Published in final edited form as:

J Am Chem Soc. 2021 September 15; 143(36): 14438–14444. doi:10.1021/jacs.1c07117.

Copper-Catalyzed Cross Coupling of Benzylic C–H Bonds and Azoles with Controlled *N*-Site Selectivity

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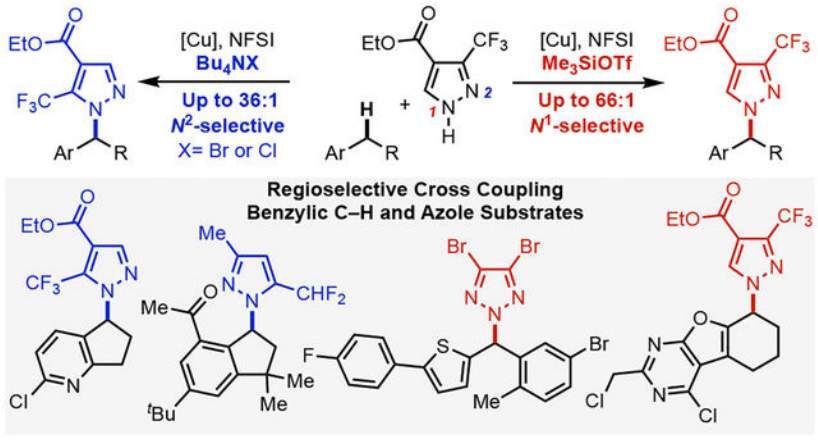
Abstract

Azoles are important motifs in medicinal chemistry, and elaboration of their structures via direct N–H/C–H coupling could have broad utility in drug discovery. The ambident reactivity of many azoles, however, presents significant selectivity challenges. Here, we report a copper-catalyzed method that achieves site-selective cross coupling pyrazoles and other N–H heterocycles with substrates bearing (hetero)benzylic C–H bonds. Excellent *N*-site selectivity is achieved, with the preferred site controlled by the identity of co-catalytic additives. This cross-coupling strategy features broad scope for both the N–H heterocycle and benzylic C–H coupling partners, enabling application of this method to complex molecule synthesis and medicinal chemistry.

Graphical Abstract



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Supporting Information.

Experimental details with supplemental notes, characterization data, and NMR spectra (PDF).

CCDC 2095281 and 2095282 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

The authors declare no competing financial interest.

Pd-[1] and Cu-catalyzed[2] C(sp^2)–N cross coupling reactions are some of the most widely used methods for pharmaceutical synthesis.[3] Recent efforts have begun prioritizing complementary methods for C(sp^3)–N coupling[4] as a means to expand the topological diversity and physiochemical properties of the resulting molecules.[3, 5] C–N coupling methods that directly functionalize C(sp^3)–H bonds bypass the need for pre-functionalized alkyl electrophiles and represent important targets for medicinal chemistry.[6] Significant progress has been made in C(sp^3)–H amination reactions that install ammonia surrogates via nitrene transfer[7] or azidation,[8] while C–H/N–H cross-coupling reactions, for example, with secondary amines/amides or N–H heterocycles, are more limited[9] and often require excess C–H substrate.[10] Here, we report a copper-catalyzed method for selective cross-coupling of azoles with (hetero)benzylic C–H substrates as the limiting reagent, affording *N*-benzylic heterocycles featured in pharmaceutical and agrochemical compounds (Figure 1A).[11–14] In addition to the challenge of C–H site selectivity, these reactions feature a second selectivity challenge arising from azoles that incorporate two (or more) nucleophilic nitrogen atoms.[15] This issue has important implications for medicinal chemistry because regioisomeric *N*-substituted azoles can have very different properties and/or bioactivity (Figure 1B).[16] The method described herein achieves excellent C–H site selectivity via hydrogen-atom transfer (HAT) from (hetero)benzylic C–H bonds (Figure 1C). Reaction with the azole coupling partners via Cu^{II}-mediated radical-polar crossover exhibits excellent N^1/N^2 site-selectivity (e.g., with pyrazoles), and variation of the reaction conditions lead to selective formation of either regioisomeric *N*-benzyl product with many coupling partners (Figure 1D).

Investigation of oxidative cross coupling of benzylic C–H substrates and N–H azoles started with ethylbenzene (**1a**) and ethyl 3-(trifluoromethyl)-1H-pyrazole-4-carboxylate (**2a**), a pyrazole featured in previous drug discovery efforts.[17] Potential reaction conditions were inspired by recent studies involving the use of copper catalysts in combination with *N*-fluorobenzenesulfonimide (NFSI) as the oxidant. Diverse nucleophilic coupling partners have been used in these reactions, including pseudohalides (cyanide,[18] azide,[8d] isocyanate[19]), alcohols,[20] carbamates,[21] and carbon-based nucleophiles ($Zn(CF_3)_2$,[22] $ArB(OH)_2$,[23] alkynes[24])[25,26] Cu^I-mediated activation of NFSI generates an *N*-centered radical that promotes selective HAT from benzylic C–H bonds, and subsequent coupling with heteroatom nucleophiles appears to favor a radical-polar crossover pathway involving formation of a benzylic cation intermediate.[8d,19,20] Complementary studies have shown that mild reductants, such as dialkylphosphites, can promote these reactions by buffering the redox state of the Cu catalyst and ensuring that both Cu^I and Cu^{II} are present in the reaction.[19,20,27]

The above mechanistic considerations guided a survey of reaction conditions. Initial screening data showed that Cu/NFSI-catalyzed oxidative coupling of **1a** and **2a** favors the N^2 isomeric product **3aa** when the reaction is conducted in chlorinated solvents PhCl and dichloromethane (DCM) (Figure 2A, entries 1–2; see Supporting Information for full screening details). Use of more polar solvents [hexafluoroisopropanol (HFIP) and $MeNO_2$] led to a switch in selectivity, favoring the N^1 isomer **3aa'** (entries 3–4). Tetrabutylammonium (TBA) bromide helped to solubilize the Cu catalyst and improved the reactivity and selectivity. Conventional ancillary ligands, such as phenanthroline or

bioxazolines, led to lower yields (see Table S1 and S2 for detailed information). A mixture of DCM:HFIP (7:3) enhanced the conversion of **1a** and improved the product yield to 71% (**3aa** + **3aa'**, entry 5). Increasing the loading of TBABr to 0.3 equiv further improved the reaction yield and increased the N^2:N^1 selectivity to 36:1 (entry 6). Optimal results results were obtained upon replacing TBABr with TBACl, affording **3aa** in 75% yield (entry 7). Further screening experiments revealed that the N^2/N^1 regioselectivity could be switched to favor the N^1 product **3aa'** with certain additives (Figure 2B, see Table S2 for additional data). The initial entries in Figure 2B show that additives with halide anions favor formation of the N^2 regioisomer **3aa**. In contrast, additives with triflate anion or Lewis acids, such as silyl triflates or BF_3•OEt_2, favor formation of the N^1 regioisomer **3aa'**. Optimal results for the formation of **3aa'** were achieved with trimethylsilyl triflate (TMSOTf) as the additive at 60 °C (67% yield; N^2:N^1 = 1:66).

The pyrazole reagent **2a** has an N–H bond at the N^1 position, as revealed by X-ray crystallography and depicted in Figure 2A (see Section 7 in the Supporting Information for details). This structure is consistent with previous reports for other electron-deficient, 3-substituted pyrazoles.[28] We postulated that the switch in pyrazole regioselectivity could arise from kinetic versus thermodynamic control over the C–N bond-forming step. Experimental data supported this hypothesis: addition of TMSOTf to **3aa** induced isomerization of this compound to **3aa'**, whereas no isomerization of **3aa'** was observed in the presence of TBABr (Figure 3A). These results suggest **3aa** is the kinetic product, and they are rationalized by the non-basic reaction conditions, which result in alkylation of the pyrazole nitrogen atom lacking the proton. Reactivity with the pyrazole N^2 lone pair (Figure 3B, top) contrasts previously reported reactivity with deprotonated pyrazolide reagents which react preferentially at the N^1 site.[28b,29] The isomerization data in Figure 3A suggests that strong Lewis acids, such as trimethylsilyl (TMS) cation, can promote isomerization via the benzylic cation and N^2-TMS species, to the thermodynamically favored N^1 product.[28b,30] The data in Figure 2A, entries 1–4 suggest that solvents capable of stabilizing charged intermediates also favor the thermodynamic product.

Access to both isomeric pyrazole coupling products is noteworthy because most coupling reactions with pyrazoles employ a base and access only the thermodynamic products.[29,31] For example, reaction of (1-bromoethyl)benzene with pyrazole **2a** affords exclusively the N^1 isomer **3aa'** (see Section 4 in the Supporting Information for details). To explore the scope of this reactivity, we evaluated numerous other C–H/N–H cross-coupling reactions with (hetero)benzylic and azole coupling partners (Figures 4 and 5). Reactions with (hetero)benzylic C–H substrates were initially tested using the TBACl conditions, which tend to be more robust and promote formation of the unique N^2-pyrazolyl product (Figure 4A). Ethylbenzene derivatives with different *p*-substituents are well tolerated (70–86%, **3aa-3da**). While the N^2 product is typically observed under these conditions, only the N^1 product **3ba'** is observed with *p*-MeO-ethylbenzene (**1b**). This result is rationalized by the stability of the benzylic carbocation, which facilitates isomerization to the thermodynamic product (cf. Figure 3). The lack of C–N coupling at tertiary C–H sites in reactions with isobutyl- and isopentylbenzene (**3ea**, **3fa**) highlights the exquisite site-selectivity of the HAT steps with the NFSI-derived imidyl radical.[8d,20] The strongly electron-withdrawing nitro

group in the indane substrate **1g** reduces the product yield (33%, **3ga**). Benzhydryl *N*-azoles, a class of compounds that exhibit aromatase inhibitory activity,[32] exhibit good reactivity (86%, **3ha**; 95%, **3ia**) and form only the N^1 regioisomers, again rationalized by the benzylic cation stability.

Benzylic pyrazoles of chromans,[33] thiophene,[14,34] and other substrates bearing oxygen-, sulfur- and nitrogen-containing heterocycles react successfully (**1j**–**1u**). These reactions demonstrate a tolerance for a formyl group (**3ka**), heteroarylbromides (**3la)**, and pyrimidines (**3ma**, **3nb**).[35] The pyridine substrate **1o** reacts in lower yield (26%, **3oa**). Substrates with two possible (hetero)benzylic sites (**1g**, **1m**, **1n**, and **1o**) generate a mixture of products, with moderate to good regioisomeric ratios (r.r.).

Pyrazoles **2a** and 3-bromopyrazole (**2b**) undergo successful late-stage reactivity with bioactive molecules. Examples include an antidiabetic intermediate **1p**, which affords only the N^1 coupling product (90%, **3pa'**); benzbromarone methyl ether (77%, **3qa**), a derivative of a xanthine oxidase inhibitor;[36] celestolide (70%, **3rb**); ibuprofen methyl ester (65%, **3sa**); an anti-inflammatory anti-allergy agent[37] (49%, **3tb**, r.r. = 7.2:1) and a precursor to a GnRH antagonist[38] (42%, **3ua**). These results were complemented with a focused assessment of the Lewis acid co-catalytic conditions (Figure 4B). These reactions lead to exclusive or high N^1 pyrazole site-selectivity in the C–N coupling reactions.

Different pyrazoles and other azole coupling partners were then tested in reactions with indane, motivated by the relevance of *N*-indanyl azoles in medicinal chemistry (Figure 5A).[39] Symmetrical 4-substituted pyrazoles, bearing fluoro, chloro, iodo, formyl, trifluoromethyl and nitro substituents, undergo coupling in good-to-excellent yields (60–82%, **3vc**-**3vh**). Other di- and trisubstituted pyrazoles with di- and trifluoromethyl (**2i**, **2j**)[17a] and sulfonyl chloride (**2k**) substituents react effectively (52–55% yields, **3vi**-**3vk**). Successful reactivity, but lower yields are observed with indazole coupling partners **2l** and **2m** (32%, **3vl**; 30%, **3vm**).[40,41] The dichloropurine derivative **2n** generates both N^9 and N^7 regioisomeric products (58% yield, N^7:N^9 = 1:1.5, **3vn**). Triazoles, including 1,2,4- and 1,2,3-isomers **2o** and **2p** and a tetrazole **2q** undergo successful reactivity (77%, **3vo**; 45%, **3vp**; 68%, **3vq**). The reaction with **2p** favors formation of the less common N^1 regioisomer (N^1:N^2 = 4.6:1),[42] consistent with the mechanistic rationale above.

Inclusion of BF_3•OEt_2 in these reactions enabled modulation of the azole regioselectivity (results with BF_3•OEt_2 were slightly better than with TMSOTf). In each of the four cases shown in Figure 5B, the favored regioisomer is different from that observed in the TBACl conditions. For example, the reaction with **2j** completely switches from N^2 to N^1 selectivity (46%, **3vj'**). In other cases, use of BF_3•OEt_2 ensures only a single isomer is formed (63%, **3vn'**; 66%, **3vp'**).

In a final assessment of the method, we explored C–N cross coupling reaction with different (hetero)benzylic and *N*-heterocyclic partners (Figure 5C). These reactions proceed in moderate-to-excellent yields. The reaction conditions show promise for heterocyclic coupling partners beyond azoles, including the beta-lactam **2s** (80%, **3ps**) and sultams **2r** and **2t** (47%, **3vr**, Figure 5A; 52%, **3tt**, Figure 5C). Reactions of the azoles **2a**, **2i**, and

2p react with the regioselectivity expected from the observation elaborated above. For example, **1p** affords the thermodynamically favored coupling product upon reaction with **2p**, reflecting the stability of benzylic cation. On the other hand, the reaction of **1w** and **2a** afforded the kinetically favored the N^2 regioisomer even with BF_3•OEt_2 as a cocatalyst (51%, **3wa**). The combined effect of BF_3•OEt_2 cocatalyst and HFIP as a cosolvent, however, supported a switch in the observed regioselectivity (46%, **3wa'**). The reaction of **1t** and **2i** affords only one of the four possible C–N coupling products (55%, **3ti**), demonstrating both C–H and N-nucleophile selectivity.

In summary, the results outlined herein introduce a unique synthetic method for direct C(sp^3)–H/N–H coupling of (hetero)benzylic substrates and azoles. Multiple features contribute to the potential impact of these methods. Perhaps the most notable feature is the ability to control the azole *N*-site selectivity, often enabling access to either regioisomeric product. Other highlights include the high-to-exclusive (hetero)benzylic C–H site selectivity, use of the C–H substrate as the limiting reagent, excellent scope for both coupling partners, and broad functional group compatibility. Overall, these C(sp^3)–N coupling methods provide efficient access to complex, pharmaceutically relevant structures, and they should find widespread utility for library synthesis and exploration of chemical space in medicinal chemistry and related disciplines.[43]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

The authors thank Ilia A. Guzei and Amelia M. Wheaton for assistance with the X-ray crystallographic characterization of **2a** and $[PhN(CH_3)_3]_2[CuBr_4]$. This work was supported by funding from the NIH (R35 GM134929). Spectroscopic instrumentation was supported by a gift from Paul. J. Bender, the NSF (CHE-1048642), and the NIH (S10 OD020022).

REFERENCES

(1). Ruiz-Castillo P; Buchwald SLApplications of Palladium-Catalyzed C–N Cross-Coupling Reactions. Chem. Rev2016, 116, 12564–12649. [PubMed: 27689804]

(2). (a)West MJ; Fyfe JWB; Vantourout JC; Watson AJBMechanistic Development and Recent Applications of the Chan–Lam Amination. Chem. Rev2019, 119, 12491–12523. [PubMed: 31756093] (b)Qiao JX; Lam PYSCopper-Promoted Carbon–Heteroatom Bond Cross-Coupling with Boronic Acids and Derivatives. Synthesis2011, 6, 829–856.

(3). Brown DG; Boström JAnalysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone?J. Med. Chem2016, 59, 4443–4458. [PubMed: 26571338]

(4). Trowbridge A; Walton SM; Gaunt MJNew Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. Chem. Rev2020, 120, 2613–2692. [PubMed: 32064858]

(5). (a)Lovering F; Bikker J; Humblet CEscape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. J. Med. Chem2009, 52, 6752–6756. [PubMed: 19827778] (b)Morley AD; Pugliese A; Birchall K; Bower J; Brennan P; Brown N; Chapman T; Drysdale M; Gilbert IH; Hoelder S; Jordan A; Ley SV; Merritt A; Miller D; Swarbrick ME; Wyatt PGFragment-Based Hit Identification: Thinking in 3D. Drug Discov. Today2013, 18, 1221–1227. [PubMed: 23906694]

(6). Cernak T; Dykstra KD; Tyagarajan S; Vachal P; Krska SWThe Medicinal Chemist's Toolbox for Late Stage Functionalization of Drug-Like Molecules. Chem. Soc. Rev2016, 45, 546–576. [PubMed: 26507237]

(7). (a)Clark JR; Feng K; Sookezian A; White MCManganese-Catalysed Benzylic C(sp^3)–H Amination for Late-Stage Functionalization. Nat. Chem2018, 10, 583–591. [PubMed: 29713037] (b)Chiappini ND; Mack JBC; Du Bois JIntermolecular C(sp^3)–H Amination of Complex Molecules. Angew. Chem. Int. Ed2018, 57, 4956–4959.

(8). (a)Sharma A; Hartwig JFMetal-Catalysed Azidation of Tertiary C–H Bonds Suitable for Late-Stage Functionalization. Nature2015, 517, 600–604. [PubMed: 25631448] (b)Huang X; Bergsten TM; Groves JTManganese-Catalyzed Late-Stage Aliphatic C–H Azidation. J. Am. Chem. Soc2015, 137, 5300–5303. [PubMed: 25871027] (c)Margrey KA; Czaplyski WL; Nicewicz DA; Alexanian EJA General Strategy for Aliphatic C–H Functionalization Enabled by Organic Photoredox Catalysis. J. Am. Chem. Soc2018, 140, 4213–4217. [PubMed: 29522330] (d)Suh S-E; Chen S-J; Mandal M; Guzei IA; Cramer CJ; Stahl SSSite-Selective Copper-Catalyzed Azidation of Benzylic C–H Bonds. J. Am. Chem. Soc2020, 142, 11388–11393. [PubMed: 32539355] (e)Niu L; Jiang C; Liang Y; Liu D; Bu F; Shi R; Chen H; Chowdhury AD; Lei AManganese-Catalyzed Oxidative Azidation of C(sp^3)–H Bonds under Electrophotocatalytic Conditions. J. Am. Chem. Soc2020, 142, 17693–17702. [PubMed: 32941025]

(9). (a)Pandey G; Laha R; Singh DBenzylic C(sp^3)–H Functionalization for C–N and C–O Bond Formation via Visible Light Photoredox Catalysis. J. Org. Chem2016, 81, 7161–7171. [PubMed: 27269307] (b)Yang Y-Z; Song R-J; Li J-HIntermolecular Anodic Oxidative Cross-Dehydrogenative C(sp^3)–N Bond-Coupling Reactions of Xanthenes with Azoles. Org. Lett2019, 21, 3228–3231. [PubMed: 30998374] (c)Hou Z-W; Liu D-J; Xiong P; Lai X-L; Song J; Xu H-CSite-Selective Electrochemical Benzylic C–H Amination. Angew. Chem. Int. Ed2020, 60, 2943–2947.(d)Hou Z-W; Li L; Wang LOrganocatalytic Electrochemical Amination of Benzylic C–H Bonds. Org. Chem. Front2021, DOI: 10.1039/D1QO00746G.

(10). (a)Song C; Dong X; Yi H; Chiang C-W; Lei ADDQ-Catalyzed Direct C(sp^3) – H Amination of Alkylheteroarenes: Synthesis of Biheteroarenes under Aerobic and Metal-Free Conditions. ACS Catal2018, 8, 2195–2199.(b)Ruan Z; Huang Z; Xu Z; Zeng S; Feng P; Sun P-HLate-Stage Azolation of Benzylic C−H Bonds Anabled by Electrooxidation. Sci. China. Chem2021, 64, 800–807.

(11). Eight of top 50 best-selling drugs contain N-benzylic heterocycles:Baumann M; Baxendale IR; Ley SV; Nikbin NBeilstein J. Org. Chem2011, 7, 442–495. [PubMed: 21647262]

(12). Taylor RD; MacCoss M; Lawson ADGRings in Drugs. J. Med. Chem2014, 57, 5845–5859. [PubMed: 24471928]

(13). Estrada AA; Feng JA; Lyssikatos JP; Sweeney ZKCompounds, Compositions, and Methods. Worldwide patent, WO2017087905 A1, 526, 2017.

(14). Hoffman TJ; Stierli D; Pitterna T; Rajan RMicrobiocidal Oxadiazole Derivatives. Worldwide patent2018158365 A1, 907, 2018.

(15). Blakemore DC; Castro L; Churcher I; Rees DC; Thomas AW; Wilson DM; Wood AOrganic Synthesis Provides Opportunities to Transform Drug Discovery. Nat. Chem2018, 10, 383–394. [PubMed: 29568051]

(16). Adams ND; Adams JL; Burgess JL; Chaudhari AM; Copeland RA; Donatelli CA; Drewry DH; Fisher KE; Hamajima T; Hardwicke MA; Huffman WF; Koretke-Brown KK; Lai ZV; McDonald OB; Nakamura H; Newlander KA; Oleykowski CA; Parrish CA; Patrick DR; Plant R; Sarpong MA; Sasaki K; Schmidt SJ; Silva DJ; Sutton D; Tang J; Thompson CS; Tummino PJ; Wang JC; Xiang H; Yang J; Dhanak DDiscovery of GSK1070916, a Potent and Selective Inhibitor of Aurora B/C Kinase. J. Med. Chem2010, 53, 3973–4001. [PubMed: 20420387]

(17). (a)Mykhailiuk PKFluorinated Pyrazoles: From Synthesis to Applications. Chem. Rev2021, 121, 1670–1715. [PubMed: 33382252] (b)Davie RL; Edwards HJ; Evans DM; Hodgson ST; Miller I; Novak AR; Smith AJ; Stocks MJHeterocyclic Derivates. Worldwide Patent2014188211 A1, 1127, 2014.

(18). Zhang W; Wang F; McCann SD; Wang D; Chen P; Stahl SS; Liu GEnantioselective Cyanation of Benzylic C–H Bonds via Copper-Catalyzed Radical Relay. Science2016, 353, 1014–1018. [PubMed: 27701109]

(19). Suh S-E; Nkulu LE; Lin S; Krska S; Stahl SSBenzylic C–H Isocyanation/Amine Coupling Sequence Enabling High-Throughput Synthesis of Pharmaceutically Relevant Ureas. Chem. Sci2021, DOI: 10.1039/D1SC02049H.

(20). Hu H; Chen S-J; Mandal M; Pratik SM; Buss JA; Krska SW; Cramer CJ; Stahl SSCopper-Catalysed Benzylic C–H Coupling with Alcohols via Radical Relay Enabled by Redox Buffering. Nat. Catal2020, 3, 358–367. [PubMed: 32368720]

(21). Liu S; Achou R; Boulanger C; Pawar G; Kumar N; Lusseau J; Robert F; Landais YCopper-Catalyzed Oxidative Benzylic C(sp^3)–H Amination: Direct Synthesis of Benzylic Carbamates. Chem. Commun2020, 56, 13013–13016.

(22). Xiao H; Liu Z; Shen H; Zhang B; Zhu L; Li CCopper-Catalyzed Late-Stage Benzylic C(Sp3)–H Trifluoromethylation. Chem2019, 5, 940–949.

(23). (a)Zhang W; Chen P; Liu GCopper-Catalyzed Arylation of Benzylic C–H bonds with Alkylarenes as the Limiting Reagents. J. Am. Chem. Soc2017, 139, 7709–7712. [PubMed: 28562032] (b)Zhang W; Wu L; Chen P; Liu GEnantioselective Arylation of Benzylic C–H Bonds by Copper-Catalyzed Radical Relay. Angew. Chem. Int. Ed2019, 58, 6425–6429.

(24). Fu L; Zhang Z; Chen P; Lin Z; Liu GEnantioselective Copper-Catalyzed Alkynylation of Benzylic C–H Bonds via Radical Relay. J. Am. Chem. Soc2020, 142, 12493–12500. [PubMed: 32539406]

(25). Wang F; Chen P; Liu GCopper-Catalyzed Radical Relay for Asymmetric Radical Transformation. Acc. Chem. Res2018, 51, 2036–2046. [PubMed: 30183262]

(26). For a survey of other examples of radical C–H functionalization reactions, see:Zhang C; Li Z-L; Gu Q-S; Liu X-YCatalytic Enantioselective C(sp^3)−H Functionalization Involving Radical Intermediates. Nat. Commun2021, 12, 475. [PubMed: 33473126]

(27). (a)Vasilopoulos A; Golden DL; Buss JA; Stahl SSCopper-Catalyzed C–H Fluorination/Functionalization Sequence Enabling Benzylic C–H Cross Coupling with Diverse Nucleophiles. Org. Lett2020, 22, 5753–5757. [PubMed: 32790420] (b)Buss JA; Vasilopoulos A; Golden DL; Stahl SSCopper-Catalyzed Functionalization of Benzylic C–H Bonds with *N*-Fluorobenzenesulfonimide: Switch from C–N to C–F Bond Formation Promoted by a Redox Buffer and Brønsted Base. Org. Lett2020, 22, 5749–5752. [PubMed: 32790419]

(28). (a)Stanovnik B; Svete JProduct Class 1: Pyrazoles. Science of Synthesis; Neier R; Bellus D, Eds.; Thieme: Stuttgart, 2002; Vol. 12, pp 15–225.(b)Ivanova AE; Burgart YV; Saloutin VI; Slepukhin PA; Borisevich SS; Khursan SLAmbident Polyfluoroalkyl-Substituted Pyrazoles in the Methylation Reactions. J. Fluor. Chem2017, 195, 47–56.(c)Jaćimović Željko. K.; Novaković SB; Bogdanović GA; Kosović M; Libowitzky E; Giester GCrystal Structure of Ethyl 3-(Trifluoromethyl)-1*H*-Pyrazole-4-Carboxylate, $C_7H_7F_3N_2O_2$. Z. Kristallogr.-New Cryst. Struct2020, 235, 1189–1190.

(29). Huang A; Wo K; Lee SYC; Kneitschel N; Chang J; Zhu K; Mello T; Bancroft L; Norman NJ; Zheng S-LRegioselective Synthesis, NMR, and Crystallographic Analysis of N1-Substituted Pyrazoles. J. Org. Chem2017, 82, 8864–8872. [PubMed: 28718639]

(30). For selected examples where cations have been used to influence *N*-regioselectivity, see: (a)Goikhman R; Jacques TL; Sames DC-H Bonds as Ubiquitous Functionality: A General Approach to Complex Arylated Pyrazoles via Sequential Regioselective *C*-Arylation and *N*-Alkylation Enabled by SEM-Group Transposition. J. Am. Chem. Soc2009, 131, 3042–3048. [PubMed: 19206533] (b)Wang X; Wang Q; Xue Y; Sun K; Wu L; Zhang BAn Organoselenium-Catalyzed N^1- and N^2-selective Aza-Wacker Reaction of Alkenes with Benzotriazoles. Chem. Commun2020, 56, 4436–4439.

(31). Hilpert LJ; Sieger SV; Haydl AM; Breit BPalladium- and Rhodium-Catalyzed Dynamic Kinetic Resolution of Racemic Internal Allenes Towards Chiral Pyrazoles. Angew. Chem. Int. Ed2019, 58, 3378–3381.

(32). Jones CD; Winter MA; Hirsch KS; Stamm N; Taylor HM; Holden HE; Davenport JD; Krumkalns EV; Suhr RGEstrogen Synthetase Inhibitors. 2. Comparison of the in Vitro Aromatase Inhibitory Activity for a Variety of Nitrogen Heterocycles Substituted with Diarylmethane or Diarylmethanol Groups. J. Med. Chem1990, 33, 416–429. [PubMed: 2296032]

(33). Wang L; Doherty G; Wang X; Tao Z-F; Brunko M; Kunzer AR; Wendt MD; Song X; Frey R; Hansen TM; Sullivan GM; Judd A; Souers AApoptosis-Inducing Agents for the Treatment of Cancer and Immune and Autoimmune Diseases. Worldwide patent2013055895 A1, 418, 2013.

(34). Zhi L; Grote M; Reddy RK; Li W; Craigo WGlucagon Receptor Antagonists. Worldwide patent2018035172 A1, 222, 2018.

(35). (a)Gangjee ATricyclic Compounds Having Antimitotic and/or Antitumor Activity and Method of Use Thereof. Worldwide patent2010006032A1, 114, 2010.(b)Aponte JC; Vaisberg AJ; Castillo D; Gonzalez G; Estevez Y; Arevalo J; Quiliano M; Zimic M; Verástegui M; Málaga E; Gilman RH; Bustamante JM; Tarleton RL; Wang Y; Franzblau SG; Pauli GF; Sauvain M; Hammond GBTrypanoside, Anti-Tuberculosis, Leishmanicidal, and Cytotoxic Activities of Tetrahydrobenzothienopyrimidines. Bioorg. & Med. Chem2010, 18, 2880–2886. [PubMed: 20356752]

(36). Schepers GBenzbromarone Therapy in Hyperuricaemia; Comparison with Allopurinol and Probenecid. J. Int. Med. Res1981, 9, 511–515. [PubMed: 7033016]

(37). Smith HWCyclopentapyrazole and tetrahydroindazole compounds. Worldwide patent8607357, 1218, 1986.

(38). Fushimi N; Yonekubo S; Ohno K; Miyagi TNitrogen-Containing Fused Ring Derivatives, Pharmaceutical Compositions Containing Them and Their Pharmaceutical Use. Japan patent5308342B2, 109, 2013.

(39). Shu S; Cai X; Li J; Feng Y; Dai A; Wang J; Yang D; Wang M-W; Liu HDesign, Synthesis, Structure–Activity Relationships, and Docking Studies of Pyrazole-Containing Derivatives as a Novel Series of Potent Glucagon Receptor Antagonists. Bioorg. & Med. Chem2016, 24, 2852–2863. [PubMed: 27161876]

(40). Indazoles tend to exist as 1*H*-tautomers:Minkin VI; Garnovskii AD; Elguero J; Katritzky AR; Denisko OVThe Tautomerism of Heterocycles: Five-Membered Rings with Two or More Heteroatoms. In Advances in Heterocyclic Chemistry; Elsevier, 2000; Vol. 76, pp 157–323.

(41). Selected methods that achieved indazole N^2-alkylations:(a)Cheung M; Boloor A; Stafford JAEfficient and Regioselective Synthesis of 2-Alkyl-2*H*-indazoles. J. Org. Chem2003, 68, 4093–4095. [PubMed: 12737599] (b)Luo G; Chen L; Dubowchik GRegioselective Protection at *N*-2 and Derivatization at *C*-3 of Indazoles. J. Org. Chem2006, 71, 5392–5395. [PubMed: 16808535] (c)Slade DJ; Pelz NF; Bodnar W; Lampe JW; Watson PSIndazoles: Regioselective Protection and Subsequent Amine Coupling Reactions. J. Org. Chem2009, 74, 6331–6334. [PubMed: 19618957]

(42). Wang X; Zhang L; Krishnamurthy D; Senanayake CH; Wipf PGeneral Solution to the Synthesis of *N*-2-Substituted 1,2,3-Triazoles *Org*. Lett2010, 12, 4632–4635.

(43). (a)Gordon EM; Barrett RW; Dower WJ; Fodor SPA; Gallop MAApplications of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic Synthesis, Library Screening Strategies, and Future Directions. J. Med. Chem1994, 37, 1385–1401. [PubMed: 8182695] (b)Thompson LA; Ellman JASynthesis and Applications of Small Molecule Libraries. Chem. Rev1996, 96, 555–600. [PubMed: 11848765]

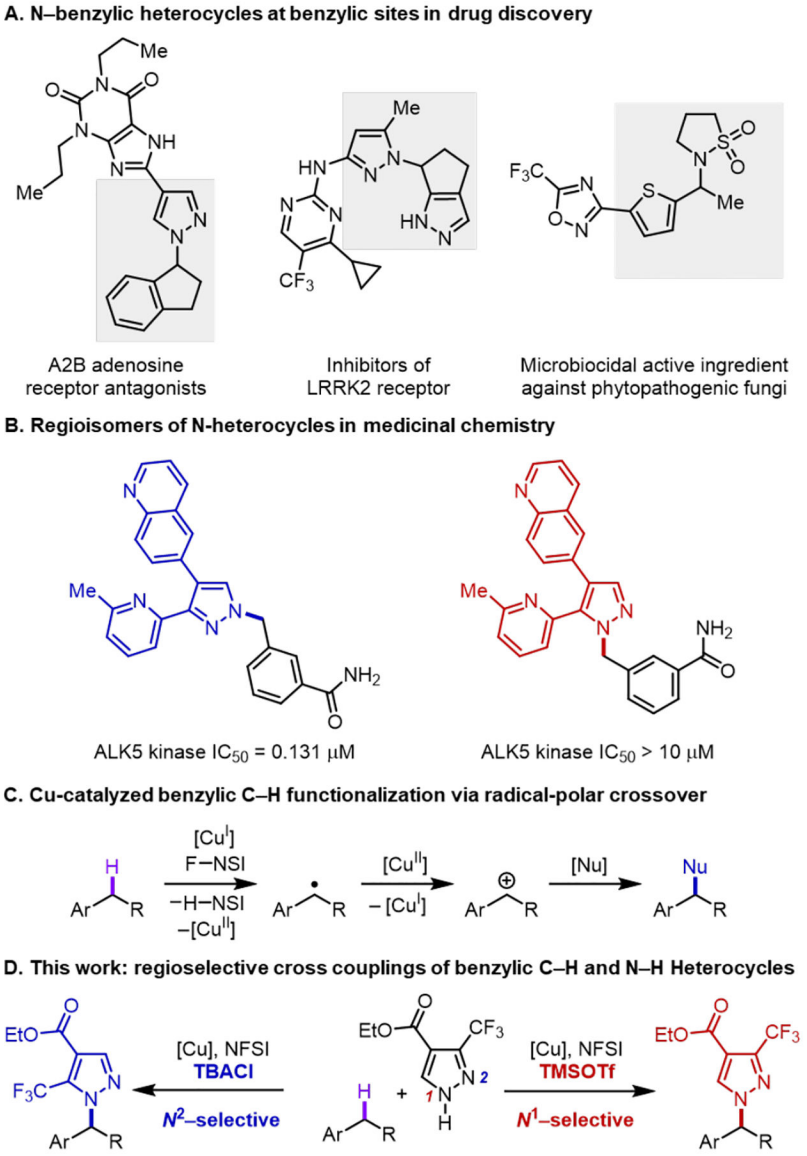
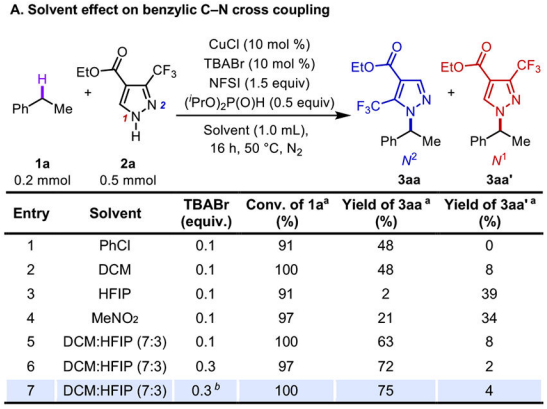


Figure 1.

(A) Importance of benzylic N-azoles in drug discovery. (B) Impact of regioselectivity of heterocyclic compounds in medicinal chemistry. (C) Copper-catalyzed regioselective cross couplings of benzylic C–H bonds and N–H heterocycles enabled by various additives.



Entry	Solvent	TBABr (equiv.)	Conv. of 1a[a] (%)	Yield of 3aa [a] (%)	Yield of 3aa' [a] (%)
1	PhCl	0.1	91	48	0
2	DCM	0.1	100	48	8
3	HFIP	0.1	91	2	39
4	$MeNO_2$	0.1	97	21	34
5	DCM:HFIP (7:3)	0.1	100	63	8
6	DCM:HFIP (7:3)	0.3	97	72	2
7	DCM:HFIP (7:3)	0.3 [b]	100	75	4

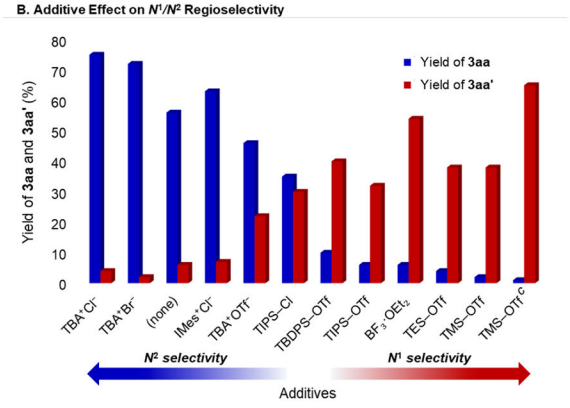


Figure 2.

Evaluation of effects of various solvents and additives on the regioselectivity. (A) Effects of solvents on benzylic C–N cross coupling reaction. (B) Regioselectivity switch observed in cross coupling of **1a** and **2a** with different additives. Conditions identical to those shown in part A, using 10 mol% additive instead of TBABr, 10 mol % $CuBr_2$ instead of CuCl, and DCM:HFIP (7:3) solvent. [a] Monitored by ^1H NMR spectroscopy, yield determined using 0.2 mmol mesitylene as internal standard. TBA, tetrabutylammonium; DCM, dichloromethane; HFIP, hexafluoroisopropanol. [b] Reaction run with TBA^+Cl^- instead of TBABr. [c] Reaction run at 60 °C.

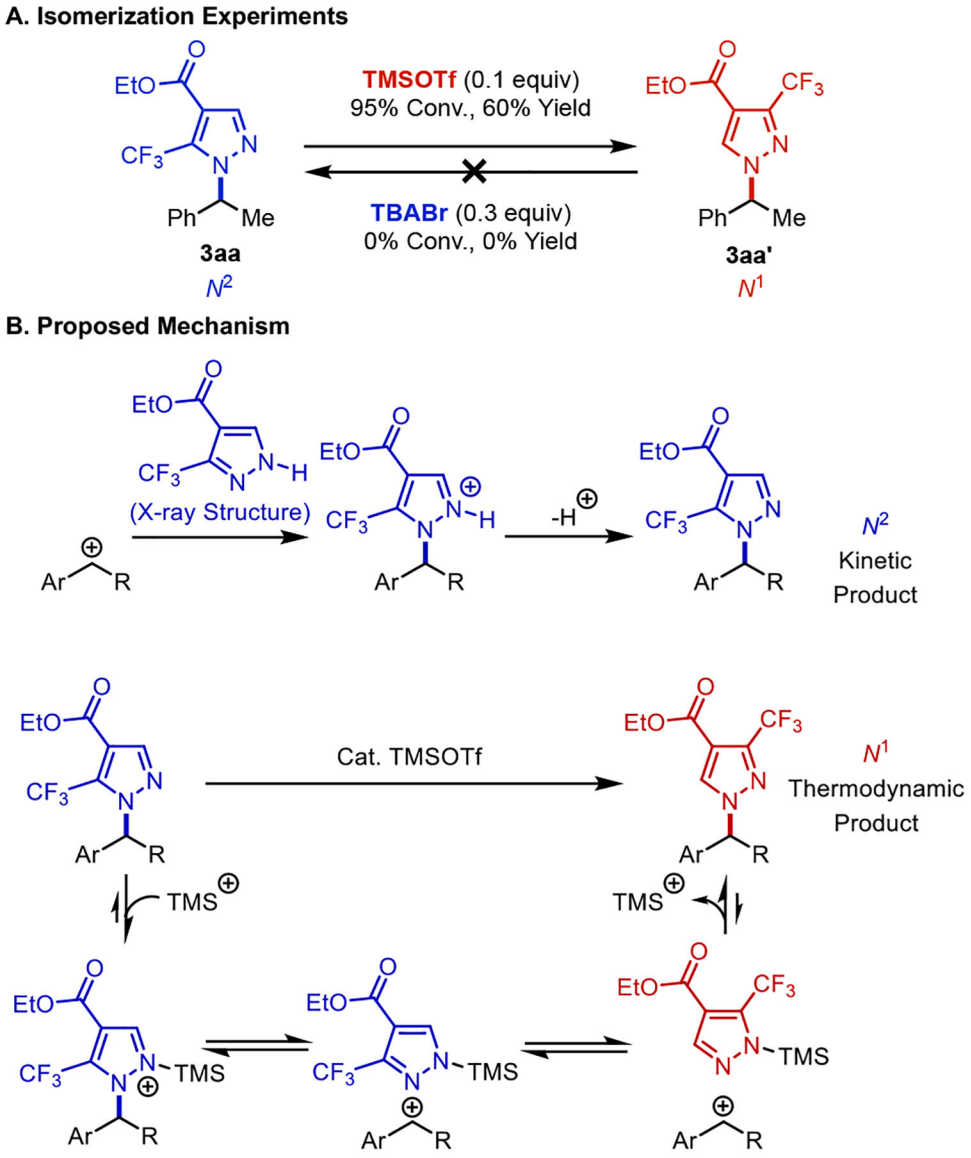


Figure 3.

Mechanistic origin of pyrazole regioselectivity. (A) N^1/N^2-isomerization test, implicating the the N^1. (B) Proposed mechanism rationalizing the influence of TMSOTf (and other Lewis acids) on the N^2/N^1 regioselectivity.

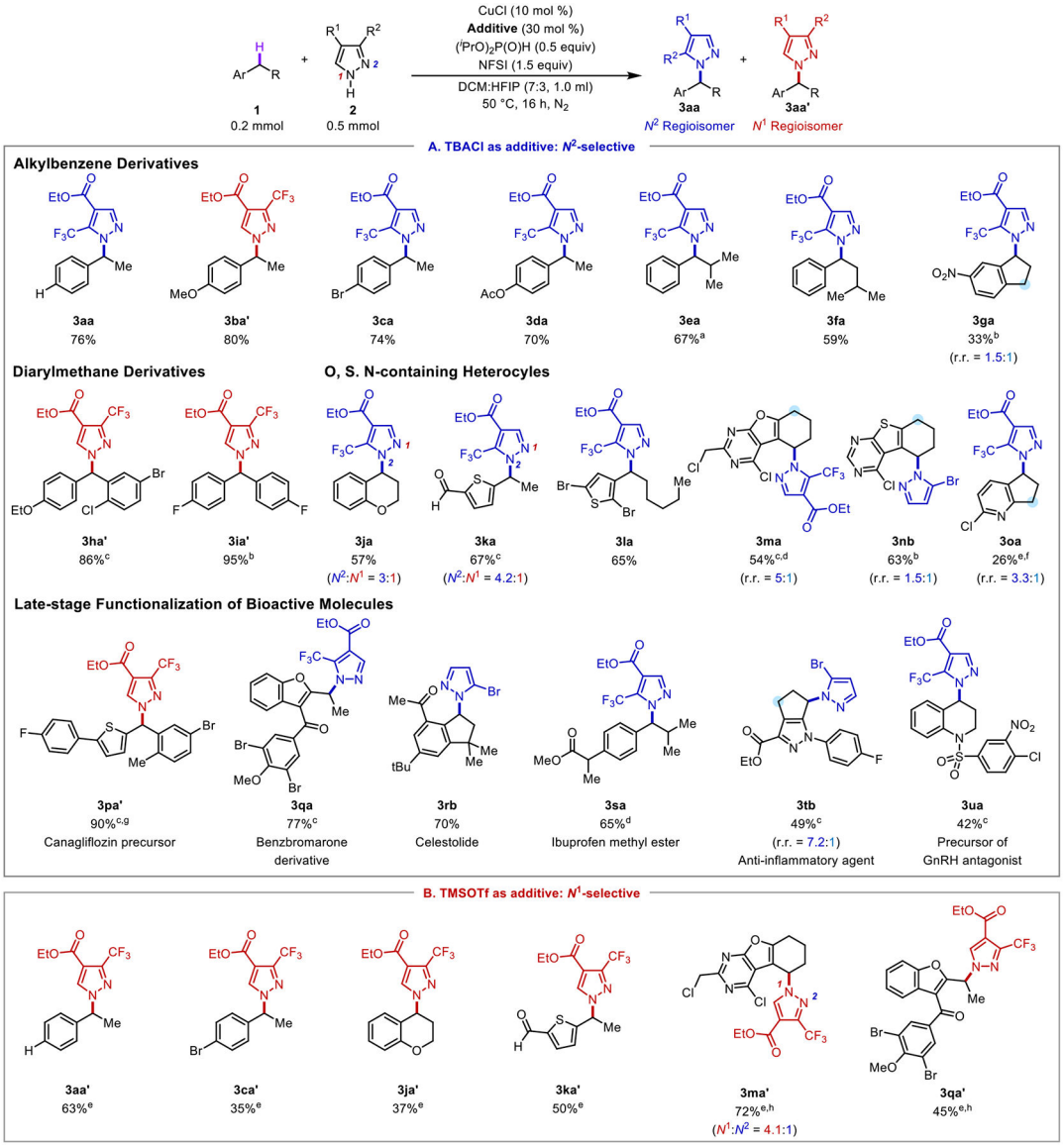


Figure 4.

Assessment of various benzylic C–H substrates in cross coupling reactions with N–H heterocycles with (A) TBACl as the additive for N^2 regioselectivity and (B) with TMSOTf as the additive for N^1 regioselectivity. Regioisomers >5% were isolated and reported. [a]Conducted in 0.5 mL DCM:HFIP (7:3). [b]Conducted with 10 mol % $CuBr_2$ and 30 mol % TBABr. [c] Conducted with 10 mol % TBACl. [d]Conducted at 40 °C. [e]Conducted at 60 °C. [f]Conducted in DCM. [g]Conducted at 30 °C. [h]Conducted with 10 mol % BF_3•OEt_2.

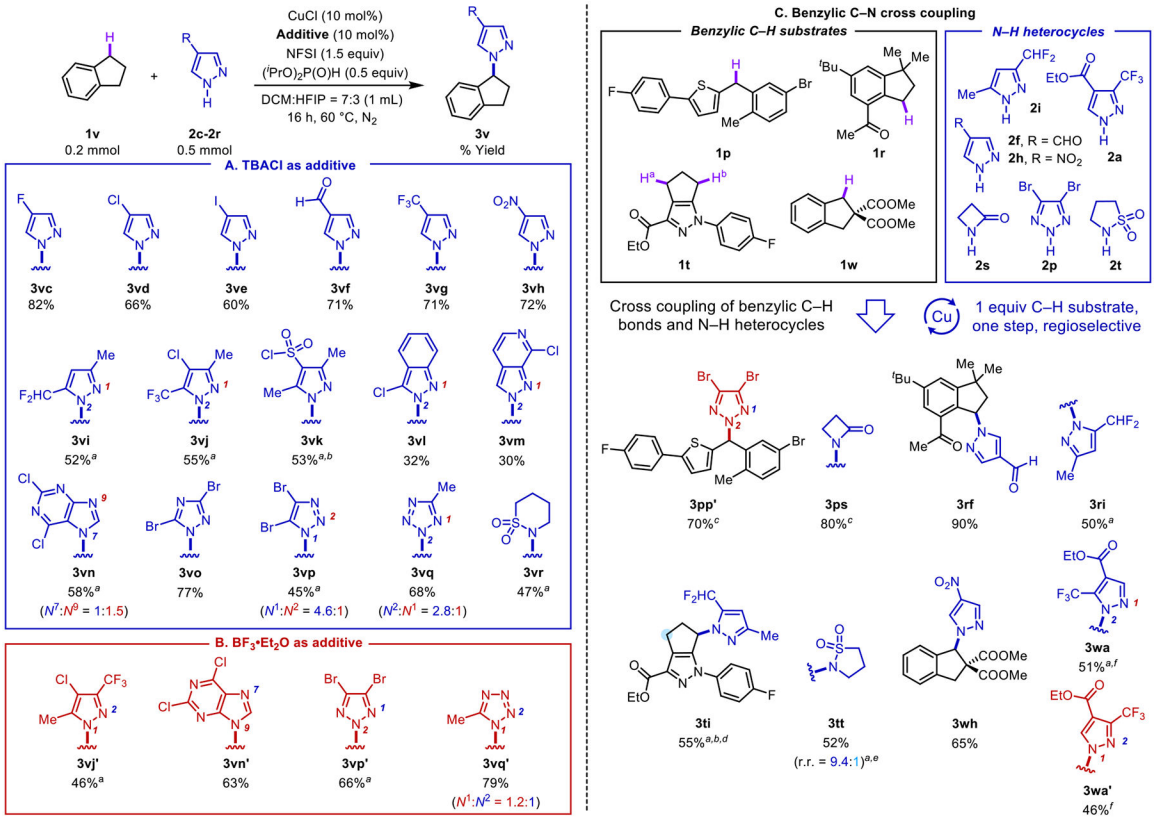


Figure 5.

Assessment of various N–H heterocycles in cross coupling reactions. Substrate scope with diverse N–H heterocycles and indane under kinetically controlled TBACl conditions (A) and in the presence of BF_3•OEt_2 as a Lewis acid cocatalyst (B). Exploration of cross-coupling reactions of diverse N–H heterocycles and (hetero)benzylic C–H scaffolds (C) under the TBACl conditions of Figure 5A, unless noted otherwise. Regioisomers formed in >5% yield were isolated. [a]Conducted in DCM. [b]Conducted at 50 °C. [c]Conducted at 30 °C. [d]Trace amount of the other benzylic regioisomer was observed. [e]Conducted at 40 °C. [f]Conducted with 10 mol % BF_3•OEt_2.