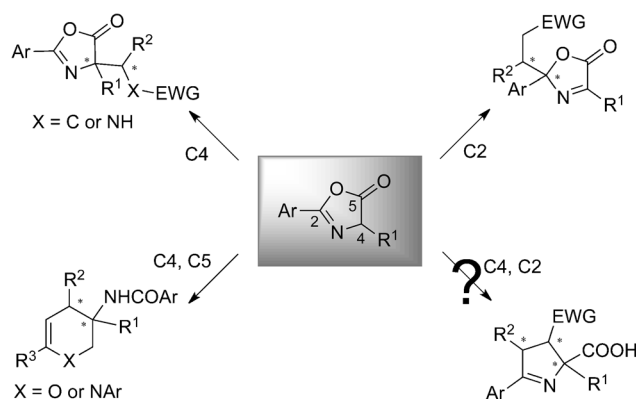


1,3-Dipolar Cycloaddition

Organocatalytic Diastereo- and Enantioselective 1,3-Dipolar Cycloaddition of Azlactones and Methyleneindolinones**

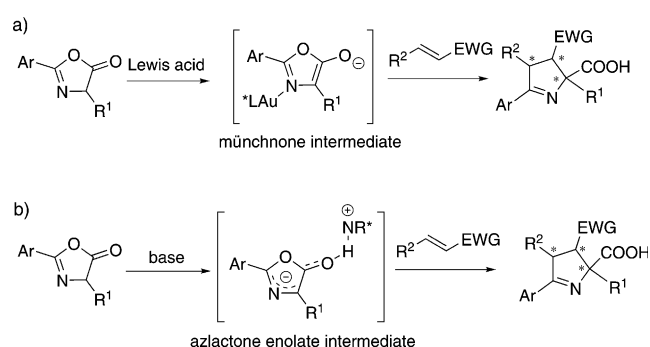
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Azlactones (oxazol-5(4*H*)-ones) possess three reactive sites at the C2, C4, and C5 atoms: both C2 and C5 are electrophilic, whereas C4 is nucleophilic. The rich reactivity of azlactones enables a wide variety of transformations, which make them extremely versatile precursors of amino acids and heterocycles.^[1–8] Recently, with the explosive development of organocatalysis, azlactones have been applied once again as substrates in many enantioselective reactions.^[1d,3–5] Typically, they have been used in organocatalytic 1,2 or 1,4-addition reactions at the C4 or C2 atom^[3,4] and [4+2] cycloaddition reactions involving the nucleophilic C4 and electrophilic C5 atoms (Scheme 1).^[5] In contrast, cycloaddition reactions,



Scheme 1. Organocatalytic addition reactions between azlactones and alkenes or imines. EWG = electron-withdrawing group.

especially asymmetric reactions, that take advantage of the nucleophilic C4 and electrophilic C2 atoms have rarely been exploited.^[6] A gold(I)-catalyzed asymmetric 1,3-dipolar cycloaddition^[7] of azlactones and electron-deficient alkenes was reported by Toste and co-workers; the stereochemical outcome of this transformation is controlled by a chiral gold-



Scheme 2. Two activation modes of azlactones as 1,3-dipoles. a) Stereochemical control by dipole formation through bonding with a chiral metal complex. b) Stereochemical control by dipole formation through interaction with a chiral base.

bonded münchnone intermediate (Scheme 2a).^[8] However, no organocatalytic asymmetric 1,3-dipolar cycloaddition of azlactones has been described previously.

We envisioned that a bifunctional thiourea/urea catalyst with a basic site might deprotonate the azlactone to reveal an enolate species in which both the C2 and C4 positions are activated (Scheme 2b). In this case, the azlactone could theoretically form a chiral dipole intermediate that would undergo an enantioselective 1,3-dipolar cycloaddition with dipolarophiles.

The 3,3'-pyrrolidonyl spirooxindole scaffold is a privileged heterocyclic motif in the large spirooxindole family not only because of its interesting biological activity, but also because of its versatility as an intermediate in the synthesis of the sophisticated spirooxindole-related natural and man-made compounds (Scheme 3).^[9] The significance of this heterocyclic motif has led to great efforts towards its synthesis.^[10] Among the established strategies, the catalytic direct enantioselective synthesis of 3,3'-pyrrolidonyl spirooxindoles by means of 1,3-dipolar cycloaddition reactions of azomethine ylides (Scheme 4) with methyleneindolinones is the most attractive.^[11,12b] However, an alternative strategy for the stereoselective construction of structurally diverse 3,3'-pyrrolidonyl spirooxindoles is still desirable.

On the basis of these previous achievements and our continuing research interest in the asymmetric construction of spirocyclic oxindoles^[12] and azlactones,^[3c,d,5f] we wondered whether azlactones could serve as mesoionic azomethine ylides (Scheme 4) in 1,3-dipolar cycloaddition reactions with methyleneindolinones.

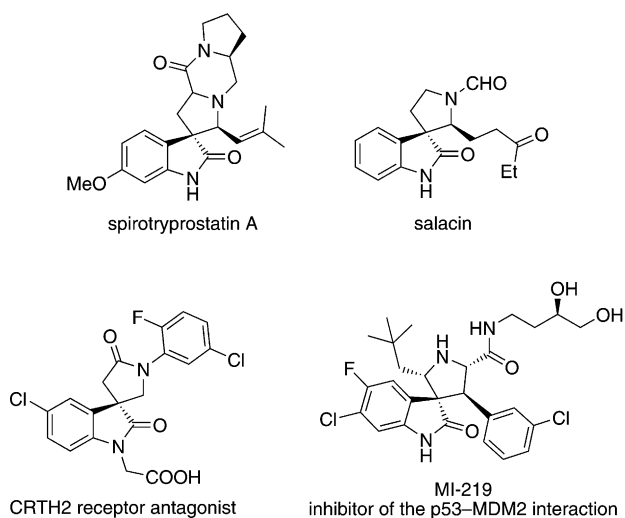
To validate our hypothesis, we began our investigation with the typical Takemoto catalyst **3a**, a chiral thiourea, for the 1,3-dipolar cycloaddition of azlactone **1a** and methylene-

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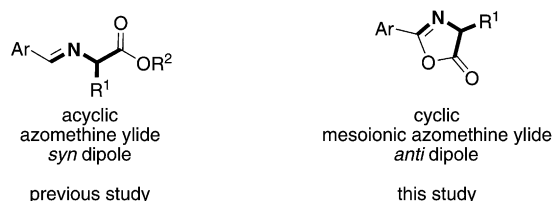
[‡] These authors contributed equally.

[**] We gratefully acknowledge financial support from the NSFC (20932003, 91213302, 21272102, 21202071) and the National S&T Major Project of China (2012ZX09504001-003). W.S. is grateful for a Scholarship Award for Distinguished Doctoral Candidates granted by the Ministry of Education, China.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201302831>.



Scheme 3. Representative naturally occurring and synthetic 3,3'-pyrroli-donyl spirooxindoles.



Scheme 4. Comparison of two types of 1,3-dipole.

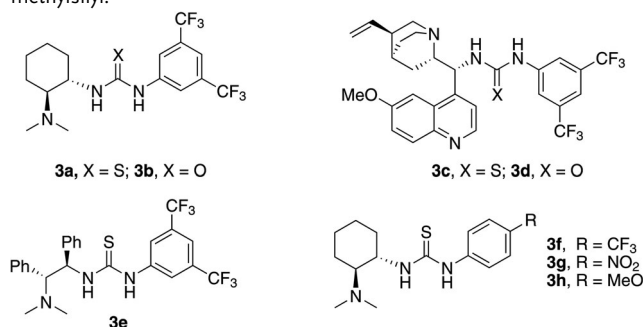
indolinone **2a** in CH_2Cl_2 at room temperature. To our delight, the reaction proceeded smoothly with almost complete conversion within 10 h. To simplify the purification of the product, the resulting mixture was then treated with methanol and TMSCHN_2 and stirred for 15 min. In this way, the esterification product **4aa** was obtained with moderate diastereoselectivity and enantioselectivity (Table 1, entry 1). Encouraged by this promising result, we then screened a representative range of bifunctional thiourea/urea catalysts derived from different privileged chiral architectures (Table 1, entries 1–8). We found that the chiral thiourea **3f** was the most effective catalyst in terms of both the diastereoselectivity and enantioselectivity of the reaction (Table 1, entry 6). Subsequent screening of solvents showed that the reaction medium had a significant effect on the reaction (Table 1, entries 6 and 9–14), and that MTBE gave the best result (Table 1, entry 14). Furthermore, lowering of the reaction temperature to 0°C had a very negative effect on both yield and selectivity (Table 1, entry 15). Thus, we chose **3f** as the catalyst and MTBE as the reaction medium and carried out all subsequent reactions at room temperature.

Having established the optimal reaction conditions, we then examined the scope of this asymmetric organocatalytic 1,3-dipolar cycloaddition. In general, the reaction proceeded with good to excellent diastereoselectivity and excellent enantioselectivity to afford the desired products in high yields (Scheme 5). We first investigated the generality of the 1,3-dipolar cycloaddition by varying the methyleneindolinone

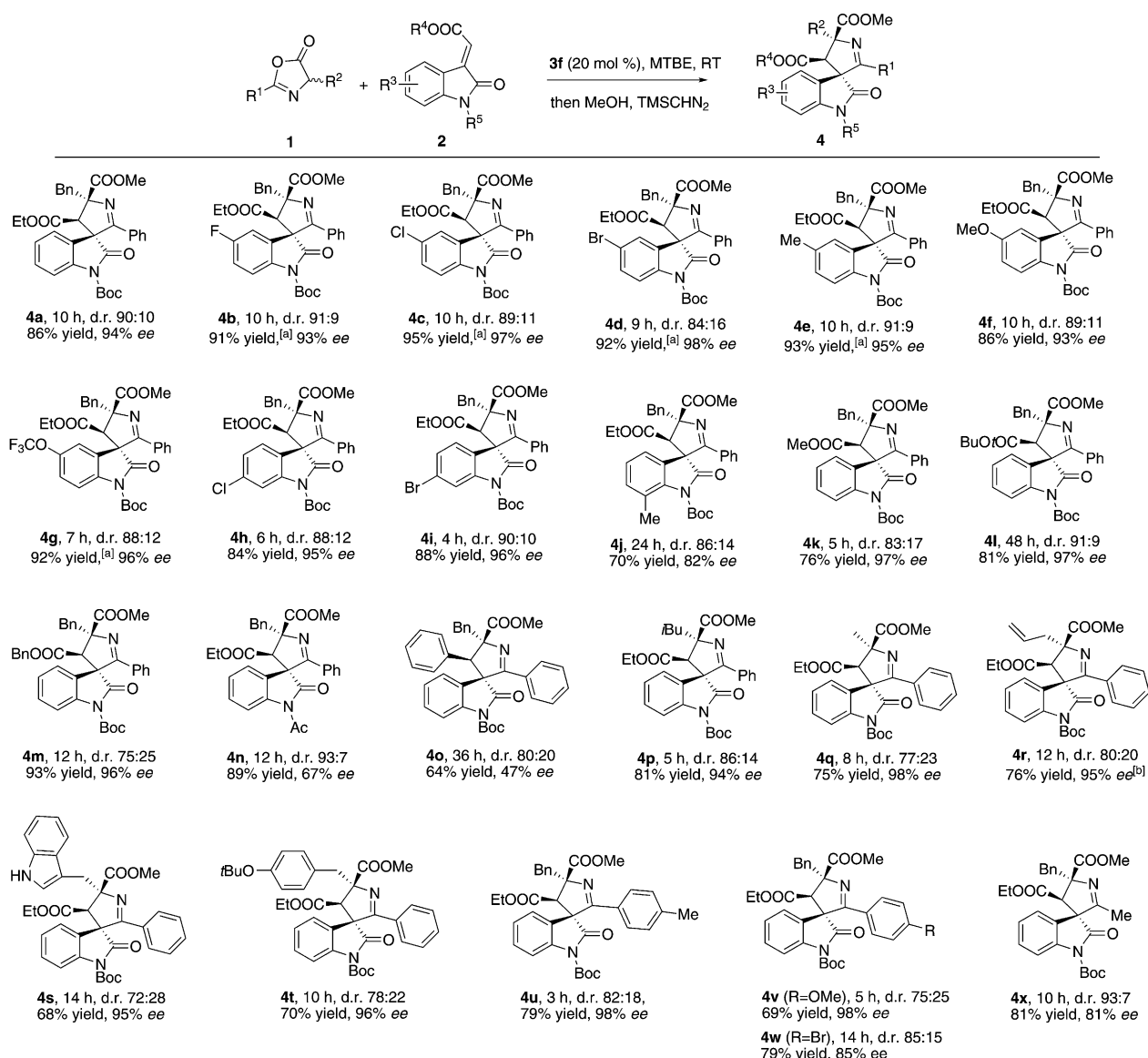
Table 1: Optimization of the 1,3-dipolar cycloaddition of azlactone **1a** and methyleneindolinone **2a**.^[a]

Entry	Cat. 3	Solvent	Conversion [%] ^[b]	d.r. ^[b]	ee [%] ^[c]
1	3a	CH_2Cl_2	99	4:1	70
2	3b	CH_2Cl_2	85	3:1	45
3	3c	CH_2Cl_2	— ^[d]	n.d.	n.d.
4	3d	CH_2Cl_2	— ^[d]	n.d.	n.d.
5	3e	CH_2Cl_2	— ^[d]	n.d.	n.d.
6	3f	CH_2Cl_2	99	12:1	85
7	3g	CH_2Cl_2	90	2:1	80
8	3h	CH_2Cl_2	96	4:1	82
9	3f	CHCl_3	98	4:1	90
10	3f	THF	89	4:1	90
11	3f	toluene	98	7.5:1	95
12	3f	ether	94	7:1	95
13	3f	CPME	96	5.5:1	96
14	3f	MTBE	99(86) ^[e]	9:1	94
15 ^[f]	3f	MTBE	70	4:1	n.d.

[a] Unless otherwise specified, the reaction was carried out on a 0.1 mmol scale in 1 mL of the solvent at room temperature with a **1a**/**2a**/**3** molar ratio of 1:1.2:0.2. [b] The diastereomeric ratio was determined by ^1H NMR spectroscopy of the crude mixture. [c] The ee value was determined by HPLC on a chiral phase (Chiralcel IA column). [d] A complex mixture was formed. [e] The yield of the isolated product is given in parenthesis. [f] The reaction was performed at 0°C . Bn = benzyl, Boc = *tert*-butoxycarbonyl, CPME = cyclopentyl methyl ether, MTBE = methyl *tert*-butyl ether, n.d. = not determined, TMS = trimethylsilyl.



substrate. Most of the reactions evaluated provided the desired product in good yield (70–95%) with good diastereoselectivity (d.r. 75:25–93:7) and moderate to excellent enantioselectivity (47–98% ee; Scheme 5, **4a–o**). Notably, the presence of an ester substituent at the alkylidene terminus of the methyleneindolinone had a minor impact on the efficiency, enantioselectivity, and diastereoselectivity of the reaction, regardless of the electronic nature, bulkiness, or position of substituents on the methyleneindolinone **2** (products **4a–m**). Unfortunately, only moderate enantioselectivity was observed and a longer reaction time was necessary when a phenyl group was incorporated at the alkylidene terminus of the methyleneindolinone (product **4o**). We then examined the scope of the reaction with respect to the azlactone substrate **1**. Azlactones derived from other amino acids were



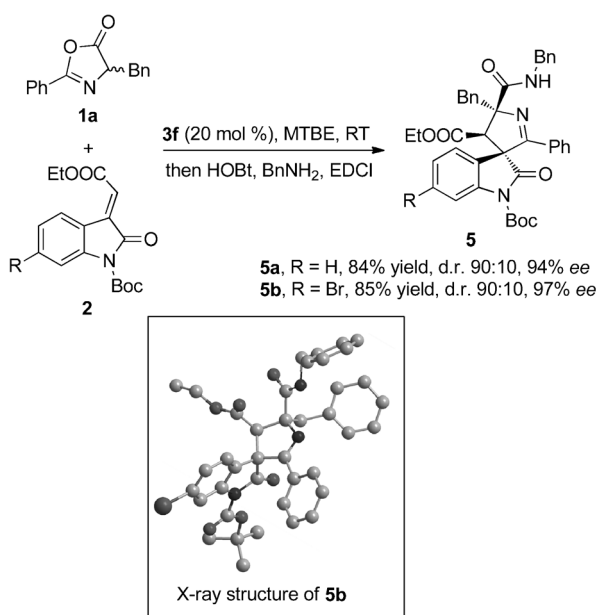
Scheme 5. Scope of the organocatalytic 1,3-dipolar cycloaddition between azlactones and methyleneindolinones. Unless otherwise specified, the reaction was carried out on a 0.1 mmol scale in MTBE (1 mL) at room temperature with a **1a/2a/3f** molar ratio of 1:1.2:0.2. The yield of the isolated major diastereoisomer is given in each case. The d.r. values were determined by ¹H NMR spectroscopy of the crude mixture. The *ee* values were determined by HPLC on a chiral phase (Chiralcel column); in each case, only the *ee* value of the major stereoisomer is reported. [a] The combined yield of both diastereoisomers is given, as the diastereoisomers were difficult to separate. [b] The *ee* value was determined after removal of the Boc protecting group.

also well tolerated (Scheme 5, **4a** and **4p–t**). Furthermore, substrates with both alkyl and aryl substituents at the C2 position can participate in the reaction, although decreased enantioselectivity was observed when azlactones with alkyl or electron-withdrawing aryl substituents were used (Scheme 5, **4u–x**). The straightforward separation of the product diastereomers by column chromatography in most cases renders this catalytic system a useful synthetic route to valuable chiral spirooxindoles.

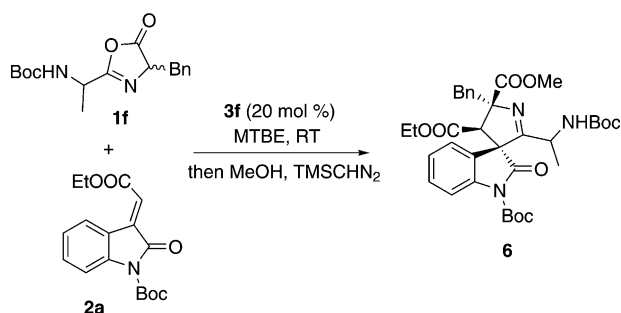
We next demonstrated this 1,3-dipolar cycloaddition as a tool for *in situ* amide formation. We chose benzylamine for the amide formation in the model reaction. Gratifyingly, when the reaction mixture was treated after completion of the

cycloaddition with HOBt, BnHN₂, and EDCI in CH₂Cl₂ at 0°C, the desired amidation product was obtained in excellent yield with excellent diastereoselectivity and enantioselectivity (Scheme 6). We also prepared an azlactone derived from a dipeptide and used it in the 1,3-dipolar cycloaddition. In this way, our methodology can be used for peptide modification (Scheme 7). The absolute configuration of the products was determined by X-ray crystallographic analysis of compound **5b**.^[13]

In summary, we have developed an unprecedented organocatalytic enantioselective 1,3-dipolar cycloaddition reaction between azlactones and methyleneindolinones that proceeds in high yield with good diastereoselectivity and good



Scheme 6. In situ amidation of the product of 1,3-dipolar cycloaddition. EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = 1-hydroxy-1H-benzotriazole.



Scheme 7. Application of the 1,3-dipolar cycloaddition to peptide modification.

to excellent enantioselectivity. To the best of our knowledge, no organocatalytic enantioselective 1,3-dipolar cycloaddition reaction of azlactones that takes advantage of the nucleophilic C4 and electrophilic C2 atoms has been reported previously. Further biological evaluation of the synthesized spirocyclic oxindole compounds is under way in our laboratory.

Experimental Section

In an ordinary vial, a methyleneindolinone **2** (0.12 mmol) was added to a stirred mixture of an azlactone **1** (0.10 mmol) and catalyst **3f** (0.01 mmol) in MTBE (1.0 mL) at room temperature. The mixture was stirred at this temperature until the reaction was complete, as monitored by TLC. Excess methanol and then TMSCHN₂ (3 equiv, 2.0 M in hexanes) were added to the reaction mixture, which was then stirred for 15 min at ambient temperature. The solvent was removed under vacuum, and the residue was purified by chromatography on silica gel (petroleum ether/AcOEt 10:1–4:1) to provide the pure desired product **4**.

Received: April 5, 2013
 Revised: May 20, 2013
 Published online: July 1, 2013

Keywords: asymmetric synthesis · azlactones · 1,3-dipolar cycloaddition · methyleneindolinones · organocatalysis

- [1] For seminal studies, see: a) J. Plöchl, *Ber. Dtsch. Chem. Ges.* **1883**, 16, 2815; b) E. Erlenmeyer, *Ber. Dtsch. Chem. Ges.* **1900**, 33, 2036; for reviews, see: c) J. S. Fisk, R. A. Mosey, J. J. Tepe, *Chem. Soc. Rev.* **2007**, 36, 1432; d) N. M. Hewlett, C. D. Hupp, J. J. Tepe, *Synthesis* **2009**, 2825; e) R. A. Mosey, J. S. Fisk, J. J. Tepe, *Tetrahedron: Asymmetry* **2008**, 19, 2755; f) A.-N. R. Alba, R. Rios, *Chem. Asian J.* **2011**, 6, 720.
- [2] For selected representative examples, see: a) J. C. Ruble, G. C. Fu, *J. Am. Chem. Soc.* **1998**, 120, 11532; b) S. A. Shaw, P. Aleman, E. Vedejs, *J. Am. Chem. Soc.* **2003**, 125, 13368; c) S. A. Shaw, P. Aleman, J. Christy, J. W. Kampf, P. Va, E. Vedejs, *J. Am. Chem. Soc.* **2006**, 128, 925; d) C. Joannes, C. P. Johnston, C. Concellón, C. Simal, D. Philp, A. D. Smith, *Angew. Chem.* **2009**, 121, 9076; *Angew. Chem. Int. Ed.* **2009**, 48, 8914; e) C. Kanta De, N. Mittal, D. Seidel, *J. Am. Chem. Soc.* **2011**, 133, 16802; f) B. M. Trost, C. Jäkel, B. Plietker, *J. Am. Chem. Soc.* **2003**, 125, 4438; g) B. M. Trost, X. Ariza, *J. Am. Chem. Soc.* **1999**, 121, 10727; h) B. M. Trost, C. B. Lee, *J. Am. Chem. Soc.* **1998**, 120, 6818; i) B. M. Trost, K. Dogra, *J. Am. Chem. Soc.* **2002**, 124, 7256; j) D. Uraguchi, Y. Asai, T. Ooi, *Angew. Chem.* **2009**, 121, 747; *Angew. Chem. Int. Ed.* **2009**, 48, 733; k) M. Weber, S. Jautze, W. Frey, R. Peters, *Chem. Eur. J.* **2012**, 18, 14792.
- [3] For selected examples of Mannich-type reactions, see: a) D. Uraguchi, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2008**, 130, 14088; b) D. Uraguchi, K. Koshimoto, T. Ooi, *Chem. Commun.* **2010**, 46, 300; c) X. Liu, L. Deng, X. Jiang, W. Yan, C. Liu, R. Wang, *Org. Lett.* **2010**, 12, 876; d) X. Liu, L. Deng, H. Song, H. Jia, R. Wang, *Org. Lett.* **2011**, 13, 1494; e) S.-H. Shi, F.-P. Huang, P. Zhu, Z.-W. Dong, X.-P. Hui, *Org. Lett.* **2012**, 14, 2010; f) W.-Q. Zhang, L.-F. Cheng, J. Yu, L.-Z. Gong, *Angew. Chem.* **2012**, 124, 4161; *Angew. Chem. Int. Ed.* **2012**, 51, 4085; for aldol-type reactions, see: g) M. Terada, H. Tanaka, K. Sorimachi, *J. Am. Chem. Soc.* **2009**, 131, 3430; h) T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, 132, 6286.
- [4] a) S. Cabrera, E. Reyes, J. Alemán, A. Milelli, S. Kobbelaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2008**, 130, 12031; b) J. Alemán, A. Milelli, S. Cabrera, E. Reyes, K. A. Jørgensen, *Chem. Eur. J.* **2008**, 14, 10958; c) H. Jiang, M. W. Paixão, D. Monge, K. A. Jørgensen, *J. Am. Chem. Soc.* **2010**, 132, 2775; d) D. Uraguchi, Y. Ueki, T. Ooi, *Science* **2009**, 326, 120; e) A.-N. R. Alba, G. Valero, T. Calbet, M. Font-Bardía, A. Moyano, R. Rios, *Chem. Eur. J.* **2010**, 16, 9884; f) A.-N. R. Alba, X. Companyó, G. Valero, A. Moyano, R. Rios, *Chem. Eur. J.* **2010**, 16, 5354; g) D. Uraguchi, Y. Ueki, A. Sugiyama, T. Ooi, *Chem. Sci.* **2013**, 4, 1308.
- [5] a) S. Dong, X. Liu, X. Chen, F. Mei, Y. Zhang, B. Gao, L. Lin, X. Feng, *J. Am. Chem. Soc.* **2010**, 132, 10650; b) S. Dong, X. Liu, Y. Zhang, L. Lin, X. Feng, *Org. Lett.* **2011**, 13, 5060; c) J. Jiang, J. Qing, L.-Z. Gong, *Chem. Eur. J.* **2009**, 15, 7031; d) M. Terada, H. Nii, *Chem. Eur. J.* **2011**, 17, 1760; e) Y. Ying, Z. Chai, H.-F. Wang, P. Li, C.-W. Zheng, G. Zhao, Y.-P. Cai, *Tetrahedron* **2011**, 67, 3337; f) X. Jiang, H. Zhu, X. Shi, Y. Zhong, Y. Li, R. Wang, *Adv. Synth. Catal.* **2013**, 355, 308.
- [6] For racemic transformations, see: a) V. Sharma, J. J. Tepe, *Org. Lett.* **2005**, 7, 5091; b) R. S. Z. Saleem, J. J. Tepe, *J. Org. Chem.* **2010**, 75, 4330; c) S. Peddibhotla, J. J. Tepe, *Synthesis* **2003**, 1433; d) S. Peddibhotla, J. J. Tepe, *J. Am. Chem. Soc.* **2004**, 126, 12776.

- [7] For reviews of 1,3-dipolar cycloaddition, see: a) *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley, New York, **1984**; b) A. Padwa, W. Pearson, *Synthetic Applications of Dipolar Cycloaddition Chemistry towards Heterocyclic and Natural Products*, Wiley-VCH, Weinheim, **2002**; c) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887; d) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863; e) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484.
- [8] a) A. D. Melhado, M. Luparia, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 12638; b) A. D. Melhado, G. W. Amarante, Z. J. Wang, M. Luparia, F. D. Toste, *J. Am. Chem. Soc.* **2011**, *133*, 3517; c) M. Martín-Rodríguez, C. Nájera, J. M. Sansano, *Synlett* **2012**, 62.
- [9] a) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; b) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209; c) H. Lin, S. J. Danishefsky, *Angew. Chem.* **2003**, *115*, 38; *Angew. Chem. Int. Ed.* **2003**, *42*, 36; d) K. Ding, Y. Lu, Z. Nikolovska-Coleska, S. Qiu, Y. Ding, W. Gao, J. Stuckey, K. Krajewski, P. P. Roller, Y. Tomita, D. A. Parrish, J. R. Deschamps, S. Wang, *J. Am. Chem. Soc.* **2005**, *127*, 10130; e) S. Shangary, D. Qin, D. McEachern, M. Liu, R. S. Miller, S. Qiu, Z. Nikolovska-Coleska, K. Ding, G. Wang, J. Chen, D. Bernard, J. Zhang, Y. Lu, Q. Gu, R. B. Shah, K. J. Pienta, X. Ling, S. Kang, M. Guo, Y. Sun, D. Yang, S. Wang, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 3933.
- [10] For reviews, see: a) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003; b) G. S. Singh, Z. Y. Desta, *Chem. Rev.* **2012**, *112*, 6104; c) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* **2012**, *41*, 7247; d) N. R. Ball-Jones, J. J. Badillo, A. K. Franz, *Org. Biomol. Chem.* **2012**, *10*, 5165; e) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381; f) L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, 355, 1023.
- [11] a) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schürmann, H. Preut, S. Ziegler, D. Rauh, H. Waldmann, *Nat. Chem.* **2010**, *2*, 735; b) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819; c) F. Shi, Z.-L. Tao, S.-W. Luo, S.-J. Tu, L.-Z. Gong, *Chem. Eur. J.* **2012**, *18*, 6885; d) L.-L. Wang, J.-F. Bai, L. Peng, L.-W. Qi, L.-N. Jia, Y.-L. Guo, X.-Y. Luo, X.-Y. Xu, L.-X. Wang, *Chem. Commun.* **2012**, 48, 5175; e) B. Tan, X. Zeng, W. W. Y. Leong, Z. Shi, C. F. Barbas III, G. Zhong, *Chem. Eur. J.* **2012**, *18*, 63.
- [12] a) X. Jiang, Y. Cao, Y. Wang, L. Liu, F. Shen, R. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 15328; b) Y. Cao, X. Jiang, L. Liu, F. Shen, F. Zhang, R. Wang, *Angew. Chem.* **2011**, *123*, 9290; *Angew. Chem. Int. Ed.* **2011**, *50*, 9124; c) W. Sun, G. Zhu, C. Wu, L. Hong, R. Wang, *Chem. Eur. J.* **2012**, *18*, 6737; d) X. Jiang, Y. Sun, J. Yao, Y. Cao, M. Kai, N. He, X. Zhang, Y. Wang, R. Wang, *Adv. Synth. Catal.* **2012**, *354*, 917; e) W. Sun, G. Zhu, C. Wu, L. Hong, R. Wang, *Chem. Eur. J.* **2012**, *18*, 13959; f) Y.-M. Cao, F.-F. Shen, F.-T. Zhang, R. Wang, *Chem. Eur. J.* **2013**, *19*, 1184; g) Q. Chen, J. Liang, S. Wang, D. Wang, R. Wang, *Chem. Commun.* **2013**, 49, 1657; h) L. Hong, M. Kai, C. Wu, W. Sun, G. Zhu, G. Li, X. Yao, R. Wang, *Chem. Commun.* **2013**, DOI: 10.1039/C3CC41507D.
- [13] CCDC 932360 (**5b**) 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.