Asymmetric Synthesis

DOI: 10.1002/ange.201104216

Enantioselective Michael/Cyclization Reaction Sequence: Scaffold-Inspired Synthesis of Spirooxindoles with Multiple Stereocenters**

*Yiming Cao, Xianxing Jiang, Luping Liu, Fangfang Shen, Futing Zhang, and Rui Wang**

Bioactive chemical compounds produced in nature act as the main source of templates and inspiration for the synthesis of compounds for the purpose of biological phenomena study and drug development.[1] As a consequence of the divergent nature of evolution, the core structural motifs of chemical compounds are limited although a myriad of natural products exist. The divergence of natural products resulting from evolution provides chemists with a prodigious starting point to design and construct collections of bioactive compounds having selected naturally occurring core scaffolds.[2]

The spirooxindole core is a privileged heterocyclic ring system that is featured in a large number of bioactive naturally occuring alkaloids and medicinally relevant compounds (Figure 1).[3] Although the significant bioactivity and preparation methods of such motifs attract the interest of chemists,[4] as reported in some elegant works,[5] the synthetic methodology to enantioselectively construct this rigid spiro-architecture containing a quaternary stereocenter remains limited. The 3,3′-pyrrolidonyl spirooxindole scaffold is an important skeleton in the larger spirooxidole family not only because of the interesting biological activities,[3c] but also because of its versatility as an intermediate in the synthesis of related and more sophisticated spirooxindole structures.[4e,6,8d,e] In addition, the spirolactam motif in such structures has also been found in various drug candidates as well as other natural product families.[7] However, the enantioselective synthesis of this kind of skeleton is rare.[8] Given the demand for new methodology for the construction of the 3,3′-pyrrolidonyl spirooxindole scaffold, we developed a simple and highly efficient synthetic method for the enantioselective construction of densely functionalized 3,3′-pyrrolidonyl spirooxindoles having three contiguous stereogenic centers.

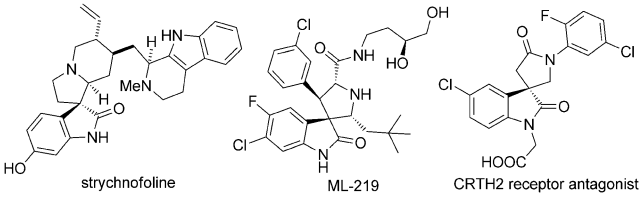
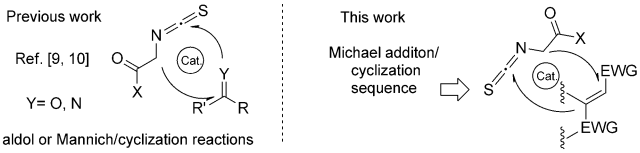


Figure 1. Spirooxindole-containing natural products and synthetic compounds.

Recently, α-isothiocyanato imides and esters emerged as two of the most attractive reactants in asymmetric organometallic or organocatalytic aldol and Mannich reactions (Scheme 1) in the synthesis the masked chiral β-hydroxyl-α-amino and α,β-diamino acid derivatives.[9] Furthermore, our group and the group of Yuan extended the utility of the α-isothiocyanato nucleophiles to the construction of optically active spirooxindoles through an aldol addition.[10] And, very recently, Shibasaki and co-workers demonstrated the utility of this method in the synthesis of nutlin analogues through a Mannich-type reaction.[9i] However, to the best of our knowledge, the Michael addition[11] using such α-isothiocyanato compounds has never been reported despite the attractiveness of the γ-lactam products bearing multiple stereocenters. The reactivity and stereoselectivity of the α-isothiocyanato compounds and electron-deficient olefins is challenging. Herein, we report the first enantioselective Michael addition/cyclization sequence of an α-isothiocyanato imide and methyleneindolinones.



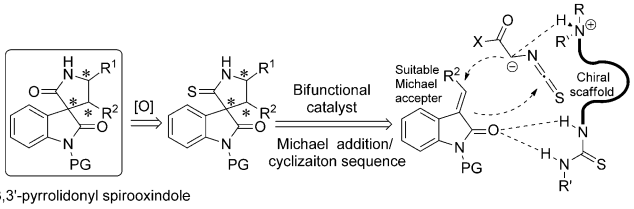
Scheme 1. Previous studies on aldol and Mannich reactions of isothiocyanato compounds and the Michael addition reported herein. EWG = electron-withdrawing group.

We envisioned that methyleneindolinones could serve as the perfect electron-deficient olefin because of its high reactivity as a Michael acceptor,[5a–f] as well as its unique structural characteristics for the construction of 3,3′-pyrrolidonyl spirooxindoles. The Lewis acid activated Michael acceptor would be expected undergo nucleophilic attack by

[*] Dr. Y.-M. Cao,[+] Dr. X.-X. Jiang,[+] L.-P. Liu, F.-F. Shen, F.-T. Zhang, Prof. Dr. R. Wang
Key Laboratory of Preclinical Study for New Drugs of Gansu Province; State Key Laboratory of Applied Organic Chemistry; Institute of Biochemistry and Molecular Biology, Lanzhou University
Lanzhou 730000 (China)
E-mail: wangrui@lzu.edu.cn
Prof. Dr. R. Wang
State Key Laboratory of Chiroscience, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong (China)
E-mail: bcrwang@polyu.edu.hk
[+] These authors contributed equally to this work.

[**] We are grateful for the grants from the National Natural Science Foundation of China (nos. 20932003 and 90813012), the Key National S&T Program "Major New Drug Development" of the Ministry of Science and Technology of China (2009ZX09503-017).
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201104216.

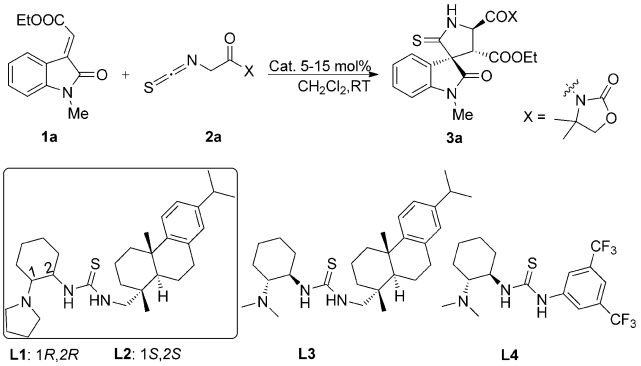
the α-isothiocyanato imide, activated by a Lewis base, with subsequent cyclization to lead to the generation of a 3,3′-thiopyrrolidonyl spirooxindole, which can then be oxidized to the 3,3′-pyrrolidonyl spirooxindole in a single transformation (Scheme 2). On the basis of our recent success in enantioselective organocatalysis using rosin-derived bifunctional thiourea catalysts developed in our group,[12,13] we surmised that this kind of organocatalyst would be suitable for catalyzing the asymmetric Michael/cyclization sequence through double activation.



Scheme 2. Strategy for the construction of the 3,3′-pyrrolidonyl spirooxindole scaffold using a bifunctional chiral catalyst. PG = protecting group.

To begin our initial investigation, several bifunctional thiourea catalysts (15 mol% catalyst) were screened to evaluate their ability to promote the Michael/cyclization reaction sequence of methyleneindolinone (**1a**) with the α-isothiocyanato imide **2a** at room temperature in CH_2Cl_2 (Table 1). Gratifyingly, the rosin-derived tertiary amine thiourea catalyst **L1** gave the desired product with greater than 99% *ee*, 10:1 d.r., and 99% yield (entry 1). The catalyst **L3** afforded **3a** in almost the same excellent enatioselectivity and with a slightly higher d.r. value, but in a relatively low product yield resulted (entry 3). The widely used catalyst **L4**[14] exhibited poor catalytic activity, and furnished the product with relatively low diastereoselectivity despite its excellent enantioselective control (entry 4). Notably, the other enatiomer of the product could also be accessed with the same excellent *ee* and d.r. values, as well as yield when **L2** was used (entry 2). When the catalyst loading was reduced to 10 mol% and 5 mol%, the same excellent results were obtained, but 36 hours were needed for completeion of the reaction when 5 mol% catalyst was used (entries 5 and 6). **L1** at a 10 mol% loading was selected for further studies in terms of efficiency.

Table 1: Studies and optimization of the reaction parameters.[a]

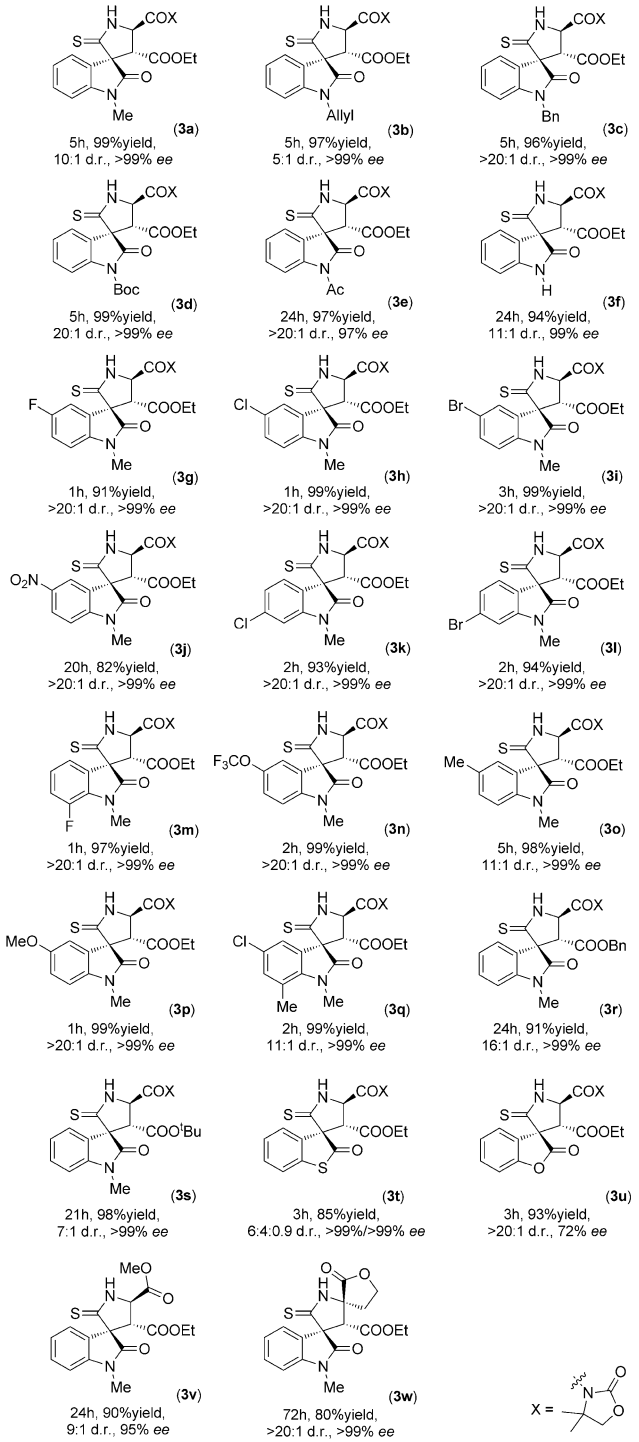


Entry	Cat. (mol%)	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**L1** (15)	3	99	10:1	>99
2	**L2** (15)	3	99	14:1	>−99
3	**L3** (15)	12	81	11:1	95
4	**L4** (15)	>72	80	6:1	95
5	**L1** (10)	5	99	10:1	>99
6	**L1** (5)	36	99	10:1	>99

[a] The reaction was performed at RT on 0.1 mmol scale with **1a** (1.1 equiv), **2a** (1.0 equiv), and catalyst in 1 mL CH_2Cl_2. [b] Yield of isolated product as a mixture of diastereoisomers. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by HPLC analysis on a chiral stationary phase.

With the established optimal reaction conditions, a variety of 3,3′-thiopyrrolidonyl spirooxindole compounds were synthesized and the results are summarized in Scheme 3. Various N-protecting groups of the methyleneindolinone having different electronic and steric parameters were tolerated, and gave the corresponding compounds in excellent yield, good to excellent diastereoselectivity, and excellent enantioselectivity (**3a**–**3f**). Both electron-donating and electron-withdrawing substituents at different positions on the aromatic ring afforded the products in greater than 99% *ee*, excellent d.r. values, and good to excellent yields (**3g**–**3q**). An increase of the steric hindrance introduced by a bulkier ester group did not affect the enantioselectivity, but decreased the d.r. value of the products and the activity of the reactions, as a longer time was needed to complete the reaction (**3r** and **3s**). Notably, when the nitrogen atom of methyleneindolinone was replaced by a sulfur or oxygen atom the reaction proceeded smoothly, thus providing the product **3t** with greater than 99% *ee* and moderate distereoselectivity, and the product **3u** with moderate enantioselectivity and excellent distereoselectivity. In addition to α-isothiocyanato imide, methyl isothiocyanato acetate was also shown to be the suitable substrate in the reaction (**3v**). Furthermore, the spirooxindole **3w** having three contiguous stereocenters, including two spiro-quaternary chiral centers, was constructed using this catalytic system and α-isothiocyanato lactone as the reactant; the product was isolated with excellent stereoseletivity and in good yield. The absolute and relative configurations of the spirooxindoles were unambiguously determined by X-ray crystallography (see the Supporting Information).

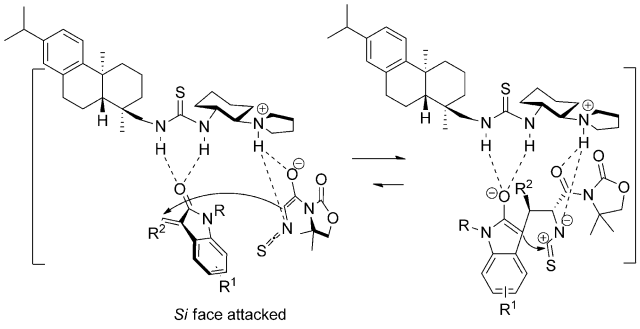
On the basis of our experimental results and recent studies,[15] we have proposed a possible model to explain the stereochemistry of the Michael/cyclization reaction sequence (Scheme 4). The electron-deficient methyleneindolinone is activated by hydrogen bonds involving the carbonyl group in the indolinone and the thiourea hydrogen atoms of the catalyst, and the α-isothiocyanato imide is enolized by deprotonation at its α-carbon atom by the tertiary amine. The *Re* face of the enolate is exposed to the methyleneindolinone and the *Si* face of the Michael acceptor is approached by the incoming nucleophile. Subsequent nucleophilic attack of the stabilized carbon anion onto the electron-defficient carbon atom of the α-isothiocyanato imide leads to the 3*R*, 4′*R*, 5′*R*-configured spirooxindole product, which is in keeping with the experimental results.



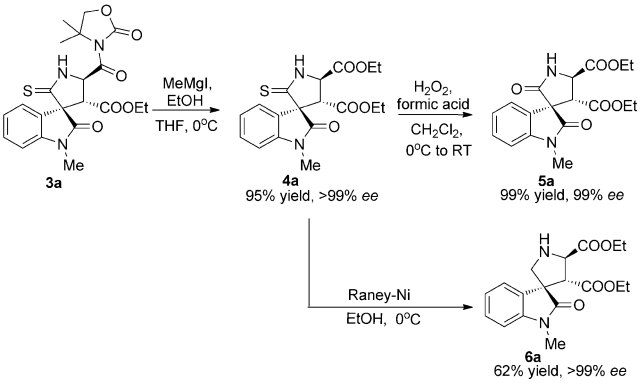
Scheme 3. Synthesized 3,3′-thiopyrrolidonyl spirooxindoles having three adjacent stereocenters by using the the established reaction conditions. The reaction time required for each substrate is given. The reported yields are of the isolated products. The *ee* and d.r. values were determined by HPLC analysis.

With the successful construction of 3,3′-thiopyrrolidonyl spirooxindoles as described above, the transformation of the cycloadduct into 3,3′-pyrrolidonyl spirooxindole was performed (Scheme 5). After the conversion of the imide into the ester using MeMgI and ethanol in THF, the γ-thiolactam moiety was smoothly oxidized to the γ-lactam by simple treatment with 30% aqueous hydrogen peroxide and formic acid in CH_2Cl_2. The 3,3′-pyrrolidonyl spirooxindole was formed in nearly quantitative yield without loss of diastereo- and enantioselectivity. Furthermore, because of the significant bioactivity of the 3,3′-pyrrolidinyl spirooxindoles,[3a,b,4] the transformation into this scaffold was also performed. Treatment of 3,3′-thiopyrrolidonyl spirooxindole with Raney Ni in ethanol gave the desulfurized product in moderate yield without change in d.r. and *ee* values.

In summary, an efficient organocatalyzed asymmetric Michael/cyclization reaction sequence of α-isothiocyanato imides, esters, and lactones with various methyleneindolinones using mild reaction conditions has been developed. This process provides a promising method for the enantioselective construction of densely functionalized 3,3′-pyrrolidonyl spirooxindoles including those having three contiguous stereogenic centers (up to 99% yield, >20:1 d.r., and >99% *ee*). Further studies into expanding the application of this approach to synthesize more promising candidates for drug discovery as well as the biological evaluation of these compounds are in progress.



Scheme 4. Proposed transition states.



Scheme 5. Transformation of the 3,3′-thiopyrrolidonyl spirooxindole into pyrrolidonyl and pyrrolidinyl spirooxindoles.

Received: June 19, 2011
Published online: August 25, 2011

Keywords: asymmetric synthesis · heterocycles · Michael addition · organocatalysis · synthetic methods

[1] a) D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461 – 477; b) J. W. H. Li, J. C. Vederas, *Science* **2009**, *325*, 161 – 165; c) K. Kumar, H. Waldmann, *Angew. Chem.* **2009**, *121*, 3272 – 3290; *Angew. Chem. Int. Ed.* **2009**, *48*, 3224 – 3242.

[2] a) M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 17272 – 17277, and references therein.

[3] a) O. Dideberg, J. Lamotte-Brasseur, L. Dupont, H. Campsteyn, M. Vermeire, L. Angenot, *Acta Crystallogr. Sect. B* **2008**, *105*, 3933 – 3938; b) S. Crosignani et al., *J. Med. Chem.* **2008**, *51*, 2227 – 2243.

[4] For recent reviews, see: a) J. J. Badillo, N. V. Hanhan, A. K. Franz, *Curr. Opin. Drug Discov. Devel.* **2010**, *13*, 758 – 776; b) F. Zhou, Y. L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381 – 1407; c) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902 – 8912; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748 – 8758; d) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003 – 3025; e) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209 – 2219.

[5] For selected recent examples, see: a) B. Tan, N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 4672 – 4675; b) B. Tan, N. R. Candeias, C. F. Barbas III, *Nat. Chem.* **2011**, *3*, 473 – 477; c) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nat. Chem.* **2010**, *2*, 735 – 740; d) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336 – 7339; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200 – 7203; e) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819 – 13825; f) B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, *129*, 12396 – 12397; g) P. R. Sebahar, R. M. Williams, *J. Am. Chem. Soc.* **2000**, *122*, 5666 – 5667.

[6] B. M. Trost, M. K. Brennan, *Org. Lett.* **2006**, *8*, 2027 – 2030.

[7] a) W. M. Kazmierski, E. Furfine, A. Spaltenstein, L. L. Wright, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3431 – 3433; b) B. Nay, N. Riache, L. Evanno, *Nat. Prod. Rep.* **2009**, *26*, 1044 – 1062.

[8] For examples of the synthesis of a chiral version of the 3,3′-pyrrolidonyl spirooxindole, see: a) M. Bella, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 3670 – 3671; b) S. Kobbelgaard, M. Bella, K. A. Jørgensen, *J. Org. Chem.* **2006**, *71*, 4980 – 4987; c) S. Sen, V. R. Potti, R. Surakanti, Y. L. N. Murthy, R. Pallepoguc, *Org. Biomol. Chem.* **2011**, *9*, 358 – 360; For examples of synthesis of achiral version of 3,3′-pyrrolidonyl spirooxindole, see: d) F. Cochard, M. Laronze, É. Prost, J.-M. Nuzillard, F. Augé, C. Petermann, P. Sigaut, J. Sapi, J.-Y. Laronze, *Eur. J. Org. Chem.* **2002**, 3481 – 3490; e) I. Allous, S. Comesse, D. Berkeš, A. Alkyat, A. Daïch, *Tetrahedron Lett.* **2009**, *50*, 4411 – 4415.

[9] For examples of the aldol reaction, see: a) M. C. Willis, G. A. Cutting, V. J.-D. Piccio, M. J. Durbin, M. P. John, *Angew. Chem.* **2005**, *117*, 1567 – 1569; *Angew. Chem. Int. Ed.* **2005**, *44*, 1543 – 1545; b) L. Li, E. G. Klauber, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 12248 – 12249; c) T. Yoshino, H. Morimoto, G. Lu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 17082 – 17083; d) M. K. Vecchione, L. Li, D. Seidel, *Chem. Commun.* **2010**, *46*, 4604 – 4606; e) X.-X. Jiang, G. Zhang, D. Fu, Y.-M. Cao, F.-F. Shen, R. Wang, *Org. Lett.* **2010**, *12*, 1544 – 1547; f) X.-H. Chen, Y. Zhu, Z. Qiao, M.-S. Xie, L.-L. Lin, X.-H. Liu, X.-M. Feng, *Chem. Eur. J.* **2010**, *16*, 10124 – 10129; For examples of Mannich-type reaction, see: g) G. A. Cutting, N. E. Stainforth, M. P. John, G. Kociok-Köhn, M. C. Willis, *J. Am. Chem. Soc.* **2007**, *129*, 10632 – 10633; h) L. Li, M. Ganesh, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 11648 – 11649; i) G. Lu, T. Yoshino, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2011**, *123*, 4473 – 4477; *Angew. Chem. Int. Ed.* **2011**, *50*, 4382 – 4385; j) Z.-G. Shi, P.-Y. Yu, P. J. Chua, G. F. Zhong, *Adv. Synth. Catal.* **2009**, *351*, 2797 – 2800; k) X.-H. Chen, S.-X. Dong, Z. Qiao, Y. Zhu, M.-S. Xie, L.-L. Lin, X.-H. Liu, X.-M. Feng, *Chem. Eur. J.* **2011**, *17*, 2583 – 2586.

[10] a) X.-X. Jiang, Y.-M. Cao, Y.-Q. Wang, L.-P. Liu, F.-F. Shen, R. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 15328 – 15333; b) W.-B. Chen, Z.-J. Wu, J. Hu, L.-F. Cun, X.-M. Zhang, W.-C. Yuan, *Org. Lett.* **2011**, *13*, 2472 – 2475.

[11] For a recent review on the Michael addition, see: J. L. Vicario, D. Badía, L. Carrillo, E. Reyes in *Organocatalytic Enantioselective Conjugate Addition Reactions* (Ed.: J. J. Spivey), The Royal Society of Chemistry, Cambridge, **2010**.

[12] For reviews on bifunctional thiourea catalysis, see: a) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713 – 5743; b) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418 – 5427; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550 – 1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520 – 1543; d) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299 – 4306.

[13] For examples of rosin-derived thiourea catalysis, see: a) X.-X. Jiang, D. Fu, G. Zhang, Y.-M. Cao, L.-P. Liu, R. Wang, *Chem. Commun.* **2010**, *46*, 4294 – 4296; b) X.-X. Jiang, Y.-F. Zhang, A. S.-C. Chan, R. Wang, *Org. Lett.* **2009**, *11*, 153 – 156; c) X.-X. Jiang, Y.-F. Zhang, X. Liu, G. Zhang, L.-H. Lai, L.-P. Wu, J.-N. Zhang, R. Wang, *J. Org. Chem.* **2009**, *74*, 5562 – 5567.

[14] T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672 – 12673.

[15] a) R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678 – 20685; b) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358 – 15374; c) S. J. Zuend, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 15872 – 15883.

