JOC The Journal of Organic Chemistry

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

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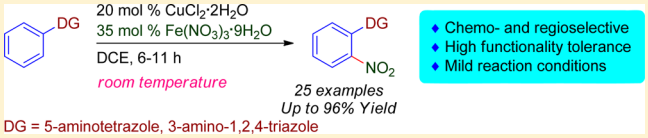
Supporting Information

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 has been described with good functional group compatibility. The procedure features the use of an 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 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 point, this process would be useful because of its mild conditions, good functional group compatibility, and freedom 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 from 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 allowed some of the above limitations to be overcome, 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]

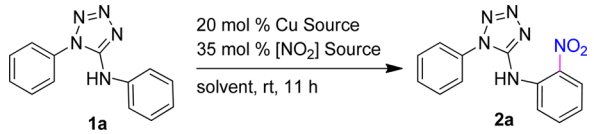
RESULTS AND DISCUSSION

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 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**−

Received: July 18, 2014
Published: August 24, 2014

Table 1. Optimization of the Reaction Conditions[a]



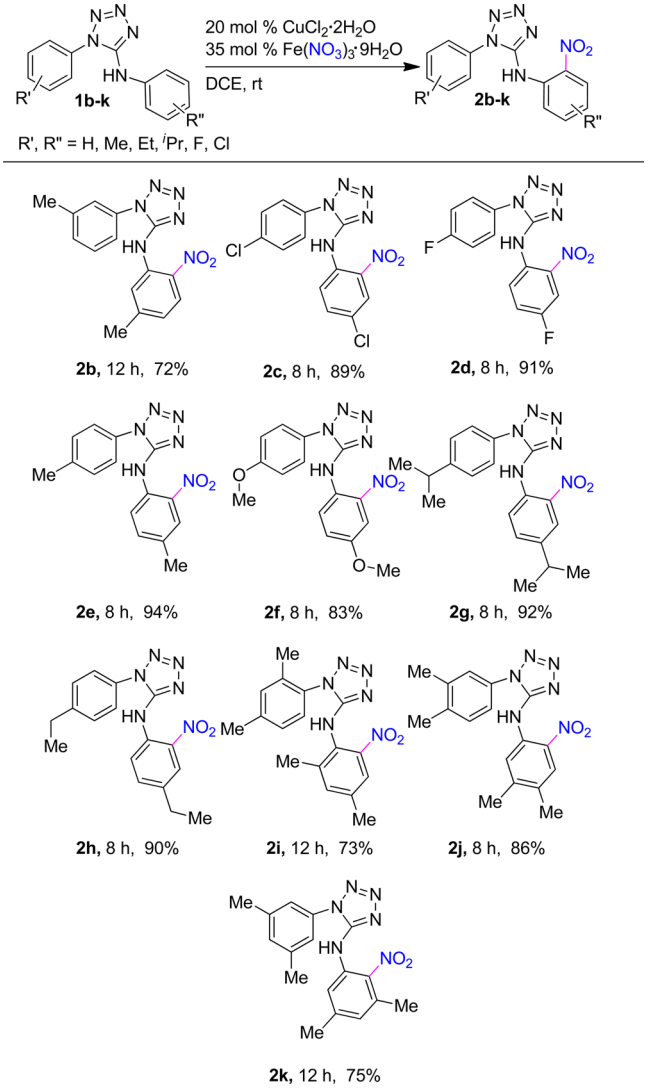
entry	Cu source (20 mol %)	[NO_2] source (35 mol %)	solvent	yield (%)
1	$Cu(OAc)_2·H_2O$	$Fe(NO_3)_3·9H_2O$	DCE	52
2	$Cu(OTf)_2$	$Fe(NO_3)_3·9H_2O$	DCE	48
3	$CuSO_4·5H_2O$	$Fe(NO_3)_3·9H_2O$	DCE	trace
4	CuI	$Fe(NO_3)_3·9H_2O$	DCE	44
5	CuCl	$Fe(NO_3)_3·9H_2O$	DCE	84
6	$CuBr_2$	$Fe(NO_3)_3·9H_2O$	DCE	86
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]$Ca(NO_3)_2·4H_2O$ (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.

h having 3-methyl, 4-chloro, 4-fluoro, 4-methyl, 4-methoxy, 4-isopropyl, and 4-ethyl substituents on the aryl rings readily led the reaction to provide the corresponding nitration products **2b–h** in 72–94% 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 73–86% yields. Next, substrates having 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 examples, the substrates **1l–p** with 2-chloro, 4-fluoro, 4-isopropyl, naphthyl, and 4-nitro substituents proceeded to produce the corresponding nitration products **2l–p** in 74–93% yields. Similarly, the substrates **1q** having 2-fluoro and 4-ethyl substituents underwent the reaction to furnish **2q** in 89% yield. Furthermore, the substrates **1r–v** containing 2,6-dimethyl, 4-methyl, 4-nitro, 4-acetanilide, and 4-cyano substituents were used to give the respective nitration products **2r–v** in 77–96% yields. Recrystallization of **2c** in CH_3CN gave single crystals whose structure was confirmed by X-ray analysis (see the Supporting Information).

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** led to reaction with greater reactivity 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

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



[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.

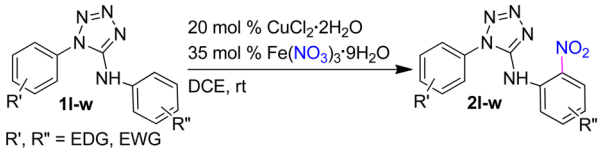
such as 4-fluoro and 4-methyl **3b** and **3c** groups readily underwent reaction to furnish **4b** and **4c** in 6 h with 82% and 87% yields, respectively.

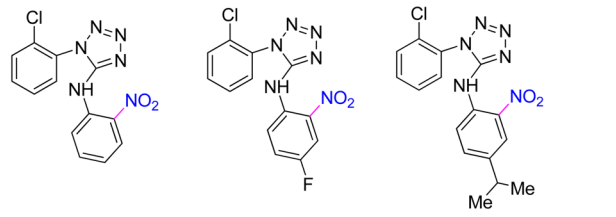
Furthermore, the protocol can be utilized for gram scale synthesis (Scheme 4). For example, the reaction of **1a** was carried out on gram scale, and the reaction occurred to afford the target molecule **2a** in 89% yield. In addition, we attempted a removal of the tetrazole directing group using the 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]

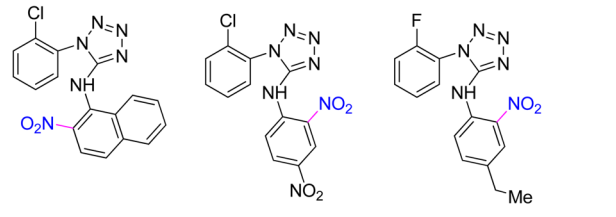
The proposed catalytic cycle is shown in Scheme 7. The intermolecular kinetic isotope experiments of the substrates **1r** and **1r-d$_3$** gave P_H/P_D = 1.2 (21% conversion), while the intramolecular kinetic isotope experiments of the substrate **1s-d** afforded P_H/P_D = 3.5 (Scheme 5).[17] These results suggest that the substrate-binding step is the product-determining step.[18] In addition, TEMPO does not inhibit the rate of the

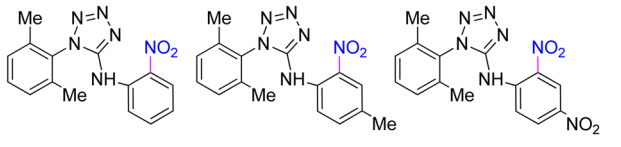
dx.doi.org/10.1021/jo501617g | J. Org. Chem. 2014, 79, 8541–8549

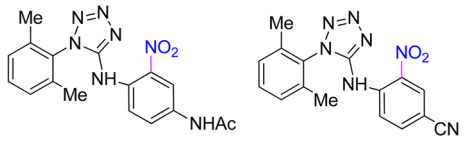
Scheme 2. *Ortho*-Nitration of Unsymmetrically Substituted *N*,1-Diaryl-5-aminotetrazoles[a]





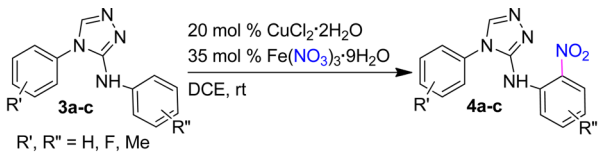


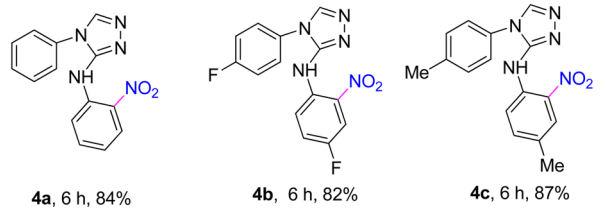




[a]Reaction conditions: *N*-phenyl-1*H*-tetrazol-5-amine **1l**–**v** (1 mmol), $CuCl_2·2H_2O$ (20 mol %), $Fe(NO_3)_3·9H_2O$ (35 mol %), DCE (3 mL), rt.

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

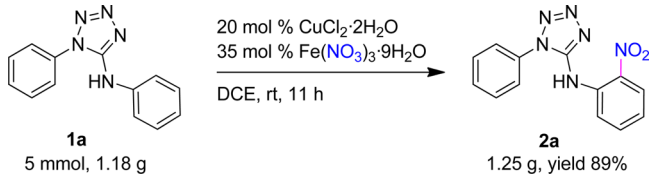
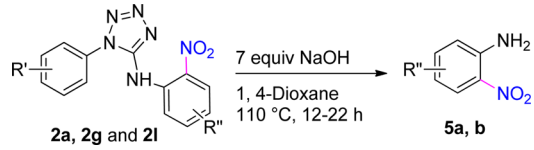


Table 2. Removal of Directing Group[a]



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.

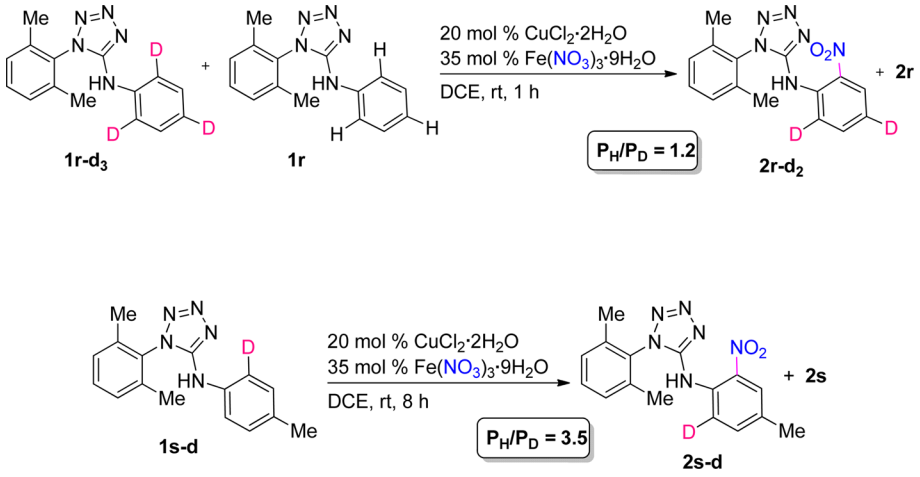
reaction, which suggests that the reaction may not involve a radical intermediate (Scheme 6).[19] In addition, the ESI-MS studies of the crude reaction mixture of **1a** before workup revealed the presence of four major species: $[\mathbf{2a} + H]^+$ and three copper complexes $\{[\mathbf{2a}·Cu]^+$, $[(\mathbf{2a})_2·Cu]^+$, 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

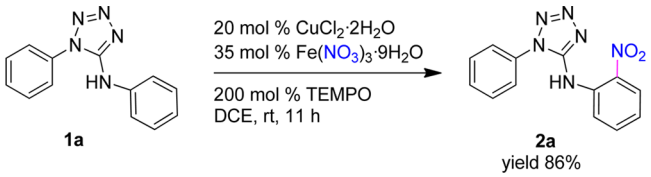
In summary, we have developed an efficient copper-catalyzed *ortho*-selective nitration of arenes using iron(III) nitrate as nitration source under mild reaction conditions. The use of inexpensive Cu catalyst and the greener nitration source provides an attractive way for the preparation of nitro arenes. 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. Because of 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.

dx.doi.org/10.1021/jo501617g | *J. Org. Chem.* 2014, 79, 8541–8549

Scheme 5. Kinetic Isotope Experiments



Scheme 6. Radical Scavenger Experiment



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] 5-Aminotetrazoles[22c] and 3-amino-1,2,4-triazoles[22b,d,e] were prepared according to reported procedures. 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) were reported in ppm, and spin−spin coupling constants (J) were given in Hz. 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 an ESI-MS instrument. Single crystals were measured on a X-ray diffractometer. Using Olex2, the structure was solved with the superflip structure solution program using charge flipping and refined with the Olex2 refine refinement package using Gauss−Newton minimization.

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, 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-1H-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 187−188 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.82 (br s, 1H), 8.98 (d, J = 8.4 Hz, 1H), 8.29 (d, J = 8.1 Hz,

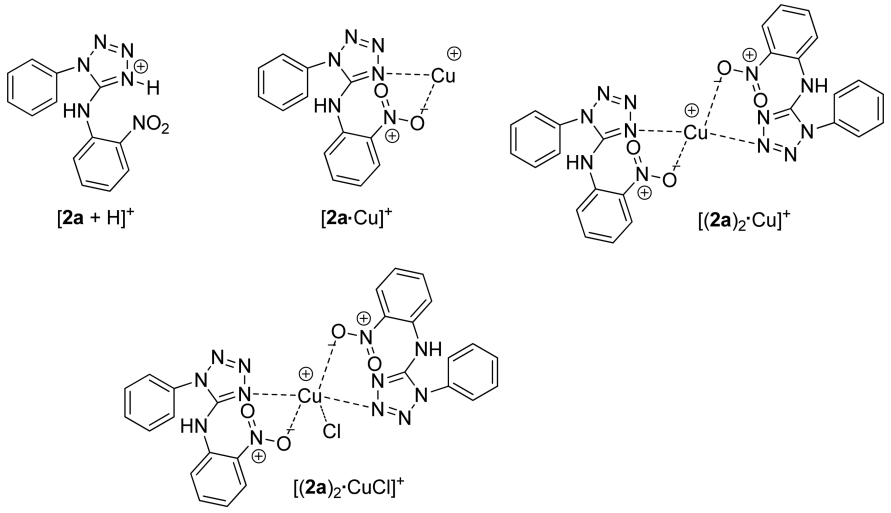
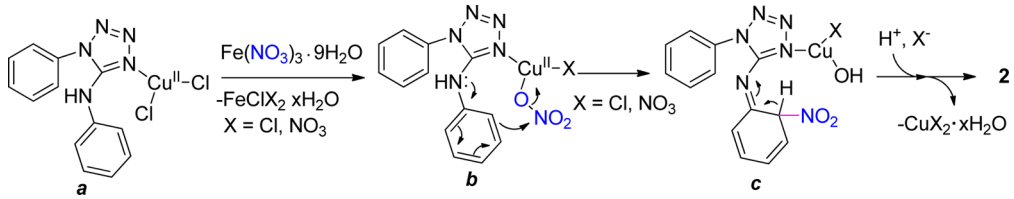


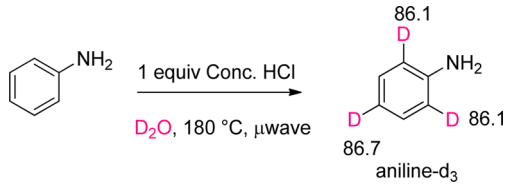
Figure 1. Major species identified using ESI-MS analysis of the reaction mixture of **1a**.

dx.doi.org/10.1021/jo501617g | J. Org. Chem. 2014, 79, 8541−8549

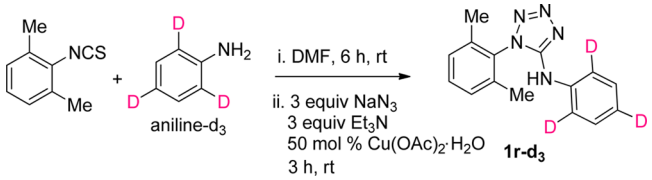
Scheme 7. Proposed Catalytic Cycle



Scheme 8



Scheme 9



1H), 7.80–7.61 (m, 6H), 7.19–7.14 (m, 1H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ 150.6, 136.9, 135.6, 134.8, 132.1, 131.0, 130.6, 126.1, 124.6, 122.2, 119.9; FT-IR (KBr) 3345, 1602, 1589, 1569, 1527, 1498, 1384, 1339, 1279, 1145, 1113, 1078, 1025, 996, 758, 739 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{10}N_6O_2$ 283.0938, found 283.0937.

N-(5-Methyl-2-nitrophenyl)-1-(m-tolyl)-1H-tetrazol-5-amine (**2b**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.68; yellow solid; 223 mg, yield 72%; mp 188–189 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.86 (br s, 1H), 8.74 (s, 1H), 8.15 (d, J = 8.7 Hz, 1H), 7.58–7.38 (m, 4H), 6.94 (d, J = 8.4 Hz, 1H), 2.50 (s, 6H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 150.7, 149.4, 141.4, 135.8, 132.9, 132.2, 131.8, 130.6, 126.4, 125.2, 123.4, 121.6, 119.9, 22.5, 21.5; FT-IR (KBr) 3095, 2921, 1608, 1541, 1493, 1450, 1378, 1340, 1293, 1125, 1094, 1055, 1033, 850, 768 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{14}N_6O_2$ 311.1251, found 311.1255.

N-(4-Chloro-2-nitrophenyl)-1-(4-chlorophenyl)-1H-tetrazol-5-amine (**2c**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow solid; 312 mg, yield 89%; mp 187–188 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.70 (br s, 1H), 8.93 (d, J = 9.2 Hz, 1H), 8.24 (d, J = 2.4 Hz, 1H), 7.71–7.64 (m, 3H), 7.56–7.53 (m, 2H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 150.5, 137.6, 137.1, 135.1, 134.3, 131.3, 130.6, 127.8, 126.0, 125.9, 121.6; FT-IR (KBr) 3259, 3108, 1604, 1556, 1542, 1502, 1417, 1338, 1275, 1247, 1094, 1006, 843, 820, 752 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_8Cl_2N_6O_2$ 351.0167, found 351.0161.

N-(4-Fluoro-2-nitrophenyl)-1-(4-fluorophenyl)-1H-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 171–172 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.62 (br s, 1H), 9.02–8.97 (m, 1H), 8.01 (dd, J = 8.1, 2.7 Hz. 1H), 7.63–7.51 (m, 3H), 7.43 (t, J = 8.4 Hz, 2H); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 165.3, (d, J = 252.0 Hz), 157.9 (d, J = 245.3 Hz), 150.6, 134.6 (d, J = 8.3 Hz), 132.2 (d, J = 2.3 Hz), 127.9 (d, J = 3.8 Hz), 127.0 (d, J = 9.0 Hz), 124.9 (d, J = 22.5 Hz), 121.8 (d, J = 6.8 Hz), 118.1 (d, J = 24.0 Hz), 112.7 (d, J = 27.0 Hz); FT-IR (KBr) 3260, 3091, 1615, 1598, 1537, 1513, 1428, 1337, 1249, 1161, 1090, 949, 843, 819, 758 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_8F_2N_6O_2$ 319.075, found 319.0758.

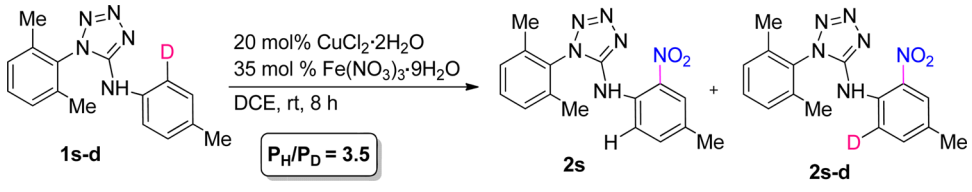
N-(4-Methyl-2-nitrophenyl)-1-(p-tolyl)-1H-tetrazol-5-amine (**2e**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.71; yellow solid; 291 mg, yield 94%; mp 193–194 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.64 (br s, 1H), 8.85 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H), 7.59 (dd, J = 9.0, 1.8 Hz. 1H), 7.48 (s, 4H), 2.50 (s, 3H), 2.41 (s, 3H); $^{13}C\{H\}$ NMR (150 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, 1656, 1604, 1562, 1526, 1489, 1334, 1281, 1109, 1093, 1015, 883, 812, 766 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{14}N_6O_2$ 311.1251, found 311.1255.

N-(4-Methoxy-2-nitrophenyl)-1-(4-methoxyphenyl)-1H-tetrazol-5-amine (**2f**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.38; brown solid; 283 mg, yield 83%; mp 166–167 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.48 (br s, 1H), 8.88 (d, J = 8.4 Hz, 1H), 7.70 (s, 1H), 7.51 (d, J = 6.9 Hz, 2H), 7.37 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 6.6 Hz, 2H), 3.92 (s, 3H), 3.86 (s, 3H); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 161.2, 154.0, 150.9, 134.8, 129.9, 126.3, 125.1, 124.4, 121.3, 115.6, 108.2, 55.9, 55.7; FT-IR (KBr) 3259, 2845, 1637, 1598, 1563, 1533, 1348, 1285, 1268, 1110, 1040, 924, 831, 799 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{14}N_6O_4$ 343.1149, found 343.1151.

N-(4-Isopropyl-2-nitrophenyl)-1-(4-isopropylphenyl)-1H-tetrazol-5-amine (**2g**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow solid; 336 mg, yield 92%; mp 116–117 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.62 (br s, 1H), 8.81 (d, J = 8.8 Hz, 1H), 8.06 (s, 1H), 7.61–7.47 (m, 5H), 3.10–3.01 (m, 1H), 3.00–2.93 (m, 1H), 1.34 (d, J = 6.8 Hz, 6H), 1.28 (d, J = 7.2 Hz, 6H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 152.0, 150.6, 143.1, 135.5, 134.6, 133.7, 129.8, 128.6, 124.4, 123.2, 119.9, 34.0, 33.1, 23.8, 23.6; FT-IR (KBr) 3258, 2963, 1628, 1596, 1560, 1537, 1519, 1460, 1341, 1277, 1252, 1153, 1088, 838 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{22}N_6O_2$ 367.1877, found 367.1878.

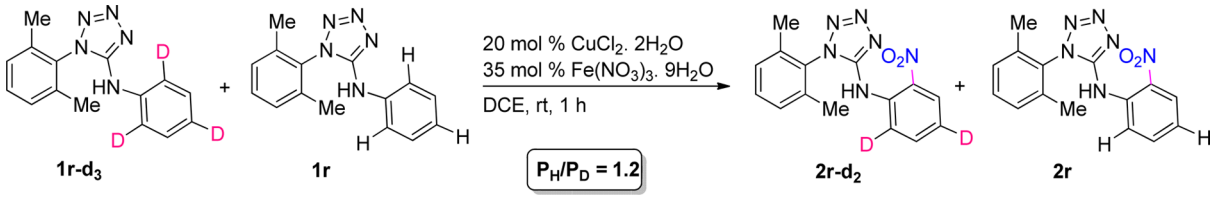
N-(4-Ethyl-2-nitrophenyl)-1-(4-ethylphenyl)-1H-tetrazol-5-amine (**2h**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.69; yellow solid; 304 mg, yield 90%; mp 115–116 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.65 (br s, 1H), 8.86 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 1.8 Hz, 1H), 7.61 (dd, J = 9.0, 1.8 Hz. 1H), 7.50 (s, 4H), 2.82 (q, J = 7.8 Hz, 2H), 2.72 (q, J = 7.8 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$) δ 150.8, 147.7, 138.7, 136.9, 134.8, 133.8, 130.1, 129.9, 124.8, 124.6,

Scheme 10



dx.doi.org/10.1021/jo501617g | J. Org. Chem. 2014, 79, 8541–8549

Scheme 11



120.1, 28.8, 27.9, 15.3, 15.2; FT-IR (KBr) 3471, 2962, 1626, 1595, 1516, 1463, 1335, 1296, 1182, 1086, 915, 834, 741 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{18}N_6O_2$ 339.1564, found 339.1568.

N-(2,4-Dimethyl-6-nitrophenyl)-1-(2,4-dimethylphenyl)-1H-tetrazol-5-amine (**2i**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; yellow solid; 246 mg, yield 73%; mp 187−188 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 9.36 (br s, 1H), 8.38 (s, 1H), 7.23 (s, 1H), 7.17 (s, 2H), 6.82 (s, 1H), 2.48 (s, 3H), 2.46 (s, 6H), 2.44 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 150.7, 145.1, 140.9, 136.4, 135.1, 133.8, 132.2, 132.1, 127.2, 121.7, 118.1, 21.9, 21.2, 21.1; FT-IR (KBr) 3095, 2772, 1608, 1540, 1493, 1377, 1340, 1294, 1248, 1125, 1093, 850, 785, 723 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{18}N_6O_2$ 339.1564, found 339.1574.

N-(4,5-Dimethyl-2-nitrophenyl)-1-(3,4-dimethylphenyl)-1H-tetrazol-5-amine (**2j**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.68; yellow solid; 290 mg, yield 86%; mp 158−159 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.55 (br s, 1H), 8.53 (s, 1H), 7.82 (s, 1H), 7.32−7.19 (m, 3H), 2.29 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H), 2.12 (s, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 150.6, 148.2, 139.9, 139.6, 133.7, 132.5, 131.5, 131.2, 129.9, 126.1, 125.3, 121.7, 120.2, 20.7, 19.9, 19.8, 19.0; FT-IR (KBr) 3266, 2921, 1624, 1594, 1561, 1529, 1449, 1375, 1324, 1259, 1093, 1015, 879, 821, 756 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{18}N_6O_2$ 339.1564, found 339.1571.

N-(3,5-Dimethyl-2-nitrophenyl)-1-(3,5-dimethylphenyl)-1H-tetrazol-5-amine (**2k**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.59; yellow solid; 253 mg, yield 75%; mp 181−182 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (br s, 1H), 8.25 (s, 1H), 7.13 (s, 1H), 7.07 (s, 2H), 6.71 (s, 1H), 2.35 (s, 9H), 2.31 (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) 3162, 2829, 1634, 1571, 1504, 1481, 1393, 1338, 1294, 1229, 1197, 1099, 894, 785, cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{18}N_6O_2$ 339.1564, found 339.1572.

1-(2-Chlorophenyl)-N-(2-nitrophenyl)-1H-tetrazol-5-amine (**2l**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.71; yellow solid; 266 mg, yield 84%; mp 135−136 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.39 (br s, 1H), 8.84 (d, J = 8.8 Hz, 1H), 8.20 (dd, J = 8.4, 1.2 Hz, 1H), 7.73−7.54 (m, 5H), 7.13 (t, J = 7.6 Hz, 1H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 151.4, 137.0, 135.6, 134.8, 133.3, 131.8, 131.6, 129.4, 129.3, 129.0, 126.2, 122.3, 119.8; FT-IR (KBr) 3288, 2964, 1598, 1564, 1533, 1501, 1441, 1342, 1287, 1137, 1096, 769, 739 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_9ClN_6O_2$ 317.0548, found 317.0558.

1-(2-Chlorophenyl)-N-(4-fluoro-2-nitrophenyl)-1H-tetrazol-5-amine (**2m**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.69; yellow solid; 289 mg, yield 87%; mp 142−143 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.26 (br s, 1H), 8.96−8.94 (m, 1H), 7.96−7.94 (m, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.67−7.64 (m, 1H), 7.59−7.50 (m, 3H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$) δ 157.1 (d, J = 247.5 Hz), 151.3, 134.6, 133.3, 132.2, 131.7, 131.5, 129.3, 129.2, 128.9, 124.7 (d, J = 22.5 Hz), 121.7, 112.5 (d, J = 28.5 Hz); FT-IR (KBr) 278, 3088, 1596, 1575, 1533, 1516, 1340, 1248, 1135, 1095, 946, 825, 777 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_8ClFN_6O_2$ 335.0454, found 335.0457.

1-(2-Chlorophenyl)-N-(4-isopropyl-2-nitrophenyl)-1H-tetrazol-5-amine (**2n**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow solid; 337 mg, yield 93%; mp 157−158 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.30 (br s, 1H), 8.77 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.65−7.53 (m, 4H), 2.95−2.90 (m, 1H), 1.24 (d, J = 6.8 Hz, 6H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 151.7, 143.6, 135.7, 134.8, 133.6, 133.3, 131.9, 131.6, 129.5, 129.0, 123.5, 120.1, 33.4, 23.8; FT-IR (KBr) 3291, 2891, 1591, 1572, 1528, 1497, 1441, 1349, 1291, 1137, 1085, 757, 727 cm^{-1}. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{15}ClN_6O_2$ 359.1018, found 359.1015.

1-(2-Chlorophenyl)-N-(2-nitronaphthalen-1-yl)-1H-tetrazol-5-amine (**2o**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; reddish yellow gummy liquid; 271 mg, yield 74%; ^1H NMR (600 MHz, $CDCl_3$) δ 8.56 (dd, J = 8.4, 0.6 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.72−7.61 (m, 3H), 7.49 (d, J = 8.4 Hz, 1H), 7.39 (td, J = 8.4, 1.2 Hz, 1H), 7.29 (dd, J = 8.4, 1.2 Hz, 1H), 7.01 (td, J = 8.4, 1.2 Hz, 1H), 6.84 (br s, 1H); $^{13}C\{H\}$ NMR (150 MHz, $CDCl_3$) δ 152.4, 134.7, 132.2, 129.2, 128.9, 128.8, 128.4, 128.1, 127.9, 125.6, 125.3, 123.8, 121.9, 121.6, 119.1; FT-IR (neat) 3256, 3113, 2925, 1585, 1549, 1511, 1350, 1289, 1170, 842, 775 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{11}ClN_6O_2$ 367.0710, found 367.0708.

1-(2-Chlorophenyl)-N-(2,4-dinitrophenyl)-1H-tetrazol-5-amine (**2p**). analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.42; orange solid; 292 mg, yield 81%; mp 189−190 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.105 (br s, 1H), 9.10 (d, J = 6.4 Hz, 1H), 8.55 (dd, J = 9.2, 2.4 Hz, 1H), 7.75 (m, 3H), 7.63 (m, 2H); $^{13}C\{H\}$ NMR (75 MHz, $CDCl_3$) δ 150.6, 141.0, 139.9, 133.6, 133.5, 131.6, 131.4, 130.9, 129.3, 129.0, 128.8, 122.6, 120.5; FT-IR (KBr) 3253, 3104, 1609, 1549, 1488, 1421, 1351, 1141, 1113, 912, 855, 841, 764, 726 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_8ClN_7O_4$ 362.0399, found 362.0390.

N-(4-Ethyl-2-nitrophenyl)-1-(2-fluorophenyl)-1H-tetrazol-5-amine (**2q**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.70; yellow solid; 292 mg, yield 89%; mp 139−140 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.42 (br s, 1H), 8.70 (d, J = 8.8 Hz, 1H), 7.98 (d, J = 1.6 Hz, 1H), 7.65−7.51 (m, 3H), 7.44−7.38 (m, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.21 (t, J = 7.6 Hz, 3H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 157.5 (d, J = 253.2 Hz), 151.5, 138.8, 136.8, 134.7, 133.6, 133.53, 133.5, 128.4, 126.1 (d, J = 3.8 Hz), 124.7, 119.9 (d, J = 9.9 Hz), 117.9 (d, J = 18.3 Hz), 27.8, 15.1; FT-IR (KBr) 3286, 2977, 1630, 1618, 1563, 1506, 1339, 1265, 1118, 1085, 891, 842, 763 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{13}FN_6O_2$ 329.1157, found 329.1152.

1-(2,6-Dimethylphenyl)-N-(2-nitrophenyl)-1H-tetrazol-5-amine (**2r**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.69; yellow solid; 283 mg, yield 91%; mp 195−196 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.21 (br s, 1H), 8.94 (dd, J = 8.8, 0.8 Hz, 1H), 8.22 (dd, J = 8.4, 1.6 Hz, 1H), 7.76 (td, J = 8.4, 1.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 7.6 Hz, 2H), 7.14 (td, J = 8.4, 1.6 Hz, 1H), 2.03 (s, 6H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 151.4, 137.1, 136.6, 135.7, 132.0, 129.7, 129.4, 126.3, 122.2, 119.9, 17.6; FT-IR (KBr) 3230, 2926, 1626, 1598, 1538, 1524, 1410, 1380, 1337, 1281, 1241, 1122, 1092, 926, 831, 772, 759 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{14}N_6O_2$ 311.1256, found 311.1248.

1-(2,6-Dimethylphenyl)-N-(4-methyl-2-nitrophenyl)-1H-tetrazol-5-amine (**2s**): analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.72; yellow solid; 305 mg, yield 96%; mp 192−193 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.05 (br s, 1H), 8.78 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 1.2 Hz, 1H), 7.54 (dd, J = 8.4, 1.6 Hz, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.28 (d, J = 7.6 Hz, 2H), 2.34 (s, 3H), 2.00 (s, 6H); $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$) δ 151.5, 138.0, 136.6, 134.5, 133.5, 132.4, 131.9, 129.6, 129.4, 125.9, 119.8, 20.5. 17.5; FT-IR

dx.doi.org/10.1021/jo501617g | J. Org. Chem. 2014, 79, 8541−8549

(KBr) 3230, 2926, 1626, 1598, 1538, 1524, 1410, 1380, 1337, 1281, 1241, 1122, 1092, 926, 831, 772, 759 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{16}N_6O_2$ 325.1408, found 325.1409.

*1-(2,6-Dimethylphenyl)-N-(2,4-dinitrophenyl)-1H-tetrazol-5-amine (**2t**):* analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.41; yellow solid; 280 mg, yield 79%; mp 189−190 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.55 (br s, 1H), 9.23 (d, J = 9.6 Hz, 1H), 9.13 (d, J = 2.4 Hz, 1H), 8.59 (dd, J = 9.6, 2.4 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.36 (d, J = 7.8 Hz, 2H), 2.02 (s, 6H); ^{13}C{H} NMR (150 MHz, $CDCl_3$) δ 150.7, 141.2, 140.0, 136.5, 133.4, 132.4, 131.1, 129.9, 129.0, 122.7, 120.7, 17.54; FT-IR (KBr) 3471, 1626, 1595, 1516, 1463, 1335, 1296, 1182, 1149, 1086, 915, 834, 741 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_7O_4$ 356.1107, found 356.1100.

*N-(4-((1-(2,6-Dimethylphenyl)-1H-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)-1H-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-4H-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)-4H-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; ^{1}H 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)-4H-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; ^{1}H 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; ^{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 Hz, 1.2, 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); ^{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).

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).

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) were added $CuCl_2{\cdot}2H_2O$ (20 mol %, 0.1 mmol, 17 mg) and $Fe(NO_3)_3{\cdot}9H_2O$ (35 mol %, 0.175 mmol, 71 mg) 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 ^{1}H 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) were added $CuCl_2{\cdot}2H_2O$ (20 mol %, 0.2 mmol, 34 mg) and $Fe(NO_3)_3{\cdot}9H_2O$ (35 mol %, 0.35 mmol, 141 mg) 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

dx.doi.org/10.1021/jo501617g | J. Org. Chem. 2014, 79, 8541−8549

determined by the ^{1}H NMR relative integration values of H_a (8.96 ppm) based on H_b (8.24 ppm).

■ ASSOCIATED CONTENT

Supporting Information

Crystal structure and data, mass spectra of the reactions 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.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the Department of Science and Technology, New Delhi, and the Council of Scientific and Industrial Research, New Delhi, for financial support. P.S. thanks UGC for SRF Fellowship. We also thank Central Instrumental Facility, IIT Guwahati, for NMR facilities. We thank Prof. V. Manivannan for discussion of the ESI-MS analysis for the reaction mixture.

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