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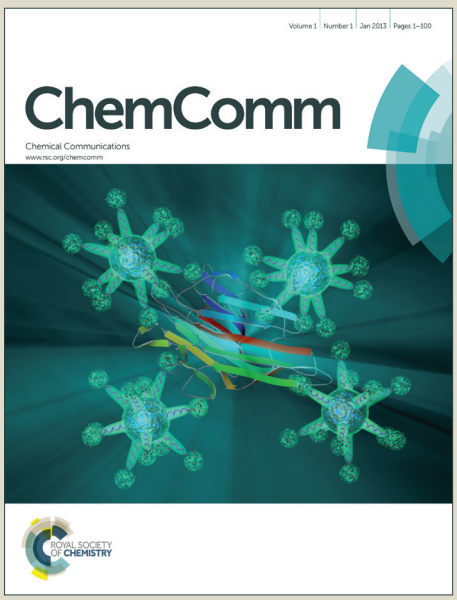

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ARTICLE TYPE

3-Pyrrolyl-oxindoles as efficient nucleophiles for organocatalytic asymmetric synthesis of structurally diverse 3,3'-disubstituted oxindole derivatives†

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A range of 3-pyrrolyl-3,3'-disubstituted oxindoles were smoothly obtained via the reaction of 3-pyrrolyl-oxindoles with nitroalkenes by organocatalyst. The usefulness of the protocol was also demonstrated by the versatile conversions of the Michael adducts into other functionalized 3,3'-disubstituted oxindoles, as well as into the analogues of some valuable natural products.

3,3'-Disubstituted oxindole framework, which contains a tetrasubstituted carbon stereocenter at the C3-position, is the structural motif frequently found in many biologically active molecules and natural products.[1] Inspired by these significant scaffolds, many elegant synthetic methods for their preparation have been developed.[1,2] Even so, considerable efforts are still being directed to the synthesis of structurally diverse 3,3'-disubstituted oxindoles on account of their application as promising drug candidates. To the best of knowledge, among the developed methods, using 3-monosubstituted oxindoles as nucleophiles reacting with different electrophiles should belong to the most straightforward methodology for constructing a tetrasubstituted carbon stereocenter at the C3-position of the oxindole framework.[2,3] Despite the substantial advancements made thus far, exploring novel 3-monosubstituted oxindoles serving as nucleophiles for stereoselective synthesis of new-type chiral 3,3'-disubstituted oxindoles is still an important target for synthetic efforts. In particular, organocatalytic synthesis of this class of molecules has received considerable attentions in recent years.[2]

Since the early report from Barbas III and co-workers on the asymmetric Michael addition of 3-alkyl-substituted oxindoles to nitroalkenes,[4] different 3-monosubstituted oxindoles as Michael donors have been used successfully for reacting with nitroalkenes to construct diverse 3,3'-disubstituted oxindoles bearing vicinal quaternary/tertiary stereocenters.[5] Notably, the nitro-compounds were chosen because of the strong electron withdrawing character and the synthetic versatility of that functional group.[6] However, to the best of knowledge, no report has yet been released relating to the use of 3-pyrrolyl-oxindoles[7] as nucleophiles for the construction of 3-pyrrolyl-3,3'-disubstituted oxindole derivatives. As part of our ongoing investigations aimed at developing new strategies for the synthesis of multifarious 3,3'-disubstituted oxindole derivatives,[8] we have found that a wide scope of optically active 3-pyrrolyl-3,3'-disubstituted oxindoles can be obtained from the Michael addition of 3-pyrrolyl-oxindoles to nitroalkenes in high yields and stereoselectivities with a chiral squaramide-substituted cinchona alkaloid catalyst. Nevertheless, studies on the extension of 3-pyrrolyl-oxindoles addition to other nucleophiles and the versatile transformations of the Michael adducts were also demonstrated. Herein, we wish to report our research progress on this subject.

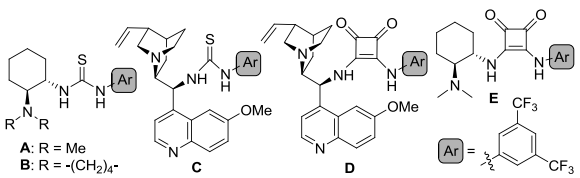

Fig. 1 Catalysts tested in the Michael addition.

To optimize the reaction conditions, the reaction of 3-pyrrolyl-oxindole **1a** and nitroalkene **2a** was employed as a model reaction. We first examined different chiral bifunctional thiourea-tertiary amine catalysts **A-C** (Figure 1). The reactions proceeded smoothly and gave the product in quantitative yields but with moderate enantioselectivities (Table 1, entries 1-3). Next, the reaction was attempted with squaramide-substituted cinchona alkaloid catalyst **D**, there was no improvement in the reactivity and diastereoselectivity, but the enantioselectivity was dramatically improved (Table 1, entry 4 vs 1-3). Another squaramide-tertiary amine catalyst **E** afforded decreased yield and ee value compared with catalyst **D** (Table 1, entry 5 vs 4). Having identified **D** as the strongest candidate of the library, we undertook a screen of solvents for the Michael addition with 10 mol % **D** at room temperature (Table 1, entries 4 and 6-9). It was observed that very good reaction rate and stereocontrol could be obtained when CH_2Cl_2 was used as solvent (Table 1, entry 8). Afterwards, different reaction temperatures and equivalent of **2a** were tested, 0 ^oC and 1.5 equiv of **2a** were found to be optimal for providing high to 94% ee value (Table 1, entries 11 vs 12). Finally, a decrease of the catalyst loading to 5 mol % had no effect on the reactivity and stereoselectivity (Table 1, entry 13). As conditions of choice, we utilized CH_2Cl_2 at 0 ^oC and 5 mol % catalyst **D** with 1.5 equiv niroalkenes to 3-pyrrolyl-oxindoles.

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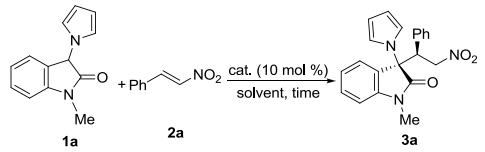
Table 1: Optimizing Reaction Conditionsa

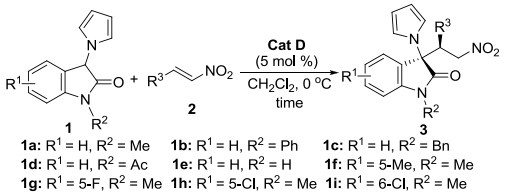


entry	solvent	cat.	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	toluene	**A**	23	95	76:24	48
2	toluene	**B**	23	97	76:24	55
3	toluene	**C**	23	96	77:23	59
4	toluene	**D**	23	98	78:22	85
5	toluene	**E**	59	83	83:17	71
6	mesitylene	**D**	48	96	76:24	88
7	$CHCl_3$	**D**	48	94	78:22	88
8	CH_2Cl_2	**D**	30	97	83:17	91
9	THF	**D**	48	89	70:30	50
10	CH_2Cl_2	**D**	72	93	86:14	93[e]
11	CH_2Cl_2	**D**	50	97	87:13	94[e,f]
12	CH_2Cl_2	**D**	108	95	88:12	94[g,f]
13	CH_2Cl_2	**D**	54	97	87:13	94[e,f,h]

[a] Unless otherwise noted, the reactions were carried out with **1a** (0.1 mmol), **2a** (0.12 mmol), and 10 mol % catalyst in solvent (2 mL) at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Determined by chiral HPLC analysis. [e] Run at 0 °C. [f] **1a** (0.1 mmol) and **2a** (0.15 mmol) were used. [g] Run at -10 °C. [h] 5 mol % **D** was used.

To explore the scope of the reaction, 3-pyrrolyl-oxindole **1a** was firstly reacted with various nitroalkenes to afford a range of 3-pyrrolyl-3,3'-disubstituted oxindoles **3b-q** containing vicinal quaternary/tertiary stereocenters in excellent yields (91-98%) with good diastereoselectivities (71:29 to 96:4 dr) and good to excellent ee values (78-99% ee) (Table 2, entries 1-16). It is interesting to note that not only the electro-donating (entries 1-4) but also the electron-withdrawing substituents (entries 5-13), as well as the position of these substituents on the *β*-benzene ring of nitroalkenes had no obvious effects on the reactivities and stereoselectivities. The introduction of a heteroaryl substituent such as the furyl and thienyl group provided the desired products **3o** and **3p** in 97% yield, 71:29 dr with 78% ee and 96% yield, 80:20 dr with 93% ee, respectively (entries 14-15). Furthermore, the bulkier group, such as 1-naphthyl was found to be compatible under the optimal conditions for giving **3q** with 98% ee value (entry 16). On the other hand, we also examined the behavior of different 3-pyrrolyl-oxindoles **1b-i**. It has been demonstrated that the *N*-methyl substituent of 3-pyrrolyl-oxindole **1a** could be replaced with other units such as *N*-phenyl or *N*-benzyl substituent (entries 17-18). Notably, *N*-Ac substituted substrate **1d** showed the surprising reaction rate (4 h) and furnished the corresponding Michael adduct in 95% yield with 68:32 dr and 82% ee (entry 19). Unprotected 3-pyrrolyl-oxindole **1e** also reacted well with nitroalkene **2a** under the standard conditions (entry 20). Ultimately, the 3-pyrrolyl-oxindole substrates with either electron-rich or electron-poor substituents on the different position of the oxindole phenyl ring were also viable under the optimal conditions, furnishing the desired products in excellent yields with high dr and ee values (entries 21-24). The absolute configuration of **3j** was determined by X-ray analysis, it contains a (*C7R,C14S*) configuration. The configurations of other products were assigned on the assumption of a uniform mechanistic pathway.[9]

Table 2: Substrate Scope for the Asymmetric Michael Addition[a]



entry	**1**	R^3	time (h)	**3**/yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	2-$MeOC_6H_4$ (**2b**)	71	**3b**/91	71:29	93
2	**1a**	3-$MeOC_6H_4$ (**2c**)	69	**3c**/96	88:12	94
3	**1a**	4-$MeOC_6H_4$ (**2d**)	64	**3d**/97	82:18	91
4	**1a**	3,4-$(MeO)_2C_6H_3$ (**2e**)	53	**3e**/94	88:12	94
5	**1a**	2-FC_6H_4 (**2f**)	57	**3f**/97	96:4	79
6	**1a**	3-FC_6H_4 (**2g**)	48	**3g**/97	89:11	94[f]
7	**1a**	4-FC_6H_4 (**2h**)	52	**3h**/96	87:13	94
8	**1a**	2-ClC_6H_4 (**2i**)	57	**3i**/94	87:13	97
9	**1a**	4-BrC_6H_4 (**2j**)	51	**3j**/96	86:14	95
10	**1a**	2,4-$Cl_2C_6H_3$ (**2k**)	53	**3k**/94	83:17	99
11	**1a**	2-$NO_2C_6H_4$ (**2l**)	57	**3l**/91	91:9	97
12	**1a**	4-$NO_2C_6H_4$ (**2m**)	52	**3m**/98	84:16	95
13	**1a**	4-CNC_6H_4 (**2n**)	52	**3n**/96	84:16[e]	84
14	**1a**	2-furyl (**1o**)	52	**3o**/97	71:29	78
15	**1a**	2-thienyl (**1p**)	52	**3p**/96	80:20	93
16	**1a**	1-naphthyl (**1q**)	60	**3q**/94	83:17	98
17	**1b**	Ph (**2a**)	53	**3r**/96	83:17	74
18	**1c**	Ph (**2a**)	50	**3s**/95	93:7	97
19	**1d**	Ph (**2a**)	4	**3t**/95	68:32	82
20	**1e**	Ph (**2a**)	50	**3u**/96	82:18	87
21	**1f**	Ph (**2a**)	75	**3v**/92	84:16	86[f]
22	**1g**	Ph (**2a**)	53	**3w**/94	85:15	94[f]
23	**1h**	Ph (**2a**)	53	**3x**/96	84:16	94
24	**1i**	Ph (**2a**)	53	**3y**/95	86:14	92

[a] Unless otherwise noted, the reactions were carried out with **1** (0.1 mmol), **2** (0.15 mmol), and catalyst **D** (5 mol %) in CH_2Cl_2 (2 mL) at 0 °C. [b]Isolated yield. [c] Determined by HPLC analysis. [d] Determined by chiral HPLC analysis. [e] Dr value was determined by ^{1}H NMR analysis. [f] %ee was determined by HPLC analysis after the derivatization.

Moreover, the reaction of 3-pyrrolyl-oxindoles with some other electrophiles was also attempted in this study (Scheme 1).[10] Under the aforementioned optimal conditions, the aldol addition of **1a** to formaldehyde (**4**) and the Mannich reaction of **1a** with isatin-derived ketimine **6** proceeded smoothly to give hydroxymethyl oxindole **3a'** and bis-3,3'-disubstituted oxindole **3c'** in good results. The α-amination of **1a** with diethyl azodicarboxylate **5** catalyzed by $(DHQD)_2PHAL$[11] was realized, furnishing 3,3'-disubstituted oxindole **3b'** bearing two nitrogen atoms at C3-position. In the presence of Takamoto catalyst **A**, **1a** was able to react with maleimide at room temperature, the

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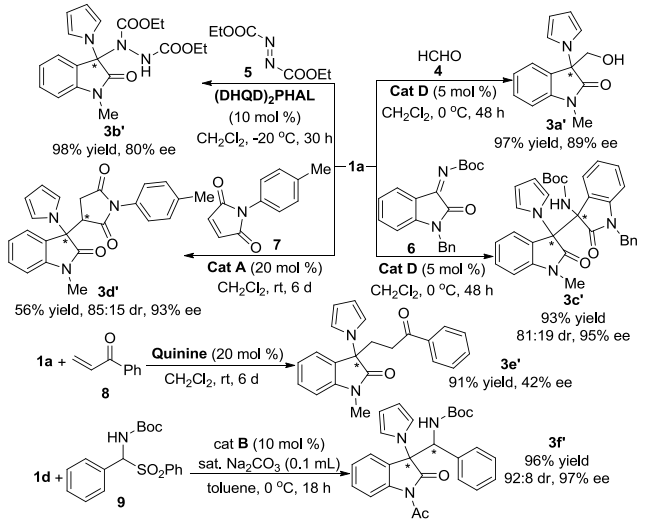
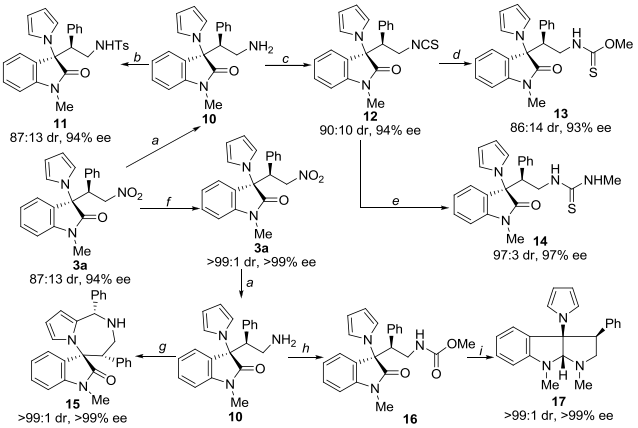
Michael adduct **3d'** was obtained in 56% yield with 85:15 dr and 93% ee but reaction time up to 6 days was needed. Additionally, asymmetric Michael addition reaction of **1a** to terminal alkene **8** with commercial quinine as catalyst was successfully examined, but giving **3e'** with only 42% ee. Finally, Mannich reaction of 3-pyrrolyl-oxindole **1d** with *N*-Boc-imine generated in situ catalyzed by catalyst **B** also occurred well and provided **3f'** in 96% yield with 92:8 dr and 97% ee.



Scheme 1 Experimental results with other electrophiles

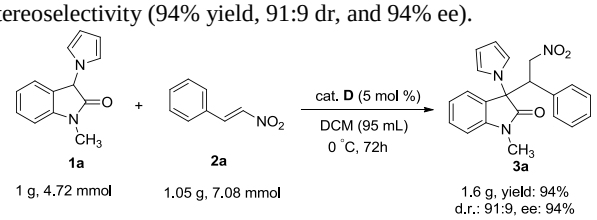
The synthetic utility of the Michael adducts was illustrated by the versatile conversions of the product **3a** into other functionalized and valuable compounds (Scheme 2).[10] The nitro group in **3a** could be converted to amine group by nickel boride reduction to give primary amine **10**. Compound **10** reacted smoothly with 4-toluene sulfonyl chloride to afford another 3,3'-disubstituted oxindole **11**. Nevertheless, the primary amine group in **10** worked well with thiophosgene, leading to *β*-isothiocyanato 3,3'-disubstituted oxindole **12**. And then the isothiocyanato group in **12** was easily transformed to *O*-methyl carbamothiouate group in **13** and 1-methyl thiourea group in **14** by treating with CH_3OH and CH_3NH_2, respectively. To our delight, recrystallization of **3a** from ethanol at room temperature resulted in the corresponding enantiopure material (>99:1 dr and >99% ee). The usefulness of our methodology was also demonstrated by the synthesis of optically active heptacyclic oxindole **15** containing three stereocentres from enantiopure **10** via an intramolecular Aza-Friedel-Crafts reaction. More importantly, a three-step transformation of enantiopure **3a** was realized to afford a pyrrolidinoindoline derivative **17**,[5j] which has a core structure similar to important natural products such as CPC-1, (-)-physostigmine, (-)-pseudophrynaminol, etc.[12] These natural product analogues might possess important biological activity and are therefore valuable for the drug discovery. Notably, the diastereo- and enantioselectivities remained at an excellent level for all of the above transformations.



[a] *Reagents and conditions*: (a) $NiCl_2\ 6H_2O$ (1.0 equiv), $NaBH_4$ (12.0 equiv), CH_3OH, 0 °C to rt, 1 h, quantitative; (b) TsCl (1.5 equiv), NEt_3 (1.0 equiv), CH_2Cl_2, 0 °C to rt, 5 h, 91% yield; (c) Thiophosgene (4.0 equiv), CH_2Cl_2, 0 °C to rt, overnight, 50% yield; (d) NaH (60% in oil, 3.0 equiv), CH_3OH, 0 °C to rt, 1 h, 95% yield; (e) Aqueous solution of CH_3NH_2 (40% w/w, 0.2 mL), 1,4-dioxane, 0 °C to rt, 2 h, 68% yield; (f) Recrystallization from ethanol at rt; (g) (*i*) $MgSO_4$, PhCHO (2.4 equiv), CH_2Cl_2, rt, 3 h; (*ii*) trifluoroacetic acid (2.0 equiv), CH_2Cl_2, rt, 3 d, 96% yield; (h) Chloromethyl formate (4.0 equiv), DMAP (0.4 equiv), Hunig's base (4.5 equiv), CH_2Cl_2, 0 °C to rt, 3 h, 88% yield; (i) $LiAlH_4$ (20.0 equiv), dry THF, 0 °C to reflux, 3 h, 22% yield.

Scheme 2 Transformation of adduct **3a** into other functionalized and valuable compounds[a]

To evaluate the practicability of this transformation, the preparation of compound **3a** was performed on a 1g scale (4.72 mmol of **1a**) with 5 mol% of catalyst **D** under the optimized conditions. As outlined in Scheme 3, the preparative-scale reaction proceeded smoothly with excellent yield and stereoselectivity (94% yield, 91:9 dr, and 94% ee).



Scheme 3 Large-Scale Experiment for the Synthesis of **3a**

In summary, the first methodology using 3-pyrrolyl-oxindoles as nucleophiles addition to nitroalkenes was developed with a chiral squaramide-substituted cinchona alkaloid catalyst. The Michael addition reactions are general and provide entry to a broad range of 3-pyrrolyl-3,3'-disubstituted oxindoles bearing vicinal quaternary/tertiary stereocenters in good to excellent yields and stereoselectivities under mild conditions. The efficient nucleophilicity of 3-pyrrolyl-oxindoles was further investigated by the reactions with some other electrophiles, also delivering the corresponding 3-pyrrolyl-3,3'-disubstituted oxindole compound with acceptable results. The usefulness of the protocol was successfully demonstrated by the versatile conversions of the adducts into other functionalized 3,3'-disubstituted oxindoles, as well as into the analogues of some valuable natural products. The biological evaluation and the studies on structure-activity relationships for these obtained chiral compounds, and the application of 3-pyrrolyl-oxindoles in other asymmetric transformations are in progress.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, spectral data of new compounds, and crystallographic data See DOI: 10.1039/b000000x/

1 (a) J. F. M. da Silva, S. J. Garden and A. C. Pinto, *J. Braz. Chem. Soc.* 2001, **12**, 273; (b) B. S. Jensen, *CNS Drug Rev.* 2002, **8**, 353; (c) H. Lin and S. J. Danishefsky, *Angew. Chem., Int. Ed.* 2003, **42,** 36; (d) C. Marti and E. M. Carreira, *Eur. J. Org. Chem*. 2003, 2209; (e) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.* 2007, **46**, 8748; (f) J. J. Badillo, N. V. Hanhan and A. K. Franz, *Curr. Opin. Drug Discov. Devel.* 2010, **13**, 758; (g) G. S. Singh and Z. Y. Desta, *Chem. Rev*. 2012, **112**, 6104.

2 For selected reviews, see: (a) B. M. Trost and M. K. Brennan, *Synthesis* 2009, 3003; (b) Y.-L. Liu and J. Zhou, *Adv. Synth. Catal*. 2010, **352**, 1381; (c) A.-N. R. Alba and R. Rios, *Chem. Asian J*. 2011, *6*, 720; (d) Shen, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 327; (e) R. Rios, *Chem. Soc. Rev.* 2012, **41**, 1060; (f) N. R. Ball-Jones, J. J. Badillo and A. K. Franz, *Org. Biomol. Chem*. 2012, **10**, 5165; (g) R. Dalpozzo, G. Bartoli and G. Bencivenni, *Chem. Soc. Rev*. 2012, **41**, 7247; (h) P. Chauhan and S. S. Chimni, *Tetrahedron: Asymmetry* 2013, **24**, 343; (i) L. Hong and R. Wang, *Adv. Synth. Catal*. 2013, **355**, 1023; (j) D. Cheng, Y. Ishihara, B. Tan and C. F., III. Barbas, *ACS Catal*. 2014, **4**, 743.

3 For selected examples on 3-prochiral oxindoles reacting with different electrophiles, see: (a) B. M. Trost and M. U. Frederiksen, *Angew. Chem., Int. Ed.* 2005, **44**, 308; (b) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura and M. Sodeoka, *J. Am. Chem. Soc*. 2005, **127**, 10164; (c) B. M. Trost and Y. Zhang, *J. Am. Chem. Soc*. 2006, **128**, 4590; (d) S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru and M. Shiro, *Angew. Chem., Int. Ed.* 2007, **46**, 8666; (e) X. Tian, K. Jiang, J. Peng, W. Du and Y.-C. Chen, *Org. Lett.* 2008, **10**, 3583; (f) K. Jiang, J. Peng, H.-L. Cui and Y.-C. Chen, *Chem. Commun.*, 2009, 3955; (g) R. He, C. Ding and K. Maruoka, *Angew. Chem., Int. Ed.* 2009, **48**, 4559; (h) Z.-Q. Qian, F. Zhou, T.-P. Du, B.-L. Wang, M. Ding, X.-L. Zhao and J. Zhou, *Chem. Commun.*, 2009, 6753; (i) P. Galzerano, G. Bencivenni, F. Pesciaioli, A. Mazzanti, B. Giannichi, L. Sambri, G. Bartoli and P. Melchiorre, *Chem. Eur. J*. 2009, **15**, 7846; (j) X. Li, Z.-G. Xi, S. Luo and J.-P. Cheng, *Org. Biomol. Chem.*, 2010, **8**, 77; (k) Y.-M. Li, X. Li, F.-Z. Peng, Z.-Q. Li, S.-T. Wu, Z.-W. Sun, H.-B. Zhang and Z.-H. Shao, *Org. Lett*. 2011, **13**, 6200; (l) T. Zhang, Z. Qiao, Y. Wang, N. Zhong, L. Liu, D. Wang and Y.-J. Chen, *Chem. Commun.*, 2013, **49**, 1636.

4 J. Bui, S. Syed and C. F. III. Barbas, *J. Am. Chem. Soc*. 2009, **131**, 8758.

5 (a) Y. Kato, M. Furutachi, Z. Chen, H. Mitsunuma, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc*. 2009, **131**, 9168; (b) R. He, S. Shirakawa and K. Maruoka, *J. Am. Chem. Soc*. 2009, **131**, 16620; (c) X. Li, B. Zhang, Z.-G. Xi, S. Luo and J.-P. Cheng, *Adv. Synth. Catal*. 2010, **352**, 416; (d) M. Ding, F. Zhou, Z.-Q. Qian and J. Zhou, *Org. Biomol. Chem.*, 2010, **8**, 2912; (e) M. Ding, F. Zhou, Y.-L. Liu, C.-H. Wang, X.-L. Zhao and J. Zhou, *Chem. Sci*. 2011, **2**, 2035; (f) X.-L. Liu, Z.-J. Wu, X.-L. Du, X.-M. Zhang and W.-C. Yuan, *J. Org. Chem*. 2011, **76**, 4008; (g) Y.-Y. Han, Z.-J. Wu, W.-B. Chen, X.-L. Du, X.-M. Zhang and W.-C. Yuan, *Org. Lett.* 2011, **13**, 5064; (h) X. Li, Y.-M. Li, F.-Z. Peng, S.-T. Wu, Z.-Q. Li, Z.-W. Sun, H.-B. Zhang and Z.-H. Shao, *Org. Lett.* 2011, **13**, 6160; (i) X. Chen, W. Zhu, W. Qian, E. Feng, Y. Zhou, J. Wang, H. Jiang, Z.-J. Yao and H. Liu, *Adv. Synth. Catal*. 2012, **354**, 2151; (j) M. Retini, G. Bergonzini and P. Melchiorre, *Chem. Commun.*, 2012, **48**, 3336; (k) C. Wang, X. Yang and D. Enders, *Chem. Eur. J*. 2012, **18**, 4832; (l) X. Dou, B. Zhou, W. Yao, F. Zhong, C. Jiang and Y. Lu, *Org. Lett.* 2013, **15**, 4920; (m) B.-D. Cui, W.-Y. Han, Z.-J. Wu, X.-M. Zhang and W.-C. Yuan, *J. Org. Chem.* 2013, **78**, 8833; (n) X. Dou, W. Yao, B. Zhou and Y. Lu, *Chem. Commun.*, 2013, **49**, 9224; (o) L. Zou, X. Bao, Y. Ma, Y. Song, J. Qu and B. Wang, *Chem. Commun.*, 2014, **50**, 5760.

6 For selected reviews about Michael additions to nitroalkenes, see: (a) O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.* 2002, 1877; (b) J. Christoffers, G. Koripelly, A. Rosiak and M. Rössle, *Synthesis* 2007, 1279; (c) S. B. Tsogoeva, *Eur. J. Org. Chem.* 2007, 1701.

7 For the synthesis of 3-pyrrolyl-oxindoles, see: (a) J. Azizian, A. R. Karimi, Z. Kazemizadeh, A. A. Mohammadi and M. Mohammadizadeh, *J. Org. Chem.* 2005, **70**, 1471; (b) B. K. Banik and M. Cardona, *Tetrahedron Lett.* 2006, **47**, 7385; (c) B. K. Banik, I. Garcia, F. R. Morales and C. Aguilar, *Heterocycl. Commun*. 2007, **13**, 109; (d) J. S. Yadav, B. V. Subba Reddy, R. Jain and C. S. Reddy, *Tetrahedron Lett*. 2007, **48**, 3295; (e) R. Sridhar, B. Srinivas, V. Pavan Kumar, V. Prakash Reddy, A. Vijay Kumar and K. Rama Rao, *Adv. Synth. Catal*. 2008, **350**, 1489; (f) M. A. Kumar, A. B. Krishna, B. H. Babu, C. B. Reddy and C. S. Reddy, *Synth. Commun*. 2008, 3456; (g) A. R. Karimi, F. Behzadi and M. M. Amini, *Tetrahedron Lett.* 2008, **49**, 5393; (h) H. M. Meshram, B. R. V. Prasad and D. A. Kumar, *Tetrahedron Lett*. 2010, **51**, 3477; (i) S. Sarkar, B. Saha and S. Naskar, *J. Chem. Res*. 2012, 581.

8 (a) W.-B. Chen, Z.-J. Wu, J. Hu, L.-F. Cun, X.-M. Zhang and W.-C. Yuan, *Org. Lett.* 2011, **13**, 2472; (b) Y.-Y. Han, W.-B. Chen, W.-Y. Han, Z.-J. Wu, X.-M. Zhang and W.-C. Yuan, *Org. Lett*. 2012, **14**, 490; (c) Y.-Y. Han, W.-Y. Han, X. Hou, X.-M. Zhang and W.-C. Yuan, *Org. Lett*. 2012, **14**, 4054; (d) Y.-H. Liao, X.-L. Liu, Z.-J. Wu, X.-L. Du, X.-M. Zhang and W.-C. Yuan, *Chem. Eur. J*. 2012, **18**, 6679; (e) X.-L. Liu, W.-Y. Han, X.-M. Zhang and W.-C. Yuan, *Org. Lett.* 2013, **15**, 1246; (f) W. Y. Han, S. W. Li, Z. J. Wu, X. M. Zhang and W. C. Yuan, *Chem. Eur. J*. 2013, **19**, 5551; (g) B.-D. Cui, J. Zuo, J.-Q. Zhao, M.-Q. Zhou, Z.-J. Wu, X.-M. Zhang and W.-C. Yuan, *J. Org. Chem*. 2014, **79**, 5305.

9 For details, see the Supporting Information.

10 For the details of reaction procedure, see the Supporting Information.

11 For selected examples on the $(DHQD)_2PHAL$-catalyzed asymmetric reaction, see: (a) D. C. Whitehead, R. Yousefi, A. Jaganathan and B. Borhan, *J. Am. Chem. Soc.*, 2010, **132**, 3298; (b) Q. Yin and S.-L. You, *Org. Lett.*, 2013, **15**, 4266; (c) M. Wilking, C. Mück-Lichtenfeld, C. G. Daniliuc and U. Hennecke, *J. Am. Chem. Soc.*, 2013, **135**, 8133; (d) Q. Yin and S.-L. You, *Org. Lett.*, 2014, **16**, 2426; (e) L. Li, C. Su, X. Liu, H. Tian and Y. Shi, *Org. Lett.*, 2014, **16**, 3728.

12 For a selected review, see U. Anthoni, C. Christophersen and P. H. Nielsen, in *Alkaloids: Chemical and Biological Perspectives*. *Vol*. **13**, Wiley, New York, 1999, p. 163. For selected examples, see: (a) J. S. Carle and C. Christophersen, *J. Am. Chem. Soc*. 1979, **101**, 4012; (b) J. S. Carle and C. Christophersen, *J. Org. Chem*. 1980, **45**, 1586; (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) A. Huang, J. J. Kodanko and L. E. Overman, *J. Am. Chem. Soc*. 2004, **126**, 14043; (e) M. Kitajima, I. Mori, K. Arai, N. Kogure and H. Takayama, *Tetrahedron Lett.* 2006, **47**, 3199.