DOI: 10.1002/ejoc.200700980

Chiral Phosphoric Acid Catalyzed Asymmetric Friedel–Crafts Alkylation of Indoles with Simple α,β-Unsaturated Aromatic Ketones

Hong-Ying Tang,[a] Ai-Dang Lu,[a] Zheng-Hong Zhou,*[a] Guo-Feng Zhao,[a] Lian-Nian He,*[a] and Chu-Chi Tang[a]

Keywords: Indoles / α,β-Unsaturated aromatic ketones / Asymmetric Friedel–Crafts alkylation / Chiral phosphoric acids / Organocatalysis

Asymmetric Michael-type Friedel–Crafts (F-C) alkylations of indoles with nonchelating α,β-unsaturated aromatic ketones catalyzed by a chiral H_8-BINOL-based phosphoric acid were investigated. The reactions took place smoothly in the presence of only 2 mol-% of catalyst at room temperature to afford the desired F-C alkylation products in good yields and with moderate enantioselectivities.

Introduction

The indole framework represents a privileged structure motif in a large number of natural products and therapeutic agents.[1] In this regard, the development of effective asymmetric routes to indole architectures has attracted much attention from organic chemists. Indole is an electron-rich heteroaromatic compound, in which the pyrrole π-system is significantly activated toward electrophilic substitution. Therefore, asymmetric Friedel–Crafts (F-C) alkylation has become a powerful strategy for the construction of indol architectures.[2] Among the F-C reactions, Michael-type F-C reactions of indoles with α,β-unsaturated carbonyl compounds have been widely investigated. A number of highly selective metal-catalyzed asymmetric F-C reactions in the presence of bidentate chelating carbonyl compounds have been developed.[3] However, the corresponding organocatalytic asymmetric process has been less widely explored. In 2002, McMillan et al. developed the first examples of asymmetric Michael-type F-C reactions between indoles and α,β-unsaturated aldehydes in the presence of benzylimidazolidinone salts derived from L-phenylalanine as the catalysts.[4] Nevertheless, such catalytic systems were inefficient for α,β-unsaturated ketones, with which poor *ee*s (25%) were observed.[5] Melchiorre et al. reported highly enantioselective (up to 96% *ee*) F-C alkylations of indoles with simple α,β-unsaturated aliphatic ketones in the presence of 20 mol-% of the D-*N*-Boc-phenylglycine salt of 9-amino(9-deoxy)epihydroquinine as the catalyst.[6] Chen et al. demonstrated that the combination of trifluoromethanesulfonic acid and the diamine derived from cinchonine (30 mol-%) was also an efficient catalytic system for asymmetric F-C reactions between indole and α,β-unsaturated aliphatic ketones, in which *ee*s of up to 89% were obtained.[7] Xu et al. described D-camphor-based sulfonic acid catalyzed (10 mol-%) asymmetric F-C alkylations of indoles with α,β-unsaturated aromatic ketones with the highest *ee* value of 58%.[8] This was the only example of a chiral Brønsted acid catalyzed process.

Despite these recent advances, there are still some drawbacks in the previously reported procedures, such as substrate limitation, the need for high catalyst loadings (10–30 mol-%), and unsatisfactory selectivities; therefore, the development of alternative catalysts for enantioselective Michael-type F-C reactions between indoles and simple α,β-unsaturated aromatic ketones would be highly desirable. Recently, chiral phosphoric acids have been shown to be versatile organocatalysts in many organic transformations.[9,10] Here we report the application of chiral phosphoric acids as Brønsted acid catalysts for the promotion of the Michael-type F-C reactions between indoles and α,β-unsaturated aromatic ketones.

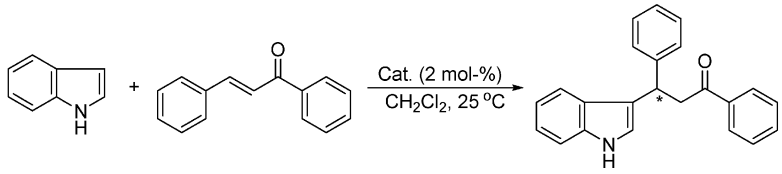
Results and Discussion

We first performed the F-C reaction between (*E*)-1,3-diphenylprop-2-en-1-one (chalcone) and indole in the presence of different BINOL phosphates **1a**–**h** and H_8-BINOL phosphates **2a**–**c** as the catalysts. Generally, chiral phosphoric acids derived from octahydrobinaphthol exhibit better catalytic activities than the corresponding binol derivatives in terms of enantioselectivity (Table 1, Entries 9–11 vs. Entries 7, 6, 3), and the best enantiomeric excess (50%,

[a] State Key Laboratory of Elemento-Organic Chemistry, Insitute of Elemento-Organic Chemistry, Nankai University
Tianjin 300071, P. R. China
Fax: +86-22-23508939
E-mail: z.h.zhou@nankai.edu.cn

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

Table 1. Screening of catalysts for the asymmetric Michael-type F-C alkylation of chalcone.[a]



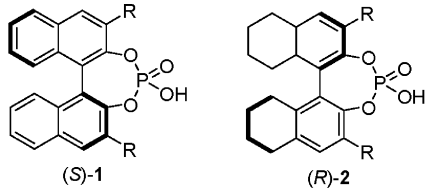
Entry	Catalyst	R	Time [h]	Yield (%)[b]	*ee* (%)[c]	Config.[d]
1	**1a**	$Ph_2P(O)$	24	61	7	(*S*)
2	**1b**	Ph	24	75	2	(*S*)
3	**1c**	4-ClC_6H_4	24	73	35	(*S*)
4	**1d**	4-MeC_6H_4	24	72	11	(*S*)
5	**1e**	4-PhC_6H_4	24	66	10	(*S*)
6	**1f**	2-naphthyl	24	73	15	(*S*)
7	**1g**	3,5-$(F_3C)_2C_6H_3$	48	73	28	(*S*)
8	**1h**	2,4,6-$tBu_3C_6H_2$	72	61	1	(*S*)
9	**2a**	3,5-$(F_3C)_2C_6H_3$	24	56	33	(*R*)
10	**2b**	2-naphthyl	24	69	46	(*R*)
11	**2c**	4-ClC_6H_4	24	87	50	(*R*)

[a] Reactions were performed on a 0.5 mmol scale of chalcone with a concentration of 0.33 mol L^{-1}. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis on an AD-H column, hexane/propan-2-ol (80:20), flow rate 1.0 mL min^{-1}, R_t = 14.95 and 16.92 min. [d] Absolute configuration of the major isomer was assigned by comparison with the literature value of optical rotation in ref.[6]

Table 1, Entry 11) was obtained when H_8-BINOL phosphate **2c** was used. The introduction of a bulky group such as 2,4,6-tri-*tert*-butylphenyl (**1h**) at the 3,3′-positions of the binol skeleton had a detrimental effect on the reaction, which became very sluggish and almost racemic product was obtained (Table 1, Entry 8).

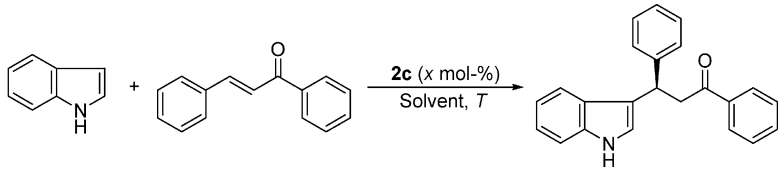
In further experiments, the solvent, reaction temperature, and catalyst loading were thoroughly examined with **2c** as the catalyst and the reaction between chalcone and indole as the model. The results are listed in Table 2.

As shown in Table 2, solvent evaluation revealed that chloroalkanes and toluene favored this transformation, and the best reaction conducts were found in dichloromethane



(Table 2, Entries 1–3 and 5). Use of protic solvents such as methanol resulted in dramatic decreases in stereoselectivity and afforded the racemic F-C adduct. Neither lowering nor increasing of the reaction temperature gave any improvement in the stereocontrol of the reaction (Table 2, Entries 10, 11 vs. Entry 1). In addition, adjusting the catalyst

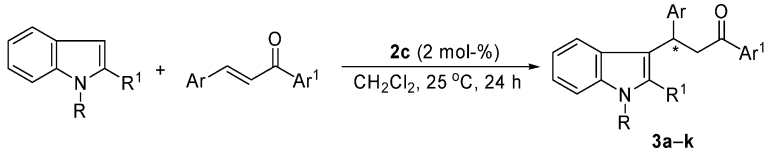
Table 2. Optimization of the reaction conditions.[a]



Entry	Solvent	**2c** [mol-%]	Temp [°C]	Yield (%)[b]	*ee* (%)[c]
1	CH_2Cl_2	2	25	87	50
2	$CHCl_3$	2	25	63	44
3	$ClCH_2CH_2Cl$	2	25	76	47
4	CH_3OH	2	25	68	0
5	toluene	2	25	78	44
6	ethyl acetate	2	25	72	22
7	THF	2	25	51	19
8	CH_2Cl_2	1	25	85	49
9	CH_2Cl_2	3	25	90	49
10	CH_2Cl_2	2	0	62	45
11	CH_2Cl_2	2	40	85	38

[a] Reactions were performed on a 0.5 mmol scale of chalcone with a concentration of 0.33 mol L^{-1}. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis on an AD-H column, hexane/propan-2-ol (80:20), flow rate 1.0 mL min^{-1}, R_t = 14.95 (major) and 16.92 (minor) min.

Table 3. Asymmetric Friedel–Crafts alkylation of indoles with different α,β-unsaturated aromatic ketones catalyzed by **2c**.[a]



Entry	R	R^1	Ar	Ar^1	Yield (%)[b]	*ee* (%)[c]	Config.
1 (**3a**)	H	H	Ph	Ph	73	56	(*R*)[d]
2 (**3b**)	CH_3	H	Ph	Ph	63	47	nd[e]
3 (**3c**)	Bn	H	Ph	Ph	92	24	nd
4 (**3d**)	H	CH_3	Ph	Ph	82	18	(*S*)[f]
5 (**3e**)	H	H	4-$H_3COC_6H_4$	4-$O_2NC_6H_4$	88	51	nd
6 (**3f**)	H	H	Ph	4-BrC_6H_4	89	39	nd
7 (**3g**)	H	H	Ph	2-ClC_6H_4	67	34	nd
8 (**3h**)	H	H	2-ClC_6H_4	Ph	71	43	nd
9 (**3i**)	H	H	4-$H_3COC_6H_4$	2-ClC_6H_4	80	36	nd
10 (**3j**)	H	H	2-$H_3COC_6H_4$	2-ClC_6H_4	69	38	nd
11 (**3k**)	H	H	2-$H_3COC_6H_4$	4-$O_2NC_6H_4$	85	51	nd

[a] Reactions were performed on a 0.5 mmol scale of enones with a concentration of 0.17 mol L^{-1}. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis on an AD-H column. [d] Absolute configuration of the major isomer was assigned by comparison with the literature value for optical rotation in ref.[6] [e] nd = not determined. [f] Absolute configuration of the major isomer was established by comparison with the reported optical rotation in ref.[11]

loading demonstrated no obvious effect on the *ee* values obtained from the reaction. For example, the use of larger or smaller amounts of phosphoric acid **2c** resulted only in slight losses of enantioselectivity (Table 2, Entries 10, 11; both are 49% *ee*).

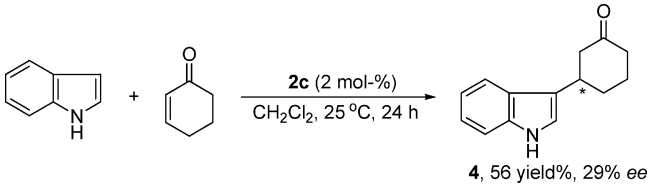
The influence of additives on the reaction was also evaluated, and it was found that the introduction of additives had a negative effect. For example, use of either acidic additives such as phenol or acetic acid or of the basic additive pyridine led to obvious decreases in *ee* values (33% *ee*, 37% *ee*, and 34% *ee*, respectively). Although significant rate acceleration was observed with molecular iodine as the additive (the reaction was complete in less than 8 h), almost racemic product (3% *ee*) was isolated, though in excellent yield.

Further studies revealed that the concentration of chalcone had an important effect on the enantioselectivity. When the concentration of chalcone was decreased to 0.17 M, the *ee* value was improved to 56%, while further decreasing the concentration to 0.13 M led to a lower selectivity of 53% *ee*.

With the optimal reaction conditions (2 mol-% of **2c** as the catalyst, 0.17 M enones, at 25 °C in dichloromethane) to hand, we then examined the scope and limitations of these stereoselective indole alkylations. The results are summarized in Table 3.

As shown in Table 3, variation of the substituents on the indole nitrogen atom revealed that the steric hindrance of the substituting group plays an important role on the reaction. For example, in relation to the result for indole (Table 3, Entry 1, 56% *ee*), the use of *N*-methylindole led to a moderate decrease in *ee* value (Table 3, Entry 2, 47% *ee*), whereas the employment of a bulkier benzyl-substituted indole resulted in a marked loss of selectivity (Table 3, Entry 3, 24% *ee*). Moreover, incorporation of a 2-methyl group also had a detrimental effect on the reaction, which gave the corresponding adduct with a sharp loss in enantioselectivity (Table 2, Entry 4, 19% *ee*). As for the substrate α,β-unsaturated aromatic ketones, generally, either introduction of an electron-deficient aryl group at the 1-position or incorporation of an electron-rich aryl group at the 1-position favored the reaction. The corresponding conjugate addition products were obtained with moderate enantioselectivities (Table 3, Entries 5–11, 34–51% *ee*s).

In addition, the optimal conditions also applied for the cyclic enones. However, both stereoselectivity and chemical yield were decreased for this type of substrate. For example, the F-C alkylation product **4** of indole with cyclohex-2-enone in the presence of 2 mol-% of **2c** was obtained in 56% yield with 29% *ee*.



Conclusions

We have developed an efficient chiral phosphoric acid organocatalyst for the asymmetric Michael-type Friedel–Crafts alkylation of indoles and simple α,β-unsaturated aromatic ketones. It is worth noting that moderate enantioselectivity has been achieved in the presence of only 2 mol-% of catalyst. This is a great advantage over other organocatalytic asymmetric version of this reaction in the limited literature reports. Mechanistic studies and further application of this type of readily available Brønsted acid catalysts in stereoselective reactions are ongoing in our laboratory.

Experimental Section

General Information: ^1H and ^{31}P NMR spectra were recorded in $CDCl_3$ with a Bruker AMX 300 or a Varian 400 MHz instrument with TMS as an internal standard for ^1H NMR and 85% H_3PO_4 as an external standard for ^{31}P NMR spectroscopy. Specific rotations were measured with a Perkin–Elmer 341MC polarimeter. Enantiomeric excesses were determined with an HP-1100 instrument (chiral column; mobile phase: hexane/*i*PrOH). Elemental analyses were conducted with a Yanaco CHN Corder MT-3 automatic analyzer. Melting points were determined with a T-4 melting point apparatus. All temperatures are uncorrected.

Synthesis of Catalysts: Catalysts **1a**–**h** and **2a**–**c** were prepared by condensation of 3,3′-substituted BINOL or H_8-BINOL and phosphorus oxychloride in the presence of pyridine and subsequent acidic hydrolysis of the corresponding chlorophosphate by a literature method.[10b]

1a: White solid. Yield 370 mg, 99%. M.p. 209–211 °C. $[\alpha]_D^{20}$ –156.2 (c = 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.78 (br. s, 1 H, OH), 7.24–7.26 (m, 4 × H_{arom}), 7.41–7.84 (m, 26 × H_{arom}) ppm. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = –0.47, 36.67, 37.39 ppm. $C_{44}H_{31}O_6P_3$ (748.61): calcd. C 70.59, H 4.17; found C 70.41, H 4.04.

General Procedure for the 2c-Catalyzed Asymmetric F-C Alkylation of Indoles with α,β-Unsaturated Aromatic Ketones: The α,β-unsaturated aromatic ketones (0.5 mmol), indoles (0.6 mmol), and catalyst **2c** (5.77 mg, 0.001 mmol) were stirred in dichloromethane (3 mL) at room temperature. The reaction was monitored by TLC analysis. After removal of the solvent, the residue was purified by column chromatograph on silica gel (200–300 mesh, gradient elution with petroleum ether/ethyl acetate) to give the desired product **3**.

(*R*)-3-(1*H*-Indol-3-yl)-1,3-diphenylpropan-1-one (3a): White solid. Yield 118 mg, 73%. M.p. 127–126 °C. $[\alpha]_D^{20}$ –17.0 (c = 1.11, $CHCl_3$), 56% *ee*. ^1H NMR ($CHCl_3$, 400 MHz): δ = 3.73 (dd, J = 7.2, 16.4 Hz, 1 H, one proton of CH_2), 3.83 (dd, J = 7.2, 16.4 Hz, 1 H, one proton of CH_2), 5.08 (t, J = 7.2 Hz, 1 H, CH), 7.00–7.04 (m, 2 × H_{arom}), 7.13–7.18 (m, 3 × H_{arom}), 7.24–7.37 (m, 4 × H_{arom}), 7.41–7.56 (m, 4 × H_{arom}), 7.94 (d, J = 8.0 Hz, 2 × H_{arom}), 7.98 (br. s, 1 H, NH) ppm. $C_{23}H_{19}NO$ (325.39): calcd. C 84.89, H 5.89, N 4.30; found C 84.76, H 6.01, N 4.08. HPLC conditions: AD-H column, hexane/propan-2-ol (80:20), flow rate 1.0 mL min^{-1}, R_t = 14.95 (major) and 16.92 (minor) min.

3-(1-Methyl-1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (3b): White solid. Yield 107 mg, 63%. M.p. 159–164 °C. $[\alpha]_D^{20}$ = –11.2 (c = 0.49, $CHCl_3$), 47% *ee*. ^1H NMR ($CHCl_3$, 400 MHz): δ = 3.72 (s, 3 H, CH_3), 3.74 (dd, J = 7.2, 16.8 Hz, 1 H, one proton of CH_2), 3.81 (dd, J = 7.2, 16.8 Hz, 1 H, one proton of CH_2), 5.06 (t, J = 7.2 Hz, 1 H, CH), 6.84 (s, 1 × H_{arom}) 7.01 (t, J = 7.2 Hz, 1 × H_{arom}), 7.14–7.20 (m, 2 × H_{arom}), 7.24–7.28 (m, 2 × H_{arom}), 7.35–7.57 (m, 6 × H_{arom}), 7.94 (d, J = 7.2 Hz, 2 × H_{arom}) ppm. $C_{24}H_{21}NO$ (339.42): calcd. C 84.92, H 6.24, N 4.13; found C 84.69, H 5.94, N 4.02. HPLC conditions: AD-H column, hexane/propan-2-ol (80:20), flow rate 1.0 mL min^{-1}, R_t = 9.22 (minor) and 11.74 (major) min.

3-(1-Benzyl-1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (3c): White solid. Yield 191 mg, 92%. M.p. 136–138 °C. $[\alpha]_D^{20}$ = –10.9 (c = 0.48, $CHCl_3$), 24% *ee*. ^1H NMR ($CHCl_3$, 400 MHz): δ = 3.73 (dd, J = 7.2, 16.4 Hz, 1 H, one proton of CH_2), 3.81 (dd, J = 7.2, 16.4 Hz, 1 H, one proton of CH_2), 5.09 (t, J = 7.2 Hz, 1 H, CH), 5.26 (s, 2 H, CH_2), 6.95 (s, 1 × H_{arom}), 6.99–7.06 (m, 3 × H_{arom}), 7.10–7.24 (m, 6 × H_{arom}), 7.28–7.30 (m, 1 × H_{arom}), 7.36–7.46 (m, 5 × H_{arom}), 7.53 (t, J = 7.6 Hz, 1 × H_{arom}), 7.91 (d, J = 7.6 Hz, 2 × H_{arom}) ppm. $C_{30}H_{25}NO$ (415.51): calcd. C 86.71, H 6.06, N 3.37; found C 86.34, H 5.82, N 3.11. HPLC conditions: AD-H column, hexane/propan-2-ol (90:10), flow rate 1.0 mL min^{-1}, R_t = 14.36 (major) and 15.16 (minor) min.

(*S*)-3-(2-Methyl-1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (3d): Viscous oil. Yield 139 mg, 82%. $[\alpha]_D^{20}$ = +6.6 (c = 2.43, $CHCl_3$), 18% *ee*. ^1H NMR ($CHCl_3$, 300 MHz): δ = 2.36 (s, 3 H, CH_3), 3.88 (dd, J = 7.2, 15.9 Hz, 1 H, one proton of CH_2), 3.95 (dd, J = 7.2, 15.9 Hz, 1 H, one proton of CH_2), 5.09 (t, J = 7.2 Hz, 1 H, CH), 6.96–7.07 (m, 2 × H_{arom}), 7.11–7.24 (m, 4 × H_{arom}), 7.33–7.38 (m, 4 × H_{arom}), 7.45–7.50 (m, 2 × H_{arom}), 7.76 (br. s, 1 H, NH), 7.87 (d, J = 7.2 Hz, 2 × H_{arom}) ppm. $C_{24}H_{21}NO$ (339.42): calcd. C 84.92, H 6.24, N 4.13; found C 84.77, H 6.03, N 3.96. HPLC conditions: AD-H column, hexane/propan-2-ol (80:20), flow rate 1.0 mL min^{-1}, R_t = 20.55 (major) and 22.37 (minor) min.

3-(1*H*-Indol-3-yl)-3-(4-methoxyphenyl)-1-(4-nitrophenyl)propan-1-one (3e): Yellow solid. Yield 176 mg, 88%, M.p. 140–141 °C. $[\alpha]_D^{20}$ = –11.3 (c = 0.53, $CHCl_3$), 51% *ee*. ^1H NMR ($CHCl_3$, 400 MHz): δ = 3.73 (dd, J = 7.2, 16.4 Hz, 1 H, one proton of CH_2), 3.75 (s, 3 H, OCH_3), 3.82 (dd, J = 7.2, 16.4 Hz, 1 H, one proton of CH_2), 4.98 (t, J = 7.2 Hz, 1 H, CH), 6.80 (d, 2 × H_{arom}), 6.98 (d, 1 × H_{arom}), 7.03 (t, 1 × H_{arom}), 7.16 (t, 1 × H_{arom}), 7.25 (d, 2 × H_{arom}), 7.33 (d, 1 × H_{arom}), 7.43 (d, J = 8.0 Hz, 1 × H_{arom}), 8.00 (d, J = 8.4 Hz, 2 × H_{arom}), 8.01 (br. s, 1 H, NH) ppm. $C_{24}H_{20}N_2O_4$ (400.41): calcd. C 71.99, H 5.03, N 7.00; found C 71.85, H 4.91, N 6.89. HPLC conditions: AD-H column, hexane/propan-2-ol (70:30), flow rate 1.0 mL min^{-1}, R_t = 27.29 (major) and 33.24 (minor) min.

1-(4-Bromophenyl)-3-(1*H*-indol-3-yl)-3-phenylpropan-1-one (3f): Pale yellow solid. Yield 180 mg, 89%. M.p. 171–173 °C. $[\alpha]_D^{20}$ = –15.9 (c = 0.91, $CHCl_3$), 39% *ee*. ^1H NMR ($CHCl_3$, 400 MHz): δ = 3.68 (dd, J = 7.2, 16.4 Hz, 1 H, one proton of CH_2), 3.78 (dd, J = 7.2, 16.4 Hz, 1 H, one proton of CH_2), 5.04 (t, J = 7.2 Hz, 1 H, CH), 6.98–7.04 (m, 3 × H_{arom}), 7.13–7.19 (m, 3 × H_{arom}), 7.32–7.35 (m, 3 × H_{arom}), 7.43 (d, J = 8.0 Hz, 1 × H_{arom}), 7.56 (d, J = 8.4 Hz, 2 × H_{arom}), 7.78 (d, J = 8.4 Hz, 2 × H_{arom}), 7.97 (br. s, 1 H, NH) ppm. $C_{23}H_{18}BrNO$ (404.29): calcd. C 68.33, H 4.49, N 3.46; found C 68.12, H 4.29, N 3.20. HPLC conditions: AD-H column, hexane/propan-2-ol (70:30), flow rate 1.0 mL min^{-1}, R_t = 12.43 (major) and 14.16 (minor) min.

1-(2-Chlorophenyl)-3-(1*H*-indol-3-yl)-3-phenylpropan-1-one (3g): White solid. Yield 121 mg, 67%. M.p. 99–101 °C. $[\alpha]_D^{20}$ = –6.8 (c = 0.56, $CHCl_3$), 34% *ee*. ^1H NMR ($CHCl_3$, 400 MHz): δ = 3.71 (dd, J = 7.2, 16.4 Hz, 1 H, one proton of CH_2), 3.79 (dd, J = 7.2, 16.4 Hz, 1 H, one proton of CH_2), 4.92 (t, J = 8.0 Hz, 1 H, CH), 6.98–7.02 (m, 2 × H_{arom}), 7.07–7.09 (m, 1 × H_{arom}), 7.12–7.19 (m, 3 × H_{arom}), 7.22–7.25 (m, 2 × H_{arom}), 7.30–7.35 (m, 4 × H_{arom}), 7.39 (t, J = 8.0 Hz, 1 × H_{arom}), 8.01 (br. s, 1 H, NH) ppm. $C_{23}H_{18}ClNO$ (359.83): calcd. C 76.77, H 5.04, N 3.89; found C 76.61, H 4.90, N 3.67. HPLC conditions: AD-H column, hexane/propan-2-ol (70:30), flow rate 1.0 mL min^{-1}, R_t = 7.08 (major) and 8.32 (minor) min.

3-(2-Chlorophenyl)-3-(1*H*-indol-3-yl)-1-phenylpropan-1-one (3h): Viscous oil. Yield 128 mg, 71%. $[\alpha]_D^{20}$ = –28.5 (c = 2.35, $CHCl_3$), 43% *ee*. ^1H NMR ($CHCl_3$, 400 MHz): δ = 3.68 (dd, J = 6.4, 16.8 Hz, 1 H, one proton of CH_2), 3.80 (dd, J = 8.0, 16.8 Hz, 1 H, one proton of CH_2), 5.54 (dd, J = 6.4, 8.0 Hz, 1 H, CH), 6.99–7.03 (m, 2 × H_{arom}), 7.10–7.16 (m, 3 × H_{arom}), 7.21–7.24 (m, 1 × H_{arom}), 7.31 (d, J = 8.0 Hz, 1 × H_{arom}), 7.38–7.46 (m, 4 × H_{arom}), 7.53–7.57 (m, 1 × H_{arom}), 7.98 (d, J = 7.2 Hz, 2 × H_{arom}), 8.01 (br. s, 1 H, NH) ppm. $C_{23}H_{18}ClNO$ (359.83): calcd. C 76.77, H 5.04, N 3.89;

found C 76.53, H 4.86, N 3.72. HPLC conditions: AD-H column, hexane/propan-2-ol (80:20), flow rate 1.0 mL min^{-1}, R_t = 11.03 (major) and 14.97 (minor) min.

1-(2-Chlorophenyl)-3-(1*H*-indol-3-yl)-3-(4-methoxyphenyl)propan-1-one (3i): White solid. Yield 156 mg, 80%. M.p. 134–136 °C. $[\alpha]_D^{20}$ = +5.49 (c = 3.28, $CHCl_3$), 36% *ee*. ^{1}H NMR ($CHCl_3$, 300 MHz): δ = 3.69 (dd, J = 7.8, 16.5 Hz, 1 H, one proton of CH_2), 3.76 (s, 3 H, OCH_3), 3.77 (dd, J = 7.8, 16.5 Hz, 1 H, one proton of CH_2), 4.87 (t, J = 7.8 Hz, 1 H, CH), 6.78 (d, J = 8.7 Hz, 2 × H_{arom}), 6.98–7.08 (m, 3 × H_{arom}), 7.10–7.18 (m, 3 × H_{arom}), 7.21 (d, J = 8.7 Hz, 2 × H_{arom}), 7.29–7.36 (m, 2 × H_{arom}), 7.40 (d, J = 8.1 Hz, 1 × H_{arom}), 8.00 (br. s, 1 H, NH) ppm. $C_{24}H_{20}ClNO_2$ (389.86): calcd. C 73.93, H 5.17, N 3.59; found C 73.74, H 5.02, N 3.27. HPLC conditions: AD-H column, hexane/propan-2-ol (80:20), flow rate 0.5 mL min^{-1}, R_t = 33.04 (minor) and 35.10 (major) min.

1-(2-Chlorophenyl)-3-(1*H*-indol-3-yl)-3-(2-methoxyphenyl)propan-1-one (3j): Colorless oil. Yield 135 mg, 69%. $[\alpha]_D^{20}$ = –6.8 (c = 1.10, $CHCl_3$), 38% *ee*. ^{1}H NMR ($CHCl_3$, 400 MHz): δ = 3.68 (dd, J = 8.8, 16.4 Hz, 1 H, one proton of CH_2), 3.78 (dd, J = 6.8, 16.4 Hz, 1 H, one proton of CH_2), 3.83 (s, 3 H, OCH_3), 5.28 (dd, J = 6.8, 8.8 Hz, 1 H, CH), 6.80 (t, J = 7.2 Hz, 1 × H_{arom}), 6.86 (d, J = 8.4 Hz, 1 × H_{arom}), 6.98–7.03 (m, 2 × H_{arom}), 7.09–7.19 (m, 5 × H_{arom}), 7.29–7.43 (m, 4 × H_{arom}), 8.07 (br. s, 1 H, NH) ppm. $C_{24}H_{20}ClNO_2$ (389.86): calcd. C 73.93, H 5.17, N 3.59; found C 73.69, H 4.98, N 3.35. HPLC conditions: AD-H column, hexane/propan-2-ol (80:20), flow rate 1.0 mL min^{-1}, R_t = 9.92 (major) and 13.20 (minor) min.

3-(1*H*-Indol-3-yl)-3-(2-methoxyphenyl)-1-(4-nitrophenyl)propan-1-one (3k): Yellow solid. Yield 170 mg, 85%. M.p. 170–172 °C. $[\alpha]_D^{20}$ = –27.6 (c = 0.34, $CHCl_3$), 51% *ee*. ^{1}H NMR ($CHCl_3$, 300 MHz): δ = 3.68 (dd, J = 6.6, 15.3 Hz, 1 H, one proton of CH_2), 3.76 (dd, J = 6.6, 15.3 Hz, 1 H, one proton of CH_2), 3.87 (s, 3 H, OCH_3), 5.37 (t, J = 6.6 Hz, 1 H, CH), 6.78–6.90 (m, 2 × H_{arom}), 6.96–7.20 (m, 6 × H_{arom}), 7.34 (t, J = 8.7 Hz, 1 × H_{arom}), 8.02 (br. s, 1 H, NH), 8.10 (d, J = 8.7 Hz, 2 × H_{arom}), 8.25 (d, J = 8.7 Hz, 2 × H_{arom}) ppm. $C_{24}H_{20}N_2O_4$ (400.41): calcd. C 71.99, H 5.03, N 7.00; found C 71.78, H 4.95, N 6.86. HPLC conditions: AD-H column, hexane/propan-2-ol (70:30), flow rate 1.0 mL min^{-1}, R_t = 18.14 (minor) and 22.03 (major) min.

3-(1*H*-Indol-3-yl)cyclohexanone (4): Colorless oil. Yield 60 mg, 56%. $[\alpha]_D^{20}$ = –4.1 (c = 0.21, $CHCl_3$), 29% *ee*. ^{1}H NMR ($CHCl_3$, 400 MHz): δ = 1.81–1.89 (m, 1 H, one proton of CH_2), 1.96–2.09 (m, 2 H, CH_2), 2.24–2.29 (m, 1 H, one proton of CH_2), 2.35–2.49 (m, 2 H, CH_2), 2.60–2.66 (m, 1 H, one proton of CH_2), 2.78–2.83 (m, 1 H, one proton of CH_2), 3.42–3.49 (m, 1 H, CH, one proton of CH_2), 6.99 (d, J = 2.0 Hz, 1 × H_{arom}), 7.13 (t, J = 7.6 Hz, 1 × H_{arom}), 7.21 (t, J = 7.6 Hz, 1 × H_{arom}), 7.38 (d, J = 7.6 Hz, 1 × H_{arom}), 7.63 (d, J = 7.6 Hz, 1 × H_{arom}), 8.01 (br. s, 1 H, NH) ppm. $C_{14}H_{15}NO$ (213.27): calcd. C 78.84, H 7.09, N 6.57; found C 78.59, H 6.84, N 6.34. HPLC conditions: AD-H column, hexane/propan-2-ol (85:15), flow rate 1.0 mL min^{-1}, R_t = 9.79 (major) and 11.86 (minor) min.

Acknowledgments

We are grateful to the National Natural Science Foundation of China (20472033, 20772058) and the Key Science and Technology Project of the Ministry of Education of China for generous financial support of our programs.

[1] a) D. J. Faulkner, *Nat. Prod. Rep.* **2002**, *19*, 1–49; b) A. Kleeman, J. Engel, B. Kutscher, D. Reichert, *Pharmaceutical Substances*, 4th ed., Thieme, New York, **2001**.

[2] For recent reviews on catalytic asymmetric Friedel–Crafts reactions, see: a) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem. Int. Ed.* **2004**, *43*, 550–556; b) K. A. Jorgensen, *Synthesis* **2003**, 1117–1125.

[3] For selected examples, see: a) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam, J. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 10780–10781; b) C. Palomo, M. Oiarbide, B. G. Kardak, J. M. Gareia, A. Linden, *J. Am. Chem. Soc.* **2005**, *127*, 4154–4155; c) D. A. Evans, K. R. Fandrick, H.-J. Song, *J. Am. Chem. Soc.* **2005**, *127*, 8942–8943.

[4] J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173.

[5] D.-P. Li, Y.-C. Guo, Y. Guo, W.-J. Xiao, *Chem. Commun.* **2006**, 799–801.

[6] G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403–1405.

[7] W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2007**, *5*, 816–821.

[8] W. Zhou, L.-W. Xu, L. Li, L. Yang, C.-G. Xia, *Eur. J. Org. Chem.* **2006**, 5225–5227.

[9] For selected reviews, see: a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; b) S. J. Connon, *Angew. Chem. Int. Ed.* **2006**, *45*, 3909–3912; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; d) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999–1010.

[10] For pioneering studies on chiral phosphoric acid catalysis, see: a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.

[11] M. Bandini, M. Fagioli, M. Garavelli, A. Melloni, V. Trigari, A. Umani-Ronchi, *J. Org. Chem.* **2004**, *69*, 7511–7518.

Received: October 17, 2007
Published Online: January 11, 2008

