

Trifluoromethylchlorosulfonylation of Alkenes: Evidence for an Inner-Sphere Mechanism by a Copper Phenanthroline Photoredox Catalyst**

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Dedicated to Henri Brunner on the occasion of his 80th birthday

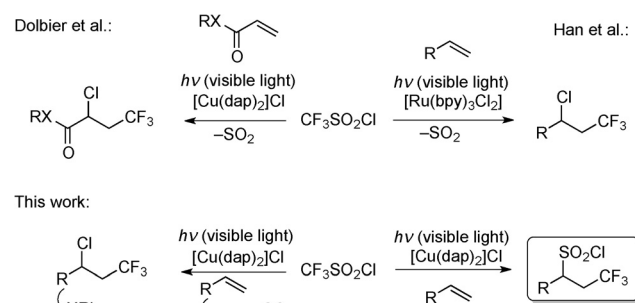
Abstract: A visible-light-mediated procedure for the unprecedented trifluoromethylchlorosulfonylation of unactivated alkenes is presented. It uses $[\text{Cu}(\text{dap})_2]\text{Cl}$ as catalyst, and contrasts with $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$, $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$, or eosin Y that exclusively give rise to trifluoromethylchlorination of the same alkenes. It is assumed that $[\text{Cu}(\text{dap})_2]\text{Cl}$ plays a dual role, that is, acting both as an electron transfer reagent as well as coordinating the reactants in the bond forming processes.

The introduction of the trifluoromethyl group into organic molecules usually leads to a significant improvement of the chemical and metabolic stability of drug candidates.^[1–3] Numerous procedures, including nucleophilic, electrophilic, or radical approaches were developed for the installation of the CF_3 group,^[4] including recent examples in which visible-light-mediated redox photocatalysis is used as key step.^[5] Ruthenium- and iridium-based complexes can effectively catalyze the cleavage of CF_3I ,^[6] Togni's reagent,^[7] Umemoto's reagent,^[8] or triflyl chloride.^[9] The role of these photoredox catalysts in such transformations is assumed in the transfer of an electron to the trifluoromethyl source by an outer-sphere mechanism, providing CF_3 radicals that undergo further transformations.

Exploring the potential of $[\text{Cu}(\text{dap})_2]\text{Cl}^{[10]}$ (−1.43 V vs. SCE; dap = 2,9-bis(*para*-anisyl)-1,10-phenanthroline) as a visible-light-driven photoredox catalyst, we report herein the unprecedented trifluoromethylchlorosulfonylation of

unactivated alkenes, suggesting an inner-sphere mechanism that determines the outcome of the reaction beyond a photo-initiated electron transfer. In contrast, commonly used ruthenium or iridium complexes or eosin Y give rise to trifluoromethylchlorination with concurrent loss of sulfur dioxide, being in agreement with an outer-sphere electron transfer mechanism commonly assumed in photoredox catalyzed ATRA (atom-transfer radical addition) reactions.^[11]

Thermal cleavage of triflyl chloride catalyzed by $[\text{Ru}(\text{Ph}_3\text{P})_2\text{Cl}_2]$ was demonstrated by Kamigata et al.^[12] for the trifluoromethylchlorination of alkenes. Han et al. showed that the same process can be achieved by photoredox catalysis using $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ (Scheme 1).^[9b] In both cases the mech-



Scheme 1. Trifluoromethylations of alkenes by visible-light photocatalysis.

anism is assumed to involve the oxidative $\text{Ru}^{2+}/\text{Ru}^{3+}$ cycle, and electron transfer to triflyl chloride is accompanied with SO_2 extrusion.

Following our development of ATRA reactions by visible light photocatalysis using $[\text{Cu}(\text{dap})_2]\text{Cl}$,^[13] we examined the feasibility of this catalyst towards trifluoromethylations of alkenes. Surprisingly, we observed that green light (LED 530 nm) irradiation of an acetonitrile solution of allylbenzene (**1a**) and triflyl chloride (2 equiv) in the presence of 1 mol % $[\text{Cu}(\text{dap})_2]\text{Cl}$ resulted in an ATRA process without SO_2 extrusion, giving rise to **2a** in moderate yield (Table 1, entry 1). The expected product **3a** was only observed in trace amounts. The presence of a base significantly improves the yield of **2a**, which was isolated in 86 % (1 mol % $[\text{Cu}(\text{dap})_2]\text{Cl}$) or 63 % (0.5 mol % $[\text{Cu}(\text{dap})_2]\text{Cl}$) yield, respectively, upon addition of K_2HPO_4 (entries 2,3). Variation of solvents (entries 4,5) results in a slight decrease in yield;

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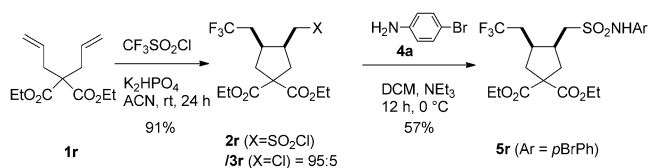
Table 1: Optimization of reaction parameters for the trifluoromethylchlorosulfonylation reaction of alkenes.^[a]

Entry	Catalyst ^[a]	Solvent ^[a]	Selectivity (2a:3a)	Yield [%]
1 ^[b]	[Cu(dap) ₂] ₂ Cl	MeCN	96:4	46
2	[Cu(dap) ₂] ₂ Cl	MeCN	95:5	86
3 ^[c]	[Cu(dap) ₂] ₂ Cl	MeCN	96:4	63
4	[Cu(dap) ₂] ₂ Cl	CH ₂ Cl ₂	93:7	73
5	[Cu(dap) ₂] ₂ Cl	DMF	54:46	71
6 ^[d]	[Cu(dap) ₂] ₂ Cl	MeCN	99:1	10
7	[Cu(MeCN) ₄] ₂ PF ₆	MeCN	15:85	7
8 ^[d]	[Cu(MeCN) ₄] ₂ PF ₆	MeCN	14:86	6
9	dap (2 mol %)	MeCN	0:100	11
10	no catalyst	MeCN	—	N.R.
11	CuOAc/1,10-phen	MeCN	—	N.R.
12	CuCl/1,10-phen	MeCN	40:60	20
13 ^[d,e,f]	CuCl/AIBN	MeCN	0:100	35
14	[Ru(bpy) ₃] ₂ Cl ₂	MeCN	4:96	84
15	[Ir(ppy) ₂](dtbbpy)]PF ₆	MeCN	11:89	75
16	Eosin Y	MeCN	3:97	80

[a] Reaction conditions: alkene (0.5 mmol), TfCl (1 mmol), K₂HPO₄ (1 mmol), catalyst (1 mol %), solvent (3 mL), irradiation at 530 nm (entries 1–14 or 455 nm entries 15–17), 24 h. [b] absence of K₂HPO₄. [c] catalyst loading 0.5 mol %. [d] dark reaction. [e] AIBN (10 mol %). [f] 100 °C. [g] bpy = 2,2'-bipyridine, ppy = 4-pyrrolidinopyridine, dtbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl, N.R. = no reaction.

moreover, the use of DMF gave both **2a** and **3a** in a nearly equimolar ratio. The combination of light, copper(I), and dap ligand is necessary for the reaction to proceed efficiently; omission of any of those resulted at best in low yields of **2a** (entries 6–10). Considering a [Cu(phenanthroline)CF₃] species, being decisive in the stoichiometric trifluoromethylation of aryl halides,^[14] CuOAc/1,10-phen was tested, but did not result in any conversion of the starting materials (entry 11). The combination of CuCl/1,10-phen was somewhat effective; however, both **2a** and **3a** were formed unselectively (entry 12). Initiation of the reaction with the combination of CuCl/AIBN under thermal conditions exclusively led to **3a** in low yield (entry 13). In contrast, established photoredox catalysts such as [Ru(bpy)₃]₂Cl₂, [Ir(ppy)₂](dtbbpy)]PF₆, and eosin Y upon irradiation close to their absorption maxima at 455 nm (entries 14–16) resulted in a net addition of CF₃Cl.

With optimized conditions in hand, we examined the scope of the reaction (Table 2, Scheme 2). Introduction of moderate donor or acceptor substituents on the aromatic ring of the parent allylbenzene far removed from the double bond



Scheme 2. Trifluoromethylchlorosulfonylation of diene **1r**.

Table 2: Substrate scope of copper-catalyzed trifluoromethylchlorosulfonylation versus trifluoromethylchlorination of alkenes.^[a]

	[Cu(dap) ₂] ₂ Cl	LED ₅₃₀ nm	SO ₂ Cl	R-CH ₂ -CH ₂ -CF ₃	2a-j
	[Cu(dap) ₂] ₂ Cl	LED ₅₃₀ nm	Cl	R-CH ₂ -CH ₂ -CF ₃	3k-q
	[Ru(bpy) ₃] ₂ Cl ₂	LED ₄₅₅ nm	Cl	R-CH ₂ -CH ₂ -CF ₃	3a,d,f

[a] Reaction conditions: alkene (1 mmol), TfCl (2 mmol), K₂HPO₄ (2 mmol), catalyst (1 mol %), acetonitrile (3 mL), irradiation at 530 nm for 24 h, compound **2i** was obtained as a mixture of two diastereomers (60:40).

had no influence on the course of the reaction, giving rise to **2a–f** in good yields. Terminal alkenes showed excellent regioselectivity (**2a–g**), whereas employing internal alkenes gave rise to mixtures of regio- and diastereoisomers (**2h**) unless symmetrical substrates (**2i** 2 diastereomers 60:40, **2j** only *trans*) were employed. The diene **1r** (Scheme 2) proved to be an excellent substrate for the trifluoromethylchlorosulfonylation, giving rise to **2r/3r** (95:5) in 91 % yield, contrasting again related [Ru(bpy)₃]₂Cl₂ catalyzed trifluoromethylations with **1r**, which proceeded only in moderate yield.^[7] The somewhat labile sulfonylchlorides **2** react readily with anilines **4** to trifluoromethylated sulfonamides **5** (Scheme 2 and Supporting Information), which allowed their formation to be unambiguously established (X-ray structure of **5d**), but also appears to be of interest in light of the relevance of sulfonamides^[20] for medicinal chemistry.

A donor atom in close proximity to the alkene functionality changes the course of the reaction in that net addition of trifluoromethyl and chloride is observed (**3k–o**). Also, **3p**

having a strong donor present was the only product that could be obtained from the corresponding alkene **1p**. In all of these cases, the reactions proceed at a considerably slower rate, showing significant amounts of unreacted starting material after 24 h. Styrenes also undergo trifluoromethylchlorination; however, mixtures of products that result from subsequent elimination of HCl are generally obtained. An exception was the electron deficient *para*-nitrostyrene that was converted exclusively into **3q** in high yield. It should be noted that no successful examples with other photoredox catalysts have been reported to date for this process employing styrenes as substrates. Very recently, Dolbier et al. reported $[\text{Cu}(\text{dap})_2]\text{Cl}$ catalyzed additions of $\text{CF}_3\text{SO}_2\text{Cl}$ to α,β -unsaturated amides and esters (that is, heteroatom-containing alkenes in close vicinity to the C,C-double bond), for which also exclusive addition of trifluoromethyl and chloride is observed,^[15] being in full agreement with the findings reported herein. When $[\text{Ru}(\text{bpy})_3]\text{Cl}_2$ is employed as catalyst for a representative number of allylbenzenes, net addition of CF_3/Cl at the double bond was exclusively observed (**3a**, **3d**, **3f** (Table 2), and **3r** (Scheme 2), being also in agreement with recent reports.^[9b]

The striking difference of $[\text{Cu}(\text{dap})_2]\text{Cl}$ to ruthenium, iridium, or eosin Y catalysts points toward the essential role of copper in the overall process, which presumably can coordinate SO_2Cl^- ,^[16,17] thus retaining it within the reactive intermediates. The quantum yield of this process was determined to be 12%, ruling out a free radical chain mechanism. We therefore reason that photoexcited $[\text{Cu}(\text{dap})_2]\text{Cl}^*$ reduces triflyl chloride by a single electron transfer (SET), with oxidation of Cu^{I} to Cu^{II} giving rise to **A** (Figure 1). From there, the trifluoromethylradical is added

demonstrates the role of copper as a ligand binding entity, given the well-known instability of free SO_2Cl^- that rapidly decomposes to SO_2 and Cl^- .^[19] The formation of *cis/trans*-**2i** and *trans*-**2j** also points to the involvement of CF_3 radicals rather than a Cu^{III} intermediate $[\text{CF}_3\text{CuSO}_2\text{Cl}]^+$, which would be expected to undergo a *cis* addition to the alkene, thus making **A** and **B** the most plausible intermediates for the process. Nevertheless, the binding of SO_2Cl^- to copper appears to be weak, which might explain the observation of trifluoromethylchlorination with alkenes that contain donor atoms. The latter might readily displace SO_2Cl^- , facilitating the extrusion of SO_2 .

In contrast the ruthenium and iridium as well as the eosin Y catalyzed reactions are likely to proceed by an outer-sphere mechanism in which upon electron transfer to $\text{CF}_3\text{SO}_2\text{Cl}$ the latter fragments with concurrent extrusion of sulfur dioxide to yield the trifluoromethyl radical and chloride, which then follows the free radical addition pathway established for photoredox catalyzed ATRA reactions.

The instrumental role of a copper-ligand environment for the course of the reaction was also seen when unfunctionalized but sterically more hindered alkenes were employed (Scheme 3). The 1,1-disubstituted alkene **1s** exclusively gave rise to the chloro adduct **3s**, while the sulfonylchloride **2s** is not observed, contrasting the course of the reaction when the terminal alkene **1c** is being used. For **1t** having a branched substituent at one alkene terminus, a mixture of chlorosulfonylated and chlorinated adducts **2t/3t** (3:1) was observed when $[\text{Cu}(\text{dap})_2]\text{Cl}$ was used as catalyst.

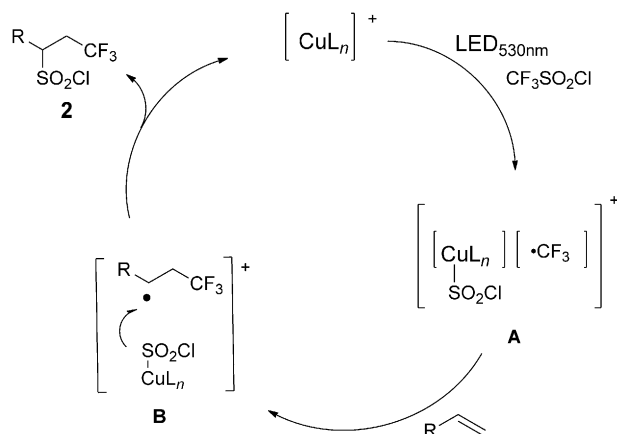
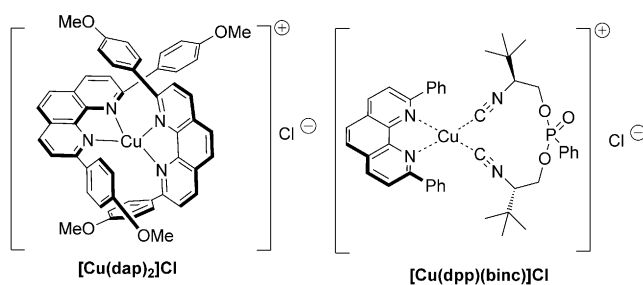
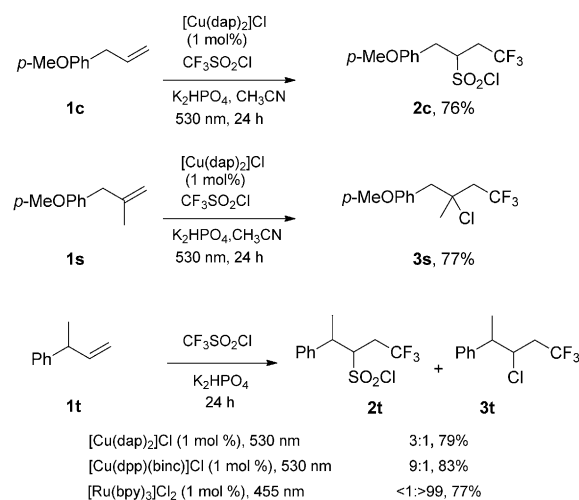


Figure 1. Proposed mechanism for $[\text{Cu}(\text{dap})_2]\text{Cl}$ -catalyzed trifluoromethylchlorosulfonylation.

to the alkene giving rise to **B**, and finally transfer of SO_2Cl from copper to the resulting radical intermediate gives rise to **2**. Mitani et al. already speculated for CuCl -UV-photocatalyzed ATRA reactions the involvement of copper as a substrate coordinating center as an alternative to a free-radical process,^[18] proposing a photoinduced oxidative addition of R-Cl to Cu^{I} , thus generating $[\text{RCu}^{\text{III}}\text{Cl}]^+$. The discovery of the trifluoromethylchlorosulfonylation reported here clearly



Scheme 3. Steric influence of substrates and catalysts on the trifluoromethylchlorosulfonylation or -chlorination of alkenes.

Significantly, using the sterically less bulky complex [Cu(dpp)(binc)]Cl significantly increases the formation of the chlorosulfonylated adduct (**2t/3t** 9:1). Obviously, steric bulk in the substrate and the catalyst disfavors the chlorosulfonylation pathway, suggesting again that this group is transferred to the alkene by a Cu-SO₂Cl intermediate but also showing its lability to easily undergo SO₂ extrusion.

In summary, we have developed the unprecedented visible-light-mediated trifluoromethylchlorosulfonylation of unactivated alkenes with triflyl chloride. [Cu(dap)₂]Cl was identified as a unique catalyst for this transformation, which in contrast to other photoredox catalysts suppresses SO₂ extrusion, thus providing the formation of new scaffolds containing a β-trifluoromethylethanesulfonyl chloride skeleton. Our study implicates that copper-catalyzed photoredox processes can be mediated in the inner sphere of a metal-ligand complex that acts at the same time as the photoelectron transfer reagent, opening up the possibility to develop copper- and photo-catalyzed asymmetric ATRA reactions.^[21]

Keywords: atom-transfer radical additions (ATRA) · chlorosulfonylation · copper · photocatalysis · trifluoromethylation

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