Chemical Science

EDGE ARTICLE

Cite this: *Chem. Sci.*, 2016, 7, 1388

Enantioselective fluorination of α-branched aldehydes and subsequent conversion to α-hydroxyacetals *via* stereospecific C–F bond cleavage†

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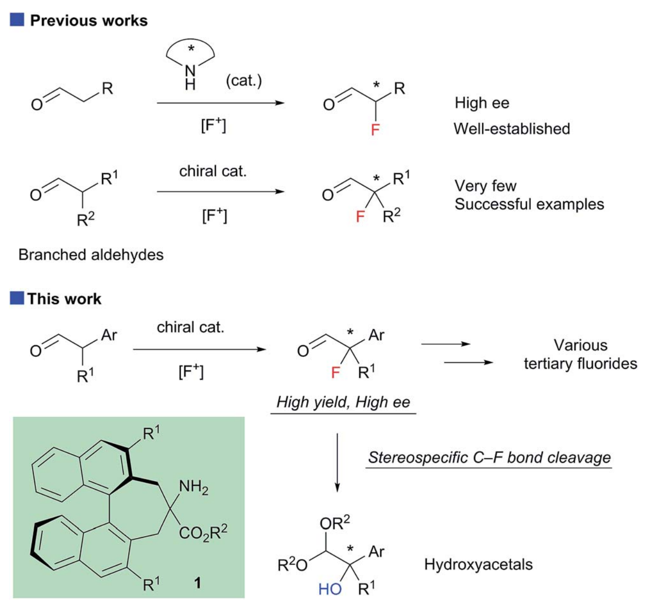
Received 16th September 2015
Accepted 14th November 2015

DOI: 10.1039/c5sc03486h

www.rsc.org/chemicalscience

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 α-fluoroaldehydes proceeded smoothly under alcoholic alkaline conditions to yield the corresponding α-hydroxyacetals in a stereospecific manner. Accordingly, the one-pot conversion of α-branched aldehydes into α-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 amine-catalyzed electrophilic fluorination of aldehydes is a highly useful method for the construction of fluorinated stereogenic centers.[5] Although this method yields α-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 α-chloroaldehydes *via* the kinetic resolution mechanism, affording α-chloro-α-fluoroaldehydes with high enantioselectivities, moderate enantioselectivities were observed when α,α-dialkylaldehydes were employed.[7] Here, we report the organocatalytic fluorination of α-branched aldehydes, using a newly developed chiral primary amine catalyst **1**; this approach affords the corresponding α-fluoroaldehydes in high chemical yields and enantioselectivities (Scheme 1). We also found that the resulting α-fluoroaldehydes could be converted into α-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,[9] and will be useful because the resulting chiral tertiary alcohols may be valuable intermediates in the synthesis of biologically active compounds.



Scheme 1 Asymmetric α-fluorination of aldehydes.

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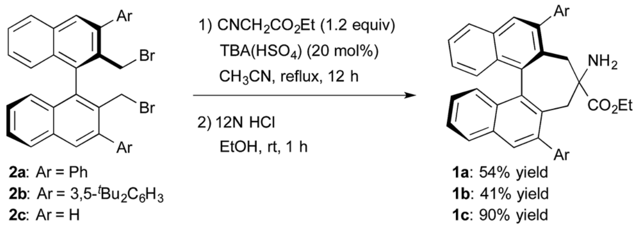
† Electronic supplementary information (ESI) available: Experimental details including characterization date, copies of ^{1}H, ^{13}C, ^{19}F NMR and HPLC traces. See DOI: 10.1039/c5sc03486h

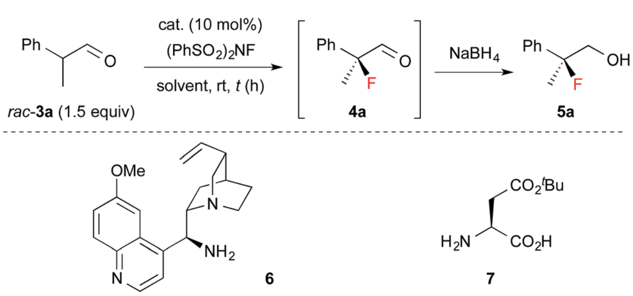


Scheme 2 Synthesis of primary amine catalysts.

The structure of the new chiral primary amine catalyst **1** is shown in Scheme 2.[10] 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.[11] 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 α-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-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% 3,5-dinitrobenzoic 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,[12] 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]

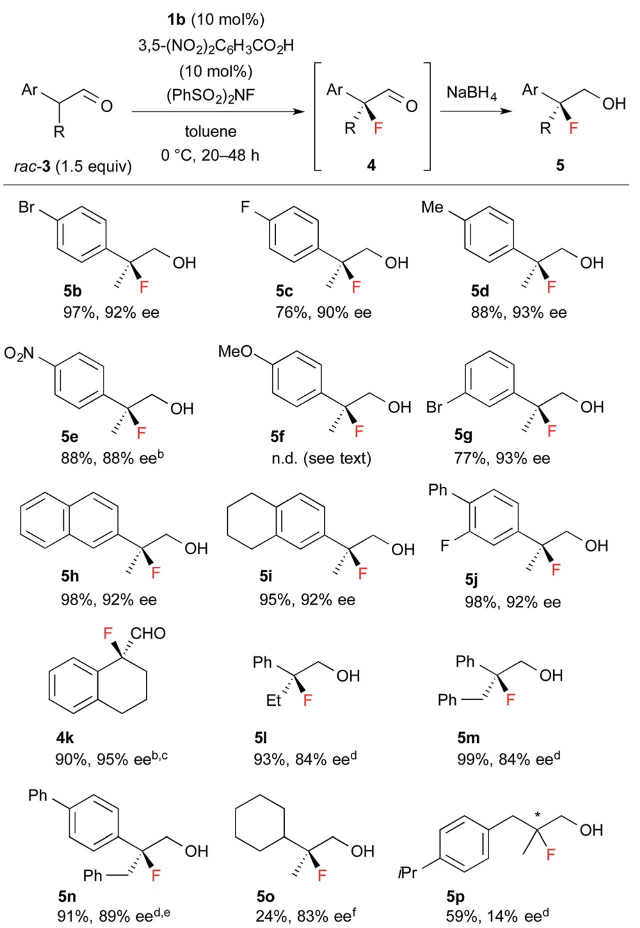
Table 1 Optimization of reaction conditions[a]



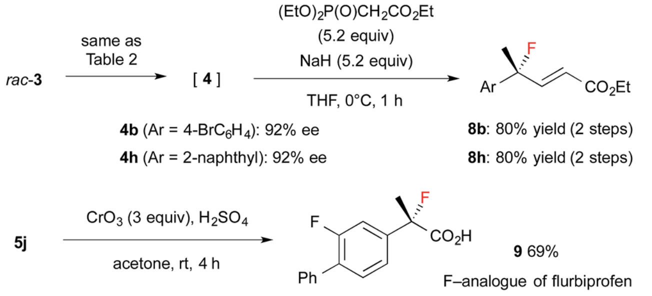
Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	Toluene	24	79	51 (*S*)
2	**1b**	Toluene	2	97	90 (*S*)
3	**1c**	Toluene	24	71	3
4	**1b**	CH_2Cl_2	18	86	74 (*S*)
5	**1b**	EtOAc	4	99	82 (*S*)
6	**1b**	^{t}BuOMe	3	97	86 (*S*)
7	**1b**	MeOH	48	<10	n.d.
8[d]	**1b**	Toluene	6	82	88 (*S*)
9[e]	**1b**	Toluene	48	73	93 (*S*)
10[e,f]	**1b**	Toluene	48	86	95 (*S*)
11[g]	**6**	$CHCl_3$	24	76	13 (*R*)
12[h]	**7**	THF	2	98	13 (*S*)

[a] Reactions were carried out with 1.5 equiv. of *rac*-**3a** based on NFSI in the presence of 10 mol% **1** unless otherwise noted. [b] Isolated yield of **5a**. [c] Absolute configuration of the major enantiomer is specified in parenthesis. [d] 1.5 equiv. of NFSI was used based on *rac*-**3a**. [e] At 0 °C. [f] 10 mol% 3,5-(NO_2)$_2$$C_6H_3CO_2H$ was used as a co-catalyst. [g] 5 mol% catalyst was used with 15 mol% TFA. [h] 20 mol% catalyst.

Table 2 Substrate scope of fluorination of **3**[a]



[a] 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_2)$_2$$C_6H_3CO_2H$. Isolated yield of **5** are described, except for **4k**. [b] Purified product contained *ca.* 5% of an inseparable by-product. [c] At rt. for 2 h. [d] At rt. for 12–24 h. [e] 20 mol% catalyst. [f] 30 mol% catalyst.



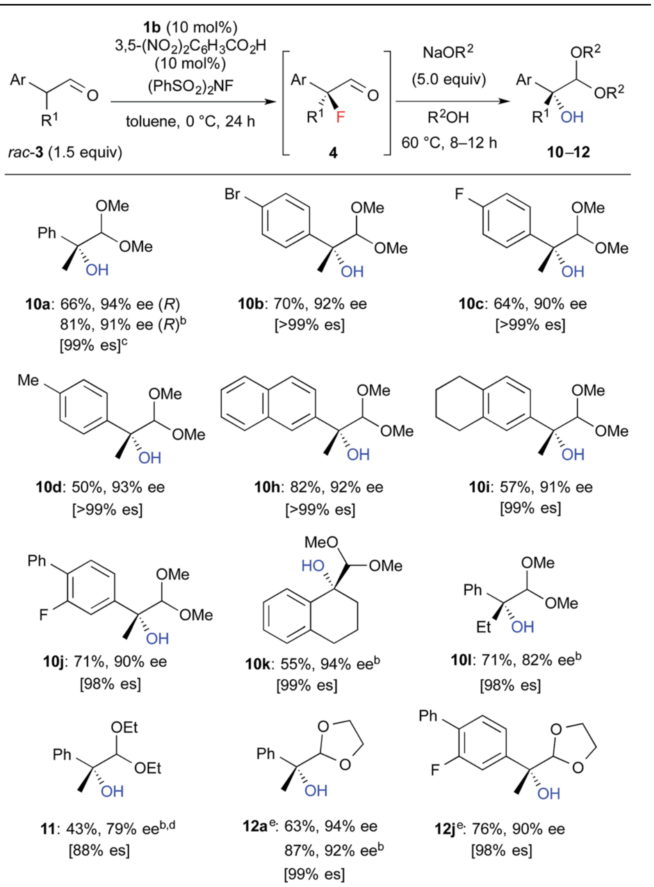
Scheme 3 Synthesis applications of α-fluoroaldehydes.

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 α-alkyl-α-aryl aldehydes were successfully fluorinated to afford the corresponding α-fluoroaldehydes in high yields with high enantioselectivities. On the other hand, the reaction with α,α-dialkyl aldehyde **3o** yielded the product with good enantioselectivity but in poor yield, while the reaction with **3p** showed 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.

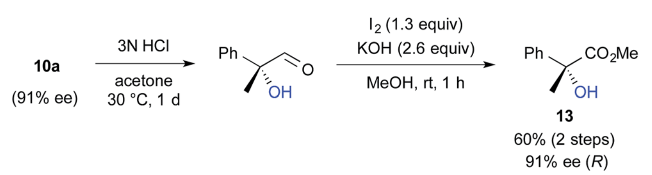
The resulting fluorides can be converted into a variety of other tertiary fluorides (Scheme 3). First, allyl fluorides **8** were synthesized by Horner–Wadsworth–Emmons reaction of α-fluoroaldehydes **4** in good yield. Next, fluorohydrine **5j** was oxidized to carboxylic acid **9**,[13] which is a 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 carbon–fluorine 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_N2-type nucleophilic substitution of sp^3-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_N2 reaction of α-chloro-α-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).[16] 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 α-hydroxy cyclic acetal **12** was obtained. The present method would be a good alternative

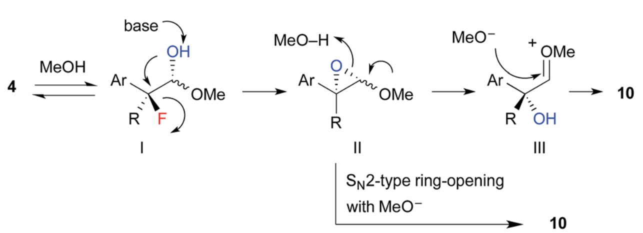
Table 3 Asymmetric synthesis of α-hydroxyacetals 10[a]



[a] Isolated yields of **10–12** from **3** are described. [b] The first step was carried out at rt. [c] es = (ee of **10–12**)/(ee of **4**). [d] The second step was carried out at rt. under reflux conditions. Purified product contained *ca.* 10% of an inseparable by-product. [e] The second step was carried out with NaH in ethylene glycol instead of $NaOR^2/R^2OH$.



Scheme 4 Synthesis of α-hydroxyesters.



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 α-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. ^{1}H NMR studies revealed that α-fluoroaldehyde **4** is in equilibrium with hemiacetal I in d_4-methanol. Upon treatment with NaOMe, epoxide II is formed *via* intramolecular S_N2 displacement, which involves the stereospecific cleavage of C–F bond. Then, regeneration of the carbonyl moiety and subsequent acetalization or direct S_N2-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 α-branched aldehydes. Further, we found that the resulting fluoroaldehydes could be converted into the corresponding α-hydroxyacetals *via* stereospecific C–F bond cleavage.

Acknowledgements

This study was supported by Daiichi Sankyo Co., Ltd. and a Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" (26105728) from MEXT, Japan. We thank the Nippon Synthetic Chemical Industry Co., Ltd. for supplying ethyl isocyanoacetate, which was used in the synthesis of the chiral amine catalyst.

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