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Cinchona Alkaloids/TMAF Combination-Catalyzed Nucleophilic Enantioselective Trifluoromethylation of Aryl Ketones

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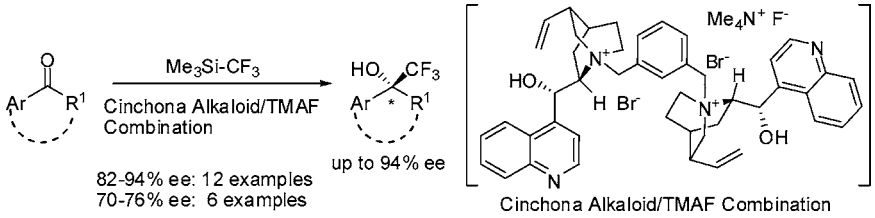
ABSTRACT



The catalytic, nucleophilic enantioselective trifluoromethylation reaction of both acyclic and cyclic aryl ketones using the Ruppert–Prakash reagent is now at hand, with an operationally simple procedure, based on the combination of ammonium bromide of cinchona alkaloids with TMAF. The procedure is reliable and general. Trifluoromethyl-substituted tetrasubstituted aryl alcohols have been synthesized in up to 94% ee.

Tetrasubstituted α-trifluoromethyl aryl alcohols, represented by $CF_3C^*(OH)R^1Ar$, have extensively provided important building blocks in the design of drug candidates.[1] Among a variety of approaches available for the synthesis of the α-trifluoromethyl aryl alcohols, enantioselective nucleophilic trifluoromethylation of aryl ketones using the Ruppert−Prakash reagent, (trifluoromethyl)trimethylsilane, Me_3SiCF_3, is surely the most straightforward operation for construction of the corresponding chiral molecules. However, chiral auxiliary based diastereoselective trifluoromethylation is still the most widely applied approach in the field with enantioselective catalysis remaining a big challenge.[2−4] We recently found 1-fluorobis(phenylsulfonyl)methane (FBSM) to be a synthetic equivalent of a fluoromethide species under the Tsuji−Trost allylic alkylation conditions, providing the palladium-catalyzed asymmetric allylic monofluoromethylation reaction with high enantiocontrol.[5a] This strategy was extended to a catalytic enantioselective monofluoromethylation reaction of in situ generated prochiral imines with

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FBSM in the presence of a chiral phase transfer catalyst.[5b] In connection with our studies on the development of a new methodology for asymmetric synthesis,[6] herein we disclose the highly enantioselective trifluoromethylation of aryl ketones with Me_3SiCF_3 catalyzed by a combination of ammonium bromides of cinchona alkaloids and tetramethylammonium fluoride (TMAF). Our approach is especially attractive because nonfluorinated prochiral substrates can be directly transformed to chiral trifluoromethylated aryl alcohols with tetrasubstituted carbon centers,[7] with unprecedentedly high enantioselectivities (up to 94% ee), using readily available chiral ammonium bromides of cinchona alkaloids and TMAF (Figure 1).

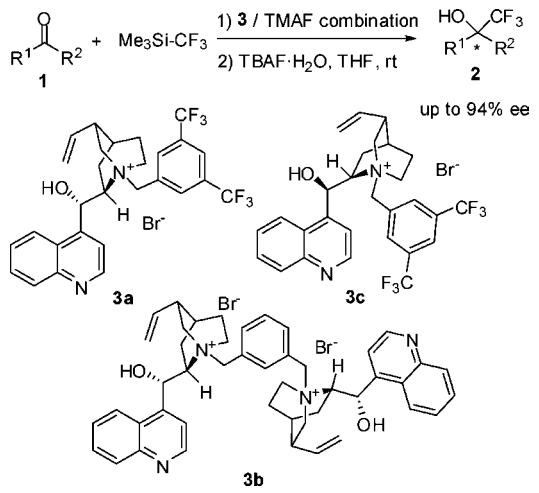

Figure 1. Chiral ammonium bromides/TMAF combination-catalyzed nucleophilic enantioselective trifluoromethylation of ketones.

Enantioselective trifluoromethylation using Me_3SiCF_3 was initially examined by Iseki et al. in 1994.[8a] Chiral ammonium fluorides derived from cinchona alkaloids catalyzed the trifluoromethylation of aryl ketones to furnish the corresponding trifluoromethylated alcohols with low to moderate enantioselectivities, up to 48% ee. After the report, considerable efforts were devoted to the development of an efficient catalytic system for the nucleophilic enantioselective trifluoromethylation reaction, but the observed enantioselectivity did not improve, except for one example reported by a Pfizer research group.[8c] The high enantioselectivity of their target α-trifluoromethyl aryl alcohol was achieved by thorough screening of chiral ammonium fluorides (92% ee). However, the catalyst did not prove to be generally applicable. Their report suggests that the enantioselectivity is highly substrate dependent and that the protocol itself is not ideal because the troublesome preparation and purification of highly hygroscopic anhydrous chiral ammonium fluorides[9] hamper the catalyst screening for each substrate. During the preparation of our manuscript, Mukaiyama et al. reported the enantioselective trifluoromethylation of aryl ketones catalyzed by ammonium phenoxides of cinchona alkaloids.[10] The enantioselectivity improved to be moderate to high. The procedure is quite interesting; however, it requires the multistep preparation of the chiral ammonium phenoxides using typical anion-exchange resins. Inasmuch as the quaternary ammonium salts of cinchona alkaloids are potential catalysts, such preparations present a formidable obstacle to their use for catalyst screening under standard experimental conditions.

We therefore focused on finding a novel catalytic system for enantioselective trifluoromethylation based on the readily accessible ammonium bromides derived from cinchona alkaloids.[11,12] We started our investigation with the reaction of methyl 2-naphthyl ketone (**1a**) with Me_3SiCF_3 and screened a broad range of additives as combination catalysts with the chiral ammonium bromide (Table 1). First, a catalytic amount of $KF/2H_2O$ was added to a mixture of **1a** and 2.0 equiv of Me_3SiCF_3 in toluene in the presence of a catalytic amount of *N*-3,5-bis(trifluoromethyl)benzylcinchoninium bromide (**3a**) at −40 °C. However, even after 1 day of stirring, the reaction did not proceed and only the starting material was detected by TLC (run 1). The poor solubility of KF in toluene presumably hampered the reaction. The polar cosolvent, dichloromethane, was added to aid in solubilization of the additive, but the situation did not improve (run 2). The reaction was then attempted using a more soluble fluoride source, $TBAH_2F_3$, in toluene/dichloromethane at −40 °C. We were encouraged to find

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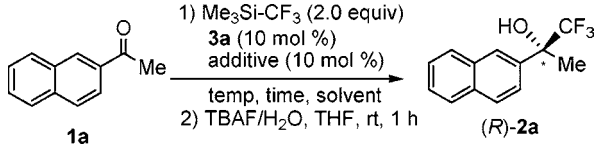
Table 1. Optimization of Additives for Enantioselective Trifluoromethylation Catalyzed by Chiral Ammonium Bromide



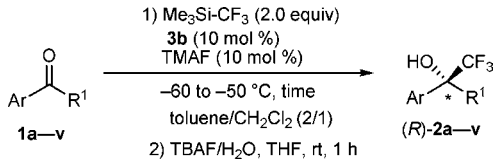
run	additive[a]	solvent	temp (°C)	time (h)	yield (%)	ee[b] (%)
1	$KF/2H_2O$	toluene	−40	24	NR[j]	–
2	$KF/2H_2O$	toluene/CH_2Cl_2[c]	−40	24	NR[j]	–
3	$TBAH_2F_3$	toluene/CH_2Cl_2[c]	−40	2	83	25
4	TBAT	toluene/CH_2Cl_2[c]	−40	2	89	18
5	LiOAc	toluene/CH_2Cl_2[c]	−40	2	99	19
6	TMAA	toluene/CH_2Cl_2[c]	−40	24	NR[j]	–
7	TBAF/H_2O	toluene/CH_2Cl_2[c]	−40	2	94	22
8	TEAF/H_2O	toluene/CH_2Cl_2[c]	−40	2	38	66
9	TMAF	toluene/CH_2Cl_2[c]	−40	8	65	70
10	TMAF	toluene/CH_2Cl_2[c]	−60	2	65	81
11	TMAF	toluene/CH_2Cl_2[d]	−60	8	70	82
12	TMAF	toluene/CH_2Cl_2[e]	−60	8	48	79
13	TMAF	toluene/CH_2Cl_2[c]	−80	2	53	80
14	TMAF	toluene	−80	24	30	72
15	TMAF	CH_2Cl_2	−80	3	56	71
16[f]	TMAF	toluene/CH_2Cl_2[c]	−80	12	98	87
17[g]	TMAF	toluene/CH_2Cl_2[c]	−60	6	87	85
18[h]	TMAF	toluene/CH_2Cl_2[c]	−60	3	70	77[i]

[a] $TBAH_2F_3$, tetrabutyl ammonium dihydrogen trifluoride; TBAT, tetrabutylammonium triphenyldifluorosilicate; TMAA, tetramethylammonium acetate; TBAF, tetrabutylammonium fluoride; TEAF, tetraethylammonium fluoride. [b] Determined by Chiralcel OD-H eluting with 5% *i*-PrOH in hexane. (*R*)-**2a** was obtained. The absolute stereochemistry of **2a** was tentatively assumed. See footnote in Table 2. [c] Toluene/CH_2Cl_2 = 2:1. [d] Toluene/CH_2Cl_2 = 1:1. [e] Toluene/CH_2Cl_2 = 1:2. [f] 20 mol % of TMAF was used. [g] Catalyst **3b** was used instead of **3a**. [h] Catalyst **3c** was used instead of **3a**. [i] (*S*)-**2a** was obtained. [j] NR: no reaction.

that trifluoromethylated adduct **2a** was formed in 83% yield with 25% ee (run 3). This preliminary result encouraged us to investigate other combinations in an attempt to improve enantioselectivity. After screening several additives (TBAT, LiOAc, TMAA, TBAF, TEAF), we found that the tetramethylammonium fluoride (TMAF) combination in toluene/dichloromethane at −40 °C affected the enantioselective trifluoromethylation of **1a** to furnish **2a** in 65% yield with 70% ee (run 9). These results clearly indicate the combined effect of the additives and chiral ammonium bromide on the enantioselectivity. The enantioselectivity was improved by lowering the temperature to −80 °C (runs 10−13). A mixed solvent system was ascertained to be suitable after screening the reaction with different ratios of toluene/dichloromethane (1:0 to 0:1, v/v, runs 10−15). When the reaction was performed in toluene/dichloromethane (2:1) at −80 °C, the best result was achieved with the catalyst combination of **3a** (10 mol %) and TMAF (20 mol %) (98% and 87% ee, run 16). It is interesting to note that biscinchoninium derivative **3b** was found to be equally effective. The CF_3 adduct was obtained in 87% yield with 85% ee when the reaction was carried out using a combination of **3b** with TMAF (10 mol %) in toluene/dichloromethane (2:1) at −60 °C (run 17). The antipode of **2a** was obtained by using the pseudoenantiomeric *N*-3,5-bis(trifluoromethyl)benzylcinchonidinium bromide (**3c**) in 70% yield with 77% ee (run 18).

With conditions optimized, the scope of our trifluoromethylation reaction using the chiral ammonium bromide/TMAF catalyst was investigated in terms of substrates (Table 2). As three types of cinchona alkaloids **3a**−**c** are almost equally effective (see runs 16−18, Table 1), the ammonium bromide **3b** was selected due to its better reactivity at −60 °C (runs 16−18 in Table 1, and entry 1 in Table 2). We found that our **3b**/TMAF combination is an extremely general catalyst for the asymmetric trifluoromethylation reaction of a broad range of alkyl aryl ketones **1a**−**m** that

Table 2. Enantioselective Trifluoromethylation of **1** with Me_3SiCF_3 Catalyzed by a **3b**/TMAF Combination[a]



entry	1	Ar	R^1	time (h)	yield (%)	ee[b] (%)
1	**1a**	naphthyl	Me	6	87	85
2[c,d,e]	**1b**	6-Me-2-naphthyl	Me	30	72	91
3	**1b**	6-Me-2-naphthyl	Me	30	74	88
4[c]	**1c**	6-MeO-naphthyl	Me	24	59	78
5	**1c**	6-MeO-naphthyl	Me	8	74	87
6[c]	**1d**	4-BrC_6H_4	Me	3	71	70
7	**1d**	4-BrC_6H_4	Me	3	81	86
8[e]	**1e**	4-BrC_6H_4	Et	12	84	93
9	**1f**	Ph	Et	14	65	82
10	**1g**	Ph	propyl	7	83	76
11[d]	**1h**	4-$MeOC_6H_4$	Me	7	84	89
12	**1i**	4-ClC_6H_4	Me	14	71	87
13	**1j**	4-FC_6H_4	Me	7	96	87
14	**1k**	4-MeC_6H_4	Me	12	94	88
15	**1l**	3-BrC_6H_4	Me	8	73	71
16[d]	**1m**	3-ClC_6H_4	Me	4	80	74
17[c,f]	**1n**	3-$NO_2C_6H_4$	Me	7	96	64
18[c,d]	**1o**	4-$NO_2C_6H_4$	Me	3	97	52
19	**1p**	1-tetralone		3	75	94
20[d,g]	**1q**	6-methoxy-1-tetralone		24	82	86
21	**1r**	1-indanone		12	34	74
22	**1s**	1-benzosuberon		2	53	73
23	**1t**	PhCH=CH	Me	3	85	70
24	**1u**	2-natphtyl	H	24	93	41
25	**1v**	$PhCH_2CH_2$	Me	6	37	10

[a] The reaction started at −60 °C, and it was kept at −60 °C to −50 °C. [b] Determined by HPLC analysis (Chiralcel OD-H, AD-H, or OJ-H eluting with 5% *i*-PrOH in hexane) or GC analysis. The absolute stereochemistry of the newly generated stereocenter in **2n** was determined by comparing retention times of HPLC analysis reported by Mukaiyama et al.,[10] and the stereochemistry of other trifluoromethylated alcohols **2** was tentatively assumed by analogy. [c] Catalyst **3a** was used instead of **3b**. [d] 20 mol % of TMAF was used. [e] The reaction was carried out at −80 °C to −70 °C. [f] The reaction was carried out in the presence of MS 4A. [g] The reaction was carried out at −50 °C to −40 °C.

have enolizable protons as well as functional groups such as halogenyl and methoxy moieties. The desired products **2a**−**m** were obtained in high yields with up to 93% ee (entries 1−16). Trifluoromethylation of nitro-activated aryl methyl ketones (**1n** and **1o**) with Me_3SiCF_3 catalyzed by the cinchona alkaloid combination shows somewhat low enantioselectivities in very high yields, due to the high reactivity of **1n**−**o** to Me_3SiCF_3 (entries 17 and 18). The absolute stereochemistry of a newly generated stereocenter in **2n** was determined by comparing retention times of HPLC analysis reported by Mukaiyama et al.,[10] and the stereochemistry of other trifluoromethylated alcohols **2** was tentatively assumed by analogy. It should be mentioned that cyclic ketones such as 1-tetralones and 1-indanone (**1p**−**s**) gave good to high enantioselectivities: the corresponding cyclic trifluoromethylated alcohols **2p**−**s** were produced with excellent enantioselectivities of 74−94% ee (entries 19−22). The results are quite impressive because these chiral cyclic α-trifluoromethylated alcohols with a quaternary carbon center **2p**−**s** are difficult to prepare by other methodologies, and the acyclic derivatives might be obtained by different strategies.[7] Furthermore, selective 1,2-addition occurred in the trifluoromethylation of *trans*-4-phenylbut-3-en-2-one (**1t**) to furnish chiral *trans*-α-trifluoromethyl allylic alcohol **2t** with a quaternary carbon center in 85% yield with 70% ee (entry 23). The **3**/TMAF combination was not effective for the enantioselective trifluoromethylation of aryl aldehyde **1u** and purely aliphatic ketone **1v** (entries 24 and 25).

In conclusion, we have devised an effective catalytic system, chiral ammonium bromide/TMAF, for the enantioselective trifluoromethylation of acyclic and cyclic aryl ketones with Me_3SiCF_3 furnishing trifluoromethylated alcohols with a tetrasubstituted carbon atom, in high yields and with very good enantioselectivities. An operationally simple procedure based on the combination strategy is particularly suitable for the introduction of a CF_3 unit into drug candidates with a complex structure. Although the reactive species in the reaction has not yet been ascertained, any combination effects and an in situ generation of chiral ammonium fluoride from the combination could not be ruled out.[11,13] The obtained high enantioselectivity could result from π-stacking interactions between the aromatic ring in the substrate and those present in the catalyst, and the details are under investigation by DFT study and X-ray crystallographic analysis of the catalysts. Enantioselective monofluoromethylation as well as difluoromethylation reactions of aryl ketones to provide the tetrasubstituted mono- and difluoromethylated alcohols are under investigation based on this strategy.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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