BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

Creating complexity

Edited by Donald Craig

Generated on 06 November 2026, 18:22

Imprint

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

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

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

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Beilstein Journal of Organic Chemistry

Creating Complexity

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Editorial

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Beilstein J. Org. Chem. **2013,** *9,* 1881–1882.
doi:10.3762/bjoc.9.220

Received: 31 July 2013
Accepted: 01 August 2013
Published: 16 September 2013

This article is part of the Thematic Series "Creating complexity".

Guest Editor: D. Craig

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The word synthesis is derived from the ancient Greek word, σύνθεσις, or 'placing with', and means literally the combination of two or more entities that together form something new [1]. Therefore, in the realm of chemistry, by definition synthesis entails combining reactants to make a product, and this almost invariably creates complexity.

Organic synthesis is widely regarded as having begun nearly two centuries ago, with Friedrich Wöhler's 1828 discovery that ammonium cyanate could be converted into urea [2]. Since that seminal finding, chemical synthesis has advanced to extents which must have been unimaginable to its early practitioners. The numerous paradigm-shifts which have taken place throughout the history of synthesis have been driven largely by a single impulse: the fascination of building sophistication from simplicity – in other words, creating complexity.

Chemical synthesis inspires chemists from many different backgrounds, and these scientists are unified in their desire to create and develop methods which enable the creation of complex target molecules from readily available starting materials. In many cases the targeted structure is a naturally occurring, biologically active entity, and over decades of research endeavour, natural products have consistently provided a rich source of inspiration. Away from the natural products arena, organic synthesis chemists are engaged in the creation of novel polymeric materials with a wide range of applications, the conception and fabrication of new supramolecular architectures, and in the exploration of new regions of chemical space in the contexts of drug discovery and development.

As synthesis nears its 200th birthday, and synthesis scientists hone the skill-sets needed to assemble structures of ever-increasing complexity, the definition of complexity is evolving. Traditionally, a complex structure was assembled one step at a time, but as synthesis matures as a discipline, synthesis chemists are searching for quicker, more efficient, more selective, less energy-intensive and more sustainable ways of creating complexity. The search for such improved methods creates additional complexity, whether they involve innovative catalyst design and synthesis, the streamlining of synthesis routes through the omission of protecting groups or the harnessing of intrinsic reactivity, or the shortening of synthesis sequences by carrying out cascade and multicomponent reactions and chemistry in flow.

This Thematic Series brings together a select group of contributors, recognised for their contributions in the areas of catalysis,

radical chemistry, stereoselective synthesis and molecular diversity. I thank them warmly for their high-quality contributions, which demonstrate the central role of organic synthesis in all its guises, in the creation of complexity.

Donald Craig

London, July 2013

References

1. http://en.wikipedia.org/wiki/Synthesis (accessed July 31, 2013).
2. Wöhler, F. *Ann. Phys.* **1828,** *88,* 253–256. doi:10.1002/andp.18280880206

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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.9.220

Beilstein Journal of Organic Chemistry

Alternaric acid: formal synthesis and related studies

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Full Research Paper

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Keywords:
formal synthesis; multicomponent coupling; natural products; silyl glyoxylates

Beilstein J. Org. Chem. **2013,** *9,* 166–172.
doi:10.3762/bjoc.9.19

Received: 24 October 2012
Accepted: 20 December 2012
Published: 24 January 2013

This article is part of the Thematic Series "Creating complexity".

Guest Editor: D. Craig

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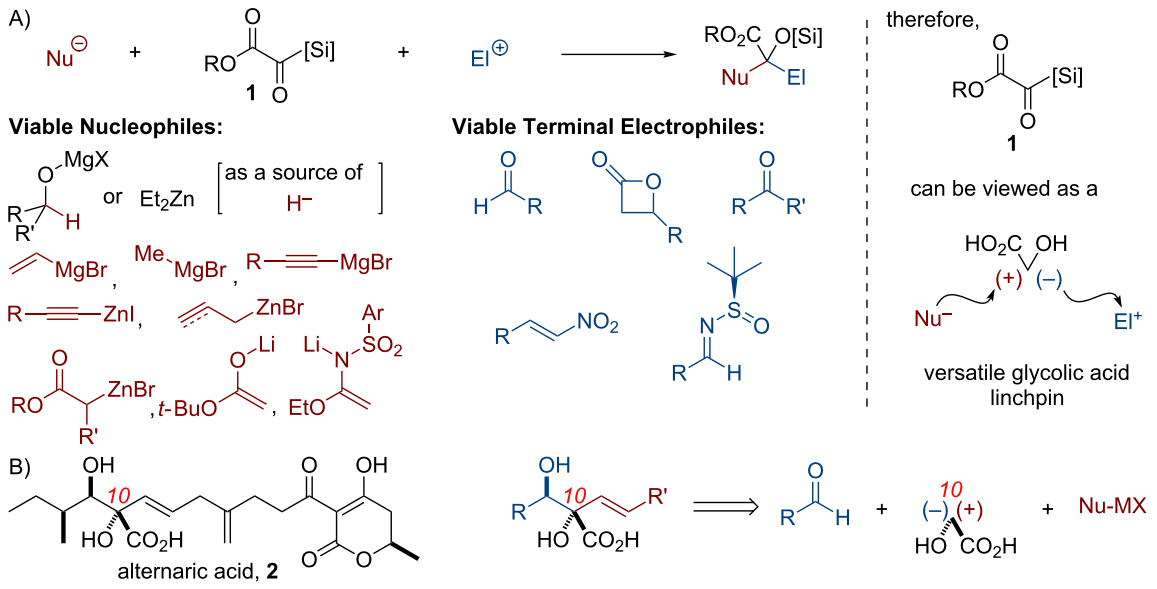
Abstract

A silyl glyoxylate three-component-coupling methodology has been exploited to achieve a formal synthesis, an analogue to an intermediate in a distinct formal synthetic route, and a third (unique) approach to the natural product alternaric acid. Highlighted in this study is the versatility of silyl glyoxylates to engage a variety of nucleophile and electrophile pairs to provide wide latitude in the approach to complex molecule synthesis.

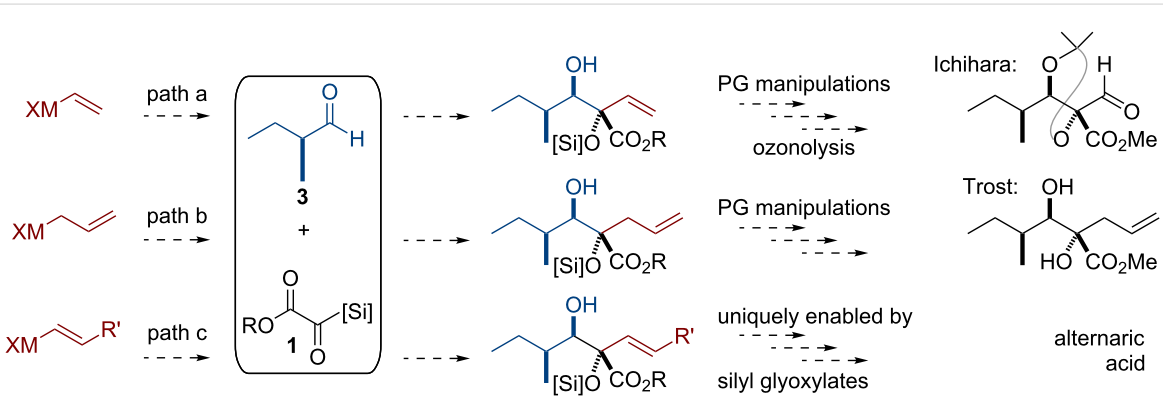
Introduction

The rapid development of molecular complexity from simple starting materials is an important goal in modern synthetic organic chemistry. In this context, streamlined one-pot transformations, cascade reactions, and multicomponent couplings have emerged as enabling tools for the synthesis of complex molecules [1,2]. Our laboratory [3-16] and others have developed [17] and employed [18,19] silyl glyoxylates **1** in a variety of synthetic endeavors, both in natural-product synthesis and synthetic methodologies [20]. Key to their use in a variety of contexts is the ability of silyl glyoxylates to function as linchpin synthons for geminal coupling of nucleophile/electrophile pairs at a glycolic acid subunit (Scheme 1A), which allows the rapid build-up of molecular complexity. Alternaric acid (**2**) [21-23] is an antifungal and phytotoxic natural product, which bears a substituted glycolic acid in the functionally and stereochemically dense core of the molecule; the potential application of silyl glyoxylate technology emerged as an attractive starting point for synthetic planning (Scheme 1B). This paper summarizes our synthetic work in this arena, which culminated in a formal synthesis, an analogue of another formal synthesis, and a unique approach to the target; each of the routes was enabled by distinct coupling partners.

Alternaric acid is a particularly interesting target to demonstrate the utility of silyl glyoxylates, as it has been the subject of one total synthesis [24], one formal synthesis [25], and a potential application of an asymmetric glycolate aldol methodology [26]. These precedents serve as fruitful comparison points for application of a silyl glyoxylate three-component coupling methodology. Scheme 2 highlights three potential avenues



Scheme 1: (A) Silyl glyoxylates as versatile reagents for three-component coupling reactions: representative nucleophiles and electrophiles. (B) Alternaric acid as a potential application of a silyl glyoxylate-enabled three-component coupling reaction.



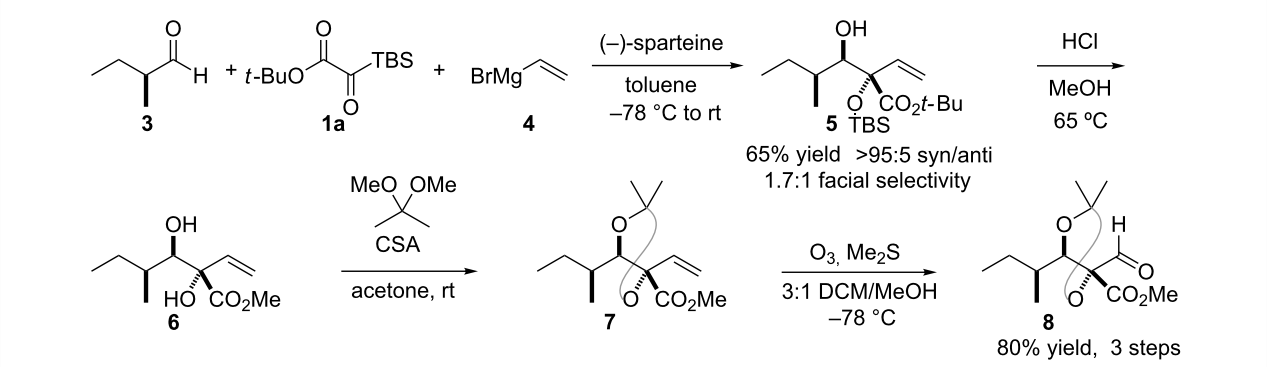
Scheme 2: Potential applications of silyl glyoxylate couplings and precedent synthetic intermediates toward the synthesis of alternaric acid.

toward the natural product and their precedents, by using the readily available (*S*)-2-methylbutanal (**3**) [27] and silyl glyoxylates **1** as two of the three key components for a coupling reaction.

Results and Discussion

Synthetic studies were initiated to explore paths a and b in Scheme 2, given the perceived rapidity with which the known intermediates could be intercepted after the proposed three-component coupling reactions. These initial studies revealed a limitation to this approach, inherent in the use of aldehyde **3** as a coupling partner: inherently poor Felkin–Anh facial selectivity with respect to the aldehyde electrophile due to minor differentiation between the Et/Me groups [28-30]. In all cases, the facial selectivity was rather poor, i.e., approximately 1.7:1, regardless of nucleophile, counterion, solvent, and temperature. Brief optimization efforts for each nucleophile thus focused on maximizing the coupling efficiency and *syn*-/*anti*-aldol selectivity (see Supporting Information File 1).

The optimal conditions for use of a vinyl nucleophile involved addition of a solution of vinylmagnesium bromide (**4**) and (−)-sparteine [31] in toluene to a solution of the *tert*-butyl silyl glyoxylate **1a** and (*S*)-2-methylbutanal (**3**) in toluene at −78 °C followed by warming to room temperature, which provided the three-component-coupling product **5** with excellent (>20:1) *syn*-/*anti*-aldol selectivity in 65% yield (Scheme 3). Ichihara's aldehyde intermediate could be intercepted in three additional



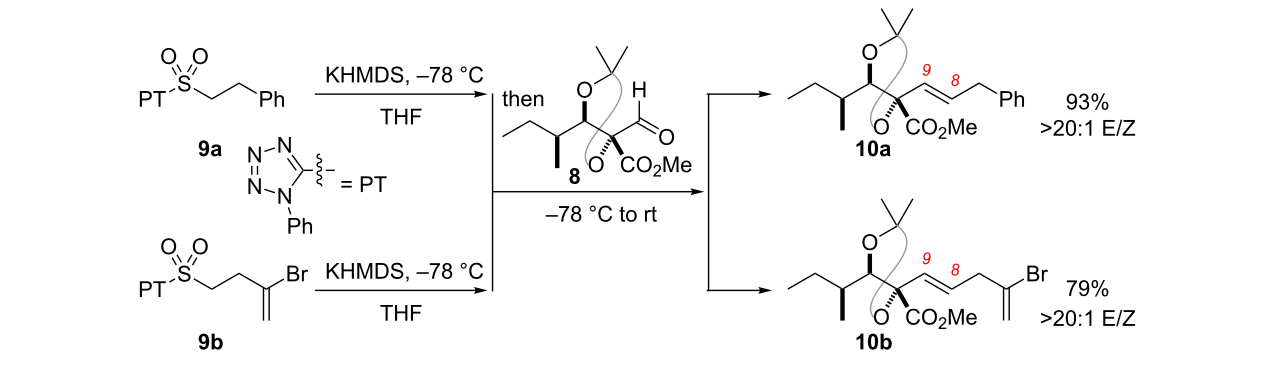
Scheme 3: Three-component coupling with a vinyl nucleophile and elaboration to Ichihara's aldehyde.

steps, in high overall yield. Simultaneous cleavage of the silyl ether and transesterification from the *tert*-butyl to the methyl ester in **6** was effected by warming in acidic methanol. Subsequent acetonide formation provided **7**, and ozonolysis afforded Ichihara's aldehyde **8** (Scheme 3).

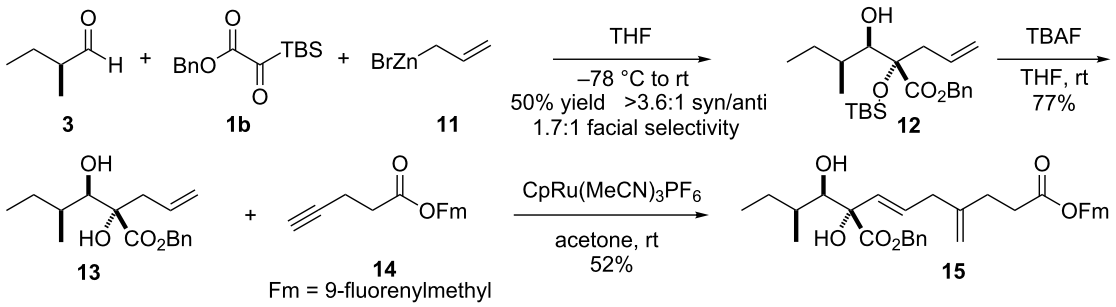
Interception of this intermediate thus constituted a formal synthesis; the precedent for the C8–C9 olefination involved a classical, three-step Julia olefination sequence [24]. To demonstrate proof-of-concept for a more step-efficient endgame, test substrates were prepared for exploration of a modified Julia olefination [32]. As shown in Scheme 4, the phenyltetrazole heteroaromatic core in sulfones **9a** and **9b** provided excellent *E*-/*Z*- selectivity for formation of the C8–C9 olefin under typical modified Julia conditions with no optimization necessary. In particular, the vinyl bromide functional handle in **10b** provides a potential avenue for elaboration to the natural product.

With the promise of the approach thus demonstrated involving the use of the vinyl nucleophile, attention shifted toward exploration of the allyl nucleophile. The best conditions for the use of an allyl nucleophile involved the addition of allylzinc bromide (**11**) in THF to a THF solution of benzyl silyl glyoxylate **1b** and (*S*)-2-methylbutanal (**3**) at 0 °C followed by warming to room temperature (Scheme 5). In the event, the three-component coupling product **12** was in 50% combined yield of all four possible diastereomers: 3.6:1 *syn*-/*anti*-selectivity and ~1.7:1 facial selectivity were observed. Thus, under these conditions both the control of enolate geometry as well as facial selectivity with respect to the aldehyde were incomplete. The four diastereomers could only be separated into *syn*/*anti* sets; within each set, the Felkin/anti-Felkin diastereomers could not be separated.

As with three-component coupling product **5**, advancement of intermediate **12** proved straightforward (Scheme 5). Deprotection of the silyl ether with TBAF afforded diol **13**, which is a benzyl ester analogue of one of Trost's substrates employed in the ruthenium-catalyzed Alder–ene reaction [25]. It too proved to be a successful substrate for the reaction with alkyne **14**, affording the 1,4-diene product **15** in 52% yield. This sequence thus demonstrated a second avenue for successful exploitation of a silyl glyoxylate coupling methodology to achieve a step-efficient approach toward the assembly of the carbon skeleton of alternaric acid.



Scheme 4: Modified Julia olefination as a step-efficient alternative endgame strategy.

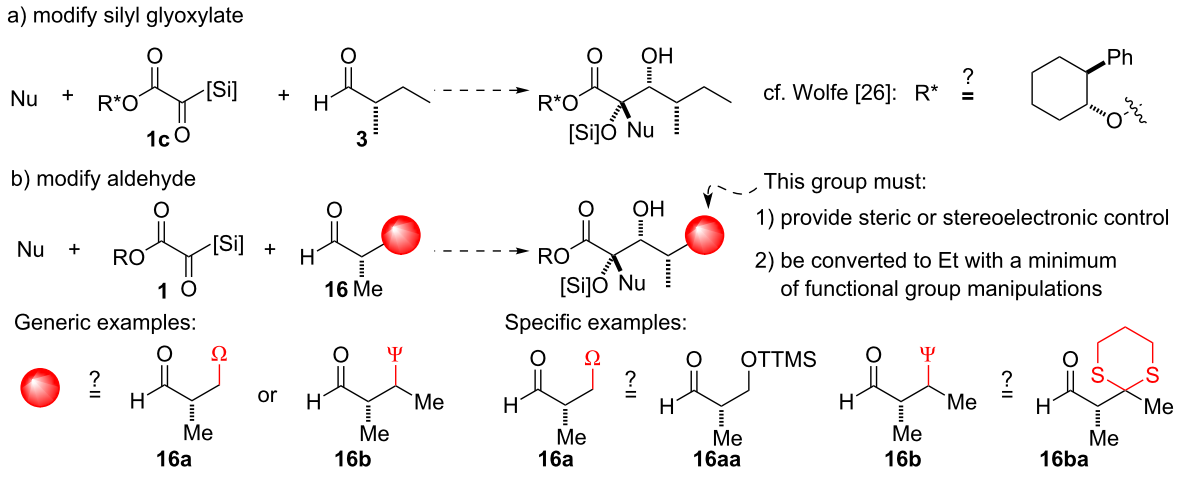


Scheme 5: Three-component coupling with an allyl nucleophile and demonstration of successful ruthenium-catalyzed Alder–ene approach.

The two approaches described above both highlighted an important limitation to the use of (*S*)-2-methylbutanal (**3**) as the third component in the silyl glyoxylate-based three-component coupling reaction: while this aldehyde directly affords the substructure of the natural product target, it is unable to adequately control the facial selectivity of the approach of the glycolate enolate revealed after nucleophile addition/[1,2]-Brook [33] rearrangement. Moreover, attempts to achieve separation of the resultant diastereomers at all synthetic intermediates in these two routes were unsuccessful. Thus, attention shifted to address the stereochemical issue.

Various approaches were considered to achieve a higher level of stereoselection in the three-component coupling reaction, which are summarized in Scheme 6 [34]. In light of the elegant precedent for overriding the moderate substrate bias from (*S*)-2-methylbutanal (**3**) [26], auxiliary modification of the silyl glyoxylate structure to generalized type **1c** could be envisioned. As hydrolysis of an ester would be required as a late-stage deprotection in any silyl glyoxylate-based approach, this modification would represent a relatively minor departure from ideality in the form of additional concession steps [35]. Alternatively, modification of the aldehyde partner, as in generalized type **16**, was also considered. For this purpose, any stereocontrolling element (Ω or Ψ in aldehyde types **16a** and **16b**, respectively) employed should meet the additional requirement that it be easily converted to a simple ethyl group to minimize the number of concession steps.

The auxiliary approach using silyl glyoxylates **1c** ([Si] = TES or TBS, Scheme 6) proved to be suboptimal: despite the successful formation of the desired three-component coupling product, yields were low and poor stereochemical control was observed. Likewise, even the extreme steric demand of the tris(trimethylsilyl) group in aldehyde **16aa** was insufficient for adequate stereocontrol in the three-component coupling reaction [34]. An additional branch point in the carbon backbone, such as in **16b**, was deemed necessary. The 1,3-dithiane group in aldehyde **16ba** was conceived as a promising candidate for a



Scheme 6: Approaches considered to address the stereochemical issue.

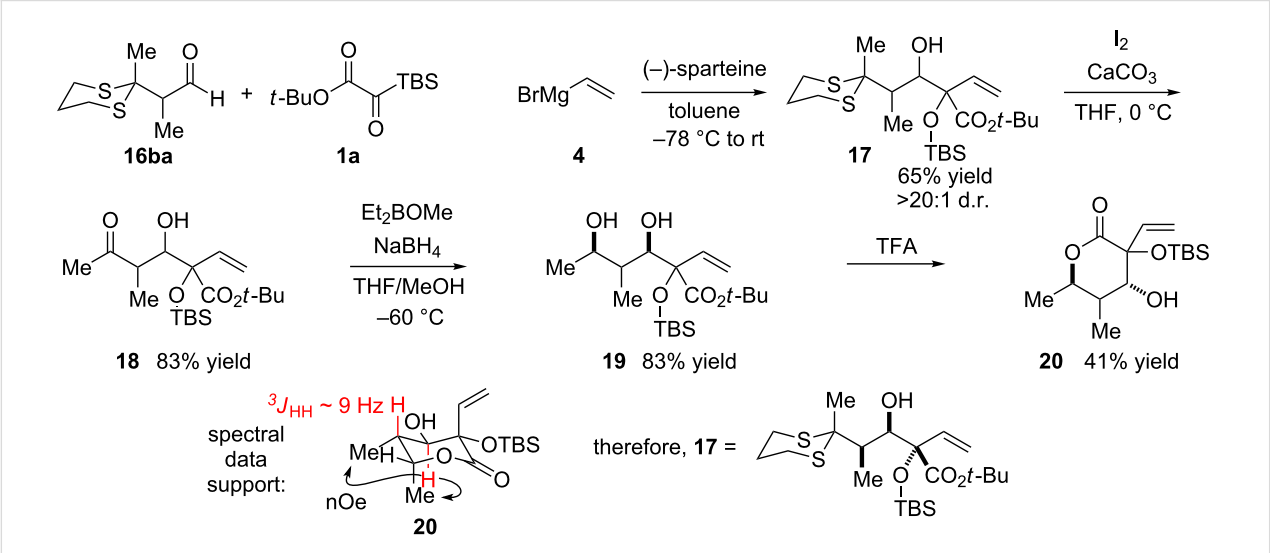
stereocontrolling element due to its large size and the wealth of precedents for single-step desulfurization to alkanes [36-40]. The racemic synthesis of the requisite aldehyde proved straightforward (see Supporting Information File 1). Most importantly, in initial three-component coupling reactions with vinyl nucleophile **4** and silyl glyoxylate **1a** under previously optimized conditions, high efficiency was achieved along with excellent (>20:1) stereochemical control for the formation of three-component-coupling product **17** (Scheme 7) [41-44]. To verify that the dithiane was acting in the desired fashion, and to rule out chelation from one of the Lewis basic sulfur atoms, derivatization to a lactone was carried out. The dithiane was cleaved to the ketone **18**, which underwent a 1,3-*syn*-selective reduction [45]. The resultant diol **19** was subjected to acidic conditions to effect cleavage of the *tert*-butyl ester and lactonization to afford **20**. The NOESY and coupling-constant data of **20** was consistent with the role of the dithiane in **16ba** as a nonchelating R_L group that led to Felkin selectivity in the three-component coupling reaction.

The complete diastereochemical control exerted by the dithiane moiety of the aldehyde **16ba** provided the impetus for exploring the use of a functionalized vinyl nucleophile in the three-component coupling reaction. Use of a more complex nucleophile would maintain the convergence of the overall synthesis, which was deemed important because (1) the route to the aldehyde component was becoming more involved; and (2) one or more additional steps for the removal of the directing group would be required. Thus, we developed a synthesis of a nucleophile that would allow the vast majority of the alternaric acid carbon skeleton to be installed through the three-component coupling reaction (Scheme 8). It began from the known allylic alcohol **21** [46], which was acetylated to afford ester **22** as prelude for reaction as a π-allyl electrophile with the Reformatsky reagent **23** derived from *tert*-butyl bromoacetate. The TMS-alkyne in **24** was deprotected with buffered TBAF to afford free alkyne **25**, and the vinyl iodide **26** was generated by hydrozirconation/iodination of the free alkyne with Schwartz's reagent [47]. The vinyl nucleophile **27** could be generated by Knochel's Mg/I exchange [48] and employed successfully in the three-component-coupling reaction with silyl glyoxylate **1a** and aldehyde **16ba** to assemble **28**, which contains the bulk of the carbon skeleton of alternaric acid. Remarkably, this highly convergent coupling allows the majority of the carbon backbone of the natural product to be assembled in a single complexity-building step.

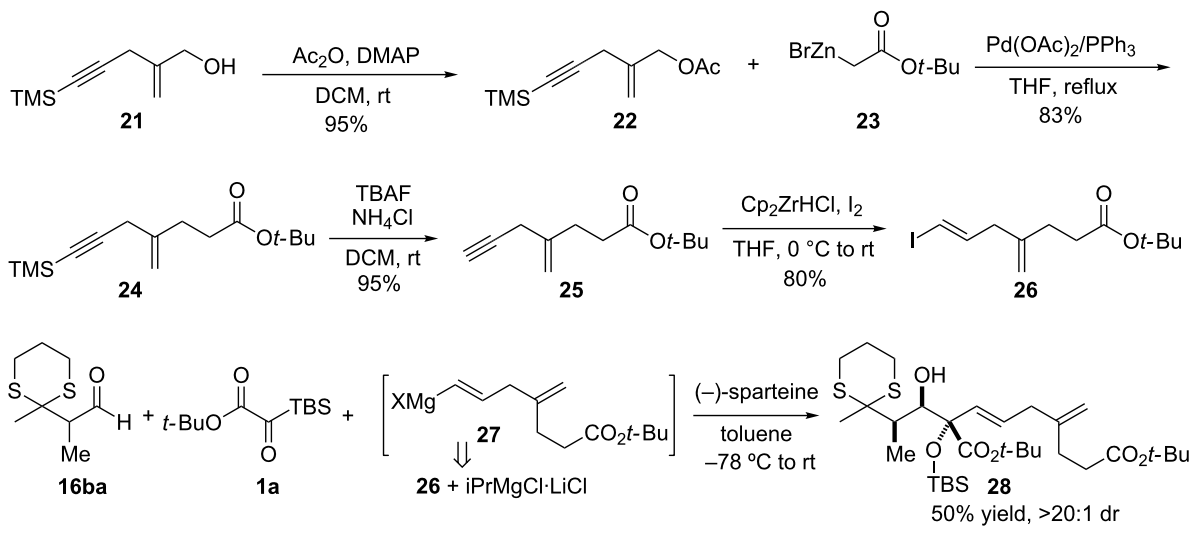
With this gratifying result, a third distinct route to alternaric acid was enabled. Most importantly, this provides the first example of such a highly functionalized nucleophile being used in a silyl glyoxylate based three-component coupling reaction. Remaining tasks for the complete formation of the natural product include desulfurization [49], deprotection [50], and appendage of the pyrone moiety [24].

Conclusion

In conclusion, we have described the application of silyl glyoxylate three-component-coupling reactions as the central feature of three distinct approaches to the total synthesis of alternaric acid. By judicious choice of coupling partner and reaction conditions, it has been possible to achieve a formal synthesis, an analogous formal synthesis via an alternative



Scheme 7: Use of a dithiane moiety to excert stereochemical control in the three-component coupling reaction and supporting evidence for its nature as a nonchelating R_L.



Scheme 8: Synthesis of a vinyl iodide for nucleophile generation and its use in a three-component coupling reaction.

route, and significant progress toward a third distinct route reliant on a highly functionalized nucleophile/electrophile combination for the construction of the majority of the natural product in a single step. In particular, this underscores the unique utility of silyl glyoxylates to serve as crucial linchpins for the coupling of a variety of nucleophile/electrophile pairs at a glycolic acid junction for the rapid development of molecular complexity.

Supporting Information

Contains additional tables and schemes for the three-component coupling reactions and approaches to address the stereochemical problem. Also contains experimental procedures, characterization, and spectral data.

Supporting Information File 1

Additional data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-19-S1.pdf]

Acknowledgements

The project described was supported by Award R01 GM084927 from the National Institute of General Medical Sciences. We thank Rebecca Cuellar for early exploratory studies and Justin Malinowski and Michael Corbett (UNC) for acquiring mass-spectral data.

References

1. Nicolaou, K. C.; Hale, C. R. H.; Nilewski, C.; Ioannidou, H. A. *Chem. Soc. Rev.* **2012,** *41,* 5185–5238. doi:10.1039/c2cs35116a
2. Rapid complexity generation in natural product total synthesis. *Chem. Soc. Rev.* **2009,** *38,* 2969–3276. doi:10.1039/b920767h
See the thematic issue for a recent compilation of reviews on this topic in the context of natural-products synthesis.
3. Nicewicz, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **2005,** *127,* 6170–6171. doi:10.1021/ja043884l
4. Linghu, X.; Satterfield, A. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2006,** *128,* 9302–9303. doi:10.1021/ja062637+
5. Nicewicz, D. A.; Brétéché, G.; Johnson, J. S.; Bryan, C.; Lautens, M. *Org. Synth.* **2008,** *85,* 278–286.
6. Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2008,** *130,* 17281–17283. doi:10.1021/ja808347q
7. Greszler, S. N.; Johnson, J. S. *Org. Lett.* **2009,** *11,* 827–830. doi:10.1021/ol802828d
8. Greszler, S. N.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2009,** *48,* 3689–3691. doi:10.1002/anie.200900215
9. Schmitt, D. C.; Johnson, J. S. *Org. Lett.* **2010,** *12,* 944–947. doi:10.1021/ol9029353
10. Steward, K. M.; Johnson, J. S. *Org. Lett.* **2010,** *12,* 2864–2867. doi:10.1021/ol100996w
11. Boyce, G. R.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2010,** *49,* 8930–8933. doi:10.1002/anie.201003470
12. Greszler, S. N.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2010,** *132,* 17393–17395. doi:10.1021/ja108848d
13. Greszler, S. N.; Malinowski, J. T.; Johnson, J. S. *Org. Lett.* **2011,** *13,* 3206–3209. doi:10.1021/ol2011192
14. Schmitt, D. C.; Lam, L.; Johnson, J. S. *Org. Lett.* **2011,** *13,* 5136–5139. doi:10.1021/ol202002r
15. Boyce, G. R.; Liu, S.; Johnson, J. S. *Org. Lett.* **2012,** *14,* 652–655. doi:10.1021/ol2033527

16. Schmitt, D. C.; Malow, E. J.; Johnson, J. S. *J. Org. Chem.* **2012,** *77,* 3246–3251. doi:10.1021/jo202679u
17. Bolm, C.; Kasyan, A.; Heider, P.; Saladin, S.; Drauz, K.; Günther, K.; Wagner, C. *Org. Lett.* **2002,** *4,* 2265–2267. doi:10.1021/ol025911n
18. Lettan, R. B.; Galliford, C. V.; Woodward, C. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009,** *131,* 8805–8814. doi:10.1021/ja808811u
19. Yao, M.; Lu, C. D. *Org. Lett.* **2011,** *13,* 2782–2785. doi:10.1021/ol201029b
20. Boyce, G. R.; Greszler, S. N.; Johnson, J. S.; Linghu, X.; Malinowski, J. T.; Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Steward, K. M. *J. Org. Chem.* **2012,** *77,* 4503–4515. doi:10.1021/jo300184h
Perspective article.
21. Brian, P. W.; Curtis, P. J.; Hemming, H. G.; Unwin, C. H.; Wright, J. M. *Nature* **1949,** *164,* 534. doi:10.1038/164534a0
22. Brian, P. W.; Curtis, P. J.; Hemming, H. G.; Jefferys, E. G.; Unwin, C. H.; Wright, J. M. *J. Gen. Microbiol.* **1951,** *5,* 619–632. doi:10.1099/00221287-5-4-619
23. Bartels-Keith, J. R. *J. Chem. Soc.* **1960,** 1662–1665. doi:10.1039/JR9600001662
24. Tabuchi, H.; Hamamoto, T.; Miki, S.; Tejima, T.; Ichihara, A. *J. Org. Chem.* **1994,** *59,* 4749–4759. doi:10.1021/jo00096a016
25. Trost, B. M.; Probst, G. D.; Schoop, A. *J. Am. Chem. Soc.* **1998,** *120,* 9228–9236. doi:10.1021/ja981540n
26. Giampietro, N. C.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2009,** *131,* 12556–12557. doi:10.1021/ja905930s
27. Anelli, P. L.; Montanari, F.; Quici, S.; Nonoshita, K.; Yamamot, H. *Org. Synth.* **1990,** *69,* 212.
28. Our results are consistent with the additions of nucleophiles to **3** (cf. [24-26]). For rare, successful examples of Me/Et differentiation, see [29,30].
29. Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997,** *119,* 7893–7894. doi:10.1021/ja971521y
30. Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001,** *123,* 6496–6502. doi:10.1021/ja0108584
31. The precise role of the (−)-sparteine is uncertain at this time. It is possible that the Lewis basic nitrogens chelate the magnesium, facilitating the reversibility of the aldolization step leading to high *syn*-selectivity. See [20], footnote 42.
32. Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002,** 2563–2585. doi:10.1039/B208078H
33. Brook, A. G. *Acc. Chem. Res.* **1974,** *7,* 77–84. doi:10.1021/ar50075a003
34. The results of efforts with silylglyoxylates **1c**, and other specific examples for the identities of Ω and Ψ, were also pursued. See Supporting Information File 1 for additional details.
35. Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010,** *75,* 4657–4673. doi:10.1021/jo1006812
36. Yang, T.-K.; Lee, D.-S.; Haas, J. Raney Nickel. *e-EROS Encyclopedia of Reagents for Organic Synthesis;* John Wiley & Sons: New York, N. Y., 2006. doi:10.1002/047084289X.rr001.pub2
37. Back, T. G.; Baron, D. L.; Yang, K. *J. Org. Chem.* **1993,** *58,* 2407–2413. doi:10.1021/jo00061a011
38. Chan, M. C.; Cheng, K. M.; Ho, K. M.; Ng, C. T.; Yam, T. M.; Wang, B. S. L.; Luh, T. Y. *J. Org. Chem.* **1988,** *53,* 4466–4471. doi:10.1021/jo00254a009
39. Becker, S.; Fort, Y.; Vanderesse, R.; Caubere, P. *Tetrahedron Lett.* **1988,** *29,* 2963–2966. doi:10.1016/0040-4039(88)85058-5
40. Becker, S.; Fort, Y.; Caubere, P. *J. Org. Chem.* **1990,** *55,* 6194–6198. doi:10.1021/jo00312a029
41. Aldehyde **16ba** has previously been used in aldol reactions; no comment on the diastereoselectivity was made, likely because it was immaterial in those applications (see [42,43]).
42. Kim, H.; Baker, J. B.; Lee, S.-U.; Park, Y.; Bolduc, K. L.; Park, H.-B.; Dickens, M. G.; Lee, D.-S.; Kim, Y.; Kim, S. H.; Hong, J. *J. Am. Chem. Soc.* **2009,** *131,* 3192–3194. doi:10.1021/ja8101192
43. Kim, H.; Baker, J. B.; Park, Y.; Park, H. B.; DeArmond, P. D.; Kim, S. H.; Fitzgerald, M. C.; Lee, D.-S.; Hong, J. *Chem.–Asian J.* **2010,** *5,* 1902–1910. doi:10.1002/asia.201000147
44. Ward, D. E.; Kazemeini, A. *J. Org. Chem.* **2012,** *77,* 10789–10803. doi:10.1021/jo302142v
While this manuscript was in review, a thorough study of the stereochemical outcomes using structurally related aldehydes was reported.
45. Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987,** *16,* 1923–1926. doi:10.1246/cl.1987.1923
46. Renaud, J.-L.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1999,** *40,* 5015–5018. doi:10.1016/S0040-4039(99)00981-8
47. Reichard, H. A.; Rieger, J. C.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2008,** *47,* 7837–7840. doi:10.1002/anie.200803031
48. Ren, H.; Krasovskiy, A.; Knochel, P. *Org. Lett.* **2004,** *6,* 4215–4217. doi:10.1021/ol048363h
49. Initial attempts to effect this transformation in a model system have demonstrated that this may not be as straightforward as anticipated. See Supporting Information File 1 for details.
50. Likewise, this may prove more difficult than anticipated; acid-promoted hydrolysis of the *tert*-butyl esters and silyl ether was planned, due to the success of such a transformation with the simpler substrate **5**, as in Scheme 3. However, substrate **28** tends to decompose when treated under a variety of acidic conditions.

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Beilstein Journal of Organic Chemistry

Some aspects of radical chemistry in the assembly of complex molecular architectures

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Review

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Keywords:
amidyls; iminyls; radical allylation; radical vinylation; xanthate transfer

Beilstein J. Org. Chem. **2013,** *9,* 557–576.
doi:10.3762/bjoc.9.61

Received: 02 January 2013
Accepted: 25 February 2013
Published: 18 March 2013

This article is part of the Thematic Series "Creating complexity" and is dedicated with respect and admiration to Professor K. C. Nicolaou.

Guest Editor: D. Craig

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Abstract

This review article describes briefly some of the radical processes developed in the authors' laboratory as they pertain to the concise assembly of complex molecular scaffolds. The emphasis is placed on the use of nitrogen-centred radicals, on the degenerate addition–transfer of xanthates, especially on its potential for intermolecular carbon–carbon bond formation, and on the generation and capture of radicals through electron transfer processes.

Introduction

Natural products exhibit an astonishing diversity of molecular architectures and structural complexity. This has spurred the development of numerous synthetic strategies for the rapid assembly of intricate carbon frameworks. In this context, reactions allowing the concomitant or sequential formation of multiple new bonds acquire a special importance [1]. Radicals, in particular, have proved to be especially apt for such a task, and numerous cascade or domino sequences have been described over the past three decades [2-5]. Radicals offer many of the properties desired by synthetic organic chemists, as compared to ionic or organometallic reactions: generally mild and neutral experimental conditions; lower sensitivity to steric hindrance; lower susceptibility to the solvent effects; lesser tendency for rearrangements and β-elimination; and a selectivity that is often complementary to that of ionic or organometallic reactions, making some protection steps superfluous. Radicals are ambiphilic species that can react with both electron-poor and electron-rich substrates, but the rates can differ by several orders of magnitude. The result is a broad spectrum of reactivity that is, paradoxically, often accompanied by a remarkable selectivity.

A major part of our research effort is directed towards the design and development of new radical processes. These include methods for the generation and capture of nitrogen-centred radicals, the degenerative transfer of xanthates and

related thiocarbonylthio derivatives, chain processes based on the chemistry of sulfonyl radicals, and electron transfer from metallic nickel to halides and oxime esters. These new reactions can be readily harnessed for the rapid creation of complex molecular structures. The present brief overview aims at giving an idea of the synthetic possibilities.

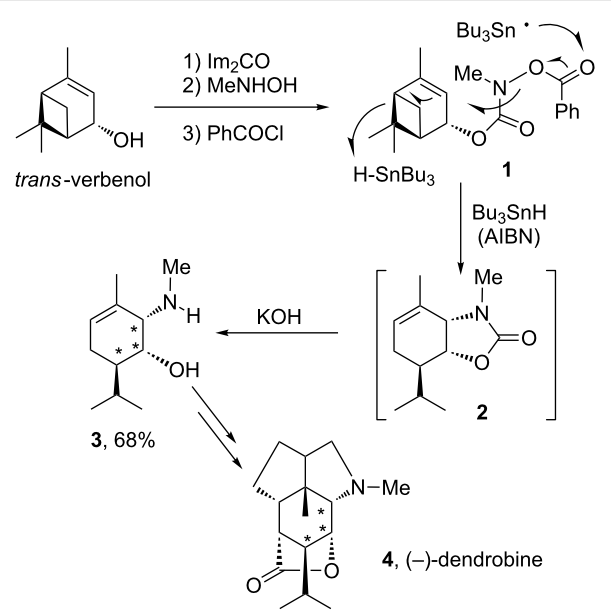
Review

Nitrogen-centred radicals

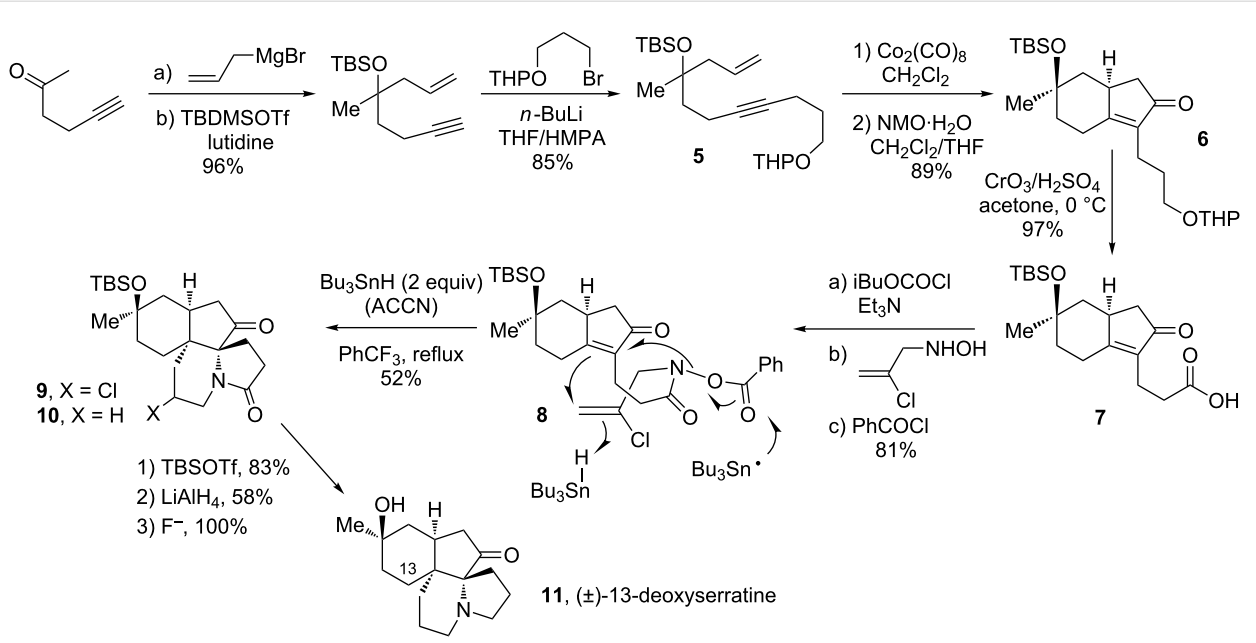
Nitrogen radicals have received little attention from synthetic organic chemists, in contrast to carbon radicals. Yet their potential for the creation of C–N bonds and for the synthesis of alkaloids is enormous [6]. One possible explanation is the lack, hitherto, of mild yet general methods for the generation of the various types of nitrogen radicals: aminyls, aminiums, iminyls, amidyls, carbamyls, ureidyls, etc.

We discovered some years ago that benzoates of hydroxamic acids, oximes and related derivatives reacted nicely with stannyl radicals to furnish the corresponding nitrogen radicals under mild conditions [7]. These could be readily incorporated into various radical sequences leading to complex nitrogen-containing scaffolds. One illustration is provided by the central transformation in the total synthesis of (–)-dendrobine (**4**), where the carbamyl radical cyclisation is followed by rupture of the cyclobutane ring [8,9]. This operation, displayed in Scheme 1, starts with benzoate **1** and results in the formation of the carbon–nitrogen bond with the correct stereochemistry and the introduction of the pendant isopropyl group present in the target. The intermediate cyclic carbamate **2** is not isolated but cleaved into aminoalcohol **3** to simplify purification. The conversion of aminoalcohol **3** into (–)-dendrobine (**4**), hinges on the use of the fabulous Pauson–Khand reaction [10,11] to introduce simultaneously the two adjacent five-membered rings.

Outlined in Scheme 2 is a very short total synthesis of (±)-13-deoxyserratine (**11**) [12,13]. The first two of the four rings in **11**



Scheme 1: Key radical step in the total synthesis of (–)-dendrobine.

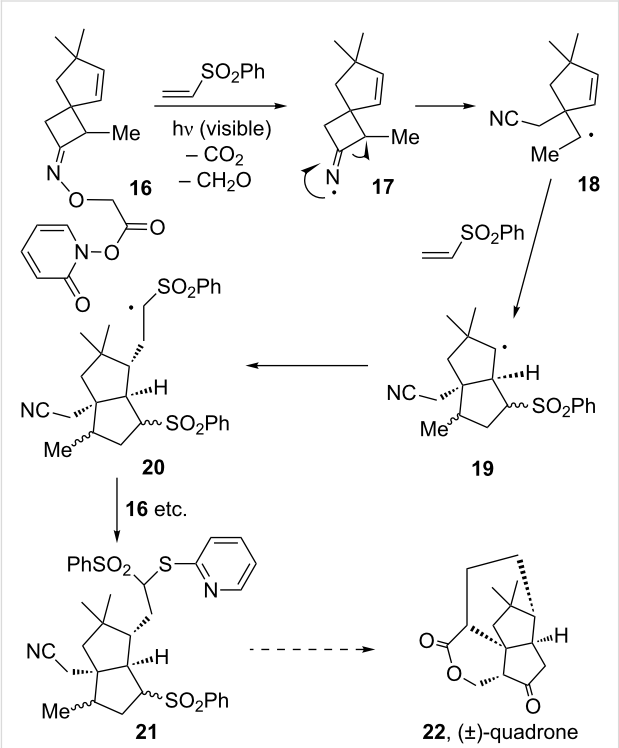


Scheme 2: Radical cascade in the total synthesis of (±)-13-deoxyserratine (ACCN = 1,1'-azobis(cyclohexanecarbonitrile)).

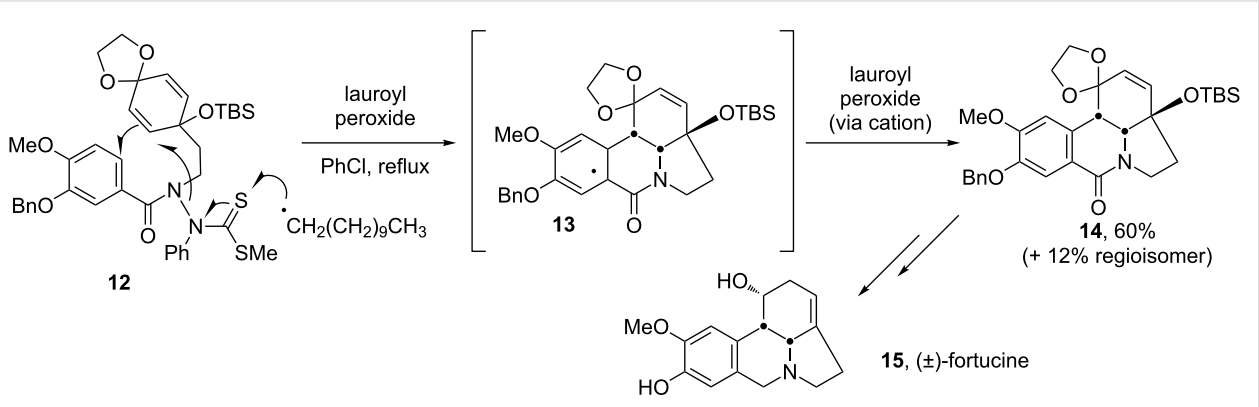
are again created through the powerful Pauson–Khand reaction starting from trivial enyne **5** and oxidation of the protected alcohol in the side-chain of cyclopentenone **6** directly into carboxylic acid **7** by using Jones' reagent. The second key step, namely the conversion of benzoate **8** into tetracycle **10**, involves the concurrent formation of two rings and two adjacent quaternary centres. The chlorine atom in **8** is deliberately introduced in order to direct the second cyclisation towards the 6-*endo* mode. The chloride in intermediate **9** is now aliphatic and not vinylic as in precursor **8**; it is therefore more susceptible to attack by stannyl radicals and the addition of an extra equivalent of tributylstannane ensures its in situ reductive removal. This domino radical cyclisation represents, in fact, a general strategy for the construction of indolizidines and pyrrolizidines, which constitute the core structure of numerous alkaloids. For pyrrolizidines, one needs simply to allow the second cyclisation to proceed in a 5-*exo* fashion by starting with an un-chlorinated substrate.

The total synthesis of fortucine (**15**), also hinges on the sequential fashioning of an indolizidine-type skeleton, with the second cyclisation taking place on an aromatic ring (Scheme 3) [14,15]. The formation of the amidyl radical in this case calls for a different precursor and does not involve a stannane reagent. The sequence is triggered by the attack of undecyl radicals on thiosemicarbazone **12**. Undecyl radicals arise from the thermal homolysis of lauroyl peroxide and decarboxylation. The lauroyl peroxide must be used in stoichiometric amounts, for it is required to oxidise the intermediate cyclohexadienyl radical **13** into its corresponding cation and thence into intermediate **14** by rapid loss of a proton.

A faster access to complexity is obtained when intermolecular steps are also involved. This increases considerably the convergence of the synthetic scheme. One such instance is pictured in Scheme 4, whereby cyclobutyliminyl radical **17**, generated from **16** by a modified Barton decarboxylation [16], undergoes a regioselective scission into secondary radical **18**, followed by an initial intermolecular addition to phenyl vinyl sulfone and closure to form the cyclopentane ring in **19**, and then by a second intermolecular addition to phenyl vinyl sulfone to furnish radical **20,** which finally evolves into the observed product **21** by transfer of the pyridylthiyl group from the starting Barton ester **16**. Even though the yield is still on the order of 40% and needs to be optimised, this sequence introduces all the carbons needed for a projected synthesis of (±)-quadrone (**22**) [17].

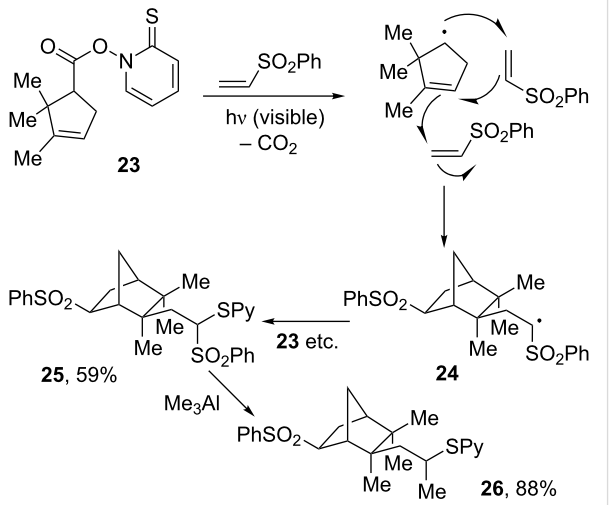


Scheme 4: Model radical sequence for the synthesis of quadrone.



Scheme 3: Formation of the complete skeleton of (±)-fortucine.

This remarkable radical cascade is in fact inspired by an earlier transformation shown in Scheme 5 and starting from simple carboxylic acid derivative **23** [18]. As in the previous sequence, radical **24**, generated following the second addition to the vinyl sulfone, is electrophilic in character and does not add further; it simply propagates the chain by reacting with the starting thiohydroxamate **23**. The complex bicyclic structure **25** is thus made in just one step. In both of these examples, three C–C bonds and one C–S bond are formed one after the other, resulting in a considerable increase in complexity. Interestingly, and not unexpectedly, the two sulfones in structures **21** and **25** have very different reactivities. For instance, exposure of bis-sulfone **25** to trimethylaluminium causes the regioselective replacement of the terminal sulfone with a methyl group to give compound **26** in good yield. The Barton decarboxylation reaction is an exceptionally powerful method that deserves without doubt a much greater attention from synthetic organic chemists.

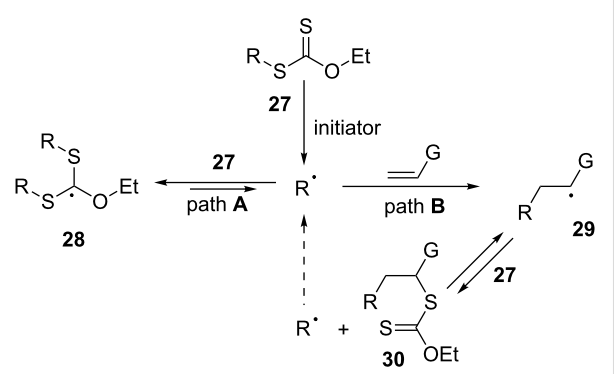


Scheme 5: Radical cascade using the Barton decarboxylation.

The degenerative transfer of xanthates

A longstanding challenge in organic synthesis has been the intermolecular creation of new carbon–carbon bonds starting with simple unactivated alkenes. The cross-metathesis constitutes at the present time one of the better solutions to this problem [19]. Another solution is the tin-free degenerative radical transfer of xanthates and related derivatives we discovered a quarter of a century ago [20]. The simplified mechanism for the addition to an alkene is depicted in Scheme 6.

The many subtle aspects embodied in the mechanism will not be discussed for lack of space, but the interested reader is directed to a recent review for a more complete description [21]. Experimentally, the procedures are simple and safe, and



Scheme 6: Simplified mechanism for the xanthate addition to alkenes.

the reagents are cheap and readily available. In the present context, two properties are especially noteworthy:

(a) The reaction of radical R· with its xanthate precursor **27** to give adduct **28** is fast but degenerate (path **A**). Radical R· is therefore continuously regenerated and acquires an extended effective lifetime. It can thus be readily captured intra- or intermolecularly, even by unactivated olefinic traps, to give finally adduct **30** (path **B**). More generally, relatively slow radical processes (additions, cyclisations, fragmentations, etc.) can be accomplished, without need for high dilution or syringe-pump techniques. This property expands considerably the scope by allowing transformations not feasible with other radical methods. The main limitation is that the initial radical R· has to be more stable than adduct radical **29** in order to bias the equilibrium in favour of product **30** and avoid the formation of oligomers by further additions of radical **29** to the alkene. Radicals R· stabilised by electron-withdrawing groups (nitrile, ketones, esters, pyridines, tetrazoles, etc.) are particularly suitable. Benzyl radicals are not reactive enough towards unactivated alkenes; they tend to accumulate in the medium and ultimately dimerise.

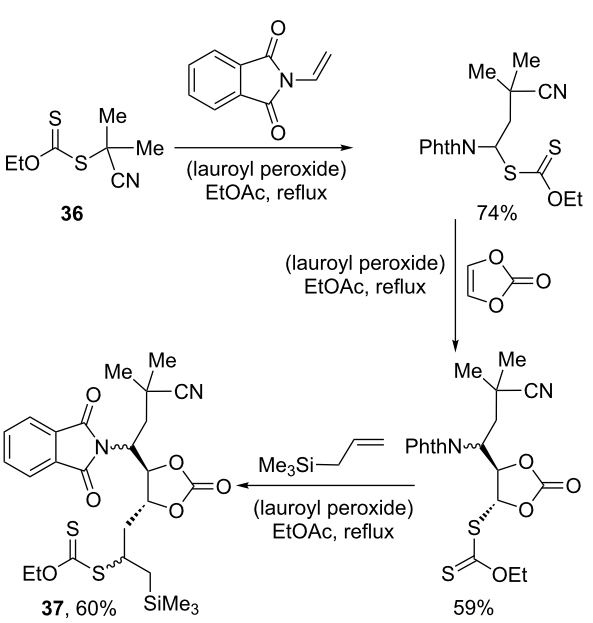
(b) The addition product, **30**, being itself a xanthate, allows the implementation of a second radical sequence, leading in turn to yet another xanthate. Alternatively, the xanthate group can be exploited as an entry into the extremely rich "ionic" chemistry of sulfur. Thus, a plethora of transformations can be easily marshalled to introduce further diversity and complexity into the structures.

By allowing intermolecular radical additions on unactivated alkenes, the xanthate transfer process opens infinite possibilities for bringing together various functional groups, which can then be made to react together. The functional groups can be present on the xanthate and/or the alkene partners. Over 2000 additions have so far been performed using more than 100

different xanthates. The few examples presented hereafter will hopefully offer a glimpse of the potential for accessing complexity.

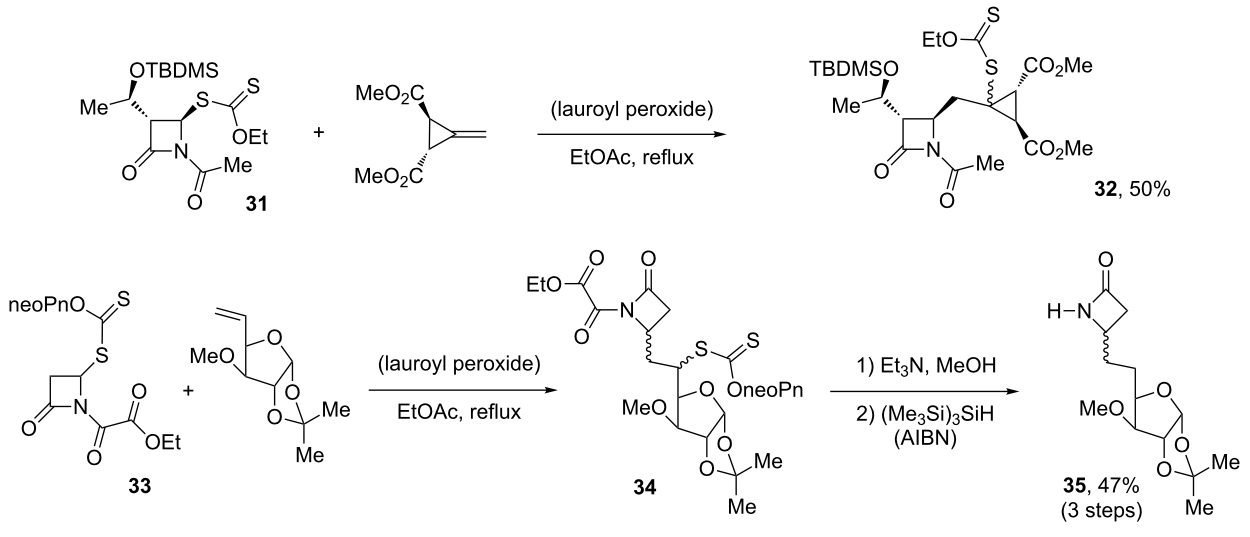
The neutral, mild experimental conditions translate into a broad tolerance for sensitive functionality. This aspect is encapsulated in the two addition reactions presented in Scheme 7 [22]. β-Lactam xanthates such as **31** and **33** can be readily added without harm to the fragile azetidinone motif and, if desired, the xanthate group may be reduced off by a number of methods, the mildest perhaps relying on tris(trimethylsilyl)silane as the reducing agent [23]. Its use is illustrated by the synthesis of the β-lactam-sugar conjugate **35**, which also highlights the possibility of cleanly removing an oxalyl group from adduct **34** without destruction of the azetidinone [24]. The synthesis of complex compounds such **32** and **35** would be very tedious by more traditional routes.

The possibility of iterating the radical addition allows for a convergent and highly modular assembly of complex scaffolds. The three successive additions outlined in Scheme 8 and leading to **37** illustrate nicely this approach [25]. One xanthate, **36**, and three different alkenes are stitched together using the same experimental conditions. The order of the additions is, however, important. One of the requirements, implicit in the general mechanism pictured in Scheme 6, is that the initial radical R· has to be more stable than adduct radical **29**, neglecting polar effects in a first approximation (again, [21] may be consulted for a more thorough discussion). A detailed inspection of the various radicals implicated in the sequence in Scheme 8 would reveal that this condition has indeed been respected.

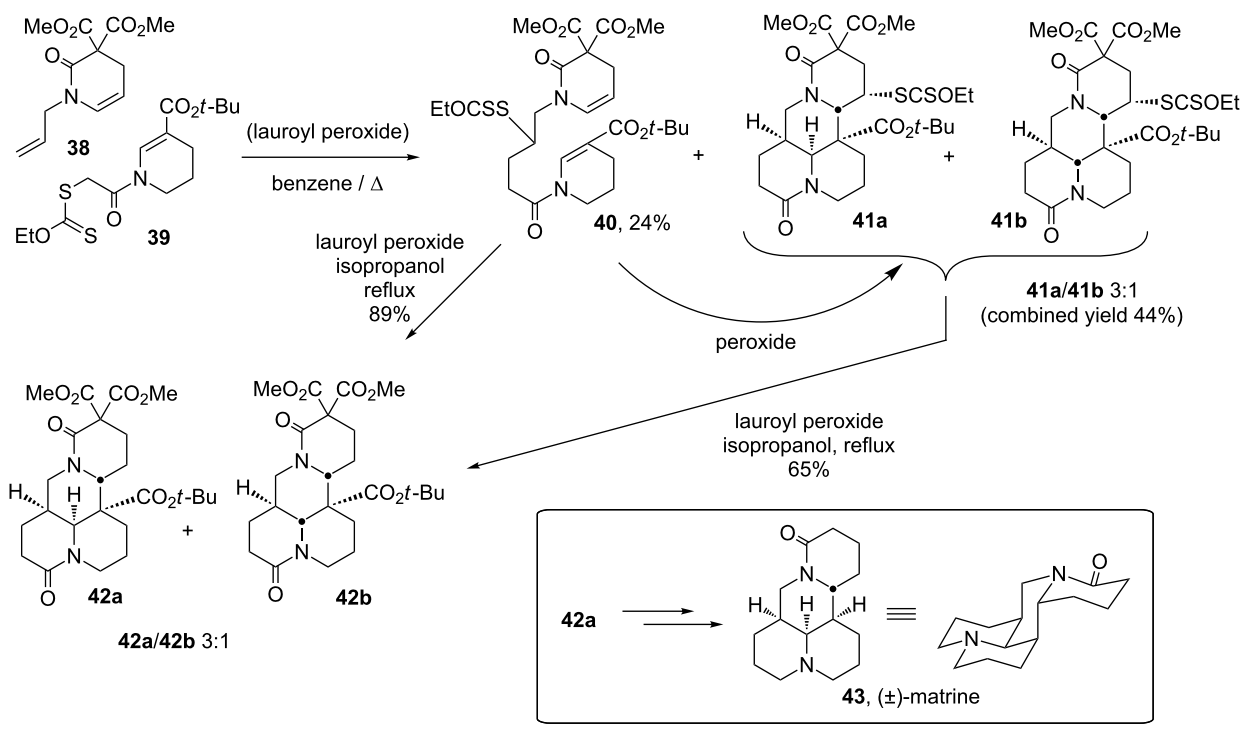


Scheme 8: Sequential additions to three different alkenes (PhthN = phthalimido).

Nevertheless, numerous variations in such sequential radical additions can be readily conceived. This is demonstrated by the key step in the total synthesis of matrine (**43**), which starts with readily available alkene **38** and xanthate **39**, and implies one intermolecular addition followed by two successive cyclisations [26]. Two isomeric tetracyclic compounds **41a** and **41b** as well as simple addition product **40** are thus obtained in good combined yield (Scheme 9). The latter may be converted into the same mixture of **41a** and **41b** by further treatment with peroxide. In practice, however, it is more convenient to subject



Scheme 7: Synthesis of β-lactam derivatives.



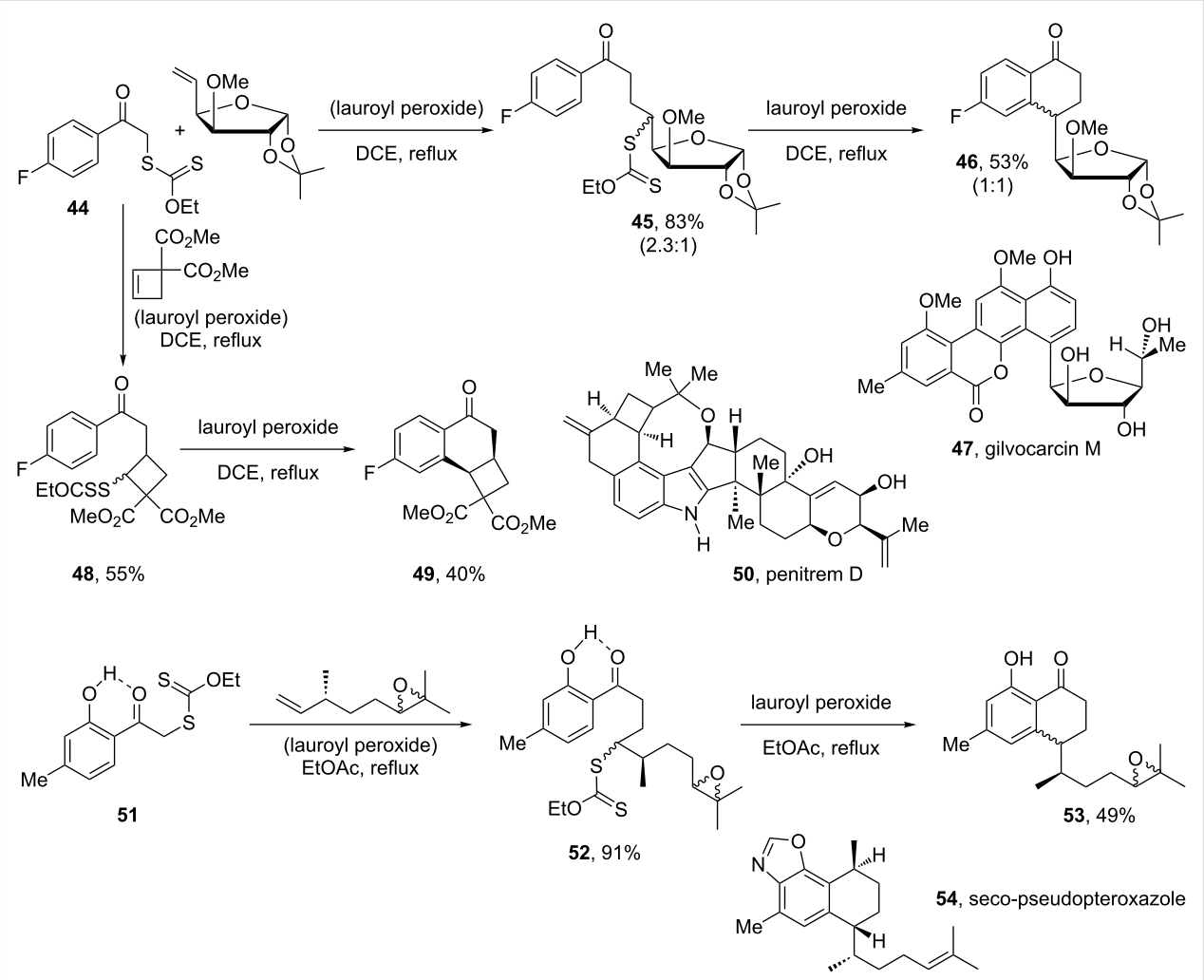
Scheme 9: Key cascade in the total synthesis of (±)-matrine (**43**).

adduct **40** separately to a reductive double cyclisation to give the epimeric mixture of **42a** and **42b**, by using isopropanol both as the solvent and source of hydrogen atoms. The mixture of **42a** and **42b** is separated at this stage and the major isomer processed into matrine (**43**) (the minor isomer has the relative stereochemistry of allo-matrine, also a natural product).

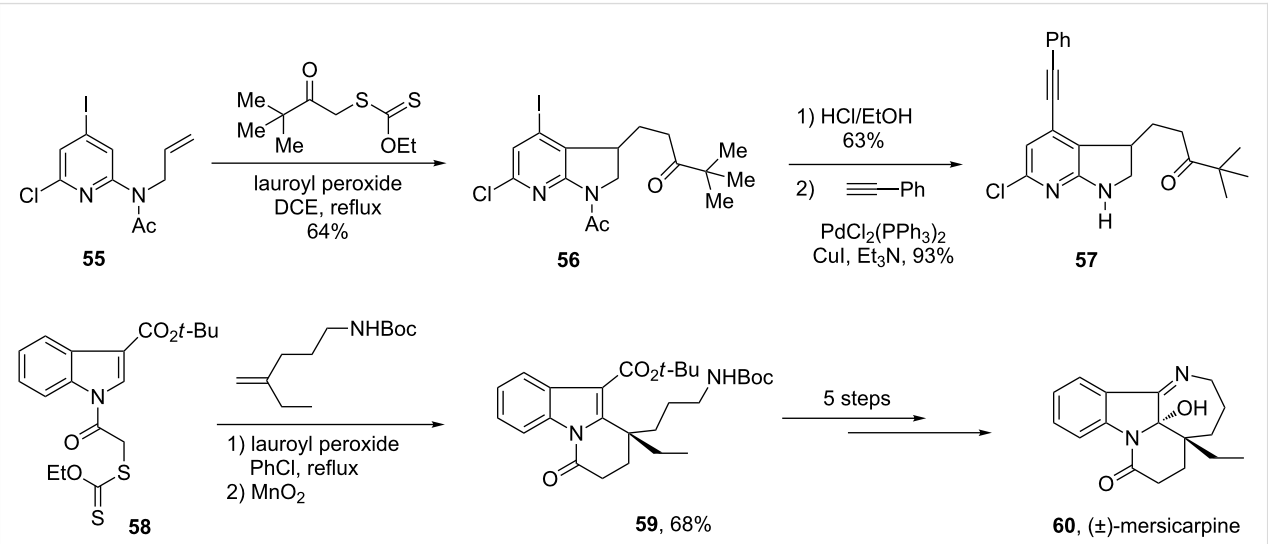
One important property of the xanthate addition–transfer process is that cross-over into a cationic manifold is possible if one of the intermediate radicals can be easily oxidised by the peroxide. The peroxide then acts as both the initiator and the stoichiometric oxidant. This is especially useful in the case of cyclisations onto aromatic or heteroaromatic rings (cf. synthesis of fortucine (**15**) in Scheme 3 above). The intermediate cyclohexadienyl radicals (analogous to radical **13**) cannot propagate the chain but are easily oxidised by the peroxide, which has to be used in stoichiometric amounts. Numerous aromatic derivatives can thus be very easily obtained. In Scheme 10, the synthesis of various tetralones is displayed. The addition of xanthate **44** to two different alkenes furnishes adducts **45** and **48**, and these can in turn be cyclised into tetralones **46** and **49**, respectively. The former represents a model study for the total synthesis of gilvocarcin M (**47**), a natural *C*-glycoside [27]; while the latter illustrates the possibility of constructing a cyclobutane-containing tricyclic motif related to the one found in penitrem D, **50** [28]. The two-step formation of tetralone **53**, starting from xanthate **51** and proceeding via adduct **52**, underscores the tolerance of the process for the presence of an epoxide and, at least in this case, of a free phenol [29]. This sequence represents an attractive potential route to seco-pseudopteroxazole, **54**, and to other congeners in this family.

In many cases, both the intermolecular addition and the ring closure can be performed in the same flask, as shown by the direct synthesis of azaindoline **56** from alkene **55** (Scheme 11) [30]. Azaindoline **56** contains at least four orthogonal sites for diversification, in addition to the obvious possibility of varying the starting xanthate. For instance, a regioselective Sonogashira coupling leading to compound **57** may be performed without affecting the less reactive chlorine substituent. The annelation commencing with xanthate **58** and furnishing indole derivative **59**, an advanced intermediate in the formal synthesis of mersicarpine (**60**), is another illustration [31]. The aromatisation process in this example was incomplete under the usual conditions and required further treatment with manganese dioxide.

The possibility of associating the radical chemistry of xanthates with various ionic reactions represents another powerful strategy for creating complexity from simple starting materials. In this approach, the radical sequence brings together the functional groups necessary for the ionic transformation. One

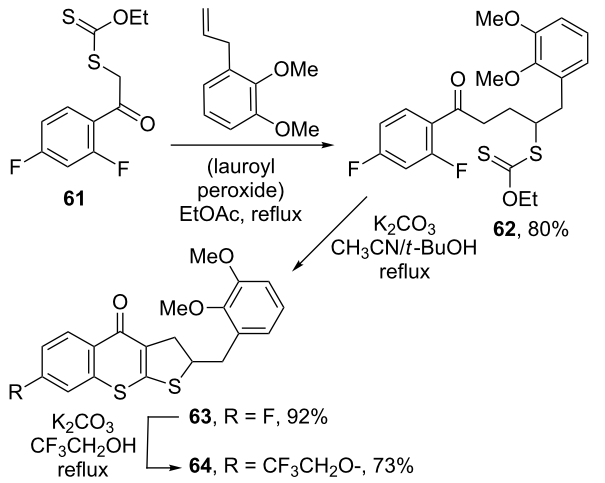


Scheme 10: Synthesis of complex tetralones.



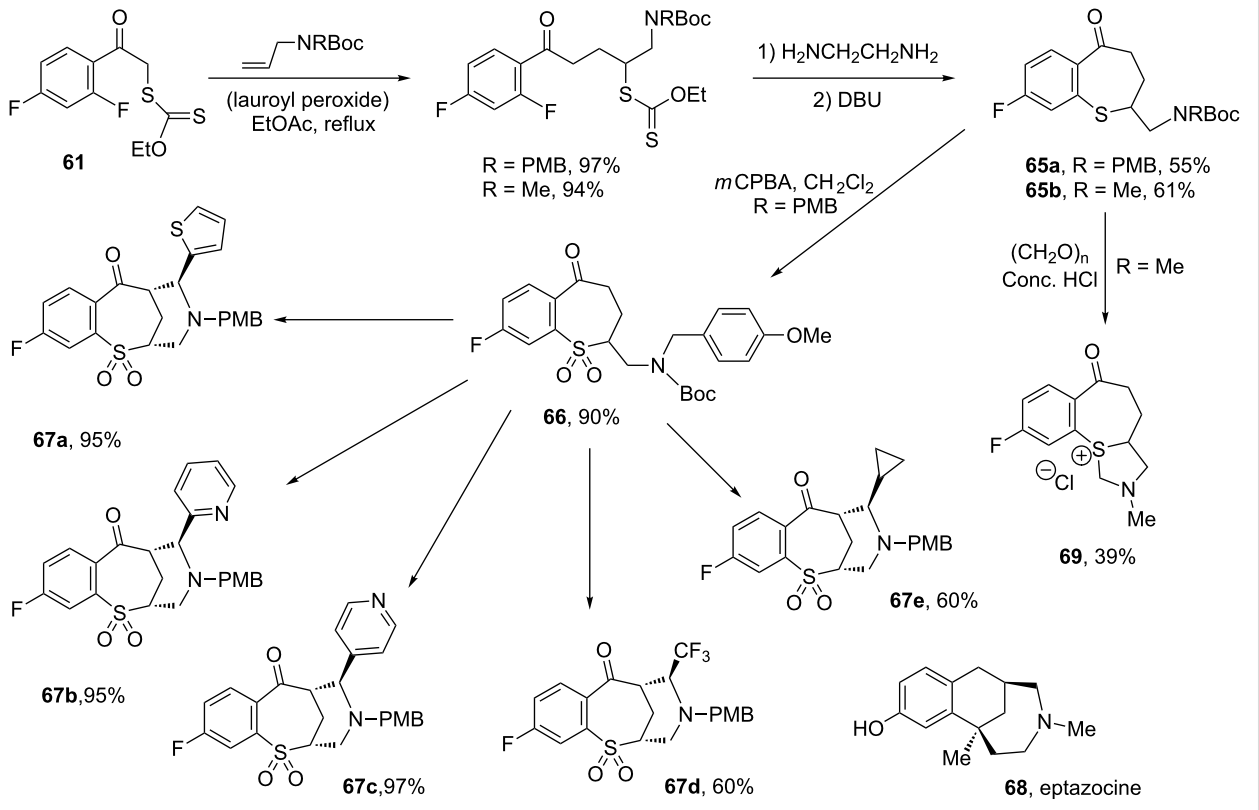
Scheme 11: Synthesis of functionalised azaindoline and indole derivatives.

example is the sequence that follows the radical addition of xanthate **61** to an alkene depicted in Scheme 12. Exposure of adduct **62** to the action of potassium carbonate, in a mixture of acetonitrile and *tert*-butanol under reflux, leads to tricyclic thiochromanone **63** in high yield [32]. This transformation involves attack of the ketone enolate on the thiocarbonyl group of the nearby xanthate, followed by substitution of the fluorine by the sulfide anion thus produced, and loss of a molecule of ethanol. Such, hitherto rare, structures can now be accessed in two easy steps that could in principle be performed in one pot. Variety is readily obtained by merely modifying the alkene or by taking advantage of the presence of the remaining fluorine to introduce different substituents, as shown by the simple formation of trifluoroethoxy derivative **64**.



Scheme 12: Synthesis of thiochromanones.

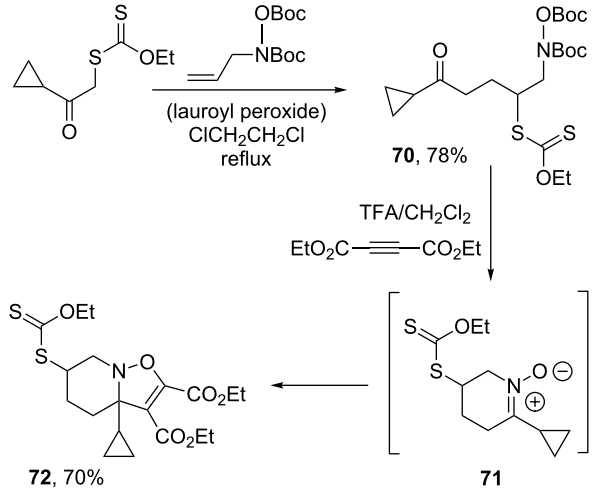
The adducts derived from xanthate **61** can be used in yet another way. Gentle aminolysis of the xanthate frees a thiol, which, under more basic conditions, displaces the *ortho*-fluorine to afford a benzothiepinone (Scheme 13) [32]. In the particular case of **65a**, oxidation to the corresponding sulfone **66** followed by a Mannich reaction with various aldehydes leads to a plethora of complex polycyclic structures **67a**–**e**, which may be viewed as analogues of eptazocine **68** [32]. Oxidation to the sulfone is necessary: when the Mannich reaction of benzothiepinone **65b** with formaldehyde was attempted, the



Scheme 13: Synthesis of complex benzothiepinones. Conditions: 1) CF3COOH; 2) RCHO / AcOH (PMB = *p*-methoxybenzyl).

reaction resulted in the formation of novel tricyclic sulfonium **69** in modest yield [32].

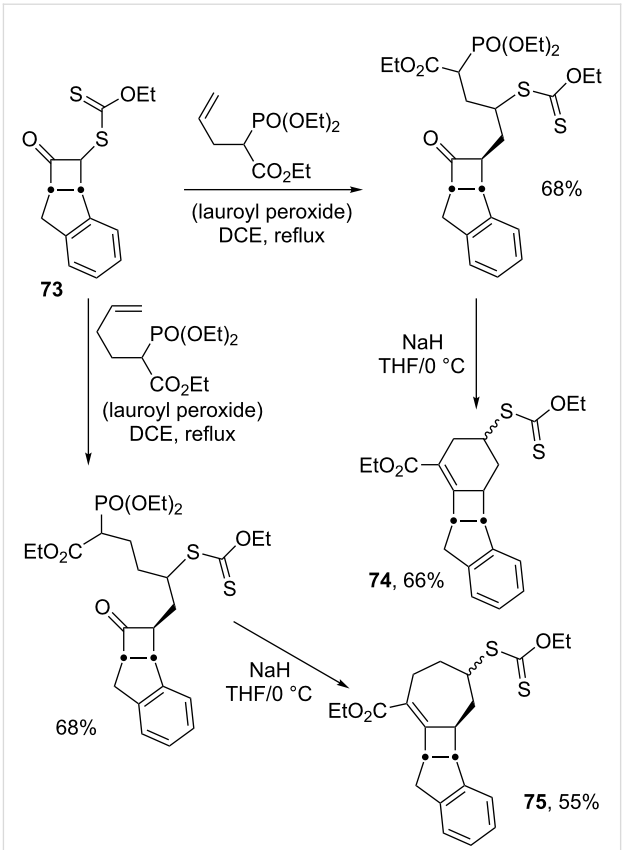
It is also possible to profit from the ability of xanthates to mediate additions to olefins containing hydroxylamine and hydrazine substituents in order to construct unusual heterocycles [33,34]. One typical illustration is presented in Scheme 14, where unmasking of the hydroxylamine in adduct **70** gives rise to cyclic nitrone **71**, which can then be intercepted by a dipolarophile placed in the medium, as shown by the ready formation of bicyclic compound **72** [33].



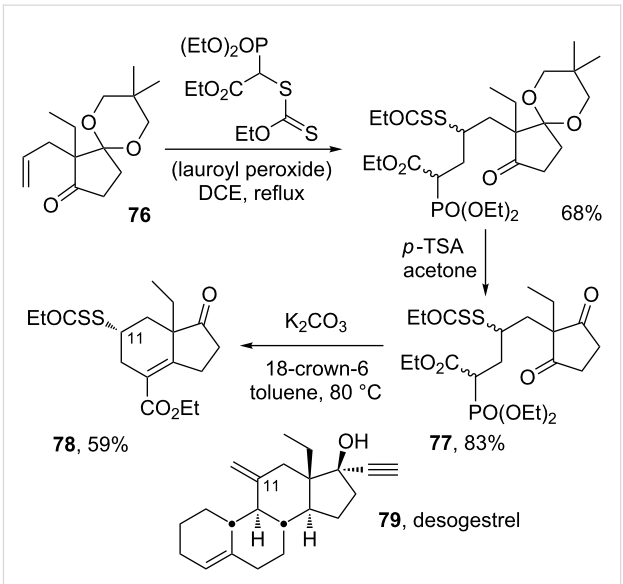
Scheme 14: Formation and capture of a cyclic nitrone.

The use of a phosphonate-containing alkene allows the assembly of numerous polycyclic structures by combining the radical addition of a ketone-bearing xanthate with an intramolecular Horner–Wadsworth–Emmons condensation. This strategy is highlighted in Scheme 15 by the synthesis of bicyclic cyclobutane derivatives **74** and **75** starting from 2-xanthyl cyclobutanone **73** [35]. Thus, depending on the distance between the terminal alkene and the phosphonate, a six- or a seven-membered ring may be fused onto the cyclobutane nucleus.

This combination represents in fact a highly flexible route to polycyclic derivatives, since it is open to numerous variations. For instance, instead of having the phosphonate group attached to the alkene, it can be part of the xanthate component. Such a modification can be used to build the CD ring system found in the highly potent steroid contraceptive desogestrel (**79**), as outlined in Scheme 16 [36]. Thus, radical addition to alkene **76** furnishes intermediate **77**, after deprotection of the second ketone group. Exposure of the latter compound to base results in the formation of bicycle **78** as one diastereomer. While the



Scheme 15: Synthesis of bicyclic cyclobutane motifs.



Scheme 16: Construction of the CD rings of steroids.

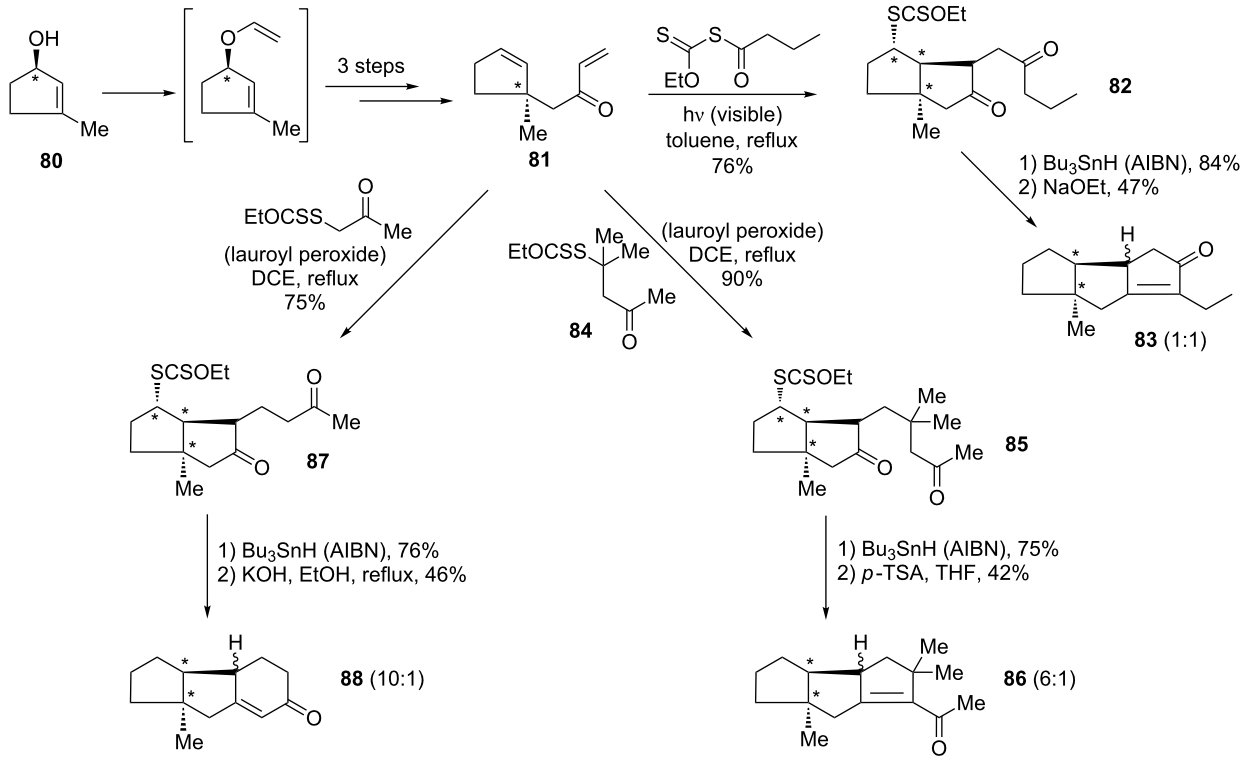
condensation could in principle take place with either of the two ketones, it occurs in fact selectively with the ketone leading to the xanthate in the equatorial position in order to avoid a 1,3-

diaxial interaction with the angular ethyl group. It is worth noting that the xanthate group conveniently occupies the 11-position (steroid numbering) and therefore allows the ready subsequent introduction of various substituents on this important position. In this quite general route to cyclohexenes, the requisite 2-allyl ketones are readily available by alkylation but also, and more importantly, by the exceedingly potent Claisen rearrangement [37], with the attending advantages of stereocontrol and chirality transfer.

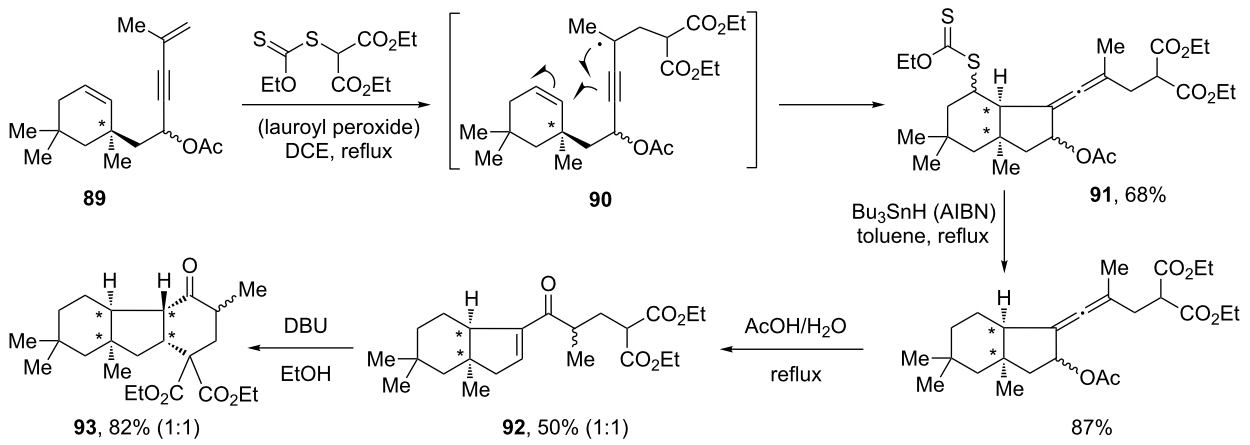
Another powerful approach to polycyclic structures is through association with Robinson-type annelations [38]. The synthesis of the precursors also exploits the Claisen rearrangement, as shown by the preparation of enone **81** from allylic alcohol **80** in Scheme 17. By varying the xanthate partner, different substitution patterns and rings may then be introduced. Two examples, **83** and **86**, in Scheme 17 illustrate the formation of triquinanes via bicyclic intermediate xanthates **82** and **85**. The former involves the addition of a butanoyl radical derived from the corresponding *S*-butanoyl xanthate, while the latter results from the addition of β-xanthyl ketone **84**. The use of an α-xanthyl ketone gives rise ultimately to a fused 6-membered ring, as shown by the formation of tricyclic product **88** from diquinane intermediate **87** [38]. In all of these transformations, the chiral information residing in the starting allylic alcohol **80** is transmitted, through the Claisen rearrangement, to various other centres (the ratios in Scheme 17 and following schemes refer to ratios of diastereoisomers). Very recently, this strategy was applied to a formal synthesis of (±)-hirsutic acid [39].

Access to polycyclic structures can be accomplished by cyclisation of propargyl radicals. Alkynes or allenes can be obtained, depending on the disposition of the internal alkene with respect to the delocalised radical [40,41]. In the sequence displayed in Scheme 18, the addition–cyclisation of a malonyl radical to enyne **89** furnishes allenyl acetate **91** by cyclisation of propargyl radical **90** [41]. Compound **91** readily undergoes reductive dexanthylation and solvolysis into enone **92**, and internal Michael addition to give tricyclic structure **93**. In this sequence too, the chirality present in the starting material **89** is initially derived from an allylic alcohol by the Claisen rearrangement and is then transmitted to the other centres.

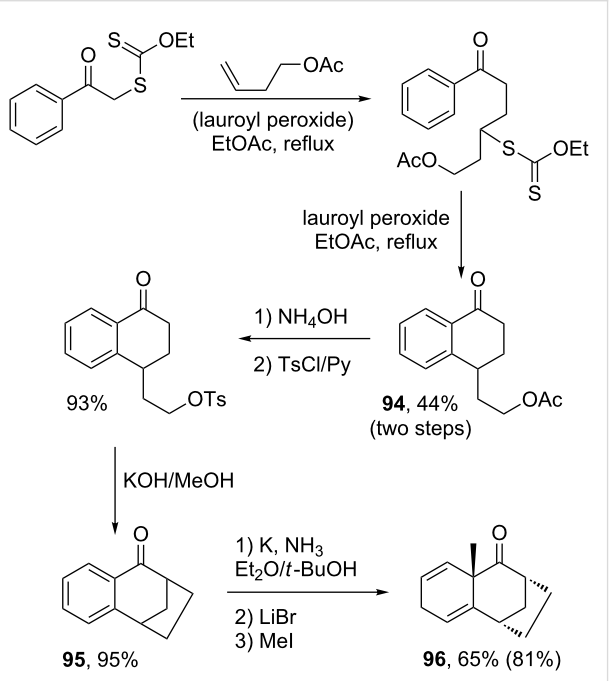
Another powerful reaction that can be associated with the radical chemistry of xanthates is the Birch reduction [42]. The radical process is employed to create the substituted aromatic motif, which is then reduced by the dissolving metal. Scheme 19 contains one such transformation, where the intermolecular radical addition is followed by ring closure to give



Scheme 17: Rapid assembly of polyquinanes.



Scheme 18: Formation of a polycyclic structure via an allene intermediate.



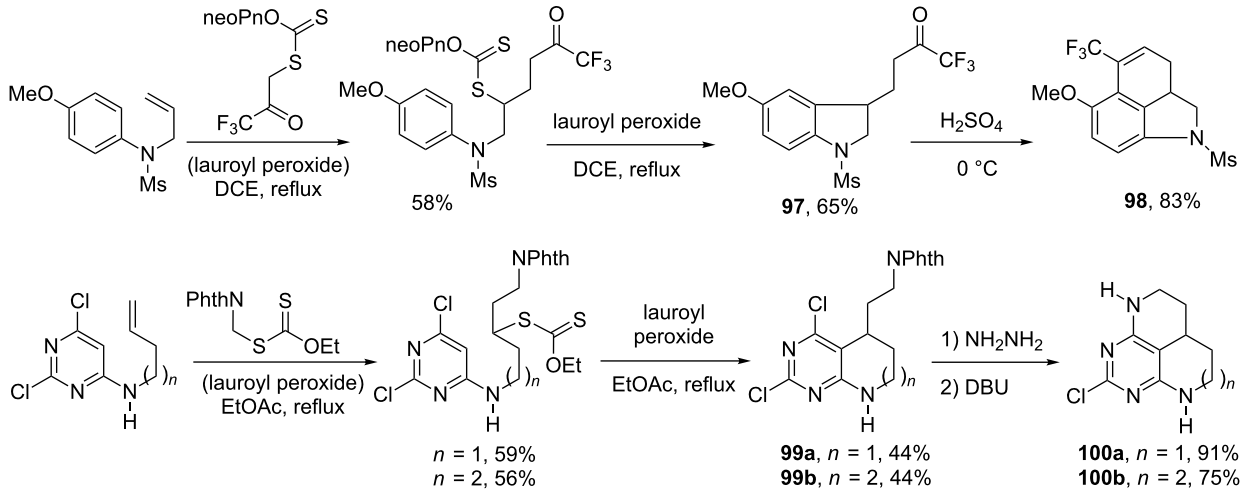
Scheme 19: A polycyclic structure via the alkylative Birch reduction.

tetralone **94**, which is easily converted into tricyclic derivative **95**. An alkylative Birch reduction finally furnishes **96** containing an angular methyl group [43]. This strategy lends itself in principle to numerous modifications, providing access to various ring combinations and substitution patterns.

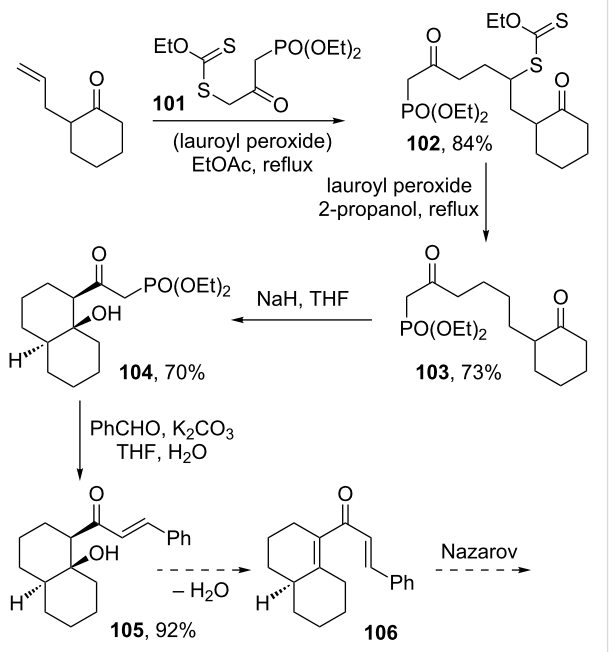
The facility of introducing polar groups such as ketones and esters through the intermolecular radical-addition step allows the association of the radical ring-closure to aromatic and heteroaromatic derivatives with ionic cyclisation processes. Two such sequences are pictured in Scheme 20. The first combines the radical addition–cyclisation leading to indoline **97** with an intramolecular Friedel–Crafts reaction to afford a tricyclic derivative **98** substituted by a trifluoromethyl group [44]. The second exploits the presence of both a protected primary amine and an easily substitutable chlorine on the pyrimidine ring in **99a**,**b** to afford two interesting tricylic compounds, one of which, **100a**, is symmetrical, and the other, **100b**, contains a seven-membered ring [45].

One path to complexity is through the use of conjunctive reagents, which can mediate an orthogonal two-directional formation of C–C bonds. In the context of xanthates, two such reagents have been studied. The first is ketophosphonyl xanthate **101**, where the intermolecular radical addition on one side of the ketone can be followed by a Horner–Wadsworth–Emmons (HWE) condensation on the other side [46]. In the transformation depicted in Scheme 21, compound **103**, obtained by the reductive dexanthylation of adduct **102** derived from 2-allylcyclohexanone, does not undergo an intramolecular HWE condensation to give a cyclooctene derivative upon treatment with sodium hydride. The formation of the cyclooctene ring is not very favourable and cannot compete with the simple aldol process leading to *trans*-decalin **104**. This compound readily undergoes HWE condensation with an external aldehyde, such as benzaldehyde. It is worth noting that β-elimination of water from the resulting product **105** would lead to dienone **106**, an interesting substrate for the Nazarov reaction which, in this case, would fuse a cyclopentenone ring on the structure.

The second reagent is chloroacetonyl xanthate **107**, which, remarkably, is able to undergo clean radical additions despite the presence of the reactive chloroketone moiety, as demonstrated by its addition to *N*-allyl-*p*-chloroacetanilide to give **108**

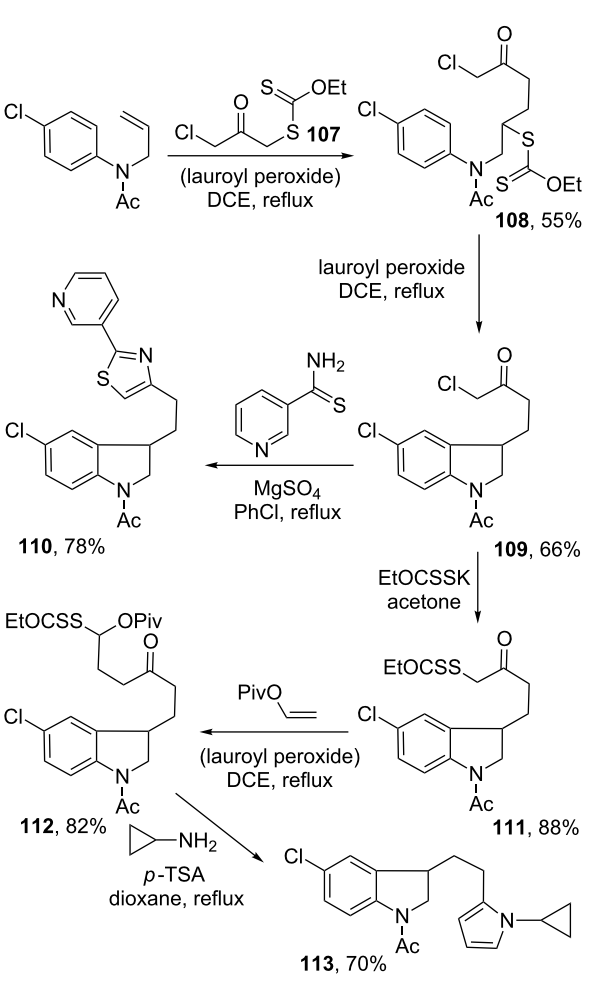


Scheme 20: Synthesis of polycyclic pyrimidines and indoline structures.



Scheme 21: Construction of a *trans*-decalin derivative.

and cyclisation of the latter into indoline **109** [47]. Diverse otherwise inaccessible chloroketones become readily available. Haloketones in general are ideal precursors for the synthesis of numerous heteroaromatic derivatives. For example, Hantzsch condensation of indoline **109** with thionicotinamide furnishes thiazole **110** (Scheme 22). Also interesting is the possibility of substituting the chlorine in **109** with a xanthate salt to form a new xanthate **111** and performing a second radical addition to a different alkene such as vinyl pivalate. The adduct, **112** in this



Scheme 22: Multiple uses of a chloroacetonyl xanthate.

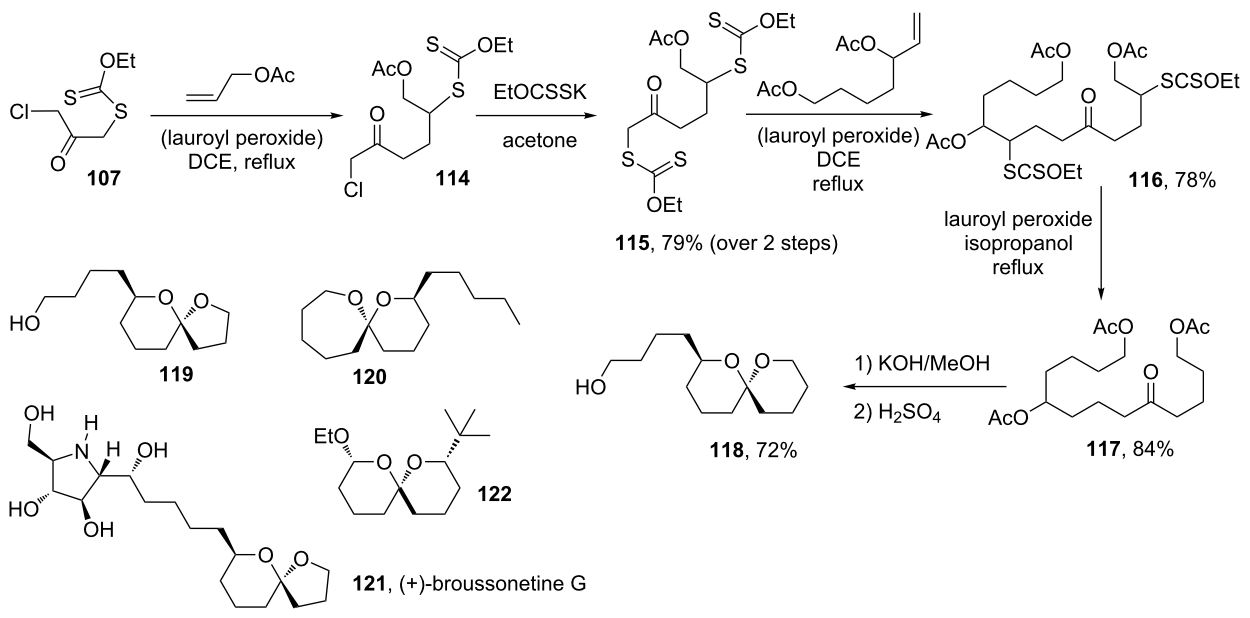
case, is the synthetic equivalent of a 1,4-keto-aldehyde and, in this capacity, can react with ammonia or primary amines, such as cyclopropylamine, to produce the corresponding pyrrole **113** by what may be viewed as a variation of the classical Paal–Knorr synthesis [47,48].

Xanthate **107** is a highly versatile reagent, since it allows the attachment of differing chains on either side of the ketone group by two consecutive intermolecular radical additions to two different alkenes. An application of this property is a simple, yet general route to spiroketals and related derivatives, as shown by the sequence in Scheme 23 [49]. Thus, addition to allyl acetate gives the expected adduct **114**, where the chlorine can be readily displaced to provide dixanthate **115**. This compound reacts with a second alkene through the xanthate group that leads to the most stable radical, namely the one adjacent to the ketone, to furnish addition product **116**. Both xanthates can be reductively removed by treatment with stoichiometric amounts of peroxide in isopropanol as the solvent, and the resulting product **117** saponified and cyclised with acid into spiroketal **118**. By choosing a vinyl or a homoallyl ester as the alkene partner, spiroketals of various ring sizes can be easily constructed. Spiroketals **119** and **120** are two such examples. The former was used in the total enantioselective synthesis of (+)-broussonetine G (**121**) [50]. If one of the alkenes contains a masked aldehyde, a bis-spiroketal such as **122** may be accessed. Furthermore, placing a 1,2- or a 1,3-diol on one of the alkenes would in principle result in the formation of a cyclic ketal. Spiro and cyclic ketals are ubiquitous in pheromones and in marine natural products [51].

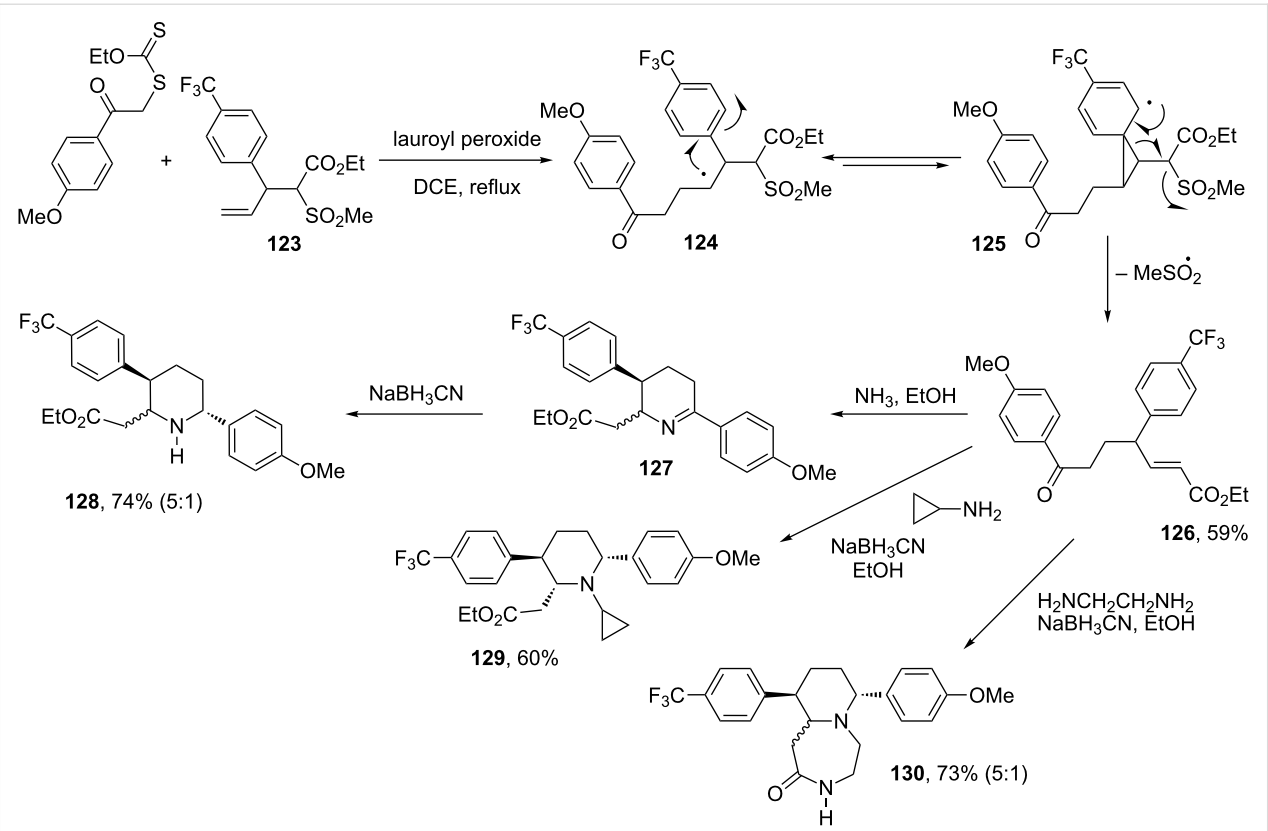
The comparatively long effective lifetime of radicals generated under the conditions of the xanthate transfer may be exploited to accomplish various difficult radical transformations. One particularly interesting process is the shifting of an aromatic ring through a radical Smiles rearrangement. In combination with the intermolecular xanthate addition, it becomes possible to rapidly assemble valuable precursors to 3-arylpiperidines. This strategy is illuminated by the synthetic outline in Scheme 24, where the intermediate radical **124** arising from addition to alkene **123** undergoes a 1,2-aryl shift via cyclopropane **125**, a process made irreversible by elimination of a methylsulfonyl radical to give ester **126** [52]. Two new C–C bonds are created, and the product now contains two electrophilic centres, a ketone and an unsaturated ester. Treatment with a primary amine or ammonia and in situ reduction of the intermediate imine **127** with sodium cyanoborohydride furnishes arylpiperidine **128** in good overall yield. Ammonia may be replaced with various primary amines, one example being cyclopropylamine, which furnishes piperidine **129** as one stereoisomer. In the case of 1,2-diaminoethane, a further cyclisation is observed leading to bicyclic piperidine **130**. All three components involved in this modular approach can be modified to provide a very broad diversity of structures.

Radical vinylations and allylations

Xanthates may be incorporated into radical processes of various kinds. Vinylation and allylation reactions are particularly appealing, in view of the importance of such transformations in organic synthesis. A number of methods were developed to this end, with perhaps the most versatile relying on the chemistry of



Scheme 23: A convergent route to spiroketals.

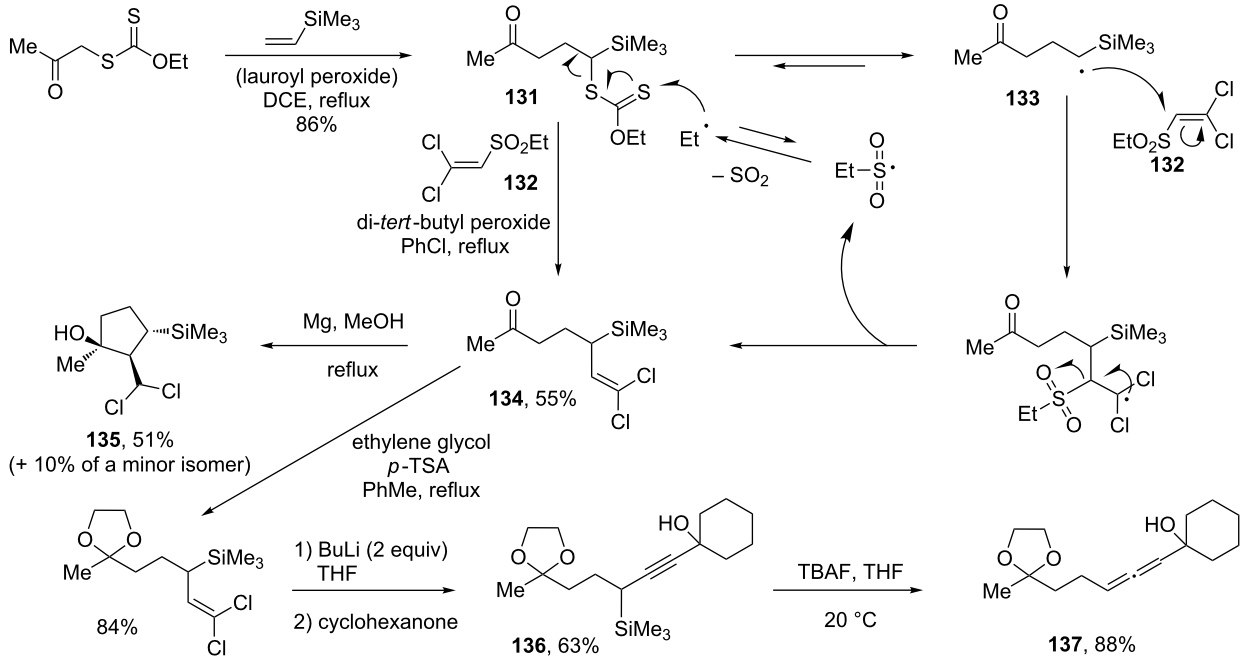


Scheme 24: A modular approach to 3-arylpiperidines.

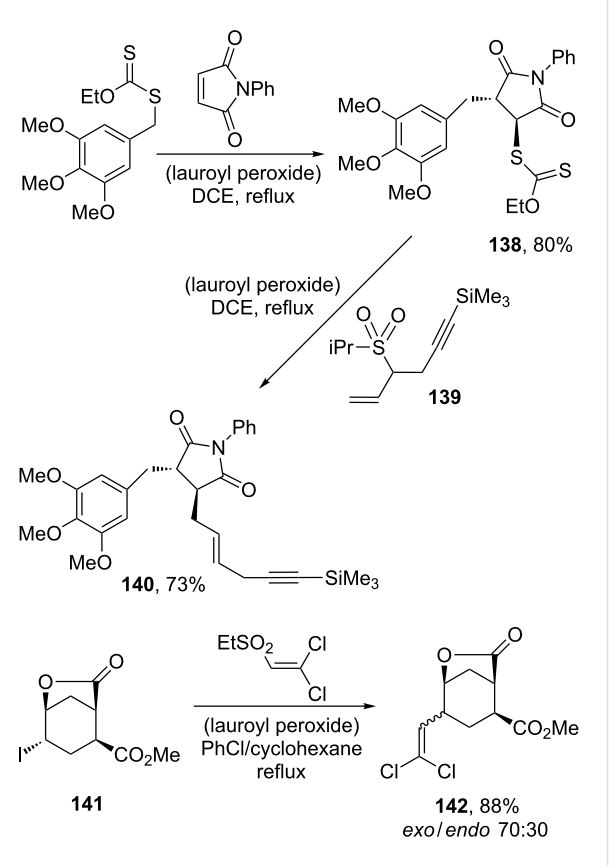
sulfones [53]. Aliphatic sulfonyl radicals are able to extrude sulfur dioxide, and the resulting carbon-centred radicals may be used in numerous ways. In particular, they can serve as chain-propagating agents for the xanthate-transfer process. An example is provided in Scheme 25 illustrating a rapid, convergent access to cyclopentanols and to functional allenes. Thus, the xanthate group in adduct **131**, derived from the radical addition to vinyl trimethylsilane, can be replaced by a dichlorovinyl motif through a second radical reaction with dichlorovinyl ethylsulfone (**132**) [54]. The ethylsulfonyl radical created in the addition–elimination process of intermediate radical **133** fragments to liberate sulfur dioxide and an ethyl radical that is capable of propagating the chain. The resulting product **134** possesses an interesting combination of functional groups. Upon treatment with magnesium turnings in methanol, this compound is converted into cyclopentanol **135** by capture of the intermediate ketyl radical by the dichlorovinyl group [55]. Alternatively, protection of the ketone and application of the Corey–Fuchs reaction followed by quenching of the acetylide with cyclohexanone furnishes propargyl silane **136**, a compound that is cleanly transformed into allene **137** upon exposure to tetrabutylammonium fluoride [54]. This approach represents perhaps the most versatile route to functional propargyl silanes. Indeed, a broad diversity of such structures becomes accessible by simply varying the starting xanthate and/or the ketone (or aldehyde) partner.

Allylations can be accomplished by applying the same concept, as shown by the sequence in Scheme 26 [56]. Again, complexity may be attained by combining the normal addition–transfer of a xanthate to an alkene with the allylation process to give fairly elaborate compounds, such as **140** obtained by reaction of adduct **138** with sulfone **139** [56]. It is interesting to note that both the vinylation and the allylation reactions are applicable to aliphatic iodides, as illustrated by the second transformation in Scheme 26 starting with iodide **141** and leading to dichlorovinyl lactone **142** [57]. It is interesting to note that while sp^2–sp^2 couplings are readily accomplished starting with vinylic or aromatic iodides using a variety of transition–metal catalysts, especially palladium-based complexes, sp^3–sp^2 couplings remain relatively rare, especially with secondary and tertiary aliphatic iodides. The present radical procedure therefore complements organometallic methods since it is most efficient with secondary and tertiary iodides, because the corresponding carbon radical is easiest to generate.

Various radical allylating agents can effect the allylation of xanthates. These include substituted allyl diphenylphosphine



Scheme 25: A convergent route to cyclopentanols and to functional allenes.

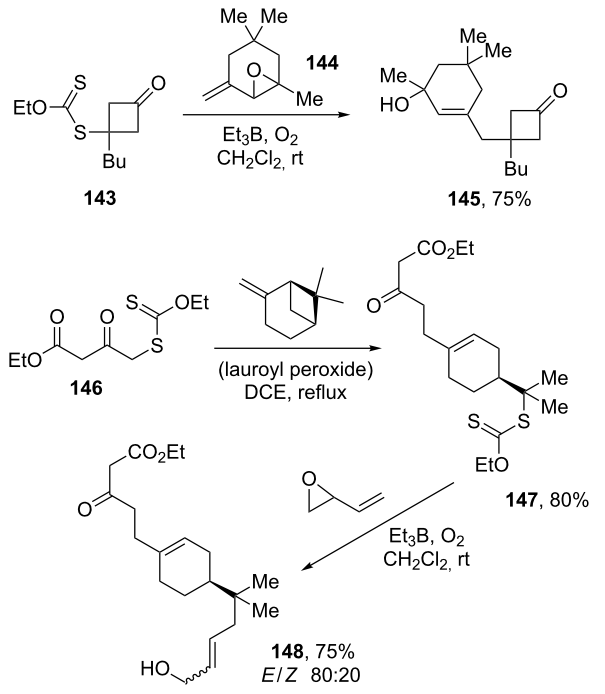


Scheme 26: Allylation and vinylation of a xanthate and an iodide.

oxides [58], vinyl epoxides [59], and allyl trimethylsilanes [60]. In the last case it is a two-step procedure. Two examples of the use of a vinyl epoxide as an allylating agent are displayed in Scheme 27 [59]. The first corresponds to the allylation of cyclobutyl xanthate **143** with vinyl epoxide **144** to yield compound **145**, while the second involves an addition–fragmentation of xanthate **146** on β-pinene to give xanthate **147**, which is then subjected to the allylation procedure with the simplest vinyl epoxide to furnish derivative **148**. It is interesting to note that the carbon–carbon bond formation takes place in ketoester xanthate **146** on the carbon bearing the least acidic hydrogens. Triethylborane, through its autoxidation, serves to initiate the process; it also quenches the intermediate alkoxy radical, liberating concomitantly an ethyl radical to propagate the chain.

Except in the cleavage of epoxides, homolytic rupture of carbon–oxygen bonds is generally a difficult process. Radicals can thus be generated next to alcohols or esters without fear of β-elimination. This constitutes a tremendous synthetic asset and explains the popularity and importance of radical-based methods for the manipulation and modification of oxygen-rich compounds such as carbohydrates and cyclitols. It is, however, possible to transform an alcohol into a leaving group in the radical sense by converting it into a fluoropyridineoxy derivative by reaction of the alkoxide anion with inexpensive 2,6-difluoropyridine [61-65]. In this manner, any allylic alcohol becomes a potential radical allylating agent. This has proved to

be a powerful route to complex alkenes, as indicated by the two examples in Scheme 28. The first represents a one-step synthesis of a steroid *C*-glycoside **149** [66], while the second illustrates a modular approach where the formation of alkene **152** is associated with the initial addition–transfer of cortisone derived xanthate **150** to vinyl acetate to provide intermediate xanthate **151** [65]. In this manner, a highly functionalised steroid containing a fluoro-substituted alkenyl side chain can be readily assembled. Both steroid products **149** and **152** would be exceedingly tedious to make by more conventional approaches.

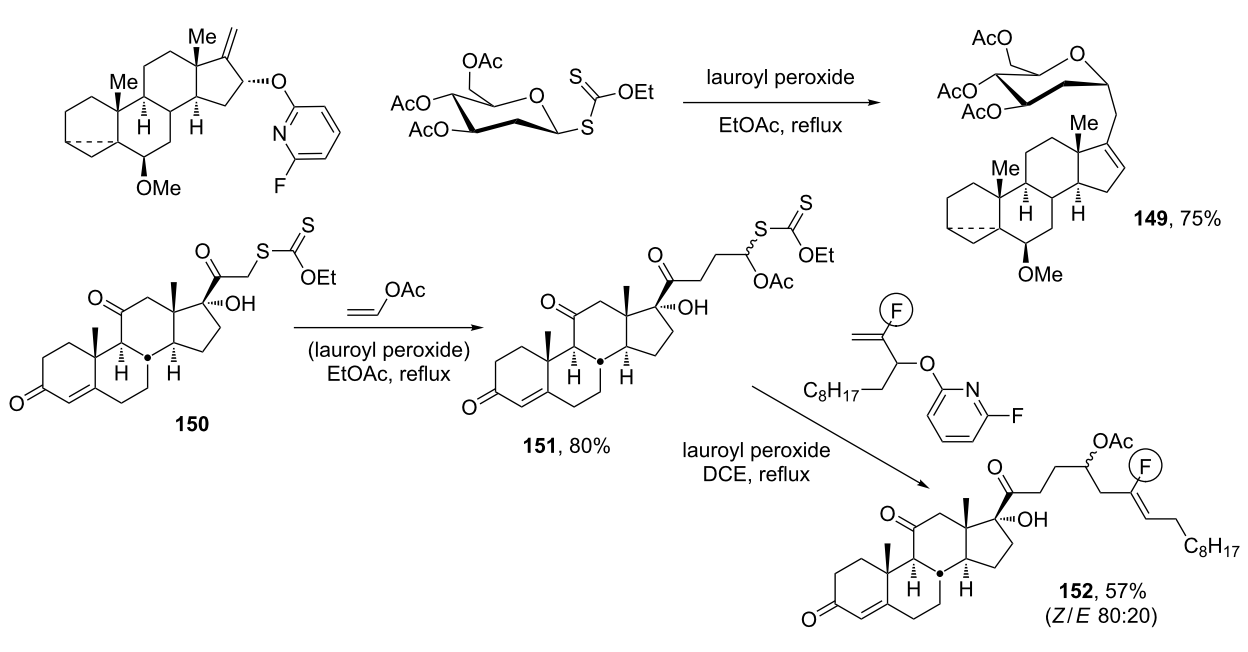


Scheme 27: Vinyl epoxides as allylating agents.

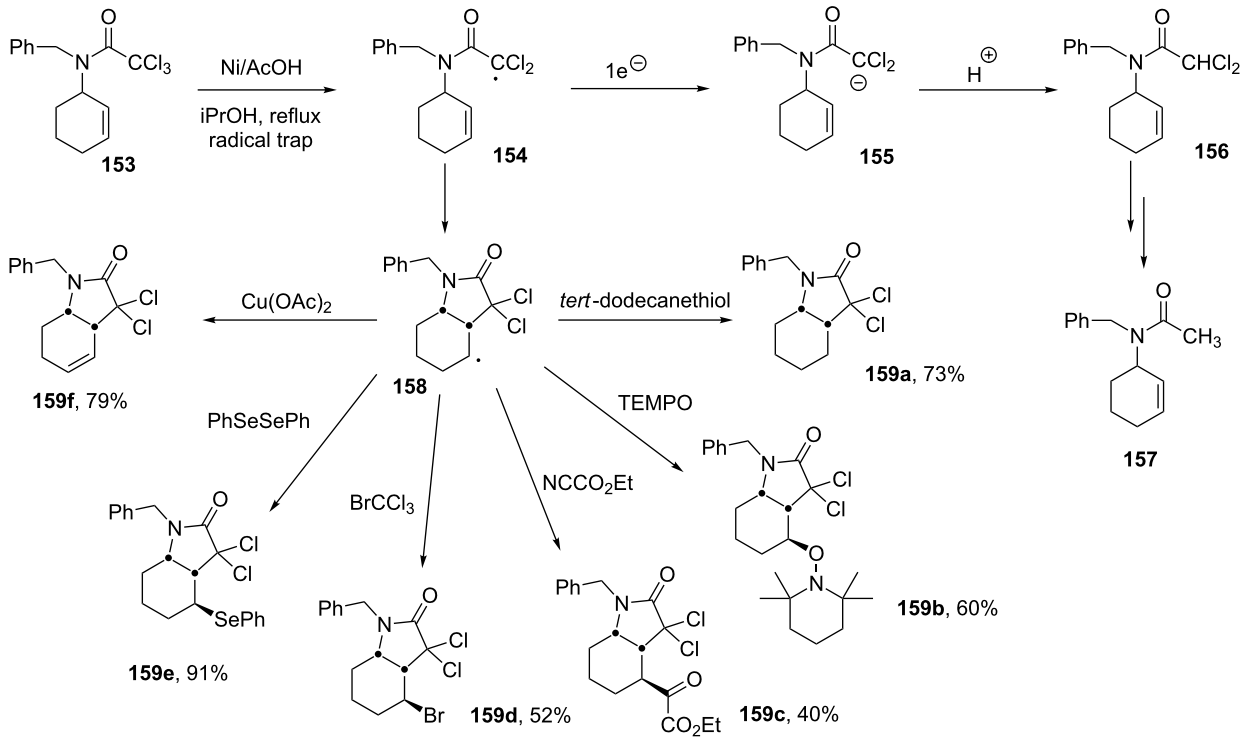
The ability to generate an alkene by the homolytic cleavage of a C–O bond is a recent development that nevertheless holds much promise. It is open to numerous variations, in particular for the synthesis of highly functionalised ketones [64] and for the stereoselective formation of di- and tri-substituted alkenes [63].

Generation of radicals by electron transfer from metallic nickel

A final topic in this brief overview concerns the use of electron transfer from metallic nickel as a means for producing and capturing radicals from selected substrates. The underlying principle is quite simple. It hinges on the observation that the intermediate radical in the dissolving metal reduction of α-halocarbonyl derivatives could be captured by an internal alkene, if the second electron transfer is slow enough. For instance, in the dechlorination of trichloroacetamide **153** with the popular zinc/acetic acid combination, the second electron transfer leading to anion **155** is too rapid to allow interception of intermediate radical **154**. No cyclisation is thus observed under these conditions, which initially afford monodechlorinated product **156** and ultimately the completely reduced material **157** (Scheme 29). In contrast, replacing zinc with plain nickel powder and diminishing the acidity of the medium by addition of a cosolvent



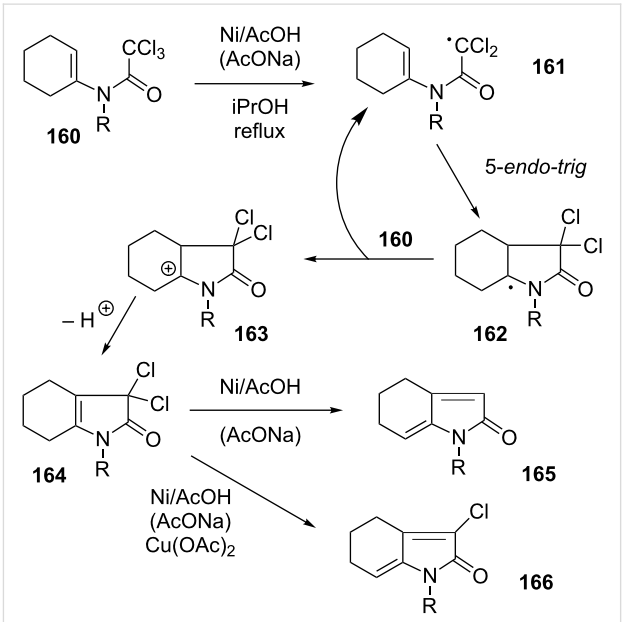
Scheme 28: Radical allylations using allylic alcohol derivatives.



Scheme 29: Synthesis of variously substituted lactams.

allows the cyclisation to proceed. The resulting secondary radical **158** is not sufficiently electrophilic in character to be reduced by the metal and can be trapped by various external reagents, as exemplified by the rich array of lactams **159a**–**f** [67]. In the case of ketoester **159c**, the reaction was carried out at room temperature [68]. The formation of unsaturated lactam **159f** is particularly interesting, since it involves the use of a mild oxidant (cupric acetate) in a reducing medium [69]. Another remarkable feature is that the nickel/acetic acid reducing system is capable of cleanly distinguishing between the starting trichloroacetamide and the dichlorolactam product. They have relatively close reduction potentials, yet the latter is reduced much more slowly under these conditions.

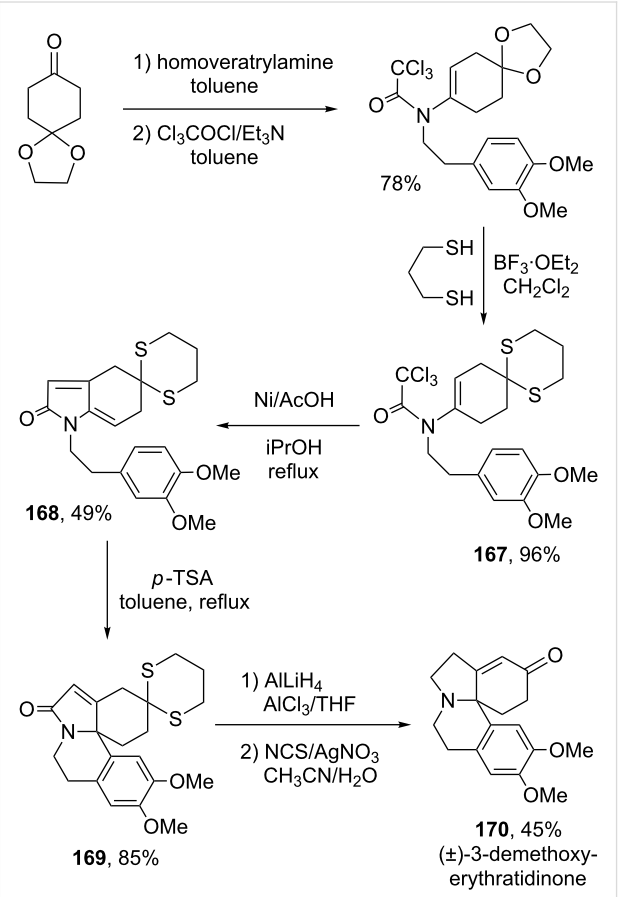
A further synthetically valuable observation is the behaviour of ene-trichloroacetamides such as **160** (Scheme 30) [70]. In this system, the intermediate radical **161** undergoes a 5-*endo* cyclisation into the easily oxidised tertiary radical **162**, which is then logically converted into cationic species **163** by electron transfer to the starting trichloroacetamide **160**. Loss of a proton finally provides unsaturated dichlorolactam **164**. This compound cannot be isolated because the chlorines are now allylic and therefore easier to reduce off than those of the starting material. Thus, a second chlorine atom is lost through reduction and the last is simply eliminated as chloride to give diene **165** as the final product. In the presence of cupric acetate additive,



Scheme 30: Nickel-mediated synthesis of unsaturated lactams.

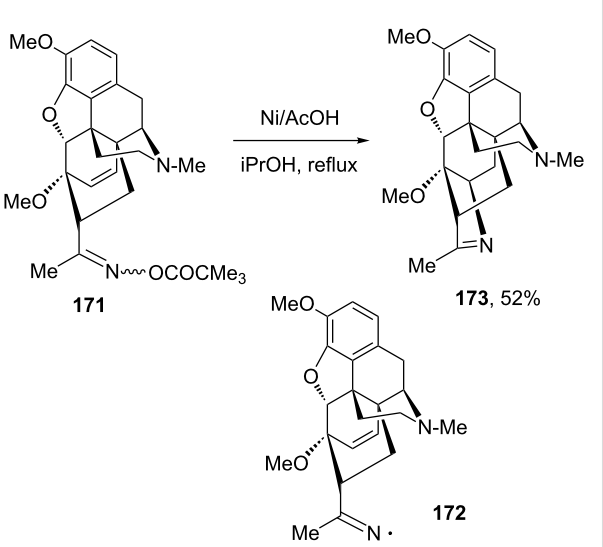
which somehow slows down the reduction, the elimination of chloride is faster than reduction, and it is chlorodiene **166** that is ultimately formed [70]. Since HCl is formally produced in these transformations, the addition of sodium acetate to buffer the medium is often beneficial.

The easy access to unsaturated lactams such as **165** and **166** may be exploited to construct complex structures by subsequent application of radical, ionic, or organometallic transformations. This is illustrated by the short, six-step total synthesis of (±)-3-demethoxy-erythratidinone (**170**) displayed in Scheme 31 [71]. In this approach, trichloroacetenamide **167**, trivially obtained in two steps from monoprotected cyclohexanedione, is subjected to the cyclisation sequence to give diene **168**, which smoothly undergoes an intramolecular Friedel–Crafts reaction to generate the last ring in intermediate **169**. Finally, reduction of the lactam and unmasking of the ketone causes the migration of the olefin to complete the synthesis of the target structure **170**.



Scheme 31: Total synthesis of (±)-3-demethoxy-erythratidinone.

The generation of radicals using nickel powder in combination with acetic acid can be extended to the production of iminyls by reduction of oxime esters [72,73]. This variant allows an easy access to pyrrolenines as underscored by the synthesis of complex structure **173** from thebain-derived oxime pivalate **171** via iminyl radical **172** (Scheme 32) [73]. In this transformation, the solvent, 2-propanol, acts as the final hydrogen atom donor to quench the carbon radical formed upon cyclisation of the iminyl.



Scheme 32: Generation and capture of an iminyl radical from an oxime ester.

Conclusion

The preceding examples showcase some of the possibilities for creating complexity by using radical processes we have developed over the years. Our research is curiosity driven, guided by a search for novelty and a thirst for understanding reaction mechanisms. Constructing complex molecular architectures is only incidental to our work, mostly a consequence of our exploration of the scope and limitations of our methods. The degenerative radical addition–transfer of xanthates is by far the most powerful radical chemistry that we have been able to discover, for it allows efficient intermolecular carbon–carbon bond formation starting with unactivated alkenes under very mild experimental conditions. Various functional groups can therefore be brought together and made to react in an infinite number of ways. Because of its convergence and tolerance, the xanthate technology offers numerous possibilities for the rapid assembly of well-decorated, intricate carbon frameworks. Much work has been done, but much more remains to be done in this never-ending quest, which will hopefully continue to take us to unexpected venues.

Acknowledgements

We are extremely grateful to our collaborators and students, whose names appear in the references, and who made this chemistry possible through their skill, dedication, and enthusiasm. We also thank the following organisations and companies that have provided financial support over the years: École Polytechnique, CNRS, MNRT, DGA, MNRT, ANR, the Alfred Kastler Foundation, CONACyT (Mexico), MECyD (Spain), the Royal Commission for the Exhibition of 1851, Rhodia, Scynexis, and Sanofi-Aventis.

References

1. Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis;* Wiley-VCH: Weinheim, Germany, 2006.
2. Renaud, P.; Sibi, M. P., Eds. *Radicals in Organic Synthesis;* Wiley-VCH: Weinheim, Germany, 2001; Vol. 1 & 2.
3. Zard, S. Z. *Radical Reactions in Organic Synthesis;* Oxford University Press: Oxford, U.K., 2003.
4. Gansäuer, A., Ed. *Radicals in Synthesis II;* Topics in Current Chemistry, Vol. 264; Springer: Berlin, Germany, 2006. doi:10.1007/11615064
5. Chatgilialoglu, C.; Studer, A., Eds. *Encyclopedia of Radicals in Chemistry, Biology and Materials;* Wiley-VCH: Weinheim, Germany, 2012.
6. Zard, S. Z. *Chem. Soc. Rev.* **2008,** *37,* 1603–1618. doi:10.1039/b613443m
   See for a recent review.
7. Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1995,** *51,* 6517–6528. doi:10.1016/0040-4020(95)00319-4
8. Cassayre, J.; Zard, S. Z. *J. Am. Chem. Soc.* **1999,** *121,* 6072–6073. doi:10.1021/ja990707p
9. Cassayre, J.; Zard, S. Z. *J. Organomet. Chem.* **2001,** *624,* 316–326. doi:10.1016/S0022-328X(01)00662-3
10. Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000,** *56,* 3263–3283. doi:10.1016/S0040-4020(00)00148-4
11. Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004,** *33,* 32–42. doi:10.1039/b300976a
12. Cassayre, J.; Gagosz, F.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2002,** *41,* 1783–1785. doi:10.1002/1521-3773(20020517)41:10<1783::AID-ANIE1783>3.0.CO;2-I
13. Callier-Dublanchet, A.-C.; Cassayre, J.; Gagosz, F.; Quiclet-Sire, B.; Sharp, L. A.; Zard, S. Z. *Tetrahedron* **2008,** *64,* 4803–4816. doi:10.1016/j.tet.2008.02.107
14. Biéchy, A.; Hachisu, S.; Quiclet-Sire, B.; Ricard, L.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2008,** *47,* 1436–1438. doi:10.1002/anie.200704996
15. Biéchy, A.; Hachisu, S.; Quiclet-Sire, B.; Ricard, L.; Zard, S. Z. *Tetrahedron* **2009,** *65,* 6730–6738. doi:10.1016/j.tet.2009.04.027
16. Boivin, J.; Fouquet, E.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1994,** *50,* 1769–1776. doi:10.1016/S0040-4020(01)80851-6
17. Zard, S. Z. *Synlett* **1996,** 1148–1154. doi:10.1055/s-1996-5698
18. Barton, D. H. R.; da Silva, E.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988,** 285–287. doi:10.1039/C39880000285
19. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003,** *125,* 11360–11370. doi:10.1021/ja0214882
20. Delduc, P.; Tailhan, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988,** 308–310. doi:10.1039/C39880000308
21. Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011,** *83,* 519–551. doi:10.1351/PAC-CON-10-08-07
    See for a recent review.
22. Quiclet-Sire, B.; Zard, S. Z. *Heterocycles* **2010,** *82,* 263–271. doi:10.3987/COM-10-S(E)39
23. Chatgilialoglu, C. *Chem. Rev.* **1995,** *95,* 1229–1251. doi:10.1021/cr00037a005
24. Cooper, R. D. G.; José, F. L. *J. Am. Chem. Soc.* **1972,** *94,* 1021–1022. doi:10.1021/ja00758a065
25. Quiclet-Sire, B.; Revol, G.; Zard, S. Z. *Tetrahedron* **2010,** *66,* 6656–6666. doi:10.1016/j.tet.2010.05.107
26. Boiteau, L.; Boivin, J.; Liard, A.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1998,** *37,* 1128–1131. doi:10.1002/(SICI)1521-3773(19980504)37:8<1128::AID-ANIE1128>3.0.CO;2-P
27. Cordero-Vargas, A.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2005,** *3,* 4432–4443. doi:10.1039/b512851j
28. Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000,** *41,* 9815–9818. doi:10.1016/S0040-4039(00)01777-9
29. Petit, L.; Zard, S. Z. *Chem. Commun.* **2010,** *46,* 5148–5150. doi:10.1039/c0cc00680g
30. Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004,** *6,* 3671–3674. doi:10.1021/ol0489649
31. Biéchy, A.; Zard, S. Z. *Org. Lett.* **2009,** *11,* 2800–2803. doi:10.1021/ol900996k
32. Boutillier, P.; Quiclet-Sire, B.; Zafar, S. N.; Zard, S. Z. *Tetrahedron: Asymmetry* **2010,** *21,* 1649–1665. doi:10.1016/j.tetasy.2010.06.006
33. Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Synlett* **2002,** 903–906. doi:10.1055/s-2002-31899
34. Quiclet-Sire, B.; Woollaston, D.; Zard, S. Z. *Tetrahedron* **2008,** *64,* 11917–11924. doi:10.1016/j.tet.2008.08.113
35. Binot, G.; Zard, S. Z. *Tetrahedron Lett.* **2003,** *44,* 7703–7706. doi:10.1016/j.tetlet.2003.09.042
36. Cholleton, N.; Gauthier-Gillaizeau, I.; Six, Y.; Zard, S. Z. *Chem. Commun.* **2000,** 535–536. doi:10.1039/b001119n
37. Martín Castro, A. M. *Chem. Rev.* **2004,** *104,* 2939–3002. doi:10.1021/cr020703u
38. Briggs, M. E.; El Qacemi, M.; Kalaï, C.; Zard, S. Z. *Tetrahedron Lett.* **2004,** *45,* 6017–6020. doi:10.1016/j.tetlet.2004.06.035
39. Revol, G.; Fuchs, C.; Zard, S. Z. *Can. J. Chem.* **2012,** *90,* 927–931. doi:10.1139/v2012-037
40. Denieul, M.-P.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996,** *37,* 5495–5498. doi:10.1016/0040-4039(96)01146-X
41. Alameda-Angulo, C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2006,** *47,* 913–916. doi:10.1016/j.tetlet.2005.11.154
42. Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986,** *3,* 35–85. doi:10.1039/np9860300035
43. Braun, M.-G. Applications de la chimie radicalaire des xanthates. Ph.D. Thesis, Ecole Polytechnique, Palaiseau, France, 2011.
44. Sortais, B. Nouvelles synthèses radicalaires d'indanes, de dérivés d'hydrazines et d'hydroxylamines. Nouvel accès aux alcaloïdes de l'ergoline et synthèse radicalaire de la mélatonine. Ph.D. Thesis, Ecole Polytechnique, Palaiseau, France, 2002.
45. Liu, Z.; Qin, L.; Zard, S. Z. *Org. Lett.* **2012,** *14,* 5976–5979. doi:10.1021/ol3028829
46. Corbet, M.; de Greef, M.; Zard, S. Z. *Org. Lett.* **2008,** *10,* 253–256. doi:10.1021/ol702590f
47. Bergeot, O.; Corsi, C.; El Qacemi, M.; Zard, S. Z. *Org. Biomol. Chem.* **2006,** *4,* 278–290. doi:10.1039/b514509k
48. Quiclet-Sire, B.; Quintero, L.; Sanchez-Jimenez, G.; Zard, S. Z. *Synlett* **2003,** 75–78. doi:10.1055/s-2003-36223
49. de Greef, M.; Zard, S. Z. *Org. Lett.* **2007,** *9,* 1773–1776. doi:10.1021/ol070488+
50. Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem., Int. Ed.* **2003,** *42,* 5987–5990. doi:10.1002/anie.200352857
51. Perron, F.; Albizati, K. F. *Chem. Rev.* **1989,** *89,* 1617–1661. doi:10.1021/cr00097a015

52. Georghe, A.; Quiclet-Sire, B.; Vila, X.; Zard, S. Z. *Tetrahedron* **2007,** *63,* 7187–7212. doi:10.1016/j.tet.2007.04.091
53. Bertrand, F.; Le Guyader, F.; Liguori, L.; Ouvry, G.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Acad. Sci., C. R. Ser. II* **2001,** *4,* 547–555. doi:10.1016/S1387-1609(01)01270-1
54. Li, Z.; Zard, S. Z. *Org. Lett.* **2009,** *11,* 2868–2871. doi:10.1021/ol900739x
55. Li, Z.; Zard, S. Z. *Tetrahedron Lett.* **2009,** *50,* 6973–6976. doi:10.1016/j.tetlet.2009.09.157
56. Charrier, N.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2008,** *47,* 9443–9446. doi:10.1002/anie.200804298
57. Bertrand, F.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **1999,** *38,* 1943–1946. doi:10.1002/(SICI)1521-3773(19990712)38:13/14<1943::AID-ANIE1943>3.0.CO;2-R
58. Ouvry, G.; Quiclet-Sire, B.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2006,** *45,* 5002–5006. doi:10.1002/anie.200601556
59. Charrier, N.; Gravestock, D.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2006,** *45,* 6520–6523. doi:10.1002/anie.200601567
60. Briggs, M. E.; Zard, S. Z. *Synlett* **2005,** 334–336. doi:10.1055/s-2004-837191
61. Charrier, N.; Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2008,** *130,* 8898–8899. doi:10.1021/ja802899m
62. Brioche, J.; Michalak, M.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2011,** *13,* 6296–6299. doi:10.1021/ol202798r
63. Braun, M.-G.; Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **2011,** *133,* 15954–15957. doi:10.1021/ja207944c
64. Debien, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2011,** *13,* 5676–5679. doi:10.1021/ol202399c
65. Debien, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2012,** *14,* 5118–5121. doi:10.1021/ol3023903
66. Kosnik, W.; Zard, S. Z. unpublished observations.
67. Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1994,** *35,* 5629–5632. doi:10.1016/S0040-4039(00)77265-0
68. Yousfi, M. Etude de nouvelles réactions radicalaires induites par le nickel en poudre. Ph.D. Thesis, Université Paris XI, Orsay, France, 1995.
69. Cassayre, J.; Dauge, D.; Zard, S. Z. *Synlett* **2000,** 471–474. doi:10.1055/s-2000-6556
70. Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron* **1998,** *54,* 1029–1040. doi:10.1016/S0040-4020(97)10204-6
71. Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1998,** *39,* 8995–8998. doi:10.1016/S0040-4039(98)02036-X
72. Boivin, J.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron Lett.* **1992,** *33,* 7849–7852. doi:10.1016/S0040-4039(00)74760-5
73. Boivin, J.; Schiano, A.-M.; Zard, S. Z.; Zhang, H. *Tetrahedron Lett.* **1999,** *40,* 4531–4534. doi:10.1016/S0040-4039(99)00720-0

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Beilstein Journal of Organic Chemistry

Synthesis of skeletally diverse alkaloid-like molecules: exploitation of metathesis substrates assembled from triplets of building blocks

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Full Research Paper

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Keywords:
alkaloids; cyclopropanes; diversity-oriented synthesis; metathesis

Beilstein J. Org. Chem. **2013,** *9,* 775–785.
doi:10.3762/bjoc.9.88

Received: 10 January 2013
Accepted: 18 March 2013
Published: 22 April 2013

This article is part of the Thematic Series "Creating complexity".

Guest Editor: D. Craig

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Abstract

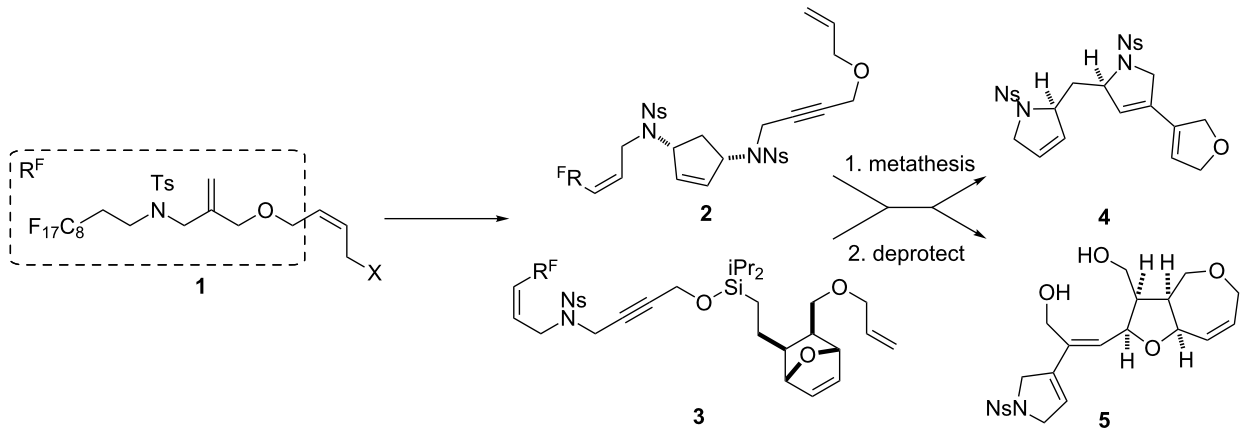
A range of metathesis substrates was assembled from triplets of unsaturated building blocks. The approach involved the iterative attachment of a propagating and a terminating building block to a fluorous-tagged initiating building block. Metathesis cascade chemistry was used to "reprogram" the molecular scaffolds. Remarkably, in one case, a cyclopropanation reaction competed with the expected metathesis cascade process. Finally, it was demonstrated that the metathesis products could be derivatised to yield the final products. At each stage, purification was facilitated by the presence of a fluorous-tagged protecting group.

Introduction

Our collective understanding of the biological relevance of chemical space has been shaped, in large part, by the historic exploration of chemical space by chemical synthesis (and biosynthesis) [1]. The scaffolds of known bioactive small molecules, in particular, play a key role in guiding the navigation of chemical space [2-4]. The field of biology-oriented synthesis (BIOS) [5], for example, uses biologically validated scaffolds [6-8] to inspire library design.

Known organic molecules populate chemical space unevenly and unsystematically. Around half of all known organic compounds are based on only 0.25% of the known molecular scaffolds [9]! This uneven coverage of chemical space is also typical of small-molecule screening collections [7,10]. Consequently, the biological relevance of most known scaffolds has been poorly explored. The field of diversity-oriented synthesis [11-13] has emerged with the specific aim of populating screening collections with diverse and novel small molecules.

We have previously developed a robust approach for the synthesis of skeletally diverse small molecules (Scheme 1) [14]. The approach relied on the synthesis of metathesis substrates by



Scheme 1: Illustrative examples of a synthetic approach to natural-product-like molecules with over eighty molecular scaffolds.

iterative attachment of simple unsaturated building blocks to a fluorous-tagged linker **1** (e.g., → **2** or **3**). Subsequently, metathesis cascade reactions were used to "reprogram" the molecular scaffolds, concomitantly releasing the products from the linker (e.g., → **4** or **5**) [14-17]. The approach enabled the combinatorial variation of molecular scaffolds, and was exploited in the synthesis of natural-product-like small molecules with unprecedented scaffold diversity (over 80 distinct scaffolds).

Although powerful, this general approach to skeletally diverse molecules had only been exemplified by varying pairs of unsaturated building blocks [14]. Thus, by exploiting the linker **1**, which is an allyl alcohol or allyl amine equivalent, all of the products were inevitably allylic alcohols or cyclic allylic amines. Here, we demonstrate that the approach is considerably more general, and that it is feasible to exploit triplets of building blocks, extending the range of diverse molecular scaffolds that may be prepared.

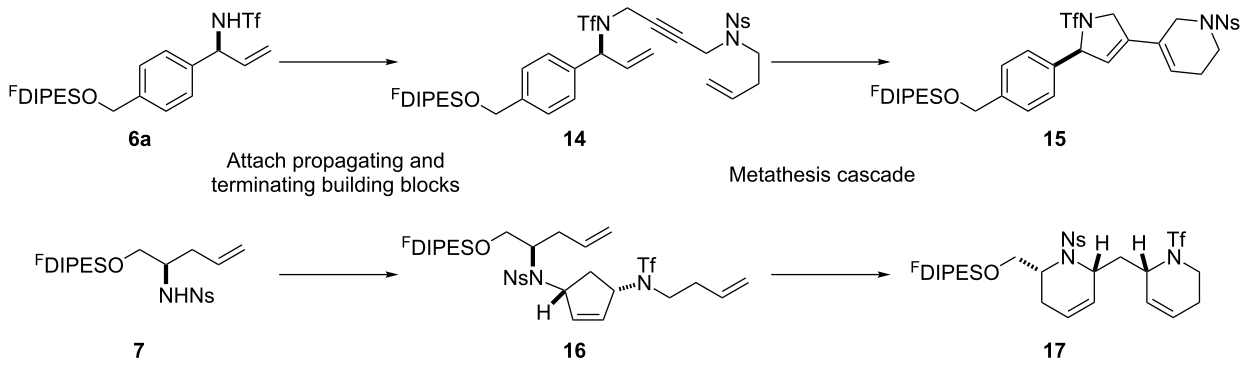
Results and Discussion

Library design

An overview of the proposed approach to the synthesis of diverse scaffolds is shown in Scheme 2. The building blocks used in this study are shown in Figure 1. It was planned to start with an "initiating" building block (e.g., **6a** or **7**) bearing a fluorous tag to facilitate the purification of synthetic intermediates [18]. Iterative attachment of a propagating and a terminating building block would yield a metathesis substrate (such as **14** or **16**). Finally, a metathesis cascade reaction would yield a product scaffold (such as **15** and **17**). It was planned that many of the product scaffolds would bear an *o*-nitrophenylsulfonyl protecting group. The combinations of building blocks were carefully chosen to ensure that, after deprotection, selective derivatisation of the product scaffolds would be possible.

Synthesis of building blocks

The initiating building blocks **6a** and **6b** were prepared by using the approach outlined in Scheme 3. The allylic alcohol **14** [19]



Scheme 2: Overview of the proposed synthetic approach. FDIPES = diisopropyl(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)silyl; Ns = *o*-nitrophenylsulfonyl.

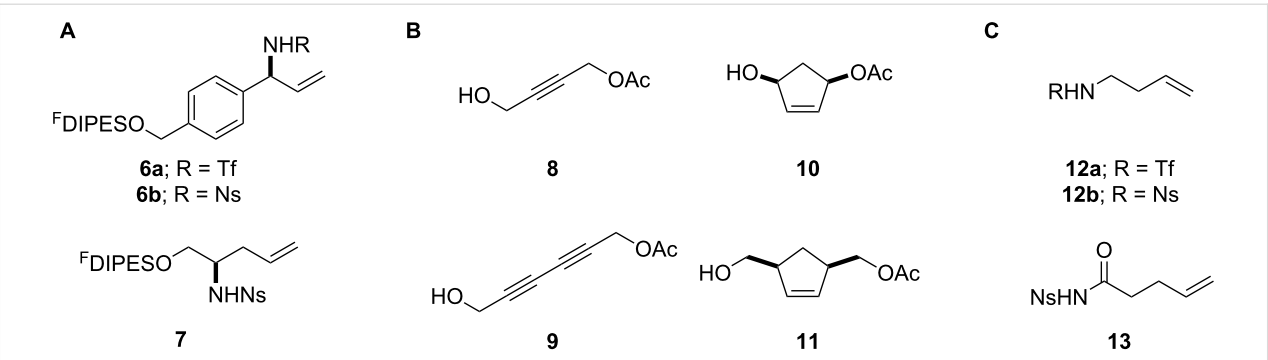
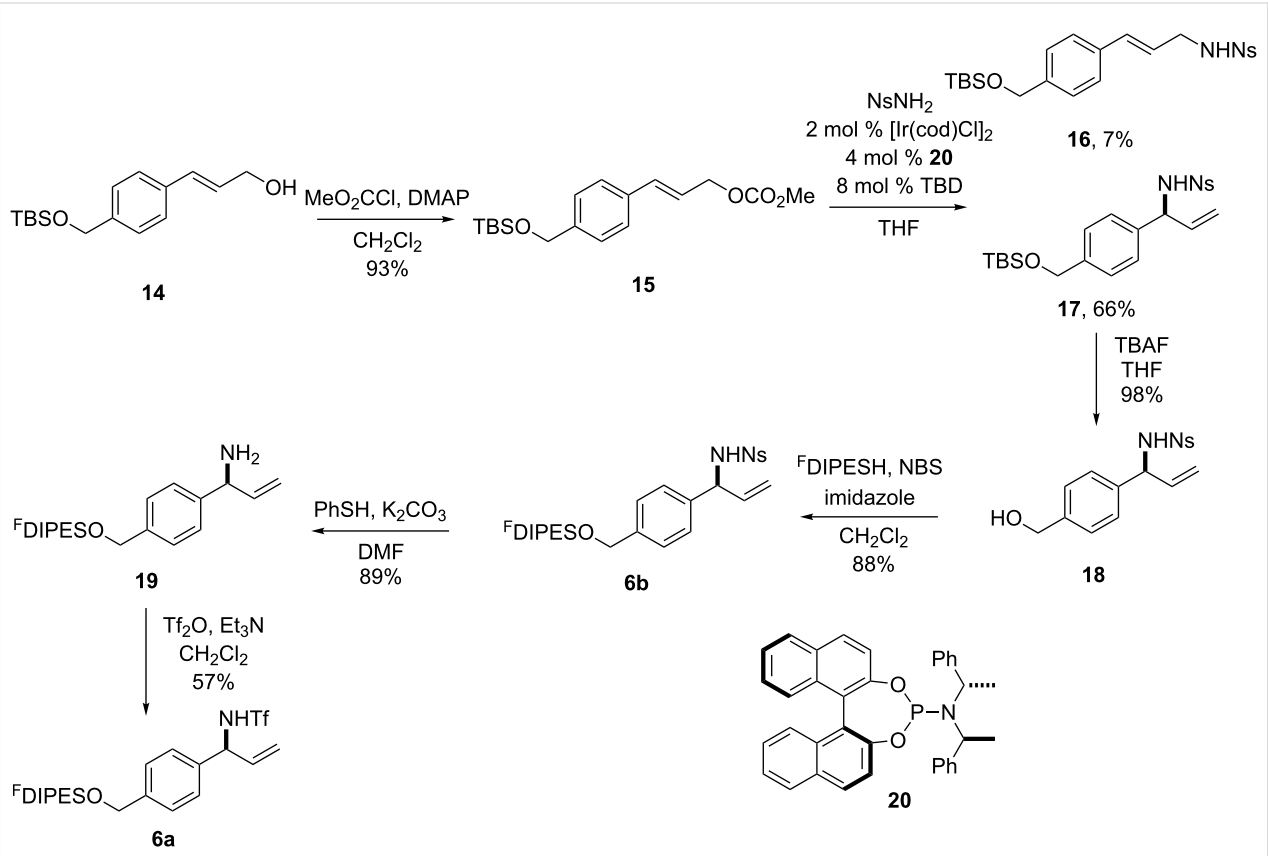


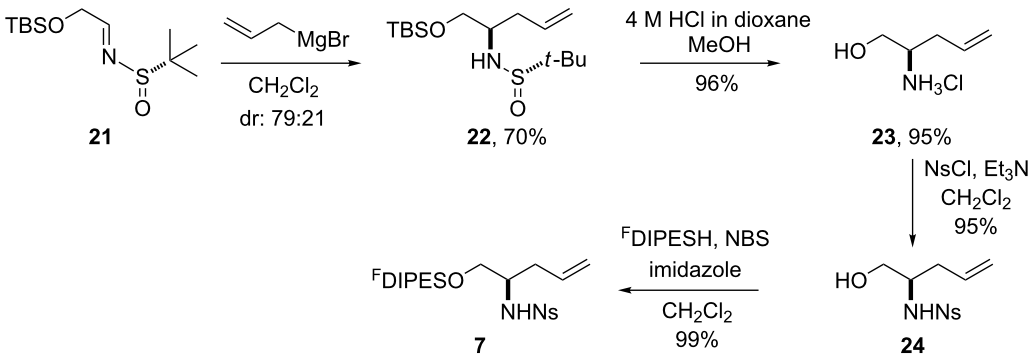
Figure 1: Structures of building blocks used in this study. Panel A: fluorous-tagged initiating building blocks. Panel B: propagating building blocks. Panel C: terminating building blocks.



Scheme 3: Synthesis of the initiating building blocks **6a** and **6b**. TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

was converted into the allylic carbonate **15** by treatment with methyl chloroformate and DMAP. The allylic carbonate **15** underwent efficient asymmetric allylic amination [20] with *o*-nitrophenylsulfonamide as the nucleophile to give the allylic sulfonamide **17** in 66% yield; in addition, the linear product **16** was also obtained in 7% yield. Desilylation of **17** (→ **18**) and reaction with diisopropyl(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl)silyl (^{F}DIPES) bromide, generated in situ from the corresponding silyl hydride, gave the fluorous-tagged building block **6b**. Finally, desulfonylation (→ **19**) and trifluoromethylsulfonylation yielded the alternative initiating building block **6a**.

The initiating building block **7** was prepared from the sulfinimine **21** by adapting a synthesis previously reported by Ellman (Scheme 4) [21]. Treatment of the sulfinimine **21** in dichloromethane with allylmagnesium bromide yielded the corresponding sulfinimides as a 79:21 mixture of diastereoiomers;



Scheme 4: Synthesis of the initiating building block **7**.

following column chromatography, the major diastereomer **22** was obtained in 70% yield, and was converted into the corresponding amino alcohol **23**. The configuration of the amino alcohol **23** was determined by conversion into the corresponding benzamide and comparison with racemic and enantiomerically enriched samples (prepared from the commercially available amino acid). Analysis by chiral HPLC indicated that the amino alcohol **23** had (*R*)-configuration. It was concluded that the sense of diastereoselectivity in the addition **21** → **22** contrasted with that reported by Ellman [21]. However, the sense of diastereoselectivity was the same as that reported for the addition of allylmagnesium bromide in dichloromethane to a similar sulfinimine [22]. The amino alcohol **23** was converted into the corresponding *o*-nitrophenylsulfonamide **24** and, hence, the fluorous-tagged building block **7**.

The propagating building blocks **8**–**11**, and the terminating building block **12b**, were prepared by using established methods [14]. The enantiomeric excess (68% ee) of the hydroxy alcohol **11** was determined by conversion into the corresponding diastereomeric *O*-methyl mandelate esters. The terminating building blocks **12a** and **13** were prepared by straightforward derivatisation of commercially available starting materials (see Supporting Information File 1).

Synthesis of metathesis substrates

Initially, the propagating building blocks **8**–**11** were attached to the fluorous-tagged initiating building blocks (**6a**, **6b** or **7**). In each case, an excess of the propagating building block, DEAD and triphenylphosphine was used. In general, the crude product was directly deacetylated. At each stage, the required fluorous-tagged product was isolated by fluorous-solid-phase extraction (F-SPE), and its purity determined by analysis by 500 MHz ^{1}H NMR spectroscopy. These results are summarised in Table 1.

The metathesis substrates were prepared by subsequent attachment of a terminating building block (**12a**, **12b** or **13**) (see Table 2). In each case, an excess of the terminating building block, DEAD and triphenylphosphine was used; the required

Table 1: Attachment of propagating building blocks to the fluorous-tagged initiating building blocks.

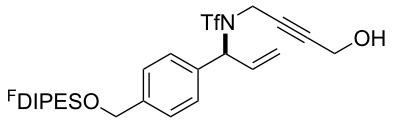
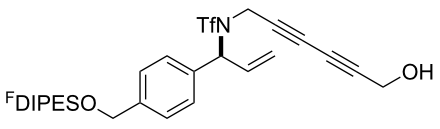
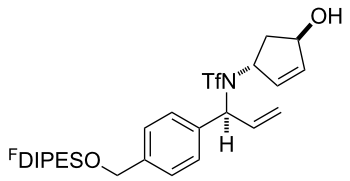
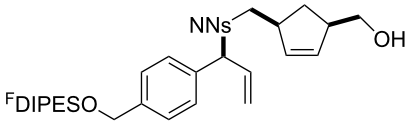
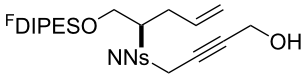
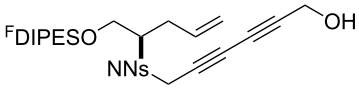
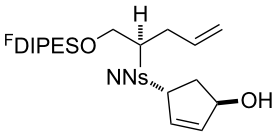
Building blocks	Attachment	Deacetylation[a]	Product
	Method[a] (mass recovery / %) {Purity[b] / %}	Mass recovery / % (Purity[b] / %)	
6a, **8**	A1 (70) {>98}	92 (92)	 **25**
6a, **9**	A2 (97) {92}	87 (93)	 **26**

Table 1: Attachment of propagating building blocks to the fluorous-tagged initiating building blocks. (continued)

6a, **10**[c]	A3 (85) {>98}	87 (98)	 **27**
6b, **11**[d]	A3 (85) {76}	85[e] (72)	 **28**
7, **8**	A3 (92) {91}	94[f]	 **29**
7, **9**	A3 (74[f])	97 (98)	 **30**
7, **10**	A3 (97) {91}	80[f]	 **31**

[a]Methods: A1: Initiating building block (1.0 equiv), propagating building block (4.0 equiv), DEAD (4.0 equiv), PPh_3 (4.0 equiv), CH_2Cl_2, 0 °C → rt then F–SPE; A2: Initiating building block (1.0 equiv), propagating building block (4.0 equiv), DEAD (2.0 equiv), PPh_3 (2.0 equiv), CH_2Cl_2, 0 °C → rt then F–SPE; A3: Initiating building block (1.0 equiv), propagating building block (4.0 equiv), DEAD (2.0 equiv), PPh_3 (2.0 equiv), THF, 0 °C → rt then F–SPE; Deacetylation: 0.025 M NH_3 in MeOH. [b]Determined by analysis of the 500 MHz ^1H NMR spectrum. [c]The building block had >98% ee. [d]The building block had 68% ee. [e]Isolated as a ca. 75:25 mixture of diastereoisomers. [f]Isolated yield of purified product (see Supporting Information File 1).

Table 2: Attachment of propagating building blocks to the fluorous-tagged initiating building blocks.

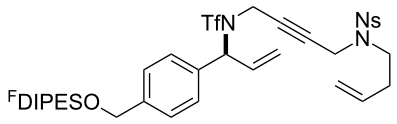
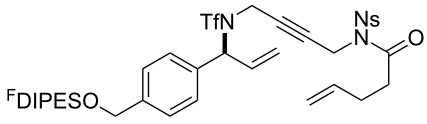
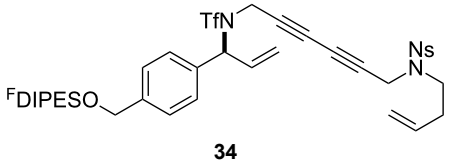
Substrate	Terminating building block	Attachment	Product
		Method[a] (mass recovery / %) {Purity[b] / %}	
25	**12b**	A4 (89) {83}	 **32**
25	**13**	A4 (89) {86}	 **33**
26	**12b**	A4 (76) {93}]	 **34**

Table 2: Attachment of propagating building blocks to the fluorous-tagged initiating building blocks. (continued)

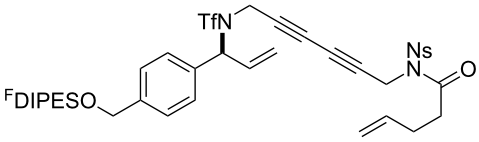
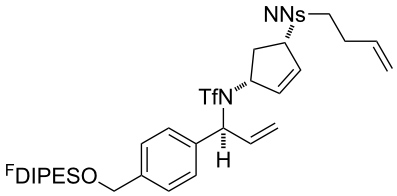
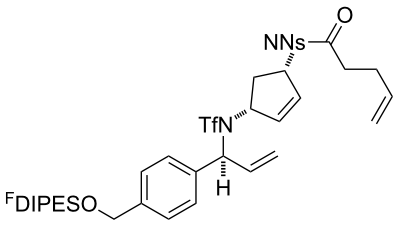
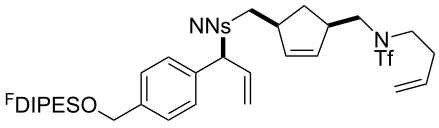
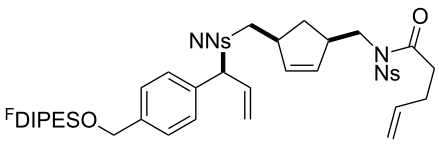
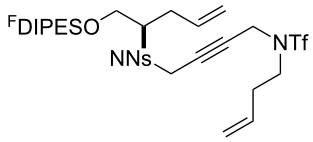
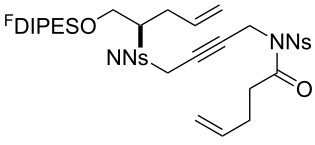
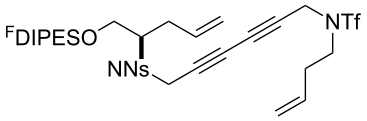
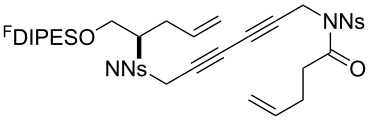
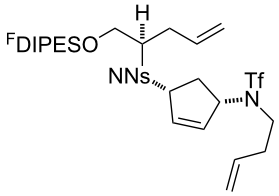
26	**13**	A4 (75) {97}	 **35**
27	**12b**	A5 (62[c])	 **36**
27	**13**	A5 (54[c])	 **37**
28[d]	**12a**	A5 (86[c,e])	 **38**
28[d]	**13**	A5 (77[c,e])	 **39**
29	**12a**	A6 (86[c])	 **40**
29	**13**	A6 (77[c])	 **41**
30	**12a**	A6 (92[c])	 **42**
30	**13**	A6 (55[c])	 **43**

Table 2: Attachment of propagating building blocks to the fluorous-tagged initiating building blocks. (continued)

31	**12a**	A6 (85[c])	 **44**

[a]Methods: A4: Substrate (1.0 equiv), propagating building block (4.0 equiv), DEAD (2.0 equiv), PPh_3 (2.0 equiv), CH_2Cl_2, 0 °C → rt then F-SPE; A5: Substrate (1.0 equiv), propagating building block (4.0 equiv), DEAD (4.0 equiv), PPh_3 (4.0 equiv), THF, 0 °C → rt then F-SPE; A6: Substrate (1.0 equiv), propagating building block (4.0 equiv), DEAD (2.0 equiv), PPh_3 (2.0 equiv), THF, 0 °C → rt then F-SPE. [b]Determined by analysis of the 500 MHz ^{1}H NMR spectrum. [c]Isolated yield of purified product. [d]The starting material was a ca. 75:25 mixture of diastereoisomers. [e]Isolated as a ca. 75:25 mixture of diastereomers.

fluorous-tagged product was isolated by solid-fluorous phase extraction (F-SPE), and its purity was determined by analysis by 500 MHz ^{1}H NMR spectroscopy.

Metathesis cascade reactions

The scaffolds of the metathesis substrates were "reprogrammed" by treatment with Hoveyda–Grubbs second-generation catalyst in either dichloromethane or *tert*-butyl methyl ether [23] (TBME). Many of the metathesis reactions were rather sluggish, and the catalyst was added portionwise until the reactions were judged to be complete by TLC analysis. After removal [24] of the catalyst by using tris(hydroxymethyl)phosphine, the metathesis products were generally purified by flash column chromatography. Finally, the *o*-nitrophenylsulfonyl groups were removed from the products. The results are summarised in Table 3.

In general, the metathesis reactions proceeded smoothly to give the expected metathesis cascade products. In the case of **39**, however, the cyclopentene did not participate in the metathesis

Table 3: Application of cascade metathesis reactions in the synthesis of diverse scaffolds and subsequent desulfonylation.

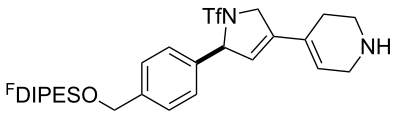
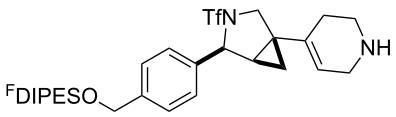
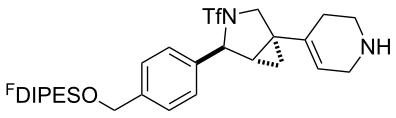
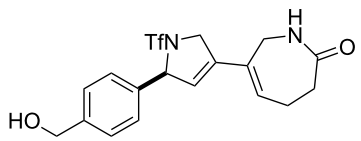
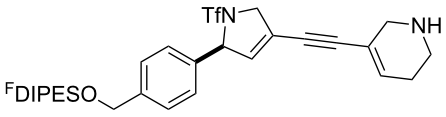
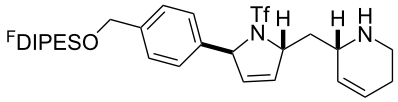
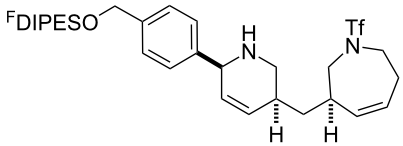
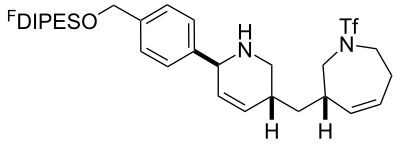
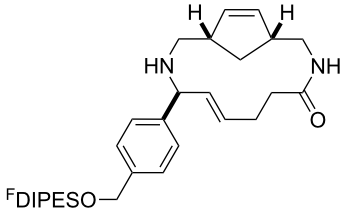
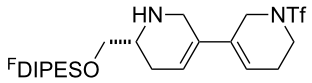
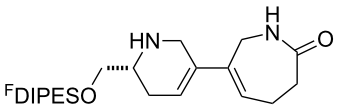
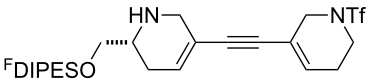
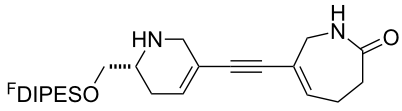
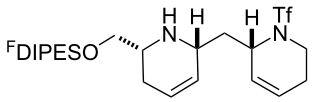
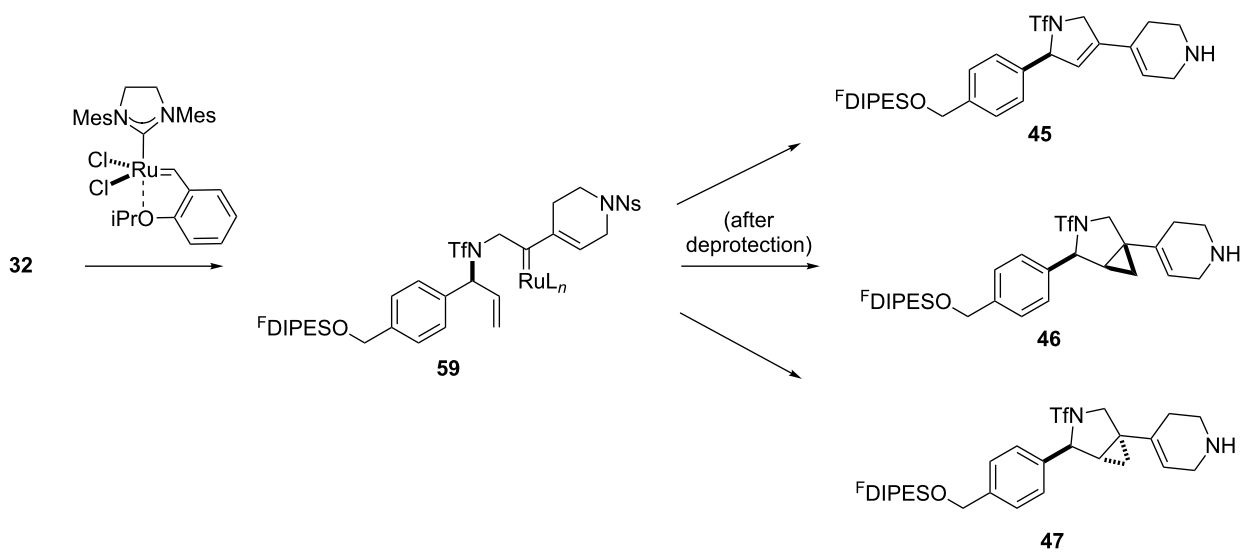
Substrate	Method[a] (mol %; time)	Product	Yield / %
32	B1 (5 + 2.5; 3 d) then C1	 **45**	**45**, 37%[b]
		 **46**	**46**, 11%[b]
		 **47**	**47**, 5%[b]
33	B1 (2 × 5; 4 d) then C1 then D	 **48**	43%[b]
34	B1 (5 + 5 + 2.5; 10 d) then C1	 **49**	49%[b] (86%[c])

Table 3: Application of cascade metathesis reactions in the synthesis of diverse scaffolds and subsequent desulfonylation. (continued)

36	B1 (4 × 5; 20 d) then C1	 **50**	77 then 81 (93%[c])
38[d]	B1 (3 × 5; 14 d) then C1	 **51**	63 then 85 (**51**)
		 **52**	29 then 94 (**52**)
39	B1 (4 × 5; 20 d) then C2	 **53**	8%[b]
40	B2 (5; 24 h) then C1	 **54**	93 then 96 (87%[c])
41	B2 (5; 24 h) then C2	 **55**	93 then 80 (93%[c])
42	B2 (3 × 5; 7 d) then C1	 **56**	76 then 92 (92%[c])
43	B2 (2 × 5; 3 d) then C2	 **57**	54 then 77 (86%[c])
44	B2 (5; 24 h) then C1	 **58**	53 then 99 (98%[c])

[a]Methods: B1: Hoveyda–Grubbs second-generation catalyst, CH_2Cl_2, 50 °C then Et_3N (86 equiv), $P(CH_2OH)_3$ (86 equiv) then silica; B2: Hoveyda–Grubbs second-generation catalyst, MTBE, 50 °C then Et_3N (86 equiv), $P(CH_2OH)_3$ (86 equiv) then silica; C1: PhSH (1.2 equiv), K_2CO_3 (3.0 equiv), DMF; C2: PhSH (2.4 equiv), K_2CO_3 (6.0 equiv), DMF; E: aq HF, MeCN–CH_2Cl_2. [b]Yield over more than one step. [c]Purity of the product determined by 500 MHz ^{1}H NMR spectroscopy. [d]The starting material was a ca. 75:25 mixture of diastereoisomers.

reaction, and the bridged macrocycle **53** was obtained in low yield. We have previously observed the formation of macrocyclic metathesis products in similar metathesis cascade reactions [14]. The formation of the cyclopropanes **46** and **47** as byproducts in the metathesis cascade reaction of **32** was remarkable [25]. Presumably, in this case, the metathesis cascade leads to the generation of the intermediate **59** (Scheme 5); the intermediate could then react to conclude the



Scheme 5: Fate of the metathesis reaction of the substrate **32**.

metathesis cascade (to give **45** after deprotection), or cyclopropanate [25] the terminal alkene (to give **46** or **47** after deprotection) (Scheme 5).

Finally, a selection of fluorous-tagged products was derivatised (typically on a 50 μmol scale) to yield a range of amides and ureas (Table 4). The fluorous tag facilitated the purification of

Table 4: Derivatisation and deprotection of final products.

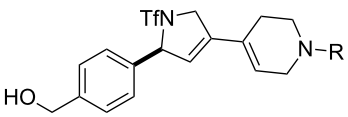
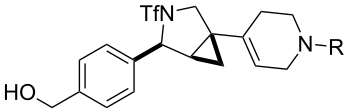
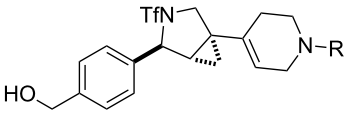
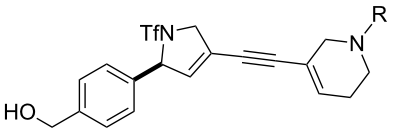
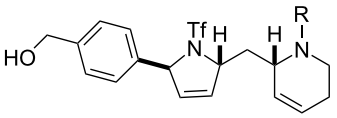
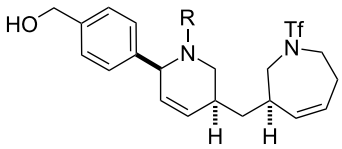
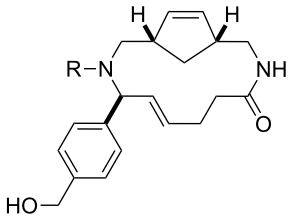
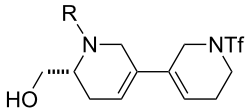
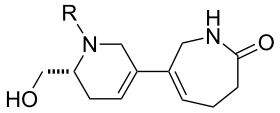
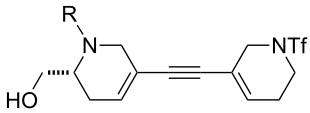
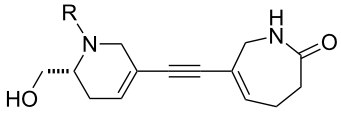
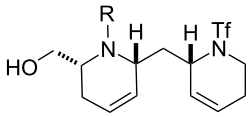
Substrate (purity[a] / %)	Product[b]		Method[c]	Yield / %
45		**60a**	D	51
		60b	E1 then D	81 then 60
		60c	E2 then D	67 then 98
		60d	E3 then D	94 then 81
46		**61b**	E1 then D	39 then 70
47		**62b**	E1 then D	43 then 63
49 (86)		**63a**	D	83
		63b	E1 then D	32 then 64
		63c	E2 then D	83 then 58
		63d	E3 then D	84 then 79
50 (93)		**64a**	D	87
		64b	E1 then D	29[d]
		64c	E2 then D	43[d]
		64d	E3 then D	34[d]

Table 4: Derivatisation and deprotection of final products. (continued)

51 (85)		**65a**	D	70
		65b	E1 then D	40[d]
		65c	E2 then D	82[d]
		65d	E3 then D	74[d]
53		**66a**	D	52
54 (87)		**67a**	D	91
		67b	E4 then D	77[d]
		67c	E2 then D	83[d]
		67d	E3 then D	42[d]
55 (93)		**68a**	D	94
		68c	E2 then D	67[d]
		68d	E3 then D	40[d]
56 (92)		**69a**	D	91
		69b	E4 then D	67[d]
		69c	E2 then D	67[d]
57 (86)		**70a**	D	47
		70c	E2 then D	59[d]
58 (98)		**71a**	D	91
		71b	E4 then D	64[d]
		71c	E2 then D	53[d]
		71d	E3 then D	29[d]

[a]Determined by analysis of the product by 500 MHz ^{1}H NMR spectroscopy. [b]The suffix refers to the identity of the R substituent: a, R = H; b, R = isoxazole-5-carbonyl; c, R = pyridine-3-carbonylamino; d, R = morpholine-4-carbonyl; [c]Methods: D: aq HF, MeCN–CH_2Cl_2; E1: isoxazole-5-carbonyl chloride (2.0 equiv), Et_3N (3.0 equiv), DMAP (1.0 equiv), CH_2Cl_2; E2: pyridine-3-isocyanate (2.0 equiv), Et_3N (3.0 equiv), DMAP (1.0 equiv), CH_2Cl_2; E3: morpholine-4-carbonyl chloride (2.0 equiv), Et_3N (3.0 equiv), DMAP (1.0 equiv), CH_2Cl_2; E4: isoxazole-5-carbonyl chloride (2.0 equiv), pyridine; [d]Yield over two steps.

the derivitised products by F-SPE. The final products **60**–**71** (Table 4) were obtained after removal of the fluorous tag by desilylation.

Conclusion

Metathesis is an extremely powerful reaction for diversity-oriented synthesis. It was demonstrated that metathesis substrates could be assembled efficiently from triplets of building blocks. Thereafter, metathesis cascades yielded a diverse range of molecular scaffolds. The diversity of the products was increased through variation of all three of the building blocks used: the initiating, the propagating, and the terminating building block.

The overall approach was facilitated by fluorous tagging of the initiating building block, allowing easy purification (by F-SPE) of synthetic intermediates and metathesis products. The presence of a fluorous tag also facilitated the purification of the

functionalised products. Evaluation of the biological activity of the final products will be reported in due course.

Supporting Information

Supporting Information File 1

Experimental and compound characterisation.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-88-S1.pdf]

Acknowledgements

We thank the European Commission for a Marie Curie International Incoming Fellowship (to S.K.M.) and the EPSRC for additional funding.

References

1. Paolini, G. V.; Shapland, R. H. B.; van Hoorn, W. P.; Mason, J. S.; Hopkins, A. L. *Nat. Biotechnol.* **2006,** *24,* 805–815. doi:10.1038/nbt1228
2. Wetzel, S.; Klein, K.; Renner, S.; Rauh, D.; Oprea, T. I.; Mutzel, P.; Waldmann, H. *Nat. Chem. Biol.* **2009,** *5,* 581–583. doi:10.1038/nchembio.187
3. Renner, S.; van Otterlo, W. A. L.; Dominguez Seoane, M.; Möcklinghoff, S.; Hofmann, B.; Wetzel, S.; Schuffenhauer, A.; Ertl, P.; Oprea, T. I.; Steinhilber, D.; Brunsveld, L.; Rauh, D.; Waldmann, H. *Nat. Chem. Biol.* **2009,** *5,* 585–592. doi:10.1038/nchembio.188
4. Hu, Y.; Wassermann, A. M.; Lounkine, E.; Bajorath, J. *J. Med. Chem.* **2010,** *53,* 752–758. doi:10.1021/jm9014229
5. Wetzel, S.; Bon, R. S.; Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011,** *50,* 10800–10826. doi:10.1002/anie.201007004
6. Evans, B. E.; Rittle, K. E.; Bock, M. G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P. *J. Med. Chem.* **1988,** *31,* 2235–2246. doi:10.1021/jm00120a002
7. Shelat, A. A.; Guy, R. K. *Nat. Chem. Biol.* **2007,** *3,* 442–446. doi:10.1038/nchembio0807-442
8. Hu, Y.; Stumpfe, D.; Bajorath, J. *J. Chem. Inf. Model.* **2011,** *51,* 1742–1753. doi:10.1021/ci200179y
9. Lipkus, A. H.; Yuan, Q.; Lucas, K. A.; Funk, S. A.; Bartelt, W. F., III; Schenck, R. J.; Trippe, A. J. *J. Org. Chem.* **2008,** *73,* 4443–4451. doi:10.1021/jo8001276
10. Krier, M.; Bret, G.; Rognan, D. *J. Chem. Inf. Model.* **2006,** *46,* 512–524. doi:10.1021/ci050352v
11. O' Connor, C. J.; Beckmann, H. S. G.; Spring, D. R. *Chem. Soc. Rev.* **2012,** *41,* 4444–4456. doi:10.1039/c2cs35023h
    See for a recent review of diversity-oriented synthesis.
12. MacLellan, P.; Nelson, A. *Chem. Commun.* **2013,** *49,* 2383–2393. doi:10.1039/c2cc38184b
    See for a recent review of diversity-oriented synthesis.
13. Nielsen, T. E.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2008,** *47,* 48–56. doi:10.1002/anie.200703073
    See for a recent review of diversity-oriented synthesis.
14. Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem., Int. Ed.* **2009,** *48,* 104–109. doi:10.1002/anie.200804486
15. Spandl, R. J.; Rudyk, H.; Spring, D. R. *Chem. Commun.* **2008,** 3001–3003. doi:10.1039/b807278g
    See for other diversity-oriented approaches that exploit metathesis chemistry.
16. Spiegel, D. A.; Schroeder, F. C.; Duvall, J. R.; Schreiber, S. L. *J. Am. Chem. Soc.* **2006,** *128,* 14766–14767. doi:10.1021/ja065724a
    See for other diversity-oriented approaches that exploit metathesis chemistry.
17. O'Leary-Steele, C.; Pedersen, P. J.; James, T.; Lanyon-Hogg, T.; Leach, S.; Hayes, J.; Nelson, A. *Chem.–Eur. J.* **2010,** *16,* 9563–9571. doi:10.1002/chem.201000707
    See for other diversity-oriented approaches that exploit metathesis chemistry.
18. Gladysz, A.; Curran, D. P.; Horváth, I. T. *Handbook of Fluorous Chemistry;* Wiley: New York, 2004. doi:10.1002/3527603905
19. Wuts, P. G. M.; Ashford, S. W.; Anderson, A. M.; Atkins, J. R. *Org. Lett.* **2003,** *5,* 1483–1485. doi:10.1021/ol034274d
20. Weinhofen, R.; Tverskoy, O.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006,** *45,* 5546–5549. doi:10.1002/anie.200601472
21. Rech, J. C.; Yato, M.; Duckett, D.; Ember, B.; LoGrosso, P. V.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007,** *129,* 490–491. doi:10.1021/ja0676004
22. Koriyama, Y.; Nozawa, A.; Hayakawa, R.; Shimizu, M. *Tetrahedron* **2002,** *58,* 9621–9628. doi:10.1016/S0040-4020(02)01250-4
23. Kuhn, K. M.; Champagne, T. M.; Hong, S. H.; Wei, W.-H.; Nickel, A.; Lee, C. W.; Virgil, S. C.; Grubbs, R. H.; Pederson, R. L. *Org. Lett.* **2010,** *12,* 984–987. doi:10.1021/ol9029808
24. Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999,** *40,* 4137–4140. doi:10.1016/S0040-4039(99)00726-1
25. Peppers, B. P.; Diver, S. T. *J. Am. Chem. Soc.* **2004,** *126,* 9524–9525. doi:10.1021/ja049079o
    See for a reaction with a similar outcome.

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doi:10.3762/bjoc.9.88

Beilstein Journal of Organic Chemistry

Aqueous reductive amination using a dendritic metal catalyst in a dialysis bag

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Full Research Paper

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Keywords:
aqueous reductive amination; cascade catalysis; compartmentalization; dendritic catalysts; dialysis

Beilstein J. Org. Chem. **2013,** *9,* 960–965.
doi:10.3762/bjoc.9.110

Received: 16 January 2013
Accepted: 02 April 2013
Published: 17 May 2013

This article is part of the Thematic Series "Creating complexity".

Guest Editor: D. Craig

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Abstract

Water-soluble dendritic iridium catalysts were synthesized by attaching a reactive metal complex to DAB-Am dendrimers via an adapted asymmetric bipyridine ligand. These dendritic catalysts were applied in the aqueous reductive amination of valine while contained in a dialysis bag. Comparable conversions were observed as for the noncompartmentalized counterparts, albeit with somewhat longer reaction times. These results clearly show that the encapsulated catalyst system is suitable to successfully drive a complex reaction mixture with various equilibrium reactions to completion.

Introduction

Cascade catalysis, a bioinspired strategy to conduct multiple consecutive catalytic steps in one pot, is attracting the attention of an increasing number of chemists [1-9]. Advantages of cascade processes include a reduction in the number of workup and purification steps, but also the fact that unstable intermediates can be immediately further reacted, or that unfavorable equilibria can be driven to the desired product. An obvious drawback of such a strategy may be the often intrinsic incompatibility of the catalysts and/or enzymes involved, which will lead to incomplete conversions. Incompatible catalysts can be physically separated in various ways, e.g., by applying biphasic reaction conditions [10], membrane reactors [11] or sol–gels [12]. Another way to circumvent incompatibility problems is to achieve compartmentalization by attaching the actual catalyst to larger particles and contain them in an environment that is accessible for the substrate molecules, but impermeable to the macromolecular catalyst. Such “pseudo-homogeneous catalysts” can, amongst other methods, be created by immobilizing soluble metal complexes on nanoparticles, either nonmagnetic [13,14] or magnetic ones [15,16], which can be contained in semipermeable membranes and hence be physically separated from other catalysts. Nanoparticles, however, may be unstable, and stabilizers, which may affect the catalyst behavior, are often necessary to prevent aggregation [17,18].

Dendrimers can also be used as scaffolds for creating macromolecular catalysts [19], which generally show only a limited loss in activity compared to their “nonexpanded” congeners

[20,21]. Such dendritic catalysts are kept in a compartment due to the macromolecular nature of these polymers, and have been utilized for purification purposes after the reaction [22] and in continuous-flow reactors during the reaction [23]. Dendritic catalysts have also been applied while enclosed in commercially available dialysis bags [24-26]. The latter examples, however, were conducted in organic, environmentally unfriendly solvents. As part of a research program, in which we focus on conducting cascade reactions catalyzed by the joint action of organometallic catalysts and enzymes, we studied possibilities to compartmentalize metal catalysts in an aqueous environment. Inspired by the aforementioned dendrimer examples, we decided to design a metallodendrimer that would show catalytic activity in a cascade process while compartmentalized under aqueous conditions. To this end, an iridium catalyst was selected that was known to be suitable for reductive amination in an aqueous environment. We showed that by applying a dendritic analogue in a dialysis device we were able to successfully drive the aqueous reductive amination of an unprotected amino acid to completion, despite the unfavorable equilibria for iminium ion formation in water. Since the dendrimer remains inside the dialysis bag due to its size, the catalyst can also be easily removed from the reaction mixture after the reaction has been completed (Figure 1).

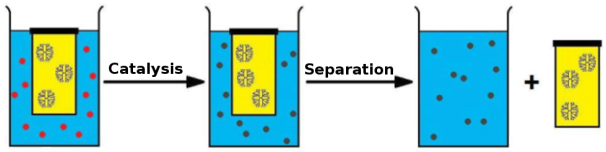
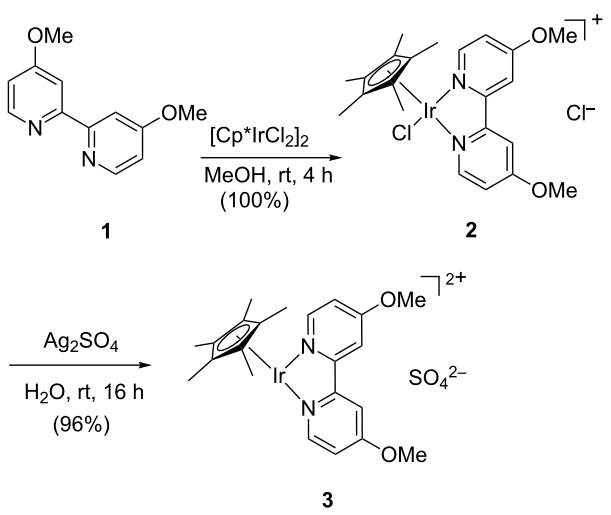


Figure 1: General approach for the use of dendritic catalysts in a dialysis bag.

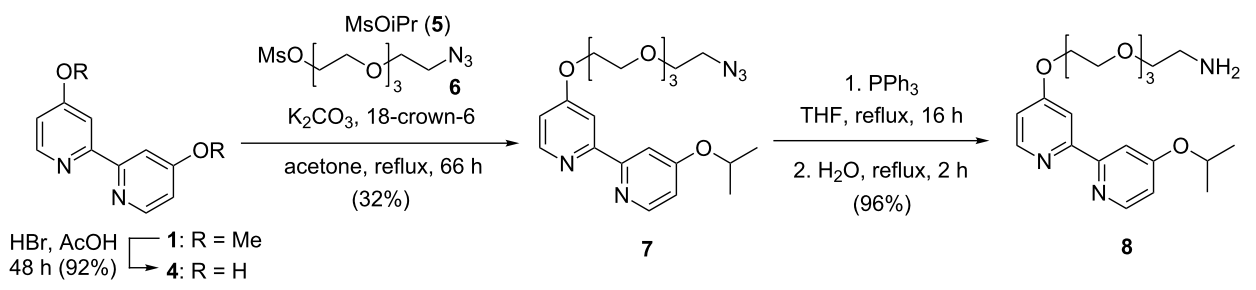
Results and Discussion

To study this approach, we selected iridium catalyst **3**, which has been previously successfully applied in aqueous reductive aminations [27]. The catalyst is based on related iridium complexes that are capable of performing transfer hydrogenation reactions, as has been documented by Fukuzumi et al. [28-30]. The water-soluble iridium catalyst **3** was prepared according to a procedure of Francis in high yield (Scheme 1) [27]. The starting material is $[Cp^*IrCl_2]_2$ which readily coordinates to bipyridine **1** to form iridium complex **2**. Subsequent abstraction of the chloride ion in the presence of Ag_2SO_4 afforded the active species **3** in excellent yield.



Scheme 1: Synthesis of water-soluble iridium catalyst **3**.

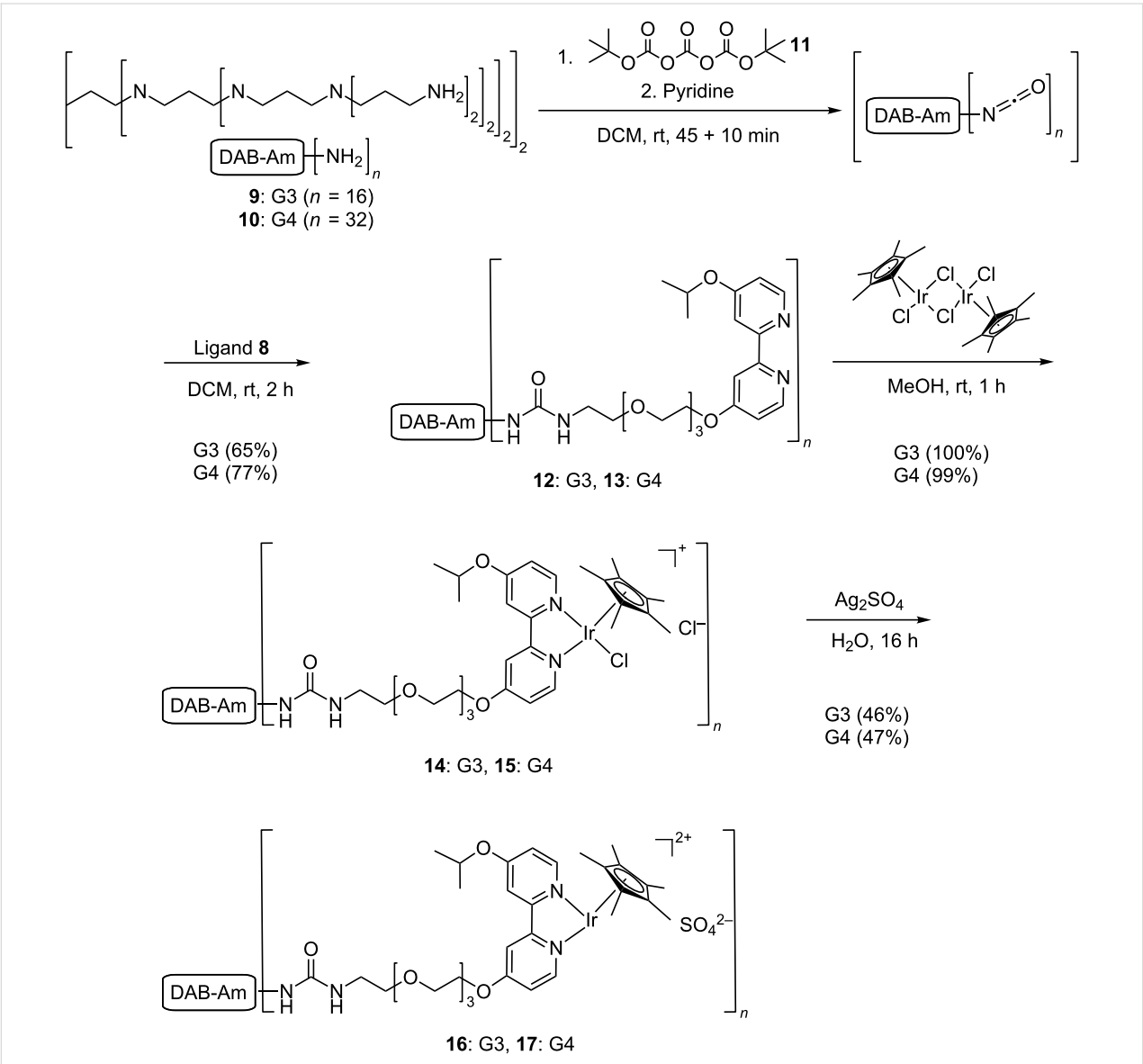
To attach catalyst **3** to a dendrimer, an amine functionality was introduced on the bipyridine ligand in three steps (Scheme 2). The first step involved demethylation of 4,4'-dimethoxy-2,2'-bipyridine (**1**) in 92% yield [31]. Monofunctionalization of the ligand will lead to the highest possible catalyst loading per dendrimer and also prevents cross-linking between dendrimers. Therefore, a 1:1 mixture of isopropyl mesylate (**5**) and tetraethylene glycol azido mesylate **6** was reacted with diol **4**, affording a mixture of the desired asymmetric bipyridine **7** and the two corresponding symmetric bipyridines. This mixture was separated by column chromatography resulting in 32% isolated yield of pure azide **7**. Subsequent Staudinger reduction and



Scheme 2: Synthesis of the desymmetrized bipyridine **8**.

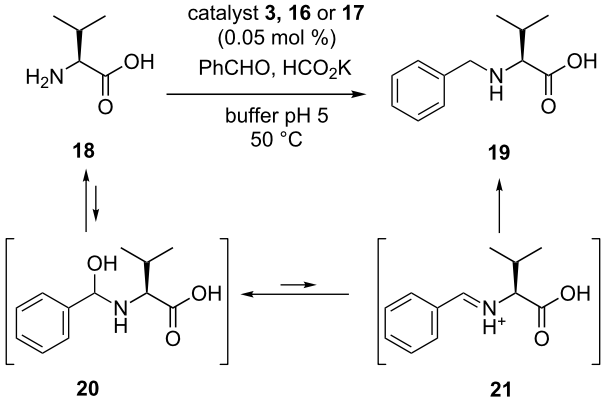
purification by acid–base extraction afforded the amine-containing ligand **8** in 96% yield.

Ligand **8** was connected to water-soluble DAB-Am dendrimers via a protocol described by Peerlings and Meijer (Scheme 3) [32]. First, a multi-isocyanate was prepared in situ by using di-*tert*-butyl tricarbonate (**11**). After the addition of pyridine to quench the excess of tricarbonate **11**, ligand **8** was added, leading to the formation of dendrimers **12** and **13** in good yields. The products were completely characterized by ^{1}H and ^{13}C NMR, thereby confirming that all amines had been reacted. Furthermore, IR spectroscopy showed signals at 1580 and 1640 cm^{-1} derived from the newly formed urea functionalities. The next reaction, coordination of iridium to the dendritic ligands in methanol, afforded the corresponding iridium complexes **14** and **15** in quantitative yield. In the final step, the complex was converted into the water-soluble dendritic catalysts **16** and **17** by overnight treatment with Ag_2SO_4 in 46 and 47% yield, respectively. During the removal of AgCl by centrifugation, some dendritic material was probably lost in the pellet, explaining the rather moderate yield of the final step. Dendrimers **16** and **17** were purified by aqueous dialysis. Unfortunately, the NMR spectra of dendrimers **14**–**17** could not be completely resolved due to the broad peaks observed as well as the low intensity of the resonances in the ^{13}C NMR measurements. However, each transformation was accompanied by a clear and complete change in chemical shift of the aromatic bipyridine peaks.



Scheme 3: Attachment of the adapted ligand **8** to the dendrimers via a multi-isocyanate coupling, followed by iridium coordination.

The reactivity of macromolecular catalysts **16** and **17** was examined in the aqueous reductive amination of valine (**18**, Scheme 4). This reaction is in fact a multistep process, in which the equilibria unfavorable in water for the formation of hemiaminal **20** and iminium ion **21** are compensated by the iridium-catalyzed reduction to form the benzylated amino acid **19**. Iridium complexes **3**, **16** and **17** were capable of reducing the intermediate imine in the presence of HCO_2K, which acted as the hydride source. The reaction was monitored by taking aliquots of the reaction mixture and by HPLC analysis. An excess of benzaldehyde was used, because it was also partially reduced to benzyl alcohol in a side reaction. The optimal pH appeared to be 5, comparable with a similar catalyst published by Fukuzumi [29,30].



Scheme 4: Catalytic reductive amination of valine (**18**) via unfavorable equilibrium reactions in water.

In the presence of the nondendritic catalyst **3**, formation of the N-alkylated amino acid **19** proceeded considerably faster than with the dendrimer-supported reductive aminations (Figure 2). However, after longer reaction times the yields were only slightly lower for the dendritic catalysts.

In order to study the same reaction with the dendritic catalysts **16** and **17** in a dialysis bag, a different setup was used based on commercially available materials. This consisted of a cup which could be closed and contained a dialysis membrane with a molecular-weight cut-off value of 2,000. We assumed that all reaction components except the catalyst would be able to pass through the membrane, turning the dialysis tube into a compartment suitable for catalysis. To verify this hypothesis, catalyst **16** was injected in the dialysis device and the reductive amination of valine was performed under otherwise identical conditions (Figure 3). HPLC analysis showed that the reaction rate and conversion were fairly similar to the noncompartmentalized aqueous reaction (Figure 4), demonstrating that mass transport

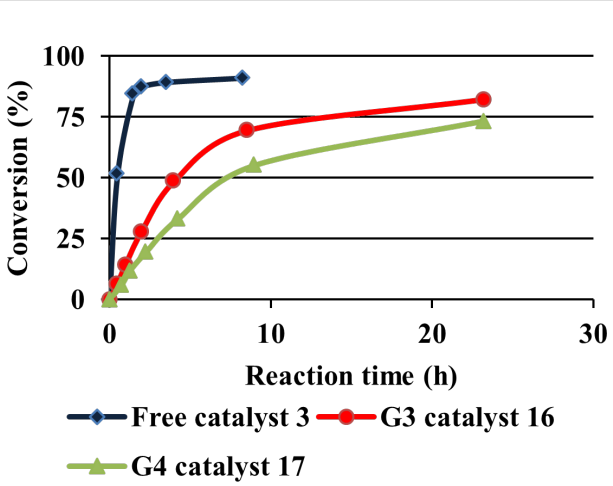


Figure 2: Formation of **19** catalyzed by the three iridium catalysts.

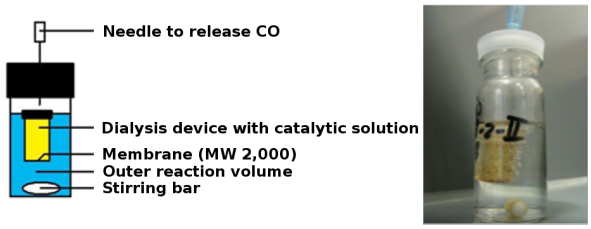


Figure 3: Reaction setup to perform compartmentalized catalysis.

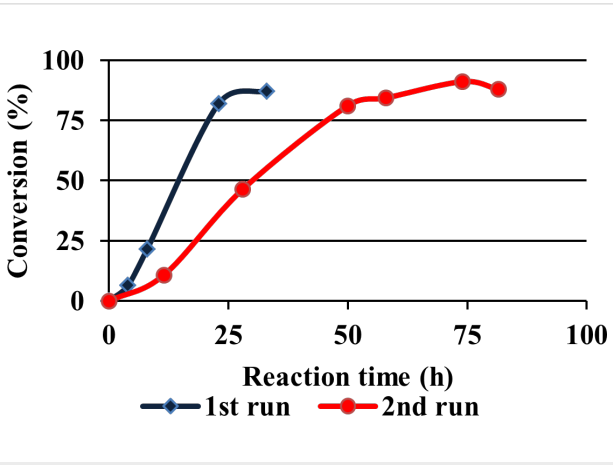


Figure 4: G3 catalyst **16** activity in dialysis device.

of the small substrate and product molecules through the membrane is hardly rate-limiting.

After the appropriate reaction time, the dialysis tube was removed from the reaction mixture, dialyzed in buffer to remove all the other reaction contents and added to a fresh reac-

tion mixture. In the second run, the recovered G3 dendrimer **16** still showed catalytic activity (Figure 4), albeit that a distinct decrease in reaction rate was observed. This phenomenon may be attributed to leakage of the catalyst through the dialysis membrane.

Similar experiments were conducted with the G4 dendrimer **17** (Figure 5). The figure shows that the reaction rate is somewhat lower, but that the conversion is fairly similar to that for the free dendritic catalyst. In contrast to the smaller G3 dendrimer **16**, however, the G4 catalyst **17** was equally active in a second run, clearly demonstrating the viability of containment of the catalyst in the dialysis bag. This result also suggests that the immobilized catalyst should be applicable in cascade reactions with reagents that are normally incompatible with the iridium complex. Since our process was successfully conducted in water, combinations with enzymes should also be possible.

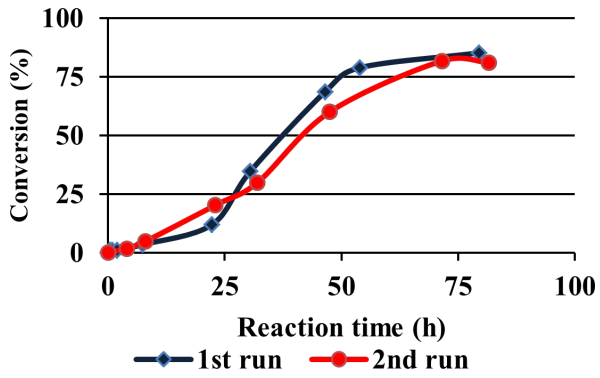


Figure 5: G4 catalyst **17** activity in subsequent runs.

Conclusion

Dendritic catalysts were successfully synthesized by connecting Ir-bipyridine complexes to third and fourth generation DAB-Am dendrimers. The dendritic catalysts showed good activity in the multistep reductive amination of a free amino acid in water, albeit that prolonged reaction times as compared to the free catalyst were required. Due to the size of the macromolecular catalysts, it was possible to employ them in a dialysis device for conducting reductive aminations of free amino acids in water. The G4 catalyst showed the same reaction rate in a second run, which validates the concept of maintaining the macromolecular catalyst in the compartment. The work described here could be more widely applicable for compartmentalization of catalytic systems in aqueous media, where the iridium system may be used either in combination with other catalysts, or with enzymes. These topics are currently under investigation in our group.

Supporting Information

Supporting Information File 1

Experimental details and spectroscopic data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-110-S1.pdf]

Supporting Information File 2

Spectra of compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-110-S2.pdf]

Acknowledgements

The National Research School Combination Catalysis (NRSC-Catalysis) is gratefully acknowledged for financial support.

References

1. Bruggink, A.; Schoevaart, R.; Kieboom, T. *Org. Process Res. Dev.* **2003,** *7,* 622–640. doi:10.1021/op0340311
2. Tietze, L. F. *Chem. Rev.* **1996,** *96,* 115–136. doi:10.1021/cr950027e
3. Zhou, J. *Chem.–Asian J.* **2010,** *5,* 422–434. doi:10.1002/asia.200900458
4. Ricca, E.; Brucher, B.; Schrittwieser, J. H. *Adv. Synth. Catal.* **2011,** *353,* 2239–2262. doi:10.1002/adsc.201100256
5. Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006,** *441,* 861–863. doi:10.1038/nature04820
6. Rueping, M.; Lin, M.-Y. *Chem.–Eur. J.* **2010,** *16,* 4169–4172. doi:10.1002/chem.201000203
7. Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007,** *46,* 1101–1104. doi:10.1002/anie.200604479
8. Babich, L.; van Hemert, L. J. C.; Bury, A.; Hartog, A. F.; Falcicchio, P.; van der Oost, J.; van Herk, T.; Wever, R.; Rutjes, F. P. J. T. *Green Chem.* **2011,** *13,* 2895–2900. doi:10.1039/c1gc15429j
9. Babich, L.; Hartog, A. F.; van Hemert, L. J. C.; Rutjes, F. P. J. T.; Wever, R. *ChemSusChem* **2012,** *5,* 2348–2353. doi:10.1002/cssc.201200468
10. Karmee, S. K.; Roosen, C.; Kohlmann, C.; Lütz, S.; Greiner, L.; Leitner, W. *Green Chem.* **2009,** *11,* 1052–1055. doi:10.1039/b820606f
11. Cantarella, L.; Gallifuoco, A.; Malandra, A.; Martínková, L.; Spera, A.; Cantarella, M. *Enzyme Microb. Technol.* **2011,** *48,* 345–350. doi:10.1016/j.enzmictec.2010.12.010
12. Gelman, F.; Blum, J.; Avnir, D. *J. Am. Chem. Soc.* **2000,** *122,* 11999–12000. doi:10.1021/ja003029b
13. Astruc, D.; Lu, F.; Aranzaes, J. R. *Angew. Chem., Int. Ed.* **2005,** *44,* 7852–7872. doi:10.1002/anie.200500766
14. Wang, S.; Zhang, M.; Zhong, L.; Zhang, W. *J. Mol. Catal. A: Chem.* **2010,** *327,* 92–100. doi:10.1016/j.molcata.2010.05.018
15. Jin, M.-J.; Lee, D.-H. *Angew. Chem., Int. Ed.* **2010,** *49,* 1119–1122. doi:10.1002/anie.200905626
16. Stevens, P. D.; Li, G.; Fan, J.; Yenb, M.; Gao, Y. *Chem. Commun.* **2005,** 4435–4437. doi:10.1039/b505424a
17. Hayek, K.; Kramer, R.; Paál, Z. *Appl. Catal., A* **1997,** *162,* 1–15. doi:10.1016/S0926-860X(97)00243-3

18. Schmidt, E.; Kleist, W.; Krumeich, F.; Mallat, T.; Baiker, A. *Chem.–Eur. J.* **2010,** *16,* 2181–2192. doi:10.1002/chem.200902517
19. Grayson, S. M.; Fréchet, J. M. J. *Chem. Rev.* **2001,** *101,* 3819–3867. doi:10.1021/cr990116h
20. Méry, D.; Astruc, D. *Coord. Chem. Rev.* **2006,** *250,* 1965–1979. doi:10.1016/j.ccr.2005.11.012
21. Knapen, J. W. J.; van der Made, A. W.; de Wilde, J. C.; van Leeuwen, P. W. N. M.; Wijkens, P.; Grove, D. M.; van Koten, G. *Nature* **1994,** *372,* 659–663. doi:10.1038/372659a0
22. Köllner, C.; Pugin, B.; Togni, A. *J. Am. Chem. Soc.* **1998,** *120,* 10274–10275. doi:10.1021/ja981137g
23. Brinkmann, N.; Giebel, D.; Lohmer, G.; Reetz, M. T.; Kragl, U. *J. Catal.* **1999,** *183,* 163–168. doi:10.1006/jcat.1999.2462
24. Pijnenburg, N. J. M.; Dijkstra, H. P.; van Koten, G.; Klein Gebbink, R. J. M. *Dalton Trans.* **2011,** *40,* 8896–8905. doi:10.1039/c1dt10502g
25. Arink, A. M.; van de Coevering, R.; Wieczorek, B.; Firet, J.; Jastrzebski, J. T. B. H.; Klein Gebbink, R. J. M.; van Koten, G. *J. Organomet. Chem.* **2004,** *689,* 3813–3819. doi:10.1016/j.jorganchem.2004.07.023
26. Gaab, M.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem.–Eur. J.* **2009,** *15,* 5450–5462. doi:10.1002/chem.200900504
27. McFarland, J. M.; Francis, M. B. *J. Am. Chem. Soc.* **2005,** *127,* 13490–13491. doi:10.1021/ja054686c
28. Abura, T.; Ogo, S.; Watanabe, Y.; Fukuzumi, S. *J. Am. Chem. Soc.* **2003,** *125,* 4149–4154. doi:10.1021/ja0288237
29. Ogo, S.; Uehara, K.; Abura, T.; Fukuzumi, S. *J. Am. Chem. Soc.* **2004,** *126,* 3020–3021. doi:10.1021/ja031633r
30. Ogo, S.; Uehara, K.; Abura, T.; Watanabe, Y.; Fukuzumi, S. *J. Am. Chem. Soc.* **2004,** *126,* 16520–16527. doi:10.1021/ja0473541
31. Hong, Y.-R.; Gorman, C. B. *J. Org. Chem.* **2003,** *68,* 9019–9025. doi:10.1021/jo0351116
32. Peerlings, H. W. I.; Meijer, E. W. *Tetrahedron Lett.* **1999,** *40,* 1021–1024. doi:10.1016/S0040-4039(98)02515-5

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Beilstein Journal of Organic Chemistry

Anionic cascade reactions. One-pot assembly of (*Z*)-chloro-*exo*-methylenetetrahydrofurans from β-hydroxyketones

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Full Research Paper

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Keywords:
acetylene addition; dichloroethylene; dimerisation; dioxanes; tetrahydrofurans

Beilstein J. Org. Chem. **2013,** *9,* 1319–1325.
doi:10.3762/bjoc.9.148

Received: 08 April 2013
Accepted: 12 June 2013
Published: 03 July 2013

This article is part of the Thematic Series "Creating complexity".

Guest Editor: D. Craig

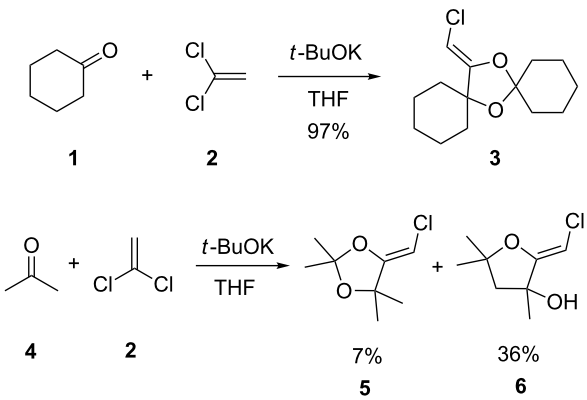
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Abstract

The assembly of (*Z*)-chloro-*exo*-methylenetetrahydrofurans by an original and connective anionic cascade sequence is reported. Base-catalysed condensation of β-hydroxyketones with 1,1-dichloroethylene generates, in moderate to good yields, the corresponding (*Z*)-chloro-*exo*-methylenetetrahydrofurans. Acidic treatment of this motif leads to several unexpected dimers, possessing unique structural features.

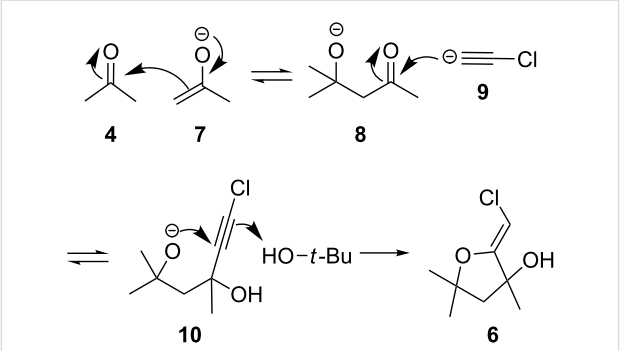
Introduction

Recently, we have shown that simple ketones reacted with 1,1-dichloroethylene, in the presence of potassium *tert*-butoxide, to afford rare (*Z*)-chloro-*exo*-methyleneketals [1-3]. This unique transformation is particularly efficient in the case of six-membered ring ketones (Scheme 1). In an attempt to extend the scope of this cascade process to acyclic ketones, acetone was submitted to the usual reaction conditions. To our surprise, the expected adduct **5** was formed in only poor yields. The major product was isolated in 36% yield and its structure was unambiguously determined as the (*Z*)-chloro-*exo*-methylenetetrahydrofuran **6**.



Scheme 1: Formation of (*Z*)-chloro-*exo*-methyleneketals.

The generation of **6** can be rationalized as depicted in Scheme 2. Under the basic conditions employed for the cascade



Scheme 2: Mechanism of formation of (*Z*)-chloro-*exo*-methylenetetrahydrofurans.

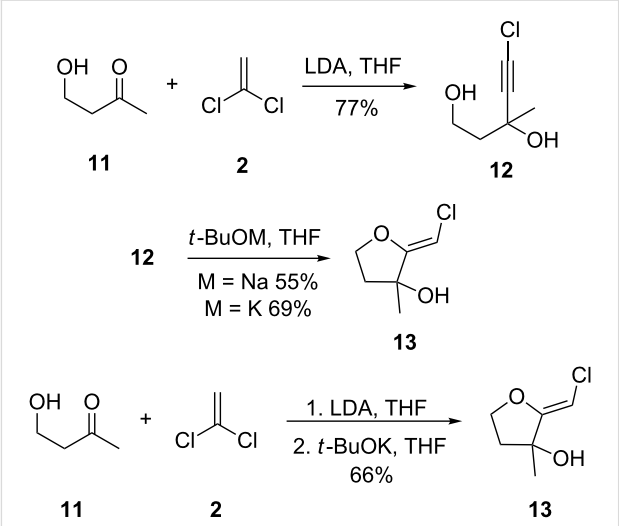
reaction, 1,1-dichloroethylene is converted into the corresponding chloro-acetylene anion **9** [4,5]. This nucleophilic species adds rapidly, though reversibly, to acetone, leading ultimately to the formation of **5**. However, in this case, competitive aldol reaction appears to take place, delivering the adduct **8**. The subsequent addition of **9** then affords the intermediate **10**, which undergoes a 5-*exo*-*dig* cyclisation, ultimately yielding the observed (*Z*)-chloro-*exo*-methylenetetrahydrofuran **6**.

This structural motif constitutes the core of several biologically active compounds, including antimicrobial agents, fungicides and interesting competitive inhibitors of *S*-adenosyl-L-homocysteine (AdoHcy) hydrolase, one of the target enzymes extensively studied in the context of antiviral chemotherapy [6-9]. Despite their utility, only a limited number of multistep methods have been described for the preparation of this subunit [10-16]. The paucity of efficient synthetic approaches towards this family of compounds and the desire to assess the scope and limitations of this method prompted us to further investigate this transformation.

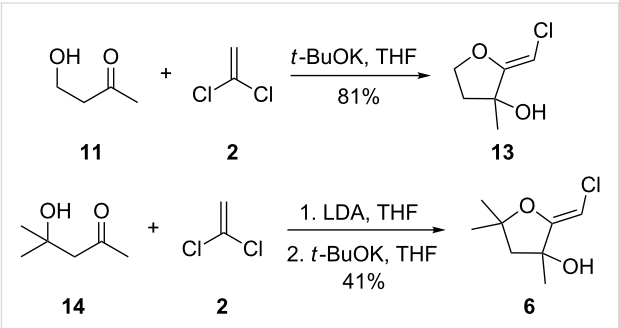
Results and Discussion

When 4-hydroxy-2-butanone (**11**) was treated with lithium chloroacetylide, generated in situ from dichloroethylene and LDA, the diol **12** was obtained in 77% yield. This adduct smoothly cyclized to **13** upon addition of sodium or potassium *tert*-butoxide, thereby supporting our mechanistic proposal. Repeating the process without isolation of the intermediate diol **12** proved to be even more efficient, affording the (*Z*)-chloro-*exo*-methylenetetrahydrofuran **13** in 66% overall yield (Scheme 3).

It is interesting to note that, in the case of the substrate **11**, the adduct **13** could be isolated in an improved 81% yield when potassium *tert*-butoxide was employed as the sole base (Scheme 4). In stark contrast, applying this procedure to the keto-alcohol **14** resulted in a mediocre 13% yield of **6**, probably due to a rapid retro-aldol reaction of the derived, rather hindered, potassium alkoxide. Applying the LDA/KO*t*-Bu protocol improved the yield to 41%.



Scheme 3: Stepwise formation of (*Z*)-chloro-*exo*-methylenetetrahydrofurans.



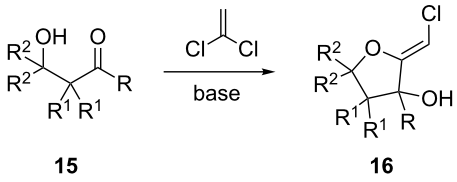
Scheme 4: Optimized protocols to form (*Z*)-chloro-*exo*-methylenetetrahydrofurans.

It thus transpires that good to excellent yields of (*Z*)-chloro-*exo*-methylenetetrahydrofurans could be obtained by the judicious choice of the bases employed to promote this cascade process. Having delineated some suitable conditions, the scope and limitations of this methodology were investigated [17-27]. Some selected examples are collected in Table 1.

As can be seen from Table 1, the reaction proves to be quite general and high-yielding for several primary alcohols (Table 1, entries 2, 3, 7 and 8). The yield was somewhat lower for two of them (Table 1, entries 4 and 6) due to rapid retro-aldol reactions and to enhanced steric hindrance, respectively. In the case of tertiary alcohols, the reaction proceeded with acceptable yields, especially in view of the one-pot nature of our procedure (Table 1, entries 1 and 5).

Having access to a broad range of substituted (*Z*)-chloro-*exo*-methylenetetrahydrofurans, a brief survey of their reactivity was performed. Several reactions involving the vinyl chloride function proved unsuccessful [28,29]. Attempts to perform oxidative rearrangement and dehydration failed and functionalisation of the hydroxy group appeared difficult [30,31]. Initially, the adduct **13** was treated with aqueous hydrochloric acid, in the hope of generating the corresponding dihydrofuran carbaldehyde **33**. Instead, the diol **34** was obtained in 52% yield as a 1:1 mixture of diastereoisomers. It thus transpires that protonation and hydration of the *exo*-methylene double bond of **13** proceeded faster than the expected rearrangement of the tertiary allylic alcohol (Scheme 5).

Table 1: Preparation of (*Z*)-chloro-*exo*-methylenetetrahydrofurans.



15 **16**

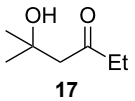
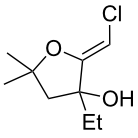
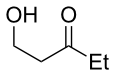
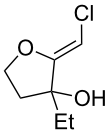
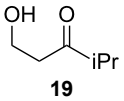
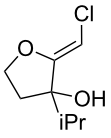
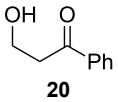
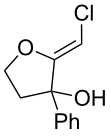
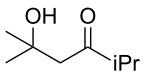
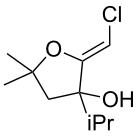
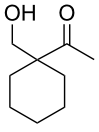
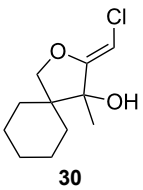
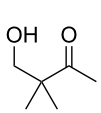
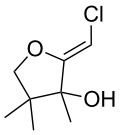
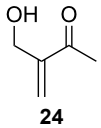
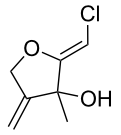
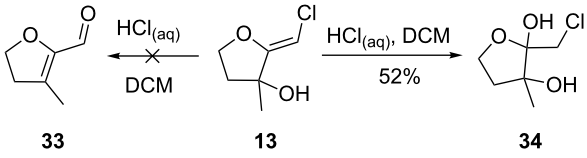
Entry	Substrate	Product	Yield[a]
1	 **17**	 **25**	39%[b]
2	 **18**	 **26**	80%[c]
3	 **19**	 **27**	73%[c]
4	 **20**	 **28**	38%[c] 47%[b]
5	 **21**	 **29**	40%[b]
6	 **22**	 **30**	42%[c]

Table 1: Preparation of (*Z*)-chloro-*exo*-methylenetetrahydrofurans. (continued)

7	 **23**	 **31**	77%[c]
8	 **24**	 **32**	10%[c] 61%[b]

[a]All yields are for pure, isolated products. [b]In these cases, 2.2 equiv of $C_2H_2Cl_2$ and 4.4 equiv of LDA were used in the first step, followed by 1 equiv of *t*-BuOK in the second step. [c]For these substrates, 2.5 equiv of $C_2H_2Cl_2$ and 5 equiv of *t*-BuOK were used to generate the acetylide.



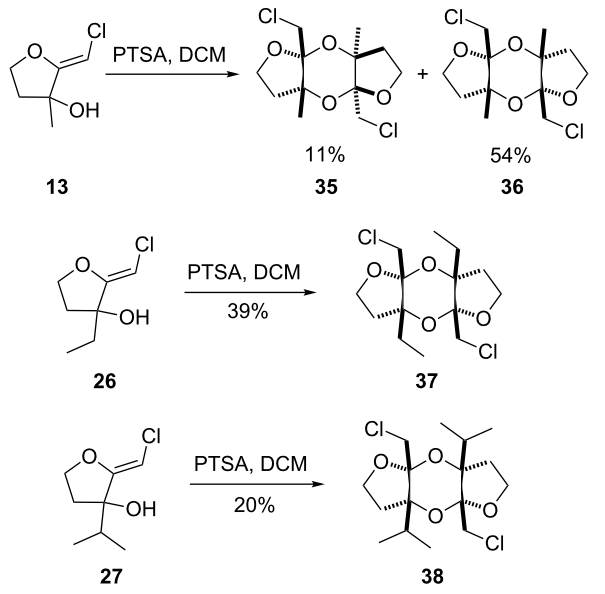
33 **13** **34**

Scheme 5: Hydration of (*Z*)-chloro-*exo*-methylenetetrahydrofurans.

To promote such an acid-catalyzed rearrangement, the (*Z*)-chloro-*exo*-methylenetetrahydrofuran **13** was treated with a catalytic amount of *para*-toluenesulfonic acid. To our surprise, the *anti*-dioxane **35** and its *syn*-derivative **36** were obtained as a 1:5 mixture of diastereoisomers that could be separated (Scheme 6). Their structure was unambiguously established by single-crystal X-ray diffraction analysis, as shown in Figure 1. Increasing the steric hindrance at the tertiary alcohol site resulted in the exclusive formation of the *syn*-dioxanes **37** and **38** respectively, albeit at the expense of the yield [32-38].

When the dimethyl adduct **6** was submitted to the same conditions, a new product [39-45] **41** was formed besides the dioxanes **39** and **40** (Scheme 7). Its structure was unambiguously established as the spirocyclic dimer **41** by single-crystal X-ray diffraction analysis. It is noteworthy that a single diastereoisomer was generated in this transformation.

The formation of these unique compounds can be rationalized as depicted in Scheme 8. Under acidic conditions, the



Scheme 6: Formation of dioxanes.

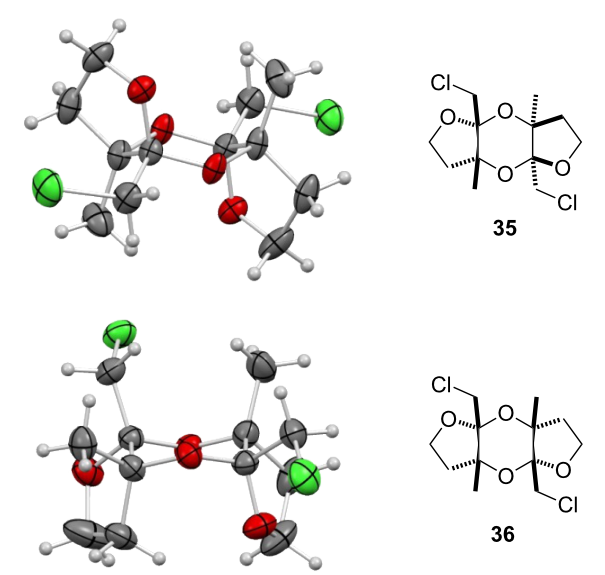
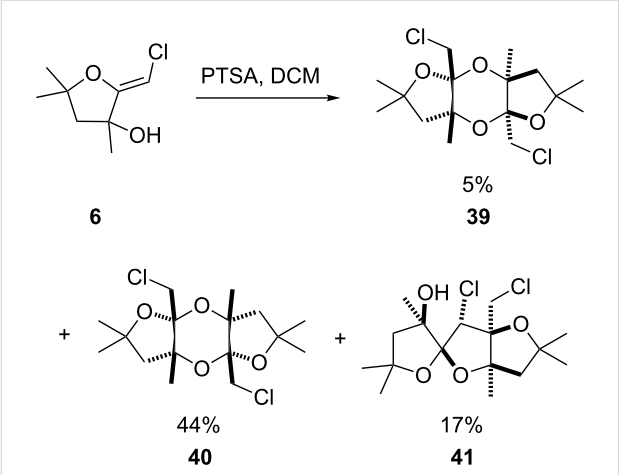
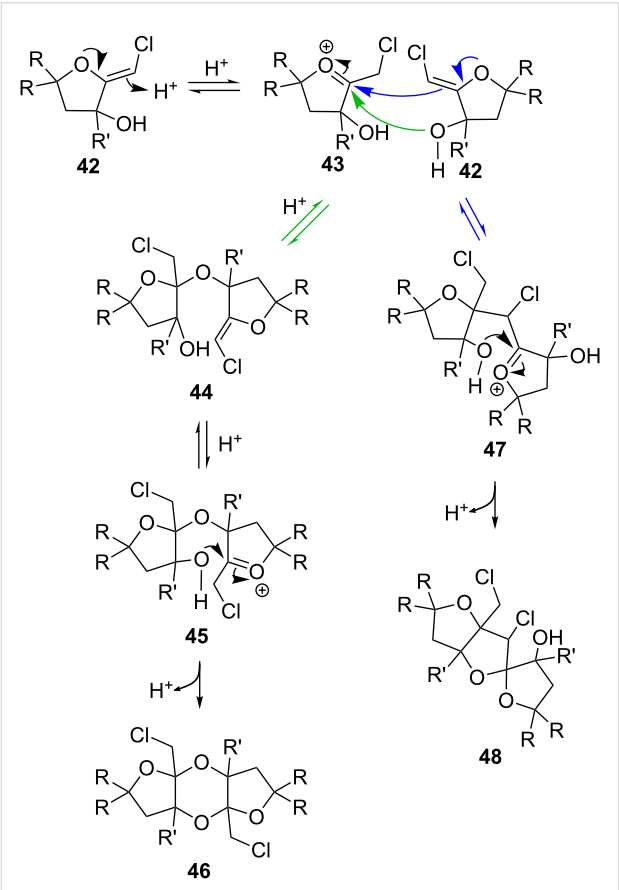


Figure 1: X-ray diffraction analysis of dioxanes **35** and **36**.

(*Z*)-chloro-*exo*-methylenetetrahydrofuran **42** is converted into the oxonium cation **43**. Subsequent capture of this intermediate **43** by a second molecule of **42** can occur via two different pathways. The first one involves the addition of the enol ether function of **42** onto **43**, leading to the creation of a new C–C bond with concomitant generation of another oxonium species **47**. Intramolecular capture of this electrophile by the pendant hydroxy substituent then delivers the spirocyclic adduct **48**. Alternatively, reaction of the tertiary alcohol of **42** with the oxonium cation **43** affords the ketal **44**. Protonation of the enol ether function, followed by 6-*exo*-*trig* cyclization, completes this sequence of events and provides the dioxane derivative **46**. Interestingly, no reaction was observed when the spirocycle **41** and the dioxanes **35**, **36** and **39** were reacted under acidic conditions, indicating that the final step is not reversible.

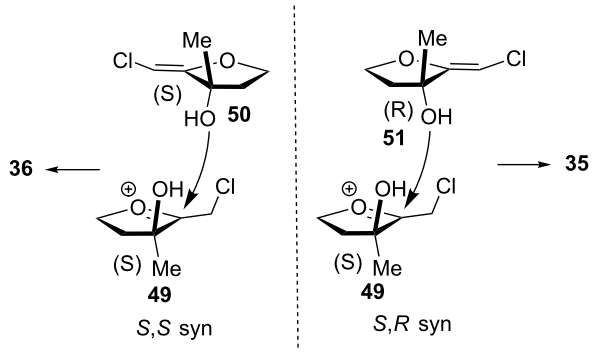


Scheme 7: Formation of a new spirocyclic dimer.



Scheme 8: Mechanism leading to dioxanes and spirocycles.

It is noteworthy that the dioxanes possess predominantly (**13**) or exclusively (**26** and **27**) the *syn–syn* relative stereochemistry at the ring junctions. This selectivity can be rationalized by an initial addition of the nucleophile *syn* to the alcohol function, as shown in Scheme 9. Interestingly, the homochiral (*S,S;R,R*)-dimer, leading to the *syn–syn* product, is preferred over the heterochiral (*S,R;R,S*)-adduct, affording the *syn–anti* isomer. Increasing the steric hindrance at the tertiary alcohol center of **49** leads to prohibitive steric repulsion during the heterodimer formation. A similar facial selectivity can explain the formation of **41** as a single diastereoisomer.



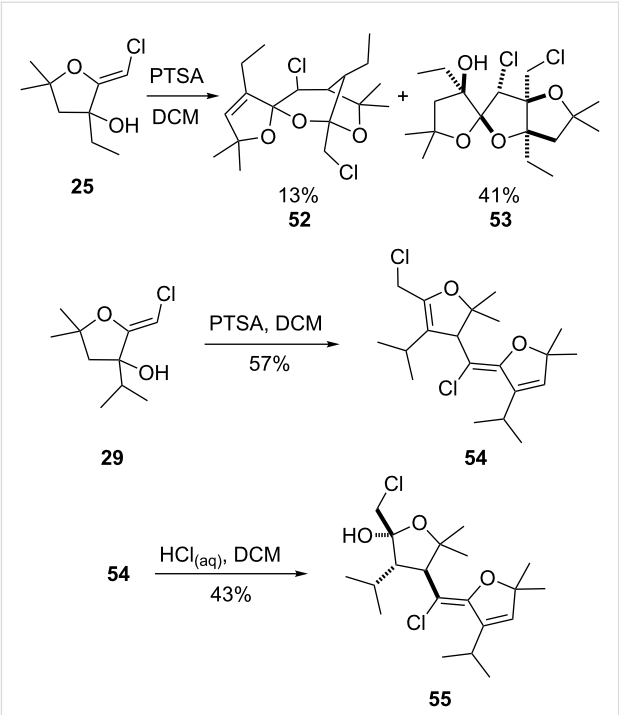
Scheme 9: (*S,S*)-*syn* and (*S,R*)-*syn* approaches.

When the adduct **25**, bearing a *gem*-dimethyl substituent was submitted to this transformation, no dioxane was observed. The major product proved to be the spirocyclic adduct **53**, accompanied by the bridged bis-ketal **52**, in 41% and 13% yield respectively (Scheme 10). Treatment of the isopropyl derivative **29** under the same acidic conditions provided the triene **54** in 57% yield. Addition of aqueous HCl generated the hemi-ketal **55** in 43% yield. The starting material was recovered in 52% yield.

The structures of compounds **53** and **55** were unambiguously established by single-crystal X-ray diffraction analysis (Figure 2).

Once again, increasing the steric effect around the tertiary alcohol function of the (*Z*)-chloro-*exo*-methylenetetrahydrofurans has a profound influence on the fate of the condensation reaction. A plausible mechanistic rationale is provided in Scheme 11.

In the presence of the *gem*-dimethyl substituent, dehydration of **42** to afford **56** appears to proceed rapidly, probably owing to a release of steric strain. The loss of water occurs especially readily when R' = Et or iPr and to a lesser extent when R' = Me, indicating that steric decompression may indeed be operational in these cases. Protonation of diene **56** leads to the



Scheme 10: Formation of a bridged dimer and a triene.

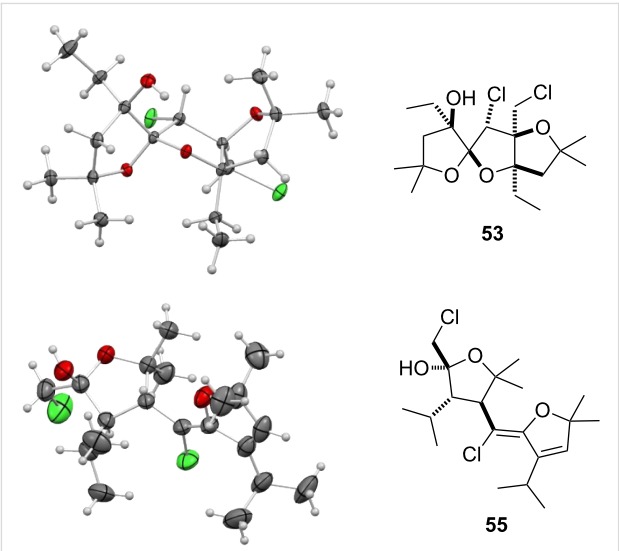
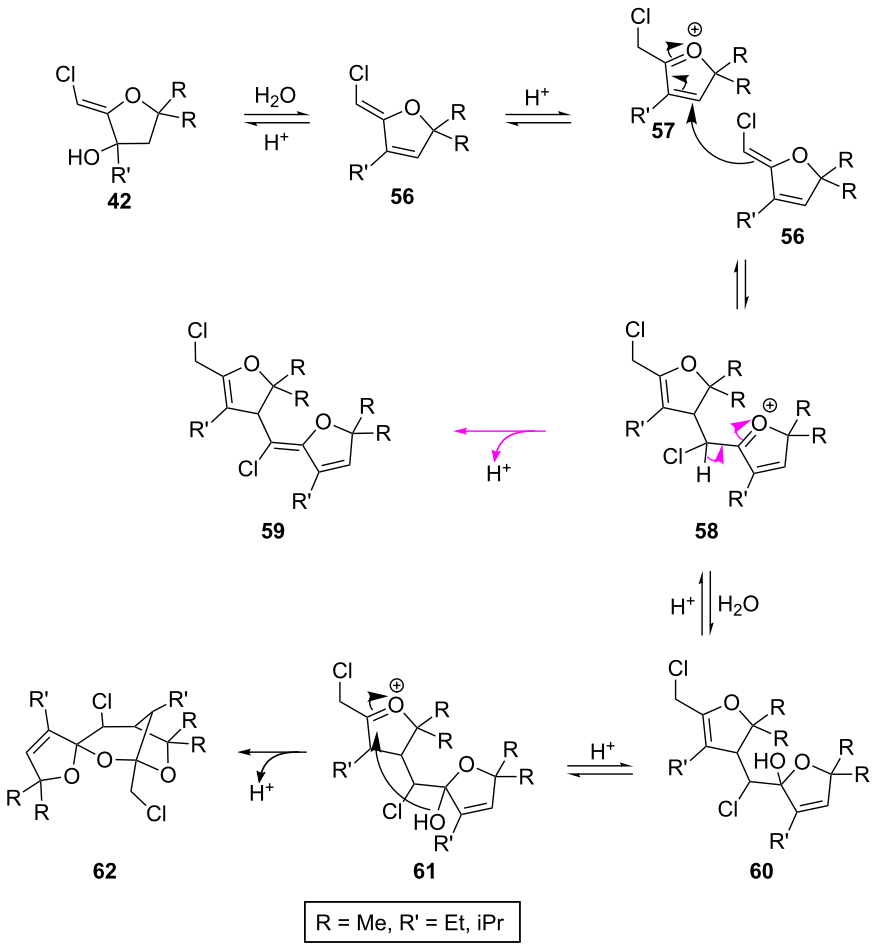


Figure 2: X-ray diffraction analysis of two new dimers.

oxonium ion **57**, which undergoes a 1,4-addition of another **56** unit, affording the new cation **58**. At this stage, two different pathways can be followed. Either carbocation **58** can lose a proton, generating the observed triene **59**, or it may undergo addition of a water molecule, affording the hemiketal **60**. Addition of a proton to the vinyl ether function, followed by intramolecular capture by the hydroxy group, finally provides the unique bridged adduct **62**.



Scheme 11: Mechanism leading to bridged and dienic dimers.

Conclusion

In summary, a unique anionic cascade process, leading to the efficient and connective assembly of (*Z*)-chloro-*exo*-methylene-tetrahydrofurans from β-hydroxyketones, has been uncovered and developed. The reactivity of this unusual motif has been briefly investigated, and dimers, possessing rather unusual structures, have been obtained. It is noteworthy that some of these dimeric products form the core of interesting biologically active compounds and of unique natural products.

Experimental

General procedure for the synthesis of chloromethylenefurans

To 40 mL of anhydrous THF, cooled to 0 °C, 1.2 mL (15.0 mmol, 2.5 equiv) of dichloroethylene and 3.37 g of potassium *tert*-butoxide were added. After 15 minutes, 700 mg (6.0 mmol, 1 equiv) of hydroxyketone in 1 mL of THF were added. After one hour, 20 mL of water was added and the mixture was neutralized with diluted sulfuric acid. The aqueous layer was extracted with 2 × 20 mL of DCM. The organic layer was dried, filtered and concentrated. The crude product was further purified by chromatography over silica gel providing 820 mg (4.6 mmol, 77%) of chloromethylenefuran **31** as a white solid. For full details, see Supporting Information File 1.

Supporting Information

Supporting Information File 1

Experimental procedures and analytical data of cited compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-148-S1.pdf]

Acknowledgements

Financial support by the Université catholique de Louvain (UCL), the Fonds pour la formation à la Recherche dans l'Industrie et dans l'Agriculture (F.R.I.A.) and the Action de Recherches Concertées (ARC 08/13-012) is gratefully acknowledged.

References

1. Schevenels, F.; Markó, I. E. *Chem. Commun.* **2011,** *47,* 3287. doi:10.1039/c0cc05186a
2. Schevenels, F.; Markó, I. E. *Org. Lett.* **2012,** *14,* 1298. doi:10.1021/ol300186s
3. Schevenels, F.; Tinant, B.; Declercq, J.-P.; Markó, I. E. *Chem.–Eur. J.* **2013,** *19,* 4335. doi:10.1002/chem.201201505
4. Viehe, H. G. *Chem. Ber.* **1959,** *92,* 1270. doi:10.1002/cber.19590920607
5. Kloster-Jenson, E. *Tetrahedron* **1971,** *27,* 33. doi:10.1016/S0040-4020(01)92395-6
6. Prakash, N. J.; Davis, G. F.; Jarvi, E. T.; Edwards, M. L.; McCarthy, J. R.; Bowlin, T. L. *Life Sci.* **1992,** *50,* 1425. doi:10.1016/0024-3205(92)90261-M
7. Buchecker, R.; Fuenfschilling, J.; Marck, G. *Mol. Cryst. Liq. Cryst. Sci. Technol., Sect. A* **1997,** *302,* 295. doi:10.1080/10587259708041840
8. Kumamoto, H.; Onuma, S.; Tanaka, H.; Kitade, Y. *Nucleic Acids Symp. Ser.* **2003,** *3,* 13. doi:10.1093/nass/3.1.13
9. Jarvi, E. T.; McCarthy, J. R.; Mehdi, S.; Matthews, D. P.; Edwards, M. L.; Prakash, N. J.; Bowlin, T. L.; Sunkara, P. S.; Bey, P. *J. Med. Chem.* **1991,** *34,* 647. doi:10.1021/jm00106a028
10. Kumamoto, H.; Onuma, S.; Tanaka, H. *J. Org. Chem.* **2004,** *69,* 72. doi:10.1021/jo030256y
11. Wnuk, S. F.; Dalley, N. K.; Robins, M. J. *J. Org. Chem.* **1993,** *58,* 111. doi:10.1021/jo00053a022
12. Xu, M.; Miao, Z.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **2005,** *88,* 2918. doi:10.1002/hlca.200590235
13. Csuk, R.; Glänzer, B. *Tetrahedron* **1991,** *47,* 1655. doi:10.1016/S0040-4020(01)96909-1
14. Gómez, A. M.; Danelón, G. O.; Pedregosa, A.; Valverde, S.; López, J. C. *Chem. Commun.* **2002,** 2024. doi:10.1039/b205121d
15. Blandino, M.; McNelis, E. *Org. Lett.* **2002,** *4,* 3387. doi:10.1021/ol026422q
16. Craig, G. W.; Sternberg, E. D.; Jones, G. H.; Moffatt, J. G. *J. Org. Chem.* **1986,** *51,* 1258. doi:10.1021/jo00358a017
17. Wasserman, H. H.; Hearn, M. J.; Cochoy, R. E. *J. Org. Chem.* **1980,** *45,* 2874. doi:10.1021/jo01302a023
18. Hitchcock, S. R.; Perron, F.; Martin, V. A.; Albizati, K. F. *Synthesis* **1990,** 1059. doi:10.1055/s-1990-27093
19. Einhorn, J.; Soulier, J.-L.; Bacquet, C.; Lelandais, D. *Can. J. Chem.* **1983,** *61,* 584. doi:10.1139/v83-104
20. Ueki, T.; Doe, M.; Morimoto, Y.; Kinoshita, T.; Tanaka, R.; Yoshihara, K. *J. Heterocycl. Chem.* **2001,** *38,* 165. doi:10.1002/jhet.5570380124
21. O'Neil, G. W.; Miller, M. M.; Carter, K. P. *Org. Lett.* **2010,** *12,* 5350. doi:10.1021/ol1024635
22. Kim, K. S.; Song, Y. H.; Lee, N. H.; Hahn, C. S. *Tetrahedron Lett.* **1986,** *27,* 2875. doi:10.1016/S0040-4039(00)84667-5
23. Schneider, C.; Hansch, M.; Weide, T. *Chem.–Eur. J.* **2006,** *11,* 3010. doi:10.1002/chem.200400951
24. Lin, K.-W.; Tsai, C.-H.; Hsieh, I.-L.; Yan, T.-H. *Org. Lett.* **2008,** *10,* 1927. doi:10.1021/ol8004326
25. Sulmon, P.; De Kimpe, N.; Schamp, N. *Org. Prep. Proced. Int.* **1989,** *21,* 91. doi:10.1080/00304948909356351
26. Trost, B. M.; Yang, H.; Thiel, O. R.; Frontier, A. J.; Brindle, C. S. *J. Am. Chem. Soc.* **2007,** *129,* 2206. doi:10.1021/ja067305j
27. Gerwick, B. C., III; Fields, S. C.; Graupner, P. R.; Schmitzer, P. R.; Brewster, W. K. Methylidene Mevalonates and their Use as Herbicides. U.S. Patent CA2527439A1, May 19, 2006.
28. Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004,** *69,* 3943. doi:10.1021/jo0498866
29. Qing, F.-L.; Wang, R.; Li, B.; Zheng, X.; Meng, W.-D. *J. Fluorine Chem.* **2003,** *120,* 21. doi:10.1016/S0022-1139(02)00279-8
30. Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977,** *42,* 682. doi:10.1021/jo00424a023
31. Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995,** *117,* 4413. doi:10.1021/ja00120a030
32. Yates, P.; Burke, P. M. *Can. J. Chem.* **1987,** *65,* 1695. doi:10.1139/v87-284
33. Martin, O. R.; Rao, S. P.; Hendricks, C. A. V.; Mahnken, R. E. *Carbohydr. Res.* **1990,** *202,* 49. doi:10.1016/0008-6215(90)84070-B
34. Adam, W.; Peters, C.; Sauter, M. *Synthesis* **1994,** 111. doi:10.1055/s-1994-25416
35. Dawid, M.; Warkentin, J. *Can. J. Chem.* **2003,** *81,* 598. doi:10.1139/v02-200
36. Timmer, M. S. M.; Stocker, B. L.; Seeberger, P. H. *J. Org. Chem.* **2006,** *71,* 8294. doi:10.1021/jo061607m
37. Mukherjee, S.; Roy, B. G.; Das, S. N.; Mandal, S. B. *Tetrahedron Lett.* **2012,** *53,* 4929. doi:10.1016/j.tetlet.2012.06.121
38. Ting, C.-M.; Wang, C.-D.; Chaudhuri, R.; Liu, R.-S. *Org. Lett.* **2011,** *13,* 1702. doi:10.1021/ol2002144
39. Chang, S.; Britton, R. *Org. Lett.* **2012,** *14,* 5844. doi:10.1021/ol302694s
40. Tlais, S. F.; Dudley, G. B. *Beilstein J. Org. Chem.* **2012,** *8,* 1287. doi:10.3762/bjoc.8.146
41. Brimble, M. A.; Finch, O. C.; Heapy, A. M.; Fraser, J. D.; Furkert, D. P.; O'Connor, P. D. *Tetrahedron* **2011,** *67,* 995. doi:10.1016/j.tet.2010.11.107
42. Tlais, S. F.; Dudley, G. B. *Org. Lett.* **2010,** *12,* 4698. doi:10.1021/ol102201z
43. Fernandes, R. A.; Ingle, A. B. *Synlett* **2010,** 158. doi:10.1055/s-0029-1218538
44. Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem.* **2009,** *74,* 2842. doi:10.1021/jo802539z
45. Seibert, S. F.; Krick, A.; Eguereva, E.; Kehraus, S.; Koenig, G. M. *Org. Lett.* **2007,** *9,* 239. doi:10.1021/ol0626802

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