Article

Enantioselective Radical Reactions and Organocatalysis

Gareth J Rowlands

Institute of Fundamental Sciences – Chemistry, Massey University (e-mail: *g.j.rowlands@massey.ac.nz*)

Introduction

…most chemists have avoided radical reactions as messy, unpredictable, unpromising, and essentially mysterious – Chryssostomos Chatgilialoglu[1]

For many years, radicals – molecules that contain a single unpaired electron – were considered too reactive to be used productively in organic synthesis. This myth has been dispelled and, somewhat ironically, it is now clear that radicals frequently offer higher levels of selectivity and predictability than analogous ionic reactions.[2] Even with increased understanding, dogma dictated that radicals could not participate in highly stereoselective reactions despite them being simple organic species, subject to the same steric and electronic interactions as all other molecules. This too has proved incorrect as the last decade has seen tremendous progress in enantioselective radical reactions.[3] The majority of naturally occurring compounds are chiral and not superimposable on their mirror images. One of the major challenges for organic chemists is to develop enantioselective reactions, *i.e.* reactions that can discriminate between mirror image enantiomers. The domination of enantioselective transformations by metal-based reagents is coming to an end as it becomes clear that small, metal-free molecules, or organocatalysts,[4] can achieve complementary reactions without recourse to potentially toxic or expensive metals.

The recent introduction of radical intermediates into organocatalysis by MacMillan[5] and Sibi[6] has attracted considerable attention and there is no doubt that the principles underpinning this methodology will have a major impact on organic synthesis. It is often overlooked that radical chemistry has always been conducive to organocatalysis, with many of the general characteristics of radicals being ideally suited for a synergistic relationship with organic-based catalysts. Radicals are largely impervious to the effects of water, display greater functional group tolerance than ionic reagents and operate over a wider pH range. It is the aim of this article to briefly outline the shared history of radicals and organocatalysis and speculate on the future directions of this profitable partnership.

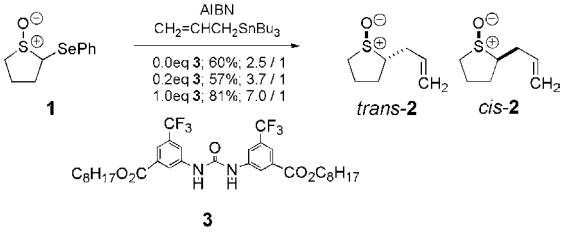
Organic Reagents and Organocatalysts in Stereoselective Radical Chemistry

When the spatial alignment of two interacting reagents is controlled, it is possible to achieve a stereoselective reaction. For this to occur, at least one of the reactants must have a well-defined shape; this can arise if either the molecule has a specific configuration or if it forms a temporary bond to a second molecule with a well-defined shape. This article will cover three strategies for achieving stereoselective radical reactions - the interaction of a substrate with a Lewis acid, the interaction of the substrate with a chiral reagent, and the temporary incorporation of chirality into the substrate.

Chiral Lewis Acid Activation

Lewis acids activate a substrate by accepting electrons and lowering the energy of the lowest unoccupied molecular orbital (LUMO) of the molecule, thus encouraging nucleophilic attack. The smallest Lewis acid is the proton and its use in catalysis is often termed Brønsted acid catalysis. The last five years have seen a renaissance in the use of Brønsted acids in asymmetric catalysis[7,8] but it is clear that the ground work was laid over a decade ago. Brønsted acids can be classified into two categories: neutral acid catalysts such as ureas, which are often termed hydrogen-bond catalysts, and stronger acid catalysts that are proton donors, such as phosphoric acids. Both classes have been employed in radical chemistry.

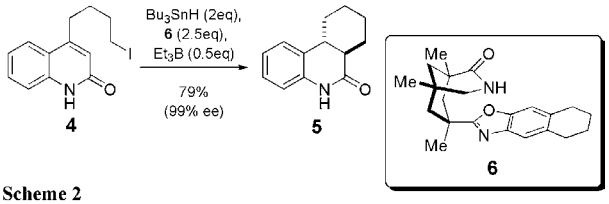
Since Jacobsen's seminal work in 1998,[9] (thio)ureas have rapidly become one of the *privileged* motifs for asymmetric organocatalysis,[8] yet the first example of a urea being used as a hydrogen-bond catalyst was four years earlier in Curran's diastereoselective allylation of cyclic sulfinyl radicals formed from **1** (Scheme 1).[10] Urea **3** was shown to increase both the yield and the *trans/cis* ratio of **2**, with as little as 0.2 equivalents of **3** increasing the ratio from 2.5/1 with no catalyst to 3.7/1. Urea **3** is thought to clamp the sulfinyl oxygen and increase the steric bulk of one face of the molecule whilst activating the incipient radical to allylation. Considering this promising result it is shocking that there have been no other reports of the use of (thio)ureas in radical chemistry.



Scheme 1

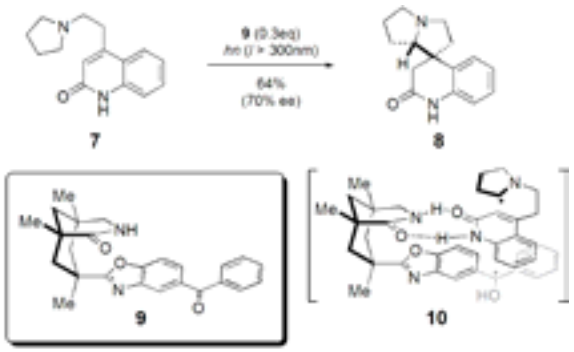
Chiral lactam **6** has been employed as a hydrogen-bond catalyst for a host of enantioselective reactions including the cyclization of iodide **4** to furnish **5** in excellent yield and selectivity (Scheme 2).[11] Lactam **6** binds to amide **4** by complementary hydrogen-bonding between carbonyl and N–H moiety and thus induces high enantioselectivity. Whilst super-stoichiometric quantities of **6** give the best results (2.5 equiv. gives 99% e.e.), use of sub-stoichiometric quantities still results in chiral amplification with just 0.1 equivalents affording **5** in 55% e.e. The correct choice of solvent is pivotal for high enantioselectivities in the catalytic variant; the reaction mixture must be heterogenous throughout the reaction with the substrate dissolving only on its complexation to **6** thus forcing cyclization

to occur in a chiral environment. The same complexing reagent has been successfully used in the enantioselective radical cyclization of piperidines[12,13] and the synthesis of fused tetracycle cyclobutanes *via* either inter- or intramolecular [2+2]-photocycloaddition reactions.[13]



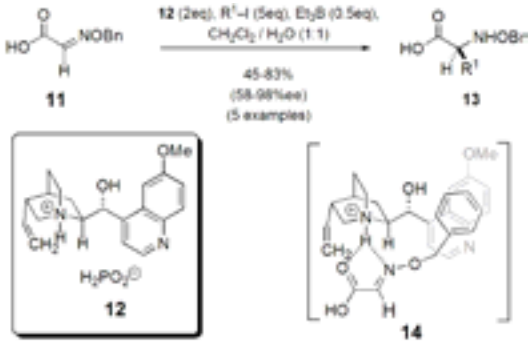
Scheme 2

An exciting variation on this system has permitted a highly enantioselective, catalytic, photoinduced electron transfer reaction that furnishes tetracycle **8** (Scheme 3).[14] Key to the success of this reaction is catalyst **9** that acts as both the chiral template and an antenna for harvesting the light required to activate the substrate. Excitation of **9** expedites electron transfer from the amine **7** to **9** and permits formation of the α-aminoalkyl radical **10**. Cyclization of the complexed radical **10** occurs from the top face as the catalyst blocks the bottom face of the alkene. Just 0.3 equivalents of **9** are required for the reaction to occur in high yield and enantioselectivity. The simplicity of this methodology and its use of just two reagents coupled with the rapid increase in molecular complexity ensure that this methodology has a bright future.



Scheme 3

A stronger Brønsted acid catalyst is the chiral quaternary ammonium salt **12** that has been used in the synthesis of amino acid derivatives **13** under mild, aqueous reaction conditions from **11** (Scheme 4).[15] Salt **12**, prepared from a *Cinchona* alkaloid and hypophosphorous acid, plays a multitude of different roles; it acts as the radical chain carrier, as a surfactant to increase the water solubility of the organic components, and as a chiral additive capable of inducing high stereoselectivity in the addition (up to 98% ee). The enantioselectivity is thought to arise from hydrogen bonding between **11** and **12** coupled with the π-stacking of the aryl groups as depicted in **14**. Whilst a catalytic variant has not been developed yet, the reaction still has many advantages over conventional nucleophilic additions: no metal reagents are utilised, all reagents are cheap and readily available, aqueous solvent mixtures are preferred to organic solvents, and the chiral amine can be recycled readily. With these benefits in mind, further applications of this and analogous systems can be anticipated in the future along with efforts to develop catalytic variants.

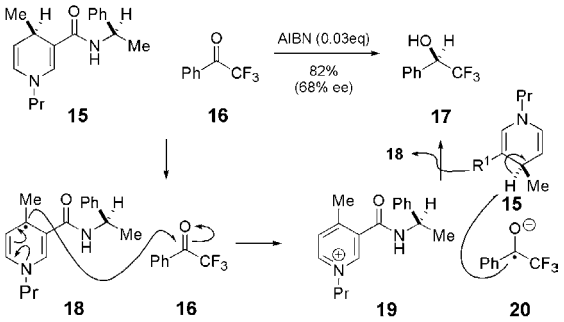


Scheme 4

Enantioselective Hydrogen Atom Transfer

It is possible to transfer a hydrogen atom from a radical chain carrier to a substrate radical in a stereoselective manner. There are two distinct methods that achieve this selectivity, the first involves an achiral hydrogen source and a chiral Lewis acid, whilst the second involves the use of a chiral hydrogen donor. Curiously, whilst the former method is the more common with metal-based systems it has not been achieved under metal-free conditions. On the other hand, the second strategy permitted some of the earliest examples of asymmetric organocatalysis.

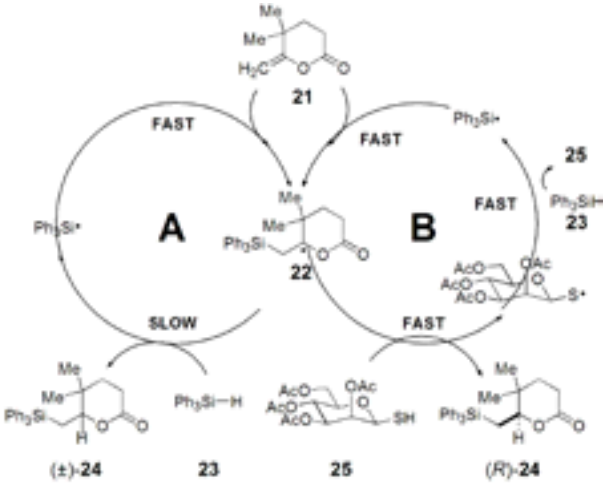
Nearly thirty years ago, Ohno synthesized nictotinamide **15** as a chiral model of the coenzyme NAD(P)H and found that it reduced certain carbonyl compounds with high selectivity (~70% e.e.).[16] Later, Tanner showed that the reaction proceeded *via* a radical pathway and was in fact the first radical chain reaction whose propagation steps contained an enantioselective hydrogen atom transfer (Scheme 5).[17] Radical initiation with azobisisobutyronitrile (AIBN) abstracts a hydrogen from **15** to give the doubly allylic stabilised radical **18**. Electron transfer from this to **16** is driven by aromatisation that provides **19** and generates the ketyl radical anion **20**. Interaction of this last intermediate with chiral hydrogen source **15** furnishes the desired product **17** and propagates the chain by reforming **18**. Once again, this reaction appears to have been consigned to history with little study outside of biochemistry reported, even though it offers an intriguing route to enantiopure alcohols.



Scheme 5

It is often forgotten that radical chain reactions rely on polarity effects for efficient propagation; smooth hydrogen atom transfer only occurs if an electrophilic radical interacts with a nucleophilic source of hydrogen or *vice versa*. If the polarities are mis-matched then the reaction will be a non-chain process and will be sluggish at best.

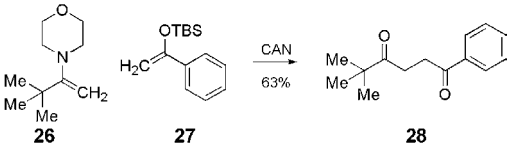
Polarity-reversal catalysts alleviate this problem, facilitating hydrogen atom transfer *via* the addition of an extra propagation step.[18,19] In the radical hydrosilylation of electron-rich alkenes such as **21**, the hydrogen atom transfer step from silane **23** to prochiral radical **22** is slow (Cycle ***A***, Scheme 6) as both donor **23** and acceptor **22** are nucleophilic. Thiol **25** acts as a polarity-reversal catalyst and overcomes this problem; the slow propagation step of the previous reaction is replaced now by two fast propagation steps (Cycle ***B***) as the thiol provides an electron deficient (or electrophilic) hydrogen atom. By making the polarity-reversal catalyst a chiral carbohydrate derivative (**25**), it is possible to enantioselectively transfer hydrogen to radical **22**. Furthermore, since **25** is regenerated in the second propagation step of Cycle ***B*** a sub-stoichiometric quantity of chiral reagent can be employed. In this example just 0.05 equivalents of **25** in the presence of a radical initiator gives lactone (*R*)-**24** in 90% yield and 95% e.e.[18] It should be noted that this is a general principle and should allow enantioselective organocatalytic radical reactions for a range of transformations. It is somewhat surprising that, with the exception of Roberts's work, very few examples of chiral polarity-reversal catalysts have been reported so this appears to be an area ripe for exploitation.



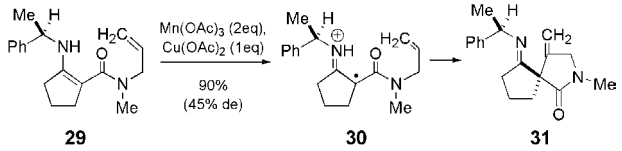
Scheme 6

Aminocatalysis/Enamine Activation

The new radical activation strategy reported by MacMillan[5] and Sibi[6] is based on aminocatalysis or enamine catalysis popularized by List and MacMillan,[20] but has its roots in older radical methodology. In 1992 Narasaka reported the cerium(IV) ammonium nitrate (CAN) mediated oxidation of an enamine **26** to a radical cation and the addition of this radical to electron rich alkenes such as **27** to give **28** (Scheme 7).[21] Whilst this undoubtedly laid the foundations for the current methodology, it was limited by the need to pre-form the enamine and because it was non-stereoselective. Arguably, Cossy reported[22] the first solution to the latter shortcoming with the manganese(III) acetate/copper(II) acetate-mediated oxidation of a chiral β-carboxamido enamine **29** to a radical cation **30** (Scheme 8). The radical then underwent cyclization to give the spirocycle **31** in moderate diastereoselectivity (45% d.e.). The enamine was formed from a primary amine and it is entirely possible that use of a secondary amine would have led to an iminium cation with less rotational freedom and thus would have resulted in better stereochemical induction. Again the reaction was limited by the need to pre-form the enamine precursor, but it clearly revealed the plausibility of this strategy for asymmetric radical chemistry.



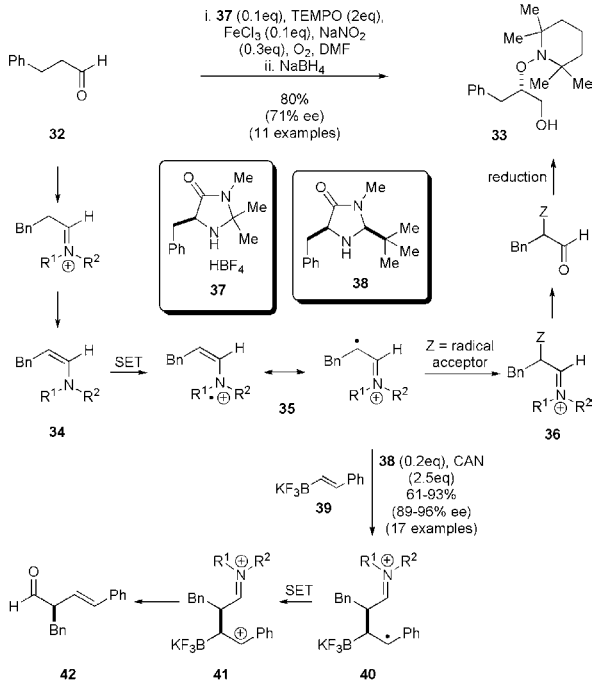
Scheme 7



Scheme 8

By refining these early examples both MacMillan[5] and Sibi[6] have developed a truly exciting method for conducting enantioselective radical reactions that shows great potential to encompass many different transformations. Both methodologies combine radical chemistry with enamine-based organocatalysis to functionalise the α-position of aldehydes; condensation of an aldehyde **32** with a sub-stoichiometric amount of a chiral secondary amine (**37** or **38**) gives enamine **34** (Scheme 9). Oxidation of the enamine by single electron transfer then furnishes iminium radical cation **35** that reacts with the appropriate radical acceptor to give the cation **36** (or **40**), which finally undergoes hydrolysis to product **33** (or **42**) and regenerates the chiral catalyst (**37** or **38**), ready to repeat the reaction. The fate of the alkyl radical **35** differentiates the two methodologies. In Sibi's methodology[6] the radical is trapped with the persistent *O*-centred 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO), resulting in the α-oxyamination of the initial aldehyde (Scheme 9). The chiral imidazolidinone **37** gives moderate to excellent enantioselectivities for a range of aldehydes, and although a variety of aryl-substituted aldehydes were tolerated, simple alkyl aldehydes containing no aromatic rings or double bonds gave no selectivity suggesting that π interactions are important.[5] The benefit of this system is that oxidation is achieved with a catalytic quantity of iron(III) chloride in conjunction with a stoichiometric amount of a co-oxidant comprised of sodium nitrite and oxygen. The disadvantage is that products of type **33** are accessible by more conventional chemistry.

MacMillan's methodology[5] appears to be more versatile and permits the reaction of the radical cation **35** with a host of electron rich acceptors including allylsilanes, silylenol ethers, heteroaromatics and alkenyl potassium trifluoroborate salts. Thus, reaction of **35** with the alkenyl potassium trifluoroborate **39** gives **40** in good yield (Scheme 9). In MacMillan's reactions two distinct oxidation steps occur; the first gives radical cation **35** whilst the second is required to oxidise radical **40** to cation **41**. As a result, the methodology currently needs an excess of the metal-based oxidant CAN. The reaction appears to be quite general as a range of aldehydes can be employed whilst the alkenyl component **39** can be alkyl- or aryl-



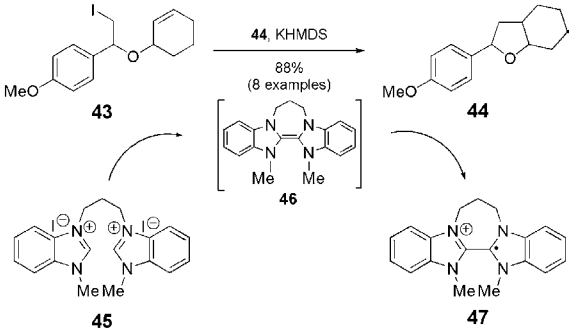
Scheme 9

substituted with little variation in the yield or selectivity. Not only does this methodology permit the facile synthesis of enantiomerically pure homoallylic aldehydes that would be difficult to form by conventional means, but also it is undoubtedly just the tip of the iceberg; it is easy to imagine this general strategy, the formation of a chiral radical cation from enamines, being employed in a wide range of novel transformations and it will be fascinating to see how this work progresses.

Currently, neither methodology is ideal. Sibi's system[6] involves a single oxidation and so appears to be limited to the addition of persistent radicals. MacMillan's protocol[5] is far more impressive in scope but it uses an excess of oxidant. A combination of the two would have a major impact on both radical chemistry and organocatalysis, and is undoubtedly being investigated.

Future Directions for Organocatalysis in Radical Chemistry

Hopefully, the discussion above has shown that most forms of organocatalysis can be applied to enantioselective radical reactions. No doubt the area will continue to develop rapidly in order to take advantage of all the benefits proffered by both radical processes and organocatalysis in terms of both clean reaction conditions and the range of transformations possible. It is obvious that the radical enamine-activation strategy will have a major impact and many new applications can be expected in the future. Improvements to the oxidation protocol that allow for use of sub-stoichiometric amounts of metal-based oxidants and more environmentally benign terminal oxidants are major goals. It will be interesting to see if the antithetical strategy, the reductive formation of radical intermediates, will be applicable to enantioselective organocatalysis. Already organic electron donors have been developed for the reduction of halides to radicals.[23] Tetraazaalkene **46** is a neutral ground-state organic molecule capable of donating an electron to a suitable acceptor due, in part, to the considerable aromatisation energy residing in its derived radical cation **47** (Scheme 10), and the stability imparted to the carbocationic centre by the adjacent nitrogen atoms. This allows **46** to reduce unactivated aryl and alkyl iodides such as **43** to C-centred radicals that can then undergo cyclization to give, *e.g.* **44**. The major drawback here is the high reactivity of **46** towards air, which requires that it normally be prepared by deprotonation of the stable salt **45** immediately prior to use. If this limitation can be overcome related reagents could be of considerable value.



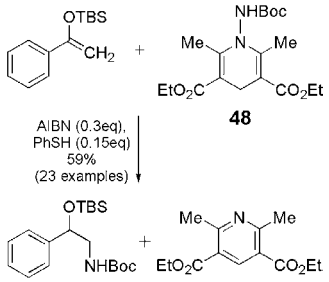
Scheme 10

The use of hydrogen-bond donor catalysts (or Brønsted acid catalysts) in radical chemistry is ripe for exploitation; the groundwork has been laid, examples of enantioselective templated reactions[11-14] and chiral proton donors[15] are known. Now it is necessary to take these precedents and pursue more general and valuable examples. It is surprising that chiral (thio)ureas have not been employed in radical additions or cyclizations. Likewise, the use of chiral phosphoric acids appears to be an obvious progression; logically, the use of chiral acids to activate various C=N moieties to radical attack would be the first step before tackling more general activation/addition methodology. It should be remembered that the last decade has seen considerable progress in the use of metal-based Lewis acids for enantioselective radical reactions whilst at the same time, Brønsted acids have begun to replace Lewis acids in many ionic transformations.[7]

The development of new chiral hydrogen atom sources as simple chain carriers or polarity-reversal catalysts is likely to continue. Not only do phosphorus hydrides show great promise as radical reagents due to their stability, low toxicity and water compatibility,[24] but also they are readily incorporated into chiral frameworks offering considerable scope for optimization. Currently, the use of chiral phosphorus hydrides has met with little success[25] perhaps because of a poor choice of chiral manifold - more sterically demanding structures may result in better diastereo- and enantioselectivities.

An interesting possibility for the development of an enantioselective transformation is the thiol-catalyzed radical transfer-hydroamination of alkenes with the N-aminated Hantzsch ester **48** (Scheme 11).[26] This reaction involves **48** as both a source of an aminyl radical and a hydrogen atom donor. The latter requires hydrogen atom transfer from a carbon atom to a carbon radical, a generally inefficient transformation that can be facilitated by the use of

a polarity reversal catalyst. The reaction proceeds in moderate yield for a range of alkenes but, more importantly, it can proceed with good diastereoselectivity (up to 90% d.e.) suggesting that possibly it could be developed into an enantioselective process either by the correct choice of polarity reversal catalyst or hydrogen-bond catalyst. Such transformations hold plenty of potential especially as they are complementary to metal-based systems, which generally give the product of Markownikov addition.



Scheme 11

Summary

It is clear that organocatalysis is going to play an important role in the future of enantioselective radical reactions. The recent reports of Sibi and MacMillan have highlighted the potential this combination displays and it is hoped that this article shows that radicals, by their very nature, have always been good partners for organocatalysis, and have in fact been employed in some of the earliest examples of this now ubiquitous field. It is also hoped that the article offers an insight into the potential of this powerful marriage of chemistries and inspires others to forget their fear of radicals and enter this fascinating field of chemistry.

References

1. Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.
2. Rowlands, G. J. *Ann. Rep. Prog. Chem., Sect. B.* **2003**, *99*, 3-20; **2004**, *100*, 33-49; **2005**, *101*, 17-32; **2006,** *102*, 17-33; **2007,** *103*, 18-34; Zard, S. Z. *Radical Reactions in Organic Synthesis*, OUP: Oxford, 2003.
3. Bar, G.; Parsons, A. F. *Chem. Soc. Rev.* **2003**, *32*, 251-263; *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications,* Curran, D. P.; Porter, N. A.; Giese, B. (Eds.), VCH: Weinheim, 1995; Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263-3295; Zimmerman, J.; Sibi, M. P. *Top. Curr. Chem.* **2006**, *263*, 107-162.
4. Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, DOI: 10.1002/anie.200704684; Pellissier, H. *Tetrahedron* **2007**, *63*, 9267-9331.
5. Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398-399; Beeson, T. D.; Mastracchio, A.; Hong, J. B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582-585; Jang, H. Y.; Hong, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004-7005.
6. Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124-4125.
7. Akiyama, T. *Chem. Rev.* **2007,** *107*, 5744-5758.
8. Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713-5743.
9. Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902.
10. Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259-3261.
11. Dressel, M.; Bach, T. *Org. Lett.* **2006**, *8*, 3145-3147.
12. Aechtner, T.; Dressel, M.; Bach, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 5849-5851; Dressel, M.; Aechtner, T.; Bach, T. *Synthesis* **2006**, 2206-2214.
13. Selig, P.; Bach, T. *J. Org. Chem.* **2006**, *71*, 5662-5673.
14. Bauer, A.; Westkamper, F.; Grimme, S.; Bach, T. *Nature* **2005**, *436*, 1139-1140.
15. Cho, D. H.; Jang, D. O. *Chem. Comm.* **2006**, 5045-5047.
16. Ohno, A.; Ikeguchi, M.; Kimura, T.; Oka, S. *J. Am. Chem. Soc.* **1979**, *101*, 7036-7040.
17. Tanner, D. D.; Kharrat, A. *J. Am. Chem. Soc.* **1988**, *110*, 2968-2970.
18. Cai, Y. D.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1376-1386.
19. Haque, M. B.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2881-2889; Haque, M. B.; Roberts, B. P. *Tetrahedron Lett.* **1996**, *37*, 9123-9126.
20. Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416-5470; Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569.
21. Narasaka, K.; Okauchi, T.; Tanaka, K.; Murakami, M. *Chem. Lett.* **1992**, 2099-2102.
22. Cossy, J.; Bouzide, A.; Leblanc, C. *J. Org. Chem.* **2000**, *65*, 7257-7265.
23. Murphy, J. A.; Khan, T. A.; Zhou, S.-z.; Thomson, D. W.; Mahesh, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1356-1360.
24. Leca, D.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Chem. Soc. Rev.* **2005**, *34*, 858-865.
25. Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. J. *Tetrahedron: Asym.* **2003**, *14*, 2849-2851.
26. Guin, J.; Fröhlich, R.; Studer, A. Angew. *Chem. Int. Ed*. **2008**, *47*, 779-782.