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Asymmetric fluorination of β-keto esters catalyzed by chiral rare earth perfluorinated organophosphates

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Abstract—Novel chiral rare earth metal complexes bearing perfluorinated binaphthyl phosphate ligand RE[(*R*)-F_8BNP]$_3$ (RE = rare earth; F_8BNP = 5,5′,6,6′,7,7′,8,8′-octafluoro-1,1′-binaphthyl-2,2′-diyl phosphate) have been synthesized and used as a catalyst for the asymmetric electrophilic fluorination reaction of β-keto esters. The use of Sc[(*R*)-F_8BNP]$_3$ catalyst in combination with 1-fluoropyridinium triflate (NFPY–OTf) as a fluorinating agent was found to give the desired α-fluoro-β-keto esters in high chemical yields and enantiomeric excesses (up to 88% ee) under mild conditions.

1. Introduction

Chiral fluoroorganic compounds have attracted much attention in various fields such as biological, medicinal, and materials chemistry.[1] For example, such compounds bearing fluorine atoms, in particular at stereogenic centers, have been effectively utilized in the mechanistic study of enzymatic reactions and also in the synthetic study of artificial medicines with some special biological activities.[2] Thus, the development of efficient methods for the direct enantioselective construction of fluorinated stereogenic carbon centers has been strongly desired. Quite recently, some useful catalytic methods using electrophilic fluorinating reagents such as Selectfluor™ or *N*-fluorobenzenesulfonimide (NFSI) have been devised.[3–7] The first successful example of a catalytic asymmetric fluorination of β-keto esters was reported by Hintermann and Togni in 2000.[4a] They used sterically hindered esters as the substrates and Selectfluor™ as a fluorinating reagent in the presence of a chiral Lewis acid catalyst [$TiCl_2$(TADDOLato)] to obtain the α-fluorinated compounds with up to 90% ee and high yields. Kim and Park also reported a successful result (69% ee), in which the chinchonine-derived quaternary ammonium salt and NFSI were employed as the effective catalyst and the fluorinating agent, respectively.[4d] In 2002, remarkable progress was brought about by Sodeoka et al. They reported that certain cationic Pd–BINAP complexes could work quite effectively as a catalyst for the asymmetric fluorination of various cyclic and acyclic β-keto esters with NFSI to attain high enantioselectivities (up to 94% ee).[4e] Furthermore, the fluorination system was successfully applied to the reaction in ionic liquids, and the catalyst could be reused 10 times without losing its high activity.[4f] More recently, some other useful methods using NFSI in the presence of bis(oxazoline)–Cu(II) or –Ni(II) catalysts have been reported.[4g–j]

As described above, useful protocols for the catalytic asymmetric α-fluorination of β-keto esters have rapidly been accumulated. However, they have some drawbacks including poor substrate-generality and the use of expensive fluorinating reagents, thus, the development of more general and practical methods is still desired. In the present study, we examined the possibility of some chiral rare earth complexes acting as a Lewis acid catalyst for the enantioselective fluorination of β-keto esters. Previously, we found that the chiral rare earth organophosphates, RE[(*R*)-BNP]$_3$, where RE = Sc or Yb and BNP = 1,1′-binaphthyl-2,2′-diyl phosphate, effectively act as a novel and storable chiral Lewis acid catalyst for the hetero-Diels–Alder reaction of aldehydes or α-keto esters with Danishefsky's diene,[8] and also for

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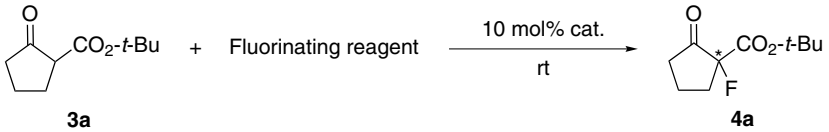
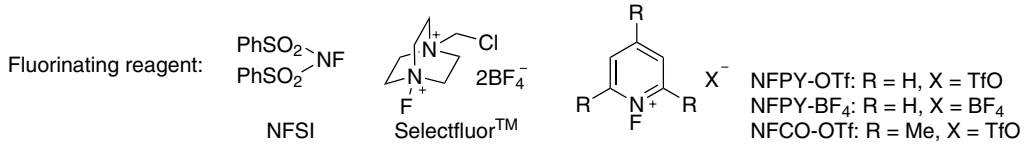
Table 1. Effect of the reaction conditions on the M[(*R*)-F_8BNP]$_3$-catalyzed asymmetric fluorination[a]



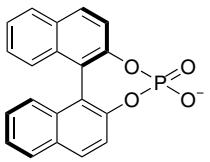
3a **4a**



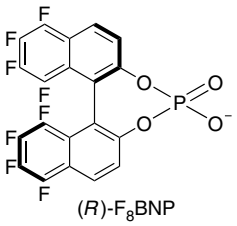
Entry	Catalyst	F-source	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	Sc[(*R*)-F_8BNP]$_3$	NFSI	CH_2Cl_2	24	85	39 (−)
2	Sc[(*R*)-F_8BNP]$_3$	Selectfluor™	CH_2Cl_2	48	7	ND[d]
3	Sc[(*R*)-F_8BNP]$_3$	NFPY–OTf	CH_2Cl_2	5	99	40 (−)
4	Sc[(*R*)-F_8BNP]$_3$	NFPY–OTf	CH_3CN	6	96	33 (−)
5	Sc[(*R*)-F_8BNP]$_3$	NFPY–OTf	THF	6	13	53 (−)
6	Sc[(*R*)-F_8BNP]$_3$	NFPY–OTf	Et_2O	6	76	60 (−)
7	Sc[(*R*)-F_8BNP]$_3$	NFPY–OTf	Toluene	6	99	79 (−)
8[e]	Sc[(*R*)-F_8BNP]$_3$	NFPY–OTf	Toluene	48	94	84 (−)
9[f]	Sc[(*R*)-F_8BNP]$_3$	NFPY–OTf	Toluene	24	12	84 (−)
10	Sc[(*R*)-F_8BNP]$_3$	NFPY–OTf	Hexane	6	52	43 (−)
11	Sc[(*R*)-F_8BNP]$_3$	NFPY–BF_4	Toluene	6	12	54 (−)
12	Sc[(*R*)-F_8BNP]$_3$	NFCO–OTf	Toluene	6	40	15 (−)
13	La[(*R*)-F_8BNP]$_3$	NFPY–OTf	Toluene	6	Trace	ND[d]
14	Gd[(*R*)-F_8BNP]$_3$	NFPY–OTf	Toluene	6	9	12 (+)
15	Yb[(*R*)-F_8BNP]$_3$	NFPY–OTf	Toluene	6	24	14 (+)
16	In[(*R*)-F_8BNP]$_3$	NFPY–OTf	Toluene	6	18	5 (+)
17	Sc[(*R*)-BNP]$_3$	NFPY–OTf	Toluene	6	57	11 (+)

[a] The reactions were carried out by using 1.2 equiv of the fluorinating reagents in the presence of 10 mol % of the catalysts at room temperature unless otherwise stated.
[b] Isolated yield.
[c] Enantiomer excess of **4a** was determined by HPLC analysis [DAICEL CHIRALPAK AD-H, 2-propanol–hexane (1:100), 0.4 mL/min, 300 nm, t_R (major) = 21.2 min, t_R (minor) = 25.9 min]. The sign of the optical rotation is shown in parentheses.
[d] Not determined.
[e] The reaction was carried out at 0 °C.
[f] The reaction was carried out at −20 °C.

the Michael addition reaction of *O*-alkylhydroxylamines to α,β-unsaturated ketones.[9] Subsequently, we first examined the efficacy of the scandium catalyst Sc[(*R*)-BNP]$_3$ for the present fluorination reaction, however, the reaction proceeded very slowly and the enantioselectivity was low (e.g., see entry 17 in Table 1). To improve this situation, we designed and prepared new chiral rare earth octafluorobinaphthyl phosphates, RE[(*R*)-F_8BNP]$_3$, which are expected to have stronger Lewis acidity than the corresponding non-fluorinated complex RE[(*R*)-BNP]$_3$, because F_8BINOL is reported to be more acidic than BINOL (pK'_a = 9.28 for F_8BINOL vs 10.28 for BINOL).[10] We report here a new and economical method using Sc[(*R*)-F_8BNP]$_3$ catalyst and 1-fluoropyridinium triflate (NFPY–OTf) for the enantioselective fluorination of β-keto esters.



(*R*)-BNP

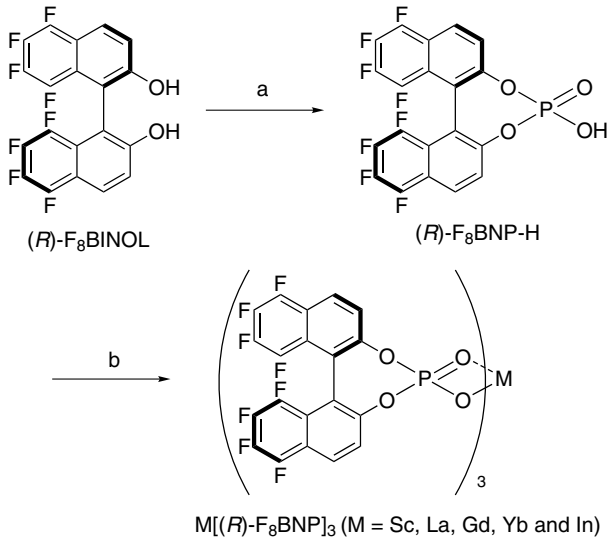


(*R*)-F_8BNP

2. Results and discussion

Enantiopure (*R*)- and (*S*)-F_8BINOL were synthesized according to the literature with a slight modification.[10a] The phosphorylation of (*R*)-F_8BINOL using phosphoryltrichloride and triethylamine in THF at 0 °C gave the corresponding chlorophosphate, which was then hydrolyzed by water in the same flask to yield the hydrogen phosphate (*R*)-F_8BNP–H as a colorless solid (Scheme 1). This compound was found to be more soluble than the corresponding non-fluorinated derivative [(*R*)-BNP–H] in common organic solvents such as THF, and it could be easily purified by recrystallization from hexane–THF. The enantiopure (*R*)-F_8BNP–H was first treated with 2% aqueous Na_2CO_3 and the resulting sodium salt was mixed with various trivalent metal chlorides (MCl_3; M = Sc, La, Gd, Yb, and In) in a 3:1 ratio and stirred at 60 °C in aqueous methanol for 19 h to yield the corresponding metal complexes M[(*R*)-F_8BNP]$_3$ as white solids.[11] They were collected by filtration, washed with water and aqueous MeOH, and then dried at 100 °C under reduced pressure before use.

The effectiveness of these novel Lewis acid catalysts, M[(*R*)-F_8BNP]$_3$, was checked by performing the

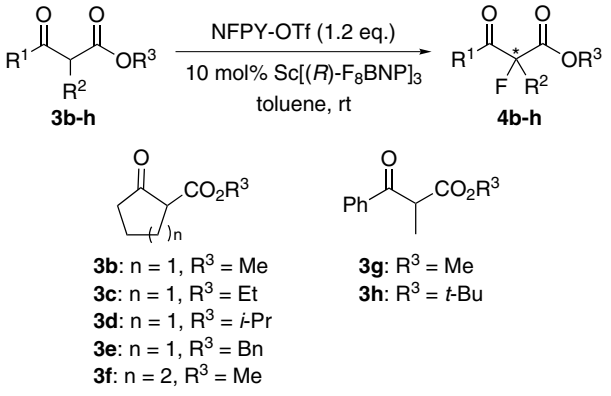


Scheme 1. Reagents and conditions: (a) $POCl_3$ (2 equiv), Et_3N (3 equiv), THF, 0 °C; H_2O, 80%; (b) 2% Na_2CO_3 aq, $MCl_3{\cdot}nH_2O$ ($n = 4$, 6, or 7) [(*R*)-F_8BNP–Na/MCl_3 = 3.5:1], MeOH/H_2O, 60 °C.

catalytic asymmetric fluorination of *tert*-butyl 2-oxocyclopentanecarboxylate **3a** with various fluorinating reagents under various conditions. Some of the results are summarized in Table 1. The reactions were carried out by using 10 mol % M[(*R*)-F_8BNP]$_3$ and 1.2 equiv of the fluorinating reagents at room temperature. The fluorination using the Sc[(*R*)-F_8BNP]$_3$ catalyst and NFSI in CH_2Cl_2 proceeded slowly to give, after 24 h, the desired α-fluoro-β-keto ester **4a** in 85% yield with 39% ee (entry 1). Selectfluor™ was found to be an unsuitable fluorinating reagent for the present catalytic reaction (entry 2). Fortunately, when NFPY–OTf was used, the reaction proceeded rapidly and the product was obtained in quantitative yield although the enantioselectivity was not satisfactory (entry 3). Screening of the reaction conditions revealed that toluene is the solvent of choice (entry 7) and when the Sc[(*R*)-F_8BNP]$_3$ catalyzed reaction was conducted at 0 °C, the desired product was obtained in high enantioselectivity (84% ee) and chemical yield (94%) (entry 8). The reaction performed at −20 °C did not improve the enantioselectivity (entry 9) and the use of other 1-fluoropyridinium salts (NFPY–BF_4 or NFCO–OTf) brought about unsatisfactory results (entries 11 and 12). As seen in entries 13–16, other metal complex catalysts were less effective than Sc[(*R*)-F_8BNP]$_3$. The importance of the octafluorinated BNP ligand (F_8BNP) is apparent from the result of the Sc[(*R*)-BNP]$_3$ catalyzed reaction (entry 17).

The optimized reaction conditions were applied to the reactions of a variety of β-keto esters (Table 2).[12] As shown in entries 1–4, various 2-oxo-cyclopentanecarboxylates **3b–d** were successfully converted to the corresponding α-fluoro-β-keto esters **4b–d** in good yields and high stereoselectivities except for the case of benzyl ester **3e** where unexpectedly low enantioselectivity was observed (entry 5). It should be noted that the most commonly used methyl ester **3b** can be an effective substrate, thus giving the desired product with 88% ee in

Table 2. The Sc[(*R*)-F_8BNP]$_3$-catalyzed fluorination of various β-keto esters[a]



Entry	Substrate	Time (h)	Yield[b] (%)	ee[c] (%)
1	**3b**	6	97	84 (−)
2[d]	**3b**	24	94	88 (−)
3	**3c**	6	87	76 (−)
4	**3d**	6	90	74 (−)
5	**3e**	6	87	47 (−)
6[e]	**3f**	48	77	81 (−)
7	**3g**	24	63	75 (+)
8	**3h**	48	16	78 (+)

[a] The reaction was carried out by using 1.2 equiv of 1-fluoropyridinium triflate (NFPY–OTf) and 10 mol % of the catalyst in toluene at room temperature unless otherwise stated.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] The reaction was carried out in presence of 20 mol % of the catalyst at 0 °C.
[e] The reaction was carried out at 0 °C.

94% yield when the reaction was carried out at 0 °C in the presence of 20 mol % of the catalyst (entry 2). Similarly, methyl 2-oxocyclohexanecarboxylate **3f** could be converted to the corresponding α-fluoro derivative with high enantioselectivity (81% ee) in good yield (entry 6). This is an advantageous point since, in existing methods, bulky esters such as *tert*-butyl esters are often required to realize such a high enantioselectivity. It is also

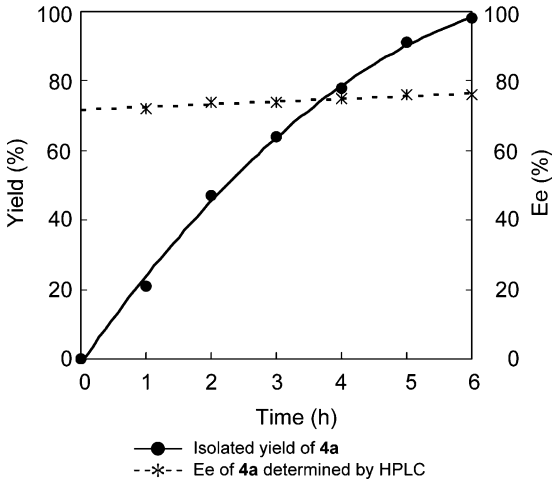


Figure 1. The time course of the yield and the enantiomeric excess of the product (c.f. entry 7 in Table 1).

important to note that the reactions of acyclic β-keto esters **3g** and **3h** showed comparable enantioselectivities to cyclic ones (entries 7 and 8).

In the present reaction, the production of pyridinium triflate increases as the fluorination reaction proceeds. Since contamination by the Brønsted acid-catalyzed nonasymmetric process was feared, the time course of the yield and the ee of the product was checked. As shown in Figure 1, the observed ee values are almost constant throughout the reaction suggesting that the scandium complex is the only catalytically active species.

3. Conclusion

A novel chiral rare earth perfluorinated binaphthyl phosphate, Sc[(*R*)-F_8BNP]$_3$, catalyzed the α-fluorination of either cyclic or acyclic β-keto esters with NFPY–OTf, thus producing the fluorinated quaternary stereogenic centers with high enantioselectivities (up to 88% ee). To the best of our knowledge, this is the first successful catalytic asymmetric fluorination using NFPY–OTf, which is commercially available, inexpensive and easy to handle. Thus, the protocol provides a new economical route to the synthesis of optically active α-fluoro-β-keto esters. The detailed mechanism of this reaction is now under investigation.

Acknowledgements

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11. The complexes were isolated as the corresponding hydrates. The detailed procedure and the physical data will be reported elsewhere.
12. *General procedure*: To a suspension of Sc[(*R*)-F_8BNP]$_3$ (15.7 mg, 0.01 mmol) and NFPY–OTf (29.6 mg, 0.12 mmol) in toluene (1 mL) was added a β-keto ester (0.1 mmol) at room temperature. After being stirred for a certain period of time, the whole mixture was passed through a short column of silica gel and eluted with ether. The eluate was then concentrated and purified by column chromatography on silica gel.