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Asymmetric Trifluoromethylation of Aldehydes and Ketones with Trifluoromethyltrimethylsilane Catalyzed by Chiral Quaternary Ammonium Fluorides

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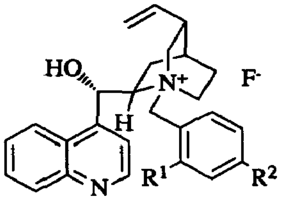
Abstract: The trifluoromethylation of aldehydes and ketones with trifluoromethyltrimethylsilane catalyzed by chiral quarternary ammmonium fluorides was carried out enantioselectively to give optically active 1-substituted-2,2,2-trifluoroethanols.

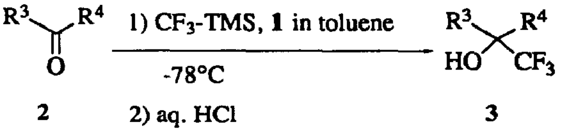
The synthesis of chiral trifluoromethylated molecules is an important aspect of organofluorine chemistry in relation to analytical and medicinal chemistry and opto-electric substances such as liquid crystals.[1] Although chiral 1-substituted-2,2,2-trifluoroethanols have been extensively prepared by enzymatic methods[1] and asymmetric synthesis (hydrogenation,[2] reduction,[3] ene-type reaction[4] and aldol condensation[5]), little research has been reported on the asymmetric introduction of a trifluoromethyl group into carbonyl compounds.

This paper presents for the first time examples of the catalytic asymmetric trifluoromethylation of aldehydes and ketones with trifluoromethyltrimethylsilane (TMS-CF_3) mediated by chiral quarternary ammonium fluorides. Nucleophilic trifluoromethylation reactions of carbonyl compounds using TMS-CF_3 catalyzed tetrabutylammonium fluoride (TBAF) as previously reported by G. A. Olah and collaborators[6] prompted the present authors to study of *N*-benzylcinchonium fluoride[7] (1) as a potential catalyst for the asymmetrical introduction of a trifluoromethyl group. Typically, trifluoromethylation was carried out by the addition of TMS-CF_3 (13 mmol) to a mixture of carbonyl compound (2) (10 mmol) and catalyst 1[8] in toluene[9] at -78°C, with stirring at the same temperature for 2 to 8 hr.[10] prior to filtration of the catalyst. The thus obtained siloxy compound was hydrolyzed to the corresponding alcohol (3) with aqueous HCl.[6] These results are summarized in Table 1.

This novel reaction should pave the way to the improved and excellent catalytic asymmetric trifluoromethylation of carbonyl compounds. Attempts are presently being made to obtain optimal optical yields through further investigation of this reaction and those related to it.



1a $R^1 = H, R^2 = CF_3$
1b $R^1 = CF_3, R^2 = CF_3$



(1)

Table1. Asymmetric Trifluoromethylation of Carbonyl Compounds with trifluoromethyltrimethylsilane Catalyzed by *N*-Benzylcinchonium Fluoride (Eq. 1)

Entry	Carbonyl Compound 2			Catalyst 1	Reaction Time	Product 3		
	R^3	R^4		(mol%)	(h)	ee(%)	Yield(%)	
1	Ph	H	**(2a)**	**1a** (10)	2	$37^{a)}$ (R)$^{b)}$	$>99^{c)}$	**(3a)**
$2^{d)}$	Ph	H	**(2a)**	**1a** (1)	2	$35^{a)}$ (R)$^{b)}$	$>99^{c)}$	**(3a)**
3	Ph	H	**(2a)**	**1b** (20)	2	$46^{a)}$ (R)$^{b)}$	$>99^{c)}$	**(3a)**
4	n-C_7H_{15}	H	**(2b)**	**1a** (20)	2	$15^{a)}$	$>99^{c)}$	**(3b)**
5	9-anthraldehyde		**(2c)**	**1a** (10)	2	$45^{e)}$ (R)$^{f)}$	$98^{g)}$	**(3c)**
6	Ph	Me	**(2d)**	**1a** (20)	2	$48^{h)}$	$91^{g)}$	**(3d)**
7	Ph	i-Pr	**(2e)**	**1a** (20)	8	$51^{h)}$	$87^{i)}$	**(3e)**

a) Enantiomeric excess was determined by GLC of the corresponding Mosher esters; b) For absolute configuration, see: Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G. *J. Chem. Soc., Chem. Commun.* 1978, 456; c) Yield was determined by GLC based on 2 using an internal standard; d) The reaction was carried out using 4A molecular sieves; e) Enantiomeric excess was determined by ^{19}F NMR of the corresponding Mosher esters; f) For absolute configuration, see: Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* 1977, *42*, 384; g) Isolated yield based on 2; h) Enantiomeric excess was determined by chiral HPLC; i) Isolated yield based on 2. Seven percent starting material was recovered.

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References and Notes

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6. a) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393; b) Krishnamurti, R.; Bellew, D. R.; Prakash, G. K. S. *J. Org. Chem.* **1991**, *56*, 984; The reaction does not proceed with a Lewis acid catalyst.
7. a) For the asymmetric Michael addition of nitromethane, see: Colonna, S.; Hiemstra, H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1978**, 238; b) for the asymmetric aldol condensation, see: Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 1507.
8. The catalyst was prepared according to Shioiri *et al.*; see method B in ref. 6b.
9. Toluene was superior to other solvents (THF, CH_2Cl_2, CH_3CN, DMF) for attaining the greatest enantioselectivity.
10. The mixture was periodically analyzed by GLC for completion of reaction.

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