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Cinchona alkaloid-derived quaternary ammonium salt combined with NaH: a facile catalyst system for the asymmetric trifluoromethylation of ketones

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ABSTRACT

Enantioselective trifluoromethylation of aromatic ketones promoted by the cinchona alkaloid-derived ammonium bromide and sodium hydride was described. A series of trifluoromethyl-substituted aryl alcohols could be obtained in up to 82% ee with 98% yield under mild conditions. A possible catalytic cycle was also presented.

Since α-trifluoromethylated alcohols play special roles in the fields of pharmacy and agrochemistry,[1] great effort has been paid to preparing these compounds.[2] Among the developed strategies,[3] employing Ruppert–Prakash reagent ($TMSCF_3$)[4] to react with carbonyl compounds had attracted great attention. Although the non-asymmetric synthesis of trifluoromethylated alcohols has been well developed,[5] the catalytic asymmetric version of tirfluoromethylation of carbonyl compounds remains a challenge. In 1994, enantioselective trifluoromethylation using chiral quaternary ammonium fluoride was investigated by Iseki et al.[6a] Then, Iseki et al. designed chiral triamino sulfonium salts for the enantioselective trifluoromethylation of aldehydes.[7] After that, asymmetric trifluoromethylation of ketones and aldehydes catalyzed by chiral ammonium fluorides was described by Caron et al.[8] Recently, the combination of biscinchoninium and TMAF (tetramethylaminofluoride) was established by Shibata and coworkers to promote the trifluoromethylation of ketones, giving the desired product in up to 94% ee.[9c]

Quaternary ammonium salts have been demonstrated as one of the most efficient catalyst system for the trifluoromethylation of aldehydes and ketones. Noteworthily, for most of these catalysts, employing F^- as the counter ion was crucial to ensure the good performance.[6,8–10] Recently, some interesting and appealing F^- free catalyst system has been developed. Mukaiyama et al. reported that the cinchonidine-derived chiral quaternary ammonium phenoxides were efficient for trifluoromethylation.[11] As well, our group has described that disodium (*R*)-binaphtholate combined with the chiral quaternary ammonium bromide to promote the enantioselective addition of $TMSCF_3$ to aromatic aldehydes.[12] Herein, we present another efficient F^- free catalyst system comprising quaternary ammonium bromide of cinchona alkaloid and NaH for the enantioselective trifluoromethylation of aryl ketones with $TMSCF_3$.

Initial studies started from that in the presence of catalytic amount of base and quinidine-derived ammonium bromide **3a**, the reaction of 2-acetonaphthone **1a** and 1.2 equiv $TMSCF_3$ underwent smoothly at −20 °C in Et_2O.[13] To our delight, the base screening showed that NaH gave the best result of 87% yield and 53% ee (Table 1, entries 1–3). Then, the quaternary ammonium salts derived from other cinchona alkaloids and 3,5-bis(trifluoromethyl) benzyl bromide were examined (Fig. 1). It was indicated that the quaternary ammonium salt **3b** derived from cinchonine could enhance the enantioselectivity to 80% ee (Table 1, entry 4). Furthermore, **3c–e** synthesized from cinchonine and some other alkyl bromides were evaluated, but unsatisfactory results were given (Table 1, entries 7–9). Configuration inversion of the product was observed, when **3** was replaced by **4** (Table 1, entries 5 and 6). Next, the influence of amount of NaH was studied. The reaction rate was gradually enhanced by increasing the amount of NaH from 5 mol % to 50 mol % without any loss of enantioselectivity (Table 1, entry 10). Further increasing the amount from 50 mol % to 100 mol % exhibited no difference in both reactivity and enantioselectivity. However, 200 mol % NaH resulted in a sharp diminution of ee value (Table 1, entry 11). Therefore, 50 mol % NaH was suitable for the reaction.

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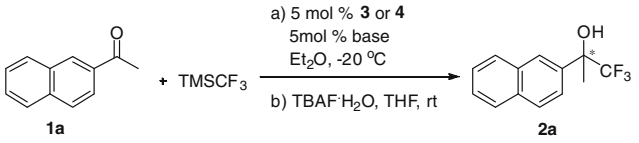
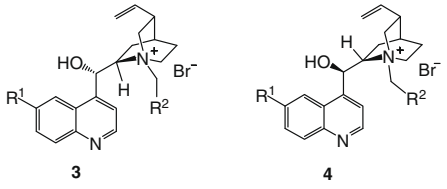
Table 1
Catalyst screening[a]



Entry	Ammonium salt	Base	Yield[b] (%)	ee[c] (%)
1	**3a**	Na_2CO_3	—	—
2	**3a**	*t*-BuOK	89	51
3	**3a**	NaH	87	53
4	**3b**	NaH	96	80
5[d]	**4a**	NaH	64	27
6[d]	**4b**	NaH	90	70
7	**3c**	NaH	77	20
8	**3d**	NaH	90	54
9	**3e**	NaH	87	56
10[e]	**3b**	NaH	97	80
11[f]	**3b**	NaH	97	43

[a] Unless otherwise noted, the reaction was carried out with 5 mol % **3** or **4**, 5 mol % NaH and 1.2 equiv $TMSCF_3$ at −20 °C in Et_2O under Ar, substrate concentration = 0.3 M. *t* = 12 h. The absolute stereochemistry of the newly generated stereocenter in **2a** was *R* which was determined by comparing specific rotation reported by Shibata et al.[9c]
[b] Isolated yield.
[c] Determined by HPLC analysis using a Chiralcel OD-H with hexane/2-propanol as an eluent.
[d] The configuration of the product was *S*.
[e] 50 mol % NaH was used, *t* = 6 h.
[f] 200 mol % NaH was used, *t* = 6 h.



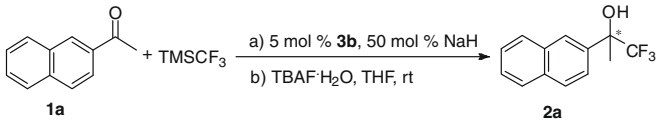
3a: R^1 = MeO R^2 = 3,5-di(trifluoromethyl)phenyl
3b: R^1 = H R^2 = 3,5-di(trifluoromethyl)phenyl
3c: R^1 = H R^2 = phenyl
3d: R^1 = H R^2 = 3,5-di(methoxyl)phenyl
3e: R^1 = H R^2 = 1-naphthyl
4a: R^1 = MeO R^2 = 3,5-di(trifluoromethyl)phenyl
4b: R^1 = H R^2 = 3,5-di(trifluoromethyl)phenyl

Figure 1. Structure of catalysts.

Solvent screening manifested that ethers except THF were suitable solvents, while toluene, CH_2Cl_2, and hexane gave poor results (Table 2, entries 1–7). Especially, the best result was achieved in isopropyl ether which was chosen as the optimal solvent afterward (Table 2, entry 7). Then, different catalyst loading, concentration and reaction temperature were examined (Table 2, entries 8–13). Lowering the catalyst loading to 2 mol %, the reactivity suffered (Table 2, entry 8). Increasing the catalyst loading and concentration led to high yield but low ee. In addition, the reaction was extremely sensitive to the temperature. Descending ee was obtained at 0 °C, and no reaction occurred at −45 °C (Table 2, entries 12 and 13). Consequently, the optimal reaction conditions were identified as: 0.2 mmol ketone, 1.2 equiv $TMSCF_3$, 5 mol % **3b**, 50 mol % NaH in $(i\text{-Pr})_2O$ (0.67 mL) at −20 °C.

Under the optimized conditions, the substrate scope was explored (Table 3). 1- and 2-Acetonaphthone were converted to the corresponding products in high yields with good enantioselectivities (Table 3, entries 1 and 2). Substituted acetophenones gave moderate to good results as well (Table 3, entries 3–8). Especially, when **1k** was subjected to the trifluoromethylation, 1,2-addition

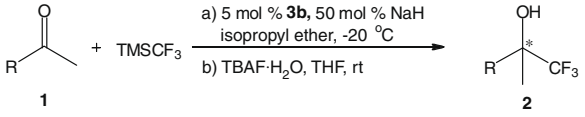
Table 2
Optimization for enantioselective trifluoromethylation of ketones catalyzed by chiral ammonium bromide[a]



Entry	Catalyst (mol %)	Solvent	Yield[b] (%)	ee[c](%)
1	5	$PhCH_3$	47	59
2	5	CH_2Cl_2	97	53
3	5	THF	94	25
4	5	Hexane	37	72
5	5	*t*-$BuOCH_3$	93	77
6	5	$PhOCH_3$	56	70
7	5	$(i\text{-Pr})_2O$	96	81
8	2	$(i\text{-Pr})_2O$	28	82
9	10	$(i\text{-Pr})_2O$	98	76
10[d]	5	$(i\text{-Pr})_2O$	32	82
11[e]	5	$(i\text{-Pr})_2O$	96	73
12[f]	5	$(i\text{-Pr})_2O$	95	75
13[g]	5	$(i\text{-Pr})_2O$	—	—

[a] Unless otherwise noted, the reaction was carried out with 5 mol % **3**, 50 mol % NaH and 1.2 equiv $TMSCF_3$ at −20 °C under Ar, substrate concentration = 0.3 M, *t* = 12 h. The absolute stereochemistry of the newly generated stereocenter in **2a** was *R* which was determined by comparing specific rotation reported by Shibata et al.[9c]
[b] Isolated yield.
[c] Determined by HPLC analysis using a Chiralcel OD-H with hexane/2-propanol as an eluent.
[d] The substrate concentration was 0.1 M.
[e] The substrate concentration was 0.5 M.
[f] The reaction temperature was 0 °C.
[g] The reaction temperature was −45 °C.

Table 3
Substrate scope for the catalytic asymmetric trifluoromethylation of ketones[a]



Entry	R	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1[d]	2-Naphthyl	**2a**	6	96	81(*R*)
2	1-Naphthyl	**2b**	6	98	82
3	2-FC_6H_4	**2c**	19	47	68
4	3-ClC_6H_4	**2d**	19	96	68
5	4-ClC_6H_4	**2e**	19	83	61
6	4-BrC_6H_4	**2f**	48	43	60
7	3-$NO_2C_6H_4$	**2g**	48	30	68(*R*)
8	4-$NO_2C_6H_4$	**2h**	24	64	50
9[d]	3-$MeOC_6H_4$	**2i**	96	38	58
10	4-MeC_6H_4	**2j**	3	70	67
11	(*E*)PhCH=CH	**2k**	22	31	59

[a] Unless otherwise noted, the reaction was carried out with 5 mol % **3b,** 50 mol % NaH and 1.2 equiv $TMSCF_3$ at −20 °C in $(i\text{-Pr})_2O$ under Ar, substrate concentration = 0.3 M.
[b] Isolated yield.
[c] Determined by HPLC analysis using Chiral columns with hexane/2-propanol as an eluent.
[d] The absolute configurations of **2a** and **2i** were determined by comparing specific rotation reported by Shibata et al.[9] and Mukaiyama et al.,[11] respectively. The stereochemistry of other trifluoromethylated alcohols **2** was tentatively assumed by analogy.

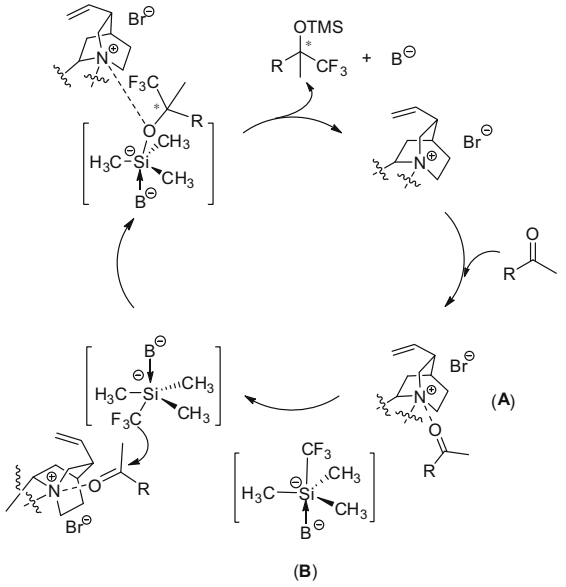


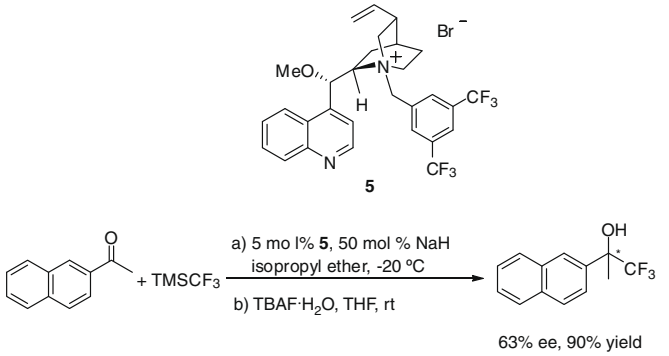
Figure 2. Proposed catalytic cycle.

occurred, furnishing α-trifluoromethyl allylic alcohol **2k** in 59% ee (Table 3, entry 11).

As depicted in Figure 2, a catalytic cycle was proposed to elucidate the reaction mechanism. First, ketone was effectively activated by the chiral N^+ cation in quaternary ammonium salt to form the intermediate **A**.[14] Meanwhile, discrimination of the enantiotopic faces of ketones happened in this step. Second, the nucleophilic reagent $TMSCF_3$ was activated by Lewis base to generate the intermediate **B**.[15] Then, the activated carbonyl group was easily attacked by CF_3^-, after which, trimethylsilylation of the resulted alkoxide quickly underwent to furnish the desired product and regenerate the catalyst.

It should be noted that there were two possible species that might act as Lewis base to activate $TMSCF_3$. One was H^- from NaH. The other was RO^- which might be produced from the deprotonation of hydroxy on quaternary ammonium salt by NaH. However, the control experiment showed that when the hydroxyl in **3b** was methylated, the reaction still proceeded smoothly and enantioselectively, affording the product in 63% ee and 90% yield (Scheme 1). Additionally, in the absence of NaH, **5** could not catalyze the reaction. Based on these observations, it was reasonable to deduce that the hydride ion in sodium hydride might serve as the efficient Lewis base to activate $TMSCF_3$.

In conclusion, the combined use of cinchonine-derived quaternary ammonium salt **3b** and NaH was established as the effective and F^- free catalytic system for the catalytic asymmetric trifluoromethylation of ketones. Adducts bearing electron-donating and electron-withdrawing groups could be obtained in moderate to good ee (up to 82%) and yield (up to 98%). Moreover, a plausible catalytic cycle was proposed to explain the mechanism.



Scheme 1. Control experiment.

Acknowledgments

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