Communication to the Editor

Asymmetric Fluorination of Cyclic Tetrasubstituted Alkenes with a Pendant Amide Groups under Dianionic Phase-Transfer Catalysis

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Asymmetric fluorination of cyclic tetrasubstituted alkenes with a pendant amide group was investigated under dianionic phase-transfer catalysis. Fluorination proceeded with high face selectivity, affording the corresponding allylic fluorides with a chiral tetrasubstituted carbon center with up to 97% enantioselective excess (ee). It should be noted that deprotonative fluorination occurred mainly in preference to intramolecular nucleophilic attack of the amide group.

Key words fluorination; asymmetric catalysis; phase-transfer catalyst; allylic fluoride; chiral tetrasubstituted carbon center

Allylic fluoride is a substructure of bioactive molecules and a useful synthetic intermediate for the preparation of organofluorine compounds. Therefore, the construction of allyl fluoride component is a current topic of interest in the field of pharmaceutical and agrochemical sciences. One of the conventional methods is deoxy-fluorination of allylic alcohols using aminosulfur trifluoride derivatives. Fluorination of allyl silanes is another promising protocol, and its asymmetric versions were independently reported by Shibata and Gouverneur. Although S$_2$ 2 reaction of allylic halides is possible with fluoride anion, recent progress of transition metal catalysis allowed for the access to various types of allylic fluoride. It is reported that allylic fluorides can be formed from simple alkenes via fluorination entailing double bond migration by deprotonation, which depends on the substrate structure and the reaction conditions.

In 2013, Toste and colleagues reported a seminal example of the deprotonative fluorination of allylic amides. The same group also applied their reaction system to allylic alcohols using the combination of a chiral phosphoric acid 4 as a precatalyst (entry 2).

As part of our halogenation program, we have been working on fluoro-functionalization of C–C double bonds as well as C–H bonds. In 2015, a highly enantioselective fluorolactonization was achieved using a hydroxyl-carboxylate phase-transfer catalyst. Based on the mechanistic study of the fluorolactonization, we designed and synthesized a novel dicarboxylate phase-transfer catalyst for commercially available electrophilic fluorinating reagent, Selectfluor, which is insoluble in non-polar organic solvent. Gratifyingly, the dicarboxylate catalyst was found to promote 6-fluorocyclization of allylic amides in a highly enantioselective manner (Chart 1a). In this study, disubstituted and trisubstituted allylic amides were tested and hydrogen bonding interaction between the amide N–H moiety and the carboxylate of the catalysts was suggested to be essential for high asymmetric induction. However, tetrasubstituted alkenes have not yet been applied to our reaction conditions. If the same reaction mode is operative, cyclization reaction through the formation of a putative β-fluorocarbocation intermediate would give dihydrooxazines with vicinal tetrasubstituted carbon centers (6-fluorocyclization). Alternatively, the stability of the carbocation intermediate may allow for deprotonation prior to intramolecular attack of the amide group to give the corresponding allylic fluoride (deprotonative fluorination). Thus, we planned to examine the fluorination of cyclic tetrasubstituted alkenes bearing a pendant amide group under the influence of our chiral dicarboxylate phase-transfer catalyst, results of which are disclosed in this report (Chart 1b).

Results and Discussion

We selected dihydronaphthalene derivative 1a as a test substrate, and several reaction conditions were examined (Table 1). At the outset, 1a was treated with Selectfluor under the optimal reaction conditions for 6-fluorocyclization using dicarboxylic acid precatalyst 4 (entry 1). The reaction afforded two products 2a and 3a in good mass balance (85%). Unlike our previous reaction (Chart 1a), allylic fluoride 3a was obtained mainly in 67% yield together with cyclized product 2a in only 18%. Interestingly, their ee values were different from each other, and 3a was obtained with higher enantiomeric excess (2a: 51% enantiomeric excess (ee), 3a: 84% ee). The reaction efficiency was significantly reduced, when simple binaphthyl dicarboxylic acid 5 was used as a precatalyst (entry 2).

Chart 1. Asymmetric Fluorination of Allylic Amides
droxyl–carboxylic acid 6 developed by us for fluorolactonization provided an almost 2:3 mixture of 2a and 3a, but their enantioselectivities were miserable (entry 3). These results clearly suggest that the dicarboxylate catalyst derived from 4 is superior to other carboxylate-type catalysts for the reaction of cyclic tetrasubstituted alkene substrates. We next examined the effect of inorganic bases (entries 4–7). Among the bases tested, K₃PO₄ gave the best results, while Na₃PO₄ was the best for reactions of acyclic allylic amides. Toluene was revealed to be the best solvent. Thus, the reactions in CH₂Cl₂ and tert-butyl methyl ether (TBME) proceeded smoothly, though with lower enantioselectivities (entries 8 and 9). Dehydrating agent, Na₂SO₄, affected the reaction profile slightly (entry 10).

Although the minor product 2a was obtained as a single stereoisomer, its relative and absolute configuration has not been determined yet. The absolute stereochemistry of the major product 3a was unambiguously determined to be S by HPLC analysis in comparison with Toste’s report. Interestingly, the stereochemistry at the fluorinated carbon center of 3a was opposite to that of the 6-endo cyclization product obtained from di- and trisubstituted allylic amides. If our working hypothesis is correct, 2a and 3a are formed from the same β-fluorocarbocation intermediate and the similar level of the enantioselectivities should be observed for both products. However, this is not the case as mentioned above. Taken together, these results indicate that the transition state leading to 3a would be distinct from that leading to 2a. Although the detail of the reaction mechanism is not clear at this moment, we speculate that deprotonation at the allylic position (methyl group) and fluorination of the alkene moiety may occur in a concerted manner. Since the basicity of the amide group did not have great impact on the reaction efficiency (vide infra), it is likely that the carboxylate anion of the chiral catalyst acts as the actual Bronsted base for deprotonation.

### Table 1. Optimization of the Reaction Conditions

| Entry | Precat. | Base | Solvent | 2a yield⁽⁻⁾/ee (%) | 3a yield⁽⁻⁾/ee (%) |
|-------|---------|------|---------|------------------|------------------|
| 1     | 4       | Na₃PO₄ | Toluene | 18/51            | 67/84            |
| 2     | 5       | Na₃PO₄ | Toluene | 10/4             | 26/3             |
| 3     | 6       | Na₃PO₄ | Toluene | 22/4             | 35/8             |
| 4     | 7       | Na₃PO₄ | Toluene | 23/5             | 77/72            |
| 5     | 4       | Na₃PO₄ | Toluene | 20/29            | 70/77            |
| 6     | 4       | K₂CO₃  | Toluene | 14/57            | 62/87            |
| 7     | 4       | K₂CO₃  | Toluene | 17/57            | 62/87            |
| 8     | 4       | K₂CO₃  | CH₂Cl₂  | 30/2             | 70/72            |
| 9     | 4       | K₂CO₃  | TBME    | 19/20            | 81/43            |

a) The reactions were carried out with catalyst (10 mol%), Selectfluor (1.5 eq), and base (1.5 eq) on a 0.1 mmol scale, unless otherwise mentioned. b) Determined NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. c) Run without Na₂SO₄. d) Isolated yield.

### Table 2. Generality of the Deprotonative Fluorination

| Entry | R¹ | R² | 4 (10 mol %) | Solvent | 25 °C, 24 h |
|-------|----|----|--------------|---------|-------------|
| 1     |    |    | K₃PO₄ (1.5 equiv) | Toluene |             |
| 2     |    |    | Na₂SO₄ | Toluene |             |
| 3a    | R = NO₂; 74%, 92% ee |
| 3c    | R = OMe; 87%, 90% ee |
| 3d    | R = CF₃; 86%, 90% ee |
| 3e    | R = CF₃; 72%, 83% ee |
| 3f    | 83%, 78% ee |
| 3g    | 79%, 78% ee |
| 3h    | 86%, 97% ee |
| 3i    | 88%, 88% ee |

Having established the optimum reaction conditions (Table 1, entry 7), we next examined the generality of the reaction (Table 2). It was found that the substituents on the aromatic
ring of the amide group did not have significant impact on the product distribution and the excellent enantioselectivity was observed for the allylic fluorides 3b-3d. Trifluoroacetamide unit was also applicable to this fluorination reaction (3e), though the ee was slightly decreased. Although a methoxy group on the tetrahydroonaphthalene framework affected the enantioselectivities, the corresponding allylic fluorides were obtained in good yield with reasonably high enantioselectivity (3f and 3g). The present fluorination could be applied to 5-membered ring and 7-membered ring substrates (3h and 3i). To our delight, 3i was obtained in 86% yield with as high as 97% ee. Furthermore, reactions of heterocyclic substrates were examined. Thus, the enantio-enriched 3-fluorochromane derivatives were obtained without difficulty (3j and 3k).

In summary, we have demonstrated the asymmetric deprotonative fluorination of cyclic tetrasubstituted allylic amides using our dianionic phase-transfer catalyst. The present fluorination reaction proceeded smoothly in preference to fluorocyclization that occurred for di- and trisubstituted allylic amides.34 Although the cyclized products were generally found to expand the scope and clarify the reaction mechanism are undergoing in our laboratory.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials. Experimental procedure and NMR spectra of isolated products.

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