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Enantioselective trifluoromethylation of aromatic aldehydes catalyzed by combinatorial catalysts

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Abstract—A new combinatorial catalyst system containing the disodium (*R*)-binaphtholate prepared in situ and a chiral quaternary ammonium salt was developed for enantioselective trifluoromethylation of aromatic aldehydes in up to 71% ee. A possible intermediate for the binaphtholate activation of the $TMSCF_3$ and a catalytic cycle were proposed based on the experiments.

1. Introduction

Trifluoromethyl-containing molecules are recognized as a useful class of compounds in drug discovery as well as synthesis of pharmaceutical and agrochemical products.[1] In the last two decades, many reliable methodologies have been developed for the introduction of a CF_3 moiety into organic compounds and trifluoromethylation has emerged.[2] Hitherto, the most convenient and widely utilized method is the Lewis base-induced nucleophilic reaction with $TMSCF_3$. For example, fluoride sources,[2d,e] *N*-heterocyclic carbene,[2f] and other Lewis bases[2g,h] have been used as nucleophilic initiators for the trifluoromethylation reaction. Nevertheless, asymmetric trifluoromethylation with $TMSCF_3$ is always a great challenge in organofluorine chemistry and only few reports have appeared.[3] Kobayashi et al. reported the asymmetric trifluoromethylation of aromatic aldehydes with $TMSCF_3$ in 40–50% ee in the presence of chiral quaternary ammonium fluoride.[3a] In addition, Caron and co-workers also described that cinchonine-derived catalyst was used in amount as low as 4 mol % in the trifluoromethylation to give the desired product in up to 92% ee.[3b] The role of fluoride in chiral quaternary ammonium fluoride[3a,b] is as Lewis base to activate the $TMSCF_3$, and there may be other Lewis bases instead of fluoride to promote the addition of $TMSCF_3$ to carbonyl compounds. Herein, we described the asymmetric trifluoromethylation of aromatic aldehydes catalyzed by disodium (*R*)-binaphtholate combined with a chiral quaternary ammonium salt. Nowadays, organic salts have been growing to become catalysts of great interest with a distinctive role in asymmetric reactions.[4] We found that inorganic and organic salts were promising Lewis bases for activation of silicon reagent in cyanosilylation of ketones with TMSCN.[4d,5a] Meanwhile, we also found that quaternary ammonium salts were remarkably effective catalysts for activation of carbonyl compounds in the same reaction.[5b] Encouraged by the results above, our interest is in using chiral organic salts in combination with chiral quaternary ammonium salts as combinatorial catalysts to promote the enantioselective trifluoromethylation of aldehydes with $TMSCF_3$.

2. Results and discussion

In a preliminary study, the disodium salts of chiral Schiff base **1a–f**, chiral disodium binaphtholates **2a–f**, and the chiral quaternary ammonium salt **3** (Fig. 1) were examined in trifluoromethylation of 2-naphthaldehyde with $TMSCF_3$. Neither sodium salts nor the quaternary ammonium salt were sufficiently effective to promote the addition of $TMSCF_3$ to the aldehyde (Table 1, entries 1–3). Only when the sodium salt and quaternary ammonium salt were used together, could the reaction proceed smoothly with a significant improvement both in reactivity and enantioselectivity (Table 1, entries 4–7). The disodium (*R*)-binaphtholate **2b** in combination with **3** exhibited the best ee value (50% ee, 87% yield, entry 7), while disodium (*S*)-binaphtholate **2a** only led to product in 38% ee (Table 1, entry 6).[6a] Decreasing the amount of **2b** from 20 to 10 mol % increased the enantioselectivity to 53% ee (Table 1, entry 8). Then the

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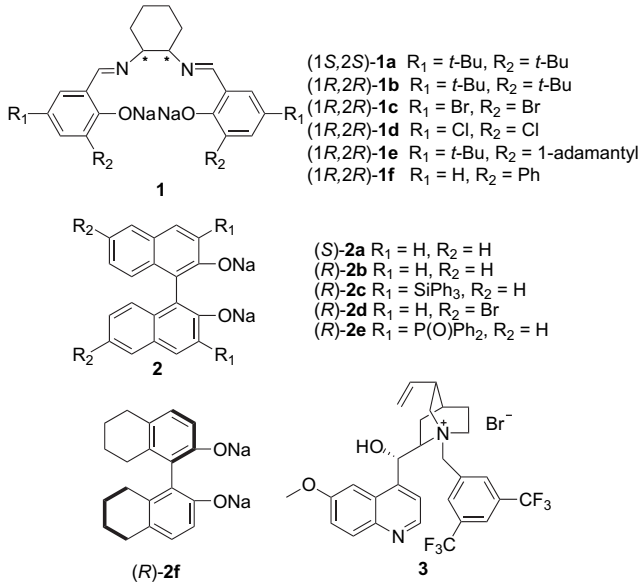
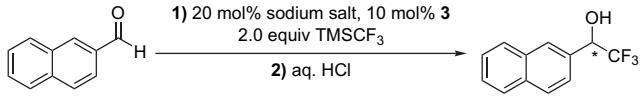


Figure 1. Combinatorial catalysts.

Table 1. Asymmetric trifluoromethylation of 2-naphthaldehyde catalyzed by organic sodium salts and **3**[a]



Entry	Sodium salt	Ammonium salt	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	—	28	37	0
2	**2a**	—	28	ND	—
3	—	**3**	24	ND	—
4	**1a**	**3**	24	93	38
5	**1b**	**3**	24	80	40
6	**2a**	**3**	24	80	38
7	**2b**	**3**	24	87	50
8[d]	**2b**	**3**	24	86	53
9[d]	**1c**	**3**	24	ND	—
10[d]	**1d**	**3**	24	ND	—
11[d]	**1e**	**3**	24	69	44
12[d]	**1f**	**3**	24	33	42
13[d]	**2c**	**3**	24	52	32
14[d]	**2d**	**3**	24	ND	—
15[d]	**2e**	**3**	24	ND	—
16[d]	**2f**	**3**	24	27	38

[a] Conditions: 20 mol % sodium salts, 10 mol % **3**, substrate concentration=0.17 M in Et_2O, −15 °C.
[b] Isolated yield, ND=not detected.
[c] The ee values were determined by HPLC on Chiralcel OD-H column.
[d] The catalyst loading of sodium salt was 10 mol %.

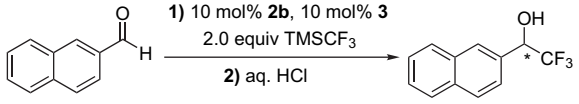
effects of the sodium salt substituents were examined. The reaction could not be performed smoothly when the sodium salts containing electron-withdrawing groups were used (Table 1, entries 9, 10, 14, and 15), and the disodium (*R*)-binaphtholate having smaller group at 3,3′-position[6b] gave better enantioselectivity (Table 1, entry 8 vs entry 13). The screening of chiral quaternary ammonium salts revealed that 3,5-bis(trifluoromethyl)-benzyl catalyst **3** was the best in this reaction.[7] Naturally, the disodium (*R*)-binaphtholate **2b** was chosen as the effective Lewis base combined with chiral quaternary ammonium salt **3** to catalyze the trifluoromethylation reaction. With these encouraging results, the effects of temperature, solvents, additive, and the method of catalyst preparation were investigated in the following experiments.

As shown in Table 2, solvent effects (Table 2, entries 1–4) demonstrated that Et_2O was the most favorable solvent. When molecular sieves were used as additive, the enantioselectivities were improved (entries 5–7), and 4 Å MS gave the best ee value (Table 2, entry 6 vs entries 5 and 7). Further investigation suggested that alkaline environment was good for the reactivity and enantioselectivity. NaOH was selected to adjust the alkalescence of the catalytic system, and the ee value was up to 69% when additional 15 mol % NaOH was added to the combinatorial catalyst system (Table 2, entry 8). Since the disodium (*R*)-binaphtholate was sensitive to moisture, in subsequent experiments, catalysts prepared in situ were chosen to test the trifluoromethylation of 2-naphthaldehyde. Consequently, the reaction performed smoothly with a little improvement in enantioselectivity (Table 2, entry 9). Then temperature effects were examined based on the new method of catalyst preparation. Increasing or lowering the temperature caused a drop both in reactivity and enantioselectivity (Table 2, entries 10 and 11).

Under the optimized conditions, a range of aromatic aldehydes were investigated, and the results are listed in Table 3. In general, *m*- and *p*-substituted benzaldehydes were tolerated well except for 4-methoxybenzaldehyde (Table 3, entry 8), and the methyl at the *m*- and *p*-position of the aromatic ring afforded similar ee value to halogen group (Table 3, entries 3–6 and 10). The piperonal and heterocyclic aromatic aldehydes gave lower ee (Table 3, entries 9 and 11).

The mechanistic detail of this conversion remains obscure. As one part of combinatorial effects, the intermediates of disodium (*R*)-binaphtholate activating the $TMSCF_3$ have

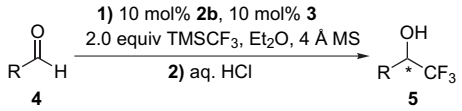
Table 2. Optimization of the solvent, temperature, additive, and the method of catalyst preparation[a]



Entry	Solvent	Temp (°C)	Additive[b]	Time (h)	Yield[c] (%)	ee[d] (%)
1	THF	−15	—	24	77	33
2	Toluene	−15	—	24	ND	—
3	CH_2Cl_2	−15	—	24	69	29
4	Et_2O	−15	—	24	86	53
5	Et_2O	−15	3 Å MS	3	71	57
6	Et_2O	−15	4 Å MS	3	62	62
7	Et_2O	−15	5 Å MS	3	50	55
8[e]	Et_2O	−15	4 Å MS	3	80	69
9[f]	Et_2O	−15	4 Å MS	2	85	71
10[f]	Et_2O	0	4 Å MS	2	75	63
11[f]	Et_2O	−45	4 Å MS	2	76	65

[a] Conditions: 10 mol % **2b**, 10 mol % **3**, substrate concentration=0.17 M in 0.6 ml Et_2O, −15 °C.
[b] The additive loading was 10 mg.
[c] Isolated yield, ND=not detected.
[d] Determined by HPLC on OD-H column.
[e] Additional 15 mol % NaOH was used.
[f] Conditions: 10 mol % **2b** prepared in situ with additional 15 mol % NaOH and 10 mol % **3**, substrate concentration=0.17 M in 0.6 ml Et_2O, −15 °C (see Section 4).

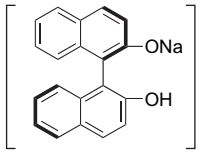
Table 3. Asymmetric trifluoromethylation of aromatic aldehydes catalyzed by combinatorial catalysts[a]



4 5

Entry	Aldehyde	Yield[b] (%)	ee[c] (%)
1	2-Naphthaldehyde (**4a**)	85	71
2	Benzaldehyde (**4b**)	72	56
3	4-Methylbenzaldehyde (**4c**)	87	60
4	3-Methylbenzaldehyde (**4d**)	88[d]	58
5	4-Chlorobenzaldehyde (**4e**)	72	50
6	3-Chlorobenzaldehyde (**4f**)	95[d]	56
7	4-Phenylbenzaldehyde (**4g**)	73	56
8	4-Methoxybenzaldehyde (**4h**)	87	41
9	Piperonal (**4i**)	95	46
10	4-Fluorobenzaldehyde (**4j**)	86[d]	57
11	2-Thiophenecarboxaldehyde (**4k**)	68[d]	45

[a] The catalyst **2b** was prepared in situ (see Section 4).
[b] Isolated yield.
[c] The ee values were determined by HPLC or GC.
[d] Isolated yield of the TMS ether.



Monosodium Binaphtholate

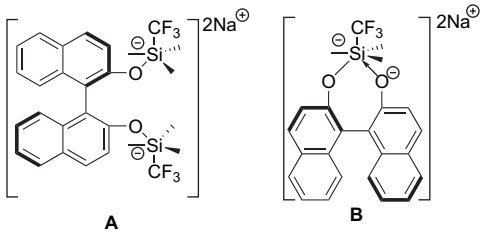


Figure 2. Intermediate of disodium binaphtholate activating the $TMSCF_3$.

two possibilities.[2h] But the reaction could not proceed when monosodium catalyst (Fig. 2) was used in combination with the quaternary ammonium salt in Et_2O. The ability of one negatively charged O atom activating the $TMSCF_3$ was not strong enough to promote the addition of $TMSCF_3$ to the aldehyde. So we speculated that the role of disodium (*R*)-binaphtholate might be as Lewis base to activate the $TMSCF_3$ and form the hexavalent intermediate **B**, not **A** (Fig. 2), and the positively charged N atom of quaternary ammonium salt attracts the O atom of the carbonyl group and thus activates the carbonyl as the other part of the combinatorial effects. A proposed catalytic cycle was afforded according to the intermediate of disodium binaphtholate activating the $TMSCF_3$ (Fig. 3).

3. Conclusion

In summary, we have developed a new chiral combinatorial catalyst system to catalyze the enantioselective addition of $TMSCF_3$ to aromatic aldehydes with reasonable yields and enantioselectivities. Moreover, a possible intermediate of binaphtholate activation of the $TMSCF_3$ and proposed catalytic cycle have been proposed based on the experiments. Further efforts will be devoted to search for effective catalyst systems that tolerate a broad range of aldehydes with higher yield and enantioselectivity.

4. Experimental

4.1. General

All reactions were carried out using anhydrous solvents and under nitrogen in over-dried tubes unless noted otherwise. Toluene, THF, and Et_2O were dried and distilled from sodium/benzophenone under nitrogen prior to use. TLC analysis was performed with glass backed plates precoated with silica gel and examined under UV (254 nm). HG/T2354-92 silica gel was used for flash chromatography (FC). Enantiomeric excesses (ee) were determined by HPLC using the corresponding commercial chiral column as stated in the experimental procedures at 23 °C with UV detection at 254 nm or chiral GC with a Varian GC system: column Chirasil DEX CB. Optical rotations were measured on the Autopol V Automatic Polarimeter. ^1H NMR spectra were recorded in $CDCl_3$ on Inova-400 (400 MHz) and were reported in parts per million using TMS (δ=0) or residual $CDCl_3$ (δ=7.26) as the reference. ^{13}C NMR spectra were recorded in $CDCl_3$ on Inova-400 (100 MHz) and were reported in parts per million relative to the central $CDCl_3$ resonance (δ=77.00).

4.1.1. General procedure for the trifluoromethylation of aromatic aldehydes (4a). A THF (0.6 mL) solution in which there were (*R*)-BINOL (2.8 mg, 0.01 mmol), NaOH (1.4 mg, 0.035 mmol), **3** (6.2 mg, 0.01 mmol), and 4 Å MS (10 mg) was stirred for 30 min at 30 °C. Then THF was evaporated under reduced pressure. 2-Naphthaldehyde (60 μL, 1.67 mol/L in toluene, 0.1 mmol) and Et_2O (0.3 mL) were added at 30 °C. At last, $TMSCF_3$ (30 μL, 0.2 mmol) and Et_2O (0.3 mL) were added at −15 °C under N_2 atmosphere. After stirring for 2 h at this temperature, the reaction was quenched. A 2 N HCl solution (1 mL) was added and the combined solution was stirred at room temperature until all TMS protected intermediate converted to product. Water (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Solvents were removed under vacuum to give the crude residue, and the crude was purified by flash chromatography on silica gel (PE/EtOAc=20:1).

4.1.1.1. (−)-2,2,2-Trifluoro-1-(2-naphthyl)ethanol (5a).[2b] $[\alpha]_D^{20}$ −23.7 (*c* 0.16, CH_2Cl_2) (71% ee), ^1H NMR (300 MHz, $CDCl_3$): δ 7.96–7.85 (m, 4H), 7.59–7.52 (m, 3H), 5.19 (q, *J*=6.6 Hz, 1H), 2.70 (s, 1H). The product was determined as 71% ee by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol=90:10, 1 mL/min). t_R (major)= 10.54 min and t_R (minor)=15.52 min.

4.1.1.2. (−)-2,2,2-Trifluoro-1-phenylethanol (5b).[2f] $[\alpha]_D^{20}$ −12.5 (*c* 0.4, CH_2Cl_2) (56% ee), ^1H NMR (400 MHz, $CDCl_3$): δ 7.49–7.47 (m, 2H), 7.42–7.40 (m, 3H), 5.02 (q, *J*=6.4 Hz, 1H), 2.92 (d, *J*=4.4, 1H). The product was determined as 56% ee by HPLC (Chiralcel OD-H,

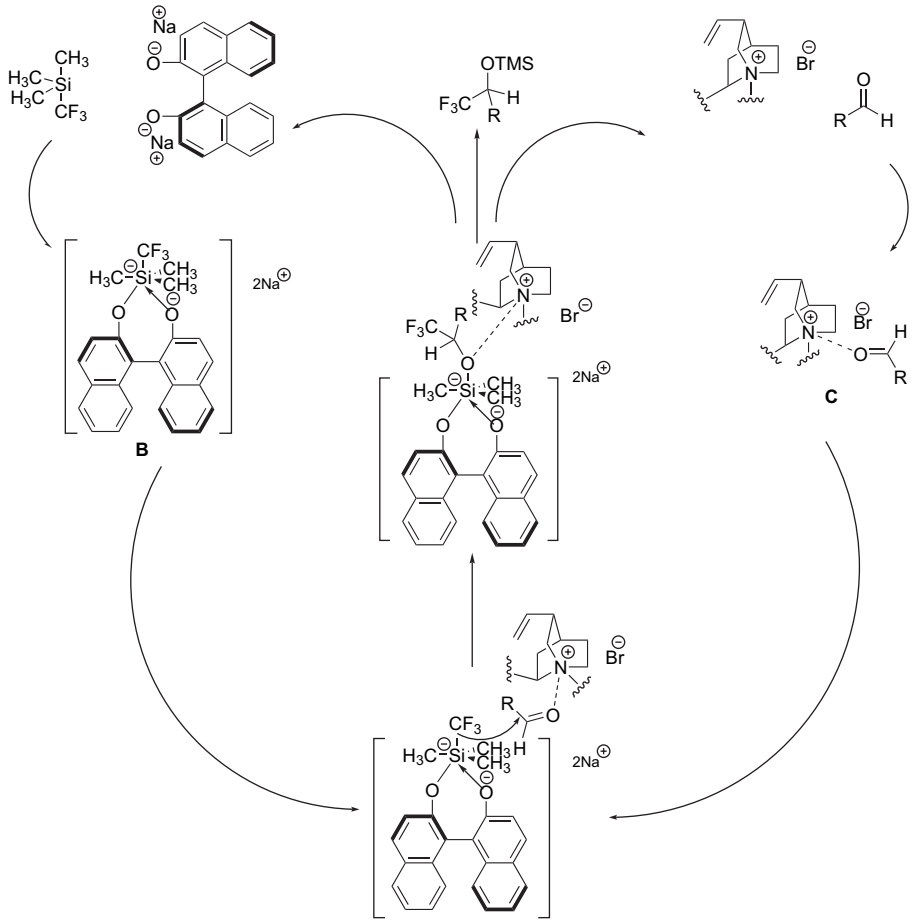


Figure 3. Proposed catalytic cycle.

n-hexane/isopropanol=99:1, 1 mL/min). t_R (major)= 35.76 min and t_R (minor)=41.43 min.

4.1.1.3. (−)-2,2,2-Trifluoro-1-*p*-tolylethanol (5c).[8a] $[\alpha]_D^{20}$ −18.4 (*c* 0.43, CH_2Cl_2) (60% ee), ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J*=7.6 Hz, 2H), 7.20 (d, *J*=7.6 Hz, 2H), 4.93 (m, 1H), 2.97 (d, *J*=4.0 Hz, 1H), 2.36 (s, 3H). The product was determined as 60% ee by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol=90:10, 1 mL/min). t_R (major)=5.81 min and t_R (minor)=7.36 min.

4.1.1.4. (−)-2,2,2-Trifluoro-1-*m*-tolylethanol (5d).[8a] $[\alpha]_D^{20}$ −13.3 (*c* 0.15, CH_2Cl_2) (58% ee), ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.21 (m, 4H), 4.96 (q, *J*= 6.8 Hz, 1H), 2.62 (d, *J*=4.4 Hz, 1H), 2.38 (s, 3H). The product was determined as 58% ee by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol=99:1, 1 mL/min). t_R (major)= 26.04 min and t_R (minor)=35.72 min.

4.1.1.5. (−)-1-(4-Chlorophenyl)-2,2,2-trifluoroethanol (5e).[2f] $[\alpha]_D^{20}$ −8.8 (*c* 0.1, CH_2Cl_2) (50% ee), ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (s, 4H), 4.98 (m, 1H), 3.21 (d, *J*=4.0 Hz, 1H). The product was determined as 50% ee by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol=90:10, 1 mL/min). t_R (major)=4.98 min and t_R (minor)=5.93 min.

4.1.1.6. (−)-1-(3-Chlorophenyl)-2,2,2-trifluoroethanol (5f).[8a] $[\alpha]_D^{20}$ −7.3 (*c* 0.22, CH_2Cl_2) (56% ee), ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.40–7.34 (m, 3H), 5.01 (q, *J*=6.4 Hz, 1H), 2.81 (d, *J*=4.0 Hz, 1H). The product was determined as 56% ee by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol=95:5, 1 mL/min). t_R (major)=7.62 min and t_R (minor)=10.83 min.

4.1.1.7. (−)-1-(4-Biphenyl)-2,2,2-trifluoroethanol (5g).[2b] $[\alpha]_D^{20}$ −7.1 (*c* 0.14, CH_2Cl_2) (56% ee), ^1H NMR (400 MHz, $CDCl_3$): δ 7.64–7.42 (m, 9H), 5.06 (m, 1H), 2.71 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 139.3, 131.8, 127.8, 126.8, 126.6, 126.3, 126.1, 123.2 (q, J_{C-F}= 281 Hz), 71.6 (q, J_{C-F}=32 Hz). HRMS (ESI) calcd for $C_{14}H_{10}F_3O$ [**5g**-H]$^-$: 251.0689, found 251.0689. The product was determined as 56% ee by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol=90:10, 1 mL/min). t_R (major)= 8.94 min and t_R (minor)=11.21 min.

4.1.1.8. (−)-2,2,2-Trifluoro-1-(4-methoxyphenyl)-ethanol (5h).[2f] $[\alpha]_D^{20}$ −8.9 (*c* 1.0, CH_2Cl_2) (41% ee), ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J*=8.8 Hz, 2H), 6.94 (d, *J*=8.8 Hz, 2H), 4.97 (q, *J*=6.8 Hz, 1H), 3.83 (s, 3H), 2.60 (d, *J*=4.4 Hz, 1H). The product was determined as 41% ee by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol= 99:1, 1 mL/min). t_R (major)=53.74 min and t_R (minor)= 58.79 min.

4.1.1.9. (−)-1-(5-Benzo[*d*][1,3]dioxolyl)-2,2,2-trifluoroethanol (5i). $[\alpha]_D^{20}$ −7.8 (*c* 0.55, CH_2Cl_2) (46% ee), ^1H NMR (400 MHz, $CDCl_3$): δ 6.97 (s, 1H), 6.92 (d, *J*=9.0 Hz, 2H), 6.81 (d, *J*=8.0 Hz, 1H), 4.92 (q, *J*=6.2 Hz,

1H), 2.72 (d, J=4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 147.9, 127.7, 124.2 (q, J_{C-F}=280 Hz), 121.6, 108.2, 107.6, 101.4, 72.6 (q, J_{C-F}=32 Hz). HRMS (ESI) calcd for $C_9H_8F_3O_3$ [**5i**+H]$^+$: 221.0420, found 221.0421. The product was determined as 46% ee by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol=90:10, 1 mL/min). t_R (major)= 8.92 min and t_R (minor)=10.00 min.

4.1.1.10. (−)-2,2,2-Trifluoro-1-(4-fluorophenyl)ethanol (5j).[8b] $[\alpha]_D^{20}$ −20 (*c* 0.02, CH_2Cl_2) (57% ee), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (t, J=6.0 Hz, 2H), 7.09 (t, J= 8.0 Hz, 2H), 5.00 (m, 1H), 2.98 (d, J=3.2 Hz, 1H). The product was determined as 57% ee by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol=90:10, 1 mL/min). t_R (major)= 4.78 min and t_R (minor)=5.42 min.

4.1.1.11. (−)-2,2,2-Trifluoro-1-(2-thiophenyl)ethanol (5k).[8c] $[\alpha]_D^{20}$ −11.4 (*c* 0.1, CH_2Cl_2) (45% ee), ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, J=5.2, 1.2 Hz, 1H), 7.21 (m, 1H), 7.05 (dd, J=4.8, 3.6 Hz, 1H), 5.29 (q, J=5.6 Hz, 1H), 2.68 (d, J=5.2 Hz, 1H). The product was determined as 45% ee by GC (Varian, CP-Chirasil DEX CB) analysis. t_R (major)=9.61 min and t_R (minor)=9.28 min.

Acknowledgements

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