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Polytriazoles as Copper(I)-Stabilizing Ligands in Catalysis

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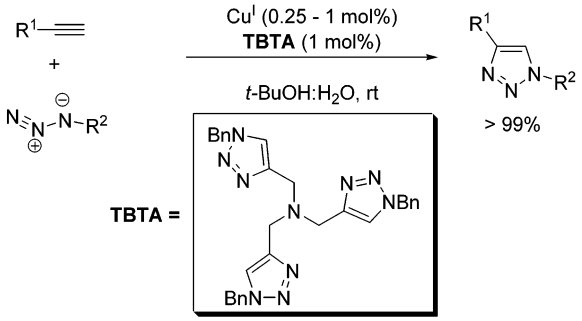
ABSTRACT



Polytriazolylamines were synthesized by the copper(I)-catalyzed ligation of azides and alkynes. The C_3-symmetric derivative, TBTA, was shown to be a powerful stabilizing ligand for copper(I), protecting it from oxidation and disproportionation, while enhancing its catalytic activity.

Copper(I) plays vital roles in chemistry[1] and biology.[2] In synthesis, it is widely used in a variety of organic transformations such as Ullmann,[3] Cadiot−Chodkiewicz,[4] and Sonogashira[5] coupling reactions and asymmetric cyclopropanations[6] to name a few. In nature, it is found in several essential metabolic enzymes that are responsible for key electrolytic redox processes involving Cu^{III}/Cu^{I} couple and for absorption and reduction of O_2.

The general thermodynamic instability of Cu^{I}, which results in its easy oxidation[7] to Cu^{II} and/or disproportionation[8] to Cu^{0} and Cu^{II}, imposes strict requirements on experimental conditions when copper(I)-mediated processes are used in the laboratory. Therefore, inert atmospheres and anhydrous solvents are usually employed. Although much has been learned about natural copper(I) environments in copper(I)-containing proteins,[9] attempts to mimic their exquisite selectivity and reactivity in the laboratory have largely relied upon supporting Cu^{I} with soft ligands such as nitriles, guanidines, imines, thiols, and halides. Unfortunately, these are either too labile and, therefore, compromise the redox stability of the metal (e.g., halides and amines), or, at the other extreme, are such strong binders that any catalytic activity of the copper center is completely suppressed (e.g., nitriles).

Our ongoing interest in developing supremely reliable reactions that are useful in both chemistry and biology prompted us to revisit the Huisgen 1,3-dipolar cycloaddition of azides and alkynes. The uniquely narrow reactivity profiles of the reactants make them ideal probes for investigation of complex biological systems. For example, we successfully

(1) Hathaway, B. J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1987; Vol. 5, pp 534−774. Krause, N., Ed. *Modern Organocopper Chemistry*; Wiley-VCH: Weinheim, 2002.

(2) Sigel, H., Ed. *Metal Ions in Biological Systems*; Dekker: New York, 1981; Vols. 12 and 13.

(3) Ullmann, F. *Liebigs Ann. Chem.* **1904**, *332*, 38.

(4) Cadiot, P.; Chokiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Dekker: New York, 1969; pp 597−647.

(5) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(6) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005.

(7) Simmons, M. G. et al. *J. Chem. Soc., Dalton Trans.* **1980**, 1827. Merrill, C. L. et al. *J. Chem. Soc., Dalton Trans.* **1984**, 2207.

(8) Ciavatta, L.; Ferri, D.; Palombari, R. *J. Inorg. Nucl. Chem.* **1983**, *23*, 1201.

(9) For recent examples see Rondelez, Y.; Bertho, G.; Reinaud, O. *Angew. Chem., Int. Ed.* **2002**, *41* (6), 1044. Rondelez, Y.; Rager, M.-N.; Duprat, A.; Reinaud, O. *J. Am. Chem. Soc.* **2002**, *124*, 1334.

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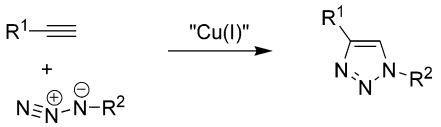
used them in the target-guided synthesis of the most potent inhibitor of acteylcholinesterase.[10] Ironically, the low reactivity of the azides and alkynes, which was essential for the success of this project, proved to be a severe handicap when a series of analogues for further studies were required. We were, therefore, pleased to have developed a new copper(I)-catalyzed regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles from azides and terminal alkynes (Scheme 1).[11] Exceptional scope, exclusive regioselectivity, and

Scheme 1. Copper(I)-Catalyzed Synthesis of 1,2,3-Triazoles



experimental simplicity have naturally placed this process among the "cream of the crop" for click chemistry endeavors.[12]

Early mechanistic investigations of this process revealed that the reaction rates of certain polyvalent substrates were unusually high, and these reactions appeared to be autocatalytic. Hence, we hypothesized that the resulting polytriazole products may serve as rate-accelerating ligands for copper(I). To our surprise, a survey of the literature revealed that [1,2,3]-triazoles have not been exploited as ligands in transition metal catalysis (perhaps, due to the lack of good methods for their synthesis). Equipped with a simple and reliable process for preparation of [1,2,3]-triazoles of diverse structure and function, we initiated a program to explore their metal binding and catalytic properties. Herein, we report the results of the studies of such ligands in the copper(I)-catalyzed formation of triazoles, the very reaction that enabled their synthesis in the first place.

The ligands were tested using a model reaction between phenylacetylene (**1**) and benzyl azide (**2**). Typically, the reaction was performed with 1−2 mol % copper(II) sulfate and 10 mol % sodium ascorbate. The latter serves as a water-soluble in situ reducing agent to generate and maintain necessary concentration of catalytically active copper(I), thereby eliminating the need for inert atmospheres and solvents and allowing isolation of the product triazoles as pure materials. To challenge our ligands, limited amounts of both copper(II) and the reducing agent were used. The reactions were carried out in a 2:1 *tert*-butyl alcohol/water solution with no effort to exclude oxygen beyond capping the vial. Several selected examples are shown in Table 1. Analogues of the promising hits were subsequently synthesized and screened to gather insight into the possible activity and mechanism of their action.

Although the early leads were far away from an ideal ligand that would keep Cu^{I} catalytically active without the need for any reducing agent and protection from oxygen, they provided a good starting point for a more rigorous screen, which employed only 1.0 mol % of the tested additive and 1.0 mol % of a copper(I) source with no reducing agent. Interestingly, the best performing ligands all share a similar structural motif: they are oligotriazole derivatives derived from propargylamine cores. This new class of ligands is capable of binding to metals by forming a five-member chelate between the N-3 of the triazole and the amine.

From various ligands shown in Table 2, one clearly stands apart in all respects: *tris*-(benzyltriazolylmethyl)amine, TBTA (entry 4).[13,14] It's tetradentate binding ability is believed to completely envelope the copper(I) center, leaving no free binding sites available for potential destabilizing interactions.[15] The tertiary amine and the [1,2,3]-triazole functionalities likely work in concert to make TBTA so efficient: the former, more basic, and sterically encumbered nitrogen, accelerates the catalysis by providing additional electron density on the metal center, while the latter, being more labile, comes off the copper center only temporarily to allow the formation of the copper(I)-acetylide/ligand complex, which is then carried through the catalytic cycle.[11a]

Cyclic voltammetry studies of this new class of ligands showed a dramatic increase in the redox potential of Cu(I)/Cu(II) by almost 300 mV (see Supporting Information), thus further supporting the proposed mode of action of these ligands.

The results of this investigation have shown that these novel oligotriazole ligands are competent in protecting copper(I) under aerobic aqueous conditions and promoting copper(I)-catalyzed transformations. The ligands appear to tightly bind to copper(I), thereby stabilizing this oxidation state of the metal, as confirmed by cyclic voltammetry. The modularity and ease of synthesis of polytriazole ligands allow rapid exploration of analogues with specifically tuned properties. TBTA has already been successfully applied in

(10) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053.

(11) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3062.

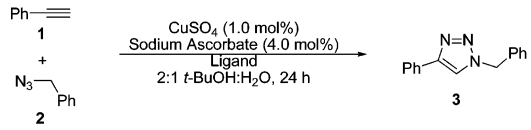
(12) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192−3193. Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686−4687. Fazio, F.; Bryan, M. C.; Blixt, O.; Paulson, J. C.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 14397−14402. Link, A. J.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 11164−11165. Deiters, A.; Cropp, T. A.; Mukherji, M.; Chin, J. W.; Anderson, J. C.; Schultz, P. G. *J. Am. Chem. Soc.* **2003**, *125*, 11782−11783. Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.

(13) While bis-triazoles from entries 2 and 3 show a stronger ligand-accelerating effect, they are not as potent in protecting the copper(I) oxidation state. This was also confirmed by further reducing the amount of the copper catalyst to 0.25 mol %. TBTA clearly outperformed all other ligands.

(14) Tripropargylamine (13.2 g; 0.1 mol) in acetonitrile (150 mL) was treated sequentially with benzyl azide (59.90 g, 0.45 mol), 2,6-lutidine (10.7 g, 0.1 mol), and $Cu(MeCN)_4PF_6$ (1.3 mol % with respect to total alkyne units). Upon addition of the copper salt, the reaction warmed and was cooled in an ice bath. After the mixture was stirred at room temperature for 3 days, a white crystalline solid precipitated from the reaction. Filtration and washing with cold acetonitrile afforded fine, white, needlelike crystals (44.9 g, 84%). Mp: 138−139 °C. ^{1}H NMR ($CDCl_3$): δ 3.70 (s, 6 H, N-CH_2-triazole), 5.49 (s, 6 H, $PhCH_2$), 7.26 (m, 6 H), 7.34 (m, 9 H), 7.67 (s, 3H, triazole). ^{13}C NMR ($CDCl_3$): δ 134.7, 129.1, 128.7, 128.0, 123.8, 54.1, 47.0. ES-MS: (*m*/*z*) 531 (MH^+). Anal. Calcd for $C_{30}H_{30}N_{10}$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.71; H, 5.73; N, 26.32. Analytically pure sample could be obtained by recrystallization of 1.00 g of TBTA from a hot 1:1 *tert*-butyl alcohol/water solution (40 mL), followed by filtration and washing with water (2 × 20 mL). The white needlelike crystals were dried under high vacuum overnight. Yield: 0.86 g, 86%.

(15) Similar mode of binding has been previously suggested for tris-oxazoline-based ligands. See: Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 3941.

Table 1. Effect of Ligands on the Copper(I)-Catalyzed Synthesis of [1,2,3]-Triazoles



	ligand	loading, mol%	yield,[a] %
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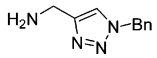
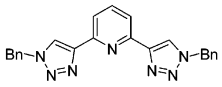
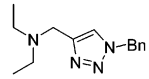
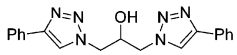
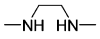
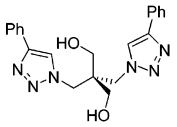
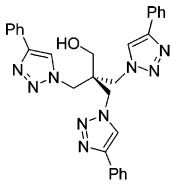
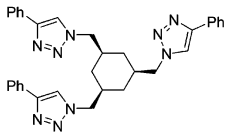
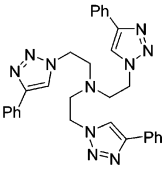
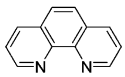
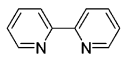
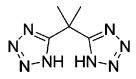
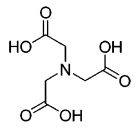
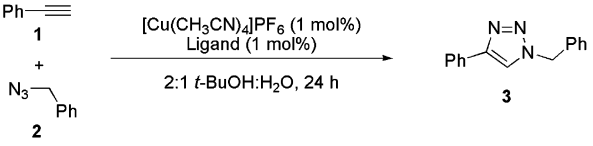
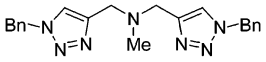
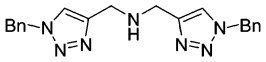
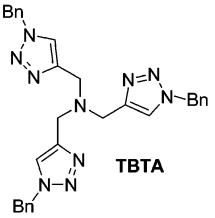
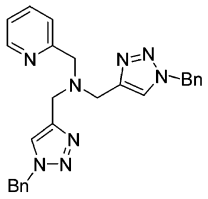
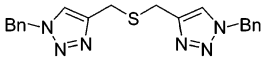
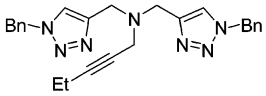
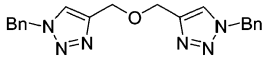
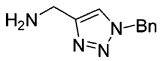
2		10	99
3		10	72
4		10	64
5		10	51
6		8	41
7		10	39
8		1	29
9		6	29
10		10	28
11		10	12
12	Et_3N	10	11
13		10	7
14		10	0
15		10[b]	0

[a] Determined by GC after 24 h and, in select cases, confirmed by product isolation. [b] Neutralized with 3 equiv of $NaHCO_3$.

Table 2. Triazoles as Stabilizing Ligands for Copper(I)



	ligand	yield,[a] %
1	none	1
2		98
3		94
4	 TBTA	84
5		39
6		28
7		21
8		17
9		4

[a] Determined by GC after 24 h and, in select cases, confirmed by product isolation.

several demanding bioconjugation studies.[12] Exploration of analogous ligands, for example, based on phosphines, is currently underway, as are further mechanistic studies and development of other applications.

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Supporting Information Available: Details of cyclic voltammetry studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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