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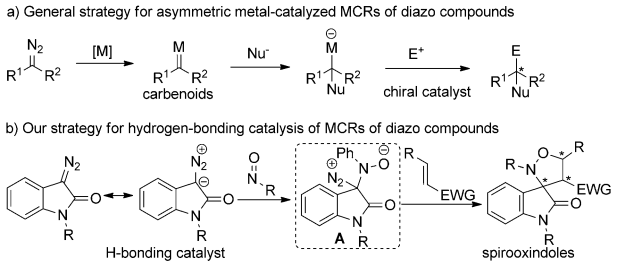
Asymmetric Construction of Spirooxindoles by Organocatalytic Multicomponent Reactions Using Diazooxindoles**

Ming-Yue Wu, Wei-Wei He, Xin-Yuan Liu, and Bin Tan**

In memory of Carlos F. Barbas III

Abstract: *The first highly diastereo- and enantioselective multicomponent reaction of diazooxindoles, nitrosoarenes, and nitroalkenes using a newly developed hydrogen-bond catalyst has been successfully developed for the efficient construction of a series of spirooxindole derivatives with excellent functional-group tolerance. Spirooxindoles are formed in excellent yields and stereoselectivities, and the method represents an unprecedented approach for trapping the active intermediate with a nitroalkene to form biologically important compounds having three contiguous stereogenic centers with excellent asymmetric induction.*

The rapid assembly of complex molecules from simple materials is a great challenge in modern organic chemistry and drug discovery.[1] For the preparation of complex molecules, multicomponent reactions (MCRs) represent a powerful chemical tool because of the atom and step economy, as well as high efficiency in generating complexity through structural modulations of each component.[2] As one of the most significant active components, diazo compounds have long been utilized for the formation of multiple carbon–carbon bonds in modern synthetic organic chemistry.[3] In particular, metal carbene species[4] generated in situ from transition metals and diazo compounds can undergo diverse reactions. Although significant progress has been made in the application of MCRs involving diazo compounds in recent years, stereoselective catalytic MCRs are still underdeveloped.[5] In 2008, Hu, Gong, and co-workers pioneered a cooperative catalytic strategy wherein the metal-associated zwitterionic intermediate generated from a diazo compound and metal undergoes an electrophilic trapping reaction with imines under the control of chiral phosphoric acids to realize high enantioselectivity.[6a] Subsequently, Hu and co-workers successfully developed a series of enantioselective MCRs by applying a similar strategy with either amines, aryl, or heteroaryl compounds as nucleophiles.[6b–d] More recently, Gong and co-workers extended this strategy to the Michael reaction of nitroalkenes with a chiral squaramide catalyst for stereocontrol.[6f] However, these reactions have encountered two major limitations (Scheme 1 a): 1) A noble metal is essential for the formation of active zwitterionic intermediates generated in situ from a diazo compound and metal; 2) Only acyclic products were formed for all of the reported MCR transformations. Thus, the development of highly enantioselective organocatalytic MCRs involving diazo compounds for the formation of complex polycyclic compounds, bearing multiple chiral centers, represents an unmet challenge and is in great demand.



Scheme 1. Asymmetric multicomponent reactions (MCRs) involving diazo compounds. EWG = electron-withdrawing group.

Spirooxindole scaffolds are the structural motifs frequently found in a large number of natural products and synthetic bioactive compounds.[7] In recent years, considerable effort[8] has been made to develop elegant methods, based on asymmetric organocatalysis, to access the structurally diverse family of chiral spirooxindoles.[9] Despite these achievements, stereoselective multicomponent synthetic methods to access polyfunctionalized spirooxindole derivatives are still highly desirable. A recent report from Zhou and co-workers demonstrated a transition-metal-catalyzed asymmetric synthesis of spirocyclopropyloxindoles from diazooxindoles and alkenes, thus opening a new avenue for the construction of spirooxindoles.[10] Inspired by these reports with diazooxindoles[11] as the substrates, and based on the reactivity of diazo compounds with organocatalysts,[12] we envisioned a novel asymmetric three-component cycloaddition reaction. As shown in Scheme 1 b, we postulated that an active intermediate (**A**) could be generated from diazooxindoles and nitroso compounds, and subsequently trapped by active alkenes. The control of the stereochemistry would be

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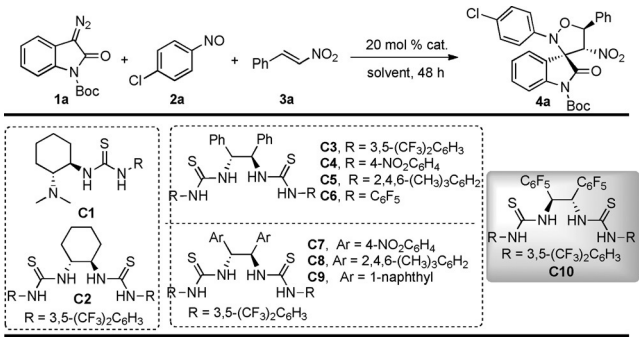
enabled by chiral hydrogen-bond catalysts,[13] thus leading to optically active spirooxindoles with an isoxazolidine ring from readily available starting materials. As part of our continued interest in the area of spirooxindole chemistry[8d,9d] and asymmetric catalysis,[14] herein, we describe the first successful example of an unprecedented and highly enantioselective organocatalytic MCR of diazooxindoles, nitrosoarenes, and nitroalkenes. Notably, the current process provides a convenient and economical route to valuable enantioenriched spirooxindole derivatives with excellent diastereo- and enantioselectivities under mild reaction conditions.

We initiated our studies by evaluating the feasibility of the multicomponent reaction of the diazooxindole **1a** with nitrosoarene[15] **2a** and nitrostyrene **3a** in the presence of the bifunctional Takemoto catalyst[16] (**C1**) in dichloromethane at 40 °C (Table 1). To our delight, the reaction proceeded

Table 1: Screening results of reaction conditions.[a]



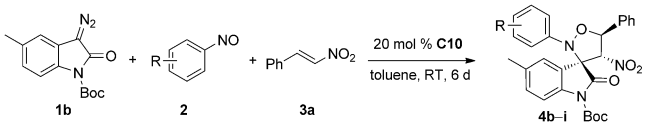
Entry	Catalyst	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**C1**	CH_2Cl_2	35	>99:1	<−5
2	**C2**	CH_2Cl_2	45	>99:1	−16
3	**C3**	CH_2Cl_2	48	>99:1	−45
4	**C3**	toluene	51	>99:1	−77
5	**C3**	MTBE	55	>99:1	−53
6	**C3**	anisole	44	>99:1	−74
7	**C3**	PhCl	49	>99:1	−76
8	**C4**	toluene	38	>99:1	−50
9	**C5**	toluene	30	>99:1	−35
10	**C6**	toluene	36	>99:1	−10
11	**C7**	toluene	46	>99:1	−74
12	**C8**	toluene	53	>99:1	−89
13	**C9**	toluene	47	>99:1	−37
14	**C10**	toluene	56	>99:1	96
15[e]	**C10**	toluene	83 (81[f])	>99:1	96

[a] Reaction conditions: Most of the solvent was removed from the reaction mixture (with **1a** (0.16 mmol), **2a** (0.16 mmol), **3a** (0.1 mmol) and 0.2 mL solvent) and then reacted at room temperature (RT) or 40 °C for 48 h (entries 1–6, at 40 °C; entries 7–18, at RT). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture with CH_2Br_2 as an internal standard. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis using a chiral stationary phase. [e] The reaction was performed at RT for 6 d. [f] Yield of isolated product. Boc = *tert*-butoxycarbonyl, MTBE = methyl *tert*-butyl ether.

smoothly to afford the desired product **4a** in moderate yield with excellent diastereoselectivity, albeit with almost no enantioselectivity (entry 1). Based on hydrogen-bonding catalysis for the synthesis of spirooxindoles,[9d] we speculated that the bis(thiourea) catalyst[17] **C2** may have a strong interaction with the oxindole moiety, thus providing the desired product with a better enantioselectivity. As expected, a slightly better yield and enantiocontrol were obtained with **C2** (entry 2). To improve enantioselectivity, we screened the bis(thiourea) catalyst **C3**, having a more flexible backbone, and it dramatically increased the enantioselectivity to 45 % *ee* (entry 3). Further solvent screening indicated that solvents had a significant influence on the enantioselectivity (entries 4–7) and toluene was identified as the best choice (entry 4). Finally, changing the structure of the aromatic ring on the skeleton and the thiourea moiety of **C3** has a significant influence on enantioselectivity (entries 8–14), thus suggesting that the electronic properties of the aniline group and the steric environment of the diamine skeleton play an important role on asymmetric induction. Among the screened catalysts, a newly developed catalyst (**C10**), with two C_6F_5 groups, gave rise to excellent results with up to 56 % yield and 96 % *ee* (entry 14). The yield of the isolated product was increased to 81 %, without decreasing the enantioselectivity, by running the reaction at room temperature for six days under almost neat conditions (entry 15).

With the optimal reaction conditions in hand, we set out to explore the substrate generality of this MCR. Various aromatic nitroso compounds were applicable and afforded the desired products as a single diastereoisomer in good yields and excellent enantioselectivities (Table 2). It was shown that

Table 2: Substrate scope of different nitroso compounds.[a]

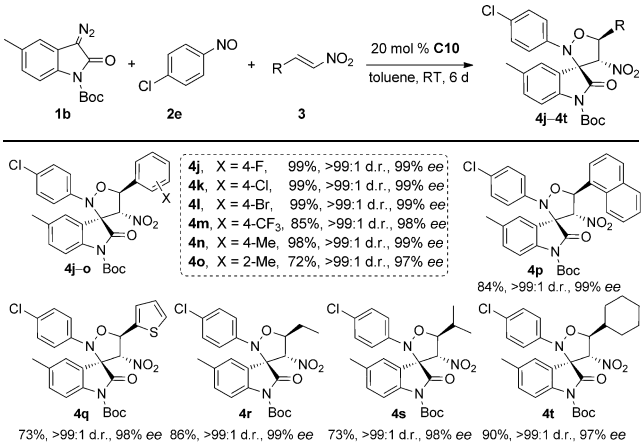


Entry	**2**	**4**	Yield [%][b]	d.r.	*ee* [%][c]
1	**2a**, R = 4-Cl	**4b**	90	>99:1	99
2	**2b**, R = 4-F	**4c**	76	>99:1	97
3	**2c**, R = 4-Br	**4d**	89	>99:1	99
4	**2d**, R = H	**4e**	81	>99:1	98
5	**2e**, R = 3-Cl	**4f**	98	>99:1	99
6	**2f**, R = 2-Cl	**4g**	78	>99:1	93
7	**2g**, R = 4-Me	**4h**	96	>99:1	98
8	**2h**, R = 3-Me	**4i**	90	>99:1	98

[a] All the reactions were conducted on a 0.1 mmol scale. [b] Yield of isolated product based on **3a**. [c] Determined by HPLC analysis using a chiral stationary phase.

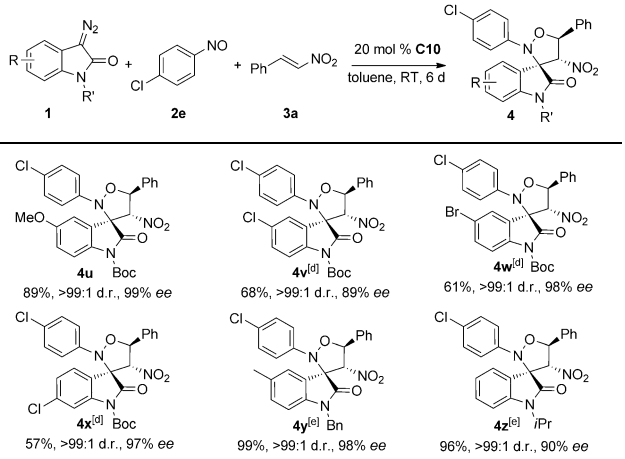
the position and the electronic nature of the substituents on the aromatic ring of **2** have limited effect on the stereoselectivity. For example, nitroso compounds bearing electron-withdrawing (R = F, Cl, Br) or electron-donating groups (R = Me) at different positions (*para*, *meta, ortho*) of the phenyl ring reacted efficiently to afford the corresponding products **4b–i** in 76–98 % yields with 93–99 % *ee* (entries 1–8). The 2-chloro substituent introduced more into sterics in the cyclization step, thus accounting for the decrease in the *ee* values (from 99 to 93 % *ee*) as compared to those of the other nitroso compounds.

Table 3: Substrate scope of different nitroalkenes.[a,b,c]



[a] All the reactions were conducted on a 0.1 mmol scale. [b] Yield of isolated product based on **3**. [c] Determined by HPLC analysis using a chiral stationary phase.

Table 4: Substrate scope of diazooxindoles.[a,b,c]

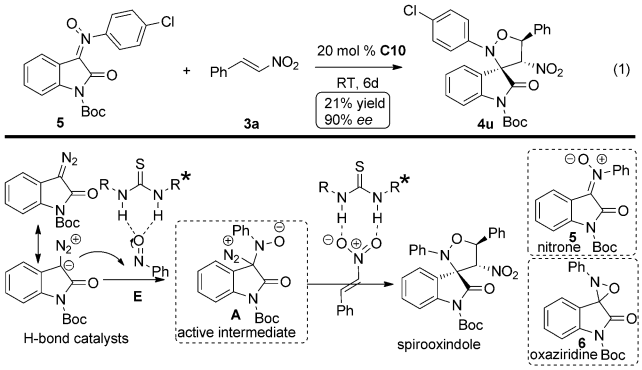


[a] All the reactions were conducted on a 0.1 mmol scale. [b] Yield of isolated product based on **3a**. [c] Determined by HPLC analysis using a chiral stationary phase. [d] The reaction was run at 40 °C, using chloroform/toluene = 1:1 as the solvent. [e] The reaction was run at 5 °C, using chloroform/toluene = 1:1 as the solvent.

We then evaluated the use of various nitroalkenes as the reactant (Table 3). Most reactions were complete within six days and gave products in good to excellent yields (72–99 %) with excellent enantioselectivities (97–99 % *ee*) and diastereoselectivities (> 99:1 d.r.). For the use of β-aryl nitroalkenes, the position and electronic properties of substituents on the aromatic ring appeared to have a very limited effect on stereoselectivity. Regardless of the type of substituents on the aromatic ring of **3**, such as electron-withdrawing (**4j**–**m**), electron-donating (**4n** and **4o**), or neutral (**4p**) groups, the reactions of these nitroalkenes gave excellent yields and stereoselectivities. The use of a nitroalkene with a thienyl group also afforded the desired product with excellent stereocontrol (**4q**). Most importantly, alkyl nitroalkenes were also suitable substrates and the desired products (**4r**–**t**) were obtained with good results under the standard reaction conditions. The absolute configuration of **4p** was determined by X-ray crystallographic analysis[18] (see Figure S1 in the Supporting Information).

Encouraged by these results, we expanded the generality of the reaction with regard to the variation of the diazooxindoles (Table 4). Although the desired products can be obtained with good stereoselectivities, the electronic properties of the aromatic ring substituents affected the reactivity of the diazo compounds. For example, under the optimal reaction conditions diazooxindoles containing electron-withdrawing groups, such as chlorine or bromine, can only produce final products with low yields because of the low reactivity. After further investigation, we modified the reaction conditions and found that acceptable yields can be achieved by increasing the temperature to 40 °C and using chloroform and toluene as a mixed solvent system (**4v**–**x**). Notably, the presence of Cl or Br at this moiety is very important for drug discovery because halides are very reactive in many transition-metal-catalyzed reactions,[19] and offer opportunities for further modifications at these positions. The protecting group (such as benzyl or isopropyl group) on the diazooxindole moiety has almost no effect on the results (**4y** and **4z**).

During the course of this study, in almost all cases, a nitrone by-product (**5**; see Scheme 2) was formed in small amounts. Therefore, we initially speculated that the key active intermediate of this multicomponent reaction might be a nitrone. To gain more insight into the reaction mechanism, we performed a control experiment by reacting **5** with the nitrostyrene **3a** under the standard reaction conditions. However, the reaction proceeded very slowly and only around 21 % yield of the desired product was obtained with excellent stereoselectivity (> 99:1 d.r., 90 % *ee*) after six days (Scheme 2), thus suggesting that the nitrone may be not the



Scheme 2. Control experiment and proposed mechanism.

exact intermediate for the current MCR and that the hydrogen-bonding catalyst may contribute to formimg the chiral intermediate **A**. Based on recent reports on the organocatalytic asymmetric nucleophilic addition of imines and diazo compounds,[12] we supposed that a more reactive intermediate (**A**), generated in situ from diazooxindole and

nirosoarene, could be directly trapped by the nitroalkene, followed by cyclization, to yield the final spirooxindole product. However, the tandem reaction of the nitroalkene with another active intermediate oxaziridine (**6**), directly generated from the **A**, could not be ruled out at the current stage (Scheme 2). The bis(thiourea) catalyst would provide a well-organized environment for asymmetric induction as well as a pocket to enable this reaction to proceed smoothly.[9d,17e]

In summary, we have developed an asymmetric MCR through the rational design of diazooxindoles, nitrosoarenes, and nitroalkenes as reaction components, thus providing a successful example of the use of diazo compounds under metal-free conditions in enantioselective MCRs. The most important feature of this transformation is the highly stereoselective MCR involving diazooxindoles as discovered through using a newly developed bis(thiourea) hydrogen-bond catalyst. A new route to access spirooxindole derivatives, with excellent functionality tolerance, in excellent yields and stereoselectivities, highlights this unprecedented approach to trapping the active intermediate with a nitroalkene to form biologically important compounds having three contiguous stereogenic centers with excellent asymmetric induction. Further studies to expand the application of this newly developed bis(thiourea) catalyst and to discover more challenging substrate combinations are ongoing in our laboratory.

Keywords: diazo compounds · enantioselectivity · heterocycles · multicomponent reactions · organocatalysis

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[1] a) H. M. L. Davies, E. J. Sorensen, *Chem. Soc. Rev.* **2009**, *38*, 2981; b) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208; c) T. Hudlicky, J. W. Reed, *Chem. Soc. Rev.* **2009**, *38*, 3117.

[2] For recent leading reviews on multicomponent reactions (MCRs), see: a) B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439; b) A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083; c) C. de Graaff, E. Ruijter, R. V. A. Orru, *Chem. Soc. Rev.* **2012**, *41*, 3969; d) S. Brauch, S. S. van Berkel, B. Westermann, *Chem. Soc. Rev.* **2013**, *42*, 4948.

[3] For selected reviews, see: a) T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091; b) Z. Zhang, J. Wang, *Tetrahedron* **2008**, *64*, 6577; c) Q. Xiao, Y. Zhang, J. Wang, *Acc. Chem. Res.* **2013**, *46*, 236.

[4] For recent reviews on metal carbenoids, see: a) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417; b) X.-L. Sun, Y. Tang, *Acc. Chem. Res.* **2008**, *41*, 937; c) M. M. Díaz-Requejo, P. J. Pérez, *Chem. Rev.* **2008**, *108*, 3379; d) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704; e) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; f) S.-F. Zhu, Q.-L. Zhou, *Acc. Chem. Res.* **2012**, *45*, 1365; g) X. Zhao, Y. Zhang, J. Wang, *Chem. Commun.* **2012**, *48*, 10162; h) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092.

[5] For recent reviews involving MCRs of diazo compounds, see: a) X. Guo, W. Hu, *Acc. Chem. Res.* **2013**, *46*, 2427; b) D. Xing, W. Hu, *Tetrahedron Lett.* **2014**, *55*, 777.

[6] For recent examples involving asymmetric metal-catalyzed MCRs of diazo compounds, see: a) W.-H. Hu, X.-F. Xu, J. Zhou, W.-J. Liu, H.-X. Huang, J. Hu, L.-P. Yang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 7782; b) J. Jiang, H.-D. Xu, J.-B. Xi, B.-Y. Ren, F.-P. Lv, X. Guo, L.-Q. Jiang, Z.-Y. Zhang, W.-H. Hu, *J. Am. Chem. Soc.* **2011**, *133*, 8428; c) H. Qiu, M. Li, L.-Q. Jiang, F.-P. Lv, L. Zan, C.-W. Zhai, M. P. Doyle, W.-H. Hu, *Nat. Chem.* **2012**, *4*, 733; d) S. Jia, D. Xing, W. Zhang, W. Hu, *Angew. Chem. Int. Ed.* **2014**, *53*, 13098; *Angew. Chem.* **2014**, *126*, 13314; e) L. Ren, X.-L. Lian, L.-Z. Gong, *Chem. Eur. J.* **2013**, *19*, 3315; f) D.-F. Chen, F. Zhao, Y. Hu, L.-Z. Gong, *Angew. Chem. Int. Ed.* **2014**, *53*, 10763; *Angew. Chem.* **2014**, *126*, 10939; g) C.-Y. Zhou, J.-C. Wang, J. Wei, Z.-J. Xu, Z. Guo, K.-H. Low, C.-M. Che, *Angew. Chem. Int. Ed.* **2012**, *51*, 11376; *Angew. Chem.* **2012**, *124*, 11538.

[7] a) R. F. Bond, J. C. A. Boeyens, C. W. Holzapfel, P. S. Steyn, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1751; b) H. Lin, S. J. Danishefsky, *Angew. Chem. Int. Ed.* **2003**, *42*, 36; *Angew. Chem.* **2003**, *115*, 38; c) C. V. Galliford, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 8748; *Angew. Chem.* **2007**, *119*, 8902; d) T. J. Greshock, A. W. Grubbs, P. Jiao, D. T. Wicklow, J. B. Gloer, R. M. Williams, *Angew. Chem. Int. Ed.* **2008**, *47*, 3573; *Angew. Chem.* **2008**, *120*, 3629; e) K. A. Miller, S. Tsukamoto, R. M. Williams, *Nat. Chem.* **2009**, *1*, 63.

[8] For reviews: a) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* **2012**, *41*, 7247; b) N. R. Ball-Jones, J. J. Badille, A. K. Franz, *Org. Biomol. Chem.* **2012**, *10*, 5165; c) L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023; d) D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas III, *ACS Catal.* **2014**, *4*, 743.

[9] For recent examples on organocatalytic asymmetric synthesis of spirooxindoles, see: a) G. Bencivenni, L. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M. Song, G. Bartoli, P. Melchiorre, *Angew. Chem. Int. Ed.* **2009**, *48*, 7200; *Angew. Chem.* **2009**, *121*, 7336; b) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819; c) X. Jiang, Y. Cao, Y. Wang, L. Liu, F. Shen, R. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 15328; d) B. Tan, G. Hernandez-Torres, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 12354; e) F. Zhong, X. Han, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* **2011**, *50*, 7837; *Angew. Chem.* **2011**, *123*, 7983; f) Z.-J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053; g) J. Peng, X. Huang, L. Jiang, H.-L. Cui, Y.-C. Chen, *Org. Lett.* **2011**, *13*, 4584; h) Y. Cao, X. Jiang, L. Liu, F. Shen, F. Zhang, R. Wang, *Angew. Chem. Int. Ed.* **2011**, *50*, 9124; *Angew. Chem.* **2011**, *123*, 9290; i) W. Sun, G. Zhu, C. Wu, G. Li, L. Hong, R. Wang, *Angew. Chem. Int. Ed.* **2013**, *52*, 8633; *Angew. Chem.* **2013**, *125*, 8795; j) L.-T. Shen, W.-Q. Jia, S. Ye, *Angew. Chem. Int. Ed.* **2013**, *52*, 585; *Angew. Chem.* **2013**, *125*, 613; k) F. Manoni, S. J. Connon, *Angew. Chem. Int. Ed.* **2014**, *53*, 2628; *Angew. Chem.* **2014**, *126*, 2666; l) B. Xiang, K. M. Belyk, R. A. Reamer, N. Yasuda, *Angew. Chem. Int. Ed.* **2014**, *53*, 8375; *Angew. Chem.* **2014**, *126*, 8515; m) K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund, K. A. Jørgensen, *J. Am. Chem. Soc.* **2015**, *137*, 1685.

[10] Z.-Y. Cao, X. Wang, C. Tan, X.-L. Zhao, J. Zhou, K. Ding, *J. Am. Chem. Soc.* **2013**, *135*, 8197.

[11] For a recent review, see: Z.-Y. Cao, Y.-H. Wang, X.-P. Zeng, J. Zhou, *Tetrahedron Lett.* **2014**, *55*, 2571.

[12] For recent examples involving organocatalytic asymmetric nucleophilic addition of imines with diazo compounds, see: a) T. Hashimoto, A. O. Galvez, K. Maruoka, *J. Am. Chem. Soc.* **2013**, *135*, 17667; b) T. Hashimoto, H. Nakatsu, K. Yamamoto, K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 9730; c) T. Hashimoto, N. Uchiyama, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 14380; d) A. A. Desai, W. D. Wulff, *J. Am. Chem. Soc.* **2010**, *132*, 13100; e) M. J. Vetticatt, A. A. Desai, W. D. Wulff, *J. Am. Chem. Soc.* **2010**, *132*, 13104; f) L. Huang, W. D. Wulff, *J. Am. Chem. Soc.* **2011**, *133*, 8892; For a review, see: g) J. N. Johnston, H. Muchalski, T. L. Troyer, *Angew. Chem. Int. Ed.* **2010**, *49*, 2290; *Angew. Chem.* **2010**, *122*, 2340.

[13] a) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187; b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; *Angew. Chem.* **2006**, *118*, 1550.

[14] a) D.-J. Cheng, L. Yan, S.-K. Tian, M.-Y. Wu, L.-X. Wang, Z.-L. Fan, S.-C. Zheng, X.-Y. Liu, B. Tan, *Angew. Chem. Int. Ed.* **2014**, *53*, 3684; *Angew. Chem.* **2014**, *126*, 3758; b) P. Yu, J.-S. Lin, L. Li, S.-C. Zheng, Y.-P. Xiong, L.-J. Zhao, B. Tan, X.-Y. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 11890; *Angew. Chem.* **2014**, *126*, 12084.

[15] For examples of organocatalytic asymmetric reactions by using nitrobenzene as an electrophile, see the pioneering work: a) G. Zhong, *Angew. Chem. Int. Ed.* **2003**, *42*, 4247; *Angew. Chem.* **2003**, *115*, 4379; b) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808; recent examples: c) M. Kawasaki, P. Li, H. Yamamoto, *Angew. Chem. Int. Ed.* **2008**, *47*, 3795; *Angew. Chem.* **2008**, *120*, 3855; d) M. Lu, D. Zhu, Y. Lu, X. Zeng, B. Tan, Z. Xu, G. Zhong, *J. Am. Chem. Soc.* **2009**, *131*, 4562; e) M. Lu, Y. Lu, D. Zhu, X. Zeng, X. Li, G. Zhong, *Angew. Chem. Int. Ed.* **2010**, *49*, 8588; *Angew. Chem.* **2010**, *122*, 8770; f) A. Yanagisawa, S. Takeshita, Y. Izumi, K. Yoshida, *J. Am. Chem. Soc.* **2010**, *132*, 5328.

[16] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119.

[17] For examples of the use of bis(thiourea) catalysts, see: a) Y. Zhang, Y. Liu, T. Kang, Z. Hu, Y. Chen, *J. Am. Chem. Soc.* **2008**, *130*, 2456; b) C. Kanta De, E. G. Klauber, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 17060; c) Y. Shi, A. Lin, H. Mao, Z. Mao, W. Li, H. Hu, C. Zhu, Y. Cheng, *Chem. Eur. J.* **2013**, *19*, 1914; d) L. Lykke, B. D. Carlsen, R. S. Rambo, K. A. Jørgensen, *J. Am. Chem. Soc.* **2014**, *136*, 11296; for a pioneering report on thiourea catalysis, see: e) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901.

[18] CCDC 1059863 (**4p**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[19] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

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