Enantioselective Friedel–Crafts Alkylation of Indoles with Aromatic α,β-Unsaturated Aldehydes Catalyzed by Diphenylprolinol Silyl Ether

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Abstract: A catalytic enantioselective Friedel–Crafts alkylation of indoles with aromatic α,β-unsaturated aldehydes has been developed. The process is promoted by (*S*)-diphenylprolinol trimethyl silyl ether to afford, after sodium borohydride mediated reduction, 3-indolyl-3-phenylpropanols in high enantioselectivities and good yields.

Key words: organocatalysis, enantioselectivity, Friedel–Crafts alkylation, indoles, aromatic α,β-unsaturated aldehydes

The Friedel–Crafts reaction of aromatic compounds is one of the most important reactions for the formation of C–C bonds and direct derivatization of aromatic compounds in organic synthesis.[1] Various aromatic compounds, including benzenes with electron-donating substituents, furans, pyrroles and indoles, have been successfully applied in a number of Friedel–Crafts reactions with electrophiles. The indole framework represents a privileged structural motif of established value in biologically active natural products and pharmaceutical compounds.[2] In this regard, the enantioselective Friedel–Crafts reaction of indoles is one of the most extensive areas of research. Catalytic enantioselective versions of this fundamental transformation have been reported, most of which use metal-based chiral complex catalysts.[3] Recently, asymmetric organocatalysis has attracted considerable attention in terms of its unique properties,[4] and there have been several reports of asymmetric Friedel–Crafts reactions of indole derivatives with organocatalysts. In 2002, MacMillan and coworkers first reported the asymmetric Friedel–Crafts reaction of indoles and *N*-alkyl indoles with alkyl α,β-unsaturated aldehydes using chiral imidazolidinones as catalysts, and demonstrated the feasibility of organocatalytic strategies based on LUMO-lowering activation of α,β-unsaturated aldehydes via the reversible formation of an iminium ion.[5] Since then, a variety of catalytic asymmetric reactions of indoles with electrophiles including alkyl α,β-unsaturated aldehydes,[6] nitroalkenes,[7] α,β-unsaturated ketones,[8] imines,[9] trifluoropyruvate,[10] and electron-rich alkenes[11] have been reported.

However, the catalytic enantioselective Friedel–Crafts alkylation of indoles with aromatic α,β-unsaturated aldehydes is not well documented. There is, so far, only one example of the Friedel–Crafts reaction of *N*-methyl indole with cinnamaldehyde,[5,6c] and no reaction of 1*H*-indole with cinnamaldehyde has been reported. The NH moiety on the indole has significant influence on its reactivity and 1*H*-indoles and *N*-alkyl indoles show different reactivities in many cases. In some reactions, 1*H*-indoles were more reactive than *N*-alkyl indoles,[8b,10] while in others, *N*-alkyl indoles were superior to 1*H*-indoles. In the enantioselective addition of indole to *N*-acyl imines reported by Antilla and co-workers, 1*H*-indole provided lower yields and enantioselectivities than *N*-alkyl indole.[9c] Due to the difference between 1*H*-indoles and *N*-alkyl indoles, the enantioselective Friedel–Crafts alkylation of 1*H*-indoles with aromatic α,β-unsaturated aldehydes is of significance.

The products from α,β-unsaturated aldehydes are more versatile than those from nitroalkenes and α,β-unsaturated ketones, and the 1*H*-indole derivatives could easily undergo further derivatization on the nitrogen atom. Therefore, the enantioselective Friedel–Crafts reactions of 1*H*-indoles and α,β-unsaturated aldehydes would afford potentially useful 3-substituted indole derivatives.

Diarylprolinol silyl ethers, which were first utilized as efficient asymmetric catalysts by Jørgensen in 2005,[12a] have now been shown to be excellent organocatalysts for a wide variety of asymmetric reactions.[12–16] However, to the best of our knowledge, its application to catalytic enantioselective Friedel–Crafts alkylation has not been reported. Herein, we would like to report the catalytic enantioselective Friedel–Crafts reaction of indoles with aromatic α,β-unsaturated aldehyde derivatives catalyzed by diphenylprolinol silyl ether (Scheme 1).

The proposed enantioselective Friedel–Crafts reaction was first examined using indole (**2a**), cinnamaldehyde (**3a**), and 15 mol% of (*S*)-**1** at room temperature in toluene. The desired Friedel–Crafts reaction product **4a** was obtained, which was reduced by sodium borohydride in situ to the corresponding γ-alcohol **5a** with moderate yield and enantioselectivity (50%, 57% ee). Addition of benzoic acid did not improve the result (Table 1, entry 2). Various solvents were then screened and, as shown in Table 1, it is noteworthy that not only the catalytic yield but also the asymmetric induction were highly dependent on the solvents employed. Among the solvents tested, polar protic methanol was found to be the best with respect to both

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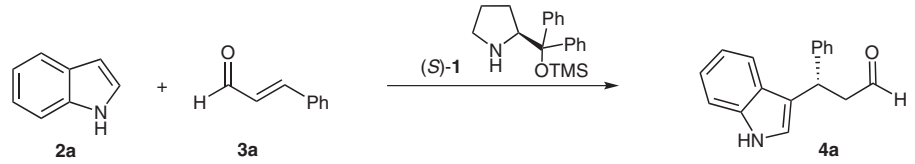
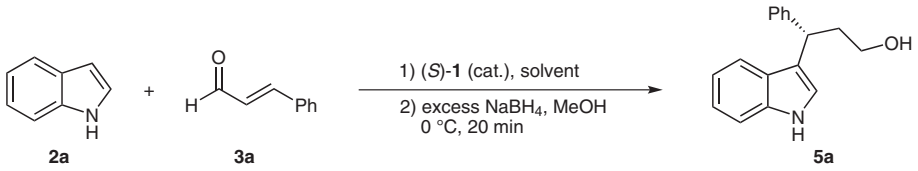


Scheme 1 Enantioselective Friedel–Crafts reaction of indole with cinnamaldehyde

the catalytic activity and the asymmetric induction (Table 1, entry 5). As expected, enantiomeric excess increased with a decrease in reaction temperature, reaching 83% ee at –10 °C, and good yield was attained after 96 h (Table 1, entry 14). After screening of the loading of the catalyst, 20 mol% was selected as the optimal amount. Thus, **5a** was formed in the presence of 20 mol% of the catalyst (*S*)-**1**, in methanol at –10 °C, with 87% yield and 86% ee, respectively (Table 1, entry 15).

Under the above optimized reaction conditions (Table 1, entry 15), the generality of the reaction was investigated; the results are summarized in Table 2. All substituted cinnamaldehydes tested were converted with very high levels of stereocontrol into the expected products **5a**–**j** (Table 2 entries 1–10). Cinnamaldehydes with electron-withdrawing groups (4-Br, 4-Cl, 4-F, 4-CF_3, 3-CF_3, 3-Cl, and 2-Cl) reacted efficiently with indole **2a** and gave good yields as well as excellent enantioselectivities (Table 2, entries 2–8). The electron-donating groups (4-Me, 4-MeO, and 2-MeO) on the aromatic ring of cinnamaldehyde were tolerated, but had a negative influence on the the yield (Table 2, entries 9–10). The Friedel–Crafts alkylation of electron-rich indoles (**2b**–**e**) afforded the corresponding products **5k**–**n** with good results (Table 2, entries 11–14). Electron-deficient indoles (5-NO_2) caused a decrease in the yield (Table 2, entry 15). As a limitation of the approach, it is worth mentioning that substitution in the α-position (α-methyl) of the cinnamaldehyde and the

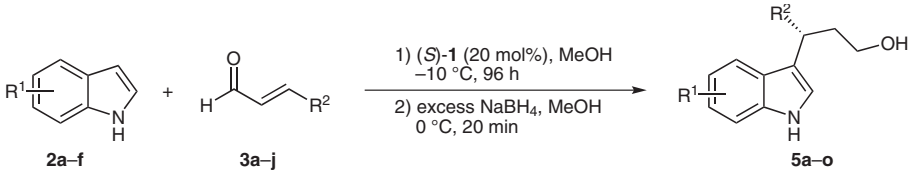
Table 1 Optimization of the Reaction Conditions[a]



Entry	Solvent	Time (h)	Temp (°C)	Cat. (mol%)	Yield (%)[b]	ee (%)[c]
1	toluene	36	r.t.	15	50	57
2	toluene	36	r.t.	15	40	50[d]
3	$CHCl_3$	36	r.t.	15	44	70
4	CH_2Cl_2	36	r.t.	15	42	60
5	MeOH	36	r.t.	15	65	73
6	EtOH	36	r.t.	15	42	49
7	MeCN	36	r.t.	15	46	72
8	THF	36	r.t.	15	33	63
9	DMF	36	r.t.	15	trace	n.d.[e]
10	MeOH	72	0	10	67	77
11	MeOH	72	0	15	70	80
12	MeOH	72	0	20	76	82
13	MeOH	96	–10	10	72	81
14	MeOH	96	–10	15	75	83
15	**MeOH**	**96**	**–10**	**20**	**87**	**86**

[a] Reaction conditions: indole (1.0 mmol), cinnamaldehyde (0.5 mmol), catalyst (*S*)-**1** (15 mol%) and solvent (1.0 mL).
[b] Isolated yield.
[c] Enantiomeric excess was determined by chiral HPLC analysis.
[d] Benzoic acid (15 mol%) was added as a co-catalyst.
[e] Not determined.

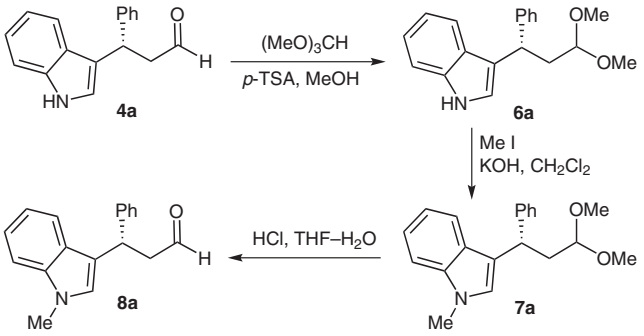
Table 2 Catalytic Asymmetric Friedel–Crafts Reaction of Substituted Indoles and Cinnamaldehydes[a]



Entry	R^1	R^2	Product	Yield (%)[b]	ee (%)[c]
1	H (**2a**)	Ph (**3a**)	**5a**	87	86
2	H (**2a**)	4-BrC_6H_4 (**3b**)	**5b**	79	91
3	H (**2a**)	4-ClC_6H_4 (**3c**)	**5c**	74	86
4	H (**2a**)	4-FC_6H_4 (**3d**)	**5d**	79	87
5	H (**2a**)	4-$F_3CC_6H_4$ (**3e**)	**5e**	72	86
6	H (**2a**)	3-$F_3CC_6H_4$ (**3f**)	**5f**	75	93
7	H (**2a**)	3-ClC_6H_4 (**3g**)	**5g**	70	89
8	H (**2a**)	2-ClC_6H_4 (**3h**)	**5h**	79	95
9	H (**2a**)	4-MeC_6H_4 (**3i**)	**5i**	56	86
10	H (**2a**)	4-$MeOC_6H_4$ (**3j**)	**5j**	63	87
11	5-MeO (**2b**)	Ph (**3a**)	**5k**	70	88
12	6-MeO (**2c**)	Ph (**3a**)	**5l**	74	87
13	5-Me (**2d**)	Ph (**3a**)	**5m**	75	87
14	7-Me (**2e**)	Ph (**3a**)	**5n**	77	94
15	5-O_2N (**2f**)	Ph (**3a**)	**5o**	60	86

[a] Reaction conditions: **2** (1.0 mmol), **3** (0.5 mmol), (*S*)-**1** (0.10 mmol), MeOH (1.0 mL).
[b] Isolated yield.
[c] Enantiomeric excess was determined by chiral HPLC analysis.

4-position (4-Me and 4-COOMe) of the indole ring had a detrimental effect on reactivity. The NH-moiety on the indole ring could not be blocked. For example, *N*-methyl indole did not react with cinnamaldehyde. This feature has already been observed in other organocatalytic Friedel–Crafts reactions of indoles believed to proceed via a dual activation mechanism.[7a,10] Alkyl α,β-unsaturated aldehydes such as crotonaldehyde seemed unreactive under our catalytic conditions.



Scheme 2 The absolute configuration of the product **5a** was determined as *S* by correlation to **8a**

For the determination of the absolute configuration of the catalytic product **5a**, we designed a route as shown in Scheme 2. From the comparison of its optical rotation with that of (*S*)-**8a**, which was synthesized by the reaction of cinnamaldehyde with 1-methylindole catalyzed by chiral imidazolidinones,[5] the absolute configuration of **5a** was determined to be 3*S*.

In summary, we have developed a highly enantioselective Friedel–Crafts reaction of indoles with aromatic α,β-unsaturated aldehydes using diphenylprolinol silyl ether as the organocatalyst. It could be a good complementary approach to MacMillan's protocol. The reaction is applicable to a variety of aromatic α,β-unsaturated aldehydes and indoles, and high enantioselectivities are attained. The approach avoids the use of any additional acid or base, and the products are potentially useful. Further investigations into synthetic applications of the method are underway.[17]

Commercial reagents were used as received, unless otherwise stated. The organocatalyst (*S*)-**1** was prepared following the procedure described in the literature. Racemates of **1** were prepared using racemic diphenylprolinol TMS-ether as the catalyst. All ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ on a Bruker Avance 400

MHz instrument with TMS as the internal standard. Chemical shifts are expressed in ppm and *J* values are given in Hz. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and integral. Data for ^{13}C NMR are reported as ppm. MS was obtained using EI ionization on an HP6989B mass spectrometer. HRMS was obtained using ESI ionization on an Apex III (7.0 tesla) Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. Melting points are uncorrected. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin–Elmer 341 digital polarimeter and are reported as follows: $[\alpha]_D^{20}$ (*c* in g per 100 mL of solvent). HPLC analysis was performed using Daicel Chiralpak AD-H and OD-H columns.

Indole Addition to α,β-Unsaturated Aldehydes (Table 2, Entry 1); Typical Procedure

To catalyst (*S*)-**1** (32 mg, 0.10 mmol, 20 mol%) dissolved in MeOH (1 mL) in a 12 mL vial at –10 °C, was added cinnamaldehyde (66 mg, 0.5 mmol). The mixture was stirred for 30 min, and indole (117 mg, 1.0 mmol) was added to the mixture. The vial was capped and the mixture was stirred at –10 °C for 96 h. Excess $NaBH_4$ (57 mg, 1.5 mmol) was added, followed by the addition of MeOH (1 mL). The –10 °C cooling bath was replaced by an ice bath, and the mixture was stirred for a further 20 min. The mixture was slowly added to sat. NH_4Cl (5 mL) at 0 °C and extracted with Et_2O (10 × 3 mL). The organic layer was collected, washed with H_2O (5 mL) and brine (5 mL), then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc–hexane, 1:1) to afford **5a**.

(*S*)-3-(1*H*-indol-3-yl)-3-phenylpropan-1-ol (5a)

Yield: 109 mg (87%); colorless oil; $[\alpha]_D^{20}$ +4.0 (*c* 0.8, $CHCl_3$); 86% ee by HPLC (Daicel Chiralpak OD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 44.6 min; τ_{minor} = 57.8 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (br s, 1 H), 7.43 (d, *J* = 7.6 Hz, 1 H), 7.22–7.31 (m, 5 H), 7.14 (dd, *J* = 8.8, 7.6 Hz, 2 H), 6.98–7.02 (m, 2 H), 4.37 (t, *J* = 7.8 Hz, 1 H), 3.60–3.67 (m, 2 H), 2.40–2.49 (m, 1 H), 2.21–2.30 (m, 1 H), 1.44 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.6, 39.2, 61.3, 110.1, 119.3, 119.5, 119.6, 121.1, 122.0, 126.1, 126.8, 127.8, 128.4, 136.5, 144.7.

EI-MS: *m*/*z* = 251 [M$^+$].

Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.77. Found: C, 81.13; H, 6.86; N, 5.47.

5b

Pale-red oil; $[\alpha]_D^{20}$ –12.0 (*c* 1.0, $CHCl_3$); 91% ee by HPLC (Daicel Chiralpak OD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 43.8 min; τ_{minor} = 66.0 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (br s, 1 H), 7.35–7.40 (m, 3 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.13–7.18 (m, 3 H), 6.99–7.03 (m, 2 H), 4.35 (t, *J* = 7.8 Hz, 1 H), 3.58–3.69 (m, 2 H), 2.38–2.47 (m, 1 H), 2.16–2.24 (m, 1 H), 1.44 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.4, 38.5, 61.0, 111.1, 119.0, 119.3, 121.1, 122.2, 126.7, 129.6, 131.4, 136.6, 143.8.

EI-MS: *m*/*z* = 329 [M$^+$; ^{79}Br], 331 [M$^+$; ^{81}Br].

Anal. Calcd for $C_{17}H_{16}BrNO$: C, 61.83; H, 4.88; N, 4.24. Found: C, 61.85; H, 4.94; N, 4.31.

5c

Pale-yellow oil; $[\alpha]_D^{20}$ –9.8 (*c* 2.0, $CHCl_3$); 86% ee by HPLC (Daicel Chiralpak AD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 27.2 min; τ_{minor} = 19.1 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (br s, 1 H), 7.40 (d, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 7.21–7.25 (m, 4 H), 7.15 (t, *J* = 7.6 Hz, 1 H), 7.00–7.05 (m, 2 H), 4.38 (t, *J* = 7.6 Hz, 1 H), 3.60–3.71 (m, 2 H), 2.40–2.47 (m, 1 H), 2.17–2.26 (m, 1 H), 1.37 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.5 (2 × C), 61.0, 111.1, 119.2, 119.3, 119.4, 121.0, 122.2, 126.7, 128.5, 129.2, 131.7, 136.6, 143.3.

EI-MS: *m*/*z* = 285 [M$^+$; ^{35}Cl], 287 [M$^+$; ^{37}Cl].

Anal. Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90. Found: C, 71.36; H, 5.69; N, 4.82.

5d

Pale-yellow oil; $[\alpha]_D^{20}$ –3.8 (*c* = 1.27, $CHCl_3$); 87% ee by HPLC (Daicel Chiralpak AD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 24.8 min; τ_{minor} = 18.4 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (br s, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.28 (d, *J* = 8.4 Hz, 1 H), 7.20–7.23 (m, 2 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 7.00 (t, *J* = 7.4 Hz, 1 H), 6.89–6.95 (m, 3 H), 4.34 (t, *J* = 7.6 Hz, 1 H), 3.56–3.66 (m, 2 H), 2.36–2.44 (m, 1 H), 2.13–2.20 (m, 1 H), 1.68 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.3, 38.6, 61.0, 111.1, 115.0, 115.2, 119.3, 119.4, 121.0, 122.1, 126.7, 129.2 (d, *J* = 7.4 Hz), 136.5, 140.4 (d, *J* = 2.3 Hz), 161.3 (d, *J* = 242.2 Hz).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{16}FNONa$: 292.1108; found: 292.1104.

EI-MS: *m*/*z* = 269 [M$^+$].

5e

Pale-yellow oil; $[\alpha]_D^{20}$ +5.6 (*c* 0.8, $CHCl_3$); 86% ee by HPLC (Daicel Chiralpak OD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 36.5 min; τ_{minor} = 56.0 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (br s, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.43 (d, *J* = 8.4 Hz, 3 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.02–7.07 (m, 2 H), 4.49 (t, *J* = 7.6 Hz, 1 H), 3.61–3.72 (m, 2 H), 2.44–2.52 (m, 1 H), 2.22–2.31 (m, 1 H), 1.65 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.3, 38.8, 60.8, 111.2, 118.5, 119.2, 119.5, 121.2, 122.3, 125.3 (q, *J* = 4.0 Hz), 125.6 (t, *J* = 280.5 Hz), 128.1, 128.2, 136.5, 149.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{16}F_3NONa$: 342.1076; found: 342.1079.

EI-MS: *m*/*z* = 319 [M$^+$].

5f

Pale-yellow oil; $[\alpha]_D^{20}$ +7.2 (*c* 2.2, $CHCl_3$); 93% ee by HPLC (Daicel Chiralpak AD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 11.3 min; τ_{minor} = 10.8 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (br s, 1 H), 7.62 (s, 2 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.33–7.38 (m, 2 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.04–7.08 (m, 2 H), 4.91 (t, *J* = 7.8 Hz, 1 H), 3.60–3.71 (m, 2 H), 2.43–2.52 (m, 1 H), 2.22–2.32 (m, 1 H), 1.79 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.4, 38.8, 60.8, 111.2, 118.5, 119.1, 119.4, 121.2, 122.2, 123.0 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 270.8 Hz), 124.4 (q, *J* = 3.8 Hz), 126.6, 128.3, 131.3 (2 × C), 136.5, 145.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{16}F_3NONa$: 342.1076; found: 342.1072.

EI-MS: *m*/*z* = 319 [M$^+$].

5g

Colorless oil; $[\alpha]_D^{20}$ –4.6 (*c* 1.33, $CHCl_3$); 89% ee by HPLC (Daicel Chiralpak AD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 18.0 min; τ_{minor} = 16.0 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (br s, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 7.27 (s, 1 H), 7.12–7.20 (m, 4 H), 7.00–7.03 (m, 2 H), 4.36 (t, *J* = 7.8 Hz, 1 H), 3.58–3.69 (m, 2 H), 2.37–2.45 (m, 1 H), 2.17–2.27 (m, 1 H), 1.76 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.4, 38.7, 60.9, 111.2, 118.8, 119.3, 119.4, 121.1, 122.2, 126.1, 126.4, 126.7, 127.9, 129.6, 134.2, 136.5, 147.0.

EI-MS: *m*/*z* = 285 [M^+; ^{35}Cl], 287 [M^+; ^{37}Cl].

Anal. Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90. Found: C, 71.55; H, 5.60; N, 4.88.

5h

Colorless oil; $[\alpha]_D^{20}$ +73.1 (*c* 2.33, $CHCl_3$); 95% ee by HPLC (Daicel Chiralpak AD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 26.7 min; τ_{minor} = 17.9 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (br s, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.34–7.36 (m, 1 H), 7.29 (d, *J* = 8.4 Hz, 1 H), 7.18–7.22 (m, 1 H), 6.99–7.15 (m, 5 H), 4.93 (t, *J* = 7.0 Hz, 1 H), 3.56–3.79 (m, 2 H), 2.41–2.45 (m, 1 H), 2.19–2.27 (m, 1 H), 1.98 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.9, 38.4, 61.2, 111.1, 118.5, 119.3, 119.4, 121.5, 122.1, 126.9, 127.1, 127.3, 129.1, 129.4, 133.5, 136.4, 142.2.

EI-MS: *m*/*z* = 285 [M^+; ^{35}Cl], 287 [M^+; ^{37}Cl].

Anal. Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90. Found: C, 71.42; H, 5.57; N, 4.90.

5i

Yellow oil; $[\alpha]_D^{20}$ –9.0 (*c* 1.13, $CHCl_3$); 86% ee by HPLC (Daicel Chiralpak OD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 38.0 min; τ_{minor} = 52.8 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (br s, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.16 (t, *J* = 7.6 Hz, 1 H), 7.09 (d, *J* = 7.6 Hz, 1 H), 7.02–7.05 (m, 2 H), 4.36 (t, *J* = 7.6 Hz, 1 H), 3.66–3.71 (m, 2 H), 2.42–2.50 (m, 1 H), 2.31 (s, 3 H), 2.23–2.28 (m, 1 H), 1.45 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 38.7, 38.8, 61.4, 111.0, 119.2, 119.5, 119.8, 121.0, 122.0, 126.9, 127.6, 129.1, 135.6, 136.5, 141.7.

EI-MS: *m*/*z* = 265 [M^+].

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.47; H, 7.19; N, 5.27.

5j

Pale-yellow oil; $[\alpha]_D^{20}$ –8.8 (*c* 0.8, $CHCl_3$); 87% ee by HPLC (Daicel Chiralpak OD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 63.7 min; τ_{minor} = 82.1 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (br s, 1 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 6.99–7.02 (m, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 4.33 (t, *J* = 7.8 Hz, 1 H), 3.75 (s, 3 H), 3.66–3.77 (m, 2 H), 2.40–2.48 (m, 1 H), 2.19–2.27 (m, 1 H), 1.36 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.4, 38.8, 55.2, 61.4, 111.0, 113.8, 119.3, 119.5, 120.0, 120.9, 122.0, 126.8, 128.7, 136.6, 136.8, 157.9.

EI-MS: *m*/*z* = 281 [M^+].

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.84; H, 6.76; N, 4.90.

5k

Yellow oil; $[\alpha]_D^{20}$ –42.5 (*c* 0.53, $CHCl_3$); 88% ee by HPLC (Daicel Chiralpak AD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 28.9 min; τ_{minor} = 98.7 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (br s, 1 H), 7.22–7.30 (m, 4 H), 7.14–7.16 (m, 2 H), 6.95 (d, *J* = 1.6 Hz, 1 H), 6.84 (d, *J* = 2.4 Hz, 1 H), 6.78 (dd, *J* = 6.4, 2.4 Hz, 1 H), 4.30 (t, *J* = 7.6 Hz, 1 H), 3.71 (s, 1 H), 3.60–3.66 (m, 2 H), 2.36–2.44 (m, 1 H), 2.18–2.27 (m, 1 H), 1.70 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.5, 39.1, 55.8, 61.2, 101.5, 111.7, 111.9, 119.2, 121.9, 126.1, 127.2, 127.8, 128.4, 131.7, 144.7, 153.6.

EI-MS: *m*/*z* = 281 [M^+].

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.87; H, 6.85; N, 4.86.

5l

Pale-yellow oil; $[\alpha]_D^{20}$ +5.3 (*c* 1.13, $CHCl_3$); 87% ee by HPLC (Daicel Chiralpak AD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 47.5 min; τ_{minor} = 41.6 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (br s, 1 H), 7.22–7.29 (m, 5 H), 7.14 (t, *J* = 7.0 Hz, 1 H), 6.85 (d, *J* = 2.0 Hz, 1 H), 6.75 (d, *J* = 2.0 Hz, 1 H), 6.66 (dd, *J* = 6.4, 2.2 Hz, 1 H), 4.29 (t, *J* = 8.0 Hz, 1 H), 3.75 (s, 1 H), 3.57–3.65 (m, 2 H), 2.36–2.44 (m, 1 H), 2.17–2.27 (m, 1 H), 1.70 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.5, 39.2, 55.6, 61.2, 94.6, 109.1, 119.4, 119.9, 120.0, 121.3, 126.1, 127.8, 128.4, 137.2, 144.8, 156.3.

EI-MS: *m*/*z* = 281 [M^+].

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.80; H, 6.77; N, 4.95.

5m

Colorless oil; $[\alpha]_D^{20}$ –26.8 (*c* 0.93, $CHCl_3$); 87% ee by HPLC (Daicel Chiralpak AD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 20.4 min; τ_{minor} = 17.0 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (br s, 1 H), 7.22–7.30 (m, 5 H), 7.13–7.16 (m, 2 H), 6.95 (d, *J* = 8.4 Hz, 1 H), 6.88 (s, 1 H), 4.31 (t, *J* = 7.8 Hz, 1 H), 3.56–3.65 (m, 2 H), 2.37–2.42 (m, 1 H), 2.36 (s, 3 H), 2.19–2.26 (m, 1 H), 1.70 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 38.7, 39.1, 61.3, 110.8, 118.8, 118.9 (2 × C), 121.3, 123.6, 126.0, 127.0, 127.8, 128.4, 134.8, 144.8.

EI-MS: *m*/*z* = 265 [M^+].

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.47; H, 7.23; N, 5.30.

5n

Colorless oil; $[\alpha]_D^{20}$ +21.3 (*c* 1.2, $CHCl_3$); 94% ee by HPLC (Daicel Chiralpak AD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 15.9 min; τ_{minor} = 17.8 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (br s, 1 H), 7.28–7.36 (m, 3 H), 7.19–7.22 (m, 2 H), 7.03 (d, *J* = 2.4 Hz, 1 H), 6.97–7.00 (m, 2 H), 4.40 (t, *J* = 7.6 Hz, 1 H), 3.66–3.71 (m, 2 H), 2.45–2.53 (m, 1 H), 2.46 (s, 3 H), 2.26–2.34 (m, 1 H), 1.68 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 38.6, 39.3, 61.3, 117.2, 119.4, 120.0, 120.2, 120.8, 122.5, 126.0, 126.3, 127.8, 128.3, 136.0, 144.8.

EI-MS: *m*/*z* = 265 [M^+].

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.35; H, 7.28; N, 5.21.

5o

Yellow solid; mp 157–159 °C; $[\alpha]_D^{20}$ –169.9 (*c* 0.67, $CHCl_3$); 86% ee by HPLC (Daicel Chiralpak AD-H column; *n*-hexane–*i*-PrOH, 90:10; flow rate: 1.0 mL/min; τ_{major} = 23.2 min; τ_{minor} = 38.8 min).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (br s, 1 H), 8.41 (s, 1 H), 8.05 (d, *J* = 9.2 Hz, 1 H), 7.19–7.36 (m, 7 H), 4.44 (t, *J* = 7.8 Hz, 1 H), 3.64–3.71 (m, 2 H), 2.42–2.48 (m, 1 H), 2.26–2.34 (m, 1 H), 1.64 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.5, 38.8, 60.8, 111.0, 116.8, 117.9, 122.6, 123.9, 126.3, 126.7, 127.7, 128.7, 139.5, 141.5, 143.6.

EI-MS: *m*/*z* = 296 [M$^+$].

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.82; H, 5.41; N, 9.46.

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References

(1) For a review, see: Olah, G. A.; Khrisnamurti, R.; Surya Prakashi, G. K. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B. M., Ed.; Pergamon: New York, **1991**, 293.

(2) (a) Sundberg, R. J. *Indoles*; Academic Press: San Diego, **1996**, 175. (b) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, **2003**.

(3) For selected metal-catalyzed procedures, see: (a) Jensen, K. B.; Thorbauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 160. (b) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. (c) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780. (d) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 901. (e) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154. (f) Evans, D. A.; Fandrick, K. R.; Song, H. *J. Am. Chem. Soc.* **2005**, *127*, 8942. (g) Takenaka, N.; Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 742. (h) Arai, T.; Yokoyama, N.; Yanagisawa, A. *Chem. Eur. J.* **2008**, *14*, 2052. (i) Arai, T.; Yokoyama, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4989.

(4) For recent reviews on organocatalysis, see for example: (a) Dalko, P. L.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (b) Seayed, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (c) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, **2007**. (d) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (e) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638.

(5) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172.

(6) (a) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482. (b) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, W.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437. (c) Bonini, B. F.; Capitò, E.; Comes-Franchini, M.; Fochi, M.; Ricci, A.; Zwanenburg, B. *Tetrahedron: Asymmetry* **2006**, *17*, 3135. (d) Li, C.; Liu, H.; Liao, J.; Cao, Y.; Liu, X.; Xiao, W. *Org. Lett.* **2007**, *9*, 1847.

(7) (a) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576. (b) Fleming, E. M.; McCabe, T.; Connon, S. J. *Tetrahedron Lett.* **2006**, *47*, 7037. (c) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 4016. (d) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464.

(8) (a) Li, D.-P.; Guo, Y.-C.; Ding, Y.; Xiao, W.-J. *Chem. Commun.* **2006**, 799. (b) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (c) Tang, H.-Y.; Lu, A.-D.; Zhou, Z.-H.; Zhao, G.-F.; He, L.-N.; Tang, C.-C. *Eur. J. Org. Chem.* **2008**, 1406.

(9) (a) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156. (b) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484. (c) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609. (d) Wanner, M. J.; Hauwert, P.; Schoemaker, H. E.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2008**, 180.

(10) Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. *Angew. Chem. Int. Ed.* **2005**, *44*, 3086.

(11) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292.

(12) For the first reports on the use of diarylprolinol silyl ethers, see: (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794. (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjasgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3703. (c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212.

(13) For selected diarylprolinol silyl ethers catalyzed α-functionalization of aldehydes, see: (a) Mossé, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361. (b) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804. (c) Ibrahem, I.; Zhao, G.-L.; Cordóva, A. *Chem. Eur. J.* **2007**, *13*, 683. (d) Aleman, J.; Cabrera, S.; Maerten, E.; Overgaard, J.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 5520. (e) Tiecco, M.; Carlone, A.; Sternativo, S.; Marini, F.; Bartoli, G.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 6882. (f) Palomo, C.; Vera, S.; Velila, I.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem. Int. Ed.* **2007**, *46*, 8054. (g) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 4722. (h) Chi, Y.; Guo, L.; Kopf, N. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 5608. (i) Shibatomi, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 5796.

(14) For selected diarylprolinol silyl ethers catalyzed β-functionalization and γ-functionalization of α,β-unsaturated aldehydes, see: (a) Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (b) Gotoh, H.; Masui, R.; Ogino, H.; Shoji, M.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 6853. (c) Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G.; Cordóva, A. *Chem. Commun.* **2007**, 849. (d) Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 4504. (e) Ibrahem, I.; Rios, R.; Vesely, J.; Hammar, P.; Eriksson, L.; Himo, F.; Cordóva, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4507. (f) Wang, Y.; Li, P.; Liang, X.; Zhang, T. Y.; Ye, J. *Chem. Commun.* **2008**, 1232. (g) Hayashi, Y.; Samanta, S.; Gotoh, H.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6634. (h) Zhao, G.-L.; Rios, R.; Vesely, J.; Eriksson, L.; Cordóva, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8468.

(15) For selected diarylprolinol silyl ethers catalyzed cascade, tandem, domino and multicomponent reactions, see: (a) Enders, D.; Huttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (b) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986. (c) Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 4922. (d) Reyes, E.; Jiang, H.; Milelli, A.; Elsner, P.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 9202. (e) Sunden, H.; Rios, R.; Ibrahem, I.; Zhao, G.; Eriksson, L.; Cordóva, A. *Adv. Synth. Catal.* **2007**, *349*, 827. (f) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886. (g) Cabrera, S.; Aleman, J.; Bolze, P.; Bertelsen, S.;

Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 121. (h) Hayashi, Y.; Gotoh, H.; Masui, R.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 4012. (i) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem. Int. Ed.* **2008**, *47*, 7539.

(16) For recent reviews on diarylprolinol silyl ethers, see: (a) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 7876. (b) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922.

(17) After our original submission of this manuscript to another journal on the 11th of March, a paper by Wang and co-workers appeared on the web on 17th March, see: Hong, L.; Wang, L.; Chen, C.; Zhang, B.; Wang, R. *Adv. Synth. Catal.* **2009**, *351*, 772.