

Visible Light-Promoted Atom Transfer Radical Cyclization of Unactivated Alkyl Iodides

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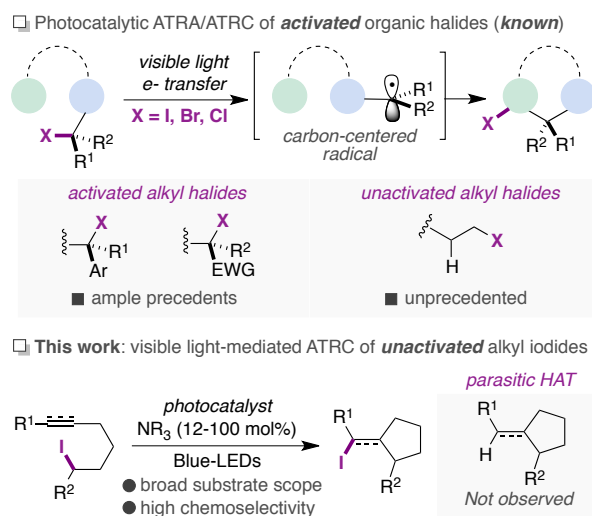
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ABSTRACT: A visible light-mediated atom transfer radical cyclization of unactivated alkyl iodides is described. This protocol operates under mild conditions and exhibits high chemoselectivity profile while avoiding parasitic hydrogen atom transfer pathways. Preliminary mechanistic studies challenge the perception that a canonical photoredox catalytic cycle is being operative.

KEYWORDS: visible light, alkyl halide, photocatalysis, atom-economy, radical cyclization.

In recent years, visible light photocatalysis has arguably gained considerable momentum for generating carbon-centered radical intermediates via single-electron transfer (SET) processes.¹ Unlike classical SET protocols based on radical initiators or metal catalysts initiated by a chemical activation mode and inner-sphere mechanisms,² photoredox catalysis offers the opportunity to promote otherwise analogous processes using simple visible light via outer-sphere mechanisms.¹ Particularly illustrative is the implementation of *redox-neutral* atom transfer radical addition (ATRA) or cyclization reactions (ATRC),³ enabling elegant bond-disconnection strategies for rapidly building up molecular complexity in a both atom- and step-economical fashion.⁴

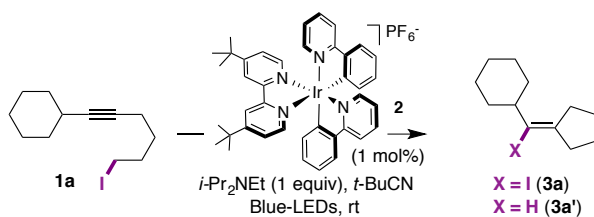


Scheme 1. Visible Light-Promoted ATRA/ATRC Reactions

At present, the portfolio of photoredox ATRA/ATRC reactions remains confined to activated organic halides possessing weak C(sp³)-X bonds adjacent to π -systems, heteroatoms or electron-withdrawing groups, thus rapidly triggering SET processes (Scheme 1, top pathways).⁵ In sharp contrast, visible-light mediated ATRA/ATRC reactions of *unactivated* alkyl halides are altogether absent from the literature. This is likely attributed to the inherent difficulties for finding photocatalysts able to match the exceptionally high redox potentials of *unactivated* alkyl halides ($E_{red} [n\text{-BuI}] = -2.5$ V vs. SCE in

MeCN).⁶ Although seminal studies by Stephenson^{7a} and Lee^{7b} elegantly showcased the ability to trigger unconventional photocatalytic *non-redox-neutral* reductive processes via hydrogen atom transfer (HAT), at the outset of our investigations it was unclear whether the inherent propensity of *in situ* generated carbon-centered radicals to undergo parasitic HAT could be tackled to efficiently promote a visible light *redox-neutral* ATRA/ATRC of unactivated alkyl halides. If successful, such strategy would provide rapid access to versatile products amenable to further functionalization via classical cross-coupling scenarios. As part of our ongoing interest in SET processes,⁸ we report herein the successful realization of a design principle capable of promoting, for the first time, a *redox-neutral* ATRA reaction of unactivated alkyl iodides under visible light irradiation. The protocol is distinguished by its mild reaction conditions, ease of execution, wide substrate scope and excellent chemoselectivity profile (Scheme 1, *bottom*). Preliminary mechanistic studies reveal an intriguing role of the amine, suggesting that a canonical photoredox cycle might not come into play, pointing towards a different scenario in which the photocatalyst is not directly involved in a SET to the corresponding alkyl iodide.

Table 1. Optimization of the Reaction Conditions.^a



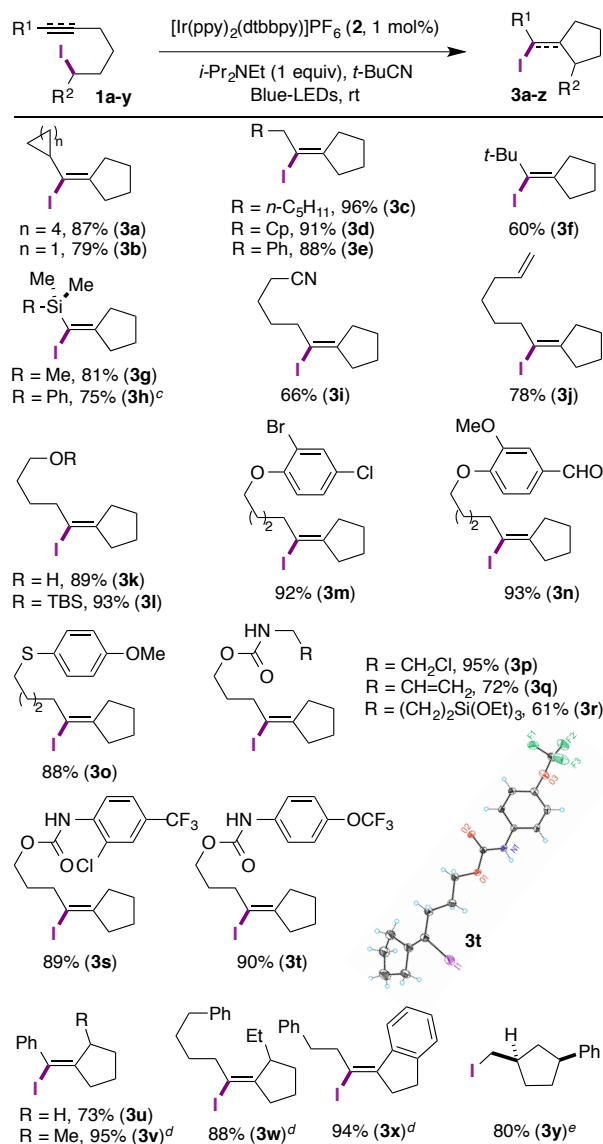
Entry	Deviation from standard conditions	3a (%) ^b	3a' (%) ^b
1	none	89(87) ^c	0
2	MeCN instead of $t\text{-BuCN}$	68	25
3	$i\text{-PrCN}$ instead of $t\text{-BuCN}$	30	11
4	$n\text{-Bu}_3\text{N}$ instead of $i\text{-Pr}_2\text{NEt}$	87	0
5	Cy_2NMe instead of $i\text{-Pr}_2\text{NEt}$	82	0
6	$i\text{-Pr}_2\text{NEt}$ (12 mol%)	83 ^d	0
7	$\text{fac-Ir}(\text{ppy})_3$ instead of 2	58	0
8	$\text{Ir}(\text{dFCF}_3\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ instead of 2	83	0
9	Using 1a-Br	0	0
10	No $i\text{-Pr}_2\text{NEt}$, no 2 or in the dark	0	0

^a **1a** (0.20 mmol), **2** (1 mol%), $i\text{-Pr}_2\text{NEt}$ (0.20 mmol) in $t\text{-BuCN}$ (0.20 M) at rt for 12 h. ^b GC yields using decane as internal standard. ^c Isolated yield. ^d 48 h reaction time.

Our investigations started with **1a** as the model substrate (Table 1). After considerable experimentation,⁹ the best results were accomplished with photocatalyst **2** in the presence of $i\text{-Pr}_2\text{NEt}$ under blue light-emitting diodes (LEDs) irradiation, obtaining 87% of **3a**. As expected, the choice of the solvent markedly influenced both yield and selectivity. While not even traces of **3a'** were observed with a protocol based on $t\text{-BuCN}$ (entry 1), solvents susceptible to undergo HAT processes generated

substantial amounts of **3a'** (entries 2 and 3).¹⁰ Although the nature of the amine did not have a significant influence on reactivity and selectivity (entries 4 and 5), it is worth noting that *catalytic* amounts of $i\text{-Pr}_2\text{NEt}$ delivered **3a** in a remarkable 83% yield, but at considerably lower rates (entry 6). The results shown in entry 1 are particularly intriguing if one takes into consideration the remarkable mismatch between redox potentials of **1a** ($E_{\text{red}} \leq -2.5$ V vs. SCE in MeCN)^{9,11} and **2** ($E_{\text{red}} [\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.51$ V vs SCE in MeCN).^{9,11,12} Indeed, we realized that stronger reducing complexes such as $\text{fac-Ir}(\text{ppy})_3$ ($E_{\text{red}} [\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -2.19$ V vs SCE in MeCN)^{1f} resulted in a significant erosion in yield, whereas stronger oxidizing $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ ($E_{\text{red}} [\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}] = -1.37$ V vs SCE in MeCN)^{1f} delivered otherwise identical yields (83%) (entry 7 vs entry 8), thus challenging the perception that a conventional SET photoredox catalytic cycle is being operative. Unfortunately, no productive formation of **3a-Br** was observed with **1a-Br**, recovering unreactive starting material (entry 9). As expected, control experiments revealed that the presence of both $i\text{-Pr}_2\text{NEt}$ and **2** under visible-light irradiation was absolutely critical for success (entries 10 and 11).

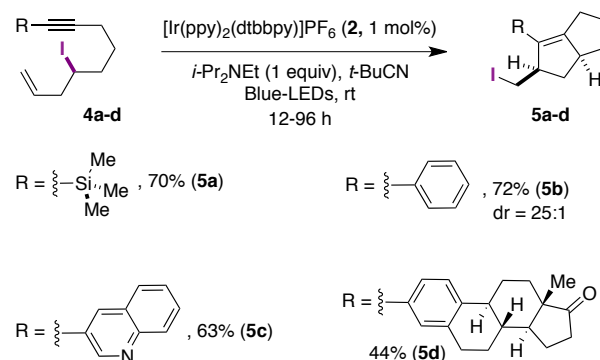
Table 2. Visible Light Photocatalytic ATRA of Unactivated Alkyl Iodides.^{a,b}



^a As for Table 1, entry 1 (12-96 h). ^b Isolated yields, average of at least two independent runs. ^c **1h** (5.80 mmol scale) with **2** (0.1 mol%). ^d $E/Z = 1:1$. ^e $\text{dr} = 10:1$.

Encouraged by these results, we next focused our attention on exploring the preparative scope of our ATRC reaction. As evident from the results compiled in Table 2, our visible light photocatalytic ATRC of unactivated alkyl iodides turned out to be highly chemoselective, as alkyl iodides possessing silyl groups (**3g**, **3h**, **3r**), nitriles (**3i**), alkenes (**3j**, **3q**), free alcohols (**3k**), silyl ethers (**3l**), aldehydes (**3n**) or carbamates (**3p-3t**), among others, could perfectly be accommodated. Notably, aryl or alkyl halides do not interfere (**3m**, **3p**, **3s**), providing an additional handle via iterative metal-catalyzed cross-coupling techniques. Interestingly, aromatic- or aliphatic-substituted alkynes could be coupled with equal ease, even for particularly challenging hindered substrate combinations (**3f-3h**). The successful preparation of **3i-**

3o and **3j-k** is particularly noteworthy; while the former indicates that intramolecular 1,5-HAT prior to iodine transfer does not compete with the efficacy of the reaction, the lack of double cyclization with a pending alcohol (**3j**) or an alkene motif (**3k**) leaves a reasonable doubt about the involvement of transient vinyl cationic species.^{5e} Moreover, the reaction of **3h** could be easily scaled up, even at 0.1 mol% loadings of **2**. Interestingly, the reaction of secondary alkyl iodides posed no problems, although equimolar E/Z mixtures were obtained for **3v** and **3w**.¹³ As shown for **3x**, we found that fused cyclopentane rings could be equally effective.



Scheme 2. Atom Transfer Double Radical Cyclization.

The successful preparation of **3a-3x** tacitly suggested that our visible light ATRC should by no means be limited to unactivated alkyl iodides bearing alkynes on the side-chain. Indeed, we found that **1y** possessing a pending alkene reacted equally well, obtaining **3y** in 80% yield. As for classical radical-type cyclizations, an excellent diastereoselectivity was observed for **3y**, invariably favoring the *cis*-isomer. In view of the significant erosion in selectivity found for **3v-3x**, we hypothesized that the utilization of secondary alkyl iodides possessing an allyl group could trigger a 5-*exo-trig* cyclization followed by rapid interconversion of the *in situ* formed vinyl radicals and a final iodine transfer, thus ultimately resulting in bicyclic skeletons via formal atom transfer double radical cyclization. As shown in Scheme 2, this turned out to be the case and **5a-d** were all obtained in good yields with high levels of diastereoselectivity under otherwise identical reaction conditions to that shown in Table 2.¹⁴ To the best of our knowledge, these results represent the first atom transfer double radical cyclization performed using photocatalysis under visible light irradiation.¹⁵ Taken together, the results of Table 2 and Scheme 2 illustrate the prospective impact of visible light-mediated *redox-neutral* ATRC reactions with unactivated alkyl iodides.

The large energy mismatch between redox potentials of **2** ($E_{\text{red}} [\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}}]$ vs $E_{\text{red}} [\text{1a}] = \sim 1$ V) suggested that a

conventional photocatalytic redox cycle might not be operative. Although quenching experiments¹⁶ indicated the involvement of a simple reductive photoredox cycle, the quantum yield of the ATRC of **1a** was found to be 2.3. While this value might fall into a radical-chain propagation scenario,¹⁷ the existence of alternate light-consuming events cannot be ruled out.¹⁸ Indeed, 12% of **3a** could be obtained *in the absence of 2* after 48 h. While higher yields of **3a** could be obtained upon increasing the light intensity or by using DMSO as solvent at higher concentrations of *i*-Pr₂NEt, it is worth noting that significant amounts of undesired **3a'** were inevitably observed in these cases, making this transformation less-synthetically attractive in the absence of **2**.⁹ Although an in depth mechanistic study should await further investigations, these results might suggest the formation of a weak charge-transfer complex¹⁹ between **1a** and *i*-Pr₂NEt, triggering a SET via *in situ* formation of an exciplex.²⁰⁻²² In line with these results, we speculate that formation of an exciplex might be accelerated via energy transfer from the triplet excited state of **2**.^{23,24} Whether chain-processes could be initiated from an exciplex²⁵ or from *in situ* generated α -amino radicals,²⁶ or if it has other mechanistic considerations is subject of ongoing studies.²⁷

In summary, we have described an unconventional photocatalytic *redox-neutral* ATRC of *unactivated* alkyl iodides under visible light irradiation. The salient features of this transformation are the mild conditions, broad scope and exquisite chemoselectivity, thus enabling the preparation of highly versatile building blocks susceptible to further functionalization. Preliminary mechanistic experiments leave some doubt about a canonical photoredox cycle. Further investigations along these lines are currently underway in our laboratories.

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ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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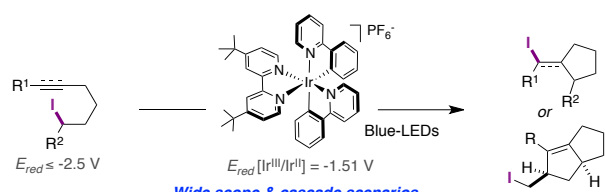
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Wide scope & cascade scenarios
Large energy mismatch (~1 V)
High chemoselectivity profile
