DOI: 10.1002/anie.201101076

Asymmetric Bromoamination of Chalcones with a Privileged *N*,*N*′-Dioxide/Scandium(III) Catalyst**

*Shao-Xu Huang and Kuiling Ding**

asymmetric catalysis · bromoamination · chalcones · *N*,*N*′-dioxides · scandium

The development of highly efficient and enantioselective catalysts is one of the greatest challenges for synthetic organic chemists,[1] in which the development of chiral ligands plays a critically important role. During the last several decades, numerous chiral ligands and their transition-metal complexes have been developed for various organic reactions. Among these chiral ligands and metal complexes, only a few have demonstrated high generality for mechanistically unrelated reactions, and they have thus been termed "privileged structures".[2] Recently, optically pure proline- or homoproline-based *N*,*N*′-dioxides[3–7] (Figure 1) were found to be powerful chiral ligands with ideal steric and electronic environments for enantioselective organocatalysis or metal-catalyzed reactions. Feng et al. have extensively explored the application of this type of chiral ligand in asymmetric catalysis in the last few years.[3–6] In particular, this type of *N*,*N*′-dioxide ligand can accommodate various metal ions[3–5] and has demonstrated excellent performance in a variety of reactions.

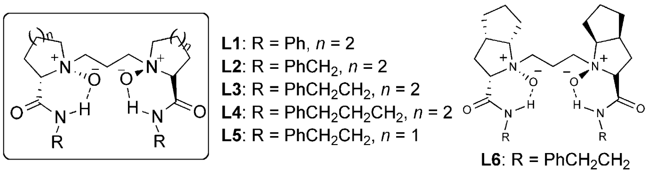


Figure 1. Representative structures of chiral *N*,*N*′-dioxide ligands.

A very recent report by Feng and co-workers has elegantly addressed a longstanding difficulty in the catalytic asymmetric vicinal bromoamination of chalcones with sulfonamide and *N*-bromosuccinimide (NBS) by using Sc^{III} complexes of *N*,*N*′-dioxide ligands as the catalyst.[7] The catalytic asymmetric difunctionalization of olefins is one of the most fundamental transformations in organic chemistry and has been widely used in organic synthesis. In contrast to many established processes for catalytic asymmetric difunctionalization of C=C bonds, such as epoxidation,[8] aziridination,[9] dihydroxylation,[10] aminohydroxylation,[11] and diamination,[12] electrophilic vicinal haloamination of olefin derivatives still presented a great challenge.

As reported by Feng et al., two difficulties must be overcome in order to realize an efficient catalytic asymmetric bromoamination of chalcones to attain chiral α-bromo-β-amino ketone derivatives. One of the concerns is the regioselectivity: chalcones usually prefer an aminobromination process through an aziridinium intermediate[13a] to afford α-amino-β-bromo ketone derivatives rather than the expected α-bromo-β-amino ketone products.[13] Therefore, driving the reaction to proceed via a bromonium ion intermediate is critically important in order to generate α-bromo-β-amino ketone products. The other difficulty is the possibility for racemization of the bromonium ion intermediate through olefin-to-olefin transfer,[14] which might reduce the enantioselectivity of the subsequent nucleophilic ring-opening process. Feng and co-workers addressed the issue of regioselectivity by using the Lewis acid $Sc(OTf)_3$ as the promoter; 4 Å molecular sieves significantly accelerated the reaction, and the desired compound was obtained as the major product in 70 % yield. They further envisaged developing the asymmetric version by employing $Sc(OTf)_3$ complexes of a variety of chiral *N*,*N*′-dioxide ligands **L1**–**L6** (Figure 1). The $Sc(OTf)_3$ complex of (*S*)-pipecolic acid derived *N*,*N*′-dioxide **L3** (10 mol %) turned out to be the most effective catalyst. Under the optimized reaction conditions, the bromoamination of chalcone **1** (R^1, $R^2 = Ph$) with *p*-toluenesulfonamide ($TsNH_2$) and NBS proceeded efficiently to give the corresponding α-bromo-β-amino ketone **2** (R^1, $R^2 = Ph$) in 99 % yield with 96 % *ee* and > 99:1 d.r. Owing to the high efficiency of the catalytic system, the catalyst loading could be decreased to 0.05 mol % without any loss of yield (99 %) and enantioselectivity (96 % *ee*). Notably, even when the catalyst loading was further reduced to 0.001 mol %, the enantioselectivity of reaction still remained at a high level (96 % *ee*) albeit with a longer reaction time and moderate yield; this demonstrates the extremely high activity and robust nature of the catalyst. It was also found that the exclusion of air and moisture was unnecessary in the manipulation. Moreover, a control experiment with a solution

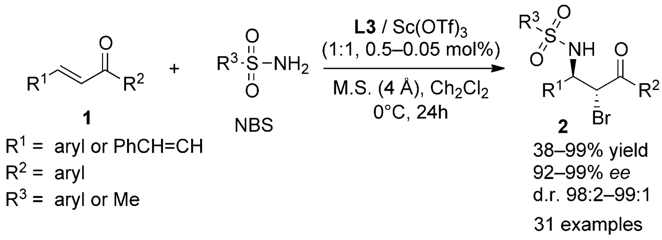
---

[*] Dr. S.-X. Huang, Prof. Dr. K. Ding
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (P.R. China)
Fax: (+86) 21-6416-6128
E-mail: kding@mail.sioc.ac.cn

[**] Financial support from the National Natural Science Foundation of China (nos. 20821002, 20923005), the Chinese Academy of Sciences, and the Major Basic Research Development Program of China (grant no. 2010CB833300) is gratefully acknowledged.

of catalyst aged for three months at room temperature showed that both the activity and the enantioselectivity of the reaction could be maintained, indicating the high stability of the catalyst. Last but not least, the preparation of **L3** is very straightforward starting from readily available industrial material by four-step reaction sequence in 55% overall yield.[15]

Under the optimized reaction conditions, the reaction of 31 chalcone derivatives having various structures, including fused-ring, multisubstituted, and heteroaryl-substituted chalcones and even rigid enones, proceeded efficiently with a catalyst loading of 0.05 mol%; the corresponding α-bromo-β-amino ketone derivatives were obtained in 80–99% yield with 90–99% *ee* and >99:1 d.r. (Scheme 1). The catalytic reaction system also tolerates a variety of sulfonamide substrates, giving the products with high *ee* and d.r. in moderate to excellent yields regardless of the substituents on the sulfonyl group. A one-pot synthesis of an optically active aziridine, a versatile building block in organic synthesis,[9] from a chalcone was also feasible by addition of Et_3N to the reaction system after the completion of bromoamination. The substrate scope of the catalysis is currently limited to chalcone derivatives, and future challenges will include the extension of the olefin substrates in particular to unfunctionalized olefins.



Scheme 1. Catalytic asymmetric vicinal bromoamination of chalcones.

The preliminary mechanistic study by Feng and coworkers is also interesting. On the basis of the regio- and stereoselectivity of the reaction, high-resolution MS and X-ray analyses of catalyst structure, and the absence of nonlinear effects, the authors proposed a mechanism based on a chiral bromonium ion along with the related transition state. As shown in Figure 2, both chalcone **1** (R^1, R^2 = Ph) and NBS are included in the coordination sphere of central Sc^{III} ion because of the oxophilicity of Sc^{III}. The intramolecular attack of bromine at the *Re* face of the chalcone yields the corresponding chiral bromonium ion, which subsequently undergoes an intermolecular nucleophilic attack of $TsNH^-$ through an S_N2 mechanism, leading to the desired product **2** (R^1, R^2 = Ph) with excellent *anti* selectivity. The regioselectivity thus can be explained on the basis of this model, since the β position of the bromonium ion intermediate has more positive charge than the α position because of the stabilizing effect of the phenyl ring. Although complete understanding of the mechanism of the present catalytic system remains a challenge, the proposed transition state outlined in Figure 2 shows that the cooperative action of activated substrates (chalcone and NBS) might be critically important for the control of the stereoselectivity of the reaction and the unusual high activity of the catalyst . Therefore, Feng's present work has provided further support for the power of cooperative catalysis[16,17] to address challenging issues, in particular the efficiency of the catalysis, and accordingly to revolutionize the chemical processes.

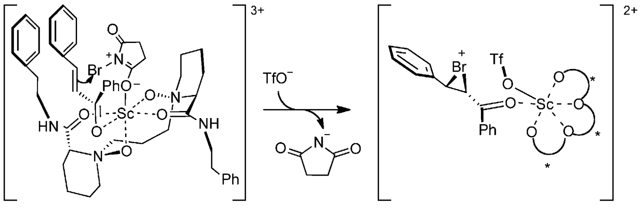


Figure 2. The proposed transition state (left) for asymmetric induction proceeding through the chiral bromonium ion intermediate (right).

In summary, the first catalytic asymmetric bromoamination of chalcones with sulfonamide and NBS has been realized by Feng et al. using an *N*,*N'*-dioxide/Sc^{III} catalyst under mild reaction conditions, affording the corresponding α-bromo-β-amino ketone derivatives with excellent regio-, diastereo-, and enantioselectivities. This work represents a significant breakthrough in the catalytic asymmetric difunctionalization of olefins. Considering the excellent performances of the *N*,*N'*-dioxide/Sc^{III} catalyst in the present reaction system and many other metal- or organocatalyzed asymmetric reactions,[3–7] it is obvious that the *N*,*N'*-dioxide molecules represent a type of privileged chiral ligands. It can be expected that the exciting results obtained with these ligands will stimulate the future efforts to understand the underlying reason for their broad applicability, and to apply this understanding to developing new reactions[18] and to solving the problems that still remain with existing catalysts.[19]

Received: February 12, 2011

---

[1] For a review, see: *Comprehensive Asymmetric Catalysis, Vol. I–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[2] T. P. Yong, E. N. Jacobsen, *Science* **2003**, *299*, 1691–1693.

[3] For examples, see: In^{III}, a) Z. P. Yu, X. H. Liu, Z. H. Dong, M. S. Xie, X. M. Feng, *Angew. Chem.* **2008**, *120*, 1328; *Angew. Chem. Int. Ed.* **2008**, *47*, 1308; Cu^{I} or Cu^{II}, b) Y. Zhu, X. H. Chen, M. S. Xie, S. X. Dong, Z. Qiao, L. L. Lin, X. H. Liu, X. M. Feng, *Chem. Eur. J.* **2010**, *16*, 11963, and references therein.

[4] For an example of Sc^{III}, see: M. S. Xie, X. H. Chen, Y. Zhu, B. Gao, L. L. Lin, X. H. Liu, X. M. Feng, *Angew. Chem.* **2010**, *122*, 3887; *Angew. Chem. Int. Ed.* **2010**, *49*, 3799, and references therein.

[5] For examples, La^{III}, see: a) Y. H. Hui, J. Jiang, W. T. Wang, W. L. Chen, Y. F. Cai, L. L. Lin, X. H. Liu, X. M. Feng, *Angew. Chem.* **2010**, *122*, 4386; *Angew. Chem. Int. Ed.* **2010**, *49*, 4290, and references therein; Ni^{II}, b) L. J. Wang, X. H. Liu, Z. H. Dong, X. Fu, X. M. Feng, *Angew. Chem.* **2008**, *120*, 8798; *Angew. Chem. Int. Ed.* **2008**, *47*, 8670; Y^{III}, c) L. Zhou, L. L. Lin, W. T. Wang, J. Ji, X. H. Liu, X. M. Feng, *Chem. Commun.* **2010**, *46*, 3601; Nd^{III}, d) K. Shen, X. H. Liu, W. T. Wang, G. Wang, W. D. Cao, W. Li, X. L. Hu, L. L. Lin, X. M. Feng, *Chem. Sci.* **2010**, *1*, 590; Mg^{II}, e) K. Zheng, Y. Yang, J. N. Zhao, C. K. Yin, L. L. Lin, X. H. Liu,

X. M. Feng, *Chem. Eur. J.* **2010**, *16*, 9969; for Ag$^{\mathrm{I}}$ and Sm$^{\mathrm{II}}$, f) Y. L. Liu, D. J. Shang, X. Zhou, Y. Zhu, L. L. Lin, X. H. Liu, X. M. Feng, *Org. Lett.* **2010**, *12*, 180.

[6] For an example of organocatalysis, see: Y. F. Cai, W. T. Wang, K. Shen, J. Wang, X. L. Hu, L. L. Lin, X. H. Liu, X. M. Feng, *Chem. Commun.* **2010**, *46*, 1250.

[7] Y. F. Cai, X. H. Liu, Y. H. Hui, J. Jiang, W. T. Wang, W. L. Chen, L. L. Lin, X. M. Feng, *Angew. Chem.* **2010**, *122*, 6296; *Angew. Chem. Int. Ed.* **2010**, *49*, 6160.

[8] For a review, see: R. A. Johnson, K. B. Sharpless, In *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed: I. Ojima), Wiley-VCH, New York, **2000**, pp. 231–280.

[9] For a review, see ref. *Comprehensive Asymmetric Catalysis*, *Vol. II* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, chap. 17.

[10] For a review, see: K. Matsumoto, T. Katsuki in *Catalytic Asymmetric Synthesis*, 3rd ed. (Ed: I. Ojima), Hoboken, Wiley-VCH, **2010**, pp. 879–882.

[11] For an example, see: G. Li, H. H. Angert, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 2995; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2813.

[12] For a review, see: F. Cardona, A. Goti, *Nat. Chem.* **2009**, *1*, 269.

[13] For examples, see: a) G. Li, S. S. R. S. Kotti, C. Timmons, *Eur. J. Org. Chem.* **2007**, 2745; b) J.-F. Wei, Z.-G. Chen, W. Lei, L.-H. Zhang, M.-Z. Wang, X.-Y. Shi, R.-T. Li, *Org. Lett.* **2009**, *11*, 4216.

[14] R. S. Brown, *Acc. Chem. Res.* **1997**, *30*, 131.

[15] W. T. Wang, X. H. Liu, W. D. Cao, J. Wang, L. L. Lin, X. M. Feng, *Chem. Eur. J.* **2010**, *16*, 1664.

[16] For reviews, see: a) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187; b) M. Shibasaki, M. Kanai, S. Matsunaga, N. Kumagai, *Acc. Chem. Res.* **2009**, *42*, 1117.

[17] For examples, see: a) J. M. Ready, E. N. Jacobsen, *Angew. Chem.* **2002**, *114*, 1432; *Angew. Chem. Int. Ed.* **2002**, *41*, 1374, and references therein; b) R. N. Loy, E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 2786; c) Z. Zhang, Z. Wang, R. Zhang, K. Ding, *Angew. Chem.* **2010**, *122*, 6898; *Angew. Chem. Int. Ed.* **2010**, *49*, 6746.

[18] For a new example, see: Y. F. Cai, X. H. Liu, J. Jiang, W. L. Chen, L. L. Lin, X. M. Feng, *J. Am. Chem. Soc.* **2011**, *133*, 5636.

[19] Note added in proof: After submission of this article, some new examples of asymmetric catalysis using this type of catalysts were reported, see: a) Y. F. Cai, X. H. Liu, J. Jiang, W. L. Chen, L. L. Lin, X. M. Feng, *J. Am. Chem. Soc.* **2011**, 133, 5636; b) K. Zheng, C. K. Yin, X. H. Liu, L. L. Lin, X. M. Feng, *Angew. Chem.* **2011**, *123*, 2621; *Angew. Chem. Int. Ed.* **2011**, *50*, 2573; c) K. Shen, X. H. Liu, G. Wang, L. L. Lin, X. M. Feng, *Angew. Chem.* **2011**, *123*, 4780; *Angew. Chem. Int. Ed.* **2011**, *50*, 4684; d) Z. Wang, Z. G. Yang, D. H. Chen, X. H. Liu, L. L. Lin, X. M. Feng, *Angew. Chem.* **2011**, *123*, 5030; *Angew. Chem. Int. Ed.* **2011**, *50*, 4928.