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Room-Temperature Cu(II)-Catalyzed Chemo- and Regioselective *Ortho*-Nitration of Arenes via C−H Functionalization

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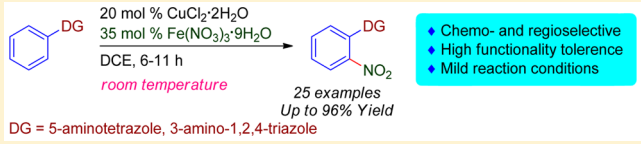
Supporting Information

ABSTRACT: An efficient Cu-catalyzed chemo- and regioselective *ortho*-nitration of *N*,1-diaryl-5-aminotetrazoles and *N*,4-diaryl-3-amino-1,2,4-triazoles have been described with good functional group compatibility. The procedure features the use of operationally simple protocol utilizing the commercially available less toxic $CuCl_2·2H_2O$ as catalyst and $Fe(NO_3)_3·9H_2O$ as nitration source at room temperature. Removal of the 5-aminotetrazole directing group has been demonstrated using base hydrolysis to afford substituted 2-nitroanilines.



INTRODUCTION

The chelation assisted direct C−H functionalization using transition-metal catalysis has recently emerged as a powerful synthetic tool for the regioselective formation of carbon−carbon and carbon−heteroatom bonds.[1] The second-row transition metals, such as Ru,[2] Rh,[3] and Pd,[4] have been considerably explored for this purpose. In contrast, the first-row transition metals have received less attention despite their high abundance in the earth's crust.[5] In particular, a few studies are focused on the copper-catalyzed aerobic C−H functionalization reactions.[6] Herein, we report an efficient copper(II)-catalyzed direct chemo- and regioselective *ortho*-nitration of *N*,1-diaryl-5-aminotetrazoles and *N*,4-diaryl-3-amino-1,2,4-triazoles in the presence of $Fe(NO_3)_3·9H_2O$ at room temperature. From an industrial standpoint, this process would be useful due to its mild conditions, good functional group compatibility, and the fact that nitric acid is not needed.

Aromatic nitro compounds are versatile building blocks in organic, medicinal, and pharmaceutical sciences as well as in chemical industry.[7] The electrophilic nitration of arenes has long been the classical synthetic approach for the preparation of the aromatic nitro compounds. However, these traditional processes often suffer due to poor selectivity and imperfect functional group tolerance under harsh conditions.[8] To overcome these drawbacks, several approaches have been explored including the *ipso*-nitration by the nitrodemetalation of an aryl C−M bond (M = B, Li),[9] the *ipso*-oxidation[10] of an amino or azide group to a nitro group, and the cross-coupling protocols of aryl halides, triflates, and nonaflates with nitrite using transition-metal catalysis (Pd or Cu).[11] Although these methods have overcome some of the above limitations, they still suffer from the requirement of prefunctionalized substrate precursors.[12] Attention has thus been recently focused on the chelation-assisted direct regioselective aromatic C−H nitrations using $Cu/AgNO_2$,[13a,d] $Rh/NaNO_2$,[13b] and $Pd/AgNO_2/NO_2$.[13c,e]

RESULTS AND DISCUSSION

N,1-Diaryl-5-aminotetrazoles and *N*,4-diaryl-3-amino-1,2,4-triazoles are structural motifs present in many compounds that are important in biological and medicinal sciences.[14,15] Their direct and selective C−H functionalization will thus be relevant to drug discovery. First, we commenced the optimization studies with *N*-aryl-1-aryl-1*H*-tetrazol-5-amine **1a** as a model substrate using a series of copper salts as catalyst with different nitro sources and solvents (Table 1). Gratifyingly, the reaction occurred selectively at the *ortho*-position of the *N*-aryl ring without affecting the 1-aryl ring to give **2a** in 95% yield when the substrate **1a** was stirred with $CuCl_2·2H_2O$ (20 mol %) and $Fe(NO_3)_3·9H_2O$ (35 mol %) in 1,2-dichloroethane (DCE) for 11 h at room temperature. In a set of copper sources screened, $CuCl_2·2H_2O$ exhibited superior results compared to $Cu(OAc)_2·H_2O$, $Cu(OTf)_2$, $CuSO_4·5H_2O$, $Cu(NO_3)_2·3H_2O$, CuI, $CuBr_2$, CuBr, and CuCl (entries 1−9). Among the nitro sources examined, $Fe(NO_3)_3·9H_2O$ gave the best results, whereas $Ca(NO_3)_2·4H_2O$, $AgNO_3$, $Bi(NO_3)_3·5H_2O$, and $NaNO_2$ afforded the target product in <26% yield (entries 10−13). DCE was found to be the solvent of choice giving the highest yield, whereas dichloromethane (DCM), toluene and CH_3CN afforded **2a** in 62−89% yields. In contrast, THF and DMF furnished inferior results (entries 14−18). Lowering the amount of the Cu source (10 mol %) led the formation of **2a** in 61% yield (entry 19). Control experiments confirmed that without the Cu source no reaction was observed and starting material **1a** was recovered intact (entry 20). In addition, the use

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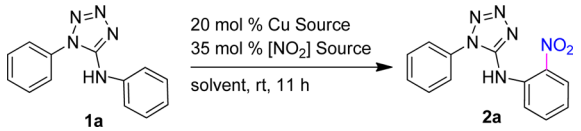
Table 1. Optimization of the Reaction Conditions[a]



entry	Cu source (20 mol %)	[NO_2] source (35 mol %)	solvent	yield (%)
1	$Cu(OAc)_2·H_2O$	$Fe(NO_3)_3·9H_2O$	DCE	52
2	$Cu(OTf)_2$	$Fe(NO_3)_3·9H_2O$	DCE	48
3	$CuSO_4·5H_2O$	$Fe(NO_3)_3·9H_2O$	DCE	trace
4	CuI	$Fe(NO_3)_3·9H_2O$	DCE	44
5	CuCl	$Fe(NO_3)_3·9H_2O$	DCE	84
6	$CuBr_2$	$Fe(NO_3)_3·9H_2O$	DCE	86
7	$Cu(NO_3)_2·3H_2O$	$Fe(NO_3)_3·9H_2O$	DCE	10
8	CuBr	$Fe(NO_3)_3·9H_2O$	DCE	74
9	$CuCl_2·2H_2O$	$Fe(NO_3)_3·9H_2O$	DCE	95
10[b]	$CuCl_2·2H_2O$	$Ca(NO_3)_2·4H_2O$	DCE	trace
11	$CuCl_2·2H_2O$	$Bi(NO_3)_3·5H_2O$	DCE	21
12[c]	$CuCl_2·2H_2O$	$AgNO_3$	DCE	26
13[d]	$CuCl_2·2H_2O$	$NaNO_2$	DCE	24
14	$CuCl_2·2H_2O$	$Fe(NO_3)_3·9H_2O$	DCM	89
15	$CuCl_2·2H_2O$	$Fe(NO_3)_3·9H_2O$	THF	trace
16	$CuCl_2·2H_2O$	$Fe(NO_3)_3·9H_2O$	toluene	74
17	$CuCl_2·2H_2O$	$Fe(NO_3)_3·9H_2O$	DMF	n.d.
18	$CuCl_2·2H_2O$	$Fe(NO_3)_3·9H_2O$	CH_3CN	62
19[e]	$CuCl_2·2H_2O$	$Fe(NO_3)_3·9H_2O$	DCE	61
20		$Fe(NO_3)_3·9H_2O$	DCE	trace
21[f]	$Cu(NO_3)_2·3H_2O$		DCE	50

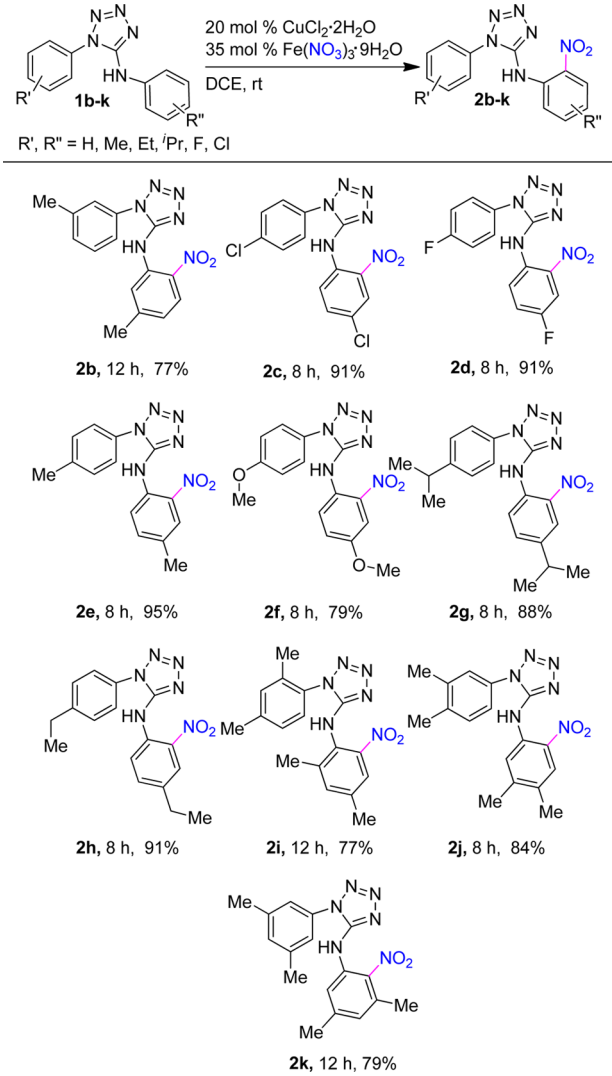
[a]Reaction conditions: *N*,1-diphenyl-1*H*-tetrazol-5-amine **1a** (1 mmol), Cu source (20 mol %), $Fe(NO_3)_3·9H_2O$ (35 mol %), solvent (3 mL), rt, 11 h. [b]$Ca(NO_3)_3·4H_2O$ (50 mol %) was used. [c]$AgNO_3$ (1.1 equiv) was used. [d]$NaNO_2$ (1.1 equiv) was used. [e]$CuCl_2·2H_2O$ (10 mol %) was used. [f]$Cu(NO_3)_2·3H_2O$ (100 mol %) was used. n.d. = not detected.

of a stoichiometric amount of $Cu(NO_3)_2·3H_2O$ without $Fe(NO_3)_3·9H_2O$ afforded **2a** in 50% yield (entry 21).

Having the optimal conditions in hand, we explored the scope of this procedure for the substrates having symmetrical substituents on the aryl rings (Scheme 1). The substrates **1b–h** having 3-methyl, 4-chloro, 4-fluoro, 4-methyl, 4-methoxy, 4-isopropyl, and 4-ethyl substituents on the aryl rings readily proceeded reaction to provide the corresponding nitration products **2b–h** in 77–95% yields. Likewise, the substrates **1i–k** containing 2,4-, 3,4-, and 3,5-dimethyl substituents could be nitrated to give the target products **2i–k** in 77–84% yields. Next, the substrates having the unsymmetrical substituents in the aryl rings were subjected to the optimized reaction conditions (Scheme 2). As above, the reaction readily occurred to give the target products in high yields. For example, the substrates **1l–p** with 2-chloro, 4-fluoro, 4-isopropyl, naphthyl, and 4-nitro substituents proceeded reaction to produce the corresponding nitration products **2l–p** in 75–94% yields. Similarly, the substrates **1q** having 2-fluoro and 4-ethyl substituents underwent reaction to furnish **2q** in 86% yield. Furthermore, the substrates **1r–v** containing 2,6-dimethyl, 4-methyl, 4-nitro, 4-acetanilide, and 4-cyano substituents reacted to give the respective nitration products **2r–v** in 77–93% yields.

The reaction conditions were also effective for the nitration of *N*,4-diaryl-3-amino-1,2,4-triazoles (Scheme 3). For example, the unsubstituted substrate **3a** reacted with greater reactivity

Scheme 1. *Ortho*-Nitration of Symmetrically Substituted *N*,1-Diaryl-5-aminotetrazoles



[a]Reaction conditions: *N*-phenyl-1*H*-tetrazol-5-amine **1b–k** (1 mmol), $CuCl_2·2H_2O$ (20 mol %), $Fe(NO_3)_3·9H_2O$ (35 mol %), DCE (3 mL), rt.

compared to the corresponding 5-aminotetrazole derivative to yield the nitration product **4a** in 6 h with 84% yield. Similarly, the substrates having symmetrical substituents such as 4-fluoro and 4-methyl **3b** and **3c** groups readily underwent the reaction to furnish **4b** and **4c** in 6 h with 82% and 87% yields, respectively.

Furthermore, the protocol can be utilized for gram-scale synthesis (Scheme 4). For example, the reaction of **1a** was carried out on gram scale, and the reaction occurred to afford the target molecule **2a** in 89% yield. In addition, we attempted a removal of the tetrazole directing group using the products **2a**, **2g**, and **2l** as representative examples (Table 2). The reaction readily occurred with NaOH in 1,4-dioxane at 110 °C to give the corresponding 2-nitroaniline derivatives in good yields.[16]

The proposed catalytic cycle is shown in Scheme 7. The intermolecular kinetic isotope experiments of the substrates **1r** and **1r-d$_3$** gave P_H/P_D = 1.2 (21% conversion), while the intramolecular kinetic isotope experiments of the substrate **1s-d**

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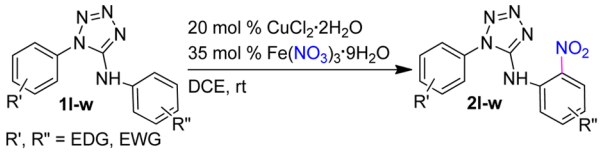
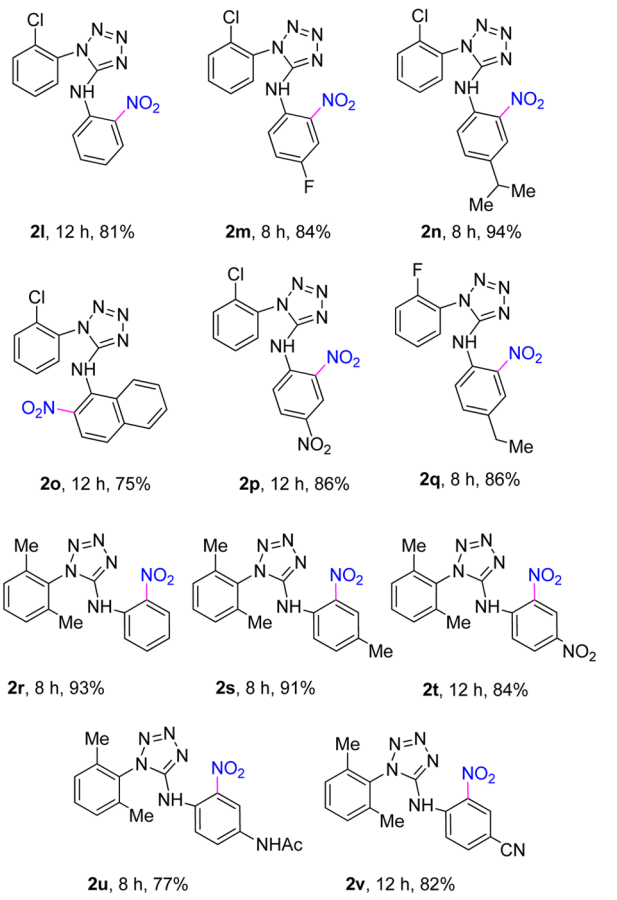
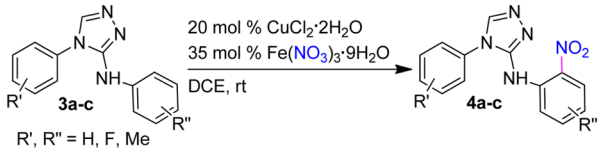
Scheme 2. *Ortho*-Nitration of Unsymmetrically Substituted *N*,1-Diaryl-5-aminotetrazoles[a]

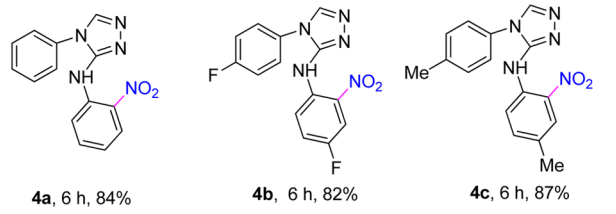




[a]Reaction conditions: *N*-phenyl-1*H*-tetrazol-5-amine **1l–v** (1 mmol), $CuCl_2·2H_2O$ (20 mol %), $Fe(NO_3)_3·9H_2O$ (35 mol %), DCE (3 mL), rt.

Scheme 3. *Ortho*-Nitration of *N*,4-Diaryl-3-amino-1,2,4-triazoles[a]





[a]Reaction conditions: *N*,4-diphenyl-4*H*-1,2,4-triazol-3-amine **3a–c** (1 mmol), $CuCl_2·2H_2O$ (20 mol %), $Fe(NO_3)_3·9H_2O$ (35 mol %), DCE (3 mL), rt.

Scheme 4. Gram-Scale Synthesis

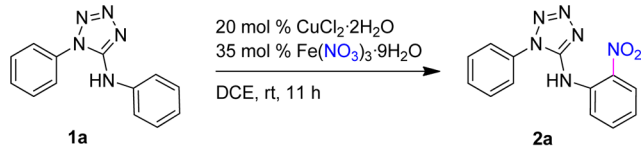
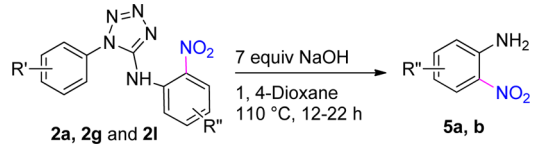
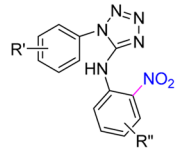
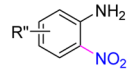


Table 2. Removal of Directing Group[a]



entry	substrate	product	time (h)	yield (%)
				
1	R', R" = H (**2a**)	R" = H (**5a**)	22	78
2	R', R" = ^{i}Pr (**2g**)	R" = ^{i}Pr (**5b**)	12	87
3	R' = 2-Cl, R" = H (**2l**)	R" = H (**5a**)	22	84

[a]Reaction conditions: **2a**, **2g**, and **2l** (1 mmol), NaOH (7.0 equiv), 1,4-dioxane (3 mL), 110 °C.

afforded P_H/P_D = 3.5 (Scheme 5).[17] These results suggest that the substrate-binding step is the product-determining step.[18] In addition, TEMPO does not inhibit the rate of the reaction, which suggests that the reaction may not involve a radical intermediate (Scheme 6).[19] In addition, the ESI-MS studies of the crude reaction mixture of **1a** before workup revealed the presence of four major species: $[\mathbf{2a} + H]^+$ and three copper complexes $\{[\mathbf{2a}·Cu]^+$, $[(\mathbf{2a})_2·Cu]^+$, and $[(\mathbf{2a})_2·CuCl]^+\}$ (see the Supporting Information) (Figure 1).[6f,20] However, attempts to isolate the species as single crystals remained unsuccessful. Furthermore, $CuCl_2·2H_2O$ and $Fe(NO_3)_3·9H_2O$ are insoluble in 1,2-dichloroethane; however, with substrate **1a** they readily dissolve to give a yellow solution, which suggests that the substrate **1a** may first bind with the hydrated $CuCl_2$ to give a soluble intermediate ***a*** that may undergo reaction with $Fe(NO_3)_3·9H_2O$ to afford the intermediate ***b*** (Scheme 7).[21] The subsequent intramolecular *ortho*-nitration via an aromatic electrophilic substitution can give the intermediate ***c***, which can afford the target product **2** and the hydrated CuX_2 to complete the catalytic cycle.

CONCLUSION

In summary, we have developed an efficient copper-catalyzed *ortho*-selective nitration of arenes using iron(III) nitrate as nitration source under mild reaction conditions. The use of inexpensive Cu catalyst and the greener nitration source provides an attractive pathway for the preparation of nitro arenes. The reaction demonstrates good functional group tolerance in attaining the product with excellent selectivity. Further, the reaction protocol is successfully extended to 3-amino-1,2,4-triazoles. Due to the versatility of nitro group in organic synthesis these studies can open new avenue for further

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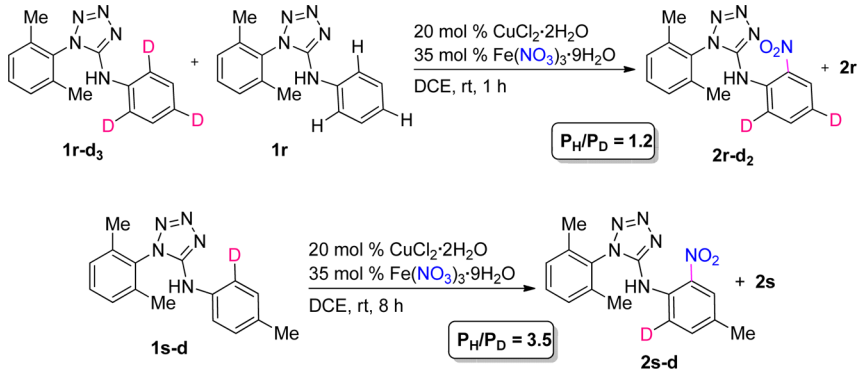
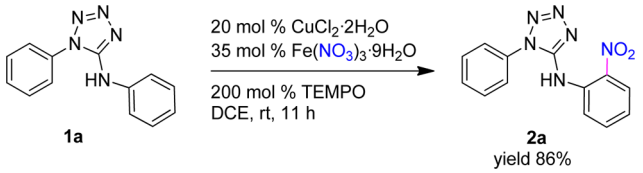
Scheme 5. Kinetic Isotope Experiments



Scheme 6. Radical Scavenger Experiment



development of 5-aminotetrazole and 3-amino-1,2,4-triazole derivatives in the area of pharmaceutical and biological sciences.

EXPERIMENTAL SECTION

General Information. $Cu(OTf)_2$ (98%), CuI (98%), and CuCl (90%) were purchased from Aldrich. $Cu(OAc)_2·H_2O$ (98%), $CuBr_2$ (98%), $Cu(NO_3)_2·3H_2O$ (99%), $CuCl_2·2H_2O$ (99%), and $Fe(NO_3)_3·9H_2O$ (98%) were purchased from Merck. $CuSO_4·5H_2O$ (99%) was obtained from Rankem. These chemicals were used as received without further purification. The solvents were purchased from commercial sources and dried according to standard procedures prior to use.[22a] 3,5-Diaminotetrazoles[22c] and amino-1,2,4-triazoles[22b,d,e] were prepared according to the reported procedure. Purification of the reaction products was carried out by column chromatography using silica gel (60−120 mesh). Analytical TLC was performed on a silica gel G/GF 254 plate. NMR spectra were recorded on 600, 400, and 300 MHz instruments using $CDCl_3$, CD_3OD, and DMSO-d_6 as solvent and Me_4Si as internal standard. Chemical shifts (δ) are reported in parts per million, and spin−spin coupling constants (J) are reported in hertz. Melting points were determined using a melting point apparatus and are uncorrected. FT-IR spectra were recorded using an IR spectrometer. High-resolution mass spectra were recorded on a Q-Tof ESI-MS instrument, and mass spectra were obtained from a ESI-MS instrument.

General Procedure for the Cu(II)-Catalyzed C−H *Ortho*-Nitration of Arenes. To a stirred solution of 1,*N*-diaryl-5-aminotetrazole **1a−v** or *N*,1,-diaryl-3-amino-1,2,4-triazoles **3a−c** (1 mmol) in DCE (3 mL) were added $CuCl_2·2H_2O$ (20 mol %, 0.2 mmol, 34.6 mg) and $Fe(NO_3)_3·9H_2O$ (35 mol %, 0.35 mmol, 141 mg) at room temperature under air. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, a saturated $NaHCO_3$ solution (5 mL) was added to the reaction mixture, and the resultant solution was extracted with ethyl acetate (3 × 10 mL) and washed with brine (2 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as eluent to afford analytically pure products.

***N*-(2-Nitrophenyl)-1-phenyl-1*H*-tetrazol-5-amine (2a):** analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.61; yellow solid; 268 mg, yield 95%; mp 186−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.79 (br s, 1H), 8.95 (d, J = 8.4 Hz, 1H), 8.26 (dd, J = 8.4, 1.2 Hz, 1H), 7.77−7.59 (m, 6H), 7.16−7.12 (m, 1H); ^{13}C{H} NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 150.8, 137.1, 135.9, 135.0, 132.4, 131.2, 130.9, 126.4, 124.8, 122.4, 120.2; FT-IR (KBr) 3228, 2854, 1598, 1564, 1538, 1525, 1381, 1336, 1280, 1121, 1092, 1019 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_{10}N_6O_2$ 283.0938, found 283.0948.

***N*-(5-Methyl-2-nitrophenyl)-1-(*m*-tolyl)-1*H*-tetrazol-5-amine (2b):** analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.66; yellow solid; 239 mg, yield 77%; mp 188−189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.84 (br s, 1H), 8.72 (s, 1H), 8.14 (d, J = 8.8 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.43−7.37 (m, 3H), 6.93 (d, J = 8.8 Hz, 1H), 2.49 (s, 3H), 2.48 (s, 3H); ^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 150.8, 149.4, 141.4, 135.9, 133.0, 132.3, 131.9, 130.6, 126.4, 125.2,

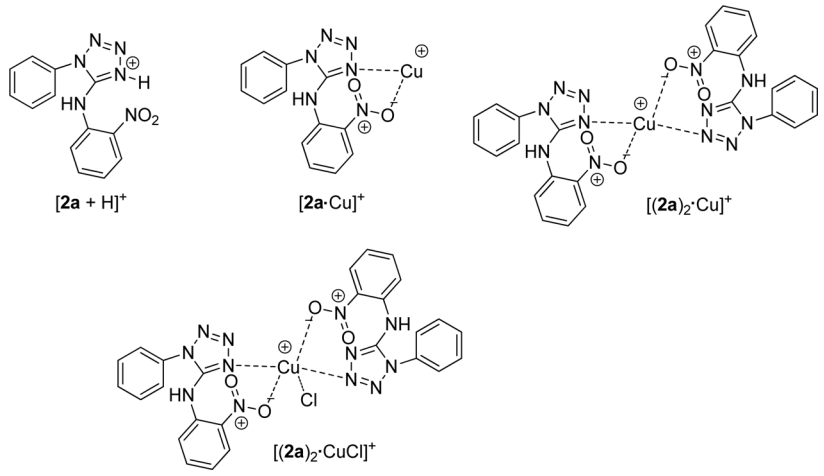


Figure 1. Major species identified using ESI-MS analysis of the reaction mixture of **1a**.

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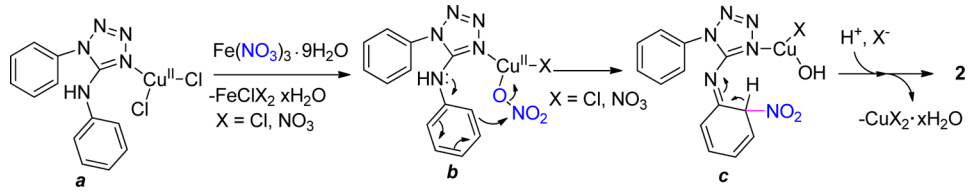
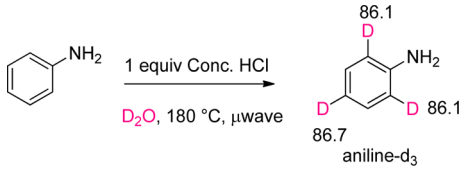
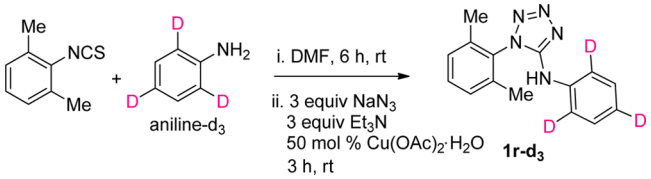
Scheme 7. Proposed Catalytic Cycle



Scheme 8



Scheme 9



123.5, 121.7, 120.0, 22.5, 21.6; FT-IR (KBr) 3095, 2923, 1592, 1534, 1489, 1324, 1281, 1161, 1091, 870, 846 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{14}N_6O_2$ 311.1251, found 311.1251.

***N*-(4-Chloro-2-nitrophenyl)-1-(4-chlorophenyl)-1*H*-tetrazol-5-amine (2c):** analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.69; yellow solid; 318 mg, yield 91%; mp 187−188 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.72 (br s, 1H), 8.96 (d, J = 9.6 Hz, 1H), 8.27 (d, J = 1.8 Hz, 1H), 7.73 (dd, J = 9.0, 1.8 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H) ; $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$) δ 150.5, 137.6, 137.2, 135.1, 134.4, 131.3, 130.7, 127.8, 126.0, 125.9, 121.7; FT-IR (KBr) 3259, 2921, 1639, 1538, 1499, 1341, 1275, 1245, 1154, 1091, 903, 838 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_8Cl_2N_6O_2$ 351.0167, found 351.0163.

***N*-(4-Fluoro-2-nitrophenyl)-1-(4-fluorophenyl)-1*H*-tetrazol-5-amine (2d):** analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.62; yellow solid; 289 mg, yield 91%; mp 170−171 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.59 (br s, 1H), 9.00−8.98 (m, 1H), 7.99 (dd, J = 8.4, 3.0 Hz,1H), 7.62−7.59 (m, 2H), 7.55−7.52 (m, 1H), 7.41−7.38 (m, 2H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$) δ 164.7 (d, J = 252.0 Hz), 157.4 (d, J = 244.5 Hz), 150.8, 134.8, 132.4, 128.2, 127.2 (d, J = 9.0 Hz), 125.0 (d, J = 22.5 Hz), 122.0 (d, J = 7.5 Hz), 118.3 (d, J = 22.5 Hz), 112.8 (d, J = 27.0 Hz); FT-IR (KBr) 3260, 3091, 2923, 1598, 1576, 1537, 1513, 1468, 1384, 1336, 1284, 1161, 1137, 1090, 949, 843 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_8F_2N_6O_2$ 319.0750, found 319.0748.

***N*-(4-Methyl-2-nitrophenyl)-1-*p*-tolyl-1*H*-tetrazol-5-amine (2e):** analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.73; yellow solid; 295 mg, yield 95%; mp 192−193 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.63 (br s, 1H), 8.83 (d, J = 8.8 Hz, 1H), 8.05 (s, 1H), 7.56 (dd, J = 8.4, 1.6 Hz, 1H), 7.45 (s, 4H), 2.48 (s, 3H), 2.38 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 150.9, 141.6, 138.1, 134.7, 133.7, 132.5, 131.4, 129.8, 126.0, 124.6, 120.1, 21.6, 20.6; FT-IR (KBr) 3083, 2922, 2852, 1594, 1524, 1463, 1333, 1303, 1247, 1116, 927, 811 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{14}N_6O_2$ 311.1251, found 311.1251.

***N*-(4-Methoxy-2-nitrophenyl)-1-(4-methoxyphenyl)-1*H*-tetrazol-5-amine (2f):** analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.36; brown solid; 270 mg, yield 79%; mp 166−167 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.45 (br s, 1H), 8.87 (d, J = 9.6 Hz, 1H), 7.69 (d, J = 2.8 Hz, 1H), 7.48−7.45 (m, 2H), 7.36 (dd, J = 9.2, 2.8 Hz, 1H), 7.15−7.11 (m, 2H), 3.90 (s, 3H), 3.85 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 161.6, 154.3, 151.2, 135.2, 130.1, 126.5, 125.3, 124.8, 121.6, 115.9, 108.6, 56.2, 55.9; FT-IR (KBr) 3259, 2924, 2852, 1599, 1562, 1534, 1384, 1348, 1268, 1245, 1024, 998, 830 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{14}N_6O_4$ 343.1149, found 343.1153.

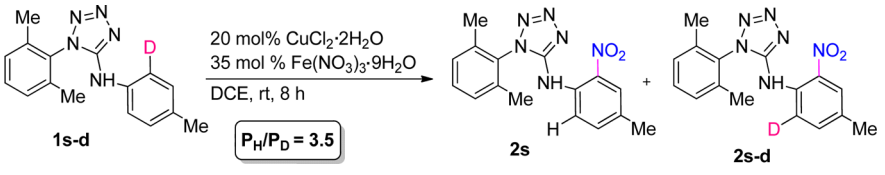
***N*-(4-Isopropyl-2-nitrophenyl)-1-(4-isopropylphenyl)-1*H*-tetrazol-5-amine (2g):** analytical TLC on silica gel, 1:5 ethyl acetate/hexane, R_f = 0.57; yellow solid; 322 mg, yield 88%; mp 116−117 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.63 (br s, 1H), 8.83 (d, J = 8.4 Hz, 1H), 8.08 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.51 (s, 4H), 3.06−2.99 (m, 1H), 2.97−2.92 (m, 1H), 1.32 (d, J = 7.2 Hz, 6H), 1.27 (d, J = 6.8 Hz, 6H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 152.3, 150.9, 143.4, 135.7, 134.8, 133.9, 130.0, 128.8, 124.5, 123.5, 120.2, 34.2, 33.4, 23.9, 23.8; FT-IR (KBr) 2963, 1627, 1596, 1535, 1518, 1425, 1338, 1283, 1252, 1087, 1013, 841 cm^{-1}. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{22}N_6O_2$ 367.1877, found 367.1884.

***N*-(4-Ethyl-2-nitrophenyl)-1-(4-ethylphenyl)-1*H*-tetrazol-5-amine (2h):** analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.69; yellow solid; 308 mg, yield 91%; mp 114−115 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.61 (br s, 1H), 8.80 (dd, J = 8.8, 0.8 Hz, 1H), 8.03 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.47 (s, 4H), 2.77 (q, J = 8.0 Hz, 2H), 2.67 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 150.8, 147.6, 138.7, 136.9, 134.7, 133.8, 130.1, 129.9, 124.8, 124.6, 120.1, 28.8, 27.9, 15.4, 15.2; FT-IR (KBr) 3245, 2960, 2926, 1596, 1559, 1531, 1516, 1384, 1335, 1251, 1183, 1086, 915, 843 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{18}N_6O_2$ 339.1564, found 339.1564.

***N*-(2,4-Dimethyl-6-nitrophenyl)-1-(2,4-dimethylphenyl)-1*H*-tetrazol-5-amine (2i):** analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.51; yellow solid; 260 mg, yield 77%; mp 188−189 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.33 (br s, 1H), 8.34 (s, 1H), 7.20 (s, 1H), 7.14 (s, 2H), 6.79 (s, 1H), 2.45 (s, 3H), 2.42 (s, 6H), 2.40 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 150.9, 145.3, 141.1, 136.7, 135.3, 133.9, 132.5, 132.3, 127.4, 121.9, 118.4, 22.1, 21.4, 21.2; FT-IR (KBr) 2922, 1615, 1544, 1493, 1377, 1344, 1294, 1249, 1091, 851 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{18}N_6O_2$ 339.1564, found 339.1565.

***N*-(4,5-Dimethyl-2-nitrophenyl)-1-(3,4-dimethylphenyl)-1*H*-tetrazol-5-amine (2j):** analytical TLC on silica gel, 1:5 ethyl acetate/hexane, R_f = 0.52; yellow solid; 284 mg, yield 84%; mp 158−159 °C;

Scheme 10



DOI: 10.1021/acs.joc.5b01021
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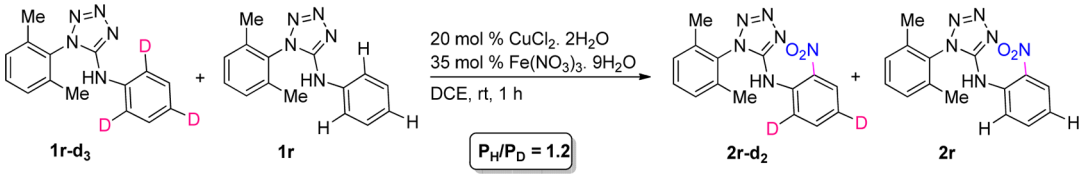
Scheme 11



^{1}H NMR (400 MHz, $CDCl_3$) δ 10.66 (br s, 1H), 8.63 (s, 1H), 7.93 (s, 1H), 7.38−7.26 (m, 3H), 2.36 (s, 3H), 2.35 (s, 3H), 2.34 (s, 3H), 2.23 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 150.7, 148.3, 140.0, 139.7, 133.8, 132.6, 131.6, 131.3, 129.9, 126.3, 125.5, 121.7, 120.3, 20.8, 19.9, 19.8, 19.1; FT-IR (KBr) 3266, 2921, 2852, 1593, 1529, 1504, 1406, 1323, 1298, 1259, 1135, 1092, 905, 892 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{18}N_6O_2$ 339.1564, found 339.1563.

***N*-(3,5-Dimethyl-2-nitrophenyl)-1-(3,5-dimethylphenyl)-1*H*-tetrazol-5-amine (2k):** analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.60; yellow solid; 267 mg, yield 79%; mp 180−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (br s, 1H), 8.30 (s, 1H), 7.18 (s, 1H), 7.12 (s, 2H), 6.76 (s, 1H), 2.40 (s, 9H), 2.37 (s, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 150.8, 145.2, 140.9, 136.5, 135.2, 133.8, 132.3, 132.2, 127.2, 121.7, 118.2, 22.0, 21.3, 21.1; FT-IR (KBr) 3094, 2922, 2844, 1606, 1539, 1491, 1339, 1293, 1249, 1093, 1033, 871, 850 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{18}N_6O_2$ 339.1564, found 339.1566.

1-(2-Chlorophenyl)-*N*-(2-nitrophenyl)-1*H*-tetrazol-5-amine (2l): analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.71; yellow solid; 256 mg, yield 81%; mp 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (br s, 1H), 8.82 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 8.4 Hz, 1H), 7.72−7.67 (m, 2H), 7.65−7.58 (m, 1H), 7.56 (d, J = 3.6 Hz, 2H), 7.09 (t, J = 8.8 Hz, 1H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 151.4, 136.9, 135.6, 134.7, 133.3, 131.8, 131.5, 129.4, 129.3, 128.9, 126.2, 122.3, 119.8; FT-IR (KBr) 3290, 3090, 2923, 1600, 1570, 1537, 1503, 1394, 1342, 1321, 1265, 1087, 887, 767, 739 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_9ClN_6O_2$ 317.0548, found 317.0547.

1-(2-Chlorophenyl)-*N*-(4-fluoro-2-nitrophenyl)-1*H*-tetrazol-5-amine (2m): analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.70; yellow solid; 281 mg, yield 84%; mp 142−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (br s, 1H), 8.96−8.92 (m, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.59−7.49 (m, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.7 (d, J = 245.5 Hz), 151.5, 133.5, 132.4, 131.9, 131.7, 129.5, 129.4, 129.0, 124.9 (d, J = 22.1 Hz), 121.9 (d, J = 7.6 Hz), 112.8 (d, J = 27.5 Hz); FT-IR (KBr) 2923, 2857, 1631, 1541, 1521, 1338, 1247, 1067, 947, 759 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_8ClFN_6O_2$ 335.0454, found 335.0462.

1-(2-Chlorophenyl)-*N*-(4-isopropyl-2-nitrophenyl)-1*H*-tetrazol-5-amine (2n): analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.69; yellow solid; 337 mg, yield 94%; mp 156−157 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.33 (br s, 1H), 8.81 (d, J = 9.0 Hz, 1H), 8.08 (d, J = 2.4 Hz, 1H), 7.74 (dd, J = 7.8, 1.2 Hz, 1H), 7.67−7.63 (m, 2H), 7.60−7.55 (m, 2H), 2.99−2.94 (m, 1H), 1.28 (d, J = 7.2 Hz, 6H); ^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 151.8, 143.7, 135.8, 134.9, 133.7, 133.4, 132.1, 131.7, 129.64, 129.60, 129.0, 123.6, 120.2, 33.5, 23.8; FT-IR (KBr) 2963, 2926, 1627, 1601, 1562, 1536, 1519, 1461, 1336, 1265, 1208, 1160, 1037, 928, 839 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{15}ClN_6O_2$ 359.1018, found 359.1021.

1-(2-Chlorophenyl)-*N*-(2-nitronaphthalen-1-yl)-1*H*-tetrazol-5-amine (2o). analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.52; reddish yellow gummy liquid; 275 mg, yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 8.8 Hz, 1H), 8.17 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.72−7.59 (m, 3H), 7.49 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 8.4 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 6.99 (t, J = 8.0 Hz, 1H), 6.84 (br s, 1H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 152.4, 134.8, 134.7, 132.2, 129.2, 128.94, 128.90, 128.8, 128.4, 128.1, 127.9, 125.6, 125.3, 123.8, 121.9, 121.5, 119.1; FT-IR (neat) 3113, 2925, 1603, 1567, 1520, 1452, 1312, 1232, 1087, 1053, 1034, 802, 772, 750 cm^{-1}. HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{11}ClN_6O_2$ 367.0710, found 367.0710.

1-(2-Chlorophenyl)-*N*-(2,4-dinitrophenyl)-1*H*-tetrazol-5-amine (2p): analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.42; orange solid; 311 mg, yield 86%; mp 189−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ 10.37 (br s, 1H), 8.86−8.85 (m, 1H), 8.81−8.78 (m, 1H), 8.34−8.31 (m, 1H), 7.54−7.46 (m, 2H), 7.43−7.38 (m, 2H); ^{13}C{H} NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 150.4, 140.6, 139.7, 133.4, 133.2, 131.1, 130.9, 130.4, 129.1, 128.7, 128.5, 122.1, 120.1; FT-IR (KBr) 3260, 3105, 2855, 1604, 1588, 1543, 1510, 1424, 1342, 1312, 1251, 1142, 1039, 912, 846, 772 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_8ClN_7O_4$ 362.0399, found 362.0398.

***N*-(4-Ethyl-2-nitrophenyl)-1-(2-fluorophenyl)-1*H*-tetrazol-5-amine (2q):** analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.72; yellow solid; 282 mg, yield 86%; mp 139−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (br s, 1H), 8.71 (d, J = 8.8 Hz, 1H), 7.99 (s, 1H), 7.67−7.51 (m, 3H), 7.44−7.39 (m, 2H), 2.64 (q, J = 8.0 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 157.5 (d, J = 253.2 Hz), 151.4, 138.8, 136.9, 134.7, 133.63, 133.60, 133.5, 128.4, 126.1 (d, J = 3.8 Hz), 124.7, 119.9 (d, J = 11.4 Hz), 117.9 (d, J = 19.0 Hz), 27.8, 15.1; FT-IR (KBr) 3276, 2964, 2926, 1597, 1536, 1505, 1416, 1343, 1300, 1110, 1088, 889, 760 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{13}FN_6O_2$ 329.1157, found 329.1155.

1-(2,6-Dimethylphenyl)-*N*-(2-nitrophenyl)-1*H*-tetrazol-5-amine (2r): analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.70; yellow solid; 288 mg, yield 93%; mp 196−197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (br s, 1H), 8.94 (d, J = 8.8 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.75 (t, J = 8.8 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.12 (t, J = 7.2 Hz, 1H), 2.03 (s, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 151.5, 137.1, 136.7, 135.8, 134.7, 132.0, 129.7, 129.4, 126.3, 122.2, 120.0, 17.60, 17.56; FT-IR (KBr) 3089, 2928, 2855, 1598, 1568, 1538, 1503, 1380, 1340, 1321, 1282, 1240, 1146, 1034, 910, 842, 740 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{14}N_6O_2$ 311.1256, found 311.1264.

1-(2,6-Dimethylphenyl)-*N*-(4-methyl-2-nitrophenyl)-1*H*-tetrazol-5-amine (2s): analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.72; yellow solid; 295 mg, yield 91%; mp 192−193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (br s, 1H), 8.78 (d, J = 8.8 Hz, 1H), 7.96 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 2.33 (s, 3H), 2.00 (s, 6H); ^{13}C{H} NMR (100 MHz, $CDCl_3$) δ 151.5, 138.0, 136.6, 134.4, 133.4, 132.3, 131.8, 129.5, 129.3, 125.8, 119.7, 20.4. 17.5; FT-IR (KBr) 3230, 3062, 2960, 2923, 1600, 1563, 1522, 1408, 1375, 1334, 1264, 1113, 1092, 1027, 924, 830 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{16}N_6O_2$ 325.1408, found 325.1416.

1-(2,6-Dimethylphenyl)-*N*-(2,4-dinitrophenyl)-1*H*-tetrazol-5-amine (2t): analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.45; yellow solid; 298 mg, yield 84%; mp 188−189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (br s, 1H), 9.21 (d, J = 9.6 Hz, 1H), 9.11 (s, 1H), 8.56 (d, J = 9.2 Hz, 1H), 7.49 (t, J = 7.2 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 2.03 (s, 6H); ^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 150.7, 141.1, 140.0, 136.5, 133.5, 132.4, 131.1, 129.9, 128.9, 122.7, 120.7, 17.6; FT-IR (KBr) 3251, 3113, 2924, 2854, 1606, 1586, 1548, 1511, 1424, 1345, 1310, 1264, 1144, 1116, 1019, 909, 842 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{13}N_7O_4$ 356.1107, found 356.1097.

***N*-(4-((1-(2,6-Dimethylphenyl)-1*H*-tetrazol-5-yl)amino)-3-nitrophenyl)acetamide (2u):** analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.48; yellow solid; 283 mg, yield 77%; mp 262−263 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (br s, 1H), 8.90 (d, J =

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9.2 Hz, 1H), 8.68 (d, J = 2.4 Hz, 1H), 7.98 (br s, 1H), 7.93 (dd, J = 9.2, 2.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 2.24 (s, 3H), 2.06 (s, 6H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$ + DMSO-d_6 + CD_3OD) δ 168.3, 150.6, 135.4, 134.4, 133.3, 130.8, 129.4, 128.45, 128.4, 126.7, 119.6, 114.7, 22.8, 16.2; FT-IR (KBr) 3334, 3238, 1674, 1611, 1546, 1360, 1296, 1273, 1260, 1091, 1016, 886, 773 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{18}N_7O_3$ 368.1471, found 368.1480.

4-((1-(2,6-Dimethylphenyl)-1*H*-tetrazol-5-yl)amino)-3-nitrobenzonitrile (2v): analytical TLC on silica gel, 1:4 ethyl acetate/hexane, R_f = 0.30; yellow solid; 275 mg, yield 82%; mp 205−206 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.42 (br s, 1H), 9.15 (d, J = 8.8 Hz, 1H), 8.53 (d, J = 2.0 Hz, 1H), 7.97 (dd, J = 9.2, 2.0 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 2H), 2.01 (s, 6H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 150.8, 139.2, 138.8, 136.5, 134.1, 132.3, 130.8, 129.8, 129.0, 121.1, 116.7, 105.8, 17.5; FT-IR (KBr) 3504, 2922, 2852, 2237, 1629, 1557, 1519, 1383, 1283, 1194, 1092, 852, 775, 674 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{13}N_7O_2$ 336.1209, found 336.1206.

***N*-(2-Nitrophenyl)-4-phenyl-4*H*-1,2,4-triazol-3-amine (4a).** analytical TLC on silica gel, 1:1 ethyl acetate/hexane, R_f = 0.40; yellow solid; 236 mg, yield 84%; mp 176−177 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.39 (br s, 1H), 8.97 (d, J = 8.4 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H), 8.11 (s, 1H), 7.67−7.58 (m, 4H), 7.43 (d, J = 7.6 Hz, 2H), 7.02 (t, J = 8.0 Hz, 1H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 149.2, 140.6, 137.2, 136.9, 134.1, 132.1, 131.0, 130.6, 126.2, 125.8, 121.0, 119.9; FT-IR (KBr) 3451, 3053, 2923, 2852, 1617, 1564, 1553, 1507, 1444, 1384, 1272, 1193, 1145, 1023, 841, 736, 609 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{11}N_5O_2$ 282.0991, found 282.0991.

***N*-(4-Fluoro-2-nitrophenyl)-4-(4-fluorophenyl)-4*H*-1,2,4-triazol-3-amine (4b):** analytical TLC on silica gel, 1:1 ethyl acetate/hexane, R_f = 0.42; reddish yellow solid; 260 mg, yield 82%; mp 189−190 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.25 (br s, 1H), 9.08−9.04 (m, 1H), 8.12 (s, 1H), 7.93 (dd, J = 8.4, 2.8 Hz, 1H), 7.50−7.43 (m, 3H), 7.39 (t, J = 8.0 Hz, 2H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 164.8 (d, J = 251.7 Hz), 156.9 (d, J = 244.0 Hz), 149.3, 140.7, 133.84 (d, J = 4.6 Hz), 133.8, 128.2 (d, J = 8.4 Hz), 127.9 (d, J = 3.0 Hz), 125.0 (d, J = 22.9 Hz), 121.7 (d, J = 7.6 Hz), 118.3 (d, J = 22.9 Hz), 112.3 (d, J = 26.7 Hz); FT-IR (KBr) 1629, 1599, 1557, 1514, 1384, 1337, 1236, 1162, 1131, 1001, 944, 878, 837, 760, 704 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_9F_2N_5O_2$ 318.0803, found 318.0802.

***N*-(4-Methyl-2-nitrophenyl)-4-*p*-tolyl-4*H*-1,2,4-triazol-3-amine (4c):** analytical TLC on silica gel, 1:1 ethyl acetate/hexane, R_f = 0.45; reddish yellow solid; 269 mg, yield 87%; mp 176−177 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.31 (br s, 1H), 8.90 (d, J = 8.8 Hz, 1H), 8.08 (s, 1H), 8.0 (s, 1H), 7.50 (d, J = 9.2 Hz, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 149.5, 141.0, 140.7, 138.1, 135.1, 133.9, 131.5, 131.0, 129.5, 125.8, 125.6, 120.0, 21.5, 20.5; FT-IR (KBr) 3471, 1731, 1632, 1598, 1514, 1449, 1386, 1238, 1163, 946, 837, 782 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{15}N_5O_2$ 310.1306, found 310.1306.

General Procedure for the Removal of Directing Group. To a stirred solution of **2a**, **2g**, and **2l** (1 mmol) in 1,4-dioxane (3 mL) was added NaOH (7.0 mmol, 280 mg) at room temperature, and the mixture was stirred at 110 °C for 12−22 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, the resultant mixture was extracted with ethyl acetate (3 × 10 mL) and washed with brine (3 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using *n*-hexane and ethyl acetate as eluent.

2-Nitroaniline (5a):[23] analytical TLC on silica gel, 1:10 ethyl acetate/hexane, R_f = 0.40; yellow solid; mp 71−72 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.4, 1.2 Hz, 1H), 7.36 (td, J = 6.6, 1.2 Hz, 1H), 6.81 (dd, J = 9.0, 1.2 Hz, 1H), 6.71 (td, J = 7.8, 1.2 Hz, 1H), 6.07 (br s, 2H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$) δ 144.9, 135.8, 132.5, 126.4, 118.9, 117.1; FT-IR (KBr) 3479, 3352, 1630, 1593, 1507, 1433, 1347, 1253, 1093, 995, 745 cm^{-1}.

4-Isopropyl-2-nitroaniline (5b): analytical TLC on silica gel, 1:10 ethyl acetate/hexane, R_f = 0.40; thick yellow liquid; 157 mg, yield 87%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 1.6 Hz, 1H), 7.28 (m, 1H), 6.77 (d, J = 8.4 Hz, 1H), 5.96 (br s, 2H), 2.86−2.83 (m, 1H), 1.23 (d, J = 6.8 Hz, 6H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 143.1, 138.1, 135.0, 127.3, 123.1, 119.0, 33.1, 23.9; FT-IR (neat) 3483, 3364, 2954, 2917, 1638, 1561, 1520, 1466, 1409, 1335, 1249, 1167, 1085, 952, 818 cm^{-1}.

Preparation of Aniline-d_3 (Scheme 8). The titled compound was prepared according to the reported procedure,[17a] and the deuterium incorporation was determined by ^1H NMR analysis of the mixture. Characterization data for the deuterated product only: 1;4 ethyl acetate/hexane, R_f = 0.32; pale brown solid; yield 85%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 2H), 3.62 (bs, 2H).

Preparation of 1-(2,6-Dimethylphenyl)-*N*-(2-nitrophenyl)-1*H*-tetrazol-5-amine-d_3 (1r-d_3) (Scheme 9). The titled compound was prepared according to the reported procedure:[22c] 3:7 ethyl acetate/hexane; R_f = 0.25; white solid; yield 74%; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, J = 8.0 Hz, 1H), 7.35 (s, 2H), 7.29 (d, J = 7.6 Hz, 2H), 6.10 (bs, 1H), 2.06 (s, 6H).

Intramolecular Kinetic Isotope Effect Study (Scheme 10). To a stirred solution of *N*-(2-deuterio-4-methylphenyl)-1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-amine[4c] **1s-d** (0.5 mmol, 140 mg) in DCE (2 mL), $CuCl_2{\cdot}2H_2O$ (20 mol %, 0.1 mmol, 17 mg) and $Fe(NO_3)_3{\cdot}9H_2O$ (35 mol %, 0.175 mmol, 71 mg) were added at room temperature under air. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After 8 h, saturated $NaHCO_3$ solution (5 mL) was added to the reaction mixture, and the resultant mixture was extracted with ethyl acetate (3 × 10 mL) and washed with brine (2 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to afford a 22:78 mixture of **2s** and **2s-d** as a yellow solid in 83% (138 mg) yield. The ratio of deuterium to hydrogen was determined from the ^1H NMR relative integration values of H_a (8.84 ppm) based on H_b (7.58 ppm).

Intermolecular Kinetic Isotope Effect Study (Scheme 11). To a stirred solution of 1-(2,6-dimethylphenyl)-*N*-phenyl-1*H*-tetrazol-5-amine (**1r**) (0.58 mmol, 156 mg) and 1-(2,6-dimethylphenyl)-*N*-(2,4,6-trideuteriophenyl)-1*H*-tetrazol-5-amine (**1r-d_3**) (0.42 mmol, 111 mg) in DCE (2 mL), $CuCl_2{\cdot}2H_2O$ (20 mol %, 0.2 mmol, 34 mg) and $Fe(NO_3)_3{\cdot}9H_2O$ (35 mol %, 0.35 mmol, 141 mg) were added at room temperature under air. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After 1.5 h, saturated $NaHCO_3$ solution (5 mL) was added to the reaction mixture, and the resultant mixture was extracted with ethyl acetate (3 × 10 mL) and washed with brine (2 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent to afford a mixture of **2r-d_2** and **2r** as a yellow solid in 18% (56 mg) yield. The ratio of deuterium to hydrogen was determined by the ^1H NMR relative integration values of H_a (8.96 ppm) based on H_b (8.24 ppm).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Mass spectra of reaction of **1a** and NMR (^1H and ^{13}C) spectra of **2a−v**, **4a−c**, aniline-d_3,**1r-d_3**, **2s-d**, **2r-d_2**, **5a**, and **5b**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01021.

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Notes

The authors declare no competing financial interest.

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