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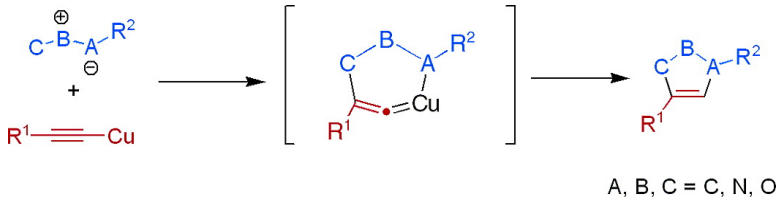

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Copper(I)-Catalyzed Synthesis of Azoles. DFT Study Predicts Unprecedented Reactivity and Intermediates

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Abstract: Huisgen's 1,3-dipolar cycloadditions become nonconcerted when copper(I) acetylides react with azides and nitrile oxides, providing ready access to 1,4-disubstituted 1,2,3-triazoles and 3,4-disubstituted isoxazoles, respectively. The process is highly reliable and exhibits an unusually wide scope with respect to both components. Computational studies revealed a stepwise mechanism involving unprecedented metallacycle intermediates, which appear to be common for a variety of dipoles.

Introduction

The copper(I)-catalyzed union of terminal alkynes and organic azides to give 1,4-disubstituted 1,2,3-triazoles[1] exhibits remarkably broad scope and exquisite selectivity. The best click reaction[2] to date, it quickly found applications in chemistry, biology, and materials science. It has enabled demanding bioconjugations involving 60 steps (with >99.8% yield per step)[3] and has been used in activity-based protein profiling (ABPP) of crude proteome homogenates,[4] for selective labeling of modified bacterial cell walls,[5] and in the synthesis of novel biologically active compounds[6] and materials.[7]

The reaction performs best in aqueous systems (including serum and whole blood[8]), succeeds over a broad temperature range (0−160 °C), is remarkably insensitive to pH (at least over the range from ca. 4 to 12), and has succeeded in the presence of all functional groups tested to date. Redox interference, most likely from the oxidation side, is easily managed.[1a] In summary, overall features of this catalytic system seem difficult to rationalize on the basis of known precedents in catalysis, biological or abiological.

Thinking up mechanistic schemes that might explain such a robust process is an interesting but daunting challenge. While most "incredible" reactivity findings remain just that, on the rare occasion that important and unprecedented reactivity is proven bona fide, it is likely to represent the signature of a new intermediate and/or a pathway. This seems to be the case at hand, as proven by the fact that this regiospecific stepwise sequence is not limited to azides, but works as well with other dipoles, such as nitrile oxides (Scheme 1).

Experimental Section

Unless stated otherwise, all reagents and solvents were purchased from commercial suppliers and were used without further purification.

Copper(I)-Catalyzed Synthesis of 1,4-Disubstituted 1,2,3-Triazoles. General Procedure A, with a Reducing Agent, As Exemplified for the Synthesis of 2*S*-17-[1-(2,3-Dihydroxypropyl)-1*H*-[1,2,3]-triazol-4-yl]-estradiol. 17-Ethynyl estradiol (888 mg, 3 mmol) and (*S*)-3-azidopropane-1,2-diol (352 mg, 3 mmol) were suspended in 12 mL of a 1:1 water/*tert*-butanol mixture. Sodium ascorbate (0.3 mmol, 300 μL of freshly prepared 1 M solution in water) was added, followed by copper(II) sulfate pentahydrate (7.5 mg, 0.03 mmol, in 100 μL of water). The heterogeneous mixture was stirred vigorously overnight, at which point it cleared and TLC analysis indicated complete consumption of the reactants. The reaction mixture was diluted with 50 mL of water and cooled in ice, and the white precipitate was collected by filtration. After being washed with cold water (2 × 25 mL), the precipitate was dried under vacuum to afford 1.17 g (94%) of pure product as an off-white powder. mp 228−230 °C. Anal. Calcd: C, 64.02; H, 7.71; N, 9.74. Found: C, 64.06; H, 7.36; N, 9.64. ^{1}H NMR ([d_6]DMSO): δ = 8.97 (s, 1H), 7.77 (s, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.45 (dd, J = 8.3 and 2.3 Hz, 1H), 6.41 (d, J = 2.3 Hz, 1H), 5.13 (m, 1H), 5.09 (d, J = 2.9 Hz, 1H), 4.83 (m, 1H), 4.46 (m, 1H), 4.21 (m, 1H), 3.81 (m, 1H), 3.26 (m, 1H), 2.67 (m, 2H), 2.35 (m, 1H), 2.08 (m, 1H), 1.96 (m, 1H), 1.89−1.77 (m, 5H), 1.63 (m, 1H), 1.48−1.12 (m, 3H), 0.91 (s, 3H), 0.74 (s, 1H). ^{13}C NMR ([d_6]DMSO): δ = 154.8, 153.8, 137.2,

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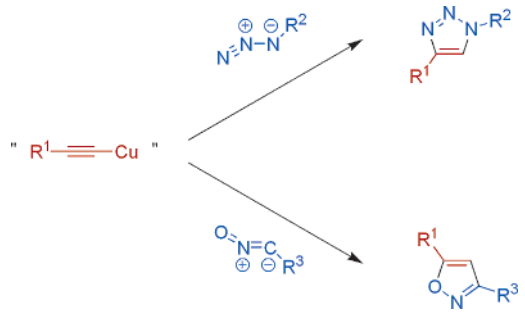
[‡] Department of Chemistry and The Skaggs Institute for Chemical Biology.

(1) (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.
(2) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004. (b) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.
(3) Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192.
(4) (a) Speers, A. E.; Cravatt, B. F. *Chem. Biol.* **2004**, *11*, 535. (b) Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686.
(5) (a) Link, A. J.; Tirrell, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 11164. (b) Deiters, A.; Cropp, T. A.; Mukherji, M.; Chin, J. W.; Anderson, J. C.; Schultz, P. G. *J. Am. Chem. Soc.* **2003**, *125*, 11782−11783.
(6) Lee, L. V.; Mitchell, M. L.; Huang, S.-J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 9588.
(7) (a) 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*, 3928−3932. (b) Díaz, D. D.; Punna, S.; Holzer, P.; McPherson, A. K.; Sharpless, K. B.; Fokin, V. V.; Finn, M. G. *J. Polym. Sci., Part A* **2004**, *42*, 4392−4403.
(8) Fokin, V. V., unpublished.

 10.1021/ja0471525 CCC: $30.25

Scheme 1. Copper-Catalyzed Synthesis of 1,2,3-Triazoles and Isoxazoles



130.4, 126.0, 123.3, 114.9, 112.7, 81.1, 70.6, 70.4, 63.2, 52.6, 47.5, 46.7, 43.2, 37.2, 32.6, 29.3, 27.2, 26.1, 23.6, 14.4.

General Procedure B, with Copper Metal as a Source of Catalytic Species, As Exemplified for 2,2-Bis((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)propane-1,3-diol. Phenylacetylene (2.04 g, 20 mmol) and 2,2-bis(azidomethyl)propane-1,3-diol (1.86 g, 10 mmol) were dissolved in a 1:2 *tert*-butyl alcohol/water mixture (50 mL). About 1 g of copper metal turnings was added, and the reaction mixture was stirred for 24 h, after which time TLC analysis indicated complete consumption of starting materials. Copper was removed, and the white product was filtered off, washed with water, and dried to yield 3.85 g (98%) of pure bis-triazole product. ^{1}H NMR (399 MHz, [d_6]DMSO): $\delta = 3.24$ (d, $^3J_{HH} = 4.8$ Hz, 4H, $-CH_2OH$), 4.50 (s, 4H, $-CH_2-$triazole), 5.09 (t, $^3J_{HH} = 4.8$ Hz, 2H, $-CH_2OH$), 7.33 (pseudo t, $J_{app} = 7.6$ Hz, 2H, *p*-H in triazole$-C_6H_5$), 7.44 (pseudo t, $J_{app} = 7.6$ Hz, 4H, *m*-H in triazole$-C_6H_5$), 7.86 (pseudo d, $J_{app} = 7.6$ Hz, 4H, *o*-H in triazole$-C_6H_5$), 8.51 (s, 2H, triazole H). ^{13}C NMR (99.75 MHz, [δ_6]DMSO): $\delta = 45.45$, 49.76, 59.96, 123.25, 125.23, 127.89, 128.91, 130.67, 146.04. ES-MS *m*/*z* (ion): 391.2 ($M + H^+$), 413.2 ($M + Na^+$). mp 211−212 °C.

Copper(I)-Catalyzed Synthesis of 3,5-Disubstituted Isoxazoles. General Procedure for Preparation of Imidoyl Chlorides. To a suspension of 10 mmol of aldehyde in a 1:1:2 mixture of H_2O/EtOH/ice (10 mL) was added 10 mmol of hydroxylamine hydrochloride, followed by 25 mmol of NaOH (as a 50% solution in water), while keeping the temperature below 30 °C. After being stirred at room temperature for 1 h, the solution was extracted with diethyl ether. The aqueous phase was acidified to pH 6 by adding concentrated HCl while keeping the temperature below 30 °C and extracted with Et_2O. The organic phase was dried over $MgSO_4$, and the solvent was evaporated to give the oxime products in 85−95% yield, which were used directly in the next reaction.

To a solution of 10 mmol of oxime in DMF (10 mL) was added 1.8 mmol of *N*-chlorosuccinimide (NCS) in one portion. (The beginning of the reaction can be detected by a slight increase of the reaction temperature. If the reaction does not start, a small amount of HCl gas can be bubbled through the solution. With the electron-deficient oximes, the reaction mixture is heated to 45 °C.) The remaining 8.2 mmol of NCS was added in small portions while keeping the temperature below 35 °C (below 60 °C for electron-deficient oximes). The mixture was stirred at room temperature for 1 h, poured into water, and extracted with diethyl ether. The organic phase was washed with brine and dried over $MgSO_4$, and the solvent was removed to give the imidoyl chloride products in 70−90% yield. They were used directly without further purification in the next reaction. Aromatic imidoyl chlorides can be stored over a long time without noticeable decomposition. However, most aliphatic imidoyl chlorides should be used soon after preparation to avoid decomposition.

General Procedure for the Synthesis of Isoxazoles from Nitrile Oxides and Alkynes, As Exemplified for 3-(4-Methoxyphenyl)-5-phenylisoxazole. *N*-Hydroxy-4-methoxy-benzenecarboximidoyl chloride (186 mg, 1 mmol) and phenylacetylene (102 mg, 1 mmol) were dissolved in 6 mL of a 1:1 *tert*-BuOH/H_2O mixture. While the mixture was being stirred, sodium ascorbate (1 M solution in water, 100 μL, 10 mol %) was added, followed by copper(II) sulfate pentahydrate (2.7 mg in 100 μL of H_2O, 2 mol %). The reaction mixture was then treated with $KHCO_3$ (4.33 mmol, 433 mg) and left stirring for 1 h at ambient temperature, after which time it was diluted with water, and the solid off-white isoxazole product was filtered off (231 mg, 92%). ^{1}H NMR ($CDCl_3$): $\delta = 3.89$ (s, 3H), 6.78 (s, 1H), 7.00 (m, 2H), 7.47 (m, 3H), 7.82 (m, 4H). ^{13}C NMR ($CDCl_3$): $\delta = 55.4$, 97.3, 114.5, 120.7, 125.8, 127.3, 128.2, 129.0, 130.2, 157.3, 159. 2, 160.6. mp 122 °C.

Computational Details

All geometries and energies presented in this study were computed using the B3LYP[9] density functional theory method as implemented in the Gaussian 98 program package.[10] Geometry optimizations were performed using the triple-ζ plus polarization basis set 6-311G(d,p), followed by single-point energy calculation using the larger basis set 6-311+G(2d,2p). Hessians were calculated at the B3LYP/6-311G(d,p) level of theory.

Solvation energies were added as single-point calculations using the conductor-like solvation model COSMO[11] at the B3LYP/6-311G(d,p) level. In this model, a cavity around the system is surrounded by a polarizable dielectric continuum. The dielectric constant was chosen as the standard value for water, $\epsilon = 80$. Some experiments were performed in acetonitrile, which has a dielectric constant of $\epsilon = 35$. As the solvation energy to a first approximation is proportional to $(1 - {}^3/_{2\epsilon})$ for large ϵ,[12] the water and acetonitrile values give almost identical solvation energies. Because we are mainly interested in relative activation barriers (reactant → transition state), the differences are not significant. All energies presented herein are enthalpies to which solvation energies are added. Zero-point energy (ZPE) effects are included.

The initial computational studies were performed with the simplest reactants, methyl azide (CH_3N_3) (or acetonitrile oxide) and propyne ($CH_3C{\equiv}CH$). The results should, however, be directly applicable to other azides, nitrile oxides, and alkynes.

Results and Discussion

(A) Experimental Evidence. Synthesis of 1,4-Disubstituted 1,2,3-Triazoles. Terminal alkynes and organic azides containing a wide range of functional groups are regiospecifically united to form the corresponding triazole products in excellent yields. Several key features set this transformation apart from most other catalytic processes: (1) it exhibits enormous scope regarding both alkynes and azides, and most functional groups do not need to be protected, (2) it proceeds well in a variety of solvent systems (while water without an organic cosolvent or water/alcohol mixtures have been used most commonly, such solvents as dimethyl sulfoxide, tetrahydrofuran, acetone, dimethylformamide, and acetonitrile have all been used success-

(9) (a) Becke, A. D. *Phys. Rev.* **1988**, *A38*, 3098. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(10) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.
(11) (a) Barone, V.; Cossi, M. *J. Phys. Chem.* **1998**, *102*, 1995. (b) Barone, B.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404.
(12) Orozco, M.; Luque, F. J. *Chem. Rev.* **2000**, *100*, 4187.

Scheme 2. Copper(I)-Catalyzed Synthesis of 1,4-Disubstituted 1,2,3-Triazoles

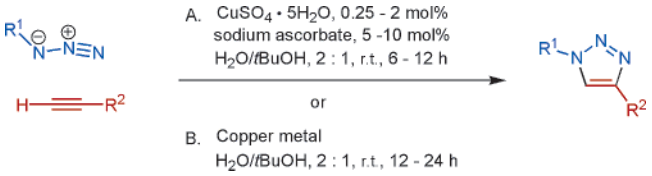
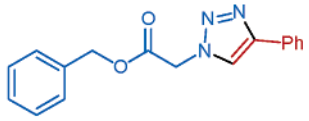
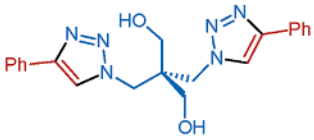
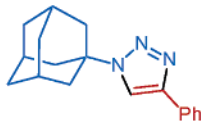
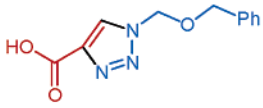
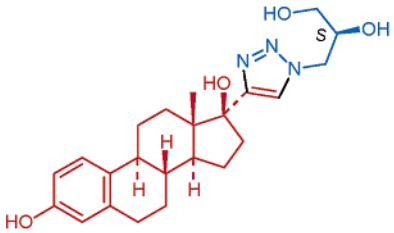
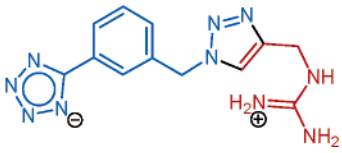


Table 1. 1,4-Disubstituted 1,2,3-Triazoles Prepared by the Cu(I)-Catalyzed Synthesis

Entry	Product	Yield, %
1		92[a]
2		98[b]
3		84[a]
4		88[a]
5		94[a]
6		88[b]

[a] Prepared by general procedure A. [b] Prepared by general procedure B.

fully), (3) it is tolerant of a wide range of pH values (although the optimal pH is usually in the range of 7−9, we have performed the reaction at pH values as low as 4 and as high as 12), (4) it performs equally well over a broad temperature range (as low as 0 °C and as high as 160 °C), and (5) pure products are usually isolated by simple filtration or extraction, without the need for chromatography or recrystallization.

Among several procedures that have been developed in our laboratories, two have emerged as the most convenient and reliable (Scheme 2). Both are performed in aqueous solvent systems at ambient temperature and do not require any special precautions.

Scheme 3. Copper(I)-Catalyzed Synthesis of 3,5-Disubstituted Isoxazoles

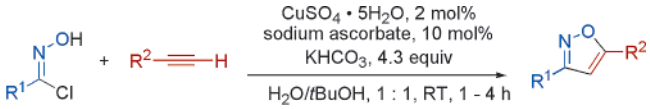
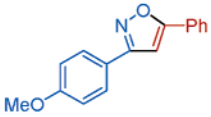
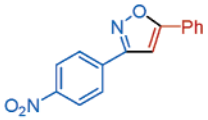
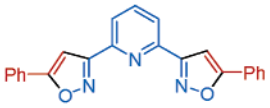
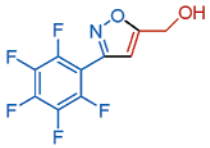
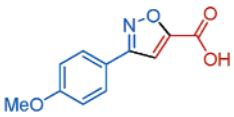
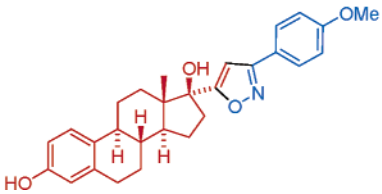


Table 2. 3,5-Disubstituted Isoxazoles Prepared by the Cu(I)-Catalyzed Synthesis

Entry	Product	Yield, %
1		92
2		74
3		83
4		76
5		74[a]
6		98

[a] This reaction was performed with the sodium propiolate; after completion, the reaction mixture was acidified with concentrated HCl and cooled to 0 °C, and the product was filtered off.

In procedure A, the "copper(II)/ascorbate system", the active catalyst is generated in situ from the Cu(II) salts (0.25−2.0 mol %) via reduction with sodium ascorbate or ascorbic acid (5−10 mol %). In addition to generating the catalyst, a slight excess of ascorbate prevents formation of the oxidative coupling products that are often observed when a Cu(I) source is used directly.[1b] In procedure B, the "copper metal system", the catalyst is introduced in the form of the copper wire or shavings. The active Cu(I) catalyst is formed via comproportionation of the Cu(II)/Cu(0) couple.[13] This procedure is especially convenient in parallel synthesis applications or when the substrates do not tolerate ascorbate or its oxidation products.

Selected examples that help to appreciate the scope of this process are presented in Table 1. All products were isolated by

(13) Ciavatta, L.; Ferri, D.; Palombari, R. *J. Inorg. Nucl. Chem.* **1980**, *42*, 593.

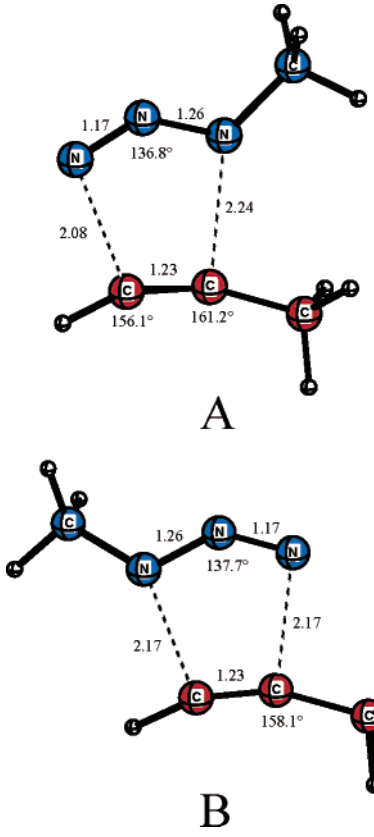


Figure 1. Optimized regioisomeric transition-state structures ((A) 1,5- and (B) 1,4-) for the uncatalyzed thermal cycloaddition reactions of methyl azide and propyne.

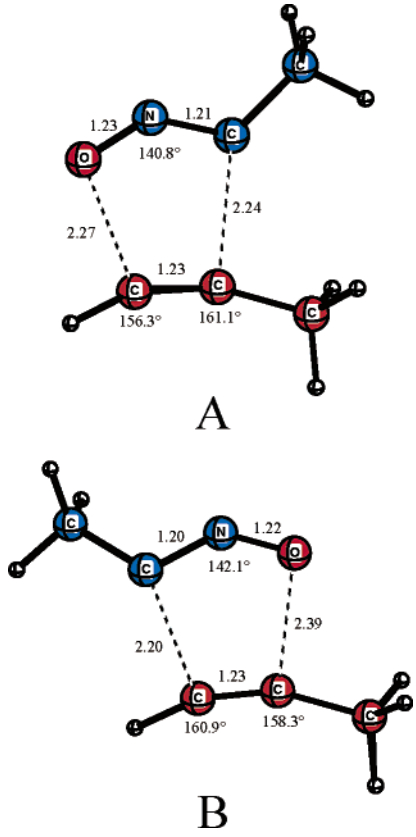


Figure 2. Optimized regioisomeric transition-state structures ((A) 3,4- and (B) 3,5-) for the uncatalyzed thermal cycloaddition reactions of acetonitrile oxide and propyne.

simple filtration as pure materials, usually as white to off-white solids, in the form they crystallized from the reaction mixture. No further purification was performed.

Synthesis of 3,5-Disubstituted Isoxazoles. Although many nitrile oxides react with alkynes at appreciable rates without a catalyst (reaction times vary widely, from several hours at 60−70 °C to several days at ambient temperature),[14] both isoxazole regioisomers are usually obtained. Particularly with reactive nitrile oxides, one encounters significant formation of byproducts, and hence lowered yields and product isolations. We were, therefore, pleased to find that copper(I) is an efficient catalyst for this system. More importantly in the present context, it served to further substantiate our mechanistic hypothesis. In fact, this was a rare occasion when a computational study predicted a novel reactivity, both qualitatively and quantitatively (vide infra).

Nitrile oxides are best prepared from the corresponding aldoximes by oxidative halogenation/dehydrohalogenation[15] (via imidoyl chlorides) immediately before they are used, because some of them, especially in the aliphatic series, cannot be stored for extended periods of time. Additionally, because the reaction is tolerant of different contaminants, the precursors can be used "as is" after preparation without purification. The catalyst is best prepared in situ by reduction of the copper(II) sulfate (1−2 mol %) with ascorbate (10 mol %), and the products are isolated as pure materials by filtration or extraction (Scheme 3).

Nitrile oxides react with copper(I) acetylides much faster than similar azides[16] (which is in good agreement with computational results, vide infra), and most reactions are complete in several hours. In general, electron-deficient nitrile oxides react slower than the electron-rich ones. Several isoxazole products obtained by the copper(I)-catalyzed synthesis are shown in Table 2.

The dramatic acceleration provided by the copper catalyst is best appreciated by comparison of the uncatalyzed cycloaddition to its copper-catalyzed counterpart. Thus, thermal cycloaddition of 4-methoxybenzonitrile oxide to phenylacetylene resulted, after 8 h at 60 °C, in a 4:1 mixture of regioisomers (in favor of the 3,5-isomer) in 62% combined yield, whereas (Table 2, entry 1) a single regioisomer in 92% yield was obtained after 1 h at ambient temperature when copper(I) catalyst was added.

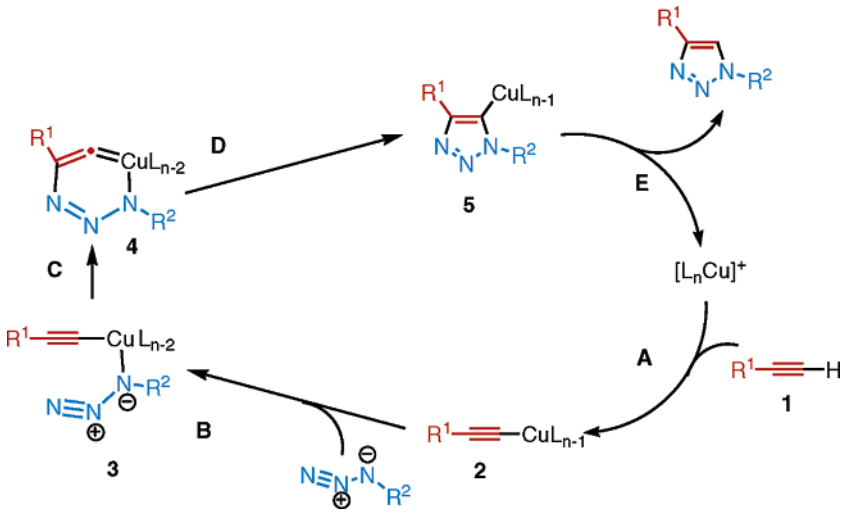
(B) Computational Studies. The Uncatalyzed, Concerted Cycloadditions. The activation barriers for the concerted reaction leading to both 1,4- and 1,5-regioisomers of the 1,2,3-triazole were found to be very close, 25.7 and 26.0 kcal/mol, respectively. Experiment supports this prediction; an ca. 1:1 mixture of the two isomers is usually formed in the thermal process. The optimized transition-state structures are shown in Figure 1. Both reactions are highly exothermic, −60.8 and

(14) (a) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 1−176. (b) Jäger, V.; Colinas, P. A. In *Heterocyclic Compounds*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002; Vol. 59, pp 363−461.

(15) (a) Grundaman, C.; Richter, R. *J. Org. Chem.* **1969**, *34*, 476. (b) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916. (c) Hallig, K.; Torssell, K. B. G.; Hazell, R. G. *Acta Chem. Scand.* **1991**, *45*, 736.

(16) The uncatalyzed cycloaddition of nitrile oxides to alkynes displays a barrier of 20.2 kcal/mol (i.e., some 6 kcal/mol lower than for the azides, hence the faster thermal reaction). The copper catalyzed reaction barrier is calculated to be 13.2 kcal/mol, a difference of 7 kcal/mol, that is, almost 5 orders of magnitude faster.

Scheme 4. Proposed Reaction Mechanism



−60.6 kcal/mol, for the 1,4- and 1,5-regioisomers, respectively. Entropy effects (not included in the present work) will somewhat reduce these numbers. From vibrational frequency calculations, they are estimated at ca. 40 eu (15 kcal/mol) at the temperatures used for these reactions.

A similar set of calculations for cycloaddition of acetonitrile oxide and propyne (Scheme 3) resulted in a 2.8 kcal/mol difference in the computed activation barriers to form the 3,4- and 3,5-regioisomers of the parent isoxazole. This difference translates to an approximate ratio of about 100:1 in favor of the 3,5-regioisomer, which agrees well with experimental observations. The overall barrier for the reaction is 20.2 kcal/mol. As expected, the process is highly exothermic (−66 kcal/mol, not accounting for entropy effects). The optimized transition-state structures are shown in Figure 2.

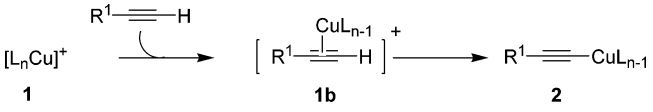
The Cu(I)-Catalyzed Variant, Stepwise and Regiospecific. Less than a week after the enormous reactivity between organic azides and the Cu(I) acetylides was found, DFT calculations by one of us (F.H.) revealed a unique qualitative and quantitative framework for understanding the mechanistic pathway outlined in Scheme 4. Despite the lack of precedent for some of its key steps and intermediates, it has become "the mechanism", for the correspondence between these unexpected, yet precise, DFT calculations and experimental evidence is striking.

Most of the calculations described below were performed with azide as the dipole. Only those instances where nitrile oxides behaved differently are highlighted. Although acetonitrile was often used as the ligand for copper (L) (because many early experiments were performed in acetonitrile), similar results were obtained when water was used as the ligand.

The sequence begins with the coordination of the alkyne to the Cu(I) species (**1**), displacing one of the acetonitrile ligands. This step was calculated to be slightly endothermic, by ca. 0.6 kcal/mol. However, with water as a ligand, the displacement process becomes exothermic by 11.7 kcal/mol. This is in good agreement with the experimental observation that the reaction proceeds much faster in aqueous solutions and does not require an amine base.

Conversion of the alkyne **1** to the acetylide **2** is well known to be involved in many C−C bond forming reactions in which Cu acetylide species are bona fide intermediates. However, present studies indicate that the initial coordination of acetylene to form π-complex **1b** (Scheme 5) lowers the pK_a of alkyne C−*H* by up to 9.8 units. These appear to be the first calculations bearing on this dramatic pK_a effect. Nevertheless, the estimate seems reasonable: with the pK_a of propyne at ∼25, lowering

Scheme 5. Formation of the Copper(I) Acetylide



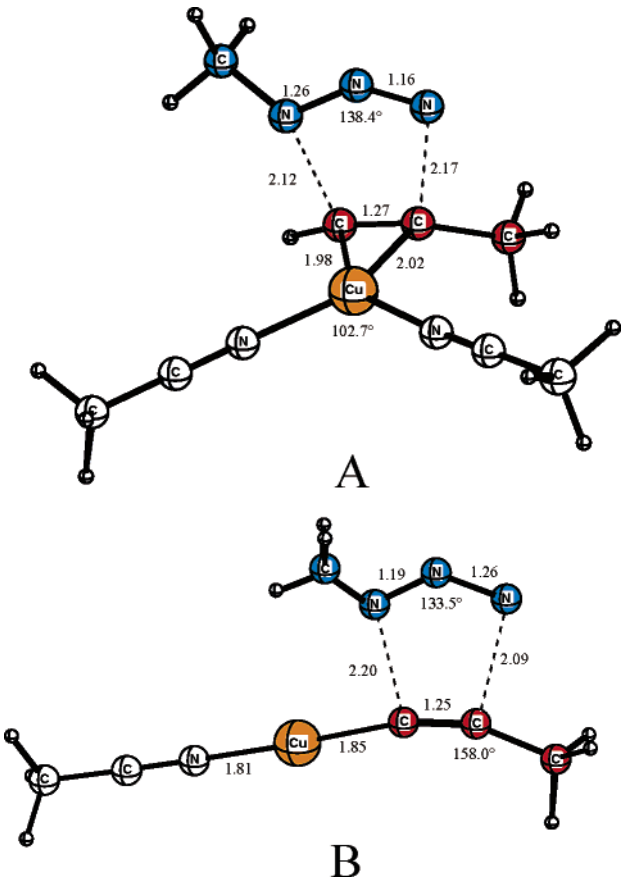
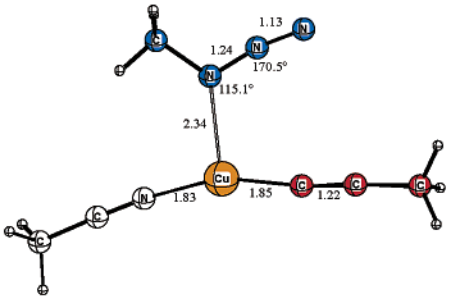
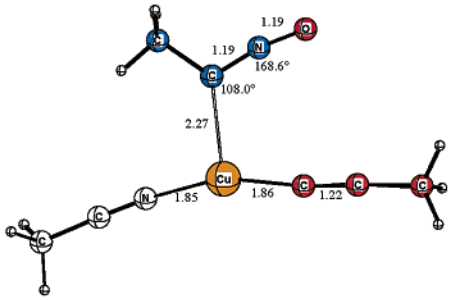
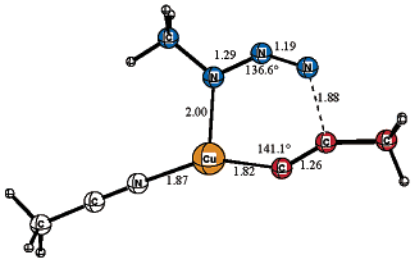
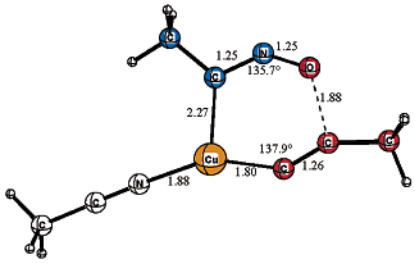
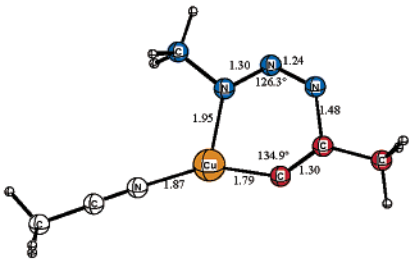
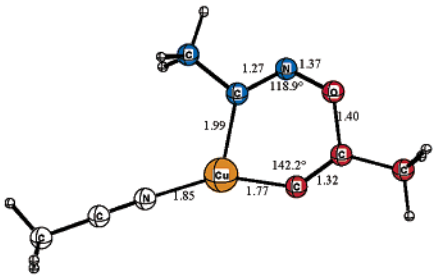
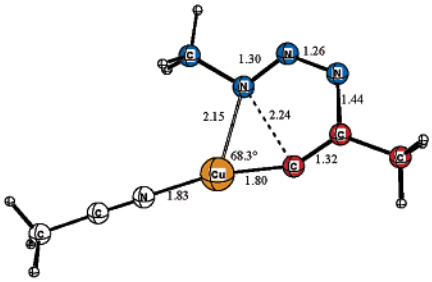
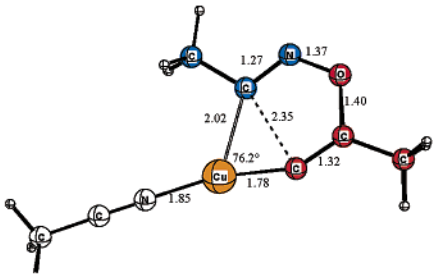
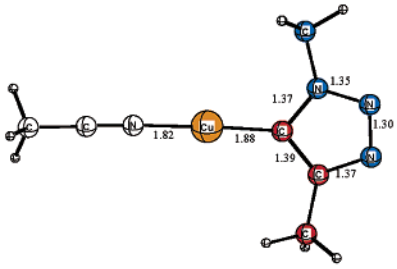
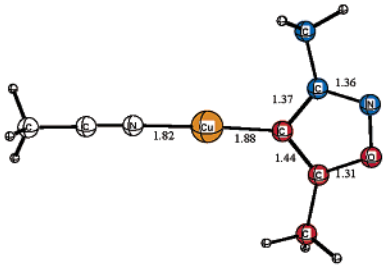


Figure 3. Optimized transition-state structures for the concerted 1,3-dipolar cycloaddition reactions between methyl azide and (A) the π-complex of copper(I) and acetylene and (B) copper(I) acetylide.

Table 3. Optimized Structures of Transition States and Intermediates

	Dipole: Azide	Dipole: Nitrile Oxide
3		
$TS_{3/4}$		
4		
$TS_{4/5}$		
5		

by 10 pK_a units makes the second step (**1b** → **2**) accessible in aqueous systems used in these studies. Furthermore, the existence of copper(I) acetylides aqueous solutions, even at acidic pH, has been previously reported.[17]

Although one could envision a mechanism in which coordination of the acetylene to the copper(I) (without its deprotonation) activates it toward a 1,3-dipolar cycloaddition, the calculated barrier for this process (optimized transition-state structure A in Figure 3) is 27.8 kcal/mol, which is even higher than that without the copper catalyst (ca. 26 kcal/mol, vide supra). In any case, among direct cycloaddition alternatives, that with the neutral acetylide **2** seems most likely. However, the barrier for this concerted process (transition structure B in Figure 3) is calculated at 23.7 kcal/mol. It is, therefore, clear that neither

(17) Mykhalichko, B. M.; Temkin, O. N.; Mys'kiv, M. G. *Russ. Chem. Rev.* **2001**, *69*, 957.

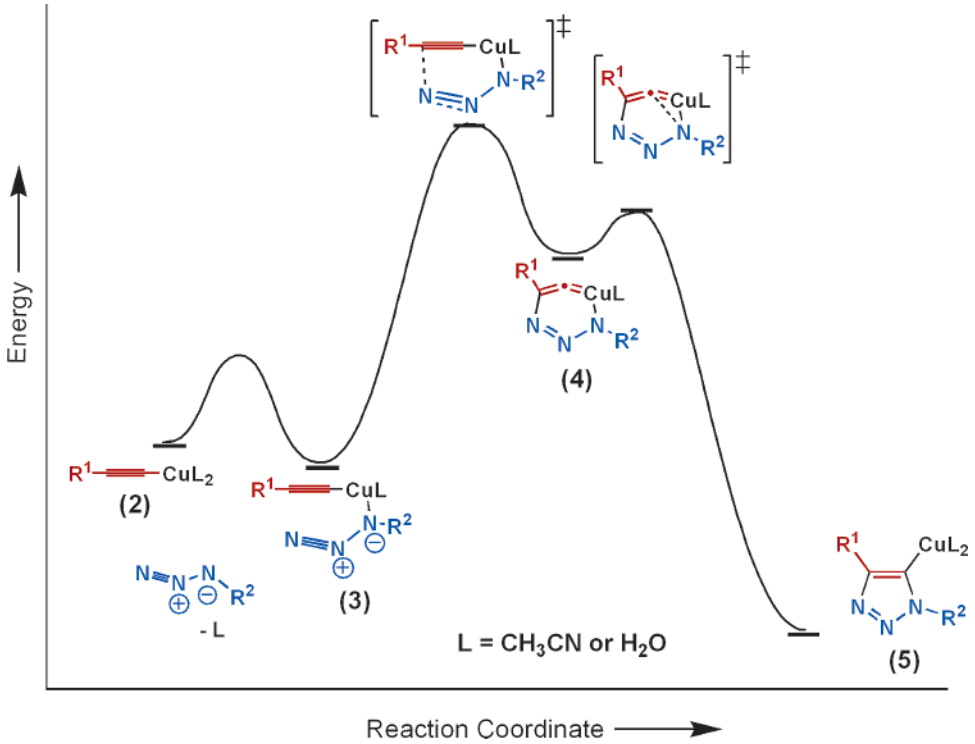


Figure 4. Schematic representation (energy vs reaction coordinate) of the reaction of copper(I) acetylides with organic azides.

of the direct cycloaddition options can explain the catalytic power of the copper observed experimentally.

Having the concerted pathways eliminated, we propose that in the next step (step B in Scheme 4) the azide replaces one of the ligands and binds to the copper atom via the nitrogen proximal to carbon, forming intermediate **3**. This is effectively a starting point for the stepwise sequence schematically represented in Figure 4. The energy of **3** is set to 0 kcal/mol. This ligand exchange step is slightly exothermic computationally (0.7 and 2.0 kcal/mol when L is acetonitrile and water, respectively). After that, the distal nitrogen of the azide in **3** attacks the C-2 carbon of the acetylide, forming the unusual six-membered copper(III) metallacycle **4**. This step is endothermic by 8.2 kcal/mol (12.6 kcal/mol when L is water), and the calculated barrier is 14.9 kcal/mol (18.7 kcal/mol when L is water), which is considerably lower than the barrier for the uncatalyzed reaction (25.7 and 26.0 kcal/mol). This explains the enormous rate acceleration of the copper(I)-catalyzed process, 7 to 8 orders of magnitude, as compared to the purely thermal cycloaddition. Similar calculations for nitrile oxides reveal that the barrier in the copper-catalyzed reaction is 13.2 kcal/mol, some 7 kcal/mol lower than for the thermal process, corresponding to a rate acceleration of 5 orders of magnitude. From classical transition-state theory, it can be deduced that a barrier of ca. 18 kcal/mol corresponds to a rate of ca. 1 per s at room temperature. An increase or decrease of the barrier by ca. 1.4 kcal/mol corresponds to a decrease or increase, correspondingly, in the rate by 1 order of magnitude. The calculated energy barriers for the stepwise reaction are therefore quite reasonable at room temperature.

From **4**, the barrier for ring contraction, which forms the triazolyl-copper derivative **5**, is very low. In fact, for the acetonitrile ligand, the transition state ($\mathbf{TS}_{4/5}$, Table 3) is 0.2 kcal/mol lower in energy than the intermediate **4**, which is, of course, an error of the method. With water as the ligand, the transition state is 3.2 kcal/mol higher than the intermediate. The optimized transition-state structures and intermediates are shown in Table 3. Proteolysis of **5** releases the triazole product, thereby completing the catalytic cycle.[18]

The proposed mechanism accounts for the key experimental observations. First, the dramatic rate increase observed in the copper-catalyzed synthesis of 1,2,3-triazoles is in excellent agreement with the computed activation barriers, which are as much as 11 kcal/mol lower than in the corresponding concerted cycloadditions. Second, the exclusive regioselectivity of the copper(I)-catalyzed processes is both predicted computationally and observed experimentally. Third, the proposed mechanism suggests that dipoles other than organic azide should engage in the analogous stepwise sequence with copper(I) acetylides. A 10^5 rate acceleration and absolute regioselectivity of the reaction of nitrile oxides with alkynes has further reinforced the fact that computational studies described above are sound and quantitatively precise. Further mechanistic investigations are currently underway and will be reported in due course.

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

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(18) Triazolyl-copper intermediate **5** can be captured with electrophiles other than proton. In fact, incorporation of deuterium at the C-5 of the triazole product is almost quantitative when the reaction is performed in D_2O.