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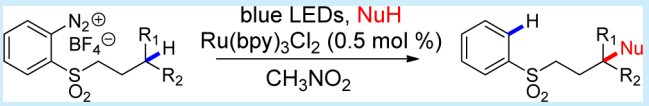
Visible-Light-Promoted Remote C−H Functionalization of *o*-Diazoniaphenyl Alkyl Sulfones

Shaofu Du, Elizabeth Ann Kimball, and Justin R. Ragains*

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803, United States

Supporting Information

ABSTRACT: Visible-light irradiation of *ortho*-diazoniaphenyl alkyl sulfones in the presence of $Ru(bpy)_3^{2+}$ results in remote Csp^3−H functionalization. Key mechanistic steps in these processes involve intramolecular hydrogen atom transfer from Csp^3−H bonds to aryl radicals to generate alkyl/benzyl radicals. Subsequent polar crossover occurs by single-electron oxidation of the alkyl/benzyl radicals to carbenium ions that then intercept nucleophiles. We have developed remote hydroxylations, etherifications, an amidation, and C−C bond formation processes using this strategy.



The selective and high-yielding conversion of inert C−H bonds to more useful functionality using intramolecular strategies has captured the imaginations of organic chemists for more than a century.[1,2] While the direction of C−H bonds into the inner sphere of transition metals (i.e., "C−H activation") or to a high-oxidation-state metal oxo species using directing groups[1] constitutes a common approach to the problem of intramolecular C−H functionalization, intramolecular hydrogen atom transfer (HAT) from an inert Csp^3−H bond to a high energy radical is an alternative approach that is gaining traction in organic synthesis.[2]

An interesting subset of transformations involving intramolecular HAT consists of a "polar crossover" step.[2j−l,n,r,s,u] For example (Scheme 1), generation of an aryl radical (**2**) via the single electron reduction of an arenediazonium ion[3] (**1**) can lead to fast ($k \approx 10^6$−10^8 s^{-1})[2i,4] intramolecular HAT with a tethered group bearing Csp^3−H bonds. While an entropically driven, chairlike 1,5-HAT dominates similar processes when the hydrogen atom is transferred to an *N*- or *O*-centered radical,[5] intramolecular hydrogen atom transfers to an *aryl radical* are somewhat harder to predict but appear to be enthalpically driven in many cases.[2i,n,u] The resulting alkyl radical (**3**) can then undergo single-electron oxidation (polar crossover) to generate a carbenium intermediate (**4**) that intercepts a nucleophile en route to C−H functionalization products (**5**) or loses a proton to generate "remote desaturation" products (**6**). This strategy has been exploited by Baran for remote desaturation[2n] and by Weinreb, Murphy, Maulide, and our group for transformations as diverse as hydroxylation, etherification, hydrazone formation, and arylation.[2j−l,r,s,u]

Previous work in our group[2u] demonstrated that remote hydroxylation and etherification could be effected with substrates such as **8** (e.g., in hydroxylation **8** → **10**, Scheme 1) bearing Tz^o[2n] sulfonate esters and sulfonamides. Use of 10 mol % of *fac*-$Ir(ppy)_3$ in conjunction with 2 equiv of aqueous HBF_4 (for liberation of a diazonium ion from the aryltriazene precursor) in 5:1 CH_3NO_2/H_2O gave optimal results while blue LED irradiation provided modest, if any, improvement in yield. Use of $H_2{}^{18}O$ demonstrated that water (and not O_2) was the oxygen source in the remote hydroxylation when a high incorporation of ^{18}O was observed, suggesting that carbenium ions are likely intermediates.

We subsequently wondered if a similar approach involving the elaboration of alkyl halides to triazene-bearing sulfones **12** (or related diazonium salts **11**) could lead to successful remote C−H functionalization. Amenability of sulfones to further manipulation would constitute an advantage with such a method. Herein, we report on the visible-light-promoted remote Csp^3−H functionalization of *o*-diazoniaphenyl alkyl sulfones (**15**, Scheme 1). Alkyl groups are derived from alkyl halides, demonstrating that our original strategy for the functionalization of alcohols and amines via Tz^o derivatives[2u] can now be applied toward alkyl halides. Further, triazene-bearing precursors proved inferior to arenediazonium tetrafluoroborate salts as substrates. To contrast with the original work involving Tz^o sulfonate esters and sulfonamides,[2u] visible-light irradiation is required for product formation while low loadings (0.5 mol %) of relatively inexpensive $Ru(bpy)_3Cl_2$ contrast with the 10 mol % loading of the relatively expensive *fac*-$Ir(ppy)_3$ that was previously required. Transformations including remote hydroxylation and etherification, a single example of amidation, a novel approach to the oxidation of a methyl ether to a ketone, and remote arylation processes are demonstrated. The systems studied here have also proven resistant to the well-known 1,5-HAT.[2,5]

Taking inspiration from our original work, we synthesized triazene-containing sulfone **16** (Figure 1) starting from 3-iodo-1-phenylpropane and probed its reactivity under conditions similar to those developed for previous remote hydroxylation procedures (10 mol % *fac*-$Ir(ppy)_3$, 5:1 CH_3NO_2/H_2O, 2 equiv of protic acid, blue LED irradiation). However, the reaction proved sluggish and low-yielding compared to results obtained

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Scheme 1. C–H Functionalization by HAT/Polar Crossover

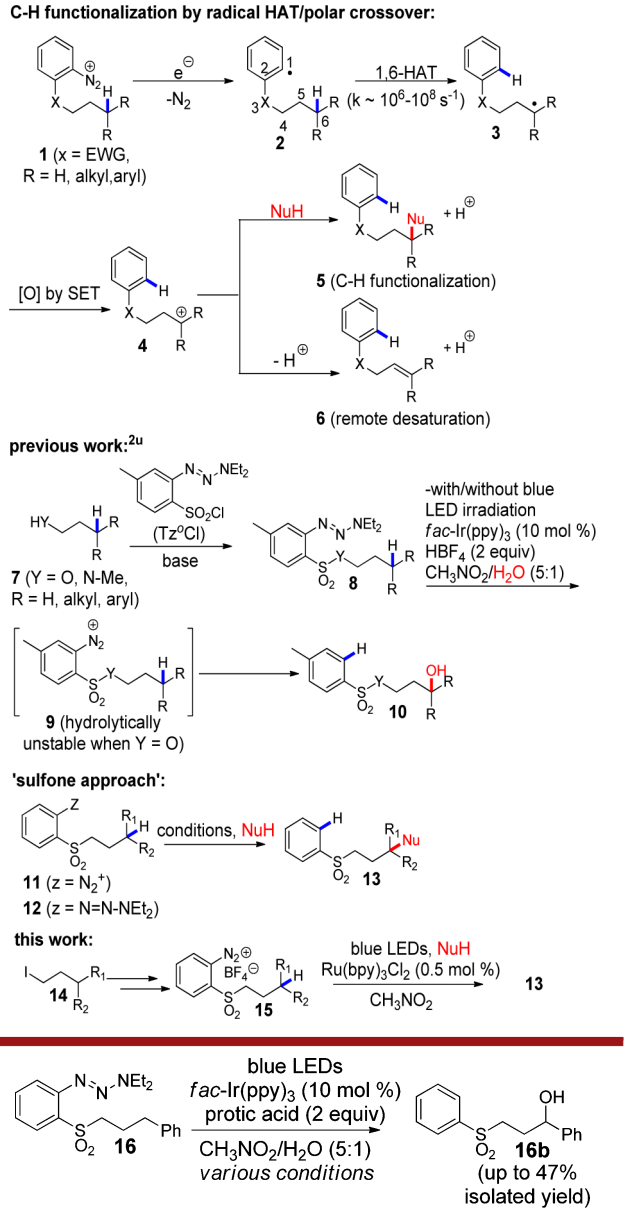
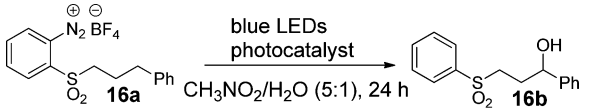


Figure 1. Initial studies with triazene-sulfone **16**.

with Tz° sulfonates.[2u] See the Supporting Information (SI) for full details. In the case of Tz° sulfonates, the arenediazonium sulfonate ester intermediates (**9**, Scheme 1) resulting from acid-promoted conversion of the Tz° triazene were hydrolytically unstable. To contrast, we believed that arenediazonium analogs **15** (Scheme 1) would be hydrolytically stable. We therefore synthesized diazonium tetrafluoroborate **16a** and subjected it to feasibility and optimization studies (Table 1; see full details in the SI). Importantly, arenediazonium tetrafluoroborate salts do not pose an explosion hazard.[6]

Blue LED irradiation of a mixture of **16a**, 5:1 CH_3NO_2/H_2O, and 10 mol % *fac*-Ir(ppy)$_3$ (entry 1, Table 1) resulted in an improved yield (relative to the Figure 1 results) of 62% of product **16b**. Decreasing the loading of *fac*-Ir(ppy)$_3$ (entry 2) gave inferior results; however, we discovered that various loadings of Ru(bpy)$_3$Cl$_2$ (entries 3–5) provided even higher yields of **16b** with the best results being obtained using only 0.5 mol % of Ru(bpy)$_3$Cl$_2$ (entry 5, 79%). The 24 h irradiation

Table 1. Feasibility and Optimization Studies with *O*-Diazoniaphenyl Alkyl Sulfone 16a[a]



entry	catalyst/mol %	yield (%)[b]
1	*fac*-Ir(ppy)$_3$/10	62
2	*fac*-Ir(ppy)$_3$/1	37
3	Ru(bpy)$_3$Cl$_2$/10	73
4	Ru(bpy)$_3$Cl$_2$/1	71
5	Ru(bpy)$_3$Cl$_2$/0.5	79
6[c]	Ru(bpy)$_3$Cl$_2$/1	68
7[d]	Ru(bpy)$_3$Cl$_2$/1	46
8	Ru(phen)$_3$(BArF)$_2$/1	60
9[e]	eosin Y/1	24
10[f]	Ru(bpy)$_3$Cl$_2$/1	33
11[g]	Ru(bpy)$_3$Cl$_2$/0	0
12[h]	Ru(bpy)$_3$Cl$_2$/1	0
13[i]	Ru(bpy)$_3$Cl$_2$/0.5	62

[a]Reaction conditions: **16a** (0.2 mmol), temp = 26–28 °C, 24 h irradiation, 10 mL of CH_3NO_2, 2 mL of H_2O. [b]Isolated yields. [c]Irradiated for 6 h. [d]Irradiated for 1 h. [e]Irradiated with green LEDs. [f]Performed reaction without freeze–pump–thaw beforehand. [g]No photocatalyst. [h]No irradiation. [i]Reaction performed on 1 mmol scale using entry 5 conditions.

time proved best (entries 5–7). Other photocatalysts such as Ru(phen)$_3$(BArF)$_2$ and eosin Y (entries 8 and 9) proved inferior to Ru(bpy)$_3$Cl$_2$. Entries 10–12 demonstrated that freeze–pump–thaw procedures before conducting the reaction are essential for high yields while Ru(bpy)$_3$Cl$_2$ and visible-light irradiation are essential. Finally, entry 13 demonstrates that the entry 5 conditions performed on 1 mmol scale result in a respectable 62% yield of **16b**. Extensive optimization can be viewed in the SI.

Encouraged by these results, we performed a substrate scope study for remote hydroxylation (Table 2). Replacing the benzylic methylene group of **16a** with the methine of **17a** resulted in alcohol **17b** (entry 1). Cyclohexane-bearing precursor **18a** gave a relatively low-yielding conversion to alcohol **18b** (entry 2) which is reminiscent of a similarly low-yielding transformation of a cyclohexane-bearing Tz° sulfonate ester.[2u] Further, the hydroxylation of benzylic hydrogens flanking electron-rich (55%, entry 3) and electron-poor (40%, entry 4) benzene rings was demonstrated. As all of the transformations screened up to this point involved 1,6-HAT, we elected to screen substrates designed to undergo 1,7- and 1,5-HAT. Aliphatic substrate **21a** gave a disappointing 16% yield of alcohol **21b** (entry 5) while the corresponding benzylic substrate gave only traces of alcohol **22b** as judged by ^{1}H NMR of the crude reaction mixture (entry 6). These results suggest that 1,7-HAT is less facile than 1,6-HAT, which contrasts with the 1,7-HAT previously observed.[2u] Conversely, we expected the benzylic substrate **23a** to undergo 1,5-HAT. To our surprise, 51% of a 1:3.45 mixture of the expected alcohol **23b** and the intramolecular biaryl coupling product **23c** was obtained (entry 7). The aliphatic substrate **24a** (entry 8) resulted in no observed alcohol products, further suggesting the recalcitrance of these systems toward 1,5-HAT even when such processes are highly exergonic.

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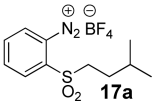
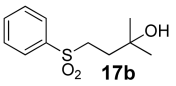
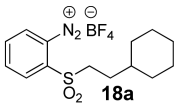
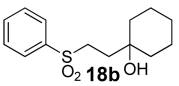
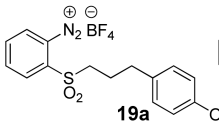
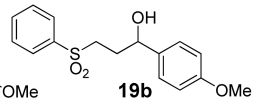
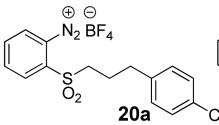
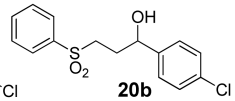
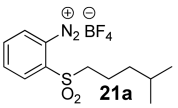
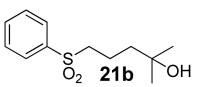
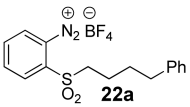
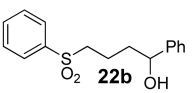
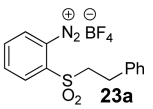
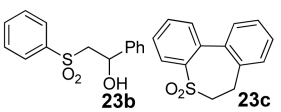
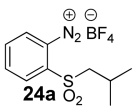
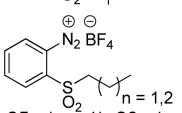
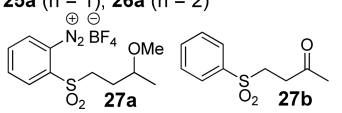
Table 2. Substrate Scope for Remote Hydroxylation[a]

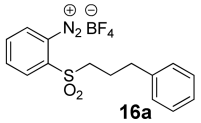
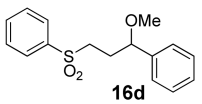
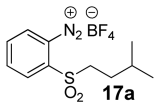
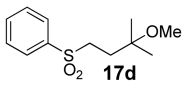
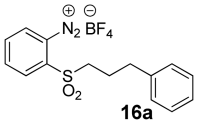
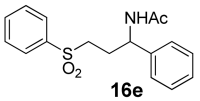
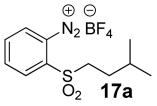
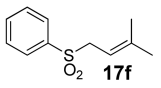
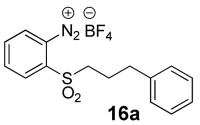
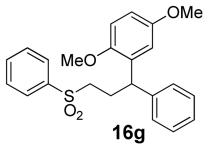
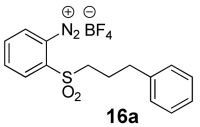
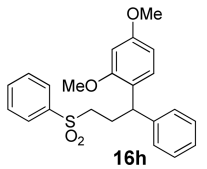
entry	substrate	product(s)	yield (%)[b]
1			52
2			28
3			55
4			40
5			16
6			trace
7			~49 (1:3.45, 23b/23c)
8		no alcohol products isolated	0
9		no alcohol products isolated	0
10			71

[a]Reaction conditions: 0.2 mmol of diazonium salt, 10 mL of CH_3NO_2, 2 mL of H_2O, temp = 26−28 °C, 24 h irradiation with blue LEDs, 0.5 mol % $Ru(bpy)_3Cl_2$. [b]Isolated yield

Further studies on the propyl and butyl sulfone intermediates **25a**/**26a** (entry 9) resulted in complex mixtures as judged by the ^{1}H NMR of crude reaction mixtures. No alcohol-containing products were isolated; however, products of simple reductive dediazoniation could be observed with NMR.[7] Finally, the methyl ether bearing substrate **27a** underwent conversion to ketone **27b** (entry 10). In this case, hydroxylation likely results in a hemiketal intermediate en route to ketone.

While previous attempts to convert Tz^o sulfonates and sulfonamides to methyl ethers using methanol as nucleophile were successful, attempts at substitution with other nucleophiles have not resulted in isolable products. With this in mind, we elected to study carbenium ion trapping with a host of nucleophiles in addition to H_2O (Table 3). Etherification (using MeOH) proceeded as expected with benzylic (entry 1) and aliphatic (entry 2) substrates. A Ritter-type amidation could also be effected with benzylic **16a** (entry 3) using wet acetonitrile; however, the aliphatic substrate **17a** (entry 4)

Table 3. Etherification, Amidation, and Arylation[a]

entry	substrate	product(s)	yield (%)[b]
1[c]			59
2[c]			38
3[d]			51
4[d]			60
5[e]			34
6[f]			19

[a]Conditions: 0.2 mmol of diazonium salt, 10 mL of CH_3NO_2, nucleophile, temp = 26−28 °C, 24 h irradiation with blue LEDs, 0.5 mol % $Ru(bpy)_3Cl_2$. [b]Isolated yields. [c]100 μL of MeOH added. [d]100 μL of CH_3CN, 0.2 mmol of H_2O added. [e]1.0 mmol of 1,4-dimethoxybenzene added. [f]1.0 mmol of 1,3-dimethoxybenzene added.

simply underwent elimination at 25 °C and at lower temperatures. We note here and in our previous work[2u] that elimination appears to be more facile with aliphatic substrates than it is with benzylic substrates. Finally, remote C−C bond formation can be effected with 1,4- and 1,3-dimethoxybenzene (entries 5, 6).

Based on our results, we propose the following mechanism for these transformations (Scheme 2). Ground state $Ru(bpy)_3^{2+}$ (λ_{max} = 452 nm)[8] absorbs a photon to generate excited state triplet $Ru(bpy)_3^{2+*}$ ($E_{1/2}$ = −0.81 V vs SCE)[8] that undergoes single-electron transfer to diazonium ion **16a**.[9] Loss of N_2 to generate aryl radical **29** is then followed by HAT to generate benzylic radical **30**.[2i,n,u] The oxidation half potentials of tertiary/secondary benzylic radicals lie in the range of ∼+ 0.1 to +0.4 V (SCE),[10] so single-electron transfer to $Ru(bpy)^{3+}$ ($E_{1/2}$ = +1.29 V, SCE)[8] that results from the oxidative quench of $Ru(bpy)_3^{2+*}$ is favorable and will lead to carbenium ions **31**.[11] Further, the high oxidation half potential of aryl radicals **29** (>+2.0 V, SCE)[12] suggests that the pre-emptive oxidation of these species to aryl cations will not compete with HAT.

The process **30** → **31** (Scheme 2) via SET to Ru indicates a closed catalytic cycle. Nevertheless, the single-electron oxidation of radicals **30** (∼+0.1 to +0.4 V, SCE) by the diazonium ion in **16a** (−0.08 V, SCE as determined with CV; see SI) may result in the formation of carbenium ions **31** and aryl radicals **29** (chain process, Scheme 2). The seemingly unfavorable electron transfer from **30** to **16a** may be mitigated

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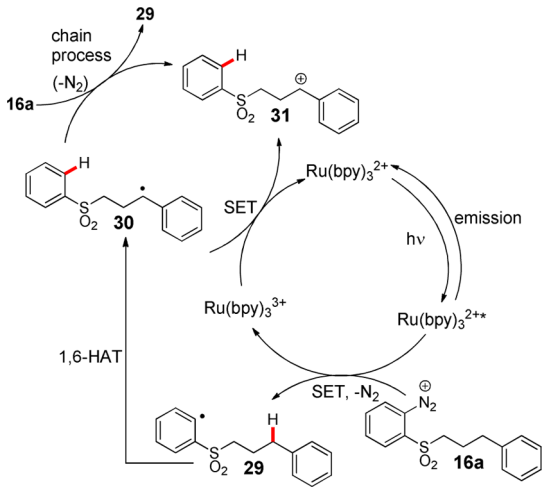
Scheme 2. Mechanistic Proposal



by the irreversible loss of N_2. Heinrich has provided evidence that processes such as these can be facile especially with the electron transfer from electron-rich tertiary benzylic radicals to electron-poor diazonium ions.[13] Ongoing work in our laboratory will distinguish between closed catalytic cycles and chain processes.

In summary, we have developed a mild, visible-light-promoted remote Csp^3–H functionalization of *ortho*-diazoniaphenyl alkyl sulfones. Key mechanistic steps in these processes include intramolecular HAT and polar crossover by single-electron oxidation of radicals to carbenium ions. We have developed remote hydroxylations, etherifications, amidations, and C–C bond formations using this strategy. A broader range of transformations than those observed with Tz^o sulfonates and sulfonamides can be effected using *ortho*-diazoniaphenyl alkyl sulfones. In addition, low loadings of relatively inexpensive $Ru(bpy)_3Cl_2$ and the necessity of visible-light irradiation distinguish the current methods from our previous report.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02650.

Experimental procedures, photograph of experimental setup, characterization data, ^1H and ^{13}C NMR spectra, CV data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jragains@lsu.edu.

ORCID

Justin R. Ragains: 0000-0002-2521-5396

Notes

The authors declare no competing financial interest.

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