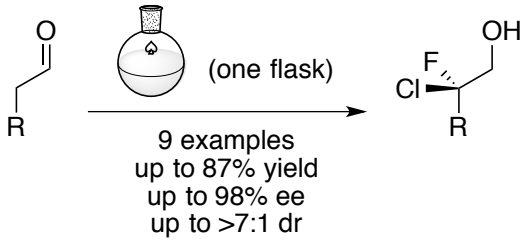
# An organocascade approach to α,α-chlorofluoroalcohols

Montgomery D. Hayes,[a] Melanie Rodriguez,[b] and Stacey E. Brenner-Moyer[a,b]*

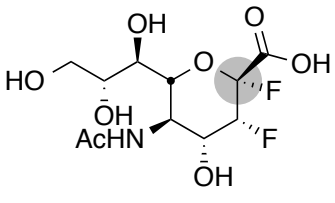
[a] Department of Chemistry, Brooklyn College, 2900 Bedford Avenue, Brooklyn, NY 11210 (USA)
[b] Present address: Department of Chemistry, Rutgers University—Newark, 73 Warren Street, Newark, NJ 07102 (USA) [Phone: (+1) 973-353-5457, Fax: (+1) 973-353-1264, E-mail: seb244@rutgers.edu]



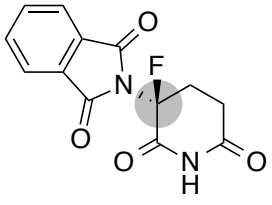

**Abstract.** Fluorinated, *tetrasubstituted*, carbon stereocenters are challenging to install enantioselectively. *Gem*-chlorofluoro compounds contain a fluorinated, tetrasubstituted stereocenter, and are an entrée into other such compounds. We report herein the first catalytic, enantioselective method to prepare *gem*-chlorofluoro compounds from unfunctionalized aldehydes. This one-pot method precludes the isolation of volatile and/or reactive α-haloaldehyde intermediates.

**Keywords:** Domino reactions; Fluorine; Organocatalysis; Synthetic Method

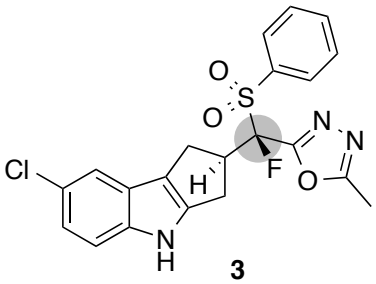
The introduction of fluorinated stereocenters has garnered much attention recently, owing to the increasing prevalence of fluorine-containing chiral drugs.[1] Fluorinated, *tetrasubstituted*, stereocenters, as exist in the compounds in Figure 1, can be a particularly challenging motif to access. Installation of this motif via asymmetric carbon-fluorine bond-forming reactions often requires the use of enantiopure starting materials or stoichiometric chiral fluorinating reagents, as in the synthesis of influenza antiviral **1** and thalidomide analog **2**, respectively.[2-3] More often, however, stereocenters of this type are introduced in racemic form, necessitating a resolution of the resulting enantio- or diastereomeric mixture, as occurred in the Hoffmann-La Roche synthesis of **3**.[4]




**1**



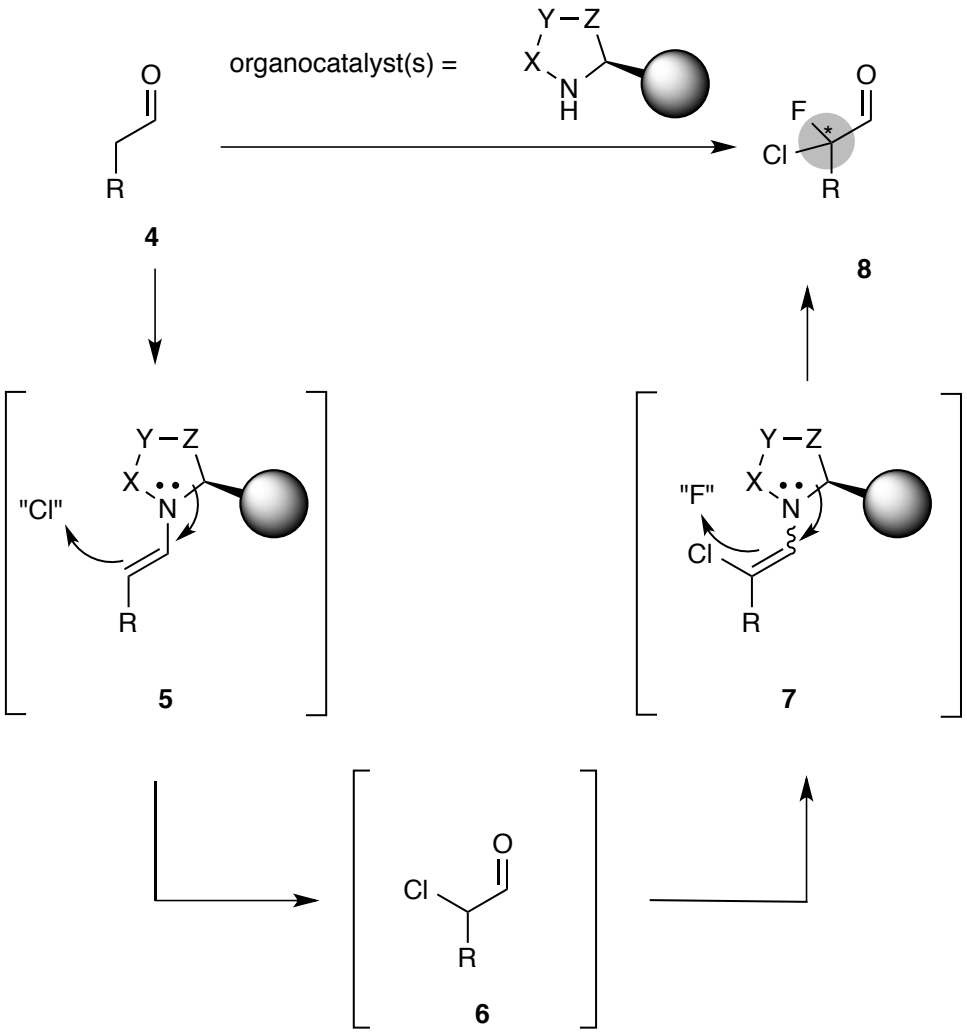

**2**




**3**

**Figure 1.** Medicinal compounds containing fluorinated, tetrasubstituted carbon stereocenters.

Chiral *gem*-chlorofluoro compounds (i.e., **8**, Scheme 1) also possess a fluorinated, tetrasubstituted, stereocenter. They may also be considered lynchpin intermediates, as $S_N2$ displacement of chlorine can potentially provide access to an array of compounds containing other fluorinated stereocenters.[5d]




**Scheme 1.** Proposed one-pot organocascade reaction.

Within the past decade, several catalytic asymmetric methods to produce enantiopure *gem*-chlorofluoro compounds have emerged. The majority of these methods are limited to β-dicarbonyl substrates.[5] Methods applicable to substrates other than β-dicarbonyl compounds require that either the carbon-fluorine or carbon-chlorine bond be in tact prior to the enantiodetermining step.[6]

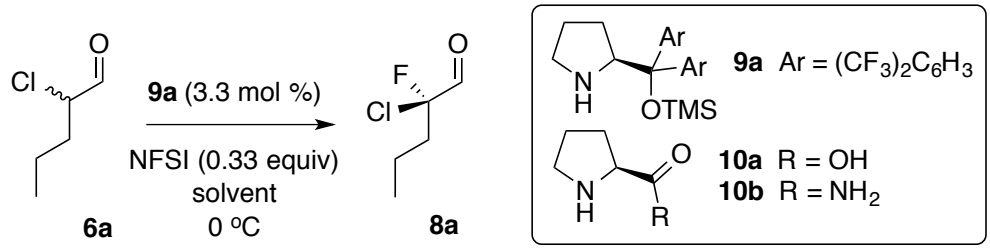
We have previously investigated organocascade reactions as efficient methods to produce fluorinated substructures of medicinal compounds.[7] Building on these studies, we envisioned that a cascade reaction combining successive enamine-catalyzed α-halogenation reactions would be an effective means of generating enantiopure *gem*-chlorofluoro compounds in one-pot starting from simple aldehyde substrates (Scheme 1). The advantages of this strategy are that it does not necessitate prior installation of one of the carbon-halogen bonds and it avoids isolation of volatile, reactive, aldehyde intermediates.

At the outset, we were well aware that the merging of two catalytic reactions into a cascade reaction poses non-trivial challenges (*vide infra*). With this realization already in mind, the starting point for the development of the cascade reaction was to assess the compatibility of the two catalytic reactions, and the goal was to develop the most operationally simple process possible. Thus, both orders of successive halogenations were initially considered,[8-9] as was the possibility of using a single catalyst/solvent system for the entire transformation.[10] Development of a cascade reaction in which the chlorination reaction was first, followed by the fluorination reaction, ultimately proved more fruitful.

Towards this end, starting with the reaction conditions reported for the enamine-catalyzed α-fluorination of α-chloroaldehydes,[6a] we examined the fluorination reaction in the presence of succinimide and pentachlorophenol, the byproducts of chlorination using the electrophilic chlorine sources *N*-chlorosuccinimide (NCS) and 2,2,3,4,5,6-hexachlorocyclohexanone,[8a] respectively (Table 1). Whereas fluorination was hampered by the presence of pentachlorophenol (18% conversion), it was unaffected by the presence of succinimide (entries 2 and 3). This result dictated the choice of NCS as the chlorine source, which, in turn, influenced the choice of catalyst for the chlorination step.

Specifically, assessment of the fluorination in the presence of catalysts reportedly effective in α-chlorinations using NCS revealed *L*-proline, **10a**,[8a] to be the top performing catalyst among those evaluated (entry 4). Some catalysts, such as of *L*-prolinamide, **10b**,[8b] failed to convert starting material into desired product (entry 5). In addition, our prior investigations had eliminated other catalysts from consideration for use in the α-chlorination step of the cascade reaction, either because they failed to produce **6a** (i.e., catalyst **9a**) or because they generated nontrivial amounts of inseparable dichlorinated byproduct.[10]

**Table 1.** Compatibility of α-fluorination and α-chlorination steps.[a]




| entry | additive | solvent | time (h) | yield (%)[b] | ee[c] (%) |
|---|---|---|---|---|---|
| 1[d] | -- | MTBE | 20 | 37 | 85 |
| 2 | succinimide | MTBE | 19 | 100 | 87 |
| 3 | $C_6Cl_5OH$ | MTBE | 19 | 18 | Nd |
| 4 | **10a** (4 mol %) | MTBE | 41 | 83 | 88 |
| 5 | **10b** (5 mol %) | MTBE | 41 | trace | -- |
| 6[e-f] | -- | $CH_2Cl_2$ | 52 | 35 | nd |
| 7[g] | **10a** (5 mol %) | MTBE: $CHCl_3$ 1.4:1 | 23 | 86 | 84 |
| 8[g] | **10a** (4 mol%), succinimide, NCS (0.2 equiv) | MTBE: $CHCl_3$ 1.4:1 | 22 | 0 | -- |

[a] Reaction conditions: **6a**, **9a** (0.033 equiv), *N*-fluorosulfonimide (NFSI, 0.33 equiv), additive (1 equiv unless indicated), solvent (0.75 M), 0 °C. [b] $^1$H NMR yield using cyclohexene as internal standard. [c] ee determined by chiral GC. [d] Isolated yield of corresponding (volatile) alcohol after reduction with $NaBH_4$. [e] Pentanal (**4a**) used instead of **6a**. [f] Reaction concentration = 1.5 M. [g] Reaction concentration = 0.45 M.

Having determined that the reaction conditions for enamine-catalyzed α-fluorinations were tolerant of NCS and L-proline, which could be used in a preceding α-chlorination step, our attention turned to establishing a solvent system for the one-pot cascade reaction. The fluorination step was low yielding in $CH_2Cl_2$, the optimal solvent for α-chlorinations of aldehydes with NCS (entry 6). It did, however, proceed smoothly using a halogenated solvent as cosolvent along with methyl *tert*-butyl ether (MTBE, entry 7).

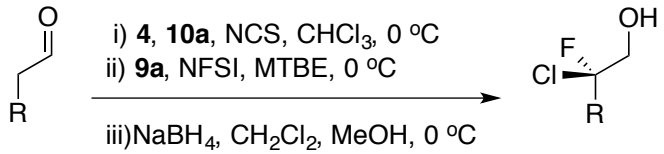
Having established that the α-fluorination reaction was compatible with the electrophilic chlorine source, catalyst and solvent for chlorination, the one-pot cascade reaction was attempted so that optimizations of the one-pot process could commence. While the first step of the cascade reaction proceeded as expected, much to our dismay, no conversion was observed in the second step. It was determined that, while the effect of succinimide, the byproduct of chlorination using NCS, on the α-fluorination reaction had already been studied, the effect of NCS itself on this reaction had not. Moreover, since 1.2 equiv of NCS were used in the chlorination step, one might expect unreacted NCS to remain during the fluorination step. Upon reexamination of the fluorination reaction, this time in the presence of NCS, indeed no α,α–chlorofluoroaldehyde was obtained (entry 8).

Thus, it seemed that use of substoichiometric quantities of NCS would be required to ensure its complete consumption. Since substoichiometric quantities of NFSI were also being employed,[6a,9b] an examination of the effect of the equivalents of these two reagents on the cascade reaction was undertaken to maximize the absolute and theoretical yield of α,α-chlorofluoroalcohol products.[10] The optimal amounts of NCS and NFSI were ultimately determined to be 0.95 and 0.7 equivalents, respectively (Table 2).

With conditions for the one-pot cascade reaction in hand, the substrate scope of this transformation was explored. Aldehydes with unbranched aliphatic R groups provided the corresponding α-chloro-α-fluoro alcohols in high yield and good ee (entries 1 and 3). Aldehydes with branched aliphatic R groups, on the other hand, resulted in higher ee's (entries 4,6,11 and 13). Pleasingly, the reaction was readily scaled ten-fold (entries 1 and 2). Additionally, conversion could be improved by running the fluorination step at room temperature, with only slight, if any, erosion of ee and/or dr (entry 4 vs. 5, 10 vs. 11, 12 vs. 13, 14). This transformation was tolerant of ether protecting groups (entry 8), other reactive functional groups (entry 9), significant steric bulk, albeit higher catalyst loadings were required in the fluorination step (entries 6-7), and adjacent stereocenters (entries 10-13). Evidently, asymmetric induction in the fluorination step is entirely

reagent controlled, as the dr was completely reversed upon subjecting **4g** to the cascade reaction conditions, followed by its enantiomer, **4h** (entry 10 vs. 12). Even an aldehyde with an activated α-carbon (i.e., R = Ph) led to product formation in high yield and ee. The absolute configuration of **11d** was established by X-ray crystallography,[11] and the configurations of all other cascade reaction products were assigned by analogy.

**Table 2.** Substrate scope of one-pot cascade reaction.[a]




| **4** | | | | **11** |
|---|---|---|---|---|
| entry | **11** | R | yield (%)[b] | ee[c-d] (%) |
| 1[e] | **a** | *n*Pr | 87 | 81 |
| 2[f] | **a** | *n*Pr | 64 | 81 |
| 3 | **b** | Bn | 71 | 86 |
| 4[g] | **c** | *i*Pr | 52 | 92 |
| 5[g-i] | **c** | *i*Pr | 70 | 89 |
| 6[i-l] | **d** | *t*Bu | 36 | 98 |
| 7[i-k,m] | **d** | *t*Bu | 54 | 92 |
| 8 | **e** | $(CH_2)_2OBn$ | 66 | 89 |
| 9[k] | **f** | $(CH_2)_6CO_2Me$ | 72 | 85 |
| 10 | **g** | (*S*)-CH(Me)$(CH_2)_3$*i*Pr | 47 | nd (8.4: 1.6) |
| 11[i] | **g** | (*S*)-CH(Me)$(CH_2)_3$*i*Pr | 57 | 99 (8.4: 1.6) |
| 12 | **h** | (*R*)-CH(Me)$(CH_2)_3$*i*Pr | 44 | nd (1.6: |

| | | | | |
|---|---|---|---|---|
| | | | | 8.4) |
| 13[i] | **h** | (*R*)-CH(Me)($CH_2$)$_3$*i*Pr | 67 | 97 (1.2: 8.8) |
| 14[i,n] | **i** | Ph | 71 | 87 |

[a] Reaction conditions: i) **4** (1 mmol), **10a** (0.05 mmol), NCS (0.95 mmol), $CHCl_3$ (1 mL), 0 °C, 19-25h, ii) **9a** (0.033 mmol), NFSI (0.7 mmol), MTBE (1.4 mL), 0 °C, 30-143h, iii) $NaBH_4$ (3.3 mmol), $CH_2Cl_2$/MeOH (2.35 mL, 3:1), 0 °C. [b] Isolated yield. [c] ee determined by chiral GC unless otherwise indicated. [d] Number in parentheses is *syn:anti* dr determined by $^{19}F$ NMR. [e] Yield is $^{1}H$ NMR yield prior to reduction using cyclohexene as internal standard. [f] Reaction run on 10 mmol scale. [g] Yield is $^{1}H$ NMR yield of purified **11** using cyclohexene as internal standard. [h] Yield and ee values are the average of duplicate reactions. [i] Step ii run at r.t. [j] **11d** is the corresponding 3,5-dinitrobenzoate derivative. [k] ee determined by chiral phase HPLC. [l] Using 0.3 mmol of catalyst **9a** in step ii. [m] Using 0.5 mmol of catalyst **9a** in step ii. [n] When step ii was run at 0 °C, ee of **11i** was 73%.

In conclusion, we have developed a catalytic, enantioselective method to produce *gem*-chlorofluoro compounds from unfunctionalized aldehyde substrates in a single flask. This cascade reaction, being a one-pot method, does not necessitate the isolation of volatile α-haloaldehyde intermediates, and is thus an improved method to produce *gem*-chlorofluoroaldehydes and -alcohols. The products of this cascade reaction are representative of a challenging class of fluorinated compounds to access efficiently in enantiopure form—those containing a fluorinated, tetrasubstituted, chiral center—and can be considered lynchpin intermediates from which to access other such fluorinated compounds. Cascade products were generated in up to 87% yield and in up to 98% ee. Investigations into the application of this methodology in the synthesis of fluorinated analogs of medicinal compounds are presently underway in our laboratory.

**Acknowledgements.** This work was supported by the National Science Foundation (CAREER-1148295) and the Alfred P. Sloan Foundation. The authors gratefully acknowledge Dr. Cliff Soll (City University of New York) and Dr. Furong Sun (University of Illinois) for the acquisition of mass spectrometry data, as well as Dr. William Brennessel (University of Rochester) for the acquisition of X-ray crystallographic data. The authors

also thank Dr. Qunsheng Guo (Rutgers University) for his assistance completing the characterization of compound **11a**.

**Supplementary Material**. Copies of $^{1}$H NMR and $^{13}$C NMR spectra and GC and/or HPLC chromatograms are contained in the Supplementary Data.

**References and Notes**

1. Qiu, X.-L.; Yue, X.; Qing, F.-L. in *Chiral Drugs: Chemistry and Biological Action* (Eds.: Lin, G.-Q.; You, Q.-D.; Cheng, J.-F.), John Wiley & Sons, Inc., Hoboken, NJ, **2011**, pp 195-252.

2. Kim, J.-H.; Resende, R.; Wennekes, T.; Chen, H.-M.; Bance, N.; Buchini, S.; Watts, A.G.; Pilling, P.; Streltsov, V.A.; Petric, M.; Liggins, R.; Barrett, S.; McKimm-Breschkin, J.L.; Niikura, M.; Withers, S.G. *Science* **2013**, *340*, 71-75.

3. Yamamoto, T.; Suzuki, Y.; Ito, E.; Tokunaga, E.; Shibata, N. *Org. Lett.* 2011, **13**, 470-473.

4. Ratni, H.; Blum-Kaelin, D.; Dehmlow, H.; Hartman, P.; Jablonski, P.; Masciadri, R.; Maugeais, C.; Patiny-Adam, A.; Panday, N.; Wright, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1654-1657.

5. a) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709-1712. b) Cho, M.J.; Kang, Y.K.; Lee, N.R.; Kim, D.Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2191-2192. c) Kang, S.H.; Kim, D.Y. *Adv. Synth. Catal.* **2010**, *352*, 2783-2786. d) Shibatomi, K.; Narayama, A.; Soga, Y.; Muto, T.; Iwasa, T. *Org. Lett.* **2011**, *13*, 2944-2947.

6. a) Shibatomi, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 5796-5798. b) Phipps, R.J.; Hiramatsu, K.; Toste, F.D. *J. Am. Chem. Soc.* **2012**, *134*, 8376-8379.

7. a) Appayee, C.; Brenner-Moyer, S.E. *Org. Lett.* **2010**, *12*, 3356-3359. b) Jones, J.H.; Appayee, C.; Brenner-Moyer, S.E. *Eur. J. Org. Chem.* **2014**, *2014*, 5273-5280.

8. Seminal references for enantioselective organocatalytic α-chlorinations of aldehydes: a) Brochu, M.P.; Brown, S.P.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2004**, *126*, 4108-4109. b) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K.A. *J. Am. Chem. Soc.* **2004**, *126*, 4790-4791.

9. Seminal references for highly enantioselective organocatalytic α-fluorinations of aldehydes: a) Beeson, T.D.; MacMillan, D.W.C. *J. Am. Chem. Soc.* **2005**, *127*, 8826-8828. b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3703-3706.

10. See Supplementary Material for full details.

11. CCDC-1019377 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.