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Teresa D. Beeson, and David W. C. MacMillan

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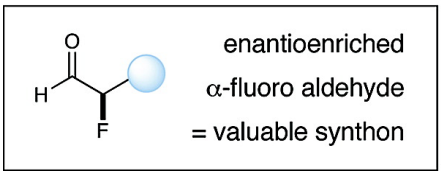
Enantioselective Organocatalytic Direct α-Fluorination



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Enantioselective Organocatalytic α-Fluorination of Aldehydes

Teresa D. Beeson and David W. C. MacMillan*

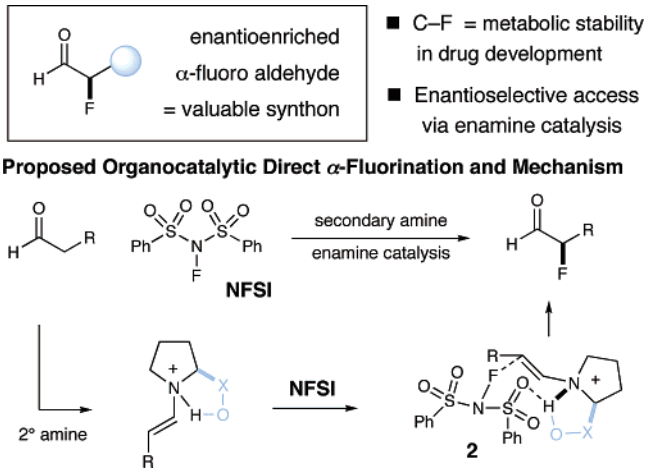
Contribution from the Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

Received March 21, 2005; E-mail: Dmacmill@caltech.edu

Abstract: The first direct enantioselective catalytic α-fluorination of aldehydes has been accomplished. The use of enamine catalysis has provided a new organocatalytic strategy for the enantioselective fluorination of aldehydes to generate α-fluoro aldehydes, an important chiral synthon for medicinal agent synthesis. The use of imidazolidinone **1** as the asymmetric catalyst has been found to mediate the fluorination of a large variety of aldehyde substrates with *N*-fluorobenzenesulfonimide serving as the electrophilic source of fluorine. A diverse spectrum of aldehyde substrates can also be accommodated in this new organocatalytic transformation. While catalyst quantities of 20 mol % were generally employed in this study, successful halogenation can be accomplished using catalyst loadings as low as 2.5 mol %.

Within the realm of drug design, the stereospecific incorporation of fluorine substituents is a powerful and widely employed tactic to circumvent metabolism issues arising from in vivo C−H bond oxidation.[1] On this basis, the catalytic production of carbon−fluorine stereogenicity has become a methodological goal of central importance to practitioners of chemical and pharmaceutical synthesis.[2] Surprisingly, however, catalytic methods for the asymmetric construction of C−F bonds are rare,[3] the majority involving α-substituted *β*-keto ester substrates that are structurally precluded from product epimerization.[4] As part of a program focused upon the development of organic catalysts for broadly useful organic reactions, we recently reported the enamine-catalyzed α-oxidation[5] and α-chlorination of aldehydes.[6] In this paper we further advance this organocatalysis concept to document an operationally trivial procedure for the enantioselective α-fluorination of aldehydes (Scheme 1). This new organofluorine reaction is founded upon the use of imidazolidinone **1**,[7] a commercial catalyst that enables rapid and enantiocontrolled C−F bond formation while being inert to product epimerization or functionalization pathways.

Scheme 1



The stereodefining step of enamine catalysis is widely believed to involve a generic platform of induction wherein a proton linchpin enforces electrophile activation in the asymmetric vicinity of a nucleophilic enamine. Provoked by the potential of developing an enantioselective aldehyde α-fluorination, we felt that an important extension of this induction paradigm might be realized using electrophilic fluorine reagents that are geometrically capable of catalyst proton-association and fluorine delivery.[8] On this basis, we identified *N*-fluorobenzenesulfonimide (NFSI) as a reagent that might participate in the requisite closed transition state **2** via sulfone-proton bonding and concomitant fluorine/enamine activation (Scheme 1). The use of NFSI as an electrophilic fluorine source was particularly

(1) For recent reviews see: (a) Böhm, H.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (b) Maienfisch, P.; Hall R. G. *Chimia* **2004**, *58*, 93. (c) Hiyama, T.; Shimizu, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 214.

(2) For reviews of fluorination see: (a) France, S.; Weatherfax, A.; Lectka, T. *Eur. J. Org. Chem.* **2005**, 475. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (c) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147. (d) Togni, A.; Mezzetti, A.; Barthazy, P.; Becker, C.; Devillers, I.; Frantz, R.; Hintermann, L.; Perseghini, M.; Sanna, M. *Chimia* **2001**, *55*, 801. (e) Davis, F. A.; Kasu, P. V. N. *Org. Prep. Proc. Int.* **1999**, *31*, 125.

(3) First catalytic asymmetric α-fluorination: Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *36*, 4359.

(4) Some recent examples of asymmetric fluorination of *β*-keto esters or *β*-keto phosphonates (a) Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46*, 1447. (b) Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, 1703. (c) Ma, J.-A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, 1007. (d) Kim D. Y. *Org. Lett.* **2002**, *4*, 545. (e) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2004**, *125*, 1357.

(5) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.

(6) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.

(7) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

(8) For reviews of N−F electrophilic fluorinating agents see: (a) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1. (b) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737. (d) Wilkinson J. A. *Chem. Rev.* **1992**, *92*, 505.

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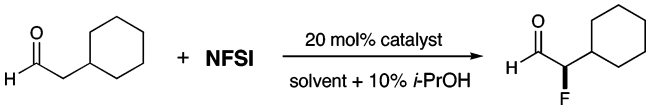
Table 1. Effect of Catalyst, Solvent, and Temperature on α-Fluorination

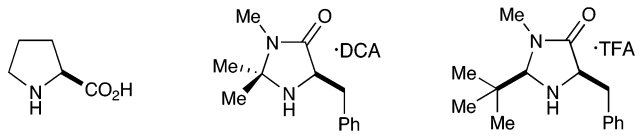


entry	catalyst	solvent	temp (°C)	time (h)	% convrsn[a]	% ee[b]
1	L-proline	THF	23	4	79	26
2	3	THF	23	0.3	96	63
3	1	THF	23	0.5	73	98
4	1	CH_3CN	23	3	75	96
5	1	EtOAc	23	0.5	84	96
6	1	acetone	23	1	89	97
7	1	$CHCl_3$	23	1	73	96
8	1	THF	4	6	97	98
9	1	THF	−10	12	98	98

[a] Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). [b] Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).

attractive, as it is an inexpensive, bench-stable solid that is readily handled by experimentalists or automated systems.[9]

As revealed in Table 1, the proposed organocatalytic α-fluorination is indeed possible with a variety of amine catalysts; however, poor stereoselectivities are observed with L-proline or imidazolidinone **3** (Table 1, entries 1 and 2, ≤63% ee). In



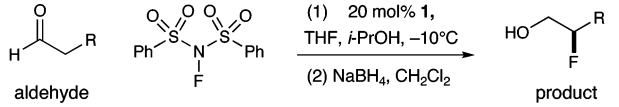
contrast, exposure of cyclohexylacetaldehyde to NFSI in the presence of imidazolidinone **1** leads to the desired α-fluoro aldehyde adduct with excellent levels of enantiocontrol (entry 3, 98% ee). A survey of reaction media with catalyst **1** reveals that a number of solvents (in combination with 10% *i*-PrOH[10]) may be utilized without significant loss in asymmetric induction or reaction efficiency (entries 3−7). It is interesting to note that carbonyl-containing solvents (e.g. acetone) do not sequester the catalyst or electrophile to an extent that is detectable (entry 6, 89% conversion, 97% ee). The impact of temperature on enantioselectivity was minimal (cf. entries 3 and 9); however, improved conversion was observed at −10 °C (entry 9). The superior levels of induction and efficiency exhibited by amine salt **1** in THF−*i*-PrOH at −10 °C to afford (*R*)-2-fluorocyclohexylacetaldehyde in 98% ee and 98% conversion prompted us to select these catalytic conditions for further exploration.

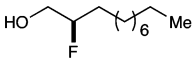
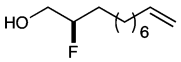
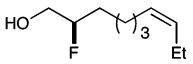
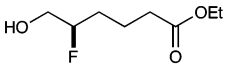
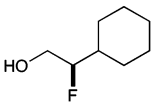
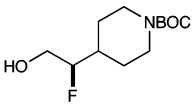
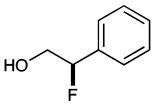
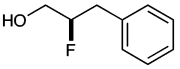
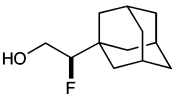
We next examined the scope of the aldehyde component in this enantioselective α-fluorination protocol. As highlighted in Table 2, a wide range of functional groups, including olefins, esters, amines, carbamates, and aryl rings, can be readily tolerated on the aldehydic substrate (entries 2−4, 6−8; 91−99% ee). Moreover, extensive variation in the steric demands of the aldehyde substituent can be realized (entries 1, 5, 7−9;

(9) (a) Development of NFSI: Differding, E.; Ofner, H. *Synlett* **1991**, 187. (b) For an investigation of the reactivity of NFSI, see: Antelo, J. M.; Crugeiras, J.; Leis, J. R.; Ríos A. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2071.

(10) While the use of *i*-PrOH as the reaction medium was less than fruitful, the addition of 10% *i*-PrOH as a cosolvent generally resulted in improved enantiocontrol and efficiency. Studies to understand this phenomenon are now underway.

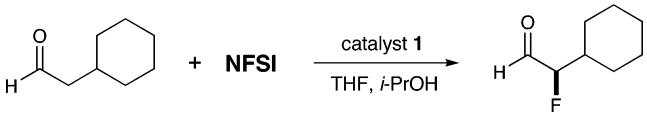
Table 2. Enantioselective α-Fluorination: Substrate Scope



entry	product	time (h)	% yield	% ee[a]
1		10	70	94
2		10	79	94
3		10	81	94
4		12	77	91
5		12	96	99[b]
6		12	85	98
7		10	54	99[b]
8		12	71	96[b]
9		12	82	98

[a] Enantiomeric excess determined by chiral HPLC analysis of the 2-naphthoyl derivative (Chiralcel OJ). [b] Enantiomeric excess determined by chiral GLC analysis (Macherey-Nagel Hydrodex-B-TBDAc).

Table 3. Effect of Catalyst Loading on Aldehyde α-Fluorination



entry	mol % catalyst 1	temp (°C)	time	% convrsn[a]	% ee[b]
1	20	23	30 min	73	98
2	20	−10	12 h	98	98
3	10	23	3 h	78	98
4	10	4	8 h	97	98
5	5	23	3 h	66	98
6	5	4	25 h	95	98
7	2.5	23	12 h	79	98

[a] Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). [b] Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).

R = nonyl, cyclohexyl, Bn, Ph, adamantyl) without loss in efficiency or enantiocontrol (54−96% yield, 94−99% ee). A catalyst exposure study has revealed that product epimerization is not observed over the indicated reaction time for any case shown in Table 2. These results serve to illustrate the remarkable capacity of imidazolidinone **1** to successfully differentiate between the aldehyde α-methylene substrates and the α-fluoro

aldehyde products. A defining example of such chemoselectivity is found in the production of (*R*)-2-fluorophenylacetaldehyde, a highly enolizable aldehyde that is configurationally stable under these mild organocatalytic conditions (entry 7, 99% ee).

Last, the effect of catalyst loading on reaction efficiency has been evaluated (Table 3). Catalyst loadings as low as 2.5 mol % can be utilized without loss in enantiocontrol (entry 7, 98% ee). In terms of operational convenience, the use of 20 mol % imidazolidinone **1** at −10 °C or of 5−10 mol % of **1** at 4 °C ensures high levels of reaction efficiency and enantioselectivity while expedient reaction times are maintained (entry 4, 4 °C, 10 mol % **1**, 97% conversion, 98% ee, 8 h; entry 6, 4 °C, 5 mol % **1**, 95% conversion, 98% ee, 25 h).

In summary, we have described the first enantioselective α-fluorination of aldehydes.[11] This mild, operationally simple, organocatalytic protocol allows direct access to carbon−fluorine stereogenicity in a wide variety of structural contexts using a commercial catalyst and electrophilic fluorine source.

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Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

JA051805F

(11) Note added in proof: After the submission of this paper, a study outlining the α-fluorination of aldehydes with low enantioselectivities was reported online: Enders, D.; Huttl, M. R. M. *Synlett* **2005**, *6*, 991.