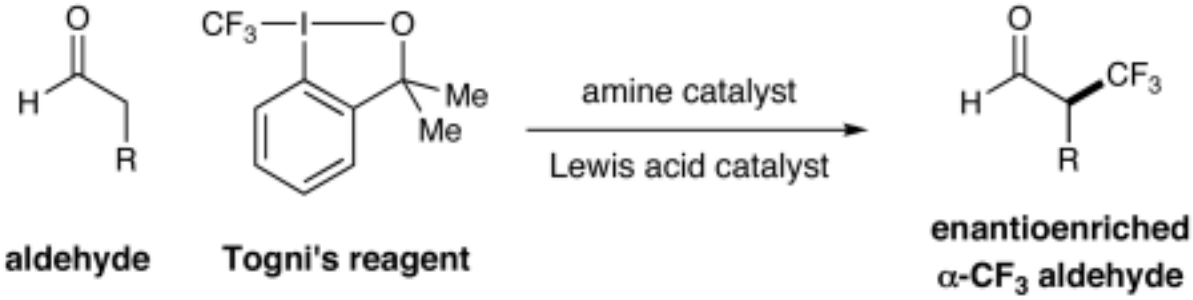
Published in final edited form as:
J Am Chem Soc. 2010 April 14; 132(14): 4986–4987. doi:10.1021/ja100748y.

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 at Princeton University, Princeton, New Jersey 08544

Abstract



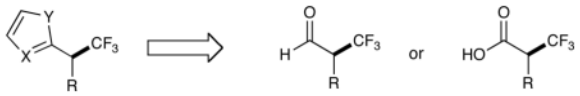
An enantioselective organocatalytic α-trifluoromethylation of aldehydes has been accomplished using a commercially available, electrophilic trifluoromethyl source. The merging of Lewis acid and organocatalysis provides a new strategy for the enantioselective construction of trifluoromethyl stereogenicity, an important chiral synthon for pharmaceutical, material, and agrochemical applications. This mild and operationally simple protocol allows rapid access to enantioenriched α-trifluoromethylated aldehydes through a non-photolytic pathway.

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] Using this alternative chemical pathway, enantioenriched α-trifluoromethyl 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, and without the requirement of a light source.

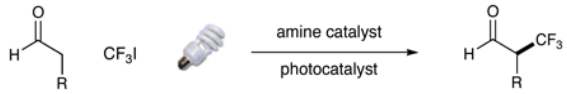
Trifluoromethyl Synthons: Novel Approaches to Stereogenic CF_3

dmacmill@princeton.edu.

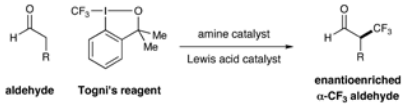
Supporting Information Available. Experimental procedures, structural proofs, and spectral data for all new compounds are provided (20 pages) (PDF).



Photoredox Organocatalysis: Weak Light ·CF_3 Generation (eq 1)[2]



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



Design Plan

Inspired by the recent studies of Togni, we hypothesized that 3,3-dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (**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] 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 Togni's reagent (**1**) should undergo Lewis acid-catalyzed bond cleavage to generate a highly electrophilic iodonium salt **2**. At the same time, condensation of amine catalyst **3** with an aldehyde substrate will generate a chiral enamine **4** that is sufficiently π-electron rich to participate in 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 **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**).

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 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 due to a post-reaction racemization pathway. Indeed, the addition of *t*-amyl alcohol was found to rescue the product optical purity in the case of the $FeCl_2$ system (we assume via in situ hemi-acetal formation, entries 7–8).[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 are also accommodated with little impact on the yield or enantiocontrol (R = *c*-hexyl, 4-piperidinyl, adamantyl; 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 11–12; 19–20:1 dr). It should be noted that catalyst **3** was ineffective in our photolytic trifluoromethylation studies,[2] providing further evidence that the protocol described herein does not involve a radical pathway.

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 provide β-CF_3 amines with only a slight reduction in optical purity (86% ee).

In summary, we introduce 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

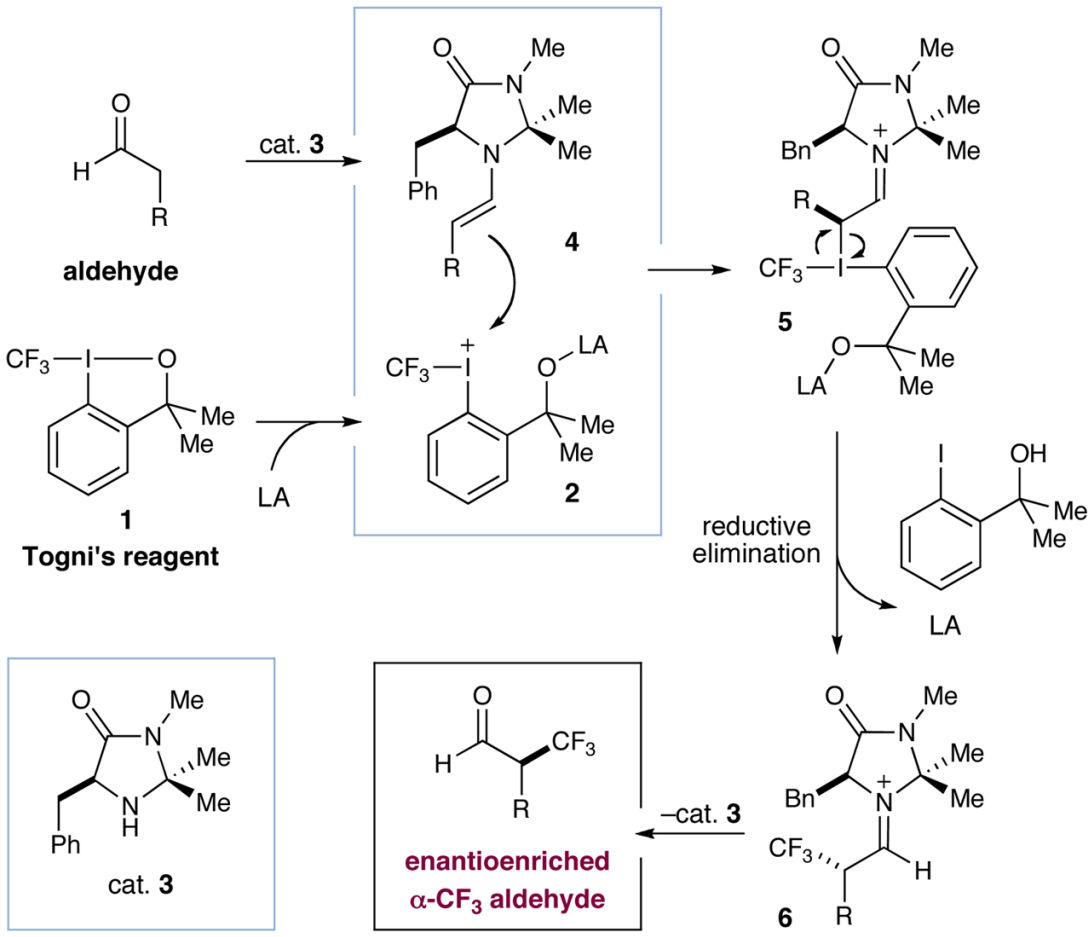
Acknowledgments

Financial support was provided by NIHGMS (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).

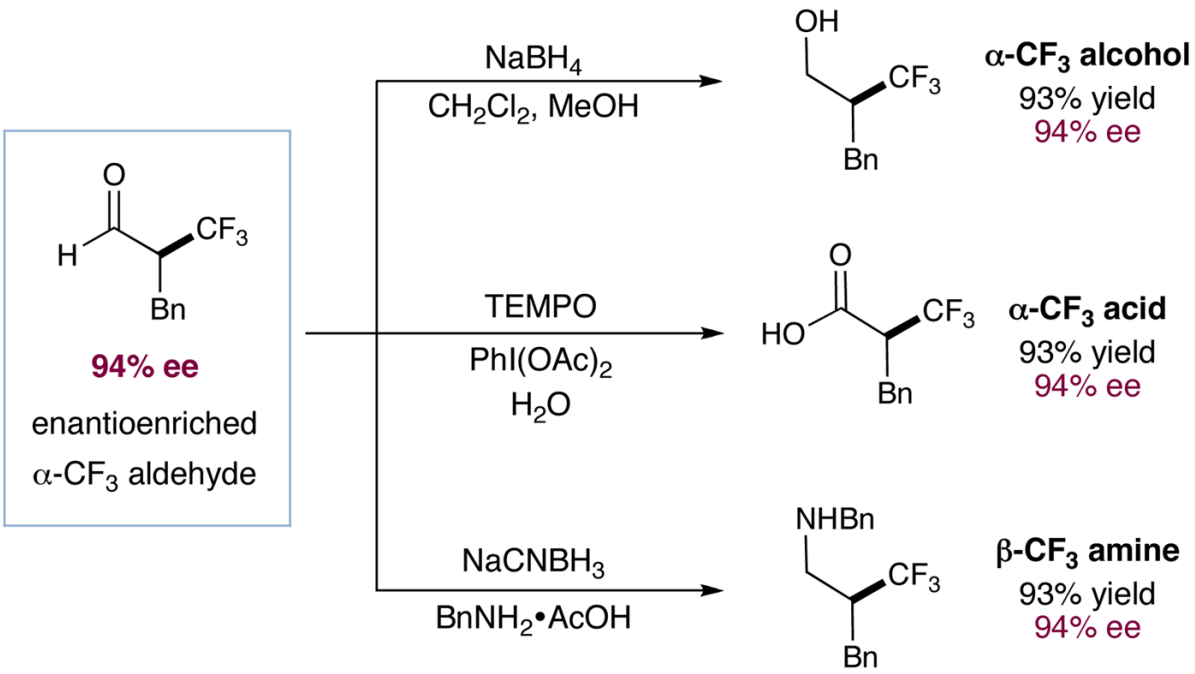
References

1. (a) Chambers, RD. Fluorine in Organic Chemistry. Wiley; New York: 1973. (b) Banks, RE.; Smart, BE.; Tatlow, JC. Organofluorine Chemistry: Principles and Commercial Applications. Plenum Press; New York: 1994. (c) Filler, R.; Kobayashi, Y.; Yagupolskii, LM. Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications. Elsevier; New York: 1993. (d) Müller K, Faeh C, Diederich F. Science 2007;317:1881. [PubMed: 17901324] (e) Pursor S, Moore PR, Swallow S, Gouverneur V. Chem Soc Rev 2008;37:320. [PubMed: 18197348]
2. (a) Nagib DA, Scott ME, MacMillan DWC. J Am Chem Soc 2009;131:10875. [PubMed: 19722670] (b) Noritake S, Shibata N, Nomura Y, Huang Y, Matsnev A, Nakamura S, Toru T, Cahard D. Org Biomol Chem 2009;7:3599–3604. [PubMed: 19675918]
3. For seminal reports of 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.
4. For seminal contributions towards other electrophilic trifluoromethylating sources, see: (a) Yagupolskii LM, Kondratenko NV, Timofeeva GN. J Org Chem USSR (Engl Transl) 1984;20:103. (b) Umemoto T, Ishihara S. Tetrahedron Lett 1990;31:3579. (c) Umemoto T, Ishihara S. J Am Chem Soc 1993;115:2156. (d) Umemoto T. Chem Rev 1996;96:1757. [PubMed: 11848810]
5. Imidazolidinone **3** can be purchased from Sigma-Aldrich as the hydrochloric acid salt (CAS: 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 4a.
7. An alternate mechanism was also considered initially wherein Togni's reagent might participate in a redox one-electron alkylation pathway.

8. Eastman K, Baran PS. Tetrahedron 2009;65:3149.
9. (a) Beeson TD, MacMillan DWC. J Am Chem Soc 2005;127:8826. [PubMed: 15954790] (b) Brochu MP, Brown SP, MacMillan DWC. J Am Chem Soc 2004;126:4108. [PubMed: 15053591]
10. Time studies have shown erosion of enantiopurity over time and the use of *t*-amyl alcohol appears to impede this post-reaction racemization.



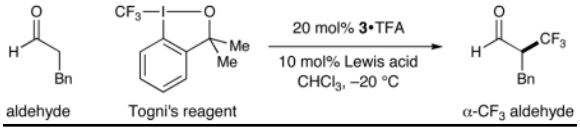
Scheme 1.
Proposed Mechanism for Direct α-Trifluoromethylation



Scheme 2.
Access to Enantioenriched Trifluoromethyl Synthons

Table 1

Effect of the Lewis Acid Catalyst on α-Trifluoromethylation



aldehyde Togni's reagent α-CF_3 aldehyde

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	$FeCl_2$ + *t*-amyl alcohol	76	91
9	CuCl[c]	86	94

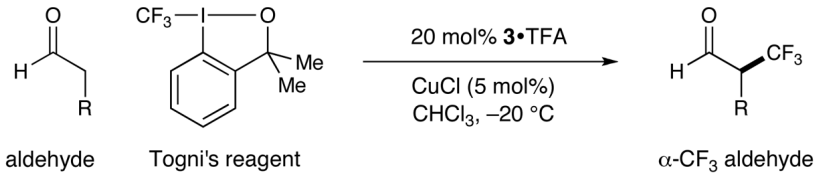
[a] Determined by ^{19}F NMR using an internal standard.

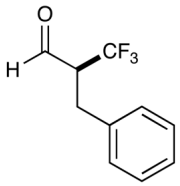
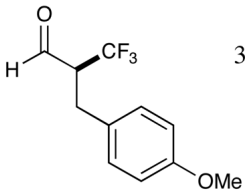
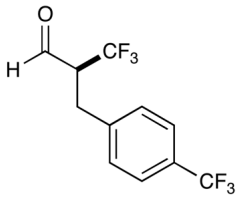
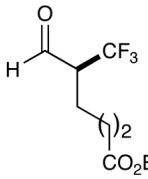
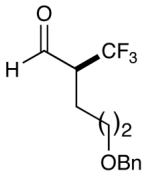
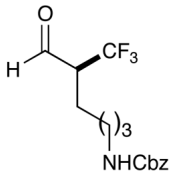
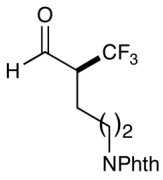
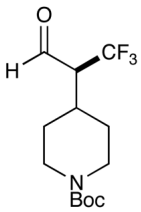
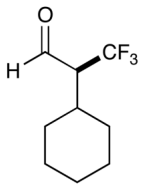
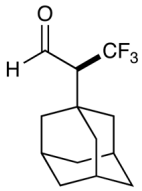
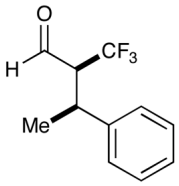
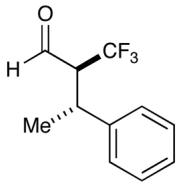
[b] Enantiomeric excess determined by chiral HPLC analysis of the corresponding alcohol.

[c] 5 mol% of Lewis acid used.

Table 2

Catalytic Enantioselective α-Trifluoromethylation: Scope



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 *t*-amyl alcohol.

[e] Yield determined by ^{19}F NMR.