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Enantioselective α-Trifluoromethylation of Aldehydes via Photoredox Organocatalysis

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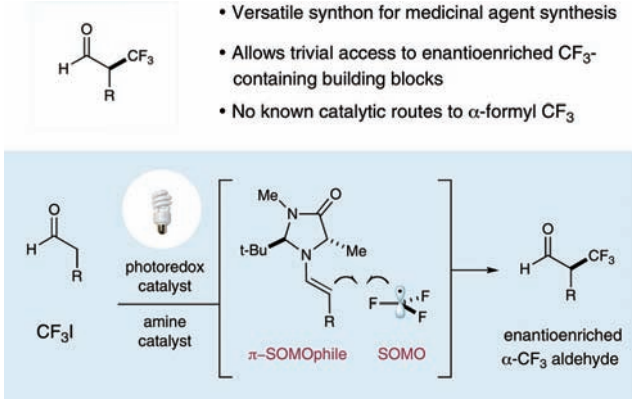
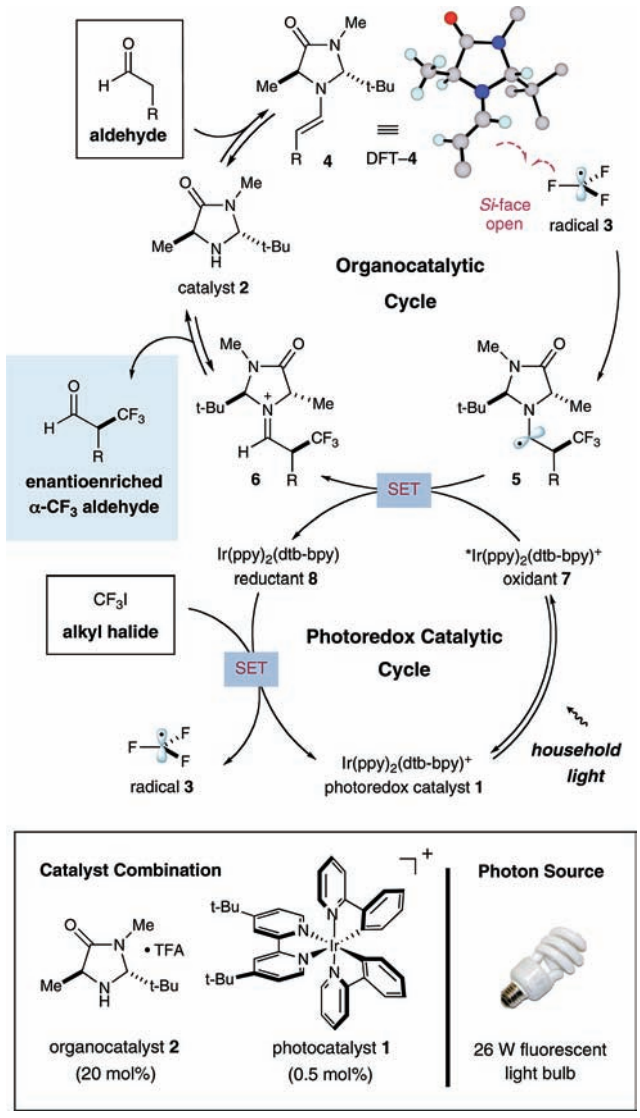
Organofluorine compounds possess unique physical properties that are exploited in a wide range of applications such as dyes, polymers, agrochemicals, and pharmaceuticals.[1] In medicinal chemistry, for example, valuable physiological properties are often conferred on "drug-like" molecules via the incorporation of CF_3 groups that enhance binding selectivity, elevate lipophilicity, and/or improve metabolic stability.[2] It is not surprising, therefore, that broad research efforts have been focused on the enantioselective construction of trifluoromethyl-containing stereogenicity.[3,4] While significant progress has been made in the arena of nucleophilic 1,2-trifluoromethylation of ketones,[5] to date, the enantioselective α-alkylfluorination of carbonyl derived enolates (or enolate equivalents) remains an elusive goal.[6,7] Herein we describe a conceptually new approach to the asymmetric α-trifluoromethylation of aldehydes via the successful merger of enamine[8] and organometallic photoredox[9,10] catalysis.



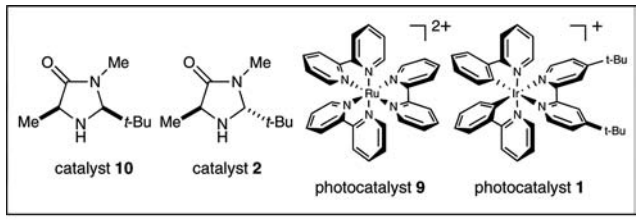
Design Plan. Recently, our laboratory introduced a new mode of organocatalytic activation, termed photoredox organocatalysis,[9] whose mechanistic foundation relies on the propensity of electrophilic radicals (derived from the reduction of an alkyl halide by a photoredox catalyst (e.g., **1**)) to combine with facially biased enamine intermediates (derived from aldehydes and chiral amine catalyst **2**). Inspired by this strategy, we hypothesized that the enantioselective α-trifluoromethylation of aldehydes should also be possible by the marriage of two similar activation pathways. As detailed in Scheme 1, we anticipated that $Ir(ppy)_2(dtb\text{-}bpy)^+$ **1**,[11] previously employed as a photosynthesis mimic, should readily accept a photon from a variety of light sources within the visible spectrum (such as a household fluorescent bulb) to populate the $^*Ir(ppy)_2(dtb\text{-}bpy)^+$ **7** excited state. Given its known tendency toward reductive quenching, we presumed that $^*Ir(ppy)_2(dtb\text{-}bpy)^+$ **7** would readily accept a single electron from a sacrificial quantity of enamine (0.5 mol %) to form a strong reductant $Ir(ppy)_2(dtb\text{-}bpy)$ **8** (−1.51 V vs SCE in CH_3CN).[12,13] At this stage we anticipated that this electron-rich iridium system **8** would participate

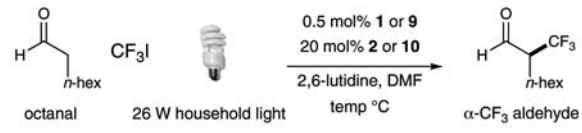
Scheme 1. Proposed Merger of Catalytic Cycles for CF_3-Alkylation



in single electron transfer (SET) with trifluoromethyl iodide (−1.22 V vs SCE in DMF)[14] to render the electrophilic radical **3**, while regenerating the photoredox catalyst **1**. In concert with this radical formation pathway, we expected that an organocatalytic cycle would initiate by condensation of the imidazolidinone catalyst **2** with an aldehyde substrate to form the enamine **4**. The merger of the two activation pathways would then occur in the key alkylation step via rapid addition of the trifluoromethyl radical **3** to the π-rich olefin **4** to form the α-amino radical **5**. Given that radical **5** should have a low barrier to oxidation,[15] a second electron transfer event with the $^*Ir(ppy)_2(dtb\text{-}bpy)^+$ **7** excited state would close the photoredox

Table 1. Enantioselective α-Trifluoromethylation: Initial Studies





entry	organocat.	photocat.	light	temp (°C)	% yield	% ee[a]
1	**10**	**9**	yes	23	51	0
2	**10**	**9**	no	23	<5	0
3	**10**	**1**	yes	23	85	0
4	**10**	**1**	yes	–20	92	52
5	**2**	**9**	yes	–20	67	87
6	**2**	**1**	yes	–20	79	99

[a] Enantiomeric excess by chiral GC analysis of the corresponding alcohol.

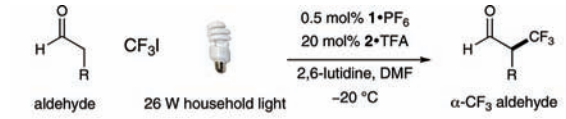
cycle and deliver the iminium ion **6**. Rapid hydrolysis of iminium **6** would then reconstitute the organocatalyst **2** while rendering the optically enriched α-CF_3 aldehyde.

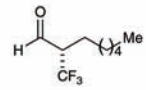
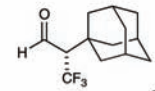
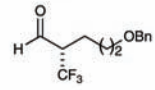
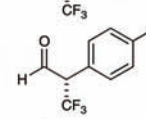
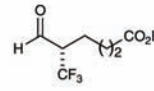
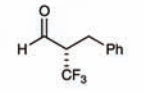
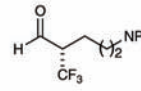
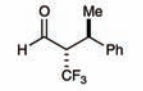
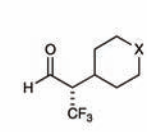
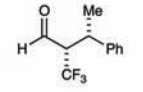
As a critical design element, we anticipated high levels of enantiocontrol resulting from positioning of the 4π-electron system of activated enamine DFT-**4** away from the bulky *tert*-butyl group, while also adopting an (*E*)-configuration to minimize nonbonding interactions.[16] In this arrangement, the methyl group on the imidazolidinone scaffold effectively shields the *Re* face, leaving the *Si* face exposed toward electrophilic radical addition.

Our photoredox fluoroalkylation was first evaluated using octanal and trifluoromethyl iodide along with imidazolidinone catalysts **2** or **10**, photoredox catalysts **1** or **9**, and a 26 W fluorescent household lamp (Table 1). Initial experiments revealed that the proposed alkylation reaction was indeed possible using a combination of $Ru(bpy)_3^{2+}$ (**9**) and the amine catalyst **10** (entry 1, 51% yield), albeit to render a racemic product. Importantly, exclusion of light from this protocol resulted in almost complete loss of catalyst efficiency (<5% yield), in accord with the photoredox mechanism outlined in Scheme 1. While the use of $Ir(ppy)_2(dtb\text{-}bpy)^+$ **1** allowed a significant increase in reaction yield (entry 3, 85%), it was not until subambient temperatures were employed that enantioinduction was observed (entry 4, −20 °C, 52% ee). Moreover, implementation of the *trans-tert*-butyl-methyl imidazolidinone catalyst **2** (along with photocatalyst **1**) provided almost perfect enantiocontrol in the trifluoromethylation step without detectable post-reaction racemization (entry 6, 79% yield, 99% ee).[17] The superior levels of induction and efficiency exhibited by the combination of organocatalyst **2** with photoredox catalyst **1** in DMF at −20 °C prompted us to select these conditions for further exploration.[18,19]

We next performed a series of experiments to determine the scope of the aldehydic component in this asymmetric trifluoromethylation protocol. As revealed in Table 2, these mild redox conditions are compatible with a wide range of functional groups including ethers, esters, amines, carbamates, and aromatic rings (entries 2−4, 6, 8, 9, 61−86% yield, 93−98% ee). Moreover, significant variation in the steric demand of the aldehyde substituent can be accommodated without loss in enantiocontrol (entries 5−7, 10, and 11, ≥90% ee).

Table 2. Enantioselective α-Trifluoromethylation: Aldehyde Scope

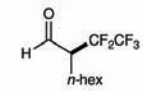
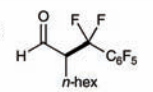
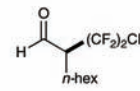
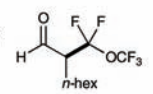
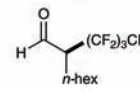
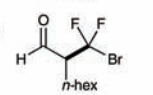
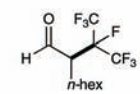
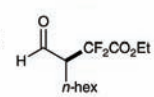


entry	product[a]	yield,[b] ee[c]	entry	product[a]	yield,[b] ee[c]
1		79% yield 99% ee	7		73% yield[d] 90% ee
2		72% yield 95% ee	8		61% yield 93% ee
3		86% yield 97% ee	9		75% yield 97% ee
4		78% yield 98% ee	10		68% yield >20:1 dr 99% ee
5 6		X = CH_2 70% yield 99% ee X = NBoc 70% yield 98% ee	11		62% yield >20:1 dr 99% ee

[a] Stereochemistry assigned by chemical correlation or by analogy. [b] Isolated yields of the corresponding alcohol. [c] Enantiomeric excess determined by chiral SFC or HPLC analysis. [d] Using catalyst **11**; ref 20.

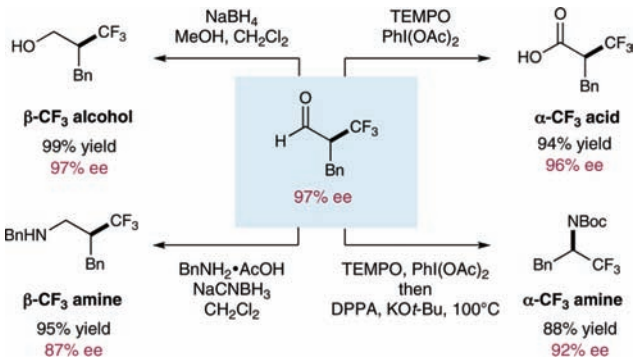
Notably, this protocol enables the formation of a benzylic-CF_3 α-formyl stereocenter without significant erosion in enantiopurity (entry 8, 61% yield, 93% ee).[21] As highlighted in entries 10 and 11, exposure of enantiopure (*R*)-3-phenyl-butyraldehyde to catalyst (2*S*,5*R*)-**2** results in the diastereoselective production of the *anti* α,β-disubstituted isomer, while the use of (*S*)-3-phenyl-butyraldehyde with the same amine catalyst affords the corresponding *syn*

Table 3. Enantioselective α-Perfluoroalkylation: Alkyl Iodide Scope

entry	product[a]	yield,[b] ee[c]	entry	product[a]	yield,[b] ee[c]
1		73% yield 96% ee	5		85% yield 98% ee
2		69% yield 99% ee	6		71% yield 99% ee
3		67% yield 96% ee	7		68% yield[d] 99% ee
4		72% yield 98% ee	8		89% yield[d] 99% ee

[a] Stereochemistry assigned by chemical correlation or by analogy. [b] Isolated yields of the corresponding alcohol. [c] Enantiomeric excess determined by chiral HPLC analysis of corresponding 2-naphthoyl ester. [d] The perfluoroalkyl bromide was employed as starting material.

Scheme 2. Access to Enantioenriched Organofluorine Synthons



adduct with high fidelity. These transformations clearly demonstrate the synthetic advantages of catalyst-enforced induction versus substrate-directed stereocontrol.

We have found that a broad range of perfluoroalkyl iodides and bromides also participate in this enantioselective alkylation reaction (Table 3). For example, *n*-perfluoroalkyl substrates of varying chain length undergo reductive radical formation and enamine addition without loss in enantiocontrol or reaction efficiency (entries 1−3 and 5−8, 67−89% yield, 96−99% ee). We have also found that the aldehyde α-functionalization step can be performed with sterically demanding coupling partners such as perfluoro-isopropyl iodides (entry 4, 72% yield, 98% ee). Moreover, benzylic, α-ester, and α-ether difluoromethylene carbons are readily incorporated as part of this new enantioselective catalytic α-carbonyl alkylation.

We fully expect that the α-trifluoromethyl aldehyde products generated in this study will be of value for the production of a variety of organofluorine synthons. As shown in Scheme 2, reduction or oxidation of the formyl group is possible to generate *β*-hydroxy and α-trifluoromethyl acids (the latter we expect will be a key building block for the formation of heterocycles that incorporate CF_3 at the benzylic position). Moreover, these aldehyde products can be employed in a reductive amination sequence without significant loss in enantioselectivity to produce *β*-trifluoromethyl amines. Last, and perhaps most important, aldehyde oxidation followed by a Curtius rearrangement allows enantioselective formation of α-trifluoromethyl amine containing stereocenters, a commonly employed amide isostere in medicinal chemistry.[2] In this case, careful selection of base and reaction temperature is essential to maintain the enantiopurity obtained in the initial alkylation step.

In summary, the first enantioselective, organocatalytic α-trifluoromethylation and α-perfluoroalkylation of aldehydes have been accomplished using a readily available iridium photocatalyst and a commercial imidazolidinone catalyst. Full details of this survey will be forthcoming.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Although $Ir(ppy)_2(dtb\text{-}bpy)PF_6$ **1** was optimal for this transformation, commercially available $Ru(bpy)_3Cl_2$ could also be used to afford the desired products in slightly diminished yields and enantioselectivities (Table 1, entry 5). **1** is available in a single step from commercially available $[Ir(ppy)_2Cl]_2$ (Sigma-Aldrich, CAS-No 92220-65-0). See ref 12.

(12) For synthesis and photophysical properties of $Ir(ppy)_2(dtb\text{-}bpy)PF_6$ **1**, see: Slinker, J. D.; Gorodetsky, A. A.; Lowry, M. S.; Wang, J.; Parker, S.; Rohl, R.; Bernhard, S.; Malliaras, G. G. *J. Am. Chem. Soc.* **2004**, *126*, 2763–2767. For a review on the photoproperties of iridium complexes, see: Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F. *Top. Curr. Chem.* **2007**, *281*, 143–203.

(13) Fluorescence quenching experiments using preformed enamine **4** (R = Bn) confirmed quenching of $*Ir(ppy)_2(dtb\text{-}bpy)PF_6$, Stern−Volmer constant = 185; see Supporting Information for details.

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(16) Performed using B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d). See ref 9.

(17) We have recently shown the disruption of a postreaction racemization pathway via design of catalyst **2** (versus catalyst **10**); see: Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5121–5124.

(18) The transformation does not proceed in the absence of the amine catalyst. The addition of 2,6-lutidine is necessary to remove hydroiodic acid that is formed during the reaction. Rapid racemization of the α-CF_3 formyl adduct was observed at room temperature but not at −20 °C.

(19) Lower reaction efficiency appears to lead to lower enantiopurity as the product is exposed to unconsumed base (i.e., Table 1, entry 5, catalyst **9**).

(20) A hitherto unreported amine catalyst **11** was employed in entry 7 (Table 2); see Supporting Information.

(21) Efficient construction of a benzylic CF_3 bond on the unsubstituted parent compound, phenylacetaldehyde, is also attainable (*cf.* 89% ^{19}F NMR yield); however facile postreaction racemization is observed.

(22) General Procedure for the Enantioselective α-Trifluoromethylation of Aldehydes: To a dry test tube were added organocatalyst **2** (0.20 equiv), photocatalyst **1** (0.005 equiv), and DMF (0.3 M). The resultant yellow solution was degassed by alternating vacuum evacuation/argon backfill (×3) at −78 °C before addition of CF_3I (∼8 equiv), followed by aldehyde (0.76 mmol, 1.0 equiv) and 2,6-lutidine (1.1 equiv). The reaction vessel was placed near a 26 W compact fluorescent light bulb in a −20 °C bath for 7.5−8 h. Upon reaction completion, the α-trifluoromethyl aldehydes were typically reduced in situ with $NaBH_4$ (10 equiv) in CH_2Cl_2 and MeOH to afford *β*-trifluoromethyl alcohols in high yield and enantioselectivity.

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