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Reversing the Regioselectivity of Halofunctionalization Reactions via Cooperative Photoredox and Copper Catalysis**

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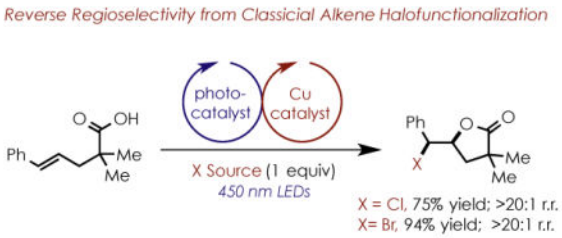
Abstract

Halofunctionalization of alkenes is a classical method for olefin difunctionalization and give rise to adducts which are found in many natural products, biologically active molecules, and offer a synthetic handle for further manipulation. Classically, this reaction is performed with an electrophilic halogen source and gives rise to regioselective formation of the halofunctionalized adducts. In this work, we demonstrate a reversal of the native regioselectivity for alkene halofunctionalization reactions through the use of an acridinium photooxidant in conjunction with a copper cocatalyst.

Graphical abstract



Keywords

organocatalysis; photoredox catalysis; radicals; Halofunctionalization; cooperative catalysis

Alkene halofunctionalizations are some of the oldest and most commonly employed reactions in organic chemistry. These transformations make it possible to rapidly build complex molecules from simple alkene starting materials and provide functional handles for further elaboration. Traditional halofunctionalization reactions proceed reliably through the formation of halonium ions, which form via nucleophilic attack at an electrophilic halogen by an alkene.[1] These intermediates are intercepted by nucleophiles at the position most capable of stabilizing positive charge due to the distortion of the halonium ion. This allows

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for the highly diastereo- and regioselective formation of halofunctionalized products (Figure 1). Recent efforts from the Borhan lab have also suggested a role for the nucleophile in activating alkenes, specifically in chlorolactonization reactions.[2] They have also provided evidence, in some cases, for a concerted mechanism in these reactions; while in other cases, formation of a carbocation intermediate was found to be favored.[2–4]

Numerous reports of enantioselective variants of traditional halofunctionalizations exploit this classic reaction manifold.[2,5,6] Typically, these proceed through activation of the electrophilic halogen source with a chiral Lewis acid,[7–9] hydrogen bond donor/acceptor,[10–12] or through the formation of a chiral electrophilic halogenating reagent in situ.[13,14] While these reports establish methods that give moderate to excellent stereoselectivity, to our knowledge there are no known methods to reliably alter the inherent regioselectivity of halofunctionalization reactions. We envisioned that an alternate method of activating alkenes could lead to the formation of the thermodynamically less favored, and in some cases, traditionally inaccessible regioisomer. Photoredox catalysis has recently been employed by our lab to activate alkenes via single electron oxidation. Indeed, our lab has used this strategy to effect anti-Markovnikov hydrofunctionalization reactions through the use of a photooxidant and a hydrogen atom donor cocatalyst.[15] Formation of a cation radical intermediate in the presence of a nucleophile leads to reversible nucleophilic attack such that the most stable distonic cation radical intermediate is more highly populated. Intercepting the radical intermediate with a radical halogen source could provide a viable method to regioselectively form the halofunctionalized products (Figure 1).

We initially noted a few potential pitfalls in the development of such a reaction: (1) Typical radical halogen sources are also capable of reacting with alkenes to directly form halonium ions. This necessitates that the catalytic pathway be much faster than background reactivity. (2) Homolysis of halogen-heteroatom bonds would lead to the production of highly reactive heteroatom centered radicals, potentially producing unwanted side products. (3) The products may be prone to decomposition or further reactivity under the reaction conditions. Particularly, benzylic halides are known to undergo rapid hydrolysis in some cases.[16]

Initially we focused on chlorolactonization as a target for development because several methods for halolactonization have recently been published and could serve as a direct comparison regarding regioselectivitiy.[17–20] In early optimization stages, several traditional stoichiometric chlorine radical sources were evaluated. In combination with **Mes-Acr-Me+** as a photocatalyst, tosyl chloride (TsCl),[21] provided an early hit for aliphatic alkenes, but proved ineffective for styrenyl substrates (Table 1, Entry 1). Other potential chlorine radical sources such as *N*-chlorosuccinimide (NCS) and *N*-chlorophthalimide (NCP) tended to produce solely the undesired regioisomer (Table 1, Entries 2 & 3). Copper (II) chloride is known to be a competent chlorine atom transfer agent in atom-transfer radical-polymerization (ATRP) reactions and although highly reversible, most copper catalysts favor the Cu(I) oxidation state.[22] Additionally, $CuCl_2$ undergoes irreversible Cl-atom transfer with carbon-centered radicals, which together made it a suitable candidate in this reaction.[23–25] We were pleased to find that employing $CuCl_2$ in MeCN as a Cl-atom source afforded small amounts of the desired regioisomer, which could be improved to a 62% yield through the use of 2,2′-bipyridine (bpy) as a supporting ligand (Table 1, Entry 4).

To avoid the use of stoichiometric metal and ligand, conditions for rendering the reaction catalytic in copper were screened. Running the reaction with 20 mol % $CuCl_2$ and ligand under air or O_2 pressure in the presence of lutidinium chloride (Lut^+Cl^-) led to the formation of unwanted oxygen trapped products and no catalyst turnover (Table 1, Entry 5). The use of stoichiometric NCP alone failed to afford desired adduct (X = Cl). However, in combination with 10 mol % $CuCl_2$/bpy, excellent yields of the chlorolactone product could be obtained (90% yield) in modest diastereoselectivity (2.3:1 dr; Table 1, Entry 6).

The use of CuCl/bpy as a catalyst gave comparable results (Table 1, Entry 7), suggesting that oxidation by NCP was generating $CuCl_2$. The use of 1,10-phenanthroline (phen) as a ligand was found to give similar yields (85% yield), but slightly improved diastereoselectivity (3.2:1 dr) and shorter reaction times (Table 1, Entry 8). In most cases, reactions reached full conversion after only 2 hours. In the absence of photocatalyst some product formation was detected (both regioisomers) but the reaction only reached 40% conversion after 18 hours (Table 1, Entry 9). When the same reaction was quenched after 2 hours, reflective of the final conditions, adduct **A** was not formed and unreacted starting material was returned. It is important to note that when both **Mes-Acr-Me+** and copper catalysts were omitted, no reaction was observed. These results, in combination with the observed formation of **B** in Entries 2 and 3 (Table 1), led us to hypothesize that, in the presence of photocatalyst, strong acid may be generated in situ[26] leading to activation of the chlorinating reagent and subsequent formation of **B**. To test this hypothesis, a reaction between NCS and the substrate was carried out in the presence of strong acid (CF_3SO_3H) and produced significant amounts of product **B** (see Supporting Information for details).

Concurrently, we developed conditions for the synthesis of the complementary bromolactone adducts. Beginning with the catalytic conditions using $CuBr_2$ and *N*-bromophthalimide (NBP) as the bromine source, the desired product was obtained in a 39% yield with significant amounts (61%) of the undesired regioisomer (Table 1, Entry 10). After some experimentation, it was determined that diethyl bromomalonate (DEBM) afforded **A** (X = Br) selectively in 97% yield (Table 1, Entry 11). It is also worth noting that no reaction occurred when the photocatalyst was omitted from the reaction mixture (Table 1, Entry 12). Omitting $CuBr_2$ and ligand from the reaction led solely to the formation of the anti-Markovnikov hydrolactonization product (Table 1, Entry 13), consistent with previous work from our lab.[27]

Once the optimized halolactonization conditions were established, we then developed a substrate scope for the transformations (Chart 1). Both conditions were successfully applied to the halolactonization of 1,2-disubstituted styrenes (**1a–1d**) in good to excellent yields (73–94%) and modest diastereoselectivities (2.1–2.5:1 dr). A trisubstituted styrene was successfully difunctionalized under the chlorination (**1e**) and bromination conditions, however the latter product was also obtained under the classical halofunctionalization conditions. Substituted, electron poor (**1f**) and rich (**1h–1i**) styrenes were viable chlorolactonization substrates while only electron poor (**1g**) and mildly rich styrenes (**1j**) were successful substrates under the bromolactonization conditions, presumably due to the instability of the electron rich benzyl bromide adducts. The versatility of the chlorolactonization conditions was further demonstrated in the chlorofunctionalization of

trisubstituted aliphatic alkenes (**1k–1l**), including a substrate bearing a TBS-protected alcohol (**1l**), albeit in a 1:1 mixture of diastereomers. We also sought to apply our conditions to 1,1-disubstituted styrenes (**1m–1q**), which are classical substrates for Markovnikov-type halofunctionalization reactions.[11,17,19] A 4,4-dimethyl substituted lactone was efficiently obtained under both conditions (**1p–1q**). Three additional substrates successfully underwent chlorolactonization in good yield (**1m–1o**). Interestingly, the presence of a geminal dimethyl group was influential in affecting the regisomeric ratio, with the substrate bearing the dimethyl group α- to the alkene (**1p**) affording a higher regioisomeric ratio (19:1 r.r.) for the tertiary halide than the substrate bearing the dimethyl group β- to the alkene (4.4:1 r.r.; **1r**). This could be due, in part, to a highly competitive uncatalyzed background reaction accelerated by a Thorpe-Ingold effect. Lastly, a benzoic acid substrate also gave benzyl chloride adduct **1s** in 65% yield and 2.5:1 r.r. We also investigated the use of additional nucleophiles including alcohols and amines under the halofunctionalization conditions. Alcohols (**1t–1v**) and a Boc-protected amine (**1w**) were also successful nucleophiles. Intermolecular reactions were also possible with acetate (**1x**) and methansulfonamide nucleophiles (**1y**).

Mechanistically, we hypothesize that these reactions follow a common starting point to our anti-Markovnikov alkene hydrofunctionalization reactions (Figure 2). As such, single electron oxidation of the alkene **1** affords reactive cation radical **2**, which can undergo reversible capture by the nucleophile to afford radical **3** after proton loss. Analogous to Cu-mediated group transfer reactions with C-centered radicals, we propose that the halide is transferred by copper, either through an inner sphere Cu(III) mechanism or an outer sphere atom transfer step, to generate product **4**.[24,28,29]

The intervening steps are perhaps less clear and require further study, however it seems likely that the stoichiometric halogenating reagent could reoxidize Cu(I) to afford the active halogenating reagent. To test the feasibility of Cu(I) oxidation by the stoichiometric halogenating reagents, UV/Vis studies were conducted. Both Cu(I) and Cu(II) complexes were generated independently and each complex has characteristic absorbances previously reported in the literature.[30,31] Solutions of the appropriate halogenating agents were then added to their respective Cu(I) complexes which were immediately oxidized, leading to the observed formation of Cu(II) complexes (See Suporting Information for details).

Turnover of **Mes-Acr-Me•** could be feasible by either an imidyl radical (**PhthN•**) or by a Cu(III) species to reset the catalytic cycle. Succinimide radical (**S•**) has been shown to undergo single electron oxidation of $Ru(bpy)_3^{2+}$ with rate constants on the order of 10^9 $M^{-1}s^{-1}$,[32] 5–6 orders of magnitude greater than that of C-H abstraction,[33] rearrangement,[32] or arene addition.[34] Combined with the sufficiently high reduction potential of **S•** (+1.96 V vs SCE),[32] it is feasible for **S•** (or **PhthN•**) to oxidize **Mes-Acr-Me•** and regenerate the photocatalyst. Both phthalimide and diethyl malonate were observed as byproducts in the crude reaction mixtures by ^1H NMR and GC-MS. This is consistent with the proposal of **S•/PhthN•** reduction and subsequent protonation. The large reduction potential for **S•** prompted us to consider the possibility of a chain mechanism in which an imidyl radical could directly oxidize the substrate. A photochemical quantum yield (Φ_R) of

~3.6% was determined for the chlorolactonization reaction to form product **1c** (see Supporting Information for details). This result is consistent with our proposed mechanism, however we cannot rule out the possibility of a highly inefficient, but productive chain propagation.

In conclusion, we have developed a new dual catalytic system consisting of an acridinium photooxidant and a copper cocatalyst that accomplishes halofunctionalization of unsaturated carboxylic acids proceeding with opposite regioselectivity from classical halolactonization conditions. These conditions are also capable of producing intra- and intermolecular adducts. We believe this class of reactions could be valuable for the synthesis of complex natural products and medicinal agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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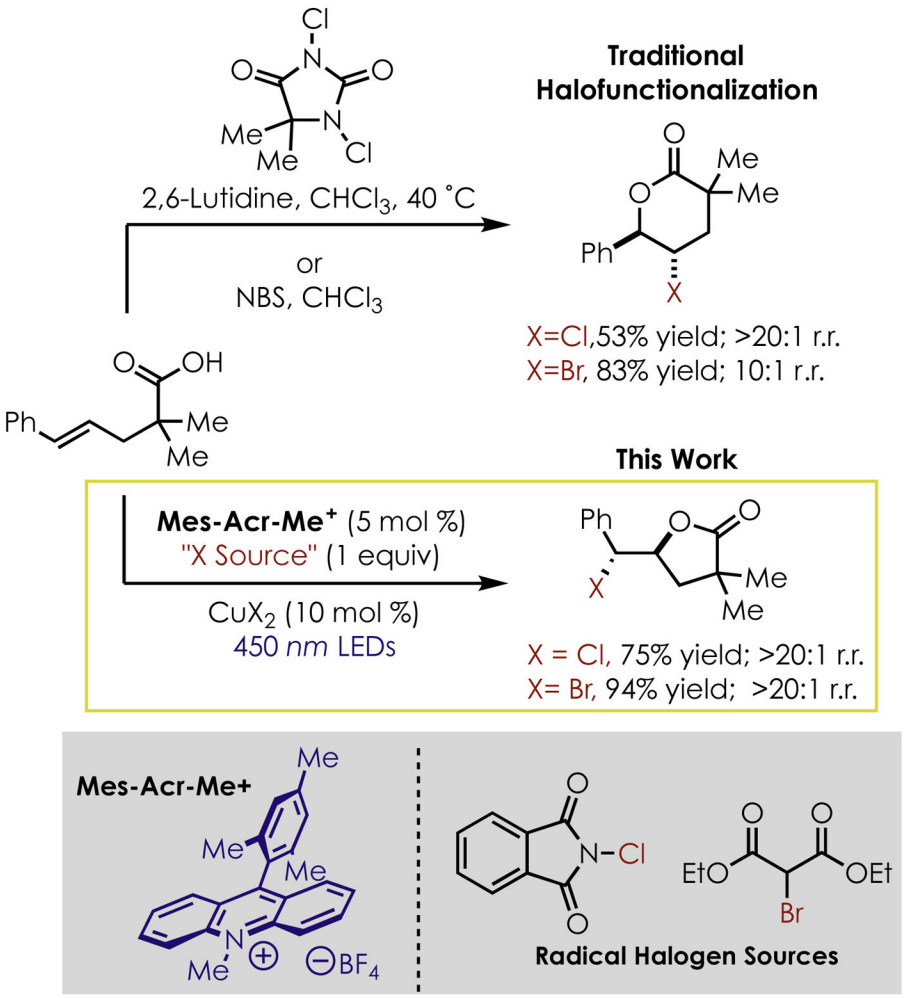


Figure 1.
Alkene Halofunctionalization – Catalytic Reversal of Regioselectivity

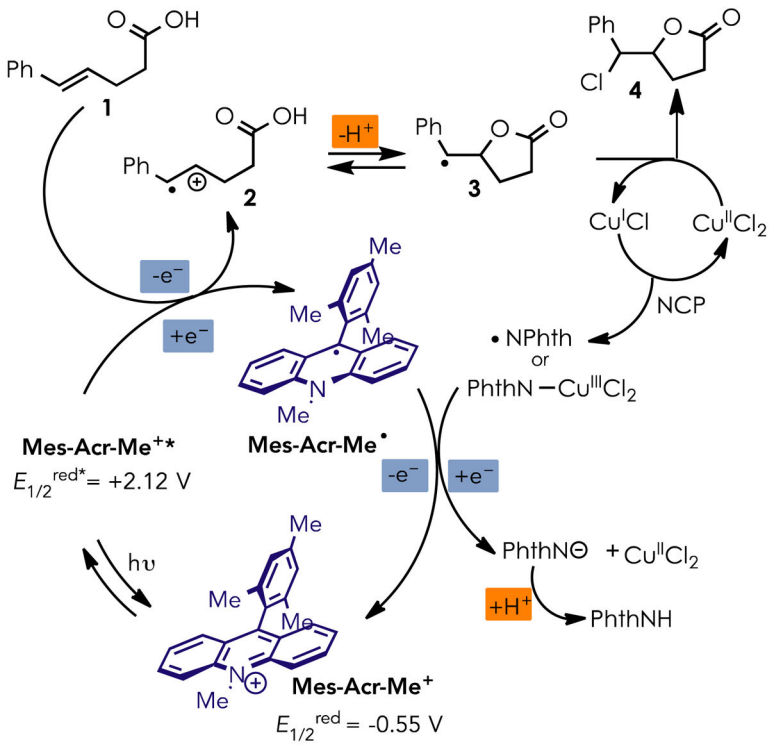


Figure 2.
Alkene Halofunctionalization – Initial Mechanistic Proposal

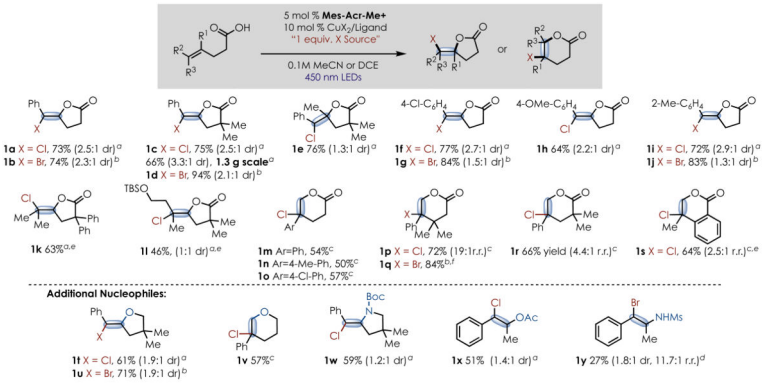


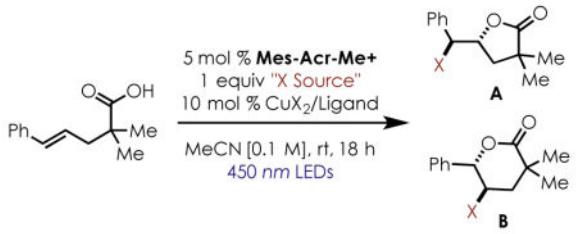
Chart 1.

Scope of the Alkene Halofunctionalization Reaction

Products isolated as single regioisomers except where noted. [a]10 mol% $CuCl_2$/phen, 1 equiv. NCP, [b]10 mol% $CuBr_2$/bpy, 1 equiv. DEBM [c]10 mol% $CuCl_2$/phen,1 equiv. NCS [d]10 mol% $CuBr_2$/phen, 1 equiv. NBP, [e]with 5.0 equiv. AcOH, [f]with 10 mol% 2,6-Lutidine. Boc=tert-butoxycarbonyl Ms=methanesulfonyl NCP=*N*-Chlorophthalimide. DEBM=Diethyl bromomalonate. NCS=*N*-Chlorosuccinimide. NBP=*N*-bromophthalimide

Table 1

Optimization of Reaction Conditions



Entry	X Source	CuX_2/Ligand	A[a]	B[a]	dr (A)
1	TsCl	—	—	—	—
2	NCS	—	—	50%	—
3	NCP	—	—	30%	—
4[b]	—	$CuCl_2$/bpy	62%	—	1.5:1
5[c]	Lut^+Cl^-	$CuCl_2$/bpy	19%	—	2.6:1
6	NCP	$CuCl_2$/bpy	90%	—	2.3:1
7	NCP	CuCl/bpy	92%	—	2.4:1
8	NCP	$CuCl_2$/phen	85%	—	3.2:1
9[d]	NCP	$CuCl_2$/phen	25%	12%	2.2:1
10	NBP	$CuBr_2$/bpy	39%	61%	3.0:1
11	DEBM	$CuBr_2$/bpy	97%	3%	2.4:1
12[d]	DEBM	$CuBr_2$/bpy	—	—	—
13	DEBM	—	—	—	—

Reactions carried out in N_2-sparged MeCN [0.1 M] under 2 LED lamps (λ_{max} = 450 nm) for 18 h.

[a] Yields were obtained of the crude reaction mixtures by ^1H NMR relative to $(Me_3Si)_2O$ internal standard.

[b] 1 equiv. of $CuCl_2$/bpy, under air.

[c] 20 mol% $CuCl_2$/bpy, in the presence of O_2.

[d] Reaction without **Mes-Acr-Me+**.