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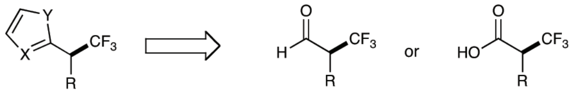
The Productive Merger of Iodonium Salts and Organocatalysis: A Non-photolytic Approach to the Enantioselective α-Trifluoromethylation of Aldehydes

Anna E. Allen and David W. C. MacMillan*
Merck Center for Catalysis, Princeton University, Princeton, New Jersey 08544

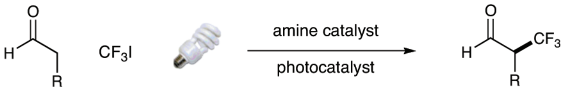
Received January 27, 2010; E-mail: dmacmill@princeton.edu

Within the realm of drug design, the stereospecific incorporation of polyfluorinated alkyl substituents is a powerful and widely employed tactic to enhance binding selectivity, elevate lipophilicity, and/or circumvent metabolism issues arising from in vivo C−H bond oxidation.[1] In particular, the catalytic production of CF_3-containing stereogenicity has become a methodological goal of central importance to practitioners of chemical and pharmaceutical synthesis.[2] Recently, we reported the first highly enantioselective α-trifluoromethylation of aldehydes using photoredox organocatalysis, a protocol that employs fluorescent household lights to generate $\cdot CF_3$ radicals that can intercept stereofacially biased enamines (eq 1).[2a] In this communication, we describe a new mechanistic (non-photolytic) approach to the same product class via the merger of Lewis acid and organocatalysis with an electrophilic trifluoromethyl alkylating reagent (eq 2).[3,4] Through this alternative chemical pathway, enantioenriched α-trifluoromethylated aldehydes (and α-CF_3 carbonyl building blocks) can be generated under mild reaction conditions using commercially available,[5] bench-stable[6] reagents and catalysts without the requirement of a light source.

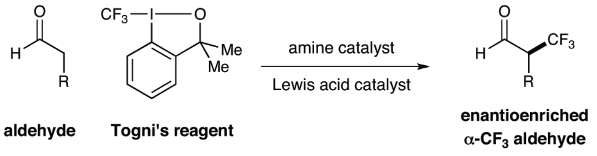
Trifluoromethyl Synthons: Novel Approaches to Stereogenic CF_3



Photoredox Organocatalysis: Weak Light $\cdot CF_3$ Generation (eq 1)[2]

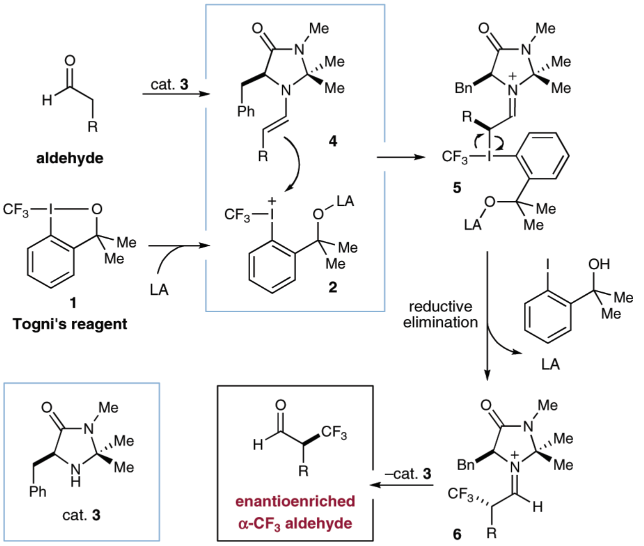


New Mechanistic Approach: Lewis Acid-Organocatalysis (eq 2)



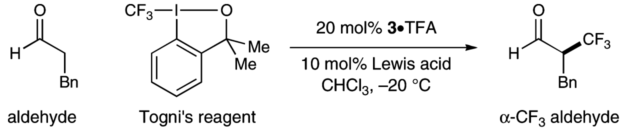
Inspired by the recent studies of Togni, we hypothesized that 3,3-dimethyl-1-trifluoromethyl-1,2-benziodoxole (Togni's reagent, **1**) might function as a trifluoromethylation agent for enamine-activated aldehydes in a manner analogous to that observed for the racemic α-alkylation of nitroesters, β-ketoesters, silyl enol ethers, and silyl ketene acetals.[3] Since **1** is generally considered to be an electrophilic species that enables C−CF_3 bond formation via an iodonium addition/reductive elimination mechanism, we felt that such hypervalent iodonic reagents might also function successfully in enamine catalysis.[7] As described in Scheme 1, we envisioned that **1** should undergo Lewis acid-catalyzed bond cleavage to generate the highly electrophilic iodonium salt **2**. At the same time, condensation of amine catalyst **3** with an aldehyde substrate should generate a chiral enamine **4** that is sufficiently π-electron-rich to participate in an enantioselective C−I bond formation with **2** via a closed-shell pathway. In accord with similar mechanisms described by Togni[3e] and Baran,[8] we expected the resulting λ^3-iodane species **5** to rapidly undergo reductive elimination with stereoretentive alkyl transfer, a step that would forge the critical C−CF_3 bond. Bifurcation of iminium ion **6** via hydrolysis would then liberate the imidazolidinone catalyst **3** along with the desired α-formyl CF_3 product. As described in previous studies,[9] we presumed that high levels of enantioinduction should be possible using catalyst **3** on the basis of enamine olefin geometry control and selective *Si*-facial exposure (via benzyl shielding of the *Re* face of enamine **4**).

Scheme 1. Proposed Mechanism for Direct α-Trifluoromethylation



The proposed α-formyl trifluoromethylation was first evaluated using hydrocinnamaldehyde, imidazolidinone **3**, and a series of Lewis acids at −20 °C (Table 1). To our delight, this new transformation was found to

Table 1. Effect of the Lewis Acid Catalyst on α-Trifluoromethylation

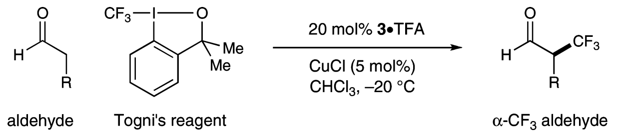


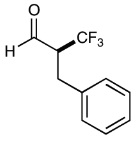
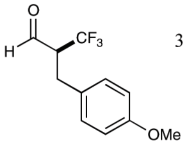
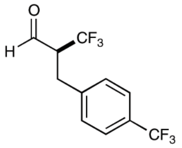
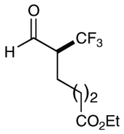
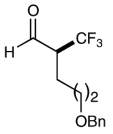
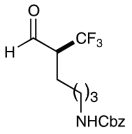
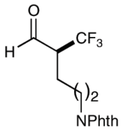
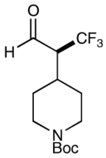
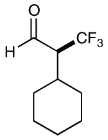
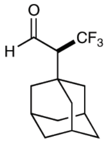
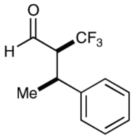
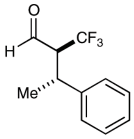
entry	Lewis acid	% yield[a]	% ee[b]
1	none	14	92
2	$FeCl_3$	7	89
3	$CuCl_2$[c]	39	87
4	$Sc(OTf)_3$	48	64
5	$Zn(NTf_2)_2$	52	66
6	$Sm(OTf)_3$	66	53
7	$FeCl_2$	80	87
8	$FeCl_2$ + *tert*-amyl alcohol	76	91
9	CuCl[c]	86	94

[a] Determined by ^{19}F NMR spectroscopy using an internal standard. [b] Enantiomeric excess was determined by chiral HPLC analysis of the corresponding alcohol. [c] Using 5 mol % Lewis acid.

10.1021/ja100748y

Table 2. Scope of Catalytic Enantioselective α-Trifluoromethylation



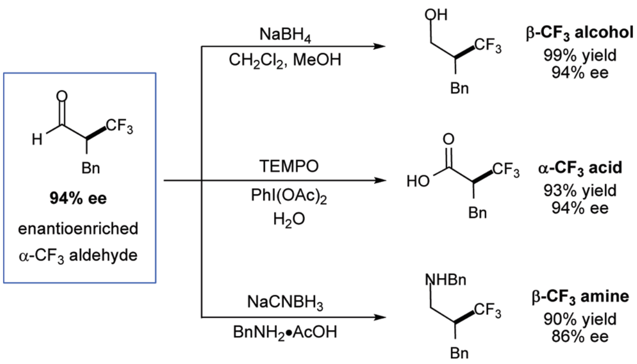
entry	product[a]	yield[b]	ee[c]
1		81% yield	94% ee
2		87% yield	96% ee
3		78% yield	93% ee
4[d]		79% yield	93% ee
5[d]		77% yield	93% ee
6		85% yield	96% ee
7		71% yield	96% ee
8[d]		80% yield	94% ee
9[d]		72% yield,[e]	94% ee
10		70% yield,[e]	97% ee
11		76% yield	>20:1 dr
12		74% yield	19:1 dr

[a] Stereochemistry assigned by chemical correlation or analogy. [b] Isolated yield of the corresponding alcohol. [c] Enantiomeric excess determined by chiral HPLC or SFC analysis. [d] Performed using FeCl$_2$ (10 mol %) and *tert*-amyl alcohol. [e] Yield determined by ^{19}F NMR spectroscopy.

be both high yielding and enantioselective using catalytic Fe(II) or Cu(I) salts. Interestingly, the use of stronger Lewis acids led to markedly lower levels of enantiomeric excess, presumably because of a post-reaction racemization pathway. Indeed, the addition of *tert*-amyl alcohol was found to rescue the product optical purity in the case of the FeCl$_2$ system (presumably via in situ hemiacetal formation; entries 7 and 8).[10] The superior levels of enantiocontrol and reaction yield obtained with CuCl and imidazolidinone **3** at −20 °C prompted us to select these conditions for further exploration.

As highlighted in Table 2, these mild Lewis acid−organocatalytic conditions tolerate a wide range of functional groups in this α-trifluoromethylation protocol, including aryl rings, ethers, esters, carbamates, and imides (entries 1−8; 71−87% yield, 93−96% ee). Sterically demanding aldehydes (R = 4-piperidinyl, cyclohexyl, adamantyl) were also accommodated with little impact on the yield or enantiocontrol (entries 8−10; 70−80% yield, 94−97% ee). In addition, enantiopure β-chiral substrates can be used for the diastereoselective construction of either the *syn*- or *anti*-α,β-disubstituted products, highlighting the remarkable catalyst control of these alkylations (entries 11 and 12; 19−20:1 dr). It should be noted that catalyst **3** was ineffective in our photolytic trifluoromethylation studies,[2a] providing further evidence that the protocol described herein does not involve a radical pathway.

Scheme 2. Access to Enantioenriched Trifluoromethyl Synthons



To highlight the utility of enantioenriched α-CF$_3$ aldehydes, we undertook their conversion to a variety of valuable organofluorine synthons. As outlined in Scheme 2, in situ reduction or oxidation of the formyl group creates enantioenriched β-CF$_3$ alcohols or α-CF$_3$ carboxylic acids with excellent stereofidelity. Moreover, reductive amination of these α-CF$_3$ aldehydes provides β-CF$_3$ amines with only a slight reduction in optical purity (86% ee).

In summary, we have introduced a new mechanistic approach to the enantioselective α-trifluoromethylation of aldehydes using only commercially available reagents. We expect that this paradigm of merging asymmetric organocatalysis (and Lewis acids) with iodonium salts will be broadly useful across many reaction types.

Acknowledgment. Financial support was provided by NIGMS (R01 01 GM093213-01) and kind gifts from Merck and Amgen. A.E.A. thanks the Natural Sciences and Engineering Research Council (NSERC) for a predoctoral fellowship (PGS D).

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

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(1) (a) Chambers, R. D. *Fluorine in Organic Chemistry*; Wiley: New York, 1973. (b) Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum Press: New York, 1994. (c) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: New York, 1993. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (e) Pursor, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.
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(3) For seminal reports on Togni's reagent and its applications, see: (a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.−Eur. J.* **2006**, *12*, 2579. (b) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754. (c) Eisenberger, P.; Kieltsch, I.; Armanino, N.; Togni, A. *Chem. Commun.* **2008**, 1575. (d) Kieltsch, I.; Eisenberger, P.; Stanek, K.; Togni, A. *Chimia* **2008**, *62*, 260. (e) Koller, R.; Stanek, K.; Stolz, D.; Aardoom, R.; Niedermann, K.; Togni, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4332.
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(5) Imidazolidinone **3** can be purchased from Sigma-Aldrich as the hydrochloric acid salt (CAS no. 278173-23-2). The hydrochloric acid salt was converted to the trifluoroacetic acid salt before use in this protocol.
(6) 3,3-Dimethyl-1-trifluoromethyl-1,2-benziodoxole can be handled in moist air without any special precautions. However, it should be stored at −20 °C to prevent slow degradation over time (see ref 3a).
(7) An alternate mechanism wherein Togni's reagent might participate in a redox one-electron alkylation pathway was also considered initially.
(8) Eastman, K.; Baran, P. S. *Tetrahedron* **2009**, *65*, 3149.
(9) (a) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826. (b) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.
(10) Time studies showed erosion of enantiopurity over time, and the use of *tert*-amyl alcohol appeared to impede this post-reaction racemization.

JA100748Y