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High-Pressure-Mediated Asymmetric Organocatalytic Hydroxyalkylation of Indoles with Trifluoromethyl Ketones

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Dedicated to Professor Janusz Jurczak on the occasion of his 75th birthday.

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Abstract: An enantioselective hydroxyalkylation of indoles and 7-azaindole with trifluoromethyl ketones was found to be effectively promoted under high-pressure conditions with a low loading of *Cinchona* alkaloids (e.g., 1–3 mol% of cinchonidine). Chiral tertiary alcohols containing a trifluoromethyl group were obtained at 9 kbar with good yield and enantioselectivity up to 89%, whereas usually merely traces of products were detected at atmospheric pressure.

Keywords: asymmetric organocatalysis; *Cinchona* alkaloids; Friedel–Crafts reaction; high-pressure effect; indoles; trifluoromethyl group

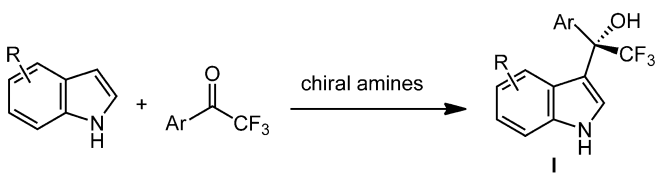
Introduction

The indole motif[1] as well as trifluoromethyl group[2] play an important role in the synthesis of biologically active compounds and in drug discovery. The presence of these two elements in one molecule seems to be particularly interesting for medicinal chemistry.[3] One possible synthetic approach for achieving this goal is functionalization of indoles at the 3-position with trifluoromethyl-containing electrophilic compounds. Of special interest are enantioselective reactions of indoles[4] with prochiral trifluoromethylated substrates,[5] for example, trifluoromethyl ketones,[6,7,8] imines[9] or α,β-unsaturated compounds.[10]

In our investigations we focused on the organocatalytic asymmetric additions of indoles to aryl or alkyl trifluoromethyl ketones (Scheme 1). We were interested to explore the possibility of utilizing chiral amines as catalysts in this reaction. Despite a number of examples of enantioselective reactions of indoles with very reactive ethyl 3,3,3-trifluoropyruvate,[3a–d,6a,7d,8] only one asymmetric approach based on Brønsted acid catalysis has been developed in an analogous reaction with simple and less reactive trifluoromethyl ketones (Scheme 1).[7a] Ma and co-workers demonstrated that chiral phosphoric acids (e.g., TRIP, 5–1 mol%) are effective catalysts in this case.[7a]

On the other hand, chiral tertiary amines were successfully applied as catalysts in reactions of indoles with 1,2-dicarbonyl compounds.[6a,11] Török et al.[6a] found that *Cinchona* alkaloids (**1a**, **1b**, **1d** and **1e**, Figure 1) are efficient catalysts for the enantioselective reaction of indoles with ethyl 3,3,3-trifluoropyruvate. Deng[11] extended the scope of the reaction to various 1,2-dicarbonyl compounds as well as aromatic aldehydes with 6′-OH *Cinchona* alkaloid derivatives (e.g., **1i**) as catalysts.

The aim of our study was to develop an amine-catalyzed asymmetric synthesis of tertiary α-trifluoromethylated alcohols **I** (Scheme 1) bearing 3-indolyl and aryl substituents, an alternative and complementary approach to Brønsted acid catalysis.[7a] The literature describes only one example of a base-catalyzed reaction of indoles with trifluoroacetophenones utilizing simple guanidines in the presence of water, and afforded racemic alcohols of type **I**.[12]



I

Scheme 1. Reaction of indoles with CF_3-ketones.

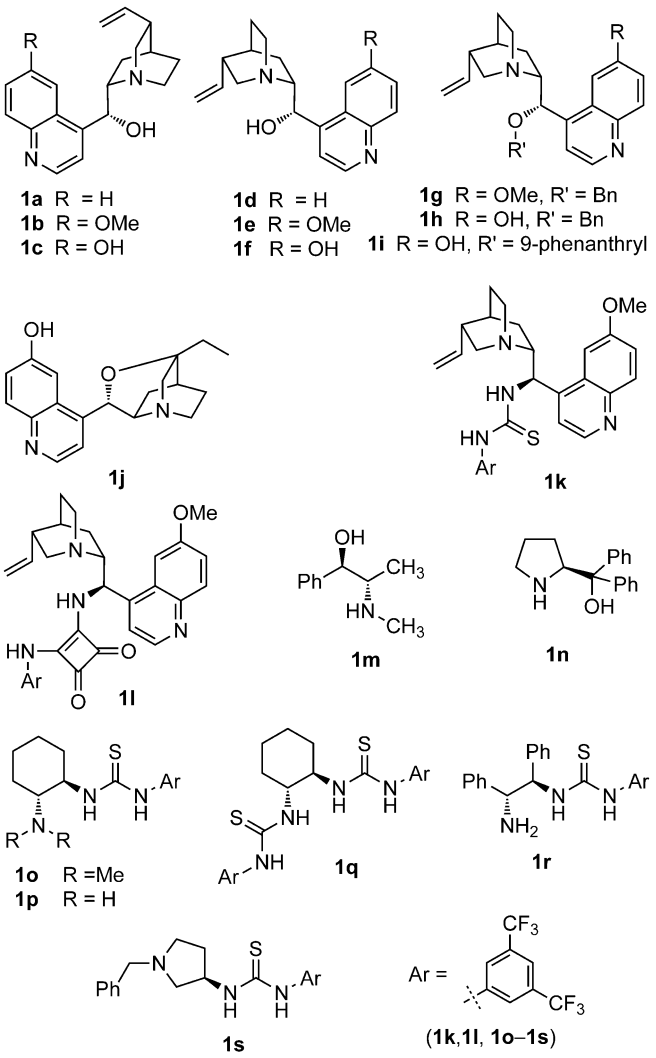


Figure 1. Organocatalysts examined in the model reaction.

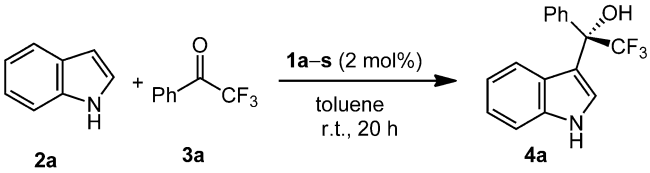
Results and Discussion

Our preliminary experiments with various chiral amines **1** (2 mol%, Figure 1) confirmed their very low activity (Table 1) in the model reaction of indole (**2a**) with trifluoroacetophenone (**3a**) under classical conditions (1 bar, room temperature, 20 h). Among the tested chiral amines cupreidine 9-*O*-benzyl ether (**1h**) turned out to be the most active catalyst. After 7 days the product **4a** was obtained with 25% yield and 58% *ee* (Table 1, entry 8). With other amines (2 mol% of **1a–f**, **1h–o**, **1q**, **1r**) only traces (<2%) of product **4a** were observed at atmospheric pressure after 20 h. Further optimization with 10 mol% of catalyst **1h** and a higher concentration of reagents leads to 26% conversion after one day and 90% after 7 days with an enantioselectivity of 60%.[13]

Encouraged by our recent results in high-pressure organocatalytic conjugate additions,[14] we decided to investigate the influence of pressure[15,16] also in the hydroxyalkylation reaction presented in Scheme 1.[17,18] However, this method of activation is useful only for reactions characterized by a negative volume of activation.[19]

Application of 2 mol% of various chiral amines containing hydrogen-bonding donors (e.g., hydroxy compounds, thioureas, squaramides) as catalysts under 8 kbar of pressure remarkably accelerated the reaction rate (Table 1). The yield substantially increased to 45–95% at 8 kbar. In the control high-pressure experiment without any catalysts we observed formation of *ca.* 5% of the product (entry 20). The presence of an amine moiety and hydrogen-bonding donors in the catalyst structure is crucial for the activ-

Table 1. Catalyst screening in the model reaction[a]



Entry	Catalyst (2 mol%)	1 bar (20 h) Yield [%][b]	8 kbar (20 h) Yield [%][b]	*er* (*R*:*S*)[c]
1	**1a**	0.3	76	10:90
2	**1b**	0.2	72	14:86
3	**1c**	0.5	83	84:16
4	**1d**	0.3	68	83:17
5	**1e**	0.1	69	79:21
6	**1f**	1[d]	84	18:82
7	**1g**	0	5	78:22
8	**1h**	4[e]	73	21:79
9	**1i**	0.5	77	11:89
10	**1j**	<0.1	85	21:79
11	**1k**	0.1	87	42.5:57.5
12	**1l**	0.4	60	58:42
13	**1m**	0.2	45	59:41
14	**1n**	1.5	46	60:40
15	**1o**	<0.1	90	31:69
16	**1p**	0.5	85	82:18
17	**1q**	<0.1	2	–
18	**1r**	0.3	49	81:19
19	**1s**	0.7	95	60:40
20	no catalyst	0	5–6[f]	–

[a] *Reaction conditions:* indole (0.5 mmol, $c = 0.5$ mol/L), trifluoroacetophenone (0.6 mmol, 1.2 equiv.), and catalyst **1** (0.01 mmol, 2 mol%) in toluene (*ca.* 0.75 mL), 20–25 °C.

[b] Determined by GC analysis using biphenyl as the internal standard.

[c] Determined by HPLC analysis using Chiralpak IB column.

[d] 14% after 7 days, *er* = 23:77.

[e] 25% after 7 days, *er* 21:79 (with 10 mol% of **1h**: 26% after 24 h; 90% after 7 days and *er* 20:80).

[f] 10% yield at 10 kbar.

ity. In contrast, the use of a chiral amine without hydrogen-bonding donors (e.g., O-protected quinidine, **1g**, entry 7) or thiourea without an amine moiety (**1q**, entry 17) resulted in very low conversion.

Among various tested amines containing hydrogen-bonding donors the most promising results in terms of conversion (>68%) and enantioselectivity (58–80% *ee*) were observed under high pressure conditions with *Cinchona* alkaloids and their demethylated derivatives, cupreine (**1c**) and cupreidine (**1f**) (entries 1–6, 8–10).[20] The presence of the phenolic OH group at C-6′ in catalysts **1c**, **1f**, **1h** and **1i** resulted in inversion of the enantioselectivity, as compared to quinine and quinidine, respectively. In contrast, with thiourea and squaramide *Cinchona* derivatives (**1k** and **1l**) a very low enantiomeric excess was achieved (entries 11 and 12). We tested also thiourea derivatives based on other chiral amines, for example, 1,2-diaminocyclohexane (**1o** and **1p**). An interesting level of enantioselectivity was observed with primary amine-thiourea **1p** (64% *ee*, entry 16). Surprisingly, use of the analogous catalyst **1n** (Takemoto's catalyst) with a tertiary amine instead of a primary one resulted in the opposite enantioselectivity (38% *ee*, entry 15).

Finally, cinchonidine (**1a**) turned out to be the best catalyst in terms of enantioselectivity (80% *ee*) as well as availability and this natural product was used in further optimization studies. A subsequent solvent screening (e.g., CH_2Cl_2, $CHCl_3$, acetonitrile, THF, MeOH)[21] revealed that toluene was the best choice.[22]

The influence of pressure in the range of 4–10 kbar on the model reaction catalyzed by 2 mol% of cinchonidine is shown in Figure 2. A pressure increase has a significant effect on the reaction rate and very good results in terms of yield were obtained at 9–10 kbar. However, the best enantioselectivity (80–82% *ee*) was observed at the 6–9 kbar pressure range.

The reaction was also investigated with higher loadings of cinchonidine (up to 5 mol%) and concentrations of reagents (1 mol/L of **2a**). In the experiment

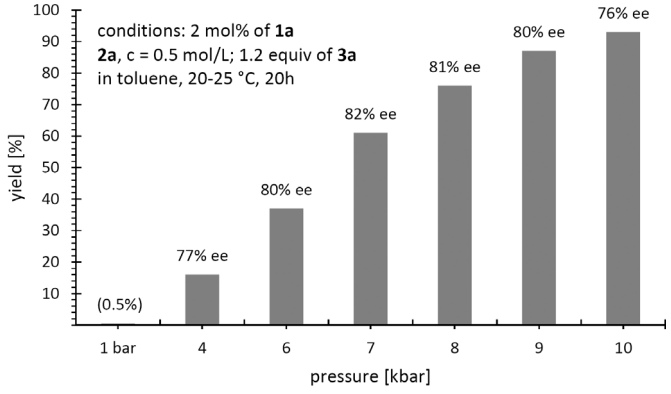


Figure 2. Effect of pressure on the model reaction.

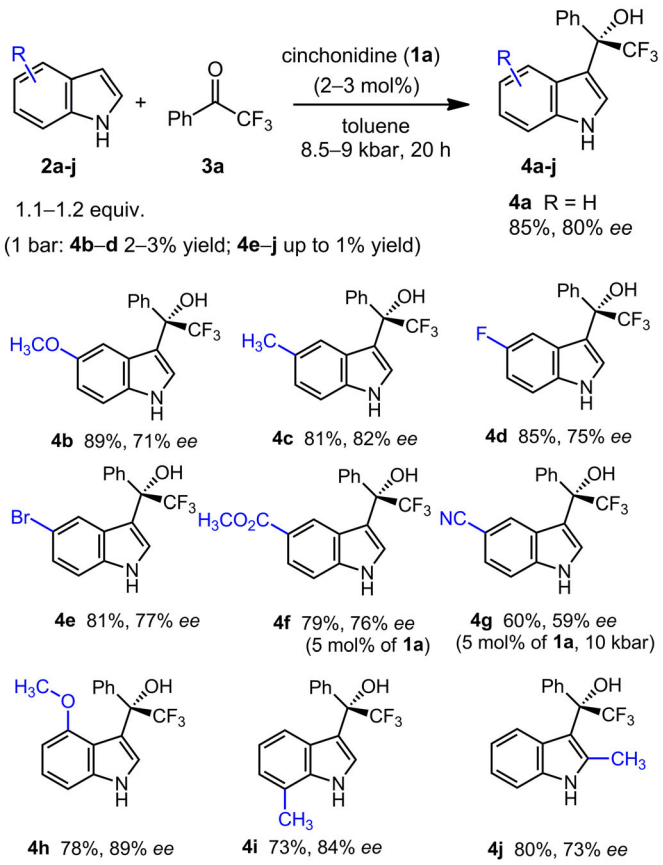
Table 2. Optimization of the model reaction[a]

Entry	mol% of **1a**	Pressure	**2a** conc. [mol/L]	Yield [%][b,c]	*ee* [%][d]
1[e]	5	1 bar	1.0	12	58
2	4	4 kbar	1.0	53	75
3	4	6 kbar	1.0	83	78
4	2	8 kbar	0.5	76 (73)	81
5	2	8 kbar	1.0	93 (91)	77
6	1	8 kbar	1.0	81	76
7	4	8 kbar	0.5	85	80
8	2	9 kbar	0.5	87 (85)	80.5
9	1	9 kbar	0.5	74	80.5
10	0.5	9 kbar	1.0	75	75.5
11[f]	4	9 kbar	0.5	62	78
12[g]	4	9 kbar	0.5	87	80.5

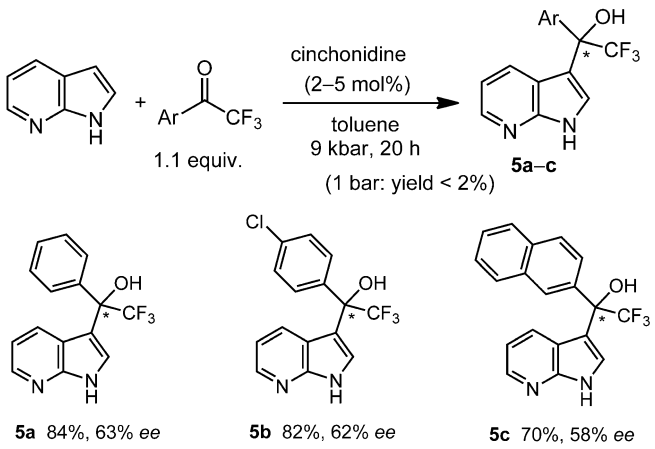
[a] *General reaction conditions:* indole (0.5 mmol), trifluoroacetophenone (0.6 mmol, 1.2 equiv.), and catalyst **1a** in toluene, 20–25 °C, 20 h.
[b] Determined by GC analysis using biphenyl as the internal standard.
[c] Isolated yield in parentheses; 2 mmol reaction scale.
[d] Determined by HPLC analysis using Chiralpak IB column.
[e] Reaction at 50 °C for 5 d.
[f] Reaction time: 4 h.
[g] Reaction time: 8 h.

carried out under atmospheric pressure at 50 °C the yield was very low even after 5 days (12%, Table 2, entry 1). We observed that a high yield (83%) can be obtained by using the same reaction mixture with 4 mol% of **1a** under 6 kbar at room temperature after 20 h (Table 2, entry 3). The reaction with a higher concentration of reactants is effective even with 1–0.5 mol% of cinchonidine under a pressure of 8–9 kbar (74–81%, entries 6 and 10) with *ee* up to 76%. Experiments with a lower concentration of reagents (0.5 mol/L of **2a**) improved the enantioselectivity up to 81% (entry 4), but the yield decreased, for example, with 2 mol% of **1a** at 8 kbar from 93% to 76% (entries 4 and 5). Application of 9 kbar pressure, 2 mol% of **1a** and 0.5 mol/L concentration of **2a** offers the best compromise in terms of yield (87%) and enantioselectivity (up to 80.5% *ee*; entry 8). The reaction time can be significantly reduced (e.g., from 20 h to 8 h) by increasing the catalyst concentration (e.g., to 4 mol%; entry 12).

To demonstrate the scope of the reaction of trifluoroacetophenone with various indoles we applied 9 kbar of pressure and 2–3 mol% of cinchonidine (Scheme 2). Products **4b–f** having in the structure various 5-substitued indoles were isolated in good yield (79–89%) and enantioselctivity in the range of 71–82% *ee*. The most problematic was the addition of the less reactive 5-cyanoindole; the product **4g** was obtained at 10 kbar with 5 mol% of **1a** in 60% yield and moderate enantioselectivity. We also tested indoles



Scheme 2. Reaction of indoles with trifluoroacetophenone.



Scheme 3. Reaction of 7-azaindole with trifluoromethyl ketones.

substituted in positions 2, 4 and 7 (see products **4h**, **4i** and **4j**). The best enantioselectivity (89%) was found with 4-methoxyindole.

The presence of a free NH in the indole ring is essential for this reaction in terms of reactivity and enantioselectivity. The use of *N*-methylindole instead of indole resulted in very low yield and loss of enantioselectivity. This observation and ^{1}H NMR spectra of **1a** with **2a** support the importance of catalyst interaction with the NH of indole (*via* hydrogen bonding with the quinuclidine part).[23] Addition of cinchonidine shifts the indole NH signal to lower field. On the other side, the hydroxy group in cinchonidine participates in hydrogen bonding activation of the carbonyl in the trifluoromethyl ketone. After addition of 2 equiv. of trifluoroacetophenone to cinchonidine, the signal from the OH group at C-9 disappeared in the ^{1}H NMR spectra.[23]

In addition, we have found that cinchonidine can also effectively catalyze the reaction of trifluoroacetophenones with 7-azaindole at 9 kbar, however the enantioselectivity is slightly lower (Scheme 3, 58–63% *ee*), as compared to indole. To the best of our knowledge, this is the first example of the use of 7-azaindoles in the enantioselective 1,2-addition to carbonyl compounds.[24]

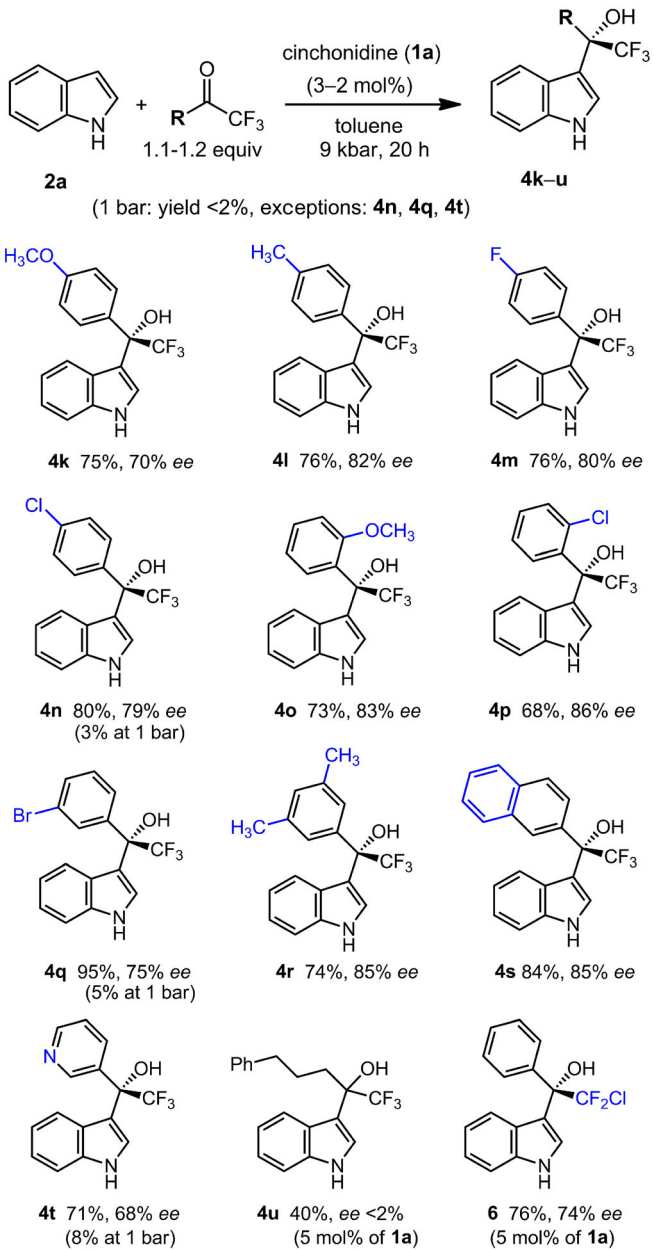
In the reaction of 7-azaindole with **3a** we also tested the possibility of an alternative approach with Brønsted acid catalysis.[7a] Application of 1 mol% of BINOL-derived phosphoric acids with 3,3′-di(2,4,6-triisopropylphenyl) groups (TRIP) failed in this reaction under atmospheric pressure as well as at high pressure.

Finally, the scope of trifluoromethyl ketones in the reaction with indole was investigated under 9 kbar (Scheme 4). The reaction works well in terms of yield and enantioselectivity with variously *para*-, *meta*- and some *ortho*- substituted trifluoroacetophenones (**4k**–**4s**) with 86–70% enantioselectivity. Moreover the hydroxyalkylation catalyzed by cinchonidine tolerates the trifluoromethyl ketone with a 3-pyridyl group (product **4t**) and 2-chloro-2,2-difluoroacetophenone (product **6**). Unfortunately, the reaction with less reactive aliphatic trifluoromethyl ketones resulted in the formation of nearly racemic alcohol **4u**. Under atmospheric pressure usually traces (yield $<2\%$) of products were observed after one day, up to 8% yield for addition to more active 3-trifluoroacetylpyridine (see **4t**).

The absolute configurations of **4a** and **4n**, obtained in the presence of cinchonidine, was determined by comparison of their optical rotations[7a] and were assigned to be (*S*). In some cases the *ee* of the alcohols **4** can be improved to $>98.0\%$ after a single crystallization (e.g., for products **4a**, **4f**, **4n**).

Conclusions

An alternative and complementary approach to the Brønsted acid-catalyzed asymmetric hydroxyalkylation of indoles with trifluoromethyl ketones is demonstrated. We have found that high pressure remarkably



Scheme 4. Reaction of indole with trifluoromethyl ketones.

accelerates the reaction of indoles and 7-azaindole with trifluoroacetophenones in the presence of low loadings of *Cinchona* alkaloids and their simple derivatives. The reaction is very slow with typical amine-based catalysts under conventional conditions. A combination of easily available cinchonidine (typically 2–3 mol%) and high pressure activation (8–9 kbar) allows an asymmetric synthesis of tertiary α-trifluoromethylated alcohols with indole and 7-azaindole heterocycles in good yields and enantioselectivities of up to 89% *ee*.

Experimental Section

Results of Solvent Screening

For the model reaction (conditions: 4 mol% of **1a**, $c_{(2a)} = 0.5$ mol/L, 1.2 equiv. of **3a**, 8 kbar, 20–25 °C, 20 h): CH_2Cl_2 (70%, 72% *ee*), $CHCl_3$ (86%, 67% *ee*), fluorobenzene (50%, 54% *ee*), chlorobenzene (72%, 70% *ee*), ethylbenzene (86%, 78% *ee*), *m*-xylene (63%, 64% *ee*), acetonitrile (71%, 63% *ee*), THF (5%), methanol (<2%).

General Procedure for Asymmetric High-Pressure-Mediated Addition of Indoles to Trifluoromethyl Ketones

A 3-mL Teflon ampoule was charged with 2–3 mol% of cinchonidine (9.0–13.5 mg), 1.5 mmol of indole and 1.65–1.8 mmol of trifluoromethyl ketone (1.1–1.2 equiv.). The Teflon ampoule was filled up with toluene and after complete dissolution of all reactants was closed. Then the Teflon ampoule with the homogeneous reaction mixture was placed in a high-pressure chamber filled with the inert liquid (hexane or petroleum ether) and the pressure was slowly increased to 9 kbar at ambient temperature (20–25 °C) by hexane compression. After the pressure was stabilized, the reaction mixture was kept under these conditions for 20 h. After decompression, the reaction mixture was directly chromatographed on silica gel to afford the tertiary α-trifluoromethylated alcohols **4**.

High-pressure reactions for isolation were carried out on a 1.0–1.5 mmol scale in 2 mL or 3 mL Teflon ampoules.[23]

Analytical Data for New Compounds

(*S*)-2,2,2-Trifluoro-1-(5-methyl-1*H*-indol-3-yl)-1-phenylethanol (4c): white solid; 81% yield; 82% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.11$ (bs, 1H, NH), 7.61–7.55 (m, 2H), 7.39–7.36 (m, 1H), 7.35–7.31 (m, 3H), 7.24 (d, $J = 8.3$ Hz, 1H), 6.98 (dd, $J = 8.3$, 1.6 Hz, 1H), 6.95–6.93 (m, 1H), 2.86 (s, 1H, OH), 2.25 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 137.6$ (C), 134.6 (C), 129.6 (C), 128.5 (CH), 127.9 (2CH), 127.6 (2CH), 125.4 (q, $J = 286.1$ Hz, CF_3), 125.3 (C), 124.4 (CH), 123.3 (q, $J = 3.1$ Hz, CH), 120.5 (CH), 113.5 (C), 110.9 (CH), 77.1 (q, $J = 29.6$ Hz, *C*-CF_3), 21.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -77.3$ (s, 3F); IR (film): $\nu = 3411$, 3033, 2921, 1486, 1450, 1271, 1164, 1040, 886, 798, 765, 719 cm^{-1}; LR-MS (ESI): $m/z = 306.1$, mass calculated for $[M+H]^+$ ($C_{17}H_{15}F_3NO$): 306.11; the enantiomeric excess was determined by HPLC analysis using a Chiralpak® IB column (hexane/*i*-PrOH: 95/5, flow rate 1.0 mL min^{-1}, $\lambda = 225$ nm): *ent*-minor $t_r = 18.2$ min and *ent*-major $t_r = 24.8$ min.

(*S*)-2,2,2-Trifluoro-1-(4-methoxy-1*H*-indol-3-yl)-1-phenylethanol (4h): white solid; 78% yield; 89% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.34$ (bs, 1H, NH), 7.55–7.49 (m, 2H), 7.34–7.26 (m, 3H), 7.19–7.16 (m, 1H), 7.11 (dd, $J = 8.2$, 7.8 Hz, 1H), 7.02 (d, $J = 8.2$ Hz, 1H), 6.49 (d, $J = 7.8$ Hz, 1H), 6.07 (s, 1H, OH), 3.62 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.3$ (C), 140.5 (C), 138.1 (C), 128.1 (CH), 127.7 (2CH), 127.6 (q, $J = 1.0$ Hz, 2CH), 125.4 (q, $J = 285.2$ Hz, CF_3), 123.5 (CH), 122.4 (q, $J = 3.1$ Hz, CH), 115.6 (C), 114.7 (C), 105.7 (CH), 101.5 (CH), ~77.1 (q overlaps with $CDCl_3$ peaks, *C*-CF_3), 55.7 (CH_3); ^{19}F NMR (376 MHz,

$CDCl_3$): $\delta = -76.1$ (s, 3F); IR (film): $\nu = 3456$, 3402, 3132, 2844, 1582, 1508, 1443, 1330, 1267, 1242, 1165, 1092, 1051, 883, 834, 739, 723 cm^{-1}; LR-MS (ESI): $m/z = 322.1$, mass calculated for $[M+H]^+$ ($C_{17}H_{15}F_3NO_2$): 322.11; the enantiomeric excess was determined by HPLC analysis using a Chiralpak® IA column (hexane/*i*-PrOH: 83/13, flow rate 1.0 mL min^{-1}, $\lambda = 225$ nm): *ent*-minor $t_r = 7.1$ min and *ent*-major $t_r = 10.6$ min.

(*R*)-2,2,2-Trifluoro-1-(1*H*-indol-3-yl)-1-(2-methoxyphenyl)ethanol (4o): white solid; 73% yield; 83% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.20$ (s, 1H, NH), 7.36–7.27 (m, 2H), 7.23–7.19 (m, 2H), 7.11 (ddd, $J = 8.2$, 7.0, 1.1 Hz, 1H), 7.03 (dm, $J = 7.8$, 1H), 7.02 (dd, $J = 8.3$, 1.0 Hz, 1H), 6.94 (ddd, $J = 8.0$, 7.0, 1.0 Hz, 1H), 6.84–6.78 (m, 1H), 6.55 (s, 1H, OH), 3.92 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 158.2 (C), 136.3 (C), 131.3 (q, $J = 1.3$ Hz, CH), 130.2 (CH), 125.6 (C), 125.4 (C), 125.7 (q, $J = 287.4$ Hz, CF_3), 123.6 (q, $J = 3.0$ Hz, CH), 122.2 (CH), 121.3 (CH), 121.3 (CH), 119.8 (CH), 113.9 (C), 112.5 (CH), 111.1 (CH), 79.5 (q, $J =$ 30.1 Hz, *C*-CF_3), 56.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -77.2$ (s, 3F); IR (film): $\nu = 3321$, 1584, 1459, 1412, 1286, 1235, 1173, 1160, 1113, 1036, 927, 743 cm^{-1}; LR-MS (ESI): $m/z = 320.1$, mass calculated for $[M-H]^-$ ($C_{17}H_{13}F_3NO_2$): 320.09; the enantiomeric excess was determined by HPLC analysis using a Chiralpak® IA column (hexane/*i*-PrOH: 88/12, flow rate 1.0 mL min^{-1}, $\lambda = 225$ nm): *ent*-major $t_r =$ 10.9 min and *ent*-minor $t_r = 12.7$ min.

(*R*)-1-(2-Chlorophenyl)-2,2,2-trifluoro-1-(1*H*-indol-3-yl)-ethanol (4p): white solid; 68% yield; 86% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.23$ (s, 1H, NH), 7.92 (dm, $J =$ 7.5 Hz, 1H), 7.38–7.30 (m, 4H), 7.27–7.25 (m, 1H), 7.17 (ddd, $J = 8.2$, 7.0, 1.1 Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 6.96 (ddd, $J = 8.1$, 7.0, 1.0 Hz, 1H), 3.75 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 136.1$ (C), 134.8 (C), 133.6 (C), 131.9 (CH), 130.1 (q, $J = 2.3$ Hz, CH), 130.0 (CH), 126.7 (CH), 125.3 (C), 125.2 (q, $J = 286.6$ Hz, CF_3), 124.1 (q, $J = 2.3$ Hz, CH), 122.5 (CH), 120.2 (2CH), 113.5 (C), 111.3 (CH), 77.6 (q, $J = 30.3$ Hz, *C*-CF_3); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta =$ −75.5 (s, 3F); IR (film): $\nu = 3411$, 3061, 1547, 1459, 1431, 1339, 1270, 1171, 1015, 929, 889, 741 cm^{-1}; LR-MS (ESI): $m/z = 324.0$, mass calculated for $[M-H]^-$ ($C_{16}H_{10}ClF_3NO$): $m/z = 324.04$; the enantiomeric excess was determined by HPLC analysis using a Chiralpak® ID column (hexane/*i*-PrOH: 90/10, flow rate 1.0 mL min^{-1}, $\lambda = 225$ nm): *ent*-minor $t_r = 6.0$ min and *ent*-major $t_r = 7.1$ min.

(*S*)-1-(3-Bromophenyl)-2,2,2-trifluoro-1-(1*H*-indol-3-yl)-ethanol (4q): white solid; 95% yield; 75% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.26$ (s, 1H, NH), 7.81 (s, 1H), 7.48–7.42 (m, 3H), 7.37 (dm, $J = 8.2$ Hz, 1H), 7.21–7.13 (m, 3H), 6.97 (ddd, $J = 8.1$, 7.0, 1.0 Hz, 1H), 2.90 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 139.9$ (C), 136.2 (C), 131.7 (CH), 130.6 (q, $J = 1.1$ Hz, CH), 129.5 (CH), 126.5 (q, $J =$ 1.0 Hz, CH), 125.0 (q, $J = 286.4$ Hz, CF_3), 124.8 (C), 123.1 (q, $J = 3.1$ Hz, CH), 122.9 (CH), 122.2 (C), 120.7 (CH), 120.5 (CH), 113.3 (C), 111.3 (CH), 76.6 (q, $J = 29.9$ Hz, *C*-CF_3); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -77.3$ (s, 3F); IR (film): $\nu = 3448$, 3411, 3066, 1459, 1421, 1338, 1273, 1164, 1040, 944, 739 cm^{-1}; LR-MS (ESI): $m/z = 367.9$, mass calculated for $[M-H]^-$ ($C_{16}H_{10}BrF_3NO$): 367.99; the enantiomeric excess was determined by HPLC analysis using a Chiralpak® IA column (hexane/*i*-PrOH: 95/5, flow rate 2.0 mL min^{-1}, $\lambda =$ 225 nm): *ent*-major $t_r = 13.0$ min and *ent*-minor $t_r = 14.7$ min.

(*S*)-2,2,2-Trifluoro-1-(1*H*-indol-3-yl)-1-(naphthalen-2-yl)-ethanol (4s): white solid; 84% yield; 85% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.23$ (bs, 1H, NH), 8.18 (bs, 1H), 7.86–7.79 (m, 2H), 7.76 (d, $J = 8.7$ Hz, 1H), 7.58 (d, $J =$ 8.7 Hz, 1H), 7.51–7.44 (m, 3H), 7.35 (dd, $J = 7.9$, 1.2 Hz, 1H), 7.16–7.10 (m, 2H), 6.89–6.84 (m, 1H), 2.98 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 136.2$ (C), 135.1 (C), 133.1 (C), 132.7 (C), 128.6 (CH), 127.6 (CH), 127.5 (CH), 127.1 (q, $J = 0.9$ Hz, CH), 126.5 (CH), 126.1 (CH), 125.4 (q, $J = 286.3$ Hz, CF_3), 125.2 (q, $J = 1.1$ Hz, CH), 125.1 (C), 123.3 (q, $J = 3.0$ Hz, CH), 122.8 (CH), 120.9 (CH), 120.3 (CH), 113.9 (C), 111.2 (CH), ~77 (q overlaps with $CDCl_3$ peaks, *C*-CF_3); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -77.0$ (s, 3F); IR (film): $\nu = 3518$, 3416, 3128, 3060, 1459, 1272, 1169, 1155, 1120, 1040, 858, 819, 745 cm^{-1}; LR-MS (ESI): $m/z = 340.1$, mass calculated for $[M-H]^-$ ($C_{20}H_{13}F_3NO$): 340.10; the enantiomeric excess was determined by HPLC analysis using a Chiralpak® ID column (hexane/*i*-PrOH: 90/10, flow rate 1.0 mL min^{-1}, $\lambda = 225$ nm): *ent*-minor $t_r = 6.5$ min and *ent*-major $t_r = 8.4$ min.

(*S*)-2,2,2-Trifluoro-1-(1*H*-indol-3-yl)-1-(pyridin-3-yl)ethanol (4t): white solid; 71% yield; 68% *ee*; ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: $\delta = 11.36$ (s, 1H, NH), 8.64 (d, $J =$ 1.8 Hz, 1H), 8.53 (dd, $J = 4.8$, 1.6 Hz, 1H), 7.87 (d, $J =$ 8.1 Hz, 1H), 7.50 (s, 1H), 7.45–7.36 (m, 2H), 7.31 (s, 1H, OH), 7.09–7.04 (m, 1H), 7.01 (d, $J = 8.0$ Hz, 1H), 6.86–6.81 (m, 1H); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: $\delta = 149.2$ (CH), 148.5 (CH), 136.5 (C), 135.2 (C), 135.1 (CH), 125.1 (C), 125.6 (q, $J = 287.5$ Hz, CF_3), 123.7 (q, $J = 2.5$ Hz, CH), 123.0 (CH), 121.5 (CH), 120.3 (CH), 119.0 (CH), 112.0 (C), 111.8 (CH), 74.9 (q, $J = 29.1$ Hz, *C*-CF_3); ^{19}F NMR [376 MHz, $(CD_3)_2SO$]: $\delta = -76.1$ (s, 3F); IR (film): $\nu = 3277$, 1424, 1264, 1247, 1166, 1041, 1028, 889, 734, 708 cm^{-1}; LR-MS (ESI): $m/z = 293.1$, mass calculated for $[M+H]^+$ ($C_{15}H_{12}F_3N_2O$): 293.09; the enantiomeric excess was determined by HPLC analysis using a Chiralpak® IC column (hexane/*i*-PrOH: 88/12, flow rate 1.0 mL min^{-1}, $\lambda = 225$ nm): *ent*-major $t_r =$ 8.8 min and *ent*-minor $t_r = 11.2$ min.

1,1,1-Trifluoro-2-(1H-indol-3-yl)-5-phenylpentan-2-ol (4u): 40% yield (conv. >80%); *ee* <2%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.13$ (bs, 1H, NH), 7.73 (d, $J = 8.1$ Hz, 1H), 7.34 (dm, $J = 8.2$ Hz, 1H), 7.25–7.03 (m, 8H), 2.72–2.50 (m, 2H), 2.42 (bs, 1H, OH), 2.36 (ddd, $J = 14.0$, 12.5, 4.6 Hz, 1H), 2.08 (ddd, $J = 14.1$, 12.1, 4.6 Hz, 1H), 1.80–1.67 (m, 1H), 1.62–1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 141.6$ (C), 136.5 (C), 128.4 (2CH), 128.3 (2CH), 126.1 (q, $J =$ 285.8 Hz, CF_3), 125.9 (CH), 125.1 (C), 123.6 (d, $J = 1.3$ Hz, CH), 122.3 (CH), 120.8 (q, $J = 1.6$ Hz, CH), 120.3 (CH), 112.4 (C), 111.4 (CH), 76.7 (q, $J = 29.6$ Hz, *C*-CF_3), 35.6 (CH_2), 34.1 (CH_2), 24.4 (CH_2); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -80.9$ (s, 3F); the enantiomeric excess was determined by HPLC analysis using a Chiralpak® IA column (hexane/*i*-PrOH: 80/20, flow rate 1.0 mL min^{-1}, $\lambda = 225$ nm): *ent*-1 $t_r =$ 5.9 min and *ent*-2 $t_r = 7.7$ min.

1-(4-Chlorophenyl)-2,2,2-trifluoro-1-(1*H*-pyrrolo[2,3-*b*]-pyridin-3-yl)ethanol (5b): white solid; 82% yield; 62% *ee*; ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: $\delta = 11.89$ (s, 1H, NH), 8.19 (d, $J = 4.5$ Hz, 1H), 7.56–7.49 (m, 3H), 7.43 (d, $J = 8.3$ Hz, 2H), 7.38 (d, $J = 7.9$ Hz, 1H), 7.29 (s, 1H, OH), 6.93 (dd, $J =$ 7.9, 4.7 Hz, 1H); ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: $\delta = 148.6$ (C), 143.2 (CH), 138.2 (C), 133.1 (C), 129.2 (CH), 128.6 (CH), 125.6 (q, $J = 287.5$ Hz, CF_3), 128.0 (2CH), 126.9, 124.0

(q, J=2.2 Hz, CH), 117.6 (C), 115.6 (CH), 111.8 (C), 75.4 (q, J=29.0 Hz, C-CF_3); ^{19}F NMR [376 MHz, $(CD_3)_2SO$]: δ=−75.4 (s, 3F); LR-MS (ESI): m/z=327.1, mass calculated for $[M+H]^+$ ($C_{15}H_{11}ClF_3N_2O$): m/z=327.05; the enantiomeric excess was determined by HPLC analysis using a Chiralpak® ID column (hexane/*i*-PrOH: 90/10, flow rate 2.0 mL min^{-1}, λ=225 nm): *ent*-minor t_r=2.8 min and *ent*-major t_r=3.9 min.

2,2,2-Trifluoro-1-(naphthalen-2-yl)-1-(1*H*-pyrrolo[2,3-*b*]-pyridin-3-yl)ethanol (5c): white solid; 70% yield; 58% *ee*; ^{1}H NMR [400 MHz, $(CD_3)_2SO$]: δ=11.90 (s, 1H, NH), 8.19 (bs, 1H), 8.17 (dd, J=4.7, 1.6 Hz, 1H), 8.00–7.88 (m, 1H), 7.87 (d, J=8.8 Hz, 1H), 7.63–7.49 (m, 4H), 7.37 (dd, J=8.0, 1.6 Hz, 1H), 6.85 (dd, J=8.0, 4.7 Hz, 1H), 7.32 (s, 1H, OH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$] δ=148,6 (C), 143.0 (CH), 136.7 (C), 132.5 (C), 132.3 (C), 128.6 (CH), 128.4 (CH), 127.4 (2CH), 126.6 (CH), 126.3 (CH), 126.2 (CH), 125.8 (q, J=287.3 Hz, CF_3), 125.2 (CH), 124.1 (q, J=2.3 Hz, CH), 117.8 (C), 115.5 (CH), 112.2 (C), 75.8 (q, J=28.8 Hz, C-CF_3); ^{19}F NMR [376 MHz, $(CD_3)_2SO$]: δ=−74.9 (s, 3F); LR-MS (ESI): m/z=343.1, mass calculated for $[M+H]^+$ ($C_{19}H_{14}F_3N_2O$): 343.11; the enantiomeric excess was determined by HPLC analysis using a Chiralpak® ID column (hexane/*i*-PrOH: 80/20, flow rate 1.0 mL min^{-1}, λ=225 nm): *ent*-minor t_r=5.7 min and *ent*-major t_r=6.5 min.

(*S*)-2-Chloro-2,2-difluoro-1-(1*H*-indol-3-yl)-1-phenylethanol (6): white solid; 76% yield; 74% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.21 (bs, 1H, NH), 7.63–7.57 (m, 2H), 7.49 (dd, J=4.6, 2.2 Hz, 1H), 7.35 (dm, J=8.2 Hz, 1H), 7.33–7.29 (m, 3H), 7.21 (d, J=8.1 Hz, 1H), 7.15 (ddd, J=8.2, 7.1, 1.1 Hz, 1H), 6.94 (ddd, J=8.1, 7.1, 0.9 Hz, 1H), 3.04 (bs, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ=138.1 (C), 136.0 (C), 131.4 (t, J=302.5 Hz, CF_2Cl), 128.4 (CH), 128.0 (t, J=1.3 Hz, 2CH), 127.7 (2CH), 125.5 (C), 123.3 (t, J=3.7 Hz, CH), 122.7 (CH), 121.1 (CH), 120.2 (CH), 114.5 (C), 111.1 (CH), 80.6 (t, J=25.4 Hz, C-CF_2Cl); ^{19}F NMR (376 MHz, $CDCl_3$): δ=−61.1 (s, 2F); IR (film): ν=3558, 3414, 3060, 1456, 1418, 1338, 1172, 1120, 1046, 998, 807, 743, 699 cm^{-1}; LR-MS (ESI): m/z=308.1, mass calculated for $[M+H]^+$ ($C_{16}H_{13}ClF_2NO$): 308.07; the enantiomeric excess was determined by HPLC analysis using a Chiralpak® IC column (hexane/*i*-PrOH: 97/3, flow rate 1.0 mL min^{-1}, λ=225 nm): *ent*-minor t_r=10.2 min and *ent*-major t_r=11.4 min.

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[21] For details see the Experimental Section.
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[23] For details see the Supporting information.
[24] There is only one example of a 7-azaindole reaction with a CF_3-ketone in the racemic version described in the literature (see ref.[12]).