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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

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

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 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*-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 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 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 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.

Supplementary Material

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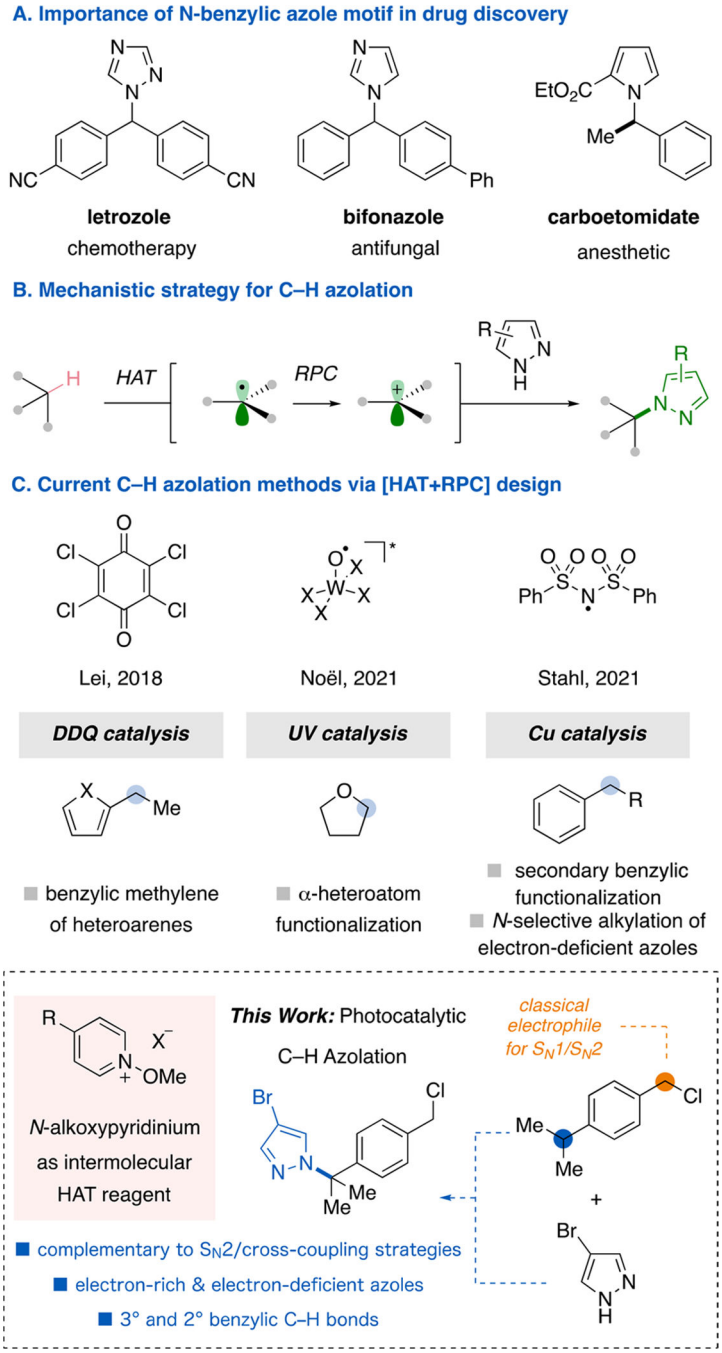

Figure 1.

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].

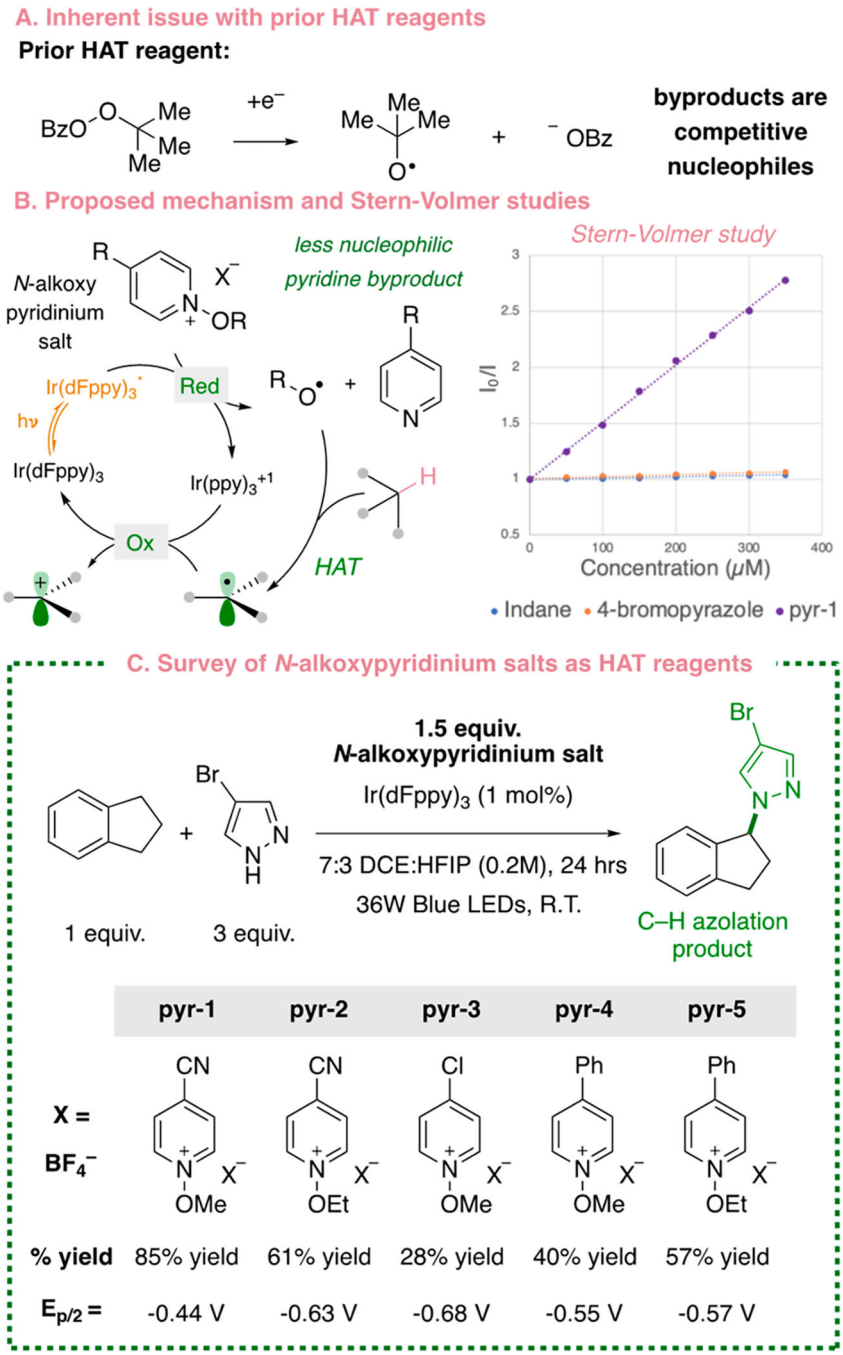

Figure 2.

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.

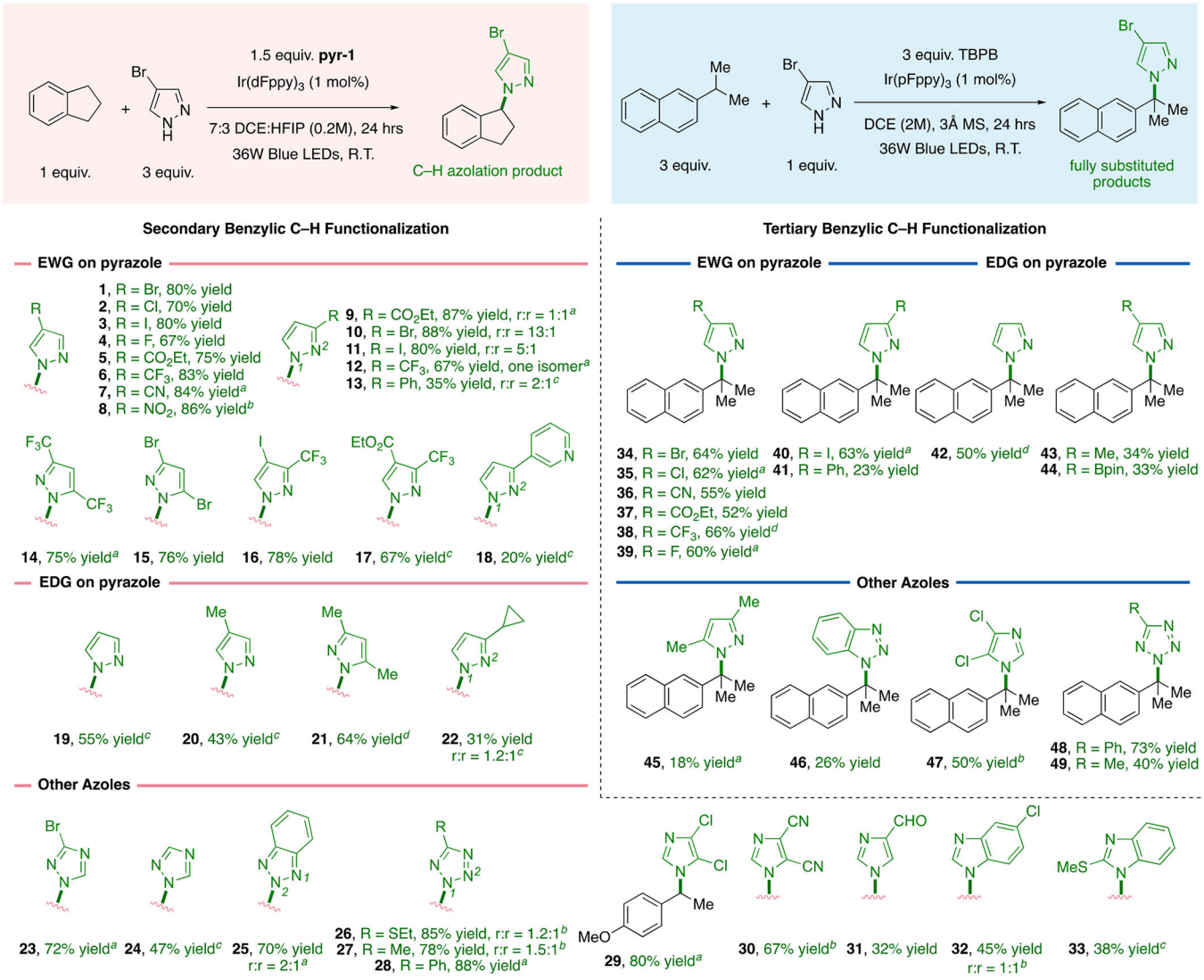

Figure 3.

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.

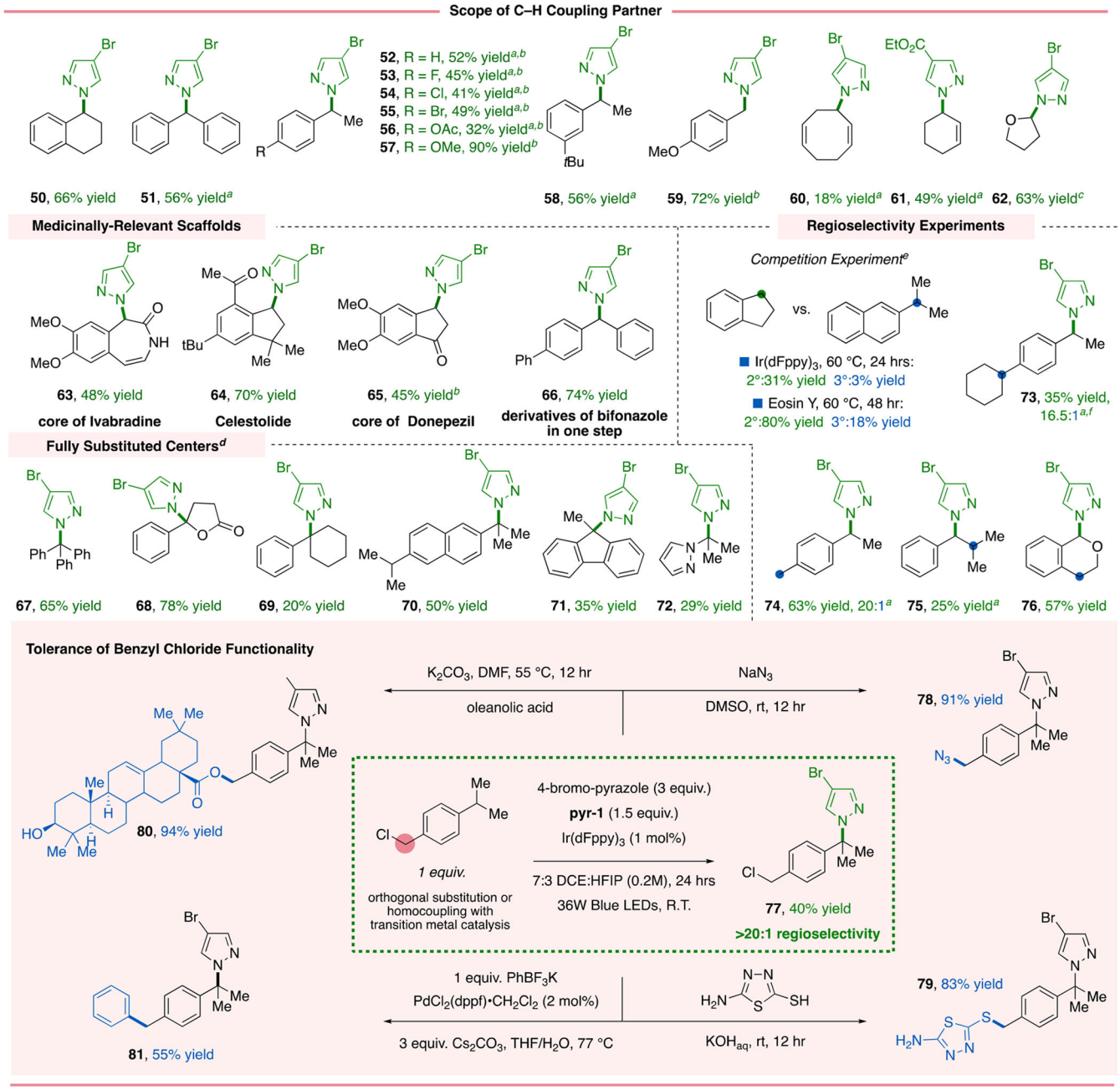

Figure 4.

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 %).

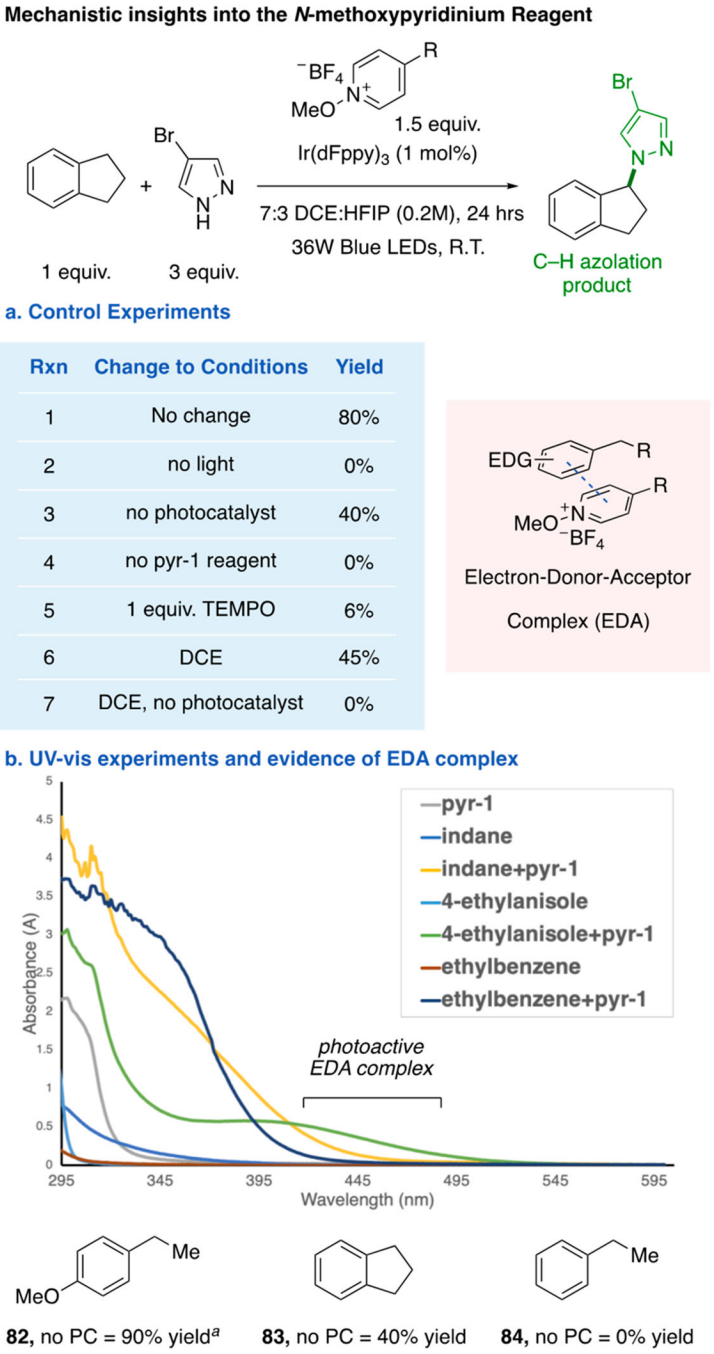

Figure 5.

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.