Asymmetric Catalysis

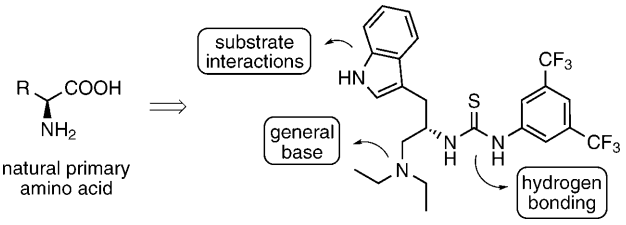
DOI: 10.1002/ange.200903635

# Asymmetric Mannich Reaction of Fluorinated Ketoesters with a Tryptophan-Derived Bifunctional Thiourea Catalyst**

*Xiao Han, Jacek Kwiatkowski, Feng Xue, Kuo-Wei Huang,* and Yixin Lu**

*In memory of George Just*

Small organic molecules capable of hydrogen-bonding interactions with substrates have found widespread application in asymmetric catalysis.[1] In particular, thiourea-based organic molecules have become the most prominent hydrogen-bond-donor catalysts in a wide variety of organic reactions. In this context, bifunctional[2] organic molecules containing a tertiary amino functionality and a thiourea moiety are remarkably useful organic catalysts.[3] Despite their tremendous utility, these bifunctional catalysts are derived from a very limited range of chiral structural scaffolds, including cyclohexane-1,2-diamine, 1,1′-binaphthyl-2,2′-diamine, and cinchona alkaloids. The development of readily accessible novel bifunctional catalysts of this nature would be highly desirable. As part of our research program towards the development of practical organocatalysts based on primary amino acids,[4] we were intrigued by the possibility of designing novel tertiary amine–thiourea catalysts on the basis of simple amino acids. The facile conversion of natural amino acids into 1,2-diamines and the availability of structurally diverse side chains make this method very attractive. To investigate the validity of this approach, we selected L-tryptophan as the chiral precursor. We reasoned that the indole moiety would be capable of engaging in aromatic and hydrogen-bonding interactions with substrates, and these effects may result in efficient chiral induction (Scheme 1).




***Scheme 1.*** Thiourea catalyst based on a primary amino acid (tryptophan).

Fluorinated molecules are of high importance in the pharmaceutical industry, and their asymmetric preparation has drawn great attention.[5] The catalytic construction of fluorinated quaternary carbon stereocenters is a formidable synthetic challenge. A number of excellent methods based on metal catalysis have been reported;[6] however, organocatalytic approaches for the creation of fluorinated quaternary centers are rather limited.[7] Recently, organocatalytic synthetic methods with fluorinated substrates have become an alternative and viable option for accessing chiral fluorinated molecules. In such approaches, racemic fluorinated nucleophiles are used as substrates. A C–C bond is formed rather than a C–F bond, and full advantage is taken of the high electronegativity and small molecular radius of the fluorine atom. We and others[8] have used fluorinated substrates in this way in organocatalytic Michael and alkylation reactions for the construction of fluorinated chiral molecules.

To assess the utility of tryptophan-based bifunctional catalysts, we chose to focus on the direct asymmetric Mannich reaction of α-fluorinated β-ketoesters, as such reactions yield structurally demanding and biologically important α-fluoro-β-amino acids. Organocatalytic asymmetric Mannich reactions of β-ketoesters and malonates were reported recently by the research groups of Schaus, Deng, and Dixon, all of whom employed organic catalysts derived from cinchona alkaloids.[9] Herein, we report that tryptophan-based bifunctional thiourea derivatives promote the asymmetric Mannich reaction of fluorinated substrates to afford highly optically enriched fluorine-containing molecules containing adjacent quaternary and tertiary stereocenters.

We selected the Mannich reaction of α-fluoro-β-ketoester **1a** with *N*-Boc imine **2a**[10] as a model reaction and examined the catalytic effects of various bifunctional catalysts (Table 1). Quinidine-derived thioureas and a quinidine-derived sulfonamide[11] gave disappointing results (Table 1, entries 1–3). On the other hand, the tryptophan-based thiourea derivatives **Trp-1**–**Trp-3** were found to be good catalysts. They afforded the Mannich product **3a** in quantitative yield and with good diastereoselectivity and enantioselectivity (Table 1, entries 4–6). Under optimized reaction conditions, the fluorinated product containing adjacent quaternary and tertiary stereo-

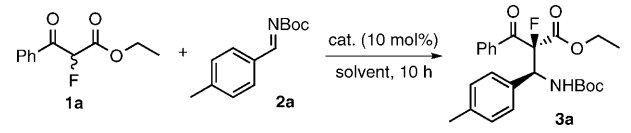
[*] X. Han, J. Kwiatkowski, Prof. Dr. F. Xue, Prof. Dr. K.-W. Huang, Prof. Dr. Y. Lu
Department of Chemistry, National University of Singapore
3 Science Drive 3, Singapore 117543 (Singapore)
Fax: (+65) 6779-1691
E-mail: hkw@nus.edu.sg
chmlyx@nus.edu.sg
Prof. Dr. Y. Lu
Medicinal Chemistry Program, Life Sciences Institute
National University of Singapore (Singapore)
J. Kwiatkowski, Prof. Dr. Y. Lu
NUS Graduate School for Integrative Sciences and Engineering (Singapore)

[**] We thank the National University of Singapore and the Ministry of Education (MOE) of Singapore (R-143-000-362-112) for generous financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200903635.

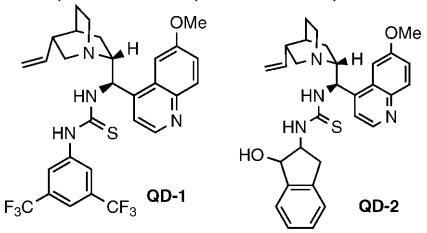

InterScience
© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

***Table 1:*** Screening of bifunctional catalysts for the asymmetric Mannich reaction of **1a** and **2a**.[a]

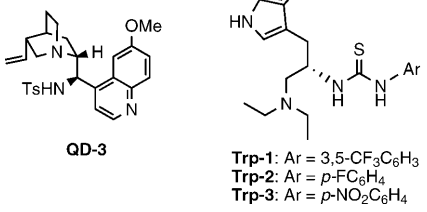



| Entry | Catalyst | *T* [°C] | Solvent | Conversion [%] | d.r. [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **QD-1** | RT | toluene | >99 | 4:1 | −43 |
| 2 | **QD-2** | RT | toluene | >99 | 3:1 | −4 |
| 3 | **QD-3** | RT | toluene | <20 | – | – |
| 4 | **Trp-1** | RT | toluene | >99 | 5:1 | 88 |
| 5 | **Trp-2** | RT | toluene | >99 | 4:1 | 59 |
| 6 | **Trp-3** | RT | toluene | >99 | 4:1 | 67 |
| 7 | **Trp-1** | RT | $CH_2Cl_2$ | >99 | 4:1 | 80 |
| 8 | **Trp-1** | RT | THF | >99 | 3:1 | 15 |
| 9 | **Trp-1** | RT | $CH_3CN$ | >99 | 5:1 | 53 |
| 10[d] | **Trp-1** | −20 | toluene | >99 | 8:1 | 93 |
| 11[e] | **Trp-1** | **−50** | **toluene** | **>99** | **9:1** | **97** |

[a] Reactions were carried out with **1a** (0.05 mmol), **2a** (0.075 mmol), and the catalyst (0.005 mmol) in the solvent (1 mL) at the specified temperature. The conversion was estimated by $^1$H NMR spectroscopic analysis of the crude product. [b] The diastereomeric ratio was determined by $^1$H NMR spectroscopic analysis of the crude product. [c] The *ee* value of the major diastereomer is given, as determined by HPLC analysis on a chiral stationary phase. [d] The reaction time was 24 h. [e] The reaction time was 48 h. Boc = *tert*-butoxycarbonyl, THF = tetrahydrofuran, Ts = *p*-toluenesulfonyl.




QD: quinidine

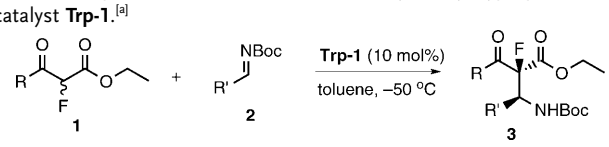



centers was obtained with d.r. 9:1 and 97% *ee* (Table 1, entry 11).

Next, we investigated the scope of the reaction. Consistently good diastereoselectivity and high enantioselectivity were observed with a wide range of aromatic α-fluorinated β-ketoesters (Table 2, entries 1–14). In the case of aliphatic ketoester substrates, although the reactions proceeded with little diastereoselectivity, the diastereomers were formed with excellent enantioselectivity (Table 2, entries 15 and 16). However, the use of the *tert*-butyl ketoester resulted in high diastereoselectivity and good enantioselectivity (Table 2, entry 17).

The Mannich reaction of alkyl imines is a daunting synthetic challenge. The results of Deng and co-workers[9b] are

***Table 2:*** Scope of the Mannich reaction catalyzed by tryptophan-based catalyst **Trp-1**.[a]




| Entry | R/R′ | *t* [h] | Yield [%][b] | d.r. [%][c] | *ee* [%][d] |
|---|---|---|---|---|---|
| 1 | *p*-$MeC_6H_4$/*p*-$MeC_6H_4$ (**3b**) | 72 | 92 | 12:1 | 97 |
| 2 | *p*-$FC_6H_4$/*p*-$MeC_6H_4$ (**3c**) | 48 | 96 | 9:1 | 96 |
| 3 | *p*-$ClC_6H_4$/*p*-$MeC_6H_4$ (**3d**) | 24 | 95 | 8:1 | 95 |
| 4 | *p*-$BrC_6H_4$/*p*-$MeC_6H_4$ (**3e**) | 20 | 92 | 7:1 | 95 |
| 5 | *p*-$NO_2C_6H_4$/*p*-$MeC_6H_4$ (**3f**) | 20 | 93 | 8:1 | 92 |
| 6 | thiophenyl/*p*-$MeC_6H_4$ (**3g**) | 24 | 95 | 4:1 | 95 |
| 7 | 2-naphthyl/*p*-$MeC_6H_4$ (**3h**) | 24 | 93 | 5:1 | 96 |
| 8 | Ph/*p*-$BrC_6H_4$ (**3i**) | 20 | 92 | 8:1 | 96 |
| 9 | *p*-$ClC_6H_4$/*p*-$BrC_6H_4$ (**3j**) | 20 | 96 | 7:1 | 95 |
| 10 | Ph/*p*-$FC_6H_4$ (**3k**) | 20 | 95 | 10:1 | 97 |
| 11 | *p*-$BrC_6H_4$/*p*-$FC_6H_4$ (**3l**) | 20 | 92 | 8:1 | 95 |
| 12 | Ph/*o*-$MeC_6H_4$ (**3m**) | 36 | 95 | 11:1 | 92 |
| 13 | Ph/*p*-$CF_3C_6H_4$ (**3n**) | 20 | 92 | 6:1 | 97 |
| 14 | Ph/*m*-$NO_2C_6H_4$ (**3o**) | 20 | 92 | 8:1 | 99 |
| 15[e] | Me/*p*-$MeC_6H_4$ (**3p**) | 24 | 90 | 1:1 | 90/93 |
| 16[e] | *i*Pr/*p*-$FC_6H_4$ (**3q**) | 36 | 93 | 1:1 | 96/97 |
| 17[e] | *t*Bu/*p*-$MeC_6H_4$ (**3r**) | 24 | 95 | >19:1 | 84 |
| 18[f] | Ph/*c*-$C_6H_{11}$ (**3s**) | 24 | 70 | 4:1 | 85 |
| 19[g] | Ph/*c*-$C_6H_{11}$ (**3t**) | 20 | 92 | 3:1 | 96 |
| 20[g] | Ph/*n*Bu (**3u**) | 20 | 93 | 3:1 | 81 |

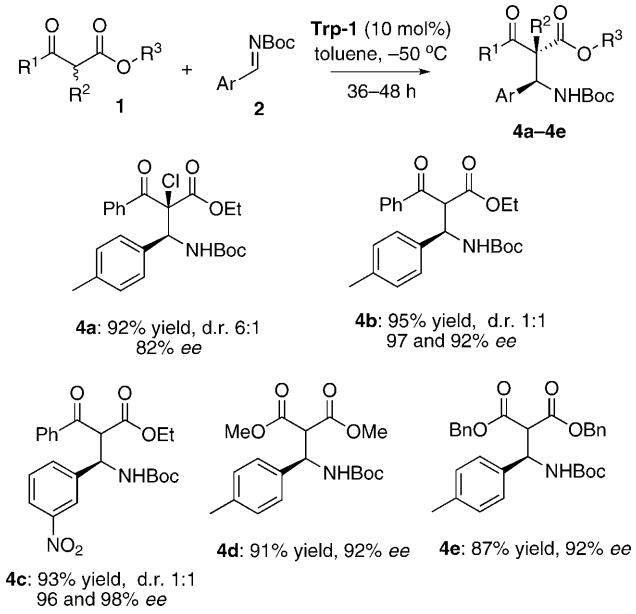
[a] Reactions were performed with the ketoester (0.05 mmol), the imine (0.075 mmol), and **Trp-1** (0.005 mmol) in toluene (1 mL). [b] Yield of the isolated product. [c] The diastereomeric ratio was determined by $^1$H NMR spectroscopic analysis of the crude product. [d] Single *ee* values are for the major diastereomer. The *ee* values were determined by HPLC analysis on a chiral phase. [e] The benzyl ester was employed instead of the ethyl ester. [f] The reaction was carried out at room temperature with 100 mol% of **Trp-1**. [g] The *N*-tosylimine was used.

the best reported for this type of reaction. In their study, high catalyst loading (100 mol%) was required for good enantioselectivity, and the yields were only moderate. By employing the *N*-Boc derivative of an alkyl imine and increasing the catalyst loading of **Trp-1**, we were able to obtain the desired Mannich product in good yield and with high enantioselectivity (Table 2, entry 18). Gratifyingly, when *N*-tosylcyclohexylmethanimine was used, the Mannich reaction proceeded very efficiently in the presence of **Trp-1** (10 mol%) to afford the desired fluorinated Mannich product with 96% *ee* (Table 2, entry 19).

Tryptophan-based **Trp-1** is a versatile catalyst for the Mannich reaction of a variety of 1,3-dicarbonyl substrates. The reactions are not limited to fluorinated substrates; nonfluorinated and chlorinated ketoesters also proved to be suitable substrates. Excellent enantioselectivity was also observed when malonates were used (Scheme 2).

We carried out density functional theory calculations to elucidate the stereochemical outcome of this novel Mannich reaction.[12] Our preliminary efforts were focused on the identification of the structure of the pre-transition-state complex. Complex **IMa** (for the formation of **3a**) was located as the most plausible intermediate. With a C–C bond distance

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 




*Scheme 2.* Mannich reaction of other ketoesters and malonates. Bn = benzyl.

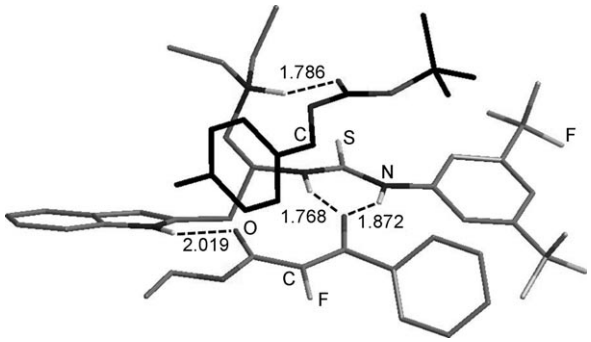
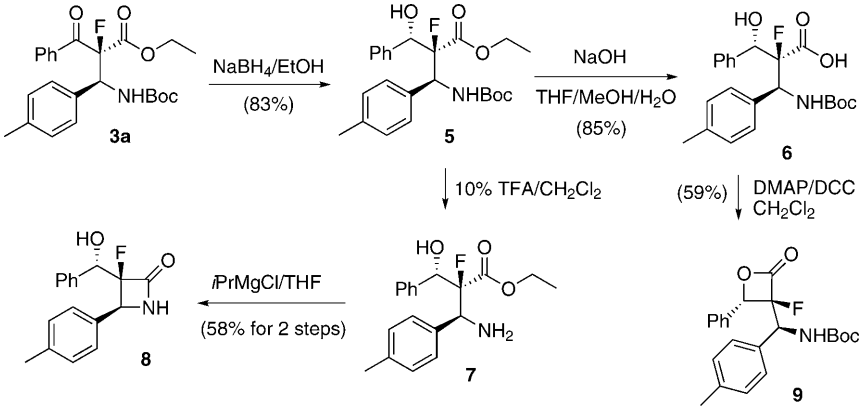



*Figure 1.* Intermediate **IMa** formed from **1a**, **2a**, and **Trp-1**. Hydrogen-bond distances are given in Å (non-hydrogen-bonded hydrogen atoms were omitted for clarity).

of 3.582 Å, it is ready to undergo the bond-forming step (Figure 1). The diethylamino group of **Trp-1** could first deprotonate **1a** to yield an ammonium group. The indole group was found to assist the thiourea moiety in binding the resulting ketoenolate through an additional N–H···O hydrogen-bonding interaction. The ammonium group could later direct and bind the incoming imine to bring it into proximity with the ketoenolate in a locked conformation.

Given the importance of β-amino acids and β-lactams[13] in biological sciences and medicinal chemistry, the synthesis of α-fluorinated analogues of these compounds is of great interest. As an illustration of the synthetic applicability of our methodology, the Mannich product **3a** was converted into α-fluoro-β-amino acid **6**, α-fluoro-β-lactam **8**, and α-fluoro-β-lactone **9** in good yields (Scheme 3). We were also able to obtain the X-ray crystal structure of lactam **8** (Figure 2).[14]

In summary, we have introduced a novel tryptophan-based bifunctional thiourea catalyst that was remarkably effective in promoting the asymmetric Mannich reaction of α-fluoro-β-ketoesters. The resulting compounds with fluorinated quaternary and tertiary stereocenters can be converted readily into α-fluoro-β-amino acids and α-fluoro-β-lactams. Preliminary computational studies suggest that the indole moiety of the catalyst plays a crucial role in substrate binding. We have shown that tertiary amine–thiourea bifunctional catalysts can be derived readily from natural amino acids; this strategy may lead to the discovery of various novel multifunctional organic catalysts. Further investigations into the reaction mechanism, the preparation of diverse bifunctional catalysts based on primary amines, and applications of these catalysts to various organic reactions are currently ongoing in our laboratories.




*Scheme 3.* Preparation of the α-fluorinated β-amino acid **6** and β-lactam **8**. DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid.

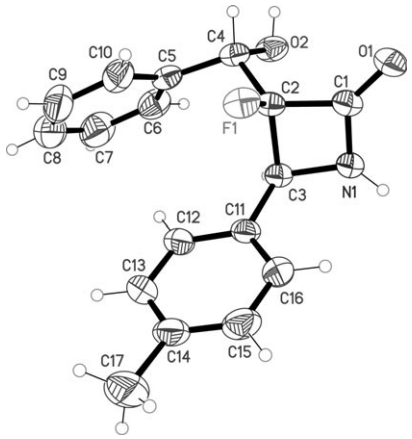



*Figure 2.* ORTEP structure of lactam **8**.


© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Received: July 3, 2009
Published online: September 8, 2009

**Keywords:** asymmetric synthesis · fluorination · Mannich reaction · organocatalysis · quaternary stereocenters

[1] a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) H. Yamamoto, K. Futatsugi, *Angew. Chem.* **2005**, *117*, 1958; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924; c) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; d) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; e) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; f) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516; g) S. J. Connon, *Chem. Commun.* **2008**, 2499.

[2] For reviews on bifunctional catalysts and multiple activation, see: a) H. Steinhagen, G. Helmchen, *Angew. Chem.* **1996**, *108*, 2489; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2339; b) J. D. Wuest, *Acc. Chem. Res.* **1999**, *32*, 81; c) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187; d) J.-A. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566; e) K. Muñiz, *Angew. Chem.* **2005**, *117*, 6780; *Angew. Chem. Int. Ed.* **2005**, *44*, 6622; f) H. Yamamoto, K. Futatsugi, *Angew. Chem.* **2005**, *117*, 1958; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924.

[3] For selected examples, see: a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; b) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170; c) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366; d) J. Wang, H. Li, X. Yu, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4293; e) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, 603; f) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967; g) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367; h) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481.

[4] For reviews on primary amino acids and primary amines in asymmetric catalysis, see: a) L.-W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807; b) L.-W. Xu, Y. Lu, *Org. Biomol. Chem.* **2008**, *6*, 2047; c) F. Peng, Z. Shao, *J. Mol. Catal. A* **2008**, *285*, 1; for relevant studies by our research group, see: d) Z. Jiang, Z. Liang, X. Wu, Y. Lu, *Chem. Commun.* **2006**, 2801; e) X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, *Adv. Synth. Catal.* **2007**, *349*, 812; f) L. Cheng, X. Wu, Y. Lu, *Org. Biomol. Chem.* **2007**, *5*, 1018; g) L. Cheng, X. Han, H. Huang, M. W. Wong, Y. Lu, *Chem. Commun.* **2007**, 4143.

[5] For recent reviews on the synthesis of fluorinated molecules, see: a) K. Mikami, Y. Itoh, M. Yamanaka, *Chem. Rev.* **2004**, *104*, 1; b) V. A. Brunet, D. O'Hagan, *Angew. Chem.* **2008**, *120*, 1198; *Angew. Chem. Int. Ed.* **2008**, *47*, 1179; c) G. K. S. Prakash, P. Beier, *Angew. Chem.* **2006**, *118*, 2228; *Angew. Chem. Int. Ed.* **2006**, *45*, 2172; d) P. M. Pihko, *Angew. Chem.* **2006**, *118*, 558; *Angew. Chem. Int. Ed.* **2006**, *45*, 544; e) M. Oestreich, *Angew. Chem.* **2005**, *117*, 2376; *Angew. Chem. Int. Ed.* **2005**, *44*, 2324; f) H. Ibrahim, A. Togni, *Chem. Commun.* **2004**, 1147; g) R. Smits, C. D. Cadicamo, K. Burger, B. Koksch, *Chem. Soc. Rev.* **2008**, *37*, 1727.

[6] For selected examples, see: a) L. Hintermann, A. Togni, *Angew. Chem.* **2000**, *112*, 4530; *Angew. Chem. Int. Ed.* **2000**, *39*, 4359; b) Y. Hamashima, K. Yagi, H. Takano, L. Tamas, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 14530; c) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc.* **2005**, *127*, 10164; d) H. R. Kim, D. Y. Kim, *Tetrahedron Lett.* **2005**, *46*, 3115; e) J.-A. Ma, D. Cahard, *Tetrahedron: Asymmetry* **2004**, *15*, 1007; f) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem.* **2005**, *117*, 4276; *Angew. Chem. Int. Ed.* **2005**, *44*, 4204; g) D. S. Reddy, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem.* **2008**, *120*, 170; *Angew. Chem. Int. Ed.* **2008**, *47*, 164; h) M. Nakamura, A. Hajra, K. Endo, E. Nakamura, *Angew. Chem.* **2005**, *117*, 7414; *Angew. Chem. Int. Ed.* **2005**, *44*, 7248; i) E. C. Burger, B. R. Barron, J. A. Tunge, *Synlett* **2007**, 2824.

[7] a) D. Y. Kim, E. J. Park, *Org. Lett.* **2002**, *4*, 545; b) S. Brandes, B. Niess, M. Bella, A. Prieto, J. Overgaard, K. A. Jørgensen, *Chem. Eur. J.* **2006**, *12*, 6039; c) T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2008**, *120*, 4225; *Angew. Chem. Int. Ed.* **2008**, *47*, 4157.

[8] a) X. Han, J. Luo, C. Liu, Y. Lu, *Chem. Commun.* **2009**, 2044; b) C. Ding, K. Mauroka, *Synlett* **2009**, 664; c) Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K.-W. Huang, M. W. Wong, C.-H. Tan, *Angew. Chem.* **2009**, *121*, 3681; *Angew. Chem. Int. Ed.* **2009**, *48*, 3627; d) G. K. S. Prakash, F. Wang, T. Stewart, T. Mathew, G. A. Olah, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4090.

[9] a) S. Lou, B. M. Taoka, A. Ting, S. E. Schaus, *J. Am. Chem. Soc.* **2005**, *127*, 11256; b) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048; c) A. L. Tillman, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1191.

[10] Imines other than the *N*-Boc imine were also examined under the same conditions at room temperature: the use of the corresponding *N*-benzylimine led to the formation of only a trace amount of the product, the *N*-*p*-methoxyphenylimine and the *N*-*p*-nitrobenzenesulfonylimine gave the products in less than 20% yield, and the *N*-benzyloxycarbonylimine afforded the Mannich products in quantitative yield with d.r. 4:1 and 75% *ee*.

[11] J. Luo, L.-W. Xu, R. A. S. Hay, Y. Lu, *Org. Lett.* **2009**, *11*, 437.

[12] See the Supporting Information for details.

[13] For the antibacterial activity and synthesis of β-lactams, see: a) J. D. Buynak, *Curr. Med. Chem.* **2004**, *11*, 1951; b) A. Brandi, S. Cicchi, F. C. Cordero, *Chem. Rev.* **2008**, *108*, 3988; c) R. Pal, S. C. Ghosh, K. Chandra, A. Basak, *Synlett* **2007**, 2321.

[14] CCDC 745901 (**8**) contains 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.

 © 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 