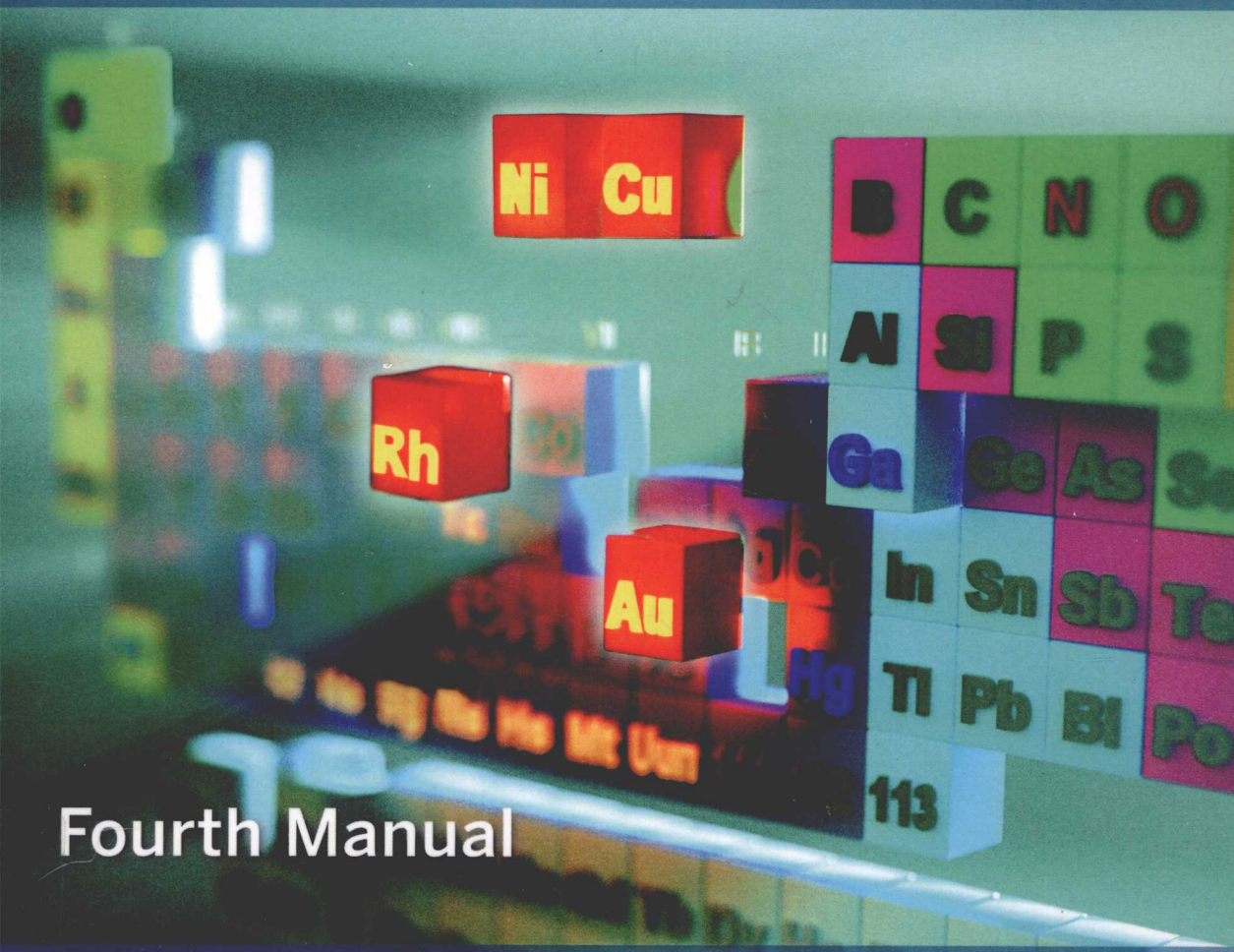
Organometallics in Synthesis



Fourth Manual

Edited by

Bruce H. Lipshutz

WILEY

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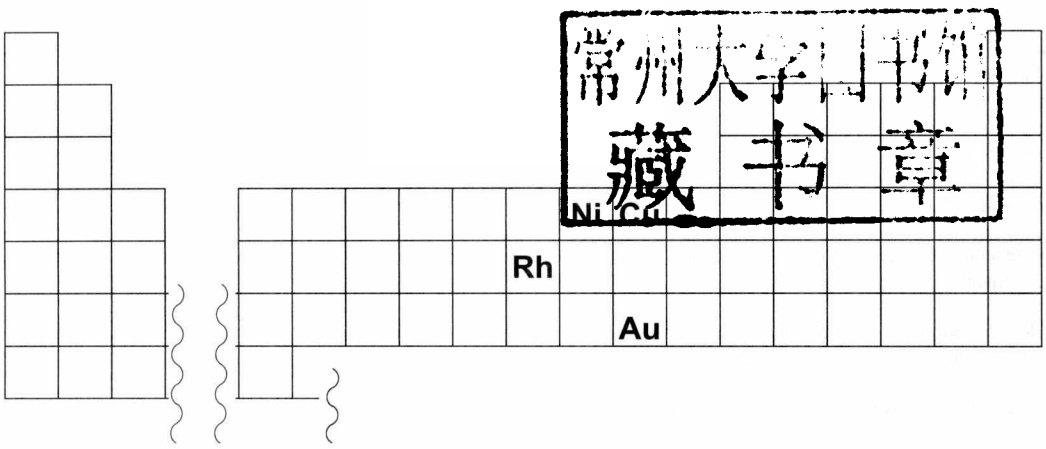

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Organometallics in Synthesis

Fourth Manual

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Preface

When the first edition of *Organometallics in Synthesis, A Manual* appeared back in 1994, it offered the community a rare, atypical source of experimental "inside information." It was a stand-alone resource of how to's and why's, written by card-carrying organic chemists with a heavy accent on organic synthesis where the C-C, C-H, and C-heteroatom bonds being made are mediated by metals that serve as either reagents or catalysts. The second edition, published in 2002, was expanded by four metals (from 7 to 11) and surpassed 1200 pages in length. And yet, it was essentially a new book. Now, more than a decade later, the third edition has just appeared. Increasing the length of this monograph, however, was no longer an option from a publishing perspective. So, to do justice to the evolving technologies associated with metals discussed in prior editions, as well as to add metals that had not been covered previously, the Manual was divided, as was the work associated with bringing each to fruition. Thus, in the third edition, Manfred Schlosser oversaw inclusion of chapters focused on organoalkali reagents, as well as those highlighting organo-silicon, -magnesium, -zinc, -iron, and -palladium chemistry, each written, again, by a "who's who" in these prominent areas.

With this fourth edition, the torch has been passed. Chapters can be found on organo-rhodium, -copper, -nickel, and -gold chemistry, where the theme is unquestionably on catalysis. And although this opus is equally split between two precious (Rh, Au) and two base (Ni, Cu) metals, the discussion is heavily, and at times exclusively, devoted to the use of each metal in catalytic quantities. Price is no longer the sole driving force; indeed, environmental considerations have become a major topic in the planning and execution of organic synthesis, regardless of the metal involved.

Three of the four contributing authors in this 4th edition are new to this series; hence, this is the first coverage in the *Manual* on rhodium, nickel, and gold chemistry. As for copper, this chapter has been completely redone; there is no redundancy whatsoever insofar as prior discussions in earlier editions are concerned. Thus, this monograph compliments the third edition beautifully. And although it may show a different name below as editor, it is likely to continue to be viewed as another worthy addition to the *Schlosser Manuals.*

Bruce H. Lipshutz
May 2013

Foreword

OMCOS Chemistry: What's the Value?

Analysis and synthesis define the main activities of chemistry that shape the material world around us. Synthesis is the only means to secure new substances and materials when non-natural products are to be studied and to be used. Present-day synthesis of complex organic chemicals is subject to challenging demands: It should be efficient and short, it should be safe and environmentally acceptable, and it should be resource efficient and proceed in high yield, being economically feasible. These concepts imply that the methods by which we do synthesis today need to be constantly challenged as to how well they meet these criteria.

Of the operations to be carried out in synthesis, those that construct the molecular skeleton are the most important and demanding. That is precisely where the development of new methods has brought substantial progress during the last 150 years, and it is in particular the application of organometallic reagents to synthesis that is indicative of the progress made. Imagine the state of synthetic methodology in which there were no organometallic reagents: You are left with certain variants of the Aldol- and Michael-additions, the alkylation of active methylene compounds, the Friedel-Crafts acylation, and the Diels-Alder addition to build the molecular skeleton of your target structures. This is hardly anything more than what nature uses in biosynthesis. Such a restricted arsenal of methods might fascinate some advocates of green chemistry, but it would not be sufficient to address the current practices and needs of medicinal chemistry. It is thus evident that adapting organometallic reagents to the needs of organic synthesis marked the progress in synthetic methodology over the last century; it enabled organic synthesis to fulfill most of the tasks in an acceptable manner, and it constitutes one of the major cultural achievements of chemistry.

Given that situation, one may hold that a *Manual* of organometallics in synthesis might be more of a historic exercise than an opus that meets the needs of today's chemists. The value of such a *Manual*, however, becomes evident when one takes the viewpoint of those that apply these methods in synthesis. Those doing actual synthesis of complex target molecules are focused on the synthesis and do not want to lose time or materials by applying methods with which they are not familiar; that is, in general, chemists doing synthesis are highly conservative regarding the methods they apply.

For instance, a survey of (arbitrarily chosen) 41 syntheses of complex natural products carried out in 1981 revealed that more than 70% of the skeleton bond-forming steps fell to enolate and Grignard reactions, the Wittig reaction and cuprate reactions, or what we would call classic organometallic reactions. In the late 1970s, a golden era of organometallics in organic synthesis started, providing the synthetic chemists with olefin metathesis; the Heck, Negishi, Suzuki, and Sonogashira reactions; and many related cross-couplings. Yet, when surveying 58 syntheses of complex natural products published in 2006, these new methods amounted to (already or merely!) 20% of the skeleton bond-forming reactions used, whereas the classic organometallic reactions men-

tioned lost only 15% of their usage. This underscores the statement that synthetic chemists are slow in taking up new (and, hopefully, more advantageous) methods as long as the older, established ones do not do too badly . The motivation to apply any method (whether old or new) depends on the practitioner's level of confidence in the scope and reliability of the method. Although a time-consuming, thorough literature search could provide this information, chemists tend to get around this and to stick with the familiar methods as long as justifiable. It is clear that it is the work of a small number of daring chemists applying newly described methods in synthesis that provided the basis for a *Manual* in which scope, usefulness, and reliability of a method can be documented. The merit of such a *Manual* is invaluable as it gives the majority of synthetic chemists the information to make a reasonable judgment as to which method might best serve their immediate synthetic needs. As the present *Manual* covers the long established organometallic methods side by side with the methods of younger vintage, it allows the synthetic chemists to make objective choices regarding the methods to be applied. The availability of such a *Manual* should reduce the reluctance of chemists to apply methods with which they are not (yet) familiar. Therefore, the fourth edition of *Organometallics in Synthesis, A Manual* is timely and a well-taken endeavor.

PROF. DR. REINHARD W. HOFFMANN

Contents

Chapter One

Organocopper Chemistry

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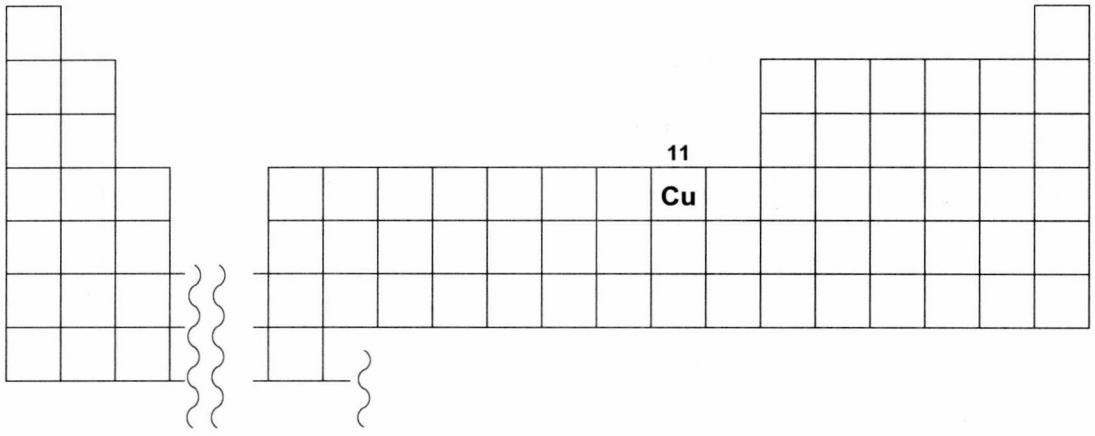


Contents

1. Introduction

Synthetic Chemistry of Cu(I): Still in Focus and "Hot"

Catalysis. It was the buzzword in the 1990s, and certainly insofar as organocopper chemistry is concerned, there has been no letup on this front in the new millennium. Very good reasons exist for this emphasis, both in terms of development of new methodologies as well as in applications. The key driver is usually the cost of waste disposal; whether copper is contained in an aqueous workup mixture, or in amounts greater than the ppm level allowed in pharmaceuticals, it requires attention. Starting with as little copper as possible in a reaction just makes sense, notwithstanding its "base" metal status. So, whereas the accent in previous versions of the *Manual* was on reagents, this chapter is organized by reaction type and focuses heavily on processes that are catalytic in copper(I). Nonetheless, attention is also directed to traditional albeit stoichiometric copper chemistry, acknowledging the fundamentals that began with Henry Gilman more than 60 years ago[1] and still are very much valued by the synthetic community today.

Within the catalysis manifold, remarkable advances have been brought to light in both asymmetric as well as achiral synthesis. As already witnessed with precious metal-based technologies, such as asymmetric hydrogenations, the metal is important, but the ligands "rule." Research over the past decade has led to several mono- and (mostly) bidentate nonracemic ligands that possess, and translate, their extraordinary innate facial biases as their derived copper complexes to a host of substrate types. Several newly discovered species now present themselves to the practitioner, where enantioselectivities are routinely in excess of 90%. On the other hand, chiral upgrades often allow industrial chemists to realize the desired high levels of enantiometric excesses (ee's) needed in pharma, thereby dettaching any real significance to the "magic" barrier of 90% ee. Nonetheless, the challenges extended by nature to chemists to achieve as close to 100% stereocontrol have not in the past, nor are they likely in the future, to be ignored. Of course, stereocontrol is not the only element that counts in such catalysis; indeed, with up-front costs for copper essentially nonexistent from the perspective of economics, it is turnover number (TON) that may dictate usage. The gap between what academicians may see as "catalytic amounts" (usually 1–5 mol%) and the required low loadings for an industrial process can be hard to fill. Hopefully, some of the progress made as highlighted in this contribution will entice our industrial colleagues.

A wealth of achiral copper chemistry is also covered; in fact, it is still the lion's share of reports in this field. Whether copper(I) in the form of its salts (CuX), perhaps (*in situ*) derived organocopper species (RCu), or even a cuprate ($R_2Cu^-M^+$), there is no denying the textbook status of this metal in organic synthesis. Nonetheless, both silver and especially gold chemistry are making astounding advances. But of the group 11 metals, copper still offers the widest variety of synthetically valued chemoselectivities. And while questions regarding mechanisms, aggregation state(s), and structure of organocopper complexes remain, tremendous progress has been

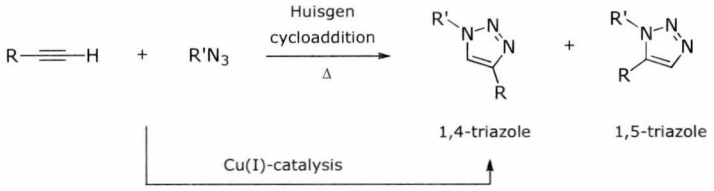
made on these fronts as well. The spirited debate throughout the 1990s on the existence, or not, of "higher order" cuprates provided new incentives for computational, structural, spectroscopic, and physical organic chemistry that has since appeared and has helped to advance the field.

As noted in earlier editions of this *Manual*, and as is true herein, this chapter is written for the practitioner who faces an ever expanding literature on organometallics. Notwithstanding the emphasis now squarely placed on catalysis, many of the same practical questions arise as highlighted previously, choices of copper salt, solvent, precursor reagent, stoichiometry, and additives, and today, there have been new variables that can play major roles, such as the choice of (*e.g.*, nonracemic) ligand, potential for heterogeneous catalysis, and the option to employ microwave assistance. Thus, with additional insights from several colleagues who have shared their experiences in organocopper chemistry, many of the "secrets to success" are again revealed in this single source. Unfortunately, however, the field is too broad for this opus to be comprehensive; indeed, tough decisions had to be made as to coverage. Thus, there are entire areas even within Cu(I)-catalyzed chemistry that are not included (*e.g.*, cyclopropanations, Diels-Alder constructions, etc.), and surely others that may cause the reader to wonder "What about ...?". The explanation is simple: Each author had a page limitation to his chapter, and it was recommended (mainly as a result of technical matters associated with binding) that the editor not violate his own rules!

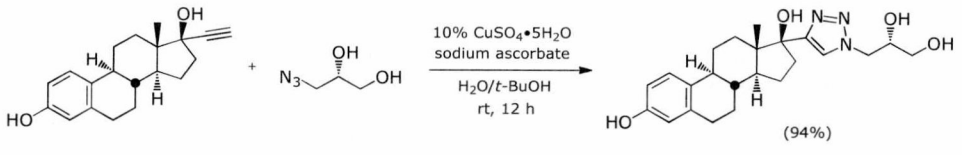
2. Click Chemistry: Just Add Copper

Reviews. Diez-Gonzalez, S. *Curr. Org. Chem.* **2011**, *15*, 2830; Diez-Gonzalez, S. *Catal. Sci Technol.* **2011**, *1*, 166; Cantillo, D.; Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Org. Biomol. Chem.* **2011**, *9*, 2952; Elchinger, P-H.; Faugeras, P-A.; Boens, B.; Brouillette, F.; Montplaisir, D.; Zerrouki, R.; Lucas, R. *Polymers*, **2011**, *3*, 1607; Becer, C. R.; Hoogenboom, R.; Schubert, U. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4900 (*metal-free*); Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952; Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018; Fokin, V. V.; Wu, P. *Aldrichimica Acta* **2007**, *40*, 7; Bock, B. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51.

The 2002 papers by the groups of Sharpless[2] at Scripps (La Jolla, CA) and Meldal[3] at the Carlsberg Laboratory (Denmark) highlighting the remarkable acceleration of Huisgen cycloadditions between organic azides[4] and terminal alkynes by Cu(I) have led to an avalanche of renewed interest in, and usage of, copper(I) in synthesis. The facility with which these two relatively high-energy educts "click" to form heteroaromatic 1,2,3-triazoles is truly impressive, and the community at large is



using this chemistry in both routine and highly innovative ways. Importantly, these otherwise thermally driven cycloadditions, which often lead to mixtures of 1,4- and 1,5-disubstituted triazoles,[5] are fully controlled in the presence of Cu(I) to afford only the 1,4-regioisomer[6] (while Ru leads to the corresponding 1,5-isomer).[7] Mechanistic details have not been fully elucidated, but significant progress has been made, most notably by Finn[8a] and Fokin,[8b] and more recently using density functional theory (DFT) calculations.[9] The data suggest involvement of copper(I) acetylides, shown to be associated within a dimeric array. Electron-withdrawing groups on the alkyne increase reactivity. A key point for the synthetic practitioner here is the acid/base chemistry that must ensue *en route* to the acetylide, implying strong potential influence of base in the medium. Indeed, it is now well accepted that selected bases can dramatically influence rates of click reactions.[6, 10] Curiously, however, the nature of the copper species selected can make a difference in the outcome, with the field narrowing in on two approaches: 1) the original Sharpless protocol using $CuSO_4$, a copper(II) salt that is readily reduced in aqueous *t*-butanol by excess sodium ascorbate (*i.e.*, the inexpensive Na salt of vitamin C).[2] Usually, *ca.* 1% $CuSO_4$ is employed in the presence of excess ascorbate, and with unhindered partners, cycloadditions occur at ambient temperatures in high yields; 2) CuI in organic solvent. Each of these is represented by the two procedures below. A third alternative involving *in situ* oxidation of Cu(0) is also available[8b] and, although considered of equal efficiency, is less frequently used.

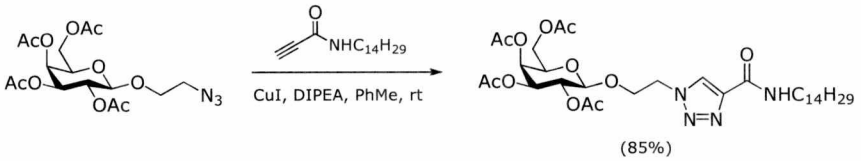


Copper(I)-catalyzed synthesis of 1,4-disubstituted 1,2,3-triazoles; general procedure. 2'S-17-[1-(2',3'-Dihydroxypropyl)-1H-[1,2,3]-triazol-4-yl]-estradiol[2]

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/*t*-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 thin layer chromatography (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.

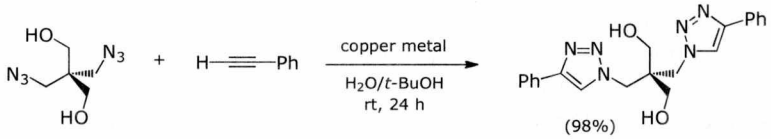
CuI-DIPEA-catalyzed click chemistry.[11]



(85%)

The azide (20 mg, 0.047 mmol), alkyne (12.7 mg, 0.047 mmol, 1 equiv), and CuI (0.9 mg, 0.004 mmol, 0.1 equiv) were dissolved in toluene (500 μL) in a glass vial (15.5 × 50 mm). To this mixture was added diisopropylethylamine (8.3 μL, 0.047 mmol, 1 equiv) and the vial was capped. After stirring for 18 h at room temperature (RT), the crude product was filtered over Celite (Sigma-Aldrich, St. Louis, MO) and purified by flash chromatography on silica gel using as eluent *n*-hexane/EtOAc (from 1:1 to 1:2). The product (28 mg) was isolated in 85% yield as a single 1,4-regioisomer as an amorphous solid; HR-MALDI-FTMS calcd. for $C_{33}H_{54}N_4O_{11}Na$ $[M + Na]^+$, 705.3681; found 705.3681.

Click chemistry with copper metal. 2,2-Bis((4-phenyl-1H-1,2,3-triazol-1-yl)-methyl)-propane-1,3-diol[8b]

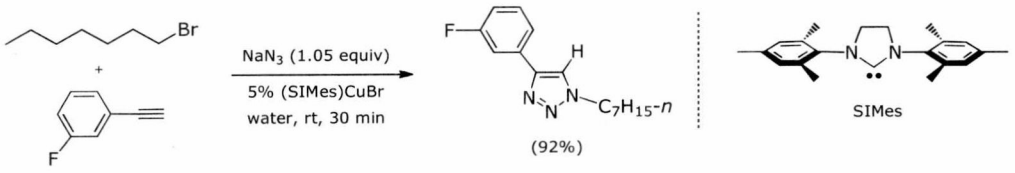


(98%)

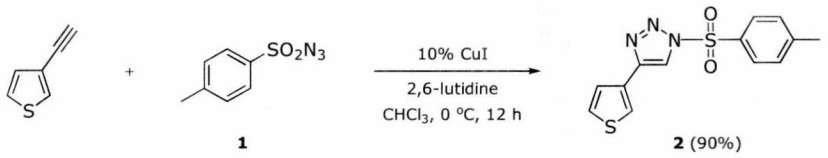
Phenylacetylene (2.04 g, 20 mmol) and 2,2-*bis*(azidomethyl)-propane-1,3-diol (1.86 g, 10 mmol) were dissolved in a 1:2 *t*-butyl alcohol/water mixture (50 mL). About 1 g of copper metal turnings was added, and the reaction mixture was stirred for 24 h; after which time, TLC analysis indicated complete 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; mp 211–212 °C; ESIMS *m/z*: 391.2 ($M + H^+$) 413.2 ($M + Na^+$).

Stabilized Cu(I) in the form of its *N*-heterocyclic carbene (NHC) complex, *e.g.*, (SIMes)CuBr (SIMes = *N,N'-bis*(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene), and the cyclohexyl analog $[(ICy)_2Cu]PF_6$, catalyzes click reactions very well in aqueous *t*-butanol, and even better in water alone.[12] Low conversions were noted in nonaqueous solvents such as tetrahydrofuran (THF), *t*-BuOH, and dichloromethane (DCM). Starting from an alkyl bromide, triazoles could be smoothly generated by *in situ* conversion to the corresponding azide (aqueous NaN_3) followed by copper-catalyzed cycloaddition. This is but one example of the potential for combining several steps in a single flask that culminates with a click reaction (*vide infra*). The

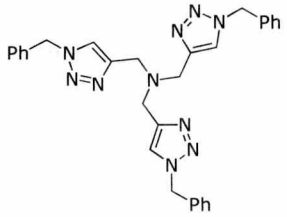
alternative use of $CuBr(Ph_3P)_3$ (0.5 mol%) in these 3-component couplings with NaN_3 (1.3 equiv) at room temperature is also best carried out in water as solvent.[13]



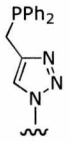
In general, as suggested by the above examples, outstanding compatibility exists among azides, 1-alkynes, and copper(I) along with the product triazoles with a vast array of other functional groups that may be present in either educt. Steric factors do exert an effect on rates. In most situations, the beneficial impact of a trialkylamine base (*e.g.*, *i*-Pr_2NEt and 1,4-diazabicyclo[2.2.2]octane [DABCO]) or others (*e.g.*, 1,8-diazabicyclo[5.4.0]undec-7-ene [DBU] and 2,6-lutidine) is used to great advantage, in particular when less soluble CuI in toluene (or even CH_3CN) is the catalyst. A recent study suggests that in the presence of catalytic amounts of HOAc, together with *i*-Pr_2NEt (1:1), rapid quenching of the intermediate copper species occurs leading to enhanced reaction rates.[14] The counterion in the Cu(I) salt (*e.g.*, Br, I, and OAc), or the Cu(II) precursor to catalytically active Cu(I) (*e.g.*, -OAc and $-NO_3$) can exert influence. Microwave assistance can reduce reaction times from hours to minutes, although yields are mostly unaffected by this mainly thermal phenomenon. Tandem events in one-pot include initial azide formation by halide substitution resulting in a net three-component coupling all under microwave irradiation (procedure below).



Remarkable is the *in situ* conversion of amines into azides by Cu(II)-catalyzed diazo transfer in a mixed aqueous environment (using trifluoromethanesulfonylazide, TfN_3), followed by click cyclization.[15] Ligands such as *tris*(benzyltriazolylmethyl)amine (TBTA) and clickphine (below) have been used to accelerate these copper-catalyzed cycloadditions.[16] Recently, conditions have been found that lead to *N*-sulfonyl-4-substituted-1,2,3-triazoles using sulfonylazides (*e.g.*, **1** to **2**), avoiding products from competing ring-opening α-diazoimino tautomers.[17a] Reactions are best run in chloroform at 0 °C using catalytic CuI, giving yields in the moderate-to-high range. In a mixed aqueous solvent environment, or water alone, the corresponding *N*-tosylated amides are formed in good yields, rather than the corresponding triazoles.[17b] Sequential displacement of α-tosyloxy ketones by azide ion and subsequent one-pot cyclization in a polyethylene glycol (PEG)/water mixture at room temperature leads to carbonyl-containing triazole derivatives.[18]

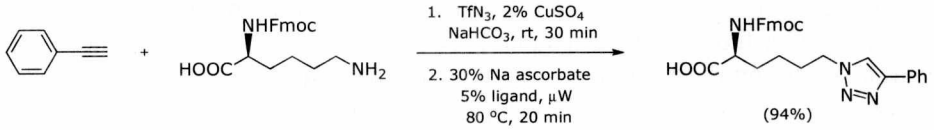


ligand TBTA



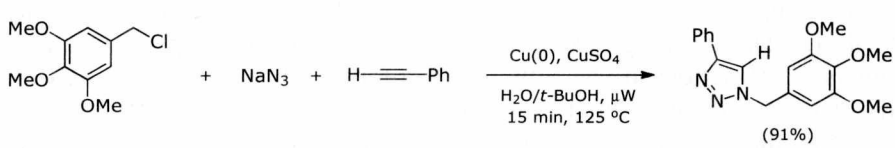
clickphine ligand

Sequential one-pot process for diazo transfer and azide-alkyne cycloaddition using $CuSO_4$ and sodium ascorbate[15]



Triflyl azide (TfN_3) was freshly prepared prior to each reaction. NaN_3 (6 equiv per substrate amine) was dissolved in a minimum volume of water (solubility of NaN_3 in water is approximately 0.4 g/mL). At 0 °C, an equal volume of DCM was added and triflic anhydride (Tf_2O; 3 equiv) was added dropwise to the vigorously stirred solution. After stirring for 2 h at 0 °C, the aqueous phase was once extracted with DCM. The combined organic phases were washed with sat. $NaHCO_3$ solution and used without further purification. The amine, Fmoc-Lys-OH (81 mg, 0.22 mmol), $CuSO_4$ (2 mol%), and $NaHCO_3$ (1 equiv) were dissolved/suspended in water (equal volume relative to DCM used for TfN_3). The TfN_3 solution was added, followed by addition of methanol until the mixture became homogeneous. The reaction was stirred at RT (*ca.* 30 min) until TLC showed complete consumption of the amine. Phenylacetylene (24 μL, 0.22 mmol) was added, then ligand TBTA (5 mol%), and then sodium ascorbate (30 mol%), and the reaction was heated to 80 °C in the microwave until complete loss of azide (≤30 min). The reaction mixture was then diluted with water and the organics extracted. Solvents were removed under reduced pressure. After flash chromatography ($CHCl_3$/MeOH/AcOH 96:3:1), the product (103 mg, 94%) was isolated as a white powder. ESIMS (MeOH): *m/z* calcd. for 495.2 $[M-H]^-$; found 495.3.

General procedure for microwave-assisted, three-component coupling reactions. 4-Phenyl-1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazole[19]



The benzylic halide (1.0 mmol), phenylacetylene (1.1 mmol), and sodium azide (1.1 mmol) were suspended in a 1:1 mixture of water and *t*-BuOH (1.5 mL each) in a 10-mL glass vial equipped with a small magnetic stirring bar. To this was added copper wire (50 mg) and copper sulfate solution (200 μL, 1 N), and the vial was tightly sealed with an aluminum/Teflon crimp top. The mixture was then irradiated using an irradiation power of 100 W (CEM Discover instrument; Matthews, NC). After completion of the reaction, the vial was cooled to 50 °C and then diluted with water (20 mL) and filtered.