BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

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Edited by Sherry R. Chemler

Generated on 05 December 2025, 16:47

Imprint

Beilstein Journal of Organic Chemistry
www.bjoc.org
ISSN 1860-5397
Email: journals-support@beilstein-institut.de

The *Beilstein Journal of Organic Chemistry* is published by the Beilstein-Institut zur Förderung der Chemischen Wissenschaften.

Beilstein-Institut zur Förderung der
Chemischen Wissenschaften
Trakehner Straße 7–9
60487 Frankfurt am Main
Germany
www.beilstein-institut.de

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Copper catalysis in organic synthesis

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Editorial
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Keywords:
copper catalysis

Beilstein J. Org. Chem. **2015,** *11,* 2252–2253.
doi:10.3762/bjoc.11.244

Received: 09 November 2015
Accepted: 13 November 2015
Published: 19 November 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Copper is a very versatile transition metal that has been used as a building material by human civilizations for over 6000 years. Copper is also an essential element, responsible for important biological processes. The title of this Thematic Series published in the Beilstein Journal of Organic Chemistry is “Copper catalysis in organic synthesis”. A web of science^{TM} topic search of “copper-catalyzed synthesis” indicated over 500 papers had been published in 2014. In point of fact, there has been a steady increase in publications on this topic since 1988. In the late 1980’s and early 1990’s, the topics centered on copper nitrene reactivity (e.g., aziridination), copper carbene chemistry, conjugate additions and cross-coupling reactions. Some of the most highly cited papers of all time on this topic are reviews on conjugate addition, cross-coupling, and [3 + 2] “Click” reaction applied to bioconjugation.

The growth in copper-catalyzed organic reactions may be driven by a couple of factors. First, copper chemistry is incredibly diverse. Depending on its oxidation state, this metal can efficiently catalyze reactions involving both one and two-electron (radical and polar) mechanisms, or both. Copper coordinates easily to heteroatoms and to π-bonds and is well-known to activate terminal alkynes. The Ullman and Goldberg C–C and C–N cross-coupling reactions were discovered over a century ago and their development has really blossomed over the past twenty years. Second, copper is an earth-abundant metal, making its use more cost effective and more sustainable than precious transition metal catalysts.

Over 25 contributions from leaders in the field of copper-catalysis from 7 countries make up this Thematic Series, “Copper catalysis in organic synthesis”. Contributions include authoritative reviews on the latest developments in copper-catalyzed Click applications, C–N cross-coupling, C–H functionalization, trifluoromethylations, asymmetric Ullmann and Goldberg couplings, asymmetric acetylide additions to carbonyl groups, radical alkylations and asymmetric conjugate additions as well as original contributions in the area of copper-catalyzed C–C cross-coupling, conjugate additions, allylic alkylations, alkene difunctionalizations, heterocycle synthesis, amide bond formation and photochemical Click reaction development.

I am grateful to the contributors and the reviewers who participated in the production of this Thematic Series. It is clear from the impact copper catalysis has had on organic synthesis that copper should be considered a first line catalyst for many organic reactions. I anticipate further growth in the field in the years to come.

Sherry R. Chemler

Buffalo, November 2015

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The definitive version of this article is the electronic one which can be found at:
doi:10.3762/bjoc.11.244

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Synthesis of alpha-tetrasubstituted triazoles by copper-catalyzed silyl deprotection/azide cycloaddition

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Full Research Paper

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Keywords:
azide; copper catalysis; multicomponent reactions; tetrasubstituted carbon; triazole

Beilstein J. Org. Chem. **2015,** *11,* 1425–1433.
doi:10.3762/bjoc.11.154

Received: 01 May 2015
Accepted: 02 July 2015
Published: 14 August 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

Propargylamines are popular substrates for triazole formation, but tetrasubstituted variants have required multistep syntheses involving stoichiometric amounts of metal. A recent cyclohexanone–amine–silylacetylene coupling forms silyl-protected tetrasubstituted propargylamines in a single copper-catalyzed step. The development of the tandem silyl deprotection–triazole formation reported herein offers rapid access to alpha-tetrasubstituted triazoles. A streamlined two-step approach to this uncommon class of hindered triazoles will accelerate exploration of their therapeutic potential. The superior activity of copper(II) triflate in the formation of triazoles from sensitive alkyne substrates extends to simple terminal alkynes.

Introduction

1,2,3-Triazoles demonstrate wide spread application in biological systems and drug development [1-12]. Copper-catalyzed azide–alkyne cycloadditions (CuAAC) regioselectively introduce a wide variety of substituents on 1,4-disubstituted 1,2,3-triazoles from the organic azide or terminal alkyne starting materials [1,2]. These Huisgen reactions [13] facilitate rapid drug screening by allowing for tracking in biological systems and the exploration of structure-activity relationships [10,14-19].

Propargylamines are a popular choice for the terminal alkyne component and form highly selective inhibitors (Figure 1) [2]. Due to the difficulty of forming tetrasubstituted propargylamines, the incorporation of deprotectable variants into triazoles is extremely rare. The Ellman group demonstrates the power of their chiral sulfinylimine protocol to synthesize propargylamine-derived alpha-tetrasubstituted triazoles (tetrasubstituted carbon bearing amine highlighted in red, Figure 1). One such triazole is a cruzain inhibitor with activity against parasite *Trypanosoma cruzi*, which causes Chagas' disease [6]. An alpha-tetrasubstituted triazole that inhibits cathepsin S can potentially treat ailments ranging from inflammation to autoimmune disorders [7,8].

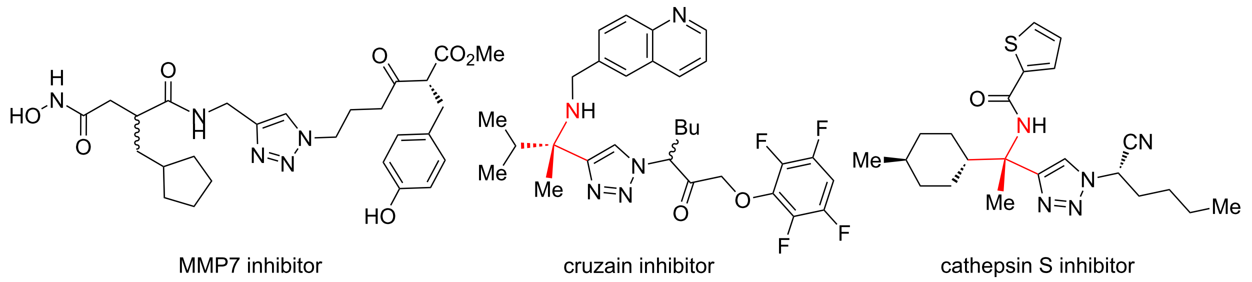

MMP7 inhibitor
cruzain inhibitor
cathepsin S inhibitor

Figure 1: A sampling of propargylamine-derived triazoles with therapeutic effects includes alpha-tetrasubstituted triazoles as cruzain and cathepsin inhibitors.

The core of the cathepsin S inhibitor is synthesized in six steps. Synthesis and isolation of an *N*-sulfinyl ketimine is followed by stoichiometric alkynylation with a trimethylsilyl-protected alkynyllithium reagent. Removal of the silyl and sulfinyl protecting groups allows for CuAAC with a resin-bound azide. Acylation of the amine followed by dehydration yields the active alpha-tetrasubstituted triazole [7].

The lengthy synthesis of tetrasubstituted propargylamine precursors limits the exploration of such alpha-tetrasubstitued triazoles. The vast majority of three-component couplings produce trisubstituted propargylamines. Copper remains the most popular catalyst for these multicomponent reactions, abbreviated as A^3 reactions to indicate the Aldehyde, Amine, and Alkyne reaction partners [20,21]. Methods for the corresponding KA^2, Ketone–Amine–Alkyne, three-component coupling reaction are rare due to the lower electrophilicity and greater steric hindrance of ketones [22-26]. Due to the release of torsional strain when the sp^2 center in the six-membered ring is attacked, cyclohexanone represents a special case as this cyclic ketone is nearly as reactive as an aldehyde [24].

The resultant tetrasubstituted (red) cyclohexylamine is found in natural alkaloids such as (–)-lycodine (Figure 2), [27] and this motif is also critical to the activity of drugs like ketamine and phencyclidine (1-(1-phenylcyclohexyl)piperidine, PCP) [28].

Tetrasubstituted carbons bearing amines can provide much higher levels of activity than the corresponding trisubstituted center. For example, fentanyl is an anesthetic that is 100 times as powerful as morphine (Figure 2) [29]. By creating a tetrasubstituted variant, the activity is increased two orders of magnitude: carfentanil is over 10,000 times as active as morphine.

Results and Discussion

Reaction optimization

The two-step/three-reaction sequence shown in Scheme 1 would streamline the synthesis of alpha-tetrasubstituted triazoles **6**. In the first step, our solvent-free copper-catalyzed three-component coupling of cyclohexanone (**1**), amines **2**, and alkynes **3** provides high yields of silyl-protected propargylic amines **4** [24,25]. Trimethylsilyl (TMS) acetylene was not stable in the presence of the copper(II) chloride catalyst, and triethylsilylacetylene did not convert cleanly to product. Triisopropylsilyl (TIPS) acetylene was found to be superior to *tert*-butyldimethylsilylacetylene as a source of silylated tetrasubstituted propargylic amines.

Although TMS-protected alkynes have been converted to triazoles via a one-pot silyl deprotection CuAAC reaction [30-33], TIPS-protected alkynes have not. As the triisopropylsilyl protecting group is more difficult to remove than the less

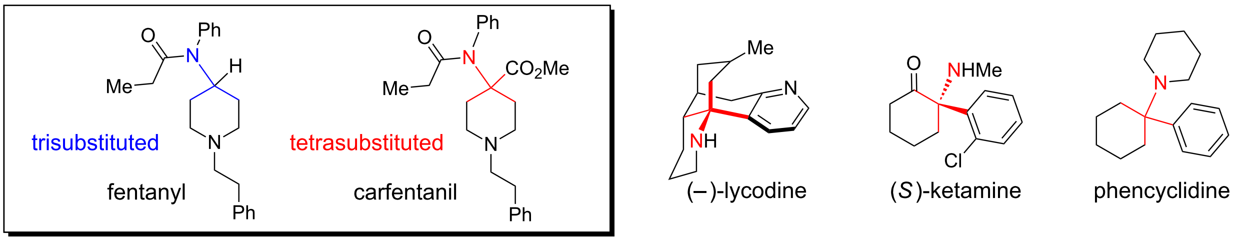
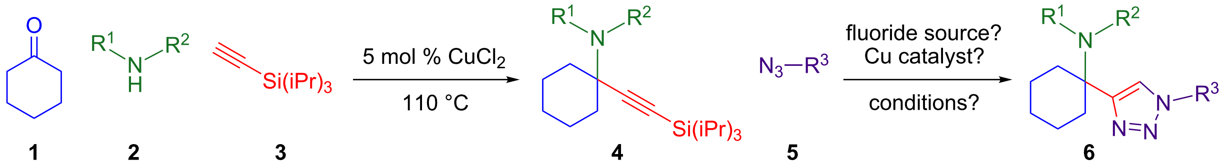

trisubstituted
fentanyl
tetrasubstituted
carfentanil
(–)-lycodine
(*S*)-ketamine
phencyclidine

Figure 2: A tetrasubstituted carbon bearing an amine (red) can provide 100-fold increase in activity compared to the trisubstituted carbon bearing an amine (blue).



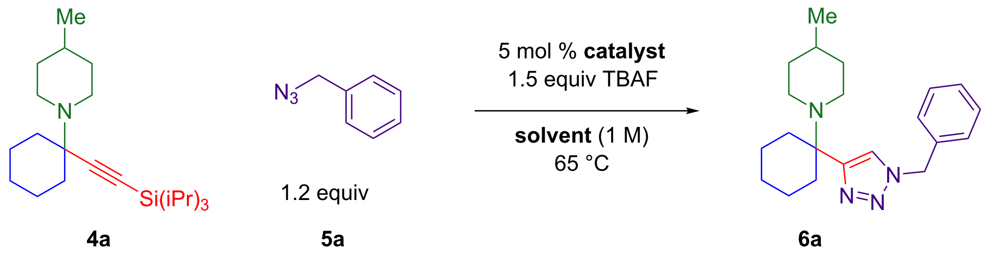
Scheme 1: KA^2 coupling followed by tandem silyl deprotection and triazole formation.

hindered trimethylsilyl, conditions for TIPS deprotection include 1.5 equiv of AgF or $Cu(OAc)_2$ combined with syringe pump addition of TBAF [34,35]. An additional difficulty is that Ellman's alpha-tetrasubstituted triazoles are synthesized by CuAAC reaction with desilylated, purified tetrasubstituted propargylic amines [6-8]. Therefore, the goal was to develop the second portion of the sequence in Scheme 1: a tandem deprotection–cycloaddition of tetrasubstituted TIPS-protected propargylamines **4** that would allow them to react in situ with various azides **5** to give hindered triazoles **6**.

As a copper(I) catalyst is required for azide–alkyne cycloaddition, the development of a method for the one-pot deprotection/CuAAC began with Cu(I) chloride and a survey of solvents reported [2] for triazole formation (Table 1). TIPS-protected propargylamine **4a** and benzyl azide (**5a**) are heated in the presence of 1.5 equivalents of TBAF (tetrabutylammonium fluoride), 5 mol % CuCl, and the solvent(s) indicated (Table 1, entries 1–6). Aqueous solvent mixtures produce only trace amounts of product at 1 h and 18 h, but methanol and *tert*-butanol provide two-thirds conversion to triazole **6a** after 18 h.

To increase the rate of reaction and to induce complete conversion to **6a**, copper(I) as well as copper(II) sources with an equal amount of sodium ascorbate as the reducing agent were tested in MeOH (Table 1, entries 6–14). All combinations of

Table 1: Optimization of silyl deprotection/cycloaddition.



Entry	Solvent[a]	Catalyst[b]	GC yield (%), 1 h	GC yield (%), 18 h
1	*t*-BuOH/H_2O (1:1 v/v)	CuCl	21	2
2	DMSO/H_2O (2:1 v/v)	CuCl	0	0
3	DMF/H_2O (1:2 v/v)	CuCl	0	0
4	THF/MeOH (1:1 v/v)	CuCl	4	34
5	*t*-BuOH	CuCl	6	62
6	MeOH	CuCl	13	65
7	MeOH	CuBr	62	63
8	MeOH	Cu Powder	24	24
9	MeOH	$CuCl_2$	72	90
10	MeOH	$CuBr_2$	65	86
11	MeOH	$CuF_2·2H_2O$	69	88
12	MeOH	$CuSO_4·5H_2O$	49	79
13	MeOH	$Cu(OAc)_2·H_2O$	46	82
14	MeOH	$Cu(OTf)_2$	39	99

[a]Entries 7–14 were carried out under an atmosphere of argon. [b]Entries 9–14 with copper(II) sources include 5 mol % of sodium ascorbate reductant.

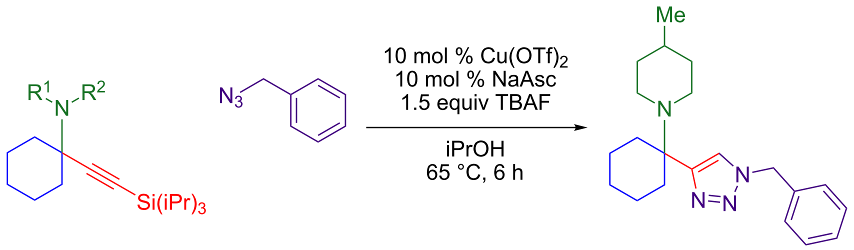
copper(II) salts with reductant provide higher GC yields (79–99%, Table 1, entries 9–14) than CuCl alone (65%, Table 1, entry 6) at 18 h – corroborating reports that CuAACs are often more efficient with copper(I) catalysts formed from the in situ reduction of copper(II) [2]. After 18 h, copper(II) chloride provides 90% GC yield (Table 1, entry 9), and copper(II) triflate unexpectedly results in quantitative GC yield of **6a** (Table 1, entry 14). Rare in CuAAC reactions, copper(II) triflate is known to form protic acid in solution, which could cause proto-desilylation [36], but this is not observed.

A broader range of green alcohol solvents [37] were assessed in the presence of the most active catalyst, in situ reduced $Cu(OTf)_2$. Isopropanol was found to provide faster conversion than methanol, ethanol, and *tert*-butanol at 1 h. A control reaction in isopropanol with in situ reduced copper(II) sources confirms that the triflate is more active than the chloride at 6 h: 67% versus 26% GC yield. Spiking the copper(II) chloride reaction with TfOH provides a similar 30% GC yield. With isopropanol as the solvent, the effect of ambient atmosphere was compared to inert atmosphere. Argon is not necessary, and an atmosphere of nitrogen provides 24% higher GC yield than air. Testing reaction concentration found no significant difference between 0.5 M to 1.0 M isopropanol but increasing the molarity to 2.0 M nearly doubles the GC yield at 18 h from 49% to 87%. Although a lower temperature of 40 °C results in incomplete conversion at 18 h, evidence of product decomposition appears at a higher temperature of 80 °C. A temperature of 60 °C provides two-thirds conversion at 1 h and 85% GC yield of triazole **6a** at 18 h. Finally, when the copper loading is varied from 2.5 mol % to 25 mol % copper(II) triflate with an equivalent loading of sodium ascorbate (NaAsc), GC yields range from 53–63%. However, isolated yields are highest with 10 mol % $Cu(OTf)_2$ plus 10 mol % NaAsc as the in situ reductant.

Substrate scope

With optimized conditions in hand, Table 2 shows the range of triisopropylsilyl cyclohexyl propargylamines that are cleanly converted to the corresponding triazole. Test substrate **6a** is isolated in 66% yield under standard conditions: 10 mol % $Cu(OTf)_2$, 10 mol % NaAsc, and 1.5 equiv TBAF in

Table 2: Tetrasubstituted silylpropargylamines form hindered triazole products.



1.0 equiv **4** | 1.2 equiv **5a** | **6**

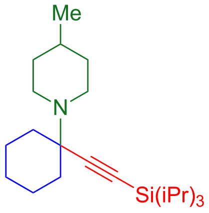
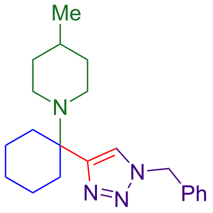
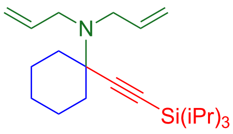
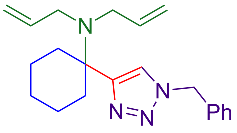
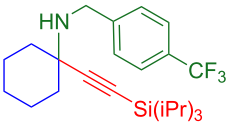
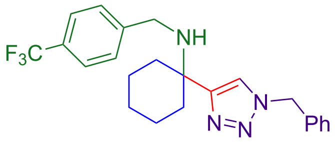
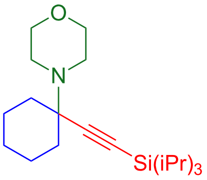
Propargylic amine **4**	Triazole product **6**
 **4a**	 **6a**, 66%
	 **6b**, 67%

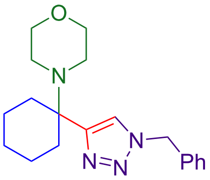
Table 2: Tetrasubstituted silylpropargylamines form hindered triazole products. (continued)



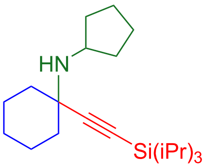


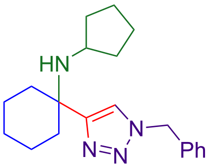
6c, 76%



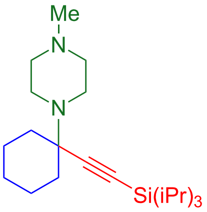


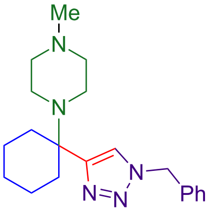
6d, 72%





6e, 65%





6f, 73%

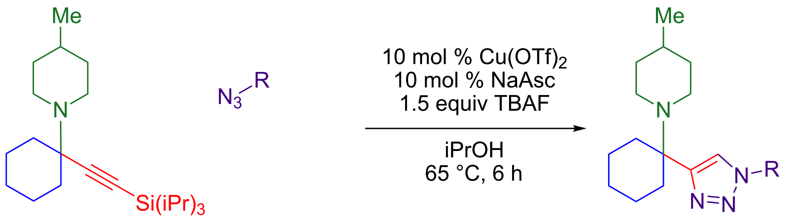
isopropanol (2.0 M) at 65 °C for 6 hours. The *N,N*-diallyl variant **6b** recrystallized in 67% yield is readily deprotectable [38]. This would allow for further elaboration in a similar fashion to the synthesis of cathepsin S inhibitor in Figure 1; *N*-deprotection followed by acylation forms the triazole amide product [6-8]. *N*-[4-(Trifluoromethyl)benzyl]triazole **6c** and morpholinyltriazole **6d** are isolated in 76% and 72% yield, respectively. Cyclopentylamine-derived **6e** and *N*-methylpiperazine-derived **6f** provide additional choices for amine substituents.

Alternate organic azides were synthesized according to known methods [39-41]. 4-Methylbenzyl azide forms triazole **6g** in a comparable yield to **6a**, but electron-poor 4-(trifluoromethyl)benzyl azide forms triazole **6h** in lower yield. Aryl and alkyl azides display parallel reactivity in the formation of triazoles **6i** and **6j**, and the HCl salt of lipophilic **6j** is isolated cleanly in 56% yield. As TIPS-protected propargylamine **4a** is utilized throughout Table 3, the lower yields observed in some cases are attributed to the intrinsic efficiency of the azide participant.

Control reactions were carried out to assess whether conditions developed for in situ silyl deprotection would otherwise affect the azide when reacting with a simpler terminal alkyne (Scheme 2). As the copper-catalyzed cycloaddition of *tert*-butylacetylene and benzyl azide proceeds in 92% yield, decomposition of the benzyl azide or non-silyl alkyne appears unlikely. Furthermore, this reaction (Scheme 2) proceeds in 92% yield without TBAF. This indicates that the sensitivity of the silyl propargylamine component causes a lower yield of the propargylamine-derived product when reacting with the same benzyl azide under the identical conditions.

This two-step sequence converts commercially available starting materials into alpha-tetrasubstituted amines via three reactions. It is important to note that triazole **6a** is formed in 65% overall yield (Scheme 3). The first step simply involves heating 5 mol % $CuCl_2$ with equimolar amounts of three starting materials, cyclohexanone (**1**), 4-methylpiperidine (**2a**), and TIPS-acetylene (**3**). As there are no added ligands, solvents, promoters, or excess starting materials, the sole byproduct in the formation of tetrasubstituted propargylamine **4a** is one equivalent of water [25]. The second step links silyl-deprotection with azide–alkyne cycloaddition, producing hindered triazoles in 6 hours. This tandem reaction was optimal with a copper(II) triflate and sodium ascorbate (NaAsc) as a mild reductant. The outcome that copper(II) triflate provides the

Table 3: Assorted azides for formation of alpha-tetrasubstituted triazoles.



1.0 equiv 1.2 equiv

4a **5** **6**

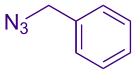
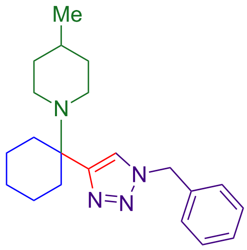
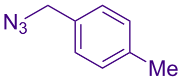
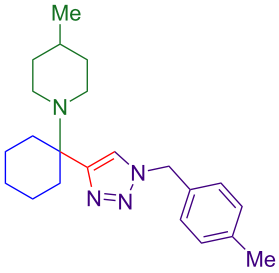
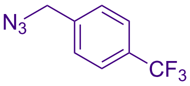
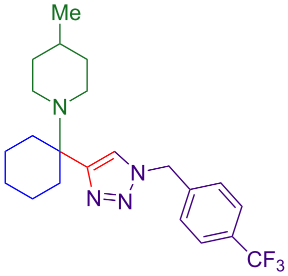
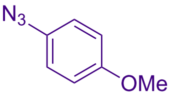
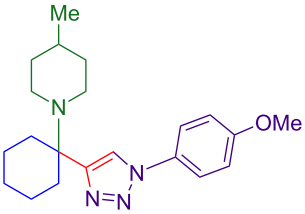
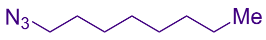
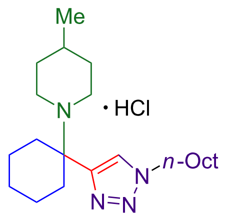
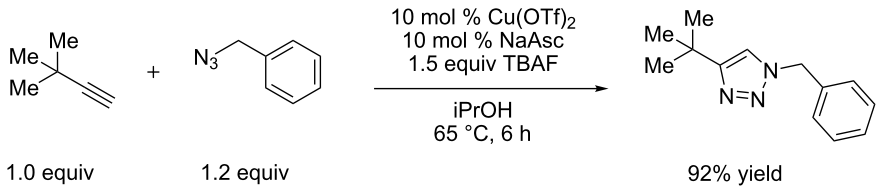
Azide **5**	Triazole product **6**
 **5a**	 **6a**, 66%
	 **6g**, 57%
	 **6h**, 29%
	 **6i**, 50%

Table 3: Assorted azides for formation of alpha-tetrasubstituted triazoles. (continued)

	 **6j**, 56%



Scheme 2: Silyl deprotection/click conditions applied to *tert*-butylacetylene. An identical yield is observed without TBAF.

highest yields for the one-pot deprotection/click reaction was unexpected as it is not known as a catalyst for azide–alkyne cycloaddition reactions [1,2].

Conclusion

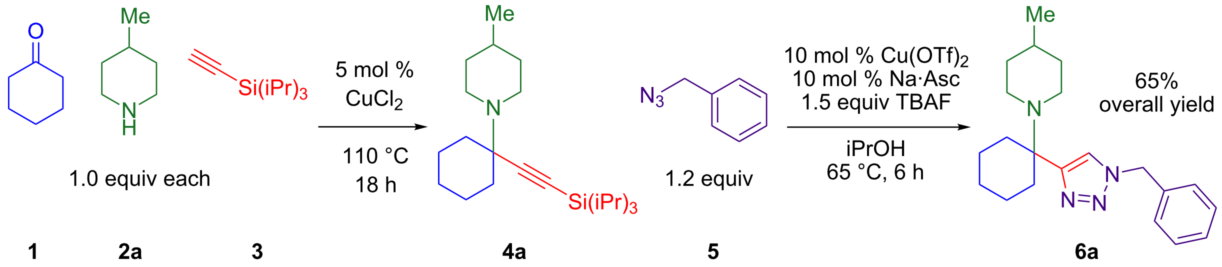
A tandem copper-catalyzed silyl deprotection/azide cycloaddition was developed for TIPS-protected tetrasubstituted propargylamines. These substrates are synthesized by a copper-catalyzed ketone–amine–alkyne (KA^2) coupling that proceeds efficiently with no additives such that an equivalent of water is the sole byproduct. This two-step sequence allows for the incorporation of tetrasubstituted carbons bearing amines at the 4-position of the 1,2,3-triazole core. The overall yield of this three-reaction sequence is high and provides rapid access to hindered triazoles in two steps from commercially available starting materials. Both steps are copper-catalyzed and convert inexpensive starting materials into high-value adducts. As the catalyst combination of copper(II) triflate and sodium ascorbate allows for the inclusion of sensitive and hindered substrates, this unprecedented method should be applicable to the robust and less hindered substrates more common in triazole literature. The power of copper catalysis will accelerate further exploration of the therapeutic potential of alpha-tetrasubstituted triazoles.

Supporting Information

The Supporting Information features experimental details, compound characterization, and copies of ^1H and ^{13}C NMR spectra of triazoles **6**.

Supporting Information File 1

Experimental details.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-154-S1.pdf]



Scheme 3: High overall yield of 1,2,3-triazole fully-substituted at the 4-position.

Acknowledgements

This material is based upon work supported by the National Science Foundation under Grant No. (NSF CAREER award CHE-1352665).

References

1. Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008,** *108,* 2952–3015. doi:10.1021/cr0783479
2. Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010,** *39,* 1302–1315. doi:10.1039/b904091a
3. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002,** *67,* 3057–3064. doi:10.1021/jo011148j
4. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002,** *41,* 2596. doi:10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4
5. Brik, A.; Muldoon, J.; Lin, Y.-C.; Elder, J. H.; Goodsell, D. S.; Olson, A. J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *ChemBioChem* **2003,** *4,* 1246–1248. doi:10.1002/cbic.200300724
6. Brak, K.; Doyle, P. S.; McKerrow, J. H.; Ellman, J. A. *J. Am. Chem. Soc.* **2008,** *130,* 6404–6410. doi:10.1021/ja710254m
7. Patterson, A. W.; Wood, W. J. L.; Hornsby, M.; Lesley, S.; Spraggon, G.; Ellman, J. A. *J. Med. Chem.* **2006,** *49,* 6298–6307. doi:10.1021/jm060701s
8. Wood, W. J. L.; Patterson, A. W.; Tsuruoka, H.; Jain, R. K.; Ellman, J. A. *J. Am. Chem. Soc.* **2005,** *127,* 15521–15527. doi:10.1021/ja0547230
9. Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005,** *127,* 15998–15999. doi:10.1021/ja054114s
10. Pagliai, F.; Pirali, T.; Del Grosso, E.; Di Brisco, R.; Tron, G. C.; Sorba, G.; Genazzani, A. A. *J. Med. Chem.* **2006,** *49,* 467–470. doi:10.1021/jm051118z
11. Srinivasan, R.; Uttamchandani, M.; Yao, S. Q. *Org. Lett.* **2006,** *8,* 713–716. doi:10.1021/ol052895w
12. Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008,** *28,* 278–308. doi:10.1002/med.20107
13. Huisgen, R. *Pure Appl. Chem.* **1989,** *61,* 613–628. doi:10.1351/pac198961040613
14. Gupte, A.; Boshoff, H. I.; Wilson, D. J.; Neres, J.; Labello, N. P.; Somu, R. V.; Xing, C.; Barry, C. E., III; Aldrich, C. C. *J. Med. Chem.* **2008,** *51,* 7495–7507. doi:10.1021/jm8008037
15. Ferreira, S. B.; Sodero, A. C. R.; Cardoso, M. F. C.; Lima, E. S.; Kaiser, C. R.; Silva, F. P., Jr.; Ferreira, V. F. *J. Med. Chem.* **2010,** *53,* 2364–2375. doi:10.1021/jm901265h
16. Van Poecke, S.; Negri, A.; Gago, F.; Van Daele, I.; Solaroli, N.; Karlsson, A.; Balzarini, J.; Van Calenbergh, S. *J. Med. Chem.* **2010,** *53,* 2902–2912. doi:10.1021/jm901532h
17. Li, Y.; Shen, M.; Zhang, Z.; Luo, J.; Pan, X.; Lu, X.; Long, H.; Wen, D.; Zhang, F.; Leng, F.; Li, Y.; Tu, Z.; Ren, X.; Ding, K. *J. Med. Chem.* **2012,** *55,* 10033–10046. doi:10.1021/jm301188x
18. Testa, C.; Scrima, M.; Grimaldi, M.; D'Ursi, A. M.; Dirain, M. L.; Lubin-Germain, N.; Singh, A.; Haskell-Luevano, C.; Chorev, M.; Rovero, P.; Papini, A. M. *J. Med. Chem.* **2014,** *57,* 9424–9434. doi:10.1021/jm501027w
19. Brik, A.; Muldoon, J.; Lin, Y.-C.; Elder, J. H.; Goodsell, D. S.; Olson, A. J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *ChemBioChem* **2003,** *4,* 1246–1248. doi:10.1002/cbic.200300724
20. Blay, G.; Monleon, A.; Pedro, J. R. *Curr. Org. Chem.* **2009,** *13,* 1498–1539. doi:10.2174/138527209789177734
21. Yoo, W. J.; Zhao, L.; Li, C.-J. *Aldrichimica Acta* **2011,** *44,* 43–51.
22. Pereshivko, O. P.; Peshkov, V. A.; Van der Eycken, E. V. *Org. Lett.* **2010,** *12,* 2638–2641. doi:10.1021/ol1008312
23. Cheng, M.; Zhang, Q.; Hu, X.-Y.; Li, B.-G.; Ji, J.-X.; Chan, A. S. C. *Adv. Synth. Catal.* **2011,** *353,* 1274–1278. doi:10.1002/adsc.201000914
24. Pierce, C. J.; Larsen, C. H. *Green Chem.* **2012,** *14,* 2672–2676. doi:10.1039/c2gc35713e
25. Palchak, Z. L.; Lussier, D. J.; Pierce, C. J.; Larsen, C. H. *Green Chem.* **2015,** *17,* 1802–1810. doi:10.1039/c4gc02318h
26. Pierce, C. J.; Nguyen, M.; Larsen, C. H. *Angew. Chem., Int. Ed.* **2012,** *51,* 12289–12292. doi:10.1002/anie.201206674
27. Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004,** *21,* 752–772. doi:10.1039/B409720N
28. Clayden, J.; Donnard, M.; Lefranc, J.; Tetlow, D. J. *Chem. Commun.* **2011,** *47,* 4624–4639. doi:10.1039/C1CC00049G
29. Vardanyan, R. S.; Hruby, V. J. *Future Med. Chem.* **2014,** *6,* 385–412. doi:10.4155/fmc.13.215
30. Aucagne, V.; Leigh, D. A. *Org. Lett.* **2006,** *8,* 4505–4507. doi:10.1021/ol061657d
31. Fletcher, J. T.; Bumgarner, B. J.; Engels, N. D.; Skoglund, D. A. *Organometallics* **2008,** *27,* 5430–5433. doi:10.1021/om800768k
32. Fletcher, J. T.; Walz, S. E.; Keeney, M. E. *Tetrahedron Lett.* **2008,** *49,* 7030–7032. doi:10.1016/j.tetlet.2008.09.136
33. Beltrán, E.; Serrano, J. L.; Sierra, T.; Giménez, R. *Org. Lett.* **2010,** *12,* 1404–1407. doi:10.1021/ol902900y
34. Escamilla, I. V.; Ramos, L. F. R.; Escalera, J. S.; Hernandez, A. A. *J. Mex. Chem. Soc.* **2011,** *55,* 133–136.
35. Heuft, M. A.; Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2001,** *3,* 2883–2886. doi:10.1021/ol016414u
36. Meyet, C. E.; Pierce, C. J.; Larsen, C. H. *Org. Lett.* **2012,** *14,* 964–967. doi:10.1021/ol2029492
37. Jessop, P. G. *Green Chem.* **2011,** *13,* 1391–1398. doi:10.1039/c0gc00797h
38. Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002,** *41,* 2535–2538. doi:10.1002/1521-3773(20020715)41:14<2535::AID-ANIE2535>3.0.CO;2-M
39. Shinde, S. S.; Chi, H. M.; Lee, B. S.; Chi, D. Y. *Tetrahedron Lett.* **2009,** *50,* 6654–6657. doi:10.1016/j.tetlet.2009.09.064
40. Asano, K.; Matsubara, S. *Org. Lett.* **2010,** *12,* 4988–4991. doi:10.1021/ol101990d
41. Rossy, C.; Majimel, J.; Delapierre, M. T.; Fouquet, E.; Felpin, F.-X. *J. Organomet. Chem.* **2014,** *755,* 78–85. doi:10.1016/j.jorganchem.2014.01.006

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doi:10.3762/bjoc.11.154

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Copper-catalyzed aerobic radical C–C bond cleavage of N–H ketimines

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Full Research Paper

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Keywords:
C–C bond cleavage; copper; ketimines; molecular oxygen; radical

Beilstein J. Org. Chem. **2015,** *11,* 1933–1943.
doi:10.3762/bjoc.11.209

Received: 23 July 2015
Accepted: 23 September 2015
Published: 19 October 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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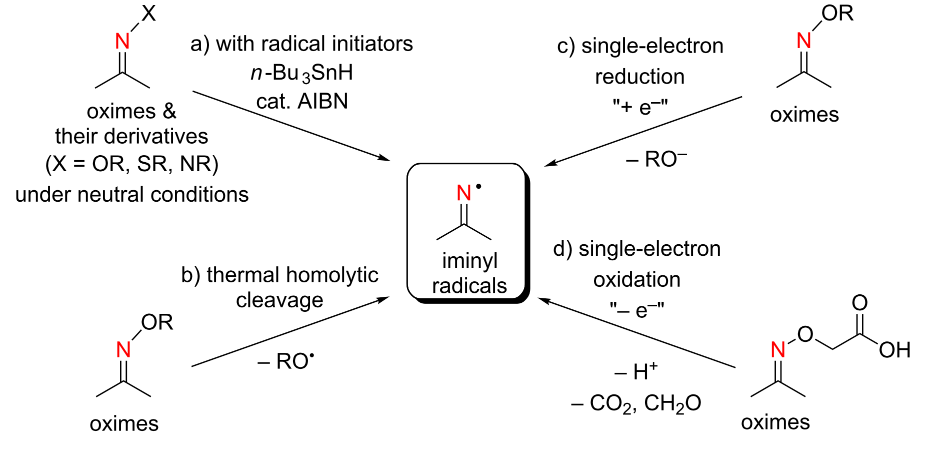
Abstract

We report herein studies on copper-catalyzed aerobic radical C–C bond cleavage of N–H ketimines. Treatment of N–H ketimines having an α-sp^3 hybridized carbon under Cu-catalyzed aerobic reaction conditions resulted in a radical fragmentation with C–C bond cleavage to give the corresponding carbonitrile and carbon radical intermediate. This radical process has been applied for the construction of oxaspirocyclohexadienones as well as in the electrophilic cyanation of Grignard reagents with pivalonitrile as a CN source.

Introduction

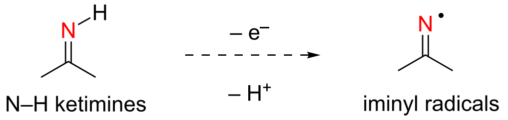
Alkylideneaminyl radicals (iminyl radicals) have been utilized for the synthesis of azaheterocycles through an intramolecular N–C bond formation with the unsaturated systems [1-6]. As precursors of iminyl radicals, readily available oximes and their derivatives have commonly been utilized. The generation of iminyl radicals involves the homolysis of the N–O bond with radical initiators [7-15] (Scheme 1a) or using thermal [16-20] or photoreaction conditions [21-27] (Scheme 1b). An alternative route to iminyl radicals is the single-electron reduction of oxime derivatives mediated by the appropriate lower valent transition metals [28-32], electron-rich organic electron donors [33-38], or sensitized photolysis [39-42] (Scheme 1c). Although the oxidative generation of iminyl radicals has also been reported, only iminooxyacetic acids have been used as the precursors when we started our studies on the oxidative reactions of N–H ketimines [43-49] (Scheme 1d).

The generation of iminyl radicals by single-electron oxidation of N–H ketimines appears to be the most atom economical method, since only protons (H^+) are produced along with the



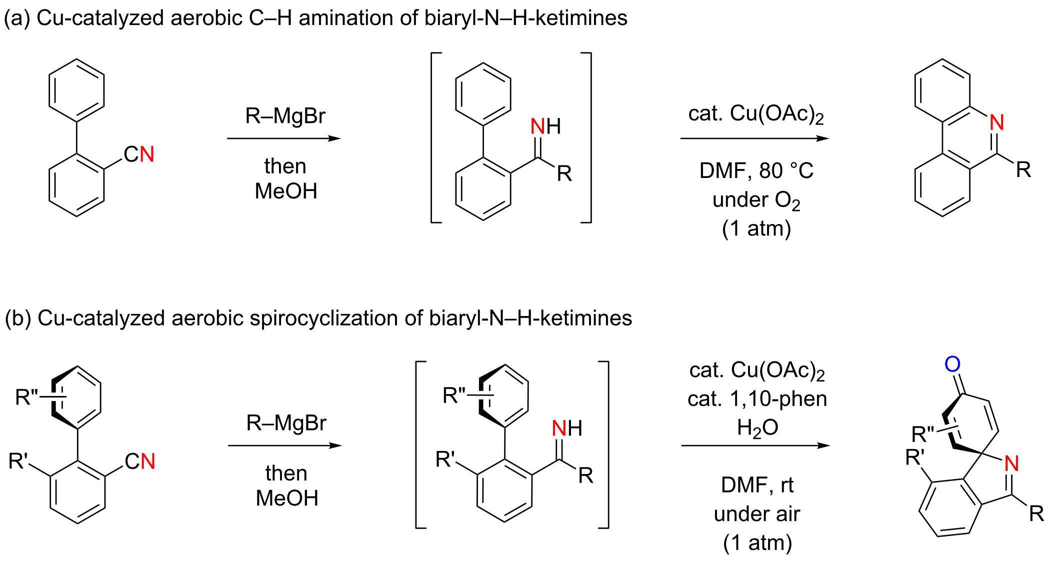
Scheme 1: Generation of iminyl radicals from oxime derivatives.

iminyl radicals (Scheme 2). However, the instability of N–H ketimines [50] limits their use as starting materials.



Scheme 2: Oxidative generation of iminyl radicals from N–H ketimines.

Recently, we have studied the chemical reactivity of N–H ketimines towards copper-catalyzed aerobic reaction conditions [51-53]. In these studies, we employed the nucleophilic addition of Grignard reagents to carbonitriles followed by protonation as one of the methods for in situ generation of N–H ketimines, which were directly subjected to Cu-catalyzed aerobic reactions without further purification [54]. In this way, biaryl N–H ketimines generated from biaryl-2-carbonitriles were found to undergo copper-catalyzed aerobic aromatic C–H amination (Scheme 3a) [52] or 1,4-aminooxygenation (spirocyclization) (Scheme 3b) [51], affording phenanthridine deriva-



Scheme 3: Copper-catalyzed aerobic reactions of in situ generated biaryl N–H ketimines.

tives and azaspirocyclohexadienones, respectively, depending on the helical sense of the biaryl axis.

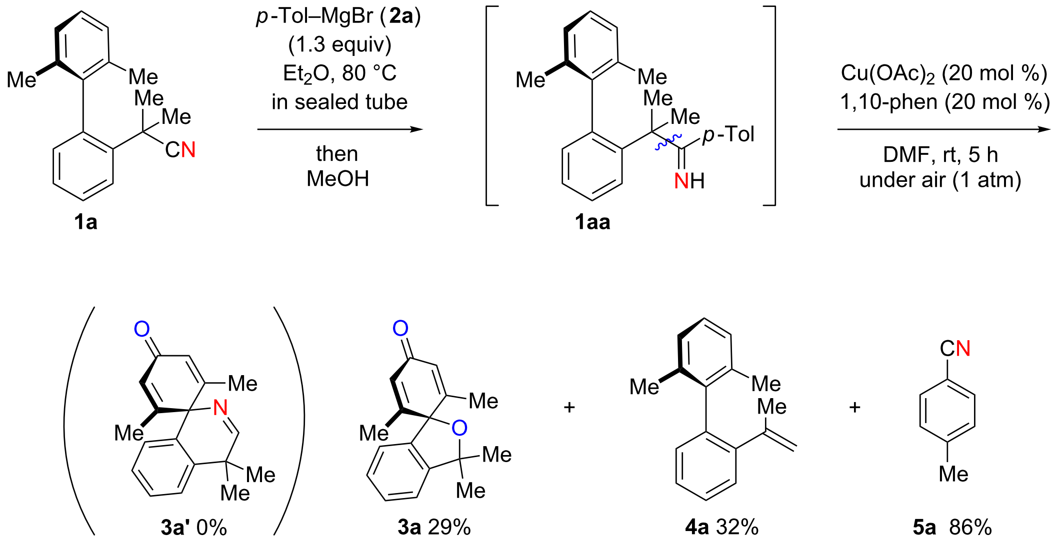
Herein we report applications of the copper-catalyzed aerobic C–C bond fission of iminyl radical species for the synthesis of oxaspirocyclohexadienones as well as the electrophilic cyanation of Grignard reagents using the readily available pivalonitrile as a CN source.

Results and Discussion

We further explored the reactivity of biaryl N–H ketimines under copper-catalyzed aerobic reaction conditions, aiming at the synthesis of 6-membered azaspirocycles such as **3a’** from carbonitrile **1a** having a quaternary sp^3-hybridized carbon center at its α-position. The reaction of *p*-tolylmagnesium bromide (**2a**) to carbonitrile **1a** proceeded smoothly in Et_2O at 80 °C in a sealed tube, generating N–H ketimine **1aa** after protonation with MeOH. Subsequently, $Cu(OAc)_2$ (20 mol %), 1,10-phen (20 mol %) and DMF (to 0.1 M final concentration) were added and stirred at room temperature under an air atmosphere (Scheme 4). Interestingly, no formation of the desired 6-membered azaspirocycle **3a’** was observed, while oxaspirocyclohexadienone **3a**, biaryl alkene **4a**, and *p*-tolunitrile (**5a**) were isolated in 29%, 32%, and 86% yields, respectively (Scheme 4).

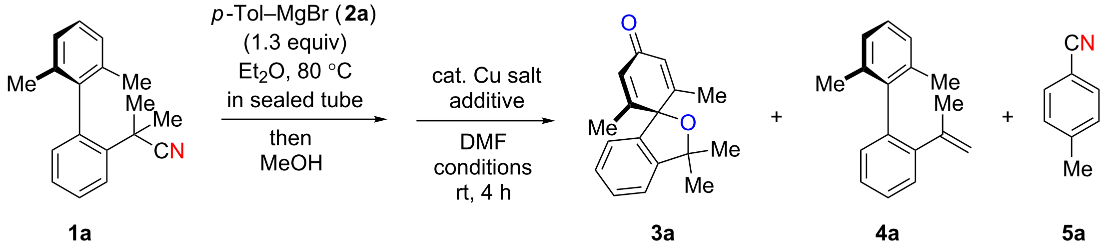
Oxaspirocyclohexadienone **3a** was formed through C–C bond cleavage from N–H ketimine intermediate **1aa** most likely via the corresponding iminyl radical, that undergoes radical fragmentation to afford the corresponding C-radical and carbonitrile **5a** [55]. Thus, it is deduced that oxaspirocyclohexadienone **3a** was formed through oxygenation of the putative C-radical. Moreover, in this transformation, the cyano group of carbonitrile **1a** is transferred to Grignard reagent **2a** to afford *p*-tolunitrile (**5a**). Considering the importance of carbonitriles in organic synthesis [56], we postulated that the cyano group transfer from simple carbonitriles onto Grignard reagents could be realized using this strategy.

Based on these preliminary results (Scheme 4), we next started to investigate the synthesis of oxaspirocyclohexadienones as the target product. Using carbonitrile **1a** and *p*-tolylmagnesium bromide (**2a**), an optimization of the reaction conditions was conducted (Table 1). Increasing the amount of the additive 1,10-phenanthroline to 40 mol % slightly improved the yield, giving **3a** in 40% yield (Table 1, entry 1). The use of 2,2’-bipyridine (bpy) provided a comparable result (Table 1, entry 2), while performing the reaction in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) led to lower yields of spirodienone **3a** (Table 1, entry 3). We therefore decided to proceed with 1,10-phenanthroline as the optimal ligand and subsequently tested different Cu(II) and Cu(I) salts (Table 1, entries 4–7). The best results were obtained using 40 mol % CuI which provided **3a** in 46% isolated yield (Table 1, entry 7). A reduction of the catalyst loading to 20 mol % slightly lowered the yield of **3a** (Table 1, entry 9) and a stoichiometric amount of catalyst did not significantly improve the yield of **3a** (Table 1, entry 10). Performing the reaction under an O_2 atmosphere did also not increase the yield of **3a** (Table 1, entry 8).



Scheme 4: Copper-catalyzed aerobic C–C bond cleavage reactions of N–H ketimines.

Table 1: Optimization of reaction conditions: oxaspirocyclohexadienone synthesis.[a]



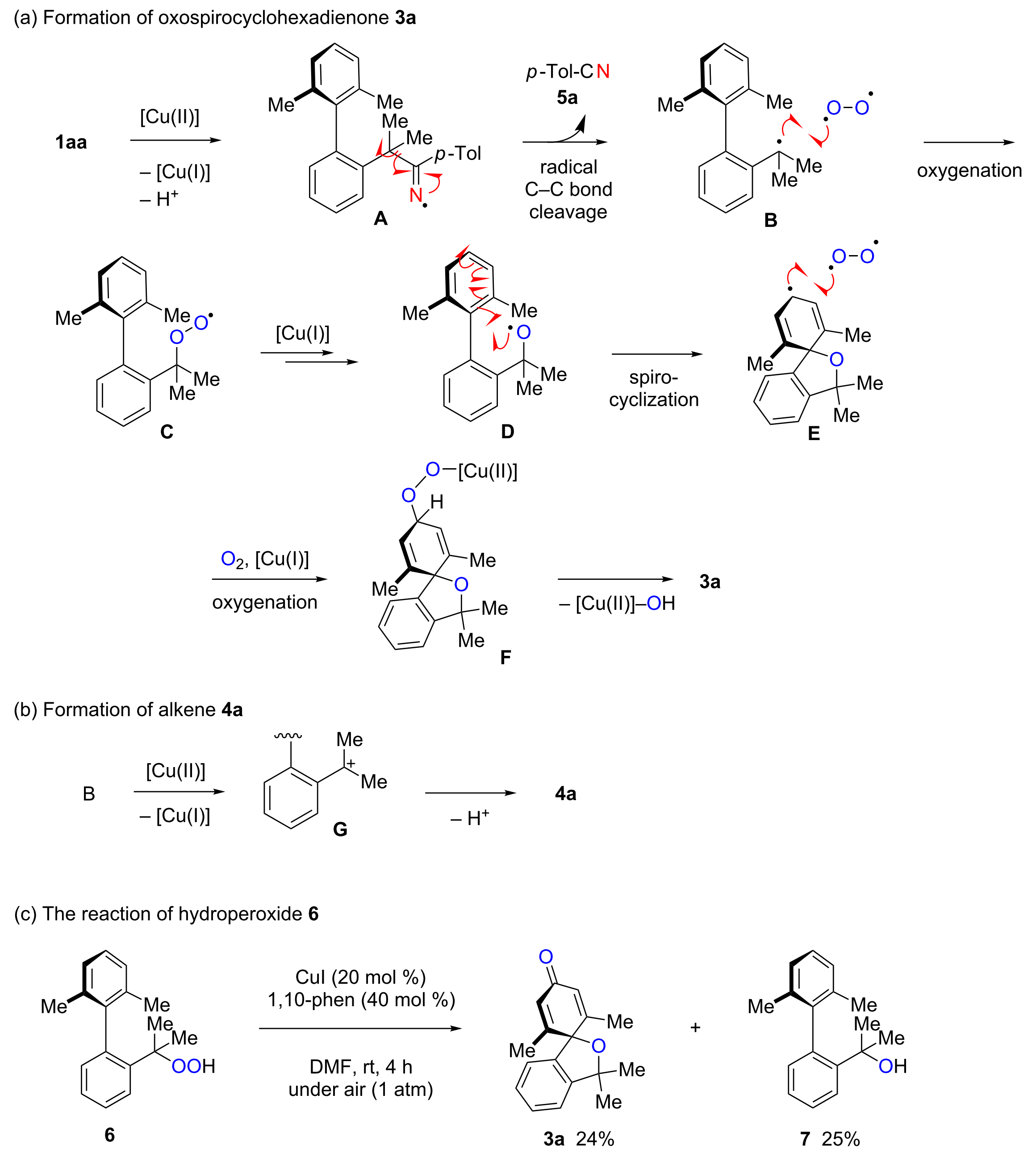
Entry	Cu salt [mol %]	Additive [mol %]	Atmosphere	Yield [%][b]		
				3a	**4a**	**5a**
1	$Cu(OAc)_2$ [20]	1,10-phen [40]	air	35 (40)	32 (31)	85 (86)
2	$Cu(OAc)_2$ [20]	bpy [40]	air	32	36	80
3	$Cu(OAc)_2$ [20]	DABCO [40]	air	10	21	87
4	$CuCl_2$ [20]	1,10-phen [40]	air	27	22	78
5	CuCl [20]	1,10-phen [40]	air	37	28	96
6	[20]	1,10-phen [40]	air	40 (40)[c]	34 (27)[c]	95 (90)[c]
7	**CuI** [20]	**1,10-phen** [40]	air	**42 (46)**[c]	**34 (28)**[c]	**92 (78)**[c]
8	CuI [20]	1,10-phen [40]	O_2	43	37	99
9	CuI [10]	1,10-phen [20]	air	37	34	95
10	CuI [100]	1,10-phen [100]	air	46	30	93

[a]All reactions were carried out using 0.5 mmol of biaryl carbonitrile **1a** with 1.3 equiv of Grignard reagent **2a** in Et_2O (0.5 mL) at 80 °C (sealed tube) for 4 h followed by the addition of MeOH (60 μL, 3.0 equiv), DMF (5 mL), Cu catalyst and additive and subsequent stirring for 4 h at rt: 1,10-phen = 1,10-phenanthroline; bpy = 2,2'-bipyridine; DABCO = 1,4-diazabicyclo[2.2.2]octane. [b]Crude yields determined by ^1H NMR based on 1,1,2,2-tetrachloroethane as an internal standard. [c]Isolated yields are given in parentheses.

A proposed reaction mechanism for the formation of oxaspirocyclohexadienone **3a**, alkene **4a**, and *p*-tolunitrile (**5a**) are depicted in Scheme 5. Single-electron oxidation of N–H ketimine **1aa** with higher valent Cu(II) species generated under the aerobic reaction conditions forms iminyl radical species **A**, that undergoes β-carbon fragmentation to give *p*-tolunitrile (**5a**) and biaryl-2-isopropyl radical **B** (Scheme 5a). The aerobic oxygenation of C-radical **B** affords peroxy radical **C**, that is presumably reduced by Cu(I) species through the Fenton-type mechanism [57] to give alkoxy radical **D** [58]. Subsequent spirocyclization of the alkoxy radical **D** onto the benzene ring affords cyclohexadienyl radical **F**, oxygenation of which followed by C=O bond formation finally provides the oxaspirocyclohexadienone product **3a**. Whereas, the oxidation of the benzylic radical **B** by the existing Cu(II) species to carbocation **G** and subsequent E1-type elimination of a proton provides biaryl alkene **4a** (Scheme 5b). The presence of alkoxy radical **D** in the reaction process could be further supported by the reaction of biaryl hydroperoxide **6**, which could be converted into the alkoxy radical **D** under copper-catalyzed aerobic reaction conditions [58]. Indeed treatment of hydroperoxide **6** under the standard reaction conditions afforded **3a** in 24% yield along with biaryl alcohol **7** in 25% yield (Scheme 5c).

While formation of biaryl alkene **4a** could not be avoided at this moment, it is still appealing to probe the potential utility of the current transformation toward the synthesis of oxaspirocyclohexadienones **3**. Therefore, the reactions of carbonitriles **1b**–**d** were examined under the current best reaction conditions (Table 1, entry 8) using *p*-tolyl Grignard reagent **2a** (Table 2). Carbonitrile **1b**, having methyl groups in ortho-positions on both aryl rings of the biaryl moiety, underwent the C–C bond fission process smoothly to afford oxaspirocyclized product **3b** and biaryl alkene **4b** in 48% and 35% yields, respectively, along with *p*-tolunitrile (**5a**) in 90% yield (Table 2, entry 1). The reactions of N–H ketimines having cyclopentyl and tetrahydropyranyl rings derived from nitriles **1c** and **1d**, respectively, afforded tricyclic oxaspirocyclohexadienones **3c** and **3d** in moderate yields along with the corresponding alkenes **4c** and **4d** as well as *p*-tolunitrile (**5a**) (Table 2, entries 2 and 3).

On the other hand, the reaction starting from carbonitrile **1e** having a strained cyclobutane ring did not form the desired oxaspirocyclohexadienone (Scheme 6). Instead, γ-bromoketone **8e** was isolated in 44% yield along with nitrile **5a** in 80% yield. The formation of γ-bromoketone **8e** is most likely caused by radical ring opening from the transient cyclobutoxy radical **I**,

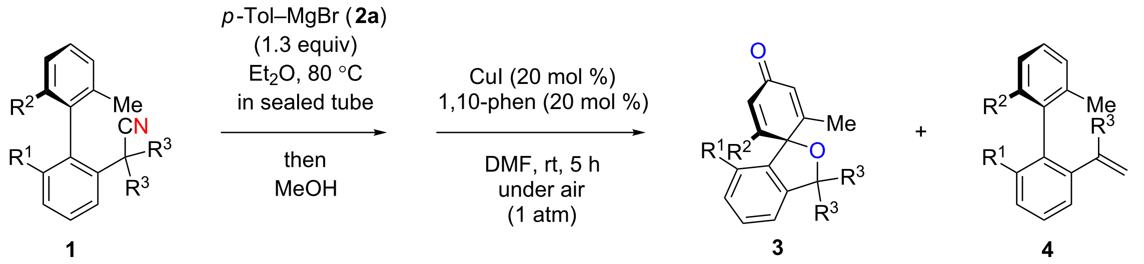


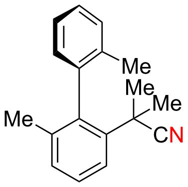
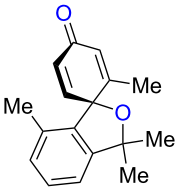
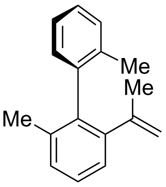
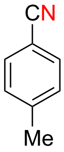
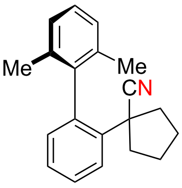
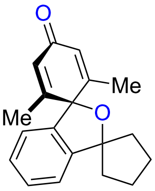
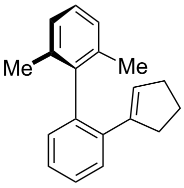
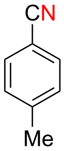
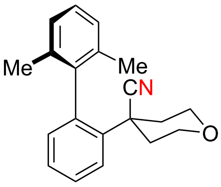
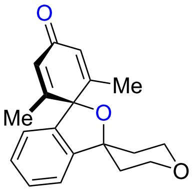
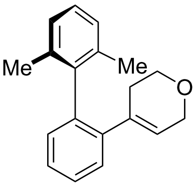
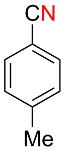
Scheme 5: Proposed reaction mechanisms for the formation of **3a**, **4a** and **5a**, and the reaction of hydroperoxide **6**.

which is driven by releasing ring strain of the cyclobutyl ring. The resulting γ-keto radical **J** subsequently undergoes radical bromination to form **8e** [59]. This result unambiguously supports the presence of the alkoxy radical intermediate during oxaspirocyclohexadienone formation in our mechanistic proposal.

Next, we turned our attention to apply the present copper-catalyzed aerobic C–C bond fission process in the electrophilic cyanation of Grignard reagents. As carbonitriles are omnipresent components in various natural products, dyes and potent pharmaceutical drugs [60-62], new and versatile routes towards this substance class are always desirable. Conventional methods to install the cyano group on aryl rings such as the Rosenmund–von Braun reaction [63] or the Sandmeyer reaction [64] require the use of stoichiometric amounts of toxic metal cyanides (such as CuCN) as the “CN” anion source [65]. Therefore, an employment of aliphatic carbonitriles which are

Table 2: Substrate scope: oxaspirocyclohexadienone synthesis.[a]



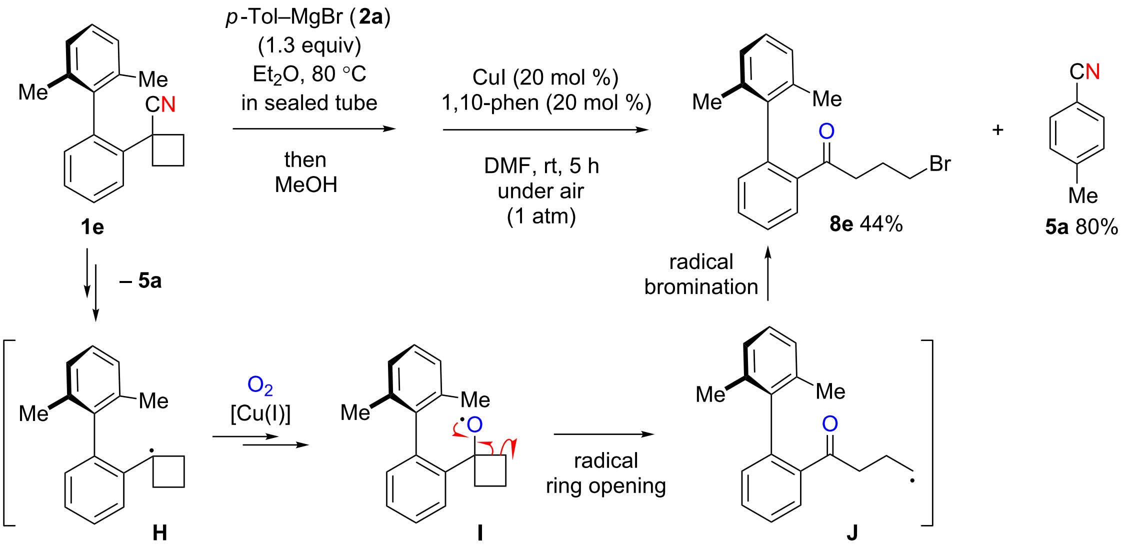
Entry	Substrate	Products[b]		
1	 **1b**	 **3b** 48%	 **4b** 35%	 **5a** 90%[c]
2	 **1c**	 **3c** 36%	 **4c** 27%	 **5a** 76%[c]
3	 **1d**	 **3d** 48%	 **4d** 40%	 **5a** 90%[c]

[a] All reactions were carried out using 0.5 mmol of biaryl carbonitrile **1** with 1.3 equiv of Grignard reagents **2a** in Et_2O (0.5 mL) at 80 °C (sealed tube) for 4 h followed by the addition of MeOH (60 µL , 3.0 equiv), DMF (5 mL), CuI (20 mol %) and 1,10-phen (40 mol %) under ambient air at rt: 1,10-phen = 1,10-phenanthroline. [b] Isolated yields. [c] ^1H NMR crude yields based on 1,1,2,2-tetrachloroethane as an internal standard.

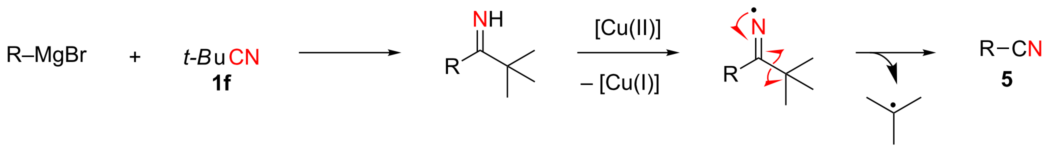
less toxic and easier to handle (such as acetonitrile [66-70], benzyl cyanide [71-76], and malononitrile [77,78]) for the "CN" surrogates has been developed more recently [79]. We envisioned that the readily available pivalonitrile (**1f**) could be a potential CN source for the electrophilic cyanation [80-86] of Grignard reagents using the present protocol (Scheme 7).

Thus pivalonitrile (**1f**) was reacted with 2-naphthylmagnesium bromide (**2b**) for formation of the corresponding N–H ketimine **1fb**, which was subsequently treated with 10 mol % of $Cu(OAc)_2$ under an O_2 atmosphere (Scheme 8). As expected, formation of 2-naphthonitrile (**5b**) was observed in 79% yield. On the other hand, the reaction in the absence of O_2 (under an Ar atmosphere) provided only 2-pivaloylnaphthalene (**9b**) in 83% yield formed through hydrolysis of unreacted N–H imine **1fb** during the aqueous work-up. Therefore molecular oxygen is indispensable to achieve the present cyanation through the C–C bond cleavage of the N–H ketimine. It was found that use of $CuBr_2$ as the catalyst resulted in formation of **5b** in higher yield (86%).

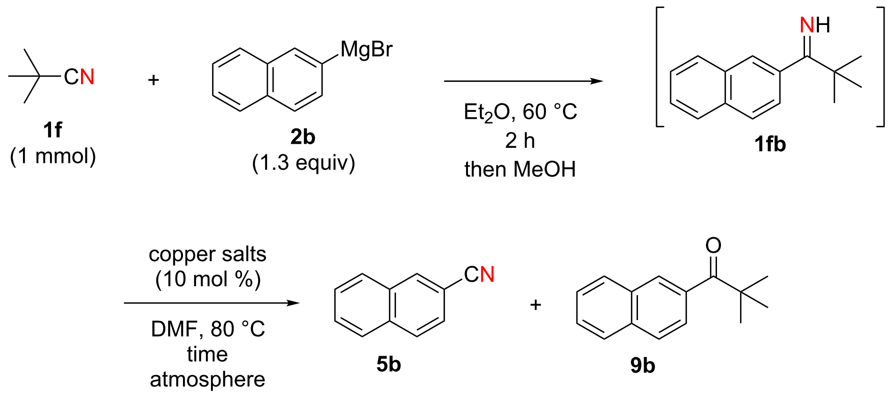
We next examined the substrate scope using different Grignard reagents (Table 3). The electrophilic cyanation proceeded smoothly even with sterically bulky Grignard reagents such as 1-naphthyl- and 2,4,6-trimethylphenyl Grignard reagents (for **5c** and **5d**) (Table 3, entries 1 and 2). Electron-rich aryl Grignard



Scheme 6: Formation of bromoketone **6e**.



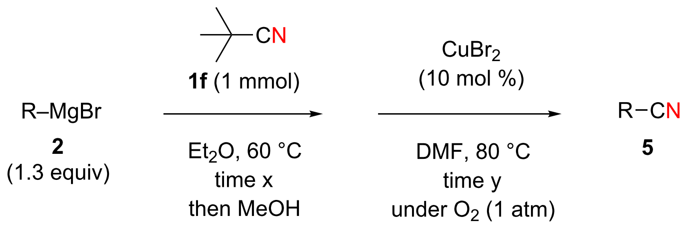
Scheme 7: Electrophilic cyanation of Grignard reagents with pivalonitrile (**1f**).

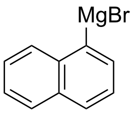
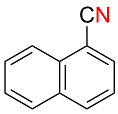
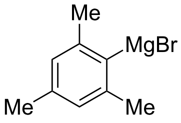
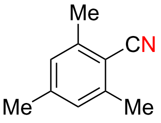
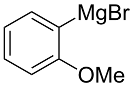
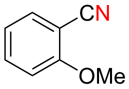
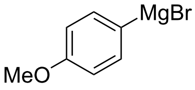
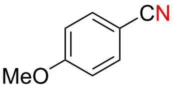
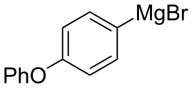
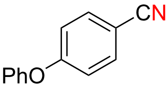
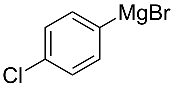
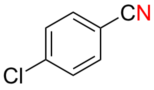
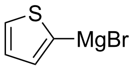
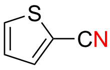
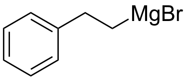
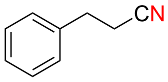


copper salts	atmosphere	time	**5b**	**9b**
$Cu(OAc)_2$	O_2	8 h	79%	0%
$Cu(OAc)_2$	Ar	24 h	0%	83%
$CuBr_2$	O_2	6 h	86%	0%

Scheme 8: Electrophilic cyanation with pivalonitrile (**1e**).

Table 3: Scope of the reaction using different Grignard reagents.[a]



Entry	R–MgBr (**2**)	Time x/y (h)	Product **5**[b]
1	 **2c**	12/18	 **5c** 76%
2[c]	 **2d**	56/19	 **5d** 81%
3[c]	 **2e**	50/18	 **5e** 67%
4	 **2f**	22/10	 **5f** 74%
5	 **2g**	48/24	 **5g** 81%
6	 **2h**	48/55	 **5h** 70%
7	 **2i**	48/24	 **5i** 63%[d]
8	 **2j**	48/48	 **5j** 47%

[a] Unless otherwise noted, the reactions were carried out using 1 mmol of pivalonitrile (**1f**) with 1.3 equiv of Grignard reagents **2** in Et_2O (1 mL) at 60 °C (sealed tube) for the time x followed by the addition of MeOH (120 μL), DMF (10 mL), and $CuBr_2$ (10 mol %), and the mixture was stirred at 80 °C for time y under an O_2 atmosphere. [b] Isolated yields. [c] The reaction was conducted using $Cu(OAc)_2$ (10 mol %) as the catalyst. [d] ^1H NMR yield.

reagents could also be used to give the corresponding benzonitriles **5e**, **5f** and **5g** in good yields (Table 3, entries 3–5). The reaction also proceeded with chlorinated substrates leaving the C–Cl bond intact (for **5h**) (Table 3, entry 6). Thiophen-2-carbonitrile (**5i**) was also prepared in 63% yield. The present method could also be applied for the cyanation of the primary alkyl Grignard reagent, phenethylmagnesium bromide (for **5j**), albeit the product yield was moderate.

Conclusion

In summary, we have demonstrated a copper-catalyzed aerobic generation of iminyl radicals from the corresponding N–H ketimines and their radical C–C bond fission. These processes could be applied for synthesis of oxaspirocyclohexadienones through spirocylization of the transient alkoxy radicals generated by aerobic oxygenation of the resulting carbon radicals. With the present protocol, the electrophilic cyanation of Grignard reagents was also established using readily available pivalonitrile as a simple CN source.

Supporting Information

Supporting Information File 1

Full experimental details and analytical data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-209-S1.pdf]

Acknowledgements

This work was supported by funding from Nanyang Technological University and Singapore Ministry of Education (Academic Research Fund Tier 2: MOE2012-T2-1-014).

References

1. Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2008,** *81,* 539–547. doi:10.1246/bcsj.81.539
2. Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005,** 4505–4519. doi:10.1002/ejoc.200500389
3. Stella, L. Nitrogen-Centered Radicals. In *Radicals in Organic Synthesis;* Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 407–426. doi:10.1002/9783527618293.ch45
4. Mikami, T.; Narasaka, K. Generation of radical species by single electron transfer reactions and their application to the development of synthetic reactions. In *Advances in Free Radical Chemistry;* Zard, S. Z., Ed.; JAI: Stanford, 1999; Vol. 2, pp 45–88. doi:10.1016/S1874-5237(99)80004-X
5. Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997,** *53,* 17543–17594. doi:10.1016/S0040-4020(97)10060-6
6. Zard, S. Z. *Synlett* **1996,** *12,* 1148–1154. doi:10.1055/s-1996-5698
7. El Kaim, L.; Meyer, C. *J. Org. Chem.* **1996,** *61,* 1556–1557. doi:10.1021/jo952173q
8. Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1995,** *36,* 8791–8794. doi:10.1016/0040-4039(95)01878-L
9. Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1995,** *51,* 6517–6528. doi:10.1016/0040-4020(95)00319-4
10. Callier, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1994,** *35,* 6109–6112. doi:10.1016/0040-4039(94)88089-1
11. Boivin, J.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron Lett.* **1994,** *35,* 249–252. doi:10.1016/S0040-4039(00)76523-3
12. Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron* **1994,** *50,* 1757–1768. doi:10.1016/S0040-4020(01)80850-4
13. Boivin, J.; Fouquet, E.; Zard, S. Z. *J. Am. Chem. Soc.* **1991,** *113,* 1055–1057. doi:10.1021/ja00003a057
14. Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron* **1994,** *50,* 1745–1756. doi:10.1016/S0040-4020(01)80849-8
15. Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron Lett.* **1990,** *31,* 3545–3548. doi:10.1016/S0040-4039(00)94438-1
16. Cai, Y.; Jalan, A.; Kobosumi, A. R.; Castle, S. T. *Org. Lett.* **2015,** *17,* 488–491. doi:10.1021/ol5035047
17. Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *Chem. Commun.* **2007,** 4041–4043. doi:10.1039/b712582h
18. Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *J. Org. Chem.* **2008,** *73,* 5558–5565. doi:10.1021/jo800847h
19. Blake, J. A.; Pratt, D. A.; Lin, S.; Walton, J. C.; Mulder, P.; Ingold, K. U. *J. Org. Chem.* **2004,** *69,* 3112–3120. doi:10.1021/jo049927y
20. Lin, X.; Stien, D.; Weinreb, S. M. *Org. Lett.* **1999,** *1,* 637–640. doi:10.1021/ol990720e
21. Faulkner, A.; Race, N. J.; Scott, J. S.; Bower, J. F. *Chem. Sci.* **2014,** *5,* 2416–2421. doi:10.1039/c4sc00652f
22. Bingham, M.; Moutrille, C.; Zard, S. Z. *Heterocycles* **2014,** *88,* 953–960. doi:10.3987/COM-13-S(S)94
23. Portela-Cubillo, F.; Lymer, J.; Scanlan, E. M.; Scott, J. S.; Walton, J. C. *Tetrahedron* **2008,** *64,* 11908–11916. doi:10.1016/j.tet.2008.08.112
24. Alonso, R.; Campos, P. J.; Rodríguez, M. A.; Sampedro, D. *J. Org. Chem.* **2008,** *73,* 2234–2239. doi:10.1021/jo7025542
25. Alonso, R.; Campos, P. J.; García, B.; Rodríguez, M. A. *Org. Lett.* **2006,** *8,* 3521–3523. doi:10.1021/ol061258i
26. Gagosz, F.; Zard, S. Z. *Synlett* **1998,** 1978–1980.
27. Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron Lett.* **1991,** *32,* 4299–4302. doi:10.1016/S0040-4039(00)92153-1
28. Zhao, M.-N.; Liang, H.; Ren, Z.-H.; Guan, Z.-H. *Synthesis* **2012,** *44,* 1501–1506. doi:10.1055/s-0031-1290779
29. Tanaka, K.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2005,** *78,* 1659–1664. doi:10.1246/bcsj.78.1659
30. Koganemaru, Y.; Kitamura, M.; Narasaka, K. *Chem. Lett.* **2002,** *31,* 784–785. doi:10.1246/cl.2002.784
31. Boivin, J.; Schiano, A.-M.; Zard, S. Z.; Zhang, H. *Tetrahedron Lett.* **1999,** *40,* 4531–4534. doi:10.1016/S0040-4039(99)00720-0
32. Boivin, J.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron Lett.* **1992,** *33,* 7849–7852. doi:10.1016/S0040-4039(00)74760-5
33. Kitamura, M.; Yoshida, M.; Kikuchi, T.; Narasaka, K. *Synthesis* **2003,** *15,* 2415–2426. doi:10.1055/s-2003-42439
34. Yoshida, M.; Kitamura, M.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **2003,** *76,* 2003–2008. doi:10.1246/bcsj.76.2003
35. Yoshida, M.; Kitamura, M.; Narasaka, K. *Chem. Lett.* **2002,** *31,* 144–145. doi:10.1246/cl.2002.144
36. Uchiyama, K.; Hayashi, Y.; Narasaka, K. *Tetrahedron* **1999,** *55,* 8915–8930. doi:10.1016/S0040-4020(99)00453-6
37. Uchiyama, K.; Ono, A.; Hayashi, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1998,** *71,* 2945–2955. doi:10.1246/bcsj.71.2945
38. Ono, A.; Uchiyama, K.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1998,** *27,* 437–438. doi:10.1246/cl.1998.437
39. Jiang, H.; An, X.; Tong, K.; Zheng, T.; Zhang, Y.; Yu, S. *Angew. Chem., Int. Ed.* **2015,** *54,* 4055–4059. doi:10.1002/anie.201411342
40. McBurney, R. T.; Slawin, A. M. Z.; Smart, L. A.; Yu, Y.; Walton, J. C. *Chem. Commun.* **2011,** *47,* 7974–7976. doi:10.1039/c1cc12720a
41. Kitamura, M.; Mori, Y.; Narasaka, K. *Tetrahedron Lett.* **2005,** *46,* 2373–2376. doi:10.1016/j.tetlet.2005.02.062
42. Mikami, T.; Narasaka, K. *Chem. Lett.* **2000,** *29,* 338–339. doi:10.1246/cl.2000.338

43. Forrester, A. R.; Gill, M.; Meyer, C. J.; Sadd, J. S.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979,** 606–611. doi:10.1039/p19790000606
44. Forrester, A. R.; Gill, M.; Sadd, J. S.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979,** 612–615. doi:10.1039/p19790000612
45. Forrester, A. R.; Gill, M.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979,** 616–620. doi:10.1039/p19790000616
46. Forrester, A. R.; Gill, M.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979,** 621–631. doi:10.1039/p19790000621
47. Forrester, A. R.; Gill, M.; Napier, R. J.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979,** 632–636. doi:10.1039/p19790000632
48. Forrester, A. R.; Gill, M.; Meyer, C. J.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1979,** 637–642. doi:10.1039/p19790000637
49. Forrester, A. R.; Napier, R. J.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1981,** 984–987. doi:10.1039/p19810000984
50. Griller, D.; Mendenhall, G. D.; Van Hoof, W.; Ingold, K. U. *J. Am. Chem. Soc.* **1974,** *96,* 6068–6070. doi:10.1021/ja00826a018
51. Tnay, Y. L.; Chen, C.; Chua, Y. Y.; Zhang, L.; Chiba, S. *Org. Lett.* **2012,** *14,* 3550–3553. doi:10.1021/ol301583y
52. Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2010,** *12,* 3682–3685. doi:10.1021/ol101490n
53. Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010,** *132,* 7266–7267. doi:10.1021/ja1027327
54. Pickard, P. L.; Tolbert, T. L. *J. Org. Chem.* **1961,** *26,* 4886–4888. doi:10.1021/jo01070a025
55. Chiba, S.; Zhang, L.; Ang, G. Y.; Hui, B. W.-Q. *Org. Lett.* **2010,** *12,* 2052–2055. doi:10.1021/ol100522z
56. Paquette, L. A. *Comprehensive Organic Transformations;* VCH Publishers, Inc./VCH Verlagsgesellschaft: New York/Weinheim, 1989. doi:10.1002/ange.19901020837
57. Rachmilovich-Calis, S.; Masarwa, A.; Meyerstein, N.; Myerstein, D.; van Eldik, R. *Chem. – Eur. J.* **2009,** *15,* 8303–8309. doi:10.1002/chem.200802572
58. Too, P. C.; Tnay, Y. L.; Chiba, S. *Beilstein J. Org. Chem.* **2013,** *9,* 1217–1225. doi:10.3762/bjoc.9.138
59. Sanjaya, S.; Chiba, S. *Tetrahedron* **2011,** *67,* 590–596. doi:10.1016/j.tet.2010.11.060
60. Fatiadi, A. J. Preparation and Synthetic Applications of Cyano Compounds. In *Triple-Bonded Functional Groups;* Patai, S.; Rappaport, Z., Eds.; John Wiley & Sons, Ltd.: Chichester, UK, 1983; Vol. 2. doi:10.1002/9780470771709.ch9
61. Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Synthesis, Patents, Applications,* 4th ed.; Thieme: Stuttgart, Germany, 2001.
62. Miller, J. S.; Manson, J. L. *Acc. Chem. Res.* **2001,** *34,* 563–570. doi:10.1021/ar0000354
63. Lindley, J. *Tetrahedron* **1984,** *40,* 1433–1456. doi:10.1016/S0040-4020(01)91791-0
64. Galli, C. *Chem. Rev.* **1988,** *88,* 765–792. doi:10.1021/cr00087a004
65. Wen, Q.; Jin, J.; Zhang, L.; Luo, Y.; Lu, P.; Wang, Y. *Tetrahedron Lett.* **2014,** *55,* 1271–1280. doi:10.1016/j.tetlet.2014.01.032
66. Zhu, Y.; Zhao, M.; Lu, W.; Li, L.; Shen, Z. *Org. Lett.* **2015,** *17,* 2602–2605. doi:10.1021/acs.orglett.5b00886
67. Pan, C.; Jin, H.; Xu, P.; Liu, X.; Cheng, Y.; Zhu, C. *J. Org. Chem.* **2013,** *78,* 9494–9498. doi:10.1021/jo4014904
68. Kou, X.; Zhao, M.; Qiao, X.; Zhu, Y.; Tong, X.; Shen, Z. *Chem. – Eur. J.* **2013,** *19,* 16880–16886. doi:10.1002/chem.201303637
69. Song, R.-J.; Wu, J.-C.; Liu, Y.; Deng, G.-B.; Wu, C.-Y.; Wei, W.-T.; Li, J.-H. *Synlett* **2012,** 2491–2496. doi:10.1055/s-0032-1317191
70. Luo, F.-H.; Chu, C.-I.; Cheng, C.-H. *Organometallics* **1998,** *17,* 1025–1030. doi:10.1021/om970842f
71. Wen, Q.; Jin, J.; Mei, Y.; Lu, P.; Wang, Y. *Eur. J. Org. Chem.* **2013,** *2013,* 4032–4036. doi:10.1002/ejoc.201300052
72. Zhang, L.; Wen, Q.; Jin, J.; Wang, C.; Lu, P.; Wang, Y. *Tetrahedron* **2013,** *69,* 4236–4240. doi:10.1016/j.tet.2013.03.089
73. Luo, Y.; Wen, Q.; Wu, Z.; Jin, J.; Lu, P.; Wang, Y. *Tetrahedron* **2013,** *69,* 8400–8404. doi:10.1016/j.tet.2013.07.063
74. Yuen, O. Y.; Choy, P. Y.; Chow, W. K.; Wong, W. T.; Kwong, F. Y. *J. Org. Chem.* **2013,** *78,* 3374–3378. doi:10.1021/jo3028278
75. Wen, Q.; Jin, J.; Hu, B.; Lu, P.; Wang, Y. *RSC Adv.* **2012,** *2,* 6167–6169. doi:10.1039/c2ra20770b
76. Jin, J.; Wen, Q.; Lu, P.; Wang, Y. *Chem. Commun.* **2012,** *48,* 9933–9935. doi:10.1039/c2cc35046g
77. Reeves, J. T.; Malapit, C. A.; Buono, F. G.; Sidhu, K. P.; Marsini, M. A.; Sader, C. A.; Fandrick, K. R.; Busacca, C. A.; Senanayake, C. H. *J. Am. Chem. Soc.* **2015,** *137,* 9481–9488. doi:10.1021/jacs.5b06136
78. Jiang, Z.; Huang, Q.; Chen, S.; Long, L.; Zhou, X. *Adv. Synth. Catal.* **2012,** *354,* 589–592. doi:10.1002/adsc.201100836
79. Wen, Q.; Lu, P.; Wang, Y. *RSC Adv.* **2014,** *4,* 47806–47826. doi:10.1039/C4RA08675A
80. Anbarasan, P.; Neumann, H.; Beller, M. *Chem. – Eur. J.* **2011,** *17,* 4217–4222. doi:10.1002/chem.201003388
81. Anbarasan, P.; Neumann, H.; Beller, M. *Chem. – Eur. J.* **2010,** *16,* 4725–4728. doi:10.1002/chem.201000086
82. Hughes, T. V.; Cava, M. P. *J. Org. Chem.* **1999,** *64,* 313–315. doi:10.1021/jo981924w
83. Koo, J. S.; Lee, J. I. *Synth. Commun.* **1996,** *26,* 3709–3713. doi:10.1080/00397919608003787
84. Klement, I.; Lennick, K.; Tucker, C. E.; Knochel, P. *Tetrahedron Lett.* **1993,** *34,* 4623–4626. doi:10.1016/S0040-4039(00)60640-8
85. van Leusen, A. M.; Jagt, J. C. *Tetrahedron Lett.* **1970,** *11,* 967–970. doi:10.1016/S0040-4039(01)97880-3
86. Foulger, N. J.; Wakefield, B. J. *Tetrahedron Lett.* **1972,** *13,* 4169–4170. doi:10.1016/S0040-4039(01)94266-2

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doi:10.3762/bjoc.11.209

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Effective ascorbate-free and photolatent click reactions in water using a photoreducible copper(II)-ethylenediamine precatalyst

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Keywords:
benzophenone photosensitizer; bioconjugation; click chemistry; copper; photoreduction

Beilstein J. Org. Chem. **2015,** *11,* 1950–1959.
doi:10.3762/bjoc.11.211

Received: 29 July 2015
Accepted: 25 September 2015
Published: 21 October 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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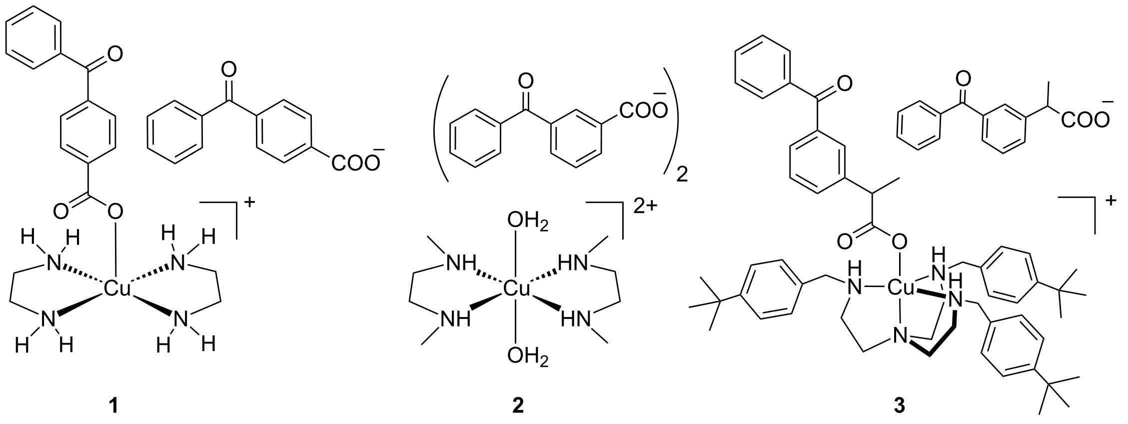
Abstract

The search for copper catalysts able to perform effectively click reactions in water in the absence of sodium ascorbate is an active area of current research with strong potential for applications in bioconjugation. The water-soluble and photoreducible copper(II)–EDA (EDA = ethylenediamine) complex **1**, which has two 4-benzoylbenzoates acting as both counterion and photosensitizer, has been synthesized and characterized by different techniques including single crystal X-ray diffraction. Highly efficient photoreduction was demonstrated when solutions of **1** in hydrogen atom donating solvents, such as THF or MeOH, were exposed to UVA radiation (350–400 nm) provided by a low pressure mercury lamp (type TLC = thin-layer chromatography, 365 nm), or by a 23 W fluorescent bulb, or by ambient/sunlight. In water, a much poorer hydrogen atom donating solvent, the photoreduction of **1** proved inefficient. Interestingly, EPR studies revealed that complex **1** could nonetheless be effectively photoreduced in water when alkynes were present in solution. The catalytic activity of **1** for click reactions involving a range of water-soluble alkynes and azides, in particular saccharides, was tested under various illumination conditions. Complex **1** was found to exhibit a photolatent character, the photogenerated copper(I) being very reactive. On irradiating aqueous reaction mixtures containing 1 mol % of **1** at 365 nm (TLC lamp) for 1 h, click reactions were shown to proceed to full conversion.

Introduction

Since the discovery in 2002 that copper(I) could catalyze the Huisgen alkyne–azide [3 + 2] cycloaddition with high selectivity for the 1,4-triazole [1,2], the so-called copper(I)-catalyzed alkyne–azide cycloaddition (CuAAC) has become a privileged reaction which is widely employed in all areas of the chemical/biological/material sciences [3,4]. Numerous copper-based catalytic systems have been developed and employed for the CuAAC [5], the main prerequisite being the generation of a copper(I) catalytic species from various homogeneous/heterogeneous precatalysts, whose oxidation states are 0, +1 or +2. A major application of the CuAAC concerns bioconjugation reactions, i.e., the covalent modification of biomolecules [6]. Such reactions typically imply water-soluble alkyne and azide reactants and should thus be performed in an aqueous medium using a water-soluble catalyst. Important limitations for such transformations are: (i) high copper loading, often used in excess with respect to the substrates, due to limited catalyst reactivity and the fact that the substrates (proteins, oligonucleotides or oligosaccharides) are typically used in dilute conditions; (ii) contamination of the products by copper salts, which should be avoided for in vivo applications and, when employed, by sodium ascorbate and/or its byproducts; (iii) side-reactions on the substrates due to the generation of reduced dioxygen-active species and/or reactive oxidized byproducts of ascorbate. In a seminal paper, Finn and coworkers addressed several of these points; they proposed an optimized catalytic system composed of $CuSO_4$, an accelerating and water-soluble tris-triazole THPTA (tris[(1-hydroxypropyl-1*H*-1,2,3-triazol-4-yl)methyl]amine) ligand with a ligand/copper ratio equal to at least 5 to effectively trap the reactive oxygenated species [7]. They also show that aminoguanidine could be added to the reaction mixture to effectively trap the reactive byproducts derived from ascorbate oxidation. Using these protective additives (excess of ligand and guanidine) bioconjugation reactions could be conducted from a Cu(II) precatalyst even when the reaction mixture is exposed to air. Optimized ligands leading to faster kinetics were later developed [8,9], allowing for instance to lower the copper loading, which is important to avoid toxicity issues for applications with living cells [9]. An interesting catalyst was reported by Gautier and coworkers based on a water-soluble Cu(I)–NHC complex, which could be used under ascorbate-free and open air conditions for the CuAAC ligation of oxidation-sensitive peptides in buffered aqueous media [10].

Recently, we developed the photoreducible copper(II) complexes **2** and **3** incorporating a tren (tren = tris(2-aminoethyl)amine) ligand derivative [11,12] or the dmeda (dmeda = *N*,*N*'-dimethylethylenediamine) ligand [13,14] (Scheme 1). Irradiation at 365 nm of the benzophenone photosensitizer (n→π* electronic transition), introduced through the carboxylate counterion, mediated a highly efficient photoinduced electron transfer process leading to a fast Cu(II) to Cu(I) reduction, the final electron source being the solvent. The photoreduction process was extremely efficient, photoreduction quantum yields (Φ_{red}) ranging from 0.17 up to around 1 being measured in good H-atom donating solvents such as MeOH or THF [11-13]. Consequently, efficient reduction could be achieved by simply exposing the solutions of the Cu(II) complexes to ambient light. Importantly, the photogenerated Cu(I) species were shown to be extremely reactive for the CuAAC reaction when conducting the reactions in organic



Scheme 1: Structures of photoactivable click catalysts **1–3**.

solvents, typically MeOH, THF or toluene. It should be noted that within the last four years, other photoreducible copper(II)-based catalytic systems applied to click chemistry have been reported [15-27], in particular for the preparation of polymers [15-24].

We wish now to report on our preliminary studies dealing with the water-soluble complex **1**, the objective being to develop photoactivable click copper(II) precatalysts which could be used in aqueous solution and ascorbate-free conditions. We describe here the synthesis and characterization of **1**, its photoreduction properties in various solvents and illumination conditions, and its catalytic properties which reveal that **1**, when illuminated, is an effective photolatent click catalyst in aqueous medium.

Results and Discussion

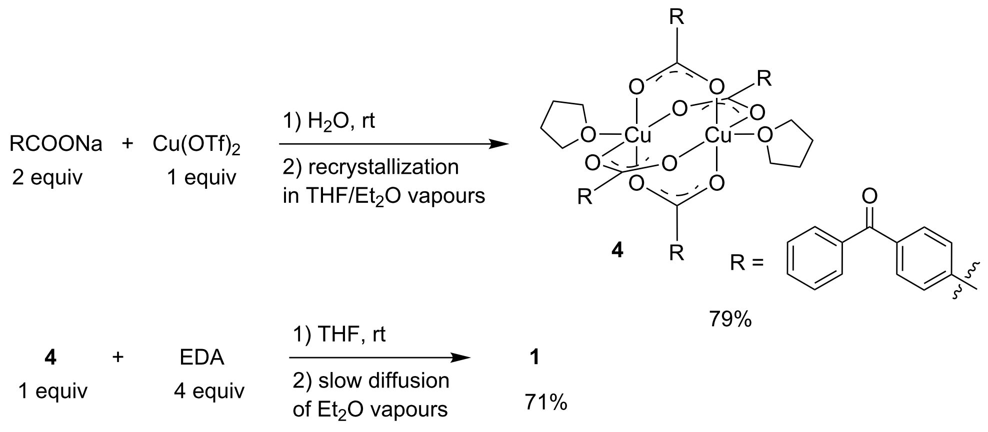
The EDA (EDA = ethylenediamine) ligand in the copper(II) complex [Cu^{II}(EDA)$_2$(4-benzoylbenzoate)](4-benzoylbenzoate) (**1**) was chosen to ensure high water solubility. Complex **1** was synthesized in two steps by first preparing the copper(II)-carboxylate dimer [Cu$_2$(4-benzoylbenzoate)$_4$(THF)$_2$] **4** which was obtained by reacting 2 equivalents of the sodium salt of the 4-benzoylbenzoic acid with Cu(OTf)$_2$ in water, the precipitate which formed being recrystallized by slow diffusion of Et$_2$O in a THF solution (Scheme 2). Then, 4 equivalents of EDA were reacted with **4** in THF, the solution immediately turned deep blue. Slow diffusion of diethyl ether vapour into the THF solution led to the crystallization of **1** as blue needles, which were recovered by filtration (71% yield).

The proposed dinuclear and mononuclear structures of **4** and **1** were confirmed by single crystal X-ray diffraction (Figure 1). The crystal structure of **4** displays the typical “paddle-wheel” of copper(II)–carboxylate complexes [28], a structure in which the two copper(II) ions are bridged by four carboxylates in a *syn–syn* configuration ($d_{Cu\cdots Cu}$ 2.613 Å), whilst two THF molecules occupy axial coordination sites.

Complex **1** displays a monomeric structure with a distorted square pyramidal geometry with the copper ion lying slightly above the basal plane formed by 4 nitrogen atoms (average $d_{Cu\cdots N}$ 2.019 Å), while an oxygen atom of a carboxylate occupies the axial site ($d_{Cu\cdots O}$ 2.294 Å). The oxygen atom of the C=O bond is participating in one intramolecular ($d_{CO\cdots HN}$ 2.140 Å) and one intermolecular ($d_{CO\cdots HN}$ 2.212 Å) hydrogen bond with hydrogen atoms of EDA ligands. The second carboxylate anion is not directly bound to the copper(II) ion, but participates in four intermolecular hydrogen bonds with hydrogen atoms of EDA (average $d_{CO\cdots HN}$ 2.125 Å) ligands of two [Cu(EDA)$_2$(4-benzoylbenzoate)]$^+$ cations.

Aqueous and THF solutions of **1** were characterized by a shift of the absorption band (d–d electronic transition) in the visible spectral region from 550 nm in water to 606 nm in THF (spectra at *t* = 0 min in Figure 2). This was ascribed to the ion-pair dissociation state of the complex with water molecules being most probably bound to the copper ions in aqueous solution, while in THF, the carboxylates interact more tightly with the copper ions. This is in agreement with the ^{1}H NMR spectra of **1**, which showed well resolved peaks for the benzophenone protons in D$_2$O, while in THF-d_8 broad resonances were observed, as expected for a compound interacting more strongly with paramagnetic copper(II) ions. It should be noted that the methylene protons of the EDA ligands are not observed.

Photoreduction studies of **1** were then conducted varying both the solvent and illumination conditions. The first experiments were carried out in quartz cuvettes to follow the disappearance of the low-energy visible light absorption band (550–600 nm)



Scheme 2: Syntheses of complexes **1** and **4**.

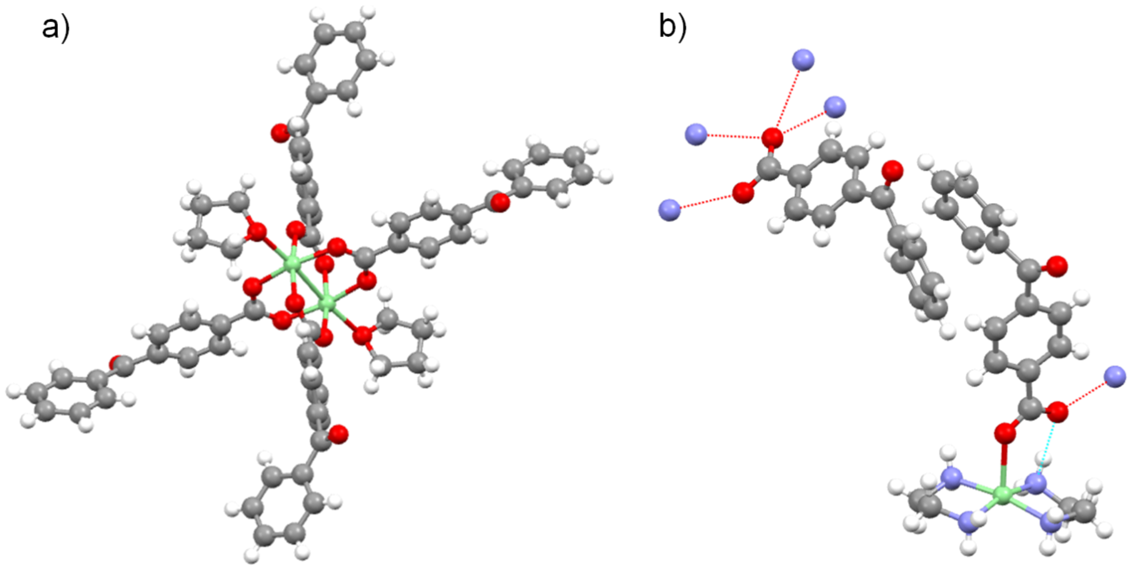


Figure 1: a) Molecular structure of **4** (a THF molecule present in the unit cell is not shown). Cu, green; C, grey; O, red; H, white; b) Molecular structure of **1** (asymmetric unit) showing the intermolecular (dashed red lines) and intramolecular (dashed blue line) H-bond interactions of the carboxylate C=O bonds with surrounding H–N bonds. Cu, green; N, blue; C, grey; O, red; H, white. CIF files for the determined structures are available as Supporting Information File 2 and Supporting Information File 3 and are also available on request from the Cambridge Crystallographic Data Centre as deposition CCDC 1414149 for **4**, and CCDC 1410011 for **1**.

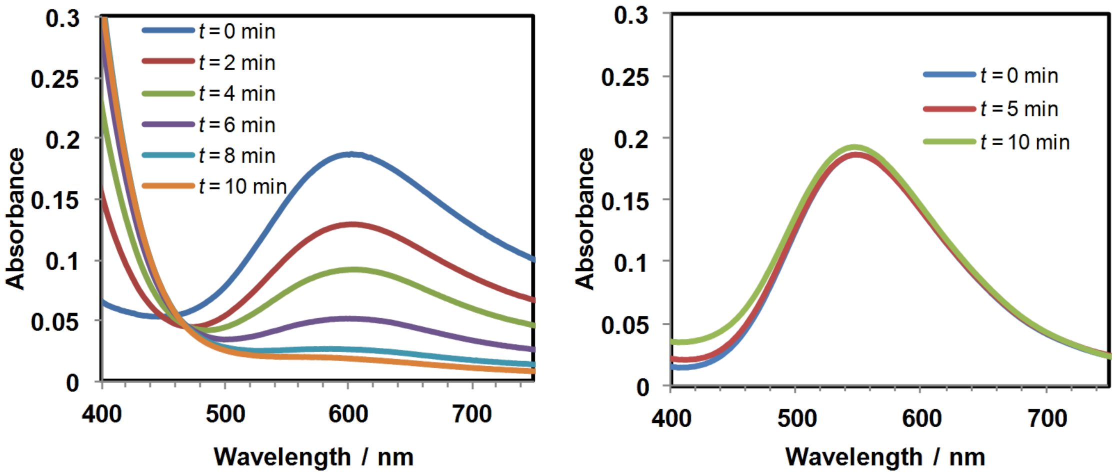


Figure 2: Evolution of the UV–vis spectra of deaerated (freeze-pump-thaw degassed, sealed quartz cuvettes) THF (left) or water (right) solutions (3 mL) of complex **1** (2 mM) under irradiation at 365 nm using a TLC lamp placed at ≈1 cm from the cuvette.

ascribed to a d–d electronic transition, which is typical for Cu^{II} complexes (d^9). The reductions were typically conducted under strictly anaerobic conditions, deaeration of the solutions being achieved either by gentle Ar bubbling through a rubber cap or, by freeze-pump-thaw cycles followed by sealing of the cell. Irradiations were performed at wavelengths compatible with the n→π* electronic transition of the benzophenone chromophore, i.e., ≈350–370 nm (UVA). Illumination of the samples at 365 nm using a TLC lamp thus represents a convenient source of light. Previous studies revealed that a 2 mM solution of **2** in THF (3 mL in a quartz cuvette with 1 cm path length) was fully reduced in ≈15 min [14]. Interestingly, the photoreduction process was found to be so effective, that the UVA photons (350–400 nm) present in sunlight/ambient light were sufficient to achieve the reduction with satisfactory rates, i.e., ≈30 min and 60 min when the samples were exposed behind a window to direct light of a sunny or a rainy day, respectively. It should also be noted that over-reduction processes leading to the formation of copper(0) nanoparticles occurred when prolonged irradiation times were applied [12,13].

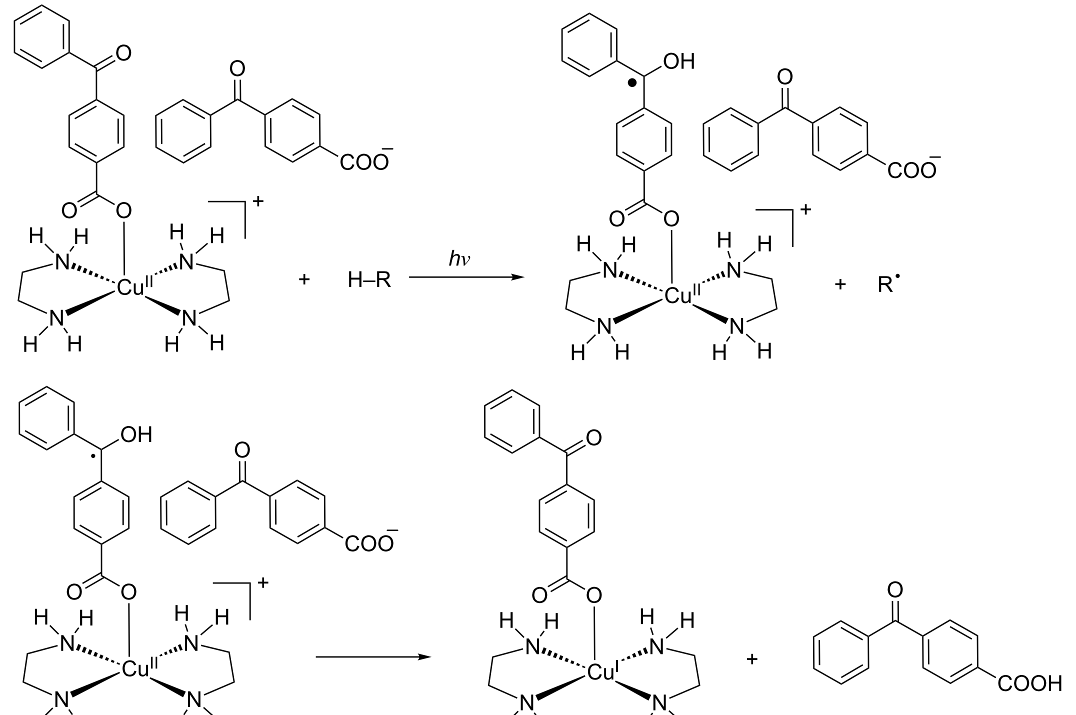
When a deaerated solution of **1** in THF was irradiated at 365 nm, a very fast change of the solution aspect was observed, the solution becoming colourless in ≈10 min as shown by UV–vis spectroscopy (Figure 2). This rate is comparable to that observed previously with the analogous complex **2**, for which a photoreduction quantum yield close to unity has been determined in THF [14]. Because of such a high efficiency, the photoreduction proceeded well under direct sunlight illumination by placing the quartz cuvette behind a window of a sunny day, ≈60% of **1** being reduced in 40 min illumination under such conditions.

When irradiations were conducted on aqueous solutions of **1**, no reduction was observed, as revealed in Figure 2. This agrees with the poor hydrogen atom donating character of H_2O (BDE = 119 kcal/mol) compared to THF (BDE = 92 kcal/mol), the reactivity of the excited triplet of benzophenone being particularly high toward the THF moiety [29].

At this stage, a reduction mechanism implying the fast generation of the ketyl radical in good hydrogen atom donating solvents, which then can reduce the copper(II) ion to generate the copper(I) and regenerate the benzophenone chromophore, could be proposed (Scheme 3). Further studies, which aim to validate this proposal, are in progress.

The poor reduction efficiency observed in water could represent a serious limitation for our goal to develop photolatent click catalysts for reactions conducted in water with water-soluble reactants. However, under catalytic conditions, i.e., in the presence of a large excess of alkyne and azide (1 mol % of **1** will be used for catalytic reactions), the reactants could be used as reducing agent. For instance, it has been previously shown that the alkynes could favor the Cu(II) to Cu(I) reduction, most probably through the well-known Glaser-type oxidative coupling [30,31]. We thus tested the reduction in the presence of the water-soluble alkynes **5**–**7**. In marked contrast with experiments conducted in pure water, the aqueous solution irradiated in the presence of alkyne **5** (50 equiv with respect to copper), rapidly evolved to become slightly cloudy. Such changes, which could be ascribed to the formation of insoluble polymeric copper(I) acetylides and/or the insoluble 3-benzoylbenzoic acid (Scheme 3), precluded the use of UV–vis spectroscopy to quantitatively analyze the reductive process. For such an analysis, EPR spectroscopy was thus employed to assess the extent of copper reduction.

In Figure 3, the EPR spectra of solutions of **1** (d^9, $S = 1/2$) recorded by irradiating the samples directly in the probe at room temperature are presented. Control experiments conducted in THF and aqueous solutions of **1** (Figure 3a and b, respectively),



Scheme 3: Proposed mechanism for the photoreduction process.

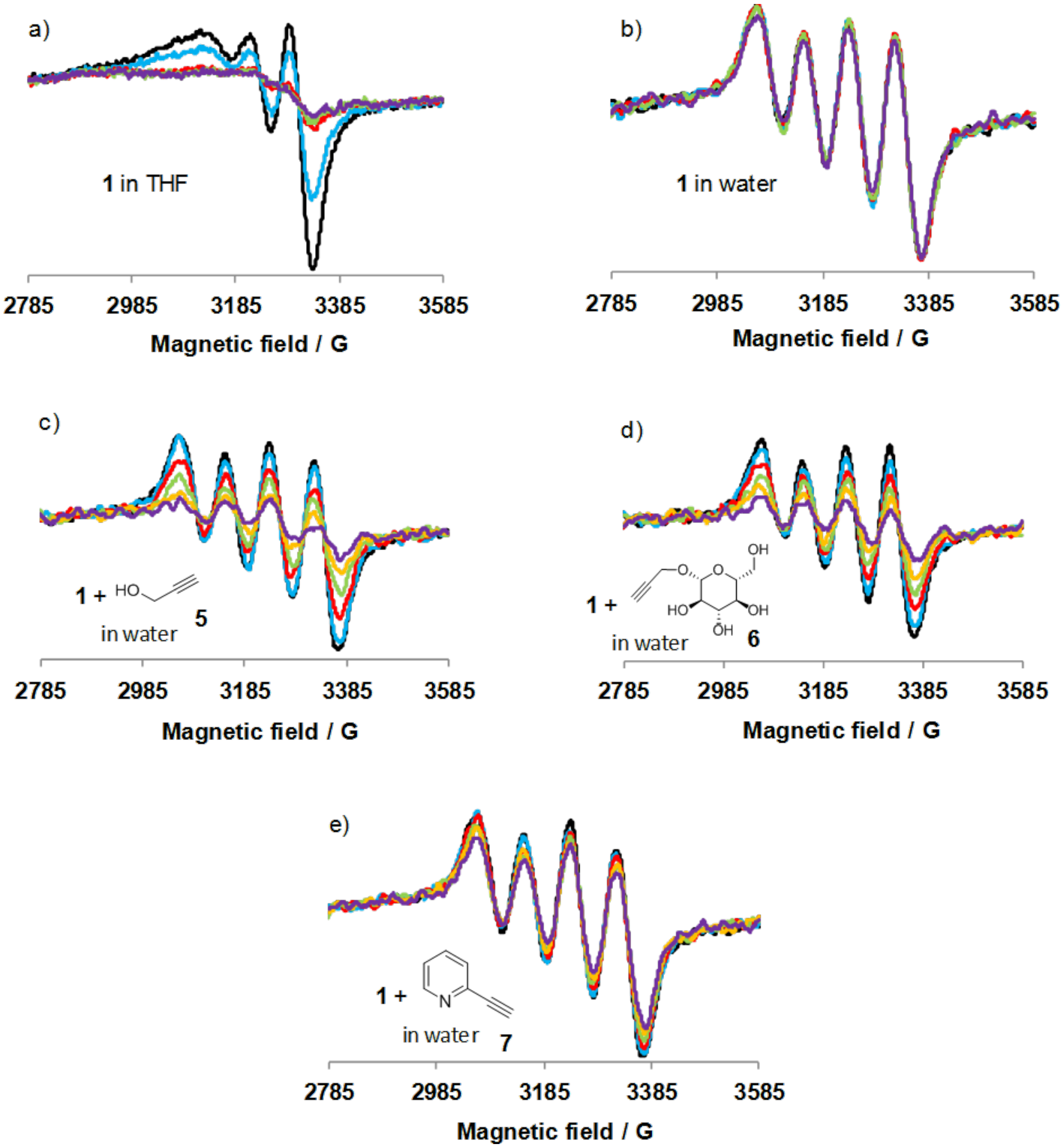


Figure 3: Evolution of the EPR spectra (X band, 298 K) of solutions of **1** under continuous irradiation (280–400 nm). A spectrum is recorded in the dark (black), then the light is switched on and the spectra (scanning time = 15 s) recorded during irradiation at times 0 s (blue), 50 s (red), 100 s (green), 150 s (orange) and 225 s (purple). a) THF solution of **1** (1 mM); b) H_2O solution of **1** (1 mM); c) H_2O solution of **1** (1 mM) and alkyne **5** (50 mM); d) H_2O solution of **1** (1 mM) and alkyne **6** (50 mM); e) H_2O solution of **1** (1 mM) and alkyne **7** (50 mM).

confirmed the results gathered by UV–vis spectroscopy, i.e., fast reduction in THF and essentially no reduction in water. In water solution, the EPR spectra displays the four well-resolved hyperfine lines, expected for Cu(II) characterized by a nuclear spin of 3/2. However, the shape of the EPR spectra are different in both solvents in agreement with the UV–vis data, i.e., a water molecule should replace the Cu-bound benzoylbenzoate in aqueous solution.

When the water-soluble alkynes **5**, **6** or **7** were added (50 equiv with respect to Cu) and the aqueous solution irradiated, a decrease of the intensity of the EPR signal was observed, in agreement with a reduction process (Figure 3c–e). In the presence of propargyl alcohol **5** or propargyl ether **6** the reductions occurred very efficiently, i.e., ≈65% of the copper(II) (estimated by integration of the EPR signal) was reduced after 250 s of irradiation. This is nonetheless slower than in THF, in which

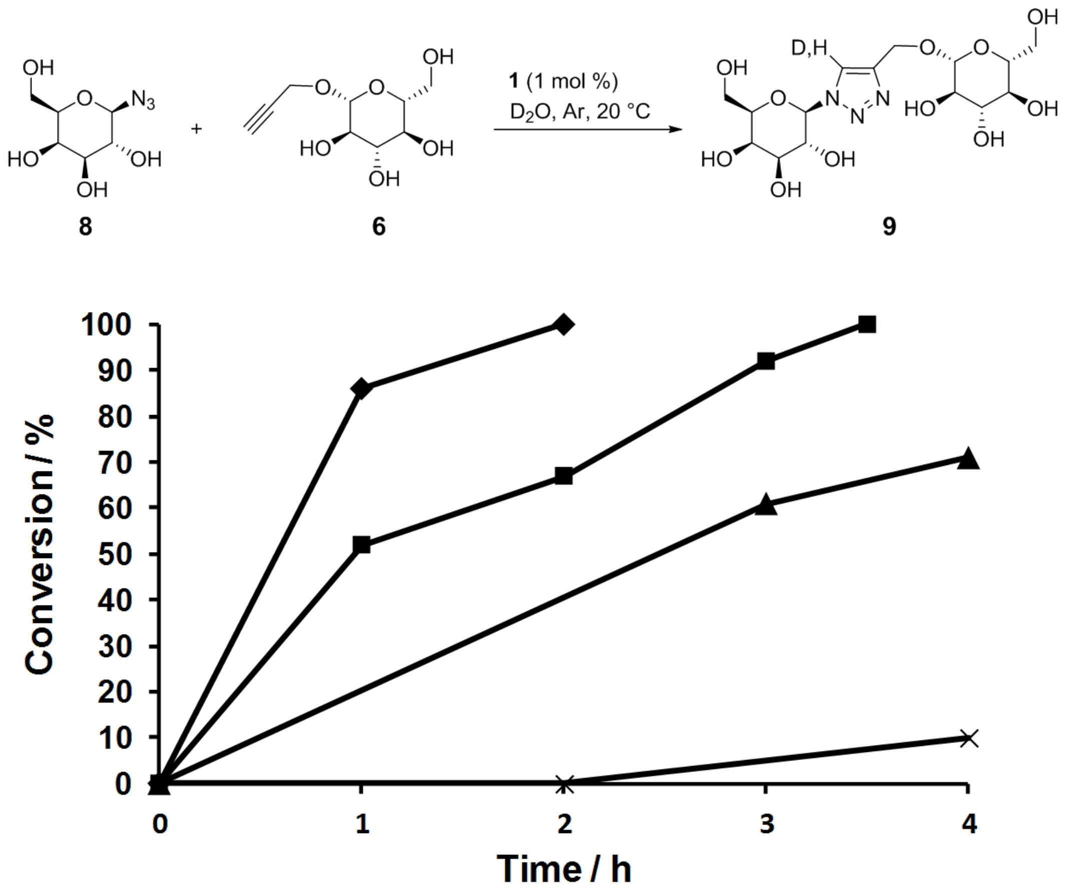


Figure 4: Reaction profiles for the formation of **9** under various illumination conditions: TLC lamp (365 nm) for 1 h, then ambient laboratory light (♦); tube in the dark (X); tube exposed to ambient laboratory light (▲); tube exposed to 23 W fluorescent bulb (■).

≈65% of **1** was reduced after only 40 s. With 2-alkynylpyridine **7**, reduction was also observed albeit at a slower rate, ≈35% of **1** being reduced after 250 s of irradiation. It is important to note that no reduction was observed in the absence of light, showing that the reduction is a photoinduced process. It also shows that if light-independent reduction is occurring, most probably through a Glaser-type oxidative coupling, it is a much slower process. At this stage, we propose that the alkynes serve as the hydrogen atom source to generate the ketyl radical of the benzophenone (Figure 2).

The photolatent properties of **1** and the reactivity of the photogenerated copper(I) species were then tested under various illumination conditions (Figure 4). Reactions between the water-soluble alkyne **6** and azide **8** were conducted in D_2O in NMR tubes, thereby allowing convenient monitoring of the reaction progress. In a typical experiment, the NMR tube was charged with **1** (1 mol %), D_2O (0.5 mL), the reactants (0.15 mmol each) and capped with a rubber septum. The whole tube was protected from light by aluminum foil, the solution was degassed by gentle Ar bubbling (20 min), and the tube was tightly capped with parafilm to limit air entry. The reactions were initiated by exposing the tubes to various light sources. In a first experiment the solution was irradiated for 1 h at 365 nm with a TLC lamp placed at ≈1 cm from the tube, and then left under ambient laboratory light. In these conditions, the reaction proceeded to full conversion in ≈2 h, 80–90% of the triazole being formed after 1 h. The triazole **9** was then isolated in 91% yield. Importantly and in marked contrast, when the tube was protected from light, no reaction occurred within 2 h, highlighting the photolatent behavior of **1**. However a slow reaction was observed, ≈10% conversion was obtained in 4 h, and 74% in 8 h. This could be ascribed to the light-independent slow generation of copper(I) through Glaser-type oxidative coupling.

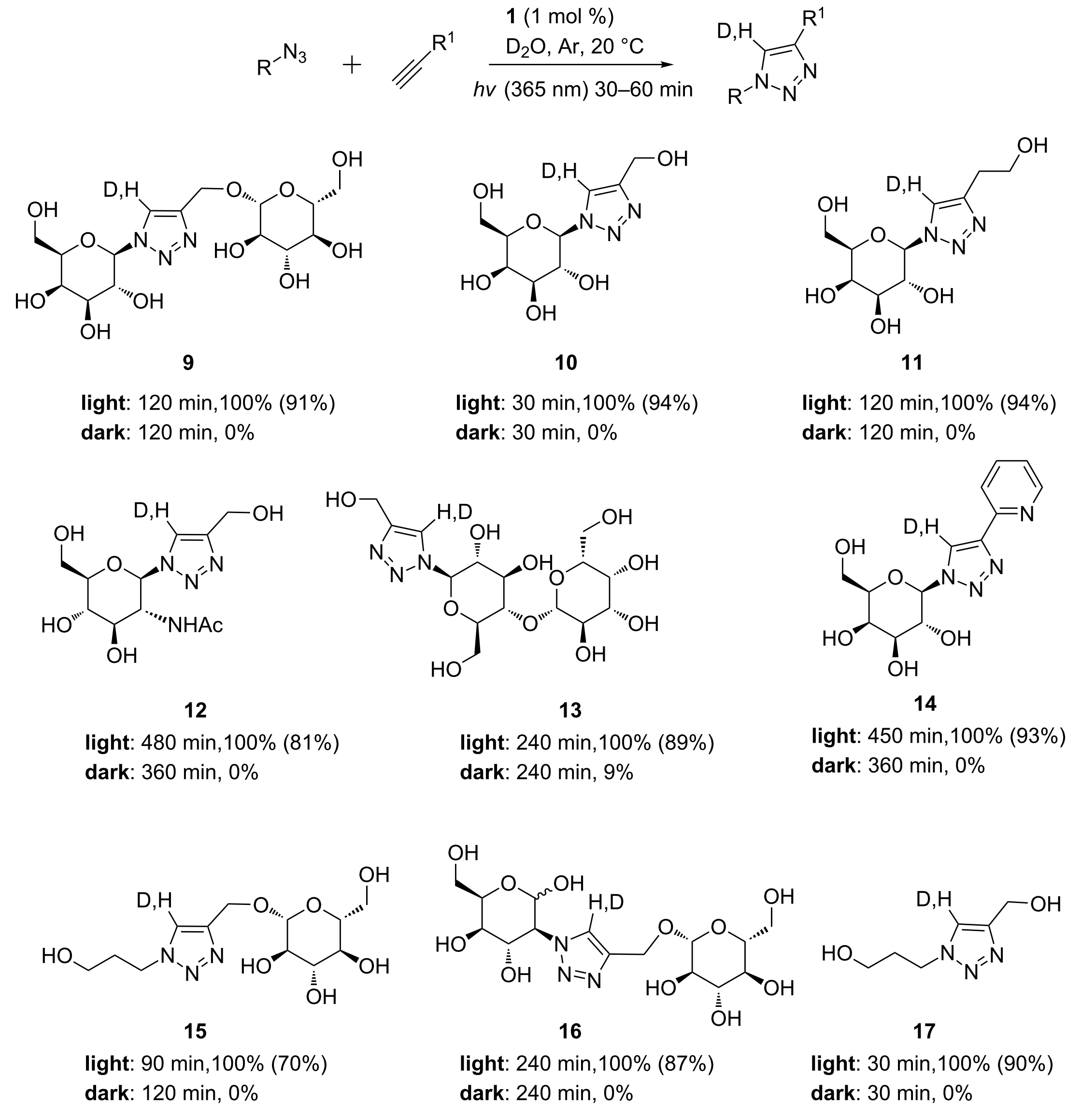
The catalytic system was found to be very sensitive to light. By simply leaving the tube exposed to ambient laboratory light after degassing, 70% conversion was reached in 4 h, the full conversion being attained in 7 h. Interestingly, from a practical viewpoint, it is possible to simply illuminate the sample with a household fluorescent bulb (23 W) which produces a significant amount of UVA photons. Using this light source, full conversion was achieved in 3.5 h, which is faster than when exposed to ambient light, but significantly slower than when exposed to TLC lamp.

Having established the most efficient illumination conditions, reactions were conducted on a range of water-soluble alkynes and azides by irradiating the NMR tubes with the TLC lamp for 1 h and then leaving it under ambient light. As seen in Scheme 4, a variety of triazoles **9**–**17** could be obtained in good isolated yields with reaction times ranging from 30 min to 8 h. Again, no or little reaction was observed when protecting the tube from light, in agreement with photolatent catalysis.

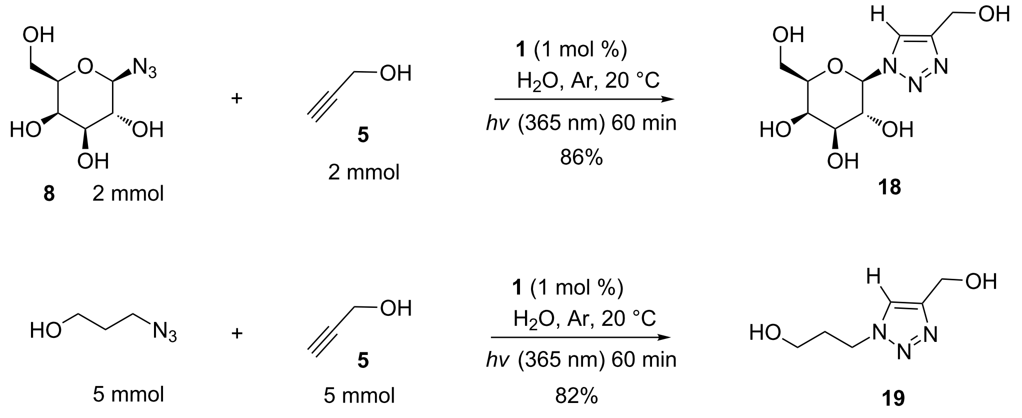
Finally, two reactions were conducted in H_2O on preparative scales in round-bottom flasks (Scheme 5). The hydrogenated triazoles **18** and **19** were obtained in 86% (0.450 g) and 82% (0.644 g) isolated yields, respectively, showing that the procedure is practical for laboratory-scale applications.

Conclusion

The copper(II) precatalyst **1** incorporating a benzophenone chromophore is easily prepared, soluble in polar solvents and water, and can be stored indefinitely under ambient conditions. It is efficiently photoreduced in THF using convenient light sources producing UVA photons. While the Cu(II) to Cu(I) reduction process in water proved inefficient we have shown, in particular using EPR spectroscopy, that the alkynes can serve as



Scheme 4: Structures, conversions and isolated yields for triazoles **9**–**17** conducted in D_2O in NMR tubes.



Scheme 5: Preparative scale synthesis of **18** and **19**.

effective and practical electron source to allow the reduction in a light-dependent process photosensitized by the benzophenone. Complex **1** proved to be an effective photolatent catalyst for reactions conducted in water involving water-soluble alkynes and azides. Combining **1** with light, thus prevents the use of sodium ascorbate as reducing agent while a copper(II) complex is employed as precatalyst. The reactions were conducted not only under ascorbate-free conditions, but also under dioxygen-free conditions, deoxygenation being conveniently performed by Ar or N_2 bubbling. Copper(I)-catalyzed processes, in particular for application in click bioconjugations, should be conducted under deaerated conditions in order to reduce copper loading due to fast Cu(I) to Cu(II) oxidation process mediated by O_2, and also to limit addition of trapping agents to capture reactive oxygen species generated through side reactions between Cu(I) and O_2.

Supporting Information

Supporting Information File 1

Experimental and analytical data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-211-S1.pdf]

Supporting Information File 2

Crystallographic Information for compound **1**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-211-S2.cif]

Supporting Information File 3

Crystallographic Information for compound **4**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-211-S3.cif]

Acknowledgments

The authors are thankful to Dr. Thierry Buffeteau for the recording of the IR spectra of complexes **1** and **4**. The University of Bordeaux, the CNRS, the Région Aquitaine, the ANR (ANR-13-BS07-0006-01), the European Research Council (FP7/2008-2013) ERC grant agreement no. 208702 and IR-RPE CNRS 3443 are gratefully acknowledged for their financial support.

References

1. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002,** *41,* 2596–2599. doi:10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4
2. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002,** *67,* 3057–3064. doi:10.1021/jo011148j
3. Themed issue: “Click chemistry: function follows form”, guest Eds Finn M. G.; Fokin, V. *Chem. Soc. Rev.* **2010,** *39,* 1231–1405.
4. Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008,** *108,* 2952–3015. doi:10.1021/cr0783479
5. Díez-González, S. *Catal. Sci. Technol.* **2011,** *1,* 166–178. doi:10.1039/c0cy00064g
6. Lim, R. K. V.; Lin, Q. *Chem. Commun.* **2010,** *46,* 1589–1600. doi:10.1039/b925931g
7. Hong, V.; Presolski, S. I.; Ma, C.; Finn, M. G. *Angew. Chem., Int. Ed.* **2009,** *48,* 9879–9883. doi:10.1002/anie.200905087
8. Presolski, S. I.; Hong, V.; Cho, S.-H.; Finn, M. G. *J. Am. Chem. Soc.* **2010,** *132,* 14570–14576. doi:10.1021/ja105743g
9. Besanceney-Webler, C.; Jiang, H.; Zheng, T.; Feng, L.; Soriano del Amo, D.; Wang, W.; Klivansky, L. M.; Marlow, F. L.; Liu, Y.; Wu, P. *Angew. Chem., Int. Ed.* **2011,** *50,* 8051–8056. doi:10.1002/anie.201101817
10. Gaulier, C.; Hospital, A.; Legeret, B.; Delmas, A. F.; Aucagne, V.; Cisnetti, F.; Gautier, A. *Chem. Commun.* **2012,** *48,* 4005–4007. doi:10.1039/c2cc30515a

11. Harmand, L.; Cadet, S.; Kauffmann, B.; Scarpantonio, L.; Batat, P.; Jonusauskas, G.; McClenaghan, N. D.; Lastécouères, D.; Vincent, J.-M. *Angew. Chem., Int. Ed.* **2012,** *51,* 7137–7141. doi:10.1002/anie.201203014
12. Harmand, L.; Lambert, R.; Scarpantonio, L.; McClenaghan, N. D.; Lastécouères, D.; Vincent, J.-M. *Chem. – Eur. J.* **2013,** *19,* 16231–16329. doi:10.1002/chem.201302032
13. Beniazza, R.; Lambert, R.; Harmand, L.; Molton, F.; Duboc, C.; Denisov, S.; Jonusauskas, G.; McClenaghan, N. D.; Lastécouères, D.; Vincent, J.-M. *Chem. – Eur. J.* **2014,** *20,* 13181–13187. doi:10.1002/chem.201404056
14. Beniazza, R.; Molton, F.; Duboc, C.; Tron, A.; McClenaghan, N. D.; Lastécouères, D.; Vincent, J.-M. *Chem. Commun.* **2015,** *51,* 9571–9574. doi:10.1039/C5CC01923K
15. Adzima, B. J.; Tao, Y.; Kloxin, C. J.; DeForest, C. A.; Anseth, K. S.; Bowman, C. N. *Nat. Chem.* **2011,** *3,* 256–259. doi:10.1038/nchem.980
16. Alzahrani, A. A.; Erbse, A. H.; Bowman, C. N. *Polym. Chem.* **2014,** *5,* 1874–1882. doi:10.1039/C3PY01064C
17. Gong, T.; Adzima, B. J.; Baker, N. H.; Bowman, C. N. *Adv. Mater.* **2013,** *25,* 2024–2028. doi:10.1002/adma.201203815
18. Gong, T.; Adzima, B. J.; Bowman, C. N. *Chem. Commun.* **2013,** *49,* 7950–7952. doi:10.1039/c3cc43637c
19. Tasdelen, M. A.; Yilmaz, G.; Iskin, B.; Yagci, Y. *Macromolecules* **2012,** *45,* 56–61. doi:10.1021/ma202438w
20. Sandmann, B.; Happ, B.; Vitz, J.; Hager, M. D.; Burtscher, P.; Moszner, N.; Schubert, U. S. *Polym. Chem.* **2013,** *14,* 3938–3942. doi:10.1039/c3py00356f
21. Demirci, G.; Tasdelen, M. A. *Eur. Polym. J.* **2015,** *66,* 282–289. doi:10.1016/j.eurpolymj.2015.02.029
22. Tinmaz, H. B.; Arslan, I.; Tasdelen, M. A. *J. Polym. Sci., Part A: Polym. Chem.* **2015,** *53,* 1687–1695. doi:10.1002/pola.27612
23. Yagci, Y.; Tasdelen, M. A.; Jockusch, S. *Polymer* **2014,** *55,* 3468–3474. doi:10.1016/j.polymer.2014.06.068
24. McBride, M. K.; Gong, T.; Nair, D. P.; Bowman, C. N. *Polymer* **2014,** *55,* 5880–5884. doi:10.1016/j.polymer.2014.08.001
25. Tasdelen, M. A.; Yagci, Y. *Tetrahedron Lett.* **2010,** *51,* 6945–6947. doi:10.1016/j.tetlet.2010.10.166
26. Dadashi-Silab, S.; Kiskan, B.; Antonietti, M.; Yagci, Y. *RSC Adv.* **2014,** *4,* 52170–52173. doi:10.1039/C4RA09954K
27. Yetiskin, O.; Dadashi-Silab, S.; Khan, S. B.; Asiri, A. M.; Yagci, Y. *Asian J. Org. Chem.* **2015,** *4,* 442–444. doi:10.1002/ajoc.201500077
28. Motreff, A.; Correa da Costa, R.; Allouchi, H.; Duttine, M.; Mathonière, C.; Duboc, C.; Vincent, J.-M. *Inorg. Chem.* **2009,** *48,* 5623–5625. doi:10.1021/ic9005218
29. Abad, S.; Boscá, F.; Domingo, L. R.; Gil, S.; Pischel, U.; Miranda, M. A. *J. Am. Chem. Soc.* **2007,** *129,* 7407–7420. doi:10.1021/ja0712827
30. Harmand, L.; Lescure, M.-H.; Candelon, N.; Duttine, M.; Lastécouères, D.; Vincent, J.-M. *Tetrahedron Lett.* **2012,** *53,* 1417–1420. doi:10.1016/j.tetlet.2012.01.035
31. Zhang, G.; Yi, H.; Zhang, G.; Deng, Y.; Bai, R.; Zhang, H.; Miller, J. T.; Kropf, A. J.; Bunel, E. E.; Lei, A. *J. Am. Chem. Soc.* **2014,** *136,* 924–926. doi:10.1021/ja410756b

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doi:10.3762/bjoc.11.211

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Chiral Cu(II)-catalyzed enantioselective β-borylation of α,β-unsaturated nitriles in water

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Full Research Paper

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Keywords:
carbon–boron bond formation; catalytic asymmetric synthesis; chiral copper(II) catalysis; β-hydroxy nitriles

Beilstein J. Org. Chem. **2015,** *11,* 2007–2011.
doi:10.3762/bjoc.11.217

Received: 25 June 2015
Accepted: 01 September 2015
Published: 27 October 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

The promising performance of copper(II) complexes was demonstrated for asymmetric boron conjugate addition to α,β-unsaturated nitriles in water. The catalyst system, which consisted of $Cu(OAc)_2$ and a chiral 2,2′-bipyridine ligand, enabled β-borylation and chiral induction in water. Subsequent protonation, which was accelerated in aqueous medium, led to high activity of this asymmetric catalysis. Both solid and liquid substrates were suitable despite being insoluble in water.

Introduction

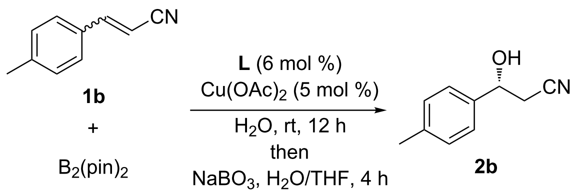
In recent years, optically active organoboranes have attracted considerable attraction as versatile synthons for the synthesis of biologically interesting compounds and of other materials. In particular, compounds with a nitrile group in the β-position with respect to the boron moiety represent an important subset of organoboron intermediates because these compounds contain two functional groups. Their C–B linkage can be transformed into C–O, C–N, as well as into C–C bonds, while retaining stereogenic centers [1-4]. The nitrile group can be transformed into a range of functional groups, such as amides [5], carboxylic acids [6], aldehydes [7], esters [8], alcohols [9], and amines [10]. Enantioselective boron conjugate addition to α,β-unsaturated nitriles provides one of the most efficient routes to chiral β-boryl nitriles. Several straightforward methods have been developed that rely on chiral Cu(I) complexes with air-sensitive phosphine ligands [11-15]. In contrast, Cu(II)-based catalysis, which has been reported recently for asymmetric boron conjugate addition, is characterized by the effective and thermodynamically stable catalysis in water. Furthermore, a broad range of α,β-unsaturated acceptors, including one example of an α,β-unsaturated nitrile, are applicable, and the reactions, which exhibit extremely high TOF values, can be performed easily without requiring the preparation of an array of chiral ligands [1,16-19]. Rapid protonation in water subsequent to β-borylation would liberate the desired adducts almost instantaneously. In addition to the synthetic utility of enantiomerically enriched β-boryl nitriles, Cu(II)-based activation of α,β-unsaturated nitriles in water is mechanistically curious. In previous reports, homogeneous catalysts composed of $Cu(OAc)_2$ were found to be more effective than insoluble $Cu(OH)_2$-based catalysts in the asymmetric β-borylation of α,β-unsaturated nitriles in water [1,19]. Herein, we describe the Cu(II)-catalyzed asymmetric boron conjugate addition of α,β-unsaturated nitriles in water.

Results and Discussion

At the outset, an aqueous solution of a chiral Cu(II) complex was formed by vigorous stirring of $Cu(OAc)_2$ with chiral 2,2′-bipyridine ligand **L** for 1 h. After successive addition of cinnamonitrile (**1a**) and bis(pinacolato)diboron, the resulting mixture was stirred at room temperature for 12 h. Subsequent oxidation by treatment with $NaBO_3$ was conducted to determine the enantioselectivity. The desired β-hydroxynitrile **2a** was obtained in 84% yield with 81% ee (Scheme 1), which is consistent with the outcome obtained when the reaction was performed at 5 °C (86% yield, 82% ee [1]). The reactions proceeded smoothly despite the fact that both solid substrates were almost completely insoluble in water. Notably, the desired β-borylated product was isolated as the β-hydroxynitrile after subsequent oxidation, with complete retention of the expected stereochemistry. β-Hydroxynitriles, which are conventionally synthesized by asymmetric addition of acetonitrile to aldehydes [6,20] or by lipase- or nitrilase-catalyzed kinetic resolution of racemic β-hydroxynitriles [21,22], are fascinating candidates for the development of many synthetically feasible derivatives.

When studying these systems, it is important to understand how the conformation of the substrate geometry correlates with its reactivity and enantioselectivity in water. The conjugated system tends to undergo Lewis acid assisted isomerization in water [18]. With three mixtures of **1b** with different *E*/*Z* ratios in hand, their activity toward boron conjugate addition and the sense of stereoselection were examined under the optimal conditions (Table 1). After stirring the reaction mixture for 12 h and subsequent oxidation, β-hydroxynitrile **2b** was obtained in the same yield and with the same enantioselectivity, irrespective of substrate geometry. Notably, the *E*/*Z* geometry of α,β-unsaturated nitrile **1b** did not have an influence on the initial reaction rate, nor was there a difference in the activity or the enantiofacial differentiation between the *E*- and *Z*-isomers.

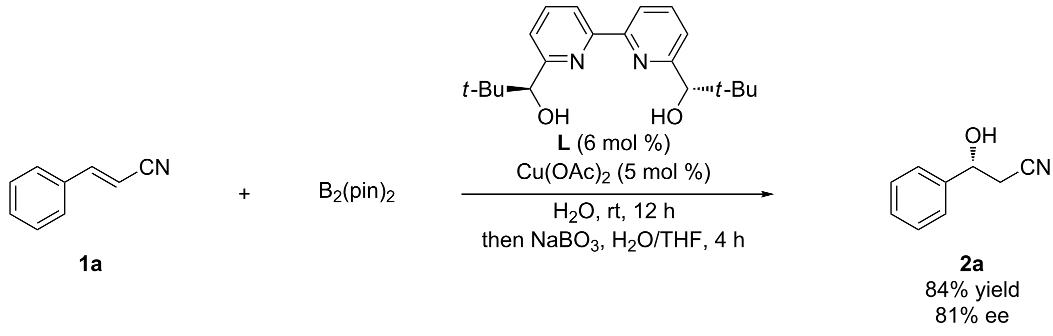
Table 1: Asymmetric β-borylation of **1b** with different configurations.



Entry	*E*/*Z* ratio of **1b**	Yield (%)^a	ee (%)^b
1	4.3:1	66	78
2	5.7:1	65	76
3	>99:<1	68	76

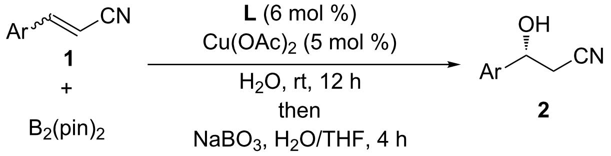
^{a}Isolated yield. ^{b}Determined by chiral HPLC analysis.

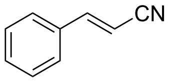
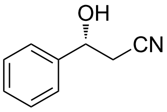
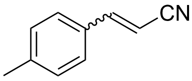
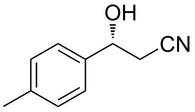
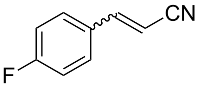
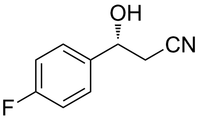
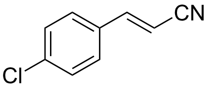
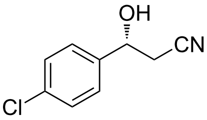
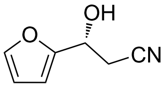
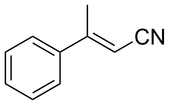
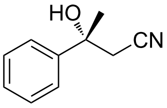
The scope of the reaction with respect to α,β-unsaturated nitriles bearing an aromatic ring was then investigated (Table 2). In addition to **1b**, electron-poor α,β-unsaturated nitriles **1c** and **1d** also reacted with the diboron reagent to give the desired products in good to high yields with good to high enantioselectivities. No significant deterioration of chiral induction was observed upon changing the electronic nature of the double bonds. Meanwhile, heterocyclic substrate **1e**, bearing a furan ring, was also tolerated under the reaction conditions and this compound underwent enantioselective β-borylation to afford β-hydroxynitrile **2e** in 87% yield with 87% ee. Remarkably, when β,β-disubstituted α,β-unsaturated nitrile **1f** was employed, the desired β-hydroxynitrile **2f** bearing a quaternary asymmetric carbon center could be successfully produced in 75% yield with 85% ee.



Scheme 1: Standard reaction conditions.

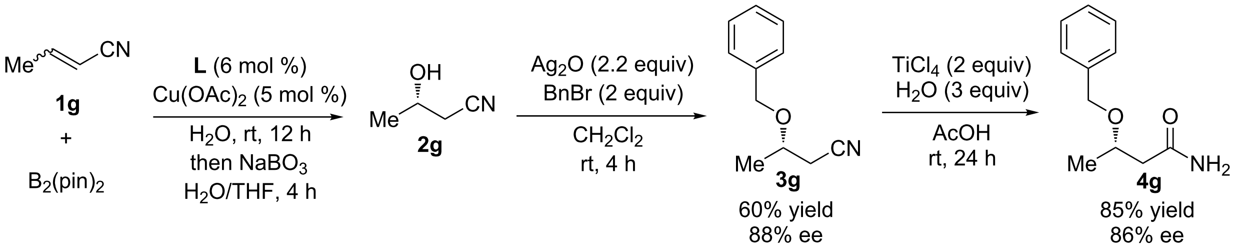
Table 2: Scope of the Cu(II)-catalyzed asymmetric borylation with respect to aromatic α,β-unsaturated nitriles.



Entry	Substrate	Product	Yield (%)[a]	ee (%)[b]
1	 **1a**	 **2a**	84	81
2	 **1b**	 **2b**	66	78
3	 **1c**	 **2c**	92	90
4	 **1d**	 **2d**	75	81
5	 **1e**	 **2e**	87	87
6	 **1f**	 **2f**	75	85

[a]Isolated yield. [b]Determined by chiral HPLC analysis.

Finally, to examine the suitability of aliphatic α,β-unsaturated nitriles as substrates for the reaction, the asymmetric β-borylation and subsequent oxidation of crotonitrile (**1g**) were attempted (Scheme 2). The obtained β-hydroxynitrile **2g** was converted into the corresponding benzyl ether **3g** in the presence of Ag$_2$O [23], followed by hydrolysis with TiCl$_4$ in AcOH



Scheme 2: Formation of aliphatic chiral β-hydroxy nitrile **2g** and its subsequent conversion into **4g**.

[24] without loss of enantiopurity of **3g**. The sense of enantioselection of **3g** was proved to be the same as that of the β-borylated aromatic products shown in Table 2, according to the reported chiral information of β-hydroxyamide **4g** [25]. It is noted that even an aliphatic α,β-unsaturated nitrile worked well under the reaction conditions to afford the desired compound in high yield with high enantioselectivity.

Conclusion

We have demonstrated that a chiral Cu(II) complex formed with chiral 2,2′-bipyridine ligand **L** constitutes a green and efficient catalyst for asymmetric boron conjugate addition of α,β-unsaturated nitriles in water. Both aromatic and aliphatic α,β-unsaturated nitriles were applicable, and both gave the corresponding chiral β-hydroxynitriles after oxidation with high enantioselectivity. In contrast to well-documented Cu(I) catalytic systems in organic solvents, Cu(II) catalysis in water does not require the use of air-sensitive phosphine ligands or strong bases. Notably, neither the chemical nor physical properties of the α,β-unsaturated nitriles had any influence on either the reactivity or the stereochemical outcome of the reaction; that is, the reaction proceeded well irrespective of whether the sample was solid or liquid, or whether the *E*- or *Z*-isomer was used.

Supporting Information

Supporting Information File 1

General procedure, analytical data and spectra of all compounds, methods for conversion.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-217-S1.pdf]

Acknowledgements

This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS), Global COE Program, The University of Tokyo, MEXT, Japan, and the Japan Science and Technology Agency (JST). P.X. thanks the JSPS for a Research Fellowship for Young Scientists.

References

1. Kitanosono, T.; Xu, P.; Kobayashi, S. *Chem. – Asian J.* **2014,** *9,* 179–188. doi:10.1002/asia.201300997
2. Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011,** *3,* 894–899. doi:10.1038/nchem.1150
3. Solé, C.; Tatla, A.; Mata, J. A.; Whiting, A.; Gulyás, H.; Fernández, E. *Chem. – Eur. J.* **2011,** *17,* 14248–14257. doi:10.1002/chem.201102081
4. Scott, H. K.; Aggarwal, V. K. *Chem. – Eur. J.* **2011,** *17,* 13124–13132. doi:10.1002/chem.201102581
5. Battilocchio, C.; Hawkins, J. M.; Ley, S. V. *Org. Lett.* **2014,** *16,* 1060–1063. doi:10.1021/ol403591c
6. Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003,** *5,* 3147–3150. doi:10.1021/ol035206u
7. Okumura, T.; Hayami, S.; Ozawa, T.; Funahashi, Y.; Maeda, Y.; Masuda, H. *Chem. Lett.* **2007,** *36,* 96–97. doi:10.1246/cl.2007.96
8. Jaroszewski, J. W.; Ettlinger, M. G. *J. Org. Chem.* **1988,** *53,* 4635–4637. doi:10.1021/jo00254a056
9. Lown, J. W.; Chauhan, S. M. S. *J. Org. Chem.* **1981,** *46,* 2479–2489. doi:10.1021/jo00325a011
10. Giannis, A.; Sandhoff, K. *Angew. Chem.* **1989,** *101,* 220–222. doi:10.1002/ange.19891010231
11. Stavber, G.; Časar, Z. *Appl. Organomet. Chem.* **2013,** *27,* 159–165. doi:10.1002/aoc.2957
12. Sole, C.; Bonet, A.; De Vries, A. H. M.; De Vries, J. G.; Lefort, L.; Gulyás, H.; Fernández, E. *Organometallics* **2012,** *31,* 7855–7861. doi:10.1021/om300194k
13. Hirsch-Weil, D.; Abboud, K. A.; Hong, S. *Chem. Commun.* **2010,** *46,* 7525–7527. doi:10.1039/c0cc02211j
14. Lee, J.-E.; Yun, J. *Angew. Chem., Int. Ed.* **2008,** *47,* 145–147. doi:10.1002/anie.200703699
15. Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006,** *8,* 4887–4889. doi:10.1021/ol061955a
16. Zhu, L.; Kitanosono, T.; Xu, P.; Kobayashi, S. *Chem. Commun.* **2015,** *51,* 11685–11688. doi:10.1039/c5cc04295j
17. Kitanosono, T.; Xu, P.; Isshiki, S.; Zhu, L.; Kobayashi, S. *Chem. Commun.* **2014,** *50,* 9336–9339. doi:10.1039/c4cc04062g
18. Kitanosono, T.; Xu, P.; Kobayashi, S. *Chem. Commun.* **2013,** *49,* 8184–8186. doi:10.1039/c3cc44324h
19. Kobayashi, S.; Xu, P.; Endo, T.; Ueno, M.; Kitanosono, T. *Angew. Chem., Int. Ed.* **2012,** *51,* 12763–12766. doi:10.1002/anie.201207343
20. Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005,** *7,* 3757–3760. doi:10.1021/ol051423e
21. Itoh, T.; Mitsukura, K.; Kanphai, W.; Takagi, Y.; Kihara, H.; Tsukube, H. *J. Org. Chem.* **1997,** *62,* 9165–9172. doi:10.1021/jo971288m
22. Kamila, S.; Zhu, D.; Biehl, E. R.; Hua, L. *Org. Lett.* **2006,** *8,* 4429–4431. doi:10.1021/ol061542+
23. Ma, D.-Y.; Wang, D.-X.; Pan, J.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2008,** *73,* 4087–4091. doi:10.1021/jo800074k
24. Mukaiyama, T.; Kamio, K.; Kobayashi, S.; Takei, H. *Chem. Lett.* **1973,** *2,* 357–358. doi:10.1246/cl.1973.357
25. Ma, D.-Y.; Zheng, Q.-Y.; Wang, D.-X.; Wang, M.-X. *Org. Lett.* **2006,** *8,* 3231–3234. doi:10.1021/ol0610688

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The definitive version of this article is the electronic one which can be found at:
doi:10.3762/bjoc.11.217

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

A new approach to ferrocene derived alkenes via copper-catalyzed olefination

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Full Research Paper

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Keywords:
catalytic olefination; copper catalysis; cyclic voltammetry; ferrocene

Beilstein J. Org. Chem. **2015,** *11,* 2072–2078.
doi:10.3762/bjoc.11.223

Received: 10 August 2015
Accepted: 15 October 2015
Published: 03 November 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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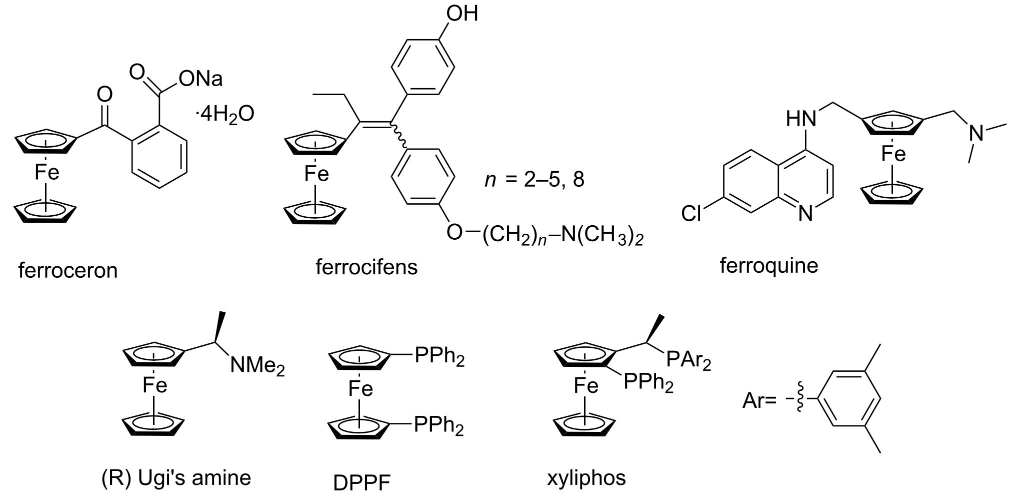
Abstract

A new approach to ferrocenyl haloalkenes and bis-alkenes was elaborated. The key procedure involves copper catalyzed olefination of *N*-unsubstituted hydrazones, obtained from ferrocene-containing carbonyl compounds and hydrazine, with polyhaloalkanes. The procedure is simple, cheap and could be applied for the utilization of environmentally harmful polyhalocarbons. The cyclic voltammetry study of the representative examples of the synthesized ferrocenyl alkenes shows the strong dependence of the cathodic behavior on the amount of vinyl groups: while for the monoalkene containing molecules no reduction is seen, the divinyl products are reduced in several steps.

Introduction

The introduction of complex functional fragments into the specified place of the target molecule is of current interest in modern synthetic chemistry [1]. From this point of view, the development of ferrocene-based molecules as crucial fragments of new materials and novel pharmacological entities is of great importance. Indeed, since the discovery of ferrocene [2] and the synthesis of the first polymer based on vinylferrocene [3], the chemistry of ferrocene and its derivatives is developing very rapidly. Ferrocene derivatives are widely applied in industry, for example, diethylferrocene is a combustion accelerator used as additive to gasoline [4]. There are many drugs containing a ferrocene fragment in their structures (Scheme 1) [5]. The



Scheme 1: Examples of ferrocene derived drugs and ligands.

ferrocene core is also a very popular scaffold for ligand design, particularly, in asymmetric catalysis (Scheme 1).

Probably, the most challenging application of ferrocenes is the production of ferrocene-containing polymers [6-8] (Scheme 2). The polymers have a set of unique properties and are used in various fields of science, technology and medicine (conducting and semiconducting materials [9], drugs [10], biosensors [11-13], liquid crystal materials [14,15], coordination polymers [16], and more [10]).

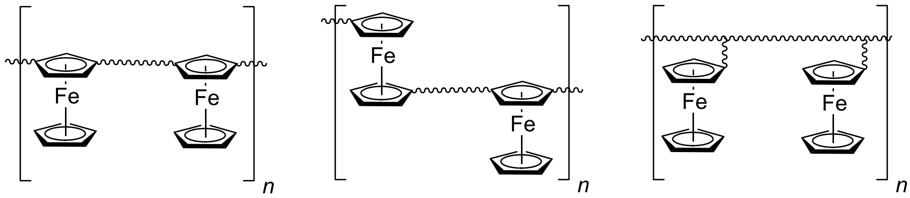
Ethynylferrocenes are one of the most popular and extremely effective starting compounds in the creation of ferrocenyl polymers. They are widely used for making both polyferrocenylvinylenes (double bond linkers) [17-21] and polyethynylferrocenes (triple bond linkers) [22-25]. There are several methods for the preparation of ethynylferrocenes [24-29]. In most cases, the key reagents for the synthesis of ethynylferrocene are the corresponding mono- and dihalogenvinylferrocene derivatives. These compounds are generally prepared using a variation of the Wittig reaction (the Corey–Fuchs reaction) using a 2–4-fold molar excess of triphenylphosphine [27-31].

Results and Discussion

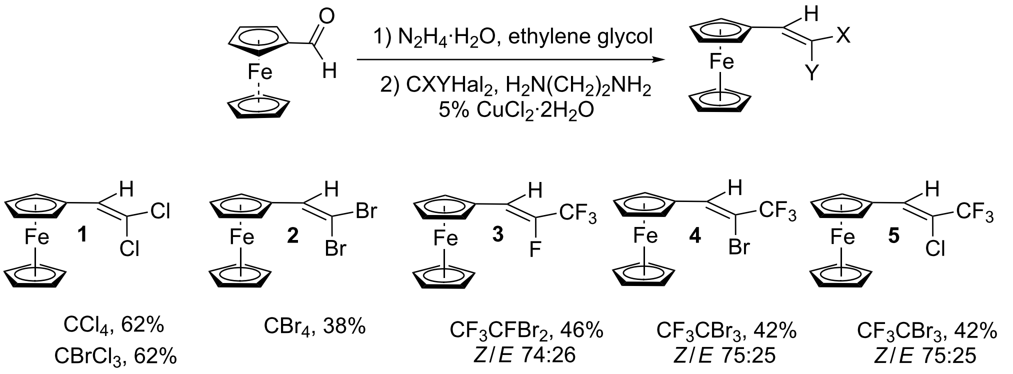
Synthesis of halovinylferrocenes

A few years ago we discovered a new reaction for a double carbon–carbon bond formation – the reaction of catalytic olefination. It was shown that the copper-catalyzed reaction of unsubstituted hydrazones of aromatic (aliphatic) aldehydes and ketones with a wide range of polyhalogenalkanes leads to the corresponding substituted ethylenes with one or two geminal halogen atoms [32-36]. In the present study, we investigated the possibility of using a catalytic olefination reaction for the synthesis of ferrocene derivatives. As a result, several well-known and previously unknown ferrocene-containing alkene compounds were obtained.

First, ferrocene carbaldehyde was investigated. It was found, that under usual conditions of the reaction (equal amount of $N_2H_4{\cdot}H_2O$, DMSO or EtOH as a solvent) the yields of the desired alkenes were not good enough. Better results were obtained in ethylene glycol with a 4-fold excess of $N_2H_4{\cdot}H_2O$ (novel media just reported for COR [37]). In this case, target alkenes were isolated in up to 62% yield. Using C2-freons fluorinated alkenes **3–5** were synthesized (Scheme 3). The reaction proceeds stereoselectively to give a mixture of isomers in which



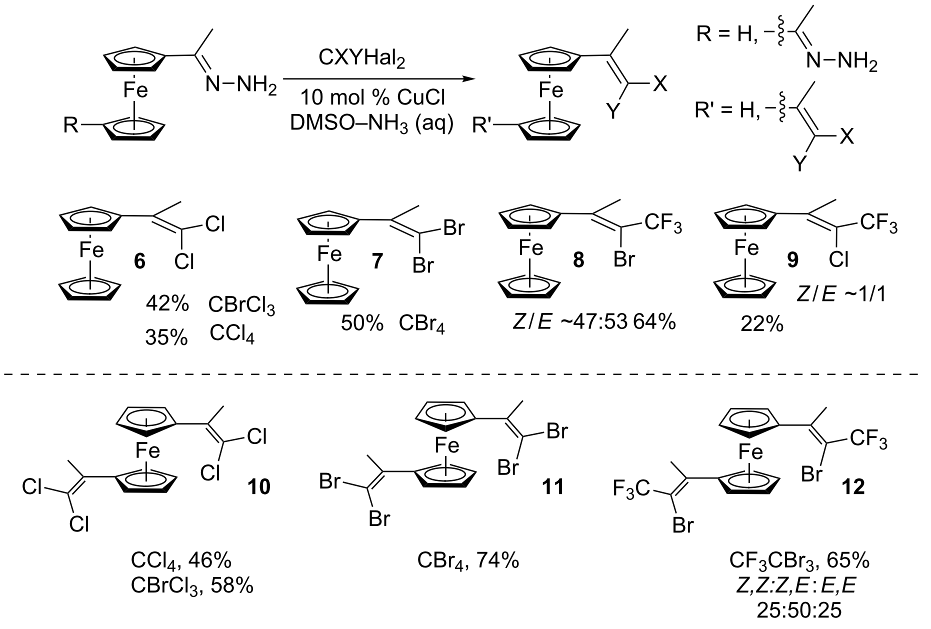
Scheme 2: Structural types of ferrocene-based polymers.



Scheme 3: Synthesis of ferrocene-derived alkenes from ferrocene carbaldehyde.

the less hindered *Z*-isomer dominates. The assignment of the isomers was easily performed by comparison of NMR spectral data with those previously reported for the *Z,E*-isomers of similar alkenes [38-40]. The trifluoromethyl group of the *Z*-isomers of compounds **3**–**5** resonates in higher field in ^{19}F NMR (**3**: −72.8 ppm, **4**: −67.1 ppm, **5**: −69.0 ppm) than that of the *E*-isomers (**3**: −67.9 ppm, **4**: −60.2 ppm, **5**: −62.4 ppm). In the case of compound **3** an additional conformation can be seen in the ^{1}H NMR spectrum. It is well-known, that $^2J_{HF}$ coupling constants in alkenes with relative *trans*-configuration of hydrogen and fluorine atoms are usually approximately twice bigger than the corresponding coupling constants in alkenes with *cis*-configuration. The values found in **3** are 36.5 Hz (*Z*-isomer by systematic nomenclature, but *trans*-configuration of H and F) and 16.2 Hz (*E*-isomer).

Acetylferrocene and 1,1'-diacetylferrocene were also involved successfully into this transformation (Scheme 4). Our preliminary study of the catalytic olefination of acetylferrocene by CF_3CBr_3 (alkene **8**) and CBr_4 (alkene **7**) indicates, that in contrast to ferrocene carbaldehyde, better results were achieved in DMSO using previously prepared hydrazones [37]. A series of ferrocene derivatives including fluorinated ones was prepared in good yields. Unsymmetrical alkenes **8** and **9** were obtained as a mixture of isomers in approximately equal amounts. Identification of the structures of the *E*- and *Z*-isomers



Scheme 4: Synthesis of ferrocene-derived alkenes from acetylferrocene and 1,1'-diacetylferrocene.

of alkene **8** was accurately performed by an X-ray crystallographic study using crystals of **8** obtained from ethanol solution (see Supporting Information File 1 and [41]). Due to the presence of two double bonds in alkene **12** the formation of three isomers (*Z,Z*, *Z,E* and *E,E*) is possible. Similar to alkenes **8** and **9** no stereoselectivity is observed to give equal numbers of *cis*- and *trans*-double bonds in the obtained molecules. As a result a 25:50:25 mixture of *Z,Z*, *Z,E* and *E,E* was formed. The higher quantity of the *Z,E*-isomer is a result of statistical doubling (in fact, the reaction gives *Z,E* and *E,Z*-alkenes which are identical).

Di- and tetrahalovinylferrocenes obtained in our work are of interest for the synthesis of ethynylferrocenes, as monomers for making ferrocene-containing polymers and as intermediates in the synthesis of ferrocene analogs of tamoxifen and other medicinally relevant molecules.

Electrochemical properties of halovinylferrocenes

The ferrocene unit possesses several exciting electrochemical characteristics, such as fast electron-transfer rate, low oxidation potential, and stability of two redox states. The combination of a ferrocene and an alkene moiety in one molecule might be of interest for the synthesis of functional devises that can be exploited in electrocatalysis, electroanalysis, and biosensing applications, since the alkene fragment could be used to graft the molecule to the polymer support or to copolymerize it with the appropriate monomers. Therefore, we have also examined the electrochemical properties of the compounds obtained. It was shown that the oxidation of the ferrocene unit proceeds in accordance to the data found in literature, whereas the reduction was found only in the case of bis(halovinyl)ferrocenes. Our results clearly indicate that the anodic and cathodic electrochemical processes proceed on different parts of the molecules. While in the anodic region the changes are localized on the iron atom, the electron transfer from the cathode occurs at a double bond.

Three representative groups of halovinylferrocenes were studied using cyclic voltammetry (Table 1). The first group was formed from three omega-dichloro derivatives **1**, **6**, and **10**. The second one was made from three omega-dibromo products **2**, **7**, and **11**, and the last group consisted of bromotrifluoromethyl molecules **4**, **8**, and **12**. Such selection allowed us to estimate the effect of the nature of substituent on the electrochemical behavior of the molecule.

All compounds are characterized by reversible oxidation waves in the range of 0.64–0.84 V that corresponds to the Fe^{2+}/Fe^{3+} redox transformation. The values of the respective oxidation potential depend mainly on the amount of the vinyl groups attached to the ferrocene core. There is also the effect of the halogen atom, though to a lesser extent compared to the effect of the amount of vinyl groups. For example, all dichloro and dibromo compounds (**1**, **2**, **6**, and **7**, one vinyl fragment) are oxidized at potentials of 0.64–0.65 V, whereas for the corresponding tetrahalo compounds (**10** and **11**, two vinyl fragments) these values are shifted to more anodic potentials, namely, 0.74 V. The same is true for trifluoromethyl ferrocenes **4**, **8**, and **12** (Figure 1).

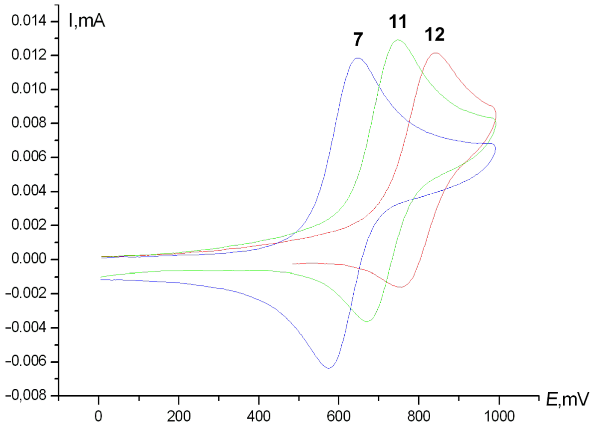


Figure 1: Typical voltammogramms of vinylferrocenes **7** (blue), **11** (green), **12** (red), anodic region.

In the cathodic region, monovinylic compounds **1**, **2**, **4**, and **6**–**8** show no reduction up to 1.80 V, whilst the corresponding divinylic molecules **10**–**12** exhibit pronounced reduction waves in the range of 0.34–1.66 V (Figure 2).

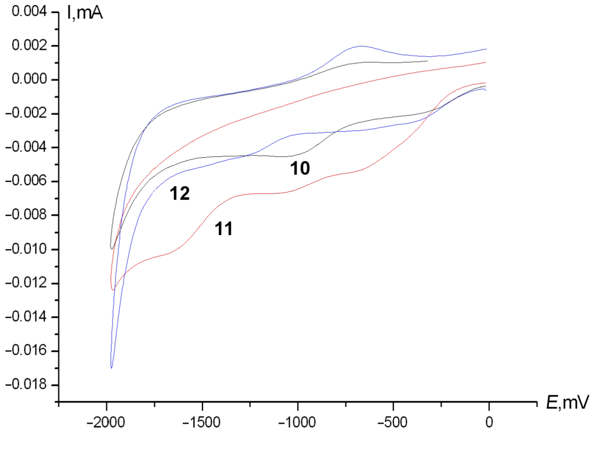
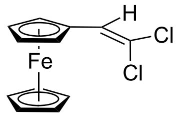
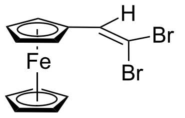
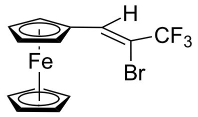
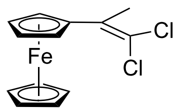
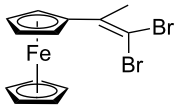
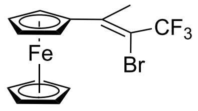
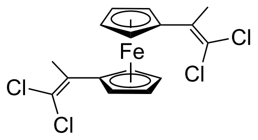
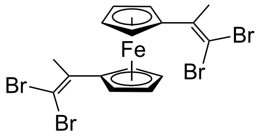
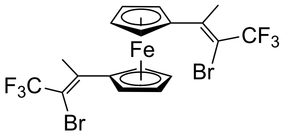


Figure 2: Typical voltammogramms of divinylferrocenes **10** (black), **11** (red), **12** (blue), cathodic region.

Table 1: Cyclic voltammetry data for selected halovinylferrocenes. Pt electrode, DMF, Ag/AgCl/KCl (sat.), Bu_4NBF_4.

Compound	E_p^{Ox}, V	$-E_p^{Red1}$, V	$-E_p^{Red2}$, V	$-E_p^{Red3}$, V
 **1**	0.646 (0.580)[a]	–	–	–
 **2**	0.651 (0.584)	–	–	–
 **4**	0.735 (0.669)	–	–	–
 **6**	0.655 (0.576)		–	–
 **7**	0.641 (0.579)	–	–	–
 **8**	0.726 (0.607)	–	–	–
 **10**	0.741 (0.675)	0.371 IR[b]	0.983 (0.763)	–
 **11**	0.740 (0.670)	0.68 IR	1.022 IR	1.66 IR
 **12**	0.836 (0.867)	0.343 IR	1.232 (0.71)	–

[a] In the case of a reversible peak the reverse potentials are shown in paranthesis. [b] IR means irreversible.

The processes behind the cathodic waves are not totally clear at the moment, but we assume that the radical-ions formed after the first electron transfer would enter the intramolecular cyclization reaction involving the second adjacent double bond with subsequent electropolymerization. The latter is confirmed by a pronounced decrease in current values (3–4 times) as compared to current values of oxidation at the iron atom. These findings allow us to state that the synthesized molecules are promising starting materials for the electrochemical synthesis of ferrocene-containing conjugated polymers.

Conclusion

In conclusion, a novel stereoselective route to ferrocenyl haloalkenes and bis-alkenes was elaborated on the basis of a catalytic olefination reaction of *N*-unsubstituted hydrazones obtained from ferrocene-containing aldehydes and ketones. Electrochemical properties of synthesized alkenes were investigated and promising electrochemical characteristics were demonstrated.

Supporting Information

Supporting Information File 1

Experimental details, analytical data and copies of NMR spectra of all synthesized compounds, X-ray data of compound **8**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-223-S1.pdf]

Acknowledgements

This work was supported by the Russian Foundation for the Basic Research (Grants no 13-03-01129-a and 14-03-91160-GFEN, investigation of electrochemical properties of halovinylferrocenes) and the Russian Science Foundation (grant no. 14-13-00083, synthesis of starting materials and halovinylferrocenes). The authors acknowledge partial support in measuring of NMR from the M.V. Lomonosov Moscow State University Program of Development.

References

1. Ananikov, V. P.; Khemchyan, L. L.; Ivanova, Yu. V.; Bukhtiyarov, V. I.; Sorokin, A. M.; Prosvirin, I. P.; Vatsadze, S. Z.; Medved'ko, A. V.; Nuriev, V. N.; Dilman, A. D.; Levin, V. V.; Koptyug, I. V.; Kovtunov, K. V.; Zhivonitko, V. V.; Likholobov, V. A.; Romanenko, A. V.; Simonov, P. A.; Nenajdenko, V. G.; Shmatova, O. I.; Muzalevskiy, V. M.; Nechaev, M. S.; Asachenko, A. F.; Morozov, O. S.; Dzhevakov, P. B.; Osipov, S. N.; Vorobyeva, D. V.; Topchiy, M. A.; Zotova, M. A.; Ponomarenko, S. A.; Borshchev, O. V.; Luponosov, Yu. N.; Rempel, A. A.; Valeeva, A. A.; Stakheev, A. Yu.; Turova, O. V.; Mashkovsky, I. S.; Sysolyatin, S. V.; Malykhin, V. V.; Bukhtiyarova, G. A.; Terent'ev, A. O.; Krylov, I. B. *Russ. Chem. Rev.* **2014,** *83,* 885–985. doi:10.1070/RC2014v83n10ABEH004471
2. Kealy, T. J.; Pauson, P. L. *Nature* **1951,** *168,* 1039–1040. doi:10.1038/1681039b0
3. Arimoto, F. S.; Haven, A. C., Jr. *J. Am. Chem. Soc.* **1955,** *77,* 6295–6297. doi:10.1021/ja01628a068
4. Tong, R.; Zhao, Y.; Wang, L.; Yu, H.; Ren, F.; Saleem, M.; Amer, W. A. *J. Organomet. Chem.* **2014,** *755,* 16–32. doi:10.1016/j.jorganchem.2013.12.052
5. Braga, S. S.; Silva, A. M. S. *Organometallics* **2013,** *32,* 5626–5639. doi:10.1021/om400446y
6. Wang, L.; Haogie, Y. *Synthesis, Properties and Application of Ferrocenyl Polymers;* Zheijang University Press, 2013.
7. Hardy, C. G.; Ren, L.; Zhang, J.; Tang, C. *Isr. J. Chem.* **2012,** *52,* 230–245. doi:10.1002/ijch.201100110
8. Heo, R. W.; Lee, T. R. *J. Organomet. Chem.* **1999,** *578,* 31–42. doi:10.1016/S0022-328X(98)01126-7
9. Deng, W.; Yamaguchi, H.; Takashima, Y.; Harada, A. *Angew. Chem.* **2007,** *119,* 5236–5239. doi:10.1002/ange.200701272
10. Neuse, E. W. *J. Inorg. Organomet. Polym. Mater.* **2005,** *15,* 3–31. doi:10.1007/s10904-004-2371-9
11. Amer, W. A.; Wang, L.; Amin, A. M.; Ma, L.; Yu, H. *J. Inorg. Organomet. Polym. Mater.* **2010,** *20,* 605–615. doi:10.1007/s10904-010-9373-6
12. Takahashi, S.; Anzai, J. *Materials* **2013,** *6,* 5742–5762. doi:10.3390/ma6125742
13. Gracia, R.; Mecerreyes, D. *Polym. Chem.* **2013,** *4,* 2206–2214. doi:10.1039/c3py21118e
14. Gao, Y.; Shreeve, J. M. *J. Inorg. Organomet. Polym. Mater.* **2007,** *17,* 19–36. doi:10.1007/s10904-006-9095-y
15. Kadkin, O. N.; Galyametdinov, Yu. G. *Russ. Chem. Rev.* **2012,** *81,* 675–699. doi:10.1070/RC2012v081n08ABEH004270
16. Horikoshi, R.; Mochida, T. *Eur. J. Inorg. Chem.* **2010,** 5355–5371. doi:10.1002/ejic.201000525
17. Dragutan, I.; Dragutan, V.; Fischer, H. *J. Inorg. Organomet. Polym. Mater.* **2008,** *18,* 311–324. doi:10.1007/s10904-008-9213-0
18. Buchmeiser, M.; Schrock, R. R. *Macromolecules* **1995,** *28,* 6642–6649. doi:10.1021/ma00123a034
19. Buchmeiser, M. R. *Macromolecules* **1997,** *30,* 2274–2277. doi:10.1021/ma961317f
20. Buchmeiser, M. R.; Schuler, N.; Kaltenhauser, G.; Ongania, K.-H.; Lagoja, I.; Wurst, K.; Schottenberger, H. *Macromolecules* **1998,** *31,* 3175–3183. doi:10.1021/ma9716948
21. Camus, A.; Faruffini, V.; Furlani, A.; Marsich, N.; Ortaggi, G.; Paolesse, R.; Russo, M. V. *Appl. Organomet. Chem.* **1988,** *2,* 533–537. doi:10.1002/aoc.590020606
22. Hudson, R. D. A. *J. Organomet. Chem.* **2001,** *637–639,* 47–69. doi:10.1016/S0022-328X(01)01142-1
23. Abd-El-Aziz, A. S. *Macromol. Rapid Commun.* **2002,** *23,* 995–1031. doi:10.1002/marc.200290003
24. Butler, I. R.; Boyes, A. L.; Kelly, G.; Quayle, S. C.; Herzig, T.; Szewczyk, J. *Inorg. Chem. Commun.* **1999,** *2,* 403–406. doi:10.1016/S1387-7003(99)00099-4
25. Plenio, H.; Hermann, J.; Sehring, A. *Chem. – Eur. J.* **2000,** *6,* 1820–1829. doi:10.1002/(SICI)1521-3765(20000515)6:10<1820::AID-CHEM1820>3.0.CO;2-A
26. Schloegl, K.; Egger, H. *Monatsh. Chem.* **1963,** *94,* 376–392.
27. Luo, S.-J.; Liu, Y.-H.; Liu, C.-M.; Liang, Y.-M.; Ma, Y.-X. *Synth. Commun.* **2000,** *30,* 1569–1572. doi:10.1080/00397910008087190
28. Clément, S.; Guyard, L.; Knorr, M.; Dilsky, S.; Strohmann, C.; Arroyo, M. *J. Organomet. Chem.* **2007,** *692,* 839–850. doi:10.1016/j.jorganchem.2006.10.039
29. Pedersen, B.; Wagner, G.; Herrmann, R.; Scherer, W.; Meerholz, K.; Schmälzlin, E.; Bräuchle, C. *J. Organomet. Chem.* **1999,** *590,* 129–137. doi:10.1016/S0022-328X(99)00440-4

30. Tsuboya, N.; Hamasaki, R.; Ito, M.; Mitsuishi, M.; Miyashita, T.; Yamamoto, Y. *J. Mater. Chem.* **2003,** *13,* 511–513. doi:10.1039/b211019a
31. Clément, S.; Guyard, L.; Knorr, M.; Gessner, V. H.; Strohmann, C. *Acta Crystallogr., Sect. E* **2009,** *65,* m334. doi:10.1107/S1600536809006102
32. Shastin, A. V.; Korotchenko, V. N.; Nenaidenko, V. G.; Balenkova, E. S. *Russ. Chem. Bull.* **1999,** *48,* 2184–2185. doi:10.1007/BF02494876
33. Shastin, A. V.; Korotchenko, V. N.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2000,** *56,* 6557–6563. doi:10.1016/S0040-4020(00)00606-2
34. Nenajdenko, V. G.; Varseev, G. N.; Korotchenko, V. N.; Shastin, A. V.; Balenkova, E. S. *J. Fluorine Chem.* **2003,** *124,* 115–118. doi:10.1016/S0022-1139(03)00199-4
35. Shastin, A. V.; Muzalevsky, V. M.; Balenkova, E. S.; Nenajdenko, V. G. *Mendeleev Commun.* **2006,** *16,* 179–180. doi:10.1070/MC2006v016n03ABEH002282
36. Muzalevskiy, V. M.; Shikhaliev, N. G.; Magerramov, A. M.; Gurbanova, N. V.; Geydarova, S. D.; Balenkova, E. S.; Shastin, A. V.; Nenajdenko, V. G. *Russ. Chem. Bull.* **2013,** *62,* 678–682. doi:10.1007/s11172-013-0091-4
37. Hirotaki, K.; Kawazoe, G.; Hanamoto, T. *J. Fluorine Chem.* **2015,** *171,* 169–173. doi:10.1016/j.jfluchem.2014.07.018
38. Nenajdenko, V. G.; Varseev, G. N.; Korotchenko, V. N.; Shastin, A. V.; Balenkova, E. S. *J. Fluorine Chem.* **2004,** *125,* 1339–1345. doi:10.1016/j.jfluchem.2004.04.002
39. Nenajdenko, V. G.; Varseev, G. N.; Shastin, A. V.; Balenkova, E. S. *J. Fluorine Chem.* **2005,** *126,* 907–913. doi:10.1016/j.jfluchem.2005.03.020
40. Korotchenko, V. N.; Shastin, A. V.; Nenajdenko, V. G.; Balenkova, E. S. *Tetrahedron* **2001,** *57,* 7519–7527. doi:10.1016/S0040-4020(01)00701-3
41. Shixaliyev, N. G.; Heydarova, S. J.; Muzalevskiy, V. M.; Nenajdenko, V. G.; Rahimova, A. G. *Azerb. Khim. Zh.* **2013,** 78–83.

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doi:10.3762/bjoc.11.223

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Copper-mediated synthesis of *N*-alkenyl-α,β-unsaturated nitrones and their conversion to tri- and tetrasubstituted pyridines

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Full Research Paper
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Keywords:
Chan–Lam; copper; nitrone; oxygen transfer; pyridine

Beilstein J. Org. Chem. **2015,** *11,* 2097–2104.
doi:10.3762/bjoc.11.226

Received: 11 August 2015
Accepted: 20 October 2015
Published: 04 November 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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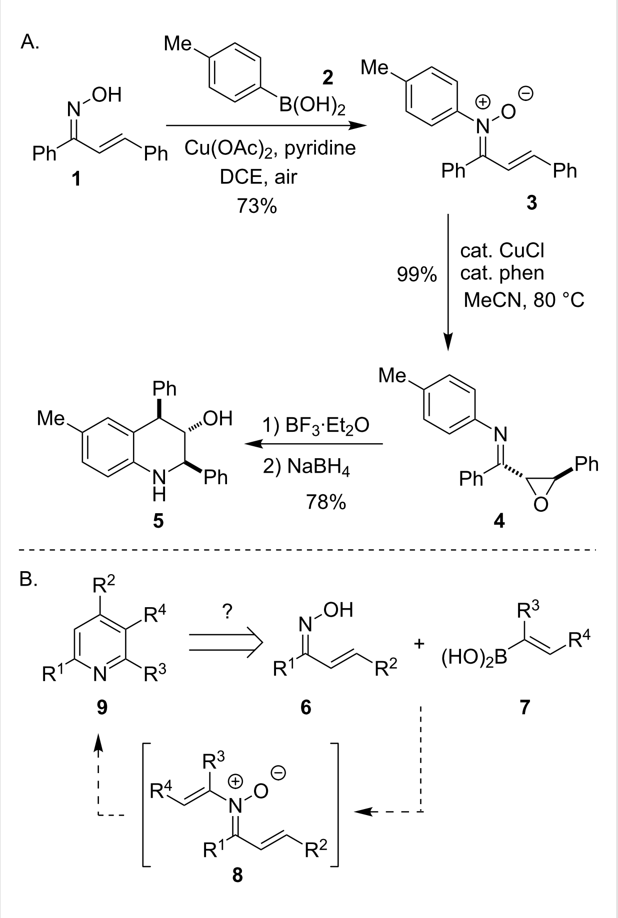
Abstract

A Chan–Lam reaction has been used to prepare *N*-alkenyl-α,β-unsaturated nitrones, which undergo a subsequent thermal rearrangement to the corresponding tri- and tetrasubstituted pyridines. The optimization and scope of these transformations is discussed. Initial mechanistic experiments suggest a reaction pathway involving oxygen transfer followed by cyclization.

Introduction

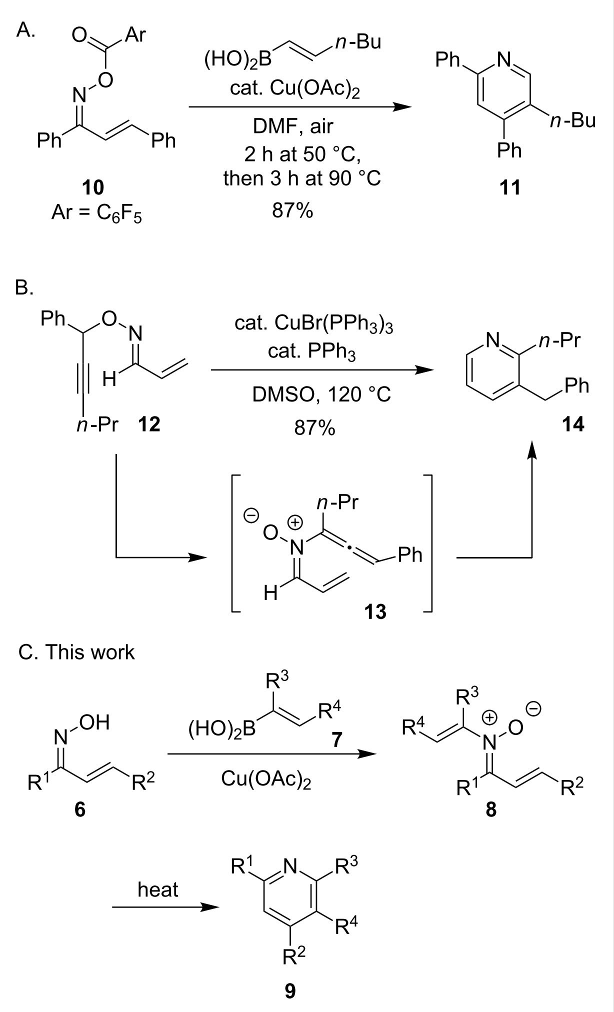
While most applications of the Chan–Lam reaction are focused on the synthesis of aryl ethers and aryl amines, our group has been interested in the use of the Chan–Lam reaction for the synthesis of *O*-alkenyl oximes and hydroxylamines, as well as *N*-alkenyl and *N*-arylnitrones [1-5]. We have discovered that when this transformation is performed with oxime and hydroxamic acid substrates, these reactive intermediates can be accessed and subsequently rearrange to a variety of challenging organic fragments and heterocyclic products [6-13]. Specifically, we reported that *N*-arylnitrones **3** can be prepared by a Chan–Lam coupling of **1** and **2** and that these compounds undergo a copper-catalyzed rearrangement to α,β-epoxyimines such as **4** [8]. Reduction of these products in the presence of a Lewis acid gave tetrahydroquinolines such as **5** (Scheme 1A). These studies encouraged us to consider if similar *N*-alkenylnitrones **8** could be accessed by a Chan–Lam coupling and transformed into the corresponding substituted pyridines **9** (Scheme 1B).

Pyridines are important heterocycles that are often found in biologically active molecules [14-21]. Due to the high demand for these compounds, there are many methods for preparing substi-



Scheme 1: Use of a Chan–Lam reaction for the synthesis of tetrahydroquinolines and potential extension to pyridines [8].

tuted pyridines through condensation reactions [22-26], cycloadditions [27-30], functionalization of parent pyridine structures [31-38], fragment couplings [39-42], and transition metal-catalyzed C–H bond functionalization of α,β-unsaturated imines and oximes [43-50]. We were inspired by the copper-catalyzed coupling of protected α,β-unsaturated oximes and alkenylboronic acids developed by Liebeskind and coworkers due to its modularity and control of regioselectivity and wondered if a Chan–Lam route to *N*-alkenylnitrones would allow us to prepare similar intermediates (Scheme 2A) [51]. Nakamura and coworkers have reported that *N*-allenylnitrones can be accessed through rearrangements of *O*-propargylic oximes and undergo similar electrocyclizations to form pyridines (Scheme 2B) [52]. Herein, we show that *N*-alkenylnitrones **8** can be prepared through a Chan–Lam coupling of α,β-unsaturated oximes **6** and an alkenylboronic acids **7** and that these compounds undergo a novel thermal rearrangement to the corresponding tri- and tetrasubstituted pyridines **9** (Scheme 2C). This use of α,β-unsaturated oxime reagents for the synthesis of pyridines is unique from transition metal-catalyzed C–H bond functionalization processes that require a regioselective migratory insertion. This route is appealing due to the modularity of the Chan–Lam coupling process, and proceeds through a pathway that is distinct from the Liebeskind copper-catalyzed C–N bond coupling and electrocyclization (Scheme 2).

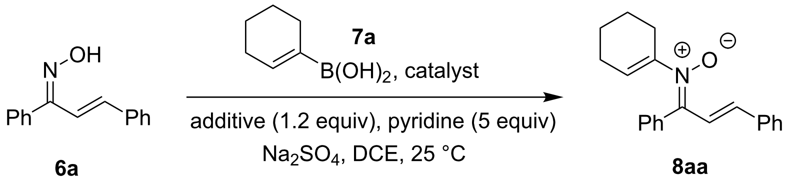


Scheme 2: Examples of pyridine synthesis from oxime precursors [51,52].

Results and Discussion

A Chan–Lam coupling between chalcone oxime **6a** and cyclohexenylboronic acid (**7a**) was initially tested using reaction conditions that we had previously identified as optimal for analogous *N*-alkenylnitrone syntheses from fluorenone oxime [7]. Nitrone **8aa** was successfully isolated in 40% yield using 2 equiv of $Cu(OAc)_2$ and the reaction conditions indicated in Table 1, entry 1. Only the *E*-nitrone isomer was observed and isolated. Decreasing the amount of copper reagent to 1 equiv had little influence on the reaction and a screen of other common copper salts only resulted in diminished yields (Table 1, entries 2–7). Further reduction of the copper loading to 10–30 mol % of $Cu(OAc)_2$ was tolerated without a decrease

Table 1: Optimization of Chan–Lam coupling for the synthesis of *N*-cyclohexenyl-α,β-unsaturated nitrones.[a]



entry	catalyst	cat. conc	additive	yield (%)[b]
1	$Cu(OAc)_2$	2 equiv	none	40
2	$Cu(OAc)_2$	1 equiv	none	46
3	CuTC	1 equiv	none	30
4	CuBr	1 equiv	none	dec
5	CuI	1 equiv	none	trace
6	$CuOTf_2$	1 equiv	none	trace
7	$Cu(TFA)_2$	1 equiv	none	trace
8	$Cu(OAc)_2$	10 mol %	none	45
9	$Cu(OAc)_2$	30 mol %	none	45
10	$Cu(OAc)_2$	10 mol %	COE	65
11	$Cu(OAc)_2$	10 mol %	NBD	58
12	$Cu(OAc)_2$	10 mol %	COD	72
13	$Cu(OAc)_2$	10 mol %	1-octene	57
14	$Cu(OAc)_2$	10 mol %	dba	51

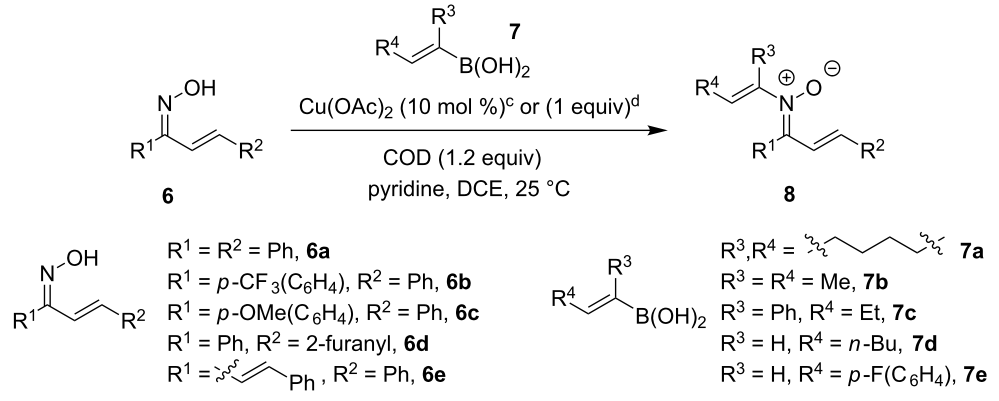
[a]Conditions: **6a** (1 equiv), **7a** (2 equiv), pyridine (5 equiv), Na_2SO_4 (8–9 equiv), 0.1 M in DCE, 25 °C, air, 18 h. [b]Determined by ^1H NMR spectroscopy using CH_2Br_2 as a reference.

in reaction efficiency (Table 1, entries 8 and 9). The key factor in improving the yield of the transformation was identified as an alkene additive. Alkene and alkyne additives have previously been observed to improve similar copper-catalyzed coupling reactions [53]. As shown in Table 1, entries 10–14, the addition of 1.2 equiv of cyclooctadiene (COD), cyclooctene (COE), norbornadiene (NBD), 1-octene, and dibenzylideneacetone (dba) all improved the yield of the Chan–Lam reaction, but COD was most efficient.

Having identified optimal conditions for the synthesis of *N*-cyclohexenylnitrone **8aa**, the scope of the nitrone synthesis was explored by varying the oxime and alkenylboronic acid reagents. As shown in Table 2, chalcone oximes with both electron-rich and electron-poor aryl substituents, as well as heteroaryl substituents, were tolerated for the transformation with electron-donating substituents providing higher yields (Table 2, entries 1–4). A significant increase in reaction efficiency was also observed for dba oxime (Table 2, entry 5). Evaluation of acyclic alkenylboronic acids further highlighted the differences between dba oxime and chalcone oximes as substrates for the Chan–Lam reaction. When dba oxime was treated with but-2-en-2-ylboronic acid, nitrone **8eb** was isolated in good yield; in contrast, treatment of chalcone oxime with but-2-en-2-ylboronic acid, resulted in the isolation of nitrone **8ab** in only 15% yield (Table 2, entries 6 and 7). Phenyl-substituted alkenylboronic acid **7c** and monosubstituted alkenylboronic acids **7d** and **7e**, were more efficient reaction partners with chalcone oxime and gave the corresponding nitrones in good to excellent yield (Table 2, entries 8–10). Acyclic alkenylboronic acids were also incompatible with the optimal conditions determined for cyclohexenylboronic acid (**7a**) and required the use of 1–2 equiv of $Cu(OAc)_2$. The use of both copper-catalyzed and copper-mediated reaction conditions with oximes **6** and alkenylboronic acids **7**, allowed for the preparation of a variety of *N*-alkenyl-α,β-unsaturated nitrones to test for further reactivity.

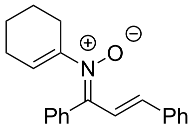
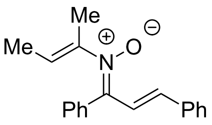
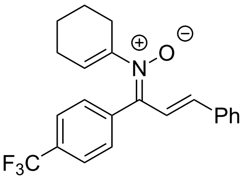
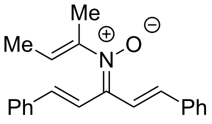
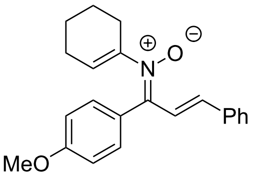
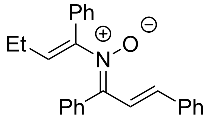
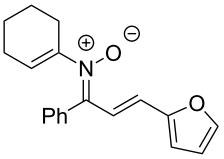
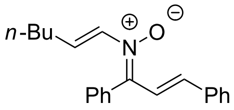
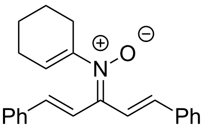
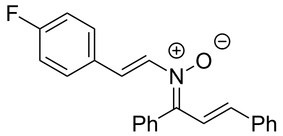
The preparation of the *N*-alkenyl-α,β-unsaturated nitrones shown in Table 2, allowed for further study of their conversion to tri- and tetrasubstituted pyridines. The preliminary evaluation of this thermal transformation with **8aa** indicated that DMSO was a more efficient reaction medium than PhMe, dioxane, or DMF (Scheme 3). As shown in Table 3, all of the chalcone nitrones were readily converted to the corresponding pyridines in good yield (Table 3, entries 1–4, 6, 8–10). In contrast, the dba nitrones gave the corresponding pyridines in attenuated yields (Table 3, entries 5 and 7). The high density of substituents and regiospecificity of the transformation due to the use of the Chan–Lam reaction for the synthesis of the nitrone

Table 2: Scope of *N*-alkenyl-α,β-unsaturated nitrone synthesis.[a]



$R^1 = R^2 = Ph$, **6a**
$R^1 = p\text{-}CF_3(C_6H_4)$, $R^2 = Ph$, **6b**
$R^1 = p\text{-}OMe(C_6H_4)$, $R^2 = Ph$, **6c**
$R^1 = Ph$, R^2 = 2-furanyl, **6d**
R^1 = , $R^2 = Ph$, **6e**

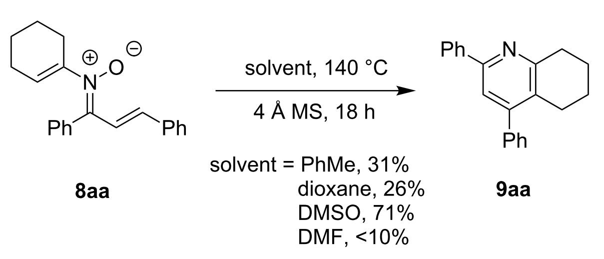
R^3,R^4 = **7a**
$R^3 = R^4 = Me$, **7b**
$R^3 = Ph$, $R^4 = Et$, **7c**
$R^3 = H$, $R^4 = n\text{-}Bu$, **7d**
$R^3 = H$, $R^4 = p\text{-}F(C_6H_4)$, **7e**

entry	8	yield (%)[b]	entry	8	yield (%)[b]
1	 **8aa**	72[c]	6	 **8ab**	15[d]
2	 **8ba**	41[c]	7	 **8eb**	68[d]
3	 **8ca**	63[c]	8	 **8ac**	57[d]
4	 **8da**	70[e]	9	 **8ad**	75[d]
5	 **8ea**	84[c]	10	 **8ae**	83[d]

[a] Conditions: **6** (1 equiv), **7** (2 equiv), pyridine (5 equiv), COD (1.2 equiv), Na_2SO_4 (8–9 equiv), 0.1 M in DCE, 25 °C, air, 18 h. [b] Percent isolated yield. [c] $Cu(OAc)_2$ (10 mol %). [d] $Cu(OAc)_2$ (1–2 equiv), pyridine (10 equiv), no COD. [e] $Cu(OAc)_2$ (10 mol %), no COD.

precursor are noteworthy and provide advantages over pyridine syntheses that require regioselective insertion reactions or nucleophilic additions.

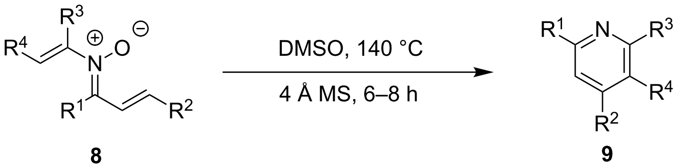
To better understand the conversion of *N*-alkenyl-α,β-unsaturated nitrones **8** to pyridines **9**, two mechanistic experiments were evaluated (Scheme 4). The conversion of nitrone **8ae** to

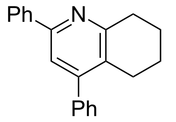
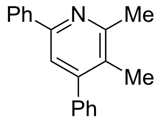
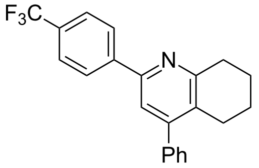
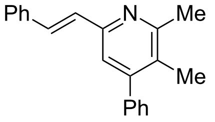
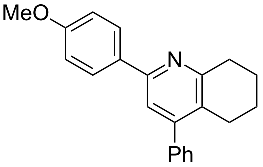
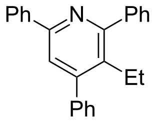
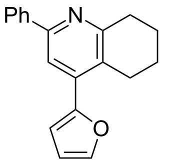
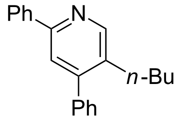
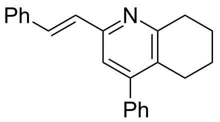
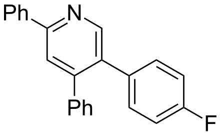


Scheme 3: Solvent effect on conversion of *N*-alkenylnitrones to pyridines.

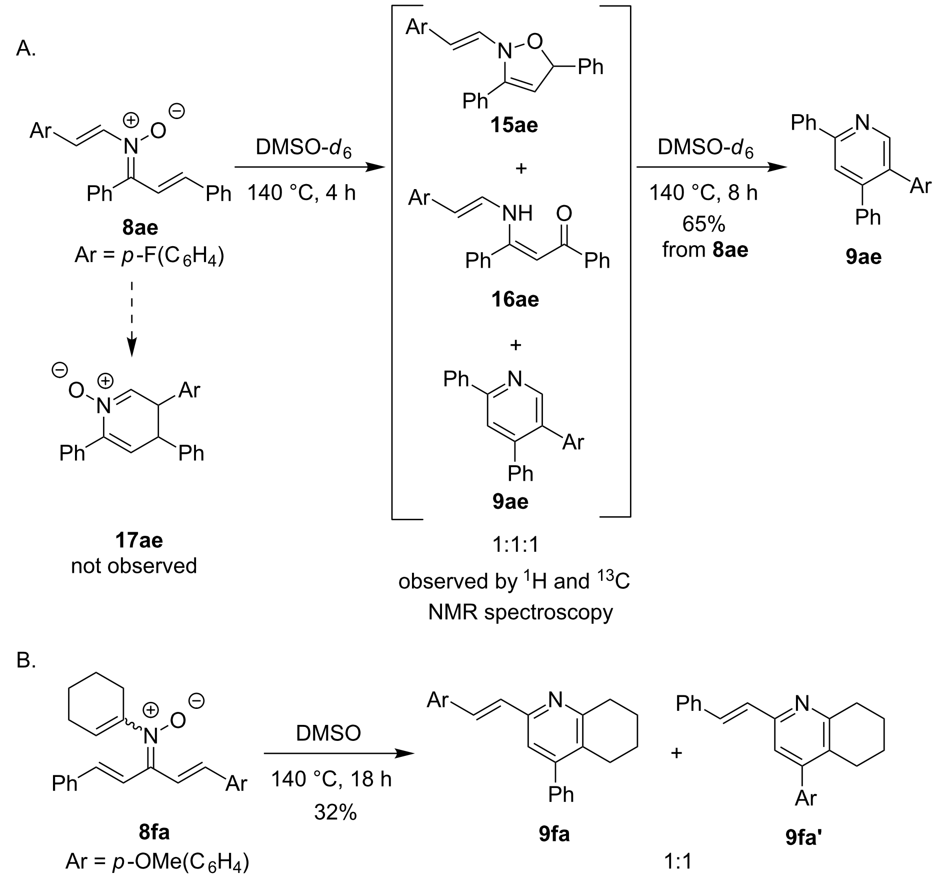
pyridine **9ae** was monitored by ^{1}H and ^{13}C NMR spectroscopy. Surprisingly, after heating **8ae** for 4 h at 140 °C in DMSO-d_6, a 1:1:1 mixture of isoxazoline **15ae**, enaminoketone **16ae**, and pyridine **9ae** was observed [54,55]. Further heating this mixture of intermediates for 4 h resulted in the sole formation of pyridine **9ae**. This experiment suggests that the conversion of nitrone **8ae** to pyridine **9ae** proceeds by oxygen transfer to give **16ae** and nucleophilic addition of the enamine to the ketone. This pathway may explain the solvent dependence that was observed for the transformation (Scheme 3). The lack of any observation of dihydropyridine *N*-oxide intermediate **17ae**

Table 3: Scope of conversion of *N*-alkenyl-α,β-unsaturated nitrones to pyridines.[a]



entry	9	yield (%)[b]	entry	9	yield (%)[b]
1	 **9aa**	71	6	 **9ab**	50
2	 **9ba**	68	7	 **9eb**	36
3	 **9ca**	64	8	 **9ac**	87
4	 **9da**	76	9	 **9ad**	71
5	 **9ea**	43	10	 **9ae**	65

[a]Conditions: **8** (1 equiv), 4 Å MS, 0.1 M in DMSO, 140 °C, 6–8 h. [b]Percent isolated yield.



Scheme 4: Mechanistic experiments.

suggests that the reaction is not proceeding through an electrocyclization and elimination process. A second experiment tested the electronic effect of this oxygen-transfer process. Unsymmetrically substituted dba nitrone **8fa** was subjected to the cyclization conditions and a 1:1 mixture of **9fa**:**9fa'** was observed. This experiment indicated a lack of any significant electronic preference for the oxygen-transfer process.

Conclusion

A new method for the preparation of tri- and tetrasubstituted pyridines has been developed that hinges on the use of a Chan–Lam coupling to construct *N*-alkenyl-α,β-unsaturated nitrone precursors from the corresponding oximes and alkenylboronic acids. This method is tolerant of a variety of chalcone- and dba-derived oxime substrates as well as both mono- and disubstituted alkenylboronic acids. Initial reaction monitoring experiments suggest that the cyclization of the *N*-alkenyl-α,β-unsaturated nitrone to the pyridine occurs through an oxygen transfer from the nitrone functionality to the β-position of the conjugated olefin followed by nucleophilic attack of the enamine.

Supporting Information

Supporting Information File 1

Experimental part.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-226-S1.pdf]

Acknowledgements

We acknowledge generous funding from ACS-PRF (DNI-50491), NSF (NSF-CHE 1212895 and 1464115), and the University of Illinois at Chicago. We also thank Mr. Furong Sun (UIUC) for mass spectrometry data.

References

1. Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011,** 829–856. doi:10.1055/s-0030-1258379
2. Partyka, D. V. *Chem. Rev.* **2011,** *111,* 1529–1595. doi:10.1021/cr1002276
3. Luo, F.; Pan, C.; Cheng, J. *Synlett* **2012,** 357–366. doi:10.1055/s-0031-1290101

4. Rao, K. S.; Wu, T.-S. *Tetrahedron* **2012,** *68,* 7735–7754. doi:10.1016/j.tet.2012.06.015
5. Petrassi, H. M.; Sharpless, K. B.; Kelly, J. W. *Org. Lett.* **2001,** *3,* 139–142. doi:10.1021/ol0003533
6. Patil, A. S.; Mo, D.-L.; Wang, H.-Y.; Mueller, D. S.; Anderson, L. L. *Angew. Chem., Int. Ed.* **2012,** *51,* 7799–7803. doi:10.1002/anie.201202704
7. Mo, D.-L.; Wink, D. A.; Anderson, L. L. *Org. Lett.* **2012,** *14,* 5180–5183. doi:10.1021/ol3022885
8. Mo, D.-L.; Anderson, L. L. *Angew. Chem., Int. Ed.* **2013,** *52,* 6722–6725. doi:10.1002/anie.201301963
9. Wang, H.-Y.; Anderson, L. L. *Org. Lett.* **2013,** *15,* 3362–3365. doi:10.1021/ol401416r
10. Kontokosta, D.; Mueller, D. S.; Wang, H.-Y.; Anderson, L. L. *Org. Lett.* **2013,** *15,* 4830–4833. doi:10.1021/ol402237w
11. Pecak, W. H.; Son, J.; Burnstine, A. J.; Anderson, L. L. *Org. Lett.* **2014,** *16,* 3440–3443. doi:10.1021/ol501230e
12. Mo, D.-L.; Pecak, W. H.; Zhao, M.; Wink, D. J.; Anderson, L. L. *Org. Lett.* **2014,** *16,* 3696–3699. doi:10.1021/ol501503a
13. Mo, D.-L.; Wink, D. J.; Anderson, L. L. *Chem. – Eur. J.* **2014,** *20,* 13217–13225. doi:10.1002/chem.201403268
14. Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011,** *54,* 3451–3479. doi:10.1021/jm200187y
15. Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006,** *4,* 2337–2347. doi:10.1039/b602413k
16. Michael, J. P. *Nat. Prod. Rep.* **2005,** *22,* 627–646. doi:10.1039/b413750g
17. Hill, M. D. *Chem. – Eur. J.* **2010,** *16,* 12052–12062. doi:10.1002/chem.201001100
18. Henry, G. D. *Tetrahedron* **2004,** *60,* 6043–6061. doi:10.1016/j.tet.2004.04.043
19. Varela, J. A.; Saá, C. *Chem. Rev.* **2003,** *103,* 3787–3802. doi:10.1021/cr030677f
20. Zeni, G.; Larock, R. L. *Chem. Rev.* **2006,** *106,* 4644–4680. doi:10.1021/cr0683966
21. Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012,** *112,* 2642–2713. doi:10.1021/cr200251d
22. Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882,** *215,* 1–82. doi:10.1002/jlac.18822150102
23. Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008,** *130,* 18–19. doi:10.1021/ja077463q
24. Bagley, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007,** 2459–2482. doi:10.1055/s-2007-986674
25. Kharchenko, V. G.; Markova, L. I.; Fedotova, O. V.; Pchelintseva, N. V. *Chem. Heterocycl. Compd.* **2003,** *39,* 1121–1142. doi:10.1023/B:COHC.0000008257.42400.9e
26. Sausins, A.; Duburs, G. *Heterocycles* **1988,** *27,* 269–289. doi:10.3987/REV-87-370
27. Boger, D. L.; Panek, J. S.; Meier, M. M. *J. Org. Chem.* **1982,** *47,* 895–897. doi:10.1021/jo00344a031
28. Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007,** *36,* 1085–1094. doi:10.1039/b607877j
29. McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005,** *127,* 5030–5031. doi:10.1021/ja0508931
30. Tanaka, R.; Yuza, A.; Watai, Y.; Suzuki, D.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005,** *127,* 7774–7780. doi:10.1021/ja050261e
31. Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004,** *104,* 2667–2722. doi:10.1021/cr020101a
32. Mongin, F.; Quéguiner, G. *Tetrahedron* **2001,** *57,* 4059–4090. doi:10.1016/S0040-4020(01)00100-4
33. Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002,** *124,* 13856–13863. doi:10.1021/ja027190t
34. Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007,** *129,* 3358–3366. doi:10.1021/ja068577p
35. Liu, S.; Sawicki, J.; Driver, T. G. *Org. Lett.* **2012,** *14,* 3744–3747. doi:10.1021/ol301606y
36. Chen, X.; Zhou, L.; Li, Y.; Xie, T.; Zhou, S. *J. Org. Chem.* **2014,** *79,* 230–239. doi:10.1021/jo4024123
37. Colombe, J. R.; Bernhardt, S.; Stathakis, C.; Buchwald, S. L.; Knochel, P. *Org. Lett.* **2013,** *15,* 5754–5757. doi:10.1021/ol402798z
38. Luzung, M. R.; Patel, J. S.; Yin, J. *J. Org. Chem.* **2010,** *75,* 8330–8332. doi:10.1021/jo1018798
39. Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006,** *128,* 4592–4593. doi:10.1021/ja060626a
40. Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007,** *129,* 10096–10097. doi:10.1021/ja073912a
41. Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008,** *130,* 8602–8603. doi:10.1021/ja803139k
42. Chen, M. Z.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012,** *134,* 1352–1356. doi:10.1021/ja2105703
43. Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008,** *130,* 3645–3651. doi:10.1021/ja7104784
44. Martin, R. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2012,** *77,* 2501–2507. doi:10.1021/jo202280e
45. Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008,** *10,* 325–328. doi:10.1021/ol7028367
46. Parthasarathy, K.; Cheng, C.-H. *Synthesis* **2009,** 1400–1402. doi:10.1055/s-0028-1088009
47. Too, P. C.; Noji, T.; Lim, Y. J.; Li, X.; Chiba, S. *Synlett* **2011,** 2789–2794. doi:10.1055/s-0031-1289556
48. Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011,** *47,* 11846–11848. doi:10.1039/C1CC15248C
49. Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2013,** *135,* 66–69. doi:10.1021/ja3104389
50. Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2014,** *136,* 2735–2738. doi:10.1021/ja412444d
51. Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008,** *130,* 6918–6919. doi:10.1021/ja8013743
52. Nakamura, I.; Zhang, D.; Terada, M. *J. Am. Chem. Soc.* **2010,** *132,* 7884–7886. doi:10.1021/ja102436z
53. Winternheimer, D. J.; Merlic, C. A. *Org. Lett.* **2010,** *12,* 2508–2510. doi:10.1021/ol100707s
54. Katritzky, A. R.; Hayden, A. E.; Kirichenko, K.; Pelphrey, P.; Ji, Y. *J. Org. Chem.* **2004,** *69,* 5108–5111. doi:10.1021/jo0496594
55. Zhang, Z.-H.; Yin, L.; Wang, Y.-M. *Adv. Synth. Catal.* **2006,** *348,* 184–190. doi:10.1002/adsc.200505268

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doi:10.3762/bjoc.11.226

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

C–H bond halogenation catalyzed or mediated by copper: an overview

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Review

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Keywords:
C(sp^2)–H bond; C(sp^3)–H bond; copper; halogenation

Beilstein J. Org. Chem. **2015,** *11,* 2132–2144.
doi:10.3762/bjoc.11.230

Received: 25 August 2015
Accepted: 22 October 2015
Published: 09 November 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

Carbon–halogen (C–X) bonds are amongst the most fundamental groups in organic synthesis, they are frequently and widely employed in the synthesis of numerous organic products. The generation of a C–X bond, therefore, constitutes an issue of universal interest. Herein, the research advances on the copper-catalyzed and mediated C–X (X = F, Cl, Br, I) bond formation via direct C–H bond transformation is reviewed.

Introduction

Organohalides are inarguably a class of most useful chemicals owing to their prevalent application in the synthesis of organic products. The versatile reactivity of C–X bonds allowed them to be used as precursors in the construction of natural products, medicinal, functional materials and agricultural chemicals [1-6]. Therefore, the research toward catalytic generation of C–X bonds constitutes a significant issue in organic synthesis. Electrophilic halogenation of electron-enriched arenes [7-9], diazotization/halogenations of anilines [10], and *ortho*-lithiation/halogenations sequence [11] among others are widely used as traditional strategies for creating C–X bonds. However, one or more problems such as poor site-selectivity, reliance on toxic halogen sources, harsh reaction conditions and/or restricted product diversity remain as challenges for these methods.

The transition metal-catalyzed C–H functionalization has recently gained considerable attention in the preparation of numerous organic molecules [12-18]. In this context, significant advances have also occurred in the C–H halogenation catalyzed by different transition metals as Pd [19-23], Rh [24,25], Ru [26], Au [27], Co [28], etc.

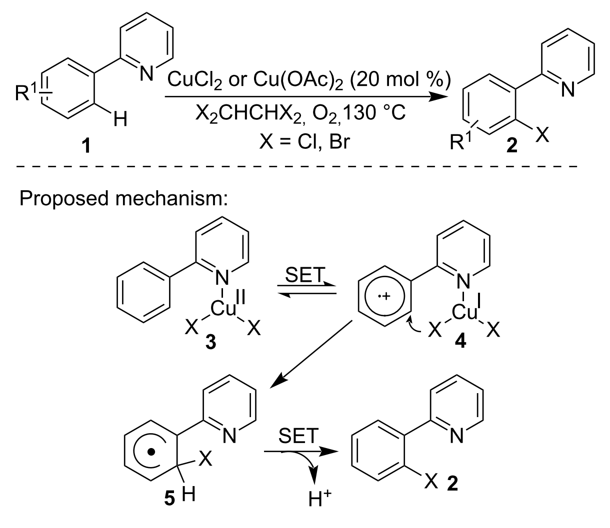
As a class of readily available and ubiquitously employed transition metal catalysts, copper catalysts have exhibited tremendous application in C–H bond functionalizations in recent years owing to their distinct advantages such as low cost, high stability and flexible forms of presence [29-31]. In the area of C–H bond halogenation, the copper catalysis also constitutes a major practical option. To show the power of copper catalysis in modern organic synthesis, herein, we would like to highlight the recent progress in the C–H bond halogenation with copper catalysis or mediation.

Review

Copper-catalyzed/mediated halogenation of the C(sp^2)–H bond

Halogenation of the arene C(sp^2)–H bond

In the synthesis of aryl halides employing the conventional electrophilic halogenation of arenes, the site selectivity was a main challenge and mixed haloarene products were frequently obtained. In 2006, Yu and co-workers [32] first realized the selective *o*-halogenation of pyridine-2-ylbenzenes **1** via C–H activation in a copper/O_2 system. As shown in Scheme 1, the presence of the pyridine ring was crucial in controlling the site selectivity by forming the copper complex **3** which enabled the selective halogenation of the *ortho* C–H bond of the phenyl ring to give products **2** via transition state **4** and **5**. The 1,1,2,2-tetrahaloethane played the roles of both reaction medium and halogen source. Notably, attempts in the chlorination of the alkene C–H bond under identical atmosphere were not successful. In the reaction process, a single electron transfer (SET) from the aryl ring to the coordinated Cu(II) complex **3** to the Cu(I) species **4** was the rate-limiting step.



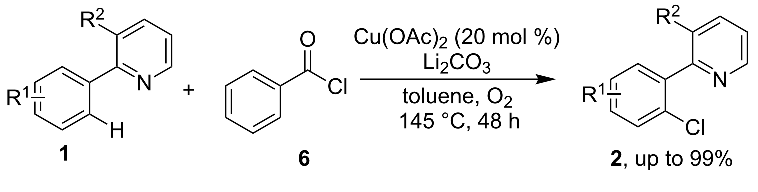
Scheme 1: Copper-catalyzed C–H bond halogenation of 2-arylpyridine.

In 2011, Cheng and co-workers discovered an alternative route of a C–H chlorination protocol of 2-arylpyridines by employing acyl chlorides **6** as chlorinating reagents [33]. A range of monochlorinated 2-arylpridines **2** were obtained in the presence of $Cu(OAc)_2$ and Li_2CO_3 under O_2 atmosphere (Scheme 2).

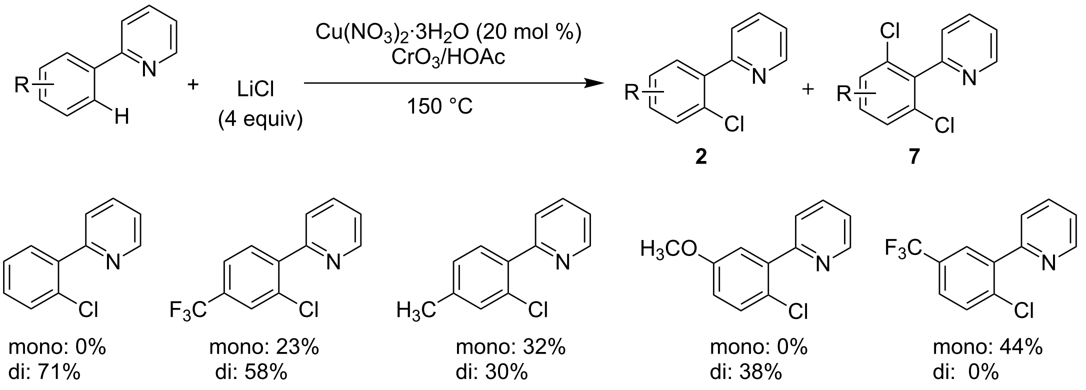
In the same year, Shen and co-workers reported the Cu-catalyzed sp^2 C–H chlorination of 2-arylpyridines by using the salt LiCl as a new chlorine source in the presence of CrO_3 and Ac_2O [34]. Due to the oxidizing potency of the CrO_3, the application scope of the method was not broad since low selectivity between monochlorinated products **2** and dichlorinated products **7** was suffered (Scheme 3).

Two years later, the same group developed a modified approach for this kind of C–H chlorination by employing lithium halide (LiCl or LiBr) as the source of halogen to react with 2-arylpyridine, which allowed the synthesis of various 2-(*o*-haloaryl)pyridines with improved selectivity towards monohalogenation in the presence of a copper catalyst [35]. As outlined in Scheme 4, the presence of molecular oxygen as the alternative oxidant enabled most entries providing monohalogenated products with a few examples giving mixed mono- and dihalogenated products.

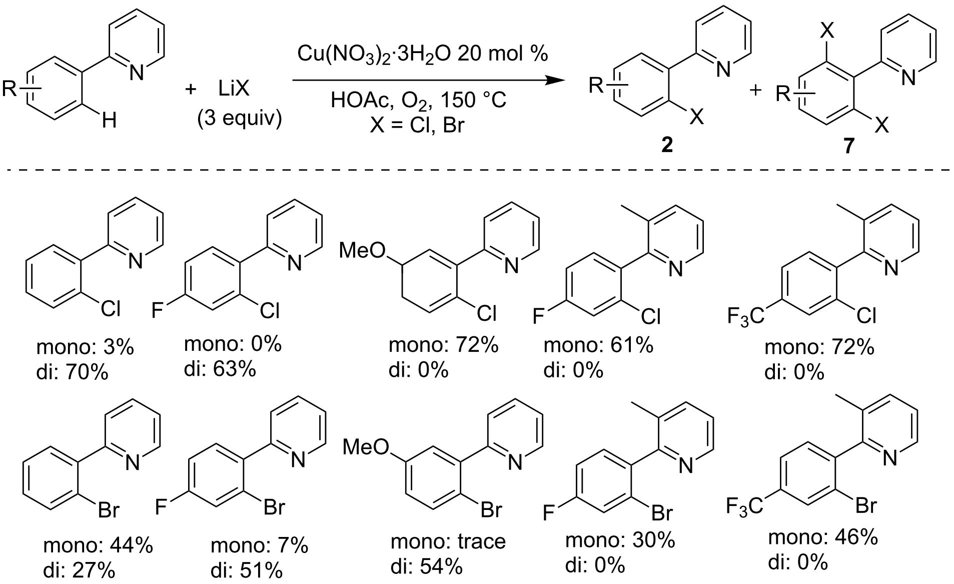
In all these known arene C–H halogenation protocols with pyridine as directing group (DG), the chemo-selectivity remained as a challenge since either mixed mono- and dihalogenated products or only one of the two potential products could be acquired. In this regard, a synthetic approach allowing the tunable synthesis of mono- and dihalogenated products was highly desirable. Recently, Han and co-workers [36] achieved successfully this kind of tunable reaction via a CuX-mediated aryl C–H halogenation with the assistance of NXS (*N*-halosuccinimide, X = Cl or Br). The application of different acids which partici-



Scheme 2: *ortho*-Chlorination of 2-arylpridines with acyl chlorides.



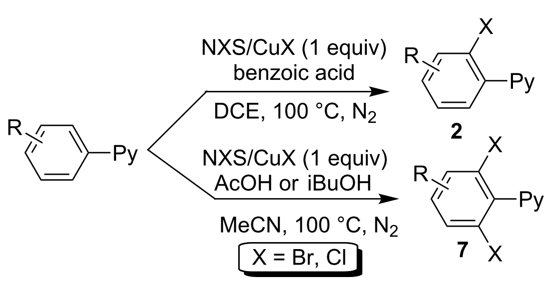
Scheme 3: Copper-catalyzed chlorination of 2-arylpyridines using LiCl.



Scheme 4: Copper-catalyzed C–H halogenation of 2-arylpyridines using LiX.

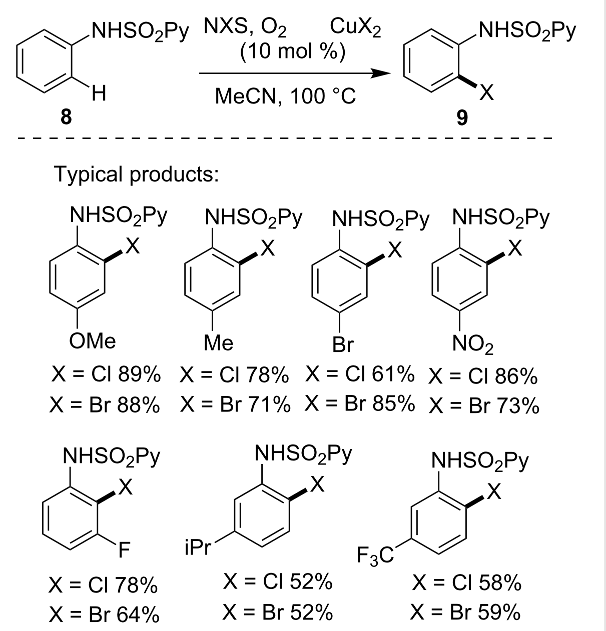
pated in the in situ formation of acyl hypohalites enabled the selective generation of products **2** and **7** (Scheme 5). Notably, the C–H iodinated product of type **2** was also observed as key intermediate in the copper-catalyzed pyridinyl-functionalized arene dimerization [37].

Besides the issue of selectivity, another major challenge in the DG-assisted C–H activation lied in the removal of the DG, which undermined the efficiency of the synthetic procedure. To alternate the hardly removable DG of the pyridine ring, Carretero and co-workers [38] devised a practical copper-catalyzed halogenation of anilines **8** containing an easily removable *N*-(2-pyridyl)sulfonyl auxiliary. In the presence of



Scheme 5: Copper-mediated selective C–H halogenations of 2-arylpyridine.

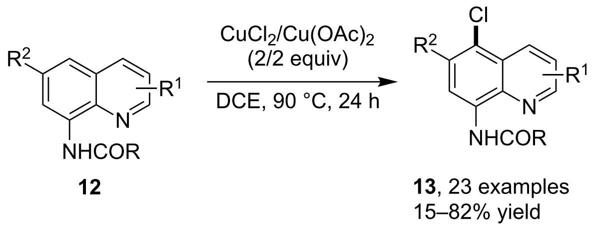
copper(II) halide catalyst and NXS (X = Cl or Br), a class of *o*-chloro/bromoanilines **9** were efficiently provided under aerobic atmosphere (Scheme 6). The *N*-(2-pyridyl)sulfonyl could be easily removed by treatment with elemental Mg in MeOH.



Scheme 6: Copper-catalyzed C–H *o*-halogenation using removable DG.

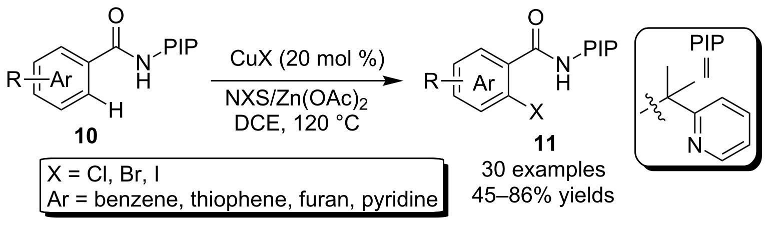
More recently, Shi and co-workers [39] reported the *ortho*-C–H halogenation of aryl-2-carboxamides **10** using PIP (2-(pyridine-2-yl)isopropylamine) as DG. As shown in Scheme 7, the copper catalyst combined with NXS (X = Cl, Br, I) and a proper additive promoted smoothly the synthesis of various *o*-haloaryl-2-carboxamides **11**. This synthetic protocol tolerated not only carbon aryls, but also various heteroaryls such as thiophene, furan and pyridine in the amide component.

Interestingly, in an earlier example studying the copper-catalyzed arene C–H methoxylation using the generally applicable quinolin-8-yl [40] as DG, Stahl et al. [41] discovered that using a CuCl/LiCl/O_2/AcOH catalytic system resulted in the formation of C-5 chlorinated quinoline, demonstrating the pivotal role of the DG in inducing the reaction pathway. These kinds of reactions were later systematically investigated by Xie and co-workers [42]. By using $Cu(OAc)_2$ as the catalyst and $CuCl_2$ as the chlorine source in DCE, a broad array of 5-chloro-8-acylaminoquinolines **13** were obtained via the selective 5-chlorination of 8-amidoquinolines **12** (Scheme 8). Control experiments in the presence of TEMPO suggested that the reaction might proceed via a C-centered free radical provided by SET between the quinoline substrate and the cupric salt.

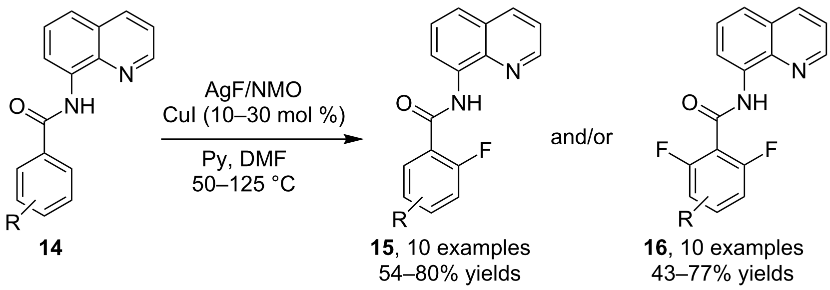


Scheme 8: Copper-catalyzed quinoline C–H chlorination.

In recent years, the formation of C–F chemical bonds received global research interest owing to the particular functions of many fluorinated chemicals. Accordingly, C–H fluorination reactions also become an issue of broad concern as such a transformation offers a straightforward route for rapid synthesis of diversity-enriched fluorinated products. On the basis of the Pd-catalyzed oxidative C–H fluorination of functionalized 8-methylquinolinyl substrates reported by Sanford et al. [43], Daugulis and co-worker [44] established in 2013 a copper-catalyzed arene C–H *o*-fluorination of *N*-(quinolin-8-yl)benzamides **14**. The mono- and/or difluorination took place in the presence of CuI, *N*-methylmorpholine *N*-oxide (NMO) and pyridine by using DMF as medium and AgF as fluorine source, providing products **15** and **16**, respectively. As happened in most cases involving the activation of two identical C–H bonds, the unsatisfactory chemo-selectivity in forming mixed products in many entries remained as a problem to address (Scheme 9).

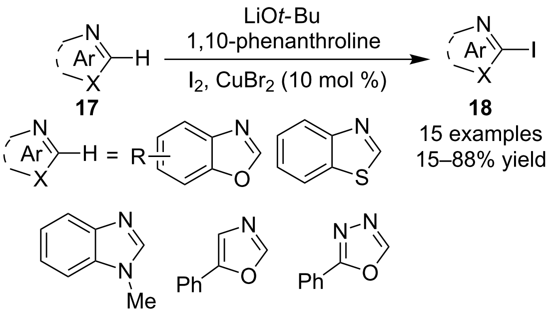


Scheme 7: Copper-catalyzed C–H halogenations using PIP as DG.



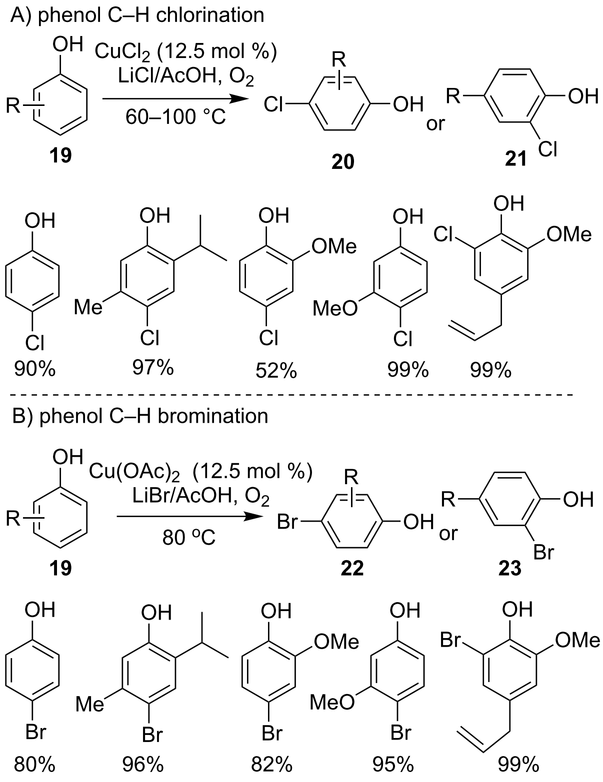
Scheme 9: Copper-catalyzed arene C–H fluorination of benzamides.

The catalytic iodination of electron deficient 1,3-azoles was recently realized by Zhao et al. Under the catalytic conditions consisting of LiO*t*-Bu, 1,10-phenanthroline and $CuBr_2$, a class of different conventional azoles **17**, including benzoxazoles, benzothiazole, *N*-methylbenzimidazole, 5-phenyloxazole and 2-phenyl-1,3,4-oxadiazole were smoothly iodinated to provide iodoheteroarenes **18** (Scheme 10) [45].



Scheme 10: Copper-catalyzed arene C–H iodination of 1,3-azoles.

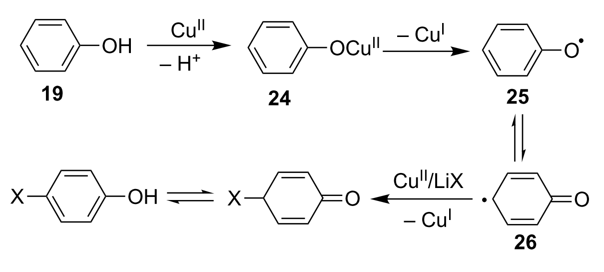
As typical electron-enriched arenes, phenols and analogous arenes tend to undergo a single-electron transfer process [46], the property of these arenes also resulted in sound attention to their C–H halogenations. In 2006, Gusevskaya and Menini [47,48] reported a highly selective method for C–H chlorination and bromination of various phenols under aerobic, copper-catalyzed conditions. As displayed in Scheme 11, the reaction of phenols **19** with 2 equiv of LiCl in the prensence of O_2 and 12.5 mol % $CuCl_2$ in acetic acid at 80 °C resulted in 93% conversion and 90% selectivity towards 4-chlorophenol **20**, and *o*-chlorinated product **21** was obtained when the *para*-site of the phenol was occupied; analogously, employing LiBr as halogen source led to the formation of equivalent brominated products **22** and **23** under modified catalytic conditions (Scheme 11).



Scheme 11: Copper-catalyzed C–H halogenations of phenols.

However, it was found that the oxidative bromination of phenols exhibited generally lower *para* regioselectivity than the corresponding chlorination [49]. Mechanistic studies on these reactions indicated that the halogenation reactions proceeded via a free radical process (Scheme 12). In the presence of a Cu(II) catalyst, the one-electron oxidation to the phenol led to the occurrence of phenoxy radical **25** via the formation of phenoxyl copper(II) salt **24**. The isomeric free radical species **26** then rapidly captured the halogen atom from LiX to give the target product via oxidation by Cu(II) and release of Cu(I). The presence of molecular oxygen regenerated the Cu(I) species to the Cu(II) catalyst via re-oxidation.

In their subsequent study, Gusevskaya et al. found that anilines were also able to be halogenated via a similar operation. However, the products were acquired as dibromoanilines via

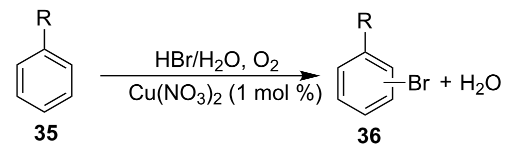


Scheme 12: Proposed mechanism for the C–H halogenation of phenols.

double C–H bromination process. On the other hand, the chlorination was found less effective due to the presence of the side transformation and formation of *N*-acetylated byproducts [50].

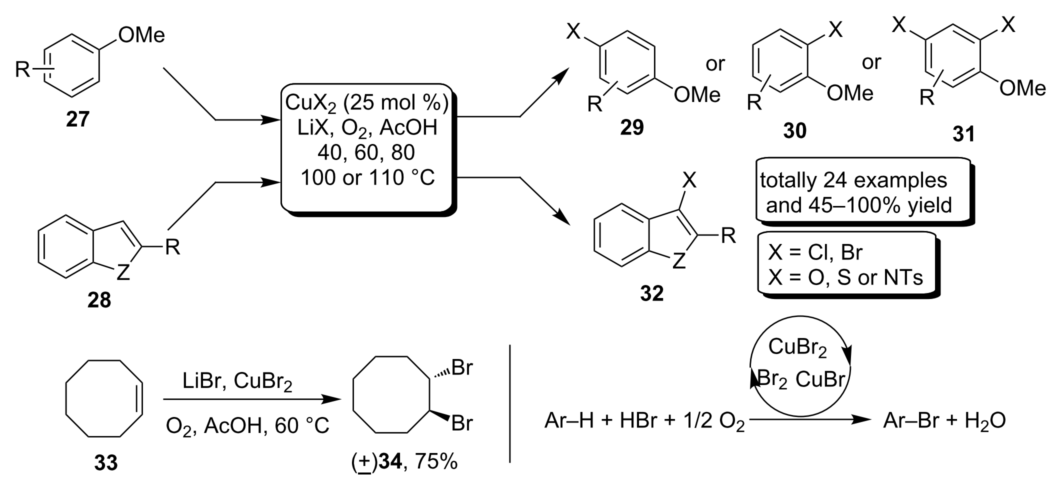
In 2009, Stahl et al. [51] reported a Cu-catalyzed aerobic C–H halogenation protocol of methoxybenzenes **27** and heteroaryls **28**. The method also employed LiX as a halogen sources which led to the production of *para*-halogenated aryls **29** and 3-haloindoles **32**, respectively. Notably, the *para*-substiuted methoxybenzenes provided *ortho*-halogenated products **30**, and employment of excessive LiX provided dihalogenated products **31** (Scheme 13). A preliminary mechanistic analysis suggested that the bromination and chlorination reactions proceeded via different pathways. According the color change in the reaction vessel, the formation of molecular bromine was hypothesized via aerobic oxidation, which suggested the copper-mediated electrophilic bromination as the reaction pathway [52,53]. In addition, the bromination experiment of cyclooctene **33** which yielded *trans*-1,2-dibromocyclooctane **34** also supported the fact that molecular bromine was generated under the catalytic conditions. On the other hand, the chlorination of **33** was not observed under the corresponding chlorination conditions, probably because the decomposition of $CuCl_2$ into CuCl and Cl_2 is much less favorable. The mechanism of the chlorination was not yet clear, but presumably the reaction was initiated by electron transfer from the arenes to the copper-catalyst.

Later on, Li and co-workers [54] developed an effective method of aerobic oxidative bromination of electron-rich arenes **35** by making use of 1 mol % $Cu(NO_3)_2$ as catalyst and 1.1 equiv HBr as additive. Brominated arenes **36** could be acquired with excellent conversions and *para*-bromination selectivity by heating at 100 °C and air atmosphere in water. Simple arenes, including toluene, anisole and cresole were all well tolerated in this transforamtion (Scheme 14).



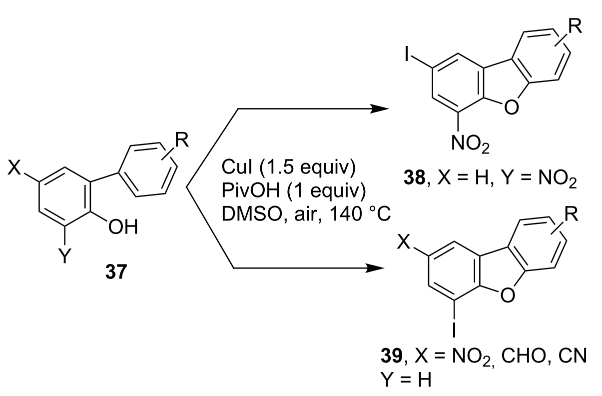
Scheme 14: Copper-catalyzed C–H bromination of arenes.

Besides the direct halogenation, a cascade reaction involving a C–H halogenation represents another important approach in preparing C–X containing compounds. Recently, Zhu and co-workers reported a new approach for the synthesis of 2 or 4-iododibenzofurans based on CuI-mediated cascade reactions wherein the C–H iodination and cycloetherification acted as key transformations [55]. As outlined in Scheme 15, in the presence of 1.5 equiv of CuI and PivOH, the EWG-functionalized *o*-arylphenols **37** underwent simultaneous C–H iodination and intramolecular C–H *o*-arylation by heating in DMSO at 140 °C,



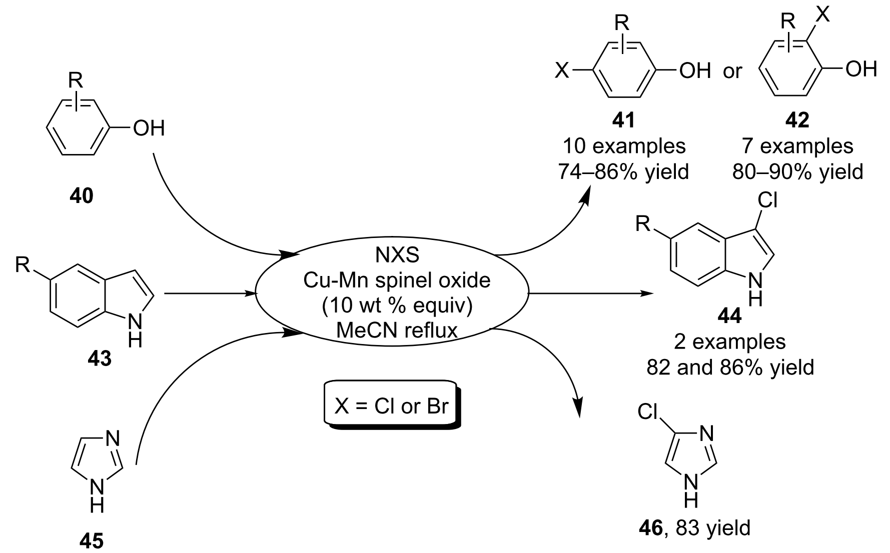
Scheme 13: Copper-catalyzed halogenation of electron enriched arenes.

which led to the production of iodinated dibenzo[*b*,*d*]furans in either the form of **38** or **39** depending on the position of the EWG. The CuI was both the catalyst and the source of iodine in the reactions. It was believed that the iodination took place via in situ generated molecular I_2 via the oxidation by molecular oxygen since the author successfully observed the presence of I_2 during chromatography process.



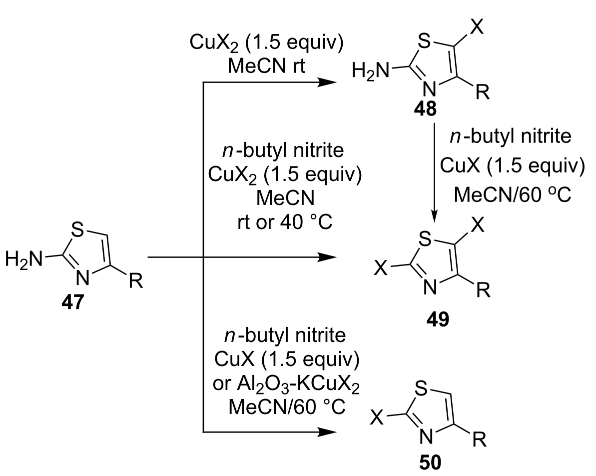
Scheme 15: CuI-mediated synthesis of iododibenzo[*b*,*d*]furans via C–H functionalization.

In the same year, Vishwakarma et al. [56] developed a catalytic approach for the halogenation of phenols and heteroarenes by using reusable Cu-Mn spinel oxide as catalyst. By employing NXS as halogen source, the Cu-Mu spinel oxide was able to catalyze the halogenation of phenols **40** to give either *para*-halogenated or *ortho*-halogenated phenols **41**/**42** in good to excellent yield and regioselectivity. In addition, the C-3 chlorination of indoles **43** and C-4 chlorination of imidazole (**45**) were also achieved under the standard reaction conditions to provide products **44** and **46**, respectively (Scheme 16).



Scheme 16: Cu-Mn spinel oxide-catalyzed phenol and heteroarene halogenation.

Because of the attractive biological functions of halogenated heteroarenes [57], the synthesis of haloheteroarenes via the corresponding arene C–H halogenations also gained extensive attention. In 2009, Pike and co-workers [58] reported the synthesis of halogenated 1,3-thiazoles using copper(II) halide as a catalyst. As shown in Scheme 17, the catalysis of copper(II) halides allowed selective halogenation of 2-amino-1,3-thiazoles **47** to give 5-halo-2-amino-1,3-thiazoles **48**, 2,5-dihalo-2-amino-1,3-thiazoles **49** or 2-halo-1,3-thiazoles **50** according to



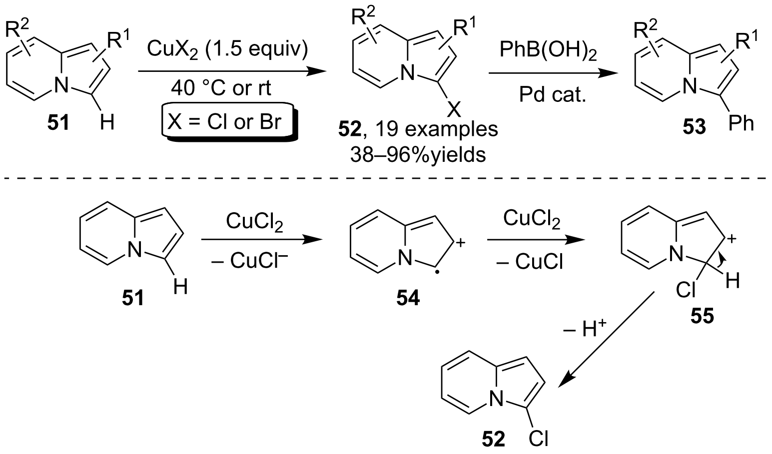
Scheme 17: Copper-catalyzed halogenations of 2-amino-1,3thiazoles.

the difference on reaction conditions such as temperature, catalyst species etc.

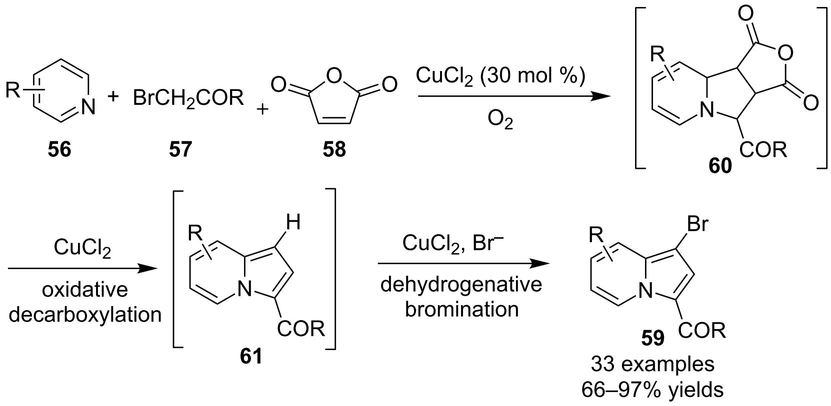
As a class of structurally interesting fused heterocycles, the indolizines received extensive research interest from the chemical and biological community [59,60]. Owing to the internal reactivity, the arene C–H bond in this arene moiety provided a facile route for elaboration. In 2009, You and Xia [61] disclosed that the Cu(II) halide was able to mediate the chlorination and bromination of indolizines **51** to afford 3-haloindolizines **52** with excellent regioselectivity. The halogenated indolizines **52** were found as highly useful platform compounds for the synthesis of 2-arylated indolizines **53** via Pd-catalyzed Suzuki–Miyaura reaction. The C–H bond activation process was believed to be initiated by the oxidation effect of the Cu(II) catalyst to give intermediate **54** which was further oxidized to provide cation intermediate **55**. The deprotection of **55** gave finally the halogenated products **52** (Scheme 18).

Rather recently, Liu and co-workers [62] reported an alternative approach to the synthesis of 3-brominated indolizines via copper-catalyzed three-component cascade reactions of pyridines **56**, α-bromoketones **57** and maleic anhydride (**58**). The construction of the products involved in the three-component annulation intermediate **60** which led to the formation of indolizine **61** via oxidative decarboxylation. And the bromination of **61** took place in situ to give products **59** via an unprecedented dehydrogenative bromination (Scheme 19).

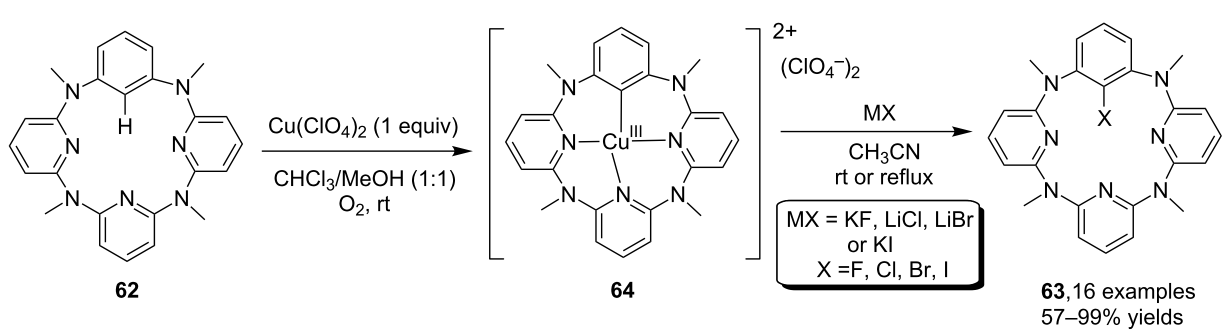
By making use of the copper-mediated arene C–H bond halogenation strategy, Wang and co-workers [63] developed an efficient method for the halogenation of azacalix[1]arene[3]pyridines **62** for the synthesis of halogenated products **63**. The synthesis of the products was mediated by the formation of Cu(III) complex **64**, as observed in the previous study [64], via the assembly of **62** and Cu(ClO$_4$)$_2$ which enabled the halogenations by using simple alkali salts



Scheme 18: Copper-mediated chlorination and bromination of indolizines.



Scheme 19: Copper-catalyzed three-component synthesis of bromoindolizines.



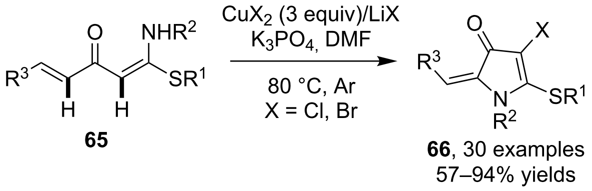
Scheme 20: Copper-mediated C–H halogenation of azacalix[1]arene[3]pyridines.

such as KF, LiCl, LiBr, KI, etc. as the source of halogen (Scheme 20).

Besides in providing various halogenated arene products, the copper-catalyzed arene C–H halogenation had also displayed important application in related C–H transformation by providing key haloarene intermediates. For examples, in the CuI-catalyzed cross arene dimerization reactions reported by Daugulis et al., the in situ formation of iodoarene intermediate was discovered as the indispensable step during the generation of the biaryl products [65].

Halogenation of the alkene C(sp^2)–H bond

Beside the arene C–H bond, the alkene C–H is another typical C(sp^2)–H bond. However, unlike the arene C–H bond, the alkene C–H bond tends to undertake difunctionalization via the cleavage of the π-bond in the presence of halogen source. Therefore, the halogenation of alkenes via C–H cleavage is much less known in literature. In 2014, Yu and co-workers [66] reported the cascade synthesis of functionalized pyrrolones **66** via the dual C–H functionalization of α-alkenoylketene *N,S*-acetals **65**. The construction of the products involved the oxidative alkene C–H amination and alkene C–H chlorination in the presence of Cu(II) halide by using LiX as the halogen source (Scheme 21).

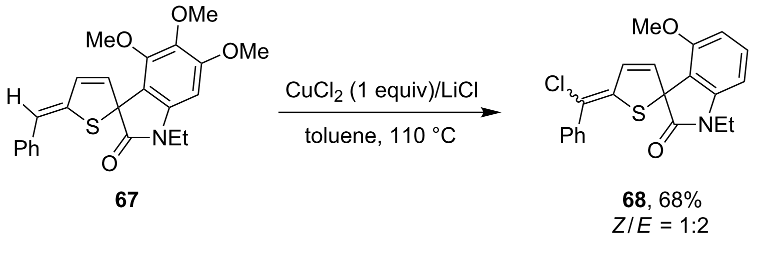


Scheme 21: Copper-mediated cascade synthesis of halogenated pyrrolones.

An earlier example of Cu-promoted alkene C–H halogenation was reported by Jiang et al. [67]. In their investigation to the transformation of α-thienylcarbinols, one of the products spirothienooxindole **67** was found to be capable of undertaking a formal alkene chlorination to provide chlorine-functionalized product **68** as mixed *Z*/*E* isomers (Scheme 22).

Halogenation of the C(sp^3)–H bond

Compared with the C(sp^2)–H bond, the C(sp^3)–H bond is the less acidic one and is therefore known as the most challenging chemical bond for direct activation. Consequently, the examples on copper-catalyzed halogenation of inactive C(sp^3)–H bond remained barely explored. In 2010, Ball and Kundu [68] developed a protocol of remote C–H chlorination of alkyl hydroperoxides by means of copper catalysis. As displayed in

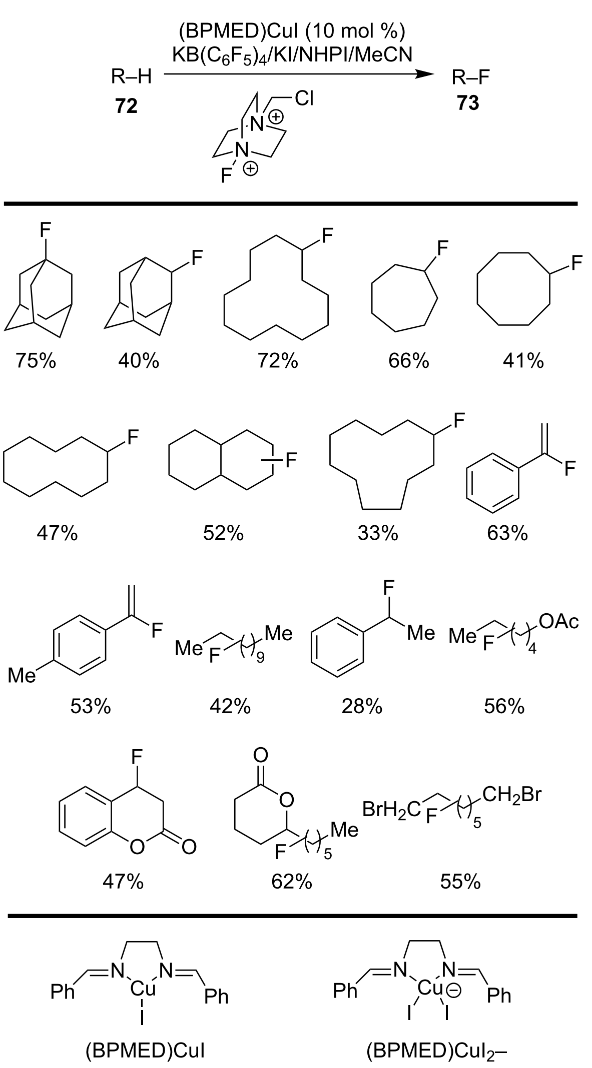


Scheme 22: Copper-mediated alkene C–H chlorination in spirothienooxindole.

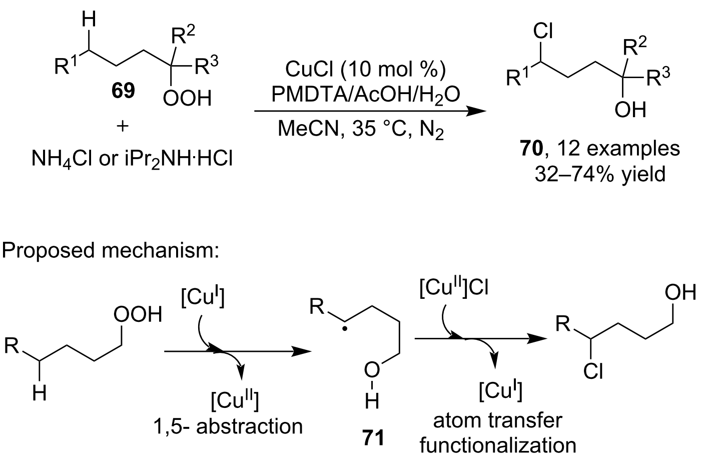
Scheme 23, the alkyl hydroperoxides **69** and proper chlorine source (NH_4Cl or $iPr_2NH \cdot HCl$) could couple each other in the presence of CuI and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) to provide γ-chlorinated alcohols **70** via an intramolecular redox process. To enable the transformation, CuCl promoted the 1,5-H abstraction and atom transfer process in the form of SET via free radical **71**.

In 2012, Lectka and co-workers [69] reported an interesting C–H fluorination method for alkynes **72** via a Cu-catalyzed aliphatic $C(sp^3)$–H functionalization. Monofluorinated products **73** were obtained by employing a catalytic system consisting of (BPMED)CuI (copper(I) bisimine complex), *N*-hydroxyphthalimide (NHPI), $KB(C_6F_5)_4$ and KI. The protocol allowed the selective fluorination of various substrates, including cycloalkanes and benzylic compounds using commercially available Selectfluor as fluorine source. According to the obtained results, the presence of $KB(C_6F_5)_4$ as the phase-transfer catalyst could accelerate the reaction rate and enhance the yield of the products. On the other hand, the KI could promote the formation of the active cuprate species $(BPMED)CuI_2^-$, thus allowing less reactive substrates to convert smoothly (Scheme 24).

Besides catalyzing the halogenation of inactive alkane substrates via a typical C–H activation, copper catalysis also exhibited important application in the electrophilic halogenation of some active methylene substrates such as ketones or esters. Although these active substrates were known to be capable of undergoing α-C–H halogenations under simple acidic or basic conditions, the problem of unsatisfactory selectivity between mono- and multihalogenation or utilization of operationally unfriendly halogenating reagents were confronted frequently and thus prevented the practical application of these

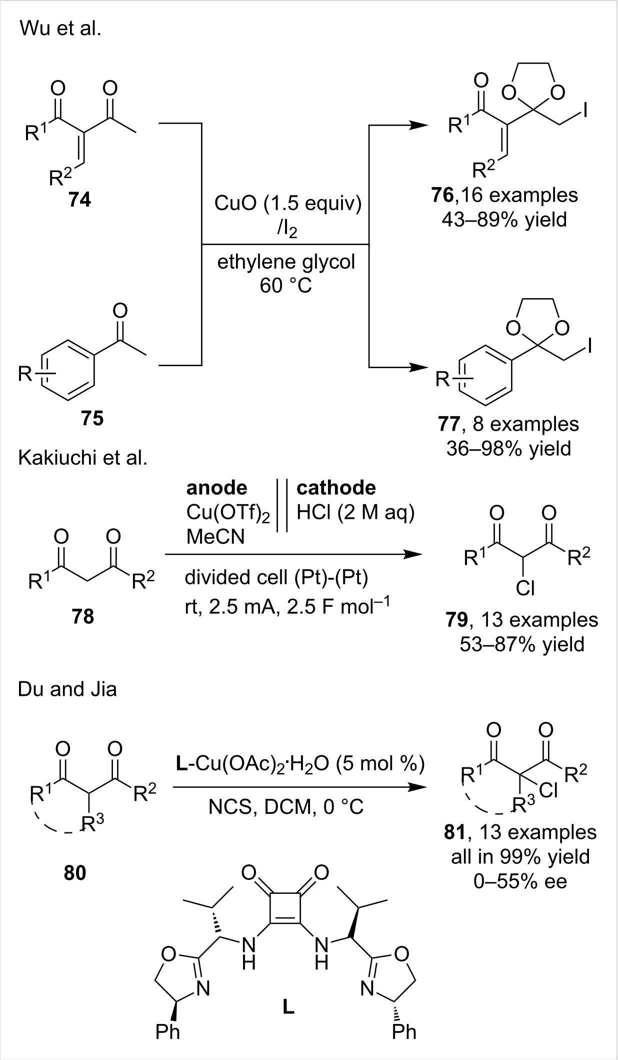


Scheme 24: Copper-catalyzed C–H fluorination of alkanes.



Scheme 23: Copper-catalyzed remote C–H chlorination of alkyl hydroperoxides.

metal-free methods. The application of copper catalysts was found as effective solution to some of these problems. For example, Wu et al. [70] reported the efficient synthesis of α-iodoketals **76** and **77** via CuO-mediated selective mono-iodination of diketones **74** and methylketones **75** in the presence of molecular iodine, respectively. The tandem transformation of a carbonyl acetalization and a iodination in sustainable ethylene glycol under mild heating provided a practical approach in the synthesis of useful protected α-haloketones (Scheme 25). Recently, Kakiuchi and co-workers [71] successfully achieved the selective mono-α-chlorination of β-keto esters/amides and 1,3-diketone **78** by employing an electrochemical synthesis via a catalysis by means of $Cu(OTf)_2$. The synthesis of chlorinated carbonyl products **79** were acquired in a divided cell using aqueous HCl as chlorine source (Scheme 25). On the other hand, Du and Jia [72] developed a route for the asymmetric chlorination of similar carbonyl substrates **80** via copper-catalyzed asymmetrical α-chlorination in the presence of a chiral ligand. The yield of all products **81** was excellent, and the enantioselectivity, however, was generally moderate (Scheme 25).



Scheme 25: Copper-catalyzed or mediated C–H halogenations of active $C(sp^3)$-bonds.

Conclusion

Due to the widespread application of halogenated chemicals in organic chemistry, the synthesis of halogenated compounds via direct halogenations of C–H bonds is amongst the most important issue of modern organic synthesis. On the basis of the traditional electrophilic substitution reaction, the occurrence of powerful new synthetic strategies such as transition metal-catalyzed C–H activation brought new opportunities to the synthesis of more diversely halogenated products by enabling the halogenation of more challenging substrates by more selective transformations. Based on the summarization in this review, it can be found that magnificent advances were made in the copper-catalyzed halogenation, allowing much more options towards the synthesis of halogenated products. On the other hand, it also should be noted that most known literatures on the area focus on the conversion of arene C–H bonds. Although elegant works on alkene C–H bond and $C(sp^3)$–H bond halogenation were also available in literature, the rare overall availability and not universal scope of application, however, demonstrated the remaining challenges in this research area. In addition, the unavailability of a practical copper-catalyzed halogenation of alkyne C(sp)–H bonds is also an issue requiring urgent attention.

Acknowledgements

The authors thank the financial support from Natural Science Foundation of China (21562024, 21202064) and Natural Science Foundation of Jiangxi Province (20142BAB213007).

References

1. *Ullmann's Encyclopedia of Industrial Chemistry,* 6th ed.; Wiley-VCH, 2002.
2. Davos, S. G. *Organotransition Metal Chemistry: Application to Organic Synthesis;* Pergamon Press: Oxford, 1982.
3. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005,** *44,* 4442–4489. doi:10.1002/anie.200500368
4. Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002,** *41,* 4176–4211. doi:10.1002/1521-3773(20021115)41:22<4176::AID-ANIE4176>3.0.CO;2-U
5. Stürmer, R. *Angew. Chem., Int. Ed.* **1999,** *38,* 3307–3308. doi:10.1002/(SICI)1521-3773(19991115)38:22<3307::AID-ANIE3307>3.0.CO;2-5
6. Butler, A.; Walker, J. V. *Chem. Rev.* **1993,** *93,* 1937–1944. doi:10.1021/cr00021a014
7. Taylor, R. *Electrophilic Aromatic Substitution;* John Wiley: New York, 1990.
8. Merkushev, E. B. *Synthesis* **1988,** 923–937. doi:10.1055/s-1988-27758

9. Dela Mare, P. D. B. *Electrophilic Halogenation;* Cambridge University Press: New York, 1976.
10. Hodgson, H. H. *Chem. Rev.* **1947,** *40,* 251–277. doi:10.1021/cr60126a003
See for a review.
11. Snieckus, V. *Chem. Rev.* **1990,** *90,* 879–933. doi:10.1021/cr00104a001
12. Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009,** *42,* 1074–1086. doi:10.1021/ar9000058
13. Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009,** *48,* 5094–5115. doi:10.1002/anie.200806273
14. Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009,** *38,* 3242–3272. doi:10.1039/b816707a
15. Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010,** *110,* 1147–1169. doi:10.1021/cr900184e
16. Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010,** *110,* 624–655. doi:10.1021/cr900005n
17. Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012,** *112,* 5879–5918. doi:10.1021/cr300153j
18. Ackermann, L. *Acc. Chem. Res.* **2014,** *47,* 281–295. doi:10.1021/ar3002798
19. Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004,** *126,* 2300–2301. doi:10.1021/ja031543m
20. Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005,** *44,* 2112–2115. doi:10.1002/anie.200462884
21. Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006,** *128,* 7416–7417. doi:10.1021/ja060232j
22. Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T. *J. Am. Chem. Soc.* **2009,** *131,* 11310–11311. doi:10.1021/ja9049228
23. Chu, L.; Xiao, K.-J.; Yu, J.-Q. *Science* **2014,** *346,* 451–455. doi:10.1126/science.1258538
24. Schröder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012,** *134,* 8298–8301. doi:10.1021/ja302631j
25. Hwang, H.; Kim, J.; Jeong, J.; Chang, S. *J. Am. Chem. Soc.* **2014,** *136,* 10770–10776. doi:10.1021/ja5053768
26. Wang, L.; Ackermann, L. *Chem. Commun.* **2014,** *50,* 1083–1085. doi:10.1039/C3CC47852A
27. Mo, F. Y.; Yan, J. M.; Qiu, D.; Li, F.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010,** *49,* 2028–2032. doi:10.1002/anie.200906699
28. Yu, D.-G.; Gensch, T.; de Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014,** *136,* 17722–17725. doi:10.1021/ja511011m
29. Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011,** *50,* 11062–11087. doi:10.1002/anie.201103945
30. Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012,** *41,* 3464–3484. doi:10.1039/c2cs15323h
31. King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010,** *132,* 12068–12073. doi:10.1021/ja1045378
32. Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006,** *128,* 6790–6791. doi:10.1021/ja061715q
33. Wang, W.; Pan, C.; Chen, F.; Cheng, J. *Chem. Commun.* **2011,** *47,* 3978–3980. doi:10.1039/c0cc05557c
34. Lu, Y.; Wang, R.; Qiao, X.; Shen, Z. *Synlett* **2011,** 1038–1042. doi:10.1055/s-0030-1259729
35. Mo, S.; Zhu, Y.; Shen, Z. *Org. Biomol. Chem.* **2013,** *11,* 2756–2760. doi:10.1039/c3ob40185e
36. Du, Z.-J.; Gao, L.-X.; Lin, Y.-J.; Han, F.-S. *ChemCatChem* **2014,** *6,* 123–126. doi:10.1002/cctc.201300734
37. Che, X.; Gobereiner, G.; Hao, X.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Tetrahedron* **2009,** *65,* 3085–3089. doi:10.1016/j.tet.2008.10.053
38. Urones, B.; Martínez, Á. M.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. *Chem. Commun.* **2013,** *49,* 11044–11046. doi:10.1039/c3cc47174h
39. Li, B.; Liu, B.; Shi, B.-F. *Chem. Commun.* **2015,** *51,* 5093–5096. doi:10.1039/C5CC00531K
40. Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005,** *127,* 13154–13155. doi:10.1021/ja054549f
41. Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S.-S. *J. Am. Chem. Soc.* **2013,** *135,* 9797–9804. doi:10.1021/ja4026424
42. Guo, H.; Chen, M.; Jiang, P.; Chen, J.; Pan, L.; Wang, M.; Xie, C.; Zhang, Y. *Tetrahedron* **2015,** *71,* 70–76. doi:10.1016/j.tet.2014.11.037
43. McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012,** *14,* 4094–4097. doi:10.1021/ol301739f
44. Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013,** *135,* 9342–9345. doi:10.1021/ja4047125
45. Zhao, X.; Ding, F.; Li, J.; Lu, K.; Lu, X.; Wang, B.; Yu, P. *Tetrahedron Lett.* **2015,** *56,* 511–513. doi:10.1016/j.tetlet.2014.12.029
46. Song, Y.-F.; van Albada, G. A.; Tang, J.; Mutikainen, I.; Turpeinen, U.; Massera, C.; Roubeau, O.; Sanchez Costa, J.; Gamez, P.; Reedijk, J. *Inorg. Chem.* **2007,** *46,* 4944–4950. doi:10.1021/ic070057n
47. Menini, L.; Gusevskaya, E. V. *Chem. Commun.* **2006,** 209–211. doi:10.1039/B513329G
48. Menini, L.; Gusevskaya, E. V. *Appl. Catal., A* **2006,** *309,* 122–128. doi:10.1016/j.apcata.2006.05.006
49. Menini, L.; Parreira, L. A.; Gusevskaya, E. V. *Tetrahedron Lett.* **2007,** *48,* 6401–6404. doi:10.1016/j.tetlet.2007.06.093
50. Menini, L.; da Cruz Santos, J. C.; Gusevskaya, E. V. *Adv. Synth. Catal.* **2008,** *350,* 2052–2058. doi:10.1002/adsc.200800223
51. Yang, L.; Lu, Z.; Stahl, S. S. *Chem. Commun.* **2009,** 6460–6462. doi:10.1039/b915487f
52. Barnes, J. C.; Hume, D. N. *Inorg. Chem.* **1963,** *2,* 444–448. doi:10.1021/ic50007a004
53. Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1965,** *30,* 587–592. doi:10.1021/jo01013a069
54. Wang, J.; Wang, W.; Li, J.-H. *Green Chem.* **2010,** *12,* 2124–2126. doi:10.1039/c0gc00328j
55. Zhao, J.; Zhang, Q.; Liu, L.; He, Y.; Li, J.; Li, J.; Zhu, Q. *Org. Lett.* **2012,** *14,* 5362–5365. doi:10.1021/ol302562a
56. Singh, P. P.; Thatikonda, T.; Kumar, K. A. A.; Sawant, S. D.; Singh, B.; Sharma, A. K.; Sharma, P. R.; Singh, D.; Vishwakarma, R. A. *J. Org. Chem.* **2012,** *77,* 5823–5828. doi:10.1021/jo300731z
57. Iso, Y.; Grajkowska, E.; Wroblewski, J. T.; Davis, J.; Goeders, N. E.; Johnson, K. M.; Sanker, S.; Roth, B. L.; Tueckmantel, W.; Kozikowski, A. P. *J. Med. Chem.* **2006,** *49,* 1080–1100. doi:10.1021/jm050570f
58. Siméon, F. G.; Wendahl, M. T.; Pike, V. W. *J. Org. Chem.* **2009,** *74,* 2578–2580. doi:10.1021/jo802799c
59. Sharma, V.; Kumar, V. *Med. Chem. Res.* **2014,** *23,* 3593–3606. doi:10.1007/s00044-014-0940-1
60. Singh, G. S.; Mmatli, E. E. *Eur. J. Med. Chem.* **2011,** *46,* 5237–5257. doi:10.1016/j.ejmech.2011.08.042
61. Xia, J.-B.; You, S.-L. *Org. Lett.* **2009,** *11,* 1187–1190. doi:10.1021/ol9000872
62. Wang, F.; Shen, Y.; Hu, H.; Wang, X.; Wu, H.; Liu, Y. *J. Org. Chem.* **2014,** *79,* 9556–9566. doi:10.1021/jo501626b

63. Yao, B.; Wang, Z.-L.; Zhang, H.; Wang, D.-X.; Zhao, L.; Wang, M.-X. *J. Org. Chem.* **2012,** *77,* 3336–3340. doi:10.1021/jo300152u
64. Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. *Chem. Sci.* **2010,** *1,* 326–330. doi:10.1039/c0sc00245c
65. Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2011,** *133,* 13577–13586. doi:10.1021/ja2047717
66. Huang, F.; Wu, P.; Wang, L.; Chen, J.; Sun, C.; Yu, Z. *Chem. Commun.* **2014,** *50,* 12479–12481. doi:10.1039/C4CC05837B
67. Yin, B.-L.; Huang, L.; Zhang, X.; Ji, F.; Jiang, H. *J. Org. Chem.* **2012,** *77,* 6365–6370. doi:10.1021/jo301039y
68. Kundu, R.; Ball, Z. T. *Org. Lett.* **2010,** *12,* 2460–2463. doi:10.1021/ol100472t
69. Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. *Angew. Chem., Int. Ed.* **2012,** *51,* 10580–10583. doi:10.1002/anie.201203642
70. Yang, Y.; Gao, M.; Shu, W.-M.; Wu, L.-M.; Zhang, D.-X.; Wu, A.-X. *Org. Biomol. Chem.* **2013,** *11,* 1226–1233. doi:10.1039/c2ob27028e
71. Tsuchida, K.; Kochi, T.; Kakiuchi, F. *Asian J. Org. Chem.* **2013,** *2,* 935–937. doi:10.1002/ajoc.201300168
72. Jia, S.-J.; Du, D.-M. *Chin. Chem. Lett.* **2014,** *25,* 1479–1484. doi:10.1016/j.cclet.2014.06.023

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Coupling of α,α-difluoro-substituted organozinc reagents with 1-bromoalkynes

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Letter

Open Access

Keywords:
1-bromoalkynes; cross-coupling; organofluorine compounds; organozinc reagents

Beilstein J. Org. Chem. **2015,** *11,* 2145–2149.
doi:10.3762/bjoc.11.231

Received: 20 August 2015
Accepted: 20 October 2015
Published: 10 November 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

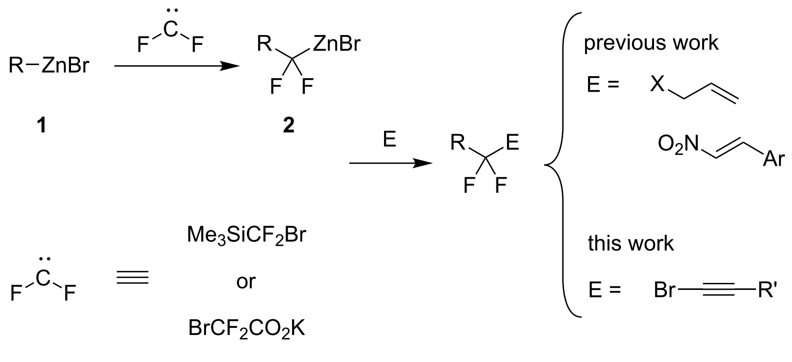
α,α-Difluoro-substituted organozinc reagents generated from conventional organozinc compounds and difluorocarbene couple with 1-bromoalkynes affording *gem*-difluorinated alkynes. The cross-coupling proceeds in the presence of catalytic amounts of copper iodide in dimethylformamide under ligand-free conditions.

Introduction

gem-Difluorinated organic compounds have attracted increasing attention nowadays due to their applicability in medicinal chemistry [1,2] and other fields. Indeed, unique stereoelectronic properties of the CF_2-unit may be exploited in conformational analysis [3-5], carbohydrate and peptide research [6,7], and reaction engineering [8,9].

Typically, the difluoromethylene fragment is created by deoxyfluorination, which requires harsh or hazardous conditions [10,11]. Alternatively, functional group manipulations starting from available CF_2-containing building blocks can be considered, but multistep sequences render this approach laborious [12-14]. Difluoro-substituted cyclopropanes and cyclopropenes constitute a specific class of compounds accessible by difluorocarbene addition to multiple bonds [15].

Recently, we proposed a general method for assembling *gem*-difluorinated structures from organozinc reagents **1**, difluorocarbene, and a terminating electrophile [16-21] (Scheme 1). (Bromodifluoromethyl)trimethylsilane [16-18] or potassium bromodifluoroacetate [19] can be used as precursors of difluorocarbene. In this process, the use of C-electrophiles is particularly important since it allows for the formation of two C–C bonds within one experimental run. Previously, as C-elec-



Scheme 1: Reaction of organozinc compounds.

trophiles in this methodology, only allylic substrates [17] and nitrostryrenes (with the NO_2 serving as a leaving group) [20], were employed. Herein, we report that 1-bromoalkynes, which are known to be involved in reactions with various organometallic compounds [22-27], can be used as suitable coupling partners for difluorinated organozinc compounds **2**. This reaction provides straightforward access to α,α-difluorinated alkynes [13,14,28-31]. Our method is based on facile zinc/copper exchange allowing for versatile couplings described for non-fluorinated organozinc compounds [32-37].

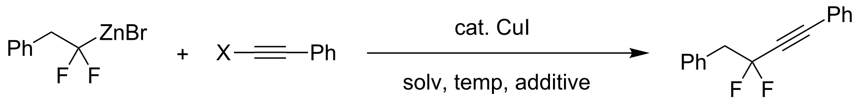
Results and Discussion

Organozinc compound **2a** generated from benzylzinc bromide was first evaluated in a reaction with haloalkynes derived from phenylacetylene (Table 1). First, most reactive iodo-substituted alkyne **3a-I** (X = I) was evaluated in the presence of copper iodide (10 mol %). Expected product **4a** was formed in 12% yield, but its yield was tripled simply by adding 2 equiv of DMF additive (Table 1, entries 1 and 2). However, in these experiments, the reaction mixtures contained about 40% of (2,2-difluoro-2-iodoethyl)benzene ($PhCH_2CF_2I$) arising from zinc/iodine exchange between **2a** and the iodoalkyne. Chloroalkyne **3a-Cl** was markedly less reactive, likely because of the strong carbon–chlorine bond. Fortunately, bromoalkyne **3a-Br** provided the best results, with the optimal conditions involving the use of DMF as a solvent and only 5 mol % of copper iodide at 0 °C to room temperature, which afforded the coupling product in 79% isolated yield (Table 1, entry 5). The addition of various ligands, as well as the use of other copper salts, did not had a beneficial effect.

Under the optimized conditions, a series of organozinc compounds **2** were coupled with bromoalkynes **3** (Table 2). Good yields of coupling products **4** were typically achieved. The reaction tolerates ester groups or TBS-protected hydroxy groups. Aromatic iodide also remains unaffected (Table 2, entry 2).

As for the mechanism, we believe that the reaction starts with the zinc/copper exchange resulting in the formation of fluorinated organocopper species **5** (Scheme 2). Compound **5** inter-

Table 1: Optimization studies.

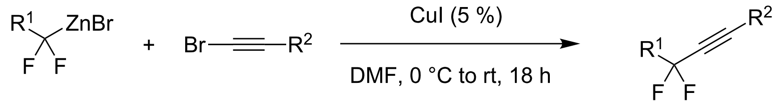


2a **3a-X** **4a**

Entry	X	**2a** (equiv)	Conditions	Solvent	CuI (equiv)	Additive (equiv)	Yield of **4a**, %[a]
1	I	2	−50 °C → rt; 4 h at rt	MeCN	0.1	–	12
2	I	1.3	−50 °C → rt; 4 h at rt	MeCN	0.1	DMF (2)	35
3	Cl	2	0 °C → rt; 16 h at rt	MeCN	0.1	DMF (2)	32
4	Br	1.5	0 °C → rt; 16 h at rt	MeCN	0.1	DMF (2)	60
5	Br	1.5	0 °C → rt; 16 h at rt	DMF	0.05	–	79[b]

[a]Determined by ^{19}F NMR with internal standard. [b]Isolated yield.

Table 2: Reaction of organozinc compounds **2** with bromoalkynes **3**.



2 (1.5 equiv) **3** **4**

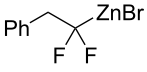
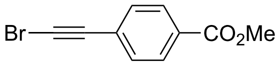
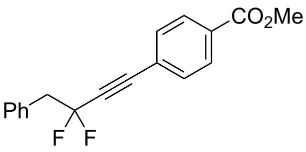
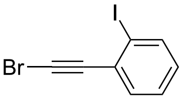
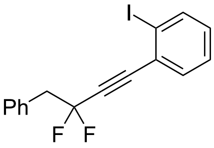
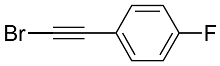
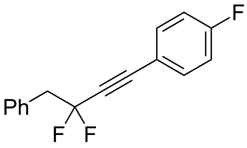
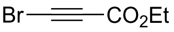
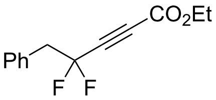
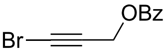
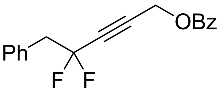
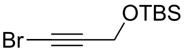
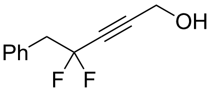
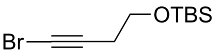
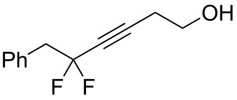
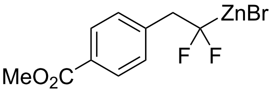
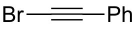
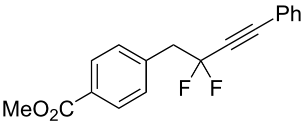
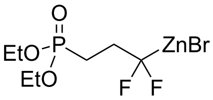
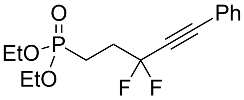
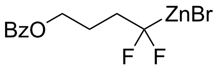
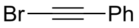
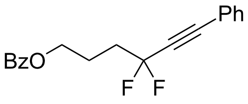
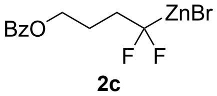
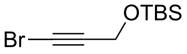
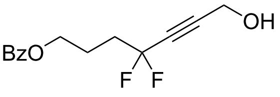
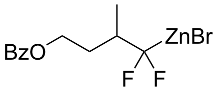
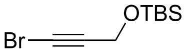
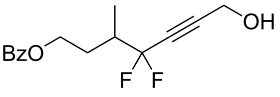
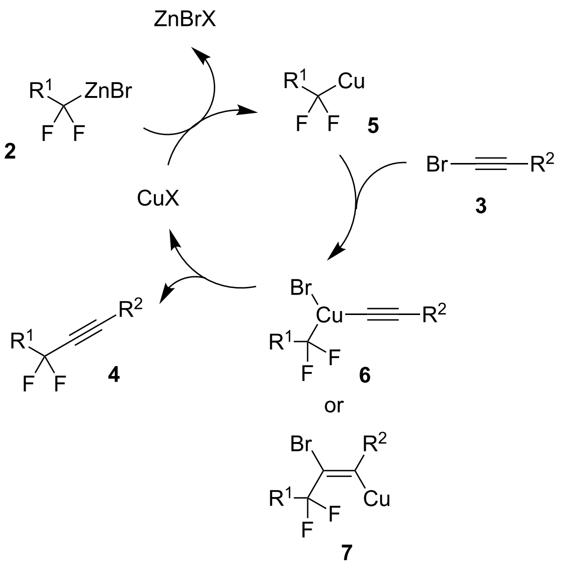
Entry	2	3	4	Yield of **4**, %[a]
1	 **2a**	 **3b**	 **4b**	84
2	**2a**	 **3c**	 **4c**	82
3	**2a**	 **3d**	 **4d**	70
4	**2a**	 **3e**	 **4e**	84
5	**2a**	 **3f**	 **4f**	67
6[b]	**2a**	 **3g**	 **4g**	80
7[b]	**2a**	 **3h**	 **4h**	75
8	 **2b**	 **3a-Br**	 **4i**	80
9	 **2e**	 **3a-Br**	 **4j**	81

Table 2: Reaction of organozinc compounds **2** with bromoalkynes **3**. (continued)

10	 **2c**	 **3a-Br**	 **4k**	72
11^b	 **2c**	 **3g**	 **4l**	71
12^b	 **2d**	 **3g**	 **4m**	62

^{a}Isolated yield. ^{b}The crude product was desilylated.

acts with bromoalkyne **3** either by oxidative addition generating copper(III) intermediate **6** or by triple bond carbometallation [38] generating copper(I) intermediate **7**. Subsequent reductive elimination (from **6**) or β-elimination (from **7**) leads to the product and regenerates the copper(I) catalyst.



Scheme 2: Proposed mechanism.

Conclusion

In summary, a method for the copper-catalyzed coupling of α,α-difluoro-substituted organozinc compounds with 1-bromoalkynes has been developed. The reaction is performed under mild conditions affording *gem*-difluoro-substituted alkynes in good yields.

Supporting Information

Supporting Information File 1

Full experimental details, compound characterization, and copies of NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-231-S1.pdf]

Acknowledgements

This work was supported by the Ministry of Science (project MD-3256.2015.3) and Russian Foundation for Basic Research (projects 14-03-00293, 14-03-31253, 13-03-12074).

References

1. Ojima, I., Ed. *Fluorine in Medicinal Chemistry and Chemical Biology;* John Wiley & Sons: Chichester, 2009.
2. Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine;* John Wiley & Sons: Hoboken, New Jersey, 2008. doi:10.1002/9780470281895
3. O'Hagan, D.; Wang, Y.; Skibinski, M.; Slawin, A. M. Z. *Pure Appl. Chem.* **2012,** *84,* 1587–1595. doi:10.1351/PAC-CON-11-09-26
4. Wang, Y.; Callejo, R.; Slawin, A. M. Z.; O'Hagan, D. *Beilstein J. Org. Chem.* **2014,** *10,* 18–25. doi:10.3762/bjoc.10.4
5. Urbina-Blanco, C. A.; Skibinski, M.; O'Hagan, D.; Nolan, S. P. *Chem. Commun.* **2013,** *49,* 7201–7203. doi:10.1039/c3cc44312d
6. Leclerc, E.; Pannecoucke, X.; Ethève-Quelquejeu, M.; Sollogoub, M. *Chem. Soc. Rev.* **2013,** *42,* 4270–4283. doi:10.1039/C2CS35403A
7. Kubyshkin, V. S.; Mykhailiuk, P. K.; Afonin, S.; Ulrich, A. S.; Komarov, I. V. *Org. Lett.* **2012,** *14,* 5254–5257. doi:10.1021/ol302412a
8. Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc. Natl. Acad. Sci. U. S. A.* **2007,** *104,* 16793–16797. doi:10.1073/pnas.0707090104

9. Codelli, J. A.; Baskin, J. M.; Agard, N. J.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2008,** *130,* 11486–11493. doi:10.1021/ja803086r
10. Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996,** *52,* 8619–8683. doi:10.1016/0040-4020(96)00311-0
11. Al-Maharik, N.; O'Hagan, D. *Aldrichimica Acta* **2011,** *44,* 65–75.
12. Qing, F.-L.; Zheng, F. *Synlett* **2011,** 1052–1072. doi:10.1055/s-0030-1259947
13. Belhomme, M.-C.; Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. – Eur. J.* **2015,** *21,* 12836–12865. doi:10.1002/chem.201501475
14. Gao, B.; Ni, C.; Hu, J. *Chimia* **2014,** *68,* 414–418. doi:10.2533/chimia.2014.414
15. Dolbier, W. R., Jr.; Battiste, M. A. *Chem. Rev.* **2003,** *103,* 1071–1098. doi:10.1021/cr010023b
16. Levin, V. V.; Zemtsov, A. A.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2013,** *15,* 917–919. doi:10.1021/ol400122k
17. Zemtsov, A. A.; Kondratyev, N. S.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2014,** *79,* 818–822. doi:10.1021/jo4024705
18. Smirnov, V. O.; Struchkova, M. I.; Arkhipov, D. E.; Korlyukov, A. A.; Dilman, A. D. *J. Org. Chem.* **2014,** *79,* 11819–11823. doi:10.1021/jo5023537
19. Levin, V. V.; Zemtsov, A. A.; Struchkova, M. I.; Dilman, A. D. *J. Fluorine Chem.* **2015,** *171,* 97–101. doi:10.1016/j.jfluchem.2014.08.021
20. Kondratyev, N. S.; Levin, V. V.; Zemtsov, A. A.; Struchkova, M. I.; Dilman, A. D. *J. Fluorine Chem.* **2015,** *176,* 89–92. doi:10.1016/j.jfluchem.2015.06.001
21. Smirnov, V. O.; Maslov, A. S.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *Russ. Chem. Bull.* **2014,** *63,* 2564–2566. doi:10.1007/s11172-014-0778-1
22. Thaler, T.; Guo, L.-N.; Mayer, P.; Knochel, P. *Angew. Chem., Int. Ed.* **2011,** *50,* 2174–2177. doi:10.1002/anie.201006879
23. Corpet, M.; Bai, X.-Z.; Gosmini, C. *Adv. Synth. Catal.* **2014,** *356,* 2937–2942. doi:10.1002/adsc.201400369
24. Cornelissen, L.; Lefrancq, M.; Riant, O. *Org. Lett.* **2014,** *16,* 3024–3027. doi:10.1021/ol501140p
25. Wang, S.; Wang, M.; Wang, L.; Wang, B.; Li, P.; Yang, J. *Tetrahedron* **2011,** *67,* 4800–4806. doi:10.1016/j.tet.2011.05.031
26. Castagnolo, D.; Botta, M. *Eur. J. Org. Chem.* **2010,** 3224–3228. doi:10.1002/ejoc.201000393
27. Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012,** *41,* 4165–4179. doi:10.1039/c2cs35034c
28. Besset, T.; Poisson, T.; Pannecoucke, X. *Eur. J. Org. Chem.* **2014,** 7220–7225. doi:10.1002/ejoc.201402937
29. Arimitsu, S.; Fernández, B.; del Pozo, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008,** *73,* 2656–2661. doi:10.1021/jo7025965
30. Hammond, G. B. *J. Fluorine Chem.* **2006,** *127,* 476–488. doi:10.1016/j.jfluchem.2005.12.024
31. Xu, B.; Mae, M.; Hong, J. A.; Li, Y.; Hammond, G. B. *Synthesis* **2006,** 803–806. doi:10.1055/s-2006-926334
32. Malosh, C. F.; Ready, J. M. *J. Am. Chem. Soc.* **2004,** *126,* 10240–10241. doi:10.1021/ja0467768
33. Thapa, S.; Kafle, A.; Gurung, S. K.; Montoya, A.; Riedel, P.; Giri, R. *Angew. Chem., Int. Ed.* **2015,** *54,* 8236–8240. doi:10.1002/anie.201502379
34. Karstens, W. F. J.; Moolenaar, M. J.; Rutjes, F. P. J. T.; Grabowska, U.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron Lett.* **1999,** *40,* 8629–8632. doi:10.1016/S0040-4039(99)01808-0
35. Knochel, P. Organomagnesium and Organozinc Chemistry. In *Organometallics in Synthesis;* Schlosser, M., Ed.; John Wiley & Sons, Inc.: Hoboken, New Jersey, 2013; pp 223–372. doi:10.1002/9781118484722.ch2
36. Knochel, P. In *Metal-Catalyzed Cross-Coupling Reactions;* Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 387–419.
37. Geurts, K.; Fletcher, S. P.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Pure Appl. Chem.* **2008,** *80,* 1025–1037. doi:10.1351/pac200880051025
38. Cahiez, G.; Gager, O.; Buendia, J. *Angew. Chem., Int. Ed.* **2010,** *49,* 1278–1281. doi:10.1002/anie.200905816

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doi:10.3762/bjoc.11.231

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Molecular-oxygen-promoted Cu-catalyzed oxidative direct amidation of nonactivated carboxylic acids with azoles

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Keywords:
amidation; azoles; Cu-catalyzed; molecular oxygen; transamidation

Beilstein J. Org. Chem. **2015,** *11,* 2158–2165.
doi:10.3762/bjoc.11.233

Received: 25 August 2015
Accepted: 26 October 2015
Published: 11 November 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

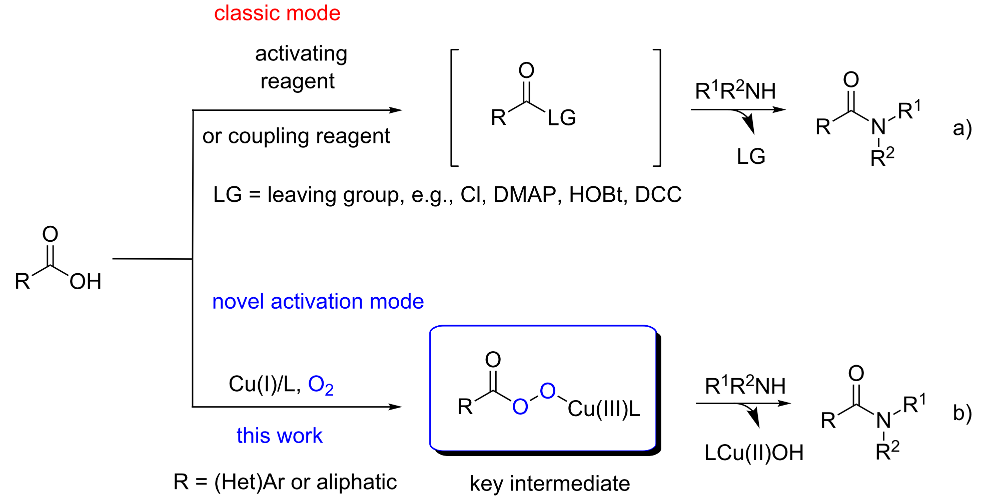
A copper-catalyzed oxidative direct formation of amides from nonactivated carboxylic acids and azoles with dioxygen as an activating reagent is reported. The azole amides were produced in good to excellent yields with a broad substrate scope. The mechanistic studies reveal that oxygen plays an essential role in the success of the amidation reactions with copper peroxycarboxylate as the key intermediate. Transamidation occurs smoothly between azole amide and a variety of amines.

Introduction

Amides are prevalent scaffolds in numerous compounds ranging from biologically active natural products to pharmaceuticals [1]. As a result, numerous methods have been developed for the formation of amides [2-7]. Despite such advances [8-21], the acylation of amines with free carboxylic acids is still the most common method employed due to the availability of the starting materials and its relatively clean process feature, whereby water is the only byproduct in the transformation [22]. However, preactivation of the free carboxylic acids is always required, and stoichiometric activating reagents or coupling reagents are mandatory in the classic methods of amide formation (Scheme 1a) [23].

In some cases, corrosive byproducts (HCl) are unavoidable and the activating reagent is difficult to remove from the system. Given the growing demand for environmentally benign synthesis [24], it is highly desirable to bring forth a green, sustainable and simple new protocol for the activation of carboxylic acids. Molecular oxygen is an ideal oxidant owing to its negligible cost, availability and sustainability [25,26]. Currently, copper-catalyzed, aerobic, oxidative transformations with dioxygen as the sole oxidant have emerged as a useful and powerful strategy to construct carbon–carbon and carbon–heteroatom bonds [27-29].

It is known that Cu(II) superoxide species are usually reported to be formed in the system, and very recently McDonald and coworkers reported an unusual nucleophilic reactivity of a special Cu(II) superoxide complex, acting as a deformylating reagent in spite of the prevailing electrophilic property common



Scheme 1: Traditional activating mode and oxidative activation mode of free carboxylic acids in amide formation.

for such a metal-bound superoxide intermediate [30]. Therefore, we envision that the newly discovered nucleophilic reactivity of Cu(II) superoxide species might lead to a novel, free carboxylic acid activation mode for amide formation: a Cu(II) superoxide species could attack the carbonyl group in an acid to afford a copper peroxycarboxylate, which might then serve as the key intermediate to make the subsequent amide formation feasible (Scheme 1b). In our work, azoles have been chosen as the amines due to their special bioactivity [31]. To the best of our knowledge, Cu salt has not yet been used for catalyzed, oxidative direct amide formation. We report the first amidation reaction from carboxylic acids with peroxycarboxylate as the key intermediate, which represents a novel activation mode with molecular oxygen as the activating reagent. Most remarkably, in sharp contrast to previous reports (which used complex N-containing ligands to form copper superoxide), inexpensive and readily available pyridine was employed as both the ligand and base in our case.

Results and Discussion

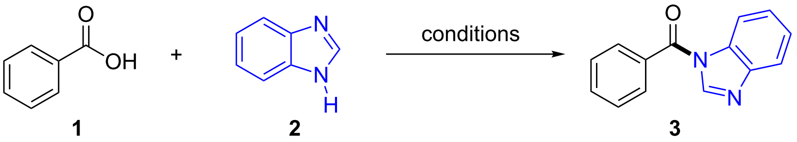
Our initial exploration commenced with benzoic acid (**1**) and benzimidazole (**2**) as the model substrates to investigate the copper-catalyzed oxidative direct amidation reaction (Table 1).

The copper salts demonstrated good activity for this novel transformation (Table 1, entries 1–5) and 85% of the desired product was obtained using 10 mol % of CuBr with pyridine (3 equiv) at 130 °C in *p*-xylene (1 mL) under O_2 in a sealed tube (Table 1, entry 4). Notably, $CuBr_2$ only gave 33% of the desired product under similar conditions (Table 1, entry 5), inferring that molecular oxygen was not just acting as an oxidant to convert Cu(I) into Cu(II), but that it might be involved in the reaction. Further screening of solvents and ligands revealed that *p*-xylene and pyridine are the optimal choices. The reaction cannot go to completion and part of the carboxylic acid remains when the amount of benzimidazole is not twice that of the carboxylic acid. The temperature affected this reaction dramatically and when the temperature was decreased to 120 °C, the yield of the desired product **3** was reduced to 31% of the corresponding GC yield (Table 1, entry 14). Copper salt, pyridine and dioxygen were all found to be pivotal to this transformation (Table 1, entries 19–21): without CuBr, no desired product was detected; in the absence of pyridine, the yield of the desired product was reduced to 46% with some unknown compounds generated; when the reactions were conducted under N_2 atmosphere or air, the desired products were either not detected or reduced to 53%.

With the optimized conditions in hand, we studied the scope and limitations of the Cu-catalyzed oxidative direct amidation reaction. First, we surveyed different carboxylic acids. To our delight, both aromatic and aliphatic carboxylic acids were competent candidates in this transformation (Scheme 2).

For aromatic carboxylic acids, various substituents on the aromatic ring were tolerable under the standard conditions, which suggests that the reaction has a broad substrate scope. Electron-donating (**4–9**, **13**, and **15–17**) and electron-withdrawing groups (**10–12**, **14**, **18**, and **19**) are also compatible in this reaction. Meanwhile, other aromatic acids such as 2-naphthylcarboxylic acid and pyrene-4-carboxylic acid also worked well under the reaction conditions, providing the desired products **20** and **21** in 59% and 88% yield, respectively. Additionally, heterocyclic acids, such as thiophene- and furan-3-carboxylic acid were well tolerated, providing the amides **22**

Table 1: Optimization of the reaction conditions.[a]



entry	catalyst (mol %)	atmosphere	ligand (equiv)	temperature	solvent	yield (%)[b]
1	CuCl (10)	O_2	pyridine (3)	130 °C	*p*-xylene	33
2	CuI (10)	O_2	pyridine (3)	130 °C	*p*-xylene	79
3	$Cu(OAc)_2$ (10)	O_2	pyridine (3)	130 °C	*p*-xylene	0
4	CuBr (10)	O_2	pyridine (3)	130 °C	*p*-xylene	97 (85)[c]
5	$CuBr_2$ (10)	O_2	pyridine (3)	130 °C	*p*-xylene	33
6	CuBr (10)	O_2	pyridine (3)	130 °C	*o*-xylene	48
7	CuBr (10)	O_2	pyridine (3)	130 °C	DMSO	no product
8	CuBr (10)	O_2	pyridine (3)	130 °C	DMF	no product
9	CuBr (10)	O_2	pyridine (3)	130 °C	toluene	4
10	CuBr (10)	O_2	1, 10-Phen (3)	130 °C	*p*-xylene	no product
11	CuBr (10)	O_2	2, 2'-bipy (3)	130 °C	*p*-xylene	no product
12	CuBr (10)	O_2	2-aminopyridine (3)	130 °C	*p*-xylene	no product
13	CuBr (10)	O_2	Et_3N (3)	130 °C	*p*-xylene	no product
14	CuBr (10)	O_2	pyridine (3)	120 °C	*p*-xylene	31
15	CuBr (10)	O_2	pyridine (0.5)	130 °C	*p*-xylene	39
16	CuBr (10)	O_2	pyridine (2)	130 °C	*p*-xylene	77
17[d]	CuBr (10)	O_2	pyridine (3)	130 °C	*p*-xylene	7
18	CuBr (10)	N_2	pyridine (3)	130 °C	*p*-xylene	no product
19	CuBr (10)	air	pyridine (3)	130 °C	*p*-xylene	53
20	–	O_2	pyridine (3)	130 °C	*p*-xylene	no product
21	CuBr (10)	O_2	–	130 °C	*p*-xylene	46

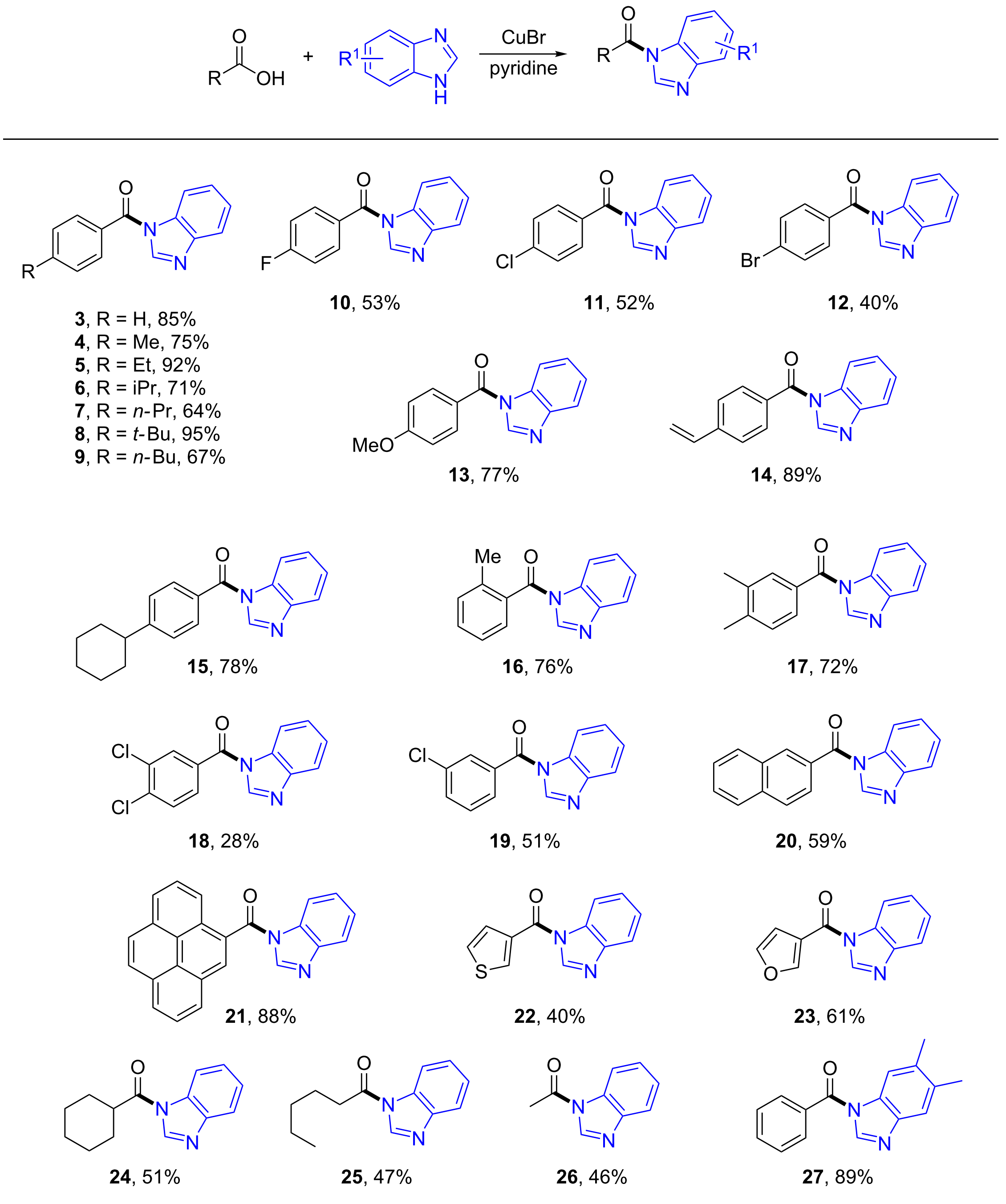
[a] Reaction conditions: all reactions were performed with a mixture of **1** (0.25 mmol), **2** (0.5 mmol), Cu salt (10 mol %), ligand, solvent (1 mL), 16 h, temp., corresponding atmosphere. [b] GC yield. [c] Isolated yield. [d] **1** (0.25 mmol), **2** (0.30 mmol).

and **23** in acceptable yields. Gratifyingly, aliphatic carboxylic acids, such as cyclohexanecarboxylic acid, hexanoic acid and acetic acid were all proven to be good substrates in this transformation and the desired products **24**, **25** and **26** were obtained in reasonable yields. Moreover, bis-substituted benzimidazole also worked very well under the standard conditions to give the desired product **27** in 89% yield.

The scope of amine was further investigated and it seems that only benzimidazole and its derivatives were good candidates in the above direct amide formation (see Scheme S1 in Supporting Information File 1 for details). However, remarkably, when 2-aminopyridine (**28**) and benzimidazole (**2**) were mixed with benzoic acid under the standard conditions, compound **29** was obtained in 45% yield instead of the predicted amide **3** (Scheme 3a). Compound **3** was not detected in the reaction. Similarly, when 2-naphthoic acid (**30**) was used instead of benzoic acid (**1**), compound **31** was afforded in 56% yield without formation of compound **20** (Scheme 3b). However, when a control experiment was conducted without benzimidazole (**2**) (Scheme 3c), compound **29** was not detected and the reaction resulted in a complex mixture of undesired compounds.

In order to determine the possibility of transamidation between compound **3** and 2-aminopyridine (**28**), azole amide **3** was mixed with 2-aminopyridine (**28**) under the standard conditions. Surprisingly, the azole amide **3** was transformed into **29** in 92% yield, which clearly demonstrated that transamidation occurred in this process (Scheme 4).

Further exploration into a variety of amines suggested that transamidation could be efficiently accomplished in the absence of the copper catalyst, pyridine and the versatile amines, including aromatic (**29**, **31**–**34**, **36** and **37**) and aliphatic (**35**, **38**–**40**), primary (**29**, **31**, **34**, **37** and **40**) and secondary (**32**, **33**, **35**, **36**, **38** and **39**). Even the amino group as a natural product (methyl L-leucinate hydrochloride, **40**) was compatible under the conditions, affording corresponding amides in good to

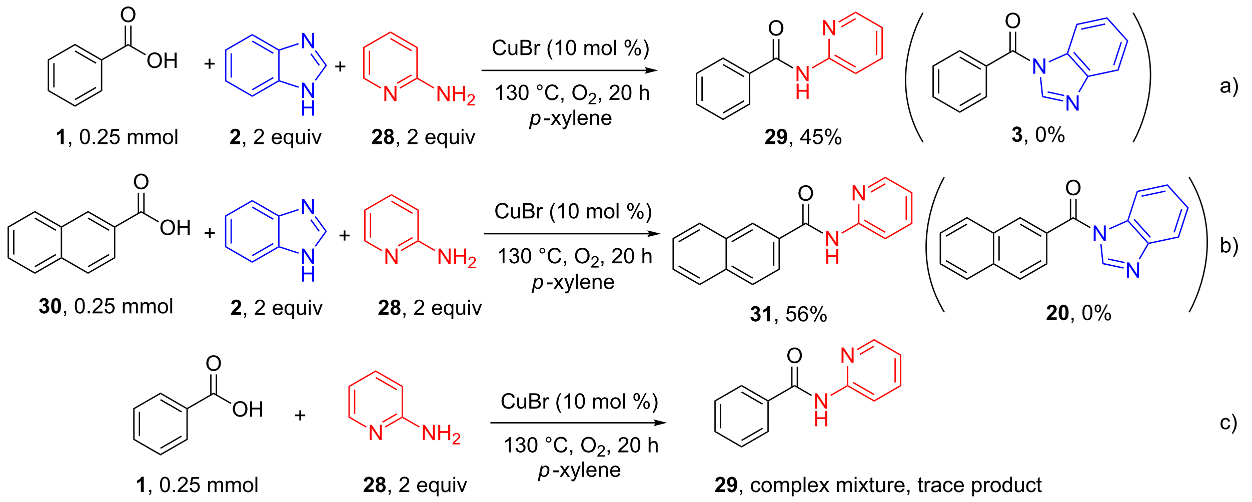


Scheme 2: Substrate scope for catalytic, direct amide formation from carboxylic acids and azoles. Reaction conditions: carboxylic acid (0.25 mmol), azole derivative (0.5 mmol), CuBr (10 mol %), pyridine (0.75 mmol), *p*-xylene (1 mL), 130 °C, 20 h, under O_2 atmosphere in a sealed tube. Isolated yield based on carboxylic acids.

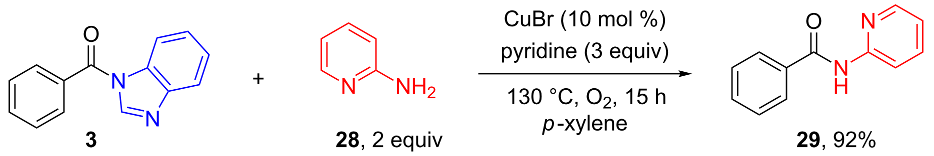
excellent yield (Scheme 5), suggesting the potential utility in complex molecule manipulation. In addition, for the carboxylic acid part, both aromatic and aliphatic (**37**) compounds were competent as well.

The amidation reaction could be easily scaled up without significant decrease in the yield (Scheme 6).

Radical trapping experiments were performed in order to gain further insight into the mechanism of the catalytic direct amide formation from nonactivated carboxylic acids. The reactions were totally inhibited by radical scavengers 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and BHT (2,6-di-*tert*-butyl-4-methylphenol), suggesting that a radical pathway might be involved in these transformations (Scheme 7).



Scheme 3: Further investigation into the scope of amine.



Scheme 4: Possible transamidation process.

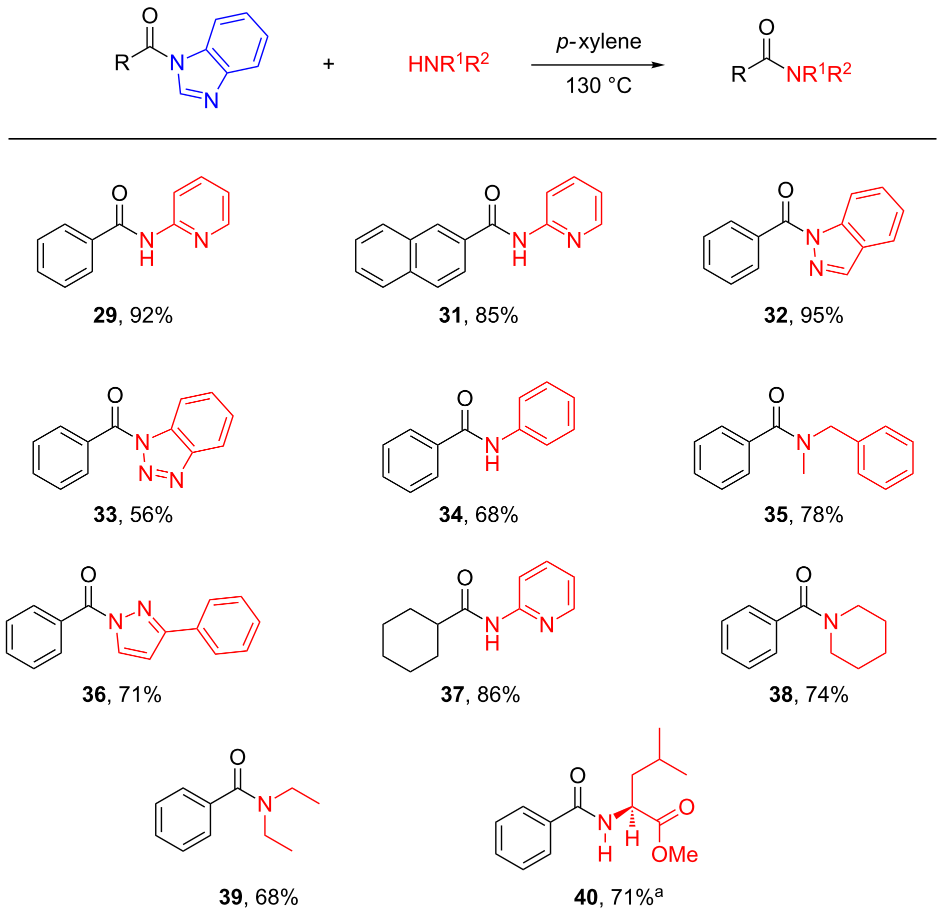
A careful look at the literature reveals that Cu(II) superoxide species were reported to be formed under our standard conditions and might act as a nucleophile to attack carbonyl groups in certain cases [30], although it was always reported as an electrophile [32]. Thus, a new intermediate, peroxycarboxylate, will be formed in our case. In order to figure out whether peroxycarboxylate acts as our key intermediate, the readily available *m*-CPBA (**41**) was used as substrate under the standard conditions and the corresponding product **19** was obtained in 54% yield (Scheme 8a).

Compared to the isolated yield from *m*-chlorophenylacetic acid (Scheme 2, **19**, 51%), we have reason to believe that the above proposed mechanism is plausible. In addition, pyridine *N*-oxide was applied to the benzoic acid standard conditions in the presence/absence of dioxygen. However, only a trace amount of the desired product **3** was ever detected, thus it was ruled out as a possible pathway (Scheme 8b).

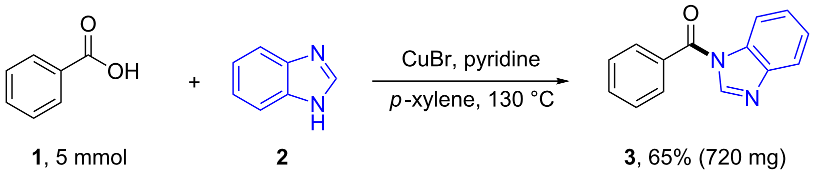
Based on the above control experiments, we postulated a tentative mechanism (Scheme 9). The copper catalyst was postulated to play dual roles in the initial activation of benzoic acid: (1) it acts as a Lewis acid to activate benzoic acid (**1**), making it vulnerable to nucleophilic attack and (2) it forms Cu(II) superoxide species [30,32-34] to attack activated benzoic acid **A** to afford intermediate **B**. Under the standard conditions, intermediate **B** was switched to intermediate **C**, once again, with the nucleophilic attack from benzimidazole (**2**) and eventually intermediate **C** was converted into the desired **3** via intermediate **D** along with the recycling of the Cu catalyst.

Conclusion

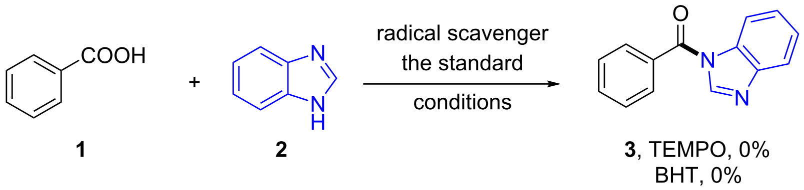
In conclusion, Cu-catalyzed oxidative direct amidation from nonactivated carboxylic acid with benzimidazoles under dioxygen atmosphere with molecular oxygen as an activating reagent has been described. Azole amides were obtained in good yield in an oxidative protocol with a very broad range of substrates. Subsequent transamidation could be performed using the prepared azole amides and a variety of amines. This reaction has many advantages, in particular the use of an inexpensive copper salt as the catalyst, the use of oxygen as both the sole terminal oxidant and activating reagent, and inexpensive and readily available starting materials. This is the first Cu-catalyzed, direct, amide formation between nonactivated carboxylic acids and benzimidazoles in coupling reagent, traditional activating, reagent-free conditions. A mechanistic study demonstrated that a peroxycarboxylate was the key intermediate. This was the first reported example in such a simple system



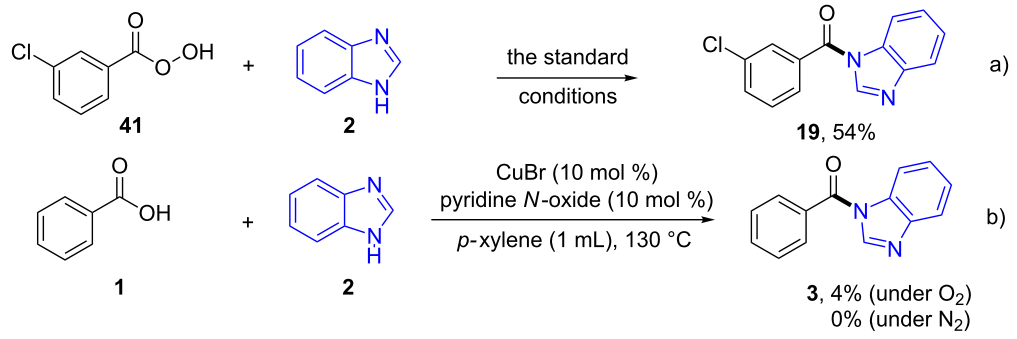
Scheme 5: Scope of the amine transamidation from benzimidazole amides. Reaction conditions: benzimidazole amide (0.25 mmol), amine (0.375 mmol), *p*-xylene (1 mL), 130 °C, sealed tube. Isolated yields. [a]Methyl L-leucinate hydrochloride as the ammonia source and Et_3N (1.5 equiv) were added, the mixture was stirred at room temperature for 3 min, then the mixture was heated to 130 °C.



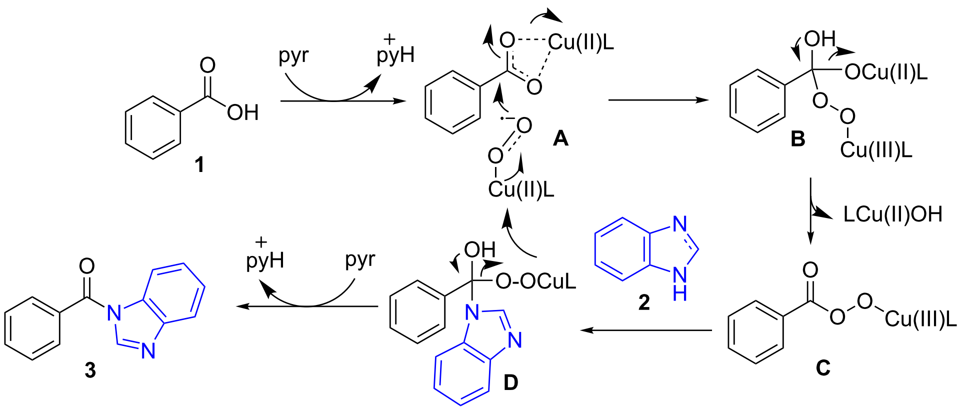
Scheme 6: Preparative scale of the reaction.



Scheme 7: Radical scavenger reaction.



Scheme 8: Control reactions.



Scheme 9: Proposed mechanism.

which could be employed in amide formation. Notably, the transamidation occurred smoothly between the azole amide and a variety of amines, thus providing versatile amides with our new strategy. Therefore, this is a very general method for azole amide formation from versatile carboxylic acids with potential application in organic synthesis.

Supporting Information

Supporting Information File 1

Experimental procedures, analytical data and NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-233-S1.pdf]

Acknowledgements

Financial support from the National Natural Science Foundation of China (21202049), the Recruitment Program of Global Experts (1000 Talents Plan), Fujian Hundred Talents Program and Program of Innovative Research Team of Huaqiao University are gratefully acknowledged.

References

1. Humphrey, M. J.; Chamberlin, R. A. *Chem. Rev.* **1997,** *97,* 2243–2266. doi:10.1021/cr950005s
2. Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009,** *38,* 606–631. doi:10.1039/B701677H
3. Mitchell, J. A.; Reid, E. E. *J. Am. Chem. Soc.* **1931,** *53,* 1879–1883. doi:10.1021/ja01356a037
4. Shepard, E. E.; Porter, H. D.; Noth, J. F.; Simmans, C. K. *J. Org. Chem.* **1952,** *17,* 568–576. doi:10.1021/jo01138a009
5. Schmidt, U.; Dietsche, M. *Angew. Chem., Int. Ed. Engl.* **1982,** *21,* 143–144. doi:10.1002/anie.198201431
6. Cheung, C. W.; Fung, H. S.; Lee, S. Y.; Qian, Y. Y.; Chan, Y. W.; Chan, K. S. *Organometallics* **2010,** *29,* 1343–1354. doi:10.1021/om9008668
7. Das, S.; Biswas, R.; Mukherjee, B. *J. Phys. Chem. B* **2015,** *119,* 274–283. doi:10.1021/jp509869d
8. Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* **2006,** *128,* 13064–13065. doi:10.1021/ja064315b
9. Ekoue-Kovi, K.; Wolf, C. *Org. Lett.* **2007,** *9,* 3429–3432. doi:10.1021/ol7014626
10. Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Kantam, M. L. *Eur. J. Org. Chem.* **2008,** 3619–3622. doi:10.1002/ejoc.200800454

11. Ghosh, S. C.; Ngiam, J. S. Y.; Chai, C. L. L.; Seayad, A. M.; Dang, T. T.; Chen, A. *Adv. Synth. Catal.* **2012,** *354,* 1407–1412. doi:10.1002/adsc.201200020
12. Prasad, V.; Kale, R. R.; Mishra, B. B.; Kumar, D.; Tiwari, V. K. *Org. Lett.* **2012,** *14,* 2936–2939. doi:10.1021/ol3012315
13. Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006,** *71,* 6652–6654. doi:10.1021/jo060847z
14. Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996,** *61,* 4196–4197. doi:10.1021/jo9606564
15. Allen, C. L.; Chhatwal, A. R.; Williams, J. M. J. *Chem. Commun.* **2012,** *48,* 666–668. doi:10.1039/C1CC15210F
16. Goh, K. S.; Tan, C.-H. *RSC Adv.* **2012,** *2,* 5536–5538. doi:10.1039/C2RA20773G
17. Subramanian, P.; Indu, S.; Kaliappan, K. P. *Org. Lett.* **2014,** *16,* 6212. doi:10.1021/ol5031266
18. Starkov, P.; Sheppard, T. D. *Org. Biomol. Chem.* **2011,** *9,* 1320–1323. doi:10.1039/C0OB01069C
19. Tan, B.; Toda, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2012,** *51,* 12538–12541. doi:10.1002/anie.201205921
20. Charville, H.; Jackson, D.; Hodges, G.; Whiting, A. *Chem. Commun.* **2010,** *46,* 1813–1823. doi:10.1039/B923093A
21. Kosal, A. D.; Wilson, E. E.; Ashfeld, B. L. *Chem. – Eur. J.* **2012,** *18,* 14444–14453. doi:10.1002/chem.201201773
22. Dunlap, F. L. *J. Am. Chem. Soc.* **1902,** *24,* 758–763. doi:10.1021/ja02022a008
23. Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955,** *77,* 1067–1068. doi:10.1021/ja01609a099
24. Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006,** *4,* 2337–2347. doi:10.1039/B602413K
25. Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005,** *105,* 2329–2364. doi:10.1021/cr050523v
26. Wang, T.; Jiao, N. *J. Am. Chem. Soc.* **2013,** *135,* 11692–11695. doi:10.1021/ja403824y
27. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003,** *42,* 5400–5449. doi:10.1002/anie.200300594
28. Bi, H.-P.; Zhao, L.; Liang, Y.-M.; Li, C.-J. *Angew. Chem., Int. Ed.* **2009,** *48,* 792–795. doi:10.1002/anie.200805122
29. Liu, J.; Liu, Q.; Yi, H.; Qin, C.; Bai, R.; Qi, X.; Lan, Y.; Lei, A. *Angew. Chem., Int. Ed.* **2014,** *53,* 502–506. doi:10.1002/anie.201308614
30. Pirovano, P.; Magherusan, A. M.; McGlynn, C.; Ure, A.; Lynes, A.; McDonald, A. R. *Angew. Chem., Int. Ed.* **2014,** *53,* 5946–5950. doi:10.1002/anie.201311152
31. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003,** *103,* 893–930. doi:10.1021/cr020033s
32. Yoon, J.; Solomon, E. I. *J. Am. Chem. Soc.* **2007,** *129,* 13127–13136. doi:10.1021/ja073947a
33. Kieber-Emmons, M. T.; Ginsbach, J. W.; Wick, P. K.; Lucas, H. R.; Helton, M. E.; Lucchese, B.; Suzuki, M.; Zuberbühler, A. D.; Karlin, K. D.; Solomon, E. I. *Angew. Chem., Int. Ed.* **2014,** *53,* 4935–4939. doi:10.1002/anie.201402166
34. Bonnot, F.; Tremey, E.; von Stetten, D.; Rat, S.; Duval, S.; Carpentier, P.; Clemancey, M.; Desbois, A.; Nivière, V. *Angew. Chem., Int. Ed.* **2014,** *53,* 5926–5930. doi:10.1002/anie.201400356

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doi:10.3762/bjoc.11.233

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Recent advances in copper-catalyzed C–H bond amidation

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Review

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Keywords:
amidation; C–H bond; cascade reactions; Copper catalysis; intermolecular; intramolecular

Beilstein J. Org. Chem. **2015,** *11,* 2209–2222.
doi:10.3762/bjoc.11.240

Received: 04 August 2015
Accepted: 29 October 2015
Published: 17 November 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

Copper catalysis has been known as a powerful tool for its ubiquitous application in organic synthesis. One of the fundamental utilities of copper catalysis is in the C–N bond formation by using carbon sources and nitrogen functional groups such as amides. In this review, the recent progress in the amidation reactions employing copper-catalyzed C–H amidation is summarized.

Introduction

The amide functional group is a fundamental fragment in nature and in both living systems and artificial chemicals. Owing to their naturally relevance to biological processes, the amides have attracted extensive research interest in numerous areas such as chemical, pharmaceutical, biological and material sciences [1-5]. For the sake of synthesizing functional amides, tremendous efforts have been made by chemists who developed many distinct methodologies towards these compounds. Typical examples on amide synthesis are the direct amidation of acids/esters/acyl chloride/anhydrides [6-11], nitrile hydrolysis [12-16], Goldberg C–N cross coupling reaction [17], aldehyde/ketone amidation [18-23], the transamidation [24-29], and oxime rearrangement [30-33], to name only a few. It is obvious that the known strategies in amide synthesis are now abundant to enable the preparation of amides as diverse as one can imagine. In this context, developing alternative synthetic approaches which are of enhanced sustainability has become a main issue of present concern in the field of amide synthesis.

As an ideal model of modern organic synthesis, the direct functionalization of inactivated C–H bonds has been proved to be a promising tool to enable atom and step economical synthesis. Inspired by the splendid advances that have taken place in the chemistry of C–H activation, the synthesis of amides has accordingly received significant progress by making use of the coupling between amino group and inert C–H bonds [34,35]. Considering the notable advances that have happened in the research of C–H amidation, it is desirable to provide a review work on this issue. Although different transition metals are known to be capable of catalyzing the C–H amidation reactions, copper is particularly advantageous because of the low cost, low toxicity and broad tolerance of copper catalysts. Therefore, the present review summarizes the advances on the copper-catalyzed C–H activation-based amidation (including related sulfonamidation and imidation) reactions under the categories of C(sp^3)–H bond amidation, C(sp^2)–H bond amidation, C(sp)–H bond amidation and cascade reactions initiated by C–H amidation.

Review

C(sp^3)–H bond amidation

Intermolecular amidation

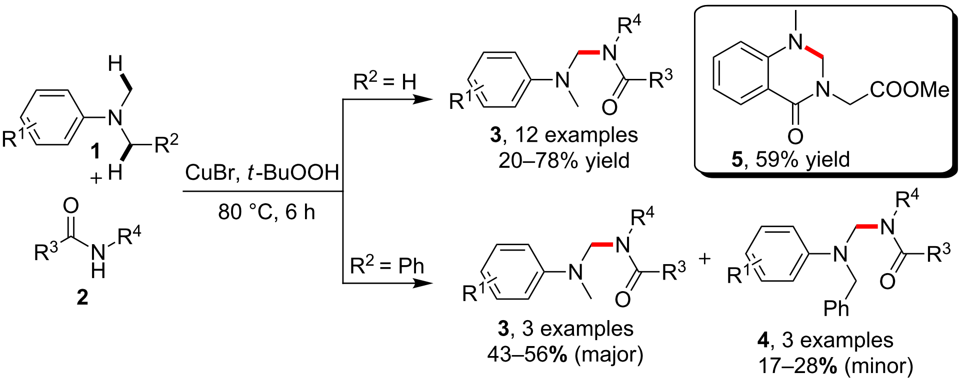
The formation of *N*-alkylamides could be traditionally accessed via nucleophilic *N*-alkylation of amides by using pre-functionalized electrophiles such as alkyl halides, alcohols or amines [36-41]. An alternative tactic which employs raw C–H bond conversion represents a revolutionary step in the synthesis of *N*-alkylamides. In 2007, Fu and co-workers [42] reported the copper-catalyzed, *tert*-butyl hydroperoxide (TBHP)-assisted C–H amidation of tertiary amines **1**. By heating at 80 °C, the C–H bond in dimethylaniline underwent direct amidation to provide products **3** in the presence of amides **2**. On the other hand, the dephenylation transformation via C–C bond cleavage took place as the main route when *N*-phenyl-*N*-methylaniline was employed as the alternative reactant, which led to the production of **3** as the main products, while corresponding products **4** via C–H bond amidation occurred as the minor ones. Notably, this kind of C–H amidation strategy could be utilized for the synthesis of cyclic product **5** via an intramolecular version (Scheme 1).

On the basis of this successful amidation of the C–H bonds adjacent to a nitrogen atom, the same group later on realized a more generally applicable protocol on the amidation of benzylic C–H bonds and C–H bonds adjacent to oxygen via an *N*-halosuccinimide- (NCS or NBS)-assisted copper-catalyzed process. As shown in Scheme 2, both cyclic and acyclic compounds **6** containing a benzylic C–H bond could be readily converted to *N*-alkylamides **8** or sulfonamides **9** via this much milder catalytic method. In addition, this modified method was also able to allow the amidation of *N,N*-dimethylanilines at room temperature with higher efficiency. One of the key intermediates was proposed to be the *N*-haloamide **10**, which was generated from the incorporation of amides and NBS/NCS. And the subsequent transformation via intermediates **11**, **12** and **13** enabled the final production of the *N*-alkylamides [43].

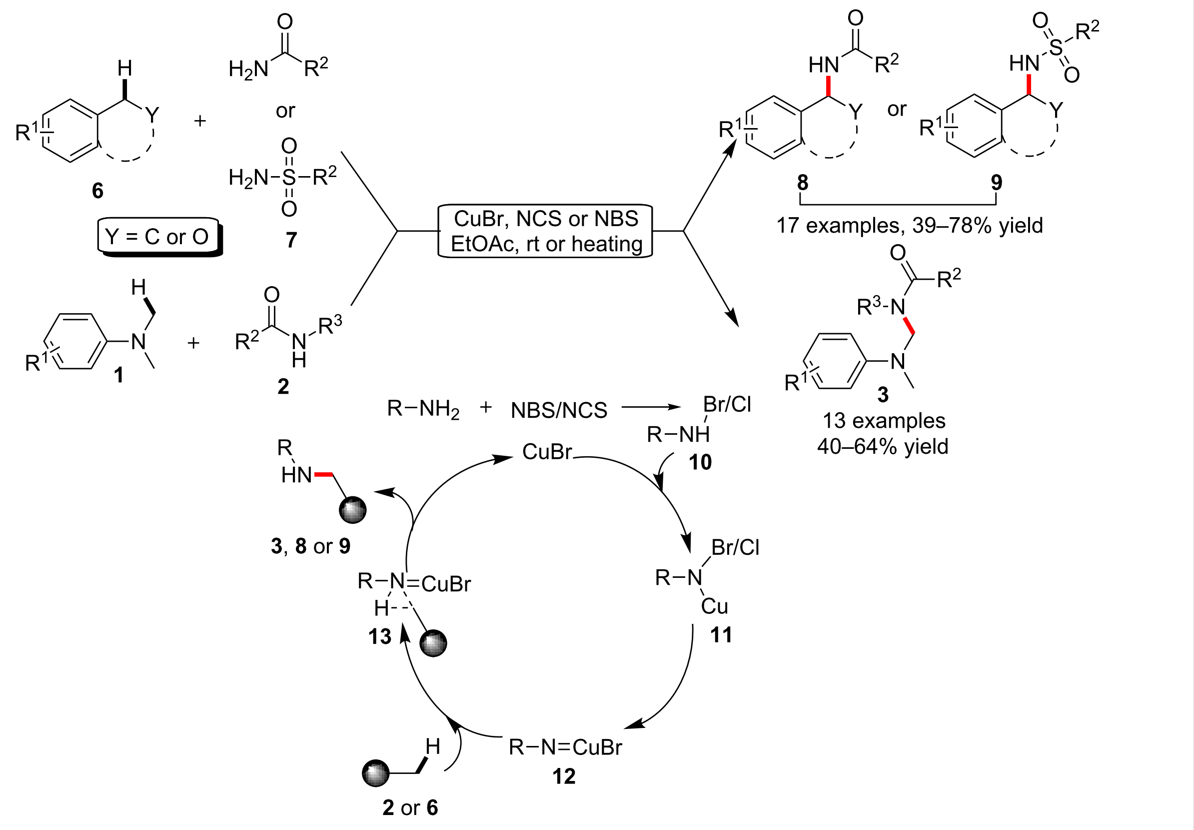
Also by means of copper catalysis, Powell et al. [44] reported the synthesis of *N*-alkylsulfonamides **16** via the C–H amidation of various sp^{3}C–H bonds such as benzylic, allylic and tertiary carbon ones (**14**) in the presence of primary or secondary sulfonamides **15** with the assistance of 1,10-phenanthroline as a ligand (Scheme 3). Notably, the asymmetric version of a similar amidation had been previously achieved by Clark et al. via copper catalysis in the presence of a chiral oxazoline ligand, which allowed the synthesis of enantioenriched products of type **16** [45].

In a subsequent study, by modifying the conditions using [MeCN]$_4$Cu(I)PF$_6$ as copper catalyst and 1,3-indanedione as the ligand, the sulfonamidation of primary benzylic C(sp^3)–H bonds in toluene were successfully performed at 23 °C in the presence of 3-CF$_3$C$_6$H$_4$CO$_3$*t*-Bu, which provides a practical approach to complement the above catalytic version on the sulfonamidation of secondary and tertiary alkyl C–H bonds (Scheme 4) [46].

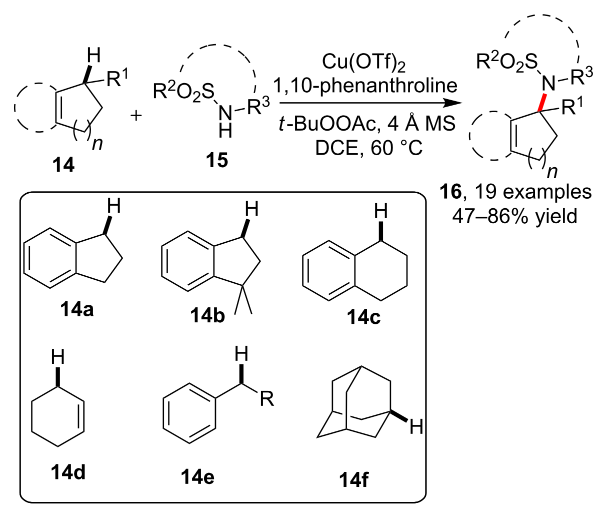
As an early known tactic with broad application, the nitrene insertion was frequently employed in the sulfonamidation of saturated C–H bonds. However, previously prepared nitrene precursors such as ArI=NTs [47] or chloramine-T [48] were required. To design a facile amidation method using this strategy, Yu and co-worker [49] developed a new method for the synthesis of tosyl-amidated esters **20** via C–H sulfonamida-



Scheme 1: Copper-catalyzed C–H amidation of tertiary amines.

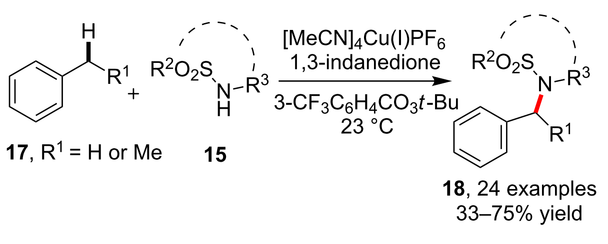


Scheme 2: Copper-catalyzed C–H amidation and sulfonamidation of tertiary amines.

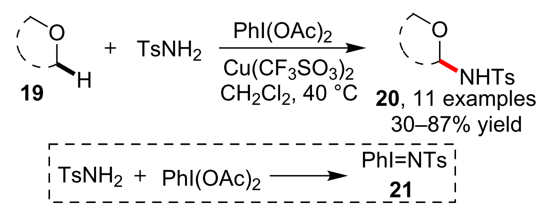


Scheme 3: Copper-catalyzed sulfonamidation of allylic C–H bonds.

tion of cyclic esters **19** under catalysis of copper(II) trifluoromethanesulfonate. The notable advantage of this protocol was that simple tosylamide had been directly used as amide nucleophile. The key point enabling the sulfonamidation transformation was the in situ generation of PhI=NTs (**21**) by employing $PhI(OAc)_2$ in the reaction (Scheme 5).



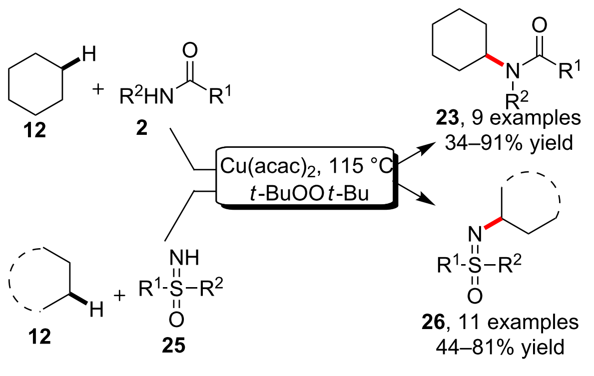
Scheme 4: Copper-catalyzed sulfonamidation of benzylic C–H bonds.



Scheme 5: Copper-catalyzed sulfonamidation of C–H bonds adjacent to oxygen.

While most known literature methods in the copper-catalyzed alkane amidation focused on the transformation of either benzylic, allylic C–H bonds or C–H bonds adjacent to nitrogen or oxygen atoms, the amidation of unactivated C–H bonds in simple linear or cyclic alkanes remained as a challenge. Recently, Hartwig and co-workers [50] successfully realized the amidation, sulfonamidation and imidation reactions of purely non-activated cyclic and linear alkanes via the catalysis of copper(I) iodide by employing 4,7-dimethoxyphenanthroline ($(OMe)_2Phen$) as the ligand and *t*-BuOO*t*-Bu as an oxidant. Heating the reaction at 100 °C allowed the synthesis of various *N*-alkylamides, sulfonamides and imides with fair to excellent yield, and the results also suggested that the catalytic method tended to selectively enable the transformation of secondary or primary C–H bonds, while the amidation of the tertiary alkyl C–H bond was not favored. More notably, the exploration on the reaction mechanism disclosed that the activation of the alkyl C–H bond was initiated by the *tert*-butoxy radical (Scheme 6).

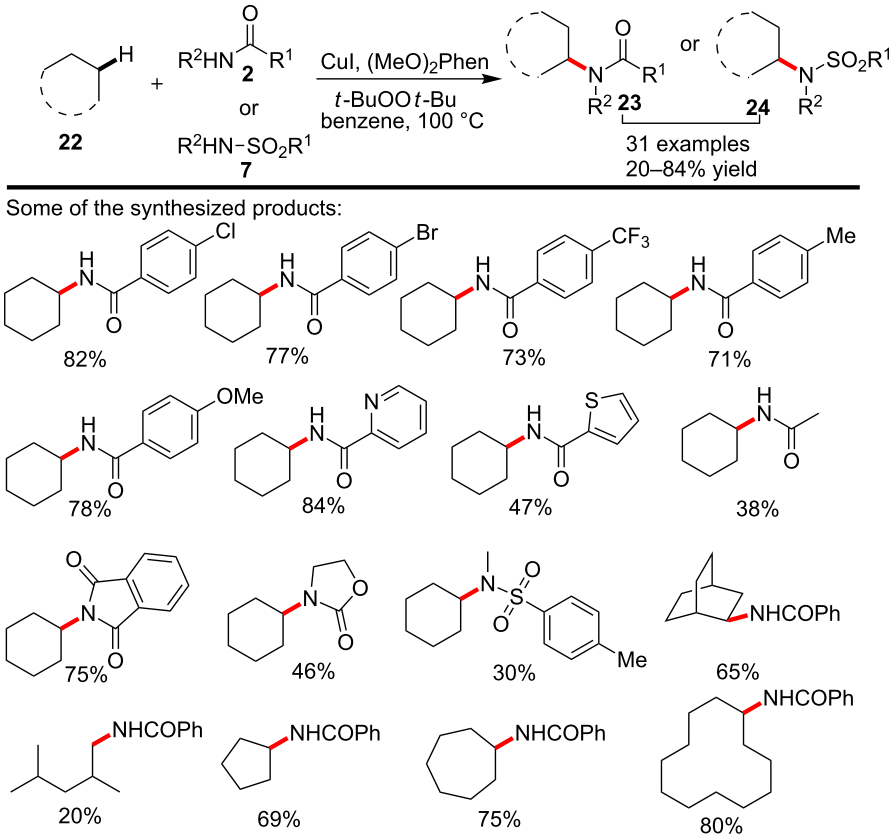
Inspired by the alkane C–H activation, Yu and Cheng et al. [51] discovered that directly heating amides in cyclohexane in the presence of $Cu(acac)_2$ and *t*-BuOO*t*-Bu enabled the C–H amidation for the synthesis of *N*-cyclohexyl amides without using a ligand or an additional solvent. More interestingly, the catalytic method was also efficiently applicable for the *N*-alkylation of sulfoximines for the synthesis of various sulfoximine derivatives (Scheme 7).



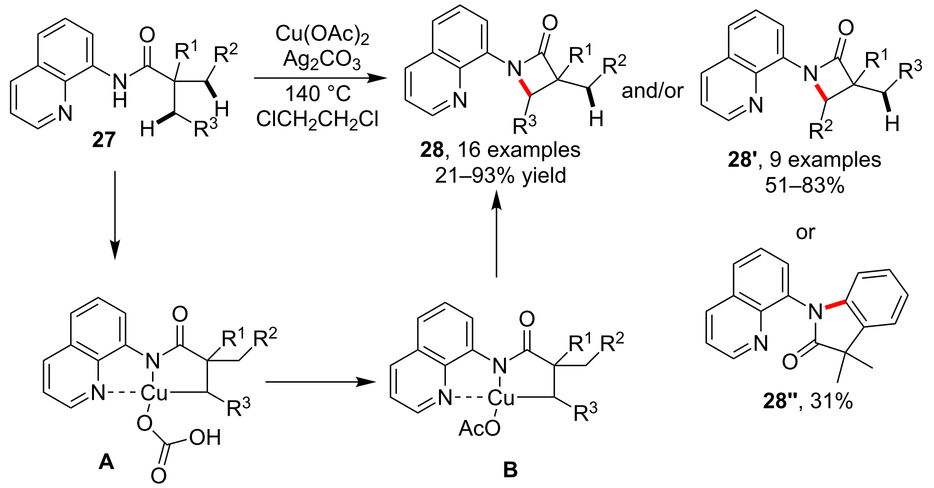
Scheme 7: Copper-catalyzed amidation and sulfonamidation of inactivated alkanes.

Intramolecular amidation

Comparing with the intermolecular amidation, the copper-catalyzed intramolecular version of the sp^3C–H amidation was much less explored. In 2014, Kuninobu and Kanai et al. [52] reported an unprecedented intramolecular $C(sp^3)$–H bond amidation for the synthesis of a lactam via chelating-group-assisted copper catalysis. As outlined in Scheme 8, the *N*-quinolin-8-yl substituted amides **27** could be smoothly trans-



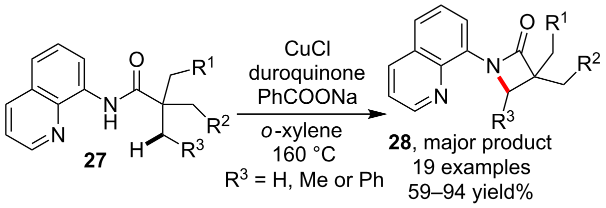
Scheme 6: Copper-catalyzed amidation and sulfonamidation of inactivated alkyl C–H bonds.



Scheme 8: Copper-catalyzed intramolecular C–H amidation for lactam synthesis.

formed into lactams **28** and/or **28'** via C–H amidation by using $Cu(OAc)_2$ as catalyst and Ag_2CO_3 as a base. In a specific case, the $C(sp^2)$–H bond could undertake the amidation to provide indolinone product **28''**. An important factor enabling the C–H bond transformation was the presence of the quinoline auxiliary which acted as a bidentate fragment to incorporate the copper catalyst and facilitate the bond cleavage and formation via intermediates **A** and **B** (Scheme 8).

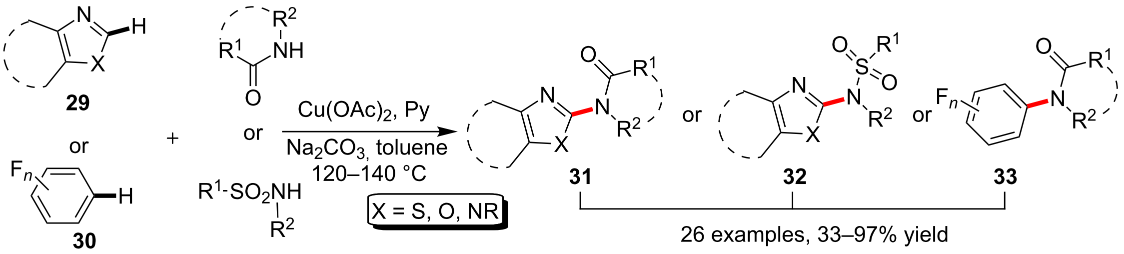
Almost at the same time, Ge et al. [53] reported a similar intramolecular C–H amidation for the synthesis of lactams using CuCl as copper catalyst. When substrates possessing more than one γ-alkyl C–H bond were used, as the case occurred in Kuninobu and Kanai's work, the primary C–H was preferably transformed over secondary C–H bonds (Scheme 9).



Scheme 9: Copper-catalyzed intramolecular C–H amidation for lactam synthesis.

$C(sp^2)$–H bond amidation

The direct transformation of $C(sp^2)$–H bonds constitutes an issue of extensive current interest. On the basis of the pioneering work in transition-metal-catalyzed activation of the C(Ar)–H bonds of electron deficient heteroaryls, Schreiber and Wang [54] attempted and achieved the $Cu(OAc)_2$-catalyzed C–H amidation/sulfonamidation of azoles **29** and polyfluorinated arenes **30** under the assistance of pyridine (Py) as ligand and base. Corresponding products **31**, **32** and **33** were readily acquired with fair to excellent yield depending on the properties of both aryl substrate and amide nucleophile (Scheme 10). It is worth to mention that Pan and co-workers recently disclosed *N*-fluorobenzene sulfonimides to be employed as the source of sulfonamide to enable the synthesis of *N*-heteroaryl sulfonimides via copper-catalyzed aryl C–H sulfonimidation [55].

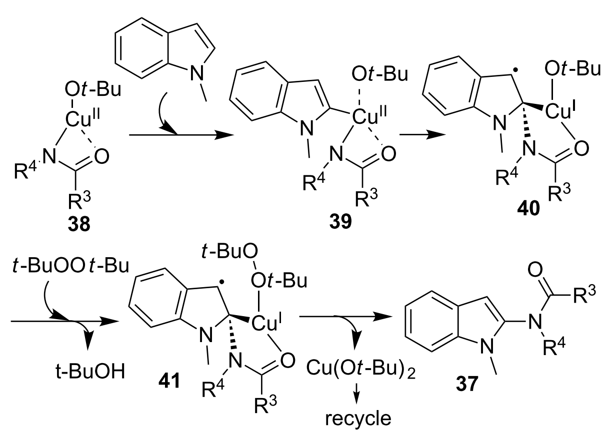


Scheme 10: Copper-catalyzed amidation/sulfonamidation of aryl C–H bonds.

In contrast to the direct transformation of the weakly acidic C–H bonds in these electron deficient arenens/heteroarenes, the amidation of normal aryl C–H bonds usually relied on the presence of a directing group (DG). In 2010, Li et al. [56] reported the *o*-amidation of 2-arylpyridines **34** via the catalysis with CuBr and oxidation with *tert*-butyl peroxide. Besides the application of *N*-substituted and unsubstituted amides in the synthesis of **35**, the sulfonamidation using $TsNH_2$ was also successfully performed. In addition, this copper-catalyzed amidation protocol was also found to be applicable for the synthesis of 2-amino-1-methylindoles **37** via C–H amidation of indoles **36** by employing benzene as the medium (Scheme 11).

While the authors proposed that the mechanism in the selective C-2 amidation of *N*-methylindoles resulted from a classical oxidative addition/reductive elimination Cu(III)/Cu(I) process, Himo and co-workers [57] provided a different Cu(II)/Cu(I) mechanism to explain the selectivity of this C-2 amidation transformation based on the study with DFT calculation. As outlined in Scheme 12, the calculation results suggested that the C-2 amidation of indole was possibly initiated by the Cu(II)-based bidentated intermediate **38**, which proceeded via a series of different intermediate states **39**–**41** to provide products **37** in the presence of *tert*-butyl peroxide.

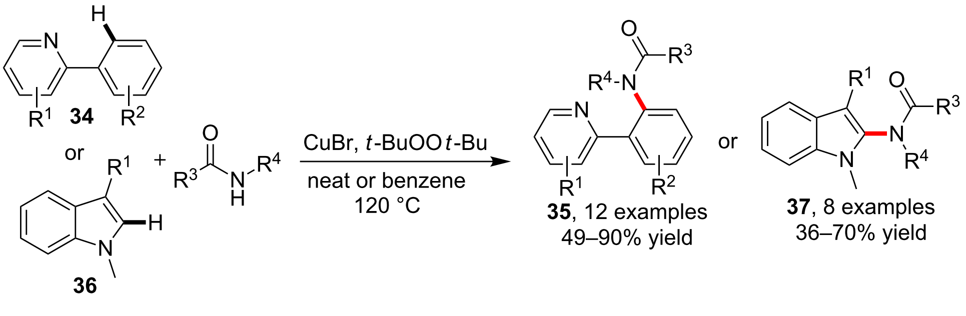
By means of the assistance of molecular oxygen, Nicholas and John [58] devised the copper-catalyzed 2-amidation and sulfonamidation of 2-arylpyridines via C–H activation. Besides the peroxide-free advantage, the C–H amination using aniline was found applicable to allow the synthesis of biarylamine. More recently, based on the DG strategy, the Yu group [59] designed the *o*-amidation of arylamides with copper catalysis under aerobic conditions. Upon systematic screening, the 2-phenyloxazole structure was found as an excellent DG to enable the *ortho*-C–H functionalization of amide **42** to provide products **43**. Under the assistance of this novel DG, this catalytic method exhibited exceptionally broad tolerance to the C–H functionalization with nitrogen nucleophiles, including amides, sulfonamides and primary arylamines. In addition, the oxazole-based DG could be easily deprotected to provide the corresponding benzoic acid **44** by heating in EtOH in the presence of KOH (Scheme 13).



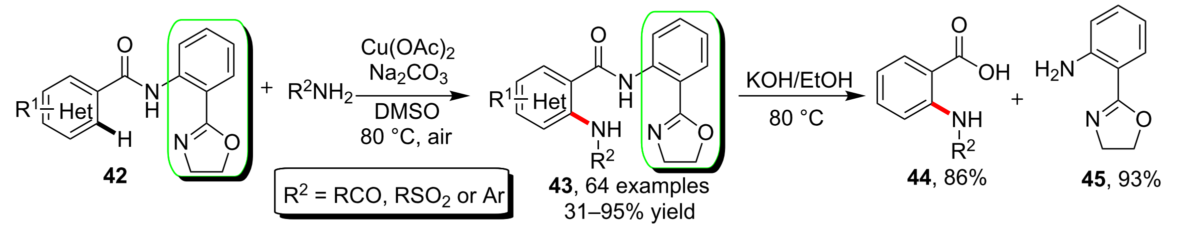
Scheme 12: Mechanism of the Cu-catalyzed C2-amidation of indoles.

As another easily available *N*-containing aromatic heterocycle, the pyrimidine ring was disclosed as useful DG in copper-catalyzed C–H activation. As reported by Shen and co-workers [60], the C–H bond in indoles **47** and benzenes **48** could be effectively activated with copper in the presence of DGs such as pyrimidin-2-yl, pyridine-2-yl or benzoyl to provide products **49** or **50** by incorporating phthalimide/saccharin **46**. Under the standard conditions, however, the reaction of benzamide with 2-phenylpyridine provided product **51** with low yield (Scheme 14).

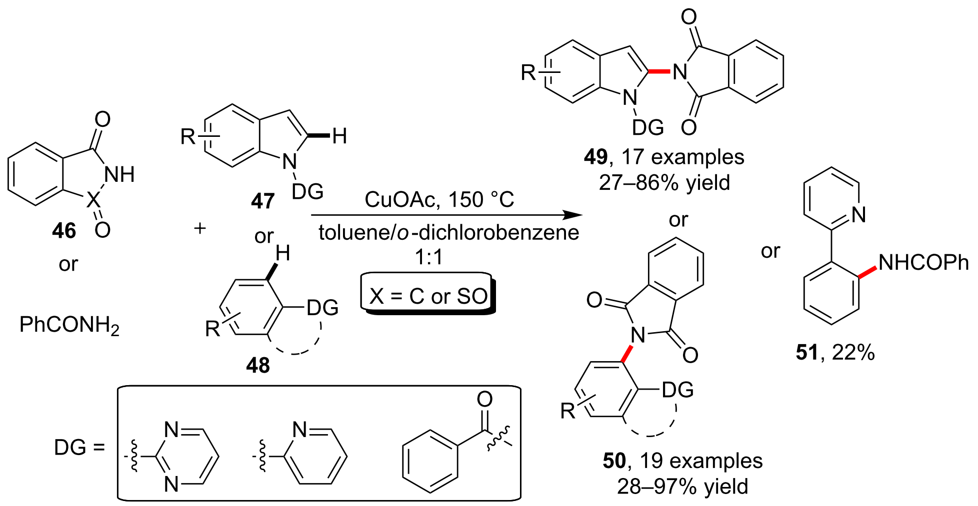
As a special aromatic system, quinoline *N*-oxides were well investigated in their reactivity for metal-catalyzed C–H activation. Based on the known results of quinoline *N*-oxide C–H alkenylation [61], arylation [62] and alkylation [63] etc, Li and co-workers [64] investigated and established the C–H amidation of quinoline *N*-oxides **52** via copper catalysis. According



Scheme 11: C–H amidation of pyridinylbenzenes and indoles.

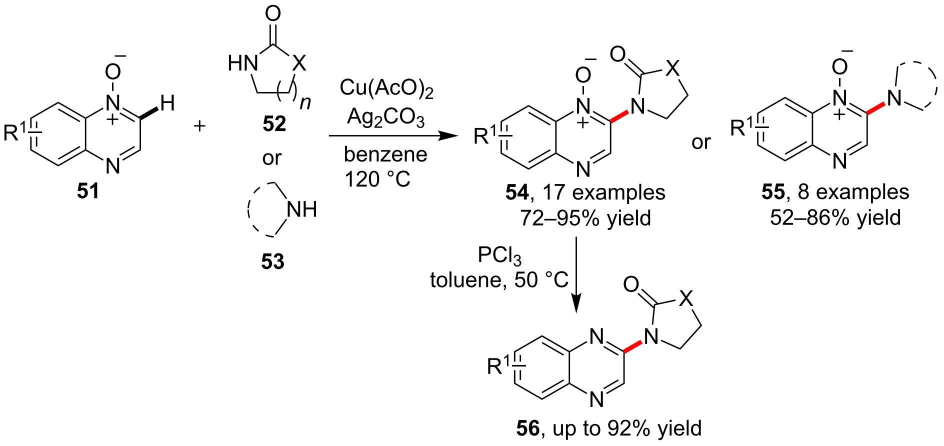


Scheme 13: Copper-catalyzed, 2-phenyl oxazole-assisted C–H amidation of benzamides.



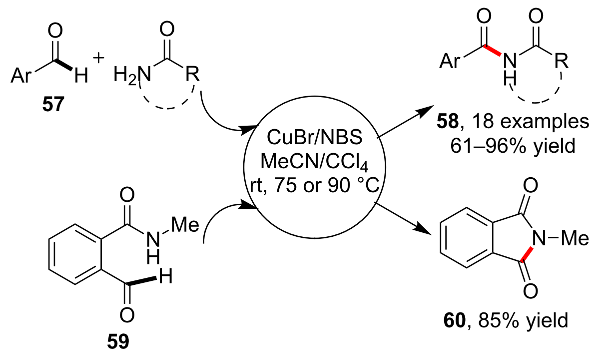
Scheme 14: DG-assisted amidation/imidation of indole and benzene C–H bonds.

their results, quinoline *N*-oxides **51** underwent C–H amidation with lactams **52** to yield 2-aminoquinoline *N*-oxides **54** with generally excellent yield. Notably, the catalytic system also allowed a C–H bond amination by using secondary amines **53** for the synthesis of 2-aminoquinoline *N*-oxides **55**. What's more, the *N*-oxides could be efficiently reduced to give the corresponding quinoline derivatives **56** by simply treating **54** with PCl_3 (Scheme 15).



Scheme 15: Copper-catalyzed C–H amination/amidation of quinoline *N*-oxides.

As another kind of conventional unsaturated hydrocarbons, the alkenes had been found to show similar reactivity with arenes in many cross coupling reactions. However, in the C–H amidation chemistry, the copper-catalyzed reactions of alkenes were rarely available. An interesting point was that the C(sp^2)–H bond at the C=O double bond had been known to possess the reactivity toward amidation via copper catalysis. In 2008, Fu and co-workers [65] reported the carbonyl C–H amidation of aryl aldehydes via the catalysis of CuBr and NBS. By simply stirring at rt, 75 or 90 °C, a variety of primary amides and lactams incorporated aldehydes **57** to yield imides **58** with moderate to excellent yield. In addition, the method also displayed sound application in the synthesis of cyclic imides such as *N*-methylphthalimide (**60**) via the intramolecular amidation of *N*-methyl-*o*-formylbenzamide (**59**) (Scheme 16).



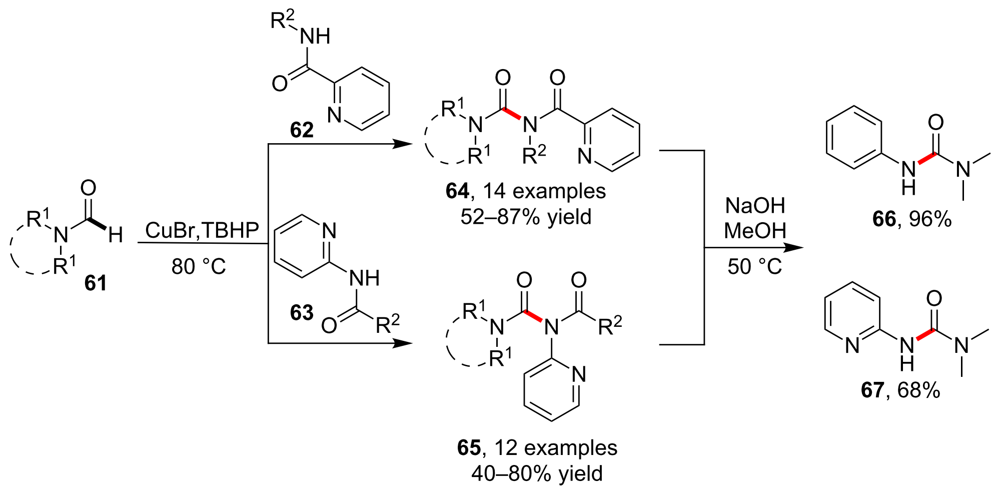
Scheme 16: Copper-catalyzed aldehyde formyl C–H amidation.

More recently, Lan et al. [66] realized the C–H amidation of *N,N*-dialkylformamides **61** using pyridine-2-yl-functionalized amides **62** or **63**. Under catalytic conditions consist of CuBr and TBHP, imides **64** and **65** were afforded, respectively. The imide products **64** and **65** could both be efficiently hydrolyzed to provide ureas **66** and **67**. The presence of the pyridine ring in substrates **62** and **63** was crucial for the conversion of the inert carbonyl C–H bond in **61** by chelating the copper catalyst (Scheme 17).

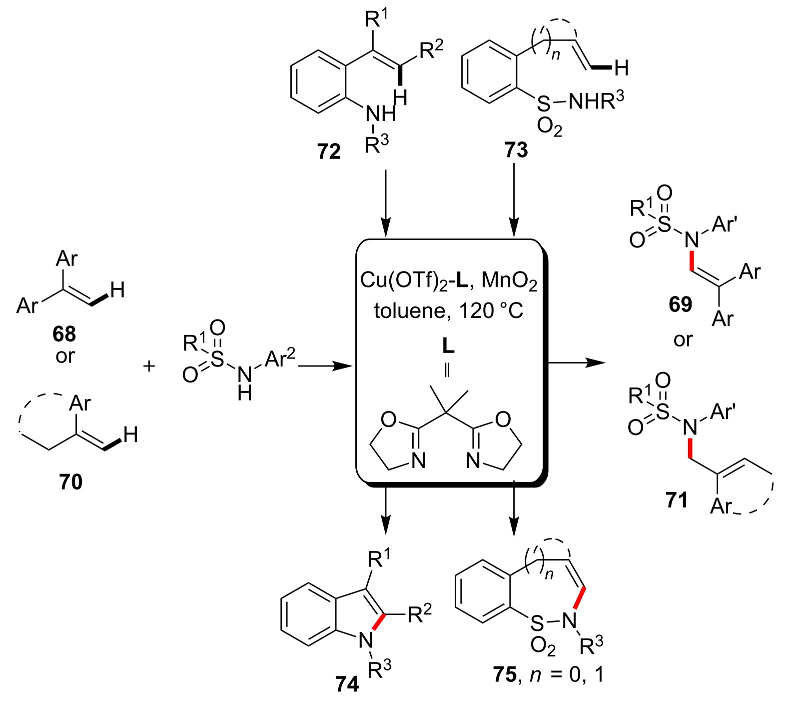
The C–H bond sulfonamidation of alkene substrates were systematically investigated by Chemler and co-workers. For example, they [67] developed the copper-catalyzed protocol for the sulfonamidation reaction of alkenes **68** via direct C–H activation to provide *N*-vinylsufonamides **69** in the presence of an oxazoline ligand. On the other hand, the reaction of allylic substrates **70** gave *N*-allylsulfonamides **71**. The catalytic approach was also well tolerable to the intramolecular version for the synthesis of indoles **74** and cyclic sulfonamides **75** by using **72** and **73** as starting materials, respectively (Scheme 18). The intramolecular version of the reaction in the synthesis of indoles was later achieved by mean of ligand-free condition via the co-catalysis of Cu(eh)$_2$ (copper(II) 2-ethylhexanoate) and TEMPO under oxygen atmosphere [68].

C(sp)–H bond amidation

The C(sp)–H bond in terminal alkynes is more acidic than equivalent alkane and alkene C–H bonds, and the alkynylation reactions by making use of direct transformations on the alkyne C–H bonds such as Sonograshira, Glaser couplings were extensively studied and utilized [69-72]. Under the inspiration of these well-known reaction models, the amidation reaction based on the activation of alkyne C–H bonds were also implemented. In 2008, Stahl et al. [73] reported the first copper-catalyzed alkyne amidation via the oxidation with molecular oxygen. The synthetic protocol exhibited excellent tolerance to the C–H

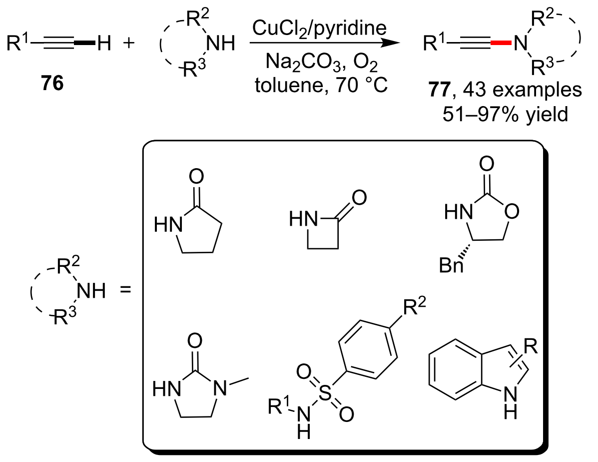


Scheme 17: Copper-catalyzed formamide C–H amidation.



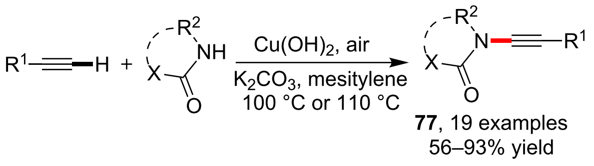
Scheme 18: Copper-catalyzed sulfonamidation of vinyl C–H bonds.

functionalization by reacting not only with lactams, but also with cyclic imides, carbamates, sulfonamides and indoles. On the other hand, the successful amidation using different alkynes, including aryl-, alkyl- and silyl-functionalized alkynes proved the broad scope of application of this method (Scheme 19).



Scheme 19: $CuCl_2$-catalyzed amidation/sulfonamidation of alkynyl C–H bonds.

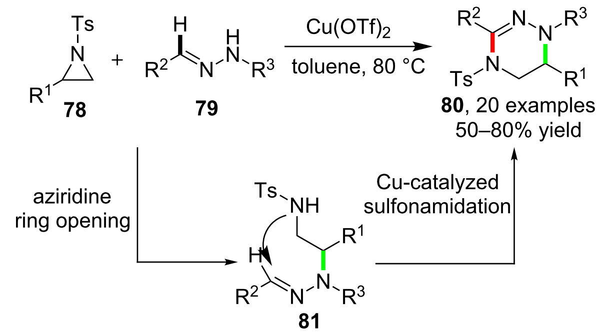
Following the design of this method, a heterogeneous catalytic protocol was later developed by Mizuno et al. [74] for the amidation of terminal alkynes using lactam, sulfonamide or cyclic carbamates. The application of $Cu(OH)_2$ as heterogeneous catalyst allowed the synthesis of ynamides **77** with moderate to excellent yield under air (Scheme 20). A latest work on this area from Truong et al. [75] showed that the heterogeneous and recyclable $Cu_2(BDC)_2(BPY)$ catalyst (BDC = benzene- 1,4-dicarboxylate; BPY = 4,4′-bipyridine) could catalyze this kind of amidation reaction with excellent selectivity to provide ynamides. Another point was that the C–H bond could also get aminated by using secondary amines such as diphenylamine.



Scheme 20: $Cu(OH)_2$-catalyzed amidation/sulfonamidation of alkynyl C–H bonds.

C–H bond amidation in cascade reactions

The success of these different kinds of C–H amidation reactions, as aforementioned, enabled the facile synthesis of diverse secondary or tertiary amides by installing a new chemical motif to the nitrogen atom. On the other hand, designing cascade reactions by employing the C–H amidation constituted another issue of extensive interest since these reactions enabled the construction of more complex and diverse products via the formation of multiple chemical bonds in one step operation. Early in 2009, Lin and Wang et al. [76] reported the cascade reactions between *N*-tosylaziridines **78** and hydrazones **79** which led to the synthesis of tetrahydrotriazines **80**. The cascade aziridine ring opening and copper-catalyzed intramolecular C–H sulfonamidation via intermediate **81** characterizes the whole reaction process (Scheme 21).

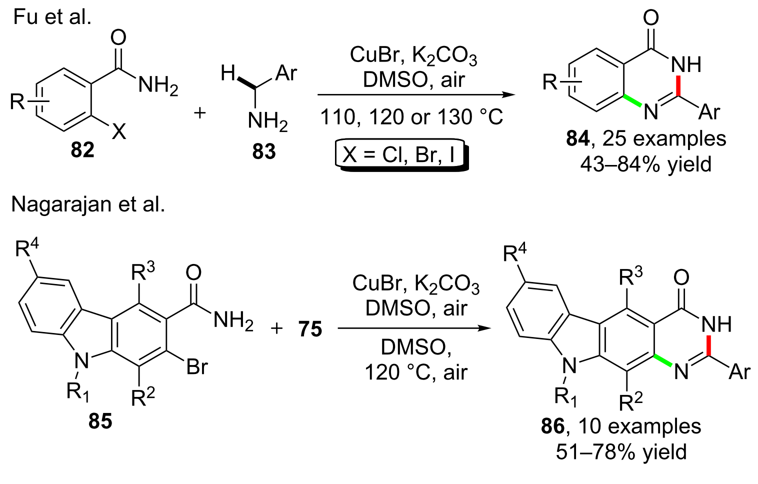


Scheme 21: Sulfonamidation-based cascade reaction for the synthesis of tetrahydrotriazines.

During their efforts in developing cascade reactions for the synthesis of heterocycles, Fu and co-workers [77] established a method for the synthesis of quinazolinones **84** through the reactions between *o*-halobenzamides **82** and benzylamines **83**. The formation of the target products were realized via a tandem Ullmann-type C–N coupling of the Ar–X bond and the amino group in **83** as well as the intramolecular amidation which was believed to assist the oxidative formation of the imine C=N bond (Scheme 22). By making use of this cascade synthetic method, Nagarajan et al. [78] finished the synthesis of various polycyclic structured quinazolinones **86** via corresponding starting materials **85** which were synthesized before by stepwise preparation (Scheme 22).

Based on a similar strategy of combining an Ullmann C–N bond formation and C–H amidation, Fu and Xu [79] also achieved the cascade reactions of o-halobenzamides **82** and (benzo)imidazoles **87** for the one-pot synthesis of (benzo)imidazoquinazolinones **88** under the catalysis of CuI and assistance of L-proline. A subsequent oxidation using molecular oxygen was required for the final formation of products. According to the results, the mechanism of the cascade reactions was proposed as shown in Scheme 23 wherein the intermediate **89** generated by Ullmann C–N coupling reaction, the bidentate copper complex **90** and **91** were assumed as the key stages of the cascade reaction. Recently, cascade reactions using analogous *o*-halobenzenesulfonamide **92** were disclosed by Wang et al. [80]. The synthesis using **92** and benzimidazoles **87** provided benzimidazole-fused cyclic sulfonamides **93**. The reaction allowed the synthesis of various products with fair to high yields with the assistance of L-proline as ligand. The expected conversion took place also in the absence of a ligand, but with evidently lower yield than the equivalent reaction with ligand (Scheme 23).

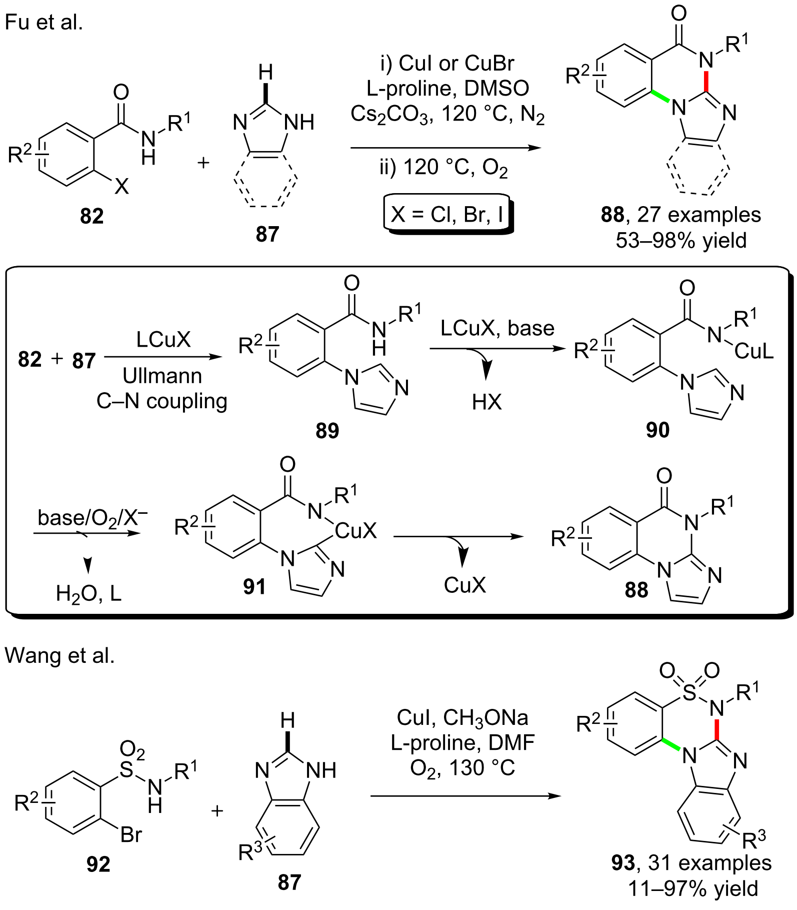
Based on a novel cascade reaction, the synthesis of quinazolinones was realized by employing *o*-aminobenzamides and methylated electron-deficient heterocycles. As reported by Han et al, the catalysis of CuCl enabled the cascade reactions between *o*-aminobenzamides **94** and 2-methylheteroaryls **95** and led to the synthesis of quinazolinones **96** via the formation of C=N and C–N bonds in the presence of Ph_2PO_2H and oxygen. For the methylated component **95**, the application



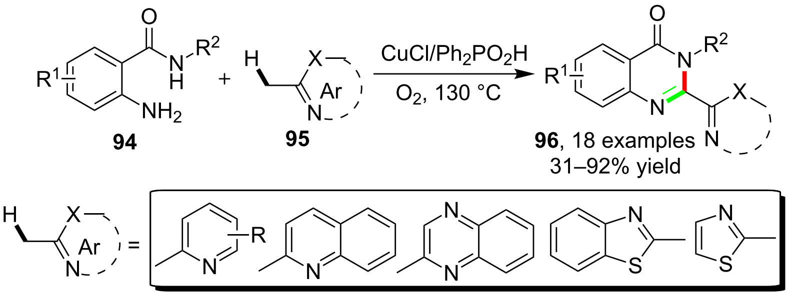
Scheme 22: Copper-catalyzed cascade reaction for the synthesis of quinazolinones.

scope of the synthesis focused on the electron deficient reactants such as 2-methylpyridine, 2-methylquinoline, 2-methylquinoxalines, 2-methylthiazole and 2-methylbenzothiazole, other methylated heterocycle such as 3-methylpyridine was not tolerated (Scheme 24) [81].

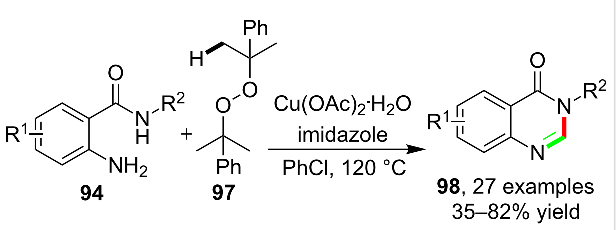
Similar quinaxolinone products were also successfully synthesized by the incorporation of *o*-aminobenzamides and a novel peroxide-based methyl donor. Wang and co-workers [82] found that the reactions of **94** with dicumyl peroxide **97** could provide 2-unsubstituted quinazolinones **98** with broad diversity. In these reactions, the dicumyl peroxide acted as the methyl donor to provide a methyl radical as the precursor of the methyl cation which was crucial for the subsequent annulation. The radical process of the reaction was also supported by the EPR experiment (Scheme 25).



Scheme 23: Copper-catalyzed cascade reactions for the synthesis of fused quinazolinones.



Scheme 24: Copper-catalyzed synthesis of quinazolinones via methyl C–H bond amidation.



Scheme 25: Dicumyl peroxide-based cascade synthesis of quinazolinones.

While most of the known C–H amidation-based cascade reactions afforded six-membered or related ring-fused products, the formation of other ring sized scaffolds such as five-membered structure were much less. An interesting cascade reaction between DG-functionalized benzamides **99** and malonates **100**, which enabled the synthesis of indolinones **101** via selective C–C and C–N bond construction, was reported by Dai and Yu et al. [83]. As outlined in Scheme 26, the presence of the oxazole-based DG was found to be the main factor in tuning the selective formation of **101**. Related control experiments suggested that the formation of intermediate **102** acquired from the copper-catalyzed C(sp^2)–C(sp^3) bond formation was the key transformation of the cascade process.

Conclusion

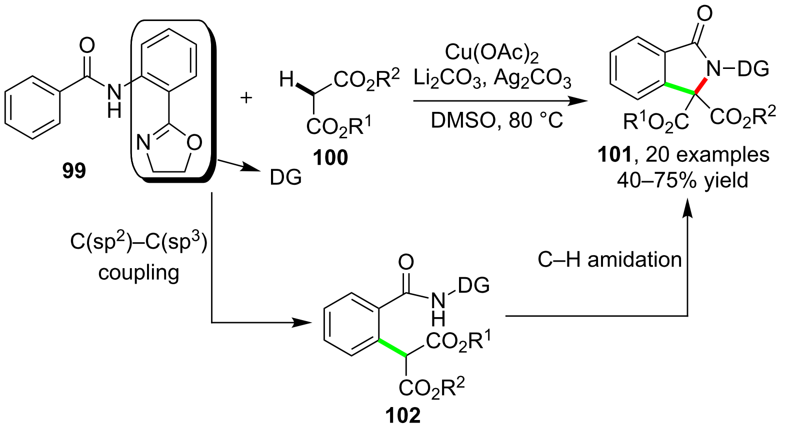
On the basis of the magnificent advances taking place in the chemistry of the C–H activation, the synthesis and elaboration of amides has won new opportunity via a more economical and simple process. With the copper-catalyzed amidation of C(sp^3)–H, C(sp^2)–H, C(sp)–H bonds, a large variety of different products have been successfully synthesized via either single bond formation or cascade construction of more than one bond. These successful examples convincingly demonstrated the application potential of the C–H amidation in organic synthesis. On the other hand, it should also be noted that challenges still remain in presently known results of C–H amidations. For example, the copper-catalyzed amidation of olefinic C(sp^2)–H bonds is still hardly available, and the heating to high temperatures for most of the C–H amidation-based transformation is another point demanding urgent improvement. The significance of the C–H amidation reactions, together with the unsolved problems in the known investigations, discloses the huge chemical space remained in the research field, and much more interesting results are expected in future from the chemistry related to the C–H amidation.

Acknowledgements

The authors thank the Natural and Science Foundation of China (no. 21562025) and Natural and Science Foundation of Jiangxi Province (no. 20151BAB203008) for financial support.

References

1. Sewald, N.; Jakubke, H. D. *Peptides: Chemistry and Biology;* Wiley-VCH: Weinheim, Germany, 2002.
2. Greenberg, A.; Breneman, C. M.; Liebman, J. F. *Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Materials Science;* Wiley-Interscience: New York, NY, U.S.A., 2000.
3. Alécio, A. C.; da Silva Bolzani, V.; Young, M. C. M.; Kato, M. J.; Furlan, M. *J. Nat. Prod.* **1998,** *61,* 637. doi:10.1021/np9703656
4. Yuan, Z. Q.; Blomberg, D.; Sethson, I.; Brickmann, K.; Ekholm, K.; Johansson, B.; Nilsson, A.; Kihlberg, J. *J. Med. Chem.* **2002,** *45,* 2512. doi:10.1021/jm0110744
5. Beckwith, A. L. J. Synthesis of amides. In *Amides;* Zabicky, J., Ed.; John Wiley & Sons: New York, NY, U.S.A., 2010.
6. Métro, T.-X.; Bonnamour, J.; Reidon, T.; Sarpoulet, J.; Martinez, J.; Lamaty, F. *Chem. Commun.* **2012,** *48,* 11781. doi:10.1039/c2cc36352f
7. Duagkamol, C.; Jaita, S.; Wangngae, S.; Phakhodee, W.; Pattarawarapan, M. *RSC Adv.* **2015,** *5,* 52624. doi:10.1039/C5RA10127A



Scheme 26: Copper-catalyzed cascade reactions for the synthesis of indolinones.

8. Khalafi-Nezhad, A.; Parhami, A.; Rad, M. N. S.; Zarea, A. *Tetrahedron Lett.* **2005,** *46,* 6879. doi:10.1016/j.tetlet.2005.08.021
9. Goossen, L. J.; Ohlmann, D. M.; Lange, P. P. *Synthesis* **2009,** 160. doi:10.1055/s-0028-1083277
10. Gernigon, N.; Al-Zoubi, R. M.; Hall, D. G. *J. Org. Chem.* **2012,** *77,* 8386. doi:10.1021/jo3013258
11. El-Faham, A.; Albericio, F. *Chem. Rev.* **2011,** *111,* 6557. doi:10.1021/cr100048w
12. Mauger, J.; Nagasawa, T.; Yamada, H. *Tetrahedron* **1989,** *45,* 1347. doi:10.1016/0040-4020(89)80133-4
13. Yamaguchi, K.; Matsushita, M.; Mizuno, N. *Angew. Chem., Int. Ed.* **2004,** *43,* 1576. doi:10.1002/anie.200353461
14. Moorthy, J. N.; Singhal, N. *J. Org. Chem.* **2005,** *70,* 1926. doi:10.1021/jo048240a
15. Battilocchio, C.; Hawkins, J. M.; Ley, S. V. *Org. Lett.* **2014,** *16,* 1060. doi:10.1021/ol403591c
16. Polshettiwar, V.; Varma, R. S. *Chem. – Eur. J.* **2009,** *15,* 1582. doi:10.1002/chem.200802264
17. Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003,** 2428. doi:10.1055/s-2003-42473
18. Ghosh, S. C.; Ngiam, J. S. Y.; Seayad, A. M.; Tuan, D. T.; Chai, C. L. L.; Chen, A. *J. Org. Chem.* **2012,** *77,* 8007. doi:10.1021/jo301252c
19. Rodríguez-Lugo, R. E.; Trincado, M.; Grützmacher, H. *ChemCatChem* **2013,** *5,* 1079. doi:10.1002/cctc.201200495
20. Saberi, D.; Heydari, A. *Appl. Organomet. Chem.* **2014,** *28,* 101. doi:10.1002/aoc.3087
21. Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* **2006,** *128,* 13064. doi:10.1021/ja064315b
22. Gao, J.; Wang, G.-W. *J. Org. Chem.* **2008,** *73,* 2955. doi:10.1021/jo800075t
23. Suto, Y.; Yamagiwa, N.; Torisawa, Y. *Tetrahedron Lett.* **2008,** *49,* 5732. doi:10.1016/j.tetlet.2008.07.075
24. Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003,** *125,* 3422. doi:10.1021/ja028242h
25. Nguyen, T. B.; Sorres, J.; Tran, M. Q.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2012,** *14,* 3202. doi:10.1021/ol301308c
26. Zhang, M.; Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Matthias, B. *Angew. Chem., Int. Ed.* **2012,** *51,* 3905. doi:10.1002/anie.201108599
27. Allen, C. L.; Atkinson, B. N.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2012,** *51,* 1383. doi:10.1002/anie.201107348
28. Becerra-Figueroa, L.; Ojeda-Porras, A.; Gamba-Sánchez, D. *J. Org. Chem.* **2014,** *79,* 4544. doi:10.1021/jo500562w
29. Fu, R.; Yang, Y.; Chen, Z.; Lai, W.; Ma, Y.; Wang, Q.; Yuan, R. *Tetrahedron* **2014,** *70,* 9492. doi:10.1016/j.tet.2014.10.066
30. Furuya, Y.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2005,** *127,* 11240. doi:10.1021/ja053441x
31. Umbreen, S.; Linker, T. *Chem. – Eur. J.* **2015,** *21,* 7340. doi:10.1002/chem.201406546
32. Hashimoto, M.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2008,** *73,* 2894. doi:10.1021/jo702277g
33. Li, Y.; Wang, K.; Qin, K.; Wang, T. *RSC Adv.* **2015,** *5,* 25365. doi:10.1039/C5RA01929J
34. Gephart, R. T., III; Warren, T. H. *Organometallics* **2012,** *31,* 7728. doi:10.1021/om300840z
35. Chemler, S. R. *Science* **2013,** *341,* 624. doi:10.1126/science.1237175
36. Kumaraswamy, G.; Pitchaiah, A.; Ramakrishna, G.; Ramakrishna, D. S.; Sadaiah, K. *Tetrahedron Lett.* **2006,** *47,* 2013. doi:10.1016/j.tetlet.2006.01.050
37. Laha, J. K.; Shah, P. U.; Jethava, K. P. *Chem. Commun.* **2013,** *49,* 7623. doi:10.1039/c3cc43835j
38. Apsunde, T. D.; Trudell, M. L. *Synthesis* **2014,** *46,* 230. doi:10.1055/s-0033-1340142
39. Yu, X.; Jiang, L.; Li, Q.; Xie, Y.; Xu, Q. *Chin. J. Chem.* **2012,** *30,* 2322. doi:10.1002/cjoc.201200462
40. Rao, S. N.; Mohan, D. C.; Adimurthy, S. *Org. Lett.* **2013,** *15,* 1496. doi:10.1021/ol4002625
41. Li, F.; Qu, P.; Ma, J.; Zou, X.; Sun, C. *ChemCatChem* **2013,** *5,* 2178. doi:10.1002/cctc.201300140
42. Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2007,** *9,* 3813. doi:10.1021/ol701715m
43. Liu, X.; Zhang, Y.; Wang, L.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008,** *73,* 6207. doi:10.1021/jo800624m
44. Pelletier, G.; Powell, D. A. *Org. Lett.* **2006,** *8,* 6031. doi:10.1021/ol062514u
45. Clark, J. S.; Roche, C. *Chem. Commun.* **2005,** 5175. doi:10.1039/b509678b
46. Powell, D. A.; Fan, H. *J. Org. Chem.* **2010,** *75,* 2726. doi:10.1021/jo100197r
47. Fructos, M. R.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2006,** *128,* 11784. doi:10.1021/ja0627850
48. Albone, D. P.; Aujla, P. S.; Taylor, P. C. *J. Org. Chem.* **1998,** *63,* 9569. doi:10.1021/jo981335q
49. He, L.; Yu, J.; Zhang, J.; Yu, X.-Q. *Org. Lett.* **2007,** *9,* 2277. doi:10.1021/ol070537i
50. Tran, B. L.; Li, B.; Driess, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014,** *136,* 2555. doi:10.1021/ja411912p
51. Teng, F.; Sun, S.; Jiang, Y.; Yu, J.-T.; Cheng, J. *Chem. Commun.* **2015,** *51,* 5902. doi:10.1039/C5CC00839E
52. Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2014,** *53,* 3496. doi:10.1002/anie.201311105
53. Wu, X.; Zhao, Y.; Zhang, G.; Ge, H. *Angew. Chem., Int. Ed.* **2014,** *53,* 3706. doi:10.1002/anie.201311263
54. Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009,** *11,* 5178. doi:10.1021/ol902079g
55. Wang, S.; Ni, Z.; Huang, X.; Wang, J.; Pan, Y. *Org. Lett.* **2014,** *16,* 5648. doi:10.1021/ol502724u
56. Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C.-J. *Adv. Synth. Catal.* **2010,** *352,* 632. doi:10.1002/adsc.200900775
57. Santoro, S.; Liao, R.-Z.; Himo, F. *J. Org. Chem.* **2011,** *76,* 9246. doi:10.1021/jo201447e
58. John, A.; Nicholas, K. M. *J. Org. Chem.* **2011,** *76,* 4158. doi:10.1021/jo200409h
59. Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014,** *136,* 3354. doi:10.1021/ja412880r
60. Xu, H.; Qiao, X.; Yang, S.; Shen, Z. *J. Org. Chem.* **2014,** *79,* 4414. doi:10.1021/jo5003592
61. Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009,** *131,* 13888. doi:10.1021/ja902762a
62. Gong, X.; Song, G.; Zhang, H.; Li, X. *Org. Lett.* **2011,** *13,* 1766. doi:10.1021/ol200306y
63. Wu, Z.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *Adv. Synth. Catal.* **2013,** *355,* 1971. doi:10.1002/adsc.201300111
64. Li, G.; Jia, C.; Sun, K. *Org. Lett.* **2013,** *15,* 5198. doi:10.1021/ol402324v
65. Wang, L.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. – Eur. J.* **2008,** *14,* 10722. doi:10.1002/chem.200801620
66. Li, X.; Li, B.; You, J.; Lan, J. *Org. Biomol. Chem.* **2013,** *11,* 1925. doi:10.1039/c3ob40094h

67. Liwosz, T. W.; Chemler, S. R. *Chem. – Eur. J.* **2013,** *19,* 12771. doi:10.1002/chem.201301800
68. Liwosz, T. W.; Chemler, S. R. *Synlett* **2015,** *26,* 335. doi:10.1055/s-0034-1379015
69. Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007,** *107,* 874. doi:10.1021/cr050992x
70. Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011,** *40,* 5084. doi:10.1039/c1cs15071e
71. Liu, Y.; Wang, C.; Wang, X.; Wan, J.-P. *Tetrahedron Lett.* **2013,** *54,* 3953. doi:10.1016/j.tetlet.2013.05.063
72. Wan, J.-P.; Cao, S.; Jing, Y. *Appl. Organomet. Chem.* **2014,** *28,* 631. doi:10.1002/aoc.3172
73. Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008,** *130,* 833. doi:10.1021/ja077406x
74. Jin, X.; Yamaguchi, K.; Mizuno, N. *Chem. Commun.* **2012,** *48,* 4974. doi:10.1039/c2cc31159c
75. Le, H. T. N.; Tran, T. V.; Phan, N. T. S.; Truong, T. *Catal. Sci. Technol.* **2015,** *5,* 851. doi:10.1039/C4CY01074D
76. Hong, D.; Lin, X.; Zhu, Y.; Lei, M.; Wang, Y. *Org. Lett.* **2009,** *11,* 5678. doi:10.1021/ol902376w
77. Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Org. Lett.* **2011,** *13,* 1274. doi:10.1021/ol1030266
78. Sreenivas, D. K.; Ramkumar, N.; Nagarajan, R. *Org. Biomol. Chem.* **2012,** *10,* 3417. doi:10.1039/c2ob07179g
79. Xu, H.; Fu, H. *Chem. – Eur. J.* **2012,** *18,* 1180. doi:10.1002/chem.201102794
80. Yang, D.; An, B.; Wei, W.; Tian, L.; Huang, B.; Wang, H. *ACS Comb. Sci.* **2015,** *17,* 113. doi:10.1021/co500125n
81. Li, Q.; Huang, Y.; Chen, T.; Zhou, Y.; Xu, Q.; Yin, S.-F.; Han, L.-B. *Org. Lett.* **2014,** *16,* 3672. doi:10.1021/ol501454j
82. Bao, Y.; Yan, Y.; Xu, K.; Su, J.; Zha, Z.; Wang, Z. *J. Org. Chem.* **2015,** *80,* 4736. doi:10.1021/acs.joc.5b00191
83. Wang, H.-L.; Shang, M.; Sun, S.-Z.; Zhou, Z.-L.; Laforteza, B. N.; Da, H.-X.; Yu, J.-Q. *Org. Lett.* **2015,** *17,* 1228. doi:10.1021/acs.orglett.5b00193

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The definitive version of this article is the electronic one which can be found at:
doi:10.3762/bjoc.11.240

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Recent developments in copper-catalyzed radical alkylations of electron-rich π-systems

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Review

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Keywords:
alkene; alkylation; alkyne; catalysis; copper; nitroalkane; radical

Beilstein J. Org. Chem. **2015,** *11,* 2278–2288.
doi:10.3762/bjoc.11.248

Received: 04 September 2015
Accepted: 04 November 2015
Published: 23 November 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

Recently, a number of papers have emerged demonstrating copper-catalyzed alkylation reactions of electron-rich small molecules. The processes are generally thought to be related to long established atom-transfer radical reactions. However, unlike classical reactions, these new transformations lead to simple alkylation products. This short review will highlight recent advances in alkylations of nitronate anions, alkenes and alkynes, as well as discuss current mechanistic understanding of these novel reactions.

Introduction

Atom transfer radical (ATR) reactions are extremely useful in organic synthesis and polymer chemistry [1]. These reactions have been used extensively in polymer chemistry because of the ability of alkyl radicals to participate in chain reactions [2-4]. They have also been used extensively in small molecule synthesis, particularly in an intramolecular cyclization setting [5-9]. However, while the ability of alkyl radicals to add to electron-rich π-systems is well established [10-13], harnessing this mode of reactivity to provide products of intermolecular alkylation would be highly valuable in organic synthesis. Although various metals have been shown to promote radical polymerizations, copper is by far the most common and effective [14].

Recently, several groups, including our own, have developed copper-catalyzed alkylation reactions of molecules containing electron-rich π-systems. These reactions all utilize alkyl halides as the alkylating agent, and deliver reactivity that is not observed in the non-catalyzed reactions. Mechanistically, it is believed that these reactions all share features of classic ATR reactions, but are distinct as they deliver simple alkylation products. These transformations represent a new paradigm in copper-catalyzed radical reactions. This article will highlight recent examples from this emergent area, including copper-catalyzed alkylation reactions of nitroalkanes, alkenes and alkynes.

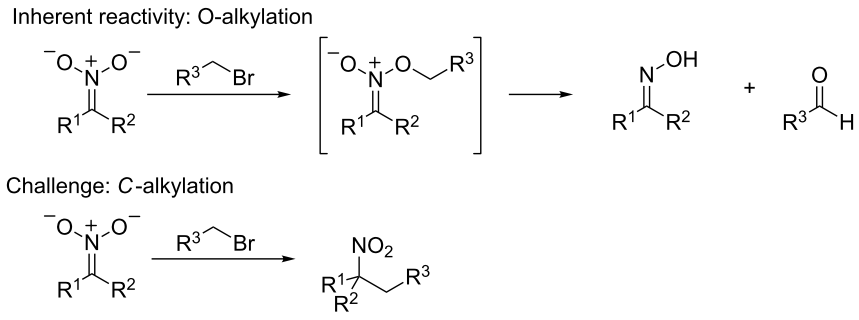
Results and Discussion

Additions to nitronate anions

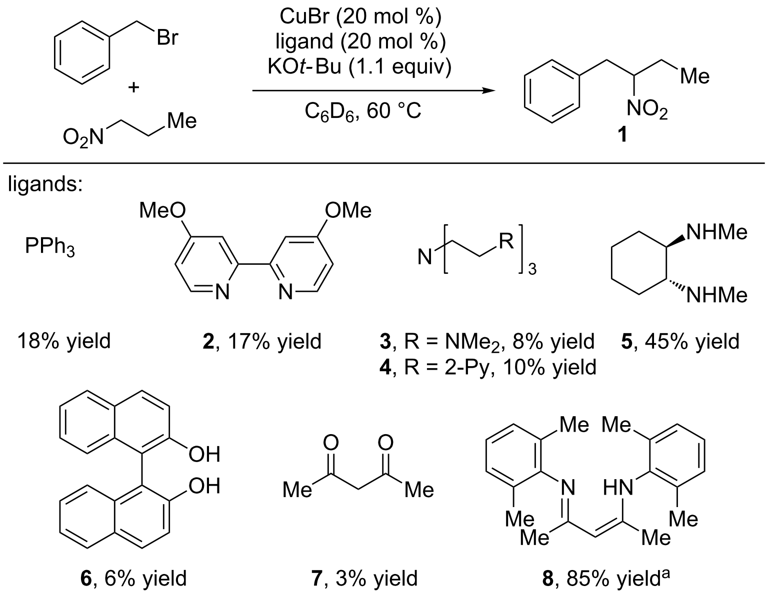
The selective *C*-alkylation of nitroalkanes with alkyl halide electrophiles is a long-standing challenge in organic synthesis (Scheme 1). This is mainly because of the propensity of nitronate anions to undergo alkylation at oxygen rather than carbon, a process that has been known for more than 60 years [15]. Recently, our group has developed a copper/diketimine catalyst system to selectively *C*-alkylate nitroalkanes [16]. While nitronate anions are known to undergo alkylation with alkyl radicals, these radicals are often accessed using highly undesirable methods such as stoichiometric alkylmetal reagents or highly complex alkylating agents [17]. Although allylation [18-23] and arylation [24-26] of nitroalkanes using palladium catalysis were known, prior to our work, no general catalytic methods for the alkylation of nitroalkanes existed.

We envisioned that the catalytic generation of an alkyl radical under copper catalysis in the presence of a nitronate anion could lead to *C*-alkylated products. In optimizing the cross coupling of nitroalkanes and benzyl halides, it was clear that the nature of the ligand had a profound effect on the reaction. Various multidentate amine ligands, which are commonly used in ATR reactions, were not effective in the reaction, affording low yields of product and significant amounts of products resulting from *O*-alkylation (Scheme 2). β-Diketimine (nacnac) ligands were determined to be highly effective for the reaction, providing high yields of *C*-alkylated products and only trace amounts of *O*-alkylated products. These types of ligands have recently found use in copper catalyzed C–H amination reactions, as reported by Warren and co-workers [27,28].

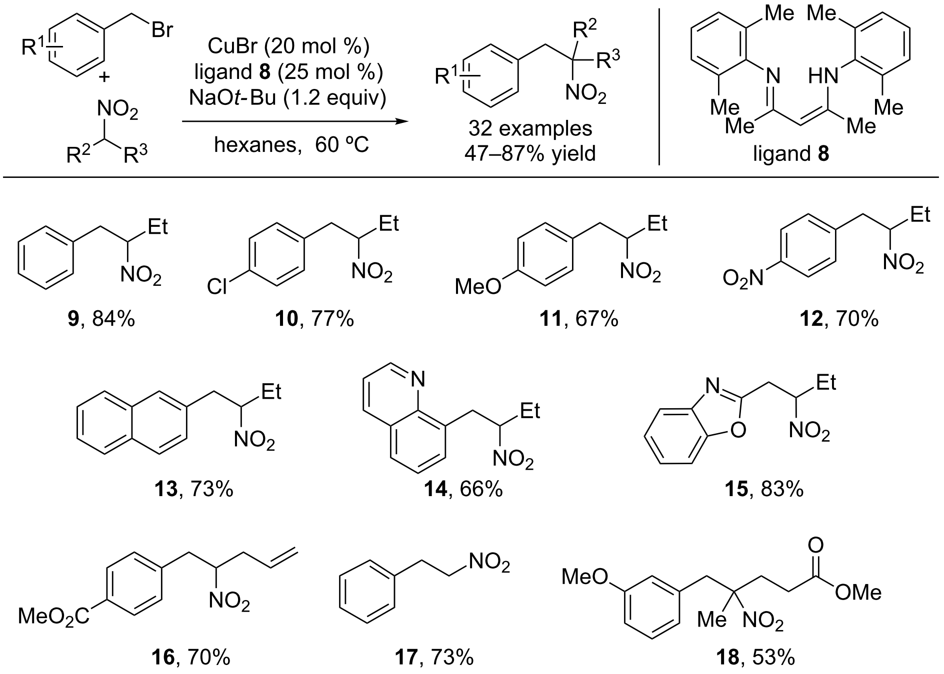
Using this mild copper-catalyzed system, β-arylnitroalkanes were produced in excellent yields (Scheme 3) [16]. The scope



Scheme 1: Reactivity of nitronate anions towards alkyl electrophiles.



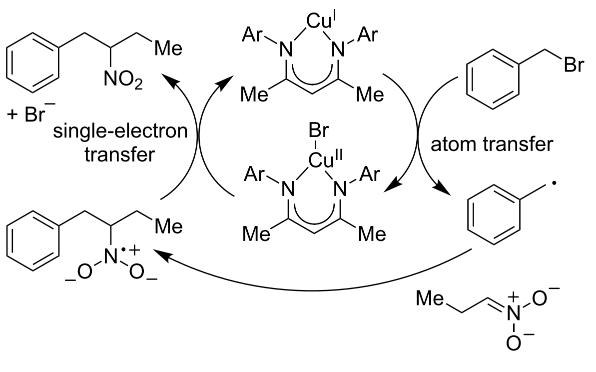
Scheme 2: Ligands tested in the alkylation of nitroalkanes with alkyl halides. [a]NaO*t*-Bu as base, hexanes as solvent.



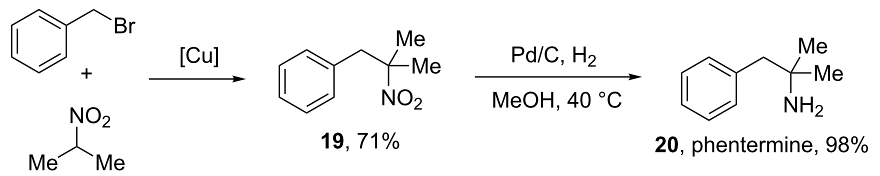
Scheme 3: Scope of the copper-catalyzed nitroalkane benzylation.

of this transformation is remarkably broad with respect to both coupling partners. Electron-rich, electron-poor and heterocyclic bromides were tolerated in very good yields. Primary and secondary nitroalkanes as well as nitromethane could be cross-coupled in excellent yields, providing access to nitroalkanes with diverse substitution patterns. Additionally, reduction of these products provides phenethylamine derivatives, many of which possess known biological activity. For instance, reduction of the fully substituted nitroalkane **19** provides phentermine (**20**), a clinically prescribed appetite suppressant (Scheme 4) [29,30].

While the precise mechanism of this transformation is not fully understood, evidence suggests that radical intermediates are involved in the bond forming step (Scheme 5). For instance, bibenzyl byproducts were observed in the cross-coupling of benzyl halides, suggesting a homodimerization of benzylic radicals. The reaction does not proceed in the presence of radical scavengers such as TEMPO. Radical clock experiments provided ring-opened products, suggesting the presence of intermediate radicals. We propose that this reaction proceeds via a thermal redox process. We hypothesize that the alkyl



Scheme 5: Possible mechanism of the thermal redox process.



Scheme 4: Application of the nitro-alkylation reaction to the synthesis of phentermine.

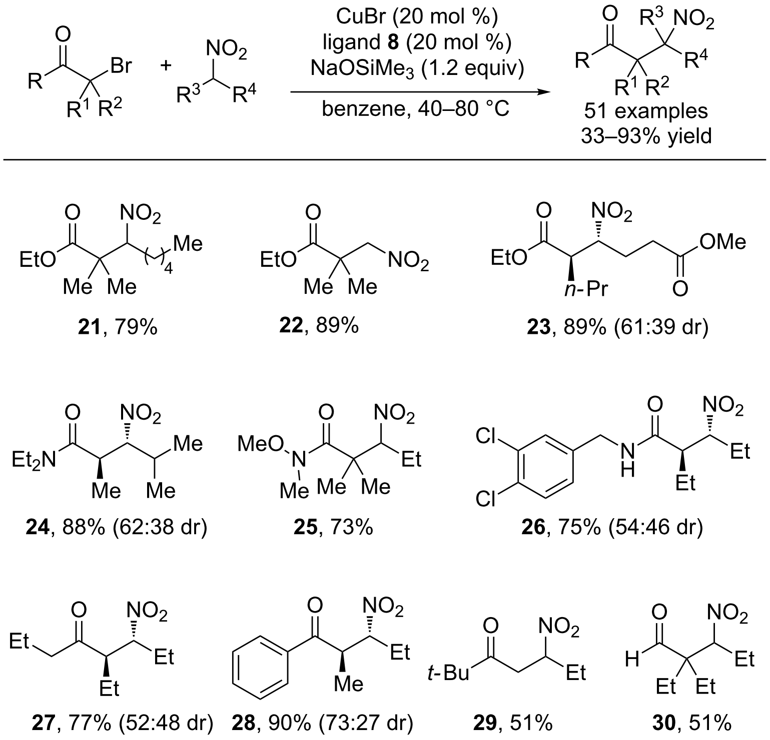
radical is formed by transfer of a bromine atom from the alkyl halide to the copper catalyst. The resultant stabilized alkyl radical then undergoes coupling with a nitronate anion, forging the C–C bond. Single electron transfer from the resultant radical anion to the Cu(II) halide results in the observed product while simultaneously reducing the metal center to regenerate the catalyst.

In subsequent studies, α-bromocarbonyls were shown to be effective coupling partners for nitronate anions under similar conditions (Scheme 6) [31]. Remarkably, α-bromo esters, ketones, amides and aldehydes all coupled efficiently with nitroalkanes to provide β-nitrocarbonyls in excellent yields. The steric threshold of this reaction is also highly notable in that β-nitrocarbonyls bearing contiguous quaternary carbons could be synthesized. Because of the ease of reduction of the nitro group, this cross-coupling procedure provides facile access to highly substituted β-amino acids (Scheme 7).

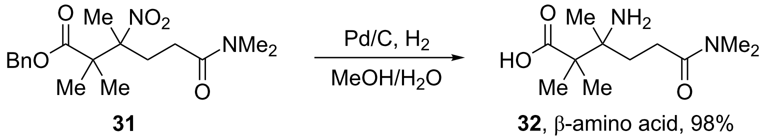
Additions to alkenes and alkynes

One of the burgeoning areas of copper-catalyzed cross-coupling chemistry is the alkenylation of alkyl halide substrates. This transformation is achieved via formation of a transient radical, addition to a π-system (an alkene or an alkyne), followed by elimination or reincorporation of a halide atom. This general scheme is outlined in Scheme 8.

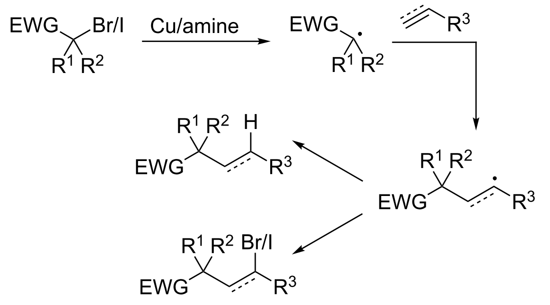
In 2013, Nishikata and co-workers reported that a copper/amine catalyst system catalyzes the alkenylation of tertiary alkyl bromides bearing an electron-withdrawing group [32]. As with many ATR reactions, multi-dentate amines were critical for the reaction. These types of ligands in conjunction with copper catalysts are known to promote the formation of stabilized carbon-centered radicals [14]. In this reaction, the putative tertiary radical undergoes addition to a styrene derivative, creating a stabilized benzylic radical. Akin to classic ATR manifolds, the authors propose that this radical abstracts a



Scheme 6: Scope of the reaction of nitroalkanes with α-bromocarbonyls.



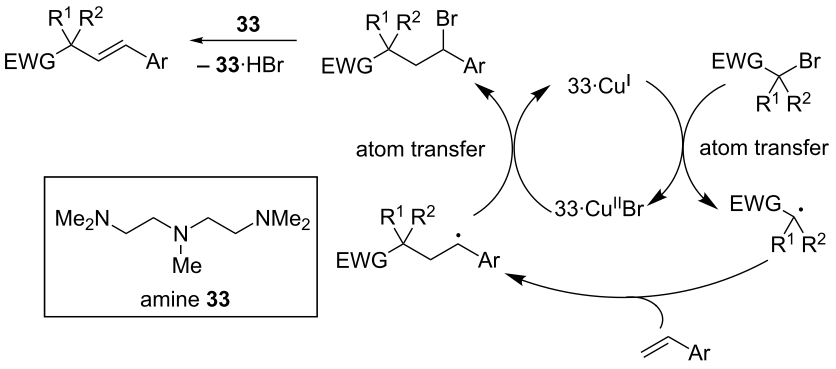
Scheme 7: Synthesis of highly congested β-amino acids.



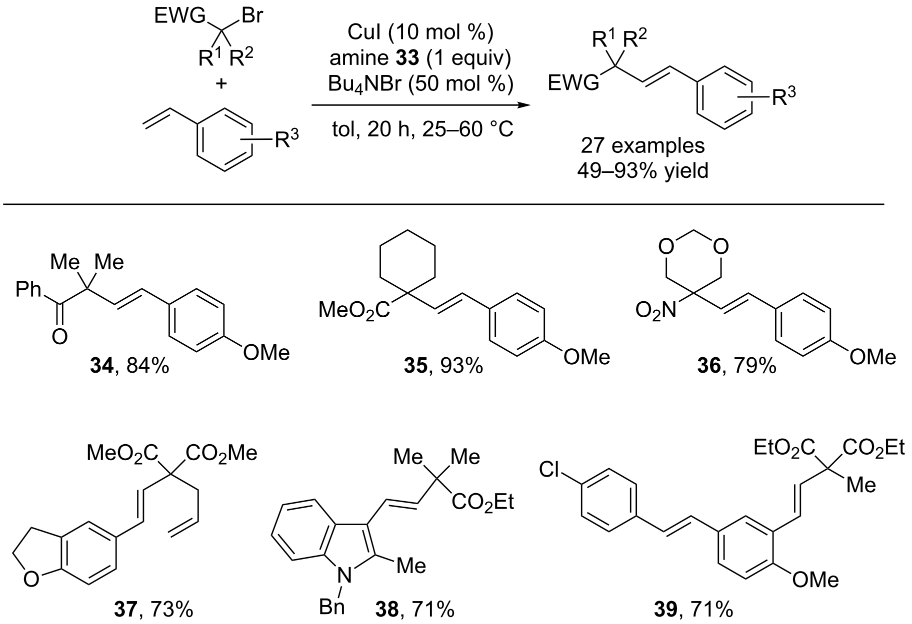
Scheme 8: Copper-catalyzed alkenylation reactions.

bromine atom from copper, regenerating the copper(I) catalyst and forming a benzylic halide. Unlike classical ATR reactions, the resultant alkyl halide then undergoes E_2 elimination, promoted by the included amine base, resulting in the observed product (Scheme 9). While the reaction conditions are similar to those utilized in atom transfer radical addition and polymerization reactions, the use of excess amine was critical for a robust alkenylation reaction and to avoid atom transfer and polymerization products.

Various electron-withdrawing groups including esters, ketones and nitro groups were tolerated in the alkyl bromide coupling partner (Scheme 10). In addition, the reaction shows excellent



Scheme 9: Proposed mechanism of the copper-catalyzed alkenylation reaction.



Scheme 10: Scope of the copper-catalyzed alkenylation of tertiary electrophiles.

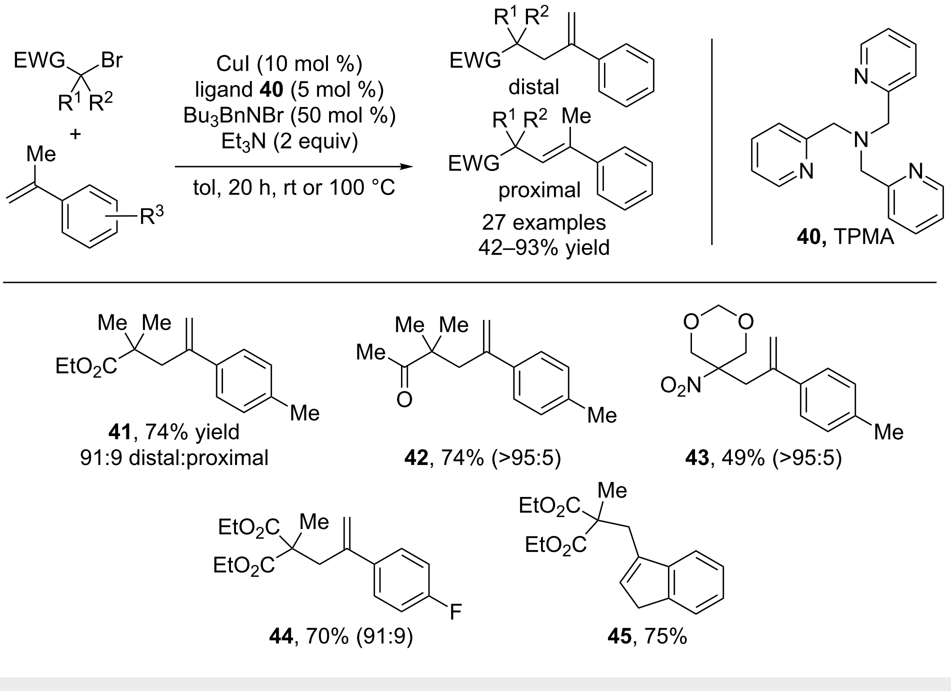
functional group compatibility with respect to the styrene coupling partner, tolerating ethers, nitriles, chlorides and amines. Notably, internal alkenes (such as **39**) were not affected during the reaction. Although the reaction proceeds via a distinct mechanism, the authors refer to the transformation as a formal Heck-type alkenylation of alkyl bromides.

As with the nitroalkane alkylation chemistry illustrated above, this reaction is a rare example of a transition metal-catalyzed cross coupling of tertiary alkyl halides. These types of reactions are often very difficult because of the propensity of the intermediate tertiary alkylmetal to undergo β-hydrogen elimination [33-35]. By developing a reaction that proceeds via tertiary alkyl radicals, these strategies have elegantly circumvented this problem and have expanded the scope of alkyl cross-coupling reactions.

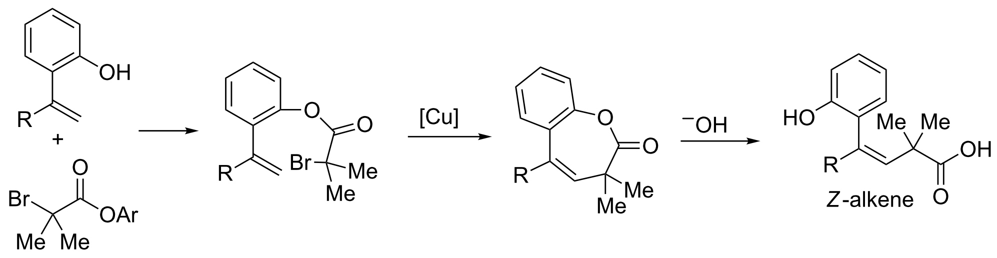
Nishikata has subsequently expanded the utility of this reaction manifold by elegant tailoring of the radical donor and acceptor [36]. If the styrene radical acceptor bears an alkyl group at the α-position, elimination happens preferentially from this position to provide exo-methylene styrenes (Scheme 11). In this case, tris(2-pyridylmethyl)amine (TPMA) was utilized as the ligand, along with excess amine base. Styrenes were produced in high yield with excellent selectivity for the exo-methylene products. The high levels of distal selectivity are proposed to arise from steric contributions. The intermediate alkyl bromide that results from the initial atom transfer possesses two possible sites of elimination. The authors propose that the distal hydrogen is more accessible to the bulky amine base. Similar to the aforementioned direct alkenylation, the reaction displays excellent functional group tolerance. α-Bromo esters, ketones, and nitroalkanes all coupled smoothly to form exo-methylene compounds. Again, excess amine was crucial to promote the desired transformation and supress polymerization.

A detachable ester group can be utilized in order to achieve *Z*-selective alkene synthesis [37]. In this protocol, an *ortho*-hydroxy substituted styrene undergoes esterification with a labile α-bromo ester. This positions the reactive radical exclusively on the face of the alkene leading to the *Z* product (Scheme 12). After cross coupling, the ester can be hydrolyzed to provide exclusively the *Z*-alkene product (Scheme 13). This protocol is complementary to the initially reported alkenylation of tertiary alkyl bromides, which resulted exclusively in *E*-alkene products.

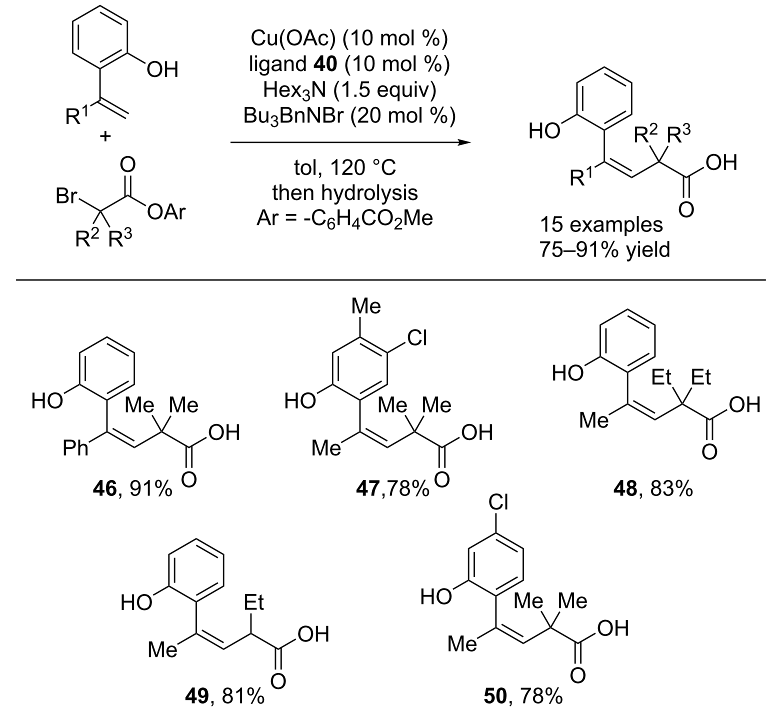
When the alkyl bromide coupling partner was changed to an α-bromo keto ester, the radical addition is followed by a tautomerization/cyclization event that provides dihydrofurans in excellent yields [38]. The radical formation/addition events proceed largely in the same manner as the aforementioned alkenylation reactions. However, the product of addition of a secondary bromo keto ester possesses an acidic α-proton. This proton can be deprotonated by diisopropylamine, and the resulting enolate cyclizes onto the newly formed benzylic halide



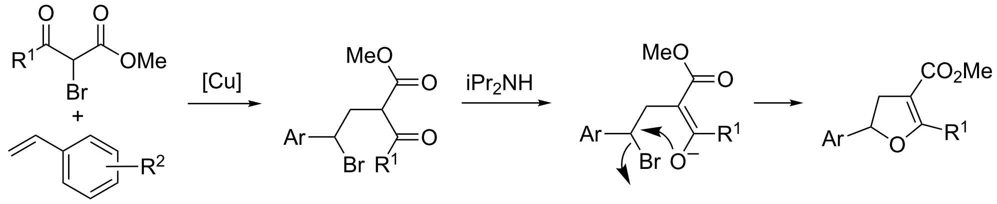
Scheme 11: Scope of the exo-methylene styrene synthesis.



Scheme 12: Phenol-directed synthesis of *Z*-alkenes.

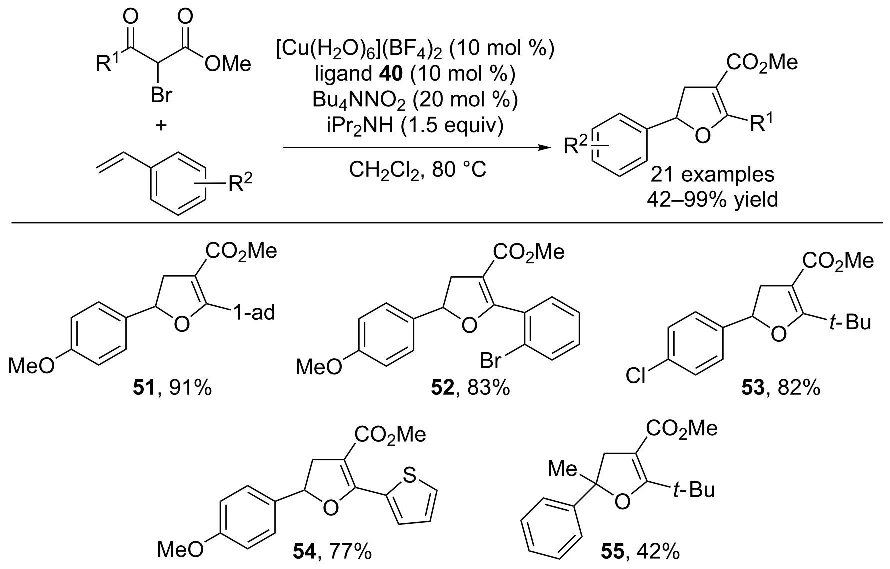


Scheme 13: Scope of the phenol-directed *Z*-alkene synthesis.



Scheme 14: Rationale for the formal [3 + 2] cycloaddition.

to form the dihydrofuran (Scheme 14). This method is formally a [3 + 2] cycloaddition of styrenes and α-bromo keto esters. Using this method, various substituted dihydrofurans were produced in high yields (Scheme 15). Electron-rich and electron-poor styrenes as well as alkyl and aryl keto esters were combined to provide diversely substituted dihydrofurans. The dihydrofurans could be easily converted into furans using DDQ in a one-pot process.

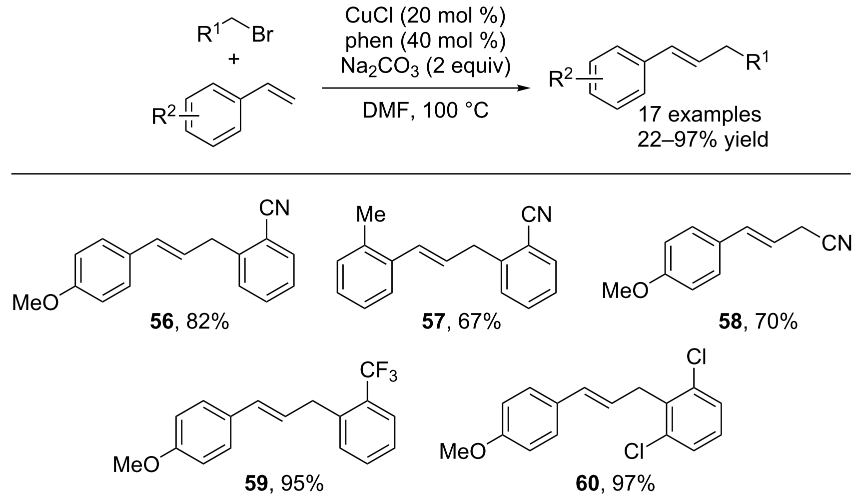


Scheme 15: Scope of the formal [3 + 2] cycloaddition.

In addition to α-bromo esters and ketones, Lei and co-workers have also recently shown that benzylic halides could undergo radical alkenylation via copper catalysis [39]. By exploiting the propensity of benzyl halides to form benzyl radicals under copper catalysis, an alkenylation similar to that developed by Nishikata was realized. Using a mixture of copper and 1,10-phenanthroline, benzylic halides were directly alkenylated using styrenes as coupling partners. Under these conditions, various allylbenzene derivatives were synthesized in very good yields (Scheme 16). Interestingly, the CuCl/phenanthroline catalyst system was also capable of cross coupling styrenes with α-bromocarbonyls and α-bromonitriles. EPR studies confirmed the presence of radical intermediates.

Additions to alkynes

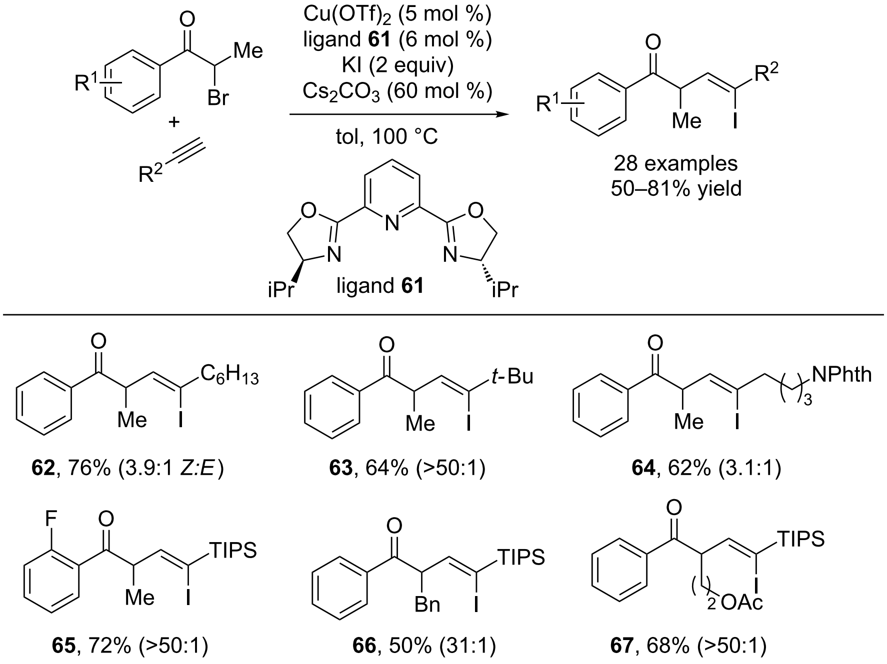
Recently, ATR type catalysts have also been used to catalyze the addition of alkyl radicals to alkynes, with reincorporation of the halide to form substituted vinyl halides. Hu and co-workers reported that a copper/PyBox catalyst system could catalyze the addition of phenacyl iodides, generated in situ from the corresponding bromides and potassium iodide, across alkynes to provide substituted vinyl iodides (Scheme 17) [40]. The process selectively forms the *Z*-alkenes. Although the *E/Z* ratios are often modest, the products are highly useful synthetic building blocks that may be used in subsequent cross-coupling reactions. The mechanism is proposed to proceed similarly to the alkenylation reactions described above. The α-iodoketone is proposed



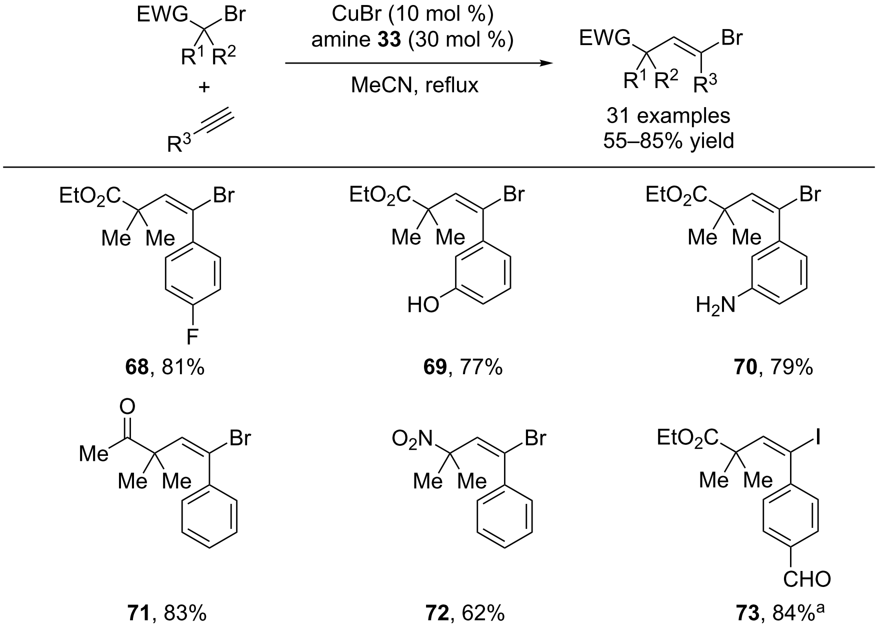
Scheme 16: Benzylation of styrenes using copper catalysis.

to form an alkyl radical, which adds to the alkyne producing an sp^2 centered radical which abstracts an iodine atom from another α-iodoketone to restart the catalytic cycle.

In a complementary protocol, Zhu and co-workers have discovered a selective *trans*-carbohalogenation of aryl alkynes [41]. A tridentate amine was used as a ligand for the copper catalyst. Using these conditions, highly valuable vinyl bromides were synthesized in excellent yields. Various functionalized tertiary alkyl bromides participated in the reaction, including those bearing esters, ketones, nitro and nitriles (Scheme 18). If the reaction was run in the presence of sodium iodide, vinyl iodides



Scheme 17: Copper-catalyzed carboiodination of alkynes.



Scheme 18: Copper-catalyzed *trans*-carbohalogenation of alkynes. [a]NaI (2 equiv) was added.

were produced. This protocol is complementary to Hu's work in that it provides products of *trans*-carbohalogenation. In an elegant one-pot procedure, enynes could be synthesized by introducing a second alkyne and a palladium catalyst to perform a tandem carbohalogenation/Sonagashira coupling.

Conclusion

Copper catalysis has recently emerged as a new means of harnessing the potential of alkyl radicals in catalytic alkylation chemistry. While the groundwork for this recent surge was laid in the development of atom-transfer radical addition and polymerization chemistry, the realization of its potential in alkylation chemistry will greatly expand the use of copper catalysis as a means for constructing complex molecular architectures. The recent groundswell in copper-catalyzed radical additions is likely to continue, with new and creative methods being developed to take advantage of the unique selectivity and reactivity observed in this class of reaction.

Acknowledgements

The University of Delaware (UD) and NIH (RO1 GM012358) are gratefully acknowledged for support. KWS is also grateful to the University of Delaware for a UD Graduate Fellowship.

References

1. Fengas, D. *Atom Transfer Reactions in Organic Synthesis;* University of Manchester: Manchester, 2001.
2. Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001,** *101,* 2921–2990. doi:10.1021/cr940534g
3. Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001,** *101,* 3689–3746. doi:10.1021/cr9901182
4. Matyjaszewski, K. *Macromolecules* **2012,** *45,* 4015–4039. doi:10.1021/ma3001719
5. Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991,** *91,* 1237–1286. doi:10.1021/cr00006a006
6. Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011,** *111,* 6513–6556. doi:10.1021/cr200164y
7. Muñoz-Molina, J. M.; Belderrain, T. R.; Pérez, P. J. *Eur. J. Inorg. Chem.* **2011,** 3155–3164. doi:10.1002/ejic.201100379
8. Clark, A. J. *Chem. Soc. Rev.* **2002,** *31,* 1–11. doi:10.1039/b107811a
9. Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994,** *94,* 519–564. doi:10.1021/cr00026a008
10. Kharasch, M. S.; Engelmann, H.; Mayo, F. R. *J. Org. Chem.* **1937,** *02,* 288–302. doi:10.1021/jo01226a011
11. Kharasch, M. S.; Jensen, E. V.; Urry, W. H. *Science* **1945,** *102,* 128. doi:10.1126/science.102.2640.128
12. Kharasch, M. S.; Urry, W. H.; Jensen, E. V. *J. Am. Chem. Soc.* **1945,** *67,* 1626. doi:10.1021/ja01225a517
13. Minisci, F. *Acc. Chem. Res.* **1975,** *8,* 165–171. doi:10.1021/ar50089a004
14. Pintauer, T.; Matyjaszewski, K. *Chem. Soc. Rev.* **2008,** *37,* 1087–1097. doi:10.1039/b714578k
15. Hass, H. B.; Bender, M. L. *J. Am. Chem. Soc.* **1949,** *71,* 1767–1769. doi:10.1021/ja01173a066
16. Gildner, P. G.; Gietter, A. A. S.; Cui, D.; Watson, D. A. *J. Am. Chem. Soc.* **2012,** *134,* 9942–9945. doi:10.1021/ja304561c
17. Ono, N. *The Nitro Group in Organic Synthesis;* Wiley-VCH: New York, 2001.
18. Aleksandrowicz, P.; Piotrowska, H.; Sas, W. *Tetrahedron* **1982,** *38,* 1321–1327. doi:10.1016/0040-4020(82)85120-X
19. Wade, P. A.; Morrow, S. D.; Hardinger, S. A. *J. Org. Chem.* **1982,** *47,* 365–367. doi:10.1021/jo00341a040
20. Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987,** *52,* 2988–2995. doi:10.1021/jo00390a007
21. Rieck, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1996,** *34,* 2687–2689. doi:10.1002/anie.199526871
22. Trost, B. M.; Surivet, J.-P. *J. Am. Chem. Soc.* **2000,** *122,* 6291–6292. doi:10.1021/ja001062s
23. Grenning, A. J.; Tunge, J. A. *Angew. Chem., Int. Ed.* **2011,** *50,* 1688–1691. doi:10.1002/anie.201006273
24. Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000,** *122,* 1360–1370. doi:10.1021/ja993912d
25. Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2001,** *67,* 106–111. doi:10.1021/jo010953v
26. Metz, A. E.; Berritt, S.; Dreher, S. D.; Kozlowski, M. C. *Org. Lett.* **2012,** *14,* 760–763. doi:10.1021/ol203303b
27. Aguila, M. J. B.; Badiei, Y. M.; Warren, T. H. *J. Am. Chem. Soc.* **2013,** *135,* 9399–9406. doi:10.1021/ja400879m
28. Jang, E. S.; McMullin, C. L.; Käß, M.; Meyer, K.; Cundari, T. R.; Warren, T. H. *J. Am. Chem. Soc.* **2014,** *136,* 10930–10940. doi:10.1021/ja5026547
29. Rubino, D. M.; Gadde, K. M. *Clin. Lipidol.* **2012,** *7,* 13–25. doi:10.2217/clp.11.65
30. O'Neil, J. M. *The Merck Index,* 14th ed.; Merck and Co., Inc.: Whitehouse Station; NJ, USA , 2006.
31. Gietter, A. A. S.; Gildner, P. G.; Cinderella, A. P.; Watson, D. A. *Org. Lett.* **2014,** *16,* 3166–3169. doi:10.1021/ol5014153
32. Nishikata, T.; Noda, Y.; Fujimoto, R.; Sakashita, T. *J. Am. Chem. Soc.* **2013,** *135,* 16372–16375. doi:10.1021/ja409661n
33. Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001,** *40,* 4544–4568. doi:10.1002/1521-3773(20011217)40:24<4544::AID-ANIE4544>3.0.CO;2-N
34. Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009,** *48,* 2656–2670. doi:10.1002/anie.200803611
35. Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011,** *111,* 1417–1492. doi:10.1021/cr100327p
36. Nishikata, T.; Nakamura, K.; Itonaga, K.; Ishikawa, S. *Org. Lett.* **2014,** *16,* 5816–5819. doi:10.1021/ol502953w
37. Nishikata, T.; Nakamura, K.; Inoue, Y.; Ishikawa, S. *Chem. Commun.* **2015,** *51,* 10154–10157. doi:10.1039/C5CC03474D
38. Ishikawa, S.; Noda, Y.; Wada, M.; Nishikata, T. *J. Org. Chem.* **2015,** *80,* 7555–7563. doi:10.1021/acs.joc.5b01139
39. Zhang, X.; Yi, H.; Liao, Z.; Zhang, G.; Fan, C.; Qin, C.; Liu, J.; Lei, A. *Org. Biomol. Chem.* **2014,** *12,* 6790–6793. doi:10.1039/C4OB00813H
40. Xu, T.; Hu, X. *Angew. Chem., Int. Ed.* **2015,** *54,* 1307–1311. doi:10.1002/anie.201410279
41. Che, C.; Zheng, H.; Zhu, G. *Org. Lett.* **2015,** *17,* 1617–1620. doi:10.1021/acs.orglett.5b00546

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doi:10.3762/bjoc.11.248

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Cu(I)-catalyzed *N,N'*-diarylation of natural diamines and polyamines with aryl iodides

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Full Research Paper

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Keywords:
amination; aryl amines; aryl iodides; copper catalysis; polyamines

Beilstein J. Org. Chem. **2015,** *11,* 2297–2305.
doi:10.3762/bjoc.11.250

Received: 02 September 2015
Accepted: 02 November 2015
Published: 24 November 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

The Cu(I)-catalyzed *N,N'*-diarylation of natural diamines and polyamines such as putrescine, cadaverine, spermine, spermidine and their homologues is described. Aryl iodides bearing electron-donating and electron-withdrawing groups have been employed in the study. The CuI/2-(isobutyryl)cyclohexanone/DMF catalytic system has found to be more efficient in the diarylation of diamines and spermine while the CuI/L-proline/EtCN system proved to be preferable for the diarylation of other tri- and tetraamines like spermidine, norspermidine and norspermine.

Introduction

Natural diamines and polyamines like putrescine (butane-1,4-diamine), spermidine (N^1-(3-aminopropyl)butane-1,4-diamine) and spermine (N^1,$N^{1'}$-(butane-1,4-diyl)dipropane-1,3-diamine) are biologically active compounds which play crucial roles in the processes of cell proliferation, apoptosis and adaptation to stress impacts. The important biological processes occur also with the participation of such diamines as propane-1,3-diamine and cadaverine (pentane-1,5-diamine), and polyamines like norspermidine (N^1-(3-aminopropyl)propane-1,3-diamine) and norspermine (N^1,$N^{1'}$-(propane-1,3-diyl)dipropane-1,3-diamine) [1]. In the early 1970s cancer cells were found to possess an excess of polyamines [2]. This fact initiated the studies of polyamines in the frames of molecular biology and biochemistry. It has been firmly established that *N*-derivatives are prospects for the creation of anticancer and antiviral medicaments. The majority of known di- and polyamine derivatives possess alkyl or benzyl substituents at the nitrogen atoms [3-8], however, the synthesis and investigation of *N*-aryl derivatives of polyamines have been addressed only recently [9-11]. For example, some *N,N'*-diphenyl-α,ω-diaminoalkanes have been found to possess respiratory stimulating effects [12], *N*-substituted putrescine and cadaverine have shown antiproliferative and cytotoxic activity [13,14], *N*-decyl and *N*-dodecyl derivatives of putrescine, *N*-(*p*-tolyl) derivatives of cadaverine and hexane-1,6-diamine have demonstrated affinity to NMDA receptors and antileishmanial activity [15-17].

Up to date no general non-catalytic approach to *N,N'*-diarylpolyamines has yet been described. Synthetic procedures are multistep [17,18] though sometimes they can be performed as one-pot syntheses [19]. Several catalytic approaches have been described in the literature. One of them employs an iridium-based catalyst with amidophosphonate as the ligand which allows to convert aminoalcohols into *N*-monoaryl-substituted diamines by the reaction with arylamines [20]. Another method uses a bimetallic catalyst (Pt–Sn/γ-Al_2O_3) in the reactions of diols with amines, and a valuable *N,N'*-diphenylhexane-1,6-diamine was obtained using this catalyst [21]. More traditional and convenient Pd(0)-catalyzed amination, proposed by Buchwald and Hartwig [22,23], was successfully applied in the synthesis of mono- and diaryl-substituted diamines and polyamines in the group of Beletskaya [24-27]. It has been shown that the secondary dialkylamino groups in linear polyamines are practically inert and this allows a selective arylation of terminal primary amino groups. The exchange of expensive palladium accompanied with toxic ligands for a much cheaper copper catalyst is one of the main trends in modern catalytic chemistry. However, in spite of numerous works dealing with Cu(I)-catalyzed arylation of monoamines, there are scarce examples of the synthesis of *N*-arylpolyamines using this method. Han and coworkers for example showed the possibility to synthesize *N*-aryldiamines using aryl iodides in the presence of CuCl under neat conditions [28], *N,N'*-diarylation of the simplest propane-1,3-diamine and butane-1,4-diamine was carried out using a CuI-metformin catalyst [29], monoarylation of mono- and diamines was studied using Cu_2O and CuO nanoparticles and CuO microparticles [30].

We initiated our studies in this field by the elaboration of Cu(I)-catalyzed *N*-arylations and *N,N'*-diarylations of the model triamine, tetraamine and oxadiamine with aryl iodides and bromides [31] and elucidated some regularities of the catalytic *N*-heteroarylation of polyamines [32]. However, it has been found that to obtain a good result, the reaction conditions (ligand, solvent, temperature) should be adjusted for a certain aryl halide/polyamine pair. In the present study we decided to undertake a thorough investigation of the Cu(I)-catalyzed *N,N'*-diarylation of natural diamines and polyamines using aryl iodides with electron-donating and electron-withdrawing substituents in order to identify conditions for the synthesis of a wide range of perspective derivatives of these di- and polyamines.

Results and Discussion

N,N'-Diarylation of diamines

The investigated diamines **1–4**, triamines **5**, **6** and tetraamines **7** and **8** as well as aryl iodides are presented on Figure 1. Di- and polyamines differ by the number of nitrogen atoms and methylene groups in the chain that dramatically influences their reactivity, as shown in our previous investigations. Aryl iodides differ by the electronic properties of the substituents and, in the case of 4- and 2-fluoroiodobenzene, by the steric hindrance at the reaction center. Also the choice of the substituents depends on the potential usefulness of corresponding *N,N'*-diaryl derivatives, for this purpose we referred to the data published in [30]. A special interest is paid to the compounds with fluorine and

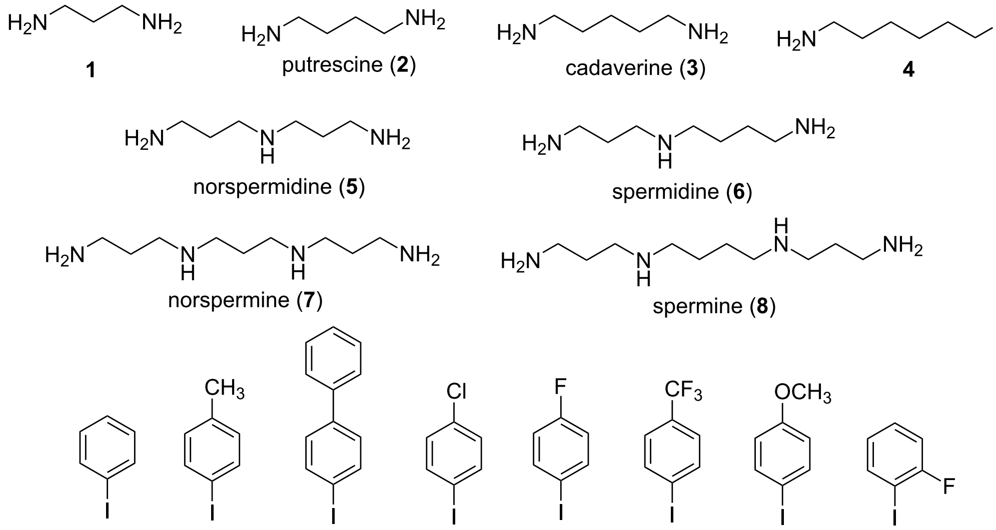


Figure 1: Diamines and polyamines studied in Cu(I)-catalyzed amination reactions.

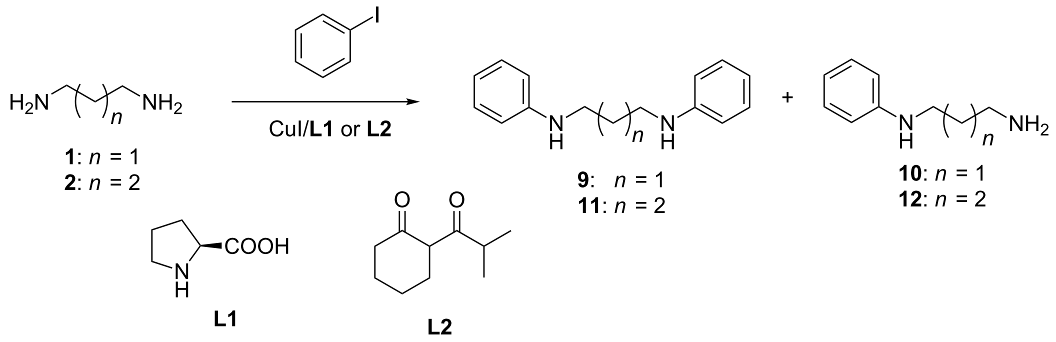
trifluoromethyl substituents as up to a quarter of pharmaceuticals contain fluorine in the aromatic or heteroaromatic ring. In this study we did not test substituted bromobenzenes as they were shown to be much less active than corresponding iodides in the copper-catalyzed amination of di- and polyamines providing mainly *N*-monoaryl derivatives [31].

On the basis of our recent investigations, in order to obtain *N,N'*-diaryl derivatives, we employed the most suitable catalytic systems, CuI/L-proline (**L1**) and CuI/2-(isobutyryl)cyclohexanone (**L2**), EtCN or DMF were used as solvents and cesium carbonate (2.5 equiv) was taken as base (Scheme 1). The reactions were run under argon for ca. 24 h using 2.5 equiv of the aryl iodides with 0.5 M concentrations of polyamines. In the case of EtCN the reactions were refluxed (ca 100 °C), in the case of DMF they were run at 110 °C. Normal catalytic loading was 5 mol % CuI and 10 mol % ligand per 1 amino group.

At first we conducted the cross-coupling reactions between the simplest iodobenzene and diamines **1** and **2** to optimize the reaction conditions (Scheme 1, Table 1). As the resulting compounds **9**–**12** are described in the literature [29,33-35], it was possible to analyze the reaction mixtures by ^{1}H and ^{13}C NMR spectroscopy and in some cases the products were isolated by column chromatography on silica gel. For example, in the proton NMR spectrum of compound **9** two signals are observed in the aliphatic part: quintet at 1.94 ppm (2H) and triplet at 3.25 ppm (4H), while the spectrum of compound **10** is characterized by three signals: quintet at 1.76 ppm (2H), broad singlet at 2.86 ppm (2H) and triplet at 3.19 ppm (2H). The signals of two compounds do not overlap and can be easily integrated.

When the reaction of diamine **1** with iodobenzene was carried out in the presence of the ligand **L1**, the yield of the target diphenyl derivative **9** did not exceed 40–45% (Table 1, entries 1 and 2), and mainly *N*-phenyl-substituted diamine **10** was formed. In the presence of the ligand **L2** the yield of **9** increased up to 75% (Table 1, entry 3). Diarylation of putrescine (**2**), on contrary, was more successful in the presence of the CuI/**L1**/EtCN catalytic system (Table 1, entry 4), and a similar result was obtained when using **L2** together with Ph$_3$P (Table 1, entry 6), while employing **L1** with triphenylphosphine led to a low conversion into diphenyl derivative **11** (Table 1, entry 5). In general, diamine **2** was found to be less reactive than propane-1,3-diamine (**1**) in the coupling with iodobenzene.

According to these preliminary results, we carried out all other reactions of diamines **1** and **2** with other aryl iodides using CuI/**L2**/DMF (10/20 mol %) catalytic system (Scheme 2, Table 2).

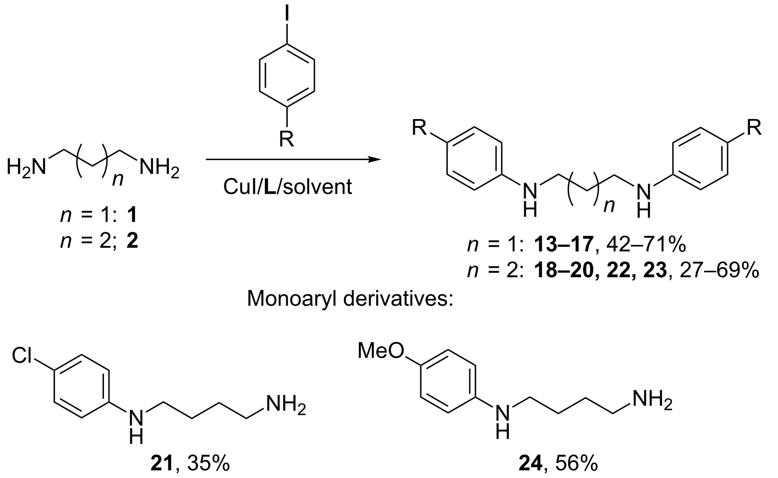


Scheme 1: *N,N'*-Diarylation of the diamines **1** and **2**.

Table 1: Optimization of the reaction conditions for the *N,N'*-diarylation of diamines **1** and **2** with iodobenzene.

Entry	Amine	Catalytic system	CuI/L, mol %	*t*, °C	Products and yields, %[a]
1	**1**	CuI/**L1**/DMF	10/20	110	**9**, 40; **10**, 60
2	**1**	CuI/**L1**/EtCN	10/20	100	**9**, 45; **10**, 55
3	**1**	CuI/**L2**/DMF	10/20	110	**9**, 75; **10**, 25
4	**2**	CuI/**L1**/EtCN	10/20	100	**11**, 60 (43); **12**, 40
5	**2**	CuI/**L1**/Ph$_3$P/EtCN	10/10/10	100	**11**, 30; **12**, 55
6	**2**	CuI/**L2**/Ph$_3$P/DMF	10/10/10	110	**11**, 53 (41); **12**, 47

[a] Isolated yields are given in brackets.



Scheme 2: Arylation of the diamines **1** and **2**.

Table 2: Arylation of the diamines **1** and **2**.

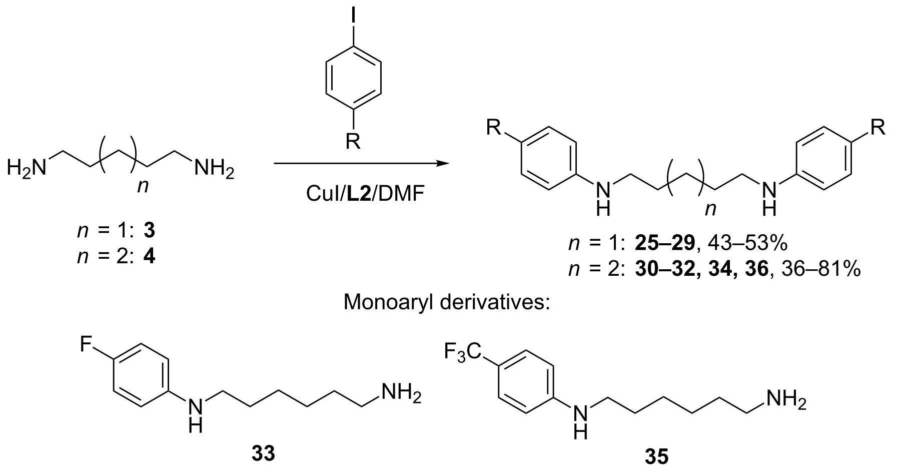
Entry	Amine	R	Catalytic system	CuI/L, mol %	Products and yields, %[a]
1	**1**	Ph	CuI/**L2**/DMF	10/20	**13**, 56
2	**1**	Cl	CuI/**L2**/DMF	10/20	**14**, 71
3	**1**	F	CuI/**L2**/DMF	10/20	**15**, 61
4	**1**	CF_3	CuI/**L2**/DMF	10/20	**16**, 42
5	**1**	OMe	CuI/**L2**/DMF	10/20	**17**, 56
6	**2**	Me	CuI/**L2**/Ph_3P/DMF	10/10/10	**18**, 30[b]
7	**2**	Me	CuI/**L2**/DMF	20/40	**18**, 60
8	**2**	Ph	CuI/**L1**/EtCN	10/20	**19**, 46
9	**2**	Cl	CuI/**L2**/DMF	10/20	**20**, 14
10	**2**	Cl	CuI/**L2**/Ph_3P/DMF	10/10/10	**20**, 27; **21**, 35
11	**2**	Cl	CuI/**L2**/Ph_3P/DMF	20/20/20	**20**, 69
12	**2**	F	CuI/**L2**/Ph_3P/DMF	20/20/20	**22**, 52
13	**2**	CF_3	CuI/**L2**/Ph_3P/DMF	10/10/10	**23**, 58
14	**2**	OMe	CuI/**L2**/Ph_3P/DMF	10/10/10	**24**, 56

[a] Yields after chromatographic isolation. [b] Yield in the reaction mixture.

The reactions with iodoarenes containing electron-withdrawing substituents ran successfully and corresponding diarylated products **13–16** were isolated in moderate to good yields (Table 2, entries 1–4). The difference in the preparative yields was due to the conditions of chromatographic isolation in each case. 4-Iodoanisole with a strong electron-donating substituent provided 56% yield of the diarylated compound **17** (Table 2, entry 5), while one could expect much lower reactivity of this compound compared to aryl iodides bearing acceptors. Diarylation of putrescine (**2**) was found to be more difficult (Scheme 2, Table 2). In the reactions with all aryl iodides we observed the formation of di- and monoarylated products in the reaction mixtures, however, only in two cases we managed to isolate the latter compounds in individual state. At first we decided to verify the efficiency of the catalytic system with **L2** and Ph_3P and tried it in the reaction with 4-iodotoluene, but the conversion of the diamine into the diarylated product **18** was low (Table 2, entry 6). Only using 20/40 mol % CuI/**L2** we managed to obtain the desired compound in a good yield (Table 2, entry 7). The same catalytic system with or without triphenylphosphine was not efficient in the coupling with 4-iodobiphenyl, however, the use of **L1** gave rise to the target diaryl derivative **19** in a moderate yield (Table 2, entry 8). On contrary, application of the ligand **L2** was more successful for aryl iodides with electron-withdrawing groups like Cl, F and CF_3, and the best results were obtained in the presence of Ph_3P (Table 2, entries 10–13), the yields of compounds **20**, **22** and **23** ranged from 52 to 69%. The reaction with 4-iodoanisole catalyzed with CuI/**L2**/Ph_3P provided 56% yield of the monoaryl derivative **24** (Table 2, entry 14); we tried other catalytic systems but they worked even worse providing low conversion of starting compounds. It should be noted that in the case of 4-chloro- and 4-fluoroiodobenzene the use of 20 mol % catalyst provided higher conversion of the starting compounds and better yields, but in the case of other aryl iodides 20 mol % catalyst led to side processes diminishing the yields of the target compounds.

Contrary to the diarylation of putrescine, the same processes with cadaverine (**3**) and hexane-1,6-diamine (**4**) proceeded without serious difficulties (Scheme 3, Table 3). The reactions of the diamine **3** with iodobenzene and other *para*-disubstituted benzenes gave the desired products in 43–53% yields in the presence of the CuI/**L2** catalytic system (Table 3, entries 1–4). Only the application of 4-iodoanisole under stated conditions gave diaryl derivative **29** in a rather poor yield (Table 3, entries 5 and 6), but the use of the ligand **L1** improved the result (Table 3, entry 7). In the case of diamine **4** the yields of the corresponding products **30–32** and **34** were somewhat lower (Table 3, entries 8–11), and with fluorinated compounds we managed to isolate also monoarylated derivatives **33** and **35** (Table 3, entries 10 and 11). It is interesting that 20/40 mol % CuI/**L2** catalytic system provided a high yield (81%) of the *N,N'*-diarylation product in the reaction with 4-iodoanisole (Table 3, entry 12). It shows that in some cases an increase in the catalyst loading can substantially enhance the yields in the reactions even with less reactive aryl halides.

Cu(I)-catalyzed amination of *ortho*-disubstituted benzenes is a challenging task as earlier we demonstrated very low reactivity



Scheme 3: Arylation of the diamines **3** and **4**.

Table 3: Arylation of the diamines **3** and **4**.

Entry	Amine	R	CuI/**L2**, mol %	Products and yields, %[a]
1	**3**	H	10/20	**25**, 50
2	**3**	Ph	10/20	**26**, 43
3	**3**	F	10/20	**27**, 53
4	**3**	CF_3	10/20	**28**, 51
5	**3**	OMe	10/20	**29**, 22
6	**3**	OMe	20/40	**29**, 22
7	**3**	OMe	20/40[b]	**29**, 52
8	**4**	H	10/20	**30**, 45
9	**4**	Ph	10/20	**31**, 36
10	**4**	F	10/20	**32**, 38; **33**, 58
11	**4**	CF_3	10/20	**34**, 34; **35**, 12
12	**4**	OMe	20/40	**36**, 81

[a]Yields after chromatographic isolation. [b]Ligand **L1** was used.

of 2-iodotoluene and 1,2-diiodobenzene [31]. Contrary to this, Pd(0)-catalyzed amination of 2-bromotoluene derivatives was quite successful [36]. In this study we tried the reaction of 2-fluoroiodobenzene with diamines **1**, **3** and **4** using the CuI/**L2** catalytic system (20/40 mol %) (Scheme 4). In the reaction with propane-1,3-diamine (**1**) only monoaryl derivative **37** was obtained in 58% yield, and with diamines **3** and **4** we managed to isolate *N,N'*-diaryl derivatives **38** and **40**, though their yields were too small (10 and 18%, respectively), the main products being *N*-(2-fluorophenyl) diamines **39** and **41**.

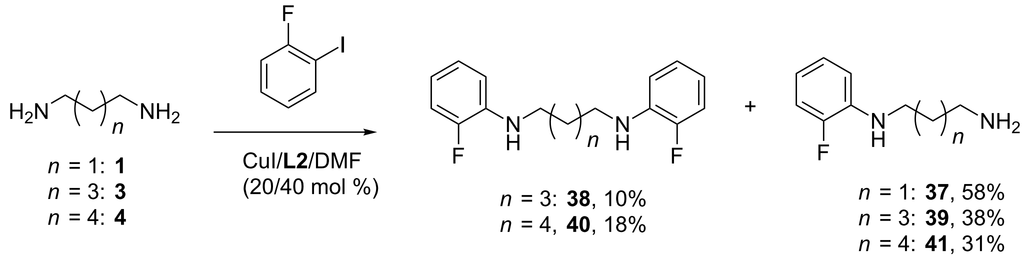
N,N'-Diarylation of tri- and tetraamines

Arylation of two primary amino groups in polyamines under Cu(I)-catalysis conditions is a more challenging task than *N,N'*-diarylation of diamines because copper-catalyzed amination is less selective than palladium-catalyzed coupling. In view of earlier obtained data we used the CuI/**L1**/EtCN catalytic system for the diarylation of the triamine **5** (Scheme 5, Table 4).

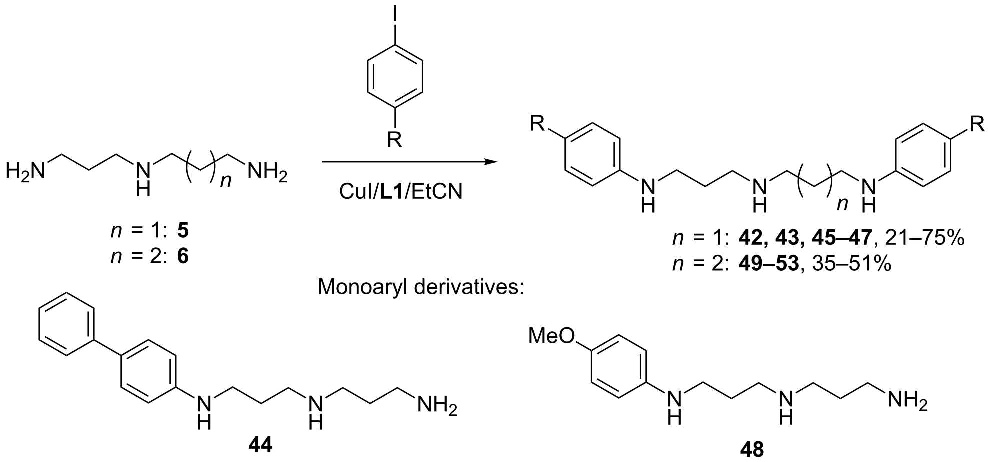
In all cases this catalytic system was efficient and corresponding *N,N'*-diaryl derivatives **42**, **45**, **46** were obtained in satisfactory yields (41–53%, Table 4, entries 1, 5 and 7) when taking 10/20 mol % of catalyst, and in the reaction with 4-iodobiphenyl 20/40 mol % catalyst allowed to increase the yield of compound **43** to 75% (Table 4, entry 4) and to obtain the diarylation product **47** with 4-iodoanisole, though in a small amount (Table 4, entry 8). The application of the CuI/**L1** system in DMF gave the same results, as the NMR spectra of the reaction mixture revealed, thus the chromatographic isolation of the combined reaction mixtures was carried out (Table 4, entries 1 and 2, 5 and 6). However, the CuI/**L2**/DMF system was not efficient at all as it strongly diminished the selectivity of the reactions.

Unsymmetrical spermidine (**6**) provided somewhat poorer yields of the diarylated derivatives **49**–**52** (Table 4, entries 9–13), and to obtain the diarylation product with the 4-iodoanisole CuI/**L2**/DMF catalytic system had to be used (Table 4, entries 14 and 15). The application of 20 mol % catalyst instead of 10 mol % helped to increase the yields in some cases (entries 11 and 15).

Easier arylation of the secondary amino groups in the tetraamines **7** and **8** (Scheme 6, Table 5) led to a loss in the



Scheme 4: Arylation of the diamines **1**, **3**, **4** with 2-fluoroiodobenzene.

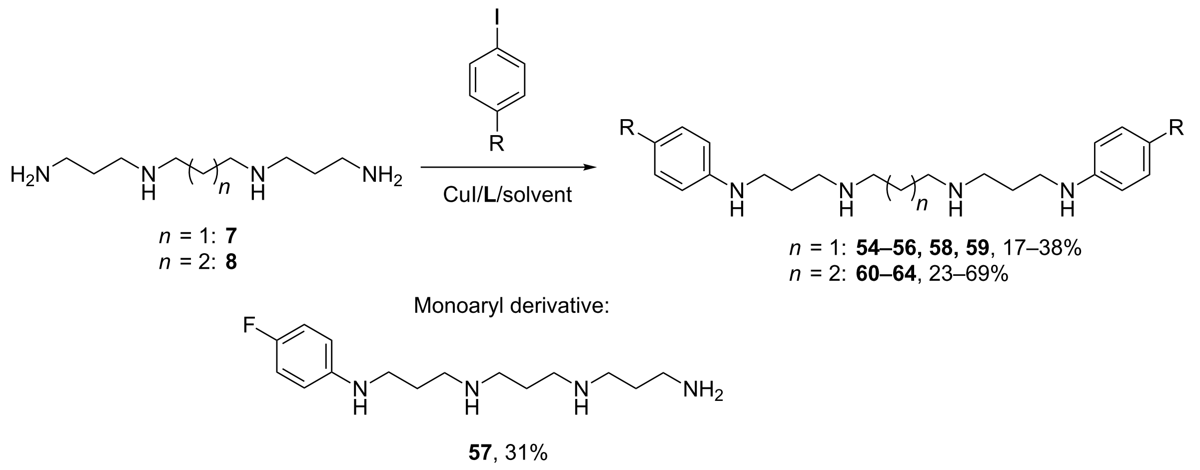


Scheme 5: Arylation of the triamines **5** and **6**.

Table 4: Arylation of the triamines **5** and **6**.

Entry	Amine	R	CuI/**L1**, mol %	Products and yields, %[a]
1	**5**	H	10/20	**42**, 41[b]
2	**5**	H	10/20[b]	
3	**5**	Ph	10/20	**43**, 13; **44**, 18
4	**5**	Ph	20/40	**43**, 75
5	**5**	F	10/20	**45**, 50[b]
6	**5**	F	20/40	
7	**5**	CF_3	10/20	**46**, 53
8	**5**	OMe	20/40	**47**, 21; **48**, 35
9	**6**	H	10/20	**49**, 36
10	**6**	Ph	10/20	**50**, 24
11	**6**	Ph	20/40	**50**, 35
12	**6**	F	10/20	**51**, 35
13	**6**	CF_3	10/20	**52**, 51
14	**6**	OMe	10/20[c]	**53**, 27
15	**6**	OMe	20/40[c]	**53**, 46

[a]Yields after chromatographic isolation. [b]DMF was used instead of EtCN, chromatography of combined reaction mixtures. [c]Ligand **L2** was used.



Scheme 6: Arylation of the tetraamines **7** and **8**.

selectivity of the process, made chromatographic isolation more tedious and less efficient, and also diminished the catalytic activity of copper due to better coordination of the cation by four nitrogen atoms which removed it from the catalytic cycle.

The *N,N'*-diarylation of the tetraamine **7** in some cases was more successful in the presence of the CuI/**L1**/EtCN catalytic system (Table 5, entries 1, 3 and 6) while CuI/**L2**/DMF gave bad results due to low conversion of the starting compounds or poor selectivity of the arylation. On contrary, the latter system was found to be more appropriate in the case of 4-iodoanisole, though the yield of the target product **59** was low even when using 10 equiv of the arylating agent (Table 5, entry 9). In the reaction with 4-fluoroiodobenzene the target compound **56** could be obtained only in the presence of the CuI/**L2**/Ph_3P system (Table 5, entry 5). The reactions with spermine (**8**) which possesses tetramethylenediamine central fragment gave better yields. In the majority of cases the system CuI/**L2**/DMF was more efficient (Table 5, entries 10, 12 and 13), CuI/**L1**/EtCN provided insufficient conversion of the starting compounds, and only with 4-iodobiphenyl it was more helpful

Table 5: Arylation of the tetraamines **7** and **8**.

Entry	Amine	R	Catalytic system	CuI/L, mol %	Products and yields, %[a]
1	**7**	H	CuI/**L1**/EtCN	10/20	**54**, 37
2	**7**	H	CuI/**L2**/DMF	10/20	**54**, 24
3	**7**	Ph[b]	CuI/**L1**/EtCN	14/28	**55**, 32
4	**7**	F	CuI/**L1**/EtCN	10/20	**56**, 6; **57**, 31
5	**7**	F	CuI/**L2**/Ph_3P/DMF	10/10/10	**56**, 37
6	**7**	CF_3	CuI/**L1**/EtCN	10/20	**58**, 38
7	**7**	CF_3	CuI/**L2**/DMF	10/20	**58**, 8
8	**7**	OMe	CuI/**L2**/DMF	20/40	**59**, 8
9	**7**	OMe[c]	CuI/**L2**/DMF	20/40	**59**, 17
10	**8**	H	CuI/**L2**/DMF	10/20	**60**, 69
11	**8**	Ph	CuI/**L1**/EtCN	10/20	**61**, 36
12	**8**	F	CuI/**L2**/DMF	10/20	**62**, 45
13	**8**	CF_3	CuI/**L2**/DMF	10/20	**63**, 41
14	**8**	OMe	CuI/**L2**/DMF	20/40	**64**, 23

[a]Yields after chromatographic isolation. [b]3.4 equiv 4-iodobiphenyl were used. [c]10 equiv 4-iodoanisole were used.

(Table 5, entry 11). The reaction with 4-iodoanisole was the most problematic and the yield of **64** even with 20 mol % of catalyst did not exceed 23% (Table 5, entry 14).

Conclusion

To sum up, the following regularities can be ruled out from the experiments: a) successful N,N'-diarylation of the diamines **1**, **3**, **4** and spermine (**8**) can be carried out in the presence of the CuI/**L2**/DMF catalytic system, while triamines **5**, **6** and norspermine (**7**) prefer the CuI/**L1**/EtCN system; b) the most problematic amines are putrescine (**2**) and norspermine (**7**) as they demand a fine tuning of the catalytic system almost for each aryl iodide; c) compounds with electron-withdrawing substituents (Cl, F, CF_3) generally produce *N,N'*-diarylated derivatives in reasonable yields, while the reactivity of electron-enriched 4-iodoanisole is lower in many cases and more catalyst is needed to afford diarylation products.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization and spectral data for synthesized compounds **11**–**64**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-250-S1.pdf]

Acknowledgements

This work was supported by the Project of the Ministry of Education and Science RFMEFI61314X0012 and by the Russian Academy of Sciences program "Elaboration of the methods for the synthesis of chemical compounds and construction of new materials".

References

1. Pegg, A. E.; Casero, R. A., Jr. *Methods Mol. Biol.* **2011,** *720,* 3–35. doi:10.1007/978-1-61779-034-8_1
2. Russell, D. H. *Polyamines in Normal and Neoplastic Growth;* Raven Press: New York, 1973.
3. Casero, R. A.; Marton, L. J. *Nat. Rev. Drug Discovery* **2007,** *6,* 373–390. doi:10.1038/nrd2243
4. Huang, Y.; Hager, E. R.; Phillips, D. L.; Dunn, V. R.; Hacker, A.; Frydman, B.; Kink, J. A.; Valasinas, A. L.; Reddy, V. K.; Marton, L. J.; Casero, R. A., Jr.; Davidson, N. E. *Clin. Cancer Res.* **2003,** *9,* 2769–2777.
5. Nowotarski, S. L.; Woster, P. M.; Casero, R. A., Jr. *Expert Rev. Mol. Med.* **2013,** *15,* e3. doi:10.1017/erm.2013.3
6. Fraser, A. V.; Woster, P. M.; Wallace, H. M. *Biochem. J.* **2002,** *367,* 307–312. doi:10.1042/bj20020156
7. Häkkinen, M. R.; Hyvönen, M. T.; Auriola, S.; Casero, R. A., Jr.; Vepsäläinen, J.; Khomutov, A. R.; Alhonen, L.; Keinänen, T. A. *Amino Acids* **2009,** *38,* 369–381. doi:10.1007/s00726-009-0429-2
8. Casero, R. A., Jr.; Woster, P. M. *J. Med. Chem.* **2001,** *44,* 1–26. doi:10.1021/jm000084m
9. Díaz, J. E.; Bisceglia, J. Á.; Mollo, M. C.; Orelli, L. R. *Tetrahedron Lett.* **2011,** *52,* 1895–1897. doi:10.1016/j.tetlet.2011.02.042
10. Bisceglia, J. Á.; García, M. B.; Massa, R.; Magri, M. L.; Zani, M.; Gutkind, G. O.; Orelli, L. R. *J. Heterocycl. Chem.* **2004,** *41,* 85–90. doi:10.1002/jhet.5570410113
11. Haffner, C. D.; Thomson, S. A.; Guo, Y.; Petrov, K.; Larkin, A.; Banker, P.; Schaaf, G.; Dickerson, S.; Gobel, J.; Gillie, D.; Condreay, J. P.; Poole, C.; Carpenter, T.; Ulrich, J. *Bioorg. Med. Chem. Lett.* **2010,** *20,* 6989–6992. doi:10.1016/j.bmcl.2010.09.131
12. Boon, W. R. *J. Chem. Soc.* **1947,** 307–318. doi:10.1039/jr9470000307

13. Burns, M. R.; LaTurner, S.; Ziemer, J.; McVean, M.; Devens, B.; Carlson, C. L.; Graminski, G. F.; Vanderwerf, S. M.; Weeks, R. S.; Carreon, J. *Bioorg. Med. Chem. Lett.* **2002,** *12,* 1263–1267. doi:10.1016/S0960-894X(02)00156-7
14. Heston, W. D. W.; Watanabe, K. A.; Pankiewicz, K. W.; Covey, D. F. *Biochem. Pharmacol.* **1987,** *36,* 1849–1852. doi:10.1016/0006-2952(87)90250-4
15. Bergeron, R. J.; Weimar, W. R.; Wu, Q.; Feng, Y.; McManis, J. S. *J. Med. Chem.* **1996,** *39,* 5257–5266. doi:10.1021/jm960545x
16. da Costa, C. F.; Coimbra, E. S.; Braga, F. G.; dos Reis, R. C. N.; da Silva, A. D.; de Almeida, M. V. *Biomed. Pharmacother.* **2009,** *63,* 40–42. doi:10.1016/j.biopha.2007.12.013
17. Reyes, M. J.; Delgado, F.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron* **2002,** *58,* 8573–8579. doi:10.1016/S0040-4020(02)00901-8
18. Hwang, J. Y.; Kim, H.-Y.; Jo, S.; Park, E.; Choi, J.; Kong, S.; Park, D.-S.; Heo, J. M.; Lee, J. S.; Ko, Y.; Choi, I.; Cechetto, J.; Kim, J.; Lee, J.; No, Z.; Windisch, M. P. *Eur. J. Med. Chem.* **2013,** *70,* 315–325. doi:10.1016/j.ejmech.2013.09.055
19. Billman, J. H.; Caswell, L. R. *J. Org. Chem.* **1951,** *16,* 1041–1046. doi:10.1021/jo50001a004
20. Blank, B.; Michlik, S.; Kempe, R. *Adv. Synth. Catal.* **2009,** *351,* 2903–2911. doi:10.1002/adsc.200900548
21. Wang, L.; He, W.; Wu, K.; He, S.; Sun, C.; Yu, Z. *Tetrahedron Lett.* **2011,** *52,* 7103–7107. doi:10.1016/j.tetlet.2011.10.100
22. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995,** *34,* 1348–1350. doi:10.1002/anie.199513481
23. Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995,** *36,* 3609–3612. doi:10.1016/0040-4039(95)00605-C
24. Beletskaya, I. P.; Bessmertnykh, A. G.; Averin, A. D.; Denat, F.; Guilard, R. *Eur. J. Org. Chem.* **2005,** 261–280. doi:10.1002/ejoc.200400456
25. Averin, A. D.; Uglov, A. N.; Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Pd-catalyzed arylation of polyamines*. In *Advances in Chemistry Research;* Taylor, J. C., Ed.; Nova Science, 2010; Vol. 4.
26. Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Tetrahedron Lett.* **1997,** *38,* 2287–2290. doi:10.1016/S0040-4039(97)00363-8
27. Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Synlett* **1999,** 1459–1461. doi:10.1055/s-1999-2837
28. Yin, H.; Jin, M.; Chen, W.; Chen, C.; Zheng, L.; Wei, P.; Han, S. *Tetrahedron Lett.* **2012,** *53,* 1265–1270. doi:10.1016/j.tetlet.2011.12.130
29. Zhang, C.; Zhan, Z.; Lei, M.; Hu, L. *Tetrahedron* **2014,** *70,* 8817–8821. doi:10.1016/j.tet.2014.10.014
30. Costa, M. V.; Viana, G. M.; de Souza, T. M.; Malta, L. F. B.; Aguiar, L. C. S. *Tetrahedron Lett.* **2013,** *54,* 2332–2335. doi:10.1016/j.tetlet.2013.02.048
31. Anokhin, M. V.; Averin, A. D.; Beletskaya, I. P. *Eur. J. Org. Chem.* **2011,** 6240–6253. doi:10.1002/ejoc.201100483
32. Anokhin, M. V.; Averin, A. D.; Panchenko, S. P.; Maloshitskaya, O. A.; Buryak, A. K.; Beletskaya, I. P. *Helv. Chim. Acta* **2015,** *98,* 47–59. doi:10.1002/hlca.201400092
33. Liu, S.; Rebros, M.; Stephens, G.; Marr, A. C. *Chem. Commun.* **2009,** 2308–2310. doi:10.1039/b820657k
34. Maruoka, K.; Banno, H.; Nonoshita, K.; Yamamoto, H. *Tetrahedron Lett.* **1989,** *30,* 1265–1266. doi:10.1016/S0040-4039(00)72731-6
35. Ramirez, M. A.; Corona, M. V.; Blanco, M. M.; Perillo, I. A.; Porcal, W.; Salerno, A. *Tetrahedron Lett.* **2010,** *51,* 5000–5002. doi:10.1016/j.tetlet.2010.07.075
36. Chernichenko, N. M.; Averin, A. D.; Buryak, A. K.; Beletskaya, I. P. *Russ. Chem. Bull.* **2014,** *63,* 2056–2063. doi:10.1007/s11172-014-0700-x

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

A concise and efficient synthesis of benzimidazo[1,2-*c*]quinazolines through CuI-catalyzed intramolecular *N*-arylations

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Full Research Paper

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Keywords:
benzimidazo[1,2-*c*]quinazoline; (bromophenyl)iodonium salt; copper catalyst; *o*-cyanoaniline; quinazolin-4(3*H*)-imine; Ullmann N-arylation

Beilstein J. Org. Chem. **2015,** *11,* 2365–2369.
doi:10.3762/bjoc.11.258

Received: 30 August 2015
Accepted: 16 November 2015
Published: 30 November 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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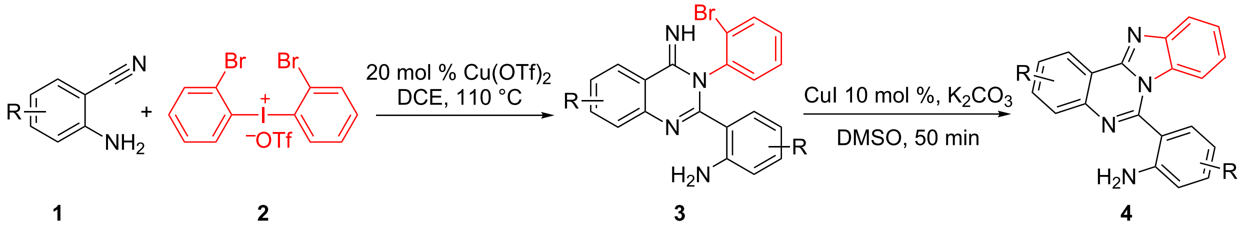
Abstract

A series of functionalized benzimidazo[1,2-*c*]quinazoline derivatives was obtained in excellent yields under mild conditions through a CuI-catalyzed Ullmann *N*-arylation starting from easily available starting materials.

Introduction

Nitrogen-containing heterocycles are ubiquitous backbones in natural products, medicine and organic materials. In addition, they are also important ligands for catalytic reactions. Recently, the conjugation of different types of azaheterocycles in the same molecule has received considerable attention since the resulting ring-fused molecules often show unique organic optoelectronic properties and bioactive activities [1,2]. Among them, benzimidazo[1,2-*c*]quinazolines were intensively investigated and promising biological activities were observed, such as anticancer, antiviral, antimicrobial, anti-inflammatory and anticonvulsant [3-5]. Indeed, some of them are already used as antimicrobial agents and lipid peroxidation inhibitors [6]. Consequently, the development of an efficient way to prepare various benzimidazo[1,2-*c*]quinazoline derivatives is highly desired. Although some methods for the synthesis of benzimidazo[1,2-*c*]quinazoline derivatives have been reported quite recently [7-12], they often require complicated starting materials that are not readily available and need harsh conditions. Herein we report a CuI-catalyzed concise and efficient method for the synthesis of benzimidazo[1,2-*c*]quinazoline derivatives through the intramolecular *N*-arylation reaction of bromo-substituted quinazolin-4(3*H*)-imines that are easily prepared from *o*-cyanoaniline (**1**) and diaryliodonium salts **2** based on our previously published method [13,14] (Scheme 1).

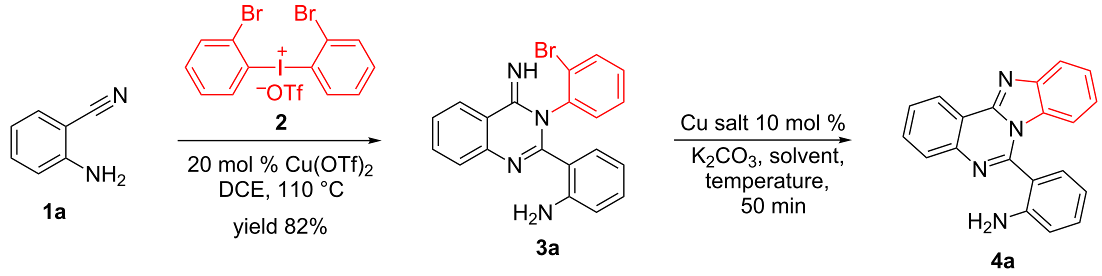


Scheme 1: CuI-catalyzed synthesis of benzimidazo[1,2-*c*]quinazolines **4** by intramolecular *N*-arylation of bromo-substituted quinazolin-4(3*H*)-imine derivatives **3**.

Results and Discussion

During the study of the synthesis of various carbocycles or heterocycles with copper catalysts [13-17], we found an interesting tandem reaction of *o*-cyanoanilines **1** and diaryliodonium salts **2** to produce quinazolin-4(3*H*)-imine derivatives **3** with Cu(OTf)$_2$ as the catalyst [13]. Encouraged by this finding, we initially attempted the reaction of *o*-cyanoaniline (**1a**) with di-(*o*-bromophenyl)iodonium salt **2**. The reaction of 2 equiv of *o*-cyanoaniline (**1a**) with **2** in DCE at 110 °C for 6 h in the presence of 20 mol % Cu(OTf)$_2$ bromo-substituted quinazolin-4(3*H*)-imine derivative **3a** in 82% isolated yield. The subsequent treatment of **3a** with CuI (0.1 equiv) and K$_2$CO$_3$ (1 equiv) in DMSO at room temperature for 50 min led to benzimidazo[1,2-*c*]quinazoline derivative **4a** in 37% yield (Table 1, entry 1). To optimize the yield of the desired product **4a** different conditions were screened. When the reaction temperature was increased to 60 °C, compound **4a** was formed in 98% yield (96% isolated, Table 1, entry 3). On the other hand, the replacement of DMSO by other solvents led to lower yields of **4a** even at elevated temperatures (Table 1, entries 5–9). Other copper salts such as Cu(OTf)$_2$, CuBr or CuCl were also able to catalyze the reaction, but they were not as efficient as CuI as the catalyst (Table 1, entries 5–9). It is worth mentioning that the imino group (sp^2) other than the amino group (sp^3) in **3a** reacted through the Cu-catalyzed Ullmann reaction [18-25].

Table 1: Optimization of reaction conditions for the synthesis of benzimidazo[1,2-c]quinazoline **4a** from quinazolin-4(3*H*)-imine derivative **3a**.

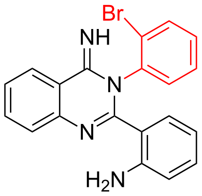
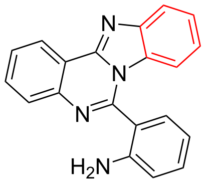
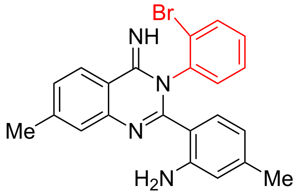
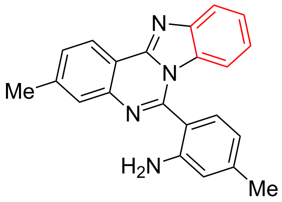
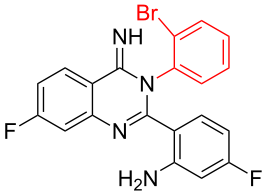
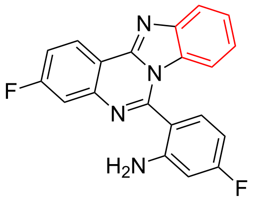
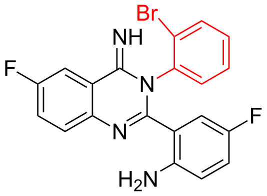
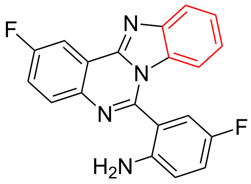
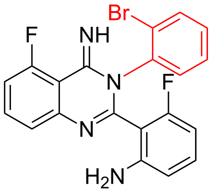
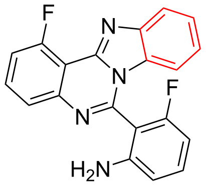
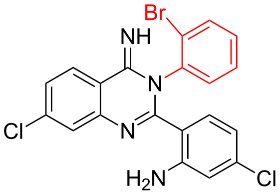
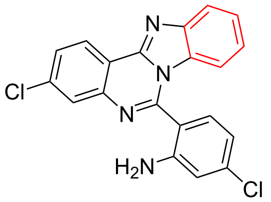


Entry	Cu salt	Temperature (°C)	Solvent	Yield (%)[a]
1	CuI	rt	DMSO	37
2	CuI	40	DMSO	72
3	CuI	60	DMSO	98 (96[b])
4	CuI	110	DMSO	98
5	CuI	110	DCE	51
6	CuI	110	CH_3CN	31
7	CuI	110	DCM	43
8	CuI	110	toluene	89
9	CuI	110	DCE	51
10	Cu(OTf)$_2$	60	DMSO	82
11	CuBr	60	DMSO	86
12	CuCl	60	DMSO	91

[a]Estimated crude yield by NMR with trichloroethylene as internal standard. [b]Isolated yield.

Inspired by the successful cyclization of quinazolin-4(3*H*)-imine **3a**, further imines were prepared and subjected to the cyclization conditions. Notably, in this protocol, after work-up, the desired bromo-substituted quinazolin-4(3*H*)-imine derivatives **3** were directly employed in the next step reaction without the need for chromatographic purification and the results are summarized in Table 2. Quinazolin-4(3*H*)-imines **3** having methyl, fluoro or chloro substituents all worked well in the

Table 2: CuI-catalyzed synthesis of benzimidazo[1,2-*c*]quinazolines **4** from bromo-substituted quinazolin-4(3*H*)-imines **3**.

Entry	Bromo-substituted quinazolin-4(3*H*)-imine **3**	Benzimidazo[1,2-*c*]quinazoline **4**	Yield[a]
1	 **3a**	 **4a**	96%
2	 **3b**	 **4b**	95%
3	 **3c**	 **4c**	95%
4	 **3d**	 **4d**	94%
5	 **3e**	 **4e**	93%
6	 **3f**	 **4f**	96%

[a]Isolated yield.

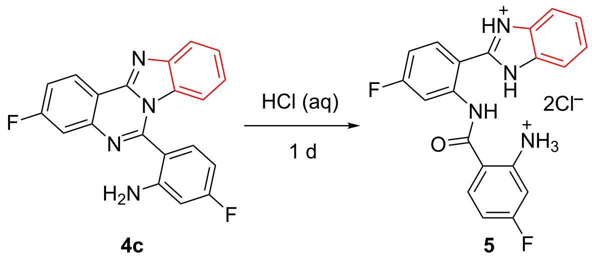
reaction and provided the corresponding quinazolines **4** in high yields (Table 2, entries 2, 3 and 6). In addition changing the position of the fluoro substituent did not affect the yield of the products (Table 2, entries 3–5).

To further expand the scope of the protocol, we attempted the synthesis of imine **3g** starting from two different nitriles. The reaction of *o*-cyanoaniline (**1a**), benzonitrile (**1g**) and di-(*o*-bromophenyl)iodonium salt **2** in the presence of $Cu(OTf)_2$ gave the desired imine **3g** together with imine **3a**. After isolation of **3g** it was further treated with 10 mol % of CuI in DMSO for 50 min to give product **4g** in quantitative yield (Scheme 2).

It is worth mentioning that during the course of our study, we observed that products **4** were not stable to acid. For example, treatment of **4c** with aqueous HCl solution led to ring-opening product **5** (Scheme 3). The structure of **5** was confirmed by X-ray diffraction analysis (Figure 1), clearly showing the cleavage of the quinazoline ring rather than the imidazole ring [26].

Conclusion

We have demonstrated a CuI-catalyzed pathway to produce functionalized benzimidazo[1,2-*c*]quinazoline derivatives from bromo-substituted quinazolin-4(3*H*)-imines through a selective intramolecular *N*-arylation reaction. The bromo-substituted quinazolin-4(3*H*)-imines are easily synthesized from readily available *o*-cyanoanilines and di-(*o*-bromophenyl)iodonium salt. The extension of the reaction and the investigation of the biological activity of the new products are currently under progress in our laboratory.



Scheme 3: Acid-promoted ring-opening reaction from quinazoline **4c** to **5**.

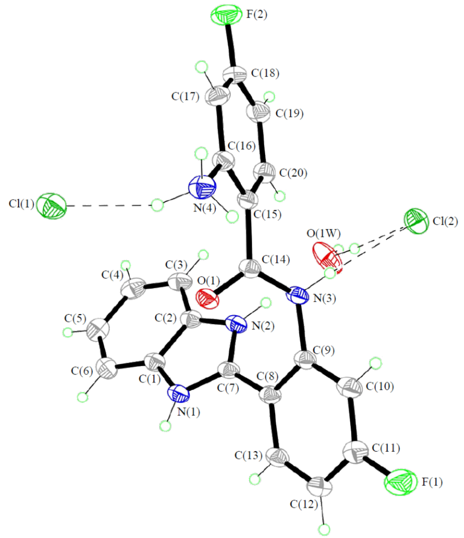
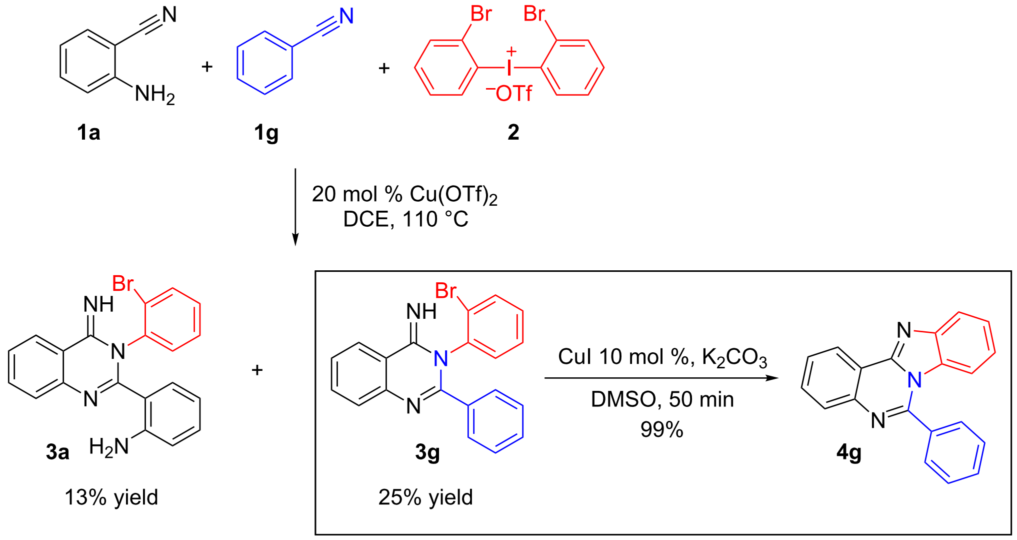


Figure 1: ORTEP drawing of **5**, $[C_{20}H_{16}F_2N_4O]{\cdot}2Cl{\cdot}H_2O$ with 35% probability ellipsoids, showing the atomic numbering scheme.



Scheme 2: Cu-catalyzed reaction of *o*-cyanoaniline (**1a**), benzonitrile (**1g**) and di-(*o*-bromophenyl)iodonium salt **2** producing imine **3g** and its subsequent cyclization in the presence of CuI.

Supporting Information

Supporting Information File 1

Full experimental procedures, characterization data, and NMR charts for compounds **3a–g** and **4a–g**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-258-S1.pdf]

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21102080, 21372138) and Tsinghua University Initiative Scientific Research Program (2011Z02150).

References

1. Michael, J. P. *Nat. Prod. Rep.* **2008,** *25,* 166–187. doi:10.1039/b612168n
2. Beniddir, M. A.; Le Borgne, E.; Iorga, B. I.; Loaëc, N.; Lozach, O.; Meijer, L.; Awang, K.; Litaudon, M. *J. Nat. Prod.* **2014,** *77,* 1117–1122. doi:10.1021/np400856h
3. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003,** *103,* 893–930. doi:10.1021/cr020033s
4. Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. *Org. Lett.* **2012,** *14,* 3894–3897. doi:10.1021/ol3016435
5. Khajavi, M. S.; Rad-moghadam, K.; Hazarkhani, H. *Synth. Commun.* **1999,** *29,* 2617–2624. doi:10.1080/00397919908086422
6. Insuasty, B. A.; Torres, H.; Quiroga, J.; Abonia, R.; Rodriguez, R.; Nogueras, M.; Sánchez, A.; Saitz, C.; Alvarez, S. L.; Zacchino, S. A. *J. Chil. Chem. Soc.* **2006,** *51,* 927–932. doi:10.4067/S0717-97072006000200018
7. Xu, S.; Lu, J.; Fu, H. *Chem. Commun.* **2011,** *47,* 5596–5598. doi:10.1039/c1cc10383k
8. Liu, Q.; Yang, H.; Jiang, Y.; Zhao, Y.; Fu, H. *RSC Adv.* **2013,** *3,* 15636–15644. doi:10.1039/c3ra41644e
9. Lamazzi, C.; Léonce, S.; Pfeiffer, B.; Renard, P.; Guillaumet, G.; Rees, C. W.; Besson, T. *Bioorg. Med. Chem. Lett.* **2000,** *10,* 2183–2185. doi:10.1016/S0960-894X(00)00427-3
10. Rohini, R.; Shanker, K.; Reddy, P. M.; Ho, Y.-P.; Ravinder, V. *Eur. J. Med. Chem.* **2009,** *44,* 3330–3339. doi:10.1016/j.ejmech.2009.03.022
11. Frère, S.; Thiéry, V.; Bailly, C.; Besson, T. *Tetrahedron* **2003,** *59,* 773–779. doi:10.1016/S0040-4020(02)01593-4
12. Molina, P.; Alajarin, M.; Vidal, A. *Tetrahedron Lett.* **1988,** *29,* 3849–3852. doi:10.1016/S0040-4039(00)82131-0
13. Pang, X.; Chen, C.; Su, X.; Li, M.; Wen, L. *Org. Lett.* **2014,** *16,* 6228–6231. doi:10.1021/ol503156g
14. Pang, X.; Lou, Z.; Li, M.; Wen, L.; Chen, C. *Eur. J. Org. Chem.* **2015,** 3361–3369. doi:10.1002/ejoc.201500161
15. Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem., Int. Ed.* **2013,** *52,* 5323–5327. doi:10.1002/anie.201300586
16. Su, X.; Chen, C.; Wang, Y.; Chen, J.; Lou, Z.; Li, M. *Chem. Commun.* **2013,** *49,* 6752–6754. doi:10.1039/C3CC43216E
17. Wang, Y.; Chen, C.; Zhang, S.; Lou, Z.; Su, X.; Wen, L. *Org. Lett.* **2013,** *15,* 4794–4797. doi:10.1021/ol402164s
18. Zhou, F.; Guo, J.; Liu, J.; Ding, K.; Yu, S.; Cai, Q. *J. Am. Chem. Soc.* **2012,** *134,* 14326–14329. doi:10.1021/ja306631z
19. Jones, G. O.; Liu, P.; Houk, K. N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010,** *132,* 6205–6213. doi:10.1021/ja100739h
20. Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002,** *102,* 1359–1470. doi:10.1021/cr000664r
21. Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006,** *106,* 2651–2710. doi:10.1021/cr0505268
22. Wen, L.-R.; Yuan, W.-K.; Li, M. *J. Org. Chem.* **2015,** *80,* 4942–4949. doi:10.1021/acs.joc.5b00288
23. Huang, X.; Yang, H.; Fu, H.; Qiao, R.; Zhao, Y. *Synthesis* **2009,** 2679–2688. doi:10.1055/s-0029-1216871
24. Wan, J.-P.; Wang, H.; Liu, Y.; Ding, H. *Org. Lett.* **2014,** *16,* 5160–5163. doi:10.1021/ol502506g
25. Liu, Y.; Wan, J.-P. *Chem. – Asian J.* **2012,** *7,* 1488–1501. doi:10.1002/asia.201101063
26. CCDC number: 1421043. The single crystal suitable for X-ray diffraction analysis was obtained by slow evaporation from a methanol/cyclohexane solution.

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doi:10.3762/bjoc.11.258

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Copper-catalyzed arylation of alkyl halides with arylaluminum reagents

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Full Research Paper

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Keywords:
alkylation; arylalkanes; copper; cross-coupling; organoaluminum

Beilstein J. Org. Chem. **2015,** *11,* 2400–2407.
doi:10.3762/bjoc.11.261

Received: 16 September 2015
Accepted: 12 November 2015
Published: 02 December 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

We report a Cu-catalyzed coupling between triarylaluminum reagents and alkyl halides to form arylalkanes. The reaction proceeds in the presence of *N*,*N*,*N'*,*N'*-tetramethyl-*o*-phenylenediamine (NN-1) as a ligand in combination with CuI as a catalyst. This catalyst system enables the coupling of primary alkyl iodides and bromides with electron-neutral and electron-rich triarylaluminum reagents and affords the cross-coupled products in good to excellent yields.

Introduction

Cross-coupling reactions represent one of the most important transformation for carbon–carbon (C–C) bond formation in organic synthesis [1-9]. These reactions, typically catalyzed by Pd and Ni, exploit a wide range of organometallic reagents of Mg, Zr, Zn, Sn, Al, B, Si and In as sources of nucleophiles. Among these metals/non-metals, Al offers a unique feature due to its high chemoselectivity and Lewis acidity [10-12]. In addition, Al also has low toxicity and is an inexpensive and earth-abundant metal. Organoaluminum reagents can be prepared directly from metallic aluminum [13-15], which further highlights the potential scope of these reagents in organic synthesis. However, despite extensive investigations and applications of organometallic reagents of Si, B, Mg, Zn and Sn in cross-coupling, the utility of organometallic complexes of Al are limited [13,14,16-21]. In many cases, direct transmetalation of organoalanes to Pd are sluggish and require $ZnCl_2$ or $CdCl_2$ to facilitate reactions through sequential transmetalations [19]. In some cases, intramolecular coordination to Al also enables the couplings of alkylalanes with organo halides [21]. Knochel [15] and Hoveyda [22] have also shown that organoaluminum reagents are capable of transmetalating to Cu-salts. Inspired by these literature reports and our recent investigations, we envisioned that organoaluminum reagents could participate as nucleophile sources in Cu-catalyzed cross-coupling reactions.

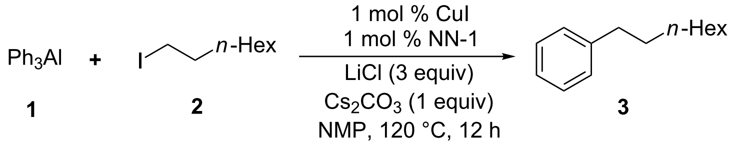
In this artcle, we show that triarylaluminum reagents are excellent coupling partners for Cu-catalyzed cross-coupling reactions. The reaction proceeds for the coupling with primary alkyl iodides and bromides in good to excellent yields.

Results and Discussion

Recently, we [23-27] and others [10,28-39] reported efficient cross-couplings of oganometallic reagents of Si, B, In, Zr, Zn, Mg and Sn with organo halides [40,41]. Under our reaction conditions, a catalyst derived from the combination of CuI and 2-(diphenylphosphino)-*N*,*N*-dimethylaniline (PN-1) remains highly effective for coupling many of these organometallic reagents with aryl halides. In order to expand the scope of our coupling reactions, we utilized the standard condtions for the reaction of commercially available Ph_3Al with 1-iodooctane using 1 mol % each of CuI and PN-1. However, the product, 1-phenyloctane (**3**), was formed only in 34% yield (Table 1, entry 1). Further optimization of the reaction conditions revealed that the coupling proceeded in 66% GC yield when the reaction was performed in NMP using 1 equivalent of Cs_2CO_3 as a base and 3 equivlents of LiCl as an additive in the absence of a ligand (Table 1, entry 2). We then screened a variety of ligands (Scheme 1) and found that *N*,*N*,*N'*,*N'*-tetramethyl-*o*-phenylenediamine (NN-1) was an efficient ligand for CuI that enabled us to increase the product yield to 81% GC yields (76% isolated, Table 1, entry 3) [10,35,42-44]. Reactions containing other PN- and NN-based ligands that are analogous to PN-1 and NN-1 (Scheme 1) afforded cross-coupled product **3** in lower yields than the reaction performed in the absence of NN-1. Reactions containing the bisphosphine ligand, *o*-bis(diphenylphosphine)benzene (PP) and anionic ligands such as 8-hydroxyquinoline (NO) and 2,2,6,6-tetramethyl-3,5-heptanedione (OO, Scheme 1) also formed the product **3** in lower yields and the reaction performed in the absence of NN-1. The reaction does not proceed in the absence of CuI (Table 1, entry 4). The cross-coupled product **3** is formed in 50% and 54% yield, respectively, in the absence of LiCl and Cs_2CO_3 (Table 1, entries 5 and 6). The reacton with 2 and 4 equivalents of LiCl also afforded product **3** in comparable yields (78% and 76%, respectively) to that of the standard reaction (Table 1, entries 7 and 8). However, excess of LiCl was found to be detrimental to the reaction (Table 1, entry 9). The reaction could also be performed at a temperature as low as 80 °C affording the coupled product **3** only in slightly lower yields than that of the standard reaction (Table 1, entries 10 and 11).

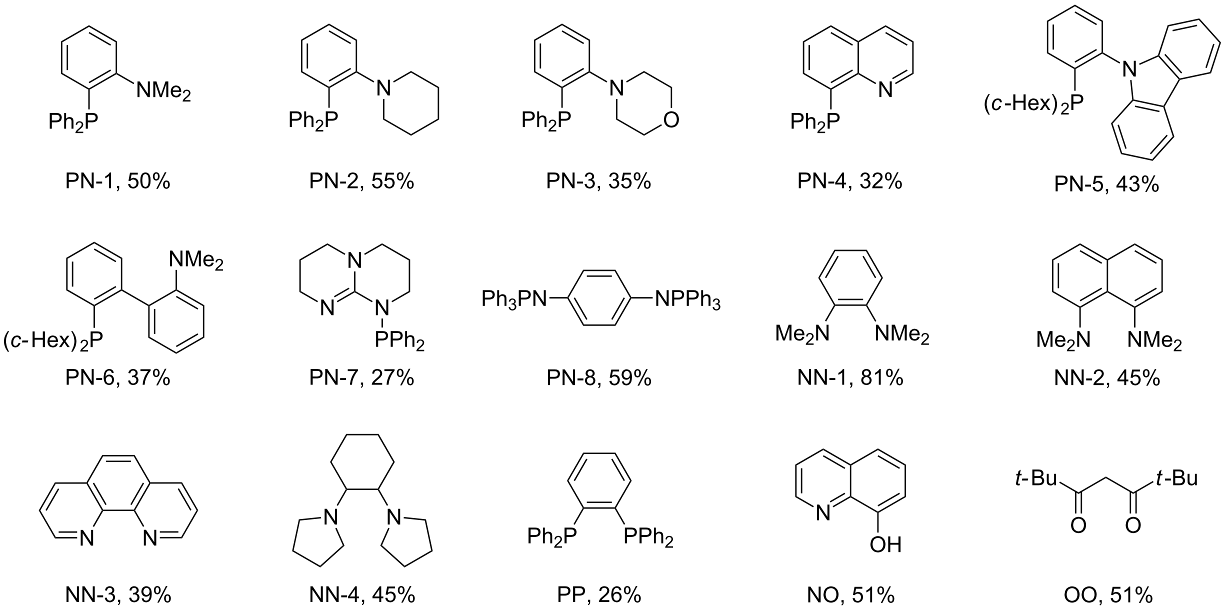
After establishing the combination of NN-1 and CuI as the best catalyst, we began to explore the substrate scope of the reaction. While the reaction proceeded in good yields with alkyl iodides (Table 2, entries 1–3) by using 1 mol % of the catalyst, reactions with alkyl bromides, which are more readily available and less expensive than alkyl iodides, required 10 mol % of NN-1/CuI (Table 2, entries 4–15). The reaction can be performed with electron-neutral and electron-rich triarylaluminum reagents [45]. The reaction tolerates a variety of functional groups on alkyl halides including highly sensitive esters

Table 1: Optimization of reaction conditions[a].



Entry	Variation from the standard conditions	Yield (%)[b]
1	PN-1 instead of NN-1 in DMF, no Cs_2CO_3	34
2	No NN-1	66
3	none	81 (76)
4	without CuI	0
5	without LiCl	50
6	without Cs_2CO_3	54
7	2 equiv LiCl	78
8	4 equiv LiCl	76
9	6 equiv LiCl	35
10	100 °C	78
11	80 °C	75

[a]Reactions were run in 0.5 mL DMF. Commercially available Ph_3Al was used. [b]GC yields (average of at least two parallel runs) calibrated against 2-nitrobiphenyl as an internal standard. Value in parenthesis is the isolated yield (1.0 mmol).



Scheme 1: Ligands used for reaction optimization.

(Table 2, entries, 5, 9 and 11), nitriles (Table 2, entries 6 and 7) and olefins (Table 2, entries 4, 8, 10, 13 and 15) [46]. With 10 mol % catalyst loading, the reaction can also be extended to the coupling of triarylaluminum reagents with benzyl bromides (Table 2, entries 12 and 14) [43].

Based on literature reports and our recent mechanistic work on Cu-catalyzed cross-couplings [23-25], we propose a catalytic cycle for the current reaction (Scheme 2). It is evident from the optimization of reaction conditions that both NN-1 and LiCl improve product yields for the current coupling of triarylalu-

Table 2: Coupling of triarylaluminum reagents with alkyl iodides and bromides[a].

$$\mathrm{Ar_3Al} + \text{Alkyl–I, Br} \xrightarrow[\text{NMP, 120 °C, 12 h}]{\substack{\text{1 or 10 mol \% CuI} \\ \text{1 or 10 mol \% PN-1}}} \text{Alkyl–Ar}$$

$$\text{[LiCl (3 equiv)], } \mathrm{Cs_2CO_3} \text{ (1 equiv)}$$

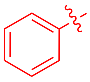
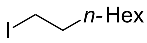
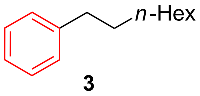
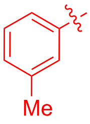
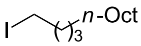
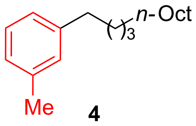
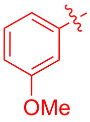
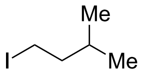
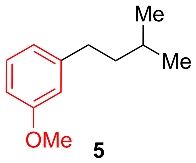
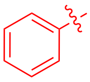
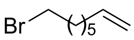
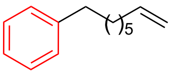
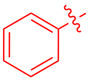
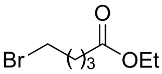
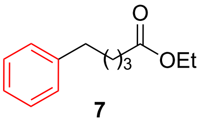
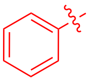
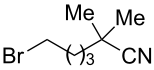
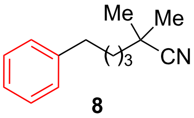
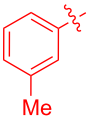
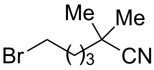
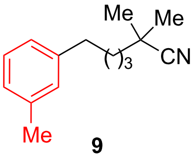
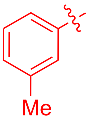
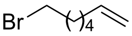
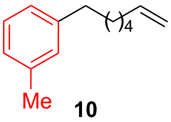
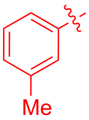
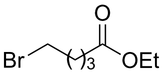
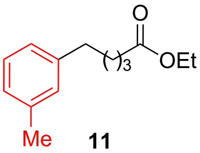
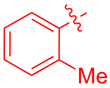
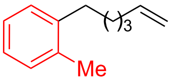
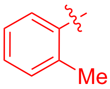
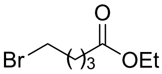
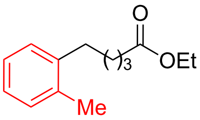
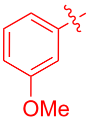
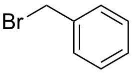
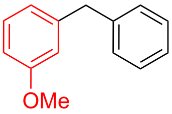
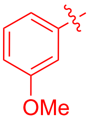
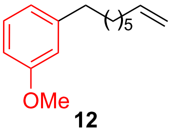
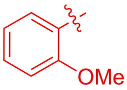
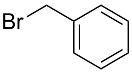
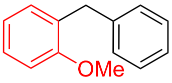
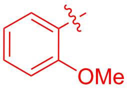
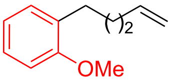
Entry	Ar in Ar_3Al	Alkyl–I,Br	Alkyl–Ar	yield (%)[b]
1			 **3**	76
2			 **4**	61
3			 **5**	49
4			 **6**	60

Table 2: Coupling of triarylaluminum reagents with alkyl iodides and bromides[a]. (continued)

5			 **7**	58
6			 **8**	71
7			 **9**	88
8			 **10**	53
9			 **11**	59
10			 **12**	46
11			 **13**	92
12			 **14**	53
13			 **12**	52
14			 **16**	68
15			 **17**	47

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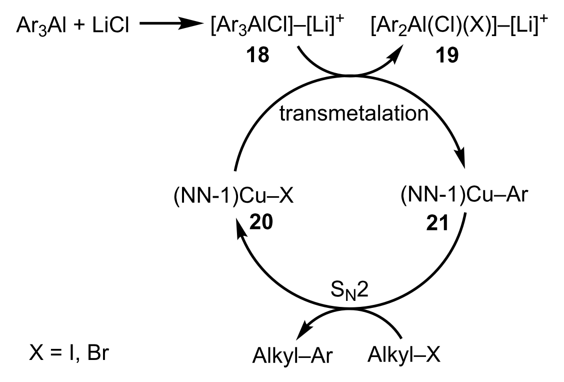
[a] Reactions were run in 5 mL DMF. Reactions for entries 1–3 were run with 1 mol % NN-1/CuI. Reactions for entries 4–15 were run with 10 mol % NN-1/CuI. Triarylaluminum reagents, except the commercially available Ph_3Al, were prepared from the reaction of 3 equivalents of ArLi reagents with $AlCl_3$ (99.99% purity) in THF at room temperature and were used without further purification. Each reaction contains 3 equivalents of LiCl, written in parenthesis below the reaction arrow, which is generated during the preparation of triarylaluminum reagents. [b] Yields are for products isolated by column chromatography from a 1.0 mmol scale reaction.

minum reagents with alkyl halides (Table 1). As such, we believe that organoaluminate complexes such as **18**, generated from the binding of LiCl to three-coordinate triarylaluminum reagents, are the actual species in solution that undergo transmetalation with NN-bound CuX (X = I, Br) to generate (NN)CuAr complexes as the reaction intermediates. Catalytically competent Cu^I-complexes that contain nitrogen-based ligands have previously been synthesized and fully characterized structurally [47-51]. Triorganoaluminum complexes are also known to form triorganoaluminate species in the presence of anions in solution [52-57]. In addition, organoaluminum reagents have been demonstrated to undergo transmetalation with Cu salts based on their participation in allylic and conjugate addition reactions [11,15,43]. Similar Cu-catalyzed couplings of organometallic reagents with alkyl electrophiles have previously been shown to proceed via an S_N2 process [34,35]. Therefore, we believe that a similar mechanistic scenario can also be envisioned in the current Cu-catalyzed cross-coupling of triarylaluminum reagents with primary alkyl halides that involves (NN)CuAr as the reaction intermediates.



Scheme 2: Proposed catalytic cycle.

Conclusion

In summary, we have developed a Cu-catalyzed coupling of triarylaluminum reagents with primary alkyl iodides and bromides. The reaction proceeds in the presence of NN-1/CuI as an effective catalyst. Electron-neutral and electron-rich triarylaluminum reagents can be coupled with a variety of alkyl iodides and bromides containing a range of sensitive functional groups such as olefins, nitriles and esters, affording the alkylated arenes in good to excellent yields.

Experimental

General information. All the reactions and handling of chemicals were done inside a nitrogen-filled glovebox unless stated otherwise. All glassware were dried in an oven before use. All commercial reagents were used as received without further purification. Anhydrous solvents and triphenylaluminum were purchased from Sigma-Aldrich. Pure triarylaluminum reagents other than Ph_3Al were synthesized following the reported procedure [56]. Ligands PN-5, PN-6, NN-2, NN-3, PP, NO and OO were purchased from commercial sources. Ligands PN-1, PN-2, PN-3, PN-4, PN-7 [58], PN-8, NN-1 [59], and NN-4 [60] were synthesized following the reported procedures [61]. ^1H and ^{13}C NMR spectra were recorded on a Bruker instrument (300 and 75 MHz, respectively) and internally referenced to the residual solvent signals of $CDCl_3$ at 7.26 and at 77.16 ppm, respectively.

General procedure for cross-coupling. To a suspension of $AlCl_3$ (133.3 mg, 1.0 mmol) in THF (2 mL) was added dropwise a solution of aryllithium (3.0 mmol, generated from the lithiation of aryl iodides with 1 equiv of *n*-BuLi in THF) at room temperature. After 45 minutes, the solvent was removed to obtain a triarylaluminum reagent containing 3 equivalents of LiCl, which was then dissolved in NMP (5 mL). Alkyl halide (1.0 mmol), CuI (1.9 mg, 0.010 mmol, for alkyl iodides; 19.0 mg, 0.10 mmol, for alkyl bromides) and NN-1 (1.6 mg, 0.010 mmol, for alkyl iodides; 16.4 mg, 0.10 mmol, for alkyl bromides) were then added to the solution of the triarylaluminum reagent. The reaction mixture was then tightly capped, taken out of the glovebox, placed in an oil bath pre-heated to 120 °C and vigorously stirred. After 12 h, the reaction mixture was cooled to room temperature, diluted with ethyl acetate (15 mL) and washed with H_2O (5 mL × 3). The aqueous fraction was extracted back with ethyl acetate (5 mL × 3) and combined with the first ethyl acetate fraction. The combined ethyl acetate fractions were dried over Na_2SO_4 and the solvent was removed on a rotary evaporator. The product was purified by silica gel column chromatography using 0–5% ethyl acetate in hexanes.

***n*-Octylbenzene (3)** [62]: The title compound **3** was obtained as a colorless oil (144 mg, 76% yield) after purification by silica gel column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 6.6 Hz, 3H), 1.29–1.32 (m, 10H), 1.58–1.68 (m, 2H), 2.62 (m, J = 8.1 Hz, 2H), 7.16–7.21 (m, 3H), 7.27–7.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.8, 29.4, 29.5, 29.6, 31.7, 32.0, 36.1, 125.7, 128.3, 128.5, 143.1; GC–MS (*m*/*z*) 190.1.

1-Dodecyl-3-methylbenzene (4): The title compound **4** was obtained as yellow oil (159 mg, 61% yield) after purification by silica gel column chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 6.3 Hz, 3H), 1.28–1.31 (m, 18H), 1.53–1.64 (m, 2H), 2.35 (s, 3H), 2.55–2.60 (m, 2H), 6.99–7.02 (m, 3H), 7.18 (t, J = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 21.6, 22.9, 27.1, 29.5, 29.6, 29.7, 29.8, 31.7, 32.1, 36.1, 45.3, 125.5, 126.4, 128.3, 129.4, 137.9, 143.1; GC–MS (*m*/*z*) 260.1.

1-Isopentyl-3-methoxybenzene (5): The title compound **5** was obtained as colorless oil (87 mg, 49% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.93 (s, 6H), 1.46–1.64 (m, 3H), 2.6 (t, *J* = 7.8 Hz, 2H), 3.80 (s, 3H), 6.71–6.80 (m, 2H), 7.12–7.38 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 22.7, 27.8, 33.9, 40.8, 55.2, 110.9, 114.3, 120.9, 129.3, 144.9, 159.7; GC–MS (*m*/*z*) 178.1.

7-Octen-1-ylbenzene (6) [63]: The title compound **6** was obtained as a colorless oil (113 mg, 60% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.33–1.41 (m, 6H), 1.60–1.65 (m, 2H), 2.00–2.08 (m, 2H), 2.61 (t, *J* = 7.5 Hz, 2H), 4.91–5.03 (m, 2H), 5.75–5.88 (m, 1H), 7.17–7.20 (m, 3H), 7.25–7.31 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 28.9, 29.1, 29.2, 31.5, 33.9, 36.0, 114.3, 125.6, 128.3, 128.5, 139.2, 142.9; GC–MS (*m*/*z*) 188.1.

Ethyl 5-phenylvalerate (7) [64]: The title compound **7** was obtained as yellow oil (120 mg, 58% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.26 (t, *J* = 9.0 Hz, 3H), 1.66–1.70 (m, 4H), 2.31–2.35 (m, 2H), 2.62–2.67 (m, 2H), 4.13 (q, *J* = 6.9 Hz, 2H), 7.17–7.22 (m, 3H), 7.26–7.32 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.3, 24.7, 33.5, 34.2, 35.6, 60.3, 125.8, 128.4, 128.4, 142.2, 173.7; GC–MS (*m*/*z*) 206.1.

2,2-Dimethyl-6-phenylhexanenitrile (8) [65]: The title compound **8** was obtained as yellow oil (143 mg, 71% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.34 (s, 6H), 1.54–1.58 (m, 4H), 1.62–1.72 (m, 2H), 2.63–2.68 (m, 2H), 7.17–7.23 (m, 3H), 7.26–7.33 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 25.0, 26.7, 31.5, 32.4, 35.7, 40.9, 125.2, 125.8, 128.4, 142.2; GC–MS (*m*/*z*) 201.1.

2,2-Dimethyl-6-(3-methylphenyl)hexanenitrile (9): The title compound **9** was obtained as yellow oil (189 mg, 88% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.35 (s, 6H), 1.55–1.59 (m, 4H), 1.63–1.72 (m, 2H), 2.36 (s, 3H), 2.61–2.67 (m, 2H), 6.99–7.02 (m, 3H), 7.19 (t, *J* = 3.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 21.4, 25.0, 26.6, 31.5, 32.3, 35.6, 41.3, 125.2, 125.3, 126.5, 128.2, 129.2, 137.8, 142.1; GC–MS (*m*/*z*) 215.1.

1-(6-Hepten-1-yl)-3-methylbenzene (10): The title compound **10** was obtained as colorless oil (100 mg, 53% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.34–1.45 (m, 4H), 1.59–1.66 (m, 2H), 2.02–2.09 (m, 2H), 2.33 (s, 3H), 2.57 (t, *J* = 7.8 Hz, 2H), 4.92–5.03 (m, 2H), 5.75–5.88 (m, 1H), 6.97–7.00 (m, 3H), 7.17 (t, *J* = 3.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 28.8, 29.7, 31.4, 33.7, 35.6, 114.2, 125.4, 126.3, 128.1, 129.2, 137.7, 139.1, 142.8; GC–MS (*m*/*z*) 188.2.

Ethyl 5-(3-methylphenyl)valerate (11) [66]: The title compound **11** was obtained as a yellow oil (130 mg, 59% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.66–1.72 (m, 4H), 2.33–2.37 (m, 5H), 2.60–2.65 (m, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 6.98–7.04 (m, 3H), 7.18 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.3, 21.5, 24.7, 31.0, 34.3, 35.6, 60.2, 125.4, 126.5, 128.3, 129.3, 137.9, 142.2, 173.7; GC–MS (*m*/*z*) 220.2.

1-(5-Hexen-1-yl)-2-methylbenzene (12) [67]: The title compound **12** was obtained as colorless oil (80 mg, 46% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.48–1.67 (m, 4H), 2.09–2.16 (m, 2H), 2.33 (s, 3H), 2.59–2.65 (m, 2H), 4.98–5.07 (m, 2H), 5.77–5.91 (m, 1H), 7.11–7.15 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 19.4, 29.1, 29.9, 33.3, 33.8, 114.6, 125.9, 125.9, 128.9, 130.2, 135.9, 139.0, 141.0; GC–MS (*m*/*z*) 174.1.

Ethyl 5-(2-methylphenyl)valerate (13) [68]: The title compound **13** was obtained as yellow oil (203 mg, 92% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.58–1.76 (m, 4H), 2.31–2.37 (m, 5H), 2.6–2.65 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 7.11–7.12 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 14.4, 19.4, 25.1, 29.8, 33.1, 34.4, 60.4, 126.0, 128.9, 130.3, 135.9, 140.5, 173.8; GC–MS (*m*/*z*) 220.2.

1-Benzyl-3-methoxybenzene (14) [69]: The title compound **14** was obtained as a light yellow oil (105 mg, 53% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.82 (s, 3H), 3.8 (s, 2H), 6.77–6.84 (m, 2H), 6.91 (t, *J* = 9.0 Hz, 1H), 7.20–7.34 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 42.0, 55.2, 111.4, 114.9, 121.4, 126.2, 128.3, 128.5, 129.5, 140.9, 142.7, 159.8; GC–MS (*m*/*z*) 198.1.

1-Methoxy-3-(oct-7-en-1-yl)benzene (15): The title compound **15** was obtained as colorless oil (113 mg, 52% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.27–1.42 (m, 4H), 1.55–1.65 (m, 4H), 2.01–2.05 (m, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 4.92–5.02 (m, 2H), 5.75–5.88 (m, 1H), 6.72–7.36 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 29.1, 29.3, 29.6, 31.4, 33.9, 35.8, 55.2, 110.9, 114.3, 121.0, 129.3, 129.8, 139.3, 144.7; GC–MS (*m*/*z*) 218.2.

1-Benzyl-2-methoxybenzene (16) [70]: The title compound **16** was obtained as light yellow oil (135 mg, 68% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 4.04 (s, 2H), 6.90–6.96 (m, 2H), 7.11–7.14 (m, 1H), 7.21–7.36 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.9, 55.4, 110.5, 120.6, 125.8, 127.5, 128.3, 129.0, 129.7, 130.4, 141.1, 157.4; GC–MS (*m*/*z*) 198.2.

1-Methoxy-2-(pent-4-en-1-yl)benzene (17) [71]: The title compound **17** was obtained as yellow oil (83 mg, 47% yield) after purification by silica gel column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64–1.74 (m, 2H), 2.08–2.15 (m, 2H), 2.61–2.66 (m, 2H), 3.83 (s, 3H), 5.01–5.08 (m, 2H), 5.80–5.94 (m, 1H), 6.84–6.92 (m, 3H), 7.15 (t, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 29.2, 33.8, 41.5, 55.4, 110.4, 114.5, 117.9, 120.4, 127.0, 139.1, 145.3, 157.2; GC–MS (*m*/*z*) 176.1.

Acknowledgments

We thank the University of New Mexico (UNM) for financial support, and upgrades to the NMR (NSF grants CHE08-40523 and CHE09-46690) and MS Facilities.

References

1. Heck, R. F. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 833 ff.
2. Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions;* Wiley-VCH: New York, 1998.
3. Negishi, E.-i.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005,** *38,* 71.
4. Fu, G. C. *Acc. Chem. Res.* **2008,** *41,* 1555–1564. doi:10.1021/ar800148f
5. Knochel, P.; Jones, P., Eds. *Organozinc Reagents: A Practical Approach;* Oxford University Press: New York, 1999.
6. Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011,** *111,* 1417–1492. doi:10.1021/cr100327p
7. Chang, W.-T. T.; Smith, R. C.; Regens, C. S.; Bailey, A. D.; Werner, N. S.; Denmark, S. E. *Org. React.* **2011,** *75,* 213–746.
8. Nakao, Y.; Hiyama, T. *Chem. Soc. Rev.* **2011,** *40,* 4893–4901. doi:10.1039/c1cs15122c
9. Sore, H. F.; Galloway, W. R. J. D.; Spring, D. R. *Chem. Soc. Rev.* **2012,** *41,* 1845–1866. doi:10.1039/C1CS15181A
10. Tsubouchi, A.; Muramatsu, D.; Takeda, T. *Angew. Chem., Int. Ed.* **2013,** *52,* 12719–12722. doi:10.1002/anie.201306882
11. Thaler, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2009,** *48,* 645–648. doi:10.1002/anie.200804446
12. Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006,** *45,* 6040–6044. doi:10.1002/anie.200601450
13. Huo, S. *Org. Lett.* **2003,** *5,* 423–425. doi:10.1021/ol0272693
14. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005,** *44,* 4442–4489. doi:10.1002/anie.200500368
15. Blümke, T. D.; Groll, K.; Karaghiosoff, K.; Knochel, P. *Org. Lett.* **2011,** *13,* 6440–6443. doi:10.1021/ol202733v
16. Chen, X.; Zhou, L.; Li, Y.; Xie, T.; Zhou, S. *J. Org. Chem.* **2014,** *79,* 230–239. doi:10.1021/jo4024123
17. Naka, H.; Uchiyama, M.; Matsumoto, Y.; Wheatley, A. E. H.; McPartlin, M.; Morey, J. V.; Kondo, Y. *J. Am. Chem. Soc.* **2007,** *129,* 1921–1930. doi:10.1021/ja064601n
18. Getmanenko, Y. A.; Twieg, R. J. *J. Org. Chem.* **2008,** *73,* 830–839. doi:10.1021/jo701812t
19. Koszinowski, K.; Böhrer, P. *Organometallics* **2009,** *28,* 771–779. doi:10.1021/om800947t
20. Lipshutz, B. H.; Bülow, G.; Lowe, R. F.; Stevens, K. L. *Tetrahedron* **1996,** *52,* 7265–7276. doi:10.1016/0040-4020(96)00250-5
21. Blum, J.; Gelman, D.; Baidossi, W.; Shakh, E.; Rosenfeld, A.; Aizenshtat, Z.; Wassermann, B. C.; Frick, M.; Heymer, B.; Schutte, S.; Wernik, S.; Schumann, H. *J. Org. Chem.* **1997,** *62,* 8681–8686. doi:10.1021/jo970822n
22. Dabrowski, J. A.; Villaume, M. T.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013,** *52,* 8156–8159. doi:10.1002/anie.201304035
23. Gurung, S. K.; Thapa, S.; Vangala, A. S.; Giri, R. *Org. Lett.* **2013,** *15,* 5378–5381. doi:10.1021/ol402701x
24. Thapa, S.; Gurung, S. K.; Dickie, D. A.; Giri, R. *Angew. Chem., Int. Ed.* **2014,** *53,* 11620–11624. doi:10.1002/anie.201407586
25. Gurung, S. K.; Thapa, S.; Kafle, A.; Dickie, D. A.; Giri, R. *Org. Lett.* **2014,** *16,* 1264–1267. doi:10.1021/ol500310u
26. Thapa, S.; Basnet, P.; Gurung, S. K.; Giri, R. *Chem. Commun.* **2015,** *51,* 4009–4012. doi:10.1039/C5CC00116A
27. Thapa, S.; Kafle, A.; Gurung, S. K.; Montoya, A.; Riedel, P.; Giri, R. *Angew. Chem., Int. Ed.* **2015,** *54,* 8236–8240. doi:10.1002/anie.201502379
28. Thathagar, M. B.; Beckers, J.; Rothenberg, G. *J. Am. Chem. Soc.* **2002,** *124,* 11858–11859. doi:10.1021/ja027716+
29. Li, J.-H.; Li, J.-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. *J. Org. Chem.* **2007,** *72,* 2053–2057. doi:10.1021/jo0623742
30. Zhou, Y.; You, W.; Smith, K. B.; Brown, M. K. *Angew. Chem., Int. Ed.* **2014,** *53,* 3475–3479. doi:10.1002/anie.201310275
31. You, W.; Brown, M. K. *J. Am. Chem. Soc.* **2014,** *136,* 14730–14733. doi:10.1021/ja509056j
32. Ito, H.; Sensui, H.-o.; Arimoto, K.; Miura, K.; Hosomi, A. *Chem. Lett.* **1997,** *26,* 639–640. doi:10.1246/cl.1997.639
33. Cornelissen, L.; Lefrancq, M.; Riant, O. *Org. Lett.* **2014,** *16,* 3024–3027. doi:10.1021/ol501140p
34. Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012,** *134,* 11124–11127. doi:10.1021/ja304848n
35. Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007,** *46,* 2086–2089. doi:10.1002/anie.200603451
36. Cahiez, G.; Gager, O.; Buendia, J. *Angew. Chem., Int. Ed.* **2010,** *49,* 1278–1281. doi:10.1002/anie.200905816
37. Mohapatra, S.; Bandyopadhyay, A.; Barma, D. K.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003,** *5,* 4759–4762. doi:10.1021/ol035458v
38. Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996,** *118,* 2748–2749. doi:10.1021/ja9541239
39. Li, J.-H.; Tang, B.-X.; Tao, L.-M.; Xie, Y.-X.; Liang, Y.; Zhang, M.-B. *J. Org. Chem.* **2006,** *71,* 7488–7490. doi:10.1021/jo061220j
40. Thapa, S.; Shrestha, B.; Gurung, S. K.; Giri, R. *Org. Biomol. Chem.* **2015,** *13,* 4816–4827. doi:10.1039/C5OB00200A
41. Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004,** *248,* 2337–2364. doi:10.1016/j.ccr.2004.09.014
42. Yang, C.-T.; Zhang, Z.-Q.; Liu, Y.-C.; Liu, L. *Angew. Chem., Int. Ed.* **2011,** *50,* 3904–3907. doi:10.1002/anie.201008007

43. Cornelissen, L.; Cirriez, V.; Vercruysse, S.; Riant, O. *Chem. Commun.* **2014,** *50,* 8018–8020. doi:10.1039/c4cc02923b
44. The reaction of Ph_3Al with 1-iodooctane using the Schlenk technique afforded cross-coupled product **3** in 72% yield.
45. Cross-coupling of electron-deficient $(4\text{-}FC_6H_4)_3Al$ with benzyl bromide afforded the product only in 18% yield.
46. The conversion of bromoolefins is generally over 90%. The low to moderate yields of the cross-coupled products could result from protodebromination of the bromoolefins.
47. Giri, R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010,** *132,* 15860–15863. doi:10.1021/ja105695s
48. Tye, J. W.; Weng, Z.; Giri, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2010,** *49,* 2185–2189. doi:10.1002/anie.200902245
49. Tye, J. W.; Weng, Z.; Johns, A. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008,** *130,* 9971–9983. doi:10.1021/ja076668w
50. Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009,** *131,* 78–88. doi:10.1021/ja0781893
51. Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008,** *130,* 15185–15192. doi:10.1021/ja805688p
52. Schiefer, M.; Hatop, H.; Roesky, H. W.; Schmidt, H.-G.; Noltemeyer, M. *Organometallics* **2002,** *21,* 1300–1303. doi:10.1021/om010690v
53. Pour, N.; Gofer, Y.; Major, D. T.; Keinan-Adamsky, K.; Gottlieb, H. E.; Aurbach, D. *Organometallics* **2013,** *32,* 3165–3173. doi:10.1021/om300865a
54. Pour, N.; Gofer, Y.; Major, D. T.; Aurbach, D. *J. Am. Chem. Soc.* **2011,** *133,* 6270–6278. doi:10.1021/ja1098512
55. Damrauer, R.; Krempp, M.; Damrauer, N. H.; Schmidt, M. W.; Gordon, M. S. *J. Am. Chem. Soc.* **1993,** *115,* 5218–5226. doi:10.1021/ja00065a038
56. Krieck, S.; Görls, H.; Westerhausen, M. *Organometallics* **2008,** *27,* 5052–5057. doi:10.1021/om800509p
57. We analyzed a mixture of Ph_3Al and LiCl using ^{27}Al NMR. No significant change was observed in the ^{27}Al NMR spectra. However, due to the strong Lewis acidic nature of Ph_3Al, formation of a small amount of $[Ph_3AlCl]^-[Li]^+$ cannot be ruled out without further experiments.
58. Dyer, P. W.; Fawcett, J.; Hanton, M. J. *Organometallics* **2008,** *27,* 5082–5087. doi:10.1021/om8005933
59. Brown, H. C.; Grayson, M. *J. Am. Chem. Soc.* **1953,** *75,* 20–24. doi:10.1021/ja01097a006
60. Periasamy, M.; Seenivasaperumal, M.; Padmaja, M.; Rao, V. D. *ARKIVOC* **2004,** No. viii, 4–11.
61. Lindner, R.; van den Bosch, B.; Lutz, M.; Reek, J. N. H.; van der Vlugt, J. I. *Organometallics* **2011,** *30,* 499–510. doi:10.1021/om100804k
62. Breitenfeld, J.; Wodrich, M. D.; Hu, X. *Organometallics* **2014,** *33,* 5708–5715. doi:10.1021/om500506y
63. Uemura, M.; Yorimitsu, H.; Oshima, K. *Chem. Commun.* **2006,** 4726–4728. doi:10.1039/b612173j
64. Di Franco, T.; Boutin, N.; Hu, X. *Synthesis* **2013,** *45,* 2949–2958. doi:10.1055/s-0033-1338544
65. Maruyama, K.; Noguchi-Yachide, T.; Sugita, K.; Hashimoto, Y.; Ishikawa, M. *Bioorg. Med. Chem. Lett.* **2010,** *20,* 6661–6666. doi:10.1016/j.bmcl.2010.09.011
66. Lipshutz, B. H.; Blomgren, P. A.; Kim, S.-K. *Tetrahedron Lett.* **1999,** *40,* 197–200. doi:10.1016/S0040-4039(98)02271-0
67. Liu, J.-H.; Yang, C.-T.; Lu, X.-Y.; Zhang, Z.-Q.; Xu, L.; Cui, M.; Lu, X.; Xiao, B.; Fu, Y.; Liu, L. *Chem. – Eur. J.* **2014,** *20,* 15334–15338. doi:10.1002/chem.201405223
68. Kori, M.; Hamamura, K.; Fuse, H.; Yamamoto, T. JP Patent JP2002/000532, 2002; p 748.
69. Dunsford, J. J.; Clark, E. R.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2015,** *54,* 5688–5692. doi:10.1002/anie.201411403
70. Tobisu, M.; Takahira, T.; Chatani, N. *Org. Lett.* **2015,** *17,* 4352–4355. doi:10.1021/acs.orglett.5b02200
71. Ellis-Davies, G. C. R.; Gilbert, A.; Heath, P.; Lane, J. C.; Warrington, J. V.; Westover, D. L. *J. Chem. Soc., Perkin Trans. 2* **1984,** 1833–1841. doi:10.1039/p29840001833

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doi:10.3762/bjoc.11.261

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Copper-catalyzed asymmetric conjugate addition of organometallic reagents to extended Michael acceptors

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Review

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Keywords:
conjugate additions; electron-deficient alkenes; enantioselective catalysis; extended Michael acceptors; organometallic nucleophiles; sequential addition

Beilstein J. Org. Chem. **2015,** *11,* 2418–2434.
doi:10.3762/bjoc.11.263

Received: 10 September 2015
Accepted: 11 November 2015
Published: 03 December 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis" and is dedicated to Professor Stephen Hanessian on the occasion of his 80th birthday.

Guest Editor: S. R. Chemler

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Abstract

The copper-catalyzed asymmetric conjugate addition (ACA) of nucleophiles onto polyenic Michael acceptors represents an attractive and powerful methodology for the synthesis of relevant chiral molecules, as it enables in a straightforward manner the sequential generation of two or more stereogenic centers. In the last decade, various chiral copper-based catalysts were evaluated in combination with different nucleophiles and Michael acceptors, and have unambiguously demonstrated their usefulness in the control of the regio- and enantioselectivity of the addition. The aim of this review is to report recent breakthroughs achieved in this challenging field.

Introduction

Amongst the variety of synthetic methods available for the formation of C–C or C–heteroatom bonds, the asymmetric conjugate addition (ACA) of nucleophiles to electron-deficient alkenes is one of the most relevant and versatile for the synthesis of complex chiral molecules [1]. Notably, the design and study of novel families of chiral enantiopure ligands has enabled a fine control of the regio- and enantioselectivity of the reaction, using a variety of nucleophilic and electrophilic substrate associations, with remarkable applications in total syntheses [2].

Polyenic electron-deficient alkenes are Michael acceptors of high synthetic interest. Indeed, they can undergo successive nucleophilic additions and therefore enable the generation of several new chiral centers [3]. On the other hand, the main challenge associated with polyenic Michael acceptors lies within the regiocontrol of the nucleophilic attack, which can occur at three different positions, at least. The regioselectivity outcome of the ACA reaction depends on many parameters, notably the metal/chiral ligand combination, the structure of the electrophile and the nature of the nucleophile. Figure 1 depicts the various scenarios that can be expected with an α,β,γ,δ-unsaturated Michael acceptor.

Amongst the variety of transition-metal-based catalytic systems that have been evaluated in ACA reactions on extended Michael acceptors [1,3], copper-based systems have been the subject of tremendous interest, which provided dramatic breakthroughs during the last two decades. This review aims to describe the early examples and recent advances in copper-catalyzed asymmetric conjugate additions of organometallic reagents to extended Michael acceptors. First, seminal reports dealing with the reactivity of extended Michael acceptors with regards to copper-based nucleophiles in stoichiometric reactions will be presented. Based on these results, research groups gained better understanding of the origin of the regioselectivity in such processes, and started to develop modern enantioselective catalytic systems. These works will be classified according to the selectivity of the addition (1,6, 1,4 then 1,8 and 1,10), while taking into account the nature of the nucleophile (dialkylzinc, Grignard or trialkylaluminium reagents).

Review

Background – first studies

The first example of achiral addition of a copper-based compound to an extended Michael acceptor was reported independently as early as 1972, by the Näf [4] and Corey [5] groups, who studied the reactivity of pentadienyl methyl ester (**1**, Figure 2). In both cases, the 1,6-conjugate addition of a stoichiometric amount of a Gilman reagent proceeded in a selective manner, affording compounds **2** and **3**. In the early 1980s, Yamamoto and co-workers also studied the reactivity of extended Michael acceptors with regard to the nature of the cuprate reagent; methyl sorbate (**4**) was chosen as a model substrate [6]. This work evidenced that a control of the regioselectivity of the reaction could be achieved with a careful choice of the copper-based nucleophile. Indeed, Yamamoto's cuprate (n-BuCu·BF$_3$) led to the 1,4-addition product **5a**, while the 1,6-adduct **5b** was selectively obtained upon reaction with a Gilman reagent. Inspired by these seminal studies, the addition of cuprates was investigated onto different Michael acceptors [7]. The reaction of dienones such as **6** (Miginiac) [8], enynones of the type **8** (Hulce) [9] or polarized enynes **10** (Krause) [10] consistently proceeded with a 1,6-selectivity, as compounds **7**, **9** and **11** were respectively identified as the major reaction product. The selective 1,6-addition of cuprates onto extended Michael acceptors featuring a terminal C–C triple bond

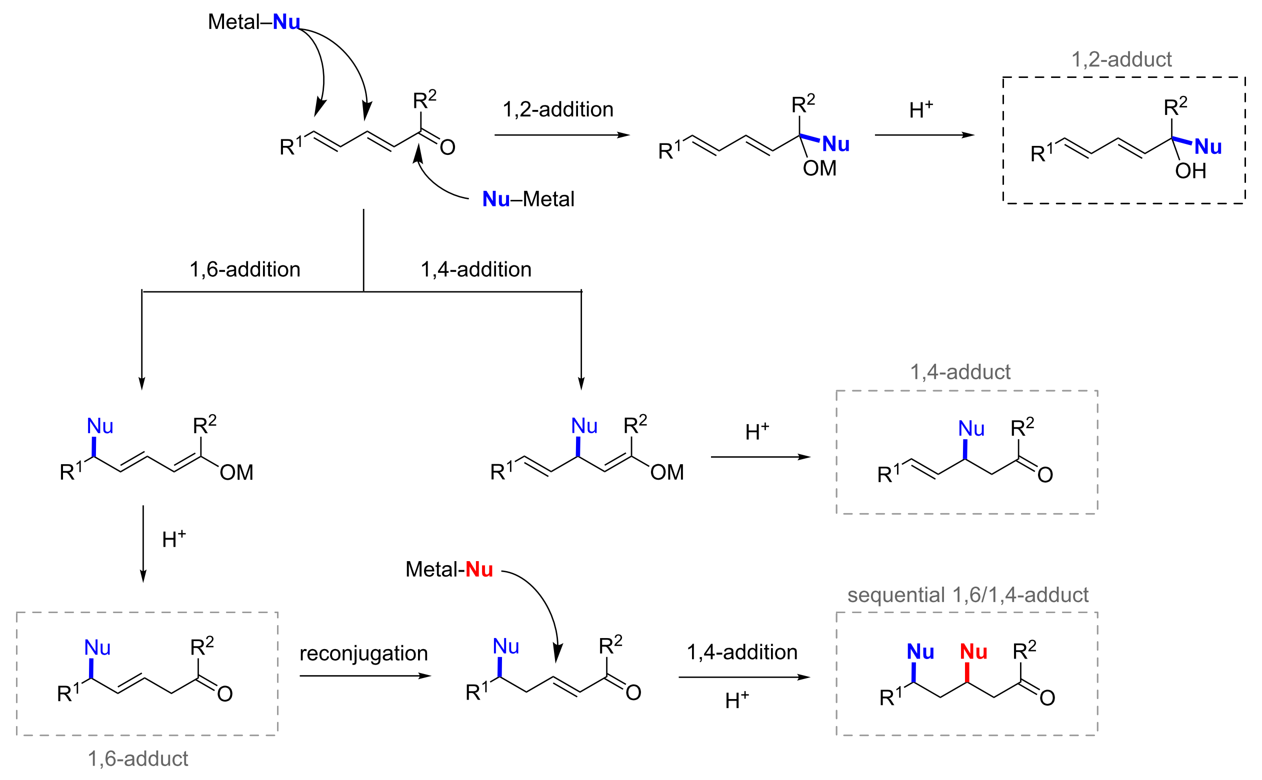


Figure 1: Possible reaction pathways in conjugate additions of nucleophiles on extended Michael acceptors.

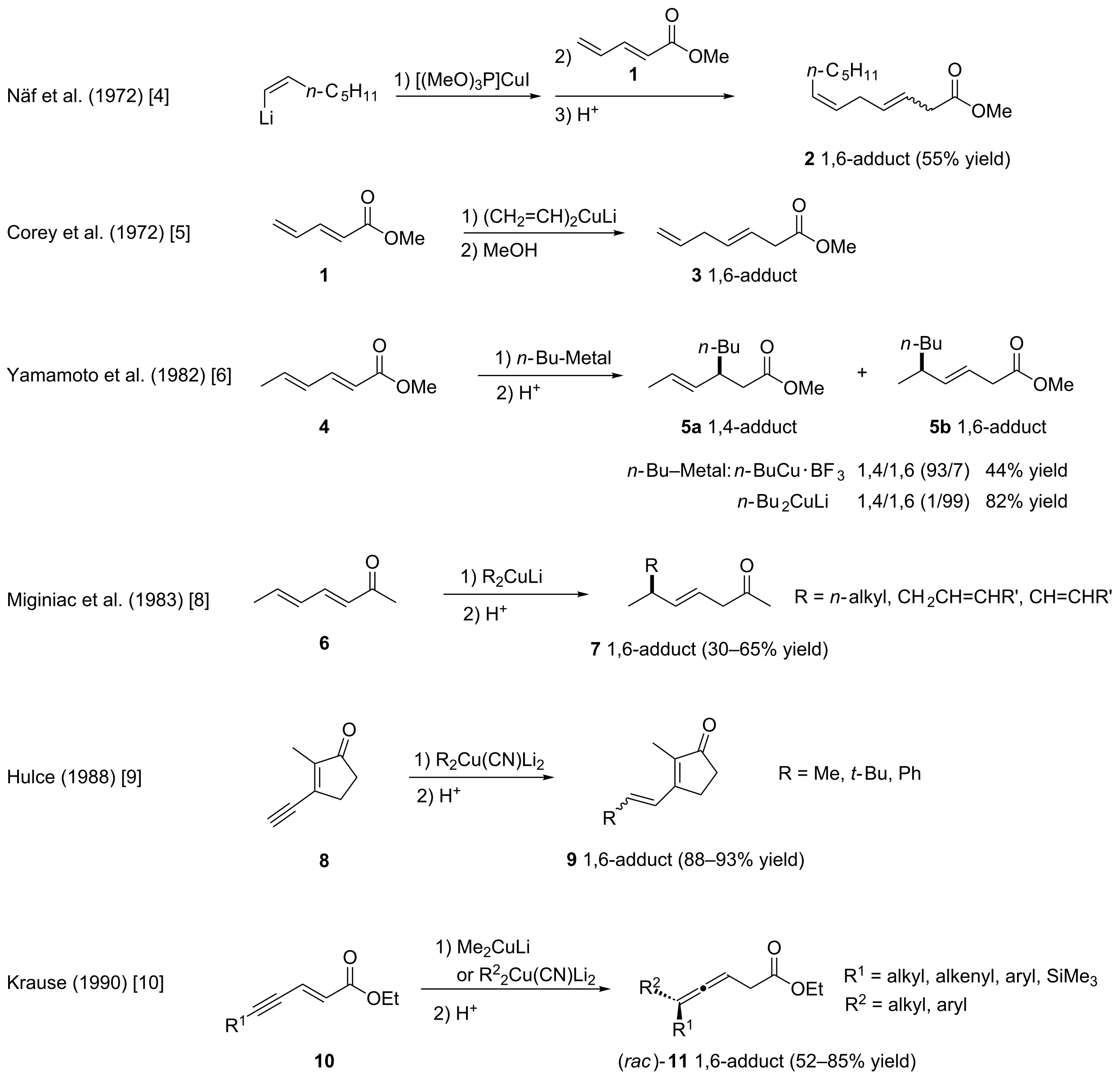


Figure 2: Early reports of conjugate addition of copper-based reagents to extended Michael acceptors.

prompted research groups to investigate thoroughly the mechanism of this reaction [11-13].

Notably, the 1,6-conjugate additions onto Michael acceptors involving copper reagents were employed in total synthesis strategies (Figure 3). Wieland and Anner took advantage of the reaction selectivity in the synthesis of steroids as early as 1967 [14]. For instance, the product (*rac*)-**13** was obtained in 43% yield by reacting a methylmagnesium bromide with the steroid derivative **12** in the presence of a substoichiometric amount of copper chloride. Ten years later, Alexakis and Posner described the addition of a vinyl Grignard reagent to the conjugated dienone **14**, affording product **15** in 66% yield, ultimately leading to pseudoguaiane [15].

The initial results regarding stoichiometric reactions of copper-based nucleophiles onto extended Michael acceptors gave the scientific community a glimpse of the great potential of such methodologies. It appeared that the regioselectivity of the reaction could be tuned by varying the nature of the copper reagent [6]. Additionally, the applications in total synthesis demonstrated that the nucleophilic copper compound could be generated in situ [14,15]. The design of efficient catalytic protocols could therefore be envisioned, enabling fine-tuning of the regio-

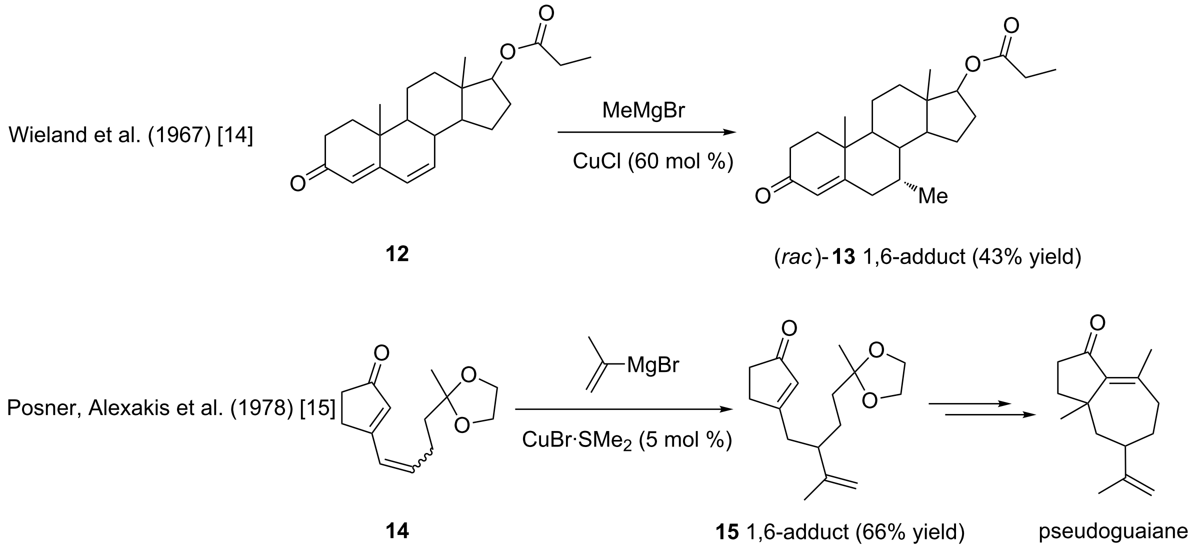


Figure 3: First applications of copper catalyzed 1,6-ACA in total synthesis.

and the enantioselectivity of the reaction. In order to tackle this challenge, many research groups extensively investigated the effect of various copper precursors, nucleophiles and Michael acceptors in catalysis, in combination with new families of chiral ligands. The results will be presented according to the selectivity of the conjugate addition; the first section will be dealing with enantioselective 1,6-additions, followed by the description of systems affording preferentially the 1,4-adduct, and a final paragraph will focus on the reactions conditions leading to 1,8- or 1,10-addition products.

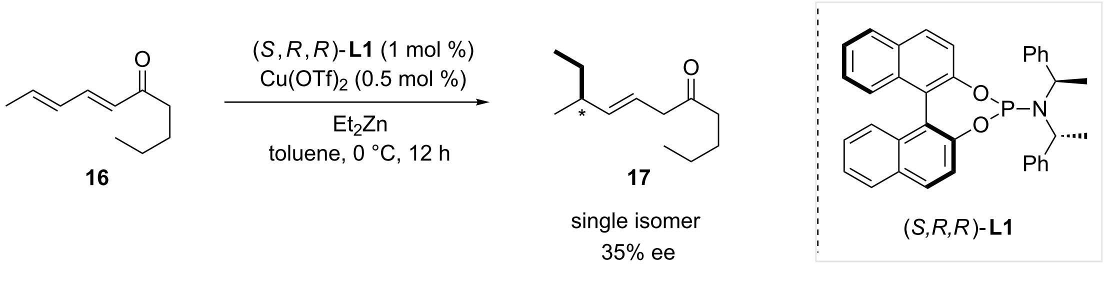
Enantioselective 1,6-addition to extended Michael acceptors

With dialkylzinc reagents

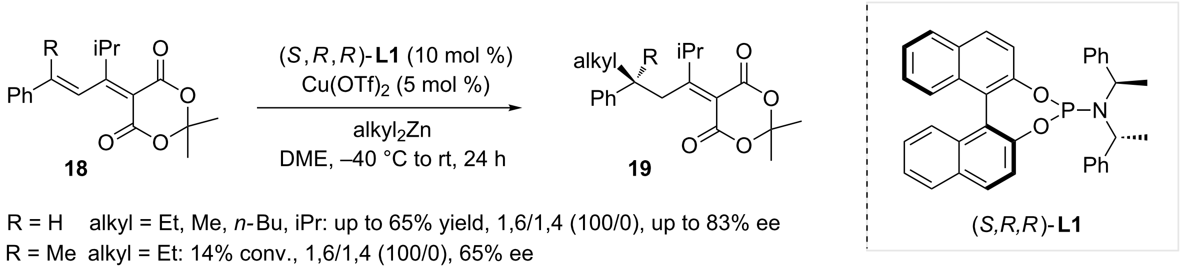
Alexakis and co-workers discovered in 2001 the first example of copper-catalyzed enantioselective 1,6-conjugate addition [16]. Using phosphoramidite ligand (*S,R,R*)-**L1** and $Cu(OTf)_2$ as the copper source, diethylzinc was added to dienone **16** with a full 1,6-regioselectivity, and an ee of 35% (Scheme 1).

In 2006, Fillion and co-workers studied the reactivity of Meldrum's acid derivatives of the type **18** with regards to ACA reactions, using dialkylzinc as nucleophiles [17]. Employing the same catalytic system as Alexakis, namely $Cu(OTf)_2$/(*S,R,R*)-**L1**, the reaction was also fully 1,6-selective, and its versatility was studied on a substrate scope. As shown in Scheme 2, tertiary and quaternary stereogenic centers could be generated using this methodology leading to products **19** in moderate to good yields and ees.

In 2008, Alexakis and Mauduit evaluated a series of different chiral ligands in ACA reactions involving polyenic Michael acceptors and various nucleophiles [18]. In this study, the addition of diethylzinc was notably investigated on cyclic dienone



Scheme 1: First example of enantioselective copper-catalyzed ACA on an extended Michael acceptor.



R = H alkyl = Et, Me, *n*-Bu, iPr: up to 65% yield, 1,6/1,4 (100/0), up to 83% ee
R = Me alkyl = Et: 14% conv., 1,6/1,4 (100/0), 65% ee

Scheme 2: Meldrum's acid derivatives as substrates in enantioselective ACA.

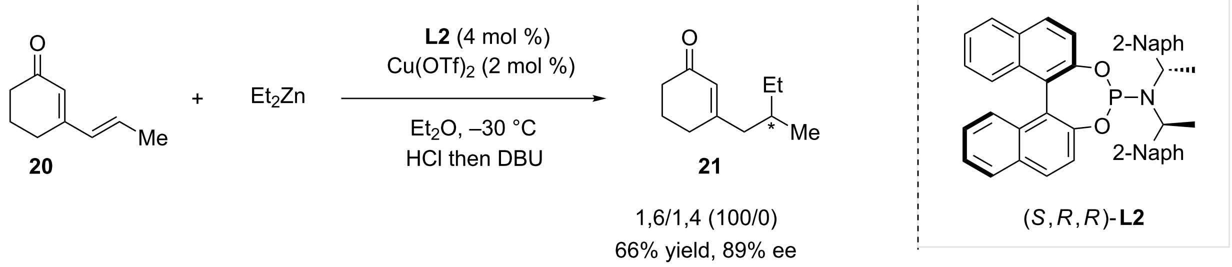
20 (Scheme 3). As regards the 1,6-conjugate addition, the highest enantioselectivity was achieved with the bulky phosphoramidite (*S,R,R*)-**L2**, to afford **21** in 66% yield and 89% ee.

Shortly after, Alexakis and Mauduit demonstrated the efficiency of the carboxylate-phosphino Schiff-base ligand DiPPAM (**L3**) in copper-catalyzed 1,6-ACA with cyclic dienones [19]. Interestingly, the reaction remained fully 1,6-regioselective, while the enantioselectivity was significantly improved. Indeed, a wide variety of substrates of the type **22** were reacted with several dialkylzinc reagents, affording the 1,6-adducts **23** with ees ranging from 93 to 99% (Scheme 4). Moreover, the reactivity of bicyclic dienone **24** was studied in these conditions, but a substantially lower enantioselectivity was recorded (**25** formed in a 40% ee). An additional study dealing with the Cu/DiPPAM-based system in the 1,6-addition demonstrated remarkable nonlinear effects (NLE) [20], which could also be observed in 1,4-ACA on both cyclic and acyclic enones.

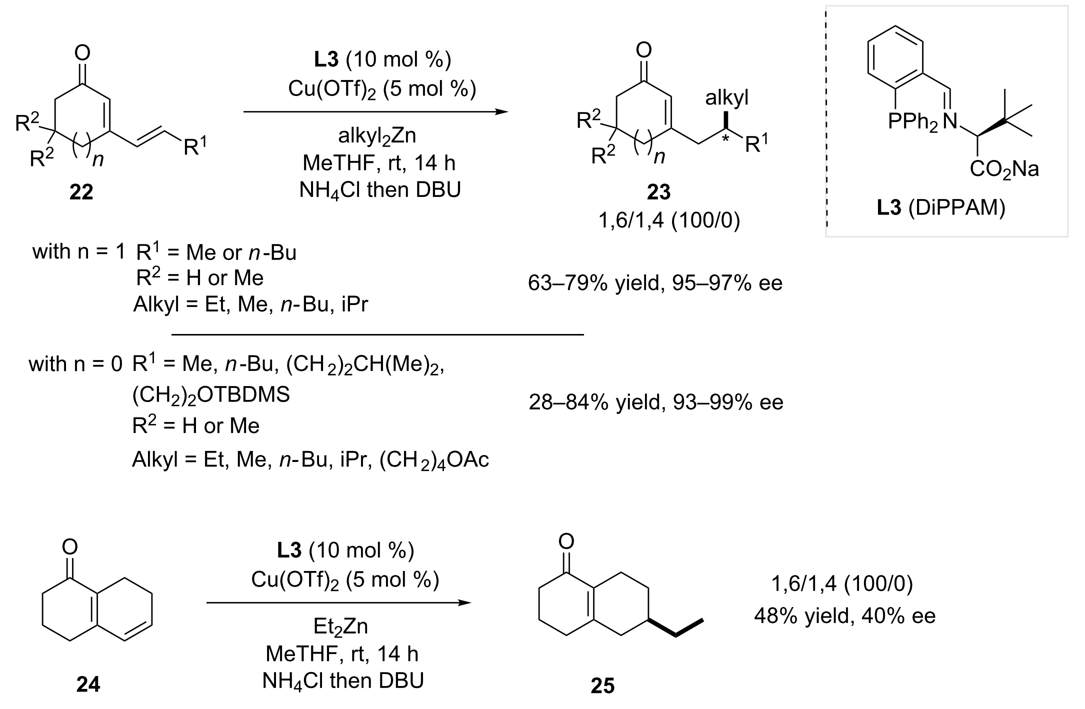
The efficiency of this copper-based catalytic system featuring DiPPAM was further tested in the reaction of linear aryldienones **26**, which are known to be significantly less reactive than their cyclic counterparts [21]. The recorded performances were also excellent, as regioselectivities up to 98/2 and enantioselectivities ranging from 88 to 98% ee were reported. In order to fully demonstrate the synthetic significance of such a methodology, compounds **27** were reconjugated in the presence of DBU and subsequently reacted in the 1,4-ACA (Scheme 5). The optimized conditions for the conversion of **28** to **29** involved copper(I) thiophene-2-carboxylate (CuTC) and (*R*)-Binap **L4,** which afforded the desired final products bearing two stereogenic centers with excellent diastereoselectivies (93–97%).

N-Heterocyclic carbenes (NHCs) have emerged, in these last two decades, as a powerful and versatile class of ligands, and appeared to be potent in many catalytic applications [22,23]. Amongst the myriad of available NHC ligands, chiral unsymmetrical NHC ligands appeared as particularly potent in asymmetric catalysis, and were investigated in copper-catalyzed conjugate additions [24]. Recently, a multicomponent synthesis enabled the facile access to a wide variety of unsymmetrical NHC precursors [25]. With this new methodology in hand, Mauduit and co-workers synthesized several bidentate chiral NHC precursors, using amino acids and amino alcohols as starting materials, and tested them in copper-catalyzed ACA [26]. Leucine-based **L5** displayed the best performance in terms of enantioselectivity, and was used in combination with $Cu(OTf)_2$ in the 1,6-ACA of cyclic dienones of the type **30** (Scheme 6). NHC ligands also enabled a total regioselectivity and ees ranging from 58 to 91%.

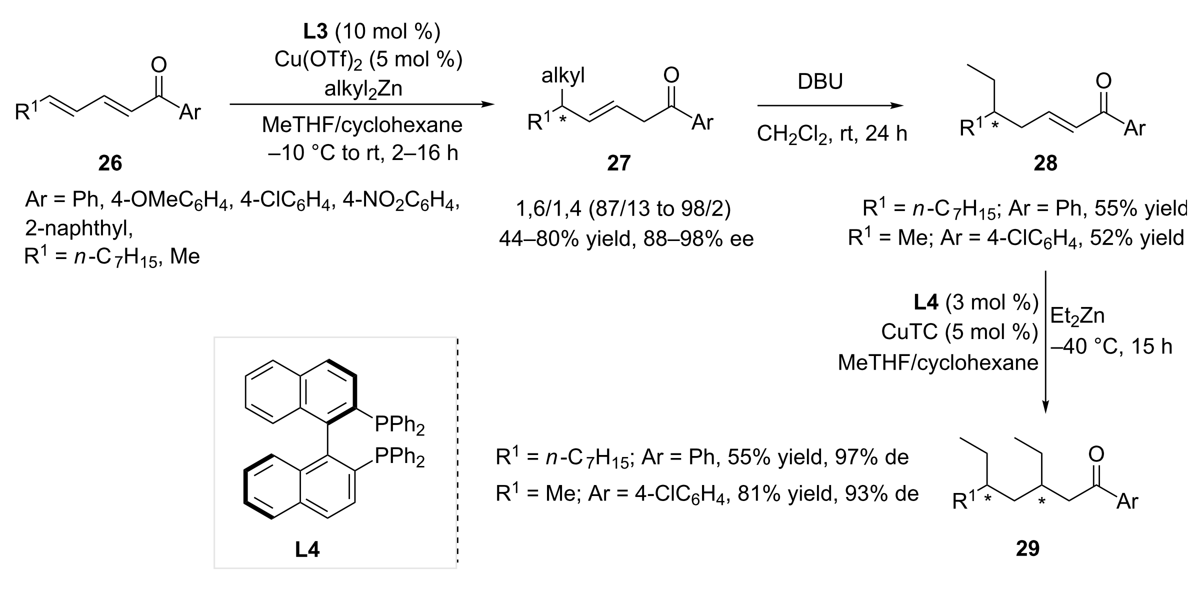
Given the efficiency of (*R*)-Binap **L4** in Cu-catalyzed 1,4-ACA on α,β-unsaturated ketones [21], the potency of other atropoiso-



Scheme 3: Reactivity of a cyclic dienone in Cu-catalyzed ACA of diethylzinc.



Scheme 4: Efficiency of DiPPAM ligand in 1,6-ACA of dialkylzinc to cyclic dienones.

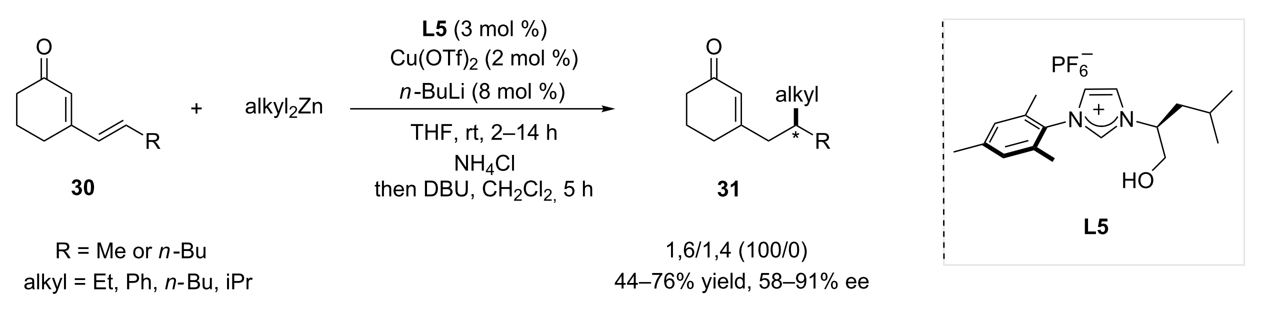


Scheme 5: Sequential 1,6/1,4-ACA reactions involving linear aryldienones.

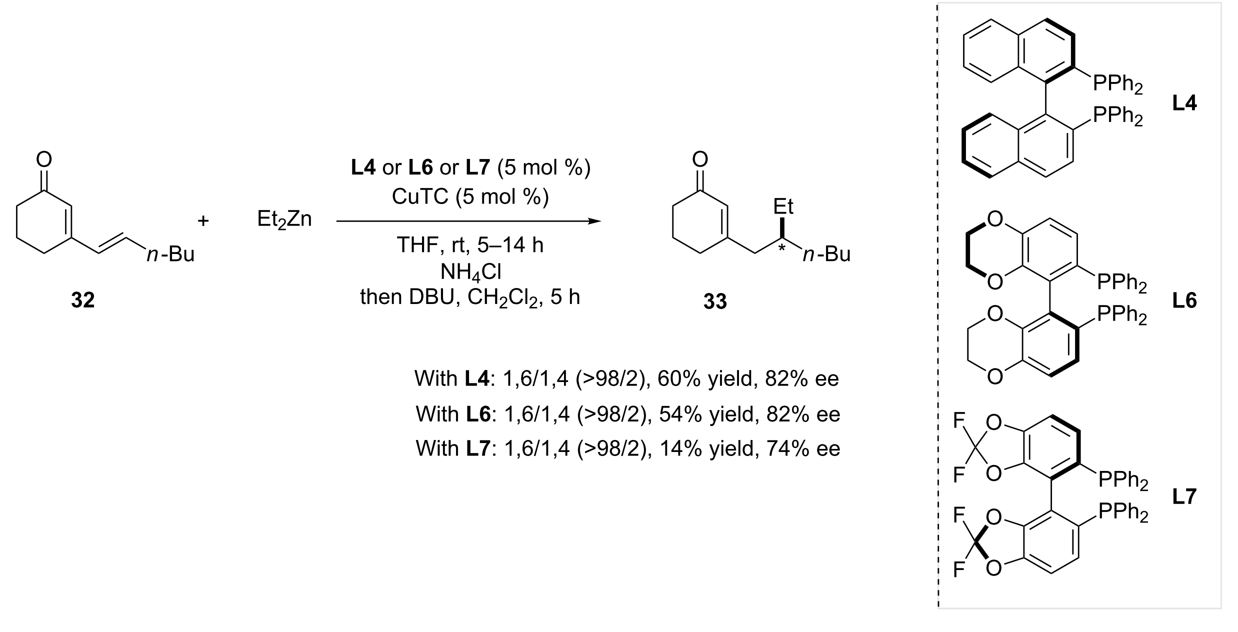
meric diphosphines was also studied in 1,4 and 1,6-conjugate additions with cyclic and linear substrates [27]. (*S*)-Synphos **L6** and (*R*)-Fluorophos **L7** were used in combination with CuTC and compared to **L4** (Scheme 7). Notably, the reaction of cyclic dienone **32** with diethylzinc proceeded at a typical catalyst loading of 5 mol %, and afforded the 1,6-adduct. Among the ligand series, **L4** proved to form the most efficient system, affording product **33** in 60% yield and 82% ee.

With Grignard reagents

Linear dienoates are another class of highly challenging extended Michael acceptors, which were the focus of a work



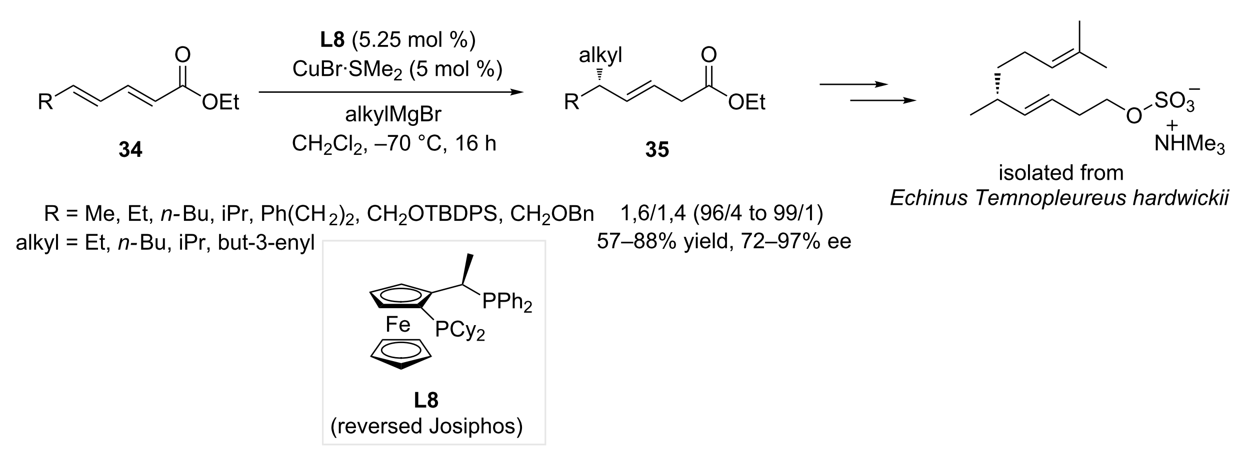
Scheme 6: Unsymmetrical hydroxyalkyl NHC ligands in 1,6-ACA of cyclic dienones.



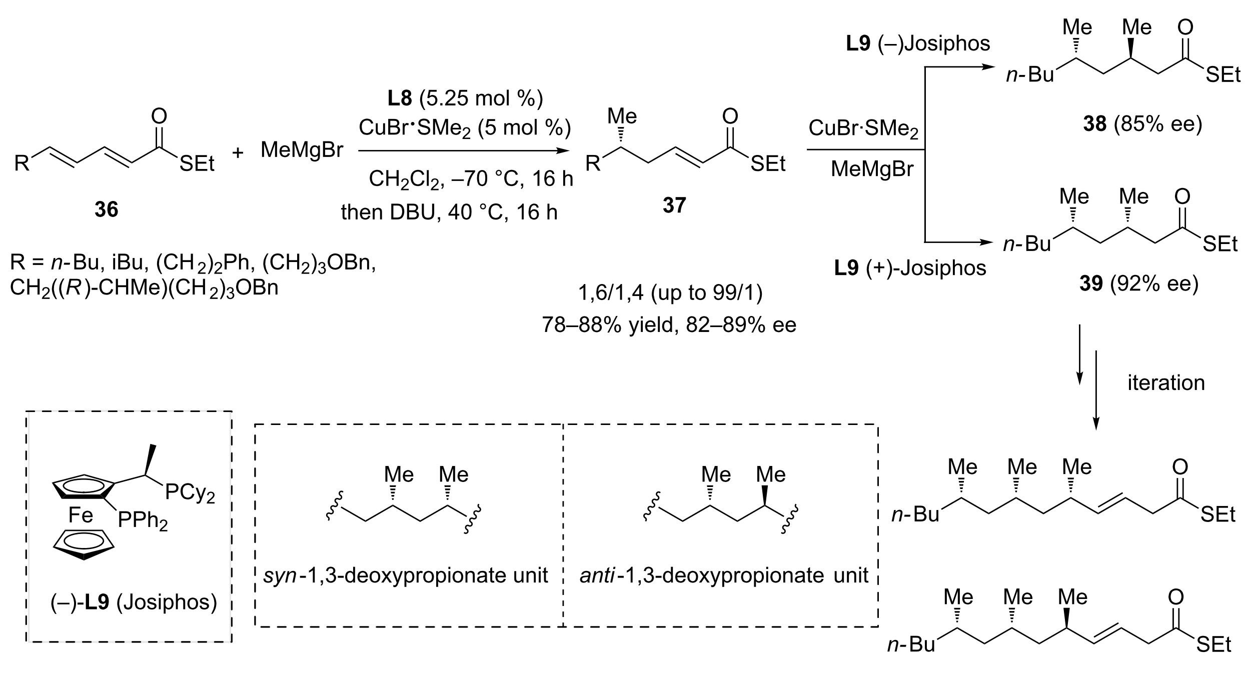
Scheme 7: Performance of atropoisomeric diphosphines in 1,6-ACA of Et_2Zn on cyclic dienones.

reported by Feringa and co-workers in 2008 [28]. In this study, the efficiency of ferrocene-based ligands was investigated for the addition of Grignard reagents onto ethyl sorbate, using $CuBr{\cdot}SMe_2$ as the copper source. Reversed Josiphos **L8** was selected as the most efficient ligand for this transformation, as a 1,6- vs 1,4-selectivity up to 99:1 could be achieved. The versatility of the catalytic system was assessed with a wide substrate scope featuring aliphatic, aromatic and functionalized dienoates **34** and various Grignard reagents. The reported products **35** were obtained in good yields (57–88%) and excellent ees (72–97%). The applicability of the method was demonstrated with the synthesis of a naturally occurring sulfated alkene, originally isolated from the echinus *Temnopleureus hardwickii* (Scheme 8).

To be noted, the latter protocol proved unsuccessful in introducing a methyl group in extended Michael acceptors through the addition of MeMgBr. A follow-up study then aimed to tackle this challenge and demonstrated that α,β,γ,δ-unsaturated thioesters **36** were the substrates of choice in order to conduct this valuable transformation (Scheme 9) [29]. A variety of α,β,γ,δ-unsaturated thioesters produced from a Horner–Wadsworth–Emmons reagent were submitted to a 1,6-ACA catalyzed by the **L8**/$CuBr{\cdot}SMe_2$ system, followed by a reconjugation reaction in the presence of DBU to selectively afford **37** (ratio between 1,6 and 1,4-ACA products ranged from 85/15 to 99/1) in high yields (78–88%) and enantioselectivities (82–89%). The obtained α,β-unsaturated thioesters **37** were subsequently reacted in a 1,4 copper-catalyzed ACA, using this time **L9** (Josiphos)/$CuBr{\cdot}SMe_2$. This approach enabled the synthesis of *anti* (**38**) or *syn* (**39**) 1,3-deoxypropionate units depending on the Josiphos enantiomer used, in both cases with good enantioselectivities (85–92% ee). Subsequent chain elongation followed by a 1,4-ACA reaction was described and



Scheme 8: Selective 1,6-ACA of Grignard reagents to acyclic dienoates, application in total synthesis.



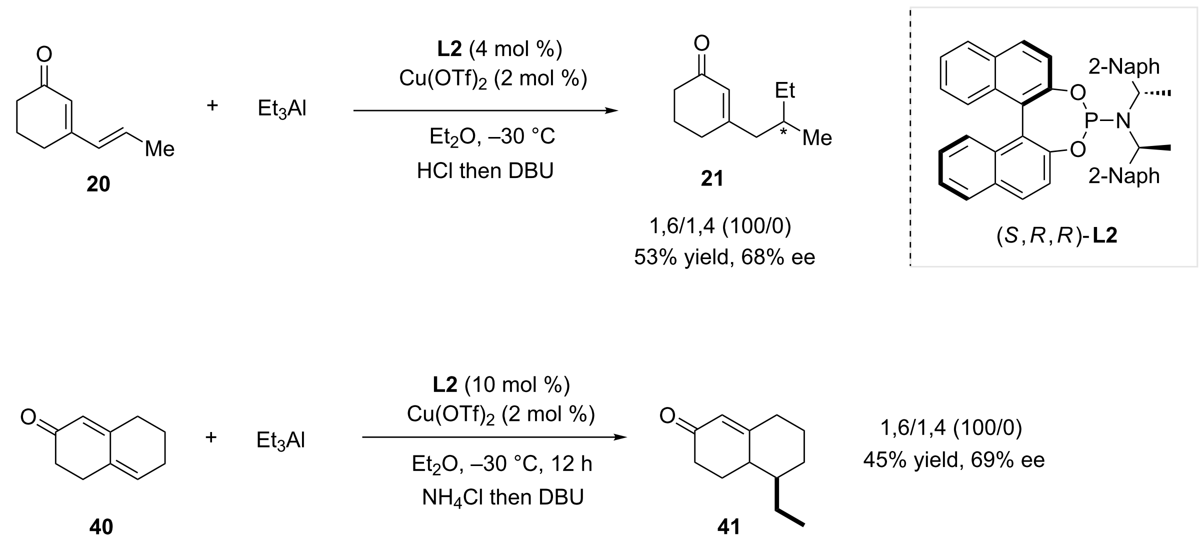
Scheme 9: Reactivity of polyenic linear thioesters towards sequential 1,6-ACA/reconjugation/1,4-ACA and production of 1,3-deoxypropionate units.

enabled the enantioselective insertion of an additional methyl group.

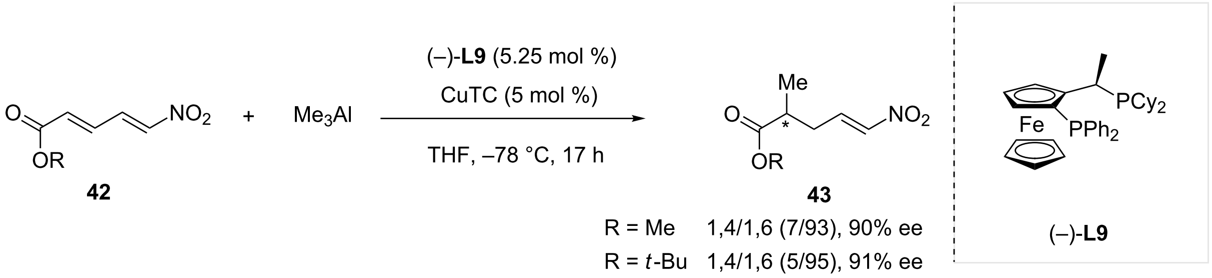
With trialkylaluminium reagents

Only a few systems are known to perform efficiently 1,6-ACA reactions using trialkylaluminium reagents as nucleophiles. In 2008, Alexakis, Mauduit and co-workers described the copper-catalyzed 1,6-ACA of triethylaluminium on cyclic α,β,γ,δ-unsaturated ketones using the phosphoramidite (*S,R,R*)-**L2** ligand [18]. The reaction of the cyclic dienone **20** selectively afforded the 1,6-adduct **21** in 53% yield and 68% ee (Scheme 10). Displaying a similar reactivity, bicyclic Michael acceptor **40** led to compound **41** in 45% yield and 69% ee.

In 2010, the Alexakis group explored the reactivity of α,β,γ,δ-unsaturated nitroolefins and nitroenynes in Cu-catalyzed ACA reactions with trialkylaluminium [30]. Several substrates were investigated affording the 1,4-adducts in most cases. However, high 1,6-selectivity with respect to the nitro group could only be observed in the reaction of nitrodienoates **42** with trimethylaluminium (Scheme 11). The most efficient catalytic system, a combination of Josiphos **L9** as chiral ligand and copper thio-



Scheme 10: 1,6-Conjugate addition of trialkylaluminium with regards to cyclic dienones.



Scheme 11: Copper-catalyzed conjugate addition of trimethylaluminium onto nitro dienoates.

phene 2-carboxylate (CuTC) afforded the desired 1,6-adducts **43** with very good regioselectivity (up to 5/95) and enantioselectivities (up to 91% ee).

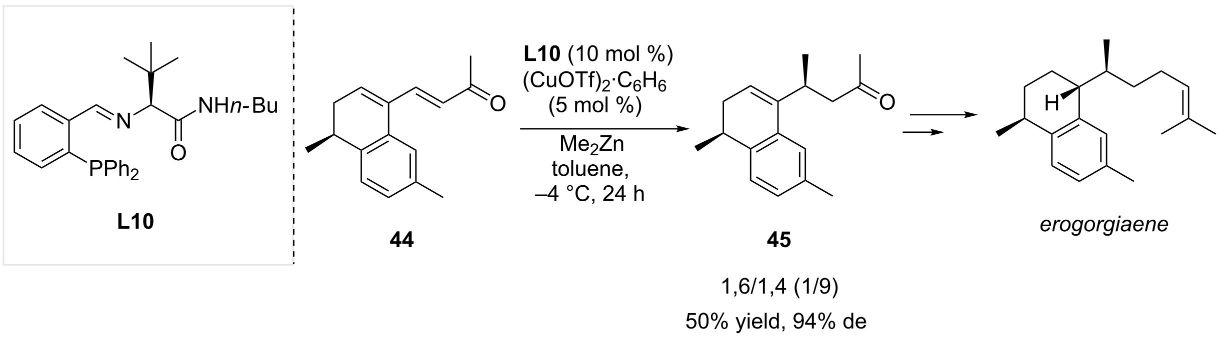
Enantioselective 1,4-addition to extended Michael acceptors

With dialkylzinc reagents

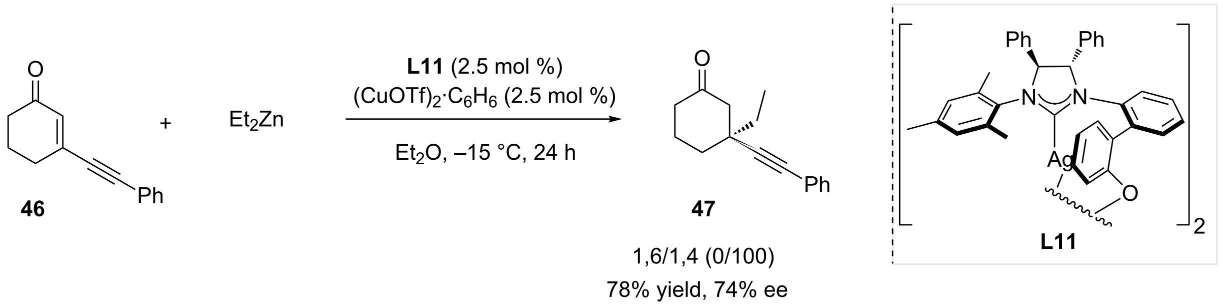
Dialkylzinc reagents are without a doubt highly potent nucleophiles in copper-catalyzed ACA often leading to 1,6-adducts onto polyconjugated electron-deficient substrates. However, examples of their use for 1,4-additions can also be found in the literature. In 2004, Hoveyda and co-workers described the total synthesis of the antimicobacterial agent erogorgiaene (Scheme 12) [31]. One of the key steps of this synthesis involved the conversion of the bicyclic extended Michael acceptor **44** to **45** through a 1,4-selective copper-catalyzed ACA. Copper(I) triflate and chiral phosphine ligand **L10** enabled this transformation to proceed with a yield of 50% and an excellent diastereoselectivity (de 94%).

The Hoveyda group was also interested in developing efficient methods for the generation of quaternary stereogenic centers from Michael acceptors via copper-catalyzed 1,4-ACA of diethylzinc onto cyclic Michael acceptors [32]. When the catalytic system was formed in situ from chiral NHC-based **L11** and $(CuOTf)_2 \cdot C_6H_6$, a large library of substrates was tested, and good yields and ees were consistently observed. Among the Michael acceptors that were submitted to the reaction conditions, cyclic enynone **46** selectively led to the 1,4-adduct **47**, and the ethyl moiety was inserted with 74% enantiomeric excess in 78% yield (Scheme 13).

Very recently, a new study dealing with the reactivity of unsaturated acyl-*N*-methylimidazole substrates in copper-catalyzed ACA was released by Mauduit, Campagne and co-workers [33]. Unsymmetrical bidentate hydroxyalkyl precursor **L12** led to the most efficient system in the insertion of methyl groups in such architectures, being highly versatile synthetic platforms [34,35]. A wide variety of α,β-unsaturated acyl-*N*-methylimidazoles



Scheme 12: Copper-catalyzed selective 1,4-ACA in total synthesis of erogorgiaene.

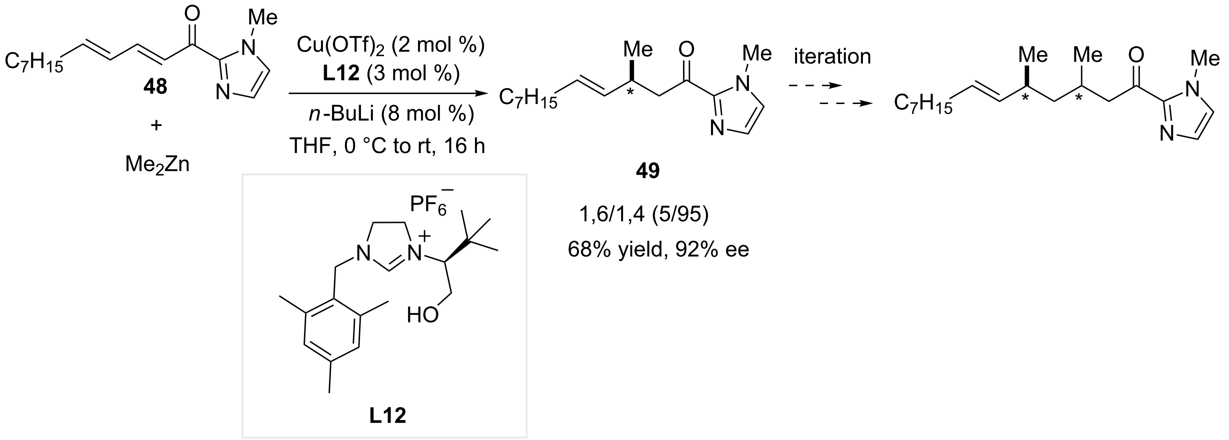


Scheme 13: 1,4-selective addition of diethylzinc onto a cyclic enynone catalyzed by a chiral NHC-based system.

could thus be reacted in high yields and enantioselectivities. Notably, the reactivity of polyenic species **48** was also investigated (Scheme 14). Interestingly, the 1,4-adduct was here formed in high regioselectivity (95%), good yield (68%) and stereoselectivity (ee 92%). Interestingly, the usefulness of the products of 1,4-ACA was demonstrated as the latter were converted into the corresponding aldehydes and subsequently used in an iterative process, leading to highly desirable 1,3-deoxypropionate units.

With Grignard reagents

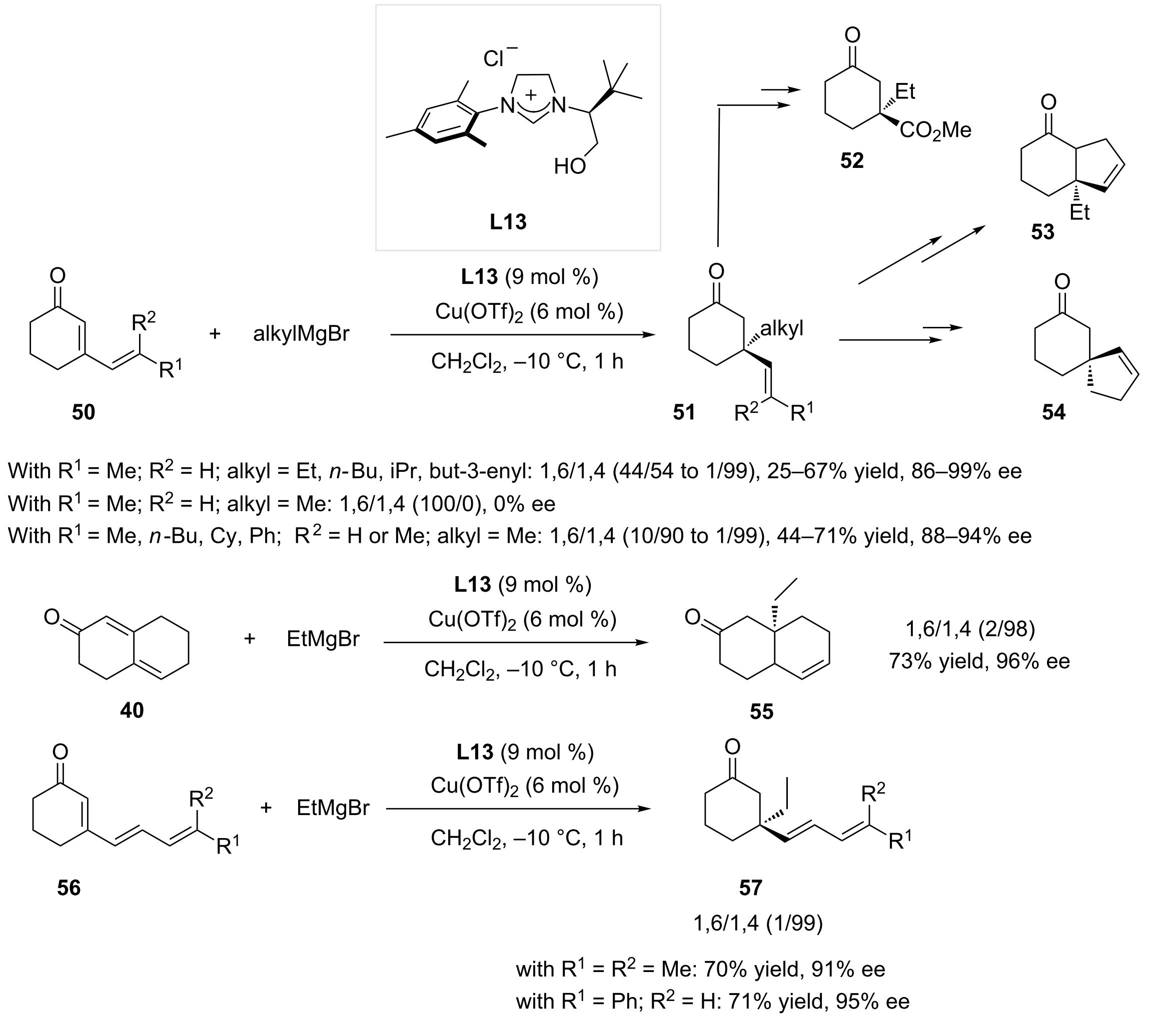
In 2008, Alexakis, Mauduit and coworkers extensively studied the influence of the parameters controlling the regioselectivity outcome of the ACA reaction with α,β,δ,γ-unsaturated ketones



Scheme 14: Cu-NHC-catalyzed 1,6-ACA of dimethylzinc onto an α,β,γ,δ-unsaturated acyl-*N*-methylimidazole.

[18]. Using a Grignard reagent as the nucleophile, it appeared that catalytic systems based on phosphoramidite ligands favored the formation of the 1,6-adduct. However, the use of catalytic systems based on an hydroxyalkyl NHC ligand ($Cu(OTf)_2$/**L13**) resulted in a surprising inversion of the regioselectivity. Indeed, the addition of ethylmagnesium bromide onto cyclic dienones occurred at the 1,4-position, affording compounds featuring an all-carbon quaternary center. The authors suggested that the chelating hydroxyalkyl chain was at the origin of this particular reactivity. The addition of other linear Grignard reagents on the substrates of the type **50** showed a near-perfect 1,4-regioselectivity, while the amount of 1,4-adduct dropped when branched nucleophiles were used. Despite this decrease in regioselectivity, the reaction remained highly enantioselective, with ees ranging from 88 to 99% for compounds **51**. Notably, attempts to add a methyl moiety through the addition of MeMgBr to the cyclic dienone featuring a disubstituted terminal double bond (R^1 = Me, R^2 = H) only resulted in an achiral 1,6-addition product. Subsequent transformations of the γ,δ-unsaturated 1,4-adducts were successfully performed: an oxidative cleavage afforded for example ketoester **52** (Scheme 15). Moreover, the in situ trapping of the addition product with acetic anhydride led to the regeneration of the lithium enolate, which was allylated and submitted to ring closing metathesis to afford the bicyclic product **53**. Finally, the RCM of the 1,4-adduct resulting from the addition of 3-butenylmagnesium bromide yielded the spiro compound **54**. Interestingly, the conversion of bicyclic compound **40** catalyzed by the same system also occurred selectively in the 4-position (**55** was formed in 73% yield, 96% ee).

The scope of the reaction was extended to many new substrates in 2012, evidencing that the 1,4-selectivity of the transforma-



With R^1 = Me; R^2 = H; alkyl = Et, *n*-Bu, iPr, but-3-enyl: 1,6/1,4 (44/54 to 1/99), 25–67% yield, 86–99% ee
With R^1 = Me; R^2 = H; alkyl = Me: 1,6/1,4 (100/0), 0% ee
With R^1 = Me, *n*-Bu, Cy, Ph; R^2 = H or Me; alkyl = Me: 1,6/1,4 (10/90 to 1/99), 44–71% yield, 88–94% ee

with R^1 = R^2 = Me: 70% yield, 91% ee
with R^1 = Ph; R^2 = H: 71% yield, 95% ee

Scheme 15: 1,4-Selectivity in conjugate addition on extended systems with the concomitant use of a chelating chiral hydroxyalkyl NHC and of a Grignard reagent.

tion remained with trienones **56**, as the polyunsaturated products **57** were obtained with good yield and excellent enantioselectivities (up to 95%) [36].

To demonstrate the high synthetic significance of a selective 1,4-ACA performed on extended systems, its implementation in the total synthesis of *ent*-riccardiphenol B was attempted using the **L13**/Cu(OTf)$_2$ system (Scheme 16) [36]. The conditions for the addition of methylmagnesium bromide were varied in order to maximize the conversion of trienone **58** towards **59**. A mixture of the three addition products was however consistently observed, and despite an ee of 85%, the conversion towards the desired product did not exceed 37%.

Cyclic enynones **60**, which are substrates of high interest for the synthetic chemist, were regioselectively converted in good yields to the 1,4-ACA products **61** with good to excellent enantioselectivity (79 to 96% ee) using the **L13**/Cu(OTf)$_2$ catalytic system [36,37]. It is important to note that the regioselectivity outcome for the addition of methyl Grignard reagent appeared to be more substrate-dependent [36]. In fact, the best 1,4-selectivities were observed with bulky R groups, as a 100/0 1,4/1,6 ratio was observed with R = TIPS while substrate **60** with R = *n*-Bu afforded a 23/77 1,4/1,6 ratio. Moreover, the obtained products **61** could be subsequently converted to the spiro compounds **62** and **63** (Scheme 17).

The same protocol was later applied to conjugated enynones featuring additional unsaturated units and a total regioselectivity towards the 1,4-adducts was recorded under the standard conditions (Scheme 17) [36]. The chiral polyconjugated products (**64**–**66**) were isolated in good yields (60 to 80% yields) with good to excellent enantioselectivity (77 to 93% ee).

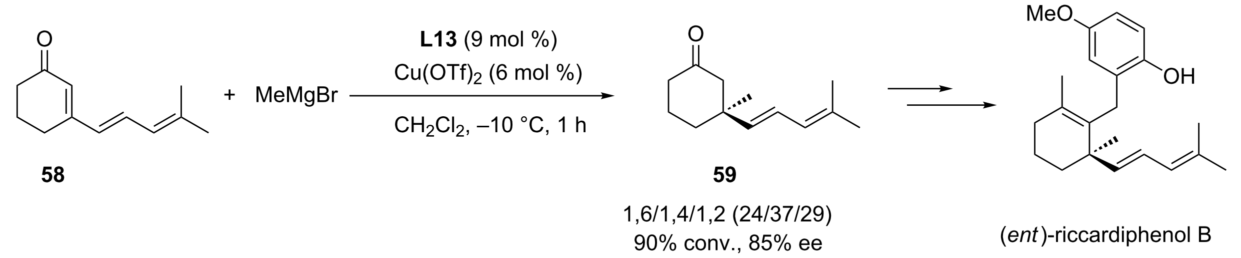
In 2013, Xie, Zhang and co-workers investigated the reactivity of extended unsaturated linear ketones in the presence of Grignard reagents, with the aim of selectively forming the 1,4-ACA adducts [38]. Various ligands were tested and the best catalytic performance was achieved using bidentate ferrocene-based ligand **L14** in combination with tetrakis(acetonitrile)copper(I) perchlorate as the copper source. The conversion of aromatic linear dienones **67** was reported with a complete regioselectivity towards the 1,4-adducts **68**. Moreover, the variation of the steric and electronic parameters of both aromatic moieties of **67** confirmed the robustness of the method, with good yields and ees obtained in most cases (Scheme 18).

With trialkylaluminium reagents

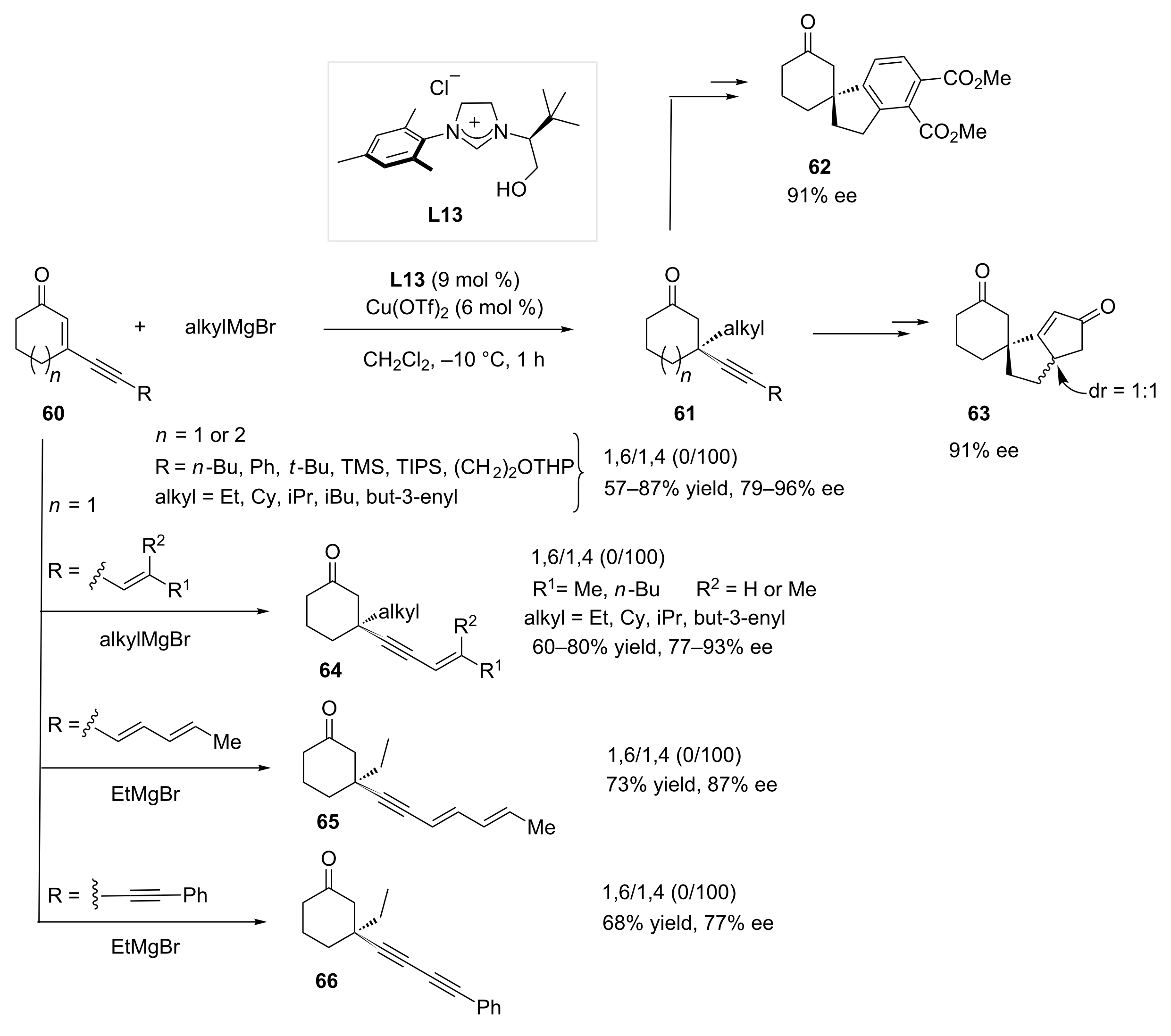
The Hoveyda group disclosed the first example of copper-catalyzed selective 1,4-ACA of low-cost trialkylaluminium reagents on extended Michael acceptors in 2008 [39]. The reported catalytic system, featuring Cu(OTf)$_2$ and sulfonated NHC-based silver complex **L15** as the ligand source, appeared as the most potent system in the conversion of cyclic enones. Enynone **69** was reacted to assess the versatility of the reaction, and a full 1,4-regioselectivity was recorded, leading to compound **70** in 71% yield and 91% ee (Scheme 19).

Another example of trialkylaluminium addition onto a cyclic extended Michael acceptor was reported in 2013, using a combination of copper(II) naphthenate (CuNaph) and SimplePhos **L16** as the catalytic system [40]. The reported methodology involved a regioselective 1,4 ACA of trimethylaluminium followed by the trapping of the aluminium enolate intermediate with (*n*-butoxymethyl)diethylamine. An oxidation–elimination sequence and a conjugate addition of a Grignard reagent to the newly formed exocyclic double bound were subsequently performed. Overall, this four-step process afforded the sterically congested cyclohexanone **72** in a 30% overall yield, with a dr of 2:1 and 96% ee (Scheme 20).

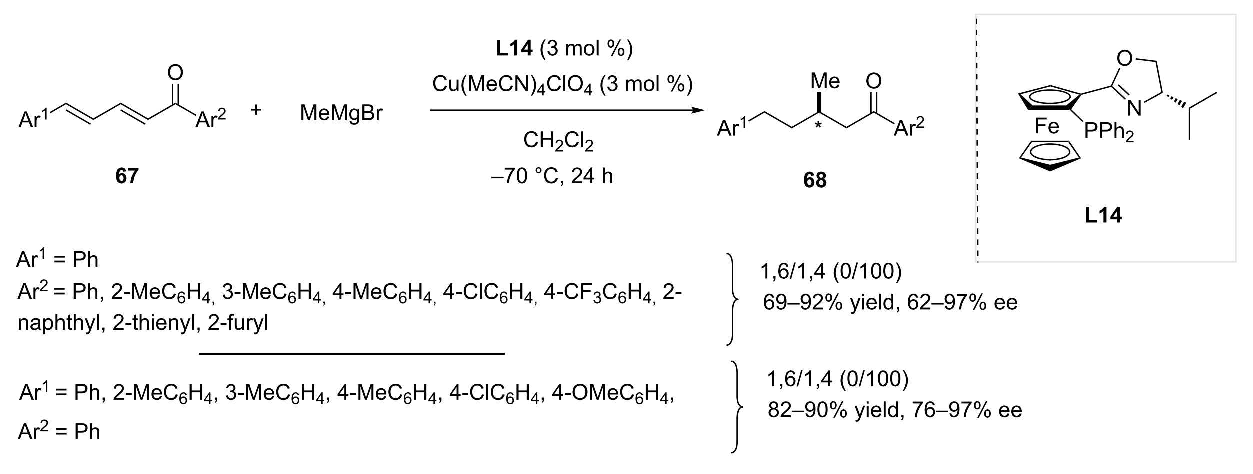
In 2012, Alexakis and Gremaud studied the reactivity of various β,γ-unsaturated α-ketoesters, which remain to date the only report dealing with such substrates in Cu-catalyzed ACA of trialkylaluminium [41]. Using the (*R*)-Binap-based system **L4**/CuTC, an excellent 1,4-selectivity was achieved with mono-unsaturated substrates. Dienic ketoester **73** was also tested with this catalytic system, and 1,4-adduct **74** was formed with a perfect regioselectivity, in high 92% yield and with a remarkable enantioselectivity of 98% (Scheme 21).



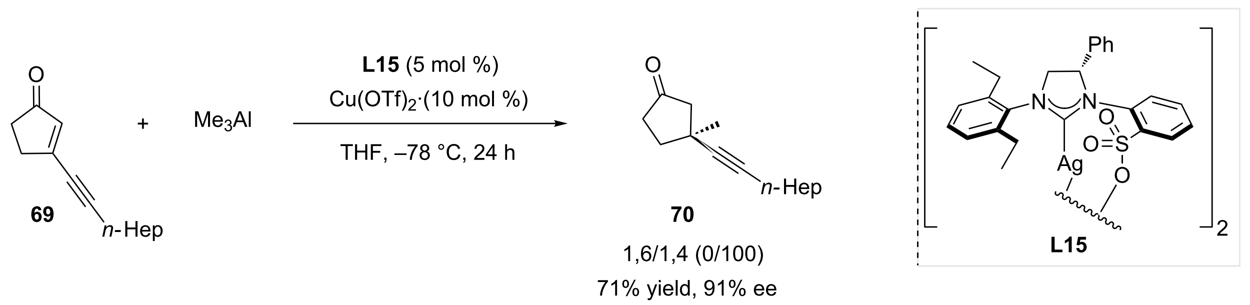
Scheme 16: Cu-NHC catalyzed 1,4-ACA as the key step in the total synthesis of *ent*-riccardiphenol B.



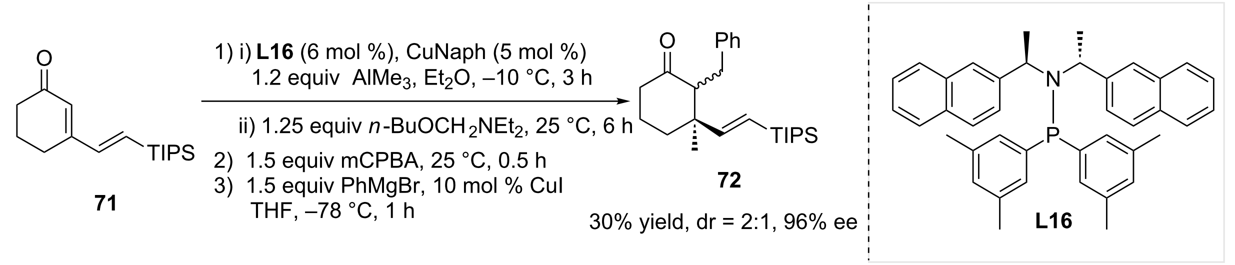
Scheme 17: Cu-NHC-catalyzed 1,4-selective ACA reactions with enynones.



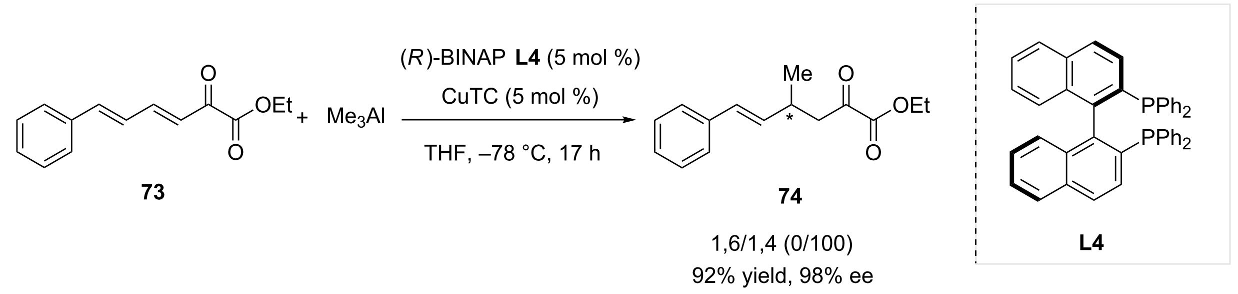
Scheme 18: Linear dienones as substrates in 1,4-asymmetric conjugate addition reactions of Grignard reagents catalyzed by a copper-based system.



Scheme 19: 1,4-ACA of trimethylaluminium to a cyclic enynone catalyzed by a copper-NHC system.



Scheme 20: Generation of a sterically encumbered chiral cyclohexanone from a polyunsaturated cyclic Michael acceptor.



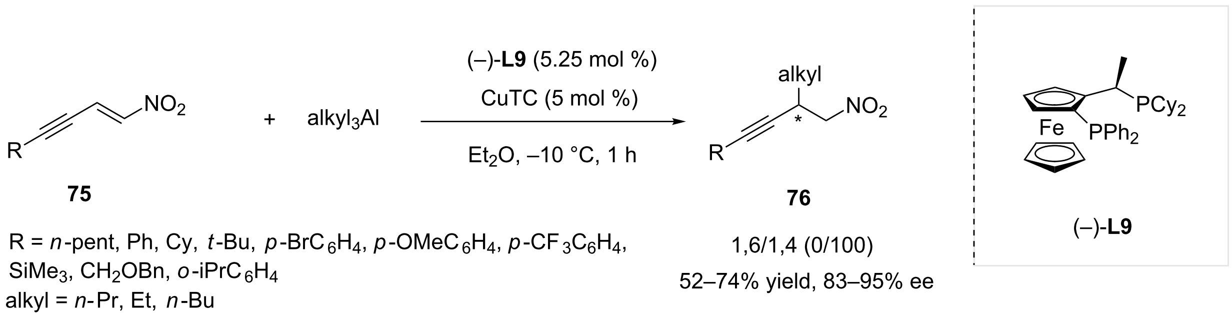
Scheme 21: Selective conversion of β,γ-unsaturated α-ketoesters in copper-catalyzed asymmetric conjugate addition.

In their report looking into the reactivity of α,β,γ,δ-unsaturated nitroolefins [30], Alexakis and co-workers could also attain a perfect 1,4-regioselectivity in the addition of trialkylaluminium reagents. Many nitroenynes such as **75** could then be converted to a wide variety of enantioenriched products **76** (83 to 95% ee) using copper thiophenecarboxylate (CuTC) as the copper source and Josiphos **L9** as chiral ligand (Scheme 22).

Additionally, a collection of nitrodienes **77** was reacted using this same methodology, and a reactivity similar to the one of nitroenynes was observed: 1,4-adducts **78** were obtained with good to very good enantioselectivity (77 to 90% ee) and perfect regioselectivity (Scheme 23).

Enantioselective 1,10- and 1,8-addition to extended Michael acceptors

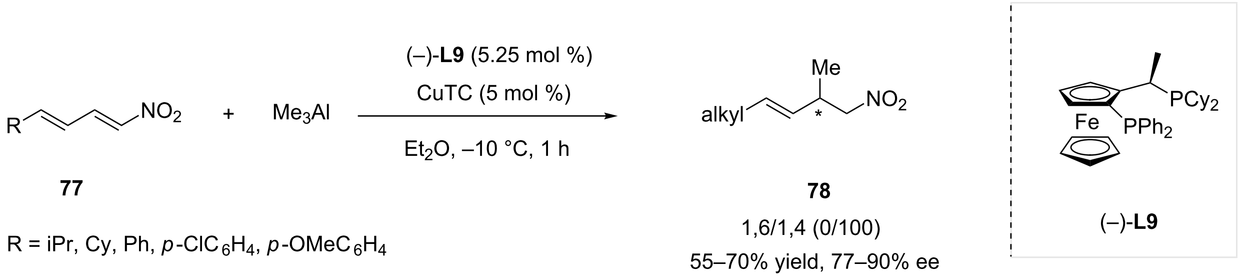
Recently, Feringa and co-workers released an extensive work dealing with the influence of various parameters in copper-catalyzed ACA of Grignard reagents on extended Michael acceptors [42]. Using “reversed Josiphos” **L8**, a well established ligand for enantio- and regioselective 1,6-additions onto dienoates [28], a wide variety of polyconjugated substrates were tested in order to gain a better insight into the reaction mechanism. Amongst the investigated electrophiles, substrates **79** (*n* = 1 or 2) could potentially undergo 1,8- or 1,10-conjugated addition, respectively. As shown in Scheme 24, the addition of the Grignard reagent occurred preferentially at the most remote



R = *n*-pent, Ph, Cy, *t*-Bu, *p*-BrC_6H_4, *p*-$OMeC_6H_4$, *p*-$CF_3C_6H_4$, $SiMe_3$, CH_2OBn, *o*-$iPrC_6H_4$
alkyl = *n*-Pr, Et, *n*-Bu

1,6/1,4 (0/100)
52–74% yield, 83–95% ee

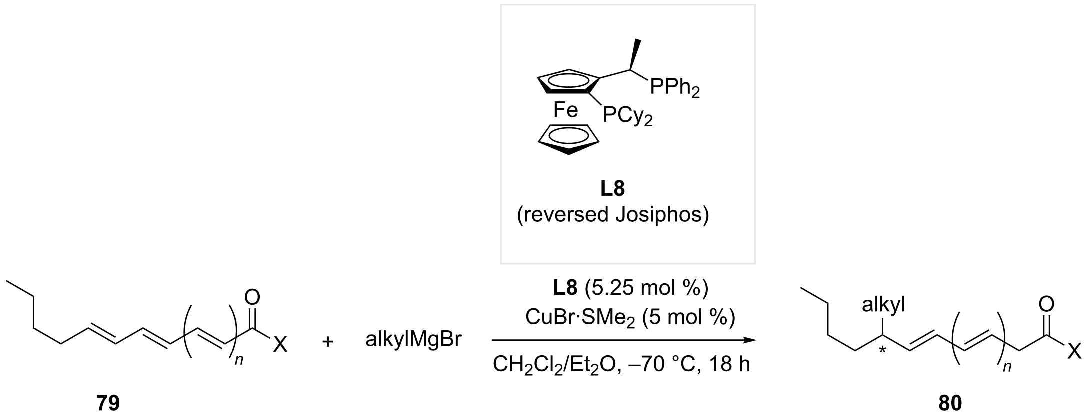
Scheme 22: Addition of trialkylaluminium compounds to nitroenynes catalyzed by **L9**/CuTC.



R = iPr, Cy, Ph, *p*-ClC_6H_4, *p*-$OMeC_6H_4$

1,6/1,4 (0/100)
55–70% yield, 77–90% ee

Scheme 23: Addition of trialkylaluminium compounds to nitrodienes catalyzed by **L9**/CuTC.



n = 1 | X = OEt; alkyl = Et 1,8/1,6/1,4 (63/8/29); 47% overall yield; 7% ee of 1,8 product
X = SEt; alkyl = Me 1,8/1,6/1,4 (86/0/14); 63% overall yield; 72% ee of 1,8 product

n = 2 | X = OEt; alkyl = Et 1,10/(1,8 + 1,6)/1,4 (49/8/43); 22% overall yield; 12% ee of 1,10 product
X = SEt; alkyl = Me 1,10/(1,8 + 1,6)/1,4 (59/0/41); 44% overall yield; 45% ee of 1,10 product

Scheme 24: Copper catalyzed 1,8- and 1,10-ACA reactions.

olefin. To be noted, polyenic esters gave a slight regioselectivity towards the 1,8- and 1,10-products and low enantioselectivities. Remarkably, only a small portion (<10%) of "intermediate" addition products (1,6-adducts when *n* = 1 and 1,6- and 1,8-adducts when *n* = 2) was detected in all cases. The nature of the substrate seemed to also have an influence since better results were obtained when the thioester was used as a starting material, in both 1,8- (63% yield, 72% ee) and 1,10-

ACA (44% yield, 45% ee). As a trend, the regio- and stereoselectivity decreased when the reacting olefin is further from the electron-withdrawing functionality. Additional studies would enable to determine the factors allowing for an improvement of the reaction outcome, as an efficient protocol allowing 3 to 4 sequential ACA reactions would be highly desirable for synthetic chemists.

Conclusion

This review attempts to give the reader an overview of the methodologies available to perform regio- and enantioselective copper-catalyzed asymmetric conjugate additions (ACA) on electron-deficient extended unsaturated systems. Since the initial discoveries looking into the conjugate addition of cuprates to extended Michael acceptors, substantial research has been undertaken to develop efficient methodologies enabling such reactions in a regio- and enantioselective manner, with significant breakthroughs. Nowadays, a number of ACA procedures with a various electron-deficient polyenic substrates (linear and cyclic dienones, dienoates, conjugated thioesters, nitroolefins and nitroenynes, enynones, unsaturated acyl-*N*-methylimidazoles and conjugated ketoesters) and nucleophiles (dialkylzinc, Grignard or trialkylaluminium reagents) are available. These protocols have shown to be highly dependent on both substrates and reaction conditions. Therefore, a variety of efficient chiral ligands is now available for the chemist willing to design synthetic routes leading to complex chiral molecules. Nonetheless, a number of potential Michael acceptors and catalytic systems have yet to be explored in order to further expand this useful toolbox.

Acknowledgements

This work was supported by the Agence Nationale de la Recherche (project SCATE, n° ANR-12-B507-0009-01 grant to SDA). MM and OB also thank the CNRS.

References

1. Mauduit, M.; Baslé, O.; Clavier, H.; Crévisy, C.; Denicourt-Nowicki, A. In *Comprehensive Organic Synthesis,* 2nd ed.; Molander, G. A.; Knochel, P., Eds.; Elsevier: Oxford, 2014; Vol. 4, pp 189–341. doi:10.1016/B978-0-08-097742-3.00406-7
2. Calvo, B. C.; Buter, J.; Minnard, A. J. Applications to the synthesis of natural products. In *Copper-Catalyzed Asymmetric Synthesis;* Alexakis, A.; Krause, N.; Woodward, S., Eds.; Wiley-VCH: Weinheim, 2014; pp 373–447. doi:10.1002/9783527664573.ch14
3. Csákÿ, A. G.; de la Herrán, G.; Murcia, M. C. *Chem. Soc. Rev.* **2010,** *39,* 4080–4102. doi:10.1039/b924486g
4. Näf, F.; Degen, P.; Ohloff, G. *Helv. Chim. Acta* **1972,** *55,* 82–85. doi:10.1002/hlca.19720550112
5. Corey, E. J.; Kim, C. U.; Chen, R. H. K.; Takeda, M. *J. Am. Chem. Soc.* **1972,** *94,* 4395–4396. doi:10.1021/ja00767a088
6. Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982,** *47,* 119–126. doi:10.1021/jo00340a026
7. Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997,** *36,* 186–204. doi:10.1002/anie.199701861
8. Barbot, F.; Kadib-Elban, A.; Miginiac, P. *J. Organomet. Chem.* **1983,** *255,* 1–9. doi:10.1016/0022-328X(83)80167-3
9. Hulce, M. *Tetrahedron Lett.* **1988,** *29,* 5851–5854. doi:10.1016/S0040-4039(00)82207-8
10. Krause, N. *Chem. Ber.* **1990,** *123,* 2173–2180. doi:10.1002/cber.19901231114
11. Mori, S.; Uerdigen, M.; Krause, N.; Morokuma, K. *Angew. Chem., Int. Ed.* **2005,** *44,* 4715–4719. doi:10.1002/anie.200462976
12. Yoshikai, N.; Yamashita, T.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005,** *44,* 4721–4723. doi:10.1002/anie.200501107
13. Yoshikai, N.; Yamashita, T.; Nakamura, E. *Chem. – Asian J.* **2006,** *1,* 322–330. doi:10.1002/asia.200600034
14. Wieland, P.; Anner, G. *Helv. Chim. Acta* **1967,** *50,* 289–296. doi:10.1002/hlca.19670500136
15. Alexakis, A.; Chapdelaine, M. J.; Posner, G. H.; Runquist, A. W. *Tetrahedron Lett.* **1978,** *19,* 4205–4208. doi:10.1016/S0040-4039(01)95182-2
16. Tissot, M.; Li, H.; Alexakis, A. Copper-catalyzed asymmetric conjugate addition and allylic substitution of organometallic reagents to extended multiple bond systems. In *Copper catalyzed asymmetric synthesis;* Alexakis, A.; Krause, N.; Woodward, S., Eds.; Wiley-VCH: Weinheim, 2014; pp 69–84. doi:10.1002/9783527664573.ch3
17. Fillion, E.; Wilsily, A.; Liao, E. T. *Tetrahedron: Asymmetry* **2006,** *17,* 2957–2959. doi:10.1016/j.tetasy.2006.11.009
18. Hénon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008,** *47,* 9122–9124. doi:10.1002/anie.200803735
19. Wencel-Delord, J.; Alexakis, A.; Crévisy, C.; Mauduit, M. *Org. Lett.* **2010,** *12,* 4335–4337. doi:10.1021/ol1017382
20. Magrez, M.; Wencel-Delord, J.; Alexakis, A.; Crévisy, C.; Mauduit, M. *Org. Lett.* **2012,** *14,* 3576–3579. doi:10.1021/ol300866p
21. Magrez-Chiquet, M.; Morin, M. S. T.; Wencel-Delord, J.; Drissi Amraoui, S.; Baslé, O.; Alexakis, A.; Crévisy, C.; Mauduit, M. *Chem. – Eur. J.* **2013,** *19,* 13663–13667. doi:10.1002/chem.201302649
22. Díez-González, S. *N-Heterocyclic Carbenes;* RSC Catalysis Series; RSC Publishing: Cambridge, 2011.
23. Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009,** *109,* 3612–3676. doi:10.1021/cr900074m
24. Clavier, H.; Coutable, L.; Guillemin, J.-C.; Mauduit, M. *Tetrahedron: Asymmetry* **2005,** *16,* 921–924. doi:10.1016/j.tetasy.2005.01.015
    See for an early example.
25. Queval, P.; Jahier, C.; Rouen, M.; Artur, I.; Legeay, J.-C.; Falivene, L.; Toupet, L.; Crévisy, C.; Cavallo, L.; Baslé, O.; Mauduit, M. *Angew. Chem., Int. Ed.* **2013,** *52,* 14103–14107. doi:10.1002/anie.201308873
26. Jahier-Diallo, C.; Morin, M. S. T.; Queval, P.; Rouen, M.; Artur, I.; Querard, P.; Toupet, L.; Crévisy, C.; Baslé, O.; Mauduit, M. *Chem. – Eur. J.* **2015,** *21,* 993–997. doi:10.1002/chem.201405765
27. Morin, M. S. T.; Vives, T.; Baslé, O.; Crévisy, C.; Ratovelomanana-Vidal, V.; Mauduit, M. *Synthesis* **2015,** *47,* 2570–2577. doi:10.1055/s-0034-1378813
28. den Hartog, T.; Harutyunyan, S. R.; Font, D.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2008,** *47,* 398–401. doi:10.1002/anie.200703702
29. den Hartog, T.; van Dijken, D. J.; Font, D.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron: Asymmetry* **2010,** *21,* 1574–1584. doi:10.1016/j.tetasy.2010.04.057

30. Tissot, M.; Müller, D.; Belot, S.; Alexakis, A. *Org. Lett.* **2010,** *12,* 2770–2773. doi:10.1021/ol100849j
31. Cesati, R. R., III; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004,** *126,* 96–101. doi:10.1021/ja0305407
32. Lee, K.-s.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006,** *128,* 7182–7184. doi:10.1021/ja062061o
33. Drissi-Amraoui, S.; Morin, M. S. T.; Crévisy, C.; Baslé, O.; Marcia de Figueiredo, R.; Mauduit, M.; Campagne, J.-M. *Angew. Chem., Int. Ed.* **2015,** *54,* 11830–11834. doi:10.1002/anie.201506189
34. Ohta, S.; Hayakawa, S.; Nishimura, K.; Okamoto, M. *Chem. Pharm. Bull.* **1987,** *35,* 1058–1069. doi:10.1248/cpb.35.1058
35. Evans, D. A.; Song, H.-J.; Fandrick, K. R. *Org. Lett.* **2006,** *8,* 3351–3354. doi:10.1021/ol061223i
36. Tissot, M.; Poggiali, D.; Henon, H.; Müller, D.; Guénée, L.; Mauduit, M.; Alexakis, A. *Chem. – Eur. J.* **2012,** *18,* 8731–8747. doi:10.1002/chem.201200502
37. Tissot, M.; Pérez-Hernàndez, A.; Müller, D.; Mauduit, M.; Alexakis, A. *Org. Lett.* **2011,** *13,* 1524–1527. doi:10.1021/ol200219m
38. Ma, Z.; Xie, F.; Yu, H.; Zhang, Y.; Wu, X.; Zhang, W. *Chem. Commun.* **2013,** *49,* 5292–5294. doi:10.1039/c3cc42088d
39. May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008,** *47,* 7358–7362. doi:10.1002/anie.200802910
40. Bleschke, C.; Tissot, M.; Müller, D.; Alexakis, A. *Org. Lett.* **2013,** *15,* 2152–2155. doi:10.1021/ol400642y
41. Gremaud, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2012,** *51,* 794–797. doi:10.1002/anie.201107324
42. den Hartog, T.; Huang, Y.; Fañanás-Mastral, M.; Meuwese, A.; Rudolph, A.; Pérez, M.; Minnaard, A. J.; Feringa, B. L. *ACS Catal.* **2015,** *5,* 560–574. doi:10.1021/cs501297s

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doi:10.3762/bjoc.11.263

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Copper-catalysed asymmetric allylic alkylation of alkylzirconocenes to racemic 3,6-dihydro-2*H*-pyrans

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Full Research Paper

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Keywords:
allylic alkylation; asymmetric catalysis; copper; design of experiments; dynamic kinetic asymmetric transformation; heterocycles; Schwartz reagent

Beilstein J. Org. Chem. **2015,** *11,* 2435–2443.
doi:10.3762/bjoc.11.264

Received: 11 September 2015
Accepted: 19 November 2015
Published: 03 December 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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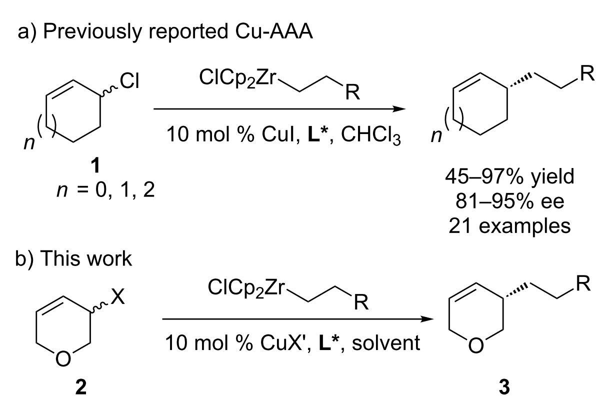
Abstract

Asymmetric allylic alkylation is a powerful reaction that allows the enantioselective formation of C–C bonds. Here we describe the asymmetric alkylation of alkylzirconium species to racemic 3,6-dihydro-2*H*-pyrans. Two systems were examined: 3-chloro-3,6-dihydro-2*H*-pyran using linear optimization (45–93% ee, up to 33% yield, 5 examples) and 3,6-dihydro-2*H*-pyran-3-yl diethyl phosphate with the assistance of a design of experiments statistical approach (83% ee, 12% yield). ^{1}H NMR spectroscopy was used to gain insight into the reaction mechanisms.

Introduction

Asymmetry is found in many natural products and biologically active molecules. Using racemic starting materials to synthesize enantiomerically enriched products is a powerful and underdeveloped strategy [1-4]. In some cases transition metal-catalysed asymmetric allylic alkylation (AAA) reactions [5-7] can be used in dynamic kinetic asymmetric transformations (DYKAT) [8-15] to provide single enantiomer products from racemic starting materials. Mechanistically some of these have been shown to occur by direct enantio-convergent transformations [16-18]. We have developed Cu-catalysed asymmetric conjugate additions of alkylzirconium reagents generated in situ by hydrometallation of terminal alkenes [19-25], and recently demonstrated that zirconium nucleophiles may undergo highly enantioselective copper-catalysed AAAs to racemic cyclic allyl halides, such as **1** (Scheme 1a) [26,27].

Tetrahydropyrans are a common motif in natural products and pharmaceuticals and are useful synthetic intermediates. However, the direct asymmetric derivatization of pyrans is rare [28] and enantiomerically enriched tetrahydropyrans are often obtained by ring-closing methods [29,30]. To extend our previously reported DYKATs beyond all-carbon electrophiles we decided to examine 3-chloro-3,6-dihydro-2*H*-pyran (**2a**, Scheme 1b). This was envisaged to be a challenging substrate.



Scheme 1: Previously reported Cu-AAA of alkylzirconium reagents to racemic allyl chlorides [26] and this work.

The presence of oxygen in the ring would modify the electronics, and likely the reactivity, of the starting material. The oxygen lone pairs on **2a** could potentially interact with the copper-catalyst or alkyl metal nucleophiles.

Results and Discussion

We first examined the in situ hydrometallation/AAA of 4-phenyl-1-butene (**4**) to racemic 3-chloro-3,6-dihydro-2*H*-pyran (**2a**, Table 1). Interestingly, no product was formed using our previously reported conditions for AAA to racemic carbocyclic substrates (CuI, ligand **A**, $CHCl_3$, Table 1, entry 1) [26] and only unreacted starting material was recovered. Different Cu salts were examined (Table 1, entries 2–7) and more strongly electron withdrawing counterions were found to provide the desired product, with $CuClO_4$ giving the best ee (70% ee, Table 1, entry 3). A solvent screen lead us to the conclusion that chlorinated solvents are best (CH_2Cl_2 (70% ee) and $CHCl_3$ (67% ee), Table 1, entries 7 and 10, respectively). Extensive examination of phosphoramidite ligands (for example, Table 1, entries 2 and 11–13) did not improve the ee. We then tested many different additives (TMSCl, AgOTf, borates, $ZrCl_4$, $Si(OEt)_4$, etc, for example Table 1, entries 14–18). Using $B(OiPr)_3$, which presumably acts as a Lewis acid, improved the ee to 80% (Table 1, entry 18) and so we re-examined different ligands using $CuClO_4$ in CH_2Cl_2 with $B(OiPr)_3$ (Table 1, entries 19–21). Derivatives of ligand **B** were tested and ligand **F** gave 83% ee (Table 1, entry 21), while electronically similar **E** was much less selective (47% ee, Table 1, entry 20). The effects of concentration, temperature and catalyst loading were also investigated (not shown) with no improvement on the enantioselectivity.

After extensive optimization, the highest enantiomeric excess obtained was only 83% ee and so we decided to examine other leaving groups (Table 2). Like allyl chloride **2a**, allyl bromide **2b** gave no desired product when using our previously reported conditions [26] (Table 2, entry 2). The use of **2b** also only gave low ee when using the conditions optimized above (38% ee, Table 2, entry 1). Allyl acetate **2c** did not give the desired product under any conditions examined, however, allyl phosphate **2d** was found to provide **5** with good selectivity (77% ee, Table 2, entry 5). 3,6-Dihydro-2*H*-pyran-3-yl diethyl phosphate (**2d**) was also the only substrate to react using our previously reported AAA conditions (CuI, ligand **A**, $CHCl_3$) [26], albeit with poor enantioselectivity (29% ee, Table 2, entry 6).

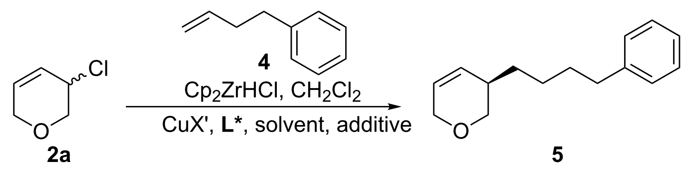
Design of experiments (DoE) [31-37] is a powerful tool for efficient screening and is commonly used in industry, since traditional one-factor-at-a-time optimization poorly covers the available parameter space and may not locate the most optimal conditions. As DoE rapidly explores the response space efficiently and can reveal interdependence of factors at no extra experimental cost, we decided to briefly examine DoE in this complex asymmetric transformation. We note that there are important limits to this investigation. Understanding what interactions give rise to asymmetric induction (particularly in transformations where mechanisms are not understood) is extremely challenging, and it is not obvious how to parameterize the multiple variables present in key factors such as ligand structure [38].

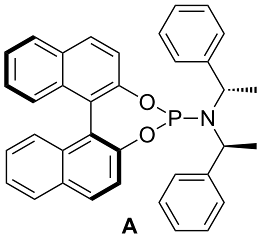
Nevertheless, a Principal Component Analysis using JMP® 12.1.0 (SAS) in 3 waves was carried out using **2d** as the starting material. In each experiment, the most promising variables were chosen based on results from previously published methods, the procedure optimised for **2a** (above), and the results of previous waves. The first wave was as a third factorial design with 3 categories: Ligand (**A**, **B**, **C**, **F** and **G**), counter-ion (ClO_4^-, I^- and OTf^-) and solvent (CH_2Cl_2, Et_2O and TBME, Table 1, entries 1–17; ● Figure 1, for more details see Supplorting Information File 1).

This first DoE study suggested that neither CuI nor TBME were good fits for the reaction (both consistently giving low ee). The combination of CuOTf in CH_2Cl_2 gave the best enantioselectivity (up to 83% ee, Table S1 entry 3, Supporting Information File 1) with ligand **G**. Unlike with **2a**, $CuClO_4$ did not give high ee with **2d**; the highest value obtained was 43% ee (Table S1, entry 14). Interestingly Et_2O gave mixed results with some low (e.g., 1% ee, Table S1, entry 1) and moderate (e.g., 56% ee, Table S1, entry 6) ee values obtained.

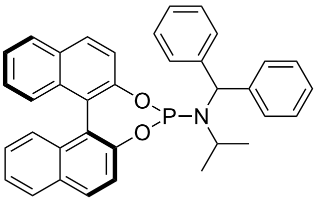
Based on those results, a second wave of DoE was designed as a 6th factorial design with 4 factors: Ligand (**G**, **H**, **I**, **J**), counter-ion (OTf and NTf_2), solvent (CH_2Cl_2, Et_2O and $CHCl_3$) and TMSCl equivalent (0, 1 and 5) (Table S1, entries

Table 1: Asymmetric alkylation to 3-chloro-3,6-dihydro-2*H*-pyran (**2a**)[a].





A



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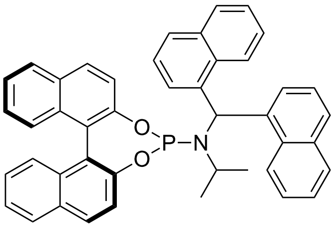

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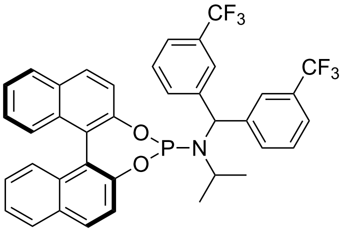

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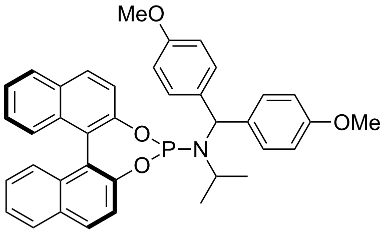

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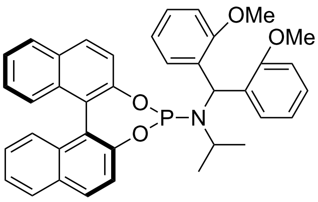
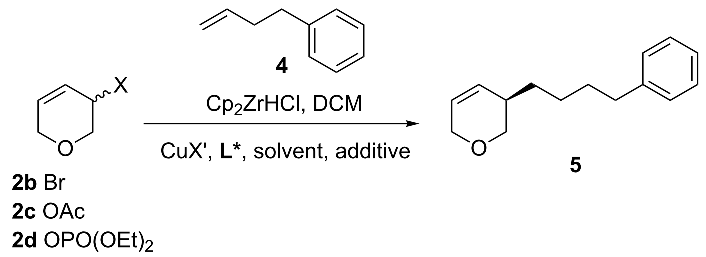


F

Entry	Copper	L*	Solvent	Additive	ee[b]
1	CuI	**A**	$CHCl_3$		NP
2	$CuClO_4$	**A**	CH_2Cl_2		68%
3	$CuClO_4$	**B**	CH_2Cl_2		70%
4	CuOTf	**B**	CH_2Cl_2		64%
5	$CuNTf_2$	**B**	CH_2Cl_2		52%
6	CuTC	**B**	CH_2Cl_2		12%
7	$CuSbF_6$	**B**	CH_2Cl_2		NP
8	$CuClO_4$	**B**	Et_2O		55%
9	$CuClO_4$	**B**	Me-THF		38%
10	$CuClO_4$	**B**	$CHCl_3$		67%
11	$CuClO_4$	**C**	CH_2Cl_2		53%
12	$CuClO_4$	**D**	CH_2Cl_2		36%
13	$CuClO_4$	**E**	CH_2Cl_2		12%
14	$CuClO_4$	**B**	CH_2Cl_2	TMSCl	73%
15	$CuClO_4$	**B**	CH_2Cl_2	$Si(OEt)_4$	63%
16	$CuClO_4$	**B**	CH_2Cl_2	$Ti(OiPr)_4$	25%
17	$CuClO_4$	**B**	CH_2Cl_2	$AlCl_3$	15%
18	$CuClO_4$	**B**	CH_2Cl_2	$B(OiPr)_3$	80%
19	$CuClO_4$	**C**	CH_2Cl_2	$B(OiPr)_3$	78%
20	$CuClO_4$	**E**	CH_2Cl_2	$B(OiPr)_3$	47%
21	$CuClO_4$	**F**	CH_2Cl_2	$B(OiPr)_3$	83%

[a]Conditions: 4-phenyl-1-butene (2.5 equiv), Cp_2ZrHCl (2.0 equiv), **2a** (1.0 equiv), Cu**L*** as specified (0.1 equiv), additive as specified (1.0 equiv), in specified solvent (2.0 mL), room temperature. [b]ee determined by HPLC. NP = no product. For more information on procedures see Supporting Information File 1.

Table 2: Effect of leaving groups.[a]



Entry	X	Copper	L*	Solvent	Additive	ee[b]
1	Br	$CuClO_4$	**F**	CH_2Cl_2	$B(O\textit{i}Pr)_3$	38%
2	Br	CuI	**A**	$CHCl_3$		NP
3	OAc	$CuClO_4$	**F**	CH_2Cl_2	$B(O\textit{i}Pr)_3$	NP
4	OAc	CuI	**A**	$CHCl_3$		NP
5	$OPO(OEt)_2$	$CuClO_4$	**F**	CH_2Cl_2	$B(O\textit{i}Pr)_3$	77%
6	$OPO(OEt)_2$	CuI	**A**	$CHCl_3$		29%

[a]Conditions: 4-phenyl-1-butene (2.5 equiv), Cp_2ZrHCl (2.0 equiv), **2** (1.0 equiv), Cu**L***(0.1 equiv), additive (1.0 equiv), in solvent (2.0 mL), room temperature. [b]ee determined by HPLC. NP = no product. For more information on procedures see Supporting Information File 1.

18–30, ♦). As mixed results were obtained with Et_2O, we decided to investigate it more thoroughly. This second study emphasizes the intrinsic challenge of finding optimum conditions in complex asymmetric reactions. Whereas CuOTf seems to work best with CH_2Cl_2 as a solvent, $CuNTf_2$ gave better enantioselectivity in Et_2O. $CHCl_3$ consistently provided lower enantioselectivity than CH_2Cl_2. In the small selection of ligands examined, **G** generally gave better results.

We designed a final study to investigate the role of various equivalents of additive (TMSCl and $B(OiPr)_3$) with CuOTf and $CuNTf_2$ in their respective favoured solvents (CH_2Cl_2 and Et_2O) (Table S1, entries 31–38, ▼). $B(OiPr)_3$ significantly lowered the ee (44% ee, Table S1, entry 33). The influence of TMSCl on the reaction was highly dependent on the other reaction parameters; $CuNTf_2$ in Et_2O with no additive gave 67% ee (Table S1, entry 34), while adding 1 equiv of TMSCl gave a slight improvement (73% ee, Table S1, entry 35) but no further improvement was observed by adding more TMSCl (5 equiv, 74% ee, Table S1, entry 36). On the other hand, using 1 equiv of TMSCl with CuOTf in CH_2Cl_2 did not modify the ee (81% ee, Table S1, entry 32), while adding 5 equiv of TMSCl was detrimental to enantioselectivity (60% ee, Table S1, entry 31).

Despite our efforts to optimise this second system, the highest enantioselectivity obtained was 83% ee, which is the same as for allyl chloride **2a**. It became clear that when using alkylzirconocene nucleophiles and Cu catalysis, derivatised 3,6-dihydro-2*H*-pyrans are difficult to obtain in high enantiomeric excess. Moreover, both optimised systems gave poor yield; 25% yield with 100% conversion from allyl chloride **2a** and 17% yield with 31% conversion from allyl phosphate **2d**.

Various alkenes were examined using the allyl chloride **2a** system (Scheme 2). The reaction showed tolerance in functional groups such as CF_3 (**6**, 75% ee) Cl (**7**, 77% ee), and cyclohexane (**8**, 88% ee). Electron rich allyl silane could also be used to introduce a TMS group (**9**, 93% ee), but all the yields were poor.

To investigate why we obtained such poor yields, and possibly shed light onto the reaction mechanism, we decided to follow both reactions in time using in situ NMR spectroscopy (Figure 2 and Figure 3). Reactions were carried out as normal, but in deuterated solvents and mixed in an NMR tube (see Supporting Information File 1). Ethylene was used as the alkylzirconium precursor as it greatly simplifies the NMR spectra. Spectra were recorded at regular intervals over time where relative concentrations are based on integration of the best resolved ^1H signal for each species and calibrated accordingly.

Through these kinetic studies, it is clear that the allyl chloride **2a** system fails because the starting material dimerises to give **11** as the major reaction product (60% isolated yield – 30 mol % by NMR) (Figure 2). This is consistent with the observed ≈100% conversion but low product yields. Presumably **11** arises from the homocoupling of allyl chloride **2a**, possibly through a π-allyl-Cu intermediate [39-43]. Although

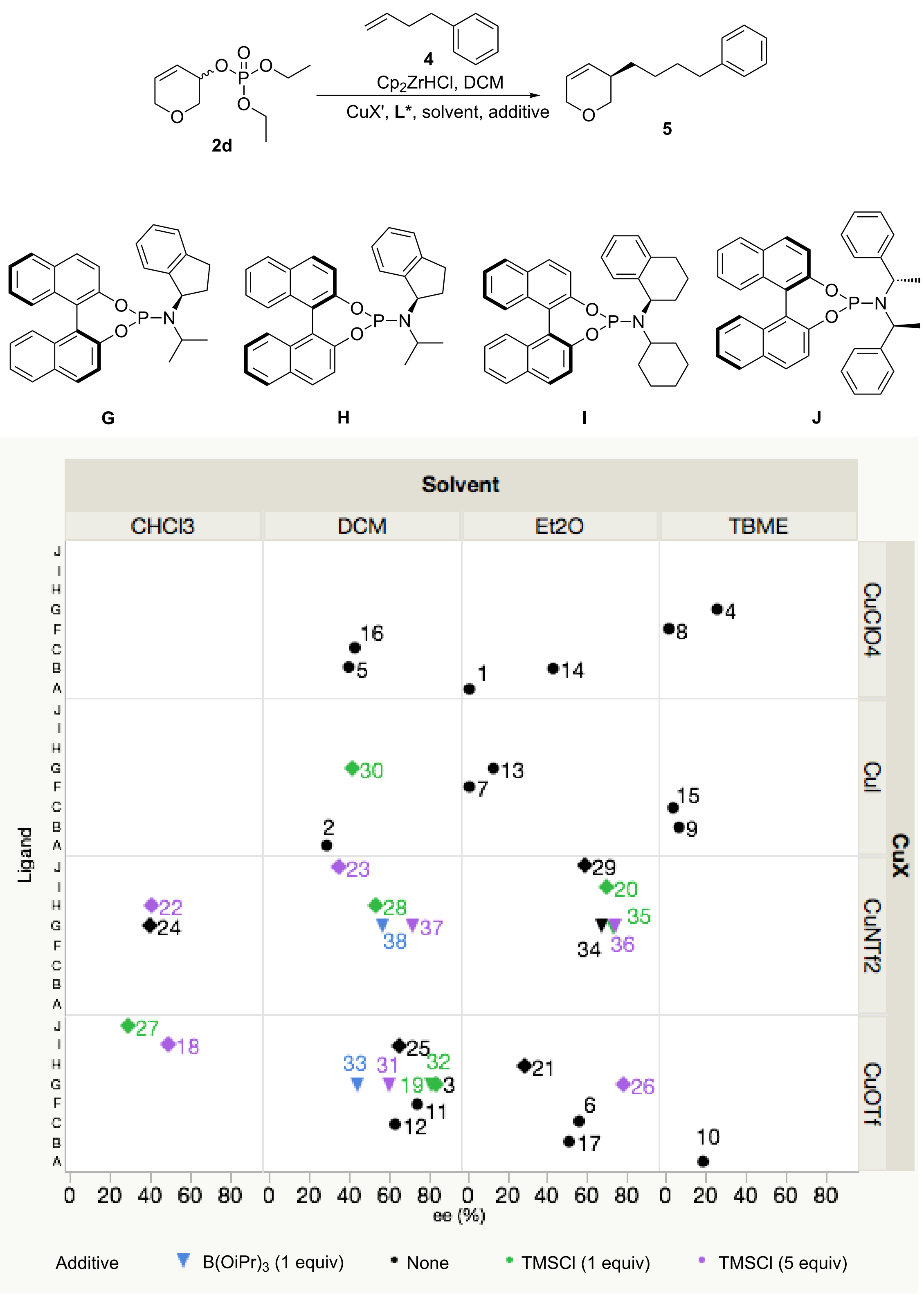
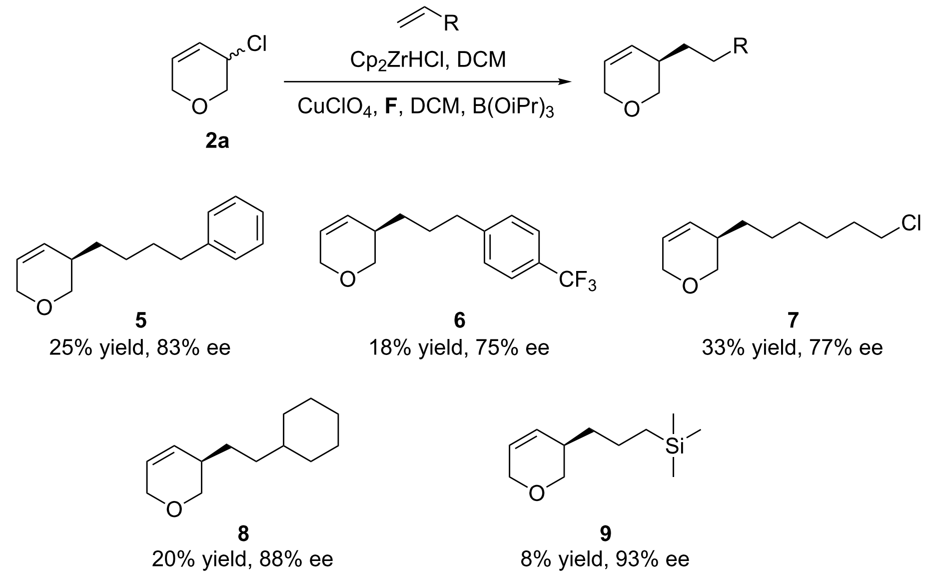


Figure 1: DoE from 3,6-dihydro-2*H*-pyran-3-yl diethyl phosphate (**2d**). Conditions: 4-phenyl-1-butene (2.5 equiv), Cp_2ZrHCl (2.0 equiv), **2d** (1.0 equiv), Cu**L*** as specified (0.1 equiv), additive as specified (1.0 equiv or 5.0 equiv), in specified solvent (2.0 mL), room temperature. ee determined by HPLC. For more information on the procedures see Supporting Information File 1. ● (wave 1, entries 1–17), ♦ (wave 2, entries 18–30), ▼ (wave 3, entries 31–38).



Scheme 2: Scope of nucleophiles. Conditions: alkene (2.5 equiv), Cp_2ZrHCl (2.0 equiv), 3-chloro-3,6-dihydro-2*H*-pyran **2a** (1.0 equiv), CuCl (10 mol %), **D** (10 mol %), $AgClO_4$ (10 mol %), $B(OiPr)_3$ (1.0 equiv), in CH_2Cl_2 (2.0 mL), room temperature. Isolated yield. ee determined by HPLC or GC. For more information see Supporting Information File 1.

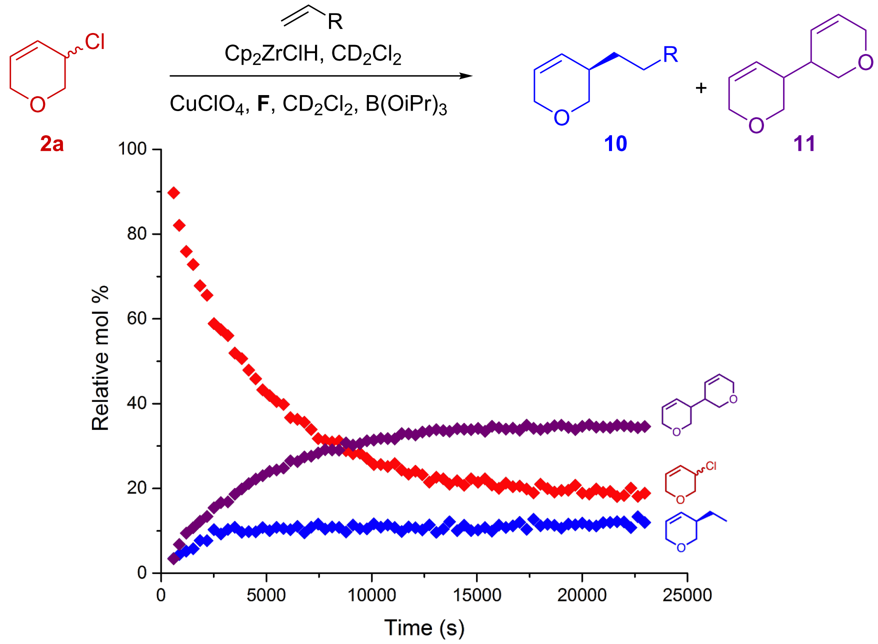


Figure 2: Reaction kinetics as monitored by in situ ^{1}H NMR spectroscopy from 3-chloro-3,6-dihydro-2*H*-pyran (**2a**).

both the conditions and leaving groups differ in the two reactions it is not clear why **2a**, but not **2d**, dimerizes. **11** can exists as 3 isomers, a meso compound and two enantiomers. Upon comparison to literature data [44], we concluded that we form a mixture of all three, as a 1:1 mixture of the meso and racemic material. Our samples did not rotate plane polarized light, emphasizing the racemic nature of the sample and suggesting that **11** is formed in a completely non-selective pathway.

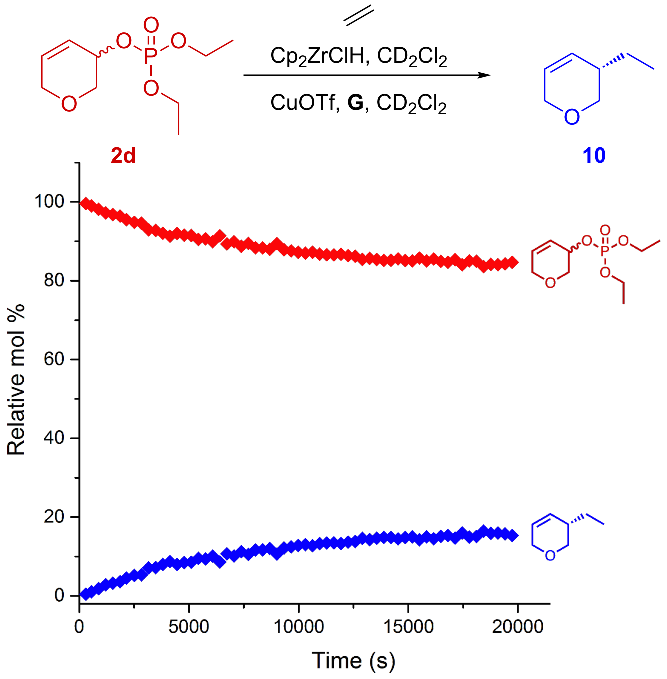


Figure 3: Reaction kinetics as monitored by in situ ^{1}H NMR spectroscopy from 3,6-dihydro-2*H*-pyran-3-yl diethyl phosphate (**2d**).

In the case of allyl phosphate **2d**, the system appears to lack reactivity and the reaction quickly dies, so that **10** (Figure 3) is formed with poor conversion, and we speculate that the phosphate leaving group inhibits the catalyst which would explain why only ~10% of product is formed.

To obtain further mechanistic information we followed the ee of these reactions in time (Figure 4 and Figure 5). In the system using chloride **2a**, the ee of product **5** remains constant throughout the reaction (~75% ee, Figure 4). Starting chloride **2a** was found to be quite robust so that we could also determine its

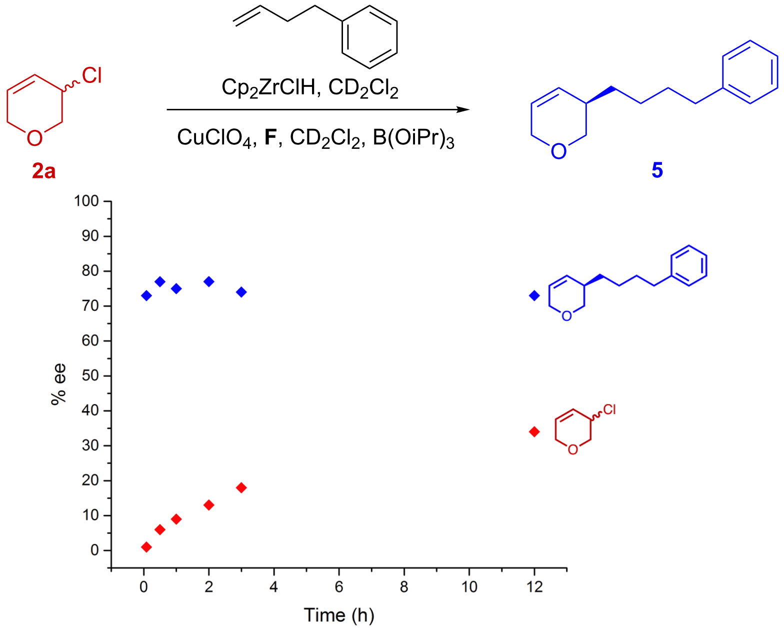


Figure 4: Kinetic ee analysis using **2a**. ee of reaction with 3-chloro-3,6-dihydro-2*H*-pyran (**2a**) as measured by removing aliquots in time.

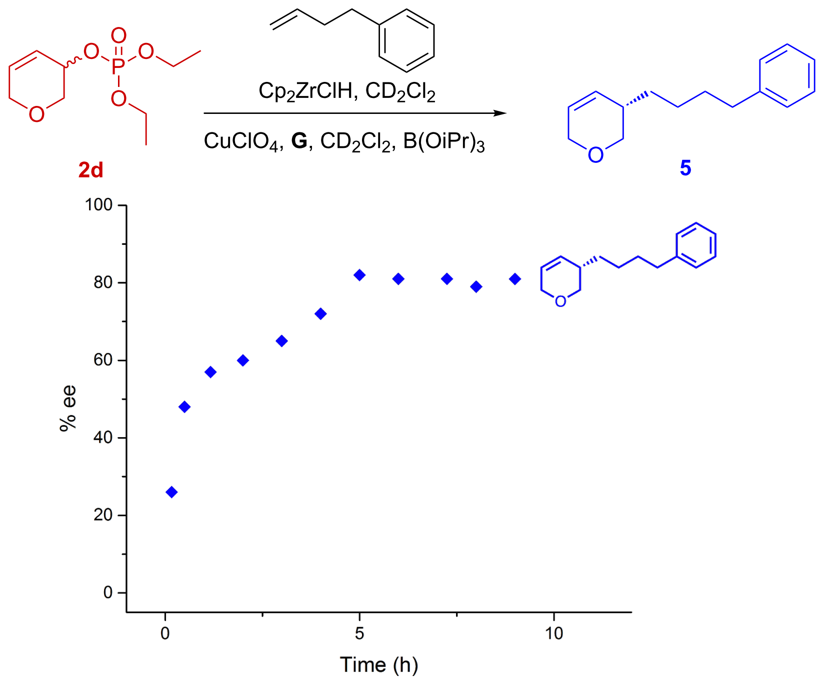


Figure 5: Kinetic ee analysis using **2d**. ee of reaction with 3,6-dihydro-2*H*-pyran-3-yl diethyl phosphate (**2d**) as measured by removing aliquots in time.

enantiomeric excess during the course of the reaction. Initially **2a** is racemic but it becomes scalemic to slowly reach 34% ee when the reaction is complete (~12 hours). From these observations and our experimental demonstration that **2a** is much more stable than all-carbocyclic **1**, it appears that **2a** undergoes kinetic resolution. However, this system is clearly complicated by the fact that the majority of **2a** is consumed during byproduct **11**'s formation.

In the phosphate system based on **2d**, the ee of product **5** was found to increase during the course of the reaction (Figure 5) so that **5** was ~26% ee after a few minutes, and increased to ~82% ee after 5 hours. Unfortunately, analytical conditions to separate the enantiomers of **2d**, so we could measure the enantiomeric excess of this starting material, could not be found. At this stage it is not possible to provide a full mechanistic rationalization of these reactions. It is also not immediately obvious how to improve yields and enantiomeric excesses. The kinetic studies suggest that the two reactions work through very different mechanisms and it strikes us as remarkable how both systems give roughly the same enantioselectivity and poor yield, yet have significantly different pathways.

Conclusion

The Cu-catalyzed AAA of alkylzirconium reagents to racemic heterocyclic electrophiles was explored. After extensive examination, two different methods for obtaining 3,6-dihydro-2*H*-pyran derivatives with respectable levels of ee (≈83% ee) were developed. Unfortunately, the yields were poor in both cases. Kinetic studies were performed to help to understand the difficulties associated with these reactions. While we were not able to resolve the issues of yield in these studies, this work reveals remarkable mechanistic diversity in Cu-catalysed asymmetric alkylation reactions to racemic starting materials.

Supporting Information

Supporting Information File 1

Additional material.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-264-S1.pdf]

Acknowledgements

The authors thank the EPSRC (EP/H003711/1) for financial support.

References

1. Faber, K. *Chem. – Eur. J.* **2001,** *7,* 5004. doi:10.1002/1521-3765(20011203)7:23<5004::AID-CHEM5004>3.0.CO;2-X
2. Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005,** *44,* 3974. doi:10.1002/anie.200460842
3. Mohr, J. T.; Ebner, D. C.; Stoltz, B. M. *Org. Biomol. Chem.* **2007,** *5,* 3571. doi:10.1039/b711159m

4. Miller, L. C.; Sarpong, R. *Chem. Soc. Rev.* **2011,** *40,* 4550. doi:10.1039/c1cs15069c
5. Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994,** *116,* 4089. doi:10.1021/ja00088a059
6. Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996,** *96,* 395. doi:10.1021/cr9409804
7. Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008,** *47,* 258. doi:10.1002/anie.200605113
8. Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001,** *30,* 321. doi:10.1039/b105464n
9. Trost, B. M.; Fandrick, D. R. *Aldrichimica Acta* **2007,** *40,* 59.
10. Norinder, J.; Bäckvall, J.-E. *Chem. – Eur. J.* **2007,** *13,* 4094. doi:10.1002/chem.200601684
11. Langlois, J.-B.; Alexakis, A. *Chem. Commun.* **2009,** 3868. doi:10.1039/b907722g
12. Langlois, J.-B.; Alexakis, A. *Adv. Synth. Catal.* **2010,** *352,* 447. doi:10.1002/adsc.200900790
13. Katcher, M. H.; Doyle, A. G. *J. Am. Chem. Soc.* **2010,** *132,* 17402. doi:10.1021/ja109120n
14. Hamilton, J. Y.; Hauser, N.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2014,** *53,* 10759. doi:10.1002/anie.201406077
15. Misale, A.; Niyomchon, S.; Luparia, M.; Maulide, N. *Angew. Chem., Int. Ed.* **2014,** *53,* 7068. doi:10.1002/anie.201309074
16. Ito, H.; Kunii, S.; Sawamura, M. *Nat. Chem.* **2010,** *2,* 972. doi:10.1038/nchem.801
17. Langlois, J.-B.; Emery, D.; Mareda, J.; Alexakis, A. *Chem. Sci.* **2012,** *3,* 1062. doi:10.1039/C2SC00868H
18. Delvos, L. B.; Oestreich, M. *Synthesis* **2015,** *47,* 924. doi:10.1055/s-0034-1380157
19. Maksymowicz, R. M.; Roth, P. M. C.; Fletcher, S. P. *Nat. Chem.* **2012,** *4,* 649. doi:10.1038/nchem.1394
20. Sidera, M.; Roth, P. M. C.; Maksymowicz, R. M.; Fletcher, S. P. *Angew. Chem., Int. Ed.* **2013,** *52,* 7995. doi:10.1002/anie.201303202
21. Maciver, E. E.; Maksymowicz, R. M.; Wilkinson, N.; Roth, P. M. C.; Fletcher, S. P. *Org. Lett.* **2014,** *16,* 3288. doi:10.1021/ol501292x
22. Roth, P. M. C.; Fletcher, S. P. *Org. Lett.* **2015,** *17,* 912. doi:10.1021/acs.orglett.5b00021
23. Rideau, E.; Mäsing, F.; Fletcher, S. P. *Synthesis* **2015,** *47,* 2217. doi:10.1055/s-0034-1379928
24. Caprioglio, D.; Fletcher, S. P. *Chem. Commun.* **2015,** *51,* 14866. doi:10.1039/C5CC05805H
25. Maksymowicz, R. M.; Bissette, A. J.; Fletcher, S. P. *Chem. – Eur. J.* **2015,** *21,* 5668. doi:10.1002/chem.201405855
26. You, H.; Rideau, E.; Sidera, M.; Fletcher, S. P. *Nature* **2015,** *517,* 351. doi:10.1038/nature14089
27. Sidera, M.; Fletcher, S. P. *Chem. Commun.* **2015,** *51,* 5044. doi:10.1039/C5CC00421G
28. Morken, J. P.; Didiuk, M. T.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1994,** *116,* 3123. doi:10.1021/ja00086a052
29. Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993,** *115,* 9856. doi:10.1021/ja00074a085
30. Clark, J. S. *Chem. Commun.* **2006,** 3571. doi:10.1039/b601839d
31. Aggarwal, V. K.; Staubitz, A. C.; Owen, M. *Org. Process Res. Dev.* **2006,** *10,* 64. doi:10.1021/op058013q
32. Weissman, S. A.; Anderson, N. G. *Org. Process Res. Dev.* **2015,** *19,* 1605. doi:10.1021/op500169m
33. Owen, M. R.; Luscombe, C.; Lai-Wah; Godbert, S.; Crookes, D. L.; Emiabata-Smith, D. *Org. Process Res. Dev.* **2001,** *5,* 308. doi:10.1021/op000024q
34. Chen, J. J.; Nugent, T. C.; Lu, C. V.; Kondapally, S.; Giannousis, P.; Wang, Y.; Wilmot, J. T. *Org. Process Res. Dev.* **2003,** *7,* 313. doi:10.1021/op034018g
35. Denmark, S. E.; Butler, C. R. *J. Am. Chem. Soc.* **2008,** *130,* 3690. doi:10.1021/ja7100888
36. Arnold, K.; Batsanov, A. S.; Davies, B.; Whiting, A. *Green Chem.* **2008,** *10,* 124. doi:10.1039/B712008G
37. Peñafiel, I.; Pastor, I. M.; Yus, M. *Eur. J. Org. Chem.* **2013,** 1479. doi:10.1002/ejoc.201201066
38. Harper, K. C.; Sigman, M. S. *J. Org. Chem.* **2013,** *78,* 2813. doi:10.1021/jo4002239
39. Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012,** *112,* 2339. doi:10.1021/cr200241f
40. Geurts, K.; Fletcher, S. P.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Pure Appl. Chem.* **2008,** *80,* 1025. doi:10.1351/pac200880051025
41. Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008,** *108,* 2796. doi:10.1021/cr0683515
42. Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008,** *108,* 2824. doi:10.1021/cr068424k
43. Alexakis, A.; Krause, N.; Woodward, S. *Copper-Catalyzed Asymmetric Synthesis;* Wiley-VCH: Weinheim, 2014. doi:10.1002/9783527664573
44. Maougal, E.; Dalençon, S.; Pearson-Long, M. S. M.; Mathé-Allainmat, M.; Lebreton, J.; Legoupy, S. *Synthesis* **2014,** *46,* 3268. doi:10.1055/s-0034-1378663

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doi:10.3762/bjoc.11.264

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Copper-catalyzed stereoselective conjugate addition of alkylboranes to alkynoates

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Full Research Paper

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Keywords:
alkylborane; alkynoate; conjugate addition; copper; multisubstituted alkene

Beilstein J. Org. Chem. **2015,** *11,* 2444–2450.
doi:10.3762/bjoc.11.265

Received: 31 August 2015
Accepted: 25 November 2015
Published: 04 December 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

A copper-catalyzed conjugate addition of alkylboron compounds (alkyl-9-BBN, prepared by hydroboration of alkenes with 9-BBN-H) to alkynoates to form β-disubstituted acrylates is reported. The addition occurred in a formal *syn*-hydroalkylation mode. The *syn* stereoselectivity was excellent regardless of the substrate structure. A variety of functional groups were compatible with the conjugate addition.

Introduction

Copper-mediated conjugate additions of organometallic reagents to alkynoates are powerful tools for the synthesis of multisubstituted alkenes [1-8]. Because of their broad availability and their compatibility with a multitude of functional groups, organoboron compounds are especially popular organometallic reagents. Recently, Yamamoto and co-workers developed copper-catalyzed conjugate additions of aryl- and allylboron compounds to alkynoates [9,10], but alkylboron compounds have not been used for these methods [11].

As related studies we reported earlier the copper-catalyzed conjugate addition of alkylboranes (alkyl-9-BBN) to imidazole-2-yl α,β-unsaturated ketones [12-14] and the copper-catalyzed three-component coupling with alkylboranes, alkynoates, and tributyltin methoxide to form trisubstituted alkenylstannanes [15]. The latter reaction pathway involved Sn-trapping of an alkenylcopper intermediate that was formed through *syn*-carbocupration of an alkylcopper(I) species across the C–C triple bond of the alkynoate. We envisioned that 1,2-hydroalkylation of the alkynoates might be possible through proton-trapping of an alkenylcopper intermediate.

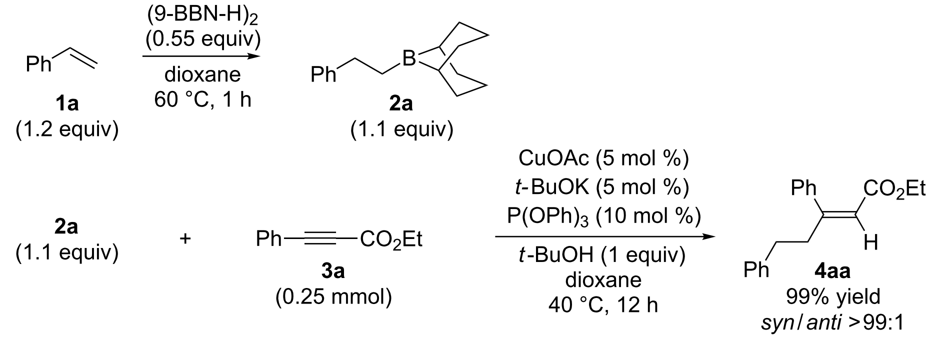
Herein, we report a copper-catalyzed conjugate addition of alkylboranes to alkynoates, providing a versatile approach to β-disubstituted acrylates [16-19]. The addition occurred in a formal *syn*-hydroalkylation mode. The *syn* stereoselectivity was excellent regardless of the substrate structure, and a variety of functional groups were tolerated in both the alkylborane and the alkynoate.

Results and Discussion

Alkylborane **2a** (0.275 mmol), which was obtained via hydroboration of styrene (**1a**) with the 9-borabicyclo[3.3.1]nonane (9-BBN-H) dimer, and ethyl 3-phenylpropiolate (**3a**, 0.25 mmol) were treated with CuOAc (5 mol %), *t*-BuOK (5 mol %), $P(OPh)_3$ (10 mol %), and *t*-BuOH (0.25 mmol) in 1,4-dioxane (1.2 mL) at 40 °C for 12 h. The reaction afforded a formal hydroalkylation product, β-disubstituted acrylate **4aa** in 99% isolated yield with >99% *syn* selectivity (Scheme 1).

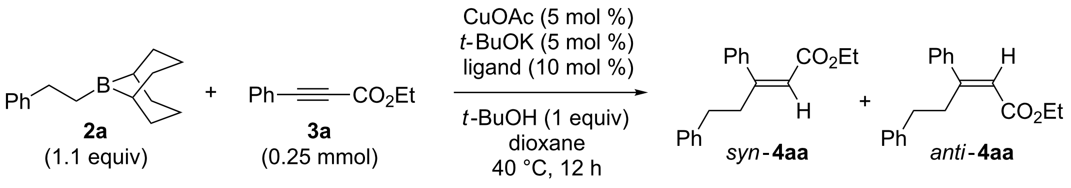
The results of ligand screening for the reaction between **2a** and **3a** are summarized in Table 1. $P(OPh)_3$ was the most effective ligand in terms of product yield and *syn* selectivity (Table 1, entry 1). The use of other monophosphine ligands such as PPh_3 and PCy_3 or the DPPE bisphopshine was also effective in promotion of the reaction, but resulted in a reduced stereoselectivity (Table 1, entries 2–4). No reaction occurred with *N*-heterocyclic carbenes (NHC) such as IMes or IPr (Table 1, entries 5 and 6). The reaction with (IMes)CuCl or (IPr)CuCl complex delivered no reaction product (data not shown). The reaction without a ligand resulted in a significantly decreased product yield while the *syn* selectivity was fairly high (Table 1, entry 7).

The use of less expensive CuCl as a copper salt was also effective to produce **4aa** in 90% yield with 99% *syn* selectivity. The reaction using MeOH as a proton source instead of *t*-BuOH caused a drastic reduction in the product yield with the syn selectivity slightly decreased (38%, *syn*/*anti* 97:3). The reduction of the yield might be due to the protonation of an alkylcopper species by the more acidic MeOH (vide infra). There



Scheme 1: Conjugate addition of alkylborane **2a** to alkynoate **3a**.

Table 1: Ligand effects.



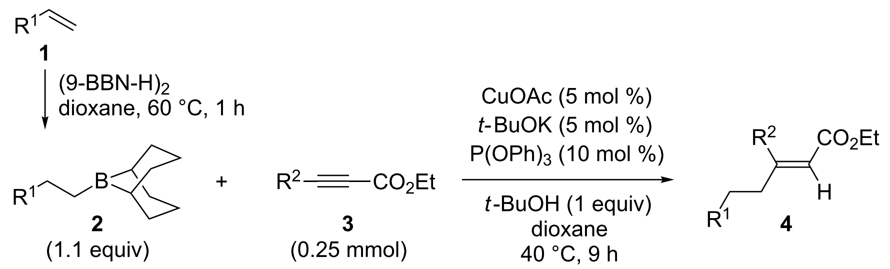
Entry	Ligand[a]	Yield [%][b]	*syn*/*anti*[c]
1	$P(OPh)_3$	99	>99:1
2	PPh_3	99	67:33
3	PCy_3	56	64:36
4	DPPE	99	83:17
5	IMes	0	–
6	IPr	0	–
7	none	37	97:3

[a] IMes: 1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene, IPr: 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene. [b] Yield determined by ^1H NMR. [c] Determined by ^1H NMR or GC analysis of the crude product.

was no reaction in the absence of a proton sourse. No hydroalkylation product at all could be found when alkyl-9-BBN **2a** was replaced by (2-phenylethyl)boronic acid pinacolate ester; the substrates hardly reacted at all.

A variety of β-disubstituted acrylates were accessible through the hydroboration–conjugate addition one-pot protocol with excellent *syn* stereoselectivities (Table 2). This protocol tolerated functional groups such as methoxy, ester, phthalimide,

Table 2: Copper-catalyzed conjugate addition of alkylboranes **2** to alkynoates 3.[a]



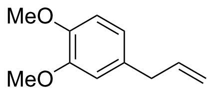
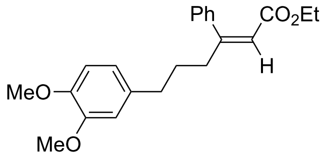
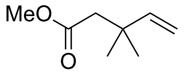
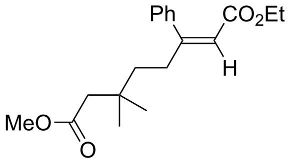
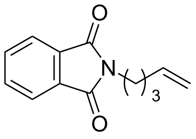
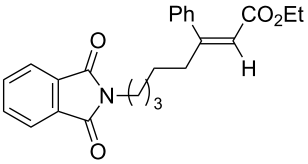
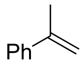
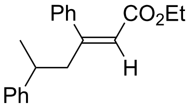
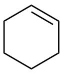
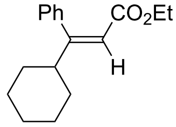
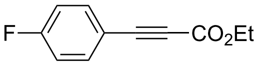
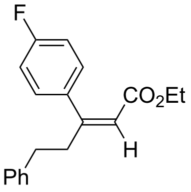
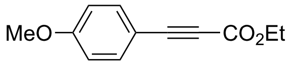
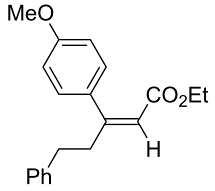
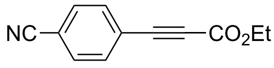
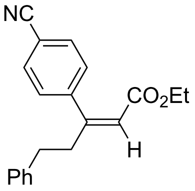
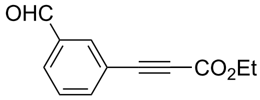
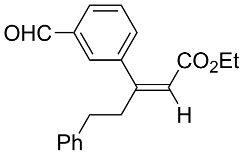
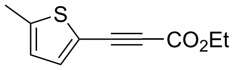
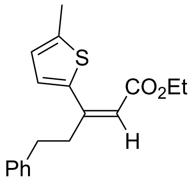
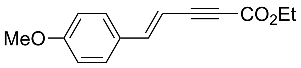
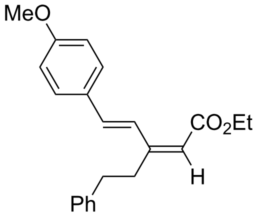
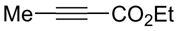
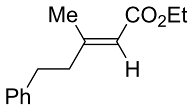
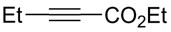
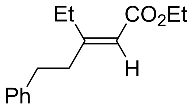
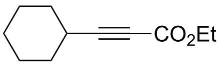
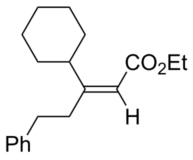
Entry	Alkene	Alkynoate	Product	Yield [%][b]	*syn*/*anti*[c]
1	 **1b**	**3a**	 **4ba**	94	99:1
2	 **1c**	**3a**	 **4ca**	99	>99:1
3	 **1d**	**3a**	 **4da**	87	99:1
4[d]	 **1e**	**3a**	 **4ea**	86	>99:1
5	 **1f**	**3a**	 **4fa**	0	–
6	**1a**	 **3b**	 **4ab**	96	98:2

Table 2: Copper-catalyzed conjugate addition of alkylboranes **2** to alkynoates 3.[a] (continued)

7	**1a**	 **3c**	 **4ac**	91	99:1
8	**1a**	 **3d**	 **4ad**	88	99:1
9	**1a**	 **3e**	 **4ae**	93	99:1
10	**1a**	 **3f**	 **4af**	95	94:6
11	**1a**	 **3g**	 **4ag**	90	>99:1
12	**1a**	 **3h**	 **4ah**	94	>99:1
13	**1a**	 **3i**	 **4ai**	98	>99:1
14	**1a**	 **3j**	 **4aj**	93	>99:1

[a] The reaction was carried out with **3** (0.25 mmol), **2** (0.275 mmol), CuOAc (5 mol %), *t*-BuOK (5 mol %), $P(OPh)_3$ (10 mol %) and *t*-BuOH (0.25 mmol) in dioxane (1.2 mL) at 40 °C for 12 h. Alkylborane **2** was prepared in advance by hydroboration of **1** with the 9-BBN-H dimer at 60 °C for 1 h and used without purification. [b] Yield of isolated product. [c] Determined by ^{1}H NMR or GC analysis of the crude product. [d] Diasteremeric ratio (1:1).

fluoro, cyano and aldehyde moieties in the alkylboranes and alkynoates (Table 2, entries 1–3, 6–9 and 11).

The data in Table 2 show the variety of functional groups attached to alkylboranes **2** that are tolerated in the reaction. The rather crowded alkylborane **2c**, which was prepared from tertiary alkyl substituted terminal alkene **1c**, reacted nicely (Table 2, entry 2). β-Branched alkylborane **2e**, prepared from α-methylstyrene (**1e**), provided **4ea** in good yield (Table 2, entry 4). Unfortunately, however, the reaction of secondary alkylboranes made from internal alkenes, did not work (Table 2, entry 5).

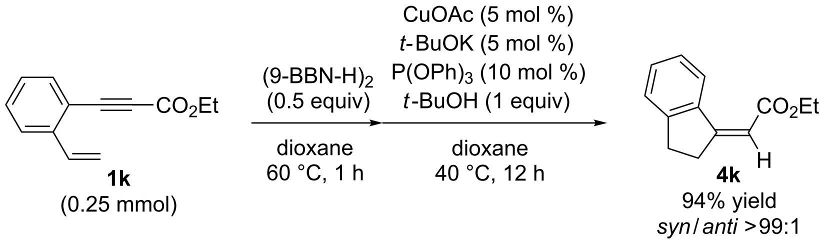
The variety of alkynoates used is also shown in Table 2. The fluoro atom and the methoxy, cyano and aldehyde groups were acceptable as *para* or *meta*-substituents on the aromatic ring at the β-positions (Table 2, entries 6–9). The alkynoate **3f** bearing a 2-thienyl group at the β-position is also compatible with the conjugate addition and gave 94% *syn* selectivity (Table 2, entry 10). The 1,3-enyne derivative **3g** reacted regioselectively to afford a conjugated 2,4-dienoate **4ag** in 90% yield with excellent *syn* selectivity (Table 2, entry 11).

Alkyl groups were also acceptable as β-substituent of the alkynoates (Table 2, entries 12–14). Alkynoate **3h** with a methyl group at the β-position reacted with an excellent stereoselectivity (Table 2, entry 12). The alkynoates with an ethyl (**3i**) or cyclohexyl group (**3j**) were also suitable substrates (Table 2, entries 13 and 14).

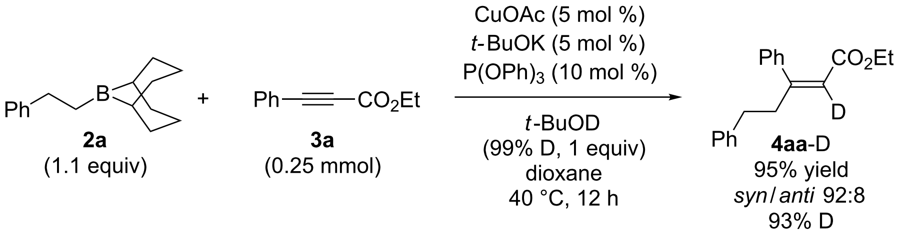
Alkene hydroboration of **1k** followed by copper-catalyzed intramolecular conjugate addition enabled the formation of the corresponding five-membered carbocycle **4k** in 94% yield with complete syn selectivity (Scheme 2).

To gain insight into the mechanism of the copper-catalyzed conjugate addition, the reaction between **2a** and **3a** with *t*-BuOD under the optimum conditions was conducted (Scheme 3). The reaction afforded **4aa**-D, which is deuterated at the α-position of the carbonyl group (93% D). The *syn* selectivity was slightly decreased due to the deuterium isotope effect: Slower D-trap caused isomerization of organocopper intermediates (vide infra). This experimental result indicates that *t*-BuOH acts as a proton source.

A possible mechanism for the present copper catalysis is proposed in Figure 1. An alkoxycopper complex (**A**) is initially formed by the reaction of CuOAc, *t*-BuOK and P(OPh)$_3$. Boron-to-cupper transmetalation between **A** and the alkylborane **2** occurs to form an alkylcopper(I) species (**B**) and a *t*-butoxyborane (9-BBN-O*t*-Bu) [12-15,20-25]. Subsequently, the alkylcopper species **B** forms a π-complex (**C**) with alkynoate **3**. Then, *syn*-carbocupration across the C–C triple bond of **C** with the assistance of Lewis acidic activation with



Scheme 2: Synthesis of five membered carbocycle.



Scheme 3: Deuterium-labeling experiment.

the *tert*-butoxyborane gave an alkenylcopper intermediate (**D**). Finally, protonolysis by *t*-BuOH produces *syn*-**4**, regenerating the alkoxycopper complex **A**.

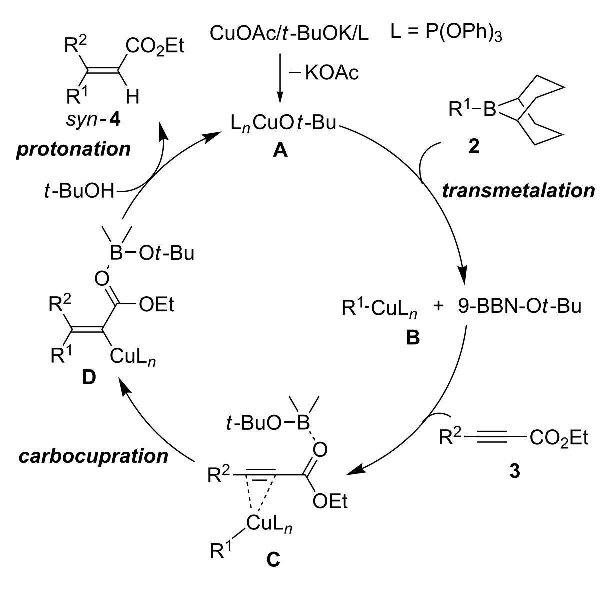


Figure 1: Possible mechanism.

The minor occurrence of *anti*-addition is likely due to the geometrical isomerization of the alkenylcopper species (**D**/**D'**) through a copper(I) allenoate complex (**E**, Figure 2) [15,26]. The resulting allenoate **E** can undergo protonolysis to form either *syn*-**4** or *anti*-**4** depending on the substituent effects of R^1 and R^2, while the isomerized alkenylcopper(I) **D'** should preferentially yield *anti*-**4**. The reduction of *syn* selectivity in the reaction with PPh$_3$, PCy$_3$ and DPPE may also be due to this isomerization (Table 1, entries 2–4).

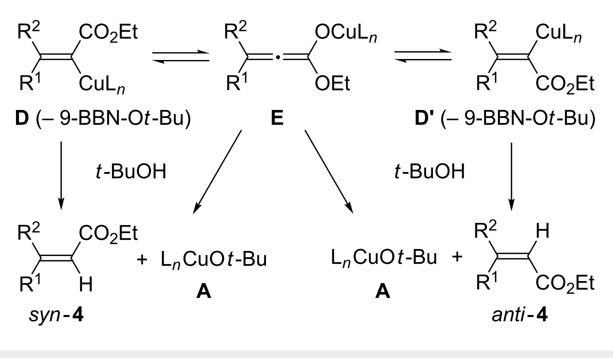


Figure 2: Isomerization of the alkenylcopper intermediates.

Conclusion

In summary, a copper-catalyzed conjugate addition of alkylboranes (alkyl-9-BBN) to alkynoates to form β-disubstituted acrylates is reported. The addition occurred in a formal *syn*-hydroalkylation mode. The stereoselectivity was excellent regardless of the substrate structure. The availability of alkylboranes through in situ alkene hydroboration is an attractive feature of this protocol and various functional groups are tolerated in both the alkylborane and alkynoate substrates.

Experimental

The reaction shown in Scheme 1 was conducted in a similar manner as described before [15]. Styrene (**1a**, 33 μL, 0.289 mmol) and (9-BBN-H)$_2$ (33.6 mg, 0.138 mmol) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon®-coated silicon rubber septum, and the vial was evacuated and filled with argon. 1,4-Dioxane (0.4 mL) was added to the vial, and the mixture was stirred at 60 °C for 1 h to prepare an alkylborane **2a**. Meanwhile, CuOAc (1.5 mg, 0.0125 mmol), P(OPh)$_3$ (6.9 μL, 0.025 mmol) and *t*-BuOK (1.4 mg, 0.0125 mmol) were placed in another vial. The vial was sealed with a Teflon®-coated silicon rubber septum, evacuated, and then filled with argon. After 1,4-dioxane (0.6 mL) was added to the vial, the mixture was stirred at 25 °C for 1 h. Next, the alkylborane solution was transferred to the vial containing the Cu(I) complex, followed by the addition of alkynoate **3a** (41.3 μL, 0.25 mmol) and *t*-BuOH (24 μL, 0.25 mmol). After 12 h stirring at 40 °C, diethyl ether was added to the mixture. The mixture was filtered through a short plug of silica gel, which was then washed with diethyl ether. After the solvent was removed under reduced pressure, flash chromatography on silica gel (0–5% EtOAc/hexane) provided **4aa** (69.4 mg, 0.248 mmol) in 99% yield with >99:1 *syn*/*anti* selectivity.

Supporting Information

Supporting Information File 1

Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra for newly synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-265-S1.pdf]

Acknowledgements

This work was supported by Grants-in-Aid for Scientic Research (B) (No. 15H03803), JSPS to H.O. and by ACT-C, JST to M.S. and by CREST, JST to M.S. K.N. thanks JSPS for scholarship support.

References

1. Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969,** *91,* 1851–1852. doi:10.1021/ja01035a045
2. Siddall, J. B.; Biskup, M.; Fried, J. H. *J. Am. Chem. Soc.* **1969,** *91,* 1853–1854. doi:10.1021/ja01035a046

3. Klein, J.; Turkel, R. M. *J. Am. Chem. Soc.* **1969,** *91,* 6186–6187. doi:10.1021/ja01050a047
4. Li, G.; Wei, H.-X.; Whittlesey, B. R.; Batrice, N. N. *J. Org. Chem.* **1999,** *64,* 1061–1064. doi:10.1021/jo981976l
5. Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989,** *30,* 4799–4802. doi:10.1016/S0040-4039(01)80511-6
6. Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Org. Chem.* **1979,** *44,* 1744–1746. doi:10.1021/jo01324a047
7. Mueller, A. J.; Jennings, M. P. *Org. Lett.* **2007,** *9,* 5327–5329. doi:10.1021/ol702546w
8. Jennings, M. P.; Sawant, K. B. *Eur. J. Org. Chem.* **2004,** 3201–3204. doi:10.1002/ejoc.200400314
9. Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Commun.* **2008,** 2010–2012. doi:10.1039/b802231c
10. Yamamoto, Y.; Yamada, S.; Nishiyama, H. *Chem. – Eur. J.* **2012,** *18,* 3153–3156. doi:10.1002/chem.201103697
11. Rajagopal, T.; Ogilvie, W. W. *Synlett* **2011,** 1113–1116. doi:10.1055/s-0030-1259933
12. Ohmiya, H.; Yoshida, M.; Sawamura, M. *Org. Lett.* **2011,** *13,* 482–485. doi:10.1021/ol102819k
13. Yoshida, M.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012,** *134,* 11896–11899. doi:10.1021/ja304481a
14. Ohmiya, H.; Shido, Y.; Yoshida, M.; Sawamura, M. *Chem. Lett.* **2011,** *40,* 928–930. doi:10.1246/cl.2011.928
15. Wakamatsu, T.; Nagao, K.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2013,** *52,* 11620–11623. doi:10.1002/anie.201305973
16. Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001,** *123,* 9918–9919. doi:10.1021/ja0165234
17. Oh, C. H.; Jung, H. H.; Kim, K. S.; Kim, N. *Angew. Chem., Int. Ed.* **2003,** *42,* 805–808. doi:10.1002/anie.200390214
18. Lin, P.-S.; Jeganmohan, M.; Cheng, C.-H. *Chem. – Eur. J.* **2008,** *14,* 11296–11299. doi:10.1002/chem.200801858
19. Bush, A. G.; Jiang, J. L.; Payne, P. R.; Ogilvie, W. W. *Tetrahedron* **2009,** *65,* 8502–8506. doi:10.1016/j.tet.2009.08.029
20. Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010,** *132,* 2895–2897. doi:10.1021/ja9109105
21. Nagao, K.; Ohmiya, H.; Sawamura, M. *Synthesis* **2012,** *44,* 1535–1541. doi:10.1055/s-0031-1290818
22. Nagao, K.; Yokobori, U.; Makida, Y.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012,** *134,* 8982–8987. doi:10.1021/ja302520h
23. Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *Org. Lett.* **2011,** *13,* 6312–6315. doi:10.1021/ol202866h
24. Shido, Y.; Yoshida, M.; Tanabe, M.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012,** *134,* 18573–18576. doi:10.1021/ja3093955
25. Hojoh, K.; Shido, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2014,** *53,* 4954–4958. doi:10.1002/anie.201402386
26. Nilsson, K.; Andersson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem. – Eur. J.* **1998,** *4,* 2051–2058. doi:10.1002/(SICI)1521-3765(19981002)4:10<2051::AID-CHEM2051>3.0.CO;2-F

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doi:10.3762/bjoc.11.265

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Synthesis of bi- and bis-1,2,3-triazoles by copper-catalyzed Huisgen cycloaddition: A family of valuable products by click chemistry

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Review

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Keywords:
bistriazoles; click chemistry; cycloaddition; homogeneous catalysis; oxidative coupling

Beilstein J. Org. Chem. **2015,** *11,* 2557–2576.
doi:10.3762/bjoc.11.276

Received: 31 August 2015
Accepted: 20 November 2015
Published: 11 December 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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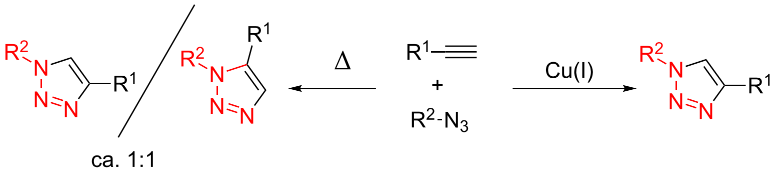
Abstract

The Cu(I)-catalyzed azide-alkyne cycloaddition reaction, also known as click chemistry, has become a useful tool for the facile formation of 1,2,3-triazoles. Specifically, the utility of this reaction has been demonstrated by the synthesis of structurally diverse bi- and bis-1,2,3-triazoles. The present review focuses on the synthesis of such bi- and bistriazoles and the importance of using copper-promoted click chemistry (CuAAC) for such transformations. In addition, the application of bitriazoles and the related CuAAC reaction in different fields, including medicinal chemistry, coordination chemistry, biochemistry, and supramolecular chemistry, have been highlighted.

Introduction

Since its discovery by Huigsen and co-workers fifty years ago [1-4], the Huisgen cycloaddition of azides to alkynes has gained much attention due to its potential to yield a wide variety of triazoles with structurally diverse and functionalized groups, especially with respect to biological activity [5-8]. Originally, this transformation was typically carried out at high temperature and resulted in a mixture of the 1,4 and 1,5 regioisomers (Scheme 1). Fortunately, representing a milestone in this field, the application of Cu(I) as the catalyst was reported by Sharpless and Meldal in 2002 [9,10]. In this work, the Huisgen reaction worked well under mild conditions, giving the desired triazoles with high yield, good regioselectivity, and quite high functional-group tolerances (Scheme 1). Since then, the so-called field of “click chemistry” has been extensively



Scheme 1: The synthesis of triazoles through the Huisgen cycloaddition of azides to alkynes.

investigated and recognized as an epoch-making progress in organic synthesis and green chemistry [11-15].

After many years of research, it was proven that the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC reaction) could be performed under various conditions according to the need of click chemistry using the catalysis of various copper salts that generate Cu(I) sources in situ [16]. As a brief summary, the copper(I)-promoted click chemistry has the following features: (1) The most preferred methods for the formation of Cu(I) involve the use of $CuSO_4$ and a reducing agent in an aqueous solution. Most commonly, a large excess of sodium ascorbate with respect to the copper catalyst is the favored reducing agent, and a water/alcohol mixture is the favored solvent. This catalyst system combines the advantage of not requiring inert gas to prevent the Cu(I) from oxidation to Cu(II) during the reaction, and not requiring the tedious work-up and purification steps. (2) Other frequently used Cu(I) sources are CuI or CuBr. In general, CuI has been used in organic solvents such as CH_3CN, THF or toluene, and the active Cu(I) species was further stabilized by the addition of excess base. In addition, many other Cu(I) salts are used in CuAAC reactions owing to improved solubility or increased rate as compared to the $CuSO_4$/sodium ascorbate or CuI catalytic system. (3) The third type of Cu(I) source is generated by the oxidation of Cu metal. The Cu(0) species (found in forms such as turnings, wire, powder or nanoparticles) in the presence or absence of Cu(II) in aqueous media also provides the key active Cu(I) in some CuAAC reactions.

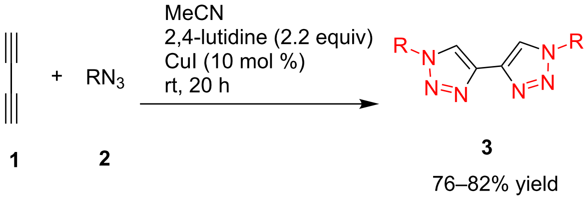
As an important supplement to the classic Huisgen cycloaddition promoted by copper catalysis, this review will deal with the copper-catalyzed syntheses of bi- and bistriazoles or their analogues by click chemistry, such as those linked directly or by spacers. The synthetic approaches for the preparation of bi- and bistriazoles are discussed in detail and their application is discussed briefly in each section. Accordingly, the following three types of bi- and bistriazoles will be primarily presented: (1) The 4,4'-linked symmetric or unsymmetrical bitriazoles. (2) The 5,5'-linked symmetric bitriazoles. (3) The bistriazoles formed through spacers from the dialkyne or diazide substrates.

Review

The synthesis of 4,4'-bitriazoles

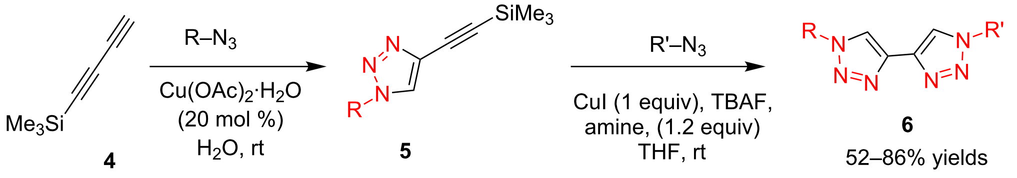
The 4,4'-bitriazoles can be realized from a double CuAAC reaction between various sources of 1,3-butadiynes with the substituted azides. In general, two different methods have been developed for the construction of the 4,4'-bitriazoles: (1) The one-pot double CuAAC reaction of 1,3-butadiyne with azides. (2) Two successive CuAAC reactions with different or same azides that require the deprotection of the second reactive site to liberate another alkyne moiety.

In 2007, Monkowius et al. reported that the 4,4'-bitriazoles **3** could be synthesized by the two-fold click reaction between 1,3-butadiyne and substituted organic azides [17], and the reaction was catalyzed by a catalytic amount of CuI in acetonitrile in the presence of 2,4-lutidine. The desired, symmetrical 4,4'-bitriazoles **3** were obtained in good yield (76–82%, Scheme 2). However, the substrate 1,3-butadiyne (**1**) is difficult to handle because of its high reactivity and instability.



Scheme 2: The synthesis of symmetrically substituted 4,4'-bitriazoles.

Later in 2009, Fiandanese et al. proposed that unsymmetrically substituted 4,4'-bi-1,2,3-triazoles can be prepared in an easy manner [18]: starting from 1-trimethylsilyl-1,3-butadiyne (**4**) the 4-(silylalkynyl)-1,2,3-triazoles **5** can be obtained after reaction with substituted azides catalyzed by $Cu(OAc)_2{\cdot}H_2O$ (0.2 equiv). After the in situ deprotection with TBAF, followed by the CuI-catalyzed click reaction with another azide in THF in the presence of 1.2 equiv of 1,1,4,7,7-pentamethyldiethylenetriamine, the unsymmetrically 4,4'-bitriazoles **6** are obtained in good yield (52–86%, Scheme 3).



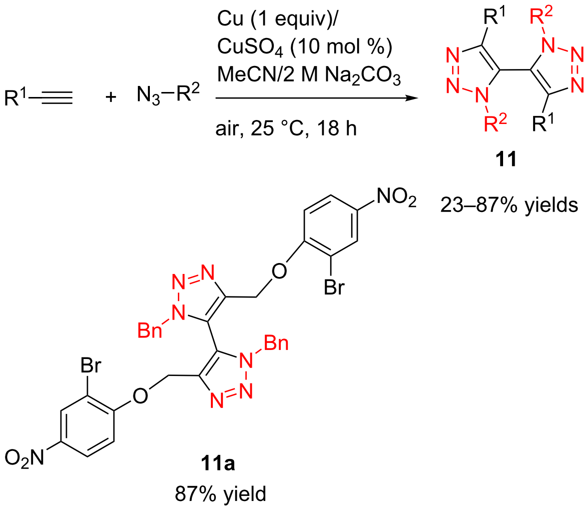
Scheme 3: The synthesis of unsymmetrically substituted 4,4'-bitriazoles.

Simpson et al. also developed this three-step procedure (CuAAC–deprotection–CuAAC) into a one-pot fashion with moderate overall yield (34–49%) [19]. Similar to Fiandanese's strategy, Aizpurua et al. developed another synthetic method [20]: Starting with the CuAAC reaction of propargyl alcohol (**7**) with different azides, followed by the sequential Swern oxidation and Ohira–Bestmann homologation provided the ethynyltriazole intermediate **9**, finally another CuAAC resulted in the formation of unsymmetrical 4,4'-bi(1,2,3-triazole)s **10** (Scheme 4).

The synthesis of 5,5'-bitriazoles

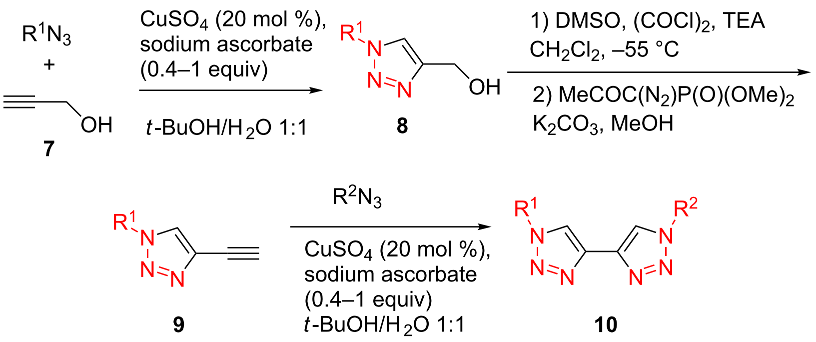
Originally, in the research of the CuAAC reaction, the 5,5'-bitriazoles were usually considered as an undesired side product or impurity in the Huisgen cycloaddition. In general, they are the oxidative coupling product of the triazole-copper species. The 5,5'-bitriazoles were usually formed as the major product by the facilitation of the reaction conditions or controlled by the starting substrate.

In 2007, Burgess and Angell successfully developed an oxidative coupling method for the preparation of 5,5'-bitriazole [21]. In this work, they were able to perform this reaction of azides and terminal alkynes with moderate to high yield by using a 1:1 mixture of MeCN/2 M aqueous Na_2CO_3 solution at 25 °C for 18 h in the presence of a catalytic amount of $CuSO_4$ (10 mol %) and one equivalent of Cu powder (Scheme 5). Obviously, this method suffered from the drawback that a stoichiometric amount of Cu powder is required to achieve the highest activity.



Scheme 5: The synthesis of 5,5'-bitriazoles.

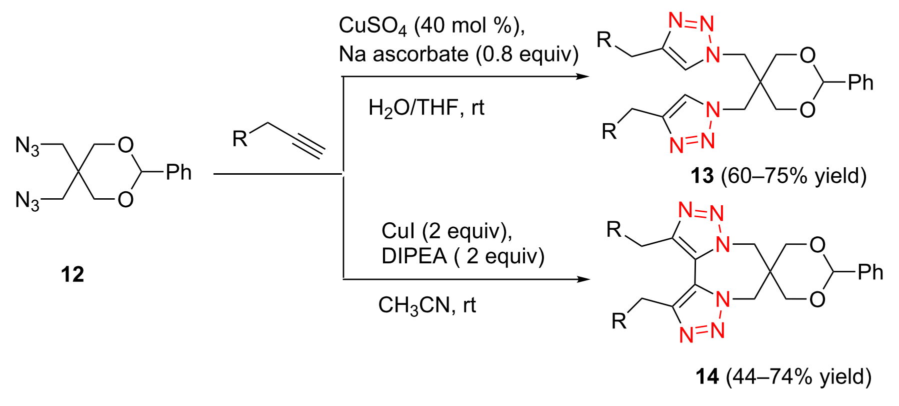
In 2010, Nandurdikar et al. linked the two (or four) molecules of NO donor prodrugs together through the triazole spacers [22], which has potential application as NO-releasing materials. They first prepared the benzylidene-protected 2,2-di(azidomethyl)propane-1,3-diol containing the conformational strain.



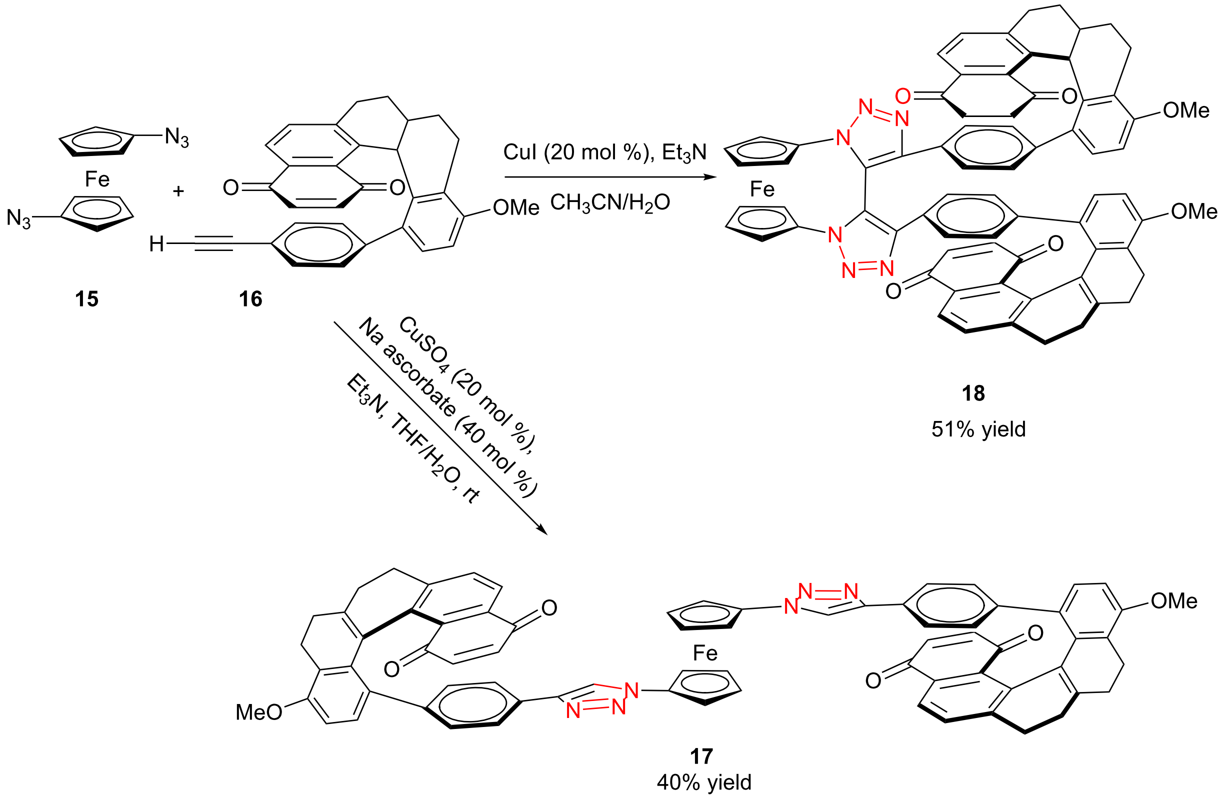
Scheme 4: The stepwise preparation of unsymmetrical 4,4'-bitriazoles.

They also investigated the click reactions with various alkynes under different conditions (Scheme 6), and found that: (1) when catalyzed with $CuSO_4$/Na ascorbate in THF/H_2O, the reaction provided the normal bistriazoles **13** with moderate to good yield (60–75%). (2) By using CuI and DIPEA in acetonitrile to perform the reaction, the sequential, CuAAC oxidative coupling gave the cyclic 5,5’-bitriazoles **14** as the major product (44–74%). They demonstrated that both the reaction conditions and the conformational effect are beneficial for the formation of the 5,5'-bitriazoles.

Similarly, Urbano and co-workers performed the CuAAC reaction of 1,1’-diazidoferrocene with ethynyl [5]-helicenequinone [23], and found the open chain bistriazolylphenylhelicenequinone **17** could be obtained in good yield when $CuSO_4$/sodium ascorbate was used in THF/H_2O (Scheme 7).



Scheme 6: The synthesis of bistriazoles and cyclic 5,5'-bitriazoles under different catalytic systems.



Scheme 7: The double CuAAC reaction between helicenequinone and 1,1'-diazidoferrocene.

However, the cyclic 5,5'-bitriazole **18** was achieved as the major product when CuI/Et_3N was used in CH_3CN.

In 2011, Cuevas-Yañez and co-workers demonstrated that temperature was the key factor for the formation of 5,5'-bitriazole [24]. In that work, it was found that the desired bitriazoles could be obtained in low to moderate yield when the CuAAC reaction was performed at low temperature (−35 °C) and high NaOH concentration. Subsequently, Jeon and co-workers reported a synthetic method for the construction of 5,5'-bitriazoles by using CuI together with 2 equiv of DIPEA [25]. The authors further demonstrated that the use of a base was also an important factor for the appropriate bitriazole yield. However, Jeon's method worked well only when the alkynes contained propargylic ethers and acetylenic amides (Scheme 8). Generally speaking, most of the above-mentioned oxidative coupling-click dimerizations merely provided the desired 5,5'-bitriazole in low yield when the alkynes or azides were linked directly with a hindered group or an aromatic moiety.

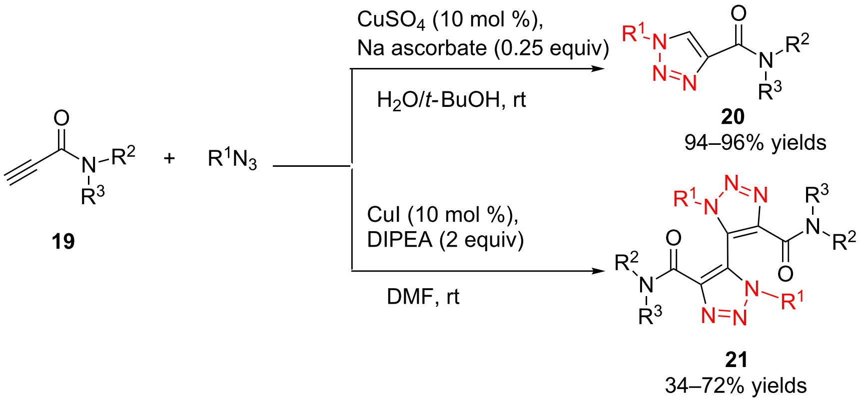
In 2012, Xu and co-workers disclosed that both the secondary and primary amine-functionalized polysiloxanes were good ligands for the copper-catalyzed Huisgen reaction of organic azides and alkynes [26]. This applied especially when the reaction was catalyzed by CuCl and mediated by the secondary amine-functionalized polysiloxanes at 0 °C in CH_2Cl_2, where the symmetrically 5,5'-coupled bitriazole was obtained as the major product (Scheme 9). All the alkynes directly linked with the aromatic moiety provided the desired bitriazoles in moderate to good yield. We believe that the key copper monotriazole intermediate formed after the first CuAAC reaction was stabilized by the secondary amine-functionalized polysiloxane, which further led to the formation of the bitriazole **22**. The chiral D-glucopyranosyl azide and phenylacetylene reacted under CuI and the secondary amine-functionalized polysiloxane catalytic system, where the desired chiral bitriazole **23** was obtained with good diastereoselectivity (85:15). Subsequently, the authors used this method to construct the novel, cyclic 5,5'-bitriazole **24** from binaphthol [27] (Scheme 10). Notably, this type of compound showed high selectivity over the recognition of I^-, possibly due to the formation of a charge-transfer complex between the I^- and the electron-deficient triazole ring.

Bistriazoles formed through spacers

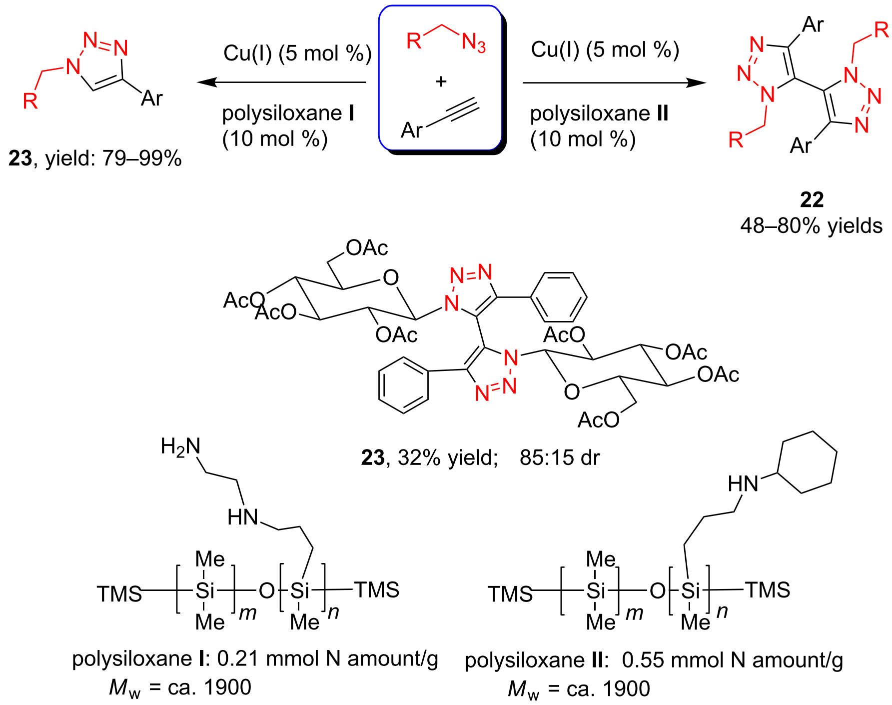
Bistriazole synthesis with dialkyne spacers

In the past years, bistriazoles with dialkyne spacers have gained significant attention for their potential application in supramolecular chemistry, pharmaceutical chemistry, biological chemistry and organometallic chemistry. The construction of bistriazoles from dialkynes is now well-developed, and three main methods are reported: (1) the one-pot CuAAC reactions of the terminal dialkynes with two equiv of the organic azides, providing the corresponding bistriazoles, which is the most popular method for the synthesis of bistriazoles with dialkyne spacers. (2) The second protocol is the sequential CuAAC–deprotection–CuAAC reaction for the construction of the bistriazoles. In general, the trialkylsilyl group was used as a temporary masking group for one of two alkyne moieties. Thus, this method provides the possibility of one molecule bearing two alkynes reacted with two different organic azides. (3) The third method involves the utilization of the substrate bearing two alkyne moieties with different reactivity in the successive Huisgen cycloaddition reactions: Huigsen reaction of the activated alkyne with the first azide and the CuAAC reaction of the nonactivated alkyne with another azide, leading to the corresponding bistriazoles.

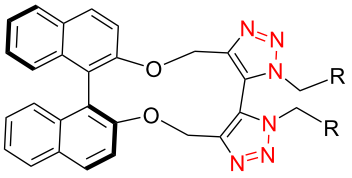
In 2006, Aucagne and Leigh reported the synthesis of the TMS-alkyne and terminal-alkyne bis-functionalized tripeptide [28].



Scheme 8: The synthesis of 1,2,3-triazoles and 5,5'-bitriazoles from acetylenic amide.



Scheme 9: The amine-functionalized polysiloxane-mediated divergent synthesis of trizaoles and bitriazoles.



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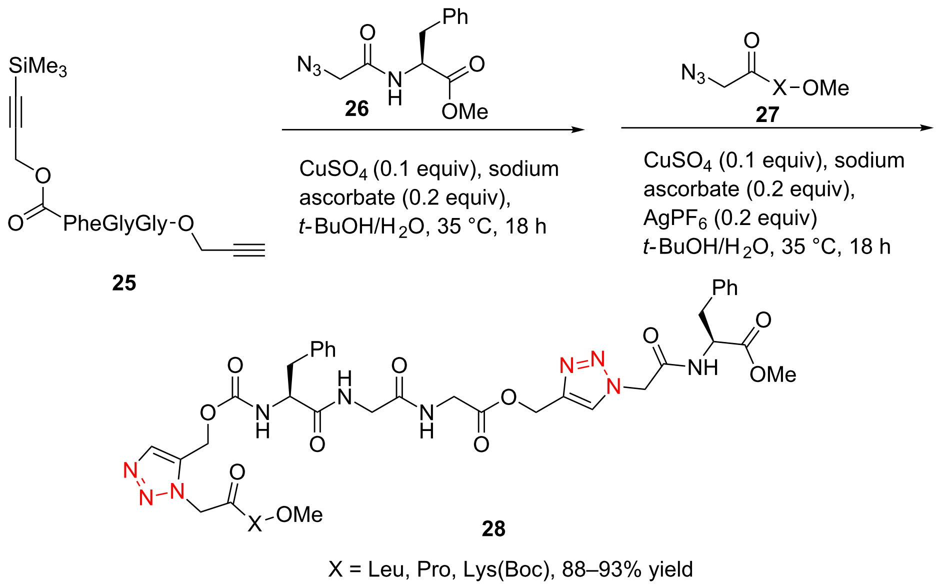
Scheme 10: The cyclic BINOL-based 5,5’-bitriazoles.

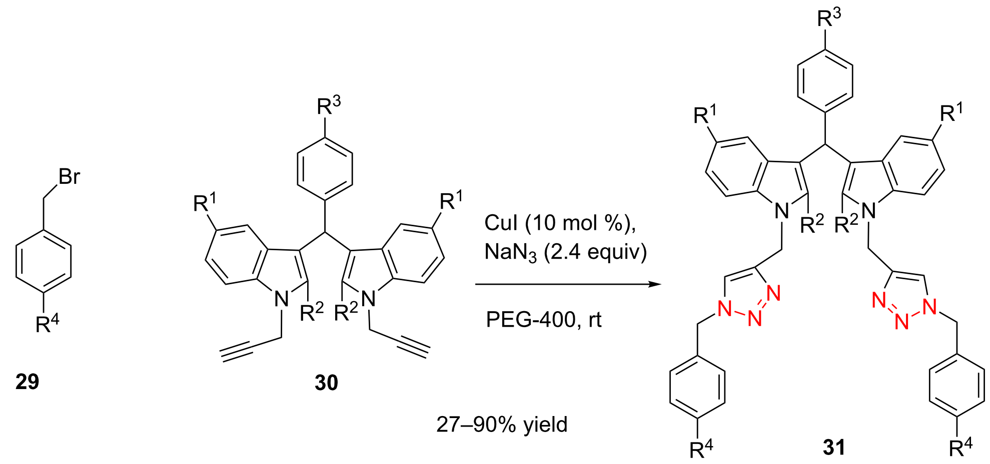
Here they used the CuAAC reaction of the terminal-alkyne-containing tripeptide **25** with the azide-containing dipeptide **26** in *t*-BuOH/H_2O, catalyzed by $CuSO_4$/sodium ascorbate, providing the first triazole-bearing intermediate (Scheme 11). They then performed the Ag(I)-catalyzed deprotection of the TMS-protected alkyne moiety, followed by another CuAAC reaction of the unmasked terminal alkyne with the second azide, giving the desired bistriazole-linked pseudononapeptides **28** in good yield (88–93%) .

In 2009, Perumal and co-workers developed a one-pot methodology [29] for the multicomponent cycloaddition of sodium azide, benzyl bromides and various *N*-propargylated bis(indolyl)arylmethanes **30** catalyzed by CuI. It was proved that this multicomponent CuAAC reaction proceeded well in PEG-400 among various solvents, mainly due to the hydrophilic and hydrophobic character of the PEG-400. As shown in Scheme 12, the CuAAC gave the desired bistriazoles **31** in good to excellent yield when electron-withdrawing groups were present in the benzyl bromides. Notably, the authors determined that all the compounds obtained showed potential biological activity.

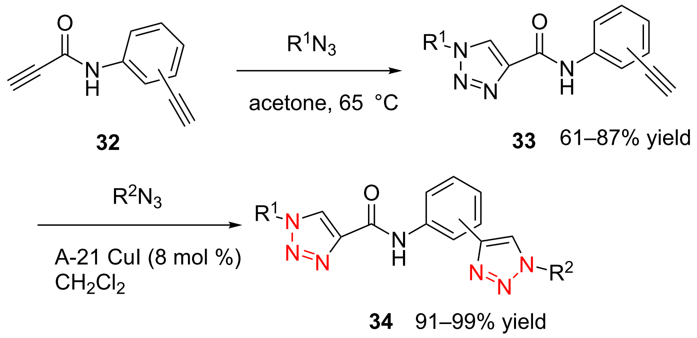
Later, in 2011, Girard et al. demonstrated that the dialkynes with functional groups could react smoothly with various organic azides without the protection–deprotection step [30]. Initially, they first chose *N*-propargylpropiolamide **32** as the substrate and found the alkyne group with neighboring electron-withdrawing amide carbonyl was reacting exclusively with the organic azide under catalyst-free reaction conditions (with or without a solvent at room temperature) to give the mono-triazole intermediate **33** in good yield. Then the nonactivated terminal alkyne reacts with another azide, catalyzed by an Amberlyst A-21/CuI system in CH_2Cl_2 to form the second triazole ring with high yield (Scheme 13). In this work, the authors further extended this method to the propiolamide, which was derived from *meta*- and *para*-ethynylaniline, where both of the substrates worked well and the desired bistriazoles **34** could be obtained by a simple trituration and filtration procedure in good yield.



Scheme 11: The one-pot click–click reactions for the synthesis of bistriazoles.



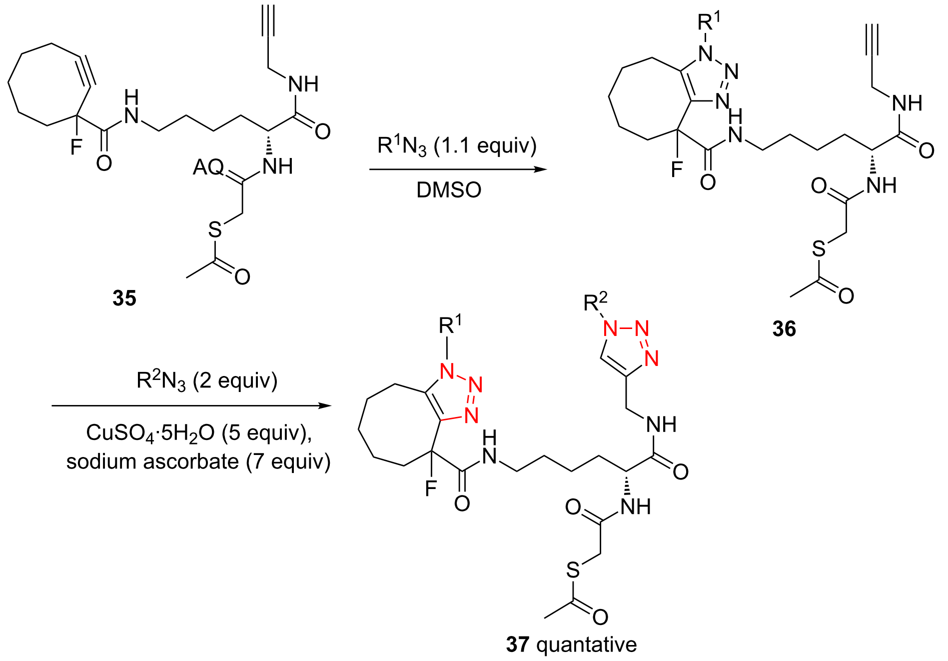
Scheme 12: The synthesis of bis(indolyl)methane-derivatized 1,2,3-bistriazoles.



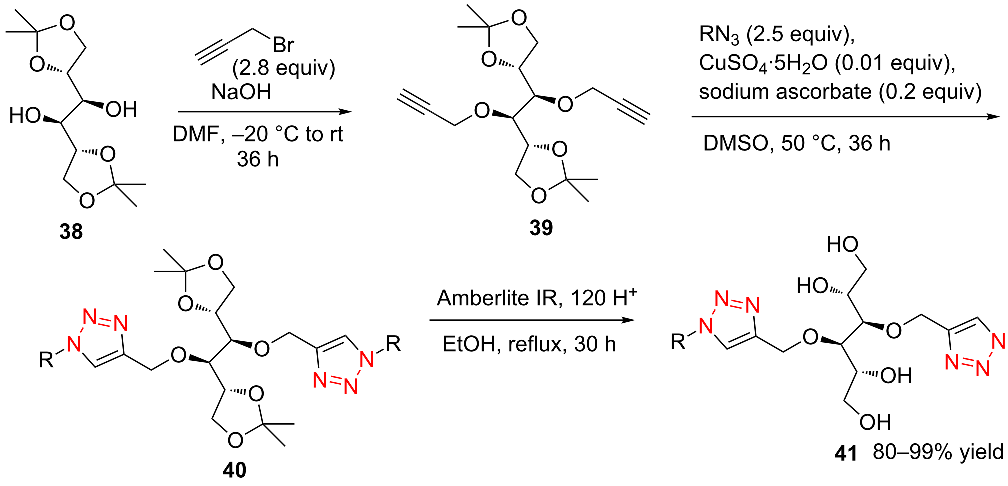
Scheme 13: The sequential, chemoselective preparation of bistriazoles.

The strain-promoted azide-alkyne cycloaddition (SPAAC) reaction could be well-performed without a Cu(I) catalyst. Such reactions are ideal for bioconjugation where no additional metal is required [31]. In 2012, Beal and co-workers incorporated the terminal alkyne and the activated cyclooctyne with two amide formation reactions [32], and then the SPAAC reaction was performed between the cyclooctyne **35** and the azides under mild conditions without the Cu(I). Notably, the CuAAC reaction between the terminal alkyne of **36** and various azides provided the desired bistriazoles **37** in good yield (Scheme 14).

Bistriazoles have potential application in the synthesis of surfactants after introducing the carbohydrate moiety. In 2012, Mohammed and co-workers selected the commercially available D-mannitol **38** as the starting material [33] in this reaction. After protection and introduction of the two alkyne groups to give dialkyne **39**, the copper-catalyzed cycloaddition occurred smoothly with the different long chain alkyl azides under the optimized reaction conditions. This provided the desired bistriazoles **40** in good yield (Scheme 15). It should be noted that the deprotection of bistriazoles **40** gives the gemini surfactants **41**



Scheme 14: The sequential SPAAC and CuAAC reaction for the preparation of bistriazoles.

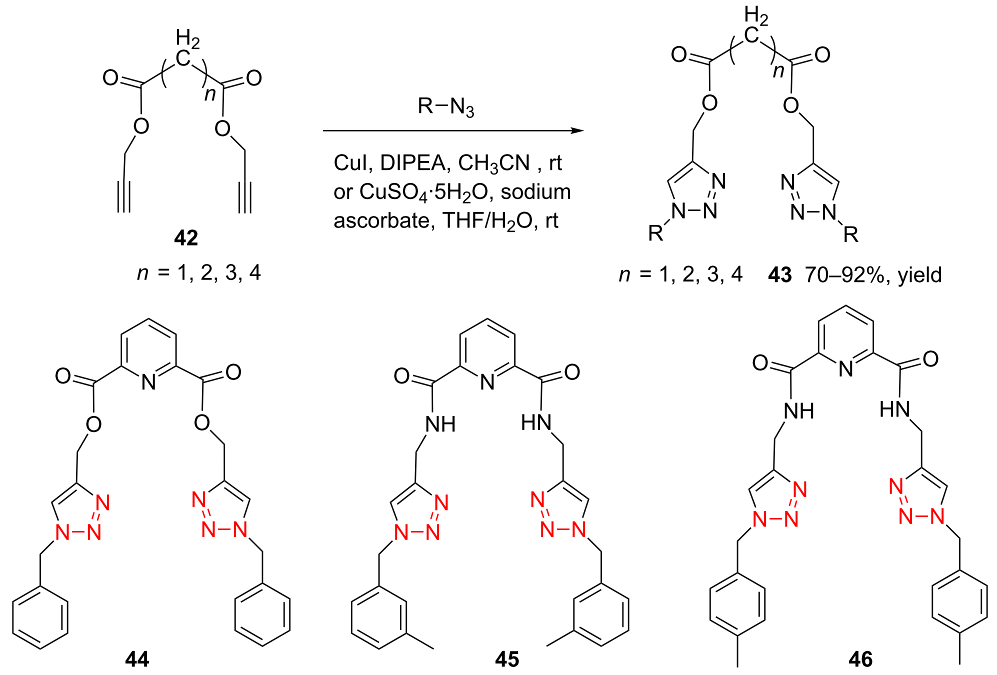


Scheme 15: The synthesis of D-mannitol-based bistriazoles.

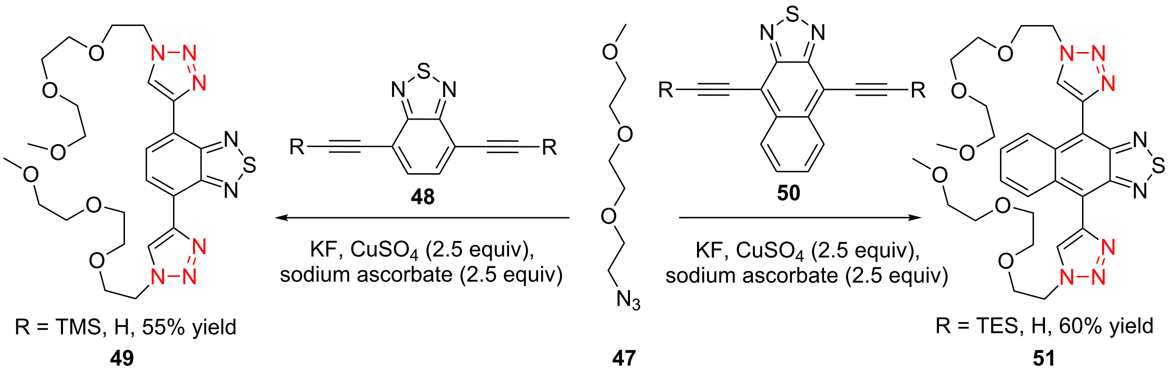
(with two hydrophobic arms and two hydrophilic heads) in high yield.

In 2012, Kaushik and co-workers prepared a series of ester-linked dialkynes from the acid dichloride and propargyl alcohol in the presence of DMAP [34]. Here, the CuAAC reaction between the dialkynes **42** and the azides provided the desired bistriazoles **43** in good yield (70–92%, Scheme 16). Interestingly, the antimicrobial activity studies revealed that compound **44** showed the highest activity against *B. subtilis* and *E. coli* due to the presence of a rigid pyridine nucleus. The authors further prepared various amide-linked bistriazoles by a three-component one-pot reaction of the amide-linked dialkynes, benzyl bromides and sodium azide catalyzed by $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in DMF [35,36]. All the obtained compounds were evaluated for in vitro cytotoxicity against a panel of five human cancer cell lines, where compounds **45** and **46** displayed the highest and broadest spectrum activity against all five cancer cell lines under study (Scheme 16).

The formation of triazole functional groups can work as a powerful auxochrome. In 2010, Bunz and co-workers used the TMS-protected diethynylbenzothiadiazoles **48** and **50** as the source of dialkynes. The CuAAC reaction was carried out with ethylene-glycol-functionalized azide **47** in the presence of $CuSO_4$ and sodium ascorbate, providing the benzo-thiadiazole-based bistriazole (**49** and **51**, Scheme 17) [37]. With the aid of the hydrophilic character of the ethylene glycol group, both of



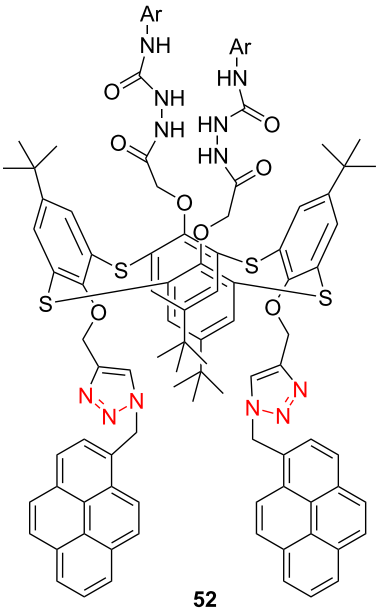
Scheme 16: The synthesis of ester-linked and amide-linked bistriazoles.



Scheme 17: The synthesis of acenothiadiazole-based bistriazoles.

the bistriazoles can be endowed with water solubility, and can effectively bind Cu(II) and Ni(II) in water.

The thiacalix[4]arenes are sulfur-bridged analogs of calix[4]arenes, which have potential application in the molecular recognition of cationic, anionic or neutral molecules. In this regard, Yamato et al. incorporated two urea moieties possessing various aryl groups and two pyrene-appended triazole rings at the opposite side of the thiacalix[4]arene cavity [38]. The authors found that receptor **52** (Scheme 18) could selectively bind Cl^- through hydrogen bonding interaction with the urea NH protons, and **52** can also bind with Ag^+ through complexation with the pyrene-appended bistriazole.



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Scheme 18: The pyrene-appended thiacalix[4]arene-based bistriazole.

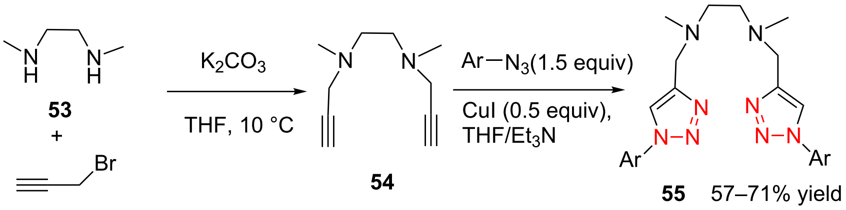
In homogeneous catalysis, functional ligands often play a key role in transition metal catalysis. Accordingly, the bistriazole derivatives could provide promising alternatives to bipyridine ligands because of their powerful nitrogen-centered coordination. In this context, Hao and co-workers have reported bistriazole-based N4 tetradentate ligands that were prepared by two CuAAC reactions in a one-pot procedure [39]. As shown in Scheme 19, these ligands exhibited good coordination properties to various metals, and the corresponding Mn(II) complexes showed good catalytic activity for the epoxidation of various aliphatic terminal olefins.

Very recently, Ulven and co-workers reported the synthesis of triazole-linked phenanthroline ligands. They were obtained by the following steps: (1) 1,10-phenanthroline-2,9-dicarbaldehyde (**56**) was treated with the Ohira–Bestmann reagent to provide the corresponding dialkyne **57**; (2) Dialkyne **57** was reacted with different azides catalyzed by the Cu(II)–TBTA complex and sodium ascorbate in a bi-phasic system of CH_2Cl_2/H_2O as the solvent, giving the desired bistriazoles **59** in good yield; (3) Deprotection of the N-Boc group with TFA, and the obtained primary amines was transformed to the corresponding primary guanidine or diisopropylguanidine analogs (**60** and **61**, Scheme 20) [40], which could be used as potential G4 DNA ligands with high selectivity over duplexed DNA.

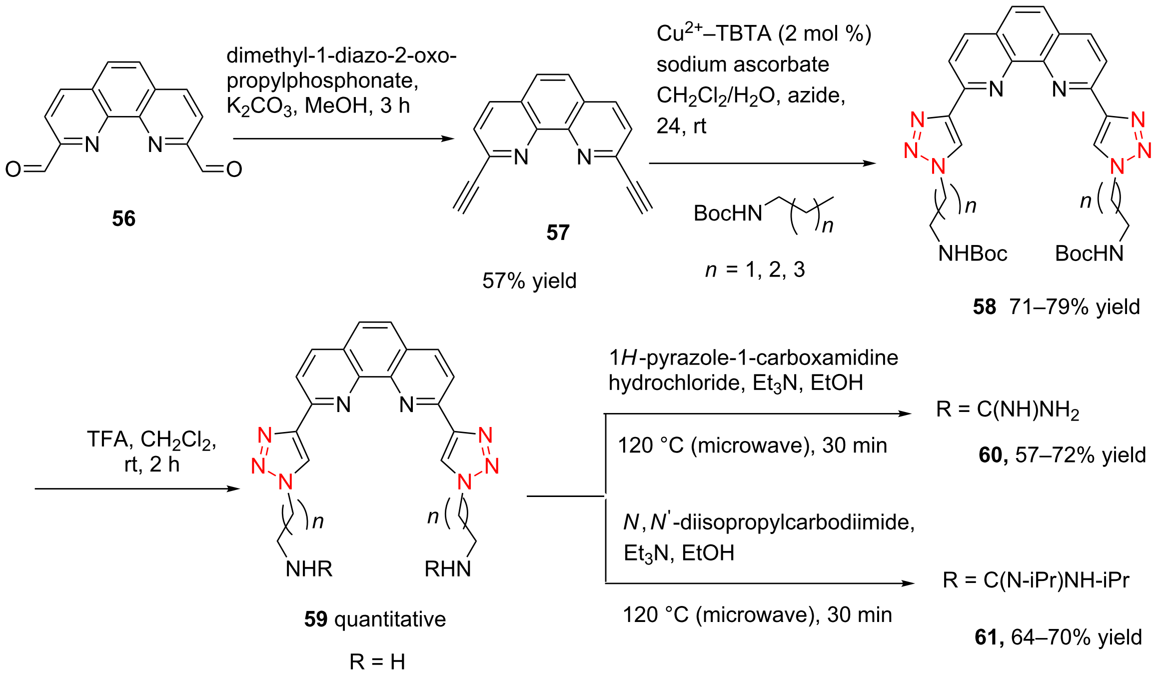
Similar to the above strategies or methods, a number of researchers have developed various dialkyne substrates with varied spacers. As shown in Table 1, the reaction conditions are summarized for comparison, including the catalysts, the solvents, and the application of the bistriazoles.

Bistriazole synthesis with diazide spacers

The spacer-linked bistriazoles could also be prepared by the CuAAC reaction of the in situ generated diazides with substitued alkynes. There are mainly two types of methods for the construction of bistriazoles from diazides: (1) Starting from the substrate-containing good-leaving groups, the diazides could be generated in situ by nucleophilic addition with NaN_3, and then the double CuAAC reactions could give the desired bistriazoles. (2) Starting from a substrate containing one azide functionality and another suitable functional group, the CuAAC reaction was performed with a terminal alkyne to provide the monotriazole compound. Subsequently, the suitable functional group was transformed into the corresponding azide for the next CuAAC reaction to give the desired bistriazoles.



Scheme 19: The synthesis of triazole-based tetradentate ligands.



Scheme 20: The synthesis of phenanthroline-2,9-bistriazoles.

Table 1: Previous reports on the copper-catalyzed Huisgen cycloaddition to bistriazoles with spacers.

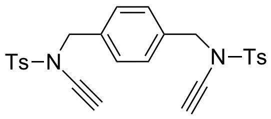
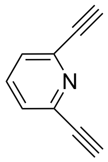
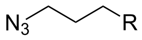
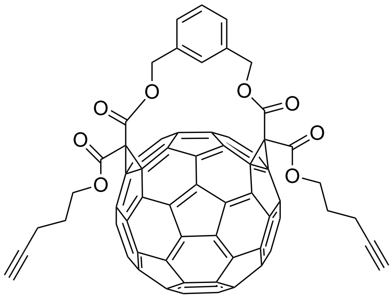
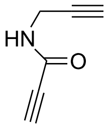
Cu source	Solvent	Spacer	Azide	Application
$CuSO_4\cdot5H_2O$, sodium ascorbate [41]	$DMSO/H_2O$		BnN_3	–
bioClick conditions [42]	–		 R = OH or Me	Complexation
$CuSO_4\cdot5H_2O$, sodium ascorbate [43]	CH_2Cl_2/H_2O		6 azidosugars	–
A-21-CuI [44]	CH_2Cl_2		$R–N_3$, R = Bn,CH_2CO_2Et, $(CH_2)_3OAc$, $(CH_2)_3OH$	–

Table 1: Previous reports on the copper-catalyzed Huisgen cycloaddition to bistriazoles with spacers. (continued)

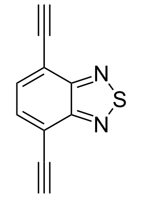
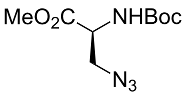
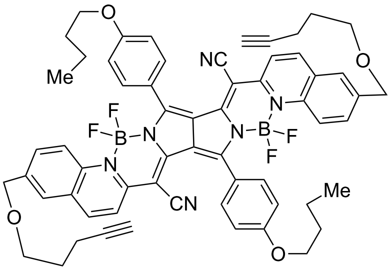
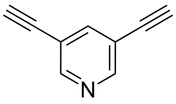
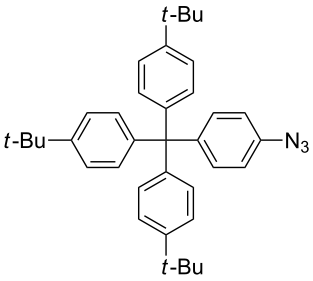
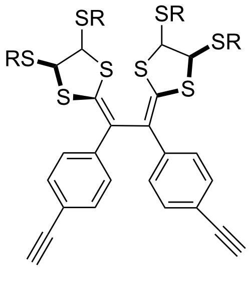
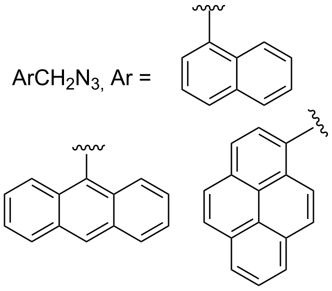
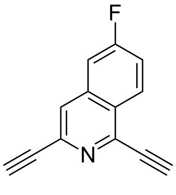
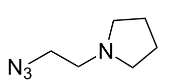
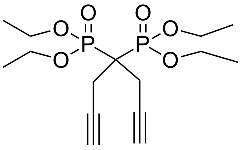
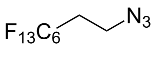
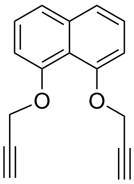
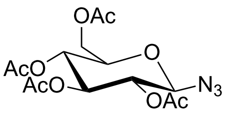
Cp*RuCl(COD) [45]	THF			Chemical sensors
$CuSO_4$, sodium ascorbate [46]	H_2O/*t*-BuOH		3 azides	Biological imaging
$[Cu(CH_3CN)_4]$ (PF_6) [47]	CH_2Cl_2			Anion recognition
CuI [48]	THF	 R = $C_{10}H_{21}$	$ArCH_2N_3$, Ar = 	Receptors for fullerenes
$CuSO_4·5H_2O$, sodium ascorbate [49]	H_2O/*t*-BuOH			Chemical sensors
$CuSO_4·5H_2O$, sodium ascorbate [50]	H_2O/*t*-BuOH		$PhCH_2N_3$, 	
$CuSO_4$, sodium ascorbate [51]	H_2O/*t*-BuOH			Chemical sensor

Table 1: Previous reports on the copper-catalyzed Huisgen cycloaddition to bistriazoles with spacers. (continued)

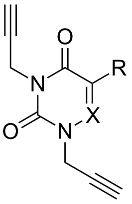
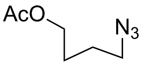
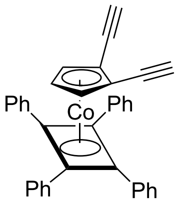
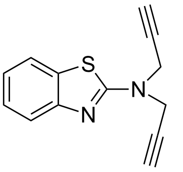
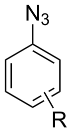
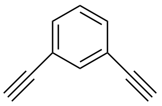
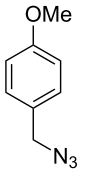
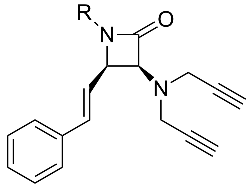
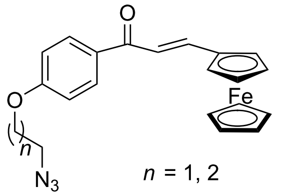
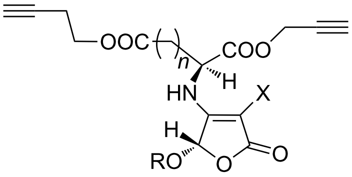
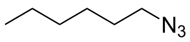
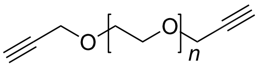
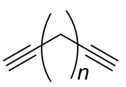
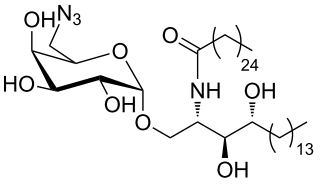
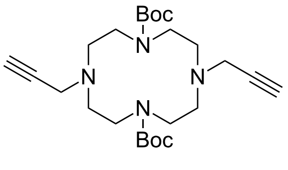
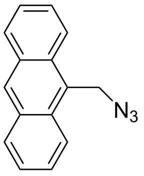
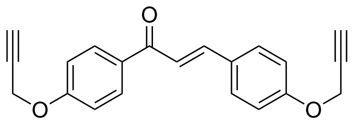
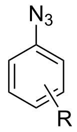
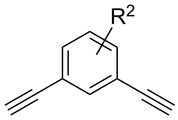
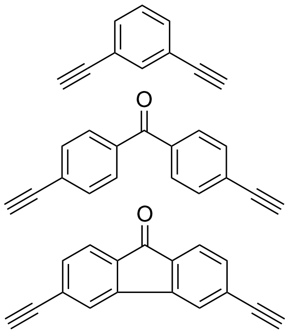
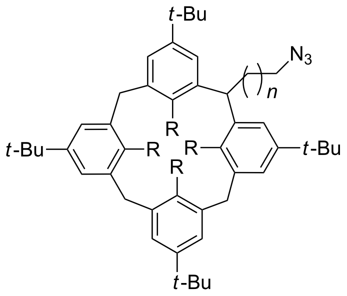
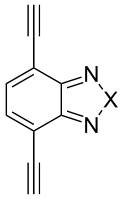
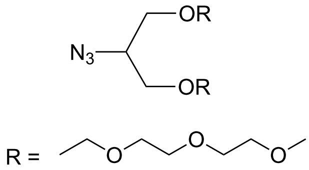
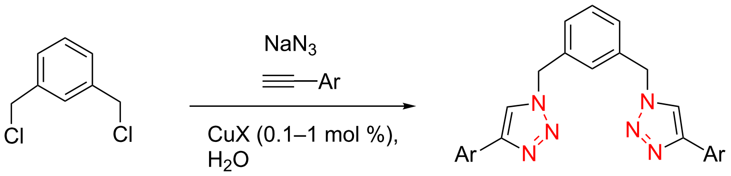
CuI [52]	–	 X = CH or N R = H or Me		Biological activity
$CuSO_4 \cdot 5H_2O$, sodium ascorbate [53]	CH_2Cl_2/H_2O		$PhCH_2N_3$	–
$CuSO_4 \cdot 5H_2O$, sodium ascorbate [54]	DMF/H_2O		 20 azides	Hemolitic activity
$CuSO_4 \cdot 5H_2O$, sodium ascorbate [55]	DMF/H_2O			Complexation
$CuSO_4 \cdot 5H_2O$, sodium ascorbate [56]	$EtOH/H_2O$		 *n* = 1, 2	Antitubercular activity
$CuSO_4 \cdot 5H_2O/Cu$ [57]	CH_3CN		$PhCH_2N_3$ 	–
$CuSO_4$, sodium ascorbate [58]	$H_2O/t\text{-}BuOH$	 *n* = 0, 2, 3, 5, 8  *n* = 4, 12, 18		Biological activity
CuI [59]	THF/H_2O			Chemical sensor

Table 1: Previous reports on the copper-catalyzed Huisgen cycloaddition to bistriazoles with spacers. (continued)

$CuSO_4·5H_2O$, sodium ascorbate [60]	H_2O/*t*-BuOH			Antioxidant, antifungal activity
$CuSO_4$, sodium ascorbate [61]	CH_2Cl_2/*t*-BuOH	 11 examples	R^1N_3	Anion bonding
CuI [62]	CH_3CN		 R = OMe, *n* = 1, 2, 4	Chemical sensors
$Cu(PPh_3)_3Br$ [63]	THF	 X = O, S, Se		Chemical sensors

In 2007, Wang and co-workers demonstrated that the one-pot three-component reaction of *ortho*- and *meta*-bis(chloromethyl)benzene (**62**), sodium azide, and terminal alkynes, catalyzed by CuX in water could provide the corresponding 1,4-disubstitued bistriazoles **63** in excellent yield [64] (Scheme 21). They found that the bistriazole could be formed during the Huisgen reaction, in which the reaction was efficiently promoted by the catalytic amount of the Cu(I) salts. For example, the three-component reaction could reach completion in the presence of only 0.2 mol % of Cu(I).

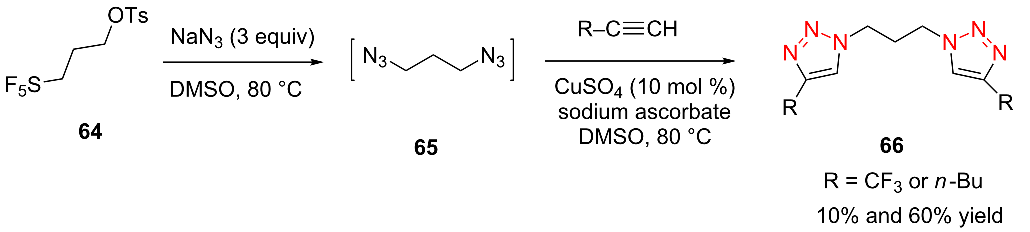
In 2010, Shreeve et al. reported that the diazides **65** could be generated in situ by the nucleophilic substitution of SF_5 and OTs groups wtih 3 equiv of NaN_3, followed by the CuAAC reaction with aliphatic alkynes, providing the desired bistriazoles **66** in moderate yield (Scheme 22) [65]. However, when



62

63 87–93% yield

Scheme 21: The three-component reaction for the synthesis of bistriazoles.

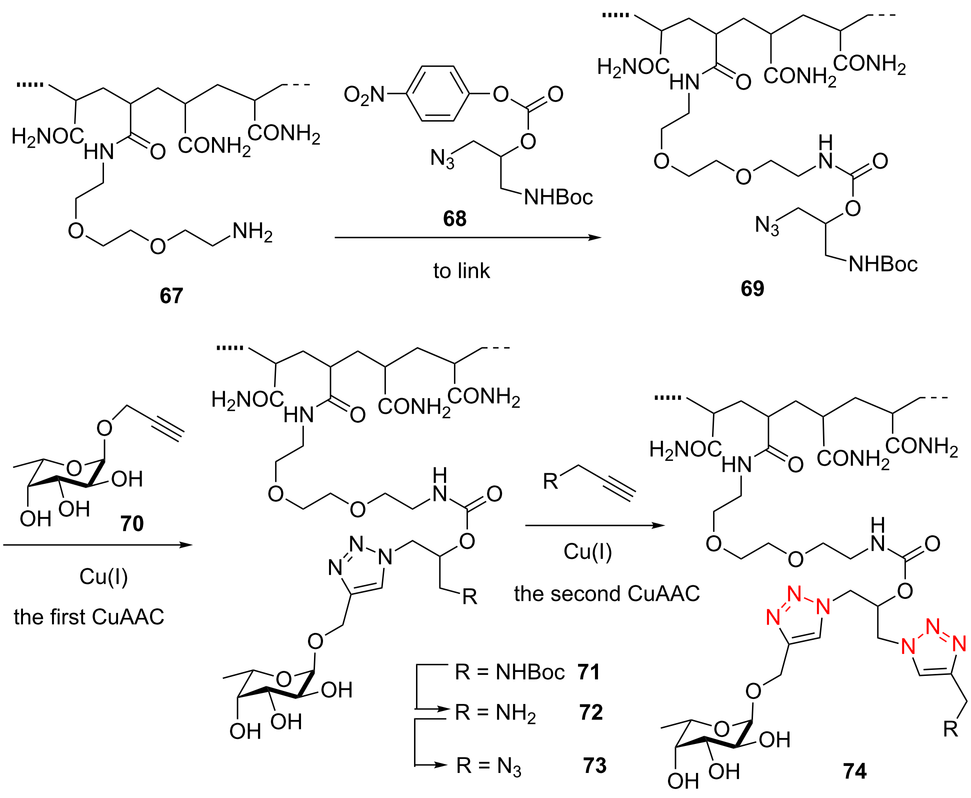


Scheme 22: The one-pot synthesis of bistriazoles.

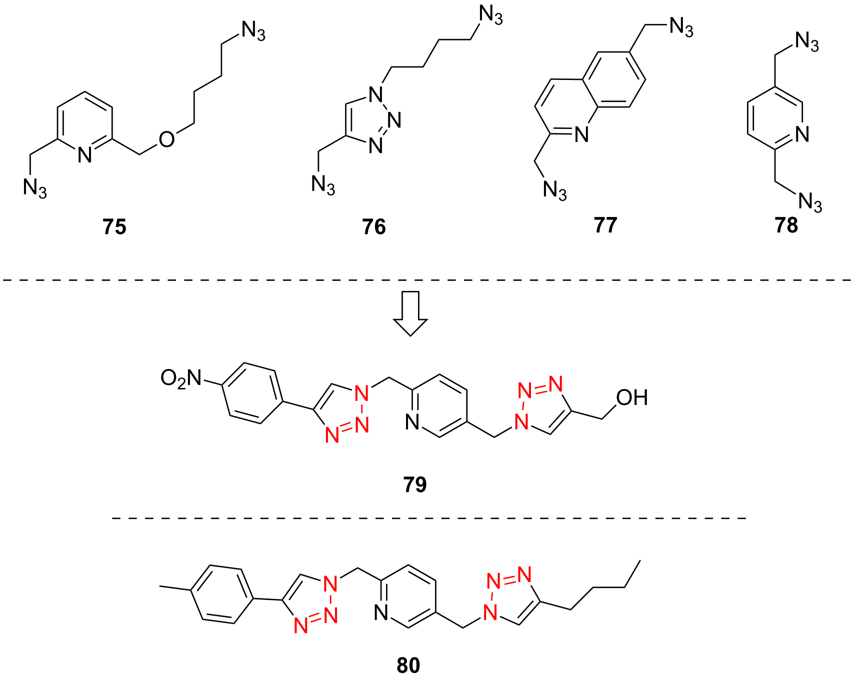
they choose the substrate SF_5-ethylbromide, only trace amounts of the triazole-containing compound was obtained even after 18 h at 60 °C due to the poor leaving ability of the Br^- compared to the OTs group.

In 2011, Bundle et al. reported the double-click method for the formation of disymmetric bistriazoles [66]. The authors introduced the azide group (**69**) by the coupling of the protected amine functionality to the polymer substrate for the first CuAAC reaction (Scheme 23). Then, the treatment of the amine-containing mono-triazole intermediate **71** with the diazo transfer agent (imidazole-1-sulfonyl azide) was performed to convert the amine group into the corresponding azide group, which provided a polymeric substrate for the second CuAAC reaction to give the desired bistriazoles (Scheme 23).

In 2009, Zhu and co-workers found that copper(II) acetate ($Cu(OAc)_2$) could catalyze the Huisgen alkyne-azide cycloaddition reactions without the addition of the reducing agents and could be produced in high yield when the substrate contains the chelating azide group [67]. Then they synthesized the bifunctional compounds with chelating azide groups and nonchelating azide groups (compounds **75**–**78**, Scheme 24) [68], by adding the $Cu(OAc)_2$. This promoted the Huisgen cycloaddition of the chelating azide with the terminal alkyne, providing the mono-



Scheme 23: The synthesis of polymer-bearing 1,2,3-bistriazole.



Scheme 24: The synthesis of bistriazoles via a sequential one-pot reaction.

triazole intermediates. Then, the introduction of the second alkyne, together with sodium ascorbate as the reducing agent, gave the desired bistriazoles in high yield. By mixing the two alkynes with different reactivities with the diazide, they developed a sequential one-pot method for the construction of the bistriazoles (**79**, **80**, etc.).

Notably, although there are many examples of the formation of spacer-linked bistriazoles from the diazide substrates, these bistriazole products were obtained with almost the same strategy as previously reported. These works are listed in Table 2 together with the reaction conditions and the applications of the corresponding bistriazoles.

Table 2: Previous reports on the copper-catalyzed Huisgen cycloaddition to bistriazoles with spacers.

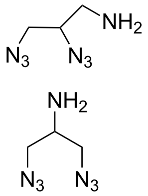
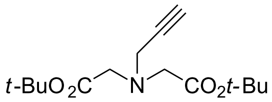
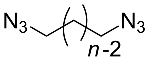
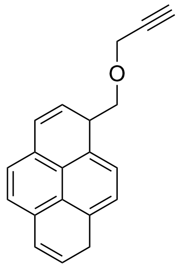
Cu source	Solvent	Spacer	Alkyne	Application
$Cu(OAc)_2$, sodium ascorbate [69]	H_2O/*t*-BuOH			Complexation
CuI [70,71]	THF/H_2O	 *n* = 3, 4, 5, 6		Chemical sensor

Table 2: Previous reports on the copper-catalyzed Huisgen cycloaddition to bistriazoles with spacers. (continued)

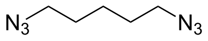
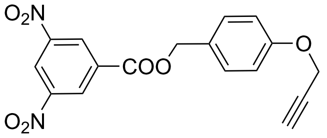
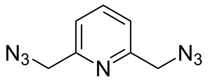
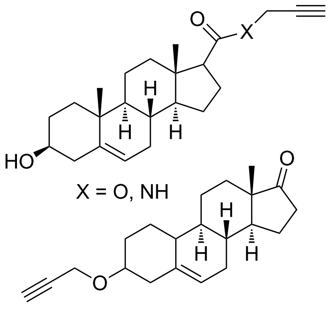
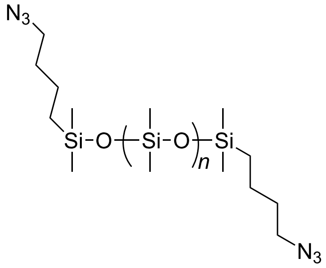
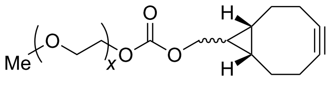
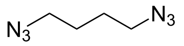
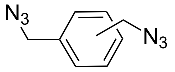
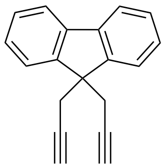
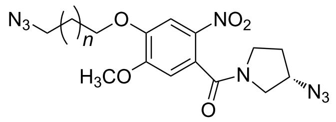
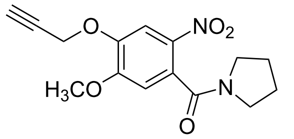
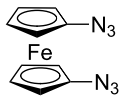
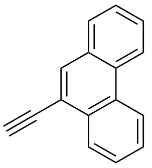
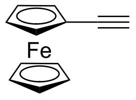
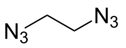
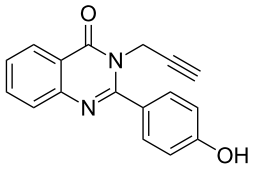
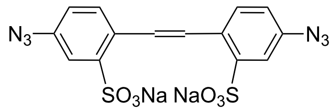
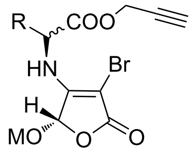
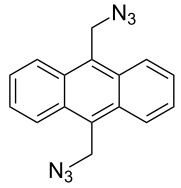
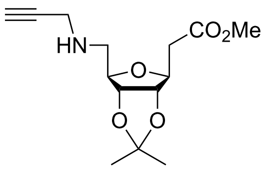
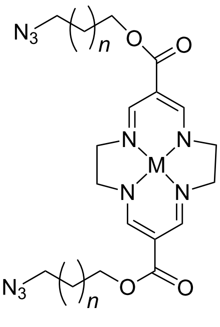
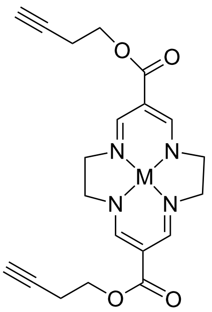
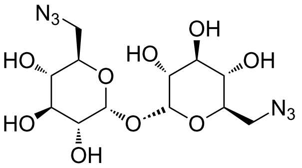
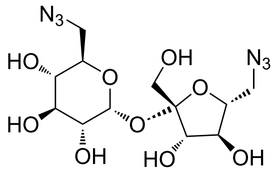
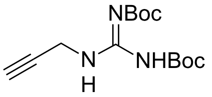
$CuSO_4 \cdot 5H_2O$, sodium ascorbate [72]	DMF/H_2O			Supermolecular chemistry
$CuSO_4 \cdot 5H_2O$, sodium ascorbate [73]	DMF		 X = O, NH	Cytotoxic activity
[74]	$CHCl_3$			Polymer chemistry
$CuSO_4 \cdot 5H_2O$, sodium ascorbate [75]	THF/H_2O	 		–
$CuSO_4 \cdot 5H_2O$, sodium ascorbate [76]	H_2O/*t*-BuOH			DNA binding
$CuSO_4 \cdot 5H_2O$, sodium ascorbate [77]	THF/H_2O		 	Receptor
$CuSO_4 \cdot 5H_2O$, sodium ascorbate [78]	DMF/H_2O			Molecular recognition
$Cu(OAc)_2/Cu$ [79]	DMSO		 R = CH_3 or $CH_2CH(CH_3)_2$	Fluorescence brightening agents

Table 2: Previous reports on the copper-catalyzed Huisgen cycloaddition to bistriazoles with spacers. (continued)

$CuSO_4$/Cu [80]	EtOH			Chemical sensor
CuI [81]	CH_2Cl_2/MeOH	 *n* = 1, 2		Electroactive receptor
$Cu(OAc)_2$ sodium ascorbate [82]	*t*-BuOH	 		Biological activity

Conclusion

During the past 15 years, the CuAAC reaction has become a powerful tool for the synthesis of a large number of 1,4-disubstituted 1,2,3-triazoles and has led to applications in almost every field of chemistry and biochemistry. In this review, we summarized the recent progress of the CuAAC reaction, together with various popular related reactions, which have unexpected potential to yield the 4,4'-, 5,5'-bitriazoles or spacer-linked bistriazoles. Nevertheless, as compared to the classic spacer-linked bistriazoles, the chemistry of 4,4'-, and 5,5'-bitriazoles (both their preparation and application) are still in their infancy. Although we restricted this review to describe only those having a bistriazole backbone, one can easily obtain a glimpse into the huge potential of bistriazoles in the broad sense when added to all other substitution possibilities. This topic, although already widely studied in the past years, is still continuously evolving and regularly brings new possibilities in click chemistry. We feel that this compilation will be beneficial to design practical approaches and better routes to improve the existing routes for the synthesis of synthetically useful bi- and bistriazoles, and we expect that the pace of discovery of the application of bi- and bistriazoles in many fields will continue to increase for some time.

Acknowledgements

This project support by the National Natural Science Founder of China (No. 21173064, 51303043, and 21472031) and Zhejiang Provincial Natural Science Foundation of China (LR14B030001) is appreciated. Z. J. Zheng also thanks the financial support of the public project of Zhejiang Province (2014C31131).

References

1. Huisgen, R. *Pure Appl. Chem.* **1989,** *61,* 613–628. doi:10.1351/pac198961040613
2. Huisgen, R.; Szeimies, G.; Möbius, L. *Chem. Ber.* **1967,** *100,* 2494–2507. doi:10.1002/cber.19671000806
3. Bastide, J.; Hamelin, J.; Texier, F.; Ven, V. Q. *Bull. Soc. Chim. Fr.* **1973,** 2555–2579.
4. Bastide, J.; Hamelin, J.; Texier, F.; Ven, V. Q. *Bull. Soc. Chim. Fr.* **1973,** 2871–2887.

5. Alvarez, R.; Velazquez, S.; San-Felix, A.; Aquaro, S.; De Clercq, E.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994,** *37,* 4185–4194. doi:10.1021/jm00050a015
6. Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000,** *43,* 953–970. doi:10.1021/jm990373e
7. Brockunier, L. L.; Parmee, E. R.; Ok, H. O.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F., Jr.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000,** *10,* 2111–2114. doi:10.1016/S0960-894X(00)00422-4
8. Fan, W.-Q.; Katritzky, A. R. In *Comprehensive heterocyclic chemistry II;* Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier Science: Oxford, 1996; Vol. 4, pp 1–126.
9. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002,** *67,* 3057–3064. doi:10.1021/jo011148j
10. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002,** *41,* 2596–2599. doi:10.1002/1521-3773(20020715)41:14<2596::AID-ANIE2596>3.0.CO;2-4
11. Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007,** *36,* 1249–1262. doi:10.1039/b613014n
12. Finn, M. G.; Fokin, V. V. *Chem. Soc. Rev.* **2010,** *39,* 1231–1232. doi:10.1039/c003740k
13. Ganesh, V.; Sudhir, V. S.; Kundu, T.; Chandrasekaran, S. *Chem. – Asian J.* **2011,** *6,* 2670–2694. doi:10.1002/asia.201100408
14. Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013,** *113,* 4905–4979. doi:10.1021/cr200409f
15. Tang, W.; Becker, M. L. *Chem. Soc. Rev.* **2014,** *43,* 7013–7039. doi:10.1039/C4CS00139G
16. Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008,** *108,* 2952–3015. doi:10.1021/cr0783479
17. Monkowius, U.; Ritter, S.; König, B.; Zabel, M.; Yersin, H. *Eur. J. Inorg. Chem.* **2007,** 4597–4606. doi:10.1002/ejic.200700479
18. Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A.; Capuzzolo, F. *Tetrahedron* **2009,** *65,* 10573–10580. doi:10.1016/j.tet.2009.10.078
19. Doak, B. C.; Scanlon, M. J.; Simpson, J. S. *Org. Lett.* **2011,** *13,* 537–539. doi:10.1021/ol102852z
20. Aizpurua, J. M.; Azcune, I.; Fratila, R. M.; Balentova, E.; Sagartzazu-Aizpurua, M.; Miranda, J. I. *Org. Lett.* **2010,** *12,* 1584–1587. doi:10.1021/ol1003127
21. Angell, Y.; Burgess, K. *Angew. Chem., Int. Ed.* **2007,** *46,* 3649–3651. doi:10.1002/anie.200700399
22. Oladeinde, O. A.; Hong, S. Y.; Holland, R. J.; Maciag, A. E.; Keefer, L. K.; Saavedra, J. E.; Nandurdikar, R. S. *Org. Lett.* **2010,** *12,* 4256–4259. doi:10.1021/ol101645k
23. del Hoyo, A. M.; Latorre, A.; Diaz, R.; Urbano, A.; Carreño, M. C. *Adv. Synth. Catal.* **2015,** *357,* 1154–1160. doi:10.1002/adsc.201400998
24. González, J.; Pérez, V. M.; Jiménez, D. O.; Lopez-Valdez, G.; Corana, D.; Cuevas-Yañez, E. *Tetrahedron Lett.* **2011,** *52,* 3514–3517. doi:10.1016/j.tetlet.2011.05.002
25. Kwon, M.; Jang, Y.; Yoon, S.; Yang, D.; Jeon, H. B. *Tetrahedron Lett.* **2012,** *53,* 1606–1609. doi:10.1016/j.tetlet.2012.01.069
26. Zheng, Z.-J.; Ye, F.; Zheng, L.-S.; Yang, K.-F.; Lai, G.-Q.; Xu, L.-W. *Chem. – Eur. J.* **2012,** *18,* 14094–14099. doi:10.1002/chem.201202472
27. Wang, C.-Y.; Zou, J.-F.; Zheng, Z.-J.; Huang, W.-S.; Li, L.; Xu, L.-W. *RSC Adv.* **2014,** *4,* 54256–54262. doi:10.1039/c4ra09589h
28. Aucagne, V.; Leigh, D. A. *Org. Lett.* **2006,** *8,* 4505–4507. doi:10.1021/ol061657d
29. Damodiran, M.; Muralidharan, D.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2009,** *19,* 3611–3614. doi:10.1016/j.bmcl.2009.04.131
30. Elamari, H.; Meganem, F.; Herscovici, J.; Girard, C. *Tetrahedron Lett.* **2011,** *52,* 658–660. doi:10.1016/j.tetlet.2010.11.141
31. Kele, P.; Mezö, G.; Achatz, D.; Wolfbeis, O. S. *Angew. Chem., Int. Ed.* **2009,** *48,* 344–347. doi:10.1002/anie.200804514
32. Beal, D. M.; Albrow, V. E.; Burslem, G.; Hitchen, L.; Fernandes, C.; Lapthorn, C.; Roberts, L. R.; Selby, M. D.; Jones, L. H. *Org. Biomol. Chem.* **2012,** *10,* 548–554. doi:10.1039/c1ob06398g
33. Mohammed, A. I.; Abboud, Z. H.; Alghanimi, A. H. O. *Tetrahedron Lett.* **2012,** *53,* 5081–5083. doi:10.1016/j.tetlet.2012.07.014
34. Lal, K.; Kumar, A.; Pavan, M. S.; Kaushik, C. P. *Bioorg. Med. Chem. Lett.* **2012,** *22,* 4353–4357. doi:10.1016/j.bmcl.2012.05.008
35. Lal, K.; Kaushik, C. P.; Kumar, K.; Kumar, A.; Qazi, A. K.; Hamid, A.; Jaglan, S. *Med. Chem. Res.* **2014,** *23,* 4761–4770. doi:10.1007/s00044-014-1038-5
36. Lal, K.; Kaushik, C. P.; Kumar, A. *Med. Chem. Res.* **2015,** *24,* 3258–3271. doi:10.1007/s00044-015-1378-9
37. Brombosz, S. M.; Appleton, A. L.; Zappas, A. J., II; Bunz, U. H. F. *Chem. Commun.* **2010,** *46,* 1419–1421. doi:10.1039/b920484a
38. Tomiyasu, H.; Shigyo, N.; Ni, X.-L.; Zeng, X.; Redshaw, C.; Yamato, T. *Tetrahedron* **2014,** *70,* 7893–7899. doi:10.1016/j.tet.2014.08.068
39. Hao, E.; Wang, Z.; Jiao, L.; Wang, S. *Dalton Trans.* **2010,** *39,* 2660–2666. doi:10.1039/b922043g
40. Nielsen, M. C.; Larsen, A. F.; Abdikadir, F. H.; Ulven, T. *Eur. J. Med. Chem.* **2014,** *72,* 119–126. doi:10.1016/j.ejmech.2013.11.027
41. Zhang, X.; Li, H.; You, L.; Tang, Y.; Hsung, R. P. *Adv. Synth. Catal.* **2006,** *348,* 2437–2442. doi:10.1002/adsc.200600404
42. Li, Y.; Huffman, J. C.; Flood, A. H. *Chem. Commun.* **2007,** 2692–2694. doi:10.1039/b703301j
43. Pereira, G. R.; Santos, L. J.; Luduvico, I.; Alves, R. B.; Pereira de Freitas, R. *Tetrahedron Lett.* **2010,** *51,* 1022–1025. doi:10.1016/j.tetlet.2009.12.050
44. Elamari, H.; Jlalia, I.; Louet, C.; Herscovici, J.; Meganem, F.; Girard, C. *Tetrahedron: Asymmetry* **2010,** *21,* 1179–1183. doi:10.1016/j.tetasy.2010.06.013
45. Ruan, Y.-B.; Yu, Y.; Li, C.; Bogliotti, N.; Tang, J.; Xie, J. *Tetrahedron* **2013,** *69,* 4603–4608. doi:10.1016/j.tet.2013.04.024
46. Zhou, M.; Zhang, X.; Bai, M.; Shen, D.; Xu, B.; Kao, J.; Ge, X.; Achilefu, S. *RSC Adv.* **2013,** *3,* 6756–6758. doi:10.1039/c3ra40441b
47. White, N. G.; Beer, P. D. *Org. Biomol. Chem.* **2013,** *11,* 1326–1333. doi:10.1039/c2ob27229f
48. Mulla, K.; Shaik, H.; Thompson, D. W.; Zhao, Y. *Org. Lett.* **2013,** *15,* 4532–4535. doi:10.1021/ol402093a
49. Midya, G. C.; Paladhi, S.; Bhowmik, S.; Saha, S.; Dash, J. *Org. Biomol. Chem.* **2013,** *11,* 3057–3063. doi:10.1039/c3ob40075a
50. Skarpos, H.; Osipov, S. N.; Vorob'eva, D. V.; Odinets, I. L.; Lork, E.; Röschenthaler, G.-V. *Org. Biomol. Chem.* **2007,** *5,* 2361–2367. doi:10.1039/b705510b
51. Hemamalini, A.; Mohan Das, T. *New J. Chem.* **2013,** *37,* 2419–2425. doi:10.1039/c3nj00072a
52. Krim, J.; Taourirte, M.; Engels, J. W. *Molecules* **2012,** *17,* 179–190. doi:10.3390/molecules17010179
53. Singh, N.; Metla, B. P. R.; Elias, A. J. *J. Organomet. Chem.* **2012,** *717,* 99–107. doi:10.1016/j.jorganchem.2012.07.023

54. Singh, M. K.; Tilak, R.; Nath, G.; Awasthi, S. K.; Agarwal, A. *Eur. J. Med. Chem.* **2013,** *63,* 635–644. doi:10.1016/j.ejmech.2013.02.027
55. Scott, S. Ø.; Gavey, E. L.; Lind, S. J.; Gordon, K. C.; Crowley, J. D. *Dalton Trans.* **2011,** *40,* 12117–12124. doi:10.1039/c1dt10551e
56. Kumar, K.; Carrère-Kremer, S.; Kremer, L.; Guérardel, Y.; Biot, C.; Kumar, V. *Dalton Trans.* **2013,** *42,* 1492–1500. doi:10.1039/c2dt32148c
57. Huo, J.-P.; Lü, M.; Wang, Z.; Li, Y. *Chin. J. Chem.* **2012,** *30,* 2411–2422. doi:10.1002/cjoc.201200638
58. Jervis, P. J.; Moulis, M.; Jukes, J.-P.; Ghadbane, H.; Cox, L. R.; Cerundolo, V.; Besra, G. S. *Carbohydr. Res.* **2012,** *356,* 152–162. doi:10.1016/j.carres.2012.02.034
59. Xu, H.-R.; Li, K.; Liu, Q.; Wu, T.-M.; Wang, M.-Q.; Hou, J.-T.; Huang, Z.; Xie, Y.-M.; Yu, X.-Q. *Analyst* **2013,** *138,* 2329–2334. doi:10.1039/c3an36789d
60. Anthony, P.; Bashir, N.; Parveen, R. *Asian J. Pharm. Sci.* **2014,** *4,* 9–13. doi:10.15272/ajbps.v4i33.501
61. Asmus, S.; Beckendorf, S.; Zurro, M.; Mück-Lichtenfeld, C.; Fröhlich, R.; Mancheño, O. G. *Chem. – Asian J.* **2014,** *9,* 2178–2186. doi:10.1002/asia.201402237
62. Fischer, C.; Weber, E. *J. Inclusion Phenom. Macrocyclic Chem.* **2014,** *79,* 151–160. doi:10.1007/s10847-013-0338-6
63. Bryant, J. J.; Lindner, B. D.; Bunz, U. H. F. *J. Org. Chem.* **2013,** *78,* 1038–1044. doi:10.1021/jo3024889
64. Wang, Z.-X.; Zhao, Z.-G. *J. Heterocycl. Chem.* **2007,** *44,* 89–92. doi:10.1002/jhet.5570440115
65. Huang, Y.; Gard, G. L.; Shreeve, J. M. *Tetrahedron Lett.* **2010,** *51,* 6951–6954. doi:10.1016/j.tetlet.2010.10.149
66. Guiard, J.; Fiege, B.; Kitov, P. I.; Peters, T.; Bundle, D. R. *Chem. – Eur. J.* **2011,** *17,* 7438–7441. doi:10.1002/chem.201003414
67. Brotherton, W. S.; Michaels, H. A.; Simmons, J. T.; Clark, R. J.; Dalal, N. S.; Zhu, L. *Org. Lett.* **2009,** *11,* 4954–4957. doi:10.1021/ol9021113
68. Yuan, Z.; Kuang, G.-C.; Clark, R. J.; Zhu, L. *Org. Lett.* **2012,** *14,* 2590–2593. doi:10.1021/ol300899n
69. Camp, C.; Dorbes, S.; Picard, C.; Benoist, E. *Tetrahedron Lett.* **2008,** *49,* 1979–1983. doi:10.1016/j.tetlet.2008.01.086
70. Hung, H.-C.; Cheng, C.-W.; Ho, I.-T.; Chung, W.-S. *Tetrahedron Lett.* **2009,** *50,* 302–305. doi:10.1016/j.tetlet.2008.10.147
71. Hung, H.-C.; Cheng, C.-W.; Wang, Y.-Y.; Chen, Y.-J.; Chung, W.-S. *Eur. J. Org. Chem.* **2009,** 6360–6366. doi:10.1002/ejoc.200900987
72. Wei, P.; Yan, X.; Li, J.; Ma, Y.; Yao, Y.; Huang, F. *Tetrahedron* **2012,** *68,* 9179–9185. doi:10.1016/j.tet.2012.09.018
73. Jurášek, M.; Džubák, P.; Sedlák, D.; Dvořáková, H.; Hajdúch, M.; Bartůněk, P.; Drašar, P. *Steroids* **2013,** *78,* 356–361. doi:10.1016/j.steroids.2012.11.016
74. Isaacman, M. J.; Corigliano, E. M.; Theogarajan, L. S. *Biomacromolecules* **2013,** *14,* 2996–3000. doi:10.1021/bm400940h
75. Rajesh, R.; Periyasami, G.; Raghunathan, R. *Tetrahedron Lett.* **2010,** *51,* 1896–1898. doi:10.1016/j.tetlet.2010.02.020
76. Kamal, A.; Shankaraiah, N.; Reddy, C. R.; Prabhakar, S.; Markandeya, N.; Srivastava, H. K.; Sastry, G. N. *Tetrahedron* **2010,** *66,* 5498–5506. doi:10.1016/j.tet.2010.05.003
77. Romero, T.; Orenes, R. A.; Tárraga, A.; Molina, P. *Organometallics* **2013,** *32,* 5740–5753. doi:10.1021/om4002457
78. Karuturi, R.; Al-Horani, R. A.; Mehta, S. C.; Gailani, D.; Desai, U. R. *J. Med. Chem.* **2013,** *56,* 2415–2428. doi:10.1021/jm301757v
79. Huo, J.-P.; Luo, J.-C.; Wu, W.; Xiong, J.-F.; Mo, G.-Z.; Wang, Z.-Y. *Ind. Eng. Chem. Res.* **2013,** *52,* 11850–11857. doi:10.1021/ie401149p
80. Huang, H.-J.; Fang, H.-Y.; Chir, J.-L.; Wu, A.-T. *Luminescence* **2011,** *26,* 518–522. doi:10.1002/bio.1263
81. Mames, I.; Wawrzyniak, U. E.; Woźny, M.; Bilewicz, R.; Korybut-Daszkiewicz, B. *Dalton Trans.* **2013,** *42,* 2382–2391. doi:10.1039/c2dt32386a
82. Westermann, B.; Dörner, S.; Brauch, S.; Schaks, A.; Heinke, R.; Stark, S.; van Delft, F. L.; van Berkel, S. S. *Carbohydr. Res.* **2013,** *371,* 61–67. doi:10.1016/j.carres.2013.02.003

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doi:10.3762/bjoc.11.276

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Recent advances in copper-catalyzed asymmetric coupling reactions

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Review

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Keywords:
asymmetric; carbon–heteroatom bond; copper; coupling

Beilstein J. Org. Chem. **2015,** *11,* 2600–2615.
doi:10.3762/bjoc.11.280

Received: 28 August 2015
Accepted: 27 November 2015
Published: 15 December 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

Copper-catalyzed (or -mediated) asymmetric coupling reactions have received significant attention over the past few years. Especially the coupling reactions of aryl or alkyl halides with nucleophiles became a very powerful tool for the formation of C–C, C–N, C–O and other carbon–heteroatom bonds as well as for the construction of heteroatom-containing ring systems. This review summarizes the recent progress in copper-catalyzed asymmetric coupling reactions for the formation of C–C and carbon–heteroatom bonds.

Introduction

Copper-mediated coupling reactions, including the Ullmann [1], Ullmann–Goldberg [2,3], Ullmann diaryl ether formation [4] and Ullmann–Hurtley condensation [5], have been reported several decades before Pd and Ni-catalyzed reactions. However, the application of these methods was limited due to their disadvantages such as the requirement of stoichiometric amounts of copper and harsh reaction conditions (high temperatures). The turn of the millennium brought about the revival of the research in this field that was initiated by the use of soluble copper salts and ligand-coordinated Cu complexes as catalysts. This allowed the reactions to be carried out under much milder conditions. In the meantime these reactions have become one of the most classic, efficient and powerful methods for the formation of C–C, C–N, C–O and other carbon–heteroatom bonds. Extensive applications have been developed in both academia and industry [6-13]. Despite the progress in recent years, the research on asymmetric coupling reactions is still relatively rare. In this review, we highlight the developments in copper-catalyzed asymmetric coupling reactions, including the asymmetric coupling of aryl halides with nucleophiles for the formation of carbon–carbon and carbon–heteroatom bonds as well as the asymmetric allylic substitution with a wide range of nucleophiles for the formation of C–C and carbon–heteroatom bonds.

Review

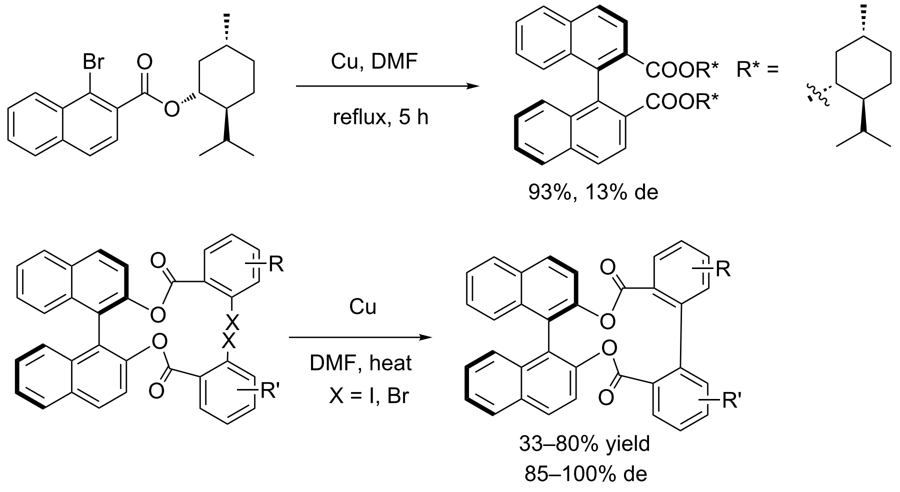
Copper-catalyzed coupling of aryl halides with nucleophiles

Chiral auxiliary-induced aryl C–C coupling

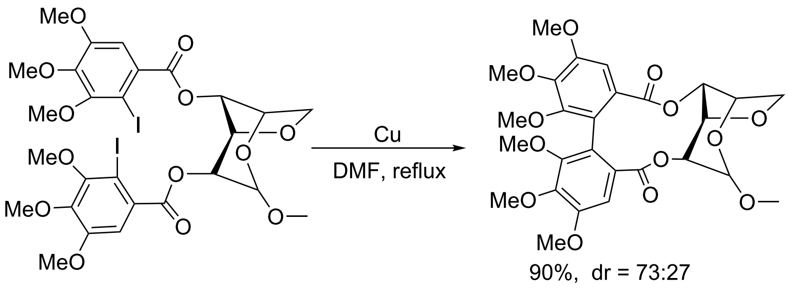
The biaryl motif is a key subunit in many natural products and axially chiral ligands. The classical Ullmann coupling is one of the most important methods for the practical synthesis of biaryls [14]. However, only few reports of an asymmetric version of the Ullmann coupling have been documented. The first attempt of an intermolecular asymmetric Ullmann coupling for the formation of biaryls was reported by Miyano and co-workers in 1980. The authors used a chiral ester group as auxiliary but only poor diastereoselectivity (13% de) was obtained [15]. A few years later, the same group took advantage of a chiral (*R*)-BINOL-bridge to link the two aromatic acids and obtained the coupling product with excellent stereocontrol (up to 100% de) (Scheme 1) [16-19].

In 1998, Martin et al. [20] applied this strategy to the asymmetric intramolecular biaryl coupling of sugar derivatives carrying 2-iodo-3,4,5-trimethoxybenzoyl substituents (Scheme 2).

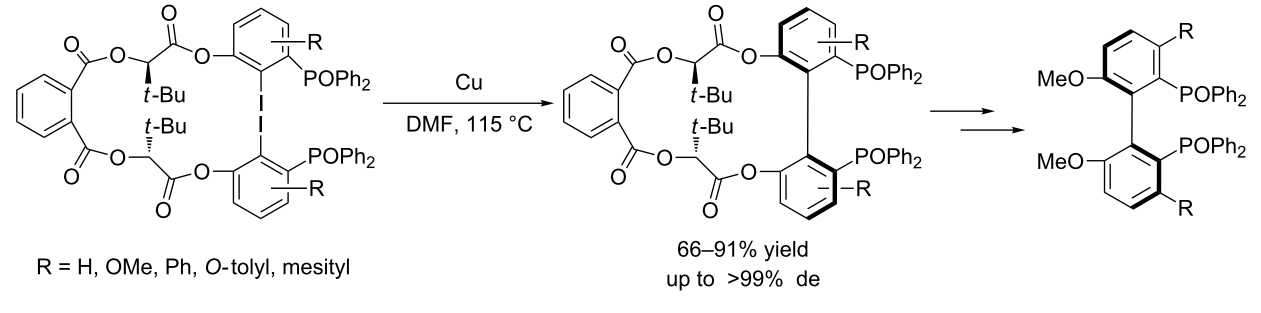
In 2006, Keay et al. [21] successfully developed an intramolecular asymmetric Ullmann coupling for the preparation of 3,3’-disubsituted MeO-BIPHEP derivatives using a chiral ester auxiliary that was easily prepared from (*R*)-2-hydroxy-3,3-dimethylbutyrate. In this reaction, only one diastereoisomer was formed during the Ullmann coupling and the auxiliary is easily prepared and removed by hydrolysis after the coupling reaction (Scheme 3).



Scheme 1: Copper-catalyzed asymmetric preparation of biaryl diacids by Ullmann coupling.



Scheme 2: Intramolecular biaryl coupling of bis(iodotrimethoxybenzoyl)hexopyranose derivatives.



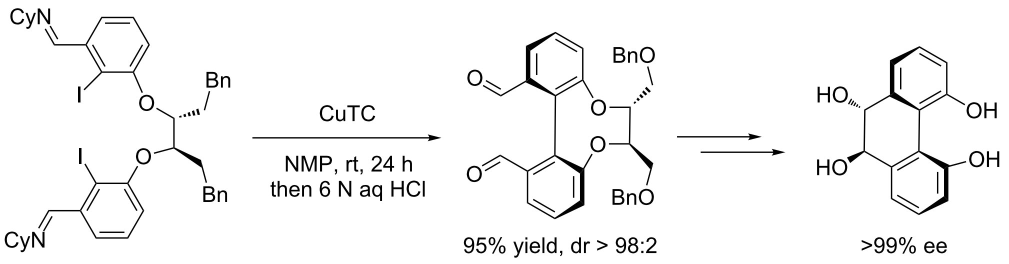
Scheme 3: Preparation of 3,3'-disubstituted MeO-BIPHEP derivatives.

In 2007, Breit et al. [22] employed a chiral tether to link two aryl halides for the enantioselective synthesis of *trans*-4,5,9,10-tetrahydroxy-9,10-dihydrophenanthrene at room temperature (Scheme 4).

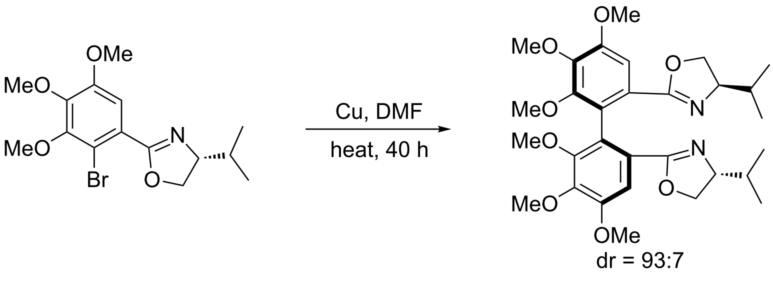
In 1994, Meyers and Nelson [23,24] developed a copper-mediated asymmetric biaryl coupling with oxazoline as the chiral auxiliary to afford the biaryl-coupling products in high diastereomeric purity (dr = 93:7, Scheme 5).

Meyers et al. also successfully applied the aforementioned strategy to the asymmetrical synthesis of many natural products [25-27] such as *O*-permethyl-tellimagrandin I (Scheme 6), (+)-gossypol (Scheme 7), (−)-mastigophorene A (Scheme 8). Based on this strategy, Lin and Zhong [28] developed an efficient method for the synthesis of Isokotanin A (Scheme 9) and Tanaka et al. [29] also used this method for the synthesis of dimethylthiaheterohelicenes, which are highly hindered C_2-symmetrical biaryls (Scheme 10).

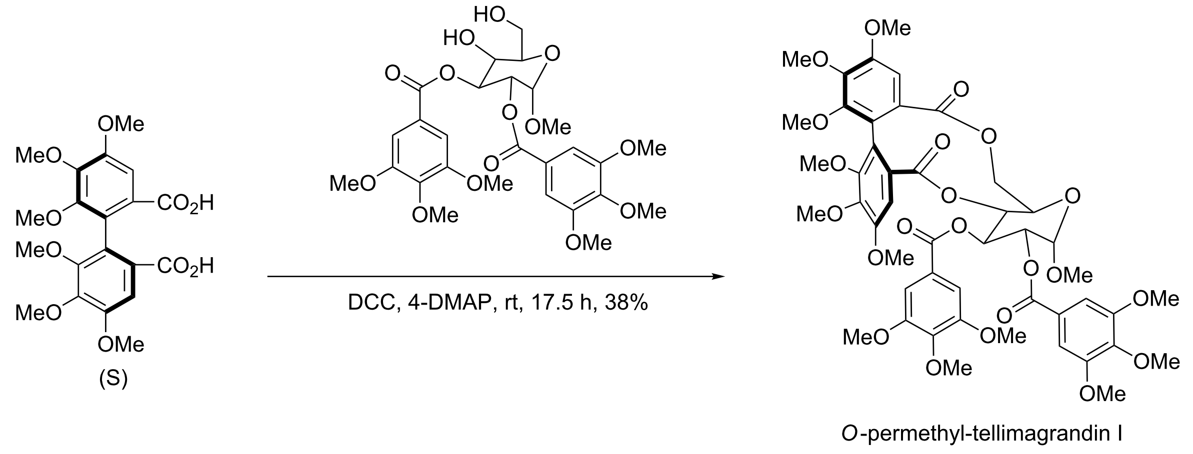
In 1994, an impressive progress was made by Lipshutz [30] in the intramolecular oxidative biaryl-coupling through the formation of higher-order cyanocuprates. The authors realized an asymmetrical intramolecular reaction by means of inexpensive optically active auxiliary bridges. The most efficient chiral auxiliary was found to be a C_2-symmetrical bridge bearing two stereogenic centers, derived from tartaric acid, giving the product as a single isomer in good yield (Scheme 11).



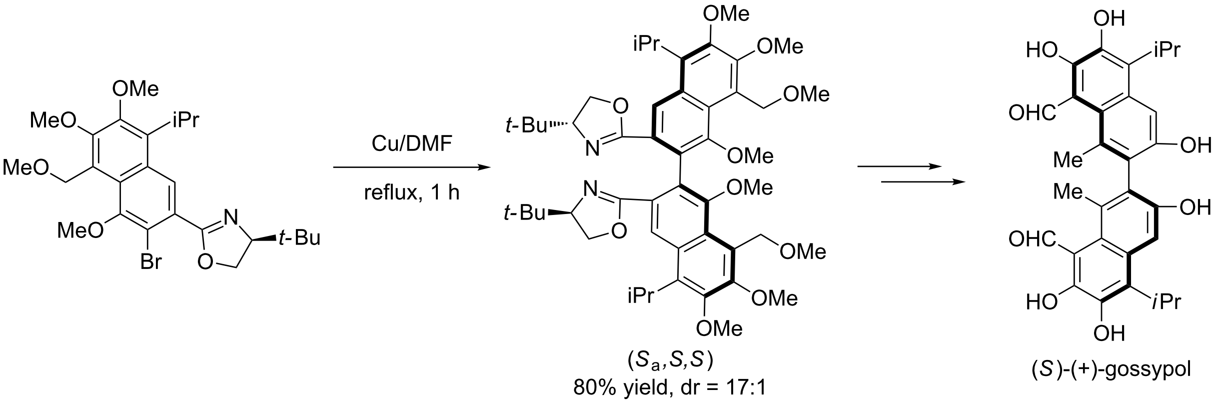
Scheme 4: Enantioselective synthesis of *trans*-4,5,9,10-tetrahydroxy-9,10-dihydrophenanthrene.



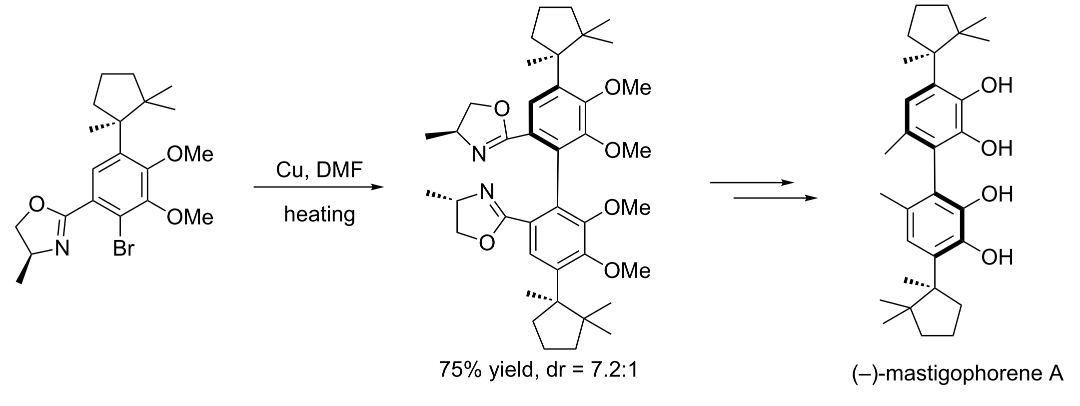
Scheme 5: Copper-catalyzed coupling of oxazoline-substituted aromatics to afford biaryl products with high diastereomeric purity.



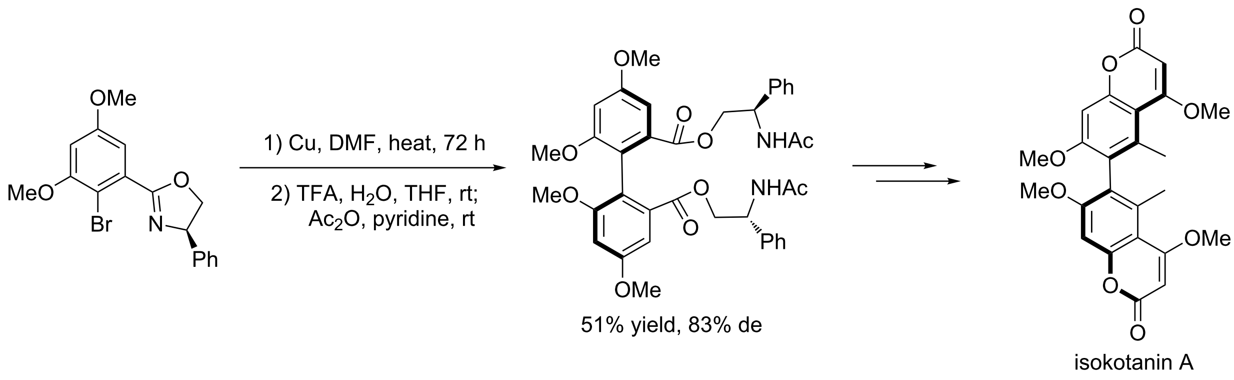
Scheme 6: Total synthesis of *O*-permethyl-tellimagrandin I.



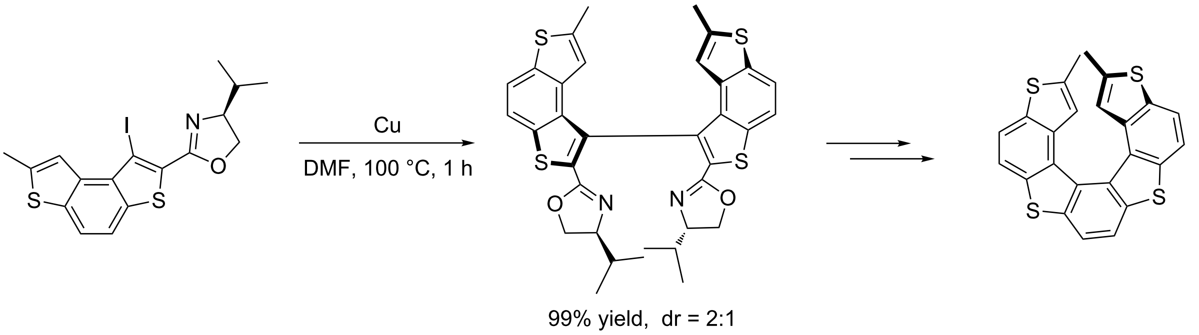
Scheme 7: Total synthesis of (+)-gossypol.



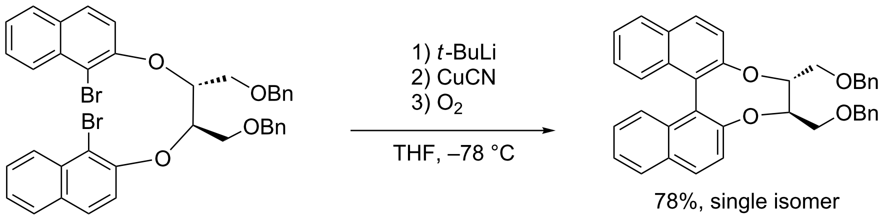
Scheme 8: Total synthesis of (−)-mastigophorene A.



Scheme 9: Total synthesis of isokotanin.



Scheme 10: Synthesis of dimethyl[7]thiaheterohelicenes.

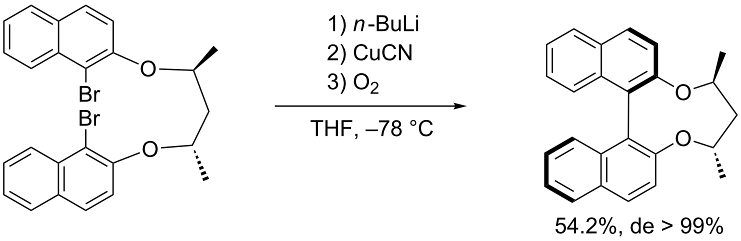


Scheme 11: Intramolecular coupling with chiral ortho-substituents.

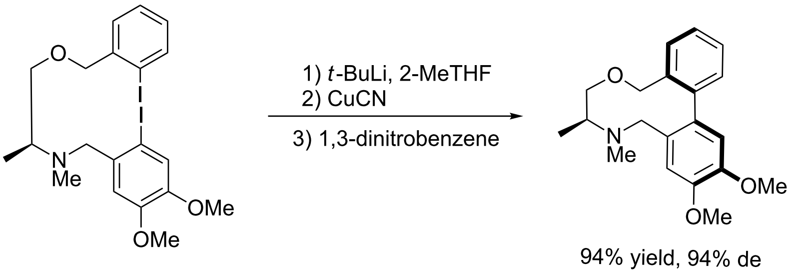
Sugimura et al. [31] expanded this method by introducing chiral 1,3-diol-derived tethers into the substrates, delivering the corresponding coupling products in excellent diastereoselectivity (Scheme 12).

Schreiber et al. [32] reported an efficient preparation of axially chiral unsymmetrical biaryl compounds in good to excellent diastereoselectivities by coupling through the formation of higher-order cuprates (Scheme 13).

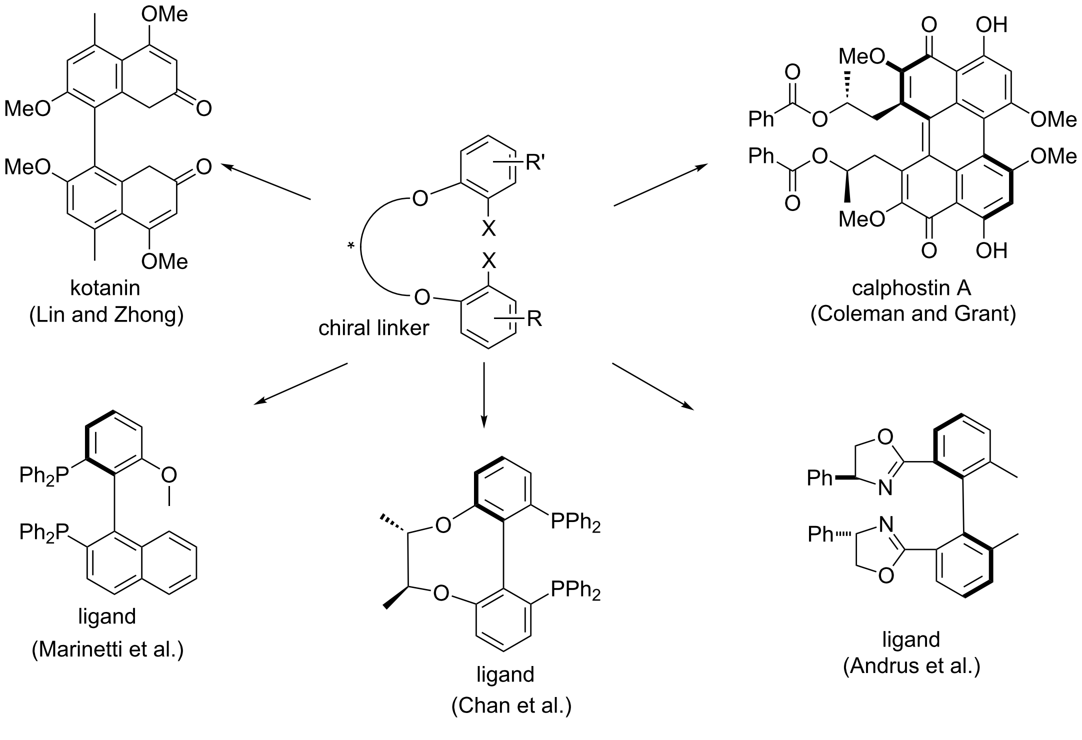
The utility of this strategy was also demonstrated by the atroposelective synthesis of many very useful axially chiral ligands and biologically important natural products. Some representative examples of these compounds are collected in Scheme 14. In 1997, Andrus et al. [33] used this method for the synthesis of enantiomerically pure bisoxazoline. Lin and Zhong [34] synthesized the natural product kotanin. Coleman and Grant [35] described an efficient synthesis of calphostin A, a potent protein kinase C inhibitor. In 2002, Marinetti et al. [36,37] employed this approach to prepare biaryl diphosphines. In 2004, Chan et al. [38] also developed a diastereoselective synthesis of chiral biphenyl diphosphine ligands by means of an intramolecular Ullmann coupling with the introduction of chiral bridged ethers.



Scheme 12: Chiral 1,3-diol-derived tethers in the diastereoselective synthesis of biaryl compounds.



Scheme 13: Synthesis of chiral unsymmetrically substituted biaryl compounds.



Scheme 14: Atroposelective synthesis of biaryl ligands and natural products by using a chiral diether linker.

Catalytic asymmetric C–C coupling

In 1929, Hurtley reported the first example of a C-arylation reaction of malonic esters with 2-bromobenzoic acid using a catalytic amount of copper-bronze or copper acetate [5]. Later on, great progress has been made in this reaction, allowing it to be carried out under practically useful and mild conditions [9-11]. However, an enantioselective version of this type of reaction remained challenging. Up to 2006 the report by Ma et al. [39] has been the only example of this type of catalytic asymmetric coupling reaction. They reacted 2-halotrifluoroacetanilides with 2-methylacetoacetates under the catalysis of CuI/*trans*-4-hydroxy-L-proline and obtained the arylated products in good yields and enantioselectivities. In this reaction, the trifluoroacetamido moiety present in the ortho position of the aryl halides plays an important role in enantiocontrol (Scheme 15).

Copper-catalyzed asymmetric aryl C–N coupling through desymmetrization and kinetic resolution strategies

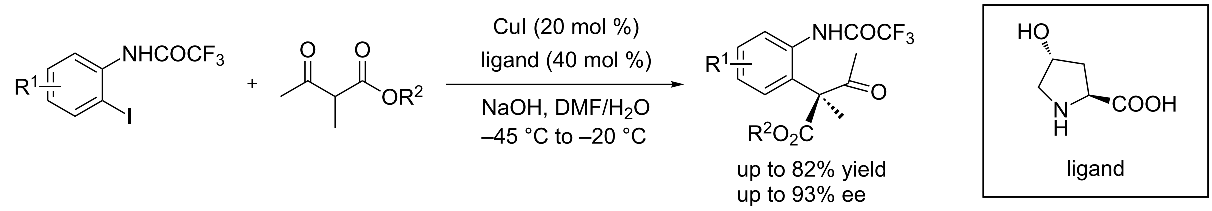
In the past, the asymmetric version of aryl C–N/O/S coupling reactions has not attracted the attention from the organic chemistry community. This may have been due to the fact that these reactions do not allow for the direct creation of new stereochemical centers. Only a few examples were reported for asymmetric N-arylation reactions using a Pd catalytic system through an “indirect” way, either by asymmetric desymmetrization or kinetic resolution [40-44]. In most cases, the enantioselectivities were not satisfactory. Recently, a copper catalytic system became another option toward asymmetric N-arylation reactions in term of improving enantioselectivity and efficiency.

In 2012, Cai et al. [45] developed the first copper-catalyzed asymmetric intramolecular Ullmann C–N coupling reaction through a desymmetrization strategy. The reaction lead to the enantioselective formation of indolines and tetrahydroquinolines in high yields and up to >99% ee (Scheme 16).

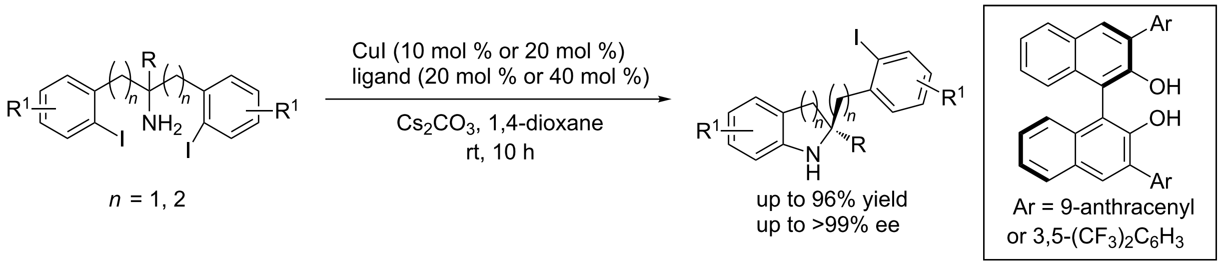
In 2014, Cai et al. [46] applied the desymmetrization strategy to construct chiral cyano-bearing all-carbon quaternary stereocenters, affording 1,2,3,4-tetrahydroquinoline analogues in good yields and excellent enantioselectivities (Scheme 17).

The same group also observed that achiral additives such as 4-(*N*,*N*-dimethylamino)pyridine caused an unexpected inversion of enantioselectivity in the Cu-catalyzed asymmetric desymmetrization of α,α-bis(2-iodobenzyl)glycines when (2*S*,3a*S*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid was used as chiral ligand [47] (Scheme 18).

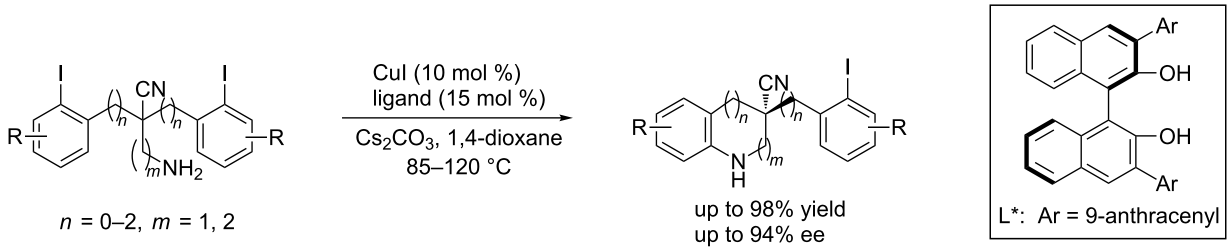
In 2015, Cai et al. reported another type of desymmetrization process, which allowed for the discrimination between two symmetric nucleophilic amine-type groups. Enantiocontrol using such substrates is more difficult in the asymmetric desymmetric aryl C–N coupling reaction because the two nucleophilic groups may serve as good chelating ligands and thus compete with the chiral ligand for binding with the copper salts.



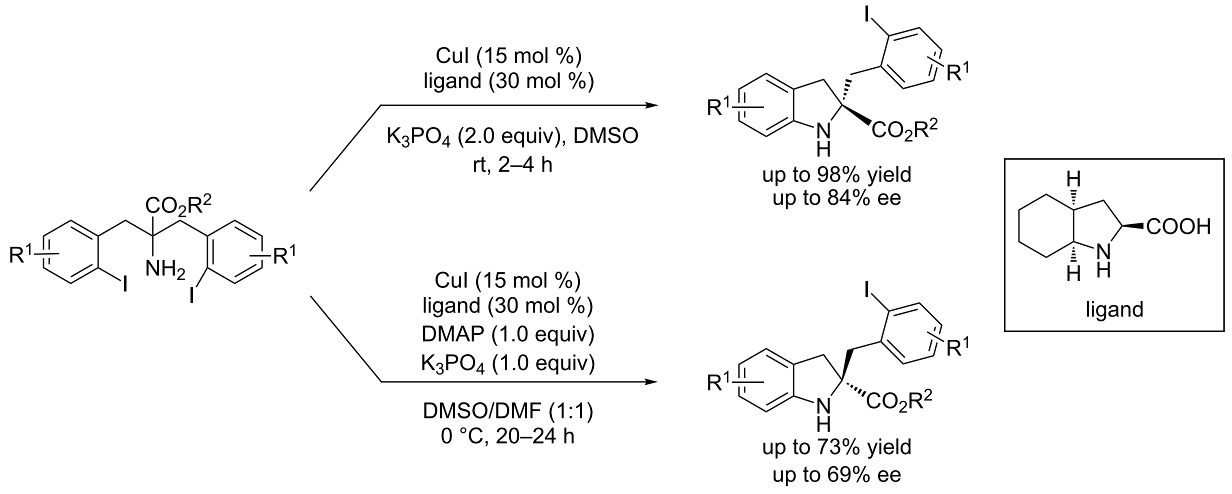
Scheme 15: Enantioselective arylation reactions of 2-methylacetoacetates.



Scheme 16: Asymmetric aryl C–N coupling reactions following a desymmetrization strategy.



Scheme 17: Construction of cyano-bearing all-carbon quaternary stereocenters.



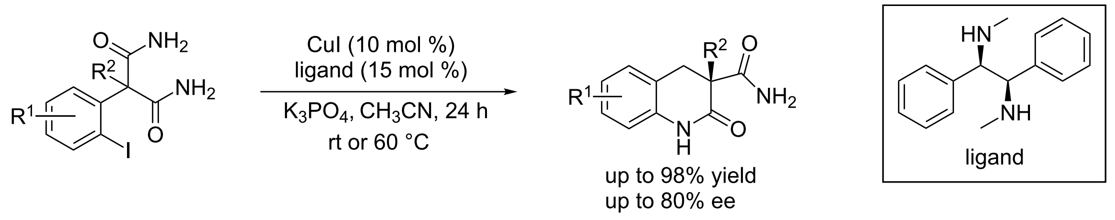
Scheme 18: An unexpected inversion of the enantioselectivity in the asymmetric C–N coupling reactions using chiral octahydro-1*H*-indole-2-carboxylic acid as the ligand.

Therefore the authors used a mono-aryl halide-substituted malonamide in the presence of a chiral CuI/1,2-diamine catalyst system and obtained the desired products in good yields and moderate enantioselectivities [48] (Scheme 19).

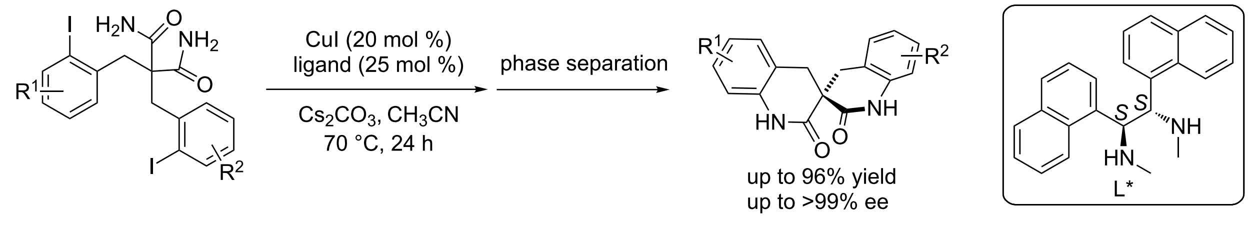
This method was further applied to a double N-arylation reaction for the enantioselective formation of spirobilactams by Cai et al. [49]. Through the combination of the copper-catalyzed double N-arylation and a simple in situ solid–solution phase separation, the spirobilatams were formed in good yields and with excellent enantioselectivities (Scheme 20).

Kinetic resolution is another strategy for asymmetric aryl C–N coupling reactions. Cai et al. [50] developed a copper-catalyzed asymmetric intramolecular N-arylation of *rac*-2-amino-3-(2-iodoaryl)propionates and *rac*-2-amino-4-(2-iodoaryl)butanoates with CuI/BINOL-derived ligands in 2013, affording the chiral coupling products and recovered starting material with high enantioselectivity (Scheme 21).

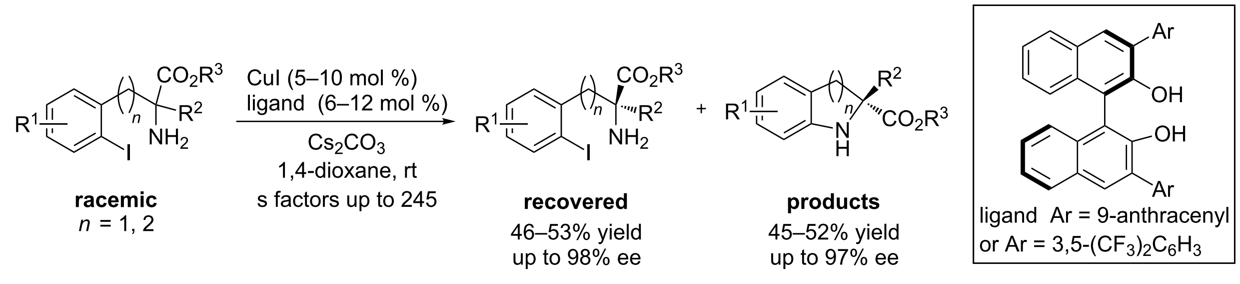
Recently, the aforementioned kinetic resolution strategy was applied to another type of substrates [51], leading to the formation of cyano-substituted quaternary stereocenters (Scheme 22).



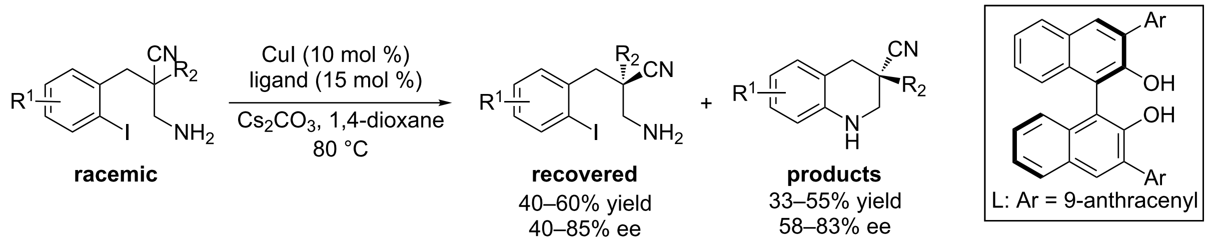
Scheme 19: Differentiation of two nucleophilic amide groups.



Scheme 20: Synthesis of spirobilactams through a double N-arylation reaction.



Scheme 21: Asymmetric N-arylation through kinetic resolution.



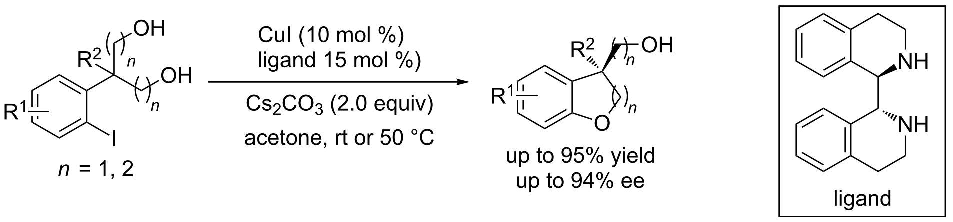
Scheme 22: Formation of cyano-substituted quaternary stereocenters through kinetic resolution.

Asymmetric C–O coupling

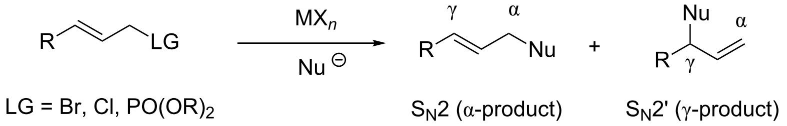
Numerous methods have been developed during the last two decades for the formation of aryl C–O bonds but asymmetric aryl C–O coupling is still a challenge [6-10]. In 2013, Beaudry and Quamar Salih reported the first copper-catalyzed asymmetric diaryl ether formation in the synthesis of (−)-myricatomentogenin, (−)-jugcathanin, (+)-galeon and (+)-pterocarine [52]. However, the enantioselectivity was poor in most cases. In 2013, Cai and co-workers [53] reported the first Pd-catalyzed highly enantioselective intermolecular aryl C–O coupling reaction for the construction of chiral (3,4-dihydro-2*H*-chromen-3-yl)methanols in good yields and high enantioselectivity by means of a desymmetrization strategy. A modified palladium catalytic system with a SDP(O) ligand was developed in 2015 for the asymmetric desymmetrization of 2-(2-halophenoxyl)-1,3-diols by the same group [54]. However, the palladium catalytic systems suffered from limited substrate scope and poor efficiency and enantioselectivity for the formation of quaternary stereocenters. Recently, Cai et al. carried out such couplings using a CuI/cyclized diamine catalytic system for the formation of 2,3-dihydrobenzofurans and analogs [55]. The copper catalytic system proved very efficient and compatible with a wide range of substrates under mild conditions. It overcame the shortcomings of the palladium catalytic system for the formation of quaternary stereocenters (Scheme 23).

Copper-catalyzed couplings of allylic halides with nucleophiles

Transition metal-catalyzed allylic substitutions are the most important process for carbon–carbon and carbon–heteroatom bond formation in organic synthesis [56-58]. Allylic substitution of the substrate with nucleophiles can afford two different products: the S_N2-product or the S_N2'-product (Scheme 24).



Scheme 23: Copper-catalyzed intramolecular desymmetric aryl C–O coupling.



Scheme 24: Transition metal-catalyzed allylic substitutions.

Usually, S_N2' regioselective allylic substitutions, which create a new stereogenic center, are more valuable. Methods that allow the S_N2' regioselective C–C bond formation have been extensively studied over the past years. In contrast to other metals (Pd, Mo, and Ir), copper-catalyzed allylic substitution reactions allow the use of nonstabilized nucleophiles including organomagnesium, organoaluminum, organozinc and organoborane reagents. Moreover, copper-catalyzed allylic substitution reactions usually proceed with high S_N2' regioselectivity, creating a new stereogenic center [59,60].

In 1995, Bäckvall et al. reported the first example of an asymmetric allylic substitution reaction catalyzed by a chiral copper complex, giving a moderate enantioselectivity (42% ee) in Grignard reactions with allylic acetates. The enantiomeric excess was later improved to 64% by using a new chiral ferrocenyl ligand [61,62]. Subsequently, great progress has been made in the development of copper-catalyzed asymmetric allylic substitution reactions. These considerable progresses have been reviewed by Hoveyda [56], Oshima [57], Alexakis [58], Feringa [59] and Diéguez [60]. In this review, we focus on the developments since 2008.

Cu-catalyzed enantioselective allylic substitutions with aryl-, alkenyl-, and allenylboronates, alkylboron compounds

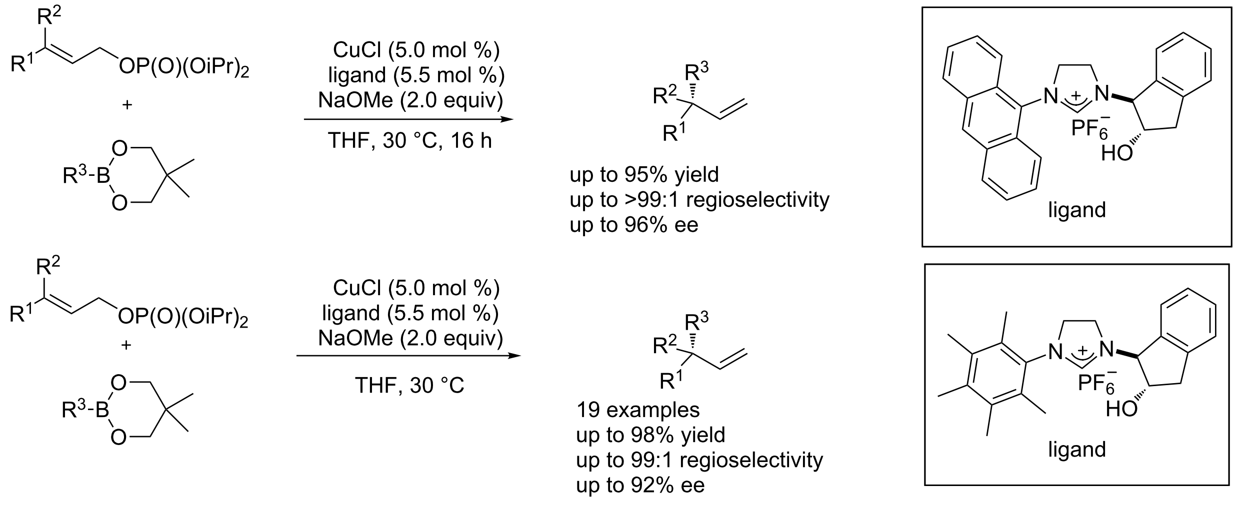
Organoboron compounds have found extensive application in coupling reactions for the construction of C–C bonds [63]. Recently, the copper-catalyzed enantioselective allylic substitutions with organoboron compounds have seen impressive progress. In 2011, Hayashi et al. [64] developed a new efficient method for the highly regioselective and enantioselective construction of tertiary carbon stereocenters by the copper/NHC-catalyzed asymmetric allylic substitution of allyl phosphates with arylboronates. Furthermore, they applied the method to the construction of quaternary carbon stereocenters with good enantioselectivity (up to 90% ee) with disubstituted allyl phosphates. The enantioselectivity was later improved to 92% ee with a new chiral catalyst (Scheme 25) [65].

In 2012, Hoveyda and Jung reported a copper/NHC-catalyzed asymmetric allylic substitution of allyl phosphates with allenylboronates [66], leading to chiral allenes bearing a tertiary or quaternary carbon stereogenic center in high yields and with excellent enantioselectivity (Scheme 26).

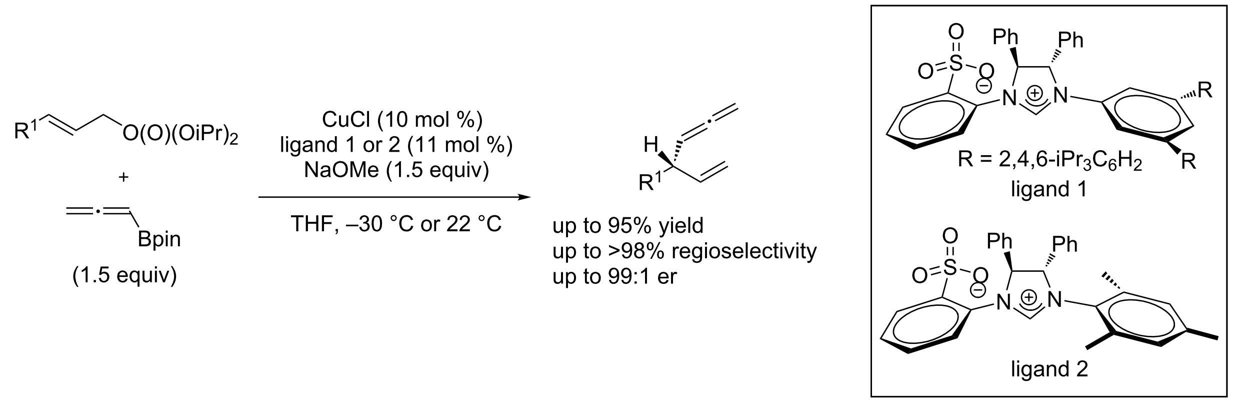
The copper/NHC catalyst system was also applied to the allylic substitution of allyl phosphates with commercially available or easily accessible vinylboron reagents, leading to chiral alkenes bearing a quaternary carbon stereocenter. The utility of this protocol was demonstrated by the concise enantioselective syntheses of the Pummerer ketone (Scheme 27) [67].

In 2012, Sawamura et al. reported a Cu(I)-DTBM-SEGPHOS-catalyzed enantioselective allylic substitution reaction with alkylboron compounds [68]. In this report, alkyl-9-BBN reagents for the first time served as nucleophiles reacting with primary allylic chlorides with excellent γ-selectivity and with high enantioselectivity (Scheme 28).

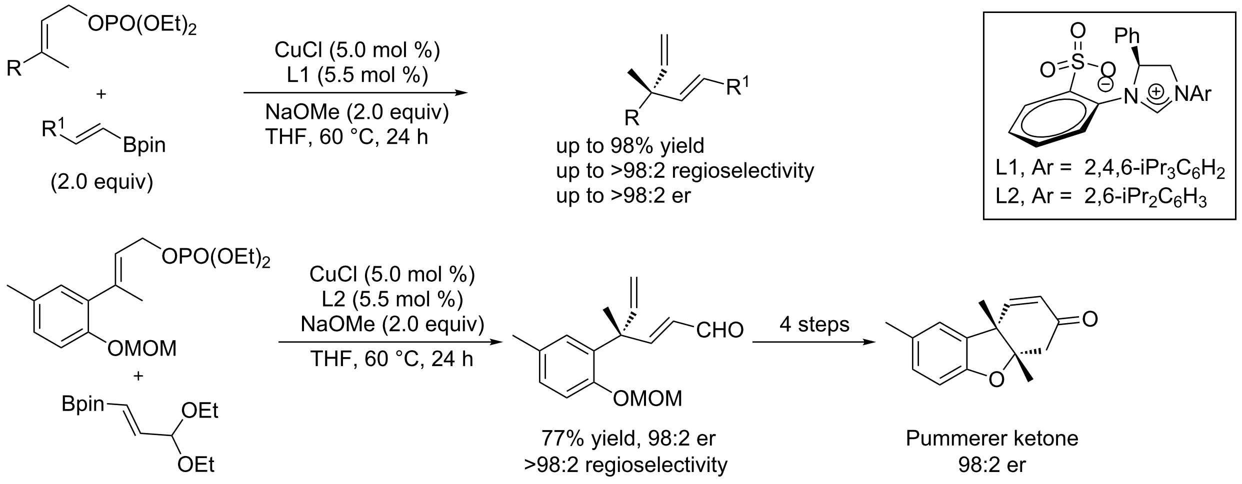
This catalytic system is however restricted to the construction of tertiary carbon stereocenters. An improved catalytic system [69,70] allowed disubstituted primary allyl chlorides to react with alkylborane (alkyl-9-BBN) for the generation of a quaternary carbon stereogenic center bearing three sp^3-alkyl groups and a vinyl group with an ee up to 90% (Scheme 29).



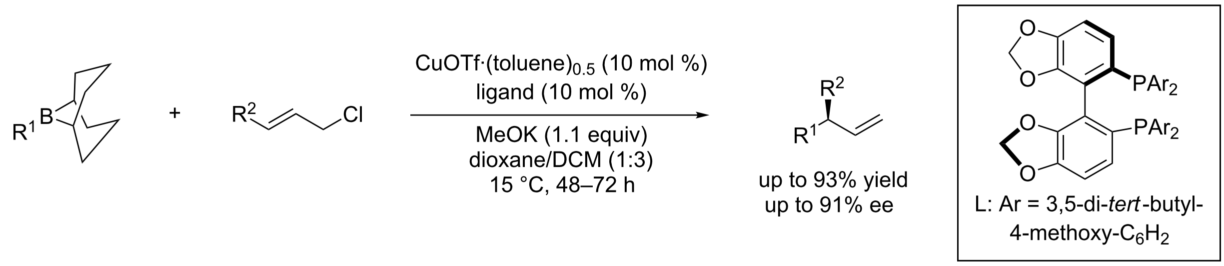
Scheme 25: Copper-catalyzed asymmetric allylic substitution of allyl phosphates.



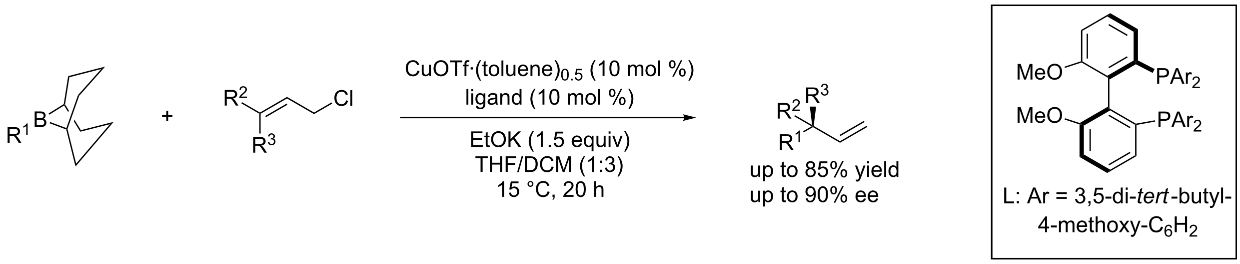
Scheme 26: Allylic substitution of allyl phosphates with allenylboronates.



Scheme 27: Allylic substitution of allyl phosphates with vinylboron.



Scheme 28: Allylic substitution of allyl phosphates with vinylboron.



Scheme 29: Construction of quaternary stereogenic carbon centers through enantioselective allylic cross-coupling.

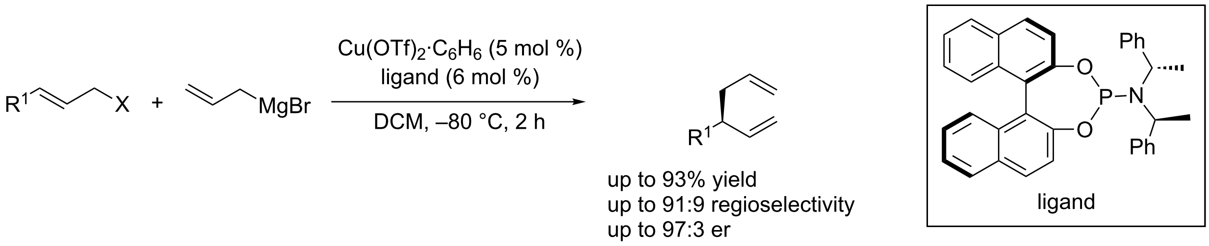
Cu-catalyzed enantioselective allylic substitutions with Grignard reagents

Transition metal-catalyzed allyl–allyl cross-coupling of allylmetal species with allylic electrophiles represents one of the powerful methods to establish 1,5-dienes. These compounds are abundant in natural terpenes as well as highly versatile intermediates in organic synthesis [71-73]. However, highly enantioselective allyl–allyl cross-coupling was only achieved by employing a Pd-catalyst system [74]. Copper-catalyzed asymmetric allylic alkylation (Cu-AAA) with allylmetal is still a great challenge. In 2013, Feringa et al. [75] reported the first copper-catalyzed highly enantioselective allyl–allyl cross-coupling of allyl Grignard reagents with allyl bromides, leading to chiral 1,5-dienes in good yield and with high enantioselectivity (Scheme 30).

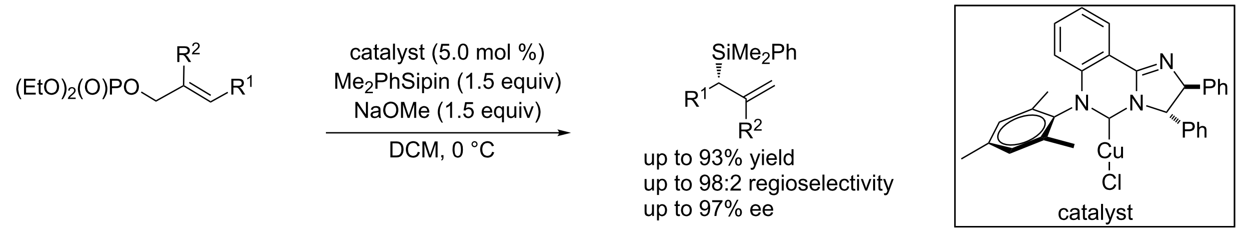
Cu-catalyzed enantioselective allylic substitutions with silylboronates

Enantioenriched allylsilanes are very useful building blocks in synthetic organic chemistry [76]. Oestreich et al. [77] reported the first example of an enantio- and regioselective allylic substitution of linear allylic chlorides and phosphates catalyzed by a Cu/NHC chiral ligand (Scheme 31).

Hayashi et al. [78] described a Cu/NHC-catalyzed asymmetric allylic substitution of allyl phosphates with silylboronates that



Scheme 30: Cu-catalyzed enantioselective allyl–allyl cross-coupling.



Scheme 31: Cu-catalyzed enantioselective allylic substitutions with silylboronates.

provides a straightforward access to chiral allylsilanes with high regio- and enantioselectivity (Scheme 32).

Cu-catalyzed enantioselective allylic substitutions with diboronates

Chiral allylboronates are useful reagents, which could be manipulated in a number of useful ways to give functionalized chiral building blocks such as allylic alcohols, amines etc. [79]. Sawamura et al. [80] developed a highly enantioselective copper-catalyzed asymmetric allylic substitution with diboronates to afford chiral allylboronates (Scheme 33).

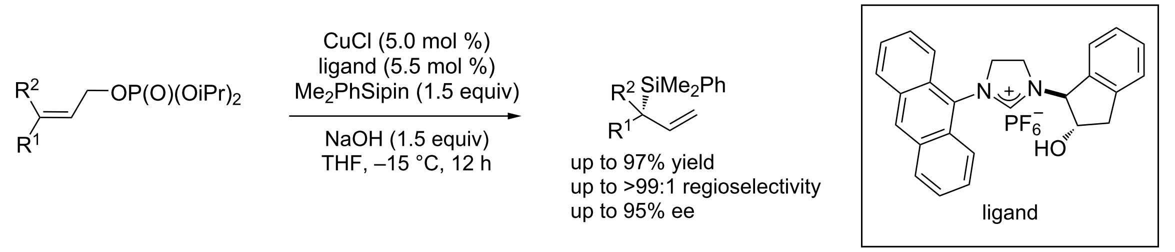
McQuade et al. [81] reported a copper/NHC-catalyzed allylic substitution of aryl ether substrates with diboron or α-substituted allylboronates in good yield and with high enantioselectivity. The reactions exhibited a wide functional-group tolerance with pure *E* or *Z* isomers or *E*/*Z* alkene mixtures (Scheme 34).

Cu-catalyzed enantioselective allylic substitutions with terminal alkynes

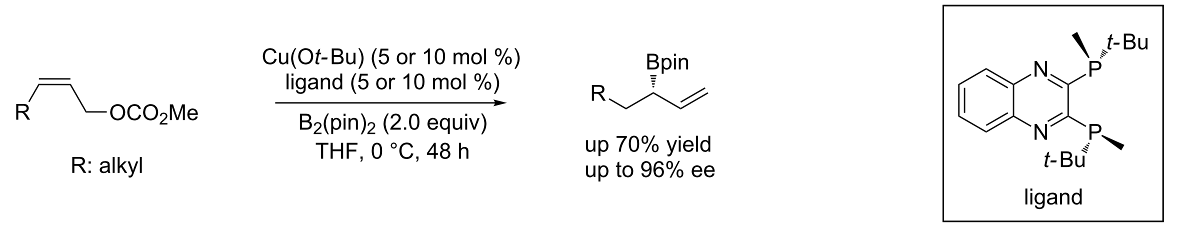
The catalytic enantioselective allylic alkylation of alkynyl nucleophiles is a powerful tool for the preparation of 1,4-enynes, which are versatile synthetic intermediates in asymmetric organic synthesis [82]. In 2014, Sawamura et al. [83] successfully developed a highly enantioselective allylic alkylation of terminal alkynes with primary allylic phosphates through a copper/NHC chiral catalyst system. The authors obtained chiral enynes with a tertiary stereocenter at the allylic propargylic position in good yield and with excellent enantioselectivity (Scheme 35).

Conclusion

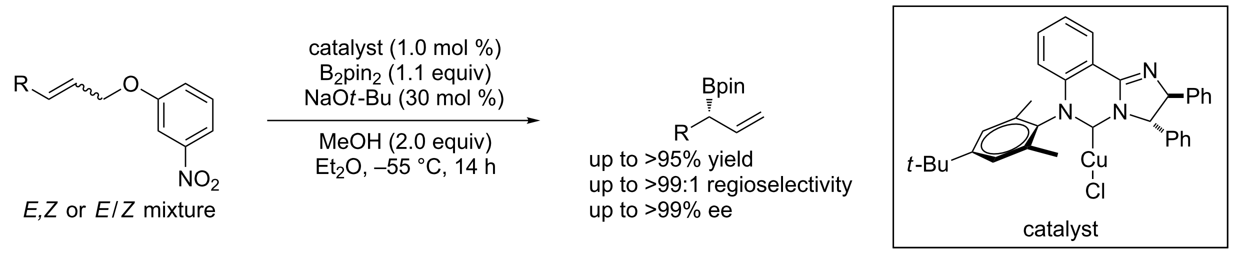
Copper-catalyzed or -mediated enantioselective carbon–carbon or carbon–heteroatom coupling reactions have been one of the most challenging areas in asymmetric catalysis in recent years. The asymmetric copper-catalyzed $C_{(Aryl)}$–$C_{(Aryl)}$ bond forma-



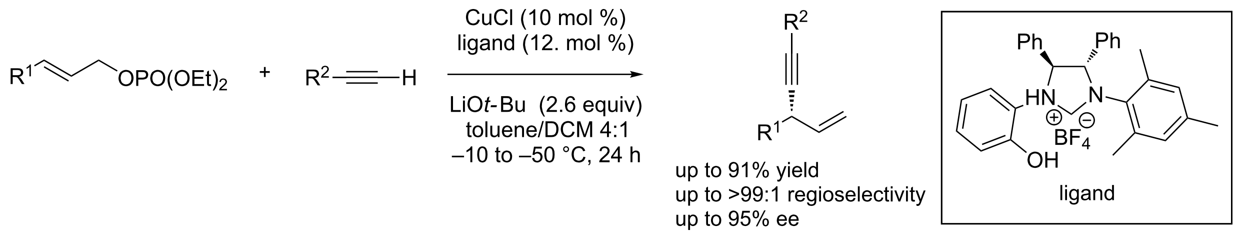
Scheme 32: Asymmetric allylic substitution of allyl phosphates with silylboronates.



Scheme 33: Stereoconvergent synthesis of chiral allylboronates.



Scheme 34: Enantioselective allylic substitutions with diboronates.



Scheme 35: Enantioselective allylic alkylations of terminal alkynes.

tion through the incorporation of a chiral ester group as auxiliary into the substrates, has emerged as a powerful tool for constructing natural products and useful ligands with axial chirality. Based on asymmetric desymmetrization and kinetic resolution strategies, a series of efficient copper-catalyzed systems have been developed for the formation of C–C, C–N, C–O bonds and the construction of nitrogen- and oxygen-containing ring systems. Despite the substantial progress that has been made in copper-catalyzed or -mediated enantioselective carbon–carbon and carbon–heteroatom coupling reactions, limitations in terms of substrate scope and catalyst efficiency still exist. In the future, the design of new ligands and improved catalyst systems are required that allow for transformations of more challenging substrates.

Acknowledgements

The authors are grateful to National Natural Science Foundation (Grant 21272234, 21572229) for the financial support.

References

1. Ullmann, F.; Bielecki, J. *Ber. Dtsch. Chem. Ges.* **1901,** *34,* 2174–2185. doi:10.1002/cber.190103402141
2. Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903,** *36,* 2382–2386. doi:10.1002/cber.190303602174
3. Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906,** *39,* 1691–1692. doi:10.1002/cber.19060390298
4. Ullmann, F.; Sponagel, P. *Ber. Dtsch. Chem. Ges.* **1905,** *38,* 2211–2212. doi:10.1002/cber.190503802176
5. Hurtley, W. R. H. *J. Chem. Soc.* **1929,** 1870–1873. doi:10.1039/jr9290001870
6. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003,** *42,* 5400–5449. doi:10.1002/anie.200300594
7. Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003,** 2428–2439. doi:10.1055/s-2003-42473
8. Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004,** *248,* 2337–2364. doi:10.1016/j.ccr.2004.09.014
9. Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008,** *108,* 3054–3131. doi:10.1021/cr8002505
10. Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009,** *48,* 6954–6971. doi:10.1002/anie.200804497
11. Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008,** *41,* 1450–1460. doi:10.1021/ar8000298
12. Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. *Chem. Soc. Rev.* **2014,** *43,* 3525–3550. doi:10.1039/c3cs60289c
13. Cai, Q.; Zhou, F. *Synlett* **2013,** *24,* 408–412. doi:10.1055/s-0032-1317866
14. Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002,** *102,* 1359–1469. doi:10.1021/cr000664r
15. Miyano, S.; Tobita, M.; Suzuki, S.; Nishikawa, Y.; Hashimoto, H. *Chem. Lett.* **1980,** *9,* 1027–1030. doi:10.1246/cl.1980.1027
16. Miyano, S.; Tobita, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1981,** *54,* 3522–3526. doi:10.1246/bcsj.54.3522
17. Miyano, S.; Handa, S.; Shimizu, K.; Tagami, K.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984,** *57,* 1943–1947. doi:10.1246/bcsj.57.1943
18. Miyano, S.; Handa, S.; Tobita, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1986,** *59,* 235–238. doi:10.1246/bcsj.59.235
19. Miyano, S.; Fukushima, H.; Handa, S.; Ito, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1988,** *61,* 3249–3254. doi:10.1246/bcsj.61.3249
20. Dai, D.; Martin, O. R. *J. Org. Chem.* **1998,** *63,* 7628–7633. doi:10.1021/jo971722k
21. Gorobets, E.; McDonald, R.; Keay, B. A. *Org. Lett.* **2006,** *8,* 1483–1485. doi:10.1021/ol060484p
22. Stavrakov, G.; Keller, M.; Breit, B. *Eur. J. Org. Chem.* **2007,** 5726–5733. doi:10.1002/ejoc.200700583

23. Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1994,** *35,* 3259–3262. doi:10.1016/S0040-4039(00)76879-1
24. Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1993,** *34,* 3061–3062. doi:10.1016/S0040-4039(00)93379-3
25. Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994,** *59,* 2577–2580. doi:10.1021/jo00088a046
26. Meyers, A. I.; Willemsen, J. J. *Chem. Commun.* **1997,** 1573–1574. doi:10.1039/A703043F
27. Degnan, A. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1999,** *121,* 2762–2769. doi:10.1021/ja984182x
28. Lin, G.-Q.; Zhong, M. *Tetrahedron Lett.* **1996,** *37,* 3015–3018. doi:10.1016/0040-4039(96)00457-1
29. Tanaka, K.; Suzuki, H.; Osuga, H. *J. Org. Chem.* **1997,** *62,* 4465–4470. doi:10.1021/jo970272t
30. Lipshutz, B. H.; Kayser, F.; Liu, Z.-P. *Angew. Chem., Int. Ed. Engl.* **1994,** *33,* 1842–1844. doi:10.1002/anie.199418421
31. Sugimura, T.; Yamada, H.; Inoue, S.; Tai, A. *Tetrahedron: Asymmetry* **1997,** *8,* 649–655. doi:10.1016/S0957-4166(97)00022-0
32. Spring, D. R.; Krishnan, S.; Schreiber, S. L. *J. Am. Chem. Soc.* **2000,** *122,* 5656–5657. doi:10.1021/ja0010507
33. Andrus, M. B.; Asgari, D.; Sclafani, J. A. *J. Org. Chem.* **1997,** *62,* 9365–9368. doi:10.1021/jo9713619
34. Lin, G.-Q.; Zhong, M. *Tetrahedron: Asymmetry* **1997,** *8,* 1369–1372. doi:10.1016/S0957-4166(97)00117-1
35. Coleman, R. S.; Grant, E. B. *J. Am. Chem. Soc.* **1995,** *117,* 10889–10904. doi:10.1021/ja00149a012
36. Michaud, G.; Bulliard, M.; Ricard, L.; Genêt, J.-P.; Marinetti, A. *Chem. – Eur. J.* **2002,** *8,* 3327–3330. doi:10.1002/1521-3765(20020802)8:15<3327::AID-CHEM3327>3.0.CO;2-F
37. Madec, J.; Michaud, G.; Genêt, J.-P.; Marinetti, A. *Tetrahedron: Asymmetry* **2004,** *15,* 2253–2261. doi:10.1016/j.tetasy.2004.05.014
38. Qiu, L.; Wu, J.; Chan, S.; Au-Yeung, T. T.-L.; Ji, J.-X.; Guo, R.; Pai, C.-C.; Zhou, Z.; Li, X.; Fan, Q.-H.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U. S. A.* **2004,** *101,* 5815–5820. doi:10.1073/pnas.0307774101
39. Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006,** *128,* 16050–16051. doi:10.1021/ja066991j
40. Takenaka, K.; Itoh, N.; Sasai, H. *Org. Lett.* **2009,** *11,* 1483–1486. doi:10.1021/ol900016g
41. Porosa, L.; Viirre, R. D. *Tetrahedron Lett.* **2009,** *50,* 4170–4173. doi:10.1016/j.tetlet.2009.04.133
42. Rossen, K.; Pye, P. J.; Maliakal, A.; Volante, R. P. *J. Org. Chem.* **1997,** *62,* 6462–6463. doi:10.1021/jo971300a
43. Tagashira, J.; Imao, D.; Yamamoto, T.; Ohta, T.; Furukawa, I.; Ito, Y. *Tetrahedron: Asymmetry* **2005,** *16,* 2307–2314. doi:10.1016/j.tetasy.2005.06.002
44. Kreis, M.; Friedmann, C. J.; Bräse, S. *Chem. – Eur. J.* **2005,** *11,* 7387–7394. doi:10.1002/chem.200500386
45. Zhou, F.; Guo, J.; Liu, J.; Ding, K.; Yu, S.; Cai, Q. *J. Am. Chem. Soc.* **2012,** *134,* 14326–14329. doi:10.1021/ja306631z
46. Zhou, F.; Cheng, G.-J.; Yang, W.; Long, Y.; Zhang, S.; Wu, Y.-D.; Zhang, X.; Cai, Q. *Angew. Chem., Int. Ed.* **2014,** *53,* 9555–9559. doi:10.1002/anie.201405575
47. Liu, J.; Yan, J.; Qin, D.; Cai, Q. *Synthesis* **2014,** *46,* 1917–1923. doi:10.1055/s-0033-1338638
48. He, N.; Huo, Y.; Liu, J.; Huang, Y.; Zhang, S.; Cai, Q. *Org. Lett.* **2015,** *17,* 374–377. doi:10.1021/ol5035386
49. Liu, J.; Tian, Y.; Shi, J.; Zhang, S.; Cai, Q. *Angew. Chem., Int. Ed.* **2015,** *54,* 10917–10920. doi:10.1002/anie.201504589
50. Yang, W.; Long, Y.; Zhang, S.; Zeng, Y.; Cai, Q. *Org. Lett.* **2013,** *15,* 3598–3601. doi:10.1021/ol401449b
51. Long, Y.; Shi, J.; Liang, H.; Zeng, Y.; Cai, Q. *Synthesis* **2015,** *47,* 2844–2850. doi:10.1055/s-0034-1380921
52. Quamar Salih, M.; Beaudry, C. M. *Org. Lett.* **2013,** *15,* 4540–4543. doi:10.1021/ol402096k
53. Yang, W.; Yan, J.; Long, Y.; Zhang, S.; Liu, J.; Zeng, Y.; Cai, Q. *Org. Lett.* **2013,** *15,* 6022–6025. doi:10.1021/ol402911y
54. Shi, J.; Wang, T.; Huang, Y.; Zhang, X.; Wu, Y.-D.; Cai, Q. *Org. Lett.* **2015,** *17,* 840–843. doi:10.1021/ol5036613
55. Yang, W.; Liu, Y.; Zhang, S.; Cai, Q. *Angew. Chem., Int. Ed.* **2015,** *54,* 8805–8808. doi:10.1002/anie.201503882
56. Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004,** 1779–1785. doi:10.1039/b401123f
57. Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005,** *44,* 4435–4439. doi:10.1002/anie.200500653
58. Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008,** 3765–3780. doi:10.1002/ejoc.200800025
59. Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008,** *108,* 2824–2852. doi:10.1021/cr068424k
60. Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008,** *108,* 2796–2823. doi:10.1021/cr0683515
61. van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* **1995,** *36,* 3059–3062. doi:10.1016/0040-4039(95)00426-D
62. Karlström, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J.-E. *Synlett* **2001,** 923–930. doi:10.1055/s-2001-14667
63. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995,** *95,* 2457–2483. doi:10.1021/cr00039a007
64. Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011,** *50,* 8656–8659. doi:10.1002/anie.201103581
65. Takeda, M.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2014,** *79,* 2354–2367. doi:10.1021/jo500068p
66. Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012,** *134,* 1490–1493. doi:10.1021/ja211269w
67. Gao, F.; Carr, J. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2012,** *51,* 6613–6617. doi:10.1002/anie.201202856
68. Shido, Y.; Yoshida, M.; Tanabe, M.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012,** *134,* 18573–18576. doi:10.1021/ja3093955
69. Hojoh, K.; Shido, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2014,** *53,* 4954–4958. doi:10.1002/anie.201402386
70. Hojoh, K.; Shido, Y.; Nagao, K.; Mori, S.; Ohmiya, H.; Sawamura, M. *Tetrahedron* **2015,** *71,* 6519–6533. doi:10.1016/j.tet.2015.05.048
71. Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994,** *50,* 6017–6028. doi:10.1016/S0040-4020(01)90454-5
72. Matsubara, R.; Jamison, T. F. *J. Am. Chem. Soc.* **2010,** *132,* 6880–6881. doi:10.1021/ja101186p
73. Nakamura, H.; Bao, M.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001,** *40,* 3208–3210. doi:10.1002/1521-3773(20010903)40:17<3208::AID-ANIE3208>3.0.CO;2-U
74. Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010,** *132,* 10686–10688. doi:10.1021/ja105161f
75. Hornillos, V.; Pérez, M.; Fañanás-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2013,** *135,* 2140–2143. doi:10.1021/ja312487r

76. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997,** *97,* 2063–2192. doi:10.1021/cr941074u
77. Delvos, L. B.; Vyas, D. J.; Oestreich, M. *Angew. Chem., Int. Ed.* **2013,** *52,* 4650–4653. doi:10.1002/anie.201300648
78. Takeda, M.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2013,** *78,* 5007–5017. doi:10.1021/jo400888b
79. Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005,** *127,* 16034–16035. doi:10.1021/ja056099x
80. Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007,** *129,* 14856–14857. doi:10.1021/ja076634o
81. Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, D. T. *J. Am. Chem. Soc.* **2011,** *133,* 2410–2413. doi:10.1021/ja1112518
82. Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011,** *133,* 4778–4781. doi:10.1021/ja2010829
83. Harada, A.; Makida, Y.; Sato, T.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2014,** *136,* 13932–13939. doi:10.1021/ja5084333

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doi:10.3762/bjoc.11.280

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Carbon–carbon bond cleavage for Cu-mediated aromatic trifluoromethylations and pentafluoroethylations

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Review

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Keywords:
β-carbon elimination; carbon–carbon bond cleavage; decarboxylation;
tetrahedral intermediate; trifluoroacetate; fluoral; trifluoromethylation

Beilstein J. Org. Chem. **2015,** *11,* 2661–2670.
doi:10.3762/bjoc.11.286

Received: 30 September 2015
Accepted: 11 December 2015
Published: 18 December 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

This short review highlights the copper-mediated fluoroalkylation using perfluoroalkylated carboxylic acid derivatives. Carbon–carbon bond cleavage of perfluoroalkylated carboxylic acid derivatives takes place in fluoroalkylation reactions at high temperature (150–200 °C) or under basic conditions to generate fluoroalkyl anion sources for the formation of fluoroalkylcopper species. The fluoroalkylation reactions, which proceed through decarboxylation or tetrahedral intermediates, are useful protocols for the synthesis of fluoroalkylated aromatics.

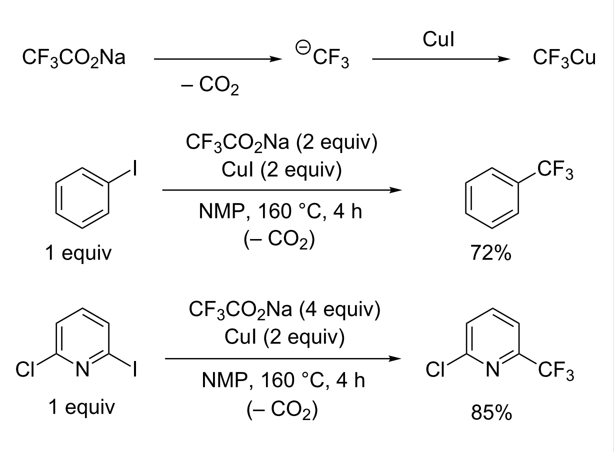
Introduction

Organofluorine compounds attract attention because of their applicability in various fields, such as medicine, agrochemical and material science. It has been widely reported that nearly 15% of pharmaceuticals and 20% of agrochemicals on the market contain fluorine atoms, including several of the top drugs. Of particular interest are compounds containing the structural motif of a (trifluoromethyl)aryl group (Ar–CF_3) [1-7]. The characteristic size, strong electron-withdrawing ability, and the high lipophilicity of the trifluoromethyl group are key properties of biologically active CF_3-containing molecules [8]. Perfluoroalkylcopper compounds ($C_nF_{2n+1}Cu$), which are soft and relatively stable perfluoroalkyl organometallic reagents ($C_nF_{2n+1}M$) with high reactivity, act as prominent cross-coupling participants in aromatic perfluoroalkylation reactions [9-32]. In order to prepare $C_nF_{2n+1}Cu$ species, several representative protocols have been reported. Among these protocols, each method has individual merit. Particularly, Ruppert–Prakash reagents ($C_nF_{2n+1}SiR_3$) have been used as the source of perfluoroalkyl anions ($C_nF_{2n+1}^-$) for the generation of $C_nF_{2n+1}Cu$. However, perfluoroalkylsilane sources are costly for large-scale operation. On the other hand, economical and useful perfluoroalkylated carboxylic acid derivatives, such as perfluoroalkylated carboxylates ($C_nF_{2n+1}CO_2Na$ or $C_nF_{2n+1}CO_2K$), halodifluoroacetates (XCF_2CO_2R), perfluoroalkyl carboxylates ($C_nF_{2n+1}CO_2R$), perfluoroalkyl ketones ($C_nF_{2n+1}COR$), and hemiaminals derived from fluoral ($CF_3C(OSiMe_3)NR_2$), can generate $C_nF_{2n+1}Cu$ via carbon–carbon bond cleavage. Herein we focus on Cu-mediated perfluoroalkylation reactions through which carbon dioxide, the esters, or the *N*-formylamines are eliminated from the perfluoroalkyl reagents.

Review

Decarboxylation of perfluoroalkylacetates

Trifluoroacetate salts are one of the most readily available trifluoromethylating agents compared to ozone-depleting CF_3Br, and expensive CF_3I. Sodium trifluoroacetate (CF_3CO_2Na) is a stable compound at room temperature. Under heating conditions (150–200 °C), CF_3CO_2Na plays the role of the CF_3^- source and [CF_3Cu] species with CuI are generated in situ. In the presence of CuI, CF_3CO_2Na undergoes trifluoromethylation with aryl halides via decarboxylation [33,34] (Scheme 1).



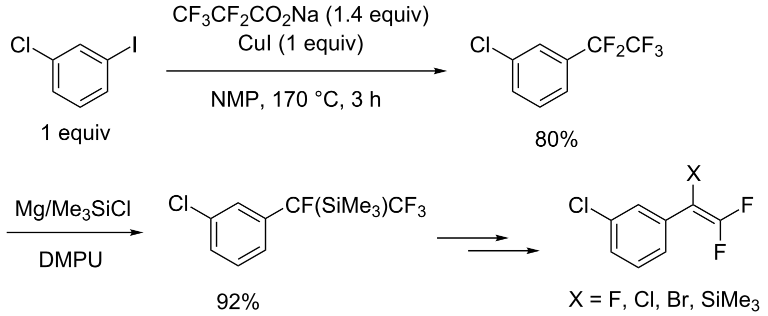
Scheme 1: Trifluoromethylation using trifluoroacetate.

A pentafluoroethyl group (C_2F_5) was fixed at the arene with sodium pentafluoropropionate [35] (Scheme 2). The reaction mechanism is similar to that of the trifluromethylation using CF_3CO_2Na [33,34]. Upon heating, the mixture of CF_3CO_2Na and CuI in NMP, 3-chloroiodobenzene underwent cross-coupling to provide the pentafluoroethylated compound in 80% yield. The pentafluoroethylated aromatic product was applied to the synthesis of 2,2-difluorostyrenes through Mg(0)-promoted defluorinative silylation followed by fluorine-ion-catalyzed 1,2-desilylative defluorination.

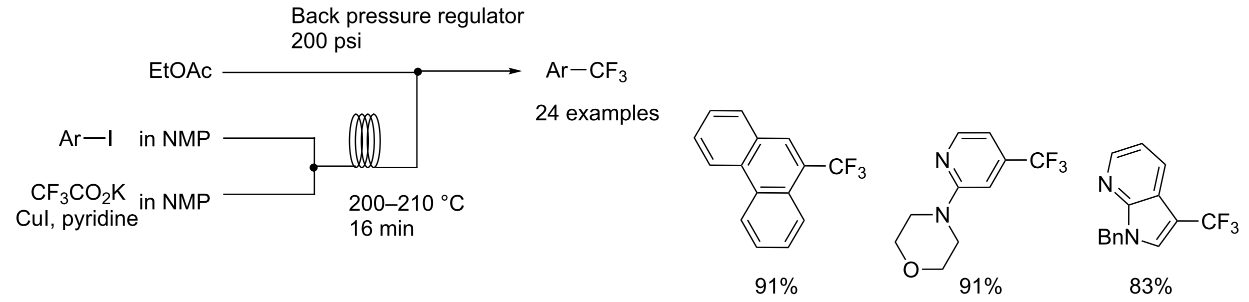
Buchwald et al. demonstrated aromatic trifluoromethylation using potassium trifluoroacetate (CF_3CO_2K), CuI and pyridine under flow conditions. Increasing the reaction temperature from 160 °C to 200 °C accelerated the decarboxylation of CF_3CO_2K [36] (Scheme 3). The trifluoromethylation using a microreactor resulted in a good yield within a short reaction time by virtue of the thermal stability of CF_3Cu and control of mixing. Taking advantage of the flow microreactor, a new protocol for scalable aromatic trifluoromethylation was developed.

From a mechanistic aspect, Vicic and co-workers explored the direct generation of CF_3Cu from CF_3CO_2Cu. The use of (N-heterocyclic carbene)copper-trifluoroacetates prepared from trifluoroacetic acid (TFA) was investigated in the decarboxylative trifluoromethylation of aryl halides [37] (Scheme 4). Not only iodobenzene but also 4-bromotoluene was trifluoromethylated by the [(NHC)Cu(TFA)] complex.

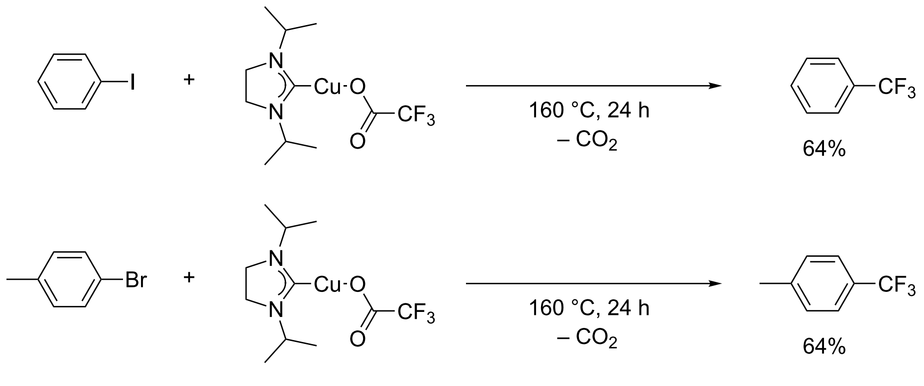
The perfluoroalkylation reactions mentioned above require a stoichiometric amount of copper reagent, whereas it was found that the addition of silver salts is effective for the copper-mediated trifluoromethylation of aryl iodides [38] (Scheme 5). The amount of copper used in the reaction was reduced to 30 or 40 mol % by adding a small amount of Ag_2O. As a related decarboxylative transformation, silver-mediated aromatic tri-



Scheme 2: Decarboxylative pentafluoroethylation and its application.

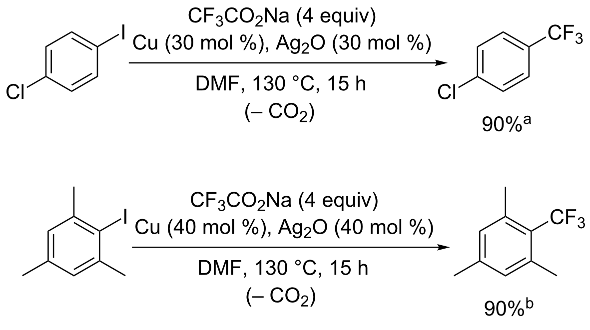


Scheme 3: Trifluoromethyation with trifluoroacetate in a flow system.



Scheme 4: Trifluoromethylation of 4-bromotoluene by [(NHC)Cu(TFA)].

fluoromethylation was recently developed. Zhang et al. reported the direct aryl C–H trifluoromethylation in which TFA works as a trifluoromethylation reagent [39] (Scheme 6). In this reaction, TFA releases a CF_3 radical via decarboxylation, which reacts with the arenes to yield trifluoromethyl-substituted products. This report suggests that TFA can act as a trifluoromethyl source in the reaction with inactivated aromatic compounds, while the control of regioselectivity is difficult.

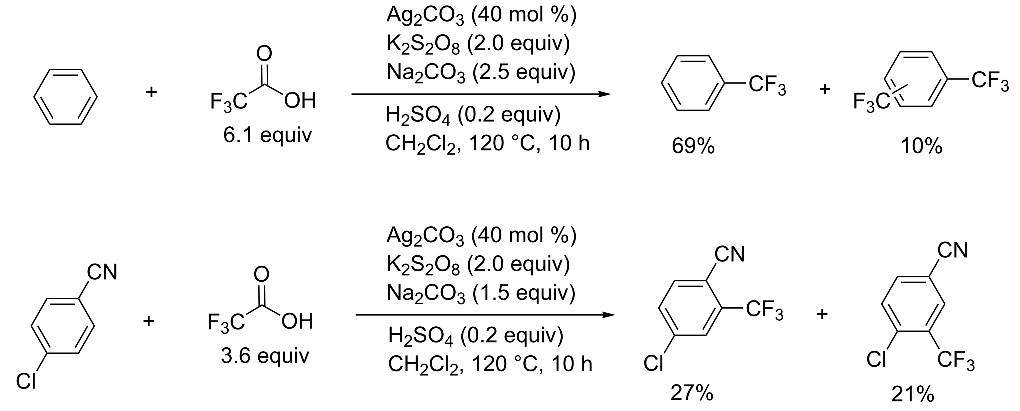


Scheme 5: Trifluoromethylation of aryl iodides with small amounts of Cu and Ag_2O. [a]The yield was determined by GC analysis. [b]The yield was determined by ^{19}F NMR analysis using CF_3CH_2OH as an internal standard.

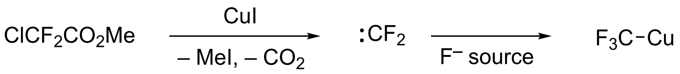
Trifluoromethylation with difluorocarbene and fluoride ions

The reaction system with $ClCF_2CO_2Me$/KF/CuI also generates CF_3Cu in situ [40,41] (Scheme 7). The demethylation of $ClCF_2CO_2Me$ proceeds by iodide, followed by decarboxylation of the resulting chlorodifluoroacetate to provide difluorocarbene (:CF_2), trapped by fluoride to give the CF_3^- species. This reacts with CuI leading to CF_3Cu.

The method described above for the trifluoromethylation of aryl iodides with $ClCF_2CO_2Me$ and fluoride can be utilized for clinical studies. Herein, we introduce one example of decarboxylative [^{18}F]trifluoromethylation for positron emission tomography (PET) studies. A synthetic methodology for [^{18}F]labelled-CF_3 arenes is desired for the application of PET imaging. The reason is that the [^{18}F] isotope has a longer half-life (110 min) than ^{13}N (10 min) or ^{15}O (2 min); however, the incorporation of [^{18}F] must be rapid and the use of the products containing [^{18}F] must be immediate. Many of the reported strategies have a limited scope of starting materials or require expensive reagents and a multistep synthesis. The [^{18}F]trifluoromethylation performed with commercially available reagents by using [^{18}F]fluoride demands no complex such as



Scheme 6: C–H trifluoromethylation of arenes using trifluoroacetic acid.



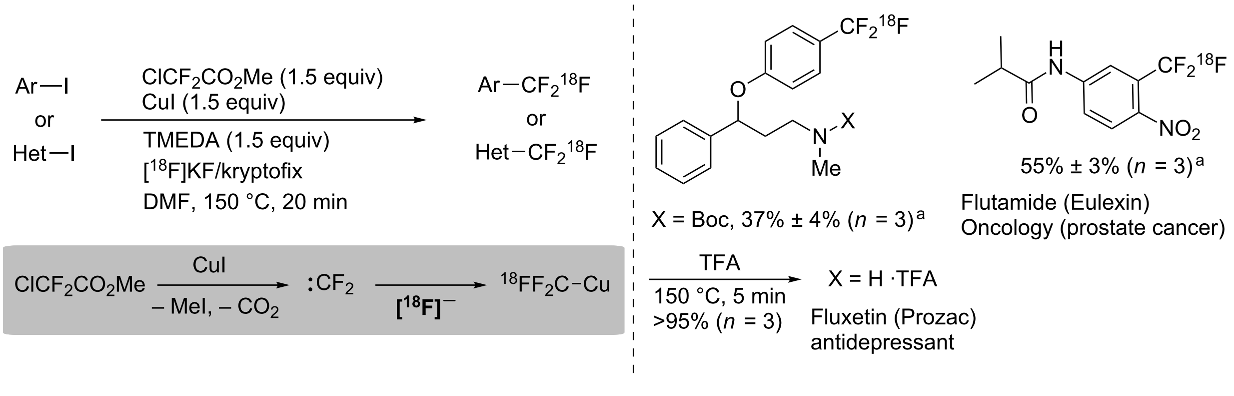
Scheme 7: CF_3Cu generated from chlorofluoroacetate and CuI.

[^{18}F]CF_2Cu, and thus the method should contribute to efficient PET imaging [42] (Scheme 8).

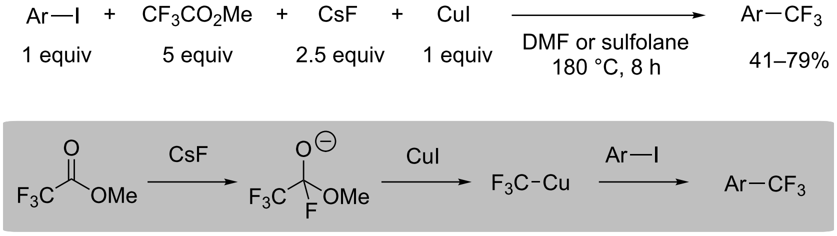
Synthesis of perfluoroalkylcopper from perfluoroalkyl ketones or esters

Langlois et al. reported that trifluoromethylation with methyl trifluoroacetate was successfully carried out in DMF or sulfolane at 180 °C [43] (Scheme 9). Methyl trifluoroacetate, which is more readily available than methyl chlorodifluoroacetate, acts as a trifluoromethylating agent. In this synthesis, the methyl trifluoroacetate/CsF/CuI system would form the tetrahedral intermediates to generate CF_3Cu species in situ. Mikami and co-workers accomplished the synthesis of CF_3Cu at room temperature with perfluoroalkyl ketone derivatives and appropriate nucleophiles. It is indicated that the CF_3Cu reagent is directly formed from tetrahedral intermediate **A** [44] (Scheme 10). The CF_3Cu reagent was applied to aromatic trifluoromethylation with aryl iodides, which have electron-withdrawing or electron-donating functional groups, in good to high yields (Scheme 11).

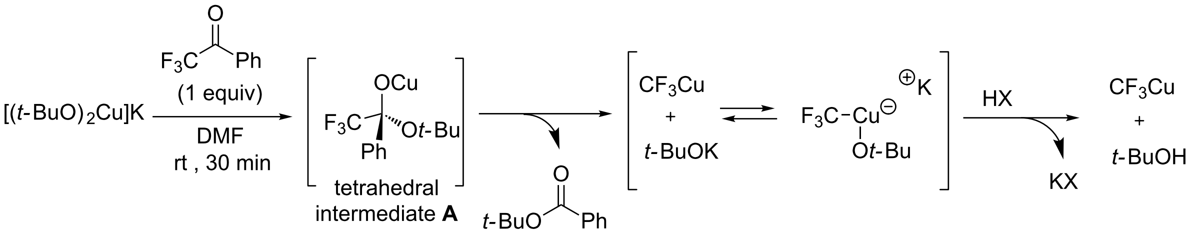
The preparation of the C_2F_5Cu reagent was investigated as well [45]. Pentafluoropropionate was reacted with CuCl salt in the presence of KO*t*-Bu to afford C_2F_5Cu. A variety of aryl bro-



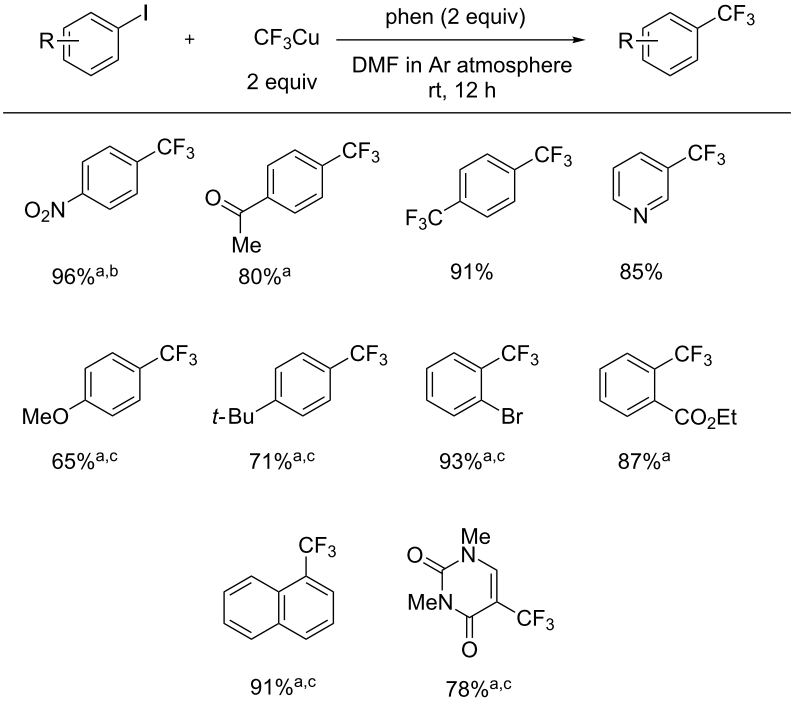
Scheme 8: [^{18}F]Trifluoromethyation with difluorocarbenes for PET. ^{a}Radiochemical yield determined by HPLC.



Scheme 9: Trifluoromethylation with trifluoroacetate and copper iodide.



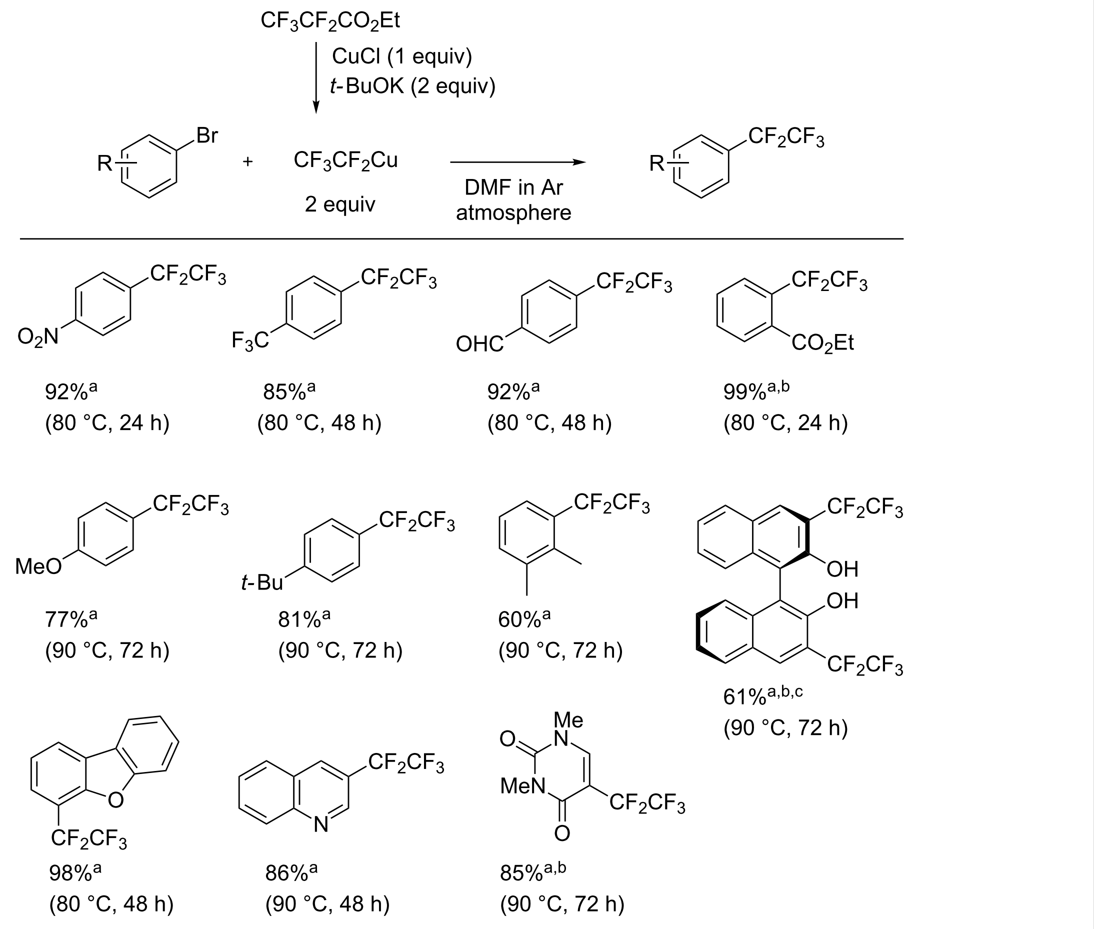
Scheme 10: Preparation of trifluoromethylcopper from trifluoromethyl ketone.



Scheme 11: Trifluoromethylation of aryl iodides. [a]Isolated yield. [b]1 equivalent each of CF_3Cu reagent and 1,10-phenanthroline were used. [c]Reaction temperature was 50 °C.

mides were reacted with C_2F_5Cu under the optimized conditions, providing pentafluoroethylated aryl products in moderate to high yield (Scheme 12).

The copper-mediated oxidative trifluoromethylation of arylboronic acids are important reactions in organic chemistry because arylboronic acids are widely used. Oxidative, aromatic



Scheme 12: Pentafluoroethylation of aryl bromides. [a]Yield was determined by ^{19}F NMR analysis using benzotrifluoride (BTF) or (trifluoromethoxy)benzene as an internal standard. [b]Isolated yield. [c]4 equivalents of CF_3CF_2Cu reagent were used.

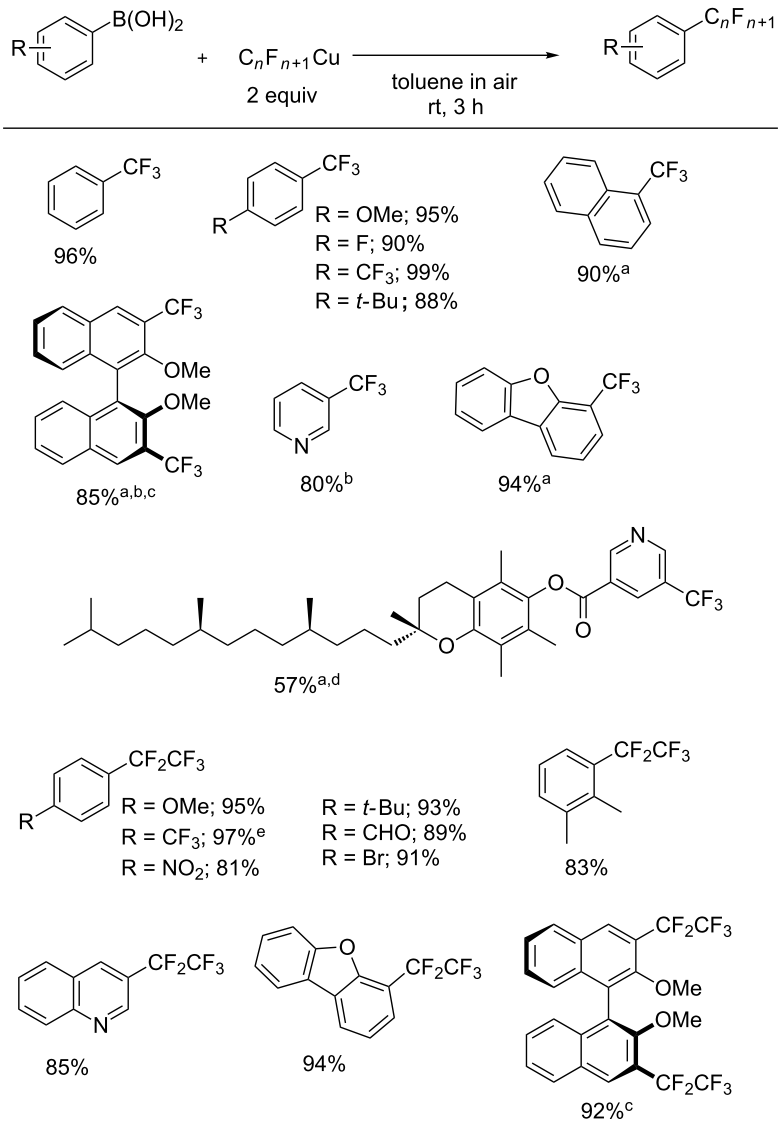
perfluoroalkylation reactions with arylboronic acid derivatives have been studied by several groups. Qing et al. and Buchwald et al. used the Ruppert–Prakash reagent (CF_3–$SiMe_3$) directly as a CF_3^- source [46,47]. From CF_3–$SiMe_3$, Hartwig et al. developed a new combination of Ir-catalyzed C–H borylation and oxidative cross-coupling using [(phen)CF_3Cu] [48]. Grushin et al. utilized fluoroform for the preparation of CF_3Cu, which participated in cross-coupling reactions with $ArB(OH)_2$ in air [49]. Starting from CF_3CO_2Et or $C_2F_5CO_2Et$, Mikami et al. obtained CF_3Cu [44] or C_2F_5Cu [45]. The substrate scope of trifluoromethylation and pentafluoroethylation suggests that CF_3Cu and C_2F_5Cu reagents are useful $C_nF_{2n+1}^-$ sources for perfluoroalkylation reactions. Furthermore, CF_3Cu and C_2F_5Cu were utilized for oxidative perfluoroalkylation reactions of arylboronic acids [44,45] (Scheme 13).

Copper-catalyzed group transfer from fluoral derivatives

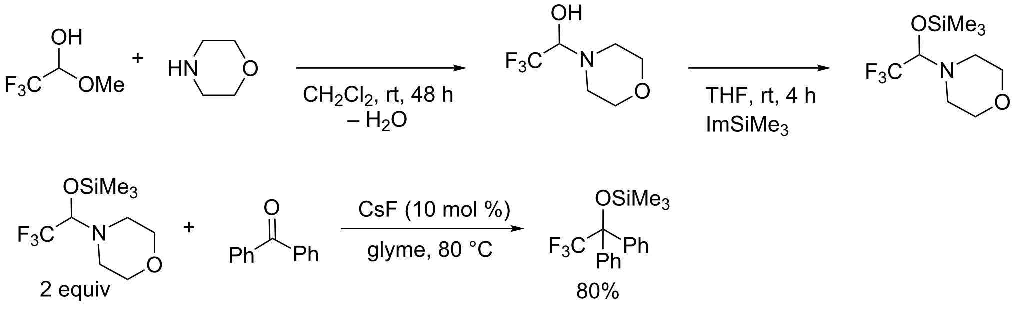
Catalytic systems in organic synthesis are desirable from an environmentally benign point of view. With regard to aromatic trifluoromethylation, the effort is devoted to reduce the copper reagents employed in the reactions. Copper-catalyzed aromatic trifluoromethylation with CF_3SiMe_3 was developed using phen as a ligand [50]. On the other hand, Billard and Langlois et al. described silylated hemiaminals of fluoral (trifluoroacetaldehyde) that act as a nucleophilic trifluoromethyl source for electrophiles such as aldehydes and ketones [51,52] (Scheme 14).

Amii and co-workers reported a copper-catalyzed aromatic trifluoromethylation from silylated hemiaminals of fluoral [53] (Scheme 15). Hemiaminal derivative **1** is readily prepared from commercially available $CF_3CH(OH)(OEt)$, which is a fluoral equivalent, and morpholine [52].

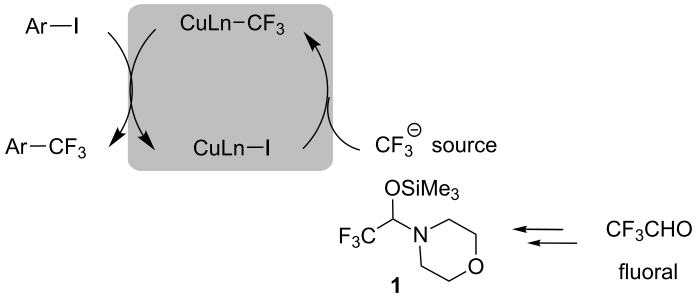
The substrate scope of the catalytic trifluoromethylation is shown in Scheme 16. Nitro, cyano, and ester groups in iodoarenes were tolerable under the reaction conditions of copper-catalyzed nucleophilic trifluoromethylation. Electron-rich iodoarenes underwent the nucleophilic trifluoromethylation to afford the corresponding trifluoromethylated benzenes.



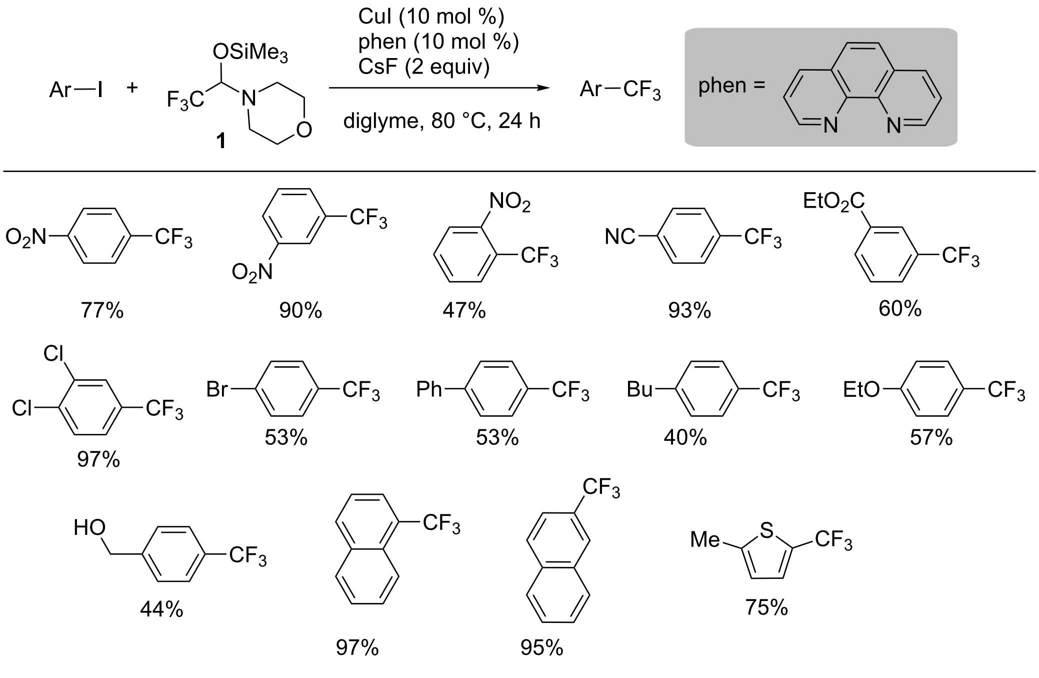
Scheme 13: Perfluoroalkylation reactions of arylboronic acids. [a]Isolated yield. [b]DMF was used instead of toluene as a solvent. [c]4 equivalents of C_nF_{n+1}Cu reagent were used. [d]Pinacolboronate ester (Bpin) was used instead of boronic acid. [e]Yield was determined by ^{19}F NMR analysis using BTF as an internal standard.



Scheme 14: Trifluoromethylation with silylated hemiaminal of fluoral.



Scheme 15: Catalytic trifluoromethylation with a fluoral derivative.



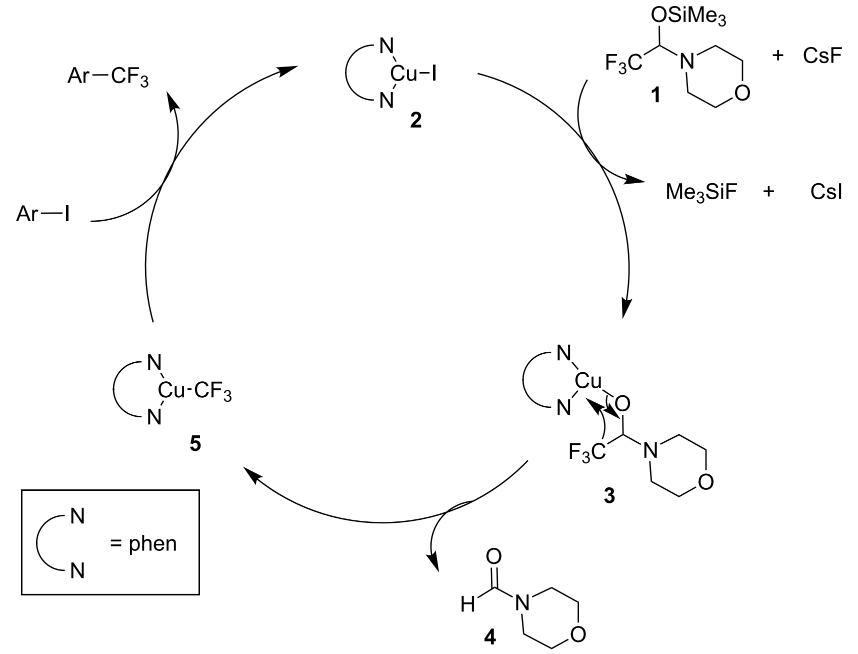
Scheme 16: The scope of Cu-catalyzed aromatic trifluoromethylation. The yield was determined by ^{19}F NMR analysis using (trifluoromethoxy)benzene as an internal standard.

Furthermore, the trifluoromethyl group was introduced into naphthalenes and thiophene with hemiaminal **1**.

A catalytic amount of copper was enough to complete the reactions. In the synthesis of trifluoromethylarenes (Ar–CF_3), the cross-coupling proceeded via the pathway shown in Scheme 17 [53]. First, the fluoride-ion-induced reaction of hemiaminal **1** with CuI-diamine complex **2** gave copper alkoxide **3**. Then the trifluoromethyl group in **3** migrates to generate the trifluoromethylcopper(I) complex **5** with the elimination of *N*-formylmorpholine (**4**) [54]. Finally, Ar–CF_3 is formed by the coupling of CF_3Cu complex **5** with Ar–I, and CuI-diamine complex **2** is regenerated.

Conclusion

Fluorine has greatly contributed to the advancement of human life and the global demand for organofluorine compounds will continue to increase. Therefore, the introduction of fluorine-containing functional groups into organic molecules is recognized as a general strategy for the design of drugs and functional materials. In fact, the research activity on selective fluorination and trifluoromethylation has reached a mature state. The progress in fluoroalkylation of organic compounds could be accelerated by the use of fluoroalkylating reagents, which are inexpensive and easy to handle. Perfluoroalkyl carboxylic acid derivatives, such as perfluoroalkyl acetates, trifluoroacetic acid, chlorodifluoroacetates, trifluoromethyl ketones and hemiami-



Scheme 17: Plausible mechanism of Cu-catalyzed aromatic trifluoromethylation [53].

nals of trifluoroacetaldehyde, are attractive perfluoroalkyl anion sources for aromatic perfluoroalkylation reactions. The generation of perfluoroalkylcopper from perfluoroalkyl carboxylic acid derivatives via carbon–carbon bond cleavage demands a high reaction temperature or basic conditions. Nevertheless, the simplicity of the operation and the reliability of higher yields would help the synthesis of fluorinated compounds in various fields.

Acknowledgements

The financial support of the Ministry of Education, Culture, Sports, Science and Technology of Japan and Japan Science and Technology Agency (JST) (ACT-C: Advanced Catalytic Transformation program for Carbon utilization) is acknowledged.

References

1. Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds: Chemistry and Application;* Springer-Verlag: Berlin, 2000. doi:10.1007/978-3-662-04164-2
2. Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications;* Wiley-VCH: Weinheim, Germany, 2004. doi:10.1002/352760393X
3. Chambers, R. D. *Fluorine in Organic Chemistry;* Blackwell: Oxford, 2004. doi:10.1002/9781444305371
4. Uneyama, K. *Organofluorine Chemistry;* Blackwell: Oxford, 2006. doi:10.1002/9780470988589
5. Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine;* John Wiley & Sons, Inc.: Hoboken, NJ, 2008. doi:10.1002/9780470281895
6. Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology;* Wiley-Blackwell: Chichester, West Sussex, 2009.
7. Gouverneur, V.; Müller, K. *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications;* World Scientific Publishing Company: London, 2012. doi:10.1142/p746
8. Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014,** *114,* 2432–2506. doi:10.1021/cr4002879
9. Lundgren, R. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010,** *49,* 9322–9324. doi:10.1002/anie.201004051
10. Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011,** *473,* 470–477. doi:10.1038/nature10108
11. Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V.-D.; Roy, S. *Tetrahedron* **2011,** *67,* 2161–2195. doi:10.1016/j.tet.2011.01.002
12. Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011,** *111,* 4475–4521. doi:10.1021/cr1004293
13. Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012,** *51,* 5048–5050. doi:10.1002/anie.201201012
14. Ye, Y.; Sanford, M. *Synlett* **2012,** *23,* 2005–2013. doi:10.1055/s-0032-1316988
15. Wu, X.-F.; Neumann, H.; Beller, M. *Chem. – Asian J.* **2012,** *7,* 1744–1745. doi:10.1002/asia.201200211
16. Jin, Z.; Hammond, G. B.; Xu, B. *Aldrichimica Acta* **2012,** *45,* 67–83.
17. Studer, A. *Angew. Chem., Int. Ed.* **2012,** *51,* 8950–8958. doi:10.1002/anie.201202624
18. Qing, F.-L. *Chin. J. Org. Chem.* **2012,** *32,* 815–824. doi:10.6023/cjoc1202021
19. Macé, Y.; Magnier, E. *Eur. J. Org. Chem.* **2012,** 2479–2494. doi:10.1002/ejoc.201101535
20. García-Monforte, M. A.; Martínez-Salvador, S.; Menjón, B. *Eur. J. Inorg. Chem.* **2012,** 4945–4966. doi:10.1002/ejic.201200620
21. Liu, T.; Shen, Q. *Eur. J. Org. Chem.* **2012,** 6679–6687. doi:10.1002/ejoc.201200648

22. Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013,** *355,* 617–626. doi:10.1002/adsc.201200764
23. Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013,** *52,* 8214–8264. doi:10.1002/anie.201206566
24. Wang, H.; Vicic, D. A. *Synlett* **2013,** *24,* 1887–1898. doi:10.1055/s-0033-1339435
25. Browne, D. L. *Angew. Chem., Int. Ed.* **2014,** *53,* 1482–1484. doi:10.1002/anie.201308997
26. Zhang, C. *Org. Biomol. Chem.* **2014,** *12,* 6580–6589. doi:10.1039/C4OB00671B
27. Sodeoka, M.; Egami, H. *Pure Appl. Chem.* **2014,** *86,* 1247–1256. doi:10.1515/pac-2013-1202
28. Xu, J.; Liu, X.; Fu, Y. *Tetrahedron Lett.* **2014,** *55,* 585–594. doi:10.1016/j.tetlet.2013.11.108
29. Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015,** *115,* 650–682. doi:10.1021/cr500223h
30. Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015,** *115,* 683–730. doi:10.1021/cr400473a
31. Ni, C.; Hu, M.; Hu, J. *Chem. Rev.* **2015,** *115,* 765–825. doi:10.1021/cr5002386
32. Alonso, C.; Martinez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015,** *115,* 1847–1935. doi:10.1021/cr500368h
33. Matsui, K.; Tobita, R.; Ando, M.; K., K. *Chem. Lett.* **1981,** *10,* 1719–1720. doi:10.1246/cl.1981.1719
34. Carr, G. E.; Chambers, R. D.; Holmes, T. F.; Parker, D. G. *J. Chem. Soc., Perkin Trans. 1* **1988,** 921–926. doi:10.1039/p19880000921
35. Nakamura, Y.; Uneyama, K. *J. Org. Chem.* **2007,** *72,* 5894–5897. doi:10.1021/jo070721h
36. Chen, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013,** *52,* 11628–11631. doi:10.1002/anie.201306094
37. McReynolds, K. A.; Lewis, R. S.; Ackerman, L. K. G.; Dubinina, G. G.; Brennessel, W. W.; Vicic, D. A. *J. Fluorine Chem.* **2010,** *131,* 1108–1112. doi:10.1016/j.jfluchem.2010.04.005
38. Li, Y.; Chen, T.; Wang, H.; Zhang, R.; Jin, K.; Wang, X.; Duan, C. *Synlett* **2011,** 1713–1716. doi:10.1055/s-0030-1260930
39. Shi, G.; Shao, C.; Pan, S.; Yu, J.; Zhang, Y. *Org. Lett.* **2015,** *17,* 38–41. doi:10.1021/ol503189j
40. MacNeil, J. G., Jr.; Burton, D. J. *J. Fluorine Chem.* **1991,** *55,* 225–227. doi:10.1016/S0022-1139(00)80126-8
41. Su, D.-B.; Duan, J.-X.; Chen, Q.-Y. *Tetrahedron Lett.* **1991,** *32,* 7689–7690. doi:10.1016/0040-4039(91)80566-O
42. Huiban, M.; Tredwell, M.; Mizuta, S.; Wan, Z.; Zhang, X.; Collier, T. L.; Gouverneur, V.; Passchier, J. *Nat. Chem.* **2013,** *5,* 941–944. doi:10.1038/nchem.1756
43. Langlois, B. R.; Roques, N. *J. Fluorine Chem.* **2007,** *128,* 1318–1325. doi:10.1016/j.jfluchem.2007.08.001
44. Serizawa, H.; Aikawa, K.; Mikami, K. *Chem. – Eur. J.* **2013,** *19,* 17692–17697. doi:10.1002/chem.201303828
45. Serizawa, H.; Aikawa, K.; Mikami, K. *Org. Lett.* **2014,** *16,* 3456–3459. doi:10.1021/ol501332g
46. Chu, L.; Qing, F.-L. *Org. Lett.* **2010,** *12,* 5060–5063. doi:10.1021/ol1023135
47. Senecal, T. D.; Parsons, A. T.; Buchwald, S. L. *J. Org. Chem.* **2011,** *76,* 1174–1176. doi:10.1021/jo1023377
48. Litvinas, N. D.; Fier, P. S.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012,** *51,* 536–539. doi:10.1002/anie.201106668
49. Novák, P.; Lishchynskyi, A.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2012,** *51,* 7767–7770. doi:10.1002/anie.201201613
50. Oishi, M.; Kondo, H.; Amii, H. *Chem. Commun.* **2009,** 1909–1911. doi:10.1039/b823249k
51. Billard, T.; Bruns, S.; Langlois, B. R. *Org. Lett.* **2000,** *2,* 2101–2103. doi:10.1021/ol005987o
52. Billard, T.; Langlois, R. B.; Blond, G. *Tetrahedron Lett.* **2000,** *41,* 8777–8780. doi:10.1016/S0040-4039(00)01552-5
53. Kondo, H.; Oishi, M.; Fujiwara, K.; Amii, H. *Adv. Synth. Catal.* **2011,** *353,* 1247–1252. doi:10.1002/adsc.201000825
54. Folléas, B.; Marek, I.; Normant, J.-F.; Saint-Jalmes, L. *Tetrahedron* **2000,** *56,* 275–283. doi:10.1016/S0040-4020(99)00951-5

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doi:10.3762/bjoc.11.286

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Enantioselective additions of copper acetylides to cyclic iminium and oxocarbenium ions

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Review

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Keywords:
catalysis; copper; enantioselectivity; iminium ion; oxocarbenium ion

Beilstein J. Org. Chem. **2015,** *11,* 2696–2706.
doi:10.3762/bjoc.11.290

Received: 16 September 2015
Accepted: 04 December 2015
Published: 22 December 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

The development of enantioselective, copper-catalyzed alkynylations of cyclic iminium and oxocarbenium ions is reviewed. The use of chiral copper-based catalysts has enabled high yields and enantioselectivites in the formation of nitrogen- and oxygen-containing heterocycles with α-stereogenic centers. This review highlights both the accomplishments and the future work needed in this important area.

Introduction

Nitrogen and oxygen heterocycles with α-stereogenic centers represent important classes of biologicially active compounds [1-7]. Enantioselective addition of chiral nucleophiles to imines, iminium ions, carbonyls, or oxocarbenium ions provides efficient access to these scaffolds. In particular, exceptional progress has been made in the addition of chiral metal acetylides. Historically, these reactions required stoichiometric amounts of both metal and chiral ligand [8], but catalytic variants are now available with a variety of metal-based catalysts [9-15]. Among these, chiral copper catalysts have been used with remarkable success in the alkynylation of cyclic iminium ion and oxocarbenium ion intermediates. This review will focus on the development of these enantioselective, copper-catalyzed alkynylations, highlighting both the accomplishments and the future work needed in this important area.

Throughout the discussion below, it is clear that there are privileged ligand architectures of these copper-catalyzed alkynylations. High enantioselectivities have been achieved with pyridine bis(oxazoline) (Pybox), bis(oxazoline) (Box), and Quinap-type ligands (Figure 1).

Review

Additions to iminium ions

Although this review will focus on enantioselective additions to cyclic electrophiles, it is worth noting that the first enantiose-

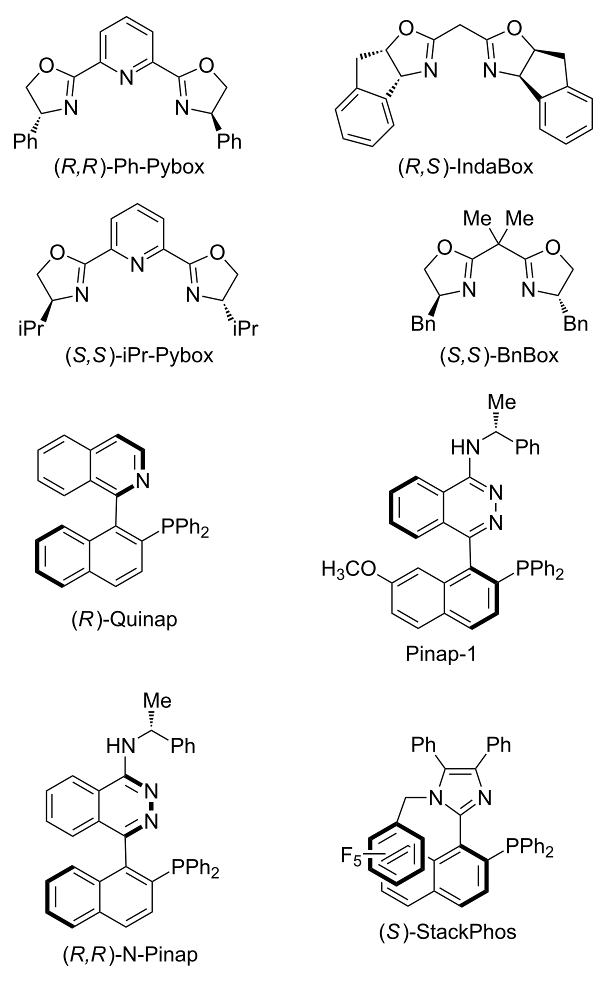
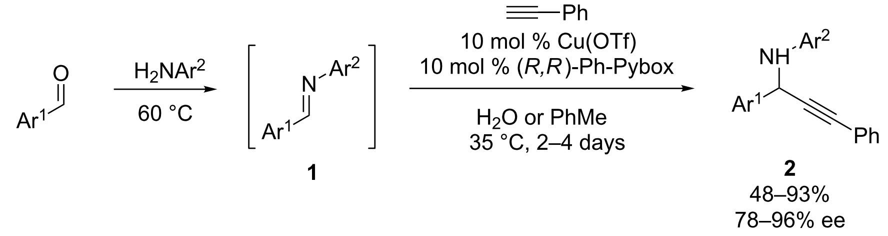


Figure 1: Chiral ligands utilized in copper-catalyzed alkynylations of cyclic iminium and oxocarbenium ions.

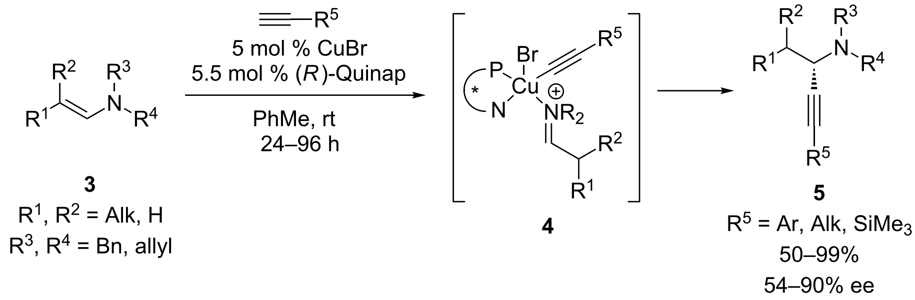
lective additions of chiral copper acetylides to imines or iminium ions utilized acyclic imine substrates. In 2002, Li and co-workers reported enantioselective alkynylations of *N*-aryl aldimines formed in situ from benzaldehydes and anilines (Scheme 1) [16,17]. This reaction employs a CuOTf/Ph-Pybox catalyst system to achieve generally high yields and ee's of propargylic amines **2**. Notably, this reaction can be carried out in H_2O, as well as PhMe. Nearly simultaneously, Knochel's group reported an enantioselective CuBr/Quinap-catalyzed alkynylation to deliver propargylic amines with alkyl substitution at the stereocenter (Scheme 2) [18-20]. In this reaction, proton transfer from the terminal alkyne to the enamine simultaneously generates the copper acetylide and iminium ion, which are proposed to both bind to the chiral copper catalyst (see **4**). A broad scope in the acetylene was observed, with arylalkynes resulting in the highest ee's. To our knowledge, these were the first enantioselective, metal-catalyzed additions of terminal alkynes to imines or iminium ions, and set the stage for subsequent development of enantioselective alkynylations of cyclic iminium ion substrates [21]. As discussed below, the catalyst systems identified in these reactions have largely informed those used for enantioselective alkynylations of cyclic electrophiles.

The first enantioselective, copper-catalyzed alkynylation of a cyclic iminium ion was reported by Li's research group in 2004 [22]. Building on their development of a cross-dehydrogenative coupling (CDC) reaction between benzylic amines and alkynes to deliver racemic products [23], the Li group developed a CuOTf/Ph-Pybox catalyst system that enables alkynylation of tetrahydroisoquinolines in moderate to good yields and enantioselectivies (Scheme 3). A particularly powerful aspect of this chemistry is that a stable tetrahydroisoquinoline **6** can be utilized as the substrate. Oxidation of the tetrahydroisoquinoline then results in formation of iminium ion **7** in situ. As in Knochel's reaction above, the highest yields and ee's were observed with arylacetylenes.

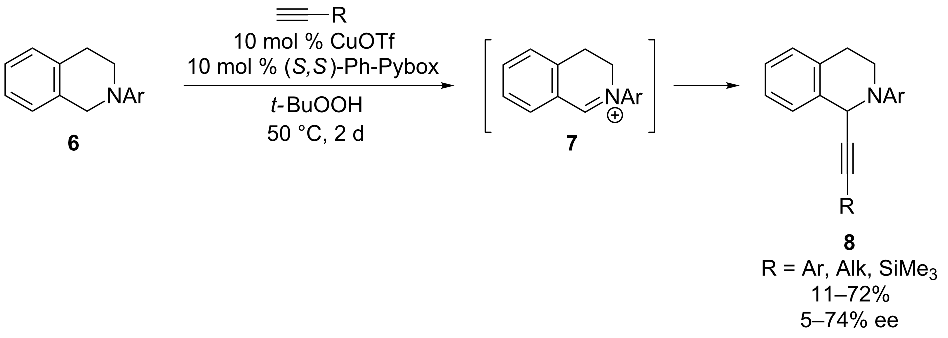
In subsequent studies of this reaction, Li investigated the intermediacy of isoquinolinium ion **9**, and found that improved yields and ee's can be achieved using this substrate and a CuBr/Quinap catalyst, despite the fact that Quinap had proven inferior to Ph-Pybox in the CDC reaction (Scheme 4) [24]. With this new catalyst and electrophile, the catalyst loading, reaction temperature, and reaction time could be reduced. Addition of alkynes with aryl, alkyl and trimethylsilyl substituents were successful, with the highest enantioselectivity observed when (trimethylsilyl)acetylene was used (94% ee).



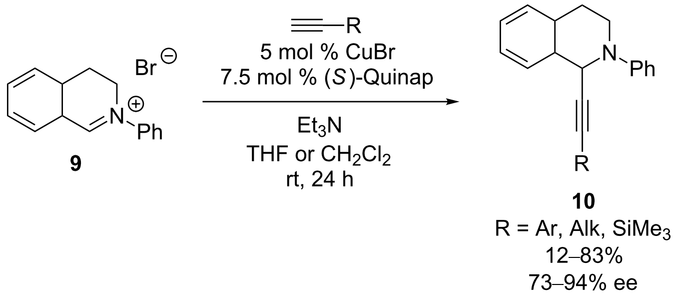
Scheme 1: Li's alkynylation of acyclic *N*-arylimines.



Scheme 2: Knochel's alkylation of acyclic *N*-alkylenamines.



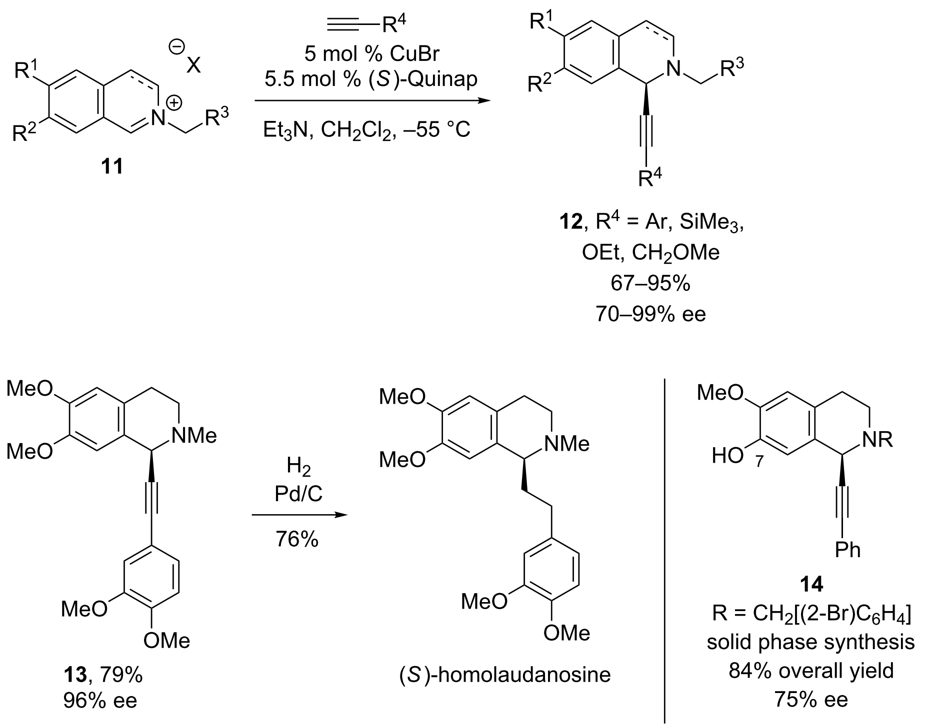
Scheme 3: Li's CDC of tetrahydroisoquinolines and alkynes.



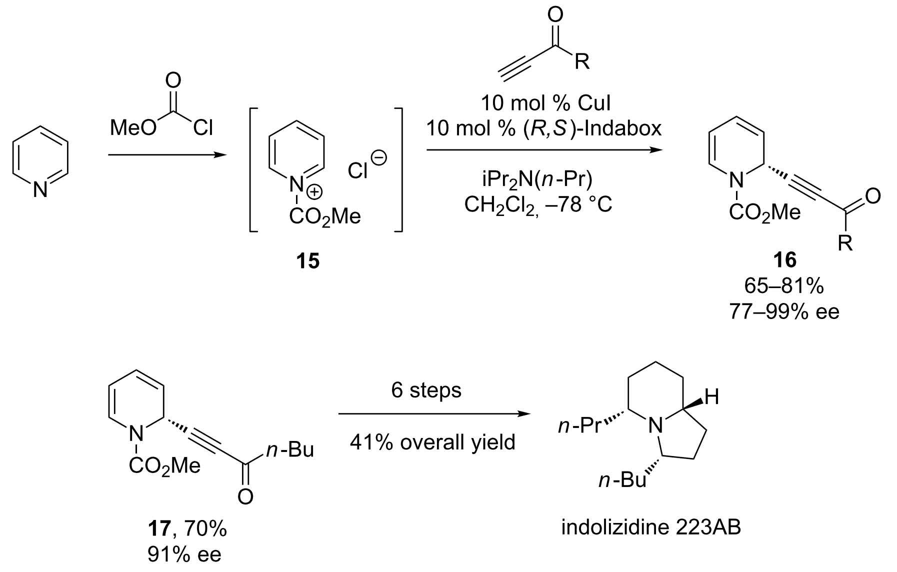
Scheme 4: Li's alkynylation of *N*-aryldihydroisoquinolinium ions.

Just before Li's report of the alkynlation of *N*-arylisoquinolinium ions, Taylor and Schreiber reported a CuBr/Quinap-catalyzed alkynylation of *N*-alkylisoquinolinium ions (Scheme 5) [25]. Similar to Li's alkynylation of *N*-arylisoquinolinium ions, alkynes with various substituents can be used successfully, and the highest ee's were observed when (trimethylsilyl)acetylene was used (99% ee). Most of the iminium ion substrates were dihydroisoquinolinium ions, but alkynylation of the aromatic isoquinolinium ion was also achieved in 67% yield and 83% ee at a higher reaction temperature (−20 °C). The authors elegantly showed the potential of this reaction in two examples. First, they reduced alkyne **13** to deliver (*S*)-homolaudanosine, a natural product from an alkaloid family with neurologic activity, in high yield and enantiopurity. They also demonstrated that this alkynylation is amenable to solid phase synthesis; alkyne **14** was prepared by alkynylation of an isoquinolinium ion linked to a polystyrene bead through the C7 hydroxy group.

In 2007, Ma and co-workers reported the first enantioselective, copper-catalyzed alkynylation of a pyridinium ion (Scheme 6) [26]. This reaction employs an *N*-acylpyridinium ion generated



Scheme 5: Schreiber's alkynylation of *N*-alkylisoquinolinium ions.



Scheme 6: Ma's alkynylation of pyridium ions.

in situ and a CuI/Indabox catalyst. Ma found that the identity of base and solvent also affect the enantioselectivity, with $iPr_2N(n\text{-}Pr)$ and CH_2Cl_2 proving best. Notably, only 1,2-addition was observed. With respect to the alkyne, activated terminal acetylenes, such as ynones and propriolates, are best for this reaction. Unactivated alkynes give products in reasonable yields (63–77%), but poor enantioselectivities (1–11% ee). However, the use of activated acetylenes provides a functional group handle for elaboration, which the authors demonstrate in the preparation of indolizidine 223AB.

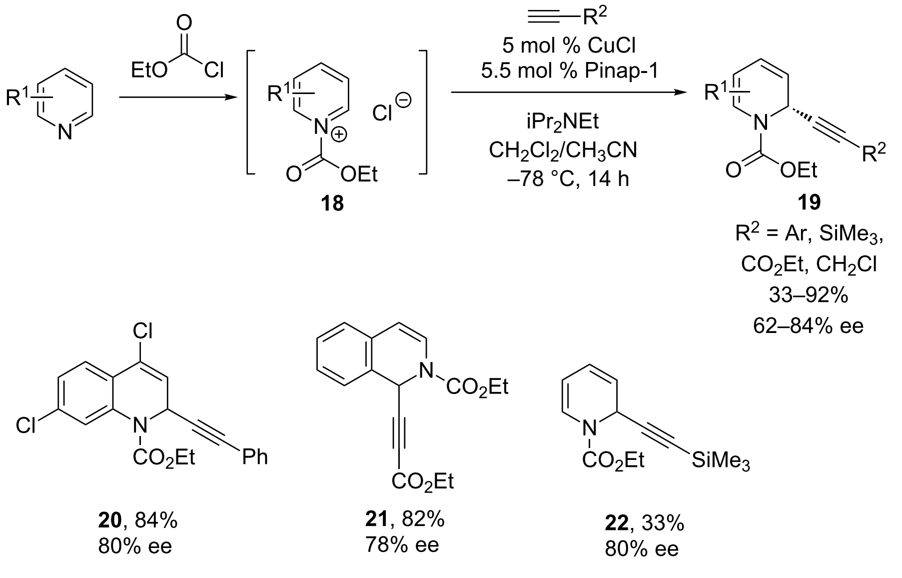
Building on their initial discovery of a non-asymmetric, copper-catalyzed, three-component coupling of pyridine, benzoyl chloride and phenylacetylene [27], the Arndtsen group tackled the challenge of developing a catalyst for the alkynylation of cyclic *N*-acyliminium ions with unactivated alkynes [28]. Using the reaction of *N*-acylquinoline and phenylacetylene as their model, they observed lower ee's with Pybox and Box ligands, and only 49% ee with Quinap. However, investigation of novel Pinap ligands led to notably higher ee's (Scheme 7) [29]. These reaction conditions enable alkynylation of quinoline (**20**), isoquinoline (**21**), and pyridine (**22**) substrates, albeit in lower yields with pyridines.

In 2011, Maruoka and co-workers investigated the use of isoquinolinium ions protected as azomethine imines [30]. The use of a CuOAc/Ph-Pybox catalyst enables the addition of a wide variety of alkynes to form isoquinolines with tertiary stereocenters in high yields and ee's (Scheme 8A). Although lower ee's were observed with *o*-tolylacetylene (43% ee) and 1-heptyne (75% ee), all other alkynes resulted in ≥85% ee. Even more impressive, the authors discovered conditions for a highly enantioselective alkynylation to form tetrasubstituted stereocenters. With 1-alkylisoquinolinium ions, high ee's could not be achieved using only a CuOAc/Ph-Pybox catalyst. Postulating that the acetate of CuOAc may facilitate proton transfer from the alkyne to the azomethine imine, a necessary step to form both the cationic iminium and the copper acetylide, Maruoka investigated the use of a chiral acid co-catalyst. With the addition of chiral Brønsted acid co-catalyst **27**, high yields and good to excellent levels of enantioselectivity were achieved in the addition of both aryl and aliphatic alkynes (Scheme 8B). The azomethine amine products **24** and **26** can be deprotected using SmI_2. To our knowledge, this report is the first and only example to date of alkynylation of an imine or iminium ion to form a chiral tetrasubstituted center with high ee.

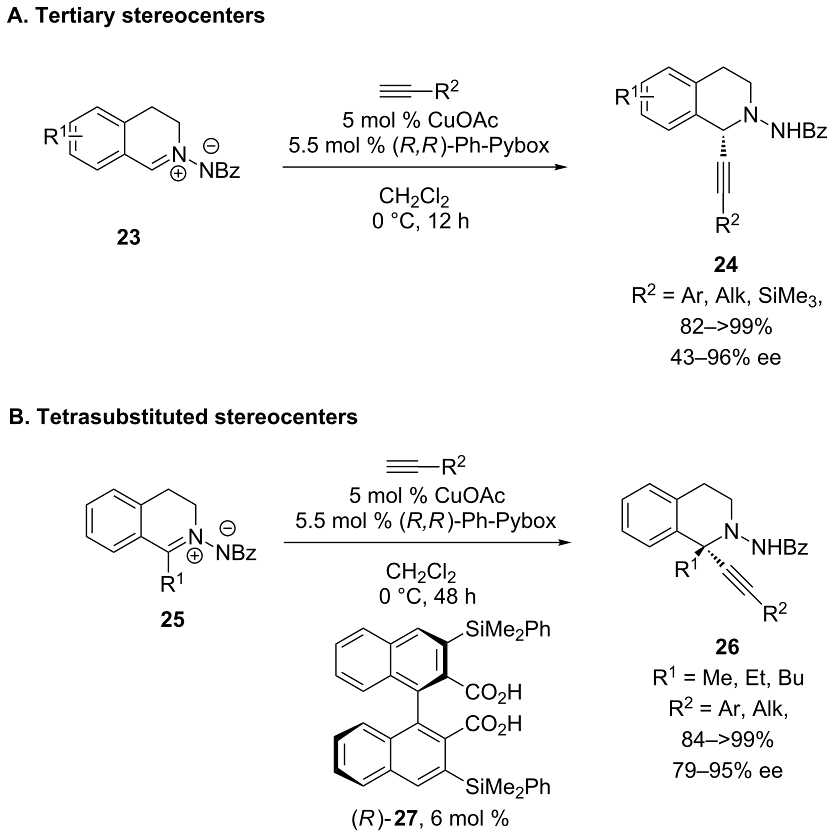
Enantioselective, copper-catalyzed alkynylations have also been accomplished under solvent-free conditions. In 2013, Su and co-workers established that the CDC reaction of *N*-aryltetrahydroisoquinolines and alkynes can be accomplished under high-speed ball-milling conditions with copper balls (Scheme 9) [31]. Under these solvent-free reaction conditions, isoquinolines **28** were formed more quickly than the in-solvent reactions previously reported, but the ee's are lower.

Recently, a new entry to isoquinolinium ions has been established. In their studies of the three-component coupling of aldehydes, amines, and alkynes (A^3 reaction), the Ma group serendipitiously discovered that isomerization of exocyclic iminium ion **30** results in the formation of endocyclic iminium ion **31** (Scheme 10) [32]. Subsequent alkynylation was accomplished using a CuI/N-Pinap catalyst to give *N*-benzylisoquinolines in exceptional yields and enantioselectivities. Notably, catalytic benzoic acid is necessary to achieve high yields. The authors hypothesize that this acid additive facilitates the iminium ion isomerization.

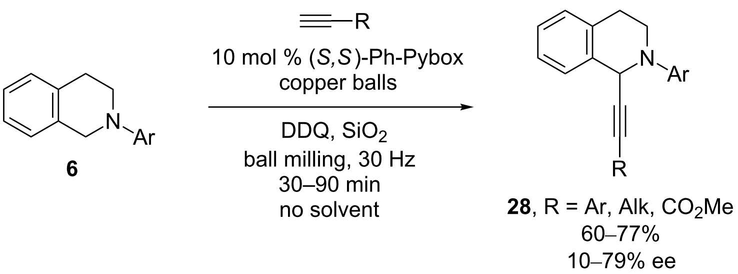
This year, several examples of improved conditions for CDC reactions have been reported. With the emergence of photoredox catalysis as a powerful technique for organic syn-



Scheme 7: Arndtsen's alkynylation of cyclic iminium ions.



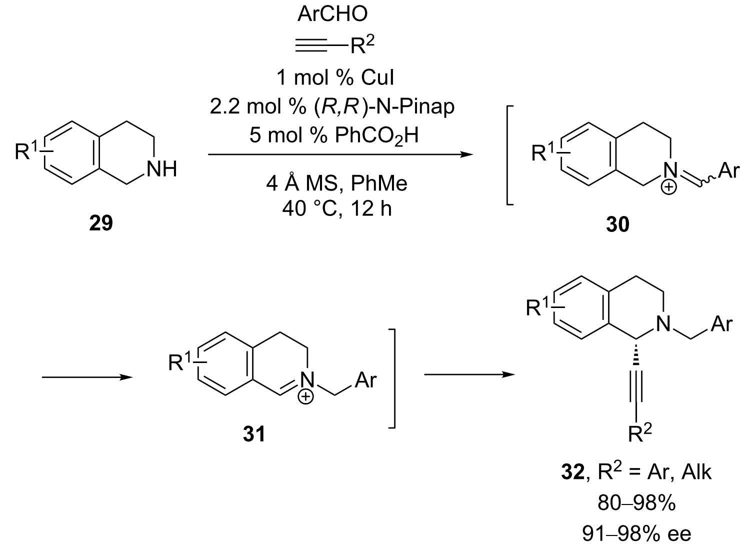
Scheme 8: Maruoka's alkynylation of azomethine imines.



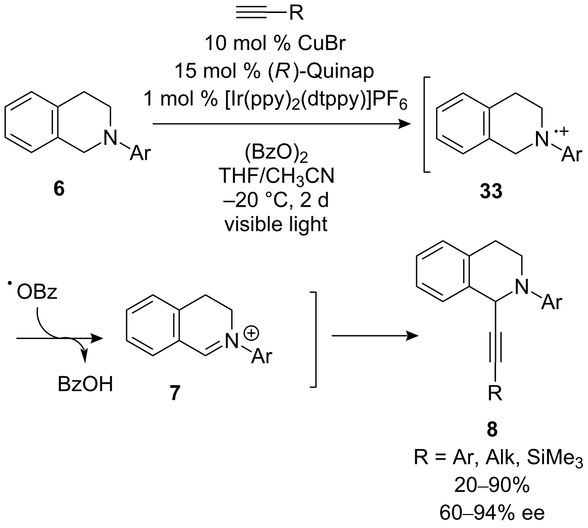
Scheme 9: Su's CDC of tetrahydroisoquinolines and alkynes under ball milling conditions.

thesis, Li's research group has discovered improved conditions for the CDC reaction of *N*-aryltetrahydroisoquinolines with alkynes (Scheme 11) [33]. By using an iridium-based photoredox catalyst in combination with benzoyl peroxide, iminium ion **7** is formed in situ. This strategy enables reduction of the reaction temperature, ultimately enabling higher enantioselectivities. With respect to the scope of alkynes, high ee's were observed with both aryl- and alkylacetylenes, but lower yields were seen with alkylacetylenes. In addition, (trimethylsilyl)acetylene can be used but in lower yield and ee (40%, 60% ee).

Also in 2015, Liu and co-workers have discovered conditions that enable the use of *N*-carbamoyltetrahydroisoquinolines in CDC reactions with alkynes (Scheme 12) [34]. These reactions utilize a CuBr/iPr-Pybox catalyst with 2,2,6,6-tetramethylpiperidine *N*-oxide as the oxidant. Liu's mechanistic experiments indicate that the reaction likely proceeds via hemiaminal **35**, formed via oxidation to an iminium ion and subsequent trapping by either EtOH or H_2O. With respect to the substrate scope, addition of arylalkynes proceeds in high yields and ee's, including those with some heteroaryl groups (**37**). Enynes can also be added, but result in lower yields and ee's, as do octyne



Scheme 10: Ma's A^3-coupling.



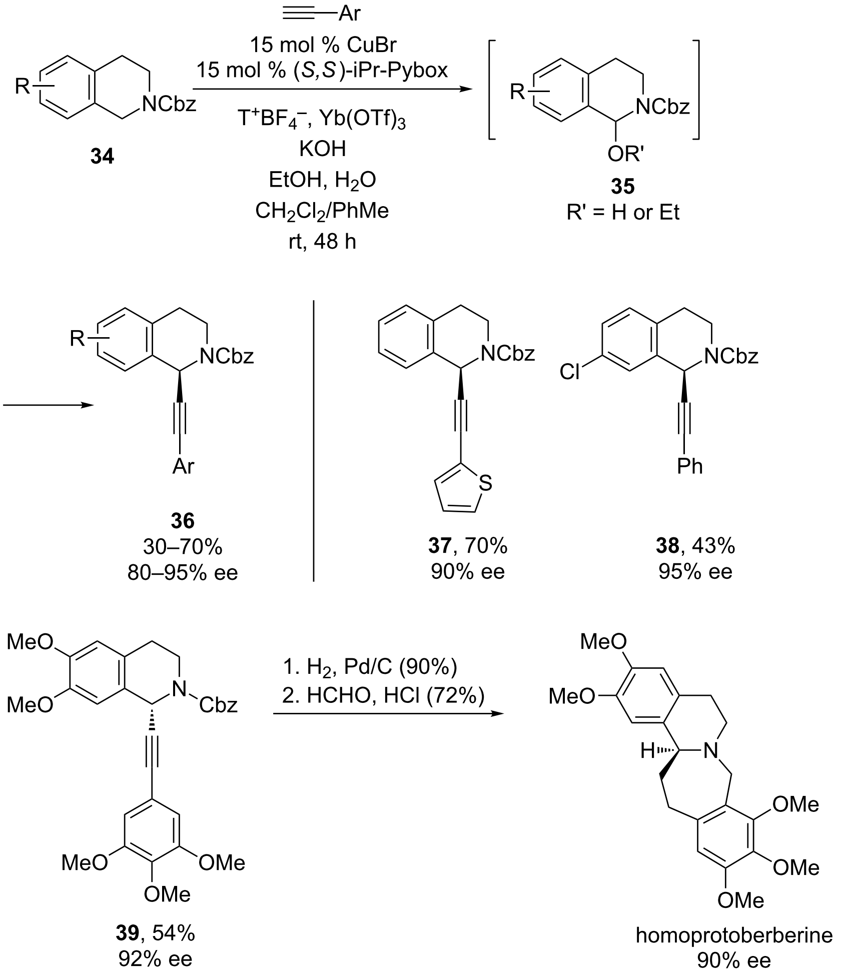
Scheme 11: Li's CDC reaction using photoredox catalysis.

and methyl propriolate. A variety of substituents are tolerated on the isoquinoline, including halides, which provides a handle for further manipulation. Furthermore, the Cbz group can be easily removed via hydrogenation, as demonstrated in Liu's efficient synthesis of homoprotoberberine.

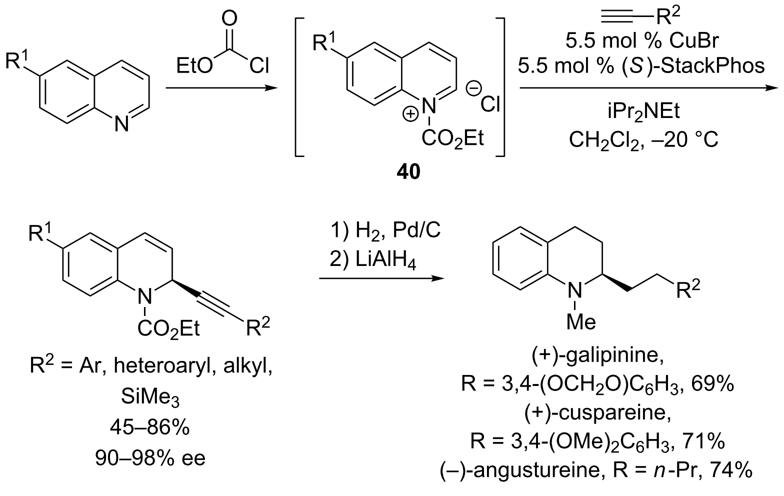
Very recently, Aponick's group reported the use of a new P,N ligand, StackPhos, for enantioselective alkynylations of quinolinium ions [35]. They hypothesized that their imidazole-based P,N ligand would provide a different bite angle than Quinap or Pinap ligands and thus enable higher ee's than previously obtained in the alkynylation of these challenging aromatic iminium ions [28]. Indeed, the CuBr/StackPhos catalyst provides generally high yields and exceptional levels of enantioselectivity in the alkynylation of *N*-carbamoylquinolinium ions **40** (Scheme 13). A broad scope was observed with the alkyne partner; additions of alkynes with aryl, heteroaryl, alkyl, and trimethylsilyl substituents result in 90–98% ee. The synthetic utility of these products, as well as their absolute configuration, was demonstrated by their reduction to the natural products (+)-galipinine, (+)-cuspareine, and (−)-angustureine.

Additions to oxocarbenium ions

Similar to the development of enantioselective, metal-catalyzed alkynylations of iminium ions, enantioselective alkynylations of cyclic oxocarbenium ions were preceded by enantioselective alkynylations of acyclic aldehyde and ketone substrates [36-54]. In particular, seminal reports by the Carreira lab demonstrated that the use of stoichiometric metal acetylides was not required to achieve addition to aldehydes; catalytic $Zn(OTf)_2$ and *N*-methylephedrine in combination with Et_3N enabled in situ formation of chiral zinc acetylides, which underwent addition to aldehydes in good yields and high enantioselectivities (Scheme 14) [38]. Since this report, a variety of metal catalysts, including copper-based catalysts [36,37,50-52], have been employed in enantioselective alkynylations of aldehydes and ketones [36-54]. However, in contrast to the efforts made in enantioselective, metal-catalyzed additions to cyclic iminium ions, much less attention has been focused on analogous reactions of cyclic oxocarbenium ions. Given the precedent in alkynylations of aldehydes and ketones, as well as the alkynyla-

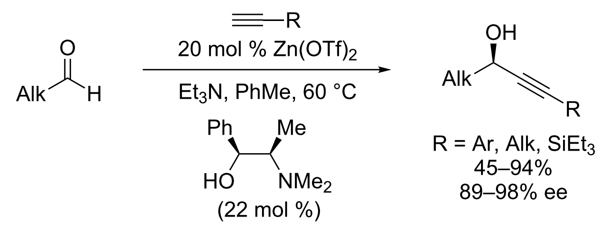


Scheme 12: Liu's CDC reaction of *N*-carbamoyltetrahydroisoquinolines. $T^+BF_4^-$ = 2,2,6,6-tetramethylpiperidine *N*-oxide tetrafluoroborate.



Scheme 13: Aponick's alkynylation of *N*-carbomoylquinolinium ions using StackPhos as ligand.

tions of iminium ions discussed above, we have pursued the development of enantioselective, metal-catalyzed alkynylation of cyclic oxocarbenium ion intermediates. In the course of these studies, we have found that copper-based catalysts are uniquely effective in promoting these alkynylations in good yields and ee's.

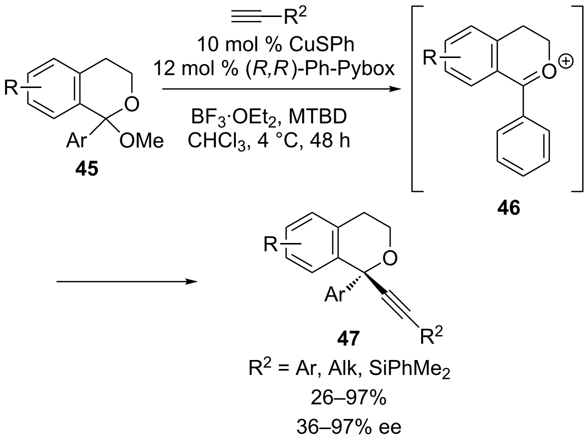


Scheme 14: Carreira's enantioselective, catalytic alkynylation of aldehydes.

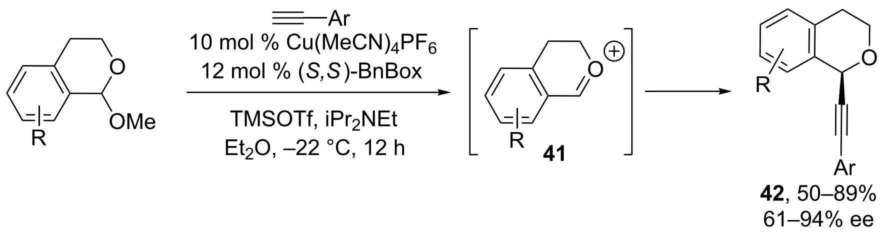
In 2011, we reported the first example of enantioselective alkynylation of a cyclic oxocarbenium ion intermediate (Scheme 15) [55]. Isochroman oxocarbenium ion **41** was formed in situ via Lewis acid-mediated ionization of a racemic acetal precursor. By using a Cu(MeCN)$_4$PF$_6$/BnBox catalyst, moderate to high yields and enantioselectivities were achieved in the addition of arylalkynes. Both yields and ee's drop with vinyl- or alkylalkynes.

Recently, we have demonstrated that enantioselective, copper-catalyzed alkynylations of oxocarbenium ions derived from chromene acetals **43** can also be achieved in high yields and ee's (Scheme 16) [56]. In this case, the reaction concentration has a significant impact on the enantioselectivity. We also observed that the alkynylation of chromene acetals with electron-donating substituents proceeds in higher ee's than less electron-rich substrates, suggesting that more stable oxocarbenium ions result in more selective reactions, potentially because they lead to later enantiodetermining transition states.

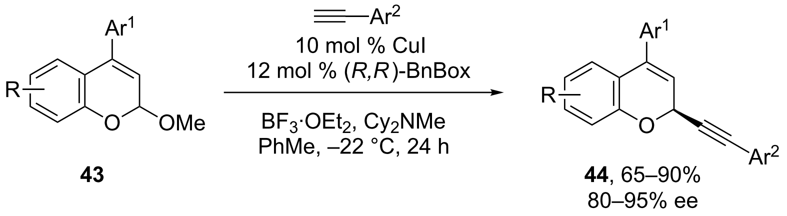
We have also discovered a CuSPh/Ph-Pybox catalyst that enables the formation of diaryl, tetrasubstituted stereocenters via an enantioselective alkynylation reaction (Scheme 17) [57].



Scheme 17: Watson's alkynylation to set diaryl tetrasubstituted stereocenters.



Scheme 15: Watson's alkynylation of isochroman oxocarbenium ions.



Scheme 16: Watson's alkynylation of chromene oxocarbenium ions.

Remarkably, by tethering one aryl group to the oxygen atom, the two faces of oxocarbenium ion **46** can be distinguished by the catalyst. In general, excellent yields and enantioselectivities were observed, although lower yields and ee's are seen with certain aliphatic alkynes. The addition of (dimethylphenylsilyl)acetylene proceeds in 53% yield and 81% ee, providing a silylalkyne that can be readily deprotected in quantitative yield for further elaboration. Notably, comparison of the ee of ligand vs ee of product revealed a significant positive nonlinear effect, indicting that catalyst aggregation occurs under these reaction conditions [58]. It is unclear at this point, whether these catalyst aggregates are on or off the catalytic cycle.

Conclusion

As described above, highly enantioselective, copper-catalyzed alkynylations of cyclic iminium and oxocarbenium ion intermediates have been achieved. α-Chiral piperidines, quinolines, isoquinolines, and benzopyrans are accessible via these reactions. The utility of these alkyne-substituted products has been demonstrated via elaboration to biologically active natural products. As evidenced by the most recent reports, particularly for iminium ions, progress is on-going to determine stable precursors to the requisite iminium ion intermediates and to identify readily removed protecting groups.

Given the potential of enantioselective, copper-catalyzed alkynylations to deliver important scaffolds, significant effort is still required to develop this class of reactions. In particular, all cyclic iminium and oxocarbenium ions utilized to date have been limited to those that form stabilized cationic intermediates (benzylic or aromatic). With few exceptions, the vast majority lack β-hydrogens, so competitive elimination reactions are not possible. Conditions to enable the use of non-stabilized iminium and oxocarbenium ions with β-hydrogens would represent an exceptional advance in this field and allow access to a wide variety of useful compounds.

In addition, little is understood about how these chiral copper catalysts provide high levels of enantioselectivity. This lack is likely due to the multiple possibilities for copper acetylide structures (monomer, dimer, dicopper acetylide, etc.) [18,59-65]. Careful mechanistic studies to elucidate the structures of chiral copper acetylides and to provide stereochemical rationale for the enantioselectivities of these reactions is needed to enable further development of catalysts in this important area.

Acknowledgements

Acknowledgement is gratefully made to the National Science Foundation (CAREER CHE 1151364) for support of this research.

References

1. Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004,** *104,* 3341–3370. doi:10.1021/cr030692k
2. Bentley, K. W. *Nat. Prod. Rep.* **2004,** *21,* 395–424. doi:10.1039/b212259f
3. Daly, J. W. *J. Med. Chem.* **2003,** *46,* 445–452. doi:10.1021/jm0204845
4. Albrecht, U.; Lalk, M.; Langer, P. *Bioorg. Med. Chem.* **2005,** *13,* 1531–1536. doi:10.1016/j.bmc.2004.12.031
5. TenBrink, R. E.; Bergh, C. L.; Duncan, J. N.; Harris, D. W.; Huff, R. M.; Lahti, R. A.; Lawson, C. F.; Lutzke, B. S.; Martin, I. J.; Rees, S. A.; Schlachter, S. K.; Sih, J. C.; Smith, M. W. *J. Med. Chem.* **1996,** *39,* 2435–2437. doi:10.1021/jm960084f
6. Xu, J.; Kjer, J.; Sendker, J.; Wray, V.; Guan, H.; Edrada, R.; Müller, W. E. G.; Bayer, M.; Lin, W.; Wu, J.; Proksch, P. *Bioorg. Med. Chem.* **2009,** *17,* 7362–7367. doi:10.1016/j.bmc.2009.08.031
7. Pierce, M. E.; Parsons, R. L., Jr.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone, P. N.; Chen, C.-y.; Tillyer, R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D.; Thompson, A. S.; Corley, E. G.; Grabowski, E. J. J.; Reamer, R.; Reider, P. J. *J. Org. Chem.* **1998,** *63,* 8536–8543. doi:10.1021/jo981170l
8. Tan, L.; Chen, C.-y.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.* **1999,** *38,* 711–713. doi:10.1002/(SICI)1521-3773(19990301)38:5<711::AID-ANIE711>3.0.CO;2-W
See for example.
9. Ahamed, M.; Todd, M. H. *Eur. J. Org. Chem.* **2010,** 5935–5942. doi:10.1002/ejoc.201000877
10. Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004,** 4095–4105. doi:10.1002/ejoc.200400246
11. Kumagai, N.; Shibasaki, M. *Bull. Chem. Soc. Jpn.* **2015,** *88,* 503–517. doi:10.1246/bcsj.20140302
12. Ohshima, T. To Catalytic Asymmetric 1,2-Alkynylation. In *Comprehensive Chirality;* Carreira, E. M.; Yamamoto, H., Eds.; Elsevier: Amsterdam, 2012; pp 355–377. doi:10.1016/B978-0-08-095167-6.00418-3
13. Pu, L. *Tetrahedron* **2003,** *59,* 9873–9886. doi:10.1016/j.tet.2003.10.042
14. Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007,** *5,* 873–888. doi:10.1039/b617746h
15. Trost, B. M.; Bartlett, M. J. Catalytic Enantioselective Addition of Terminal Alkynes to Carbonyls. In *Modern Alkyne Chemistry;* Trost, B. M.; Li, C.-J., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2014; pp 201–238. doi:10.1002/9783527677894.ch8
16. Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002,** *124,* 5638–5639. doi:10.1021/ja026007t
17. Wei, C.; Mague, J. T.; Li, C.-J. *Proc. Natl. Acad. Sci. U. S. A.* **2004,** *101,* 5749–5754. doi:10.1073/pnas.0307150101
18. Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002,** *41,* 2535–2538. doi:10.1002/1521-3773(20020715)41:14<2535::AID-ANIE2535>3.0.CO;2-M
19. Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. – Eur. J.* **2003,** *9,* 2797–2811. doi:10.1002/chem.200204691
20. Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003,** *42,* 5763–5766. doi:10.1002/anie.200352578

21. Yin, L.; Otsuka, Y.; Takada, H.; Mouri, S.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2013,** *15,* 698–701. doi:10.1021/ol3035609
See for a recent example of enantioselective, copper-catalyzed alkynlation of acyclic ketoimines.
22. Li, Z.; Li, C.-J. *Org. Lett.* **2004,** *6,* 4997–4999. doi:10.1021/ol047814v
23. Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004,** *126,* 11810–11811. doi:10.1021/ja0460763
24. Li, Z.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006,** *17,* 590–597. doi:10.1016/j.tetasy.2006.02.007
25. Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2006,** *8,* 143–146. doi:10.1021/ol0526165
26. Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007,** *129,* 9300–9301. doi:10.1021/ja0734849
27. Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004,** *6,* 1107–1110. doi:10.1021/ol036462+
28. Black, D. A.; Beveridge, R. E.; Arndtsen, B. A. *J. Org. Chem.* **2008,** *73,* 1906–1910. doi:10.1021/jo702293h
29. Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004,** *43,* 5971–5973. doi:10.1002/anie.200461286
See for the initial report of Pinap ligands.
30. Hashimoto, T.; Omote, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2011,** *50,* 8952–8955. doi:10.1002/anie.201104017
31. Yu, J.; Li, Z.; Jia, K.; Jiang, Z.; Liu, M.; Su, W. *Tetrahedron Lett.* **2013,** *54,* 2006–2009. doi:10.1016/j.tetlet.2013.02.007
32. Lin, W.; Cao, T.; Fan, W.; Han, Y.; Kuang, J.; Luo, H.; Miao, B.; Tang, X.; Yu, Q.; Yuan, W.; Zhang, J.; Zhu, C.; Ma, S. *Angew. Chem., Int. Ed.* **2014,** *53,* 277–281. doi:10.1002/anie.201308699
33. Perepichka, I.; Kundu, S.; Hearne, Z.; Li, C.-J. *Org. Biomol. Chem.* **2015,** *13,* 447–451. doi:10.1039/C4OB02138J
34. Sun, S.; Li, C.; Floreancig, P. E.; Lou, H.; Liu, L. *Org. Lett.* **2015,** *17,* 1684–1687. doi:10.1021/acs.orglett.5b00447
35. Pappoppula, M.; Cardoso, F. S. P.; Garrett, B. O.; Aponick, A. *Angew. Chem., Int. Ed.* **2015,** *54,* 15202–15206. doi:10.1002/anie.201507848
36. Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2007,** *9,* 3901–3904. doi:10.1021/ol701534n
37. Asano, Y.; Ito, H.; Hara, K.; Sawamura, M. *Organometallics* **2008,** *27,* 5984–5996. doi:10.1021/om800667c
38. Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001,** *123,* 9687–9688. doi:10.1021/ja016378u
39. Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002,** *4,* 2605–2606. doi:10.1021/ol026282k
40. Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000,** *122,* 1806–1807. doi:10.1021/ja993838z
41. Ito, J.-i.; Asai, R.; Nishiyama, H. *Org. Lett.* **2010,** *12,* 3860–3862. doi:10.1021/ol1015338
42. Koyuncu, H.; Dogan, Ö. *Org. Lett.* **2007,** *9,* 3477–3479. doi:10.1021/ol701535y
43. Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005,** *127,* 13760–13761. doi:10.1021/ja053946n
44. Trost, B. M.; Chan, V. S.; Yamamoto, D. *J. Am. Chem. Soc.* **2010,** *132,* 5186–5192. doi:10.1021/ja910656b
45. Yang, F.; Xi, P.; Yang, L.; Lan, J.; Xie, R.; You, J. *J. Org. Chem.* **2007,** *72,* 5457–5460. doi:10.1021/jo0707535
46. Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002,** *124,* 12636–12637. doi:10.1021/ja025541y
47. Lu, G.; Li, X.; Chan, W. L.; Chan, A. S. C. *Chem. Commun.* **2002,** 172–173. doi:10.1039/b107817h
48. Moore, D.; Pu, L. *Org. Lett.* **2002,** *4,* 1855–1857. doi:10.1021/ol025825n
49. Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002,** *4,* 4143–4146. doi:10.1021/ol026921r
50. Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003,** *42,* 5057–5058. doi:10.1002/anie.200352013
51. Lu, G.; Li, X.; Li, Y.-M.; Kwong, F. Y.; Chan, A. S. C. *Adv. Synth. Catal.* **2006,** *348,* 1926–1933. doi:10.1002/adsc.200606078
52. Motoki, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007,** *9,* 2997–3000. doi:10.1021/ol071003k
53. Chen, C.; Hong, L.; Xu, Z.-Q.; Liu, L.; Wang, R. *Org. Lett.* **2006,** *8,* 2277–2280. doi:10.1021/ol060526+
54. Zhou, S.; Chen, C.-R.; Gau, H.-M. *Org. Lett.* **2010,** *12,* 48–51. doi:10.1021/ol902454n
55. Maity, P.; Srinivas, H. D.; Watson, M. P. *J. Am. Chem. Soc.* **2011,** *133,* 17142–17145. doi:10.1021/ja207585p
56. Srinivas, H. D.; Maity, P.; Yap, G. P. A.; Watson, M. P. *J. Org. Chem.* **2015,** *80,* 4003–4016. doi:10.1021/acs.joc.5b00364
57. Dasgupta, S.; Rivas, T.; Watson, M. P. *Angew. Chem., Int. Ed.* **2015,** *54,* 14154–14158. doi:10.1002/anie.201507373
58. Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998,** *37,* 2922–2959. doi:10.1002/(SICI)1521-3773(19981116)37:21<2922::AID-ANIE2922>3.0.CO;2-1
59. Díez, J.; Gamasa, M. P.; Panera, M. *Inorg. Chem.* **2006,** *45,* 10043–10045. doi:10.1021/ic061453t
60. Panera, M. a.; Díez, J.; Merino, I.; Rubio, E.; Gamasa, M. P. *Inorg. Chem.* **2009,** *48,* 11147–11160. doi:10.1021/ic901527x
61. Nakajima, K.; Shibata, M.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2015,** *137,* 2472–2475. doi:10.1021/jacs.5b00004
62. Ahlquist, M.; Fokin, V. V. *Organometallics* **2007,** *26,* 4389–4391. doi:10.1021/om700669v
63. Díez, J.; Gamasa, M. P.; Gimeno, J.; Aguirre, A.; García-Granda, S.; Holubova, J.; Falvello, L. R. *Organometallics* **1999,** *18,* 662–669. doi:10.1021/om980592i
64. Mealli, C.; Godinho, S. S. M. C.; Calhorda, M. J. *Organometallics* **2001,** *20,* 1734–1742. doi:10.1021/om0009132
65. Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005,** *44,* 2210–2215. doi:10.1002/anie.200461496

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doi:10.3762/bjoc.11.290

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Copper-catalyzed aminooxygenation of styrenes with *N*-fluorobenzenesulfonimide and *N*-hydroxyphthalimide derivatives

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Letter

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Keywords:
aminooxygenation of styrenes; copper catalysts;
N-fluorobenzenesulfonimide; *N*-hydroxyphthalimide derivatives

Beilstein J. Org. Chem. **2015,** *11,* 2721–2726.
doi:10.3762/bjoc.11.293

Received: 16 September 2015
Accepted: 10 December 2015
Published: 24 December 2015

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

A copper-catalyzed aminooxygenation reaction of styrenes with *N*-fluorobenzenesulfonimide and *N*-hydroxyphthalimide derivatives has been developed. The aminooxygenation product could be converted into the corresponding alcohol or free amine through the cleavage of the N–O or C–N bond of the *N*-hydroxyphthalimide moiety.

Findings

Direct aminooxygenation of alkenes provides a straightforward and powerful approach to construct the 1,2-aminoalcohol skeleton [1], which is ubiquitous in bioactive compounds (such as the drugs bestatin (**1**) and tamiflu (**2**), the natural products Al-77-B (**3**) and hapolosin (**4**); Figure 1) [2] and has also been widely used as chiral ligands and auxiliaries in asymmetric synthesis [3]. Therefore, the development of a new aminooxygenation reaction is still highly attractive [4]. Most of the existing aminooxygenation reactions involve an intramolecular cyclization step [5-33] to provide various valuable cyclic compounds. Comparatively, methods for an intermolecular three-component aminooxygenation reaction are considerably less established. In 2006, Stahl and co-workers reported a Pd-catalyzed aminooxygenation reaction of alkenes with phthalimide and (diacetoxyiodo)benzene through *cis*-aminopalladation and S_N2 C–O bond formation [34]. In 2013, Zhu and co-workers described an *n*-Bu_4NI-catalyzed aminooxygenation of inactive alkenes with benzotriazole and water which underwent a nitrogen-centred radical addition and a nucleophilic oxygen attack [35]. Very recently, Studer and co-workers presented an aminooxygenation of alkenes with *N*-fluorobenzenesulfonimide (NFSI) and sodium 2,2,6,6-tetramethylpiperidine-1-olate (TEMPONa) via nitrogen-centred radical addition to the alkene followed by trapping of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) [36].

NFSI is a very interesting reagent. Besides classic electrophilic fluorination reagent [37], it has been used not only as fluoride-

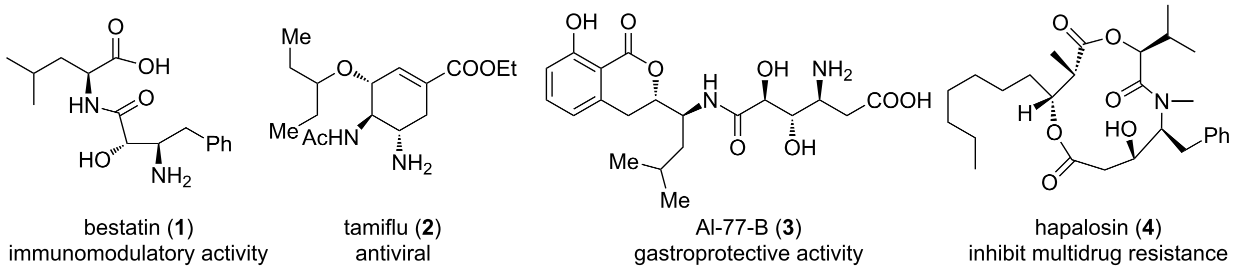
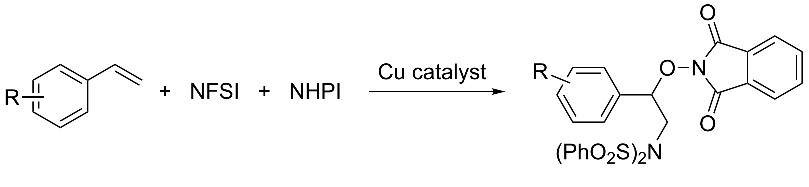


Figure 1: Bioactive compounds containing 1,2-aminoalcohol motif.

atom transfer reagent [38-40] but also as nucleophilic/radical amination reagent [41]. We are highly interested in the multiple reaction modes of NFSI [37-41], especially as a nitrogen-centred radical. In this context, we have realized copper-catalyzed benzylic sp^3 C–H amination [42], aminative multiple functionalization of alkynes [43], diamination, aminocyanation [44] and aminofluorination of alkenes [45], as well as amination of allenes [46]. Encouraged by these results, we try to develop copper-catalyzed aminooxygenation of alkenes by using NFSI. Herein, we report a simple and efficient copper-catalyzed three-component aminooxygenation reaction of styrenes with NFSI and *N*-hydroxyphthalimide (NHPI) derivatives (Scheme 1).

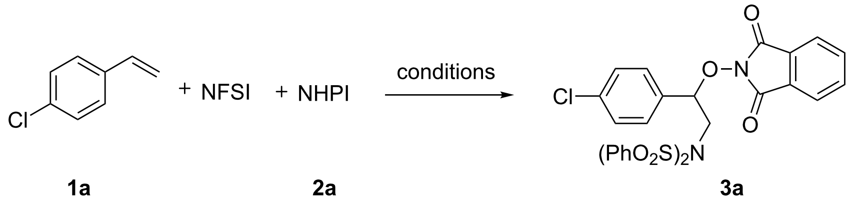
Initially, we conducted the three-component amnooxygenation of styrene **1a** with NFSI and NHPI (**2a**). After the reaction of **1a** (0.3 mmol), NFSI (0.3 mmol, 1.0 equiv) and **2a** (0.45 mmol, 1.5 equiv) was performed in the presence of Cu(OTf)$_2$ (10 mol %) in dichloromethane (DCM, 2 mL) under nitrogen atmosphere at 70 °C for 10.0 h, the desired aminooxygenation product **3a** was obtained in 39% yield (Table 1, entry 1). A variety of copper salts such as CuCl, CuBr, CuI, [(CH$_3$CN)$_4$Cu]PF$_6$, CuCN, Cu(acac)$_2$, Cu(OAc)$_2$, CuBr$_2$ and CuCl$_2$ were examined (Table 1, entries 2–10). We found that CuCl$_2$ was the most effective catalyst, affording **3a** in 55% yield (Table 1, entry 10). No reaction was observed in the absence of copper salts (Table 1, entry 11). Next, the reaction solvents were scanned. 1,2-Dichloroethane (DCE) and CH$_3$CN were not efficient solvents, providing **3a** in 9% and 20% yields, respectively (Table 1, entries 12 and 13). Using CHCl$_3$ as the solvent, only a trace amount of **3a** was observed (Table 1, entry 14). No reaction occurred in the solvents DMF, DMSO and THF (Table 1, entries 15–17). A relatively lower temperature (45 °C) only afforded a trace amount of **3a** (Table 1, entry 18). Increasing the temperature to 90 °C or 110 °C, **3a** was obtained in 45% and 40% yields, respectively (Table 1, entries 19 and 20). The ratio of substrates distinctly influenced the reaction (Table 1, entries 21–23). Changing the ratio from 1:1:1.5 (**1a**:NFSI:**2a**) to 1:2:2 or 1:2:3 (**2a**:NFSI:**1a**) led to much better yields (Table 1, entries 21 and 22). To our delight, when the ratio was 1:4:3 (**2a**:NFSI:**1a**), **3a** was obtained in 76% yield (Table 1, entry 23).

With the optimized reaction conditions in hand (Table 1, entry 23), the scope of this copper-catalyzed aminooxygenation reaction was examined (Figure 2). Styrenes with electron-withdrawing (**1a**–**f**) or electron-donating (**1h** and **1i**) groups were viable, providing the corresponding 1,2-aminoalcohol derivatives in good yields. It is worth noting that functionalities such as F, Cl, Br, CN, and NO$_2$ groups, which could easily undergo further transformations, were intact after the reaction (**3a**–**e**). The structure of **3e** was confirmed by X-ray crystallographic analysis [47]. The substituent at the *ortho* (**3j** and **3k**) or *meta* (**3l**) position of the aromatic ring did not hinder the reaction (41–55% yields). Similarly, for disubstituted (**1m**) and trisubstituted (**1n**) substrates, the aminooxygenation underwent smoothly, providing the corresponding products **3m** (51%) and **3n** (53%). The *trans*-β-methylstyrene (**1o**) afforded the desired



Scheme 1: Copper-catalyzed radical aminooxygenation reaction of styrenes.

Table 1: The optimization of reaction conditions[a].



Entry[a]	Catalyst	Solvent	Temp (°C)	Yield[b] (%)
1	$Cu(OTf)_2$	DCM	70	39
2	CuCl	DCM	70	48
3	CuBr	DCM	70	43
4	CuI	DCM	70	30
5	$[(CH_3CN)_4Cu]PF_6$	DCM	70	50
6	CuCN	DCM	70	16
7	$Cu(acac)_2$	DCM	70	48
8	$Cu(OAc)_2$	DCM	70	51
9	$CuBr_2$	DCM	70	54
10	$CuCl_2$	DCM	70	55
11	none	DCM	70	NR[c]
12	$CuCl_2$	DCE	70	9
13	$CuCl_2$	CH_3CN	70	20
14	$CuCl_2$	$CHCl_3$	70	trace
15	$CuCl_2$	DMF	70	NR[c]
16	$CuCl_2$	DMSO	70	NR[c]
17	$CuCl_2$	THF	70	NR[c]
18	$CuCl_2$	DCM	45	trace
19	$CuCl_2$	DCM	90	45
20	$CuCl_2$	DCM	110	40
21[d]	$CuCl_2$	DCM	70	70
22[e]	$CuCl_2$	DCM	70	73
23[f]	**$CuCl_2$**	**DCM**	**70**	**76**

[a]Reaction conditions: **1a** (0.3 mmol), NFSI (0.3 mmol, 1.0 equiv), **2a** (0.45 mmol, 1.5 equiv), catalyst (10 mol %), solvent (2.0 mL), N_2, 10.0 h.
[b]Isolated yields. [c]NR: no reaction. [d]**1a**:NFSI:**2a** = 2.0:2.0:1.0 [e]**1a**:NFSI:**2a** = 3.0:2.0:1.0. [f]**1a**:NFSI:**2a** = 3.0:4.0:1.0.

product **3o** in a low yield (15%). In addition, NHPI derivatives **2b** and **2c** were suitable nitrogen sources and the desired **3p** and **3q** were obtained in 56% and 64%, respectively. For 4-methoxystyrene (**1r**), no aminooxygenation reaction occurred.

Based on these experimental results and our previous investigations [42-46,48], a plausible mechanism for the copper-catalyzed three-component aminooxygenation of styrenes with NFSI an NHPI is shown in Scheme 2. Initially, the oxidation of Cu(I) with NFSI provided F–Cu(III)–N complex **I**, which could transform into a copper(II)-stabilized benzenesulfonimide radical **II** through a redox isomerization equilibrium. Next, the intermolecular radical addition of **II** to styrene **1g** took place, producing benzylic radical **III** and Cu(II)–F species **IV**. The combination of the intermediates **III** and **IV** gave the Cu(III) species **V** having a C–Cu bond, which reacted with **2a** to generate Cu(III)–O species **VI**, along with the loss of HF. Finally, the reductive elimination of **VI** afforded aminooxygenation product **3g**.

Finally, we tried to investigate the synthetic value of our new aminooxygenation method. Then, the selective reduction of **3g** was conducted (Scheme 3). The cleavage of the N–O bond in **3g** readily occurred with $Mo(CO)_6/Et_3N$ at 80 °C to give alcohol **4** [36] in 67% yield. Treatment of **3g** with $NH_2NH_2 \cdot H_2O$ under mild conditions (25 °C) in $CHCl_3/MeOH$ gave free amine **5** in 70% yield.

In summary, we have developed a novel copper-catalyzed three-component aminooxygenation reaction of styrenes with NFSI and NHPI derivatives. Furthermore, the aminooxygenation product could be easily converted into the corresponding

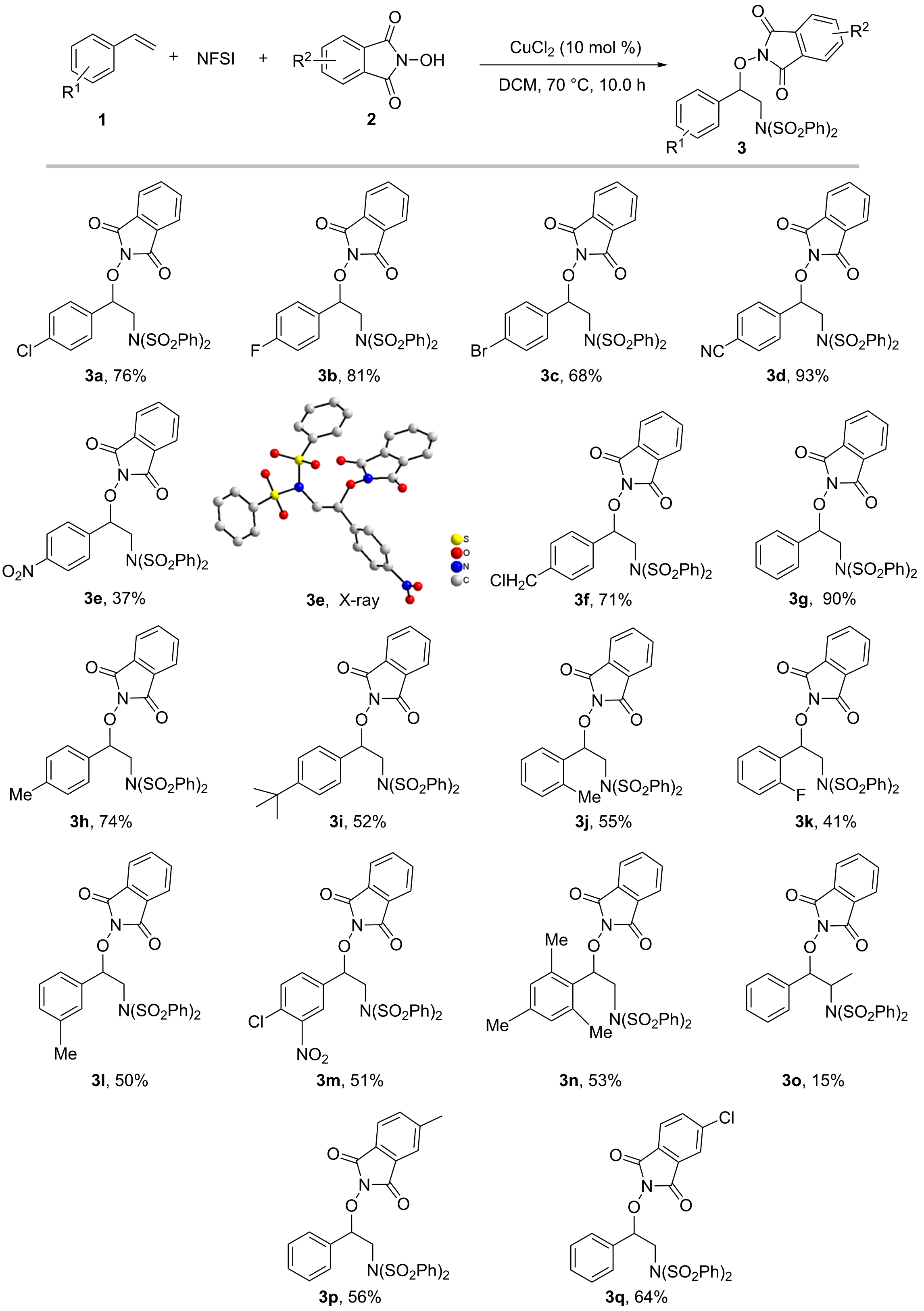
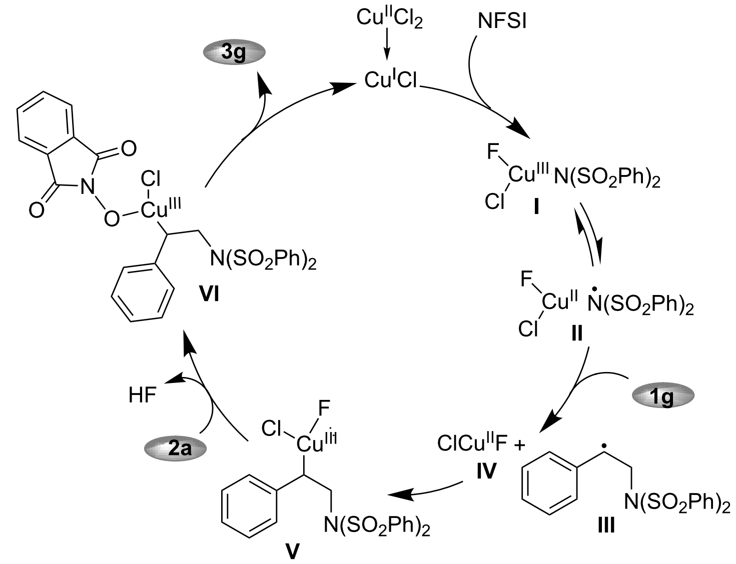
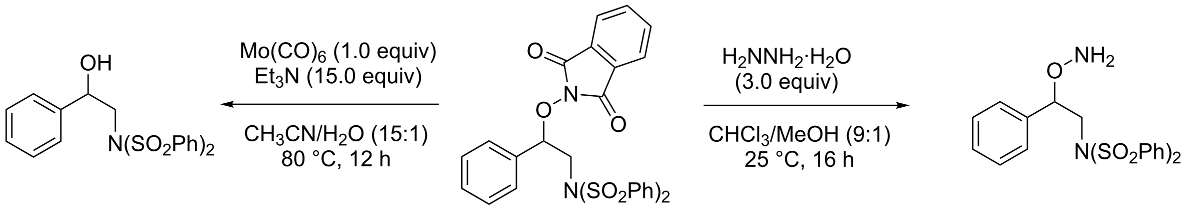


Figure 2: The copper-catalyzed three-component aminooxygenation of styrenes with NFSI and NHPI derivatives. Reaction conditions: **1** (0.9 mmol, 3.0 equiv), NFSI (1.2 mmol, 4.0 equiv), **2** (0.3 mmol, 1.0 equiv), $CuCl_2$ (10 mol %), DCM (2.0 mL), N_2, 70 °C, 10.0 h. Isolated yields.



Scheme 2: The plausible mechanism.



Scheme 3: Selective reduction of the aminooxygenation product.

alcohol or free amine through the cleavage of the N–O or C–N bond of the NHPI moiety. Further studies are underway in our lab.

Supporting Information

Supporting Information File 1

Experimental part.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-293-S1.pdf]

Acknowledgements

We acknowledge support for this work from the National NSF of China (21172033, 21372041 and 21302017).

References

1. Bergmeier, S. C. *Tetrahedron* **2000,** *56,* 2561–2576. doi:10.1016/S0040-4020(00)00149-6
2. Shimojima, Y.; Hayashi, H. *J. Med. Chem.* **1983,** *26,* 1370–1374. doi:10.1021/jm00364a007
3. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996,** *96,* 835–876. doi:10.1021/cr9500038
4. Donohoe, T. J.; Callens, C. K. A.; Flores, A.; Lacy, A. R.; Rathi, A. H. *Chem. – Eur. J.* **2011,** *17,* 58–76. doi:10.1002/chem.201002323
5. Noack, M.; Göttlich, R. *Chem. Commun.* **2002,** 536–537. doi:10.1039/b111656h
6. Szolcsányi, P.; Gracza, T. *Chem. Commun.* **2005,** 3948–3950. doi:10.1039/b506731f
7. Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008,** *10,* 5039–5042. doi:10.1021/ol8022165
8. Muñiz, K.; Iglesias, A.; Fang, Y. *Chem. Commun.* **2009,** 5591–5593. doi:10.1039/B912139K
9. Borsini, E.; Broggini, G.; Fasana, A.; Galli, S.; Khansaa, M.; Piarulli, U.; Rigamonti, M. *Adv. Synth. Catal.* **2011,** *353,* 985–994. doi:10.1002/adsc.201000889
10. Broggini, G.; Barbera, V.; Beccalli, E. M.; Chiacchio, U.; Fasana, A.; Galli, S.; Gazzola, S. *Adv. Synth. Catal.* **2013,** *355,* 1640–1648. doi:10.1002/adsc.201300104
11. Liu, G.-S.; Zhang, Y.-Q.; Yuan, Y.-A.; Xu, H. *J. Am. Chem. Soc.* **2013,** *135,* 3343–3346. doi:10.1021/ja311923z

12. Zhang, Y.-Q.; Yuan, Y.-A.; Liu, G.-S.; Xu, H. *Org. Lett.* **2013,** *15,* 3910–3913. doi:10.1021/ol401666e
13. Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005,** *127,* 7690–7691. doi:10.1021/ja051406k
14. Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem.* **2007,** *72,* 3896–3905. doi:10.1021/jo070321u
15. Chemler, S. R. *J. Organomet. Chem.* **2011,** *696,* 150–158. doi:10.1016/j.jorganchem.2010.08.041
16. Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008,** *130,* 17638–17639. doi:10.1021/ja806585m
17. Chemler, S. R. *Org. Biomol. Chem.* **2009,** *7,* 3009–3019. doi:10.1039/b907743j
18. Sherman, E. S.; Chemler, S. R. *Adv. Synth. Catal.* **2009,** *351,* 467–471. doi:10.1002/adsc.200800705
19. Paderes, M. C.; Chemler, S. R. *Org. Lett.* **2009,** *11,* 1915–1918. doi:10.1021/ol9003492
20. Karyakarte, S. D.; Smith, T. P.; Chemler, S. R. *J. Org. Chem.* **2012,** *77,* 7755–7760. doi:10.1021/jo3013226
21. Paderes, M. C.; Chemler, S. R. *Eur. J. Org. Chem.* **2011,** 3679–3684. doi:10.1002/ejoc.201100444
22. de Haro, T.; Nevado, C. *Angew. Chem., Int. Ed.* **2011,** *123,* 936–940. doi:10.1002/ange.201005763
23. Mancheno, D. E.; Thornton, A. R.; Stoll, A. H.; Kong, A.; Blakey, S. B. *Org. Lett.* **2010,** *12,* 4110–4113. doi:10.1021/ol101702w
24. Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011,** *50,* 5678–5681. doi:10.1002/anie.201100362
25. Sanjaya, S.; Chiba, S. *Org. Lett.* **2012,** *14,* 5342–5345. doi:10.1021/ol302525m
26. Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007,** *46,* 5737–5740. doi:10.1002/anie.200701454
27. Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011,** *133,* 11402–11405. doi:10.1021/ja204255e
28. Han, B.; Yang, X.-L.; Fang, R.; Yu, W.; Wang, C.; Duan, X.-Y.; Liu, S. *Angew. Chem., Int. Ed.* **2012,** *51,* 8816–8820. doi:10.1002/anie.201203799
29. Sequeira, F. C.; Chemler, S. R. *Org. Lett.* **2012,** *14,* 4482–4485. doi:10.1021/ol301984b
30. Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. *J. Am. Chem. Soc.* **2007,** *129,* 1866–1867. doi:10.1021/ja067894t
31. Michaelis, D. J.; Ischay, M. A.; Yoon, T. P. *J. Am. Chem. Soc.* **2008,** *130,* 6610–6615. doi:10.1021/ja800495r
32. Williamson, K. S.; Yoon, T. P. *J. Am. Chem. Soc.* **2010,** *132,* 4570–4571. doi:10.1021/ja1013536
33. Benkovics, T.; Guzei, I. A.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2010,** *49,* 9153–9157. doi:10.1002/anie.201004635
34. Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006,** *128,* 7179–7181. doi:10.1021/ja061706h
35. Xue, Q.; Xie, J.; Xu, P.; Hu, K.; Cheng, Y.; Zhu, C. *ACS Catal.* **2013,** *3,* 1365–1368. doi:10.1021/cs400250m
36. Li, Y.; Hartmann, M.; Daniliuc, C. G.; Studer, A. *Chem. Commun.* **2015,** *51,* 5706–5709. doi:10.1039/C5CC00591D
37. Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008,** *108,* PR1–PR43. doi:10.1021/cr800221v
38. Rueda-Becerril, M.; Sazepin, C. C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquin, J.-F.; Sammis, G. M. *J. Am. Chem. Soc.* **2012,** *134,* 4026–4029. doi:10.1021/ja211679v
39. Halperin, S. D.; Fan, H.; Chang, S.; Martin, R. E.; Britton, R. *Angew. Chem., Int. Ed.* **2014,** *53,* 4690–4693. doi:10.1002/anie.201400420
40. Sibi, M. P.; Landais, Y. *Angew. Chem., Int. Ed.* **2013,** *52,* 3570–3572. doi:10.1002/anie.201209583
41. Li, Y.; Zhang, Q. *Synthesis* **2015,** *47,* 159–174. doi:10.1055/s-0034-1379396
42. Ni, Z.; Zhang, Q.; Xiong, T.; Zheng, Y.; Li, Y.; Zhang, H.; Zhang, J.; Liu, Q. *Angew. Chem., Int. Ed.* **2012,** *51,* 1244–1247. doi:10.1002/anie.201107427
43. Zheng, G.; Li, Y.; Han, J.; Xiong, T.; Zhang, Q. *Nat. Commun.* **2015,** *6,* No. 7011. doi:10.1038/ncomms8011
44. Zhang, H.; Pu, W.; Xiong, T.; Li, Y.; Zhou, X.; Sun, K.; Liu, Q.; Zhang, Q. *Angew. Chem., Int. Ed.* **2013,** *52,* 2529–2533. doi:10.1002/anie.201209142
45. Zhang, H.; Song, Y.; Zhao, J.; Zhang, J.; Zhang, Q. *Angew. Chem., Int. Ed.* **2014,** *53,* 11079–11083. doi:10.1002/anie.201406797
46. Zhang, G.; Xiong, T.; Wang, Z.; Xu, G.; Wang, X.; Zhang, Q. *Angew. Chem., Int. Ed.* **2015,** *54,* 12649–12653. doi:10.1002/anie.201506066
47. The X-ray crystallographic coordinates for the structure of compound **3e** reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number 1422654.
48. Sun, K.; Li, Y.; Zhang, Q. *Sci. China: Chem.* **2015,** *58,* 1354–1358. doi:10.1007/s11426-015-5385-y

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Copper-catalyzed intermolecular oxyamination of olefins using carboxylic acids and *O*-benzoylhydroxylamines

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Letter

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Keywords:
copper; electrophilic amination; olefin oxyamination

Beilstein J. Org. Chem. **2016,** *12,* 22–28.
doi:10.3762/bjoc.12.4

Received: 30 October 2015
Accepted: 11 December 2015
Published: 07 January 2016

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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Abstract

This paper reports a novel approach for the direct and facile synthesis of 1,2-oxyamino moieties via an intermolecular copper-catalyzed oxyamination of olefins. This strategy utilizes *O*-benzoylhydroxylamines as an electrophilic amine source and carboxylic acids as a nucleophilic oxygen source to achieve a modular difunctionalization of olefins. The reaction proceeded in a regioselective manner with moderate to good yields, exhibiting a broad scope of carboxylic acid, amine, and olefin substrates.

Introduction

The 1,2-oxyamino motif is highly valuable and found in a vast range of biologically active natural products, pharmaceuticals, and agrochemicals (Figure 1) [1,2]. Representative examples include salmeterol (Advair®), a β_2-adrenergic receptor agonist [3]; lumefantrine, an antimalarial drug [4]; ifenprodil, an *N*-methyl-D-aspartate (NMDA) antagonist [5]; and tebuconazole, a commercial fungicide [6].

With the importance of 1,2-oxyamino motifs as privileged pharmacophores, the development of facile and efficient access to this class of molecules is highly valued. Toward this end, intermolecular olefin oxyamination allows for direct and modular installation of both oxygen and amino groups to readily available olefins in a single step, representing a powerful and appealing approach over multistep sequences [7-9]. Sharpless reported the first examples of this strategy using osmium tetroxide and amines to generate imido osmium intermediates (Scheme 1A) [10-12]. Although this transformation has received extensive application, the development of less toxic olefin oxyamination methods is greatly desired. In 2006, Stahl and Liu reported a palladium-catalyzed introduction of phthalimide (HNPhth) and acetate functionalities to terminal allylic and homoallylic ethers in the presence of an iodine oxidant (Scheme 1B) [13]. The Yoon lab also developed copper- and iron-catalyzed olefin difunctionalization reactions with oxaziridine derivatives to create 1,3-oxazolidines, which were readily

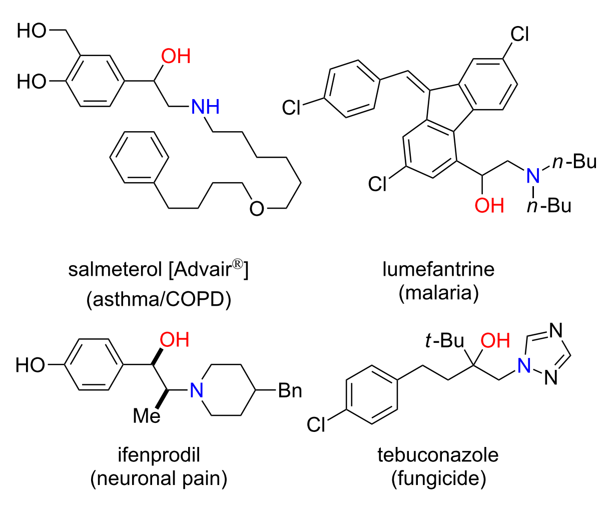
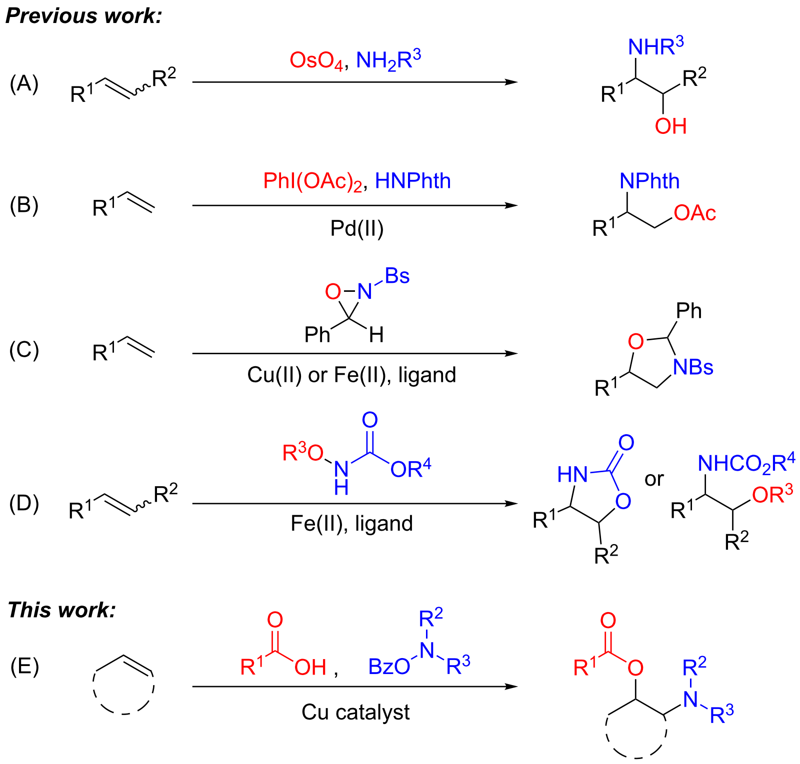


Figure 1: Examples of valuable 1,2-oxyamino-containing molecules.

converted to the 1,2-oxyamino functionality (Scheme 1C) [14,15]. Recently, the Xu lab developed another iron-catalyzed intermolecular olefin-oxyamination reaction with *O*-alkylhydroxylamides to construct either 1,2-oxyamino or 2-oxazolidinone motifs (Scheme 1D) [16]. Metal-free intermolecular oxyamination reactions have also been accomplished; examples were reported by the Zhu lab with the use of peroxides [17] and by the Studer lab with the use of hypervalent iodo-azide reagents [18]. Furthermore, the intramolecular oxyamination of olefins with a tethered amino or oxygen functionality has been achieved for the construction of a variety of 1,2-oxyamino products, using palladium [19,20], platinum [21], gold [22], copper [23-26], free-radical initiators [27-29], hypervalent iodine [30], and electrochemical oxidation [31-33], as well as an analogous intramolecular electrophilic amino lactonization from our group [34].

Despite these important achievements, current intermolecular olefin oxyamination reactions are often restricted by the use of specific amino and oxygen precursors, limiting the structural diversity of 1,2-oxyamino products. For example, most oxyamination methods are limited to the installation of amide or sulfonamide derivatives. The direct installation of electron-rich amino groups, especially tertiary cyclic amines, remains an unsolved problem. Furthermore, most methods employ inflexible oxygen sources, such as TEMPO and acetate. Herein, we envisioned that a copper-catalyzed intermolecular olefin oxyamination could be achieved using *O*-acylhydroxylamines as an electrophilic amino precursor [35-39] and carboxylic acids as a nucleophilic oxygen source (Scheme 1E). The proposed transformation, integrating an electrophilic amination with a nucleophilic oxygenation, builds upon our recent development



Scheme 1: Strategies for intermolecular olefin oxyamination.

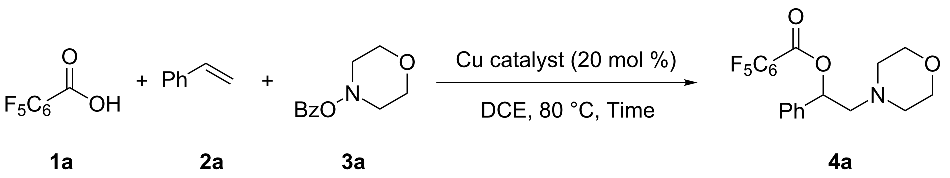
in copper-catalyzed olefin difunctionalization, such as copper-catalyzed diamination [40] and amino lactonization [34]. This strategy overcomes common issues of chemo- and regioselectivity associated with adding two different nucleophiles and simultaneously eliminates the need for an external oxidant. Particularly advantageous is the direct addition of electron-rich amino groups, especially tertiary amines, which are difficult to access by other known methods. Furthermore, *O*-acylhydroxylamines are synthetically straightforward and benchtop stable, serving as attractive amine precursors [41,42]. Overall, the development of such a three-component transformation offers an appealing oxyamination strategy complementary to existing methods.

Results and Discussion

Our investigation began with the use of pentafluorobenzoic acid (**1a**) as the oxygen source and 4-benzoyloxymorpholine (**3a**) as the nitrogen source in the proposed intermolecular oxyamination of styrene (**2a**, Table 1). Copper was found to be effective and critical to promote the formation of oxyamination product **4a** with excellent regioselectivity, as **4a** was not observed in the absence of a catalyst (Table 1, entry 1). Among a variety of copper salts (Table 1, entries 2–7), $Cu(OAc)_2$ proved superior as a catalyst (Table 1, entry 2). When the stoichiometry of each reactant was examined for this three-component transformation, decreasing the amount of **1a** resulted in lower yields (Table 1, entry 2 vs 8), while decreasing the amount of **3a** had no effect (Table 1, entry 2 vs 9). Increasing the amount of **2a** led to a noticeable improvement (Table 1, entry 9 vs 12). Finally, the optimal conditions were established with three equivalents of both **1a** and **2a**, providing **4a** in a clean 78% isolation yield (Table 1, entry 13) [43].

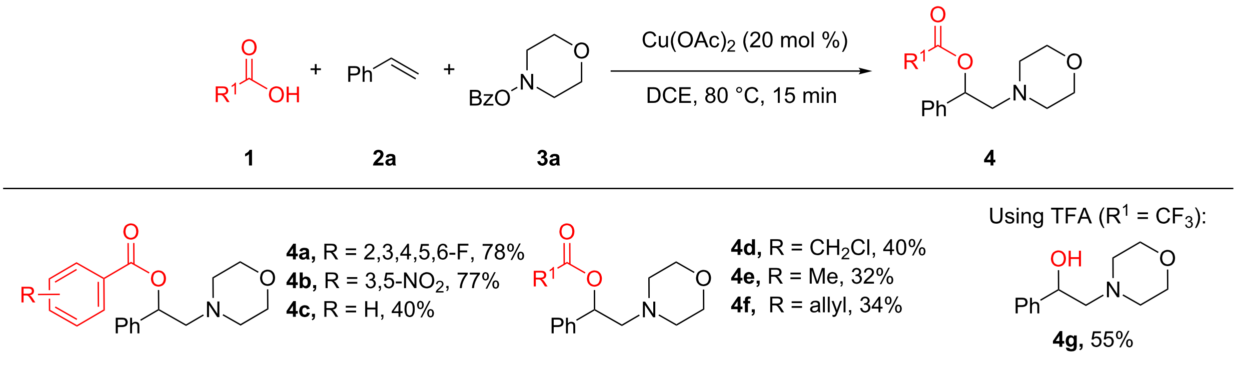
With established oxyamination conditions in hand, the scope of carboxylic acids in this transformation was examined using olefin **2a** and *O*-benzoylhydroxylamine **3a** (Scheme 2). Both aryl and alkyl carboxylic acid derivatives proved to be viable substrates, smoothly providing 1,2-oxyamino products **4a–g**. Carboxylic acids containing a nitro group (**4b**), a halide group (**4d**), or an allyl group (**4f**) were tolerated, demonstrating the broad functional group compatibility of the reaction conditions. It is notable that higher efficiencies were observed in the reactions with more acidic benzoic acids, indicating a correlation of their reactivity to their acidity which remains to be further clarified [44]. Furthermore, when trifluoroacetic acid was employed as an oxygen source, the free 1,2-amino alcohol **4g** was isolated, possibly due to the labile hydrolysis of the trifluoroacetate group.

Table 1: Optimization of copper-catalyzed intermolecular oxyamination.[a]



Entry	Reactants (equiv)			Catalyst	Time[b]	**4a** (%)[c]
	1a	**2a**	**3a**			
1	2	1	2	–	24 h	0
2	2	1	2	$Cu(OAc)_2$	15 min	63
3	2	1	2	$Cu(OTf)_2$	15 min	45
4	2	1	2	$CuCl_2$	15 min	60
5	2	1	2	$Cu(TFA)_2$	15 min	47
6	2	1	2	Cu(OAc)	15 min	59
7	2	1	2	CuI	60 min	52
8	1	1	2	$Cu(OAc)_2$	15 min	48
9	2	1	1	$Cu(OAc)_2$	15 min	63
10	3	1	1	$Cu(OAc)_2$	15 min	71
11	1	2	2	$Cu(OAc)_2$	15 min	77
12	2	2	1	$Cu(OAc)_2$	15 min	85
13	**3**	**3**	**1**	**$Cu(OAc)_2$**	**15 min**	**99 (78)**[d]

[a]Reaction conditions: **1a**, **2a**, **3a**, catalyst (20 mol %), DCE (1.0 mL), 80 °C. [b]Time required for consumption of **2a**. [c]Only the indicated isomer was observed. Yields determined by ^1H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard. [d]Isolated yield. OAc = acetate, OTf = trifluoromethanesulfonate, TFA = trifluoroacetate.

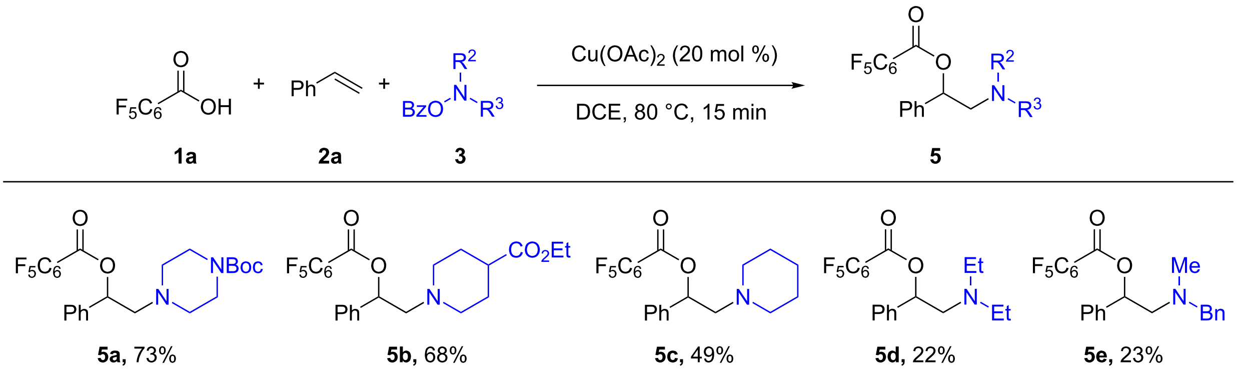


Scheme 2: Examples of carboxylic acids in the olefin oxyamination reaction. Reaction conditions: **1** (1.2 mmol, 3.0 equiv), **2a** (3.0 equiv), **3a** (1.0 equiv), $Cu(OAc)_2$ (20 mol %), DCE (2.0 mL), 80 °C, 15 min. Isolated yields.

Next, the scope of *O*-benzoylhydroxylamines was examined with carboxylic acid **1a** and olefin **2a** (Scheme 3). In the reactions with cyclic *O*-benzoylhydroxylamines, **5a–c** were readily formed in good yields, while acyclic amine products **5d** and **5e** were formed less effectively. Likely, the electronic and steric nature of the acyclic *O*-benzoylhydroxylamines may affect the stability of the corresponding amino intermediates, and result in facile breakdown of the amine precursors to the corresponding free amine. It should be noted that the benzyl group on the amine **5e** can be readily cleaved for the construction of a secondary amine.

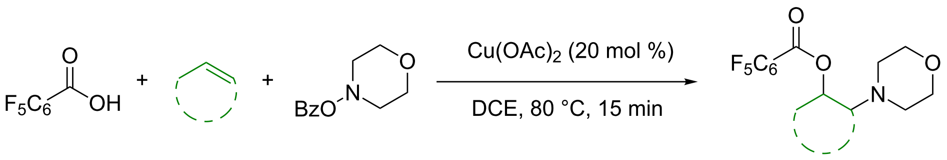
Finally, the scope of olefins for the transformation was examined including both aryl and alkyl olefins (Table 2). First, styrene derivatives bearing a variety of substitutions on the aryl ring, including both electron-donating and electron-withdrawing groups, were all effective in providing the 1,2-oxyaminated products with exclusive regioselectivity (Table 2, entries 1–6). Interestingly, the products derived from electron-rich styrene substrates (i.e., **6a**, **6b**, **6e**) were formed in higher yields than those from electron-deficient ones (i.e., **6c** and **6f**). The reactions with simple olefins also provided desired products, yet in poor yields (Table 2, entries 7 and 8). These results indicate that olefin substrates capable of stabilizing a possible electron-deficient intermediate (carbon cation or radical) are likely favored in this transformation. Furthermore, 1,2-disubstituted olefins were also viable substrates (Table 2, entries 9–11). Particularly exciting is the formation of **6j** and **6k** in excellent diastereoselectivity. In contrast, acyclic 1,2-oxyamino product **6i** was formed as a 1:1 mixture of two diastereomers. These results suggest a contribution of the structural conformation to the diastereoselective outcome of the reaction. Yet, 1,1-disubstituted olefins were not effective, likely due to the increased steric hindrance in the oxygenation step (Table 2, entry 12).

Currently, the mechanistic details of this copper-catalyzed oxyamination reaction remain unclear. In the control experiment with the absence of *O*-benzoylhydroxylamine, both carboxylic acid and olefin substrates were fully recovered, suggesting the critical role of *O*-benzoylhydroxylamine in the

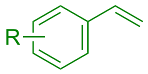
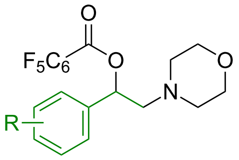
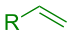
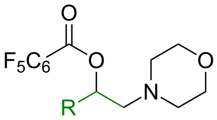
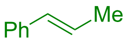
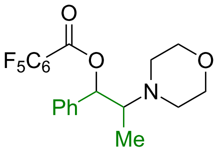
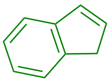
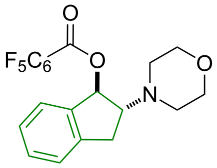
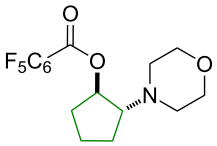
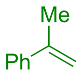
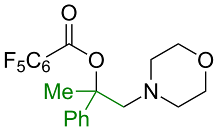


Scheme 3: Examples of *O*-benzoylhydroxylamines in the olefin oxyamination reaction. Reaction conditions: **1a** (1.2 mmol, 3.0 equiv), **2a** (3.0 equiv), **3** (1.0 equiv), $Cu(OAc)_2$ (20 mol %), DCE (2.0 mL), 80 °C, 15 min. Isolated yields.

Table 2: Examples of olefins in intermolecular oxyamination reaction.[a]



1a **2** **3a** **6**

Entry	Olefin	Product		Yield (%)[b]
1 2 3 4 5 6			**6a**, R = 2–OMe **6b**, R = 3–OMe **6c**, R = 3–F **6d**, R = 4–Me **6e**, R = 4–OMe **6f**, R = 4–Cl	83 71 57 81 69 70
7 8			**6g**, R = CH_2TMS **6h**, R = TMS	19 9
9			**6i**	69 (1:1 dr)[c]
10			**6j**	89 (7:1 dr)[c]
11			**6k**	35 (>20:1 dr)[c]
12			**6l**	<15%[d]

[a] Reaction conditions: **1a** (1.2 mmol, 3.0 equiv), **2** (3.0 equiv), **3a** (1.0 equiv), $Cu(OAc)_2$ (20 mol %), DCE (2.0 mL), 80 °C, 15 min. [b] Isolated yields. [c] dr = diastereomeric ratio, determined by ^{1}H NMR of the crude reaction mixture. Major diastereomer shown. Relative stereochemistry of **6j** determined by X-ray analysis. [d] Product containing minor inseparable impurities.

activation of copper catalyst for the initiation of this reaction. Further investigations are underway for a better understanding of the reaction pathway.

Conclusion

In summary, we have developed a copper-catalyzed three-component intermolecular oxyamination of olefins using carboxylic acids and *O*-benzoylhydroxylamines. This reaction allows for rapid access to a variety of 1,2-oxyamino products in a modular manner with excellent regioselectivity. It offers an appealing oxyamination method, especially for the construction of electron-rich tertiary amines. Future efforts will be undertaken for a better understanding of the reaction mechanism and for the development of an asymmetric version.

Supporting Information

Supporting Information File 1

Full experimental details, characterization data and crystallographic data for **6j**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-4-S1.pdf]

Acknowledgements

We acknowledge the financial support from Duke University for this work and the fellowships from the Burroughs Wellcome Endowment (B.N.H.). We also thank Dr. George Dubay for assistance with HRMS experiments and Dr. Roger Sommer for assistance with X-ray crystallography.

References

1. Bergmeier, S. C. *Tetrahedron* **2000,** *56,* 2561–2576. doi:10.1016/S0040-4020(00)00149-6
2. Donohoe, T. J.; Callens, C. K. A.; Flores, A.; Lacy, A. R.; Rathi, A. H. *Chem. – Eur. J.* **2011,** *17,* 58–76. doi:10.1002/chem.201002323
3. Calverley, P. M. A.; Anderson, J. A.; Celli, B.; Ferguson, G. T.; Jenkins, C.; Jones, P. W.; Yates, J. C.; Vestbo, J. *N. Engl. J. Med.* **2007,** *356,* 775–789. doi:10.1056/NEJMoa063070
4. von Seidlein, L.; Jaffar, S.; Pinder, M.; Haywood, M.; Snounou, G.; Gemperli, B.; Gathmann, I.; Royce, C.; Greenwood, B. *J. Infect. Dis.* **1997,** *176,* 1113–1116. doi:10.1086/516524
5. Williams, K. *Mol. Pharmacol.* **1993,** *44,* 851–859.
6. Cabras, P.; Angioni, A.; Garau, V. L.; Melis, M.; Pirisi, F. M.; Minelli, E. V.; Cabitza, F.; Cubeddu, M. *J. Agric. Food Chem.* **1997,** *45,* 2708–2710. doi:10.1021/jf960939x
7. Hassner, A.; Lorber, M. E.; Heathcock, C. H. *J. Org. Chem.* **1967,** *32,* 540–549. doi:10.1021/jo01278a006
8. Bäckvall, J.-E. *Tetrahedron Lett.* **1975,** *16,* 2225–2228. doi:10.1016/S0040-4039(00)72683-9
9. Kuszpit, M. R.; Giletto, M. B.; Jones, C. L.; Bethel, T. K.; Tepe, J. J. *J. Org. Chem.* **2015,** *80,* 1440–1445. doi:10.1021/jo502369d
10. Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975,** *97,* 2305–2307. doi:10.1021/ja00841a071
11. Sharpless, K. B.; Chong, A. O.; Oshima, K. *J. Org. Chem.* **1976,** *41,* 177–179. doi:10.1021/jo00863a052
12. Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996,** *35,* 451–454. doi:10.1002/anie.199604511
13. Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006,** *128,* 7179–7181. doi:10.1021/ja061706h
14. Michaelis, D. J.; Shaffer, C. J.; Yoon, T. P. *J. Am. Chem. Soc.* **2007,** *129,* 1866–1867. doi:10.1021/ja067894t
15. Williamson, K. S.; Yoon, T. P. *J. Am. Chem. Soc.* **2012,** *134,* 12370–12373. doi:10.1021/ja3046684
16. Lu, D.-F.; Zhu, C.-L.; Jia, Z.-X.; Xu, H. *J. Am. Chem. Soc.* **2014,** *136,* 13186–13189. doi:10.1021/ja508057u
17. Xue, Q.; Xie, J.; Xu, P.; Hu, K.; Cheng, Y.; Zhu, C. *ACS Catal.* **2013,** *3,* 1365–1368. doi:10.1021/cs400250m
18. Zhang, B.; Studer, A. *Org. Lett.* **2013,** *15,* 4548–4551. doi:10.1021/ol402106x
19. Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007,** *46,* 5737–5740. doi:10.1002/anie.200701454
20. Zhu, H.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2014,** *136,* 1766–1769. doi:10.1021/ja412023b
21. Muñiz, K.; Iglesias, A.; Fang, Y. *Chem. Commun.* **2009,** 5591–5593. doi:10.1039/b912139k
22. de Haro, T.; Nevado, C. *Angew. Chem., Int. Ed.* **2011,** *50,* 906–910. doi:10.1002/anie.201005763
23. Mancheno, D. E.; Thornton, A. R.; Stoll, A. H.; Kong, A.; Blakey, S. B. *Org. Lett.* **2010,** *12,* 4110–4113. doi:10.1021/ol101702w
24. Karila, D.; Leman, L.; Dodd, R. H. *Org. Lett.* **2011,** *13,* 5830–5833. doi:10.1021/ol202436a
25. Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008,** *130,* 17638–17639. doi:10.1021/ja806585m
26. Paderes, M. C.; Keister, J. B.; Chemler, S. R. *J. Org. Chem.* **2013,** *78,* 506–515. doi:10.1021/jo3023632
27. Schmidt, V. A.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011,** *133,* 11402–11405. doi:10.1021/ja204255e
28. Han, B.; Yang, X.-L.; Fang, R.; Yu, W.; Wang, C.; Duan, X.-Y.; Liu, S. *Angew. Chem., Int. Ed.* **2012,** *51,* 8816–8820. doi:10.1002/anie.201203799
29. Duan, X.-Y.; Zhou, N.-N.; Fang, R.; Yang, X.-L.; Yu, W.; Han, B. *Angew. Chem., Int. Ed.* **2014,** *53,* 3158–3162. doi:10.1002/anie.201309918
30. Wardrop, D. J.; Bowen, E. G.; Forslund, R. E.; Sussman, A. D.; Weerasekera, S. L. *J. Am. Chem. Soc.* **2010,** *132,* 1188–1189. doi:10.1021/ja9069997
31. Xu, H.-C.; Moeller, K. D. *J. Am. Chem. Soc.* **2008,** *130,* 13542–13543. doi:10.1021/ja806259z
32. Xu, H.-C.; Campbell, J. M.; Moeller, K. D. *J. Org. Chem.* **2014,** *79,* 379–391. doi:10.1021/jo402623r
33. Xu, F.; Zhu, L.; Zhu, S.; Yan, X.; Xu, H.-C. *Chem. – Eur. J.* **2014,** *20,* 12740–12744. doi:10.1002/chem.201404078
34. Hemric, B. N.; Shen, K.; Wang, Q. Unpublished work.
35. Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012,** *51,* 3642–3645. doi:10.1002/anie.201108773
36. Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013,** *135,* 15746–15749. doi:10.1021/ja4092819
37. McDonald, S. L.; Hendrick, C. E.; Wang, Q. *Angew. Chem., Int. Ed.* **2014,** *53,* 4667–4670. doi:10.1002/anie.201311029
38. McDonald, S. L.; Wang, Q. *Angew. Chem., Int. Ed.* **2014,** *53,* 1867–1871. doi:10.1002/anie.201308890
39. Yan, X.; Yang, X.; Xi, C. *Catal. Sci. Technol.* **2014,** *4,* 4169–4177. doi:10.1039/C4CY00773E
40. Shen, K.; Wang, Q. *Chem. Sci.* **2015,** *6,* 4279–4283. doi:10.1039/C5SC00897B
41. Biloski, A. J.; Ganem, B. *Synthesis* **1983,** 537–538. doi:10.1055/s-1983-30410
42. Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006,** *71,* 219–224. doi:10.1021/jo051999h
43. Excess equivalents of carboxylic acid **1a** and olefin **2a** were observed as the only significant impurities in the crude reaction mixture.
44. In the absence of external carboxylic acids, **4c** was observed in ca. 7% yield (determined by ^{1}H NMR), which was likely formed via the nucleophilic trapping by benzoic acid derived from **3a**. Furthermore, **4c** was observed in ca. 5% yield in the oxyamination reactions of some carboxylic acid sources (e.g., **4d–f**), but not in the reaction with stronger carboxylic acids (e.g., **4a,b**, **4g**).

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The definitive version of this article is the electronic one which can be found at:
doi:10.3762/bjoc.12.4

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Copper-mediated arylation with arylboronic acids: Facile and modular synthesis of triarylmethanes

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Full Research Paper

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Keywords:
copper; modular synthesis; triarylmethanes

Beilstein J. Org. Chem. **2016,** *12,* 496–504.
doi:10.3762/bjoc.12.49

Received: 22 November 2015
Accepted: 04 March 2016
Published: 11 March 2016

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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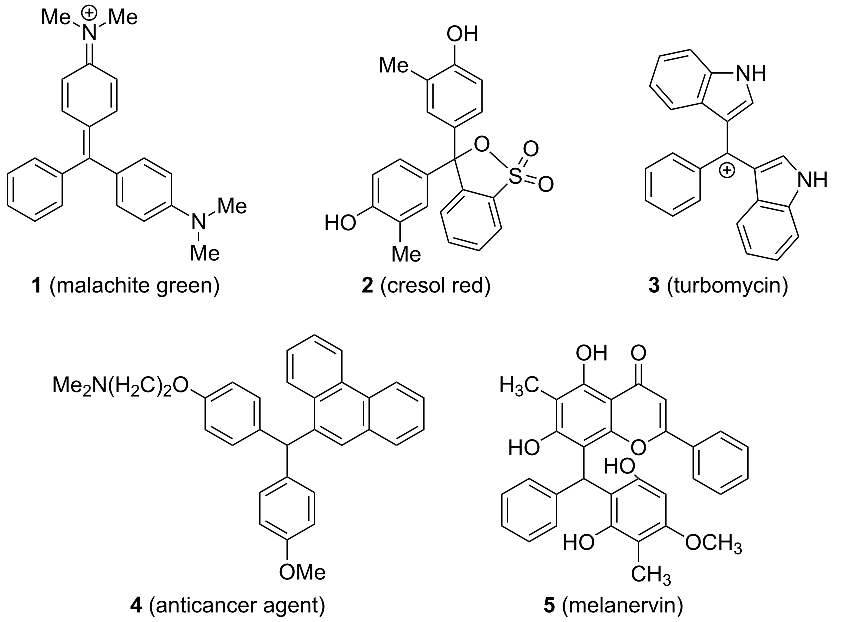
Abstract

A facile and modular synthesis of triarylmethanes was achieved in good yield via a two-step sequence in which the final step is the copper(II)-catalyzed arylation of diarylmethanols with arylboronic acids. By using this protocol a variety of symmetrical and unsymmetrical triarylmethanes were synthesized. As an application of the newly developed methodology, we demonstrate a high-yielding synthesis of the triarylmethane intermediate towards an anti-breast-cancer drug candidate.

Introduction

The triarylmethanes form an exclusive group of organic molecules wherein three aryl groups are attached to the central sp^3-hybridized carbon atom bearing a hydrogen atom [1-4]. Although the group can be restricted to such molecules, many closely related derivatives that have a triarylmethane motif (like those having a heteroatom attached to the central carbon atom or the central carbon is sp^2 hybridized) have been included in this class [5]. Molecules with a triarylmethane motif are ubiquitous and found mainly in technologically and medicinally relevant molecules like dyes [6-9], pH indicators [10-12], fluorescent probes [13-18] and antibacterial drugs [19]. For example, malachite green (**1**) is a dye, cresol red (**2**) is a pH indicator and turbomycin (**3**) is an antibacterial medicinal drug (Figure 1). Genuine triarylmethane **4**, having three different aryl groups on the central CH, is a proven anti-breast-cancer agent [20]. In addition to **4**, several other triarylmethanes exhibit interesting biological activity, including oestrogen receptor binding affinity [21], inhibition of hepatic cholesterol [22], inhibition of aldose reductase [23], antiproliferative [24], antiviral, cytotoxic [25], antifungal [26], anti-HIV [27-29] and antibacterial activity [30]. Although rare, there are a few natural products, for example, melanervin (**5**), a flavanoid bearing the triarylmethane motif [31,32].

Triarylmethanes are typically synthesized by a Friedel–Crafts-type substitution of the three alkoxy groups in a trialkyl ortho-

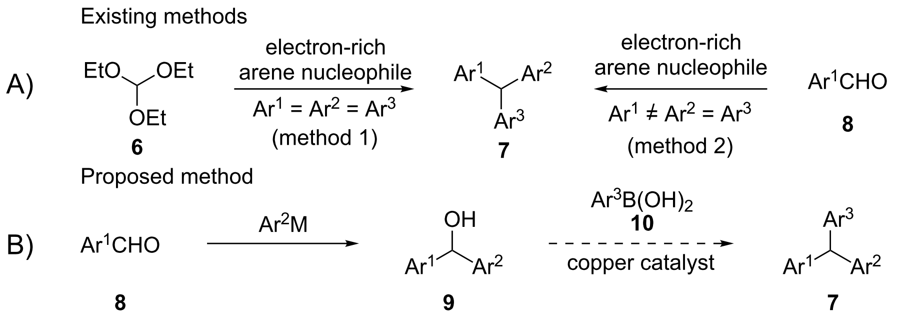


1 (malachite green) **2** (cresol red) **3** (turbomycin)

4 (anticancer agent) **5** (melanervin)

Figure 1: Representative examples of triarylmethanes.

formate (Scheme 1A, method 1) [33-35] or by sequential two-step addition of electron-rich aromatic nucleophiles to activated arene aldehydes followed by substitution of the resulting hydroxy group with another electron-rich aromatic compound (Scheme 1A, method 2) [36-39]. Both of the approaches are limited in scope and suffer from drawbacks such as (a) electron-rich aromatic systems that are required as nucleophiles and therefore, not amenable for the synthesis of triarylmethanes with electron-withdrawing groups, (b) the regioselectivity in the substitution at the aromatic ring that depends on the *ortho*- or *para*-directing nature of the substituent and also by the steric hindrance offered by the substitution, (c) the methods are rarely modular and not suitable for the preparation of triarylmethanes with three different aryl groups, and finaly, (d) Lewis [40,41] or protic acids [42] are required to catalyze the reactions. To overcome the above-mentioned difficulties, many efforts have recently been directed towards transition metal-catalyzed cross-couplings [43-48] or CH arylation followed by an arylative desulfonation [49,50]. The coupling reactions provide an opportunity to install an unactivated aryl group on a carbon bearing two more aryl groups to synthesize the triarylmethane motif. Recently, we reported a copper-catalyzed C–C bond formation by substitution of the labile C(4)SMe group in 4*H*-chromenes or C(3)–OH in isoindolinones with aryl/alkenyl groups by employing the corresponding boronic acids [51,52]. Continuing these efforts, we designed a copper-catalyzed synthesis of a variety of triarylmethanes through substitution of C(sp^3)–OH in diarylmethanols with arylboronic acids (Scheme 1B). We reasoned that since diarylmethanols with two different aromatic rings can be made by a wide variety of methods [53,54] (e.g., addition of an aryl carbanion to an aryl aldehyde and a further step with a variety of aryl boronic acids), it should be possible to provide a



Scheme 1: General methods and proposed method for the synthesis of triarylmethanes.

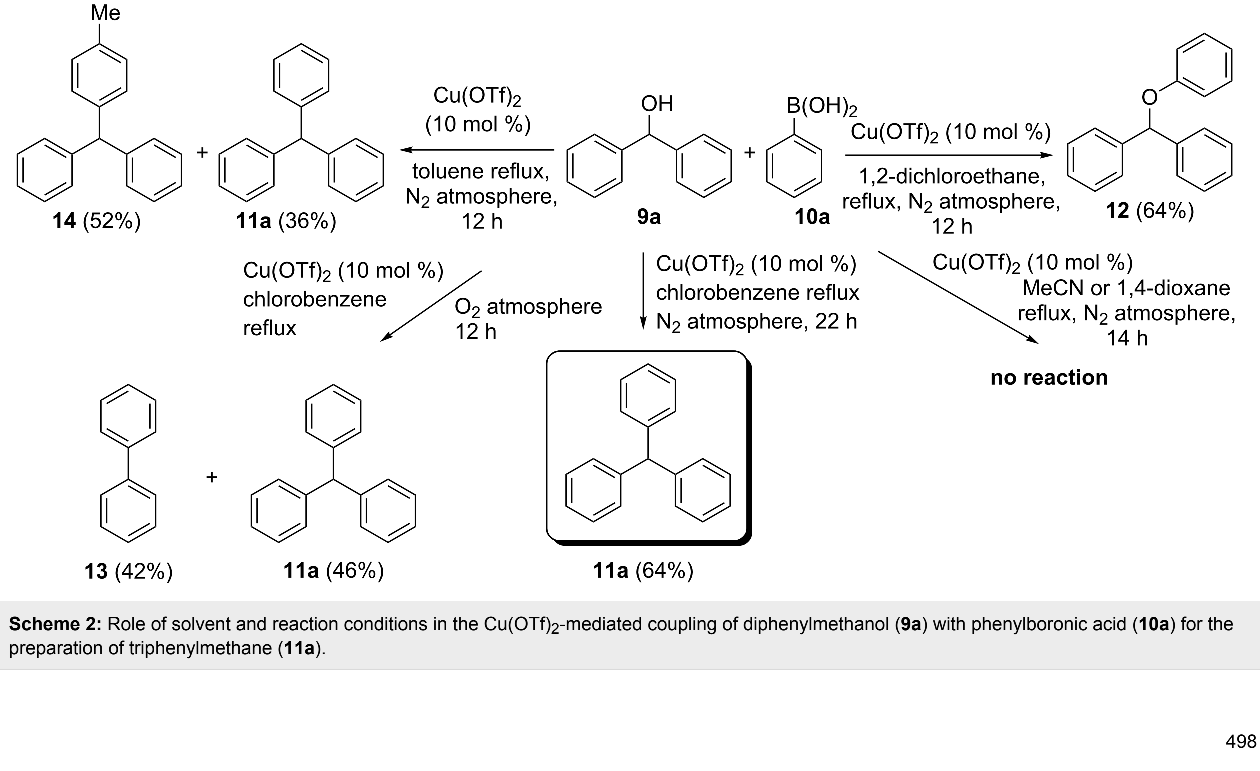
unique opportunity for the modular synthesis of unsymmetrical triarylmethanes. If successful, the method could provide an opportunity for the synthesis of a combinatorial library of the coveted molecules. Herein, we report a copper(II) triflate-catalyzed modular synthesis of triarylmethanes by employing diarylmethanols **9** and arylboronic acids **10**. It is advantageous to employ a base metal catalyst such as copper(II) triflate instead of palladium [55,56] or nickel (Ni) [57] catalysts and to avoid the use of phosphine ligands as it is less expensive and more readily facilitates purification.

Results and Discussion

We selected the copper-mediated cross-coupling reaction of diphenylmethanol (**9a**) with phenylboronic acid (**10a**) for the synthesis of triphenylmethane (**11a**) to optimize the reaction conditions and catalyst loading. Based on our accrued experience [52], in a first attempt, we employed $Cu(OTf)_2$ (10 mol %) in refluxing 1,2-dichlorethane (DCE) to effect C–C coupling, but the reaction provided (phenoxymethylene)dibenzene (**12**) as the only product formed through the C–O coupling (Chan–Lam–Evans coupling product) [58-60] in 64% yield.

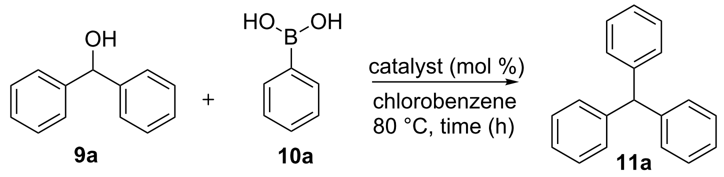
To obtain the desired triphenylmethane (**11a**) as the sole product, we screened various alternative solvents (Scheme 2). Of the solvents investigated, toluene gave a mixture of triphenylmethane (**11a**) and the toluene-incorporated product (*p*-tolylmethylene)dibenzene (**14**) in 36% and 52% yield, respectively (Scheme 2). Solvents like acetonitrile (polar, aprotic) and dioxane (oxygenated, aprotic) did not provide the triphenylmethane (**11a**). On the other hand, the higher-boiling, nonpolar chlorobenzene (Scheme 2) at 80 °C provided the coupled product triphenylmethane (**11a**) in 64% yield. When the reaction was conducted under oxygen atmosphere, the yield of **11a** fell to 46%. Under these aerobic conditions, we isolated biphenyl (**13**) generated through homocoupling of phenylboronic acid. Attempts to improve the yield by the use of bases such as Na_2CO_3 (10 mol %) and K_2CO_3 (10 mol %) were not successful. The yield of triphenylmethane (**11a**) was further reduced in these cases. The base was employed to trap the boric acid, which is likely to be the side product of the reaction. From the above experiments, we concluded that chlorobenzene was the most suitable solvent for the synthesis of triphenylmethane (**11a**).

Next, we turned our attention to evaluate different copper salts to optimize the yield of triphenylmethane (**11a**); these efforts have been summarized in Table 1. We screened various Cu(II) catalysts such as $Cu(OAc)_2$ (64%, Table 1, entry 1), $Cu(CF_3COO)_2$ (46%, Table 1, entry 2) $Cu(acac)_2$ (36%, Table 1, entry 3), $CuSO_4{\cdot}5H_2O$ (36%, Table 1, entry 4), $CuBr_2$ (14%, Table 1, entry 5), $CuCl_2{\cdot}2H_2O$ (24%, Table 1, entry 6) and CuO (no reaction, Table 1, entry 8), which did not provide the desired triphenylmethane (**11a**) in better yield. However, 20 mol % of $Cu(OTf)_2$ (Table 1, entry 17) delivered the desired triphenylmethane (**11a**) in good yield (78%) after chromatographic purification. We screened other borderline Lewis acids such as $Sc(OTf)_3$, $Yb(OTf)_3$, $Zn(OTf)_2$ and $Fe(OTf)_3$, but the reaction did not afford triphenylmethane (**11a**) at all, which indicated that Cu(II) and not TfOH is responsible for the transformation. Thus, the optimal conditions for the copper-mediated



Scheme 2: Role of solvent and reaction conditions in the $Cu(OTf)_2$-mediated coupling of diphenylmethanol (**9a**) with phenylboronic acid (**10a**) for the preparation of triphenylmethane (**11a**).

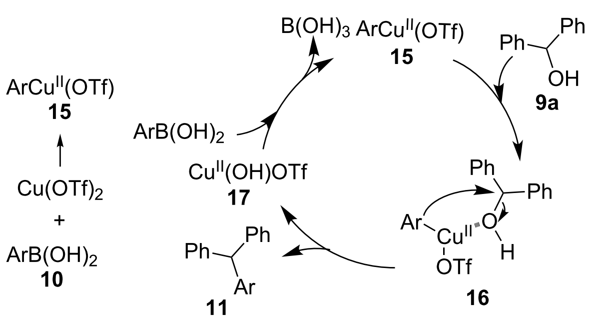
Table 1: Screening of metal catalysts for the arylation reaction.



Entry	Catalyst	Time (h)	Catalyst (mol %)	Yield (%)[a]
1	$Cu(OAc)_2·H_2O$	21	10	64
2	$Cu(OOCCF_3)_2$	18	10	46
3	$Cu(acac)_2$	21	10	36
4	$CuSO_4·5H_2O$	19	10	36
5	$CuBr_2$	16	10	14
6	$CuCl_2·H_2O$	16	10	24
7	$Cu(OTf)_2$	21	10	68
8	CuO	12	10	n.r.
9	CuI	21	10	42
10	CuBr	21	10	14
11	CuCl	19	10	28
12	Cu_2O	12	10	n.r.
13	$Cu(I)BrSMe_2$	12	10	n.r.
14	$Cu(PPh_3)_2Br$	12	10	n.r.
15	CuMeSal	21	10	42
16	CuTc	21	10	27
17	**$Cu(OTf)_2$**	**18**	**20**	**78**
18	$Sc(OTf)_3$	12	10	n.r.
19	$Fe(OTf)_3$	12	10	n.r.
20	$Zn(OTf)_2$	12	10	n.r.
21	$Yb(OTf)_3$	12	10	n.r.

[a] n.r. = no reaction.

coupling involve heating equimolar amounts of diphenylmethanol (**9a**) and phenylboronic acid (**10a**) in chlorobenzene at 80 °C in the presence of 20 mol % of $Cu(OTf)_2$ under a blanket of oxygen-free nitrogen.



Scheme 3: A plausible mechanism for the formation of triarylmethanes **11**.

Based on the above observations, we propose a mechanism for the copper-mediated coupling of phenylboronic acid with diphenylmethanol, leading to triphenylmethane and boric acid (Scheme 3). At the start of the cascade, the first step is the transmetallation of the copper(II) into phenylboronic acid to form reactive PhCu(OTf) (**15**) and $B(OH)_2(OTf)$ [61]. The intermediate **15** then reacts with diphenylmethanol **9** to provide the intermediate **16**. Formation of the intermediate **16** can be attributed to Lewis acidic characteristics of **15** and Lewis basic characteristics of diphenylmethanol (**9a**). The crucial C–C bond formation with simultaneous C–O bond cleavage subsequently occurs in **16** to give the triarylmethane **11** and copper(OH)(OTf) (**17**). The reaction of **17** with arylboronic acid **10** regenerates **15** and results in the formation of stable boric acid. The driving force for the triarylmethane formation is the generation of a stable C–C bond in **11**, a Cu–O bond in **17**, and boric acid at the cost of weak Ar–Cu and C–OH bonds in **16** and **9**, respectively [52].

With the optimized reaction conditions in hand, we examined the scope of the cross-coupling reaction for the synthesis of a variety of triarylmethanes from diphenylmethanol (**9a**). Ten more arylboronic acids were employed in the coupling reaction and good yields (77–92%) of the corresponding triarylmethanes **11b–k** were realized (Table 2). The arylboronic acids **10b–k** were selected considering their structural diversity and electron density in the aryl ring. Efficient cross-coupling could be noted irrespective of the presence of strongly electron-withdrawing (**10b**,**c** to **11b**,**c**; Table 2, entries 1 and 2), mildly electron-withdrawing (**10d**,**e** to **11d**,**e**; Table 2, entries 3 and 4), strongly electron-donating (**10f** to **11f**; Table 2, entry 5) or mildly electron-donating (**10g** to **11g**; Table 2, entry 6) groups at the C(4) position of the phenyl ring. The robust nature of the protocol was demonstrated by reacting *ortho*-methoxyphenylboronic acid (**10h**) to efficiently generate the desired triarylmethane **11h** (Table 2, entry 7). The transformation showed that apart from the insensitivity towards electronic effects, the copper-mediated cross-coupling reaction is not very sensitive to steric crowding in the neighborhood of the reaction center. Next, we employed heteroaromatic boronic acids, such as furan-2-ylboronic acid (**10i**; Table 2, entry 8), thiophen-2-ylboronic acid (**10j**; Table 2, entry 9) and benzo[*b*]thiophen-2-ylboronic acid (**10k**; Table 2, entry 10) in the coupling reaction and the reactions furnished the corresponding triarylmethanes **11a–k** in excellent yield. The transformations showed that heteroaromatic groups, including those bearing a sulfur atom, react efficiently to provide triarylmethanes.

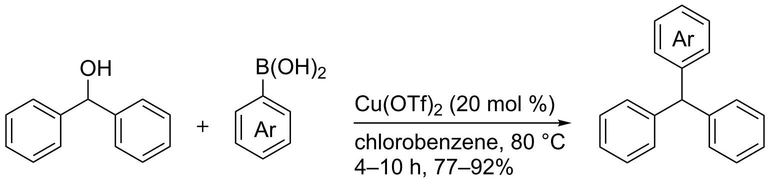
However, when we employed 2,6-dimethoxyphenylboronic acid **10l**, surprisingly, we isolated the triarylmethane **11l**, in which the C–C bond formation took place on the C(3) carbon of the 2,6-dimethoxyphenylboronic acid instead of the C(1) carbon, as illustrated in **11m** (Scheme 4). Structure of **11l** was readily confirmed on the basis of ^{13}C NMR and DEPT-135 spectra. We surmise that the initially formed, transmetallated product **18** rearranged to the more stable **18a** before it could react with diphenylmethanol (**9a**, Scheme 4).

The scope of the copper-catalyzed coupling reaction of diarylmethanols **9b–d** with phenylboronic acid (**10a**) was explored by changing one or both of the aryl rings in the diarylmethanol (Table 3) [62]. The copper-catalyzed reaction of phenyl(pyren-1-yl)methanol (**9b**) with phenylboronic acid (**10a**) was very facile and the product triarylmethane **11n** was obtained in 72% yield (Table 3, entry 1). Similarly, the reaction of anthracen-9-yl(phenyl)methanol (**9c**) with phenylboronic acid (**10a**) provided the corresponding triarylmethane **11o** in 82% yield (Table 3, entry 2). The last example in the genre is interesting, as one of the aryl rings is ferrocene in **11p**. The reaction of ferrocene-1-yl(phenyl)methanol (**9d**) with phenyboronic acid (**10a**) was facile and it provided diphenylmethylferrocene (**11p**) without any difficulty in 71% yield.

Modular synthesis of triarylmethanes

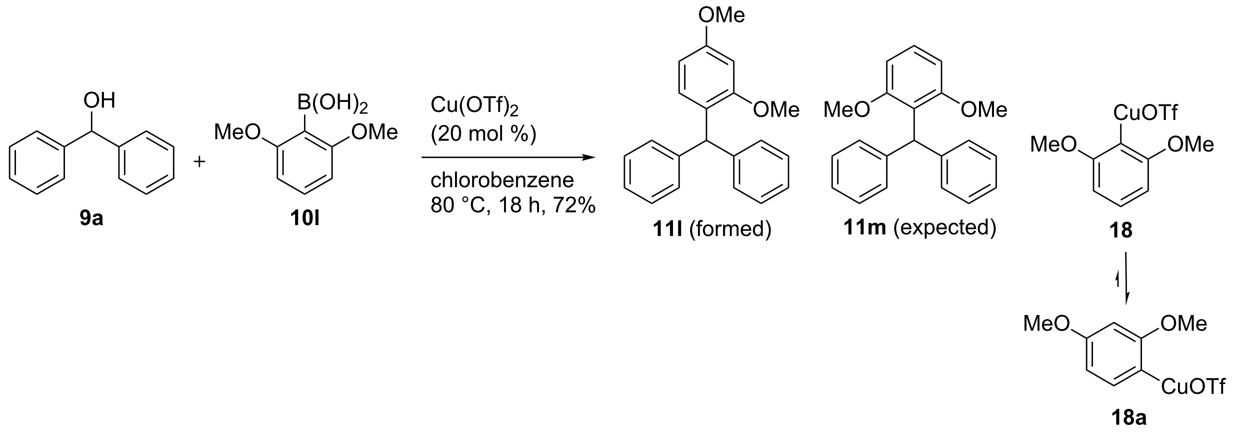
The synthetic method that we developed, through which three different aromatic rings on the central carbon can be assembled in a two-step protocol, is modular in nature. The first step is the synthesis of diarylmethanol and the second step is the replacement of the hydroxy group in the resulting diarylmethanol by a third aryl group by employing arylboronic acid under copper catalysis. As a proof of principle, we present the synthesis of

Table 2: Scope of the Cu-catalyzed arylation with various arylboronic acids.



9a **10b–k** **11b–k**

Entry	Ar in arylboronic acid	Triarylmethane	Time (h)	Yield (%)
1	**10b**: 4-$CF_3C_6H_4$	**11b**	4	92
2	**10c**: 4-FC_6H_4	**11c**	10	77
3	**10d**: 4-ClC_6H_4	**11d**	6	79
4	**10e**: 4-BrC_6H_4	**11e**	4	91
5	**10f**: 4-$MeOC_6H_4$	**11f**	5	81
6	**10g**: 4-MeC_6H_4	**11g**	6	81
7	**10h**: 2,5-$(OMe)_2C_6H_3$	**11h**	6	88
8	**10i**: 2-furyl	**11i**	8	85
9	**10j**: 2-thiophenyl	**11j**	8	89
10	**10k**: 2-benzothiophenyl	**11k**	10	86



Scheme 4: Copper-catalyzed C–C bond formation synthesis of triarylmethane **10l**.

Table 3: Scope of diarylmethanol **9b–d** in the copper-catalyzed coupling reaction.

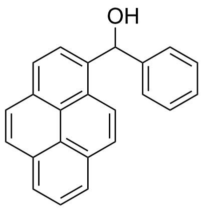
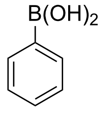
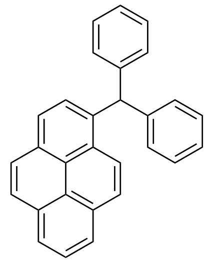
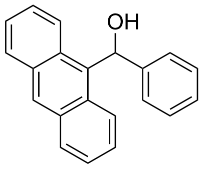
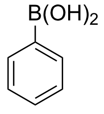
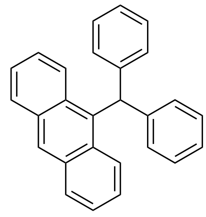
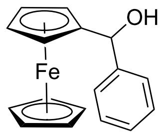
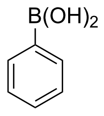
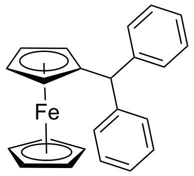
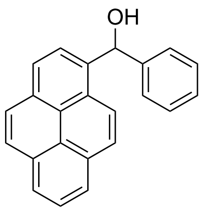
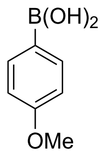
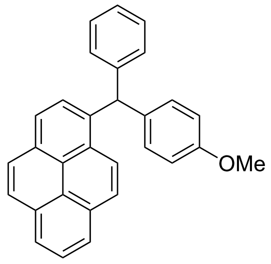
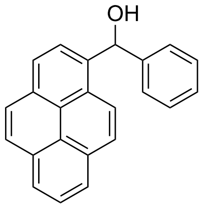
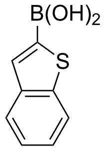
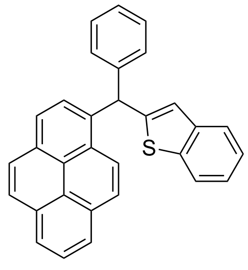
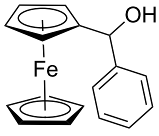
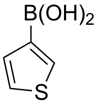
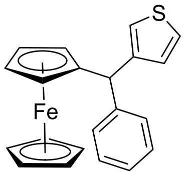
Entry	Diarylmethanol	Arylboronic acid	Triarylmethane^a
1	 **9b**	 **10a**	 **11n** (14 h, 72%)
2	 **9c**	 **10a**	 **11o** (16 h, 83%)
3	 **9d**	 **10a**	 **11p** (16 h, 71%)
4	 **9b**	 **10f**	 **11q** (16 h, 68%)

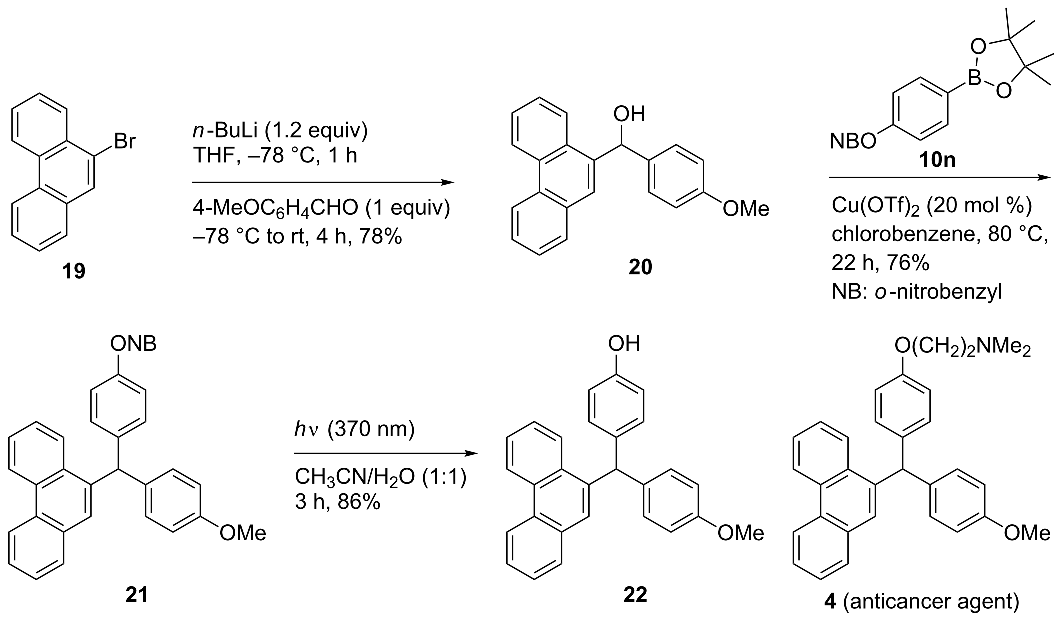
Table 3: Scope of diarylmethanol **9b–d** in the copper-catalyzed coupling reaction. (continued)

5	 **9b**	 **10k**	 **11r** (12 h, 72%)
6	 **9d**	 **10m**	 **11s** (4 h, 64%)

[a] Time required for completion of the reaction and yield of the isolated and purified triarylmethanes are given in the parenthesis.

three examples of triarylmethanes **11q–s** that bear three different aromatic rings (Table 3). The copper-catalyzed coupling reaction of phenyl(pyren-1-yl)methanol (**9b**) with 4-methoxyphenylboronic acid (**10f**) and benzo[*b*]thiophen-2-ylboronic acid (**10k**) provided the respective pyrene-containing unsymmetrical triarylmethanes **11q–r** in good yields (Table 3). Next, the coupling reaction of phenyl(ferrocenyl)methanol (**9d**) with thiophen-3-ylboronic acid (**10m**) provided triarylmethane **11s**, which has ferrocene, thiophene and phenyl rings installed on the central carbon. The triarylmethane **11s** was found to be unstable when kept as a solution in hexane. However, the compound was stable as a solid for at least two months when refrigerated (+5 °C).

To demonstrate an application of our newly developed $Cu(OTf)_2$-catalyzed C–C coupling reaction for the synthesis of triarylmethanes, we designed a synthesis of the precursor **22** (Scheme 5) for the anti-breast-cancer agent **4** (Figure 1). Any method for the synthesis of **4** needs to take into account that it has two phenyl rings with different alkoxy groups at the respec-



Scheme 5: Synthesis of anti-breast-cancer agent intermediate **22**.

tive C(4) position. We reasoned that one of the aryl groups could be a part of diarylmethanol and the other of the arylboronic acid. We designed the protection of the C(4) hydroxy group in the arylboronic aicd with the photolabile 2-nitrobenzyl (NB) group, so that it can be removed without affecting the rest of the molecule. The synthesis of triarylmethane **22** began with the preparation of the starting diarylmethanol **20**, which was accomplished by the addition the anion from 9-bromophenanthrene [63] **19** to 4-methoxybenzaldehdye. The resulting diarylmethanol **20** was treated with bis(pinacolato)diboron [64] **10n**, which has an 2-nitrobenzyl protecting group on the phenolic hydroxy group [52]. The reaction was conducted in the presence of 20 mol % $Cu(OTf)_2$ under optimized conditions, providing triarylmethane **21** in 76% yield. Deprotection of the phenolic hydroxy group in **21** was facile under photocatalytic conditions by using UV LED lamps in wet acetonitrile. The reaction furnished the synthetic intermediate **22** in 86% yield [52]. Since the intermediate **22** has been previously converted into the drug candidate **4** [49], our efforts constitute a formal, alternate synthesis.

Conclusion

In conclusion, we have demonstrated a facile $Cu(OTf)_2$-catalyzed synthesis of a variety of triarylmethanes from readily available diarylmethanols and arylboronic acids. This method is a novel synthetic approach for the preparation of multisubstituted triarylmethanes starting from easily preparable diarylmethanols and commercially available arylboronic acids. Structurally diverse, unsymmetrical triarylmethanes were prepared by employing this methodology. As an application to the newly developed methodology, we achieved a facile synthesis of the penultimate intermediate of an anti-breast-cancer agent. Hopefully the work described here will stimulate further work for the synthesis of a wide variety of triarylmethanes with tailor-made properties.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, details of the NMR structural determination of all new compounds and copies of ^{1}H, ^{13}C NMR and DEPT-135 spectra for all compounds prepared.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-49-S1.pdf]

Acknowledgements

H.S.P.R thanks UGC, UGC-SAP, CSIR and DST-FIST for financial assistance. A.V.R thanks CSIR for a fellowship. We thank CIF, Pondicherry University for recording spectra.

References

1. Mondal, S.; Panda, G. *RSC Adv.* **2014,** *4,* 28317–28358. doi:10.1039/c4ra01341g
2. Nair, V.; Thomas, S.; Mathew, S. C.; Abhilash, K. G. *Tetrahedron* **2006,** *62,* 6731–6747. doi:10.1016/j.tet.2006.04.081
3. Shchepinov, M. S.; Korshun, V. A. *Chem. Soc. Rev.* **2003,** *32,* 170–180. doi:10.1039/b008900l
4. Duxbury, D. F. *Chem. Rev.* **1993,** *93,* 381–433. doi:10.1021/cr00017a018
5. Oda, M.; Kawase, T.; Wei, C. *Pure Appl. Chem.* **1996,** *68,* 267–274. doi:10.1351/pac199668020267
6. Mason, C. D.; Nord, F. F. *J. Org. Chem.* **1951,** *16,* 722–727. doi:10.1021/jo01145a011
7. Ghaisas, V. V.; Kane, B. J.; Nord, F. F. *J. Org. Chem.* **1958,** *23,* 560–565. doi:10.1021/jo01098a016
8. Irie, M. *J. Am. Chem. Soc.* **1983,** *105,* 2078–2079. doi:10.1021/ja00345a075
9. Muthyala, R.; Katritzky, A. R.; Lan, X. *Dyes Pigm.* **1994,** *25,* 303–324. doi:10.1016/0143-7208(94)87017-9
10. Rottman, C.; Grader, G.; De Hazan, Y.; Melchior, S.; Avnir, D. *J. Am. Chem. Soc.* **1999,** *121,* 8533–8543. doi:10.1021/ja991269p
11. Yamaguchi, K.; Tamura, Z.; Maeda, M. *Anal. Sci.* **1997,** *13,* 521–522. doi:10.2116/analsci.13.521
12. Heger, D.; Klánová, J.; Klán, P. *J. Phys. Chem. B* **2006,** *110,* 1277–1287. doi:10.1021/jp0553683
13. Miura, T.; Urano, Y.; Tanaka, K.; Nagano, T.; Ohkubo, K.; Fukuzumi, S. *J. Am. Chem. Soc.* **2003,** *125,* 8666–8671. doi:10.1021/ja035282s
14. Haugland, R. P. Molecular Probes. *The Molecular Probes Handbook. A Guide to Fluorescent Probes and Labeling Technologies,* 10th ed.; Life Technologies Corporation: Eugene, USA, 2005.
15. Urano, Y.; Kamiya, M.; Kanada, K.; Ueno, T.; Hirose, K.; Nagano, T. *J. Am. Chem. Soc.* **2005,** *127,* 4888–4894. doi:10.1021/ja043919h
16. Abe, H.; Wang, J.; Furukawa, K.; Oki, K.; Uda, M.; Tsuneda, S.; Ito, Y. *Bioconjugate Chem.* **2008,** *19,* 1219–1226. doi:10.1021/bc800014d
17. Kim, H. N.; Lee, M. H.; Kim, H. J.; Kim, J. S.; Yoon, J. *Chem. Soc. Rev.* **2008,** *37,* 1465–1472. doi:10.1039/b802497a
18. Beija, M.; Afonso, C. A. M.; Martinho, J. M. G. *Chem. Soc. Rev.* **2009,** *38,* 2410–2433. doi:10.1039/b901612k
19. Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2008,** *18,* 289–292. doi:10.1016/j.bmcl.2007.10.083
20. Shagufta; Srivastava, A. K.; Sharma, R.; Mishra, R.; Balapure, A. K.; Murthy, P. S. R.; Panda, G. *Bioorg. Med. Chem.* **2006,** *14,* 1497–1505. doi:10.1016/j.bmc.2005.10.002
21. Bindal, R. D.; Golab, J. T.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1990,** *112,* 7861–7868. doi:10.1021/ja00178a003
22. Jendralla, H.; Granzer, E.; von Kerekjarto, B.; Krause, R.; Schacht, U.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Kesseler, K.; Wess, G.; Chen, L.-J.; Granata, S.; Herchen, J.; Kleine, H.; Schüssler, H.; Wagner, K. *J. Med. Chem.* **1991,** *34,* 2962–2983. doi:10.1021/jm00114a004
23. Costantino, L.; Ferrari, A. M.; Gamberini, M. C.; Rastelli, G. *Bioorg. Med. Chem.* **2002,** *10,* 3923–3931. doi:10.1016/S0968-0896(02)00318-8
24. Al-Qawasmeh, R. A.; Lee, Y.; Cao, M.-Y.; Gu, X.; Vassilakos, A.; Wright, J. A.; Young, A. *Bioorg. Med. Chem. Lett.* **2004,** *14,* 347–350. doi:10.1016/j.bmcl.2003.11.004
25. Mibu, N.; Yokomizo, K.; Uyeda, M.; Sumoto, K. *Chem. Pharm. Bull.* **2003,** *51,* 1325–1327. doi:10.1248/cpb.51.1325

26. Schultz, T. W.; Sinks, G. D.; Cronin, M. T. D. *Environ. Toxicol.* **2002,** *17,* 14–23. doi:10.1002/tox.10027
27. Wang, P.; Kozlowski, J.; Cushman, M. *J. Org. Chem.* **1992,** *57,* 3861–3866. doi:10.1021/jo00040a027
28. Long, Y.-Q.; Jiang, X.-H.; Dayam, R.; Sanchez, T.; Shoemaker, R.; Sei, S.; Neamati, N. *J. Med. Chem.* **2004,** *47,* 2561–2573. doi:10.1021/jm030559k
29. Cushman, M.; Kanamathareddy, S.; De Clerq, E.; Schols, D.; Goldman, M. E.; Bowen, J. A. *J. Med. Chem.* **1991,** *34,* 337–342. doi:10.1021/jm00105a053
30. Parmar, V. S.; Bisht, K. S.; Jain, R.; Singh, S.; Sharma, S. K.; Gupta, S.; Malhotra, S.; Tyagi, O. D.; Vardhan, A.; Pati, H. N. *Indian J. Chem., Sect. B* **1996,** *35,* 220–232.
31. Bindal, R. D.; Katzenellenbogen, J. A. *J. Med. Chem.* **1988,** *31,* 1978–1983. doi:10.1021/jm00118a020
32. Seligmann, O.; Wagner, H. *Tetrahedron* **1981,** *37,* 2601–2606. doi:10.1016/S0040-4020(01)98963-X
33. Pindur, U.; Müller, J. *J. Heterocycl. Chem.* **1987,** *24,* 289–290. doi:10.1002/jhet.5570240156
34. Witzel, H.; Pindur, U. *J. Heterocycl. Chem.* **1988,** *25,* 907–910. doi:10.1002/jhet.5570250339
35. Sato, T.; Higuchi, S.; Ito, K. *Lett. Org. Chem.* **2007,** *4,* 595–600. doi:10.2174/157017807782795574
36. Podder, S.; Choudhury, J.; Roy, U. K.; Roy, S. *J. Org. Chem.* **2007,** *72,* 3100–3103. doi:10.1021/jo062633n
37. Kodomari, M.; Nagamatsu, M.; Akaike, M.; Aoyama, T. *Tetrahedron Lett.* **2008,** *49,* 2537–2540. doi:10.1016/j.tetlet.2008.02.117
38. Yamamoto, Y.; Itonaga, K. *Chem. – Eur. J.* **2008,** *14,* 10705–10715. doi:10.1002/chem.200801105
39. Genovese, S.; Epifano, F.; Pelucchini, C.; Curini, M. *Eur. J. Org. Chem.* **2009,** 1132–1135. doi:10.1002/ejoc.200801115
40. Hikawa, H.; Suzuki, H.; Azumaya, I. *J. Org. Chem.* **2013,** *78,* 12128–12135. doi:10.1021/jo402151g
41. Li, Z.; Duan, Z.; Kang, J.; Wang, H.; Yu, L.; Wu, Y. *Tetrahedron* **2008,** *64,* 1924–1930. doi:10.1016/j.tet.2007.11.080
42. Shirakawa, S.; Kobayashi, S. *Org. Lett.* **2007,** *9,* 311–314. doi:10.1021/ol062813j
43. Thirupathi, P.; Kim, S. S. *Tetrahedron* **2010,** *66,* 2995–3003. doi:10.1016/j.tet.2010.02.063
44. Shacklady-McAtee, D. M.; Roberts, K. M.; Basch, C. H.; Song, Y.-G.; Watson, M. P. *Tetrahedron* **2014,** *70,* 4257–4263. doi:10.1016/j.tet.2014.03.039
45. Harris, M. R.; Hanna, L. E.; Greene, M. A.; Moore, C. E.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013,** *135,* 3303–3306. doi:10.1021/ja311783k
46. Zhou, Q.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013,** *135,* 3307–3310. doi:10.1021/ja312087x
47. Tabuchi, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2014,** *79,* 5401–5411. doi:10.1021/jo5010636
48. Matthew, S. C.; Glasspoole, B. W.; Eisenberger, P.; Crudden, C. M. *J. Am. Chem. Soc.* **2014,** *136,* 5828–5831. doi:10.1021/ja412159g
49. Nambo, M.; Crudden, C. M. *Angew. Chem., Int. Ed.* **2014,** *53,* 742–746. doi:10.1002/anie.201307019
50. Nambo, M.; Crudden, C. M. *ACS Catal.* **2015,** *5,* 4734–4742. doi:10.1021/acscatal.5b00909
51. Rao, H. S. P.; Rao, A. V. B. *Eur. J. Org. Chem.* **2014,** 3646–3655. doi:10.1002/ejoc.201402003
52. Rao, H. S. P.; Rao, A. V. B. *J. Org. Chem.* **2015,** *80,* 1506–1516. doi:10.1021/jo502446k
53. Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998,** *37,* 1701–1703. doi:10.1002/(SICI)1521-3773(19980703)37:12<1701::AID-ANIE1701>3.0.CO;2-U
54. Majumdar, K. K.; Cheng, C.-H. *Org. Lett.* **2000,** *2,* 2295–2298. doi:10.1021/ol006064w
55. Niwa, T.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2007,** *9,* 2373–2375. doi:10.1021/ol0708119
56. Yu, J.-Y.; Kuwano, R. *Org. Lett.* **2008,** *10,* 973–976. doi:10.1021/ol800078j
57. Cao, X.; Sha, S.-C.; Li, M.; Kim, B.-S.; Morgan, C.; Huang, R.; Yang, X.; Walsh, P. J. *Chem. Sci.* **2016,** *7,* 611–618. doi:10.1039/C5SC03704B
58. Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998,** *39,* 2933–2936. doi:10.1016/S0040-4039(98)00503-6
59. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998,** *39,* 2941–2944. doi:10.1016/S0040-4039(98)00504-8
60. Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998,** *39,* 2937–2940. doi:10.1016/S0040-4039(98)00502-4
61. Itoh, T.; Shimizu, Y.; Kanai, M. *Org. Lett.* **2014,** *16,* 2736–2739. doi:10.1021/ol501022d
62. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *VOGEL's Textbook of Practical Organic Chemistry,* 5th ed.; John Wiley & Sons: New York, 2077; pp 523 ff.
63. Kodomari, M.; Satoh, H.; Yoshitomi, S. *J. Org. Chem.* **1988,** *53,* 2093–2094. doi:10.1021/jo00244a046
64. Lu, J.; Guan, Z.-Z.; Gao, J.-W.; Zhang, Z.-H. *Appl. Organomet. Chem.* **2011,** *25,* 537–541. doi:10.1002/aoc.1799

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doi:10.3762/bjoc.12.49

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Studies on the synthesis of peptides containing dehydrovaline and dehydroisoleucine based on copper-mediated enamide formation

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Full Research Paper

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Keywords:
catalysis; dehydroamino acids; Hartwig–Buchwald reaction; myxovalargin; peptides

Beilstein J. Org. Chem. **2016,** *12,* 564–570.
doi:10.3762/bjoc.12.55

Received: 03 December 2015
Accepted: 02 March 2016
Published: 22 March 2016

This article is part of the Thematic Series "Copper catalysis in organic synthesis".

Guest Editor: S. R. Chemler

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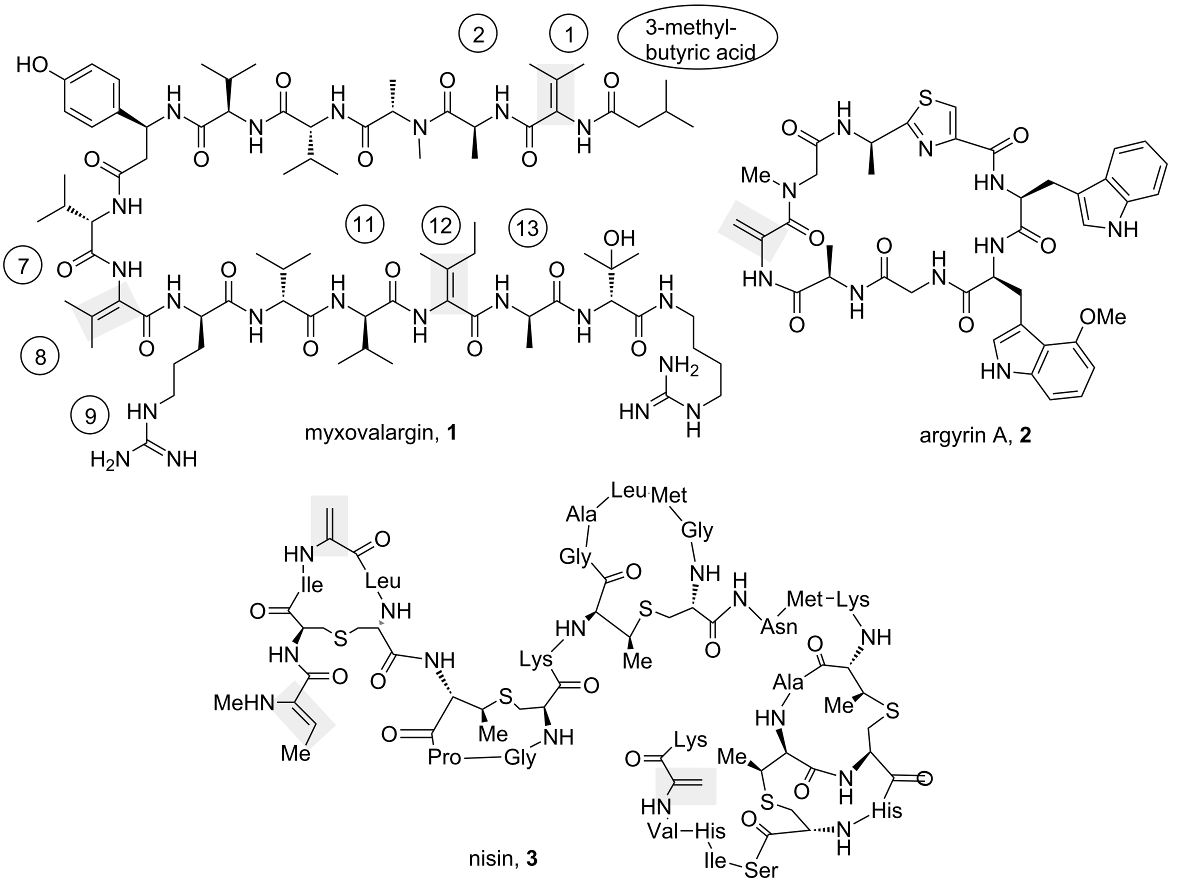
Abstract

The preparation of peptide fragments containing dehydrovaline and dehydroisoleucine moieties present in the antibiotic myxovalargin is reported. Peptide formation is based on a copper-mediated C–N cross-coupling protocol between an acyl amide and a peptidic vinyl iodide. The presence of a neighboring arginine in the vinyl iodide posed a challenge with respect to the choice of the protecting group and the reaction conditions. It was found that ornithine – a suitable precursor – is better suited than arginine for achieving good yields for the C–N cross-coupling reaction. The optimized conditions were utilized for the synthesis of peptides **32**, **33**, **39** and **40** containing a neighboring ornithine as well as for the tripeptide **44** containing dehydroisoleucine with the correct stereochemistry.

Introduction

Dehydroamino acids [1] are rare amino acids that are constituents of many oligopeptides from microbial sources. Typical examples are myxovalargin (**1**), argyrin (**2**) and nisin (**3**, Scheme 1).

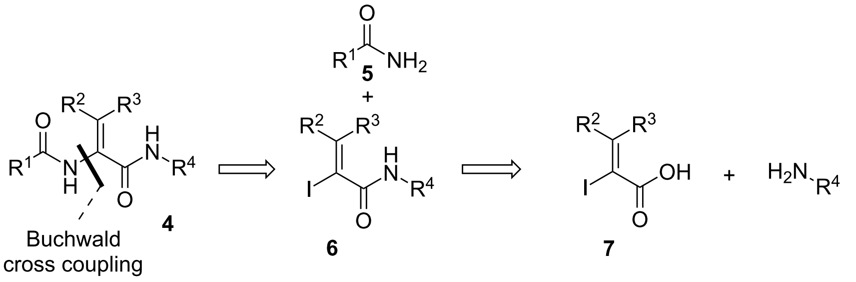
Dehydroamino acids and peptides are characterized by the presence of an olefinic double bond conjugated with the carboxyl or peptidic carbonyl group. Besides being α,β-unsaturated acids or amides, respectively, they can also be regarded as enamines. Due to the lack of reactivity of the amino group as well as the carboxylate, dehydroamino acids have hardly employed as building blocks in peptide synthesis. Therefore, the olefinic double bond is commonly introduced after the peptide backbone is assembled and typically this is achieved by elimination when a leaving group occupies the β-position [2]. Especially peptides containing dehydroalanine as found in argyrin (**2**) can be prepared from a precursor that contains a selenide substituent in the β-position [3]. Peptides that bear the doubly branched dehydroamino acids dehydrovaline or dehydroisoleucine, e.g., found in myxovalargin (**1**), are much more challenging to



Scheme 1: Selected examples of oligopeptides bearing dehydroamino acid moieties: myxovalargin (**1**), argyrin A (**2**) and nisin (**3**) (in myxovalargin dehydroamino acids and neighboring amino acids are numbered).

prepare due to steric hindrance in the β-position and the issue of regiocontrol during elimination [4,5], as β-elimination of a tertiary alcohol group often leads to the terminal instead of the conjugated alkene.

Principally, enamides can also be prepared by the copper-mediated C–N coupling between a vinyl halide **6** and an amide **5** as reported by Ogawa and co-workers in 1991 [6]. Later, the group of Porco showed that copper(I) thiophencarboxylate is a suitable catalyst to promote this reaction in the presence of cesium carbonate as base and *N*-methylpyrrolidone (NMP) as solvent [7,8]. Buchwald et al. [9] simplified the conditions by demonstrating that copper(I) iodide, potassium carbonate and the ligand *N*,*N*-dimethylethylenediamine can be used instead. Finally, Ma and co-workers [10] further modified the conditions using copper(I) iodide, cesium carbonate and *N*,*N*-dimethylglycine in 1,4-dioxane. Recently, Inoue applied this cross-coupling protocol to the synthesis of peptides (Scheme 2)



Scheme 2: The Buchwald cross-coupling reaction in the preparation of peptides containing dehydroamino acids **4**.

[11,12] as demonstrated in the total synthesis of Yaku'amide A [13].

As part of our study on the total synthesis of myxovalargin (**1**), a secondary metabolite from *Myxococcus fulvus* with antibacterial activity [14,15], we report on copper-mediated cross-coupling chemistry to create peptide fragments bearing dehydrovaline and dehydroisoleucine. We faced difficulties to use the reported conditions for the C–N cross coupling in the preparation of myxovalargin peptide fragments mainly because of the steric hindrance of β,β'-disubstituted dehydroamino acids created. Additionally, the neighboring amino acid, especially arginine or ornithine, a precursor for preparing arginine (amino acid number 9 in **1**), can be made responsible. Thus, this report covers our efforts to optimize the copper-mediated cross-coupling reaction in the preparation of dehydroamino acid containing peptide fragments present in myxovalargin (peptides containing amino acids 3-methylbutyric acid 1, 2, 7–9 and 11–13).

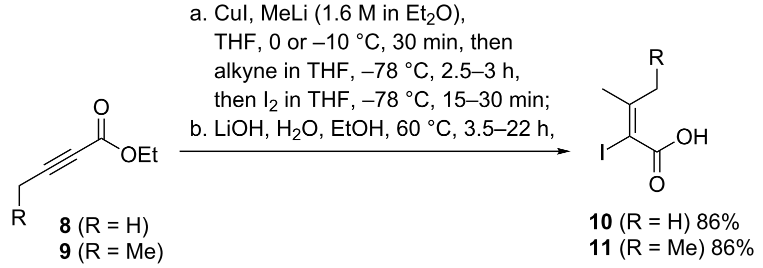
Results and Discussion

First vinyl iodide **10**, representing dehydrovaline, was prepared by an established sequence starting from alkynyl ester **8**. Under similar conditions vinyl iodide **11** which resembles dehydroisoleucine was obtained as a single diastereoisomer starting from alkynyl ester **9** (Scheme 3). The stereochemistry of the ethyl ester of **11** was determined NMR spectroscopically including nOe experiments (see Supporting Information File 1). Next, vinyl iodide **10** was subjected to amidation with L-alanine methylate (resembling position 2 in myxovalargin) using the reagent system PyAOP, HOAt, DIPEA to yield amide **12** (Table 1). Now, the stage was set to optimize the C–N coupling conditions using amide **13** as coupling partner, the 3-methylbutyric acid located at the terminus of myxovalargin (**1**).

Under the published conditions [13] (vinyl iodide (1.5 equiv), amide (1.0 equiv), CuI (0.6 equiv), Cs_2CO_3 (2.0 equiv), *N*,*N*-dimethylethylenediamine **16** (4.05 equiv), 1,4-dioxane, 90 °C) we did not encounter the formation of enamide **14** but instead only the hydrolysis product **15** was isolated which might have resulted from the presence of oxygen in the solvent. Therefore, we decreased the temperature and only degassed 1,4-dioxane was used in order to avoid oxidation and formation of copper(II) which can act as a Lewis acid. These changes provided peptide **14** (Table 1, entry 1) but this result turned out not to be reproducible. Instead, when the reaction time was extended, only the formation of the α-ketoamide **15** was encountered (Table 1, entry 2). Change of the solvent to THF or toluene as well as the use of palladium catalysts [16] or the use of additives such as HMPA mainly led to substantial decomposition of vinyl iodide **12**. At room temperature only small amounts of product were formed but the vinyl iodide was stable (Table 1, entry 3). The presence of the ligand was essential and the choice of other amines such as tetramethylethylendiamine (TMEDA) (Table 1, entry 4) or piperidine-2-carboxylate did not lead to product formation (Table 1, entry 5).

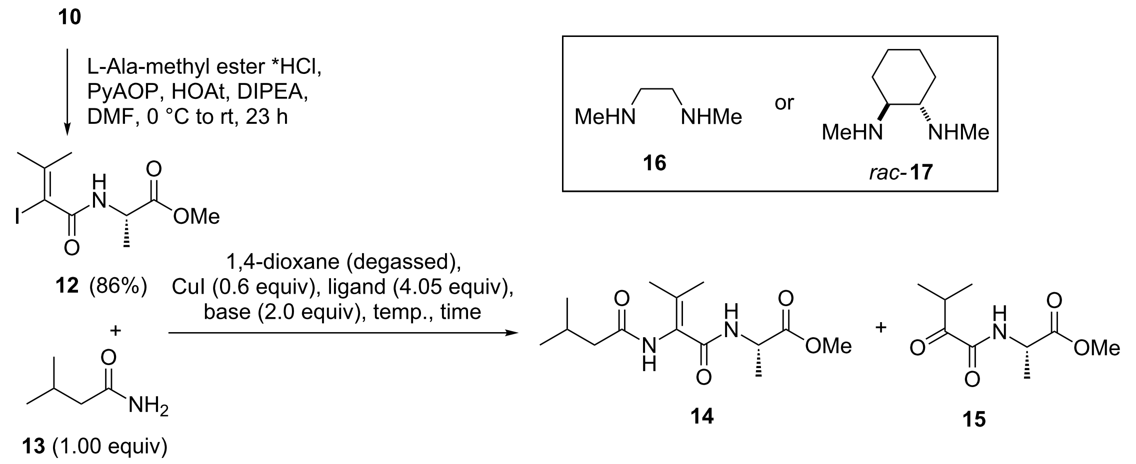
However, (*rac*)-*trans*-*N*,*N*-dimethyl-1,2-cyclohexanediamine (**17**) [9] in combination with cesium carbonate or potassium carbonate, the latter being superior to the former base, in 1,4-dioxane provided conditions that allowed us to prepare the coupling product **14** at room temperature. When raising the temperature to 50 °C the desired coupling product was isolated in 35% yield along with a substantial amount of starting vinyl iodide (Table 1, entry 6). When *N*,*N*-dimethylethylenediamine (**16**) was employed under these conditions instead, the coupling product formed only in traces. When potassium carbonate was exchanged by sodium carbonate the yield dropped to 25% under the optimized conditions (Table 1, entry 8).

Next, we tested these reaction conditions for the preparation of the other dehydrovaline bearing peptide fragment of myxovalargin **1** (amino acids 7–9). First, dipeptides **18**–**21** and methyl esters **22** and **23** were *N*-acylated with vinyl iodide **10** to yield peptidic vinyl iodides **24**–**29** in commonly good yields (Scheme 4). The coupling partners **18**–**23** (synthesis see Supporting Information File 1) all contain arginine or the precursor amino acid ornithine and they differ in the choice of the protecting group. These variations are important for gaining



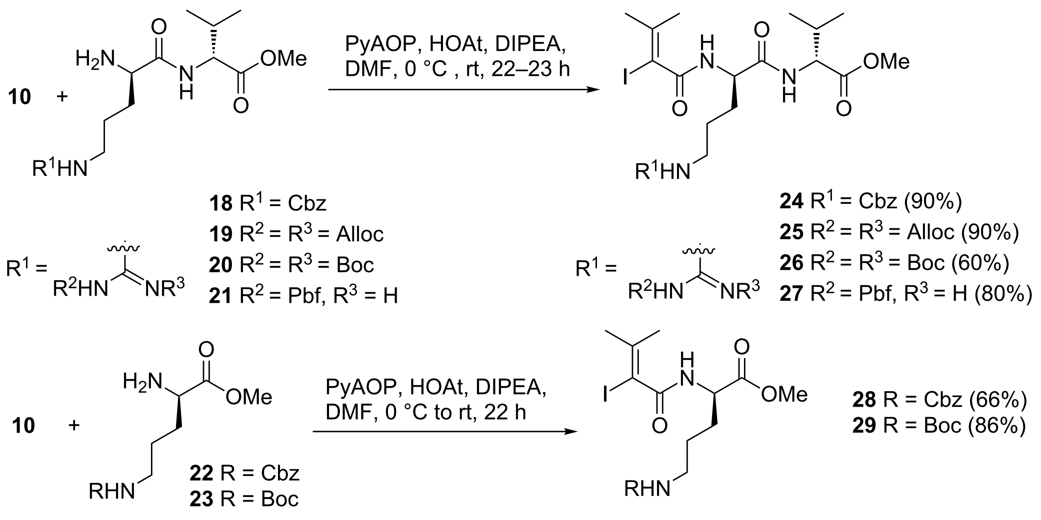
Scheme 3: Syntheses of vinyl iodides **10** and **11**.

Table 1: Formation of amide **12** and optimization of C–N cross coupling reaction.



entry	conditions	**12** (equiv)	**12** (% reisolated)	**14** (% yield)	**15** (% yield)
1	**16**, Cs_2CO_3, 16 h, 50 °C	1.5	–	31	–
2	**16**, Cs_2CO_3, 26 h, 50 °C	1.5	–	0	nd
3	**16**, Cs_2CO_3, 24 h, rt	1.5	60	~15	0
4[a]	TMEDA, Cs_2CO_3, 20 h, rt	1.5		no reaction	
5[a]	piperidine-2-carboxylate, K_2CO_3, 20 h, rt	1.5		no reaction	
6	**17**, K_2CO_3, 22 h, 50 °C	2.0	43	35	0
7	**17**, K_2CO_3, 20 h, 70 °C	2.0	57	35	0
8	**17**, Na_2CO_3, 20 h, 70 °C	2.0	66	25	0

[a] CuI (1.0 equiv) was used instead of 0.6 equiv of CuI.



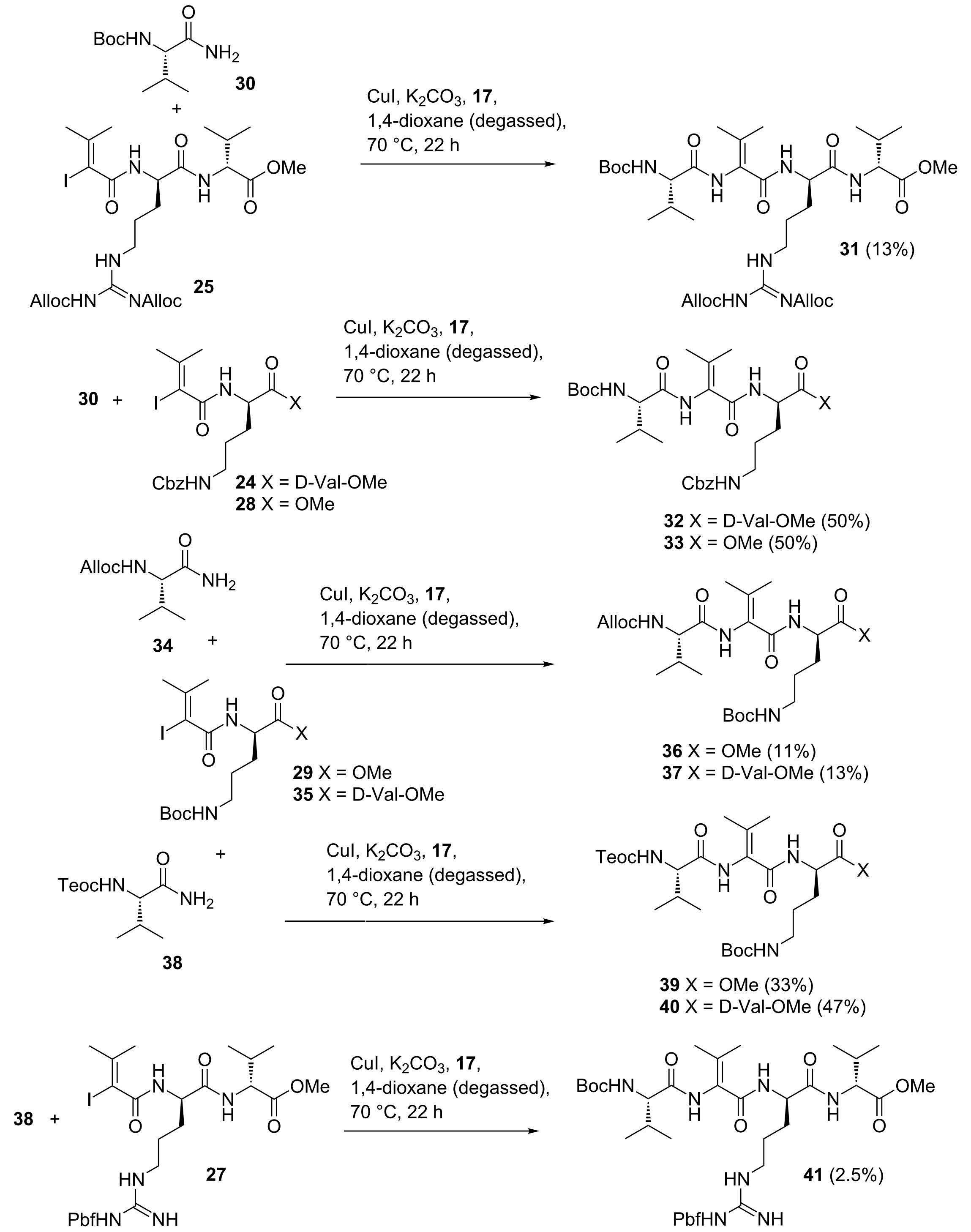
Scheme 4: Preparation of vinyl iodides **24**–**29** (Cbz = benzyloxycarbonyl, Alloc = allyloxycarbonyl, Boc = *tert*-butyloxycarbonyl, Pbf = 2,2,4,6,7-pentamethyldihydrobenzofurane-5-sulfonyl).

flexibility towards the end of the total synthesis when the guanidine group has either to be liberated by the removal of the protecting groups or used for the introduction to the corresponding ornithine residue.

These results demonstrate that the copper-mediated cross-coupling reaction depends on the functional groups present in the peptide containing the vinyl iodide moiety and on the chosen protecting groups. Vinyl iodides bearing an arginine moiety gave a significantly reduced yield of the desired cross-coupling product compared to the corresponding ornithine derivatives.

Furthermore, it turned out that the Alloc and Pbf protecting groups are not compatible for this enamide forming protocol. The best results were obtained by using the Boc-protected amide **30** and ornithine-containing vinyl iodides **24** and **28** (Scheme 5).

It needs to be noted that the presence of a Cbz protecting group in dehydrooligopeptides is problematic, because it cannot be cleaved without simultaneously reducing the acyl enamide. We



Scheme 5: Copper-mediated C–N cross-coupling of dehydropeptides **31–33**, **36**, **37**, and **39–41**.

found that the Teoc protecting group is better suited to be removed from oligoamides **39** and **40**, respectively, which were formed from amide **38** and vinyl iodides **29** and **35** (Scheme 5) [17]. Facile removal of the Teoc group was achieved within 24 h at room temperature in quantitative yield using a 1 M solution in TBAF in THF.

With these results in hand we next coupled amide **42** with Boc-protected valine-derived amide **43**. To our delight, the coupling proceeded in an improved yield of 48% without scrambling of the stereochemistry of the olefinic double bond (Scheme 6). We based the stereochemical assignment on NMR spectroscopy which included nOe experiments.

Conclusion

In conclusion, we report on the synthesis of dehydrovaline and dehydroisoleucine-containing oligopeptides as found in the peptide antibiotic myxovalargin using a C–N cross-coupling approach. Substantial optimization of the reaction conditions and the choice of the protecting group became necessary when the dehydrovaline-containing oligopeptide based on ornithine was synthesized. For the copper-mediated Buchwald C–N coupling reaction, (*rac*)-*trans*-*N*,*N*-dimethyl-1,2-cyclohexandiamine was the ligand of choice in combination with potassium carbonate as base. In our case, the usage of Boc and Teoc protection groups in the cross-coupling reaction gave the best results. By using the optimized reaction conditions the dehydroisoleucine peptide was synthesized without scrambling of stereochemistry. In summary, we showed that the C–N coupling reaction is a powerful tool to straight forwardly build-up of sterically hindered dehydroamino acid-containing peptide fragments.

Supporting Information

Supporting Information File 1

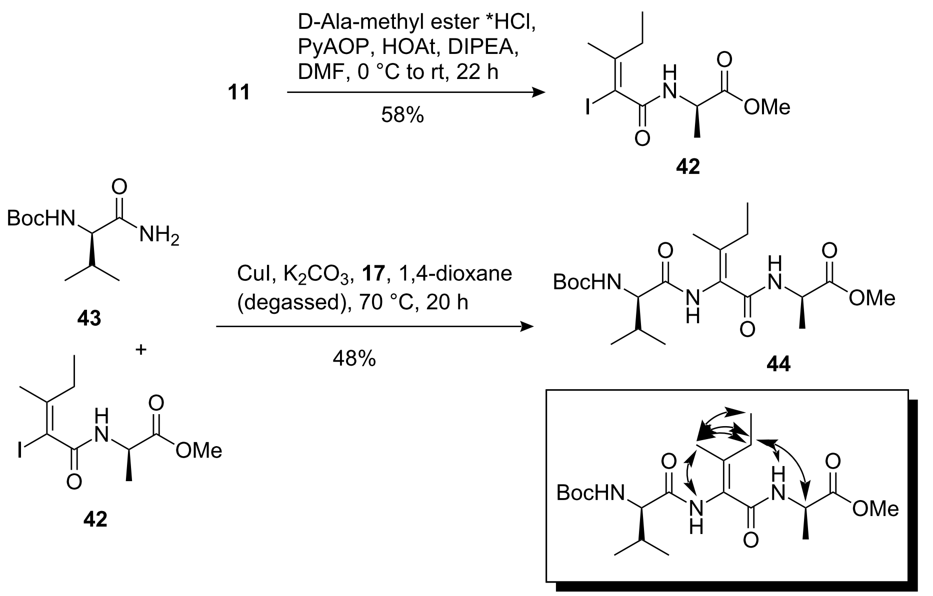
Syntheses and analytical descriptions of reagents and peptides and copies of ^{1}H and ^{13}C NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-55-S1.pdf]

Acknowledgements

We thank the Beilstein-Institut for generously supporting Franziska Gille with a Ph.D. scholarship.

References

1. Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997,** *97,* 2243–2266. doi:10.1021/cr950005s
2. Kazmaier, U. Synthesis and Chemistry of α,β-Dehydroamino Acids. In *Amino Acids, Peptides and Proteins in Organic Chemistry;* Hughes, A. B., Ed.; Wiley-VCH: Weinheim, 2009; Vol. 2, pp 3–34.
3. Ley, S. V.; Priour, C.; Heusser, C. *Org. Lett.* **2002,** *4,* 711–714. doi:10.1021/ol017184m
4. Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988,** 159–172. doi:10.1055/s-1988-27503
5. Bonauer, C.; Walenzyk, T.; König, B. *Synthesis* **2006,** 1–20. doi:10.1055/s-2005-921759
6. Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991,** *20,* 1443–1446. doi:10.1246/cl.1991.1443



Scheme 6: C–N coupling reaction between amide **43** and vinyl iodide **42**; formation of dehydroisoleucine containing peptide **44**. nOe assignments (tripeptide corresponds to amino acids 11–13 in myxovalargin (**1**)).

7. Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000,** *2,* 1333–1336. doi:10.1021/ol005800t
8. Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003,** *125,* 7889–7901. doi:10.1021/ja0352350
9. Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003,** *5,* 3667–3669. doi:10.1021/ol035355c
10. Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004,** *6,* 1809–1812. doi:10.1021/ol049464i
11. Kuranaga, T.; Sesoko, Y.; Inoue, M. *Nat. Prod. Rep.* **2014,** *31,* 514–532. doi:10.1039/c3np70103d
12. Evano, G.; Theunissen, C.; Pradal, A. *Nat. Prod. Rep.* **2013,** *30,* 1467–1489. doi:10.1039/c3np70071b
13. Kuranaga, T.; Sesoko, Y.; Sakata, K.; Maeda, N.; Hayata, A.; Inoue, M. *J. Am. Chem. Soc.* **2013,** *135,* 5467–5474. doi:10.1021/ja401457h
14. Irschik, H.; Gerth, K.; Kemmer, T.; Steinmetz, H.; Reichenbach, H. *J. Antibiot.* **1983,** *36,* 6–12. doi:10.7164/antibiotics.36.6
15. Irschik, H.; Reichenbach, H. *J. Antibiot.* **1985,** *38,* 1237–1245. doi:10.7164/antibiotics.38.1237
16. Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003,** *125,* 6653–6655. doi:10.1021/ja035483w
17. Gille, F.; Kirschning, A. unpublished results.

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