Asymmetric Catalysis

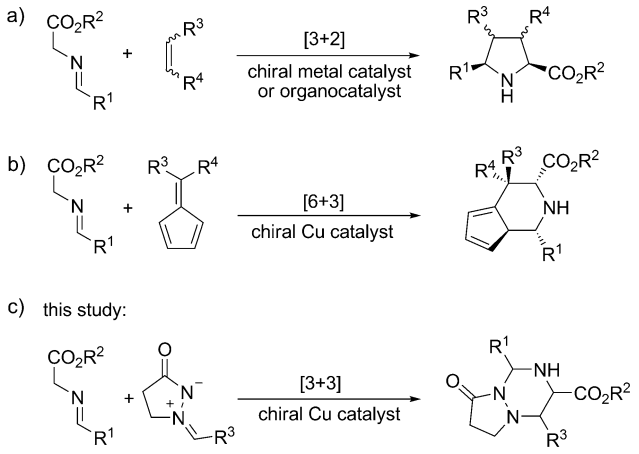
DOI: 10.1002/anie.201307317

# Enantioselective Copper-Catalyzed [3+3] Cycloaddition of Azomethine Ylides with Azomethine Imines**

*Hongchao Guo,* Honglei Liu, Fu-Lin Zhu, Risong Na, Hui Jiang, Yang Wu, Lei Zhang, Zhen Li, Hao Yu, Bo Wang, Yumei Xiao, Xiang-Ping Hu,* and Min Wang*

The 1,3-dipolar cycloaddition has been established as a reliable and powerful tool for the synthesis of heterocyclic compounds from simple starting materials.[1] In particular, the catalytic asymmetric 1,3-dipolar [3+2] cycloaddition of azomethine ylides with electron-deficient alkenes for the enantioselective preparation of structurally diverse pyrrolidines is probably one of the most studied asymmetric 1,3-dipolar cycloaddition reactions (Scheme 1 a),[2,3] and considerable progress has been made since the pioneering contributions from the research groups of Jørgensen[4] and Zhang.[5]

However, in the past decade, most studies on the cycloaddition chemistry of azomethine ylides have been focused on the development of chiral catalysts for asymmetric [3+2] cycloaddition with electron-deficient alkenes as the reaction partner; other types of cycloaddition reactions (e.g., [3+3] or [3+4] cycloaddition) with azomethine ylides as one of the reaction partners have received little attention. Only recently, a novel cycloaddition reaction, the catalytic enantioselective [6+3] cycloaddition of azomethine ylides with fulvene to provide stereochemically rich piperidine derivatives, was developed independently by the research groups of Waldmann[6] and Wang[7] (Scheme 1 b). At present, the development of new and efficient catalytic enantioselective higher-order cycloaddition reactions to access chiral six- and seven-membered rings and even larger heterocycles constitutes an important challenge. It was recently demonstrated that the zwitterion (which could be considered as a dipole) formed by the conjugate addition of a phosphine to an allenoate reacted with another kind of dipole in the form of azomethine imines in [3+2], [3+3], [4+3], and [3+2+3] cycloaddition reactions.[8] Inspired by this study, we conceived that a metal-catalyzed asymmetric cycloaddition of a dipole with a dipole might be feasible. Such a reaction has never been explored in the cycloaddition chemistry of azomethine ylides. We envisaged that azomethine imines, which have been used extensively as 1,3-dipoles in various metal-catalyzed and organocatalytic cycloaddition reactions,[9] might serve as a three-atom synthon in a metal-catalyzed cycloaddition of azomethine ylides and undergo [3+3] cycloaddition to give biologically important hexahydro-8*H*-pyrazolo[1,2-*a*][1,2,4]triazin-8-one derivatives (Scheme 1 c).[10] Herein, we report the first asymmetric [3+3] cycloaddition of azomethine ylides with azomethine imines under the catalysis of a copper complex with a chiral ferrocenyl P,N ligand to provide 8-oxohexahydro-6*H*-pyrazolo[1,2-*a*][1,2,4]triazine-3-carboxylate derivatives with high diastereo- and enantioselectivities (Scheme 1 c).




***Scheme 1.*** Asymmetric cycloaddition reactions of azomethine ylides.

Both azomethine ylides and azomethine imines are versatile 1,3-dipoles and can be prepared readily from aldehydes. We began the study by examining the reaction between the azomethine ylide precursor **1a** and the azomethine imine **2a** (Table 1) in the presence of different metals, chiral ligands, and bases in several solvents. Numerous combinations of various commonly used chiral ligands, such as 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (binap), segphos, the Trost diphosphine, Fesulphos, Taniaphos, quinap, box, phox, Fc-phox, bpe, and Duphos,[2h] metal salts, such as $Ag^{I}$, $Cu^{I}$, $Cu^{II}$, $Zn^{II}$, and $Ca^{II}$ salts, bases, such as $Et_3N$, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), $i$Pr$_2$NEt, $CsCO_3$, KO$t$Bu, $K_2CO_3$, potassium hexamethyldisilazide (KHMDS), and LiOH, and solvents, such as THF, $CH_2Cl_2$, and toluene, were tested. The target product in

[*] Prof. Dr. H. Guo, H. Liu, Dr. R. Na, H. Jiang, Y. Wu, L. Zhang, Z. Li, H. Yu, B. Wang, Dr. Y. Xiao, Prof. Dr. M. Wang
Department of Applied Chemistry, China Agricultural University
2 West Yuanmingyuan Road, Beijing 100193 (China)
E-mail: hchguo@cau.edu.cn
F.-L. Zhu, Prof. Dr. X.-P. Hu
Dalian Institute of Chemical Physics
Chinese Academy of Sciences
Dalian 116023 (China)
E-mail: xiangping@dicp.ac.cn

[**] This research was supported by the NSFC (21172253, 21372256), NCET-11-0481, the National Scientific and Technology Supporting Program of China (2011BAE06B05-5), the National S&T Pillar Program of China (2012BAK25B03), and Nutrichem. X.-P.H. also thanks the DICP for the financial support.

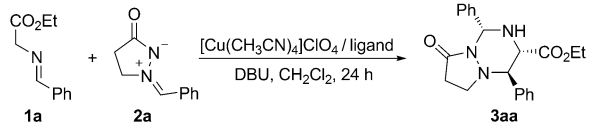
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201307317.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

Scheme 1c was generally obtained in very poor yield with very poor enantioselectivity. The combination binap/AgOAc/DBU afforded the best results, but the highest yield and *ee* value were only 30 and 33%, respectively.

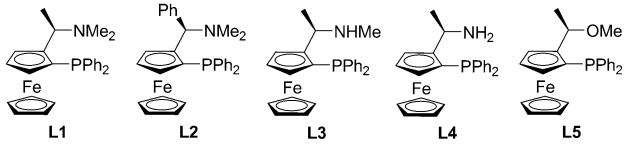
Finally, we turned our attention to ferrocenyl P,N ligands, which have been employed in asymmetric [3+2] cycloaddition reactions of azomethine ylides with electron-deficient alkenes.[2h] The screening experiments conducted with these chiral ligands are summarized in Table 1. To our delight, with $[Cu(CH_3CN)_4]ClO_4$ (10 mol%), **L1**, and dichloromethane as the solvent at 25°C, the target product **3aa** was obtained in 81% yield with 72% *ee* and excellent diastereoselectivity (Table 1, entry 1). When ligand **L2** was used, both the yield and the enantioselectivity were improved somewhat (85% yield, 77% *ee*; Table 1, entry 2). The catalyst generated from ligand **L3** promoted the cycloaddition with 74% *ee* but in moderate 50% yield (Table 1, entry 3). When ligand **L4** was employed, little conversion was observed (Table 1, entry 4). Interestingly, the Cu catalyst formed with the ferrocenyl P,O ligand **L5** also promoted the reaction to afford the target product in 70% yield, albeit with moderate 37% *ee* (Table 1, entry 5). With **L1** or **L2** as the chiral ligand, a further improvement in enantioselectivity was achieved by lowering the reaction temperature (Table 1, entries 6–8): With the Cu–**L1** catalyst at 0°C in $CH_2Cl_2$, the [3+3] cycloadduct was produced in 81% yield with 80% *ee*. However, when the Cu–**L2** catalyst (10 mol%) was used at 0 and −5°C, the *ee* value of the product increased markedly to 90 and 95%, respectively, with no significant erosion of the yield (85 and 78%; Table 1, entries 7 and 8) with respect to that of the reactions at 25°C (entries 1 and 2).[11] The relative and absolute configuration of **3aa** was assigned by X-ray crystal-structure analysis of the analogue **3al** obtained from the annulation of **1a** with the azomethine imine **2l** (Table 3)[12] and comparison of the optical rotation of the two compounds and NMR spectroscopic data.

***Table 1:*** Study of the reaction conditions.[a]



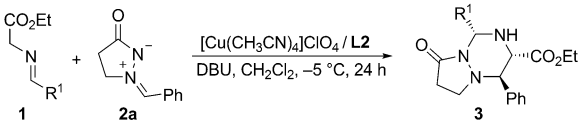

| Entry | Ligand | *T* [°C] | Yield [%][b] | d.r.[c] | *ee* [%][c] |
|---|---|---|---|---|---|
| 1 | **L1** | 25 | 81 | >20:1 | 72 |
| 2 | **L2** | 25 | 85 | >20:1 | 77 |
| 3 | **L3** | 25 | 50 | >20:1 | 74 |
| 4 | **L4** | 25 | trace | – | – |
| 5 | **L5** | 25 | 70 | >20:1 | 37 |
| 6 | **L1** | 0 | 81 | >20:1 | 80 |
| 7 | **L2** | 0 | 85 | >20:1 | 90 |
| 8 | **L2** | −5 | 78 | >20:1 | 95 |

[a] Unless otherwise indicated, reactions were carried out with **1a** (0.3 mmol), **2a** (0.33 mmol), $[Cu(CH_3CN)_4]ClO_4$ (0.03 mmol), the ligand (0.033 mmol), and DBU (0.033 mmol) in $CH_2Cl_2$ (3 mL) for 24 h. [b] Yield of the isolated product after chromatographic purification. [c] The diastereomeric ratio and *ee* value were determined by HPLC analysis on a chiral stationary phase. The product is levorotatory.




We first examined the scope of the reaction with respect to the azomethine ylide substrate under the optimized reaction conditions. A range of azomethine ylides derived from precursors **1** were tested in the [3+3] cycloaddition with azomethine imine **2a**. These functionalized azomethine ylides were converted efficiently into the corresponding products **3aa–ja** in 71–89% yield with 83–96% *ee* (Table 2). Good reactivity and stereoselectivity were observed for azomethine ylides with either electron-donating or electron-withdrawing groups on the benzene ring (Table 2, entries 1–9). In particular, the reaction of the azomethine ylide derived from the precursor **1f** with a 4-chlorophenyl group produced the bicyclic product **3fa** with the highest selectivity (96% *ee*) in 86% yield (Table 2, entry 6). The azomethine ylide bearing a 2-naphthyl group also underwent the desired [3+3] cycloaddition with **2a** to give the corresponding pyrazolo[1,2-*a*][1,2,4]triazine derivative in 72% yield with 90% *ee* (Table 2, entry 10). Unfortunately, azomethine ylides derived from aliphatic aldehydes were not viable substrates. The strong electron-donating effect of alkyl groups on azomethine ylides might lead to a decrease in activity of the ylides in the cycloaddition reaction.

***Table 2:*** Copper-catalyzed [3+3] cycloaddition of azomethine ylides with azomethine imine **2a**.[a]



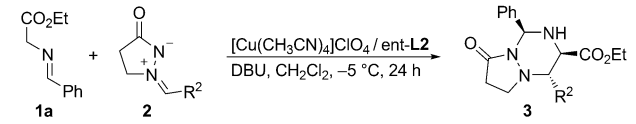

| Entry | **1** | $R^1$ | **3** | Yield [%][b] | d.r.[c] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **1a** | $C_6H_5$ | **3aa** | 78 | >20:1 | 95 |
| 2 | **1b** | 4-$MeC_6H_4$ | **3ba** | 71 | 14:1 | 88 |
| 3 | **1c** | 4-$FC_6H_4$ | **3ca** | 76 | >20:1 | 90 |
| 4 | **1d** | 2-$ClC_6H_4$ | **3da** | 81 | >20:1 | 91 |
| 5 | **1e** | 3-$ClC_6H_4$ | **3ea** | 81 | >20:1 | 94 |
| 6 | **1f** | 4-$ClC_6H_4$ | **3fa** | 86 | >20:1 | 96 |
| 7 | **1g** | 2-$BrC_6H_4$ | **3ga** | 75 | >20:1 | 83 |
| 8 | **1h** | 4-$BrC_6H_4$ | **3ha** | 82 | >20:1 | 90 |
| 9 | **1i** | 4-$CF_3C_6H_4$ | **3ia** | 89 | >20:1 | 95 |
| 10 | **1j** | 2-naphthyl | **3ja** | 72 | >20:1 | 90 |

[a] Unless otherwise indicated, reactions were carried out with **1** (0.3 mmol), **2a** (0.33 mmol), $[Cu(CH_3CN)_4]ClO_4$ (0.03 mmol), **L2** (0.033 mmol), and DBU (0.033 mmol) in $CH_2Cl_2$ (3 mL) at −5°C for 24 h. [b] Yield of the isolated product. [c] The diastereomeric ratio and *ee* value were determined by HPLC analysis on a chiral stationary phase. The products are levorotatory. When there were more than two diastereomers, the diastereomeric ratio given is the ratio of the amount of the major diastereomer to the total amount of other diastereomers.

Next, we investigated the reactivity of various azomethine imines **2** with the azomethine ylide derived from precursor **1a** as the reaction partner. The enantiomer of ligand **L2** was used

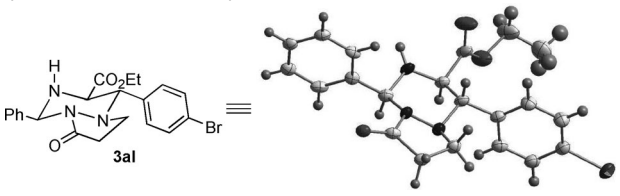

© 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

***Table 3:*** Copper-catalyzed [3+3] cycloaddition of azomethine ylide **1a** with azomethine imines.[a]



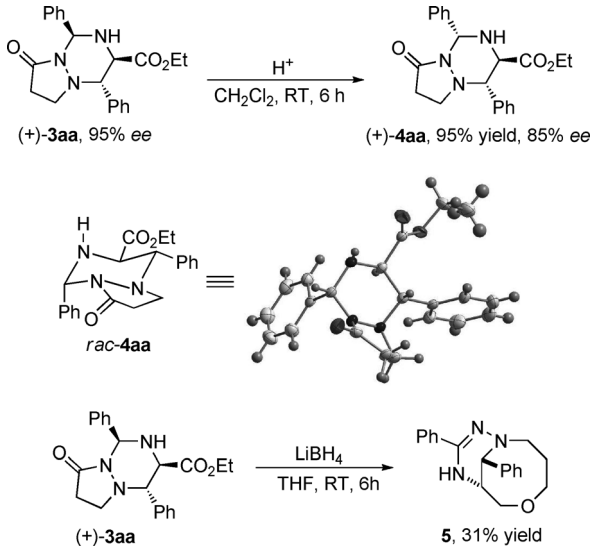

| Entry | 2 | $R^2$ | 3 | Yield [%][b] | d.r.[c] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **2b** | 4-$MeC_6H_4$ | **3ab** | 60 | >20:1 | 85 |
| 2 | **2c** | 4-$MeOC_6H_4$ | **3ac** | 73 | >20:1 | 84 |
| 3 | **2d** | 2-$FC_6H_4$ | **3ad** | 80 | 10:1 | 93 |
| 4 | **2e** | 3-$FC_6H_4$ | **3ae** | 70 | >20:1 | 93 |
| 5 | **2f** | 4-$FC_6H_4$ | **3af** | 68 | >20:1 | 91 |
| 6 | **2g** | 2-$ClC_6H_4$ | **3ag** | 79 | 10:1 | 92 |
| 7 | **2h** | 3-$ClC_6H_4$ | **3ah** | 70 | 18:1 | 90 |
| 8 | **2i** | 4-$ClC_6H_4$ | **3ai** | 70 | >20:1 | 87 |
| 9 | **2j** | 2-$BrC_6H_4$ | **3aj** | 77 | 2:1 | 91 |
| 10 | **2k** | 3-$BrC_6H_4$ | **3ak** | 76 | >20:1 | 90 |
| 11 | **2l** | 4-$BrC_6H_4$ | **3al** | 83 | >20:1 | 90 |
| 12 | **2m** | 4-$CF_3C_6H_4$ | **3am** | 78 | >20:1 | 83 |
| 13[d] | **2n** | 4-$CNC_6H_4$ | **3an** | 73 | >20:1 | 90 |
| 14 | **2o** | 2-naphthyl | **3ao** | 75 | >20:1 | 89 |

[a] Unless otherwise indicated, reactions were carried out with **1a** (0.3 mmol), **2** (0.33 mmol), $[Cu(CH_3CN)_4]ClO_4$ (0.03 mmol), *ent*-**L2** (0.033 mmol), and DBU (0.033 mmol) in $CH_2Cl_2$ (3 mL) for 24 h. For entries 3, 6, 7, and 9–11, the reactions were performed at 0°C for 18 h. [b] Yield of the isolated product. [c] The diastereomeric ratio and *ee* value were determined by HPLC analysis on a chiral stationary phase. The products are dextrorotatory. When there were more than two diastereomers, the diastereomeric ratio given is the ratio of the amount of the major diastereomer to the total amount of other diastereomers. [d] DBU (0.0225 mmol, 7.5 mol%) was used.




as the chiral ligand in the reactions. With the Cu–*ent*-**L2** catalyst (10 mol%), a variety of azomethine imines **2b–o** smoothly underwent the cycloaddition to provide the corresponding heterocyclic products **3** in 60–83% yield with 83–93% *ee* (Table 3). In general, the azomethine imines with electron-withdrawing groups on the benzene ring showed better enantioselectivity than those with electron-donating groups (Table 3, entries 1 and 2 versus entries 3–13). An *ortho* substituent on the benzene ring had a negative effect on the diastereoselectivity of the reaction (Table 3, entries 3, 6, and 9), probably as a result of the steric hindrance caused by three contiguous functional groups, namely, the ester group, the *ortho*-substituted phenyl group, and the pyrazolidin-3-one ring. The 2-naphthaldehyde-derived azomethine imine **2o** was also a viable substrate and underwent an efficient [3+3] cycloaddition with **1a** to give the product **3ao** in high yield with good enantioselectivity (Table 3, entry 14). The X-ray crystallographic structure of product **3al**[12] showed that the six-membered ring of the bicyclic structure adopts a chair conformation, and that all substituents on the six-membered ring occupy the five equatorial positions; this arrangement enables the structure to be very stable. Unfortunately, like aliphatic azomethine ylides, azomethine imines derived from aliphatic aldehydes were not viable substrates.

Under acidic conditions, a very interesting epimerization of the products **3** occurred to give their diastereomers **4**. For example, when the product (+)-**3aa** was treated with acetic acid (1 equiv) in dichloromethane for 6 h, its diastereomer (+)-**4aa** was obtained in 95% yield with a certain loss of optical purity (Scheme 2). The relative and absolute configuration of (+)-**4aa** was assigned by X-ray crystal-structure




***Scheme 2.*** Epimerization and synthetic elaboration of product **3aa**.

analysis of the compound *rac*-**4aa**[13] and (+)-**4aj** formed by the epimerization of the product (+)-**3aj**.[12] As compared with the product (+)-**3aa**, the configuration at C1 has been inverted in (+)-**4aa**, and the phenyl substituent at this carbon atom occupies the axial position in the chair conformation. The treatment of product (+)-**3aa** with $LiBH_4$ in THF afforded a bicyclic heterocyclic compound **5** with an interesting structure in 31% yield. Unfortunately, although product **5** was formed as a single diastereomer, it was racemic.

In conclusion, we have developed a copper-catalyzed highly diastereo- and enantioselective [3+3] cycloaddition of azomethine ylides with azomethine imines in the presence of ferrocenyl P,N chiral ligands. Since azomethine ylides, azomethine imines, and ferrocenyl P,N chiral ligands are highly accessible compounds, the reaction provides concise and expedient access to a variety of optically active hexahydro-8*H*-pyrazolo[1,2-*a*][1,2,4]triazin-8-one derivatives with potential biological activity. The high efficiency observed in this reaction suggests that more cycloaddition reactions of 1,3-dipoles with 1,3-dipoles could be anticipated. Further exploration of the reaction mechanism and expansion of the scope of the reaction to include other kinds of azomethine ylide and azomethine imine substrates are under way.

Received: August 20, 2013
Published online: October 2, 2013

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

**Keywords:** asymmetric catalysis · azomethine imines · azomethine ylides · copper · [3+3] cycloaddition

[1] For selected reviews, see: a) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863 – 909; b) K. V. Gothelf in *Cycloaddition Reactions in Organic Synthesis* (Eds.: S. Kobayashi, K. A. Jørgensen), Wiley-VCH, Weinheim, **2002**, pp. 211 – 247; c) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry—Toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, Hoboken, **2003**; d) T. Hashimoto, K. Maruoka in *Handbook of Cyclization Reactions* (Ed.: S. Ma), Wiley-VCH, Weinheim, **2009**, chap. 3, pp. 87 – 168.

[2] For selected reviews, see: a) C. Nájera, J. M. Sansano, *Angew. Chem.* **2005**, *117*, 6428 – 6432; *Angew. Chem. Int. Ed.* **2005**, *44*, 6272 – 6276; b) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765 – 2809; c) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484 – 4517; d) H. Pellissier, *Tetrahedron* **2007**, *63*, 3235 – 3285; e) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887 – 2902; f) B. Engels, M. Christl, *Angew. Chem.* **2009**, *121*, 8110 – 8112; *Angew. Chem. Int. Ed.* **2009**, *48*, 7968 – 7970; g) A. de Cózar, F. P. Cossío, *Phys. Chem. Chem. Phys.* **2011**, *13*, 10858 – 10868; h) J. Adrio, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6784 – 6794.

[3] For selected examples of [3+2] cycloaddition reactions, see: a) C. Chen, X. Li, S. L. Schreiber, *J. Am. Chem. Soc.* **2003**, *125*, 10174 – 10175; b) T. F. Knöpfel, P. Aschwanden, T. Ichikawa, T. Watanabe, E. M. Carreira, *Angew. Chem.* **2004**, *116*, 6097 – 6099; *Angew. Chem. Int. Ed.* **2004**, *43*, 5971 – 5973; c) W. Zeng, Y.-G. Zhou, *Org. Lett.* **2005**, *7*, 5055 – 5058; d) S. Cabrera, R. G. Arrayás, J. C. Carretero, *J. Am. Chem. Soc.* **2005**, *127*, 16394 – 16395; e) X.-X. Yan, Q. Peng, Y. Zhang, K. Zhang, W. Hong, X.-L. Hou, Y.-D. Wu, *Angew. Chem.* **2006**, *118*, 2013 – 2017; *Angew. Chem. Int. Ed.* **2006**, *45*, 1979 – 1983; f) W. Zeng, G.-Y. Chen, Y.-G. Zhou, Y.-X. Li, *J. Am. Chem. Soc.* **2007**, *129*, 750 – 751; g) S. Saito, T. Tsubogo, S. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 5364 – 5365; h) J. L. Vicario, S. Reboredo, D. Badía, L. Carrillo, *Angew. Chem.* **2007**, *119*, 5260 – 5262; *Angew. Chem. Int. Ed.* **2007**, *46*, 5168 – 5170; i) X.-H. Chen, W.-Q. Zhang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 5652 – 5653; j) C. Nájera, M. D. G. Retamosa, J. M. Sansano, *Angew. Chem.* **2008**, *120*, 6144 – 6147; *Angew. Chem. Int. Ed.* **2008**, *47*, 6055 – 6058; k) S.-i. Fukuzawa, H. Oki, *Org. Lett.* **2008**, *10*, 1747 – 1750; l) Y.-K. Liu, H. Liu, W. Du, L. Yue, Y.-C. Chen, *Chem. Eur. J.* **2008**, *14*, 9873 – 9877; m) T. Arai, N. Yokoyama, A. Mishiro, H. Sato, *Angew. Chem.* **2010**, *122*, 8067 – 8070; *Angew. Chem. Int. Ed.* **2010**, *49*, 7895 – 7898; n) Z.-Y. Xue, T.-L. Liu, Z. Lu, H. Huang, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2010**, *46*, 1727 – 729; o) T. Arai, A. Mishiro, N. Yokoyama, K. Suzuki, H. Sato, *J. Am. Chem. Soc.* **2010**, *132*, 5338 – 5339; p) I. Oura, K. Shimizu, K. Ogata, S.-i. Fukuzawa, *Org. Lett.* **2010**, *12*, 1752 – 1755; q) C. Zhang, S.-B. Yu, X.-P. Hu, D.-Y. Wang, Z. Zheng, *Org. Lett.* **2010**, *12*, 5542 – 5545; r) Y. Yamashita, X.-X. Guo, R. Takashita, S. Kobayashi, *J. Am. Chem. Soc.* **2010**, *132*, 3262 – 3263; s) R. Robles-Machín, I. Alonso, J. Adrio, J. C. Carretero, *Chem. Eur. J.* **2010**, *16*, 5286 – 5291; t) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nat. Chem.* **2010**, *2*, 735 – 740; u) H. Y. Kim, J.-Y. Li, S. Kim, K. Oh, *J. Am. Chem. Soc.* **2011**, *133*, 20750 – 20753; v) L. He, X.-H. Chen, D.-N. Wang, S.-W. Luo, W.-Q. Zhang, J. Yu, L. Ren, L.-Z. Gong, *J. Am. Chem. Soc.* **2011**, *133*, 13504 – 13518; w) T.-L. Liu, Z.-L. He, Q.-H. Li, H.-Y. Tao, C.-J. Wang, *Adv. Synth. Catal.* **2011**, *353*, 1713 – 1719; x) Y. Yamashita, T. Imaizumi, S. Kobayashi, *Angew. Chem.* **2011**, *123*, 4995 – 4998; *Angew. Chem. Int. Ed.* **2011**, *50*, 4893 – 4896; y) T.-L. Liu, Z.-L. He, H.-Y. Tao, Y.-P. Cai, C.-J. Wang, *Chem. Commun.* **2011**, *47*, 2616 – 2618; z) H.-L. Teng, H. Huang, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2011**, *47*, 5494 – 5496; aa) T.-L. Liu, Z.-L. He, C.-J. Wang, *Chem. Commun.* **2011**, *47*, 9600 – 9602; ab) Q.-H. Li, M.-C. Tong, J. Li, H.-Y. Tao, C.-J. Wang, *Chem. Commun.* **2011**, *47*, 11110 – 11112; ac) S. Reboredo, E. Reyes, J. L. Vicario, D. Badía, L. Carrillo, A. Cózar, F. P. Cossío, *Chem. Eur. J.* **2012**, *18*, 7179 – 7188; ad) M. Potowski, M. Schürmann, H. Preut, A. P. Antonchick, H. Waldmann, *Nat. Chem. Biol.* **2012**, *8*, 428 – 430; ae) E. Conde, D. Bello, A. de Cózar, M. Sánchez, M. A. Vázquez, F. P. Cossío, *Chem. Sci.* **2012**, *3*, 1486 – 1491; af) M. González-Esguevillas, J. Adrio, J. C. Carretero, *Chem. Commun.* **2012**, *48*, 2149 – 2151.

[4] A. S. Gothelf, K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 4410 – 4412; *Angew. Chem. Int. Ed.* **2002**, *41*, 4236 – 4238.

[5] J. M. Longmire, B. Wang, X. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13400 – 13401.

[6] a) M. Potowski, J. O. Bauer, C. Strohmann, A. P. Antonchick, H. Waldmann, *Angew. Chem.* **2012**, *124*, 9650 – 9654; *Angew. Chem. Int. Ed.* **2012**, *51*, 9512 – 9516; b) M. Potowski, A. P. Antonchick, H. Waldmann, *Chem. Commun.* **2013**, *49*, 7800 – 7802.

[7] Z.-L. He, H.-L. Teng, C.-J. Wang, *Angew. Chem.* **2013**, *125*, 3006 – 3010; *Angew. Chem. Int. Ed.* **2013**, *52*, 2934 – 2938.

[8] a) R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard, III, H. Guo, O. Kwon, *J. Am. Chem. Soc.* **2011**, *133*, 13337 – 13348; b) C. Jing, R. Na, B. Wang, H. Liu, L. Zhang, J. Liu, M. Wang, J. Zhong, O. Kwon, H. Guo, *Adv. Synth. Catal.* **2012**, *354*, 1023 – 1034; c) J. Liu, H. Liu, R. Na, G. Wang, Z. Li, H. Yu, M. Wang, J. Zhong, H. Guo, *Chem. Lett.* **2012**, *41*, 218 – 230.

[9] For examples of the cycloaddition of azomethine imines, see: a) R. Shintani, G. C. Fu, *J. Am. Chem. Soc.* **2003**, *125*, 10778 – 10779; b) A. Suárez, C. W. Downey, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 11244 – 11245; c) R. Shintani, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 6330 – 6331; d) W. Chen, X.-H. Yuan, R. Li, W. Du, Y. Wu, L.-S. Ding, Y.-C. Chen, *Adv. Synth. Catal.* **2006**, *348*, 1818 – 1822; e) A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 5334 – 5335; f) H. Suga, A. Funyu, A. Kakehi, *Org. Lett.* **2007**, *9*, 97 – 100; g) R. Shintani, M. Murakami, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 12356 – 12357; h) W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen, *Angew. Chem.* **2007**, *119*, 7811 – 7814; *Angew. Chem. Int. Ed.* **2007**, *46*, 7667 – 7670; i) M. P. Sibi, D. Rane, L. M. Stanley, T. Soeta, *Org. Lett.* **2008**, *10*, 2971 – 2974; j) C. Perreault, S. R. Goudreau, L. E. Zimmer, A. B. Charette, *Org. Lett.* **2008**, *10*, 689 – 692; k) N. D. Shapiro, Y. Shi, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 11654 – 11655; l) M. Keller, A. S. S. Sido, P. Pale, J. Sommer, *Chem. Eur. J.* **2009**, *15*, 2810 – 2817; m) T. Hashimoto, Y. Maeda, M. Omote, H. Nakatsu, K. Maruoka, *J. Am. Chem. Soc.* **2010**, *132*, 4076 – 4077; n) T. Hashimoto, M. Omote, K. Maruoka, *Angew. Chem.* **2011**, *123*, 3551 – 3554; *Angew. Chem. Int. Ed.* **2011**, *50*, 3489 – 3492; o) K. Yoshimura, T. Oishi, K. Yamaguchi, N. Mizuno, *Chem. Eur. J.* **2011**, *17*, 3827 – 3831; p) T. Imaizumi, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2012**, *134*, 20049 – 20052; q) W. Zhou, X. X. Li, G. H. Li, Y. Wu, Z. L. Chen, *Chem. Commun.* **2013**, *49*, 3552 – 3554; r) J. T. Li, X. J. Lian, X. H. Liu, L. L. Lin, X. M. Feng, *Chem. Eur. J.* **2013**, *19*, 5134 – 5140; s) Y. Qian, P. J. Zavalij, W. H. Hu, M. P. Doyle, *Org. Lett.* **2013**, *15*, 1564 – 1567; t) X. F. Xu, X. C. Xu, P. Y. Zavalij, M. P. Doyle, *Chem. Commun.* **2013**, *49*, 2762 – 2764; u) Y.-Y. Zhou, J. Li, L. Ling, S.-H. Liao, X.-L. Sun, Y.-X. Li, L.-J. Wang, Y. Tang, *Angew. Chem.* **2013**, *125*, 1492 – 1496; *Angew. Chem. Int. Ed.* **2013**, *52*, 1452 – 1456.

[10] a) M. M. Badran, M. A. H. Ismail, N. Abdu, M. Abdel-Hakeem, *Alexandria J. Pharm. Sci.* **1999**, *13*, 101 – 106; b) K. Thiele, C. J. S. Gordon, J. Fischer, U. Jahn, Eur. Pat. Appl. EP 28660, **1981** [*Chem. Abstr.* **1981**, *95*, 103328]; c) Z. Zhu, W. J. Greenlee, D. J. Cole, D. A. Pissarnitski, G. V. Gallo, H. Li, H. B. Josien, J. Qin, C. E. Knutson, M. Mandal, M. L. Vicarel, M. Rajagopalan, P. K.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 

Dhondi, R. Xu, Z.-Y. Sun, T. A. Bara, X. Huang, X. Zhu, Z. Zhao, J. W. Clader, A. Palani, T. Asberom, T. McCracken, C. E. Bennett, PCT Int. Appl. WO 2010054067, **2010** [*Chem. Abstr.* **2010**, *152*, 548137].

[11] Ligand **L2** with 98% *ee* was used. By further increasing the optical purity of the chiral ligand, it might be possible to improve the enantioselectivity of the reaction further. The use of a reduced amount of DBU sometimes led to an improvement in the enantioselectivity of the reaction. For example, with 7.5 mol% of DBU at −5°C, the *ee* value of **3aa** could be increased to 98%.

[12] CCDC 951058 ((+)-**3al**), 951059 ((+)-**4aj**), 951060 ((+)-**3ae**), and 951061 (racemic **4aa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] A single crystal of (+)-**4aa** has not yet been obtained, although the growth of a suitable crystal has been attempted under various conditions.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 