Organocatalytic enantioselective indole alkylations of α,β-unsaturated ketones†

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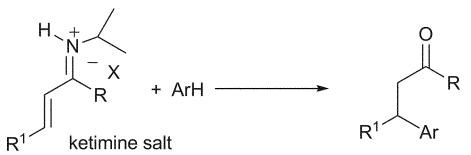
The C3-selective enantioselective Michael-type Friedel–Crafts alkylations of indoles with nonchelating α,β-unsaturated alkyl ketones, catalysed by a chiral primary amine derived from natural cinchonine, were investigated. The reactions, in the presence of 30 mol% catalyst, were smoothly conducted at 0 to −20 °C. Moderate to good ee (47–89%) has been achieved.

Introduction

The Friedel–Crafts reaction and its enantioselective variants have been employed as a powerful carbon–carbon bond forming process.[1] The application of the reaction to the alkylations of indoles triggered special interest because the indole framework has been widely identified in a large amount of natural products and medicinal agents.[2] Although numerous acid-catalysed Michael-type additions of electron-rich indoles to α,β-unsaturated carbonyl compounds have been reported, the asymmetric process has been less explored.[3] Previous examples utilised oxazoline-based metal complexes as the chiral catalysts, and high enantioselectivity has been achieved for the Michael acceptors with bidentate structures.[4] However, only one example has been presented with nonchelating α,β-unsaturated aryl ketones (up to 89% ee) catalysed by a chiral [Al(salen)Cl] complex, and very low ee (11%) was obtained for simple α,β-unsaturated alkyl ketones.[5] On the other hand, MacMillan *et al.* developed a versatile protocol for the asymmetric Michael-type Friedel–Crafts reactions between various aromatic compounds and α,β-unsaturated aldehydes, employing benzyl imidazolidinone salts derived from L-phenylalanine as the LUMO-lowering activation organocatalysts.[6,7] Nevertheless, such a catalytic system was inefficient for the stereoselective addition of indoles to α,β-unsaturated ketones, and poor ee (25%) has been observed.[8] Therefore, the development of alternative catalysts for the enantioselective Friedel–Crafts reactions between indoles and simple α,β-unsaturated ketones is highly desirable.

During our continuing studies on organocatalysis based on the iminium strategy,[9] we are interested in the undeveloped asymmetric reaction between indoles and α,β-unsaturated ketones catalysed by chiral aminocatalysts.[10] However, we found that a very sluggish activating rate, or even inert capacity was generally observed for secondary amines which we have successfully applied in the reactions of α,β-unsaturated aldehydes. We realised that the formation of the iminium cation between the α,β-unsaturated ketone and a secondary amine would be relatively unfavoured because of steric hindrance. It could be envisaged that the generation of a ketimine cation from a primary amine salt and the ketone carbonyl should be much more practicable. Thus the LUMO energy of the α,β-unsaturated system could be lowered, and the Michael-type coupling reaction would be facilitated [eqn (1)].[11]



(1)

Results and discussion

Inspired by this initiative, primary amines **1a–1d** with various chiral scaffolds (Fig. 1) were screened in the reaction of indole **2a** and α,β-unsaturated ketone **3a** in the presence of acidic additive. Amino alcohol **1a** was inert for the coupling reaction (Table 1, entry 1), and the desired C3-selective Friedel–Crafts alkylation product **4aa** was obtained in a racemic form with alanamide **1b**[12] (entry 2). Gratifyingly, we found that the diamine compound **1c** derived from natural cinchonine[13] showed promising catalytic activity in the combination with 2 equiv. of CF_3SO_3H, and **4aa** was cleanly obtained in 26% isolated yield with 56% ee after 12 h at ambient temperature, while a large amount of starting materials remained unchanged in this period of time (entry 3). A lower ee was attained in the presence of 9-amino-9-deoxyepiquinine **1d**[13] (entry 4). Subsequently, a range of reaction conditions with diamine **1c** were further investigated in order to improve the catalytic efficacy. $HClO_4$ salt gave faster reaction but the ee was much lower (entry 5). *p*-TsOH salt was less efficient (entry 6) and TFA salt showed almost no catalytic activity (entry 7).

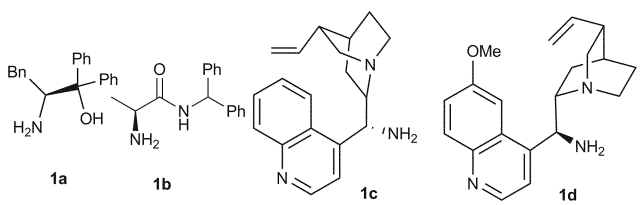


Fig. 1 Structures of the chiral primary amine catalysts.

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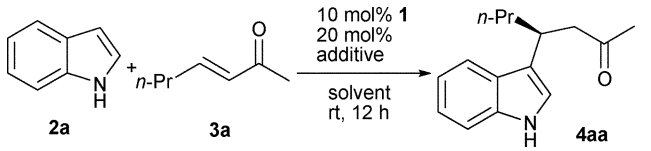
† Electronic supplementary information (ESI) available: NMR and HPLC spectra of the products. See DOI: 10.1039/b616504d

Table 1 Screening studies of the asymmetric Friedel–Crafts reaction of indole **2a** and α,β-unsaturated ketone **3a**[a]



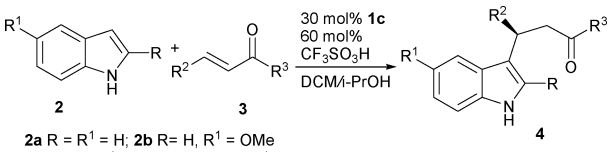
Entry	Catalyst	Solvent	Additive	Yield[b] (%)	Ee[c] (%)
1[d]	**1a**	THF	CF_3SO_3H	—	—
2[d]	**1b**	THF	CF_3SO_3H	30	0
3	**1c**	THF	CF_3SO_3H	26	56
4	**1d**	THF	CF_3SO_3H	35	35
5	**1c**	THF	$HClO_4$	60	22
6	**1c**	THF	*p*-TsOH	13	58
7	**1c**	THF	CF_3COOH	Trace	—
8	**1c**	DCM	CF_3SO_3H	13	51
9	**1c**	DCM–*i*-PrOH	CF_3SO_3H	44	58
10	**1c**	THF–*i*-PrOH	CF_3SO_3H	44	36
11	**1c**	DCM–MeOH	CF_3SO_3H	99	26
12[e]	**1c**	DCM–*i*-PrOH	CF_3SO_3H	52	65
13[f]	**1c**	DCM–*i*-PrOH	CF_3SO_3H	70	75

[a] Unless otherwise noted, the reaction was conducted with **2a** (0.1 mmol), **3a** (0.2 mmol), catalyst **1** (0.01 mmol) and acidic additive (0.02 mmol) in a solvent (1 mL) at room temperature for 12 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Adding 0.01 mmol of CF_3SO_3H. [e] At −10 °C for 6 d. [f] At −20 °C with 30 mol% of **1c** for 6d.

Although slow reaction was observed in pure DCM catalysed by **1c**–$(CF_3SO_3H)_2$ (entry 8), it was found that adding 15% *i*-PrOH (v/v) could accelerate the reaction (entry 9).[6b] However, the ee was decreased in the mixture of THF–*i*-PrOH (entry 10). Excellent yield was obtained in the mixture of DCM–MeOH but the ee was disappointing (entry 11). Finally we conducted the Friedel–Crafts alkylation at lower temperature. The reaction became sluggish with 10 mol% of **1c** at −10 °C, 65% ee with 52% yield was obtained after 6 days (entry 12). Nevertheless, up to 75% ee with better yield was achieved catalysed by 30 mol% of **1c** at −20 °C (entry 13).[14]

With the reaction conditions in hand, we then examined the scope and limitations of enantioselective indole alkylations catalysed by 30 mol% of **1c**. The reaction results are summarised in Table 2. Lower reactivity was observed in the reaction of indole **2a** with unsaturated ketone **3b** with a branched β-substitution while a good ee (82%) was obtained (entry 2). The alkylation reactions with β-aryl unsaturated ketones **3c** and **3d** were conducted at 0 °C, and moderate ee was observed (entries 3 and 4). A much higher ee was achieved in the reaction of indole **2a** and ethyl enone **3e** (entry 5). On the other hand, 5-methoxyindole **2b** generally gave higher enantioselectivity in the Friedel–Crafts reactions with various α,β-unsaturated ketones. The coupling reactions with alkyl-substituted substrates **3a** and **3b** were sluggish but good ees were achieved (entries 6–9). In contrast, high reactivity was noted for β-aryl enone **3d** with moderate enantioselectivity (entries 10 and 11). Much lower ees were obtained for enones **3f** and **3g** with electron-donating substitution (entries 12 and 13). High ees were attained for β-aryl enones **3e**, **3h** and **3i** with bulkier alkyl group at 0 °C (entries 14–17), but lower reactivity was observed for enone **3h** (entry 16). The ee was moderate in the case of cyclic enone **3j** (entry 18). The enantioselectivity also decreased when indole

Table 2 Asymmetric Friedel–Crafts alkylations of indoles **2** with α,β-unsaturated ketone **3**[a]



2a R = R^1 = H; **2b** R= H, R^1 = OMe
2c R= H, R^1 = Br; **2d** R= CH_3, R^1 = H

Entry	**2**	R^2	R^3 (**3**)	*T* (°C)/*t* (d)	**4**	Yield[b] (%)	Ee[c] (%)
1	**2a**	*n*-Pr	CH_3 (**3a**)	−20/6	**4aa**	70	75
2	**2a**	*i*-Pr	CH_3 (**3b**)	−10/6	**4ab**	35	82
3	**2a**	Ph	CH_3 (**3c**)	0/3	**4ac**	72	65
4	**2a**	*p*-Cl-Ph	CH_3 (**3d**)	0/3	**4ad**	61	64
5	**2a**	Ph	C_2H_5 (**3e**)	0/6	**4ae**	47	81
6	**2b**	*n*-Pr	CH_3 (**3a**)	−10/6	**4ba**	74	78
7				−20/6		43	84
8	**2b**	*i*-Pr	CH_3 (**3b**)	0/4	**4bb**	42	81
9				−20/6		23	86
10	**2b**	*p*-Cl-Ph	CH_3 (**3d**)	0/2	**4bd**	99	70
11				−20/6		70	72
12	**2b**	*p*-MeO-Ph	CH_3 (**3f**)	0/7	**4bf**	93	47
13	**2b**	2-Thienyl	CH_3 (**3g**)	0/7	**4bg**	83	50
14	**2b**	Ph	C_2H_5 (**3e**)	0/3	**4be**	91	85
15				−20/6		16	89
16	**2b**	*p*-Cl-Ph	C_2H_5 (**3h**)	0/7	**4bh**	41	88[d]
17	**2b**	Ph	C_3H_7 (**3i**)	0/5	**4bi**	78	87
18	**2b**	$–C_3H_6–$	(**3j**)	−20/8	**4bj**	82	56
19	**2c**	*n*-Pr	CH_3 (**3a**)	0/6	**4ca**	72	59
20	**2d**	*n*-Pr	CH_3 (**3a**)	−20/6	**4da**	99	65
21	**2d**	*i*-Pr	CH_3 (**3b**)	−20/6	**4db**	78	82

[a] Reaction conditions: **2** (0.1 mmol), **3** (0.2 mmol), catalyst **1c** (0.03 mmol) and CF_3SO_3H (0.06 mmol) were stirred in DCM–*i*-PrOH (85 : 15, 1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configuration was determined to be (*R*) by X-ray analysis, and the other products were assigned accordingly.

2c with an electron-withdrawing substitution was applied. In addition, we explored the asymmetric Friedel–Crafts reaction of 2-methylindole **2d**. Interestingly, better reactivity was observed in the reaction with β-alkyl enones compared with indole **2a**, and good ee was obtained using enone **3b** as the acceptor (entries 20 and 21).

In order to determine the absolute configuration of the Friedel–Crafts products, single crystals suitable for X-ray crystallographic analysis were obtained from compound **4bh** bearing a chlorine atom. Over 99% ee could be gained after two recrystallizations of **4bh** (88% ee) from a mixture of ethyl acetate and hexane. The absolute configuration of **4bh** was determined to be (*R*) in the benzylic carbon (Fig. 2).‡ Subsequently, we proposed a possible transitional model for the stereocontrol. As illustrated in Fig. 3, the ketimine cation between **1c** and α,β-unsaturated ketone **3h**

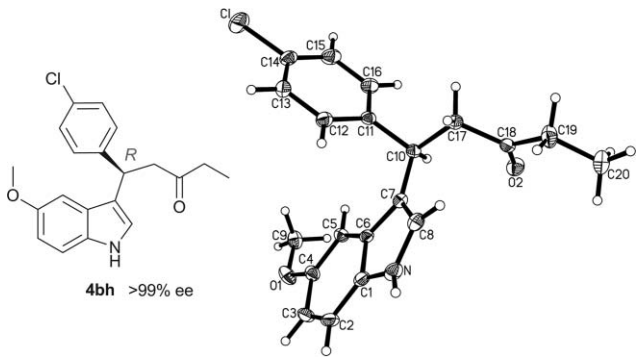


Fig. 2 X-Ray structure of enantiopure **4bh**. Thermal ellipsoids are shown at 30% probability.

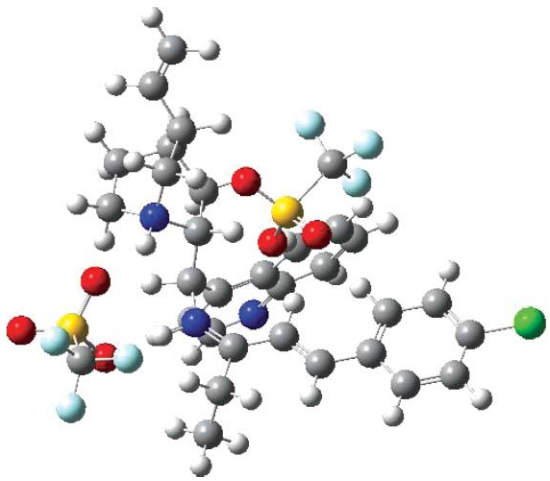


Fig. 3 Plausible iminium ion in the asymmetric Friedel–Crafts reaction.

‡ Crystal data for enantiopure **4bh** $C_{20}H_{20}ClNO_2$ (341.82), orthorhombic, space group $P2_12_12_1$, $a = 5.1480(1)$, $b = 15.8080(3)$, $c = 21.3073(5)$ Å, $U = 1733.98(6)$ Å^3, $Z = 4$, specimen $0.55 \times 0.19 \times 0.16$ mm^3, $T = 153(2)$ K, Mac Science M18XHF22-SRA diffractometer, absorption coefficient 0.232 mm^{-1}, reflections collected/unique 17187/3985 [R(int) = 0.0185], refinement by full-matrix least-squares on F^2, data/restraints/parameters 3985/0/224, goodness-of-fit on $F^2 = 1.008$, final R indices [$I > 2\sigma(I)$] $R1 = 0.0296$, $wR2 = 0.0778$, R indices (all data) $R1 = 0.0302$, $wR2 = 0.0782$, absolute structure parameter 0.02(5), extinction coefficient 0.0117(15), largest diff. peak and hole 0.375 and −0.442 e Å^{-3}. CCDC reference number 624251. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b616504d

might adopt a *trans*-conformation. Then nucleophilic attack from *re*-face of the iminium ion would give the desired (*R*)-product.[15]

Conclusions

In conclusion, we have demonstrated for the first time that a chiral primary amine derived from natural cinchonine was an efficient organocatalyst for the asymmetric Michael-type Friedel–Crafts alkylations of indoles and α,β-unsaturated alkyl ketones. Moderate to high enantioselectivity (47–89% ee) has been achieved. To our knowledge, this is the best result for this type of reactions in the limited literature reports. Further expansion of the asymmetric Friedel–Crafts reactions, mechanistic studies and application of the readily available and inexpensive primary aminocatalysts in other environmentally benign stereoselective reactions are actively under way in our laboratory.[16]

Experimental

General methods

TLC was performed on glass-backed silica plates. Column chromatography was performed using silica gel (200–300 mesh) eluting with ethyl acetate and petroleum ether. NMR was recorded on Bruker 300 or 400 MHz spectrometers. Chemical shifts were reported in ppm down field from tetramethylsilane with the solvent resonance as the internal standard. ESI HRMS was recorded on a Bruker Apex-2. Enantiomeric excess was determined by HPLC analysis on Chiralpak columns. All other reagents were used without purification as commercially available.

General procedure for Friedel–Crafts alkylations of indoles with α,β-unsaturated ketones

α,β-Unsaturated ketones **3** (0.2 mmol), indole **2** (0.1 mmol) and catalyst **1c** 8.8 mg (0.03 mmol) were stirred in a mixture of DCM and *i*-PrOH (85 : 15, v/v, 1.0 mL) at the desired temperature. Then CF_3SO_3H 5.3 μL (0.06 mmol) was added. The reaction was maintained at this temperature and monitored by TLC analysis. Then the solution was diluted with Et_2O (10 mL), washed with water, dried, and concentrated. The residue was chromatographed on silica gel to give the desired product **4**.

4-(1*H*-Indol-3-yl)heptan-2-one (4aa). 70% yield. $[a]_D^{20}$ +11.0 ($c = 0.22$, CH_2Cl_2), 75% ee. The enantiomeric excess was determined by HPLC on Chiralpak AS column (5% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, $t_{minor} = 23.69$ min, $t_{major} = 26.28$ min. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.03$ (br s, 1H), 7.66 (d, $J = 8.0$ Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.20–7.07 (m, 2H), 6.95 (d, $J = 2.4$ Hz, 1H), 3.50–3.44 (m, 1H), 2.89 (dd, $J = 15.6$, 7.6 Hz, 1H), 2.79 (dd, $J = 15.8$, 7.2 Hz, 1H), 2.02 (s, 3H), 1.78–1.62 (m, 2H), 1.31–1.21 (m, 2H), 0.85 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 208.9$, 136.5, 126.5, 121.9, 121.2, 119.3, 119.2, 119.0, 111.2, 50.2, 38.1, 32.6, 30.4, 20.7, 14.0. ESI HRMS: calcd. for $C_{15}H_{19}NO + Na$ 252.1364, found 252.1356.

4-(1*H*-Indol-3-yl)-5-methylhexan-2-one (4ab). 35% yield. $[a]_D^{20}$ +5.0 ($c = 0.16$, CH_2Cl_2), 82% ee. The enantiomeric excess was determined by HPLC on Chiralpak AS column (5% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, $t_{minor} = 25.40$ min, $t_{major} = 34.18$ min. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.07$ (br s, 1H), 7.65

(d, $J = 8.0$ Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.18 (t, $J = 7.2$ Hz, 1H), 7.11 (d, $J = 7.2$ Hz, 1H), 6.93 (d, $J = 2.0$ Hz, 1H), 3.37–3.31 (m, 1H), 2.93–2.81 (m, 2H), 2.09–2.02 (m, 1H), 1.98 (s, 3H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.87 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 209.3$, 136.3, 127.2, 121.9, 121.8, 119.4, 119.1, 117.5, 111.1, 47.0, 39.3, 32.6, 30.1, 20.5, 20.4. ESI HRMS: calcd. for $C_{15}H_{19}NO$ + Na 252.1364, found 252.1351.

4-(1*H*-Indol-3-yl)-4-phenylbutan-2-one (4ac). 72% yield. $[\alpha]_D^{20}$ −25.3 ($c = 0.4$, CH_2Cl_2), 65% ee. The enantiomeric excess was determined by HPLC on Chiralpak AS column (30% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, $t_{minor} = 8.15$ min, $t_{major} = 7.37$ min. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.02$ (br s, 1H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.33–6.98 (m, 9H), 4.83 (t, $J = 7.6$ Hz, 1H), 3.25 (dd, $J = 16.2$, 7.6 Hz, 1H), 3.16 (dd, $J = 16.0$, 8.0 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 207.9$, 143.9, 136.5, 128.4, 127.6, 126.3, 122.0, 121.3, 119.3, 118.5, 111.1, 50.2, 38.3, 30.3. ESI HRMS: calcd. for $C_{18}H_{17}NO$ + Na 286.1208, found 286.1191.

4-(4-Chlorophenyl)-4-(1*H*-indol-3-yl)butan-2-one (4ad). 61% yield. $[\alpha]_D^{20}$ −12.2 ($c = 0.36$, CH_2Cl_2), 64% ee. The enantiomeric excess was determined by HPLC on Chiralpak AS column (30% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, $t_{minor} = 7.81$ min, $t_{major} = 6.82$ min. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.04$ (br s, 1H), 7.38–7.32 (m, 2H), 7.25–7.14 (m, 5H), 7.05–6.97 (m, 2H), 4.81 (t, $J = 7.6$ Hz, 1H), 3.24 (dd, $J = 16.2$, 7.2 Hz, 1H), 3.13 (dd, $J = 16.4$, 8.0 Hz, 1H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 207.2$, 142.5, 136.6, 132.0, 129.1, 128.6, 126.3, 122.3, 121.3, 119.5, 119.3, 118.4, 111.2 50.0, 37.6, 30.4. ESI HRMS: calcd. for $C_{18}H_{16}ClNO$ + Na 320.0818, found 320.0813.

1-(1*H*-Indol-3-yl)-1-phenylpentan-3-one (4ae). 47% yield. $[\alpha]_D^{20}$ −18.6 ($c = 0.22$, CH_2Cl_2), 81% ee. The enantiomeric excess was determined by HPLC on Chiralpak AS column (30% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, $t_{minor} = 6.60$ min, $t_{major} = 5.69$ min. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.01$ (br s, 1H), 7.42 (d, $J = 8.8$ Hz, 1H), 7.33–7.23 (m, 5H), 7.18–7.12 (m, 2H), 7.03–6.98 (m, 2H), 4.85 (t, $J = 7.6$ Hz, 1H), 3.23 (dd, $J = 15.8$, 7.6 Hz, 1H), 3.14 (dd, $J = 15.8$, 8.0 Hz, 1H), 2.43–2.24 (m, 2H), 0.94 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 210.2$, 144.0, 136.6, 128.4, 127.7, 126.5, 126.3, 122.1, 121.3, 119.5, 119.4, 119.0, 111.1, 49.1, 38.4, 36.4, 7.5. ESI HRMS: calcd. for $C_{19}H_{19}NO$ + Na 300.1364, found 300.1349.

4-(5-Methoxy-1*H*-indol-3-yl)heptan-2-one (4ba). 43% yield. $[\alpha]_D^{20}$ +8.6 ($c = 0.36$, CH_2Cl_2), 84% ee. The enantiomeric excess was determined by HPLC on Chiralpak AD column (10% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, $t_{minor} = 13.21$ min, $t_{major} = 11.75$ min. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.94$ (br s, 1H), 7.23 (d, $J = 8.4$ Hz, 1H), 7.09 (d, $J = 2.8$ Hz, 1H), 6.94 (d, $J = 2.4$ Hz, 1H), 6.85 (dd, $J = 8.4$, 2.4 Hz, 1H), 3.88 (s, 3H), 3.48–3.41 (m, 1H), 2.87 (dd, $J = 15.8$, 7.2 Hz, 1H), 2.78 (dd, $J = 16.0$, 6.8 Hz, 1H), 2.04 (s, 3H), 1.78–1.62 (m, 2H), 1.36–1.23 (m, 2H), 0.87 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 208.9$, 153.7, 131.7, 127.0, 121.9, 118.8, 111.8, 111.7, 101.5, 56.0, 50.1, 38.0, 32.4, 30.5, 20.7, 14.1. ESI HRMS: calcd. for $C_{16}H_{21}NO_2$ + Na 282.1470, found 282.1454.

4-(5-Methoxy-1*H*-indol-3-yl)-5-methylhexan-2-one (4bb). 23% yield. $[\alpha]_D^{20}$ −6.0 ($c = 0.25$, CH_2Cl_2), 86% ee. The enantiomeric excess was determined by HPLC on Chiralpak AD column (10% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, $t_{minor} = 12.08$ min, $t_{major} = 13.07$ min. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.06$ (br s, 1H), 7.22 (d, $J = 8.8$ Hz, 1H), 7.08 (d, $J = 2.0$ Hz, 1H), 6.90 (d, $J = 2.0$ Hz, 1H), 6.84 (dd, $J = 2.0$, 9.0 Hz, 1H), 3.87 (s, 3H), 3.32–3.27 (m, 1H), 2.90–2.81 (m, 2H), 2.08–2.01 (m, 1H), 1.99 (s, 3H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 209.5$, 153.7, 131.5, 127.6, 122.7, 117.2, 111.7, 111.6, 101.6, 55.9, 46.9, 39.2, 32.6, 30.1, 20.5, 20.3. ESI HRMS: calcd. for $C_{16}H_{21}NO_2$ + Na 282.1470, found 282.1457.

4-(4-Chlorophenyl)-4-(5-methoxy-1*H*-indol-3-yl)butan-2-one (4bd). 70% yield. $[\alpha]_D^{20}$ +20.6 ($c = 0.66$, CH_2Cl_2), 72% ee. The enantiomeric excess was determined by HPLC on Chiralpak AD column (10% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, $t_{minor} = 32.58$ min, $t_{major} = 20.86$ min. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.02$ (br s, 1H), 7.22–7.17 (m, 5H), 6.92 (d, $J = 2.0$ Hz, 1H), 6.81 (dd, $J = 8.6$, 2.4 Hz, 1H), 6.77 (d, $J = 2.4$ Hz, 1H), 4.75 (t, $J = 7.6$ Hz, 3H), 3.74 (s, 3H), 3.21 (dd, $J = 16.2$, 7.2 Hz, 1H), 3.11 (dd, $J = 16.0$, 8.0 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 207.3$, 153.8, 142.5, 132.0, 131.7, 129.1, 128.5, 126.7, 122.0, 118.0, 112.2, 111.9, 101.3, 55.8, 49.9, 37.5, 30.4. ESI HRMS: calcd. for $C_{19}H_{18}ClNO_2$ + Na 350.0924, found 350.0914.

4-(5-Methoxy-1*H*-indol-3-yl)-4-(4-methoxyphenyl)butan-2-one (4bf). 93% yield. $[\alpha]_D^{20}$ +8.3 ($c = 0.6$, CH_2Cl_2), 47% ee. The enantiomeric excess was determined by HPLC on Chiralpak AD column (15% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, $t_{minor} = 27.20$ min, $t_{major} = 20.76$ min. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.99$ (br s, 1H), 7.23–7.16 (m, 4H), 6.92 (d, $J = 2.4$ Hz, 1H), 6.83–6.78 (m, 3H), 4.72 (t, $J = 7.6$ Hz, 3H), 3.74 (s, 6H), 3.19 (dd, $J = 15.8$, 7.2 Hz, 1H), 3.11 (dd, $J = 16.0$, 8.0 Hz, 1H), 2.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 207.9$, 157.9, 153.7, 136.0, 131.7, 128.6, 126.9, 121.9, 118.8, 113.8, 112.0, 111.8, 101.5, 55.8, 55.2, 50.4, 37.5, 30.4. ESI HRMS: calcd. for $C_{20}H_{21}NO_3$ + Na 346.1419, found 346.1428.

4-(5-Methoxy-1*H*-indol-3-yl)-4-(thiophen-2-yl)butan-2-one (4bg). 83% yield. $[\alpha]_D^{20}$ +6.2 ($c = 0.5$, CH_2Cl_2), 50% ee. The enantiomeric excess was determined by HPLC on Chiralpak AD column (15% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, $t_{minor} = 19.68$ min, $t_{major} = 17.30$ min. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.99$ (br s, 1H), 7.20 (d, $J = 8.8$ Hz, 1H), 7.10 (t, $J = 3.6$ Hz, 1H), 6.99 (d, $J = 2.4$ Hz, 1H), 6.93 (d, $J = 2.0$ Hz, 1H), 6.88 (d, $J = 3.6$ Hz, 2H), 6.83 (dd, $J = 8.8$, 2.4 Hz, 1H), 5.07 (t, $J = 7.6$ Hz, 1H), 3.78 (s, 3H), 3.25 (d, $J = 7.6$ Hz, 2H), 2.09 (S, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 207.1$, 153.9, 148.4, 131.6, 126.5, 124.1, 123.5, 122.2, 118.3, 112.2, 111.9, 101.3, 55.8, 50.8, 33.4, 30.5. ESI HRMS: calcd. for $C_{17}H_{17}NO_2S$ + Na 322.0878, found: 322.0866.

1-(5-Methoxy-1*H*-indol-3-yl)-1-phenylpentan-3-one (4be). 91% yield. $[\alpha]_D^{20}$ +0.6 ($c = 0.5$, CH_2Cl_2), 85% ee. The enantiomeric excess was determined by HPLC on Chiralpak AD column (10% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, $t_{minor} = 37.15$ min, $t_{major} = 20.68$ min. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.98$ (br s, 1H), 7.31–7.14 (m, 6H), 6.93 (d, $J = 2.4$ Hz, 1H), 6.82–6.78 (m, 2H), 4.79 (t, $J = 7.6$ Hz, 1H), 3.73 (s, 3H), 3.21 (dd, $J = 15.8$, 7.6 Hz, 1H), 3.12 (dd, $J = 16.0$, 8.0 Hz, 1H), 2.41–2.25 (m, 2H), 0.94 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 210.3$, 153.7, 144.0, 131.7, 128.4, 127.7, 126.9, 126.3, 122.0, 118.6, 112.1, 111.8, 101.4, 55.8, 49.0, 38.3, 36.5, 7.5. ESI HRMS: calcd. for $C_{20}H_{21}NO_2$ + Na 330.1470, found 330.1461.

1-(4-Chlorophenyl)-1-(5-methoxy-1*H*-indol-3-yl)pentan-3-one (4bh). 41% yield. $[\alpha]_D^{20}$ +13.3 (c = 0.24, CH_2Cl_2), 88% ee. The enantiomeric excess was determined by HPLC on Chiralpak AD column (10% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, t_{minor} = 32.79 min, t_{major} = 19.02 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (br s, 1H), 7.25–7.20 (m, 5H), 6.95 (d, J = 2.0 Hz, 1H), 6.82 (dd, J = 13.4, 2.4 Hz, 1H), 6.78 (d, J = 2.4 Hz, 1H), 4.78 (t, J = 7.2 Hz, 3H), 3.75 (s, 3H), 3.20 (dd, J = 16.0, 6.8 Hz, 1H), 3.10 (dd, J = 16.0, 8.0 Hz, 1H), 2.43–2.27 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.8, 153.9, 142.6, 132.0, 131.7, 129.1, 128.5, 126.7, 122.0, 118.3, 112.2, 111.8, 101.4, 55.8, 48.7, 37.6, 36.6, 7.5. ESI HRMS: calcd. for $C_{20}H_{20}ClNO_2$ + Na 364.1080, found 364.1080.

1-(5-Methoxy-1*H*-indol-3-yl)-1-phenylhexan-3-one (4bi). 78% yield. $[\alpha]_D^{20}$ +1.3 (c = 0.38, CH_2Cl_2), 87% ee. The enantiomeric excess was determined by HPLC on Chiralpak AD column (10% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, t_{minor} = 31.07 min, t_{major} = 17.98 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (br s, 1H), 7.32–7.24 (m, 4H), 7.20–7.14 (m, 2H), 6.93 (d, J = 2.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 8.4, 2.4 Hz, 1H), 4.81 (t, J = 7.6 Hz, 1H), 3.74 (s, 3H), 3.20 (dd, J = 16.0, 7.2 Hz, 1H), 3.13 (dd, J = 16.0, 8.0 Hz, 1H), 2.38–2.23 (m, 2H), 1.55–1.46 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.8, 153.7, 144.0, 131.7, 128.4, 127.7, 126.9, 126.3, 122.0, 118.7, 112.1, 111.7, 101.4, 55.8, 49.3, 45.3, 38.2, 16.9, 13.6. ESI HRMS: calcd. for $C_{21}H_{23}NO_2$ + Na 344.1626, found 344.1636.

3-(5-Methoxy-1*H*-indol-3-yl)cyclohexanone (4bj). 82% yield. $[\alpha]_D^{20}$ −1.8 (c = 0.4, CH_2Cl_2), 56% ee. The enantiomeric excess was determined by HPLC on Chiralpak AD column (10% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, t_{minor} = 27.97 min, t_{major} = 34.58 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (br s, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.6, 2.4 Hz, 1H), 3.83 (s, 3H), 3.43–3.36 (m, 1H), 2.82–2.77 (m, 1H), 2.62–2.56 (m, 1H), 2.50–2.36 (m, 2H), 2.28–2.22 (m, 1H), 2.10–2.02 (m, 1H), 1.99–1.77 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.9, 153.8, 131.6, 126.5, 121.1, 119.3, 112.2, 112.0, 100.9, 56.0, 48.0, 41.5, 35.8, 31.5, 24.9. ESI HRMS: calcd. for $C_{15}H_{17}NO_2$ + Na 266.1157, found 266.1148.

4-(5-Bromo-1*H*-indol-3-yl)heptan-2-one (4ca). 72% yield. $[\alpha]_D^{20}$ +4.8 (c = 0.4, CH_2Cl_2), 59% ee. The enantiomeric excess was determined by HPLC on Chiralpak AD column (3% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, t_{minor} = 26.01 min, t_{major} = 24.29 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (br s, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.26–7.18 (m, 2H), 6.94 (d, J = 2.4 Hz, 1H), 3.43–3.38 (m, 1H), 2.88–2.75 (m, 2H), 2.03 (s, 3H), 1.76–1.61 (m, 2H), 1.27–1.18 (m, 2H), 0.86 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.7, 135.1, 128.2, 124.7, 122.5, 121.7, 118.6, 112.7, 112.4, 49.9, 37.9, 32.4, 30.4, 20.7, 14.0. ESI HRMS: calcd. for $C_{15}H_{18}BrNO$ + Na 330.0469, found 330.0461.

4-(2-Methyl-1*H*-indol-3-yl)heptan-2-one (4da). 99% yield. $[\alpha]_D^{20}$ +18.2 (c = 0.34, CH_2Cl_2), 65% ee. The enantiomeric excess was determined by HPLC on Chiralpak AD column (5% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, t_{minor} = 13.90 min, t_{major} = 10.83 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (br s, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 7.2 Hz, 1H), 7.10–7.02 (m, 2H), 3.42–3.34 (m, 1H), 3.04 (dd, J = 13.4, 8.0 Hz, 1H), 2.81 (dd, J = 16.0, 6.0 Hz, 1H), 2.37 (s, 3H), 1.94 (s, 3H), 1.91–1.82 (m, 1H), 1.69–1.61 (m, 1H), 1.26–1.10 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.0, 135.6, 131.4, 127.1, 120.6, 118.9, 118.8, 113.3, 110.4, 49.3, 37.3, 32.4, 30.7, 21.0, 14.0, 12.0. ESI HRMS: calcd. for $C_{16}H_{21}NO$ + Na 266.1521, found 266.1506.

5-Methyl-4-(2-methyl-1*H*-indol-3-yl)hexan-2-one (4db). 78% yield. $[\alpha]_D^{20}$ +35.9 (c = 0.44, CH_2Cl_2), 82% ee. The enantiomeric excess was determined by HPLC on Chiralpak AD column (10% 2-propanol–hexane, 1 mL min^{-1}), UV 254 nm, t_{minor} = 7.42 min, t_{major} = 6.32 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (br s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.10–7.01 (m, 2H), 3.14–3.01 (m, 2H), 2.88 (dd, J = 14.4, 3.6 Hz, 1H), 2.36 (s, 3H), 2.20–2.10 (m, 1H), 1.86 (s, 3H), 1.04 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.5, 135.5, 131.9, 127.3, 120.5, 119.2, 118.8, 113.1, 110.4, 46.7, 40.0, 32.4, 30.7, 21.5, 21.4, 12.1. ESI HRMS: calcd. for $C_{16}H_{21}NO$ + Na 266.1521, found 266.1528.

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