Iodine(III)-Mediated Photochemical C-H Azolation

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Abstract: Radical chemistry is an important enabling tool for organic synthesis but can be plagued by the lack of comprehensive polarity and therefore reactivity analysis scheme. Herein we have formulated a systematic radical polarity analysis framework for the projection of radical reactivity patterns. An iodine(III)-mediated photochemical C-H azolation reaction has been envisaged and developed based on the set of empirical guidelines. The synthesis features an environmentally benign reagent, a mild reaction condition, an operationally simple protocol, and a broad substrate scope. The inclusive demonstration of reactivity for ether, thioether, amide, benzylic, and allylic C-H bonds promises synthetic utility in a pervasive range of application settings.

Keywords: Radical Polarity Analysis; C-H Azolation; Iodine(III) Reagent; Photochemical Reaction; Ether, Thioether, Amide, Benzylic, and Allylic C-H Bonds.

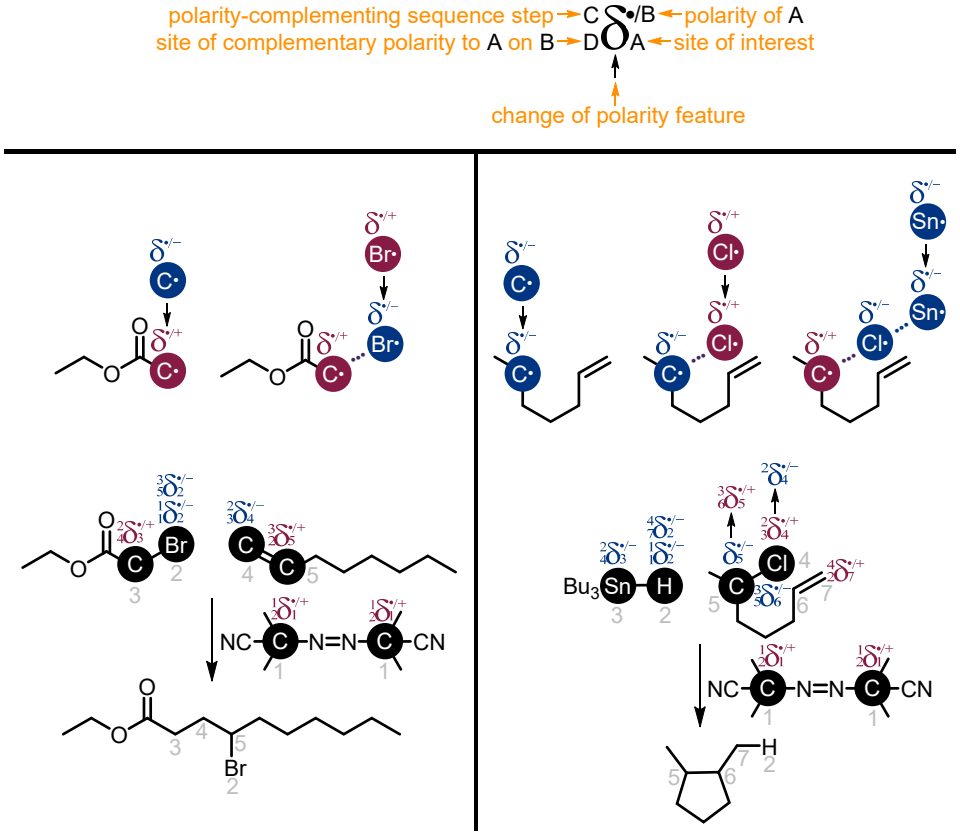
Radical chemistry is an important branch of organic transformations that involves the reactive species of unpaired electrons.[1] This reaction modality has contributed to the development of innovative synthetic methodologies of significant scientific and industrial values.[2] Despite the tremendous advances, an enduring perception of radical reactions as the chaotic and intractable events prevents rational deliberation of the radical reactivity patterns. Indeed, radical reactions are typically illustrated with the association and dissociation of atomic and molecular fragments; a methodical thermodynamic and kinetic metric is generally adopted to account for the bonding and bond dissociation processes; as opposed to the polar reaction counterpart, no comprehensive conceptually intuitive polarity analysis scheme has been established as the foundational framework for delineating radical pathways and cascades.[3] With these fundamental limitations in mind, we have undertaken the initiative to formulate a systematic set of empirical polarity analysis guidelines for the projection of radical reactivity patterns.

Herein the radical polarity analysis framework is built upon the key premise that atomic and molecular radical fragments of defined polarity features serve as the building blocks for organic molecules and reactive units for organic transformations. With radical polarity categorized into electrophilic ($\delta^{\cdot/+}$; here the "$\cdot$" symbol indicates a radical species) and nucleophilic ($\delta^{\cdot/-}$) variants, the following radical polarity analysis rules are proposed (Scheme 1):[4] 1. Radicals can be divided into the primitive type and derivative type;[1] a primitive radical is the one perceivable by a bond scission process from a molecule, and a derivative radical is the non-primitive one perceivable in a

radical-molecule substitution process or a radical-unsaturated bond addition process, 2. Many initiator-type primitive radicals are electrophilic, and the derivative radicals can be electrophilic or nucleophilic, 3. The assignment of polarity has been compiled for carbon- and heteroatom-centered radicals (electrophilic or nucleophilic, largely depending on the element, also depending on the structural context and reaction context),[5] 4. There can exist joint radical effect and disjoint radical effect; the joint radical effect refers to a phenomenon that the polarity of a radical can be influenced by a covalently bonded, jointed structure as perceived along the reaction trajectory; the disjoint radical effect refers to a phenomenon that the polarity of a radical can be influenced by a non-covalently associated, disjointed structure, 5. Polarity matching, the complementation of polarity between two sites of interest, one electrophilic and one nucleophilic, is a key predictive guiding principle for creating a favored bonding state,[6] 6. With the collective experimental reactivity accumulated for intramolecular radical-alkene cyclization reactions, for an electron-rich alkene, the electrophilic radical coupling C-site is a nucleophilic radical, and the other C-site is an electrophilic radical; for an electron-deficient alkene, the nucleophilic radical coupling C-site is an electrophilic radical, and the other C-site is also an electrophilic radical (as a corollary to proposition 5), 7. Radical-radical coupling and radical-molecule substitution favors electrophilic-nucleophilic radical bonding as the reactive mode (as a corollary to proposition 5), 8. Radical-unsaturated bond addition reaction favors electrophilic-electron-rich and nucleophilic-electron-deficient radical-unsaturated bond coupling (as a corollary to proposition 5), 9. Radical-molecule substitution favors small molecular

fragment as the radical bonding partner,[1] 10. Photochemical radical reaction can differ in the reactive mode as compared to the thermal reaction.[7]

Scheme 1. Radical Polarity Analysis: Notation (Top) and Illustration of Joint Radical Effect, Disjoint Radical Effect, and Polarity Matching (Bottom)



An illustrative example is the atom transfer radical addition (ATRA) of ethyl 2-bromoacetate to 1-octene (Scheme 1).[8] For ethyl 2-bromoacetate, the joint radical effect from ethylcarbonyl structure (electron-withdrawing) transitions the polarity of neighboring C radical site from $\delta^{\cdot/-}$ to $\delta^{\cdot/+}$; correspondingly, the disjoint radical effect from this C radical site ($\delta^{\cdot/+}$) transitions the polarity of Br radical from $\delta^{\cdot/+}$ to $\delta^{\cdot/-}$. For this ATRA C-C bonding transformation, the polarity matching between C1 ($\delta^{\cdot/+}$) (initiator 2,2'-azobis(isobutyronitrile), or AIBN) and Br2 ($\delta^{\cdot/-}$) initiates the reaction; the polarity matching between C3 ($\delta^{\cdot/+}$) and C4 ($\delta^{\cdot/-}$), C5 ($\delta^{\cdot/+}$) and Br2 ($\delta^{\cdot/-}$) propagates the

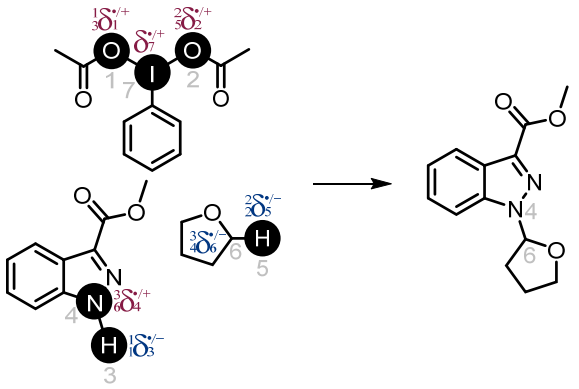
reaction.[9] Another exemplary reaction is the intramolecular reductive cyclization (IRC) of 6-chloro-1-heptene enabled by Bu_3SnH (Scheme 1). In this case, the disjoint radical effect from the Sn radical ($\delta^{\cdot/-}$) transitions the polarity of Cl radical from $\delta^{\cdot/+}$ to $\delta^{\cdot/-}$, and the disjoint radical effect from this Cl radical site ($\delta^{\cdot/-}$) transitions the polarity of neighboring C radical from $\delta^{\cdot/-}$ to $\delta^{\cdot/+}$.[10] For this IRC C-C bonding transformation, the polarity matching can be established, at initiation, between C1 ($\delta^{\cdot/+}$) (AIBN) and H2 ($\delta^{\cdot/-}$), and at propagation, Sn3 ($\delta^{\cdot/-}$) and Cl4 ($\delta^{\cdot/+}$; subsequent transition to $\delta^{\cdot/-}$), C5 (transition from $\delta^{\cdot/-}$ to $\delta^{\cdot/+}$) and C6 ($\delta^{\cdot/-}$), C7 ($\delta^{\cdot/+}$) and H2 ($\delta^{\cdot/-}$).

It should be noted that radical polarity analysis is inherently multifaceted and intricate (e.g., electronic and steric effects, intramolecular versus intermolecular reaction, ambiphilicity, radical-polar crossover)[11] and as such, an expansive prospect on the above rules is expected to contribute substantially to the rational development of synthetically useful radical reactions.

With the radical polarity analysis framework established, we next seek the application of these rules to the development of radical reactions. A reaction of broad synthetic utility, the C-N bond coupling, is selected as the target test case (Scheme 2). With phenyliodine(III) diacetate (PIDA) exploited as the oxidative mediator, and methyl 1*H*-indazole-3-carboxylate (**1a**) and tetrahydrofuran (**2a**) as the coupling partners, the polarity matching can be envisioned at O1 ($\delta^{\cdot/+}$) and H3 ($\delta^{\cdot/-}$), O2 ($\delta^{\cdot/+}$) and H5 ($\delta^{\cdot/-}$), N4 ($\delta^{\cdot/+}$) and C6 ($\delta^{\cdot/-}$) for the production of **3aa**. Herein, we report the photochemical achievement of such a polarity-matched transformation. In particular, this iodine(III)-mediated, visible light-enabled C-H azolation method features a cost-

effective and environmentally benign reagent, a mild reaction condition, a simple operation protocol, and a broad substrate scope.

Scheme 2. Radical Polarity Analysis for Iodine(III)-Mediated Photochemical C-H Azolation



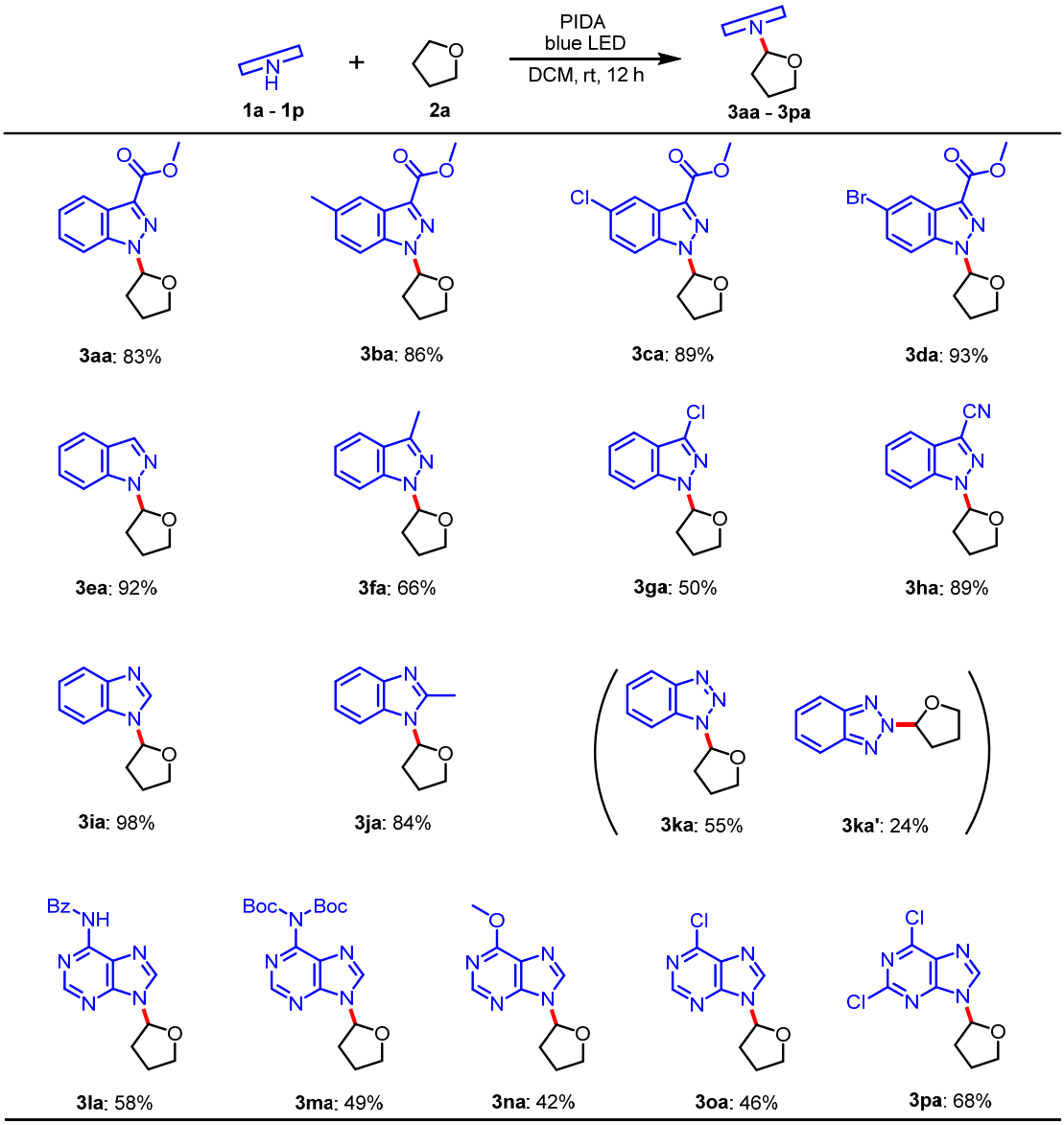
C-H azolation has been relentlessly pursued in the past for the prevalence of azole skeletons[12] in natural products, pharmaceutical compounds,[13] and functional materials.[14] Methodology development has been focused largely on thermochemical transformations. A plethora of synthetic protocols have been established, based on either direct oxidative or catalytic oxidative coupling.[15] Despite the success, each of these protocols is generally limited by a narrow substrate scope[16], applicable only to a portion of the ether, thioether, amide, benzylic, and allylic C-H bonds (herein, for ether, thioether, and amide, the C-H bond refers to the one α to the heteroatom).[17] Photochemical transformations, due to the fundamental divergence in reactivity associated with excited-state dynamics, have recently been experimented in search for a unified C-H bond coupling protocol. In this regard, the initial advances still witness the bifurcated regime: synthetic utility for either ether (decatungstate, *tert*-butyl hydroperoxide, or TBHP; [Acr^+-Mes][ClO_4^-], air)[18] or benzylic ($Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, $CBrCl_3$, K_2CO_3; [Acr^+-Mes][ClO_4^-], K_2HPO_4, CBr_4)[19]

C-H bond. Only two recent protocols document notable progress toward fulfillment of the unified promise of photochemical approach. One covers the ether, benzylic, and allylic C-H bond regime ($Ir(dFppy)_3$,[20] *p*-cyano-*N*-methoxypyridinium tetrafluoroborate), and the other covers the ether, thioether, amide, and benzylic C-H bond regime (2,3-dichloro-5,6-dicyano-1,4-benzoquinone, or DDQ, *tert*-butyl nitrite, or TBN, O_2).[21] In comparison, the PIDA protocol reported herein encompasses the full regime of ether, thioether, amide, benzylic, and allylic C-H bonds; in addition, this single-component reagent-mediated protocol obviates the need for either a precious metal (Ir) or a toxic compound (DDQ). As such, this method provides an ideal orthogonal C-H functionalization tool that complements the conventional nucleophilic substitution and transition metal-catalyzed cross-coupling synthesis.

We commence the survey of reaction conditions for the C-N bond coupling between reactants **1a** and **2a** under PIDA and 456 nm light irradiation at the 0.2 mmol scale. Room temperature (rt) reaction under 2.0 equiv PIDA in dichloromethane (DCM) for 12 h proceeds to a 67% yield for the expected product **3aa**. A variation of oxidative mediator to 1-hydroxy-1,2-benziodoxol-3-one (BI-OH), 1-acetoxy-1,2-benziodoxol-3-one (BI-OAc), Dess-Martin periodinane ($BI\text{-}(OAc)_3$), and phenyliodine(III) bis(trifluoroacetate) (PIFA) offers a yield of trace, 80%, 75%, and 53%, respectively. A reduction of PIDA quantity to 1.5 equiv raises the yield to 83% (optimized condition and yield; yield at 10.0 mmol scale: 79%). A switch of solvent to 1,2-dichloroethane (DCE), CH_3CN, and ^{t}BuOH is not beneficial, decreasing the yield to 76%, 48%, and trace, respectively. A reversal back to DCM under 1.0 equiv PIDA provides a 69%

yield.

Scheme 3. Substrate Scope of Azoles I[a]

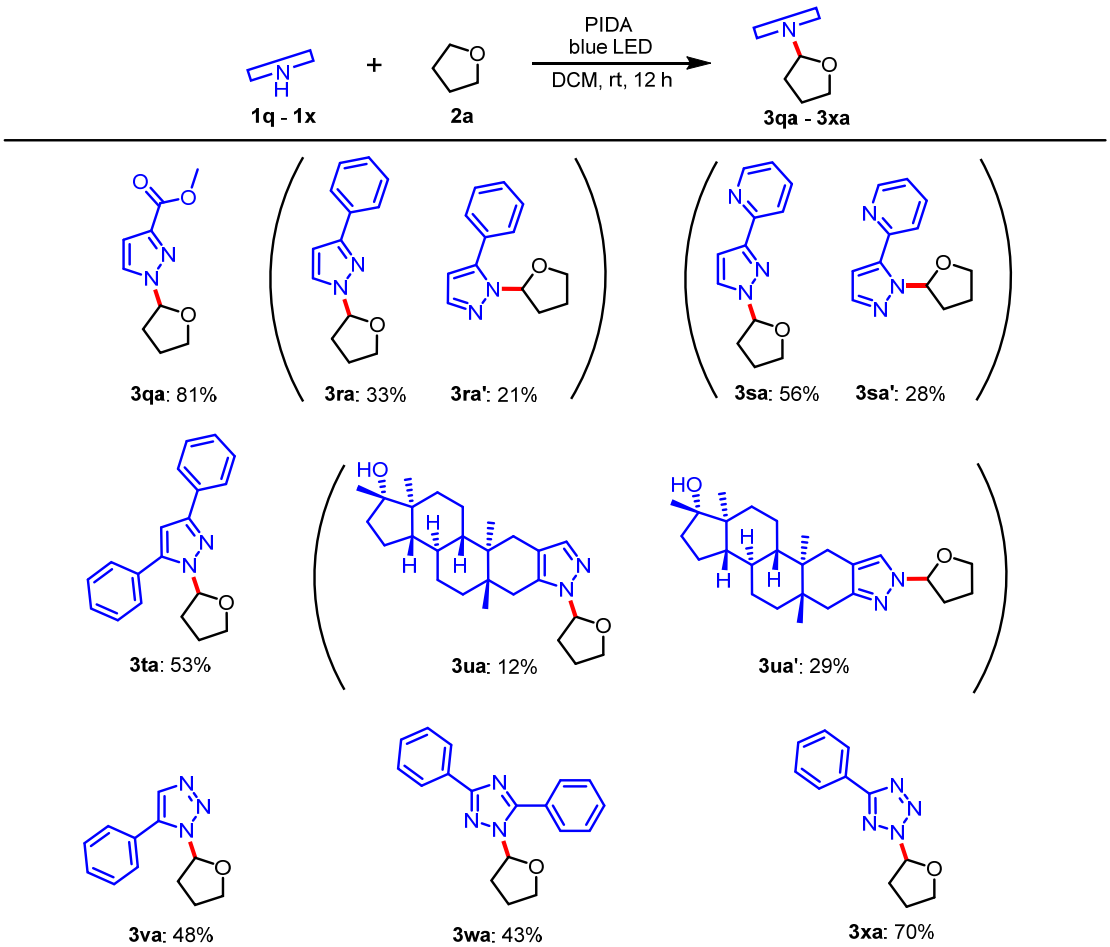


[a]Reaction conditions: **1** (0.20 mmol), **2a** (10.0 equiv), PIDA (1.5 equiv), DCM (1.0 mL); Under blue LED light, 12 h.

With the reaction condition optimized, we next set out to explore the substrate scope. The azole side is examined first, with **2a** engaged as the coupling partner (Schemes 3 and 4). The placement of an extra substituent at C5 of indazole ring of **1a**, irrespective of the electronic character, leads to an increased yield (Me, **1b**, 86%; Cl, **1c**, 89%; Br, **1d**, 93%). A reversal back to pristine 1*H*-indazole (**1e**) gives a yield of

92%. A substitution at C3 of **1e** negatively impacts the yield to a varied extent (Me, **1f**, 66%; Cl, **1g**, 50%; CN, **1h**, 89%). The pristine 1*H*-benzimidazole (**1i**) affords, essentially, a quantitative product yield (98%). A 2-Me substitution (**1j**) lowers the yield to 84%. The pristine benzotriazole (1*H* or 2*H*, **1k**) generates a mixture of products (1*H*, 55%, 2*H*, 24%). For the purine ring, a moderate yield is generally observed (6-benzamido, **1l**, 58%; 6-bis(*tert*-butoxycarbonyl)amino, **1m**, 49%; 6-MeO, **1n**, 42%; 6-Cl, **1o**, 46%; 2-Cl-6-Cl, **1p**, 68%). For the pyrazole ring, depending on the substituent, mono substitution allows access to either a regioselective single product (3-methoxycarbonyl, **1q**, 81%) or a mixture of products (3-phenyl, **1r**, 1*H*, 33%, 2*H*, 21%;

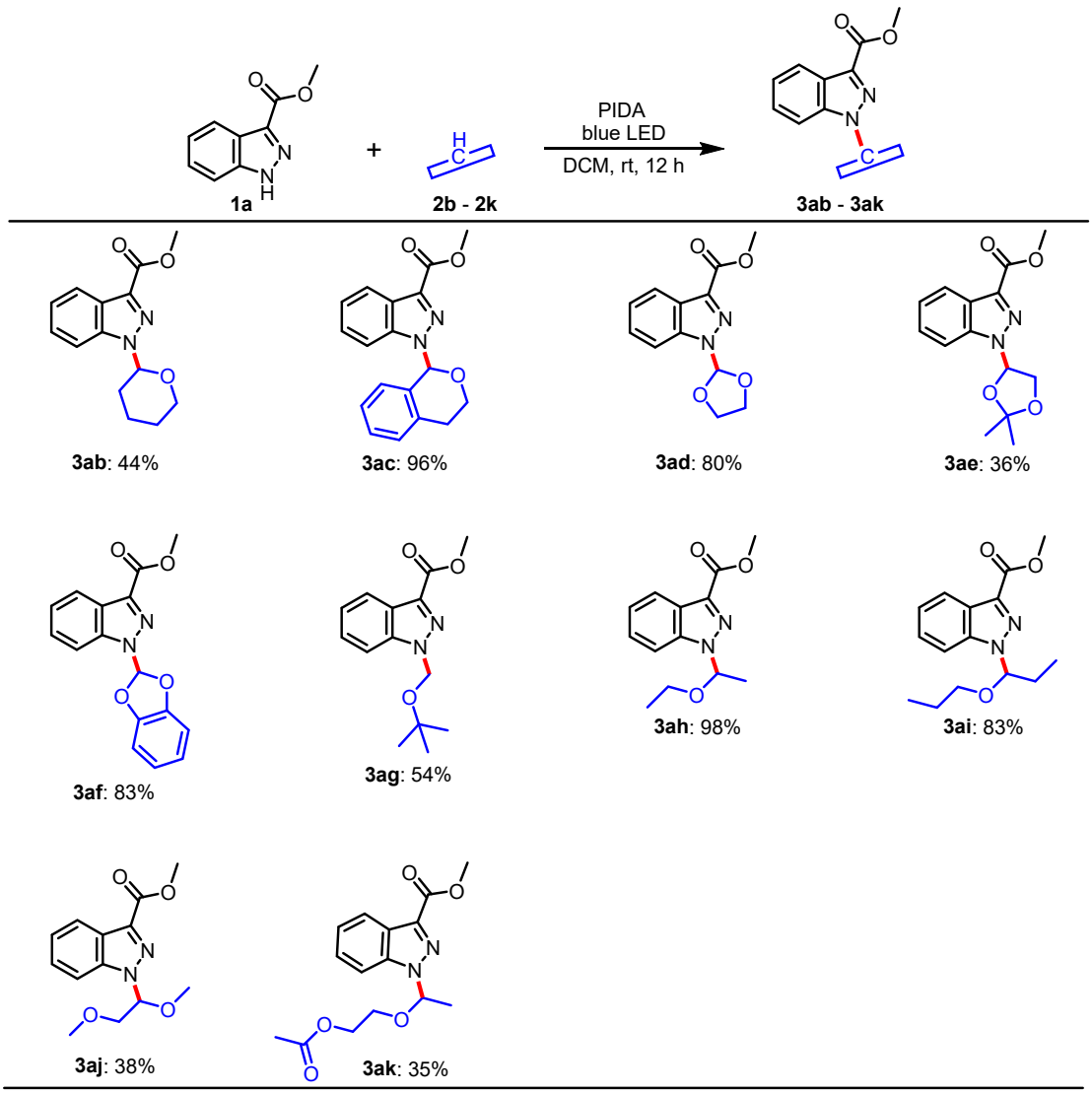
Scheme 4. Substrate Scope of Azoles II[a]



[a]Reaction conditions: **1** (0.20 mmol), **2a** (10.0 equiv), PIDA (1.5 equiv), DCM (1.0 mL); Under blue LED light, 12 h.

3-(2-pyridyl), **1s**, 1*H*, 56%, 2*H*, 28%). The double substitution (3-phenyl-5- phenyl, **1t**, 53%) is also compatible with the reaction. Notable is that stanozolol (**1u**), a complex drug bearing a pyrazole ring, is a competent substrate (1*H*, 12%, 2*H*, 29%). Extension into the 1,2,3-triazole (**1v**, 48%), 1,2,4-triazole (**1w**, 43%), and tetrazole (**1x**, 70%) realm proves to be viable.

Scheme 5. Substrate Scope of C-H Bonds I[a]

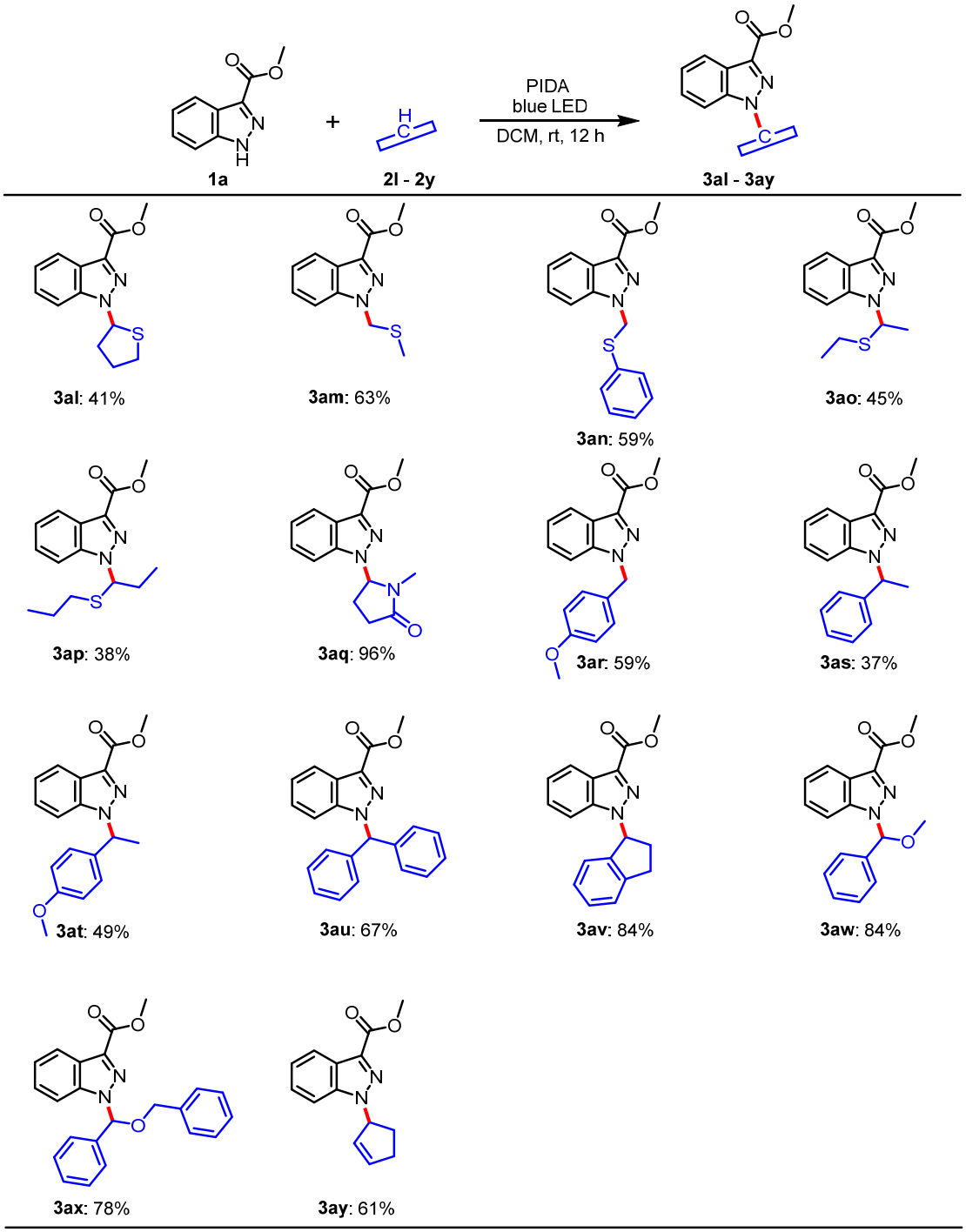


[a]Reaction conditions: **1a** (0.20 mmol), **2** (10.0 equiv), PIDA (1.5 equiv), DCM (1.0 mL); Under blue LED light, 12 h.

With the azole side substrate scope examined, we then embark on the investigation of C-H bond substrate scope, with **1a** as the coupling partner (Schemes 5 and 6). Ring

expansion from **2a** to tetrahydropyran (**2b**) diminishes the yield to 44%. A fusion of benzene ring (isochromane, **2c**) restores the yield to 96%. Dioxolane (**2d**, 80%) exhibits the regioselective reactivity at C2. The blocking of C2 with two Me groups (**2e**, 36%) exposes the reactivity at C4. A fusion of benzene ring to **2d** (benzodioxole, **2f**, 83%) maintains the respective product yield. A structural change of ether configuration from the ring to the open-chain type is tolerated, with the yield dictated by the structural feature (methyl *tert*-butyl ether, **2g**, 54%; diethyl ether, **2h**, 98%; di(*n*-propyl) ether, **2i**, 83%; 1,2-dimethoxyethane, **2j**, 38%; 2-ethoxyethyl acetate, **2k**, 35%). A switch from ether to thioether leads to a reduced yield, due to the susceptibility to oxidation. For tetrahydrothiophene (**2l**), a 41% yield is identified, approximately halved as compared to **2a**. Whereas a slightly increased yield is spotted for dimethyl sulfide (**2m**, 63%)and methyl phenyl sulfide (**2n**, 59%), a similarly halved yield is observed for diethyl sulfide (**2o**, 45%) and di(*n*-propyl) sulfide (**2p**, 38%) as referenced to **2i** and **2j**, respectively. Notably, a full structural switch to amide (**2q**) witnesses a near-quantitative product yield (96%). Further, benzylic C-H bond can also be accepted as the coupling partner. Again, the yield is correlated with the structural feature of the substrate: 4-methoxytoluene (**2r**) gives a 59% yield, and ethylbenzene (**2s**, 37%) and 1-methoxy-4-ethylbenzene (**2t**, 49%) manifest a lower yield than diphenylmethane (**2u**, 67%); a ring configuration in indane (**2v**, 84%) is beneficial for the reaction. An ether-benzylic-intersected C-H bond (**2w**, 84%; **2x**, 78%), as expected, can deliver the product in a great yield. As a closing case, allylic C-H bond (cyclopentene, **2y**, 61%) can also undergo the reaction smoothly.

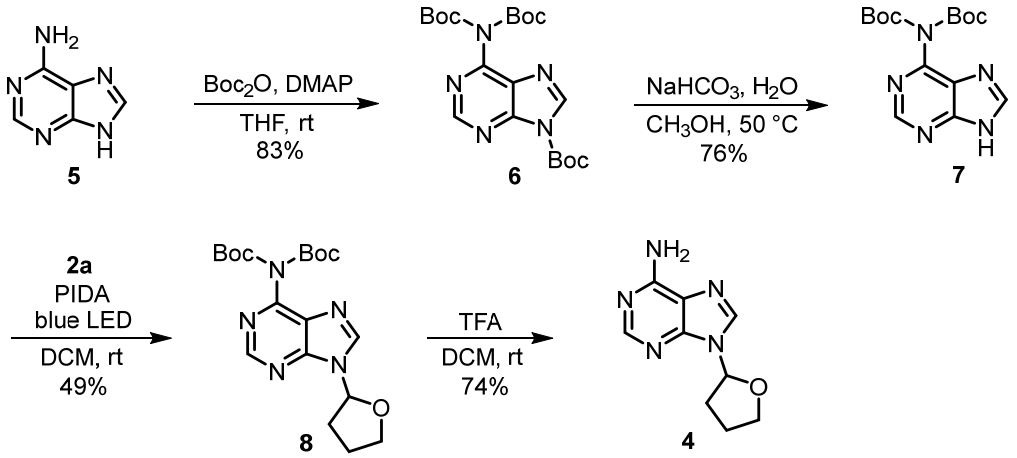
Scheme 6. Substrate Scope of C-H Bonds II[a]



[a]Reaction conditions: **1a** (0.20 mmol), **2** (10.0 equiv), PIDA (1.5 equiv), DCM (1.0 mL); Under blue LED light, 12 h.

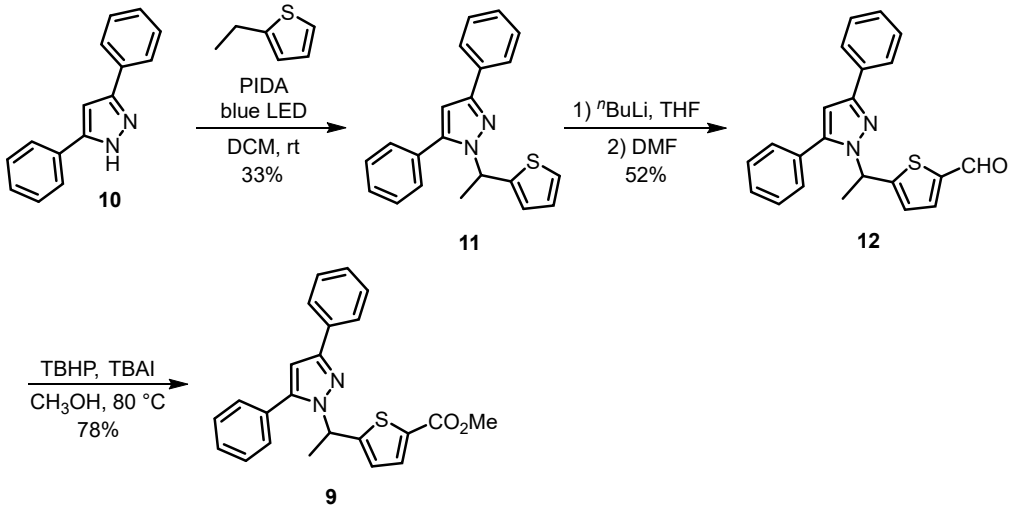
With the broad substrate scope demonstrated, we next pursue the synthetic utility of the protocol in the real application settings. The first product targeted is an adenylate cyclase inhibitor, 9-(tetrahydrofuran-2-yl)-9*H*-purin-6-amine (**4**) (Scheme 7). The synthesis starts with 9*H*-purin-6-amine (**5**), proceeding through the initial

Scheme 7. Synthesis of 4



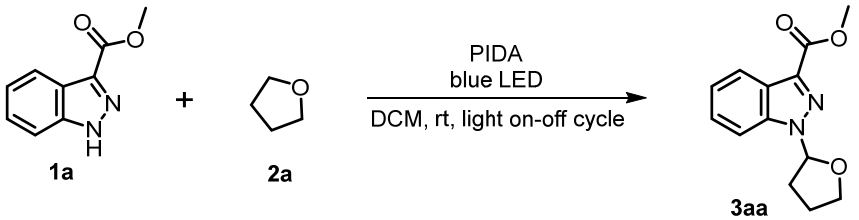
tert-butyloxycarbonyl (Boc) protection of 6-amino and 9-N*H* groups to **6** (83%), subsequent protection of 6-amino and 9-N*H* groups to **6** (83%), subsequent selected deprotection of 9-N-Boc group under basic condition to **7** (or **1m**, 76%) and protocol application coupling of 9-N*H* with **2a** to **8** (49%), and final deprotection of 6-amino-(Boc)$_2$ under acidic condition to **4** (74%). The second product targeted is methyl 5-(1-(3,5-diphenyl-1*H*-pyrazol-1-yl)ethyl)thiophene-2-carboxylate (**9**) (Scheme 8),[22] as pyrazole derivatives are frequently privileged pharmaceutical candidates. The synthesis starts with 3,5-diphenyl-1*H*-pyrazole (**10**), proceeding through the initial protocol

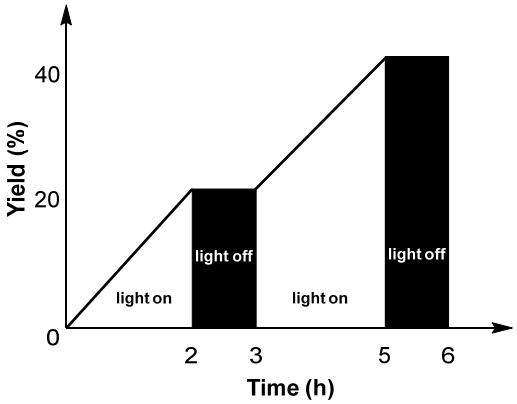
Scheme 8. Synthesis of 9



application coupling of 1-N*H* with 2-ethylthiophene (applicable to thiophene C2-benzylic C-H bond) to **11** (33%), subsequent formylation to **12** (52%), and final aldehyde group oxidation to acid followed by methyl esterification to **9** (78%).

Scheme 9. Light On-Off Experiment

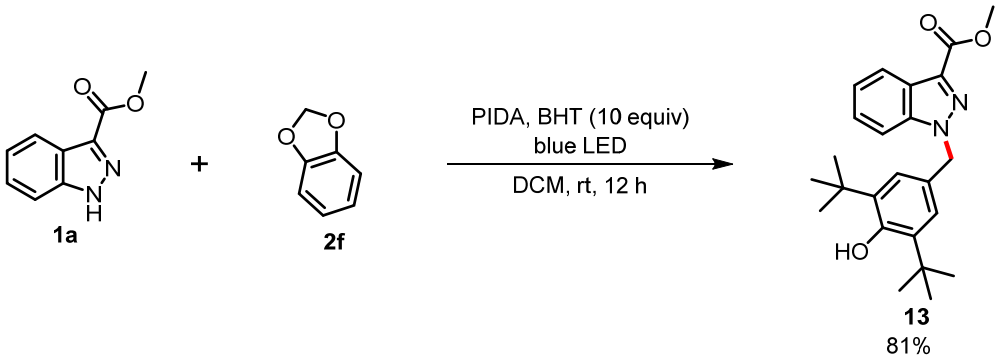




With the synthetic aspect of C-H azolation concluded, we then conduct two experiments to interrogate the reaction mechanism. The first is a light on-off cycle experiment (Scheme 9). Indeed, a reaction between **1a** and **2a** proceeds to 22% yield of **3aa** for the 2 h light-on period and stays paused for the 1 h light-off period; likewise, the reaction mirrors the 19%-pause pattern (total yield: 41%) for the next 2 h-1 h light on-off duration. This supports the photochemical instead of thermochemical nature of the reaction. The second is a radical trapping experiment (Scheme 10). An otherwise optimized-condition reaction between **1a** and **2f**, with the extra inclusion of 10 equiv butylated hydroxytoluene (BHT), identifies an adduct of **1a** and BHT (**13**, 81%). This supports the radical nature of the reaction and further, azole, instead of C-H bond, as

the reactant for initial generation of radical species, consistent with the mechanistic proposal from the radical polarity analysis.

Scheme 10. Mechanistic Experiment



In summary, radical polarity analysis has been proposed herein as a foundational tool for the projection of radical reactivity patterns. An iodine(III)-mediated photochemical C-H azolation reaction has been developed based on this analysis framework. The reaction is environmentally benign, experimentally mild, and operationally simple. Significantly, a broad coverage of ether, thioether, amide, benzylic, and allylic C-H bonds has been achieved, promising the wide-ranging utility of the established synthetic protocol in real application settings.

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