Enantioselective fluorination of β-keto esters using a PEG-bound urea-containing chiral quaternary ammonium salt catalyst

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Abstract

The asymmetric fluorination of *β*-keto esters with *N*-fluorobisbenzenesulphonimide (NFSI) catalyzed by a PEG-bound urea-containing chiral quaternary ammonium salt is developed. The corresponding products were obtained in good yields and enantioselectivities. The catalyst structure facilitated its recovery and multiple reuse without any loss of activity.

Keywords: Asymmetric fluorination, *β*-keto esters, PEG-bound chiral catalyst

Introduction

Recently, bifunctional chiral quaternary ammonium salt phase transfer catalysts have received much attention for their powerful catalytic activities and steroselectivities in the asymmetric synthesis.[1] Of particular note are the scaffolds of urea,[2-4] thiourea[5] and binaphthols,[6] which produced some leading quaternary ammonium salt molecules that exhibit good catalytic activity and steroselectivity. However, these expensive catalysts suffered from the difficulty of recovery, purification and reuse. Immobilization of the catalyst offers a solution to the problem. Among the polymeric matrixes available, an attractive catalyst support for is polyethylene glycol (PEG), because it is soluble in many organic solvents but can be precipitated with diethyl ether.[7] A PEG-bound catalyst is not only easy to purify and recycle, but is also able to operate in homogeneous conditions. In 2014, Waser reported a urea-containing quaternary ammonium salt **1** (Figure 1), which can promote the enantioselective fluorination of β-keto esters in high yields and ee values.[8] Here, we report a method for the preparation of PEG-supported urea-containing quaternary ammonium salt (**3**) and its application to the asymmetric fluorination of *β*-keto esters.

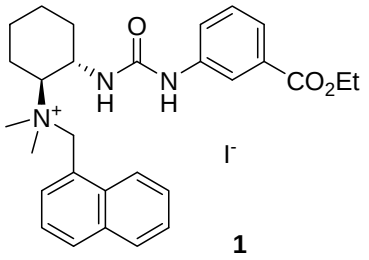
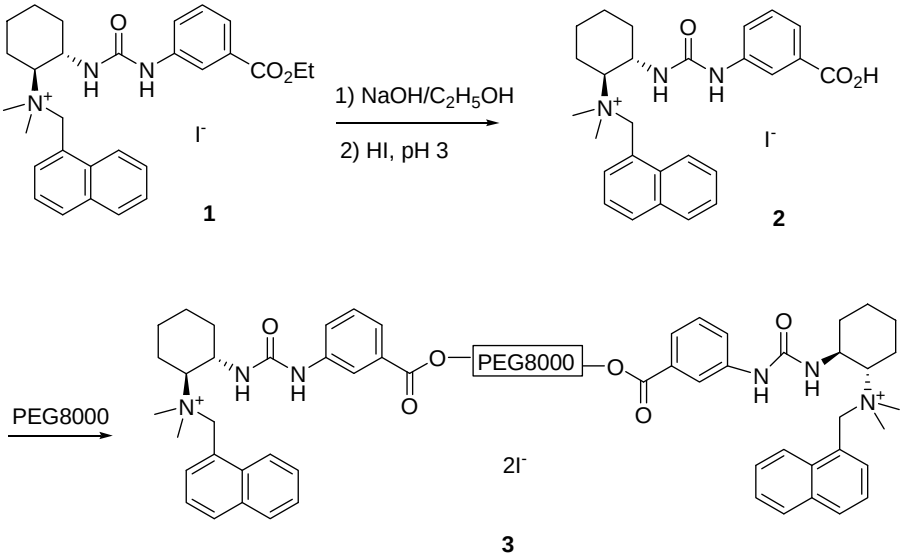


Figure 1. The structure of catalyst **1**.

Results and Discussion

To attach compound **1** to the soluble support PEG 8000, we hydrolyzed **1** with aqueous NaOH, followed by acidification with HI, whereby the ester group was completely converted into a carboxyl group The salt **2** was separated from the reaction mixture, and esterified with PEG 8000 in the presence of *p*-TsOH. After precipitation of the PEG-bound catalyst by diethyl ether, we obtained a catalyst **3** in 78% purity. The synthetic route is outlined in Scheme 1.



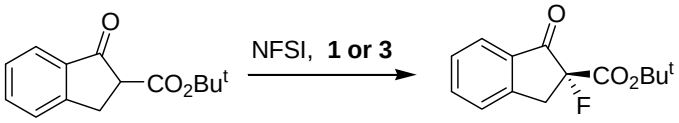
Scheme 1. Preparation of the PEG-supported catalyst **3**.

To assess the efficacy of the polymer-bound catalyst, we chose the reaction of the β-keto ester **4a** with *N*-fluorobisbenzenesulphonimide (NFSI) in *m*-xylene and aqueous K_3PO_4 (0.5 M) at 0 ºC in the presence of **3** (1 mol %) or **1** (2 mol %), respectively, for 24h. It was found that the catalytic activity and the asymmetric induction of **3** are comparable to the homogeneous **1** under the reaction conditions (Table 1, entries 1 and 2). We focused on the use of **3** for further screening efforts. Dropping the temperature to -10 ºC distinctly improved the enantioselectivity

(Table 1, entry 3). The selectivity was not improved further by carrying out the reaction at -20 ºC with a prolonged reaction time (Table 1, entry 4).

When more concentrated aqueous K_3PO_4 (2 M) was used as an additive, the enantioselectivity observed in the product was slightly increased (Table 1, entry 5). Other solvents were tried, but the results indicated that *m*-xylene was the best choice.

Table 1. Effects of additives, temperature and solvents on the fluorination



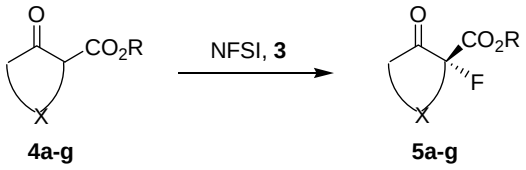
4a **5a**

Entry	Catalyst	t (ºC)	Additive	Solvent	Time (h)	Yield (%)[a]	ee (%)[b]
1	**1**	0	K_3PO_4 (0.5 M)	*m*-xylene	24	95	80
2	**3**	0	K_3PO_4 (0.5 M)	*m*-xylene	24	95	81
3	**3**	-10	K_3PO_4 (0.5 M)	*m*-xylene	32	94	84
4	**3**	-20	K_3PO_4 (0.5 M)	*m*-xylene	48	95	84
5	**3**	-10	K_3PO_4 (2 M)	*m*-xylene	48	95	85
6	**3**	-10	K_3PO_4 (2 M)	toluene	32	93	69
7	**3**	-10	K_3PO_4 (2 M)	CH_2Cl_2	30	92	56

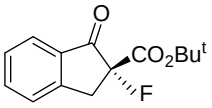
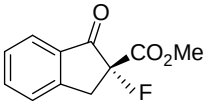
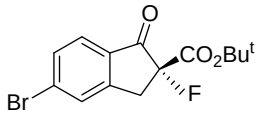
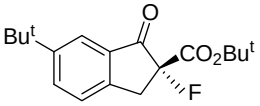
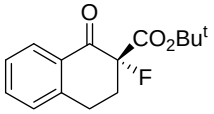
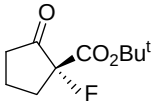
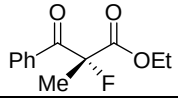
[a] Isolated yield. [b] ee was determined by HPLC analysis.

Employing the optimized conditions (Table 1, entry 5), the scope of the method in the fluorination reaction was investigated. The results were summarized in Table 2. The nature of the ester group has a great influence on the ee value of the product. For example, a tertiary butyl ester gave a product ee value of 85% (Table 2, entry 1), while the corresponding methyl ester gave the lower selectivity of 72% ee (Table 2, entry 2). The effect of the substituent identity and substitution pattern on the phenyl ring was also studied. Both electron-withdrawing and electron-donating substituents gave the desired products in high enantioselectivity and reasonable yields (Table 2, entries 3 and 4). The substitution at the 5- or 6-position on the aromatic ring of the substrate did not obviously influence the efficiency of the asymmetric induction (Table 2, entries 3 and 4). Substrates with a six-membered ring also underwent the fluorination reaction smoothly and a good ee value and yield were obtained (Table 2, entry 5). Good results were also obtained when a monocyclic five-membered ring *β*-keto ester was employed (Table 2, entry 6). However, the acyclic ester ethyl α-benzoylpropionate gave a product in low yield and enantioselectivity (Table 2, entry 7).

Table 2. Fluorination of *β*-keto esters catalyzed by **3** in aqueous K_3PO_4 (2 M) and *m*-xylene



4a-g **5a-g**

Entry	Product		Yield (%)[a]	ee (%)[b]
1		**5a**	96	85
2		**5b**	93	72
3		**5c**	78	84
4		**5d**	76	70
5		**5e**	70	73
6		**5f**	69	79
7		**5g**	39	23

[a] Isolated yield. [b] ee was determined by HPLC analysis.

Recycling of catalyst **3** was also studied. The catalyst **3** already employed in entry 1 of Table 2 was reused a second time in the fluorination of **4a** to give the product **5a** in 96% yield and 85% ee. The recovered catalyst **3** was recycled 6 times without showing any decrease in the catalytic activity.

Conclusion

In summary, PEG-bound urea-containing quaternary ammonium salt homogeneous catalyst has been successfully applied in the enantioselective fluorination reactions of *β*-keto esters. The corresponding products could be obtained with good enantioselectivity in excellent yields when

NFSI was used as fluorination reagent. The PEG-bound catalyst was proved to facilitate the recovery and reuse without affecting the chemical yield and enantioselectivity.

Experimental Section

General. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Varian Mercury 400 Plus instrument with TMS as internal standard for ^{1}H NMR, and $CDCl_3$ for ^{13}C NMR. $CFCl_3$ served as an internal standard for ^{19}F NMR. High-performance liquid chromatography (HPLC) was conducted on an Agilent 1100 liquid chromatograph; HPLC analysis using Diacel chiralcel OD-H column. The urea-containing quaternary ammonium salt **1** was prepared according to reference 8, in optical purity of 99.7% by recrystallization from EtOH / EtOAc.

Preparation of catalyst 3

A solution of **1** (6 g, 10 mmol) and NaOH (440 mg, 11 mmol, 1 mol·L^{-1}) in C_2H_5OH (12 mL) was stirred at room temperature for 1.5 h. After adjusting the pH to 3 with aqueous HI solution (1 mol·L^{-1}), the mixture was concentrated to dryness under reduced pressure. Dry CH_2Cl_2 (10 mL) was added to the residue and stirred for 10 min. The solid was filtered off and washed well with more dry CH_2Cl_2. The organic phases were combined, and PEG 8000 (8 g, 1 mmol) and *p*-toluenesulfonic acid (0.14 g) was added. The mixture was placed in a pressure-resistant test tube provided with a magnetic stirring bar. The tube was sealed with a septum, placed in the CEM MW device, and subjected to MW irradiation using a power of 100W at 100 °C for 10 min. Upon completion of the reaction, cold diethyl ether (120 mL) was added to the mixture to precipitate the catalyst **3**. This was filtered off, thoroughly washed with ice-cold C_2H_5OH, and dried *in vacuo*. In this way 78 % of the polymer was converted to the desired product (purity of catalyst **3** was determined based on the iodine content, found to be 2.17% by Volhard's method).

General procedure for the asymmetric fluorination of *β*-keto esters. Aqueous K_3PO_4 (0.25 mL, 1.2 mmol, 2 mol·L^{-1}) was added to a mixture of β-keto ester **4** (1.0 mmol) and catalyst **3** (0.12g, 0.01 mmol) or catalyst **1** (0.01g, 0.02 mmol) in *m*-xylene (10 mL) and the mixture was cooled to -10 °C. *N*-Fluorobisbenzenesulphonimide (NFSI, 0.38g, 1.2 mmol) was added portionwise over 1h, and the mixture was vigorously stirred for 48 h under an Ar atmosphere. The mixture was concentrated to *ca.* 3 mL under reduced pressure. Ten volumes (*ca.* 30 ml) of Et_2O were slowly added to the residue with stirring. The crystalline polymer was collected by filtration, washing and drying *in vacuo*, and reused for later reactions. All the filtrate was concentrated under reduced pressure and purified by silica gel column chromatography to give the products **5a-g** in the reported yields.

2-Fluoro-1-oxoindan-2-carboxylic acid *tert*-butyl ester (5a). Colourless oil; R_f 0.4, hexane / EtOAc 10:1; $[a]_D^{25}$ +3.2° (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* 7.6 Hz, 1H), 7.67 (t, *J* 7.6 Hz, 1H), 7.48 (d, *J* 7.4 Hz, 1H), 7.44 (t, *J* 6.8 Hz, 1H), 3.71 (dd, *J* 17.6, 10.9 Hz,

1H), 3.37 (dd, *J* 22.8, 17.6 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8 (d, *J* 17.9 Hz), 166.0 (d, *J* 27.9 Hz), 150.9 (d, *J* 3.5 Hz), 136.5, 133.5, 128.4, 126.4, 125.5, 94.3 (d, *J* 202.1 Hz), 84.2, 38.3 (d, *J* 24.1 Hz), 27.8; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ –162.6 (dd, *J* 22.8, 10.8 Hz); The enantiomeric excess was determined to be 85% by HPLC (Chiralcel OD-H, i-PrOH / hexane 1 / 200, 1.0mL / min, 254 nm), t_{minor} 24.9 min, t_{major} 32.3 min; HRMS (ESI) Calcd for $C_{14}H_{15}FO_3$ $[M+NH_4]^+$ 268.1345, found 268.1348.

2-Fluoro-1-oxoindan-2-carboxylic acid methyl ester (5b). White solid, mp 78–81 °C (EtOAc/hexanes); R_f 0.3, hexane / EtOAc 5:1; $[\alpha]_D^{25}$ -27.1° (c 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* 7.6 Hz, 1H), 7.70 (t, *J* 7.6 Hz, 1H), 7.48 (m, 2H), 3.82 (m, 3H), 3.80 (dd, *J* 17.5, 11.7 Hz, 1H), 3.42 (dd, *J* 23.3, 11.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2 (d, *J* 18.1 Hz), 167.7 (d, *J* 27.6 Hz), 150.9 (d, *J* 3.8 Hz), 136.7, 133.1, 128.7, 126.6, 125.7, 94.6 (d, *J* 201.9 Hz), 53.2, 38.2 (d, *J* 23.0 Hz); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -165.7 (dd, *J* 23.0, 11.2 Hz); The enantiomeric excess was determined to be 72% by HPLC (Chiralcel OD-H, i-PrOH / hexane 5 / 95, 1.0mL / min, 254 nm), t_{major} 28.0 min, t_{minor} 36.3 min; HRMS (ESI) Calcd for $C_{11}H_9FO_3$ $[M+H]^+$ 209.0608, found 209.0611.

5-Bromo-2-fluoro-1-oxoindan-2-carboxylic acid *tert*-butyl ester (5c). Colourless oil; R_f 0.37, hexane / EtOAc 4:1; $[a]_D^{25}$ -28.2°(c 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.69 (m, 2H), 7.66-7.57 (m, 1H), 3.75 (dd, *J* 17.6, 11.1 Hz, 1H), 3.38 (dd, *J* 23.0, 17.7 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0 (d, *J* 18.6 Hz), 165.9 (d, *J* 29.8 Hz), 153.0 (d, *J* 3.8 Hz), 132.5 (d, *J* 1.3 Hz), 132.1, 132.0, 129.9 (d, *J* 1.1 Hz), 126.8, 94.5 (d, *J* 201.6 Hz), 84.5, 38.0 (d, *J* 24.8 Hz), 27.9; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -163.5 (dd, *J* 22.5, 11.3 Hz); The enantiomeric excess was determined to be 84% by HPLC (Chiralcel OD-H, i-PrOH / hexane 5 / 95, 1.0mL / min, 254 nm), t_{major} 12.2 min, t_{minor} 14.1 min; HRMS (ESI) Calcd. for $C_{14}H_{14}BrFO_3$ $[M+NH_4]^+$ 346.0448, Found 346.0451.

6-tert-Butyl-2-fluoro-1-oxoindan-2-carboxylic acid *tert*-butyl ester (5d). Pale yellow oil; R_f 0.4, hexane / EtOAc 5:1; $[a]_D^{25}$ +9.9°(c 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.69 (m, 1H), 7.73 (d, *J* 7.5 Hz, 1H), 7.40 (d, *J* 7.5 Hz, 1H), 3.77 (dd, *J* 17.0, 11.1 Hz, 1H), 3.38 (dd, *J* 23.0, 17.7 Hz, 1H), 1.46 (s, 9H), 1.37(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.9 (d, *J* 16.6 Hz), 167.0 (d, *J* 27.5 Hz), 152.1, 148.9 (d, *J* 3.8 Hz), 134.5, 133.4, 126.0, 122.0, 95.0 (d, *J* 200.1 Hz), 84.2, 38.2 (d, *J* 23.8 Hz), 35.0, 31.1, 28.0; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ-164.3 (dd, *J* 23.0, 11.2 Hz); The enantiomeric excess was determined to be 70% by HPLC (Chiralcel OD-H, i-PrOH / hexane 5 / 95, 1.0mL / min, 254 nm), t_{major} 7.5 min, t_{minor} 8.1 min; HRMS (ESI) Calcd. for $C_{18}H_{23}FO_3$ (M^+) 324.1969, found 324.1971.

2-Fluoro-1-oxotetralone-2-carboxylic acid *tert*-butyl ester (5e). Colourless oil; R_f 0.16, hexane / EtOAc 1:8; $[\alpha]_D^{20}$ +6.4°(c 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08-8.07 (m, 1H), 7.58-7.54 (m, 1H), 7.38-7.36 (m, 1H), 7.29 (t, *J* 7.5 Hz, 1H), 7.20 (d, *J* 7.5 Hz, 1H), 2.93-3.19 (m, 2H),2.48-2.30 (m, 1H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5 (d, *J* 19.0 Hz), 166.8 (d, *J* 26.0 Hz), 153.1, 134.6, 130.4, 128.7, 128.4, 125.2, 94.3 (d, *J* 192.8 Hz), 84.5, 38.0, 28.1, 21.8; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -163.6 (dd, *J* 19.4, 11.0 Hz); The enantiomeric excess was determined to be 73% by HPLC (Chiralcel OD-H, i-PrOH / hexane 8 / 92, 1.0mL /

min, 254 nm), t_{major} 10.6 min, t_{minor} 11.7 min; HRMS (ESI) Calcd for $C_{15}H_{17}FO_3$ $[M+NH_4]^+$ 282.1500, found 282.1510.

2-Fluoro-1-oxocyclopentane-2-carboxylic acid *tert*-butyl ester (5f). Colourless oil; R_f 0.3, hexane / EtOAc 4:1; $[\alpha]_D^{20}$ +44.4°(c 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62-2.43 (m, 3H), 2.40-2.20 (m, 1H), 2.21-2.01 (m, 2H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4 (d, *J* 17.4 Hz), 167.5 (d, *J* 27.3 Hz), 94.8 (d, *J* 199.8 Hz), 84.0, 35.6, 33.8 (d, *J* 21.0 Hz), 27.7, 18.0 (d, *J* 4.0 Hz); ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -165.8(dd, *J* 22.0, 16.5 Hz); The enantiomeric excess was determined to be 79% by HPLC (Chiralcel OD-H, i-PrOH / hexane 5 / 95, 1.0mL / min, 254 nm), t_{minor} 8.6 min, t_{major} 9.9 min; HRMS (ESI) Calcd for $C_{10}H_{15}FO_3$ $[M+NH_4]^+$ 220.1344, found 220.1350.

2-Fluoro-2-methyl-3-oxo-3-phenylpropanoic acid ethyl ester (5g). Colourless oil; R_f 0.5, hexane / EtOAc 20:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.72 (m, 5H), 4.29-4.22 (m, 2H), 1.90-1.85 (m, 3H), 1.20-1.17(m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7 (d, *J* 20.3 Hz), 168.5 (d, *J* 24.1 Hz), 133.8, 133.3, 130.9, 129.9, 129.7, 129.6, 128.9, 90.9 (d, *J* 197.5 Hz), 62.5,13.8; ^{19}F NMR ($CDCl_3$, 376.5 MHz) δ -148.2 (dd, *J* 22.2, 11.3 Hz) ; The enantiomeric excess was determined to be 23% by HPLC (Chiralcel OD-H, i-PrOH / hexane 10 / 90, 1.0mL / min, 254 nm), t_{major} 14.36 min, t_{minor} 16.39 min; HRMS Calcd for $C_{13}H_{13}FO_3$ 224.0850, found 224.0849.

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