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Catalytic Hydrotrifluoromethylation of Unactivated Alkenes

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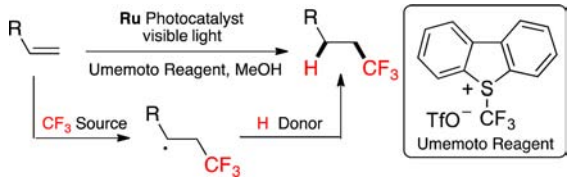
Supporting Information

ABSTRACT: A visible-light-mediated hydrotrifluoromethylation of unactivated alkenes that uses the Umemoto reagent as the CF_3 source and MeOH as the reductant is disclosed. This effective transformation operates at room temperature in the presence of 5 mol % $Ru(bpy)_3Cl_2$; the process is characterized by its operational simplicity and functional group tolerance.

Unactivated alkenes are among the most abundant and commonly used carbon feedstocks in the synthesis of commodity chemicals.[1] For this reason, a myriad of catalytic reactions are available for the functionalization of alkenes that form carbon–carbon or carbon–heteroatom bonds.[2] Direct hydroalkylation is a fundamentally important transformation that emcompasses a broad spectrum of applications ranging from industrial processes to the synthesis of pharmaceutical agents.[3] Despite enormous progress in the field, hydrotrifluoromethylation remains underdeveloped; this is in contrast to hydroperfluoroalkylation.[4] In fact, among all the processes involving an alkene and a trifluoromethyl source,[5] no example of catalytic hydrotrifluoromethylation of unactivated alkenes is extant. In view of the importance of trifluoromethyl substitution onto small molecules for the pharmaceutical, agrochemical, and material industries,[6] the availability of a mild and functional-group-tolerant method for vicinal hydrotrifluoromethylation of unactivated olefins is of interest.

To engineer a net fluoroform addition to alkenes, we considered what catalytic processes would potentially be suitable. We envisioned a general mechanism in which the trifluoromethyl group and the hydrogen atom would stem from separate reagent sources. The ability of photoredox catalysts[7] such as $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (bpy = 2,2′-bipyridine) or *fac*-$Ir(ppy)_3$ (ppy = 2-phenylpyridinato) to promote atom transfer radical addition (ATRA) of trifluoromethyl iodide to olefins served as a starting point for reaction development.[8] We reasoned that direct net fluoroform addition could be achieved if one could favor hydrogen abstraction[9] from a competent reducing agent following the C–CF_3 bond-forming event. This strategy was thus adopted, building on the previously disclosed reductive radical cyclization of alkyl bromides tethered to unactivated π systems.[10] Herein we report a reductive intermolecular process that consists of a net regioselective addition of CF_3H onto alkenes (Scheme 1). This hydrotrifluoromethylation uses the Umemoto reagent as the CF_3 source and methanol as the hydrogen donor. This operationally simple protocol can readily be used to install a terminal CF_3 group on a broad range of simple and complex alkenes. Alternative methods to access these seemingly simple products are surprisingly very limited.[11]

Scheme 1. Regioselective Hydrotrifluoromethylation of Alkenes



Examination and optimization of the reaction parameters were explored using $Ru(bpy)_3Cl_2{\cdot}6H_2O$ as the photoredox catalyst and 5-hexenyl benzoate (**1a**) as the substrate in conjunction with various sources of CF_3 radical and hydride donors (Table 1). The reactions were performed with 5 mol % Ru catalyst under visible-light irradiation. The use of trifluoromethyl iodide (**I**) and Hantzsch ester (**VI**) with or without *i*-Pr_2NEt in dimethyl sulfoxide (DMSO) led mainly to the ATRA product (Table 1, entries 1 and 2). Replacing **I** with Togni reagent **III** or **IV** gave the desired hydrotrifluoromethylated product **2a**; however, the yield did not exceed 22% (Table 1, entries 3 and 4). The Umemoto reagent (**V**) was superior to other CF_3 sources when the reaction was conducted in *N*,*N*-dimethylformamide (DMF) or MeOH (Table 1, entries 5–7). The potential role of methanol as a hydrogen atom donor[12] encouraged us to conduct control experiments in the absence of Hantzsch ester. Alkene **1a** underwent ATRA with CF_3I/*i*-Pr_2NEt (Table 1, entries 8 and 9), and the use of trifluoromethylsulfonyl chloride (**II**) gave the product resulting from net CF_3Cl addition after 30 h (Table 1, entry 10). Togni reagents **III** and **IV** led mainly to decomposition (Table 1, entries 11 and 12). Gratifyingly, Umemoto reagent **V** in methanol gave a 67% yield of **2a** resulting from net fluoroform

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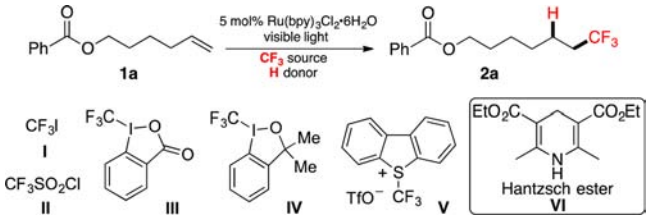
Table 1. Optimization of the Reaction Parameters



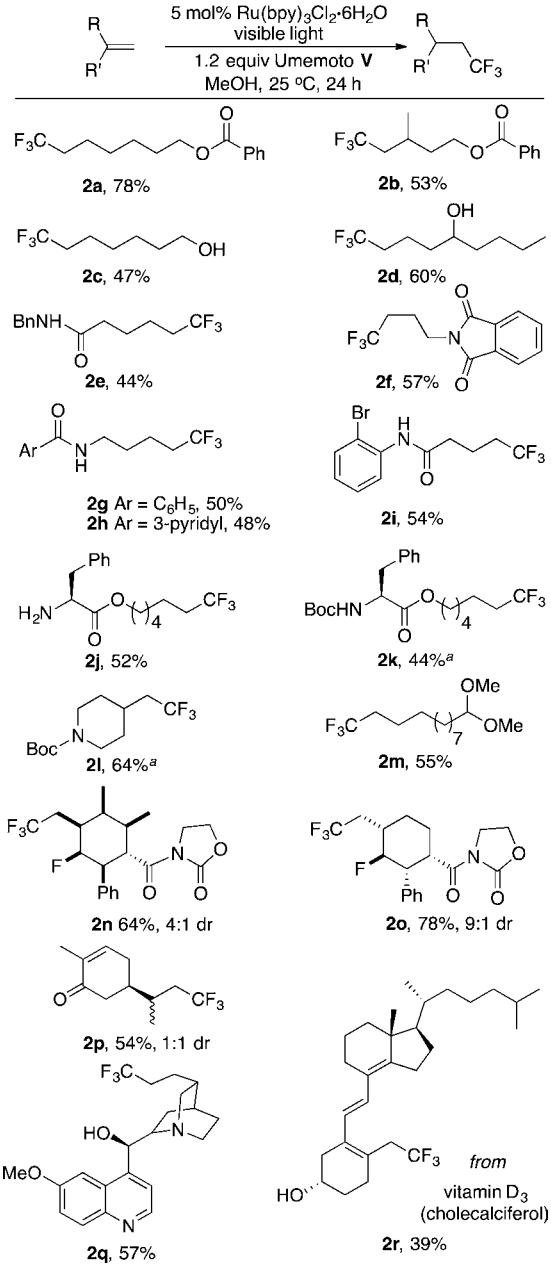
entry	CF_3 source[a]	additive	solvent[b]	conv. (%)[c]	yield (%)[c]
1	**I**	**VI**[d]	DMSO	45	<2[e]
2	**I**	**VI**,[d] *i*-Pr_2NEt[f]	DMSO	69	<4[e]
3	**III**	**VI**[d]	DMSO	47	22
4	**IV**	**VI**[d]	DMSO	50	17
5	**V**	**VI**[d]	DMSO	58	24
6	**V**	**VI**[d]	DMF	64	30
7	**V**	**VI**	MeOH	45	35
8	**I**	–	MeOH	–[g]	–
9	**I**	*i*-Pr_2NEt[f]	MeOH	>95	–[h]
10	**II**	–	MeOH	>95	–[i]
11	**III**	–	MeOH	65	13
12	**IV**	–	MeOH	86	–
13	**V**	–	MeOH	>95	67
14[j]	**V**	–	MeOH	>95	69
15[k]	**V**	–	MeOH	>95	<5
16	**V**	–	EtOH	>95	22
17	**V**	–	*i*PrOH	>95	10
18	**V**	Na_2HPO_4	MeOH	>95	60
19	**V**	*i*-Pr_2NEt[f]	MeOH	80	13
20	**V**	pyridine[l]	MeOH	90	75

[a]1.2 equiv of **II**–**V** or 10 equiv of **I**. [b]0.25 M. [c]Determined by ^{19}F NMR integration relative to an internal standard ($C_6H_5CF_3$). [d]2 equiv. [e]38% yield of the ATRA product. [f]2 equiv. [g]No reaction. [h]79% yield of the ATRA product. [i]53% yield of the adduct resulting from *net* CF_3Cl addition. [j]Reagent **V** with BF_4^- as the counteranion. [k]5 mol % $[Ir(ppy)_2(dtbbpy)]PF_6$. [l]1.2 equiv.

addition in the absence of Hantzsch ester (Table 1, entry 13). The counterion of the Umemoto reagent had little influence on the product outcome (Table 1, entry 14). The use of $[Ir(ppy)_2(dtbbpy)]PF_6$ (dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) instead of $Ru(bpy)_3Cl_2{\cdot}6H_2O$ led to complete consumption of **1a**, and only trace quantities of **2a** (<5%) were detected (Table 1, entry 15). Alternative alcohols such as EtOH or *i*-PrOH were less effective (Table 1, entries 16 and 17). The presence of 1.2 equiv of pyridine proved to be slightly beneficial, but trace amounts of the product resulting from competitive oxytrifluoromethylation were seen with this additive. Control experiments authenticated the importance of both light and the Ru catalyst for reactivity. Thus, under the optimized conditions,[13] the Ru-catalyzed reaction of alkene **1a** with 1.2 equiv of Umemoto reagent **V** in MeOH at room temperature afforded exclusively the trifluoromethylated product **2a** as a single regioisomer.

Unactivated terminal monosubstituted and geminally disubstituted alkenes participated in the hydrotrifluoromethylation effectively (Scheme 2). Typically, the reactions were performed in the absence of pyridine. A wide range of substrates and functional groups were tolerated, including esters, unprotected and protected alcohols, protected amines, amides, imides, carbamates, enones, (hetero)arenes, and oxazolidinones. The hydrotrifluoromethylation of undec-10-enal occurred with concomitant acetalization, suggesting that an acid, presumably

Scheme 2. Substrate Scope of the Hydrotrifluoromethylation



[a]1.2 equiv of pyridine.

trifluoromethanesulfonic acid, is generated in solution. The trifluoromethylated acetal **2m** was obtained in 55% yield under the standard reaction conditions. In a similar vein, the deprotected trifluoromethylated amine **2j** was isolated in 52% yield from the corresponding protected *N*-Boc-amino ester precursor. For this reaction, the addition of 1.2 equiv of pyridine prevented *N*-Boc deprotection, affording **2k** instead of **2j**; however, the presence of base could not suppress acetalization for substrates with an aldehyde functionality.

Cyclic fluorinated substrates made available by electrophilic fluorination of the corresponding allylsilanes[14] underwent catalytic hydrotrifluoromethylation to afford **2n** and **2o** in yields of 64 and 78% (4:1 and 9:1 dr), respectively. Pleasingly, this reaction allowed for the direct hydrotrifluoromethylation of more complex starting materials such as (*R*)-carvone and quinine. For (*R*)-carvone, which contains two inequivalent

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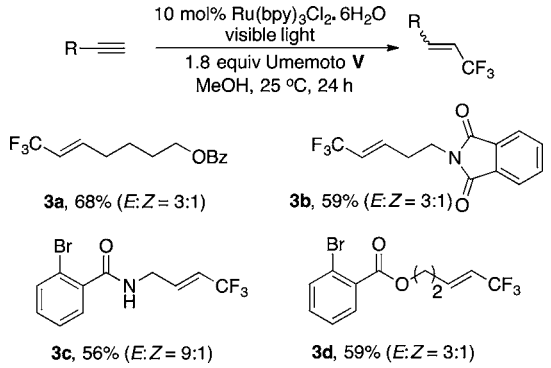
alkenes, the reaction chemoselectively targeted the electron-rich exocyclic alkene, affording product **2p** in 54% yield (1:1 dr). Quinine was readily transformed into **2q** in 57% yield. Under the standard reaction conditions, vitamin D3 afforded **2r**, the product of allylic trifluoromethylation rather than net fluoroform addition.

The hydrotrifluoromethylation of alkynes was also successful (Scheme 3). The highest yields were observed when the

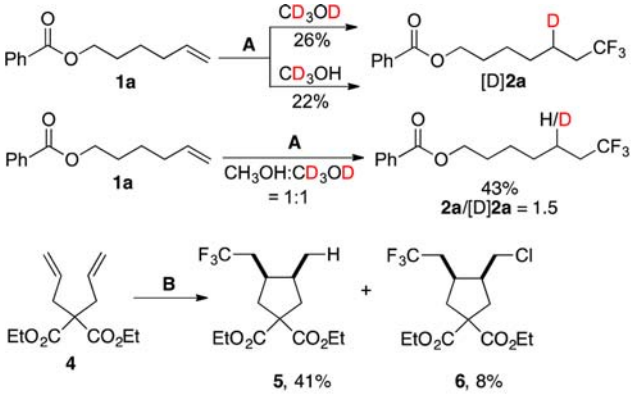
Scheme 3. Hydrotrifluoromethylation of Alkynes



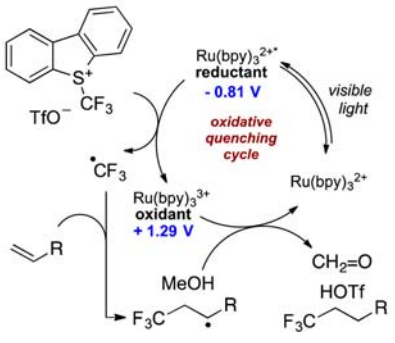
reaction was performed in the presence of 10 mol % $Ru(bpy)_3Cl_2{\cdot}6H_2O$ and 1.8 equiv of Umemoto reagent **V** in methanol at room temperature. Under these conditions, trifluoromethylated alkenes **3a–d** were isolated in yields of up to 68% as mixtures of *E*/*Z* isomers.

We probed the mechanism of the reaction by replacing CH_3OH with CD_3OD and CD_3OH (Scheme 4). The exclusive

Scheme 4. Mechanistic Investigations



A: Umemoto **V** (1.2 equiv), $Ru(bpy)_3Cl_2$ (5 mol%), visible light, 25 °C, 24 h
B: Umemoto **V** (1.2 equiv), $Ru(bpy)_3Cl_2$ (5 mol%), pyridine (1.2 equiv), visible light, 25 °C, 24 h



formation of the deuterated product [D]**2a** in both reactions unambiguously confirmed that the α-C–H bond of methanol serves as the hydrogen atom source. When the reaction was carried out in a 1:1 mixture of CH_3OH and CD_3OD, the product distribution revealed a mechanistically significant normal kinetic isotope effect (k_H/k_D = 1.5). Next, diene **4** was submitted to the reaction conditions and was found to give cyclized product *syn*-**5** in 41% yield along with the cyclized chlorinated byproduct *syn*-**6** (8% yield). The observed cyclization event is consistent with the presence of a CF_3 radical intermediate in this hydrotrifluoromethylation reaction. Collectively, these data strongly suggest a radical-based mechanism. It is well-established that irradiation of $Ru(bpy)_3Cl_2$ with visible light (λ_{max} = 452 nm) leads to the excited-state species $Ru(bpy)_3^{2+*}$, which enters either an oxidative or reductive quenching cycle.[7] We propose that the present hydrotrifluoromethylation occurs through an oxidative quenching cycle of $Ru(bpy)_3^{2+*}$. The reduction potential of Umemoto reagent **V** (−0.25 V vs SCE in CH_3CN)[15] is compatible with the reduction step using excited-state $Ru(bpy)_3^{2+*}$. This implies that single electron transfer (SET) reduction of **V** would be concurrent with the oxidation of $Ru(bpy)_3^{2+*}$ to $Ru(bpy)_3^{3+}$ (−0.81 V vs SCE in CH_3CN).[7,16] The resulting Umemoto radical anion could collapse to generate an electrophilic $CF_3^{\bullet}$ species, which would be well-suited to add regioselectively to the alkene substrate. The resultant carbon radical would subsequently be converted to the hydrotrifluoromethylation product. This last event would require the participation of methanol as the hydrogen atom donor and of the strong oxidant $Ru(bpy)_3^{3+}$ (+1.29 V vs SCE in CH_3CN).[7,16] Upon oxidation of methanol, $Ru(bpy)_3^{3+}$ is converted into the ground-state photocatalyst $Ru(bpy)_3^{2+}$.[17] A reductive quenching pathway was dismissed because oxidation of MeOH takes place at potentials greater than +1.5 V vs SCE on a glassy carbon electrode and $Ru(bpy)_3^{2+}$ (+0.77 V vs SCE in CH_3CN) is a weaker oxidant than $Ru(bpy)_3^{3+}$.[7,16]

In conclusion, we have reported our initial examination of the hydrotrifluoromethylation of unactivated alkenes using visible-light-activated $Ru(bpy)_3Cl_2{\cdot}6H_2O$. The studies detailed herein have resulted in a novel method that allows *net* fluoroform addition across alkenes and alkynes in a regioselective manner under mild conditions (room temperature). The catalytic cycle employs the Umemoto reagent as the CF_3 source and methanol as both the solvent and the hydrogen atom donor. The substrate scope and operational simplicity make this reaction an attractive method for medicinal chemistry and other applications.[18]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, additional optimization studies, and analytical data and spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) While this manuscript was under review, a report disclosing the silver-catalyzed hydrotrifluoromethylation of unactivated alkenes with CF_3SiMe_3 appeared. See: Wu, X.; Chu, L.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2013**, DOI: 10.1002/anie.201208971.