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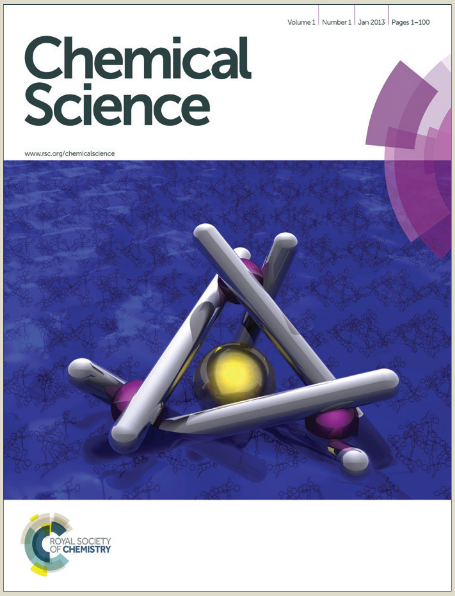

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ARTICLE TYPE

Stereoselective Construction of All-Carbon Quaternary Center by Means of Chiral Phosphoric Acid: Highly Enantioselective Friedel-Crafts Reaction of Indoles with β,β-Disubstituted Nitroalkenes

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We describe herein a chiral phosphoric acid catalyzed Friedel-Crafts reaction of indoles with β-alkoxycarbonyl-β-disubstituted nitroalkenes. A wide variety of substrates participated in this reaction to afford indoles having all-carbon quaternary centers with excellent selectivities (up to 97% ee). Further investigation suggested that the olefin geometry and the employment of NH-indole derivatives are responsible for both reactivity and selectivity.

Introduction

The indole skeleton is prevalent in many biologically active compounds, natural products, and industrially useful compounds. Because of their important biological activities, the development of new approaches for the synthesis of enantio-enriched indole derivatives is a subject of considerable interest.

In this context, the asymmetric Friedel-Crafts reaction of indoles with various electrophiles is one of the most straightforward methods to afford chiral indole derivatives.[1] Much effort has been expended on the development of novel and effective methods.[2–6] However, most of the Michael-type asymmetric Friedel-Crafts reactions reported so far have focused on β-monosubstituted electron-deficient alkenes. The corresponding reactions with β,β-disubstituted olefins are conspicuously limited despite the fact that those processes offer synthetically useful, chiral indole derivatives with all-carbon quaternary center. The intrinsic steric hindrance around the β-carbon dramatically decreases the reactivity, thereby lending stereocontrol of the new bond-forming step extremely difficult.[7]

The first asymmetric Friedel-Crafts reaction of indoles with β,β-disubstituted electron-deficient alkenes was reported by Kwiatkowski and coworkers by means of cinchona alkaloid in 2012.[8] Although the results were striking, one of the drawbacks was the moderate to good selectivities (48–80% ees). The first excellent enantioselective Friedel-Crafts reaction for the construction of an all-carbon quaternary center was accomplished by Jia and coworkers with a chiral Ni-BOX complex in 2013.[9] The CF_3-containing all-carbon quaternary center was elegantly controlled with up to 97% ee. Quite recently, Arai and coworkers achieved a highly enantioselective Friedel-Crafts reaction of indole with nitrostyrene derived from isatin.[10] Zhang subsequently found that an α,β-unsaturated aldehyde derived from isatin was also a good counterpart for the reaction by means of the Hayashi-Jørgensen catalyst.[11] In spite of such achievements, the development of new and effective methods for the asymmetric construction of all-carbon quaternary centers remains a challenge.

We wish to report herein the first example of a chiral phosphoric acid catalyzed enantioselective Friedel-Crafts reaction of indoles with β,β-disubstituted nitroalkenes. The key to achieve this goal is the employment of a nitroalkene having an ester group (electron-withdrawing moiety) at the β-position,[12] and the desired products with all-carbon quaternary centers were obtained with good to excellent selectivities (up to 97% ee).[13, 14]

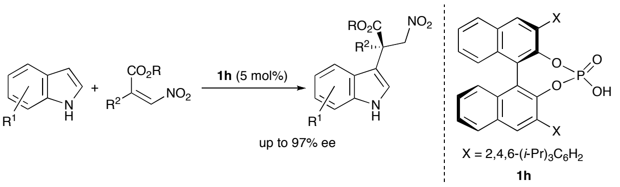
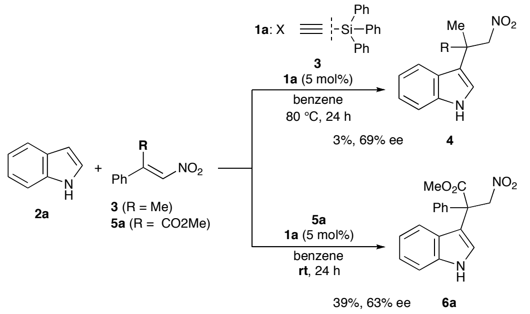


Figure 1. Enantioselective Friedel-Crafts reaction of indoles with β-alkoxycarbonyl nitroalkenes.

Results and Discussion

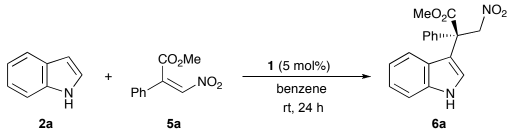
The first trial was conducted by using α-methyl-β-nitrostyrene **3** and chiral phosphoric acid **1a** (X= $SiPh_3$),[15] which exhibited excellent selectivity in the Friedel-Crafts reaction of indole (**2a**) with the simple β-monosubstituted nitroalkenes we previously developed.[6a] Adduct **4** was obtained with good selectivity (69% ee), but the chemical yield was miserably low (3%). Altering the reaction conditions (catalyst, solvent, reaction temperature, and additive) improved neither chemical yield nor enantioselectivity. Fortunately, changing the nitrostyrene moiety from **3** to α-methoxycarbonyl-β-nitrostyrene **5a** offered promising results. The reaction proceeded under mild conditions (room temperature, cf. 80 °C in the case of **3**) and desired compound **6a** was obtained in 39% yield with 63% ee.



Scheme 1. Reactivity difference of substituent (Me vs CO$_2$Me).

Entry 1 shows the results when **1a** was used. Examination of the catalyst suggested that bulkiness of the catalyst was the key to achieving excellent selectivity (Entries 2–8). In contrast to the low selectivity when **1b** having an electron-withdrawing group was used, the use of catalysts having sterically hindered groups, such as a 9-anthryl group and a mesityl group, led to good selectivity (63% ee in each case, Entries 3 and 4). 2,4,6-Triisopropylphenyl-substituted catalyst (TRIP) **1h** turned out to be the most effective in terms of selectivity (88% ee), although the chemical yield was low (24%). We already found that the addition of molecular sieves had a beneficial effect on the chiral phosphoric acid catalyzed Friedel-Crafts reaction of indole with β-monosubstituted nitroalkenes.[6a,c] The addition of molecular sieves 5Å dramatically enhanced the reactivity to give the corresponding adduct **6a** in 74% yield without erosion of selectivity (88% ee, Entry 9). Employment of the mixed solvent system (cyclohexane/CH$_2$Cl$_2$ = 4/1, v/v) further enhanced both chemical yield and enantioselectivity of **6a** to excellent levels (91% with 92% ee, Entry 11).

Table 1. Screening for catalyst (*R*)-**1**.[a]



Entry	X	Yield [%][b]	Ee [%][c]
1	SiPh$_3$ (**1a**)	39	63
2	4-NO$_2$C$_6$H$_4$ (**1b**)	10	7
3	9-Anthryl (**1c**)	13	63
4	2,4,6-Me$_3$C$_6$H$_2$ (**1d**)	24	63
5	2,6-(*i*Pr)$_2$-4-PhC$_6$H$_2$ (**1e**)	75	76
6	2,6-(*i*Pr)$_2$-4-(9-Anthryl)C$_6$H$_2$ (**1f**)	38	70
7	2,6-(*i*Pr)$_2$C$_6$H$_3$ (**1g**)	16	49
8	2,4,6-(*i*Pr)$_3$C$_6$H$_2$ (**1h**)	24	88
9[d]	2,4,6-(*i*Pr)$_3$C$_6$H$_2$ (**1h**)	74	88
10[d,e]	2,4,6-(*i*Pr)$_3$C$_6$H$_2$ (**1h**)	89	90
11[d,e,f]	2,4,6-(*i*Pr)$_3$C$_6$H$_2$ (**1h**)	91	92

[a] Unless otherwise noted, all reactions were conducted with 0.20 mmol of **2a** and 0.40 mmol of nitrostyrene **5a** in the presence of chiral phosphoric acid **1** (5 mol%) in benzene (1.0 mL) at room temperature. [b] Isolated yield. [c] DAICEL CHIRALCEL AD-H®, flow rate = 1.0 mL/min, hexane/*i*PrOH = 10/1. [d] MS5Å was added. [e] *c*-hexane/CH$_2$Cl$_2$ (v/v = 4/1) was used instead of benzene. [f] 1.5 equiv. of **5a** was employed.

The reaction outcome was little sensitive to variation of the ester moiety (Figure 2). Corresponding adducts **6b**–**e** having ethyl, isopropyl, *tert*-butyl, and benzyl esters were obtained with excellent selectivities (over 86% ee). The selectivity of **6e** that had a benzyl ester moiety, in particular, was almost perfect, although the chemical yield was moderate (67%, 97% ee). Based on these results, an examination of the substrate scope was conducted using nitroalkene with methyl ester.

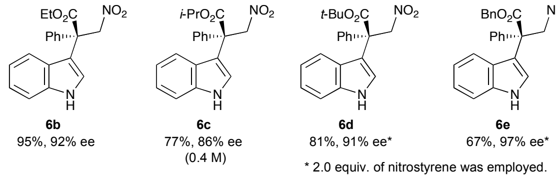
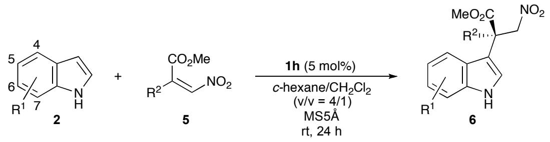


Figure 2. Effect of ester group.

The substrate scope of this asymmetric reaction is illustrated in Table 2.[16] Nitrostyrenes having *p*-tolyl, *p*-methoxyphenyl, *p*-trifluoromethylphenyl, 2-naphthyl, and 2-thienyl groups afforded corresponding adducts (**6f**–**j**) with excellent selectivities (≥ 89% ee, entries 1–5). As expected, the position of the substituent on the aromatic ring of nitrostyrene was important to realize good chemical yield: whereas nitrostyrene with an *m*-tolyl group afforded adduct **6k** in good chemical yield with excellent selectivity (70%, 91% ee, entry 6), **5l** with an *o*-tolyl group did not lead to the formation of the desired adduct (entry 7). In addition, this method is applicable to aliphatic nitroalkenes, albeit with moderate chemical yields (≥ 85% ee, entries 8 and 9).

Indoles with various substituents at 5,6,7-positions afforded corresponding adducts **6o**–**v** in good yields with excellent selectivities (88–94% ee, entries 10–17) regardless of the electronic circumstances. It should be noted that 7-methylindole afforded corresponding adduct **6v** with excellent selectivity (88% ee, entry 17) although 7-methylindole led to low selectivity in the asymmetric Friedel–Crafts reaction with α,β-unsaturated acyl phosphonates (19% ee).[6b] 2-Methylindole, however, led to both low enantioselectivity and low chemical yield (41%, 26% ee). The absolute configurations of those products were surmised as depicted in Figure 2 and Tables 1 and 2 by analogy to **6a**, whose absolute stereochemistry was unambiguously established by single-crystal X-ray analysis after some transformations (*vide infra*).

Table 2. Substrate scope.[a]

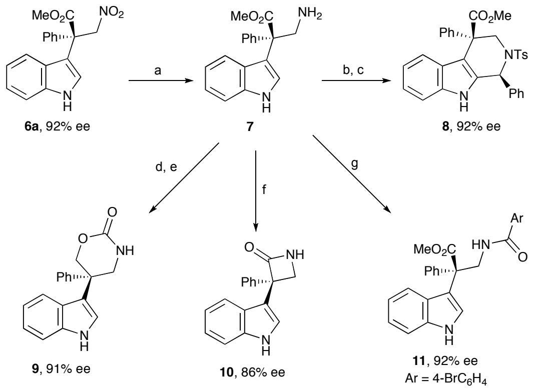


Entry	R^1	R^2	**6**	Yield [%][b]	Ee [%][c]
1	H (**2a**)	4-MeC$_6$H$_4$ (**5f**)	**6f**	87	89
2[d]	H (**2a**)	4-MeOC$_6$H$_4$ (**5g**)	**6g**	81	89
3[e]	H (**2a**)	4-CF$_3$C$_6$H$_4$ (**5h**)	**6h**	72	93
4[f]	H (**2a**)	2-Naphthyl (**5i**)	**6i**	88	90
5	H (**2a**)	2-Thienyl (**5j**)	**6j**	75	89
6	H (**2a**)	3-MeC$_6$H$_4$ (**5k**)	**6k**	70	91
7	H (**2a**)	2-MeC$_6$H$_4$ (**5l**)	**6l**	trace	–

8	H (**2a**)	$PhCH_2CH_2$ (**5m**)	**6m**	52	87
9	H (**2a**)	Bu (**5n**)	**6n**	43	85
10	5-Me (**2b**)	Ph (**5a**)	**6o**	87	93
11	5-OBn (**2c**)	Ph (**5a**)	**6p**	80	90
12	5-F (**2d**)	Ph (**5a**)	**6q**	72	94
13	5-Cl (**2e**)	Ph (**5a**)	**6r**	72	94
14[e]	5-Br (**2f**)	Ph (**5a**)	**6s**	75	91
15[e]	5-I (**2g**)	Ph (**5a**)	**6t**	57	91
16[f]	6-Cl (**2h**)	Ph (**5a**)	**6u**	61	89
17[g]	7-Me (**2i**)	Ph (**5a**)	**6v**	88	88
18[e]	2-Me (**2j**)	Ph (**5a**)	**6w**	41	26

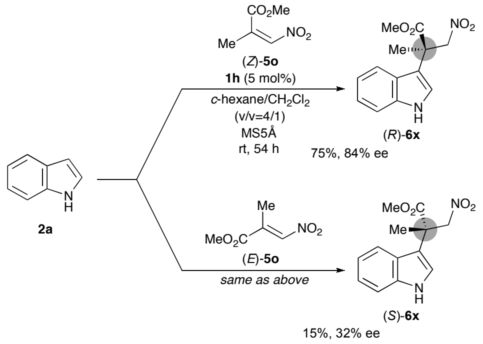
[a] Unless otherwise noted, all reactions were conducted with 0.20 mmol of **2** and 0.30 mmol of nitrostyrene **5** in the presence of chiral phosphoric acid **1h** (5 mol%) and MS5A in cyclohexane/CH_2Cl_2 (v/v = 4/1, 1.0 mL). [b] Isolated yield. [c] Enantiomeric excess was determined with a chiral stationary phase. [d] 53 h. [e] 0.5 mL of cyclohexane/CH_2Cl_2 (v/v = 4/1) was employed. [f] 67 h. [g] 48 h.

The quaternary stereogenic center thus constructed was maintained through some transformations (Scheme 2). The reduction of the nitro group by the combination of $NaBH_4$ and $NiCl_2$•$6H_2O$ followed by the Pictet-Spengler reaction with benzaldehyde afforded tetrahydro-β-carboline **8**, which is found in many useful biologically active compounds, in 78% yield.[3c,17] Synthetically important cyclic carbamate **9** and β-lactam **10** were also obtained from primary amine **7** with almost retaining the chiral information. Bromobenzamide **11** gave a nice single crystal whose X-ray analysis allowed us to determine the absolute configuration.[18]



Scheme 2. Further transformations to more complex framework. Conditions: (a) $NaBH_4$ (5.0 equiv.), $NiCl_2$•$6H_2O$ (1.2 equiv.), MeOH, rt, 60 min; (b) PhCHO (1.2 equiv.), CF_3CO_2H, $MgSO_4$, CH_2Cl_2, rt, 48 h, 97% (2 steps, single diastereomer); (c) TsCl (5.0 equiv.), Et_3N (6.0 equiv.), CH_2Cl_2, reflux, 6 h, 80%, 92% ee; (d) $LiAlH_4$ (1.5 equiv.), THF, 0 °C, 10 min; (e) triphosgene (0.5 equiv.), *i*Pr_2NEt, CH_2Cl_2, 0 °C, 3 h, 70%, 91% ee (3 steps); (f) *i*PrMgBr (8.0 equiv.), THF, rt, 1 h, 50%, 86% ee (2 steps); (g) 4-bromobenzoyl chloride (1.5 equiv.), pyridine (2.0 equiv.), DMAP, CH_2Cl_2, rt, 4.5 h, 70%, 92% ee (2 steps).

Further examination revealed that the enantioselectivity was strongly governed by the olefin geometry (Scheme 3). (*Z*)-β-Methyl nitroalkene **5o** afforded corresponding adduct **6x** in 75% yield with 84% ee in favor of the *R*-isomer. On the other hand, the *S*-isomer was favored in the reaction of (*E*)-nitroalkene **5o**, albeit with lower enantioselectivity (32% ee). These results suggest that indole attacks the same enantioface of the nitroalkene moiety irrespective of the geometry of alkene, and the *syn*-orientation of the ester group and the nitro group is the key to achieve both good chemical yield and excellent selectivity.



Scheme 3. Effect of alkene geometry.

The NH group of indole derivatives is also responsible for both reactivity and selectivity (Figure 3). *N*-Methylindole (**12**) afforded adduct **13** in low yield with considerably low selectivity (20%, 8% ee). This result clearly suggests that the Friedel-Crafts reaction proceeded via a 12-membered-ring transition state[19,20] in which concomitant activation of the indole N–H moiety by phosphoryl oxygen and the nitro group by a Brønsted acidic site is involved.

The proposed transition state model of this reaction is illustrated in the lower part of Figure 3. Due to the steric repulsion between the indole (or nitroalkene) and the triisopropylphenyl group at 3,3'-positions of the catalyst, the indole and the nitroalkene assume an *endo* orientation,[19i,20a] thereby affording the *R*-isomer. The low reactivity and selectivity in (*E*)-nitroalkenes are ascribed to the steric repulsion between the R group of alkene and the catalyst.

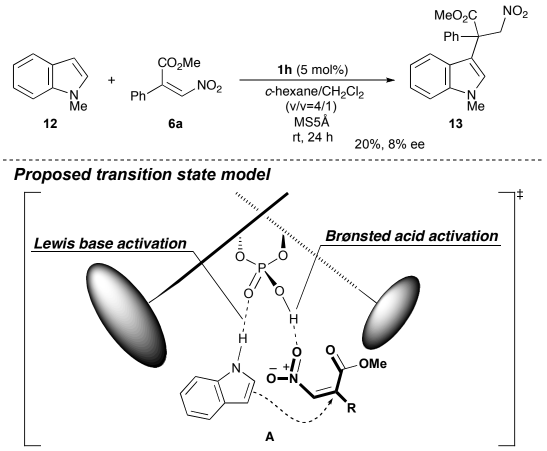


Figure 3. Reaction of *N*-Me indole moiety and proposed transition state model.

Conclusions

In summary, we have developed a highly enantioselective Friedel-Crafts reaction of indoles with β-alkoxycarbonyl-β-disubstituted nitroalkenes. The salient feature of the reaction is that the enantioselectivity of the all-carbon quaternary stereogenic center, which is considered the most challenging target in the field of asymmetric reactions, could be very well controlled (up to 97% ee). Furthermore, the corresponding adduct was readily converted into synthetically useful tetrahydro-β-carboline, cyclic carbamate, and β-lactam without erosion of chiral information. Further work is underway to clarify the details of the stereocontrol mechanism and its application to other asymmetric reactions for the construction of all-carbon quaternary centers.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data for all new compounds. See DOI: 10.1039/b000000x/

1 For reviews, see: (a) D. Roca-Lopez, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* 2010, **21**, 2561; (b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* 2007, **107**, 5471.

2 For a review on chiral Brønsted acid catalyzed Friedel–Crafts alkylation, see: (a) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* 2009, **38**, 2190. Selected examples, see: (b) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* 2002, **124**, 1172; (c) Y.-Q. Wang, J. Song, R. Hong, H. Li, L. Deng, *J. Am. Chem. Soc.* 2006, **128**, 8156; (d) M. Terada, K. Sorimachi, *J. Am. Chem. Soc.* 2007, **129**, 292; (e) Q. Kang, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* 2007, **129**, 1484; (f) G. B. Rowland, E. B. Rowland, Y. Liang, J. A. Perman, J. C. Antilla, *Org. Lett.* 2007, **9**, 2609; (g) Y.-X. Jia, J. Zhang, S.-F. Zhu, C.-M. Zhang, Q.-L. Zhou, *Angew. Chem. Int. Ed.* 2007, **46**, 5565; (h) H.-Y. Tang, A.-D. Lu, Z.-H. Zhou, G.-F. Zhao, L.-N. He, C.-C. Tang, *Eur. J. Org. Chem.* 2008, 1406; (i) Y.-F. Sheng, Q. Gu, A.-J. Zhang, S.-L. You, *J. Org. Chem.* 2009, **74**, 6899; (j) W. Kashikura, J. Itoh, K. Mori, T. Akiyama, *Chem. Asian. J.* 2010, **5**, 470; (k) Y. Qian, G. Ma, A. Lv, H.-L. Zhu, J. Zhao, V. H. Rawal, *Chem. Commun.* 2010, **46**, 3004; (l) L.-Y. Chen, H. He, W.-H. Chan, A. W. M. Lee, *J. Org. Chem.* 2011, **76**, 7141; (m) T. Courant, S. Kumarn, L. He, P. Retailleau, G. Masson, *Adv, Synth. Catal,* 2013, **355**, 836.

3 The selected examples of Michael-type Friedel-Crafts reaction of indoles with β-monosubstituted nitroalkenes, see: (a) W. Wang, J. Wang, H. Li, *Angew. Chem. Int. Ed.* 2005, **44**, 1369; (b) W. Zhuang, R. G. Hazell, K. A. Jørgensen, *Org. Biomol. Chem.* 2005, **3**, 2566; (c) R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem. Int. Ed.* 2005, **44**, 6576; (d) Y.-X. Jia, S.-F. Zhu, Y. Yang, L.-X. Wang, Q.-L. Zhou, *J. Org. Chem.* 2006, **71**, 75; (e) S.-F. Lu, D.-M. Du, J. Xu, *Org. Lett.* 2006, **8**, 2115; (f) E. M. Fleming, T. McCabe, S. J. Connon, *Tetrahedron*, 2006, **47**, 7037; (g) M. Ganesh, D. Seidel, *J. Am. Chem. Soc.* **2008**, 130, 16464; (h) N. Yokoyama, T. Arai, *Chem. Commun.* 2009, 3285; (i) H. Liu, D.-M Du,. *Adv. Synth. Catal.* 2010, **352**, 1113; (j) H. Y. Kim, S. Kim, K. Oh, *Angew. Chem., Int. Ed.* 2010, **49**, 4476; (k) F. Guo, G. Lai, S. Xiong, S. Wang, Z. Wang, *Chem. Eur. J.* 2010, **16**, 6438; (l) N. Takenaka, J. Chen, B. Captain, R. S. Sarangthem, A. Chandrakumar, *J. Am. Chem. Soc.* 2010, **132**, 4536; (m) J. Wu, X. Li, F. Wu, B. Wan, *Org. Lett.* 2011, **13**, 4834.

4 The selected examples of Michael-type Friedel-Crafts reaction of indoles with α,β-unsaturated carbonyl compounds, see: (a) H.-Y. Tang, A.-D. Lu, Z.-H. Zhou, G.-F. Zhao, L.-N. He, C.-C. Tang, *Eur. J. Org. Chem.* 2008, 1406; (b) A. Scettri, R. Villano, M. R. Acocella, *Molecules*, 2009, **14**, 3030; (c) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem. Int. Ed.* 2008, **47**, 593; d) S. Adachi, F. Tanaka, K. Watanabe, T. Harada, *Org. Lett.* 2009, **11**, 5206; (e) N. Madhavan, T. Takatani, C. D. Sherrill, M. Weck, *Chem. Eur. J.,* 2009, **15**, 1186; (f) A. J. Boersma, B. L. Feringa, G. Roelfes, *Angew. Chem. Int. Ed.* 2009, **48**, 3346; (g) H. Jiang, M. W. Paixão, D. Monge, K. A. Jørgensen, *J. Am. Chem. Soc.* 2010, **132**, 2775.

5 The selected examples of the Michael reaction of carbonyl compounds with β-monosubstituted nitroalkenes, see: (a) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* 2005, **44**, 4212; (b) C. Palomo, S. Vera, A. Mielgo, E. Gómez-Bengoa, *Angew. Chem. Int. Ed.* 2006, **45**, 5984; (c) M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem. Int. Ed.* 2008, **47**, 1871; (d) P. García-García, A. Ladépêche, R. Halder, B. List, *Angew. Chem. Int. Ed.* 2008, **47**, 4719; (f) H. Uehara, C.F. Barbas III, *Angew. Chem. Int. Ed.* 2009, **48**, 9848; (g) M. Wiesner, M. Neuburger, H. Wennemers, *Chem. Eur. J.* 2009, **15**, 10103; (h) M. Wiesner, G. Upert, G. Angelici, H. Wennemers, *J. Am. Chem. Soc.* 2010, **132**, 6; (i) S. Belot, A. Quintard, N. Krause, A. Alexakis, *Adv. Synth. Catal.* 2010, **352**, 667; (j) M. Wiesner, H. Wennemers, *Synthesis* 2010, 1568; (k) S. Zhu, S. Yu, Y. Wang, D. Ma, *Angew. Chem. Int. Ed.* 2010, **49**, 4656; (l) Y. Arakawa, M. Wiesner, H. Wennemers, *Adv. Synth. Catal.* 2011, **353**, 1201; (m) H. Rahaman, Á. Madarász, I. Pápai, P. M. Pihko, *Angew. Chem. Int. Ed.* 2011, **50**, 6123.

6 For Michael-type asymmetric Friedel-Crafts reaction developed by our group under chiral phosphoric acid catalysis, see: (a) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem. Int. Ed.* 2008, **47**, 4016; (b) P. Bachu, T. Akiyama, *Chem. Commun.* 2010, **46**, 4112; (c) T. Sakamoto, J. Itoh, K. Mori, T. Akiyama, *Org. Biomol. Chem.* 2010, **8**, 5448.

7 For the asymmetric Michael reaction of β,β-disubstituted α,β-unsaturated carbonyl compounds with CH_3NO_2, see: (a) C. E. T. Mitchell, S. E. Brenner, S. V. Ley, *Chem. Commun.* 2005, 5346; (b) P. Li, Y. Wang, X. Liang, J. Ye, *Chem. Commun.* 2008, 3302; (c) P. Kwiatkowski, K. Dudziński, D. Łyżwa, *Org. Lett.* 2011, **13**, 3624; (d) K. Akagawa, K. Kudo, *Angew. Chem. Int. Ed.* 2012, **51**, 12786. For the asymmetric cyanation of β,β-disubstituted α,β-unsaturated carbonyl compounds or nitroalkenes, see: (e) C. Mazet, E. N. Jacobsen, *Angew. Chem. Int. Ed.* 2008, **47**, 1762; (f) L. Bernardi, F. Fini, M. Fochi, A. Ricci, *Synlett* 2008, 1857; (g) Y. Tanaka, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* 2010, **132**, 8862. For the reaction of β-CF_3-substituted-α,β-unsaturated ketone with OH-NH_2, see: (h) K. Matoba, H. Kawai, T. Furukawa, A. Kusuda, E. Tokunaga, S. Nakamura, M. Shiro, N. Shibata, *Angew. Chem. Int. Ed.* 2010, **49**, 5762.

8 D. Łyżwa, K. Dudziński, P. Kwiatkowski, *Org. Lett.* 2012, **14**, 1540.

9 J.-R. Gao, H. Wu, B. Xiang, W.-B. Yu, L. Han, Y.-X. Jia, *J. Am. Chem. Soc.* 2013, **135**, 2983.

10 T. Arai, Y. Yamamoto, A. Awata, K. Kamiya, M. Ishibashi, M. A. Arai, *Angew. Chem. Int. Ed.* 2013, **52**, 2486.

11 (a) R. Liu, J. Zhang, *Org. Lett.* 2013, 15, 2266. Reaction with malonate: (b) R. Liu, J. Zhang, *Chem. Eur. J.* 2013, **19**, 7319.

12 For the asymmetric Michael reaction of β-alkoxycarbonyl nitrostyrene with aldehyde, see: R. Kastl, H. Wennemers, *Angew. Chem. Int. Ed.* 2013, **52**, 7228.

13 During preparation of the manuscript, Gong and Meggers reported the same kind of of Michael-type asymmetric Friedel-Crafts reaction of indole with β,β-disubstituted nitroalkenes catalyzed by Ni-BOX complex, L.-A. Chen, X. Tang, J. Xi, W. Xu, L. Gong, E. Meggers, *Angew. Chem. Int. Ed.* 2013, **52**, 14021.

14 After submission of the manuscript, Jia and co-workers reported the similar reaction with chiral Ni-BOX complex, see: Weng, J.-Q.;

Deng, Q.-M.; Wu, L.; Xu, K.; Wu, H.; Liu, R.-R.; Gao, J.-R.; Jia, Y.-X. *Org. Lett.* DOI: 10.1021/ol403480v.

15 (a) T. Akiyama, Itoh, J. K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* 2004, 43, 1566; (b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* 2004, **126**, 5356. For reviews on chiral phosphoric acid catalysis, see: (c) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* 2006, **348**, 999; (d) S. J. Connon, *Angew. Chem. Int. Ed.* 2006, **45**, 3909; (e) M. Terada, *Chem. Commun.* 2008, 4097; (f) M. Terada, *Synlett*, 2010, 1929; (g) A. Zamfir, S. Schenker, M. Freund, S. M. Tsogoeva, *Org. Biomol. Chem.* 2010, **8**, 5262; (h) M. Terada, *Curr. Org. Chem.* 2011, **15**, 2227; (i) M. Rueping, A. Kuenkel, I. Atodiresei, *Chem. Soc. Rev.* 2011, **40**, 4539. See also references cited therein.

16 The configuration of α-methoxycarbonyl-β-nitrostyrene **5h** was determined to be *Z* by X-ray analysis, and those of the other substrates were determined by analogy.

17 The relative stereochemisry of **8** was determined by X-ray analysis of the *N*-free tetrahydro-β-carboline (CCDC-982411).

18 CCDC-971880 and CCDC-971879 contain the supplementary crystallographic data of **5h** and **11**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

19 For theoretical studies on chiral phosphoric acid catalysis, see: (a) M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* 2007, **129**, 6756; (b) L. Simón, J. M. Goodman, *J. Am. Chem. Soc.* 2008, **130**, 8741; (c) M. Yamanaka, T. Hirata, *J. Org. Chem.* 2009, **74**, 3266; (d) T. Akiyama, H. Morita, P. Bachu, K. Mori, M. Yamanaka, T. Hirata, *Tetrahedron* 2009, **65**, 4950; (e) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* 2009, **131**, 13819; (f) F.-Q. Shi, B.-A Song, *Org. Biomol. Chem.* 2009, **7**, 1292; (g) N. Nan Li, X.-H. Chen, J. Song, S.-W. Luo, W. Fan, L.-Z. Gong, *J. Am. Chem. Soc.* 2009, **131**, 15301; (h) T. Marcelli, P. Hammar, F. Himo, *Adv. Synth. Catal.* 2009, **351**, 525; (i) L. Simón, J. M. Goodman, *J. Org. Chem.* 2010, **75**, 589; (j) S. Xu, Z. Wang, Y. Li, X. Zhang, H. Wang, K. Ding, *Chem. Eur. J.* 2010, **16**, 3021; (k) Q. Cai, C. Zheng, S.-L. You, *Angew. Chem. Int. Ed.* 2010, **49**, 8666; (l) L. He, X.-H. Chen, D.-N. Wang, S.-W. Luo, W.-Q. Zhang, J. Yu, L. Ren, L.-Z. Gong, *J. Am. Chem. Soc.* 2011, **133**, 13504; (m) L. Simón, J. M. Goodman, *J. Org. Chem.* 2011, **76**, 1775; (n) F. Shi, S.-W. Luo, Z.-L. Tao, L. He, J. Yu, S.-J. Tu, L.-Z. Gong, *Org. Lett.* 2011, **13**, 4680; (o) M. N. Grayson, S. C. Pellegrinet, J. M. Goodman, *J. Am. Chem. Soc.* 2012, **134**, 2716; (p) F. Shi, G.-J. Xing, Z.-L. Tao, S.-W. Luo, S.-J. Tu, L.-Z. Gong, *J. Org. Chem.* 2012, **77**, 6970; (q) H. Wang, P. Jain, J. C. Antilla, K. N. Houk, *J. Org. Chem.* 2013, **78**, 1208; (r) Y. Shibata, M. Yamanaka, *J. Org. Chem.* 2013, **78**, 3731.

20 For a theoretical study on chiral phosphoric acid catalyzed Friedel-Crafts reaction of indole with nitrostyrene, see: (a) T. Hirata, M. Yamanaka, *Chem. Asian J.* 2011, **6**, 510. For DFT calculation of Friedel-Crafts reaction of 4,7-dihydroindole with nitrostyrene, see: b) C. Zheng, Y.-F. Sheng, Y.-X. Li, S.-L. You, *Tetrahedron* 2010, **66**, 2875.