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Letter

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Diastereodivergent Access to *Syn* and *Anti* 3,4-Substituted *β*-Fluoropyrrolidines: Enhancing or Reversing Substrate Preference

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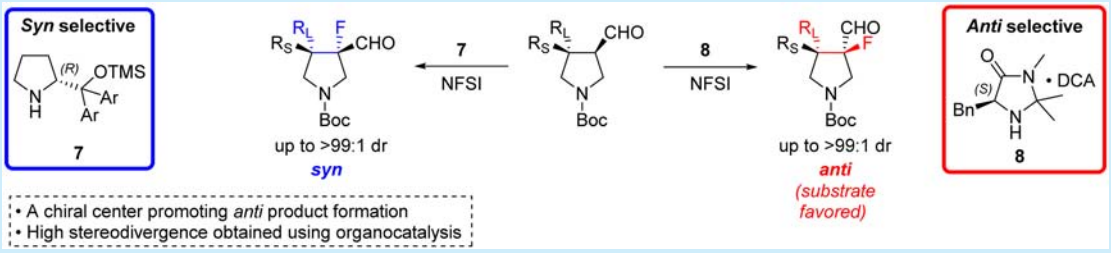
Supporting Information



ABSTRACT: A practical diastereodivergent access to *β*-fluoropyrrolidines with two adjacent stereocenters has been demonstrated, by either enhancing or completely reversing the substrate control, in the diastereoselective fluorination of a series of diverse pyrrolidinyl carbaldehydes using organocatalysis. Furthermore, enamine catalysis has been successfully utilized for kinetic resolution, obtaining a fluorinated *β*-prolinol analogue with two adjacent tetrasubstituted chiral centers in 95% *ee* from a racemic substrate.

The incorporation of fluorine as a substitute for hydrogen has had a significant impact on molecule design in drug discovery, providing medicinal chemists with a broad collection of scaffolds with attractive properties, and the possibility of fine-tuning existing scaffolds.[1−6] In particular, fluorine placed in close proximity to an amine functionality can alter the electron density and pK_a and thereby influence the pharmacokinetic profile of a compound.[7] However, the synthetic challenge of introducing fluorine in more advanced structures still limits the full exploitation of this unique element from a medicinal chemistry point of view.[8,9] The pyrrolidine scaffold is a widely occurring motif in biologically active compounds, and fluorinated analogues are emerging that exploits the physicochemical impact of H/F replacement.[10,11] Introduction of fluorine at the *β*-position of the pyrrolidine scaffold has a noticeable effect on the pK_a. However, chiral *β*-fluoropyrrolidines have previously mostly been prepared from relatively expensive fluorine containing starting materials, where the stereochemical course of the synthesis is controlled by the substrate.[12−14] The importance of controlling both the relative and absolute configurations is supported by the very different biological properties of 3,4-substituted pyrrolidines; e.g., *cis*-3,4-pyrrolidines are reported as selective serotonin inhibitors, whereas the *trans*-diastereomers had little or no activity.[15] In contrast, *trans*-3,4-substituted pyrrolidines have been developed as renin inhibitors.[16] Although it is possible to introduce fluorine on chiral polysubstituted (i.e., 3,4-substituted) pyrrolidines, there are no examples reported where this is done with high control of the stereochemical outcome. We were therefore interested in exploring the strategy for the diastereodivergent fluorination of pyrrolidines as presented in Figure 1.

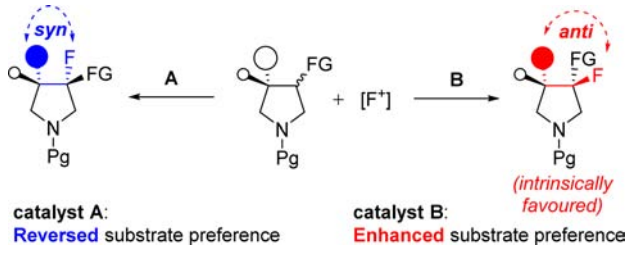


Figure 1. Diastereodivergent fluorination of chiral polysubstituted pyrrolidines. [F$^+$] = Achiral electrophilic fluorine source. FG = functional group (e.g., ester, aldehyde, amide or cyano group). The circles represent differently sized substituents.

Based on the well-established methodology of organocatalytic *α*-functionalization of aldehydes,[17] we envisioned that the aldehyde functionality would serve as an ideal handle, allowing diastereodifferentiation through enamine formation with a chiral amine. In addition, the resulting product would allow rapid chemical access to a variety of fluorinated derivatives, due to the synthetic versatility of aldehydes.[18] While the fluorination of aldehydes has been studied extensively for *α*-monosubstituted aldehydes,[19] the formation of tetrasubstituted fluorinated

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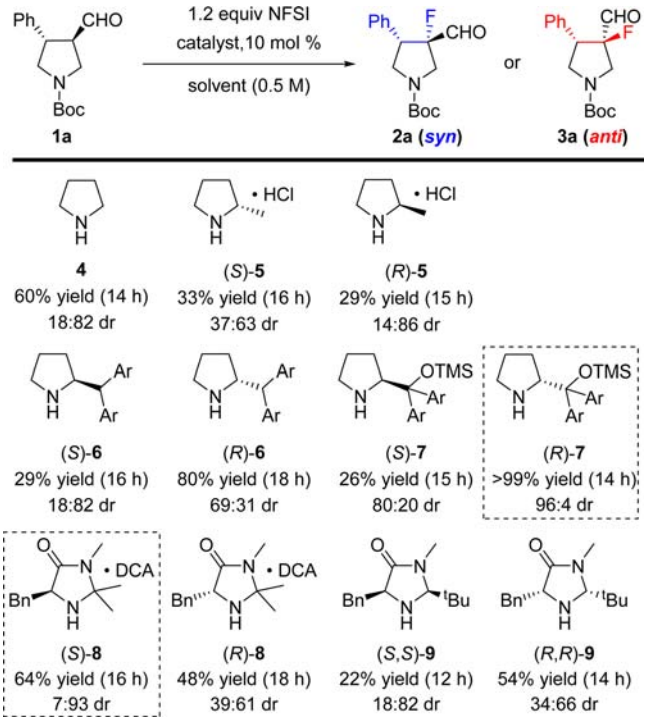
stereocenters is more synthetically challenging. The enantioselective fluorination of α-branched aldehydes, using primary amine catalysis, was recently demonstrated for a series of substrates with one chiral center,[20] whereas the diastereodivergent fluorination of aldehydes bearing two stereogenic centers remains unprecedented. Herein, the practical application of two different organocatalysts for the construction of tetrasubstituted fluorinated stereocenters, adjacent to a chiral center, is presented. A series of optically pure pyrrolidines **1a**–**g** were synthesized from α,β-unsaturated esters that underwent [3 + 2] cycloaddition with an azomethine ylide to provide the *trans*-3,4-substituted pyrrolidine ring system. Subsequent reduction followed by chiral supercritical fluid chromatographic (SFC) separation, *N*-debenzylation, *N*-Boc-protection, and oxidation afforded the aldehydes **1a**–**g**.[21a] The catalyst screening began by examining the effect of pyrrolidine catalysis on the enantiomerically pure aldehyde **1a**, using commercially available *N*-fluorobenzenesulfonimide (NFSI) as the fluorinating agent.[21b] The reaction provided a mixture of the corresponding fluorinated aldehydes **2a** and **3a** in 60% yield, with an 18:82 dr, where the only chiral information directing the stereochemical outcome was present in the substrate (Scheme 1, cat. **4**). Thus,

Scheme 1. Screening of Organocatalysts[a]



[a]The reactions were performed using 0.1 mmol of **1a** at 40 °C with reaction times in parentheses. Methyl-*tert*-butylether (MTBE) was used as solvent for all of the reactions except for **5** and **8**, where a 9:1 mixture of THF/*i*-PrOH was used. Ar = 3,5-$(F_3C)_2C_6H_3$, DCA = 2,2-dichloroacetic acid. Yields reported after silica gel chromatography. The dr was determined by LCMS analysis of the crude reaction mixture after reduction to the corresponding alcohols. A 20 mol % loading was used for **4** and **8**.

the *anti*-product **3a** was formed in majority, as a result of fluorine approaching the least hindered enamine face. The choice of solvent, fluorinating agent, and catalyst loading for the screening (Scheme 1) was based on previously successful fluorination reactions reported in literature, although the temperature was increased from rt to 40 °C to ensure full conversion of **1a**.[19a,c] For each chiral catalyst **5**–**9**, both enantiomers were examined.

When a methyl group was introduced in the catalyst ((*S*)-**5** and (*R*)-**5**), a chiral match/mismatch behavior was observed, leading to a modest improvement of selectivity for (*R*)-**5**. Encouragingly, the reversal of the stereochemical outcome of the reaction obtained by (*R*)-**6**, now favoring **2a**, occurred as a consequence of catalyst control. This behavior was further enhanced with the prolinol derived catalyst (*R*)-**7** that proved to catalyze the formation of the desired synthetically more challenging *syn* product **2a** in both high yield and dr.[22] However, the (*S*)-**7** enantiomer also favored the formation of **2a** albeit in low yield. We found it surprising that both enantiomers of catalyst **7** were selective toward the same nonsubstrate preferred product, an effect we propose could be a consequence of different enamine rotational isomers reacting with the fluorinating agent. The best catalyst for enhancing the *anti*-selectivity, to favor **3a**, was found to be the imidazolidinone (*S*)-**8**. The ability of secondary amine catalysts to direct the geometry of the iminium bond being formed in enamine reactions has been supported computationally.[23] We qualitatively use the ability of such catalyst-induced diastereofacial discrimination to rationalize the observed diastereodivergence (Figure 2a and b).

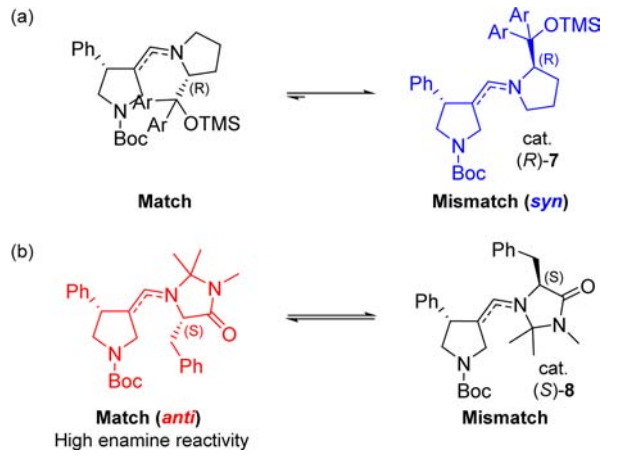


Figure 2. Iminium-enamine rotational isomers used to rationalize the observed outcome of asymmetric induction based on a presumed preference for the enamine double bond to adopt the (Z)-configuration.

These complementing properties of the two catalysts (*R*)-**7** and (*S*)-**8** allowed for a high control of the stereochemical outcome in the fluorination of **1a**. The substrate scope was subsequently examined, and as can be seen in Table 1, these two catalysts allowed the successful and stereochemically controlled fluorination of a variety of pyrrolidinyl carbaldehydes **1a**–**g** (Table 1) featuring aliphatic, aromatic, and heteroaromatic substituents, and also a case of vicinal tetrasubstituted stereocenters (Table 1, **2b** and **3b**). The aldehydes **1a**–**g** were initially fluorinated using **4** to quantify the intrinsic diastereocontrol of the substrate. When applying the diastereodivergent fluorination protocol for an *N*-benzyl protected analogue of **1d**, no significant formation of the desired product was observed. However, by employing the *N*-Boc-protecting group instead, the syntheses of **2d** and **3d** proceeded in good yields and with excellent diastereoselectivities. For **1c**, having only a methyl substituent on the 4-position and thus being the substrate with the least steric bulk, it was possible to both significantly enhance substrate

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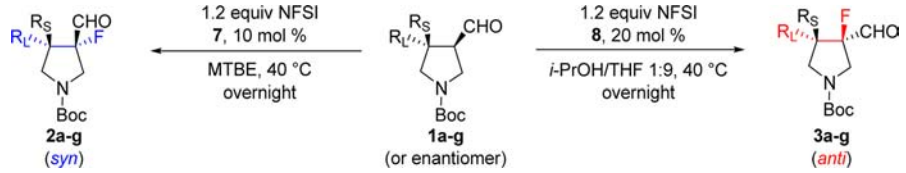
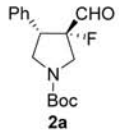
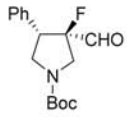
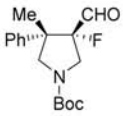
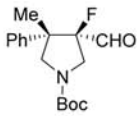
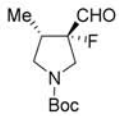
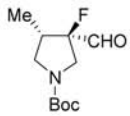
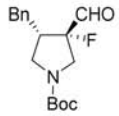
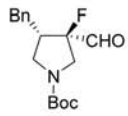
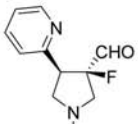
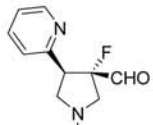
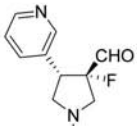
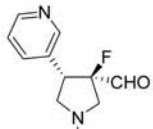
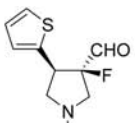
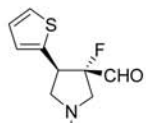
Table 1. Diastereodivergent Fluorination of Pyrrolidinyl Carbaldehydes Featuring Vicinal Stereocenters[a]



	catalyst 7				catalyst 8				catalyst 4	
products[e] *syn*	7 (*R*) or (*S*)	dr (*syn*:*anti*) isolated[b] (crude)[c]	yield[d] [%]	products[e] *anti*	8 (*R*) or (*S*)	dr (*syn*:*anti*) isolated[b] (crude)[c]	yield[d] [%]	dr[f,g] (*syn*:*anti*) (crude)[c]	yield[d] [%]
 **2a**	(*R*)	98:2 (96:4)	>99 (14 h)	 **3a**	(*S*)	2:98 (7:93)	64 (16 h)	(18:82)	60 (14 h)
 **2b**	(*R*)	98:2 (96:4)	74 (14 h)	 **3b**	(*S*)	1:>99 (7:93)	59 (16 h)	(13:87)	42 (14 h)
 **2c**	(*R*)	94:6 (97:3)	87 (16 h)	 **3c**	(*S*)[h]	10:90 (13:87)	62 (18 h)	(43:57)	49 (16 h)
 **2d**	(*R*)	>99:1 (98:2)	76 (16 h)	 **3d**	(*S*)[h]	2:98 (6:94)	51 (18 h)	(27:73)	20 (14 h)
 **2e**	(*S*)[g]	>99:1 (95:5)	79 (16 h)	 **3e**	(*R*)	1:>99 (1:99)	44 (20 h)	(23:77)	12 (20 h)
 **2f**	(*R*)[g]	96:4 (97:3)	72 (16 h)	 **3f**	(*S*)	1:>99 (2:98)	65 (20 h)	(24:76)	13 (20 h)
 **2g**	(*S*)	89:11 (89:11)	83 (14 h)	 **3g**	(*R*)	1:99 (2:98)	73 (18 h)	(20:80)	43 (16 h)

[a] R_S = H or Me, R_L = Ph, Me, Bn, 2-Pyr, 3-Pyr, 2-Thienyl. [b] Determined by ^{1}H NMR analysis after silica gel chromatography. [c] Determined by LCMS analysis of the crude reaction mixture after reduction to the corresponding alcohols on an analytical scale. [d] Isolated yields; reaction times in parentheses. [e] The absolute configurations of **1a–g** were assigned by comparison with data reported in the literature and by analogy; see the Supporting Information for further details. The *ee* of **1a–g** were >98%. [f] The relative configurations of **2a–g** and **3a–g** were assigned using heteronuclear NOESY analysis; by analogy, see the Supporting Information for details. [g] 20 mol % catalyst loading was used. [h] 10 mol % catalyst loading was used.

control and also reverse the diastereoselectivity using (*S*)-**8** and (*R*)-**7**, respectively. Even in the case of **1b**, where the intrinsic dr from pyrrolidine catalysis was as high as 13:87, it was possible to reverse the selectivity using (*R*)-**7** in 74% yield.

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For racemic **1b** (*rac*-**1b**), we also examined the use of (*R*)-**7** for kinetic resolution. This was achieved using a substoichiometric amount of NFSI, preferentially allowing fluorination of the most reactive enamine enantiomer formed after condensation with the organocatalyst (Figure 3). The fluorination provided **11b** in

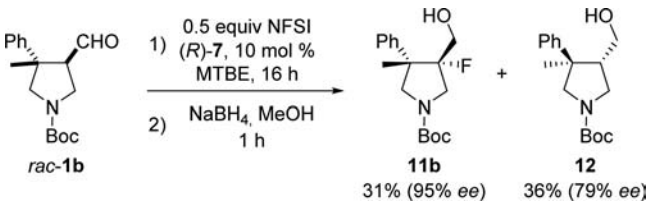

Figure 3. Kinetic resolution of *rac*-**1b** by (*R*)-**7**. Trace amount of the *anti*-product was removed by silica gel chromatography (96:4 dr), and the yields reported are after purification.

95% *ee*, affirming a highly selective and thus practically useful discovery.[24] In addition, the resolved starting material was recovered in 79% *ee* as the corresponding alcohol **12**. There is to our knowledge no examples in literature of enamine catalysis applied for chiral resolution of α-branched aldehydes bearing more than one stereocenter.[25]

In conclusion, we have demonstrated the preparation of a series of β-fluorinated pyrrolidines that are interesting scaffolds from a medicinal chemistry point of view. This was achieved starting from advanced α-branched aldehydes, and the products were obtained in both high yields and excellent diastereoselectivities. Furthermore, we have employed organocatalysis for kinetic resolution of a racemic substrate, furnishing a fluorinated prolinol **11b** with vicinal stereogenic centers in 95% *ee*.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00293.

The full experimental details, the protocols for synthesis of substrates, characterization data for new compounds, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(21) (a) Detailed synthetic protocols for the synthesis of substrates **1a−g** can be found in the Supporting Information. (b) Additional results from the screening of organocatalysts can be found in the Supporting Information.

(22) For a recent review, see: Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 13860−13874.

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(24) Kinetic resolution using catalyst **8** on *rac*-**1b** provided the expected *anti* diastereomer **13b** in 34% yield with no *ee*; see the Supporting Information.

(25) For kinetic resolution of racemic α-alkyl-α-chloroaldehydes with one chiral center, yielding the corresponding chlorofluoroaldehydes selectively, see: Shibatomi, K.; Okimi, T.; Abe, Y.; Narayama, A.; Nakamura, N.; Iwasa, S. *Beilstein J. Org. Chem.* **2014**, *10*, 323−331.

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