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Asymmetric Dearomative Fluorination of 2-Naphthols with Dicarboxylate Phase-Transfer Catalyst

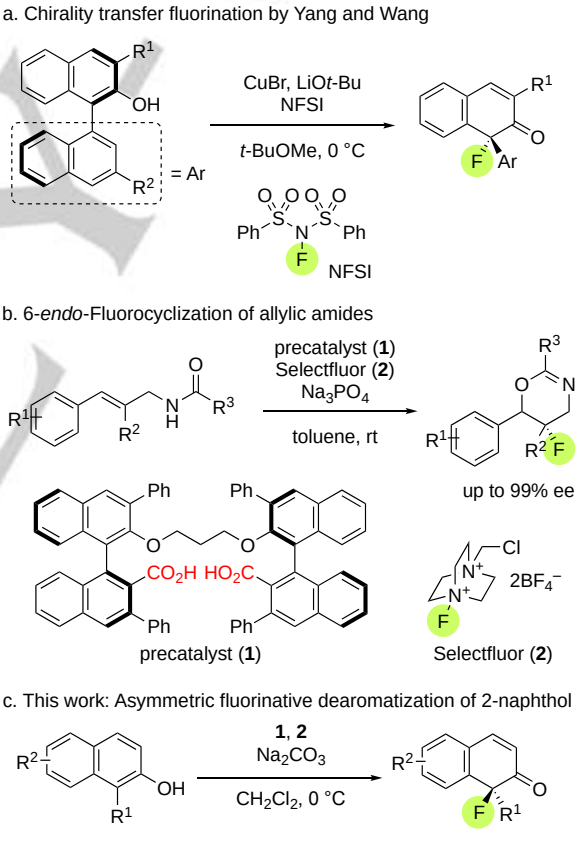
Hiromichi Egami, Taiki Rouno, Tomoki Niwa, Kousuke Masuda, Kenji Yamashita, and Yoshitaka Hamashima*

Abstract: A linked dicarboxylate phase-transfer catalyst enables smooth asymmetric dearomative fluorination of 2-naphthols with Selectfluor under mild conditions to give the corresponding 1-fluoronaphthalenone derivatives in a highly enantioselective manner. This reaction, which is compatible with various functional groups, is the first example of catalytic asymmetric fluorination of 2-naphthols, and is expected to be useful in the synthesis of bioactive molecules.

Organofluorine compounds have found widespread applications in the pharmaceutical and agrochemical sciences,[1] and various types of fluorinative transformations have been reported.[2] However, dearomative fluorination of electron-rich aromatic compounds has been less well studied.[3] Dearomatization is a versatile strategy for the construction of three-dimensional molecules, not only in biosynthesis, but also in synthetic organic chemistry, and considerable attention has been directed to the development of asymmetric dearomatization reactions.[4] In this context, 2-naphthol derivatives are expected to be useful substrates for dearomative fluorination, because the resulting naphthalenone framework containing a transformable conjugated enone unit is present in many naturally occurring bioactive compounds.[5]

Although Toste reported pioneering work on asymmetric dearomative fluorination of phenol derivatives (followed by dimerization via Diels-Alder reaction) using chiral phosphate phase-transfer catalysis,[6] the reaction system was not examined for 2-naphthols. In 2018, Yang and Wang reported copper-catalyzed chirality transfer-type fluorinative dearomatization of axially chiral 1-substituted 2-naphthols (Scheme 1a).[7] However, while various types of enantioselective dearomatization reactions of 2-naphthols[8] have been investigated, catalytic asymmetric dearomative fluorination of 2-naphthols has no precedent in the literature.

We have been working on several types of fluorofunctionalization of organic molecules,[9] and we recently developed a dicarboxylate phase-transfer catalyst **1** for Selectfluor (**2**) to form a chiral fluorinating reagent in situ; this proved to be highly effective for enantioselective 6-*endo*-fluorocyclization and deprotonative fluorination of allylic amides (Scheme 1b).[10] The high enantioselectivity observed in these reactions can be rationalized as arising from hydrogen-bonding interaction between the carboxylate ion of the catalyst and the N–H group of the substrate amide (*vide infra*). This consideration prompted us to examine a phenolic hydroxyl group as a hydrogen bond donor; since its acidity is much higher than that of simple amides, we expected that it would interact more effectively with the dicarboxylate phase-transfer catalyst. In this report, we present the first example of catalytic asymmetric dearomative fluorination of 2-naphthols using our dianionic phase-transfer catalyst (Scheme 1c).



Scheme 1. Prior reactions and the present enantioselective dearomative fluorination of 2-naphthols.

In order to optimize the reaction conditions, 1-phenyl-2-naphthol (**3a**) was chosen as a test substrate (Table 1). First, the conditions established in the previous study [10a] were applied to this substrate. To our delight, the desired dearomative fluorination occurred preferentially to give the product **4a** in 58% yield with 71% ee (entry 1). To improve the reaction efficiency, reaction parameters such as base, solvent, and temperature were screened. Inorganic bases affected the chemical yield, but

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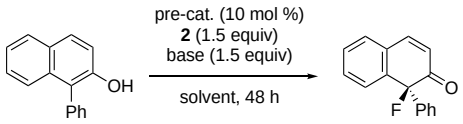
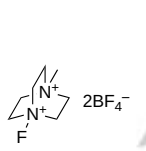
Table 1. Optimization of the reaction conditions.[a]



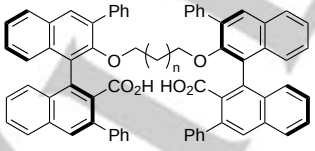
3a **4a**

entry	base	solvent	pre-cat.	temp. (°C)	yield (%)[b]	ee (%)
1	Na_3PO_4	toluene	**1**	rt	58	71
2	Na_2HPO_4	toluene	**1**	rt	81	69
3	Na_2CO_3	toluene	**1**	rt	quant.	70
4	K_3CO_3	toluene	**1**	rt	54	67
5	Na_2CO_3	benzene	**1**	rt	91	77
6	Na_2CO_3	ClC_6H_5	**1**	rt	84	85
7	Na_2CO_3	$CHCl_3$	**1**	rt	91	81
8[c]	Na_2CO_3	CH_2Cl_2	**1**	rt	97	86
9[d]	Na_2CO_3	CH_2Cl_2	**1**	0	quant. (97)[e]	93
10[f,g]	Na_2CO_3	CH_2Cl_2	**1**	0	95	83
11[f,h]	Na_2CO_3	CH_2Cl_2	**1**	0	trace	-
12[c]	Na_2CO_3	CH_2Cl_2	TRIP	rt	79	-26
13[f]	Na_2CO_3	CH_2Cl_2	**5**	0	89	-61
14[f]	Na_2CO_3	CH_2Cl_2	**6**	0	81	24
15[f]	Na_2CO_3	CH_2Cl_2	**7**	0	78	-15
16[f]	Na_2CO_3	CH_2Cl_2	-	0	39	-

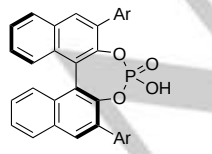
[a] The reactions were carried out with **1** (10 mol %), **2** (1.5 equiv), and base (1.5 equiv) on a 0.1 mmol scale, unless otherwise mentioned. [b] Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c] Run for 24 h. [d] Run for 18 h. [e] Isolated yield. [f] Run for 36 h. [g] Run with Selectfluor II instead of **2**. [h] Run with NSFI instead of **2**.



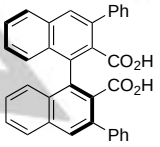
Selectfluor II



1: n = 1, **5**: n = 2, **6**: n = 3



TRIP: Ar = 2,4,6-tri(*i*-Pr)C_6H_2



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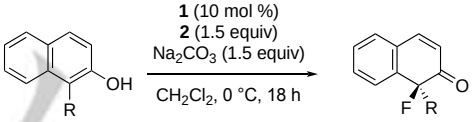
had little influence on the enantioselectivity (entries 1-4). Among the solvents examined, chlorinated solvents gave higher enantioselectivity (entries 3, 5-8). In CH_2Cl_2 at 0 °C, the enantioselectivity was as high as 93% (entry 9). When Selectfluor II was used in place of **2**, the product **4a** was formed in high yield, albeit with somewhat lower enantioselectivity (entry 10). In contrast, *N*-fluorobenzenesulfonamide (NFSI) was totally ineffective (entry 11). The following control experiments clearly indicate the superiority of our dicarboxylate catalyst over other chiral anionic catalysts. Thus, when a phosphoric acid precatalyst (TRIP) was tested, no reaction occurred at 0 °C. Although the reaction proceeded smoothly at room temperature, the enantioselectivity was only moderate (entry 12). The use of **5** or **6** having a longer alkyl linker resulted in lower enantioselectivity (entries 13 and 14). In addition, simple binaphthyl dicarboxylic acid **7** was not effective for this fluorination reaction (entry 15). These results suggest the importance of the presence of two carboxylate units at an appropriate distance. Interestingly, **4a** was formed even in the absence of **1** (entry 16). This indicates that the phase-transfer ability of **1** is high enough to overcome the background racemic reaction. It is noteworthy that the undesired aromatic fluorinative substitution reaction was not observed under the optimal conditions. Considering that several fluorinated products are formed in the homogenous reaction in MeCN, phase-transfer catalysis appears to be essential for the clean synthesis of fluorinated naphthalenone derivatives.

Table 2. Asymmetric fluorination of 1-substituted 2-naphthols.[a]



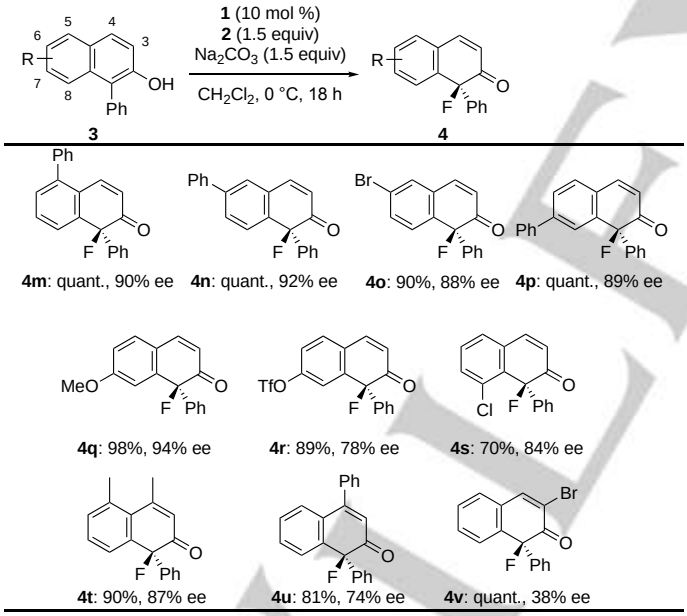
3 **4**

entry	R		yield (%)[b]	ee (%)
1	4-MeO-C_6H_4	**b**	86	83
2	4-F-C_6H_4	**c**	86	92
3	4-CHO-C_6H_4	**d**	91	92
4	3-CHO-C_6H_4	**e**	87	88
5	3,5-diCl-C_6H_3	**f**	95	85
6	2-naphthyl	**g**	91	85
7	3-thiophenyl	**h**	90	92
8	cyclohexyl	**i**	97	93
9	*i*-Pr	**j**	98	89
10	allyl	**k**	95	83
11[c]	Me	**l**	92	81

[a] The reactions were carried out with **1** (10 mol %), **2** (1.5 equiv), and Na_2CO_3 (1.5 equiv) on a 0.1 mmol scale, unless otherwise mentioned. [b] Isolated yield. [c] Run for 48 h.

Having established the optimized reaction conditions, we examined the fluorination reaction of various 1-substituted 2-naphthols (Table 2). An electron-donating methoxy group slightly reduced the enantioselectivity, although the reaction proceeded regioselectively without concomitant formation of the aromatic fluorination product (entry 1). It is noteworthy that aromatic aldehyde, which is readily oxidizable, could tolerate this reaction (entries 3 and 4), and the desired products were obtained in high yield with 92% and 88% ee, respectively. The fluorination is also applicable to heteroaromatic compounds. For example, a thiophene derivative was converted to the dearomatized product without difficulty (entry 7), whereas the homogeneous reaction afforded a complex mixture. In addition to aromatic substituents, 2-naphthols with an aliphatic substituent were examined. As shown in entries 8 and 9, cyclohexane- and isopropyl-substituted compounds underwent the fluorination reaction with high enantioselectivity. In addition, smaller substituents such as a methyl and an allyl group were also available (entries 10 and 11). It is noteworthy that the dearomative fluorination proceeded predominantly even in the presence of an alkene moiety (entry 10).

Table 3. Asymmetric fluorination of disubstituted 2-naphthols.[a]



[a] The reactions were carried out with **1** (10 mol %), **2** (1.5 equiv), and Na_2CO_3 (1.5 equiv) on a 0.1 mmol scale, unless otherwise mentioned.

We next investigated multiply substituted 2-naphthol derivatives. As shown in Table 3, the reaction showed broad generality with respect to the substitution pattern on the naphthalene ring. The 5-phenyl-substituted compound **3m** provided **4m** in high yield with 90% ee. The reaction was compatible with substitution at the 6- and 7-positions, affording the desired products with good to excellent enantioselectivity (**4n**-**4r**). It is noteworthy that bromo and triflate groups tolerate the reaction, and can therefore serve as useful handles for further transformation (**4o**, **4r**). Interestingly, the reaction of **3s** having a substituent at the 8-position proceeded in a highly enantioselective manner, even though the chlorine atom is close to the reaction site. A methyl group at the 4-position did not have a significant impact. For example, **4t** was obtained in 90% yield with 87% ee, though the enantioselectivity was somewhat reduced by a bulkier phenyl group at the 4-position (**4u**). Unfortunately, the incorporation of a substituent at the 3-position decreased the enantioselectivity (**4v**), suggesting that the difference in steric demand between the *C*1 and *C*3 positions is crucial for achieving high face selectivity at the naphthalene ring.

A tentative model of the reaction mechanism is shown in Figure 1, although the details remain to be elucidated. Dicarboxylate catalyst **A** generated in situ undergoes ion exchange reaction with Selectfluor (**2**), which is almost insoluble in CH_2Cl_2, allowing for the transfer of **2** from the solid phase to the liquid phase to give a chiral Selectfluor **B**.[11] Since ^{1}H NMR experiments suggested a hydrogen-bonding interaction between 2-naphthol and the carboxylate catalyst **A**,[10,12] we consider that the phenolic substrate forms a ternary assembly **C**, which is important not only for acceleration of the reaction, but also for enantioface discrimination. The absolute configuration of the products was deduced to be *S* on the basis of an X-ray analysis of enantio-pure **4a** (Figure 2).[13]

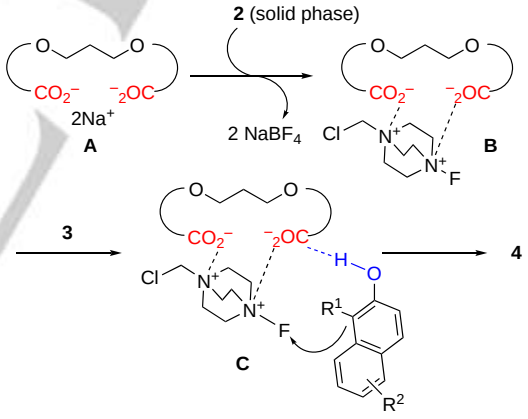
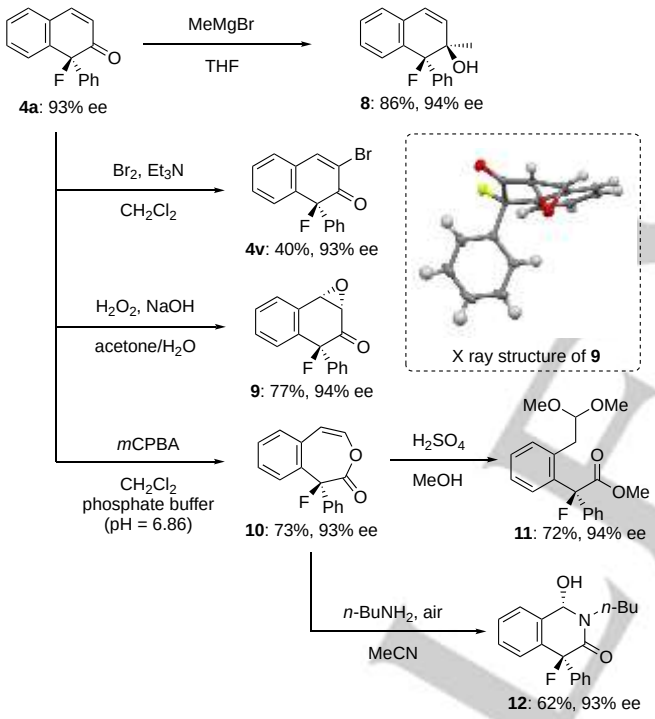


Figure 1. Proposed mechanism.

Figure 2. X-ray structure of **4a**.

To confirm the utility of the reaction, we examined the conversion of the fluorinated product **4a**, as shown in Scheme 2.

When **4a** was treated with MeMgBr at –78 °C, tertiary alcohol **8** was obtained as a single diastereomer, the stereochemistry of which was determined by NMR analysis after methyl ether formation.[12] In addition, α-bromination proceeded without difficulty, offering an alternative route to **4v**. Since the bromo group within **4v** can be in principle transformed by means of cross-coupling reactions, this compound should be a convenient platform for further derivatization. Furthermore, epoxidation occurred smoothly to afford **9** in a diastereoselective manner when H_2O_2 was used as an oxidant under basic conditions. The stereochemistry of **9** was determined by X-ray analysis.[14] In contrast, treatment with *m*-chloroperbenzoic acid (*m*CPBA) predominantly provided Baeyer-Villiger product **10**. When **10** was exposed to acidic conditions in MeOH, the ring-opening product **11** was obtained in good yield. Interestingly, the 6-membered hemiaminal **12** was formed in the reaction with *n*-butylamine under aerobic conditions.[11,15]



Scheme 2. Transformations of **4a**.

In summary, we present the first successful methodology for asymmetric dearomative fluorination of 2-naphthols, enabling the construction of chiral fluorinated naphthalenone derivatives. The reaction proceeds smoothly under dianionic phase-transfer catalysis conditions, and various functional groups are well tolerated. The utility of the products was demonstrated by the derivatization of **4a**. Considering the potentially high reactivity of the ketone group with heteroatom-based nucleophiles within biomolecules, [1,16] we believe that the availability of chiral fluorinated naphthalenones and their derivatives will facilitate drug development. Further investigation of this reaction system is ongoing in our laboratory.

Experimental Section

General procedure for the dearomative fluorination of 2-naphthols: To a solution of **3a** (22.0 mg, 0.1 mmol), **1** (9.7 mg, 10 mol %), and Na_2CO_3 (15.9 mg, 1.5 equiv) in CH_2Cl_2 (0.5 mL) was added Selectfluor (53.1 mg, 1.5 equiv) at 0 °C. The reaction mixture was stirred for 18 h at 0 °C, then diluted with EtOAc, and filtered through a pad of Celite. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (*n*-hexane / ethyl acetate = 5/1) to provide **4a** as a colorless solid (23.1 mg, 97%). The ee was determined by chiral HPLC analysis to be 93%.

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Keywords: fluorination • dearomatization • asymmetric reaction • phase-transfer catalyst • naphthol

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[12] See the supporting information.

[13] CCDC 1981709 contains the supplementary crystallographic data for this paper.

[14] CCDC 1994834 contains the supplementary crystallographic data for this paper.

[15] The details of the mechanism are not clear, but we assume that an enamine intermediate, which is formed after addition of *n*-butylamine and condensation between the resulting aldehyde and excess amine, undergoes auto-oxidation resulting in C–C bond cleavage.

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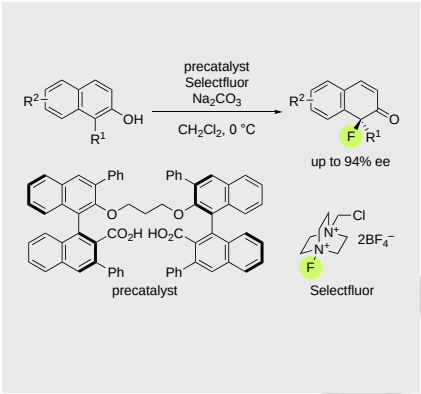
Our dianionic phase-transfer catalyst enables fluorinative dearomatization of 2-naphthols with Selectfluor to afford the fluorinated naphthalenone derivatives in good yield with high enantioselectivity. Various functional groups are tolerated under the reaction conditions.



*Hiromichi Egami, Taiki Rouno, Tomoki Niwa, Kousuke Masuda, Kenji Yamashita, and Yoshitaka Hamashima**

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Asymmetric Dearomative Fluorination of 2-Naphthols with Dianionic Phase-Transfer Catalyst