Communications

Catalytic Asymmetric Fluorination of α-Chloro-β-ketoesters in the Presence of Chiral Palladium Complexes

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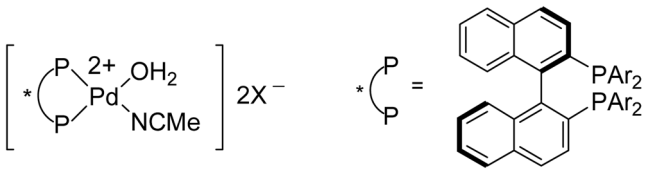
The chemistry of organic fluorine compounds is a rapidly developing area of research because of their importance in biochemical and medicinal applications and material science.[1] Introduction of fluorine atom into biologically active compounds often leads to improvement of chemical and physical properties of the parent compounds due to unique properties of the fluorine atom.[2] 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.[3] The development of effective methodologies for the preparation of stereoselectively fluorinated compounds having a fluorine atom at a stereogenic carbon center is critical in order to further advances of fluorine chemistry.[4] Until now, a number of enantioselective fluorinations have been achieved by reagent-controlled and catalytic enantioseletive fluorination.[5] Recently, several groups have been reported the catalytic enantioselective fluorination of active methine derivatives using chiral Lewis acids[6] such as Binap-Pd(II) and transition metal-bis(oxazoline) complexes and organocatalysts[7] such as cinchonine-derived quaternary ammonium salt, imidazolidinone, and proline derivatives.

A few synthetic methods for the preparation of α-chloro-α-fluoro-β-ketoesters have been reported. In general, α-chloro-α-fluoro-β-ketoesters were prepared by the electrophilic fluorination of α-chloro-β-ketoesters using NFSI or F_2 in the presence of formic acid.[8] Togni has recently reported the first catalytic enantioselective synthesis of α-chloro-α-fluoro-β-ketoesters using chiral titanium complexes with up to 65% selectivity.[9]



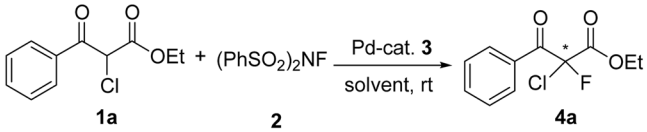
3a: Ar = Ph: (*R*)-BINAP, X = OTf
3b: Ar = Ph: (*R*)-BINAP, X = BF_4
3c: Ar = Ph: (*R*)-BINAP, X = SbF_6
3d: Ar = Ph: (*R*)-BINAP, X = PF_6
3e: Ar = 4-methylphenyl: (*R*)-Tol-BINAP, X = PF_6
3f: Ar = 3,5-dimethylphenyl: (*R*)-Xylyl-BINAP, X = BF_4

Figure 1. Chiral palladium complexes **3**.

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[10] we reported the catalytic enantioselective α-fluorination and α-amination of β-ketoesters with excellent enantioselectivity which promoted by chiral ammonium salts and chiral palladium complexes.[7f,10a] In this letter, we wish to report the catalytic enantioseletive electrophilic α-fluorination of α-chloro-β-ketoesters using chiral palladium complexes **3** which are air- and moisture-stable.

To determine suitable reaction condition for the catalytic enantioselcetive fluorination of α-chloro-β-ketoesters **1**, we first examined electrophilic fluorination of 1-chloro benzoylacetate **1a** with *N*-fluorobenzenesulfonimide (NFSI) in the presence of 5 mol% of **3a** in MeOH at room temperature (Table 1). As can be seen from Table 1, the fluorinated

Table 1. Optimization of the reaction conditions

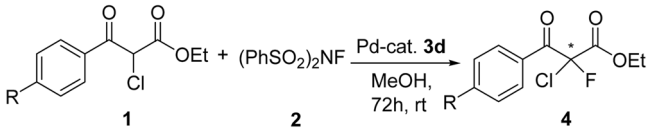


1a **2** **4a**

Entry	Catalyst	Solvent	Time (h)	Yield[a] (%)	Ee[b] (%)
1	**3a**	MeOH	118	87	65
2	**3b**	MeOH	66	65	61
3	**3c**	MeOH	118	88	65
4	**3d**	MeOH	72	90	75
5	**3e**	MeOH	72	71	67
6	**3f**	MeOH	72	71	66
7	**3d**	Toluene	72	41	69
8	**3d**	Acetone	72	88	67
9	**3d**	THF	72	74	67
10[c]	**3d**	MeOH	125	85	11
11[d]	**3d**	MeOH	125	0	–

[a]Isolated yields. [b]Enantiopurity was determined by HPLC analysis using with a chiralcel OB-H column. [c]Reaction carried out using Selectfluor™ as fluorination reagent. [d]Reaction carried out using 1-fluoropyridinium triflate as fluorination reagent.

Table 2. Catalytic asymmetric fluorination of α-chloro-β-ketoesters



Entry	R	Yield[a] (%)	Ee[b] (%)
1	H	**4a**, 90	75
2	MeO	**4b**, 94	65
3	CH_3	**4c**, 79	63
4	Br	**4d**, 94	77
5	CF_3	**4e**, 88	76

[a]Isolated yields. [b]Enantiomeric excess determined by chiral HPLC analysis using with a chiralcel OB-H and OJ columns.

product was obtained with 87% yield with 65% ee after 118 h (entry 1). To improve the enantioselectivity, we examined a series of chiral diphosphine ligands. When (*R*)-phenyl-BINAP palladium complex **3d** was used, the enantioselectivity was improved to 75% ee (entry 4). Concerning the solvent, there are no significant effects on enantioselectivity. NFSI was more effective fluorinating agent than Selectfluor in this reaction under the same condition (entries 4 and 10). Using 1-fluoropyridinium triflate as fluorination reagent under similar conditions, the reaction was not proceeded (entry 11).

To examine the generality of the catalytic enantioselective fluorination of α-chloro-β-ketoesters **1** by using chiral palladium complex **3d**, we studied the fluorination of α-chloro-β-ketoester derivatives **1** under optimum reaction condition. As it can be seen by the results summarized in Table 2, the corresponding α-chloro-α-fluoro-β-ketoesters **4** were obtained in moderate to excellent yields with high enantioselctivities (63-77% ee).[11]

In summary, we have accomplished the efficient catalytic enantioselective electrophilic α-fluorination of various α-chloro-β-ketoesters **1** with good enantioselectivity (up to 77% ee) using palladium complex **3d** as chiral catalyst. It should be noted that this fluorination reaction proceeded well using air- and moisture-stable chiral palladium complexes in environmentally benign alcoholic solvent. This catalytic enantioselective fluorination in MeOH has been shown to be practical from environmental and economical points of view. Current efforts are toward developing synthetic applications of this a-fluorination reaction.

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11. **Typical procedure for the fluorination of 1-chloro benzoylacetate 1a:** To a stirred solution of 1-chloro benzoylacetate **1a** (67.9 mg, 0.3 mmol) and palladium catalyst **3d** (16.1 mg, 0.015 mmol) in MeOH (1.5 mL) was added NFSI (113.5 mg, 0.36 mmol) at room temperature. Reaction mixture was stirred for 118 h at room temperature. The mixture was diluted with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and purified by flash chromatography (ethyl acetate:hexane = 1:9) to afford 1-chloro-1-fluoro benzoylacetate **4a** (66.1 mg, 90%): $[\alpha]_D^{21} = -18.1$ (c = 0.695, $CHCl_3$, 75% ee); ^1H NMR (200 MHz, $CDCl_3$) 1.27 (t, *J* = 7.1 Hz, 3H), 4.36 (q, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 2H), ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 64.2, 103.0 (d, *J* = 263.1), 128.8, 130.9, 130.1 (d, *J* = 4), 134.7, 163.0 (d, *J* = 26.6), 184.6 (d, *J* = 26.8), ^{19}F NMR (282 MHz, $CDCl_3$) δ −117.05, R_t HPLC (95:5, *n*-hexane: *i*-PrOH, 254 nm, 0.5 mL/min) Chiralcel OB-H column, t_R = 12.7 min (minor), t_R = 13.7 min (major).