Intramolecular Homolytic Substitution Enabled by Photoredox Catalysis: Sulfur, Phosphorus, and Silicon Heterocycle Synthesis from Aryl Halides

Alberto F. Garrido-Castro,^{†,§} Noelia Salaverri,^{†,§} M. Carmen Maestro,^{*,†} and José Alemán^{*,†,‡}

[†]Department of Organic Chemistry, Universidad Autónoma de Madrid, Madrid 28049, Spain

[‡]Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, Madrid 28049, Spain

Supporting Information

ABSTRACT: Aryl radical generation and manipulation constitutes a long-standing challenge in organic synthesis. Photocatalytic single-electron reduction of aryl halides has been established as a premier activation pathway to reach these intermediates. The current study integrates the conceptual simplicity of the classical intramolecular homolytic substitution with the practicality of the modern photocatalytic approach. Predicated on an efficient metal-free dehalogenation of aryl halides under mild organo-photoredox conditions,



sulfur, phosphorus, and silicon heteroatoms capture the $C(sp^2)$ -centered radical in an intramolecular fashion.

ryl synthons have continued to fulfill an incredibly valuable Arole in organic chemistry for decades. Countless arylation protocols based on two-electron reductions of aryl halides have surfaced.¹ Complementary to ionic chemistry, Single-Electron Transfer (SET) reductive dehalogenation of aryl halides can give access to $C(sp^2)$ -centered radicals. These species serve as relevant intermediates in organic synthesis, and also feature a reactivity profile which completes the general portfolio of arylation methods.² The most common reducing methods employ either a hydride source to induce halide abstraction³ or photochemical cleavage of the $C(sp^2)-X$ bond.⁴ The former regularly hinges on stoichiometric amounts of toxic and unstable metal-based H atom donors and radical initiators (such as tributyltin hydride and AIBN, respectively). The latter has traditionally enabled photolytic dehalogenation under highly energetic light irradiation (λ < 300 nm), thus restricting applicability and establishing a strict relationship between the substrate and its photophysical properties.

The recent renaissance of photochemistry has led to transcendent developments, unlocking new bond constructions based on newly identified photocatalysts capable of acting in the visible or near-visible light end of the spectrum.⁵ In this regard, the generation of $C(sp^2)$ -centered radicals has benefitted greatly.⁶ Most precursors include an activating group that aids the radical generation by lowering the reduction potential, e.g., aryl diazonium salts, diaryliodonium salts, or aryl sulfonyl chlorides (>-1.0 V vs SCE). Alternatively, less-reactive aryl halides present larger reduction potentials (<-1.5 V vs SCE), although they remain the most convenient precursor due to availability and stability.

Therefore, SET reductive dehalogenation has been a main target in the field of photocatalysis, yet the majority of the findings merely report hydrogenation protocols.⁷ The formation

of new C–C or C–heteroatom bonds based on this strategy remains markedly more appealing (Scheme 1, top). Intermolecular versions of these events have proven to be quite challenging, as superstoichiometric amounts of radical trapping





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agents are often required for adequate functionalization of the aryl radical (Scheme 1A).⁸ Intriguingly, the intramolecular variant has been less studied; only a short number of examples restricted to C–C bond formation have been reported in the literature (Scheme 1B).⁹ Nonetheless, the photocatalytic intramolecular formation of C–heteroatom bonds has not been described to the best of our knowledge (Scheme 1C), although the heterocycles obtained through this synthetic route represent highly relevant targets (Scheme 1, bottom). Through careful evaluation of pioneering works in the field of the intramolecular homolytic substitution (S_Hi),¹⁰ implementation of a modern photocatalytic approach could serve as an ideal activation pathway to help overcome previous limitations and provide synthetic intermediates en route to these valuable heterocyclic scaffolds (Scheme 1, bottom).¹¹

We thus identified a straightforward sulfur-based heterocycle preparation to be an ideal starting point for our research.¹² Initial reductive dehalogenations were performed with brominated sulfinamide **1a** (Table 1). Several highly reducing organo-

Table 1. Optimization of the Photocatalytic S_Hi



^{*a*}Reaction conditions: 0.1 mmol scale using 1.0 equiv of sulfinamide 1, 5 mol % of photocatalyst 2, and 2.5 equiv of DIPEA ($^{i}Pr_{2}EtN$) in 1.0 mL of MeCN. ^{*b*}380 mW single LED. See Supporting Information for detailed experimental setup. ^{*c*}Determined by ¹H NMR analysis of the crude mixture. ^{*d*}Absence of DIPEA results in <5% conversion. ^{*c*}Isolated yield after flash chromatography. DIPEA = *N*,*N*-diisopropylethylamine, PTH = 10-phenylphenothiazine, Naph-PTH = 10-(1naphthyl)phenothiazine.

photocatalysts^{5d,13} (entries 1–3) and solvents (see Supporting Information (SI) for detailed optimization studies) were tested in the presence of a sacrificial electron donor (Hünig's base, DIPEA). Irradiation at near-visible light (365 nm) of PTH **2a** as a photocatalyst (5 mol %) in MeCN yielded the best results, albeit resulting in moderate formation of sulfinamide **3a** (entry 1, 44% conversion). In spite of the extensive efforts made to optimize this reaction, bromo-derivative **1a** displayed moderate reactivity.¹⁴ Therefore, iodinated sulfinamide **1b** was subjected to numerous photocatalysts, reaching improved conversions with organic dyes Eosin Y **2d** (entry 4) and Rhodamine 6G **2e** (entry 5), and PTH (entry 6), under visible light irradiation, although longer reaction times were required. Gratifyingly, irradiation of PTH at a slightly more energetic wavelength (385 nm) led to full conversion of **1b** and an 85% isolated yield of product **3a** after only 3 h (entry 7). Control experiments confirmed that PTH, DIPEA, and light irradiation are necessary for the reaction to take place (entries 8–9).

The nature of the leaving group (LG) was studied next, as depicted in Scheme 2. *tert*-Butyl (t Bu) had already been

Scheme 2. Evaluation of the Leaving Group in Sulfinamide 1^a



^{*a*}Reaction conditions: 0.1 mmol scale using 1.0 equiv of sulfinamide 1, 5 mol % of PTH, and 2.5 equiv of DIPEA in 1.0 mL of MeCN for 3 h. Isolated yields are indicated under each entry.

confirmed as a good LG throughout the optimization studies. Furthermore, other alkyl chains such as isopropyl (1c) and *n*butyl (1d) displayed similar efficiency, yielding cyclic sulfinamide 3a in equally impressive fashion. On the other hand, irradiation of p-tolyl sulfinamide 1e under the present conditions resulted in a decrease in yield,¹⁵ presumably due to the higher bond dissociation energy associated to $C(sp^2)-S$ bonds.¹⁶ This set of results indicates that the reaction behaves similarly regardless of the alkyl substitution on the starting sulfinamide. Thus, the rate-determining step of the reaction should be the reductive dehalogenation of the aryl halide. In addition, the stereochemical outcome of the reaction at the sulfur atom was determined. When the reaction was carried out with enantiopure sulfinamide (R)-1b (>99% ee), cyclic sulfinamide (S)-3a was obtained without loss of enantiopurity and complete inversion of configuration (>99% ee; see SI), in accordance with an S_{Hi} mechanism.^{12,17} Consequently, 'Bu was deemed a suitable LG stemming from Ellman's accessible sulfinamide, which is capable of enforcing exquisite stereocontrol on the reaction.

With the optimized conditions in hand, a host of structurally diverse sulfinyl derivatives were subjected to the newly developed photocatalytic protocol (Scheme 3). The reaction was found to be amenable to electron-donating and electronwithdrawing substitution on the aromatic ring, affording the corresponding products in good yields (3b-3d). Impressively, o-substitution on the aryl iodide was well tolerated (3d). Conventional reductive dehalogenations have lacked selectivity as a result of the highly reducing conditions often employed to access radical intermediates. In this context, brominated sulfinamides 1i and 1j provided a remarkable display of chemoselectivity when subjected to irradiation at 420 nm, observing exclusive cyclization at the iodinated positions, while the bromide functionalities remained intact (3e and 3f). Notably, indole- and guinoline-based iodides also underwent efficient cyclization, delivering tricyclic heterocycles 3g and 3h in good yields. Moreover, the presence of a stereogenic center at the benzylic position did not alter the reaction outcome, maintaining its stereochemical information at the benzyl site and undergoing inversion of configuration at the sulfur atom (3i).¹⁸

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Scheme 3. Scope of the Photocatalytic S_{Hi} with Sulfinyl Derivatives 1^{a}



^{*a*}Reaction conditions: 0.1 mmol scale using 1.0 equiv of sulfinyl derivative 1, 5 mol % of PTH, and 2.5 equiv of DIPEA in 1.0 mL of MeCN for 3 h. Isolated yields are indicated under each entry. ^{*b*}Reaction performed on a 1.0 mmol scale. ^{*c*}Reaction mixture irradiated for 6 h. ^{*d*}Reaction mixture irradiated at 420 nm. ^{*c*}Yield determined by ¹H NMR using PhMe as internal standard. ^{*f*}Determined by ¹H NMR.

An additional challenge surfaced when the formation of sixmembered cyclic sulfinamide **3j** was attempted. The unsubstituted starting material (**1n**, R'' = H) features an N-H bond capable of engaging in a 1,5-Hydrogen Atom Transfer (HAT) event with the C(sp²)-radical, leading to undesired hydrogenation over cyclization. Nevertheless, this issue was bypassed upon N-alkylation of the open sulfinamide (**1o**, R'' = Me), affording cyclic N-methyl sulfinamide **3j**. Lastly, the method was also successfully implemented in the preparation of other heterocycles in excellent yields such as five- and six-membered sultines (**3k** and **3l**) and five-membered cyclic sulfoxide (**3m**).

Encouraged by the generality and efficiency of this photocatalytic system throughout the synthesis of different sulfurbased heterocycles, we wondered if this protocol could be expanded further. Phosphorus and silicon have showcased the ability to participate in S_{Hi} processes,¹⁹ although it remains largely unexplored under photocatalytic conditions. Consequently, phosphites 4 (Scheme 4A) and silyl ethers 6 (Scheme 4B) were quickly identified as intriguing candidates.

Phosphonate esters hold an important role in pharmaceutical chemistry, serving as the corresponding prodrug of biologically active phosphonic acids, such as tenofovir or fosmidomycin.²⁰ Among the multiple synthetic routes which grant access to these prized organophosphorus compounds, phosphites have been described to undergo $S_{\rm H}i$ —concurrent with oxidation from P(III) to P(V)—delivering these Arbuzov-type products.²¹ In this regard, a series of phosphites were evaluated (see SI for detailed studies). Iodinated derivatives proved difficult to work

Scheme 4. (A) Scope of the Photocatalytic S_Hi with Phosphites 4^{*a*}; (B) Scope of the Photocatalytic S_Hi with Silyl Ethers 6^{*b*}



^aReaction conditions: 0.1 mmol scale using 1.0 equiv of phosphite 4, 20 mol % of PTH and 2.5 equiv of DIPEA in 1.0 mL of MeCN for 16 h. Isolated yields are indicated under each entry. ^bReaction conditions: 0.1 mmol scale using 1.0 equiv of silyl ether 6, 5 mol % of PTH, and 2.5 equiv of DIPEA in 1.0 mL of MeCN. Yields determined by ¹H NMR using PhMe as internal standard, and reaction times are indicated under each entry.

with due to background photolytic cleavage of the C–I bond, leading to hydrogenated byproduct formation.²² Given this lack of control, focus shifted to bromo-derivatives in an attempt to harness the aryl radical generation in a milder way. To our delight, homobenzylic phosphite **4a** was successfully debrominated to afford the hexacyclic phosphonate **5a** (Scheme 4A), for which an increase in catalyst loading (20 mol %) and reaction time (16 h) was essential. Subsequently, a brief structural scope evaluation was conducted on this system. Electron-donating substitution (**4b**) and the chloride functionality (**4c**) were tolerated, affording phosphonates **5b** and **5c** in synthetically useful yields.²³

Silvl groups represent a useful functionality in organic synthesis. They can act as "placeholders" for further functionalizations, including alcohol formation via oxidation and Hiyama-type cross-couplings with electrophiles.²⁴ Accordingly, the expansion of this photocatalytic reaction to achieve $C(sp^2)$ -Si bond formation could be valuable (Scheme 4B). Tris(trimethylsilyl)-substituted silyl ethers 6 were selected as precursors, since the TMS group is known to be a good LG in $S_{\rm H}$ i reactions.²⁵ Iodinated starting materials proved unstable once again, so aryl bromides were employed instead. We were pleased to find that the reaction worked well under the standard photocatalytic conditions (5 mol % of PTH, short reaction times) with the less-reactive bromine-substituted ring 6a, affording cyclic silyl ether 7a in good yield. In this case, electron-rich and electron-poor aromatic rings could be studied, providing swift formation of products 7b and 7c, respectively.

Finally, chloro-derivative 7**d** was readily accessed under these mild conditions.

A plausible mechanism for the photocatalytic S_{Hi} reaction is represented in Scheme 5. First, the photocatalyst (PTH) reaches

Scheme 5. Mechanistic Proposal for the Photocatalytic S_Hi



its highly reducing excited state ($E^{red} PTH^{\bullet+}/PTH^* = -2.1 V vs SCE$)^{5d,13} upon absorption of light. The photoexcited catalyst would then engage in an SET event with the corresponding aryl halide (E^{red} ca. -1.5 to -2.0 V vs SCE),^{6c,14a} generating the anion radical of the substrate through an oxidative quenching pathway. Stern–Volmer quenching studies have shown the inability of trialkylamines to quench PTH*. Therefore, the excited catalyst is interacting with the aryl halide¹³ (see SI). Ensuing mesolytic cleavage of the C(sp²)–X bond results in the release of a halide anion (X⁻) and formation of the aryl radical.^{14a} At this point, the S_Hi process should become strictly substrate-dependent, as the aryl radical interacts with each heteroatom in a different manner:

- (i) The lone pair on the S atom would take part in the $C(sp^2)-S$ bond-forming event, while the homolytic scission of the $S-C(sp^3)$ bond would lead to the ^tBu radical release. This is taking place through a concerted process, confirmed by the enantiopurity (>99% ee) of compound (S)-3a.
- (ii) The aryl radical would initially attack the P(III) atom, forming the new C(sp²)-P bond as the unstable phosphoranyl radical is generated. Ethyl radical release followed by oxidative rearrangement to P(V) would then render the final aryl phosphonate.
- (iii) The aryl radical would begin C(sp²)–Si bond formation in concert with Si–SiMe₃ homolytic bond dissociation, resulting in silyl ether cyclization and TMS radical release.

Lastly, regeneration of PTH through reduction of its oxidized form $(E_{1/2}^{\text{ox}} \text{ PTH/PTH}^{\bullet+} = +0.68 \text{ V vs SCE})^{5d,13}$ using Hünig's base as a sacrificial electron donor $(E^{\text{ox}} \text{ DIPEA/DIPEA}^{\bullet+} = +0.94 \text{ V vs SCE}$; see SI) closes the photocatalytic cycle.

The generation and reactivity of aryl radicals represents an extraordinary challenge in single-electron chemistry. In this context, the intramolecular capture of the valuable $C(sp^2)$ -centered radical intermediate with multiple heteroatoms— unexplored under photocatalytic conditions to the best of our knowledge—is herein disclosed. Through reductive dehalogenation of aryl halides, this efficient, metal-free protocol gives access to diverse heterocycles, ranging from S-based sulfinamides and sultines to P- and Si-centric benzofused structures. From a mechanistic standpoint, all $C(sp^2)$ -heteroatom bond-forming events are believed to occur through an intramolecular

homolytic substitution at the different heteroatoms studied under this protocol.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01911.

General experimental procedures, optimization studies, compound synthesis and characterization data, mechanistic studies, and NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: carmen.maestro@uam.es. *E-mail: jose.aleman@uam.es.

ORCID 🔍

Alberto F. Garrido-Castro: 0000-0001-7262-7986 M. Carmen Maestro: 0000-0002-5639-9714 José Alemán: 0000-0003-0164-1777

Author Contributions

[§]A.F.G.-C. and N.S. contributed equally.

Notes

The authors declare no competing financial interest.

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