DOI: 10.1002/adsc.200505165

Stereoselective Construction of Quaternary Stereocenters

Jens Christoffers,* Angelika Baro

Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany
Fax: (+49)-711-685-4269, e-mail: jchr@oc.uni-stuttgart.de

Received: April 20, 2005; Accepted: July 16, 2005

Abstract: Quaternary stereocenters are a particular challenge for stereoselective synthesis. With a central view on this specific structural issue, selected examples from the recent literature are highlighted in order to evaluate the state of the art of asymmetric C–C bond formation. The review is divided into sections on addition and substitution reactions, rearrangements and cycloaddition reactions.

Keywords: asymmetric catalysis; asymmetric synthesis; C–C coupling; chiral auxiliaries; quaternary stereocenters; synthetic methods

1 Introduction

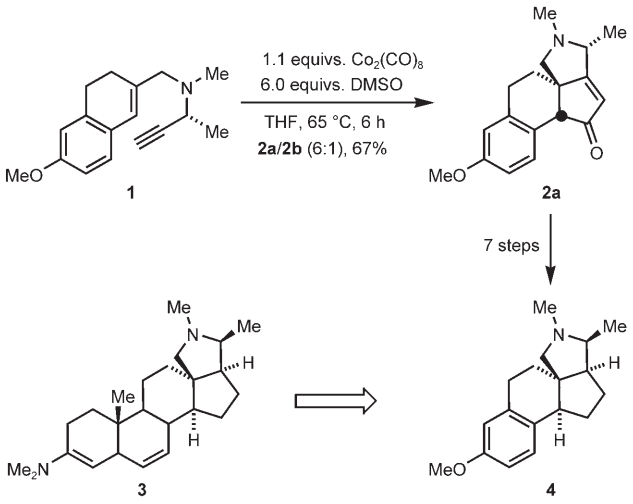
The challenge of controlling the configuration of asymmetric centers is crucial in modern organic synthesis. Today a broad repertoire of chiral auxiliaries, reagents and catalysts allows for the stereoselective construction of tertiary stereocenters with high reliability in most cases. In contrast, the formation of a quaternary stereocenter often turns out to be more problematic. Therefore, this issue remains the ultimate touchstone of every enantioselective procedure.

Quaternary stereocenters – this specific structural issue has been reviewed by several authors in the past years.[1] The intention of this review is to highlight selected examples from the newer literature (end of 2003 until begin of 2005), which have not been covered in a recent monograph.[1i] Certainly, this collection cannot be comprehensive, but must be regarded as a personal choice of the authors. Moreover, a rather narrow definition of a quaternary, i.e., all carbon-substituted, carbon atom is used herein, excluding tertiary alcohols, ethers, amines, etc., although a large number of extremely interesting articles dealing with these structural issues can be found in the recent literature.[2–6] Nevertheless, enantioselective as well as diastereoselective work is presented herein. Apart from catalytic asymmetric processes which are, of course, of central interest today, the use of chiral auxiliaries should also be considered. Despite their stoichiometric application, chiral auxiliaries are of great practical relevance.

Quaternary stereocenters can be found not only in a wide range of important and useful compounds in pharmaceutical and medicinal contexts, but also in a large variety of natural products. As already mentioned, it is almost impossible to cover this issue completely. As a spotlight, the formal total synthesis of the steroidal alkaloid (+)-conessine (**3**) will be mentioned as an introduction (Scheme 1).[7] Jiang and Xu prepared the optically active enyne **1** from 6-methoxy-1-tetralone and a propargylic amine in four steps with 63% yield, which was then converted with a stoichiometric amount of $Co_2(CO)_8$ in an asymmetric Pauson–Khand reaction[8] to give the optically active tetracyclic compound **2a** together with a small amount of its unwanted diastereoisomer **2b**. Compound **2a** was further converted in seven synthetic steps and 59% yield to give the BCDE ring precursor **4** of the natural product **3**.

Jens Christoffers was born in Germany in 1966. After receiving his Diploma from the Universität Marburg (Germany) in 1992 he moved together with Prof. K. H. Dötz to Bonn (Germany), where he completed his doctorate in 1994 on Fischer carbene complexes and Pauson–Khand reactions. He got in touch with zirconocene catalysis during a post-doctoral stay with Prof. R. G. Bergman in Berkeley (USA). In 1996 he started his independent career at the Technische Universität Berlin (Germany) and finished his Habilitation with Prof. S. Blechert in 2000. He has been Professor of Organic Chemistry at the Universität Stuttgart (Germany) since 2001. His current research interests are in the fields of asymmetric catalysis, synthesis of heterocyclic compounds and catalytic oxidation reactions utilizing molecular oxygen.

Angelika Baro was born in Stadtoldendorf (Germany). She studied chemistry at the Georg-August-Universität Göttingen (Germany), where she received in 1987 her PhD degree in Clinical Biochemistry under supervision of Prof. H. D. Söling. Since 1991 she has been scientific staff member at the Institut für Organische Chemie, Universität Stuttgart (Germany).

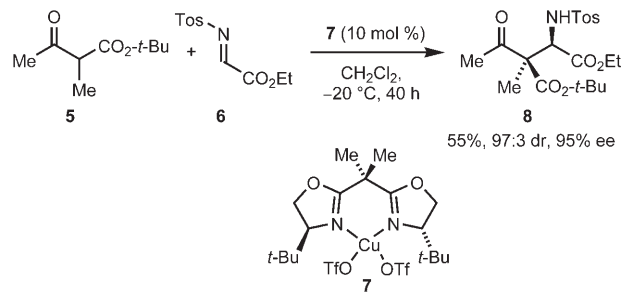


Scheme 1. Formal total synthesis of (+)-conessine (**3**) by asymmetric Pauson–Khand reaction.

2 Addition and Substitution Reactions

2.1 Asymmetric Mannich Reaction

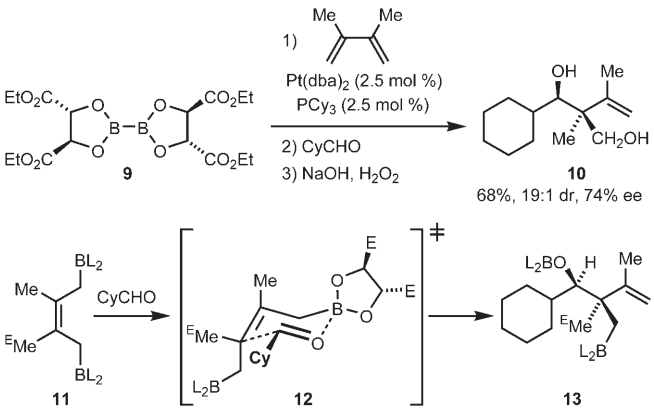
The Mannich reaction, defined as the addition of an enol to an (*in situ* generated) aldiminium ion, provides access to a β-amino carbonyl structural motif and is therefore complementary to an aza-Michael addition.[9] In asymmetric Mannich reactions, an amino group, normally at a secondary, sometimes a tertiary carbon center, is generated.[10] Examples of quaternary stereocenter formation are very rare, one of which was reported by Jørgensen and coworkers.[11] A chiral Lewis acid catalyst prepared from an L-*tert*-leucine derived BOX-ligand and $Cu(OTf)_2$ converts malonates with α-aldiminoester **6** in high yield and stereoselectivity if 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) is used as a stoichiometric additive. However, no quaternary stereocenters are formed in these cases. The reaction with β-oxo esters like **5** (Scheme 2) proceeds without HFIP as additive and products like **8**, bearing adjacent tertiary and quaternary stereocenters, are obtained with high stereoselectivity, although the yields are moderate.



Scheme 2. Asymmetric Mannich reaction with optically active BOX-Cu(II) catalyst.

2.2 Asymmetric Allylboration Reactions

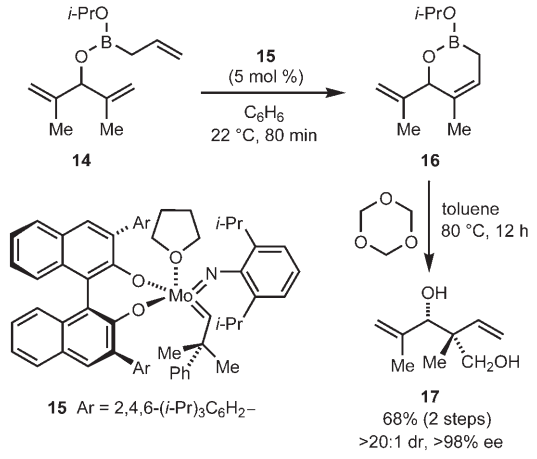
The chiral auxiliary-based allylboration reaction is an excellent tool to prepare optically active secondary homoallylic alcohols.[12] Recently, Morken and Morgan reported a three-step, one-flask sequence of diboration and allylboration (with subsequent oxidative work-up) yielding 1,3-diols with a quaternary stereocenter.[13] In the first step, a *Z*-selective Pt-catalyzed 1,4-addition of diboronate **9** (derived from L-diethyl tartrate) across di-



Scheme 3. Sequence of diboration-allylboration with oxidative work-up yielding homoallylic 1,3-diols with a quaternary stereocenter (E = CO_2Et).

methylbutadiene occurs to give a 1,4-diboryl-2-butene derivative **11**, which is further converted with, for example, cyclohexanecarbaldehyde (CyCHO) to afford, after work-up with NaOOH, the diol **10** with a tertiary and quaternary stereocenter (Scheme 3). The diastereomeric ratio is high (>19:1), whereas yield and enantioselectivity are moderate. A mechanistic rationale for the stereochemical outcome of the reaction involves a chair-like transition state **12** with the cyclohexyl residue Cy of the carbaldehyde (CyCHO) in an equatorial position.[12e] The two ester groups E of the tartrate-derived boronate auxiliary favour a front side coordination of the aldehyde to the boron resulting in an intermediate **13** with the (*E*)-methyl group (^{E}Me) in an anti-configuration to the OH.

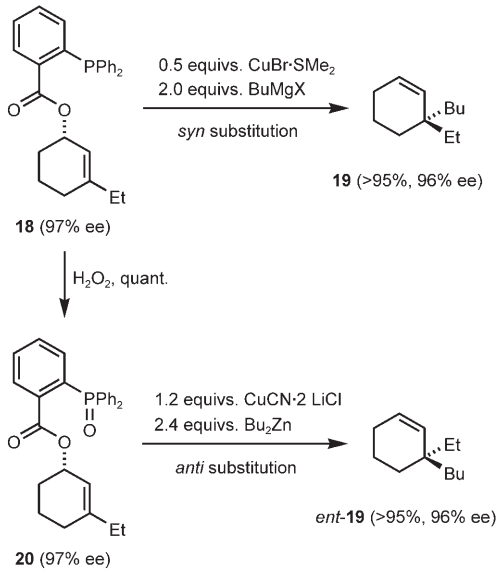
A second example reported by Schrock and Hoveyda et al.[14] starts with allylboronate **14** bearing a pentadienol residue. Derivative **14** was submitted to asymmetric ring-closing metathesis using one of the optically active Mo catalysts, **15**, developed by the authors.[15] The intermediate oxaboracycle **16** was heated with trioxane to give (after aqueous work-up) homoallylic 1,3-diol **17** with good overall yield and excellent stereoselectivity (Scheme 4).



Scheme 4. Sequence of asymmetric ring-closing metathesis and allylboration.

2.3 Allylic Substitutions with Organocopper Reagents

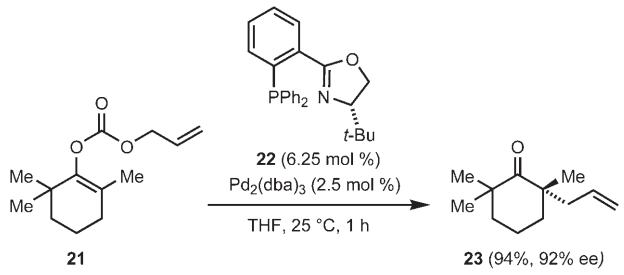
Allylation reactions play a dominating role among asymmetric C–C bond formation processes, because both electrophilic (allylic esters or halides) and nucleophilic species (allylmetal reagents) are capable of allylic inversion and therefore show enhanced reactivity. Consequently, numerous reports on the formation of quaternary stereocenters with allylic reagents are found in the literature.[16] The S_N2' displacement of allylic esters with organocuprates is a feature often applied for the generation of quaternary stereocenters.[17] *ortho*-Diphenylphosphanylbenzoic acid (o-DPPB) has been introduced by Breit and co-workers[18] as a catalyst- or reagent-directing group. They have reported on o-DPPB and its derived phosphane oxide as a stereochemistry switch in allylic substitution reactions.[19] o-DPPB usually behaves as a reagent-directing group which leads to *syn*-substitution of substrate **18** with a BuCu reagent. The optically active hydrocarbon **19** is therefore obtained with quantitative regioselectivity and stereospecificity (Scheme 5). On the other hand, oxidized phosphane **20** gives *anti*-substitution products *ent*-**19**. Here, the o-DPPB oxide moiety shields the back face of the C–C double bond, and thus, the oxidation state of the phosphane acts as a configuration switch in the allylic substitution.



Scheme 5. Stereospecific and stereodivergent construction of quaternary carbon centers by directed/non-directed allylic substitution.

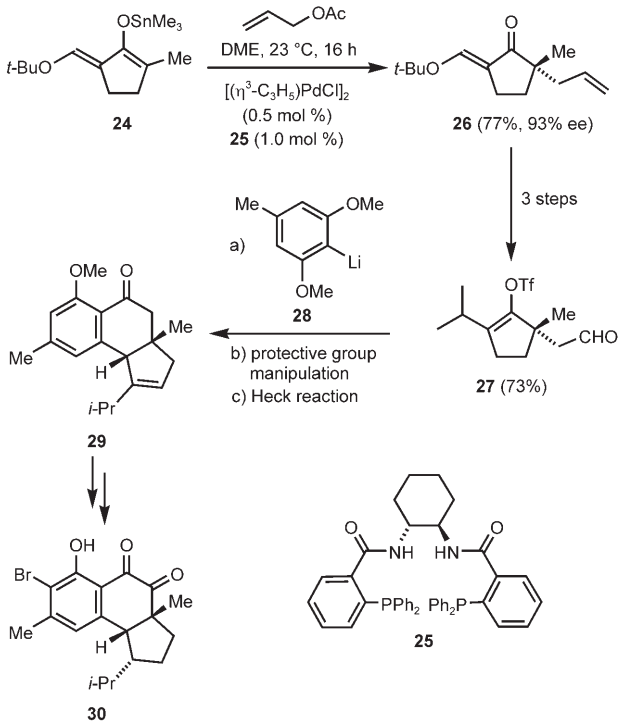
2.4 Palladium-Catalyzed Asymmetric Allylic Substitution Reactions

Palladium-catalyzed enantioselective allylation chemistry has played a key role in the evolution of catalytic asymmetric C–C bond forming reactions.[20] The racemic decarboxylative alkylation of allyl enol carbonates can be traced back to reports of Tsuji in the 1980s.[21] Stoltz and Behenna recently published the first asymmetric version of this Tsuji allylation.[22] The P,N ligand **22**[23] was used for intramolecular conversion of enol carbonate **21** to ketone **23** (Scheme 6). Both yield and stereoselectivity were good.



Scheme 6. Enantioselective Tsuji enol carbonate allylation.

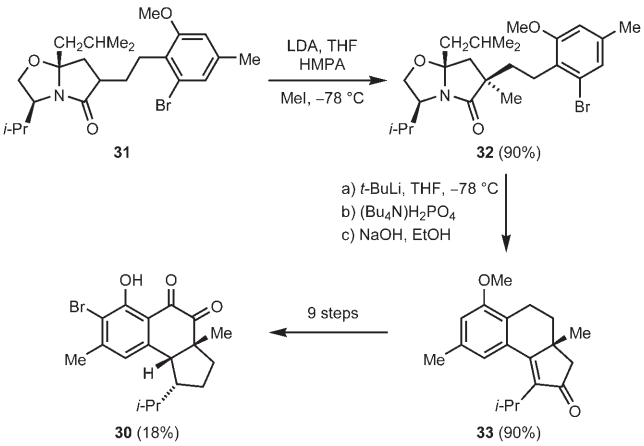
Among many others, Helmchen, Pfaltz[24] and Trost have made leading contributions to the field of asymmetric allylic alkylation reactions (AAA). In the recent literature, some examples of quaternary stereocenter formation by AAA are found.[25] As a representative example, the synthesis of hamigeran B (**30**), a marine natural product with powerful activity against herpes and polio viruses, by Trost and co-workers is briefly mentioned here (Scheme 7).[26] The stereoinducing key step is a Pd-catalyzed asymmetric allylation of simple ketone enolates,[27] which is based on *in situ* formation of the trimethylstannyl enol ether **24**. By application of the "standard Trost ligand" **25**, the obvious disadvantage of using stoichiometric tin reagents is compensated for by the high yield and stereoselectivity of product **26** (77%, 93% ee). The latter is further transformed in three steps to aldehyde **27** (73% overall yield), which is treated, without prior isolation, with the aryllithium species **28**. After oxidation and some protective group manipulation (four steps with 57% yield), Heck reaction furnished tricyclic compound **29** (58%, together with three by-products), which could be further elaborated to the target **30**.



Scheme 7. A short and concise asymmetric synthesis of hamigeran B (**30**).

2.5 Alkylation Reactions

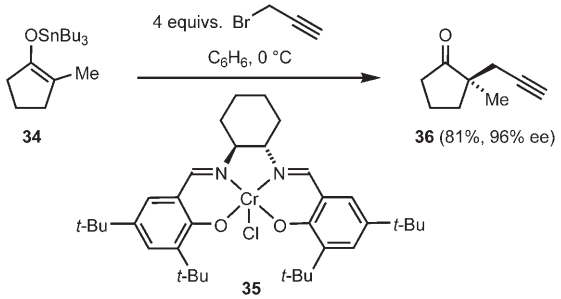
Another approach to hamigeran B (**30**) was reported by Clive et al., who used a chiral auxiliary prepared from L-valine.[28] After introduction of the arylethyl side chain into **31**, the bicyclic lactam was α-deprotonated (LDA, THF) to be subsequently stereoselectively alkylated (MeI, HMPA) from the less hindered face of the substrate yielding the α-quaternary lactam **32** together with a small amount of the unwanted diastereoisomer (18:1 dr) (Scheme 8). After lithium-halogen exchange with *t*-BuLi, the intramolecular addition of the aryllithium to the lactam carbonyl group starts an elegant reaction cascade, which further proceeds with Brønsted acid-catalyzed aminal hydrolysis and finally ends up with the aldol condensation product **33**. Considering this rather complex sequence of carbonyl group trans-



Scheme 8. Stereoselective synthesis of hamigeran B (**30**) applying a chiral auxiliary derived from L-valine.

formations, the overall yield of 90% is excellent. Compound **33** can be elaborated to yield the natural product **30** (18% yield over nine steps).

Catalytic asymmetric α-alkylations of β-dicarbonyl compounds nowadays can be achieved with chiral phase transfer catalysts, a topic which has been reviewed very recently.[29] If simple ketones are used as substrates, however, the respective reactions become much more difficult. A newer method was reported by Jacobsen and Doyle[30] which, similar to the results of Trost et al. for the AAA, is based on the stoichiometric application of organotin compounds. Tributylstannyloxycycloalkenes like **34** are converted with a four-fold excess of electrophiles such as allyl bromide, propargyl bromide, benzyl bromide, methyl iodide, or ethyl iodoacetate to provide the respective α-quaternary cycloalkanones **36** in excellent yields and stereoselectivities (Scheme 9). Among several catalysts investigated by the authors, the optically active Cr(III)-salen complex **35** has been identified to give optimal results.

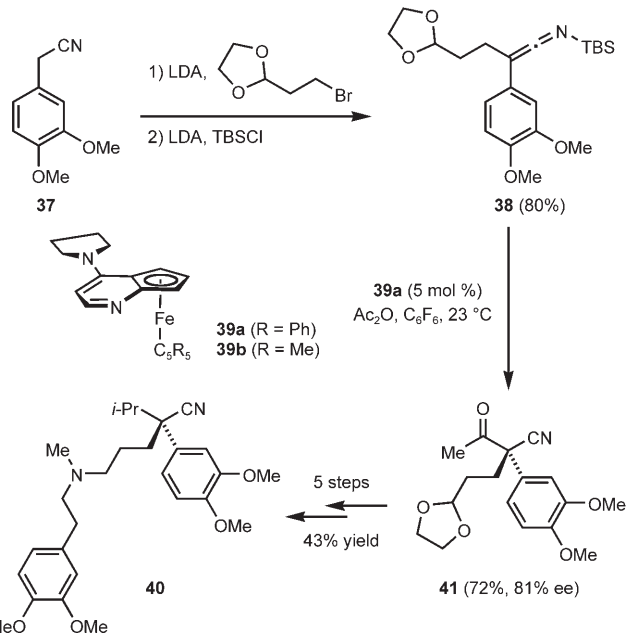


Scheme 9. Enantioselective alkylations of tributyltin enolates catalyzed by Cr(salen)Cl.

2.6 Asymmetric Acylations

Fu and co-workers have developed planar chiral DMAP analogues like **39** and successfully applied them as nucleophilic catalysts in asymmetric synthesis.[31] In extension of their work on asymmetric silyl ketene acetal acylations,[32] they reported on the asymmetric synthesis of the calcium-channel blocker (*S*)-verapamil (**40**) by acylation of silyl ketene imines.[33]

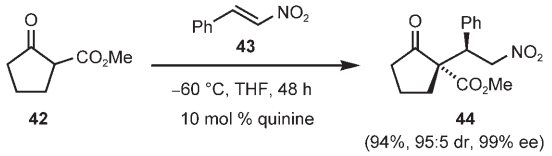
The silyl ketene imine **38** was formed in two steps by *C*-alkylation and subsequent *N*-silylation of arylacetonitrile **37** (Scheme 10). Compound **38** is essentially inert to acylation reagents such as Ac_2O; however, in the presence of catalytic amounts of chiral ferrocene derivative **39a** it smoothly furnishes the α-cyanoketone **41**. The target quaternary stereocenter is hereby formed with 81% ee selectivity. Further elaboration of this intermediate product by a sequence including ketone-olefination and reductive amination yielded the optically active drug **40** in five steps with 43% overall yield.



Scheme 10. Synthesis of (*S*)-verapamil (**40**) by asymmetric acylation of silyl ketene imines.

2.7 Michael Addition

The conjugate addition of stabilized enolates to acceptor-activated olefins is one of the most important reactions to construct asymmetric quaternary stereocenters.[34] Newer developments have been highlighted recently.[35] An organocatalytic example of quaternary stereocenter formation was published by Deng and coworkers.[36] Products like **44** with adjacent quaternary and tertiary stereocenters are formed almost independently of the constitution of the Michael donor (cyclic and acyclic β-oxo esters, β-diketones, α-acyllactams, α-nitro and α-cyano esters) and tolerating a broad substitution pattern in the β-position of the nitroethylene derivative **43**. At temperatures of -60 to $-20\,^{\circ}C$ the yields are in the range of 75–95% and the selectivities are generally excellent (up to 99% ee, dr up to 98:2). Quinine or quinidine itself or simple derivatives thereof are applied as the organocatalysts. Scheme 11 shows a representative example.



Scheme 11. Organocatalytic Michael addition to nitroolefins.

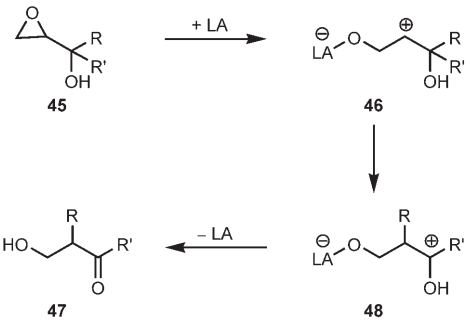
3 Rearrangements

3.1 Semipinacol Rearrangements

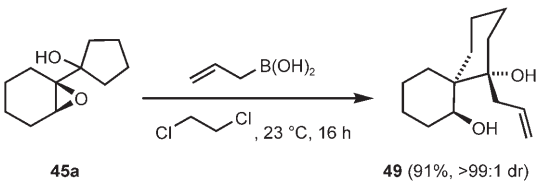
Epoxides are important starting materials for the stereoselective formation of quaternary stereocenters in complex carbon skeletons. Many diastereo- and enantioselective examples can be found in the recent literature.[37] α-Hydroxyalkyloxiranes **45** can be ring-opened with Lewis acids (LA) to generate carbenium ions **46**, which undergo a 1,2-alkyl shift[38] to yield β-hydroxy ketones as final products **47** (Scheme 12). Due to its similarity to the rearrangements of carbenium ions generated by acid-catalyzed dehydratization of 1,2-diols, this process is called a semipinacol rearrangement and has been utilized by a number of research groups.[39]

Tu and coworkers have developed a number of reaction sequences initiated by semipinacol rearrangements. Two of those will be presented here. As depicted in Scheme 13, intermediate carboxonium species **48** can be trapped by an alkylboronic acid yielding a tertiary alcohol **49** with an α-quaternary stereocenter.[40] The reaction sequence is highly stereospecific. In the case of conversion of **45a**, only one diastereomer of the product is observed. The role of boron is not only to activate the intermediate ketone **47** for allylboration via a six-membered cyclic transition state, but also to act as the Lewis acid for epoxide opening. α-Hydroxyepoxides **45** are readily available by epoxidation of the corresponding allylic alcohols.

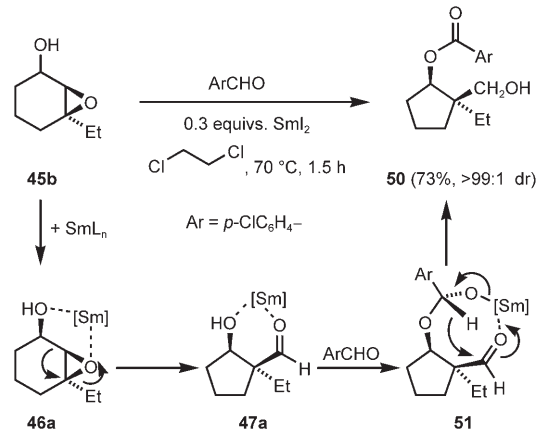
In the presence of a stoichiometric amount of *p*-chlorobenzaldehyde and SmI_2 as catalyst, the aldehyde function in intermediate **47a** (Scheme 14) is reduced to a primary alcohol in the final product **50**.[41] Reduction occurs by samarium-assisted intramolecular hydride migration of a hemiacetal of the benzaldehyde derivative and the secondary alcohol function (structure **51** in Scheme 14). Consequently, the benzaldehyde moiety ends up in the oxidation state of a carboxylic acid in product **50**.



Scheme 12. Semipinacol rearrangement.



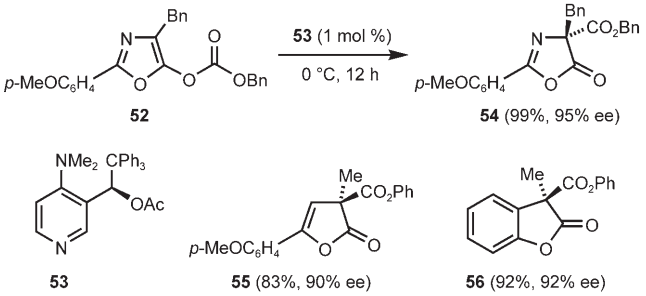
Scheme 13. Tandem semipinacol rearrangement/alkylation of α-epoxy alcohols.



Scheme 14. Samarium-catalyzed tandem semipinacol rearrangement/Tishchenko reaction.

3.2 1,2-Acyl Migrations

Optically active azlactones such as **54** are valuable precursors for α-quaternary amino acid derivatives. These heterocycles can be obtained by nucleophile-catalyzed rearrangements of oxazolylcarbonates **52**. Vedejs et al. have applied a chiral DMAP derivative **53**, developed in their laboratory, as organocatalyst for this asymmetric 1,2-acyl shift. With only 1 mol % of the catalyst excellent conversions and selectivities are realized at 0 °C. Scheme 15 shows an example. This method can be carried forward to furyl and benzofuryl carbonates yielding the corresponding α-quaternary lactones **55** and **56**.[42]

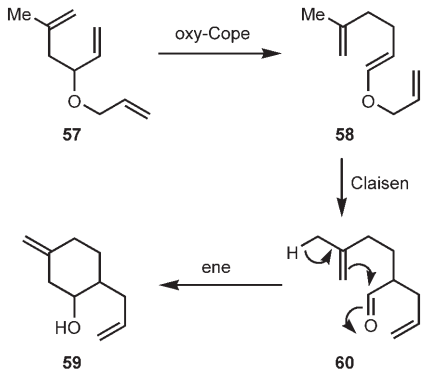


Scheme 15. Chiral DMAP as organocatalyst for 1,2-acyl shifts.

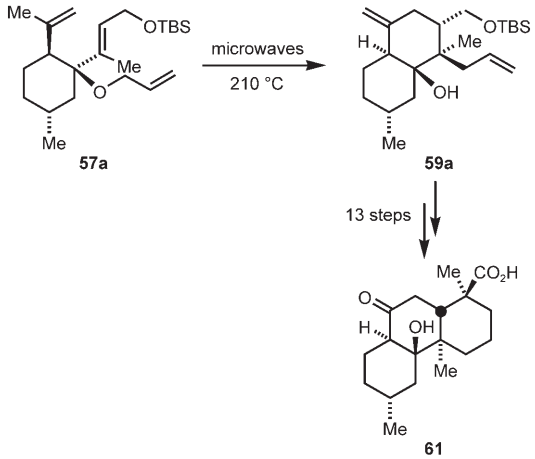
3.3 Oxy-Cope/Claisen/Ene Cascade

Due to their high stereospecificity, Cope[43] and Claisen[44] reactions are valuable tools for stereoselective C–C bond formation. Sauer and Barriault developed a sequence leading to highly functional cyclohexanol derivatives by a reaction cascade consisting of an oxy-Cope and Claisen rearrangement followed by an intramolecular ene reaction as the final step. A simplifying sketch of this sequence is depicted in Scheme 16 (only the relevant carbon skeleton is given, substituents are omitted for the sake of clarity).[45]

The authors have since pointed out the efficiency of their sequence in converting allyl ether **57a** into decalin **59a**, a precursor for the preparation of the tricyclic natural product analogue **61** (Scheme 17).[46] The reaction sequence takes place upon short heating in a microwave oven. The tandem pericyclic reaction is initiated by an oxy-Cope rearrangement to generate *in situ* a macrocyclic species, which spontaneously rearranges *via* a Claisen [3,3] shift reaction to another macrocyclic ketone. The latter is poised to cyclize *via* a transannular carbonyl ene reaction to give decalin **59a**. The stereochemical outcome of the complete sequence is governed by the preferential conformation of both intermediate macrocyclic species at the transition state for the Claisen and ene reactions.



Scheme 16. Tandem oxy-Cope/Claisen/ene reaction.



Scheme 17. Preparation of a wiedemannic acid analogue **61**.

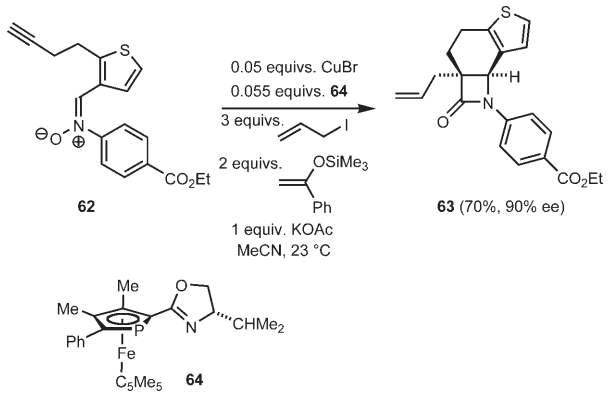
4 Cycloaddition Reactions

4.1 [3+2] Cycloadditions

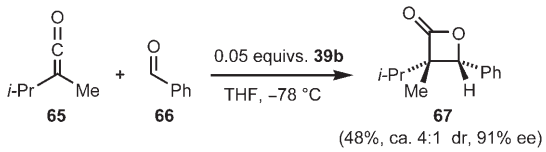
β-Lactams are a widespread structural motif for pharmaceutically important products. A rather unusual access to this four-membered heterocycle is the so-called Kinugasa reaction, which is essentially a [3+2] dipolar cycloaddition of an alkyne with a nitrone followed by ring contraction. Fu and coworkers recently reported an asymmetric copper-catalyzed variant of this cycloaddition process.[47] Extending their previous studies, the authors were aiming to trap a copper-enolate (copper-ketene-hemiaminal), which is presumed to be an intermediate species in the overall reaction sequence, with electrophilic alkylating agents.[48] Scheme 18 highlights their results. In the presence of a mixture of a silyl enol ether and KOAc as a base, alkyne-nitrone **62** underwent cyclization followed by α-alkylation with an excess of allyl iodide in good yield and selectivity. The planar chiral phosphaferrocene-oxazoline **64** was used as the ligand for the copper catalyst. Thus, two C–C bonds, a C–N bond, two new rings (including a β-lactam), a carbonyl group, and adjacent tertiary and quaternary stereocenters can be generated in a single cyclization-alkylation sequence.

4.2 [2+2] Cycloadditions

Another example of asymmetric cycloaddition reactions catalyzed by planar chiral ferrocenes is the [2+2] cycloaddition of dialkylketenes **65** with aromatic aldehydes **66**.[49] As depicted in Scheme 19, in the pres-



Scheme 18. Asymmetric copper-catalyzed Kinugasa reaction/alkylation sequence.



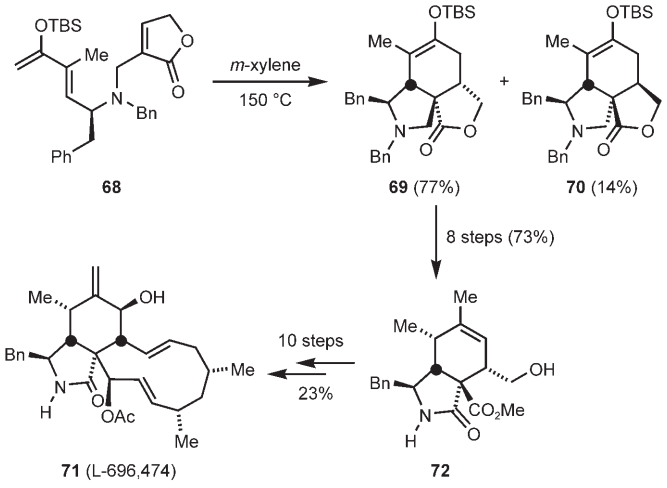
Scheme 19. Organocatalytic β-lactone formation.

ence of the ferrocene catalyst **39b** (Scheme 10) β-lactones **67** with adjacent quaternary and tertiary stereocenters are formed with high enantioselectivity, although yield and dr are moderate. Remarkably, the yield (and, of course, also stereoselectivity) dramatically decreased at temperatures higher than $-78\,^{\circ}C$.

4.3 [4+2] Cycloadditions

Myers and Haidle have reported an enantioselective, modular and general route to cytochalasins, namely L-696,474 and cytochalasin B, which are structurally complex fungal metabolites with a range of biological effects including promising anti-tumor and antiviral properties.[50] One of the key steps is a diastereoselective intramolecular Diels–Alder reaction of an optically active precursor **68** which originates from L-phenylalanine in 8 steps with 58% yield (Scheme 20).

Best conditions turned out to be high temperatures (refluxing xylene) by using glassware passivated by prior silylation. Under these conditions two diastereoisomeric products **69** and **70** bearing four adjacent stereocenters were obtained, one of them quaternary. These diastereoisomers could be separated easily by chromatography. The major product **69** gave single crystals suitable for X-ray analysis, which established the desired *endo* configuration. Tricyclic lactone **69** was further elaborated to give bicyclic lactam **72** (73% yield over eight steps),



Scheme 20. Intramolecular Diels–Alder reaction *en route* to cytochalasin L-696,474.

which can be transformed in 10 steps (23%) into one of the target compounds L-696,474 (**71**). The overall longest linear sequence from L-phenylalanine to **71** consists of 27 steps (6.2% overall yield).

5 Conclusion

Several new methods and strategies for the enantioselective synthesis of quaternary carbon centers have been developed in the recent years. Only a small selection from a very active area of research has been presented in this review. Nevertheless, there is still a great demand for new processes and for optimization of the known ones, since they do not always meet the requirements of modern synthetic organic chemistry. In particular, flexibility and versatility with regard to substrates and functional groups, atom-economy, efficiency, and simple performance are standards, which a modern synthetic method ought to fulfil, and moreover, chiral auxiliaries and ligands should be readily accessible. As a primary goal, however, the development of catalytic asymmetric reactions suitable for the generation of quaternary stereocenters remains a particular challenge for synthetic organic chemists.

References and Notes

[1] Reviews: a) E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci.* USA **2004**, *101*, 11943–11948; b) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367; c) D. J. Ramon, M. Yus, *Curr. Org. Chem.* **2004**, *8*, 149–183; d) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105–10146; e) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725–4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597; f) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; g) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037–2066; h) S. F. Martin, *Tetrahedron* **1980**, *36*, 419–460; see also: i) J. Christoffers, A. Baro (Eds.), *Quaternary Stereocenters – Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, **2005**.

[2] Nucleophilic addition to ketones: a) K. Funabashi, M. Jachmann, M. Kanai, M. Shibasaki, *Angew. Chem.* **2003**, *115*, 5647–5650; *Angew. Chem. Int. Ed.* **2003**, *42*, 5489–5492; b) M. Langner, C. Bolm, *Angew. Chem.* **2004**, *116*, 6110–6113; *Angew. Chem. Int. Ed.* **2004**, *43*, 5984–5987; c) P. G. Cozzi, S. Alesi, *Chem. Commun.* **2004**, 2448–2449; d) S.-G. Wang, H. R. Tsai, K. Chen, *Tetrahedron Lett.* **2004**, *45*, 6183–6185.

[3] Nucleophilic addition to ketimines: a) S. Saaby, K. Nakama, M. A. Lie, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 6145–6154; b) W. Zhuang, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 4576–4578; *Angew. Chem. Int. Ed.* **2004**, *43*, 4476–4478.

[4] Enantioselective cyanosilylation: a) S.-K. Tian, R. Hong, L. Deng, *J. Am. Chem. Soc.* **2003**, *125*, 9900–9901; b) F.-X. Chen, H. Zhou, X. Liu, B. Qin, X. Feng, G. Zhang, Y. Jiang, *Chem. Eur. J.* **2004**, *10*, 4790–4797.

[5] Stereospecific carbene insertions: a) Y. Masaki, H. Arasaki, M. Iwata, *Chem. Lett.* **2003**, *32*, 4–5; b) H. Arasaki, M. Iwata, D. Nishimura, A. Itoh, Y. Masaki, *Synlett* **2004**, 546–548.

[6] Enzymatic resolution of tertiary alcohols: E. Henke, U. T. Bornscheuer, R. D. Schmid, J. Pleiss, *ChemBioChem* **2003**, *4*, 485–493.

[7] B. Jiang, M. Xu, *Angew. Chem.* **2004**, *116*, 2597–2600; *Angew. Chem. Int. Ed.* **2004**, *43*, 2543–2546.

[8] Reviews: a) M. Rodriguez Rivero, J. Adrio, J. C. Carretero, *Synlett* **2005**, 26–41; b) M. A. Pericàs, J. Balsells, J. Castro, I. Marchueta, A. Moyano, A. Riera, J. Vázquez, X. Verdaguer, *Pure Appl. Chem*. **2002**, *74*, 167–174; c) K. M. Brummond, J. L. Kent, *Tetrahedron* **2000**, *56*, 3263–3283; d) S. L. Buchwald, F. A. Hicks, in: *Comprehensive Asymmetric Catalysis I–III*, Vol. II, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin **1999**, pp. 491–510; e) S. T. Ingate, J. Marco-Contelles, *Org. Prep. Proc. Int.* **1998**, *30*, 121–143.

[9] Reviews: a) M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096–1122; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070; b) A. Cordova, *Acc. Chem. Res.* **2004**, *37*, 102–112.

[10] Y. Hamashima, N. Sasamoto, D. Hotta, H. Somei, N. Umebayashi, M. Sodeoka, *Angew. Chem.* **2005**, *117*, 1549–1553; *Angew. Chem. Int. Ed.* **2005**, *44*, 1525–1529.

[11] M. Marigo, A. Kjærsgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2359–2367.

[12] a) M. Gravel, H. Lachance, X. Lu, D. G. Hall, *Synthesis* **2004**, 1290–1302; b) P. Veeraraghavan Ramachandran, M. V. R. Reddy, H. C. Brown, *Pure Appl. Chem.* **2003**, *75*, 1263–1275; c) P. Veeraraghavan Ramachandran, *Aldrichimica Acta* **2002**, *35*, 23–35; d) R. W. Hoffmann, *Pure Appl. Chem.* **1988**, *60*, 123–130; e) W. R. Roush, L. K. Hoong, M. A. J. Palmer, J. C. Park, *J. Org. Chem.* **1990**, *55*, 4109–4117.

[13] J. B. Morgan, J. P. Morken, *Org. Lett.* **2003**, *5*, 2573–2575.

[14] J. A. Jernelius, R. R. Schrock, A. H. Hoveyda, *Tetrahedron* **2004**, *60*, 7345–7351.

[15] a) A. H. Hoveyda, R. R. Schrock, *Comprehensive Asymmetric Catalysis, Supplement*, Springer, Berlin, **2004**, *1*, 207–233; b) R. R. Schrock, A. H. Hoveyda, *Angew. Chem.* **2003**, *115*, 4740–4782; *Angew. Chem. Int. Ed.* **2003**, *42*, 4592–4633; c) A. H. Hoveyda, R. R. Schrock, *Chem. Eur. J.* **2001**, *7*, 945–950.

[16] a) G. Sklute, D. Amsallem, A. Shabli, J. P. Varghese, I. Marek, *J. Am. Chem. Soc.* **2003**, *125*, 11776–11777; b) R. S. Grainger, A. Patel, *Chem. Commun.* **2003**, 1072–1073; c) B. Cardinal-David, B. Guérin, Y. Guindon, *J. Org. Chem.* **2005**, *70*, 776–784; d) H. Ohmiya, T. Tsuji, H. Yorimitsu, K. Oshima, *Chem. Eur. J.* **2004**, *10*, 5640–5648; e) N. T. Patil, H. Wu, I. Kadota, Y. Yamamoto, *J. Org. Chem.* **2004**, *69*, 8745–8750; f) S. Kezuka, K. Kanemoto, R. Takeuchi, *Tetrahedron Lett.* **2004**, *45*, 6403–6406.

[17] a) J. E. Tønder, M. Hosseini, A. B. Ahrenst, D. Tanner, *Org. Biomol. Chem.* **2004**, *2*, 1447–1455; b) C. Spino, C. Godbout, C. Beaulieu, M. Harter, T. M. Mwene-Mbeja, L. Boisvert, *J. Am. Chem. Soc.* **2004**, *126*, 13312–13319.

[18] a) B. Breit, in: *Organic Synthesis Highlights V*, (Eds.: H.-G. Schmalz, T. Wirth), Wiley-VCH, Weinheim, **2003**, pp. 68–81; b) B. Breit, *Chem. Eur. J.* **2000**, *6*, 1519–1524.

[19] B. Breit, P. Demel, C. Studte, *Angew. Chem.* **2004**, *116*, 3874–3877; *Angew. Chem. Int. Ed.* **2004**, *43*, 3786–3789.

[20] a) B. M. Trost, C. Lee, in: *Catalytic Asymmetric Synthesis*, (Ed.: I. Ojima), 2nd edn., Wiley-VCH, New York, **2000**, pp. 593–649; b) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422; c) B. M. Trost, *J. Org. Chem.* **2004**, *69*, 5813–5837.

[21] J. Tsuji, I. Minami, *Acc. Chem. Res.* **1987**, *20*, 140–145.

[22] D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.

[23] Recent review: P. J. Guiry, C. P. Saunders, *Adv. Synth. Catal.* **2004**, *346*, 497–537.

[24] G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336–345.

[25] a) X.-L. Hou, N. Sun, *Org. Lett.* **2004**, *6*, 4399–4401; b) B. M. Trost, M. U. Frederiksen, *Angew. Chem.* **2005**, *117*, 312–314; *Angew. Chem. Int. Ed.* **2005**, *44*, 308–310.

[26] B. M. Trost, C. Pissot-Soldermann, I. Chen, *Chem. Eur. J.* **2005**, *11*, 951–959.

[27] B. M. Trost, G. M. Schroeder, *Chem. Eur. J.* **2005**, *11*, 174–184.

[28] D. L. J. Clive, J. Wang, *J. Org. Chem.* **2004**, *69*, 2773–2784.

[29] Recent examples: a) E. J. Park, M. H. Kim, D. Y. Kim, *J. Org. Chem.* **2004**, *69*, 6897–6899; b) M. Kitamura, S. Shirakawa, K. Maruoka, *Angew. Chem.* **2005**, *117*, 1573–1575; *Angew. Chem. Int. Ed.* **2005**, *44*, 1549–1551; recent reviews: c) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013–3028; d) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506–517; e) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518–525.

[30] A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 62–63.

[31] a) G. C. Fu, *Acc. Chem. Res.* **2004**, *37*, 542–547; b) G. C. Fu, *Pure Appl. Chem.* **2002**, *74*, 33–36; c) G. C. Fu, *Pure Appl. Chem.* **2001**, *73*, 347–349; d) G. C. Fu, *Acc. Chem. Res.* **2000**, *33*, 412–420.

[32] A. H. Mermerian, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 4050–4051.

[33] A. H. Mermerian, G. C. Fu, *Angew. Chem.* **2005**, *117*, 971–974; *Angew. Chem. Int. Ed.* **2005**, *44*, 949–952.

[34] a) T. Satoh, S. Sugiyama, Y. Kamide, H. Ota, *Tetrahedron* **2003**, *59*, 4327–4336; b) D. Bensa, T. Constantieux, J. Rodriguez, *Synthesis* **2004**, 923–927.

[35] J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726–1728; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688–1690.

[36] H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107–110; *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108.

[37] a) D. F. Taber, Y. He, M. Xu, *J. Am. Chem. Soc.* **2004**, *126*, 13900–13901; b) M. Pineschi, F. Del Moro, P. Crotti,

V. Di Bussolo, F. Macchia, *J. Org. Chem.* **2004**, *69*, 2099–2105; c) J. E. Tønder, D. Tanner, *Tetrahedron* **2003**, *59*, 6937–6945.
[38] For a nice example of a Stevens [1,2] shift, see: D. Muroni, A. Saba, N. Culeddu, *Tetrahedron: Asymmetry* **2004**, *15*, 2609–2614.
[39] a) B. M. Wang, Z. L. Song, C. A. Fan, Y. Q. Tu, W. M. Chen, *Synlett* **2003**, 1497–1499; b) O. L. Epstein, J. K. Cha, *Angew. Chem.* **2005**, *117*, 123–125; *Angew. Chem. Int. Ed.* **2005**, *44*, 121–123; c) G. R. Dake, M. D. B. Fenster, M. Fleury, B. O. Patrick, *J. Org. Chem.* **2004**, *69*, 5676–5683; d) X. Li, B.-M. Wang, X.-Z. Zhao, S.-H. Gao, Y.-Q. Tu, D.-R. Li, *Chin. J. Chem.* **2004**, *22*, 1177–1182.
[40] X.-D. Hu, C.-A. Fan, F.-M. Zhang, Y. Q. Tu, *Angew. Chem.* **2004**, *116*, 1734–1737; *Angew. Chem. Int. Ed.* **2004**, *43*, 1702–1705.
[41] C.-A. Fan, X.-D. Hu, Y.-Q. Tu, B.-M. Wang, Z.-L. Song, *Chem. Eur. J.* **2003**, *9*, 4301–4310.
[42] S. A. Shaw, P. Aleman, E. Vedejs, *J. Am. Chem. Soc.* **2003**, *125*, 13368–13369.
[43] W. P. Malachowski, M. Banerji, *Tetrahedron Lett.* **2004**, *45*, 8183–8185.
[44] a) G. Nordmann, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 4978–4979; b) P. Beaulieu, W. W. Ogilvie, *Tetrahedron Lett.* **2003**, *44*, 8883–8885.
[45] a) E. L. O. Sauer, L. Barriault, *J. Am. Chem. Soc.* **2004**, *126*, 8569–8575; b) J. A. Farand, I. Denissova, L. Barriault, *Heterocycles* **2004**, *62*, 735–748.
[46] E. L. O. Sauer, L. Barriault, *Org. Lett.* **2004**, *6*, 3329–3332.
[47] M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 4572–4573.
[48] R. Shintani, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4216–4219; *Angew. Chem. Int. Ed.* **2003**, *42*, 4082–4085.
[49] J. E. Wilson, G. C. Fu, *Angew. Chem.* **2004**, *116*, 6518–6520; *Angew. Chem. Int. Ed.* **2004**, *43*, 6358–6360.
[50] A. M. Haidle, A. G. Myers, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12048–12053.

