Catalytic Enantioselective Fluorination of α-Cyano Esters by Phase-Transfer Catalysis Using Chiral Quaternary Ammonium Salts

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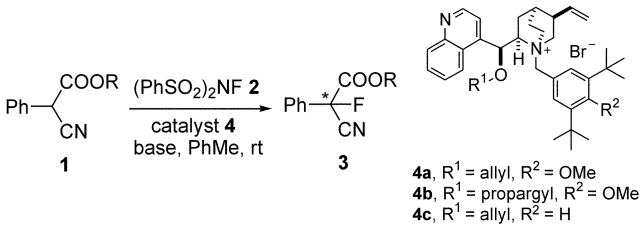
The chemistry of bioactive organofluorine compounds is a rapidly developing area of research because of their importance in biochemical and medicinal application.[1] Chiral organofluorine compounds are interesting and important materials with uses in analytical, biological and medicinal chemistry.[2] In particular, chiral acyclic monofluoro compounds have many applications such as chiral building blocks,[3] chiral derivatization reagents,[4] and synthetic intermediates for organic synthesis.[5] Recent advances in synthetic methodology of electrophilic enantioselective fluorinations by Shibata, Cahard, Togni, Sodeoka and us have led to significant improvements over the past few years.[6,7] A number of enantioselective fluorination of β-keto esters has been achieved by reagent-controlled enantioselective fluorination,[8] alkaloid/Selectrofluor combination,[6a-6e] and catalytic enantioselective fluorination using chiral titanium or palladium complex.[6f,6g] However, few examples have been demonstrated to date for enantioselective fluorination of α-cyano acetates, and only enantioselective fluorination using cinchona alkaloid/Selectrofluor combination has proved to be promising as an alternate strategy. The total absence of an efficient catalytic reaction for enantioselective fluorination of α-cyano acetates prompted us to embark in a study aimed at the development of such a reaction.

As part of our research program related to the development of effective cinchona alkaloid-derived phase-transfer catalysts,[9] we report the catalytic enantioselective fluorination of β-keto esters promoted by a cinchonine-derived quaternary ammonium salts as a phase-transfer catalyst.[7] In this paper, we wish to report the catalytic entioselective electrophilic fluorination of α-cyano acetates using the cinchona alkaloid derived quaternary ammonium salts **4**.

To determine suitable reaction conditions for the catalytic enantioselective electrophilic fluorination of α-cyano acetates, we initially investigated the reaction system with methyl α-cyano phenylacetate **1a** using *N*-fluorobenzenesulfonimide **2** as the electrophilic fluorinating agent in the presence of 10 mol% of catalyst **4** in toluene at room temperature (Table 1).

The effects of base has been investigated first, and as shown in Table 1, the compound (−)-**3a** was always formed under the various reaction conditions as the excessive enantiomer, which should be the case because all of the catalysts used possess the same chirality. Catalyst **4b** having *O*-propargyl group showed higher catalytic efficiency than others in terms of yields and enantioselectivity in the presence of Cs_2CO_3 as a base (entry 7). It has been also found that Cs_2CO_3 was the more effective base in this reaction than others such as CsOH, K_2CO_3, and KOH. Furthermore, we also investigated the effect of ester group on enantioselectivity (entries 7 and 10-12). The best results have been obtained with *p*-nitrobenzyl ester of substrate **3d** (73% ee). As we expected, the reaction was proceeded but the enantioselectivity was 0% ee in the case without chiral phase-transfer catalyst. Interesting is solvent effect, *i.e.* the reagent-controlled and catalytic enantioselective fluorination procedures were generally proceeded more efficiently in polar solvents such as acetonitrile.[6a-6e] In contrast, this reaction was complete within 30 min in nonpolar solvent at room temperature.[10] To examine the generality of the

Table 1. Influence of phase-transfer catalysts, bases, and ester group of α-cyano acetate **1**



entry	R	catalyst	base	yields (%)	ee[a] (%)
1	Me	**4a**	K_2CO_3	**3a**, 52	25
2	Me	**4a**	KOH	**3a**, 64	26
3	Me	**4a**	Cs_2CO_3	**3a**, 71	45
4	Me	**4a**	CsOH	**3a**, 47	35
5	Me	**4b**	K_2CO_3	**3a**, 49	15
6	Me	**4b**	KOH	**3a**, 52	25
7	Me	**4b**	Cs_2CO_3	**3a**, 76	50
8	Me	**4b**	CsOH	**3a**, 72	15
9	Me	**4c**	Cs_2CO_3	**3a**, 46	16
10	Et	**4b**	Cs_2CO_3	**3b**, 65	42
11	benzyl	**4b**	Cs_2CO_3	**3c**, 77	61
12	*p*-nitrobenzyl	**4b**	Cs_2CO_3	**3d**, 76	73

[a]Enantiopurity was determined by HPLC analysis with Chiralcel OJ (for **3a** and **3b**) or Chiralpak AD (for **3c** and **3d**) columns.

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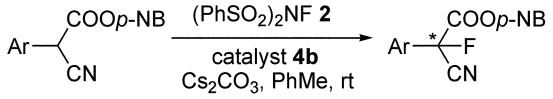
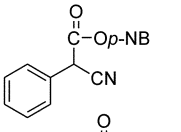
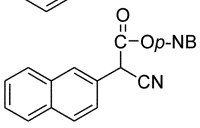
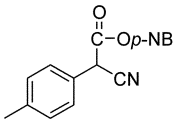
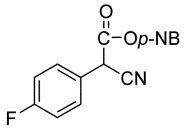
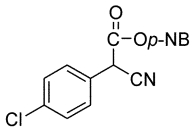
Table 2. Catalytic enantioselective fluorination of **1** with phase-transfer catalyst **4b**



1 **3**

α-cyano acetate	yield (%)	ee[a] (%)
	**3d**, 76	73
	**3e**, 71	76
	**3f**, 64	72
	**3g**, 76	73
	**3h**, 72	76

[a]Enantiopurity was determined by HPLC analysis with a Chiralpak AD column.

enantioselective fluorination using chiral phase-transfer catalyst **4b**, we studied the fluorination of α-cyano esters **1d-1h** (Table 2). The fluorination reaction was carried out at room temperature. As can be seen by the results summarized in Table 2, all of the corresponding α-cyano α-fluoro esters **3d-3h** were obtained in high yields with moderate selectivities.

We have developed a mild and practical catalytic enantioselective fluorination using a chiral phase-transfer catalyst with *N*-fluorobenzenesulfonimide. α-Cyano acetate derivatives were fluorinated enantioselectively to give the corresponding α-fluoro compounds in high yields with good to moderate enantiomeric excess under phase-transfer conditions. We are currently involved in the extension of this convenient fluorination process to other enolizable substrates and are investigating the applicability of phase-transfer catalysts to other asymmetric phase-transfer processes.

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10. *General procedure for the fluorination of α-cyano acetates:* To a stirred solution of α-cyano acetate (0.3 mmol), Cs_2CO_3 (33 mg, 0.1 mmol) in toluene (3 mL) was added chiral cinchonium salt **4b** (l9 mg, 0.03 mmol) at room temperature. Reaction mixture was stirred for 1 h at room temperature. *N*-fluorobenzenesulfonimide (95 mg, 0.3 mmole) was added slowly for 1-2 min. After 30 min, the mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (silica gel, ethyl acetate : hexane = 1 : 8) to afford the α-cyano α-fluoro acetate.