Cl atoms having a marked anionic character.[30] This feature is also realized, but to a lesser extent, in the M−Cl bonds of complexes **2**–**6**.

The present study illustrates for the first time the ability of an $\alpha$-cyclodextrin cavity to recognize a transition metal M−Cl bond through weak Cl$\cdots$H-5 interactions in the solid state as well as in solution. The fact that such subtle interactions could be observed in non-aqueous media is a consequence of the absence of stronger competing supramolecular forces, such as the hydrophobic effect, which usually plays a prevailing role in the formation of CD inclusion complexes. Overall these results illustrate the potential of modified cyclodextrins as second-sphere ligands.

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[26] Crystal structure analysis of $\mathbf{2}\cdot C_4H_8O$: crystals suitable for X-ray diffraction were obtained by slow diffusion of pentane into a butanone solution of the complex. Crystal data: $M_r = 1782.98$, hexagonal, space group $P6_522$, $a = b = 14.8846(3)$, $c = 67.0615(15)$ Å, $V = 12867.0(5)$ Å$^3$, $Z = 6$, $\rho_{calcd} = 1.381$ g cm$^{-3}$, Mo$_{K\alpha}$radiation ($\lambda = 0.71073$ Å), $\mu = 0.395$ mm$^{-1}$. Data were collected on a Bruker SMART 1000 CCD system at 133(2) K. The structure was solved by direct methods and refined on $F_o^2$ by full-matrix least squares (program SHELXL-97, G. M. Sheldrick, University of Göttingen). All non-hydrogen atoms were refined anisotropically; hydrogen atoms were included using a riding model. The absolute configuration (and thus the enantiomeric space group assignment) was determined by a Flack $x$ parameter of $-0.07(3)$. Refinement proceeded to $wR2 = 0.1025$ for all 5529 reflections and $R1 = 0.0413$ for data with $I > 2\sigma(I)$. The compound crystallizes with a butanone molecule positioned inside the cyclodextrin cavity. CCDC-181579 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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[29] The behavior of the CD cavity towards the "$RuCl_2(CO)_2$" unit strongly contrasts with that of a recently reported *p-tert*-butylcalix[4]-arene-derived diphosphane. Upon complexation, the latter favors inclusion of a "Ru−CO" rod over that of a "Ru−Cl" fragment; see reference [6].

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# A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes[**]

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Valery V. Fokin,* and K. Barry Sharpless*

Huisgen 1,3-dipolar cycloadditions[1] are exergonic fusion processes that unite two unsaturated reactants and provide fast access to an enormous variety of five-membered hetero-

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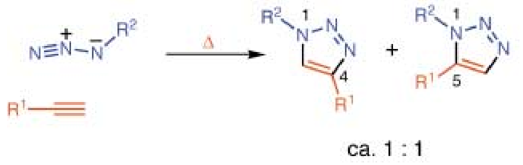
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

cycles.[2] The cycloaddition of azides and alkynes to give triazoles[3] is arguably the most useful member of this family. However, likely because of concerns about the safety of working with organic azides, synthetic chemists, in both pure and applied fields, have not given this transformation the special attention it deserves. Although the actual cycloaddition step may be faster and/or more regioselective for 1,3-dipoles other than azide, the latter is by far the most convenient to introduce and to carry hidden through many synthetic steps. Indeed, it appears to be the only three-atom dipole which is nearly devoid of side reactions.

Azides usually make fleeting appearances in organic synthesis: they serve as one of the most reliable means to introduce a nitrogen substituent through the reaction $-\text{R}-\text{X} \rightarrow [\text{R}-\text{N}_3] \rightarrow \text{R}-\text{NH}_2$. The azide intermediate is shown in brackets because it is generally reduced straightaway to the amine.[4] Despite this "azidophobia", we have learned to work safely with azides because they are the most crucial functional group for click chemistry endeavors.[5] Ironically, what makes azides unique for click chemistry purposes is their extraordinary stability toward $H_2O$, $O_2$, and the majority of organic synthesis conditions.[6] The spring-loaded nature of the azide group remains invisible unless a good dipolarophile is favorably presented.[7] However, even then the desired triazole-forming cycloaddition may require elevated temperatures and, usually results in a mixture of the 1,4 and 1,5 regioisomers [Eq. (1)].[1, 8]

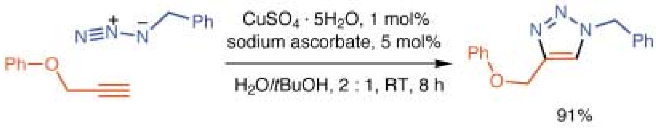


(1)

Since efforts to control this 1,4- versus 1,5-regioselectivity problem have so far met with varying success,[9] we were pleased to find this copper(I)-catalyzed reaction sequence which regiospecifically unites azides and terminal acetylenes to give only 1,4-disubstituted 1,2,3-triazoles.[10] The process is experimentally simple and appears to have enormous scope.

While a number of copper(I) sources can be used directly (see below), we found that the catalyst is better prepared in situ by reduction of $Cu^{II}$ salts, which are less costly and often purer than $Cu^{I}$ salts ($CuSO_4 \cdot 5\,H_2O$ serves well). As the reductant, ascorbic acid and/or sodium ascorbate proved to be excellent[11] for they allow preparation of a broad spectrum of 1,4-triazole products in high yields and purity at 0.25–2 mol% catalyst loading. The reaction appears to be very forgiving and does not require any special precautions. It proceeds to completion in 6 to 36 hours at ambient temperature in a variety of solvents, including aqueous *tert*-butyl alcohol or ethanol and, very importantly, water with no organic co-solvent.[12] Although most experiments were performed at near neutral pH values, the catalysis seems to proceed well at pH values ranging from approximately 4 to 12. In other words, this is a very robust catalytic process, which is so insensitive to the usual reaction parameters as to strain credulity.[13]

The reaction between phenyl propargyl ether and benzylazide in the presence of 5 mol% of sodium ascorbate and 1 mol% of copper(II) sulfate in a 2:1 mixture of water and *tert*-butyl alcohol furnished the 1,4-disubstituted triazole product in 91% yield after stirring for eight hours at room temperature in a capped scintillation vial, but otherwise with no effort to exclude oxygen [Eq. (2)]. The regiochemistry of the product was established by NOE experiments and confirmed by an X-ray crystallographic analysis.[14] For comparison, the thermal reaction (neat, 92 °C, 18 h) between these substrates gives both regioisomers in a ratio of 1.6:1 in favor of the 1,4 isomer.



(2)

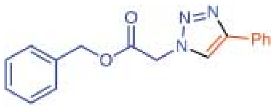
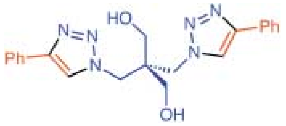
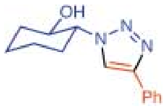
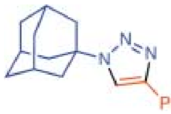
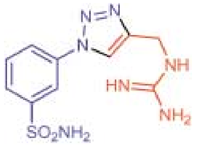
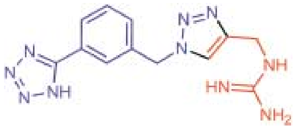
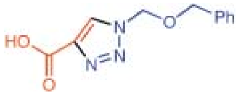
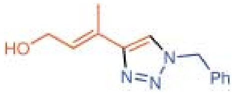
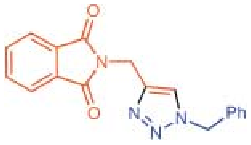
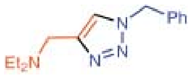
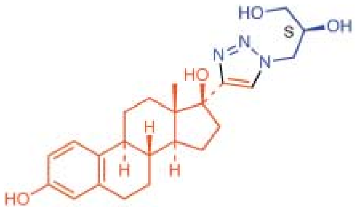
The scope of this copper-catalyzed triazole synthesis is partly revealed by the examples in Table 1; the lack of functional group interference is especially noteworthy. These triazoles are obtained by using a procedure which generally involves little more than stirring the reagents and filtering off pure products. Variously substituted primary, secondary, tertiary, and aromatic azides readily participate in this transformation. Tolerance for variations in the acetylene component is also excellent.

Copper(I) salts, for example, CuI, $CuOTf \cdot C_6H_6$, and $[Cu(NCCH_3)_4][PF_6]$, can also be used directly in the absence of a reducing agent. These reactions usually require acetonitrile as co-solvent and one equivalent of a nitrogen base (for example, 2,6-lutidine, triethylamine, diisopropylethylamine, or pyridine). However, formation of undesired by-products, primarily diacetylenes, bis-triazoles, and 5-hydroxytriazoles, was often observed.[10, 15] This complication with the direct use of $Cu^{I}$ species was minimized when 2,6-lutidine was used, and exclusion of oxygen further improved product purity and yield.[16] Even though a broad range of both acetylene and azide components react readily in the acetonitrile system, we prefer the even more reliable and simple $Cu^{II}$/ascorbate aqueous system (with or without co-solvents and amine buffers/additives).

Our mechanistic proposal for the catalytic cycle is shown in Scheme 1. It begins unexceptionally with formation of the copper(I) acetylide **I**[17] (as expected, no reaction is observed with internal alkynes), but then gets interesting. Extensive density functional theory calculations[18] offer compelling evidence which strongly disfavors—by about 12–15 kcal—the concerted [2+3] cycloaddition (B-direct) and points to a stepwise, annealing sequence (B-1 → B-2 → B-3, hence the term "ligation"), which proceeds via the intriguing six-membered copper-containing intermediate **III**.[19]

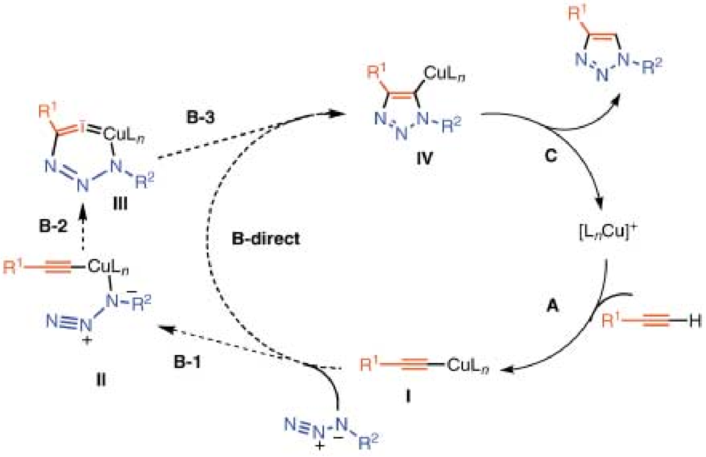
In conclusion, the $Cu^{I}$-catalyzed transformation described here—a high-yielding and simple to perform "fusion" process leading to a thermally and hydrolytically stable triazole connection—is an ideal addition to the family of click reactions. The process exhibits broad scope and provides

Table 1. Synthesis of 1,4-disubstituted 1,2,3-triazoles catalyzed by Cu$^I$ ions in the presence of ascorbate.[a]

| Entry | Product | Yield [%] |
|---|---|---|
| 1 |  | 92 |
| 2 |  | 93 |
| 3 |  | 82 |
| 4 |  | 84 |
| 5 |  | 91 |
| 6 |  | 88 |
| 7 |  | 88 |
| 8 |  | 84 |
| 9 |  | 88 |
| 10 |  | 90 |
| 11 |  | 94 |

[a] All reactions were carried out in water with *tert*-butyl alcohol as co-solvent, 0.25–0.5 M in reactants, with 1 mol% of $CuSO_4$ and 10 mol% of sodium ascorbate, and were complete in 12–24 h.

1,4-disubstituted 1,2,3-triazole products in excellent yields and near perfect regioselectivity. The fact that this "unstoppable" reactivity[20] of copper(I) acetylides with organic azides remained unrevealed until now, despite the great body of research on copper-mediated organic synthesis over the last seventy years, is extraordinary. It can only be attributed to the often irrational fear of azides and is just another indication of the untapped potential of this underappreciated functional group. Above all, what this new catalytic process seems to offer is an unprecedented level of selectivity, reliability, and scope for those organic synthesis endeavors which depend on the creation of covalent links between diverse building blocks. Several studies which highlight the capabilities of the process, as well as studies hoping to achieve better mechanistic understanding of its unique reactivity features, are currently underway and will be reported in due course.



Scheme 1. Proposed catalytic cycle for the Cu$^I$-catalyzed ligation.

## Experimental Section

General procedure (entry 11, Table 1): 17-ethynylestradiol (888 mg, 3 mmol) and (*S*)-3-azidopropane-1,2-diol (352 mg, 3 mmol) were suspended in a 1:1 mixture of water and *tert*-butyl alcohol (12 mL). 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 water (50 mL), cooled in ice, and the white precipitate was collected by filtration. After washing the precipitate with cold water (2 × 25 mL), it was dried under vacuum to afford 1.17 g (94%) of pure product as an off-white powder. M.p. 228–230 °C. Elemental analysis calcd for $C_{23}H_{31}N_3O_4$: C 64.02, H 7.71, N 9.74%; found: C 64.06, H 7.36, N 9.64%. $^1H$ NMR ($[D_6]DMSO$) $\delta = 8.97$ (s, 1H), 7.77 (s, 1H), 6.95 (d, $J = 8.3$ Hz, 1H), 6.45 (dd, $J = 8.3, 2.3$ 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, 3H), 1.63 (m, 1H), 1.48–1.12 (m, 6H), 0.91 (s, 3H), 0.74 ppm (s, 1H); $^{13}C$ NMR ($[D_6]DMSO$) $\delta = 154.8$, 153.8, 137.2, 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 ppm.

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[7] In fact, it was the razor sharp reactivity window for this cycloaddition process which spawned our "in situ click chemistry" ideas—an approach which recently resulted in the discovery of the most potent noncovalent inhibitor of acetylcholinesterase known to date: W. G. Lewis, L. G. Green, F. Grynszpan, Z. Radic, P. R. Carlier, P. Taylor, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 1095–1099; *Angew. Chem. Int. Ed.* **2002**, *41*, 1053–1057.

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[9] P. Zanirato, *J. Chem. Soc. Perkin Trans. 1* **1991**, 2789–2796; D. J. Hlasta, J. A. Ackerman *J. Org. Chem.* **1994**, *59*, 6184–6189; C. A. Booth, D. Philp, *Tetrahedron Lett.* **1998**, *39*, 6987–6990; S. J. Howell, N. Spencer, D. Philp, *Tetrahedron* **2001**, *57*, 4945–4954; W. L. Mock, T. A. Irra, J. P. Wepsiec, M. Adhya, *J. Org. Chem.* **1989**, *54*, 5302–5308; W. L. Mock, *Top. Curr. Chem.* **1995**, *175*, 1–24; J. Chen, J. Rebek, Jr., *Org. Lett.* **2002**, *4*, 327–329; J. W. Wijnen, R. A. Steiner, J. B. F. N. Engberts, *Tetrahedron Lett.* **1995**, *36*, 5389–5392; M. P. Repasky, W. L. Jorgensen, *Faraday Discuss.* **1998**, *110*, 379–389.

[10] While this manuscript was in preparation, an independent account of copper-catalyzed synthesis of 1,4-triazoles from azides and terminal acetylenes on solid support was reported: C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057.

[11] For a review of reactions of L-ascorbic acid with transition metals, see M. B. Davies, *Polyhedron* **1992**, *11*, 285–321, and references therein; redox properties of ascorbic acid are summarized in C. Creutz, *Inorg. Chem.* **1981**, *20*, 4449.

[12] The starting materials do not need to be dissolved in the reaction solvent. The reaction seems to proceed just as efficiently as long as adequate stirring is maintained.

[13] Amazingly, even $Cu^0$ can be used as a source of the catalytic species. Although these reactions may take longer to proceed to completion, the experimental procedure is exceedingly simple. For example, bistriazole shown in entry 2 (Table 1) was obtained in quantitative yield after stirring the corresponding azide and acetylene components for 24 h with about 1 g of coiled copper metal turnings. The turnings were removed at the end of the reaction, and the pure white product was collected by simple filtration.

[14] CCDC 186236 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[15] For a recent summary of the reactions of copper(I) complexes with dioxygen, see S. Schindler, *Eur. J. Inorg. Chem.* **2000**, 2311–2326 and A. G. Blackman, W. B. Tolman in *Structure and Bonding, Vol. 97* (Ed: B. Meunier), Springer, Berlin, **2000**, pp. 179–211.

[16] For example, ethyl propiolate and benzylazide furnished the corresponding 1,4-triazole in 55% yield when this procedure was used, but only a trace amount of the product was obtained with one equivalent of triethylamine and without exclusion of oxygen.

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[19] M. P. Doyle, M. A. McKervey, T. Ye in *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1997**, pp. 163–248.

[20] The reaction proceeded equally well even in human plasma (protein loading 65–85 $mg\,mL^{-1}$, $C_{azide} = C_{alkyne} = 5\,mM$; $C_{Cu^+} = 100\,\mu M$), which indicates that the copper species remained available for the catalysis despite being heavily bound to plasma proteins.

# Electronic and Steric Effects on Catalysts for $CO_2$/Epoxide Polymerization: Subtle Modifications Resulting in Superior Activities**

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Carbon dioxide is an attractive chemical feedstock. In addition to the fact that $CO_2$ is an inexpensive substance of practically inexhaustible supply, it is also nonflammable and exhibits low toxicity.[1–3] Since $CO_2$ is believed to contribute significantly to global warming, its removal from the atmosphere has added environmental benefits. Consequently, the alternating copolymerization of carbon dioxide with epoxides to aliphatic polycarbonates has been a topic of increasing

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