Organocatalytic Asymmetric Friedel-Crafts Alkylation of Indoles with Simple α,β -Unsaturated Ketones

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General Methods. The ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts (δ) are referenced to residual signals of the solvents (CHCl_3 – 7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR). Coupling constants are given in Hz. Carbon types were determined by DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.¹ Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Mass spectra were obtained from the Department of Organic Chemistry “A. Mangini” Mass Spectroscopy facility. Optical rotations are reported as follows: $[\alpha]_D^{25}$ (c in g per 100 mL, solvent). All reactions were carried out in air and using undistilled solvent, without any precautions to exclude moisture unless otherwise noted.

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.² Indoles **1** and **4a-d** were purchased from Aldrich and used as received. α,β -Unsaturated ketones **2a-e**, **2h** and **2j-k** were purchased from Aldrich or Lancaster and used as received. Enones **2f** and **2g** were prepared by Wittig reaction between commercially available acetylmethylene-triphenylphosphorane and hydrocinnamaldehyde or ethyl glyoxalate, respectively, (DCM/48 h/RT). Enones **2i**³ and **2l**⁴ were synthesized following the literature procedures. *N*-protected amino acids were purchased from Aldrich or Fluka and used as received. Chiral primary amines **A** and **B** were purchased from Aldrich and used as received.

9-Amino(9-deoxy)*epi*-hydroquinine **C** was prepared from commercially available hydroquinine following the literature procedure.⁵

Determination of Enantiomeric Purity. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H or AS-H columns and Daicel Chiralcel OD-H with *i*-PrOH/hexane as the eluent were used. HPLC traces were compared to racemic samples prepared by InBr_3 -catalyzed F-C reaction.⁶

Determination of Absolute Configuration. The absolute configurations of the optically active compounds **3d**⁷, **3f**⁸ and **3l**⁹ were determined on the basis of the measured optical rotations that were compared with literature values. All other absolute configurations were assigned by analogy based on an uniform reaction mechanism and the uniform elution order observed in the HPLC chromatograms.

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Organocatalytic Asymmetric Addition of Indole to *E*-Benzylidenacetone 2a

Catalyst Screen.

Table S1. Catalyst screen.^a

Amine	Acid	Conversion (%) ^b	ee (%) ^c
	TFA	18	0
	TFA	90	0
L-Proline	-	0	-
	-	0	-
	TFA (20 mol%)	<5%	<5%
	TFA	85	-16
	 40mol%	0	-
	TFA	73	29

TFA	18	5
-	0	-
TFA (20 mol%)	80	6
TFA (20 mol%)	0	-
9-Epi-QD-NH₂	TFA (40 mol%)	22	53
9-Epi-HQ-NH₂	TFA (20 mol%)	23	61
9-Epi-HQ-NH₂	TFA (40 mol%)	44	65

^a Open-air reactions were carried out in undistilled toluene using a 1.2:1 ratio of **1** to **2a**, 20 mol% of the catalyst, 40 mol% of the acid on a 0.2 mmol scale. ^b Determined by ¹H NMR of the crude mixture. ^c ee of **3a** was determined by HPLC analysis on a Daicel Chiralpak AD-H column.

Acidic Additives Screen.^a

Table S2. Acidic Additives Screen.^a

Acid	Conv (%) – 24h ^b	ee (%) ^c
TFA (20 mol%)	23	61
TFA	44	65
CF ₃ SO ₃ H	18	31
p-NO ₂ -Benzoic acid	7	80
o-NO ₂ -Benzoic acid	24	79
Ph-CH ₂ -COOH	No reaction	-
No reaction	-
p-TSA	20	59
25	82
THF / 2	88
AcOEt / 5	78
CHCl ₃ / 23	82

^a Open-air reactions were carried out in undistilled solvent using a 1.2:1 ratio of **1** to **2a**, 20 mol% of the catalyst, 40 mol% of the acid on a 0.2 mmol scale. ^b Determined by ¹H NMR of the crude mixture. ^c ee of **3a** was determined by HPLC analysis (AD-H column).

Amino acids Screen.^a

Table S3: Amino acids Screen.^a

Aminoacid	Conv (%) – 24h ^b	ee (%) ^c
-	No reaction	
BocHN-CH ₂ -COOH	<5	85
BocHN-CH(COOH)-CH ₂ -t-Bu (L)	7 20 (5days)	89
BocHN-CH(COOH)-CH ₂ -t-Bu (L) + TFA 10 mol% 10 mol%	12	76
BocHN-CH(COOH)-CH ₂ -C ₆ H ₄ -OH (L)	No reaction	-
BocHN-CH(COOH)-CH ₂ -Indole (L)	6	78
BocHN-CH(COOH)-CH ₂ -i-Pr (L)	6	89
BocHN-CH(COOH)-CH ₂ -i-Bu (L)	5	90
BocHN-CH(COOH)-CH ₂ -Bn (D)	9	89
BocHN-CH(COOH)-CH ₂ -Bn (L)	8	90
BocHN-CH(COOH)-CH ₂ -Bn (RAC)	9	89
H ₂ N-CH(COOH)-CH ₂ -Bn (L)	No reaction	-

$\begin{array}{c} \text{CbzHN} \text{---} \text{CH} \text{---} \text{COOH} \\ \\ \text{(L)} \text{---} \text{Bn} \end{array}$	10	85
$\begin{array}{c} \text{FmocHN} \text{---} \text{CH} \text{---} \text{COOH} \\ \\ \text{(L)} \text{---} \text{Bn} \end{array}$	<5	86
$\begin{array}{c} \text{Boc} \\ \\ \text{Me} \text{---} \text{N} \text{---} \text{CH} \text{---} \text{COOH} \\ \\ \text{(L)} \text{---} \text{Bn} \end{array}$	<5 (48h)	84
$\begin{array}{c} \text{BocHN} \text{---} \text{CH} \text{---} \text{COOH} \\ \\ \text{(L)} \text{---} \text{Ph} \end{array}$	16	90
$\begin{array}{c} \text{BocHN} \text{---} \text{CH} \text{---} \text{COOH} \\ \\ \text{(RAC)} \text{---} \text{Ph} \end{array}$	18	92
$\begin{array}{c} \text{BocHN} \text{---} \text{CH} \text{---} \text{COOH} \\ \\ \text{(D)} \text{---} \text{Ph} \end{array}$	21	93
$\begin{array}{c} \text{BocHN} \text{---} \text{CH} \text{---} \text{COOH} \\ \\ \text{(D)} \text{---} \text{Ph} \end{array}$	>95	87^d
$\begin{array}{c} \text{BocHN} \text{---} \text{CH} \text{---} \text{COOH} \\ \\ \text{(D)} \text{---} \text{Ph} \end{array}$ 20 mol%	62	87 ^d

^a Open-air reactions were carried out in undistilled toluene using a 1.2:1 ratio of **1** to **2a**, 20 mol% of the catalyst, 40 mol% of the acid on a 0.2 mmol scale. ^b Determined by ¹H NMR of the crude mixture. ^c ee of **3a** was determined by HPLC analysis (AD-H column). ^d 70 °C reaction temperature.

Optimisation of the Standard Reaction Parameters.

Table S3. Standard Reaction Parameters.

solvent	[2a] ₀	<i>T</i> (°C)	Conversion (%) ^b	ee (%) ^c
toluene	0.25 M	70	>95	87
toluene: 9 <i>i</i> -PrOH : 1	0.25 M	70	90	85
H ₂ O: 9 THF: 1	0.25 M	70	>95	36
CH ₃ Cl	0.25 M	70	>95	80
THF	0.25 M	70	14	56
(<i>n</i> -Bu) ₂ O	0.25 M	70	42	87
toluene	0.1 M	70	50	90
toluene	0.5 M	70	>95	84
toluene	1 M	50	>95	78
EtOH	1 M	50	84	62
toluene	0.2 M	70	>95 (90)^d	88

^a Open-air reactions were carried out in undistilled solvent using a 1.2:1 ratio of **1** to **2a**, 20 mol% of the catalyst, 40 mol% of the acid on a 0.2 mmol scale. ^b Determined by ¹H NMR of the crude mixture. ^c ee of **3a** was determined by HPLC analysis (AD-H column). ^d Isolated yield is reported in parenthesis.

Experimental Procedures

General Procedure for the Organocatalytic Asymmetric Friedel-Crafts Alkylation of Indoles with Simple α,β -Unsaturated Ketones. All the reactions were carried out in undistilled toluene without any precautions to exclude water. In an ordinary test tube equipped with a magnetic stirring bar, 9-Amino(9-deoxy)*epi*-hydroquinine **C** (0.04 mmol, 13.0 mg) was dissolved in 1 mL of toluene. After addition of 0.08 mmol (20 mg) of D-*N*-Boc-phenylglycine, the solution was stirred for 5 minutes at room temperature. After addition of α,β -unsaturated ketones (0.2 mmol), the mixture was stirred at the indicated temperature for 10 minutes. Then indole derivatives (0.24 mmol) was added in one portion, the tube was closed with a rubber stopper and stirring was continued for the indicated time (24-96 h). Then the crude reaction mixture was diluted with hexane (2 mL) and flushed through a plug of silica, using hexane/Et₂O 1/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography to yield the desired F-C-adduct.

(S)-4-(1*H*-Indol-3-yl)-4-phenyl-butan-2-one^{10,11} - **3a** (Table 2, entries 1-2).

The reaction was carried out at 70 °C for 24 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 85/15) as a white foam in 90% yield and 88% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 10.2 min; τ_{major} = 10.8 min). $[\alpha]_D^{25}$ = +20.3 (c = 0.95, CHCl₃, 88% ee). ¹H NMR (400 MHz, CDCl₃): δ = 2.07 (s, 3H), 3.16 (dd, J = 7.6, 16.0 Hz, 1H), 3.25 (dd, J = 7.6, 16.0 Hz, 1H), 4.84 (t, J = 7.6 Hz, 1H), 6.96-6.99 (m, 1H), 7.00-7.05 (m, 1H), 7.12-7.20 (m, 2H), 7.23-7.33 (m, 5H), 7.42 (d, J = 8 Hz, 1H), 8.02 (br s, 1H); ¹³C NMR (150 MHz, CDCl₃): δ = 30.3 (CH₃), 38.4 (CH), 50.3 (CH₂), 111.1 (CH), 118.8 (C), 119.39 (CH), 119.41 (CH), 121.3 (CH), 122.1 (CH), 126.4 (CH), 126.5 (C), 127.7 (CH), 128.5 (CH), 136.6 (C), 143.9 (C), 207.6 (C).

(S)-4-(4-Chloro-phenyl)-4-(1*H*-indol-3-yl)-butan-2-one – **3b** (Table 2, entry

3). The reaction was carried out at 70 °C for 24 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 7/3) as a white foam in 92% yield and 89% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 9.6 min; τ_{major} = 11.5 min). $[\alpha]_D^{25}$ = +10.9 (c = 1.04, CHCl₃, 89% ee). HRMS: m/z calcd for C₁₈H₁₆NOCl: 297.092043; found: 297.09175. ¹H NMR (400 MHz, CDCl₃): δ = 2.12 (s, 3H), 3.16 (dd, J = 8.0, 16.0 Hz, 1H), 3.27 (dd, J = 7.2, 16.0 Hz, 1H), 4.85 (t, J = 7.2 Hz, 1H), 6.97-7.00 (m, 1H), 7.04-

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7.09 (m, 1H), 7.17-7.22 (m, 1H), 7.24-7.30 (m, 4H), 7.33-7.36 (m 1H), 7.40-7.44 (m 1H), 8.11 (br s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ = 30.4 (CH_3), 37.6 (CH), 50.0 (CH_2), 111.2 (CH), 118.3 (C), 119.2 (CH), 119.5 (CH), 121.2 (CH), 122.2 (CH), 126.3 (C), 128.5 (CH), 129.1 (CH), 131.9 (C), 136.6 (C), 142.5 (C), 207.2 (C).

(R)-4-(1H-Indol-3-yl)-4-thiophen-2-yl-butan-2-one – 3c (Table 2, entry 4).

The reaction was carried out at 70 °C for 48 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a yellowish oil in 92% yield and 84% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 10.4 min; τ_{major} = 12.1 min). $[\alpha]_{\text{D}}^{25}$ = + 2.88 (c = 0.47, CHCl_3 , 84% ee). HRMS: m/z calcd for $\text{C}_{16}\text{H}_{15}\text{NOS}$: 269.08743; found: 269.087. ^1H NMR (400 MHz, CDCl_3): δ = 2.11 (s, 3H), 3.24-3.34 (m, 2H), 5.14 (t, J = 7.6 Hz, 1H), 6.88-6.92 (m, 2H), 7.03-7.13 (m, 3H), 7.16-7.20 (m, 1H), 7.33-7.36 (m 1H), 7.52-7.56 (m 1H), 8.07 (br s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ = 30.5 (CH_3), 33.5 (CH), 50.9 (CH_2), 111.3 (CH), 118.5 (C), 119.3 (CH), 119.5 (CH), 121.6 (CH), 122.2 (CH), 123.5 (CH), 124.1 (CH), 126.1 (C), 126.5 (CH), 136.5 (C), 148.5 (C), 207.0 (C).

(R)-4-(1H-Indol-3-yl)-pentan-2-one^{7,11} – 3d (Table 2, entry 5). The reaction

was carried out at 40°C for 70 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 6/4) as a colourless oil in 98% yield and 87% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 12.5 min; τ_{minor} = 14.6 min). $[\alpha]_{\text{D}}^{25}$ = - 5.1 (c = 0.96, CHCl_3 , 87% ee; Lit.⁷ $[\alpha]_{\text{D}}^{25}$ = - 3.6, (R)-**3d**, (c = 0.55, CHCl_3 , 30% ee). ^1H NMR (400 MHz, CDCl_3): δ = 1.39 (d, J = 6.8, 3H), 2.10 (s, 3H), 2.71 (dd, J = 8.4, 16.0 Hz, 1H), 2.94 (dd, J = 6.0, 16.0 Hz, 1H), 3.60-3.70 (m, 1H), 6.96-6.98 (m, 1H), 7.10-7.15 (m, 1H), 7.18-7.22 (m, 1H), 7.35-7.38 (m, 1H), 7.63-7.67 (m, 1H), 7.96 (br s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ = 21.2 (CH_3), 27.0 (CH), 30.4 (CH_3), 51.5 (CH_2), 111.2 (CH), 119.1 (CH), 119.3 (CH), 120.1 (CH), 121.1 (C), 122.1 (CH), 126.3 (C), 136.5 (C), 208.6 (C).

(R)-4-(1H-Indol-3-yl)-nonan-2-one – 3e (Table 2, entries 6-7). The reaction was carried out at RT for 96 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/Et₂O = 7/3) as a colourless oil in

91% yield and 93% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (95/5 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 24.1 min; τ_{minor} = 25.5 min). $[\alpha]_D^{25}$ = - 35.7 (c = 1.01, CHCl₃, 93% ee). HRMS: m/z calcd for C₁₇H₂₃NO: 257.17796; found: 257.1777. ¹H NMR (400 MHz, CDCl₃): δ = 0.80-0.84 (m, 3H), 1.19-1.29 (m, 6H), 1.64-1.80 (m, 2H), 2.02 (s, 3H), 2.80 (dd, J = 6.8, 16.0 Hz, 1H), 2.89 (dd, J = 7.2, 16.0 Hz, 1H), 3.43-3.53 (m, 1H), 6.96-6.98 (m, 1H), 7.08-7.13 (m, 1H), 7.16-7.22 (m, 1H), 7.35 (d, J = 8.4, 1H), 7.65 (d, J = 8.4, 1H), 7.99 (br s, 1H); ¹³C NMR (150 MHz, CDCl₃): δ = 14.0 (CH₃), 22.5 (CH₂), 27.2 (CH₂), 30.4 (CH₃), 31.7 (CH₂), 32.9 (CH), 35.8 (CH₂), 50.2 (CH₂), 111.3 (CH), 118.9 (C), 119.1 (CH), 119.2 (CH), 121.2 (CH), 121.8 (CH), 126.5 (C), 136.5 (C), 209.2 (C).

(R)-4-(1H-Indol-3-yl)-6-phenyl-hexan-2-one⁸ – 3f (Table 2, entry 8). The reaction was carried out at RT for 96 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a colourless

viscous oil in 67% yield and 93% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 11.5 min, τ_{minor} = 12.6 min). $[\alpha]_D^{25}$ = - 9.2 (c = 0.85, CH₂Cl₂, 93% ee; Lit.⁸ $[\alpha]_D^{25}$ = + 12.6, (S)-**3f**, (c = 1.0, CH₂Cl₂, 94.6% ee). ¹H NMR (400 MHz, CDCl₃): δ = 2.00 (s, 3H), 2.01-2.18 (m, 2H), 2.52-2.62 (m, 2H), 2.84 (dd, J = 7.2, 16.0 Hz, 1H), 2.93 (dd, J = 7.6, 16.0 Hz, 1H), 3.48-3.56 (m, 1H), 7.01 (d, J = 2.4, 1H), 7.09-7.28 (m, 6H), 7.26-7.40 (m, 1H), 7.37 (d, J = 8.0, 1H), 7.65 (d, J = 8.0, 1H), 8.04 (br s, 1H); ¹³C NMR (150 MHz, CDCl₃): δ = 30.4 (CH₃), 32.6 (CH), 33.9 (CH₂), 37.4 (CH₂), 50.2 (CH₂), 111.3 (CH), 118.4 (C), 119.3 (CH), 121.5 (CH), 122.0 (CH), 125.7 (CH), 126.4 (C), 128.2 (CH), 128.4 (CH), 136.6 (C), 142.3 (C), 211.3 (C).

(R)-2-(1H-Indol-3-yl)-4-oxo-hexanoic acid ethyl ester – 3g (Table 2, entry 9).

The reaction was carried out at 50 °C for 66 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 65/35) as a white solid in 99% yield and 95% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (75/25 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 10.9 min, τ_{minor} = 16.2 min). $[\alpha]_D^{25}$ = - 106.4 (c = 1.04, CHCl₃, 95% ee). HRMS: m/z calcd for C₁₅H₁₇NO₃: 259.12084; found: 259.1210. ¹H NMR (400 MHz, CDCl₃): δ = 1.19 (t, J = 7.2 Hz, 3H), 2.18 (s, 3H), 2.85 (dd, J =

4.8, 18.0 Hz, 1H), 3.51 (dd, J = 10.4, 18.0 Hz, 1H), 4.08 (dq, J = 7.2, 10.8 Hz, 1H), 4.18 (dq, J = 7.2, 10.8 Hz, 1H), 4.40 (dd, J = 4.8, 10.4 Hz, 1H), 7.06 (d, J = 2.4 Hz, 1H), 7.12-7.23 (m, 2H), 7.35 (dt, J = 0.8, 8.0 Hz, 1H), 7.71-7.73 (d, J = 8.4 Hz, 1H), 8.25 (br s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ = 14.0 (CH_3), 29.9 (CH_3), 37.8 (CH), 46.2 (CH_2), 61.0 (CH_2), 111.3 (CH), 112.8 (C), 119.2 (CH), 119.7 (CH), 122.1 (CH), 122.3 (CH), 126.1 (C), 136.2 (C), 173.8 (C), 206.9 (C).

3-(1H-Indol-3-yl)-cyclohexanone^{10,12} – **3h** (Table 2, entry 10). The reaction was carried out at 40 °C for 70 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 75/25) as a colourless oil in 65% yield and 78% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 9.3 min, τ_{minor} = 10.9 min). $[\alpha]_{\text{D}}^{25}$ = +11.1 (c = 0.51, CHCl_3 , 78% ee). ^1H NMR (400 MHz, CDCl_3): δ = 1.80-2.10 (m, 3H), 2.24-2.50 (m, 3H), 2.60-2.68 (m, 1H), 2.78-2.85 (m, 1H), 3.42-3.49 (m, 1H), 6.97-7.00 (m, 1H), 7.10-7.15 (m, 1H), 7.19-7.23 (m, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 8.09 (br s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ = 24.9 (CH_2), 31.7 (CH_2), 35.9 (CH), 41.5 (CH_2), 48.1 (CH_2), 111.3 (CH), 119.0 (CH), 119.3 (CH), 119.7 (C), 120.3 (CH), 122.2 (CH), 126.1 (C), 136.4 (C), 211.8 (C).

(S)-1-(1H-Indol-3-yl)-1-phenyl-pentan-3-one – **3i** (Table 2, entry 11). The reaction was carried out at 70 °C for 72 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 8/2) as a white solid in 56% yield and 95% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 9.4 min; τ_{major} = 10.1 min). $[\alpha]_{\text{D}}^{25}$ = +38.2 (c = 0.77, CHCl_3 , 95% ee). HRMS: m/z calcd for $\text{C}_{19}\text{H}_{19}\text{NO}$: 277.14666; found: 277.146. ^1H NMR (400 MHz, CDCl_3): δ = 0.95 (t, J = 7.2, 3H), 2.25-2.44 (m, 2H), 3.15 (dd, J = 8.0, 16.0 Hz, 1H), 3.24 (dd, J = 7.2, 16.0 Hz, 1H), 4.86 (t, J = 7.2 Hz, 1H), 6.98-7.00 (m, 1H), 7.01-7.05 (m, 1H), 7.13-7.20 (m, 2H), 7.24-7.34 (m, 5H), 7.42-7.46 (m, 1H), 8.01 (br s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ = 7.55 (CH_3), 36.4 (CH_2), 38.3 (CH), 49.1 (CH_2), 111.1 (CH), 119.0 (C), 119.39 (CH), 119.47 (CH), 121.3 (CH), 122.1 (CH), 126.3 (CH), 126.5 (C), 127.7 (CH), 128.4 (CH), 136.6 (C), 144.0 (C), 210.2 (C).

¹² P. Magnus, J. Lacour, P. A. Evans, P. Rigollier, H. Tobler *J. Am. Chem. Soc.* **1998**, *120*, 12486.

(S)-1-(1H-Indol-3-yl)-1,3-diphenyl-propan-1-one⁶ – 3j (Table 2, entry 12).

The reaction was carried out at 70 °C for 96 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/AcOEt = 85/15 to 6/4) as a white solid in 78% yield and 82% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 16.9 min; τ_{major} = 18.9 min). $[\alpha]_D^{25}$ = + 23.3 (c = 0.82, CHCl₃, 82% ee). ¹H NMR (400 MHz, CDCl₃): δ = 3.73 (dd, J = 7.6, 16.8 Hz, 1H), 3.83 (dd, J = 7.2, 16.8 Hz, 1H), 5.08 (t, J = 7.2 Hz, 1H), 6.98-7.00 (m, 1H), 7.00-7.05 (m, 1H), 7.13-7.20 (m, 2H), 7.24-7.38 (m, 5H), 7.41-7.46 (m, 3H), 7.52-7.56 (m, 1H), 7.92-7.95 (m, 2H), 7.98 (br s, 1H); ¹³C NMR (150 MHz, CDCl₃): δ = 38.2 (CH), 45.2 (CH₂), 111.1 (CH), 119.28 (C), 119.38 (CH), 119.52 (CH), 121.4 (CH), 122.1 (CH), 126.3 (CH), 126.6 (C), 127.8 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 132.9 (CH), 136.6 (C), 137.1 (C), 144.2 (C), 198.6 (C).

(R)-5-(1H-Indol-3-yl)-hexan-3-one – 3k¹³ (Table 2, entry 13). The reaction

was carried out at 50 °C for 72 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/ Et₂O = 7/3) as a colourless oil in 76% yield and 96% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 7.3 min; τ_{major} = 7.7 min). $[\alpha]_D^{25}$ = - 8.5 (c = 0.93, CHCl₃, 96% ee). HRMS: m/z calcd for C₁₄H₁₇NO: 215.13101; found: 215.130. ¹H NMR (400 MHz, CDCl₃): δ = 1.00 (t, J = 7.2, 3H), 1.39 (d, J = 7.2, 3H), 2.37 (q, J = 7.2, 2H), 2.69 (dd, J = 8.4, 16.0 Hz, 1H), 2.92 (dd, J = 5.6, 16.0 Hz, 1H), 3.62-3.72 (m, 1H), 6.96-6.98 (m, 1H), 7.10-7.15 (m, 1H), 7.18-7.22 (m, 1H), 7.34-7.37 (m, 1H), 7.64-7.68 (m, 1H), 8.00 (br s, 1H); ¹³C NMR (150 MHz, CDCl₃): δ = 7.7 (CH₃), 21.2 (CH₃), 27.1 (CH), 36.4 (CH₂), 50.2 (CH₂), 111.2 (CH), 119.15 (CH), 119.19 (CH), 120.1 (CH), 121.2 (C), 122.0 (CH), 126.2 (C), 136.5 (C), 211.3 (C).

(R)-5-(1H-Indol-3-yl)-1-phenyl-butan-1-one – 3l⁶ (Table 2, entry 14). The

reaction was carried out at 70 °C for 90 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/ AcOEt = 85/15) as a white solid in 94% yield and 70% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 11.3 min; τ_{major} = 12.5 min). $[\alpha]_D^{25}$ = + 14.2 (c = 1.22, CHCl₃, 70% ee; Lit.⁹ $[\alpha]_D^{25}$ = + 7.4, (R)-**3l**, (c = 1.0, CHCl₃, 64% ee). ¹H NMR (400 MHz, CDCl₃): δ = 1.47 (d, J = 6.8, 3H), 3.26 (dd, J = 8.8, 16.4 Hz, 1H), 3.49 (dd, J = 4.8, 16.4 Hz,

¹³ T. C. Wabnitz, J.-Q. Yu, J. B. Spencer, *Chem. Eur. J.* **2004**, *10*, 484.

1H), 3.81-3.91 (m, 1H), 7.00-7.04 (m, 1H), 7.14 (t, J = 6.8 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 7.2 Hz, 2H), 8.00 (br s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ = 21.0 (CH_3), 27.1 (CH), 46.4 (CH_2), 111.3 (CH), 119.19 (CH), 119.21 (CH), 120.1 (CH), 121.5 (C), 122.0 (CH), 126.3 (C), 128.1 (CH), 128.5 (CH), 132.9 (CH), 136.5 (C), 137.3 (C), 199.8 (C).

(R)-4-(2-Methyl-1H-indol-3-yl)-nonan-2-one – 5a (Table 3, entries 2 and 3).

The reaction was carried out at RT for 24 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 7/3) as a yellowish oil in 87% yield and 94% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 7.2 min, τ_{minor} = 8.3 min). $[\alpha]_{\text{D}}^{25}$ = - 32.3 (c = 0.98, CHCl_3 , 94% ee). HRMS: m/z calcd for $\text{C}_{18}\text{H}_{25}\text{NO}$: 271.19361; found: 271.1942. ^1H NMR (400 MHz, CDCl_3): δ = 0.79-0.84 (m, 3H), 1.08-1.28 (m, 6H), 1.65-1.75 (m, 1H), 1.80-1.90 (m, 1H), 1.95 (s, 3H), 2.38 (s, 3H), 2.81 (dd, J = 6.0, 16.0 Hz, 1H), 3.05 (dd, J = 4.4, 16.0 Hz, 1H), 3.33-3.40 (m, 1H), 7.02-7.12 (m, 2H), 7.24-7.28 (m, 1H), 7.69 (d, J = 7.6, 1H), 7.75 (br s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ = 12.0 (CH_3), 14.0 (CH_3), 22.6 (CH_2), 27.6 (CH_2), 30.7 (CH_3), 31.7 (CH_2), 32.6 (CH), 35.1 (CH_2), 49.3 (CH_2), 110.4 (CH), 113.3 (C), 118.8 (CH), 118.9 (CH), 120.6 (CH), 127.1 (C), 131.4 (C), 135.6 (C), 209.0 (C).

(R)-4-(5-Chloro-1H-indol-3-yl)-nonan-2-one – 5b (Table 3, entry 4). The

reaction was carried out at 40 °C for 96 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/ Et_2O = 7/3) as a yellowish oil in 74% yield and 92% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (95/5 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 22.5 min, τ_{minor} = 23.8 min). $[\alpha]_{\text{D}}^{25}$ = - 16.9 (c = 0.92, CHCl_3 , 92% ee). HRMS: m/z calcd for $\text{C}_{17}\text{H}_{22}\text{NOCl}$: 291.13899; found: 291.1390. ^1H NMR (400 MHz, CDCl_3): δ = 0.80-0.86 (m, 3H), 1.18-1.26 (m, 6H), 1.62-1.76 (m, 2H), 2.03 (s, 3H), 2.78 (dd, J = 6.8, 16.0 Hz, 1H), 2.85 (dd, J = 7.6, 16.0 Hz, 1H), 3.37-3.44 (m, 1H), 6.97 (d, J = 2.4 Hz, 1H), 7.12 (dd, J = 2.0, 8.8 Hz, 1H), 7.24 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 2.4, 1H), 8.13 (br s, 1H); ^{13}C NMR (150 MHz, CDCl_3): δ = 14.0 (CH_3), 22.5 (CH_2), 27.2 (CH_2), 30.4 (CH_3), 31.7 (CH_2), 32.7 (CH), 35.7 (CH_2), 50.0 (CH_2), 112.3 (CH), 118.7 (CH), 118.9 (C), 122.1 (CH), 122.7 (CH), 124.9 (C), 127.6 (C), 134.8 (C), 208.7 (C).

(R)-4-(5-Methoxy-1H-indol-3-yl)-nonan-2-one – 5c (Table 3, entry 5). The reaction was carried out at RT for 40 h using 20 mol% of amine **C** and 40 mol% of D-*N*-Boc-phenylglycine following the general procedure. The title compound was isolated by column chromatography (hexane/Et₂O = 6/4) as a colourless oil in 76% yield and 93% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (85/15 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 8.7 min; τ_{major} = 9.2 min). $[\alpha]_{\text{D}}^{25}$ = -16.8 (c = 1.0, CHCl₃, 93% ee). HRMS: m/z calcd for C₁₈H₂₅NO₂: 287.18853; found: 287.1884. ¹H NMR (400 MHz, CDCl₃): δ = 0.82-0.86 (m, 3H), 1.22-1.27 (m, 6H), 1.64-1.78 (m, 2H), 2.03 (s, 3H), 2.78 (dd, J = 6.8, 16.0 Hz, 1H), 2.86 (dd, J = 7.2, 16.0 Hz, 1H), 3.39-3.46 (m, 1H), 3.88 (s, 3H), 6.85 (dd, J = 2.4, 8.8 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 7.09 (d, J = 2.4 Hz, 1H), 7.22 (dd, J = 0.4, 8.8 Hz, 1H), 7.99 (br s, 1H); ¹³C NMR (150 MHz, CDCl₃): δ = 14.0 (CH₃), 22.5 (CH₂), 27.2 (CH₂), 30.4 (CH₃), 31.8 (CH₂), 32.7 (CH), 35.7 (CH₂), 50.1 (CH₂), 55.9 (CH₃), 101.4 (CH), 111.7 (CH), 111.8 (CH), 118.7 (C), 121.9 (CH), 126.9 (C), 131.6 (C), 153.6 (C), 209.0 (C).