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Visible-Light-Driven Neutral Nitrogen Radical Mediated Intermolecular Styrene Difunctionalization

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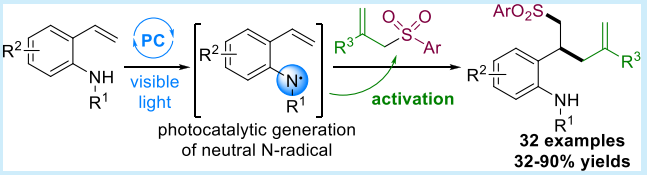
Supporting Information

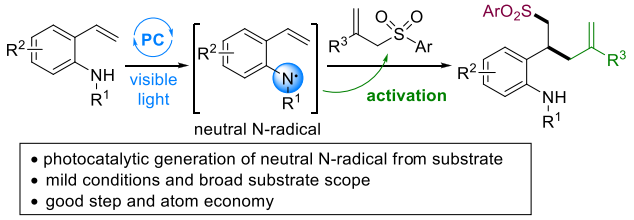
ABSTRACT: A neutral nitrogen radical-mediation strategy, wherein the existing N−H moiety of substrates serves as a neutral nitrogen radical precursor to enable room-temperature intermolecular radical difunctionalization of styrenes under photoredox catalysis, is reported. The reaction shows high functional group tolerance and substrate scope with respect to both components, giving the corresponding products with generally good yields. Preliminary control experiments and DFT calculations are performed to explain the reaction mechanism.



The use of the existing functional group of substrate as a catalyst or activator precursor to in situ generate an transient reactive species to trigger otherwise inaccessible or challenging reactions is an ideal strategy.[1] Given the unique capability of the photoredox catalysis in generation of various highly reactive species,[2] we hypothesized that application of photoredox catalysis to these substrates containing a photosensitizing group would probably offer an opportunity for new chemical reaction design. With the evolution of the photocatalysis,[2] the chemistry of nitrogen-centered radicals (NCRs) has witnessed remarkable advances in recent years and emerged as a key synthetic platform for the creation of C−N bonds and nitrogen-containing molecules.[3,4] More recently, increasing attention has also been devoted to application of this radical species class to inert C−H bond activation because of their unique HAT properties[5] as well as C−C bond cleavage,[6] thus enabling a diverse range of remote site-selective functionalizations. These versatile reactivity modes of NCRs are attributed to their different configurations and nucleophilic or electrophilic properties caused by the N-hybridization and substituents. Despite these significant advances, to the best of our knowledge, use of NCRs to mediate intermolecular radical reaction has never been reported. In our efforts to develop NCR-mediated radical functionalization of alkenes, we found that the protecting groups on nitrogen atom had an obvious effect on their reactivity modes.[4a,6b]

Moreover, considering the extensive studies on photocatalytic activation and transformation of amines, we speculated that the existing amine moiety of certain substrates might serve as a NCR radical precursor. For proof of concept, we focused on 2-vinylanilines as suitable candidates (Scheme 1).[7] Herein, we reported that in situ generated neutral NCRs by photoredox catalysis enabled an efficient intermolecular difunctionalization of 2-vinylanilines using allyl sulfones.[8] This protocol provides a new complementary access to diversely substituted anilines and sulfonyl-containing compounds.[9] To our knowledge, there is no precedent for such a radical transformation.

Scheme 1. Design of Neutral Nitrogen Radical (NCR)-Mediated Styrene Difunctionalization



Our studies commenced with an examination of reaction conditions to test the reaction of model substrates **1a** and **2a** (Table 1). An extensive screening of commonly used photocatalysts, solvents, and bases identified that the designed reaction did indeed occur to furnish product **3aa** in 87% NMR yield when $Ir(ppy)_2bpyPF_6$ was used as catalyst and K_2CO_3 as base in DMF under 7 W blue LED illumination at room temperature (entry 1).[10] In the control experiments, no product **3aa** was detected in the absence of photocatalyst, base, or light, and large amounts of both starting materials remained intact (entries 2−4). A slightly prolonged reaction time increased the NMR yield to 92% (entry 5), and 88% isolated yield of **3aa** was obtained when the reaction was carried out on a 0.2 mmol scale (Scheme 2). In contrast to many precedents that typically used allyl sulfones as ally radical precursors,[8] the current protocol allows convergent incorporation of both allyl and sulfonyl moieties into the final products.[9]

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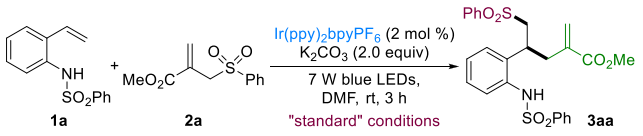
Table 1. Condition Optimization[a]



entry	variation from standard conditions	yield[b] (%)
1	none	87
2	no $Ir(ppy)_2bpyPF_6$	<5
3	no K_2CO_3	<5
4	no light	<5
5	4 h	92

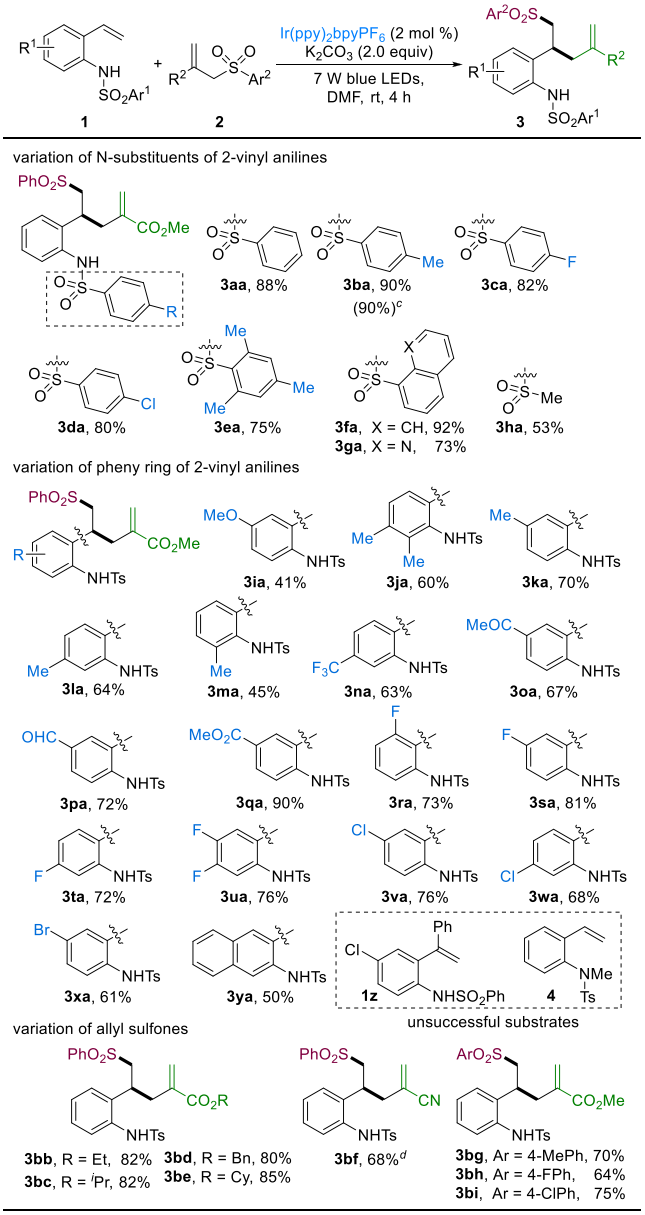
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), $Ir(ppy)_2bpyPF_6$ (0.002 mmol, 2 mol %), K_2CO_3 (0.2 mmol), DMF (2 mL), 7 W blue LEDs, rt, 3 h. [b]Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

The optimized reaction conditions show broad substrate scope and high functional group tolerance with respect to both reaction components. Scheme 2 provides a series of representative examples. For instance, a wide variety of functional groups such as methyl, fluoro, and chloride could be incorporated into the phenyl ring of the arylsulfone moiety in 2-vinylanilines, and products **3ba**–**3da** are obtained in 80–90% yields. As shown in the synthesis of product **3ea**, sterically congested substrate was also compatible with the reaction. The reactions with substrates **1f** and **1g** bearing fused aromatic or heteroaromatic groups also proceeded smoothly to afford **3fa** and **3g** with good yields. Notably, substrate **1h** with a methylsulfonyl group on the nitrogen atom reacted well with **2a** to give **3ha** in 53% yield. To demonstrate the scalability of this protocol, a gram-scale reaction of **1b** and **2a** was also performed, and product **3ba** was still obtained in 90% yield.

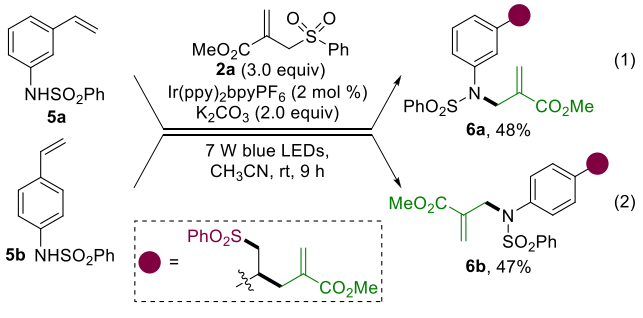
We then proceeded to examine the effect of substitution pattern of the phenyl ring of 2-vinylanilines on the reaction. A series of *N*-tosyl-substituted 2-vinylanilines **1i**–**1x** with electron-donating (e.g., MeO, Me) or electron-withdrawing (e.g., CF_3, COMe, CHO, CO_2Me, F, Cl, Br) groups at the different positions were all well tolerated. The corresponding products **3ia**–**3xa** were obtained in high yields in most cases. In particular, these biologically relevant functionalities such as ketone, aldehyde, and ester also highlighted the potential medicinal use of the products. Moreover, halogen atoms, including F (**3ra**–**3ua**), Cl (**3va**–**3wa**), and Br (**3xa**), provided a convenient handle for further synthetic elaborations at the halogenated positions. *N*-Tosyl-3-vinylnaphthalen-2-amine **1y** also reacted well with **2a** to furnish product **3ya** in acceptable yield. However, the reaction is very sensitive to the substitution pattern of the vinyl moiety. As demonstrated in the case of substrate **1z**, no alkene difunctionalization product can be detected under the standard conditions. We attribute the poor reaction efficiency to the steric hindrance. In good agreement with our design plan, it is found that the N–H moiety of the substrate is critical to the desired reaction. For example, the substrate **4** with a tertiary amine proved to be ineffective in the transformation. This result also suggests the possible involvement of nitrogen radical mediation strategy in activation of substrates.

To further display the synthetic potential of this protocol, we also extended the current catalytic system to include 3-vinylaniline **5a** and 4-vinylaniline **5b** (eqs 1 and 2). Interestingly, both substrates reacted smoothly with **2a** to give highly functionalized anilines **6a** and **6b** in good yields, which resulted from a sequential alkene radical difunctionalization and thermal aza-addition reaction.

Scheme 2. Scope of Neutral NCR-Mediated Intermolecular Difunctionalization of 2-Vinylanilines[a,b]



[a]Conditions: **1** (0.2 mmol), **2** (0.6 mmol), $Ir(ppy)_2bpyPF_6$ (0.004 mmol, 2 mol %), K_2CO_3 (0.4 mmol), DMF (4 mL), 7 W blue LEDs, rt, 4 h. [b]Isolated yields. [c]Gram-scale reaction. [d]Using CH_3CN as solvent.



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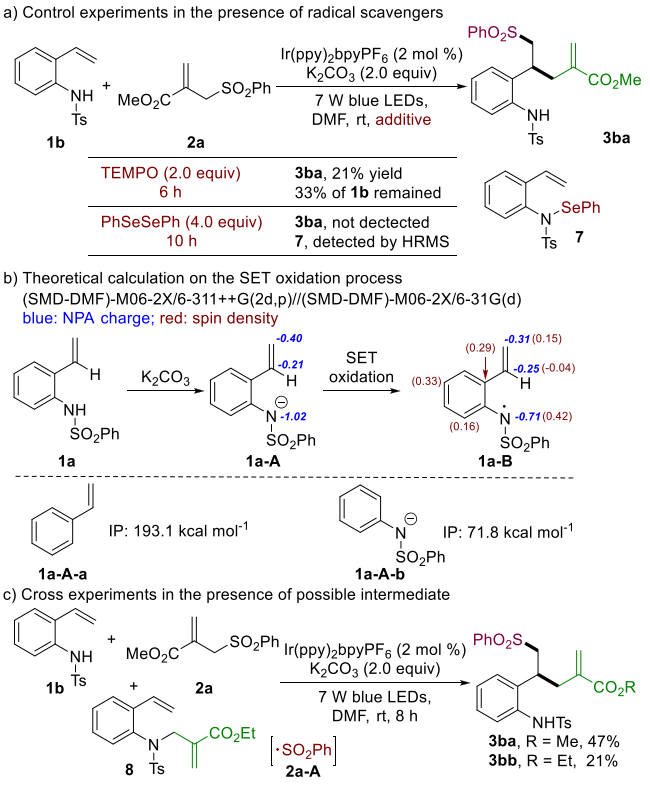
To gain some insight into the mechanism, we first carried out several control experiments with substrates **1b** and **2a** (Scheme 3a). Upon addition of commonly used radical scavengers

Scheme 3. Mechanistic Studies



TEMPO or PhSeSePh, significant or complete inhibition of target reaction was observed. Notably, selenide adduct **7** was detected by HRMS, which is indicative of the nitrogen radical engaged in the process. In accordance with the optimization studies (Table 1, entry 3), luminescence-quenching experiments of **1a** also revealed that only in the presence of base K_2CO_3 can substrate **1a** efficiently quench the excited-state photocatalyst. Moreover, the ^1H NMR analysis of **1a** disclosed that the addition of K_2CO_3 led to complete deprotonation of **1a** and its full conversion to nitrogen anion intermediate **1a-A**.[10] In principle, both the vinyl and nitrogen anion moieties of **1a-A** would undergo visible-light-induced SET oxidation by the excited-state photocatalyst.[4,11] The computed ionization potentials (IP) of styrene **1a-A-a** and *N*-phenylbenzenesulfonamide anion **1a-A-b** are 193.1 and 71.8 kcal mol^{-1}, respectively (Scheme 3b),[12] indicating that the nitrogen anion moiety is a stronger electron donor and thus should be the most likely site of SET oxidation. This is corroborated by the computed spin-density distribution in radical **1a-B** in which the spin density is mainly localized at the nitrogen atom. Taken together, these results suggest that the nitrogen anion moiety should be more easily oxidized than the vinyl group and N-radical is involved as a mediator.

Allyl sulfones are a well-established class of radical acceptors;[8] thus, we hypothesized that the in situ formed N-radical might initially activate the allyl sulfones by radical addition to the alkene moiety. We then carried out the crossover experiment by subjecting **1b**, **2a**, and two equimolar amounts of presynthesized aniline **8** to the standard conditions (Scheme 3c). In addition to the formation of routine coupling product **3ba** resulting from **1b** and **2a**, we also isolated product **3bb** in 21% yield, lending support to the intermediacy of **8** in the process. This result also suggests the involvement of sulfonyl radical **2a-A** in the reaction.

We then examined the possible application of this strategy in the intermolecular reaction of simple styrene **9** and allyl sulfone **2a** by using aniline substrate **1b** as a radical catalyst (eq 3). In addition to the formation of normal product **3ba** (58% yield),

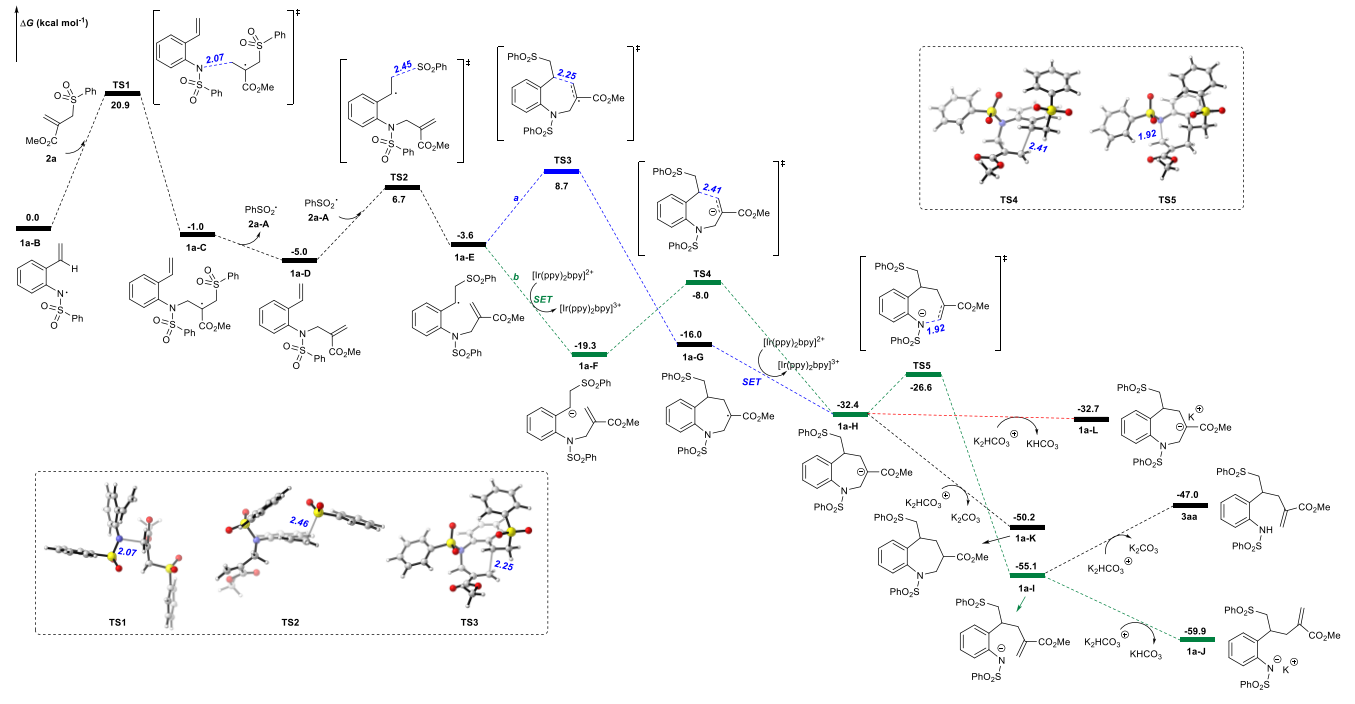


Figure 1. Free energy diagram of the reaction of *N*-radical **1a-B** and substrate **2a** calculated at the SMD-M06-2X/[6-311++G(2d, p)-SDD(Ir)]//SMD-M06-2X/[6-31G(d)-LANL2DZ(Ir)] level of theory.

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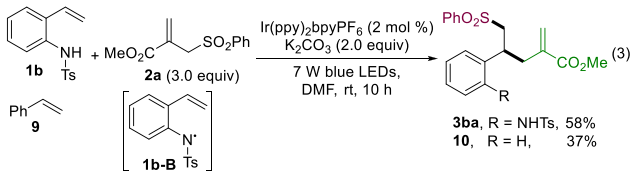
pleasingly, we could also isolate the addition product **10** in 37% yield, which implied that substrate **1b**-derived N-radical **1b-B** could also mediate the reaction between styrene **9** and allyl sulfone **2a**.



To better understand the mechanism of the reaction, we conducted DFT calculations at the SMD-M06-2X/[6-311++G(2d, p)-SDD(Ir)]//SMD-M06-2X/[6-31G(d)-LANL2DZ-(Ir)] level of theory.[12] As shown in Figure 1, addition of the in situ formed N-radical **1a-B** to the olefinic double bond in **2a** via transition state **TS1** to afford intermediate **1a-C** requires an activation free energy of 20.9 kcal mol^{-1}. The radical intermediate **1a-C** could readily release a sulfonyl radical **2a-A** to generate **1a-D**, which is located 4.0 kcal mol^{-1} below the intermediate **1a-C**. Notably, the control experiment of **1a** and **2a** without photocatalyst and visible light irradiation demonstrated that thermal S_N2' substitution among them did not occur, and no **1a-D** or sulfinate was observed.[10] Thus, an alternative pathway involving thermal S_N2' substitution between **1a** and **2a** and photocatalytic SET oxidation should not be involved in our reaction system.[13] Then, radical addition of **2a-A** to the olefin moiety of **1a-C** via **TS2** leads to a benzyl radical **1a-E** with a barrier of 11.7 kcal mol^{-1} relative to **1a-D**. Subsequently, intermediate **1a-E** could either undergo radical cyclization (pathway a) or SET reduction by the reduced-state photocatalyst $[Ir(ppy)_2bpy]^{2+}$ (pathway b). The calculation shows that SET reduction of **1a-E** by $[Ir(ppy)_2bpy]^{2+}$ is more facile than the radical cyclization. Intermediate **1a-F** undergoes an intramolecular Michael addition via **TS4** to give a seven-membered-ring anion **1a-H**, which has a barrier of 11.3 $kcalmol^{-1}$. Notably, **1a-H** is more stable than **1a-F** by 13.1 $kcalmol^{-1}$ as the negative charge is stabilized by the adjacent electron-withdrawing ester group. A retro-Michael addition reaction via **TS5** to form a nitrogen anion intermediate **1a-I** has a barrier of only 5.8 kcal mol^{-1} with respect to **1a-H**. Intermediate **1a-I** could either abstract an H^+ or K^+ from $K_2HCO_3^+$. The formation of potassium salt **1a-J** is energetically favored over **3aa** by ca. 13 kcal mol^{-1}. Post-treatment of **1a-J** will give the final product **3aa**. However, both **1a-K** and **1a-L** are thermodynamically less stable than the ring-opened product **1a-J** by at least 9 kcal mol^{-1}. This is consistent with experimental observations that no seven-membered-ring side product was observed.

It should be noted that a chain pathway might also be possible,[14] particularly in the reaction of **5a** and **5b**. The in situ formed sulfonyl radical **2a-A** can also be added to the alkene moiety of another molecule of substrate to generate benzylic radical, which can then be trapped by allyl sulfone **2a** to give the expected product. The reaction of **9** and **2a** might also proceed through this pathway (eq 3).

In conclusion, we have described the validation of a photogenerated neutral NCR-mediation strategy for the first time to achieve intermolecular radical difunctionalization of styrenes under mild conditions.[15] The existing amine moiety of the substrates serves as a neutral nitrogen radical precursor. Considering the prevalence and significance of amine functionality, we thus expect this advance will propel the development of a wide range of radical transformations using this strategy as well as nitrogen radical catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01362.

Experimental procedures, full analysis data for new compounds, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1870689−1870690 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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