Enantioselective Alkylation of α-Fluoro-β-Keto Esters by Asymmetric Phase-Transfer Catalysis

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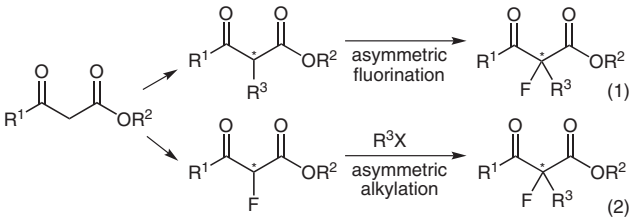
Abstract: Highly enantioselective alkylation of *tert*-butyl α-fluoro-β-keto esters can be effected by the use of *N*-spiro chiral quaternary ammonium salt as chiral phase-transfer catalyst, as a complementary approach to the asymmetric fluorination of α-alkyl-β-keto esters.

Key words: phase-transfer catalysis, alkylations, asymmetric catalysis, esters, alkyl halides

The recent significant expansion in the use of organofluorine compounds has attracted the attention in various scientific fields including organic, agricultural, medicinal, and material chemistry.[1] Among these, one of the most fascinating aspects of organofluorine chemistry is the asymmetric synthesis of fluorinated molecules.[2] Accordingly, various asymmetric approaches have been developed for this purpose. For example, there are two possibilities of preparing optically active organofluorine compounds as shown in Scheme 1. Asymmetric fluorination of carbonyl substrates such as β-keto esters is a well-known approach for obtaining optically active organofluorine compounds (Scheme 1, eq. 1).[3] Alternatively, asymmetric alkylation of α-fluorocarbonyl substrates would give similar organofluorine compounds (Scheme 1, eq. 2). The advantage of the latter strategy is the ready availability of various organofluorine compounds in optically active forms by changing the alkylating agent (R^3 in Scheme 1). In addition, the use of asymmetric phase-transfer catalysis would be most preferable from the practical viewpoint.[4] Here, we wish to report asymmetric alkylation of α-fluoro-β-keto esters catalyzed by *N*-spiro chiral quaternary ammonium bromide (*S,S*)-**1** under phase-transfer conditions.

Asymmetric benzylation of ethyl 2-fluoro-3-oxo-3-phenylpropanoate (**2a**) in toluene catalyzed by 1 mol% *N*-spiro chiral quaternary ammonium bromide (*S,S*)-**1** in the presence of 33% aqueous K_2CO_3 was initially carried out in consideration of our extensive researches on the use of (*S,S*)-**1** for various asymmetric phase-transfer alkylations.[5,6] However, the observed enantioselectivity of the product **3a** was found to be moderate (48% ee in entry 1 of Table 1). Switching the ethyl ester **2a** to the corresponding *tert*-butyl ester **2b** enhanced the enantioselectivity (78% ee in entry 2). Then, the effect of base was

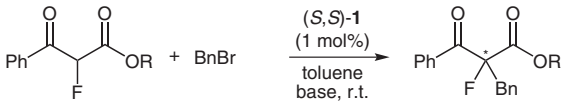


Scheme 1 Two distinctive approaches for the syntheses of α-alkyl-α-fluoro-β-keto esters

examined by asymmetric benzylation of *tert*-butyl 2-fluoro-3-oxo-3-phenylpropanoate (**2b**) in toluene with 1 mol% of (*S,S*)-**1** (Figure 1) under similar phase-transfer conditions to furnish **3b**, and among these, the use of 10% aqueous CsOH was found to be most preferable in terms of both reactivity and selectivity (entry 5 vs. 2–4).

We also examined the effect of temperature and solvent by asymmetric benzylation of *tert*-butyl 2-fluoro-3-oxo-3-phenylpropanoate (**2b**) in toluene with 10% aqueous CsOH catalyzed by 1 mol% of (*S,S*)-**1** under similar phase-transfer conditions as shown in Table 2. In toluene solvent, the use of lower temperature enhanced the enantioselectivity (entry 2 vs. 1). The use of aromatic solvents such as toluene, *o*-xylene, and mesitylene generally gave

Table 1 Asymmetric Alkylation of Ethyl or *tert*-Butyl 2-Fluoro-3-oxo-3-phenylpropanoates **2** and Benzyl Bromide – Effect of Base[a]



2a R = Et
2b R = *t*-Bu

3a R = Et
3b R = *t*-Bu

Entry	R	Base	Time (h)	Yield (%)[b]	ee (%)[c]
1	Et	33% K_2CO_3	12	93	48
2	*t*-Bu	33% K_2CO_3	12	77	78
3	*t*-Bu	50% Cs_2CO_3	24	86	77
4	*t*-Bu	50% K_3PO_4	24	66	69
5	*t*-Bu	10% CsOH	2	64	77

[a] The asymmetric alkylation of ethyl 2-fluoro-3-oxo-3-phenylpropanoate (**2a**, 0.10 mmol) with benzyl bromide (0.12 mmol) and aq base (1.0 mL) in the presence of 1 mol% of catalyst (*S,S*)-**1** in toluene (2.0 mL) at r.t. under the given reaction time.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

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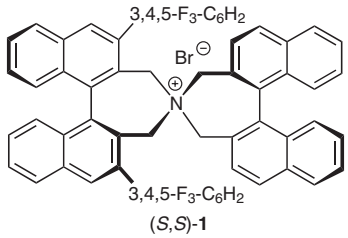
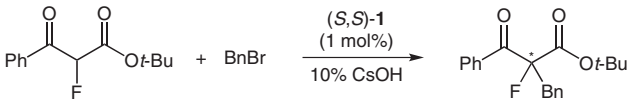


Figure 1

Table 2 Asymmetric Alkylation of *tert*-Butyl 2-Fluoro-3-oxo-3-phenylpropanoate (**2b**) and Benzyl Bromide – Effect of Temperature and Solvent[a]



Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	toluene	r.t.	2	64	77
2	toluene	0	7	56	84
3	*o*-xylene	0	7	81	85
4	TBME	0	7	62	80
5	CPME	0	7	50	82
6	mesitylene	0	7	86	85
7[d]	mesitylene	0	16	82	85

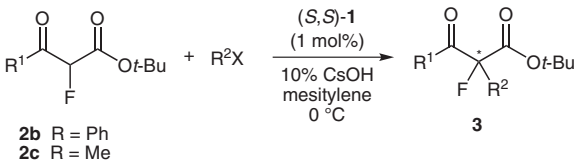
[a] The asymmetric alkylation of *tert*-butyl 2-fluoro-3-oxo-3-phenylpropanoate (**2b**, 0.10 mmol) with benzyl bromide (0.12 mmol) and 10% aq CsOH (1.0 mL) in the presence of 1 mol% of catalyst (*S*,*S*)-**1** in solvent (2.0 mL) at r.t. or 0 °C under the given reaction time.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Use of 10% aq CsOH (2 equiv).

better enantioselectivity than ethereal solvents such as *tert*-butyl methyl ether (TBME) and cyclopentyl methyl ether (CPME).

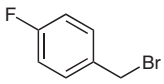
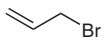
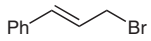
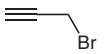
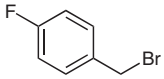
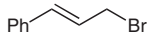
With the optimized conditions in hand, the scope and limitation of this asymmetric alkylation of α-fluoro-β-keto esters was summarized as shown in Table 3.[7] In addition to substituted benzyl bromide, various alkyl halides such as allylic and simple alkyl halides can be employable (entries 1–5). Unfortunately, asymmetric alkylation with propargyl bromide led to the eminent loss of enantioselectivity (entry 6). Use of another α-fluoro-β-keto ester such as *tert*-butyl 2-fluoro-3-oxobutanoate (**2c**) as nucleophile also exhibited similar reactivity and enantioselectivity (entries 7 and 8).

This approach is also applicable to the asymmetric conjugate addition of *tert*-butyl 2-fluoro-3-oxo-3-phenylpropanoate (**2b**) to methyl vinyl ketone with Na_2CO_3 in the presence of a catalytic amount (1 mol%) of (*S*,*S*)-**1** in mesitylene at –20 °C for 24 hours and then at 0 °C for 10 hours

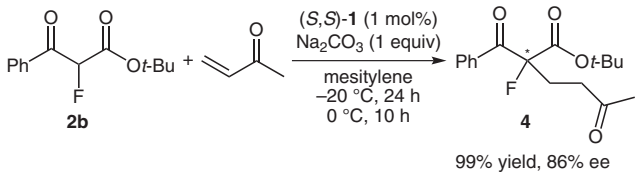
Table 3 Asymmetric Alkylation of α-Fluoro-β-Keto Esters **2b** and **2c** with Several Alkyl Halides Catalyzed by (*S*,*S*)-**1**[a]



2b R = Ph
2c R = Me

Entry	R^1	R^2X	Time (h)	Yield (%)[b]	ee (%)[c]
1	Ph	BnBr	16	82	85
2	Ph		12	87	88
3	Ph		36	81	81
4	Ph		15	89	86
5	Ph	MeI	36	80	78
6	Ph		36	68	65
7	Me		8	79	80
8	Me		8	85	68

[a] The asymmetric alkylation of *tert*-butyl 2-fluoro-3-oxo-3-phenylpropanoate (**2b**) or *tert*-butyl 2-fluoro-3-oxobutanoate (**2c**, 0.10 mmol) with alkyl halide (0.12 mmol) and 10% aq CsOH (0.2 mmol) in the presence of 1 mol% of catalyst (*S*,*S*)-**1** in mesitylene (2.0 mL) at 0 °C under the given reaction time.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.



Scheme 2

to afford the corresponding conjugate adduct **4** in 99% yield with high enantioselectivity.

In conclusion, we succeeded in obtaining various α-alkyl-α-fluoro-β-keto esters with high enantioselectivity by using the phase-transfer-catalyzed asymmetric alkylation of *tert*-butyl 2-fluoro-3-oxo-3-phenylpropanoate and *tert*-butyl 2-fluoro-3-oxobutanoate as a key asymmetric induction step.

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(7) **Typical Procedure for the Catalytic Asymmetric Alkylation of *tert*-Butyl 2-Fluoro-3-oxo-3-phenylpropanoate (2b) under Phase-Transfer Conditions**

To a solution of phase-transfer catalyst (*S*,*S*)-**1** (0.001 mmol, 0.9 mg) and **2b** (0.10 mmol, 23.6 mg) in mesitylene (2 mL) was added benzyl bromide (0.12 mmol, 14.0 μL), and the mixture was cooled to 0 °C. After adding 10% aq CsOH (0.3 mL, ca. 0.2 mmol) to this mixture, the reaction mixture was vigorously stirred until the completion of the reaction. The mixture was then poured into sat. aq NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on SiO_2 to give *tert*-butyl 2-benzyl-2-fluoro-3-oxo-3-phenylpropanoate (**3b**) as a colorless oil [82% (26.8 mg), 85% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralpak OD, hexane–2-PrOH (300:1), flow rate = 0.5 mL/min, 254 nm, t_R = 18.8 min(minor) and 21.7 min(major)]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–8.02 (2 H, m, ArH), 7.53–7.58 (1 H, m, ArH), 7.41–7.44 (2 H, m, ArH), 7.25–7.30 (5 H, m, ArH), 3.46–3.68 (2 H, m, $PhCH_2$), 1.29 (9 H, s, *t*-Bu).