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

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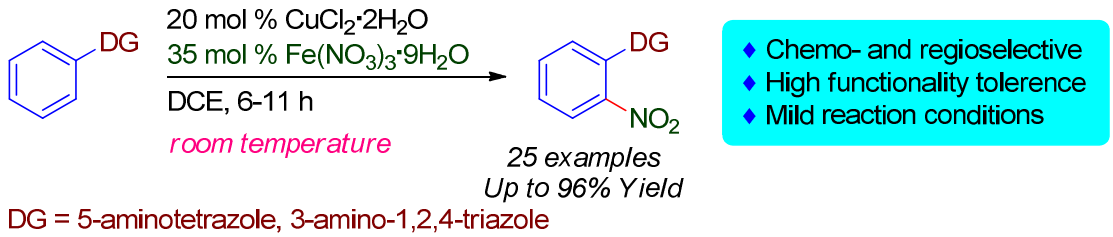

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ABSTRACT: An efficient Cu-catalyzed chemo- and regioselective *ortho*-nitration of *N*,1,-diaryl-5-aminotetrazoles and *N*,4,-diaryl-3-amino-1,2,4-triazoles have been described with good functional group compatibility. The procedure features the use 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 crust.[5] In particular, a few studies are focused on the copper catalyzed aerobic C-H functionalization reactions.[6] Herein, we wish to 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 $Fe(NO_3)_3 \cdot 9H_2O$ at room temperature. From an industrial point, this process would be useful due to its mild conditions, good functional group compatibility and free from the use of nitric acid.

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 led to overcome some of the above limitations, still they 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]

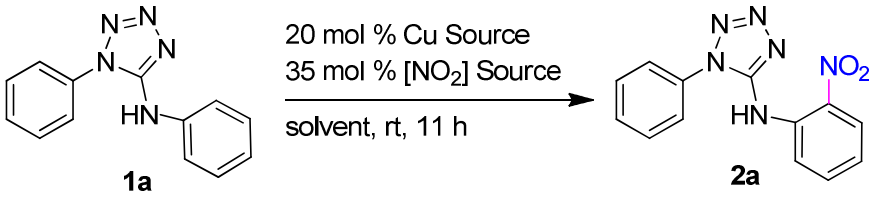
RESULTS AND DISCUSSION

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 experiment confirmed that without the Cu-source, no reaction was observed and starting material **1a** was recovered intact (entry 20). In addition, the use of 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

Table 1. Optimization of the Reaction Conditions[a] (Reproduced from *J. Org. Chem.* **2014**, *79*, 8541. Copyright 2015 American Chemical Society)



entry	Cu source (20 mol %)	[NO_2] source (35 mol %)	solvent	yield (%)
1	$Cu(OAc)_2 \cdot H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	52
2	$Cu(OTf)_2$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	48
3	$CuSO_4 \cdot 5H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	trace
4	CuI	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	44
5	CuCl	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	84
6	$CuBr_2$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	86
7	$Cu(NO_3)_2 \cdot 3H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	10
8	CuBr	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	74
9	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	95
10[b]	$CuCl_2 \cdot 2H_2O$	$Ca(NO_3)_2 \cdot 4H_2O$	DCE	trace
11	$CuCl_2 \cdot 2H_2O$	$Bi(NO_3)_3 \cdot 5H_2O$	DCE	21
12[c]	$CuCl_2 \cdot 2H_2O$	$AgNO_3$	DCE	26
13[d]	$CuCl_2 \cdot 2H_2O$	$NaNO_2$	DCE	24
14	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DCM	89
15	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	THF	trace
16	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	toluene	74
17	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DMF	n.d.
18	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	CH_3CN	62
19[e]	$CuCl_2 \cdot 2H_2O$	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	61
20	-	$Fe(NO_3)_3 \cdot 9H_2O$	DCE	trace
21[f]	$Cu(NO_3)_2 \cdot 3H_2O$	-	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] $Ca(NO_3)_3{\cdot}4H_2O$ (50 mol %) was used. [c] $AgNO_3$ (1.1 equiv) was used. [d] $NaNO_2$ (1.1 equiv) was used. [e] $CuCl_2{\cdot}2H_2O$ (10 mol %) was used. [f] $Cu(NO_3)_2{\cdot}3H_2O$ (100 mol %) was used. n.d. = not detected.

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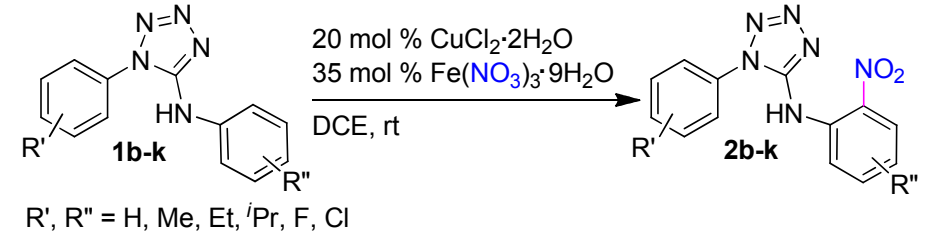
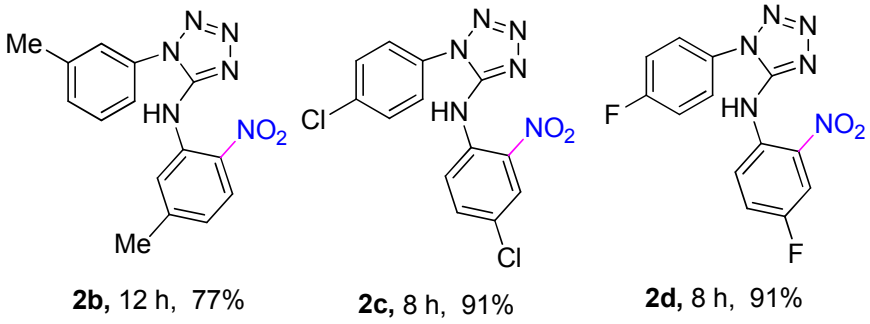
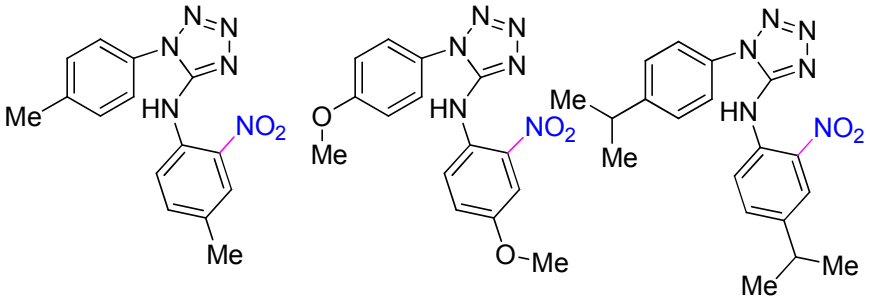
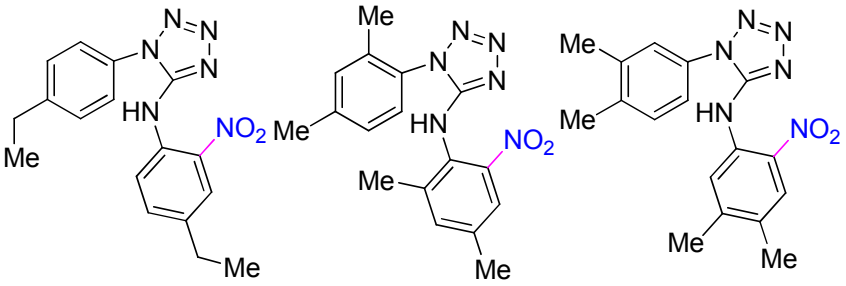




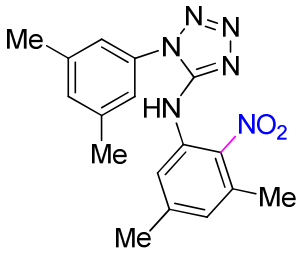
2b, 12 h, 77% **2c,** 8 h, 91% **2d,** 8 h, 91%



2e, 8 h, 95% **2f,** 8 h, 79% **2g,** 8 h, 88%



2h, 8 h, 91% **2i,** 12 h, 77% **2j,** 8 h, 84%



2k, 12 h, 79%

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

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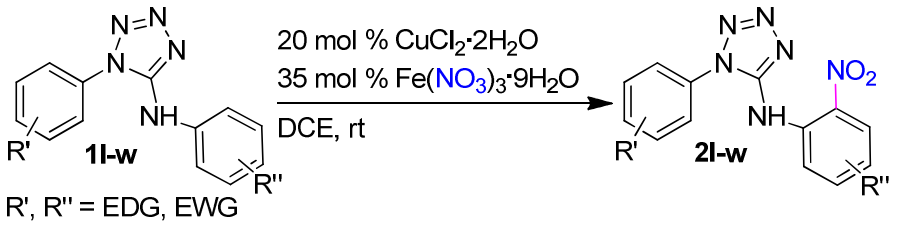
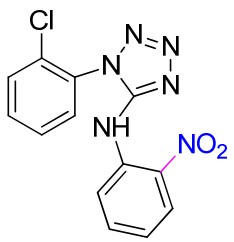
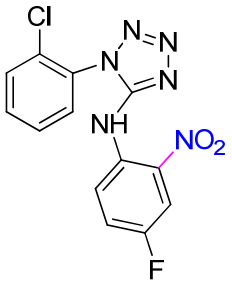
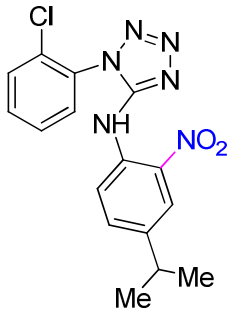




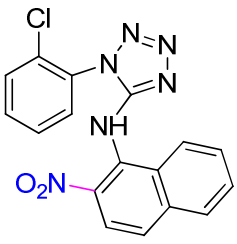
2l, 12 h, 81%



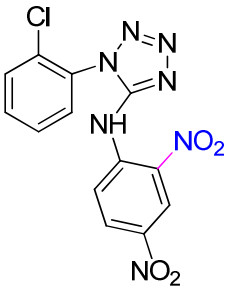
2m, 8 h, 84%



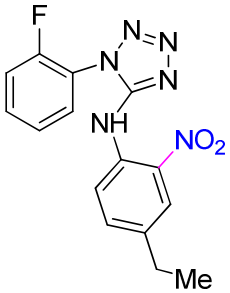
2n, 8 h, 94%



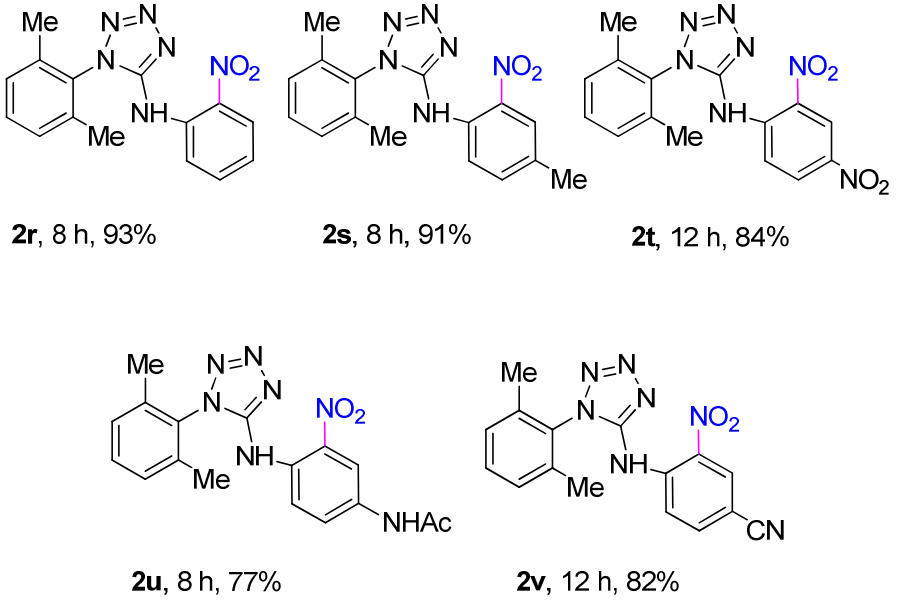
2o, 12 h, 75%



2p, 12 h, 86%

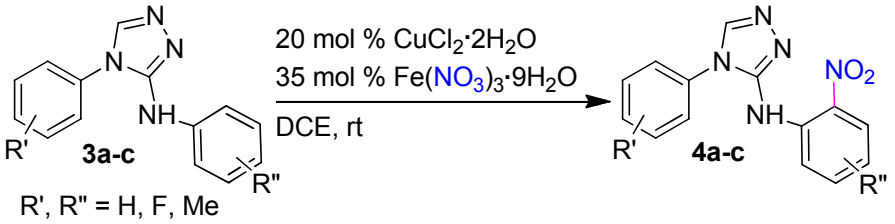


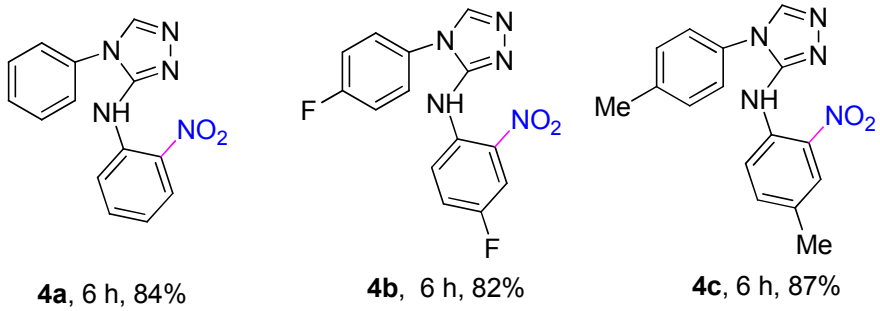
2q, 8 h, 86%



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

Scheme 3. *Ortho*-Nitration of *N*,4-Diaryl-3-amino-1,2,4-triazoles[a] (Reproduced from *J. Org. Chem.* **2014**, *79*, 8541. Copyright 2015 American Chemical Society)





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

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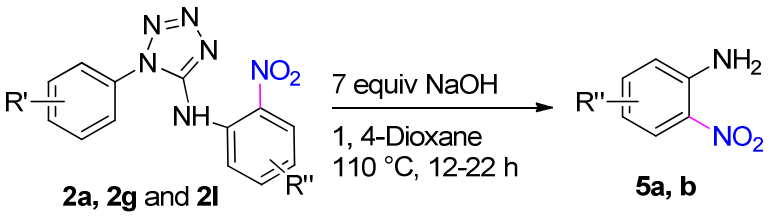
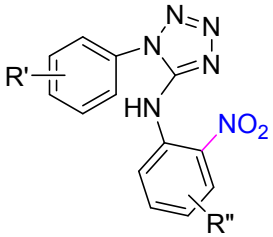
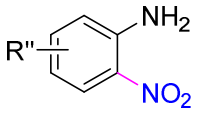
optimized reaction conditions (Scheme 2). As above, the reaction readily occurred to give the target products in high yields. For examples, the substrates **1l-p** with 2-chloro, 4-fluoro, 4-isopropyl, naphthyl and 4-nitro substituents proceeded reaction to produce the corresponding nitration products **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 were proceeded reaction 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 examples, the unsubstituted substrate **3a** proceeded reaction with greater reactivity compared to the corresponding 5-amino-tetrazole 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 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 in 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 ^{o}C to give the corresponding 2-nitroaniline derivatives in good yields.[16]

Table 2. Removal of Directing Group[a] (Reproduced from *J. Org. Chem.* **2014**, *79*, 8541. Copyright 2015 American Chemical Society)



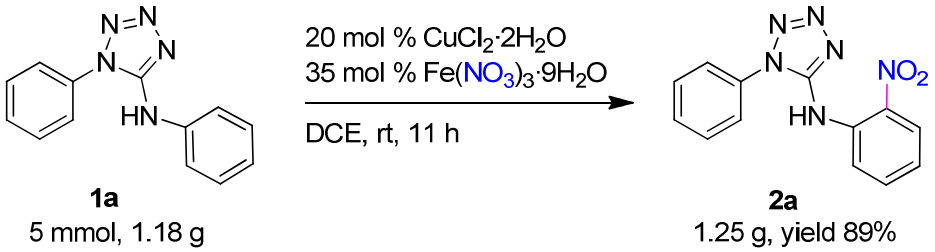
entry	substrate	product	time (h)	yield (%)
				
1	R', R" = H (**2a**)	R" = H (**5a**)	22	78
2	R', R" = ^{i}Pr (**2g**)	R" = ^{i}Pr (**5b**)	12	87
3	R' = 2-Cl, R" = H (**2l**)	R" = H (**5a**)	22	84

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

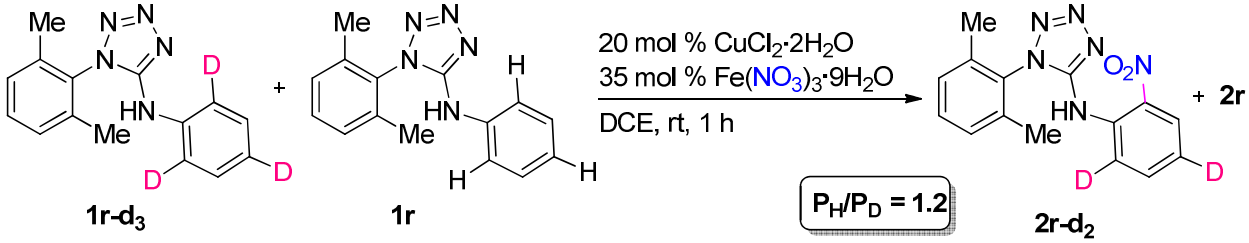
The proposed catalytic cycle is shown in Scheme 7. The intermolecular kinetic isotope experiments of the substrates **1r** and **1r-D3** gave P_H/P_D = 1.2 (21% conversion), while the intramolecular kinetic isotope experiments of the substrate **1s-D** afforded P_H/P_D = 3.5 (Scheme 5).[17] These results 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 work up revealed the presence of four major species: $[\mathbf{2a} + H]^+$ and three copper complexes $\{[\mathbf{2a}\cdot Cu]^+$, $[(\mathbf{2a})_2\cdot Cu]^+$ and $[(\mathbf{2a})_2\cdot CuCl]^+\}$ (see supporting information) (Figure 1).[6f,20] However, attempts to isolate the species as single crystals remained unsuccessful. Furthermore, $CuCl_2\cdot 2H_2O$ and $Fe(NO_3)_3\cdot 9H_2O$ are insoluble in 1,2-dichloroethane, however,

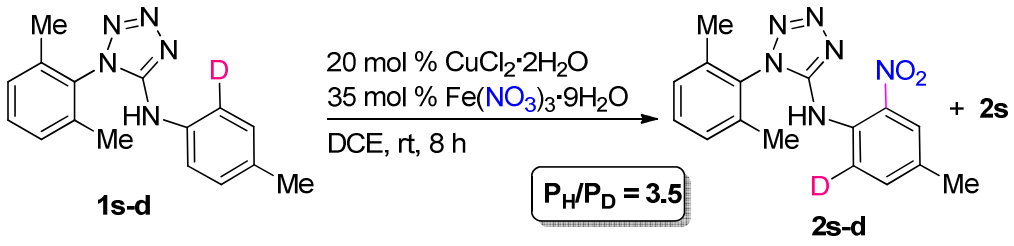
with substrate **1a** they readily dissolve to give a yellow solution, which suggest that the substrate **1a** may first bind with the hydrated $CuCl_2$ to give a soluble intermediate ***a*** that may undergo reaction with $Fe(NO_3)_3{\cdot}9H_2O$ to afford the intermediate ***b*** (Scheme 7).[21] The 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.

Scheme 4. Gram Scale Synthesis (Reproduced from *J. Org. Chem.* **2014**, *79*, 8541. Copyright 2015 American Chemical Society)

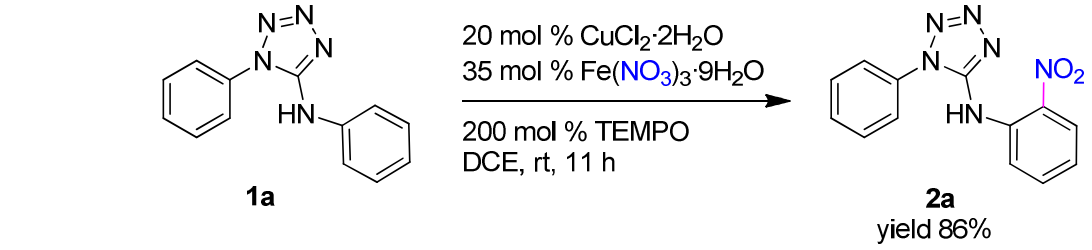


Scheme 5. Kinetic Isotope Experiments (Reproduced from *J. Org. Chem.* **2014**, *79*, 8541. Copyright 2015 American Chemical Society)





Scheme 6. Radical Scavenger Experiment (Reproduced from *J. Org. Chem.* **2014**, *79*, 8541. Copyright 2015 American Chemical Society)



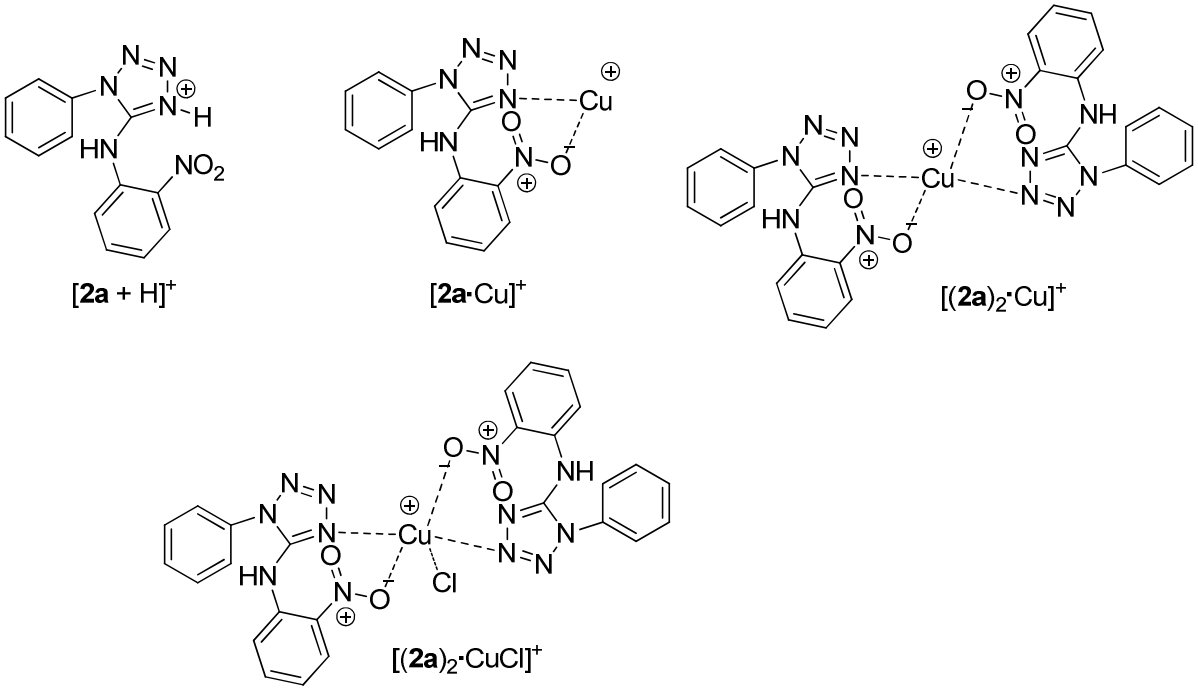
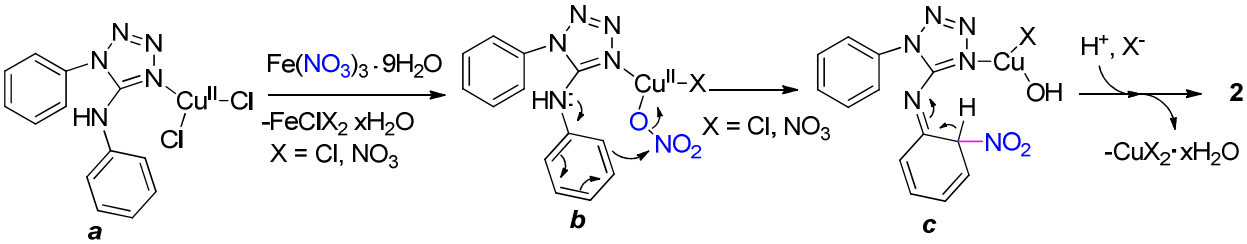


Figure 1. Major species identified using ESI-MS analysis of the reaction mixture of **1a**. (Reproduced from *J. Org. Chem.* **2014**, *79*, 8541. Copyright 2015 American Chemical Society)

Scheme 7. Proposed Catalytic Cycle (Reproduced from *J. Org. Chem.* **2014**, *79*, 8541. Copyright 2015 American Chemical Society)



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 way 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 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. $Cu(OAc)_2{\cdot}H_2O$ (98%), $CuBr_2$ (98%), $Cu(NO_3)_2{\cdot}3H_2O$ (99%), $CuCl_2{\cdot}2H_2O$ (99%) and $Fe(NO_3)_3{\cdot}9H_2O$ (98%) were purchased from Merck. $CuSO_4{\cdot}5H_2O$ (99%) was obtained from Rankem. These chemicals were used as received without further purification. The solvents were purchased from commercial source and dried according to standard procedure prior to use.[22a] 3-5-Aminotetrazoles[22c] and amino-1,2,4-triazoles[22b,d-e] were prepared according to reported procedure. Purification of the reaction products was carried out by column chromatography using silica gel (60-120 mesh). Analytical TLC was performed on 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) were reported in ppm and spin-spin coupling constants (J) were given in Hz. Melting points were determined using

melting point apparatus and are uncorrected. FT-IR spectra were recorded using 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), $CuCl_2{\cdot}2H_2O$ (20 mol %, 0.2 mmol, 34.6 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 completion, saturated $NaHCO_3$ solution (5 mL) was added to the reaction mixture, and the resultant solution was extracted with ethyl acetate (3 x 10 mL) and washed with brine (2 x 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,

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; ^1H 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; ^1H 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; ^1H 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; ^1H 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; ^1H 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* = 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; ^{1}H 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; ^{1}H 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.

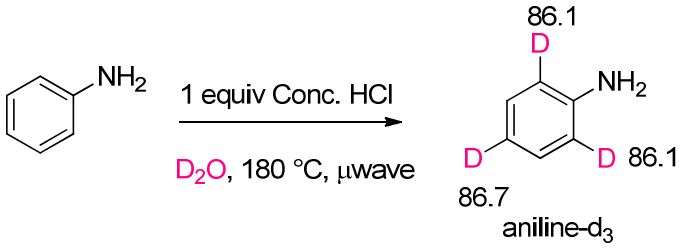
General Procedure for the Removal of Directing Group. To a stirred solution of **2a**, **2g** and **2l** (1 mmol) in 1,4-dioxane (3 mL), NaOH (7.0 mmol, 280 mg) was added at room temperature, and the mixture was stirred at 110 °C for 12-22 h. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, the resultant mixture was extracted with ethyl acetate (3 x 10 mL) and washed with brine (3 x 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; ^{1}H 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}.

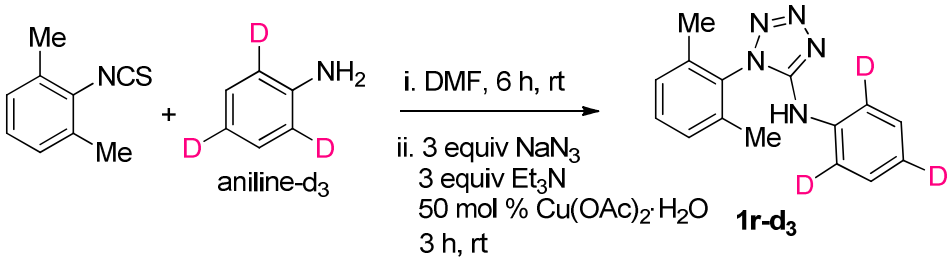
4-Isopropyl-2-nitroaniline 5b. Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.40; thick yellow liquid; 157 mg, yield 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 1.6 Hz, 1H), 7.28 (m, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 5.96 (br s, 2H), 2.86-2.83 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 6H); ^{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 ^{1}H 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%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 2H), 3.62 (bs, 2H).



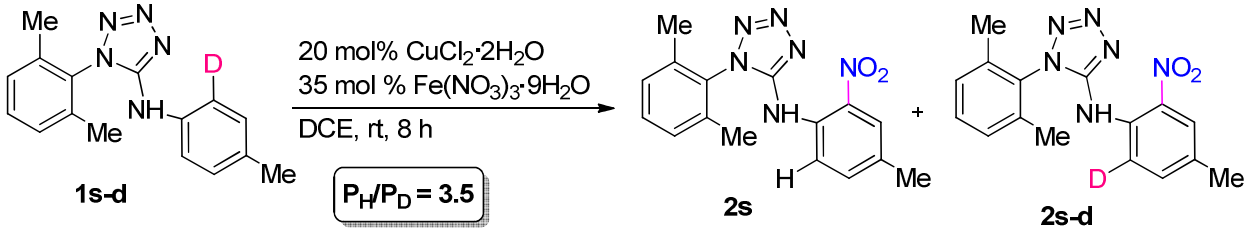
Scheme 8 (Reproduced from *J. Org. Chem.* **2014**, *79*, 8541. Copyright 2015 American Chemical Society)

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%; ^{1}H 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).



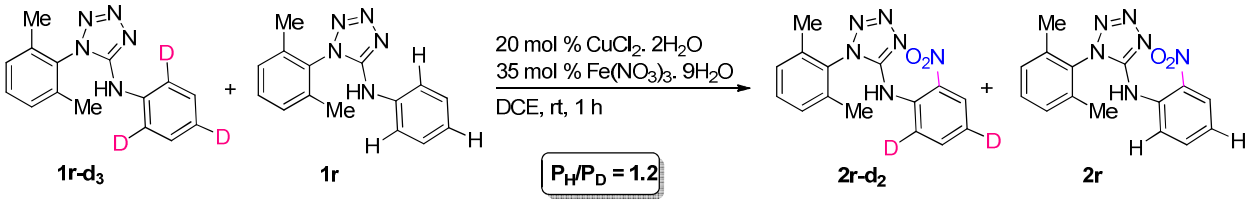
Scheme 9 (Reproduced from *J. Org. Chem.* **2014**, *79*, 8541. Copyright 2015 American Chemical Society)

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 x 10 mL) and washed with brine (2 x 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 ^{1}H NMR relative integration values of H_a (8.84 ppm) based on H_b (7.58 ppm).



Scheme 10 (Reproduced from *J. Org. Chem.* **2014**, *79*, 8541. Copyright 2015 American Chemical Society)

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 x 10 mL) and washed with brine (2 x 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 ^{1}H NMR relative integration values of H_a (8.96 ppm) based on H_b (8.24 ppm).



Scheme 11 (Reproduced from *J. Org. Chem.* **2014**, *79*, 8541. Copyright 2015 American Chemical Society)

ASSOCIATED CONTENT

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Supporting Information

Mass spectra of reaction of **1a** and NMR (^{1}H and ^{13}C) spectra of **2a-v**, **4a-c**, aniline-d_3,**1r-d_3**, **2s-d**, **2r-d_2**, **5a** and **5b**. This material is available free of charge via the internet at http://pubs.acs.org.

Notes

†Revised manuscript of Sadhu, P.; Alla, S. K.; Punniyamurthy, T. *J. Org. Chem.* **2014**, *79*, 8541; *J. Org. Chem.* **2015**, *80*, 3358

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