Cooperative Phosphine-Photoredox Catalysis Enables N–H Activation of Azoles for Intermolecular Olefin Hydroamination

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ABSTRACT: Catalytic intermolecular olefin hydroamination is an enabling synthetic strategy that offers direct and atom-economical access to a variety of nitrogen-containing compounds from abundant feedstocks. However, despite numerous advances in catalyst design and reaction development, hydroamination of N–H azoles with unactivated olefins remains an unsolved problem in synthesis. We report a dual phosphine and photoredox catalytic protocol for the hydroamination of numerous structurally diverse and medicinally relevant N–H azoles with unactivated olefins. Hydroamination proceeds with high anti-Markovnikov regioselectivity and *N*-site selectivity. The mild conditions and high functional group tolerance of the reaction permit the rapid construction of molecular complexity and late-stage functionalization of bioactive compounds. N–H bond activation is proposed to proceed via polar addition of the N–H heterocycle to a phosphine radical cation, followed by P–N α-scission from a phosphoranyl radical intermediate. Reactivity and *N*-site selectivity are classified by heterocycle N–H BDFE and nitrogen-centered radical (NCR) spin density, respectively, which can serve as a useful predictive aid in extending the reaction to unseen azoles.

INTRODUCTION

The prevalence of nitrogen heterocycles in natural products, pharmaceuticals, and agrochemicals, has fueled a demand for new methodologies that enable their synthesis and diversification.[1-3] While strategies for *N*-arylation of azoles have been extensively developed, fewer modern catalytic methods exist for *N*-alkylation.[4-7] *N*-Aryl azoles are much more common in pharmaceuticals than *N*-alkyl azoles, which may in part be due to the challenge of achieving mild, efficient, and selective azole alkylation. Regardless, given the growing recognition of the importance of C(sp^3) incorporation in new drugs and agrochemicals,[8-10] the development of broadly applicable methods for *N*-alkylation of N–H azoles represents an important goal.

Well-established approaches for N–C(sp^3) bond formation rely on nucleophilic addition of *N*-centered nucleophiles to an electrophile, such as an alkyl (pseudo)halide or carbonyl compound.[11] However, the low nucleophilicity of N–H azoles often necessitates harsh reaction conditions that are incompatible with incorporation of secondary or tertiary aliphatic substituents and are not applicable in complex settings.[12, 13] Recently, photo- and electrochemical methods have emerged as a powerful alternative approach toward azole *N*-alkylation with a diverse set of electrophiles, providing regioselective product formation under mild conditions.[14-16] These strategies typically rely on the formation of *C*-centered radicals or carbocation intermediates from abundant precursors, such as alkyl halides, alkyl carboxylic acids, alkanes, or redox-active esters (**Figure 1**A). Even with the development of these important synthetic technologies, there is a need for mechanistically distinct approaches that show tolerance across many medicinally relevant heterocycle classes, enable access to products with complementary chemo- and regioselectivity, and engage different classes of feedstocks.

Intermolecular olefin hydroamination represents an attractive strategy for the alkylation of N–H azoles due to its atom-economy and the availability of olefin feedstocks.[17] However, because most N–H substrates and olefins are nucleophilic, a catalyst is necessary to mediate their reaction.[18] Numerous advances have been made in transition metal-catalyzed intermolecular hydroamination, but only a single report describes the reaction of an N–H azole class, N–H indoles, with unactivated olefins.[19] Although remarkable, the scope is limited to indoles and only accommodates terminal olefins with Markovnikov selectivity. Similarly, important progress has been made in photocatalytic hydroamination with heterocycles via nucleophilic addition to an olefin radical cation, but no reports demonstrate formation of *N*-alkylazole products using unactivated olefins (**Figure 1**B).[20] A complementary approach involves the formation of electrophilic *N*-centered radicals (NCRs), since their reaction with unactivated olefins is polarity matched.[21, 22] The Knowles group, amongst others, has contributed new photocatalytic approaches to N–H activation of a variety of classes of amines and (sulfon)amides.[23] However, N–H azoles have not been reported. Recent work by the groups of Zhang[24] and Chen[25] have demonstrated the feasibility of alkene hydroamination via heterocylic NCRs using *N*-functionalized azoles, such as *N*-pyridinium salts and hydroxybenzotriazoles, respectively. Thus, identification of a mild and general strategy for N–H bond activation of azoles could prove highly enabling in the development of this and numerous other reactions that deliver medicinally relevant heterocyclic products.

The Doyle group recently reported a phosphine-photoredox catalytic platform that activates N–H bonds of primary sulfonamides (BDFE ~105 kcal/mol) and delivers NCRs via α-scission of the P–N bond of a phosphoranyl radical intermediate.[26] We questioned whether this strategy could be extended to N–H azoles and selected to evaluate substrates with a wide range of N–H BDFEs (68–117 kcal/mol) (**Figure 1**C). Nevertheless, the ambident reactivity of many N–

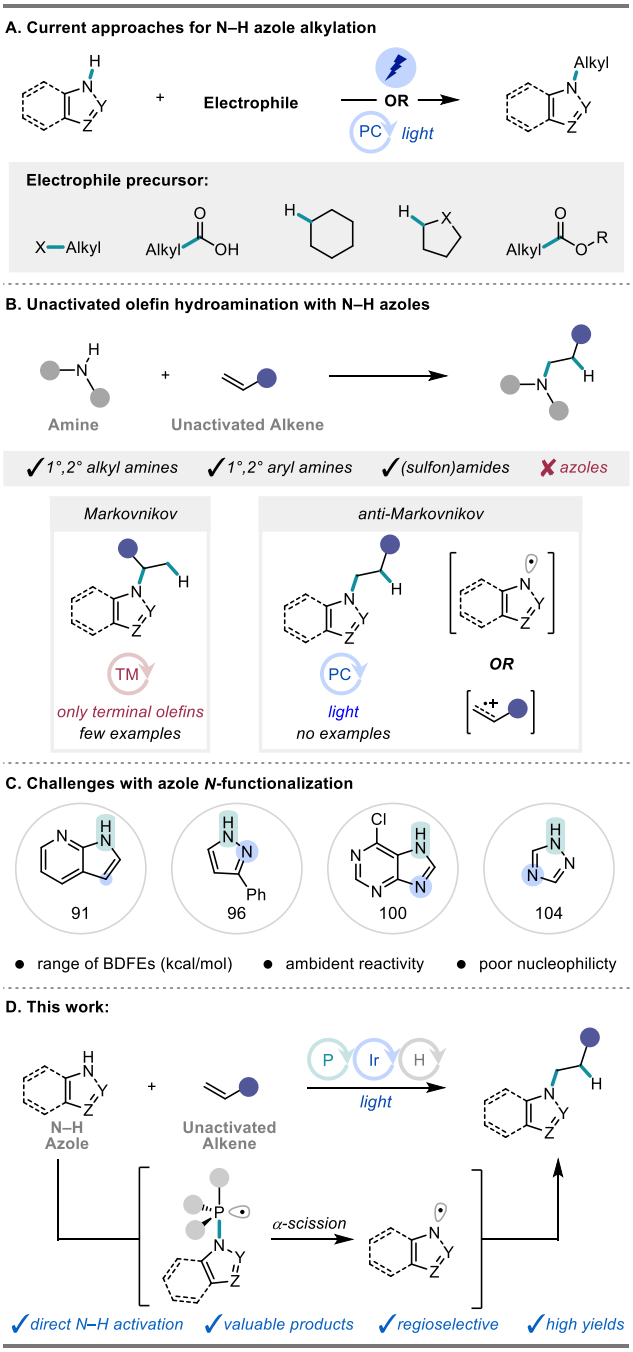
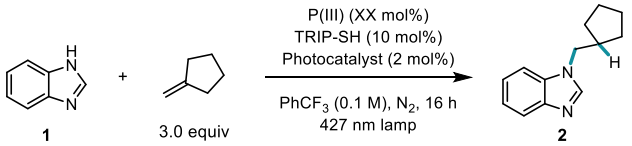


Figure 1. Synthesis of *N*-alkylazoles and limitations.

H azoles and their low nucleophilicity presents a potential challenge to their use under this protocol; nucleophilic addition to a phosphine radical cation affords the phosphoranyl radical intermediate and we had previously found that this step was sensitive to the steric hindrance of sulfonamide substrates, where primary sulfonamides reacted selectively over secondary sulfonamides. Despite this concern, we anticipated that the modularity of the dual catalytic system would offer an opportunity to identify an efficient protocol. Here we demonstrate a general method for *N*-alkylation of a variety of azoles by intermolecular anti-Markovnikov hydroamination of unactivated olefins using the combination of phosphine and photoredox catalysts under visible light irradiation (**Figure 1**D).

Table 1. Optimization Studies



Entry[a]	Phosphine	(P mol%)	Photocatalyst	Yield (%)[b]
1	PCy_3	2.5	PC 1	55
2	PCy_3	5	PC 1	59
3	PCy_3	10	PC 1	71
4	PCy_3	20	PC 1	38
5	PCy_3	40	PC 1	32
6	PAd_2*n*-Bu	10	PC 1	45
7	PAd_3	10	PC 1	45
8	PCy_2Ph	10	PC 1	58
9	BrettPhos	10	PC 1	2
10	DavePhos	10	PC 1	0
11	PPh_3	10	PC 1	8
12	PCy_3	10	PC 2	32
13	PCy_3	10	PC 3	16
14[c]	PCy_3	10	PC 1	**82**
Entry[a]	**Deviation from optimal conditions (Entry 3)**			**Yield (%)[b]**
15	No Phosphine			0
16	No Photocatalyst			0
17	No TRIP-SH			0
18	No Light			0

PC 1: $[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$; $*Ir^{III}/Ir^{II}$ = +0.97 V vs SCE

PC 2: $[Ir(ppy)_2(dtbbpy)]PF_6$; $*Ir^{III}/Ir^{II}$ = +0.66 V vs SCE

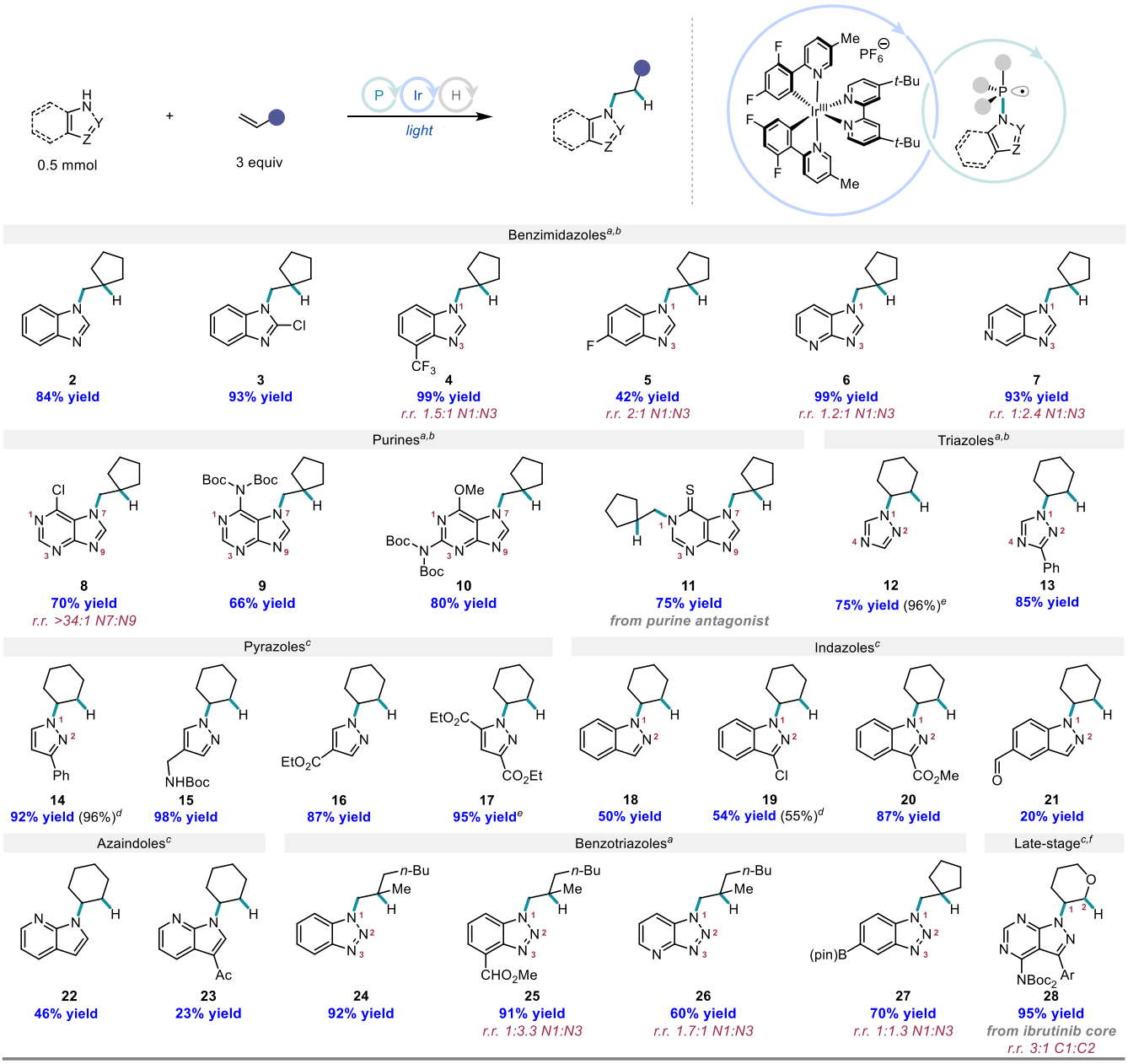
PC 3: $[Ir(dF(CF_3)ppy)_2(4,4'\text{-}dCF_3bpy)]PF_6$; $*Ir^{III}/Ir^{II}$ = +1.65 V vs SCE

[a]Reactions were performed on a 0.1 mmol scale with 1.0 equiv of benzimidazole and 3.0 equiv of methylenecyclopentane under irradiation with 427 nm lamp (34 W) at 50% light intensity. [b]Yield was determined by ^{1}H NMR spectroscopic analysis against 1,3,5-trimethoxybenzene as an internal standard. [c]427 nm lamp intensity set to 100% instead of 50%.

RESULTS AND DISCUSSION

Reaction Development. We commenced reaction optimization using benzimidazole (**1**) and methylenecyclopentane as model substrates. On the basis of our previously disclosed sulfonamide hydroamidation, we first explored the use of tricyclohexylphosphine (PCy_3), $[Ir(dF(Me)ppy)_2(dtbbpy)]PF_6$ ($*Ir^{III}/Ir^{II}$ = +0.97 V vs SCE in MeCN), and tri*iso*propylbenzenethiol (TRIP-SH) as catalysts for the transformation. Hydroamination product **2** was formed in 55% yield using 2.5 mol% PCy_3, 2 mol% photocatalyst, and 10 mol% TRIP-SH with a 427 nm lamp (34 W) at 50% intensity (**Table 1**, entry 1). While an increase in product yield was observed when the phosphine loading was increased from 2.5 to 10 mol%, increasing the loading further led to a decrease in product formation, presumably due to competitive addition of phosphine to the phosphine radical cation (**Table 1**, entries 2–5). Alternative commercially available trialkylphosphines also provided *N*-alkylated product in good yield (**Table 1**, entries 6–7). Although dicyclohexylphenylphosphine (PCy_2Ph) afforded **2** in 58% yield, phosphines with more complex aryl substituents,

Scheme 1. Azole Scope.



Reactions were performed on a 0.5 mmol scale reacting 1.0 equiv of azole with 3.0 equiv of olefin using PCy_3 (10 mol%) or PPh_3 (20 mol%) with $[Ir(dF(Me)ppy)_2dtbbpy]PF_6$ (2 mol%), and TRIP-SH (10 mol%) irradiating with a 427 nm lamp at 50% intensity for 16 hours. Isolated yield reported as an average of two runs. [a]PCy_3 was used as phosphine catalyst. [b]427 nm lamp light intensity was set to 100%. [c]PPh_3 was used as the phosphine catalyst. [d]Yields are reflective of reactions set-up using Schlenk technique instead of in a glovebox. [e]Yield determined by ^1H NMR with comparison to internal standard. [f]Ar = *p*-Ph–O–Ph.

such as BrettPhos and DavePhos, were essentially unreactive (**Table 1**, entries 8–10). Moreover, triphenylphosphine (PPh_3) formed product in only 8% yield (**Table 1**, entry 11). Examining photocatalysts with various excited-state oxidation potentials demonstrated that **PC 1** is optimal for this method, presumably because it delivers a strong driving force for the generation of the phosphine radical cation (**Table 1**, entries 12–13). Product formation was improved to 82% yield when the light intensity of the 427 nm lamp (34 W) was increased from 50% to 100% (**Table 1**, entry 14). Finally, control experiments indicated that no product formation occurs in the absence of phosphine catalyst, photocatalyst, hydrogen atom transfer (HAT) catalyst, or irradiation (**Table 1**, entries 15–18).

Azole Scope. With the optimized protocol in hand, we investigated the scope of *N*-alkylation with various azole classes. Notably, we found that for certain N–H azoles, use of 20 mol% PPh_3 instead of PCy_3 under otherwise identical reaction conditions was necessary to achieve efficient hydroamination (See SI for details). Moreover, results employing PPh_3 as the catalyst were reproducible using Schlenk technique, as indicated in **Scheme 1**. We first examined substituted benzimidazoles and discovered that substituents at

numerous positions around the ring are compatible with the method. A 93% yield of **3** was obtained using 2-chlorobenzimidazole, a common precursor for the synthesis of antihistaminic norastemizole. Fluorinated substrates substituted at the 4- and 5-positions, such as 4-trifluoromethylbenzimidazole and 5-fluoro-benzimidazole, provided *N*-alkylated products **4** and **5** in 99 and 42% yield, respectively. Moreover, 4- and 5-azabenzimidazoles have been shown to have medicinal significance due to their biophysical and biochemical properties among a multitude of diseases.[27] We found that these N–H azoles delivered products **6** and **7** in excellent yield. Unfortunately, low *N*-site selectivity is observed for the hydroamination of unsymmetric benzimidazoles. However, we found that the regioisomers are separable by chromatography and thus offer an opportunity to access a library of *N*-alkylated benzimidazoles from readily available precursors. With the success of benzimidazoles, we set out to explore the compatibility of our method with other privileged N–H azoles.

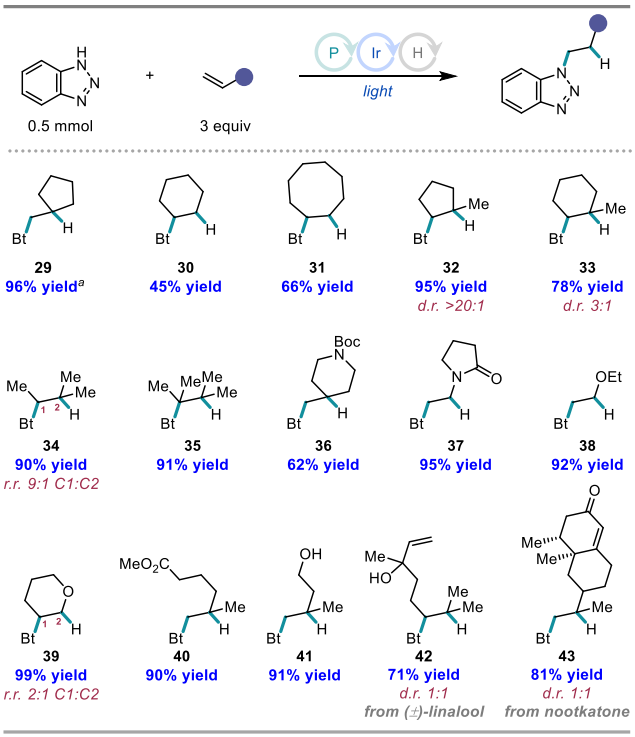
Purines are the most abundant nitrogenous azoles in nature, serving as constituents of nucleic acids.[28] Current approaches to N^7-alkylated purines rely on laborious synthetic manipulations or methods that provide the N^9-alkylated isomer as the major product.[29, 30] Therefore, we were excited to find that purines were not only competent substrates for the phosphine/photoredox hydroamination protocol, but they also delivered high N^7-alkylation selectivity as confirmed by X-ray structure determination. For example, readily available 6-chloropurine afforded **8** in 70% yield with nearly exclusive N^7 selectivity (>20:1 N^7:N^9). Derivatives of adenine, guanine, and 6-mercaptopurine also afforded products in high yields (**9**–**11**).

As triazoles, pyrazoles, and indazoles have been frequently employed in medicinal chemistry, we investigated these N–H azole classes as well. Although these azoles tend to be plagued with ambident reactivity, where multiple *N*- and *C*- atoms are reactive, the hydroamination reaction of these nucleophiles delivered exclusive N^1-alkylated isomers. Unsubstituted 1,2,4-triazole and 3-phenyltriazole were converted to products **12** and **13** in high yields. Moreover, pyrazoles bearing phenyl (**14**), carbamate (**15**), and ester (**16**–**17**) substituents were well-tolerated. Unsubstituted indazole (**18**) and 3-substituted indazoles **19** and **20** also underwent hydroamination in good yields. Finally, as a testament to the mild conditions and complementary functional group tolerance of this method compared to polar chemistry and transition metal catalysis for *N*-alkylation, we found that an aldehyde-functional group was tolerated, delivering indazole derivative **21**, albeit in 20% yield.

We then turned our attention to 7-azaindole, a well-established motif within various anti-cancer agents, and benzotriazoles, which are also important building blocks for drug discovery.[31] Both heterocycles are competent substrates under the hydroamination conditions. 7-azaindoles deliver exclusive *N*- rather than *C*-alkylated products **22** and **23**. Benzotriazole was found to react with 2-methylheptene to provide **24** in 92% yield with exclusive N^1-alkylation. However, modest N^1 and N^3 selectivity was observed when using substituted benzotriazoles as substrates (**25** and **26**). Additionally, 5-pinacol boronic ester-benzotriazole formed product **27** in 30% yield, demonstrating compatibility of labile functionality to the reaction conditions and delivering a product with a modular handle for further diversification. Finally, to highlight the versatility of the method for late-stage synthesis, we tested *N*-alkylation of the Boc-protected heterocyclic core of ibrutinib. The hydroamination protocol could enable the generation of a library of N^1-alkylated ibrutinib derivatives at a late-stage as highlighted by the synthesis of **28,** which was formed in 95% yield, and features an N^1-tetrahydropyran whereas ibrutinib possesses an N^1-piperidine.

Olefin Scope. Next, we evaluated the scope of the olefin partner using benzotriazole,[32] a useful heterocyclic building block with applications in pharmaceuticals,[33] corrosion inhibitors,[34] materials,[35] and supramolecular ligands (**Scheme 2**).[36] Both linear and cyclic 1,1-disubstituted olefins are highly reactive in this system providing **24** and **29** in 92% and 96% yield, respectively. Cyclohexene and cyclooctene afforded **30** and **31**, demonstrating that internal olefins of various ring sizes are competent coupling partners. Additionally, cyclic and acyclic trisubstituted olefins afforded the desired hydroamination products **32**–**34** in 78–95% yield and tetramethylethylene reacted to give **35** in excellent yield. Notably, **34** was obtained as separable regioisomers, delivering anti-Markovnikov and Markovnikov products in a 9:1 ratio. DFT computations were consistent with the experimental ratio and support that the product selectivity is dependent on the rate of NCR addition to the olefin (See SI for details).

Scheme 2. Olefin Scope.



Reactions were performed on a 0.5 mmol scale reacting 1.0 equiv of benzotriazole with 3.0 equiv of olefin using PCy_3 (10 mol%) with $[Ir(dF(Me)ppy)_2dtbbpy]PF_6$ (2 mol%), and TRIP-SH (10 mol%) irradiating with a 427 nm lamp at 50% intensity for 16 hours. Isolated yield reported as an average of two runs. [a]Yield reproduced after 2 hours using standard conditions.

We also observed that a wide variety of functional groups were well-tolerated on the olefin partner, including carbamates (**36**), lactams (**37**), acyclic (**38**) and cyclic ethers (**39**), as well as esters (**40**) and unprotected primary alcohols (**41**). (±)-Linalool underwent regioselective hydroamination favoring reaction at the more electron-rich trisubstituted olefin in the presence of the monosubstituted olefin (**42**). Nootkatone, an insect repellant, also reacts in good yield with exclusive addition of benzotriazole to the 1,1-disubstituted olefin over the α,β-unsaturated ketone (**43**). Although this reaction is applicable to a variety of alkene partners, monosubstituted terminal aliphatic and styrenyl olefins represent limitations of the current protocol. Overall, this method offers a new strategy to access a diverse array of valuable products from N–H azoles and unactivated or electron-rich olefins.

Mechanistic Investigation. On the basis of our prior mechanistic work on sulfonamide hydroamination and the similarity in reaction conditions between the N–H azole and sulfonamide hydroaminations, we envisioned the catalytic cycle depicted in **Figure 2**A. Blue light irradiation of the iridium photocatalyst, followed by single-electron transfer (SET) between the excited photocatalyst and phosphine **A** delivers a reduced photocatalyst and phosphine radical cation **B**. Subsequent nucleophilic addition of azole **D** would form phosphoranyl radical intermediate **C**. α-Scission of the P–N bond of **C** regenerates the phosphine catalyst **A** and liberates an *N*-centered radical **E**. C–N bond formation between **E** the olefin partner furnishes a *C*-centered radical **F** that undergoes HAT with the thiol catalyst. SET of thiyl radical **I** with the reduced photocatalyst, followed by proton transfer (PT) regenerates the HAT catalyst and completes the catalytic cycle.

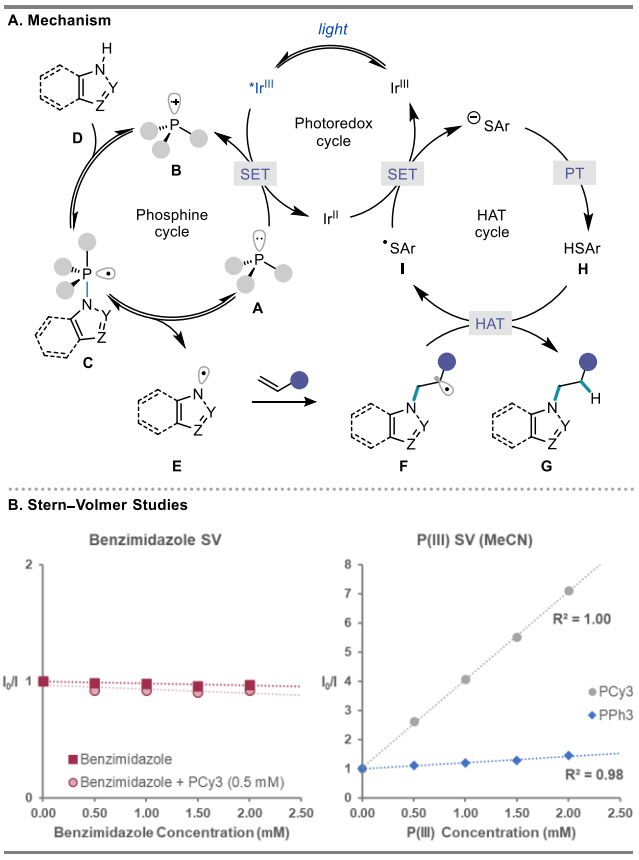


Figure 2. Mechanism and Stern–Volmer studies.

In addition to phosphorus-mediated α-scission, we considered two other mechanistic scenarios: 1) direct oxidation of the N–H azole substrate by the excited photocatalyst and 2) N–H activation via a proton-coupled electron transfer (PCET) pathway. We conducted Stern–Volmer studies to assess both pathways using the photocatalyst and four azole classes: benzimidazole, benzotriazole, indazole, and 7-azaindole. In all cases, we observed that the photocatalyst is not quenched by the azole substrate alone nor when combined with the corresponding phosphine at a constant concentration, as showcased for benzimidazole (**Figure 2**B, *left*). In contrast, the excited photocatalyst undergoes concentration-dependent quenching by PCy_3 and PPh_3, which is consistent with the formation of a phosphine radical cation, a key intermediate in the proposed mechanism (**Figure 2**B, *right*). Altogether, the studies support the proposed catalytic cycle.

During the course of our scope studies, we collected reactivity data on the hydroamination of cyclohexene or methylene cyclopentane with 105 substituted N–H azoles, some of which showed limited or no reactivity under the standard reaction conditions (see SI for full list). We therefore sought to build a model that could identify unreactive substrates ahead of experimental evaluation and offer mechanistic insight into the factors governing reactivity and selectivity. We posited nucleophilicity of the azole could dictate the rate of addition to the phosphine radical cation and pK_a may influence the deprotonation step necessary to form the phosphoranyl radical intermediate. Additionally, the N–H BDFE relates to the thermodynamics of the α-scission step and the *N*-atom charge could be responsible for the rate of olefin addition to generate the C–N bond.[37] To investigate these hypotheses, we used DFT computations on the N–H azoles to extract molecular and atomic properties such as pK_a, atomic charge, and N–H BDFE.

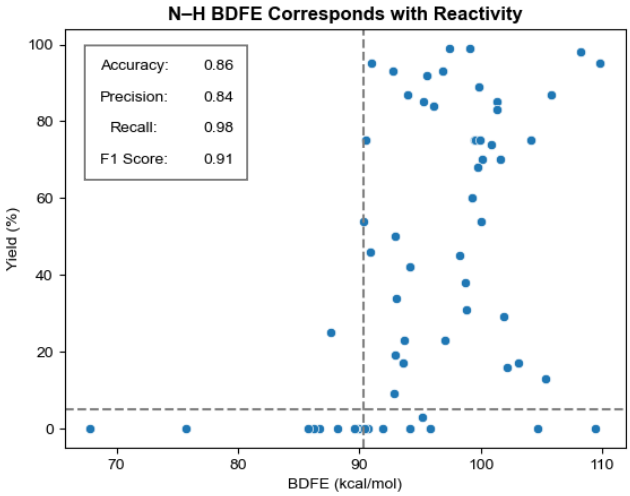


Figure 3. N–H BDFE corresponds with reactivity.

After removing substrates bearing incompatible functional groups (amides, anilines, bromides, and iodides), we observed a reactivity threshold with the BDFE of the N–H azole, where substrates with BDFEs below ~90 kcal/mol are unreactive (**Figure 3**). Due to the relation of N–H BDFE values and NCR stability, it is likely that azoles with BDFEs

below the threshold have high concentrations of the NCR relative to phosphoranyl radical; reversible or slow addition of these NCRs to the alkene could lead to unproductive back-electron transfer (BET) or other decomposition pathways. One false negative is found in this classification. This substrate, 3-phenylindazole, is structurally similar to other reactive azoles and possesses stronger concentration of the HOMO and spin density on nitrogen, which may make up for the low BDFE. Conversely, the false positive examples in the classification have HOMOs that are not concentrated on the *N*-atom expected to undergo alkylation (See SI for details). Thus, while it is likely a combination of multiple factors that lead to productive reactivity, this simple BDFE classification can serve as a predictive tool for pre-screening N–H azoles that are likely to be effective under the catalytic protocol.

Finally, we questioned the origin of regioselectivity for ambident azoles. We posited that high concentration of spin density relates to the favorable site of reactivity. Indeed, NCR spin density calculations are consistent with this proposal, wherein the major isomer of *N*-alkylation corresponds to the *N*-atom with highest spin density in the NCR. However, differences in spin density do not capture the magnitude of the experimental selectivity observed (**Figure 4**) (See SI for details).

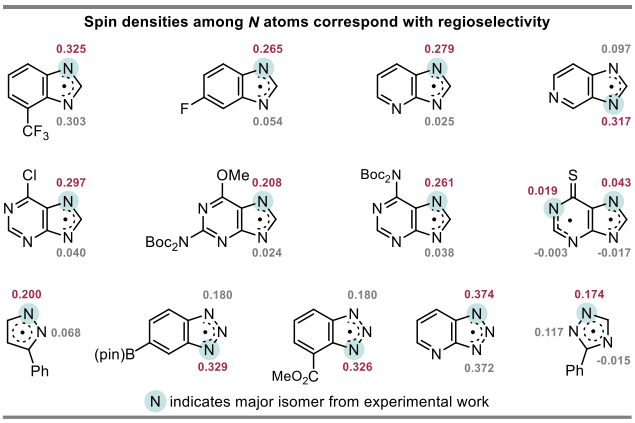


Figure 4. NCR spin densities and regioselectivity. Calculations performed at the (U)M06-2X/Def2-TZVP/SMD(Toluene)//(U)M06-2X/Def2-SVP level of theory.

CONCLUSION

In conclusion, we have showcased the application of phosphine-photoredox catalysis to the generation of *N*-centered radicals from a variety of azole classes via activation of N–H bonds. The catalytic protocol was applied to the chemo- and regioselective synthesis of valuable *N*-alkylated azoles via the intermolecular anti-Markovnikov hydroamination of unactivated olefins. Mechanistic studies support the azole radical generation proceeds via α-scission of a phosphoranyl radical intermediate. A threshold was identified for reactivity which correlates well with N–H BDFEs. Moreover, regioselectivity corresponds with NCR spin density. This study expands the synthetic utility of the phosphoranyl radical α-scission activation mode.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, experimental data, and characterization and spectral data for new compounds (PDF).

Data from quantum mechaniscs calculations (.csv)

Accession Codes

CCDC 2341285 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc. cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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