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Enantioselective Fluorination of β-Ketoesters Catalyzed by Chiral Sodium Phosphate: Remarkable Enhancement of Reactivity by Simultaneous Utilization of Metal Enolate and Metal Phosphate

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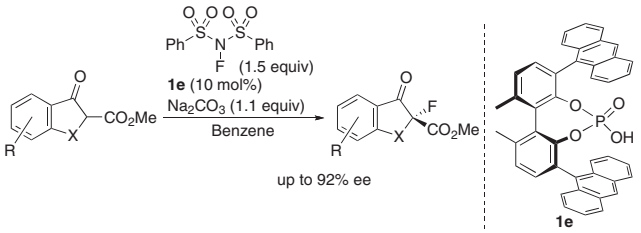
A highly enantioselective fluorination of β-ketoesters catalyzed by chiral sodium phosphate is achieved. In this process, the simultaneous formation of sodium enolate and sodium phosphate under basic conditions is the key to achieving excellent selectivity. Indanone derivatives as well as benzofuranone derivatives could be employed in this reaction to afford the fluorinated adducts in good yields with good to excellent enantioselectivities.

Because of the increasing importance of fluorinated compounds in pharmaceuticals and pesticides, the introduction of fluorine atoms in organic molecules has attracted much interest in recent years.[1] In particular, there have been numerous moves to develop a variety of enantioselective reactions.[2]

The catalytic enantioselective fluorination of β-ketoesters was achieved by Hintermann and Togni in 2000.[3] Although excellent enantioselectivity was accomplished with the Ti-TADDOL catalyst (90% ee), only one substrate with an extremely bulky 2,4,6-triisopropylphenylmethyl ester was presented in their report. Recent advances in metal-catalyzed asymmetric reactions have furthered the applicability of substrates.[4] One of the limitations, however, is that bulky *t*-butyl or adamantyl esters have to be employed most of the time to achieve excellent enantioselectivity as methyl ester yields moderate to low selectivity.

In contrast to the progress made in metal-catalyzed reactions, the asymmetric fluorination reaction that employs an organocatalyst still has much room for improvement.[5–7] The first organocatalytic enantioselective fluorination of β-ketoesters was developed by Park and Kim,[5a] in which cinchona alkaloids worked as a phase-transfer catalyst to afford α-fluoro β-ketoesters in excellent yields with moderate enantioselectivities. Quite recently, Maruoka (chiral quaternary ammonium phase-transfer catalyst)[5c] and Hu (chiral thiourea catalyst)[5d] independently developed a highly enantioselective fluorination reaction of β-ketoesters. As regards chiral phosphoric acid catalysis,[8,9] Inanaga's group developed a chiral scandium perfluorobinaphthyl phosphate-catalyzed asymmetric reaction of β-ketoesters, in which moderate to good selectivities were achieved.[10] Except for the work of Hu and Inanaga, excellent selectivity could be achieved with only a bulky *t*-butyl group on the ester moiety and hence, there is a great demand for the development of a new method that is able to use a large variety of substrates.

We wish to report herein an asymmetric fluorination reaction catalyzed by in situ generated chiral sodium phosphate derived from chiral phosphoric acid (Scheme 1).[11] Two active species (sodium enolate and sodium phosphate) were formed simultaneously under basic conditions and the corresponding



Scheme 1. Enantioselective fluorination of β-ketoesters catalyzed by chiral phosphoric acid.

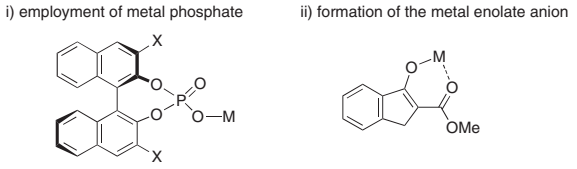
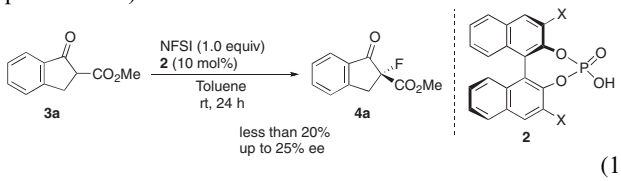


Figure 1. Two solutions for enhancing reactivity.

α-fluoro β-ketoesters, including methyl, ethyl, and benzyl esters, were obtained in excellent yields with good to excellent enantioselectivities.

In our initial examination conducted with chiral phosphoric acid **2** as the catalyst, we found that phosphoric acid itself is not sufficient to achieve the desired reaction. In spite of our exhaustive investigations that were aimed at achieving high selectivities, desired fluorinated adduct **4a** was obtained in modest chemical yield with low selectivity (less than 20% yield, up to 25% ee).

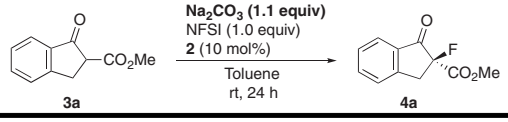


(1)

To overcome this daunting reactivity issue, improvement of both catalytic ability and substrate reactivity is required. Based on the reports of Ishihara[12] and Antilla[13] on the enantioselective reaction catalyzed by a chiral metal phosphate, we hypothesized that the following two solutions would meet our purpose (Figure 1): (1) employment of a metal phosphate in place of phosphoric acid itself and (2) formation of a metal enolate anion. We anticipated that the concomitant employment of these two species would lead to a dramatic enhancement of reactivity.

The simplest way to simultaneously form the above-mentioned two active species is to add a slight excess (1.1 equiv) of an inorganic base to the reaction mixture. As expected, the

Table 1. Screening for catalysts under basic conditions[a]



3a 4a

Entry	X	Yield/%	ee/%[b]
1	2,4,6-(*i*Pr)$_3$C$_6$H$_2$ (**2a**)	77	20
2	3-CF$_3$-4-NO$_2$C$_6$H$_3$ (**2b**)	97	7
3	3,4,5-(MeO)$_3$C$_6$H$_2$ (**2c**)	84	0
4	SiPh$_3$ (**2d**)	78	9
5	9-anthryl (**2e**)	87	77
6	9-anthryl (**1e**)	76	−79
7[c]	9-anthryl (**1e**)	96	−90

[a]Unless otherwise noted, all reactions were performed with 0.20 mmol β-ketoester **3**, 0.20 mmol NFSI, 0.22 mmol Na_2CO_3, and 10 mol % **2** in toluene (2.0 mL) at room temperature. [b]Enantiomeric excess was determined with a chiral stationary phase. [c]Benzene was employed as the reaction solvent.

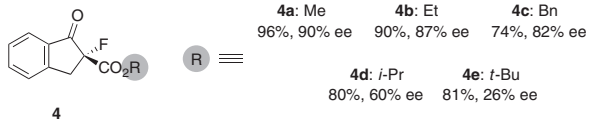


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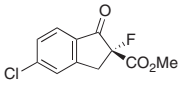
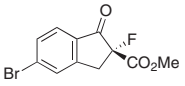
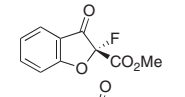
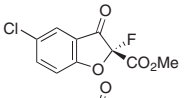
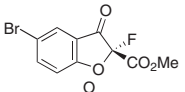
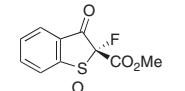
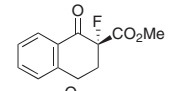
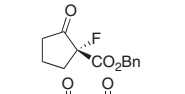
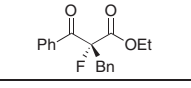
Figure 2. Effect of the ester group.

addition of Na_2CO_3 significantly improved the chemical yield (Table 1). Corresponding product **4a** was obtained in good to excellent chemical yields in all cases (≥76%). Fortunately, phosphoric acid **2e** bearing a 9-anthryl group dramatically improved the selectivity to 77% ee (87% yield, Entry 5). A slight improvement in selectivity was observed with (*S*)-biphenyl-type catalyst **1e** (76% yield, −79% ee, Entry 6). Changing the reaction solvent from toluene to benzene improved the selectivity markedly and corresponding adduct **4a** was obtained in 96% yield with −90% ee (Entry 7).[14,15]

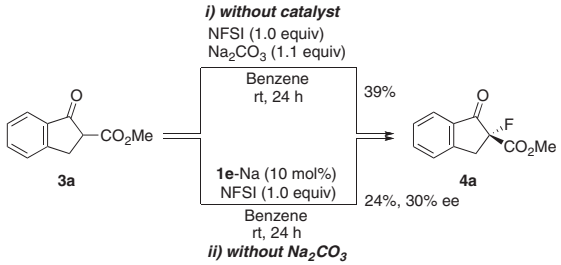
Next, we sought to examine the applicability of this reaction. A survey of the ester group revealed that a small ester group was suitable for this asymmetric reaction (Figure 2). High selectivities were achieved when substrates with ethyl and benzyl esters were employed (87% ee in **4b**, 82% ee in **4c**, respectively). On the other hand, sterically hindered isopropyl and *t*-butyl esters led to low selectivities (≤60% ee). These results suggest that our fluorination reaction may be used together with hitherto reported methods, in which a bulky ester group (such as *t*-butyl ester) exhibited excellent selectivity.

Table 2 lists the results of further examination of the substrate scope. Here we find that the substituents on the aromatic ring have an almost negligible effect on the reaction. The obtained fluorinated adducts **4f** and **4g** with chloro and bromo atoms at 5-position had good to excellent selectivities (89% ee and 70% ee, respectively, Entries 1 and 2). This method could be applied to ketoesters derived from salicylic acid to afford corresponding adducts **4h**–**4j** in good yields with excellent selectivities (88–92% ee, Entries 3–5). Good selectivity was also observed in thio-analogue **4k** (75% ee, Entry 6). In contrast to the favorable results gained with the five-membered ring substrates, 6-membered ring substrate **3l** gave a product

Table 2. Substrate scope[a]

Entry	Product		Time /h	Yield /%	ee /%[b]
1		**4f**	48	92	89
2		**4g**	27	92	70
3		**4h**	26	98	88
4		**4i**	37	85	92
5		**4j**	37	90	91
6		**4k**	42	48	75
7		**4l**	33	98	42
8		**4m**	44	63	33
9		**4n**	48	7	29

[a]Unless otherwise noted, all reactions were performed with 0.20 mmol β-ketoester **3**, 0.20 mmol NFSI, 0.22 mmol Na_2CO_3, and 10 mol % **1e** in benzene (2.0 mL) at room temperature. [b]Enantiomeric excess was determined with a chiral stationary phase.



Scheme 2. Effect of metal phosphate and metal enolate.

with decreased selectivity (42% ee, Entry 7). This is possibly due to the loss of structural rigidity compared with indanone derivatives. Further examination revealed that both the aromatic ring and the ketoester ring structure are important to achieve high selectivity: both benzyl 2-oxocyclopentanecarboxylate (**3m**) and methyl 2-benzyl-3-oxo-3-phenylpropanoate (**3n**) resulted in low selectivity (33% ee and 29% ee, respectively, Entries 8 and 9).[16]

As we have expected, the simultaneous formation of metal phosphate and metal enolate is crucial for this reaction (Scheme 2). A low chemical yield was observed in the absence of a phosphoric acid catalyst (39%, 24 h). When the reaction was conducted without Na_2CO_3 (sodium phosphate of **1e** was

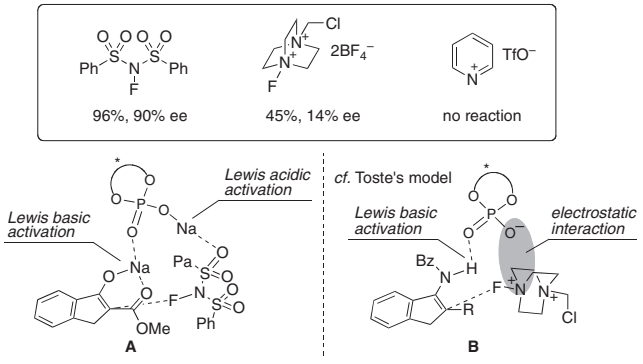


Figure 3. Examination of fluorinating reagent and proposed transition state model.

prepared in situ), corresponding adduct **4a** was obtained in 24% yield with 30% ee.

Quite recently, Toste's group achieved a chiral sodium phosphate-catalyzed enantioselective fluorination of enamide derived from indanone under almost identical reaction conditions to our method (*ent*-**2a**, Selectfluor®, Na_2CO_3, hexane, room temperature).[11b] However, desired compound **4a** was obtained in low yield with very low enantioselectivity (45%, 14% ee) with Selectfluor® under our optimum conditions. In addition, the reaction did not proceed to completion when *N*-fluoropyridinium triflate was used.[10] These results clearly indicate that the transition state of the present reaction is totally different from that of Toste's group (**B** in Figure 3). Based on the above arguments, we assumed that our fluorination reaction would proceed via twelve-membered ring transition state model **A** as shown in Figure 3, wherein sodium phosphate worked as a bifunctional catalyst [(1) Lewis basic activation of sodium enolate moiety by phosphoryl oxygen and (2) Lewis acidic activation of sulfonyl group of NFSI by sodium atom of phosphate moiety].

In summary, a highly enantioselective fluorination of β-ketoesters was achieved based on a chiral metal phosphate strategy. A variety of substrates derived from indanone and benzofuranone could be employed in this reaction to afford fluorinated adducts in good yields with good to excellent selectivities. Further investigation to develop novel reactions by use of the simultaneous formation of metal phosphate and metal enolate is under way in our laboratory.

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15 The absolute configuration of **4a** was determined by the comparison of optical rotation of the reported datum in ref 5c.

16 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

