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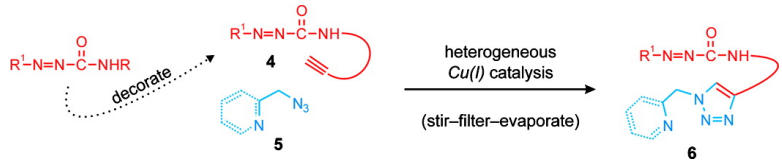

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Concise and Diversity-Oriented Synthesis of Ligand Arm-Functionalized Azoamides

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Azoamides, previously established as bioactive intracellular GSH-depleting agents, were decorated with a terminal alkyne moiety to **4** and then were transformed, by copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC), into different ligand-arm functionalized azoamides **6**. Azides **5** having ligand-arms amenable for binding to platinum(II) were selected for this study. Because, for the fragile azoamides **4**, the typically employed reaction conditions for CuAAC failed, several alternative solvents and copper catalysts were tested. Excellent results were obtained with copper(II) sulfate pentahydrate/metallic copper and especially with heterogeneous catalysts, such as copper-in-charcoal, cupric oxide, and cuprous oxide. The heterogeneous catalysts were employed to obtain the desired products in almost quantitative yields by a simple three-step "stir−filter−evaporate" protocol with no or negligible contamination with copper impurities. This is of particular importance because compounds **6** have been designed for coordination.

Introduction

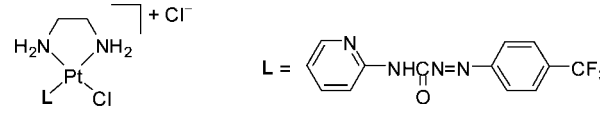
We have demonstrated that azoamides oxidize thiols to the corresponding disulfides.[1] The oxidative properties of azoamides can be finely tuned through the choice of groups attached directly to the diazene −N=N− moiety (R^1, Table 1), which is especially important if they are designed to target intracellular thiols such as glutathione (GSH). GSH constitutes one of the main cellular defenses in tumor cells against platinum anticancer drugs (e.g., cisplatin), and through binding to platinum, it causes the resistance that the tumors acquire after the initial treatment.[2] This indicated that in a combined azoamide−cisplatin treatment, the GSH-depleting azoamides should lead to the reversal of the acquired resistances. Indeed, when tested on different tumor-cell lines, azoamides have been shown to decrease the intracellular GSH concentration and thus inhibit their growth.[3] They reduced the survival of some cisplatin-resistant sublines and, in combined treatments, exhibited a synergistic effect with cisplatin. In this connection, we recently prepared complex [PtCl(en)(**L**)]Cl (Figure 1, en=ethylenediamine), in which the azoamide ligand **L** was coordinated to Pt(II) through the pyridine nitrogen atom.[4] This hybrid molecule with a dual mode of action combined advantages of azoamides and chloroplatinum(II) structural motif, exhibiting higher cytotoxicity against T24 bladder carcinoma cells in comparison to the parent [PtCl(dimethyl sulfoxide)(en)]Cl, for example.[4]

The above-mentioned success encouraged us to screen an array of platinum complexes with azoamide carrier groups. The preparation of ligand **L**, however, is a multistep process and any structural modification would require repeating the lengthy reaction sequences. Thus, we decided to search for a quick and practical methodology that would potentially afford a diverse library of azoamides having specific oxidative properties and being functionalized with appropriate ligand-arms for coordination to platinum in different modes.[5]

Results and Discussion

The most efficient route to the azoamides is the addition of hydrazines to isocyanates,[6] with the subsequent oxidation of the semicarbazides.[1,7] Although both azoamides and semicarbazides are relatively stable and quite indifferent to solvents and pH, these may not be prone to more rigorous reaction conditions and reagents, potentially required if one desires to install or modify the ligand-arm in one of the later steps of the preparative sequence. Recently, the groups of Meldal and Sharpless developed a copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC).[8] Because this "click" reaction has been well documented for its remarkably mild reaction conditions, broad scope, and exquisite selectivity,[9] we envisioned that it has all of the necessary features to become a conjugation method for the synthesis of ligand-arm substituted azoamides **6** (Table 2). In combination with the promising chemistry, the 1,2,3-triazole connection bridge in **6** seemed to be the linker of choice between the azoamide and the ligand arm (R^2) because of its thermal, hydrolytical, and metabolical stability, at least for the purpose of an initial screening for a potential lead compound.

Alkyne-Functionalized Azoamides. The alkyne-functionalized azoamides **4** (Table 1), selected for this study were



[PtCl(en)(**L**)]Cl

Figure 1. Structure of [PtCl(en)(L)]Cl.

* To whom correspondence should be addressed. E-mail: janez.kosmrlj@fkkt.uni-lj.si.

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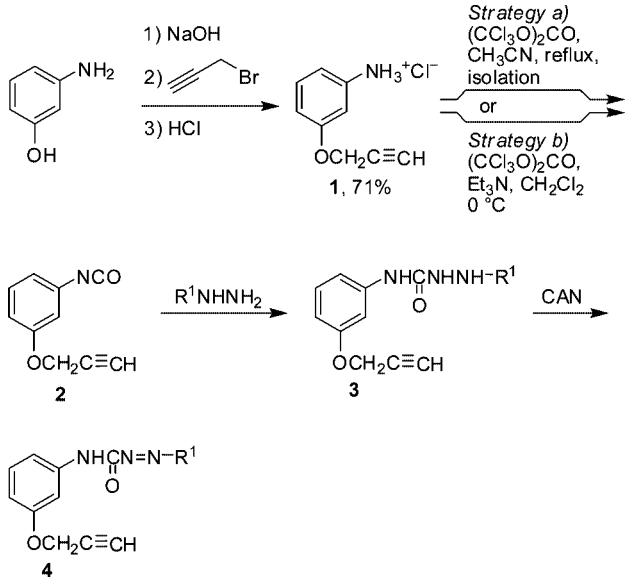
Table 1. Synthesis of Alkyne-Functionalized Azoamides **4**



entry	R^1	**3**, yield (%)[a]	**4**, yield (%)[a,b]
1	4-CF_3-C_6H_4−	**3a**, 94[c]	**4a**, 96
2	4-CF_3-C_6H_4−	**3a**, 77[d]	
3	C_6F_5−	**3b**, 98[c]	**4b**, 85
4	C_6F_5−	**3b**, 80[d]	
5	4-CH_3-C_6H_4−	**3c**, 54[c]	**4c**, 95
6	4-CH_3-C_6H_4−	**3c**, 80[d]	
7	4-Cl-C_6H_4−	**3d**, 78[c]	**4d**, 94
8	4-NO_2-C_6H_4−	**3e**, 79[c]	**4e**, 97
9	4-CH_3O-C_6H_4−	**3f**, 40[c,e]	**4f**, 86

[a] Yields of isolated pure products. [b] From **3**. [c] Over two steps from **1** (strategy b). [d] From **2** (strategy a). [e] **3f′** was also isolated in 21% yield.

easily prepared starting from 3-aminophenol. The phenolate ion generated from 3-aminophenol and sodium hydroxide was allowed to react with propargyl bromide to give oily 3-(prop-2-ynyloxy)aniline. Because this compound turned out to be unstable, it was transformed into its hydrochloride **1** for purification and storage purposes.

For the preparation of 3-(prop-2-ynyloxy)phenyl isocyanate **2** in the next step, we selected the reaction with triphosgene.[10] Two strategies were considered: (a) preparation and isolation and (b) in situ generation (Table 1). For strategy a compound **1** was refluxed with triphosgene in acetonitrile without additives.[11] Volatiles were removed by evaporation, and isocyanate **2** was isolated in 44−55% yield (several consecutive experiments at 2−170 mmol scales) by vacuum distillation. For strategy b, isocyanate **2** was prepared in dichloromethane using triethylamine as a base, at 0 °C and was used immediately in the next step without isolation.

Isocyanate **2**, either isolated or prepared in situ, was in the next step let to react with hydrazines (R^1NHNH_2) into the corresponding semicarbazides **3** (Table 1). The selection of R^1 at the hydrazines was made to test different electron-withdrawing and -releasing groups and, importantly, on the basis of our previous findings in which prop-2-ynyloxy-unsubstituted analogues of **4** proved to have promising bioactivities.[3,4] Although it was experimentally more practical to prepare and use a stock of isocyanate **2**, strategy b turned out to be more efficient in terms of the overall yields of semicarbazides **3** from aniline **1** (compare entries 1 and 2, 3 and 4, 5 and 6). The moderate yield of **3f** was caused by the formation of undesired 1,3-disubstituted semicarbazide **3f′** (21%, Table 1, entry 9, Figure 2).[12]

Semicarbazides **3** were oxidized with CAN in methanol to azoamides **4** (Table 1). A simple extractive workup afforded the products in excellent yields with more than 95% purity, as determined by ^{1}H NMR.

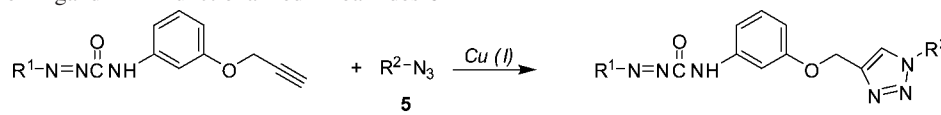
Azides. The syntheses of azides **5a**−**d** (Figure 3), having different ligand arms R^2 known for their potential ability to coordinate platinum(II), were based on literature precedents. These were easily accessible from halogenides by halogen substitution with sodium azide (**5a**, **b**, **d**) or from amines by the diazo-transfer reaction (**5c**). Azides **5a**[13] and **5d**[14] have already been used as click components.

Ligand-Arm Functionalized Azoamides. To test the conjugation strategy from Table 2, we initially conducted a set of experiments with **4a** and **5a** employing various reaction conditions. We introduced Cu(I) from $(CF_3SO_3Cu)_2 \cdot C_6H_6$ either without additives or in combination with Cu(I)-stabilizing *tris*-(benzyltriazolylmethyl)amine (TBTA).[15] Although the Cu(I) required for the CuAAC reaction has often been conveniently generated by the in situ reduction of Cu(II) with sodium ascorbate,[9] for the synthesis of **6a**, this was not appropriate because ascorbate reduces the azoamide to the semicarbazide. Different mixtures of water and alcohols (*t*-BuOH, *i*-PrOH, EtOH, MeOH), commonly used for this transformation, were screened as reaction solvents. Unfortunately, all of the combinations tested were unsuccessful, resulting in long reaction times of as much as a week and yielding substantial amounts of undefined side products. The reactants usually turned into a gummy material that stuck to the reaction vessel and the magnetic stirring bar, thus preventing the reaction from going to completion. The catalyst was also found to be very sensitive to air, even in the presence of TBTA. In combination, these issues resulted in irreproducible experiments in terms of the reaction time and yield of **6a**. Other acetylene (**4a**−**f**)/azide (**5a**−**d**) combinations that were tested failed similarly.

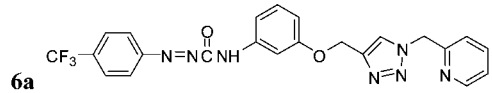
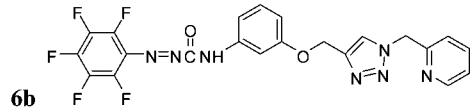
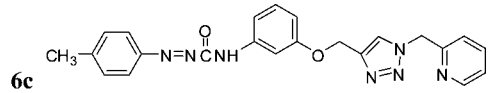
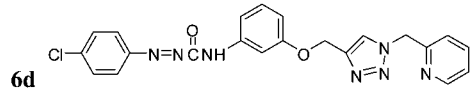
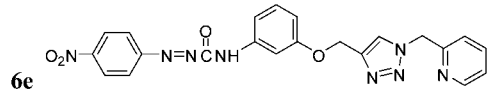
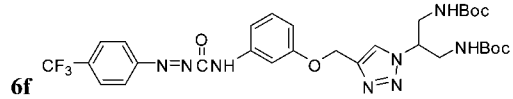
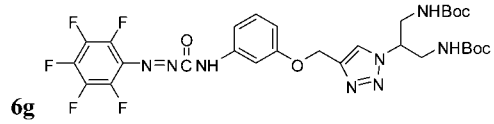
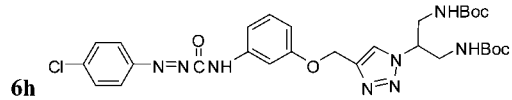
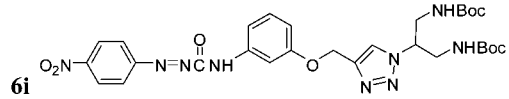
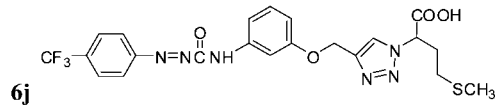
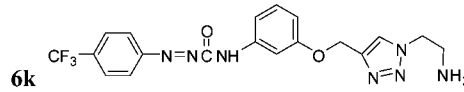
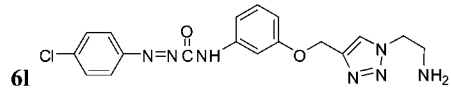
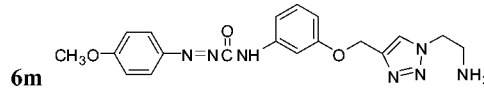
Considering the above results, we changed the reaction solvent to dimethyl sulfoxide (DMSO) and the source of Cu(I) to $CuSO_4 \cdot 5H_2O$/metallic copper,[16] which should provide good solubility of the reactants, and a constant source of Cu(I). We were delighted to find that the reaction of **4a** with an equimolar amount of **5a** was completed within 40 min (Table 2, entry 1). No exclusion of aerial oxygen was required. An extractive workup with saturated aqueous ammonium chloride and dichloromethane furnished the pure product **6a** in a 95% yield. The ammonium chloride workup was found to be effective in extracting copper ions from the product, which is of particular importance because compounds **6** are designed for coordination and could potentially be contaminated with a substantial amount of copper. Crude **6a** contained 45 ppm of copper, as determined by atomic absorption spectroscopy (AAS). It should be noted that the results were reproducible in several consecutive experiments. Metallic copper was recovered and reused. As shown in Table 2, the above protocol was also highly successful in the cycloadditions of other alkynes **4** with azides **5**.

Recently, copper-in-charcoal (Cu/C) has been described as a simple, inexpensive, robust, and efficient heterogeneous

Table 2. Synthesis of Ligand-Arm Functionalized Azoamides **6**[a]



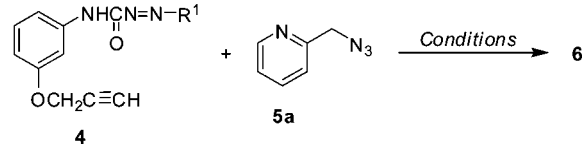
4 **5** **6**

Entry	Alkyne	Azide	mol % $CuSO_4 \cdot 5H_2O$	Reaction time	Product **6**	Yield (%)[b]
1	**4a**	**5a**	11	40 min	 **6a**	95
2	**4b**	**5a**	19	30 min	 **6b**	97
3	**4c**	**5a**	10	40 min	 **6c**	73
4	**4d**	**5a**	20	30 min	 **6d**	87
5	**4e**	**5a**	19	15 min	 **6e**	90
6	**4a**	**5b**	11	5 h	 **6f**	97
7	**4b**	**5b**	19	2 h	 **6g**	76
8	**4d**	**5b**	9	6 h	 **6h**	96
9	**4e**	**5b**	10	1 h	 **6i**	96
10	**4a**	**5c**	19	2 h	 **6j**	93
11	**4a**	**5d**	11	30 min	 **6k**	74
12	**4d**	**5d**	5	10 min	 **6l**	95
13	**4f**	**5d**	12	5 min	 **6m**	87

[a] Reaction conditions: **4**, **5** (1.00−1.05 equiv), $CuSO_4 \cdot 5H_2O$, granular copper (3.8 equiv), DMSO (2 mL/mmol of **4**), air, room temp. [b] Yields of isolated pure products.

catalyst for CuAAC.[17] For our purposes, this catalyst seemed to be an attractive alternative from the following two reasons. The catalyst requires no reducing agent for CuAAC reactions, and no or negligible leaching of copper from a charcoal matrix into the reaction solvent was expected, which should substantially simplify the isolation of ligand-arm functionalized azoamides **6**. In a test reaction, mixing alkyne **4a** with an equimolar amount of azide **5a** in DMSO-d_6 at room temperature in the presence of 20 mol % Cu/C and 0.8 equiv of triethylamine, the cycloaddition was completed within 10 min. The catalyst was filtered off, and ^{1}H NMR spectrum was recorded, which indicated complete consumption of starting compounds and pure product **6a** (Table 3, entry 1). No reaction was observed in the absence of triethylamine

Table 3. Heterogeneous CuAAC of Alkynes **4** and Azide **5a**[a]



entry	alkyne	aditive (equiv)	time	**6**, yield (%)[b]
		catalyst: Cu/C (0.2 equiv)		
1	**4a**	Et_3N(0.8)	10 min[c]	**6a**, 100[d]
2	**4a**	none	24 h[c]	−[e]
3	**4a**	Et_3N(0.8)	30 min	**6a**, 90
4	**4c**	Et_3N(0.8)	30 min	**6c**, 98
5	**4d**	Et_3N(0.8)	30 min	**6d**, 97
		catalyst: CuO[f]		
6	**4a**	Et_3N(0.8)	7 h	**6a**, 99
7	**4c**	Et_3N(0.8)	5 h	**6c**, 99
8	**4d**	none	15 h	**6d**, 98
9	**4d**	Et_3N(0.8)	5 h	**6d**, 99
10	**4e**	Et_3N(0.8)	24	**6e**, 72
		catalyst: Cu_2O[g]		
11	**4a**	Et_3N(0.8)	5 h	**6a**, 92
12	**4a**	Et_3N(0.8)	20 h[h]	**6a**, 98
13	**4c**	Et_3N(0.8)	3 h	**6c**, 98
14	**4d**	none	10 h	**6d**, 99
15	**4d**	Et_3N(0.8)	8 h	**6d**, 99
16	**4e**	Et_3N(0.8)	24	**6e**, 80

[a] Reaction conditions: **4** (0.1 mmol), **5** (1.03 equiv), catalyst, additive, MeOH (0.5 mL), air, room temp. [b] Yields of isolated crude products, >95% pure as determined by ^{1}H NMR. [c] DMSO-d_6 was used as a reaction solvent. [d] Quantitative conversion, as determined by ^{1}H NMR. [e] No reaction. [f] 28 mg of CuO was used. [g] 50 mg of Cu_2O was used. [h] 5 mg of Cu_2O was used.

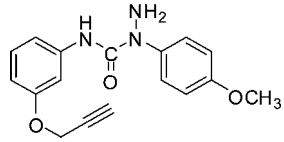


Figure 2. 1,3-Disubstituted semicarbazide **3f′**.

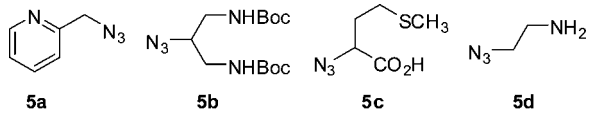


Figure 3. Azides **5** (R^2-N_3).

(entry 2). Screening again for a greener solvent, we were delighted to find out that the reactions could efficiently be conducted in methanol. In all the experiments from Table 3, entries 3−5, the isolation of products **6** was achieved by simple filtration and solvent evaporation. As judged by ^{1}H NMR spectra, crude products were over 95% pure, whereas the absence of any line-shape broadening indicated no or negligible contamination with paramagnetic copper impurities.

In the search for a commercial heterogeneous copper catalyst, cupric oxide and cuprous oxide were next examined. As demonstrated in Table 3, entries 6−16, clean reactions and simple isolation with nearly quantitative isolated yields of pure products **6** (analogous to those prepared by Cu/C protocol) qualified the above two catalysts. Longer reaction times and slightly lower yields in the case of **6e** were associated with low solubility of the nitro-substituted alkyne **4e** in the reaction medium (entries 10, 16). Although the CuAAC took place without additives, the rates of the reactions could be accelerated by the addition of triethylamine (compare entries 8 with 9 and 14 with 15). Different catalyst loadings were also examined (compare entries 11 and 12); however, the actual catalyst loading for the heterogeneous catalysts, such as pure cupric oxide and cuprous oxide, depends on several factors including the catalytically active species and surface area. No attempts of the actual catalyst loadings in these cases were made at this point of the research. On the basis of preliminary experiments, the cupric oxide and cuprous oxide, as well as the copper-in-charcoal, used for the synthesis of triazoles **6** could potentially be recovered and reused. Our results are in contrast to the recent literature, reporting that cuprous oxide showed very low activity for CuAAC, whereas cupric oxide was inactive.[18]

All CuAAC reactions under this investigation were completely regioselective, as judged by the ^{1}H NMR of the crude reaction products. The 1,4-disubstitution at the 1,2,3-triazoles **6** was confirmed by NOE between H-5^{triazole} and the nearby protons of R^2 groups.

Conclusion

A modular entry enabling the preparation of diverse ligand arm-functionalized azoamides **6** is presented. The key step is based on click chemistry between fragile alkyne-azoamides **4** and azides **5**. Because, in these reactions, typical Sharpless conditions failed, several alternative solvents and copper catalysts were examined. Excellent results were obtained using copper(II) sulfate pentahydrate/metallic copper, whereas truly a practical reaction protocol involved heterogeneous catalysts copper-in-charcoal, and commercial cupric oxide and cuprous oxide. While the reactions with copper-in-charcoal required a basic additive, this was not necessary for efficient catalysis with cupric oxide and cuprous oxide. Using heterogeneous catalysts, we achieved the isolation of pure products **6** by simple filtration and solvent evaporation. The results suggested no or negligible contamination of products with copper, which is particularly important because compounds **6** have been designed for coordination. Scope and limitations of cupric oxide and cuprous oxide as catalysts for CuAAC will be investigated. We believe these could find broader application, especially in automated combinatorial chemistry. Employing suitable ligand arms, we will explore azoamides **6** as potential bioactive ligands in novel cisplatin analogues, hybrid molecules with a potential dual mode of action in anticancer treatment.

Experimental Section

General Considerations. General procedures are presented in detail in the Supporting Information. **Caution:** *The handling of azides is dangerous because of their potentially explosive character. Although, in our hands, azides* **5a−d** *did not appear to be shock sensitive, the compounds should be handled with great care. Neat azides must not be heated or distilled, and all reactions should be carried out on a small scale. The use of a safety shield is highly recommended.*

Typical Procedure for the Synthesis of Triazoles 6 Using $CuSO_4 \cdot 5H_2O$/Cu(0) (Table 2). A mixture of an appropriate azoamide **4** (0.25 mmol), azide **5** (0.25−0.26 mmol), $CuSO_4 \cdot 5H_2O$ (3.1−12.5 mg, 5−20 mol %, Table 2), and granular copper (60 mg, 0.94 mmol, 3.8 equiv) in DMSO (0.5 mL) was stirred for the time indicated in Table 2. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and filtered, and the filtrate was washed with saturated aq. NH_4Cl (2 × 30

mL) and brine (10 mL). Each time the product was back-extracted from the water layers with few milliliters of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent of the filtrate was removed in vacuo to give pure **6**, as determined by ^{1}H NMR (in some instances the only impurity was a small amount of DMSO, which could easily be removed by column chromatography on silica gel or recrystallization). This procedure was applied for the synthesis of **6a**−**m**. For **6j**, **l**, and **m**, a modified isolation procedure[12] afforded higher yields of the products.

General Procedure for the Synthesis of Triazoles 6a, c−e using Cu/C, CuO, or Cu_2O (Table 3). A scintillation vial was equipped with a stirring bar and charged with an appropriate azoamide **4** (0.10 mmol) and an appropriate catalyst (Table 3). A stock solution of 2-(azidomethyl)pyridine (**5a**) in MeOH (0.5 mL, 0.21 mM, 0.105 mmol) was added, followed by triethylamine (8.0 mg, 0.08 mmol) where appropriate (Table 3). The reaction mixture was stirred in the presence of air for the time indicated in Table 3, diluted with MeOH (1 mL), and filtered through a pad of Celite. The vial and Celite pad were rinsed with MeOH, and the filtrate was evaporated to dryness to give pure triazole **6**, as determined by ^{1}H NMR.

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Note Added after ASAP Publication. Due to a production error, the name of the first author in references 1 and 7 was spelled incorrectly; the corrected version published ASAP October 18, 2008.

Supporting Information Available. Experimental procedures for all the reactions and characterization data for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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