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Creative approaches towards the synthesis of 2,5-dihydro- furans, thiophenes, and pyrroles. One method does not fit all!

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A single method is never sufficient, which is why there is a great need for developing many diverse and creative approaches towards every chemical substrate class. This statement is supported by the contents of this perspective in addition to providing the reader with a helpful synthetic roadmap for selecting a suitable method for the building blocks being discussed. Detailed in this review are eight different synthetic approaches that provide access to valuable 2,5-dihydro- furan, thiophene and pyrrole building blocks. Each approach is briefly presented and its limits discussed. The strengths and weaknesses of each approach are further highlighted with a graphical table summary at the end. This summary clearly drives home the point that for every chemical substrate class we need many good methods in order to provide access to every member of each class.

Introduction

It is clear that the need for operationally simple atom-efficient methods with as broad substrate scope as possible will always be great. It is important to emphasize that one type of chemical transformation can rarely provide universal access to all substrate permutations of a given class. Efforts should be devoted to developing a series of complementary practical synthetic methods that together can provide access to every member of a substrate class. Such practical new synthetic methods can have a significant impact since a large number of research areas rely on building new molecular architectures either for fundamental or industrial applications. This perspective presents a case study of how eight very diverse and creative synthetic approaches collectively provide access to many structural permutations of an important heterocyclic class (Fig. 1).

Five-membered heterocycles are essential building blocks that are frequently used in the pharmaceutical and commodity chemical industry. For example, more than 95% of pharmaceuticals contain at least one heterocyclic fragment. Our group has dedicated substantial efforts to developing a useful synthetic approach that can afford access to a broad range of 2,5-dihydro- furan, thiophene and pyrrole products. These products are very attractive building blocks *en route* to natural products, pharmaceuticals, materials and commodity chemicals. The 3,4-unsaturation of these heterocycles is a particularly attractive feature, as it enables straightforward access to reduced, oxidized and further functionalized members of these three important structural families. Members of the furan family can be found in thousands of natural products, bulk commodity chemicals, and pharmaceutical agents.[1] Thiophenes are used for a number of practical applications such as pharmaceuticals and materials.[2] A significant number of marketed

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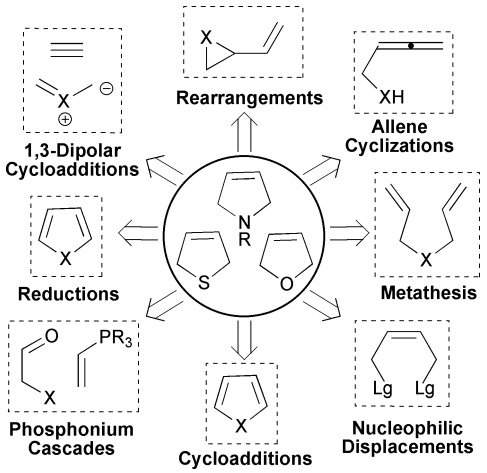


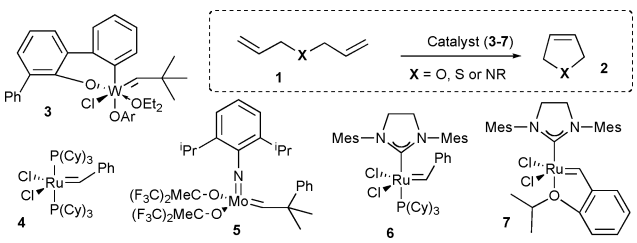
Fig. 1 Eight retrosynthetic approaches for 2,5-dihydro- furans, thiophenes and pyrroles.

and approved drugs contain a pyrrolidine core, with the most commonly employed derivatives being proline or azabicyclics.[3] The tropane core (which is [3.2.1]-azabicyclic), for example, is the structural backbone of many very successful therapeutics.[4]

The eight distinct 2,5-dihydro- furan, thiophene and pyrrole retrosynthetic approaches that are the focus of this perspective are highlighted in Fig. 1. In our discussion we have chosen not to cover any synthetic methods that form either fused aromatic products or those that are sp^2-hybridized at either the 2- or 5-positions, which also excludes lactones, lactams and such derivatives. Finally, the only methods discussed are those that are considered "general" in that they allow access to all three heterocycle classes. Although this stipulation seems very restrictive, only a few notable methods are not discussed. Each synthetic approach is discussed in the following sections. A brief outline is followed by reaction comments and literature examples highlighting their strengths. Whenever possible, we have chosen natural product examples.

1. Ring-closing metathesis (RCM)

Metathesis reactions, and ring-closing metathesis (RCM) in particular, have in the last fifteen years revolutionized how organic chemists design and assemble molecules.[5] Not surprisingly this new synthetic approach was quickly applied to the construction of 2,5-dihydro- furan, thiophene and pyrrole products (Scheme 1, **2**). Early efforts utilized tungsten (**3**),[6] ruthenium and molybdenum catalysts, with Grubbs (**4**)[7] and Schrock (**5**)[8] catalysts featured most prominently. In accessing simple heterocyclic products, the primary challenges that were encountered were



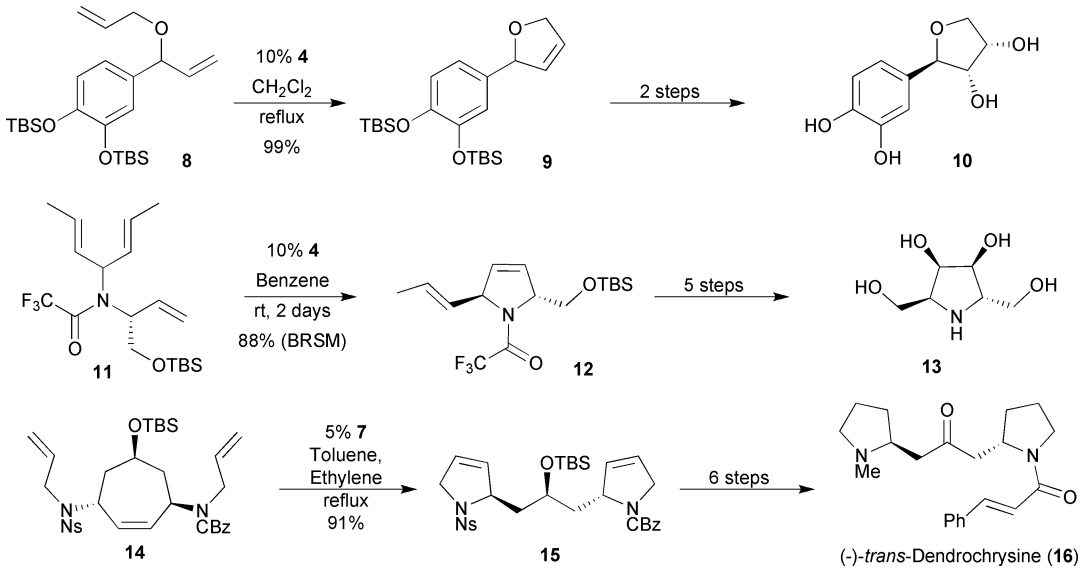
Scheme 1 Synthesis of 2,5-dihydro- furans, thiophenes and pyrroles using metathesis.

catalyst inhibition by sulfide[9] and free amine substrates[10] as well as unwanted olefin isomerization of dihydrofuran products.[11] Many of these challenges have since been overcome. Second-generation ruthenium catalysts such as **6**[12] and **7**[13] have led the way because of their attractive air-stability and functional group compatibility. For example, by utilizing suitably protected diallylamines, 3-pyrrolines can now be readily accessed.[14] Diallyl sulfides are now manageable substrates,[15] although challenges still exist and in many cases sulfones[16] are used as substitutes. The dihydrofuran olefin isomerization challenge has been addressed by using a benzoquinone additive.[17] Tetrasubstituted and strained bicyclic substrates continue to be very challenging for ring-closing metathesis, although recent new catalyst developments indicate that the tetrasubstituted products will soon be more accessible.[18] From a retrosynthetic point of view metathesis is less appealing for 2,5-substituted substrates, as synthesis of the requisite starting materials can be challenging at times. Additionally, the fact that a large amount of solvent is usually needed coupled with high catalyst cost, non-trivial catalyst removal and toxicity challenges often makes the scale-up less attractive.

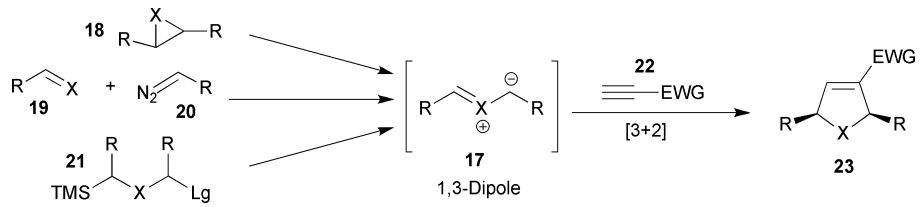
This new synthetic approach has been utilized for natural product synthesis with great success (Scheme 2). Most examples reported to date have employed this strategy to access 3-pyrrolines *en route* to a target natural product. Lack of dihydro- or tetrahydrothiophene-containing natural products probably accounts for the fact that no such 2,5-dihydrothiophene examples exist. Aryl furan natural product **10** was easily assembled from benzylic allyl ether **8** using Grubbs' first-generation catalyst.[19] Blechert has taken advantage of ring-closing metathesis to access azasugar **13**[20] and the natural product (−)-*trans*-dendrochrysine **16**[21] from trienes **11** and **14** respectively. The second example is a particularly attractive application of this strategy, as two 3-pyrroline rings are constructed in a single step.

2. [3+2] Dipolar cycloadditions

Dipolar cycloadditions are an important class of reactions within the field of organic chemistry.[22] Prominently featured as a member of this class are [3+2] dipolar cycloadditions. Dipoles, such as **17** (Scheme 3), when coupled with an alkyne (**22**), provide ready access to 2,5-dihydro- furan, thiophene and pyrrole products (**23**).[23] This strategy has been shown to be feasible for all three heteroatoms (O, N and S), although most reported examples are on generating and using azomethine ylides for constructing 2,5-dihydropyrroles. Generating the requisite 1,3-dipole (**17**) is one of the main challenges for this approach. Summarized in Scheme 3 are the three most commonly used strategies for generating the dipole. Thermal or Lewis acid catalyzed opening of oxiranes or aziridines (**18**) have been reported extensively.[24] This approach is not very general, and requires very specific functionalization to proceed favorably. Imines, carbonyl and thiocarbonyl groups (**19**) can be converted in a single step to **17** upon treatment with the appropriate metal carbene, which in most cases originates from a diazo precursor (**20**).[25] This strategy is most commonly employed for carbonyl starting materials. The third approach, which relies on precursors such as **21** (Lg = leaving group), is the preferred method for accessing azomethine ylides. Another major challenge of this approach is reactivity and regioselectivity. In most cases symmetrical activated alkynes such as acetylene



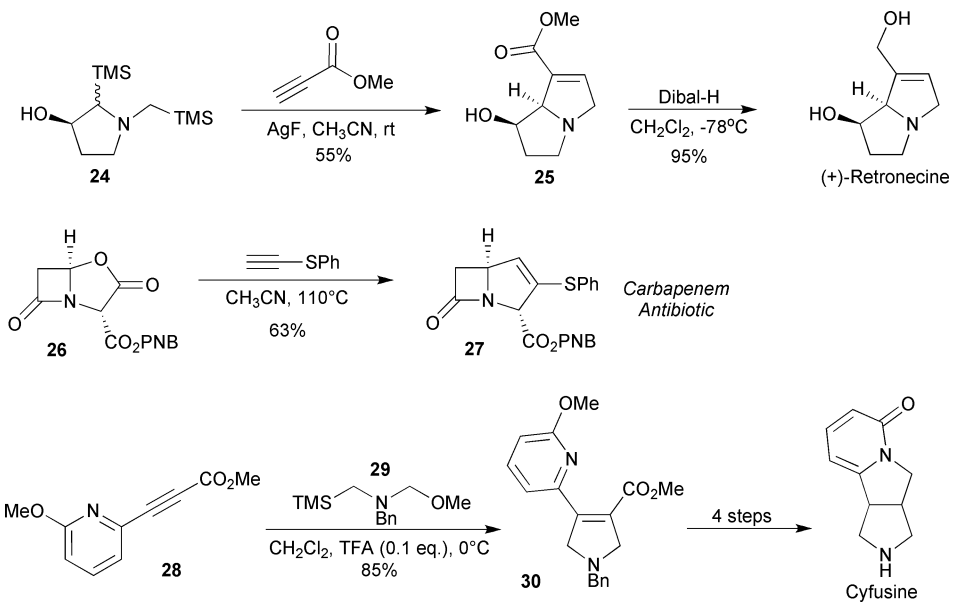
Scheme 2 Natural product total synthesis using ring-closing metathesis.



Scheme 3 Synthesis of 2,5-dihydro- furans, thiophenes and pyrroles using [3+2] cycloadditions.

dicarboxylates or diphenylacetylenes are needed. In general, this synthetic strategy is almost exclusively used to synthesize 2,5-dihydropyrroles, although intramolecular oxonium ylide variants have been popularized by Padwa and coworkers.[26] If the above conditions are met, functional group compatibility tends to be good.

This synthetic approach has found its place in natural product synthesis, but as is evident from the three examples in Scheme 4, these cases have been primarily limited to alkaloid synthesis. The natural product retronecine has been assembled in two steps from a disilylated pyrrolidine (**24**). The intermediate azomethine ylide was generated using silver fluoride and then trapped with methyl propiolate to form pyrrolizidine core **25**.[27] In an interesting approach, the core of carbapenam antibiotics (**27**) was assembled from oxazolidone **26**. The dipole was generated by thermolyzing



Scheme 4 Natural product total synthesis using [3+2] cycloadditions.

26, which released carbon dioxide and allowed trapping of the ylide with an alkyne.[28] As part of a vigorous research program, which recently resulted in the approval of varenicline (Chantix®), researchers at Pfizer have used an azomethine ylide approach to rapidly assembly a novel cytisine-inspired structure (cyfusine). Ynoate **28** and silyl aminal **29** were coupled under acidic conditions to form **30**, which was then converted in four additional steps to cyfusine.[29]

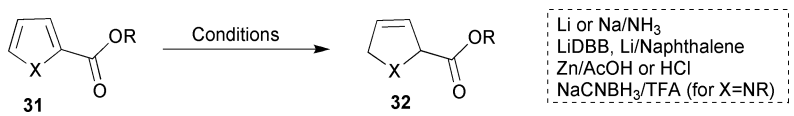
3. Birch reductions

The dissolving metal reduction (Birch reductions) of furans, pyrroles and thiophenes is one of the earlier reported strategies for accessing the target building blocks (Scheme 5).[30] Classically, these dissolving metal reductions are performed in the presence of sodium or lithium in ammonia, although now lithium di-*tert*-butylbiphenyl (LiDBB) or similar reagents are more likely to be used. Many of these aromatic compounds can also be reduced without using dissolving metals. In such cases, the reagents of choice are commonly zinc or sodium cyanoborohydride. The nature of substituents tends to be critical for success. For all practical purposes this otherwise attractive approach tends to be mostly limited to substrates having at least one electron-withdrawing group in the 2-position of the aromatic ring. What is particularly attractive about this approach is that the *in situ*-generated carbanion can be trapped with useful electrophiles. This reductive strategy can be accomplished asymmetrically using either a chiral proton source or chiral auxiliary. When these promising asymmetric solutions are coupled with an *in situ* alkylation, it seems clear that this strategy can hold its own against other methods for a range of useful substrates.

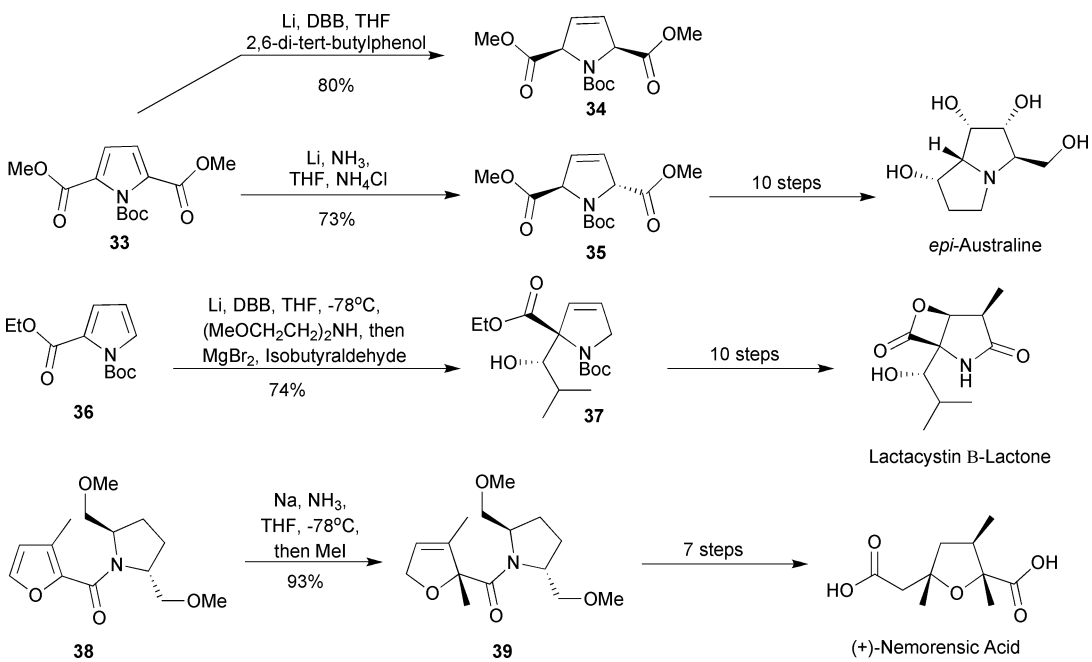
Donohoe and coworkers have led the way in this area for some time now, which is reflected by the fact that all the examples detailed in Scheme 6 are the work of his research group. Showcasing the strengths of this strategy, Donohoe has demonstrated that symmetrical pyrrole substrates (**33**) can be reduced to either the 2,5-*cis* (**34**) or 2,5-*trans* (**35**) products by using the appropriate reducing agent and proton source.[31] This particular *trans*-product (**35**) has been advanced to the natural product *epi*-australine.[32] In his synthetic approach towards the lactacystin β-lactone, the intermediate anion generated during the reduction process is coupled *in situ* with isobutyraldehyde to afford **37** as a single diastereomer.[33] In his synthetic approach towards the natural product nemorensic acid, Donohoe uses a C_2-symmetric pyrrolidine chiral auxiliary (**38**) to very effectively (30:1 dr) control the methylation of the anion generated during the Birch reduction.[34] Intermediate **39** was then advanced to the natural product in seven additional steps. Although these are all very impressive applications of this synthetic strategy, they also clearly highlight the fact that this approach is not yet very practical for aromatic precursors lacking an electron-withdrawing group.

4. Vinyl- oxirane, thiirane and aziridine rearrangements

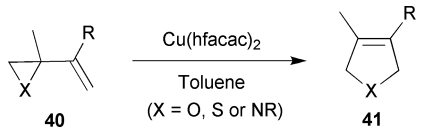
Our research group has recently demonstrated that a wide range of vinyl- oxirane,[35] thiirane[36] and aziridine[37] substrates (Scheme 7, **40**) can be rearranged efficiently to the corresponding



Scheme 5 Birch reduction of aromatic building blocks.



Scheme 6 Natural product total synthesis using Birch reductions.



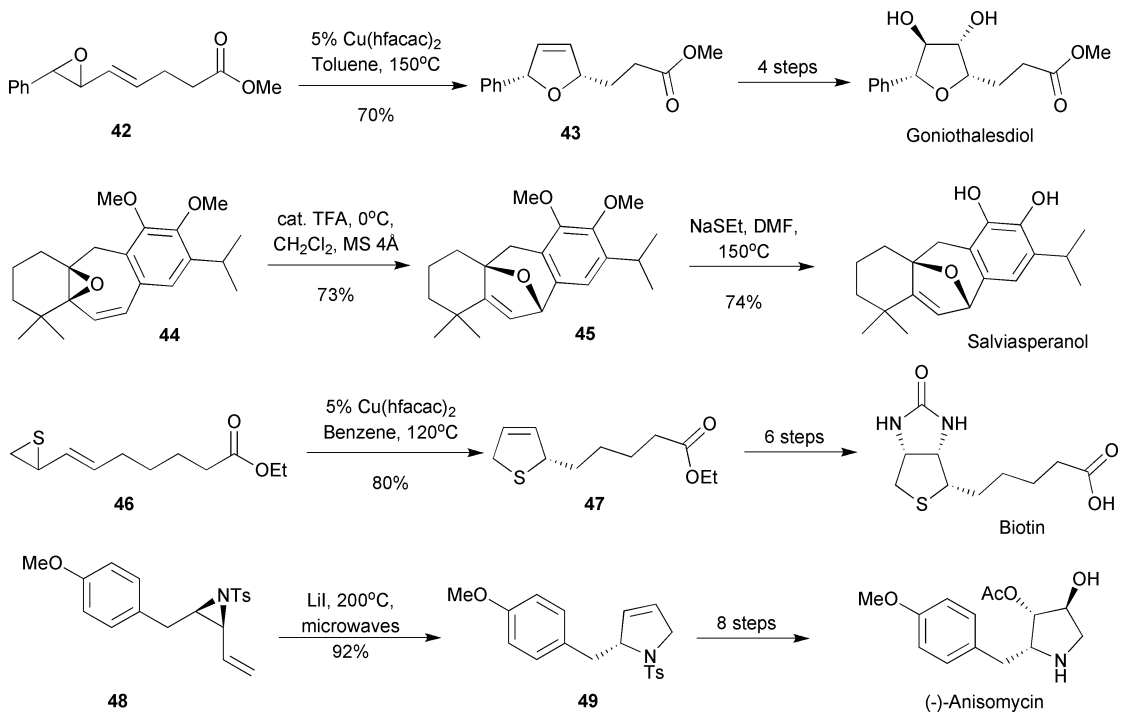
Scheme 7 Rearrangement of vinyl- oxiranes, thiiranes and aziridines.

2,5-dihydro- furan, thiophene and pyrrole products (**41**) by using copper(II) hexafluoroacetylacetonate as a catalyst. Prior to our work in this area there were scattered reports of success for a narrow range of vinyl- oxirane and aziridine substrates, but there were no reports of a vinyl thiirane rearrangement. For example, it has been known since the 1960's that certain simple vinyl aziridines can be rearranged thermally[38] under very forcing conditions, and in the 1980's Oshima showed that triene monoaziridines can be rearranged in the presence of a palladium catalyst,[39] while simple vinyl aziridines did not. Acid-catalyzed vinyl oxirane rearrangements have been known for a long time. It is important to note that most of these examples are rigged for success in that the detrimental competing hydride shift cannot occur. Our copper-catalyzed rearrangement is the optimal approach for all substrate categories and again the only approach that can be applied to vinyl thiiranes. In addition, we have shown the substrate scope to be very broad.

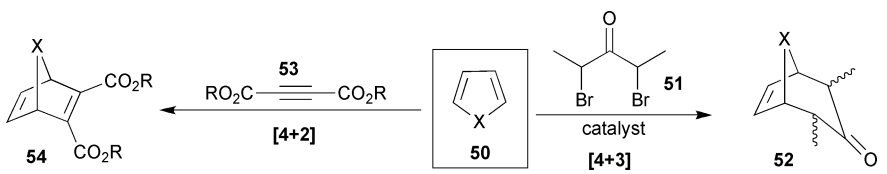
This powerful synthetic strategy has also found its place in the field of natural product total synthesis (Scheme 8). Our group has recently completed the total synthesis of goniothalesdiol by stereoselectively rearranging vinyl oxirane **42** to 2,5-dihydrofuran **43**, which could be converted to the natural product in four additional steps.[40] Sarpong and coworkers used trifluoroacetic acid to ring-expand **44** to oxabicyclic product **45** in their synthetic approach towards salviasperanol.[41] Yields are high for this substrate since the competing hydride shift is not possible. Majetich used the same conditions for a very similar substrate in his approach towards salviasperanol.[42] We showcased our novel copper-catalyzed vinyl thiirane rearrangement by converting **46** to 2,5-dihydrothiophene **47** *en route* to a formal synthesis of biotin.[36] Somfai has shown that vinyl aziridine **48** can be rearranged under forcing microwave conditions to pyrroline **49** in the presence of lithium iodide.[43] He then advanced this product to an intermediate in Hall's total synthesis of anisomycin.[44] This last approach works for a limited range of substrates.

5. [4+2] and [4+3] cycloadditions

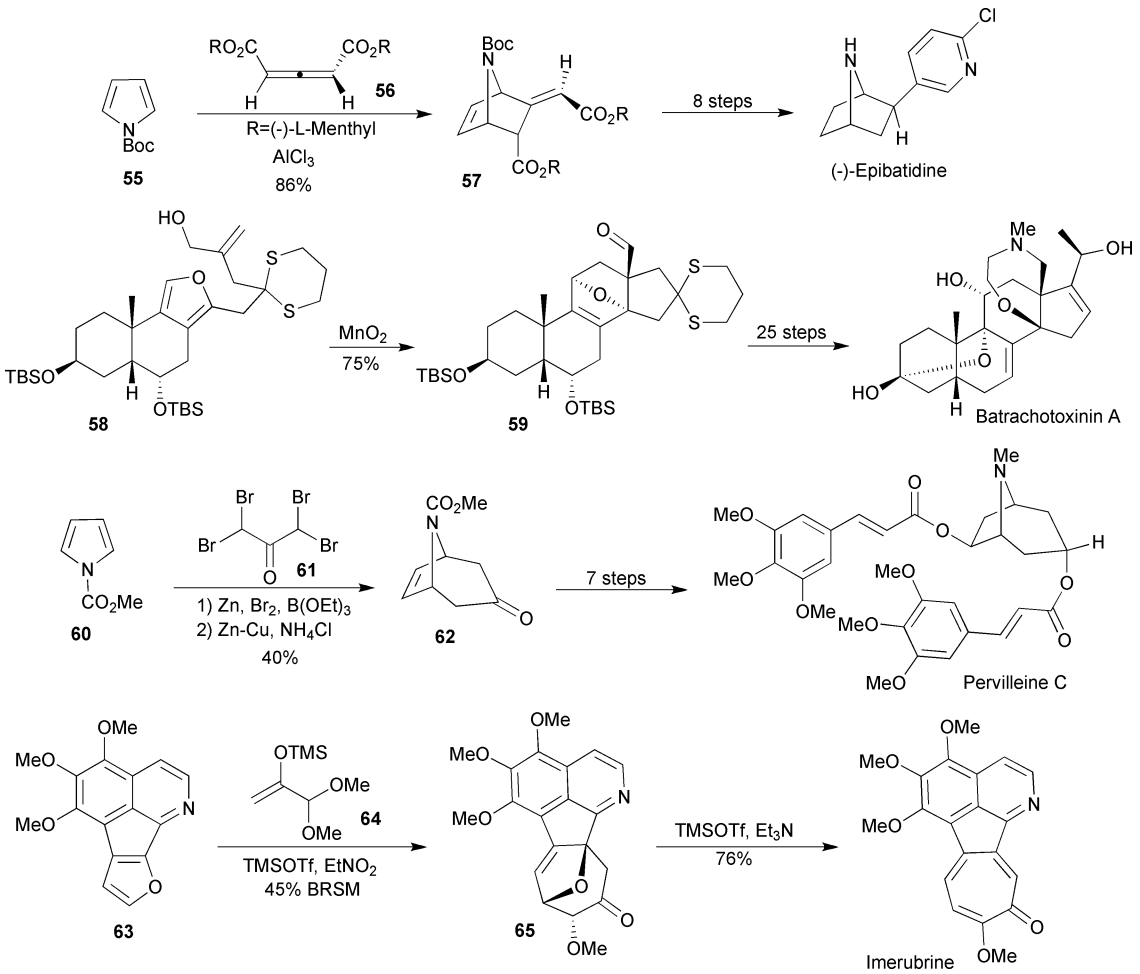
Although [4+2] and [4+3] cycloadditions of furans, thiophenes and pyrroles provide access to a very narrow spectrum of 2,5-dihydrofuran, thiophene and pyrrole products, we have included these two cycloaddition approaches in our survey because the resulting oxa-, aza and thiobicyclic products are hard to access using other methods (Scheme 9). These two approaches do not work very well



Scheme 8 Natural product total synthesis using vinyl- oxiranes, thiiranes and aziridines.



Scheme 9 [4+2] and [4+3] cycloadditions of furans, thiophenes and pyrroles.



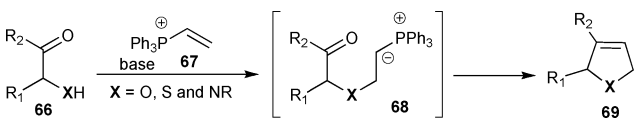
Scheme 10 Natural product total synthesis using [4+2] and [4+3] cycloadditions.

for thiophenes,[45] although this limitation can be partly remedied by using sulfone derivatives.[46] The Diels–Alder reaction of furans and pyrroles require in most cases very active dienophiles for the reaction to succeed.[47] The oxyallyl cations classically used for these [4+3] cycloadditions can be generated in many different ways, but originate in most cases from halo ketones or similary activated ketone precursors.[48] These halo ketones are converted to the oxyallyl cation by treatment with zinc metal. This approach is in most cases limited to simple substitution patterns and many functional groups are not well tolerated.

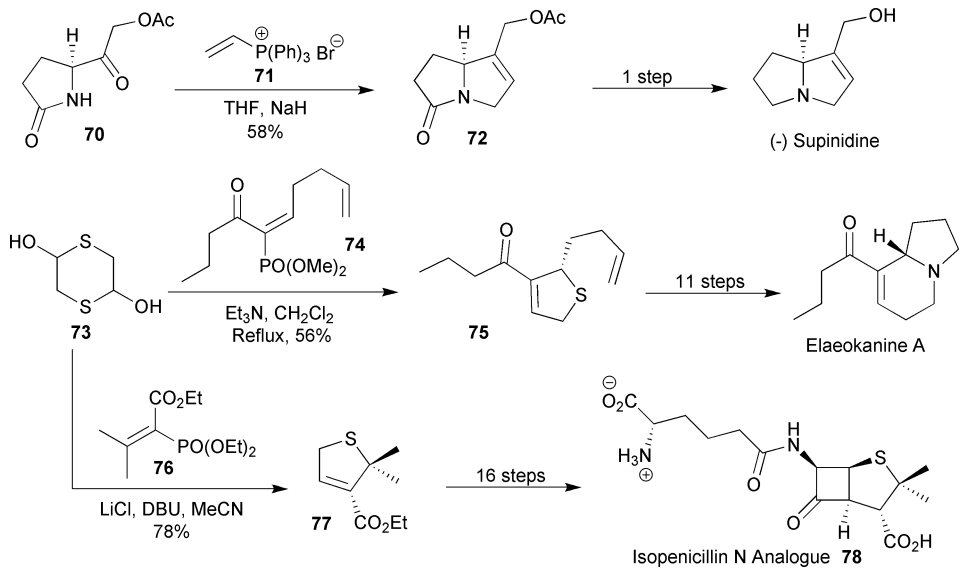
These cycloadditions have been used for the total synthesis of a number of natural products (Scheme 10). Epibatidine has been a favoured playground for evaluating different synthetic methods and strategies. Azabicyclic product **57** was nicely assembled by fusing chiral allene **56** to pyrrole **55** in the presence of aluminium trichloride.[49] This intermediate was then advanced to a known ketone that had previously been converted to epibatidine by Trudell and coworkers.[50] Kishi employed furan **58** as a dienophile in an intramolecular Diels–Alder reaction with an *in situ*-generated methacrolein moiety. The resulting product (**59**) was then eventually converted to batrachotoxinin A.[51] The anti-cancer agent pervilleine C was recently synthesized. Its tropane core (**62**) was constructed by coupling pyrrole **60** with tetrabromoketone **61**, and the resulting cycloadduct was debrominated.[52] The natural product imerubrine has been efficiently assembled by reacting the oxyallyl cation generated from **64** with furan **63**. The oxabicyclic cycloadduct (**65**) was then converted in a single step to the natural product.[53]

6. Vinyl phosphonium cascade

In the 1960's Schweizer demonstrated that various nucleophiles, including R_2NH, RSH, ROH and R_2PH, could be added to vinyl phosphonium salts (**67**, Scheme 11). When a carbonyl group (**66**) was tethered to these nucleophiles the ylide generated *in situ* underwent a Wittig olefination, thus allowing ready access to all three heterocyclic families (**69**) in a single operation.[54] This is an attractive two-component coupling reaction using readily available starting materials. When amines and alcohols are used as nucleophiles, the vinylphosphonium salt is often activated by an additional stabilizing group (such as arylsulfones and



Scheme 11 Vinyl phosphonium cascade.



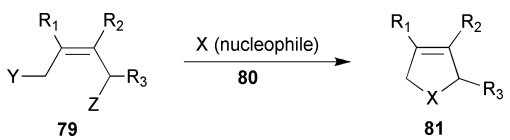
Scheme 12 Natural product total synthesis using vinyl phosphonium cascades.

arylsulfoxides) to ensure a successful Michael addition step. This multicomponent coupling strategy struggles when the vinyl phophonium salt is substituted in the β-postion, although thiols are in most cases sufficiently nucleophilic to be successful. The phosphonium salt in certain situations can be replaced by the phosphoryl ester with comparable results. The amine nucleophiles need to be electron-deficient such as amides or sulfonamides in order for the cascade to be successful. This method is one of the better methods discussed in this review to construct 2,5-dihydrothiophenes.

This exciting synthetic approach has also found its place in natural product synthesis (Scheme 12). Hewson has nicely demonstrated that the pyrrolizidine alkaloid supinidine can be rapidly assembled in two steps from lactam **70**.[55] Dihydrothiophenes **75** and **77** were both accessed in a single step from 1,4-dithiane-2,5-diol (**73**) upon treatment with vinyl phosphonates **74** and **76** respectively. Enone **75** was advanced to elaeokanine A[56] while enoate **77** was further functionalized to isopenicillin analogue **78**.[57]

7. Nucleophilic displacements

One of the oldest approaches to 2,5-dihydro- furans, thiophenes and pyrroles is simple nucleophilic displacement using either an internal or external nucleophile (Scheme 13). By using an appropriately functionalized *Z*-olefin with two leaving groups (Y and Z, **79**) a sulfur or nitrogen based nucleophile (X, **80**) can be used to form the product (**81**) directly. In practice, this method is rarely used and those few literature examples are mostly limited to unsubstituted cases. In most applications Y or Z is the desired heteroatom and the other is the leaving group, which is usually a halide, sulfonate ester or a hydroxy group. What makes this synthetic approach most unattractive is the need for a multistep route for constructing a highly functionalized *Z*-olefin (**79**). Once precursors like **79** are accessed, the cyclization tends to occur without problems.

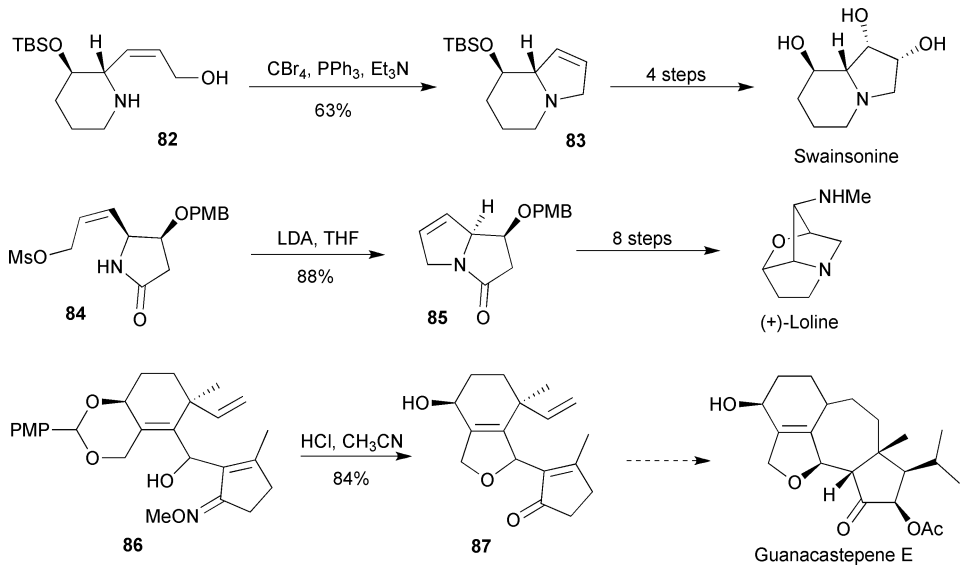


Scheme 13 Nucleophilic displacements.

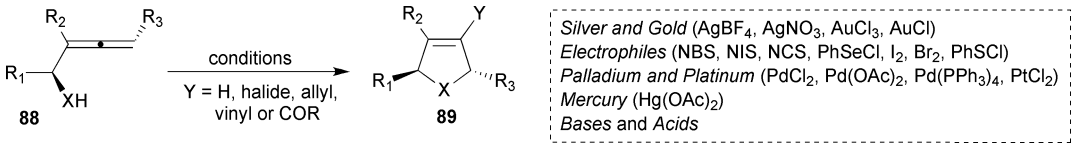
Three natural product examples utilizing this strategy are presented in Scheme 14. Swainsonine's fused bicyclic core was completed by *in situ* activation and cyclization of allylic alcohol **82** to **83**.[58] Substrate-controlled dihydroxylation and protecting group manipulations then afforded the natural product. A similar core (**85**) was stitched together by cyclizing a lithiolactam onto an allylic sulfonate ester (**84**). White and coworkers then advanced this intermediate to the bridged bicyclic alkaloid (+)-loline.[59] In his approach towards the guanacastepene family of natural product, Sorensen cyclized a triene triol (**86**) to a fused 2,5-dihydrofuran (**87**).[60]

8. Allene cyclizations

The cyclization of an allenic alcohol (**88**, Scheme 15) to a 2,5-dihydrofuran (**89**) in the presence of either a base[61] or mercury salts[62] was first reported forty years ago. In 1979 Claesson demonstrated that pyrrolines could be accessed similarly upon treatment with Ag(I) catalysts.[63] In the late 1980's Liebeskind and coworkers reported that palladium could catalyze this cyclization and that the resulting vinyl palladate could be cross-coupled *in situ* with an olefin (Y = vinyl).[64] Since then a number of halide, selenium and sulfur electrophiles have also been shown to aid this cyclization while at the same time incorporating a functional handle (Y = Cl, Br, I, PhS, PhSe).[65] This powerful transformation has been revisited in the last eight years as part of what could only be described as a gold[66] and silver[67] catalyst rush. For example, Krause has shown Au(I) and Au(III) catalysts to be ideally suited for 2,5-dihydrothiophene formation.[68] These efforts have greatly expanded the scope of this transformation, which in our opinion firmly ranks as one of the best current methods to access 2,5-dihydro- furans, thiophenes and pyrroles.

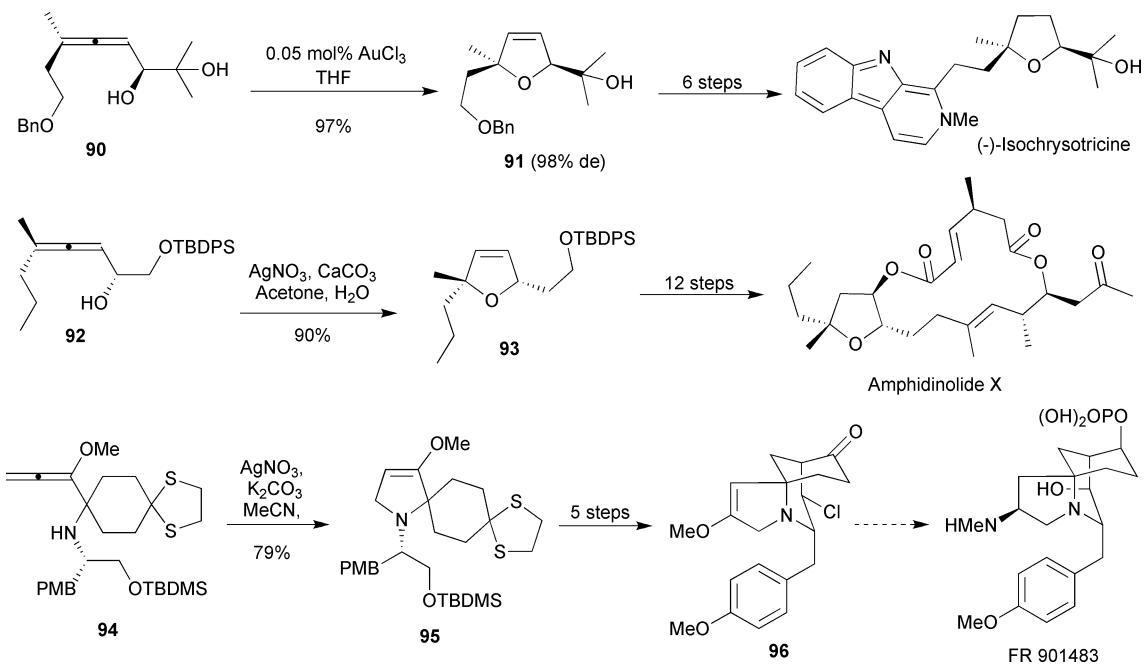


Scheme 14 Natural product total synthesis using nucleophilic displacements.



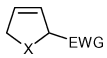
Scheme 15 Cyclizations of allenic alcohols, amines and thiols.

The allene precious metal rush has not surprisingly found its way to natural product total synthesis. Shown in Scheme 16 are three nice applications of this useful cyclization approach. Krause has used a gold(III) catalyst for cyclizing allene **90** in high yield and stereoselectivity to dihydrofuran **91** *en route* to the natural product (–)-isochrysotricine.[69] Fürstner and colleagues have used the classic silver nitrate cyclization conditions to advance allenic alcohol **92** to dihydrofuran **93**. This key intermediate was then utilized to complete the first total synthesis of amphidinolide X.[70] Although **96** has not been converted to FR 901493, Reissig has showcased an efficient cyclization of an amino allene **94** to pyrrolidine **95** that could then be converted in five additional steps to **96**.[71]



Scheme 16 Total synthesis of natural products using allene cyclizations.

Table 1 Comparison of the eight synthetic approaches for accessing classic product constructs[a]

Synthetic approach					
Ring-closing metathesis (RCM)	++	++	–	–	+
[3+2] Cycloaddition	–	+	–	+	++
Birch reduction	–	+	–	–	++
[1,3]-Rearrangement	++	+	+	++	+
[4+2]/[4+3] Cycloadditions	–	–	++	–	–
Vinylphosphine cyclization cascade	+	–	–	+	+
Nucleophilic substitution	+	–	–	+	+
Allene cyclization	+	+	–	+	+

[a] Key: ++, very good; +, fair; –, poor.

Conclusions

For a chemist planning to use any of these methods in a synthesis, perhaps one of the best ways to summarize the strengths and weakness of the eight synthetic approaches discussed in this Perspective is to graphically tabulate this information. We have chosen the five classic product classes shown in Table 1 as indicators of the effectiveness of these methods. Our ranking system uses ++ (very good), + (fair) and – (poor) to describe the effectiveness of the reaction of interest for a given substrate class. This graphic presentation also serves very well to highlight the need for further improving existing methods and to develop new approaches. For many of these substrate classes, there are no good choices, as for example, in the case of the bridged bicyclic substrate class. We are particularly proud of the fact that our contributions to this area, the copper-catalyzed rearrangement of vinyl- oxiranes, thiiranes and aziridines, allows access to all five product classes. It is important to note that this table does not take into account the difficulty of preparing the synthetic precursors or factors such as cost, toxicity, scalability or solvent use. Inclusion of these factors would be quite complex and would undoubtedly further highlight just how much need there is for better methods.

In conclusion, it is important to reiterate that there is no such thing as a general synthetic method. Instead it is the collection of good methods, each with its unique benefits and substrate scope, that truly provides access to the general product landscape. It is our belief that this approachable summary will be of great value to chemists planning on constructing a member of a specific structural class.

References

1 (*a*) F. M. Dean, *Naturally Occurring Oxygen Ring Compounds*, Butterworths, London, 1963, Chapter 1, p 1; (*b*) B. A. Keay, P. W. Dibble, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Elsevier, Oxford, 1997, Vol. 2, pp. 395–436; (*c*) M. C. Elliot, *J. Chem. Perkin Trans. I.*, 2002, 2301–2323; (*d*) J. C. Harmange and B. Figadere, *Tetrahedron: Asymmetry*, 1993, **4**, 1711–1754.

2 (*a*) E. Campaigne, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, Vol. 4, pp. 909–934; (*b*) R. K. Russell, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Elsevier, Oxford, 1997, Vol. 2, pp. 679–729; (*c*) J. B. Sperry and D. L. Wright, *Curr. Opin. Drug Discovery Dev.*, 2005, **8**, 723–740; (*d*) I. Osaka and R. D. McCullough, *Acc. Chem. Res.*, 2008, **41**, 1202–1214; (*e*) I. F. Perepichka, D. F. Perepichka, H. Meng and F. Wudl, *Adv. Mater.*, 2005, **17**, 2281–2305.

3 (*a*) G. W. Gribble, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Elsevier, Oxford, 1997, Vol. 2, pp. 395–436; (*b*) R. J. Sundberg, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, 1984, Vol. 4, pp. 370–376; (*c*) F. Bellina and R. Rossi, *Tetrahedron*, 2006, **62**, 7213–7256; (*d*) D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435–446.

4 (*a*) G. Fodor and R. Dharanipragada, *Nat. Prod. Rep.*, 1991, 603–612; (*b*) G. Fodor and R. Dharanipragada, *Nat. Prod. Rep.*, 1986, 181–184; (*c*) G. Fodor and R. Dharanipragada, *Nat. Prod. Rep.*, 1985, 221–225; (*d*) G. Fodor and R. Dharanipragada, *Nat. Prod. Rep.*, 1984, 231–234; (*e*) G. Fodor and R. Dharanipragada, *Nat. Prod. Rep.*, 1988, 67–72; (*f*) G. Fodor and R. Dharanipragada, *Nat. Prod. Rep.*, 1990, 539–548; (*g*) G. Fodor and R. Dharanipragada, *Nat. Prod. Rep.*, 1994, 443–450; (*h*) G. Fodor and R. Dharanipragada, *Nat. Prod. Rep.*, 1993, 199–206.

5 (*a*) F. X. Felpin and J. Lebreton, *Eur. J. Org,. Chem.*, 2003, 3693–3712; (*b*) T. G. Kilroy, T. P. O'Sullivan and P. J. Guiry, *Eur. J. Org,. Chem.*, 2005, 4929–4949.

6 (*a*) J. L. Couturier, K. Tanaka, M. Leconte and J. M. Basset, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 112–115; (*b*) S. Pagano, A. Mutch, F. Lefebvre and J. M. Basset, *J. Molecular. Catalysis A,*, 1998, **133**, 61–65.

7 (*a*) G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, 1992, **114**, 7324–7325; (*b*) G. C. Fu, S. T. Nguyen and R. H. Grubbs, *J. Am Chem. Soc.*, 1993, **115**, 9856–9857.

8 (*a*) G. C. Bazan, J. H. Oskam, H. N. Cho, L. Y. Park and R. R. Schrock, *J. Am. Chem. Soc.*, 1991, **113**, 6899–6907; (*b*) D. S. La, J. B. Alexander, D. R. Cefalo, D. D. Graf, A. H. Hoveyda and R. R. Schrock, *J. Am. Chem. Soc.*, 1998, **120**, 9720–9721.

9 A. Smulik, A. J. Giessert and S. T. Diver, *Tetrahedron Lett.*, 2002, **43**, 209–211.

10 Q. Yang, W. J. Xiao and Z. Yu, *Org. Lett.*, 2005, **7**, 871–874.

11 (*a*) B. Schmidt, *Eur. J. Org. Chem.*, 2003, 816–819; (*b*) A. E. Sutton, B. A. Seigal, D. F. Finnegan and M. L. Snapper, *J. Am. Chem. Soc.*, 2002, **124**, 13390–13391; (*c*) B. Schmidt, *J. Org. Chem.*, 2004, **69**, 7672–7687.

12 M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953–956.

13 J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus and A. H. Hoveyda, *J. Am. Chem. Soc.*, 1999, **121**, 791–799.

14 (*a*) G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, 1992, **114**, 7324–7325; (*b*) G. C. Fu, S. T. Nguyen and H. Grubbs, *J. Am. Chem. Soc.*, 1993, **115**, 9856–9857.

15 G. Spagnol, M.-P. Heck, S. P. Nolan and C. Mioskowski, *Org. Lett.*, 2002, **4**, 1767–1770.

16 Q. Yao, *Org. Lett.*, 2002, **4**, 427–430.

17 S. H. Hong, D. P. Sanders, C. W. Lee and R. H. Grubbs, *J. Am. Chem. Soc.*, 2005, **127**, 17160–17161.

18 (*a*) J. M. Berlin, K. Campbell, T. Ritter, T. W. Funk, A. Chlenov and R. H. Grubbs, *Org. Lett.*, 2007, **9**, 1339–1342; (*b*) I. C. Stewart, T. Ung, A. A. Pletnev, J. M. Berlin, R. H. Grubbs and Y. Schrodi, *Org. Lett.*, 2007, **9**, 1589–1592.

19 M. Fermenia-Rios, C. M. Garcia-Pajon, R. Hernandez-Galan, A. J. Macias-Sanchez and I. G. Collado, *Biorg. Med. Chem. Lett.*, 2006, **16**, 5836–5839.

20 C. M. Huwe and S. Blechert, *Synthesis*, 1997, 61–67.
21 M. Dochnahl, S. R. Schultz and S. Blechert, *Synlett*, 2007, 2599–2601.
22 (*a*) K. V. Gothelf and K. A. Jorgensen, *Chem Rev.*, 1998, **98**, 863–910; (*b*) L. M. Stanley and M. P. Sibi, *Chem Rev.*, 2008, **108**, 2887–2902.
23 (*a*) H. Pellissier, *Tetrahedron*, 2007, **63**, 3235–3285; (*b*) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765–2810; (*c*) W. H. Pearson and P. Stoy, *Synlett*, 2003, 903–921.
24 (*a*) R. Huisgen, *Angewandte Chemie*, 1977, **89**, 589–602; (*b*) J. Brokatzky and W. Eberbach, *Chemische Berichte*, 1981, **114**, 384–388; (*c*) W. Eberbach and J. C. Carre, *Chemische Berichte*, 1983, **116**, 563–586; (*d*) A. G. Schultz, R. R. Staib and K. K. Eng, *J. Org. Chem.*, 1987, **52**, 2968–2972; (*e*) P. Clawson, P. M. Lunn and D. A. Whiting, *J. Chem. Soc. Perkin Trans. I*, 1990, 159–162; (*f*) K. Ishii, T. Sone, Y. Shimada, T. Shigeyama, M. Noji and S. Sugiyama, *Tetrahedron*, 2004, **60**, 10887–10898.
25 (*a*) R. Huisgen and P. de March, *J. Am. Chem. Soc.*, 1982, **104**, 4953–4954; (*b*) R. Huisgen and X. Li, *Heterocycles*, 1983, **20**, 2363–2368; (*c*) J. S. Clark, *Nitrogen, Oxygen, Sulfur Ylide Chemistry*, 2002, 1–113; (*d*) C. V. Galliford, M. A. Beenen, S. T. Nguyen and K. A. Scheidt, *Org. Lett.*, 2003, **5**, 3487–3490.
26 (*a*) A. Padwa and M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223–269; (*b*) A. Padwa, *Topics in Current Chemistry*, 1997, **189**, 121–158; (*c*) A. Padwa and S. F. Hornbuckle, *Chem. Rev.*, 1991, **91**, 263–309; (*d*) A. Padwa, *Acc. Chem. Res.*, 1991, **24**, 22–28; (*e*) A. Padwa and K. E. Krumpe, *Tetrahedron*, 1992, **48**, 5385–5453; (*f*) A. Padwa, *Angew. Chem.*, 1976, **88**, 131–144.
27 G. Pandey and G. Lakshmaiah, *Synlett*, 1994, 277–278.
28 S. R. Martel, R. Wiesdale, T. Gallagher, L. D. Hall, M. F. Mahon, R. H. Bradbury and N. J. Hales, *J. Am. Chem. Soc.*, 1997, **119**, 2309–2310.
29 D. Yohannes, K. Procko, L. A. Lebel, C. B. Fox and B. T. O'Neill, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2316–2319.
30 P. W. Rabideau and Z. Marcinow, *Organic Reactions*, 1992, **42**, 1–334.
31 T. J. Donohoe, C. E. Headley, R. P. Cousins and A. Cowley, *Org. Lett.*, 2003, **5**, 999–1002.
32 T. J. Donohoe and H. O. Sintim, *Org. Lett.*, 2004, **6**, 2003–2006.
33 T. J. Donohoe, H. O. Sintim, L. Sisangia and J. D. Harling, *Angew. Chem. Int. Ed. Engl.*, 2004, **43**, 2293–2296.
34 (*a*) T. J. Donohoe, J.-P. Guillermin, C. Frampton and D. S. Walter, *Chem. Commun.*, 2000, 465–466; (*b*) T. J. Donohoe, J.-P. Guillermin and D. S. Walter, *J. Chem. Soc. Perkin Trans. I*, 2002, 1369–1375.
35 L. A. Batory, C. E. McInnis and J. T. Njardarson, *J. Am. Chem. Soc.*, 2006, **128**, 16054–16055.
36 E. Rogers, H. Araki, L. A. Batory, C. E. McInnis and J. T. Njardarson, *J. Am. Chem. Soc.*, 2007, **129**, 2768–2769.
37 M. Brichacek, D. E. Lee and J. T. Njardarson, *Org. Lett.*, 2008, **10**, 5023–5026.
38 R. S. Atkinson and C. W. Rees, *Chem. Commun.*, 1967, 1230–1230.
39 K. Fugami, Y. Morizawa, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, 1985, **26**, 857–860.
40 M. Brichacek, L. A. Batory and J. T. Njardarson, unpublished results.
41 E. M. Simmons and R. Sarpong, *Org. Lett.*, 2006, **8**, 2883–2886.
42 G. Majetich, G. Zou and J. Grove, *Org. Lett.*, 2008, **10**, 85–87.
43 S. Hirner and P. Somfai, *Synlett*, 2005, 3099–3102.
44 D. P. Schumacher and S. S. Hall, *J. Am. Chem. Soc.*, 1982, **104**, 6076–6080.
45 K. Kumamoto, I. Fukada and H. Kotsuki, *Angew. Chem. Int. Ed. Engl.*, 2004, **43**, 2015–2017.
46 (*a*) Y. Li, T. Thiemann, T. Sawada, S. Mataka and M. Tashiro, *J. Org. Chem.*, 1997, **62**, 7926–7936; (*b*) K. Torssell, *Acta Chem. Scand. Ser. B*, 1976, **B30**, 353–357.
47 (*a*) C. O. Kappe, S. S. Murphree and A. Padwa, *Tetrahedron*, 1997, **53**, 14179–14233; (*b*) I. Hemeon, C. DeAmicis, H. Jenkins, P. Scammells and R. D. Singer, *Synlett*, 2002, 1815–1818; (*c*) M. G. B. Drew, A. V. George, N. S. Isaacs and H. S. Rzepa, *J. Chem. Soc. Perkin. Trans. I*, 1985, 1277–1284.
48 (*a*) S. J. Jin, J. R. Choi, J. Oh, D. Lee and J. K. Cha, *J. Am. Chem. Soc.*, 1995, **117**, 10914–10921; (*b*) M. R. Ashcroft and H. M. R. Hoffmann, *Organic Syntheses*, 1978, **58**, 17–24; (*c*) H. Takaya, S. Makino, Y. Hayakawa and R. Noyori, *J. Am. Chem. Soc.*, 1978, **100**, 1765–1777.
49 M. Node, K. Nishide, T. Fujiwara and S. Ichihashi, *Chem. Commun.*, 1998, 2363–2364.
50 C. Zhang and M. C. Trudell, *J. Org. Chem.*, 1996, **61**, 7189–7191.
51 M. Kurosu, L. R. Marcin, T. J. Grinsteiner and Y. Kishi, *J. Am. Chem. Soc.*, 1998, **120**, 6627–6628.
52 K. Kulkarni, A. Y. Zhao, A. W. Purcell and P. Perlmutter, *Synlett*, 2008, 2209–2212.
53 J. C. Lee and J. K. Cha, *J. Am. Chem. Soc.*, 2001, **123**, 3243–3246.
54 (*a*) E. E. Schweizer, *J. Am. Chem. Soc.*, 1964, **86**, 2744–2744; (*b*) E. E. Schweizer and J. G. Lieber, *J. Org. Chem.*, 1968, **33**, 583–584; (*c*) J. M. McIntosh, H. B. Goodbrand and G. M. Masse, *J. Org. Chem.*, 1974, **39**, 202–206.
55 C. M. Boynton, A. T. Hewson and D. Mitchell, *J. Chem. Soc. Perkin Trans. I*, 2000, 3599–3602.
56 N. A. Khatri, H. F. Schmitthenner, J. Shringarpure and S. M. Weinreb, *J. Am. Chem. Soc.*, 1981, **103**, 6387–6393.
57 A. C. Ferguson, R. M. Adlington, D. H. Martyres, P. J. Rutledge, A. Cowley and J. E. Baldwin, *Tetrahedron*, 2003, **59**, 8233–8243.
58 C. Mukai, Y.-I. Sugimoto, K. Miyazawa, S. Yamaguchi and M. Hanaoka, *J. Org. Chem.*, 1998, **63**, 6281–6287.
59 P. R. Blakemore, S.-K. Kim, V. K. Schulze, J. D. White and A. F. T. Yokochi, *J. Chem. Soc., Perkin 1*, 2001, 1831–1845.
60 W. D. Shipe and E. J. Sorensen, *Org. Lett.*, 2002, **4**, 2063–2066.
61 S. Hoff, L. Brandsma and J. F. Arens, *Recueil des Travaux Chimiques des Pays-Bas*, 1969, **88**, 609–619.
62 F. Toda and K. Akagi, *Tetrahedron*, 1969, **25**, 3795–3799.
63 A. Claesson, C. Sahlberg and K. Luthman, *Acta Chemica Scandinavica, Series B: Organic Chemistry and Biochemisry*, 1979, **B33**, 309–310.
64 J. S. Prasad and L. S. Liebeskind, *Tetrahedron Lett.*, 1988, **29**, 4257–4260.
65 (*a*) P. L. Beaulieu, V. M. Morisset and D. G. Garratt, *Tetrahedron Lett.*, 1980, **21**, 129–132; (*b*) J. A. Marshall and X. J. Wang, *J. Org. Chem.*, 1991, **56**, 4913–4918; (*c*) A. J. Bridges and R. D. Thomas, *J. Chem. Soc. Chem. Commun.*, 1984, 694–695; (*d*) Schultz-Fademrecht, M. Zimmermann, R. Frohlich and D. Hoppe, *Synlett*, 2003, 1969–1972; (*e*) A. Horvath, J. Benner and J. E. Backvall, *Eur. J. Org. Chem.*, 2004, 3240–3243; (*f*) C. J. T. Hyland and L. S. Hegedus, *J. Org. Chem.*, 2006, **71**, 8658–8660.
66 (*a*) A. Hoffmann-Roder and N. Krause, *Org. Lett.*, 2001, **3**, 2537–2538; (*b*) N. Morita and N. Krause, *Org. Lett.*, 2004, **6**, 4121–4123; (*c*) P. H. Lee, H. Kim, K. Lee, M. Kim, K. Noh, H. Kim and D. Seomoon, *Angew. Chem. Int. Ed.*, 2005, **44**, 1840–1843; (*d*) A. S. K. Hashmi, M. C. Blanco, D. Fischer and J. W. Bats, *Eur. J. Org. Chem.*, 2006, 1387–1389; (*e*) N. Morita and N. Krause, *Eur. J. Org. Chem.*, 2006, 4634–4641.
67 (*a*) R. K. Dieter and H. Yu, *Org. Lett.*, 2001, **3**, 3855–3858; (*b*) D. Xu, Z. Li and Shenming Ma, *Chem. Eur. J.*, 2002, **8**, 5012–5018; (*c*) A. S. Golubev, N. N. Sergeeva, L. Hennig, A. F. Kolomiets and K. Burger, *Tetrahedron*, 2003, **59**, 1389–1394; (*d*) M. A. Chowdhury and H. U. Reissig, *Synlett*, 2006, 2383–2386; (*e*) B. Alcaide, P. Almendros and R. Rodriguez-Acebes, *J. Org. Chem.*, 2006, **71**, 2346–2351; (*f*) R. K. Dieter, N. Chen and V. K. Gore, *J. Org. Chem.*, 2006, **71**, 8755–8760; (*g*) B. Mitasev and K. M. Brummond, *Synlett*, 2006, 3100–3104.
68 N. Morita and N. Krause, *Angew. Chem. Int. Ed. Engl.*, 2006, **45**, 1897–1899.
69 F. Volz and N. Krause, *Org. Biomol. Chem*, 2007, **5**, 1519–1521.
70 (*a*) O. Lepage, E. Kattnig and A. Furstner, *J. Am. Chem. Soc.*, 2004, **126**, 15970–15971; (*b*) A. Furstner, E. Kattnig and O. Lepage, *J. Am. Chem. Soc.*, 2006, **128**, 9194–9204.
71 S. Kaden and H.-U. Reissig, *Org. Lett.*, 2006, **8**, 4763–4766.

