Asymmetric Catalysis

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Asymmetric Fluorination of α-Aryl Acetic Acid Derivatives with the Catalytic System $NiCl_2$–Binap/R_3SiOTf/2,6-Lutidine**

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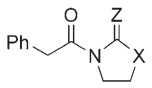
Dedicated to Professor Masakatsu Shibasaki on the occasion of his 60th birthday

As a reflection of the importance of organofluorine compounds in medicinal and agricultural chemistry and materials science,[1] catalytic asymmetric fluorination has been attracting increasing attention.[2,3] We and others have developed elegant systems for the catalytic asymmetric fluorination of carbonyl compounds, including β-ketoesters,[4] β-ketophosphonates,[5] cyanoacetates,[6] oxindoles,[7] and primary aldehydes.[8] In contrast, the preparation of chiral α-fluorocarboxylic acids has not been explored as thoroughly, even though such compounds have great potential in medicinal chemistry.[9] Only a few synthetically useful diastereoselective fluorination reactions of ester equivalents are known.[10,11] No catalytic method has been developed so far, probably owing to the difficulty in the in situ generation of metal enolates (or enols) of ester equivalents under catalytic conditions.

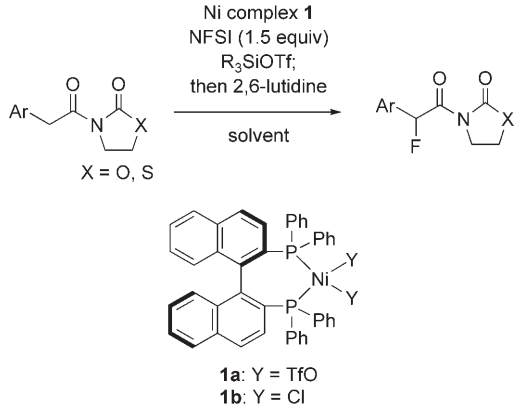
We reported recently a unique reaction in which tandem asymmetric fluorination–methanolysis of an *N*-Boc-protected oxindole yielded a chiral monofluorinated aryl acetate (Boc = *tert*-butoxycarbonyl).[12] To our knowledge, this reaction is the only catalytic asymmetric synthesis of an α-fluorinated ester through a fluorination reaction so far. However, the ester moiety was formed indirectly through opening of the oxindole ring; the structures of available starting materials are thus highly restricted. As the aryl acetic acid moiety is found in various important medicines, such as nonsteroidal anti-inflammatory drugs, the availability of chiral α-monofluorinated aryl acetic acids is expected to be useful for drug synthesis. As part of our research on the synthesis of chiral organofluorine compounds, we present herein a novel catalytic asymmetric fluorination of (2-aryl acetyl)thia- and oxazolidin-2-ones with the unique reaction system Ni^{II}–binap/R_3SiOTf/2,6-lutidine (Scheme 1; binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, Tf = trifluoromethanesulfonyl).

We first tested compounds **2**–**4**, expected to react via a bidentate metal enolate, in the fluorination reaction.[13]



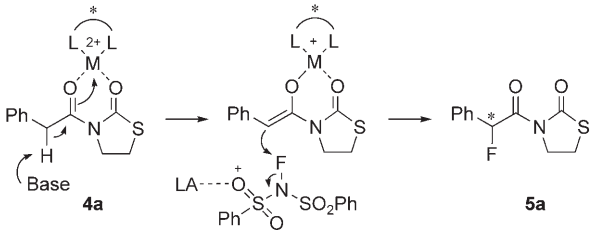
2: X = Z = S
3: X = O, Z = S
4a: X = S, Z = O
4b: X = Z = O

Although *N*-acyl thiazolinethiones were used successfully in a direct catalytic asymmetric aldol reaction,[14] **2** and the related compound **3** were found to be unstable in the presence of *N*-fluorobenzenesulfonimide (NFSI), probably owing to the high reactivity of the C=S group towards the electrophilic fluorine atom. In contrast, substrates **4a** and **4b** with an oxycarbonyl group were insensitive to NFSI. As we could not isolate the fluorinated product derived from **4b**, and one of the enantiomers of the product was inseparable from **4b** by HPLC on a chiral phase, we initially selected **4a** as a model compound.



Scheme 1. Catalytic asymmetric fluorination.

We anticipated that cooperative activation by a cationic metal complex and an organic base would promote the formation of a metal enolate from **4a** (Scheme 2)[15] and



Scheme 2. Concept for the catalytic fluorination of **4a**.

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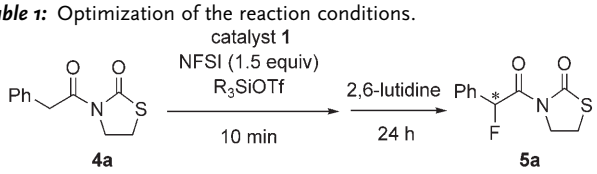
examined a variety of reaction conditions. We varied the metal complex, the organic base, the fluorine source, and the solvent. Unfortunately, however, no reaction occurred with any combination of reagents tested. Previously, we had observed that independent simultaneous activation of both the nucleophile and the electrophile is highly effective in promoting C–C bond-forming reactions.[16] We hypothesized that the desired fluorination reaction might occur if the NFSI reagent was activated strongly, even though the amount of the enolate formed in situ might be very small. Consequently, we examined the effect of supplementary Lewis acids (Scheme 2). It was expected that a chiral metal complex with two vacant binding sites would activate **4a** preferentially through bidentate complexation, whereas a monodentate secondary Lewis acid would interact with NFSI. A recent report by Evans and Thomson supported the validity of this idea.[17]

We tested several chiral metal complexes[18] and supplementary Lewis acids[19] and found that the concurrent use of the Ni^{II} complex **1a** and Me_3SiOTf was effective.[20] When Me_3SiOTf (1 equiv) was added as a supplementary Lewis acid, the reaction of **4a** proceeded smoothly in the presence of **1a** (10 mol%) and 2,6-lutidine (1 equiv) to afford the desired product **5a** in 99% yield with 28% *ee* (Table 1, entry 1). The

Table 1: Optimization of the reaction conditions.



Entry	Catalyst ([mol%])	R_3SiOTf [equiv] (R)	Base [equiv]	Solvent	*T* [°C]	Yield[a] [%]	*ee*[b] [%]
1	**1a** (10)	1 (Me)	1	CH_2Cl_2	RT[c]	99	28
2	**1a** (10)	1 (Me)	–	CH_2Cl_2	RT[c]	n.r.	–
3	**1a** (10)	–	3	CH_2Cl_2	RT[c]	n.r.	–
4	–	2 (Me)	3	CH_2Cl_2	RT[c]	85	–
5	**1a** (10)	1 (Me)	1	CH_2Cl_2	−20	64	68
6	**1a** (10)	1.5 (Me)	1.5	CH_2Cl_2	−20	90	68
7	**1b** (10)	1.5 (Me)	1.5	CH_2Cl_2	−20	95	68
8	**1b** (10)	1.5 (Et)	1.5	CH_2Cl_2	−20	99	70
9	**1b** (10)	1.5 (Et)	1.5	toluene	−20	99	88
10	**1b** (10)	0.5 (Et)	1.5	toluene	−20	98	88
11	**1b** (10)	0.25 (Et)	1.5	toluene	−20	77	86
12	**1b** (5)	0.75 (Et)	1.5	toluene	−20	99	88
13	**1b** (5)	0.5 (Et)	1.5	toluene	−20	96	86
14	**1b** (2.5)	0.5 (Et)	1.5	toluene	−20	91	76

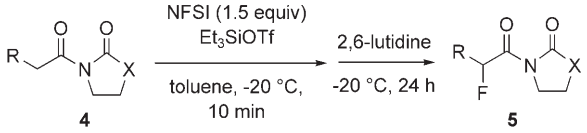
[a] Yield of the isolated product. [b] The *ee* value was determined by HPLC on a chiral phase. [c] Room temperature: 23–25 °C.

results shown in entries 2–4 of Table 1 indicate that the triad Ni^{II}/Me_3SiOTf/2,6-lutidine is necessary for high conversion and enantioselectivity. However, the observation that the fluorination reaction proceeds in the absence of the Ni complex (Table 1, entry 4) indicates that the low *ee* value of the product in entry 1 is associated with the spontaneous fluorination of the silyl enolate of **4a** generated in situ. When the reaction was carried out at −20 °C, the uncatalyzed racemic pathway was suppressed considerably, and the *ee* value of **5a** was improved to 68% (Table 1, entries 5 and 6). Interestingly, the neutral $NiCl_2$–binap complex **1b** could also be used as an effective catalyst precursor and gave comparable results (95%, 68% *ee*; Table 1, entry 7). Thus, the same active species appears to be operative in the reactions with **1a** and **1b**. The use of **1b** is convenient in practical terms, as **1b** is bench stable.

While the nonstereoselective reaction to give the racemic product was promoted by Me_3SiOTf and 2,6-lutidine in CH_2Cl_2 even at −20 °C, no reaction was observed in toluene. When Et_3SiOTf and toluene were used in the presence of **1b** and 2,6-lutidine, the reaction proceeded smoothly to give **5a** in quantitative yield with the highest enantioselectivity observed in this study (88% *ee*; Table 1, entry 9). It was possible to apply a substoichiometric amount of Et_3SiOTf (about 0.25 equiv; Table 1, entries 9–11), however, a stoichiometric amount of the base was required for a high chemical yield.[21,22] Furthermore, the quantity of the catalyst could be decreased to 5 mol% without significant deterioration of the reaction efficiency. A drop in the selectivity was finally observed when 2.5 mol% of **1b** was used (Table 1, entries 12–14). It is interesting that no formation of a difluorinated compound and no racemization of the monofluorinated product were observed in these reactions.[23]

With these optimized conditions established, we next examined the generality of this reaction. As shown in Table 2, the reaction is applicable to a variety of α-aryl acetic acid derivatives. The electronic nature of the aromatic ring did not appear to affect the reactivity of the *para*-substituted substrates **4c** and **4d**, which underwent the fluorination reaction smoothly with high enantioselectivity (Table 2, entries 2 and 3). When 5 mol% of **1b** was used, decreased chemical yield and enantioselectivity were observed with the

Table 2: Catalytic asymmetric fluorination.

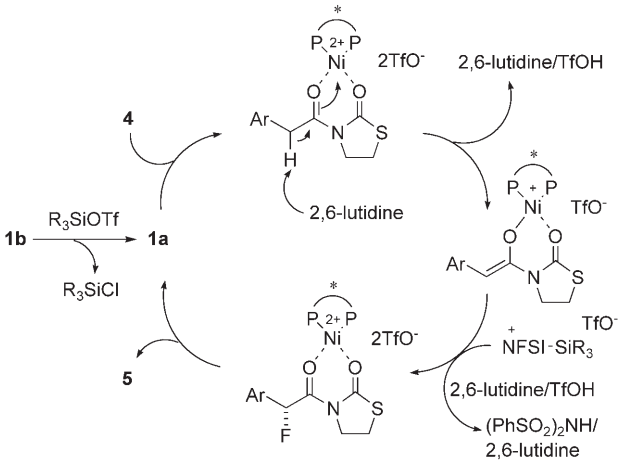


Entry	4	X	R	**1b** [mol%]	Et_3SiOTf [equiv]	Yield[a] [%]	*ee*[b] [%]
1	**4a**	S	Ph	5	0.75	99	88
2	**4c**	S	*p*-FC_6H_4	5	0.75	90	83
3	**4d**	S	*p*-$MeOC_6H_4$	5	0.75	92	81
4	**4e**	S	*m*-$MeOC_6H_4$	5	0.75	56	69
5	**4e**	S	*m*-$MeOC_6H_4$	10	1.5	95	82
6	**4f**	S	*o*-$MeOC_6H_4$	5	0.75	73	61
7	**4f**	S	*o*-$MeOC_6H_4$	10	1.5	87	78
8	**4g**	S	2-naphthyl	10	1.5	99	83
9	**4h**	S	1-naphthyl	5	0.75	94	87
10	**4b**	O	Ph	10	1.5	95	87
11[c]	**4i**	S	*n*-propyl	10	1.5	15	11

[a] Yield of the isolated product. [b] The *ee* value was determined by HPLC on a chiral phase. [c] The reaction was carried out at room temperature.

corresponding *ortho*- and *meta*-methoxy-substituted substrates (Table 2, entries 4 and 6), but satisfactory results were obtained when 10 mol% of the catalyst was used (entries 5 and 7). The reactions of the bulkier naphthyl-substituted substrates **4g** and **4h** also afforded the desired products in excellent yield with high enantioselectivity (Table 2, entries 8 and 9). Under these optimized conditions, **4b** was converted completely into the desired product **5b**, which was isolated in 95% yield with 87% *ee* (Table 2, entry 10). Unfortunately, however, this method for the catalytic asymmetric α-monofluorination of carboxylic acid derivatives is not applicable to (3-alkanoyl)thiazolin-2-ones, such as **4i**, probably as a result of their insufficient acidity (Table 2, entry 11).

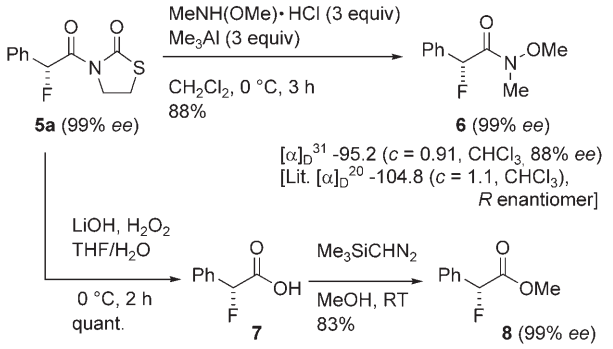
A plausible catalytic cycle is outlined in Scheme 3. ^{31}P NMR spectroscopic studies indicated that two Cl anions on the complex **1b** were replaced by TfO anions when **1b** was



Scheme 3. Proposed catalytic cycle.

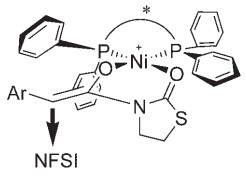
treated with excess R_3SiOTf.[23] The cationic complex **1a** formed in situ and 2,6-lutidine act cooperatively to give the chiral Ni enolate. This Ni enolate with the *Z* configuration reacts with NFSI, and the dissociation of the product from the Ni complex completes the catalytic cycle. ^{1}H and ^{19}F NMR spectroscopic studies showed an interaction between Et_3SiOTf and NFSI. Although the exact role of R_3SiOTf is unclear, it is likely that it enhances the electrophilicity of NFSI. Alternatively, R_3SiOTf might reduce the acidity of the substrate. However, a control experiment with the silyl enolate preformed in situ indicated that the silyl enolate was not involved in the reaction.[24] It appears that the formation of the Ni enolate is more favorable than the formation of the achiral silyl enolate. The putative role(s) of the supplementary Lewis acid in our system should be distinct from the action of Me_3SiOTf in the Evans aldol reaction, in which it is proposed to trap the nickel aldolate intermediate.[14]

Compound **5a** was converted into the Weinreb amide **6** according to a literature procedure (Scheme 4).[10b] The absolute configuration of **5a** was determined to be *R* by



Scheme 4. Transformation of **5a**.

comparing the optical rotation of **6** with the reported value. The sense of face selectivity observed in this reaction can be explained by postulating the involvement of the bidentate nickel enolate.[17]



To confirm the utility of our fluorination reaction, **5a** was converted into the corresponding carboxylic acid **7** (Scheme 4). The recrystallization of **5a** from CH_2Cl_2/Et_2O (1:9) yielded racemic prisms, and almost optically pure **5a** was obtained from the mother liquid (88%, 99% *ee*). When exposed to hydrolytic conditions, **5a** was converted quantitatively into the carboxylic acid **7**. To our delight, analysis of the corresponding methyl ester by HPLC on a chiral phase confirmed that no loss of optical purity had occurred.[25] For the synthesis of α-fluorocarboxylic acids, the organocatalytic fluorination of primary aldehydes is likely to be an appropriate choice. However, the conversion of the products into the corresponding acids has not yet been demonstrated, probably as a result of the instability of α-fluoroaldehydes.[8] Furthermore, chiral α-fluoroketones and 2-fluoroalcohols can be synthesized in principle from **5** and **6** according to the procedure of Davis and co-workers.[10] Thus, we expect the present methodology to be useful in providing a variety of optically active fluorine-containing compounds.

In summary, we have developed the first catalytic asymmetric fluorination reaction for ester equivalents. In the presence of a $NiCl_2$–binap/R_3SiOTf/2,6-lutidine triad, the monofluorinated compounds were formed with high enantioselectivity (88% *ee*) and up to 99% yield. Furthermore, the conversion of the fluorinated product into the corresponding carboxylic acid was achieved. Although the exact role of R_3SiOTf remains to be elucidated, we believe that the present three-component activation system has the potential for application to novel reactions. Further investigations into the substrate scope and reaction mechanism are in progress.

Experimental Section

Representative procedure: Compound **4a** (22 mg, 0.1 mmol), the nickel complex **1b** (3.8 mg, 0.005 mmol, 5 mol%), and NFSI (47.4 mg, 0.15 mmol) were placed in a dry reaction tube. Toluene (0.1 mL) and triethylsilyl triflate (17 μL, 0.75 equiv) were added at −20 °C under an atmosphere of dry nitrogen. After 10 min, 2,6-lutidine (18 μL, 0.15 mmol) was added, and the resulting mixture was stirred at −20 °C for 24 h. Saturated aqueous NaCl was then added to quench the reaction, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, the solvent was evaporated, and the crude product was purified by flash column chromatography (SiO_2, hexane/chloroform/ethyl acetate 5:1:1) to afford **5a** as a white solid. The *ee* value of the product was determined by HPLC on a chiral phase. $[\alpha]_D^{31} = -92.1$ ($c = 1.0$, $CHCl_3$; 82% *ee*); HPLC (Daicel Chiralcel AD-H, *n*-hexane/isopropyl alcohol 9:1, 1.0 mL min^{-1}, 254 nm): t_R(major) = 14.3 min, t_R(minor) = 16.5 min; IR (neat): $\tilde{\nu} = 2953$, 1687, 1358, 1286, 1240, 1178, 1154, 1067, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.25$–3.35 (m, 2H), 4.12–4.27 (m, 2H), 6.81 (d, $J = 48.5$ Hz, 1H), 7.37–7.41 (m, 3H), 7.51–7.53 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 25.6, 46.7, 89.6 (d, $J = 178.6$ Hz), 128.5 (d, $J = 5.0$ Hz), 128.8 (d, $J =$ 1.6 Hz), 130.0 (d, $J = 3.2$ Hz), 133.5 (d, $J = 19.8$ Hz), 168.1 (d, $J =$ 27.2 Hz), 172.5 ppm; ^{19}F NMR (376 Hz, $CDCl_3$, CF_3COOH): $\delta =$ −95.2 ppm (d, $J = 48.5$ Hz); FABMS (*m*-nitrobenzylalcohol): *m*/*z* 262 $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{11}H_{10}FNNaO_2S$: 262.0314 $[M+Na]^+$; found: 262.0311.

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[17] D. A. Evans, R. J. Thomson, *J. Am. Chem. Soc.* **2005**, *127*, 10506; $BF_3{\cdot}OEt_2$ (3 equiv) was used as an external activator to form an oxonium intermediate from methyl orthoformate.
[18] Metal–binap complexes of Pd^{II}, Pt^{II}, and Ag^{I} and metal–bisoxazoline complexes of Cu^{II}, Zn^{II}, Ni^{II}, Pd^{II}, and Pt^{II} gave almost racemic products under similar conditions.
[19] The reaction with Bu_2BOTf as a supplementary Lewis acid proceeded with no enantioselectivity, and the reaction with $BF_3{\cdot}OEt_2$ did not proceed at all.
[20] The nickel complexes used in these studies were prepared according to the procedure described by Evans and Thomson.[17]
[21] When 0.5 equivalents of 2,6-lutidine were used, the reaction did not proceed to completion: The product was formed in 42% yield with 43% *ee* when the reaction was carried out in CH_2Cl_2 at room temperature.
[22] The use of other bases, including Et_3N, iPr_2NEt, pyridine, and 2,6-di(*tert*-butyl)pyridine, led to less satisfactory results.
[23] Details of these experiments will be discussed in a full paper.
[24] The treatment of **4a** with Et_3SiOTf and 2,6-lutidine at room temperature gave the corresponding silyl enolate in 78% yield with 22% unchanged **4a**. When this reaction mixture was subjected to the fluorination conditions at −20 °C for 24 h, **5a** was obtained in 29% yield with 64% *ee*. The enantioselective

fluorination of the remaining **4a** and the uncatalyzed reaction of a small amount of the silyl enolate account for the observed low chemical yield and moderate enantioselectivity. If the formation of the silyl enolate and transmetalation are involved, a higher chemical yield and a comparable *ee* value should be observed.

[25] In contrast, when chiral 2-acyl oxazolidin-2-ones were used as substrates, the optical purity of the fluorinated compounds decreased considerably during hydrolysis.[10a]