Journal of Fluorine Chemistry 148 (2013) 19–29

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

The enantioselective trifluoromethylation of aromatic aldehydes by quaternary ammonium bromide and (IPr)CuF at low catalyst loading

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ARTICLE INFO

Article history:
Received 11 December 2012
Received in revised form 25 January 2013
Accepted 26 January 2013
Available online 5 February 2013

Keywords:
Aldehyde
Asymmetric catalysis
Carbene copper species
Quaternary ammonium salt
Trifluoromethylation

ABSTRACT

A general catalytic enantioselective trifluoromethylation of aromatic aldehydes using (IPr)CuF and quinidine-derived quaternary ammonium salt as catalysts has been developed. A wide range of aromatic aldehydes are converted to the corresponding products in up to 92% yield and 81% ee at 2 mol% of catalyst loading.

1. Introduction

Due to their unique properties and unusual reactivities, fluorinated compounds have found extensive applications in the fields of materials, pharmaceuticals, and agrochemicals [1]. Trifluoromethylated organic compounds have recently emerged expansively as promising biologically active motifs for drug design [2]. As a consequence, many groups are committed to the introduction of trifluoromethyl group into organic compounds [3]. Another point of interest in medicinal chemistry is the fact that the number of chiral drugs on the market has been rapidly increasing [4]. These lead us to explore efficient method for constructing optically pure trifluoromethylated compounds to provide attractive surrogates for drug candidates [5,1d]. Among them, direct trifluoromethylation is simple and therefore promising as an industrial process. Indeed, after the initial discovery of trifluoromethylation reaction of carbonyl compounds with Me_3SiCF_3 (Ruppert–Prakash reagent) by Prakash group [6], considerable efforts have been devoted to the development of different catalytic systems to activate Me_3SiCF_3. Although synthesis of racemic trifluoromethylated alcohols with Me_3SiCF_3 has been competitively studied in recent years, highly enantioselective trifluoromethylation of aromatic aldehydes is difficult to be achieved [7].

Kobayashi and coworkers firstly selected *N*-[4-(trifluoromethyl)benzyl]cinchonium fluoride as catalyst for the reaction and the corresponding trifluoromethylated alcohols were provided in ee values of 40–50% in 1994 [8]. Following this work, a lot of stereo-selective variants were developed in recent years [9], such as chiral ammonium salts and triaminosulfonium salts. However, enantioselectivities were low to moderate. Furthermore, Feng discovered that a combination of disodium (*R*)-binaphtholate and *cinchona* alkaloid-derived quaternary ammonium salts afforded the products of trifluoromethylation of aromatic aldehydes in up to 71% ee by 10 mol% of catalyst [10], while the enantioselectivities were low around 40% ee for electron-rich aromatic aldehydes. The subsequently developed asymmetric approaches were documented by Shibata [11]. They used 1 mol% of chiral crown ether and 10 mol% base as the catalyst. But the ee values just reached 44%. In contrast to the enantioselective trifluoromethylation of aromatic aldehydes, better results of ketones were acquired [12]. In the later papers, the best enantioselectivity for ketones was recorded as 94% ee by Shibata, while aryl aldehyde only got 41% ee using 10 mol% of the same catalyst *cinchona* alkaloid-derived ammonium bromide salt and $Me_4N^+F^-$. The enantioselective trifluoromethylation of aromatic aldehydes is still improvable. Previously, we communicated an enantioselective trifluoromethylation reaction of aromatic aldehydes with (IPr)CuF (IPr = 1,3-bis(2′,6′-di-*iso*-propylphenyl)imidazol-2-ylidene) and quaternary ammonium salt [13]. Herein, the effects of catalyst structure (**1a–g**, **2**, **3**, **4a–d**), reaction parameters, structure of substrates (**5a–u**)

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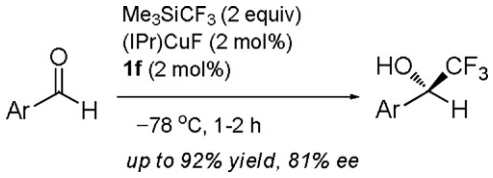
http://dx.doi.org/10.1016/j.jfluchem.2013.01.027



Scheme 1. Enantioselective trifluoromethylation of aldehydes catalyzed by quaternary ammonium bromide and (IPr)CuF.

including the heterocyclic aromatic aldehyde (**5d**), and the plausible catalytic cycle are described in full length (Scheme 1).

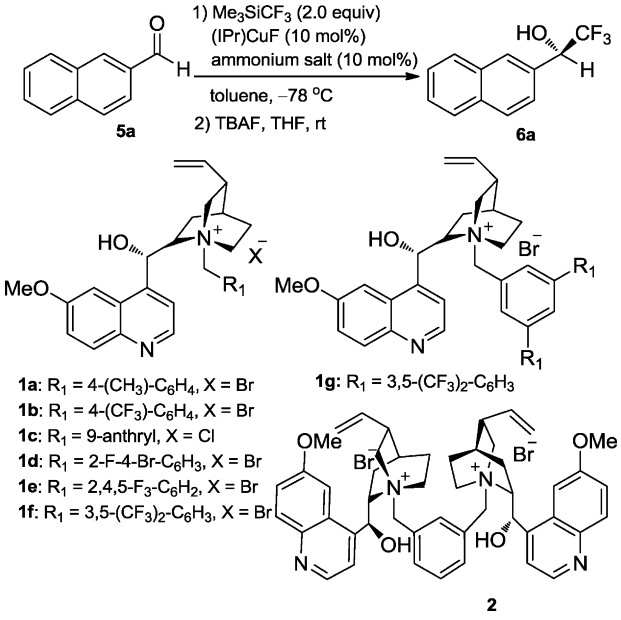
2. Results and discussion

The model reaction was conducted with 2-naphthaldehyde (**5a**) and Me_3SiCF_3 (2 equiv.) in toluene at −78 °C. Initially, a variety of quinidine-derived quaternary ammonium salts (**1a–g**, **2**) were examined with different *N*-substituent at 10 mol% catalyst loading with results shown in Table 1. *N*-(4-Methylbenzyl) ammonium bromide salt (**1a**) led to the desired product in 20% ee albeit in good yield (Table 1, entry 1). When **1b** possessing a 4-trifluoromethyl benzyl group at the nitrogen atom of quinidine was used, the reaction afforded **6a** in 90% yield and 35% ee (entry 2). It was noteworthy that **1c** bearing a hindering *N*-9-anthrylmethylene group gave nearly racemic product (entry 3). Better enantioselectivities were obtained with catalyst **1d** and **1e** bearing electron-withdrawing groups (entries 4 and 5). Additionally, both bulky substituent at the nitrogen atom and enhanced electron-withdrawing strength caused a significant improvement in enantioselectivity. Accordingly, catalyst **1f** and **1g** greatly increased the ee values to 69% and 63%, respectively (entries 6 and 7). However, C_2-symmetric dimeric catalyst **2** derived from quinidine gave a disappointing result of 45% yield and 21% ee (entry 8).

The steric effect of substituent at C-6 was also evaluated. As shown in Table 2, both 3 with a small H at C-6 derived from cinchonine and **4a** with a bulky cyclopentyloxyl instead gave lower ee values than methoxy group (Table 2, entries 1–2 vs. entry 6 of Table 1). Modification of the catalyst motif revealed that the C-9 hydroxyl group had to be unprotected to maintain good chiral inductive capability. Thus, C-9-protected **4b** led to a decreased yield and 45% ee (entry 3), suggesting a live hydrogen bond and a possible π–π stacking between the benzyl moiety of catalyst and the aromatic portion of substrate as well [14]. Considering the indispensability of free hydroxyl group of the quinidine for achieving high enantiocontrol, deprotection of *O*-methyl yielded **4c**. However, the result was disappointing with it (entry 4), which indicated that one more free hydroxyl group at C-6 disturbed the hydrogen bond of C-9-OH and π–π stacking interactions. Furthermore, C-6-OH and C-9-*O*-benzylated catalyst **4d** decreased the enantioselectivity to 21% ee (entry 5). Based on the results of catalyst screening, **1f** gave the highest enantioselectivity.

In view of the role of H-bond in this cooperative catalyst, other additives were introduced into the reaction mixture with results listed in Table 3. Without any proton additive, the ee value was up to 69% (Table 1, entry 6). Proton sources such as (*R*)-BINOL ((*R*)-1,1′-binaphthalen-2,2′-diol) and (*R*)-2,2,2-trifluoro-1-(naphthalen-2-yl)ethanol gave no conversion (Table 3, entries 1–2). When

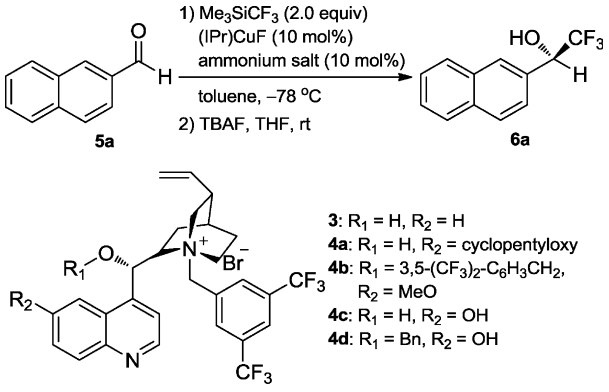
Table 1
Effect of *N*-substituents of quinidine-derived quaternary ammonium salts on the enantioselectivity.[a]



Entry	Ammonium salt (mol%)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a** (10)	1	87	20 (*R*)[d]
2	**1b** (10)	1	90	35
3	**1c** (10)	1	90	2
4	**1d** (10)	1	89	53
5	**1e** (10)	1	93	57
6	**1f** (10)	1	92	69
7	**1g** (10)	1	86	63
8	**2** (10)	4	45	21

[a] Reaction conditions: **5a** (0.2 mmol), (IPr)CuF (10 mol%), Me_3SiCF_3 (0.4 mmol, 2 equiv.), [**5a**] = 0.25 mol L^{-1} in toluene (0.8 mL), −78 °C, stirring under Ar atmosphere.
[b] Isolated yield.
[c] Determined by chiral HPLC on Chiralcel OJ-H.
[d] The absolute configuration of the **6a** was assigned by comparing HPLC retention time and the sign of optical rotation value with that of literature [Ref. 12b].
TBAF = tetrabutylammonium fluoride.

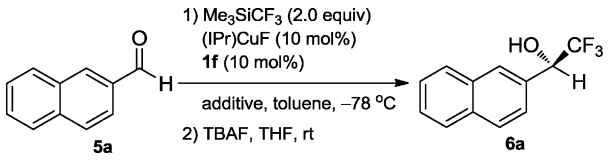
Table 2
Effect of hydroxy groups at C-6 and C-9 on the enantioselectivity.[a]



Entry	Ammonium salt (mol%)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**3** (10)	2	83	20
2	**4a** (10)	1	90	46
3	**4b** (10)	1	85	45
4	**4c** (10)	12	43	17
5	**4d** (10)	12	37	21

[a] Reaction conditions: **5a** (0.2 mmol), (IPr)CuF (10 mol%), Me_3SiCF_3 (0.4 mmol, 2 equiv.), [**5a**] = 0.25 mol L^{-1} in toluene (0.8 mL), −78 °C, stirring under Ar atmosphere.
[b] Isolated yield.
[c] Determined by chiral HPLC on Chiralcel OJ-H.

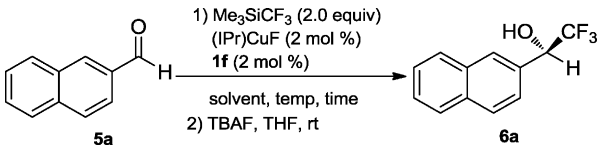
Table 3
Effect of additive on the model reaction.[a]



Entry	Additive (mol%)	Time (h)	Yield[b] (%)	ee[c] (%)
1	(*R*)-BINOL (10)	12	–	–
2	(*R*)-2,2,2-trifluoro-1-(naphthalen-2-yl)ethanol (10)	4	–	–
3	(*R*)-BNPH (10)	12	Trace	ND
4	Me_3SiCl (100)	2	–	–
5[d]	4 Å MS	1	92	68

[a] Reaction conditions: **5a** (0.2 mmol), (IPr)CuF (0.02 mmol, 10 mol%), 1f (0.02 mmol, 10 mol%), Me_3SiCF_3 (0.4 mmol, 2 equiv.), [**5a**] = 0.25 mol L^{-1} in toluene (0.8 mL), −78 °C, stirring under Ar atmosphere.
[b] Isolated yield.
[c] Determined by chiral HPLC on Chiralcel OJ-H.
[d] 10 mg 4 Å MS was used. ND = not detected.

Table 5
Effects of solvent on the model reaction.[a]



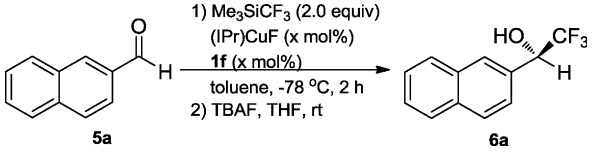
Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	Toluene	−78	1	90	75
2	2-Chlorotoluene	−20	2	92	35
3	Et_2O	−78	4	41	37
4	Hexane	−78	4	37	6
5	THF	−78	2	88	29
6	CH_3CN	−20	2	85	0
7	CH_2Cl_2	−78	1	87	40

[a] Reaction conditions: **5a** (0.2 mmol), Me_3SiCF_3 (0.4 mmol, 2 equiv.), (IPr)CuF (0.004 mmol, 2 mol%), 1f (0.004 mmol, 2 mol%), [**5a**] = 0.33 mol L^{-1}, stirring under Ar atmosphere.
[b] Isolated yield.
[c] Determined by chiral HPLC on Chiralcel OJ-H.

the protonic acid (*R*)-BNPH ((*R*)-1,1′-binaphthyl-2,2′-diyl phosphoric acid) was added, only trace product was obtained (entry 3). Proton additives destroyed the catalytic capability of the cooperative catalysts. Me_3SiCl suppressed the reaction completely (entry 4). Molecular sieves had no effect on the catalyst efficiency (entry 5).

To obtain the optimum reaction condition further optimization on catalyst loading, reaction temperature substrate concentration and other copper complexes was performed (Table 4). Reasonably, as reducing the catalyst loading from 10 mol% to 2 mol% at 0.25 mol L^{-1} of 2-naphthaldehyde, the yields and ee values of product **6a** had no significant effect (entries 1 and 2). Further decrease of the catalyst loading to 1 mol% resulted in a deleterious effect on the reaction conversion even at higher concentration of 0.5 mol L^{-1} and longer reaction time, but without decrease of enantioselectivity (entries 3–4). To our delight, when the reaction was run at 0.33 mol L^{-1} of aldehyde concentration, better enantioselectivity 75% ee was afforded at 2 mol% of catalyst loading (entry 5). Higher concentration of the substrate

Table 4
Effect of catalyst loading, reaction temperature and concentration on the model reaction.[a]



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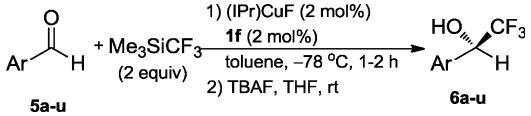
Entry	Ammonium salt (mol%)	(IPr)CuF (mol%)	Concn[b] (mol L^{-1})	Yield[c] (%)	ee[d] (%)
1	**1f** (5)	5	0.25	89	67
2	**1f** (2)	2	0.25	92	68
3[e]	**1f** (1)	1	0.25	52	66
4	**1f** (1)	1	0.50	50	67
5	**1f** (2)	2	0.33	90	75
6	**1f** (2)	2	0.50	89	67
7[f]	**1f** (2)	2	0.33	92	47
8[g]	**1f** (2)	2	0.33	87	24
9[h]	**1f** (10)	–	0.33	86	53
10[i,j]	**1f** (10)	–	0.33	NR	-

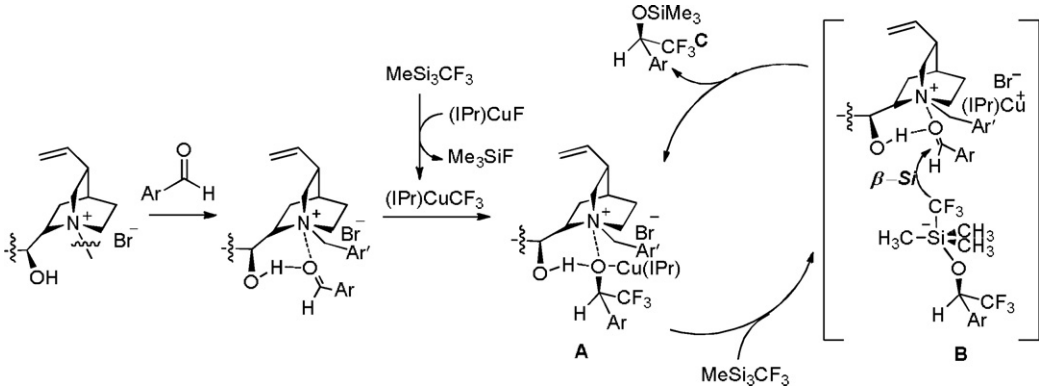
[a] Reaction conditions: **5a** (0.2 mmol), Me_3SiCF_3 (0.4 mmol, 2 equiv.), −78 °C, stirring under Ar atmosphere.
[b] Concentration of **5a**.
[c] Isolated yield.
[d] Determined by chiral HPLC on Chiralcel OJ-H.
[e] The reaction time was 4 h.
[f] The reaction was carried out at −40 °C.
[g] The reaction was carried out at −20 °C.
[h] $CuF(PPh_3)_3$ (10 mol%) instead of (IPr)CuF was used.
[i] CuF_2 (10 mol%) and (S)-BINAP (10 mol%) instead of (IPr)CuF was used.
[j] The reaction was carried out at 0 °C.

Table 6
Scope of substrate.[a]



Entry	5	Ar	Time (h)	Yield[b] (%)	ee[c] (%)
1	**5a**	2-Naphthyl	1	90	75 (98)[d]
2	**5b**	1-Naphthyl	2	88	60
3[e]	**5c**	C_6H_5	2	80	60
4	**5d**	2-Pyridyl	2	89	42
5	**5e**	4-BrC_6H_4	2	81	57
6	**5f**	3-BrC_6H_4	2	82	52
7[e]	**5g**	4-ClC_6H_4	2	83	51
8[e]	**5h**	3-ClC_6H_4	2	83	51
9[e]	**5i**	4-FC_6H_4	2	79	45
10[e]	**5j**	3-FC_6H_4	2	87	51
11	**5k**	4-MeC_6H_4	1	88	68
12	**5l**	4-PhC_6H_4	1	90	66
13	**5m**	3-$PhOC_6H_4$	1	87	60
14	**5n**	4-$MeOC_6H_4$	1	85	67
15	**5o**	3-$MeOC_6H_4$	1	89	74
16	**5p**	2-$MeOC_6H_4$	1	88	73
17	**5q**	6-MeO-2-naphthyl	2	83	53
18	**5r**	3,4-$O(CH_2)C_6H_3$	2	92	81
19	**5s**	3,4-$O(CH_2)_2C_6H_3$	2	92	79
20	**5t**	4-$(C_3H_5O)C_6H_4$	2	80	67
21	**5u**	4-$C_2H_5SC_6H_4$	2	85	73

[a] Reaction conditions: **5a–u** (0.2 mmol), (IPr)CuF (0.004 mmol, 2 mol%), 1f (0.004 mmol, 2 mol%), Me_3SiCF_3 (0.4 mmol, 2 equiv.), [**5**] = 0.33 mol L^{-1} in toluene (0.6 mL), −78 °C, stirring under Ar atmosphere.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OJ-H, OD-H, AD-H, and AS-H). The absolute configuration of **6a** was assigned by comparing HPLC retention time and the sign of optical rotation value with that of literature [Ref. 12b]. Others (**6b–u**) were assumed by analogy.
[d] The ee value in parentheses was obtained after recrystallization.
[e] The reaction was carried out at −20 °C.



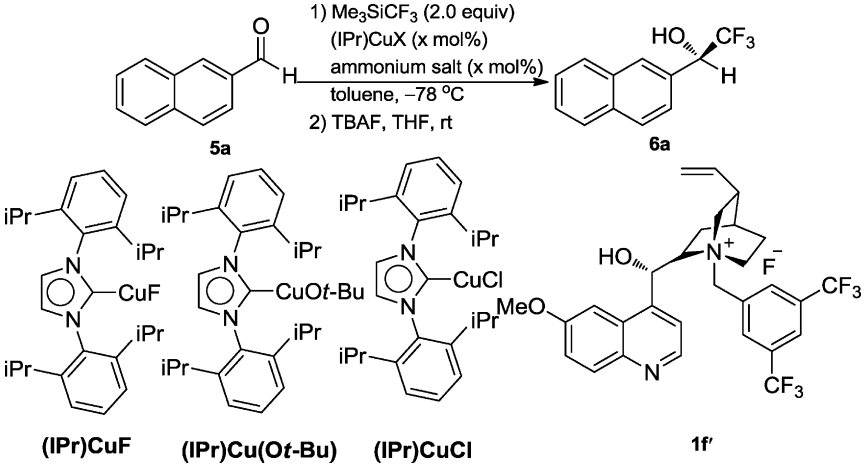
Scheme 2. Proposed catalytic cycle.

(0.5 mol L^{-1}) eroded the enantioselectivity obviously to 67% ee. Elevation of the reaction temperature from −78 °C to −40 °C and −20 °C decreased enantioselectivity stepwise from 75% ee to 47% ee and 24% ee, respectively (entries 7 and 8). Other copper complexes were also tested and the results were summarized in entry 9 and 10. $CuF(PPh_3)_3$ and **1f** led to relative lower ee values while CuF_2/(S)-BINAP and **1f** gave no conversion.

With **1f** as the catalyst, the solvent effect on the model reaction was subsequently investigated. Solvents exhibited strong effect on the catalyst capability. As shown in Table 5, when toluene was used, the reaction was furnished in 75% ee (entry 1). 2-Chlorotoluene and Et_2O gave poor results (entries 2 and 3). In hexane, the cooperative catalyst nearly lost its enantioselective capability (entry 4). THF, CH_3CN and CH_2Cl_2 afforded **6a** with excellent yields, however, the ee values were decreased sharply (entries 5–7). Consequently, the optimal reaction conditions are as follows: 2 mol% of (IPr)CuF, 2 mol% of **1f**, substrate concentration 0.33 mol L^{-1} in toluene, and −78 °C.

With the optimal reaction condition in hands, the substrate generality was evaluated (Table 6). For aldehydes (**5a**–**c**) without substituent, almost all of the corresponding products could be obtained in high yields and high enantioselectivities (entries 1–3). After a simple recrystallization the enantiopurity of **6a** was increased from 75% to 98% ee easily (entry 1). The heterocyclic aromatic aldehyde (**5d**) gave lower ee value and good yield (entry 4). This is the first report of directly enantioselective trifluoromethylation of heterocyclic aromatic aldehydes up to date. On the other hand, F, Cl, Br-substituted aldehydes (**5e**–**j**) worked well for this reaction and provided the products in moderate enantioselectivities (entries 5–10).

Table 7
Control experiments.[a]



Entry	Ammonium salt (mol%)	(IPr)CuX (mol%)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1f** (2)	–	4	NR	–
2	–	(IPr)CuF (2)	4	Trace	ND
3	**1f** (2)	(IPr)CuF (2)	1	90	75
4	**1f** (2)	(IPr)Cu(O*t*-Bu) (2)	4	57	45
5	**1f** (2)	(IPr)CuCl (2)	4	NR	–
6	**1f′** (5)	–	36	87	57
7	**1f′** (5)	(IPr)CuCl (5)	48	84	67
8[d]	**1f** (5)	–	12	76	52
9[d]	**1f** (5)	(IPr)CuF (5)	12	79	59

[a] Reaction conditions: **5a** (0.2 mmol), Me_3SiCF_3 (0.4 mmol, 2 equiv.), toluene (0.6 mL), −78 °C, stirring under Ar atmosphere.
[b] Isolated yield.
[c] Determined by HPLC analysis on Chiralcel OJ-H.
[d] Sodium salt of (*R*)-**6a** (99% ee, 10 mol%) was added. ND = not detected. NR = no reaction.

To our satisfaction, electron-donating aromatic aldehydes reacted very well under the optimal reaction condition to give **6k**–**u** with good to high enantioselectivities (entries 11–21). For aldehydes (**5n**–**p**) with methoxy group on different positions of the phenyl ring were well tolerated in the present system with good to high enantioselectivities (67–74% ee) (entries 14–16). Significantly, we were pleased to find that epoxy replaced aromatic substrates (**5r**–**s**) were trifluoromethylated with excellent yields and good enantioselectivities (81% ee and 79% ee, respectively, entries 18–19). The highest enantioselectivity 81% ee (entry 18) was recorded in the case of **5r** compared to 46% ee in the literature [10]. It should be mentioned that functional aldehydes and hetero-substitutional were also suitable to the reaction. 4-(Allyloxy)benzaldehyde (**5t**) and 4-(ethylthio)benzaldehyde (**5u**) were converted into the alcohols in 67% ee and 73% ee, respectively (entries 20 and 21). To the best of our knowledge, this represents the most general process for the catalytic enantioselective trifluoromethylation of aromatic aldehydes to date.

To gain more information about the reaction mechanism and fundamental catalytic steps, a family of (IPr)CuX were applied to the model reaction under optimum reaction conditions as controlled reactions (Table 7). Neither (IPr)CuF nor the chiral quaternary ammonium salt was sufficiently effective to promote the addition of Me_3SiCF_3 to aldehyde even after 4 h (entries 1, 2 vs. entry 3). However, in the presence of **1f** (IPr)Cu(O*t*-Bu) produced **6a** with 45% ee while (IPr)CuCl and **1f** gave no product (entries 4 and 5). Nevertheless, quaternary ammonium fluoride salt **1f′** gave the product in 87% yield and 57% ee (entry 6). In combination with (IPr)CuCl, the enantioselectivity increased to 67% ee (entry 7). We supposed that the fluoride ion might act as an initiator to generate the active [(IPr)CuCF_3] and other copper species. Considering the generation of carbene copper alkoxides in the catalytic cycle [15], in the absence of (IPr)CuF, the (*R*)-sodium 2,2,2-trifluoro-1-(naphthalen-2-yl)ethanolate was added to enhance the enantioselectivity. However, the ee value decreased to 52% (entry 8). After the (IPr)CuF was used together, the ee value increased to 59% (entry 9). These observations indicated (IPr)CuF was the key factor for the high performance of the cooperative catalyst.

Based on the experimental observations, the plausible catalytic cycle was proposed (Scheme 2). First, aldehyde was effectively activated by the chiral N^+ cation. At the same time, (IPr)CuF reacted with Me_3SiCF_3 to transfer a CF_3 group to copper and furnished the active [(IPr)CuCF_3] which underwent nucleophilic attack to the activated carbonyl group forming intermediate **A**. The presence of copper species may further enhance the chiral communications between the quaternary ammonium salt and the substrates. The formation of alkoxide intermediate **A**, subsequent association and thus activation of Me_3SiCF_3 arranged the new transition state **B** effectively allowing the release of product **C** and regeneration of **A** simultaneously.

3. Conclusion

In conclusion, a general catalytic enantioselective trifluoromethylation of aromatic aldehydes using (IPr)CuF and quinidine-derived quaternary ammonium salts as the catalyst as well as the plausible catalytic cycle have been developed. This process proceeds through [(IPr)CuCF_3] and (IPr)Cu-alkoxide to give the product. It furnishes a wide range of substrates to the corresponding products with the highest levels of enantiomeric excess recorded in the literature thus far including the first example of directly enantioselective trifluoromethylation of heterocyclic aromatic aldehydes. In particular, the results obtained with electron-donating aldehydes are remarkable. On the other hand, the hydroxy group at the position of C-9 of quaternary ammonium salts has a significant influence on the yield and enantioselectivity. Moreover, The reaction requires only 2 mol% of the (IPr)CuF and chiral ammonium salt, to the best of our knowledge, the lowest catalyst loading for the enantioselective trifluoromethylation of aromatic aldehydes up to date. Further investigations would be directed toward extension of this cooperative catalyst in other asymmetric reactions.

4. Experimental

All reactions were carried out under argon atmosphere using typical vacuum-line techniques unless otherwise noted. The ^1H NMR (400 MHz) spectra for solution in $CDCl_3$ and DMSO-d_6 were recorded on Bruker Avance 400 or Varian Mercury 400. Chemical shifts were reported downfield in ppm from tetramethylsilane ($CDCl_3$, δ = 7.26; DMSO-d_6, δ = 2.50). Spectra were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration and assignment. ^{13}C NMR spectra were collected on a Bruker Avance 400 or a Varian Mercury 400 (100 MHz) with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane ($CDCl_3$, δ = 77.0; DMSO-d_6, δ = 39.5). The IR spectra were recorded on Thermo Scientific Nicolet iS10 with KBr pellets. Elemental analyses were performed on an Elementar Vario MICRO CUBE instrument. Enantiomeric excesses were determined by HPLC on Shimadzu LC-20A apparatus with Chiralpak OJ-H, AS-H, OD-H and AD-H. Optical rotations were measured on a Krüss P8000 polarimeter. HRMS was recorded on Bruker Apex IV FTMS. All melting points were determined on a XT4A melting point apparatus without correction. Analytical thin layer chromatography (TLC) was performed using F254 pre-coated silica gel plate. Column chromatography was performed with silica gel (200–300 mesh). Petroleum ether (PE) had a boiling point range of 60–90 °C.

4.1. Enantioselective trifluoromethylation reaction of aldehydes; general procedure

To a stirred solution of (IPr)CuF (1.9 mg, 0.004 mmol, 2 mol%) and *N*-(3,5-ditrifluoromethylbenzyl)quinidinium bromide (**1f**) (2.6 mg, 0.004 mmol, 2 mol%) in toluene (0.6 mL) was added aryl aldehydes (**5a**–**u**, 0.2 mmol) at −78 °C under argon atmosphere. Then this mixture was kept at −78 °C for 10 min. After that, Me_3SiCF_3 (60 μL, 0.4 mmol, 2 equiv.) was added drop-wise. After stirring for 1–2 h at −78 °C, the reaction was quenched with water. Aqueous layer was extracted with EtOAc (15 mL × 3), and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product *O*-TMS ether was treated with *n*-Bu_4NF (0.2 mL, 1 M in THF, 0.2 mmol) in THF (2.0 mL) at room temperature until full conversion to the final product. The resulting mixture was concentrated under reduced pressure, and purified by column chromatography with silica gel (PE/EtOAc = 20/1, V/V) to give trifluoromethylated alcohols (**6a**–**u**).

4.2. (R)-2,2,2-Trifluoro-1-(naphthalen-2-yl)ethanol [10] (*6a*)

Yield: 90%; white solid; mp 76–78 °C; $[\alpha]_D^{25}$ −24.7 (*c* 0.21, CH_2Cl_2) [lit.[10] $[\alpha]_D^{20}$ −23.7 (*c* 0.16, CH_2Cl_2, 71% ee)]; IR (KBr): 3374, 3062, 1602, 1507, 1341, 1247, 1262, 1193, 1124, 1085, 822, 792, 763, 752, 702, 486 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.86 (m, 4H), 7.59–7.51 (m, 3H), 5.19 (m, 1H), 2.77 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.8, 132.9, 131.3, 128.5, 128.3, 127.8, 127.4, 126.9, 126.6, 124.4 (q, *J* = 281.2 Hz), 124.3, 73.0 (q, *J* = 31.9 Hz). The ee was determined by HPLC on Chiralpak OJ-H (*n*-hexane/*i*-PrOH = 80/20, V/V, 1.0 mL/min, 254 nm), t_R(major) = 10.7 min, t_S(minor) = 15.4 min, 75% ee.

*4.3. (R)-2,2,2-Trifluoro-1-(naphthalen-1-yl)ethanol [12b] (**6b**)*

Yield: 88%; colorless oil; $[\alpha]_D^{25}$ −14.6 (*c* 0.47, CH_2Cl_2); IR (KBr): 3421, 3046, 2927, 2847, 1515, 1399, 1355, 1264, 1167, 1126, 1093, 1030, 877, 781, 698, 632, 538 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.4 Hz, 1H), 7.93–7.91 (m, 2H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.60–7.53 (m, 3H), 5.90 (m, 1H), 2.78 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.1, 130.3, 129.1, 126.1, 125.8, 125.2, 124.7 (q, *J* = 281.7 Hz), 122.8, 69.0 (q, *J* = 32.0 Hz). The ee was determined by HPLC on Chiralpak AS-H (*n*-hexane/*i*-PrOH = 98/2, V/V, 1.0 mL/min, 254 nm), t_R(major) = 16.7 min, t_S(minor) = 19.8 min, 60% ee.

*4.4. (R)-2,2,2-Trifluoro-1-phenylethanol [10] (**6c**)*

Yield: 80%; colorless oil; $[\alpha]_D^{25}$ −13.1 (*c* 0.28, CH_2Cl_2) [lit.[10] $[\alpha]_D^{20}$ −12.5 (*c* 0.40, CH_2Cl_2, 56% ee)]; IR (KBr): 3410, 2927, 2851, 2360, 2342, 1457, 1206, 1171, 1127, 1093, 1063, 1029, 860, 760, 705, 633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.47 (m, 2H), 7.42–7.40 (m, 3H), 5.10 (q, *J* = 6.6 Hz, 1H), 2.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.0, 129.6, 128.7, 127.5, 124.3 (q, *J* = 281.0 Hz), 72.9 (q, *J* = 32.0 Hz). The ee was determined by HPLC on Chiralpak OJ-H (*n*-hexane/*i*-PrOH = 95/5, V/V, 1.0 mL/min, 254 nm), t_R(major) = 21.3 min, t_S(minor) = 29.4 min, 60% ee.

*4.5. (R)-2,2,2-Trifluoro-1-(pyridin-2-yl)ethanol [16] (**6d**)*

Yield: 89%; colorless oil; $[\alpha]_D^{19}$ −7.1 (*c* 0.10, CH_2Cl_2); IR (KBr): 3092, 2863, 1622, 1421, 1354, 1271, 1228, 1203, 1119, 1081, 1068, 717, 653, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 4.4 Hz, 1H), 7.80 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.45–7.38 (m, 2H), 5.04 (q, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.0, 148.3, 137.3, 124.5, 124.1 (q, *J* = 281.8 Hz), 122.7, 70.7 (q, *J* = 31.9 Hz). The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, V/V, 1.0 mL/min, 254 nm), t_S(minor) = 17.1 min, t_R(major) = 23.2 min, 42% ee.

*4.6. (R)-1-(4-Bromophenyl)-2,2,2-trifluoroethanol [17] (**6e**)*

Yield: 81%; colorless oil; $[\alpha]_D^{25}$ −11.5 (*c* 0.24, CH_2Cl_2) [lit.[17] $[\alpha]_D^{20}$ −1.3 (*c* 1.04, EtOH, 12% ee)]; IR (KBr): 3420, 2921, 2353, 1596, 1491, 1406, 1356, 1267, 1097, 1012, 871, 847, 807, 726, 667, 586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.52 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 4.97 (q, *J* = 6.4 Hz, 1H), 2.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.8, 131.9, 129.1, 124.0 (q, *J* = 281.1 Hz), 123.8, 72.2 (q, *J* = 32.1 Hz). The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, V/V, 1.0 mL/min, 254 nm), t_R(major) = 9.1 min, t_S(minor) = 12.6 min, 57% ee.

*4.7. (R)-1-(3-Bromophenyl)-2,2,2-trifluoroethanol [18] (**6f**)*

Yield: 82%; colorless oil; $[\alpha]_D^{25}$ −7.3 (*c* 0.11, CH_2Cl_2).

IR (KBr): 3409, 3062, 2925, 1574, 1430, 1355, 1255, 1178, 1100, 1076, 997, 838, 784, 677, 630, 532, 453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (s, 1H), 7.55–7.52 (m, 1H), 7.40–7.38 (d, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 5.00–4.95 (m, 1H), 3.01 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.3, 130.3, 124.0 (q, *J* = 281.1 Hz), 123.2, 116.7, 114.7, 114.5, 72.2 (q, *J* = 32.1 Hz). The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, V/V, 1.0 mL/min, 254 nm), t_R(major) = 8.8 min, t_S(minor) = 14.4 min, 51% ee.

*4.8. (R)-1-(4-Chlorophenyl)-2,2,2-trifluoroethanol [10] (**6g**)*

Yield: 83%; colorless oil; $[\alpha]_D^{25}$ −8.3 (*c* 0.13, CH_2Cl_2) [lit.[10] $[\alpha]_D^{20}$ −8.8 (*c* 0.10, CH_2Cl_2, 50% ee)]; IR (KBr): 3431, 2919, 1576, 1492, 1346, 1267, 1197, 1097, 870, 847, 811, 667, 586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.38 (m, 4H), 5.04–4.98 (m, 1H), 2.72 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 132.4, 129.0, 128.9, 124.1 (q, *J* = 281.1 Hz), 72.3 (q, *J* = 32.1 Hz); The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, V/V, 1.0 mL/min, 254 nm), t_R(major) = 8.0 min, t_S(minor) = 10.9 min, 52% ee.

*4.9. (R)-1-(3-Chlorophenyl)-2,2,2-trifluoroethanol [10] (**6h**)*

Yield: 83%; colorless oil; $[\alpha]_D^{19}$ −6.5 (*c* 0.09, CH_2Cl_2) [lit.[10] $[\alpha]_D^{20}$ −7.3 (*c* 0.22, CH_2Cl_2, 56% ee)]; IR (KBr): 3407, 3066, 2925, 1601, 1578, 1477, 1433, 1412, 1355, 1267, 1177, 1131, 907, 742, 722, 696, 631, 535 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (s, 1H), 7.43–7.29 (m, 3H), 5.02 (m, 1H), 2.98 (t, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8, 134.7, 129.9, 129.8, 127.7, 125.7, 124.0 (q, *J* = 281.1 Hz), 72.2 (q, *J* = 32.2 Hz). The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, V/V, 1.0 mL/min, 254 nm), t_R(major) = 8.2 min, t_S(minor) = 11.4 min, 50% ee.

*4.10. (R)-2,2,2-Trifluoro-1-(4-fluorophenyl)ethanol [10] (**6i**)*

Yield: 79%; colorless oil; $[\alpha]_D^{19}$ −11.5 (*c* 0.07, CH_2Cl_2) [lit.[10] $[\alpha]_D^{20}$ −20 (*c* 0.02, CH_2Cl_2, 57% ee)]; IR (KBr): 3415, 2925, 1609, 1514, 1358, 1271, 1232, 1174, 1128, 1074, 873, 855, 821, 693, 575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.44 (m, 2H), 7.12–7.07 (m, 2H), 5.00 (m, 1H), 3.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6 (d, *J* = 247.5 Hz), 129.9 (d, *J* = 1.9 Hz), 129.4 (d, *J* = 8.5 Hz), 124.2 (q, *J* = 280.9 Hz), 115.6 (d, *J* = 21.7 Hz), 72.2 (q, *J* = 32.0 Hz). The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, V/V, 1.0 mL/min, 254 nm), t_R(major) = 14.7 min, t_S(minor) = 20.2 min, 45% ee.

*4.11. (R)-2,2,2-Trifluoro-1-(3-fluorophenyl)ethanol [19] (**6j**)*

Yield: 87%; colorless oil; $[\alpha]_D^{19}$ −19.3 (*c* 0.13, CH_2Cl_2) [lit.[19] $[\alpha]_D^{26}$ −18.6 (*c* 0.5, $CHCl_3$, 47% ee)]; IR (KBr): 3421, 2923, 1610, 1491, 1296, 1258, 1128, 841, 788, 718 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.35 (m, 1H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.13–7.08 (m, 1H), 5.02 (m, 1H), 2.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8 (d, *J* = 245.9 Hz), 136.3, 130.2 (d, *J* = 8.2 Hz), 124.1 (q, *J* = 281.1 Hz), 123.2, 116.5 (d, *J* = 21.0 Hz), 114.6 (d, *J* = 23.0 Hz), 72.2 (q, *J* = 32.1 Hz); The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, V/V, 1.0 mL/min, 254 nm), t_R(major) = 7.7 min, t_S(minor) = 9.5 min, 52% ee.

*4.12. (R)-2,2,2-Trifluoro-1-(p-tolyl)ethanol [10] (**6k**)*

Yield: 88%; colorless oil; $[\alpha]_D^{25}$ −12.7 (*c* 0.18, CH_2Cl_2) [lit.[10] $[\alpha]_D^{20}$ −18.4 (*c* 0.43, CH_2Cl_2, 60% ee)]; IR (KBr): 3421, 3046, 2927, 2847, 1515, 1399, 1355, 1264, 1167, 1126, 1093, 1030, 1001, 877, 781, 698, 632, 538, 525, 455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 2H), 4.97 (m, 1H), 2.73 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.6, 131.1, 129.4, 127.4, 124.3 (q, *J* = 280.9 Hz), 72.8 (q, *J* = 31.9 Hz), 21.3. The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 97/3, V/V, 1.0 mL/min, 254 nm), t_R(major) = 13.3 min, t_S(minor) = 17.7 min, 68% ee.

*4.13. (R)-1-([1,1′-Biphenyl]-4-yl)-2,2,2-trifluoroethanol [10] (**6l**)*

Yield: 90%; white solid; mp 113–114 °C; $[\alpha]_D^{28}$ −18.5 (*c* 0.40, CH_2Cl_2) [lit.[10] $[\alpha]_D^{20}$ −7.1 (*c* 0.14, CH_2Cl_2, 56% ee)]; IR (KBr): 3364, 1490, 1408, 1352, 1256, 1198, 1173, 1158, 1130, 1075, 1006, 855, 823, 764, 743, 726, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.54 (m, 6H), 7.47–7.43 (m, 2H), 7.39–7.35 (m, 1H), 5.07 (m, 1H), 2.70 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 142.5, 140.3, 132.9, 128.9, 127.9, 127.7, 127.4, 127.2, 124.3 (q, *J* = 281.0 Hz), 72.7 (q, *J* = 32.0 Hz). The ee was determined by HPLC on Daicel Chiralpak OD-H (*n*-hexane/*i*-PrOH = 90/10, V/V, 1.0 mL/min, 254 nm), t_R(major) = 10.0 min, t_S(minor) = 12.8 min, 66% ee.

4.14. (R)-2,2,2-Trifluoro-1-(3-phenoxyphenyl)ethanol [20] (**6m**)

Yield: 87%; colorless oil; $[\alpha]_D^{25}$ −8.8 (*c* 0.50, CH_2Cl_2); IR (KBr): 3447, 2926, 2843, 2357, 1606, 1491, 1458, 1438, 1262, 1170, 1126, 1044, 839, 788, 710, 631, 556 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.32 (m, 3H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.14–7.10 (m, 2H), 7.04–7.00 (m, 3H), 4.96 (m, 1H), 2.75 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 156.4, 135.6, 129.7, 129.6, 123.8 (q, *J* = 281.0 Hz), 123.4, 121.8, 119.3, 118.8, 117.5, 72.2 (q, *J* = 32.0 Hz). The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, V/V, 1.0 mL/min, 254 nm), t_R(major) = 13.9 min, t_S(minor) = 28.6 min, 60% ee.

4.15. (R)-2,2,2-Trifluoro-1-(4-methoxyphenyl)ethanol [10] (**6n**)

Yield: 85%; colorless oil; $[\alpha]_D^{25}$ −13.6 (*c* 0.27, CH_2Cl_2) [lit.[10] $[\alpha]_D^{20}$ −8.9 (*c* 1.00, CH_2Cl_2, 41% ee)]; IR (KBr): 3445, 3008, 2918, 2842, 1614, 1587, 1517, 1465, 1444, 1356, 1252, 1207, 1171, 1127, 1075, 1031, 850, 819, 695, 589, 520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 4.97 (q, *J* = 3.2 Hz, 1H), 3.82 (s, 3H), 2.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 128.8, 126.2, 124.4 (q, *J* = 281.0 Hz), 114.1, 72.5 (q, *J* = 32.0 Hz), 55.3. The ee was determined by HPLC on Chiralpak OJ-H (*n*-hexane/*i*-PrOH = 95/5, V/V, 1.0 mL/min, 254 nm), t_R(major) = 34.8 min, t_S(minor) = 38.5 min, 67% ee.

4.16. (R)-2,2,2-Trifluoro-1-(3-methoxyphenyl)ethanol [21] (**6o**)

Yield: 89%; colorless oil; $[\alpha]_D^{25}$ −13.6 (*c* 0.13, CH_2Cl_2); IR (KBr): 3442, 2926, 2843, 1357, 1605, 1589, 1491, 1458, 1438, 1262, 1170, 1126, 1044, 933, 839, 788, 760, 710, 631, 556 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 1H), 7.04 (d, *J* = 7.6 Hz, 2H), 6.95–6.92 (m, 1H), 4.98 (m, 1H), 3.82 (s, 3H), 2.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 135.5, 129.7, 124.2 (q, *J* = 281.1 Hz), 119.8, 115.1, 113.0, 72.8 (q, *J* = 31.8 Hz), 55.4. The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 95/5, V/V, 1.0 mL/min, 254 nm), t_R(major) = 20.7 min, t_S(minor) = 28.0 min, 74% ee.

4.17. (R)-2,2,2-Trifluoro-1-(2-methoxyphenyl)ethanol [12b] (**6p**)

Yield: 88%; colorless oil; $[\alpha]_D^{25}$ −11.7 (*c* 0.24, CH_2Cl_2); IR (KBr): 3441, 3012, 2946, 2845, 1605, 1591, 1496, 1466, 1442, 1358, 1249, 1171, 1131, 1027, 871, 829, 781, 627, 593, 574, 538, 498 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.34 (m, 2H), 7.00 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 5.27 (m, 1H), 3.86 (s, 3H), 3.75 (q, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 130.6, 129.3, 124.7 (q, *J* = 282.0 Hz), 122.1, 121.1, 111.3, 69.9 (q, *J* = 32.5 Hz), 55.8. The ee was determined by HPLC on Chiralpak OJ-H (*n*-hexane/*i*-PrOH = 97/3, V/V, 1.0 mL/min, 254 nm), t_S(minor) = 23.5 min, t_R(major) = 27.4 min, 74% ee.

4.18. (R)-2,2,2-Trifluoro-1-(6-methoxynaphthalen-2-yl)-ethanol [20] (**6q**)

Yield: 88%; white solid; m.p. 85–87 °C; $[\alpha]_D^{25}$ −13.9 (*c* 0.11, CH_2Cl_2); IR (KBr): 3265, 2924, 2838, 1632, 1509, 1489, 1468, 1267, 1173, 1128, 1080, 1033, 1018, 859, 727, 690, 474 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1H), 7.75 (t, *J* = 7.8 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.17 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.13 (d, *J* = 2.8 Hz, 1H), 5.13 (m, 1H), 3.92 (s, 3H), 2.80 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 135.1, 129.8, 129.1, 128.4, 127.4, 127.2, 125.9, 124.4 (q, *J* = 281.1 Hz), 119.5, 105.7, 73.0 (q, *J* = 31.9 Hz), 55.4. The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 90/10, V/V, 1.0 mL/min, 254 nm), t_R(major) = 10.3 min, t_S(minor) = 20.6 min, 51% ee.

4.19. (R)-1-(Benzo[d][1,3]dioxol-5-yl)-2,2,2-trifluoroethan-ol [10] (**6r**)

Yield: 92%; colorless oil; $[\alpha]_D^{25}$ −16.7 (*c* 0.48, CH_2Cl_2) [lit.[10] $[\alpha]_D^{20}$ −7.8 (*c* 0.55, CH_2Cl_2, 46% ee)]; IR (KBr): 3454, 2906, 2772, 1855, 1602, 1506, 1492, 1448, 1351, 1251, 1170, 1124, 1040, 930, 872, 810, 793, 730, 704, 636, 654, 560 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.96 (s, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 2H), 4.90 (m, 1H), 2.90 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 148.0, 127.8, 124.3 (q, *J* = 281.0 Hz), 121.6, 108.3, 107.7, 101.4, 72.6 (q, *J* = 32.0 Hz). The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 97/3, V/V, 1.0 mL/min, 254 nm), t_R(major) = 27.9 min, t_S(minor) = 34.7 min, 81% ee.

4.20. (R)-1-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2,2,2-trifluoroethanol [22] (**6s**)

Yield: 92%; colorless oil; $[\alpha]_D^{25}$ −16.3 (*c* 0.54, CH_2Cl_2); IR (KBr): 3458, 2928, 1539, 1511, 1461, 1437, 1314, 1291, 1260, 1171, 1125, 1067, 921, 888, 846, 816, 725, 703, 664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.00 (s, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 4.90 (m, 1H), 4.27 (s, 4H), 2.90 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 143.6, 127.2, 124.3 (q, *J* = 281.0 Hz), 120.6, 117.5, 116.6, 72.4 (q, *J* = 32.0 Hz), 64.4, 64.3. The ee was determined by HPLC on Chiralpak OD-H (*n*-hexane/*i*-PrOH = 97/3, V/V, 1.0 mL/min, 254 nm), t_S(minor) = 44.9 min, t_R(major) = 50.4 - min, 79% ee.

4.21. (R)-1-(4-(Allyloxy)phenyl)-2,2,2-trifluoroethanol (**6t**)

Yield: 80%; white solid; mp 49–50 °C; $[\alpha]_D^{25}$ −19.3 (*c* 0.20, CH_2Cl_2); IR (KBr): 3408, 2929, 2863, 1888, 1614, 1515, 1428, 1324, 1305, 1247, 1178, 1117, 1070, 1013, 940, 871, 802, 693, 589 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.4 Hz, 2H), 6.95–6.92 (m, 2H), 6.10–6.00 (m, 1H), 5.41 (qd, *J* = 1.6, 17.2 Hz, 1H), 5.29 (qd, *J* = 1.2, 10.8 Hz, 1H), 4.98–4.92 (m, 1H), 4.54 (td, *J* = 1.6, 5.2 Hz, 2H), 2.61 (br, 1H); ^{13}C NMR (100 MHz, CDCl3): δ = 159.5, 133.0, 128.8, 126.3, 124.4 (q, *J* = 281.0 Hz), 117.9, 114.9, 72.5 (q, *J* = 32.0 Hz), 68.9; Anal. Calcd for $C_{11}H_{11}F_3O_2$: C, 56.90; H, 4.77. Found: C, 57.12; H, 4.87. The ee was determined by HPLC on Chiralpak AD-H (*n*-hexane/*i*-PrOH = 97/3, V/V, 1.0 mL/min, 254 nm), t_S(minor) = 18.0 min, t_R(major) = 20.2 min, 66% ee.

4.22. (R)-1-(4-(Ethylthio)phenyl)-2,2,2-trifluoroethanol (**6u**)

Yield: 85%; white solid; mp 47–49 °C; $[\alpha]_D^{25}$ −16.7 (*c* 0.63, CH_2Cl_2); IR (KBr): 3356, 2974, 2928, 2873, 1601, 1496, 1406, 1351, 1255, 1135, 1093, 1071, 1013, 868, 848, 811, 793, 680, 586, 496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 4.93–4.50 (m, 1H), 2.96 (q, *J* = 7.2 Hz, 2H), 2.70 (s, 1H), 1.33 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 131.1, 128.3, 127.9, 124.2 (q, *J* = 281.0 Hz), 72.5 (q, *J* = 32.0 Hz), 27.1, 14.2; Anal. Calcd for $C_{10}H_{11}F_3OS$: C, 50.84; H, 4.69. Found: C, 51.23; H, 4.76. The ee was determined by HPLC on Chiralpak OJ-H (*n*-hexane/*i*-PrOH = 95/5, V/V, 1.0 mL/min, 254 nm), t_R(major) = 26.2 min, t_S(minor) = 30.2 min, 73% ee.

4.23. (IPr)CuF preparation; general procedure

4.23.1. [1,3-Bis(2,6-di-iso-propylphenyl)imidazol-2-ylidene] copper(I) chloride, (IPr)CuCl [23]

An oven-dried Schlenk flask containing 1,3-bis(2,6-di-*iso*-propylphenyl) imidazolium chloride (849.0 mg, 2.00 mmol), CuCl (198.0 mg, 2.00 mmol), NaO*t*-Bu (192.0 mg, 2.00 mmol) was evacuated and refilled with argon three times. THF (10 mL) were added to this Schlenk flask. The resulting suspension was stirred at room temperature for 4 h. Then, it was filtered through Celite in glovebox.

Yield: 81%; white powder; IR (KBr): 3160, 3137, 3070, 2968, 2926, 2869, 1963, 1577, 1469, 1456, 1405, 1383, 1327, 1114, 1104, 1212, 1058, 937, 946, 809, 765, 742, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (t, J = 8.0 Hz, 2H), 7.29 (d, J = 7.6 Hz, 4H), 7.11 (s, 2H), 2.53–2.60 (m, 4H), 1.30 (d, J = 12 Hz, 12H), 1.22 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.6, 145.6, 134.4, 130.6, 124.2, 123.2, 28.8, 24.9, 23.9.

4.23.2. [1,3-Bis(2,6-di-iso-propylphenyl)imidazol-2-ylidene]-copper(I) tert-butoxide, (IPr)Cu(Ot-Bu) [24]

In a glovebox, a 30 mL round-bottom flask was charged with (IPr)CuCl (969.0 mg, 2.00 mmol) and NaO*t*-Bu (192.0 mg, 2.00 mmol). Anhydrous THF (12.0 mL) was added. The resulting opaque brown solution was stirred for 2.0 h. It was filtered through Celite in glovebox and concentrated in vacuo.

Yield: 79%; off-white powder; IR (KBr): 3396, 3136, 3073, 2263, 2927, 2869, 1593, 1470, 1407, 1385, 1364, 1330, 1213, 1060, 935, 805, 758, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (t, J = 8.0 Hz, 2H), 7.29 (d, J = 7.6 Hz, 4H), 7.11 (s, 2H), 2.53–2.60 (m, 4H), 1.30 (d, J = 6.8 Hz, 12H), 1.26 (s, 9H), 1.22 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.6, 145.6, 134.4, 130.6, 124.2, 123.2, 31.2, 28.8, 24.9, 23.9.

4.23.3. [1,3-Bis(2,6-di-iso-propylphenyl)imidazol-2-ylidene]-copper(I) fluoride, (IPr)CuF [15f]

In glovebox, (IPr)CuO*t*-Bu (1043 mg, 2.00 mmol) and benzene (18 mL) were added to a 50 mL round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with a rubber septum and took out from the glovebox. Triethylamine tris(hydrofluoride) (110.0 μL, 0.67 mmol, 0.33 equiv.) was added via a syringe. The resulting white suspension was stirred for 6 h at room temperature. The solvent was removed under reduced pressure. In the glovebox, the white solid was suspended in hexane (5 mL), filtered, and washed with hexane (5 mL).

Yield: 85%; white powder; IR (KBr): 3166, 3138, 3076, 3031, 1963, 2926, 2869, 1591, 1467, 1402, 1362, 1329, 1276, 1209, 1181, 1061, 944, 807, 766, 744, 699, 560, 542 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (t, J = 8.0 Hz, 2H), 7.29 (d, J = 7.6 Hz, 4H), 7.14 (s, 2H), 2.51–2.58 (m, 4H), 1.30 (d, J = 6.8 Hz, 12H), 1.22 (d, J = 6.8 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.5, 145.6, 134.6, 130.5, 124.2, 123.2, 28.8, 24.7, 24.0.

4.24. Ammonium bromides of cinchona alkaloids; general procedure

To a flame-dried flask equipped with a magnetic stirring bar and a condenser was added with cinchona alkaloids (1 mmol), toluene (5 mL), and benzyl bromide derivatives (1.2 mmol, 1.2 equiv.). The mixture was heated at 80 °C until a TLC analysis showing that the starting material was completely consumed. Cooled to room temperature and poured onto Et_2O (30 mL) with stirring, the resulting suspension was stirred for another 1 h. Then the precipitate was purified by flash chromatography (MeOH/EtOAc = 1/10, V/V).

4.24.1. N-(4-Methylbenzyl)quinidinium bromide (**1a**)

Yield: 80%; white solid; mp 240 °C (decomp.); $[\alpha]_D^{28}$ +154.3 (*c* 0.35, CH_3OH); IR (KBr): 3406, 3054, 1620, 1585, 1508, 1467, 1417, 1353, 1255, 1239, 1227, 1125, 1037, 1002, 928, 931, 816 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.81 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 5.2 Hz, 1H), 7.77 (d, J = 4.4 Hz, 1H), 7.60 (t, J = 3.8 Hz, 2H), 7.50 (dd, J = 9.2, 2.0 Hz, 1H), 7.44 (s, 1H), 7.38 (d, J = 7.6 Hz, 2H), 6.84 (s, 1H), 6.53 (s, 1H), 6.03 (ddd, J = 17.6, 10.0, 7.2 Hz, 1H), 5.25 (s, 1H), 5.22 (d, J = 6.0 Hz, 1H), 5.00 (d, J = 12.8 Hz, 1H), 4.72 (d, J = 12.8 Hz, 1H), 4.23–4.19 (m, 1H), 4.07 (s, 3H), 3.96–3.94 (m, 1H), 3.85 (t, J = 9.2 Hz, 1H), 3.48 (t, J = 11.4 Hz, 1H), 2.90 (q, J = 9.6 Hz, 1H), 2.66 (q, J = 8.4 Hz, 1H), 2.39 (s, 4H), 1.89 (s, 1H), 1.76 (t, J = 8.8 Hz, 2H), 1.12–1.05 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.9, 147.9, 144.2, 144.0, 140.4, 137.7, 134.0, 131.9, 130.1, 125.9, 125.2, 121.9, 120.8, 117.5, 102.8, 67.7, 65.1, 63.6, 56.4, 56.1, 54.2, 37.2, 26.9, 23.6, 21.4, 21.1; HRMS calcd for $[C_{28}H_{33}N_2O_2]^+$: 429.2536, found 429.2540.

4.24.2. N-(4-Trifluoromethylbenzyl)quinidinium bromide (**1b**) [25]

Yield: 87%; white solid; mp 218 °C (decomp.); $[\alpha]_D^{28}$ +184.2 (*c* 0.15, CH_3OH); IR (KBr): 3398, 3209, 2954, 1621, 1589, 1509, 1373, 1427, 1325, 1227, 1241, 1170, 1125, 1068, 1021, 1003, 934, 864, 832 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.82 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.97 (dd, J = 10.4, 9.2 Hz, 4H), 7.77 (d, J = 4.4 Hz, 1H), 7.51 (dd, J = 9.2, 2.4 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 3.6 Hz, 1H), 6.52 (s, 1H), 6.03 (ddd, J = 17.4, 10.5, 6.9 Hz, 1H), 5.25 (s, 1H), 5.10 (d, J = 8.4 Hz, 2H), 4.85 (d, J = 12.8 Hz, 1H), 4.28–4.22 (m, 1H), 4.06 (s, 3H), 4.02–4.00 (m, 1H), 3.86 (t, J = 9.4 Hz, 1H), 3.50 (t, J = 11.4 Hz, 1H), 3.00–2.90 (m, 1H), 2.69–2.63 (m, 1H), 2.40 (t, J = 11.4 Hz, 1H), 1.91 (s, 1H), 1.79–1.75 (m, 2H), 1.15–1.07 (m, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.0, 147.9, 144.2, 143.8, 137.7, 135.1, 133.0, 131.9, 130.9 (q, J = 31.8 Hz), 126.4, 126.3, 125.9, 123.1, 121.7, 120.8, 117.5, 103.0, 68.1, 65.2, 62.9, 56.5, 56.2, 54.5, 37.2, 26.8, 23.6, 21.1.

4.24.3. N-(9-Anthrylmethyl)quinidinium chloride (**1c**) [26]

Yield: 80%; light yellow solid; m.p. 161 °C (decomp.) (lit.[26] mp 160 °C, decomp.); $[\alpha]_D^{28}$ +390.0 (*c* 0.12, CH_3OH); IR (KBr): 3394, 3183, 1621, 1508, 1458, 1473, 1431, 1258, 1362, 1240, 1227, 1029, 922, 864, 744 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.98 (s, 1H), 8.86 (d, J = 4.4 Hz, 1H), 8.79 (d, J = 9.2 Hz, 1H), 8.70 (d, J = 9.2 Hz, 1H), 8.28 (dd, J = 8.2, 3.0 Hz, 2H), 8.05 (d, J = 9.2 Hz, 1H), 7.90 (d, J = 4.4 Hz, 1H), 7.82–7.74 (m, 3H), 7.69–7.64 (m, 3H), 7.53 (dd, J = 7.6, 2.4 Hz, 1H), 6.98 (s, 1H), 6.33 (d, J = 14.4 Hz, 1H), 6.03 (ddd, J = 17.2, 10.2, 7.2 Hz, 1H), 5.88 (d, J = 14.0 Hz, 1H), 5.18 (d, J = 10.4 Hz, 1H), 5.08 (d, J = 17.2 Hz, 1H), 4.46 (t, J = 9.2 Hz, 2H), 4.21 (s, 4H), 3.18 (t, J = 11.2 Hz, 1H), 2.62–2.54 (m, 1H), 2.46–2.35 (m,2H), 1.78 (s, 1H), 1.69 (d, J = 8.4 Hz, 1H), 1.56–1.53 (m, 1H), 1.10–1.04 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.9, 147.9, 144.3, 137.9, 133.5, 133.3, 132.5, 131.8, 131.7, 131.6, 130.2, 128.3, 128.0, 126.1, 126.0, 125.3, 125.0, 122.3, 121.0, 119.3, 117.5, 103.2, 67.9, 65.7, 56.5, 56.1, 55.8, 55.6, 37.7, 26.1, 24.2, 21.6.

4.24.4. N-(2-F-4-Br-benzyl)quinidinium bromide (**1d**)

Yield: 79%; white solid; m.p. 174–176 °C (decomp.); $[\alpha]_D^{28}$ +143.3 (*c* 0.14, CH_3OH); IR (KBr): 3387, 3198, 3006, 1621, 1520, 1473, 1460, 1431, 1338, 1259, 1241, 1205, 1113, 1026, 851, 828, 719 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.81 (d, J = 4.4 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.87–7.76 (m, 3H), 7.67 (dd, J = 8.4, 1.6 Hz, 1H), 7.50 (dd, J = 9.2, 2.0 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 6.51 (s, 1H), 6.03 (ddd, J = 17.2, 10.4, 6.8 Hz, 1H), 5.25–5.23 (m, 2H), 5.06 (d, J = 12.4 Hz, 1H), 4.77 (d, J = 12.4 Hz, 1H), 4.19 (t, J = 9.6 Hz, 1H), 4.06 (s, 3H), 3.97–3.85 (m, 2H), 3.44 (t, J = 11.2 Hz, 1H), 3.12 (q, J = 10.0 Hz, 1H), 2.68–2.62 (m,1H), 2.36 (t, J = 11.2 Hz, 1H), 2.00 (s, 1H), 1.82–1.75 (m, 2H), 1.10–1.03 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.1 (d, J = 252.2 Hz), 157.9, 147.9, 144.2, 143.8, 137.6, 131.9, 129.0, 125.8, 125.5 (d, J = 10.1 Hz), 121.9, 120.7, 120.3 (d, J = 25.7 Hz), 117.5, 115.4 (d, J = 13.7 Hz), 102.8, 67.9, 65.3, 56.8, 56.1, 54.7, 37.4, 26.6, 23.7, 21.0; HRMS calcd for $[C_{33}H_{35}F_6N_2O_2]^+$: 511.1391, found 511.1398.

4.24.5. N-*(2,4,5-Trifluorobenzyl)quinidinium bromide (**1e**)*

Yield: 69%; white solid; m.p. 182–185 °C (decomp.); $[\alpha]_D^{28}$ +194.8 (*c* 0.19, CH_3OH); IR (KBr): 3394, 3198, 3006, 1621, 1520, 1473, 1469, 1431, 1338, 1259, 1241, 1226, 1205, 1158, 1113, 1026, 851, 828, 719 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.82 (d, *J* = 4.4 Hz, 1H), 8.16–8.10 (m, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.91–7.85 (m, 1H), 7.76 (d, *J* = 4.4 Hz, 1H), 7.50 (dd, *J* = 9.6, 2.8 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 6.84 (d, *J* = 2.8 Hz, 1H), 6.50 (s, 1H), 6.03 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.26–5.21 (m, 2H), 5.01 (d, *J* = 12.8 Hz, 1H), 4.77 (d, *J* = 13.6 Hz, 1H), 4.23–4.18 (m, 1H), 4.06 (s, 3H), 3.94–3.82 (m, 2H), 3.49 (t, *J* = 11.4 Hz, 1H), 3.22–3.15 (m, 1H), 2.67–2.60 (m, 1H), 2.36 (t, *J* = 11.8 Hz, 1H), 1.90 (s, 1H), 1.84–1.75 (m, 2H), 1.10–1.05 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.0 (ddd, *J* = 244.1, 9.9, 2.3 Hz), 157.9, 151.5 (dt, *J* = 251.2, 13.6 Hz), 147.9, 146.7 (ddd, *J* = 241.8, 12.6, 2.4 Hz), 144.2, 143.7, 137.7, 131.9, 125.9, 123.8 (dd, *J* = 19.1, 2.7 Hz), 122.0, 120.7, 117.6, 112.8 (dt, *J* = 17.0, 5.6 Hz), 107.5 (dd, *J* = 29.5, 21.4 Hz), 102.7, 68.0, 65.3, 56.4, 56.1, 56.0, 54.7, 37.5, 26.6, 23.7, 21.0; HRMS calcd for $[C_{27}H_{28}F_3N_2O_2]^+$: 469.2097, found 469.2098.

4.24.6. N-*(3,5-Ditrifluoromethylbenzyl)quinidinium bromide (**1f**) [27]*

Yield: 85%; white solid; mp 177 °C (decomp.); $[\alpha]_D^{28}$ +176.1 (*c* 0.19, CH_3OH); IR (KBr): 3394, 3201, 2954, 2664, 1622, 1509, 1473, 1432, 1374, 1281, 1214, 1226, 1178, 1135, 1027, 1005, 866, 905, 843, 828, 709, 682 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.82 (d, *J* = 4.8 Hz, 1H), 8.56 (s, 2H), 8.38 (s, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.77 (d, *J* = 4.4 Hz, 1H), 7.53 (dd, *J* = 7.2, 2.4 Hz 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 6.78 (d, *J* = 3.2 Hz, 1H), 6.48 (s, 1H), 6.04 (ddd, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.28 (d, *J* = 2.8 Hz, 1H), 5.22 (d, *J* = 12.4 Hz, 2H), 5.01 (d, *J* = 12.8 Hz, 1H), 4.34 (t, *J* = 10.0 Hz, 1H), 4.10–4.13 (m, 1H), 4.06 (s, 3H), 3.80 (t, *J* = 9.4 Hz, 1H), 3.48 (t, *J* = 11.4 Hz, 1H), 3.04 (q, *J* = 9.6 Hz, 1H), 2.62 (q, *J* = 8.4 Hz, 1H), 2.42 (t, *J* = 11.6 Hz, 1H), 1.91 (s, 1H), 1.85–1.72 (m, 2H), 1.20–1.13 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.1, 147.9, 144.2, 143.7, 137.8, 135.1, 132.0, 131.7, 131.3 (q, *J* = 33.1 Hz), 130.1, 126.0, 125.0, 124.6 (q, *J* = 4.1 Hz), 123.7 (q, *J* = 271.3 Hz), 121.5, 120.9, 117.6, 103.1, 68.4, 65.2, 61.8, 56.3, 56.2, 54.7, 37.4, 26.9, 23.6, 21.1.

4.24.7. N-*(3,3″,5,5″-Tetrakis(trifluoromethyl)-1,1′:3′,1″-terbenzyl)quinidinium bromide (**1g**) [27]*

Yield: 71%; white solid; mp 186 °C (decomp.); $[\alpha]_D^{28}$ +129.5 (*c* 0.14, CH_3OH); IR (KBr): 3402, 3196, 2946, 1711, 1621, 1509, 1432, 1280, 1239, 1226, 1176, 1134, 1029, 1002, 900, 885, 844, 827, 718, 704, 683, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.39 (d, *J* = 4.4 Hz, 1H), 8.29 (s, 2H), 8.00 (s, 4H), 7.84 (s, 2H), 7.69 (d, *J* = 6.0 Hz, 2H), 7.60 (s, 1H), 7.42 (s, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.71 (d, *J* = 5.6 Hz, 1H), 6.44 (s, 1H), 6.00 (s, 2H), 5.88 (ddd, *J* = 17.0, 10.2, 7.0 Hz, 1H), 5.23–5.17 (m, 2H), 4.66 (t, *J* = 10.0 Hz, 1H), 4.36 (t, *J* = 10.0 Hz, 1H),4.10 (t, *J* = 9.0 Hz, 1H), 3.77 (s, 3H), 3.34 (t, *J* = 11.2, 1H), 2.98 (q, *J* = 10.0 Hz, 1H), 2.28–2.43 (m, 2H), 1.82 (s, 1H), 1.78 (d, *J* = 8.4 Hz, 2H), 0.90–0.83 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.8, 147.0, 143.9, 142.1, 139.8, 135.1, 133.1, 132.5 (q, *J* = 33.4 Hz), 131.5, 130.2, 127.3, 127.2, 127.1, 126.0, 123.1 (q, *J* = 272.0 Hz), 122.1 (q, *J* = 3.4 Hz), 120.4, 120.1, 118.4, 102.8, 68.2, 66.8, 61.5, 56.9, 56.3, 54.5, 38.1, 27.1, 24.0, 21.7.

*4.24.8. 1,3-Bis(quinidinium-*N*-methylene)benzene dibromide (**2**) [27]*

A mixture of quinidine (324.4 mg, 1.0 mmol) with α,α′-dibromo-m-xylene (132.0 mg, 0.5 mmol) in a mixture of ethanol (1 mL), DMF (1.2 mL), and chloroform (0.4 mL) was stirred at 100 °C for 8 h. After cooling the reaction mixture to room temperature, the reaction mixture was diluted with methanol (40 mL) and then added to ether (200 mL) dropwise with stirring. The solid precipitated was filtered. The resulting precipitate was purified by flash chromatography (MeOH/EtOAc = 1/10, V/V).

Yield: 75%; white solid; mp 218 °C (decomp.); $[\alpha]_D^{28}$ +197.2 (*c* 0.14, CH_3OH); IR (KBr): 3386, 2951, 2361, 1621, 1590, 1509, 1473, 1459, 1431, 1358, 1241, 1227, 1207, 1026, 1001, 934, 866, 828, 717, 855 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.82 (d, *J* = 4.0 Hz, 2H), 8.07 (s, 1H), 8.03 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 4.4 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 2H), 6.83 (d, *J* = 3.2 Hz, 2H), 6.56 (s, 2H), 6.03 (ddd, *J* = 16.8, 10.4, 6.8 Hz, 2H), 5.22–5.12 (m, 6H), 4.82 (d, *J* = 12.4 Hz, 2H), 4.24–4.19 (m, 2H), 4.09–3.99 (m, 8H), 3.85–3.80 (m, 2H), 3.53–3.47 (m, 2H), 3.27–3.22 (m, 2H), 2.77–2.70 (m, 2H), 2.42 (t, *J* = 11.4 Hz, 2H), 1.91 (s, 2H), 1.76–1.74 (m, 4H), 1.16–1.12 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.0, 147.9, 144.2, 143.9, 139.2, 137.7, 135.7, 131.9, 130.2, 129.0, 125.9, 121.8, 120.9, 117.5, 102.8, 68.0, 65.1, 63.3, 56.2, 54.1, 37.3, 26.9, 23.5, 21.1.

4.24.9. N-*(3,5-Ditrifluoromethylbenzyl)cinchonium bromide (**3**) [27]*

Yield 72%; white solid; m.p. 237 °C (decomp.); $[\alpha]_D^{28}$ +153.1 (*c* 0.12, CH_3OH); IR (KBr): 3411, 3220, 3018, 2956, 1510, 1460, 1372, 1279, 1238, 1179, 1135, 920, 763, 710, 683 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 9.00 (d, *J* = 4.4 Hz, 1H), 8.59 (s, 2H), 8.37 (d, *J* = 4.8 Hz, 1H), 8.34 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 6.8 Hz, 1H), 7.84 (d, *J* = 4.4 Hz 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 3.6 Hz, 1H), 6.50 (s, 1H), 6.01 (ddd, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.32 (d, *J* = 12.4 Hz, 1H), 5.28 (s, 1H), 5.24 (d, *J* = 3.2 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 4.34 (t, *J* = 9.6 Hz, 1H), 4.04 (t, *J* = 7.6 Hz, 1H), 3.90 (t, *J* = 9.2 Hz, 1H), 3.50 (t, *J* = 11.2 Hz, 1H), 3.03 (q, *J* = 10.0 Hz, 1H), 2.62 (q, *J* = 8.4 Hz, 1H), 2.32 (t, *J* = 11.6 Hz, 1H), 1.89 (s, 1H), 1.80–1.75 (m, 2H), 1.13–1.06 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 147.9, 144.2, 143.7, 137.7, 135.1, 131.9, 131.7, 131.3 (q, *J* = 33.0 Hz), 127.7, 125.1, 123.7 (q, *J* = 271.3 Hz), 121.4, 120.9, 117.6, 103.1, 68.5, 65.2, 61.8, 56.2, 54.7, 37.4, 26.9, 23.6, 21.0.

4.24.10. N-*(3,5-Ditrifluoromethylbenzyl)-6′-(cyclopentyloxy)-quinidinium bromide (**4a**)*

Yield: 62%; white solid; m.p. 165–169 °C (decomp.); $[\alpha]_D^{28}$ + 116.5 (*c* 0.17, CH_2Cl_2); IR (KBr): 3427, 3201, 2961, 1712, 1619, 1507, 1461, 1373, 1281, 1239, 1223, 1177, 1138 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 4.8 Hz, 1H), 8.31 (s, 2H), 7.85 (s,1H), 7.80 (d, *J* = 9.2 Hz, 1H), 7.73 (d, *J* = 4.8 Hz, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.05 (dd, *J* = 9.8, 2.4 Hz, 1H), 6.66 (d, *J* = 6.0 Hz, 1H), 6.47 (s, 1H), 6.23 (d, *J* = 12.4 Hz, 1H), 6.02 (d, *J* = 12.4 Hz, 1H), 5.87 (ddd, *J* = 17.6, 10.4, 7.2 Hz, 1H), 5.25 (d, *J* = 9.6 Hz, 1H), 5.20 (s, 1H), 4.79 (t, *J* = 5.6 Hz, 1H), 4.64 (m, 1H), 4.23 (t, *J* = 9.6 Hz, 2H), 3.19 (t, *J* = 11.6, 1H), 3.09 (q, *J* = 7.2 Hz, 1H), 2.73 (q, *J* = 9.6 Hz, 1H), 2.42 (q, *J* = 8.8 Hz, 1H), 2.31 (t, *J* = 12.8 Hz, 1H), 1.90–1.82 (m, 8H), 1.65–1.63 (m, 2H), 1.00–0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 146.7, 143.6, 142.0, 134.8, 133.8, 132.0 (q, *J* = 33.9 Hz), 131.3, 130.4, 126.3, 122.6 (q, *J* = 271.9 Hz), 121.1, 120.4, 118.5, 105.2, 79.9, 68.6, 67.7, 60.3, 56.6, 54.5, 46.1, 37.9, 32.9, 27.1, 24.2, 23.9, 21.9; HRMS calcd for $[C_{33}H_{35}F_6N_2O_2]^+$: 605.2597, found 605.2598.

4.24.11. N-*(3,5-Ditrifluoromethyl)benzyl-O(9)-(3,5-ditrifluoro-methylbenzyl)quinidinium bromide (**4b**)*

To a suspension of *N*-(3,5-ditrifluoromethylbenzyl)-quinidinium bromide (632.5 mg, 1.0 mmol) in dichloromethane (3 mL) was added 3,5-ditrifluoro-methylbenzyl bromide (920.0 μL, 5.0 mmol) and 50% aqueous KOH (560.0 μL, 5.0 mmol). The resulting mixture was stirred vigorously at room temperature for 4 h. The mixture was diluted with water (5 mL) and extracted with dichloromethane (3× 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude solid was purified by flash chromatography (MeOH/EtOAc = 1/10, V/V).

Yield: 63%; white solid; mp 150 °C (decomp.); $[\alpha]_D^{28}$ +78.1 (*c* 0.31, CH_2Cl_2); IR (KBr): 3420, 2961, 1622, 1508, 1475, 1433, 1372, 1280, 1241, 1227, 1177, 1135, 1030, 902, 843, 828, 707, 683 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.80 (d, *J* = 2.8 Hz, 1H), 8.53 (s, 2H), 8.39 (s, 1H), 8.27 (s, 2H), 8.09 (s, 1H), 8.04 (d, *J* = 9.2 Hz, 1H), 7.75 (d, *J* = 1.2 Hz, 1H), 7.56–7.48 (m, 2H), 6.57 (s, 1H), 6.01–5.96 (m, 1H), 5.19–5.02 (m, 5H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.07 (s, 4H), 3.86–3.83 (m, 1H), 3.58–3.52 (m, 1H), 3.00–2.93 (m, 1H), 2.64 (d, *J* = 9.2 Hz, 2H), 1.98 (s, 1H), 1.81–1.74 (m, 2H),1.45–1.42 (m, 1H), 0.86–0.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.6, 158.8, 146.7, 146.6, 146.5, 145.0, 141.3, 139.4, 137.8, 137.7, 134.9, 134.5, 134.4, 134.3, 132.5 (q, *J* = 33.0 Hz), 131.6, 130.2, 128.2 (q, *J* = 33.0 Hz), 124.6, 124.5, 124.4, 123.1 (q, *J* = 271.7 Hz), 122.7 (q, *J* = 271.9 Hz), 122.3 (q, *J* = 2.8 Hz), 118.2, 101.7, 73.1, 69.4, 67.5, 61.5, 61.4, 56.1, 55.1, 37.7, 26.9, 23.6, 21.9, 11.0; HRMS calcd for $[C_{38}H_{33}F_{12}N_2O_2]^+$: 777.2344, found 777.2331.

4.24.12. N-*(3,5-Ditrifluoromethyl)benzyl-6′-hydroxyquinidi-nium bromide (**4c**)*

Ethanethiol (2.30 mL, 30.8 mmol) was added under argon atmosphere to a stirred suspension of sodium hydride (370.0 mg, 15.4 mmol) in dry DMF (15 mL). Quinidine (500 mg, 1.5 mmol) in dry DMF (7.5 mL) was added dropwise and the reaction mixture was stirred at 110 °C for 13 h. The solvent and excess ethanethiol were removed under reduced pressure. Then the 3,5-ditrifluoromethylbenzyl bromide (675.4 mg, 2.2 mmol) was added in THF (9 mL). The reaction mixture was refluxed and monitored by TLC analysis. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (MeOH/EtOAc = 1/20, V/V).

Yield 52%; white solid; mp 258 °C (decomp.); $[\alpha]_D^{28}$ +182.3 (*c* 0.16, CH_3OH); IR (KBr): 3369, 3234, 1622, 1531, 1469, 1217, 1181, 1135, 1003, 927, 905, 864, 842, 736, 709, 683 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.06 (s, 1H), 8.75 (d, *J* = 4.4 Hz, 1H), 8.63 (s, 2H), 8.37 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 4.4 Hz, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.38 (dd, *J* = 9.0, 2.2 Hz, 1H), 6.68 (d, *J* = 3.6 Hz, 1H), 6.32 (s, 1H), 6.02 (ddd, *J* = 17.4, 10.5, 6.9 Hz, 1H), 5.38 (d, *J* = 12.4 Hz, 1H), 5.26–5.19 (m, 3H), 4.32 (t, *J* = 9.6 Hz, 1H), 4.13 (t, *J* = 9.6 Hz, 1H), 3.92 (t, *J* = 9.6 Hz, 1H), 3.49 (t, *J* = 11.2 Hz, 1H), 3.12–3.05 (m, 1H), 2.65–2.59 (m, 1H), 2.33 (t, *J* = 11.6 Hz, 1H), 1.89 (s, 1H), 1.83–1.78 (m, 2H), 1.17–1.09 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.5, 147.2, 143.4, 143.1, 137.7, 135.2, 131.9, 131.7, 131.2 (q, *J* = 33.0 Hz), 126.1, 124.6 (q, *J* = 3.2 Hz), 123.7 (q, *J* = 271.8 Hz), 122.2, 120.4, 117.6, 105.1, 68.2, 65.3, 60.9, 56.3, 54.7, 37.3, 26.9, 23.6, 21.0; HRMS calcd for $[C_{28}H_{27}F_6N_2O_2]^+$: 537.1971, found 537.1959.

4.24.13. N-*(3,5-Ditrifluoromethyl)benzyl-9-O-benzyl-6′-hydroxyquinidinium bromide (**4d**)*

Sodium hydride (96.0 mg, 4.0 mmol) was added to a solution of quinidine (324.4 mg, 1.0 mmol) in dry DMF (5 mL). Benzyl chloride (173 μL, 1.5 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 20 h and quenched by water. The aqueous phase was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, concentrated in vacuo to afford yellowish oil, which was used without purification. Ethanethiol (434.0 μL, 5.8 mmol) was added to a stirred suspension of sodium hydride (139.3 mg, 5.8 mmol) in dry DMF (3 mL). The yellowish oil (300 mg) in dry DMF (3 mL) was added dropwise and the reaction mixture was stirred at 110 °C for 15 h. The solvent and excess ethanethiol were removed under reduced pressure. The crude product was added the 3,5-ditrifluoromethylbenzyl bromide (336.2 mg, 1.1 mmol) in THF (6 mL). The reaction mixture was refluxed and monitored by TLC analysis. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (MeOH/EtOAc = 1/20, V/V). The product was obtained as pale white solid.

Yield 46%; pale white solid; mp 246 °C (decomp.); $[\alpha]_D^{28}$ +68.9 (*c* 0.33, CH_3OH); IR (KBr): 3462, 2950, 1622, 1601, 1497, 1463, 1427, 1375, 1280, 1245, 1181, 1135, 1083, 903, 845, 748, 683, 483 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.26 (s, 1H), 8.83 (d, *J* = 3.6 Hz, 1H), 8.27 (s, 1H), 8.05 (d, *J* = 9.2 Hz, 2H), 7.97 (s,1H), 7.72–7.70 (m, 1H), 7.58–7.39 (m, 7H), 6.34 (d, *J* = 12.0 Hz, 1H), 6.05 (s, 1H), 5.93 (ddd, *J* = 17.0, 10.0, 7.2 Hz, 1H), 5.37 (d, *J* = 10.4 Hz, 1H), 5.24–5.13 (m, 2H), 5.07 (d, *J* = 12.4 Hz, 1H), 4.53 (t, *J* = 9.4 Hz, 1H), 4.33–4.29 (m, 2H), 4.16–4.11 (m, 1H), 3.75 (d, *J* = 12.0 Hz, 1H), 3.06 (t, *J* = 11.4 Hz, 1H), 2.75–2.67 (m, 1H), 2.51–2.36 (m, 2H), 2.02 (s, 1H), 1.95 (t, *J* = 10.4 Hz, 1H), 1.17–1.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 157.4, 146.4, 144.1, 136.7, 135.8, 134.9, 134.0, 132.6 (q, *J* = 34.3 Hz), 132.3, 131.9, 130.9, 129.9, 129.8, 129.5, 129.4, 128.9, 125.9, 123.8, 122.7 (q, *J* = 272.4 Hz), 118.7, 104.8, 73.5, 72.0, 66.5, 59.4, 56.1, 54.4, 37.7, 27.0, 23.5, 21.7; HRMS calcd for $[C_{35}H_{33}F_6N_2O_2]^+$: 627.2440, found 627.2434.

4.24.14. N-*(3,5-Ditrifluoromethylbenzyl)quinidinium fluoride (**1f**)*

The column of Amberlyst A-26 (OH^- form, 500 mg) was washed with methanol. A solution of the *N*-(3,5-ditrifluoromethylbenzyl)-quinidinium bromide (126.2 mg, 0.2 mmol) in methanol (5 mL) was slowly passed through the column and the column then washed with methanol. The eluent was neutralized until pH = 7 with HF and the solvents were removed in vacuo. The residue was coevaporated with toluene three times and dried under vacuum overnight and the chiral ammonium fluoride was used without further purification.

Yield: 89%; light yellow solid; mp 190 °C (decomp.); $[\alpha]_D^{28}$ +127.2 (*c* 0.14, CH_3OH); IR (KBr): 3462, 2950, 1622, 1601, 1497, 1463, 1427, 1375, 1280, 1245, 1181, 1135, 1083, 903, 845, 748, 683, 483 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 8.83 (d, *J* = 4.4 Hz, 1H), 8.53 (s, 2H), 8.38 (s,1H), 8.05 (d, *J* = 9.2 Hz, 1H), 7.78 (d, *J* = 4.4 Hz, 1H), 7.55 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 6.75 (d, *J* = 2.8 Hz, 1H), 6.46 (s, 1H), 6.05 (ddd, *J* = 17.6, 10.4, 7.2 Hz, 1H), 5.24–5.29 (m, 2H), 5.14 (d, *J* = 12.8 Hz, 1H), 4.97 (d, *J* = 12.8 Hz, 1H), 4.32 (t, *J* = 9.2 Hz, 1H), 4.05 (s, 3H), 4.03 (t, *J* = 12.0, 1H), 3.78 (t, *J* = 10.0 Hz, 1H), 3.49 (t, *J* = 11.4, 1H), 3.13–2.99 (m, 1H), 2.62 (q, *J* = 2.4 Hz, 1H), 2.43 (t, *J* = 11.4 Hz, 1H), 1.92 (s, 1H), 1.83–1.76 (m, 2H), 1.46–1.20 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.1, 147.9, 144.1, 143.8, 137.7, 135.1, 132.0, 131.7, 131.3 (q, *J* = 33.1 Hz), 126.0, 124.7 (q, *J* = 1.9 Hz), 123.7 (q, *J* = 271.8 Hz), 121.4, 120.9, 117.6, 103.2, 68.5, 65.3, 61.9, 56.2, 54.8, 46.3, 44.7, 37.4, 26.9, 23.6, 21.0; HRMS calcd for $[C_{29}H_{29}F_6N_2O_2]^+$: 551.2127, found 551.2135.

Acknowledgements

We thank National Natural Science Foundation of China (20972016, 21172018) and Beijing Institute of Technology for the financial support.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2013.01.027.

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