JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

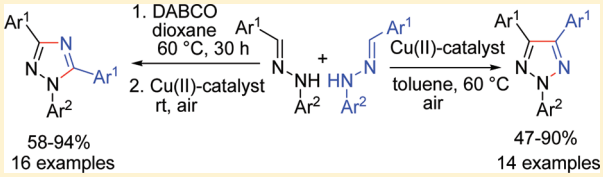
Copper(II)-Catalyzed Aerobic Oxidative Synthesis of Substituted 1,2,3- and 1,2,4-Triazoles from Bisarylhydrazones via C−H Functionalization/C−C/N−N/C−N Bonds Formation

Murali Mohan Guru and Tharmalingam Punniyamurthy*

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India

Supporting Information

ABSTRACT: An unprecedented copper(II)-catalyzed aerobic oxidative synthesis of 2,4,5-triaryl-1,2,3-triazoles and 1,3,5-triaryl-1,2,4-triazoles from bisarylhydrazones as the common starting precursor has been achieved via cascade C−H functionalization/C−C/N−N/C−N bonds formation under mild reaction conditions. One of the enthralling outcomes of this strategy is the copper(II)-catalyzed room temperature C−H functionalization/C−N bond formation in presence of air, which has been accomplished during the synthesis of substituted 1,2,4-triazoles. This new class of compounds could give prospective luminescence as an iconic component in the area of pharmaceutical and biological sciences. The intermediates for both the processes have been isolated to elucidate the mechanistic scenario.



INTRODUCTION

The functionalization of C−H bonds has emerged to be a powerful strategy for its increased efficiency and ideality of new synthetic routes. The most alluring aspect in this context is the construction of the heterocyclic compounds through transition-metal-catalyzed C−H activation.[1] Although for the most part, rhodium-,[2] ruthenium-,[3] and palladium-based[4] catalysts are contributing to the dramatic resurgence of interest in carbon−carbon or carbon−heteroatom bond formation by the cleavage of ubiquitous C−H bonds, the use of copper[5] catalysts can also be beneficial for achieving the same, a pivotal advantage with respect to cost and toxicity. Our contribution in this field has been modest,[5h,i] and our contention was to extend this strategy for the synthesis of heterocycles, such as substituted triazoles, which have found versatile applications in biological, material, and medicinal sciences.[6,7]

1,2,3-Triazoles are an important class of heterocycles because of their pharmacological properties like antifungal,[6i] antiviral,[6j] and anticoccidiostatic activities.[6k] Because of limitations of the traditional Huisgen azide−alkyne dipolar cycloaddition (AAC) processes,[8] metal-catalyzed AAC reactions[9] have enabled the assembly of diversely *N*-1-substituted 1,2,3-triazoles under relatively mild reaction conditions. However, the synthesis of another subset *N*-2-substituted 1,2,3-triazoles, widely used as biologically active compounds such as orexin receptor antagonist (MK-4305),[6d] SYK kinase inhibitors,[6l] and ALK5 inhibitors,[6m] has remained a challenging task to the scientific endeavor.[10] To get *N*-2-aryl-1,2,3-triazoles, the usual strategy involves N-arylation of 1,2,3-triazoles, which are limited because of the regioselectivity problem.[6e,l,11] Recently, the C−N cross-coupling reactions of aryl halides with 1,2,3-triazoles has been employed for *N*-2 selective arylation of 1,2,3-triazoles by incorporating C-4- and C-5-substituents on the heteroarenes[12] or by using bulky ligand.[13]

On the other hand, 1,2,4-triazoles have received considerable attention in biological and pharmaceutical fields, as they display potent biological properties such as antibacterial[7f] and antifungal[7g] activities. Furthermore, *N*-1-aryl-1,2,4-triazoles such as ICL670 (deferasirox), an orally active iron chelator, is very useful in iron overload therapy.[7e] There are only a few studies available for the synthesis of substituted 1,2,4-triazoles.[14] A particularly interesting scaffold of these heterocycles is 1,3,5-trisubstituted 1,2,4-triazoles that could be constructed either by heterocyclization of primary amidines via acylamidine intermediate[15] or through oxidative cyclization of triazenes.[16] Pertinent to the present research, there appears hardly any precedent for the catalytic one-pot regioselective synthesis of fully substituted triazoles from the same starting precursor under aerobic conditions. The present method uses the readily accessible bisarylhydrazones as only substrate and offers a new route for the regioselective synthesis of both 2,4,5-triaryl-1,2,3-triazoles and 1,3,5-triaryl-1,2,4-triazoles via a cascade copper(II)-catalyzed aerobic oxidative C−H functionalization/C−C/N−N/C−N bonds formation (Scheme 1).

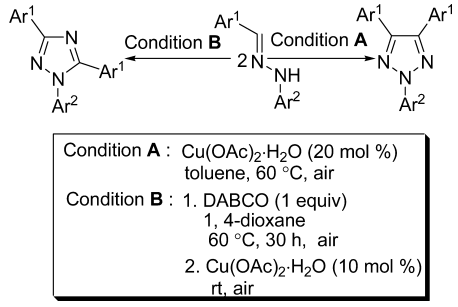
RESULTS AND DISCUSSION

In our recent study[5i] and from the literature reports,[17] we have found that bisarylhydrazones are unstable at elevated temperature. With this finding, when we initiated our new approach with the reaction of bisarylhydrazone **1a** in presence of 20 mol % $Cu(OAc)_2·H_2O$ in toluene at 60 °C under air, gratifyingly, we got 1,2,3-triazole 2a in 75% yield after 6 h (see the Supporting Information). Other reaction parameters were examined with **1a** as a model substrate. Anhydrous $Cu(OAc)_2$

Received: March 21, 2012
Published: May 9, 2012

   dx.doi.org/10.1021/jo300592t | J. Org. Chem. 2012, 77, 5063−5073

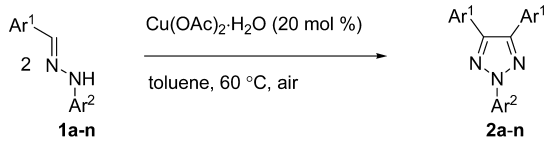
Scheme 1. Cu(II)-Catalyzed C−H Functionalization of Bisarylhydrazones

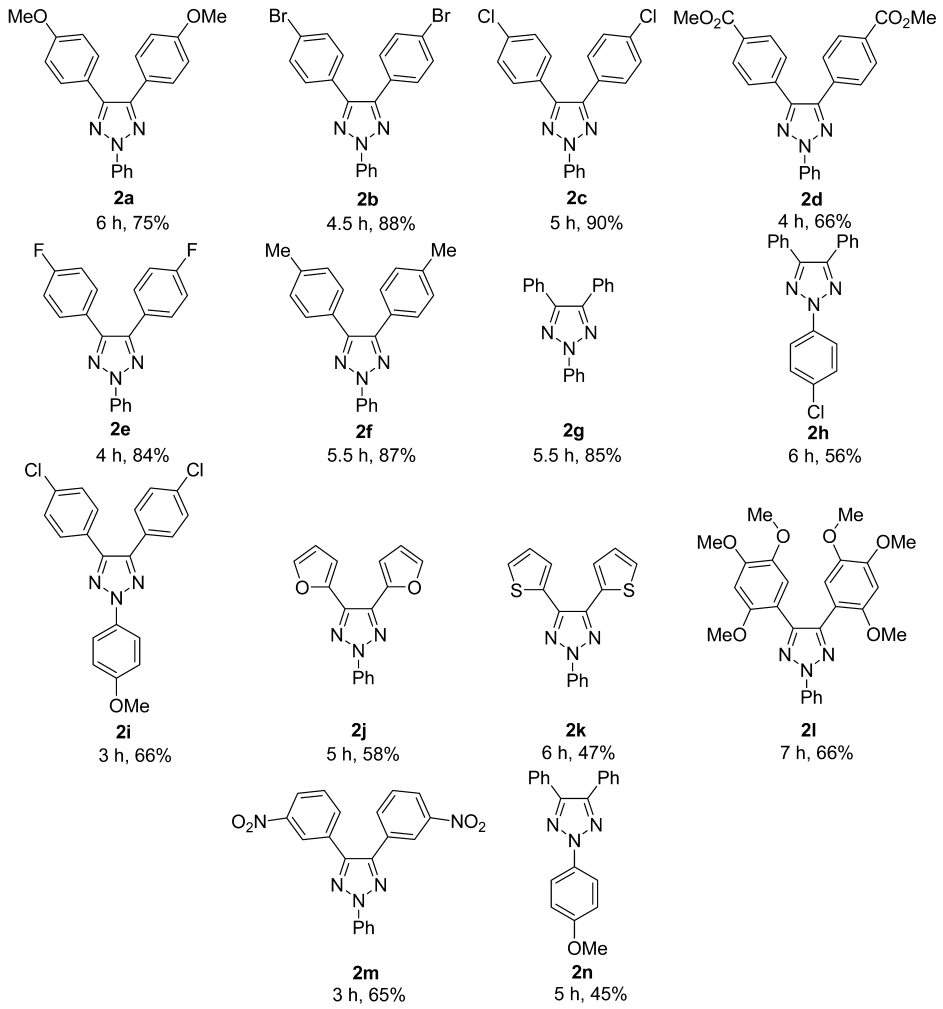


was found to be slightly less efficient than the hydrated one, whereas other copper salts gave inferior results. In polar solvents such as dioxane, DMSO, and THF, the product **2a** was obtained in trace to moderate yield. Use of molecular oxygen led to the formation of **2a** in 74% yield, while the reaction utilizing aqueous 30% H_2O_2 afforded **2a** in 65% yield. In contrast, under nitrogen atmosphere, the yield of the target compound 2a was reduced to 30%. A similar result was observed when either the reaction temperature (40 °C) or the amount of the copper source (10 mol %) was reduced. Control experiment confirmed that without the copper source, the product **2a** was not obtained. In brief, condition **A** provided the best results for the synthesis of 2,4,5-triaryl-1,2,3-triazoles (Scheme 1).

During further investigation of the reaction conditions, intriguingly, we found that bisarylhydrazone **1a** could readily undergo reaction with an organic base such as Et_3N in toluene at 60 °C for 30 h under air to give an intermediate that could

Table 1. Copper(II)-Catalyzed Synthesis of 2,4,5-Triaryl-1,2,3-Triazoles[a−c]





[a]Conditions: Bisarylhydrazones **1a−n** (0.5 mmol) and $Cu(OAc)_2·H_2O$ (20 mol %) were stirred in toluene (2 mL) at 60 °C under air. [b]Aldehydes (5−10%) were obtained as byproduct. [c]Isolated yield.

dx.doi.org/10.1021/jo300592t | J. Org. Chem. 2012, 77, 5063−5073

Scheme 2. Copper(II)-Catalyzed Synthesis of Unsymmetrically Substituted 1,2,3-Triazole

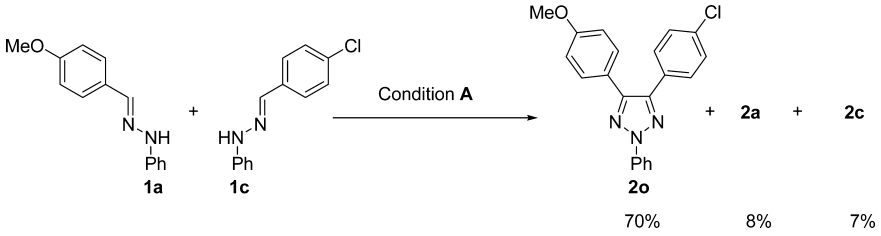
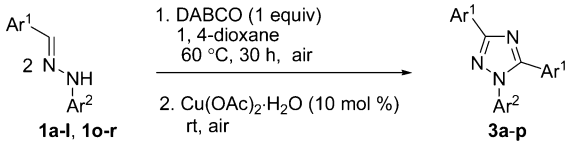
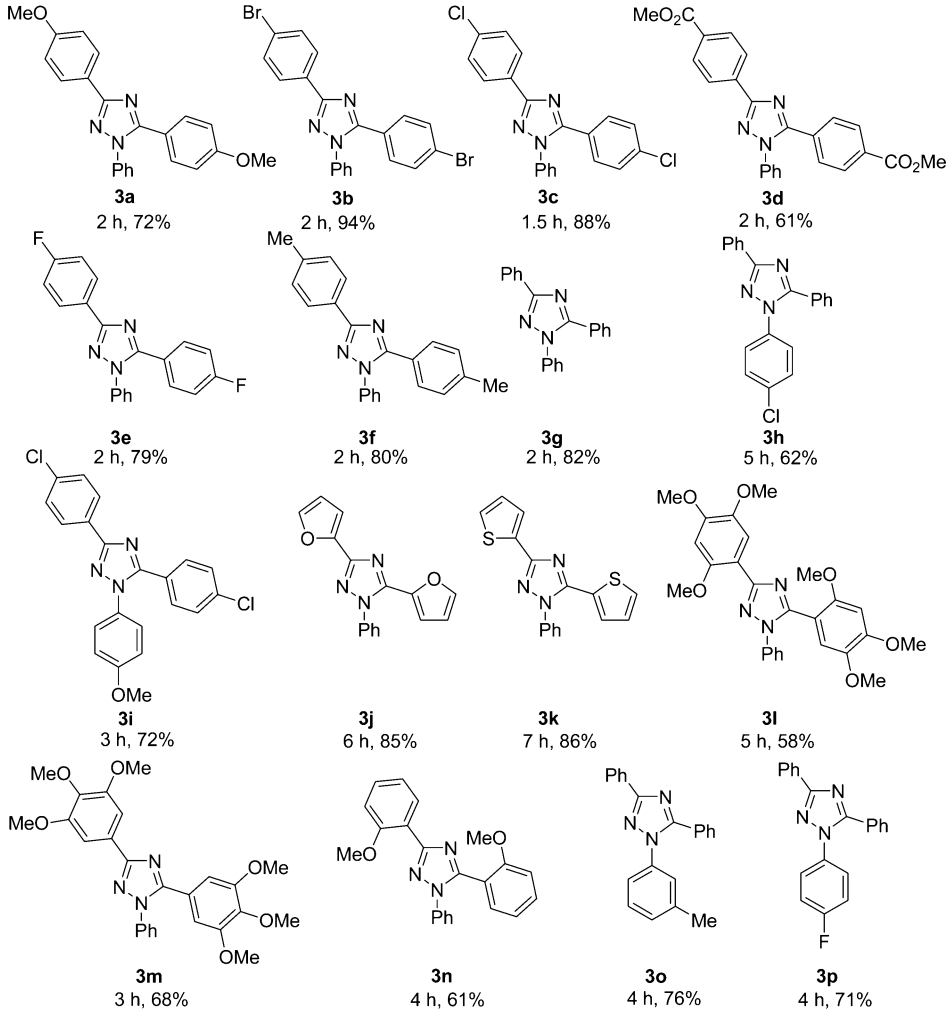


Table 2. Copper(II)-Catalyzed Synthesis of 1,3,5-Triaryl-1,2,4-Triazoles[a–c]



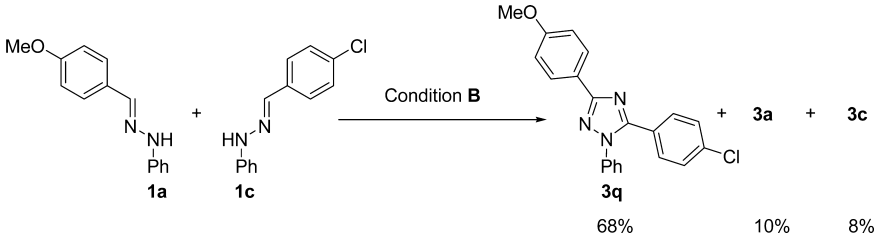


[a]Conditions: Bisarylhydrazones **1a–l** and **1o–r** (0.5 mmol) in the presence of DABCO (1 equiv) were stirred in dioxane (2 mL) at 60 °C for 30 h under air, the resulting mixture was treated with $Cu(OAc)_2·H_2O$ (10 mol %) at rt under air, and the stirring was continued for the appropriate time. [b]Aldehydes (2–10%) were obtained as byproduct. [c]Isolated yield.

proceed reaction further with 10 mol % $Cu(OAc)_2·H_2O$ at room temperature to afford 1,3,5-triaryl-1,2,4-triazole **3a** in 55% yield (see the Supporting Information). Having this important result in our hand, we went on further to screen the other reaction parameters with **1a** as a model substrate. Employing other organic bases and solvents led to find DABCO and dioxane as the choice of base and solvent, respectively. In contrast, the reactions with inorganic bases were found to be ineffective. The catalytic activity of the other copper sources such as $Cu(OAc)_2$, $CuCl_2$, $Cu(OTf)_2$, CuCl, and CuI was

dx.doi.org/10.1021/jo300592t | J. Org. Chem. 2012, 77, 5063–5073

Scheme 3. Copper(II)-Catalyzed Synthesis of Unsymmetrically Substituted 1,2,4-Triazole



examined, and Cu(II) salts were found to be superior to Cu(I) salts to afford the product **3a** in high yield. When the amount of the copper source (5 mol %) or quantity of the base (0.5 equiv) was reduced, the yield of **3a** was significantly dropped. Control experiment revealed that in the absence of the copper source, no cyclization was observed to give the target heterocycle **3a**. As a whole, condition **B** was fascinated to be the best for the synthesis of 1,3,5-triaryl-1,2,4-triazoles (Scheme 1).

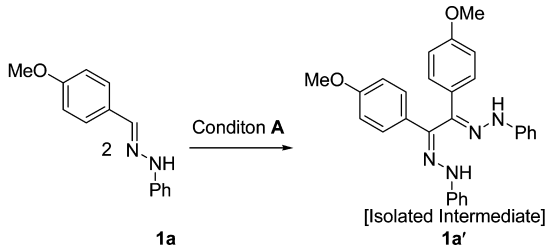
Substrate Scope for the Synthesis of 1,2,3-Triazoles (Condition A). Having the optimal conditions in hand, we set out to explore the scope of the reactions of a wide range of readily accessible bisarylhydrazones by employing condition **A**. The reaction was general, and a series of substrates readily proceeded cyclization to give the target molecules in moderate to high yields. For example, bisarylhydrazones **1a**–**n** underwent reaction to give the substituted 1,2,3-triazoles **2a**–**n** in 45–90% yields (Table 1). Bisarylhydrazones **1b**–**e**, **1h**, and **1m** bearing electron-withdrawing substituents on the arenes led to give **2b**–**e**, **2h**, and **2m** in 56–90% yields. While bisarylhydrazones **1a**, **1f**, and **1n** having electron-donating substituents on the aryl rings proceeded cyclization to afford the corresponding heterocycles **2a**, **2f**, and **2n** in 45–87% yield. Furthermore, bisarylhydrazone **1i** having both electron-withdrawing and electron-donating substituents on the arenes could afford the target heterocycle **2i** in 66% yield. The substrate **1g** with unsubstituted arenes afforded **2g** in 85% yield. The substrate **1l** bearing trimethoxy substituents on the aryl ring underwent reaction to provide the substituted 1,2,3-triazole **2l** in 66% yield. Arylhydrazones **1j** and **1k** containing furanyl and thiophenyl moieties also proceeded cyclization to provide the target heterocycles **2j** and **2k**, respectively, in moderate yield. Under this condition, alkyl arylhydrazones were not stable and underwent decomposition to give aldehydes. For structural confirmation, the single crystal of the compound **2f**, grown from acetonitrile solution, was analyzed by single crystal X-ray analysis (see the Supporting Information).

Synthesis of Unsymmetrically Substituted 1,2,3-Triazole. The reaction condition **A** was also compatible for the synthesis of unsymmetrical 2,4,5-triaryl-1,2,3-triazoles. For an example, bisarylhydrazones **1a** and **1c** readily proceeded in reaction to give the unsymmetrical 2,4,5-triaryl-1,2,3-triazole **2o** in 70% yield along with the symmetrically substituted 1,2,3-triazoles **2a** and **2c** as minor products (Scheme 2).

Substrate Scope for the Synthesis of 1,2,4-Triazoles (Condition B). Next, we explored the scope for the synthesis of 1,3,5-triayl-1,2,4-triazoles **3a**–**p** with optimal condition **B** (Table 2). Bisarylhydrazones **1b**–**e**, **1h**, and **1r** bearing electron-withdrawing groups on the aryl rings proceeded cyclization to give the corresponding substituted triazoles **3b**–**e**, **3h**, and **3p** in 61–94% yield. Furthermore, the substrates **1a**, **1f,g**, and **1p,q** bearing H or electron-donating substituents on the aryl rings afforded the target heterocycles **3a**, **3f,g** and **3n,o**, respectively, in 61–82% yield. Bisarylhydrazone **1i** with both electron-donating and -withdrawing substituents on the aryl ring cyclized to give 1,2,4-triazole **3i** in 72% yield. In addition, bisarylhydrazones **1l** and **1o** having trimethoxy substituents in the aromatic rings could be converted into the corresponding substituted 1,2,4-triazoles **3l** and **3m** in 58–68% yield. Furthermore, the substrates **1j** and **1k** underwent reaction to give substituted 1,2,4-triazoles **3j** and **3k**, respectively, in 85–86% yield. The single crystal of the compound **3c** obtained from acetonitrile solution was analyzed by X-ray analysis (see the Supporting Information).

Synthesis of Unsymmetrically Substituted 1,2,4-Triazole. The reaction condition **B** could also be readily employed for the synthesis of unsymmetrical 1,3,5-triaryl-1,2,4-triazoles. For an example, a 1:1 mixture of hydrazones **1a** and **1c** underwent reaction to give the corresponding unsymmetrical 1,2,4-triazole **3q** in 68% yield along with the symmetrical 1,2,4-triazoles **3a** and **3c** as minor products (Scheme 3).

Mechanistic Studies of the Synthesis of 1,2,3-Triazoles 2a–n. During the transformation of bisarylhydrazone **1a** to give the substituted 1,2,3-triazole **2a**, we were able to isolate the intermediate **1a′** (eq 1) as crystals, a dimer of **1a**,



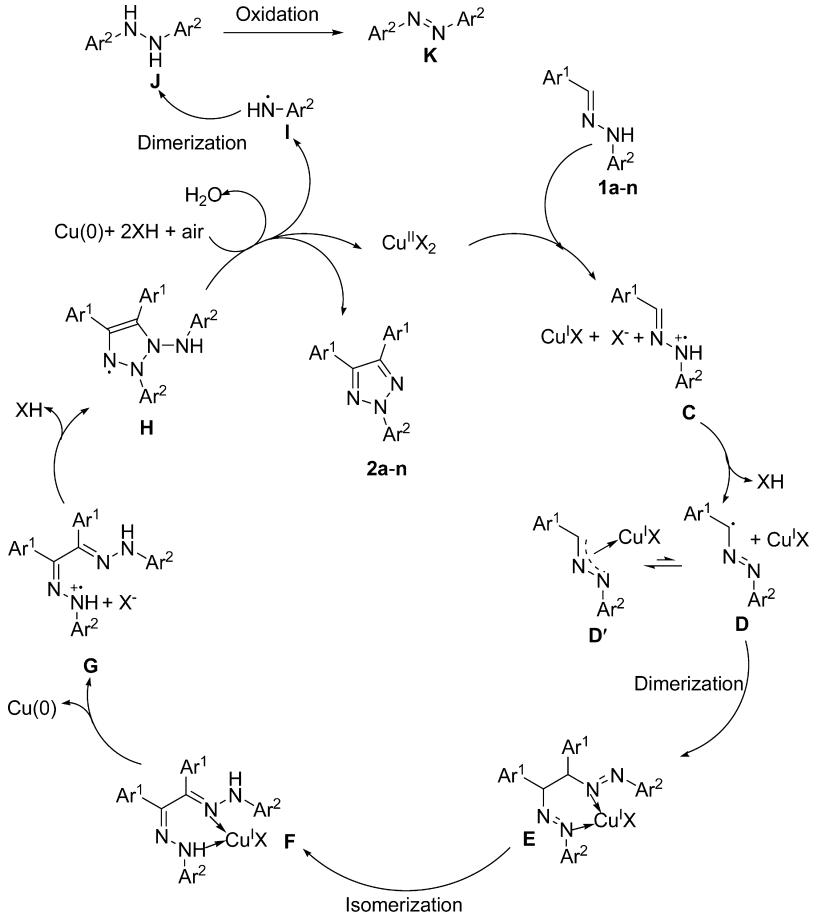
(1)

whose structure was confirmed by single crystal X-ray analysis (see the Supporting Information). Next, to get insight about whether the reaction involves a radical pathway, a radical inhibition test was carried out. When TEMPO, an effective radical scavenger, was added to the reaction mixture, the progress of the reaction was significantly slowed and a mixture of **2a** (7%) and unreacted **1a** (55%) was isolated (see the Supporting Information). This result clearly suggests that the reaction may involve radical intermediate.

On the basis of the above experimental observations and literature reports,[18] a plausible pathway for the synthesis of substituted 1,2,3-triazoles has been proposed (Scheme 4). Thus, bisarylhydrazones **1a**–**n** may transform into the radical cation **C** via single-electron transfer (SET) to Cu(II)X_2. The intermediate **C** could then transform into **D** by the elimination of HX. Dimerization of **D** could lead to the formation of **E**, which could isomerize to afford the intermediate **F**. The latter could form a radical cation **G** by reductive elimination of elemental copper through SET process. The generation of

dx.doi.org/10.1021/jo300592t | J. Org. Chem. 2012, 77, 5063–5073

Scheme 4. Proposed Catalytic Cycle for the Synthesis of Substituted 1,2,3-Triazoles



metallic copper(0) was confirmed by powder XRD analysis (Figure 1). The sharp peaks at 43.20°, 50.29°, and 73.98°

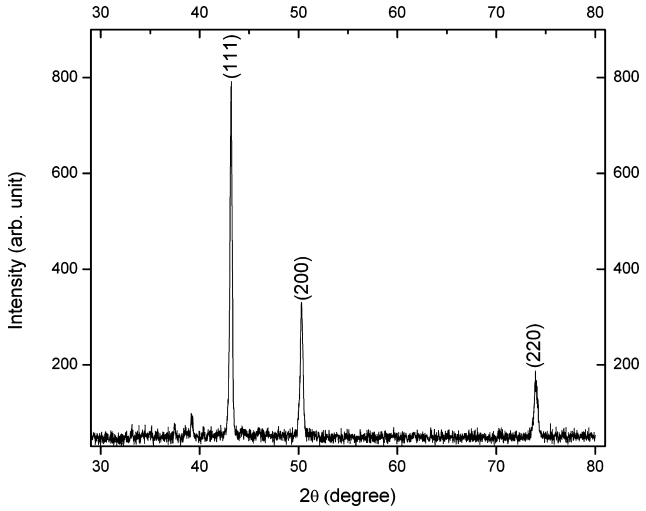
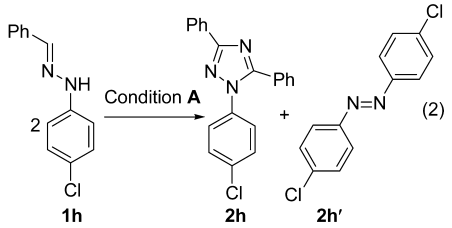
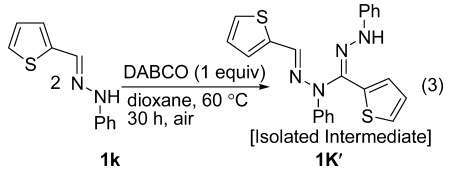


Figure 1. Powder XRD analysis of the recovered copper(0) species.

correspond to the (111), (200), and (220) planes of face-centered cubic copper(0) (with space group *Fm*3m, JCPDS 03-1005).[19] Elimination of HX followed by cyclization of **G** may lead to the formation of **H**, which could afford the target heterocycles **2a**–**n** via elimination of the radical intermediate **I**. Dimerization of **I** may give **J**, which could readily undergo oxidation under air to give the more stable azo compound **K**, which was confirmed by single crystal X-ray analysis of **2h′** (see the Supporting Information), a byproduct, formed during the transformation of **1h** to **2h** (eq 2). The reduced copper(0) species may be reoxidized by air to regenerate the active copper(II) species to complete the catalytic cycle.[5h,14e]

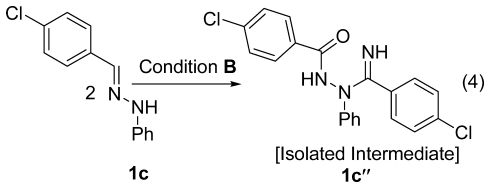




Mechanistic Studies of the Synthesis of 1,2,4-Triazoles 3a–p. To demonstrate the mechanism for the synthesis of 1,2,4-triazoles **3a**–**p**, the intermediate **1K′**, formed from **1k** in presence of organic base (eq 3), was isolated, and its

dx.doi.org/10.1021/jo300592t | J. Org. Chem. 2012, 77, 5063–5073

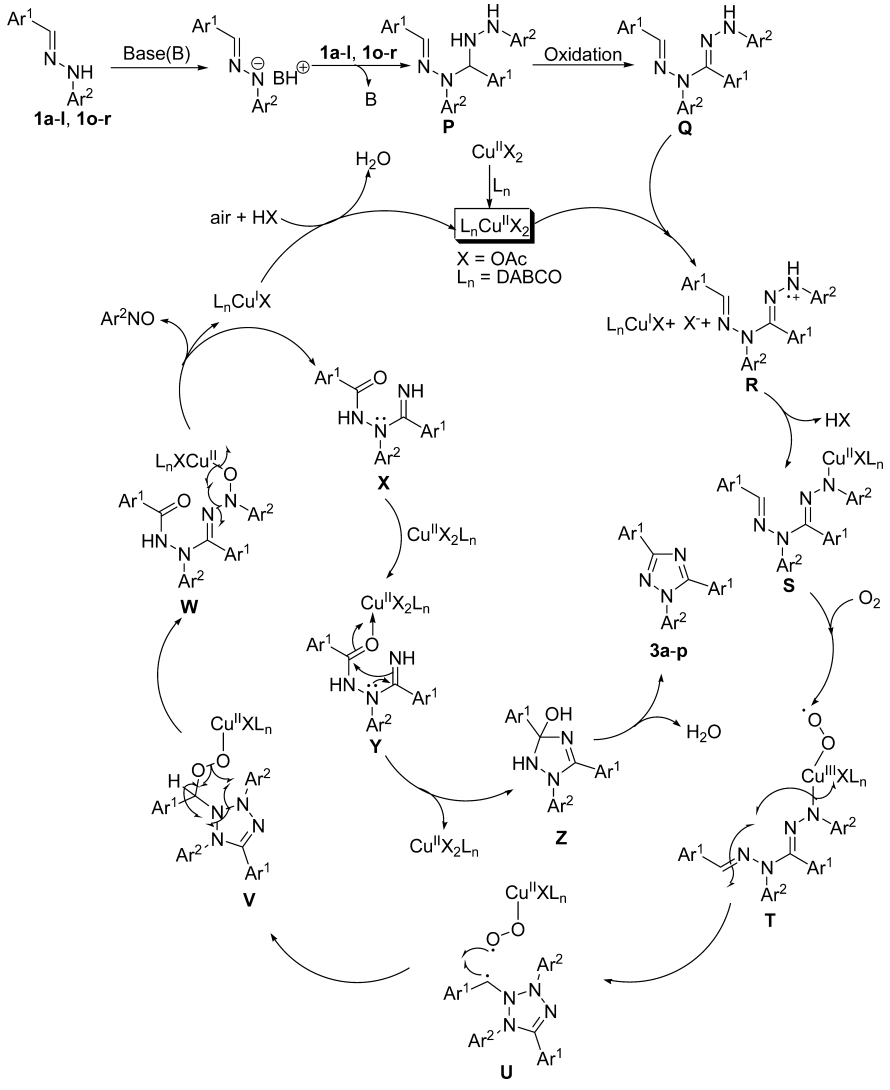
structure was confirmed by single crystal X-ray analysis (see the Supporting Information). To our delight, the intermediate **1c″** has also been isolated from **1c** when it was treated with organic base for 30 h followed by the addition of copper catalyst in presence of air (eq 4). Furthermore, the keto imine



intermediate **1c″**, whose structure was confirmed by X-ray analysis (see the Supporting Information), readily proceeded with cyclization to give the substituted 1,2,4-triazole **3c** when the reaction was prolonged. To see whether DABCO has any role in the cyclization step, the reaction of the dimeric intermediate **1K′** was investigated with 10 mol % $Cu(OAC)_2·H_2O$ in dioxane at room temperature under air. However, no cyclization was observed, and the intermediate **1K′** was isolated intact. In contrast, when DABCO was added, the reaction proceeded efficiently to afford the target heterocycle **3k**. These results clearly suggest that DABCO is not only acting as a base but also playing a crucial role of an effective ligand for the copper(II)-catalyzed oxidative cyclization to give the target heterocycles **3a−p**.

The literature reports on copper-catalyzed aerobic oxidative transformations developed by Chiba[20] and Stahl[21] facilitate to unravel the mechanistic route for the synthesis of substituted 1,2,4-triazoles. Observed experimental results and the literature precedent on copper-catalyzed aerobic oxidative processes[22] suggest that the base may mediate the dimerization of bisarylhydrazones **1a−l** and **1o−r** to give **P** via C−N bond formation (Scheme 5). The aerobic oxidation of **P** could give **Q**, which may lead to the formation of the radical cation **R** by single-electron transfer to copper(II) complex derived from copper(II)-salt with DABCO. The radical intermediate **R** may react with copper(I) complex to give copper(II) species **S** by elimination of HX. Aerobic oxidation of **S** may provide the copper(III)-superoxo species **T**. Heterocyclization of **T** may lead to the formation of benzylic radical **U**, which may further be converted into copper(II)-peroxo species **V**.[20a] Rearrangement of **V** could form the intermediate **W**, which with elimination of nirosoarenes[23] and copper(I) complex may afford keto imine intermediate **X** by abstracting hydrogen either

Scheme 5. Plausible Catalytic Cycle for the Synthesis of Substituted 1,2,4-Triazoles

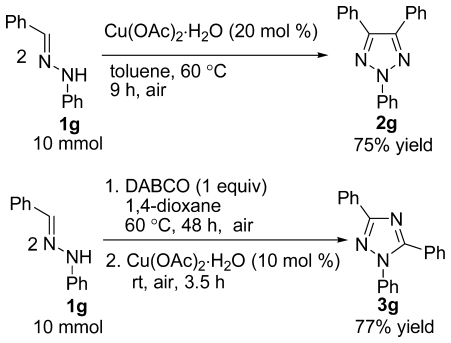


dx.doi.org/10.1021/jo300592t | J. Org. Chem. 2012, 77, 5063−5073

from water generated during the reaction or from intermediate **Q**. The Lewis acid assisted heterocyclization of **X** may lead to the target azaheterocycles **3a**–**p** via **Y** and **Z**. The active copper(II) complex could be regenerated by the aerobic oxidation of copper(I) complex in presence of HX.

Finally, the scale up of the conditions **A** and **B** were studied with **1g** as a substrate (Scheme 6). As anticipated, the reactions were efficient and afforded the corresponding target heterocycles **2g** and **3g** in 75 and 77% yield, respectively, with slightly longer reaction time.

Scheme 6. Gram Scale Synthesis of Substituted Triazoles



CONCLUSIONS

In summary, the intriguing chemistry of copper(II)-catalyzed oxidative C–H functionalization of bisarylhydrazones for the regioselective synthesis of 2,4,5-triaryl-1,2,3-triazoles and 1,3,5-triaryl-1,2,4-triazoles have been exploited under aerobic conditions. This strategy, carried out under mild reaction conditions, could be explored in large synthetic scope with wide functional group compatibility from the readily accessible substrates. The ground breaking feature with this protocol involves the synthesis of 1,3,5-triaryl-1,2,4-triazoles by copper(II)-catalyzed C–H functionalization at room temperature using aerobic oxygen as an oxidant. This could introduce a new incarnation to the scientific endeavor for copper-catalyzed room temperature C–H functionalization. Although we have isolated the reactive intermediates to unravel the mechanistic ubiquity, the detailed mechanism of each elementary step is still to be illuminated.

EXPERIMENTAL SECTION

General Procedure for Copper(II)-Catalyzed Synthesis of 2,4,5-Triaryl-1,2,3-Triazoles. Bisarylhydrazones **1a**–**n** (0.5 mmol) and $Cu(OAc)_2·H_2O$ (20 mol %, 20.0 mg) were stirred at 60 °C in toluene (2 mL) under air. After stirring for the appropriate time, the reaction mixture was cooled to room temperature and passed through a short pad of silica gel using hexane followed by a mixture of ethyl acetate and hexane as eluent to accomplish the target 2,4,5-triaryl-1,2,3-triazoles **2a**–**n** in analytically pure form.

Typical Procedure for Copper(II)-Catalyzed Synthesis of Unsymmetrical 2,4,5-Triaryl-1,2,3-Triazole 2o. Bisarylhydrazones **1a** (0.25 mmol, 56.6 mg) and **1c** (0.25 mmol, 57.7 mg) with $Cu(OAc)_2·H_2O$ (20 mol %, 20.0 mg) were stirred at 60 °C in toluene (2 mL) under air. After stirring for 6 h, the reaction mixture was cooled to room temperature and passed through a short pad of silica gel using hexane followed by a mixture of ethyl acetate and hexane as eluent to accomplish the target 2,4,5-triaryl-1,2,3-triazole **2o** in 70% (63.3 mg) yield along with symmetrical 2,4,5-triaryl-1,2,3-triazoles **2a** and **2c** in 8% (7.1 mg) and 7% (6.4 mg) yield, respectively.

Typical Procedure for Gram Scale Synthesis of 2,4,5-Triphenyl-1,2,3-Triazole 2g. Bisphenylhydrazone **1g** (10 mmol, 1.96 g) and $Cu(OAc)_2·H_2O$ (20 mol %, 0.40 g) were stirred at 60 °C in toluene (40 mL) under air for 9 h. After cooling to room temperature, the reaction mixture was passed through a short pad of silica gel using hexane followed by a mixture of ethyl acetate and hexane as eluent to afford the target 2,4,5-tripenyl-1,2,3-triazole **2g** in 75% (1.11 g) yield.

4,5-Bis(4-methoxyphenyl)-2-phenyl-2*H*-1,2,3-triazole 2a. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.40; colorless solid: yield 75% (67.0 mg); mp 134–135 °C (lit.[24] mp 133 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.8 Hz, 4H), 7.50 (t, J = 8.0 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 8.8 Hz, 4H), 3.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 145.6, 139.9, 129.8, 129.3, 127.1, 123.4, 118.6, 114.1, 55.33, 55.27; FT-IR (KBr) 2966, 2934, 1614, 1598, 1526, 1493, 1459, 1443, 1435, 1300, 1274, 1248, 1177, 1027 cm^{-1}; m/z (ESI-MS) 358.16 $[M + H]^+$. Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.86; H, 5.34; N, 11.81.

4,5-Bis(4-bromophenyl)-2-phenyl-2*H*-1,2,3-triazole 2b. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane R_f = 0.50; colorless solid: yield 88% (100.0 mg); mp 159–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.0 Hz, 2H), 7.55–7.42 (m, 10H), 7.38 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 139.6, 132.0, 130.0, 129.6, 129.4, 127.8, 123.2, 118.9; FT-IR (KBr) 2917, 1651, 1597, 1497, 1486, 1455, 1392, 1372, 1309, 1284, 1262, 1078, 1072, 1013 cm^{-1}; m/z (ESI-MS) 453.96, 455.97, 457.96 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}Br_2N_3$: C, 52.78; H, 2.88; N, 9.23. Found: C, 52.87; H, 2.87; N, 9.18.

4,5-Bis(4-chlorophenyl)-2-phenyl-2*H*-1,2,3-triazole 2c. Analytical TLC on silica gel, 1:49 ethyl acetate/hexane R_f = 0.60; colorless solid: yield 90% (82.4 mg); mp 156–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 8.8 Hz, 4H), 7.50 (t, J = 7.6 Hz, 2H), 7.38–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 139.6, 135.0, 129.8, 129.4, 129.1, 127.8, 118.9; FT-IR (KBr) 1637, 1598, 1496, 1456, 1396, 1372, 1310, 1285, 1264, 1092, 1071, 1016 cm^{-1}; m/z (ESI-MS) 366.06 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}Cl_2N_3$: C, 65.59; H, 3.58; N, 11.47. Found: C, 65.66; H, 3.60; N, 11.42.

4,5-Bis(4-carbomethoxyphenyl)-2-phenyl-2*H*-1,2,3-triazole 2d. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; colorless solid: yield 66% (68.2 mg); mp 160–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 8.0 Hz, 4H), 7.70 (d, J = 8.0 Hz, 4H), 7.53 (t, J = 8.0 Hz, 2H), 7.40 (t, J = 7.6 Hz, 1H), 3.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 145.1, 139.3, 134.8, 130.2, 129.9, 129.3, 128.3, 127.9, 118.8, 52.2; FT-IR (KBr) 2945, 2923, 1717, 1614, 1593, 1497, 1432, 1404, 1311, 1277, 1176, 1103, 1015 cm^{-1}; m/z (ESI-MS) 414.16 $[M + H]^+$. Anal. Calcd for $C_{24}H_{19}N_3O_4$: C, 69.72; H, 4.63; N, 10.16. Found: C, 69.65; H, 4.64; N, 10.19.

4,5-Bis(4-fluorophenyl)-2-phenyl-2*H*-1,2,3-triazole 2e. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; colorless solid: yield 84% (70.0 mg); mp 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.4 Hz, 2H), 7.61–7.57 (m, 4H), 7.51 (t, J = 8.0 Hz, 2H), 7.37–7.33 (m, 1H), 7.11–7.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 162.0, 145.0, 139.7, 130.4, 130.3, 129.4, 127.7, 126.9, 118.8, 116.0, 115.8; FT-IR (KBr) 3067, 1605, 1594, 1522, 1498, 1456, 1263, 1225, 1156, 1070 cm^{-1}; m/z (ESI-MS) 334.14 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}F_2N_3$: C, 72.06; H, 3.93; N, 12.61. Found: C, 72.13; H, 3.92; N, 12.56.

2-Phenyl-4,5-di-*p*-tolyl-2*H*-1,2,3-triazole 2f. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.50; colorless solid: yield 87% (70.8 mg); mp 144–145 °C (lit.[25] mp 145–146 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.0 Hz, 4H), 7.50 (t, J = 8.0 Hz, 2H), 7.35–7.31 (m, 1H), 7.20 (d, J = 8.4 Hz, 4H), 2.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 139.9, 138.5, 129.4, 129.3, 128.5, 128.1, 127.3, 118.8, 21.5; FT-IR (KBr) 3034, 3019, 2912, 1615, 1596, 1496, 1455, 1372, 1288, 1266, 1070 cm^{-1}; m/z (ESI-MS) 326.17 $[M + H]^+$. Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.15; H, 5.90; N, 12.95.

dx.doi.org/10.1021/jo300592t | J. Org. Chem. 2012, 77, 5063–5073

2,4,5-Triphenyl-2*H*-1,2,3-triazole 2g. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.45; colorless solid: yield 85% (63.2 mg); mp 123−124 °C (lit.[25] mp 124−125 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.4 Hz, 2H), 7.74−7.72 (m, 4H), 7.55 (t, J = 8.0 Hz, 2H), 7.47−7.43 (m, 6H), 7.40 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 139.9, 130.9, 129.4, 128.7, 128.6, 127.5, 118.8; FT-IR (KBr) 1632, 1597, 1496, 1458, 1441, 1375, 1322, 1289, 1266, 1074 cm^{-1}; m/z (ESI-MS) 298.15 $[M + H]^+$. Anal. Calcd for $C_{20}H_{15}N_3$: C, 80.78; H, 5.08; N, 14.13. Found: C, 80.73; H, 5.10; N, 14.17.

2-(4-Chlorophenyl)-4,5-diphenyl-2*H*-1,2,3-triazole 2h. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.70; colorless solid: yield 56% (46.5 mg); mp 95−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 9.2 Hz, 2H), 7.66−7.63 (m, 4H), 7.47 (d, J = 8.8 Hz, 2H), 7.41−7.39 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 138.4, 133.1, 130.7, 129.5, 129.0, 128.8, 128.6, 120.1; FT-IR (KBr) 3054, 2917, 1492, 1456, 1439, 1410, 1371, 1286, 1263, 1088, 1067 cm^{-1}; m/z (ESI-MS) 332.08 $[M + H]^+$. Anal. Calcd for $C_{20}H_{14}ClN_3$: C, 72.40; H, 4.25; N, 12.66. Found: C, 72.49; H, 4.23; N, 12.61.

4,5-Bis(4-chlorophenyl)-2-(4-methoxyphenyl)-2*H*-1,2,3-triazole 2i. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; colorless solid: yield 66% (65.4 mg); mp 127−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 9.2 Hz, 2H), 7.54−7.52 (m, 4H), 7.37−7.35 (m, 4H), 7.00 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 144.5, 134.8, 133.5, 129.8, 129.3, 129.1, 120.4, 114.5, 55.7; FT-IR (KBr) 2962, 2923, 1632, 1603, 1510, 1451, 1393, 1297, 1258, 1163, 1093, 1030 cm^{-1}; m/z (ESI-MS) 396.09 $[M + H]^+$. Anal. Calcd for $C_{21}H_{15}Cl_2N_3O$: C, 63.65; H, 3.82; N, 10.60. Found: C, 63.74; H, 3.83; N, 10.55.

4,5-Di(furan-2-yl)-2-phenyl-2*H*-1,2,3-triazole 2j. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.60; yellow solid: yield 58% (40.2 mg); mp 75−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.4 Hz, 2H), 7.654−7.652 (m, 2H), 7.56−7.44 (m, 2H), 7.43−7.30 (m, 1H), 7.09−7.08 (m, 2H), 6.61−6.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 143.3, 139.5, 137.4, 129.4, 128.0, 119.2, 111.7, 110.8; FT-IR (KBr) 2963, 1594, 1513, 1491, 1425, 1369, 1294, 1261, 1095, 1030 cm^{-1}; m/z (ESI-MS) 278.07 $[M + H]^+$. Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.39; H, 3.98; N, 15.11.

2-Phenyl-4,5-di(thiophen-2-yl)-2*H*-1,2,3-triazole 2k. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.70; orange solid: yield 47% (36.4 mg); mp 80−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.8 Hz, 2H), 7.50−7.40 (m, 5H), 7.37 (d, J = 7.6 Hz, 2H), 7.10−7.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 139.5, 131.6, 129.7, 129.4, 127.8, 127.7, 127.1, 119.0; FT-IR (KBr) 2961, 1593, 1494, 1421, 1261, 1093, 1026 cm^{-1}; m/z (ESI-MS) 310.05 $[M + H]^+$. Anal. Calcd for $C_{16}H_{11}N_3S_2$: C, 62.11; H, 3.58; N, 13.58; S, 20.73. Found: C, 62.02; H, 3.56; N, 13.63; S, 20.79.

4,5-Bis(2,4,5-trimethoxyphenyl)-2-phenyl-2*H*-1,2,3-triazole 2l. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.60; brown solid: yield 66% (78.8 mg); mp 138−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.4 Hz, 2H), 7.33−7.29 (m, 2H), 7.16−7.12 (m, 1H), 6.98 (s, 2H), 6.37 (s, 2H), 3.73 (s, 6H), 3.69 (s, 6H), 3.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 149.7, 144.9, 142.7, 139.6, 128.9, 126.6, 118.3, 113.6, 112.6, 97.4, 56.2, 55.8; FT-IR (KBr) 2935, 2842, 1614, 1596, 1527, 1497, 1461, 1436, 1399, 1379, 1291, 1261, 1210, 1175, 1102, 1029 cm^{-1}; m/z (ESI-MS) 478.21 $[M + H]^+$. Anal. Calcd for $C_{26}H_{27}N_3O_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.31; H, 5.69; N, 8.85.

4,5-Bis(3-nitrophenyl)-2-phenyl-2*H*-1,2,3-triazole 2m. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.50; colorless solid: yield 65% (62.9 mg); mp 152−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55−8.54 (m, 2H), 8.29−8.27 (m, 2H), 8.20 (d, J = 8.4 Hz, 2H), 7.92−7.90 (m, 2H), 7.62−7.52 (m, 4H), 7.44 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 143.9, 139.2, 134.0, 131.9, 130.1, 129.8, 129.6, 128.5, 123.9, 123.3, 119.0; FT-IR (KBr) 1595, 1537, 1509, 1488, 1466, 1374, 1347, 1303, 1262, 1168, 1100, 1072, 1023 cm^{-1}; m/z (ESI-MS) 388.12 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}N_5O_4$: C, 62.01; H, 3.38; N, 18.08. Found: C, 62.09; H, 3.37; N, 18.05.

2-(4-Methoxyphenyl)-4,5-diphenyl-2*H*-1,2,3-triazole[26] 2n. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.70; colorless solid: yield 45% (36.8 mg); mp 103−104 °C (lit.[26] mp 101−102 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.8 Hz, 2H), 7.63−7.61 (m, 4H), 7.39−7.37 (m, 6H), 7.00 (d, J = 9.2 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 145.7, 128.8, 128.7, 128.6, 124.5, 120.4, 114.5, 114.3, 55.7; FT-IR (KBr) 2963, 2928, 1603, 1577, 1511, 1459, 1440, 1294, 1260, 1176, 1144, 1102, 1024 cm^{-1}; m/z (ESI-MS) 328.15 $[M + H]^+$. Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 77.11; H, 5.21; N, 12.81.

4-(4-Chlorophenyl)-5-(4-methoxyphenyl)-2-phenyl-2*H*-1,2,3-triazole 2o. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.40; colorless solid: yield 70% (63.3 mg); mp 98−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 2H), 7.40−7.33 (m, 4H), 7.28−7.26 (m, 2H), 7.16−7.11 (m, 3H), 6.73−6.71 (m, 2H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 145.9, 144.5, 139.7, 134.6, 129.8, 129.7, 129.5, 129.3, 128.9, 127.4, 122.9, 118.7, 114.2, 55.3; FT-IR (KBr) 2962, 1614, 1599, 1497, 1458, 1251, 1175, 1092, 1032 cm^{-1}; m/z (ESI-MS) 362.12 $[M + H]^+$. Anal. Calcd for $C_{21}H_{16}ClN_3O$: C, 69.71; H, 4.46; N, 11.61. Found: C, 69.80; H, 4.44; N, 11.58.

General Procedure for Copper(II)-Catalyzed Synthesis of 1,3,5-Triaryl-1,2,4-Triazoles. Bisarylhydrazones **1a−l** and **1o−r** (0.5 mmol) with DABCO (1 equiv, 56.1 mg) were stirred in dioxane (2 mL) at 60 °C for 30 h under air. After cooling to room temperature, $Cu(OAc)_2{\cdot}H_2O$ (10 mol %, 10.0 mg) was added in the same pot, and the stirring was continued for the appropriate time at room temperature under air. After completion of the reaction, the solvent was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel using ethyl acetate and hexane as eluent to afford the desired heterocycles **3a−p** in analytically pure form.

Typical Procedure for Copper(II)-Catalyzed Synthesis of Unsymmetrical 1,3,5-Triaryl-1,2,4-Triazole 3q. Bisarylhydrazones **1a** (0.25 mmol, 56.6 mg) and **1c** (0.25 mmol, 57.7 mg) with DABCO (1 equiv, 56.1 mg) were stirred in dioxane (2 mL) at 60 °C for 30 h under air. After cooling to room temperature, $Cu(OAc)_2{\cdot}H_2O$ (10 mol %, 10.0 mg) was added in the same pot, and the stirring was continued for 3 h at room temperature under air. After completion of the reaction, the solvent was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel using ethyl acetate and hexane as eluent to afford unsymmetrical 1,3,5-triaryl-1,2,4-triazole **3q** in 68% (61.5 mg) yield along with symmetrical 1,3,5-triaryl-1,2,4-triazoles **3a** and **3c** in 10% (8.9 mg) and 8% (7.3 mg) yield, respectively.

Typical Procedure for Gram Scale Synthesis of 1,3,5-Triphenyl-1,2,4-Triazole 3g. Bisphenylhydrazone **1g** (10 mmol, 1.97 g) and DABCO (10 mmol, 1.12 g) were stirred in dioxane (40 mL) at 60 °C for 48 h under air. After cooling to room temperature, $Cu(OAc)_2{\cdot}H_2O$ (10 mol %, 0.20 g) was added in the same pot, and the stirring was continued for 3.5 h at room temperature under air. The solvent was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel using ethyl acetate and hexane as eluent to afford 1,3,5-triphenyl-1,2,4-triazole **3g** in 77% (1.14 g) yield.

3,5-Bis(4-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 3a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; colorless solid: yield 72% (64.3 mg); mp 132−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.34−7.31 (m, 5H), 6.94 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 8.0 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 160.7, 160.5, 154.3, 138.4, 130.3, 129.2, 128.5, 127.8, 125.3, 123.5, 120.2, 113.8, 55.0; FT-IR (KBr) 2939, 2837, 1611, 1577, 1531, 1498, 1482, 1465, 1426, 1390, 1345, 1301, 1255, 1172, 1108, 1031 cm^{-1}; m/z (ESI-MS) 358.18 $[M + H]^+$. Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.01; H, 5.35; N, 11.73.

3,5-Bis(4-bromophenyl)-1-phenyl-1*H*-1,2,4-triazole 3b. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.50; gummy liquid: yield 94% (106.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.49−7.37 (m, 9H); ^{13}C

dx.doi.org/10.1021/jo300592t | J. Org. Chem. 2012, 77, 5063−5073

NMR (100 MHz, $CDCl_3$) δ 161.1, 153.7, 138.0, 131.81, 131.75, 130.4, 129.6, 129.5, 129.1, 128.1, 126.7, 125.3, 124.7, 123.7; FT-IR (KBr) 2961, 1638, 1597, 1497, 1470, 1456, 1416, 1404, 1339, 1262, 1173, 1139, 1094, 1070, 1012 cm^{-1}; m/z (ESI-MS) 453.96, 455.93, 457.95 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}Br_2N_3$: C, 52.78; H, 2.88; N, 9.23. Found: C, 52.72; H, 2.89; N, 9.25.

3,5-Bis(4-chlorophenyl)-1-phenyl-1*H*-1,2,4-triazole 3c. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.50; colorless solid: yield 88% (80.6 mg); mp 133−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.4 Hz, 2H), 7.48−7.38 (m, 9H), 7.33 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 153.8, 138.0, 136.3, 135.4, 130.2, 129.6, 129.2, 128.9, 128.7, 127.9, 127.2, 126.2, 125.4, 112.7; FT-IR (KBr) 1644, 1598, 1498, 1471, 1455, 1408, 1337, 1178, 1136, 1086, 1014 cm^{-1}; m/z (ESI-MS) 366.07 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}Cl_2N_3$: C, 65.59; H, 3.58; N, 11.47. Found: C, 65.68; H, 3.56; N, 11.44.

3,5-Bis(4-carbomethoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 3d. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.30; colorless solid: yield 61% (63.1 mg); mp 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.4 Hz, 2H), 8.13 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.46−7.43 (m, 2H), 7.42−7.37 (m, 3H), 3.92 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 166.3, 161.3, 154.1, 137.9, 134.8, 131.9, 131.5, 130.9, 130.0, 129.8, 129.7, 129.4, 129.0, 126.5, 125.5, 52.4, 52.2; FT-IR (KBr) 2923, 2851, 1719, 1637, 1613, 1497, 1434, 1418, 1341, 1277, 1138, 1108, 1017 cm^{-1}; m/z (ESI-MS) 414.17 $[M + H]^+$. Anal. Calcd for $C_{24}H_{19}N_3O_4$: C, 69.72; H, 4.63; N, 10.16. Found: C, 69.64; H, 4.61; N, 10.21.

3,5-Bis(4-fluorophenyl)-1-phenyl-1*H*-1,2,4-triazole 3e. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.45; colorless solid: yield 79% (65.8 mg); mp 101−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21−8.17 (m, 2H), 7.55−7.51 (m, 2H), 7.45−7.38 (m, 5H), 7.15 (t, J = 8.8 Hz, 2H), 7.06 (t, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 161.8, 160.4, 153.2, 137.5, 130.5, 130.4, 128.9, 128.6, 128.4, 128.0, 127.9, 126.4, 124.8, 123.5, 115.3, 115.12, 115.06, 114.9; FT-IR (KBr) 3061, 1604, 1599, 1529, 1499, 1483, 1462, 1451, 1422, 1385, 1343, 1217, 1159, 1141, 1098 cm^{-1}; m/z (ESI-MS) 334.13 $[M + H]^+$. Anal. Calcd for $C_{20}H_{13}F_2N_3$: C, 72.06; H, 3.93; N, 12.61. Found: C, 72.13; H, 3.94; N, 12.57.

1-Phenyl-3,5-di-*p*-tolyl-1*H*-1,2,4-triazole 3f. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.40; colorless solid: yield 80% (65.1 mg); mp 115−116 °C (lit.[27] mp 116.5−117 °C) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz, 2H), 7.46−7.41 (m, 7H), 7.28 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 154.4, 139.8, 138.9, 138.2, 129.1, 128.99, 128.96, 128.6, 128.3, 127.9, 126.3, 125.1, 124.9, 21.14, 21.05; FT-IR (KBr) 3025, 2919, 2857, 1613, 1595, 1499, 1478, 1462, 1417, 1389, 1344, 1262, 1178, 1139, 1021 cm^{-1}; m/z (ESI-MS) 326.19 $[M + H]^+$. Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.12; H, 5.92; N, 12.96.

1,3,5-Triphenyl-1*H*-1,2,4-triazole 3g. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.65; colorless solid: yield 82% (61.0 mg); mp 105−106 °C (lit.[28] mp 104−105 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 7.2 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.42−7.20 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 154.5, 138.1, 130.7, 129.8, 129.3, 129.2, 128.8, 128.6, 128.5, 128.4, 127.8, 126.4, 125.2; FT-IR (KBr) 3062, 2923, 1594, 1517, 1496, 1478, 1442, 1397, 1352, 1272, 1262, 1172, 1138, 1070, 1027 cm^{-1}; m/z (ESI-MS) 298.14 $[M + H]^+$. Anal. Calcd for $C_{20}H_{15}N_3$: C, 80.78; H, 5.08; N, 14.13. Found: C, 80.85; H, 5.06; N, 14.09.

1-(4-Chlorophenyl)-3,5-diphenyl-1*H*-1,2,4-triazole 3h. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.35; colorless solid: yield 62% (51.4 mg); mp 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 6.8 Hz, 2H), 7.54 (d, J = 6.8 Hz, 2H), 7.45−7.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 154.8, 136.8, 134.5, 130.6, 130.2, 129.6, 129.0, 128.8, 128.7, 127.8, 126.6, 126.5; FT-IR (KBr) 3066, 2923, 1519, 1494, 1478, 1443, 1396, 1352, 1171, 1141, 1094, 1016 cm^{-1}; m/z (ESI-MS) 332.08 $[M + H]^+$. Anal. Calcd for $C_{20}H_{14}ClN_3$: C, 72.40; H, 4.25; N, 12.66. Found: C, 72.31; H, 4.24; N, 12.71.

3,5-Bis(4-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-1,2,4-triazole 3i. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.50; colorless solid: yield 72% (71.3 mg); mp 191−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.33−7.28 (m, 4H), 6.96 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 160.1, 153.9, 136.4, 135.5, 130.6, 130.2, 128.92, 128.86, 128.5, 127.8, 126.9, 125.9, 114.7, 55.5; FT-IR (KBr) 2955, 2928, 1599, 1509, 1469, 1459, 1424, 1406, 1307, 1251, 1170, 1137, 1102, 1087, 1027, 1013 cm^{-1}; m/z (ESI-MS) 396.08 $[M + H]^+$. Anal. Calcd for $C_{21}H_{15}Cl_2N_3O$: C, 63.65; H, 3.82; N, 10.60. Found: C, 63.55; H, 3.83; N, 10.64.

3,5-Di(furan-2-yl)-1-phenyl-1*H*-1,2,4-triazole 3j. Analytical TLC on silica gel, 1:5 ethyl acetate/hexane R_f = 0.30; gummy liquid: yield 85% (58.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.4 Hz, 1H), 7.53−7.45 (m, 5H), 7.36−7.32 (m, 1H), 7.11−7.10 (m, 1H), 6.52−6.51 (m, 2H), 6.41−6.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 155.0, 144.3, 144.1, 143.2, 137.4, 129.4, 129.1, 128.7, 125.8, 119.9, 113.1, 111.5, 109.9; FT-IR (KBr) 2963, 1599, 1508, 1497, 1437, 1319, 1261, 1094, 1075, 1016 cm^{-1}; m/z (ESI-MS) 278.11 $[M + H]^+$. Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.23; H, 4.01; N, 15.19.

1-Phenyl-3,5-di(thiophen-2-yl)-1*H*-1,2,4-triazole 3k. Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; gummy liquid: yield 86% (66.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 3.6 Hz, 1H), 7.54−7.49 (m, 5H), 7.39−7.36 (m, 2H), 7.12−7.10 (m, 1H), 7.08 (d, J = 4.0 Hz, 1H), 6.96−6.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 149.0, 136.6, 132.3, 129.1, 128.8, 128.3, 128.0, 126.9, 126.8, 126.0, 125.9; FT-IR (KBr) 3090, 3071, 1594, 1549, 1499, 1469, 1451, 1434, 1393, 1314, 1229, 1107, 1075 cm^{-1}; m/z (ESI-MS) 310.02 $[M + H]^+$. Anal. Calcd for $C_{16}H_{11}N_3S_2$: C, 62.11; H, 3.58; N, 13.58; S, 20.73. Found: C, 62.19; H, 3.57; N, 13.54; S, 20.70.

3,5-Bis(2,4,5-trimethoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 3l. Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.20; gummy liquid: yield 58% (69.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.35−7.26 (m, 5H), 7.17 (s, 1H), 6.61 (s, 1H), 6.33 (s, 1H), 3.90−3.88 (m, 9H), 3.85 (s, 6H), 3.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 159.6, 152.1, 151.4, 151.1, 150.2, 142.9, 142.7, 138.8, 128.3, 127.3, 122.9, 113.7, 113.5, 111.4, 108.3, 98.1, 96.7, 59.9, 56.7, 56.1, 55.6, 54.9, 53.3; FT-IR (KBr) 2933, 2840, 1612, 1504, 1465, 1437, 1375, 1276, 1214, 1171, 1028 cm^{-1}; m/z (ESI-MS) 478.18 $[M + H]^+$. Anal. Calcd for $C_{26}H_{27}N_3O_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.50; H, 5.68; N, 8.76.

3,5-Bis(3,4,5-trimethoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 3m. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.40; gummy liquid: yield 68% (81.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 7H), 6.64−6.60 (m, 2H), 3.79−3.66 (m, 12H), 3.52−3.47 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 154.2, 153.1, 152.7, 139.1, 138.8, 138.0, 129.1, 128.7, 125.8, 125.5, 122.3, 106.0, 103.3, 60.4, 55.8, 55.5; FT-IR (KBr) 2932, 2846, 1590, 1497, 1486, 1463, 1418, 1347, 1234, 1127, 1004 cm^{-1}; m/z (ESI-MS) 478.17 $[M + H]^+$. Anal. Calcd for $C_{26}H_{27}N_3O_6$: C, 65.40; H, 5.70; N, 8.80. Found: C, 65.48; H, 5.71; N, 8.75.

3,5-Bis(2-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 3n. Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.40; gummy liquid: yield 61% (54.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.6 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.42−7.26 (m, 7H), 7.06−7.00 (m, 3H), 6.78 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 3.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 157.5, 156.5, 151.9, 138.9, 131.8, 131.4, 131.0, 130.4, 128.6, 127.7, 123.2, 120.8, 120.4, 111.9, 111.7, 111.6, 111.2, 55.7, 54.6; FT-IR (KBr) 2923, 1629, 1603, 1583, 1498, 1462, 1250, 1160, 1105, 1023 cm^{-1}; m/z (ESI-MS) 358.13 $[M + H]^+$. Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.85; H, 5.37; N, 11.81.

3,5-Diphenyl-1-*m*-tolyl-1*H*-1,2,4-triazole 3o. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; colorless liquid: yield 76% (59.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 6.8 Hz, 2H), 7.58 (d, J = 6.8 Hz, 2H), 7.49−7.22 (m, 9H), 7.14 (d, J = 8.0 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 154.8, 139.8, 138.3, 130.9, 130.0, 129.7, 129.5, 129.2, 129.1, 128.7, 128.6, 128.2, 126.7, 126.1, 122.7, 21.4; FT-IR (KBr) 3064, 2956, 2917, 1610,

dx.doi.org/10.1021/jo300592t | J. Org. Chem. 2012, 77, 5063−5073

1591, 1517, 1491, 1478, 1443, 1395, 1352, 1262, 1173, 1137, 1071, 1027, 1012 cm^{-1}; *m/z* (ESI-MS) 312.17 $[M + H]^+$. Anal. Calcd for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50; N, 13.49. Found: C, 81.08; H, 5.48; N, 13.44.

1-(4-Fluorophenyl)-3,5-diphenyl-1*H*-1,2,4-triazole 3p. Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.40; orange solid: yield 71% (56.0 mg); mp 100−101 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 6.8 Hz, 2H), 7.54−7.47 (m, 2H), 7.46−7.34 (m, 8H), 7.14−7.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 162.1, 161.3, 155.0, 134.5, 130.7, 130.3, 129.7, 129.1, 128.81, 128.76, 127.9, 127.5, 127.4, 126.7, 116.7, 116.4; FT-IR (KBr) 2923, 2851, 1637, 1509, 1478, 1440, 1399, 1352, 1219, 1155, 1097, 1067 cm^{-1}; *m/z* (ESI-MS) 316.13 $[M + H]^+$. Anal. Calcd for $C_{20}H_{14}FN_3$: C, 76.18; H, 4.47; N, 13.33. Found: C, 76.11; H, 4.45; N, 13.39.

5-(4-Chlorophenyl)-3-(4-methoxyphenyl)-1-phenyl-1*H*-1,2,4-triazole 3q. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.40; colorless solid: yield 68% (61.5 mg); mp 149−151 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.2 Hz, 2H), 7.48−7.40 (m, 7H), 7.33 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 9.2 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 153.4, 138.0, 136.1, 130.2, 129.44, 129.37, 128.9, 128.8, 128.0, 127.8, 125.4, 123.2, 114.0, 55.2; FT-IR (KBr) 2991, 1613, 1596, 1499, 1471, 1440, 1424, 1250, 1169, 1092, 1027 cm^{-1}; *m/z* (ESI-MS) 362.09 $[M + H]^+$. Anal. Calcd for $C_{21}H_{16}ClN_3O$: C, 69.71; H, 4.46; N, 11.61. Found: C, 69.60; H, 4.48; N, 11.64.

■ ASSOCIATED CONTENT

Supporting Information

General information, optimization tables, crystal structures and data (CIF), and NMR (^1H and ^{13}C) spectra of **2a−o** and **3a−q**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tpunni@iitg.ernet.in.

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.

■ REFERENCES

(1) For examples, see: (a) Espino, C. G.; Wehn, P. M.; Chow, J.; Bois, J. D. *J. Am. Chem. Soc.* **2001**, *123*, 6935. (b) Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250. (c) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (d) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (e) Neumann, J. J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892. (f) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (g) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (h) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, *132*, 13217. (i) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (j) Cho, S. H.; Kim, J. Y.; Kwak., J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (k) Lu, Z.; Stahl, S. S. *Org. Lett.* **2012**, *14*, 1234. (l) Ueda, S.; Okada, T.; Nagasawa, H. *Chem. Commun.* **2010**, 2462. (m) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (n) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (o) Tang, S.; Peng, P.; Wang, Z.-Q.; Tang, B.-X.; Deng, C.-L.; Li, J.-H.; Zhong, P.; Wang, N.-X. *Org. Lett.* **2008**, *10*, 1875. (p) Inamoto, K.; Hasegawa, C.; Kawasaki, J.; Hiroya, K.; Doi, T. *Adv. Synth. Catal.* **2010**, *352*, 2643. (q) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (r) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147. (s) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627. (t) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288. (u) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. Am. Chem. Soc.* **2010**, *132*, 9602. (v) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

(2) For examples of Rh-catalyzed reactions, see: (a) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500. (b) Fiori, K. W.; Bios, J. D. *J. Am. Chem. Soc.* **2007**, *129*, 562. (c) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094. (d) Gong, T.-J.; Xiao, B.; Liu, Z.-J.; Wan, J.; Xu, J.; Luo, D.-F.; Fu, Y.; Liu, L. *Org. Lett.* **2011**, *13*, 3235. (e) Park, S. H.; Kim, J. Y.; Chang, S. *Org. Lett.* **2011**, *13*, 2372. (f) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616. (g) Patureau, F. W.; Nimphius, C.; Glorius, F. *Org. Lett.* **2011**, *13*, 6346. (h) DeAngelis, A.; Shurtleff, V. W.; Dmitrenko, O.; Fox, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 1650. (i) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (j) Zhang, H.-J.; Bolm, C. *Org. Lett.* **2011**, *13*, 3900.

(3) For examples of Ru-catalysed reactions, see: (a) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 3856. (b) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (c) Simon, M.-O.; Genet, J.-P.; Darses, S. *Org. Lett.* **2010**, *12*, 3038. (d) Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 706. (e) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153. (f) Kwon, K.-H.; Lee, D. W.; Yi, C. S. *Organometallics* **2010**, *29*, 5748.

(4) For some examples, see: (a) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222. (b) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972. (c) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (d) Garcia-Rubiá, A.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511. (e) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (f) Daugulis, O.; Do, H,-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (g) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (h) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (i) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144. (j) Nishikata, T.; Abela, A. R.; Lipshutz, B. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 781. (k) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (l) Ackermann, L.; Althammer, A.; Fenner, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 201.

(5) For some examples, see: (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (b) Xiong, T.; Li, Y.; Bi, X.; Lv, Y.; Zhang, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 7140. (c) Bellina, F.; Rossi, S. *Adv. Synth. Catal.* **2010**, *352*, 1223. (d) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522. (e) Ueda, S.; Nagasawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6411. (f) Ueda, S.; Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272. (g) Chen, X.; Hao, X. S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (h) Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *Org. Lett.* **2011**, *13*, 1194. (i) Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *J. Org. Chem.* **2011**, *76*, 5295. (j) Moure, M. J.; SanMartin, R.; Dominguez, E. *Angew. Chem., Int. Ed.* **2012**, *124*, 3274. (k) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (l) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (m) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (n) Park, E. J.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 17268.

(6) For applications of substituted 1,2,3-triazoles, see: (a) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. (c) Watanabe, T.; Umezawa, Y.; Takahashi, Y.; Akamatsu, Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5807. (d) Cox, C. D.; Breslin, M. J.; Whitman, D. B.; Schreier, J. D.; McGaughey, G. B.; Bogusky, M. J.; Roecker, A. J.; Mercer, S. P.; Bednar, R. A.; Lemaire, W.; Bruno, J. G.; Reiss, D. R.; Meacham Harrell, C.; Murphy, K. L.; Garson, S. L.; Doran, S. M.; Prueksaritanont, T.; Anderson, W. B.; Tang, C.; Roller, S.; Cabalu, T. D.; Cui, D.; Hartman, G. D.; Young, S. D.; Koblan, K. S.; Winrow, C. J.; Renger, J. J.; Coleman, P. J. *J. Med. Chem.* **2010**, *53*, 5320. (e) Baxter, C. A.; Cleator, E.; Brands, K. M. J.; Edwards, J. S.; Reamer,

R. A.; Sheen, F. J.; Stewart, G. W.; Strotman, N. A.; Wallace, D. J. *Org. Process Res. Dev.* **2011**, *15*, 367. (f) Wu, P.; Fokin, V. V. *Aldrichimica Acta* **2007**, *40*, 7. (g) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928. (h) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046. (i) Aher, N. G.; Pore, V. S.; Mishra, N. N.; Kumar, A.; Shukla, P. K.; Sharma, A.; Bhat, M. K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 759. (j) Zhou, L.; Amer, A.; Korn, M.; Burda, R.; Balzarini, J.; De Clercq, E.; Kern, E. R.; Torrence, P. F. *Antiviral Chem. Chemother.* **2005**, *16*, 375. (k) Bochis, R. J.; Chabala, J. C.; Harris, E.; Peterson, L. H.; Barash, L.; Beattie, T.; Brown, J. E.; Graham, D. W.; Waksmunski, F. S. *J. Med. Chem.* **1991**, *34*, 2843. (l) Jia, Z. J.; Venkataramani, C.; Huang, W.; Mehrotra, M.; Song, Y.; Xu, Q.; Bauer, S. M.; Pandey, A. WO2009136995, 2009. (m) Kim, D.-K.; Kim, J.; Park, H.-J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2401.

(7) For applications of substituted 1,2,4-triazoles, see: (a) Al-Masoudi, A.; Al-Soud, Y. A.; Al-Salihi, N. J.; Al-Masoudi, N. A. *Chem. Heterocycl. Compd.* **2006**, *42*, 1377. (b) Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Csoeregh, I.; Hesselink, W.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 3112. (c) Cho, I. H.; Park, H. J.; Noh, J. Y.; Ryu, H. C.; Park, S. W.; Jung, S. H.; Lee, S. H.; Kim, J. H.; Lim, J. W.; Lyu, C. S.; Kim, D. H.; Kim, Y. H.; Yeon, K. J.; Chae, M. Y.; Min, I. K.; Jin, H. T.; Kang, K. R. WO2004014878, 2004. (d) Nicolaou, K. C.; Pratt, B. A.; Arseniyadis, S.; Wartmann, M.; O'Brate, A.; Giannakakou, P. *ChemMedChem* **2006**, *1*, 41. (e) Nisbet-Brown, E.; Olivieri, N. F.; Giardina, P. J.; Grady, R. W.; Neufeld, E. J.; Séchaud, R.; Krebs-Brown, A. J.; Anderson, J. R.; Alberti, D.; Sizer, K. C.; Nathan, D. G. *Lancet* **2003**, *361*, 1597. (f) Sui, Z.; Guan, J.; Hlasta, D. J.; Macielag, M. J.; Foleno, B. D.; Goldschmidt, R. M.; Loeloff, M. J.; Webb, G. C.; Barrett, J. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1929. (g) Kaku, Y.; Tsuruoka, A.; Kakinuma, H.; Tsukada, I.; Yanagisawa, M.; Naito, T. *Chem. Pharm. Bull.* **1998**, *46*, 1125.

(8) Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984.

(9) For some representative examples of metal-catalyzed AAC, see: (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (c) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680. (d) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998. (e) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 1730. (f) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem* **2010**, *8*, 4503.

(10) For examples, see: (a) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786. (b) Zhang, Y.; Li, X.; Li, J.; Chen, J.; Meng, X.; Zhao, M.; Chen, B. *Org. Lett.* **2012**, *14*, 26. (c) Kalisiak, J.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3171. (d) Wang, X. -J.; Zhang, L.; Krishnamurthy, D.; Senanayake, C. H.; Wipf, P. *Org. Lett.* **2010**, *12*, 4632. (e) Wang, X.-J.; Zhang, L.; Lee, H.; Haddad, N.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5026. (f) Chen, Y.; Liu, Y.; Petersen, J. L.; Shi, X. *Chem. Commun.* **2008**, 3254. (g) Tang, W.-J.; Hu, Y.-Z. *Synth. Commun.* **2006**, *36*, 2461.

(11) (a) Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 934. (b) Balachandran, K. S.; Hiryakkanavar, I.; George, M. V. *Tetrahedron* **1975**, *31*, 1171.

(12) Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389.

(13) Ueda, S.; Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8944.

(14) For examples, see: (a) Moulin, A.; Bibian, M.; Blayo, A.-L.; Habnouni, S. E.; Martinez, J.; Fehrentz, J.-A. *Chem. Rev.* **2010**, *110*, 1809. (b) Saleem, R. S. Z.; Tepe, J. J. *J. Org. Chem.* **2010**, *75*, 4330. (c) Katritzky, A. R.; Qi, M.; Feng, D.; Zhang, G.; Griffith, M. C.; Watson, K. *Org. Lett.* **1999**, *1*, 1189. (d) Stocks, M. J.; Cheshire, D. R.; Reynolds, R. *Org. Lett.* **2004**, *6*, 2969. (e) Ueda, S.; Nagasawa, H. *J. Am. Chem. Soc.* **2009**, *131*, 15080. (f) Zhang, J.-P.; Lin, Y.-Y.; Huang, X.-C.; Chen, X.-M. *J. Am. Chem. Soc.* **2005**, *127*, 5495. (g) Boyle, J. T. A.; Grundon, M. F.; Scott, M. D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 207.

(15) (a) Staben, S. T.; Blaquiere, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 325. (b) Castanedo, G. M.; Seng, P. S.; Blaquiere, N.; Trapp, S.; Staben, S. T. *J. Org. Chem.* **2011**, *76*, 1177.

(16) (a) Paulvannan, K.; Hale, R.; Sedehi, D.; Chen, T. *Tetrahedron* **2001**, *57*, 9677. (b) Paulvannan, K.; Chen, T.; Hale, R. *Tetrahedron* **2000**, *56*, 8071.

(17) For the stability of hydrazones, see: (a) Johnson, S. M.; Petrassi, H. M.; Palaninathan, S. K.; Mohamedmohaideen, N. N.; Purkey, H. E.; Nochols, C.; Chiang, K. P.; Walkup, T.; Sacchettini, J. C.; Sharpless, K. B.; Kelly, J. W. *J. Med. Chem.* **2005**, *48*, 1576. (b) Kalia, J.; Raines, R. T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7523.

(18) For examples on the reactivity of radical cations, see: (a) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 2550. (b) Pacansky, J.; McLean, A. D.; Miller, M. D. *J. Phys. Chem.* **1990**, *94*, 90. (c) Lu, S.; Jin, T.; Kwon, E.; Bao, M.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 802. (d) Yan, R.-L.; Yan, H.; Ma, C.; Ren, Z.-Y.; Gao, X.-A.; Huang, G.-S.; Liang, Y.-M. *J. Org. Chem.* **2012**, *77*, 2024. (e) Bhatnagar, I.; George, M. V. *J. Org. Chem.* **1967**, *32*, 2252.

(19) Radi, A.; Pradhan, D.; Sohn, Y.; Leung, K. T. *ACS Nano* **2010**, *4*, 1553.

(20) (a) Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2011**, *13*, 1622. (b) Toh, K. K.; Wang, Y.-F.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 13942. (c) Wang, Y.-F.; Zhu, X.; Chiba, S. *J. Am. Chem. Soc.* **2012**, *134*, 3679. (d) Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 7266.

(21) (a) Hewgley, J. B.; Stahl, S. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 12232. (b) King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044. (c) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196. (d) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068.

(22) For examples of Cu-catalyzed oxidative reactions, see: (a) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (b) Zhang, C.; Xu, Z.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11088. (c) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (d) Wang, J.; Wang, J.; Zhu, Y.; Lu, P.; Wang, Y. *Chem. Commun.* **2011**, *47*, 3275. (e) Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678. (f) Wei, W.; Hu, X.-Y.; Yan, X.-W.; Zhang, Q.; Cheng, M.; Ji, J.-X. *Chem. Commun.* **2012**, *48*, 305. (g) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158. (h) Li, Y.; Xie, Y.; Zhang, R.; Jin, K.; Wang, X.; Duan, C. *J. Org. Chem.* **2011**, *76*, 5444. (i) Borduas, N.; Powell, D. A. *J. Org. Chem.* **2008**, *73*, 7822. (j) Gao, Y.; Wang, G.; Chen, L.; Xu, P.; Zhao, Y.; Zhou, Y.; Han, L.-B. *J. Am. Chem. Soc.* **2009**, *131*, 7956. (k) Chu, L.; Quing, F.-L. *Org. Lett.* **2010**, *12*, 5060. (l) Berrino, R.; Cacchi, S.; Fabrizi, G.; Goggiamani, A. *J. Org. Chem.* **2012**, *77*, 2537. (m) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078. (n) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298. (o) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317. (p) Lucas, H. R.; Li, L.; Narducci Sarjeant, A. A.; Vance, M. A.; Solomon, E. I.; Karlin, K. D. *J. Am. Chem. Soc.* **2009**, *131*, 3230. (q) Mayasaka, M.; Hirano, K.; Satoh, T.; Kawalczyk, R.; Bolm, C.; Miura, M. *Org. Lett.* **2011**, *13*, 359.

(23) The nitrosoarenes have been isolated as byproduct during the synthesis of substituted 1,2,4-triazoles.

(24) Balachandran, K. S.; Hiryakkanavar, I.; George, M. V. *Tetrahedron* **1975**, *31*, 1171.

(25) Bhat, V.; Dixit, V. M.; Ugarker, B. G.; Trozzolo, A. M.; George, M. V. *J. Org. Chem.* **1979**, *44*, 2957.

(26) Butler, R. N.; Hanniffy, J. M.; Stephens, J. C.; Burke, L. A. *J. Org. Chem.* **2008**, *73*, 1354.

(27) Siegrist, A. E. *Helv. Chim. Acta* **1967**, *50*, 906.

(28) Barr, J. J.; Storr, R. C. *J. Chem. Soc., Perkin Trans. 1* **1979**, 185.