BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

C–H Functionalization/activation in organic synthesis

Edited by Richmond Sarpong

Generated on 07 November 2026, 18:36

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

The copyright to this document as a whole, which is published in the *Beilstein Journal of Organic Chemistry*, is held by the Beilstein-Institut zur Förderung der Chemischen Wissenschaften. The copyright to the individual articles in this document is held by the respective authors, subject to a Creative Commons Attribution license.

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

C–H Functionalization/activation in organic synthesis

Richmond Sarpong

Editorial

Open Access

Address:
Department of Chemistry, University of California, Berkeley, 841A Latimer Hall, Berkeley, CA 94720, USA

Email:
Richmond Sarpong - rsarpong@berkeley.edu

Keywords:
C–H activation; C–H functionalization

Beilstein J. Org. Chem. **2016,** *12,* 2315–2316.
doi:10.3762/bjoc.12.224

Received: 19 September 2016
Accepted: 29 September 2016
Published: 03 November 2016

This article is part of the Thematic Series "C–H Functionalization/activation in organic synthesis".

Guest Editor: R. Sarpong

© 2016 Sarpong; licensee Beilstein-Institut.
License and terms: see end of document.

The last decade has seen an explosion in research reports in the area of C–H functionalization/activation in organic synthesis. This is not surprising. What is surprising is that it took many in the synthetic organic community this long to fully embrace this exciting and enabling technology. After all, organic compounds mainly consist of a carbon skeleton that bears a large number of hydrogens. It is therefore highly desirable to be able to take advantage of the myriad of C–H groups in organic molecules as functional handles for bond formation, and in some cases, bond-breaking processes.

"Modern" C–H functionalization/activation can trace its roots to the "clarion call" by Bergman and co-workers [1] in a famous *Accounts of Chemical Research* paper in 1995 where the potential for this reaction was discussed. The community has responded and today, there are investigators from all branches of chemistry, chemical biology, and engineering that are pursuing new powerful methods and strategies to achieve C–H functionalization/activation reactions. The growth in popularity of C–H functionalization/activation in organic synthesis can be attributed to the desire to implement more sustainable methods for synthesis and to achieve novel reactivity and selectivity in building molecules. A lot of exciting progress has been made in a short period of time and the stage has been set for even more far-reaching developments in the future.

In this Thematic Series, a collection of 10 contributions from researchers in the area of C–H functionalization from Europe, United States, Japan, China, India, and Brazil is presented. These contributions include full accounts on primary research in the area of C–H functionalization/activation and reviews that focus on aspects of this exciting field. The powerful C_{sp}^2 functionalization of heterocycles provides access to value-added compounds as reported by Itami et al. [2], Chatani et al. [3] and Waser et al. [4]. Alternatively, the C_{sp}^2 functionalization of benzenoids is equally powerful and affords interesting opportunities as described by Lipshutz et al. [5], Bisai et al. [6] and Chen et al. [7]. The emerging power of controlled and selective C_{sp}^3 functionalization is also captured in this series with contributions from Wang et al. [8], May et al. [9], Machado et al. [10] and Dai et al. [11].

I am grateful to all those that have participated in making this Thematic Series, first and foremost, the authors. I am also thankful to the reviewers, who made many constructive suggestions. Overall, it is clear that the field of C–H functionalization/

activation in all its varied forms is an exciting area of modern synthetic chemistry and in many ways is revolutionizing synthetic organic chemistry. This Thematic Series provides a view into this burgeoning and exciting world.

Richmond Sarpong

Berkeley, September 2016

References

1. Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995,** *28,* 154–162. doi:10.1021/ar00051a009
2. Hata, K.; Ito, H.; Segawa, Y.; Itami, K. *Beilstein J. Org. Chem.* **2015,** *11,* 2737–2746. doi:10.3762/bjoc.11.295
3. Tobisu, M.; Igarashi, T.; Chatani, N. *Beilstein J. Org. Chem.* **2016,** *12,* 654–661. doi:10.3762/bjoc.12.65
4. Tolnai, G. L.; Brand, J. P.; Waser, J. *Beilstein J. Org. Chem.* **2016,** *12,* 745–749. doi:10.3762/bjoc.12.74
5. Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *Beilstein J. Org. Chem.* **2016,** *12,* 1040–1064. doi:10.3762/bjoc.12.99
6. Kumar, N.; Ghosh, S.; Bhunia, S.; Bisai, A. *Beilstein J. Org. Chem.* **2016,** *12,* 1153–1169. doi:10.3762/bjoc.12.111
7. Nack, W. A.; Wang, X.; Wang, B.; He, G.; Chen, G. *Beilstein J. Org. Chem.* **2016,** *12,* 1243–1249. doi:10.3762/bjoc.12.119
8. Wang, B.; Qiu, D.; Zhang, Y.; Wang, J. *Beilstein J. Org. Chem.* **2016,** *12,* 796–804. doi:10.3762/bjoc.12.78
9. Shih, J.-L.; Chen, P.-A.; May, J. A. *Beilstein J. Org. Chem.* **2016,** *12,* 985–999. doi:10.3762/bjoc.12.97
10. Santiago, J. V.; Machado, A. H. L. *Beilstein J. Org. Chem.* **2016,** *12,* 882–902. doi:10.3762/bjoc.12.87
11. Ye, Z.; Gettys, K. E.; Dai, M. *Beilstein J. Org. Chem.* **2016,** *12,* 702–715. doi:10.3762/bjoc.12.70

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.224

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Pyridylidene ligand facilitates gold-catalyzed oxidative C–H arylation of heterocycles

Kazuhiro Hata[1], Hideto Ito[1], Yasutomo Segawa*[1,2] and Kenichiro Itami*[1,2,3]

Full Research Paper

Open Access

Address:
[1]Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan, [2]JST, ERATO, Itami Molecular Nanocarbon Project, Nagoya University, Chikusa, Nagoya 464-8602, Japan and [3]Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, Chikusa, Nagoya 464-8602, Japan

Email:
Yasutomo Segawa* - ysegawa@nagoya-u.jp; Kenichiro Itami* - itami@chem.nagoya-u.ac.jp

* Corresponding author

Keywords:
carbene ligand; C–H arylation; gold catalysis

Beilstein J. Org. Chem. **2015,** *11,* 2737–2746.
doi:10.3762/bjoc.11.295

Received: 20 September 2015
Accepted: 09 December 2015
Published: 28 December 2015

This article is part of the Thematic Series "C–H Functionalization/activation in organic synthesis".

Guest Editor: R. Sarpong

© 2015 Hata et al; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

Triaryl-2-pyridylidene effectively facilitates the gold-catalyzed oxidative C–H arylation of heteroarenes with arylsilanes as a unique electron-donating ligand on gold. The employment of the 2-pyridylidene ligand, which is one of the strongest electron-donating N-heterocyclic carbenes, resulted in the rate acceleration of the C–H arylation reaction of heterocycles over conventional ligands such as triphenylphosphine and a classical N-heterocyclic carbene. In situ observation and isolation of the 2-pyridylidene-gold(III) species, as well as a DFT study, indicated unusual stability of gold(III) species stabilized by strong electron donation from the 2-pyridylidene ligand. Thus, the gold(I)-to-gold(III) oxidation process is thought to be facilitated by the highly electron-donating 2-pyridylidene ligand.

Introduction

Over the past decade, gold salts and complexes have emerged as unique catalysts for the transformation of alkynes, alkenes and allenes [1-30]. In most of the gold-catalyzed reactions, phosphines, N-heterocyclic carbenes, pyridines and salen ligands have been applied as ligands for controlling the stability of catalysts, and chemo-, regio- and enantioselectivities of the reactions [31-36]. Recent advances in the gold-catalyzed reactions are represented by oxidative coupling that is expected to proceed through a gold(I)/gold(III) catalytic cycle [37-81]. In particular, the elegant works of Lloyd-Jones and Russell on gold-catalyzed oxidative C–H arylation of simple arenes with arylsilanes have led the way to novel gold-catalyzed reactions that could not be achieved with other transition metals [68,69]. In these reactions, the oxidation of gold(I) to gold(III) is thought to be a key step in the catalytic cycle consisting of transmetalation with arylsilane, C–H activation and reductive elimination [69]. While gold(I) complexes bearing various ligands are used as gold(III) precursors, it remains unclear whether ligands can still coordinate to the gold center or not under such oxidative reaction conditions. For example, tri-

phenylphosphine is easily oxidized to triphenylphosphine oxide by a hypervalent iodine reagent that has been used as an oxidant for gold-catalyzed C–H arylation [69]. Appropriate ligands that are tolerant to the oxidative conditions would offer numerous benefits such as high activity and stability of gold catalyst, thereby achieving otherwise-difficult oxidative transformations [37-40].

Recently, we have introduced highly electron-donating triaryl-2-pyridylidene (PyC: pyridine-based carbene) [82-84] as a new type of nonclassical N-heterocyclic carbene [85-102]. We demonstrated that the PyC ligand is one of the strongest electron-donating carbene ligands to a gold(I) species (Figure 1) [83]. The AuCl(PyC) complex is very stable, even in air and moisture, and isolable by column chromatography on silica gel. Thus we envisioned that a gold complex with strongly electron-donating PyC would promote the gold(I)-to-gold(III) oxidation process, facilitating oxidative coupling reactions. Herein we report that the PyC ligand facilitates gold-catalyzed oxidative C–H arylation of hereroarenes that has been known to be very sluggish with typical ligand systems [68-72]. In this paper, the C–H arylation reactions of isoxazole, indole, and benzothiophene are presented. In addition, direct observation and isolation of PyC-gold(III) complexes are described.

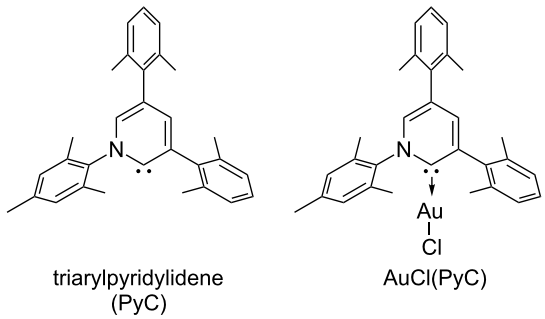


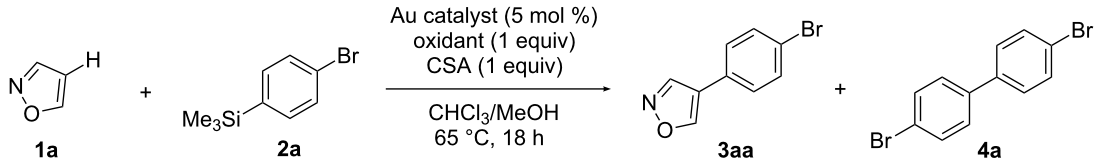
Figure 1: Triaryl-2-pyridylidene (PyC) and PyC-gold(I) complex (AuCl(PyC)).

Results and Discussion

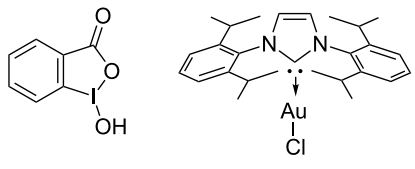
Ligand effect of PyC in gold-catalyzed aromatic C–H arylation

In this study, we selected the gold-catalyzed oxidative C–H arylation of arenes with arylsilanes [68,69], reported by Lloyd-Jones and Russell, to test the ligand effect of PyC (Table 1).

Table 1: Effect of ligand and oxidant in gold-catalyzed oxidative C–H arylation of isoxazole **1a**.[a]



Entry	Au catalyst	Oxidant	Yield [%][b]	
			3aa	**4a**
1	$AuCl(PPh_3)$	IBA	10	7
2	AuCl(IPr)	IBA	0	0
3	AuCl(PyC)	IBA	30	12
4	AuCl(PyC)	$PhI(OAc)_2$	4	5
5	AuCl(PyC)	$PhI(OCOCF_3)_2$	3	4
6[c]	AuCl(PyC)	PhI(OH)(OTs)	9	5
7[d]	AuCl(PyC)	IBA	13	5
8[c]	AuCl(PyC)	IBA	0	9
9[e]	AuCl(PyC)	IBA	3	36



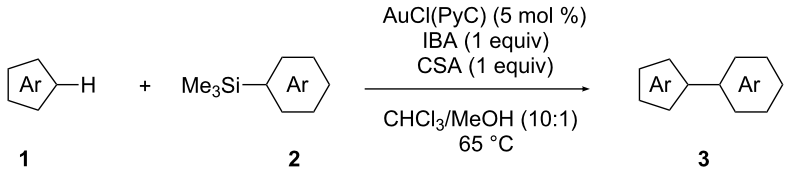
[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.20 mmol), Au catalyst (5 mol %), oxidant (0.20 mmol), (+)-10-camphorsulfonic acid (CSA, 0.20 mmol), $CHCl_3$/MeOH (10:1, 1.1 mL), 65 °C. [b]Determined by GC analysis with *n*-nonane as an internal standard. [c]Without CSA. [d]$TsOH{\cdot}H_2O$ was used instead of CSA. [e]$CHCl_3$ (1.0 mL) was used as solvent.

Likely due to the low stability of electron-rich heteroarene substrates toward oxidative conditions [103-107], their original conditions usually do not work well for these substrates. For example, when isoxazole (**1a**: 1 equiv) [108-111] was treated with 1-bromo-4-(trimethylsilyl)benzene (**2a**: 1 equiv) in chloroform/methanol solution at 65 °C in the presence of AuCl(PPh_3) (5 mol %), iodosobenzoic acid (IBA: 1 equiv) and (+)-10-camphorsulfonic acid (CSA: 1 equiv), the corresponding C–H arylation product **3aa** was obtained in only 10% yield (Table 1, entry 1). Although the application of IPr, a conventional NHC ligand, to the reaction did not afford **3aa** at all (Table 1, entry 2), PyC promoted the reaction with higher yield of 4-arylisoxazole **3aa** under these conditions (30%, Table 1, entry 3). In the AuCl(PyC)-catalyzed reaction, **1a** was fully consumed, and 4,4'-dibromobiphenyl (**4a**) derived from the homocoupling of arylsilane **2a** was also detected. Furthermore, a significant amount of methyl 2-iodobenzoate (**5**) was generated through the esterification of a co-product (2-iodobenzoic acid) with methanol. We also tested other iodine(III) reagents such as $PhI(OAc)_2$, $PhI(OCOCF_3)_2$ and PhI(OH)(OTs), but they all resulted in lower yields than IBA mainly due to the formation of diaryliodonium $PhI(4\text{-}BrC_6H_4)^+$ produced by the reaction with arylsilane **2a** (Table 1, entries 4–6) [69]. Using *p*-toluenesulfonic acid (TsOH) instead of CSA was less effective (Table 1, entry 7). It was clearly seen that both CSA and methanol had a significant effect on the reaction progress (Table 1, entries 8 and 9). Nevertheless, the highest yield achieved by the use of AuCl(PyC) may be attributed to the highly electron-donating nature of the PyC ligand.

Oxidative C–H arylation of heteroarenes with arylsilanes catalyzed by AuCl(PyC)

Having discovered the positive effect of using PyC as a ligand, we further examined the C–H arylation of various heteroarenes with arylsilanes (Table 2). It should be noted that all of the examined heteroarenes were not successfully applied in the previous gold-catalyzed C–H arylation. The reactions of **1a** with halogenated aryltrimethylsilanes **2a** and **2b** afforded coupling products **3aa** and **3ab** in 14% and 15% isolated yields, respectively (Table 2, entries 1 and 2) [112]. 5-Methylisoxazole (**1b**) was arylated with bromo-, fluoro- and trifluoromethyl-substituted aryltrimethylsilanes, **2a**, **2b** and **2c**, respectively, to give the corresponding 4-aryl-5-methylisoxazoles, **3ba**, **3bb** and **3bc**, respectively, in higher efficiency as compared

Table 2: AuCl(PyC)-catalyzed oxidative C–H arylation of heteroarenes with arylsilanes.[a]



1 **2** **3**

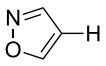
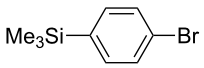
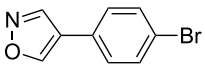
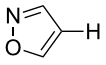
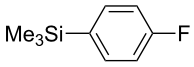
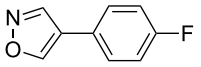
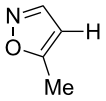
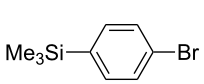
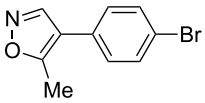
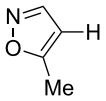
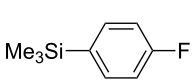
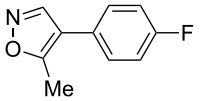
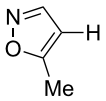
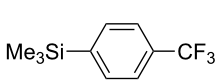
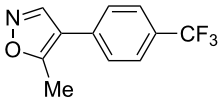
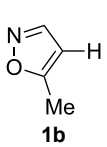
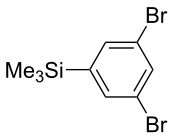
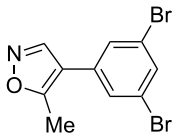
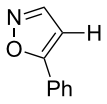
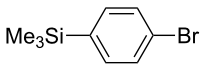
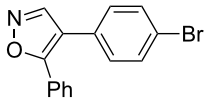
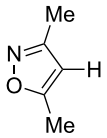
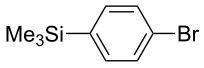
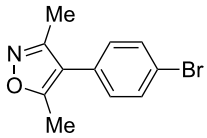
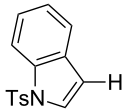
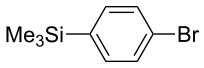
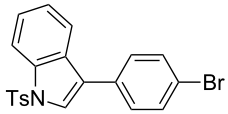
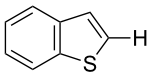
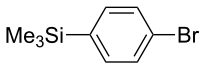
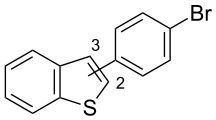
Entry	1	2	3	Yield[b]
1	 **1a**	 **2a**	 **3aa**	14%
2	 **1a**	 **2b**	 **3ab**	15%
3	 **1b**	 **2a**	 **3ba**	55%
4	 **1b**	 **2b**	 **3bb**	54%
5	 **1b**	 **2c**	 **3bc**	33%

Table 2: AuCl(PyC)-catalyzed oxidative C–H arylation of heteroarenes with arylsilanes.[a] (continued)

6	 **1b**	 **2d**	 **3bd**	13%
7	 **1c**	 **2a**	 **3ca**	28%
8	 **1d**	 **2a**	 **3da**	17%
9	 **1e**	 **2a**	 **3ea**	44%
10	 **1f**	 **2a**	 **3fa** (C2):**3fa'** (C3) = 83:17	22%

[a]Reaction conditions: **1** (0.20 mmol), **2** (0.20 mmol), AuCl(PyC) (5 mol %), IBA (0.20 mmol), CSA (0.20 mmol), $CHCl_3$/MeOH (10:1, 1.1 mL), 65 °C, 18–48 h. [b]Isolated yield.

with **1a** (Table 2, entries 3–5). This may be due to the higher tolerability of **1b** than **1a** toward undesired decomposition [113]. The introduction of the 3,5-dibromophenyl group onto methylisoxazole **1b** resulted in lower yield of heterobiaryl **3bd** (Table 2, entry 6). In the reaction of 5-phenylisoxazole (**1c**), the selective arylation at the C4 position occurred without any arylation at the phenyl group (Table 2, entry 7). 3,5-Dimethylisoxazole (**1d**) showed low reactivity, likely due to the steric hindrance, but the reaction gave sterically congested heterobiaryl **3da** in 17% yield (Table 2, entry 8). In the case of the reaction of indole **1e**, 3-arylindole **3ea** was exclusively obtained in 44% yield (Table 2, entry 9). On the other hand, arylation of benzo[*b*]thiophene (**1f**) mainly afforded 2-arylbenzothiophene **3fa** along with a small amount of 3-arylbenzothiophene **3fa'** (Table 2, entry 10).

Reaction progress analysis

To further unveil the ligand effect of PyC, time-production profiles of coupling product **3ba** were investigated for the reaction of **1b** and **2a** with AuCl(PyC), AuCl(PPh_3) and AuCl(IPr). The yield of **3ba** was determined by GC analysis, whereas the consumption of IBA (oxidant) was estimated by the production of methyl 2-iodobenzoate (**5**). The reaction plots with AuCl(PyC), AuCl(PPh_3) and AuCl(IPr) are depicted in Figure 2. Noteworthy observations are as follows: (i) the reaction with AuCl(PyC) was fastest among those with three catalysts (Figure 2a), (ii) the induction periods with regard to the formation of **3ba** were found in the reactions using AuCl(PyC) and AuCl(PPh_3) (Figure 2a,b), and (iii) the oxidant consumption began at the reaction initiation for all catalysts (Figure 2c). In the reaction using AuCl(PyC), the coupling product **3ba** was generated after a shorter induction period of about 3 h and reached 60% yield after 50 h (Figure 2a). On the other hand, the reaction using AuCl(PPh_3) began after a longer induction period (ca. 5 h), and the yield of **3ba** did not exceed the yield with AuCl(PyC) even after 100 h (see Supporting Information File 1 for details). No coupling product was produced with AuCl(IPr) although the consumption of about 10% of IBA was observed.

Mechanistic considerations

Based on the above results and the literature [68-75], we propose the reaction mechanism of the gold-catalyzed C–H arylation of heteroarenes with arylsilanes as shown in Scheme 1. A gold(I) complex **A** is first oxidized to gold(III)

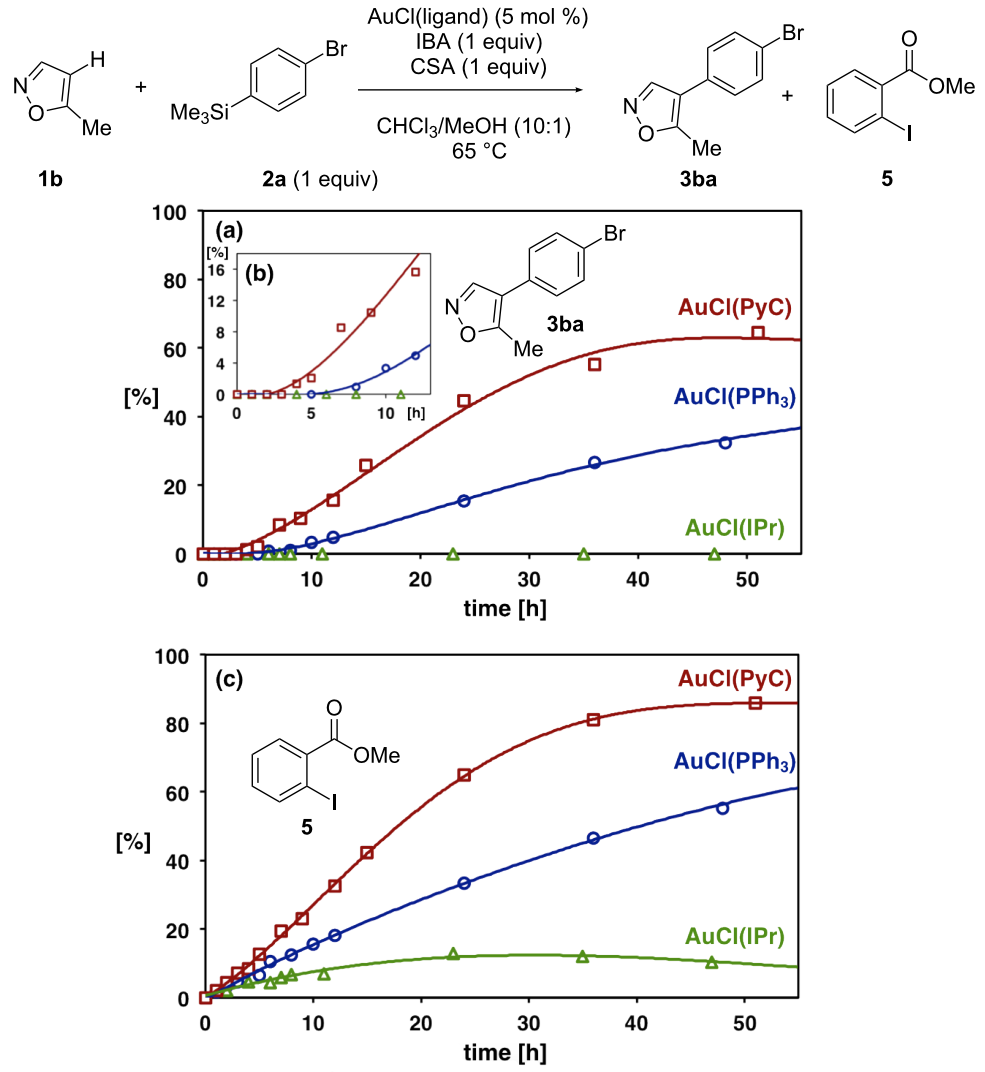
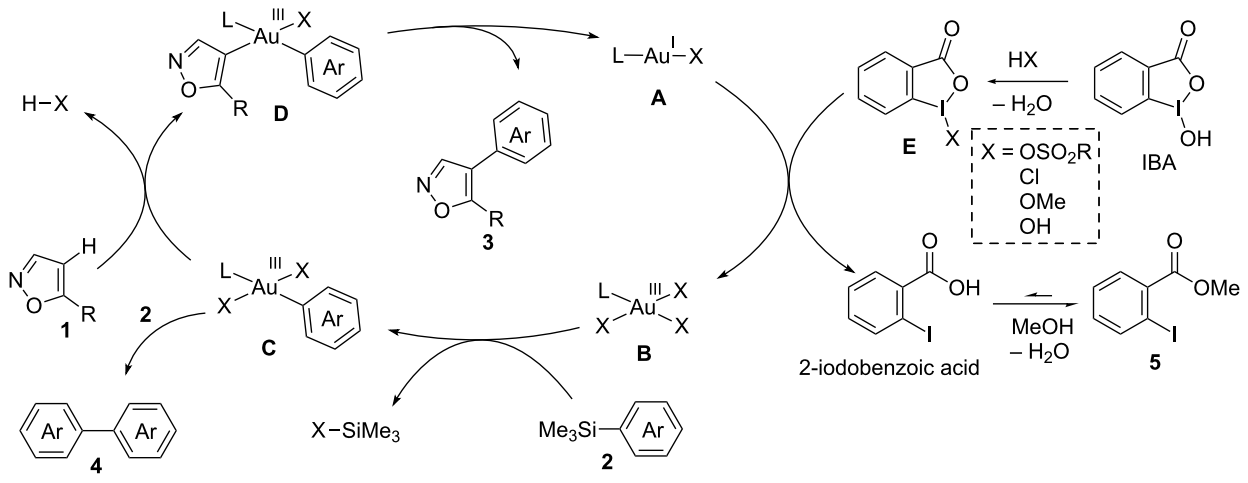


Figure 2: Yield–time profiles of 4-(4-bromophenyl)-5-methylisoxazole (**3ba**) and methyl 2-iodobenzoate (**5**) with AuCl(PyC), AuCl(PPh_3) and AuCl(IPr). (a) Yield of **3ba**. (b) Magnified figure of (a). (c) Yield of **5**. All yields were determined by GC analysis with *n*-nonane as an internal standard.



Scheme 1: Plausible reaction mechanism of gold-catalyzed oxidative C–H arylation of heteroarenes with arylsilanes.

species **B** by the iodine(III) reagent **E** derived from IBA by the exchange of a hydroxy group with an existing acid such as CSA, HCl and MeOH. We independently confirmed that the esterification of 2-iodobenzoic acid takes place to give **5** under the reaction conditions; 2-iodobenzoic acid was smoothly converted to **5** in chloroform/methanol solution at 65 °C. Transmetalation of gold(III) complex **B** with arylsilane **2** affords monoarylated gold(III) intermediate **C**. The electrophilic metalation of heteroarene **1** with **C** with concurrent generation of an acid (HX) produces diarylated gold(III) species **D**. Finally, the reductive elimination from **D** releases the coupling product **3** along with the regeneration of gold(I) species **A**. The side reaction leading to the homocoupling product of arylsilane **4** likely occurs via over-transmetalation of monoarylated gold(III) species **C** with arylsilane **2** or disproportionation of **C** [67-81].

Oxidation process of gold

In all reaction progress experiments with the three gold catalysts (Figure 2), the consumption of IBA (production of **5**) was observed to some extent even in the induction period. Taking the possible reaction mechanism into consideration, the oxidation of gold(I) to gold(III) by the oxidant may occur during the induction period. While it is unclear what is oxidized in these reactions, we hypothesize that the highly electron-donating PyC ligand facilitates the oxidation of gold(I) to gold(III). As triphenylphosphine is known to be easily oxidized to triphenylphosphine oxide under the current oxidative conditions, the ligand-free gold(III) species is thought to be an active species in the arylation reaction with AuCl(PPh_3) [69]. While the IPr-gold(I) complex is known to undergo oxidation to an IPr-gold(III) species [114], its inactiveness in the current reaction indicates that the electron-donating capability is not high enough to facilitate this process.

Direct observation and isolation of PyC-gold(III) complex

To verify our hypothesis that PyC accelerates the gold(I)-to-gold(III) oxidation, we attempted the direct observation and the isolation of the PyC-gold(III) complex. First of all, the gold(III) complex $AuCl_3$(PyC) was newly synthesized by treating AuCl(PyC) with $PhICl_2$ (see Experimental section and Supporting Information File 1 for details) [114]. The X-ray crystallographic analysis was successfully accomplished with a colorless single crystal of $AuCl_3$(PyC), which was recrystallized from nitrobenzene and pentane (Figure 3) [115]. The X-ray crystal structure shows that the four gold bonds are in a planar surface, and the pyridylidene face and the added two chlorine atoms are in vertical positions. The ligand arrangement is quite similar to a series of reported NHC–$AuCl_3$ complexes [114].

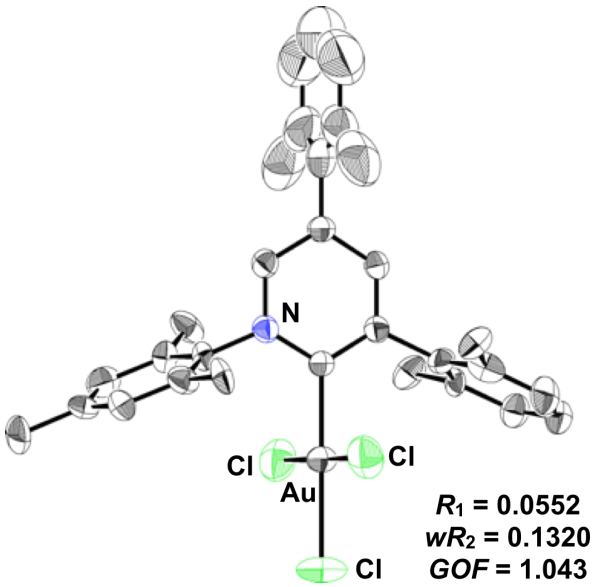
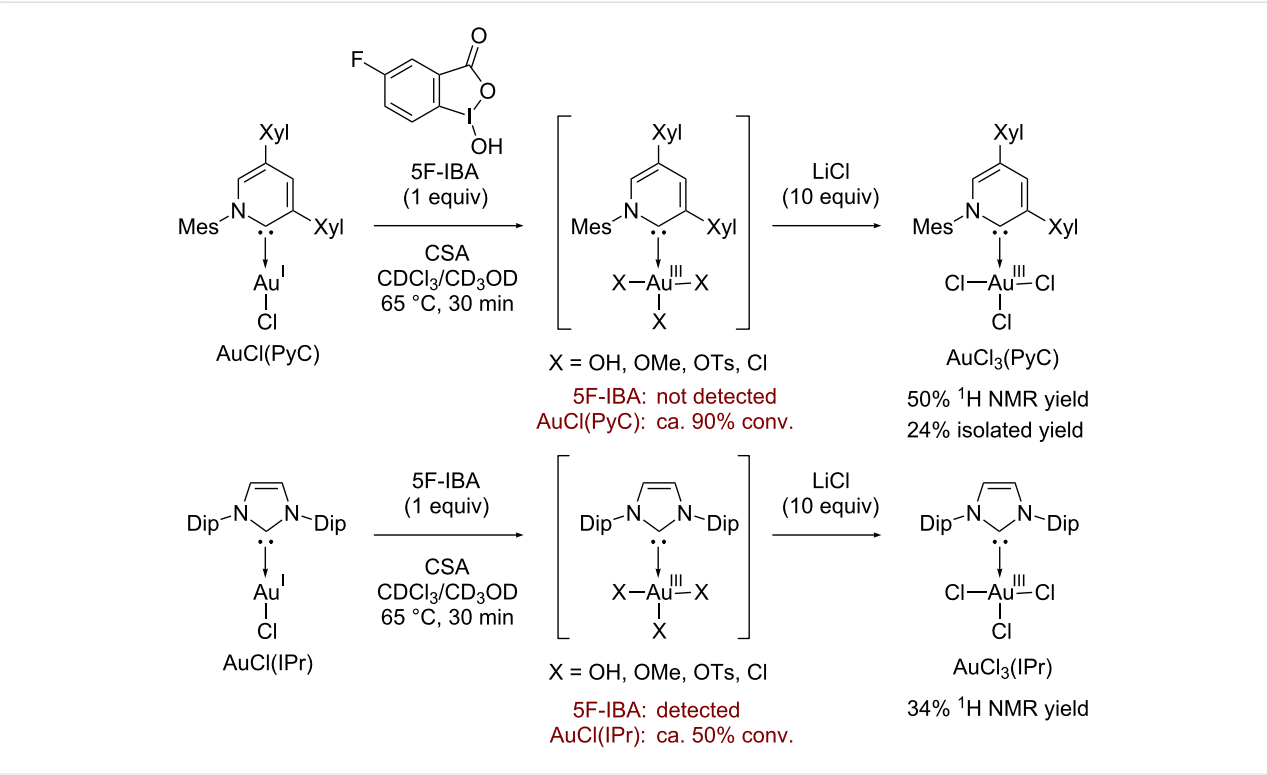


Figure 3: ORTEP drawing of $AuCl_3$(PyC) with 50% probability. Hydrogen atoms and solvent are omitted for clarity.

With the authentic $AuCl_3$(PyC) in hand, we next carried out the direct observation of PyC-gold(III) species under the catalytic conditions. The treatment of AuCl(PyC) with 5-fluoroiodosobenzoic acid (5F-IBA) and CSA in $CDCl_3/CD_3OD$ at 65 °C resulted in the full consumption of 5F-IBA within 30 min (monitored by ^{19}F NMR). While the resulting mixture seemed to contain several PyC-gold(III) complexes, the formation of various gold(III) species bearing hydroxy, methoxy, sulfoxy and chloro groups made the analysis and isolation difficult. However, the subsequent addition of excess LiCl enabled us to detect the gold(III) species as $AuCl_3$(PyC) by ^1H and ^{13}C NMR analyses. The ^1H NMR analysis revealed that about 90% of AuCl(PyC) was consumed and $AuCl_3$(PyC) was produced in 50% NMR yield. Fortunately, the isolation from the messy crude mixtures was accomplished to give $AuCl_3$(PyC) in 24% isolated yield. We also conducted the same experiment with the AuCl(IPr) complex. From the ^{19}F and ^1H NMR analyses, approximately half of AuCl(IPr) and oxidant 5F-IBA remained unreacted after heating for 30 min, and $AuCl_3$(IPr) was observed only in 34% ^1H NMR yield [114] (Scheme 2).

These observations on gold(III) species support our hypothesis that the highly electron-donating PyC ligand strongly coordinates to a gold center and promotes the gold(I)-to-gold(III) oxidation by stabilizing a gold(III) species without dissociation. An IPr-gold(III) complex is known to be stable, but the lower electron-donation ability of IPr than that of PyC seems to result in the inefficient oxidation of AuCl(IPr). DFT calculations on the oxidation process of the AuCl(ligand) to $AuCl_3$(ligand) also



Scheme 2: Direct observation and isolation of carbene-gold(III) complex. Mes = 2,4,6-$Me_3C_6H_2$, Xyl = 2,6-$Me_2C_6H_3$, Dip = 2,6-$iPr_2C_6H_3$.

clarified the advantage of the PyC ligand over IPr by 3.6 kcal mol^{-1} (see Supporting Information File 1 for details). While it still remains unclear how the PyC ligand affects the transmetalation, C–H metalation and reductive elimination steps, we believe that the strongly electron-donating PyC not only facilitates gold(I)-to-gold(III) oxidation in catalysis but also prolongs the catalyst lifetime by preventing the ligand dissociation and formation of inactive gold nanoparticles.

Conclusion

In summary, we have developed the oxidative C–H arylation of heteroarenes with arylsilanes catalyzed by PyC-gold complex and revealed the advantageous features of using the PyC ligand. From the reaction progress, experiments and stoichiometric oxidation of gold(I) complexes, we conclude that the highly electron-donating PyC ligand promotes the gold(I)-to-gold(III) oxidation and stabilizes the gold(III) species, thereby facilitating the oxidative coupling reactions.

Experimental

Preparation of triarylpyridylidene-gold(I) chloride [AuCl(PyC)]: A 10 mL Schlenk tube containing a stir bar was dried under vacuum and filled with N_2 after cooling to room temperature. Ag_2O (232 mg, 1.0 mmol) and $NBu_4Cl{\cdot}H_2O$ (1.39 g, 5.0 mmol) were added to the solution of 3,5-bis(2,6-dimethylphenyl)-1-mesitylpyridin-1-ium triflate (730 mg, 1.0 mmol) in 1,2-dichloroethane (5.0 mL). The mixture was stirred at room temperature for 2 h, and $AuCl(SMe_2)$ (11.5 mg, 0.10 mmol) was then added to the reaction mixture. The reaction mixture was further stirred overnight, and the addition of $CHCl_3$ (50 mL) to the mixture gave a white precipitate. The suspension was filtered off and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluents: MeOH/$CHCl_3$ 1:20) and recrystallized from $CHCl_3$/toluene at room temperature to give a pure AuCl(PyC)/toluene complex (286 mg, 40%) as a pale yellow crystal. The addition of $CHCl_3$ and the concentration in vacuum yielded a pure AuCl(PyC) complex without toluene as white powder. The characterization data for AuCl(PyC) corresponded to the reported values [83].

General procedure for AuCl(PyC)-catalyzed oxidative C–H arylation of heteroarenes with arylsilanes: AuCl(PyC) (6.4 mg, 0.010 μmol, 5.0 mol %), heteroarene **1** (0.20 mmol), and aryltrimethylsilane **2** (0.20 mmol), 2-iodosobenzoic acid (IBA, 53 mg, 0.20 mmol), 10-camphorsulfonic acid (CSA) (47 mg, 0.20 mmol) and a stir bar were placed in a screw test tube, and dry $CHCl_3$/MeOH (1.0 mL/0.10 mL) was added under N_2 atmosphere. The tube was sealed with a cap equipped with a Teflon®-coated silicon rubber septum, and the mixture was stirred at 65 °C for 18–48 h. The reaction was quenched by addition of excess saturated aqueous $NaHCO_3$, the aqueous layer

was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the coupling product **3** (Table 2).

Oxidation of AuCl(PyC): The oxidation of AuCl(PyC) was performed according to the literature [16]. $PhICl_2$ (54.8 mg, 0.20 mmol) was added into a solution of AuCl(PyC) (128 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) under N_2 atmosphere. After stirring at room temperature for 19 h, the reaction mixture was filtered through a pad of Celite®. The filtrate was poured into hexane and the resulting precipitate was collected by filtration to obtain pure $AuCl_3$(PyC) as a white solid (140 mg, 99%). The colorless single crystal used for X-ray diffraction analysis was obtained by recrystallization from nitrobenzene and pentane. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.17 (d, J = 2.1 Hz, 1H), 7.90 (d, J = 2.1 Hz, 1H), 7.29 (td, J = 7.6, 2.7 Hz, 2H), 7.19 (d, J = 7.6 Hz, 2H), 7.16 (d, J = 7.6 Hz, 2H), 7.07 (s, 2H), 2.36 (s, 3H), 2.28 (s, 12H), 2.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.5 (CH), 149.6 (4°), 146.6 (CH), 144.7 (CH), 141.9 (4°), 141.5 (4°), 138.5 (4°), 136.4 (4°), 135.6 (4°), 135.6 (4°), 133.2 (4°), 132.2 (4°), 130.4 (CH), 129.9 (CH), 129.7 (CH), 128.3 (4°), 128.3 (CH), 22.1 (CH_3), 21.1 (CH_3), 20.9 (CH_3), 19.3 (CH_3); HRMS (ESI+) m/z: $[M - Cl + MeOH]^+$ calcd for $C_{31}H_{35}AuCl_2NO$, 704.1756; found, 704.1722.

In situ observation and isolation of $AuCl_3$(PyC): AuCl(PyC) (12.8 mg, 0.020 mmol), 5-fluoroiodosobenzoic acid (5F-IBA, 5.6 mg, 0.020 mmol) and CSA (4.6 mg, 0.020 mmol) were placed in an NMR tube, and $CDCl_3/CD_3OD$ (10:1, 0.60 mL) was added under N_2 atmosphere. The tube was sealed with a cap equipped with a Teflon®-coated silicon rubber septum and heated at 65 °C for 30 min. After cooling to room temperature, LiCl (8.4 mg, 0.20 mmol) was added. 1,1,2,2-Tetrachloroethane was added as an internal standard and an NMR yield of $AuCl_3$(PyC) was estimated by ^{1}H NMR spectroscopy. The solvent was removed in vacuum, and the residue was dissolved in EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated in vacuum to afford the crude mixture. The crude mixture was further washed with Et_2O to give pure $AuCl_3$(PyC) as a white powder (3.4 mg, 24%, Scheme 2).

Supporting Information

Supporting Information File 1

Experimental procedures, spectra of new compounds, CIF data, and details of the computational study.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-11-295-S1.pdf]

Acknowledgements

This work was supported by the ERATO program from JST (K.I.) and the Funding Program for KAKENHI from MEXT (26810057 to H.I. and 23750038 to Y.S.). K.H. is a recipient of the JSPS research fellowship for young scientists. ITbM is supported by the World Premier International Research Center (WPI) Initiative (Japan).

References

1. Arcadi, A. *Chem. Rev.* **2008,** *108,* 3266–3325. doi:10.1021/cr068435d
2. Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008,** *37,* 1766–1775. doi:10.1039/b615629k
3. Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008,** *108,* 3239–3265. doi:10.1021/cr068434l
4. Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008,** *37,* 1776–1782. doi:10.1039/b711132k
5. Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008,** *108,* 3395–3442. doi:10.1021/cr050041j
6. Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011,** *111,* 1657–1712. doi:10.1021/cr100414u
7. Huang, H.; Zhou, Y.; Liu, H. *Beilstein J. Org. Chem.* **2011,** *7,* 897–936. doi:10.3762/bjoc.7.103
8. Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012,** *41,* 2448–2462. doi:10.1039/C1CS15279C
9. Abbiati, G.; Marinelli, F.; Rossi, E.; Arcadi, A. *Isr. J. Chem.* **2013,** *53,* 856–868. doi:10.1002/ijch.201300040
10. Chiarucci, M.; Bandini, M. *Beilstein J. Org. Chem.* **2013,** *9,* 2586–2614. doi:10.3762/bjoc.9.294
11. López, F.; Mascareñas, J. L. *Beilstein J. Org. Chem.* **2013,** *9,* 2250–2264. doi:10.3762/bjoc.9.264
12. Nunes dos Santos Comprido, L.; Hashmi, A. S. K. *Isr. J. Chem.* **2013,** *53,* 883–891. doi:10.1002/ijch.201300072
13. Ohno, H. *Isr. J. Chem.* **2013,** *53,* 869–882. doi:10.1002/ijch.201300054
14. Abbiati, G.; Rossi, E. *Beilstein J. Org. Chem.* **2014,** *10,* 481–513. doi:10.3762/bjoc.10.46
15. Muratore, M. E.; Homs, A.; Obradors, C.; Echavarren, A. M. *Chem. – Asian J.* **2014,** *9,* 3066–3082. doi:10.1002/asia.201402395
16. Xie, J.; Pan, C.; Abdukader, A.; Zhu, C. *Chem. Soc. Rev.* **2014,** *43,* 5245–5256. doi:10.1039/C4CS00004H
17. Yang, W.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2014,** *43,* 2941–2955. doi:10.1039/c3cs60441a
18. Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015,** *115,* 9028–9072. doi:10.1021/cr500691k
19. Qian, D.; Zhang, J. *Chem. Soc. Rev.* **2015,** *44,* 677–698. doi:10.1039/C4CS00304G
20. Soriano, E.; Marco-Contelles, J. *Acc. Chem. Res.* **2009,** *42,* 1026–1036. doi:10.1021/ar800200m
21. Gaillard, S.; Cazin, C. S. J.; Nolan, S. P. *Acc. Chem. Res.* **2012,** *45,* 778–787. doi:10.1021/ar200188f
22. Alcaide, B.; Almendros, P. *Acc. Chem. Res.* **2014,** *47,* 939–952. doi:10.1021/ar4002558
23. Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014,** *47,* 953–965. doi:10.1021/ar4002334
24. Fürstner, A. *Acc. Chem. Res.* **2014,** *47,* 925–938. doi:10.1021/ar4001789
25. Hashmi, A. S. K. *Acc. Chem. Res.* **2014,** *47,* 864–876. doi:10.1021/ar500015k

26. Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014,** *47,* 902–912. doi:10.1021/ar400174p
27. Wang, Y.-M.; Lackner, A. D.; Toste, F. D. *Acc. Chem. Res.* **2014,** *47,* 889–901. doi:10.1021/ar400188g
28. Yeom, H.-S.; Shin, S. *Acc. Chem. Res.* **2014,** *47,* 966–977. doi:10.1021/ar4001839
29. Zhang, D.-H.; Tang, X.-Y.; Shi, M. *Acc. Chem. Res.* **2014,** *47,* 913–924. doi:10.1021/ar400159r
30. Zhang, L. *Acc. Chem. Res.* **2014,** *47,* 877–888. doi:10.1021/ar400181x
31. For ligand effects in gold-catalyzed reactions, see references [32-36].
32. Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008,** *108,* 3351–3378. doi:10.1021/cr068430g
33. Alcarazo, M.; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem., Int. Ed.* **2010,** *49,* 2542–2546. doi:10.1002/anie.200907194
34. Nolan, S. P. *Acc. Chem. Res.* **2011,** *44,* 91–100. doi:10.1021/ar1000764
35. Cera, G.; Bandini, M. *Isr. J. Chem.* **2013,** *53,* 848–855. doi:10.1002/ijch.201300029
36. Gatineau, D.; Goddard, J.-P.; Mouriès-Mansuy, V.; Fensterbank, L. *Isr. J. Chem.* **2013,** *53,* 892–900. doi:10.1002/ijch.201300059
37. For selected reviews on gold-catalyzed oxidative C–C coupling reactions, see references [38-40].
38. Hopkinson, M. N.; Gee, A. D.; Gouverneur, V. *Chem. – Eur. J.* **2011,** *17,* 8248–8262. doi:10.1002/chem.201100736
39. Wegner, H. A.; Auzias, M. *Angew. Chem., Int. Ed.* **2011,** *50,* 8236–8247. doi:10.1002/anie.201101603
40. Brand, J. P.; Li, Y.; Waser, J. *Isr. J. Chem.* **2013,** *53,* 901–910. doi:10.1002/ijch.201300044
41. For recent examples of oxidative heteroarylation of alkene through gold(I)/gold(III) catalytic cycle, see references [42-52].
42. Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem., Int. Ed.* **2009,** *48,* 3112–3115. doi:10.1002/anie.200900585
43. Ball, L. T.; Green, M.; Lloyd-Jones, G. C.; Russell, C. A. *Org. Lett.* **2010,** *12,* 4724–4727. doi:10.1021/ol1019162
44. Brenzovich, W. E., Jr.; Benitez, D.; Lackner, A. D.; Shunatona, H. P.; Tkatchouk, E.; Goddard, W. A., III; Toste, F. D. *Angew. Chem., Int. Ed.* **2010,** *49,* 5519–5522. doi:10.1002/anie.201002739
45. Brenzovich, W. E., Jr.; Brazeau, J.-F.; Toste, F. D. *Org. Lett.* **2010,** *12,* 4728–4731. doi:10.1021/ol102194c
46. Hopkinson, M. N.; Tessier, A.; Salisbury, A.; Giuffredi, G. T.; Combettes, L. E.; Gee, A. D.; Gouverneur, V. *Chem. – Eur. J.* **2010,** *16,* 4739–4743. doi:10.1002/chem.201000322
47. Melhado, A. D.; Brenzovich, W. E., Jr.; Lackner, A. D.; Toste, F. D. *J. Am. Chem. Soc.* **2010,** *132,* 8885–8887. doi:10.1021/ja1034123
48. Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010,** *132,* 1474–1475. doi:10.1021/ja909555d
49. Zhang, G.; Luo, Y.; Wang, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2011,** *50,* 4450–4454. doi:10.1002/anie.201100293
50. Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *Chem. – Eur. J.* **2012,** *18,* 2931–2937. doi:10.1002/chem.201103061
51. Zhang, R.; Xu, Q.; Chen, K.; Gu, P.; Shi, M. *Eur. J. Org. Chem.* **2013,** 7366–7371. doi:10.1002/ejoc.201300896
52. Zhu, S.; Ye, L.; Wu, W.; Jiang, H. *Tetrahedron* **2013,** *69,* 10375–10383. doi:10.1016/j.tet.2013.09.097
53. For recent examples of gold-catalyzed C–C bond forming oxidative coupling reaction, see references [54-66].
54. Jones, C. J.; Taube, D.; Ziatdinov, V. R.; Periana, R. A.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A., III. *Angew. Chem., Int. Ed.* **2004,** *43,* 4626–4629. doi:10.1002/anie.200461055
55. Wegner, H. A.; Ahles, S.; Neuburger, M. *Chem. – Eur. J.* **2008,** *14,* 11310–11313. doi:10.1002/chem.200801848
56. Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009,** *48,* 9346–9349. doi:10.1002/anie.200905419
57. Cui, L.; Zhang, G.; Zhang, L. *Bioorg. Med. Chem. Lett.* **2009,** *19,* 3884–3887. doi:10.1016/j.bmcl.2009.03.127
58. Peng, Y.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2009,** *131,* 5062–5063. doi:10.1021/ja901048w
59. Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010,** *49,* 7304–7307. doi:10.1002/anie.201003179
60. de Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010,** *132,* 1512–1513. doi:10.1021/ja909726h
61. Hopkinson, M. N.; Ross, J. E.; Giuffredi, G. T.; Gee, A. D.; Gouverneur, V. *Org. Lett.* **2010,** *12,* 4904–4907. doi:10.1021/ol102061k
62. Qian, D.; Zhang, J. *Beilstein J. Org. Chem.* **2011,** *7,* 808–812. doi:10.3762/bjoc.7.92
63. Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem. – Eur. J.* **2012,** *18,* 5655–5666. doi:10.1002/chem.201200200
64. Levin, M. D.; Toste, F. D. *Angew. Chem., Int. Ed.* **2014,** *53,* 6211–6215. doi:10.1002/anie.201402924
65. Ma, Y.; Zhang, S.; Yang, S.; Song, F.; You, J. *Angew. Chem., Int. Ed.* **2014,** *53,* 7870–7874. doi:10.1002/anie.201402475
66. Peng, H.; Xi, Y.; Ronaghi, N.; Dong, B.; Akhmedov, N. G.; Shi, X. *J. Am. Chem. Soc.* **2014,** *136,* 13174–13177. doi:10.1021/ja5078365
67. For gold-catalyzed oxidative C–H arylation of arenes, see references [68-72].
68. Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *Science* **2012,** *337,* 1644–1648. doi:10.1126/science.1225709
69. Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *J. Am. Chem. Soc.* **2014,** *136,* 254–264. doi:10.1021/ja408712e
70. Kar, A.; Mangu, N.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Chem. Commun.* **2008,** 386–388. doi:10.1039/B714928J
71. Kar, A.; Mangu, N.; Kaiser, H. M.; Tse, M. K. *J. Organomet. Chem.* **2009,** *694,* 524–537. doi:10.1016/j.jorganchem.2008.11.016
72. Wu, Q.; Du, C.; Huang, Y.; Liu, X.; Long, Z.; Song, F.; You, J. *Chem. Sci.* **2015,** *6,* 288–293. doi:10.1039/C4SC02070G
73. For selected mechanistic investigations on gold(I)/gold(III) redox processes, see references [74-84].
74. Mankad, N. P.; Toste, F. D. *J. Am. Chem. Soc.* **2010,** *132,* 12859–12861. doi:10.1021/ja106257n
75. Tkatchouk, E.; Mankad, N. P.; Benitez, D.; Goddard, W. A., III; Toste, F. D. *J. Am. Chem. Soc.* **2011,** *133,* 14293–14300. doi:10.1021/ja2012627
76. Hofer, M.; Nevado, C. *Eur. J. Inorg. Chem.* **2012,** 1338–1341. doi:10.1002/ejic.201100956
77. Cambeiro, X. C.; Boorman, T. C.; Lu, P.; Larrosa, I. *Angew. Chem., Int. Ed.* **2013,** *52,* 1781–1784. doi:10.1002/anie.201209007
78. Hofer, M.; Nevado, C. *Tetrahedron* **2013,** *69,* 5751–5757. doi:10.1016/j.tet.2013.04.029
79. Hofer, M.; Gomez-Bengoa, E.; Nevado, C. *Organometallics* **2014,** *33,* 1328–1332. doi:10.1021/om400884s
80. Winston, M. S.; Wolf, W. J.; Toste, F. D. *J. Am. Chem. Soc.* **2014,** *136,* 7777–7782. doi:10.1021/ja503974x

81. Wolf, W. J.; Winston, M. S.; Toste, F. D. *Nat. Chem.* **2014,** *6,* 159–164. doi:10.1038/nchem.1822
82. For our contributions to the synthesis, complexation of pyridylidene ligands, see references [83] and [84].
83. Hata, K.; Segawa, Y.; Itami, K. *Chem. Commun.* **2012,** *48,* 6642–6644. doi:10.1039/c2cc33184e
84. Yoshidomi, T.; Segawa, Y.; Itami, K. *Chem. Commun.* **2013,** *49,* 5648–5650. doi:10.1039/c3cc42655f
85. For the synthesis and DFT calculation of pyridylidene, see references [86-92].
86. Raubenheimer, H. G.; Toerien, J. G.; Kruger, G. J.; Otte, R.; van Zyl, W.; Olivier, P. *J. Organomet. Chem.* **1994,** *466,* 291–295. doi:10.1016/0022-328X(94)88058-1
87. Strasser, C. E.; Stander-Grobler, E.; Schuster, O.; Cronje, S.; Raubenheimer, H. G. *Eur. J. Inorg. Chem.* **2009,** 1905–1912. doi:10.1002/ejic.200801180
88. Roselló-Merino, M.; Díez, J.; Conejero, S. *Chem. Commun.* **2010,** *46,* 9247–9249. doi:10.1039/c0cc03935g
89. Hollóczki, O.; Nyulászi, L. *J. Org. Chem.* **2008,** *73,* 4794–4799. doi:10.1021/jo8000035
90. Kassaee, M. Z.; Shakib, F. A.; Momeni, M. R.; Ghambarian, M.; Musavi, S. M. *Tetrahedron* **2009,** *65,* 10093–10098. doi:10.1016/j.tet.2009.09.043
91. Tukov, A. A.; Normand, A. T.; Nechaev, M. S. *Dalton Trans.* **2009,** 7015–7028. doi:10.1039/b906969k
92. Wang, L.; Kong, L.; Li, Y.; Ganguly, R.; Kinjo, R. *Chem. Commun.* **2015,** *51,* 12419–12422. doi:10.1039/C5CC04091D
93. For the synthesis and characterization of nonclassical carbenes, see references [94-96].
94. Canac, Y.; Soleilhavoup, M.; Conejero, S.; Bertrand, G. *J. Organomet. Chem.* **2004,** *689,* 3857–3865. doi:10.1016/j.jorganchem.2004.02.005
95. Melaimi, M.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2010,** *49,* 8810–8849. doi:10.1002/anie.201000165
96. Martin, D.; Melaimi, M.; Soleilhavoup, M.; Bertrand, G. *Organometallics* **2011,** *30,* 5304–5313. doi:10.1021/om200650x
97. For nonclassical carbene-gold complexes in catalytic reactions, see references [98-102]
98. Zeng, X.; Frey, G. D.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2009,** *131,* 8690–8696. doi:10.1021/ja902051m
99. Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2011,** *50,* 5560–5563. doi:10.1002/anie.201100740
100. López-Gómez, M. J.; Martin, D.; Bertrand, G. *Chem. Commun.* **2013,** *49,* 4483–4485. doi:10.1039/c3cc41279b
101. Hu, X.; Martin, D.; Melaimi, M.; Bertrand, G. *J. Am. Chem. Soc.* **2014,** *136,* 13594–13597. doi:10.1021/ja507788r
102. Jin, L.; Weinberger, D. S.; Melaimi, M.; Moore, C. E.; Rheingold, A. L.; Bertrand, G. *Angew. Chem., Int. Ed.* **2014,** *53,* 9059–9063. doi:10.1002/anie.201404665
103. Electron-rich arenes show the reactivity toward dehydrogenative homo- and cross-coupling reaction under oxidative conditions without metal oxidants. For related examples, see references [104-107].
104. Ito, H.; Ueda, K.; Itami, K. Cross-Dehydrogenative-Coupling Reactions without Metals. In *From C–H to C–C Bonds: Cross-Dehydrogenative-Coupling;* Li, C.-J., Ed.; The Royal Society of Chemistry, 2015; pp 153–196. doi:10.1039/9781782620082-00153
105. Jean, A.; Cantat, J.; Bérard, D.; Bouchu, D.; Canesi, S. *Org. Lett.* **2007,** *9,* 2553–2556. doi:10.1021/ol070941h
106. Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009,** *131,* 1668–1669. doi:10.1021/ja808940n
107. Morimoto, K.; Yamaoka, N.; Ogawa, C.; Nakae, T.; Fujioka, H.; Dohi, T.; Kita, Y. *Org. Lett.* **2010,** *12,* 3804–3807. doi:10.1021/ol101498r
108. For palladium-catalyzed C–H arylation of isoxazole, see references [109-111].
109. Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007,** *9,* 1449–1451. doi:10.1021/ol0702324
110. Fall, Y.; Reynaud, C.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2009,** 4041–4050. doi:10.1002/ejoc.200900309
111. Roger, J.; Požgan, F.; Doucet, H. *Adv. Synth. Catal.* **2010,** *352,* 696–710. doi:10.1002/adsc.200900793
112. Higher volatility of products resulted in the lower isolated yields.
113. In the presence of 10 mol % of AuCl(PyC), the reaction of **1b** and **2a** gave lower yield of **3ba** (33% GC yield) with significant amount of homo-coupling product of **2a** (4,4'-dibromobiphenyl) being observed.
114. Gaillard, S.; Bantreil, X.; Slawin, A. M. Z.; Nolan, S. P. *Dalton Trans.* **2009,** 6967–6971. doi:10.1039/b907109a
See for the synthesis and characterization of $AuCl_3$(IPr) complex.
115. Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-1045812 [$AuCl_3$(PyC)]. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.11.295

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Iridium/N-heterocyclic carbene-catalyzed C–H borylation of arenes by diisopropylaminoborane

Mamoru Tobisu*[1,2], Takuya Igarashi[2] and Naoto Chatani*[2]

Full Research Paper

Open Access

Address:
[1]Center for Atomic and Molecular Technologies, Graduate School of Engineering, Osaka University, Osaka 565-0871, Japan and
[2]Department of Applied Chemistry, Faculty of Engineering, Osaka University, Osaka 565-0871, Japan

Email:
Mamoru Tobisu* - tobisu@chem.eng.osaka-u.ac.jp; Naoto Chatani* - chatani@chem.eng.osaka-u.ac.jp

* Corresponding author

Keywords:
boronic acid; C–H borylation; iridium; N-heterocyclic carbene

Beilstein J. Org. Chem. **2016,** *12,* 654–661.
doi:10.3762/bjoc.12.65

Received: 22 January 2016
Accepted: 21 March 2016
Published: 07 April 2016

This article is part of the Thematic Series "C–H Functionalization/activation in organic synthesis".

Guest Editor: R. Sarpong

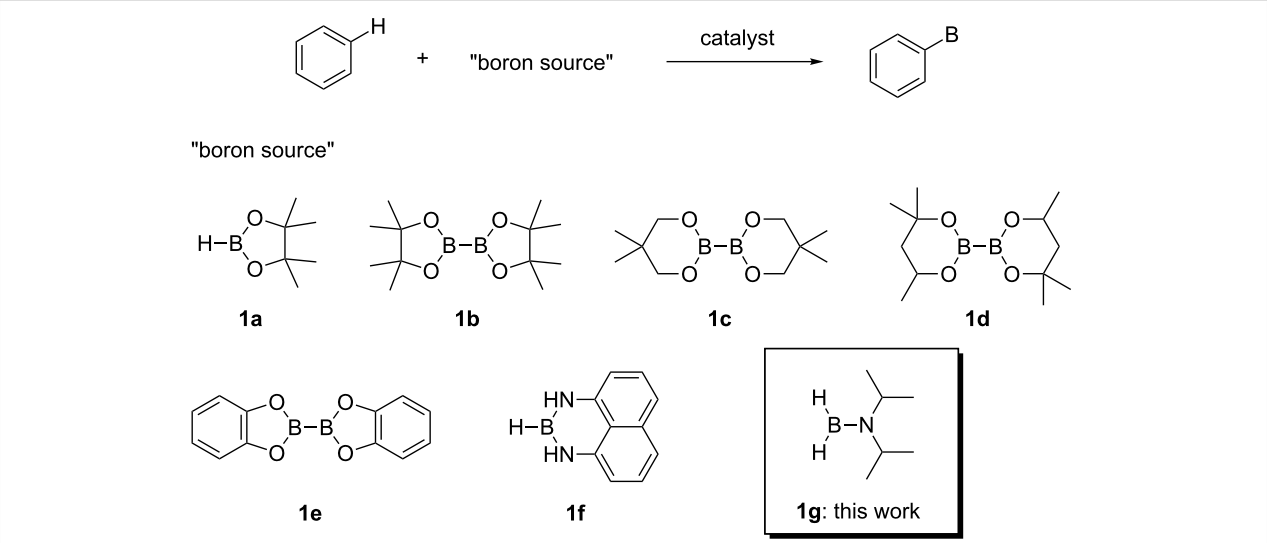
© 2016 Tobisu et al; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

Catalytic C–H borylation of arenes has been widely used in organic synthesis because it allows the introduction of a versatile boron functionality directly onto simple, unfunctionalized arenes. We report herein the use of diisopropylaminoborane as a boron source in C–H borylation of arenes. An iridium(I) complex with 1,3-dicyclohexylimidazol-2-ylidene is found to efficiently catalyze the borylation of arenes and heteroarenes. The resulting aminoborylated products can be converted to the corresponding boronic acid derivatives simply by treatment with suitable diols or diamines.

Introduction

Catalytic C–H borylation of arenes has become an essential tool in organic synthesis [1]. The eminent features of this methodology include 1) no directing group is needed, allowing the direct functionalization of simple arenes; 2) the regioselectivity is readily predictable based on steric factors; 3) the resulting boryl group is versatile and can be converted into a variety of carbon- or heteroatom-based substituents. An iridium complex in conjunction with 4,4'-di-*tert*-butylbipyridine (dtbpy) developed by Ishiyama, Miyaura and Hartwig has served as the state-of-the-art catalyst for C–H borylation of arenes [2]. In addition to the Ir/dtbpy system, various other catalytic systems have also been developed. For example, base metals such as Fe [3-6], Co [7] and Ni [8,9] have been shown to be viable metal centers for the use as C–H borylation catalysts. We also reported the first use of a Pt catalyst that enables C–H borylation of simple hindered arenes such as mesitylene [10,11]. Metal-free C–H borylation has also been reported [12]. Ligand modification has been used to control the regioselectivity of C–H borylation reactions; for example, in the *ortho*-selective C–H borylation of arenes containing a directing group [13], and to improve the *meta*/*para*-selectivity of monosubstituted benzenes [14,15]. Despite considerable progress in the C–H borylation reaction, the scope of the boryl group that can be introduced is relatively limited (Scheme 1). The most commonly used boron sources



Scheme 1: Catalytic C–H borylation of arenes and related reported boron sources.

are pinacolborane (HBpin, **1a**) and bis(pinacolato)diboron (B_2pin_2, **1b**), which form pinacol esters of arylboronic acids. Although the pinacol ester products prepared in these reactions are amenable to a range of transformations, their reactivity is generally lower than that of the corresponding boronic acids. Because of this lower reactivity, several transformations require deprotection of a pinacol ester under oxidative conditions (e.g., $NaIO_4$) [16]. Hartwig reported that the Ir/dtbpy system is also able to introduce more reactive neopentyl and hexylene glycolate esters and catecolates using the corresponding diboron reagents **1c**, **1d**, and **1e**, respectively [17,18]. Suginome reported that an Ir/1,2-diphenylphosphinoethane catalyst can promote C–H borylation using 1,8-naphthalenediaminatoborane (**1f**) [19]. The resulting diaminonaphthalene (dan)-protected arylboronic acid is synthetically useful because it can be readily deprotected with a dilute aqueous acid [20].

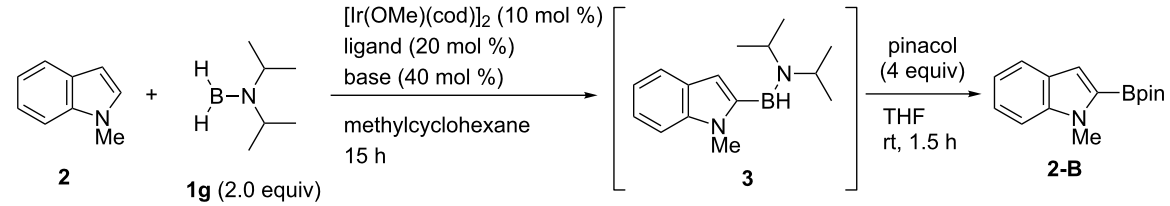
We envisioned that diisopropylaminoborane (**1g**) [21] could be a useful boron source because the resulting aminoborylated products are sufficiently labile to be converted into various boron derivatives by treatment with protecting groups in a one-pot reaction sequence. The reactivity of **1g** has previously been well-exploited in catalytic borylation of aryl halides [22-27]. Herein, we report the C–H borylation of arenes using **1g** catalyzed by an Ir/N-heterocyclic carbene (NHC) system.

Results and Discussion

On the basis of a superior reactivity of indoles in several C–H borylation reactions [7-9], we initially examined the borylation of indole **2** with aminoborane **1g** using an iridium catalyst under forcing conditions (140 °C, 15 h). Although all the attempts to isolate an initially formed aminoborylated product **3** were not successful, its formation was confirmed by ^{11}B NMR (δ = 40.7 ppm in cyclohexane-d_{12}). The crude reaction mixture was treated with pinacol and the yield of the product was estimated by ^1H NMR spectroscopy. Using dtbpy, the common ligand for iridium-catalyzed C–H borylation [2], the reaction failed to give **2-B** under these conditions (Table 1, entry 1). Several mono- and diphosphine ligands were found to be active for the formation of **2-B**, but the best yield was only 21% (Table 1, entries 2–6). Our success in C–H borylation using NHC ligands [8,10] led us to investigate a series of NHC ligands for this process. Among the NHC ligands examined, 1,3-dicyclohexylimidazol-2-ylidene (ICy) [28-33] was found to be most effective, giving **2-B** in 33% yield with a 2-/3-borylation ratio of 88:12 (Table 1, entry 9). It should be noted that [Ir(cod)(ICy)$_2$](CF$_3$CO$_2$) was previously reported to promote C–H borylation of arenes using HBpin [34]. Further optimization using an ICy ligand determined that decreasing the reaction temperature to 110 °C and shortening the reaction time to 4 h markedly improved the yield of **2-B** (72%) with near complete regioselectivity (99:1) (Table 1, entry 12).

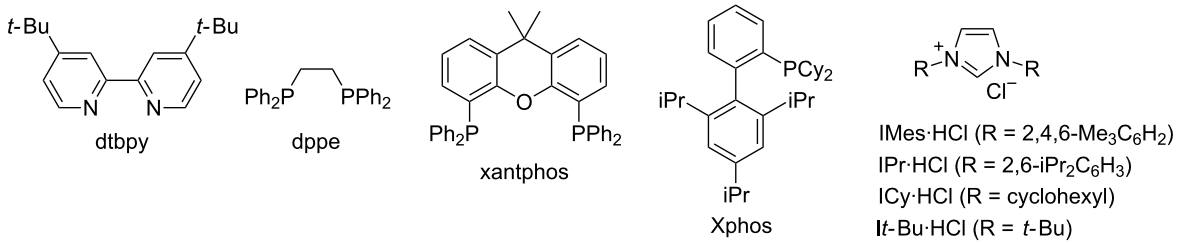
Having optimized the conditions, we next explored the scope of Ir/ICy-catalyzed borylation of heteroarene substrates using **1g** (Table 2). Functionalized indoles, such as those containing methoxy, fluoro, bromo and chloro substituents, all underwent the borylation to form the corresponding 2-borylated products **4-B**, **5-B**, **6-B** and **7-B**, respectively (Table 2, entries 1–4). When 1,4-dimethylindole (**8**) was used, 2-borylated product **8-B** was formed exclusively with no borylation occurring at the benzylic position (Table 2, entry 5) [8,35,36]. Benzothiophenes readily gave 2-borylated products using our system, as exemplified by the high yields obtained from **9** and **10** (Table 2, entries 6 and

Table 1: Effect of the ligand on the Ir-catalyzed borylation of **2** with **1g**.[a]



2 **1g** (2.0 equiv) **3** **2-B**

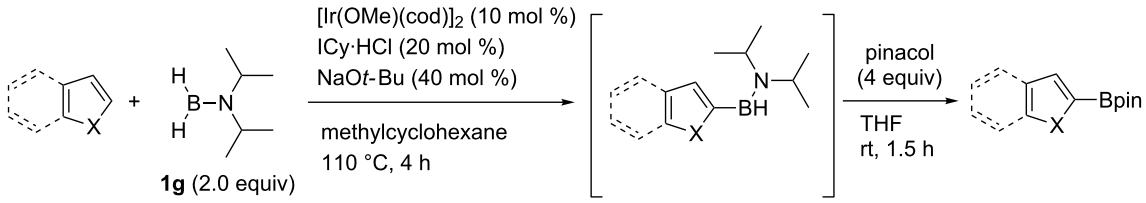
Entry	Ligand	Base	Temperature [°C]	NMR yield[b] [%]	2-Isomer/3-Isomer
1	dtbpy	none	140	trace	–
2	PPh_3	none	140	21	57/43
3	PCy_3	none	140	3	>99/1
4	dppe	none	140	2	>99/1
5	xantphos	none	140	18	56/44
6	Xphos	none	140	19	71/29
7	IMes·HCl	NaO*t*-Bu	140	5	>99/1
8	IPr·HCl	NaO*t*-Bu	140	3	>99/1
9	ICy·HCl	NaO*t*-Bu	140	33	88/12
10	I*t*-Bu·HCl	NaO*t*-Bu	140	0	–
11	ICy·HCl	NaO*t*-Bu	110	58	95/5
12	ICy·HCl	NaO*t*-Bu	110	72 (65)[c]	99/1



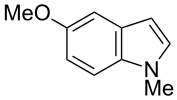
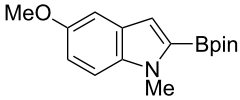
IMes·HCl (R = 2,4,6-$Me_3C_6H_2$)
IPr·HCl (R = 2,6-$iPr_2C_6H_3$)
ICy·HCl (R = cyclohexyl)
I*t*-Bu·HCl (R = *t*-Bu)

[a]Reaction conditions: **2** (0.50 mmol), **1g** (1.0 mmol), $[Ir(OMe)(cod)]_2$ (0.050 mmol), ligand (0.10 mmol), NaO*t*-Bu (0.20 mmol) in methylcyclohexane (1.0 mL) at 140 °C for 15 h. After treatment with pinacol (2.0 mmol), the borylated product was converted to the corresponding pinacolate. [b]The yield refers to a combined NMR yield of 2- and 3-borylated products. [c]Isolated yield.

Table 2: Scope of the heteroarene substrates.[a]

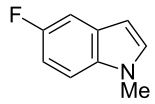
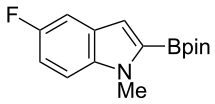
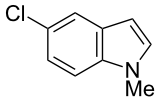
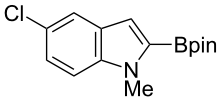
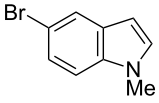
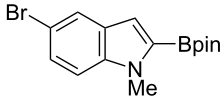
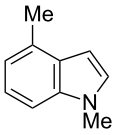
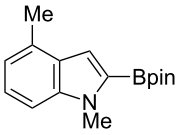
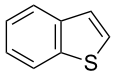
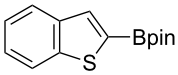
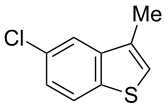
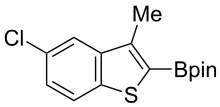
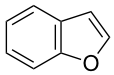
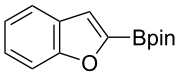
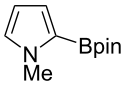
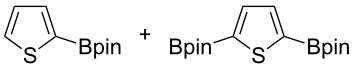
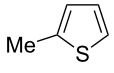
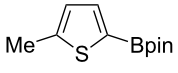
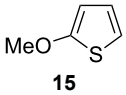
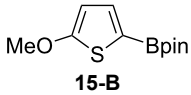
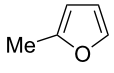
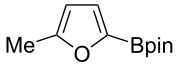


1g (2.0 equiv)

Entry	Heteroarene	Product	Isolated yield (NMR yield) [%]
1			48 (51)

4 **4-B**

Table 2: Scope of the heteroarene substrates.[a] (continued)

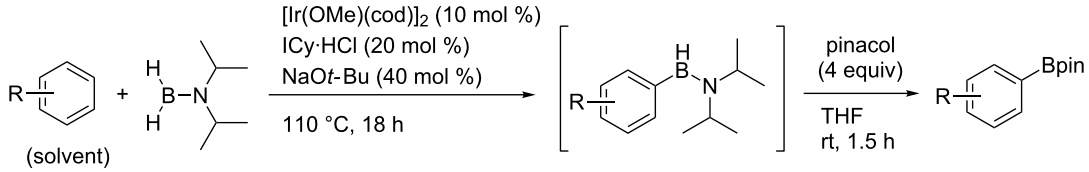
2	 **5**	 **5-B**	75 (82)
3	 **6**	 **6-B**	66 (66)
4	 **7**	 **7-B**	50 (55)[b]
5	 **8**	 **8-B**	51 (58)
6	 **9**	 **9-B**	94 (>99)
7	 **10**	 **10-B**	91 (99)
8	 **11**	 **11-B**	65 (87)
9	 **12**	 **12-B**	0 50 (52)[c]
10	 **13**	 **13-B** **13-2B**	71 (91) **13-B**:**13-2B** = 1.1:1
11	 **14**	 **14-B**	96 (>99)
12	 **15**	 **15-B**	91 (>99)
13	 **16**	 **16-B**	68 (92)

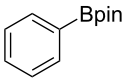
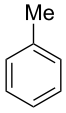
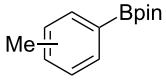
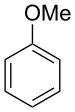
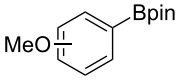
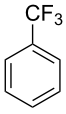
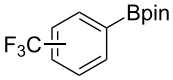
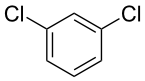
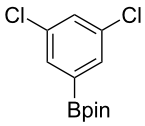
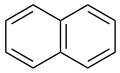
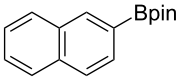
[a]Reaction conditions: heteroarene (0.50 mmol), **1g** (1.0 mmol), $[Ir(OMe)(cod)]_2$ (0.050 mmol), ICy·HCl (0.10 mmol), NaO*t*-Bu (0.20 mmol) in methylcyclohexane (1.0 mL) at 110 °C for 4 h. After treatment with pinacol (2.0 mmol), the borylated product was converted to the corresponding pinacolate. In cases where NMR yield is modest, the recovered starting heteroarene can account for the material balance, unless otherwise noted. bDebrominative borylation also occurred with a yield of 6%. [c]Run using 1.0 mL of *N*-methylpyrrole instead of methylcyclohexane.

7). Although benzofuran **11** was borylated at the 2-position successfully, the isolated yield was somewhat lower than the yield calculated from the ^{1}H NMR data, probably because of the instability of **11-B** during isolation (Table 2, entry 8). Our protocol was able to borylate non-benzofused five-membered heteroarenes. Pyrrole **12** was much less reactive than indoles, and required neat conditions to obtain a modest yield of the borylated product **12-B** (Table 2, entry 9). Thiophene (**13**) afforded a 1.1:1 mixture of 2-borylated and 2,5-diborylated products under our standard conditions (Table 2, entry 10). 2-Substituted thiophenes **14** and **15** and furan **16** were borylated successfully at the 5-positions (Table 2, entries 11–13). Electron-deficient heteroarenes such as pyridine and quinolone failed to form the borylated product under the current conditions.

We next turned our attention to the borylation of benzene derivatives. Unfortunately, benzene derivatives proved to be much less reactive than heteroarenes when borylated with **1g**. For example, Ir/ICy-catalyzed borylation of benzene with **1g** afforded **17-B** in 48% isolated yield even when the reaction was conducted under neat conditions (Table 3, entry 1) (see the Supporting Information File 1 for details on the optimization for the borylation of benzene). Borylation was relatively independent

Table 3: Scope of the arene substrates.[a]



Entry	Arene	Product	Isolated yield [%]	Ratio of *o/m/p* isomers
1	 **17**	 **17-B**	48	–
2	 **18**	 **18-B**	42	0/64/36
3	 **19**	 **19-B**	35	0/60/40
4	 **20**	 **20-B**	49	0/76/24
5	 **21**	 **21-B**	31	–
6[b]	 **22**	 **22-B**	50	–

[a]Reaction conditions: arene (1.0 mL), **1g** (0.50 mmol), $[Ir(OMe)(cod)]_2$ (0.050 mmol), ICy·HCl (0.10 mmol), NaO*t*-Bu (0.20 mmol) at 110 °C for 15 h. After treatment with pinacol (2.0 mmol), the borylated product was converted to the corresponding pinacolate. [b]Naphthalene (3.0 mmol) was used in methylcyclohexane (1.0 mL).

of the electronic nature of the arene substrates, as indicated by the similar yields and regioselectivity observed with toluene, anisole and trifluoromethylbenzene (Table 3, entries 2–4). Similar to the reported C–H borylation using other boron sources, 1,3-disubstituted benzenes were borylated at the 5-position in a regioselective manner (Table 3, entry 5). Naphthalene also underwent borylation with **1g** at the less hindered 2-position (Table 3, entry 6).

Our protocol was performed on a gram scale without any difficulty using a lower loading of the iridium catalyst (Scheme 2, top). Using **1g** as the boron source in C–H borylation reactions has the synthetic advantage of allowing various substituents to be introduced onto the boron atom during the work-up stage simply by changing the reagents added. For example, addition of different diols delivered the corresponding boronic esters **10-Bnep** and **10-Bmep** (Scheme 2, bottom). It was also possible to introduce Suginome's dan group, which allows us to use the borylated products in more elaborate manner, such as iterative cross-coupling reactions [20].

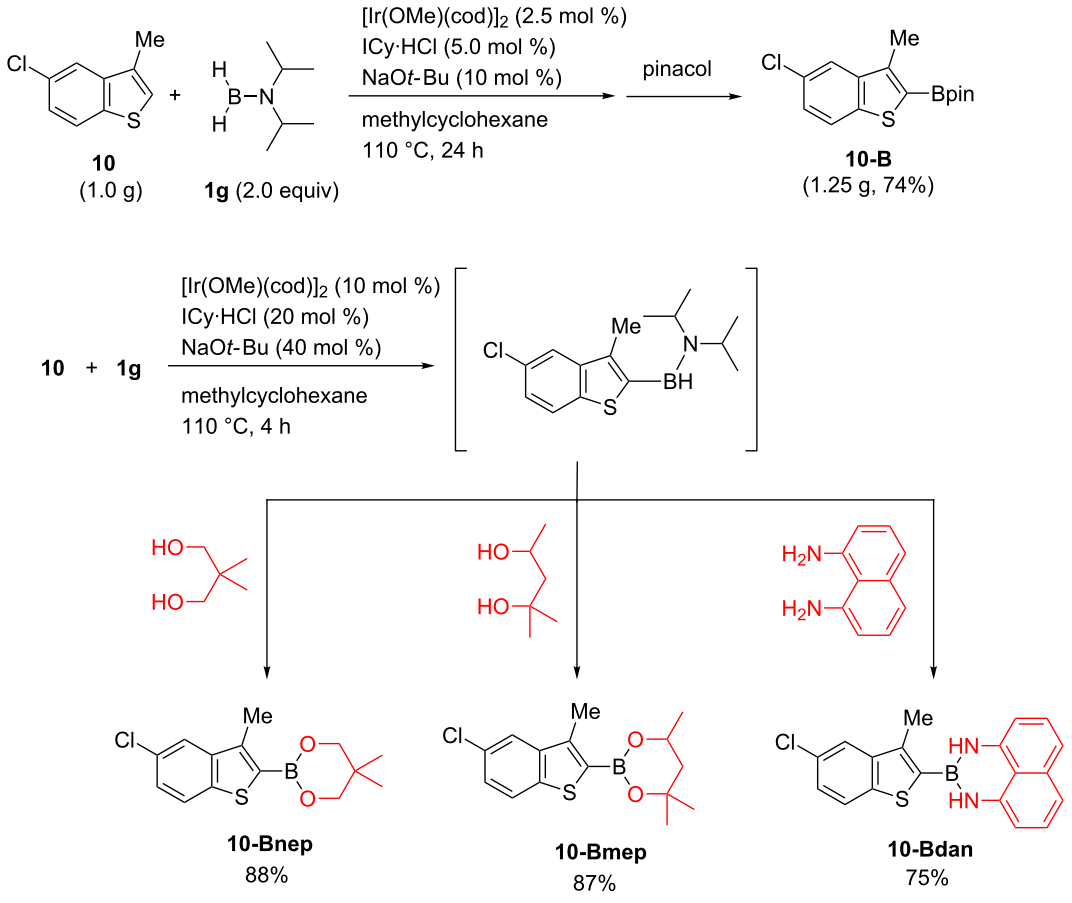
Conclusion

We have developed a C–H borylation of arenes and heteroarenes using diisopropylaminoborane as a borylating reagent. An iridium(I) complex bearing an ICy ligand was the most efficient catalyst. The initially formed aminoborylated products can readily be converted to the corresponding organoboron compounds bearing various boron-protecting groups.

Experimental

Procedure for the Ir-catalyzed borylation of heteroarenes using **1g**

In a glovebox filled with nitrogen, $[Ir(OMe)(cod)]_2$ (33.1 mg, 0.050 mmol, 0.10 equiv), ICy·HCl (26.2 mg, 0.10 mmol, 0.20 equiv), NaO*t*-Bu (19.2 mg, 0.20 mmol, 0.40 equiv) and methylcyclohexane (1.0 mL) were added to a 10 mL sample vial with a Teflon-sealed screwcap, and stirred for 5 min at room temperature. A heteroarene (0.50 mmol, 1.0 equiv) and **1g** (113.1 mg, 2.0 equiv) were added, and then the cap was screwed on seal the vial. The vial was stirred at 110 °C for 4 h. The reaction mixture was cooled to room temperature. Pinacol



Scheme 2: Scalability and derivatization.

(236 mg, 2.0 mmol) in THF (2.0 mL) was added and the reaction mixture was stirred under N_2 at room temperature for 1.5 h. The crude mixture was filtered through a pad of Celite and eluted with EtOAc. The filtrate was concentrated in vacuo and sampled for analysis by ^{1}H NMR spectroscopy using 1,2-dichloroethane as an internal standard. The residue was purified by flash column chromatography over silica gel eluting with hexane/EtOAc. Product-containing fractions were concentrated in vacuo to give a pure borylated product.

Supporting Information

Supporting Information File 1

Experimental procedures, data for optimization studies and copies of ^{1}H and ^{13}C NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-65-S1.pdf]

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from MEXT, Japan and ACT-C from JST, Japan. We also thank the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for their assistance with HRMS.

References

1. Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010,** *110,* 890. doi:10.1021/cr900206p
2. Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002,** *124,* 390. doi:10.1021/ja0173019
3. Hatanaka, T.; Ohki, Y.; Tatsumi, K. *Chem. – Asian J.* **2010,** *5,* 1657. doi:10.1002/asia.201000140
4. Yan, G.; Jiang, Y.; Kuang, C.; Wang, S.; Liu, H.; Zhang, Y.; Wang, J. *Chem. Commun.* **2010,** *46,* 3170. doi:10.1039/b926945b
5. Dombray, T.; Werncke, C. G.; Jiang, S.; Grellier, M.; Vendier, L.; Bontemps, S.; Sortais, J.-B.; Sabo-Etienne, S.; Darcel, C. *J. Am. Chem. Soc.* **2015,** *137,* 4062. doi:10.1021/jacs.5b00895
6. Mazzacano, T. J.; Mankad, N. P. *J. Am. Chem. Soc.* **2013,** *135,* 17258. doi:10.1021/ja408861p
   See for Cu–Fe mixed catalyst.
7. Obligacion, J. V.; Semproni, S. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2014,** *136,* 4133. doi:10.1021/ja500712z
8. Furukawa, T.; Tobisu, M.; Chatani, N. *Chem. Commun.* **2015,** *51,* 6508. doi:10.1039/C5CC01378J
9. Zhang, H.; Hagihara, S.; Itami, K. *Chem. Lett.* **2015,** *44,* 779. doi:10.1246/cl.150154
10. Furukawa, T.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015,** *137,* 12211. doi:10.1021/jacs.5b07677
11. Takaya, J.; Ito, S.; Nomoto, H.; Saito, N.; Kirai, N.; Iwasawa, N. *Chem. Commun.* **2015,** *51,* 17662. doi:10.1039/C5CC07263H
12. Légaré, M.-A.; Courtemanche, M.-A.; Rochette, É.; Fontaine, F.-G. *Science* **2015,** *349,* 513. doi:10.1126/science.aab3591
13. Ros, A.; Fernández, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014,** *43,* 3229. doi:10.1039/c3cs60418g
    See for a review.
14. Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem.* **2015,** *7,* 712. doi:10.1038/nchem.2322
    See for directed meta-borylation.
15. Saito, Y.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2015,** *137,* 5193. doi:10.1021/jacs.5b02052
16. Tzschucke, C. C.; Murphy, J. M.; Hartwig, J. F. *Org. Lett.* **2007,** *9,* 761. doi:10.1021/ol062902w
17. Liskey, C. W.; Hartwig, J. F. *Synthesis* **2013,** *45,* 1837. doi:10.1055/s-0033-1338863
18. Liskey, C. W.; Wei, C. S.; Pahls, D. R.; Hartwig, J. F. *Chem. Commun.* **2009,** 5603. doi:10.1039/b913949d
19. Iwadate, N.; Suginome, M. *J. Organomet. Chem.* **2009,** *694,* 1713. doi:10.1016/j.jorganchem.2008.11.068
20. Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007,** *129,* 758. doi:10.1021/ja067975p
21. Köster, R.; Bellut, H.; Hattori, S. *Justus Liebigs Ann. Chem.* **1968,** *720,* 1. doi:10.1002/jlac.19687200102
22. Euzenat, L.; Horhant, D.; Ribourdouille, Y.; Duriez, C.; Alcaraz, G.; Vaultier, M. *Chem. Commun.* **2003,** 2280. doi:10.1039/B306874A
23. Pasumansky, L.; Haddenham, D.; Clary, J. W.; Fisher, G. B.; Goralski, C. T.; Singaram, B. *J. Org. Chem.* **2008,** *73,* 1898. doi:10.1021/jo702271c
24. Marciasini, L.; Richy, N.; Vaultier, M.; Pucheault, M. *Chem. Commun.* **2012,** *48,* 1553. doi:10.1039/C1CC14605J
25. Marciasini, L. D.; Richy, N.; Vaultier, M.; Pucheault, M. *Adv. Synth. Catal.* **2013,** *355,* 1083. doi:10.1002/adsc.201200942
26. Guerrand, H. D. S.; Marciasini, L. D.; Jousseaume, M.; Vaultier, M.; Pucheault, M. *Chem. – Eur. J.* **2014,** *20,* 5573. doi:10.1002/chem.201304861
27. Marciasini, L.; Cacciuttolo, B.; Vaultier, M.; Pucheault, M. *Org. Lett.* **2015,** *17,* 3532. doi:10.1021/acs.orglett.5b01620
28. Tobisu, M.; Yasutome, A.; Kinuta, H.; Nakamura, K.; Chatani, N. *Org. Lett.* **2014,** *16,* 5572. doi:10.1021/ol502583h
29. Tobisu, M.; Takahira, T.; Ohtsuki, A.; Chatani, N. *Org. Lett.* **2015,** *17,* 680. doi:10.1021/ol503707m
30. Tobisu, M.; Takahira, T.; Chatani, N. *Org. Lett.* **2015,** *17,* 4352. doi:10.1021/acs.orglett.5b02200
31. Tobisu, M.; Morioka, T.; Ohtsuki, A.; Chatani, N. *Chem. Sci.* **2015,** *6,* 3410. doi:10.1039/C5SC00305A
32. Morioka, T.; Nishizawa, A.; Nakamura, K.; Tobisu, M.; Chatani, N. *Chem. Lett.* **2015,** *44,* 1729. doi:10.1246/cl.150936
33. Nakamura, K.; Tobisu, M.; Chatani, N. *Org. Lett.* **2015,** *17,* 6142. doi:10.1021/acs.orglett.5b03151
34. Frey, G. D.; Rentzsch, C. F.; von Preysing, D.; Scherg, T.; Mühlhofer, M.; Herdtweck, E.; Herrmann, W. A. *J. Organomet. Chem.* **2006,** *691,* 5725. doi:10.1016/j.jorganchem.2006.08.099
35. Ishiyama, T.; Ishida, K.; Takagi, J.; Miyaura, N. *Chem. Lett.* **2001,** *30,* 1082. doi:10.1246/cl.2001.1082
36. Larsen, M. A.; Wilson, C. V.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015,** *137,* 8633. doi:10.1021/jacs.5b04899

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.65

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Opportunities and challenges for direct C–H functionalization of piperazines

Zhishi Ye, Kristen E. Gettys and Mingji Dai*

Review

Open Access

Address:
Department of Chemistry and Center for Cancer Research, Purdue University, West Lafayette, Indiana 47907, United States

Email:
Mingji Dai* - mjdai@purdue.edu

* Corresponding author

Keywords:
α-lithiation; C–H functionalization; heterocycle; photoredox catalysis; piperazine

Beilstein J. Org. Chem. **2016,** *12,* 702–715.
doi:10.3762/bjoc.12.70

Received: 20 January 2016
Accepted: 21 March 2016
Published: 13 April 2016

This article is part of the Thematic Series "C–H Functionalization/activation in organic synthesis".

Guest Editor: R. Sarpong

© 2016 Ye et al; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

Piperazine ranks within the top three most utilized N-heterocyclic moieties in FDA-approved small-molecule pharmaceuticals. Herein we summarize the current synthetic methods available to perform C–H functionalization on piperazines in order to lend structural diversity to this privileged drug scaffold. Multiple approaches such as those involving α-lithiation trapping, transition-metal-catalyzed α-C–H functionalizations, and photoredox catalysis are discussed. We also highlight the difficulties experienced when successful methods for α-C–H functionalization of acyclic amines and saturated mono-nitrogen heterocyclic compounds (such as piperidines and pyrrolidines) were applied to piperazine substrates.

Introduction

Piperazine is one of the most important saturated N-heterocycles frequently found in life-saving small-molecule pharmaceuticals [1]. In a recent statistical study done by Njardarson and co-workers, piperazine ranks among the top three N-heterocycles along with pyridine and piperidine in the U.S. FDA-approved pharmaceuticals [2]. Due to its broad utilization, piperazine has been considered as a privileged scaffold in drug discovery to combat various human diseases (Figure 1). For example, Imatinib (also marketed as Gleevec), a BCR-Abl tyrosine kinase inhibitor, is used in the treatment of multiple cancers with high response rate [3]. Sildenafil, sold as Viagra, is an important medication for treating erectile dysfunction as well as pulmonary arterial hypertension [4]. Indinavir, a protease inhibitor, is used to treat HIV/AIDS [5]. Gatifloxacin is an important fluoroquinolone antibiotic [6]. Despite the high frequency appearance of piperazines in small-molecule pharmaceuticals, over 80% only contain substituents at the two nitrogen atoms and a very small fraction of them have simple carbon substitutions (methyl or carboxylate). Recently, other substituents such as aryl and alkyl groups started to appear on the α-carbons of piperazine rings of various important lead compounds in the pipeline of drug discovery [7-9]. Vestipitant, a neurokinin-1

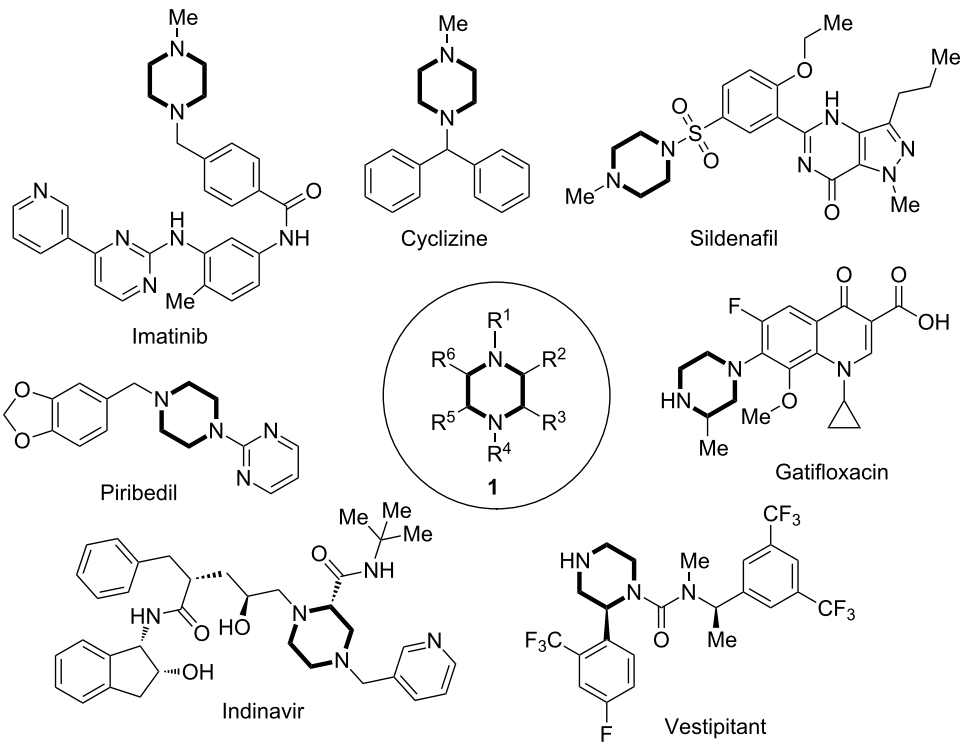


Figure 1: Selected piperazine-containing small-molecule pharmaceuticals.

antagonist, is an example which is currently in clinical trials for the treatment of anxiety and tinnitus [7]. However, such cases are rare and there is still a significant lack of structural diversity in piperazine-containing pharmaceuticals and small-molecule collections mainly due to the lack of efficient and reliable methods to quickly access carbon-substituted piperazines in regioselective and stereoselective manners.

The common and traditional way to synthesize α-carbon-substituted piperazines is through de novo construction of the six-membered ring with starting materials such as amino acids and diamines followed by oxidation level adjustment (Figure 2, path a) [10]. This approach is generally lengthy, not flexible, and the substitution pattern highly depends on the availability of the starting materials. Recently, advances have been made to address some of these issues encountered in the synthesis of carbon-substituted piperazines [11]. For example, Bode and co-workers have developed a tin (Sn) amine protocol (SnAP) to synthesize piperazines and other N-heterocyles from aldehydes [12-14]. Aggarwal and co-workers have developed a formal [4 + 2] procotocl utilizing vinyl sulfonium salts and diamines as starting materials [15-17]. Carreira et al. have developed a ring expansion of 3-oxetanone to synthesize substituted piperazines [18]. Transition metal (such as Ti, Au, and Pd) catalyzed cyclizations of linear starting materials have been used by several groups including the Schafer, Nelson, Huang, and Wolfe groups to synthesize carbon-substituted piperazines [19-22]. Mendoza et al. have developed a [3 + 3] dimerization of azomethine to synthesize highly substituted piperazines [23]. Notably, Stoltz and co-workers recently developed an enantioselective synthesis of piperazin-2-ones and piperazines using a palladium-catalyzed asymmetric allylic alkylation [24]. The most straightfor-

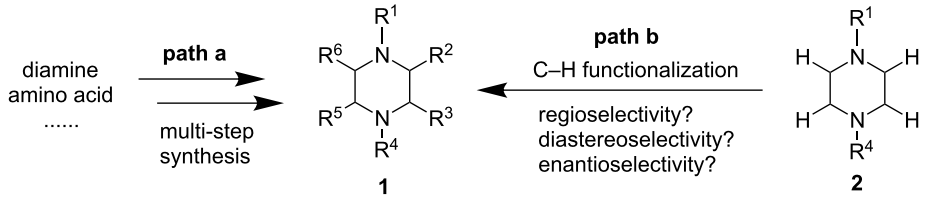


Figure 2: Strategies for the synthesis of carbon-substituted piperazines.

ward and attractive way of synthesizing α-carbon-substituted piperazines is the selective (regioselective, diastereoselective, and enantioselective) activation and functionalization of the existing C–H bonds of piperazine substrates (Figure 2, path b). Although there have been major advancements made in the field of direct sp^3 C–H bond activation and functionalization adjacent to nitrogen in saturated N-heterocycles and acyclic amines [25-27], C–H functionalization of piperazines has been a daunting challenge. In comparison to the well-studied pyrrolidine and piperidine systems, the existence of the second ring-bound nitrogen in piperazines either causes various side reactions or inhibits or diminishes the reactivity of the C–H bond. This review summarizes the current status and challenges of direct C–H bond functionalization of piperazines.

Review

Direct α-C–H lithiation trapping

Since the seminal discovery made by Beak and Lee [28,29], α-functionalization of *N*-Boc-protected nitrogen heterocycles via direct α-C–H lithiation trapping has been a straightforward and effective method to introduce various substituents on the α-carbon atoms [30,31]. Corresponding enantioselective versions have also been developed using chiral diamines as ligands to allow access to enantioenriched α-substituted nitrogen heterocycles. However, most of the success has been made in the territory of *N*-Boc-pyrrolidine [32,33] and *N*-Boc-piperidine [34-36], especially with regard to the asymmetric versions. The addition of the second nitrogen atom in piperazines significantly increases the reaction difficulty and complexity and only limited examples of direct α-C–H lithiation trapping of piperazines have been reported.

The first examples of direct α-lithiation of *N*-Boc-protected piperazines were reported by van Maarseveen and co-workers in 2005 [37], sixteen years after Beak and Lee's seminal discovery. Van Maarseveen et al. have developed two sets of reaction conditions: one uses various electrophiles to directly trap the α-lithiation product derived from treating *N*-Boc-protected piperazines with *sec*-BuLi at –78 °C (Figure 3, conditions A) while the other converts the α-lithiation product to an α-Cu intermediate via transmetallation followed by electrophilic trapping (conditions B). As shown in Figure 3, conditions A generally work better for electrophiles such as TMSCl and Bu_3SnCl whereas conditions B are more suitable for alkyl electrophiles. Van Maarseveen and co-workers also noted that the substituents on the distal nitrogen, while lacking proximity to the reaction center, have a significant impact on the overall result.

In 2010, Coldham and co-workers reported a direct α-functionalziation of *N*-Boc-*N'*-*tert*-butylpiperazines (Figure 4) [38]. Under the conditions of *sec*-BuLi and TMEDA, substituents such as TMS, Bu_3Sn, Me, CHO, and CO_2H could be installed on the *N*-Boc α-carbon in good yields. In general, the bulky *tert*-butyl group on the distal nitrogen gave better results than small alkyl groups such as methyl or benzyl groups.

Both van Maarseveen and Coldham's cases required the use of TMEDA and the reaction takes place at –78 °C, a reaction temperature which requires a considerable amount of energy to maintain when the reaction is conducted on a production scale (multikilogram or more) [39]. In order to circumvent these operational issues, O'Brien, Campos, and co-workers de-

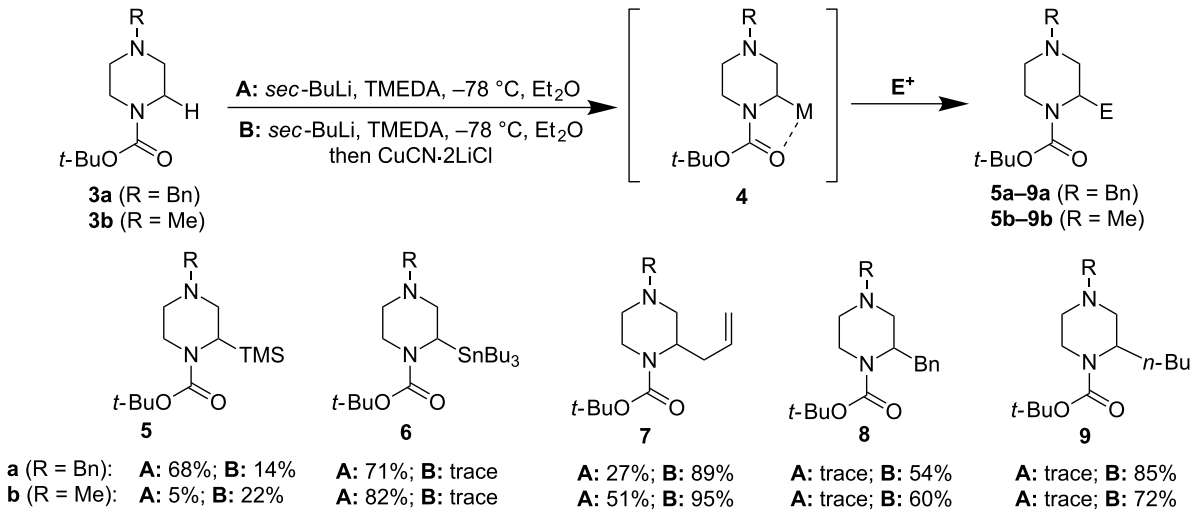


Figure 3: The first α-lithiation of *N*-Boc-protected piperazines by van Maarseveen et al. in 2005 [37].

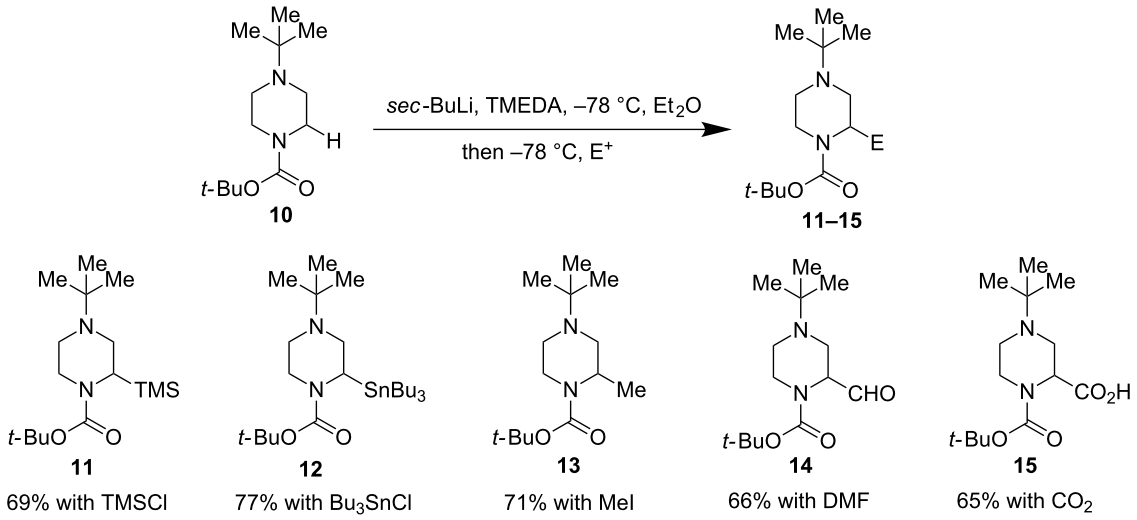


Figure 4: α-Lithiation of *N*-Boc-*N'-tert*-butyl piperazines by Coldham et al. in 2010 [38].

veloped a diamine-free lithiation trapping process to functionalize *N*-Boc-heterocycles including piperazines using *sec*-BuLi in THF (Figure 5) [40]. This simple and effective diamine-free procedure allowed the reaction to take place at −30 °C, which is more desirable than −78 °C in process chemistry. Under the new reaction conditions, electrophiles such as TMSCl, MeO_2CCl, DMF, Ph_2CO, and PhBr (via a Negishi coupling process) can be used to install the corresponding substituents on the α-carbon of *N*-Boc-*N*'-benzylpiperazines in good yield. Notably, the O'Brien–Campos conditions work well for *N*-Boc-pyrrolidine and imidazolidine, but not for *N*-Boc-piperidine (cf. **20**).

Asymmetric direct α-C–H lithiation trapping

Advances of enantioselective α-functionalization of *N*-Boc-protected saturated mono-nitrogen heterocycles via the lithiation trapping sequence using chiral diamines such as (−)-sparteine and (+)-sparteine surrogates as ligands have been made. However, the progress for the enantioselective α-functionalization of *N*-Boc-protected piperazines is surprisingly slow and very few examples have been reported. There remains a demand for a general versatile method to efficiently synthesize enantioenriched α-substituted piperazines. The first example of a *sec*-BuLi/(−)-sparteine-mediated asymmetric deprotonation of *N*-Boc-*N'-tert*-butylpiperazine was reported by McDermott et

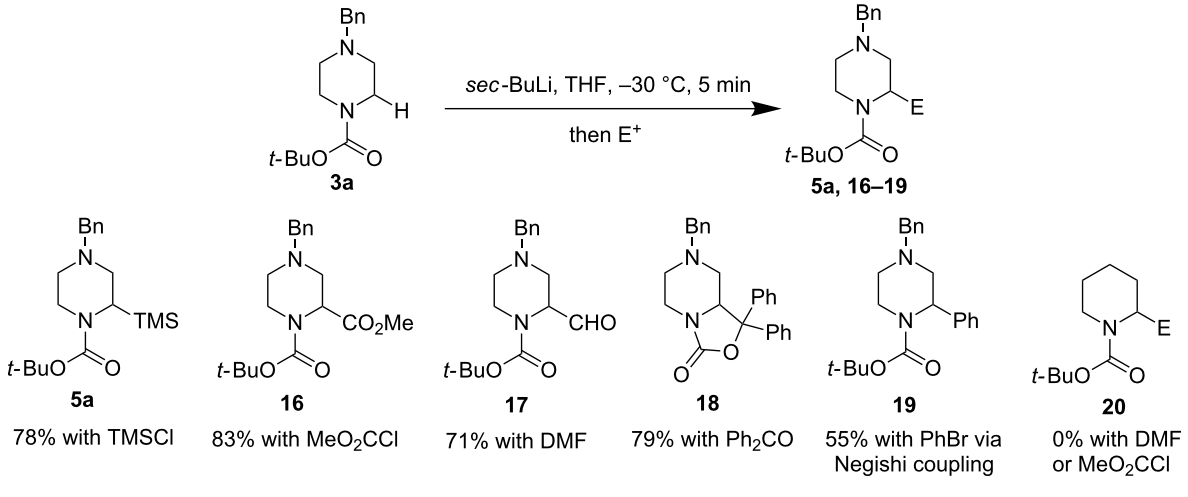


Figure 5: Diamine-free α-lithiation of *N*-Boc-piperazines by O'Brien, Campos, et al. in 2010 [40].

al. in 2008 (Figure 6) [41]. In two steps (asymmetric deprotonation followed by a carbon dioxide quench and coupling with *N*-benzylpiperazine, **22**) product **23** was produced in 48% yield with 89:11 enantioselectivity favoring the *R*-configuration of the newly generated carbon center.

In contrast to the direct asymmetric deprotonation, Coldham and co-workers developed a dynamic thermodynamic resolution (DTR) of the lithiated *N*-Boc-*N*'-alkylpiperazines by taking advantage of the configurational lability of the lithiated carbanion at elevated temperatures (higher than −50 °C) [38]. After generation of the lithiated *N*-Boc-*N*'-alkylpiperazines with *sec*-BuLi and TMEDA at −78 °C, the reaction was warmed up to −30 °C with addition of a chiral ligand. The chiral ligand coordinates with the racemic lithiation product to give a diastereomeric mixture which can be resolved under thermodynamic or kinetic control with electrophilic quench by a variety of electrophiles. After evaluating a few chiral diamino-alkoxide ligands, ligand **24** was identified as a superior choice. As shown in Figure 7, the result was not optimal with only 30–75% of the desired α-substituted products being obtained and the enantiomeric ratio (er) ranging from 60:40 to 81:19. The substituents are restricted to TMS, Bu_3Sn, Me, CHO, and CO_2H.

O'Brien and co-workers reported another asymmetric lithiation trapping of *N*-Boc-protected saturated heterocycles at temperatures above −78 °C in 2013 [42]. Good yields and high enantioselectivity were obtained for *N*-Boc-pyrrolidines when (−)-sparteine or (+)-sparteine surrogate **28** was used. The reactions could be conducted at −30 or −20 °C with a slight drop of the enantiomeric ratio in comparison to the results at −78 °C. They also reported one example of asymmetric lithiation trapping of

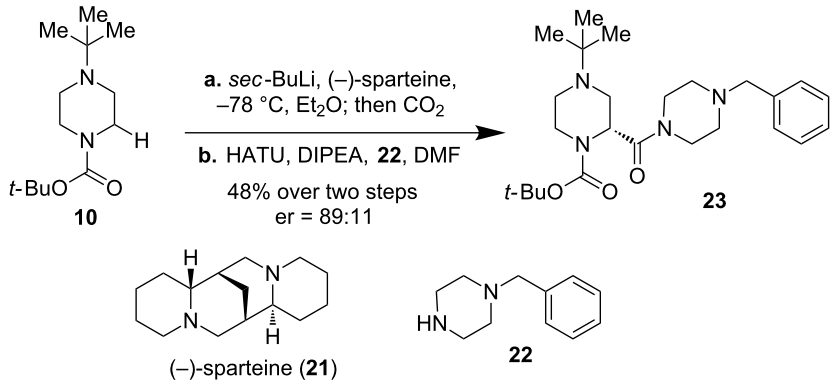


Figure 6: The first enantioselective α-lithiation of *N*-Boc-piperazines by McDermott et al. in 2008 [41].

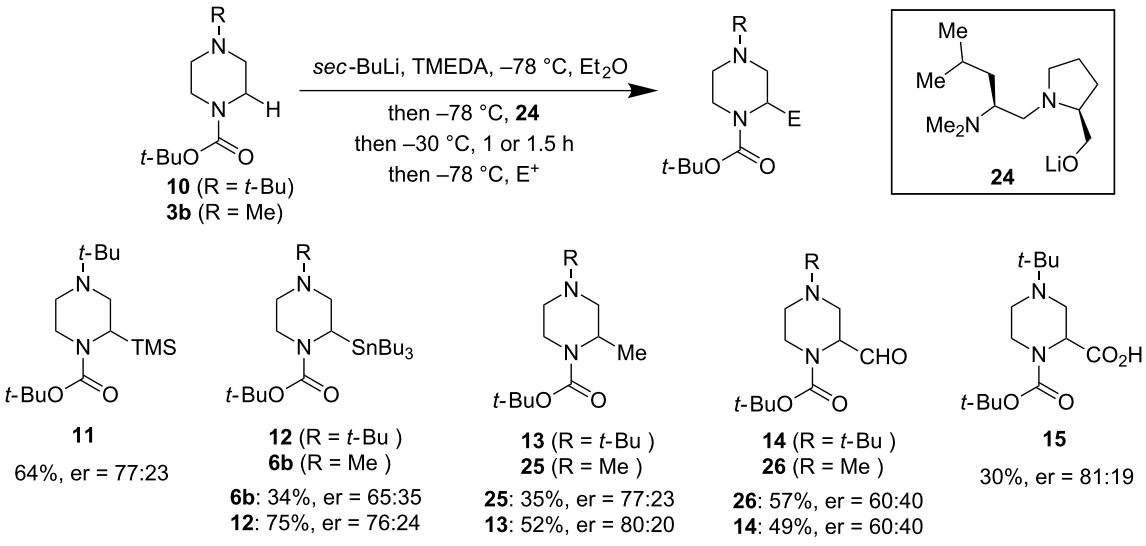


Figure 7: Dynamic thermodynamic resolution of lithiated of *N*-Boc-piperazines by Coldham et al. in 2010 [38].

N-Boc-piperazine **10** using a combination of *sec*-BuLi and **28** to produce (*S*)-**30** with an 89:11 er. In 2015, O'Brien and co-workers expanded this work and reported an elegant and detailed study of asymmetric lithiation trapping of *N*-Boc-piperazines [43]. With the help of in situ IR spectroscopy, they were able to monitor the reaction process and establish the side reactions responsible for the observed byproduct formation (cf. **29**). As shown in Figure 8, a good to excellent selectivity could be obtained for the introduction of CO_2Me, Bu_3Sn, and CONH*t*-Bu groups although installation of the TMS group was found to be problematic. Similar to the Coldham discovery, they also noted that the distal *N*-alkyl substituents have a profound effect on the overall reaction yield and enantioselectivity, with the bulkier alkyl substituents giving better results. The rationale is that the bulky alkyl substituent on the distal nitrogen atom is likely preventing this nitrogen from attacking the electrophile and triggers an elimination process which would yield a byproduct like **29**.

Of particular interest, when benzophenone (Ph_2CO) was used to trap the α-lithiation product of *N*-Boc-*N*'-alkylpiperazines, in addition to the desired products (**18**, **34**, and **35**), a significant amount of oxidized product **36** was obtained (Figure 9). The formation of this byproduct is proposed to be a sequential single-electron oxidation of the alkyllithium intermediate by benzophenone. Again, the use of a bulky alkyl group on the

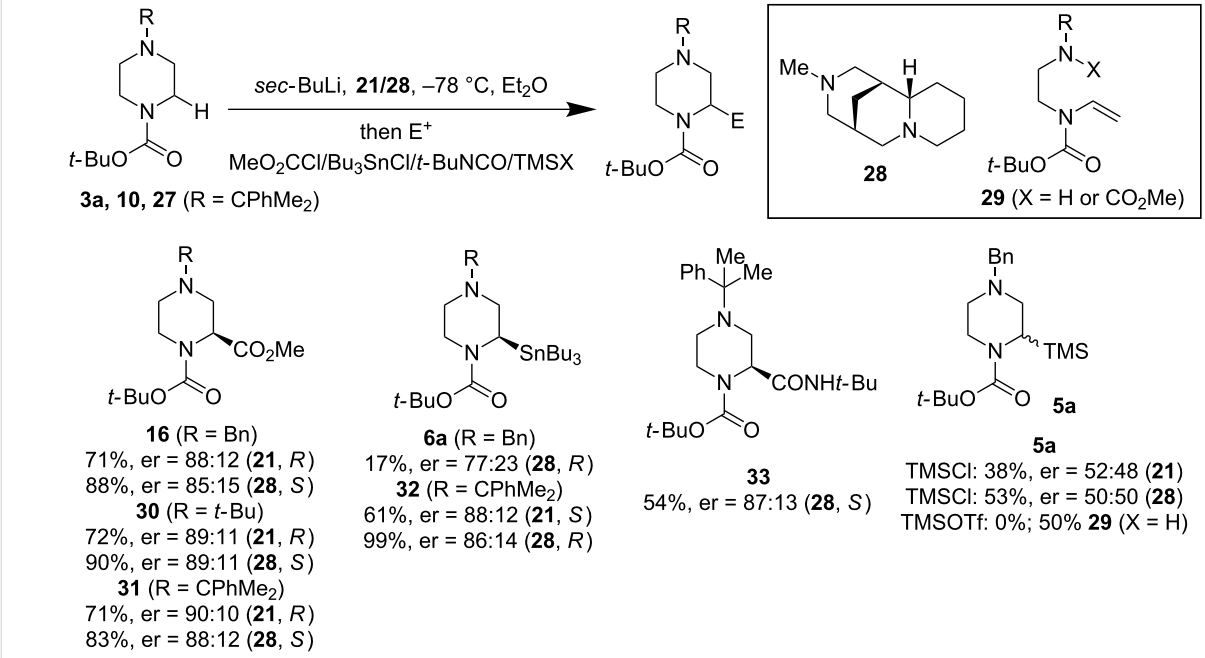


Figure 8: Enantioselective α-lithiation of *N*-Boc-*N*'-alkylpiperazines by O'Brien et al. in 2013 and 2016 [42,43].

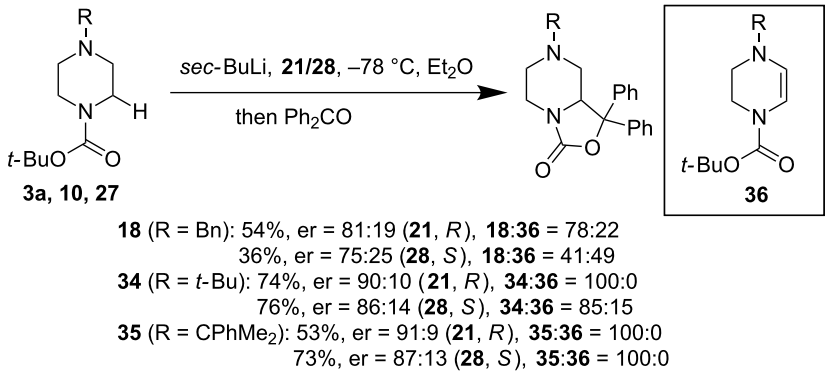


Figure 9: Asymmetric α-functionalization of *N*-Boc-piperazines with Ph_2CO by O'Brien et al. in 2016 [43].

distal nitrogen atom was seen to help reduce byproduct **36** and the desired α-functionalization product was obtained in good yield and enantioselectivity.

In order to prepare enantiopure α-functionalized piperazines, O'Brien and co-workers used a stereogenic α-methylbenzyl on the distal nitrogen atom. The α-methylbenzyl group is bulky enough to prevent the aforementioned side reactions and the resulting diastereomeric α-functionalized piperazines could then afford good separation. Furthermore, this "chiral auxiliary" can be removed upon catalytic hydrogenation. As shown in Figure 10, a variety of substituents could be installed on the α-position (yield of the major product was given). Notably, when (+)-sparteine surrogate **28** was used as a ligand, product **38** was produced in 90% yield with 95:5 diastereoselectivity, but once the chiral amine ligand was simply switched from **28** to (−)-sparteine (**21**), product **39** was produced in only 49% yield with poor diastereoselectivity (67:33). This result indicates a mismatched case of (−)-sparteine and the (*S*)-α-methylbenzyl group even though the chiral center of the "chiral auxiliary" is quite far away from the newly established chiral center. This issue is easily circumvented by using a matched case of (−)-sparteine and the (*R*)-α-methylbenzyl group (**40**).

The α-methyl-substituted piperazine is an important structural motif. Installation of a methyl group on a drug candidate is often seen to have a positive effect on improving the drug candidate's activity and properties, as the so-called as the "magic methyl effect" [44]. Direct enantioselective α-methylation of piperazines however, has been a great synthetic challenge and an effective method still needs to be developed. O'Brien and co-workers also reported their work towards a solution to this problem. As shown in Figure 11, they have tried various reaction conditions to achieve an enantioselective methylation of the α-lithiation intermediate of *N*-Boc-*N*'-alkylpiperazines by using different diamines (TMEDA, **21**, and **28**) as well as the "chiral auxiliary" strategy. While the result is not yet optimal, a significant progress has been made. Due to the low reactivity of MeI and Me_2SO_4, a diamine switch strategy of replacing the bulky chiral diamines (**21**/**28**) with the less hindered TMEDA has been put in place to improve the reactivity of the alkyllithium intermediate and gave a 48% yield of (*S*)-**46** with an 87:13 enantiomeric ratio (Figure 11, reaction 1). The use of more reactive MeOTf with α-methylbenzyl chiral auxiliary on the distal nitrogen atom was not fruitful (Figure 11, reaction 2); a significant amount of elimination product **47** or **50** was produced in these cases. To date, a combination of the di-

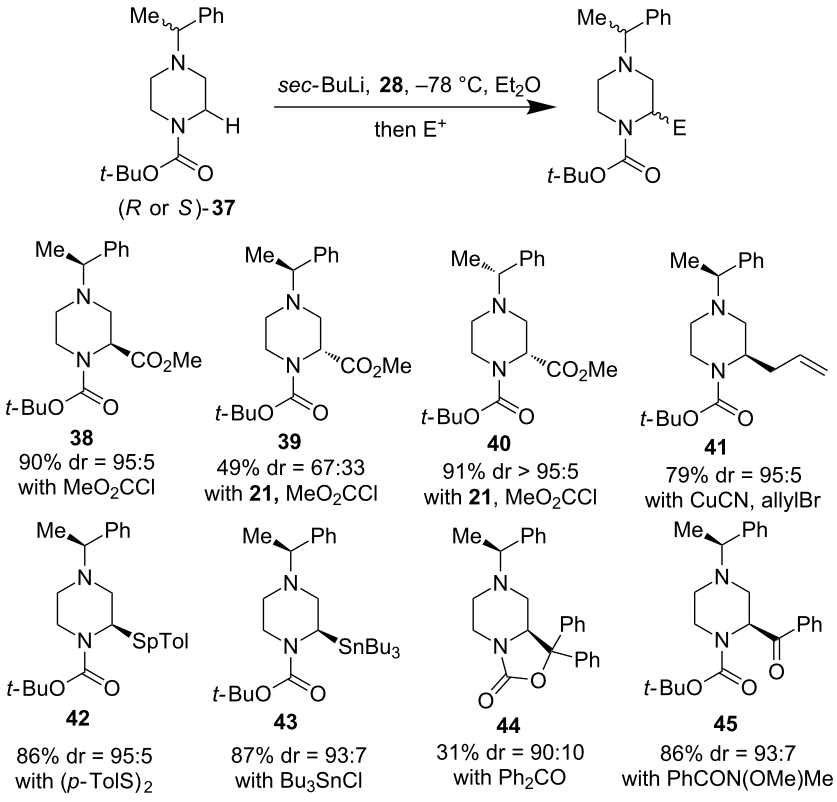


Figure 10: A "chiral auxiliary" strategy toward enantiopure α-functionalized piperazines by O'Brien et al. 2016 [43].

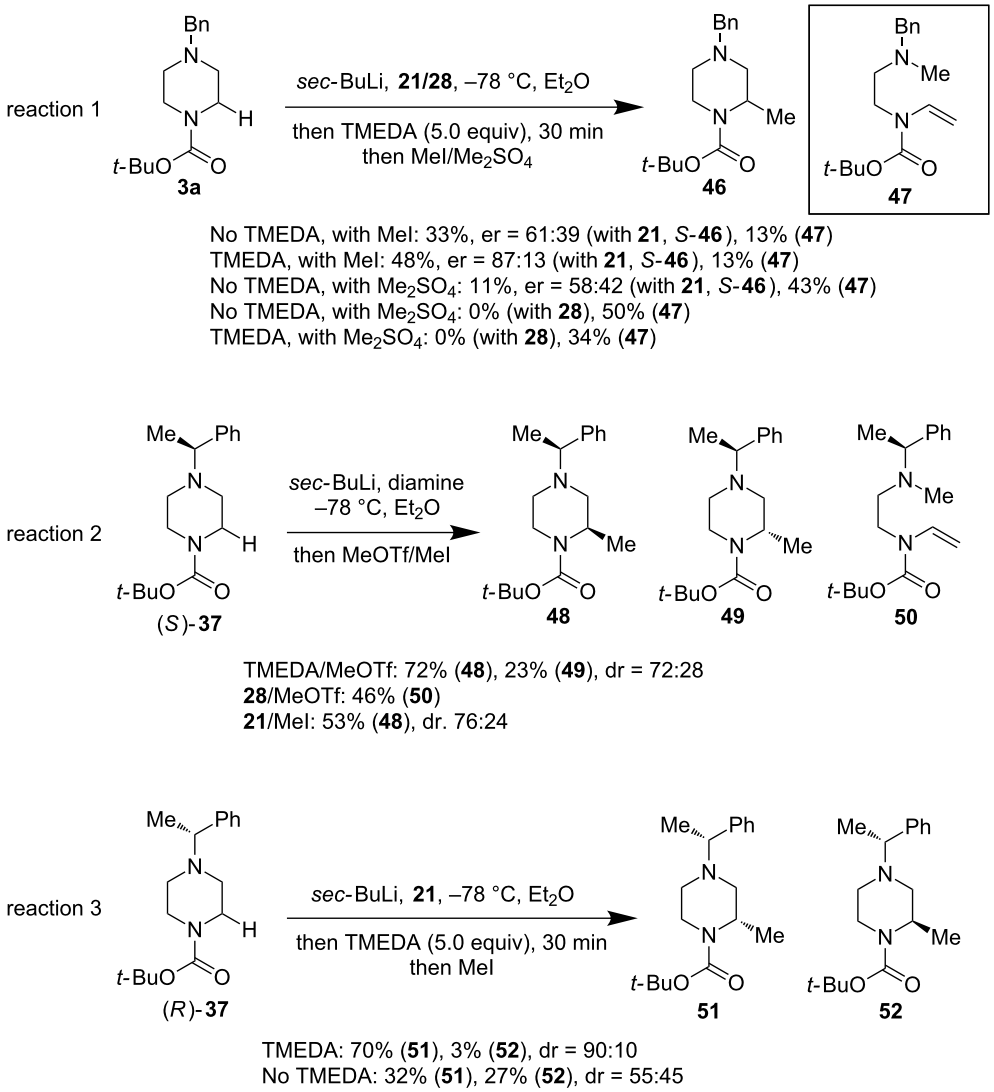


Figure 11: Installation of methyl group at the α-position of piperazines by O'Brien et al. 2016 [43].

amine switch strategy and α-methylbenzyl chiral auxiliary strategy has been reported to give the best results and produce **51** in 70% yield and 90:10 diastereoselectivity (Figure 11, reaction 3).

O'Brien and co-workers also reported a stereoselective synthesis of enantiopure 2,6-*trans*- and 2,5-*trans*-piperazines via a second α-lithiation trapping of carbon-substituted *N*-Boc-piperazines (Figure 12). In the cases of **41** and **48**, 2,6-*trans*-piperazine products **54**, **55**, or **56** were produced in excellent stereroselectivity and good yield. The predominant formation of the 2,6-*trans*-piperazine products is presumably due to a Boc-directed equatorial lithiation trapping with the existing allyl or methyl group in the axial position to avoid strong $A^{1,3}$-interaction with the Boc group. In the case of **53**, an equatorial lithiation trapping with the existing methyl group in the equatorial position gave 2,5-*trans*-piperazine **57**.

In summary, promising progress has been made in the direct α-lithiation trapping of *N*-Boc-protected piperazines, including enantioselective versions. So far, these methods are limited by narrow electrophile scopes and often low enantioselectivities rendering further developments necessary.

Transition-metal-catalyzed α-C–H functionalization

Transition-metal-catalyzed direct sp^3 C–H bond functionalization at the α-carbon of both cyclic and acyclic amines have been

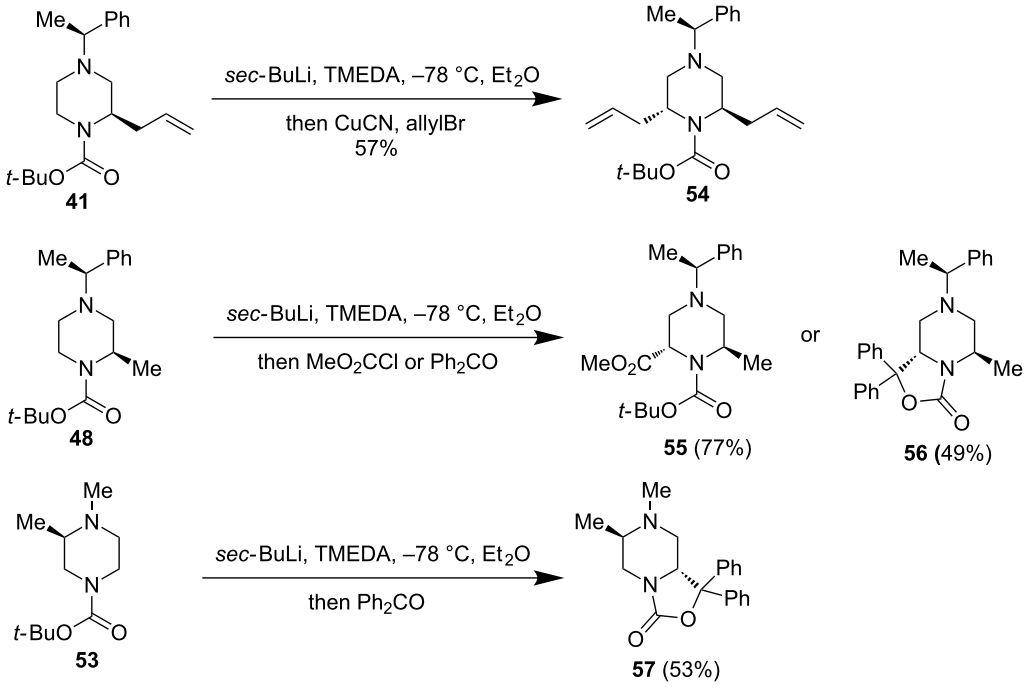


Figure 12: α-Lithiation trapping of *C*-substituted *N*-Boc-piperazines by O'Brien et al. 2016 [43].

a fertile research field [45-47]. In the case of saturated *N*-heterocycles however, most of the efforts have been focused on directed α-C–H functionalization of pyrrolidines and piperidines [48-50]. Little progress has been made in transition-metal-catalyzed α-C–H functionalization of piperazines presumably due to the low reactivity and the undesired competitive pathways caused by the addition of the second nitrogen in the six-membered ring [51]. As of yet only a few examples have been reported so far and are far from being general and practical; no enantioselective versions have been shown.

Rhodium-catalyzed dehydrogenative carbonylation

In 1997, Murai and co-workers reported a novel Rh-catalyzed α-C–H-functionalization reaction of *N*-(2-pyridinyl)piperazines with carbon monoxide and terminal olefins (Figure 13) [52]. Their previous work on pyridinyl group-directed Rh-catalyzed carbonylation at sp^3 C–H bonds adjacent to the nitrogen atom in other alkylamines such as pyrrolidine, piperidine, and tetrahydroisoquinoline [53,54] gave the carbonylation product directly. However, when piperazine substrates were used, an additional formal dehydrogenation process took place before the carbonylation reaction. As shown in Figure 13, under the conditions of 15 atm of carbon monoxide and ethylene, $Rh_4(CO)_{12}$ catalyst, and toluene at 160 °C, dehydrogenation and propionylation of *N*-(2-pyridinyl)piperazines took place to give various tetrahydropiperazines. Similar to the α-C–H lithiation trapping strategy, the substituents on the distal nitrogen have a profound effect on the overall yield with alkyl groups giving better yields than aryl and acyl groups. Other olefins such *tert*-butylethylene and cyclopentene can be used as well, but the yields were significantly lower (cf. **63** and **64**). The scope of the directing 2-pyridinyl group can be expanded to electron-withdrawing groups such as ester and trifluoromethyl, while maintaining excellent yields. Regioselectivity issues have been encountered in the case of C_3-substituted piperazine substrates resulting in a mixture of **70** and **71**. Notably, when 1-hexene was used, a mixture of **73**–**75** was produced. When the 2-pyridinyl directing group was switched to simple aryl groups, only dehydrogenation products were observed. Overall, the result is promising, but this method has quite a limited substrate scope and yields only dehydrogenated products after C–H functionalization instead of the desired fully saturated piperazines. It also highlights the challenges provided by the extra nitrogen of piperazine in comparison to pyrrolidine and piperidine substrates.

Tantalum-catalyzed hydroaminoalkylation

In continuation of their efforts in developing new catalysts and methods for hydroaminoalkylation at the α-position of amines, Schafer and co-workers reported an elegant tantalum-catalyzed hydroaminoalkylation for the synthesis of α-alkylated *N*-heterocycles from the corresponding heterocycles and alkenes [55]. Along with piperidine and azepane substrates, piperazine substrates of type **76** react smoothly with terminal olefins (**78**) in the presence of 10 mol % of catalyst **77** in toluene at 165 °C (Figure 14). Despite the high temperature, the reaction provi-

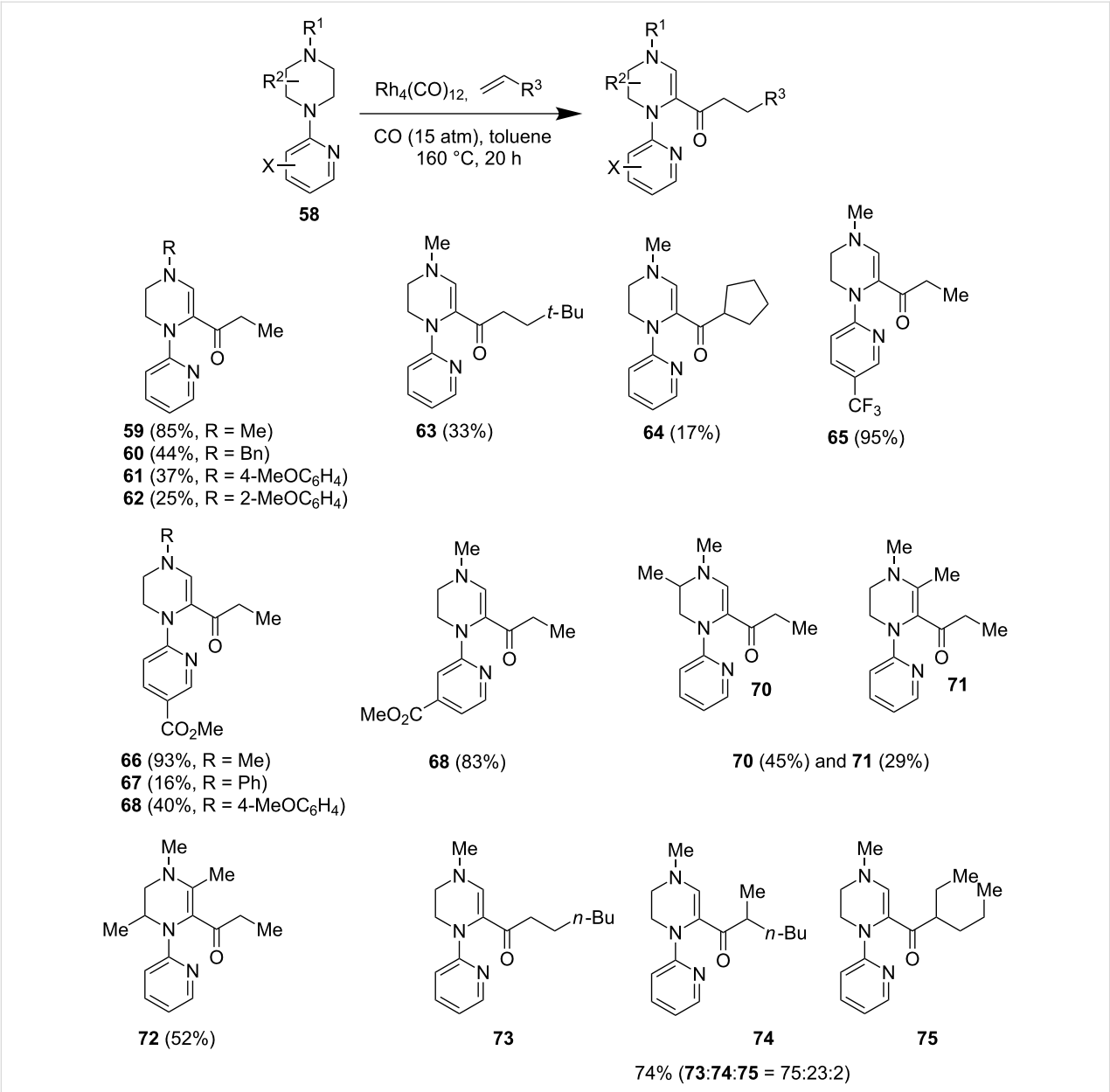


Figure 13: Rh-catalyzed reactions of *N*-(2-pyridinyl)piperazines by Murai et al. in 1997 [52].

ded α-alkylated piperazines **79**–**83** in good yield. The reaction is atom-economic and does not require directing groups which sets it apart from previously discussed models. Simple mono-alkylated or -arylated piperazines and terminal olefins were used as starting materials. The reaction proceeds with excellent regio- and diastereoselectivity which is presumably due to a regio- and stereoselective alkene insertion into the strained metalla-aziridine intermediate **84**.

Photoredox catalysis

Visible-light photoredox catalysis has emerged as a powerful platform for organic small-molecule functionalization [56-58]. One important application of photoredox catalysis is direct sp^3 C–H activation and functionalization [59-61]. Among the recent advances, direct photoredox redox C–H activation of the α-position of amines has been an efficient and versatile method to functionalize amines, particularly saturated N-heterocycles [62-66]. However, photoredox catalysis for direct α-C–H functionalization of piperazines is very limited and only a few examples have been reported by MacMillan and co-workers (Figure 15) [63,65,66]. Using a high-throughput and automated workflow platform, they have discovered a photoredox-catalyzed C–H arylation of *N*-arylamines with 1,4-dicyanobenzene (**88**) to produce pharmaceutically important benzylic amines.

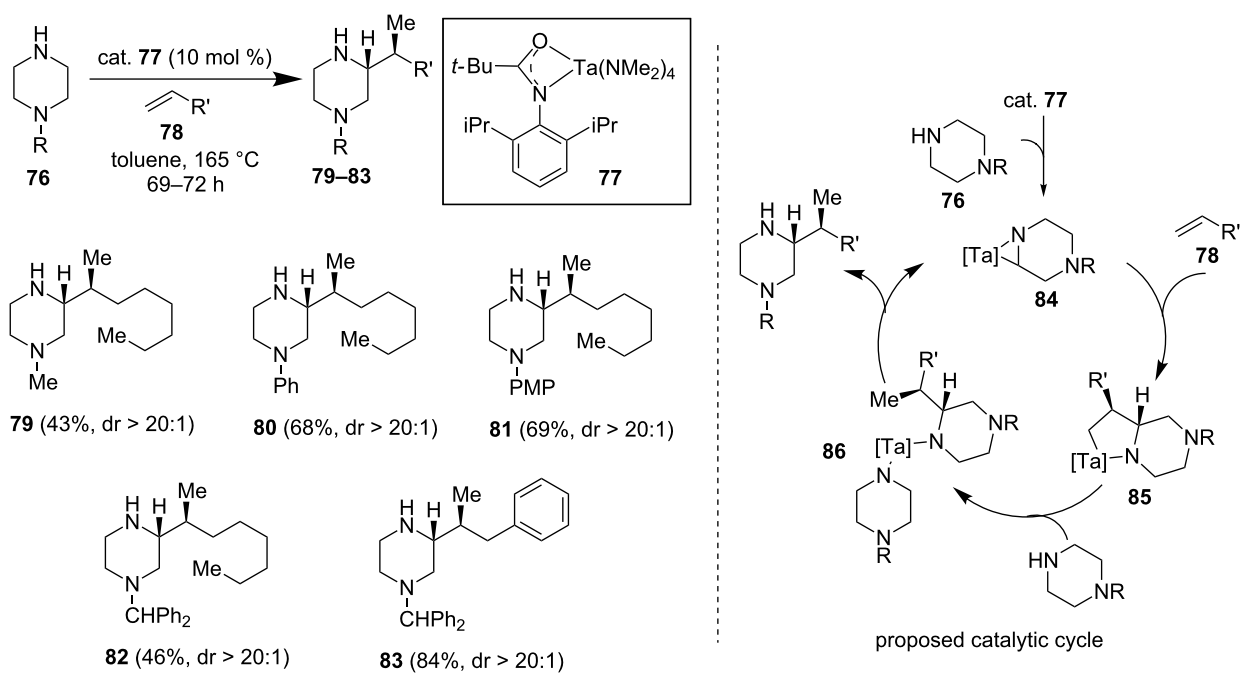


Figure 14: Ta-catalyzed hydroaminoalkylation of piperazines by Schafer et al. in 2013 [55].

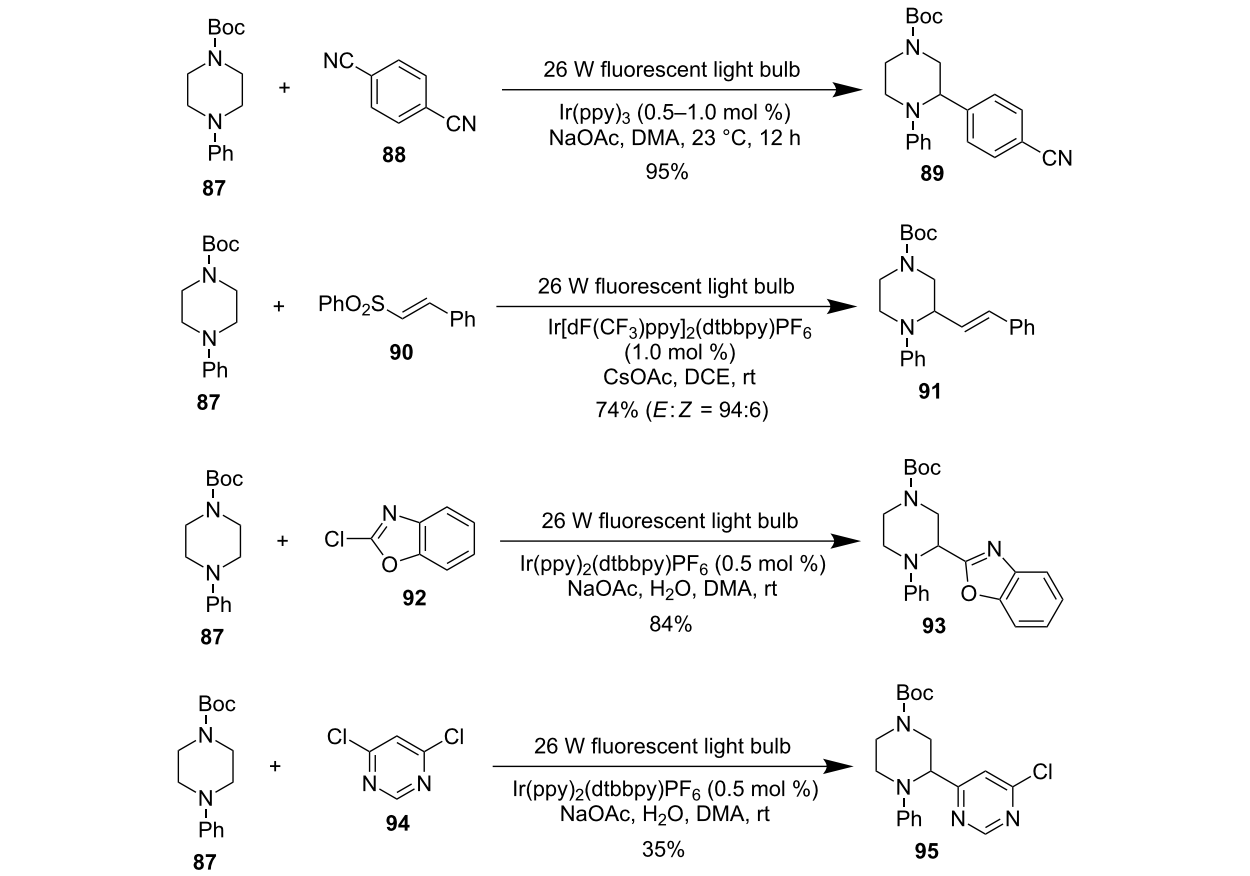


Figure 15: Photoredox catalysis for α-C–H functionalization of piperazines by MacMillan et al. in 2011 and 2014 [63,65,66].

This reaction works well with piperazine substrate **87** to synthesize the α-arylated piperazine **89** in 95% yield with $Ir(ppy)_3$ as the catalyst [63]. In another report, MacMillan et al. showed that under similar photoredox conditions, **87** could couple with vinyl sulfone **90** to provide α-vinylation product **91** in 74% yield with excellent *E*/*Z* selectivity [65]. They also discovered that piperazine **87** could couple with heteroaryl chlorides **92** and **94** to obtain products **93** and **95** in 84% and 35% yield, respectively [66]. These results represent a breakthrough in the direct α-C–H functionalization of piperazines. The generation and trapping of the α-amino radical derived from **87** with radical acceptors under mild photoredox catalysis conditions could avoid the aforementioned side reactions associated with direct α-lithiation trapping and transition-metal-catalyzed C–H functionalization of piperazines. However, the involvement of an α-amino radical in the reaction process adds another layer of difficulty in achieving enantioselective versions of these transformations.

Copper-catalyzed C–H oxidation

In an effort to establish a chemical toolkit to rapidly deliver oxidized drug metabolites, Touré, Sames and co-workers have discovered that piperazines could be oxidized to diketopiperazines as well as ring fragmented products under aerobic conditions with copper salt catalysts [67]. For example, when the antipsychotic drug aripiprazole (**96**) was treated with a catalytic amount of CuI under air or oxygen in DMSO at 120 °C, 2,3-diketopiperazine **97** was produced in 30% yield along with a 15% yield of urea product **98** (Figure 16). This method, despite its relatively low yield and selectivity, does offer a rapid way to access potential drug metabolites or analogs for further biological evaluations.

Free radical approach

In 1994, Undheim and co-workers developed a radical relay strategy, using a progression from an aryl radical to an α-amine radical followed by trapping with acrylate, to functionalize the α-position of amines [68]. The strategy works for morpholine and piperazine substrates, but the yields for the latter are generally low, ranging from 12% to 41% (Figure 17).

Anodic oxidation strategy

Another uncommon way to perform α-position functionalization is using electroorganic chemistry [69]. As shown in Figure 18, bisformyl protected piperazine **106** could be converted to **107** in 91% yield under anodic oxidation conditions at 500 g scale [70]. While this method is limited and only allows for functionalization with alkoxy groups, the resulting aminal products can be further diversified into other carbon-substituted piperazine products.

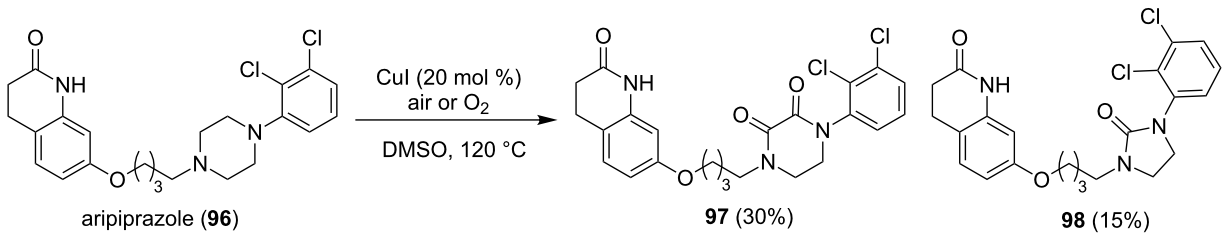


Figure 16: Copper-catalyzed aerobic C–H oxidation of piperazines by Touré, Sames, et al. in 2013 [67].

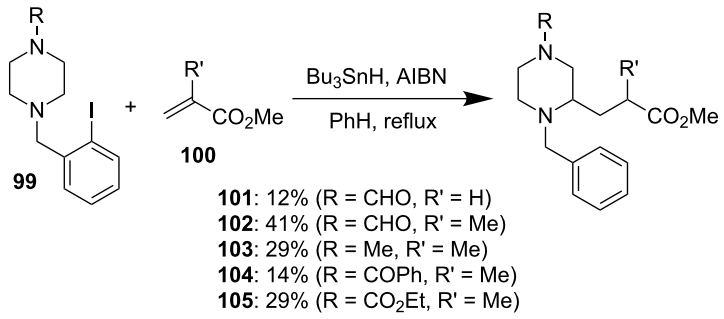


Figure 17: Free radical approach by Undheim et al. in 1994 [68].

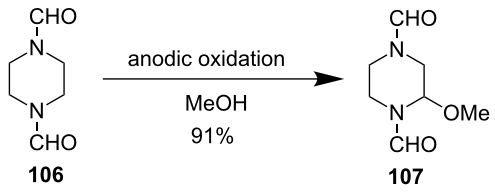


Figure 18: Anodic oxidation approach by Nyberg et al. in 1976 [70].

Conclusion

In summary, despite the importance and necessity of substituted piperazines in medicinal chemistry, there is still a lack of general and practical methods to directly and stereoselectively introduce substituents on the α-carbons of piperazines. So far most of the efforts focus on direct α-C–H lithiation trapping, transition-metal-catalyzed α-C–H functionalization of piperazines, and photoredox catalysis. While some progress has been made, there is still a long way to go, as most of these methods are far from general and practical. Many of the known methods have a very narrow substrate scope and give poor reaction yields. The enantioselective C–H functionalization of piperazines has been a barren field despite the advances made with other saturated N-heterocycles. The addition of the second nitrogen makes piperazine behave very differently in comparison to the corresponding pyrrolidine and piperidine systems. It either creates various side reactions such as the undesired elimination or dehydrogenation pathways or diminishes the reactivity of the α-C–H bond. In order to overcome these intrinsic reactivity issues, new synthetic methods and novel catalyst systems are necessary. These engagements are important because general and practical regioselective, diastereoselective, and enantioselective C–H functionalizations of piperazines are expected to significantly enhance the structural diversity and availability of piperazine-containing small-molecule collections in the pharmaceutical industry.

Acknowledgements

We thank the Purdue University for financial support.

References

1. Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014,** *57,* 5845. doi:10.1021/jm4017625
2. Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014,** *57,* 10257. doi:10.1021/jm501100b
3. Stegmeier, F.; Warmuth, M.; Sellers, W. R.; Dorsch, M. *Clin. Pharmacol. Ther. (Hoboken, NJ, U. S.)* **2010,** *87,* 543. doi:10.1038/clpt.2009.297
4. Lue, T. F. *N. Engl. J. Med.* **2000,** *342,* 1802. doi:10.1056/NEJM200006153422407
5. Vacca, J. P.; Dorsey, B. D.; Schleif, W. A.; Levin, R. B.; McDaniel, S. L.; Darke, P. L.; Zugay, J.; Quintero, J. C.; Blahy, O. M.; Roth, E.; Sardana, V. V.; Schlabach, A. J.; Graham, P. I.; Condra, J. H.; Gotlib, L.; Holloway, M. K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *Proc. Natl. Acad. Sci. U. S. A.* **1994,** *91,* 4096. doi:10.1073/pnas.91.9.4096
6. Burka, J. M.; Bower, K. S.; Vanroekel, R. C.; Stutzman, R. D.; Kuzmowych, C. P.; Howard, R. S. *Am. J. Ophthalmol.* **2005,** *140,* 83. doi:10.1016/j.ajo.2005.02.037
7. Di Fabio, R.; Griffante, C.; Alvaro, G.; Pentassuglia, G.; Pizzi, D. A.; Donati, D.; Rossi, T.; Guercio, G.; Mattioli, M.; Cimarosti, Z.; Marchioro, C.; Provera, S.; Zonzini, L.; Montanari, D.; Melotto, S.; Gerrard, P. A.; Trist, D. G.; Ratti, E.; Corsi, M. *J. Med. Chem.* **2009,** *52,* 3238. doi:10.1021/jm900023b
8. Leonard, D. M. *J. Med. Chem.* **1997,** *40,* 2971. doi:10.1021/jm970226l
9. Matsuo, M.; Hagiwara, D.; Manabe, T.; Konishi, N.; Shigenaga, S.; Murano, K.; Matsuda, H.; Miyake, H. 1-Benzoyl-2-(indolyl-3-alkyl)-piperazine derivatives as neurokinin receptor antagonists. PCT Int. Appl. WO9637489A1, Nov 28, 1996.
10. Sánchez-Roselló, M.; Delgado, O.; Mateu, N.; Trabanco, A. A.; Van Gool, M.; Fustero, S. *J. Org. Chem.* **2014,** *79,* 5887. doi:10.1021/jo500832j See for a leading reference.
11. Vo, C.-V. T.; Bode, J. W. *J. Org. Chem.* **2014,** *79,* 2809. doi:10.1021/jo5001252 See for a review.
12. Vo, C.-V. T.; Mikutis, G.; Bode, J. W. *Angew. Chem., Int. Ed.* **2013,** *52,* 1705. doi:10.1002/anie.201208064
13. Vo, C.-V. T.; Luescher, M. U.; Bode, J. W. *Nat. Chem.* **2014,** *6,* 310. doi:10.1038/nchem.1878
14. Luescher, M. U.; Vo, C.-V. T.; Bode, J. W. *Org. Lett.* **2014,** *16,* 1236. doi:10.1021/ol500210z
15. Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2008,** *47,* 3784. doi:10.1002/anie.200800373
16. Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2009,** *11,* 257. doi:10.1021/ol8023727
17. Matlock, J. V.; Svejstrup, T. D.; Songara, P.; Overington, S.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2015,** *17,* 5044. doi:10.1021/acs.orglett.5b02516
18. Ruider, S. A.; Müller, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013,** *52,* 11908. doi:10.1002/anie.201306563
19. Zhai, H.; Borzenko, A.; Lau, Y. Y.; Ahn, S. H.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2012,** *51,* 12219. doi:10.1002/anie.201206826
20. James, T.; Simpson, I.; Grant, J. A.; Sridharan, V.; Nelson, A. *Org. Lett.* **2013,** *15,* 6094. doi:10.1021/ol402988s
21. Yao, L.-F.; Wang, Y.; Huang, K.-W. *Org. Chem. Front.* **2015,** *2,* 721. doi:10.1039/C5QO00060B
22. Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2007,** *9,* 3279. doi:10.1021/ol071241f
23. Suárez-Pantiga, S.; Colas, K.; Johansson, M. J.; Mendoza, A. *Angew. Chem., Int. Ed.* **2015,** *54,* 14094. doi:10.1002/anie.201505608
24. Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2015,** *54,* 179. doi:10.1002/anie.201408609
25. Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. – Eur. J.* **2012,** *18,* 10092. doi:10.1002/chem.201201539
26. Campos, K. R. *Chem. Soc. Rev.* **2007,** *36,* 1069. doi:10.1039/B607547A

27. Beatty, J. W.; Stephenson, C. R. J. *Acc. Chem. Res.* **2015,** *48,* 1474. doi:10.1021/acs.accounts.5b00068
28. Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989,** *30,* 1197. doi:10.1016/S0040-4039(00)72714-6
29. Beak, P.; Lee, W. K. *J. Org. Chem.* **1993,** *58,* 1109. doi:10.1021/jo00057a024
30. Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996,** *29,* 552. doi:10.1021/ar950142b
31. Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000,** *33,* 715. doi:10.1021/ar000077s
32. Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991,** *113,* 9708. doi:10.1021/ja00025a066
33. Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994,** *116,* 3231. doi:10.1021/ja00087a008
34. Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002,** *124,* 1889. doi:10.1021/ja012169y
35. Coldham, I.; O'Brien, P.; Patel, J. J.; Raimbault, S.; Sanderson, A. J.; Stead, D.; Whittaker, D. T. E. *Tetrahedron: Asymmetry* **2007,** *18,* 2113. doi:10.1016/j.tetasy.2007.09.001
36. Stead, D.; Carbone, G.; O'Brien, P.; Campos, K. R.; Coldham, I.; Sanderson, A. *J. Am. Chem. Soc.* **2010,** *132,* 7260. doi:10.1021/ja102043e
37. Berkheij, M.; van der Sluis, L.; Sewing, C.; den Boer, D. J.; Terpstra, J. W.; Hiemstra, H.; Iwema Bakker, W. I.; van den Hoogenband, A.; van Maarseveen, J. H. *Tetrahedron Lett.* **2005,** *46,* 2369. doi:10.1016/j.tetlet.2005.02.085
38. Robinson, S. P.; Sheikh, N. S.; Baxter, C. A.; Coldham, I. *Tetrahedron Lett.* **2010,** *51,* 3642. doi:10.1016/j.tetlet.2010.05.019
39. Bennie, L. S.; Kerr, W. J.; Middleditch, M.; Watson, A. J. B. *Chem. Commun.* **2011,** *47,* 2264. doi:10.1039/c0cc04939e
40. Barker, G.; O'Brien, P.; Campos, K. R. *Org. Lett.* **2010,** *12,* 4176. doi:10.1021/ol1017799
41. McDermott, B. P.; Campbell, A. D.; Ertan, A. *Synlett* **2008,** 875. doi:10.1055/s-2008-1042905
42. Gelardi, G.; Barker, G.; O'Brien, P.; Blakemore, D. C. *Org. Lett.* **2013,** *15,* 5424. doi:10.1021/ol402395j
43. Firth, J. D.; O'Brien, P.; Ferris, L. *J. Am. Chem. Soc.* **2016,** *138,* 651. doi:10.1021/jacs.5b11288
44. Schönherr, H.; Cernak, T. *Angew. Chem., Int. Ed.* **2013,** *52,* 12256. doi:10.1002/anie.201303207
45. Li, C.-J. *Acc. Chem. Res.* **2009,** *42,* 335. doi:10.1021/ar800164n
46. Doye, S. *Angew. Chem., Int. Ed. Engl.* **2001,** *40,* 3351. doi:10.1002/1521-3773(20010917)40:18<3351::AID-ANIE3351>3.0.CO;2-B
47. Murahashi, S.-I. *Angew. Chem., Int. Ed. Engl.* **1995,** *34,* 2443. doi:10.1002/anie.199524431
48. Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006,** *128,* 14220. doi:10.1021/ja064481j
49. Spangler, J. E.; Kobayashi, Y.; Verma, P.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015,** *137,* 11876. doi:10.1021/jacs.5b06740
50. Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013,** *135,* 10946. doi:10.1021/ja4054114
51. Gribkov, D. V.; Pastine, S. J.; Schnürch, M.; Sames, D. *J. Am. Chem. Soc.* **2007,** *129,* 11750. doi:10.1021/ja072577n
52. Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Organometallics* **1997,** *16,* 3615. doi:10.1021/om970372p
53. Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000,** *122,* 12882. doi:10.1021/ja002561w
54. Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001,** *123,* 10935. doi:10.1021/ja011540e
55. Payne, P. R.; Garcia, P.; Eisenberger, P.; Yim, J. C.-H.; Schafer, L. L. *Org. Lett.* **2013,** *15,* 2182. doi:10.1021/ol400729v
56. Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013,** *113,* 5322. doi:10.1021/cr300503r
57. Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012,** *77,* 1617. doi:10.1021/jo202538x
58. Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011,** *40,* 102. doi:10.1039/B913880N
59. Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013,** *339,* 1593. doi:10.1126/science.1232993
60. Qvortrup, K.; Rankic, D. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014,** *136,* 626. doi:10.1021/ja411596q
61. Terrett, J. A.; Clift, M. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014,** *136,* 6858. doi:10.1021/ja502639e
62. Hu, J.; Wang, J.; Nguyen, T. H.; Zheng, N. *Beilstein J. Org. Chem.* **2013,** *9,* 1977. doi:10.3762/bjoc.9.234
63. McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011,** *334,* 1114. doi:10.1126/science.1213920
64. Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012,** *134,* 3338. doi:10.1021/ja211770y
65. Noble, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014,** *136,* 11602. doi:10.1021/ja506094d
66. Prier, C. K.; MacMillan, D. W. C. *Chem. Sci.* **2014,** *5,* 4173. doi:10.1039/C4SC02155J
67. Genovino, J.; Lütz, S.; Sames, D.; Touré, B. B. *J. Am. Chem. Soc.* **2013,** *135,* 12346. doi:10.1021/ja405471h
68. Williams, L.; Booth, S. E.; Undheim, K. *Tetrahedron* **1994,** *50,* 13697. doi:10.1016/S0040-4020(01)85682-9
69. Shono, T. *Tetrahedron* **1984,** *40,* 811. doi:10.1016/S0040-4020(01)91472-3
70. Nyberg, K.; Servin, R. *Acta Chem. Scand., Ser. B* **1976,** *30,* 640. doi:10.3891/acta.chem.scand.30b-0640

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.70

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Gold-catalyzed direct alkynylation of tryptophan in peptides using TIPS-EBX

Gergely L. Tolnai[1,2], Jonathan P. Brand[1,3] and Jerome Waser[*1]

Letter

Open Access

Address:
[1]Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne, Switzerland, [2]Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden and [3]Givaudan, Chemin de la parfumerie 5, 1214 Vernier, Switzerland

Email:
Jerome Waser[*] - jerome.waser@epfl.ch

* Corresponding author

Keywords:
alkynes; C–H functionalization; gold catalysis; hypervalent iodine; peptides

Beilstein J. Org. Chem. **2016,** *12,* 745–749.
doi:10.3762/bjoc.12.74

Received: 07 February 2016
Accepted: 06 April 2016
Published: 19 April 2016

This article is part of the Thematic Series "C–H Functionalization/activation in organic synthesis".

Guest Editor: R. Sarpong

© 2016 Tolnai et al; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

The selective functionalization of peptides containing only natural amino acids is important for the modification of biomolecules. In particular, the installation of an alkyne as a useful handle for bioconjugation is highly attractive, but the use of a carbon linker is usually required. Herein, we report the gold-catalyzed direct alkynylation of tryptophan in peptides using the hypervalent iodine reagent TIPS-EBX (1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one). The reaction proceeded in 50–78% yield under mild conditions and could be applied to peptides containing other nucleophilic and aromatic amino acids, such as serine, phenylalanine or tyrosine.

Introduction

Alkynes have always been important building blocks in synthetic organic chemistry. Recently, they have attracted also strong interest for applications in materials science and chemical biology [1]. One of the most important transformations of alkynes is the copper-catalyzed [3 + 2] cycloaddition with azides, which can be performed under mild conditions in the presence of multiple functional groups, and has therefore found broad applications for the modification of biomolecules and polymers [2-5]. But before the unique reactivity of the triple bond can be unravelled, it is necessary to introduce it onto the desired molecules. In this context, the modification of natural peptides and proteins is highly attractive, and it has been the target of intensive research in the last decades (Figure 1) [6-11]. The functionalization of highly reactive cysteine, lysine and the N-terminus has been particularly successful [12-17], whereas the more challenging modification of the electron-rich aromatic residues of tyrosine [18-20] and tryptophan [21-31] has been the focus of recent interest. As tryptophan is a rare amino acid, its functionalization is especially interesting. It has been achieved in the past for example by Francis and co-workers and

Ball and co-workers using rhodium-catalyzed carbene-insertion reactions [21-23] or via direct C–H arylation [24-29]. If the installation of alkynes on peptides or proteins is desired, an indirect method using a linker is used, for example an alkylation reaction of cysteine. The direct introduction of an alkyne onto the biomolecule would be interesting to profit from modified electronic and spectroscopic properties. However, the direct alkynylation of peptides or proteins is usually based on the use of the Sonogashira reaction, which requires modified non-natural amino acids [32,33].

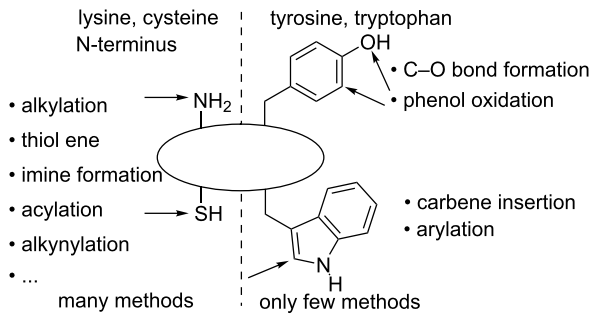
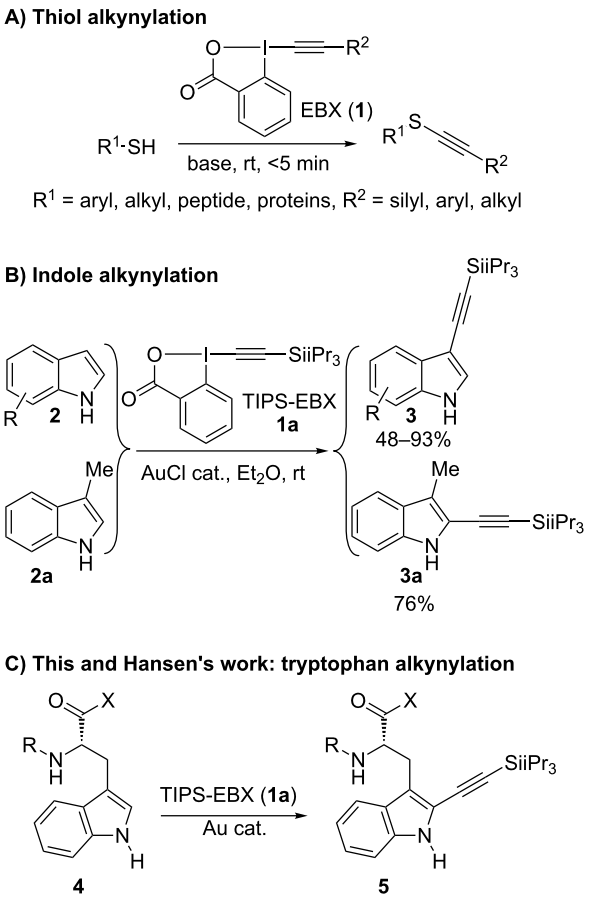


Figure 1: Functionalization of natural peptides and proteins: state of the art.

In 2013, our group reported the alkynylation of thiols using the hypervalent iodine reagent TIPS-EBX (**1a**, 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one) (Scheme 1A) [34]. The reaction was almost instantaneous. It was highly chemoselective for thiols in the presence of other nucleophilic functional groups. The alkynylation could be therefore applied to cysteine-containing peptides. The scope of the reaction could be later extended to a broad range of aliphatic and aromatic alkynes [35]. In 2015, the efficiency of the reaction for the functionalization of proteins both in cell lysates and in the living cell was finally demonstrated [36].

Even if the alkynylation of cysteines is an important method, thiols are often part of disulfide bonds in folded proteins, and therefore difficult to access. Reduction and unfolding, or protein engineering to install more accessible cysteines, are usually required. For these reasons, it is important to develop selective alkynylation methods in order to functionalize other amino acids. The direct C–H functionalization of aromatic compounds is an attractive method for the modification of biomolecules without the need for non-natural amino acids. However, the multiple functional groups present in biomolecules make such a process highly challenging. Based on our previous work on the alkynylation of indoles using TIPS-EBX (**1a**) and a gold catalysis [37,38], we wondered if this transformation could be extend-



Scheme 1: Alkynylation with EBX reagents.

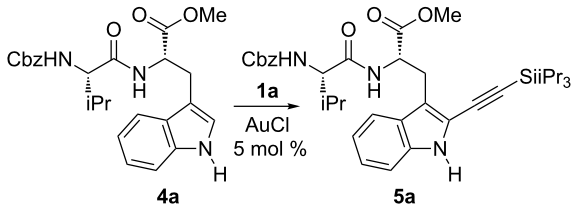
ed to tryptophan-containing peptides. Even if the reaction gave C3-alkynylation for C3-unsubstituted indoles, we demonstrated that C2-alkynylation could be achieved on skatole (**2a**, Scheme 1B) [37]. Very recently, Hansen et al. indeed reported a modified protocol using a gold catalyst and TIPS-EBX (**1a**) for the alkynylation of tryptophan-containing peptides and even proteins (Scheme 1C) [39]. This recent disclosure motivated us to report our own work on this transformation, resulting in an efficient direct alkynylation of tryptophan-containing peptides.

Results and Discussion

We started our investigation by attempting the alkynylation of valine-tryptophan dipeptide **4a** as model substrate (Table 1). An often used carboxybenzyl (Cbz, Z) protecting group was chosen. Examining this substrate will tell if C2-alkynylation is possible in the presence of an ester, a carbamate and an amide protecting group. A promising result was obtained with 5 mol % gold chloride as catalyst at room temperature in acetonitrile (Table 1, entry 1). Although the reaction did not go to completion even after two days, the desired C2 alkynylation

product **5a** was obtained in 44% yield. The yield could be increased to 72% when the reaction was performed at 40 °C (Table 1, entry 2). No further improvement was observed at higher temperature (Table 1, entry 3). The product **5a** could also be obtained in a broad range of other solvents, as long as the solubility of the substrate **4a** and TIPS-EBX (**1a**) was sufficient (Table 1, entries 4–8). The best yield was obtained in acetonitrile (Table 1, entry 2). Although the presence of water slowed down the reaction, the desired product could still be obtained in 41% yield (Table 1, entry 9). Monitoring the reaction over time showed that 34% of product **5a** was already formed after 20 min (Table 1, entry 10), but the reaction then slowed down significantly, with 67% yield after 10 h and 78% after 24 h (Table 1, entries 11 and 12). At this point, a conversion higher than 90% was achieved, with no significant improvement after a longer reaction time.

Table 1: Optimization of the alkynylation of dipeptide **4a**.



entry	solvent	time (h)	*T* (°C)	yield[a]
1	CH_3CN	48	23	44%
2	CH_3CN	48	40	72%
3	CH_3CN	48	60	67%
4	iPrOH	48	40	60%
5	MeOH	48	40	50%
6	acetone	48	40	39%
7	CH_2Cl_2	48	40	63%
8	DMSO	48	40	38%
9	CH_3CN 5% H_2O	48	40	41%
10	CH_3CN	0.3	40	34%
11	CH_3CN	10	40	67%
12	CH_3CN	24	40	78%

[a]Reaction conditions: 0.20 mmol **4a**, 0.24 mmol TIPS-EBX (**1a**), 0.010 mmol AuCl in 2 mL solvent were stirred at the indicated temperature and time. Isolated yields after column chromatography are given.

With the optimized conditions in hand, we investigated the scope of the reaction with different amino acids in the dipeptide (Scheme 2). With glycine as second amino acid, the desired product **5b** could be obtained in 66% yield. The reaction was selective for tryptophan in the presence of other aromatic amino acids, such as phenylalanine or tyrosine (products **5c** and **5d**). Serine and proline containing dipeptides **5e** and **5f** could also be obtained in 64% and 53% yield, respectively. The reaction was therefore general for dipeptides bearing tryptophan at the C-terminus. On the other hand, only traces of alkynylated dipeptide **5g** with a tryptophan at the N-terminus could be obtained under these reaction conditions. A first example of valine–tryptophan–valine tripeptide was also examined, and product **5h** was isolated in 50% yield, demonstrating that alkynylation of tryptophan inside a peptide chain was possible. Unfortunately, only limited conversion was observed with N- or C-terminus unprotected peptides. Nevertheless, Hansen and co-workers recently demonstrated that N- and C-termini unprotected peptides, as well as more complex peptides and even proteins, could be alkynylated using modified reaction conditions (10 mol % $AuCl(SMe_2)$, three equivalents TIPS-EBX (**1a**) and 2 mol % trifluoroacetic acid as co-catalyst) [39]. They also demonstrated that the obtained silylalkyne products can be easily deprotected with fluoride sources to allow bioconjugation via cycloaddition with azides.

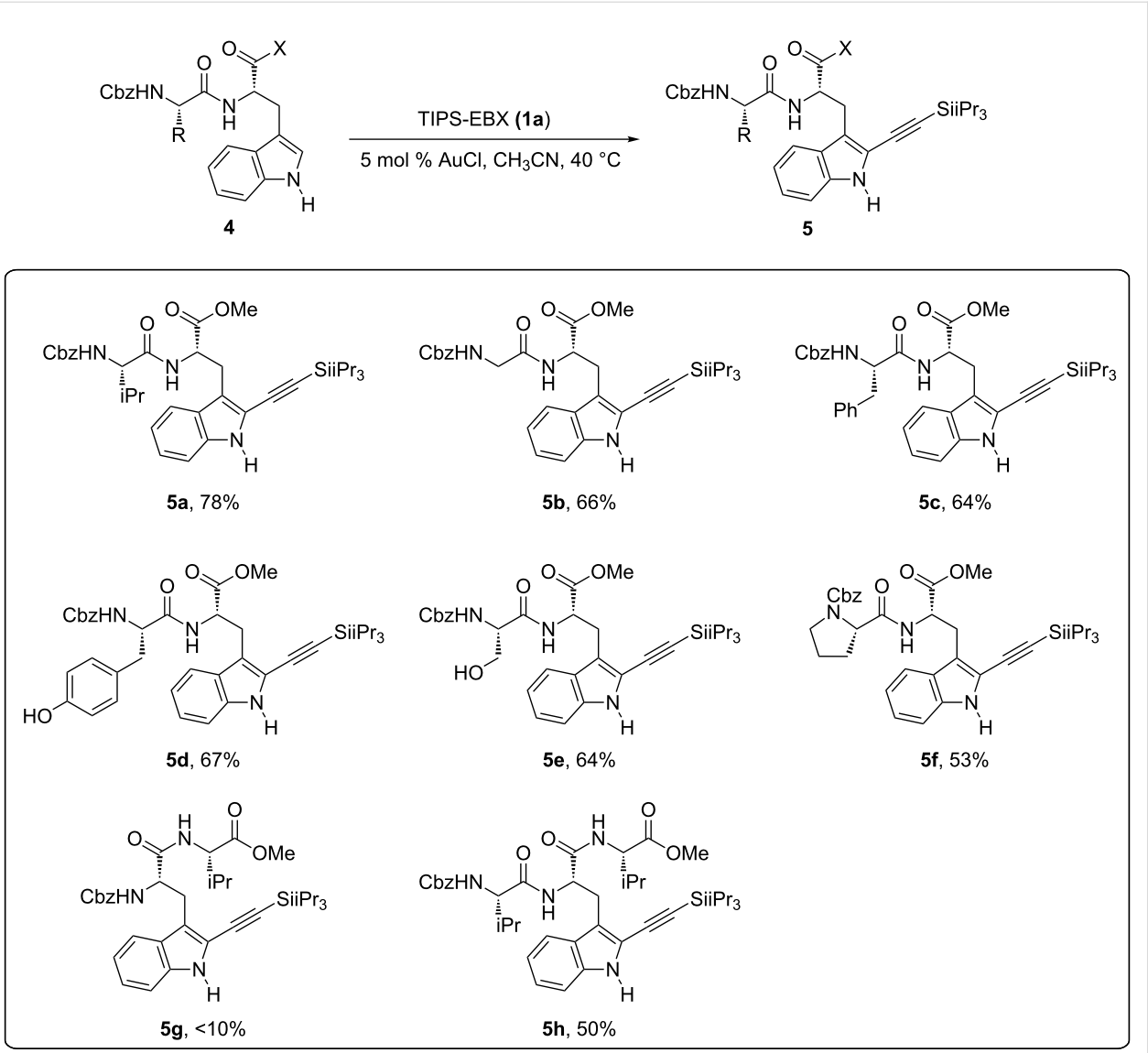
Conclusion

In conclusion, our work combined with the results of Hansen and co-workers has demonstrated that the gold-catalyzed alkynylation of indoles could be extended to tryptophan in peptides. When considering the scarcity of methods allowing the modification of tryptophan under mild conditions without requiring the installation of non-natural amino acids, the transformation will be highly useful for bioconjugation. A current limitation of the developed alkynylation reaction is the requirement for organic solvents. Investigations are currently ongoing in our laboratory for the development of water-compatible reagents and catalysts.

Experimental

General procedure for the gold-catalyzed alkynylation

The starting peptide **4** (0.20 mmol, 1 equiv) and TIPS-EBX (**1a**, 0.240 mmol, 103 mg, 1.2 equiv) were added into a 5 mL test tube equipped with a stirring bar. Acetonitrile (2 mL) was added, then the reaction mixture was stirred at 40 °C for 2 min. Gold(I) chloride (2.3 mg, 10 μmol, 0.05 equiv) was added in one portion. The reaction tube was sealed and stirring was continued for 24 h at 40 °C. Afterwards, the mixture was diluted with EtOAc (50 mL), and the organic layer was washed with a mixture of water (2.5 mL) and conc. $NaHCO_3$ solution (2.5 mL), and then with brine (20 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting yellow oil was purified by column chromatography (SiO_2, hexane/EtOAc 3:1 to 2:3). The product was dried under reduced pressure, and washed into a vial with Et_2O. The solvent was evaporated under vacuum and dried under high vacuum (ca. 10^{-2} mbar) for several hours.



Scheme 2: Alkynylation of tryptophan-containing peptides.

Supporting Information

Supporting Information File 1

Experimental procedure and characterization data for all compounds. NMR spectra of new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-74-S1.pdf]

Acknowledgements

We thank the EPFL for funding and F. Hoffmann-La Roche Ltd. for an unrestricted research grant. The work of G.L.T. was supported by a Sciex-NMS^{ch} fellowship of the Swiss confederation.

References

1. Diederich, F.; Stang, P. J.; Tykwinski, R. R., Eds. *Acetylene Chemistry: Chemistry, Biology and Material Science;* Wiley-VCH: Weinheim, Germany, 2005.
2. 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
3. Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007,** *46,* 1018. doi:10.1002/anie.200604050
4. Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008,** *108,* 2952. doi:10.1021/cr0783479
5. McKay, C. S.; Finn, M. G. *Chem. Biol.* **2014,** *21,* 1075. doi:10.1016/j.chembiol.2014.09.002
6. Stephanopoulos, N.; Francis, M. B. *Nat. Chem. Biol.* **2011,** *7,* 876. doi:10.1038/nchembio.720

7. Takaoka, Y.; Ojida, A.; Hamachi, I. *Angew. Chem., Int. Ed.* **2013,** *52,* 4088. doi:10.1002/anie.201207089
8. Patterson, D. M.; Nazarova, L. A.; Prescher, J. A. *ACS Chem. Biol.* **2014,** *9,* 592. doi:10.1021/cb400828a
9. Yang, M.; Li, J.; Chen, P. R. *Chem. Soc. Rev.* **2014,** *43,* 6511. doi:10.1039/C4CS00117F
10. Boutureira, O.; Bernardes, G. J. L. *Chem. Rev.* **2015,** *115,* 2174. doi:10.1021/cr500399p
11. Koniev, O.; Wagner, A. *Chem. Soc. Rev.* **2015,** *44,* 5495. doi:10.1039/C5CS00048C
12. Chalker, J. M.; Bernardes, G. J. L.; Davis, B. G. *Acc. Chem. Res.* **2011,** *44,* 730. doi:10.1021/ar200056q
13. Kundu, R.; Ball, Z. T. *Chem. Commun.* **2013,** *49,* 4166. doi:10.1039/C2CC37323H
14. Toda, N.; Asano, S.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2013,** *52,* 12592. doi:10.1002/anie.201306241
15. Abbas, A.; Xing, B.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2014,** *53,* 7491. doi:10.1002/anie.201403121
16. Obermeyer, A. C.; Jarman, J. B.; Francis, M. B. *J. Am. Chem. Soc.* **2014,** *136,* 9572. doi:10.1021/ja500728c
17. Vinogradova, E. V.; Zhang, C.; Spokoyny, A. M.; Pentelute, B. L.; Buchwald, S. L. *Nature* **2015,** *526,* 687. doi:10.1038/nature15739
18. Joshi, N. S.; Whitaker, L. R.; Francis, M. B. *J. Am. Chem. Soc.* **2004,** *126,* 15942. doi:10.1021/ja0439017
19. Tilley, S. D.; Francis, M. B. *J. Am. Chem. Soc.* **2006,** *128,* 1080. doi:10.1021/ja057106k
20. Ban, H.; Gavrilyuk, J.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2010,** *132,* 1523. doi:10.1021/ja909062q
21. Antos, J. M.; Francis, M. B. *J. Am. Chem. Soc.* **2004,** *126,* 10256. doi:10.1021/ja047272c
22. Antos, J. M.; McFarland, J. M.; Iavarone, A. T.; Francis, M. B. *J. Am. Chem. Soc.* **2009,** *131,* 6301. doi:10.1021/ja900094h
23. Popp, B. V.; Ball, Z. T. *J. Am. Chem. Soc.* **2010,** *132,* 6660. doi:10.1021/ja101456c
24. Ruiz-Rodríguez, J.; Albericio, F.; Lavilla, R. *Chem. – Eur. J.* **2010,** *16,* 1124. doi:10.1002/chem.200902676
25. Preciado, S.; Mendive-Tapia, L.; Albericio, F.; Lavilla, R. *J. Org. Chem.* **2013,** *78,* 8129. doi:10.1021/jo400961x
26. Mendive-Tapia, L.; Preciado, S.; Garcia, J.; Ramon, R.; Kielland, N.; Albericio, F.; Lavilla, R. *Nat. Commun.* **2015,** *6,* No. 7160. doi:10.1038/ncomms8160
27. Williams, T. J.; Reay, A. J.; Whitwood, A. C.; Fairlamb, I. J. S. *Chem. Commun.* **2014,** *50,* 3052. doi:10.1039/c3cc48481e
28. Reay, A. J.; Williams, T. J.; Fairlamb, I. J. S. *Org. Biomol. Chem.* **2015,** *13,* 8298. doi:10.1039/C5OB01174D
29. Zhu, Y.; Bauer, M.; Ackermann, L. *Chem. – Eur. J.* **2015,** *21,* 9980. doi:10.1002/chem.201501831
30. Perekalin, D. S.; Novikov, V. V.; Pavlov, A. A.; Ivanov, I. A.; Anisimova, N. Yu.; Kopylov, A. N.; Volkov, D. S.; Seregina, I. F.; Bolshov, M. A.; Kudinov, A. R. *Chem. – Eur. J.* **2015,** *21,* 4923. doi:10.1002/chem.201406510
31. Siti, W.; Khan, A. K.; de Hoog, H.-P. M.; Liedberg, B.; Nallani, M. *Org. Biomol. Chem.* **2015,** *13,* 3202. doi:10.1039/C4OB02025A
32. Kodama, K.; Fukuzawa, S.; Nakayama, H.; Sakamoto, K.; Kigawa, T.; Yabuki, T.; Matsuda, N.; Shirouzu, M.; Takio, K.; Yokoyama, S.; Tachibana, K. *ChemBioChem* **2007,** *8,* 232. doi:10.1002/cbic.200600432
33. Li, N.; Lim, R. K. V.; Edwardraja, S.; Lin, Q. *J. Am. Chem. Soc.* **2011,** *133,* 15316. doi:10.1021/ja2066913
34. Frei, R.; Waser, J. *J. Am. Chem. Soc.* **2013,** *135,* 9620. doi:10.1021/ja4044196
35. Frei, R.; Wodrich, M. D.; Hari, D. P.; Borin, P.-A.; Chauvier, C.; Waser, J. *J. Am. Chem. Soc.* **2014,** *136,* 16563. doi:10.1021/ja5083014
36. Abegg, D.; Frei, R.; Cerato, L.; Prasad Hari, D.; Wang, C.; Waser, J.; Adibekian, A. *Angew. Chem., Int. Ed.* **2015,** *54,* 10852. doi:10.1002/anie.201505641
37. Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009,** *48,* 9346. doi:10.1002/anie.200905419
38. Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013,** *15,* 112. doi:10.1021/ol3031389
39. Hansen, M. B.; Hubálek, F.; Skrydstrup, T.; Hoeg-Jensen, T. *Chem. – Eur. J.* **2016,** *22,* 1572. doi:10.1002/chem.201504462

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.74

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Recent advances in C(sp^3)–H bond functionalization via metal–carbene insertions

Bo Wang, Di Qiu, Yan Zhang and Jianbo Wang*

Review

Open Access

Address:
Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China

Email:
Jianbo Wang* - wangjb@pku.edu.cn

* Corresponding author

Keywords:
alkane; diazo compounds; C–H bond functionalization; C–H bond insertion; metal–carbene; site-selectivity

Beilstein J. Org. Chem. **2016,** *12,* 796–804.
doi:10.3762/bjoc.12.78

Received: 01 February 2016
Accepted: 06 April 2016
Published: 25 April 2016

This article is part of the Thematic Series "C–H Functionalization/activation in organic synthesis".

Guest Editor: R. Sarpong

© 2016 Wang et al; licensee Beilstein-Institut.
License and terms: see end of document.

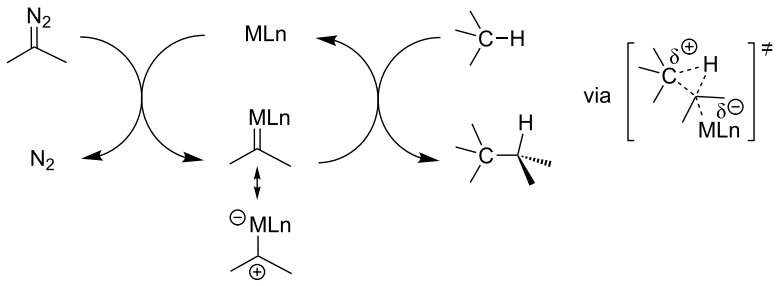
Abstract

The recent development of intermolecular C–H insertion in the application of C(sp^3)–H bond functionalizations, especially for light alkanes, is reviewed. The challenging problem of regioselectivity in C–H bond insertions has been tackled by the use of sterically bulky metal catalysts, such as metal porphyrins and silver(I) complexes. In some cases, high regioselectivity and enantioselectivity have been achieved in the C–H bond insertion of small alkanes. This review highlights the most recent accomplishments in this field.

Introduction

Direct functionalization of inactivated C–H bonds, especially C(sp^3)–H bonds, have attracted significant attentions in recent years. The C(sp^3)–H bond activation strategies based on radical reactions and transition metal catalysis have been explored, alongside the development of various directing groups for controlling the site-selectivity of the reaction. Regardless of the great efforts devoted to the field, the intermolecular C(sp^3)–H bond activation of simple alkanes still remains a formidable challenge, obviously attributed to the inertness and ubiquitous nature of simple aliphatic C(sp^3)–H bonds. In this context, catalytic metal–carbene C(sp^3)–H bond insertion represents an alternative and unique approach for this purpose.

Metal–carbene insertion into a C(sp^3)–H bond, well-recognized as one of the typical reactions of carbene species, have been studied extensively over the decades [1-8]. Mechanistically, the C(sp^3)–H bond insertion reaction is considered to follow a concerted reaction pathway with a three-center two electron transition state (Scheme 1). Since late transition metals, typically Rh(II) complexes, are most commonly employed as the catalysts, the carbenic carbon of the metal–carbene species is positively charged in general, as shown by the resonance structure. Consequently, when the electron-deficient carbenic carbon approaches the C(sp^3)–H bonds, the C–H bonds with high electron density will react preferentially [9]. However, the site-



Scheme 1: Pathway for transition-metal-catalyzed carbene insertion into C(sp^3)–H bonds.

selectivity of C(sp^3)–H bond insertion is also affected by steric factors. High regioselectivity of C(sp^3)–H bond insertions has been observed in intramolecular reactions in most cases, in which the C(sp^3)–H bond positioned 5 atoms away from the carbene center will normally react preferentially (1,5 C–H insertion). However, 1,3-, 1,4, and 1,6 C–H insertions are also possible, depending on the substrates and the catalysts. Although the site-selectivity of intramolecular metal–carbene C(sp^3)–H bond insertion is affected by the combination of factors such as steric and electronic factors as well as catalysts, high site-selectivity is generally achievable, which makes this type of reaction a valuable tool for the construction of carbocycles from readily available starting materials [1-6].

While most of the site-selective metal–carbene C(sp^3)–H bond insertions are based on intramolecular reaction systems, or with relatively active C–H bonds, such as allylic, benzylic or the C–H bonds adjacent to the oxygen or nitrogen, the corresponding site-selective metal–carbene insertion into simple aliphatic C(sp^3)–H bonds has also been challenged in intermolecular reaction systems and one has witnessed some exciting advances along this line. Thus, it would be an appropriate time to summarize the field in connection with direct C–H bond functionalization. Since catalytic metal–carbene C(sp^3)–H bond insertions have been discussed in a series of excellent reviews [1-8], this short article will highlight the most recent developments in the field, with the emphasis on simple aliphatic C(sp^3)–H bond insertions.

Review

Metal carbene C(sp^3)–H bond insertions into relatively active C–H bonds

Compared to ordinary aliphatic C(sp^3)–H bonds, the C(sp^3)–H bonds located at allylic and benzylic sites and those at the α-position of oxygen or nitrogen, show high activity because of the stabilization of the partial positive charge developed in the transition state of the metal–carbene C–H bond insertion process. Such type of intramolecular metal–carbene C–H insertions shows high selectivities in many cases [10-20], and they have been successfully incorporated into the steps in natural product synthesis. Herein some selected recent examples are highlighted.

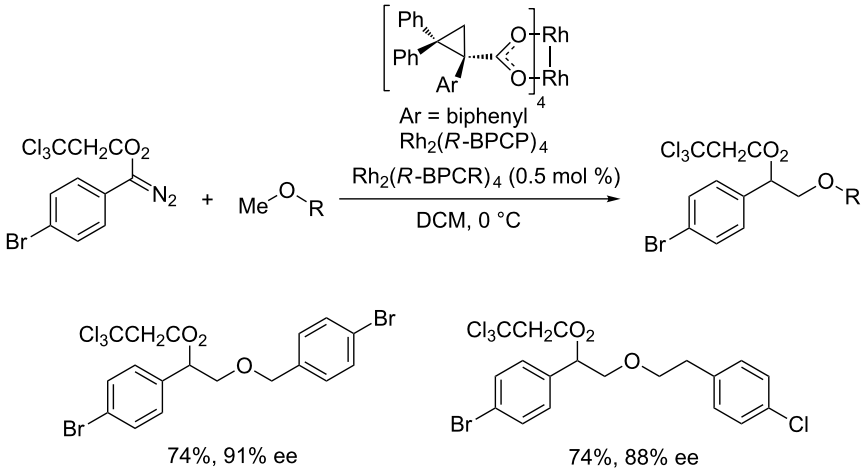
The C–H bond insertions at the α-positions of oxygen or nitrogen

Attributed to the stabilizing effect of oxygen and nitrogen toward the positive charge development at the neighboring positions, the metal–carbene C–H bond insertions at these positions are favored. Davies and co-workers have recently reported a highly site-selective and enantioselective C–H bond insertion of methyl ethers [21]. The use of 2,2,2-trichloroethyl aryldiazoacetates, in combination with sterically crowded chiral Rh(II) catalysts Rh_2(*R*-BPCP)$_4$, enhances the site-selectivity and the enantioselectivity of the reaction. Interestingly, the C–H bonds of a methyl group show high reactivity over the secondary C–H bonds, even the secondary benzylic C–H bonds (Scheme 2). Notably, for the site-selectivity of carbene insertion into primary, secondary and tertiary C–H bonds, the electronic and steric factors operate in the opposite directions. It is thus possible to tune or even revise the selectivity by judicious combination of reagents and catalysts.

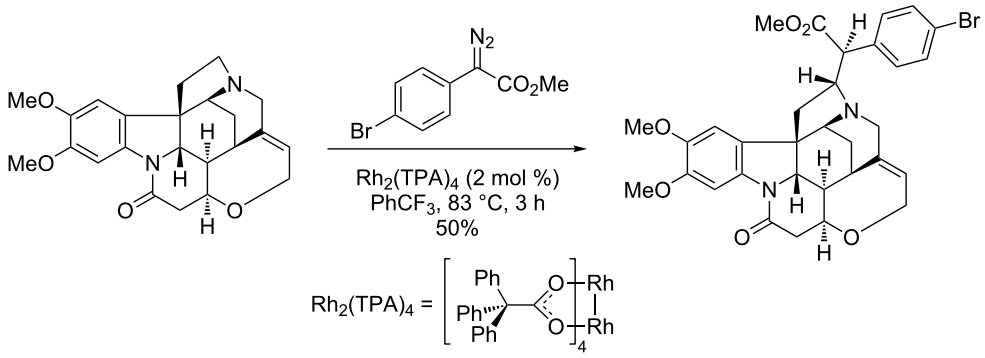
Rh(II)-catalyzed site-selective and enantioselective intramolecular carbene insertion into the C–H bond at the α-position of a tertiary amine have been previously established by Davies and co-workers [22-24]. Recently, this methodology has been used in the late-stage C–H functionalization of complex alkaloids and drug molecules (Scheme 3) [25].

C–H bond insertions at the allylic and benzylic positions

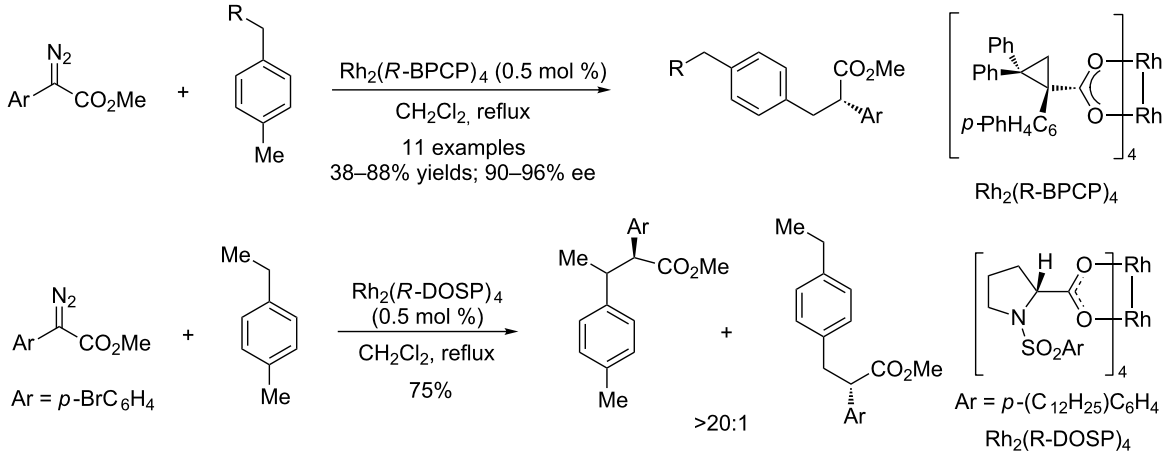
Metal–carbene C–H insertion is also favored for allylic and benzylic sites. In 2014, Davies and co-workers reported an enantioselective C–H insertion catalyzed by chiral dirhodium catalysts. The reaction took place selectively at the primary C–H bond when chiral Rh(II) catalyst Rh_2(R-BPCP)$_4$ is employed. However, when chiral Rh(II) catalyst Rh_2(R-DOSP)$_4$ is used, secondary C–H bond insertion becomes predominant



Scheme 2: Rh(II)-catalyzed site-selective and enantioselective C–H functionalization of methyl ether.



Scheme 3: Late-stage C–H functionalization with Rh(II)-catalyzed carbene C(sp^3)–H insertion.



Scheme 4: The Rh(II)-catalyzed selective carbene insertion into benzylic C–H bonds.

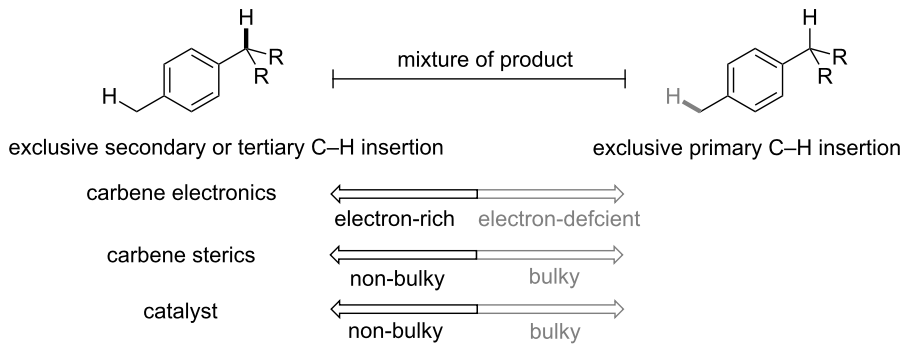
(Scheme 4) [26]. Subsequently, an extensive structure–selectivity relationship was carried out by Davies and Sigman [27]. The quantitative analysis of the substrate and the reagent shows that a non-bulky electron-rich carbene and a non-bulky catalyst prefer secondary or tertiary C–H bonds, while bulky electron-deficient carbene and bulky catalysts prefer primary C–H bonds (Scheme 5). Such quantitative understanding is very useful for the design of reagent/catalyst combination to achieve high selectivity of unactivated C(sp^3)–H bond functionalization.

Metal carbene insertion into aliphatic C(sp^3)–H bonds of light alkanes

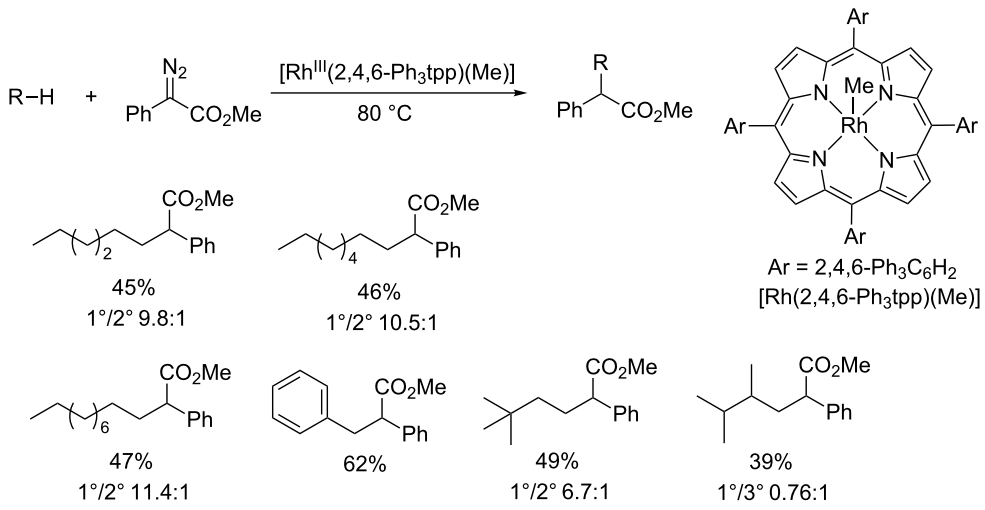
Site-selective metal–carbene insertion into simple aliphatic C(sp^3)–H bonds is generally more challenging simply because of the ubiquitous nature of C(sp^3)–H bonds and the little difference between different C(sp^3)–H bonds. The investigation in this field is focused on the development of novel transition metal catalysts through judicious combination of metal and ligands. In 1982, Callot and Metz reported Rh(III) porphyrins catalyzed intermolecular C–H insertion, which showed an extraordinary selectivity for 1° C–H bonds [28]. Other metal porphyrin complexes, such as Os [29], Fe, Cu, Ag [30], can also serve as catalysts for C–H insertions, although the C–H insertions with these catalysts are generally less efficient.

More recently, Che and co-workers developed a highly site-selective intermolecular insertion into primary C–H bonds catalyzed by robust and sterically encumbered [Rh^{III}(2,4,6-Ph_3tpp)Me]. Presumably attributed to the large steric hindrance of 2,4,6-Ph_3tpp, the reaction for *n*-alkanes afforded a high 1°/2° ratio of up to 11.4:1 (Scheme 6) [31]. The results further demonstrate that steric bulkiness of the catalyst can override the electronic preference for secondary C(sp^3)–H bond insertions.

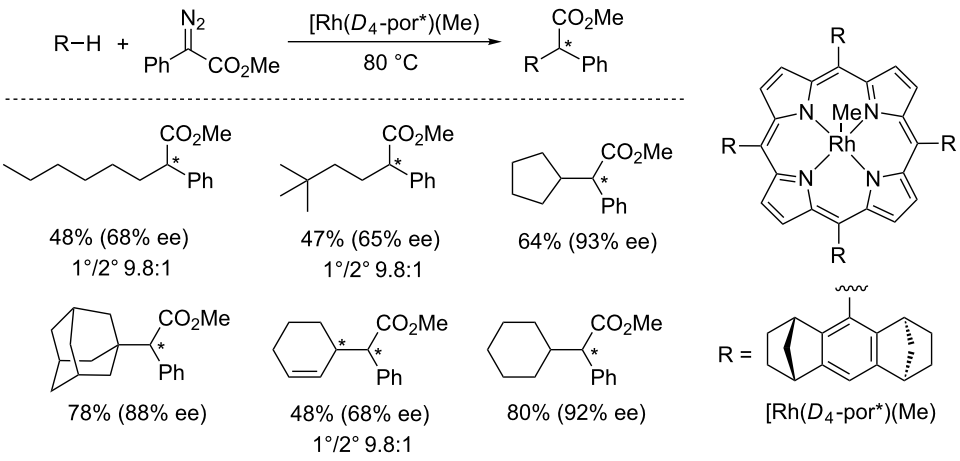
By employing chiral porphyrins D_4-por*, the enantioselective intermolecular carbene insertion into C(sp^3)–H bonds was achieved with moderate to high selectivities (Scheme 7). Besides, the reaction of diazo compounds with benzylic, allylic



Scheme 5: The structure–selectivity relationship.



Scheme 6: Rh-porphyrin complexes for catalytic intermolecular C–H insertions.



Scheme 7: Asymmetric intermolecular C(sp^3)–H insertion with chiral Rh-porphyrin catalyst.

and alkane C(sp^3)–H bonds afforded the insertion products in up to 80% yield and with up to 93% ee.

Pérez and co-workers have explored different types of catalysts based on copper and silver in metal–carbene C(sp^3)–H insertions. Tris(pyrazoly)borate complexes of copper (TpCu) [32-34] and silver (TpAg) [35-37] have been employed for C(sp^3)–H insertion of alkanes (Figure 1). Compared to Rh(II) catalysts, these coinage metal-based catalysts are generally less efficient in carbene-transfer reactions, thus requiring a high catalyst loading in general. However, this drawback is compensated by much lower cost of these metals than rhodium.

In 2008, Pérez, Díaz-Requejo and Etienne reported a perfluorinated F_{21}-tris(pyrazoly)borate (F_{21}-Tp) scorpionate ligand, which enhanced alkane C–H functionalization by carbene insertion with (F_{21}-Tp)Cu and (F_{21}-Tp)Ag catalysts (Figure 1) [38]. In particular, with silver catalyst remarkably low catalyst loading (ca. 0.5%), and high turnover number (up to 200), have been achieved when the reaction was carried out with hexane and EDA (Scheme 8).

The high reactivity of silver-based catalysts encouraged further investigations on its applications in aliphatic C(sp^3)–H insertions. The metal–carbene C–H bond insertion with methane, the ultimate simple alkane, thus becomes an attractive goal along this line. However, the major obstacle to achieve the methane C–H bond functionalization through metal–carbene C–H insertion is the low reactivity of the methane C–H bond as compared to most of the C–H bonds in organic compounds. This

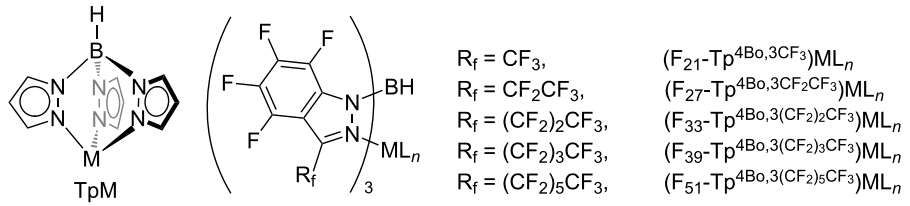
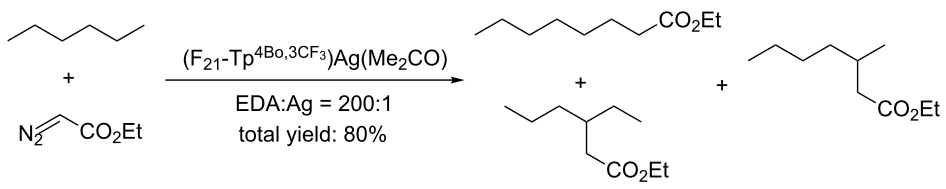


Figure 1: The structure of TpM catalysts.



Scheme 8: Ag-Tpx-catalyzed intermolecular C–H insertion between EDA and alkanes.

impedes the use of most organic solvents, while the gaseous nature of methane makes it impossible to form a homogenous reaction system without a solvent.

Pérez and co-workers addressed this problem by using supercritical carbon dioxide ($scCO_2$) as the reaction medium. Methane can be dissolved in $scCO_2$. Moreover, the electron-deficient nature of CO_2 will prevent its reaction with the highly reactive metal–carbene species, which are electrophilic in nature. In 2011, Pérez, Etienne and Asensio achieved the Tp^xAg catalyzed C–H insertion of methane in supercritical CO_2 (Scheme 9) [39]. The reaction between methane and EDA formed ethyl propionate in 19% yield (based on EDA) at 40 °C over 14 h in the presence of silver-perfluorinated catalysts (F_n-Tp^xAg). Other gaseous alkanes, including ethane, propane, butane and isobutene, have also been functionalized with the same catalytic system with EDA [40]. Notably, the site-selectivities of the C–H insertion of pentane in $scCO_2$ media are essentially identical as compared to the corresponding reaction with pentane as the solvent.

More recently, a new borate ligand, hydrotris((3,5-bis(trifluoromethyl)-4-bromo)pyrazol-1-yl)borate ($Tp^{(CF3)2,Br}$), was introduced and similar C–H bond functionalization of methane was achieved by $Tp^{(CF3)2,Br}$ ML (M = Cu, Ag; L = MeCN or THF) (Figure 2) [41]. A detailed investigation on the TpML-type catalysts was also carried out [42]. Notably, the copper complex $Tp^{(CF3)2,Br}Cu$ (NCMe) is soluble in methane/$scCO_2$, thus forming a homogenous catalytic system.

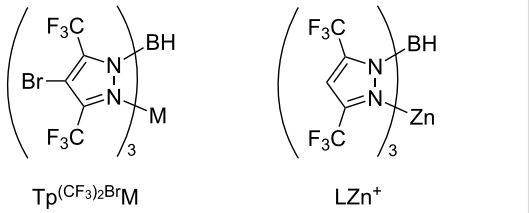
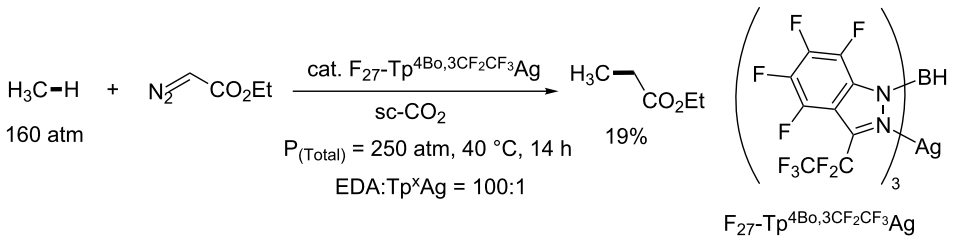
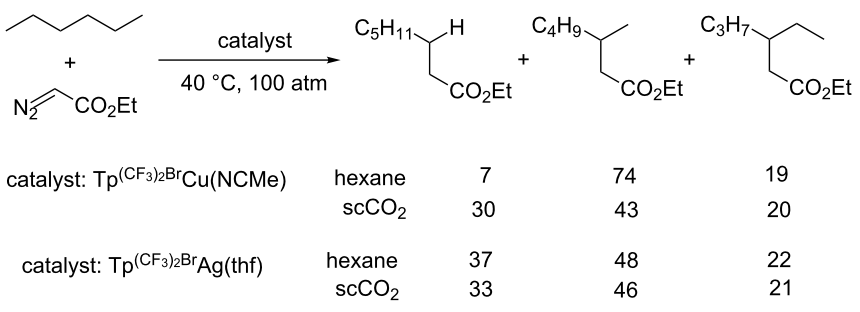


Figure 2: Structure of TpM-type catalysts.

With the new borate ligand, depending on the metal of the catalyst, different selectivities were observed when the reaction medium is changed from alkane to $scCO_2$ (Scheme 10) [43]. When $scCO_2$ was used as the solvent for the C–H insertion of hexane, a significant increase in the functionalization of the primary sites was observed in the presence of $Tp^{(CF3)2,Br}Cu$(MeCN); while hexane and $scCO_2$ made little difference as compared to $Tp^{(CF3)2,Br}Ag$(thf) catalyzed reactions. These results may be related to the interaction of the ligand with carbon dioxide. A net electron density flux from the metal center to the ligand and to carbon dioxide was supported by experimental data and DFT studies. Such interaction increases the electrophilicity of the carbene moiety and thus lowers the activation energy for C–H bond insertion.



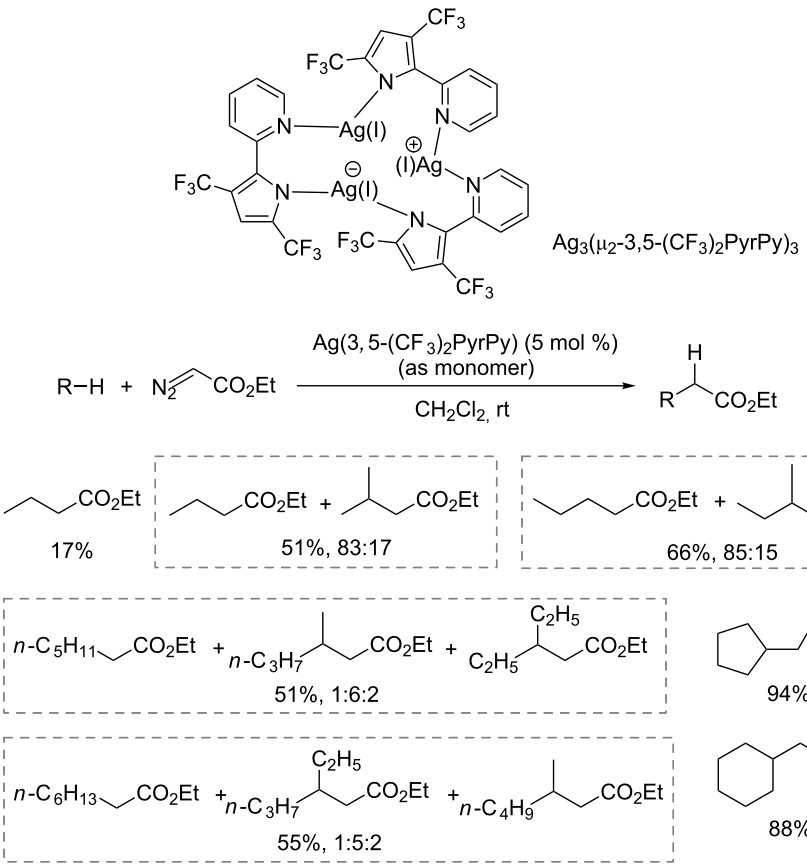
Scheme 9: Ag-Tpx-catalyzed C–H insertion of methane with EDA in $scCO_2$.



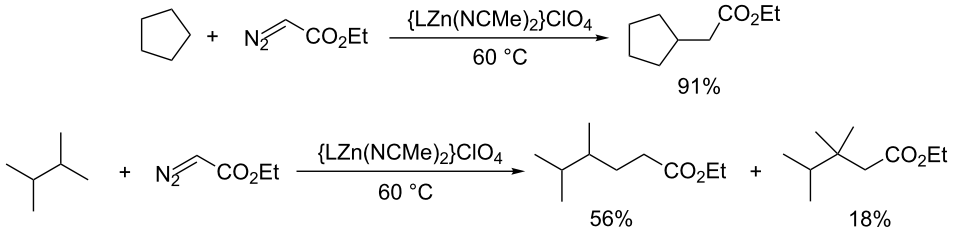
Scheme 10: Comparison of site-selectivities of C–H insertion in different reaction media.

Other ligands have also been explored for the metal–carbene C(sp^3)–H insertion of simple alkanes. Mindiola and Caulton reported carbene C–H insertion catalyzed by a trinuclear cluster $Ag_3(\mu_2\text{-}3,5\text{-}(CF_3)_2PyrPy)_3$ (3,5-$(CF_3)_2$PyrPy = 3,5-bis(trifluoromethyl)-2,2'-pyridylpyrrolide) [44]. The C–H bond insertion of ethane, propane, butane and more heavier alkanes have been achieved except for methane (Scheme 11). The DFT studies suggested that formation of the silver carbene complex was the rate-determining step for alkane substrates such as ethane and propane. As for methane, the overall rate-determining step was carbene insertion into the C–H bond, attributed to the inertness of the methane C–H bond. As a result, the side reactions of the highly active metallocarbene intermediate override the C–H insertion.

Zinc catalysts, which were seldom used for metal–carbene C–H insertions, have been recently explored in the C–H insertion between EDA with alkanes [45]. A detailed computational study of the likely intermediate suggests that it is best described as a zinc-bound carbocation rather than a zinc carbene (Scheme 12). Notably, Zn is a cheap, earth-abundant 3d metal, thus making it attractive as catalyst for C–H bond functionalization.



Scheme 11: C(sp^3)–H bond insertion catalyzed by trinuclear cluster Ag.



Scheme 12: Zn(II)-catalyzed C(sp^3)–H bond insertion.

Conclusion

The intermolecular metal–carbene insertion represents a direct approach for the C–H bond functionalization of aliphatic C(sp^3)–H bonds. While some progresses have been made in this area, significant challenge remains. From the selected examples summarized in this review it is obvious that the main issue is the balance of reactivity and selectivity. The factors governing the reactivity and site-selectivity of metal–carbene C–H insertion include: 1) the electrophilicity of the metal–carbene bond; 2) the nucleophilicity of the targeted C–H bond; 3) the steric bulk of the ligand around the metal; 4) the steric bulk of the substituents around the targeted C–H bond. While secondary and tertiary C(sp^3)–H bonds are favored toward the electron-deficient carbenic carbon center in terms of electronic effects, they are unfavored in terms of steric hindrance. The primary C(sp^3)–H bonds operate in the opposite way. Further studies in this area will be focused on the development of novel catalysts as well as the perceptive combination of catalyst/substrates in order to achieve highly selective C(sp^3)–H bond insertions.

Acknowledgements

Financial support by 973 Program (No. 2015CB856600) and NSFC (Grant 21472004 and 21472004) is gratefully acknowledged.

References

1. Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003,** *103,* 2861–2904. doi:10.1021/cr0200217
2. Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010,** *110,* 704–724. doi:10.1021/cr900239n
3. Taber, D. F.; Stiriba, S.-E. *Chem. – Eur. J.* **1998,** *4,* 990–992. doi:10.1002/(SICI)1521-3765(19980615)4:6<990::AID-CHEM990>3.0.CO;2-U
4. Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev.* **2009,** *38,* 3061–3071. doi:10.1039/b901170f
5. Egger, J.; Carreira, E. M. *Nat. Prod. Rep.* **2014,** *31,* 449–455. doi:10.1039/c3np70084d
6. Lombard, F. J.; Coster, M. J. *Org. Biomol. Chem.* **2015,** *13,* 6419–6431. doi:10.1039/c5ob00311c
7. Che, C.-M.; Lo, V. K.-Y.; Zhou, C.-Y.; Huang, J.-S. *Chem. Soc. Rev.* **2011,** *40,* 1950–1975. doi:10.1039/c0cs00142b
8. Caballero, A.; Díaz-Requejo, M. M.; Fructos, M. R.; Olmos, A.; Urbano, J.; Pérez, P. J. *Dalton Trans.* **2015,** *44,* 20295–20307. doi:10.1039/c5dt03450g
9. Wang, J.; Chen, B.; Bao, J. *J. Org. Chem.* **1998,** *63,* 1853–1862. doi:10.1021/jo971747j
10. Suematsu, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009,** *131,* 14218–14219. doi:10.1021/ja9065267
11. Owens, C. P.; Varela-Álvarez, A.; Boyarskikh, V.; Musaev, D. G.; Davies, H. M. L.; Blakey, S. B. *Chem. Sci.* **2013,** *4,* 2590–2596. doi:10.1039/c3sc50886b
12. Davies, H. M. L.; Jin, Q. *Tetrahedron: Asymmetry* **2003,** *14,* 941–949. doi:10.1016/s0957-4166(03)00154-x
13. Bykowski, D.; Wu, K.-H.; Doyle, M. P. *J. Am. Chem. Soc.* **2006,** *128,* 16038–16039. doi:10.1021/ja066452e
14. Hilt, G.; Galbiati, F. *Org. Lett.* **2006,** *8,* 2195–2198. doi:10.1021/ol060739z
15. Nadeau, E.; Ventura, D. L.; Brekan, J. A.; Davies, H. M. L. *J. Org. Chem.* **2010,** *75,* 1927–1939. doi:10.1021/jo902644f
16. Hansen, J. H.; Gregg, T. M.; Ovalles, S. R.; Lian, Y.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011,** *133,* 5076–5085. doi:10.1021/ja111408v
17. Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011,** *133,* 11940–11943. doi:10.1021/ja2051155
18. Lian, Y.; Hardcastle, K. I.; Davies, H. M. L. *Angew. Chem., Int. Ed.* **2011,** *50,* 9370–9373. doi:10.1002/anie.201103568
19. McMills, M. C.; Humes, R. J.; Pavlyuk, O. M. *Tetrahedron Lett.* **2012,** *53,* 849–851. doi:10.1016/j.tetlet.2011.12.019
20. Wang, H.; Li, G.; Engle, K. M.; Yu, J.-Q.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013,** *135,* 6774–6777. doi:10.1021/ja401731d
21. Guptill, D. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014,** *136,* 17718–17721. doi:10.1021/ja5107404
22. Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002,** *41,* 2197–2199. doi:10.1002/1521-3773(20020617)41:12<2197::AID-ANIE2197>3.0.CO;2-N
23. Davies, H. M. L.; Jin, Q. *Org. Lett.* **2004,** *6,* 1769–1772. doi:10.1021/ol0495467
24. Davies, H. M. L.; Ni, A. *Chem. Commun.* **2006,** 3110–3112. doi:10.1039/B605047F
25. He, J.; Hamann, L. G.; Davies, H. M. L.; Beckwith, R. E. J. *Nat. Commun.* **2015,** *6,* No. 5943. doi:10.1038/ncomms6943
26. Qin, C.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014,** *136,* 9792–9796. doi:10.1021/ja504797x
27. Bess, E. N.; Guptill, D. M.; Davies, H. M. L.; Sigman, M. S. *Chem. Sci.* **2015,** *6,* 3057–3062. doi:10.1039/c5sc00357a
28. Callot, H. J.; Metz, F. *Tetrahedron Lett.* **1982,** *23,* 4321–4324. doi:10.1016/s0040-4039(00)85590-2
29. Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M. *Chem. Commun.* **2003,** 1362–1363. doi:10.1039/b300441d
30. Mbuvi, H. M.; Woo, L. K. *Organometallics* **2008,** *27,* 637–645. doi:10.1021/om7007502
31. Thu, H.-Y.; Tong, G. S.-M.; Huang, J.-S.; Chan, S. L.-F.; Deng, Q.-H.; Che, C.-M. *Angew. Chem., Int. Ed.* **2008,** *47,* 9747–9751. doi:10.1002/anie.200803157
32. Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2002,** *124,* 896–897. doi:10.1021/ja016798j
33. Caballero, A.; Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2003,** *125,* 1446–1447. doi:10.1021/ja0291484
34. Caballero, A.; Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *Organometallics* **2003,** *22,* 4145–4150. doi:10.1021/om034002e
35. Dias, H. V. R.; Browning, R. G.; Richey, S. A.; Lovely, C. J. *Organometallics* **2004,** *23,* 1200–1202. doi:10.1021/om0499198
36. Dias, H. V. R.; Browning, R. G.; Richey, S. A.; Lovely, C. J. *Organometallics* **2005,** *24,* 5784. doi:10.1021/om050832b
37. Urbano, J.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics* **2005,** *24,* 1528–1532. doi:10.1021/om050024k
38. Despagnet-Ayoub, E.; Jacob, K.; Vendier, L.; Etienne, M.; Álvarez, E.; Caballero, A.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics* **2008,** *27,* 4779–4787. doi:10.1021/om800531a

39. Caballero, A.; Despagnet-Ayoub, E.; Díaz-Requejo, M. M.; Díaz-Rodríguez, A.; González-Núñez, M. E.; Mello, R.; Muñoz, B. K.; Ojo, W.-S.; Asensio, G.; Etienne, M.; Pérez, P. J. *Science* **2011,** *332,* 835–838. doi:10.1126/science.1204131
40. Fuentes, M. A.; Olmos, A.; Muñoz, B. K.; Jacob, K.; González-Núñez, M. E.; Mello, R.; Asensio, G.; Caballero, A.; Etienne, M.; Pérez, P. J. *Chem. – Eur. J.* **2014,** *20,* 11013–11018. doi:10.1002/chem.201403217
41. Gava, R.; Olmos, A.; Noverges, B.; Varea, T.; Álvarez, E.; Belderrain, T. R.; Caballero, A.; Asensio, G.; Pérez, P. J. *ACS Catal.* **2015,** *5,* 3726–3730. doi:10.1021/acscatal.5b00718
42. Caballero, A.; Pérez, P. J. *J. Organomet. Chem.* **2015,** *793,* 108–113. doi:10.1016/j.jorganchem.2015.02.029
43. Gava, R.; Olmos, A.; Noverges, B.; Varea, T.; Funes-Ardoiz, I.; Belderrain, T. R.; Caballero, A.; Maseras, F.; Asensio, G.; Pérez, P. J. *ChemCatChem* **2015,** *7,* 3254–3260. doi:10.1002/cctc.201500610
44. Flores, J. A.; Komine, N.; Pal, K.; Pinter, B.; Pink, M.; Chen, C.-H.; Caulton, K. G.; Mindiola, D. J. *ACS Catal.* **2012,** *2,* 2066–2078. doi:10.1021/cs300256b
45. Kulkarni, N. V.; Dash, C.; Jayaratna, N. B.; Ridlen, S. G.; Khani, S. K.; Das, A.; Kou, X.; Yousufuddin, M.; Cundari, T. R.; Dias, H. V. R. *Inorg. Chem.* **2015,** *54,* 11043–11045. doi:10.1021/acs.inorgchem.5b02134

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.78

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Enantioselective carbenoid insertion into C(sp^3)–H bonds

J. V. Santiago and A. H. L. Machado*

Review

Open Access

Address:
Grupo de Tecnologia em Síntese Orgânica, Instituto de Química, Universidade de Brasília, Campus Universitário Darcy Ribeiro, 4478, CEP 70904-970, Asa Norte, Brasília-DF, Brasil

Email:
A. H. L. Machado* - nagelo@unb.br

* Corresponding author

Keywords:
C–H activation; chiral catalysis; diazo compounds; total synthesis

Beilstein J. Org. Chem. **2016,** *12,* 882–902.
doi:10.3762/bjoc.12.87

Received: 01 February 2016
Accepted: 09 April 2016
Published: 04 May 2016

This article is part of the Thematic Series "C–H Functionalization/activation in organic synthesis" and is dedicated to Prof. Dr. Hugo Jorge Monteiro for his outstanding contributions for carbenoid insertion into C(sp^3)–H bonds and the development of organic synthesis in Brazil.

Guest Editor: R. Sarpong

© 2016 Santiago and Machado; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

The enantioselective carbenoid insertion into C(sp^3)–H bonds is an important tool for the synthesis of complex molecules due to the high control of enantioselectivity in the formation of stereogenic centers. This paper presents a brief review of the early issues, related mechanistic studies and recent applications on this chemistry area.

Introduction

One of the major challenges met in organic synthesis is the formation of carbon–carbon bonds, in particular in a stereoselective way. Nucleophilic substitution reactions, radical reactions, cross-coupling reactions and the Heck reaction are well-known approaches available to this goal. These reactions are based on the polar characteristic of the carbon–halogen or carbon–pseudohalogen bonds, as a result of the electronegativity difference between these atoms. Despite the proven success of these transformations, they are limited to pre-functionalization of the chemical structure of interest with halogen atoms or pseudohalogen functional groups.

One approach that has been gaining increasing attention, by not requiring the presence of a strongly polarized chemical bond, is the C(sp^3)–H bonds activation by carbenoids [1]. The enantioselective insertion of these organometallic species into these non-polarized bonds is a recent topic in the chemical literature, when compared to the first reports of carbenoid chemistry around the 1950s.

Carbene is a molecule bearing a functional group with a divalent neutral carbon. This structural framework results in the presence of a nonbonding electron pair that may adopt two electronic configurations: singlet and triplet (Figure 1). A carbenoid is an organometallic complex where the carbene acts as a neutral ligand to a metal center. This ensures a greater stability of the carbene, allows the modulation of its reactivity, and controls the chemo-, regio- and stereoselectivity in reactions.

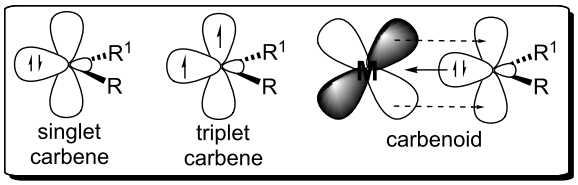


Figure 1: Singlet carbene, triplet carbene and carbenoids.

The activation of the C(sp^3)–H bond needs an appropriate interaction between the carbenoid intermediate and the carbon atom of the C(sp^3)–H. Depending on the electronic demand of the substituent attached to the carbene carbon atom, the insertion reaction can be more or less selective. Very electrophilic carbenoid intermediates, for example, display little regio- and stereoselectivity, favoring the occurrence of side reactions. A less electrophilic carbenoid intermediate, on the other hand, has a lower reactivity, but its regio- and stereoselectivity are better [2].

The electrophilicity of the carbenoid intermediate is related to the substituents present in its structure. Electron-withdrawing groups (EWGs) increase the electrophilicity of the carbon atom in the carbenoid and electron-donating groups (EDGs) act with the opposite effect. Due to these observations, a carbenoid intermediate can be divided in three different classes based on the electronic nature of the chemical groups attached to its structure: acceptor, donor/acceptor and acceptor/acceptor (Figure 2) [2]. The modification of the substituents on the carbenoid intermediate can change its reactivity and hence the selectivity of the carbenoid reaction.

The most commonly used diazo compounds rely on the formation of a donor/acceptor carbenoid intermediate type. The EWG increases the electrophilicity and reactivity of the donor/acceptor carbenoid, while an EDG increases its stability and selectivity [2].

Despite the importance of the electronic factors to the reactivity and selectivity of carbenoid intermediates, steric and conformational effects are also determining factors for carbenoid chemistry. Steric as well as electronic factors and the chemical properties of the ligands around the metal center also determine significantly the type of insertion performed by the carbenoid intermediate. The complexes used for the formation of carbenoids in enantioselective insertion reactions must present a balance between steric and electronic factors, to promote the formation of a specific enantiomer.

The search for the best balance of these properties of the carbenoid intermediates was also sought through the use of different metals such as copper [3], rhodium [4], iron [5], ruthenium [6], iridium [7], osmium [8], and others. From these, copper and rhodium have been the most frequently used ones in carbenoid insertion reactions.

Copper carbenoids having a higher electrophilic character display a great reactivity, but little selectivity in insertion reactions. Despite these features, only recently the insertion of chiral copper carbenoids into a C(sp^3)–H bond has gained special attention, as in the works of Muler and Boléa [9], Flynn [10], Stattery [11] and their respective co-workers. The most selective copper carbenoids are those generated from chiral bis(oxazoline) ligands in the presence of copper(I) triflate (CuOTf) (Figure 3).

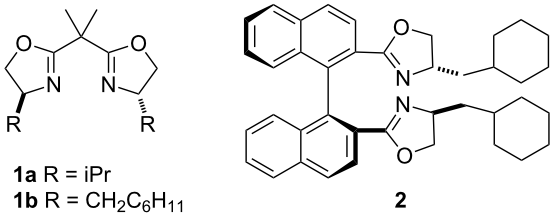


Figure 3: Chiral bis(oxazoline) ligands used in enantioselective copper carbenoid insertion.

The rhodium carbenoid intermediates are prferably used in enantioselective insertion reactions. They are more often found as dirhodium(II) complexes. Only one of the two metal atoms present in the chemical structure effectively participates in the

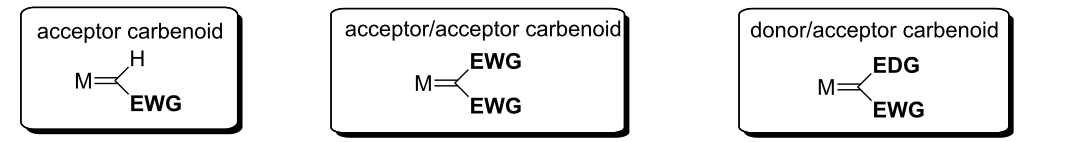


Figure 2: Classification of the carbenoid intermediates by the electronic nature of the groups attached to the divalent carbene carbon.

insertion reaction. The other rhodium atom withdraws electron density from the rhodium atom involved in the insertion mechanism increasing therefore its electrophilic character [12]. Four specific types of chiral rhodium(II) complexes can be found as catalyst in enantioselective insertion reactions of carbenoids in C(sp^3)–H bonds: carboxylates [13-19], carboxamides [20-23], phosphates [24,25], and ortho-arylphosphines [26-30].

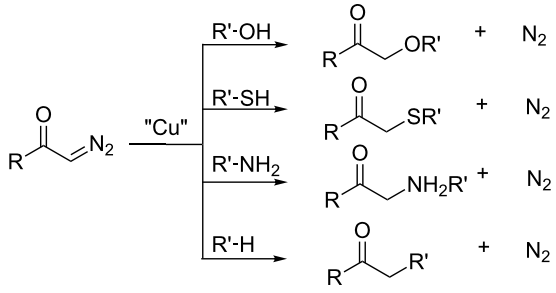
This work aims to review the chemical literature, since 2009 [31,32] until the end of 2015, concerning the development of catalytic systems able to promote enantioselective carbenoid insertion into C(sp^3)–H bonds, the mechanistic aspects recently discovered to the known catalytic systems and the application of these synthetic tools to the organic synthesis of natural products.

Review

Historic perspective on the carbenoid reaction insertion into X–H bonds

One of the former works to address the chemistry of carbenoid was reported in 1952 by Peter Yates, although the author does not specifically use the term carbenoid, but – carbene–copper complex (Scheme 1) [3]. In his opinion, the copper catalyst promotes the decomposition of diazoketones to afford "free carbenes", the chemical intermediates responsible for the insertion reaction in X–H bonds (X = O, S, N, or C).

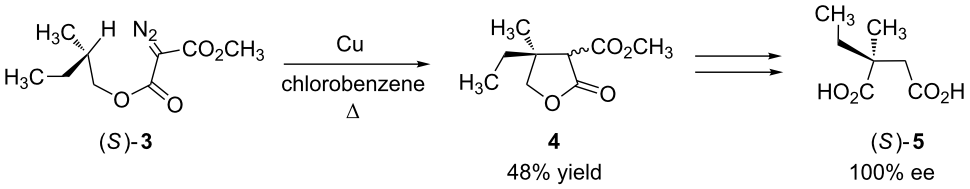
Ledon et al, in 1973, showed a very important feature of the carbenoid insertions into C(sp^3)–H bonds. The intramolecular reaction of the chiral diazomalonate (*S*)-**3** led to the insertion of the carbenoid intermediate into the C(sp^3)–H of the stereogenic center with full retention of the asymmetric carbon configuration (Scheme 2) [33].



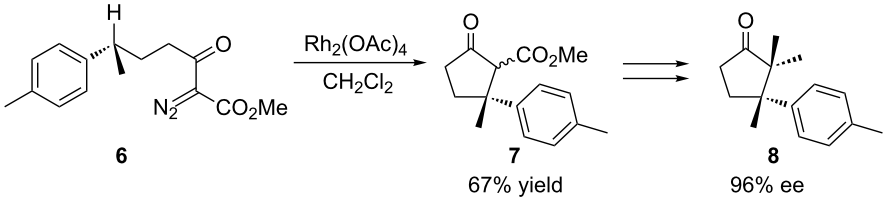
Scheme 1: Pioneering work of Peter Yates on the carbenoid insertion reaction into X–H bonds (where X = O, S, N, or C).

The authors demonstrated that an insertion reaction in C(sp^3)–H bonds only occurs with considerable yield when small amounts of copper powder or copper salts, such as $CuSO_4$ and CuCN, were employed. Even using the term "carbenoid", the work does not present the formation of a copper carbenoid intermediate. It only suggests an insertion reaction occurring through free carbenes with copper working only as a catalyst to promote the carbene formation.

In 1985, Taber and coworkers reported the synthesis of (+)-α-cuparenone (**8**) through the construction of a five-membered ring prepared by an enantioselective carbenoid insertion into a C(sp^3)–H bond (Scheme 3) [34]. To carry out the cyclization, the carbenoid was formed by the action of $Rh_2(OAc)_4$ on the diazo compound **6**. That intermediate intramolecularly inserted into the C(sp^3)–H bond of the asymmetric carbon to yield ketoester **7** in 67% yield. This latter compound was converted to (+)-α-cuparenone (**8**) in 26% yield and 96% enantiomeric excess.



Scheme 2: Copper carbenoid insertion into C(sp^3)–H bond of a stereogenic center with full retention of the asymmetric carbon configuration.

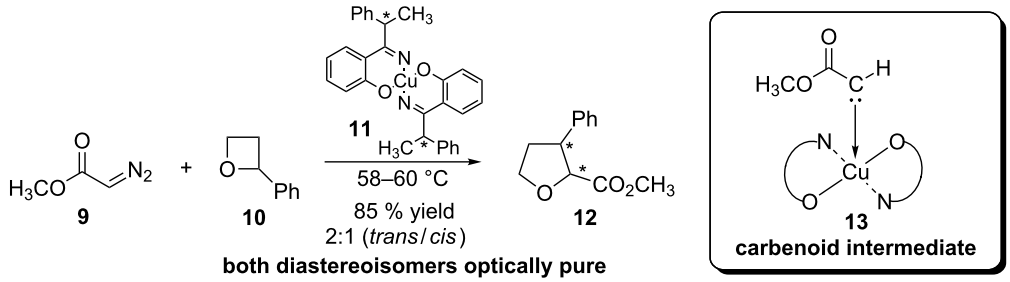


Scheme 3: Carbenoid insertion into a C(sp^3)–H bond as the key step of the Taber's (+)-α-cuparenone (**8**) synthesis.

In the late 1980s, many studies have been published by Taber [35], Sonawane [36], Doyle [37] and their respective coworkers regarding the regiochemistry of carbenoid insertion into C(sp^3)–H bonds, and also the steric and electronic factors related to this insertion.

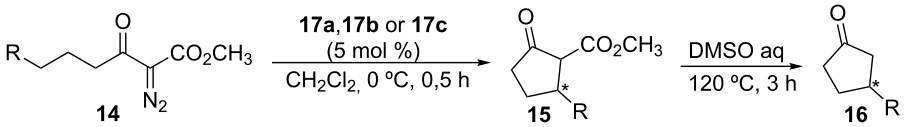
The first example of an enantioselective carbenoid insertion reaction in chemical bonds catalyzed by chiral metal complexes was introduced in 1966 by Noyori and coworkers (Scheme 4) [38]. In addition to the novelty of the use of the chiral copper complex **11** for controlling the enantioselectivity, the authors proposed the participation of the copper carbenoid **13**, formed from the reaction between the copper complex **11** and methyl diazoacetate **9** as active intermediate in the catalytic cycle of this transformation.

From the 1990s, the enantioselective carbenoid insertion into C(sp^3)–H bonds starts to be better discussed in the literature. Ikegami and coworkers reported the enantioselective insertion of α-diazo-β-ketoesters into C(sp^3)–H bonds catalyzed by rhodium carboxylate complexes in their homochiral form (Table 1) [39]. Modest enantiomeric excesses were provided by

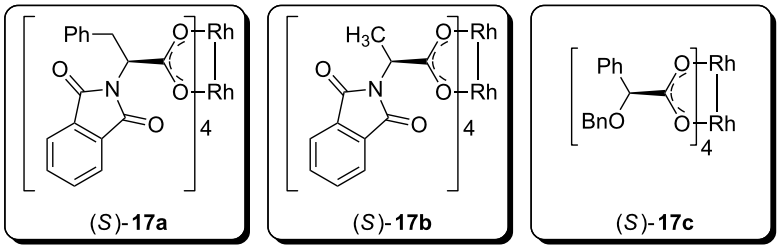


Scheme 4: First enantioselective carbenoid insertion into C–O bonds catalyzed by chiral metallic complexes.

Table 1: Enantioselective insertion of α-diazo-β-ketoesters into C(sp^3)–H bonds catalyzed by chiral rhodium(II) complexes **17a**, **17b** and **17c**.



R = CH_3, C_5H_{11}, $CH{=}CH_2$, Ph



R	catalyst	yield (%)	ee (%)	configuration of **16**
CH_3	**17a**	76	24	*R*
CH_3	**17b**	73	24	*R*
CH_3	**17c**	75	10	*S*
C_5H_{11}	**17a**	43	29	*R*
$CH{=}CH_2$	**17a**	44	38	*R*
$CH{=}CH_2$	**17b**	39	35	*R*
$CH{=}CH_2$	**17c**	44	30	*S*
Ph	**17a**	96	46	*R*
Ph	**17b**	87	43	*R*
Ph	**17c**	73	13	*S*

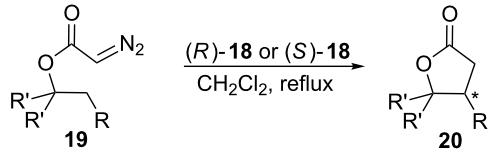
the three tested catalysts. The reactions carried out with complex **17a** and **17b** show very similar stereoselectivity, forming the *R*-enantiomer of compound **16** as the main product after decarboxylation reaction. The catalyst **17c** showed opposite enantioselectivity when compared to the catalysts **17a** and **17b**, with the *S*-enantiomer formed as the major product.

In 1991, Doyle and coworkers published asymmetric synthesis of lactones from alkyl diazoacetates in high enantioselectivity by intramolecular rhodium carbenoid insertion into C(sp^3)–H [40]. In this work, the authors introduced the enantiomeric rhodium(II) carboxamides complexes (*R*)-**18** and (*S*)-**18** (Figure 4).

The authors could observe the enantioselective formation of the lactones **20** with high enantiomeric excess (Table 2). The carbenoid formed by (*S*)-**18** favored the *S* configuration at the generated stereogenic center for most of the prepared lactones. The opposite preference, *R* configuration at the new stereogenic center of **20**, was reported to the use of the enantiomeric rhodium complex (*R*)-**18**. When substrate **19f** reacts under catalysis of rhodium(II) carboxamide complexes (*R*)-**18** and (*S*)-**18**, the configuration of the new stereogenic center of **20f** was reversed, probably due to the lack of the oxygen atom in the substituent R, as suggested by the authors.

In 1997, Davies and Hansen reported the intermolecular carbenoid insertion into C(sp^3)–H catalyzed by rhodium complex (*S*)-**23** with good to excellent enantioselective control (Scheme 5) [41]. The best results were observed when the reaction was carried out at room temperature. A wide range of substituent groups were evaluated at *para* position of the aryldiazoacetate aromatic ring. The cyclic hydrocarbon reagents, also used as solvent, were cyclopentane, cyclohexane and cycloheptane.

Table 2: Enantioselective intramolecular insertion of carbenoids into C(sp^3)–H bonds catalyzed by rhodium (II) carboxamides complexes (*R*)-**18** and (*S*)-**18**.



a: R = CH_3O, R' = H
b: R = CH_3CH_2O, R' = H
c: R = $PhCH_2O$, R' = H
d: CH_3O, R' = CH_3
e: R = $PhCH_2O$, R' = CH_3
f: R = Ph, R' = H

Reagent	catalyst	yield (%)	ee (%)	configuration of **20**
19a	(*S*)-**18**	62	91	*S*
19a	(*R*)-**18**	73	91	*R*
19b	(*S*)-**18**	64	89	*S*
19b	(*R*)-**18**	63	89	*R*
19c	(*S*)-**18**	64	87	*S*
19c	(*R*)-**18**	69	87	*R*
19d	(*S*)-**18**	68	56	*S*
19d	(*R*)-**18**	70	57	*R*
19e	(*S*)-**18**	85	51	*S*
19f	(*S*)-**18**	42	46	*R*
19f	(*R*)-**18**	34	45	*S*

Two factors are noteworthy in this work. Unlike the carboxamide complexes (*R*)-**18** and (*S*)-**18** previously reported by Doyle and coworkers (Table 2), where the complexation of the chiral ligand to rhodium atoms occurs through the carboxamide group, in the new chiral catalyst (*S*)-**23** the rhodium atoms are complexed to the chiral ligands by the carboxylate group, similar to those chiral complexes presented by Ikegami and coworkers (Table 1). Another important feature of this work is, unlike to the work that preceded it, that the new stereogenic center is formed on the carbenoid carbon coordinated to the

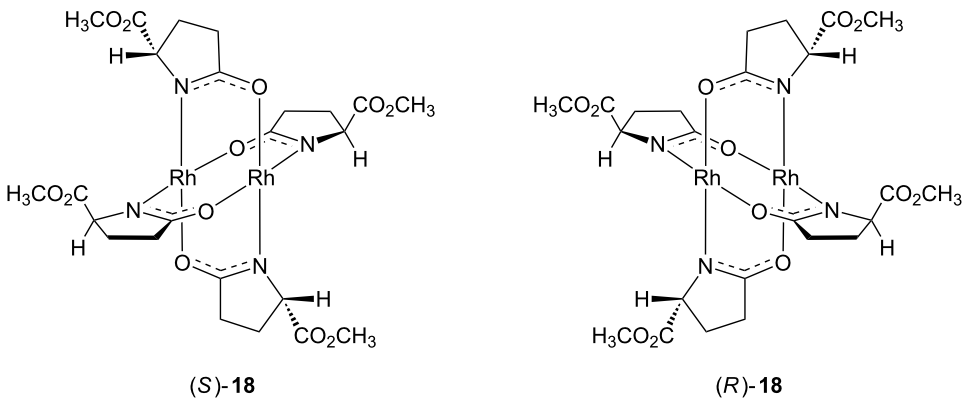
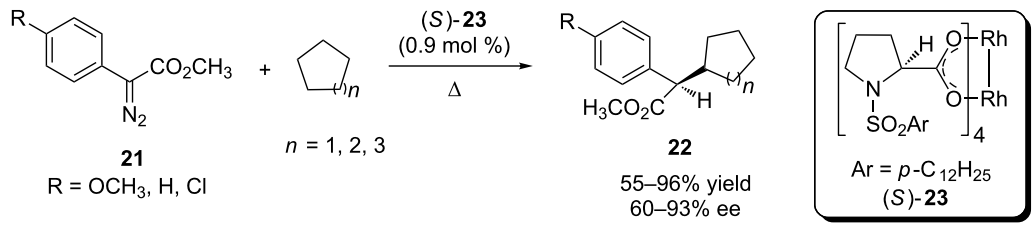


Figure 4: Chemical structures of complexes (*R*)-**18** and (*S*)-**18**.



Scheme 5: Asymmetric carbenoid insertions into C(sp^3)–H bonds of cycloalkanes catalyzed by chiral rhodium carboxylate complexes.

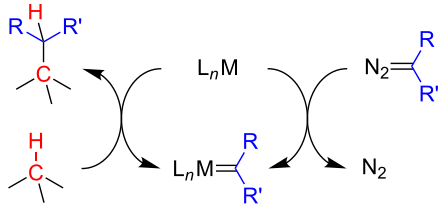
metal rhodium center and not on carbon-containing the C(sp^3)–H bond activated by the carbenoid moiety.

The authors also reported in this work the insertion into the C(sp^3)–H bond of tetrahydrofuran. This reaction showed good yield, regio-, diastereo- and enantioselectivity and represents the first example of the formation of a new stereogenic center out of the diazoacetate scaffold by an intermolecular carbenoid insertion into C(sp^3)–H bond (Scheme 6).

Mechanism of the carbenoid insertion into the C(sp^3)–H bond

Nakamura [12] and Doyle [37] were the first to do important contributions to the comprehension of the mechanism of this catalytic cycle. In a simplified form, the mechanism of the carbenoid insertion into a C(sp^3)–H bond can be represented as outlined in Scheme 7.

Nakamura et al. investigated the dirhodium tetracarboxylate-mediated carbenoid insertion reaction into C(sp^3)–H bonds in more detail using the relationship between the transition-state structures and their corresponding free energies obtained by DFT investigation (Scheme 8) [12]. The insertion step primarily consists in the formation of the metal carbenoid **29** by the interaction of the diazo compound **28** and the dirhodium complex **27**. In sequence, the reaction proceeds through the transition state **TS-30** to release N_2, and yields the carbenoid **31**. The divalent carbon attached to the rhodium atom starts to interact with the hydrogen of the C(sp^3)–H bond of the compound **32** to form the van der Waals complex **33** which undergoes through

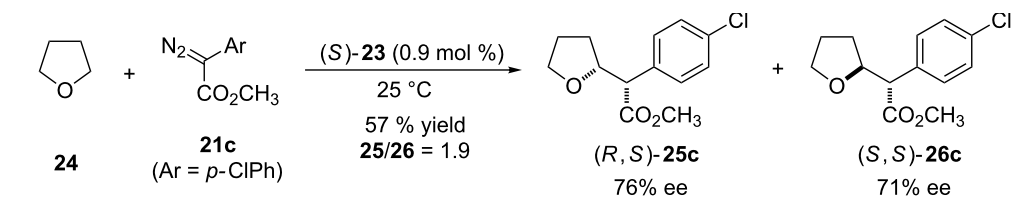


Scheme 7: Simplified mechanism of the carbenoid insertion into a C(sp^3)–H bond.

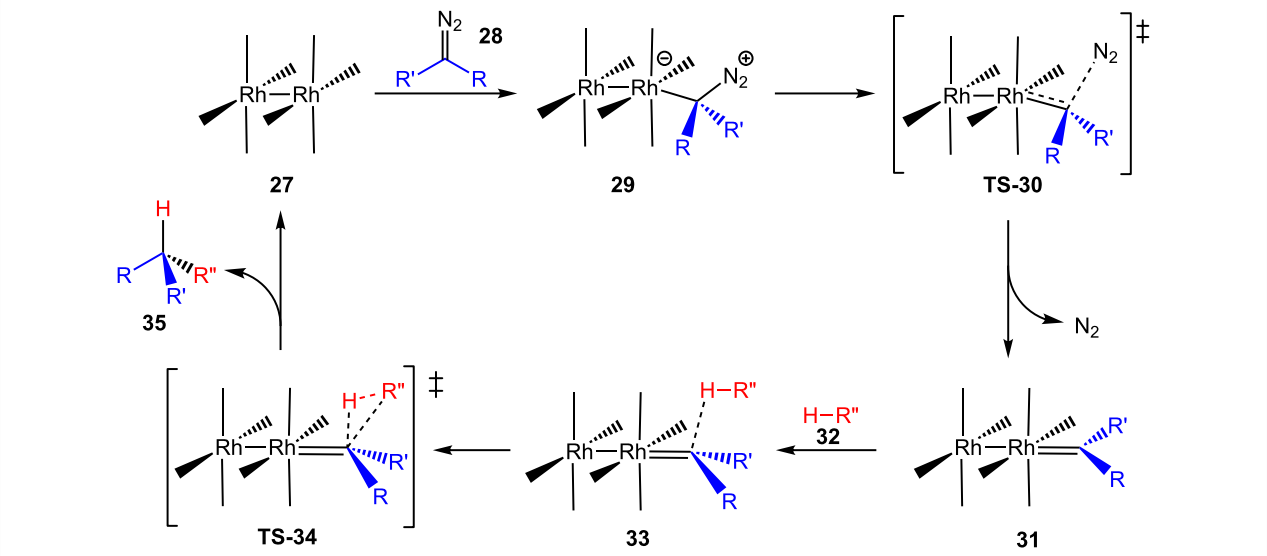
the transition state **TS-34** to the product of the carbenoid insertion reaction **35**, regenerating the dirhodium complex **27**.

In 2009, Davies and coworkers reported a DFT investigation of the relationship between the electronic characteristics of the substituent X attached to the carbenoid divalent carbon and the selectivity toward carbenoid insertion into σ C(sp^3)–H bonds (Scheme 9) [42].

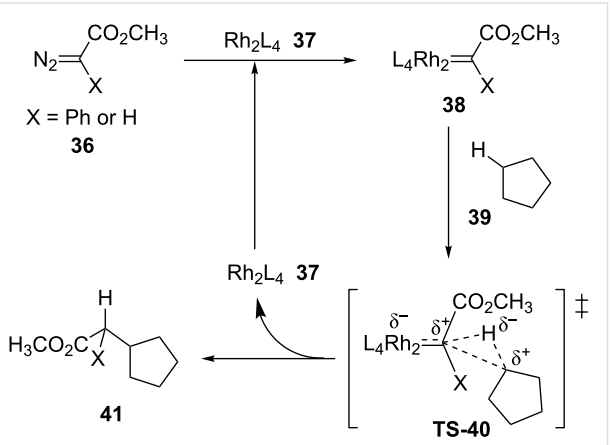
The authors found an exergonic carbenoid formation step and proposed two reasons for the selectivity toward insertion of this carbenoid into σ C(sp^3)–H when X = Ph or H. The first reason concerns the relative stability of the carbenoids **38-Ph** and **38-H**. The first one, prepared from the donor/acceptor diazo compound **36-Ph**, is 10.9 kcal more stable than the carbenoid **38-H** obtained from the acceptor diazo compound **36-H**. This observation was attributed to the stabilization of the partial positive charge on the divalent carbon of the transition state **TS-40** provided by the phenyl donor group. The second reason



Scheme 6: First diastereo and enantioselective intermolecular carbenoid insertion into tetrahydrofuran C(sp^3)–H bond.



Scheme 8: Nakamura's carbenoid insertion into a C(sp^3)–H bond catalytic cycle.



Scheme 9: Investigation of the relationship between the electronic characteristics of the substituent X attached to the carbenoid divalent carbon and the selectivity of the carbenoid insertion into σ C(sp^3)–H bonds.

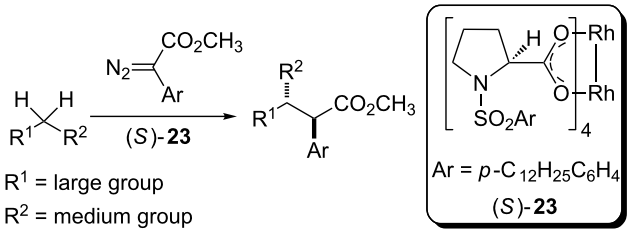
concerns the large difference between the activation energy of these reactions which relies on the development of steric strain through the transitions state **TS-40**, less important when X = H. This study provided a simple empirical model able to predict the stereoselectivity of the intermolecular insertion of donor/acceptor dirhodium carbenoids into C(sp^3)–H bonds properly validated by the results obtained by this research group during the development of the chiral catalyst (*S*)-**23** (Scheme 10).

Recent studies concerning the enantioselective carbenoid insertion into C(sp^3)–H bonds

From 2000, the study of carbenoid chemistry has become more comprehensive. The focus of most recently published works is the development of new catalysts for carbenoid insertion reactions into C(sp^3)–H bonds and also the insertion into X–H bonds, where X = N, O, S, Si and others.

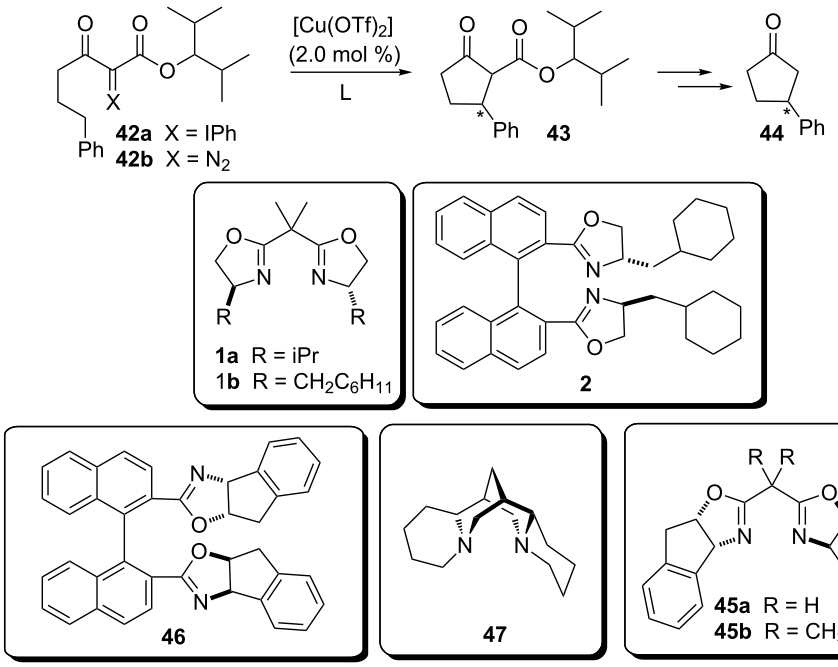
Copper-based chiral catalysts

In 2002, Müller and Boléa published a study evaluating the enantioselective insertion of copper carbenoids formed from phenyliodonium ylides and diazo compounds (Table 3) [9]. This work is particularly important because, at that time, the carbenoids derived from rhodium complexes were the most used for insertion reactions in C(sp^3)–H bonds.



Scheme 10: Empirical model to predict the stereoselectivity of the donor/acceptor dirhodium carbenoid insertion into C(sp^3)–H catalyzed by (*S*)-**23**.

Table 3: Enantioselective intramolecular insertion of copper carbenoids derived from phenyliodonium ylides and diazo compounds.



L[a]	yield (%) from 42a[a]	ee (%)	yield (%) from **42b**[b]	ee (%)
1a	51	(*R*)-**42**	38	(*R*)-**15**
1b	49	(*R*)-**38**	32	(*R*)-**18**
45a	52	(*S*)-**72**	14	(*S*)-**31**
45b	46	(*S*)-**17**	55	(*S*)-**22**
2	46	(*R*)-**59**	35	(*R*)-**60**
46[c]	47	(*S*)-**67**	17	(*S*)-**51**
47	11	(*S*)-**57**	32	(*S*)-**18**

[a]CH_2Cl_2 at 0 °C; [b]$ClCH_2CH_2Cl$ at 65 °C; [c]Ligand **46** was used in 70% de. When **42a** was cyclized by **46** with de > 98%, the ee of the product **43** increased to 70% ee favoring the same stereoisomer (*S*).

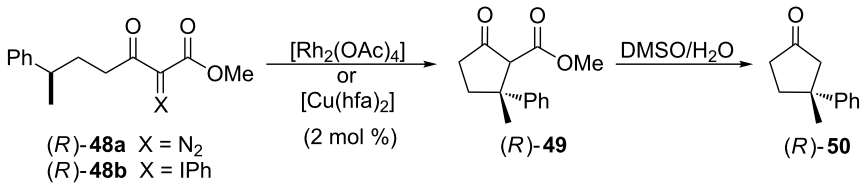
Comparing the results of Table 3, the same enantiomer was obtained mainly for both carbenoid precursors, ylide **42a** and the diazo compound **42b.** The authors suggested the formation of the same chiral copper carbenoid intermediate by the reaction of the in situ prepared chiral copper complexes with both **42a** and **42b** to provide the observed insertion products.

The reactions with phenyliodonium ylides **42a** showed better ee when compared to that done with diazo compounds **42b**. The authors attributed this observation to the large difference between the reaction temperatures, 0 °C to ylides versus 65 °C to diazo compounds. Higher temperatures increase the carbenoid formation rate by the chiral copper complexes as well as the carbene formation rate by direct decomposition of the precursors **42a** and **42b**. The competition between carbene insertion and chiral carbenoid insertion into C(sp^3)–H bonds decreases the enantioselectivity of this transformation.

To confirm the copper carbenoid formation and its participation on the insertion reactions, the authors prepared the carbenoid precursors (*R*)-**48a** and (*R*)-**48b** and submit them to $Rh_2(OAc)_4$ or $Cu(hfa)_2$ catalysis (Table 4). All reactions maintained the configuration of the asymmetric carbon where de insertion happened, independent to the carbenoid precursor and the catalyst, a strong evidence of the carbenoid intermediates formation.

In 2010, Maguire et al. studied the enantioselective insertion of copper carbenoid derived from α-diazosulfones into C(sp^3)–H bonds [10]. In this work, the authors produced cyclic sulfones (thiopyrans) **52** with high enantioselectivity by using a combination of 5 mol % of copper chloride salt, 6 mol % of ligand **1c** and 6 mol % of sodium tetrakis[(3,5-tri-fluoromethyl)phenyl]borate (NaBARF). The cyclic sulfones **52** were obtained in good yields and excellent enantiomeric

Table 4: Experimental evidences of the carbenoid formation from (*R*)-**48a** and (*R*)-**48b** and its intramolecular insertion into C(sp^3)–H bonds.



precursor	catalyst	time	(*R*)-**49** yield (%)	ee (%)
(*R*)-**48a**	$[Rh_2(OAc)_4]$	30 min	59	>98
(*R*)-**48a**	$[Cu(hfa)_2]$	3h	54	>98
(*R*)-**48b**	$[Rh_2(OAc)_4]$	3h	57	>98
(*R*)-**48b**	$[Cu(hfa)_2]$	3h	36	>98

excesses (85–98%) favoring the *cis*-1,2-di-substituted stereoisomer (Table 5).

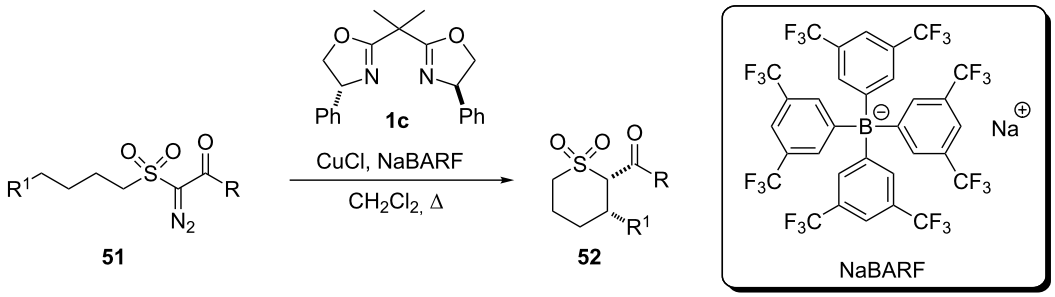
The authors also performed the copper carbenoid insertion reaction to yield five-membered cyclic sulfones **54**, under similar experimental conditions, in moderate yields and enantiomeric excesses of the *trans* stereoisomer (Table 6).

Independent to the size of the product, the authors emphasize the low dependence of the enantioselectivity with respect to the structural nature of the substrates where the lowest results are observed for the substrate **51h** (R = CH_3). In contrast, the reaction times showed to be more dependent on the chemical structure of the substrates.

This research group has focused a lot of efforts to better comprehend the scope of this catalytic system, especially on features concerning the BARF salt effect [43,44] and electronic effects on the aromatic rings of the chiral ligands [45].

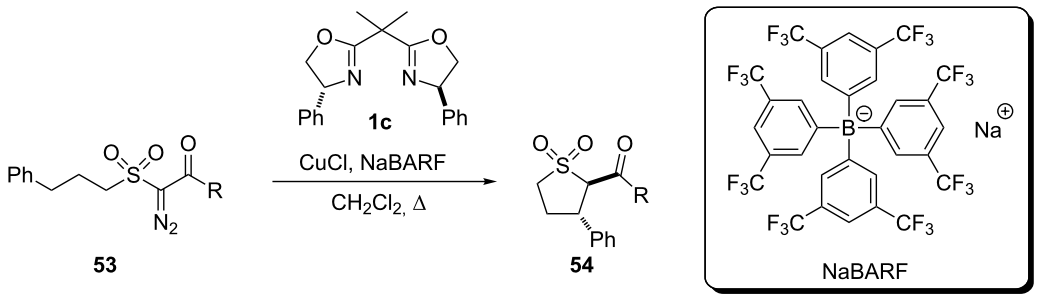
In 2014, Maguire at al reported the syntheses of *N*-heterocycles by the enantioselective insertion of copper carbenoids to

Table 5: Insertion of asymmetric copper carbenoid C(sp^3)–H bonds to prepare thiopyrans **52**.



diazo compound	R	R^1	time (h)	**52** yield (%)	ee (%)
51a	OCH_3	Ph	5	47	98
51b	OCH_3	4-tolyl	5	64	96
51c	OCH_3	4-anisyl	22	56	91
51d	OCH_3	4-nitrophenyl	2,5	–	–
51e	OCH_3	benzyl	7	42	96
51f	OCH_3	ethyl	16	68	97
51g	OBn	octyl	22	66	90
51h	CH_3	Ph	22	30	85
51i	Ph	Ph	6	49	97

Table 6: Asymmetric insertion of copper carbenoids in C(sp^3)–H bonds to prepare five-membered cyclic sulfones **54**.



diazo compound	R	time (h)	**54** yield (%)	ee (%)
53a	OCH_3	5	57	60
53b	CH_3	3	40	40

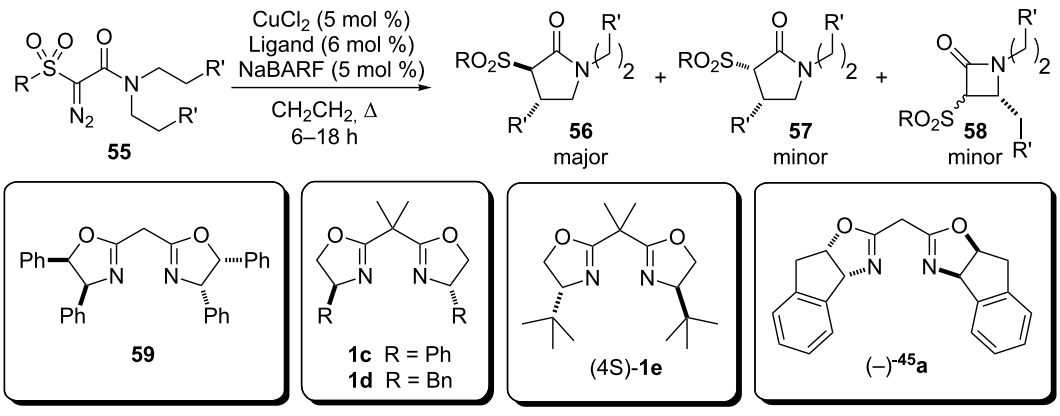
α-nitrogen C(sp^3)–H bonds of amides (Scheme 11) [46]. A wide range of bis(oxazolines) were evaluated as chiral ligands in dry dichloromethane with NaBARF as additive. Three catalytic systems, based on ligands (−)-**45a**, (+)-**45a** and (4*S*)-**1e**, showed a better performance (>82% ee). The transformation was regio and stereoselective where the main product was *trans*-γ-lactam (**56**). The chiral rhodium complexes (*S*)-**17**, (*S*)-**18** and (*S*)-**23** were also evaluated and yielded similar regio- and diastereoselectivity, however, with lower enantioselectivity when compared to the bis(oxazoline)/$CuCl_2$/NaBARF catalytic system.

Attempts to heterogeneous catalysis using chiral copper complexes were also done. Fraile et al reported, in 2011, the copper catalyst **60** for enantioselective insertion of carbenoid into *O*-heterocycles C(sp^3)–H bonds (Table 7) [47,48]. The reaction was performed under homogeneous and heterogeneous conditions, with laponite as support for the catalyst. The reaction afforded moderate yields, diastereomeric ratio and enantioselectivity under both conditions. The supported catalytic system was reused over three cycles with no performance decrease. The same heterogeneous catalyst was also used to perform an enantioselective insertion of the carbenoid into benzylic C(sp^3)–H bonds and similar results were observed [49].

In 2011, the same research group developed a new heterogeneous copper catalyst for carbenoid insertion into C(sp^3)–H bonds [50]. The solid support was based on SiO_2/Al_2O_3 and, after addition of ligand **1c** to the reaction media, the reaction afforded moderate yields, diastereomeric ratio and enantioselectivity. These catalysts were reused over three cycles with progressive yield and enantioselectivity decrease.

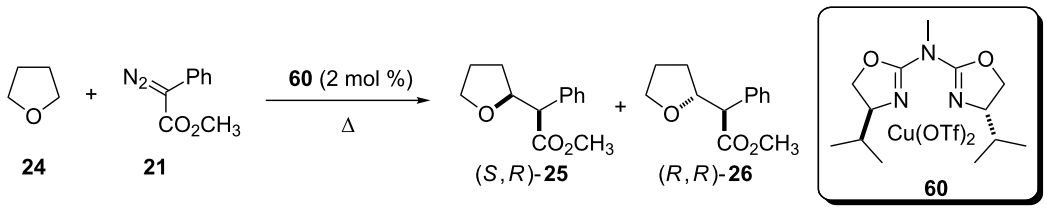
Iridium-based chiral catalysts

Most recently, chiral iridium complexes have been used as catalyst for insertion reactions in C(sp^3)–H bonds. In 2009, Suematsu and Katsuki published the first study addressed to the



Scheme 11: Asymmetric insertion of copper carbenoids in C(sp^3)–H bonds to prepare *trans*-γ-lactam.

Table 7: Asymmetric insertion of copper carbenoids into tetrahydrofuran C(sp^3)–H bonds under heterogeneous reaction condition.



conditions	% yield	**25**/**26**	**25** ee (%)
homogeneous	74	56:44	64
heterogeneous	50	59:41	62

use of iridium-based chiral complexes as catalyst for the formation of carbenoid intermediates (Figure 5) [51]. The authors conducted insertion reactions in C(sp^3)–H bonds in a diastereo- and enantioselective manner. For enantioselective insertion reactions the authors tested two specific iridium complexes, **61a** and **61b**.

The authors used a wide range of α-substituted α-diazoacetates for performing insertion into substrates such as tetrahydrofuran (**24**) and 1,4-cyclohexadiene (**62**). Using these two compounds, the authors evaluated the best conditions for carrying out the reaction. When the iridium-catalyzed insertion reaction of carbenoids into tetrahydrofurans C(sp^3)–H bond was performed at room temperature, the authors reported the formation of dimers of α-substituted α-diazoacetates as the main products of this reaction. This issue was circumvented when low temperatures, −50 °C, were used and the insertion reaction occurred with considerable yields and good enantiomeric excess (Table 8). According to the authors, the low temperature could

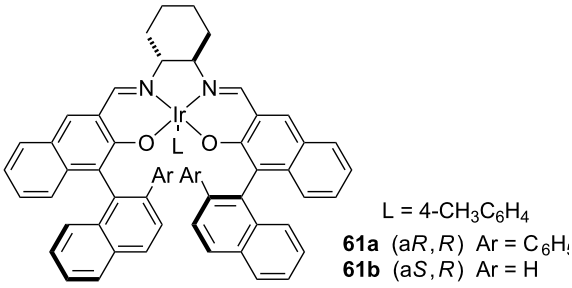
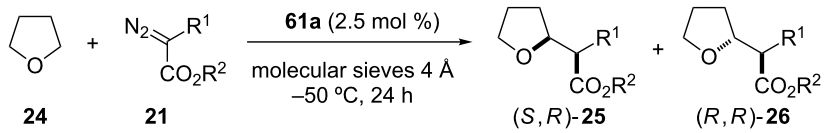


Figure 5: Iridium catalysts used by Suematsu and Katsuki for carbenoid insertion into C(sp^3)–H bonds.

Table 8: Intermolecular insertion of chiral iridium carbenoid into THF C(sp^3)–H bond.



diazo compound	R^1	R^2	**25**:**26**	**25** yield (%)	**25** ee (%)
21a	C_6H_5	Me	13:1	75	95
21b	*p*-$MeOC_6H_4$	Me	>20:1	64	97
21c	*p*-ClC_6H_4	Me	19:1	82	94
21d	*p*-MeC_6H_4	Me	19:1	71	97
21e	*p*-BrC_6H_4	Me	>20:1	76	93
21f	*m*-$MeOC_6H_4$	Me	9:1	75	97
21g	*m*-ClC_6H_4	Me	>20:1	82	95
21h	2-naphthyl	Me	>20:1	80	98
21i	*o*-$MeOC_6H_4$	Me	>20:1	9	95
21j	Me	t-Bu	13:1	70	90

reduce some type of steric strain on the transition state of the insertion reaction and avoid the dimer formation.

For the insertion reaction of iridium carbenoid into the 1,4-cyclohexadiene (**62**) bis-allylic C(sp^3)–H bond the authors observed the formation of two products, one resulting from iridium carbenoid insertion into the C(sp^3)–H bond (**63**) and the other as a result of the cyclopropanation reaction (**64**, Table 9).

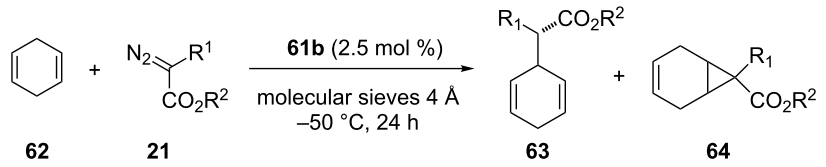
Both examples reported by Suematsu and Katsuki showed very good yields and excellent enantiomeric excesses of the products. This work is noteworthy because it is the first report in the literature of an enantioselective insertion of an iridium carbenoid into C(sp^3)–H bonds.

Che and coworkers introduced the first porphyrin-based chiral iridium catalyst (−)-**65** to insertion of carbenoids into C(sp^3)–H bonds [52]. The reaction with 1,4-cyclohexadiene was promoted by 1 mol % of the catalyst at low temperatures to affords the product in high yields and enantioselectivity (Scheme 12).

The same catalytic system was applied to carbenoid insertions into tetrahydrofuran C(sp^3)–H bonds (Scheme 13). The reaction afforded the desired product in a regioselective way and high diastereoselectivity, ranging from 2.5:1 to >20:1, favoring the *anti*-product, in a complementary sense when compared to the results reported by Suematsu and Katsuki for iridium catalyst **61a** (Table 8). Poor to excellent yields and high enantioselectivity were reported for the main product.

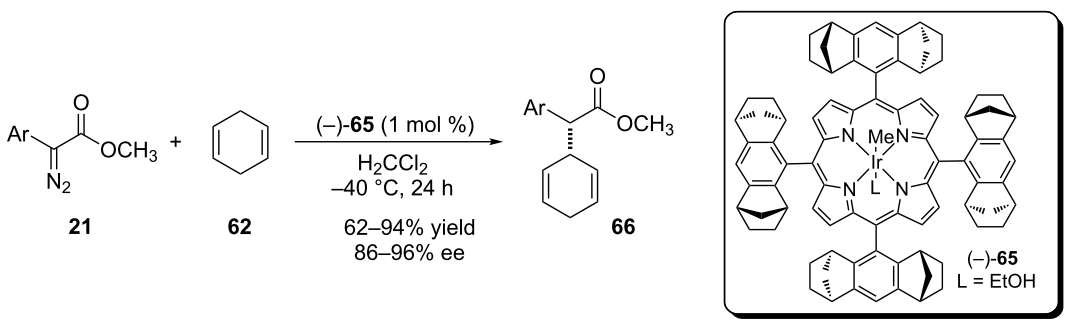
The chiral porphyrin-based iridium complex (−)-**65** was also used by the same research group to catalyze the intramolecular carbenoid insertion into C(sp^3)–H bonds and affords the synthe-

Table 9: Intermolecular insertion of chiral iridium carbenoids into the 1,4-cyclohexadiene (**62**) bis-allylic C(sp^3)–H bond.



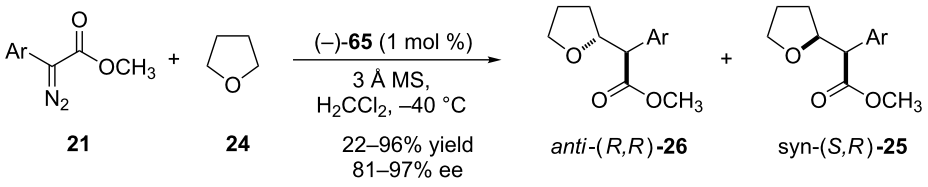
62 **21** **63** **64**

diazo compound	R^1	R^2	**63**:**64**	**63** yield (%)	ee (%) o
21a	C_6H_5	Me	>20:1	91	94
21b	*p*-$MeOC_6H_4$	Me	>20:1	39	90
21c	*p*-ClC_6H_4	Me	>20:1	79	95
21f	*m*-$MeOC_6H_4$	Me	>20:1	95	96
21g	*m*-ClC_6H_4	Me	>20:1	80	99
21i	*o*-$MeOC_6H_4$	Me	>20:1	54	97
21k	o-ClC_6H_4	Me	>20:1	53	99
21l	3,4-$Cl_2C_6H_3$	Me	>20:1	95	99
21m	3-Thienyl	C_2H_4Cl	>20:1	67	97
21n	Me	Et	>20:1	68	83
21o	Me	t-Bu	>20:1	84	>99



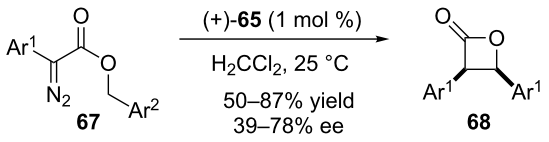
21 **62** **66**

Scheme 12: Chiral porphyrin iridium complex catalyzes the carbenoid insertion into bis-allylic C(sp^3)–H bonds.



Scheme 13: Chiral porphyrin iridium complex catalyzes the carbenoid insertion into tetrahydrofuran C(sp^3)–H bonds.

sis of *cis*-β-lactones in a wide range of yields and enantioselectivities (Scheme 14) [53]. The reaction time was dependent on the chemical structure of the group Ar^1 (*p*-CH_3Ph = 24 h; *p*-FPh, *m*-ClPh, *m*-BrPh = 10 min) and the enantioselectivity drops from 70–80% ee to less than 50% ee when Ar^1 is *m*-ClPh or *m*-BrPh.



Scheme 14: Chiral porphyrin–iridium complex catalyzes the intramolecular carbenoid insertion into C(sp^3)–H bonds to afford the synthesis of *cis*-β-lactones.

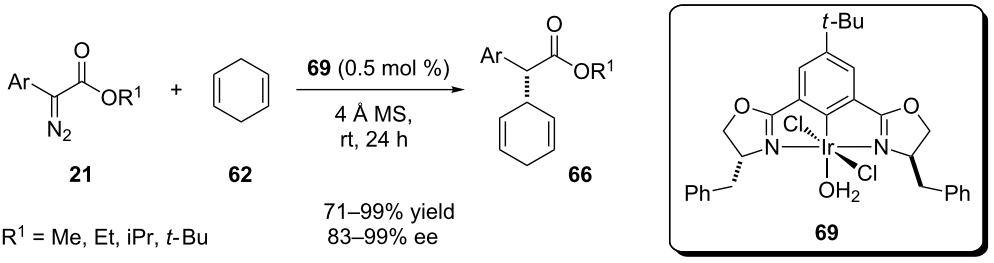
In 2013, Davies, Blakey and coworkers reported a new iridium catalyst to perform a carbenoid insertion into the C(sp^3)–H bond (Scheme 15) [54]. The reactions were performed at room temperature and low catalyst loading (0.5 mol %) to afford the desired product in high yield and enantioselectivity. To reduce the amount of cyclohexadiene, the reaction was also performed in trifluorotoluene, resulting in a yield decrease (93% when 1,4-cyclohexadiene was solvent and reagent; 60% when 2,5 equivalents of cyclohexadiene and $PhCF_3$ as solvent where used) but with almost the same enantioselectivity.

Rhodium-based chiral catalysts

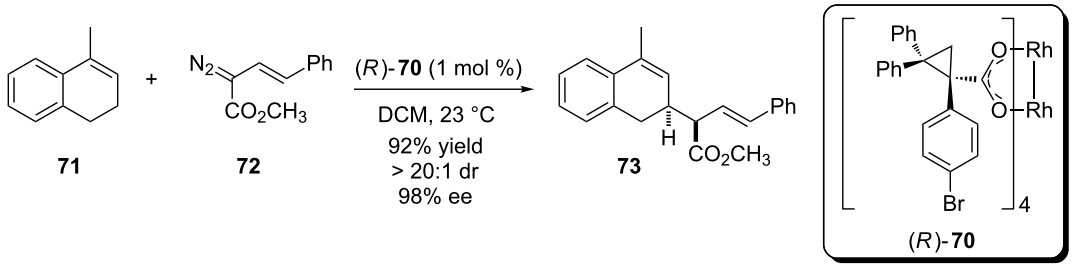
Since the pioneering reports by Ikegami [39], Doyle [40] and Davies [41] introducing their dirhodium chiral catalysts, these complexes have been the most frequently used and studied catalysts for enantioselective insertion of carbenoids into C(sp^3)–H [55]. It is noteworthy the intensive contribution of the Davies research group which reported important works related to regioselectivity and stereoselectivity [56], and chemoselectivity [57] of this transformation.

In 2011, Davies et al reported a chiral rhodium complex based on a new cyclopropylcarboxylate ligand (Scheme 16) [58]. Among the various transformations promoted by this new catalyst we can find enantioselective carbenoid insertion into the endocyclic allylic C(sp^3)–H bond of **71** followed by the Cope rearrangement and retro-Cope strategy previously described by the same research group [59]. The product was obtained in excellent yield, diastereo- and enantioselectivity.

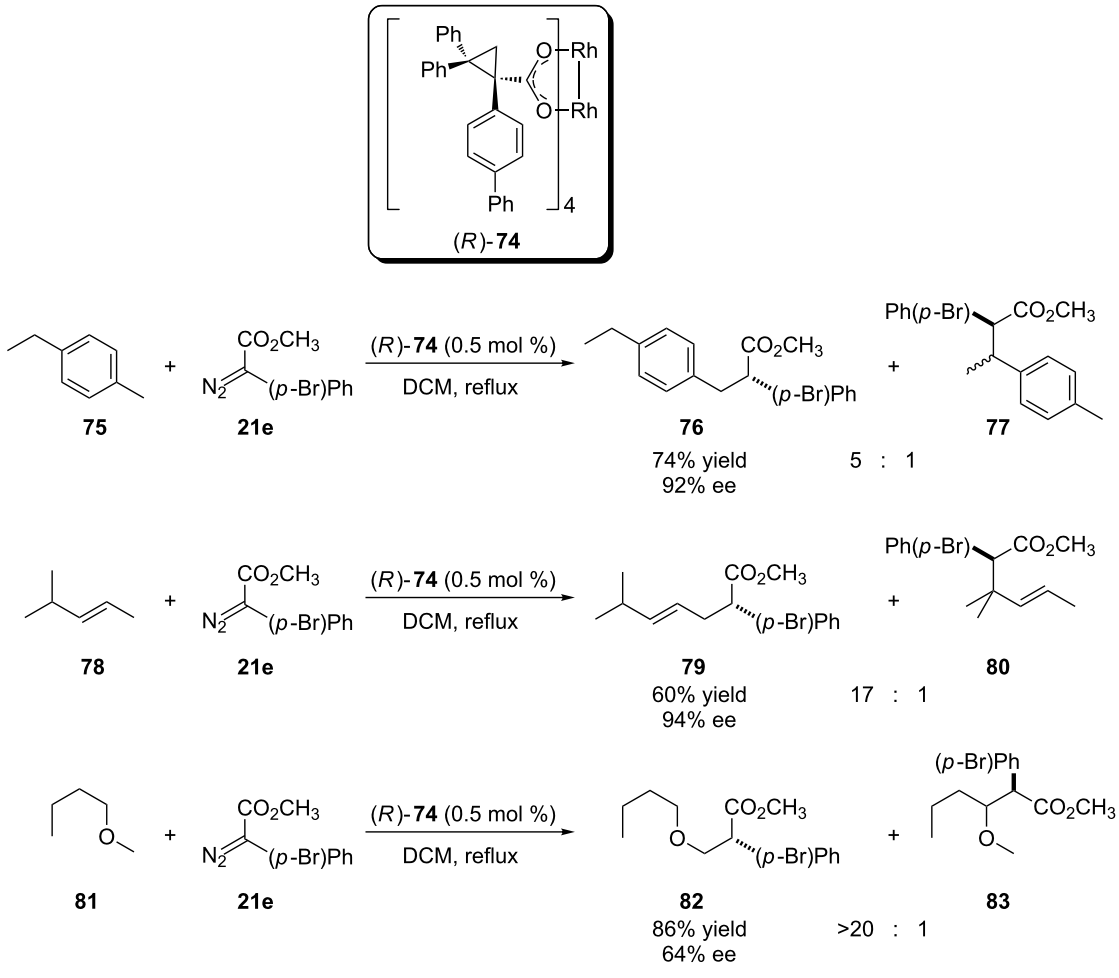
Later, the same authors showed a new chiral rhodium complex (*R*)-**74** based on an analogue cyclopropylcarboxylate ligand (Scheme 17) [60]. This new ligand favors the regiochemistry of rhodium carbenoid insertion into primary C(sp^3)–H activated bonds even in the presence of activated secondary C(sp^3)–H bonds. This preference stems from the greater volume of the ligand and the consequent greater steric strain in the transition state that leads to the minor insertion product at activated secondary C(sp^3)–H bonds. Substrates with benzylic bond, allylic and α-oxygen C(sp^3)–H were submitted to the new catalyst, under dichloromethane reflux, and led to the preferential formation of the insertion products into primary carbon, (from 5:1 to >20:1), high yields and enantioselectivity, higher than 90% ee, 88% ee and 64% ee, respectively.



Scheme 15: Chiral bis(oxazoline)–iridium complex catalyzes the carbenoid insertion into bis-allylic C(sp^3)–H bonds.

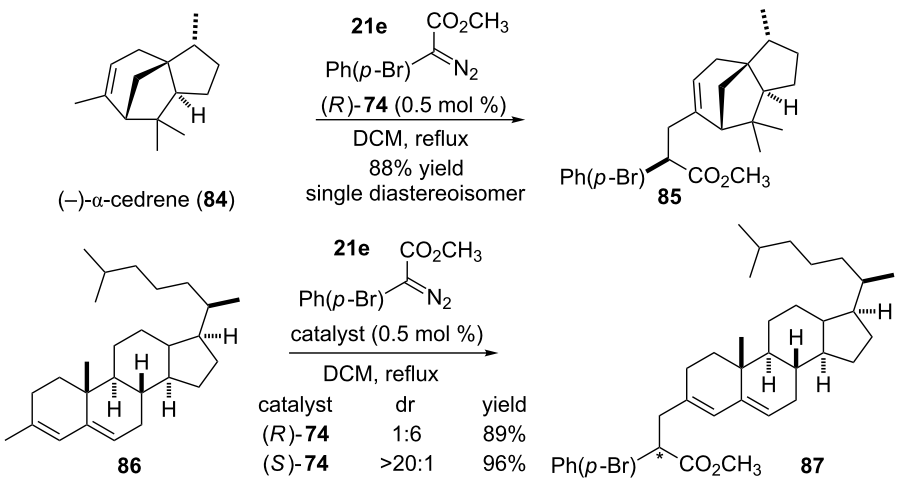


Scheme 16: New cyclopropylcarboxylate-based chiral catalyst to enantioselective carbenoid insertion into the endocyclic allylic C(sp^3)–H bond.



Scheme 17: Regio- and enantioselective carbenoid insertion into the C(sp^3)–H bond catalyzed by a new bulky cyclopropylcarboxylate-based chiral dirhodium complex (*R*)-**74**.

The authors also employed this catalyst in the functionalization of the (−)-α-cedrene and a steroidal nucleus, both substrates containing primary, secondary and tertiary allylic C(sp^3)–H bonds (Scheme 18). In both cases, was only observed the formation of the regioisomer derived from carbenoid insertion into the primary allylic position with excellent yield and high diastereoselectivity. For the steroidal substrate, the catalyst (*R*)-**74** favored the formation of a new center with *R* configuration in a 6:1 diastereoisomeric ratio. The use of the enantiomeric catalyst, (*S*)-**74**, yielded the product with *S* configuration at the new stereogenic center with a higher diastereoisomeric ratio (>20:1).



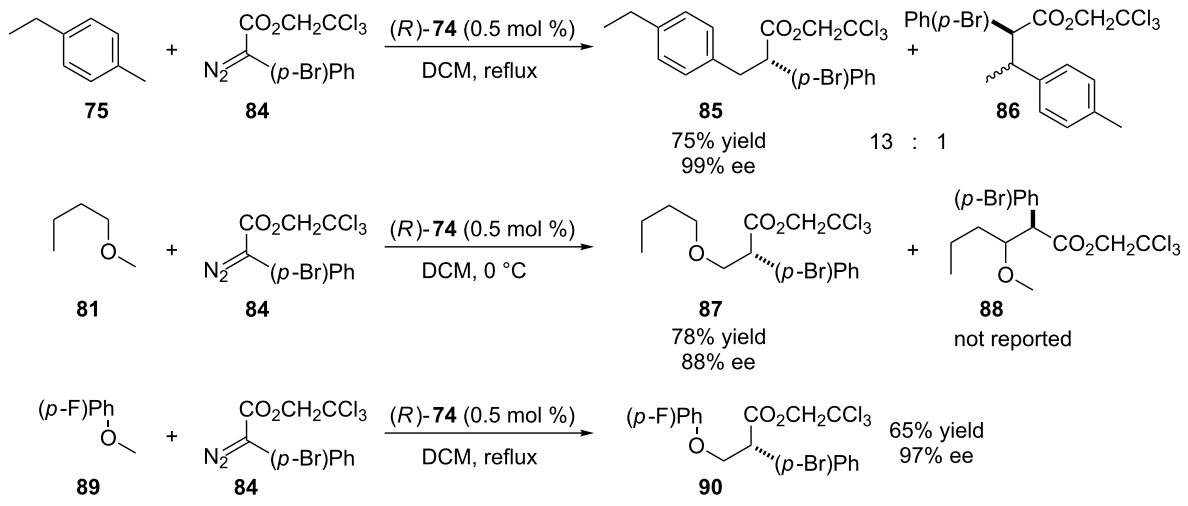
Scheme 18: Regio and diastereoselective carbenoid insertion into the C(sp^3)–H bond catalyzed by a new bulky cyclopropylcarboxylate-based chiral dirhodium complex.

In 2014, Davies and coworkers expand the scope of catalyst (*R*)-**74** by combining it with 2,2,2-trichloroethyl (TCE) aryldiazoacetates (Scheme 19) [61]. When compared with the use of traditional methylaryldiazoacetates (Scheme 17), an improved enantioselectivity of the insertion product **85** was observed combined with superior regiochemistry, favoring the rhodium carbenoid insertion into primary C(sp^3)–H activated bonds even in the presence of activated secondary C(sp^3)–H bonds.

Another important contribution addressed by this work was the C(sp^3)–H bond functionalization of methyl ethers even in the presence of other activated C(sp^3)–H bonds. A wide range of methyl ethers were regioselectively functionalized, also with improved enantioselectivity, by the use of TCE aryldiazoacetates in combination with (*R*)-**47**, here exemplified by the reaction between methyl ether **81** and the TCE aryldiazoacetate **84**. The comparison of this result with that presented at Scheme 17 shows a significant increase of the enantioselectivity.

TCE heteroaryldiazoacetates were also successfully employed for the formation of the rhodium carbenoid insertion products in superior yields when compared to the reaction with methyl aryldiazoacetates. TCE aryldiazoacetates reduced significantly the carbene dimerization allowing the reduction of the TCE diazoacetate addition time from 1.5 hours to 5 seconds.

The deactivated aryl methyl ether **84** was also functionalized by the use of TCE aryldiazoacetates in combination with (*R*)-**47** in



Scheme 19: 2,2,2-Trichloroethyl (TCE) aryldiazoacetates to improve the scope, regio- and enantioselective of the carbenoid insertion into primary C(sp^3)–Hs bond by (*R*)-**74**.

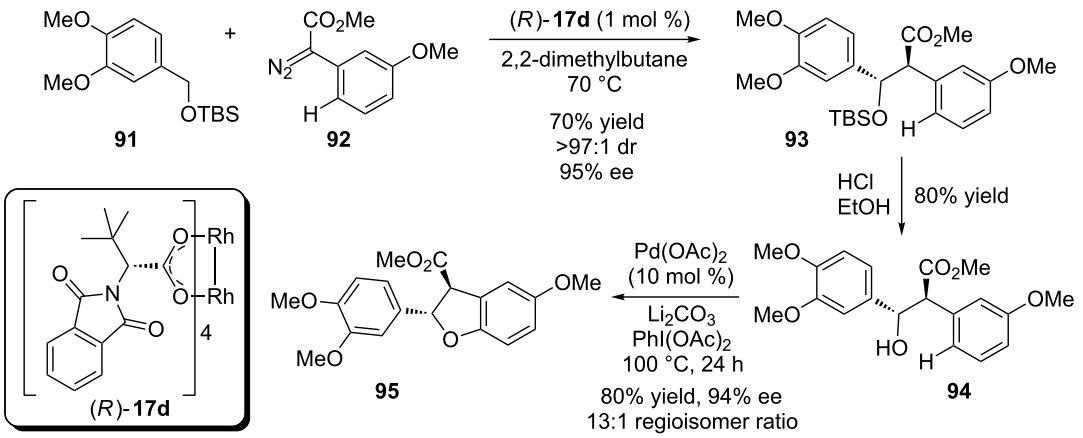
good yield and excellent enantioselectivity. The reaction between **84** and the methyl aryldiazoacetate **21e** afforded the insertion product in only 15% yield.

In 2013, Davies, Yo et al reported a new strategy to construct 2,3-dihydrobenzofurans based on a sequential enantioselective rhodium catalyzed carbenoid insertion into a C(sp^3)–H bond followed by a palladium C(sp^2)–H bond activation to build a new C–O bond (Scheme 20) [62]. A wide range of benzyl silyl ethers and diazo compounds were tested providing the desired 2,3-dihydrobenzofuran in good yields and excellent diastereo- and enantioselectivity. Later, this strategy was further used by Davies, Zakarian and coworkers to access the total synthesis of (−)-maoecrystal V [63].

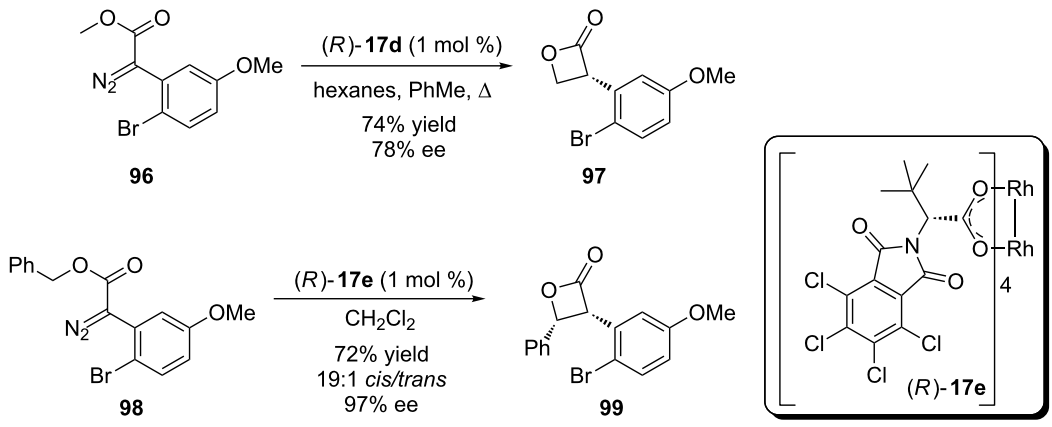
During this study, the authors observed an unexpected result when *ortho*–halosubstituted diazo compounds were used. Here the formation of a β-lactone by the carbenoid insertion into the C(sp^3)–H bond of the alkyl substituent of the alkoxy moiety of the ester (Scheme 21). The authors decided to investigate this observation and reported a more detailed study concerning the synthesis of *cis*-disubstituted β-lactones in high yield, diastereo- and enantioselectivity [64].

Total syntheses of 2,3-dihydrobenzofurans containing natural products have also been recently reported independently by Hashimoto [65,66] and Kan [67] based on an enantioselective intramolecular rhodium carbenoid insertion into C(sp^3)–H bonds.

In 2012, Pavlyuk and coworkers performed the synthesis of azacycloalkenes by rhodium carbenoid insertion into C(sp^3)–H bonds, and subsequent ring closing olefin metathesis (RCM) [68]. The insertion of the rhodium carbenoids derived from



Scheme 20: Sequential C–H functionalization approach to 2,3-dihydrobenzofurans.



Scheme 21: Enantioselective intramolecular rhodium carbenoid insertion into C(sp^3)–H bonds to afford *cis*-disubstituted β-lactones.

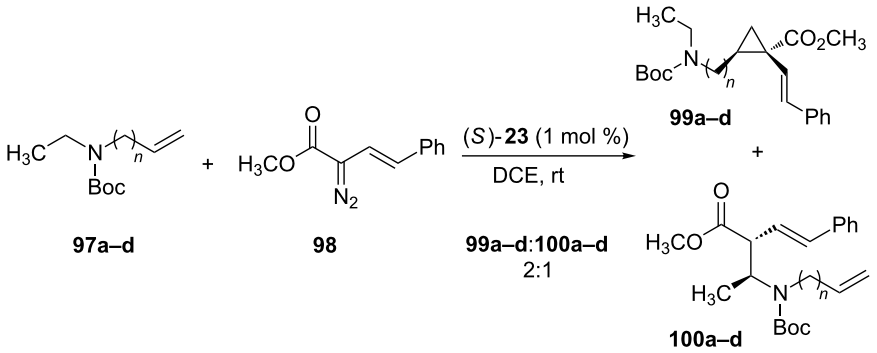
vinyl diazoacetate into the C(sp^3)–H bonds of the alkenylcarbamates **97a–d** yields two reaction products (Table 10). The major one (**99a–d**) was the result of the cyclopropanation reaction of the double bond present in **97a–d**. The minor product (**100a–d**) was the desired one, resulting from the insertion reaction on the C(sp^3)–H bond α to the nitrogen atom.

The carbenoid insertion reaction into C(sp^3)–H bonds was regioselective for substrates **97a–d**, even when there was an allylic and α-nitrogen C(sp^3)–H bond in substrate **97a**. The authors also point out that the **66**:**67** ratio was 2:1 regardless of the rhodium source ($Rh_2(OAc)_4$, $Rh_2(pfb)_4$, $Rh_2(TFA)_4$, $Rh_2(TPA)_4$) or solvents (hexane, benzene) used in this reaction.

The dienes **100a–d** were submitted to 2nd-generation Grubbs–Hoveyda catalyst (**101**), under dichloroethane reflux, to afford the desired azacycloalkenes **102a–c** in 95–98% yield and 92–95 % ee (Table 11). Only the diene **100d** did not cyclize and did not afford the nine-membered heterocycle by this methodology.

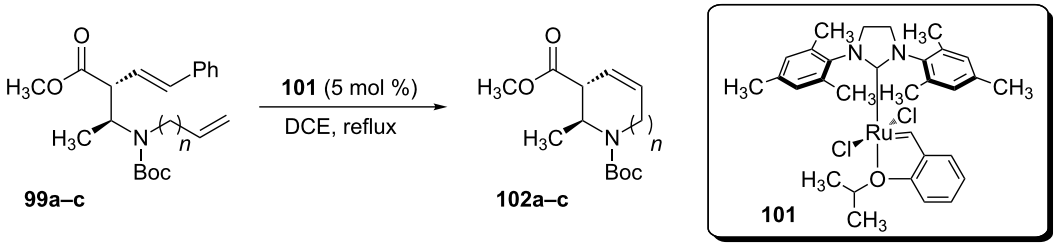
In 2015, Hashimoto et al reported the synthesis of methyl 2-vinyltetrahydropyran-3-carboxylates (**104**) by an enantioselective rhodium carbenoid insertion into C(sp^3)–H bond strategy [69]. The desired product was obtained in very good yield and excellent diastereo- and enantioselectivity favoring the *cis* isomer (Scheme 22).

Table 10: Cyclopropanation/Insertion rhodium carbenoid reactions into C(sp^3)–H reported by Pavlyuk and coworkers.

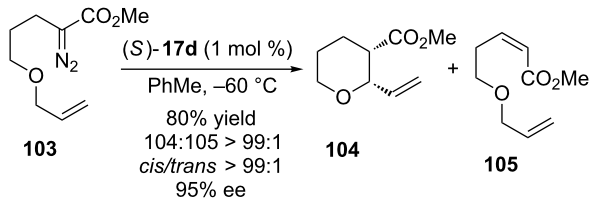


alkenylcarbamate	*n*	**99** yield (%)	de (%)	ee (%)	**100** yield (%)	de (%)	ee (%)
97a	1	64	95	96	32	90	92
97b	2	61	98	92	30	94	90
97c	3	59	98	95	28	98	85
97d	4	55	98	92	27	98	83

Table 11: Syntheses of *N*-heterocycles by RCM reported by Pavlyuk and coworkers.



diene	*n*	**102** yield (%)	de (%)	ee (%)
99a	1	98	>98	93
99b	2	96	>98	95
99c	3	95	>98	92

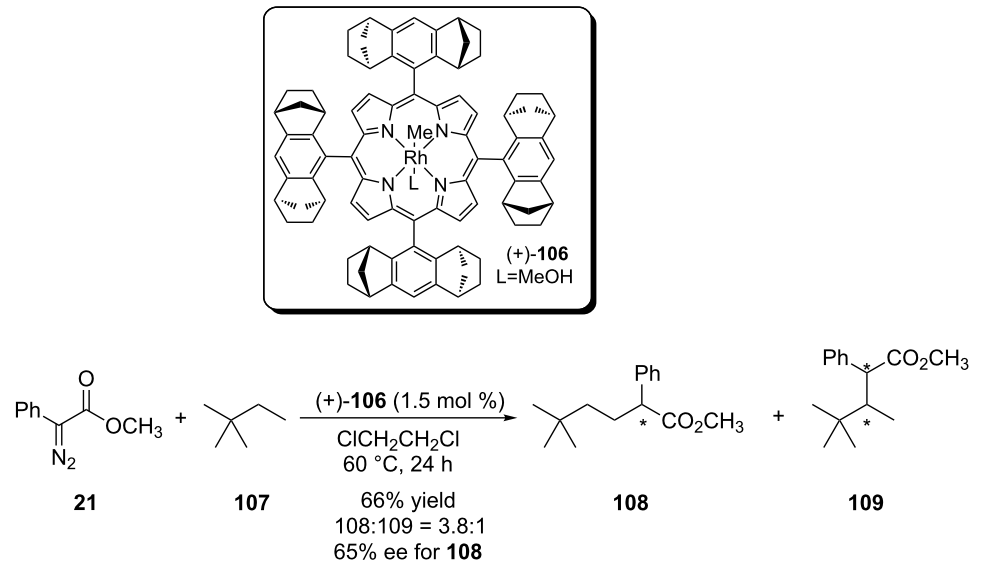


Scheme 22: Enantioselective intramolecular rhodium carbenoid insertion into C(sp^3)–H bonds to afford *cis*-2-vinyltetrahydropyran-3-carboxylates.

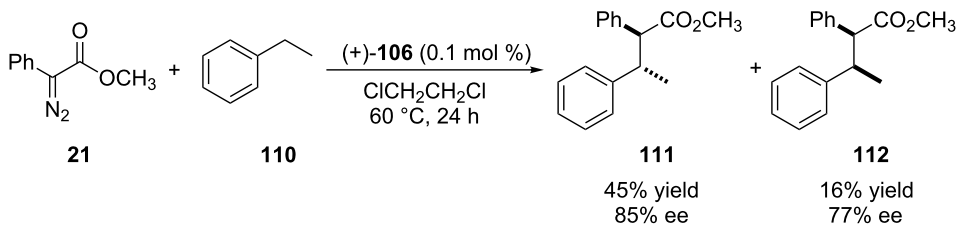
An interesting work was reported by Che and coworkers concerning the first rhodium porphyrin-based catalyst for enantioselective carbenoid insertion into C(sp^3)–H bonds [70]. The reaction with acyclic alkanes showed regioselectivity in favor of the formation of the insertion product into primary carbons in modest stereoselectivity (Scheme 23). The preference for the reaction in less hindered carbon was attributed to high steric demand required by the chiral ligand in the transition state of the carbenoid insertion step in the C(sp^3)–H bond.

Cyclic alkanes were also tested with yields ranging from 64–80% and enantioselectivities between 88 and 92% ee. The reaction with cyclohexane was conducted on a gram scale and, after 10 hours of reaction, 2.88 g (73% yield) were obtained of the carbenoid insertion product in 91% ee. Cyclohexene showed high regioselectivity for the carbenoid insertion of the allylic C(sp^3)–H bond, 43% yield, 71% ee and a 60:40 diastereoisomeric ratio. The formation of the cyclopropanation product was also observed in 14% yield. Ethylbenzene (**110**) was used and also showed high regioselectivity favoring the carbenoid insertion into benzylic C(sp^3)–H bonds (Scheme 24). The diastereoisomers **111** and **112** were obtained in 45% yield and 16%, respectively, and moderate stereoselectivity was observed in both products.

Few examples of attempts to develop heterogeneous catalytic systems based on chiral rhodium complexes were also done. In 2010, Hashimoto and coworkers reported the synthesis of a highly robust polymer-supported chiral dirhodium(II) complex [71]. The chiral part of the catalyst was based on the



Scheme 23: First rhodium porphyrin-based catalyst for enantioselective carbenoid insertion into C(sp^3)–H bond.



Scheme 24: Rhodium porphyrin-based catalyst for enantioselective carbenoid insertion into benzylic C(sp^3)–H bond.

N-phthaloyl-(S)-amino rhodium carboxylate (*S*)-**17d**. Two substrates were submitted to the enantioselective carbenoid insertion into the C(sp^3)–H bond in toluene as solvent and at temperatures ranging from −78 °C to −60 °C. The desired products were obtained in yields up to 80% and enantioselectivity up to 90%, even after 15 recycles of the catalyst.

Jones, Davies and coworkers also recently published a new heterogeneous catalytic cycle base on homogeneous catalyst (*S*)-**23** [72]. The chiral scaffold was covalently supported on silica surface through an organic linker and was tested in a tandem enantioselective carbenoid insertion into C(sp^3)–H bond/Cope rearrangement. The reactions afforded good yields and excellent enantioselectivity. The recycling of the catalyst was evaluated in a cyclopropanation reaction and no significant decrease on its performance could be observed after five runs.

Conclusion

The efforts focused on the development of the enantioselective insertion of carbenoids into C(sp^3)–H bonds have provided a wide range of catalytic systems to the chemical community able to perform this transformation and to introduce new C–C bonds in a enantiocontrolled way. The chiral rhodium catalysts are the state of art of this synthetic tool. However, rhodium is an expensive metal and increases the cost of the chemical process despite the low catalyst loads found in literature.

Despite the good results presented until today, the use of the reported chiral iridium catalysts is even more expensive than the use of other metals such as rhodium, copper and ruthenium, for example. Efforts should be directed toward the development of simpler ligands specially those based on inexpensive chiral building blocks like amino acids and sugars.

The examples of works focused on copper-based catalysts are growing in number and quality. Among the well-known metals able to react with diazo compounds to afford carbenoid intermediates, copper is inexpensive and has a wide range of well-established chiral ligands able to be tested and to inspire the rational design of new ligands.

For all metals commonly used in this transformation, more efforts should be focused towards the development of new and robust heterogeneous catalytic systems. This strategy can reduce the costs related to metals like rhodium or iridium and can also contribute to reduce the disposal of these metals in the environment.

Acknowledgements

We thank the Brazilian National Research Council (CNPq, Gran Nos. 477418/2013-9), the Brazilian Coordination for the Improvement of Higher Education Level Personnel (CAPES), Distrito Federal Research Foundation (FAPDF, Gran Nos. 193.001.049/2015), FINEP-MCT and DPP-UnB for financial support and fellowships.

References

1. Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010,** *110,* 704–724. doi:10.1021/cr900239n
2. Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003,** *103,* 2861–2904. doi:10.1021/cr0200217
3. Yates, P. *J. Am. Chem. Soc.* **1952,** *74,* 5376–5381. doi:10.1021/ja01141a047
4. Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982,** *47,* 4808–4809. doi:10.1021/jo00145a050
5. Mbuvi, H. M.; Woo, L. K. *Organometallics* **2008,** *27,* 637–645. doi:10.1021/om7007502
6. Maas, G.; Werle, T.; Alt, M.; Mayer, D. *Tetrahedron* **1993,** *49,* 881–888. doi:10.1016/S0040-4020(01)80330-6
7. Kubo, T.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* **2000,** 625–626. doi:10.1039/B000518P
8. Woo, L. K.; Smith, D. A. *Organometallics* **1992,** *11,* 2344–2346. doi:10.1021/om00043a011
9. Müller, P.; Boléa, C. *Helv. Chim. Acta* **2002,** *85,* 483–494. doi:10.1002/1522-2675(200202)85:2<483::AID-HLCA483>3.0.CO;2-Q
10. Flynn, C. J.; Elcoate, C. J.; Lawrence, S. E.; Maguire, A. R. *J. Am. Chem. Soc.* **2010,** *132,* 1184–1185. doi:10.1021/ja909713a
11. Slattery, C. N.; Maguire, A. R. *Tetrahedron Lett.* **2013,** *54,* 2799–2801. doi:10.1016/j.tetlet.2013.03.078
12. Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002,** *124,* 7181–7192. doi:10.1021/ja017823o
13. Ye, T.; García, F. C.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1995,** 1373–1379. doi:10.1039/P19950001373
14. Ye, T.; McKervey, M. A.; Brandes, B. D.; Doyle, M. P. *Tetrahedron Lett.* **1994,** *35,* 7269–7272. doi:10.1016/0040-4039(94)85379-7
15. Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc., Chem. Commun.* **1990,** 361–362. doi:10.1039/C39900000361
16. McKervey, M. A.; Ye, T. *J. Chem. Soc., Chem. Commun.* **1992,** 823–824. doi:10.1039/C39920000823
17. Roos, G. H. P.; McKervey, M. A. *Synth. Commun.* **1992,** *22,* 1751–1756. doi:10.1080/00397919208020494
18. Doyle, M. P. *Chem. Rev.* **1986,** *86,* 919–939. doi:10.1021/cr00075a013
19. Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1999,** *121,* 1417–1418. doi:10.1021/ja983748e
20. Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosh, R. *J. Am. Chem. Soc.* **1993,** *115,* 9968–9978. doi:10.1021/ja00075a013
21. Timmons, D. J.; Doyle, M. P. *J. Organomet. Chem.* **2001,** *617–618,* 98–104. doi:10.1016/S0022-328X(00)00637-9
22. Doyle, M. P.; Ren, T. The Influence of Ligands on Dirhodium(II) on Reactivity and Selectivity in Metal Carbene Reactions. In *Progress in Inorganic Chemistry;* Karlin, K. D., Ed.; John Wiley & Sons: Hoboken, NJ, U.S.A., 2001; Vol. 49, pp 113–168. doi:10.1002/9780470166512.ch2
23. Doyle, M. P. *Russ. Chem. Bull.* **1999,** *48,* 16–20. doi:10.1007/BF02494393

24. McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992,** *33,* 5983–5986. doi:10.1016/S0040-4039(00)61106-1
25. Pirrung, M. C.; Zhang, J. *Tetrahedron Lett.* **1992,** *33,* 5987–5990. doi:10.1016/S0040-4039(00)61107-3
26. Estevan, F.; Herbst, K.; Lahuerta, P.; Barberis, M.; Pérez-Prieto, J. *Organometallics* **2001,** *20,* 950–957. doi:10.1021/om0010060
27. Estevan, F.; Lahuerta, P.; Pérez-Prieto, J.; Sanaú, M.; Stiriba, S.-E.; Ubeda, M. A. *Organometallics* **1997,** *16,* 880–886. doi:10.1021/om9608162
28. Taber, D. F.; Malcolm, S. C.; Bieger, K.; Lahuerta, P.; Sanaú, M.; Stiriba, S.-E.; Pérez-Prieto, J.; Monge, M. A. *J. Am. Chem. Soc.* **1999,** *121,* 860–861. doi:10.1021/ja9819559
29. Estevan, F.; Lahuerta, P.; Pérez-Prieto, J.; Pereira, I.; Stiriba, S.-E. *Organometallics* **1998,** *17,* 3442–3447. doi:10.1021/om971070q
30. Lahuerta, P.; Pereira, I.; Pérez-Prieto, J.; Sanaú, M.; Stiriba, S.-E.; Taber, D. F. *J. Organomet. Chem.* **2000,** *612,* 36–45. doi:10.1016/S0022-328X(00)00357-0
31. Davies, H. M. L.; Denton, J. R. *Chem. Soc. Rev.* **2009,** *38,* 3061–3071. doi:10.1039/b901170f
32. Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009,** *38,* 3242–3272. doi:10.1039/b816707a
33. Ledon, H.; Linstrumelle, G.; Julia, S. *Tetrahedron Lett.* **1973,** *14,* 25–28. doi:10.1016/S0040-4039(01)95567-4
34. Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985,** *107,* 196–199. doi:10.1021/ja00287a035
35. Taber, D. F.; Ruckle, R. E. *J. Am. Chem. Soc.* **1986,** *108,* 7686–7693. doi:10.1021/ja00284a037
36. Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *J. Org. Chem.* **1991,** *56,* 1434–1439. doi:10.1021/jo00004a019
37. Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993,** *115,* 958–964. doi:10.1021/ja00056a021
38. Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966,** *43,* 5239–5244. doi:10.1016/S0040-4039(01)89263-7
39. Hashimoto, S.-i.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990,** *31,* 5173–5174. doi:10.1016/S0040-4039(00)97834-1
40. Doyle, M. P.; Van Oeveren, A.; Westrum, L. J.; Protopopova, M. N.; Clayton, T. W., Jr. *J. Am. Chem. Soc.* **1991,** *113,* 8982–8984. doi:10.1021/ja00023a077
41. Davies, H. W. L.; Hansen, T. *J. Am. Chem. Soc.* **1997,** *119,* 9075–9076. doi:10.1021/ja971915p
42. Hansen, J.; Autschbach, J.; Davies, H. M. L. *J. Org. Chem.* **2009,** *74,* 6555–6563. doi:10.1021/jo9009968
43. Slattery, C. N.; Clarke, L.-A.; O'Neill, S.; Ring, A.; Ford, A.; Maguire, A. R. *Synlett* **2012,** 765–767. doi:10.1055/s-0031-1290598
44. Slattery, C. N.; Clarke, L.-A.; Ford, A.; Maguire, A. R. *Tetrahedron* **2013,** *69,* 1297–1301. doi:10.1016/j.tet.2012.12.003
45. Slattery, C. N.; O'Keeffe, S.; Maguire, A. R. *Tetrahedron: Asymmetry* **2013,** *24,* 1265–1275. doi:10.1016/j.tetasy.2013.09.009
46. Clarke, L. A.; Ring, A.; Ford, A.; Sinha, A. S.; Lawrence, S. E.; Maguire, A. R. *Org. Biomol. Chem.* **2014,** *12,* 7612–7628. doi:10.1039/c4ob01430h
47. Fraile, J. M.; García, J. I.; Mayoral, J. A.; Roldán, M. *Org. Lett.* **2007,** *9,* 731–733. doi:10.1021/ol070092y
48. Fraile, J. M.; López-Ram-de-Viu, P.; Mayoral, J. A.; Roldán, M.; Santafé-Valero, J. *Org. Biomol. Chem.* **2011,** *9,* 6075–6081. doi:10.1039/c1ob05499f
49. Fraile, J. M.; Mayoral, J. A.; Muñoz, A. M.; Santafé-Valero, J. *Tetrahedron* **2013,** *69,* 7360–7364. doi:10.1016/j.tet.2013.06.088
50. Fraile, J. M.; Mayoral, J. A.; Ravasio, N.; Roldán, M.; Sordelli, L.; Zaccheria, F. *J. Catal.* **2011,** *281,* 273–278. doi:10.1016/j.jcat.2011.05.008
51. Suematsu, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009,** *131,* 14218–14219. doi:10.1021/ja9065267
52. Wang, J.-C.; Xu, Z.-J.; Guo, Z.; Deng, Q.-H.; Zhuo, C.-Y.; Wan, X.-L.; Che, C.-M. *Chem. Commun.* **2012,** *48,* 4299–4301. doi:10.1039/c2cc30441d
53. Wang, J.-C.; Zhang, Y.; Xu, Z.-J.; Lo, V. K.-Y.; Che, C.-M. *ACS Catal.* **2013,** *3,* 1144–1148. doi:10.1021/cs4001656
54. Owens, C. P.; Varela-Álvarez, A.; Boyarskikh, V.; Musaev, D. G.; Davies, H. M. L.; Blakey, S. B. *Chem. Sci.* **2013,** *4,* 2590–2596. doi:10.1039/c3sc50886b
55. Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015,** *115,* 9981–10080. doi:10.1021/acs.chemrev.5b00121
56. Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011,** *40,* 1857–1869. doi:10.1039/C0CS00217H
57. Nadeau, E.; Ventura, D. L.; Brekan, J. A.; Davies, H. M. L. *J. Org. Chem.* **2010,** *75,* 1927–1939. doi:10.1021/jo902644f
58. Qin, C.; Boyarskikh, V.; Hansen, J. H.; Hardcastle, K. I.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011,** *133,* 19198–19204. doi:10.1021/ja2074104
59. Davies, H. M. L.; Lian, Y. *Acc. Chem. Res.* **2012,** *45,* 923–935. doi:10.1021/ar300013t
60. Qin, C.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014,** *136,* 9792–9796. doi:10.1021/ja504797x
61. Guptill, D. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014,** *136,* 17718–17721. doi:10.1021/ja5107404
62. Wang, H.; Li, G.; Engle, K. M.; Yu, J.-Q.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013,** *135,* 6774–6777. doi:10.1021/ja401731d
63. Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014,** *136,* 17738–17749. doi:10.1021/ja510573v
64. Fu, L.; Wang, H.; Davies, H. M. L. *Org. Lett.* **2014,** *16,* 3036–3039. doi:10.1021/ol5011505
65. Natori, Y.; Tsutsui, H.; Sato, N.; Nakamura, S.; Nambu, H.; Shiro, M.; Hashimoto, S. *J. Org. Chem.* **2009,** *74,* 4418–4421. doi:10.1021/jo900502d
66. Ito, M.; Namie, R.; Krishnamurthi, J.; Miyamae, H.; Takeda, K.; Nambu, H.; Hashimoto, S. *Synlett* **2014,** 288–292. doi:10.1055/s-0033-1340291
67. Wakimoto, T.; Miyata, K.; Ohuchi, H.; Asakawa, T.; Nukaya, H.; Suwa, Y.; Kan, T. *Org. Lett.* **2011,** *13,* 2789–2791. doi:10.1021/ol200728w
68. McMills, M. C.; Humes, R. J.; Pavlyuk, O. M. *Tetrahedron Lett.* **2012,** *53,* 849–851. doi:10.1016/j.tetlet.2011.12.019
69. Ito, M.; Kondo, Y.; Nambu, H.; Anada, M.; Takeda, K.; Hashimoto, S. *Tetrahedron Lett.* **2015,** *56,* 1397–1400. doi:10.1016/j.tetlet.2015.01.125
70. Thu, H.-Y.; Tong, G. S.-M.; Huang, J.-S.; Chan, S. L.-F.; Deng, Q.-H.; Che, C.-M. *Angew. Chem., Int. Ed.* **2008,** *47,* 9747–9751. doi:10.1002/anie.200803157
71. Takeda, K.; Oohara, T.; Anada, M.; Nambu, H.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2010,** *49,* 6979–6983. doi:10.1002/anie.201003730
72. Chepiga, K. M.; Feng, Y.; Brunelli, N. A.; Jones, C. W.; Davies, H. M. L. *Org. Lett.* **2013,** *15,* 6136–6139. doi:10.1021/ol403006r

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.87

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

The synthesis of functionalized bridged polycycles via C–H bond insertion

Jiun-Le Shih, Po-An Chen and Jeremy A. May*

Review

Open Access

Address:
Department of Chemistry, University of Houston, 3585 Cullen Blvd., Fleming Bldg. Room 112, Houston, TX 77204-5003, United States

Email:
Jeremy A. May* - jmay@uh.edu

* Corresponding author

Keywords:
bridged rings; carbene; cascade reaction; C–H bond insertion; nitrene

Beilstein J. Org. Chem. **2016,** *12,* 985–999.
doi:10.3762/bjoc.12.97

Received: 11 February 2016
Accepted: 28 April 2016
Published: 17 May 2016

This article is part of the Thematic Series "C–H Functionalization/activation in organic synthesis".

Guest Editor: R. Sarpong

© 2016 Shih et al; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

This review presents examples from the chemical literature of syntheses of bridged-polycyclic products via C–H bond insertion by carbenes and nitrenes. Applications to natural product synthesis, a description of the essential elements in substrate-controlled reactions, and mechanistic details of transformations are presented. Overall, these transformations allow the construction of important ring systems rapidly and efficiently, though additional catalyst development is needed.

Introduction

Bridged polycyclic natural products are an inviting challenge to the synthetic chemist for their rich display of functional groups, densely packed structures, and inherent architectural three-dimensionality. Many of these compounds exhibit biological activity that is potentially useful (Figure 1) [1-12]. Of these, some exhibit exquisite selectivity for a single target, presumably because their rigid structures restrict molecular conformations for binding to multiple biological entities. Given the natural scarcity of most of these compounds, few have been extensively screened for biological activity, and some have not been tested at all.

Unsurprisingly, many synthetic strategies for the construction of bridged rings have been reported. These methods usually rely on existing functional groups to build the rings, consequently leading to the synthesis of a single isomer. To access a different isomer, either the synthetic sequence must be revised to install the key functional groups at alternative positions, or the synthetic strategy must be completely altered as the original method is not capable of synthesizing other isomers. For example, multiple research groups have shown that the bridged bicyclo[2.2.2]octane core **1** of maoecrystal V may be constructed via an intramolecular Diels–Alder reaction from a functionali-

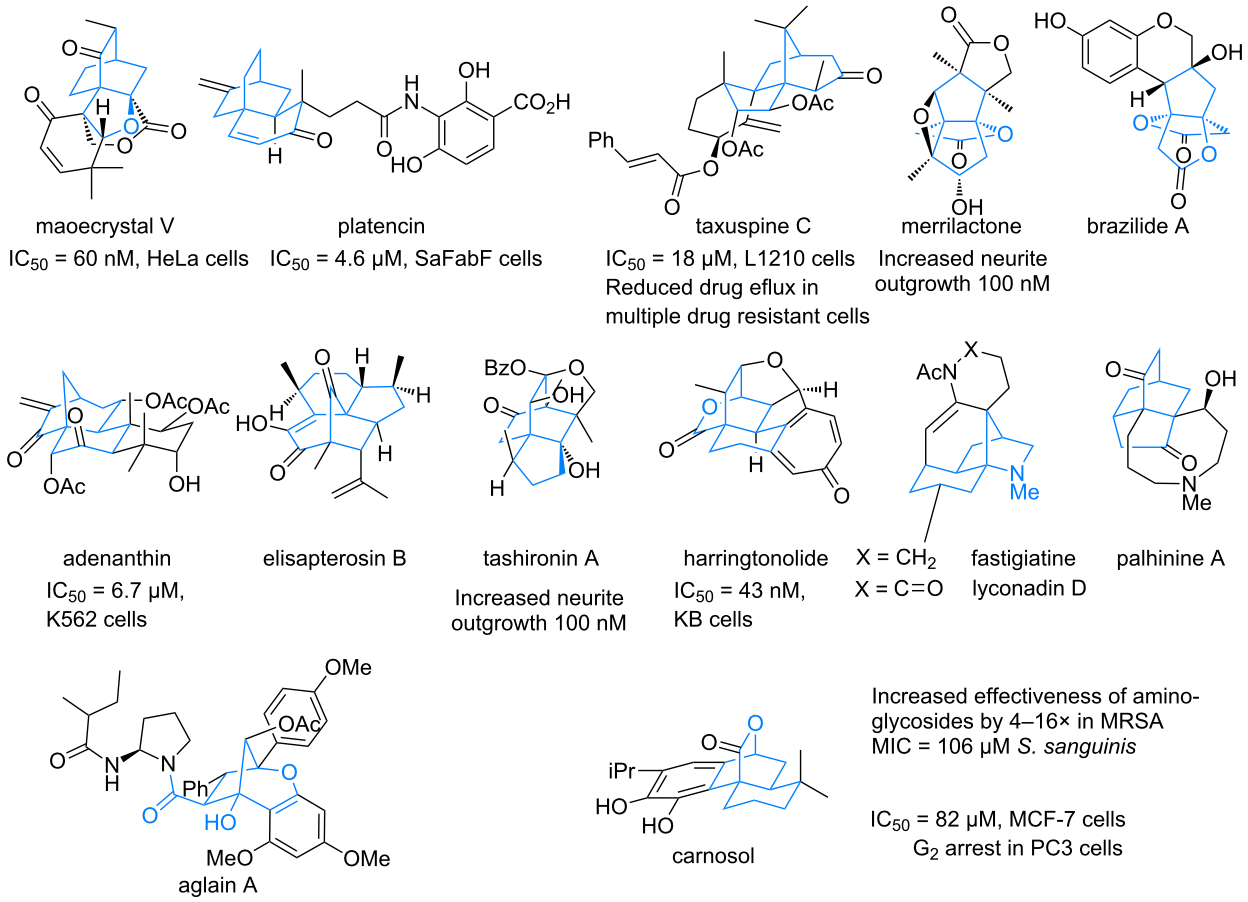


Figure 1: Bridged polycyclic natural products.

zed 1,3-diene like **2** (Figure 2) [13-16]. However, such a reaction would not be applicable to synthesize the bicyclo[3.2.1]-octane core **3** of taxuspine C, as the mechanistic requirements in a Diels–Alder cycloaddition are not met with a 1,4-diene.

Strategies that may access multiple structural isomers of bridged polycycles from a common intermediate offer multiple advantages: saved time and effort by avoiding the validation of new strategies for each target, accumulated understanding of the

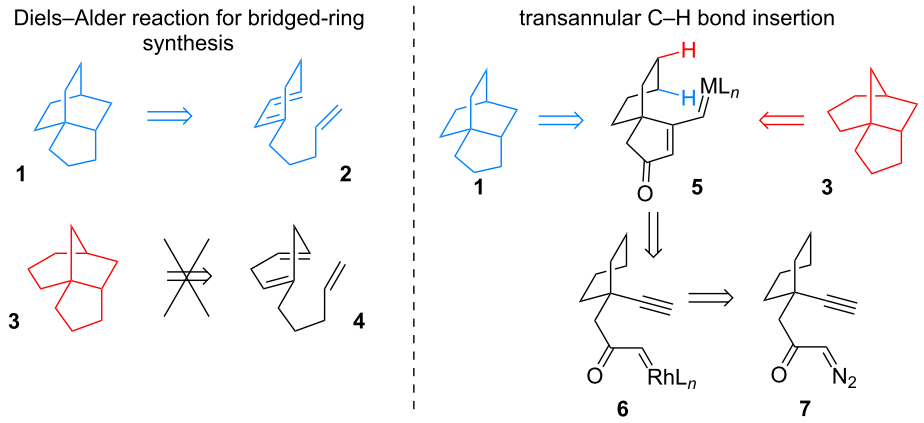


Figure 2: Strategic limitations.

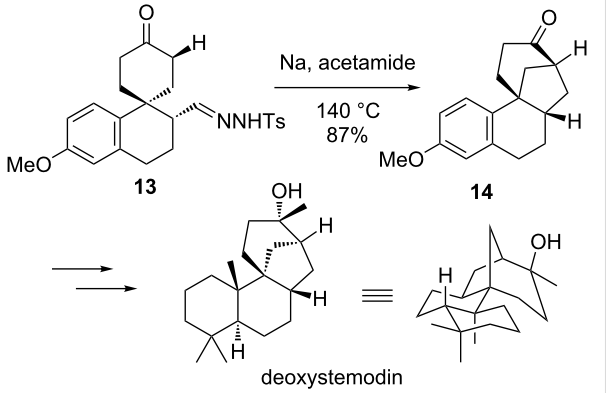
key reactions in the strategy for higher yields and improved efficiency, and rapid access to multiple targets from a single intermediate produced on large scale that may be stored until needed [17]. The C–H bond insertion has great potential as a method to access different polycyclic isomers (e.g., **1** or **3**) through C–C or C–N bond formation from a carbene or nitrene, respectively, without having to preinstall functional groups at those positions (Figure 2). Ideally, the choice of catalyst or reagent would control the product formed. The transformation of **5** to **1** or **3** could occur in a single-bond-forming event, or multiple rings could be synthesized in a cascade reaction (i.e., **6** to **1** or **3**).

This review highlights strategies that leverage C–H bond insertion by carbenes and nitrenes to construct bridged polycycles. This key bond-forming event may construct the bridged ring, or it may construct an additional ring fused to an existing bridged bicycle to synthesize the bridged-polycyclic product. While some examples of bridged-azacycle formation via N–H bond insertion are known (Scheme 1) [18,19], they are less common. We note that the development of synthetic methods to access the goal portrayed in Figure 2 is still in the early stages, with most of the work discussed having been reported within the last decade. Taken together, this work has elucidated many of the substrate factors that control the reaction. The development of catalysts to control isomer formation has yet to be achieved, though it is our hope that this review will inspire efforts for their development. We have organized this review by the catalyst used, with free carbenes first, followed by Cu, Rh, Au, Pt, and then W-catalyzed reactions.

Review

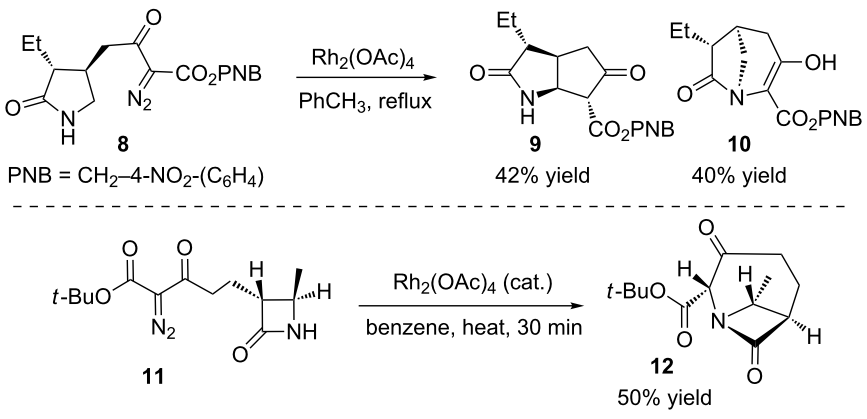
Metal-free reactions

While transition metal catalysis has seen widespread adoption for carbene and nitrene reactions, it is not necessary for a controlled reaction in all cases. Chatterjee reported an early example of building bridged-polycyclic intermediates using metal-free carbenes in 1979 (Scheme 2) [20]. Exposing the tosylhydrazone **13** to base and heat generated an alkyl carbene that inserted into the C–H bond of an adjacent ring. Surprisingly, the insertion reaction was more rapid than a 1,2-hydride shift or rearrangement, and the bridged product **14** was obtained in 87% yield. This compound was advanced to synthesize the natural product deoxystemodin [21-25].



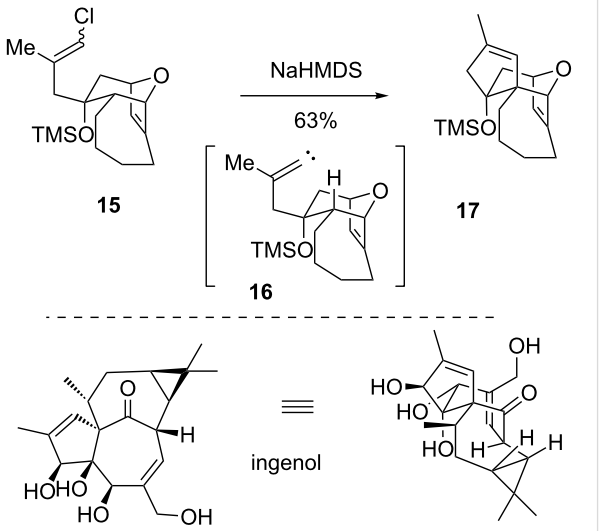
Scheme 2: The synthesis of deoxystemodin.

Grainger reported an approach to synthesize the bridged core of ingenol via C–H insertion (Scheme 3) [26]. Here, an existing bridged ring with a pendant vinyl chloride was synthesized (see **15**). The addition of base promoted the formation of a vinylidene carbene **16**, which then inserted into the more electron-rich methine C–H bond to generate the fused cyclopentenyl ring in **17**. While this intermediate was not advanced in a total synthesis of the natural product, it demonstrates the potential of the strategy. Additionally, the reaction was described to proceed through the lowest energy conformation of the carbene interme-



Scheme 1: Bridged rings from N–H bond insertions.

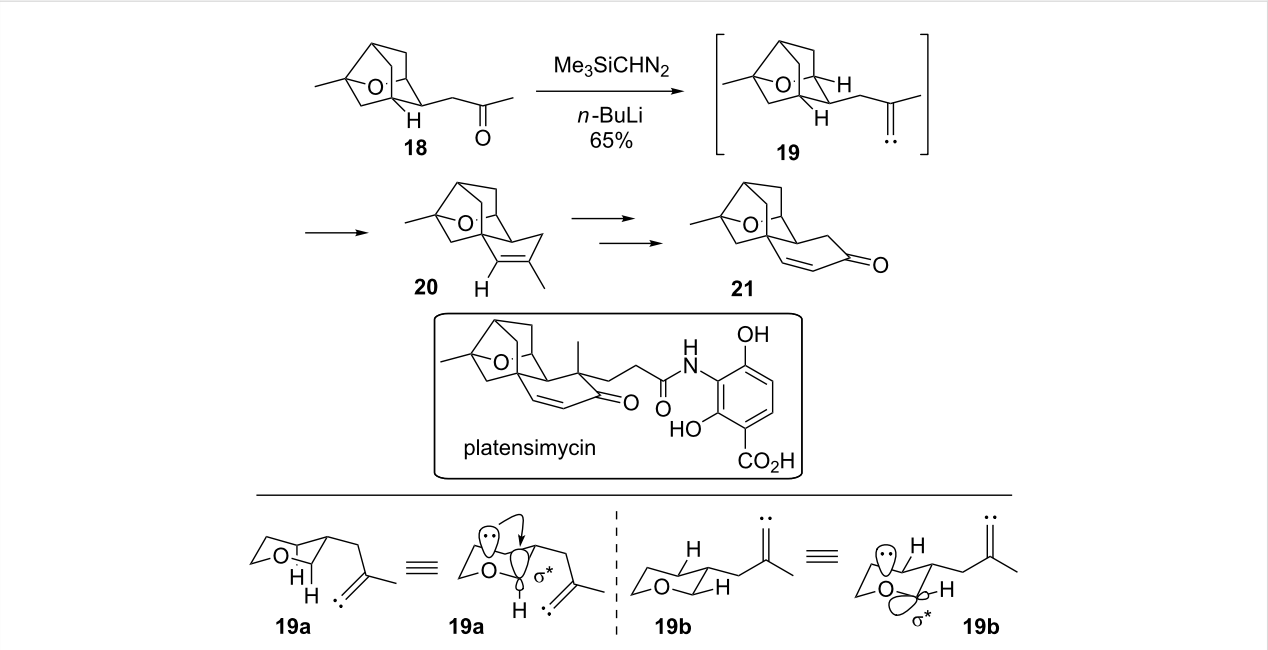
diate **16**, but an extensive study of conformational effects was not reported.



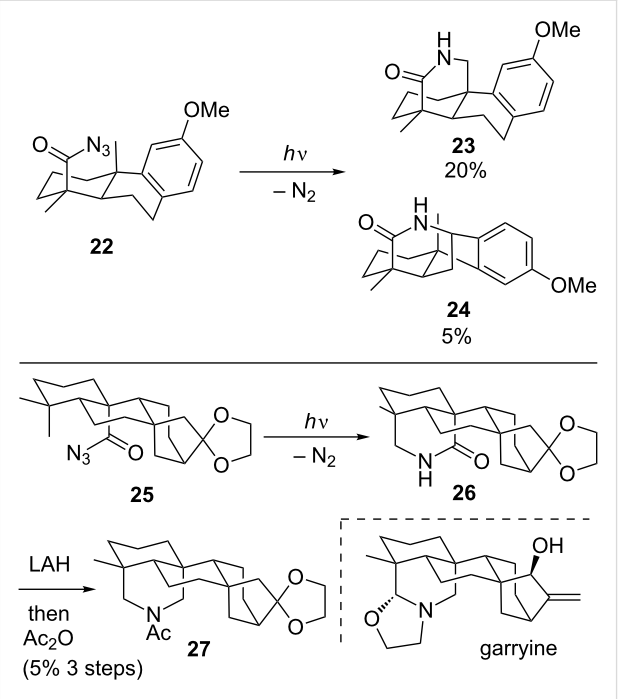
Scheme 3: A model system for ingenol.

More recently, Lee showed that vinylidene carbenes could be used to build the ring-fused bridged system **21** found in platensimycin (Scheme 4) [27]. The vinylidene carbene **19** preferentially inserted into the C–H bond further from the oxygen, which is contrary to many intramolecular studies that have found that heteroatoms accelerate C–H bond insertion at adjacent carbons. The Lee group performed further studies on the electronic effects of the oxygen on the rate of bond insertion, and concluded that the ability of the oxygen lone pair to align with the σ* orbital of the C–H bond targeted for insertion (see illustration **19a**) is required for rate acceleration. Equatorial C–H bonds adjacent to endocyclic oxygens cannot achieve the correct orbital alignment (see illustration **19b**), and so the electronegativity of the oxygen actually deactivates insertion into the equatorial C–H bond. This is the case for carbene **19**, since the alkyl bridge locks its conformation in such a way that prevents an activating alignment, and the oxygen acts as an inductive electron-withdrawing group. The alkene in the cyclopentene of **20** was oxidatively cleaved, and then an aldol condensation gave the cyclohexenone **21**, which was an intermediate in Nicolau's platensimycin synthesis [28].

Carbenes are not the only species that have been used to build bridged polycycles without metal catalysts. Masamune demonstrated that the nitrene generated from the acyl azide **22** via ultraviolet irradiation inserted into a nearby methyl group to give **23** (Scheme 5) [29,30]. Competition with a transannular benzylic C–H insertion to give **24** was a minor outcome. This initial study provided a model system to confirm the proposed stereochemistry of atisine. A later study using the substrate **25** that lacked the benzylic C–H bond led to a formal total synthesis of garryine, which is closely related to atisine. The initial lactam **26** that was formed by methyl C–H insertion was quite unstable, and so it was quickly converted to the acetamide **27**. Advancing that intermediate intercepted a route to garryine completed by Pelletier [31].



Scheme 4: Formal synthesis of platensimycin.



Scheme 5: The formal synthesis of gerryine.

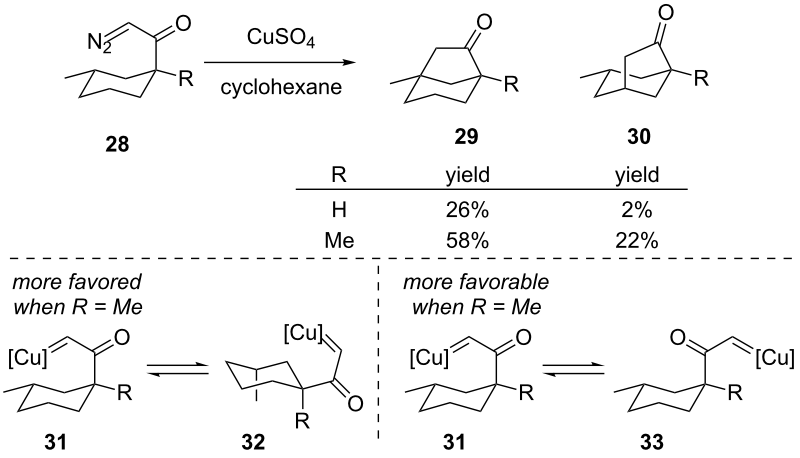
Metal-catalyzed reactions

Copper

The earliest example to our knowledge of transition metal catalysis for the formation of bridged rings via C–H bond insertion was Wolff's use of copper (Scheme 6) [32,33]. Silver was also examined as a possible catalyst, but then a Wolff rearrangement was the primary outcome. The major product with copper was insertion into the more electron-rich methine to give bicyclo[3.2.1]octane **29**. The yields of both transannular C–H insertion products were increased relative to the Wolff rearrangement when a methyl group was present on the cyclohexyl carbon bearing the diazoketone (**28**, R = Me). There are two reasons this methyl substituent affects the reaction: firstly, it helps favor a ring conformation where the copper carbene derived from the diazoketone is axially disposed (see **32**) and thus is closer to the C–H bonds for insertion. Secondly, the methyl group helps bias the rotation about the ketone–cyclohexyl bond so that the carbene may be conformationally disposed over the ring as shown in **31** instead of the exocyclic conformation **33**.

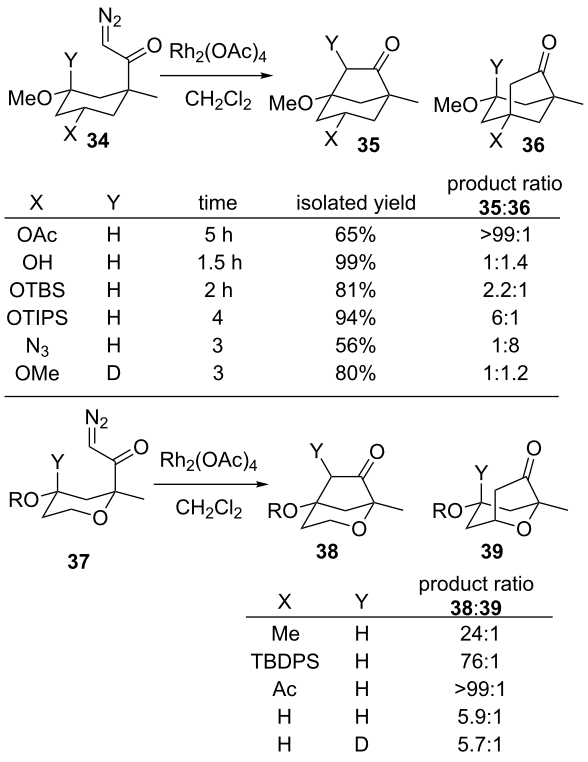
Rhodium

The most common metal seen in C–H bond insertions for the formation of bridged rings is rhodium. Adams used $Rh_2(OAc)_4$ to further develop Wolff's early work to determine selectivity patterns for transannular insertions (Scheme 7) [34,35]. His group examined the effects of heteroatom substituents such as ethers and an azide in the 3-methoxycyclohexyl substrate **34**. The observed patterns largely mirrored those found in intramolecular C–H bond insertions to form monocyclic and fused bicyclic rings [36-59]. The stronger the electron donor, the greater the observed insertion at the C–H bond on the carbon with that donor. For example, insertion at the methoxy-substituted carbon to give **35** (X = OAc) occurred more rapidly than at an acetoxy-substituted carbon to form **36**. Sterics also seemed to play a role, as insertion near a TIPS ether in **36** (X = OTIPS) was less than that for a TBS ether (**36**, X = OTBS) [60]. A hydroxy group had a similar effect to the methoxy substituent, and the azide was the only group to activate the C–H bond more than a methoxy group. Interestingly, the endocyclic oxygen in substrate **37** was not nearly as effective at activating the adjacent C–H bond for insertion to give **39** as the exocyclic oxygen was to provide **38**, even when the exocyclic oxygen was acetylated. This is likely related to the effects observed by Lee (Scheme 4). The Adams group also looked for a deuterium



Scheme 6: Copper-catalyzed bridged-ring synthesis.

kinetic isotope effect for insertion in both **34** (Y = D, X = OMe) and **37** (Y = D, R = H). Only a small difference in relative rates between C–H and C–D bond insertion was seen for either substrate (e.g., compare **35** to **36**, Y = D, X = OMe). Adams proposed that a late transition state must be operative for insertion, and so the isotope effect was not pronounced.



X	Y	time	isolated yield	product ratio 35:36
OAc	H	5 h	65%	>99:1
OH	H	1.5 h	99%	1:1.4
OTBS	H	2 h	81%	2.2:1
OTIPS	H	4	94%	6:1
N_3	H	3	56%	1:8
OMe	D	3	80%	1:1.2

X	Y	product ratio 38:39
Me	H	24:1
TBDPS	H	76:1
Ac	H	>99:1
H	H	5.9:1
H	D	5.7:1

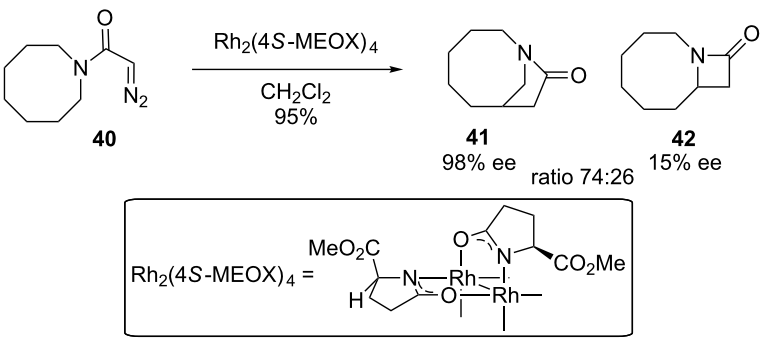
Scheme 7: Factors influencing insertion selectivity.

Doyle expanded the scope of the potential bridged products through the use of diazoacetamides (Scheme 8) [61]. He found an important example of a transformation where the ratio of gamma vs beta-lactam formation could be controlled to a significant extent by catalyst choice. In particular, $Rh_2(4S\text{-MEOX})_4$ favored the bridged γ-lactam **41** over the fused β-lactam **42** in about a 3:1 ratio. The conformation of the cyclooctyl ring may also play a role in the selectivity as discussed below.

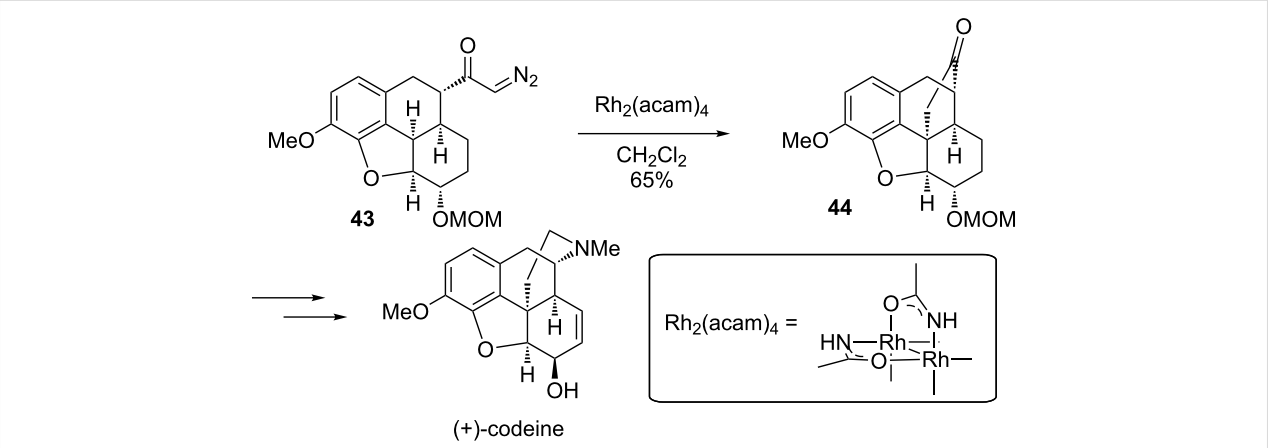
The White group used rhodium dimers as catalysts to form the central quaternary carbon of (+)-codeine (Scheme 9) [62]. This insertion into the benzylic methine of **43** was quite selective, with only a single reported product. The formation of this hindered carbon stereocenter could be potentially quite difficult otherwise. While a slightly better yield for the insertion was obtained if the OMOM ether was replaced with a ketone functional group, that product was problematic in attempts to advance it to codeine. It is notable that the intramolecular C–H bond insertion to form the bridged polycycle was significantly faster than an intermolecular insertion into the MOM acetal methylene, which would be electronically activated by the two flanking oxygen substituents.

Later, Magnus showed that a conformationally flexible fused bicycle like **45** was also viable as a substrate for bridged-ring synthesis (Scheme 10) [63]. While a conformational flip to the other chair form **47** is perhaps more favored energetically, the insertion into the proximal C–H bonds in **47** would lead to a cyclobutanone, which is apparently slower than the ring flip and transannular insertion by an axially disposed ketocarbene into an axial C–H bond. Magnus noted that **46** bears a striking resemblance to the bridged polycyclic lactone core of irroratin and proposed that this method could be used for its synthesis.

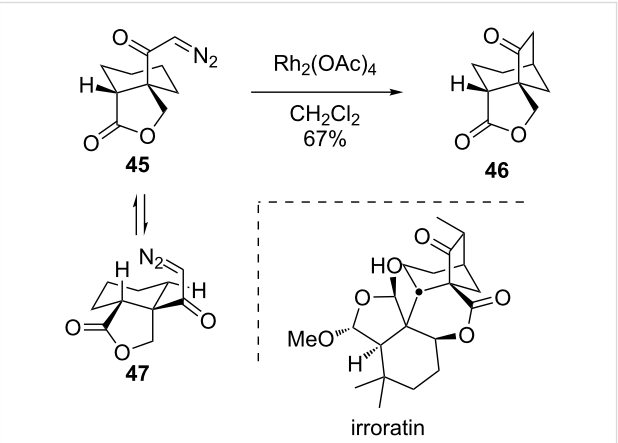
The discovery by Du Bois that carbenes and nitrenes generated from sulfonate esters prefer 6-membered ring formation (i.e., 1,6-insertion) opened the door for easy access to 1,3-functionalized products via C–H insertion [64,65]. The sulfonate can be a useful functional group for subsequent transformations, also. If used in the presence of an attached ring as in **48**, the 1,6-insertion produced the bridged-bicyclic product **49** (Scheme 11) [66].



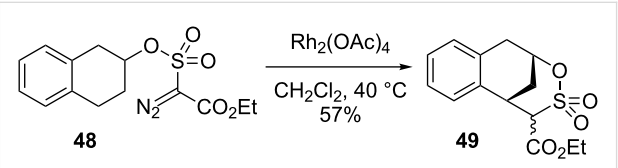
Scheme 8: Bridged-lactam formation.



Scheme 9: The total synthesis of (+)-codeine.

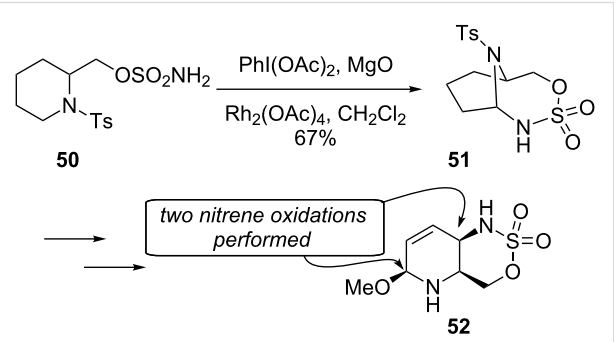


Scheme 10: A model system for irroratin.



Scheme 11: The utility of 1,6-insertion.

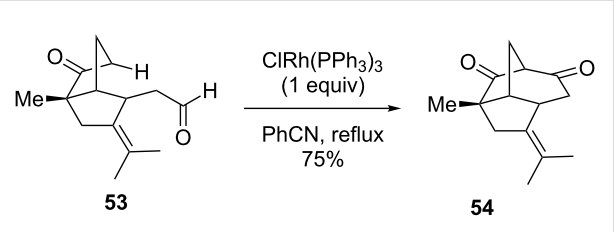
The Compain group leveraged this innovation in the synthesis of functionalized piperidines (Scheme 12) [67]. By using the piperidine **50**, an initial insertion into the amine-activated C–H bond generated the tosylamine-bridged bicycle **51**. The aminal in **51** could be transformed to a methyl hemiaminal, and then later a second C–H bond insertion by another nitrene targeted the less activated C–H bond to form the ring-fused piperidine **52**. Thus, the pendant sulfonamide acted as a tool for multiple remote functionalizations on the piperidine ring. Many examples of the sequence with different piperidines were also reported. The resulting 3-amino-2,6-disubstituted piperidines



Scheme 12: Piperidine functionalization.

like **52** are known to display anti-allergic and anti-inflammatory activities.

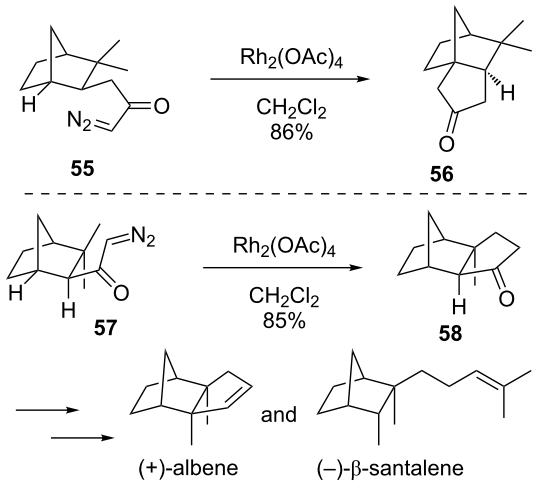
Rao generated a bridged polycycle via a formal C–H bond insertion using Wilkinson's catalyst ($RhCl(PPh_3)_3$) instead of the usual rhodium(II) dimer (Scheme 13) [68]. Rather than starting with a diazoketone, ester, or amide, Wilkinson's catalyst may generate an active organorhodium intermediate through insertion into the acyl C–H bond of the aldehyde **53**. A subsequent transannular C–H functionalization at the site of a weakly acidic proton then produces the bridged product **54**. While an innovative transformation, it should be noted that a



Scheme 13: Wilkinson's catalyst for C–H bond insertion.

full equivalent of Wilkinson's catalyst is needed as there is no catalytic turnover observed.

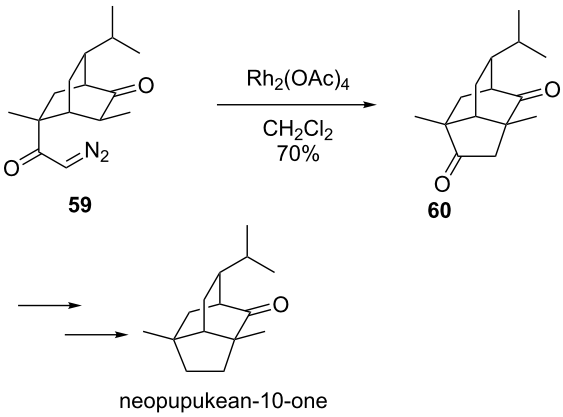
Bridged polycycles may also be accessed synthetically by the formation of a new ring on an existing bridged bicycle via C–H bond insertion. Early results for this approach using rhodium(II) dimers were disclosed by Sonowane [69,70]. He found that the tether length of the diazoketone to the bridged ring had a profound effect on the preferred C–H insertion location (Scheme 14). As has been noted for other intramolecular insertions [42-65], five-membered ring formation is generally preferred over other ring sizes. Thus, the diazopropanone-substituted norbornane **55** saw insertion into the bridgehead C–H methine to generate the cyclopentanone-fused norbornane **56**. However, the shorter tether in diazoethanone-substituted **57** would form a cyclobutanone-fused product if bridgehead insertion occurred, and so insertion into a methyl C–H bond was preferred to give a different cyclopentanone-fused norbornane, **58**. This latter intermediate was used in the total syntheses of (+)-albene and (−)-β-santalene.



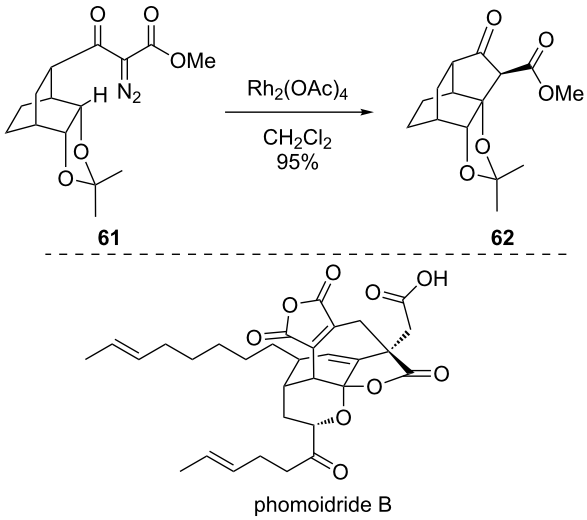
Scheme 14: Bridgehead insertion and the total synthesis of albene and santalene.

Srikrishna found that caged polycycles could be similarly formed via a transannular insertion [71-75]. His group synthesized isotwistanes (2)-neopupukean-4,10-dione, (2)-neopupukean-10-one (shown), 2-thiocyanatoneopupukeanane, (−)-2-pupukeanone, (−)-4-thiocyanatoneopupukeanane, and (±)-9-isocyanoneopupukeanane from carvone all with a nearly identical strategy to that in Scheme 15.

The Wood group applied a similar strategy toward the synthesis of phomoidride B (Scheme 16) [76]. While this strategy was ultimately not productive for the total synthesis of the natural



Scheme 15: The total synthesis of neopupukean-10-one.

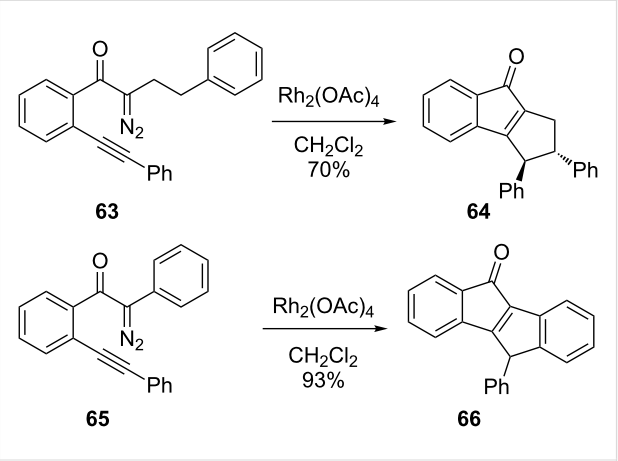


Scheme 16: An approach to phomoidride B.

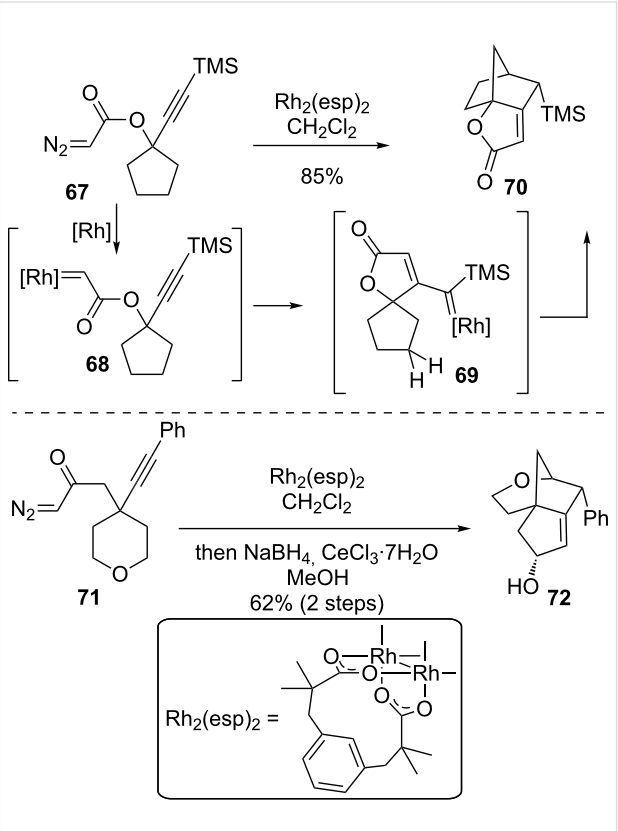
product, it did synthesize the key synthetic intermediate **62** very rapidly by taking advantage of insertion into the ether-activated C–H bond of **61**.

A carbene cascade reaction coupled with C–H bond insertion offers the potential to build both the bridged bicycle and additional fused rings in a single reaction (see Figure 2). The foundation of this strategy was laid by Hoye and Padwa [77-85]. Some substrates with a well-defined C–H bond insertion as the final step were reported, though these generally produced fused polycycles (Scheme 17) [86].

The May group took advantage of this cascade to synthesize bridged polycycles from monocyclic precursors [87-89]. Both diazoesters and diazoketones were examined for their potential to initiate the cascade (Scheme 18). While the exact mechanis-



Scheme 17: Carbene cascade for fused bicycles.

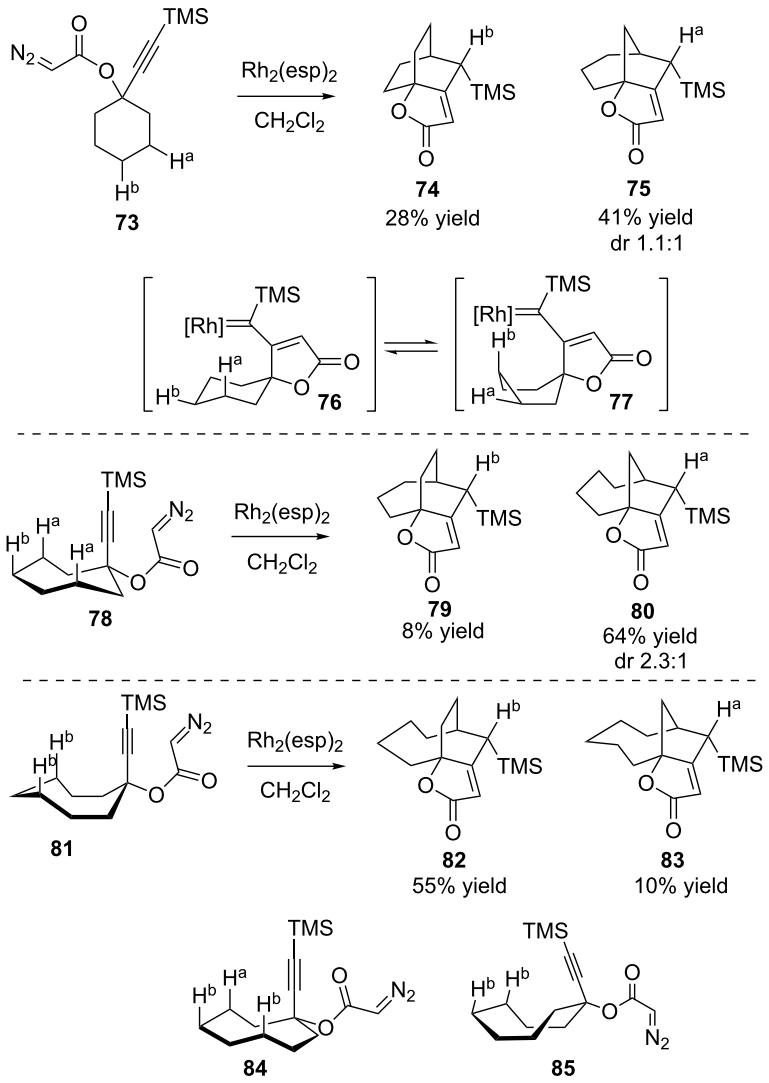


Scheme 18: Cascade formation of bridged rings.

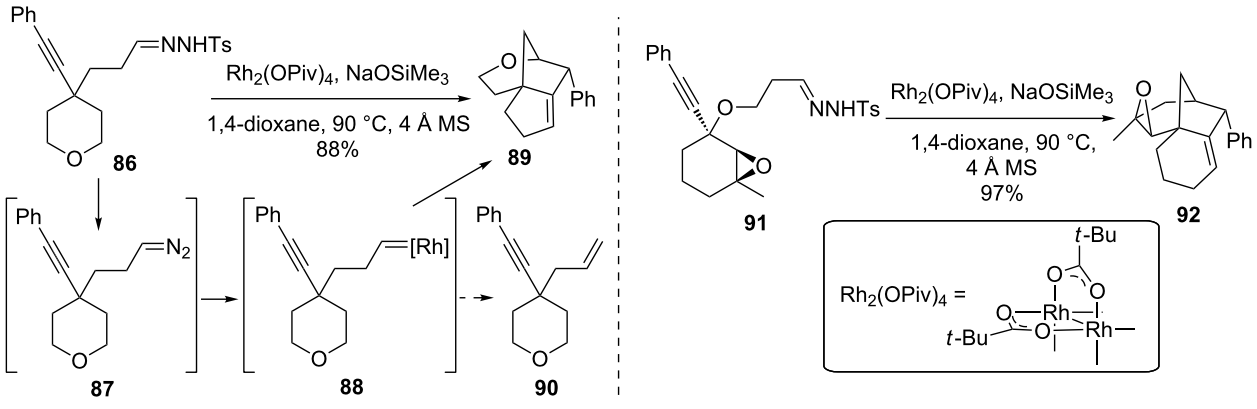
tic intermediates for this transformation have not been conclusively defined [90], the reaction may be thought of as proceeding through an initial dediazotization to form a rhodium carbene, **68**, reaction with the alkyne to generate the butenolide carbene **69** or its reactive equivalent, and then C–H insertion into a cyclopentyl methylene. Insertion into a methylene adjacent to the spirocyclic center in **69** would create a highly strained spirocyclic cyclobutane ring having an sp^2 carbon center. Thus, the bicyclo[2.2.1]heptane **70** is the major product, but a sterically hindered catalyst such as $Rh_2(esp)_2$ or $Rh_2(OPiv)_4$ is needed to prevent dimerization of the diazoacetate. These catalysts are presumed to protect the carbene intermediates from intermolecular reactions long enough to adopt the correct conformation for bridged-ring formation.

An exploration of the effect of substrate ring sizes demonstrated that the substrate conformation has as much control for insertion selectivity as electronics and size of the ring being formed. The conformational flexibility of the cyclohexyl ring in **73** led to a product ratio that roughly corresponded to the prevalence of the two non-equivalent methylenes available for insertion, suggesting that the barriers for insertion into the 3 position from conformation **76** was similar to that for the 4 position from conformation **77** (Scheme 19). This similarity in rates makes the substrate **73** suitable as a test case to find a catalyst to control the product isomer formed in the reaction as envisioned in Figure 2. The cycloheptyl and cyclooctyl rings showed a stronger intrinsic product isomer preference, however. Assuming that the carbene (or reactive equivalent) generated from the alkyne after butenolide formation (see **76**) will need to be in an axial orientation for a transannular C–H bond insertion, the lowest energy ring conformation **78** may be drawn for the cycloheptyl ring [91] with the alkyne representing the reactive carbene. The depiction of conformation **78** shows that the most accessible C–H bonds are likely to be C–H^a at the 3 position. The observed product distribution supports this analysis, as the bicyclo[4.2.1]nonane **80** is the major product. A similar analysis for the cyclooctyl substrate leads to **81** as the most likely conformation [91]. Here, the most available C–H bonds for insertion would give bicyclo[4.2.2]decane **82**, which would require the formation of a new 6-membered ring instead of a 5-membered ring, though the latter is typically preferred in intramolecular reactions [36-59]. Nevertheless, **82** was produced as the major product, with the minor product coming from the predicted second-most preferred conformation **84**.

The May group also showed that the cascade reaction could be initiated from hydrazones. In the course of this work, it was discovered that $NaOSiMe_3$ was a superior base for hydrazone to diazo conversion (i.e., **86** to **87**, Scheme 20) [89]. Surprisingly, no reaction was observed in the absence of the Rh catalyst, suggesting that it may be involved in the transformation of the hydrazone to **87**. While the intermediate alkyl carbene **88** could potentially undergo a 1,2-hydride shift to give the alkene **90** in a Bamford–Stevens-like transformation, the reaction with the adjacent alkyne proved to be much faster to provide the bridged-polycyclic product **89**. The conditions employed were sufficiently mild and chemoselective that the epoxide in cyclohexane **91** remained intact in the reaction to form **92**.



Scheme 19: Conformational effects.



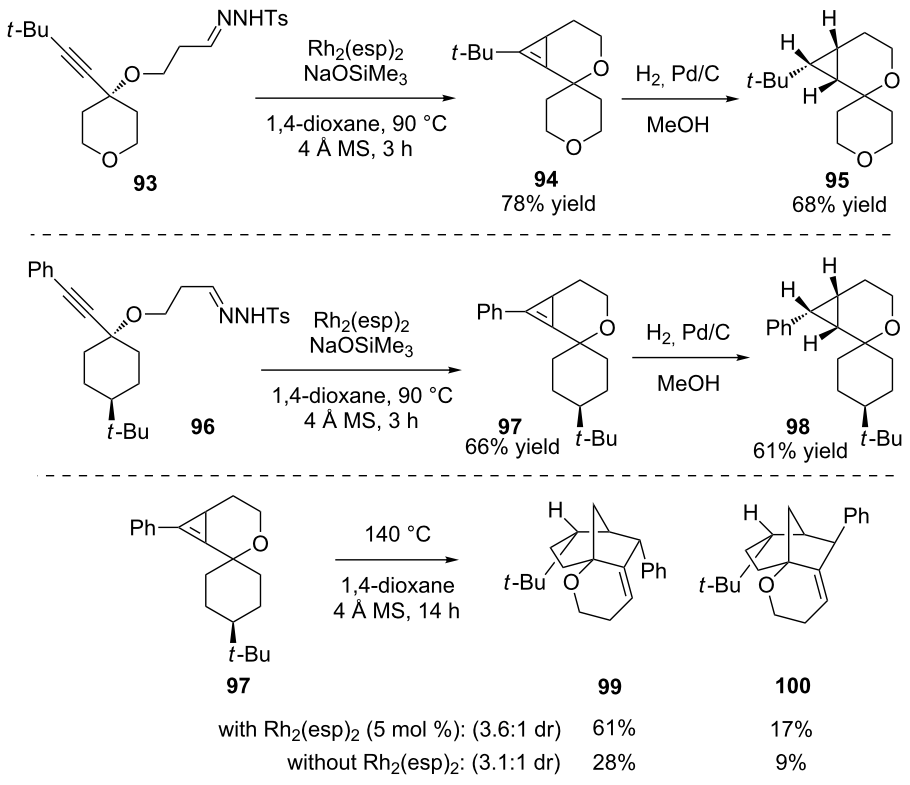
Scheme 20: Hydrazone cascade reaction.

The use of substrates with a 3-atom tether to the hydrazone and sterically large substituents allowed the isolation and characterization of mechanistic intermediates from the cascade reaction when it was conducted at 90 °C (Scheme 21). This confirmed some prior proposals of a cyclopropene intermediate [92], as the cyclopropene **97** reacted [93,94] to form the same products as the hydrazone **96** did directly when heated to 140 °C.

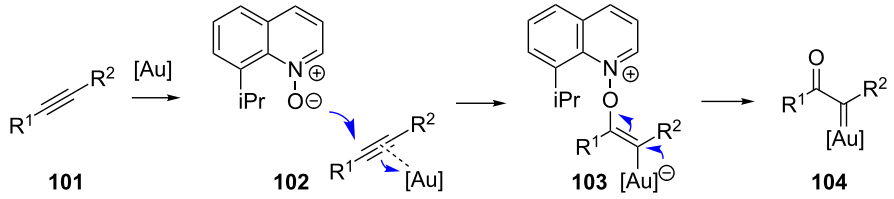
Gold

The work by the May group was soon followed by gold-promoted carbene/alkyne cascades. These cascades rely on Zhang's discovery that the use of pyridine *N*-oxides allow for the formation of gold ketocarbenes **104** from alkynes (Scheme 22) [95]. Those carbenes are then capable of further transformations, including C–H bond insertion and the reaction with other alkynes. Notably, this approach avoids the use of unstable diazo compounds.

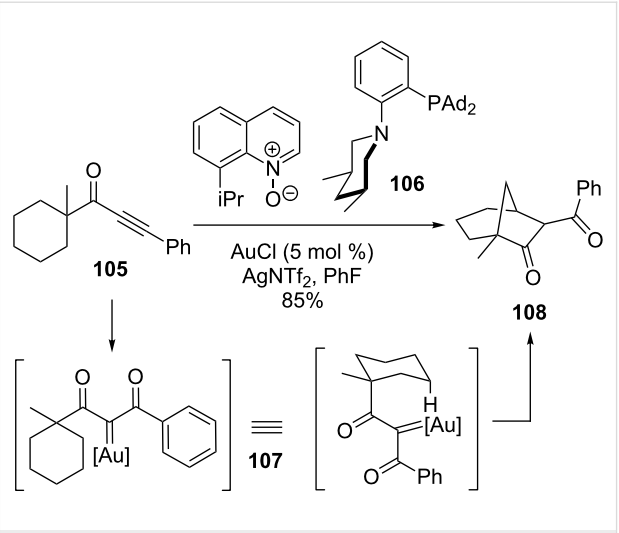
The Zhang group also demonstrated that the gold carbenes generated from alkynes can produce bridged bicycles from C–H bond insertion (Scheme 23) [96]. This was first implemented by transannular insertion via **107** to give the bicyclo[3.2.1]octane **108**. The diastereoselectivity of the process was not reported. Again, dual gold catalysts were used with a pyridinium oxide oxidant. Notably, a hindered ligand was again necessary for bridged-bicycle formation – in this case the diadamantyl phosphine **106**. The Thorpe–Ingold effect was also found to be highly beneficial for the reaction. An interesting mechanistic study using a less selective substrate showed that the same array of products could be obtained from either an alkynyl ketone or



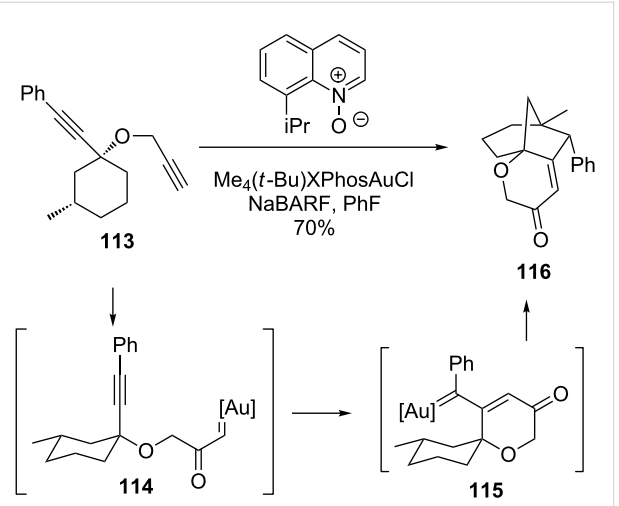
Scheme 21: Mechanistic studies.



Scheme 22: Gold carbene formation from alkynes.



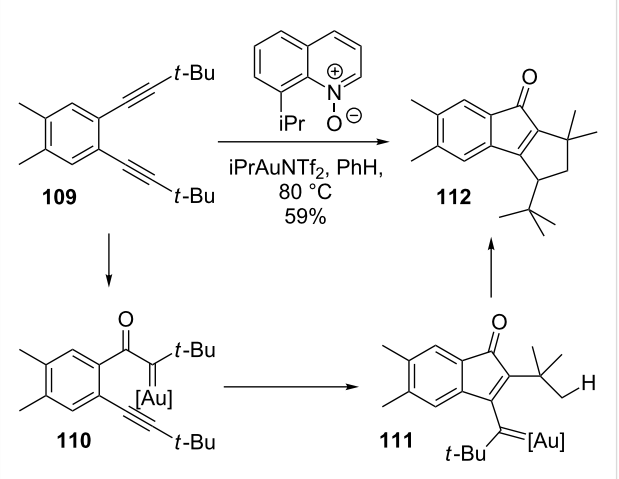
Scheme 23: Au-catalyzed bridged-bicycle formation.



Scheme 25: Gold carbene/alkyne cascade with C–H bond insertion.

the corresponding diazoketones. The product distribution was the same for either starting material, though the latter took 4 days to go to completion instead of 2 hours. Unlike the studies by Adams (Scheme 7), a significant deuterium kinetic isotope effect of 2.34 was seen for C–H insertion with gold catalysis.

Hashmi demonstrated the viability of dual gold catalysis for carbene/alkyne cascades with diynes like **109**, which gave products from either a 1,2-methyl shift (not shown) or a C–H bond insertion to form enone **112** (Scheme 24) [97]. Though this report provided proof of principle, it focused on the generation of fused polycyclic products.



Scheme 24: Gold carbene/alkyne cascade.

Zheng demonstrated that an alkyne cascade could generate bridged polycyclic products like **116** from simple diyne precursors highly reminiscent of the May group's substrates (Scheme 25) [98]. Here, a single gold species was used that contained a sterically bulky *t*-Bu-XPhos ligand. Many examples of the synthesis of ring-fused bridged bicycles were shown in a very nice demonstration of the reaction.

Platinum

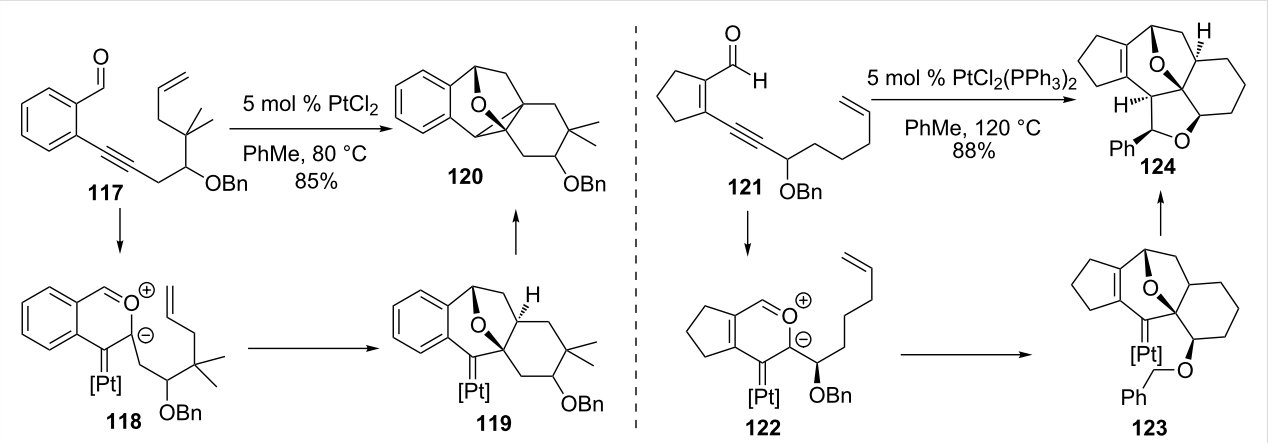
Recent examples have used less common metals as catalysts for C–H bond insertion. Oh used platinum to generate intermediate 1,3-dipoles like **118** and **122**, which then undergo a cycloaddition to generate **119** or **123**, respectively (Scheme 26) [99-101]. Here, the reactivity of those carbenes diverges. Carbene **119**, which has a distal benzyl ether, undergoes a methine C–H bond insertion to form the caged cyclopropyl ring system in **120**. Alternatively, the proximity of the methylene of the benzyl ether in **123** allows for a benzylic C–H insertion to generate the bridged polycycle **124**.

Tungsten

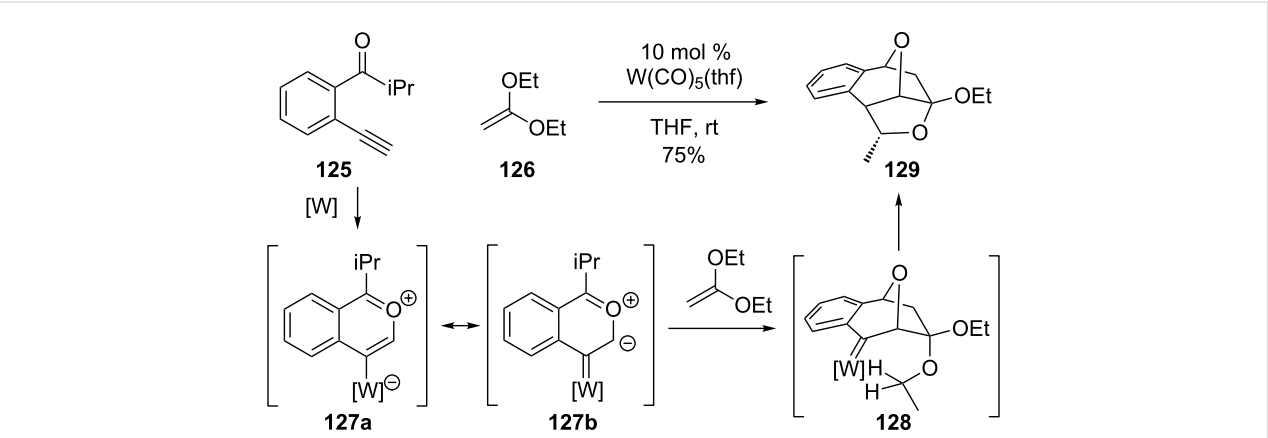
Iwasawa demonstrated a similar strategy for bridged-polycycle synthesis using a tungsten catalyst (Scheme 27) [102,103]. Again, the formation of a 1,3-dipole (see **127**) allows for a cycloaddition, though this example is intermolecular in nature. One of the ethereal ethyl groups in **128** is consequently poised for C–H bond insertion by the tungsten carbene to give **129** as a single diastereomer.

Conclusion

Many of the early examples of bridged-polycycle synthesis via C–H bond insertion arose from strategies targeting the total synthesis of natural products. The results of these early efforts led to useful reaction conditions, a better understanding of stereoelectronic effects involved in the insertions, and inspiration for subsequent efforts of greater complexity. The transannular C–H



Scheme 26: Platinum cascades.



Scheme 27: Tungsten cascade.

bond insertion by an axially disposed carbene group that is needed for bridged-ring formation occurs readily, but pathways that lead to fused products having less ring strain or that lead to dimer formation must be excluded by catalyst control or reaction protocols (e.g., slow addition of substrate). As a result of the studies reported herein, many representative core systems for natural products have been synthesized, and our understanding of substrate control is becoming much better defined. In the future, greater catalyst control for these reactions should be pursued. Ideally, the catalyst would dictate the diastereoselectivity, the enantioselectivity, and the location of C–H bond insertion to provide any of the possible product isomers selectively on demand.

Acknowledgements

The authors are grateful to the Welch Foundation (grant E-1744) and the NSF (grant CHE-1352439) for financial support. J-L.S. is grateful for support by CBIP (UH) and the Studying Abroad Scholarship of Taiwan.

References

1. Li, S.-H.; Wang, J.; Niu, X.-M.; Shen, Y.-H.; Zhang, H.-J.; Sun, H.-D.; Li, M.-L.; Tian, Q.-E.; Lu, Y.; Cao, P.; Zheng, Q.-T. *Org. Lett.* **2004,** *6,* 4327–4330. doi:10.1021/ol0481535
2. Jayasuriya, H.; Herath, K. B.; Zhang, C.; Zink, D. L.; Basilio, A.; Genilloud, O.; Diez, M. T.; Vicente, F.; Gonzalez, I.; Salazar, O.; Pelaez, F.; Cummings, R.; Ha, S.; Wang, J.; Singh, S. B. *Angew. Chem., Int. Ed.* **2007,** *46,* 4684–4688. doi:10.1002/anie.200701058
3. Kobayashi, J.; Ogiwara, A.; Hosoyama, H.; Shigemori, H.; Yoshida, N.; Sasaki, T.; Li, Y.; Iwasaki, S.; Naito, M.; Tsuruo, T. *Tetrahedron* **1994,** *50,* 7401–7416. doi:10.1016/S0040-4020(01)90470-3
4. Huang, J.-m.; Yokoyama, R.; Yang, C.-s.; Fukuyama, Y. *Tetrahedron Lett.* **2000,** *41,* 6111–6114. doi:10.1016/S0040-4039(00)01023-6
5. Yang, B. O.; Ke, C.-Q.; He, Z.-S.; Yang, Y.-p.; Ye, Y. *Tetrahedron Lett.* **2002,** *43,* 1731–1733. doi:10.1016/S0040-4039(02)00109-0
6. Xu, Y.-l.; Sun, H.-d.; Wang, D.-z.; Iwashita, T.; Komura, H.; Kozuka, M.; Naya, K.; Kubo, I. *Tetrahedron Lett.* **1987,** *28,* 499–502. doi:10.1016/S0040-4039(00)95765-4

7. Rodríguez, A. D.; Ramírez, C.; Rodríguez, I. I.; Barnes, C. L. *J. Org. Chem.* **2000,** *65,* 1390–1398. doi:10.1021/jo9914869
8. Huang, J. -m.; Fukuyama, Y.; Yang, C.-s.; Minami, H.; Tanaka, M. *Chem. Pharm. Bull.* **2000,** *48,* 657–659. doi:10.1248/cpb.48.657
9. Buta, J. G.; Flippen, J. L.; Lusby, W. R. *J. Org. Chem.* **1978,** *43,* 1002–1003. doi:10.1021/jo00399a047
10. Gerard, R. V.; Maclean, D. B.; Fagianni, R.; Lock, C. J. *Can. J. Chem.* **1986,** *64,* 943–949. doi:10.1139/v86-157
11. Zhao, F.-W.; Sun, Q.-Y.; Yang, F.-M.; Hu, G.-W.; Luo, J.-F.; Tang, G.-H.; Wang, Y.-H.; Long, C.-L. *Org. Lett.* **2010,** *12,* 3922–3925. doi:10.1021/ol101602n
12. Brieskorn, C. H.; Fuchs, A.; Bredenberg, J. B.-s.; Mcchesney, J. D.; Wenkert, E. *J. Org. Chem.* **1964,** *29,* 2293–2298. doi:10.1021/jo01031a044
13. Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010,** *132,* 16745–16746. doi:10.1021/ja108907x
14. Peng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2012,** *134,* 18860–18867. doi:10.1021/ja309905j
15. Lu, P.; Gu, Z.; Zakarian, A. *J. Am. Chem. Soc.* **2013,** *135,* 14552–14555. doi:10.1021/ja408231t
16. Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014,** *136,* 17738–17740. doi:10.1021/ja510573v
17. Ko, H. M.; Dong, G. *Nat. Chem.* **2014,** *6,* 739–744. doi:10.1038/nchem.1989
18. Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989,** *111,* 1073–1081. doi:10.1021/ja00185a043
19. Szostak, M.; Aubé, J. *Chem. Rev.* **2013,** *113,* 5701–5765. doi:10.1021/cr4000144
20. Chatterjee, S. *J. Chem. Soc., Chem. Commun.* **1979,** 622–623. doi:10.1039/c39790000622
21. Other work published at the same time as reference [20] by Chatterjee has been called into question. While no issues have been raised with the work referenced herein, we refer the reader to references [22-25] to evaluate the reliability of reference [20].
22. Paquette, L. A.; Han, Y. K. *J. Org. Chem.* **1979,** *44,* 4014–4016. doi:10.1021/jo01336a071
23. Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981,** *103,* 1835–1838. doi:10.1021/ja00397a044
24. Cornforth, J. *Tetrahedron Lett.* **1980,** *21,* 709–710. doi:10.1016/S0040-4039(00)71452-3
25. Cornforth, J.; Pengelly, T. *Tetrahedron Lett.* **1982,** *23,* 2213–2216. doi:10.1016/S0040-4039(00)87303-7
26. Grainger, R. S.; Owoare, R. B. *Org. Lett.* **2004,** *6,* 2961–2964. doi:10.1021/ol048911r
27. Yun, S. Y.; Zheng, J.-C.; Lee, D. *J. Am. Chem. Soc.* **2009,** *131,* 8413–8415. doi:10.1021/ja903526g
28. Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2006,** *45,* 7086–7090. doi:10.1002/anie.200603892
29. Masamune, S. *J. Am. Chem. Soc.* **1964,** *86,* 290–291. doi:10.1021/ja01056a042
30. Masamune, S. *J. Am. Chem. Soc.* **1964,** *86,* 291–292. doi:10.1021/ja01056a043
31. Pelletier, S. W.; Parthasarathy, P. C. *Tetrahedron Lett.* **1963,** *4,* 205–208. doi:10.1016/S0040-4039(01)90607-0
32. Wolff, S.; Agosta, W. C. *J. Org. Chem.* **1973,** *38,* 1694–1696. doi:10.1021/jo00949a017
33. Agosta, W. C.; Wolff, S. *J. Org. Chem.* **1975,** *40,* 1027–1030. doi:10.1021/jo00896a006
34. Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994,** *116,* 3296–3305. doi:10.1021/ja00087a016
35. Spero, D. M.; Adams, J. *Tetrahedron Lett.* **1992,** *33,* 1143–1146. doi:10.1016/S0040-4039(00)91880-X
36. Doyle, M. P.; Bagheri, V.; Pearson, M. M.; Edwards, J. D. *Tetrahedron Lett.* **1989,** *30,* 7001–7004. doi:10.1016/S0040-4039(01)93408-2
37. Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991,** *56,* 820–829. doi:10.1021/jo00002a058
38. Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Daniel, K. L. *Tetrahedron Lett.* **1992,** *33,* 7819–7822. doi:10.1016/S0040-4039(00)74752-6
39. Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992,** *114,* 1874–1876. doi:10.1021/ja00031a048
40. Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993,** *115,* 8669–8680. doi:10.1021/ja00072a021
41. Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993,** *115,* 958–964. doi:10.1021/ja00056a021
42. Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996,** *61,* 9146–9155. doi:10.1021/jo961607u
43. Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996,** *118,* 8837–8846. doi:10.1021/ja961682m
44. Timmons, D. J.; Doyle, M. P. *J. Organomet. Chem.* **2001,** *617–618,* 98–104. doi:10.1016/S0022-328X(00)00637-9
45. Doyle, M. P.; Hu, W.; Wee, A. G. H.; Wang, Z.; Duncan, S. C. *Org. Lett.* **2003,** *5,* 407–410. doi:10.1021/ol027157b
46. Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982,** *47,* 4808–4809. doi:10.1021/jo00145a050
47. Taber, D. F.; Ruckle, R. E., Jr. *Tetrahedron Lett.* **1985,** *26,* 3059–3062. doi:10.1016/S0040-4039(00)98618-0
48. Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986,** *108,* 7686–7693. doi:10.1021/ja00284a037
49. Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992,** *57,* 436–441. doi:10.1021/jo00028a011
50. Taber, D. F.; You, K. K. *J. Am. Chem. Soc.* **1995,** *117,* 5757–5762. doi:10.1021/ja00126a015
51. Taber, D. F.; Song, Y. *J. Org. Chem.* **1996,** *61,* 6706–6712. doi:10.1021/jo960758u
52. Taber, D. F.; Kamfia, K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996,** *118,* 547–556. doi:10.1021/ja9515213
53. Taber, D. F.; Christos, T. E. *Tetrahedron Lett.* **1997,** *38,* 4927–4930. doi:10.1016/S0040-4039(97)01081-2
54. Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **1998,** *63,* 3717–3721. doi:10.1021/jo9803434
55. Hashimoto, S.-i.; Watanabe, N.; Ikegami, S. *J. Chem. Soc., Chem. Commun.* **1992,** 1508–1510. doi:10.1039/C39920001508
56. Hashimoto, S.-i.; Watanabe, N.; Ikegami, S. *Synlett* **1994,** 353–355. doi:10.1055/s-1994-22852
57. Anada, M.; Sugimoto, T.; Watanabe, N.; Nakajima, M.; Hashimoto, S.-i. *Heterocycles* **1999,** *50,* 969–980. doi:10.3987/COM-98-S(H)95
58. Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1999,** *121,* 1417–1418. doi:10.1021/ja983748e

59. Sulikowski, G. A.; Cha, K. L.; Sulikowski, M. M. *Tetrahedron: Asymmetry* **1998,** *9,* 3145–3169. doi:10.1016/S0957-4166(98)00342-5
60. Liang, H.; Hu, L.; Corey, E. J. *Org. Lett.* **2011,** *13,* 4120–4123. doi:10.1021/ol201640y
61. Doyle, M. P.; Kalinin, A. V. *Synlett* **1995,** 1075–1076. doi:10.1055/s-1995-5176
62. White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1999,** *64,* 7871–7884. doi:10.1021/jo990905z
63. Magnus, P.; Rainey, T.; Lynch, V. *Tetrahedron Lett.* **2003,** *44,* 2459–2461. doi:10.1016/S0040-4039(03)00336-8
64. Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001,** *123,* 6935–6936. doi:10.1021/ja011033x
65. Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003,** *5,* 4823–4826. doi:10.1021/ol035776u
66. Wolckenhauer, S. A.; Devlin, A. S.; du Bois, J. *Org. Lett.* **2007,** *9,* 4363–4366. doi:10.1021/ol701950d
67. Toumieux, S.; Compain, P.; Martin, O. R. *J. Org. Chem.* **2008,** *73,* 2155–2162. doi:10.1021/jo702350u
68. John Biju, P.; Subba Rao, G. S. R. *Chem. Commun.* **1999,** 2225–2226. doi:10.1039/a906904f
69. Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *J. Org. Chem.* **1991,** *56,* 1434–1439. doi:10.1021/jo00004a019
70. Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *J. Org. Chem.* **2001,** *56,* 1434–1439. doi:10.1021/jo00004a019
71. Srikrishna, A.; Gharpure, S. J. *Chem. Commun.* **1998,** 1589–1590. doi:10.1039/a804001j
72. Srikrishna, A.; Gharpure, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000,** 3191–3193. doi:10.1039/b005943i
73. Srikrishna, A.; Ravi Kumar, P.; Gharpure, S. J. *Tetrahedron Lett.* **2001,** *42,* 3929–3931. doi:10.1016/S0040-4039(01)00585-8
74. Srikrishna, A.; Gharpure, S. J. *J. Org. Chem.* **2001,** *66,* 4379–4385. doi:10.1021/jo0102765
75. Srikrishna, A.; Satyanarayana, G. *Tetrahedron* **2005,** *61,* 8855–8859. doi:10.1016/j.tet.2005.07.016
76. Spiegel, D. A.; Njardarson, J. T.; Wood, J. L. *Tetrahedron* **2002,** *58,* 6545–6554. doi:10.1016/S0040-4020(02)00664-6
77. Padwa, A.; Krumpe, K. E.; Zhi, L. *Tetrahedron Lett.* **1989,** *30,* 2633–2636. doi:10.1016/S0040-4039(00)99084-1
78. Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996,** *96,* 223–270. doi:10.1021/cr950022h
79. Padwa, A. *Molecules* **2001,** *6,* 1–12. doi:10.3390/60100001
80. Padwa, A. *Chem. Soc. Rev.* **2009,** *38,* 3072. doi:10.1039/b816701j
81. Korkowski, P. F.; Hoye, T. R.; Rydberg, D. B. *J. Am. Chem. Soc.* **1988,** *110,* 2676–2678. doi:10.1021/ja00216a066
82. Hoye, T. R.; Dinsmore, C. J.; Johnson, D. S.; Korkowski, P. F. *J. Org. Chem.* **1990,** *55,* 4518–4520. doi:10.1021/jo00302a010
83. Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1991,** *32,* 3755–3758. doi:10.1016/S0040-4039(00)79368-3
84. Hoye, T. R.; Dinsmore, C. J. *Tetrahedron Lett.* **1992,** *33,* 169–172. doi:10.1016/0040-4039(92)88041-3
85. Hoye, T. R.; Vyvyan, J. R. *J. Org. Chem.* **1995,** *60,* 4184–4195. doi:10.1021/jo00118a040
86. Padwa, A.; Weingarten, M. D. *J. Org. Chem.* **2000,** *65,* 3722–3732. doi:10.1021/jo991938h
87. Jansone-Popova, S.; May, J. A. *J. Am. Chem. Soc.* **2012,** *134,* 17877–17880. doi:10.1021/ja308305z
88. Jansone-Popova, S.; Le, P. Q.; May, J. A. *Tetrahedron* **2014,** *70,* 4118–4127. doi:10.1016/j.tet.2014.03.060
89. Le, P. Q.; May, J. A. *J. Am. Chem. Soc.* **2015,** *137,* 12219–12222. doi:10.1021/jacs.5b08157
90. Hoye, T. R.; Dinsmore, C. J. *J. Am. Chem. Soc.* **1991,** *113,* 4343–4345. doi:10.1021/ja00011a055
91. Anslyn, E. V.; Dougherty, D. A. Strain and Stability. *Modern Physical Organic Chemistry;* University Science Books: Sausalito, CA, 2006; pp 65–137.
92. Mykytka, J. P.; Jones, W. M. *J. Am. Chem. Soc.* **1975,** *97,* 5933–5935. doi:10.1021/ja00853a059
93. Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007,** *107,* 3117–3179. doi:10.1021/cr050988l
94. Baird, M. S. *Chem. Rev.* **2003,** *103,* 1271–1294. doi:10.1021/cr010021r
95. Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012,** *134,* 31–34. doi:10.1021/ja2091992
96. Wang, Y.; Zheng, Z.; Zhang, L. *J. Am. Chem. Soc.* **2015,** *137,* 5316–5319. doi:10.1021/jacs.5b02280
97. Nösel, P.; dos Santos Comprido, L. N.; Lauterbach, T.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *J. Am. Chem. Soc.* **2013,** *135,* 15662–15666. doi:10.1021/ja4085385
98. Zheng, Z.; Zhang, L. *Org. Chem. Front.* **2015,** *2,* 1556–1560. doi:10.1039/C5QO00308C
99. Kim, J. H.; Ray, D.; Hong, C. S.; Han, J. W.; Oh, C. H. *Chem. Commun.* **2013,** *49,* 5690–5692. doi:10.1039/c3cc42525h
100. Oh, C. H.; Lee, J. H.; Lee, S. M.; Yi, H. J.; Hong, C. S. *Chem. – Eur. J.* **2009,** *15,* 71–74. doi:10.1002/chem.200801887
101. Oh, C. H.; Yi, H. J.; Lee, J. H.; Lim, D. H. *Chem. Commun.* **2010,** *46,* 3007–3009. doi:10.1039/C001495H
102. Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001,** *123,* 5814–5815. doi:10.1021/ja010478i
103. Kusama, H.; Funami, H.; Shido, M.; Hara, Y.; Takaya, A. J.; Iwasawa, N. *J. Am. Chem. Soc.* **2005,** *127,* 2709–2716. doi:10.1021/ja044194k

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.97

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Cationic Pd(II)-catalyzed C–H activation/cross-coupling reactions at room temperature: synthetic and mechanistic studies

Takashi Nishikata, Alexander R. Abela, Shenlin Huang and Bruce H. Lipshutz*

Full Research Paper

Open Access

Address:
Department of Chemistry & Biochemistry, University of California, Santa Barbara, CA 93106, USA

Email:
Bruce H. Lipshutz* - lipshutz@chem.ucsb.edu

* Corresponding author

Keywords:
arylation; cationic palladium; C–H functionalization; green chemistry; olefination

Beilstein J. Org. Chem. **2016,** *12,* 1040–1064.
doi:10.3762/bjoc.12.99

Received: 18 January 2016
Accepted: 28 April 2016
Published: 20 May 2016

This article is part of the Thematic Series "C–H Functionalization/activation in organic synthesis".

Guest Editor: R. Sarpong

© 2016 Nishikata et al; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

Cationic palladium(II) complexes have been found to be highly reactive towards aromatic C–H activation of arylureas at room temperature. A commercially available catalyst $[Pd(MeCN)_4](BF_4)_2$ or a nitrile-free cationic palladium(II) complex generated in situ from the reaction of $Pd(OAc)_2$ and HBF_4, effectively catalyzes C–H activation/cross-coupling reactions between aryl iodides, arylboronic acids and acrylates under milder conditions than those previously reported. The nature of the directing group was found to be critical for achieving room temperature conditions, with the urea moiety the most effective in promoting facile coupling reactions at an *ortho* C–H position. This methodology has been utilized in a streamlined and efficient synthesis of boscalid, an agent produced on the kiloton scale annually and used to control a range of plant pathogens in broadacre and horticultural crops. Mechanistic investigations led to a proposed catalytic cycle involving three steps: (1) C–H activation to generate a cationic palladacycle; (2) reaction of the cationic palladacycle with an aryl iodide, arylboronic acid or acrylate, and (3) regeneration of the active cationic palladium catalyst. The reaction between a cationic palladium(II) complex and arylurea allowed the formation and isolation of the corresponding palladacycle intermediate, characterized by X-ray analysis. Roles of various additives in the stepwise process have also been studied.

Introduction

Transition metal-catalyzed, direct functionalization of aryl C–H bonds has made enormous progress over the past decade, and continues to attract a great deal of attention due to the highly efficient routes now available for elaborating aromatic rings. While reactions of this type have been known for decades [1-71], serious challenges remain in achieving reactivity and selectivity due to the inertness and ubiquity of C–H bonds. High temperatures are frequently required to realize aromatic C–H

functionalization (>120 °C), increasing the potential for side reactions and functional group compatibility issues. Indeed, C–H activation transformations until recently have rarely proceeded at ambient temperature due to the typically low reactivity of these positions [72-79]. In the case of palladium-catalyzed C–H activation, the crucial, namesake "C–H activation" step typically involves a C–H to C–Pd refunctionalization, generating a reactive aryl-palladium species that is poised for further transformations.

Three approaches (Figure 1) have generally been employed to enhance the reactivity and promote the key metalation/C–H bond cleavage step: (1) tuning of the reaction conditions through inclusion of various additives such as metal salts [1-22], or strong acids such as TFA or HOAc, in addition to the application of heat, although it is not always clear which steps within the overall mechanism are most directly effected under these conditions; (2) in a major subset of C–H activation chemistry, internally chelating *ortho*-directing groups [71-85] have been found to effectively promote selective C–H activation, typically by aiding in the formation of a palladacycle intermediate. Careful tuning of the structure of the directing group, with functionalities including a variety of nitrogen-containing moieties, such as amides [86,87], *N*-heterocycles [88,89], imines [90,91], pyridine *N*-oxide [92], amines [93,94], as well as a variety of others [1-71], has been found to profoundly impact reactivity; (3) tuning of ligands around the transition metal catalyst center has emerged as an especially powerful means of enhancing and controlling reactivity in these processes [95-107].

A fourth approach with considerable potential, and which appears to have received considerably less attention, involves tuning the cationicity of the transition metal catalyst [72-79]. Literature studies have suggested that certain anionic ligands on palladium, such as acetate or carbonate, may assist C–H bond cleavage by acting as internal bases as part of a concerted metalation–deprotonation (CMD) pathway, particularly in the case of less electron-rich arenes (Scheme 1, top) [34,108-119]. In other arrays, particularly those with more electron-rich substituents, evidence suggests an electrophilic aromatic substitution mechanism may be operative. In these instances, electron-poor catalysts, such as those generated from the reaction of Pd(II) and TFA, have in some cases been shown to be especially effective. We reasoned that substitution with a more distant coordinating anion would result in a highly Lewis acidic, dicationic palladium species that might be still more reactive in the electrophilic palladation step, potentially gaining entry to C–H activation under even milder reaction conditions for selected couplings than have previously been observed (Scheme 1, bottom) [120-122].

Metal cations, in general, are well known to increase the reactivity of C–C and C–N double bonds due to their Lewis acidity. Cationic palladium complexes [123], in particular, possess a wide breadth of reactivity, having been used to catalyze Diels–Alder [124,125], aldol and Mannich reactions [126-128], Wacker oxidations [129], polymerizations of alkenes [130,131], and asymmetric 1,4-additions with arylboronic [132-134], arylbismuth [135], and arylsilicon [136] reagents. Although carbocations react with arenes through electrophilic aromatic hydro-

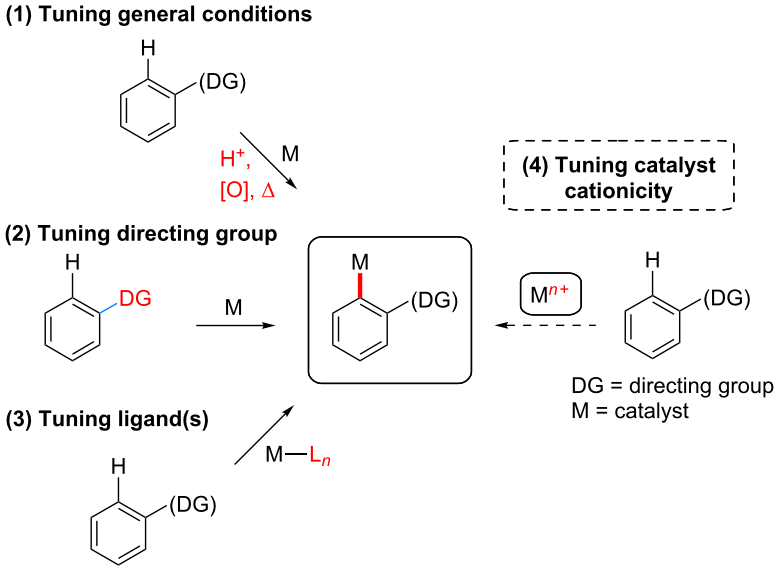
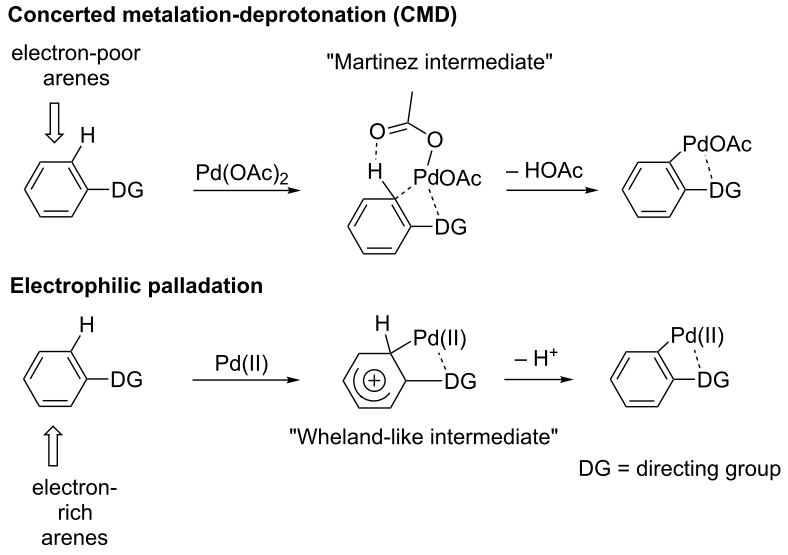


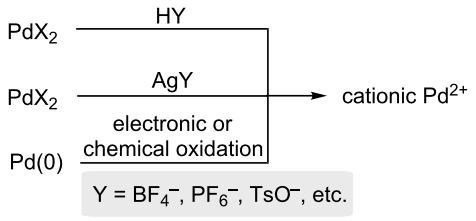
Figure 1: Road map to enhanced C–H activation reactivity.



Scheme 1: Concerted metalation–deprotonation and elelectrophilic palladation pathways for C–H activation.

gen substitution in a Friedel–Crafts reaction, the potential for metal cations to participate in similar chemistry has been far less widely examined. A cationic palladium-catalyzed electrophilic aromatic C–H substitution without basic anions [137-142] would hold considerable promise as an alternative and potentially milder approach to achieving valued C–H activation/coupling reactions.

While several cationic palladium complexes are commercially available, they may also be generated in situ via a variety of routes (Scheme 2), including: (a) reaction of a palladium complex with a non-coordinating anion source, usually an acid or metal salt; (b) reaction of Pd(II) halide complexes and silver salts [143-145]; (c) electronic oxidation of Pd(0) [146]; and (d) chemical oxidation of Pd(0) with HBF_4, $Cu(BF_4)_2$ or $AgBF_4$ [136,147,148].



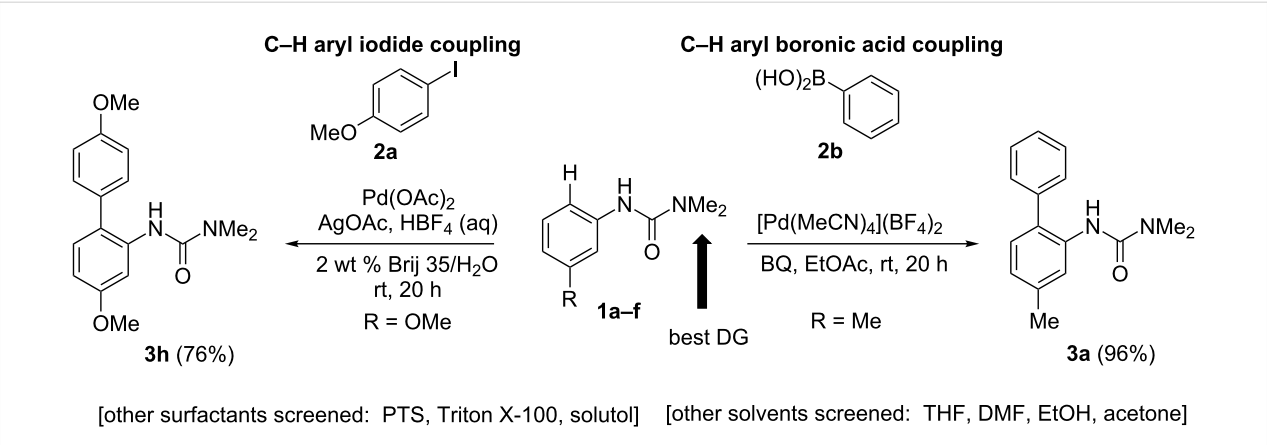
Scheme 2: Routes for generation of cationic palladium(II) species.

We have previously reported that cationic palladium-catalyzed C–H arylations of arylureas [121,122] and Fujiwara–Moritani reactions of anilide derivatives [148] can be effected at room temperature. In this account we disclose, in addition to full details associated with this C–H activation chemistry, additional applications of room temperature Fujiwara–Moritani reactions including a synthesis of the herbicide boscalid, as well as spectroscopic and mechanistic studies.

Results and Discussion

C–H arylations of arylureas with aryl iodides and arylboronic acids

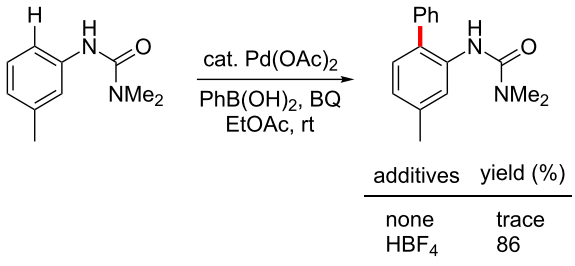
Among the most conceptually attractive approaches to aromatic C–H activation is the efficient synthesis of biaryls through direct arylation reactions. The widespread availability of aryl iodides and arylboronic acids make them appealing arylating agents [149-171]. Previously reported C–H activation reaction conditions employing these reagents, however, have typically required high temperatures to obtain the desired coupling products in good yields. In order to successfully carry out these reactions at ambient temperature, several considerations must be addressed, as illustrated in Figure 1. Optimization studies initially focused on the choice of an *ortho*-directing group together with a cationic palladium(II) catalyst. Although the combination of acetanilide together with a palladium(II) catalyst lead to the corresponding palladacycle, as reported by Tremont [172], in the presence of **2a**, $Pd(OAc)_2$, HBF_4 and AgOAc at room temperature, acetyl or isopropyl anilides afford essentially no product. Only after heating to 50 °C did substrate **1a** react with iodide **2a**. The corresponding pivaloylanilide is also known to serve as an effective directing group at 130 °C, but at room temperature a poor yield was obtained. Only the dimethylurea analog gave satisfactory conversion to the desired biaryl, thus arriving at optimized conditions, as shown in Scheme 3 (left). By contrast, the Daugulis group and others



Scheme 3: Optimized conditions for C–H arylations at room temperature.

[173,174] have demonstrated Pd-catalyzed *ortho*-arylations of anilides at temperatures typically greater than 100 °C, and the Sanford group has also studied similar transformations involving diaryliodonium salts [175]. Arylureas have recently been noticed to be more active coupling partners for C–H functionalizations as opposed to anilides, especially at lower temperatures [176]. A number of strong acids have been previously utilized in C–H activation reactions [1-22], e.g., HBF_4 was found to be critical for generation of biaryl **3h** in good yield. The structure of the *ortho*-arylated product was confirmed by X-ray analysis. While similar reactions, in addition to requiring high temperatures, have typically employed strong acids such as TFA as the organic solvent, here 2 wt % solutions of selected surfactants in water were found to be excellent reaction media, providing an additional environmentally appealing feature to this protocol. While good yields could be obtained using the first generation surfactant PTS (polyoxyethanyl α-tocopheryl sebacate) [121,177,178], several other amphiphiles that are both less costly and are items of commerce gave comparable results. Using commercialy available Brij 35 (2 wt %) in water [179-183] afforded the best levels of conversion and thus, overall yields, while in its absence (i.e.,"on water"), there was a noticeable drop in the extent of conversion. In addition, lower loadings of HBF_4, silver salt, or the palladium catalyst also gave inferior results.

In the case of C–H activation/Suzuki–Miyaura coupling reactions, the commercially available, pre-formed cationic Pd(II) catalyst $[Pd(MeCN)_4](BF_4)_2$ [184], was found to efficiently catalyze the reaction between arylureas and arylboronic acids. On the other hand, C–H arylations with aryl iodides catalyzed by $[Pd(MeCN)_4](BF_4)_2$ did not give any of the desired products (see mechanistic discussion; vide infra). Various neutral palladium catalysts were examined, such as $Pd(OAc)_2$, $PdCl_2L_n$, $Pd_2(dba)_3$, in the absence of added acid, but none led to cross-coupling at room temperature. 1,4-Benzoquinone (BQ) was found to be an effective additive in promoting the reaction, while addition of stoichiometric metal salts (e.g., silver or copper salts) was unnecessary. Moreover, in this case organic solvents were far more effective as the reaction medium than was water, possibly due to BQ solubility issues. EtOAc, rather than EtOH and THF was the most effective (Scheme 3, right), while other organic solvents (e.g., DMF) gave low-to-moderate yields of product **3a**. Although reduced amounts of both phenylboronic acid (**2b**) and BQ still gave excellent yields, lower catalyst loadings caused slower reactions. A neutral palladium(II) complex, $Pd(OAc)_2$, showed no catalytic acitivity, whereas catalytic $Pd(OAc)_2$ in the presence of stoichiometric HBF_4 reacted with an arylurea and arylboronic acid to afford the biaryl in high yield (Scheme 4).



Scheme 4: Biaryl formation catalyzed by $Pd(OAc)_2$.

Representative results for the reactions between aryl iodides and arylboronic acids are summarized in Figure 2. These arylations tolerate various combinations of substrates and reagents having electron-withdrawing or electron-donating groups, as well as sterically hindered aromatic rings, all taking place at room temperature. Suzuki–Miyaura-type C–H coupling reactions are typically more tolerant of electron-withdrawing groups (**3d**, **3f**, **3k**) and *ortho*-substitution (**3g**) on the aryl ring. On the other hand,

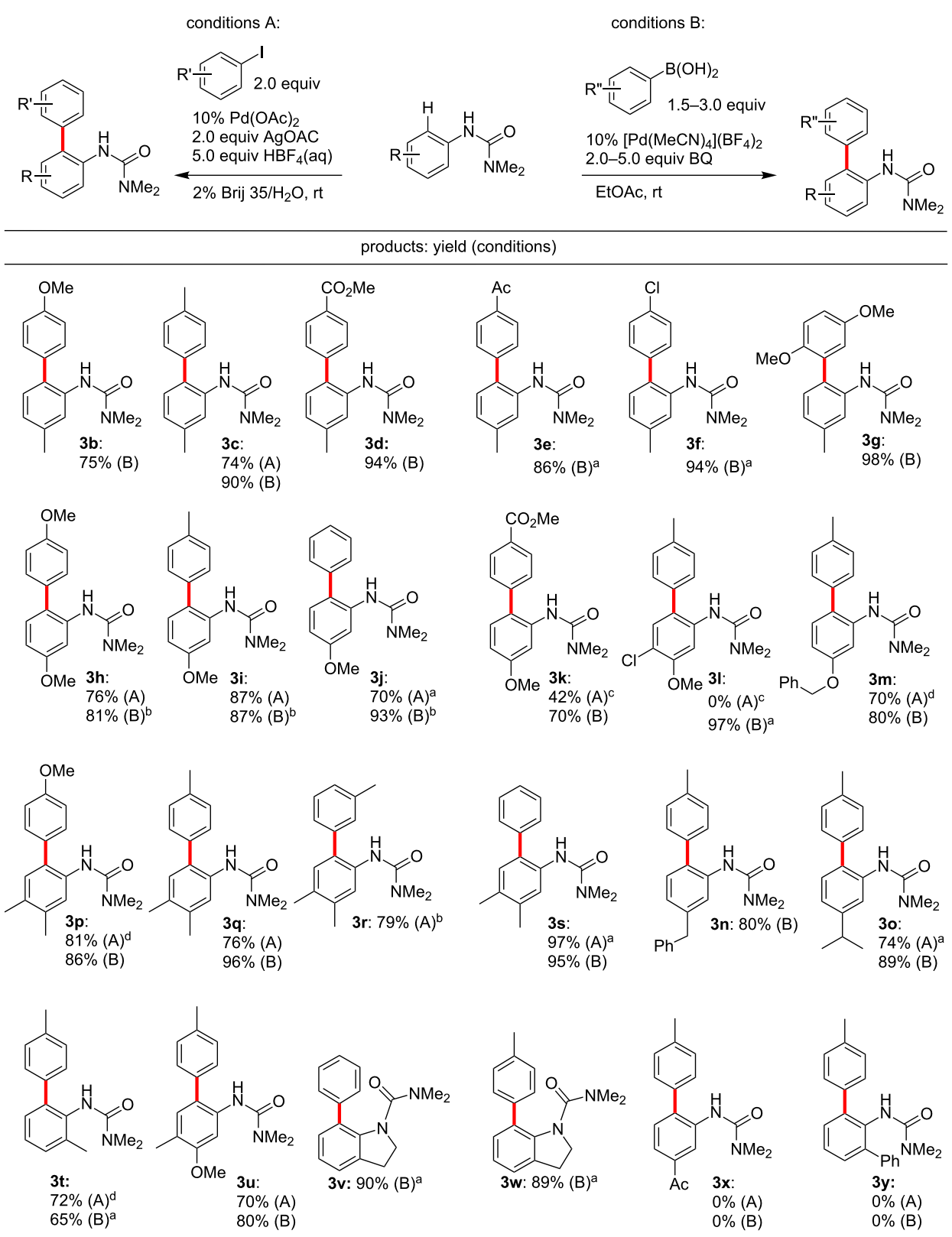


Figure 2: C–H arylation results. Conditions A: Conducted at rt for 20 h in 2 wt % Brij 35/water (1 mL) with 10 mol % $Pd(OAc)_2$, AgOAc (2 equiv), HBF_4 (5 equiv), arylurea (**1**, 0.25 mmol), and ArI (2.0 equiv). Conditions B: Conducted at rt for 20 h in EtOAc (1 mL) with 10 mol % $[Pd(MeCN)_4](BF_4)_2$, BQ (2 or 5 equiv), arylurea (**1**, 0.25 mmol), and $ArB(OH)_2$ (1.5 or 3 equiv). [a]Run for 48 h. [b]2 equiv of BQ. [c]Run for 96 h. [d]Run for 72 h.

the reaction with 4-methoxycarbonylphenyl iodide, for example, gave a low yield of product **3k**. Arylureas having only an electron-withdrawing group showed no reactivity towards coupling under either set of conditions (**3x**), consistent with an electrophilic aromatic substitution pathway in the initial C–H activation step by a cationic palladium(II) species (vide infra). Arylureas with various alkyl substituents in the *ortho*-position, including cyclic arrays, gave good isolated yields (**3t**, **3v**, **3w**), whereas a 2-phenyl substituted arylurea did not participate in the C–H activation/coupling reaction under these conditions (**3y**). Overall, C–H Suzuki–Miyaura coupling reactions were applicable to a broader substrate scope than the corresponding reaction with aryl iodides, although the latter protocol remains appealing for a variety of cross-coupling combinations due to both the convenience of aryl iodides as substrates, and the use of water as the gross reaction medium.

Especially noteworthy are the numerous examples of aniline derivatives lacking *ortho*- or *meta*-substitution, which have previously been shown to be prone to double arylation (Figure 3). Since literature conditions generally employ elevated temperatures, directed C–H arylations have often suffered from uncontrollable double arylation in symmetrical or unsubstituted substrates [1-22,173,174]. At ambient temperatures, however, coupling reactions on these more challenging substrate types underwent selective *mono*-arylations in water (Figure 3). In fact, doubly arylated products were rather difficult to generate under these room temperature conditions, not unexpected given the previously described low reactivity of ureas already possessing an *ortho*-aryl substituent [121,122].

A 1-naphthylurea also gave excellent selectivity at room temperature (Scheme 5). When this substrate was subjected to optimized conditions for the boronic acid C–H coupling, the corresponding singly *ortho*-arylated product was obtained in 97% yield solely as the 2-aryl isomer, as confirmed by ^{1}H NMR and X-ray crystallography. Generally, it is difficult to efficiently control the selectivity between the C2 and C8 positions in naphthalene rings towards a single isomeric C–H activation product [163,174,185-189].

Fujiwara–Moritani reactions

Following these results on biaryl constructions via C–H activation at room temperature, we next sought to apply our cationic

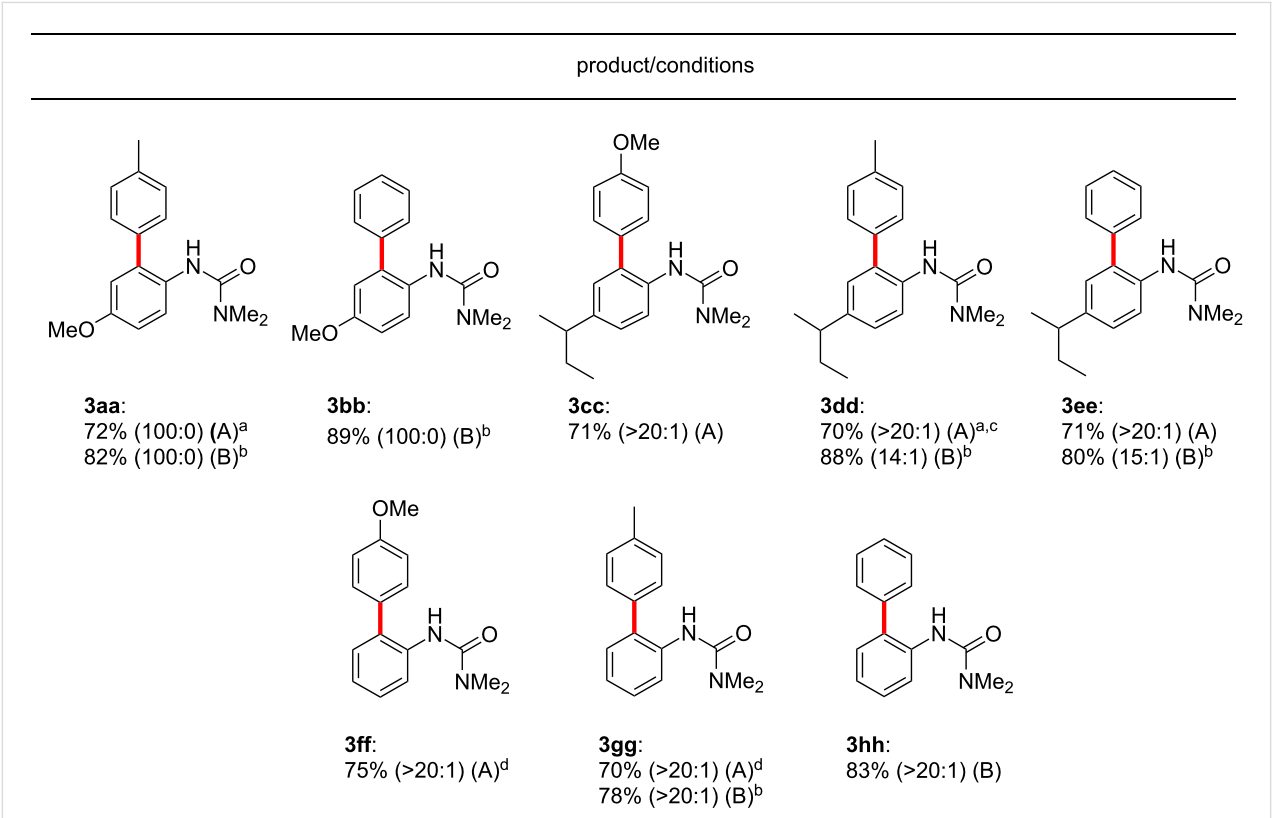
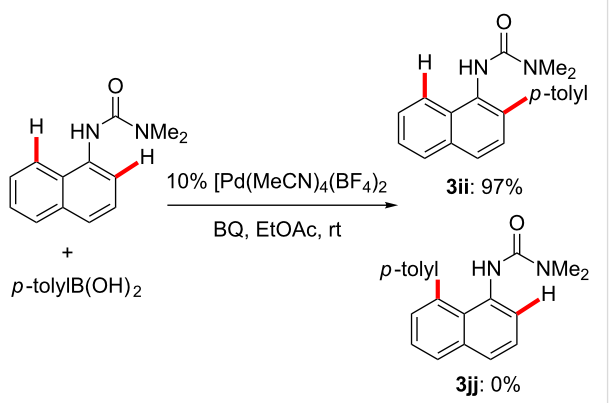


Figure 3: Monoarylations in water at rt. Conditions A: Conducted at rt for 20 h in 2 wt % Brij 35/water with 10 mol % $Pd(OAc)_2$, AgOAc (2 equiv), HBF_4 (5 equiv), arylurea (**1**, 0.25 mmol), and ArI (**2**, 1.5 equiv). Conditions B: Conducted at rt for 20 h in EtOAc with 10 mol % $[Pd(MeCN)_4](BF_4)_2$, BQ (5 equiv), arylurea (**1**, 0.25 mmol), and $ArB(OH)_2$ (**2**, 1.5 equiv). The ratios of single:double arylation determined by ^{1}H NMR are shown in the parentheses. [a]Run for 48 h. [b]1.2 equiv of $ArB(OH)_2$. [c]1.2 equiv of ArI. [d]Run for 72 h.



Scheme 5: Selective arylation of a 1-naphthylurea derivative.

palladium(II) conditions to the venerable Fujiwara–Moritani reaction. As reported back in 1967, this direct aryl olefination reaction is among the first palladium-catalyzed C–H activation reactions to be described [190-192]. Subsequent studies have generally resorted to elevated temperatures (80–160 °C) and anhydrous conditions, and in many cases high pressures of CO or O_2 are also required in order to carry out these Heck-like coupling reactions [1-22,193-203]. Additional progress of note includes coupling reactions with arenes containing an *ortho*-directing group [1-22,45-51,193-203], as well as a *meta*-selective Fujiwara–Moritani reaction [204,205]. A recent report employing arylureas as the C–H coupling partner achieved limited coupling at ambient temperature, with most examples requiring heating to 60 °C [74,206].

We have previously reported a methodology enabling Fujiwara–Moritani reactions to be run in water at room temperature using the cationic palladium catalyst $[Pd(MeCN)_4](BF_4)_2$ (Figure 4, **5a**–**c**, conditions A). While this reaction proceeded with a number of alkyl anilide derivatives, as well as ureas as directing groups (**5c**), the substrate scope was otherwise somewhat limited; only anilides possessing a strongly donating alkoxy group *meta* to the directing group (*para* to the position

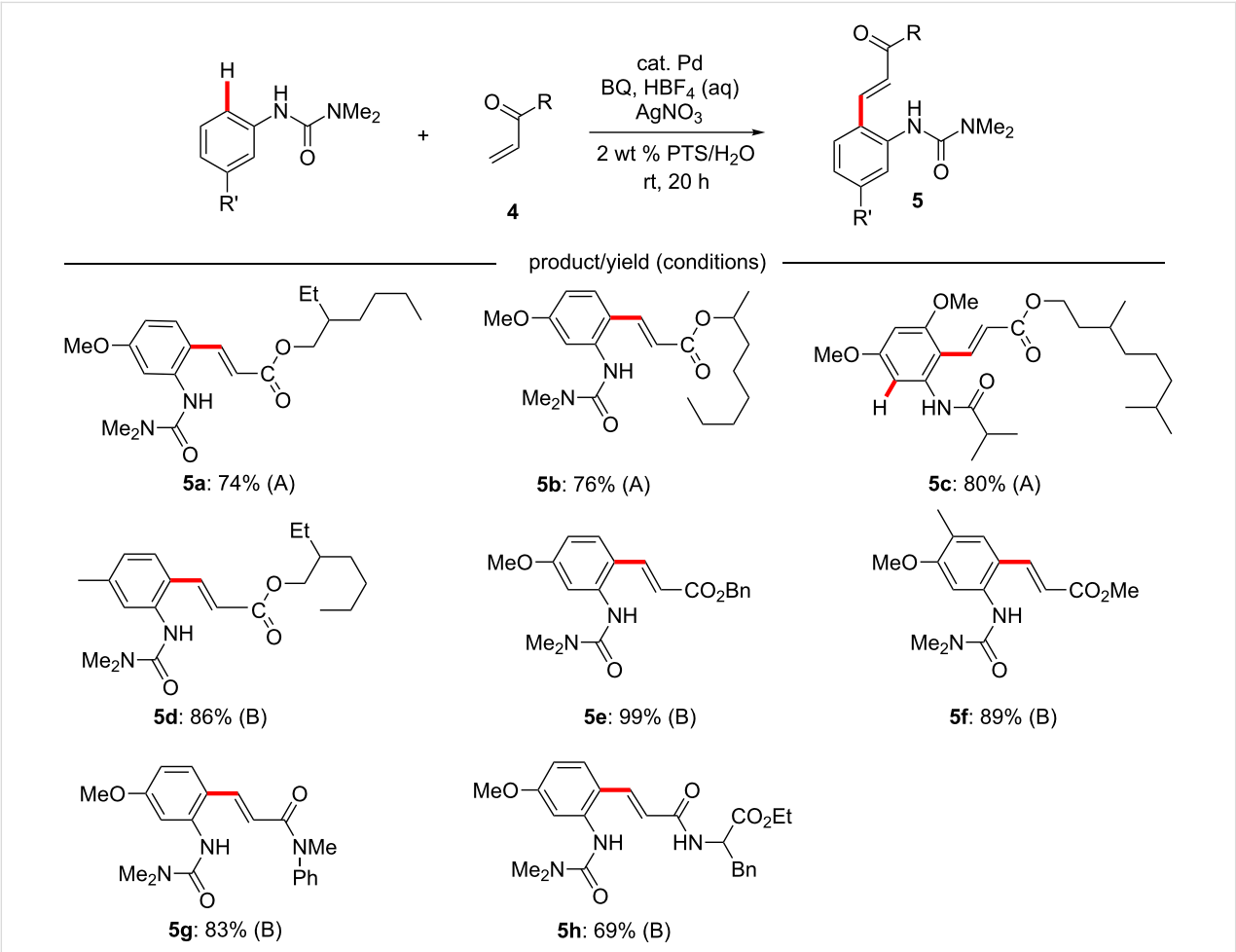


Figure 4: Fujiwara–Moritani coupling rreactions in water. Conditions A: 10 mol % $[Pd(MeCN)_4](BF_4)_2$, 1 equiv BQ, 2 equiv $AgNO_3$, 2 wt % PTS/water, rt, 20 h. Conditions B: 10 mol % $Pd(OAc)_2$, 1 equiv BQ, 2 equiv AgOAc, 5 equiv HBF_4 aq, 2 wt % Brij 35/water, rt, 20 h.

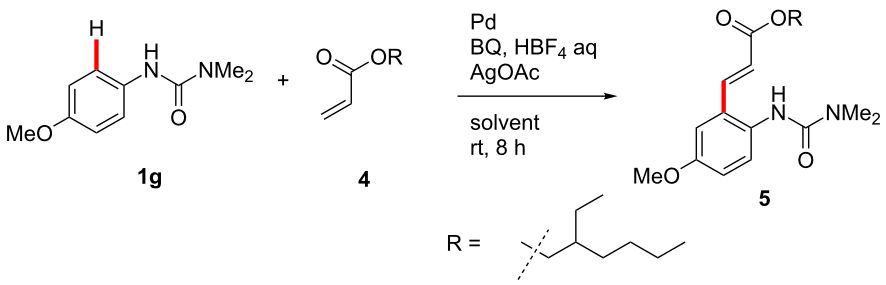
where the C–H activation would occur) were reactive. However, we have since found that use of acetonitrile-free, in situ generated cationic palladium with arylureas as the directing group expanded the substrate scope to include reactions with 3-alkyl-substituted ureas, as well as a wider variety of acrylates and even some acrylamides (Figure 4, **5d**–**h**, conditions B). Many combinations of acrylates and more challenging arylureas, however, did not produce the desired product in satisfactory yields, and the reaction still required the use of stoichiometric silver salts in addition to benzoquinone.

To overcome these limitations, further optimization of the catalyst system was conducted (Figure 5). A combination of $AgNO_3$ or AgOAc and BQ was critical to obtain good yields of the same products formed earlier in water (vide supra), but as seen previously in the corresponding Suzuki–Miyaura reactions, a switch to EtOAc obviated the need for a silver salt. In the presence of BQ and HBF_4, the reaction of **1g** and acrylate **4** was efficiently catalyzed by $Pd(OAc)_2$ (Figure 5, runs 3 and 4). Lower loadings of BQ and HBF_4 also gave good results (Figure 5, runs 5 and 7). Much lower loading of HBF_4, however, afforded a low yield of product **5** (Figure 5, run 8). In the absence of acid or BQ, the product was not obtained (Figure 5, runs 6 and 9). The pre-formed cationic palladium(II) complex, $[Pd(MeCN)_4](BF_4)_2$, was also found to effectively catalyze the reaction between **1g** and ester **4** at room temperature, without additional acid, although somewhat longer reaction times were necessary (Figure 5, run 10). Despite the presence of two potentially reactive *ortho*-aromatic C–H bonds in **1g**, the mono-acrylated product was obtained exclusively.

Under optimized conditions, various acrylates and amides can be synthesized via C–H activation reactions (Figure 6). Methyl acrylate, which did not show good general reactivity with arylureas under previous conditions, could be coupled in excellent yields (**5i**, **5j**, **5k**). As previously mentioned, a drawback characteristic of several *ortho*-directed C–H activation cross-coupling approaches has been the undesired coupling at both sites *ortho*- to the directing group. These new conditions completely inhibited second-stage alkenylation, thereby generating singly derivatized arylureas in good yields (**5l**, **5m**, **5n**). Arylureas containing halogens, which are slightly electron-deficient but provide useful synthetic handles for subsequent functionalization, reacted cleanly to form the desired products (**5p**, **5q**). Arylureas bearing *ortho*-alkyl substituents also gave excellent yields (**5o**, **5r**), while acrylamides having simple amine or amino acid moieties also participated in cross-coupling reactions with the arylurea to produce the corresponding amide derivatives in moderate to good yields (**5s**, **5t**).

Total synthesis of boscalid® via C–H activation

The rationale behind the attention recently accorded C–H activation chemistry has been based, in part, on its potential to streamline routes towards valuable synthetic targets. As a demonstration of the utility of our C–H activation approach, we



run	cat	BQ	AgOAc	HBF_4	yield(%)
1	$Pd(OAc)_2$	1	2	5	38[a]
2	$Pd(OAc)_2$	1	2	5	93
3	$Pd(OAc)_2$	3	0	1	96 (7 h)
4	$Pd(OAc)_2$	3	0	1	97 (4 h)
5	$Pd(OAc)_2$	1.5	0	1	92 (4 h)
6	$Pd(OAc)_2$	0	0	1	trace (7 h)
7	$Pd(OAc)_2$	3	0	0.5	93 (7 h)
8	$Pd(OAc)_2$	3	0	0.2	40 (4 h)
9	$Pd(OAc)_2$	3	0	0	0 (20 h)
10	$[Pd(MeCN)_4](BF_4)_2$	3	0	0	88 (20 h)

Figure 5: Optimization. Conducted at rt for 8 h or as otherwise noted in EtOAc with 10 mol % Pd catalyst, AgOAc, HBF_4, arylurea (**1g**, 0.25 mmol), BQ and acrylate (**2c**, 2.0 equiv). [a]2 wt % Brij 35 in water instead of EtOAc.

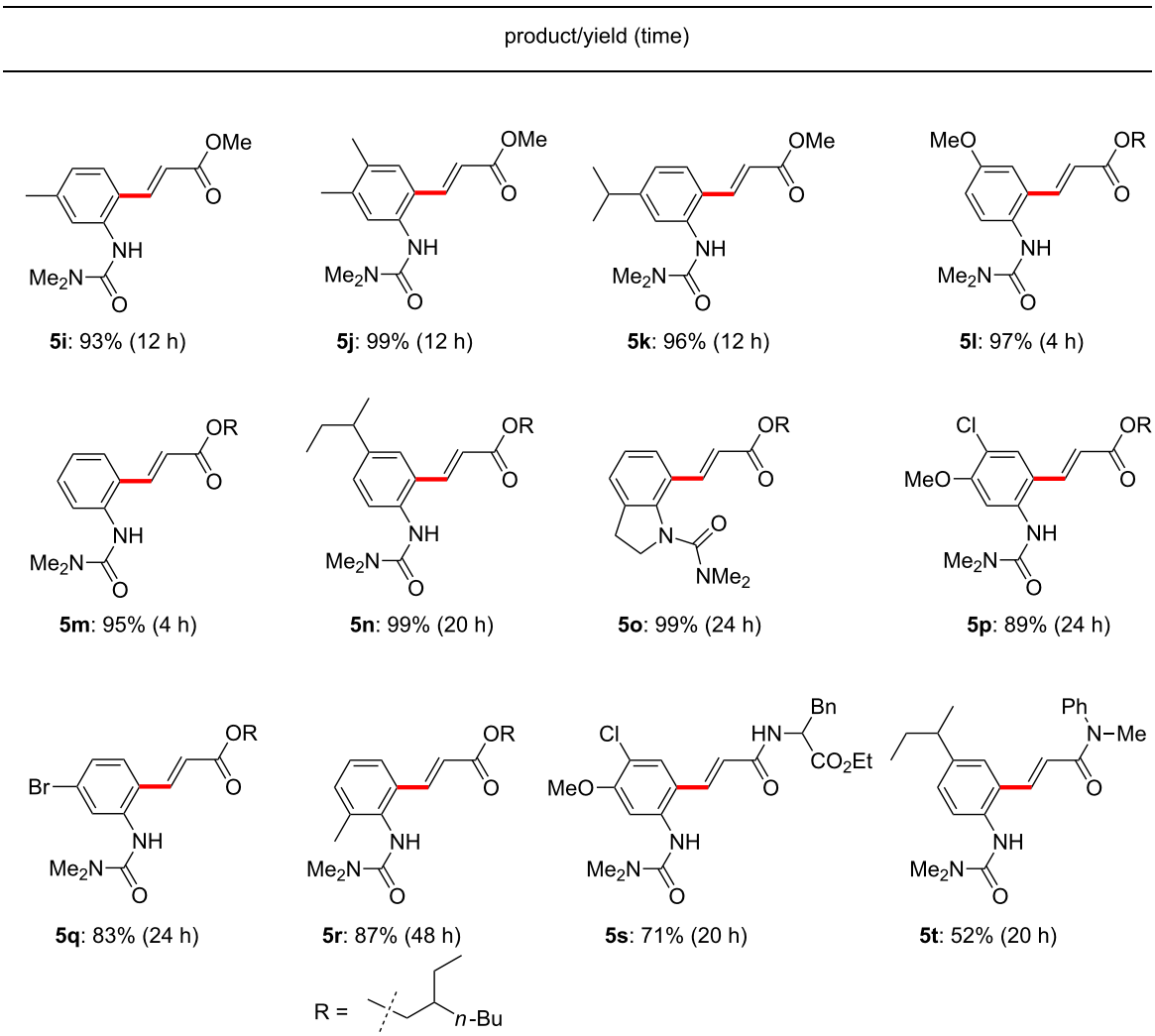


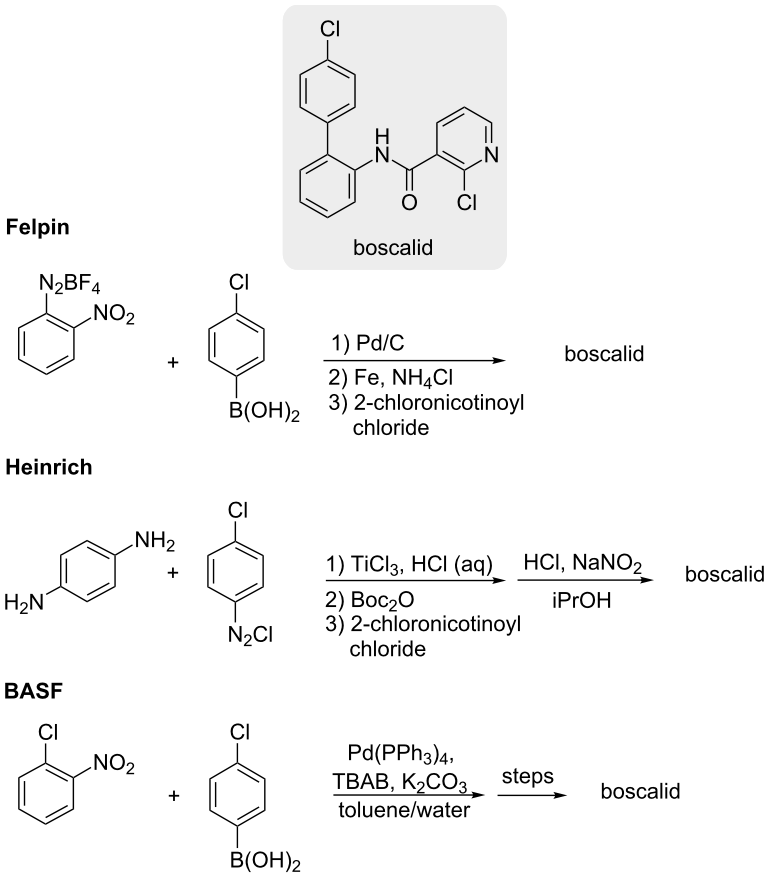
Figure 6: Representative results in EtOAc. Conducted at rt in EtOAc with 10 mol % $Pd(OAc)_2$, HBF_4 (1 equiv), arylurea (**1**, 0.25 mmol), BQ (3 equiv) and acrylate (**2**, 2.0 equiv).

chose to synthesize boscalid®, a pesticide currently prepared on a yearly kiloton scale by means of a traditional Suzuki–Miyaura coupling. It is used to control a range of plant pathogens in broadacre and horticultural crops (Scheme 6) [207]. Felpin and co-workers have reported its synthesis starting from aryldiazonium salts [208], while the Heinrich group has employed a free-radical biaryl cross-coupling of diaminobenzene promoted by $TiCl_3$ [209]. A number of additional syntheses can also be found in the literature [86,210]. Moreover, the BASF has patented routes using a traditional Suzuki–Miyaura cross-coupling in the presence of 0.5 mol % Pd catalyst to reach the same nitro-intermediate found in the Felpin route [211-213].

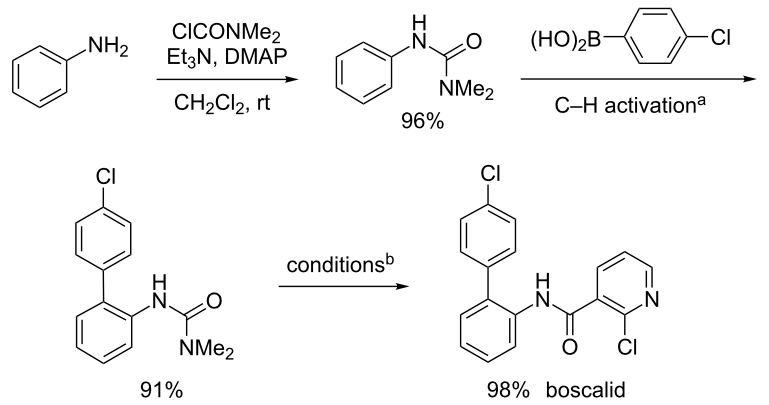
Many of these syntheses require large excesses of iron or other stoichiometric metals to obtain high yields (Scheme 6). As shown in Scheme 7, a synthesis that proceeds via a C–H activation strategy, however, might provide a highly efficient, alternative route originating from just aniline. The corresponding phenylurea can be prepared in high yield (96%), which is then subjected to C–H Suzuki–Miyaura coupling at room temperature (91%). Sequential deprotection and acylation with 2-chloronicotinoyl chloride result in boscalid in four steps in an overall yield of 86%, which compares favorably with all known routes to this pesticide shown in Scheme 6 [86,208-213].

Mechanistic insight

Although there have been a number of mechanistic studies on C–H activation reactions involving neutral palladium species [34,108-119], those catalyzed by cationic palladium have been much less thoroughly examined. We hypothesized that our catalytic cycles for the Fujiwara–Moritani, arylboronic acid, and aryl iodide coupling reactions catalyzed by cationic palladium



Scheme 6: Previous syntheses of boscalid®.

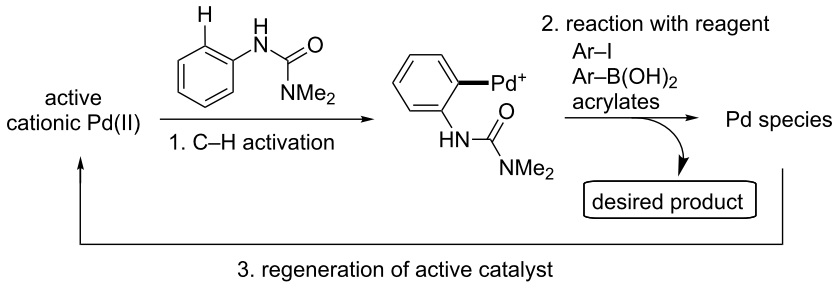


Scheme 7: Synthesis of boscalid®. [a]Conducted at rt for 20 h in EtOAc with 10 mol % $[Pd(MeCN)_4](BF_4)_2$, BQ (5 equiv), arylurea (**1**, 0.25 mmol), and $ArB(OH)_2$ (**2**, 1.5 equiv). [b]NaOH, dioxane/water, reflux, then 2-chloronicotinoyl chloride, Et_3N, THF, rt.

complexes are composed of three key steps; (1) aromatic C–H activation by cationic palladium; (2) reaction of the resulting intermediate (a cationic palladacycle) with a corresponding reagent; and (3) re-generation of the active catalyst (Scheme 8). In order to test this hypothesis we explored the viability of each of these individual steps.

The C–H activation step

Although aromatic C–H bond activation through palladacycle [214] generation is a critical step in the *ortho*-directed, activation/cross-coupling sequence, many of its specific mechanistic features are still controversial. Previous studies with arylureas [73,206,215] have formulated a palladacycle as the likely initial



Scheme 8: Hypothetical reaction sequence for cationic Pd(II)-catalyzed aromatic C–H activation reactions.

intermediate associated with palladation and subsequent C–H bond cleavage.

In order to confirm palladacycle formation in our reactions with arylureas, the dicationic palladium complex $[Pd(MeCN)_4](BF_4)_2$ was exposed to one equivalent of 3-methoxyphenylurea **1f** at room temperature for 20 minutes (Scheme 9). This stoichiometric reaction led to the corresponding palladacycle **6** in 95% yield, without the aid of additives (i.e., no Ag salt or protic acid). In harmony, in situ-generated cationic palladium from the reaction of $Pd(OAc)_2$ and HBF_4 gave the same palladacycle upon addition of acetonitrile, as confirmed by NMR. The facile formation of this species supports the intermediacy of a palladacycle in the catalytic cycle. The structure of the isolated palladacycle was confirmed by X-ray analysis [216].

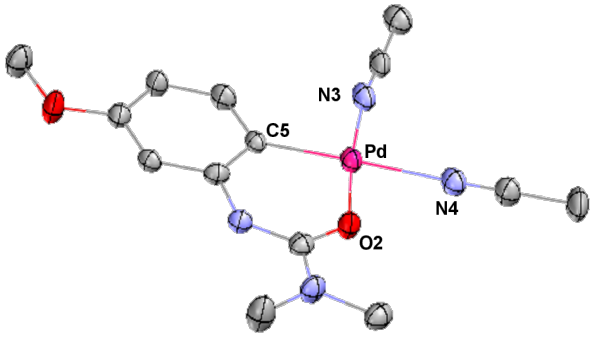
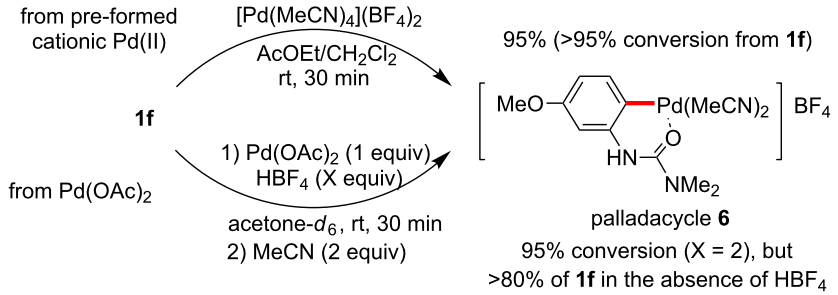


Figure 7: X-ray structure of palladacycle **6** with thermal ellipsoids at the 50% probability level. BF_4 and hydrogen atoms were omitted for clarity. Selected bond length (Å): Pd–C(5) = 1.980, Pd–N(3) = 1.995, Pd–N(4) = 2.126, Pd–O(2) = 1.988. Selected angles (°): C(5)–Pd–N(3) = 94.15, N(3)–Pd–N(4) = 87.81, N(4)–Pd–O(2) = 86.07, O(2)–Pd–C(5) = 91.98.

An ORTEP plot for palladacycle **6** is shown in Figure 7. The molecular structure consists of a Pd atom with an arylurea and two molecules of acetonitrile assembled in a square-planar geometry around the metal. The sum of the angles around Pd is 360.01°. The C(5)–Pd–O(2) angle (91.98°) is slightly larger than that of N(3)–Pd–N(4) (87.81°), but it is similar to the angles of neutral $PdCl_2(Ph_2PCH_2CH_2CH_2PPh_2)$(dppp)) (angle of P–Pd–P: 90.58°) having a six-membered ring conformation [217], and palladacycles reported previously [73,206,215]. The length of the Pd–N4 bond, (2.126 Å), is slightly longer than those of Pd–N(3), Pd–C(5), Pd–O(2) bonds, likely due to a trans effect of the strong σ-donor aryl group as has been observed in a related urea palladacycle [73,215]. The bond length of Pd–N is 1.96 Å in $[Pd(MeCN)_4](BF_4)_2$.

NMR spectroscopic studies on the reaction between a cationic Pd(II) complex and an arylurea to generate a palladacycle are illustrated in Figure 8. The pure palladacycle from pre-formed cationic palladium $[Pd(MeCN)_4](BF_4)_2$ is shown as spectrum in Figure 8A. Generally, monocationic arylpalladium(II) com-



Scheme 9: Palladacycle formation.

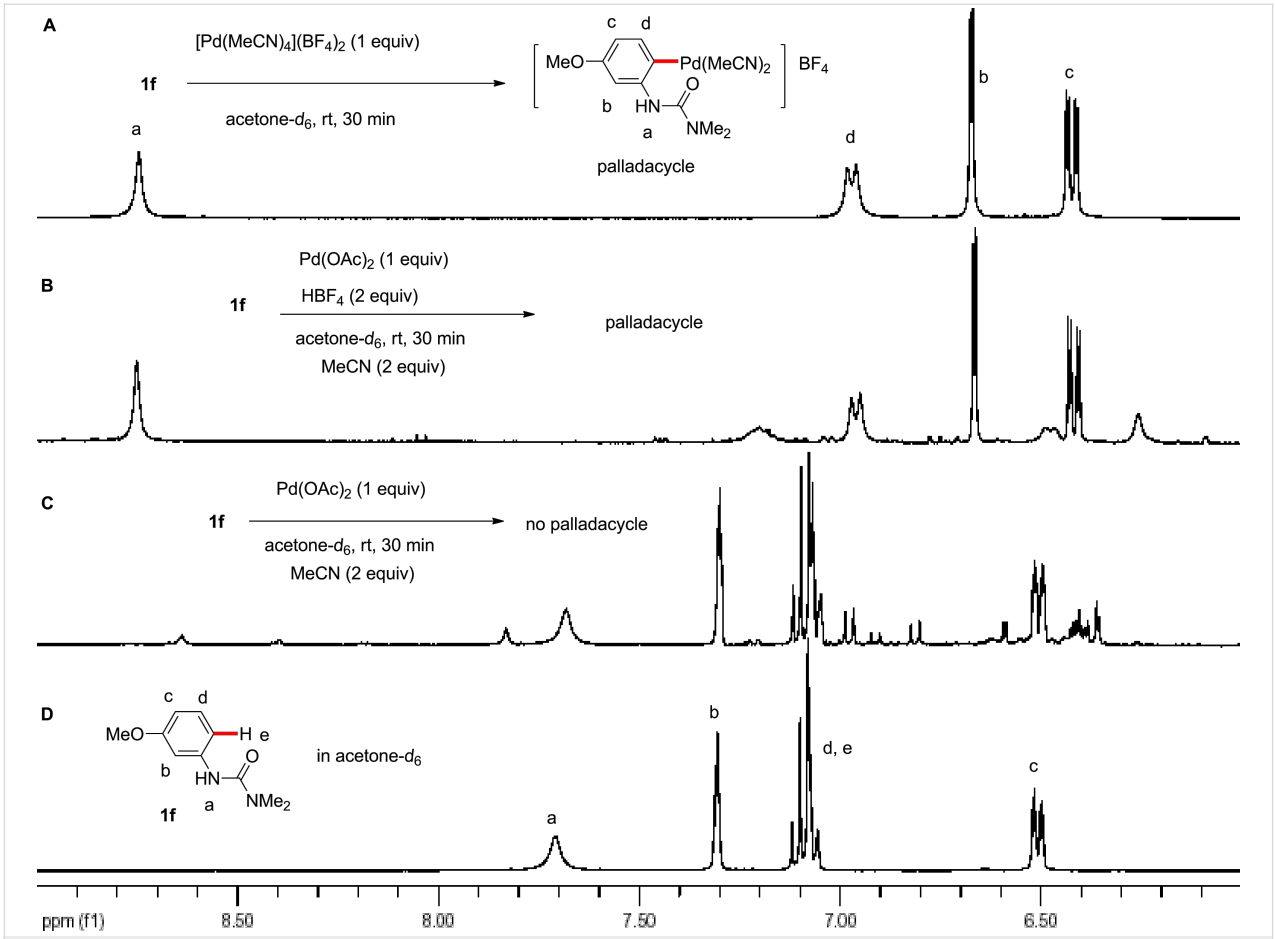


Figure 8: NMR studies. A: The reaction of $[Pd(MeCN)_4](BF_4)_2$ and 3-$MeOC_6H_4NHCONMe_2$ in acetone-d_6. B: The reaction of $Pd(OAc)_2$ and 3-$MeOC_6H_4NHCONMe_2$ in the presence of HBF_4 and MeCN in acetone-d_6. C: The reaction of $Pd(OAc)_2$ and 3-$MeOC_6H_4NHCONMe_2$ in the presence of MeCN in acetone-d_6. D: 3-$MeOC_6H_4NHCONMe_2$ in acetone-d_6.

plexes without strongly coordinating ligands are unstable even at low temperatures [218-220]; nonetheless, this cationic palladacycle, aided by the presence of strongly coordinating MeCN, was found to be quite stable at room temperature. While the in situ generated cationic palladium species from the reaction of $Pd(OAc)_2$ and HBF_4 gave the same palladacycle upon treatment with the arylurea (spectrum Figure 8B), the reaction in the absence of HBF_4 did not result in palladacycle formation (spectrum Figure 8C). Here, essentially no conversion of the starting material was detected by ^1H NMR in acetone-d_6 (spectrum Figure 8D). Indeed, for reactions starting from $Pd(OAc)_2$, no cross-coupling product was observed without adding a BF_4^- source for the Fujiwara–Moritani reaction (Figure 5, run 9), Suzuki–Miyaura coupling (Scheme 4), and arylation with aryl iodide [121,122,150]. HBF_4 apparently acts as an acetate scavenger to generate the active cationic palladium(II) species (Scheme 10).

$$Pd(OAc)_2 \xrightarrow[-\ AcOH]{HBF_4} [Pd(II)L_n](BF_4)_2$$

Scheme 10: The generation of cationic Pd(II) from $Pd(OAc)_2$.

As discussed previously herein, there are several routes available for cyclopalladation and C–H bond cleavage, most notably the concerted metalation-deprotection (CMD) or electrophilic palladation pathways (Scheme 1) [221-224]. Although control experiments had previously indicated the importance of conditions involving cationic palladium for achieving overall reaction conversion, our studies of palladacycle formation suggest that a cationic palladium catalyst is specifically required for the initial C–H activation step itself. Since the crystal structure of **6** (Figure 7) is indicative of a monocationic palladacycle, the cationicity of the metal may still play a role as well in subsequent steps. However, the much higher reactivity of a cationic Pd species (even under acetate-free conditions), the lack of effectiveness of $Pd(OAc)_2$ alone in palladacycle formation, and the observed reactivity trends that strongly favor more electron-rich arylureas, all appear to be most consistent with an

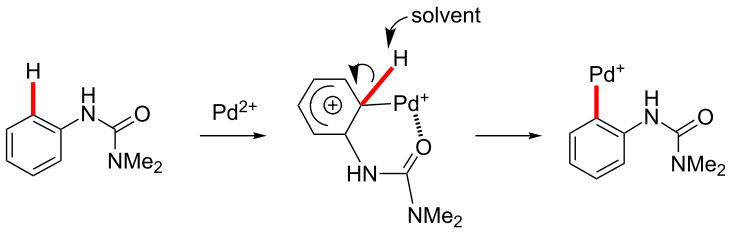
electrophilic palladation pathway over a CMD mechanism (Scheme 11). However, it is appreciated that further study might provide additional insight on this point.

Reactions of palladacycle **6** with Ph–I, $PhB(OH)_2$, and an acrylate

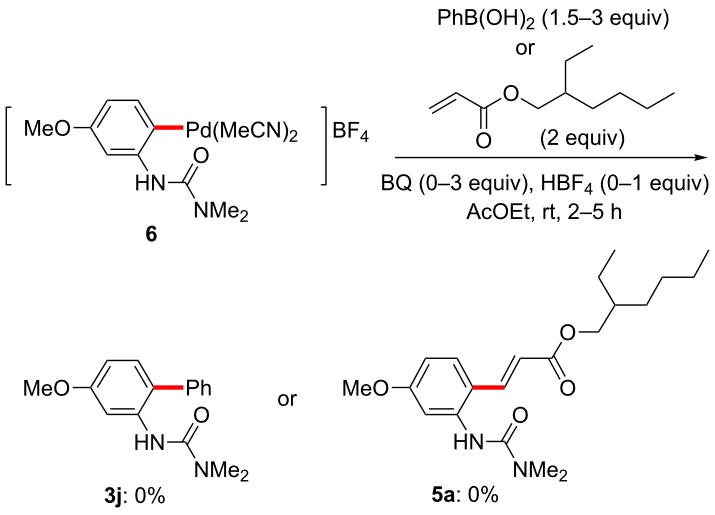
Having demonstrated the potential for facile palladacycle formation at room temperature, we next examined the reactivity of this intermediate with coupling partners for each of the three reaction types studied. Stoichiometric reactions between the isolated palladacycle **6** and an acrylate or arylboronic acid were first attempted at room temperature (Scheme 12). Initial experiments, however, resulted in no formation of the desired products. Although the palladacycles were subjected to various conditions in the presence of BQ and HBF_4, the anticipated reaction did not proceed from isolated catalyst complexes containing the stabilizing ligand MeCN.

Although the initial C–H activation step proceeded readily in the presence of MeCN in these stoichiometric reactions, subsequent reactions of the palladacycle with acrylates, arylboronic acids, and aryl iodides appeared to be significantly suppressed by the presence of stoichiometric MeCN. The inhibitory effect of this ligand had been previously observed in the coupling reactions of aryl iodides (in which even 40 mol % of MeCN was enough to almost completely shut down the reaction) [121]. In a cationic palladium(II) complex-catalyzed 1,4-addition of arylsilane, the nitrile-free cationic Pd(II) catalyst was much more effective than a PhCN-containing cationic palladium(II) complex towards transmetallations with arylsilicon-containing partners and insertion of mono-cationic arylpalladium(II) species into olefins [136]. The detrimental effect of MeCN under our C–H activation conditions was further established through a series of reactions as illustrated in Scheme 13. Under optimized conditions previously determined, where C–H functionalized products were obtained in good yields, in the presence of added MeCN (1 equiv relative to **1f**) all three reactions were completely inhibited, in all likelihood due to its strong coordinating ability as a ligand on cationic palladium.

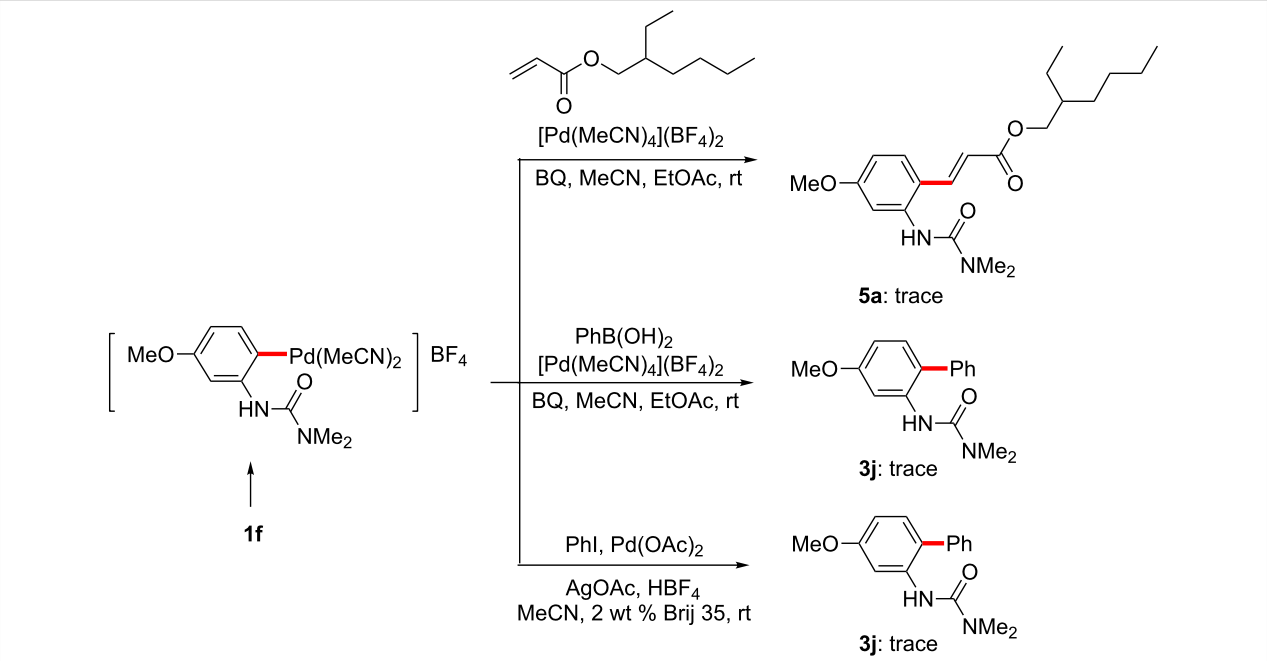
On the other hand, when nitrile-free conditions were applied to urea **1f**, with in situ-generated palladacycle (from $Pd(OAc)_2$ and



Scheme 11: Electrophilic substitution of aromatic hydrogen by cationic palladium(II) species.



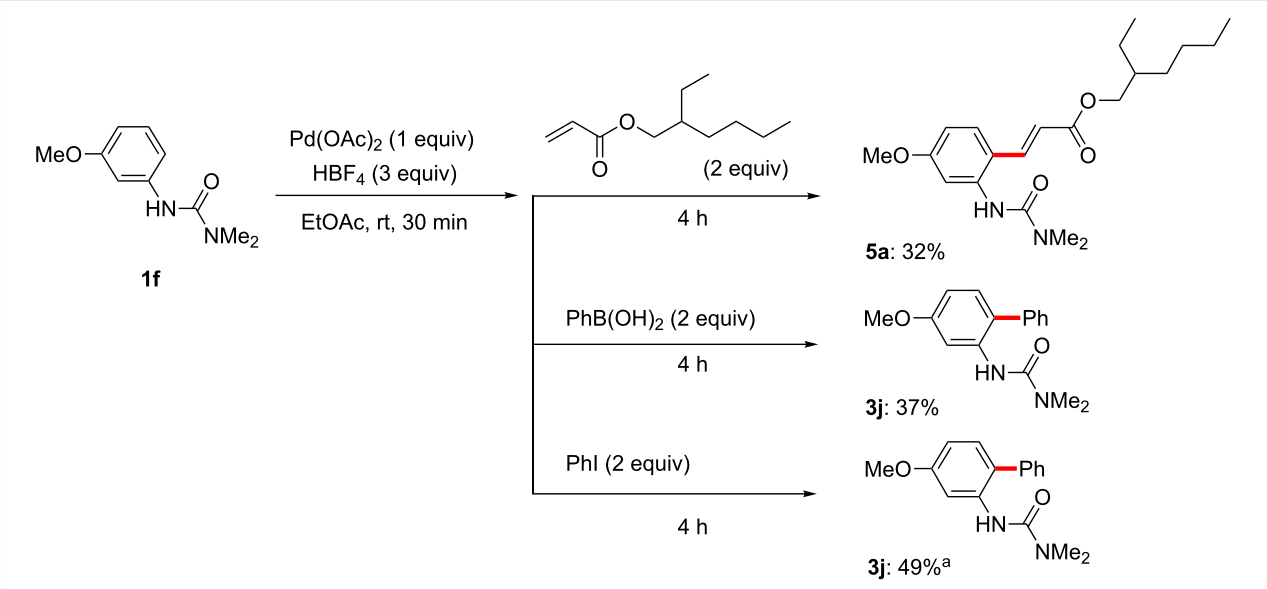
Scheme 12: Attempted reactions of palladacycle **6**.



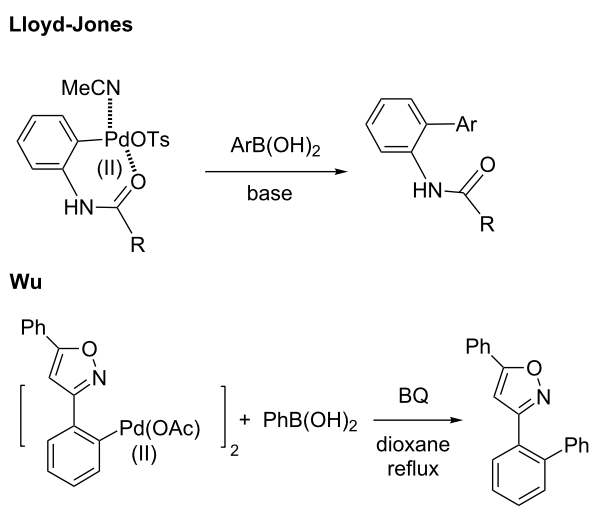
Scheme 13: The impact of MeCN on C-H activation/coupling reactions.

HBF_4; Figure 8), followed by addition of the usual reagents, each reaction proceeded to give the anticipated acrylated/arylated product (Scheme 14; unoptimized yields). Notably, all three stoichiometric reactions now proceeded in the absence of other additives, such as BQ or Ag(I) salts, which are required for the catalytic versions to proceed efficiently.

Although Lloyd-Jones and Booker-Milburn also reported the reaction of a urea-derived palladacycle and arylboronic acid in the presence of base in THF under reflux conditions to produce the corresponding coupling product, our cationic palladacycle underwent coupling without added base (Scheme 15) [178]. In fact, it has been previously shown that cationic palladium species can undergo transmetalation with an arylboronic acid in the absence of base even at 0 °C [219,220]. Wu and co-workers have also reported the interesting reactivities of neutral palladacycles with arylboronic acids (Scheme 15). Under their conditions, BQ and high temperature were critical to obtain the prod-



Scheme 14: Stoichiometric MeCN-free reactions. [a]2% Brij 35 was used instead of EtOAc.



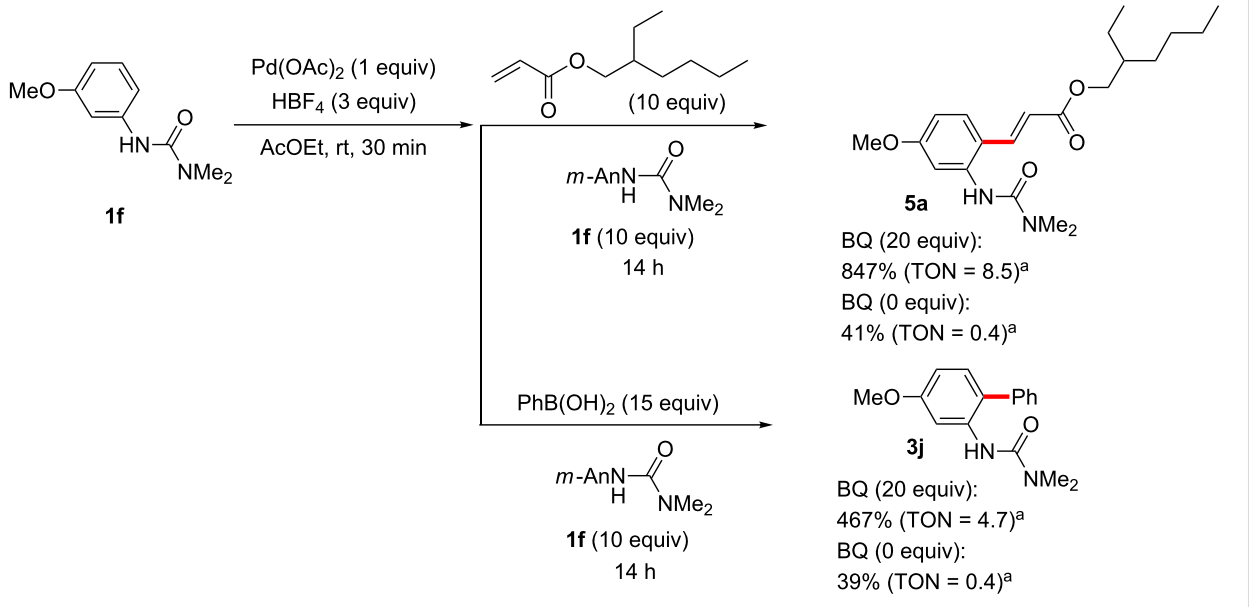
Scheme 15: The reactions of divalent palladacycles.

uct from their 5-membered isoxazoline-containing palladacycle [160,168,225]. Although BQ is sometimes used as a ligand for palladium to accelerate reductive elimination [103,226-230], its presence was not necessary in our stoichiometric reaction of a cationic 6-membered ring palladacycle.

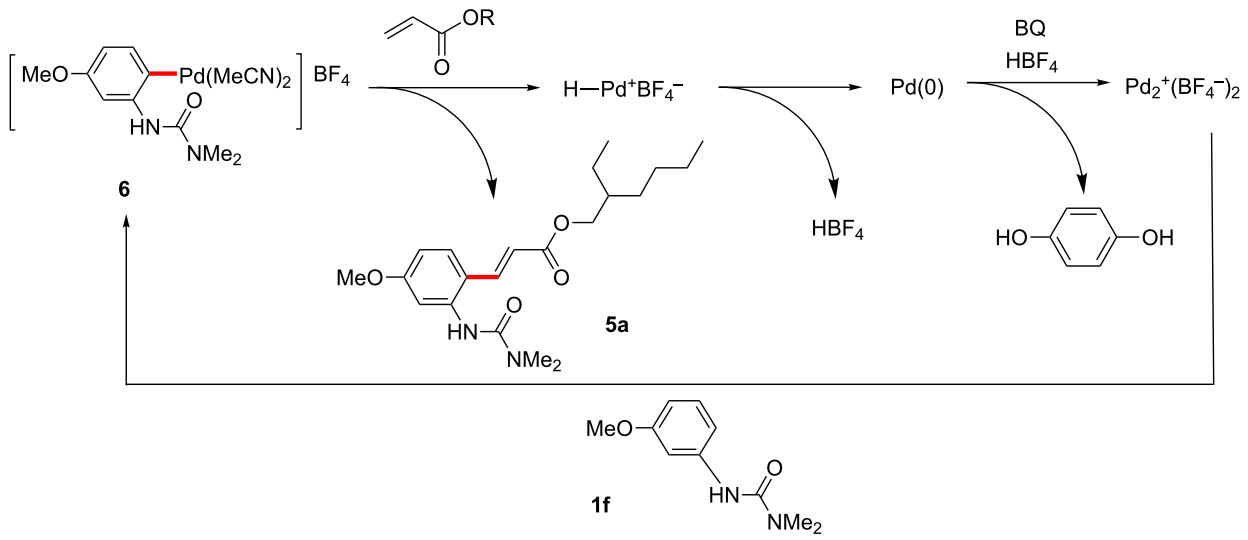
Regeneration of active catalyst; the roles of additives BQ, AgOAc, and HBF_4

As shown in previous sections herein, both the formation of palladacycles from arylureas and their subsequent coupling reactions with acrylates, arylboronic acids, and aryl iodides proceed under stoichiometric palladium conditions in the absence of additives, such as BQ and AgOAc, which had been necessary in the corresponding optimized catalytic reactions. To establish the roles of these additives, the reaction of the palladacycle in the presence of excesses of both coupling partners was carried out (Scheme 16). In Fujiwara–Moritani and Suzuki–Miyaura coupling reactions, 41 and 39% of the products (isolated yields based on the palladacycle) were obtained, respectively, in the absence of BQ, indicating that no catalyst turnover was occurring without this additive. When 20 equivalents of BQ were added, along with the coupling partners, however, 847% (TON = 8.5) and 467% (TON = 4.7) yields of the products were obtained, respectively, supporting a key role for BQ in regeneration of the active dicationic species ($PdL_4(BF_4)_2$).

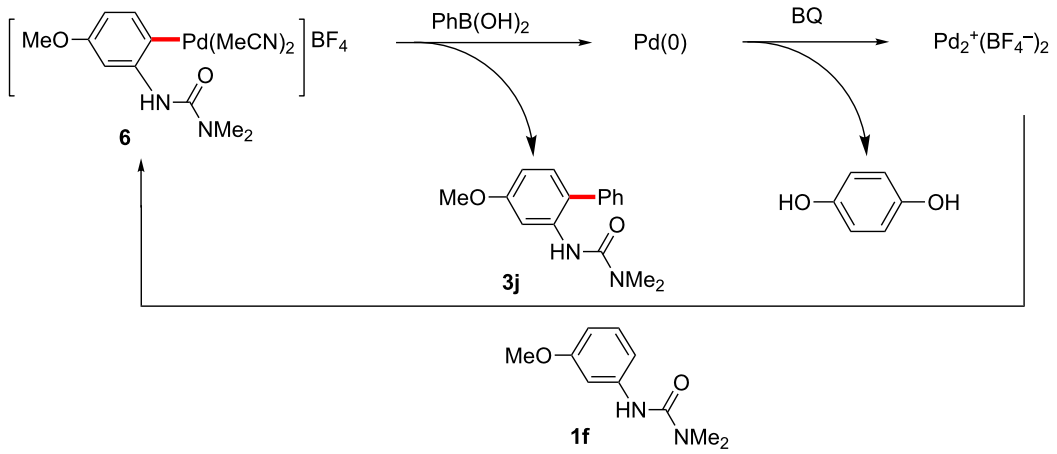
Benzoquinone (BQ) has been well studied as an oxidant for Pd(0) to Pd(II) processes, generating hydroquinone as a byproduct. For the Fujiwara–Moritani coupling, addition of the palladacycle **6** to an acrylate followed by β-hydride elimination and reductive elimination of $HPd^+BF_4^-$ would result in a Pd(0) species unable to participate in palladacycle formation until it is oxidized by BQ to $Pd^{2+}(BF_4)_2$, whereupon it reacts with another equivalent of arylurea (Scheme 17) [231]. Similarly, BQ's role in C–H coupling of boronic acids would likely be to oxidize Pd(0) to Pd(II) after the product forming step (Scheme 18). Transmetallation between the palladacycle and arylboronic acid followed by reductive elimination would give the expected product and Pd(0), where the metal can be subsequently oxidized with BQ.



Scheme 16: Role of BQ in stoichiometric Fujiwara–Moritani and Suzuki–Miyaura coupling reactions. [a]Yields based on Pd.



Scheme 17: Proposed role of BQ in Fujiwara–Moritani reactions.

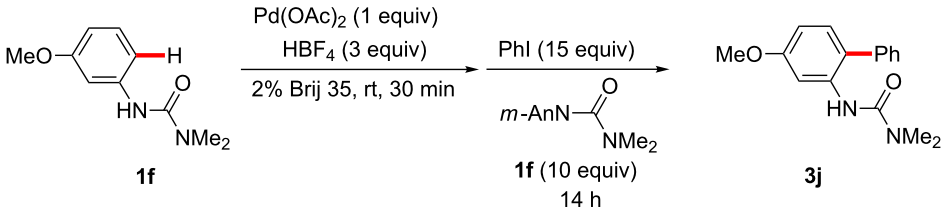


Scheme 18: Proposed role of BQ in Suzuki–Miyaura coupling reactions.

In the reaction with aryl iodides, when an excess of coupling partner was employed, a yield of ca. 90% (TON = 0.9) of the product was obtained with or without additional HBF_4 (Scheme 19), in this case indicating that no catalyst turnover was occurring in the absence of a Ag(I) salt. Surprisingly, when 15 equivalents of AgOAc were added along with an excess of both coupling partners, but without the addition of HBF_4 beyond the three equivalents required for initial palladacycle formation, no coupling product was observed. Under these conditions, a large excess of acetate anion relative to BF_4^- would exist, which may decrease the cationicity of the cationic palladium(II) species formed in the initial cyclopalladation (Scheme 20), or otherwise disrupt the reaction sequence subsequent to palladacycle formation. On the other hand, the reaction in the presence of both silver salt and excess of HBF_4 gave the corresponding product in 342% yield relative to palladium (TON = 3.4) (Scheme 19).

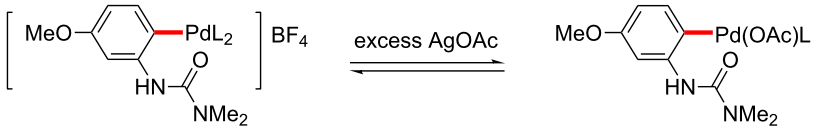
Based on these results, the proposed roles of silver and acid are shown in Scheme 21. After the coupling of the palladacycle and aryl iodide, I–$Pd^+BF_4^-$ is generated, which is catalytically inactive. Then, I–$Pd^+BF_4^-$ reacts with AgOAc and HBF_4 to regenerate active cationic $Pd^{2+}(BF_4^-)_2$. Under this proposed sequence, AgOAc would primarily act, therefore, as an iodide scavenger.

In our previous studies it was found that when $AgBF_4$ was used in place of AgOAc under optimized conditions for C–H arylation with aryl iodides, HBF_4 (or any other added acid) was unnecessary for the catalytic reaction to occur. Here, since

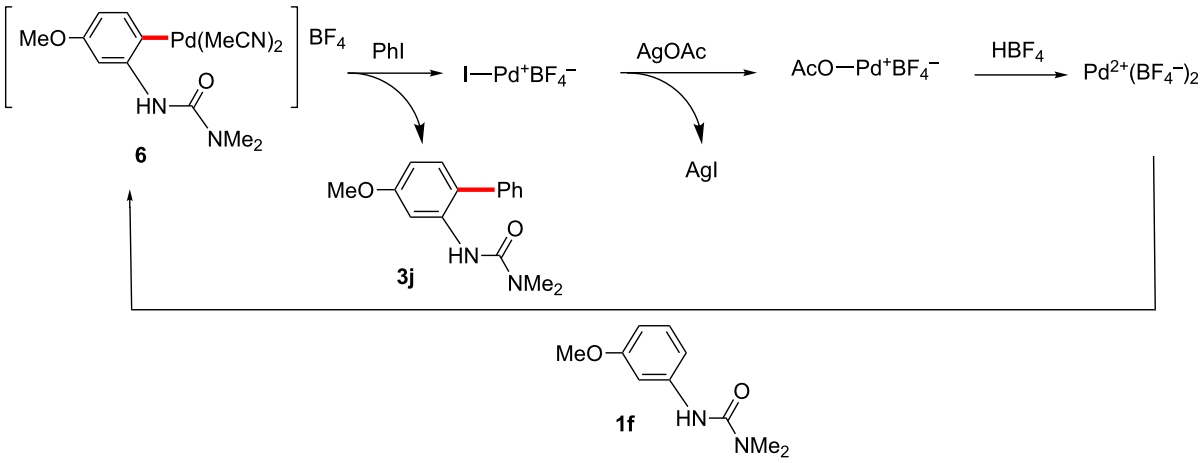


AgOAc (equiv)	HBF_4 (equiv)	yield[a]	TON
15	50	342	3.4
0	50	87	0.9
15	0	0	0
0	0	94	0.9

Scheme 19: Stoichiometric C–H arylation of iodobenzene. [a]Yields based on Pd.



Scheme 20: Impact of acetate on the cationicity of Pd.



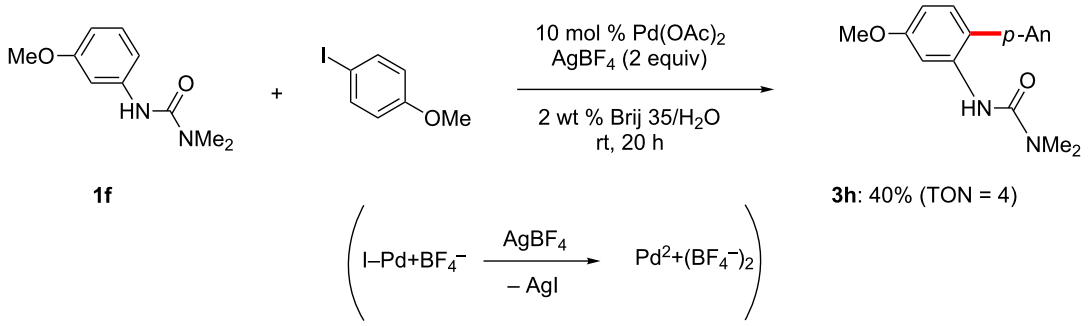
Scheme 21: Roles of additives in C–H arylation.

$AgBF_4$ apparently reacts with $I–Pd^+BF_4^-$ to produce catalytically active $Pd^{2+}(BF_4)_2^-$ (Scheme 22), and there are no stoichiometric quantities of competing acetate anions, additional acid is not needed to produce and maintain active catalyst.

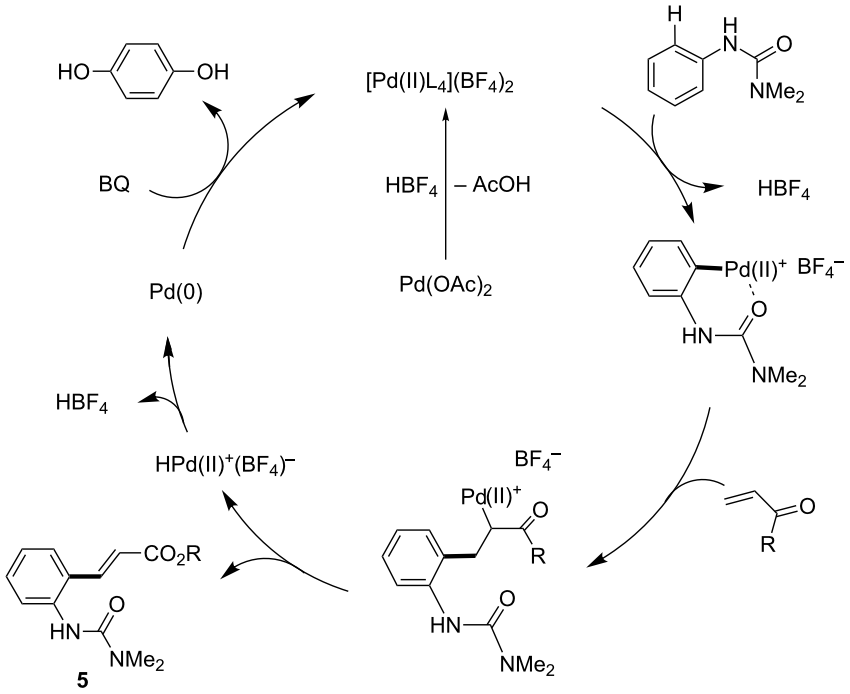
Proposed mechanisms

Our results have demonstrated that a dicationic palladium complex effectively catalyzes C–H activation of arylureas at room temperature. Based on these studies of the major steps for each reaction, proposed catalytic cycles are illustrated below.

Fujiwara–Moritani reactions. At the first stage of the catalytic cycle, an active divalent cationic palladium species is generated from the reaction of a neutral complex, $Pd(OAc)_2$, and HBF_4 [232]. This reaction results in the formation of a monocationic arylpalladium(II) palladacycle, likely via a Wheland-like intermediate (Scheme 23) [233-237]. The product-forming portion of the cycle may proceed in a manner resembling a traditional Heck cross-coupling. In this case, addition of the palladacycle to an acrylate followed by β-hydride elimination yields the corresponding product **5**. As previously demon-



Scheme 22: Cross-coupling in the presence of $AgBF_4$.

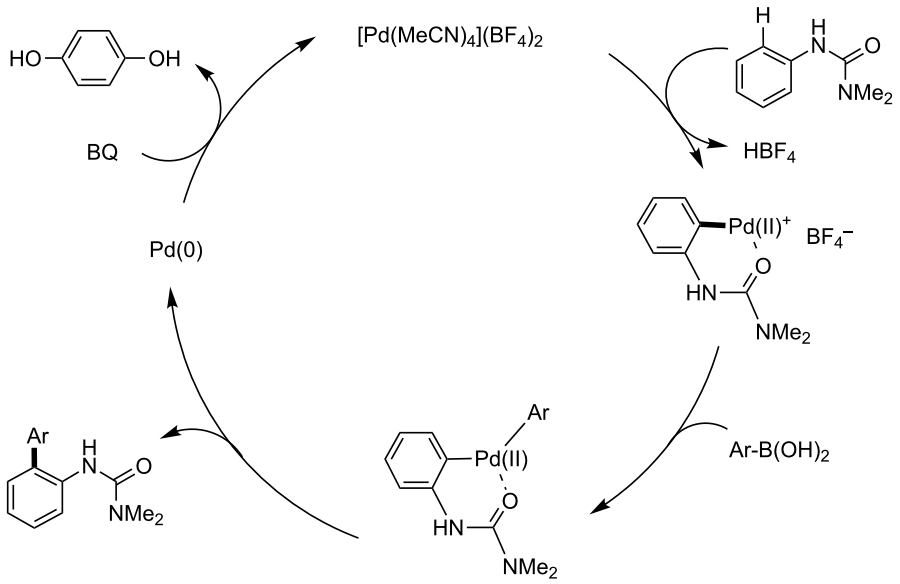


Scheme 23: A proposed catalytic cycle for Fujiwara–Moritani reactions.

strated in palladium-catalyzed Mizoroki–Heck reactions [238-240], insertion of a alkenyl double bond into C–Pd^+ present within the cationic palladacyle is facile, owing to the high Lewis acidity of the metal center. This is a noteworthy advantage associated with the use of cationic palladium(II) catalysts. Finally, BQ oxidizes the Pd(0) that is reductively eliminated from the $HPd(II)^+BF_4^-$ formed to regenerate the active cationic palladium species $Pd^{2+}(BF_4)_2^-$.

C–H boronic acid coupling reactions. Unlike traditional Suzuki–Miyaura coupling reactions [241-243], C–H coupling reactions catalyzed by a cationic palladium(II) complex require an oxidant instead of a strong base, but otherwise likely share a number of features with this widely used C–C bond-forming process. The reaction also presumably starts from the generation of a cationic palladacycle, which may undergo a facile transmetalation with an arylboronic acid without prior activation by base (Scheme 24) [241-248]. This step is followed by reductive elimination of a diarylpalladium(II) species, affording the coupling product and Pd(0). The resulting Pd(0) is then oxidized with BQ to regenerate the dicationic palladium species, which can re-enter the catalytic cycle.

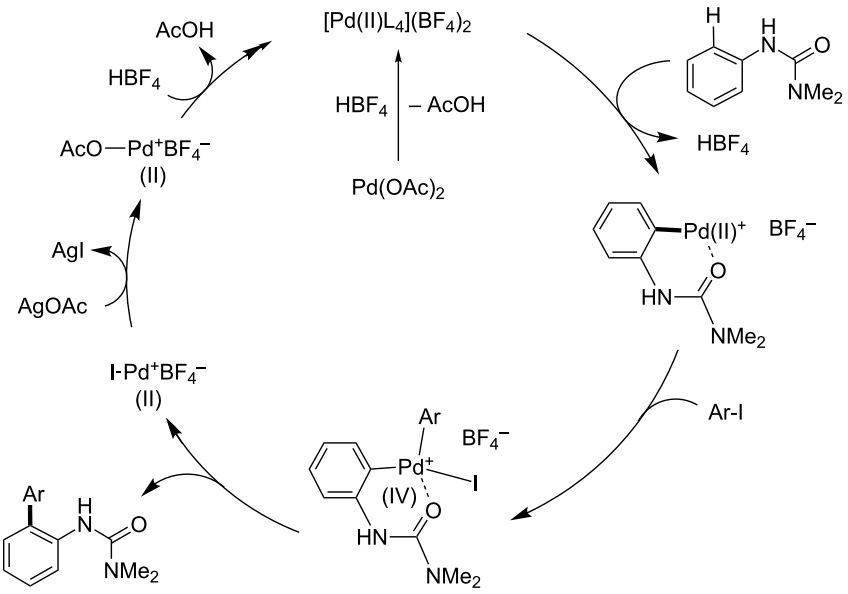
Arylation with an aryl iodide. Coupling reactions of aryl iodides have fewer similarities in terms of traditional cross-coupling reactions compared with features characteristic of other room temperature C–H activations we have studied, and are more difficult to rationalize with a Pd(II)/Pd(0) catalytic cycle.



Scheme 24: Proposed catalytic cycle of C–H activation/Suzuki–Miyaura coupling reactions.

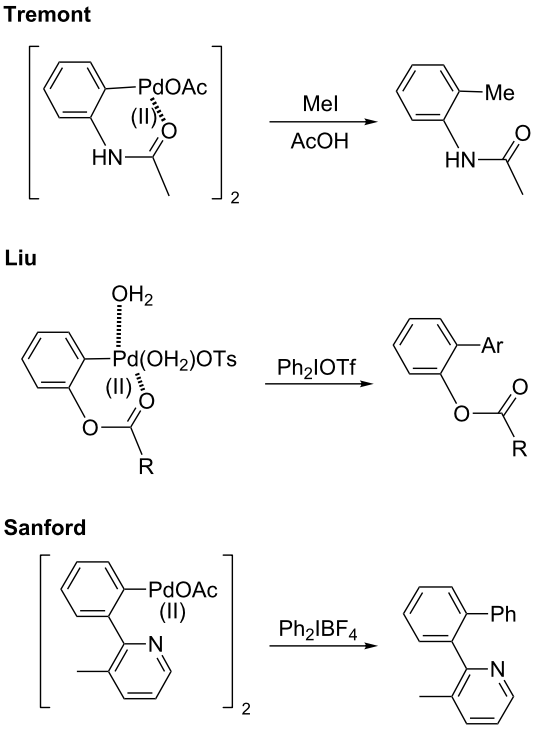
Hence, a possible Pd(II)/Pd(IV) catalytic cycle, similar to that previously proposed by Daugulis [8], is proposed below (Scheme 25). A mono-cationic palladium intermediate reacts with the aryl iodide, albeit in a poorly understood step of the sequence. Stoichiometric studies reveal that this step occurs in the absence of AgOAc, and in fact its presence in excess relative to HBF_4 inhibits the reaction (Scheme 19). In one possible pathway, an oxidative addition to the aryl iodide would provide a Pd(IV) intermediate, which could then rapidly reductively eliminate in the C–C bond forming step. The resulting I–Pd(II)–X species could then be converted back to the active cationic palladium species through reactions with the silver salt and HBF_4 (or in situ generated $AgBF_4$).

The specific nature of the reaction between the palladacycle and aryl iodide and resulting intermediate is lacking in details. It is known that divalent palladacycles react with alkyl iodides or diaryliodonium salts, and this process likely involves a Pd(IV)



Scheme 25: A proposed catalytic cycle for C–H arylation involving a Pd(IV) intermediate.

intermediate. Tremont and co-workers previously proposed a Pd(IV) intermediate in C–H alkylation of acetoanilides and alkyl iodides [172]. In this case the reaction of a divalent palladacycle and MeI readily occurred at room temperature and was shown not to proceed through a radical pathway. Notably, in 2011 Vicente and co-workers obtained the crystal structure of a Pd(IV) complex obtained by the room temperature oxidative addition of an internally-chelated Pd(II) species into an aryl iodide, and demonstrated this species' competence as a pre-catalyst for C–H olefinations. Liu [73] and Sanford reported the stoichiometric reaction of palladacycles and aryliodonium salts at high temperature to give the corresponding products through Pd(II)/Pd(IV) or Pd(III)/Pd(III) dimeric species bridged by acetates (Scheme 26) [68,175,249,250]. Sequences involving Pd(III) intermediates have been suggested as alternatives to Pd(II)/Pd(IV) cycles in some cases, but most well-studied examples involve Pd(III)/Pd(III) dimers formed with the aid of bridging anionic ligands such as acetate or nitrate [251,252] that do not match as well with the cationic palladium conditions employed here. Silver-mediated one electron oxidations to form monomeric Pd(III) complexes have also been studied [251], but the successful implementation of silver-free conditions with stoichiometric palladium herein would appear to eliminate this as a key step. To the best of our knowledge, the existence of Pd(IV) complexes has yet to be conclusively demonstrated from the oxidative addition of anilide-derived, divalent palladacycles into aryl halides, although formation of octahedral Pd(IV) complexes from *N*-substituted biphenyl palladacycles that possess similar highly planar structures as found in the urea-derived palladacycle (Figure 7) have been well studied [253-255].



Scheme 26: Selected reactions of divalent palladacycles.

Conclusion

In conclusion, we have demonstrated that a dicationic palladium complex enables facile C–H activation reactions of arylureas with aryl iodides, arylboronic acids, and acrylates at room temperature. In many cases nanomicelles in water can be used in place of organic solvents, allowing for some of the mildest and environmentally responsible conditions yet achieved in C–H activation chemistry. The practical value of this approach has been further demonstrated with an efficient, streamlined application to the synthesis of the herbicide boscalid. Mechanistic investigations revealed that a dicationic Pd(II) complex reacts readily with an arylurea to rapidly produce a mono-cationic palladacycle at room temperature, and this likely, catalytically competent species has been characterized by X-ray crystallography. Experiments revealed that a highly cationic palladium complex is required for the formation of this palladacycle at room temperature. While some key steps, including the precise nature of the reaction between this cationic palladacycle and aryl iodides, require further clarification, studies using stoichiometric palladium have provided insight into the roles of additives HBF_4, BQ, and AgOAc, as well as the crucial steps of each reaction's catalytic cycle. Lastly, this study highlights the advantages of dicationic palladium complexes in synthesis, and their tolerance to aqueous media. Such cationic reagent/medium combinations, potentially applicable to other group 10 metals, and Ni in particular, may well offer related synthetic opportunities.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization of all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-99-S1.pdf]

Supporting Information File 2

Crystal structure of **6**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-99-S2.cif]

Supporting Information File 3

Crystal structure of **6** No 2.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-99-S3.pdf]

Acknowledgements

We warmly thank the NIH for support of this work (GM 86485), and Johnson Matthey (Dr. Thomas Colacot) for supplying the $Pd(OAc)_2$ used in this work.

References

1. Godula, K.; Sames, D. *Science* **2006,** *312,* 67–72. doi:10.1126/science.1114731
2. Deprez, N. R.; Sanford, M. S. *Inorg. Chem.* **2007,** *46,* 1924–1935. doi:10.1021/ic0620337
3. Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007,** *107,* 174–238. doi:10.1021/cr0509760
4. Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008,** *41,* 222–234. doi:10.1021/ar700133y
5. Kakiuchi, F.; Kochi, T. *Synthesis* **2008,** 3013–3039. doi:10.1055/s-2008-1067256
6. Thansandote, P.; Lautens, M. *Chem. – Eur. J.* **2009,** *15,* 5874–5883. doi:10.1002/chem.200900281
7. Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009,** *48,* 5094–5115. doi:10.1002/anie.200806273
8. Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009,** *42,* 1074–1086. doi:10.1021/ar9000058
9. Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009,** *38,* 3242–3272. doi:10.1039/b816707a
10. Storr, T. E.; Baumann, C. G.; Thatcher, R. J.; De Ornellas, S.; Whitwood, A. C.; Fairlamb, I. J. S. *J. Org. Chem.* **2009,** *74,* 5810–5821. doi:10.1021/jo9012282
11. Zhang, M. *Adv. Synth. Catal.* **2009,** *351,* 2243–2270. doi:10.1002/adsc.200900426
12. Vedernikov, A. N. *Chem. Commun.* **2009,** 4781–4790. doi:10.1039/b907036b
13. Muñiz, K. *Angew. Chem., Int. Ed.* **2009,** *48,* 9412–9423. doi:10.1002/anie.200903671
14. Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010,** *110,* 624–655. doi:10.1021/cr900005n
15. Bellina, F.; Rossi, R. *Chem. Rev.* **2010,** *110,* 1082–1146. doi:10.1021/cr9000836
16. Scheuermann, C. J. *Chem. – Asian J.* **2010,** *5,* 436–451. doi:10.1002/asia.200900487
17. Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010,** *110,* 890–931. doi:10.1021/cr900206p
18. Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010,** *110,* 1147–1169. doi:10.1021/cr900184e
19. Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. – Eur. J.* **2010,** *16,* 2654–2672. doi:10.1002/chem.200902374
20. Mousseau, J. J.; Charette, A. B. *Acc. Chem. Res.* **2013,** *46,* 412–424. doi:10.1021/ar300185z
21. Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012,** *45,* 936–946. doi:10.1021/ar300014f
22. Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015,** *115,* 1622–1651. doi:10.1021/cr500410y
23. Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014,** *136,* 898–901. doi:10.1021/ja411715v
24. Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013,** *52,* 11726–11743. doi:10.1002/anie.201301451
25. Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J.-Q. *Nat. Chem.* **2014,** *6,* 146–150. doi:10.1038/nchem.1836
26. Thuy-Boun, P. S.; Villa, G.; Dang, D.; Richardson, P.; Su, S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013,** *135,* 17508–17513. doi:10.1021/ja409014v
27. Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007,** *129,* 5332–5333. doi:10.1021/ja070388z
28. Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002,** *124,* 3202–3203. doi:10.1021/ja017351d
29. Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002,** *124,* 13964–13965. doi:10.1021/ja0281129
30. Kakiuchi, F.; Sonoda, M.; Tsujimoto, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1999,** *28,* 1083–1088. doi:10.1246/cl.1999.1083
31. Cook, A. K.; Emmert, M. H.; Sanford, M. S. *Org. Lett.* **2013,** *15,* 5428–5431. doi:10.1021/ol4024248
32. Cheng, X.-F.; Li, Y.; Su, Y.-M.; Yin, F.; Wang, J.-Y.; Sheng, J.; Vora, H. U.; Wang, X.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013,** *135,* 1236–1239. doi:10.1021/ja311259x
33. Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006,** *8,* 1141–1144. doi:10.1021/ol0530272
34. Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008,** *130,* 13285–13293. doi:10.1021/ja8045519
35. Kim, H.; Shin, K.; Chang, S. *J. Am. Chem. Soc.* **2014,** *136,* 5904–5907. doi:10.1021/ja502270y
36. Foo, K.; Sella, E.; Thomé, I.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2014,** *136,* 5279–5282. doi:10.1021/ja501879c
37. Matsubara, T.; Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2014,** *136,* 646–649. doi:10.1021/ja412521k
38. Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011,** *133,* 1466–1474. doi:10.1021/ja108450m
39. Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011,** *133,* 1694–1697. doi:10.1021/ja1101695
40. Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010,** *132,* 6900–6901. doi:10.1021/ja101939r
41. Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008,** *130,* 10066–10067. doi:10.1021/ja803397y
42. Dick, A. R.; Remy, M. S.; Kampf, J. W.; Sanford, M. S. *Organometallics* **2007,** *26,* 1365–1370. doi:10.1021/om061052l
43. He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013,** *135,* 3387–3390. doi:10.1021/ja400648w
44. Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009,** *11,* 3250–3252. doi:10.1021/ol901049r
45. Vora, H. U.; Silvestri, A. P.; Engelin, C. J.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2014,** *53,* 2683–2686. doi:10.1002/anie.201310539
46. García-Rubia, A.; Urones, B.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2011,** *50,* 10927–10931. doi:10.1002/anie.201105611
47. Nakao, Y.; Yada, A.; Ebata, S.; Hiyama, T. *J. Am. Chem. Soc.* **2007,** *129,* 2428–2429. doi:10.1021/ja067364x
48. Satoh, T.; Nishinaka, Y.; Miura, M.; Nomura, M. *Chem. Lett.* **1999,** *28,* 615–618. doi:10.1246/cl.1999.615
49. Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007,** *9,* 1407–1409. doi:10.1021/ol070406h
50. Lee, G. T.; Jiang, X.; Prasad, K.; Repič, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005,** *347,* 1921–1924. doi:10.1002/adsc.200505202
51. Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003,** *5,* 2759–2761. doi:10.1021/ol035083d
52. Furukawa, T.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015,** *137,* 12211–12214. doi:10.1021/jacs.5b07677

53. Cho, S. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013,** *135,* 8157–8160. doi:10.1021/ja403462b
54. Kawamorita, S.; Murakami, R.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.* **2013,** *135,* 2947–2950. doi:10.1021/ja3126239
55. Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009,** *131,* 5058–5059. doi:10.1021/ja9008419
56. Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008,** *130,* 7534–7535. doi:10.1021/ja8015878
57. Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005,** *127,* 14263–14278. doi:10.1021/ja053433g
58. Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002,** *124,* 390–391. doi:10.1021/ja0173019
59. Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000,** *287,* 1995. doi:10.1126/science.287.5460.1995
60. Cho, J.-Y.; Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **2000,** *122,* 12868–12869. doi:10.1021/ja0013069
61. Tse, M. K.; Cho, J.-Y.; Smith, M. R., III. *Org. Lett.* **2001,** *3,* 2831–2833. doi:10.1021/ol0162668
62. Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009,** *131,* 3466–3467. doi:10.1021/ja900200g
63. Yu, W.-Y.; Sit, W. N.; Lai, K.-M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008,** *130,* 3304–3306. doi:10.1021/ja710555g
64. Chu, L.; Wang, X.-C.; Moore, C. E.; Rheingold, A. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013,** *135,* 16344–16347. doi:10.1021/ja408864c
65. Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009,** *131,* 7520–7521. doi:10.1021/ja901352k
66. Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008,** *47,* 6452–6455. doi:10.1002/anie.200802187
67. Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007,** *129,* 15142–15143. doi:10.1021/ja077866q
68. Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006,** *128,* 7134–7135. doi:10.1021/ja061943k
69. Powers, D. C.; Ritter, T. *Nat. Chem.* **2009,** *1,* 302–309. doi:10.1038/nchem.246
70. Jia, X.; Zhang, S.; Wang, W.; Luo, F.; Cheng, J. *Org. Lett.* **2009,** *11,* 3120–3123. doi:10.1021/ol900934g
71. Ma, S.; Villa, G.; Thuy-Boun, P. S.; Homs, A.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2014,** *53,* 734–737. doi:10.1002/anie.201305388
72. Hesp, K. D.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2011,** *133,* 11430–11433. doi:10.1021/ja203495c
73. Xiao, B.; Fu, Y.; Xu, J.; Gong, T.-J.; Dai, J.-J.; Yi, J.; Liu, L. *J. Am. Chem. Soc.* **2010,** *132,* 468–469. doi:10.1021/ja909818n
74. Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009,** *48,* 9346–9349. doi:10.1002/anie.200905419
75. Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002,** *124,* 1586–1587. doi:10.1021/ja0176907
76. Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002,** *41,* 3056–3058. doi:10.1002/1521-3773(20020816)41:16<3056::AID-ANIE3056>3.0.CO;2-#
77. Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008,** *130,* 3276–3277. doi:10.1021/ja7107068
78. Chary, B. C.; Kim, S.; Park, Y.; Kim, J.; Lee, P. H. *Org. Lett.* **2013,** *15,* 2692–2695. doi:10.1021/ol4009987
79. Yang, F.; Song, F.; Li, W.; Lan, J.; You, J. *RSC Adv.* **2013,** *3,* 9649–9652. doi:10.1039/c3ra41981a
80. Kakiuchi, F.; Murai, S. *Org. Synth.* **2003,** *80,* 104–110. doi:10.15227/orgsyn.080.0104
81. Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1997,** *70,* 3117–3128. doi:10.1246/bcsj.70.3117
82. Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995,** *68,* 62–83. doi:10.1246/bcsj.68.62
83. Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. *J. Organomet. Chem.* **1995,** *504,* 151–152. doi:10.1016/0022-328X(95)05607-Q
84. Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Pure Appl. Chem.* **1994,** *66,* 1527–1534. doi:10.1351/pac199466071527
85. Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993,** *366,* 529–531. doi:10.1038/366529a0
86. Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007,** *129,* 6066–6067. doi:10.1021/ja070767s
87. Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008,** *47,* 1115–1118. doi:10.1002/anie.200704092
88. Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008,** *10,* 2299–2302. doi:10.1021/ol800773x
89. Kakiuchi, F.; Sato, T.; Yamauchi, M.; Chatani, N.; Murai, S. *Chem. Lett.* **1999,** *28,* 19–20. doi:10.1246/cl.1999.19
90. Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004,** *126,* 9542–9543. doi:10.1021/ja046831c
91. Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006,** *128,* 9048–9049. doi:10.1021/ja062856v
92. Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008,** *130,* 3266–3267. doi:10.1021/ja710451s
93. Lazareva, A.; Daugulis, O. *Org. Lett.* **2006,** *8,* 5211–5213. doi:10.1021/ol061919b
94. Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007,** *129,* 7666–7673. doi:10.1021/ja070588a
95. Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem.* **2015,** *7,* 712–717. doi:10.1038/nchem.2322
96. He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014,** *343,* 1216–1220. doi:10.1126/science.1249198
97. Iwai, T.; Harada, T.; Hara, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2013,** *52,* 12322–12326. doi:10.1002/anie.201306769
98. Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun.* **2010,** *46,* 159–161. doi:10.1039/B910298A
99. Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010,** *327,* 315–319. doi:10.1126/science.1182512
100. Stang, E. M.; White, M. C. *Nat. Chem.* **2009,** *1,* 547–551. doi:10.1038/nchem.351
101. Lafrance, M.; Lopointe, D.; Fagnou, K. *Tetrahedron* **2008,** *64,* 6015–6020. doi:10.1016/j.tet.2008.01.057
102. Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2008,** *130,* 3316–3318. doi:10.1021/ja710206u
103. Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006,** *45,* 2619–2622. doi:10.1002/anie.200504450
104. Saiki, T.; Nishio, Y.; Ishiyama, T.; Miyaura, N. *Organometallics* **2006,** *25,* 6068–6073. doi:10.1021/om050968+
105. Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005,** *127,* 6970–6971. doi:10.1021/ja0500198
106. Tsukada, N.; Mitsuboshi, T.; Setoguchi, H.; Inoue, Y. *J. Am. Chem. Soc.* **2003,** *125,* 12102–12103. doi:10.1021/ja0375075

107. Gray, J. B.; Cook, A. K.; Sanford, M. S. *ACS Catal.* **2013,** *3,* 700–703. doi:10.1021/cs300786j
108. Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010,** *110,* 749–823. doi:10.1021/cr900315k
109. Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009,** *131,* 17050–17051. doi:10.1021/ja906935c
110. Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009,** *131,* 9651–9653. doi:10.1021/ja901952h
111. García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007,** *129,* 6880–6886. doi:10.1021/ja071034a
112. Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006,** *128,* 16496–16497. doi:10.1021/ja067144j
113. Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006,** 1253–1264. doi:10.1039/b515481m
114. García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006,** *128,* 1066–1067. doi:10.1021/ja056165v
115. Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005,** *127,* 13754–13755. doi:10.1021/ja052047w
116. Maleckis, A.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2013,** *135,* 6618–6625. doi:10.1021/ja401557m
117. Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005,** *127,* 12790–12791. doi:10.1021/ja0541940
118. Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics* **2000,** *19,* 3895–3908. doi:10.1021/om000002s
119. Horino, H.; Inoue, N. *J. Org. Chem.* **1981,** *46,* 4416–4422. doi:10.1021/jo00335a019
120. Zudin, V. N.; Chinakov, V. D.; Nekipelov, V. M.; Rogov, V. A.; Likholobov, V. A.; Yermakov, Yu. I. *J. Mol. Catal.* **1989,** *52,* 27–48. doi:10.1016/0304-5102(89)80080-X
121. Nishikata, T.; Abela, A. R.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2010,** *49,* 781–784. doi:10.1002/anie.200905967
122. Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010,** *132,* 4978–4979. doi:10.1021/ja910973a
123. Yamamoto, A. *J. Organomet. Chem.* **1995,** *500,* 337–348. doi:10.1016/0022-328X(95)00521-Q
124. Oi, S.; Kashiwagi, K.; Inoue, Y. *Tetrahedron Lett.* **1998,** *39,* 6253–6256. doi:10.1016/S0040-4039(98)01288-X
125. Oi, S.; Kashiwagi, K.; Terada, E.; Ohuchi, K.; Inoue, Y. *Tetrahedron Lett.* **1996,** *37,* 6351–6354. doi:10.1016/0040-4039(96)01369-X
126. Sodeoka, M.; Hamashima, Y. *Chem. Commun.* **2009,** 5787–5798. doi:10.1039/b911015a
127. Sodeoka, M.; Hamashima, Y. *Bull. Chem. Soc. Jpn.* **2005,** *78,* 941–956. doi:10.1246/bcsj.78.941
128. Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999,** *121,* 5450–5458. doi:10.1021/ja9902827
129. Gaunt, M. J.; Spencer, J. B. *Org. Lett.* **2001,** *3,* 25–28. doi:10.1021/ol0066882
130. Chen, C.; Luo, S.; Jordan, R. F. *J. Am. Chem. Soc.* **2010,** *132,* 5273–5284. doi:10.1021/ja100491y
131. Brookhart, M.; Wagner, M. I.; Balavoine, G. G. A.; Haddou, H. A. *J. Am. Chem. Soc.* **1994,** *116,* 3641–3642. doi:10.1021/ja00087a077
132. Yamamoto, Y.; Nishikata, T.; Miyaura, N. *Pure Appl. Chem.* **2008,** *80,* 807–817. doi:10.1351/pac200880050807
133. Miyaura, N. *Synlett* **2009,** 2039–2042. doi:10.1055/s-0029-1217555
134. Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Angew. Chem., Int. Ed.* **2003,** *42,* 2768–2770. doi:10.1002/anie.200350888
135. Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* **2004,** 1822–1823. doi:10.1039/b407272c
136. Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Chem. Lett.* **2003,** *32,* 752–753. doi:10.1246/cl.2003.752
137. Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008,** *130,* 2926–2927. doi:10.1021/ja710731a
138. Stuart, D. R.; Fagnou, K. *Science* **2007,** *316,* 1172–1175. doi:10.1126/science.1141956
139. Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006,** *128,* 4972–4973. doi:10.1021/ja060809x
140. Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002,** *41,* 1569–1572. doi:10.1002/1521-3773(20020503)41:9<1569::AID-ANIE1569>3.0.CO;2-8
141. Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000,** *287,* 1992–1995. doi:10.1126/science.287.5460.1992
142. Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998,** *71,* 467–473. doi:10.1246/bcsj.71.467
143. Albano, V. G.; Di Serio, M.; Monari, M.; Orabona, I.; Panunzi, A.; Ruffo, F. *Inorg. Chem.* **2002,** *41,* 2672–2677. doi:10.1021/ic011059p
144. Liston, D. J.; Lee, Y. J.; Scheidt, W. R.; Reed, C. A. *J. Am. Chem. Soc.* **1989,** *111,* 6643–6648. doi:10.1021/ja00199a025
145. Davis, J. A.; Hartley, E. R.; Muray, S. G. *J. Chem. Soc., Dalton Trans.* **1980,** 2246–2249. doi:10.1039/dt9800002246
146. Amatore, C.; Jutand, A.; Mederious, M. J.; Mottier, L. *J. Electroanal. Chem.* **1997,** *422,* 125–132. doi:10.1016/S0022-0728(96)04901-7
147. Grushin, V. V. *Chem. Rev.* **1996,** *96,* 2011–2034. doi:10.1021/cr950272y
148. Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010,** *12,* 1972–1975. doi:10.1021/ol100331h
149. Ricci, P.; Krämer, K.; Cambeiro, X. C.; Larrosa, I. *J. Am. Chem. Soc.* **2013,** *135,* 13258–13261. doi:10.1021/ja405936s
150. Join, B.; Yamamoto, T.; Itami, K. *Angew. Chem., Int. Ed.* **2009,** *48,* 3644–3647. doi:10.1002/anie.200806358
151. Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009,** *131,* 3291–3306. doi:10.1021/ja808332k
152. Yang, F.; Wu, Y.; Li, Y.; Wang, B.; Zhang, J. *Tetrahedron* **2009,** *65,* 914–919. doi:10.1016/j.tet.2008.11.001
153. Scarborough, C. C.; McDonald, R. I.; Hartmann, C.; Sazama, G. T.; Bergant, A.; Stahl, S. S. *J. Org. Chem.* **2009,** *74,* 2613–2615. doi:10.1021/jo802632v
154. Kim, J.; Jo, M.; So, W.; No, Z. *Tetrahedron Lett.* **2009,** *50,* 1229–1362. doi:10.1016/j.tetlet.2009.01.010
155. Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008,** *130,* 10848–10849. doi:10.1021/ja802533u
156. Li, D.-D.; Yuan, T.-T.; Wang, G.-W. *J. Org. Chem.* **2012,** *77,* 3341–3347. doi:10.1021/jo300126n
157. Chen, F.; Min, Q.-Q.; Zhang, X. *J. Org. Chem.* **2012,** *77,* 2992–2998. doi:10.1021/jo300036d
158. Liang, Z.; Feng, R.; Yin, H.; Zhang, Y. *Org. Lett.* **2013,** *15,* 4544–4547. doi:10.1021/ol402207g
159. Shi, B.-S.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010,** *132,* 460–461. doi:10.1021/ja909571z
160. Chu, J.-H.; Tsai, S.-L.; Wu, M.-J. *Synthesis* **2009,** 3757–3764. doi:10.1055/s-0029-1217014
161. Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008,** *47,* 4882–4886. doi:10.1002/anie.200801030
162. Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008,** *130,* 7190–7191. doi:10.1021/ja801355s

163. Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008,** *130,* 17676–17677. doi:10.1021/ja806681z
164. Kirchberg, S.; Vogler, T.; Studer, A. *Synlett* **2008,** 2841–2845. doi:10.1055/s-0028-1083546
165. Vogler, T.; Studer, A. *Org. Lett.* **2008,** *10,* 129–131. doi:10.1021/ol702659a
166. Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007,** *129,* 3510–3511. doi:10.1021/ja0701614
167. Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006,** *128,* 12634–12635. doi:10.1021/ja0646747
168. Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003,** *125,* 1698–1699. doi:10.1021/ja029273f
169. Liang, Z.; Yao, J.; Wang, K.; Li, H.; Zhang, Y. *Chem. – Eur. J.* **2013,** *19,* 16825–16831. doi:10.1002/chem.201301229
170. Meng, X.; Kim, S. *J. Org. Chem.* **2013,** *78,* 11247–11251. doi:10.1021/jo401716p
171. Yamaguchi, K.; Kondo, H.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2013,** *4,* 3753–3757. doi:10.1039/c3sc51206a
172. Tremont, S. J.; Ur Rahman, H. *J. Am. Chem. Soc.* **1984,** *106,* 5759–5760. doi:10.1021/ja00331a073
173. Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2007,** *72,* 7720–7725. doi:10.1021/jo701387m
174. Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005,** *44,* 4046–4048. doi:10.1002/anie.200500589
175. Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005,** *127,* 7330–7331. doi:10.1021/ja051402f
176. Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009,** *48,* 1830–1833. doi:10.1002/anie.200805842
177. Nishikata, T.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009,** *131,* 12103–12105. doi:10.1021/ja905082c
178. Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2009,** *11,* 2377–2379. doi:10.1021/ol900235s
179. Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta* **2008,** *41,* 58–72.
180. Ohnmacht, S. A.; Mamone, P.; Culshaw, A. J.; Greaney, M. F. *Chem. Commun.* **2008,** 1241–1243. doi:10.1039/b719466h
181. Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008,** *10,* 2717–2720. doi:10.1021/ol800869g
182. Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007,** *46,* 7996–8000. doi:10.1002/anie.200702141
183. Herrerías, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007,** *107,* 2546–2562. doi:10.1021/cr050980b
184. Mitsudo, K.; Kaide, T.; Nakamoto, E.; Yoshida, K.; Tanaka, H. *J. Am. Chem. Soc.* **2007,** *129,* 2246–2247. doi:10.1021/ja069043r
185. Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005,** *70,* 3113–3119. doi:10.1021/jo050031i
186. Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003,** *68,* 8669–8682. doi:10.1021/jo030157k
187. Oi, S.; Watanabe, S.-i.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003,** *44,* 8665–8668. doi:10.1016/j.tetlet.2003.09.151
188. Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001,** *3,* 2579–2581. doi:10.1021/ol016257z
189. Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998,** 2439–2440. doi:10.1039/a806790b
190. Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969,** *91,* 7166–7169. doi:10.1021/ja01053a047
191. Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Lett.* **1968,** *9,* 633–636. doi:10.1016/S0040-4039(01)98820-3
192. Moritani, S.; Fujiwara, Y. *Tetrahedron Lett.* **1967,** *8,* 1119–1122. doi:10.1016/S0040-4039(00)90648-8
193. Jiao, L.-Y.; Oestreich, M. *Org. Lett.* **2013,** *15,* 5374–5377. doi:10.1021/ol402687t
194. Wang, L.; Liu, S.; Li, Z.; Yu, Y. *Org. Lett.* **2011,** *13,* 6137–6139. doi:10.1021/ol202738j
195. Rauf, W.; Thompson, A. L.; Brown, J. M. *Dalton Trans.* **2010,** *39,* 10414–10421. doi:10.1039/c0dt00378f
196. Wu, J.; Cui, X.; Chen, L.; Jiang, G.; Wu, Y. *J. Am. Chem. Soc.* **2009,** *131,* 13888–13889. doi:10.1021/ja902762a
197. Aouf, C.; Thiery, E.; Le Bras, J.; Muzart, J. *Org. Lett.* **2009,** *11,* 4096–4099. doi:10.1021/ol901570p
198. Cheng, D.; Gallagher, T. *Org. Lett.* **2009,** *11,* 2639–2641. doi:10.1021/ol900627q
199. Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008,** *130,* 9254–9256. doi:10.1021/ja8026295
200. Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003,** *42,* 3512–3515. doi:10.1002/anie.200351524
201. Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003,** *125,* 1476–1477. doi:10.1021/ja028903a
202. Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001,** *123,* 337–338. doi:10.1021/ja003361n
203. Meng, X.; Kim, S. *Org. Lett.* **2013,** *15,* 1910–1913. doi:10.1021/ol400565r
204. Dai, H.-X.; Li, G.; Zhang, X.-G.; Stephan, A. F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013,** *135,* 7567–7571. doi:10.1021/ja400659s
205. Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009,** *131,* 5072–5074. doi:10.1021/ja900327e
206. Rauf, W.; Thompson, A. L.; Brown, J. M. *Chem. Commun.* **2009,** 3874–3876. doi:10.1039/b905717j
207. Rouhi, A. M. *Chem. Eng. News* **2004,** *82,* 49–58.
208. Felpin, F.-X.; Fouquet, E.; Zakri, C. *Adv. Synth. Catal.* **2009,** *351,* 649–650. doi:10.1002/adsc.200800783
209. Wetzel, A.; Ehrhardt, V.; Heinrich, M. R. *Angew. Chem., Int. Ed.* **2008,** *47,* 9130–9133. doi:10.1002/anie.200803785
210. Spivey, A. C.; Tseng, C.-C.; Hannah, J. P.; Gripton, C. J. P.; de Fraine, P.; Parr, N. J.; Scicinski, J. J. *Chem. Commun.* **2007,** 2926–2928. doi:10.1039/B707517K
211. Ehrenfreund, J.; Lamberth, C.; Tobler, H.; Walter, H. Biphenyl derivatives and their use as fungicides. WO Patent WO 2004058723, July 15, 2004.
212. Eicken, K.; Rack, M.; Wetterich, F.; Ammermann, E.; Lorenz, G.; Strathmann, S. Biphenylamide. German Patent DE 19735224, Feb 18, 1999.
213. Eicken, K.; Rang, H.; Harreus, A.; Goetz, N.; Ammermann, E.; Lorenz, G.; Strathmann, S. Bisphenylamide. German Patent DE19531813, March 6, 1997.
214. Urriolabeitia, E. P. Oxidative Addition and Transmetallation. In *Palladacycles: Synthesis, Characterization and Applications;* Dupont, J.; Pfeffer, M., Eds.; Wiley-VCH: Weinheim, Germany, 2008.
215. Roiban, G.-D.; Serrano, E.; Soler, T.; Contel, M.; Grosu, I.; Cativiela, C.; Urriolabeitia, E. P. *Organometallics* **2010,** *29,* 1428–1435. doi:10.1021/om901068f
216. The palladacycle is very stable and did not release the corresponding arylurea after 2–3 weeks in wet solvent.
217. Steffen, W. L.; Palenik, G. J. *Inorg. Chem.* **1976,** *15,* 2432–2439. doi:10.1021/ic50164a025
218. Ludwig, M.; Strömberg, S.; Svensson, M.; Åkermark, B. *Organometallics* **1999,** *18,* 970–975. doi:10.1021/om9803265

219. Nishikata, T.; Yamamoto, Y.; Gridnev, I. D.; Miyaura, N. *Organometallics* **2005,** *24,* 5025–5032. doi:10.1021/om050678t
220. Nishikata, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **2004,** *23,* 4317–4324. doi:10.1021/om0498044
221. Albrecht, M. *Chem. Rev.* **2010,** *110,* 576–623. doi:10.1021/cr900279a
222. Chatani, N., Ed. *Directed Metallation;* Topics in Organometallic Chemistry, Vol. 24; Springer: Berlin, Germany, 2007.
223. Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006,** *4,* 4041–4047. doi:10.1039/B611094K
224. Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005,** *105,* 2527–2572. doi:10.1021/cr030681r
225. Chu, J.-H.; Chen, C.-C.; Wu, M.-J. *Organometallics* **2008,** *27,* 5173–5176. doi:10.1021/om800606c
226. Pérez-Rodríguez, M.; Braga, A. A. C.; Garcia-Melchor, M.; Pérez-Temprano, M. H.; Casares, J. A.; Ujaque, G.; de Lera, A. R.; Alvarez, R.; Maseras, F.; Espinet, P. *J. Am. Chem. Soc.* **2009,** *131,* 3650–3657. doi:10.1021/ja808036j
227. Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B. *Chem. – Eur. J.* **2001,** *7,* 2481–2485. doi:10.1002/1521-3765(20010601)7:11<2481::AID-CHEM24810>3.0.CO;2-2
228. Szabó, K. J. *Organometallics* **1998,** *17,* 1677–1686. doi:10.1021/om9800344
229. Bäckvall, J. E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984,** *49,* 4619–4631. doi:10.1021/jo00198a010
230. Temple, J. S.; Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982,** *104,* 1310–1315. doi:10.1021/ja00369a028
231. 1,4-Dihydroxybenzene was confirmed by ^{1}H, and ^{13}C NMR and GC–MS analysis.
232. Some previous C–H activation reactions catalyzed by $Pd(OAc)_2$ require high temperature to generate a cationic species. TFA or *p*-TsOH led to room temperature C–H activation only when catalyzed by $Pd(OAc)_2$ probably due to generation of a cationic Pd(II) species.
233. Crociani, B.; Di Bianca, F.; Uguagliati, P.; Canovese, L.; Berton, A. *J. Chem. Soc., Dalton Trans.* **1991,** 71–79. doi:10.1039/DT9910000071
234. Eaborn, C.; Odell, K. J.; Pidcock, A. *J. Chem. Soc., Dalton Trans.* **1978,** 357–368. doi:10.1039/DT9780000357
235. Foresee, L. N.; Tunge, J. A. *Organometallics* **2005,** *24,* 6440–6444. doi:10.1021/om0507225
236. Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000,** *122,* 7252–7263. doi:10.1021/ja0005845
237. We have not yet obtained strong proof of this species based on either a kinetic or an isotope effect study.
238. Kawataka, F.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1995,** *68,* 654–660. doi:10.1246/bcsj.68.654
239. Karabelas, K.; Hallberg, A. *J. Org. Chem.* **1986,** *51,* 5286–5290. doi:10.1021/jo00376a044
240. Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985,** *50,* 3896–3900. doi:10.1021/jo00220a042
241. Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009,** *48,* 9240–9261. doi:10.1002/anie.200904306
242. Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008,** *41,* 1461. doi:10.1021/ar800036s
243. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995,** *95,* 2457–2483. doi:10.1021/cr00039a007
244. Sicre, C.; Braga, A. A. C.; Maseras, F.; Magdalena Cid, M. *Tetrahedron* **2008,** *64,* 7437–7650. doi:10.1016/j.tet.2008.05.018
245. Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005,** *127,* 9298–9307. doi:10.1021/ja050583i
246. Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998,** *63,* 461–470. doi:10.1021/jo971681s
247. Pantcheva, I.; Nishihara, Y.; Osakada, K. *Organometallics* **2005,** *24,* 3815–3817. doi:10.1021/om049050t
248. Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007,** *129,* 1876–1877. doi:10.1021/ja068587q
249. Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009,** *131,* 11234–11241. doi:10.1021/ja904116k
250. Cotton, F. A.; Koshevoy, I. O.; Lahuerta, P.; Murillo, C. A.; Sanaú, M.; Ubeda, M. A.; Zhao, Q. *J. Am. Chem. Soc.* **2006,** *128,* 13674–13675. doi:10.1021/ja0656595
251. Powers, D. C.; Ritter, T. Palladium(III) in Synthesis and Catalysis. In *Higher Oxidation State Organopalladium and Platinum Chemistry;* Canty, A. J., Ed.; Topics in Organometallic Chemistry, Vol. 35; Springer: Berlin, Germany, 2011; pp 129–156. doi:10.1007/978-3-642-17429-2_6
252. Powers, D. C.; Xiao, D. Y.; Geibel, M. A. L.; Ritter, T. *J. Am. Chem. Soc.* **2010,** *132,* 14530–14536. doi:10.1021/ja1054274
253. Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010,** *110,* 824–889. doi:10.1021/cr9003242
254. Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009,** *131,* 10974–10983. doi:10.1021/ja9014474
255. Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008,** *41,* 1512–1522. doi:10.1021/ar800040u

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.99

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Synthesis of 2-oxindoles via 'transition-metal-free' intramolecular dehydrogenative coupling (IDC) of sp^2 C–H and sp^3 C–H bonds

Nivesh Kumar‡, Santanu Ghosh‡, Subhajit Bhunia and Alakesh Bisai*

Full Research Paper

Open Access

Address:
Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal Bypass Road, Bhauri, Bhopal – 462 066, Madhya Pradesh, India

Email:
Alakesh Bisai* - alakesh@iiserb.ac.in

* Corresponding author ‡ Equal contributors

Keywords:
C−H functionalization; intramolecular dehydrogenative coupling (IDC); iodine; *N*-iodosuccinimide; oxidants; 2-oxindoles

Beilstein J. Org. Chem. **2016,** *12,* 1153–1169.
doi:10.3762/bjoc.12.111

Received: 13 February 2016
Accepted: 16 May 2016
Published: 08 June 2016

This article is part of the Thematic Series "C–H Functionalization/activation in organic synthesis".

Guest Editor: R. Sarpong

© 2016 Kumar et al; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

The synthesis of a variety of 2-oxindoles bearing an all-carbon quaternary center at the pseudo benzylic position has been achieved via a 'transition-metal-free' intramolecular dehydrogenative coupling (IDC). The construction of 2-oxindole moieties was carried out through formation of carbon–carbon bonds using KO*t*-Bu-catalyzed one pot C-alkylation of β-*N*-arylamido esters with alkyl halides followed by a dehydrogenative coupling. Experimental evidences indicated toward a radical-mediated path for this reaction.

Introduction

The C−H functionalization is an attractive synthetic strategy used in organic synthesis for the development of atom- and step-economical routes [1-10]. In recent years it was witnessed a mushrooming growth in the number of reports in the literature owing to the efficiency of the oxidative coupling of two C–H bonds [also termed as cross-dehydrogenative-coupling (CDC)] in the formation of C–C bonds [11-16]. This was facilitated by the introduction of transition metals in organic synthesis providing an amazing tool to explore these oxidative coupling reactions in an efficient manner. However, despite the associated advantages, these methodologies require one or two metal catalysts for efficient reactions, which are sometimes undesirable [17-21]. Therefore, an alternate strategy to carry out these transformations under 'transition-metal-free' conditions has recently gained immense importance.

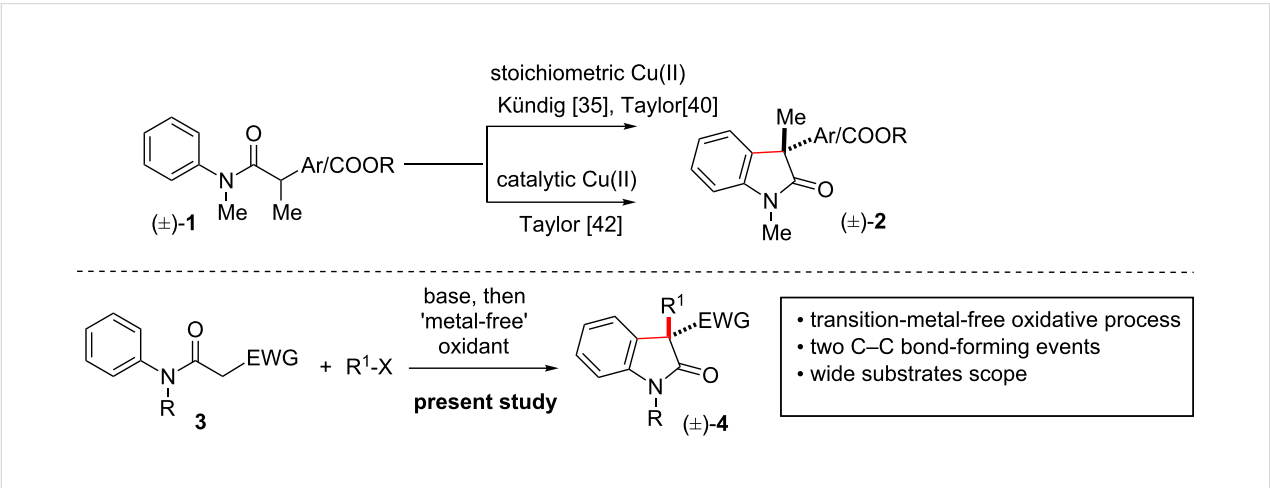
2-Oxindoles having all carbon quaternary centres at the pseudobenzylic position are common structural scaffolds in many naturally occurring alkaloids of biological relevance [22-25]. These heterocyclic motifs especially exist in indole alkaloids with a wide spectrum of biological and pharmacological properties and hence are very attractive as well as challenging

synthetic targets [26]. Selected examples for the synthesis of 2-oxindole include an intramolecular homolytic aromatic substitution on the aryl ring by an amidyl radical formed by homolysis of a C–X bond [27-30], single electron transfer (SET) to a α-halo anilides followed by halide elimination [31,32], and the formation of an aryl radical followed by a 1,5-hydrogen atom translocation [33,34]. Out of these strategies, the initial two require specifically functionalized precursors such as the presence of an *o*-halogen, an *o*-selenium, or an *o*-xanthate, respectively. One of the direct approaches to 2-oxindoles could be a one-electron oxidation of an amide enolate as shown in Scheme 1. Toward this end, in 2009, Kündig and co-workers have developed a novel route to 3,3-disubstituted-2-oxindoles while working on asymmetric synthesis of 3,3-disubstituted-2-oxindoles via a Pd-catalyzed (chiral *N*-heterocyclic carbene as ligands) intramolecular α-arylation of an amide [35-37]. For this 'intramolecular dehydrogenative coupling' (IDC) of Csp^2-H and Csp^3-H they used 2.2 equiv of $CuCl_2$ and 5 equiv of NaO*t*-Bu [38,39].

In the same year, Taylor and co-workers independently reported synthesis of 2-oxindoles in the presence of $Cu(OAc)_2 \cdot H_2O$ as oxidant (Scheme 1) [40-44]. Experimental evidence suggests involvement of a free-radical process in the addition of α-carbonylalkyl radicals to the phenyl ring. The α-carbonylalkyl radicals were formed by Cu(II)-mediated oxidation of the respective enolate precursors. In 2010, Yu and co-workers have reported the synthesis of 3-acetyloxindoles via Ag_2O-mediated intramolecular oxidative coupling [45]. For the past few years, our group is engaged in the development of efficient methodologies for the synthesis of 2-oxindoles with intriguing ring systems. To this end, recently, we have reported a transition-metal-free ‘intramolecular-dehydrogenative-coupling' (IDC) strategy to access such 2-oxindole moieties through a C-alkylation followed by an oxidative construction of the C–C bond (Scheme 1) [46]. Applying the aforementioned strategy, we were able to synthesize several 3-alkyl-2-oxindoles bearing ester functionalities at the pseudobenzylic position from β-*N*-arylamido allyl, methallyl, dimethylallyl, and geranyl esters. Here, in this article, we disclose the scope and limitations of 'transition-metal-free' IDC of Csp^2-H and Csp^3-H using iodine and *N*-iodosuccinimide (NIS) as oxidants. In addition, we have also demonstrated the synthetic utility of oxidative coupling products in the syntheses of 3-substituted-2-oxindoles, via a decarboxylative protonation on 2-oxindoles bearing an benzylester or *para*-methoxybenzyl ester at the 3-position in presence of a catalytic amount of Pd on activated charcoal. We have also shown the direct installation of allyl, prenyl, *reverse*-prenyl, or geranyl groups at the 3-position of 2-oxindole using Pd-catalyzed decarboxylative strategies [47].

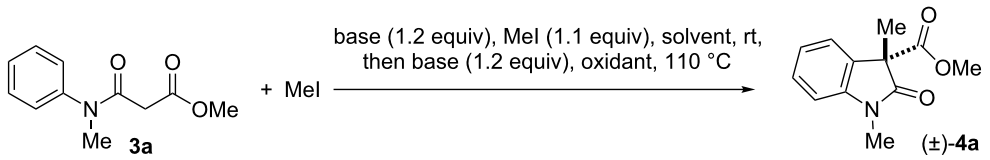
Results and Discussion

We decided to use iodine as an oxidant for the synthesis of 2-oxindoles [48-53], starting from β-*N*-arylamido ester **3a** and methyl iodide as the substrates (Table 1). An elaborate optimization study suggested that the methylation can be done in the presence of 1.2 equivalents of KO*t*-Bu and 1.1 equivalents of methyl iodide. This was accompanied with an oxidative coupling using 1.2 equivalents of KO*t*-Bu and iodine to afford the desired product in 65% yield (Table 1, entries 1 and 2). Optimization studies in search of suitable solvent, potential bases, oxidants etc. yielded the desired product in good yields i.e. 85%, 88%, and 90% in THF, dioxane, and DMSO, respectively (Table 1, entries 3, 5, and 8). However, in non-polar aromatic solvents like xylene, benzene, and toluene, poor yields (43–49%, Table 1, entries 4, 6, and 7) of products were observed with reactions being unclean (mixture of products) [54]. KO*t*-Bu was superior over other bases used in this reaction like



Scheme 1: Synthesis of 2-oxindoles via oxidative processes.

Table 1: Optimization of intramolecular-dehydrogenative-coupling (IDC)[a].



entry	solvent	base	Alkylations at 25 °C	oxidants	time	% **4a**[b,c]
1.	DMF	*t*-BuOK	20 min	1.5 equiv I_2	6 h	65%
2.	DMF	*t*-BuOK	20 min	1.2 equiv I_2	3 h	62%
3.	THF	*t*-BuOK	30 min	1.2 equiv I_2	3 h	85%
4.	xylene	*t*-BuOK	45 min	1.2 equiv I_2	1 h	49%[d]
5.	dioxane	*t*-BuOK	20 min	1.2 equiv I_2	2 h	88%
6.	benzene	*t*-BuOK	50 min	1.2 equiv I_2	2 h	43%[d]
7.	toluene	*t*-BuOK	45 min	1.2 equiv I_2	1 h	45%[d]
8.	DMSO	*t*-BuOK	20 min	1.2 equiv I_2	30 min	90%
9.	DMSO	NaH	20 min	1.2 equiv I_2	30 min	33%
10.	DMSO	NaOMe	2 h	1.2 equiv I_2	30 min	–[e]
11.	DMSO	K_2CO_3	1 h[f]	–	–	–
12.	DMSO	CS_2CO_3	2 h	1.5 equiv I_2	30 min	26%[g]
13.	DMSO	*t*-BuONa	30 min	1.5 equiv I_2	30 min	–[g]
14.	**DMSO**	***t*-BuOK**	**15 min**	**1.2 equiv I_2**	**30 min**	**90%**
15.	DMSO	*t*-BuOK	15 min	0.6 equiv I_2	1 h	54%
16.	DMSO	*t*-BuOK	15 min	0.3 equiv I_2	1 h	29%
17.	DMSO	*t*-BuOK	15 min	1.2 equiv PIDA	30 min	82%
18.	DMSO	*t*-BuOK	15 min	1.2 equiv DBDMH[h]	30 min	16%[g]
19.	DMSO	*t*-BuOK	15 min	1.2 equivICl	30 min	69%
20.	**DMSO**	***t*-BuOK**	**15 min**	**1.2 equiv NIS**	**30 min**	**84%**
21.	DMSO	*t*-BuOK	15 min	1.2 equiv NBS	30 min	75%
22.	DMSO	*t*-BuOK	15 min	1.2 equiv NCS	30 min	58%
23.	DMSO	*t*-BuOK	15 min	1.0 equivTCICA[i]	30 min	62%
24.	DMSO	*t*-BuOK	15 min	0.5 equivTCICA[i]	30 min	56%

[a] Entries 1–18 have been reproduced from our preliminary communication (reference [46]. [b]Reactions were carried out on a 0.25 mmol of **3a** with 0.275 mmol of methyl iodide in presence of 0.30 mmol of base in 1 mL of solvent at 25 °C for specified time for alkylations and 0.275 mmol of oxidant in presence of 0.30 mmol of base under heating at 110 °C for oxidative coupling steps, unless noted otherwise. [c]Isolated yields of **4a** after column chromatography. [d]Mixture of products were observed for rest of the mass balance. [e]C-methylation as major product. [f]Starting material was recovered (92%). [g]Decomposition of starting materials. [h]DBDMH (1,3-dibromo-5,5-dimethylhydantoin) as oxidant. [i]TCICA (trichloroisocyanuric acid).

NaH, NaOMe, K_2CO_3, Cs_2CO_3, and NaO*t*-Bu (Table 1, entries 9–13). Among other metal-free oxidants, iodosobenzenediacetate (PIDA), DBDMH (1,3-dibromo-5,5-dimethylhydantoin), and ICl afforded 2-oxindole **4a** in 82%, 16%, and 69%, respectively (Table 1, entries 17–19). Later, we turned our attention to *N*-halo succinimides as potential oxidants in our methodology [53]. Interestingly, *N*-iodosuccinimide (NIS), *N*-bromosuccinimide (NBS), and *N*-chlorosuccinimide (NCS) afforded **4a** in 84%, 75%, and 58% yields, respectively (Table 1, entries 20–22). However, trichloroisocyanuric acid (TCICA) is found to be inefficient in oxidative coupling and afforded 56–62% yields of **4a** (Table 1, entries 23 and 24). In the absence of iodine or NIS, no product was formed. Eventually, the combination of 1.2 equivalents of iodine (conditions A) or NIS (conditions B) were found to be the best and chosen for further studies (Table 1, entries 14 and 20).

Next, the substrate scope of the reaction was explored as shown in Figure 1. A variety of substrates were prepared by a coupling reaction of *N*-methyl arylamines and monoalkyl malonates/cyanoacetic acids. Under optimized conditions A and B, various β-*N*-arylamido esters and nitriles (**3**) were subjected to a one-pot alkylations using 1.2 equivalents of KO*t*-Bu to produce C-alkylated intermediate **5** followed by oxidative cou-

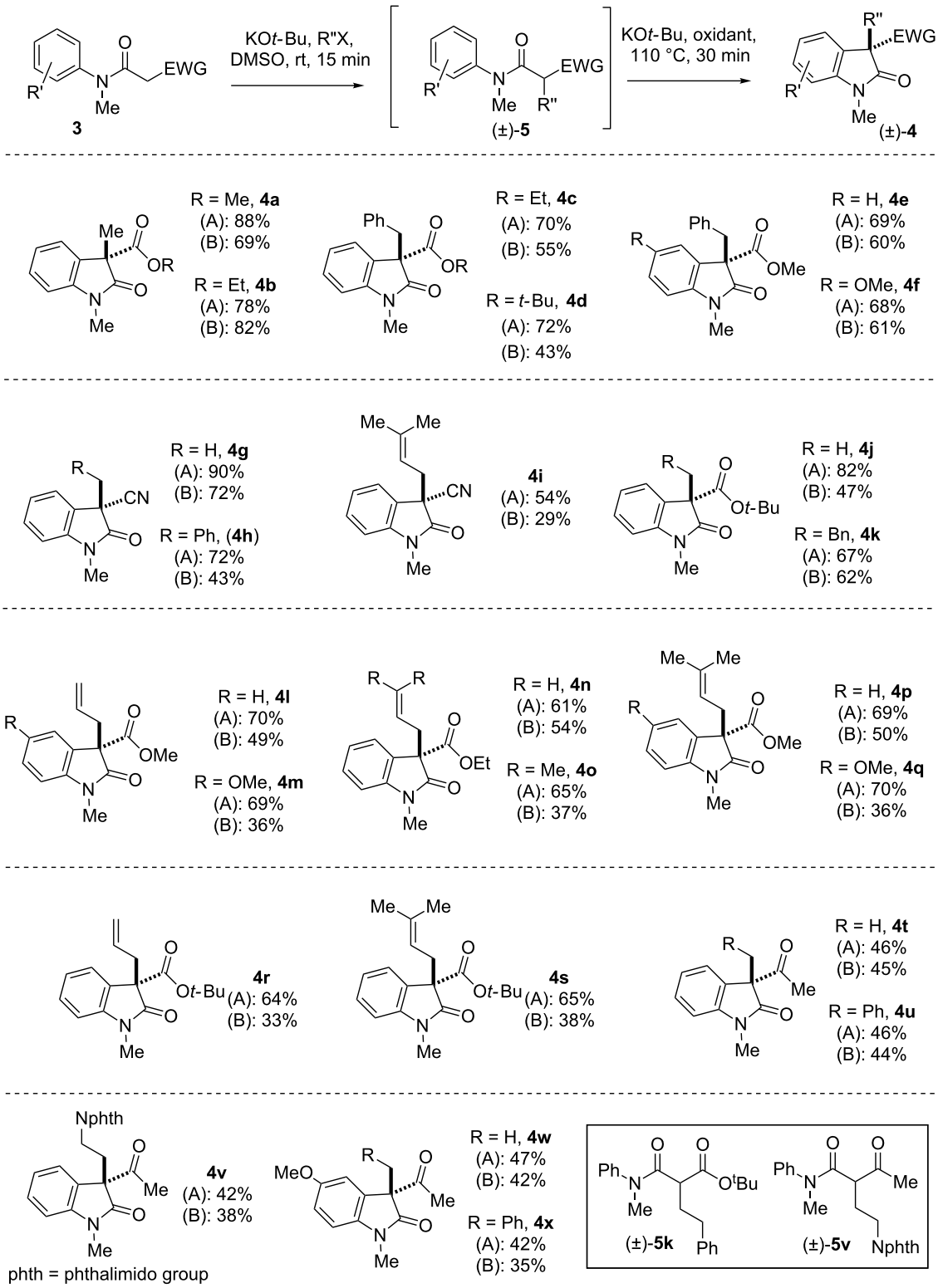


Figure 1: Substrates scope of one-pot 'transition-metal-free' IDC. The syntheses of compounds **4a**–**s** according to method A have been reproduced from reference [46]. Conditions A: KO*t*-Bu, iodine; conditions B: KO*t*-Bu, NIS.

pling using 1.2 equivalents iodine or NIS. Gratifyingly, it was found that a range of β-*N*-arylamido esters (**3a–s**) and β-*N*-arylamido ketones (**3t–x**) underwent intramolecular dehydrogenative coupling (IDC) under both conditions A and B to afford a wide range of 2-oxindoles (**4a–x**) having an all-carbon quaternary center in high yields. However, we observed that in case of 2-oxindoles **4v** and **4k**, a two-step protocol is necessary, where in first step C-alkylation of β-*N*-arylamido ketone was carried out using 1.2 equivalents of KO*t*-Bu to afford products **5v** and **5k**, respectively (Figure 1), followed by a second oxidative coupling reaction in the presence of iodine or NIS.

We envisioned that the oxidative coupling products containing benzyl or *p*-methoxybenzyl ester could be effective intermediates for the synthesis of 3-monosubstituted 2-oxindoles via deprotection of the benzyl group followed by decarboxylative protonation in presence of a catalytic amount of Pd on activated charcoal under hydrogenolysis. Thus, we explored the substrate scope using β-*N*-arylamido benzyl ester or β-*N*-arylamido *p*-methoxybenzyl ester as starting materials for the oxidative coupling reaction shown in Figure 2. Towards this end, β-*N*-aryl amido benzylester or β-*N*-arylamido p-methoxybenzyl ester **3** were subjected to an one pot alkylation to generate the intermediate **7** followed by oxidative coupling reaction using our optimized conditions A and B to furnish products of type (±)-**6** in good yields (Figure 2). For the synthesis of compound (±)-**6g**, we followed a two-step protocol: In first step a C-alkylation of β-*N*-arylamido benzylester in presence of 1.2 equivalents of NaH and alkylating agent afford compound (±)-**7g** in good yields (74%), followed by an oxidative coupling in presence of 1.2 equivalents of KO*t*-Bu and iodine or NIS as oxidant.

Next, we focussed our attention to prenylated, *reverse*-prenylated, and geranylated hexahydropyrrolo[2,3-*b*]indole alkaloids showing broad biological activities [55-61]. For the synthesis of these compounds, we thought of utilizing the Pd-catalyzed decarboxylative strategy to install the prenyl, *reverse*-prenyl, or

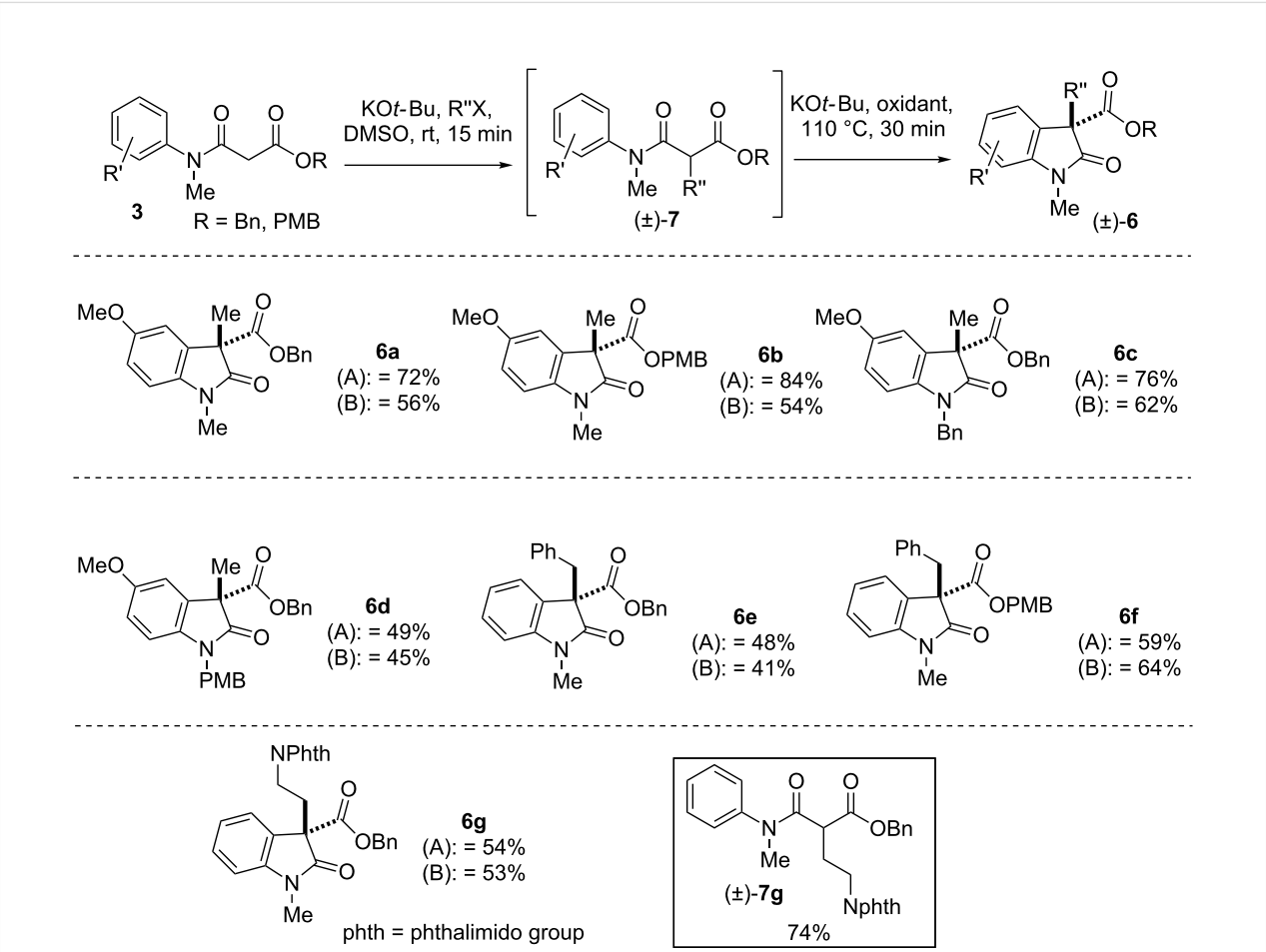


Figure 2: Further substrates scope of one-pot 'transition metal-free' IDC. Conditions A: KO*t*-Bu, iodine; conditions B: KO*t*-Bu, NIS.

geranyl group at the 3-position of 2-oxindole starting from the corresponding β-amido esters such as **8** [47]. This further extended the methodology to a variety of β-*N*-arylamido esters containing allyl, methallyl, dimethylallyl, and geranyl ester groups (**9**). It is noteworthy that, the substrate of type **9** could undergo smooth IDC in the presence of iodine (conditions A) to provide an access to compounds **8** in synthetically useful yields (Figure 3).

Noticeably, we could directly construct the 2-oxindoles with a geranyl group at the 3-position using geranyl bromide as an alkylating agent. Upon a subsequent oxidative coupling step, products in good yields (**8q–s**, Figure 3) were formed using conditions A. Later, the IDC was extended to substrates having β-*N*-arylamido geranyl esters to afford compounds **8t–v** (Figure 3). These compounds could be excellent substrates for carrying out Tsuji–Trost decarboxylative geranylations/*reverse*-

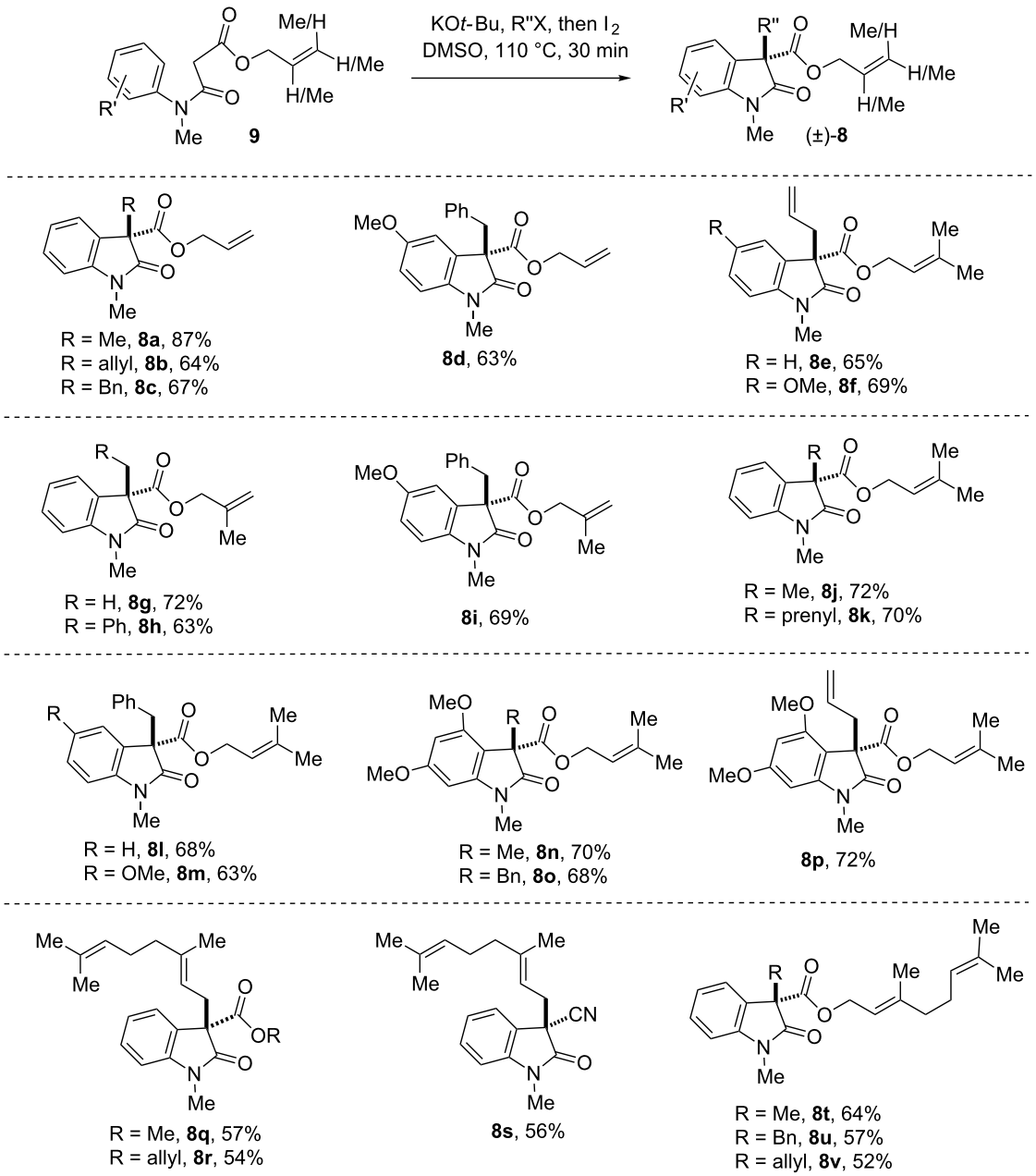


Figure 3: Substrates scope of 'transition-metal-free' IDC using KO*t*-Bu/I_2. Reproduced from [46].

geranylations [62,63]. However, conditions B (NIS) were found unsuccessful in case of β-*N*-arylamidoallyl, methallyl, dimethylallyl, and geranyl esters **9**. We speculate that the olefin functionality of substrates might be reacting with NIS (conditions B) faster than iodine (conditions A). Although our iodine-mediated IDC is successful in most of the cases, however, in few cases we have seen moderate yields of products. Thus, we decided to carry out IDC in the presence of organic bases as well.

Thus, for an alternative approach to 2-oxindoles bearing allyl, methallyl, dimethylallyl, and geranyl esters, we were interested for IDC using simple organic bases such as triethylamine, pyridine, and DABCO (Table 2) [64]. It was found that IDC can operate in the presence of organic bases to afford products only in 25–34% yields of 2-oxindoles (Table 2, entries 1, 2 and 4). These reactions were always associated with unreacted starting material (28–51%) and decomposition of the rest of the mass balance. Interestingly, when the base was changed to DBU (using 1.5 equiv DBU and 1.2 equiv of iodine) the desired 2-oxindole was isolated in 82% (conditions C).

With this result in hand, we thought of exploring IDC using C-alkylated substrates **10**. For this purpose, a variety of C-alkylated β-*N*-arylamidoallyl, methallyl, dimethylallyl, and geranyl esters **10** were synthesized in good yields as per Figure 4. These substrates were then utilized in IDC-promoted by DBU/I_2 and the results are summarized in Figure 5. Interestingly, under this conditions, we can synthesize a variety of 2-oxindoles **8** in moderate to good yields.

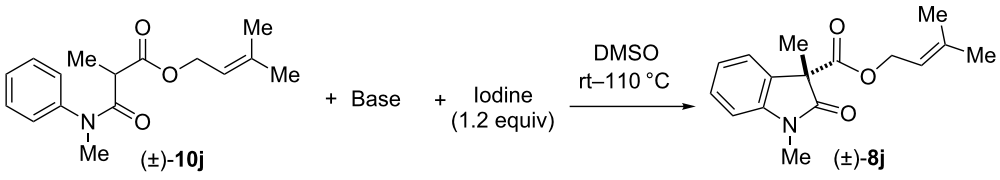
There are a large number of indole alkaloids bearing a 3-arylated-2-oxindole moiety that are known for their various biological activities [65-67]. In a quest for such structural scaffolds, C-arylated substrates (±)-**11a–d** were subjected to standard reaction conditions to afford compound **12a–d** (Scheme 2). To our pleasure, C-arylated β-*N*-arylamidoesters (±)-**11a–d** afforded products (±)-**12a–d** in 59–89% yield after 1 h under conditions A and B.

Our synthetic methodology was further explored in the construction of spiro-fused oxindole ring systems (Scheme 3). The spiro-fused oxindoles such as coerulescine (**15a**) [68-72], horsfiline (**15b**) [73], and elacomine (**16**), are prevalently found in a huge number of indole-based alkaloids having analgesic properties. Our oxidative methodology offered us a direct access to the core structures of these alkaloids under the optimized IDC conditions in high yields (Scheme 3).

Next, we thought of carrying out the IDC without alkylations of compounds **3a** and **b** and **17a** and **b** (Scheme 4). Unfortunately, we could not isolate products due to decomposition under optimized IDC conditions. It was noticed that changing the solvent to THF effected very fast (within 5 minutes) dimerization of **3a** and **b** at room temperature to afford **18a** and **b** as sole products in 91–93% yield and in up to >20:1 dr (Scheme 4). This shows that formation of a stabilized tertiary radical probably facilitates the IDC process for the syntheses of 2-oxindoles.

However, if a tertiary radical is responsible for the oxidative process, then one would realize the formation of dimeric

Table 2: IDC in the presence of organic bases. Reproduced from [46].



entry	base	time	% of **8j**	% of **10j**
1.	pyridine	12 h	29	30
2.	Et_3N	12 h	25	28
3.	**DBU**	**40 min**	**82**	**–**
4.	DABCO	12 h	34	51

[a]Reactions were carried out on a 0.25 mmol of **10j** using 0.50 mmol of base and 0.275 mmol of iodine in 1 mL of solvent for specified time.

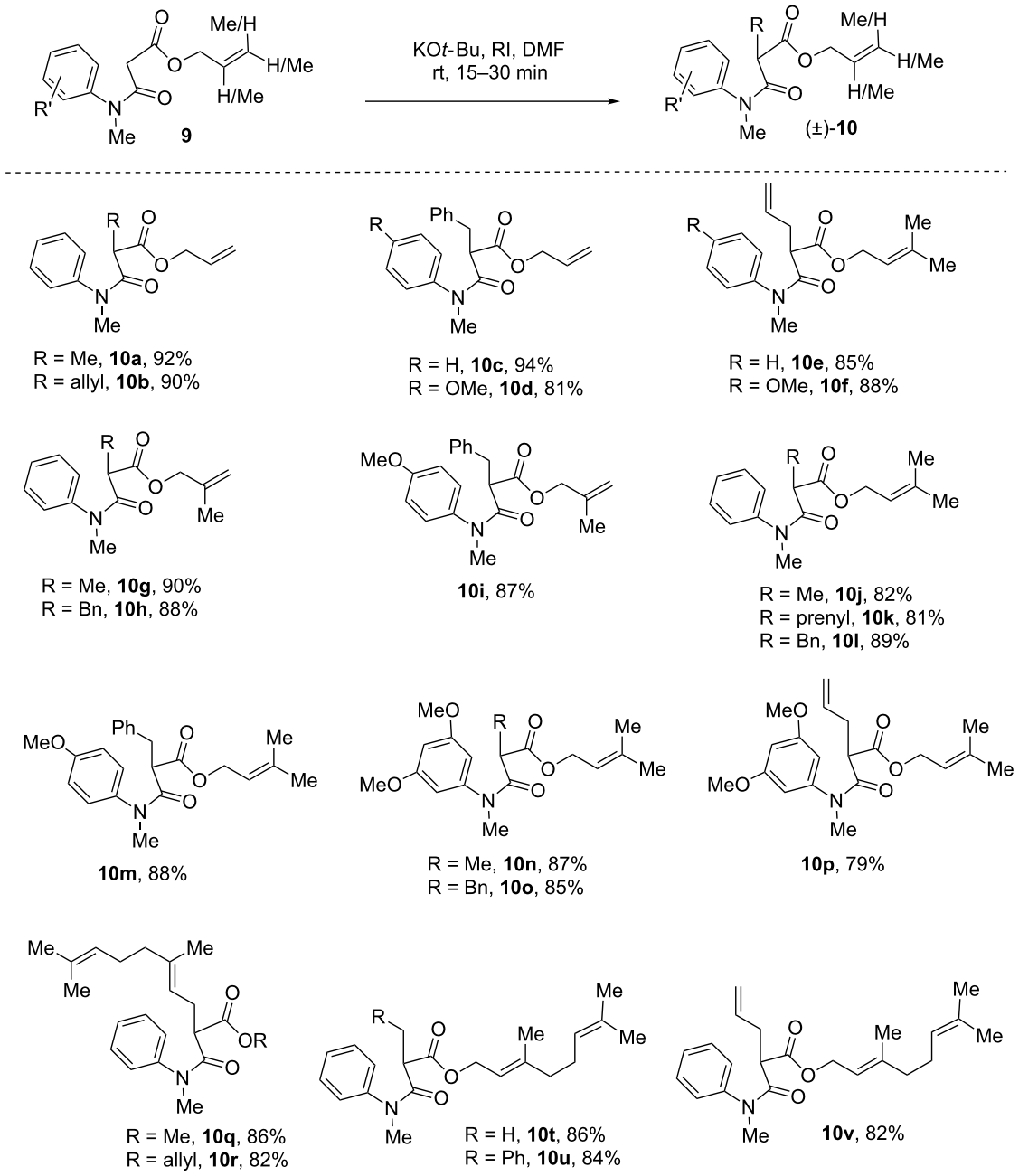


Figure 4: C-Alkylation of anilides using KO*t*-Bu.

2-oxindoles sharing vicinal all-carbon quaternary centers from dimeric β-*N*-arylamidoesters **18a** and **b** (Scheme 4). The reason behind our interest towards this direction was due to the prevalence of various dimeric cyclotryptamine alkaloids containing 3a,3a'-bis-pyrrolo[2,3-*b*]indole subunits (core structure of alkaloids **22a** and **b**, see, Scheme 5) [74-77], sharing a vicinal all-carbon quaternary stereogenic centers with extreme steric congestion at the C3a–C3a' σ-bond as well as the attendant lability of this linkage. Under the optimized conditions, one-pot dimerization of β-*N*-arylamido ester **3a** and **b** and **9a** took place

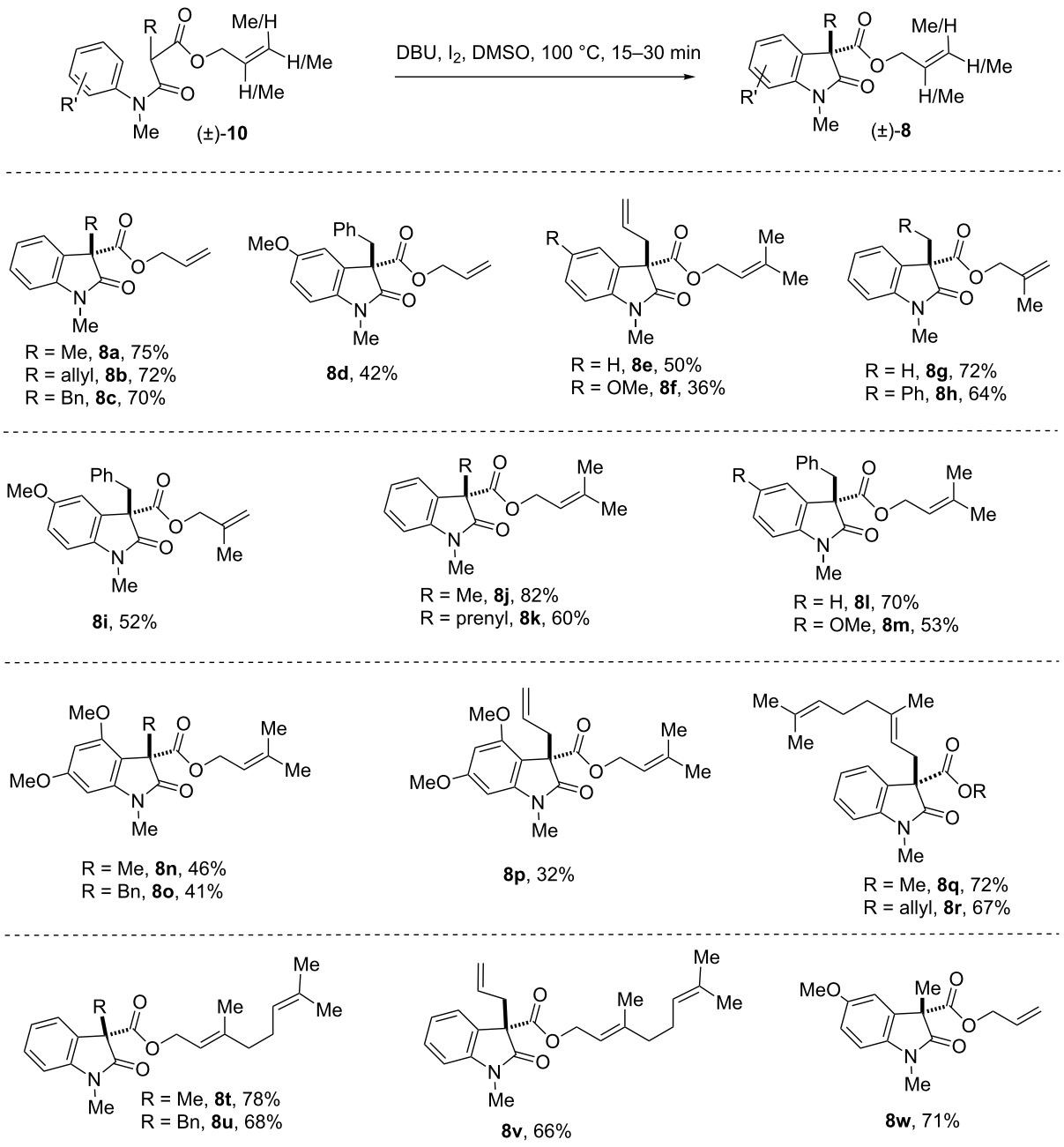
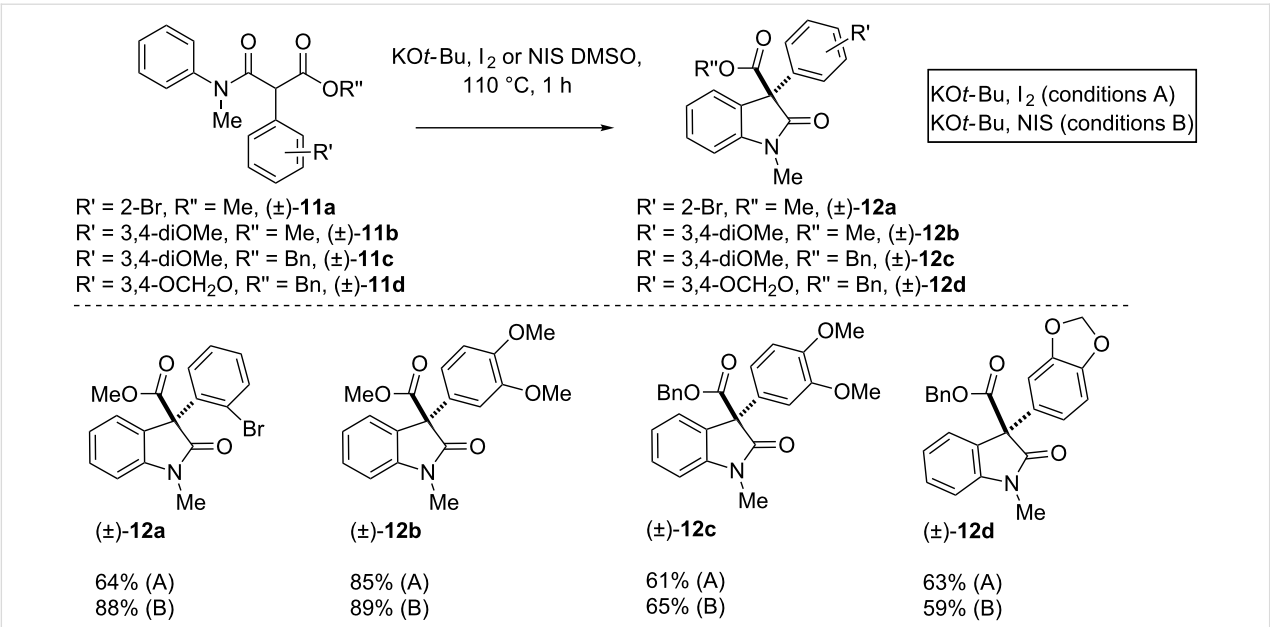
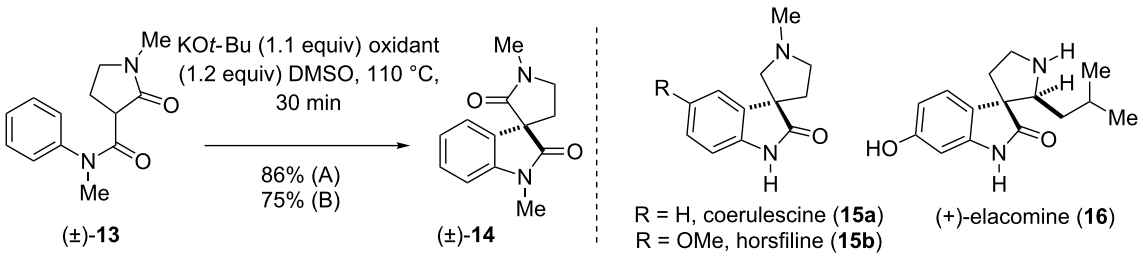


Figure 5: Substrates scope of 'transition-metal-free' IDC of C-alkylated anilides using DBU/I_2.

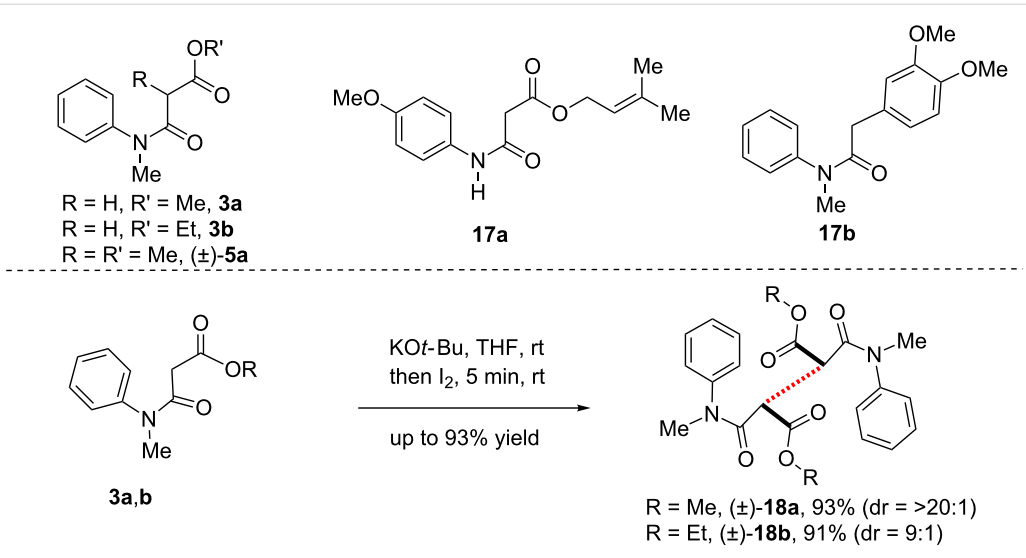
in the presence of 1.2 equivalents of KO*t*-Bu and I_2 followed by a double IDC on treatment with 1.2 equivalents of KO*t*-Bu and I_2 affording the dimeric 2-oxindoles (±)-**19a–c** in poor to moderate yields (26–45% yield and 2:1 dr) along with 15–18% isolation of dimeric β-*N*-arylamidoesters (±)-**18a–c** (Scheme 5). This transformation is an efficient one-pot formation of three consecutive carbon–carbon bonds. X-ray crystal structure determination of (±)-**19b** proved the outcome of the reaction unambiguously. It was noteworthy to observe Pd-catalyzed highly enantio-, chemo-, and diastereoselective double decarboxylative allylations on dimeric β-*N*-arylamido allyl ester **19c** to yield the enantiopure compounds of type **20a** and **b** in good yields



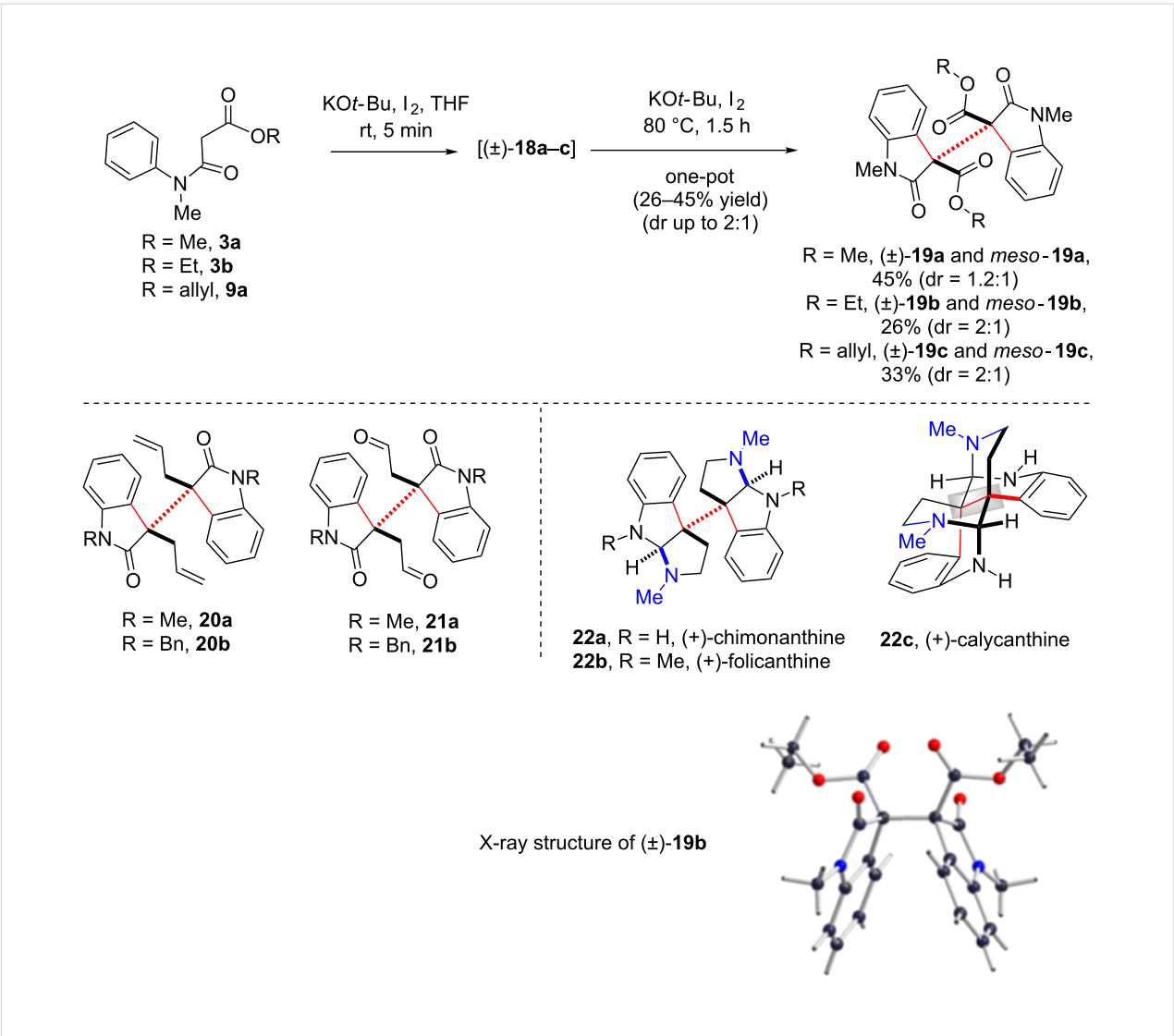
Scheme 2: Oxidative coupling of C-arylated anilides (±)-**11a–d**. The synthesis of **12b** as per method A has been reproduced from reference [46].



Scheme 3: Synthesis of spirocyclic product through IDC The synthesis of **14** as per method A has been reproduced from reference [46]. Conditions A: KO*t*-Bu, iodine; conditions B: KO*t*-Bu, NIS.



Scheme 4: Dimerization of β-*N*-aryl-amidoesters **3a** and **b**. Reproduced from [46].



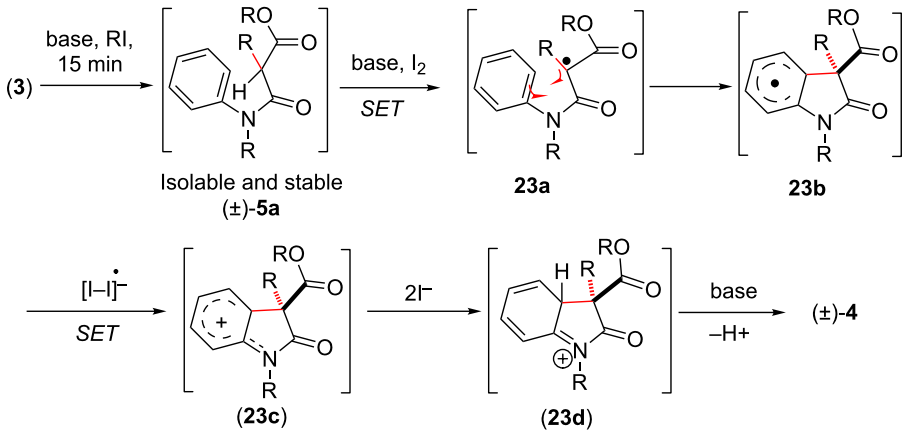
Scheme 5: Synthesis of dimeric 2-oxindoles utilizing IDC. The syntheses of **19a** and **b** have been reproduced from [46].

[78-81]. Especially, enantioenriched **20b** is the advanced intermediate for the total syntheses of 3a,3a'-bispyrrolo[2,3-*b*]indole alkaloids, chimonanthine (**22a**), folicanthine (**22b**), and their rearranged skeleton such as calycanthine (**22c**) (Scheme 5) [78].

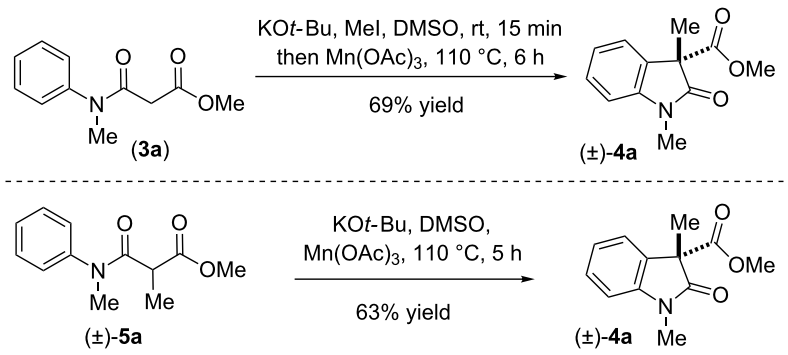
In all the cases, IDC was feasible with substrates having substituents at the carbon atom α- to the amides. This gave a clue for a radical-mediated process where a single electron transfer (SET) mechanism might be operating. A tentative mechanism has been proposed in Scheme 6, the reaction can adopt a SET mechanism leading to the intermediate **23a**, after C-alkylation. Compound **23a** in turn gets converted into intermediate aryl radical **23b**. From this intermediate another intermediate aryl carbocation **23c** is formed by transferring a single electron to the oxidant. Carbocation **23c** is stabilized by the amide nitrogen as shown in **23d**. Eventually, in the presence of base, rearomatization of **23d** takes place to afford the final product of the oxidative coupling reaction.

Kündig et al. in their oxidative coupling process using 2.2 equivalent of $CuCl_2$ showed that it is important to have a tertiary carbon α- to the amide for the process to be radical mediated [38,39]. Also, it is well evident from literature that the oxidation processes using $Mn(OAc)_3$ as oxidant follow a radical pathway [82-86]. In fact, the reaction of **3a** also afforded 2-oxindole **4a** in 69% yield when the oxidative coupling was carried out in presence of 1.2 equiv of $Mn(OAc)_3$ (Scheme 7). A similar result was also observed when reaction was carried out using C-methyl β-*N*-arylamido ester **5a** (Scheme 7) [82-86].

However, one can't rule out the possibility of a substitution reaction on C-iodo product **24** from the adjacent aryl group

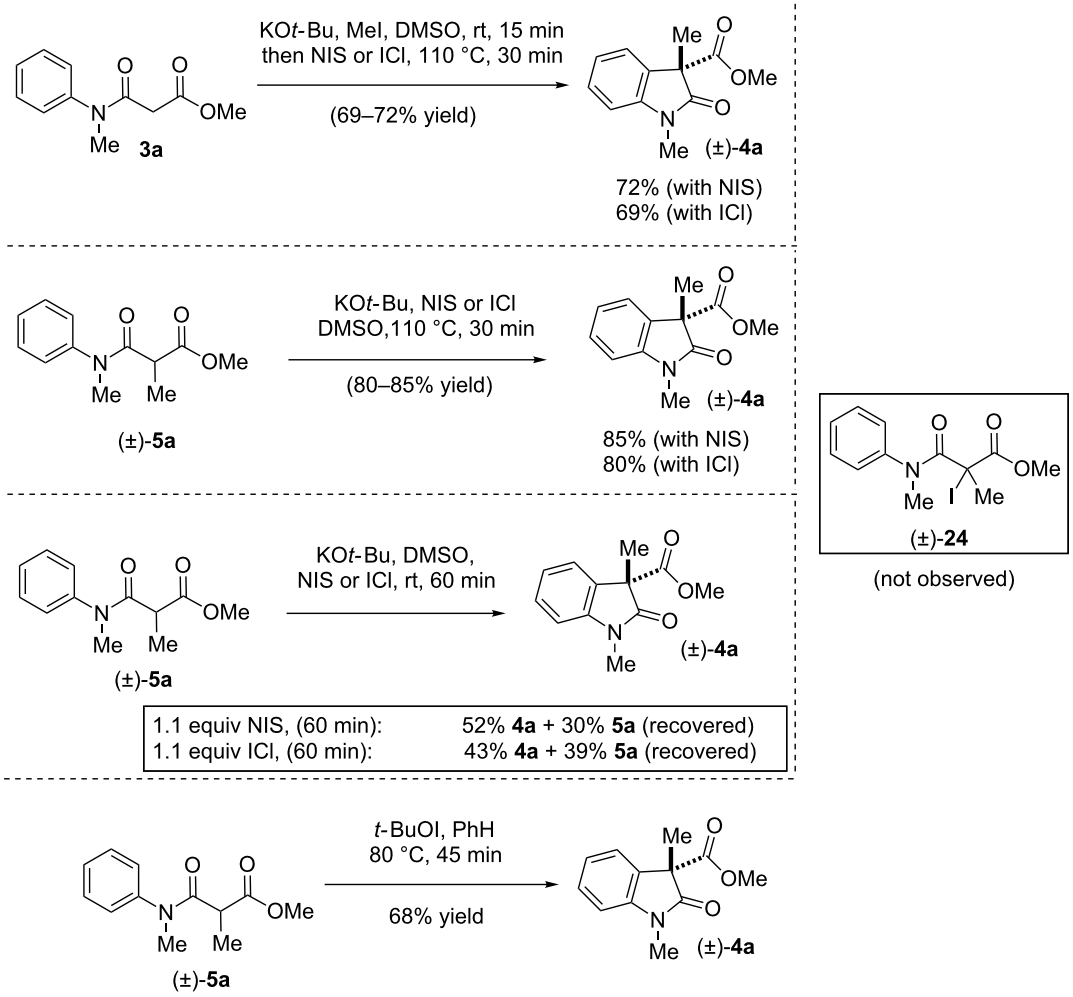


Scheme 6: Plausible mechanism of 'transition-metal-free' IDC The mechanistic consideration in Scheme 6 has been reproduced from [46].



Scheme 7: Intramolecular-dehydrogenative-coupling (IDC) of **3a** and **5a**. Reproduced from [46].

(Scheme 8). Thus, the possibilty of the addition at the 2-position of electron-rich *N*-acylated aniline **3a** to the tertiary iodide intermediate was also investigated. Towards this, we thought of synthesizing the C-iodo intermediate using *N*-iodosuccinimide (NIS) or ICl in the presence of a base. Surprisingly, our all effort to prepare C-iodo compound **24** in the presence of KO*t*-Bu as a base only led to formation of 2-oxindole **4a** in 72% and 69% yields, respectively (Scheme 8). Along the same line, C-methyl β-*N*-arylamido ester **5a** also afforded product **4a** in 80–85% yield when the reaction was carried out at elevated temperature (Scheme 8). We thought there could be the possibility of a substitution reaction of iodide compound **24** prepared in-situ to form directly 2-oxindole **4a** under elevated temperature. Thus, it was decided to carry out the C-iodination at room temperature, where substitution reactions would be unlikely, considering the fact that the substitution has to occur at the sterically congested tertiary iodide **24**. However, to our surprise, when C-iodination of **5a** was carried out at rt, we found that it also afforded 2-oxindole **4a** in 30–39% yield along with 43–52% of recovered starting material (Scheme 8) and no trace of C-iodide **24** was observed. These results suggest that, NIS and ICl also acts as oxidants and helping in a single electron transfer (SET) in the oxidative coupling reaction [87,88]. It is also well evident in the literature that, these can also be used as oxidants in variety of oxidative coupling reactions [87,88]. Further, oxidative coupling of **5a** was carried out in presence of well-known *t*-BuOI, which generally goes through a radical-mediated pathway [89,90]. Towards this, when the oxidative coupling was carried out in presence of in situ generated *t*-BuOI [91], the reaction afforded oxidative coupling product (±)-**4a** in 68% yield, which is also probably indicating a radical pathway of the reaction (Scheme 8).

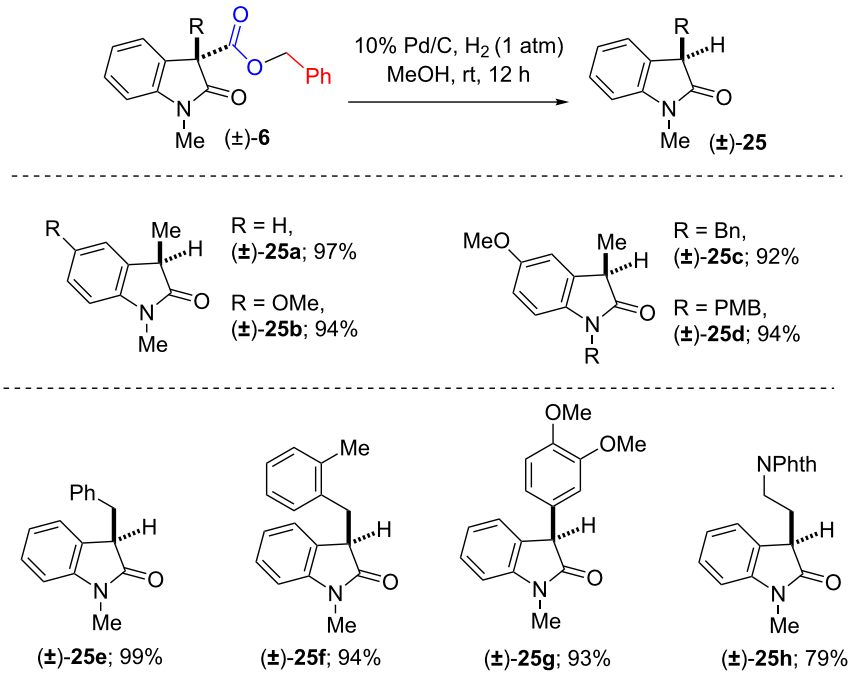


Scheme 8: IDC of **3a** and **5a** using different oxidants. Reproduced from [46].

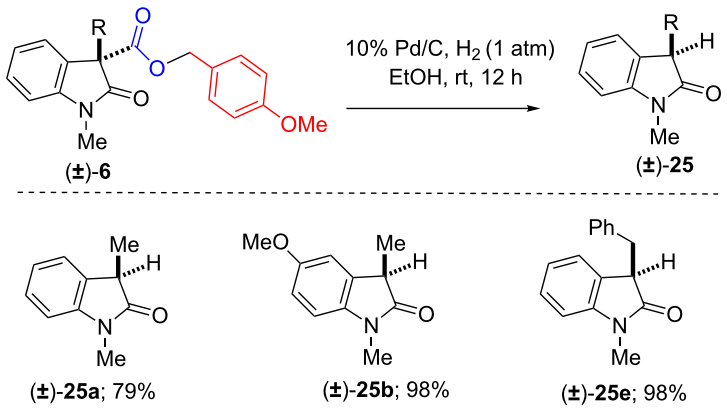
Shifting our attention towards the synthetic application of our IDC methodology, we put forward our effort towards the synthesis of 3-alkylated or arylated 2-oxindoles. Towards this, we subjected to react, the oxidative coupling products (±)-**6,** (±)-**12c** and **d** having benzyl (Bn) or *p*-methoxybenzyl (PMB) esters with a catalytic amount of Pd on activated charcoal (10% Pd on charcoal) under atmospheric pressure of hydrogen gas in MeOH/EtOH (Scheme 9).

Interestingly, we observed that the oxidative coupling products undergo deprotection of benzyl or p-methoxybenzyl group and provided the intermediate carboxylic acid, followed by decarboxylative protonation in the same pot gave us the desired products (±)-**25a**–**h** in excellent yields (Scheme 9 and Scheme 10).

Later, we envisioned that the oxidative coupling products having allyl, methallyl, dimethylallyl esters after Trost–Tsuji decarboxylative allylations could serve as an interesting platform for complex natural product synthesis after further synthetic elaboration and functionalization. A few substrates were treated under decarboxylative allylation (DcA) conditions in the presence of 10 mol % of $Pd(PPh_3)_4$ in refluxing tetrahydrofuran (7–8 h), which afforded products **26a**–**d** in up to 99% yield (Scheme 11). Interestingly, oxidative coupling products with dimethylallyl esters **8j** underwent smooth decarboxylative



Scheme 9: Synthesis of 3-substituted-2-oxindoles from benzyl esters.

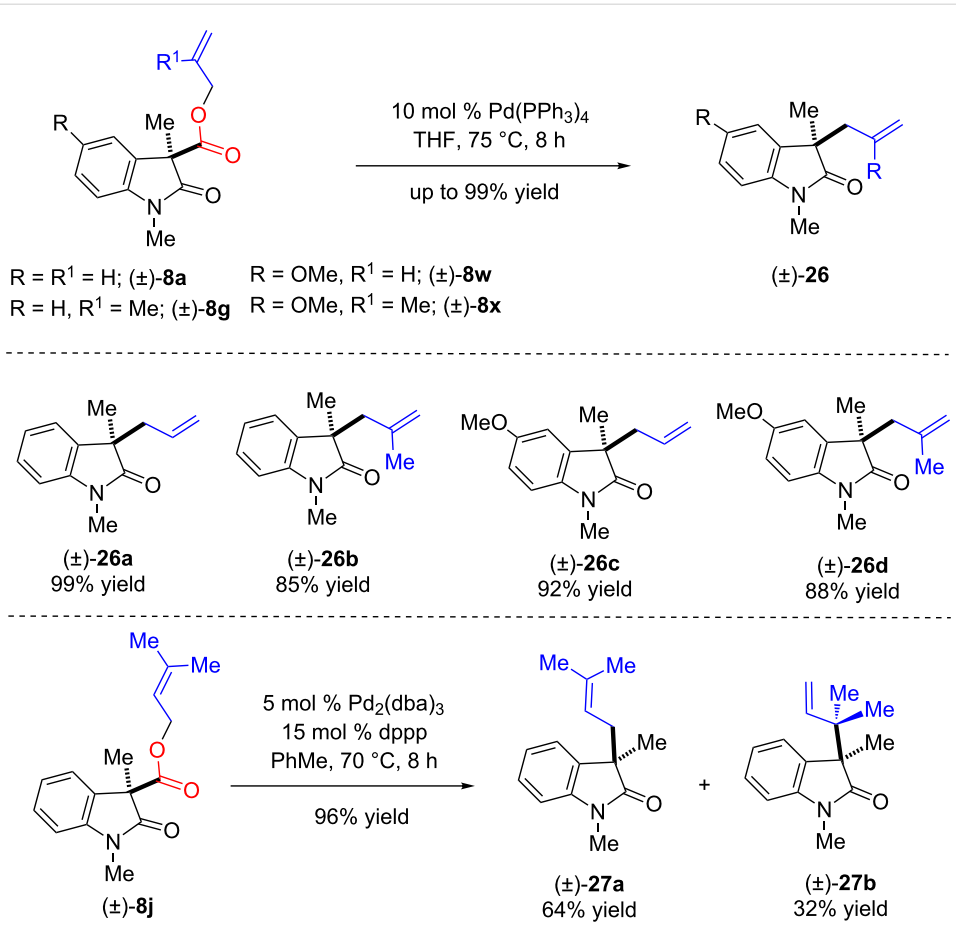


Scheme 10: 3-Substituted-2-oxindoles from p-methoxybenzyl esters.

prenylation and *reverse*-prenylation in the presence of 5 mol % of $Pd_2(dba)_3$ and 15 mol % dppp in refluxing toluene (7–8 h, 96% yields) to afford prenylated (**27a**) and *reverse*-prenylated (**27b**) structures in 64% and 32% yield, respectively (Scheme 11) [92,93]. These structures commonly occur in many hexahydropyrrolo[2,3-*b*]indole-based alkaloids.

Conclusion

In summary, we have successfully demonstrated the synthesis of 2-oxindoles bearing an all-carbon quaternary center applying a 'transition-metal-free' intramolecular dehydrogenative coupling (IDC) strategy. The methodology has been broadly applied to a wide range of substrates affording 2-oxindoles in good yields in a facile one-pot C-alkylation concomitant with oxidative coupling strategy. These products serve as a great synthetic platform for several indole-based natural products. The methodology demonstrated here has several advantages: (i) C-alkylations can be carried in same pot; (ii) simple oxidants like iodine and *N*-iodosuccinimide (NIS) could be used in the absence of any transition metal which may be toxic and (iii)



Scheme 11: Synthetic elaboration using Tsuji–Trost reactions. Reproduced from [46].

substrates with a scope of further functionalization work equally well. The easy handling and the low cost of the reagents involved in this synthetic methodology offers profound opportunities to expand and explore the use of IDC in organic synthesis. Further applications of this strategy are under active investigation in our laboratory.

Supporting Information

Supporting Information File 1

Copies of ^{1}H, and ^{13}C NMR spectra for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-111-S1.pdf]

Acknowledgements

Financial support from the Department of Science and Technology (DST) through FAST-TRACK scheme (SB/FT/CS-54/2011) and the Council of Scientific and Industrial Research (CSIR) [02(0013)/11/EMR-II], Govt. of India is gratefully acknowledged. N.K., S.G., and S.B. thank the CSIR, New Delhi, for predoctoral fellowships. We sincerely thank Dr. Subahdip De, Dr. Badrinath N. Kakde, and Dr. Amit Adhikary for preliminary studies. Facilities from the Department of Chemistry, IISER Bhopal is gratefully acknowledged.

References

1. Dyker, G., Ed. *Handbook of C-H Transformations: Applications in Organic Synthesis;* 2005; Vol. 2.
2. Stuart, D. R.; Fagnou, K. *Science* **2007,** *316,* 1172. doi:10.1126/science.1141956
3. Ashenhurst, J. A. *Chem. Soc. Rev.* **2010,** *39,* 540. doi:10.1039/B907809F
4. Le Bras, J.; Muzart, J. *Chem. Rev.* **2011,** *111,* 1170. doi:10.1021/cr100209d
5. Rossi, R.; Bellina, F.; Lessi, M. *Synthesis* **2010,** 4131. doi:10.1055/s-0030-1258262
6. Scheuermann, C. J. *Chem. – Asian J.* **2010,** *5,* 436. doi:10.1002/asia.200900487
7. You, S.-l.; Xia, J.-B. *Top. Curr. Chem.* **2010,** *292,* 165. doi:10.1007/128_2009_18
8. Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009,** *38,* 3010. doi:10.1039/b821200g

9. Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010,** *75,* 4657. doi:10.1021/jo1006812
10. Hendrickson, J. B. *J. Am. Chem. Soc.* **1975,** *97,* 5784. doi:10.1021/ja00853a023
11. Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011,** *40,* 5068. doi:10.1039/c1cs15082k
12. Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011,** *111,* 1215. doi:10.1021/cr100280d
13. McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009,** *38,* 2447. doi:10.1039/b805701j
14. Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011,** *111,* 1780. doi:10.1021/cr100379j
15. Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000,** *39,* 2632. doi:10.1002/1521-3773(20000804)39:15<2632::AID-ANIE2632>3.0.CO;2-F
16. Li, C.-J. *Acc. Chem. Res.* **2009,** *42,* 335. doi:10.1021/ar800164n
17. Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U. S. A.* **2006,** *103,* 8928. doi:10.1073/pnas.0601687103
18. Li, C.-J.; Li, Z. *Pure Appl. Chem.* **2006,** *78,* 935. doi:10.1351/pac200678050935
19. Yoo, W.-J.; Li, C.-J. *Top. Curr. Chem.* **2010,** *292,* 281. doi:10.1007/128_2009_17
20. Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006,** *128,* 4242. doi:10.1021/ja060050p
    See for metal-free CDC.
21. Uyanik, M.; Ishihara, K. *ChemCatChem* **2012,** *4,* 177. doi:10.1002/cctc.201100352
22. Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003,** 2209. doi:10.1002/ejoc.200300050
23. Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011,** 6821. doi:10.1002/ejoc.201100836
24. Roth, G. J.; Heckel, A.; Colbatzky, F.; Handschuh, S.; Kley, J.; Lehmann-Lintz, T.; Lotz, R.; Tontsch-Grunt, U.; Walter, R.; Hilberg, F. *J. Med. Chem.* **2009,** *52,* 4466. doi:10.1021/jm900431g
25. Rudrangi, S. R. S.; Bontha, V. K.; Manda, V. R.; Bethi, S. *Asian J. Res. Chem.* **2011,** *4,* 335.
26. Trost, B. M.; Brennan, M. K. *Synthesis* **2009,** 3003. doi:10.1055/s-0029-1216975
27. Nishio, T.; Iseki, K.; Araki, N.; Miyazaki, T. *Helv. Chim. Acta* **2005,** *88,* 35. doi:10.1002/hlca.200490294
28. Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.* **1994,** *35,* 1719. doi:10.1016/0040-4039(94)88328-9
29. Murphy, J. A.; Tripoli, R.; Khan, T. A.; Mail, U. W. *Org. Lett.* **2005,** *7,* 3287. doi:10.1021/ol051095i
30. Teichert, A.; Jantos, K.; Harms, K.; Studer, A. *Org. Lett.* **2004,** *6,* 3477. doi:10.1021/ol048759t
31. Zhu, J.; Zhang, W.; Zhang, L.; Liu, J.; Zheng, J.; Hu, J. *J. Org. Chem.* **2010,** *75,* 5505. doi:10.1021/jo1005262
32. Ju, X.; Liang, Y.; Jia, P.; Li, W.; Yu, W. *Org. Biomol. Chem.* **2012,** *10,* 498. doi:10.1039/C1OB06652H
33. Khan, T. A.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. *Org. Lett.* **2003,** *5,* 2971. doi:10.1021/ol035173i
34. Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004,** *43,* 95. doi:10.1002/anie.200352419
35. Kündig, E. P.; Seidel, T. M.; Jia, Y.-X.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2007,** *46,* 8484. doi:10.1002/anie.200703408
36. Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kündig, E. P. *Chem. Commun.* **2008,** 4040. doi:10.1039/b810858g
37. Jia, Y.-X.; Katayev, D.; Bernardinelli, G.; Seidel, T. M.; Kündig, E. P. *Chem. – Eur. J.* **2010,** *16,* 6300. doi:10.1002/chem.201000031
38. Jia, Y. X.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009,** *48,* 1636. doi:10.1002/anie.200805652
    See for oxidative coupling using 2.2 equiv of $CuCl_2$.
39. Dey, C.; Kündig, E. P. *Chem. Commun.* **2012,** 3064. doi:10.1039/c2cc17871k
40. Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009,** 3249. doi:10.1039/b903516h
    See for oxidative coupling using 1.0 equiv of $Cu(OAc)_2{\cdot}H_2O$.
41. Pugh, D. S.; Klein, J. E. M. N.; Perry, A.; Taylor, R. J. K. *Synlett* **2010,** 934. doi:10.1055/s-0029-1219392
42. Klein, J. E. M. N.; Perry, A.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2010,** *12,* 3446. doi:10.1021/ol1012668
    See for coupling using 5–10 mol % of $Cu(OAc)_2{\cdot}H_2O$.
43. Moody, C. L.; Franckevičius, V.; Drouhin, P.; Klein, J. E. M. N.; Taylor, R. J. K. *Tetrahedron Lett.* **2012,** *53,* 1897. doi:10.1016/j.tetlet.2012.01.120
44. Pugh, D. S.; Taylor, R. J. K. *Org. Synth.* **2012,** *89,* 438. doi:10.15227/orgsyn.089.0438
45. Yu, Z.; Ma, L.; Yu, W. *Synlett* **2010,** 2607. doi:10.1055/s-0030-1258584
46. Ghosh, S.; De, S.; Kakde, B. N.; Bhunia, S.; Adhikary, A.; Bisai, A. *Org. Lett.* **2012,** *14,* 5864. doi:10.1021/ol302767w
    See for a preliminary communication from our group.
47. Trost, B. M.; Malhotra, S.; Chan, W. H. *J. Am. Chem. Soc.* **2011,** *133,* 7328. doi:10.1021/ja2020873
    See for Pd-catalyzed asymmetric prenylations and geranylations.
48. Smit, W. A.; Bochkov, A. F.; Caple, R. *Organic Synthesis: The Science behind the Art;* Royal Society of Chemistry: Cambridge, 1998.
49. Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis;* John Wiley & Sons: New York, 1995.
50. Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004,** *104,* 1383. doi:10.1021/cr0306900
51. Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008,** *108,* 5299. doi:10.1021/cr800332c
52. Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008,** *130,* 7222. doi:10.1021/ja8028069
53. West, S. P.; Bisai, A.; Lim, A. D.; Narayan, R. R.; Sarpong, R. *J. Am. Chem. Soc.* **2009,** *131,* 11187. doi:10.1021/ja903868n
54. Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011,** *133,* 19960. doi:10.1021/ja2087085
    Due to electron-rich species, aromatic solvents can take part in oxidative coupling reactions. See for an example.
55. Jensen, B. S. *CNS Drug Rev.* **2002,** *8,* 353. doi:10.1111/j.1527-3458.2002.tb00233.x
56. Oleynek, J. J.; Sedlock, D. M.; Barrow, C. J.; Appell, K. C.; Casiano, F.; Haycock, D.; Ward, S. J.; Kaplita, P.; Gillum, A. M. *J. Antibiot.* **1994,** *47,* 399. doi:10.7164/antibiotics.47.399
57. Yu, Q.-S.; Holloway, H. W.; Flippen-Anderson, J. L.; Hoffman, B.; Brossi, A.; Greig, N. H. *J. Med. Chem.* **2001,** *44,* 4062. doi:10.1021/jm010080x
58. Yu, Q.-S.; Zhu, X.; Holloway, H. W.; Whittaker, N. F.; Brossi, A.; Greig, N. H. *J. Med. Chem.* **2002,** *45,* 3684. doi:10.1021/jm010491d
59. Luo, W.; Yu, Q.-S.; Zhan, M.; Parrish, D.; Deschamps, J. R.; Kulkarni, S. S.; Holloway, H. W.; Alley, G. M.; Lahiri, D. K.; Brossi, A.; Greig, N. H. *J. Med. Chem.* **2005,** *48,* 986. doi:10.1021/jm049309+
60. Kobayashi, J.; Ishibashi, M. *Alkaloids* **1992,** *41,* 41.
61. Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003,** *42,* 36. doi:10.1002/anie.200390048

62. Okada, M.; Sato, I.; Cho, S. J.; Dubnau, D.; Sakagami, Y. *Tetrahedron* **2006,** *62,* 8907. doi:10.1016/j.tet.2006.06.074
See for the isolation of geranylated hexahydropyrrolo[2,3-*b*]indole alkaloids.
63. Rochfort, S. J.; Moore, S.; Craft, C.; Martin, N. H.; Van Wagoner, R. M.; Wright, J. L. C. *J. Nat. Prod.* **2009,** *72,* 1773. doi:10.1021/np900282j
64. One-pot alkylations followed by dehydrogenative-coupling was unsuccessful, thus, IDC was carried out C-alkylated substrates such as **10**.
65. Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003,** *42,* 4961. doi:10.1002/anie.200352577
66. Nicolaou, K. C.; Hao, J.; Reddy, M. V.; BheemaRao, P.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Guiseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004,** *126,* 12897. doi:10.1021/ja040093a
67. Wu, Q.-X.; Crew, M. S.; Draskovic, M.; Sohn, J.; Johnson, T. A.; Tenney, K.; Valeriote, F. A.; Yao, X.-J.; Bjeldanes, L. F.; Crews, P. *Org. Lett.* **2010,** *12,* 4458. doi:10.1021/ol101396n
68. Francke, W.; Kitching, W. *Curr. Org. Chem.* **2001,** *5,* 233. doi:10.2174/1385272013375652
69. Rosenberg, S.; Leino, R. *Synthesis* **2009,** 2651. doi:10.1055/s-0029-1216892
70. Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999,** *121,* 2147. doi:10.1021/ja983788i
71. Deppermann, N.; Thomanek, H.; Prenzel, A. H. G. P.; Maison, W. *J. Org. Chem.* **2010,** *75,* 5994. doi:10.1021/jo101401z
72. Trost, B. M.; Brennan, M. K. *Org. Lett.* **2006,** *8,* 2027. doi:10.1021/ol060298j
73. De, S.; Das, M. K.; Bhunia, S.; Bisai, A. *Org. Lett.* **2015,** *17,* 5922. doi:10.1021/acs.orglett.5b03082
See for our approach using a thiourea catalyzed aldol reaction with paraformaldehyde.
74. May, J. A.; Stoltz, B. M. *Tetrahedron* **2006,** *62,* 5262. doi:10.1016/j.tet.2006.01.105
75. Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007,** *46,* 5488. doi:10.1002/anie.200700612
76. Schmidt, M. A.; Movassaghi, M. *Synlett* **2008,** 313. doi:10.1055/s-2008-1032060
77. Ghosh, S.; Chaudhuri, S.; Bisai, A. *Org. Lett.* **2015,** *17,* 1373. doi:10.1021/acs.orglett.5b00032
78. Ghosh, S.; Chaudhuri, S.; Bisai, A. *Chem. – Eur. J.* **2015,** *21,* 17479. doi:10.1002/chem.201502878
See for an enantioselective approach using a key Pd-catalyzed decarboxylative allylation from our group.
79. Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999,** *121,* 7702. doi:10.1021/ja991714g
See for an asymmetric sequential processes to set a vicinal all-carbon quaternary stereocenter.
80. Trost, B. M.; Osipov, M. *Angew. Chem., Int. Ed.* **2013,** *52,* 9176. doi:10.1002/anie.201302805
81. Ghosh, S.; Bhunia, S.; Kakde, B. N.; De, S.; Bisai, A. *Chem. Commun.* **2014,** *50,* 2434. doi:10.1039/c3cc49064e
82. Heiba, E. I.; Dessau, R. M.; Koehl, W. J., Jr. *J. Am. Chem. Soc.* **1968,** *90,* 2706. doi:10.1021/ja01012a051
See for a Mn(III)-mediated radical process.
83. Bush, J. B., Jr.; Finkbeiner, H. *J. Am. Chem. Soc.* **1968,** *90,* 5903. doi:10.1021/ja01023a048
84. Nikishin, G. I.; Vinogradov, M. G.; Fedorova, T. M. *J. Chem. Soc., Chem. Commun.* **1973,** 693. doi:10.1039/C39730000693
85. Corey, E. J.; Kang, M. *J. Am. Chem. Soc.* **1984,** *106,* 5384. doi:10.1021/ja00330a076
86. Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994,** *94,* 519. doi:10.1021/cr00026a008
87. Newhouse, T.; Lewsi, C. A.; Eastman, K. J.; Baran, P. S. *J. Am. Chem. Soc.* **2010,** *132,* 7119. doi:10.1021/ja1009458
88. Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011,** *50,* 2716. doi:10.1002/anie.201008048
89. Akhtar, M.; Barton, D. H. R. *J. Am. Chem. Soc.* **1964,** *86,* 1528. doi:10.1021/ja01062a016
90. Montoro, R.; Wirth, T. *Org. Lett.* **2003,** *5,* 4729. doi:10.1021/ol0359012
91. Preparation of *t*-BuOI: A flame-dried round-bottom flask was charged with 0.6 mmol of *t*-BuONa in 0.5 mL of benzene. To this solution was added 0.6 mmol of I_2 at room temperature. This solution was directly used for the oxidative coupling (see, reference [90]).
92. Ruchti, J.; Carreira, E. M. *J. Am. Chem. Soc.* **2014,** *136,* 16756. doi:10.1021/ja509893s
93. Thandavamurthy, K.; Sharma, D.; Porwal, S. K.; Ray, D.; Viswanathan, R. *J. Org. Chem.* **2014,** *79,* 10049. doi:10.1021/jo501651z

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at:
doi:10.3762/bjoc.12.111

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Palladium-catalyzed picolinamide-directed iodination of remote *ortho*-C−H bonds of arenes: Synthesis of tetrahydroquinolines

William A. Nack[1], Xinmou Wang[2], Bo Wang[3], Gang He[*1] and Gong Chen[*1,2,3]

Full Research Paper

Open Access

Address:
[1]Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, United States, [2]State Key Laboratory and Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China and [3]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, China

Email:
Gang He[*] - hegang@nankai.eud.cn; Gong Chen[*] - gongchen@nankai.edu.cn

* Corresponding author

Keywords:
iodination; palladium; remote C–H activation; tetrahydroquinoline

Beilstein J. Org. Chem. **2016,** *12,* 1243–1249.
doi:10.3762/bjoc.12.119

Received: 24 March 2016
Accepted: 05 June 2016
Published: 17 June 2016

This article is part of the Thematic Series "C–H Functionalization/activation in organic synthesis".

Guest Editor: R. Sarpong

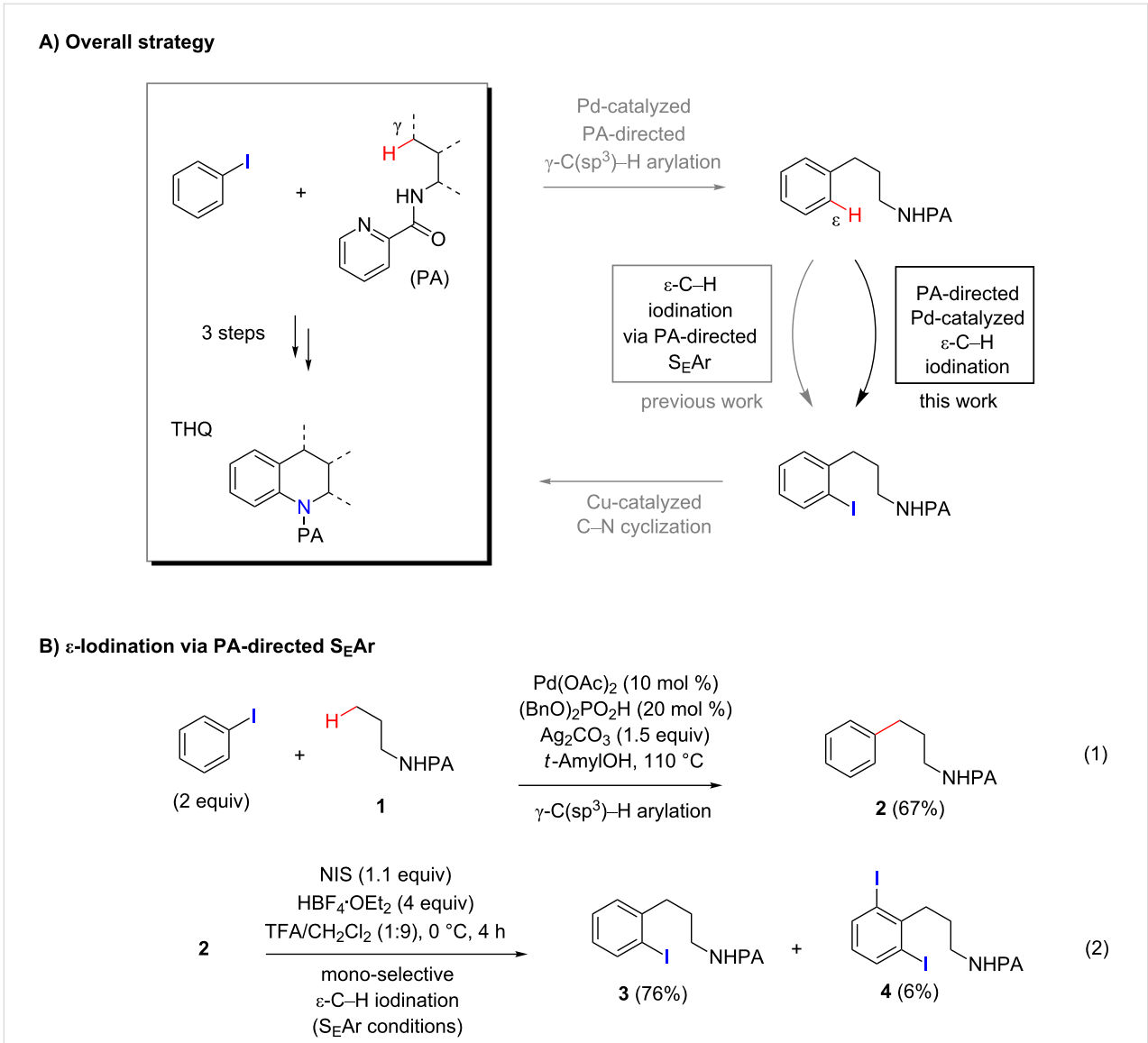
© 2016 Nack et al.; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

A new palladium-catalyzed picolinamide (PA)-directed *ortho*-iodination reaction of ε-C(sp^2)−H bonds of γ-arylpropylamine substrates is reported. This reaction proceeds selectively with a variety of γ-arylpropylamines bearing strongly electron-donating or withdrawing substituents, complementing our previously reported PA-directed electrophilic aromatic substitution approach to this transformation. As demonstrated herein, a three step sequence of Pd-catalyzed γ-C(sp^3)−H arylation, Pd-catalyzed ε-C(sp^2)−H iodination, and Cu-catalyzed C−N cyclization enables a streamlined synthesis of tetrahydroquinolines bearing diverse substitution patterns.

Introduction

Tetrahydroquinoline (THQ) is an important *N*-heterocyclic scaffold found in many natural products and pharmaceutical agents [1,2]. Efficient and generally applicable methods for the synthesis of THQs with complex substitution patterns are still in great demand [3-7]. Recently, we reported a synthetic strategy for THQs based on picolinamide (PA)-directed sequential C−H functionalization reactions starting from readily accessible aryl iodide and alkylamine precursors (Scheme 1) [8]. Alkylpicolinamides were first subjected to Pd-catalyzed γ-C(sp^3)−H arylation with aryl iodides to form γ-arylpropylpicolinamides [9-20]. These γ-arylpropylpicolinamides were then selectively iodinated at the remote ε-C(sp^2)−H position via a rarely precedented PA-directed electrophilic aromatic substitution (S_EAr) reaction (Scheme 1, reaction 2) [21,22]. Copper-catalyzed intramolecular C−N cyclization of these *ortho*-iodinated intermediates provided PA-coupled THQ products in good yields.



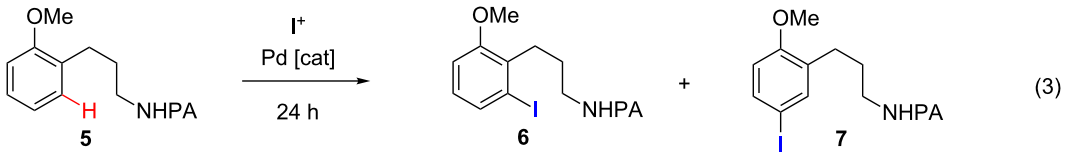
Scheme 1: New synthetic strategy for THQs via PA-directed C−H functionalization.

Although ε-C−H iodination via directed S_EAr proceeds with excellent yield and mono-selectivity for many γ-arylpropylpicolinamides, the scope of these PA-directed S_EAr reactions is limited to arenes bearing moderate electron-donating or withdrawing groups. Arene substrates bearing strongly electron-donating substituents typically gave substantial amounts of undesired iodinated side products via competing innate S_EAr processes, and arene substrates bearing strongly electron-withdrawing substituents were often unreactive. Herein, we report our development of a Pd-catalyzed PA-directed iodination reaction of ε-C(sp^2)−H bonds of γ-arylpropylpicolinamides. This Pd-catalyzed reaction is complementary in scope to the directed S_EAr iodination approach and allows for the efficient synthesis of a broad range of THQs with diverse substitution patterns.

Results and Discussion

Methods for metal-catalyzed halogenation of *ortho* C−H bonds at the more remote ε position are scarce, in contrast to the large number of *ortho* C−H halogenation reactions of arenes effected by more proximal directing groups [23-33]. Fundamentally, it is challenging to achieve efficient reactions through kinetically unfavorable seven-membered palladacycle intermediates. Furthermore, the electrophilic reagents used for C–H halogenation can often react with arenes through undirected S_EAr pathways, which need to be suppressed for regioselectivity. To address this issue upfront, we commenced our study of Pd-catalyzed ε-C−H halogenation with 3-arylpropylpicolinamide **5** bearing a strongly electron-donating OMe group (Table 1, see Supporting Information File 1 for the preparation of **5**). Iodina-

Table 1: Optimization of Pd-catalyzed *ortho* C−H iodination of **5**.[a]



entry	reagents (equiv)	solvent	temperature (°C)	yield (%)[b] 6	7
1	NIS (1.5), $HBF_4{\cdot}EtO_2$ (4.0)	T/D[c]	0	<2	68
2	NIS (1.5)	T/D	0	<2	82
3	$Pd(OAc)_2$ (10 mol %), NIS (1.5)	chlorobenzene	110	<2	74
4	$Pd(OAc)_2$ (10 mol %), NaI (1.5), $NaIO_3$ (1.5), $K_2S_2O_8$ (2.0)	*n*-BuOH	110	<2	<2
5	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $K_2S_2O_8$ (2)	DMF	110	<2	60
6	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0)	DMF	110	43	25
7	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0), K_2CO_3 (1.0)	DMF	110	14	11
8	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0), $KHCO_3$ (2.0)	DMF	110	45	12
9	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0), $KHCO_3$ (1.0)	DMF	110	75 (72)[d]	9 (5)[d]
10	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0), Na_2CO_3 (1.0)	DMF	110	80	8
11	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0), $KHCO_3$ (1.0)	dichloroethane	110	16	58
12	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0), $KHCO_3$ (1.0)	dioxane	110	13	65
13	I_2 (2.0), $PhI(OAc)_2$ (2.0), $KHCO_3$ (1.0)	DMF	110	<2	64

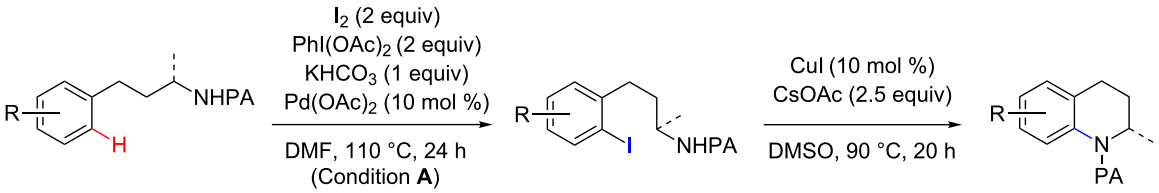
[a]All screening reactions were carried out in a 10 mL glass vial on a 0.2 mmol scale: [b]Yields are based on ^1H NMR analysis of the reaction mixture using CH_2Br_2 as internal standard; [c]T/D: TFA (T)/CH_2Cl_2 (D); [d]isolated yield.

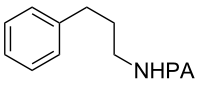
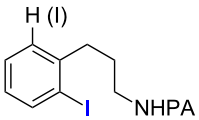
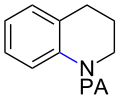
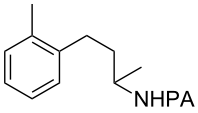
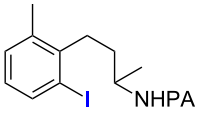
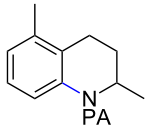
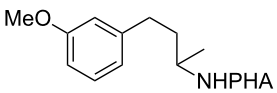
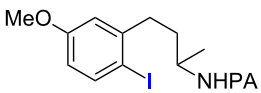
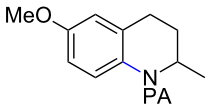
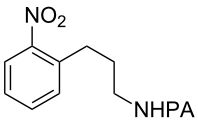
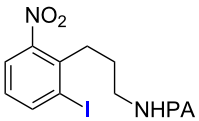
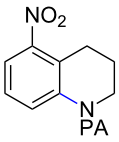
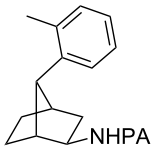
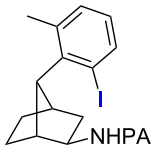
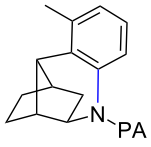
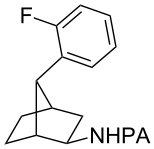
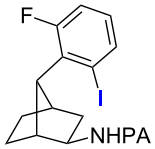
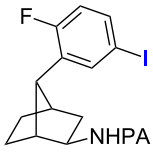
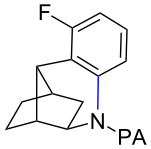
tion of **5** under our previous S_EAr protocol gave undirected iodination product **7** as the major product; only a trace amount of *ortho*-iodination product **6** was detected (Table 1, entries 1 and 2). Iodination of **5** under a variety of Pd-catalyzed oxidative conditions gave either low conversion or poor regioselectivity (Table 1, entries 3–5). To our delight, the use of a combination of 2 equiv of I_2 and 2 equiv of $PhI(OAc)_2$ in DMF at 110 °C gave the desired product **6** in good yield and moderate selectivity. Similar conditions were reported by Yu to effect the Pd-catalyzed NHTf-directed iodination of δ-C(sp^2)−H bonds of β-phenylethyl triflamides [33]. IOAc generated in situ is believed to be the active iodinating species. DMF was found to be the best solvent for this reaction (Table 1, entry 9 vs 11 and 12). Moreover, we found that the choice of alkali carbonate base was important: replacing K_2CO_3 with $KHCO_3$ or Na_2CO_3 gave notably improved yields and ortho selectivity (Table 1, entries 9 and 10) [34,35]. By analogy with similar Pd-catalyzed directed C–H halogenation reactions, we speculate that the catalytic cycle follows a sequence of C−H palladation, oxidative addition and reductive elimination [36,37].

With the best conditions in hand (Table 1, entries 9 and 10), we then examined the substrate scope of this Pd-catalyzed iodination of γ-arylpropylpicolinamides (Table 2). The γ-arylpropylpicolinamides were prepared from the corresponding *N*-alkylpicolinamides and aryl iodides under our $(BnO)_2PO_2H$-promoted Pd-catalyzed γ-C(sp^3)−H arylation conditions (see Supporting Information File 1 for details). The substrate scope was chosen to complement the S_EAr method, which is notably incompatible with NO_2, F and OMe substituents. In contrast to the mono-selectivity of the directed S_EAr approach (reaction 2, Scheme 1), iodination of γ-phenylpropylpicolinamide **2** bearing two equivalent *ortho* C−H bonds under Pd-catalyzed conditions A gave a mixture of mono-iodinated **3** and *ortho* diiodinated product **4**. However, no *para*-iodinated side product was formed. With 4 equiv of $PhI(OAc)_2/I_2$ and 1 equiv of $KHCO_3$, **4** can be formed as the major product in 69% yield.

Arenes bearing *meta*-substituents (e.g., **12**) were selectively iodinated at the less hindered *ortho* position. Pd-catalyzed iodination of substrate **15** bearing a strongly electron-withdrawing

Table 2: Substrate scope of Pd-catalyzed ε-C−H iodination and Cu-catalyzed C−N cyclization to form THQs[a].



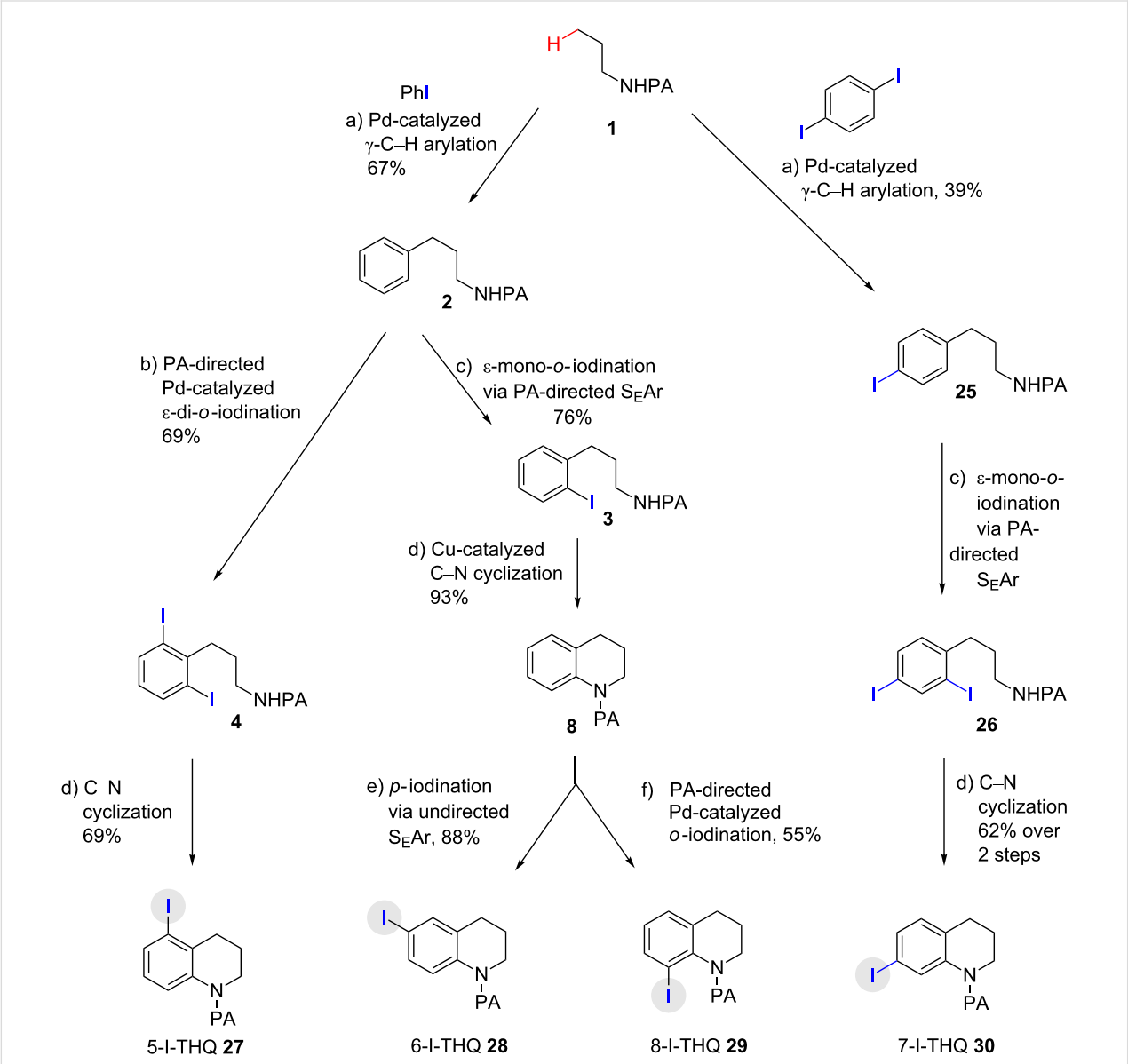
C–H arylation[b]	iodination		C–N cyclization
	Pd catalyzed	directed S_EAr	
 **2** (67%)	 **3** (mono-I, 47%) + **4** (di-I, 25%)[c]	**3** (76%) + **4** (6%)	 **8** (93%)
 **9** (81%)	 **10** (75%)	**10** (60%) (*o*/*x* = 5:3)[c]	 **11** (96%)
 **12** (81%)	 **13** (68%)	**13** (50%) (*o*/*x* = 5:4)[c]	 **14** (94%)
 **15** (28%)	 **16** (68%)	NR	 **17** (47%)
 **18** (60%)	 **19** (56%)	**19** (20%) (*o*/*x* = 1:4)[c]	 **20** (85%)
 **21** (95%)	 **22** (53% or 85%[d])	 **23** (90%) X-ray	 **24** (78%)

[a]Yields are based on isolated product on a 0.2 mmol scale; [b]see reaction 1 in Scheme 1B for conditions for Pd-catalyzed C−H arylation; [c]di: *ortho*-diiodinated isomer, *x*: mixture of other iodinated isomers; [d]conditions B: I_2 (2 equiv), $PhI(OAc)_2$ (2 equiv), $Pd(OAc)_2$ (10 mol %), Na_2CO_3 (1 equiv), DMF, 110 °C, 24 h.

NO_2 group also proceeded smoothly to give **16**; this substrate is unreactive to directed S_EAr. The rigid arylnorbornane scaffold **18** is incompatible with directed S_EAr, but was iodinated selectively at the ortho position under Pd-catalyzed conditions without the formation of regioisomeric side products. The strong *para*-directing effect exerted by aryl fluoride substituents overrides directed S_EAr selectivity [38,39]. Thus, we observed only *para*-iodinated compound **23** when **21** was subjected to the directed S_EAr protocol. In contrast, using our Pd-catalyzed iodination (conditions B), *ortho*-iodinated product **22** was obtained

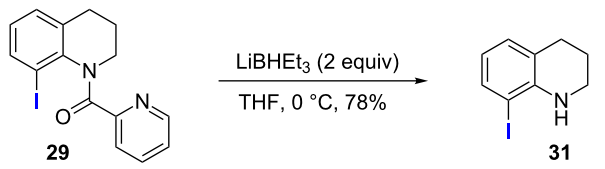
via Pd-catalyzed iodination as the only product in excellent yield. The iodinated intermediates could be readily cyclized under our previously reported Cu-catalyzed conditions to give PA-coupled THQ products with various substitution patterns in good yields (Scheme 2) [8].

As shown in Scheme 2, Pd-catalyzed PA-directed ε-C−H iodination can be used in concert with PA-directed γ-C−H arylation, PA-directed S_EAr iodination, and undirected S_EAr iodination to quickly access THQs **27**–**30** bearing iodo groups at different positions on the arene ring [40-42]. *Ortho*-diiodinated product **4** was obtained from **2** in 69% yield using optimized Pd-catalyzed ε-C–H iodination conditions, and Cu-catalyzed C–N cyclization of **4** gave 5-iodo-THQ **27**. PA-THQ **8** was susceptible to iodination at two positions. Under undirected S_EAr conditions, 6-iodo-THQ **28** was produced in excellent yield and regioselectivity. Alternatively, a Pd-catalyzed C–H iodination reaction of **8** was developed which provides 8-iodo-THQ **29**. Pd-catalyzed C−H arylation of **1** with *para*-diiodobenzene under the standard arylation conditions gave **25** in moderate yield. Iodination of **25** via PA-directed S_EAr gave diiodinated compound **26**, which was cyclized under Cu catalysis to give



Scheme 2: Preparation of iodo-substituted THQs via PA-directed C−H functionalization strategy. a) ArI (2 equiv), $Pd(OAc)_2$ (10 mol %), $(BnO)_2PO_2H$ (20 mol %), Ag_2CO_3 (1.5 equiv), *t*-AmylOH, 110 °C, 24h; b) $Pd(OAc)_2$ (10 mol %), I_2 (4 equiv), $PhI(OAc)_2$ (4 equiv), $KHCO_3$ (1 equiv), 130 °C, DMF, 24 h; c) NIS (1.1 equiv), $HBF_4{\cdot}OEt_2$ (4), TFA/DCM (1:9), 2.5 mM, 0 °C, 4 h; d) CuI (10 mol %), CsOAc (2.5 equiv), DMSO, Ar, 90 °C, 20 h; e) NIS (1.1 equiv), TFA/DCM (1:9), 2.5 mM, rt, 16 h; f) $Pd(OAc)_2$ (15 mol %), NIS (2.5 equiv), α,α,α-trifluorotoluene, Ar, 100 °C, 24 h.

7-iodo-THQ **30** in good yield. The PA group of 8-iodo-THQ **29** was readily removed with $LiBHEt_3$ to give **31** (Scheme 3) [10].



Scheme 3: Removal of PA auxiliary from THQ product.

Conclusion

In summary, we have developed a new palladium-catalyzed picolinamide (PA)-directed iodination reaction of ε-C(sp^2)−H bonds of γ-arylpropylamine substrates. This method works well for arenes with a broad range of substituents and offers a complementary scope to our previously reported PA-directed S_EAr approach. This Pd-catalyzed PA-directed ε-C−H iodination can be used in concert with the PA-directed γ-C−H arylation, PA-directed S_EAr iodination, undirected S_EAr iodination, and Cu-catalyzed C−N cyclization to quickly access tetrahydroquinolines bearing diverse substitution patterns from readily accessible starting materials.

Supporting Information

Supporting Information File 1

Detailed synthetic procedures and characterizations of all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-119-S1.pdf]

Acknowledgements

We gratefully acknowledge financial support from the State Key Laboratory of Elemento-Organic Chemistry at Nankai University and the Pennsylvania State University.

References

1. Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996,** *51,* 15031. doi:10.1016/S0040-4020(96)00911-8
2. Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2011,** *111,* 7157. doi:10.1021/cr100307m
3. Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006,** *128,* 13070. doi:10.1021/ja064676r
4. Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009,** *131,* 4598. doi:10.1021/ja900806q
5. Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009,** *131,* 9182. doi:10.1021/ja903547q
6. Rousseaux, S.; Liégault, B.; Fagnou, K. *Chem. Sci.* **2012,** *3,* 244. doi:10.1039/C1SC00458A
7. Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2012,** *51,* 12842. doi:10.1002/anie.201207959
8. Nack, W. A.; He, G.; Zhang, S.-Y.; Chen, G. *Org. Lett.* **2013,** *15,* 3440. doi:10.1021/ol4015078
9. Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005,** *127,* 13154. doi:10.1021/ja054549f
10. Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012,** *134,* 7. doi:10.1021/ja210959p
11. Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013,** *78,* 9689. doi:10.1021/jo4013628
12. He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011,** *50,* 5192. doi:10.1002/anie.201100984
13. Zhao, Y.; Chen, G. *Org. Lett.* **2011,** *13,* 4850. doi:10.1021/ol201930e
14. He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012,** *134,* 3. doi:10.1021/ja210660g
15. Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012,** *134,* 7313. doi:10.1021/ja3023972
16. He, G.; Lu, C.; Zhao, Y.; Nack, W. A.; Chen, G. *Org. Lett.* **2012,** *14,* 2944. doi:10.1021/ol301352v
17. Zhao, Y.; He, G.; Nack, W. A.; Chen, G. *Org. Lett.* **2012,** *14,* 2948. doi:10.1021/ol301214u
18. Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013,** *135,* 2124. doi:10.1021/ja312277g
19. Roman, D. S.; Charette, A. B. *Org. Lett.* **2013,** *15,* 4394. doi:10.1021/ol401931s
20. Huang, L.; Li, Q.; Wang, C.; Qi, C. *J. Org. Chem.* **2013,** *78,* 3030. doi:10.1021/jo400017v
21. Barluenga, J.; Álvarez-Gutiérrez, J. M.; Ballesteros, A.; González, J. M. *Angew. Chem., Int. Ed.* **2007,** *46,* 1281. doi:10.1002/anie.200603631
22. Espuña, G.; Arsequell, G.; Valencia, G.; Barluenga, J.; Álvarez-Gutiérrez, J. M.; Ballesteros, A.; González, J. M. *Angew. Chem., Int. Ed.* **2004,** *43,* 325. doi:10.1002/anie.200352464
23. Lu, C.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Tetrahedron* **2014,** *70,* 4197. doi:10.1016/j.tet.2014.02.070
See for our recent report on Pd-catalyzed PA-directed *ortho* C−H halogenation of benzylamine substrates.
24. Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006,** *62,* 11483. doi:10.1016/j.tet.2006.06.075
25. Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006,** *128,* 7416. doi:10.1021/ja060232j
26. Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008,** *47,* 5215. doi:10.1002/anie.200705613
27. Mo, F.; Yan, J. M.; Qiu, D.; Li, F.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010,** *49,* 2028. doi:10.1002/anie.200906699
28. Schröder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012,** *134,* 8298. doi:10.1021/ja302631j
29. Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997,** *62,* 2. doi:10.1021/jo961876k
30. Leblanc, M.; Fagnou, K. *Org. Lett.* **2005,** *7,* 2849. doi:10.1021/ol0505959
31. Li, J.-J.; Giri, R.; Yu, J.-Q. *Tetrahedron* **2008,** *64,* 6979. doi:10.1016/j.tet.2008.03.026
32. Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012,** *486,* 518. doi:10.1038/nature11158
33. Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008,** *47,* 6452. doi:10.1002/anie.200802187
34. Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009,** *48,* 5094. doi:10.1002/anie.200806273
35. Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010,** *110,* 1147. doi:10.1021/cr900184e

36. Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012,** *134,* 11948. doi:10.1021/ja305259n
Alkali cations (e.g., Na^+, K^+) might play a useful role in this PA-directed C–H functionalization reaction. See for mechanistic investigations on related reaction systems.
37. Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011,** *133,* 12984. doi:10.1021/ja206002m
38. Ault, A. *J. Chem. Educ.* **1966,** *43,* 329. doi:10.1021/ed043p329
39. Rosenthal, J.; Schuster, D. I. *J. Chem. Educ.* **2003,** *80,* 679. doi:10.1021/ed080p679
40. Thansandote, P.; Lautens, M. *Chem. – Eur. J.* **2009,** *15,* 5874. doi:10.1002/chem.200900281
41. Mei, T.-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J.-Q. *Synthesis* **2012,** *44,* 1778. doi:10.1055/s-0031-1289766
42. Nack, W. A.; Chen, G. *Synlett* **2015,** *26,* 2505. doi:10.1055/s-0034-1381051

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.119

BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Direct arylation catalysis with chloro[8-(dimesitylboryl)quinoline-κN]copper(I)

Sem Raj Tamang and James D. Hoefelmeyer*

Full Research Paper

Open Access

Address:
Department of Chemistry, University of South Dakota, 414 E. Clark St., Vermillion, SD 57069, USA

Email:
James D. Hoefelmeyer* - jhoefelm@usd.edu

* Corresponding author

Keywords:
catalysis; C–C coupling; C–H activation; copper; direct arylation

Beilstein J. Org. Chem. **2016,** *12,* 2757–2762.
doi:10.3762/bjoc.12.272

Received: 22 September 2016
Accepted: 30 November 2016
Published: 15 December 2016

This article is part of the Thematic Series "C–H Functionalization/activation in organic synthesis".

Guest Editor: R. Sarpong

© 2016 Tamang and Hoefelmeyer; licensee Beilstein-Institut.
License and terms: see end of document.

Abstract

We report direct arylation of arylhalides with unactivated sp^2 C–H bonds in benzene and naphthalene using a copper(I) catalyst featuring an ambiphilic ligand, (quinolin-8-yl)dimesitylborane. Direct arylation could be achieved with 0.2 mol % catalyst and 3 equivalents of base (KO(*t*-Bu)) at 80 °C to afford TON ≈160–190 over 40 hours.

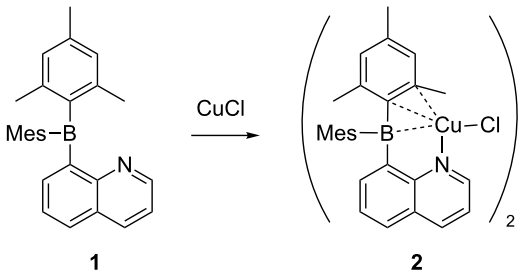
Introduction

Coupling of aryl C–C bonds is invaluable in organic synthesis, and has been the subject of much research with the aim to lower cost and improve atom efficiency [1-5]. The earliest and most developed methods involve the reaction of C–M (M = Li, B, Mg, Si, Sn, Zn) with C–X (X = halide, triflate, tosylate, or aryliodide (as Ar_2I^+)) using Pd-based catalysts. These methods achieve coupling of aryl C–C bonds with high activity and selectivity; however, the reactants are quite expensive and there is significant opportunity to improve the atom efficiency. Additionally, there is impetus to utilize less expensive metal catalysts or even metal-free reactions. Recently, there has been rapid progress toward the use of C–H bonds as a reactive functional group [6]. While it would be highly desirable to utilize C–H/C–H coupling reactions [7], low reactivity and selectivity are significant obstacles. The use of directing groups can improve the selectivity, but could contribute additional reaction steps and expense. Therefore, C–X/C–H (X = halogen) direct arylations are an important avenue of investigation that may represent a balance between cost, activity, and selectivity [8-13].

The C–X/C–H direct arylation reaction can be achieved with X = halogen, triflate, tosylate [14], $B(OH)_2$ [15-20], SnR_3 [21], $Si(OR)_3$ [22], or with the use of aryliodonium salts [23]; wherein halogen atoms represent the most cost-effective and atom-efficient functional group. The reactions typically utilize expensive transition metal catalysts (Pd, Rh, Ir) at high loadings (typically 10 mol %), and require a large amount of strong

base (typically 3 equivalents KO(*t*-Bu)). There has been some success using inexpensive first-row transition metals (Fe [24,25], Co [26-28], Ni [29-33], and Cu [34-37]) or an aluminum-based metal-organic framework [38], and there are several reports of metal-free direct arylation reactions in which the reaction is promoted with 2–3 equivalents KO(*t*-Bu) and (typically) 10–30 mol % of an additive [39-48].

The use of ambiphilic molecules as ligands for transition metals has given rise to an important new class of catalysts [49]. In previous work from our laboratory, we prepared the intramolecular frustrated Lewis pair 8-quinolyldimesitylborane (**1**) and its complexes with Cu(I), Ag(I), and Pd(II) [50]. Recently, we reported the Pd(II) complex catalyzed Heck-type C–C coupling [51]. The observation may implicate reductive elimination and oxidative addition can cycle repeatedly on the palladium center coordinated to **1**. With this in mind, we sought to utilize the Cu(I) complex, chloro[8-(dimesitylboryl)quinoline-κN]copper(I) (**2**, Scheme 1), and investigate its performance as a catalyst for direct arylation reactions. We note that compound **2** consists of the ambiphilic ligand **1** coordinated to Cu(I) via nitrogen atom coordination and an η^3-BCC interaction [52]. Herein we report the use of the preformed catalyst **2** and demonstrate good activity for C–X/C–H direct arylation reactions.

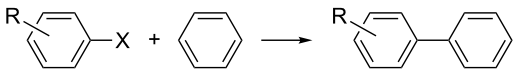


Scheme 1: Coordination of Cu(I) with the ambiphilic ligand **1** to form the catalyst **2**.

Results and Discussion

The results of direct arylation catalysis are summarized in Table 1. We performed the reaction of iodobenzene with benzene/DMF (10:1 v/v) at 80 °C using a catalyst loading of 2 mol % of **2** and 30 equivalents KO(*t*-Bu) (Table 1, entry 1). After 10 hours the yield of biphenyl was 94% according to GC–MS analysis. A control reaction (Table 1, entry 4) of iodobenzene with benzene/DMF (10:1 v/v) using 2 mol % Cu(I)Br and 30 equivalents KO(*t*-Bu) gave 5% yield of biphenyl after 10 hours. Reactions performed in the absence of catalyst, using 3 or 30 equivalents KO(*t*-Bu) gave no reaction (Table 1, entries 5 and 6). While the high yield of the direct arylation suggests

Table 1: Coupling reaction of aryl halides with benzene. Reactions were carried out with 4 mL of benzene and 0.4 mL of DMF.



entry	catalyst	cat. (mol %)	KO(*t*-Bu) (equiv)	X	R[a]	time (h)	yield (%)
1	2	2	30	I	H	10	94
2	2	2	30	I	*p*-OMe	20	77
3	2	2	30	I	*p*-NO_2	20	<1
4	CuBr	2	30	I	H	10	5
5	none	0	30	I	H	10	0
6	none	0	3	I	H	10	0
7	2	2	0	I	H	10	0
8	2	0.5	3	I	*p*-OMe	40	70
9	2	0.5	3	I	H	40	85
10	2	0.5	3	I	*p*-CH_3	40	52
11	2	0.3	3	I	*o*-OMe	40	53
12	2	0.3	3	I	H	40	36
13	2	0.3	3	I	*p*-CH_3	40	25
14	2	0.3	3	I	*p*-OH	40	0
15	2	0.3	3	Br	*m*-Cl	40	4
16	2	0.3	3	Br	*m*-CH_3	40	8
17	2	0.2	3	I	*p*-OMe	40	33
18	2	0.2	3	I	H[b]	40	43

[a]Functional group on the aryl halide. [b]Reaction of naphthalene (2 g) with iodobenzene and 0.4 mL DMF.

that the product cannot be exclusively obtained from homocoupling of iodobenzene, we performed additional experiments to demonstrate a heterocoupling pathway. The coupling of benzene with *p*-iodoanisole at 2 mol % loading of catalyst **2** was evaluated (Table 1, entry 2). We were pleased to find that the reaction yielded 4-methoxybiphenyl according to GC–MS analysis, and the isolated yield after flash column chromatography was 77%. Encouraged by these findings, we attempted the reaction with lower catalyst loadings and 3 equivalents KO(*t*-Bu). The reaction of iodobenzene with benzene with catalyst loading of 0.5 mol % gave biphenyl in isolated yield of 85% (Table 1, entry 9). The reaction of *p*-iodoanisole with benzene using 0.2 or 0.3 mol % of catalyst **2** gave 4-methoxybiphenyl in isolated yields of 33% and 53%, respectively, which indicate a TON ≈190 (Table 1, entries 11 and 17). The reaction of *p*-iodotoluene and benzene (Table 1, entries 10 and 13) with 3 equivalents KO(*t*-Bu) gave 4-methylbiphenyl in yields of 25% and 52% using 0.3 and 0.5 mol % of catalyst **2**, respectively (TON ≈170 for the latter). The reactions of *p*-iodophenol (Table 1, entry 14) or *p*-nitroiodobenzene (Table 1, entry 3) with benzene were very sluggish with only trace quantities (<1% yield) of products. The coupling of *m*-bromotoluene and *m*-bromochlorobenzene with benzene proceeded more slowly (Table 1, entries 15 and 16). The yields of 3-methylbiphenyl and 3-chlorobiphenyl at catalyst loading of 0.3 mol % and 3 equivalents KO(*t*-Bu) were 8% and 4%, respectively. In all of the reactions, we note that metallic precipitates did not form, and the solutions did not become dark.

Activation of the sp^2 C–H bonds in naphthalene was possible as well. The reaction of iodobenzene in neat naphthalene at 85 °C using 0.2 mol % catalyst and 3 equivalents KO(*t*-Bu) gave a ≈2:1 ratio of 1-phenylnaphthalene and 2-phenylnaphthalene in a total yield of 43% (Table 1, entry 18). The observed substitution ratio is typical of substitutions on naphthalene under kinetic control that tend to favor the alpha C–H bonds due better resonance stabilization effects [53]. Importantly, we note the alpha protons are slightly more acidic than the beta protons [54].

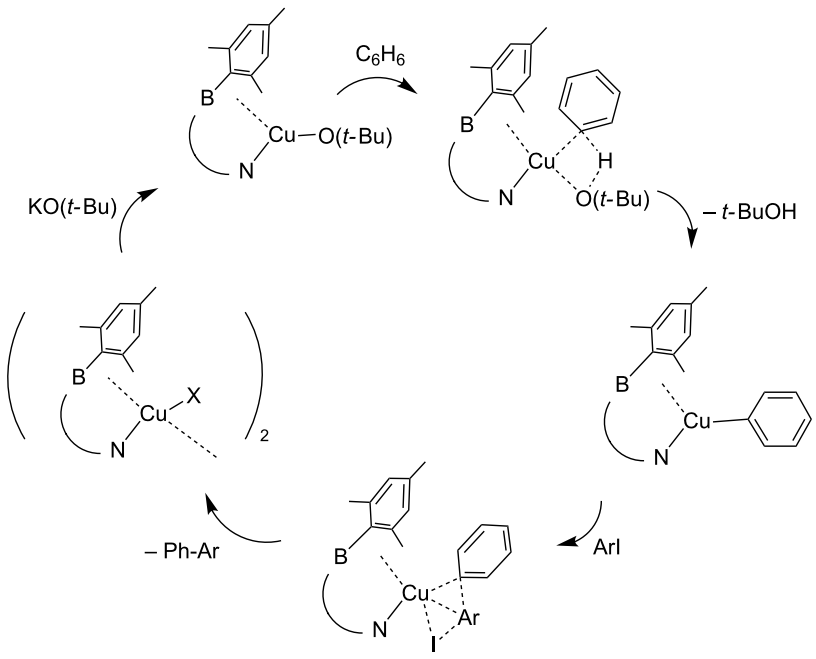
The mechanism of Cu catalyzed coupling reactions and, more specifically, direct arylation have been the subject of intense interest. Mechanistic models appear to diverge along those favoring oxidative addition/reductive elimination via Cu(I)/Cu(III) versus proposals favoring a single electron transfer (SET) pathway [55,56].

In the base-promoted SET mechanism [57], electron donation to ArI leads to a short-lived radical anion $ArI^{\bullet-}$ that decomposes to I^- and $Ar^{\bullet}$. The Ar radical undergoes homolytic aromatic substitution with benzene to form a biaryl radical, and deprotonation gives a biaryl radical anion that transfers one electron to ArI to begin the cycle anew. The mechanism explains the metal-free direct arylation catalysis, but there has been some question about the initiation step. As KO(*t*-Bu) does not have sufficient reducing power to generate $ArI^{\bullet-}$, it has been proposed that initiation could arise from the reaction of ArI and KO(*t*-Bu) to form benzyne or that organic electron donors form in situ with suitable additives under the basic conditions of the reaction [58-60]. For example, observation of faster direct arylation in the presence of DMF led to proposals of deprotonated DMF as one electron donor [61] or forming a dibasic -enediol in situ as an electron donor [62].

While the SET mechanism has drawn much interest, our observation of large rate enhancement upon addition of the preformed catalyst **2** may be better described with a metalation–deprotonation step followed by oxidative addition/reductive elimination (Scheme 2) [63]. Thus, $t\text{-BuO}^-$ substitutes the halogen ligand on **2**, followed by deprotonation–metalation of benzene, followed by oxidative addition of the arylhalide, and finally reductive elimination of the biaryl. The molecule **2** may be uniquely suited for this pathway. The electron-rich Cu(I) in the (L-Z)Cu(OR) intermediate may be well-stabilized by boron as a Z-type ligand, and the mesityl groups surrounding boron may favor the association of arenes for the deprotonation–metalation and the oxidative addition steps. Wang et al. proposed concerted metalation–deprotonation via a sigma bond metathesis involving a cyclic 4-membered transition state, followed by oxidative addition of ArI to Cu(I) [63]. Oxidative addition of arylhalide to Cu(I) produces Cu(III) intermediates, for which there is substantial evidence [64-67]. However, under catalytic conditions, there is no requirement that the copper catalyst pass through an intermediate with a formal oxidation state of +3, which may undoubtedly have a large activation energy. Rather, a concerted pathway through a 4-membered transition state will have less localization of charge. A concerted process for coupling of nucleophiles with arylhalides on copper centers have been proposed by Bacon [68] and were elaborated by Litvak [69] who proposed SET within the 4-membered transition state. It is noteworthy that modern DFT calculations [63] also produce cyclic transition states.

Conclusion

In conclusion, we observe direct arylation reactions (C–X/C–H; X = halogen) catalyzed by a Cu(I) center stabilized by an ambiphilic ligand. The activation of stable sp^2 C–H bonds in benzene and naphthalene occurs as a result of the catalysis. We favor a mechanism involving 4-membered cyclic transition states for metalation–deprotonation followed by concerted oxidative addition/reductive elimination. The scope of reactivity, including functional group tolerance on the reactants, types of C–H bonds that can be activated, selectivity of C–H bond acti-



Scheme 2: Proposed mechanism of direct arylation catalyzed by **2** (X = Cl/I; Ar = aryl).

vation, further optimization studies, and new catalyst design will be topics for further study. The initial results are very encouraging in that an inexpensive copper catalyst at low loading exhibited good activity for the reaction. The observation of high activity using a preformed copper catalyst may assist in the development of new catalysts.

Experimental

General. Compounds **1** and **2** were prepared according to the literature [50]. All organic reagents and solvents were obtained from commercial sources and used without further purification. A GCMS-QP2010SE gas chromatograph–mass spectrometer (Shimadzu Corp., Kyoto, Japan) was used for GC–MS analyses. NMR spectra were recorded on an Avance 400 MHz spectrometer (Bruker, Billerica, MA, USA).

Catalysis experiments. A 50 mL roundbottom flask was charged with 0.5 mmol of aryl halide, benzene (4 mL) and 1.5 mmol of KO(*t*-Bu). The flask was fitted with a reflux condenser left open to air. Then, a solution of catalyst dissolved in 420 μL DMF was added to the reaction. The reaction was then stirred and refluxed for 40 h. The reaction was worked up by extraction with ether and washed with deionized H_2O. The organic phase was collected and dried over anhydrous sodium sulfate. The residue was purified by flash column chromatography. NMR spectra of isolated products matched well with the literature.

Supporting Information

Supporting Information File 1

NMR spectra and GC–MS data of the products.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-272-S1.pdf]

Acknowledgements

This work was made possible through funds from the National Science Foundation grant nos. EPS-0554609 (single crystal X-ray diffractometer and glovebox), CHE-1229035 (400 MHz NMR spectrometer), and DGE-0903685 (graduate student support).

References

1. Diederich, F.; Stang, P. J., Eds. *Metal-catalyzed cross-coupling reactions;* Wiley VCH: Weinheim, 1998.
2. Negishi, E. *Angew. Chem., Int. Ed.* **2011,** *50,* 6738–6764. doi:10.1002/anie.201101380
3. Suzuki, A. *Angew. Chem., Int. Ed.* **2011,** *50,* 6722–6737. doi:10.1002/anie.201101379
4. Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002,** *102,* 1359–1470. doi:10.1021/cr000664r
5. Zhao, D.; You, J.; Hu, C. *Chem. – Eur. J.* **2011,** *17,* 5466–5492. doi:10.1002/chem.201003039

6. Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012,** *51,* 10236–10254. doi:10.1002/anie.201203269
7. Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011,** *40,* 5068–5083. doi:10.1039/c1cs15082k
8. Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007,** *107,* 174–238. doi:10.1021/cr0509760
9. McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009,** *38,* 2447–2464. doi:10.1039/b805701j
10. Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009,** *48,* 9792–9826. doi:10.1002/anie.200902996
11. Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009,** *42,* 1074–1086. doi:10.1021/ar9000058
12. Mousseau, J. J.; Charette, A. B. *Acc. Chem. Res.* **2013,** *46,* 412–424. doi:10.1021/ar300185z
13. Rossi, R.; Bellina, F.; Lessi, M.; Manzini, C. *Adv. Synth. Catal.* **2014,** *356,* 17–117. doi:10.1002/adsc.201300922
14. Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006,** *45,* 2619–2622. doi:10.1002/anie.200504450
15. Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008,** *47,* 1473–1476. doi:10.1002/anie.200704619
16. Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010,** *132,* 13194–13196. doi:10.1021/ja1066459
17. Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010,** *132,* 4978–4979. doi:10.1021/ja910973a
18. Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008,** *10,* 3607–3609. doi:10.1021/ol8013717
19. Vogler, T.; Studer, A. *Org. Lett.* **2008,** *10,* 129–131. doi:10.1021/ol702659a
20. Wen, J.; Zhang, J.; Chen, S.-Y.; Li, J.; Yu, X.-Q. *Angew. Chem., Int. Ed.* **2008,** *47,* 8897–8900. doi:10.1002/anie.200802526
21. Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998,** 2439–2440. doi:10.1039/a806790b
22. Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2010,** *49,* 2202–2205. doi:10.1002/anie.200906996
23. Phipps, R. J.; Gaunt, M. J. *Science* **2009,** *323,* 1593–1597. doi:10.1126/science.1169975
24. Vallée, F.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2010,** *132,* 1514–1516. doi:10.1021/ja910687u
25. Liu, W.; Cao, H.; Lei, A. *Angew. Chem., Int. Ed.* **2010,** *49,* 2004–2008. doi:10.1002/anie.200906870
26. Liu, W.; Cao, H.; Xin, J.; Jin, L.; Lei, A. *Chem. – Eur. J.* **2011,** *17,* 3588–3592. doi:10.1002/chem.201002290
27. Pieber, B.; Cantillo, D.; Kappe, C. O. *Chem. – Eur. J.* **2012,** *18,* 5047–5055. doi:10.1002/chem.201103748
28. Chan, T. L.; To, C. T.; Liao, B.-S.; Liu, S.-T.; Chan, K. S. *Eur. J. Inorg. Chem.* **2012,** 485–489. doi:10.1002/ejic.201100780
29. Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009,** *11,* 1733–1736. doi:10.1021/ol9001587
30. Kobayashi, O.; Uraguchi, D.; Yamakawa, T. *Org. Lett.* **2009,** *11,* 2679–2682. doi:10.1021/ol900778m
31. Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013,** 19–30. doi:10.1002/ejoc.201200914
32. Yamamoto, T.; Muto, K.; Komiyama, M.; Canivet, J.; Yamaguchi, J.; Itami, K. *Chem. – Eur. J.* **2011,** *17,* 10113–10122. doi:10.1002/chem.201101091
33. Yokota, A.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014,** *79,* 11922–11932. doi:10.1021/jo501697n
34. Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007,** *129,* 12404–12405. doi:10.1021/ja075802+
35. Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008,** *130,* 1128–1129. doi:10.1021/ja077862l
36. Yoshizumi, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2008,** *49,* 1598–1600. doi:10.1016/j.tetlet.2008.01.042
37. Liu, W.; Hou, F. *Appl. Organomet. Chem.* **2015,** *29,* 368–371. doi:10.1002/aoc.3300
38. Liu, H.; Yin, B.; Gao, Z.; Li, Y.; Jiang, H. *Chem. Commun.* **2012,** *48,* 2033–2035. doi:10.1039/c2cc16790e
39. Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008,** *10,* 4673–4676. doi:10.1021/ol8019764
40. Shirakawa, E.; Itoh, K.-i.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010,** *132,* 15537–15539. doi:10.1021/ja1080822
41. Liu, W.; Tian, F.; Wang, X.; Yu, H.; Bi, Y. *Chem. Commun.* **2013,** *49,* 2983–2985. doi:10.1039/c3cc40695d
42. Liu, W.; Xu, L.; Bi, Y. *RSC Adv.* **2014,** *4,* 44943–44947. doi:10.1039/C4RA07688E
43. Liu, W.; Xu, L. *Tetrahedron* **2015,** *71,* 4974–4981. doi:10.1016/j.tet.2015.05.082
44. Wu, Y.; Choy, P. Y.; Kwong, F. Y. *Asian J. Org. Chem.* **2014,** *3,* 1262–1265. doi:10.1002/ajoc.201402181
45. Wu, Y.; Choy, P. Y.; Kwong, F. Y. *Org. Biomol. Chem.* **2014,** *12,* 6820–6823. doi:10.1039/C4OB01211A
46. Dewanji, A.; Murarka, S.; Curran, D. P.; Studer, A. *Org. Lett.* **2013,** *15,* 6102–6105. doi:10.1021/ol402995e
47. Ng, Y. S.; Chan, C. S.; Chan, K. S. *Tetrahedron Lett.* **2012,** *53,* 3911–3914. doi:10.1016/j.tetlet.2012.05.073
48. Gai, L.; To, C. T.; Chan, K. S. *Tetrahedron Lett.* **2014,** *55,* 6373–6376. doi:10.1016/j.tetlet.2014.09.131
49. Bouhadir, G.; Bourissou, D. *Chem. Soc. Rev.* **2016,** *45,* 1065–1079. doi:10.1039/C5CS00697J
50. Son, J.-H.; Pudenz, M. A.; Hoefelmeyer, J. D. *Dalton Trans.* **2010,** *39,* 11081–11090. doi:10.1039/c0dt00798f
51. Tamang, S. R.; Hoefelmeyer, J. D. *Molecules* **2015,** *20,* 12979–12991. doi:10.3390/molecules200712979
52. Emslie, D. J. H.; Cowie, B. E.; Kolpin, K. B. *Dalton Trans.* **2012,** *41,* 1101–1117. doi:10.1039/C1DT11271F
53. Field, L. D.; Sternhell, S.; Wilton, H. V. *J. Chem. Educ.* **1999,** *76,* 1246–1247. doi:10.1021/ed076p1246
54. Streitwieser, A., Jr.; Lawler, R. G.; Perrin, C. *J. Am. Chem. Soc.* **1965,** *87,* 5383–5388. doi:10.1021/ja00951a023
55. Sperotto, E.; van Klink, G. P. M.; van Koten, G.; de Vries, J. G. *Dalton Trans.* **2010,** *39,* 10338–10351. doi:10.1039/c0dt00674b
56. Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. *Chem. Soc. Rev.* **2014,** *43,* 3525–3550. doi:10.1039/c3cs60289c
57. Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011,** *50,* 5018–5022. doi:10.1002/anie.201101597
58. Zhou, S.; Anderson, G. M.; Mondal, B.; Doni, E.; Ironmonger, V.; Kranz, M.; Tuttle, T.; Murphy, J. A. *Chem. Sci.* **2014,** *5,* 476–482. doi:10.1039/C3SC52315B
59. Patil, M. *J. Org. Chem.* **2016,** *81,* 632–639. doi:10.1021/acs.joc.5b02438
60. Zhang, L.; Yang, H.; Jiao, L. *J. Am. Chem. Soc.* **2016,** *138,* 7151–7160. doi:10.1021/jacs.6b03442
61. Drapeau, M. P.; Fabre, I.; Grimaud, L.; Ciofini, I.; Ollevier, T.; Taillefer, M. *Angew. Chem., Int. Ed.* **2015,** *54,* 10587–10591. doi:10.1002/anie.201502332

62. Barham, J. P.; Coulthard, G.; Emery, K. J.; Doni, E.; Cumine, F.; Nocera, G.; John, M. P.; Berlouis, L. E. A.; McGuire, T.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2016,** *138,* 7402–7410. doi:10.1021/jacs.6b03282
63. Wang, M.; Fan, T.; Lin, Z. *Organometallics* **2012,** *31,* 560–569. doi:10.1021/om2007612
64. Casitas, A.; Ribas, X. *Chem. Sci.* **2013,** *4,* 2301–2318. doi:10.1039/c3sc21818j
65. Ichiishi, N.; Canty, A. J.; Yates, B. F.; Sanford, M. S. *Organometallics* **2014,** *33,* 5525–5534. doi:10.1021/om5007903
66. Casitas, A.; Canta, M.; Solà, M.; Costas, M.; Ribas, X. *J. Am. Chem. Soc.* **2011,** *133,* 19386–19392. doi:10.1021/ja2058567
67. Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. *Chem. Sci.* **2010,** *1,* 326–330. doi:10.1039/c0sc00245c
68. Bacon, R. G. R.; Hill, H. A. O. *J. Chem. Soc.* **1964,** 1097–1107. doi:10.1039/jr9640001097
69. Litvak, V. V.; Shein, S. M. *Zh. Org. Khim.* **1974,** *10,* 2360–2366.

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (http://www.beilstein-journals.org/bjoc)

The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.12.272