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Mild and General Access to Diverse 1*H*-Benzotriazoles via Diboron-Mediated N–OH Deoxygenation and Palladium-Catalyzed C–C and C–N Bond Formation

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Abstract

Benzotriazoles are a highly important class of compounds with broad-ranging applications in such diverse areas as medicinal chemistry, as auxiliaries in organic synthesis, in metallurgical applications, in aircraft deicing and brake fluids, and as antifog agents in photography. Although there are numerous approaches to N-substituted benzotriazoles, the essentially one general method to N-unsubstituted benzotriazoles is via diazotization of *o*-phenylenediamines, which can be limited by the availability of suitable precursors. Other methods to N-unsubstituted benzotriazoles are quite specialized. Although reduction of 1-hydroxy-1*H*-benzotriazoles is known the reactions are not particularly convenient or broadly applicable. This presents a limitation for easy access to and availability of diverse benzotriazoles. Herein, we demonstrate a new, broadly applicable method to diverse 1*H*-benzotriazoles via a mild diboron-reagent mediated deoxygenation of 1-hydroxy-1*H*-benzotriazoles. We have also evaluated sequential deoxygenation and Pd-mediated C–C and C–N bond formation as a one-pot process for further diversification of the benzotriazole moiety. However, results indicated that purification of the deoxygenation product prior to the Pd-mediated reaction is critical to the success of such reactions. The overall chemistry allows for facile access to a variety of new benzotriazoles. Along with the several examples presented, a discussion of the advantages of the approaches is described, as also a possible mechanism for the deoxygenation process.

Keywords

1-hydroxy-1*H*-benzotriazole; benzotriazole; diboron; reduction; deoxygenation

Introduction

As a class, benzotriazoles (Bts) are highly important in a variety of applications. As examples, benzotriazole (Bt) and its derivatives are medicinally and pharmacologically

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important, and many have significant antiviral activities.^[1-3] Bt has been used for decades as a corrosion inhibitor for copper and copper alloys such as brass and bronze. Mechanisms by which Bt inhibits corrosion of copper have been intensely investigated.^[4] Because of its corrosion inhibiting properties of non-ferrous metals, Bt as well as 4- and 5-methyl Bt are components in dishwashing detergent.^[5] Bts are also found in formulations that contact metals, such as aircraft deicing and brake fluids, and in metal-cutting fluids.^[6] In photographic applications Bts are used as antifog agents.^[7]

Bts are also powerful entities in synthesis. As examples; Bt is a versatile synthetic auxiliary in diverse transformations,^[8] aminoacyl Bt derivatives (several now commercially available) are reagents for peptide assembly and synthesis of peptide conjugates,^[9] and Bts have been used as ligands in cross-coupling reactions.^[10]

By contrast to the numerous methods for synthesis of N-substituted Bts (see the Supporting Information for a compilation of several methods), there are far fewer ones to N-unsubstituted Bts, i.e., 1*H*-benzotriazoles (1*H*-Bts). The most common approach, limited by the availability of appropriate precursors, is via diazotization of *ortho*-phenylenediamines (Scheme 1, eq 1). When appropriate precursors are available, this method can be used for synthesis of both 1*H*-Bts and N-substituted Bts^[11,12] The syntheses of alizapride, an antiemetic used for treating postoperative nausea and vomiting,^[13] and the aromatase inhibitor vorazole,^[14] exemplify this chemistry (structures shown in Scheme 1).

Some other specialized approaches to 1*H*-Bts are shown in Scheme 1. These involve diazo transfer (eq 2),^[15] oxidation of an *ortho*-acetamidophenylhydrazine by Cl₂ (eq 3),^[16] high-temperature and high-pressure reaction of benzimidazolones with NaNO₂ (eq 4),^[17] and reaction of benzo-1,2,4-triazin-3-(2*H*)-one with ethereal chloramine (eq 5).^[18]

A general approach to 1*H*-Bts would be the reduction of 1-hydroxy-1*H*-Bts and methods for this have been reported. Limited use of SmI₂ and PCl₃ has been reported to deoxygenate polymer-bound 1-hydroxy-1*H*-Bt.^[19] From the amount of the resulting polymer loading reported, significant excesses of PCl₃ and SmI₂ seem to be needed for this reduction, and these methods have not been assessed for general applicability. Other reductions involving the use of Fe powder in dilute HCl at 86°C,^[20] H₂/Et₃N/FeCl₂/Pt-C at 80°C and at 0.6 MPa (~6 atm),^[21] and Pb/Al/H₂O with dropwise addition of HCl at 100°C^[22] have been reported in the patent literature. The conditions used do not appear particularly convenient and could pose functional group incompatibilities.

We have recently become interested in the scope of reductions that can be mediated by diboron reagents. Such reagents have been briefly investigated for the reduction of three amine N-oxides,^[23] and in prior work we had discovered an unusual deoxygenation of *O*⁶-(benzotriazolyl)inosine and deoxyinosine with bis(pinacolato)diboron [(pinB)₂] and Cs₂CO₃.^[24] These had led us to develop a general reduction of amine N-oxides to amines using (pinB)₂ and bis(catecholato)diboron [(catB)₂], and such reactions could also be conducted in water.^[25] Although reduction of the *zwitterionic* amine N-oxides was readily accomplished, an intriguing question is whether *charge neutral* N–OH bonds, such as those in 1-hydroxy-1*H*-Bts, can be reduced to NH groups by diboron reagents.

Results and Discussion

Feasibility of the N–OH → NH reduction was tested with commercially available HOBt and HOAt using (pinB)₂, (catB)₂, and B₂(OH)₄. MeCN and H₂O were tested as solvents, and DBU and Et₃N were tested as bases. Results from these initial experiments are shown in Table 1.

From the preliminary analysis, several factors come to light. (a) All three diboron reagents tested are effective for the reduction, both in MeCN and in water, but reactions in water present some product isolation problems. (b) Reactions benefit significantly by addition of a base, indicating that deprotonation of HOBt and HOAt facilitates reaction at the boron center. In MeCN/H₂O the *pK_a* values of HOBt and HOAt are estimated at ~5.7 and ~4.0, respectively.^[26] Thus, 1-hydroxy-1*H*-Bts can be readily deprotonated by Et₃N and DBU. (c) B₂(OH)₄ is more reactive than (pinB)₂, consistent with a recent observation.^[27] (d) In the reduction of HOAt (**2**) formation of a significant polar material, possibly an amine adduct, was observed. This diminished over an 8 h reaction time to yield 1*H*-7-azabenzotriazole in excellent yield. In this case, use of Cs₂CO₃ eliminated this problem, producing a relatively fast reaction, but workup was cumbersome due to a pasty nature of the reaction mixture. When 0.5 or 1 equiv of Et₃N was added to a solution of HOAt in MeCN, a polar material formed in each case. These adducts were isolated and ¹H NMR obtained and these clearly showed resonances from Et₃N (see the mechanistic discussion below and the Supporting Information). The formation of an adduct is comparable to hydrazine adducts with 1-hydroxyazabenzotriazoles.^[28]

Next, several new 1-hydroxy-1*H*-Bts **3–7** and 1-hydroxy-1*H*-4-azaBt **8** were synthesized by known methods^[26,28,29] (Scheme 2, *Caution*^[30]), essentially via a facile reaction of *ortho*-chloro or *ortho*-fluoro nitro aromatic compounds with hydrazine. Further, halo nitro aromatics are exceptionally activated toward oxidative addition to Pd and there are substantial differences in the ease with which this occurs for various C-halogen bonds. This can be leveraged for generating additional compound diversity with dihalo nitro aromatic compounds. To demonstrate this, compounds **9–11** were readily synthesized from 4-bromo-1-fluoro-2-nitrobenzene via reactions with phenyl-, 1-naphthyl-, and 3-thienylboronic acids using Pd(PPh₃)₄ followed by reaction with hydrazine.

The 1-hydroxy-1*H*-Bts **1–11** were subjected to reaction with B₂(OH)₄ (1.2 equiv) and Et₃N (1.2 equiv) at 50°C in MeCN, which were determined to be optimal. Highly efficient reduction was observed in each case with isolated product yields of 90% (Scheme 3). Reactions were complete within 30 min except for compounds **2** and **8**, which required 8 h reaction times.

Further diversification of the benzotriazoles was then considered. Because boron-based byproducts are generally considered benign we evaluated a tandem deoxygenation C–C cross coupling approach to substituted Bts as a one-pot process. For this, compound **7** was deoxygenated with B₂(OH)₄/Et₃N in MeCN at 50°C. The crude reaction mixture was evaporated and reactions were performed with four arylboronic acids (data shown in parenthesis in Table 2).

For this attempted one-pot conversion, the combination of $\text{Pd}(\text{PPh}_3)_4$ (0.2 equiv)/2 M aq Na_2CO_3 in 1,4-dioxane at 100°C proved to be ineffective. On the other hand, dichloro[1,1'-bis(dicyclohexylphosphinyl)ferrocene]palladium(II) [$\text{PdCl}_2(\text{dcpf})$] (0.2 equiv)/ K_3PO_4 (2 equiv) in 1,4-dioxane at 100°C led to product formation in some cases but the reactions were capricious. Similarly, we attempted aryl amination as a two-step, one-pot process using compound **7**, but the reactions were unsuccessful with a variety of catalysts. These data showed that the deoxygenation byproducts could have a detrimental effect on the Pd-catalyzed reactions, contrary to expectation. However, due to the relatively sparse literature on such Pd-mediated reactions of benzotriazoles in comparison to other aromatic systems, we needed to ascertain whether the reactions themselves were problematic or whether such conversions could be effectively conducted in a more general manner. Therefore, we evaluated reactions of purified benzotriazole **18** with arylboronic acids and arylamines, the results from which are shown in Table 2.

These data evidenced that Pd-catalyzed C–C and C–N reactions can be conducted in a general manner and that the deoxygenation byproducts could inhibit these processes. Because compounds **20**, **21**, and **22** have been prepared either from 4-bromo-1-fluoro-2-nitrobenzene or from bromo benzotriazole **18**, we have compared the two approaches. Table 3 shows the overall three-step yields from the two sequences.

Between the two approaches Method 1 appears to be superior at least in the cases tested. There is another advantage to Method 1. Because halo nitrobenzenes are very reactive, simple $\text{Pd}(\text{PPh}_3)_4$ is adequate for C–C bond formation. Nevertheless, both approaches are eminently useful depending upon specific needs. In contrast to the possibility for C–C cross coupling prior to assembly of the benzotriazole moiety, it is less desirable to perform C–N bond formation on a dihalo nitro aromatic due to the possibility of unwanted $\text{S}_{\text{N}}\text{Ar}$ displacement of halide. Thus, the amination reactions are better conducted on the assembled benzotriazole.

We have also analyzed the possible mechanism of this reaction by ^1H and ^{11}B NMR. When HOBt and HOAt were independently exposed to Et_3N in $\text{MeCN-}d_3$, significant upfield shifts of the aromatic resonances were observed. This would be consistent with the formation of an electron-rich system by deprotonation. Because the reduction of HOAt is slower than that of HOBt, $(\text{pinB})_2$ was added to the HOAt/ Et_3N mixture in $\text{MeCN-}d_3$ and stirred at 50°C . Aliquots were taken at regular intervals and assessed by ^1H and ^{11}B NMR. During the course of the reaction, the ^1H NMR spectrum showed disappearance of the resonances of what is presumably AtO^- and formation of a set of resonances corresponding to product. However, these new resonances were also upfield shifted. Addition of an aliquot of the reaction mixture to pure 1*H*-7-azabenzotriazole also caused an upfield shift its resonances indicating a presently unknown interaction with the reaction components. Purification of the products however led to proton resonances at the expected chemical shifts.

Acquisition of ^{11}B NMR data of the reaction involving HOAt, Et_3N , and $(\text{pinB})_2$ in $\text{MeCN-}d_3$ over a 3 h timeframe showed resonances from $(\text{pinB})_2$ ($\delta = 30.6$ ppm) and presumably $(\text{pinB})_2\text{O}$ ($\delta = 22.4$ ppm). Prolonged heating resulted in other ^{11}B resonances, possibly due to interactions of the nitrogenated compounds with the boron-containing materials. Although

the deoxygenation of pyridine N-oxides by (pinB)₂ was more readily discerned by NMR^[23] as compared to the conversion herein, we propose the mechanism shown in Scheme 4, where either the N-hydroxy and/or the N-oxide Bt tautomer^[31] can be involved.

Conclusions

In summary, we have disclosed a previously unknown, mild, and general approach to 1*H*-benzotriazoles via a diboron reagent-mediated N–O deoxygenation of 1-hydroxy-1*H*-benzotriazoles. Using differential reactivities of C-halogen bonds towards Pd catalysts, additional compound diversity can be easily attained. Also, C-halogen bonds that can be reduced under other reductive conditions remain unaffected under these conditions. This offers a synthetic advantage for subsequent manipulations, such as the metal-catalyzed reactions described. In this context, we have evaluated a two-step, one-pot deoxygenation/Pd-catalysis protocol. However, we have found that removal of the deoxygenation byproducts is essential for successful catalysis reactions. We have demonstrated diversification of the benzotriazole moiety via three Pd-catalyzed approaches, all of which appear generally applicable: (a) C–C bond formation prior to formation of the 1-hydroxy-1*H*-benzotriazoles and then deoxygenation, (b) C–C bond formation on the deoxygenated product, and (c) C–N bond formation on the deoxygenated product. This chemistry further demonstrates an untapped potential of diboron reagents for novel transformations such as the N–OH → NH reduction shown here, and complements the reduction of amine N-oxides by diboron reagents.

Experimental Section

General Experimental Considerations

Thin-layer chromatography was performed on 200 μm aluminum-foil-backed silica gel plates. Bis(pinacolato)diboron (pinB)₂, bis(catecholato)diboron (catB)₂, tetrahydroxydiboron B₂(OH)₄, all arylboronic acids, arylamines, PdCl₂(dcpf), Pd₂(dba)₃, ^tBu₃P, and all other reagents were obtained from commercial suppliers and were used without further purification. Column chromatographic purifications were performed on 100–200 mesh silica gel. MeCN was distilled over CaH₂, 1,4-dioxane was distilled over NaBH₄ and then freshly distilled over Na prior to use. EtOAc and hexanes were distilled over CaSO₄, and commercial CH₂Cl₂ was redistilled. Other commercially available compounds were used without further purification. ¹H NMR spectra were recorded at 400 MHz in the solvents indicated and are referenced to residual protonated solvent resonances. ¹³C NMR spectra were recorded at 100 MHz in the solvents indicated and are referenced to the solvent resonances. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are in hertz (Hz). Standard abbreviations are used to designate resonance multiplicities. ¹⁹F NMR spectra were recorded at 376 MHz in the solvents indicated.

Synthesis of Precursors to Compounds 9, 10 and 11 ^[32]

4-Fluoro-3-nitrobiphenyl—In a 100 mL oven-dried, round-bottomed flask equipped with a stirring bar were placed 5-bromo-2-fluoronitrobenzene (2.0 g, 9.13 mmol) and

phenylboronic acid (1.22 g, 10.0 mmol) in 1:1 toluene/EtOH (40 mL). Aqueous 2 M Na₂CO₃ (10 mL) was added, the mixture was sparged with argon gas for 5 min, and Pd(PPh₃)₄ (0.31 g, 3 mol %) was added. The reaction mixture was heated at reflux for 2 h and monitored by TLC. Upon completion of the reaction the mixture was concentrated, diluted with EtOAc, and washed with water. The aqueous layer was extracted with EtOAc (2x). The organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. Chromatography of the crude material on a silica gel column using 5% EtOAc in hexanes gave the title compound as a pale yellow solid (1.88 g, 95% yield). *R_f* (SiO₂/10% EtOAc in hexanes) = 0.53. ¹H NMR (400 MHz, CDCl₃): δ 8.25 (dd, *J* = 2.1, 7.0 Hz, Ar-H, 2H), 7.84–7.80 (m, Ar-H, 1H), 7.56 (dd, *J* = 2.0, 8.5 Hz, Ar-H, 1H), 7.49–7.39 (m, Ar-H, 3H), 7.37 (t, *J* = 9.6 Hz, Ar-H, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 154.6 (d, *J*_{C-F} = 264.1 Hz), 138.3 (d, *J*_{C-F} = 3.8 Hz), 137.6, 133.8 (d, *J*_{C-F} = 8.4 Hz), 129.1, 128.5, 126.9, 124.2 (d, *J*_{C-F} = 2.2 Hz), 118.7 (d, *J*_{C-F} = 20.5 Hz). ¹⁹F NMR (376 MHz, CDCl₃): δ -120.3.

1-(4-Fluoro-3-nitrophenyl)naphthalene—Synthesized as described for 4-fluoro-3-nitrobiphenyl, using 5-bromo-2-fluoronitrobenzene (2.0 g, 9.13 mmol), naphthalen-1-ylboronic acid, (1.72 g, 10.0 mmol), 2 M aqueous Na₂CO₃ (10 mL), and Pd(PPh₃)₄ (0.31 g, 3 mol %) in 1:1 toluene/EtOH (40 mL) at reflux for 2 h. Workup as described above and chromatography of the crude material on a silica gel column using 5% EtOAc in hexanes gave the title compound as an off-white solid (2.19 g, 90% yield). *R_f* (SiO₂/10% EtOAc in hexanes) = 0.53. ¹H NMR (400 MHz, CDCl₃): δ 8.16 (dd, *J* = 2.2, 7.2 Hz, Ar-H, 1H), 8.92 (dd, *J* = 4.8, 7.6 Hz, Ar-H, 2H), 7.72–7.69 (m, Ar-H, 2H), 7.53–7.44 (m, Ar-H, 3H), 7.40–7.35 (m, Ar-H, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 154.7 (d, *J*_{C-F} = 264.1 Hz), 137.6 (d, *J*_{C-F} = 4.6 Hz), 137.2 (d, *J*_{C-F} = 8.0 Hz), 136.9, 136.3, 133.8, 131.0, 128.9, 128.6, 127.2, 127.1, 126.8, 126.2, 125.2, 124.7, 118.2 (d, *J*_{C-F} = 21.2 Hz). ¹⁹F NMR (376 MHz, CDCl₃): δ -119.8.

3-(4-Fluoro-3-nitrophenyl)thiophene—Synthesized as described for 4-fluoro-3-nitrobiphenyl, using 5-bromo-2-fluoronitrobenzene (2.0 g, 9.13 mmol), 3-thienylboronic acid, (1.28 g, 10.0 mmol), 2 M aqueous Na₂CO₃ (10 mL), and Pd(PPh₃)₄ (0.31 g, 3 mol %) in 1:1 toluene/EtOH (40 mL), at reflux for 2 h. Workup as described above and chromatography of the crude material on a silica gel column using 5% EtOAc in hexanes gave the title compound as an as off-white solid (1.87 g, 92% yield). *R_f* (SiO₂/10% EtOAc in hexanes) = 0.43. ¹H NMR (400 MHz, CDCl₃): δ 8.24 (dd, *J* = 2.1, 7.0 Hz, Ar-H, 1H), 7.83–7.79 (m, Ar-H, 1H), 7.51 (d, *J* = 4.0 Hz, Ar-H, 1H), 7.45 (t, *J* = 4.0 Hz, Ar-H, 1H), 7.36–7.25 (m, Ar-H, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 154.4 (d, *J*_{C-F} = 264.1 Hz), 138.7, 137.5, 133.0 (d, *J*_{C-F} = 8.4 Hz), 127.4, 125.7, 123.5 (d, *J*_{C-F} = 2.3 Hz), 121.9, 118.7 (d, *J*_{C-F} = 21.2 Hz). ¹⁹F NMR (376 MHz, CDCl₃): δ -120.2.

General Procedure for the Synthesis of 1-Hydroxy-1*H*-benzotriazoles

A mixture of the appropriate *ortho*-chloronitro- or *ortho*-fluoronitrobenzene and hydrazine hydrate were heated at reflux in absolute EtOH for the period of time indicated for each compound. After removal of the solvent under reduced pressure, the residue was dissolved in 10% aqueous Na₂CO₃. The solution was extracted with Et₂O to remove any starting

material and then acidified with concentrated HCl to precipitate the product, which was filtered, washed with water, and dried to obtain the various 1-hydroxy-1*H*-benzotriazoles.

5-Chloro-1*H*-benzo[d][1,2,3]triazol-1-ol (3)—Synthesized using 2,4-dichloro-1-nitrobenzene (1.5 g, 7.85 mmol) and hydrazine hydrate (0.77 mL, 15.70 mmol) in absolute EtOH (10 mL) at reflux over 36 h. After removal of the solvent under reduced pressure, the residue was dissolved in 10% aqueous Na₂CO₃ (20 mL). The solution was extracted with Et₂O (30 mL) and then acidified with concentrated HCl. The precipitated product was filtered, washed with water, and dried to obtain compound **3** as an off-white solid (1.13 g, 85% yield). *R_f* (SiO₂/10% MeOH, 1% Et₃N in CH₂Cl₂) = 0.37. IR (KBr): 3461, 1342 and 747 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.85 (br s, OH, 1H), 8.14 (s, Ar-H, 1H), 7.80 (d, *J* = 8.7 Hz, Ar-H, 1H), 7.58 (d, *J* = 8.7 Hz, Ar-H, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 143.3, 129.1, 127.9, 126.6, 118.4, 111.2. HRMS (ESI/TOF) *m/z* calcd for C₆H₅ClN₃O [M + H]⁺ 170.0116, found 170.0126.

4,5-Dichloro-1*H*-benzo[d][1,2,3]triazol-1-ol (4)—Synthesized using 1,2,3-trichloro-4-nitrobenzene (1.5 g, 6.66 mmol) and hydrazine hydrate (0.65 mL, 13.33 mmol) in absolute EtOH (10 mL) at reflux over 36 h. After removal of the solvent under reduced pressure, the residue was dissolved in 10% aqueous Na₂CO₃ (20 mL). The solution was extracted with Et₂O (30 mL) and then acidified with concentrated HCl. The precipitated product was filtered, washed with water, and dried to obtain compound **4** as a white solid (1.04 g, 77% yield). *R_f* (SiO₂/10% MeOH, 1% Et₃N in CH₂Cl₂) = 0.40. IR (KBr): 3494, 1385, and 796 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.59 (d, 1H, Ar-H, *J* = 8.8 Hz), 7.55 (d, 1H, Ar-H, *J* = 8.8 Hz). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 140.8, 127.7, 127.5, 126.7, 120.9, 110.2. HRMS (ESI/TOF) *m/z* calcd for C₆H₄Cl₂N₃O [M + H]⁺ 203.9726, found 203.9724.

6-Methyl-1*H*-benzo[d][1,2,3]triazol-1-ol (5).^[33]—Synthesized using 1-chloro-4-methyl-2-nitrobenzene (1.0 g, 5.84 mmol) and hydrazine hydrate (0.57 mL, 11.69 mmol) in absolute EtOH (8 mL) at reflux over 24 h. After removal of the solvent under reduced pressure, the residue was dissolved in 10% aqueous Na₂CO₃ (20 mL). The solution was extracted with Et₂O (30 mL) and then acidified with concentrated HCl. The precipitated product was filtered, washed with water, and dried to obtain compound **5** as a white solid (0.56 g, 65% yield). *R_f* (SiO₂/10% MeOH, 1% Et₃N in CH₂Cl₂) = 0.34. IR (KBr): 3431, 1388, and 809 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.24 (br s, OH, 1H), 7.87 (d, *J* = 8.5 Hz, Ar-H, 1H), 7.49 (s, Ar-H, 1H), 7.25 (d, *J* = 8.5 Hz, Ar-H, 1H), 2.49 (s, CH₃, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 141.6, 137.6, 128.2, 126.8, 118.6, 108.3, 21.3. HRMS (ESI/TOF) *m/z* calcd for C₇H₈N₃O [M + H]⁺ 150.0662, found 150.0659.

5-(Trifluoromethyl)-1*H*-benzo[d][1,2,3]triazol-1-ol (6)—Synthesized using 2-chloro-1-nitro-4-(trifluoromethyl)benzene (2.0 g, 8.88 mmol) and hydrazine hydrate (0.88 g, 17.76 mmol) in absolute EtOH (13 mL) at reflux over 24 h. After removal of the solvent under reduced pressure, the residue was dissolved in 10% aqueous Na₂CO₃ (25 mL). The solution was extracted with Et₂O (30 mL) and then acidified with concentrated HCl. The precipitated product was filtered, washed with water, and dried to obtain compound **6** as a white solid (1.08 g, 60% yield). *R_f* (SiO₂/10% MeOH, 1% Et₃N in CH₂Cl₂) = 0.33. IR

(KBr): 3437, 1330, and 809 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 14.0 (br s, OH, 1H), 8.51 (s, Ar-H, 1H), 7.99 (d, $J = 8.7$ Hz, Ar-H, 1H), 7.85 (d, $J = 8.7$ Hz, Ar-H, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 141.9, 129.2, 124.7 (q, $J_{\text{C-F}} = 270.9$ Hz), 125.3 (q, $J_{\text{C-F}} = 31.8$ Hz), 123.5, 117.9 (d, $J_{\text{C-F}} = 4.6$ Hz), 111.3. ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$): δ -63.2 (with internal standard TFA- d $\delta = -78.5$ ppm). HRMS (ESI/TOF) m/z calcd for $\text{C}_7\text{H}_5\text{F}_3\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$ 204.0380, found 204.0391.

6-Bromo-1H-benzo[d][1,2,3]triazol-1-ol (7)—Synthesized using 4-bromo-1-fluoro-2-nitrobenzene (3.0 g, 13.70 mmol) and hydrazine hydrate (1.34 mL, 27.40 mmol) in absolute EtOH (20 mL) at reflux over 24 h. After removal of the solvent under reduced pressure, the residue was dissolved in 10% aqueous Na_2CO_3 (30 mL). The solution was extracted with Et_2O (30 mL) and then acidified with concentrated HCl. The precipitated product was filtered, washed with water, and dried to obtain compound **7** as an off-white solid (2.48 g, 85% yield). R_f ($\text{SiO}_2/10\%$ MeOH, 1% Et_3N in CH_2Cl_2) = 0.38. IR (KBr): 3436, 1206 and 803 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 13.45 (br s, OH, 1H), 7.96 (m, Ar-H, 2H), 7.52 (d, $J = 8.5$ Hz, Ar-H, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 141.7, 128.7, 127.6, 120.9, 120.2, 112.2. HRMS (ESI/TOF) m/z calcd for $\text{C}_6\text{H}_5\text{BrN}_3\text{O}$ $[\text{M} + \text{H}]^+$ 213.9611, found 213.9614.

1H-[1,2,3]triazolo[4,5-b]pyridin-1-ol (8) [26]—Synthesized using 2-chloro-3-nitropyridine (1.0 g, 6.32 mmol) and hydrazine hydrate (0.62 mL, 12.64 mmol) in absolute EtOH (10 mL) at reflux over 24 h. After removal of the solvent under reduced pressure, the residue was dissolved in 10% aqueous Na_2CO_3 (20 mL). The solution was extracted with Et_2O (20 mL) to remove the starting material and aqueous layer was acidified with concentrated HCl. The product that precipitated slowly over 12 h was filtered, washed with water, and dried to obtain compound **8** as an off-white solid (0.68 g, 80% yield). R_f ($\text{SiO}_2/10\%$ MeOH, 1% Et_3N in CH_2Cl_2) = 0.21. IR (KBr): 3457, 1396, and 777 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.36 (dd, $J = 1.5, 4.1$ Hz, Ar-H, 1H), 7.91–7.89 (m, Ar-H, 1H), 7.03–7.00 (m, Ar-H, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 153.8, 146.5, 120.8, 118.9, 116.3. HRMS (ESI/TOF) m/z calcd for $\text{C}_5\text{H}_5\text{N}_4\text{O}$ $[\text{M} + \text{H}]^+$ 137.0458, found 137.0475.

6-Phenyl-1H-benzo[d][1,2,3]triazol-1-ol (9)—Synthesized using 4-fluoro-3-nitrobiphenyl (1.0 g, 4.67 mmol) and hydrazine hydrate (0.45 mL, 9.34 mL) in absolute EtOH (8 mL) at reflux over 24 h. After removal of the solvent under reduced pressure, the residue was dissolved in 10% aqueous Na_2CO_3 (20 mL). The solution was extracted with Et_2O (20 mL) and then acidified with concentrated HCl. The precipitated product was filtered, washed with water, and dried to obtain compound **9** as a white solid (0.89 g, 92% yield). R_f ($\text{SiO}_2/10\%$ MeOH, 1% Et_3N in CH_2Cl_2) = 0.42. IR (KBr): 3565, 1088, and 695 cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.77 (d, $J = 8.5$ Hz, Ar-H, 1H), 7.62 (d, $J = 7.4$, Hz, Ar-H 2H), 7.55 (s, Ar-H, 1H), 7.47 (t, $J = 8.11$ Hz, Ar-H, 3H), 7.37 (t, $J = 7.2$ Hz, Ar-H, 1H). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 142.9, 140.7, 136.3, 129.3, 128.5, 127.6, 127.4, 123.1, 119.1, 108.6. HRMS (ESI/TOF) m/z calcd for $\text{C}_{12}\text{H}_{10}\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$ 212.0819, found 212.0823.

6-(Naphthalen-1-yl)-1*H*-benzo[*d*][1,2,3]triazol-1-ol (10)—Synthesized using 1-(4-fluoro-3-nitrophenyl) naphthalene (1.0 g, 3.74 mmol) and hydrazine hydrate (0.36 mL, 7.48 mmol) in absolute EtOH (8 mL) at reflux over 24 h. After removal of the solvent under reduced pressure, the residue was dissolved in 10% aqueous Na₂CO₃ (20 mL). The solution was extracted with Et₂O (30 mL) and then acidified with concentrated HCl. The precipitated product was filtered, washed with water, and dried to obtain compound **10** as a white solid (0.80 g, 82% yield). *R_f* (SiO₂/10% MeOH, 1% Et₃N in CH₂Cl₂) = 0.41. IR (KBr): 3448, 1300, and 754 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.98 (br s, OH, 1H), 8.11 (d, *J* = 8.5 Hz, Ar-H, 1H), 8.05 (t, *J* = 8.5 Hz, Ar-H, 2H), 7.80 (d, *J* = 8.3 Hz, Ar-H, 1H), 7.74 (s, Ar-H, 1H), 7.64–7.48 (m, Ar-H, 5H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 142.2, 139.0, 138.5, 133.3, 130.8, 128.3, 128.2, 128.1, 127.3, 126.9, 126.5, 126.0, 125.5, 125.0, 118.9, 110.2. HRMS (ESI/TOF) *m/z* calcd for C₁₆H₁₂N₃O [M + H]⁺ 262.0975, found 262.0977.

6-(Thien-3-yl)-1*H*-benzo[*d*][1,2,3]triazol-1-ol (11)—Synthesized using 3-(4-fluoro-3-nitrophenyl)thiophene (1.0 g, 4.47 mmol) and hydrazine hydrate (0.44 mL, 8.95 mmol) in absolute EtOH (10 mL) at reflux over 24 h. After removal of the solvent under reduced pressure, the residue was dissolved in 10% aqueous Na₂CO₃ (20 mL). The solution was extracted with Et₂O (20 mL) and then acidified with concentrated HCl. The precipitated product was filtered, washed with water, and dried to obtain compound **11** as a white solid (0.87 g, 90% yield). *R_f* (SiO₂/10% MeOH, 1% Et₃N in CH₂Cl₂) = 0.33. IR (KBr): 3408, 1370, and 773 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.87 (s, Ar-H, 1H), 7.81 (d, *J* = 8.7 Hz, Ar-H, 1H), 7.68 (s, Ar-H, 1H), 7.64–7.60 (m, Ar-H, 2H), 7.54 (d, *J* = 4.8 Hz, Ar-H, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 142.2, 141.1, 132.2, 128.2, 127.1, 126.4, 122.8, 121.4, 118.9, 106.6. HRMS (ESI/TOF) *m/z* calcd for C₁₀H₈N₃SO [M + H]⁺ 218.0383, found 218.0382.

General Procedure for the Synthesis of Benzotriazoles

In a clean, dry 8 mL vial equipped with a stirring bar, the 1-hydroxy-1*H*-benzotriazole was dissolved in MeCN. Et₃N (1.2 equiv) was added followed and the reaction mixture was stirred at room temperature for 30 min. Then B₂(OH)₄ (1.2 equiv) was added and the resulting reaction mixture was stirred for 30 min (8 h for precursors **2** and **8**) at 50°C. After completion of the reaction, the mixture was concentrated and crude material was purified by chromatography on a silica gel column by elution with 10–50% EtOAc in hexanes and in the case of compound **13** with 0–5% MeOH in CH₂Cl₂.

1*H*-Benzo[*d*][1,2,3]triazole (12)—Synthesized using 1*H*-benzo[*d*][1,2,3]triazol-1-ol (200 mg, 1.48 mmol), Et₃N (0.24 mL, 1.77 mmol), and B₂(OH)₄ (159 mg, 1.77 mmol) in MeCN (2 mL) over 30 min at 50°C. Evaporation of the volatiles and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **12** as a white solid (168 mg, 95% yield). *R_f* (SiO₂/50% EtOAc in hexanes) = 0.46. IR (KBr): 3468, 1207 and 740 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 7.95 (dd, *J* = 3.1, 6.3 Hz, Ar-H, 2H), 7.47 (dd, *J* = 3.1, 6.3 Hz, Ar-H, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 138.7, 125.4, 114.9. HRMS (ESI/TOF) *m/z* calcd for C₆H₆N₃ [M + H]⁺ 120.0557, found 120.0562.

3H-[1,2,3]triazolo[4,5-*b*]pyridine (13)—Synthesized using 3H-[1,2,3]triazolo[4,5-*b*]pyridin-3-ol (200 mg, 1.47 mmol), Et₃N (0.24 mL, 1.76 mmol), and B₂(OH)₄ (158 mg, 1.76 mmol) in MeCN (2 mL) over 8 h at 50°C. Evaporation of the volatiles and chromatography of the crude material on a silica gel column by gradient elution with MeOH in CH₂Cl₂ gave compound **13** as a white solid (166 mg, 95% yield). *R_f* (SiO₂/10% MeOH in CH₂Cl₂) = 0.10. IR (KBr): 3436, 1399, and 783 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): 8.75 (dd, *J* = 1.2, 4.1 Hz, Ar-H, 1H), 8.47 (dd, *J* = 1.0, 8.3 Hz, Ar-H, 1H), 7.54 (dd, *J* = 4.4, 8.3 Hz, Ar-H, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 151.2, 149.3, 130.9, 124.9, 120.9. HRMS (ESI/TOF) *m/z* calcd for C₅H₅N₄ [M + H]⁺ 121.0509, found 121.0513.

5-Chloro-1H-benzo[*d*][1,2,3]triazole (14).^[22]—Synthesized using 5-chloro-1H-benzo[*d*][1,2,3]triazol-1-ol (200 mg, 1.17 mmol), Et₃N (0.19 mL, 1.41 mmol), and B₂(OH)₄ (142 mg, 1.41 mmol) in MeCN (1.6 mL) over 30 min at 50°C. Evaporation of the volatiles and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **14** as a white solid (166 mg, 92% yield). *R_f* (SiO₂/50% EtOAc in hexanes) = 0.44. IR (KBr): 3454, 1392, and 800 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 15.86 (br s, 1H, NH), 8.01 (s, 1H, Ar-H), 7.95 (d, 1H, Ar-H, *J* = 8.7 Hz), 7.44 (d, 1H, Ar-H, *J* = 8.7 Hz). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 139.4, 138.2, 130.6, 126.2, 117.0, 114.5. HRMS (ESI/TOF) *m/z* calcd for C₆H₅ClN₃ [M + H]⁺ 154.0167, found 154.0164.

4,5-Dichloro-1H-benzo[*d*][1,2,3]triazole (15)—Synthesized using 4,5-dichloro-1H-benzo[*d*][1,2,3]triazol-1-ol (200 mg, 0.98 mmol), Et₃N (0.16 mL, 1.18 mmol), and B₂(OH)₄ (106 mg, 1.18 mmol) in MeCN (1.3 mL) over 30 min at 50°C. Evaporation of the volatiles and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **15** as a white solid (171 mg, 93% yield). *R_f* (SiO₂/50% EtOAc in hexanes) = 0.40. IR (KBr): 3458, 1439, and 809 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): 7.93 (d, *J* = 8.8 Hz, Ar-H, 1H), 7.66 (d, *J* = 8.8 Hz, Ar-H, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 139.6, 137.6, 128.2, 127.9, 118.7, 114.5. HRMS (ESI/TOF) *m/z* calcd for C₆H₄Cl₂N₃ [M + H]⁺ 187.9777, found 187.9789.

6-Methyl-1H-benzo[*d*][1,2,3]triazole (16).^[22]—Synthesized using 6-methyl-1H-benzo[*d*][1,2,3]triazol-1-ol (200 mg, 1.34 mmol), Et₃N (0.22 mL, 1.61 mmol), and B₂(OH)₄ (144 mg, 1.61 mmol) in MeCN (1.81 mL) over 30 min at 50°C. Evaporation of the volatiles and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **16** as a white solid (160 mg, 90% yield). *R_f* (SiO₂/50% EtOAc in hexanes) = 0.40. IR (KBr): 3456, 1440, and 795 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆, 100°C): δ 15.21 (brs, 1H, NH), 7.79 (d, 1H, Ar-H, *J* = 4.8 Hz), 7.62 (s, 1H, Ar-H), 7.26 (d, 1H, Ar-H, *J* = 8.0 Hz), 2.47 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 138.8, 138.1, 135.9, 127.3, 115.4, 113.0. HRMS (ESI/TOF) *m/z* calcd for C₇H₈N₃ [M + H]⁺ 134.0713, found 134.0707.

5-(Trifluoromethyl)-1H-benzo[d][1,2,3]triazole (17)—Synthesized using 5-(trifluoromethyl)-1H-benzo[d][1,2,3]triazol-1-ol (200 mg, 0.98 mmol), Et₃N (0.16 mL, 1.18 mmol), and B₂(OH)₄ (105 mg, 1.18 mmol) in MeCN (1.3 mL) over 30 min at 50°C. Evaporation of the volatiles and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **17** as a white solid (169 mg, 92% yield). *R_f* (SiO₂/50% EtOAc in hexanes) = 0.43. IR (KBr): 3467, 1326 and 824 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆ + 1 drop TFA-*d*): δ 16.04 (br s, NH, 1H), 8.42 (s, Ar-H, 1H), 8.13 (d, *J* = 8.8 Hz, Ar-H, 1H), 7.77 (d, *J* = 8.8 Hz, Ar-H, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop TFA-*d*): δ 140.0, 138.7, 124.6 (q, C-F, *J* = 270.2 Hz), 126.1 (q, C-F, *J* = 31.9 Hz), 122.4 (d, C-F, *J* = 3.0 Hz), 115.5, 114.9 (d, C-F, *J* = 3.8 Hz). ¹⁹F NMR (376 MHz, DMSO-*d*₆): δ -59.7. HRMS (ESI/TOF) *m/z* calcd for C₇H₅F₃N₃ [M + H]⁺ 188.0436, found 188.0439.

6-Bromo-1H-benzo[d][1,2,3]triazole (18)—Synthesized using 6-bromo-1H-benzo[d][1,2,3]triazol-1-ol (200 mg, 0.93 mmol), Et₃N (0.15 mL, 1.12 mmol), and B₂(OH)₄ (101 mg, 1.12 mmol) in CH₃CN (1.3 mL) over 30 min at 50°C. Evaporation of the volatiles and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **18** as a white solid (170 mg, 92% yield). *R_f* (SiO₂/50% EtOAc in hexanes) = 0.50. IR (KBr): 3436, 1206, and 803 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 15.89 (br s, NH, 1H), 8.20 (s, Ar-H, 1H), 7.92 (d, *J* = 8.0 Hz, Ar-H, 1H), 7.58 (t, *J* = 4.5 Hz, Ar-H, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 139.8, 137.9, 128.5, 118.3, 117.5, 116.9. HRMS (ESI/TOF) *m/z* calcd for C₆H₅BrN₃ [M + H]⁺ 197.9662, found 197.9651.

1H-[1,2,3]triazolo[4,5-*b*]pyridine (19 same as compound 13)—Synthesized using 1H-[1,2,3]triazolo[4,5-*b*]pyridine (200 mg, 1.47 mmol), Et₃N (0.40 mL, 2.94 mmol), and B₂(OH)₄ (263.5 mg, 2.94 mmol) in MeCN (2 mL) over 8 h at 50°C. Evaporation of the volatiles and chromatography of the crude material on a silica gel column by gradient elution with MeOH in CH₂Cl₂ gave compound **19** as a white solid (158 mg, 90% yield). *R_f* (SiO₂/70% EtOAc in hexanes) = 0.33. IR (KBr): 3433, 1400, and 785 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆ + 1 drop TFA-*d*): δ 15.90 (br s, NH, 1H), 8.75 (dd, *J* = 1.2, 4.3 Hz, Ar-H, 1H), 8.47 (dd, *J* = 1.0, 8.0 Hz, Ar-H, 1H), 7.54 (dd, *J* = 4.4, 8.2 Hz, Ar-H, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 151.4, 149.4, 131.2, 125.2, 121.1. HRMS (ESI/TOF) *m/z* calcd for C₅H₅N₄ [M + H]⁺ 121.0509, found 121.0524.

6-Phenyl-1H-benzo[d][1,2,3]triazole (20)—Synthesized using 6-phenyl-1H-benzo[d][1,2,3]triazol-1-ol (200 mg, 0.94 mmol), Et₃N (0.15 mL, 1.13 mmol), and B₂(OH)₄ (102 mg, 1.13 mmol) in MeCN (1.3 mL) over 30 min at 50°C. Evaporation of the volatiles and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **20** as a white solid (175 mg, 95% yield). *R_f* SiO₂/50% EtOAc in hexanes = 0.43. IR (KBr): 3435, 1209, and 609 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 15.78 (br s, NH, 1H), 8.14 (s, Ar-H, 1H), 8.02 (d, *J* = 8.0 Hz, Ar-H, 1H), 7.78 (t, *J* = 7.5 Hz, Ar-H, 3H), 7.53 (t, *J* = 8.0 Hz, Ar-H, 2H), 7.43 (t, *J* = 7.3 Hz, Ar-H, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop TFA-*d*): δ 140.5, 139.6, 138.9, 138.6, 129.3, 127.9, 127.7, 125.5,

115.8, 112.5. HRMS (ESI/TOF) m/z calcd for $C_{12}H_{10}N_3$ $[M + H]^+$ 196.0870, found 196.0872.

6-(Naphthalen-1-yl)-1H-benzo[d][1,2,3]triazole (21)—Synthesized using 6-(naphthalen-1-yl)-1H-benzo[d][1,2,3]triazol-1-ol (200 mg, 0.76 mmol), Et_3N (0.12 mL, 0.91 mmol), and $B_2(OH)_4$ (82.4 mg, 0.91 mmol) in MeCN (1 mL) over 30 min at 50°C. Evaporation of the volatiles and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **21** as a white solid (176 mg, 94% yield). R_f (SiO_2 /50% EtOAc in hexanes) = 0.50. IR (KBr): 3467, 1203, and 774 cm^{-1} . 1H NMR (400 MHz, DMSO- d_6): δ 15.83 (br s, NH, 1H), 8.07–7.97 (m, Ar-H, 4H), 7.80 (d, J = 8.4 Hz, Ar-H, 1H), 7.63–7.47 (m, Ar-H, 5H). ^{13}C NMR (100 MHz, DMSO- d_6): δ 138.9, 133.3, 130.9, 128.3, 127.8, 127.3, 126.4, 125.9, 125.5, 125.1. HRMS (ESI/TOF) m/z calcd for $C_{16}H_{12}N_3$ $[M + H]^+$ 246.1026, found 246.1030.

6-(Thien-3-yl)-1H-benzo[d][1,2,3]triazole (22)—Synthesized using 6-(thien-3-yl)-1H-benzo[d][1,2,3]triazol-1-ol (200 mg, 0.92 mmol), Et_3N (0.15 mL, 1.10 mmol), and $B_2(OH)_4$ (99.1 mg, 1.10 mmol) in MeCN (1.2 mL) over 30 min at 50°C. Evaporation of the volatiles and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **22** as a white solid (166 mg, 90% yield). R_f (SiO_2 /50% EtOAc in hexanes) = 0.41. IR (KBr): 3485, 1203, and 780 cm^{-1} . 1H NMR (400 MHz, DMSO- d_6 + 1 drop of TFA- d): δ 8.20 (s, Ar-H, 1H), 8.00 (s, Ar-H, 1H), 7.96 (d, J = 8.5 Hz, Ar-H, 1H), 7.85 (d, J = 8.8 Hz, Ar-H, 1H), 7.70–7.68 (m, Ar-H, 2H). ^{13}C NMR (100 MHz, DMSO- d_6 + 1 drop TFA- d): δ 141.5, 139.3, 138.9, 133.4, 127.4, 126.8, 125.0, 121.9, 115.9, 111.4. HRMS (ESI/TOF) m/z calcd for $C_{10}H_8N_3S$ $[M + H]^+$ 202.0434, found 202.0443.

General Procedure for C–C Cross-Coupling Reactions of 6-Bromo-1H-benzo[d][1,2,3]triazole with Arylboronic Acids

In a clean, dry 8 mL vial equipped with a stirring bar, 6-bromo-1H-benzo[d][1,2,3]triazole was dissolved in anhydrous 1,4-dioxane. The arylboronic acid and K_3PO_4 were added, the mixture was sparged with argon gas, and then $PdCl_2(dcpf)$ was added. The vial was capped and the mixture was stirred for 16 h at 100°C. Upon completion of the reaction, the mixture was concentrated under reduced pressure, and the crude material was purified by chromatography on a silica gel column by gradient elution with 10–50% EtOAc in hexanes and in the case of compound **24** with 0–3% MeOH in CH_2Cl_2 .

6-Phenyl-1H-benzo[d][1,2,3]triazole (20)—Synthesized using 6-bromo-1H-benzo[d][1,2,3]triazole (200 mg, 1.01 mmol), phenylboronic acid (246 mg, 2.02 mmol), K_3PO_4 (428 mg, 12.32 mmol), and $PdCl_2(dcpf)$ (152 mg, 0.202 mmol) in 1,4-dioxane (1.3 mL) over 16 h at 100°C. Chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **20** as a pale brown solid (179 mg, 90% yield).

6-(Naphthalen-1-yl)-1H-benzo[d][1,2,3]triazole (21)—Synthesized using 6-bromo-1H-benzo[d][1,2,3]triazole (200 mg, 1.01 mmol), naphthalen-1-ylboronic acid (347 mg, 2.02 mmol), K_3PO_4 (428 mg, 12.32 mmol), and $PdCl_2(dcpf)$ (152 mg, 0.202 mmol) in anhydrous 1,4-dioxane (1.3 mL) over 16 h at 100°C. Chromatography of the crude material

on a silica gel column by gradient elution with EtOAc in hexanes gave compound **21** as a pale brown solid (195 mg, 78% yield).

6-(Thien-3-yl)-1H-benzo[d][1,2,3]triazole (22)—Synthesized using 6-bromo-1H-benzo[d][1,2,3]triazole (200 mg, 1.01 mmol), 3-thienylboronic acid (258 mg, 2.02 mmol), K₃PO₄ (428 mg, 12.32 mmol), and PdCl₂(dcpf) (152 mg, 0.202 mmol) in anhydrous 1,4-dioxane (1.3 mL) over 16 h at 100°C. Chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **22** as a pale brown solid (180 mg, 88% yield).

6-(4-Methoxyphenyl)-1H-benzo[d][1,2,3]triazole (23)—Synthesized using 6-bromo-1H-benzo[d][1,2,3]triazole (200 mg, 1.01 mmol), *para*-methoxyphenyl-boronic acid (311 mg, 2.02 mmol), K₃PO₄ (428 mg, 12.32 mmol), and PdCl₂(dcpf) (152 mg, 0.202 mmol) in anhydrous 1,4-dioxane (1.3 mL) over 16 h at 100°C. Chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **23** as a pale brown solid (172 mg, 75% yield). *R_f* (SiO₂/50% EtOAc in hexanes) = 0.41. IR (KBr): 3391, 1604, and 808 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 8.06 (s, Ar-H, 1H), 7.98 (d, *J* = 8.5 Hz, Ar-H, 1H), 7.72 (d, *J* = 8.8 Hz, Ar-H, 3H), 7.08 (d, *J* = 8.5 Hz Ar-H, 2H), 3.85 (s, CH₃, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 139.1, 138.7, 138.1, 132.5, 128.6, 125.5, 115.7, 114.6, 111.3, 55.2. HRMS (ESI/TOF) *m/z* calcd for C₁₃H₁₂N₃O [M + H]⁺ 226.0975, found 226.0981.

4-(1H-Benzo[d][1,2,3]triazol-6-yl)-3,5-dimethylisoxazole (24)—Synthesized from 6-bromo-1H-benzo[d][1,2,3]triazole (200 mg, 1.01 mmol), 3,5-dimethylisoxazol-4-ylboronic acid (283 mg, 2.02 mmol), K₃PO₄ (428 mg, 12.32 mmol), and PdCl₂(dcpf) (152 mg, 0.202 mmol) in anhydrous 1,4-dioxane (1.3 mL) over 16 h at 100°C. Chromatography of the crude material on a silica gel column using gradient elution with MeOH in CH₂Cl₂ gave compound **24** as a pale brown solid (131 mg, 60% yield). *R_f* (SiO₂/10% MeOH in CH₂Cl₂) = 0.41. IR (KBr): 3468, 1634, 1195, and 798 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 8.02 (d, *J* = 8.3 Hz, Ar-H, 1H), 7.93 (s, Ar-H, 1H), 7.46 (d, *J* = 8.0 Hz, Ar-H, 1H), 2.45 (s, CH₃, 3H), 2.27 (s, CH₃, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 165.5, 139.3, 138.1, 127.4, 126.9, 116.0, 115.4, 115.2, 11.3, 10.4. HRMS (ESI/TOF) *m/z* calcd for C₁₁H₁₁N₄O [M + H]⁺ 215.0928, found 215.0939.

General Procedure for C–N Bond-Forming Reactions of 6-Bromo-1H-benzo[d][1,2,3]triazole with Arylamines

In a clean, and dry 8 mL vial equipped with a stirring bar, 6-bromo-1H-benzo[d][1,2,3]triazole was dissolved in anhydrous 1,4-dioxane. The arylamine was added, the mixture was sparged with argon gas, and then ^tBuONa, Pd₂(dba)₃, and ^tBu₃P were added. The vial was capped and the mixture was stirred for 6 h at 100°C. Upon completion of the reaction, the mixture was diluted with CH₂Cl₂, filtered through Celite, and concentrated under reduced pressure. The crude material was purified by chromatography on a silica gel column by gradient elution with 10–50% EtOAc in hexanes and in the case of compound **29** with 0–5% MeOH in CH₂Cl₂.

***N*-(4-Methylphenyl)-1*H*-benzo[*d*][1,2,3]triazol-6-amine (25)**—Synthesized using 6-bromo-1*H*-benzo[*d*][1,2,3]triazole (150 mg, 0.76 mmol), *para*-toluidine (243 mg, 2.28 mmol), ^tBuONa (73 mg, 1.52 mmol), Pd₂(dba)₃ (69.5 mg, 0.076 mmol), and ^tBu₃P (23.0 mg, 0.114 mmol) in anhydrous 1,4-dioxane (0.9 mL) over 6 h at 100°C. Workup of the reaction mixture and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **25** as a pale brown solid (135 mg, 80% yield). *R_f* (SiO₂/50% EtOAc in hexanes) = 0.40. IR (KBr): 3483, 3391, 1515, and 808 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 15.05 (br s, NH, 1H), 7.81 (d, *J* = 8.9 Hz, Ar-H, 1H), 7.20 (d, *J* = 1.5 Hz, Ar-H, 1H), 7.14–7.09 (m, Ar-H, 5H), 2.24 (s, CH₃, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop TFA-*d*): δ 143.8, 140.0, 129.9, 129.6, 118.7, 116.8, 91.4, 20.3. HRMS (ESI/TOF) *m/z* calcd for C₁₃H₁₃N₄ [M + H]⁺ 225.1135, found 225.1142.

***N*-(Naphthalen-1-yl)-1*H*-benzo[*d*][1,2,3]triazol-6-amine (26)**—Synthesized using 6-bromo-1*H*-benzo[*d*][1,2,3]triazole (200 mg, 1.01 mmol), naphthalen-1-amine (433 mg, 3.03 mmol), ^tBuONa (193 mg, 2.02 mmol), Pd₂(dba)₃ (94.2 mg, 0.101 mmol), and ^tBu₃P (30.6 mg, 0.151 mmol) in 1,4-dioxane (1.0 mL) over 6 h at 100°C. Workup of the reaction mixture and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **26** as a pale brown solid (191 mg, 72% yield). *R_f* (SiO₂/50% EtOAc in hexanes) = 0.42. IR (KBr): 3478, 3390, 1521, and 791 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 8.17 (d, *J* = 7.6 Hz, Ar-H, 1H), 7.95 (d, *J* = 8.3 Hz, Ar-H, 1H), 7.86 (d, *J* = 8.9 Hz, Ar-H, 1H), 7.64 (d, *J* = 7.6 Hz, Ar-H, 1H), 7.56–7.44 (m, Ar-H, 4H), 7.27 (d, *J* = 8.9 Hz, Ar-H, 1H), 7.00 (d, *J* = 1.3 Hz, Ar-H, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 145.2, 138.7, 137.6, 136.3, 134.6, 128.3, 127.8, 126.2, 125.5, 123.0, 117.9, 1177.8, 116.8, 116.7, 94.1. HRMS (ESI/TOF) *m/z* calcd for C₁₆H₁₃N₄ [M + H]⁺ 261.1135, found 261.1148.

***N*-(4-Methoxyphenyl)-1*H*-benzo[*d*][1,2,3]triazol-6-amine (27)**—Synthesized using 6-bromo-1*H*-benzo[*d*][1,2,3]triazole (150 mg, 0.76 mmol), *p*-anisidine (280 mg, 2.28 mmol), ^tBuONa (73 mg, 1.52 mmol), Pd₂(dba)₃ (69.5 mg, 0.076 mmol), and ^tBu₃P (23.0 mg, 0.114 mmol) in 1,4-dioxane (0.85 mL) over 6 h at 100°C. Workup of the reaction mixture and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **27** as a pale brown solid (127 mg, 70% yield). *R_f* (SiO₂/50% EtOAc in hexanes) = 0.31. IR (KBr): 3467, 3391, 1510, and 804 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆): δ 14.92 (br s, NH, 1H), 8.18 (s, NH, 1H), 7.79 (s, Ar-H, 1H), 7.14–6.94 (m, Ar-H, 6H), 3.74 (s, CH₃, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆): δ 154.5, 145.3, 138.9, 135.3, 134.5, 121.8, 119.1, 116.0, 114.6, 89.5, 55.2. HRMS (ESI/TOF) *m/z* calcd for C₁₃H₁₃N₄O [M + H]⁺ 241.1084, found 241.1086.

***N*-(1*H*-Benzo[*d*][1,2,3]triazol-6-yl)isoquinolin-5-amine (28)**—Synthesized using 6-bromo-1*H*-benzo[*d*][1,2,3]triazole (200 mg, 1.01 mmol), isoquinolin-5-amine (436 mg, 3.03 mmol), ^tBuONa (193 mg, 2.02 mmol), Pd₂(dba)₃ (92.4 mg, 0.101 mmol), and ^tBu₃P (30 mg, 0.151 mmol) in anhydrous 1,4-dioxane (1 mL) over 6 h at 100°C. Workup of the reaction mixture and chromatography of the crude material on a silica gel column by gradient elution with EtOAc in hexanes gave compound **28** as brown solid (178 mg, 68% yield). *R_f* (SiO₂/10% MeOH in CH₂Cl₂) = 0.54. IR (KBr): 3437, 3272, 1518, 1387, and 824

cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆ + 1 drop TFA-*d*): δ 9.91 (s, Ar-H, 1H), 8.73 (s, Ar-H, 2H), 8.12 (d, *J* = 7.8 Hz, Ar-H, 1H), 7.97–7.89 (m, Ar-H, 3H), 7.45 (s, Ar-H, 1H), 7.37 (d, *J* = 8.8 Hz, Ar-H, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop TFA-*d*): δ 147.5, 141.6, 140.3, 138.0, 137.3, 131.6, 131.1, 130.7, 128.6, 122.6, 121.2, 120.7, 119.5, 117.8, 99.7. HRMS (ESI/TOF) *m/z* calcd for C₁₅H₁₂N₅ [M + H]⁺ 262.1087, found 262.1099.

4-(1*H*-Benzo[*d*][1,2,3]triazol-6-ylamino)benzonitrile (29)—Synthesized using 6-bromo-1*H*-benzo[*d*][1,2,3]triazole (150 mg, 0.76 mmol), *para*-aminobenzonitrile (269 mg, 2.28 mmol), ^tBuONa (73 mg, 1.52 mmol), Pd₂(dba)₃ (69.5 mg, 0.076 mmol), and ^tBu₃P (23 mg, 0.114 mmol) in anhydrous 1,4-dioxane (0.85 mL) over 6 h at 100°C. Workup of the reaction mixture and chromatography of the crude material on a silica gel column by gradient elution with MeOH in CH₂Cl₂ gave compound **29** as a pale brown solid (116 mg, 65% yield). *R_f* (SiO₂/70% EtOAc in hexanes) = 0.40. IR (KBr): 3436, 3338, 2212, 1606, and 805 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 7.94 (d, *J* = 8.7 Hz, Ar-H, 1H), 7.65 (d, *J* = 8.7 Hz, Ar-H, 2H), 7.56 (d, *J* = 1.5 Hz, Ar-H, 1H), 7.28 (dd, *J* = 1.8, 8.8 Hz, Ar-H, 1H), 7.22 (d, *J* = 8.8 Hz, Ar-H, 2H). ¹³C NMR (100 MHz, DMSO-*d*₆ + 1 drop of TFA-*d*): δ 148.1, 139.6, 137.9, 137.2, 133.8, 120.0, 119.9, 117.7, 115.2, 100.6, 100.2. HRMS (ESI/TOF) *m/z* calcd for C₁₃H₁₀N₅ [M + H]⁺ 236.0931, found 236.0933.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1. Other Methods for the Synthesis of 1*H*-Benzotriazoles.

Scheme 2.

1-Hydroxy-1H-benzotriazoles selected for the analysis and yields of those synthesized.

Scheme 3.
Various 1H-benzotriazoles synthesized.

Scheme 4.

A possible mechanism for the deoxygenation.

Table 1

Evaluation of Conditions for the Deoxygenation of HOBt (1) and HOAt (2).

Entry	Substrate	Conditions ^[a]	Conversion, yield (%) ^[b]
1	1	(pinB) ₂ , MeCN, rt, 12 h	~5%, NA
2	1	(pinB) ₂ , MeCN, 50°C, 24 h	~50%, NA
3	1	(pinB) ₂ , MeCN, 80°C, 12 h	~95%, 92
4	2	(pinB) ₂ , MeCN, 80°C, 12 h	~95%, 90
5	1	(pinB) ₂ DBU, MeCN, 50°C, 1 h	100%, 96
6	1	(pinB) ₂ , Et ₃ N, MeCN, 50°C, 0.5 h	100%, 98
7	2	(pinB) ₂ , Et ₃ N, MeCN, 50°C, 8 h	100%, 94
8	1	B ₂ (OH) ₄ , H ₂ O, 85°C, 6 h	100%, 95
9 ^[c]	2	B ₂ (OH) ₄ , H ₂ O, 85°C, 12 h	95%, 75
10	1	(catB) ₂ , Et ₃ N, MeCN, 50°C, 0.5 h	100%, 90
11	2	(catB) ₂ , Et ₃ N, MeCN, 50°C, 0.5 h	100%, 88
12	1	B ₂ (OH) ₄ , Et ₃ N, MeCN, rt, 1.2 h	98%, 95
13	1	B ₂ (OH) ₄ , Et ₃ N, MeCN, 50°C, 0.5 h	100%, 95
14	2	B ₂ (OH) ₄ , Et ₃ N, MeCN, 50°C, 8 h	100%, 92
15	1	B ₂ (OH) ₄ , Cs ₂ CO ₃ , MeCN, 50°C, 1 h	98%, 92
16	2	B ₂ (OH) ₄ , Cs ₂ CO ₃ , MeCN, 50°C, 1 h	100%, 95
17	1	B ₂ (OH) ₄ , K ₃ PO ₄ , H ₂ O, 85°C, 24 h	~10%, NA ^[d]

^[a] Reactions were performed with 1.2 equiv of the diboron reagent and where applicable 1.2 eq of base.

^[b] Yields reported are of isolated and purified products.

^[c] Reaction required 1.7 equiv of B₂(OH)₄.

^[d] Multiple spots were observed by TLC.

Table 2

Diversification of 1*H*-Benzotriazoles via Pd-catalyzed C–C and C–N Bond Formation.

Entry	ArB(OH) ₂ or ArNH ₂	Product	Compound: yield ^[a]
1			20 : 90%, 99.6 ^[b] (60) ^{[c].[d]}
2			21 : 78%, 99.8 ^[b] (NR) ^[e]
3			22 : 88%, 99.8 ^[b] (42) ^{[c].[d]}
4			23 : 75%, 99.1 ^[b] (45) ^{[c].[d]}
5			24 : 60%, 99.1 ^[b]
6			25 : 50%, 99.1 ^[b]
7			26 : 72%, 99.2 ^[b]
8			27 : 70%, 99.5 ^[b]

Entry	ArB(OH) ₂ or ArNH ₂	Product	Compound: yield ^[a]
9			28 : 68%, 98.2 ^[b]
10			29 : 65%, 99.7 ^[b]

^[a]Yields reported are of isolated and purified products.

^[b]Purity by UPLC analysis.

^[c]Yield for the two-step, one-pot reaction.

^[d]A significant amount of compound **18** from the deoxygenation step remained.

^[e]No reaction was observed in the two-step, one-pot reaction, and only compound **18** from the deoxygenation step remained.

Table 3

Comparison of Two Methods for Diversification via C-C Bond Formation.

Entry	Final product	Overall yield via method 1 ^[a] v/s method 2 ^[b]
1		20: 83% v/s 70%
2		21: 69% v/s 61%
3		22: 74% v/s 69%

^[a] Method 1: C-C reaction of 4-bromo-1-fluoro-2-nitrobenzene with the arylboronic acid, construction of the hydroxybenzotriazole, and then deoxygenation.

^[b] Method 2: synthesis of compound **7**, deoxygenation to benzotriazole **18**, and then C-C reaction with the arylboronic acid.