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Cross-Dehydrogenative Coupling of Azoles with α-C(sp^3)−H of Ethers and Thioethers under Metal-Free Conditions: Functionalization of H−N Azoles via C−H Activation

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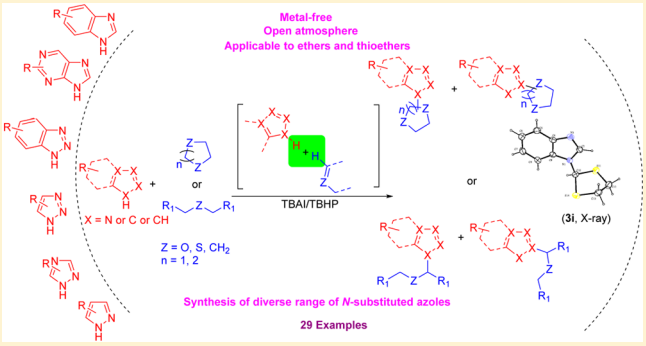
Supporting Information

ABSTRACT: A metal-free cross-dehydrogenative coupling method for the synthesis of *N*-substituted azoles has been developed. The TBAI/TBHP system catalyzed the coupling of azoles with ethers and thioethers via α-C(sp^3)−H activation. Under the optimized conditions, a diverse range of un/substituted azoles such as 1*H*-benzimidazole, 9*H*-purine, 1*H*-benzotriazole, 1*H*-1,2,3-triazole, 1*H*-1,2,4-triazole, and 1*H*-pyrazole were successfully employed for coupling with various ethers and thioethers such as tetrahydrofuran, tetrahydropyran, 1,4-dioxane, diethyl ether, tetrahydrothiophene, and 1,3-dithiolane.



N-Substituted azoles, particularly *N*-alkylated azoles, represent an important class of compounds because of their common occurrence in medicinally important products (some examples are given in Figure 1)[1] as well as their use as precursors for *N*-heterocyclic carbenes and ionic liquids.[2] In view the importance of *N*-substituted azoles, the development of new synthetic methods for the functionalization of azoles is of great interest. Traditionally, *N*-alkylated azoles have been synthesized by coupling of azoles with electrophiles (Figure 2). These reactions normally require harsh conditions and often result in over-alkylation.[3] In the past decade, there has been great interest in the exploration and development of metal-catalyzed and metal-free organocatalyzed C−H bond activation/functionalization methods for C−C, C−O, and C−N bonds.[4−6] In this direction, Pan et al.[7] applied an Fe/TBHP-catalyzed C−H activation strategy for the *N*-alkylation of azoles (as shown in Figure 2). Moreover, in recent years, metal-free organocatalytic systems such as tetrabutylammonium iodide (TBAI)/*tert*-butyl hydroperoxide (TBHP) have also been extensively explored for C−H activation/functionalization.[8]

In continuation of our interest in the development of C−H activation/functionalization methods,[9] here we have developed a general cross-dehydrogenative coupling (CDC) method for the coupling of azoles with α-C(sp^3)−H of ethers and thioethers under metal-free conditions using TBAI in the presence of TBHP to active the α-C(sp^3)−H of ethers and thioethers. The present method has wide applicability and successfully works with diverse un/substituted azoles such as 1*H*-benzimidazole, 9*H*-purine, 1*H*-benzotriazole, 1*H*-1,2,3-triazole, 1*H*-1,2,4-triazole, and 1*H*-pyrazole.

To optimize the reaction conditions, 1*H*-benzimidazole (**1**) and tetrahydrofuran (THF, **2**) were used as coupling partners, and the results of the optimization studies are summarized in Table 1. In the first instance, coupling of **1** with THF in the presence of 10 mol % TBAI and 2 equiv of 70% aqueous TBHP in 1,2-dichloroethane (DCE) gave the expected coupled product **3a** in 45% yield (Table 1, entry a), as confirmed by NMR and MS analyses. Increasing the amount of TBHP from 2 to 3.5 equiv afforded a 72% yield of the coupled product **3a** (entry b). Further increases in the amount of TBHP did not affect the formation of **3a** (results not shown). Changing the amount of THF also affected the yield, as decreasing the amount of THF from 15 to 5 equiv lowered the yield of **3a** from 72% to 60% (entries c and d). When the reaction was performed in neat THF, no improvement was noticed (entry e). Changing the solvent from DCE to ethyl acetate (EtOAc) also did not show any improvement (entry f). The effect of temperature was also studied: when the reaction was conducted at rt, the coupled product **3a** was observed in 50% yield, but the reaction took a comparatively longer time (entry g). Changing the source of iodide ions to sodium iodide (NaI) or potassium

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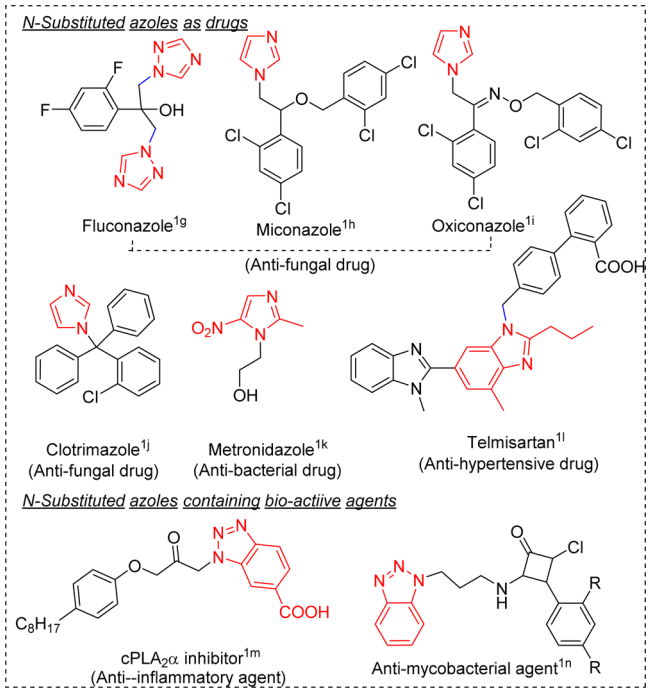


Figure 1. Medicinally important *N*-substituted azoles.

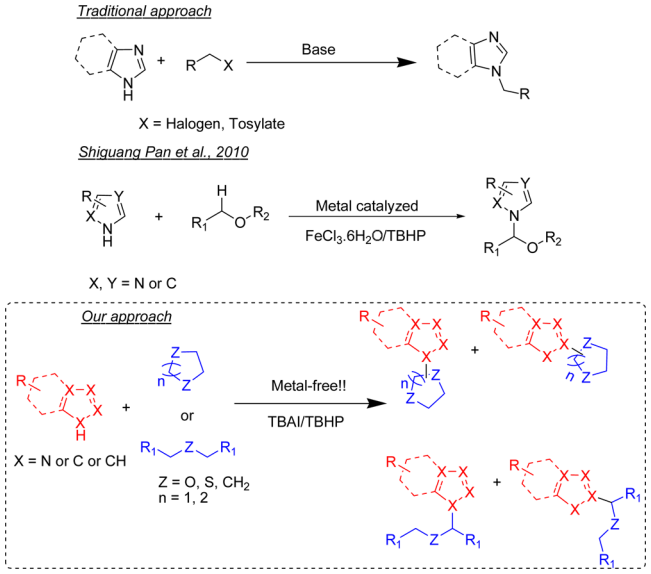


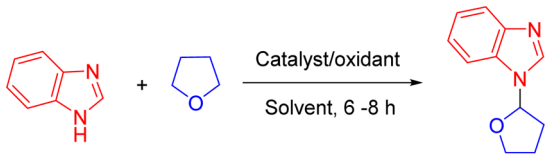
Figure 2. Previous and present approaches for the alkylation of *N*-azoles.

iodide (KI) was also tried, but neither gave better results (entries h and i). With molecular iodine (I_2), the expected coupled product **3a** was observed in only 55% yield (entry j). In the absence of TBHP, no coupling was observed (entry k). On the basis of the above results, the best coupling conditions involved 15 equiv of THF, 10 mol % TBAI, and 3.5 equiv of TBHP in DCE as the solvent at 80 °C.

To know the generality of the optimized conditions, the couplings of various un/substituted 1*H*-benzimidazoles with ethers and thioethers were also investigated, and the results are given in Table 2. The presence of substitution on the 1*H*-benzimidazole greatly affects the formation of the coupled products. Coupling of 5,6-dimethyl-1*H*-benzimidazole with THF gave the corresponding product **3b** in an excellent yield of 82%. Coupling of 6-bromo-1*H*-benzimidazole with THF gave a mixture of unseparable regioisomers **3c** and **3c′** in an overall yield of 78%. 1*H*-Benzimidazole **1** underwent coupling with 1,4-dioxane to give **3d** in 30% yield, while on the other hand, coupling of 5,6-dimethyl-1*H*-benzimidazole with 1,4-dioxane afforded **3e** in 65% yield. Similarly, coupling of 6-bromo-1*H*-benzimidazole to 1,4-dioxane gave an unseparable mixture of regioisomers **3f** and **3f′** in an overall yield of 55%.

Under the optimized conditions, un/substituted 1*H*-benzimidazoles also underwent coupling with tetrahydrothiophene to give the corresponding coupled products in moderate to good yields. When 1*H*-benzimidazole **1** was coupled with tetrahydrothiophene, the corresponding product **3g** was observed in 48% yield. 5,6-Dimethylbenzimidazole underwent coupling with tetrahydrothiophene to give **3h** in 62% yield. Benzimidazole **1** also underwent coupling with 1,3-dithiolane to

Table 1. Optimization Studies[a]



1 2 3a

entry	ether **2** (equiv)	catalyst	oxidant (equiv)[c]	solvent	*T* (°C)	yield (%)[d]
a	THF (15)	TBAI (0.1)	TBHP (2)	DCE	80	45
b	THF (15)	TBAI (0.1)	TBHP (3.5)	DCE	80	72
c	THF (10)	TBAI (0.1)	TBHP (3.5)	DCE	80	70
d	THF (5)	TBAI (0.1)	TBHP (3.5)	DCE	80	60
e[b]	THF	TBAI (0.1)	TBHP (3.5)	–	80	70
f	THF (15)	TBAI (0.1)	TBHP (3.5)	EtOAc	80	70
g	THF (15)	TBAI (0.1)	TBHP (3.5)	DCE	rt	50
h	THF (15)	NaI (1)	TBHP (3.5)	DCE	80	65
i	THF (15)	KI(1)	TBHP (3.5)	DCE	80	65
j	THF (15)	I_2 (1)	TBHP (3.5)	DCE	rt	55
k	THF (15)	TBAI (0.1)	–	DCE	80	0

[a]All of the reactions were performed with 1 mmol of azole. [b]Performed using THF as the solvent. [c]70% aqueous TBHP. [d]Isolated yields.

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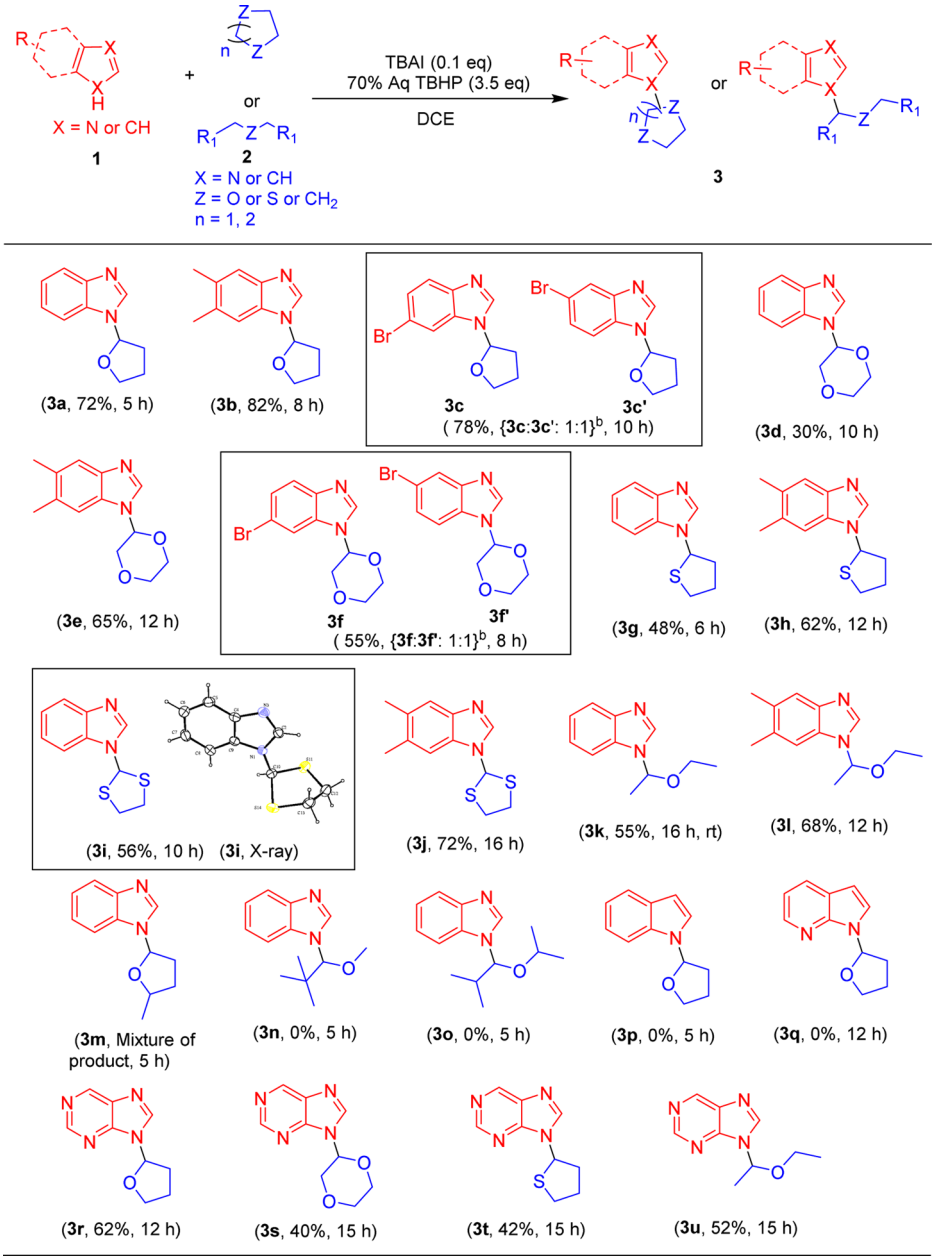
Table 2. Coupling of Un/substituted Azoles with Ethers/Thioethers[a]



[a]Reaction conditions (unless otherwise noted): azole **1** (1 mmol), ether/thioether **2** (15 mmol), DCE (15 mL), 80 °C. Isolated yields are shown. [b]The ratio was revealed by $^{1}H/^{13}C$ NMR spectroscopy.

afford 1-(1,3-dithiolan-2-yl)-1*H*-benzo[*d*]imidazole (**3i**) in 56% yield. The structure of **3i** was also confirmed by X-ray crystallography (details are given in the Supporting Information). 5,6-Dimethylbenzimidazole also underwent coupling with 1,3-dithiolane to give **3j** in 72% yield. The optimized conditions also worked with alicyclic ethers such as diethyl ether, giving corresponding coupled product **3k** in 55% yield. Coupled product **3l** was formed in 68% yield by the reaction between 5,6-dimethylbenzimidazole and diethyl ether. When a substituted cyclic ether such as 2-methyltetrahydrofuran was tried, a mixture of products was observed. Apart from diethyl ether, other alicyclic ethers such as diisopropyl ether and *tert*-butyl methyl ether did not work under the optimized conditions. *N*-Heterocycles such as indole and 7-azaindole also did not work under the optimized conditions. Interestingly when purine was tried, the coupling reaction proceeded, giving the coupled products in good to moderate yields. Coupling of purine with THF, 1,4-dioxane, tetrahydrothiophene, and diethyl ether gave the corresponding coupled products **3r**, **3s**, **3t**, and **3u** in yields of 62%, 40%, 42% and 52%, respectively. 1*H*-Benzimidazoles containing electron-donating groups gave comparatively better yields.

Next, we extended the reaction to other azoles, such as 1*H*-1,2,3-benzotriazole and various 1*H*-1,2,3-triazoles, and the optimized method worked efficiently, giving separable regioisomeric mixtures of the corresponding coupled products in moderate to good yields (Table 3). When 1*H*-1,2,3-benzotriazole was treated with THF under the optimized conditions, a separable mixture of regioisomers **5a** and **5a′** was observed in 65% and 33% yield, respectively. 1,4-Dioxane also

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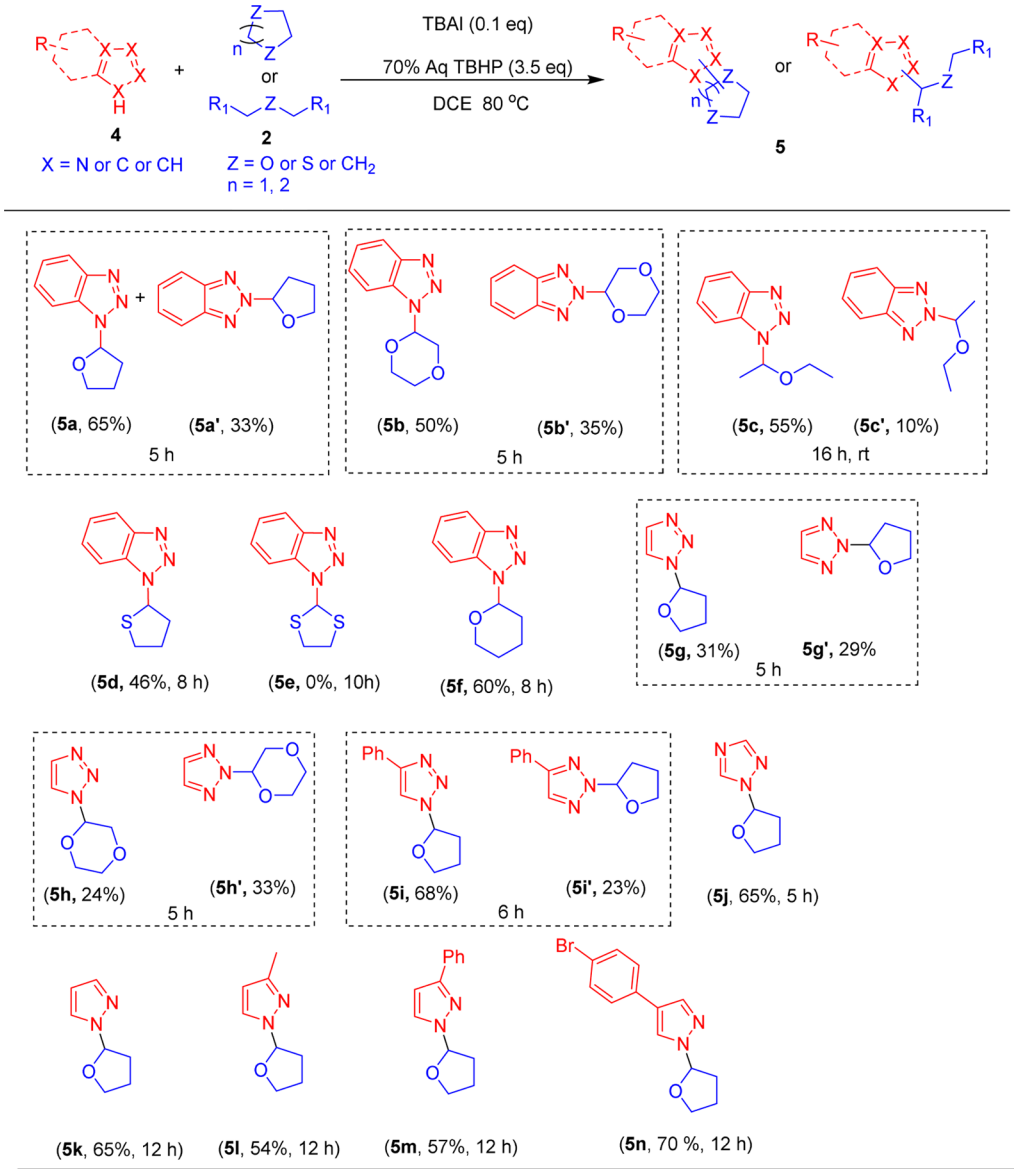
Table 3. Coupling of Un/substituted Azoles with Ethers/Thioethers[a]



[a]Reaction conditions (unless otherwise noted): azole **4** (1 mmol), ether/thioether **2** (15 mmol), DCE (15 mL), 80 °C. Isolated yields are shown.

underwent coupling smoothly to give a separable mixture of regioisomers **5b** and **5b′** in 50% and 35% yield, respectively. Similarly, 1*H*-1,2,3-benzotriazole also underwent coupling with diethyl ether to give a mixture of regioisomers **5c** and **5c′** in 55% and 10% yield, respectively. 1*H*-1,2,3-Benzotriazole also underwent coupling with tetrahydrothiophene to afford the coupled product **5d** in 46% yield as the major isolable regioisomer. 1,3-Dithiolane did not work with benzotriazole, but pyran coupled successfully to give **5f** in 60% yield as the major isolable regioisomer. 1*H*-1,2,3-Triazole underwent coupling with THF to give the corresponding separable mixture of regioisomers **5g** and **5g′** in 31 and 29% yield, respectively. Under the optimized conditions, 1*H*-1,2,3-triazole also coupled with 1,4-dioxane, and a mixture of regioisomers **5h** and **5h′** was isolated in 24 and 33% yield, respectively. 4-Phenyl-1*H*-1,2,3-triazole also underwent coupling with THF, giving a separable mixture of regioisomers **5i** and **5i′** in 68 and 23% yield, respectively. To our delight, the optimized method also worked with 1*H*-1,2,4-triazole, which underwent coupling with THF to give the corresponding coupled product **5j** in 65% yield. Coupling of 1*H*-pyrazole with THF under the optimized conditions gave the corresponding coupled product **5k** in 65% yield. 3-Methyl- and 3-phenyl-1*H*-pyrazole also underwent coupling with THF to give the respective coupled products **5l** and **5m** in 54 and 57% yield, respectively. 4-(4-Bromophenyl)-1*H*-pyrazole also worked under the optimized conditions, giving coupled product **5n** in 70% yield.

To gain insight into the reaction mechanism involved for the coupling of azoles with ethers/thioethers, some experiments were conducted. When the coupling of benzimidazole with THF was performed in the presence of the free-radical scavenger 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), the yield of the coupled product **3a** decreased drastically and the formation of the THF−TEMPO coupled product **6** was observed, confirming the involvement of a free-radical pathway. Surprisingly, even in the presence of 10 equiv of TEMPO, the formation of the coupled product was not completely suppressed (Scheme 1), indicating the initial formation of

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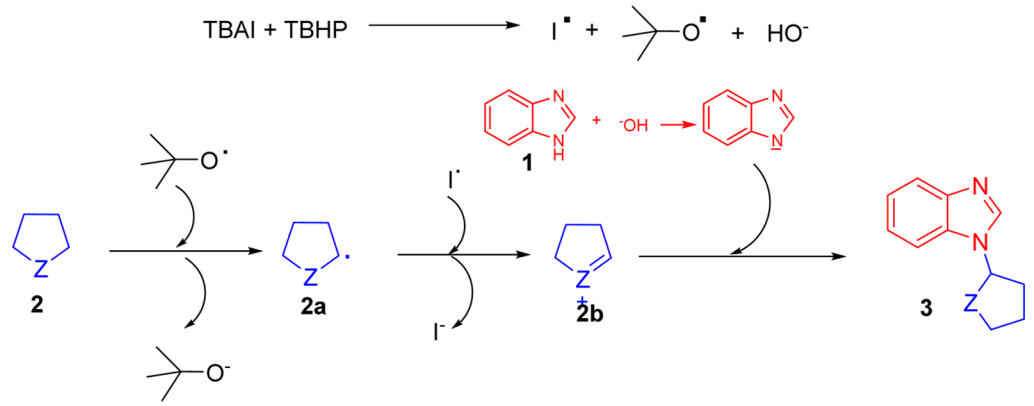
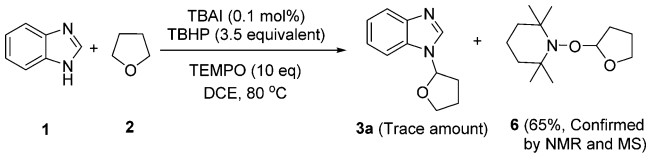


Figure 3. Plausible mechanism for the coupling of azoles with ethers/thioethers.

Scheme 1. Coupling in the Presence of a Free-Radical Scavenger



radical **2a** followed by immediate conversion into cation **2b** (as observed earlier),[7,8] which is attacked by the azole to give the *N*-alkylated product. On the basis of the literature[7,8] and our experimental findings, a plausible mechanism would involve the intermediacy of a radical/oxonium or thionium ion and follow the path depicted in Figure 3.

In conclusion, we have developed a general, metal-free, TBAI/TBHP-catalyzed method for the *N*-alkylation of azoles via α-C(sp^3)−H activation of ethers and thioethers. The optimized method works successfully with diverse ranges of un/substituted azoles and ethers/thioethers. Moreover, the present method gives a diverse range of *N*-substituted azoles that can be explored for pharmacological applications and as synthons/intermediates in organic synthesis.

EXPERIMENTAL SECTION

General Information. ^{1}H, ^{13}C, and DEPT NMR spectra were recorded on a 400 MHz spectrometer using $CDCl_3$ as the solvent. Melting points were recorded on a digital melting point apparatus. HRMS spectra were recorded on a UHD-Q-TOF HRMS instrument. MALDI MS spectra were recorded on MALDI-TOF mass spectrometer using 2,5-dihydroxybenzoic acid/ α-cyano-4-hydroxycinnamic acid as the matrix in acetonitrile/water containing 0.01% TFA. GC−MS data were obtained using a GC−EI mass spectrometer. Three-dimensional X-ray intensity diffraction data for a block-shaped single crystal were recorded on an X-ray diffractometer equipped with a CCD camera.

General Procedure for the Synthesis of Compounds in Table 2. Azole **1** (1*H*-benzimidazole, 5,6-dimethyl-1*H*-benzimidazole, 6-bromo-1*H*-benzimidazole, or 9*H*-purine) (1 mmol), ether/thiother **2** (15 mmol), TBHP (3.5 mmol, 70% in water), and TBAI (0.01 mmol) were dissolved in 8 mL of DCE solvent. The reaction mixture was refluxed until the starting material was consumed. After completion of the reaction, the solvent was evaporated from the reaction mixture, and the residue was extracted with ethyl acetate solvent. The product was purified by flash chromatography using a 1% methanol and DCM solvent system.

General Procedure for the Synthesis of Compounds in Table 3. Azole **4** (1*H*-benzotriazole, 1*H*-1,2,3-triazole, 1*H*-1,2,4-triazole, pyrazole) (1 mmol), ether/thioether **2** (15 mmol), TBHP (3.5 mmol, 70% in water), and TBAI (0.01 mmol) were dissolved in 8 mL of DCE solvent. The reaction mixture was refluxed until the starting material was consumed. After completion of the reaction, the solvent was evaporated from the reaction mixture, and the residue was extracted with ethyl acetate solvent. The product was purified by flash chromatography using a 15% ethyl acetate and hexane solvent system. (Note: we observed that products containing 1*H*-1,2,3-triazole underwent degradation upon storage at room temperature).

Spectral Data. *1-(Tetrahydrofuran-2-yl)-1H-benzo[d]imidazole (**3a**) (IIIM/724/1572/CN/18).*[7] Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.85−7.75 (m, 1H), 7.50−7.42 (m, 1H), 7.36−7.25 (m, 2H), 6.19 (dd, J = 5.6, 4.0 Hz, 1H), 4.23−4.17 (m, 1H), 4.10−4.04 (m, 1H), 2.52−2.44 (m, 2H), 2.19−2.12 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 144.1, 140.2, 132.6, 123.1, 122.5, 120.3, 110.5, 86.0, 68.9, 31.8, 24.2; HRMS (ESI+) calcd for $C_{11}H_{13}N_2O$ 189.1028 ([M + H]$^+$), found 189.1028.

*5,6-Dimethyl-1-(tetrahydrofuran-2-yl)-1H-benzo[d]imidazole (**3b**) (IIIM/724/1572/CN/65).* Colorless liquid; TLC R_f = 0.6 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.55 (s, 1H), 7.23 (s, 1H), 6.14 (t, J = 4.7 Hz, 1H), 4.17 (dd, J = 14.7, 7.1 Hz, 1H), 4.05 (dd, J = 15.3, 7.7 Hz, 1H), 2.50−2.30 (m, 8H), 2.15 (dd, J = 14.3, 7.1 Hz, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 142.9, 139.5, 132.2, 131.3, 131.2, 120.3, 110.6, 85.9, 68.8, 31.7, 24.2, 20.5, 20.2; HRMS (ESI+) calcd for $C_{13}H_{17}N_2O$ 217.1341 ([M + H]$^+$), found 217.1349.

*6-Bromo-1-(tetrahydrofuran-2-yl)-1H-benzo[d]imidazole (**3c**) (IIIM/724/1572/CN/48) and 5-Bromo-1-(tetrahydrofuran-2-yl)-1H-benzo[d]imidazole (**3c′**) (IIIM/724/1572/CN/48).* The ratio was calculated by ^{1}H and ^{13}C NMR analysis. Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.91 (s, 0.47H), 7.63 (d, J = 8.7 Hz, 1H), 7.33 (dd, J = 22.5, 8.5 Hz, 1.51H), 6.10 (dd, J = 5.8, 2.8 Hz, 1H), 4.19−4.09 (m, 1H), 4.08−3.99 (m, 1H), 2.50−2.30 (m, 2H), 2.19−1.98 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 141.2, 140.8, 126.1, 125.8, 123.0, 121.4, 116.4, 115.5, 113.7, 111.8, 86.1, 69.0, 31.8, 24.1; HRMS (ESI+) calcd for $C_{11}H_{12}BrN_2O$ 267.0133 ([M + H]$^+$), found 267.0139.

*1-(1,4-Dioxan-2-yl)-1H-benzo[d]imidazole (**3d**) (IIIM/724/1572/CN/27).*[10] Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.75 (d, J = 6.0 Hz, 1H), 7.44 (d, J = 5.6 Hz, 1H), 7.29−7.18 (m, 2H), 5.63 (s, 1H), 4.07 (d, J = 4.6 Hz, 2H), 3.88−3.59 (m, 4H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 143.2, 141.4, 133.1, 123.6, 122.9, 120.3, 110.6, 78.5, 67.9, 66.4, 63.4; HRMS (ESI+) calcd for $C_{11}H_{13}N_2O_2$ 205.0977 ([M + H]$^+$), found 205.0978.

*1-(1,4-Dioxan-2-yl)-5,6-dimethyl-1H-benzo[d]imidazole (**3e**) (IIIM/724/1572/CN/67).* Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.57 (s, 1H), 7.28 (s, 1H), 5.65 (t, J = 3.6 Hz, 1H), 4.45 (t, J = 6.1 Hz, 1H), 4.24−4.06 (m, 1H), 3.97−3.75 (m, 4H), 2.38 (d, J = 7.3 Hz, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 142.5, 140.8, 132.7, 131.7, 131.4,

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120.3, 110.7, 78.5, 68.1, 66.4, 63.4, 20.5, 20.2; HRMS (ESI+) calcd for $C_{13}H_{17}N_2O_2$ 233.1290 ([M + H]$^+$), found 233.1293.

*6-Bromo-1-(1,4-dioxan-2-yl)-1H-benzo[d]imidazole (**3f**) (IIIM/724/1572/CN/61) and 5-Bromo-1-(1,4-dioxan-2-yl)-1H-benzo[d]-imidazole (**3f′**) (IIIM/724/1572/CN/61).* The ratio was calculated by ^{1}H and ^{13}C NMR analysis. Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.8 Hz, 1H), 7.90 (s, 0.46H), 7.66−7.57 (m, 1H), 7.35 (d, J = 4.8 Hz, 1.30H), 5.66−5.55 (m, 1H), 4.15−3.99 (m, 2H), 3.89−3.63 (m, 4H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 142.6, 142.2, 126.5, 126.2, 123.3, 121.7, 116.8, 115.8, 113.9, 111.9, 78.5, 67.8, 66.4, 63.1; HRMS (ESI+) calcd for $C_{11}H_{12}BrN_2O_2$ 283.0082 ([M + H]$^+$), found 283.0084.

*1-(Tetrahydrothiophen-2-yl)-1H-benzo[d]imidazole (**3g**) (IIIM/724/1572/CN/23).* Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.40 (d, J = 6.9 Hz, 1H), 7.28−7.09 (m, 2H), 6.00 (s, 1H), 3.29−3.16 (m, 1H), 2.97 (dd, J = 16.0, 9.3 Hz, 1H), 2.39−2.15 (m, 4H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 144.3, 141.8, 133.3, 122.9, 122.5, 120.5, 110.0, 63.0, 38.2, 33.0, 28.7; HRMS (ESI+) calcd for $C_{11}H_{13}N_2S$ 205.0799 ([M + H]$^+$), found 205.0797.

*5,6-Dimethyl-1-(tetrahydrothiophen-2-yl)-1H-benzo[d]imidazole (**3h**) (IIIM/724/1572/CN/68).* Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.48 (s, 1H), 7.14 (s, 1H), 5.99−5.87 (m, 1H), 3.22 (dd, J = 10.2, 6.2 Hz, 1H), 2.96 (dd, J = 16.0, 9.2 Hz, 1H), 2.41−2.23 (m, 8H), 2.22−2.08 (m, 1H), 2.06−1.89 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 142.1, 140.0, 131.0, 130.8, 130.3, 119.5, 109.1, 61.9, 37.1, 31.9, 27.6, 19.6, 19.2; HRMS (ESI+) calcd for $C_{13}H_{17}N_2S$ 233.1112 ([M + H]$^+$), found 233.1128.

*1-(1,3-Dithiolan-2-yl)-1H-benzo[d]imidazole (**3i**) (IIIM/724/1572/CN/38).* White solid; mp 110 °C; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.73 (dd, J = 6.6, 2.0 Hz, 1H), 7.42 (dd, J = 6.6, 1.9 Hz, 1H), 7.29−7.22 (m, 2H), 7.00 (s, 1H), 3.54−3.32 (m, 4H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 144.5, 141.4, 132.8, 123.3, 122.9, 120.6, 110.4, 65.8, 39.5; HRMS (ESI+) calcd for $C_{10}H_{11}N_2S_2$ 223.0364 ([M + H]$^+$), found 223.0368.

*1-(1,3-Dithiolan-2-yl)-5,6-dimethyl-1H-benzo[d]imidazole (**3j**) (IIIM/724/1572/CN/69).* White solid; mp 135 °C; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.54 (s, 1H), 7.24 (s, 1H), 7.01 (s, 1H), 3.58−3.40 (m, 4H), 2.39 (d, J = 16.5 Hz, 6H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 143.1, 140.7, 132.5, 131.8, 131.6, 120.6, 110.5, 65.8, 39.5, 20.6, 20.2; HRMS (ESI+) calcd for $C_{12}H_{15}N_2S_2$ 251.0677 ([M + H]$^+$), found 251.0694.

*1-(1-Ethoxyethyl)-1H-benzo[d]imidazole (**3k**) (IIIM/724/1572/CN/20).*[7] (Note: reactions with ethers were carried out at room temperature with longer reaction times.) Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.78 (dd, J = 5.3, 2.9 Hz, 1H), 7.60−7.49 (m, 1H), 7.27 (dd, J = 5.8, 2.9 Hz, 2H), 5.68 (q, J = 5.9 Hz, 1H), 3.45−3.35 (m, 1H), 3.31−3.18 (m, 1H), 1.73 (d, J = 6.0 Hz, 3H), 1.10 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 142.8, 140.0, 131.3, 122.2, 121.6, 119.2, 110.0, 82.2, 63.0, 21.1, 13.7; HRMS (ESI+) calcd for $C_{11}H_{15}N_2O$ 191.1184 ([M + H]$^+$), found 191.1185.

*1-(1-Ethoxyethyl)-5,6-dimethyl-1H-benzo[d]imidazole (**3l**) (IIIM/724/1572/CN/66).* Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.49 (s, 1H), 7.27 (s, 1H), 5.52 (q, J = 6.0 Hz, 1H), 3.35 (dd, J = 15.7, 7.3 Hz, 1H), 3.23 (dd, J = 15.1, 7.8 Hz, 1H), 2.30 (d, J = 8.1 Hz, 6H), 1.69 (d, J = 6.0 Hz, 3H), 1.08 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 142.8, 140.3, 132.2, 131.4, 131.0, 120.3, 111.1, 82.9, 63.9, 22.1, 20.5, 20.2, 14.8; HRMS (ESI+) calcd for $C_{13}H_{19}N_2O$ 219.1497 ([M + H]$^+$), found 219.1505.

*9-(Tetrahydrofuran-2-yl)-9H-purine (**3r**) (IIIM/724/1572/CN/53).* Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.99 (s, 1H), 8.23 (s, 1H), 6.40 (dd, J = 6.2, 2.9 Hz, 1H), 4.32 (dd, J = 14.3, 7.0 Hz, 1H), 4.11 (dd, J = 15.4, 7.6 Hz, 1H), 2.73−2.46 (m, 2H), 2.27−2.11 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 152.3, 150.5, 148.5, 143.4, 134.7, 85.9, 69.9, 32.3, 24.3; HRMS (ESI+) calcd for $C_9H_{11}N_4O$ 191.0933 ([M + H]$^+$), found 191.0927.

*9-(1,4-Dioxan-2-yl)-9H-purine (**3s**) (IIIM/724/1572/CN/58).* Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.95 (s, 1H), 8.46 (s, 1H), 6.05−5.94 (m, 1H), 4.15 (dd, J = 11.8, 1.3 Hz, 1H), 4.06 (dd, J = 12.0, 5.7 Hz, 1H), 3.91−3.81 (m, 4H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 152.9, 151.0, 148.8, 143.7, 133.8, 77.2, 68.3, 66.2, 64.3; HRMS (ESI+) calcd for $C_9H_{11}N_4O_2$ 207.0882 ([M + H]$^+$), found 207.0878.

*9-(Tetrahydrothiophen-2-yl)-9H-purine (**3t**) (IIIM/724/1572/CN/59).* Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.93 (s, 1H), 8.45 (s, 1H), 6.37−6.21 (m, 1H), 3.31−3.26 (m, 1H), 3.03−2.97 (m, 1H), 2.41−2.32 (m, 2H), 2.31−2.15 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 152.4, 150.9, 148.7, 144.5, 134.9, 62.0, 38.9, 33.3, 28.7; HRMS (ESI+) calcd for $C_9H_{11}N_4S$ 207.0704 ([M + H]$^+$), found 207.0696.

*9-(1-Ethoxyethyl)-9H-purine (**3u**) (IIIM/724/1572/CN/62).* Colorless liquid; TLC R_f = 0.5 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.92 (s, 1H), 8.26 (s, 1H), 6.00 (q, J = 6.0 Hz, 1H), 3.56−3.39 (m, 1H), 3.35−3.19 (m, 1H), 1.74 (d, J = 6.0 Hz, 3H), 1.11 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 152.7, 151.1, 148.7, 142.7, 134.0, 80.8, 64.8, 22.4, 14.7; HRMS (ESI+) calcd for $C_9H_{13}N_4O$ 193.1089 ([M + H]$^+$), found 193.1088.

*1-(Tetrahydrofuran-2-yl)-1H-benzo[d][1,2,3]triazole (**5a**) (IIIM/724/1572/CN/21(a)).*[10] Colorless liquid; TLC R_f = 0.4 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 6.44 (dd, J = 6.5, 1.6 Hz, 1H), 4.10−3.88 (m, 2H), 3.20−3.10 (m, 1H), 2.57−2.47 (m, 1H), 2.32−2.43 (m, 1H), 2.19−2.04 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 146.2, 132.8, 127.5, 124.1, 119.7, 110.4, 87.9, 69.2, 30.8, 24.3; HRMS (ESI+) calcd for $C_{10}H_{12}N_3O$ 190.0980 ([M + H]$^+$), found 190.0856; MALDI TOF MS calcd for $C_{10}H_{12}N_3O$ ([M + H]$^+$) 190.0980, found 190.0971.

*2-(Tetrahydrofuran-2-yl)-2H-benzo[d][1,2,3]triazole (**5a′**) (IIIM/724/1572/CN/21(b)).* Colorless liquid; TLC R_f = 0.8 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 6.4, 2.9 Hz, 2H), 7.38 (dd, J = 6.5, 2.8 Hz, 2H), 6.60 (d, J = 4.8 Hz, 1H), 4.33 (dd, J = 14.0, 7.4 Hz, 1H), 4.13 (dd, J = 14.3, 7.4 Hz, 1H), 2.77−2.54 (m, 1H), 2.54−2.45 (m, 2H), 2.17−2.09 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 144.2, 126.6, 118.4, 94.1, 70.2, 32.3, 24.3; HRMS (ESI+) calcd for $C_{10}H_{12}N_3O$ 190.0980 ([M + H]$^+$), found 190.0854; MALDI TOF MS calcd for $C_{10}H_{12}N_3O$ ([M + H]$^+$) 190.0980, found 190.0997.

*1-(1,4-Dioxan-2-yl)-1H-benzo[d][1,2,3]triazole (**5b**) (IIIM/724/1572/CN/29(a)).*[10] White solid; mp 85 °C; TLC R_f = 0.4 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.3 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 6.10 (dd, J = 7.2, 2.8 Hz, 1H), 4.54 (dd, J = 11.8, 7.3 Hz, 1H), 4.24 (dd, J = 11.9, 2.7 Hz, 1H), 4.03−3.80 (m, 4H); ^{13}C NMR (100.16 MHz, $CDCl_3$) δ 146.0, 132.5, 127.9, 124.4, 120.1, 110.6, 82.0, 67.3, 65.9, 65.3; HRMS (ESI+) calcd for $C_{10}H_{12}N_3O_2$ 206.0930 ([M + H]$^+$), found 206.0925.

*2-(1,4-Dioxan-2-yl)-2H-benzo[d][1,2,3]triazole (**5b′**) (IIIM/724/1572/CN/29(b)).* White solid; mp 85 °C; TLC R_f = 0.8 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, J = 6.6, 3.0 Hz, 2H), 7.42 (dd, J = 6.6, 3.0 Hz, 2H), 6.12 (dd, J = 6.4, 2.8 Hz, 1H), 4.52 (dd, J = 11.9, 6.5 Hz, 1H), 4.22 (dd, J = 11.9, 2.7 Hz, 1H), 4.15−4.07 (m, 1H), 4.05−3.94 (m, 1H), 3.90 (t, J = 3.0 Hz, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 144.3, 127.1, 118.6, 86.4, 67.6, 65.7, 65.2; HRMS (ESI+) calcd for $C_{10}H_{12}N_3O_2$ 206.0930 ([M + H]$^+$), found 206.0932.

*1-(1-Ethoxyethyl)-1H-benzo[d][1,2,3]triazole (**5c**) (IIIM/724/1572/CN/22(a)).* Colorless liquid; TLC R_f = 0.5 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 6.19 (q, J = 6.1 Hz, 1H), 3.55−3.40 (m, 1H), 3.24−3.10 (m, 1H), 1.79 (d, J = 6.1 Hz, 3H), 1.06 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 146.8, 131.1, 127.4, 124.1, 120.0, 111.1, 87.0, 64.3, 21.1, 14.7; HRMS (ESI+) calcd for $C_{10}H_{14}N_3O$ 192.1137 ([M + H]$^+$), found 192.1009;

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GC−MS(EI) m/z (relative intensity) 192.2 (M^+, 2.1), 176.3 (4.65), 147.4 (100), 119.5 (53.98), 91.3 (88.3), 64.4 (37.04), 45.4 (77.61).

*2-(1-Ethoxyethyl)-2H-benzo[d][1,2,3]triazole (**5c′**) (IIIM/724/1572/CN/22(b)).* Colorless liquid; TLC R_f = 0.8 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, J = 5.9, 2.4 Hz, 2H), 7.33 (dd, J = 6.0, 2.3 Hz, 2H), 6.00 (q, J = 5.8 Hz, 1H), 3.59−3.42 (m, 1H), 3.36−3.17 (m, 1H), 1.85 (d, J = 5.9 Hz, 3H), 1.09 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 144.1, 126.7, 118.5, 91.5, 65.1, 21.5, 14.6; HRMS (ESI+) calcd for $C_{10}H_{14}N_3O$ 192.1137 ([M + H]$^+$), found 192.1009; GC−MS(EI) m/z (relative intensity) 192.2 (M^+, 2.2), 176.3 (5.7), 147.4 (100), 119.4 (68.2), 91.3 (86.6), 77.3 (33.54), 64.4 (41).

*1-(Tetrahydrothiophen-2-yl)-1H-benzo[d][1,2,3]triazole (**5d**) (IIIM/724/1572/CN/24).* Colorless liquid; TLC R_f = 0.5 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 6.44−6.35 (m, 1H), 3.31−3.20 (m, 1H), 3.13−2.99 (m, 1H), 2.94−2.84 (m, 1H), 2.57−2.36 (m, 2H), 2.32−2.22 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 146.4, 132.1, 127.1, 123.9, 120.3, 110.3, 65.9, 37.1, 33.8, 29.9; HRMS (ESI+) calcd for $C_{10}H_{12}N_3S$ 206.0752 ([M + H]$^+$), found 206.0621; MALDI TOF MS calcd for $C_{10}H_{11}N_3S$ ([M + H]$^+$) 206.0752, found 206.0724.

*1-(Tetrahydro-2H-pyran-2-yl)-1H-benzo[d][1,2,3]triazole (**5f**) (IIIM/724/1582/CN/01).* Colorless liquid; TLC R_f = 0.4 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 6.05 (dd, J = 8.2, 2.8 Hz, 1H), 3.96 (dd, J = 11.6, 4.4 Hz, 1H), 3.86−3.72 (m, 1H), 2.71−2.56 (m, 1H), 2.29−2.11 (m, 2H), 1.87−1.68 (m, 3H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 146.2, 132.5, 127.4, 124.1, 119.8, 111.1, 85.6, 66.8, 29.2, 24.9, 21.4; HRMS (ESI+) calcd for $C_{11}H_{13}N_3O$ 204.1137 ([M + H]$^+$), found 204.1002; MALDI TOF MS calcd for $C_{11}H_{13}N_3O$ ([M + H]$^+$) 204.1137, found 204.1145.

*1-(Tetrahydrofuran-2-yl)-1H-1,2,3-triazole (**5g**) (IIIM/724/1572/CN/30(a)).* Colorless liquid; TLC R_f = 0.3 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 2H), 6.25 (d, J = 6.5 Hz, 1H), 4.18−3.99 (m, 2H), 2.80−2.65 (m, 1H), 2.50−2.40 (m, 1H), 2.16−2.09 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 133.6, 122.0, 89.4, 69.6, 32.2, 23.8; HRMS (ESI+) calcd for $C_6H_{10}N_3O$ 140.0824 ([M + H]$^+$), found 140.0771.

*2-(Tetrahydrofuran-2-yl)-2H-1,2,3-triazole (**5g′**) (IIIM/724/1572/CN/30(b)).* Colorless liquid; TLC R_f = 0.7 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 2H), 6.39−6.26 (m, 1H), 4.16 (dd, J = 13.9, 7.4 Hz, 1H), 4.04 (dd, J = 13.9, 7.6 Hz, 1H), 2.72−2.56 (m, 1H), 2.45−2.36 (m, 2H), 2.20−2.01 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 134.5, 92.1, 69.5, 31.3, 24.4; HRMS (ESI+) calcd for $C_6H_{10}N_3O$ 140.0824 ([M + H]$^+$), found 140.0815; MALDI TOF MS calcd for $C_6H_9N_3O$ ([M + H]$^+$) 140.0824, found 140.0839.

*1-(1,4-Dioxan-2-yl)-1H-1,2,3-triazole (**5h**) (IIIM/724/1572/CN/31(a)).* Colorless liquid; TLC R_f = 0.3 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.70 (s, 1H), 5.84 (s, 1H), 4.12 (dd, J = 11.9, 2.0 Hz, 1H), 4.01 (dd, J = 11.9, 5.9 Hz, 1H), 3.91−3.67 (m, 4H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 133.7, 122.7, 81.8, 68.2, 66.0, 64.3; HRMS (ESI+) calcd for $C_6H_{10}N_3O_2$ 156.0773 ([M + H]$^+$), found 156.0764.

*2-(1,4-Dioxan-2-yl)-2H-1,2,3-triazole (**5h′**) (IIIM/724/1572/CN/31(b)).* Colorless liquid; TLC R_f = 0.7 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 2H), 5.78 (dd, J = 7.1, 2.6 Hz, 1H), 4.27 (dd, J = 11.7, 7.3 Hz, 1H), 4.03 (dd, J = 11.8, 2.5 Hz, 1H), 3.95−3.84 (m, 2H), 3.80−3.70 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 135.2, 84.8, 67.5, 65.8, 65.4; HRMS (ESI+) calcd for $C_6H_{10}N_3O_2$ 156.0773 ([M + H]$^+$), found 156.0764.

*4-Phenyl-1-(tetrahydrofuran-2-yl)-1H-1,2,3-triazole (**5i**) (IIIM/724/1572/CN/39(a)).* Colorless liquid; TLC R_f = 0.3 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.70 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 6.26−6.19 (m, 1H), 4.09 (dd, J = 14.3, 7.4 Hz, 1H), 3.94 (dd, J = 14.1, 7.4 Hz, 1H), 2.63−2.52 (m, 1H), 2.41−2.22 (m, 2H), 2.03−1.88 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 148.0, 131.4, 130.3, 128.8, 128.5, 126.0, 92.3, 69.5, 31.3, 24.5; HRMS (ESI+) calcd for $C_{12}H_{14}N_3O$ 216.1137 ([M + H]$^+$), found 216.1134.

*4-Phenyl-2-(tetrahydrofuran-2-yl)-2H-1,2,3-triazole (**5i′**) (IIIM/724/1572/CN/39(b)).* Colorless liquid; TLC R_f = 0.7 (30% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.75−7.69 (m, 2H), 7.35 (t, J = 7.3 Hz, 2H), 7.27 (t, J = 7.3 Hz, 1H), 6.29−6.23 (m, 1H), 4.13 (dd, J = 14.4, 7.3 Hz, 1H), 3.99 (dd, J = 14.1, 7.3 Hz, 1H), 2.68−2.56 (m, 1H), 2.45−2.27 (m, 2H), 2.10−1.96 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 148.0, 131.4, 130.3, 128.8, 128.5, 126.0, 92.3, 69.5, 31.3, 24.4; HRMS (ESI+) calcd for $C_{12}H_{14}N_3O$ 216.1137 ([M + H]$^+$), found 216.1132; MALDI TOF MS calcd for $C_{12}H_{13}N_3O$ ([M + H]$^+$) 216.1137, found 216.1156.

*1-(Tetrahydrofuran-2-yl)-1H-1,2,4-triazole (**5j**) (IIIM/724/1572/CN/34).*[1] Colorless liquid; TLC R_f = 0.4 (50% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.97 (s, 1H), 6.12−6.02 (m, 1H), 4.18 (dd, J = 13.4, 8.0 Hz, 1H), 4.04 (dd, J = 15.4, 7.6 Hz, 1H), 2.60−2.53 (m, 1H), 2.43−2.33 (m, 1H), 2.21−1.99 (m, 2H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 151.7, 142.1, 88.9, 69.6, 32.2, 23.5; HRMS (ESI+) calcd for $C_6H_{10}N_3O$ 140.0824 ([M + H]$^+$), found 140.0829.

*1-(Tetrahydrofuran-2-yl)-1H-pyrazole (**5k**) (IIIM/724/1572/CN/47).* Colorless liquid; TLC R_f = 0.4 (20% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 2H), 6.20 (s, 1H), 5.93 (d, J = 6.3 Hz, 1H), 4.05 (dd, J = 14.1, 7.6 Hz, 1H), 3.91 (dd, J = 14.8, 7.4 Hz, 1H), 2.58−2.45 (m, 1H), 2.34−2.22 (m, 1H), 2.18−2.04 (m, 1H), 2.01−1.93 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 139.8, 128.0, 105.6, 90.0, 69.1, 31.7, 24.4; HRMS (ESI+) calcd for $C_7H_{10}N_2O$ 139.0871 ([M + H]$^+$), found 139.0859.

*3-Methyl-1-(tetrahydrofuran-2-yl)-1H-pyrazole (**5l**) (IIIM/724/1572/CN/50).* Colorless liquid; TLC R_f = 0.4 (20% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 5.97 (s, 1H), 5.89−5.79 (m, 1H), 4.05 (dd, J = 14.3, 7.0 Hz, 1H), 3.89 (dd, J = 14.5, 7.2 Hz, 1H), 2.56−2.41 (m, 1H), 2.34−2.16 (m, 4H), 2.14−2.03 (m, 1H), 2.01−1.91 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 149.2, 128.6, 105.4, 89.8, 69.0, 31.6, 24.5, 13.5; HRMS (ESI+) calcd for $C_8H_{13}N_2O$ 153.1028 ([M + H]$^+$), found 153.1025.

*3-Phenyl-1-(tetrahydrofuran-2-yl)-1H-pyrazole (**5m**) (IIIM/724/1572/CN/44).* Colorless liquid; TLC R_f = 0.4 (20% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.4 Hz, 2H), 7.51 (d, J = 1.9 Hz, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.21 (dd, J = 14.3, 6.8 Hz, 1H), 6.50 (d, J = 2.0 Hz, 1H), 5.96 (dd, J = 6.3, 1.8 Hz, 1H), 4.11 (dd, J = 13.6, 7.8 Hz, 1H), 3.94 (dd, J = 15.0, 7.4 Hz, 1H), 2.65−2.51 (m, 1H), 2.33−2.23 (m, 1H), 2.21−2.09 (m, 1H), 2.02−1.94 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 151.7, 133.6, 129.1, 128.5, 127.4, 125.7, 102.9, 90.3, 69.2, 31.9, 24.3; HRMS (ESI+) calcd for $C_{13}H_{15}N_2O$ 215.1184 ([M + H]$^+$), found 215.1198.

*4-(4-Bromophenyl)-1-(tetrahydrofuran-2-yl)-1H-pyrazole (**5n**) (IIIM/724/1572/CN/37).* Colorless liquid; TLC R_f = 0.4 (20% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 4.1 Hz, 2H), 7.61 (s, 1H), 7.53 (d, J = 7.0 Hz, 2H), 6.57 (d, J = 1.3 Hz, 1H), 6.05 (d, J = 5.2 Hz, 1H), 4.20 (dd, J = 12.5, 7.0 Hz, 1H), 4.04 (dd, J = 14.2, 7.0 Hz, 1H), 2.74−2.62 (m, 1H), 2.43−2.34 (m, 1H), 2.32−2.18 (m, 1H), 2.10−2.01 (m, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 150.7, 132.6, 131.6, 129.3, 127.2, 121.4, 102.8, 90.3, 69.4, 32.0, 24.3; HRMS (ESI+) calcd for $C_{13}H_{14}BrN_2O$ 293.0290 ([M + H]$^+$), found 293.0287.

*2,2,6,6-Tetramethyl-1-((tetrahydrofuran-2-yl)oxy)piperidine (**6**) (IIIM/724/1572/CN/55).* Colorless liquid; TLC R_f = 0.8 (5% EtOAC/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (d, J = 4.5 Hz, 1H), 3.84−3.69 (m, 2H), 2.00−1.78 (m, 4H), 1.40 (d, J = 6.5 Hz, 6H), 1.20−0.87 (m, 12H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 109.5, 66.6, 60.1, 58.6, 40.0, 39.6, 33.8, 33.3, 31.2, 23.8, 20.4, 20.0, 17.2; HRMS (ESI+) calcd for $C_{13}H_{26}NO_2$ 228.1964 ([M + H]$^+$), found 228.1961.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR and MS spectra, XRD analysis details, and a CIF file for **3i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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