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Catalytic enantioselective fluorination of α-cyano acetates catalyzed by chiral palladium complexes

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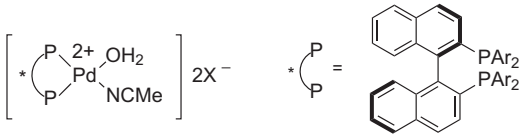
Abstract—The catalytic enantioselective electrophilic fluorination promoted chiral palladium complexes is described. Treatment of α-cyano acetates with *N*-fluorobenzenesulfonimide as the fluorine source under mild reaction conditions afforded the corresponding α-cyano α-fluoro acetates in high yields with excellent enantiomeric excesses (85–99% ee).

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 containing a fluorine atom bonded directly to a stereogenic center have been utilized in studies of enzyme mechanisms and as intermediates in asymmetric syntheses.[2] Chiral α-fluoro α-cyano acetate derivatives have useful applications such as chiral synthetic intermediates for organic synthesis[2] and derivatization reagents.[3] The development of effective methodologies for the preparation of new selectively fluorinated, stereochemically defined compounds is critical to further advances of fluorine chemistry.[4] Until now, a number of enantioselective fluorination of β-keto esters has been achieved by reagent-controlled and catalytic enantioselective fluorination.[4e,5] Recently, the efficient example of a catalytic enantioselective fluorination of β-keto esters was reported by Sodeoka and co-workers.[5c] They examined the reaction of several substrates with a chiral palladium complex, and reported an excellent enantioselection (83–94% ee). However, few examples have been demonstrated to date for enantioselective fluorination of α-cyano acetates, and only enantioselective fluorination using cinchona alkaloid/Selectfluor™ combination has proved to be promising as an alternate strategy.[6] The total absence of a catalytic enantioselective fluorination of α-cyano acetates prompted us to embark in a study aimed at the development of such a reaction.

As part of the research program related to the development of synthetic methods for the enantioselective construction of stereogenic quaternary carbon centers,[7] we report the catalytic enantioselective fluorination of α-cyano acetates promoted by chiral quaternary ammonium salts.[7a] In this letter, we wish to report the catalytic enantioselective electrophilic fluorination of α-cyano acetates using chiral palladium complexes **1**–**3** (Fig. 1).[8]

To determine suitable reaction conditions for the catalytic enantioselective electrophilic fluorination of α-cyano acetates, we initially investigated the reaction system with α-cyano phenylacetate **4** using *N*-fluorobenzenesulfonimide (NFSI) as the electrophilic fluorinating



1a: Ar = Ph: (*R*)-BINAP, X = BF_4
1b: Ar = Ph: (*R*)-BINAP, X = OTf
1c: Ar = Ph: (*R*)-BINAP, X = SF_6
1d: Ar = Ph: (*R*)-BINAP, X = PF_6
2: Ar = 4-methylphenyl: (*R*)-Tol-BINAP, X = PF_6
3: Ar = 3,5-dimethylphenyl: (*R*)-Xylyl-BINAP, X = PF_6

Figure 1.

Keywords: Chiral palladium complexes; Fluorination; Asymmetric reactions.
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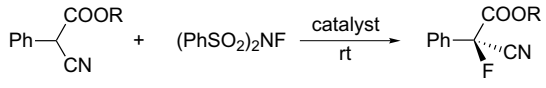
Table 1. Optimization of the reaction conditions



4a-f **5a-f**

Entry	R	Catalyst	Solvent	Time (h)	Yield (%)	ee[a] (%)
1	**4a**, Me	**1d**	MeOH	12.5	**5a**, 56	67
2	**4b**, Et	**1d**	MeOH	13.5	**5b**, 79	79
3	**4c**, Bn	**1d**	MeOH	12.5	**5c**, 75	81
4	**4d**, *p*-NO_2, Bn	**1d**	MeOH	12	**5d**, 75	75
5	**4e**, $CHPh_2$	**1d**	MeOH	10	**5e**, 62	83
6	**4f**, *t*-Bu	**1d**	MeOH	29	**5f**, 72	89
7[b]	**4f**, *t*-Bu	**1d**	MeOH	60	**5f**, 83	99
8[c]	**4f**, *t*-Bu	**1d**	MeOH	11	**5f**, 59	99
9	**4f**, *t*-Bu	**1a**	MeOH	48	**5f**, 61	97
10	**4f**, *t*-Bu	**1b**	MeOH	48	**5f**, 88	93
11	**4f**, *t*-Bu	**1c**	MeOH	48	**5f**, 62	93
12	**4f**, *t*-Bu	**2**	MeOH	24	**5f**, 80	89
13	**4f**, *t*-Bu	**3**	MeOH	29	**5f**, 71	79
14[d]	**4f**, *t*-Bu	**1d**	MeOH	48	**5f**, 81	59
15	**4f**, *t*-Bu	**1d**	EtOH	19	**5f**, 82	81
16	**4f**, *t*-Bu	**1d**	THF	25	**5f**, 74	87
17	**4f**, *t*-Bu	**1d**	Acetone	50	**5f**, 10	60

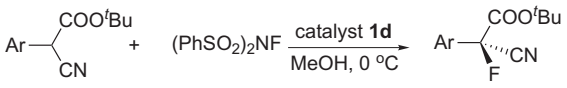
[a] Enantiomeric excess determined by chiral HPLC using Chiralcel OJ (for **5a**–**c**) Chiralpak AD (for **5d**–**f**) column.
[b] Reaction carried out at 0 °C.
[c] Reaction carried out at −40 °C.
[d] Reaction carried out using Selectfluor™ as fluorinating reagent.

agent in the presence of 5 mol % of catalyst **1d** in MeOH at room temperature (Table 1).[9] We first examined the effect of ester group on enantioselectivity (entries 1–6). The best results have been obtained with *tert*-butyl ester of substrate **4f**. Lowering the temperature to 0 and −40 °C with catalyst **1d** dramatically increased enantioselectivities up to 99% ee (entries 6–8). Catalyst **1d** was a more effective than other catalysts (entries 7–13). Concerning the solvent, the use of MeOH gave the best results, whereas the fluorination in EtOH and acetone led to lower yields and enantioselectivities (entries 6–8, 15–17). NFSI was a more effective fluorinating agent than Selectfluor™ in this reaction under the same condition (entries 6 and 14).[10]

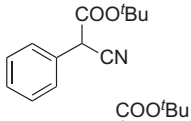
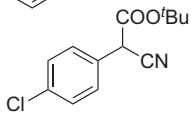
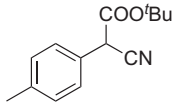
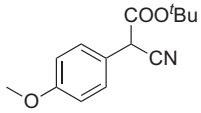
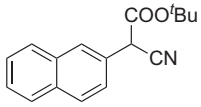
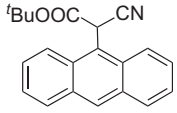
To examine the generality of the catalytic enantioselective fluorination of α-cyano acetates **4** by using chiral palladium complex **1d**, we studied the fluorination of various α-cyano acetates **4f**–**k**. As it can be seen by the results summarized in Table 2, the corresponding α-cyano α-fluoro acetates **5f**–**k** were obtained in moderate to excellent yields and excellent enantioselectivities. Unfortunately, the fluorination of α-alkyl substituted α-cyano acetates did not proceeds in these reaction conditions.

In summary, we have accomplished the first catalytic enantioselective fluorination of α-cyano acetates **4** with excellent enantioselectivity (85–99% ee). Current efforts are toward developing synthetic applications and a mechanistic elucidation of this fluorination reaction.

Table 2. Catalytic enantioselective fluorination of α-cyano acetates



4f-k **5f-k**

α-Cyano acetate	Time (h)	Yield (%)	ee[a] (%)
	60	**5f**, 83	99 [*R*][c]
	17	**5g**, 94[b]	85
	60	**5h**, 85	93 [*R*][c]
	72	**5i**, 85[d]	99
	60	**5j**, 88	93
	52	**5k**, 42[b,e]	91

[a] Enantiopurity of **5** was determined by HPLC analysis with Chiralpak AD and Chiralcel OJ (for **5i**) columns.
[b] Reaction carried out at room temperature.
[c] Absolute configuration was determined by comparison of the optical rotation of the corresponding acid with the literature value.[3,6b]
[d] Reaction carried out using catalyst **1a**.
[e] Reaction carried out using THF–MeOH (1:1).

Acknowledgements

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9. General procedure for the fluorination of α-cyano acetates: To a stirred solution of α-cyano acetate (0.3 mmol), catalyst **1d** (16.2 mg, 0.015 mmol) in MeOH (3 mL) was added *N*-fluorobenzenesulfonimide (94.6 mg, 0.3 mmol) at room temperature. Reaction mixture was stirred for 10–72 h at room temperature. The mixture was diluted with saturated NH_4Cl solution (20 mL) and extracted with ethyl ether (2×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (silica gel, ethyl acetate–hexane = 1:15) to afford the α-cyano α-fluoro acetate.
10. No reaction was observed in MeOH using *N*-fluoropyridinium triflate.