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Asymmetric Fluorolactonization with a Bifunctional Hydroxyl Carboxylate Catalyst

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Supporting Information

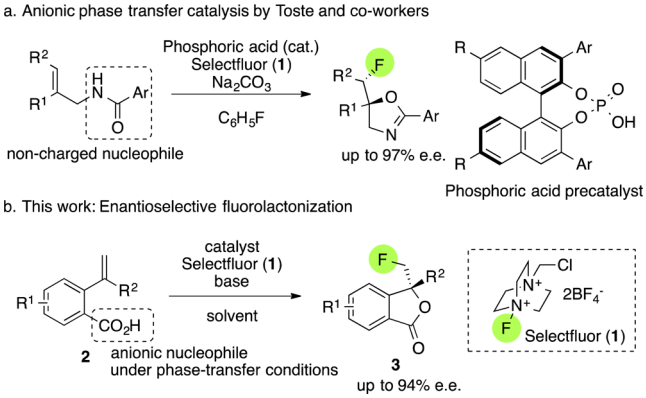
ABSTRACT: We report the first successful example of a highly enantioselective fluorolactonization with an electrophilic fluorinating reagent, Selectfluor®, in the presence of a novel bifunctional organocatalyst. The catalyst design includes a carboxylate anion functioning as a phase-transfer agent and a benzyl alcohol unit to capture the substrate through hydrogen bonding. Fluorinated isobenzofuranones were obtained in good yields with up to 94% ee (97:3 er). On the basis of mechanistic studies, we propose a unique reaction mechanism with potential for further applications.

Although fluorine is the 13th most abundant element on earth, very few natural products contain fluorine atom(s). However, artificial organofluorine compounds have found widespread applications in pharmaceuticals, agrochemicals, and fine chemicals as well as in materials science.[1] Thus, the development of efficient methods to synthesize chiral fluorinated compounds is highly desirable.[2] In this context, catalytic asymmetric fluorofunctionalization of alkenes would be a powerful method to obtain structurally diverse fluorinated compounds for structure−activity relationship studies. However, such reactions remain largely unexplored, with only a few exceptions that require a stoichiometric amount of chiral source.[3]

In 2011, Toste and co-workers reported a conceptually new approach in which a chiral phosphate anion acts as an anionic phase-transfer catalyst to bring a reactive electrophilic fluorinating reagent, Selectfluor® (**1**),[4] which is insoluble in nonpolar solvents, into the liquid phase, thereby suppressing the undesired background reaction to give the racemic product (Scheme 1a).[5] Although further applications were reported,[6] this strategy is effective only for reactions of alkenes with noncharged pronucleophiles such as amides and is not applicable to alkenes bearing anionic nucleophiles. We envisaged that various types of fluorinated analogues of medicinally important heterocycles could be synthesized in a single step if acidic pronucleophiles such as carboxylic acids, sulfonamides, and phenols were available as pendant nucleophiles.

Following our work on bromolactonization,[7] we became interested in asymmetric fluorolactonization of ene−carboxylic acids. While a variety of asymmetric halolactonization reactions with heavier halogens (Cl^+, Br^+, I^+) have recently been developed,[8] fluorolactonization had not been reported in either a stoichiometric or a catalytic version before we started the project. Since isobenzofuranone derivatives are found in various bioactive compounds,[9] we selected the fluorination of *o*-vinylbenzoic acid derivatives **2** as a model reaction (Scheme 1b).[10] Herein we report the first successful example of a highly enantioselective fluorolactonization catalyzed by a newly developed bifunctional organocatalyst.

Scheme 1. Asymmetric Fluorodifunctionalizations of C−C Double Bonds



Although the basic concept of anionic phase-transfer catalysis seemed promising for our purpose, we were aware that simple application of chiral phosphate anion catalysts might be difficult for the following reasons. First, the substrate carboxylate anion generated under basic phase-transfer conditions can act as an achiral phase-transfer catalyst to promote the undesired racemic reaction (Figure 1a). Second, either flexible ion pairing of the substrate anion with Selectfluor® or loose salt bridging between the catalyst and the substrate anion would result in low asymmetric induction (Figure 1b). In accord with these considerations, a representative phosphoric acid (TRIP), which gave high enantioselectivity in the fluorocyclization of allylic amides,[5,6] was found to be almost ineffective in our initial experiments.[11]

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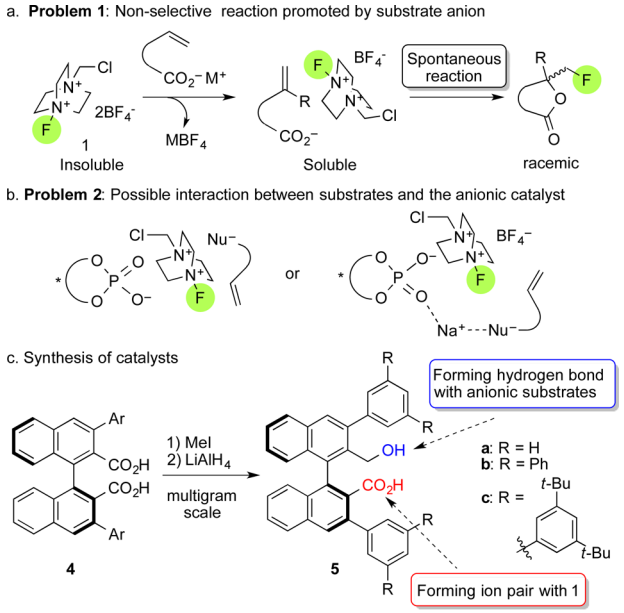


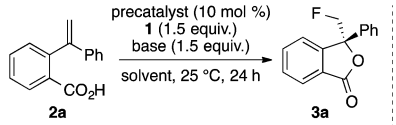
Figure 1. (a, b) Problems in the development of fluorolactonization reactions and (c) synthesis of our catalyst.

To overcome the possible problems illustrated in Figure 1a,b, the catalyst is required not only to transport **1** efficiently to the liquid phase but also to undergo an associative interaction with the anionic substrate. Therefore, the catalyst should be equipped with an anion to form an ion pair with **1** and a hydrogen-bond donor to fix the substrate anion. Because we had observed in our early experiments that the substrate **2** acts as a phase-transfer catalyst precursor (vide infra) and because various synthetic methods are available to introduce a carboxyl group into binaphthol, we selected a carboxylate anion as a key functionality. As a hydrogen-bond donor, we planned to install a hydroxyl group. These considerations led us to design the novel bifunctional precatalysts **5** (Figure 1c). Even though these catalysts are equivalent to the substrate anion in terms of electronic charge, we assumed that better transport of **1** would be achieved by increasing the hydrophobicity of the catalyst, thereby minimizing the background reaction promoted by the substrate anion. Consequently, we expected that catalyst **5** would form a ternary complex by accommodating both **1** and the substrate into the chiral pocket. To test our hypothesis, we synthesized a series of novel catalysts **5** on a multigram scale from C_2-symmetric dicarboxylic acids **4**, which were originally developed by Maruoka et al.,[12] via monoesterification[13] followed by reduction with $LiAlH_4$.[11]

These catalyst precursors were evaluated for fluorolactonization of **2a** (Table 1). As the size of the substituent increased, the catalyst efficiency greatly improved (entries 1–3). To our delight, **3a** was obtained in 84% yield with 83% ee when **5c** was used as a precatalyst (entry 3). Further optimization revealed that the combination of Na_3PO_4 as a base[14] and Na_2SO_4 as a dehydrating agent in cyclohexane gave the best results (entry 9). This fluorolactonization was successfully scaled up without difficulty (entry 10). Interestingly, the reaction with Selectfluor® II gave a lower enantioselectivity (entry 12). As illustrated in Figure 1a, the reaction without precatalyst **5** also proceeded to give racemic **3a** in 51% yield (entry 13).

Having established the optimum reaction conditions, we next examined the generality of the reaction (Table 2). Various aryl-

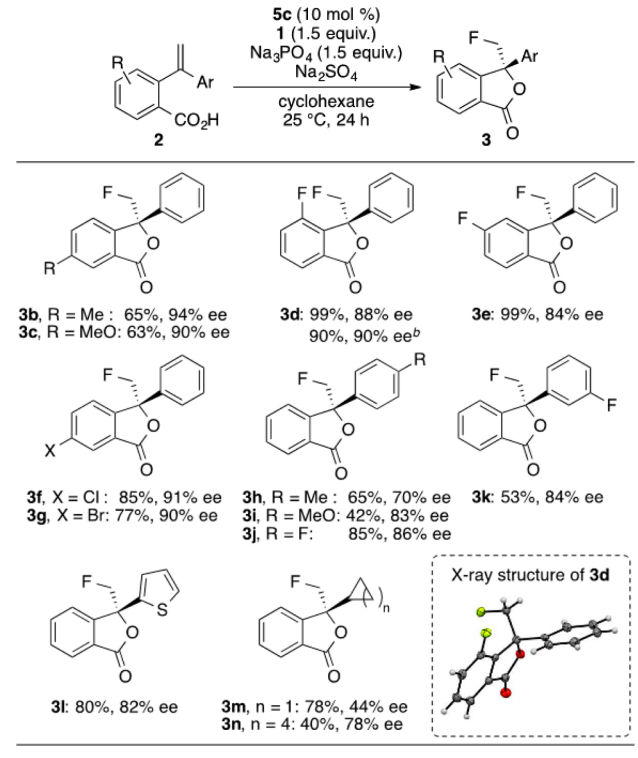
Table 1. Optimization of the Reaction Conditions[a]



entry	precatalyst	solvent	base	yield (%)[b]	ee (%)
1	**5a**	toluene	Na_3PO_4	30	33
2	**5b**	toluene	Na_3PO_4	37	68
3	**5c**	toluene	Na_3PO_4	84	83
4	**5c**	toluene	K_3PO_4	44	18
5	**5c**	toluene	K_2CO_3	78	45
6	**5c**	toluene	Na_2CO_3	quant	59
7	**5c**	*n*-hexane	Na_3PO_4	77	87
8	**5c**	*c*-hexane	Na_3PO_4	85	88
9[c]	**5c**	*c*-hexane	Na_3PO_4	quant (99)[d]	88
10[c,e]	**5c**	*c*-hexane	Na_3PO_4	80[d]	88
11[c,f]	**5c**	*c*-hexane	Na_3PO_4	64	90
12[g]	**5c**	*c*-hexane	Na_3PO_4	80	67
13	–	*c*-hexane	Na_3PO_4	51	–

[a]The reactions were carried out with precatalyst **5**, **1**, and the base in 1 mL of the solvent on a 0.1 mmol scale, unless otherwise noted. [b]Determined by ^{1}H NMR analysis using dibromoethane as an internal standard. [c]Run with Na_2SO_4. [d]Isolated yield. [e]Run on a 0.5 mmol scale. [f]Run at 15 °C. [g]Run with Selectfluor® II instead of **1**.

Table 2. Substrate Scope[a]



[a]The reactions were run on a 0.1 mmol scale, unless otherwise noted. [b]Run for 48 h on a 0.5 mmol scale.

substituted vinylbenzoic acids underwent the fluorination reaction efficiently to give the desired fluorinated isobenzofuranons **3** in a highly enantioselective manner. A single recrystallization gave optically pure **3d** (>99% ee), and X-ray analysis revealed its absolute stereochemistry to be *R*. In addition, the reaction was applicable to some alkyl-substituted

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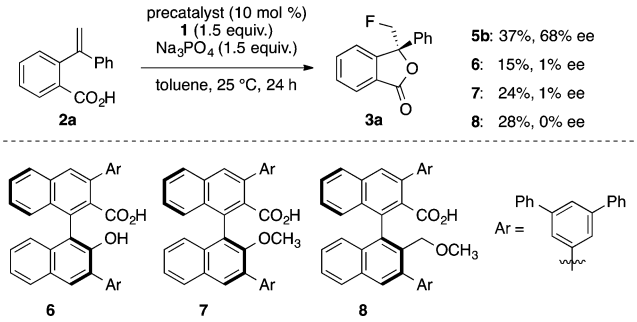
substrates, and the reactions proceeded with good enantioselectivity (**3m**, **3n**).[15]

During the course of the catalyst screening, we were able to confirm the importance of the primary hydroxyl group within the catalyst. With **5b** as the reference precatalyst, we examined the catalytic ability of structurally analogous precatalysts **6**–**8** (Scheme 2). While **5b** gave fluorolactone **3a** with 68% ee in toluene, only negligible asymmetric induction was observed in the reactions using precatalysts **6**–**8** under identical conditions. These results clearly indicate that the presence of a primary hydroxyl group at an appropriate position is important to achieve high asymmetric induction.

Scheme 2. Fluorolactonization with Other Analogous Acids as Precatalysts



To gain further information regarding the reaction mechanism, NMR experiments were performed in toluene-d_8, as toluene also gave good results (Table 1, entry 3). Selectfluor® (**1**) was not detected by ^{1}H NMR or ^{19}F NMR spectroscopy even in the presence of inorganic salts (Na_3PO_4 and Na_2SO_4).[11] These results indicate that **1** is insoluble in toluene-d_8 and exclude the possibility that the inorganic salts function as phase-transfer agents.

Upon treatment of **5c** with Na_3PO_4 (5 equiv), peaks characteristic of **5c** disappeared and broad signals were observed in the ^{1}H NMR spectrum, suggesting that the carboxylate anion catalyst forms aggregates. Interestingly, when an equimolar amount of **2a** was added to this mixture, a set of sharp peaks appeared again.[11] This observation suggests that the substrate interferes with aggregation of the catalyst, forming a 1:1 complex **9** (Figure 2). Upon addition of **1** to this mixture, a characteristic peak at 50.9 ppm, which could be attributed to the N$^+$–F unit of **1**,[16] appeared in the ^{19}F NMR spectrum in addition to peaks of BF_4^- (−156.1 and −156.2 ppm).[11,16] Although these signals cannot be assigned at present, this observation strongly suggests that the catalyst forms the putative ion pair with **1**.

On the basis of these observations, we propose the following reaction mechanism (Figure 2). The acid **5** tends to aggregate after deprotonation, but the substrate facilitates dissociation to give binary complex **9** consisting of the catalyst and the substrate. This complex may be responsible for the better transport of **1** compared with that by the catalyst aggregate because the N$^+$–F unit was not detected in the absence of **2**.[11] Then **9** reacts with **1** to generate the active fluorinating species **10** in the liquid phase. Since a positive nonlinear correlation was observed between the ee of the product and that of the catalyst,[11] we speculate that two catalyst molecules may be involved in the fluorination step (**10**, X^- = **5**$^-$ or **9**$^-$).[5] However, we cannot rule out the possibility that the observed nonlinear effect is due to pre-equilibration between the actual catalyst and the catalyst aggregate and that a ternary complex **10** (X^- = **2**$^-$ or BF_4^-) might be operative. Fluorine is delivered to the substrate, affording intermediate **11** with release of fluorolactone **3**. The ion exchange reaction, followed by association with the substrate anion, would complete the catalytic cycle. Taking into account the results shown in Scheme 2, it is likely that the hydroxyl group within **5c** plays a key role in the interaction with the substrate. The hydroxyl group might also participate in hydrogen-bond formation with the neighboring carboxylate anion to fix its position. The high enantioselectivity observed in our reaction indicates that the catalyst-controlled reaction is much faster than the substrate-mediated reaction, presumably because of the high phase-transfer ability arising from the hydrophobic environment and the presence of polar functionalities.

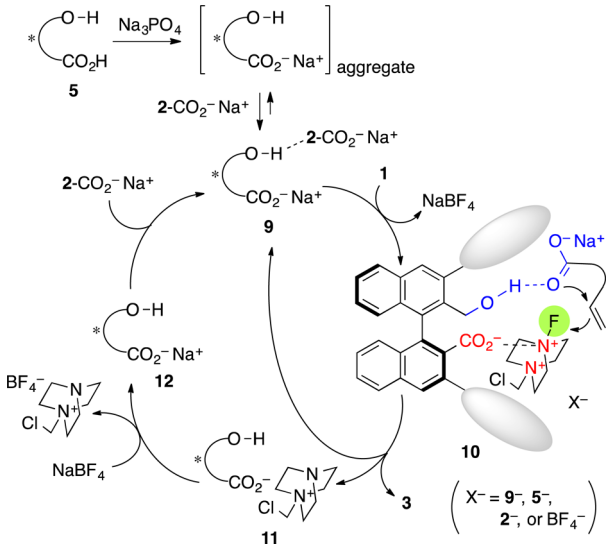


Figure 2. Proposed catalytic cycle.

In summary, we have presented the first successful example of catalytic asymmetric fluorolactonization using a newly designed anionic phase-transfer catalyst having a hydrogen-bond donor site. Fluorolactonization of *o*-vinylbenzoic acids proceeded smoothly to give the corresponding fluorinated isobenzofuranones in good yields with high to excellent enantioselectivities. Experiments using structural analogues of **5** indicated that the combination of a carboxylate anion with a benzyl alcohol moiety is essential for high asymmetric induction. NMR experiments supported our hypothesis that the catalyst holds the substrate anion and a cationic fluorinating reagent in a chiral pocket. We consider this type of unsymmetrical bifunctional catalyst to have great potential for the synthesis of enantioenriched fluorinated compounds. Further studies are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06546.

Detailed experimental procedures and spectroscopic data for product characterization (PDF)
Crystallographic data for **3d** (CIF)
Crystallographic data for **S7** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) Among the inorganic bases examined, Na_3PO_4 gave the best selectivity. According to the recent report by Rueping,[10] carbonate anion can mediate phase transfer of **1** in *n*-hexane, suggesting that the decreased ee value may be due to the background reaction promoted by Na_2CO_3 (Table 1, entry 6).

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