Organocatalytic Michael addition of unprotected 3-substituted oxindoles to nitroolefins†

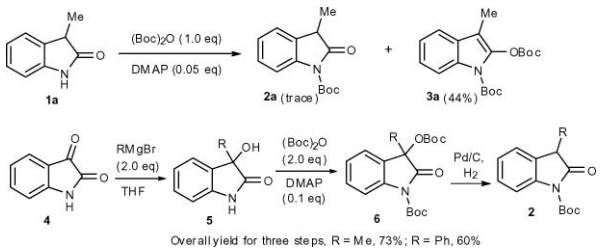
Miao Ding, Feng Zhou, Zi-Qing Qian and Jian Zhou*

Received 9th March 2010, Accepted 4th May 2010
First published as an Advance Article on the web 17th May 2010
DOI: 10.1039/c004037a

Quinidine was found to catalyze the Michael addition of unprotected 3-substituted oxindoles to nitroolefins in excellent yield and moderate to good diastereoselectivity. Bifunctional quinidine derived thiourea catalyst 10 could catalyze this reaction to afford the major diastereomer in up to 85% ee.

The catalytic asymmetric synthesis of oxindoles bearing a tetrasubstituted carbon stereocenter at the 3-position has received much attention, because 3,3-disubstituted oxindole structural motif is widely presented in natural products, drugs and pharmaceutically active compounds.[1] Among the synthetic strategies developed to date,[2] the catalytic asymmetric direct functionalization of 3-substituted oxindoles is probably the most versatile method to construct all-carbon or heteroatom-containing tetrasubstituted carbon stereocenter at the C3 position, *via* alkylation,[3] Mannich,[4] fluorination,[5] hydroxylation,[6] aldol,[7] amination[8] and Michael addition reaction.[9] However, N-protected 3-substituted oxindoles were used in most of these protocols, and only very limited examples were based on the use of unprotected 3-substituted oxindoles **1**.[4b,7a–b,8a–b,9b]

The difficulty in the direct functionalization of unprotected 3-substituted oxindoles **1** was possibly due to the high pK_a value of C–H bond at the C3 position, considering the pK_a value of oxindole is 18.2.[10] To facilitate the deprotonative activation, the introduction of electron-withdrawing protecting group to the nitrogen moiety might lower down the pK_a value, for example, N-acetyl oxindole has a pK_a value of 13.0, much lower than that of oxindole.[10] Accordingly, N-Boc protected 3-substituted oxindole **2** is most commonly used for reaction design, allowing easier deprotonative activation and better enantiofacial control owing to the bulky shielding group. However, it took three steps to obtain N-Boc protected oxindole **2** from isatins **4**, with the sacrifice of one more equivalent of $(Boc)_2O$ (Scheme 1).[11] The direct protection of 3-substituted oxindole **1** with Boc group was reported to be problematic due to the competitive O- and N-reactivity. Even using the new method recently introduced by Trost *et al*,[11] the yield of the N-Boc 3-substituted oxindole is still moderate. Since the oxindole moiety in most of the natural products, drugs and bioactive compounds is without protecting groups, it is more atom economical and convenient to use unprotected 3-substituted oxindole **1** for reaction development.



Scheme 1 The synthesis of N-Boc 3-substituted oxindole **2**.

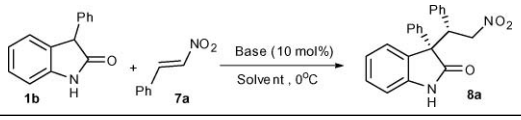
As part of a program directed at the synthesis of 3,3-disubstituted oxindoles for biological evaluation, we have developed a highly enantioselective amination of unprotected 3-substituted oxindoles **1**.[8b] We also focused on the Michael addition of unprotected oxindole derivative **1** to nitroolefins,[12] because the desired adducts are very useful in organic synthesis. During our investigation, Barbas III[9c] and Shibasaki[9d] independently reported the highly enantioselective Michael addition of N-Boc protected 3-alkylsubstituted oxindole **2** to nitroolefins, respectively. Maruoka reported chiral PTC-catalyzed base-free Michael addition of N-Boc protected 3-arylsubstituted oxindole **2** to nitroolefins.[9e] Later, Luo and Cheng reported the Michael addition of N-phenyl 3-substituted oxindole to nitroolefins.[9g] To the best of our knowledge, the Michael addition of unprotected 3-substituted oxindole to nitroolefins has not been reported. Here we wish to report our preliminary results in this communication.

We began reaction development by optimizing reaction parameters for the Michael addition of 3-phenyloxindole **1b** with nitroolefin **7a**. The solvent effect was first evaluated by treating compound **1b** and nitroolefin **7a** in the presence of 10 mol% of CD at 0 °C. As shown in Table 1, the reaction proceeded well in all the screened solvents except cyclohexane (entries 1–7), possibly due to poor solubility of oxindole **1b** in cyclohexane. Generally, the reaction could finish within two days, affording the desired product **8a** in moderate diastereoselectivity. The dr was determined by ^{1}H NMR analysis of the crude reaction mixture. Since reaction in acetone afforded the best diastereoselectivity (entry 3), the evaluation of different bases was carried out using acetone as the solvent. Not only organic but inorganic bases could serve as catalyst for this reaction, but the base obviously influenced the dr of the product. K_2CO_3 and Cs_2CO_3 could readily catalyze this reaction, but afforded the two diastereomers of product **8a** in almost equal amount (entries 8 and 9). Organic bases such as triethylamine, DBU, *i*-Pr_2NEt and TMEDA all afforded inferior dr than cinchonidine (entries 10–13). To our delight, QD could improve the dr to 5.0 : 1.0. We also tried the addition of molecular sieves or lowering temperature to further improve the diastereoselectivity, but no obvious improvement was obtained.

Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry, East China Normal University, 3663 N. Zhongshan Road, Shanghai 200062, (P. R. China). E-mail: jzhou@chem.ecnu.edu.cn; Fax: +86-21-62234560; Tel: +86-21-62234560

† Electronic supplementary information (ESI) available: General experimental procedures and spectral data. See DOI: 10.1039/c004037a

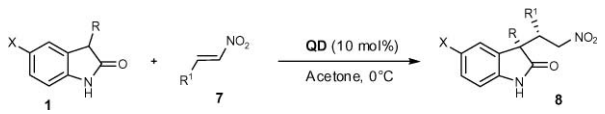
Table 1 Reaction optimization



Entry[a]	Base	Solvent	Conv.[b]	Dr[c]
1	CD	CH_2Cl_2	Full	2.1 : 1.0
2	CD	Toluene	Full	1.8 : 1.0
3	CD	Acetone	Full	2.7 : 1.0
4	CD	*t*-BuOMe	Full	2.1 : 1.0
5	CD	CH_3CN	Full	1.8 : 1.0
6	CD	THF	Full	2.6 : 1.0
7	CD	*c*-Hexane	<10%	1.7 : 1.0
8	K_2CO_3	Acetone	Full	1.0 : 1.1
9	Cs_2CO_3	Acetone	Full	1.0 : 1.0
10	Et_3N	Acetone	Full	2.0 : 1.0
11	DBU	Acetone	Full	1.2 : 1.0
12	*i*-Pr_2NEt	Acetone	Full	2.0 : 1.0
13	TMEDA	Acetone	Full	2.3 : 1.0
14	QD	Acetone	Full	5.0 : 1.0

[a] Reaction scale: 0.1 mmol; [b] Monitored by TLC analysis and confirmed by ^{1}H NMR analysis of the crude reaction mixture; [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Abbreviations: CD (cinchonidine), DBU (1,8-diazabicyclo[5,4,0]undec-7-ene), TMEDA (N, N, N′,N′-tetramethylethylenediamine), QD (quinidine).

Table 2 Substrate scope

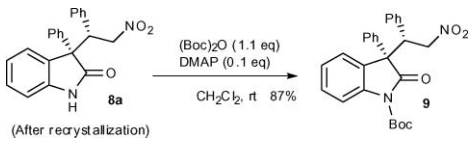


Entry[a]	X	R	R[11]	8c	Yield[b](%)	Dr[c]
1	H	Ph	Ph	**8a**	96	5.0 : 1.0
2	F	Ph	Ph	**8b**	87	4.3 : 1.0
3	Br	Ph	Ph	**8c**	95	4.3 : 1.0
4	H	2-Naphthyl	Ph	**8d**	92	5.0 : 1.0
5	H	*p*-ClC_6H_4	Ph	**8e**	95	4.7 : 1.0
6	H	Ph	*p*-$CF_3C_6H_4$	**8f**	95	2.3 : 1.0
7	H	Ph	*p*-ClC_6H_4	**8g**	92	4.5 : 1.0
8	H	Ph	2,4-$Cl_2C_6H_3$	**8h**	85	3.0 : 1.0
9	H	Ph	2-Naphthyl	**8i**	92	4.8 : 1.0
10	H	Ph	2-Thienyl	**8j**	95	4.3 : 1.0
11	H	Ph	2-Furanyl	**8k**	75	2.4 : 1.0
12	H	Ph	*n*-Bu	**8l**	95	1.7 : 1.0
13	H	Ph	*i*-Bu	**8m**	78	3.0 : 1.0
14[d]	H	Ph	Ph	**8n**	61	1.6 : 1.0

[a] Reaction scale: 0.25 mmol; [b] Isolated yield; [c] Determined by ^{1}H NMR analysis of the crude reaction mixture; [d] At room temperature.

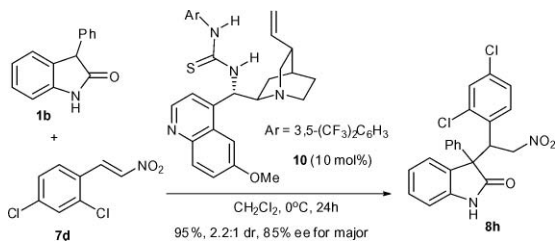
Based on the above optimization studies, we next examined the substrate scope of different 3-substituted oxindole **1** and nitroolefins **7** in acetone at 0 °C, using 10 mol% of quinidine as catalyst (Table 2). All 3-aryloxindoles worked well to afford the desired product in excellent yield. The substituents on C5 position of oxindole or different aryl substituents on the C3 position had small impact on the diastereoselectivity of the reaction, and all afforded good diastereoselectivity (entries 1–5). The substituent of nitroolefin **7** influenced the dr of the reaction to some extent. In the case of substituted nitrostyrenes, the substituent on the phenyl ring lowered the diastereoselectivity of the reaction, compared with nitroolefin **7a** (entries 6–8). Both 1-(2-napthyl)-2- and 1-(2-thienyl)-2-nitroethene afforded the desired products in good dr and excellent yield (entries 9–10). However, product **8k** derived from 1-(2-furyl)-2-nitroethene was obtained in lower yield and moderate dr (entry 11). Alkyl nitroolefins were also workable under the reaction condition, but afforded the product in lower dr (entries 12 and 13). Less reactive 3-alkyloxindoles were also tried. For example, 3-benzyloxindole reacted with nitroolefin **7a** at room temperature for two days to afford product **8n** in 61% yield with moderate dr (1.6 : 1.0, entry 14).

The relative configuration of the product **8a** was assigned *via* conversion to known compound **9**.[9e] By comparing the ^{1}H NMR data with the literature report, the relative configuration of the product **8a** was finally determined as shown in the eqn (1). It should be noted that the stereochemistry shown in Table 1, 2 and eqn (1) was referred to relative configuration, not absolute configuration. Those of other products **8b–8l** were tentatively assigned by analogy.



(1)

We also tried to develop a catalytic asymmetric Michael addition of unprotected oxindoles **1** to nitroolefins **7**. Reaction optimization revealed that the catalyst structure significantly influenced the enantioselectivity of the product (see ESI†). Compared with other quinidine derivatives examined, bifunctional cinchona alkaloid-based thiourea catalyst **10** turned out to be the most enantioselective catalyst,[13] which could promote the reaction of oxindole **1b** and nitroolefin **7d** to afford product **8h** in up to 85% ee for major diastereomer with moderate dr (2.2 : 1.0), using CH_2Cl_2 as the solvent at 0 °C. Unfortunately, only the enantiomeric excess of product **8h** could be analyzed by now, since we can not separate the diastereomers and enantiomers of other Michael adducts (**8a–g** and **8i–n**) by chiral HPLC.



(2)

In conclusion, we developed the first example of Michael addition of unprotected 3-substituted oxindoles to nitroolefins. Under the catalysis of quinidine, fourteen examples of 3,3-disubstituted oxindole derivatives, with two adjacent quaternary-tertiary carbon centers, were synthesized in excellent yield and moderate to good diastereoselectivity. The simple and mild reaction conditions including air-tolerance, together with the usefulness of the product, make our method very useful. Initial investigation revealed that alkaloid-based thiourea catalyst was a highly enantioselective catalyst for this transformation, affording the desired product in up to 85% ee with moderate diastereoselectivity. Based on the evaluation of the different catalysts derived from cinchona alkaloids, the development of new bifunctional chiral cinchona alkaloids catalyst might be promising to expand

the substrate scope and to improve the diastereoselectivity and enantioselectivity, which is now underway in our lab.

The financial support from the Natural Science Foundation of China (20902025) and East China Normal University are highly appreciated.

Notes and references

1 For reviews, see: (*a*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (*b*) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209; (*c*) S. Hibino and T. Choshi, *Nat. Prod. Rep.*, 2001, **18**, 66.

2 For a review, see: (*a*) B. M. Trost and M. K. Brennan, *Synthesis*, 2009, 3303; (*b*) for intramolecular coupling reactions, see: T. Matsuura, L. E. Overman and D. J. Poon, *J. Am. Chem. Soc.*, 1998, **120**, 6500; (*c*) A. B. Dounay, K. Hatanaka, J. J. Kodanko, M. Oestreich, L. E. Overman, L. A. Pfeifer and M. M. Weiss, *J. Am. Chem. Soc.*, 2003, **125**, 6261; (*d*) C. A. Busacca, D. Grossbach, R. C. So, E. M. O'Brien and E. M. Spinelli, *Org. Lett.*, 2003, **5**, 595; (*e*) A. Pinto, Y. Jia, L. Neuville and J. Zhu, *Chem.–Eur. J.*, 2007, **13**, 961; (*f*) S. Lee and J. F. Hartwig, *J. Org. Chem.*, 2001, **66**, 3402; (*g*) E. P. Kündig, T. M. Seidel, Y. Jia and G. Bernardinelli, *Angew. Chem., Int. Ed.*, 2007, **46**, 8484; (*h*) Y.-X. Jia, J. M. Hillgren, E. L. Watson, S. P. Marsden and E. P. Kündig, *Chem. Commun.*, 2008, 4040; (*i*) Y. Yasui, H. Kamisaki and Y. Takemoto, *Org. Lett.*, 2008, **10**, 3303; (*j*) for nucleophilic additions to isatins, see: R. Shintani, M. Inoue and T. Hayashi, *Angew. Chem., Int. Ed.*, 2006, **45**, 3353; (*k*) D. Tomita, K. Yamatsugu, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 6946; (*l*) J. Itoh, S. B. Han and M. J. Krische, *Angew. Chem., Int. Ed.*, 2009, **48**, 6313; (*m*) G. Luppi, P. G. Cozzi, M. Monari, B. Kaptein, Q. B. Broxterman and C. Tomasini, *J. Org. Chem.*, 2005, **70**, 7418; (*n*) S. Nakamura, N. Hara, H. Nakashima, K. Kubo, N. Shibata and T. Toru, *Chem.–Eur. J.*, 2008, **14**, 8079; (*o*) T. Itoh, H. Ishikawa and Y. Hayashi, *Org. Lett.*, 2009, **11**, 3854; (*p*) F. Xue, S. Zhang, L. Liu, W. Duan and W. Wang, *Chem.–Asian J.*, 2009, **4**, 1664; (*q*) N. V. Hanhan, A. H. Sahin, T. W. Chang, J. C. Fettinger and A. K. Franz, *Angew. Chem., Int. Ed.*, 2010, **49**, 744; (*r*) for other methods, see: I. D. Hills and G. C. Fu, *Angew. Chem., Int. Ed.*, 2003, **42**, 3921; (*s*) T. A. Duffey, S. A. Shaw and E. Vedejs, *J. Am. Chem. Soc.*, 2009, **131**, 14; (*t*) E. C. Linton and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2008, **130**, 16162; (*u*) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 7200; (*v*) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 13819; (*w*) S. Ma, X. Han, S. Krishnan, S. C. Virgil and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2009, **48**, 8037; (*x*) B. M. Trost, N. Cramer and S. M. Silverman, *J. Am. Chem. Soc.*, 2007, **129**, 12396.

3 (*a*) T. B. K. Lee and G. S. K. Wong, *J. Org. Chem.*, 1991, **56**, 872; (*b*) B. M. Trost and M. U. Frederiksen, *Angew. Chem., Int. Ed.*, 2005, **44**, 308; (*c*) B. M. Trost and Y. Zhang, *J. Am. Chem. Soc.*, 2006, **128**, 4590; (*d*) B. M. Trost and Y. Zhang, *J. Am. Chem. Soc.*, 2007, **129**, 14548; (*e*) B. M. Trost and Y. Zhang, *Chem.–Eur. J.*, 2010, **16**, 296; (*f*) K. Jiang, J. Peng, H.-L. Cui and Y.-C. Chen, *Chem. Commun.*, 2009, 3955.

4 (*a*) X. Tian, K. Jiang, J. Peng, W. Du and Y.-C. Chen, *Org. Lett.*, 2008, **10**, 3583; (*b*) L. Cheng, L. Liu, H. Jia, D. Wang and Y.-J. Chen, *J. Org. Chem.*, 2009, **74**, 4650.

5 (*a*) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura and M. Sodeoka, *J. Am. Chem. Soc.*, 2005, **127**, 10164; (*b*) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru and S. Kanemasa, *Angew. Chem., Int. Ed.*, 2005, **44**, 4204; (*c*) T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru and M. Shiro, *Angew. Chem., Int. Ed.*, 2008, **47**, 4157.

6 (*a*) T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru and S. Kanemasa, *J. Am. Chem. Soc.*, 2006, **128**, 16488; (*b*) D. Sano, K. Nagata and T. Itoh, *Org. Lett.*, 2008, **10**, 1593.

7 (*a*) S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru and M. Shiro, *Angew. Chem., Int. Ed.*, 2007, **46**, 8666; (*b*) K. Shen, X. Liu, K. Zheng, W. Li, X. Hu, L. Lin and X. Feng, *Chem.–Eur. J.*, 2010, **16**, 3736; (*c*) S. Kobayashi, M. Kobubo, K. Kawasumi and T. Nagano, *Chem.–Asian J.*, 2010, **5**, 490.

8 (*a*) L. Cheng, L. Liu, D. Wang and Y.-J. Chen, *Org. Lett.*, 2009, **11**, 3874; (*b*) Z.-Q. Qian, F. Zhou, T.-P. Du, B.-L. Wang, M. Ding, X.-L. Zhao and J. Zhou, *Chem. Commun.*, 2009, 6753; (*c*) T. Bui, M. Borregan and C. F. Barbas III, *J. Org. Chem.*, 2009, **74**, 8935; (*d*) S. Mouri, Z. Chen, H. Mitsunuma, M. Furutachi, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 1255.

9 (*a*) R. He, C. Ding and K. Maruoka, *Angew. Chem., Int. Ed.*, 2009, **48**, 4559; (*b*) P. Galzerano, G. Bencivenni, F. Pesciaioli, A. Mazzanti, B. Giannichi, L. Sambri, G. Bartoli and P. Melchiorre, *Chem.–Eur. J.*, 2009, **15**, 7846; (*c*) T. Bui, S. Syed and C. F. Barbas III, *J. Am. Chem. Soc.*, 2009, **131**, 8758; (*d*) Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 9168; (*e*) R. He, S. Shirakawa and K. Maruoka, *J. Am. Chem. Soc.*, 2009, **131**, 16620; (*f*) X. Li, Z.-G. Xi, S. Luo and J.-P. Cheng, *Org. Biomol. Chem.*, 2010, **8**, 77; (*g*) X. Li, B. Zhang, Z.-G. Xi, S. Luo and J.-P. Cheng, *Adv. Synth. Catal.*, 2010, **352**, 416.

10 F. G. Bordwell and H. E. Fried, *J. Org. Chem.*, 1991, **56**, 4218.

11 Please see the surpporting information of ref. 5a, also see: B. M. Trost, Y. Zhang and T. Zhang, *J. Org. Chem.*, 2009, **74**, 5115.

12 For reviews on the application of nitroolefins in asymmetric Michael addition, see: (*a*) O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.*, 2002, 1877; (*b*) A. Alexakis and C. Benhaim, *Eur. J. Org. Chem.*, 2002, 3221; (*c*) D. Almasi, D. A. Alonso and C. Nájera, *Tetrahedron: Asymmetry*, 2007, **18**, 299; (*d*) J. L. Vicario, D. Badía and L. Carrillo, *Synthesis*, 2007, 2065; (*e*) S. Mukhrjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (*f*) T. Jerphagnon, M. G. Pizzuti, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, 2009, **38**, 1039; (*g*) for some selected examples, see: Y. Sui, L. Liu, J.-L. Zhao, D Wang and Y.-J. Chen, *Tetrahedron*, 2007, **63**, 5173; (*h*) B. M. Trost and C. Müller, *J. Am. Chem. Soc.*, 2008, **130**, 2438; (*i*) R. P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem., Int. Ed.*, 2005, **44**, 6576; (*j*) Y.-X. Jia, S.-F. Zhu, Y. Yang and Q.-L. Zhou, *J. Org. Chem.*, 2006, **71**, 75; (*k*) T.-Y. Liu, H.-L. Cui, Q. Chai, J. Long, B.-J. Li, Y. Wu, L.-S. Ding and Y.-C. Chen, *Chem. Commun.*, 2007, 2228; (*l*) C.-L. Cao, M.-C. Ye, X.-L. Sun and Y. Tang, *Org. Lett.*, 2006, **8**, 2901; (*m*) M. Nielsen, W. Zhuang and K. A. Jørgensen, *Tetrahedron*, 2007, **63**, 5849; (*n*) J. Wu, D. M. Mampreian and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2005, **127**, 4584; (*o*) L. Bernardi, F. Fini, M. Fochi and A. Ricci, *Synlett*, 2008, 1857; (*p*) N. J. A. Martin, X. Cheng and B. List, *J. Am. Chem. Soc.*, 2008, **130**, 13862; (*q*) P. García-García, A. Ladépêche, R. Halder and B. List, *Angew. Chem., Int. Ed.*, 2008, **47**, 4719; (*r*) Y.-F. Sheng, Q. Gu, A.-J. Zhang and S.-L. You, *J. Org. Chem.*, 2009, **74**, 6899; (*s*) H. Liu, S.-F. Lu, J. Xu and D.-M. Du, *Chem.–Asian J.*, 2008, **3**, 1111; (*t*) C.-L. Cao, Y.-Y. Zhou, J. Zhou, X.-L. Sun, Y. Tang, Y.-X. Li, C.-Y. Li and J. Sun, *Chem. Eur. J.*, 2009, **15**, 11384.

13 For a review about catalyst **10**, see: (*a*) S. J. Connon, *Chem. Commun.*, 2008, 2499; (*b*) For pioneer work on this catalyst, see: B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding and Y. Wu, *Synlett*, 2005, 603; (*c*) B. Vakulya, S. Varga, A. Csámpai and T. Soós, *Org. Lett.*, 2005, **7**, 1967; (*d*) S. H. McCooey and S. J. Connon, *Angew. Chem., Int. Ed.*, 2005, **44**, 6367; (*e*) J. Ye, D. J. Dixon and P. S. Hynes, *Chem. Commun.*, 2005, 4481.

