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Enantioselective Fluorination of Spirocyclic β-Prolinals Using Enamine Catalysis

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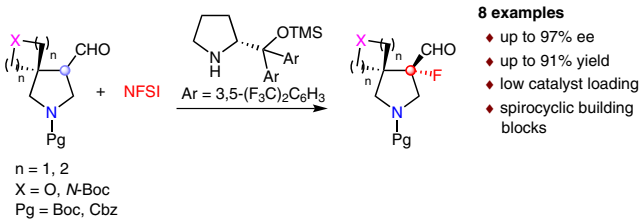

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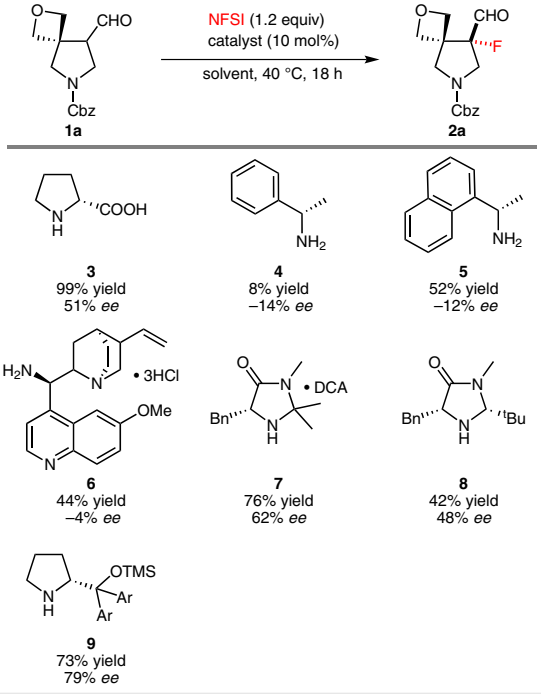
Abstract A series of spirocyclic carbaldehydes were successfully fluorinated using enamine catalysis, furnishing the corresponding tertiary fluorides in both high yields and enantioselectivities. The fluorinated spirocycles provide a set of novel building blocks interesting from a medicinal chemistry point of view.

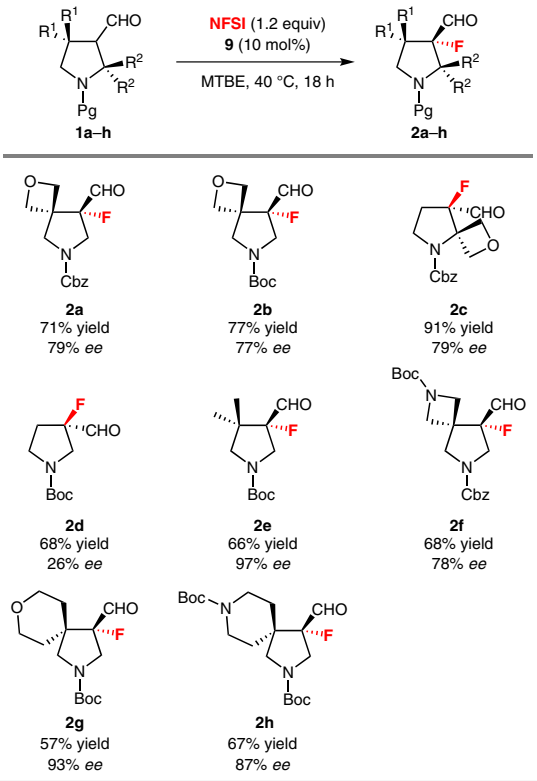
Key words spirocycles, organocatalysis, enantioselective catalysis, fluorination, asymmetric synthesis

In modern drug discovery, the ability to tailor the properties of lead compounds by selective introduction of fluorine, affecting parameters such as permeability, pK_a, and potency, has provided medicinal chemists with a useful tool for a more innovative design of active pharmaceutical ingredients.[1] Despite the potentially rewarding impact of introducing fluorine, accessing more advanced fluorinated scaffolds is mainly limited by a lack of synthetic methodology.[2] Another important parameter in medicinal chemistry research is the synthetic accessibility of spatially diverse building blocks with a defined three-dimensional geometry. The control of molecular geometry provides the possibility for better vectorization, allowing functional groups to be directed towards regions that are optimal for target interaction.[3] Spirocyclic building blocks constitute a structurally attractive compound class, in many ways similar to regular saturated heterocycles. However, the conformational constraints of the spirocyclic structures allow access to different chemical space relative to the native heterocycles, thus providing medicinal chemists with increased building-block diversity. Herein, we present the enantioselective fluorination of spirocyclic carbaldehydes to yield a range of novel fluorinated building blocks, successfully facilitated using enamine catalysis, a subject that has been thoroughly studied for nonbranched aldehydes a decade ago.[4] However, only recently were a series of simple acyclic α-branched aldehydes fluorinated with high enantioselectivity employing primary amines as organocatalysts.[5] Based on the well-established methodology for α-monosubstituted aldehydes using a commercially available fluorine source, *N*-fluorobenzenesulfonimide (NFSI), the fluorination of the spirocyclic compound **1a** comprised of an oxetane and a pyrrodine was examined. In these reactions a series of structurally different organocatalysts in methyl *tert*-butyl ether (MTBE) or a mixture of THF and *i*-PrOH at 40 °C were tested (Scheme 1).[4a,b,6] The reaction catalyzed by proline furnished the fluorinated aldehyde **2a** in high yield, although with moderate control of the stereochemical outcome. The use of three branched chiral primary amines as catalysts furnished the opposite enantiomer of **2a**, albeit with poor selectivity. The use of imidazolidinone catalyst **7** showed an increased enantioselectivity relative to proline and provided **2a** in 76% yield. Encouragingly, well-known silylated diaryl prolinol **9** catalyzed the fluorination of **1a** in both high yield and with 79% ee. In order to further establish the substrate scope of the enantioselective fluorination using **9** on spirocyclic frameworks, a range of pyrrolidine-based substrates **1a–h** were prepared using either a 1,3-dipolar cycloaddition protocol or an intramolecular cyclization approach.[7]

The scope of the enantioselective fluorination of spirocyclic carbaldehydes was initially examined by studying the tolerability of different carbamate-based *N*-protecting groups by comparing the enantioselectivity in the fluorination of **1a** and **1b** (Scheme 2). As the fluorination of the *N*-Boc-protected analogue **1b** furnished the corresponding product **2b** in high yield with 77% ee, an outcome similar to what was obtained for **2a**, the *N*-protecting group seemed



Scheme 1 Reactions performed on 0.1 mmol scale. Solvent = MTBE (0.2 M) for **4**, **5** and **9**, whereas *i*-PrOH–THF (1:9, 0.2 M) was used for **3**, **6**–**8**. The yields reported are isolated yields. The experiment with **9** was also conducted using 1 mol% catalyst with no loss in ee, albeit with significantly decreased conversion after 18 h. Ar = 3,5-$(F_3C)_2C_6H_3$, DCA = 2,2-dichloroacetic acid. The ee was determined using chiral SFC after reduction to the corresponding alcohol.



Scheme 2 The ee was determined using chiral SFC after reduction to the corresponding alcohol or on a *p*-nitrobenzoyl derivative; see the Supporting Information for further details. The yields reported correspond to the isolated yields of the fluorinated aldehydes.

to have little influence on the enantioselectivity. However, when an *N*-benzyl protecting group was used, the reaction yielded only trace amounts of the desired product.

A similar level of enantioselectivity was observed for **1c**, where the spirooxetane is attached to the other side of the aldehyde on the pyrrolidine scaffold relative to **1a**. In the case of **2d**, without branching at the β-positions, an expected loss of enantioselectivity was observed. We propose that this result is a consequence of lower differentiation of the two α-substituents leading to a mixture of *E*- and *Z*-enamine intermediates, which give different stereochemical outcome, and not due to insufficient face shielding of the catalyst. When the pyrrolidine was substituted with *gem*-dimethyl substituents in place of the oxetane ring, as was the case for **1e**, the enantioselectivity drastically increased to 97% ee in the formation of **2e**, presumably due to the increased steric demand of the *gem*-dimethyl groups, and thus better control of the enamine *E*/*Z* ratio, relatively to the more strained oxetane ring. The substrate scope was further extended to include a spiroazetidine moiety (**1f**), bearing a *N*-Cbz group, and thus orthogonally protected to the pyrrolidine nitrogen. This provides an opportunity for diversification upon further functionalization of either the pyrrolidine or azetidine unit after chemoselective *N*-deprotection. The fluorination protocol using **9** as catalyst also tolerated six-membered rings spiro-fused at the 4-position of the pyrrolidine, including a tetrahydropyranyl (**2g**) and an *N*-Boc-protected piperidine (**2h**), furnishing the fluorinated products in high yields and enantioselectivities.

The absolute configuration of **2e** was confirmed using X-ray crystallography for **10**, a crystalline derivative of **2e**, being the product formed in highest ee (Figure 1). Furthermore, the absolute configuration of **2e** was also confirmed by vibrational circular dichroism (VCD) analysis of the corresponding alcohol.[8]

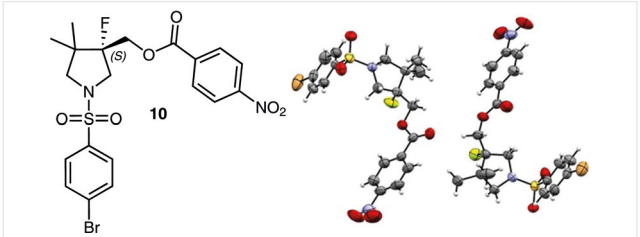
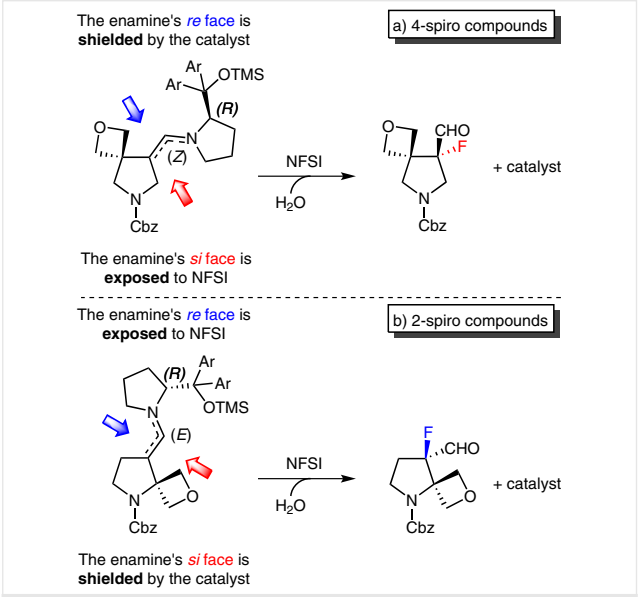


Figure 1 ORTEP diagram of **10** showing two molecules of **10** in the asymmetric unit cell. The crystals were obtained from boiling EtOH

The reaction mechanisms of stereoselective reactions of aldehydes catalyzed by secondary amines have been studied previously.[9] Based on these studies, we rationalize the stereochemical outcome imposed by catalyst **9** by the sum of two effects: the pyrrolidine substituents' impact on the enamine's *E*/*Z* equilibrium, resulting in a distinct enamine configuration, and the face-shielding ability of the catalyst, ultimately controlling the asymmetric induction (Scheme 3). Thus, a high enamine *E*/*Z* equilibrium constant combined with a fast equilibration rate relative to the rate of fluorination should allow for a high control of the enantioselectivity.[10]



Scheme 3 Enamine transition-state geometries used to rationalize the observed stereochemical outcome of the fluorination reactions

For the substrates spiro-fused at the 4-position (Scheme 3, a), the *Z*-enamine is presumed to be dominant having the pyrrolidine ring of the catalyst placed farthest away from the oxetane, and the steric bulk of the catalyst away from the *N*-Cbz group, leaving the *si* face exposed to fluorination. In contrast, the *re* face is presumed to be the most accessible site of fluorination for the substrates substituted at the 2-position due to a predominant presence of the *E*-enamine based on similar rationalization of minimizing steric interactions (Scheme 3, b).

In conclusion; a series of fluorinated spirocyclic carbaldehydes were successfully prepared in high yields and enantioselectivities using enamine catalysis, demonstrating the synthetic accessibility of such building blocks interesting in particular from a medicinal chemistry point of view.[11]

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588100.

References and Notes

(1) (a) Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K. *J. Med. Chem.* **2015**, *58*, 9041. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(2) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315.

(3) Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257.

(4) (a) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3703. (b) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826. (c) Steiner, D. D.; Mase, N.; Barbas, C. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 3706. (d) Enders, D.; Huttl, M. R. M. *Synlett* **2005**, 991. For a comprehensive review on amine catalysis, see: (e) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138.

(5) For initial fluorinations of α-branched aldehydes with up to 90% ee and moderate yields, see: (a) Brandes, S.; Niess, B.; Bella, M.; Prieto, A.; Overgaard, J.; Jørgensen, K. A. *Chem. Eur. J.* **2006**, *12*, 6039. (b) Witten, M. R.; Jacobsen, E. N. *Org. Lett.* **2015**, *17*, 2772. (c) Shibatomi, K.; Kitahara, K.; Okimi, T.; Abe, Y.; Iwasa, S. *Chem. Sci.* **2016**, *7*, 1388.

(6) For recent findings on organocatalytic fluorination of aldehydes bearing two chiral centers, see: (a) Fjelbye, K.; Marigo, M.; Clausen, R. P.; Juhl, K. *Org. Lett.* **2016**, *18*, 1170. (b) Hu, X.; Lawer, A.; Peterson, M. B.; Iranmanesh, H.; Ball, G. E.; Hunter, L. *Org. Lett.* **2016**, *18*, 662.

(7) For the synthesis of the spirocyclic structures, see: Fjelbye, K.; Marigo, M.; Clausen, R. P.; Juhl, K. *Synlett* **2016**, DOI: 10.1055/s-0036-1588902.

(8) For further details on the determination of absolute stereochemistry, see the Supporting Information.

(9) (a) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273. (b) Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 6722.

(10) For a mechanistic study of enamine catalysis on α-branched aldehydes, see: Bures, J.; Armstrong, A.; Blackmond, D. G. *Chem. Sci.* **2012**, *3*, 1273.

(11) **General Procedure for the Enantioselective Fluorination of Aldehydes**
To a solution of **1a–h** in MTBE (0.5 M) was added catalyst (*R*)-**9** (10 mol%), and the mixture was stirred for 5 min at r.t. after which *N*-fluorobenzenesulfonimide (NFSI, 1.2 equiv) was added, and the resulting mixture was stirred at 40 °C for 18 h.

Subsequently, the reaction mixture was diluted with MTBE and passed through a filter directly onto SiO_2 for flash chromatographic purification to yield the desired product.

Benzyl (*S*)-8-Fluoro-8-formyl-2-oxa-6-azaspiro[3.4]octane-6-carboxylate (2a)

The enantioselective fluorination procedure provided **2a** (76 mg, 0.259 mmol, 71% yield, 79% ee) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.10–10.07 (m, 1 H), 7.39–7.30 (m, 5 H), 5.14–5.12 (m, 2 H), 4.88–4.39 (m, 4 H), 4.06–3.50 (m, 4 H); conformers and hydrate formation. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 196.7 (d, *J* = 33.2 Hz), 196.4 (d, *J* = 33.0 Hz), 154.6, 154.4, 136.3, 136.0, 128.6, 128.5, 128.5, 128.3, 128.2, 128.1, 128.0, 97.6, 97.5, 96.3, 96.2, 96.1, 96.0, 76.4–76.2 (m), 74.2–73.7 (m), 73.2–72.8 (m), 67.5, 67.3, 55.9, 55.7, 55.1, 54.9, 53.4, 52.9, 51.8–51.0 (m), 50.9, 29.8–29.0 (m); conformers. ^{19}F NMR (471 MHz, $CDCl_3$): δ = –173.08, –174.16; conformers. ESI-HRMS: *m/z* calcd for $C_{15}H_{17}FNO_4$ [MH^+]: 294.1136; found: 294.1137. $[\alpha]_D^{22}$ +9.9 (*c* 0.27, $CHCl_3$, 79% ee).