Photocatalytic Generation of 2-Azolyl Radicals; Intermediates for the Azolylation of Arenes and Heteroarenes via C–H Functionalization.

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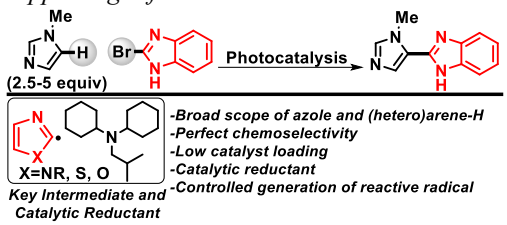
Supporting Information Placeholder

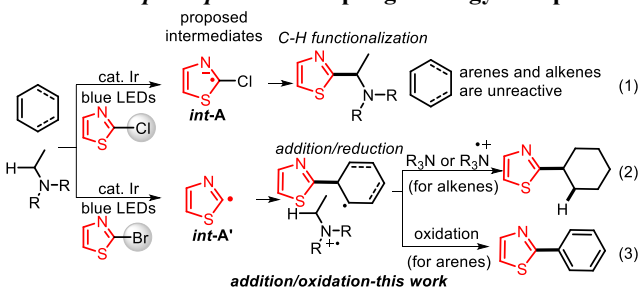


ABSTRACT: The 2-azolyl radical is generated from 2-bromoazoles via photocatalysis. It is a powerful intermediate for the intermolecular arylation of unmodified (hetero)arenes. The reaction is characterized by mild conditions, operational simplicity, tolerance toward functional and sterically demanding groups, broad scope, and anti-Minisci selectivity. A working mechanism is provided and a low-solubility amine is essential for successful coupling. The utility of the reaction is demonstrated via late-stage functionalization of methyl estrone and application toward other bromoarenes.

Azoles are a privileged motif frequently found in natural products,[1] pharmaceuticals,[2] and functional materials.[3] In all cases, they display diverse behavior depending upon substituent patterns. Consequently, a great deal of attention has been invested in the development of both *de novo* synthesis[4] as well as the functionalization of preexisting azole cores, which collectively allow a relatively versatile synthesis of azoles.[5] Often azoles can be synthesized via either strategy and both have distinct advantages (i.e., scaling vs. diversification), giving relevance to the development of both strategies. Within the latter strategy, the most prominent methods rely on lithiation[6] by either C–H deprotonation or lithium-halogen exchange. Alternatively, Pd-mediated cross-couplings[5] have also been extensively developed. In both cases, reactivity patterns and limitations are well established. Thus, there is a need to find new, unexplored, reactive azole intermediates in hope that they may provide new directions and possibilities for this important motif.

As a part of our program, we have commenced a systematic study of photocatalyst-mediated electron transfer from amines to 2-haloazoles with a particular interest in the nature, reactivity, and utility of the intermediates that can be generated by electron transfer (Scheme 1). In this context, we have seen that the nature and reactivity of the intermediate formed depends exclusively upon the halogen attached at the 2-position of the azole. We observed that 2-chloroazoles undergo C–H functionalization of aliphatic amines-even in the presence of alkenes and arenes (Scheme 1, eq 1).[7] In contrast, when 2-bromoazoles are subjected to similar conditions, the azole core undergoes addition to alkenes and subsequent reduction to give net hydroazolylation of the alkene (Scheme 1, eq 2).[8] Herein, we sought to capitalize on the ability to form a presumed azolyl radical by finding conditions that would allow the same intermediate to undergo direct intermolecular addition to arenes followed by subsequent oxidation and rearomatization (Scheme 1, eq 3). The realization of this reaction is significant in part because it entails simultaneous reduction of the 2-bromoazole and oxidation of the arene-H. If possible, it would allow simple and direct access to an important motif from widely available starting materials.

Scheme 1. C*sp*^{2}–C*sp*^{3} Cross-coupling Strategy Comparison

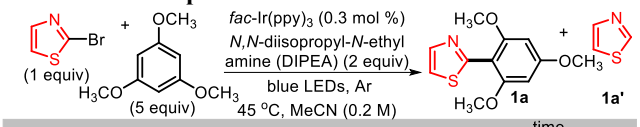


The stoichiometric generation of reactive radicals, often gives rise to undesired reaction pathways, such as reduction, unselective addition, and oligomerization, which can impose severe limitations on the scope of intermolecular reactions. In contrast, the photocatalytic generation of the reactive radical species can significantly reduce the amount of most of these side products-albeit often at the expense of scope.[7a,8] This is in part a result of the catalytic generation and transient nature of the reactive species, which helps minimize undesired pathways. Additionally, the reactivity of the amine can be tuned by structural modification, and can serve as a reaction handle.

The most significant side reaction that is observed is Hydrogen Atom Transfer (HAT) to the azolyl radical, which results in hydrodebromination of the bromoazole, **1a'** (Table 1). Careful tracking of the electrons would suggest it may be possible to use an oxidative quenching mechanism to initiate the chemistry, with the rearomatization process ultimately serving as the electron source.[9] The advantage would be the ability to avoid using a reductant that also serves as the H-atom source.[8] Thus, eliminating the amine might allow us to avoid

the undesired reduction pathway altogether. Unfortunately, this was not a viable pathway because in the absence of amine, no reaction occurs, even though *fac*-Ir(ppy)$_3$ is very reducing from its excited state (-1.73 V vs. SCE) (Table 1, entry 12). Along this line, Stephenson demonstrated that *N,N*-diphenyl-4-methoxyaniline, which is devoid of easily transferable hydrogens, could serve as an electron donor to bromomalonates, and addition of this amine helped avoid reduction of the bromides.[10] However, in the present case, no reaction occurred in the presence of this amine (Table 1, entry 2). Previously,[8] we used the low solubility of certain amines to increase the yields in the related photocatalytic alkylation reaction in which competitive reduction of the azole was also problematic (Scheme 1, eq 2). Consequently, we performed a screen of low solubility amines.[11] We found that bulky *N*-cyclohexyl-*N*-isobutyl-*N*-cyclohexanamine,[12] which is far less soluble in MeCN at 23 °C than diisopropylethylamine which is reasonably soluble, (0.01 M vs 1.3 M) gave an increased amount of the desired product (Table 1, entry 3 vs 1).

Table 1. Optimization of Reaction Conditions



entry	modifications	1a/1a'[a]	time, h	conv[a]
1.	none	52:48	21	100%
2.	*N,N*-diphenyl-4-methoxyaniline instead of DIPEA	na	20	0%
3.[b]	(*c*Hex)$_2$N*i*Bu instead of DIPEA	68:32	20	100%
4.	(*c*Hex)$_2$N*i*Bu, at 15 °C	92:8	20	39%
5.	(*c*Hex)$_2$N*i*Bu, at 30 °C	84:16	20	100%
6.	(*c*Hex)$_2$N*i*Bu, at 60 °C	49:51	20	100%
7.	(*c*Hex)$_2$N*i*Bu, 30 °C, 3.0 equiv of arene-H	78:22	20	100%
8.	(*c*Hex)$_2$N*i*Bu, 30 °C, 1.2 equiv of arene-H	42:58	20	<45%[c]
9.	(*c*Hex)$_2$N*i*Bu, 30 °C, 3.0 equiv of arene-H, but at 0.05 M	94:6	20	100%
10.	**30 °C, 3.0 equiv of arene-H, 0.05 M, but 0.5 equiv (*c*Hex)$_2$N*i*Bu, 2 equiv K_2CO_3**	**95:5**	**20**	**100%**
11.	Entry 10, but Ir(*t*buppy)$_3$ instead of Ir(ppy)$_3$	86:14	20	<45%[c]
12.	Entry 10, but exposed to air	72:28	19	31%[d]
13.[e]	Entry 10, no light, no amine, or no Ir(ppy)$_3$	na	19	<2%

[a]Determined by ^{1}H NMR. [b]See supporting information for entire amine investigation. [c]Reaction did not proceed with extended time. [d]Conversion to undesired product. [e]Three separate experiments.

We next evaluated the effect of temperature and found that lowering the temperature led to an increase in product ratio, though at lower temperature the reaction becomes sluggish (Table 1, entries 3-6). It is likely that both effects are due to a decreased amount of soluble amine at lower temperatures (0.00075 M at 15 °C). We next explored the effect of the concentration of arene (Table 1, entries 7 and 8). Dropping the arene loading from 5.0 equivalents to 3.0 resulted in only a slight decrease in product. However, further decrease to 1.2 equivalents led to both a decrease in the **1a**:**1a'** ratio as well as incomplete conversion despite extended reaction times.

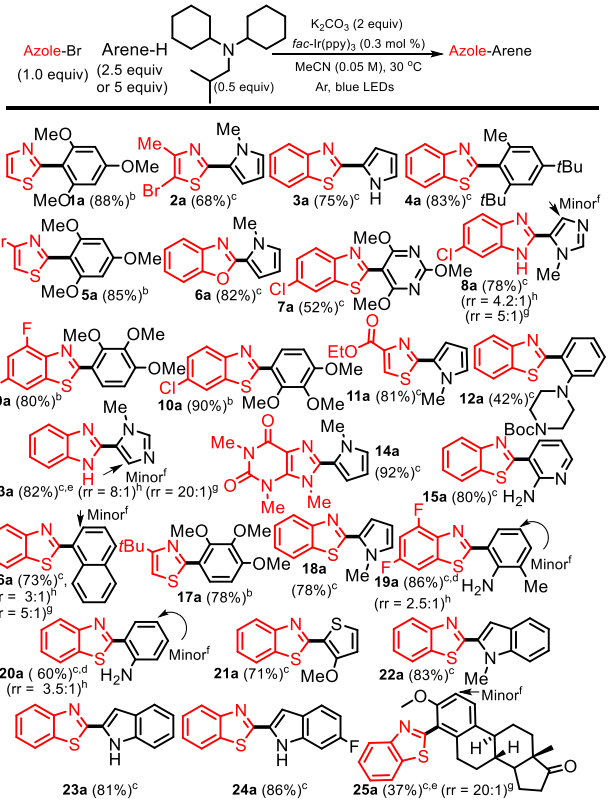
Assessment of the overall concentration of the reaction revealed that 0.05 M was superior to 0.2 M (Table 1, entries 9 vs. 7), giving **1a**:**1a'** in a 94:6 ratio. We believed the amine was playing two roles in the reaction. The first was to serve as a reductant, which is responsible for the C–Br fragmentation. The second was to sequester the HBr that was formed under the reaction conditions. However, we speculated that rearomatization may serve to propagate the reaction[13] and possibly regenerate the amine. To test this, we added a stoichiometric, non-redox active base, K_2CO_3, which would allow us to lower the amine loading to a substoichiometric amount (Table 1, entry 10 vs. 9). Indeed, we found that using only 0.5 equiv of amine resulted in nearly identical **1a**:**1a'** ratio. Finally, control experiments confirmed the necessity of light, amine, and photocatalyst.

Using the optimal conditions (Table 1, entry 10), an isolated yield of 88% of **1a** was obtained and we began to explore the scope of the reaction (Scheme 2). The reaction worked remarkably well across all of the azoles investigated, thiazoles, benzothiazoles, benzoxazoles, and benzimidazoles, as well as purine derivatives. The selectivity of the reaction for the 2-bromo of azole derivatives is absolute, allowing the presence of other bromine and chlorine substituents (**2a**, **5a**, **8a**, **10a**) that could be used for further elaboration. Additionally, there was no evidence of the bromoazole (or its product) serving as the arene-H partner.

In general, the azolyl radical appears electrophilic in nature, nonetheless, the scope of the arene-H was remarkably broad.[14] The reaction worked well with electron rich benzene derivatives (**1a**, **5a**, **9a**, **10a**, and **17a**) and sterically hindered benzenes **4a**.

Commonly, pyrroles- and indoles-azoles are made via cyclodehydration or isomerization of the pyrroles and indole precursor to form the azole heterocyle rather than cross-coupling because of the rapid protiodeborylation of 2-heteroatom boronic acids.[15] However, simple unmodified pyrroles coupled efficiently, requiring only 2.5 equivalents of the pyrroles or indole partner. The coupling worked well for *N*-substituted pyrroles and indoles (**2a**, **6a**, **11a**, **14a**, and **18a**) and should immediately simplify the synthesis of such motifs.[11]

Scheme 2. The Photocatalytic Azolylation of Arenes and Heteroarenes



[a]Yields are of isolated products after chromatography. [b]5 equiv of Arene-H is used in the reaction. [c]2.5 equiv of Arene-H is used in the reaction. [d]Both isomers are separable on flash charomatography and yield includes mass of all isolated isomers. [e]Yield of shown isomer only. Regioisomeric ratio (rr), [g]isolated rr, [h]crude rr, determined on crude material via ^{1}H NMR. [f]Site of azolylation of minor regioisomer.

The transformation also works equally well for *N*-unsubstituted pyrroles and indoles (**3a**, **23a**, and **24a**), which typically undergo *N*-azolylation, thus providing an orthogonal type of reactivity from the same substrates.[16]

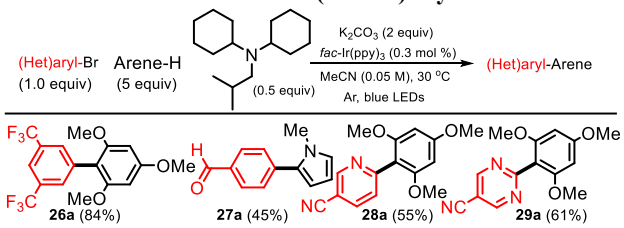
2-Azolyl thiophenes are typically synthesized via Pd-mediated coupling of 2-metallated thiophenes and 2-bromoazoles.[17] Using the developed protocol, 3-methoxy thio-

phene is cleanly coupled to the bromoazole **21a** without pre-functionalization of the thiophene to deliver the azole-3-alkoxy thiophene motif, which is frequently investigated because of its nonlinear optical response.[18]

The coupling of 2-aminopyridine took place smoothly, giving a single isomer **15a**. Normally, these same reagents give rise to C–N coupling, but this is not observed and again demonstrates the orthogonality of the reaction to currently used methods.[19] 2-Bromo-6-chlorobenzothiazole underwent smooth coupling with trimethoxy pyrimidine (**7a**) to give the fully substituted pyrimidine.[20] *N*-Alkyl imidazoles (**8a** and **13a**) undergo smooth coupling with 2-bromoimidazoles, albeit at somewhat diminished rates compared to more electron rich arene-Hs. This type of biazole has frequently been investigated because of the array of biological activity it displays, and its synthesis is usually accomplished via cyclodehydration or cross-coupling with an organometallic.[21] In contrast to acid-,[22] copper-,[23] or palladium-catalyzed[24] processes in which anilines undergo *N*-substitution with 2-bromoazoles, in the current protocol, both tertiary and primary anilines give the ortho-substituted products as the major to exclusive product (**12a**, **19a**, and **20a**) with the para-substituted aniline making up the mass balance. Addition of the radical to naphthalene affords mono α-azolylation as the major product with some β-addition product (rr 3:1, **16a**). The generation of azolyl radical takes place under very mild conditions and appears to be quite compatible with all the functional groups that were tested. Furthermore, no arene-related by-products are observed, suggesting the method might be useful for late-stage azolylylation of pharmaceuticals, in which a major goal is to derivatize the molecule with minimal time and effort.

To demonstrate this, we examined the photocatalytic azolylation reaction of commercially available methylestrone, in which derivatization of the carbonyl has already led to an FDA approved oral contraceptive (mestranol). Although the yield was modest due to low solubility of the substrate, we were able to isolate 37% of the desired product as a single regioisomer in which the C–H was benzothiazolylated at C_4, providing a functionalization strategy and suggesting that the photocatalytic C–H azolylation of arenes may be generally useful for late-stage functionalizations.

Scheme 3. Reaction of Other (Hetero)Aryl Bromides.



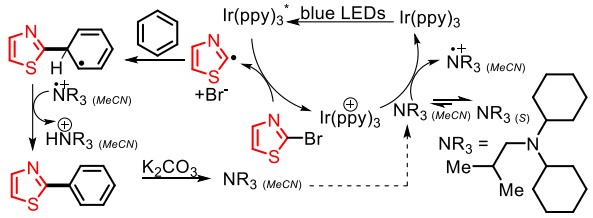
While we have been primarily focused on the functionalization of arenes with azoles, in theory this process of electron transfer, radical anion fragmentation, addition, and rearomatization should extend beyond azoles. Thus, we subjected a few reducible (hetero)aryl bromides to the reaction conditions.[25] Modest to good yields could be obtained using the standard conditions without any further optimization (Scheme 3). Given the substantial differences between azoles and these electronically diverse arenes, these results are encouraging, and optimization would likely lead to improved yields.

Our working mechanism is outlined below (Scheme 4). Initially, absorption of a photon by the photocatalyst results in a long-lived excited state catalyst, $Ir(ppy)_3^*$.[26] Plausible arguments can be made for both oxidative and reductive quenching, but ultimately both result in electron transfer to the bromoazole, which is ultimately responsible for the formation of the reactive intermediate. Electron transfer to the 2-bromoazole gives an azolyl radical after fragmentation of the C–Br bond.[27] In light of our earlier work with 2-chloroazoles[7a] and the distinct behavior of these intermediates (Scheme 1, eq 1 vs. eqs 2 and 3) we believe that a radical anion of the bromoazole is likely formed, but is short-lived and rapidly gives rise to the azolyl radical by unimolecular fragmentation of the C–Br bond.[28] The azolyl radical undergoes addition to the arene with regioselectivity that depends primarily upon the electronics of the arene–H substrate. Because the azolyl radical is generated under slightly basic conditions, as opposed to the strongly acidic conditions typical of the Minisci reaction, both the polarity of the heterocycles and the traditional Minisci-regioselectivities are reversed.[29]

Addition of the azolyl radical to the arene gives rise to a cyclohexadienyl radical. In the last step, rearomatization occurs. There are several possible pathways through which this may be accomplished. It may occur through 1) electron transfer to the amine radical cation along with deprotonation of the resulting cyclohexadienyl cation, 2) propagation,[13] i.e., transfer of the electron to another bromoazole along with deprotonation of the cyclohexadienyl cation, 3) transfer of the electron to an excited state catalyst along with deprotonation of a cyclohexadienyl cation or 4) deprotonation to generate a cyclohexadienyl radical anion stabilized by the presence of conjugated azole, which would rearomatize upon loss of an electron to one of the aforementioned potential oxidants. It is reasonable to assume that the dominant rearomatization mechanism is dependent upon the exact nature of the arene-H.

It is important to note that the key azolyl radical can undergo undesired hydrogen atom abstraction from either the amine or the amine radical cation.[8] Consequently, keeping the concentration of the amine low is one vital aspect to avoiding reduction of the bromoazole.[30] Previously, the use of sparingly soluble amines proved effective at decreasing undesired reduction in the photocatalytic reductive alkylation.[8] Again, we see that an amine that exhibits low solubility maintains a low concentration throughout the reaction. This allows electron transfer to occur at sufficient rates to facilitate the overall process while surpressing HAT and reduction of the bromoazole. Given that only substoichiometric amounts of amine are needed, it is possible that the amine is being regenerated under the reaction conditions, but this feature could also be a result of a propagation reaction in which the amine is only needed for initiation step.[13]

Scheme 4. Mechanistic Hypothesis.



Given the ability of the reaction to engage such a wide range of ubiquitous arenes and heteroarenes, the operational simplicity of the reaction, and the interest in such products, we expect that this reaction can immediately help those trying to explore the chemical space about a (hetero)arene-azole core. The developement of this C–H functionalization reaction is a consequence of the exploration of the azolyl intermediate and prompts further exploration of important motifs such as the azole, which could lead to significant advances in our technical ability to synthesize other priveledged scaffolds.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, additional optimization experiments, and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interests.

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(11) See Supporting Information for more details.
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