Asymmetric Synthesis

DOI: 10.1002/anie.201003114

Enantioselective Halocyclization Reactions for the Synthesis of Chiral Cyclic Compounds**

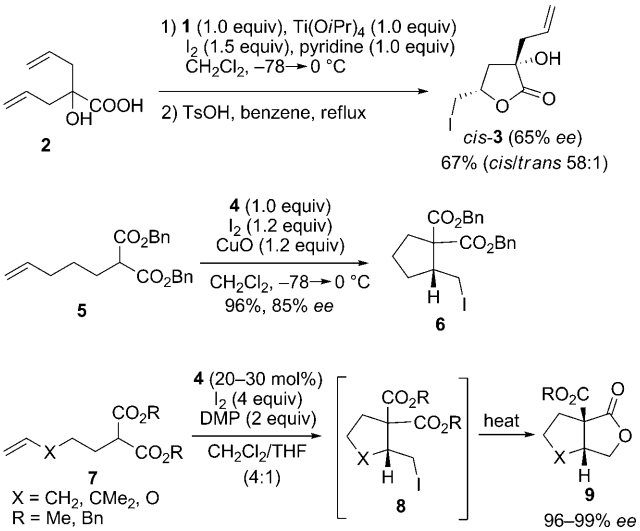
*Guofei Chen and Shengming Ma**

asymmetric synthesis · cyclization · electrophilic addition · halogenation · homogeneous catalysis

Nowadays it is relatively easy to develop a transition-metal-catalyzed enantioselective reaction owing to the wide availability of chiral ligands able to smoothly coordinate with metals to afford a variety of chiral catalysts. Although diastereoselective electrophilic cyclizations with chiral electrophilic selenium reagents have been realized with excellent diastereoselectivities in many cases,[1–3] the enantioselective cyclization of nonchiral unsaturated substrates with nonchiral electrophiles is challenging, as it is difficult to install the required chirality. Thus, in addition to the metal-mediated approach, conceptually new chiral reagents have to be developed that can interact with electrophiles to induce asymmetry before the background racemic reaction occurs. In this Highlight, we comment on recent advances in this area.

In 1992, Taguchi and co-workers reported a desymmetrizing enantioselective iodolactonization reaction of 2-allyl-2-hydroxy-4-pentenoic acid (**2**) with I_2 in the presence of 1 equivalent of a titanium complex generated from (Me,Ph)-taddol (**1**) and Ti(O*i*Pr)$_4$ to afford the corresponding γ-lactone *cis*-**3** with 65% *ee* (Scheme 1).[4a] Interestingly, the iodocarbocyclization of dibenzyl 2-(4-pentenyl)malonate (**5**) with I_2, CuO, and the chiral titanium taddolate **4** (1.0 equiv) produced **6** in 96% yield with 85% *ee*.[4b] When 2,6-dimethoxypyridine (DMP) was used instead of CuO as the base, the reaction could even be carried out in CH_2Cl_2/THF (4:1) with a catalytic amount of the chiral titanium taddolate **4** (20–30 mol%) to give **8**, which upon heating afforded bicyclic lactones **9** with 96–99% *ee*![4c–e] The high enantioselectivity of this reaction may be attributed to the strong coordination between the chiral titanium taddolate **4** and the malonate moiety in the substrates.

Later, Kang and co-workers developed[5] a catalytic enantioselective iodoetherification to form tetrahydrofurans **12** with up to 90% *ee* by using the combination of the chiral



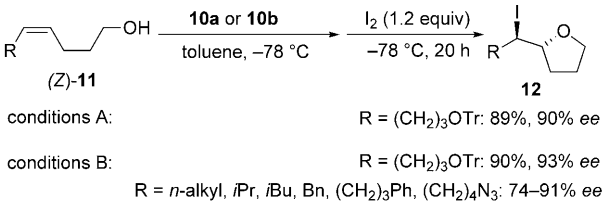
Scheme 1. Iodocarbocyclization with chiral titanium taddolates. Bn = benzyl, Ts = *p*-toluenesulfonyl.

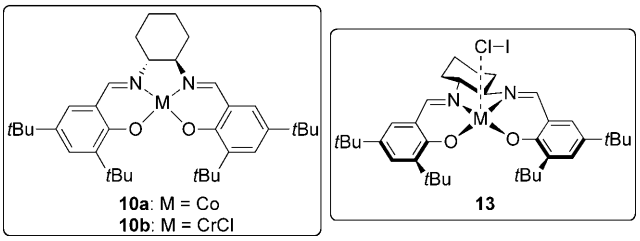
salen–Co complex **10a** (0.3 equiv) and *N*-chlorosuccinimide (NCS; 0.75 equiv; Scheme 2).[5a] With the salen–Cr complex **10b**, 7 mol% of the catalyst was enough for enantioselective iodocyclization with up to 93% *ee*.[5b] It is thought that NCS first reacts with the iodide anion to release ICl slowly, which is crucial for minimization of the background reaction, and that the intermediate **13** generated from ICl and the salen–metal catalyst **10** determines the enantioselectivity.[5b] When **10a** was used as the catalyst,[5a] I_2 was added first, and then the substrate was added over 8 h with a syringe pump; when **10b** was used as the catalyst, the substrate was added first, and then the I_2 was added in one portion.[5b]

Recently, instead of chiral metal catalysts, a stoichiometric amount of the binol-based phosphoramidite **14** was used to induce enantioselectivity in the asymmetric iodocarbocyclization of alkadienyl or alkatrienyl arenes **15** to afford the

[*] G. Chen, Prof. Dr. S. Ma
Laboratory of Molecular Recognition and Synthesis Department of Chemistry, Zhejiang University
Hangzhou 310027, Zhejiang (P.R. China)
Fax: (+86) 21-6416-7510
E-mail: masm@mail.sioc.ac.cn

[**] Financial support from the Major State Basic Research and Development Program (2006CB806105) and the National Natural Science Foundation of China (20732005) for our research in a related area is appreciated.

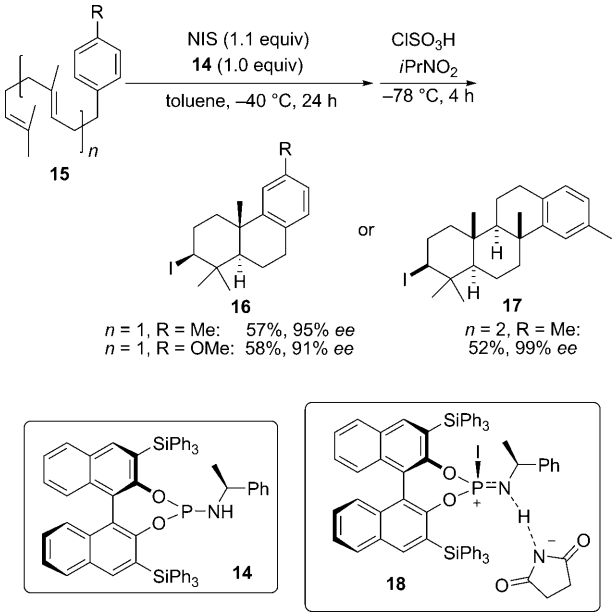




Scheme 2. Iodocyclization with chiral salen-based metal complexes. Conditions A: **10a** (30 mol%), NCS (0.75 equiv); conditions B: **10b** (7 mol%), NCS (0.7 equiv), K_2CO_3 (0.5 equiv). Tr = triphenylmethyl (trityl).

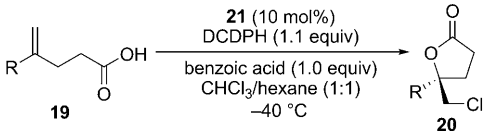
product **16** or **17** with up to 99% *ee* (Scheme 3).[6] In this reaction, the phenyl ring acts as the nucleophile. The low reactivity and rotation-restrained nature of intermediate **18**, generated in situ from the chiral binol-based phosphoramidite **14** and NIS in toluene, were considered to be responsible for the high enantioselectivity of the reaction. However, the corresponding enantioselective bromocyclization and chlorocyclization were inefficient.

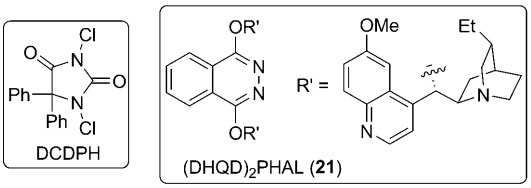
Chiral amines, such as 2-((1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)pyridine,[7a] (*R*)-1,2,3,4-tetrahydronaphth-1-ylamine,[7b–c] *N*-methylephedrine,[7d] dihydroquinidine benzoylate,[8a] and cinchonidine[8b] have also been tested for such enantioselective electrophilic cyclizations, with very limited success. Such a cyclization reaction even proceeded with just

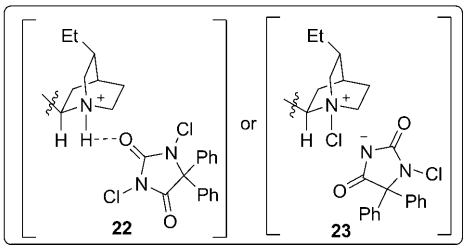


Scheme 3. Iodocarbocyclization with binol-based phosphoramidites. NIS = *N*-iodosuccinimide.

30 mol% of the cinchonidine salt, although the enantioselectivities were still low.[8c] These trials paved the way for the further development of enantioselective reactions of this type. Recently, a breakthrough came from the Borhan group: the catalytic enantioselective chlorolactonization of 4-aryl-substituted 4-pentenoic acids **19** through the interaction of $(DHQD)_2PHAL$ (**21**; 10 mol%) with 1,3-dichloro-5,5-diphenylhydantoin (DCDPH) to afford lactones **20** with high enantioselectivities (up to 89% *ee*; Scheme 4).[9] The associative complex **22** or **23** between catalyst **21** and DCDPH is





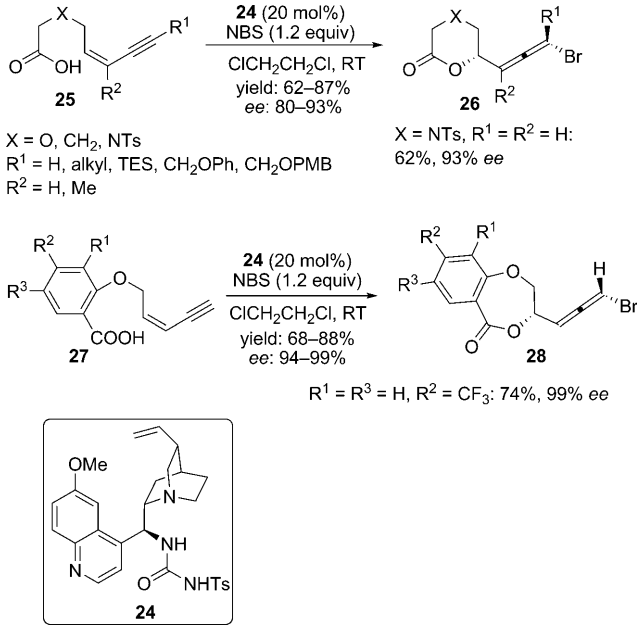


Scheme 4. Catalytic enantioselective chlorolactonization with **21**.

thought to be the crucial intermediate responsible for the high enantioselectivity. With $(DHQ)_2PHAL$, the opposite enantiomer, *ent*-**20**, was formed. The enantioselectivity is much higher than that observed for previous approaches.[5e,7b]

Another breakthrough was made by Tang and co-workers, who reported an impressive highly enantioselective bromolactonization of 5-en-7-ynyl acids **25** and 6-en-8-ynyl acids **27** in the presence of the quinuclidine-based urea catalyst **24** (20 mol%) to afford allenyl bromides **26** and **28** with up to 99% *ee* (Scheme 5).[10] Catalyst **24** may serve as a bifunctional catalyst to activate the system through deprotonation of the acid and the formation of hydrogen bonds with NBS; in these processes, the quinuclidine and urea groups are both critical. Owing to the presence of the conjugated C–C triple bond, not only the lactone ring, but also a synthetically useful chiral allenyl bromide functionality was formed.

In conclusion, highly enantioselective electrophilic halocyclizations have been developed on the basis of either the interaction of a chiral Lewis acid with an unsaturated



Scheme 5. Catalytic enantioselective bromolactonization with **24**. NBS = *N*-bromosuccinimide, PMB = *p*-methoxybenzyl, TES = triethylsilyl.

substrate or the generation of a chiral electrophilic intermediate in situ from an electrophile and a chiral reagent. The impressive aspect of the catalytic reactions is that the reactivity of the chiral electrophilic or nucleophilic species formed in situ must be much higher than that of the original nonchiral electrophile or nucleophile to ensure the high enantioselectivity observed. The future of this chemistry will rely on better understanding of the working models, so that various effective combinations of electrophiles or nucleophiles and chiral reagents, including Lewis acids, chiral amines, and other new chiral promoters, can be found for the enantioselective synthesis of different chiral cyclic compounds. Furthermore, only alkenes with a nucleophilic functionality were used as substrates in most cases; future attention must be paid to reactions of substrates containing allenes and different combinations of unsaturated bonds with a nucleophilic functionality. This research area will surely attract high interest in the near future.

Received: May 23, 2010
Published online: September 13, 2010

[1] a) Y. Nishibayashi, S. K. Srivastava, H. Takada, S. Fukuzawa, S. Uemura, *J. Chem. Soc. Chem. Commun.* **1995**, 2321; b) T. G. Back, B. P. Dyck, *Chem. Commun.* **1996**, 2567; c) T. G. Back, B. P. Dyck, S. Nan, *Tetrahedron* **1999**, *55*, 3191; d) T. G. Back, Z. Moussa, M. Parvez, *J. Org. Chem.* **2002**, *67*, 499; e) K. Fujita, K. Murata, M. Iwaoka, S. Tomoda, *J. Chem. Soc. Chem. Commun.* **1995**, 1641; f) K. Fujita, K. Murata, M. Iwaoka, S. Tomoda, *Tetrahedron* **1997**, *53*, 2029.
[2] T. Wirth, *Angew. Chem.* **1995**, *107*, 1872; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1726.
[3] a) R. Déziel, E. Malenfant, *J. Org. Chem.* **1995**, *60*, 4660; b) R. Déziel, E. Malenfant, C. Thibault, S. Fréchette, M. Gravel, *Tetrahedron Lett.* **1997**, *38*, 4753; c) R. Déziel, E. Malenfant, C. Thibault, *Tetrahedron Lett.* **1998**, *39*, 5493.
[4] a) O. Kitagawa, T. Hanano, K. Tanabe, M. Shiro, T. Taguchi, *J. Chem. Soc. Chem. Commun.* **1992**, 1005; b) T. Inoue, O. Kitagawa, S. Kurumizawa, O. Ochiai, T. Taguchi, *Tetrahedron Lett.* **1995**, *36*, 1479; c) T. Inoue, O. Kitagawa, O. Ochiai, M. Shiro, T. Taguchi, *Tetrahedron Lett.* **1995**, *36*, 9333; d) T. Inoue, O. Kitagawa, A. Saito, T. Taguchi, *J. Org. Chem.* **1997**, *62*, 7384; e) O. Kitagawa, T. Taguchi, *Synlett* **1999**, 1191.
[5] a) S. H. Kang, S. B. Lee, C. M. Park, *J. Am. Chem. Soc.* **2003**, *125*, 15748; b) H. Y. Kwon, C. M. Park, S. B. Lee, J.-H. Youn, S. H. Kang, *Chem. Eur. J.* **2008**, *14*, 1023; for similar studies, see: c) S. H. Kang, C. M. Park, S. B. Lee, M. Kim, *Synlett* **2004**, 1279; d) S. H. Kang, S. Y. Kang, C. M. Park, H. Y. Kwon, M. Kim, *Pure Appl. Chem.* **2005**, *77*, 1269; e) Z. Ning, R. Jin, J. Ding, L. Gao, *Synlett* **2009**, 2291.
[6] A. Sakakura, A. Ukai, K. Ishihara, *Nature* **2007**, *445*, 900.
[7] a) X.-L. Cui, R. S. Brown, *J. Org. Chem.* **2000**, *65*, 5653; b) J. Haas, S. Piguel, T. Wirth, *Org. Lett.* **2002**, *4*, 297; c) J. Haas, S. Bissmire, T. Wirth, *Chem. Eur. J.* **2005**, *11*, 5777; d) J. M. Garnier, S. Robin, G. Rousseau, *Eur. J. Org. Chem.* **2007**, 3281.
[8] a) R. B. Grossman, R. J. Trupp, *Can. J. Chem.* **1998**, *76*, 1233; b) M. Wang, L. X. Gao, W. Yue, W. P. Mai, *Synth. Commun.* **2004**, *34*, 1023; c) M. Wang, L. X. Gao, W. P. Mai, A. X. Xia, F. Wang, S. B. Zhang, *J. Org. Chem.* **2004**, *69*, 2874.
[9] D. C. Whitehead, R. Yousefi, A. Jaganathan, B. Borhan, *J. Am. Chem. Soc.* **2010**, *132*, 3298.
[10] W. Zhang, S. Zheng, N. Liu, J. B. Werness, I. A. Guzei, W. Tang, *J. Am. Chem. Soc.* **2010**, *132*, 3664.

