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Communication

Azolation of Benzylic C−H Bonds via Photoredox-Catalyzed Carbocation Generation

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ABSTRACT: A visible-light photoredox-catalyzed method is reported that enables the coupling between benzylic C−H substrates and N−H azoles. Classically, medicinally relevant *N*-benzyl azoles are produced via harsh substitution conditions between the azole and a benzyl electrophile in the presence of strong bases at high temperatures. Use of C−H bonds as the alkylating partner streamlines the preparation of these important motifs. In this work, we report the use of *N*-alkoxypyridinium salts as a critically enabling reagent for the development of a general C(sp^3)−H azolation. The platform enables the alkylation of electron-deficient, -neutral, and -rich azoles with a range of C−H bonds, most notably secondary and tertiary partners. Moreover, the protocol is mild enough to tolerate benzyl electrophiles, thus offering an orthogonal approach to existing S_N2 and cross-coupling methods.

N-Benzyl azoles are an abundant motif in drug discovery,[1] with key examples including letrozole,[2] bifonazole,[3] and carboetomidate[4] (Figure 1). Such motifs exhibit widespread utility as active compounds across a number of disease areas and medical uses. Generally, azoles, such as pyrazoles, possess tempered nucleophilicity relative to halides or carboxylates.[5] Thus, their alkylation via substitution reactions typically requires harsh conditions. Indeed, the preparation of the C−N bond of letrozole relies on an S_N2-type protocol with triazole and a benzyl electrophile (halide/tosylate) at 100 °C with strong base.[6] Additionally, benzyl electrophiles are prone to hydrolysis and often require extra preparatory steps. Thus, a need exists for new mild and streamlined protocols to be developed. In addition, a strategy that differs from classical transition metal cross-coupling conditions would also allow for an expanded substrate scope to include electron-rich azoles, organoboranes, and alkyl, aryl, and benzyl/allyl halides to maximize synthetic route opportunities.[7]

Recently, alternative alkylating partners have been investigated, with carboxylic acids being a particularly attractive option.[8] Although they are abundant and provide a handle for accessing radicals and carbocations, their activation requires acyl group manipulations or strong oxidants to facilitate the decarboxylation. By contrast, C−H bonds represent the most prevalent functionality in organic compounds; accordingly, rendering them reactive for C−X bond formation would be greatly advantageous toward the goal of a streamlined reaction platform.[9] The primary advantage of C−H functionalization methods is a decrease in preparatory steps of reagents and eventual use for the rapid diversification of late-stage targets.

A handful of methods have demonstrated that single-electron oxidization of arenes can activate the benzylic C−H positions toward subsequent functionalization, albeit requiring high oxidation potentials.[10] In the past few years, a mechanistic strategy for expanding the C−H scope employs a hydrogen-atom transfer (HAT) event prior to a (radical) oxidation (i.e., radical−polar crossover, RPC).[11] Notably, the combination of HAT and RPC has been engineered into one catalytic cycle utilizing different HAT species: Lei and co-workers used the phenoxy radical of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ);[12] the Noël group employed a UV-activated decatungstate catalyst;[13] and the Stahl group leveraged a sulfonimide radical derived from *N*-fluorobenzenesulfonimide (NFSI) in conjugation with copper catalysis.[14] While all three methods proceed via a carbocation intermediate, noticeably lacking in the scope of each protocol is the formation of fully substituted centers arising from *in situ*-generated tertiary carbocations. Recently, our group,[15] concurrently with the Doyle group,[16] published a visible-light photoredox-catalyzed [HAT+RPC] mechanism that can engage classically weak nucleophiles, including fluoride, and readily forge fully substituted centers from tertiary C−H precursors. We hypothesized that the established platform could be extended to the formation of an array of *N*-benzyl azoles, including those bearing fully substituted centers. In addition, these works demonstrated the power of photoredox catalysis to mediate a formal hydride abstraction with two different types of HAT reagents: *tert*-butyl peroxybenzoate (TBPB) and *N*-acyloxyphthalimide. Thus far, only photoredox platforms have exhibited such modularity in the examination of stereoelectronically diverse HAT reagents for the [HAT+RPC] process. Herein we report the implementation of *N*-alkoxypyridinium salts in this process. Simple *N*-alkoxypyridinium salts can be readily prepared in one step and offer an electronically tunable HAT scaffold.[17,18] Finally, mechanistic evidence suggests that an electron-donor−acceptor (EDA) complex may be operable for

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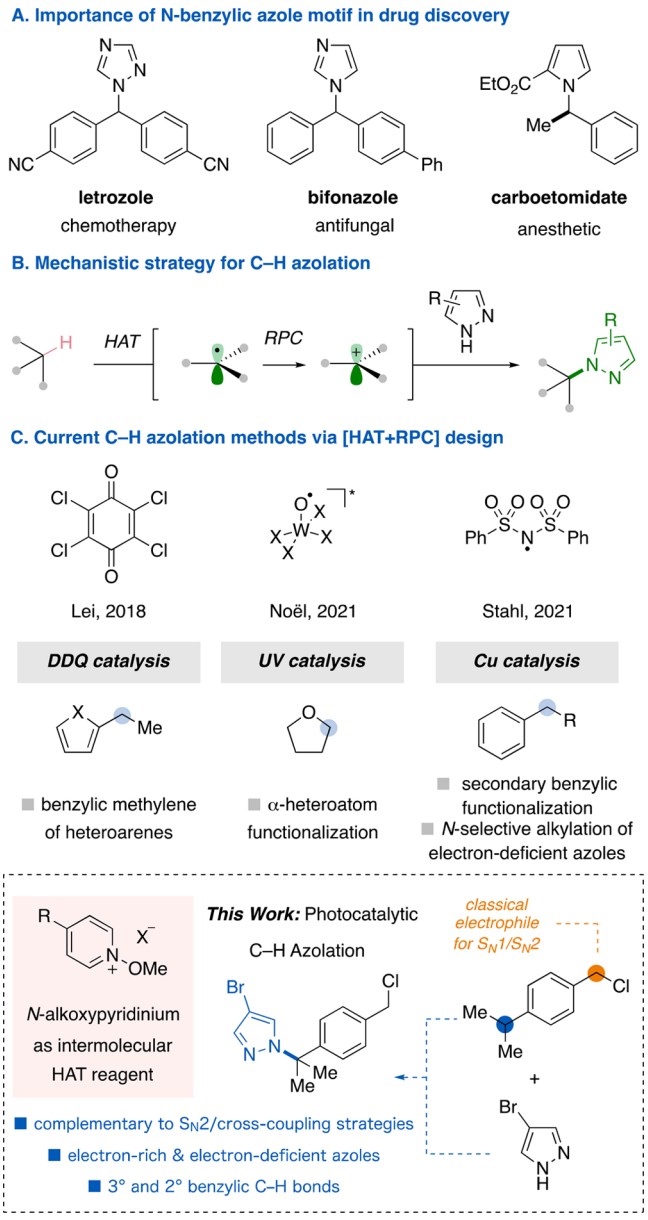

Figure 1. Background on C−H azolation methods. (A) *N*-benzyl azoles are attractive pharmaceutical motifs. (B) Recent mechanism for C−H functionalization. (C) Current C−H azolation methods utilizing [HAT+RPC].

activating the pyridinium reagents for certain electron-rich benzylic partners.[19]

Our efforts toward the development of a C−H azolation protocol initiated with the use of TBPB to facilitate the HAT event. Although successful in our prior work for C−H fluorination with nucleophilic fluoride (N = 10.8−13.2),[20] switching to less nucleophilic coupling partners such as pyrazoles (N = 8.9−9.6) resulted in competitive trapping of the carbocation by both benzoate (N = 16.8) and *tert*-butanol (N = 5.4)[5] byproducts (Figure 2A). Work by Hong,[21] Li,[22] and Lakhdar[23] has demonstrated that *N*-alkoxypyridinium reagents can facilitate intermolecular HAT processes at P−H, C(sp^2)−H, Si−H, and α-oxy C(sp^3)−H bonds.[24] We hypothesized that this reagent could also be used for the intermolecular abstraction of H· at benzylic C(sp^3)−H bonds in the desired transformation (Figure 2B). While *N*-

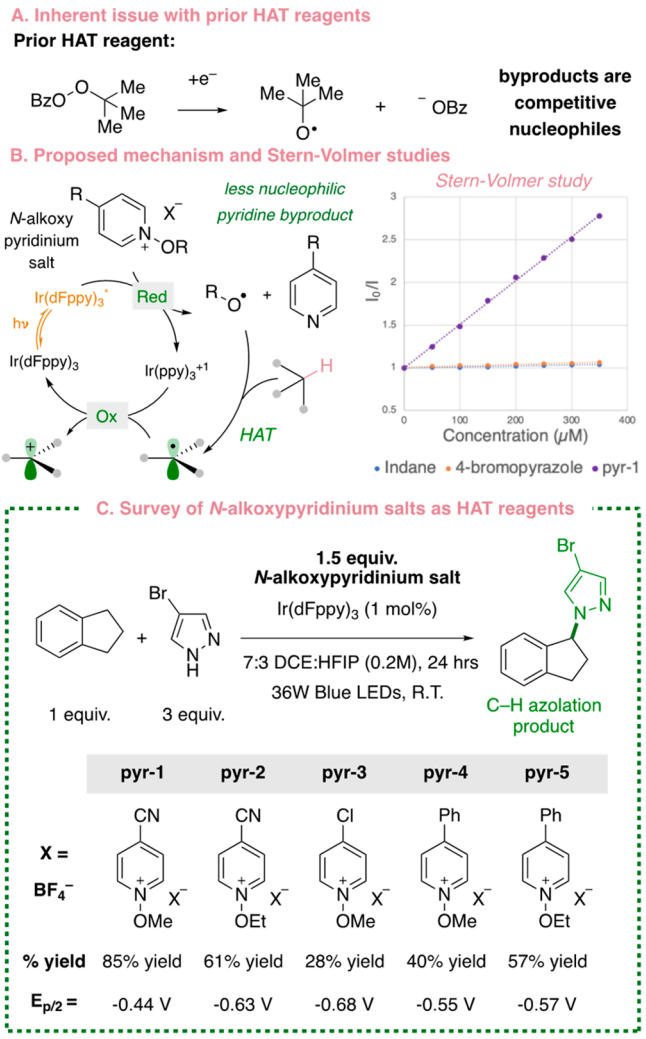

Figure 2. Optimization with *N*-alkoxypyridinium reagents. (A) Use of TBPB can lead to competitive nucleophiles. (B) Proposed mechanism and Stern−Volmer experiment. (C) Optimization of the *N*-alkoxypyridinium scaffold.

alkoxypyridiniums bearing long-chain alkyl groups have been used for intramolecular 1,5-HAT processes,[25] they have not been used widely for intermolecular efforts at C(sp^3)−H bonds.[22] The pyridinium reagents would be particularly attractive in the desired transformation, as reductive fragmentation would reduce the generation of competitive nucleophilic byproducts (Figure 2B). Accordingly, we rapidly synthesized a suite of *N*-methoxy- and *N*-ethoxypyridinum reagents.[26] With indane and 4-bromopyrazole as our model substrates, we delightfully observed the desired C−H azolation product (Figure 2C).

Electron-withdrawing *p*-cyanopyridinium **pyr-1** was discovered to result in higher product formation, possibly due to a lower reduction potential (see the Supporting Information). Stern−Volmer experiments corroborated an interaction between the excited state of the photocatalyst and **pyr-1**. Next, we explored the generality of the substrate scope.

Starting with an exploration of azoles (Figure 3), an array of electron-withdrawing groups at the 4-position of pyrazole were well-tolerated, including other halides (**2**−**4**), esters (**5**), and trifluoromethyl (**6**), cyano (**7**), and nitro groups (**8**). Substitution at the 3-position of pyrazole also resulted in

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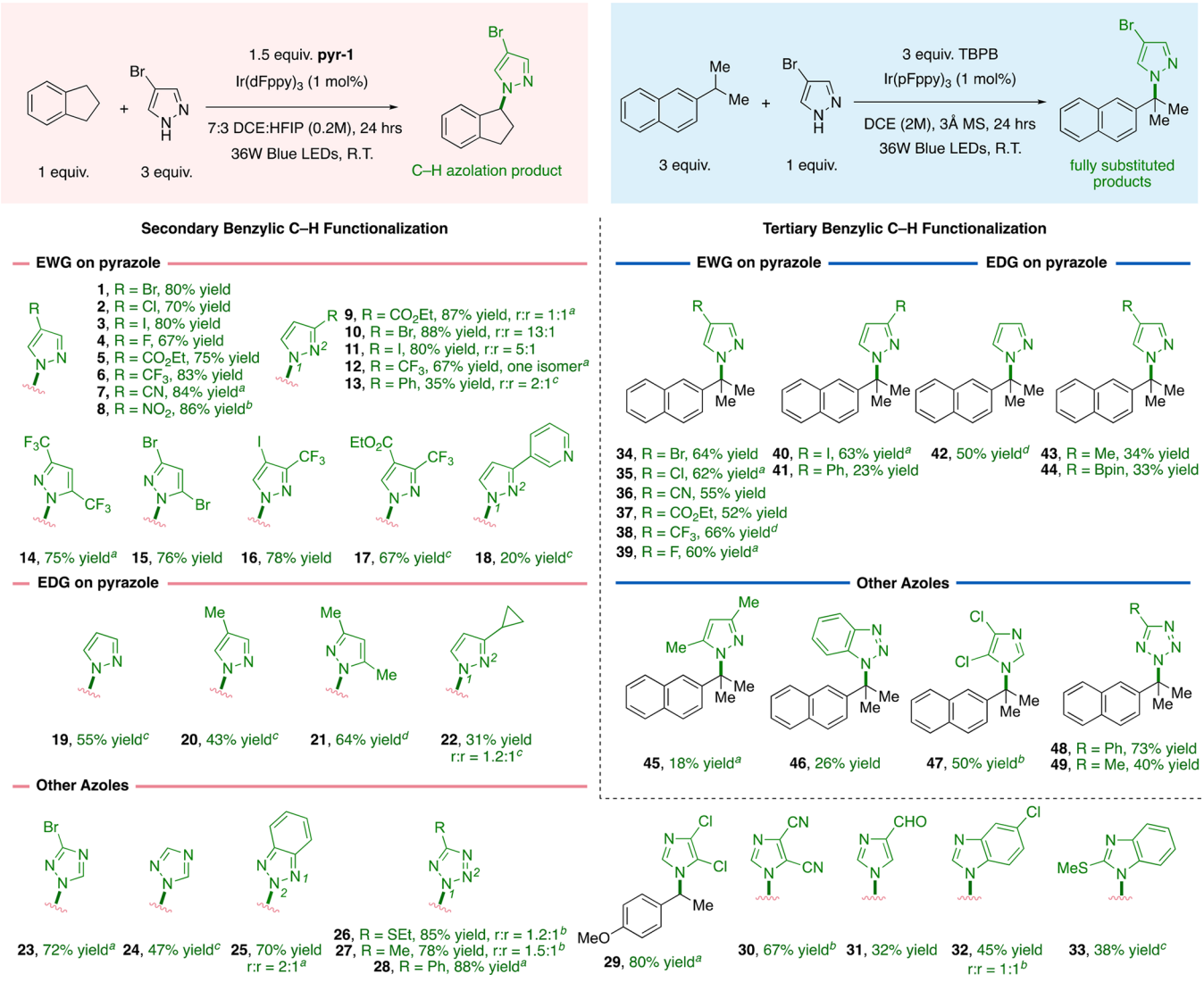

Figure 3. Azole scope for secondary and tertiary benzylic C−H substrates. Reactions were run on a 0.5 mmol scale. DCE = 1,2-dichloroethane. HFIP = hexafluoroisopropanol. [a]48 h. [b]72 h. [c]60 °C. [d]96 h.

good to excellent yields (**9**−**13**). Difunctionalized pyrazoles afforded high yields of the products (**14**−**17**), and an extended heterocycle was also successful in the protocol (**18**). Excitingly, more electron-rich pyrazoles were successfully alkylated with our system, representing a class of substrates that are not compatible with base-metal-catalyzed strategies due to potential catalyst poisoning (**19**−**22**). Furthermore, 1,2,3- and 1,2,4-triazoles ($N \approx 7.7$) were also viable nucleophiles, as was benzotriazole (**23**−**25**).[26] Substituted tetrazoles, imidazoles, and benzimidazoles were also viable substrates (**26**−**33**).

Given the minimal effect of steric hindrance observed, we questioned whether the photoredox-catalyzed [HAT+RPC] platform could enable the functionalization of tertiary benzylic C−H bonds. To the best of our knowledge, the synthesis of fully substituted carbon centers has not been reported in prior C−H azolation methods with the [HAT+RPC] formula, despite the enhanced carbocation stability. Classically, tertiary benzyl halides/tosylates are unstable and/or prepared with harsh reagents (strong acids) and expensive oxidants.[27] Moreover, the carboxylic acid equivalent of 2-isopropylnaphthalene is not widely available from commercial vendors. The use of C−H alternatives thus represents an advantage in terms of synthetic ease and available resources. Gratifyingly, 2-isopropylnaphthalene could be readily functionalized with a wide array of azoles using TBPB as the HAT reagent. Currently, we postulate that a methyl radical could be the most effective H-atom abstractor for tertiary benzylic C−H sites, which can be derived from ·O*t*Bu via a facile β-scission.[16,28] Various 4- and 3-substituted pyrazoles were successfully alkylated (**34**−**41**), with the latter being functionalized at the less sterically hindered nitrogen. Electron-rich pyrazoles also afforded the products in modest yields (**42**−**44**). Notably, **44** contains a nucleophilic arylboron functionality that would not be tolerated by transition metal approaches. Moreover, the strength of the carbocation strategy was highlighted with the alkylation of 3,5-dimethylpyrazole to give sterically congested adduct **45**, albeit in low yield. Finally, the protocol was also successful at producing fully substituted tetrazole, imidazole, and (benzo)triazole C−N adducts (**46**−**49**).[29]

Next, we examined the generality of the benzylic C−H scope. Methylene sites on both cyclic and acyclic precursors afforded appreciable yields of C−N products (**50**−**57**). Diphenylmethane, a common motif in drug targets (Figure 1a), worked in good yield (**51**). Electron-deficient functional

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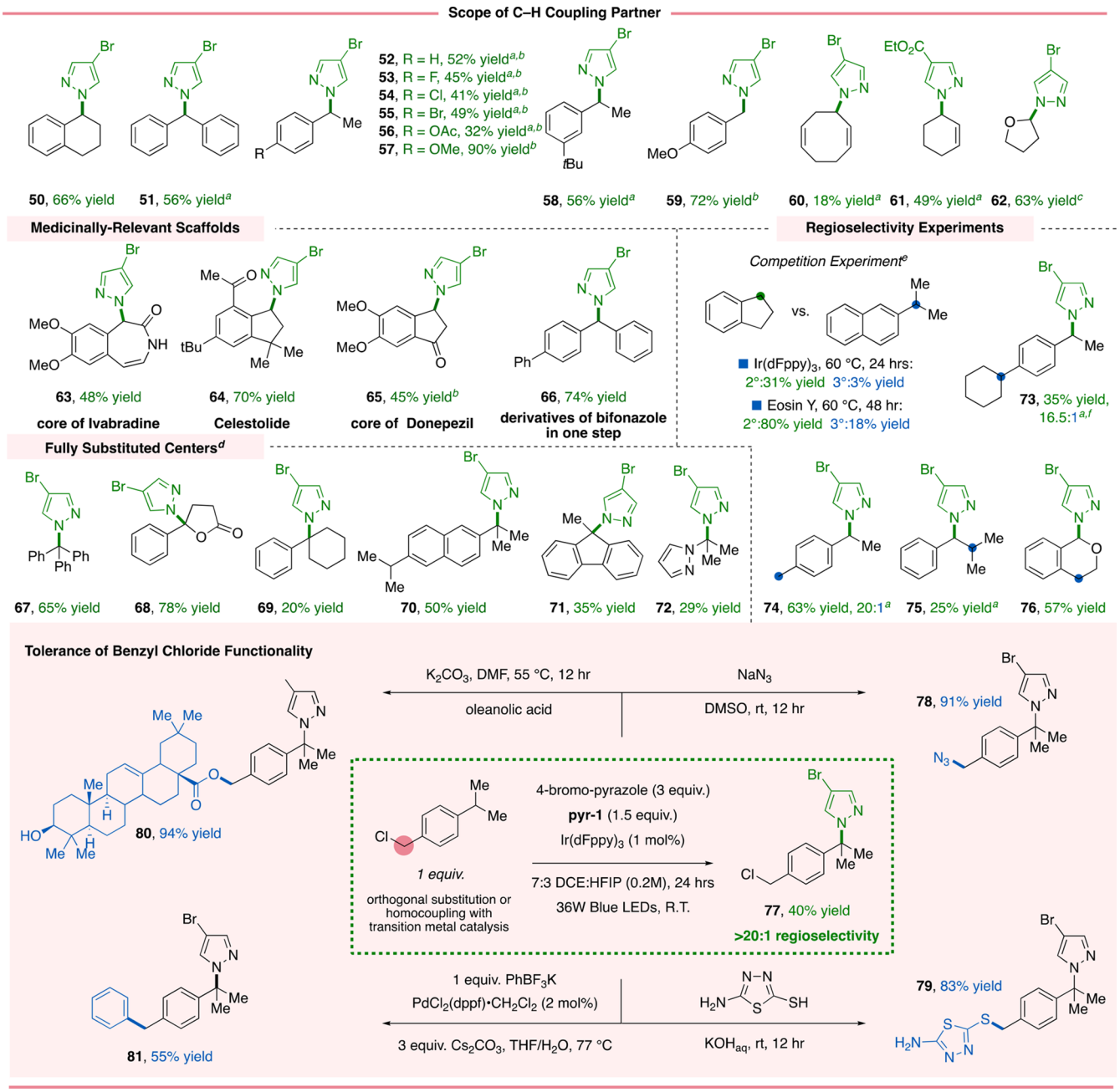

Figure 4. Scope of the C–H reaction partner. [a]60 °C. [b]48 h. [c]Tetrahydrofuran (5 equiv). [d]Conditions: hydrocarbon (3 equiv), azole (1 equiv), and TBPB (3 equiv) as indicated in Figure 3. [e]1 equiv of C–H precursor, azole (3 equiv), and **pyr-1** (1.5 equiv). [f]Eosin Y (5 mol %).

groups at the para position did not significantly hinder the reaction efficiency (**52**–**56**); nevertheless, higher yields were observed with electron-donating groups (**57**). Notably, our carbocation-generating protocol is permissible of aryl bromide and chloride motifs, allowing for the retention of functional handles for further derivatization via classical cross-coupling catalysis. Meta substitution was also well-tolerated (**58**). The primary benzylic substrate leading to **59** represents another class of substrates not demonstrated in other [HAT+RPC] strategies for azolation. C–H functionalization of allylic positions was achieved, giving **60** and **61** in 18% and 49% yield, respectively. Lastly, α-oxy C–H sites were also viable substrates for the visible-light-mediated azolation (**62**).

Next, we sought to apply the method to late-stage functionalization of pharmaceutical scaffolds. The seven-membered cyclic core of ivabradine, used in the treatment of heart failure, was successfully elaborated at the α-benzylic site in 48% yield (**63**). Celestolide (**64**, 70% yield) and the core of donepezil (**65**, 45% yield) also underwent C–H azolation with the [HAT+RPC] protocol in appreciable yields. Lastly, we demonstrated that azole derivatives of the antifungal agent bifonazole (**66**) can be readily prepared in one step from commercially available 4-benzylbiphenyl. These examples demonstrate the utility of direct functionalization of benzylic C–H bonds as opposed to the established multistep processes involving conversion of a benzyl alcohol to a benzyl chloride followed by harsh conditions.[30]

Next, an array of other tertiary benzylic C–H partners were translated to fully substituted products (**67**–**71**). γ-Phenyl-lactone gave sterically congested **68** in good yield, as did

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phenylcyclohexane (**69**). Monofunctionalization of compounds containing two tertiary benzylic sites was successful (**70**), and last, installation of a congested C−N center on 9-methylfluorene was realized (**71**). Notably, for substrates **68**−**71**, the corresponding benzyl chlorides or carboxylic acids are either commercially unavailable or prohibitively expensive. Excitingly, compound **72** was successfully prepared, demonstrating potential for the azolation of heteroarene C−H substrates.

To probe regioselectivity, a competition experiment was conducted. Using **pyr-1**, a preference for azolation at indane over 2-isopropylnaphthalene was observed. High selectivity for the secondary position of **73** (16.3:1) was congruent with this finding. The protocol appears to be selective for secondary benzylic C−H sites over primary benzylic (**74**) and aliphatic tertiary (**75**) sites and is completely selective for α-oxy benzylic positions over secondary benzylic ones (**76**; see the Supporting Information).

Finally, we sought to evaluate the specificity and orthogonality of our photocatalytic C−H azolation. Classically, letrazole and bifonazole are prepared via S_N2-type reactions on benzyl chlorides with heat and strong bases.[6,30] As depicted in Figure 4, this platform is sufficiently mild to tolerate the preparation of **77** in 40% yield with no detection of the S_N2 product (>20:1 regioselectivity). Subsequently, high yields were achieved for S_N2 azidation (**78**), thiolation (**79**), and esterification (**80**) substitution reactions. Furthermore, the benzyl chloride functionality could also serve as an electrophile in a Pd-catalyzed cross-coupling (**81**).[31]

Lastly, pyridinium salts have been reported to participate in EDA complexes.[18,23b,c,32] Control experiments suggested that when HFIP is added as a cosolvent, an EDA complex could be operable, on the basis of the observation of product without photocatalyst and an observed bathochromic shift in the UV−vis spectra (Figure 5b). Presumably, the EDA complex facilitates oxidation of the arene, which triggers fragmentation of **pyr-1** to release a methoxy radical. Subsequent HAT at the benzylic position of the resultant arene radical cation can generate the benzylic carbocation.[33] Further UV−vis studies indicated that only electron-rich substrates form an EDA complex (see the Supporting Information), suggesting that other substrates may follow a photocatalyst-mediated mechanism.

In conclusion, we have successfully developed a benzylic C−H azolation reaction via a photoredox-catalyzed formal hydride abstraction mechanism. An *N*-methoxypyridinium salt was used as an effective intermolecular HAT reagent at benzylic C(sp^3)−H bonds. We have demonstrated the generality of the method, as it includes the alkylation of a plethora of azoles. Additionally, a broad C−H partner scope was established, including the alkylation of secondary and tertiary benzylic C−H sites, the latter of which afford a direct and simplified route to *N*-*tert*-alkyl azole motifs. Importantly, we showcase the complementary nature of our reaction conditions to classical S_N2 and transition metal cross-coupling conditions, which are two current state-of-the-art technologies for forging alkylated azole products. Lastly, mechanistic studies suggest that a plausible EDA mechanism is operable for certain C−H substrates.

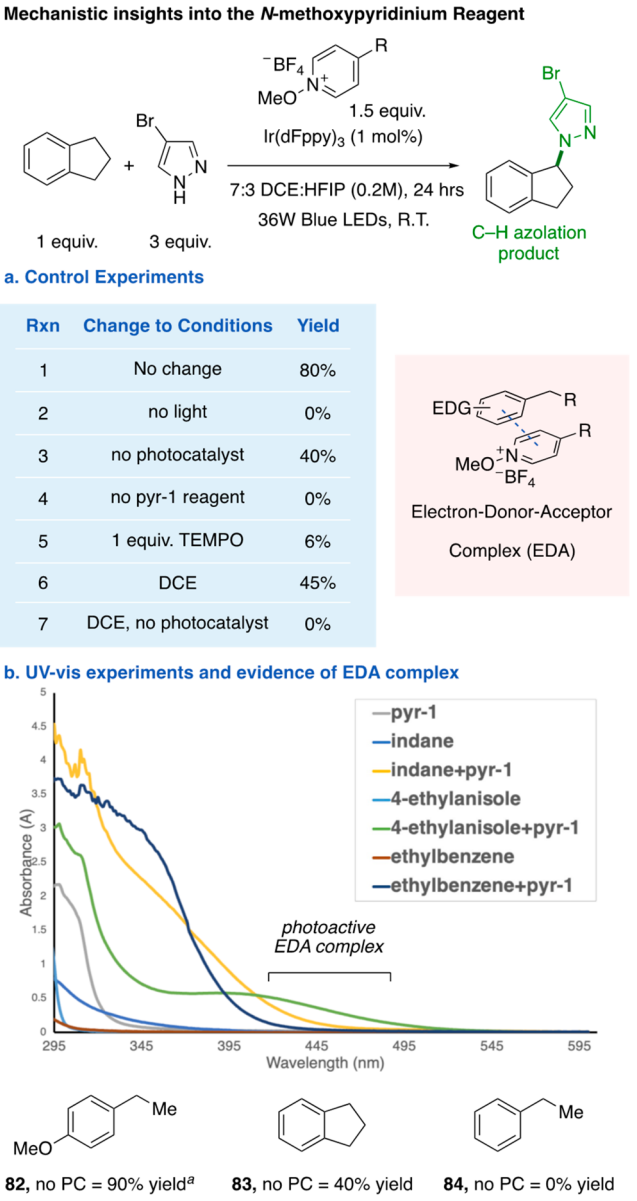

Figure 5. Mechanistic studies. (a) Control experiments for optimized conditions. (b) UV−vis experiments to probe for EDA complex formation and yields of substrates without photocatalyst (PC). [a]48 h.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c12850.

Additional experimental details, characterization data, optimization, and relevant spectra (PDF)

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Notes

The authors declare no competing financial interest.

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