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Photocatalytic, Intermolecular Olefin Alkylcarbofunctionalization Triggered by Haloalkyl Radicals Generated via Halogen Atom Transfer

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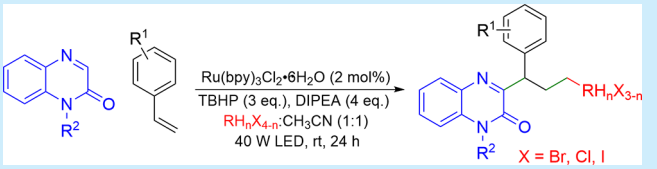
ABSTRACT: A visible-light-mediated, haloalkyl-radical-initiated, three-component olefin difunctionalization is reported. The application of haloalkyl radicals generated via halogen atom abstraction by α-aminoalkyl radicals has been demonstrated for accessing a new halogenated chemical space. Overall, the alkylcarbofunctionalization of styrenes was accomplished by employing them as (poly)haloalkyl radical acceptors and subsequent C−C bond formation with quinoxalinones.



The generation of halogen-containing organic molecules is an area of high contemporary interest, primarily due to the increasing importance and prevalence of fluorinated and chlorinated molecules in medicine.[1−3] Approximately 40% of the currently marketed drugs possess at least one halogen atom,[4] and new halogenated molecules continue to be approved as pharmaceuticals,[5] thereby fueling interest in new synthetic methods that lead to halogen incorporation. Among synthetic paradigms that have enabled the expansion of halogenated chemical space, transformations involving α-aminoalkyl radicals as halogen atom transfer (XAT) agents are at the forefront. Doyle et al. developed copper-ion-catalyzed haloalkylative difunctionalization of olefins using the XAT strategy (Figure 1a).[6−8] Leonori and co-workers demonstrated a photochemical strategy for XAT by generating alkyl radicals from iodo- and bromoalkanes via α-aminoalkyl radicals.[9] Although no halogen atoms were incorporated in the product, control of oxidative conditions led to sp^3−sp^3, sp^2−sp^3, and sp^3−sp^3 C−C bond formations (Figure 1b). These seminal contributions highlight the transformative potential and impact of XAT-derived radical species. Among current challenges, establishing greater control over the generation and reactivity of radical species arising via halogen atom transfers and the creation of complex molecules via more intricate reaction design are the next frontier. Our lab has been interested in olefin difunctionalization in the context of halogenated molecule synthesis, and we envisioned a three-component system wherein the initial haloalkyl radical would react with an olefin and the resulting radical species would then be trapped in a second C−C bond-forming event. Among strategies for olefin alkylcarbofunctionalizations (in the non-halogenated realm), the nickel-catalyzed, radical-initiated three-component systems were pioneered by Baran[10] and Giri,[11−13] who employed organozinc reagents to install one of

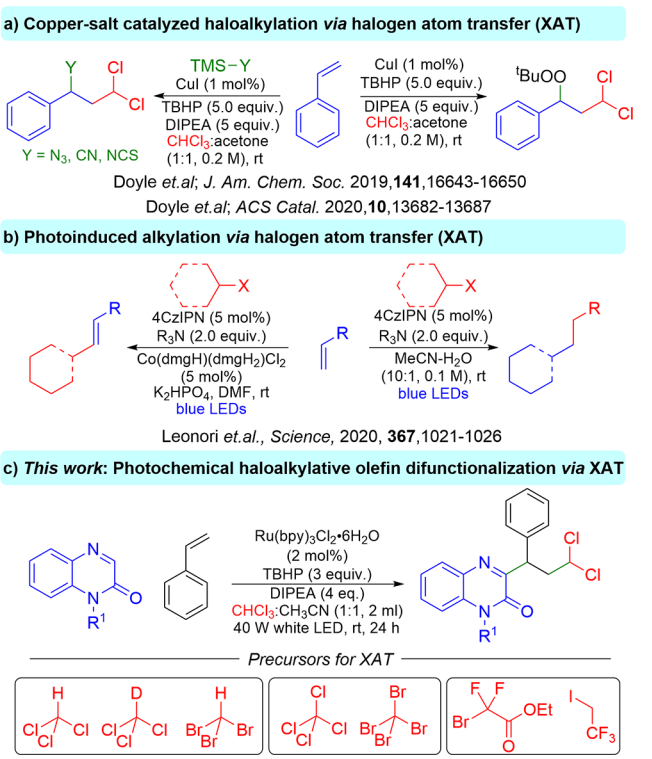


Figure 1. Halogen atom transfer strategies for olefin functionalization.

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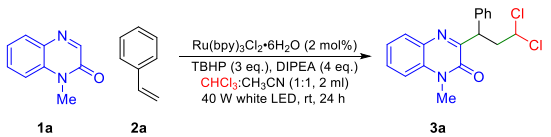
the alkyl/aryl components. Subsequent work by Nevado,[14] Chu,[15] and Koh[16] demonstrated the effectiveness of directing groups and iodoalkane precursors under reductive conditions, thereby obviating the need for organozinc reagents. More recently, a combination of photoredox and nickel catalysis has also been employed for activating alkyl oxalates,[15] alkyl silicates,[17] and α-silylamines[18] for three-component functionalization of C=C bonds. The use of carbon-centered radicals generated via homolysis of C−H bonds has limitations in three-component transformations, and newer studies[18] continue to improve the scope and selectivity. Notwithstanding the creative contributions in radical-initiated olefin alkylcarbofunctionalizations, the reliance on functionalized radical precursors, directing groups, and organonickel intermediates imposes limits on their scope, one of them being their incompatibility with most haloalkyl radicals. Our strategy involves generation of haloalkyl radical through light-induced XAT, its interception by styrene, and subsequent quenching of the resulting radical by quinoxalinone to ultimately construct two C−C bonds. Among design principles that would allow chemoselectivity without directing groups and organometallic intermediates, the choice of the two π systems involved is key from the standpoint of their reactivity with radicals and their compatibility with the conditions required for XAT.[19]

We started our investigation with quinoxalinone **1a** and styrene (**2a**) as the dichloromethyl radical acceptor. We discovered that diisopropylethylamine (DIPEA) was the most effective base and that triethylamine afforded a low yield while TMEDA was not effective (Table 1, entries 2 and 3). Among photocatalysts, eosin Y and Rose Bengal resulted in slightly diminished yields of the product (72% and 59%, respectively; Table 1, entries 5 and 6). Replacing the photocatalyst with CuI resulted in product formation in only 22% yield (Table 1, entry 7). MeCN was the most effective solvent, and acetone, DMF, and DMSO resulted in lower yields (Table 1, entries 8−10). Attempts to employ cumene hydroperoxide and di-*tert*-butyl peroxide resulted in significantly reduced yields (Table 1, entries 11 and 12). Irradiation with blue LEDs (12 W) resulted in a 46% yield of the desired product (Table 1, entry 13). Control experiments revealed that photocatalyst, amine, light, and oxidant are crucial for this transformation (Table 1, entries 14−17) and that a substoichiometric amount of DIPEA leads to poor yields.[20] Accordingly, the optimized conditions emerged to include MeCN as the solvent, $Ru(bpy)_3Cl_2$ as the photocatalyst, TBHP as the oxidant, DIPEA as the XAT reagent, and 40 W LED as the light source, which afforded **3a** in 80% isolated yield (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	deviation from standard conditions	yield of **3a** (%)
1	none	80
2	Et_3N instead of DIPEA	34
3	TMEDA instead of DIPEA	0
4	DABCO instead of DIPEA	27
5	eosin Y	72
6	Rose Bengal	59
7	CuI	22
8	acetone instead of MeCN	60
9	DMF instead of MeCN	52
10	DMSO instead of MeCN	52
11	cumene hydroperoxide instead of TBHP	52
12	di-*tert*-butyl peroxide instead of TBHP	13
13	blue LEDs (12 W)	46
14	without DIPEA	0
15	without light	0
16	without photocatalyst	0
17	without TBHP	42

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (1.5 mmol), TBHP (3 equiv), DIPEA (5 equiv), $Ru(bpy)_3Cl_2$ (2 mol %), MeCN:$CHCl_3$ (1:1, 2 mL), 40 W white LED, rt, under N_2.

A range of alkyl halides were examined, as depicted in Figure 2. Among trihalo precursors, deuterated chloroform afforded

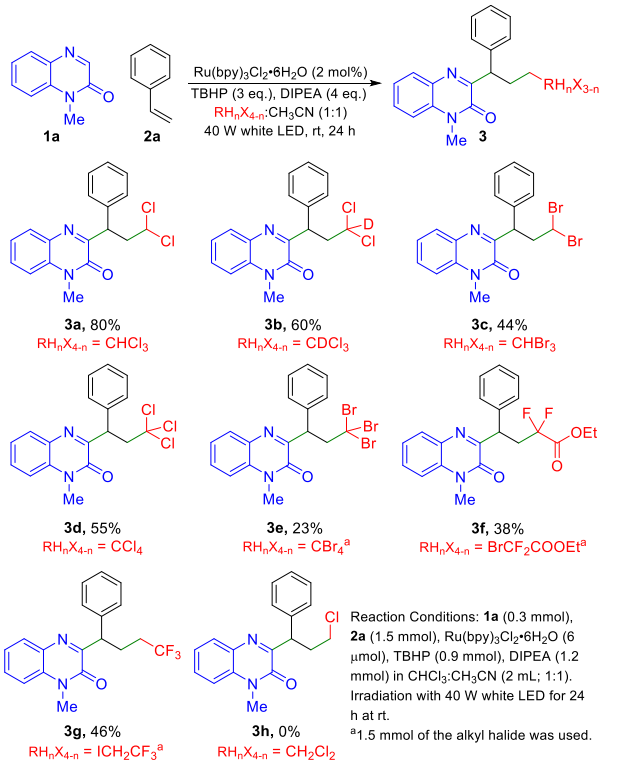


Figure 2. Reaction scope: alkyl halides.

the dichloro derivative **3b** in 60% yield, while bromoform resulted in the dibromo derivative **3c** in 44% yield. Carbon tetrachloride and carbon tetrabromide were also viable precursors, although the yield was significantly higher for the trichloro derivative **3d** compared to the tribromo product **3e**. When bromodifluoroethyl acetate was employed, the difluoro product **3f** was obtained in 38% yield. Trifluoroethyl iodide also afforded the corresponding product **3g** in 46% yield. No product formation was observed in the case of dichloromethane. The lower yields in the case of bromoform, carbon tetrabromide, and bromodifluoroethyl acetate may be due to the fast polymerization of styrene.[21]

We next explored the substrate scope with respect to quinoxalin-2(1*H*)-ones (Figure 3). Variation of the nitrogen substituent on the quinoxalin-2(1*H*)-one, such as ethyl, propyl, and butyl, afforded products in good to moderate yields (**4a**−**4c**). Allyl and propargyl substituents were tolerated well, and products **4d** and **4e** were obtained in 81% and 85% yield,

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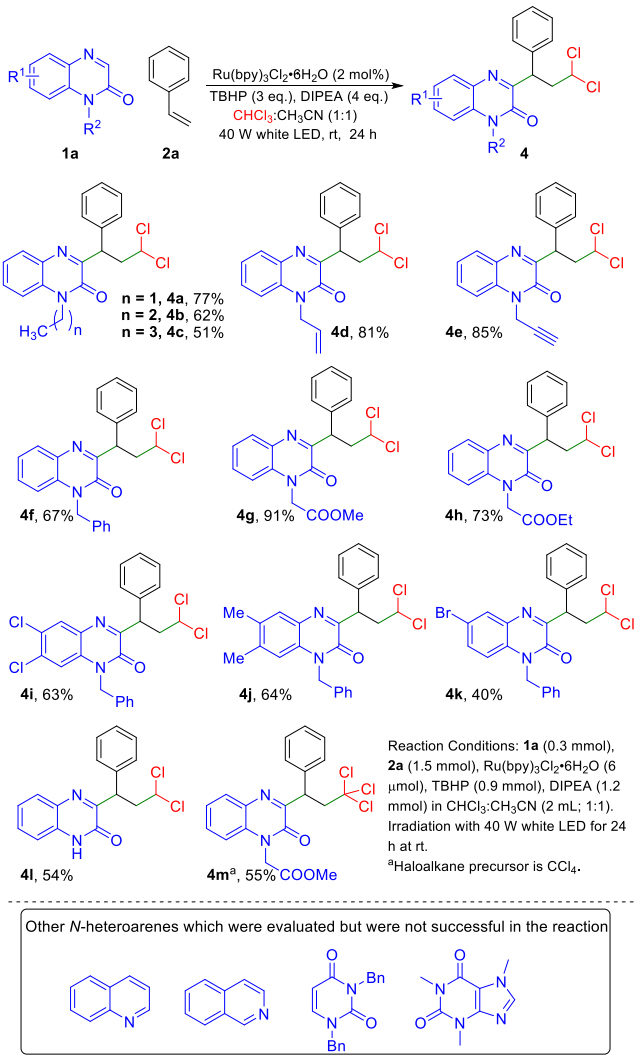

Figure 3. Reaction scope: quinoxalinones.

respectively. Precursors with benzyl and carboxymethyl substituents also performed well, affording products in high yields (Figure 3, **4f**–**4h**). While chloro and methyl substitutions on the benzene ring of the quinoxalinone led to product formation in good yields (**4i** and **4j**), the bromo derivative afforded a diminished yield (**4k**). Application of a quinoxalinone with free *N*-H afforded the corresponding product **4l** in 54% yield. The carboxymethyl analogue derived from carbon tetrachloride (**4m**) was obtained in 55% yield. We also evaluated some other N-heteroarenes such as caffeine, quinoline, isoquinoline, and pyrimidinedione, but they did not lead to a successful reaction.

A variety of substituted styrenes were also evaluated, and the results are depicted in Figure 4. Electron-donating substituents generally performed better, as exemplified by the *p*-OMe-substituted precursor (product **5b**, Figure 4). Halogen substituents resulted in modest yields (**5c**–**5e**), and the trifluoromethyl derivative **5f** was obtained in 45% yield. However, *p*-chloromethylstyrene afforded the corresponding product **5g** in good yield (78%). Interestingly, the methoxy substituent at the *meta* position led to poorer yield (43%) than the one at the *ortho* position (67%) (**5h** and **5i**, respectively), reflecting that more electron-rich styrenes typically afforded better yields. A thiophene-derived alkene also reacted

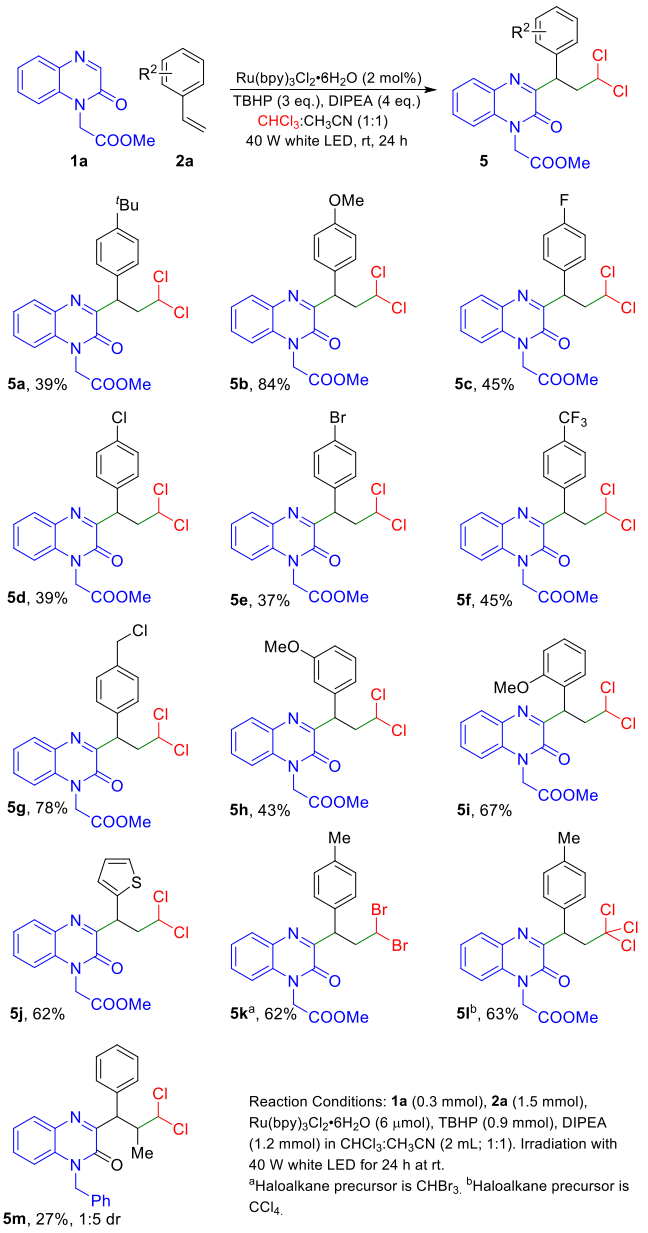

Figure 4. Reaction scope: styrenes.

smoothly, affording the derivative **5j** in 62% yield. Application of bromoform and carbon tetrachloride with *p*-Me-substituted styrene resulted in the corresponding products **5k** and **5l** in 62% and 63% yield, respectively.

We performed experiments with TEMPO and BHT under otherwise identical conditions and observed that product formation was completely suppressed, indicating the involvement of radical intermediates. We also observed the TEMPO and BHT[22] adducts with DIPEA[23] when the reaction mixture was subjected to mass spectrometry (Figure 5a). Stern–Volmer studies revealed that the fluorescence emission of the excited-state catalyst is quenched by DIPEA but not by ^{t}BuOOH or quinoxalinone **1a** (Figure 5b). This indicates that DIPEA engages in SET with the photoexcited Ru(II) species that results in reductive quenching leading to a Ru(I) species. The quantum yield for a reaction performed for 30 min (in 24% yield) was determined to be ∼22, indicating that radical chain processes may be involved in the mechanism.[20] Together

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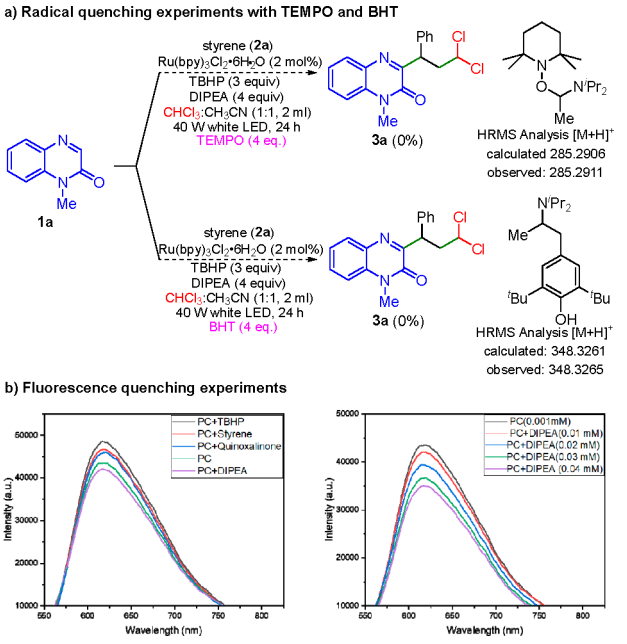

Figure 5. (a) Radical quenching experiments and (b) fluorescence quenching experiments (PC = photocatalyst).

with the results of other control experiments outlined in Table 1 and information in the literature,[24] we propose a plausible mechanism as outlined in Figure 6. The excited photocatalyst

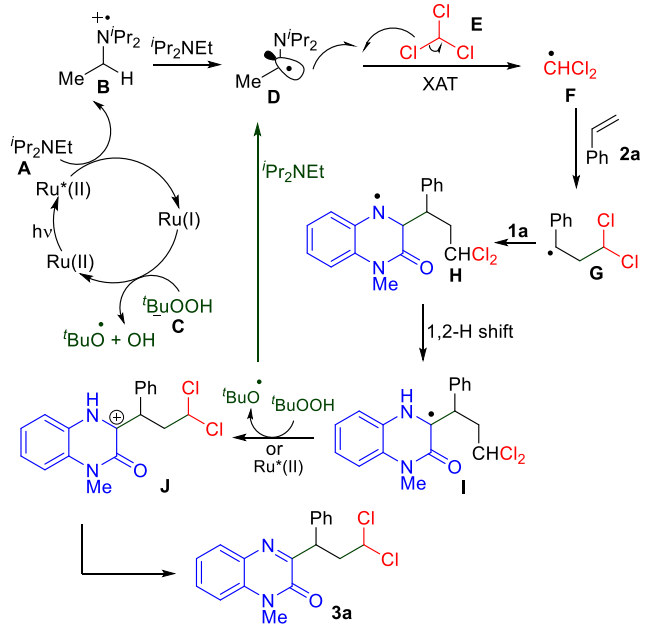

Figure 6. Proposed mechanism.

undergoes reductive quenching with DIPEA to form amine radical cation **B** and the Ru(I) species. Radical **B** is deprotonated with DIPEA to give α-amino radical **D**, which then abstracts a halogen atom from the halogenated precursor. The resulting halomethyl radical (**F**) then adds to styrene to afford benzylic radical **G**, which is trapped by quinoxalinone, resulting in the N-centered radical **H**. Subsequent transposition to the carbon-centered radical **I**[25] and its oxidation leads to cation **J**, which undergoes elimination to afford the final product. A radical chain process could be involved at this stage, wherein the *tert*-butoxy radical could engage in a hydrogen atom transfer with DIPEA resulting in the generation of α-amino radical **D**.

In conclusion, we have developed a visible-light-mediated, three-component haloalkylative functionalization of styrenes. The use of radicals generated via halogen atom transfer in initiating this intermolecular transformation was demonstrated. A variety of readily available halogenated precursors were employed to populate new halogenated chemical space. The reaction occurs under mild conditions, features good substrate scope, and can be performed on a gram scale. The elements of reaction design (and outcome) are complementary to the Ni-catalyzed alkylcarbofunctionalizations and offer an opportunity to establish this protocol as a valuable tool for multicomponent reaction development.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c01800.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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