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### Enantioselective fluorination of $\alpha$ -branched aldehydes and subsequent conversion to $\alpha$ hydroxyacetals via stereospecific C-F bond cleavage\*

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The highly enantioselective fluorination of α-branched aldehydes was achieved using newly developed chiral primary amine catalyst **1**. Furthermore, the C-F bond cleavage of the resulting  $\alpha$ -fluoroaldehydes proceeded smoothly under alcoholic alkaline conditions to yield the corresponding  $\alpha$ -hydroxyacetals in a stereospecific manner. Accordingly, the one-pot conversion of  $\alpha$ -branched aldehydes into  $\alpha$ -hydroxyacetals was achieved for the first time in high enantioselectivity.

Enantioselective construction of fluorinated chiral stereogenic centers is synthetically important, because the resulting fluorides are expected to be useful intermediates for fluorinated drugs and agricultural agents.1 Despite the extraordinary interest in practical synthetic methodologies towards chiral tertiary fluorides, until very recently, catalytic enantioselective methods capable of introducing fluorine atoms onto a tertiary carbon center have been primarily limited to the fluorination of active methine compounds.2-4 The chiral secondary aminecatalyzed electrophilic fluorination of aldehydes is a highly useful method for the construction of fluorinated stereogenic centers.<sup>5</sup> Although this method yields  $\alpha$ -fluoroaldehydes with high enantioselectivity when α-monosubstituted aldehydes are used as substrates, fluorination of α-branched aldehydes with secondary amine catalysts generally exhibits low enantioselectivity.5a,5b To the best of our knowledge, there are only three reports on the enantioselective fluorination of α-branched aldehydes yielding tertiary fluorides with acceptable enantiopurity.6-8 Notably, Jørgensen and co-workers reported the asymmetric fluorination of *α*-alkyl-*α*-aryl aldehydes achieving high enantioselectivity (up to 90% ee) with a new primary amine catalyst with non-biaryl atropisomeric chirality.6 However, the isolated yields of the fluorinated products were not satisfactory for some reasons. Although we also reported the asymmetric fluorination of  $\alpha$ -chloroaldehydes via the kinetic resolution mechanism, affording a-chloro-a-fluoroaldehydes with high moderate enantioselectivities enantioselectivities, were observed when  $\alpha, \alpha$ -dialkylaldehydes were employed.<sup>7</sup> Here, we

report the organocatalytic fluorination of α-branched aldehydes, using a newly developed chiral primary amine catalyst 1; this approach affords the corresponding  $\alpha$ -fluoroaldehydes in high chemical yields and enantioselectivities (Scheme 1). We also found that the resulting  $\alpha$ -fluoroaldehydes could be converted into a-hydroxyacetals, bearing chiral tertiary alcohol moieties, and their optical purity could be maintained, which suggested that the reaction proceeded via a stereospecific C-F bond cleavage. These results shed new light on C-F bond activation,<sup>9</sup> and will be useful because the resulting chiral tertiary alcohols may be valuable intermediates in the synthesis of biologically active compounds.

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Scheme 1 Asymmetric  $\alpha$ -fluorination of aldehydes.

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Scheme 2 Synthesis of primary amine catalysts.

The structure of the new chiral primary amine catalyst **1** is shown in Scheme 2.<sup>10</sup> An ester moiety and substituents at the 3,3'-positions on the binaphthyl backbone are expected to influence the chirality of the resulting products. Catalyst **1** was synthesized according to the procedure shown in Scheme 2. First, (*R*)-3,3'-diaryl-2,2'-bis(bromomethyl)-1,1'-binaphthyl (2) was prepared from commercially available (*R*)-BINOL *via* a reported procedure.<sup>11</sup> Compound **2** was then converted into the desired amino ester **1** *via* alkylative cyclization with ethyl isocyanoacetate and subsequent acid hydrolysis of the isocyano group.

Next, **1** was applied in the enantioselective fluorination of  $\alpha$ -branched aldehydes (Table 1). Fluorination of 2-phenylpropanal (**3a**) was carried out with *N*-fluorobenzenesulfonimide (NFSI) in the presence of 10 mol% **1a** to yield 2-fluoro-2-



<sup>*a*</sup> Reactions were carried out with 1.5 equiv. of *rac*-**3a** based on NFSI in the presence of 10 mol% **1** unless otherwise noted. <sup>*b*</sup> Isolated yield of **5a**. <sup>*c*</sup> Absolute configuration of the major enantiomer is specified in parenthesis. <sup>*d*</sup> 1.5 equiv. of NFSI was used based on *rac*-**3a**. <sup>*e*</sup> At 0 °C. <sup>*f*</sup> 10 mol% 3,5-(NO<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CO<sub>2</sub>H was used as a co-catalyst. <sup>*g*</sup> 5 mol% catalyst was used with 15 mol% TFA. <sup>*h*</sup> 20 mol% catalyst.

phenylpropanal (4a) in a high conversion. The fluorinated product was isolated after reduction to primary alcohol 5a, due to difficulties in the purification of 4a. Thus, 5a was isolated in a sufficiently high chemical yield, but with poor enantioselectivity (entry 1). To our delight, the enantioselectivity of the fluorination dramatically improved to 90% ee by employing catalyst 1b, which has bulky aryl substituents at the 3,3'-positions (entry 2). As expected, the use of catalyst 1c without aryl substituents in the 3,3'-positions yielded a nearly racemic product (entry 3). The optimal solvent for the reaction was found to be toluene (entries 4-7). The enantioselectivity and reaction rate were slightly increased by adding 10 mol% 3,5dinitrobenzoic acid as a co-catalyst (entry 10). We also confirmed that chiral primary amines 6 and 7, which were reported to induce high enantioselectivity in the amination of α-branched aldehydes,<sup>12</sup> were ineffective in the fluorination of 3a (entries 11 and 12). The absolute configuration of 5a was determined to be S, by comparison of its optical rotation with that of the reported value.6



<sup>*a*</sup> Reactions were carried out with 1.5 equiv. of *rac*-3 based on NFSI in the presence of 10 mol% **1b** and 3,5-(NO<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CO<sub>2</sub>H. Isolated yield of 5 are described, except for **4k**. <sup>*b*</sup> Purified product contained *ca*. 5% of an inseparable by-product. <sup>*c*</sup> At rt. for 2 h. <sup>*d*</sup> At rt. for 12–24 h. <sup>*e*</sup> 20 mol% catalyst. <sup>*f*</sup> 30 mol% catalyst.



Encouraged by the results obtained with amine catalyst **1b**, we attempted to expand the substrate scope of the fluorination reaction. As summarized in Table 2, various  $\alpha$ -alkyl- $\alpha$ -aryl aldehydes were successfully fluorinated to afford the corresponding  $\alpha$ -fluoroaldehydes in high yields with high enantioselectivities. On the other hand, the reaction with  $\alpha$ , $\alpha$ -dialkyl aldehyde **3o** yielded the product with good enantioselectivity but in poor yield, while the reaction with **3p** showed



<sup>a</sup> Isolated yields of 10-12 from 3 are described. <sup>b</sup> The first step was

carried out at rt. <sup>c</sup> es = (ee of 10-12)/(ee of 4). <sup>d</sup> The second step was

carried out at rt. under reflux conditions. Purified product contained

ca. 10% of an inseparable by-product.<sup>e</sup> The second step was carried

out with NaH in ethylene glycol instead of NaOR<sup>2</sup>/R<sup>2</sup>OH.

disappointingly low enantioselectivity. Although it was observed that the reaction with **3f** yield the corresponding fluoroaldehyde **4f** in good conversion by NMR measurement of the reaction mixture, reduction of **4f** to **5f** gave a complicated mixture, thus we could not determine those enantiopurity.

The resulting fluorides can be converted into a variety of other tertiary fluorides (Scheme 3). First, allyl fluorides 8 were synthesized by Horner–Wadsworth–Emmons reaction of  $\alpha$ -fluoroaldehydes 4 in good yield. Next, fluorohydrine 5j was oxidized to carboxylic acid 9,<sup>13</sup> which is a fluorinated analogue of a non-steroidal anti-inflammatory agent, flurbiprofen.

We further investigated the synthetic utility of α-fluoroaldehydes 4. Although, in general, the cleavage of carbonfluorine bonds is not facile due to the strength of the bond, methods for C-F bond activation have recently garnered significant interest.9 The S<sub>N</sub>2-type nucleophilic substitution of sp<sup>3</sup>-alkylfluorides is known to be a challenging reaction; in particular, there are very few examples of the substitution of tertiary alkylfluorides.14 We recently reported that the S<sub>N</sub>2 reaction of a-chloro-a-keto esters with sodium azide and alkylthiols proceeds smoothly, despite the fact that the reaction occurs at a tertiary carbon.15 This finding encouraged us to examine the nucleophilic substitution of α-fluoroaldehydes 4. First, typical nucleophiles such as sodium azide and alkylthiols were surveyed, but the desired product was not obtained. Eventually, we found that treatment of 4a with NaOMe in methonal yielded the corresponding α-hydroxyacetal 10a in a good conversion (Table 3).<sup>16</sup> Due to the difficulties in purifying 4a, enantioselective fluorination of 3a and subsequent hydroxyacetalization were performed in a one-pot fashion. Notably, the enantiopurity of 10a was nearly the same as that of 4a. This result indicated that the C-F bond cleavage occurred in a stereospecific manner. As summarized in Table 3, various α-hydroxyacetals 10 were synthesized in good yields with high enantioselectivities *via* the sequential fluorination-alkaline treatment. When the second step was carried out with NaH in ethylene glycol, the corresponding  $\alpha$ -hydroxy cyclic acetal 12 was obtained. The present method would be a good alternative







Scheme 5 Proposed reaction mechanism.

to direct oxidation of α-branched aldehydes.8,17 Our method does not require the use of any explosive oxidant and simultaneously protects the carbonyl group. The resulting 10a could be easily converted into  $\alpha$ -hydroxy ester 13 without loss of enantiopurity (Scheme 4). The absolute configuration of 13 was determined to be R, by comparison of reported optical rotation values;18 these results confirmed that this transformation involved the Walden inversion.

The proposed reaction mechanism for the formation of hydroxyacetals 10 is shown in Scheme 5. <sup>1</sup>H NMR studies revealed that  $\alpha$ -fluoroaldehyde 4 is in equilibrium with hemiacetal I in d<sub>4</sub>-methanol. Upon treatment with NaOMe, epoxide II is formed via intramolecular S<sub>N</sub>2 displacement, which involves the stereospecific cleavage of C-F bond. Then, regeneration of the carbonyl moiety and subsequent acetalization or direct S<sub>N</sub>2-type ring opening of II with methoxide affords hydroxyacetal 10.

#### Conclusions

In conclusion, we developed a new class of chiral primary amine catalysts and successfully applied them in the enantioselective fluorination of  $\alpha$ -branched aldehydes. Further, we found that the resulting fluoroaldehydes could be converted into the corresponding α-hydroxyacetals via stereospecific C-F bond cleavage.

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