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A Simple Primary Amine Catalyst for Enantioselective α-Hydroxylations and α-Fluorinations of Branched Aldehydes

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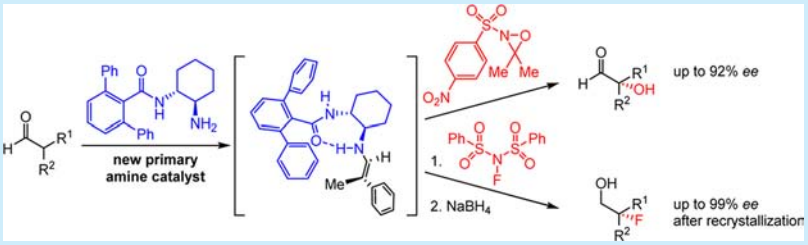
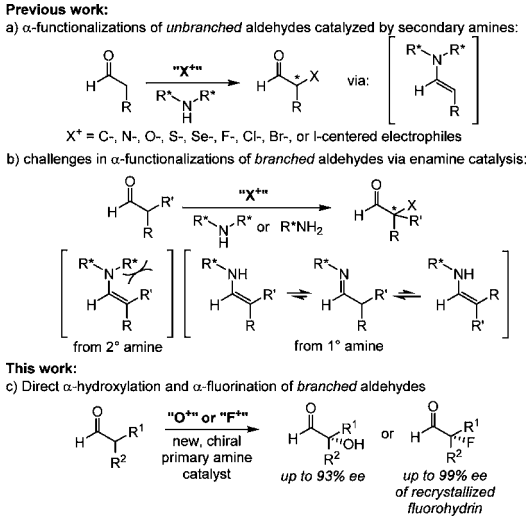
Supporting Information



ABSTRACT: A new primary amine catalyst for the asymmetric α-hydroxylation and α-fluorination of α-branched aldehydes is described. The products of the title transformations are generated in excellent yields with high enantioselectivities. Both processes can be performed within short reaction times and on gram scale. The similarity in results obtained in both reactions, combined with computational evidence, implies a common basis for stereoinduction and the possibility of a general catalytic mechanism for α-functionalizations. Promising initial results in α-amination and α-chlorination reactions support this hypothesis.

Aminocatalysis via enamine intermediates has emerged as a proven strategy for direct α-functionalization of carbonyl compounds, providing access to chiral products bearing new C−C, C−N, and C−X (X = halogen or chalcogen) linkages in an enantiocontrolled manner. This approach is especially well-developed in reactions of unbranched aldehydes to form α-trisubstituted products (Scheme 1a) using chiral secondary amine catalysts.[1] In contrast, highly enantioselective α-functionalizations of α-branched aldehydes, which represent efficient approaches to multifunctional compounds bearing tetrasubstituted, stereogenic centers (Scheme 1b), are far less well-developed.[2] With few exceptions, secondary amines are ineffective catalysts for reactions of α-branched aldehydes, a phenomenon ascribable to the steric demands of the reacting partners.[3] Primary amines form less hindered enamine intermediates, but introduce other problems such as unfavorable tautomer equilibria and poorer control of *E*/*Z* selectivity.[4] With these considerations in mind, we have sought to develop an effective and general catalyst for functionalization of α-branched aldehydes. We report herein a simple, new primary amine catalyst that effectively promotes highly enantioselective α-hydroxylations and α-fluorinations of α,α-disubstituted aldehydes (Scheme 1c) under simple conditions and on preparative scales.

Scheme 1. Asymmetric Catalytic α-Functionalizations via Enamine Catalysis



Most likely because of the problems inherent to primary amine-derived enamines outlined in Scheme 1b,[3−5] primary amines have been investigated far less intensively than secondary amines in aminocatalysis, despite the central role of lysine as Nature's enamine catalyst in aldolases, decarboxylases, and dehydratases.[6] Nonetheless, over the past several years, various new classes of chiral primary amines have been identified and shown to be effective in promoting enantioselective α-functionalizations of hindered carbonyl compounds. In the context of C−O and C−F bond-forming reactions, List et al. found primary amine catalysts to perform better than pyrrolidine derivatives in the α-benzoyloxylation of ketones and α-branched aldehydes.[7] Similarly, the Jørgensen[8] and Barbas[9] groups were unable to use secondary amine catalysts to effect the α-fluorination of branched aldehydes in greater than 50% *ee*, but Jørgensen et al. later demonstrated that an axially chiral primary

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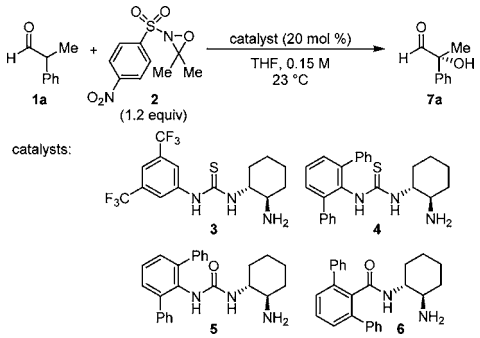
amine catalyst could be employed to prepare the same tertiary fluorides in up to 90% *ee*, albeit with low to moderate yields.[10]

Our group[11] and others[12] have investigated bifunctional primary aminothioureas designed to engage in activation of hindered carbonyls via formation of nucleophilic enamines with simultaneous activation of the electrophilic reacting partner via H-bond catalysis. This principle has been applied successfully in C−C bond-forming reactions of α-branched aldehydes, including conjugate additions[11a] and simple alkylations.[11b] We hypothesized that a similar cooperative mechanism might be applied to α-oxidation reactions, with the H-bond donor activating a sulfonyl-based electrophile. We chose to examine both the α-hydroxylation (Table 1) and α-fluorination (Table 2)

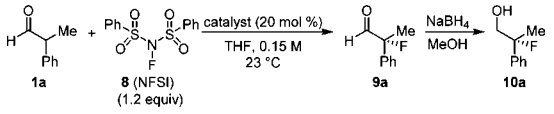
Table 1. Optimization of the α-Hydroxylation[a]



entry	cat.	additive(s)	time (h)	conversion[b] (%)	*ee*[c] (%)
1	**3**	–	90	61	22
2	**4**	–	90	61	51
3	**5**	–	90	56	59
4	**6**	–	16	73	75
5	**6**	TFA (20 mol %)	2	87	73
6	**6**	$NaHCO_3$ (1.5 equiv)	48	72	71
7	**6**	TFA (20 mol %) + $NaHCO_3$ (1.5 equiv)	4	85	87

[a]Reactions performed on 0.15 mmol scale. [b]Determined by GC analysis. [c]Determined by HPLC analysis of reduced diol using commercial columns with chiral stationary phases.

Table 2. Optimization of the α-Fluorination[a]



entry	cat.	additive(s)	time (h)	conversion[b] (%)	*ee*[c] (%)
1	**3**	–	90	70	31
2	**4**	–	90	72	59
3	**5**	–	90	60	67
4	**6**	–	16	74	78
5	**6**	TFA (20 mol %)	2	64	80
6	**6**	$NaHCO_3$ (1.5 equiv)	4	82	79
7	**6**	TFA (20 mol %) + $NaHCO_3$ (1.5 equiv)	4	83	83

[a]Reactions performed on 0.15 mmol scale. [b]Conversion to aldehyde **9a** determined by GC analysis of crude reaction mixture. [c]Determined by HPLC analysis of fluorohydrin **10a** using commercial columns with chiral stationary phases.

of racemic aldehyde **1a** as model reactions.[13,14] The *N*-sulfonyloxaziridine **2** (Table 1) was selected as a potentially practical reagent for α-hydroxylations.[15] This oxaziridine, developed by the Yoon group, is crystalline, bench-stable, and readily accessible on multigram scales.[16] The commercially available and widely used NFSI (**8**) was selected as the fluorinating reagent. The volatility of fluoroaldehyde **9a** and its instability on silica gel necessitated its *in situ* reduction to fluorohydrin **10a** for isolation and analysis.[8,10,17]

The primary aminothiourea **3**[11b] catalyzed both model reactions (Tables 1 and 2) with promising results, affording the desired α-oxidation products with low enantioselectivity (entries 1). The more hindered aminothiourea **4**[18] and its urea analog **5** displayed very similar reactivity but significantly higher enantioselectivities relative to **3** (entries 2 and 3). Given that the thiourea or urea components of **4** and **5** are effectively blocked by the sterically demanding 2,6-diphenylaryl group, these latter results raised the question of whether the dual H-bond components of these catalysts were engaged directly in the catalytic mechanism. Indeed, the dual H-bond donor proved unnecessary, as the simple benzamide analog **6** displayed substantially higher reactivity and enantioselectivity in both transformations (entries 4). While further modification of the chiral diamine catalyst structure did not afford additional improvements,[13] introduction of achiral acid and base additives had a pronounced beneficial effect.[19] Thus, strongly acidic organic acids such as trifluoroacetic acid (TFA) provided significant rate enhancements in both reactions (entries 5), and the combination of TFA and $NaHCO_3$ as additives afforded a cooperative enhancement in both rate and enantioselectivity for the two reactions (entries 7).[13,20]

With the results of these preliminary optimization studies in hand, we explored the scope of the α-functionalizations in reactions carried out at 1.00 mmol of aldehyde. In adjusting the conditions for this larger scale, we found that the overall reaction concentration could be doubled and the amount of electrophile and $NaHCO_3$ decreased to 1.0 equiv each without deleterious effect, thus improving the efficiency of the overall processes. With this optimized protocol, α-hydroxyaldehyde **7a** was produced in the model reaction in 90% *ee* and 95% isolated yield (Scheme 2). Substitution on the aromatic ring of the aldehyde was generally well tolerated (**7b**–**l**), although ortho-substituted substrates underwent oxidation with slower reaction rates and lower enantioselectivity (**7f**). Smaller heteroaromatic rings (**7m**), α-ethyl-substituted aldehydes (**7n**), and α,α-dialkyl branched aldehydes (**7o**) also underwent α-oxidation, albeit with significantly lower (<80%) enantioselectivities.

The α-fluorination was also investigated in 1.00 mmol scale reactions under conditions strictly analogous to those employed in the α-hydroxylation reaction (Scheme 3). Although lower enantioselectivities are generally obtained in the fluorination reaction, similar scope and limitations were observed in the two transformations. In particular, substituted arylpropionaldehyde derivatives generally undergo α-fluorination with consistent results. Furthermore, the enantiomeric purity of many of the fluorohydrins could be upgraded by recrystallization.[13] As in the α-hydroxylation reaction, α-ethyl-substituted aldehydes and α,α-dialkyl branched aldehydes afforded α-fluorination products (**10n** and **10o**, respectively) with significantly lower (<70%) enantioselectivities.

Both reactions were scaled up successfully to generate over a gram of hydroxyaldehyde **7a** or fluoroalcohol **10a** (Scheme 4). Higher enantioselectivity was obtained in the α-hydroxylation when the reaction was performed at reduced temperature, although longer reaction times were required.[21] In the case of the

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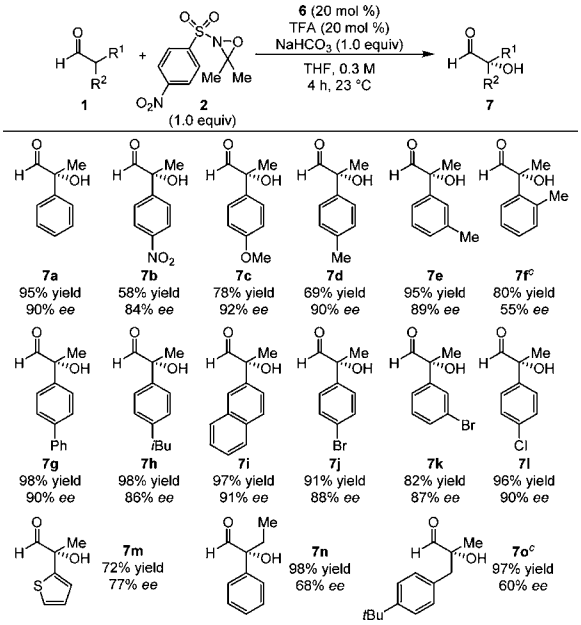
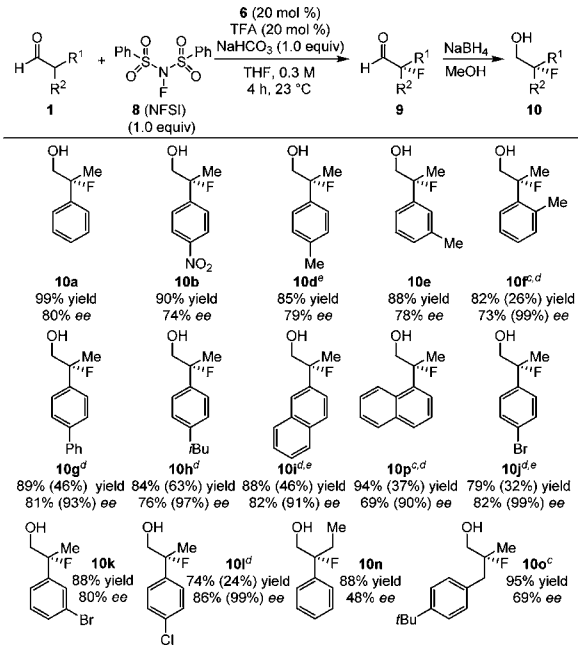
Scheme 2. Scope of the α-Hydroxylation[a,b]



[a]Reactions performed on 1.00 mmol scale. Absolute configurations assigned based on comparison of optical rotations to published data.[13] [b]The *ee* determined by HPLC analysis of reduced diol using commercial columns with chiral stationary phases. [c]20 h.

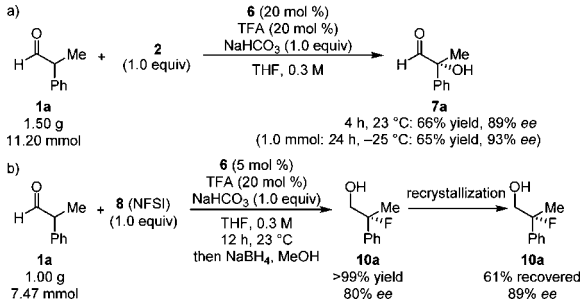
Scheme 3. Scope of the α-Fluorination[a,b]



[a]Reactions performed on 1.00 mmol scale. Absolute configurations assigned based on comparison of optical rotations to published data.[13] [b]The *ee* determined by HPLC analysis using commercial columns with chiral stationary phases. [c]20 h. [d]Numbers in parentheses correspond to isolated yield and *ee* after recrystallization. [e]Absolute configuration confirmed by X-ray crystallography.[13]

fluorination, the loading of catalyst **6** could be decreased to 5 mol % to achieve a quantitative yield of **10a** within 12 h.[22] Recrystallization from hexanes provided the tertiary fluoride in upgraded *ee*.[13]

Scheme 4. Gram-Scale α-Functionalizations



The viability of putative enamine intermediate **11a** (Figure 1) was confirmed by MS analysis of a reaction mixture lacking

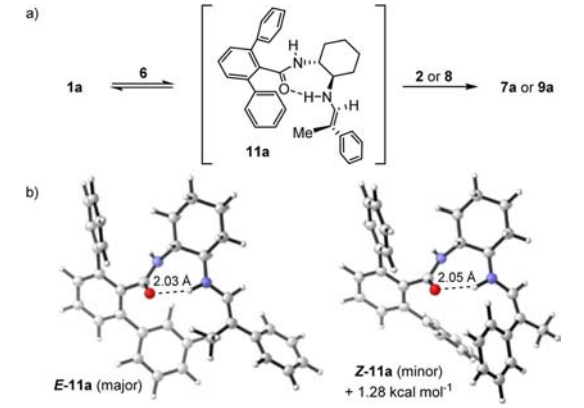


Figure 1. (a) Formation of proposed intermediate enamine **11a**. (b) Lowest energy calculated structures (B3LYP/6-31G(d)) for *E*-enamine **11a** leading to observed major enantiomers (*R*)-**7a** and (*R*)-**9a** (left) and *Z*-enamine **11a** leading to minor enantiomers (*S*)-**7a** and (*S*)-**9a**.

oxaziridine **2** or NFSI (**8**).[13] We anticipated that a detailed understanding of the conformational properties of this enamine might help elucidate a model for stereoinduction and inform further reaction design. Computational analysis of **11a** predicted a lowest energy structure in which an intramolecular H-bond between the benzamide carbonyl and enamine NH serves to rigidify the catalyst backbone. The terphenyl moiety projects one of its aryl rings directly behind one face of the enamine, likely blocking access to incoming electrophile **2** or **8** (Figure 1b, left). This analysis of ***E*-11a** correctly predicts the predominant (*R*)-configuration of products **7a** and **9a**. The corresponding enamine stereoisomer ***Z*-11a** (Figure 1b, right) is calculated to lie 1.28 kcal mol^{-1} higher in energy, a result attributable to steric interactions between the aryl group of the substrate and one of the phenyl substituents of the catalyst.

This stereochemical analysis raises the possibility that enantioselectivity in reactions of branched aldehydes catalyzed by **6** is dictated primarily by the *E*/*Z* ratio of the enamine intermediates,[20] and that other electrophiles or oxidants may be expected to react with the same sense and similar levels of stereoinduction. Preliminary results for an α-amination (Scheme 5a)[2] and the first asymmetric α-chlorination (Scheme 5b) of a branched aldehyde support this hypothesis, with α-substitution products **13** and **15** obtained in 85% and 66% *ee*, respectively; these unoptimized results are encouraging starting points for future reaction development.

In conclusion, the new aminobenzamide catalyst **6** promotes efficient α-hydroxylations and α-fluorinations of α,α-disubsti-

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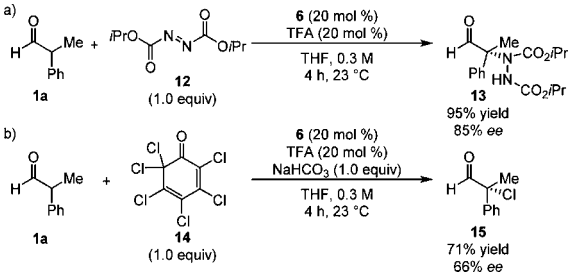
Scheme 5. Additional α-Functionalization Reactions Catalyzed by Benzamide 6



tuted aldehyde substrates in excellent yields, high enantioselectivities, and short reaction times. Experimental and computational studies indicate that stereoselectivity may be defined and limited by the *E*/*Z* ratio of the key enamine intermediates. Our ongoing efforts are directed toward applying this insight toward the development of more selective catalysts with a broader scope, with the ultimate goal of devising a broadly general engine for α-functionalizations of branched aldehydes.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, syntheses of substrates and catalyst **6**, characterization data for all new compounds, NMR spectra and HPLC traces for α-functionalization products, geometries and energies of calculated stationary points, and crystallographic information (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01193.

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Notes

The authors declare no competing financial interest.

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(19) Acid and base additives are well-precedented promoters of enamine-catalyzed transformations. See refs 1, 2, 7b, and 11b. See also: Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2011**, *133*, 1738.

(20) The effect of various additives on enantioselectivity may be ascribed to their influence on the equilibrium *E*/*Z* ratio of enamine intermediate **11**. Different bases behave quite differently, indicating a strong dependence on the identity of the countercation. See the SI for details.

(21) No improvement in the enantioselectivities of α-fluorination were observed in reactions carried out at −25 °C.

(22) Reduction in catalyst loading below 20 mol % in the α-hydroxylation resulted in diminished yields. See the SI for details.

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