DOI: 10.1002/ejoc.200500483

Cu^{I}-Catalyzed Alkyne–Azide "Click" Cycloadditions from a Mechanistic and Synthetic Perspective

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Keywords: Click chemistry / Cycloaddition / Heterocycles / Molecular diversity / Azides

Cu^{I}-catalyzed alkyne–azide cycloaddition provides 1,4-disubstituted 1,2,3-triazoles with such efficiency and scope that the transformation has been described as "click" chemistry. An overview of the mechanism of this remarkable reaction is presented as a means to explain the myriad of experimental results, particularly the various methods of catalyst generation, solvent and substrate effects, and choice of base or ligand. Both solution-phase and solid-phase results are comprehensively examined.

1. Introduction to the Cu^{I}-Catalyzed Alkyne–Azide "Click" Cycloaddition

Although demand for new chemical materials and biologically active molecules continues to grow, chemists have hardly begun to explore the vast pool of potentially active compounds.[1] The emerging field of "click chemistry," a newly identified classification for a set of powerful and selective reactions that form heteroatom links, offers a unique approach to this problem.[2] Reactions defined as "click" reactions require only benign reaction conditions and simple workup and purification procedures and can still rapidly create molecular diversity through the use of reactive modular building blocks.[2] By focusing the search for new compounds only on those available through these reliable and efficient reactions, click chemistry may accelerate the process of discovery and optimization.

Sharpless and co-workers have identified a number of reactions that meet the criteria for click chemistry,[2] arguably the most powerful of which discovered to date is the Cu^{I}-catalyzed variant of the Huisgen 1,3-dipolar cycloaddition[3] of azides and alkynes to afford 1,2,3-triazoles. As is not uncommon in organic synthesis, this reaction owes its usefulness in part to the ease with which azides and alkynes can be introduced into a molecule and their relative stability under a variety of conditions. Azides and alkynes are essentially inert to most biological and organic conditions, including highly functionalized biological molecules, molecular oxygen, water, and the majority of common reaction conditions in organic synthesis.[4,5] In most cases, the

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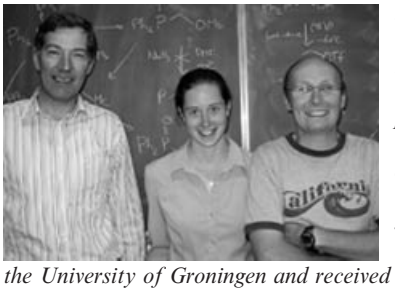


Jan van Maarseveen was born in Enschede, The Netherlands, in 1963. He studied chemistry at the University of Nijmegen and received his Ph. D. at this university with Prof. Binne Zwanenburg and Dr. Hans W. Scheeren in 1994. In the same year, he joined Solvay-Pharmaceuticals (Weesp, The Netherlands) as a group leader in the Medicinal Chemistry Department. He was appointed associate professor at the University of Amsterdam in 1999. In 2004 he joined the Ghadiri group at The Scripps Research Institute (La Jolla, USA) briefly to develop new methods for cyclic peptide synthesis using click chemistry. His current research interests are the development of novel synthetic methodology to enable difficult peptide cyclizations, homogeneous catalysis and the combination of organic synthesis and biology.

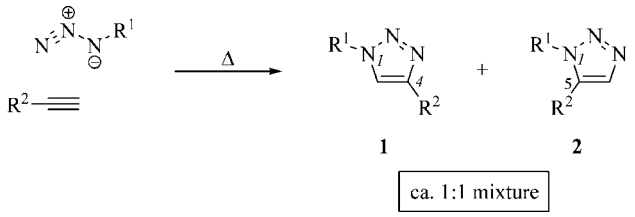
Henk Hiemstra was born in Dronrijp, Friesland, The Netherlands, in 1952. He studied chemistry at the University of Groningen and received his PhD. at this university with Prof. Hans Wynberg in 1980. After a postdoctoral stay with Prof. Barry M. Trost at the University of Wisconsin, Madison, USA, he was appointed at the University of Amsterdam in 1982. He was promoted to full professor of organic synthesis in 1997. His favorite research areas are new synthetic methodology and the total synthesis of natural products.

Victoria Bock was born in Webster, Texas, USA, in 1981. She received her B. A. in chemistry from Williams College (Williamstown, Massachusetts, USA) in 2004. She is currently studying at the University of Amsterdam in an international MSc. program.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

two functionalities can be installed when convenient and remain unaffected through a number of subsequent transformations.[6] In particular, despite the thermodynamic favorability of azide decomposition, kinetic factors allow aliphatic azides to remain nearly invisible until presented with a good dipolarophile.[5]

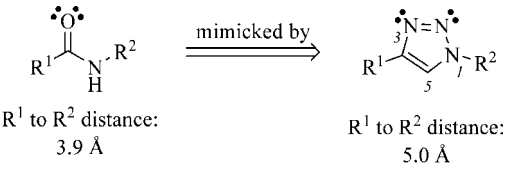
In fact, this kinetic stability of alkynes and azides is directly responsible for their slow cycloaddition, which generally requires elevated temperatures and long reaction times.[7,8] Good regioselectivity in the uncatalyzed Huisgen-type cycloaddition is observed for coupling reactions involving highly electron-deficient terminal alkynes,[9] but reactions with other alkynes usually afford mixtures of the 1,4- and 1,5-regioisomers (Scheme 1).[7]



Scheme 1. Products of thermal 1,3-cycloaddition.

Thus, only following the recent discovery of the advantages of Cu^{I}-catalyzed alkyne–azide coupling, reported independently by the Sharpless[5] and Meldal[10] groups, did the main benefits of this cycloaddition become clear. Cu^{I} catalysis dramatically improves regioselectivity to afford the 1,4-regioisomer exclusively (**1**, Scheme 1) and increases the reaction rate up to 10^7 times,[11] eliminating the need for elevated temperatures. This high-yielding reaction tolerates a variety of functional groups and affords the 1,2,3-triazole product with minimal work-up and purification,[5,10] an ideal click reaction.

Further interest in this reaction stems from the interesting biological activity of 1,2,3-triazoles. These heterocycles function as rigid linking units that can mimic the atom placement and electronic properties of a peptide bond without the same susceptibility to hydrolytic cleavage (Scheme 2).[2b,12] Some structural differences between triazoles and amide bonds of course exist; most notably, the extra atom in the triazole backbone leads to a calculated increase in R^1–R^2 distance of 1.1 Å over the typical amide bond (Scheme 2). Triazoles also possess a much stronger dipole moment than an amide bond,[13] but this may actually enhance peptide bond mimicry by increasing the hydrogen bond donor and acceptor properties of the triazole. In addition to the possibility of both the N(2) and N(3) triazole atoms acting as hydrogen-bond acceptors, the strong dipole may polarize the C(5) proton to such a degree that it can function as a hydrogen-bond donor, like the amide proton.[12b,14] Perhaps due in part to their ability to mimic certain aspects of a peptide bond, many known 1,2,3-triazoles possess varied biological activity, including *anti*-HIV activity,[15] selective β_3 adrenergic receptor inhibition,[16] *anti*-bacterial activity,[17] potent *anti*-histamine activity,[18] and more.[19,20]



Scheme 2. Topological and electronic similarities of amides and 1,2,3-triazoles.

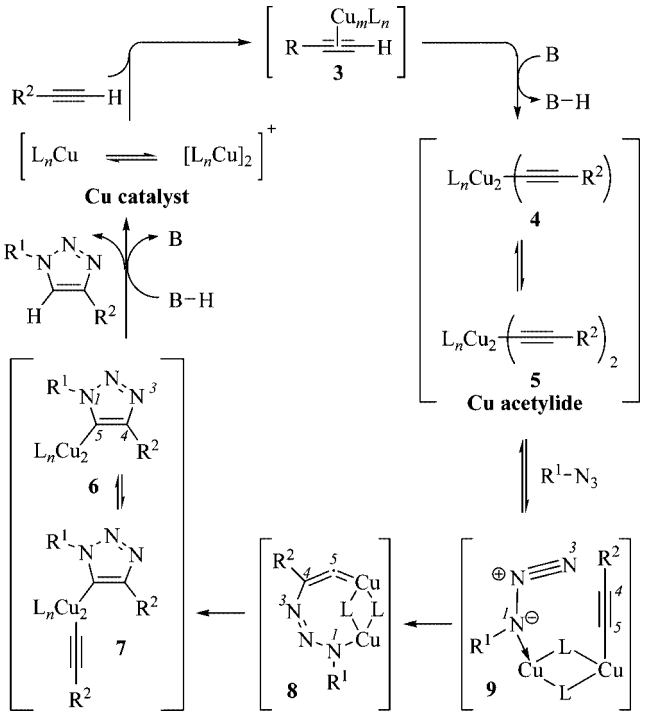
Since the initial discovery of Cu^{I}-catalyzed alkyne–azide coupling, numerous successful examples have been recorded in the literature, but as of yet, no systematic study of optimal conditions has been reported. Further, conditions have varied widely, particularly with respect to generation of the active Cu^{I} species. Sources of Cu^{I} include Cu^{I} salts, most commonly copper iodide,[10] in-situ reduction of Cu^{II} salts, particularly Cu^{II} sulfate,[5] and comproportionation of Cu^0 and Cu^{II}.[21] Recent reports suggest that nitrogen-based ligands can stabilize the Cu^{I} oxidation state under aerobic, aqueous conditions and promote the desired transformation.[22] Steric factors and electronic effects may also play a role in the success of this click chemistry.[10] Herein, we report a mechanism-based approach to unraveling the myriad of results reported since the discovery of Cu^{I}-catalyzed alkyne–azide coupling.

2. Mechanism of Cu^{I}-Catalyzed Alkyne–Azide Coupling

2.1 Mechanistic Outline of Cu^{I}-Catalyzed Alkyne–Azide Coupling

Any mechanism put forth for Cu^{I}-catalyzed alkyne–azide coupling should explain the body of experimental evidence that makes this transformation so unique. It tolerates most organic functional groups and shows a wide scope with respect to both alkyne and azide reactants. The reaction proceeds in a variety of solvents, tolerates a wide range of pH values, and performs well over a broad temperature range. To this end, researchers at The Scripps Institute in La Jolla, California, USA have proposed a stepwise mechanism on the basis of calculations and kinetic studies (Scheme 3).[21c,23]

Although the thermal dipolar cycloaddition of azides and alkynes occurs through a concerted mechanism, DFT calculations on monomeric copper acetylide complexes indicate that the concerted mechanism is strongly disfavored relative to a stepwise mechanism (Scheme 3). Although one can imagine, for example, direct, concerted cycloaddition of a copper–acetylene π complex with the appropriate azide, the calculated activation barrier for this process exceeds that of the uncatalyzed process, and the lowest barrier found for any concerted process is 23.7 kcal/mol,[21c] too high to be responsible for significant rate effect of Cu^{I} catalysis. Stepwise cycloaddition catalyzed by a monomeric Cu^{I} species lowers the activation barrier relative to the uncatalyzed process by as much as 11 kcal/mol, which



Scheme 3. Proposed outline of species involved in the catalytic cycle.

is sufficient to explain the incredible rate enhancement observed under Cu^{I} catalysis.[21c]

Based on earlier precedent of Cu^{I} insertion into terminal alkynes[24] and experimental evidence indicating that internal alkynes show no activity in this reaction,[5,10] researchers propose that the stepwise catalytic cycle begins with formation of a Cu^{I} acetylide species via the π complex **3** (Scheme 3). Alkyne π complexation requires ligand dissociation and is endothermic in acetonitrile by 0.6 kcal/mol. In aqueous solution, however, the formation of copper species **4** is exothermic by 11.7 kcal/mol, a result consistent with experimental findings of a rate acceleration in water. Calculations also indicate that copper coordination lowers the pK_a of the alkyne C–H by up to 9.8 pH units, thus making deprotonation in aqueous systems possible without the addition of a base.[21c] Although no prior calculations have shown such a significant effect on pK_a, Cu^{I} acetylides have been found in aqueous solution, even at acidic pH.[25]

Recent kinetic studies indicate that the rate of the catalytic process is second order in copper, but that with increasing copper concentrations, less reactive species such as metal aggregates form.[23] These results suggest that a dynamically changing family of different Cu^{I} acetylide species may exist in solution, depending on the reaction conditions.[26] Even π complexes may play a role, further complicating matters. While the role of the second copper atom seems to be activation of the azide functionality as in dimer **9** (Scheme 3), π complexation of a terminally bound acetylide to a proximal copper atom may also occur. This complexation doubtlessly changes the reactivity of the acetylide and likely increases acetylide activity toward cyclization by reducing the alkyne electron density.[10,26]

Overall, however, surprisingly little is known about the nature of the copper acetylide complexes active in Cu^{I}-catalyzed alkyne–azide coupling, even though evidence suggests that these species determine in large part the rate and success of catalysis. Under conditions of excess copper, the reaction was found to be between first and second order in alkyne concentration, suggesting either that two pathways, involving one and two acetylenes, respectively, are operative or that the preferred pathway requires two acetylenes but is inhibited at higher concentrations.[23] In the latter case, higher concentrations of the alkyne may in effect coordinatively saturate the copper ion, due to the Cu^{I} preference for alkyne ligands over azide ligands, preventing the azide from binding and reducing the overall rate. Commercially available copper acetylides, which are presumably already saturated with alkyne, show no catalytic activity, emphasizing the importance of labile ligand dissociation to catalysis, and as of yet, only one known[27] copper species has been shown to catalyze triazole formation.[23] Although questions about the nature of Cu^{I} acetylene complexes still exist, the current evidence indicates that the copper acetylide species involved in catalysis requires two metal centers, one or two alkyne ligands, and other labile ligands that allow for competitive azide binding.

Following the formation of the active copper acetylide species, azide displacement of one ligand generates a copper acetylide-azide complex, such as the dicopper species **9** (Scheme 3). Subsequent cyclization has been explored only for monomeric copper species,[21c] but we can imagine a similar process occurring for dimeric copper complexes. Complexation of the azide activates it toward nucleophilic attack of acetylide carbon C(4) at N(3) of the azide (numbers based on traditional triazole nomenclature), generating metallocycle **8**.[28] Consistent with this mechanism, experimental results indicate that electron-withdrawing substituents on the alkyne accelerate Cu^{I}-catalyzed alkyne–azide coupling.[10,26b] This metallocycle positions the bound azide properly for subsequent ring contraction by a transannular association of the N(1) lone pair of electrons with the C(5)–Cu π* orbital. Calculations indicate that ring contraction in the monomeric case ensues from the metallocycle intermediate with almost no barrier;[21c] the difference in ring size for dimeric complexes may change the kinetics slightly, but most likely the transformation from metallocycle **8** into triazole-copper derivative **6** is similarly fast.

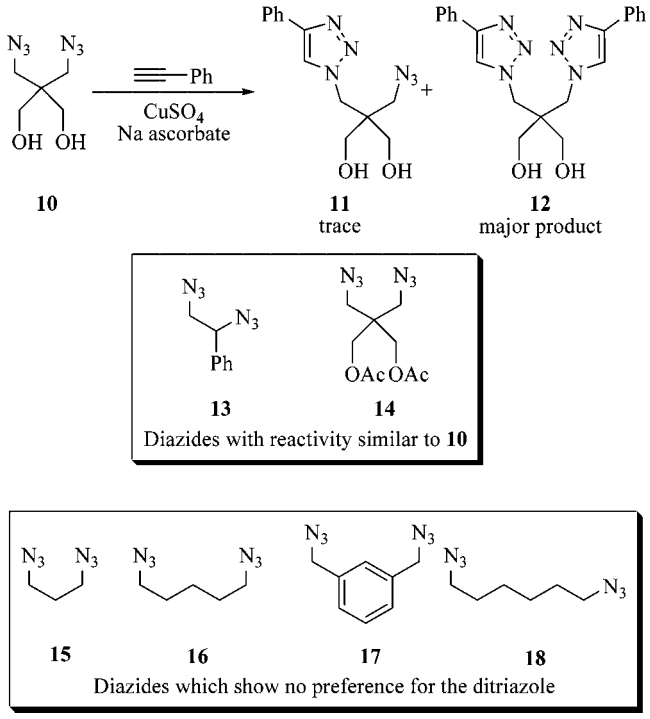
Protonation of triazole-copper derivative **7** followed by dissociation of the product ends the reaction and regenerates the catalyst (Scheme 3). Limited deuteration studies suggest that protonation occurs through interaction with a protonated external base or solvent molecule,[21c,23] but further studies are needed to conclusively establish the proton source.

2.2 Mechanistic Studies

Although kinetic and computational studies provide this broad mechanistic outline, recent unexpected experimental

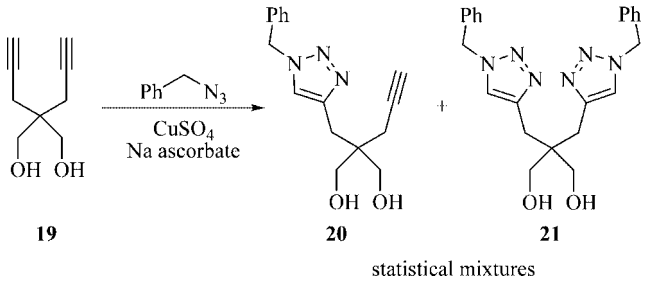
results add more questions into the precise nature of the reactive intermediates. In particular, the role of π complexation in the catalytically-active species remains uncertain. Finn and co-workers evoke π complexation as a means of positioning substrates to explain the unusual cyclodimerization observed during an attempted cyclization of a peptide on the solid phase, but other factors such as influence from the resin and copper–peptide interactions may also contribute to the anomalous results.[29]

Further, π complexation may also activate a terminally-bound copper acetylene toward cycloaddition. Such activation may help explain unusual product distributions observed for various diazides and dialkynes subjected to Cu^{I}-catalyzed alkyne–azide coupling.[23] Reaction of diazide **10** with phenylacetylene affords the ditriazole **12** as the major product (Scheme 4), even under conditions of excess diazide, while reaction of the analogous dialkyne **19** with benzyl azide provides a statistical mixture of the monotriazole **20** and the ditriazole **21** (Scheme 5) Kinetic studies indicate that during the cycloaddition of the diazide **10**, a low level of monotriazole **11** forms and remains constant throughout the reaction, while the monotriazole **20** builds up initially before leveling off in a manner consistent with two sequential reactions of approximately equal rates.



Scheme 4. Reactivity of diazides toward Cu^{I}-catalyzed cycloaddition.

Only conformational constrained diazides such as **10**, **13**, and **14** show this activity (Scheme 4), indicating that the first triazole must be held in close proximity to the azide for this effect to occur.[23] Reactions of diazide **10** show no evidence of autocatalysis, and no rate acceleration was observed in the coupling of phenylacetylene and benzyl azide upon addition of the ditriazole **12**. These results suggest

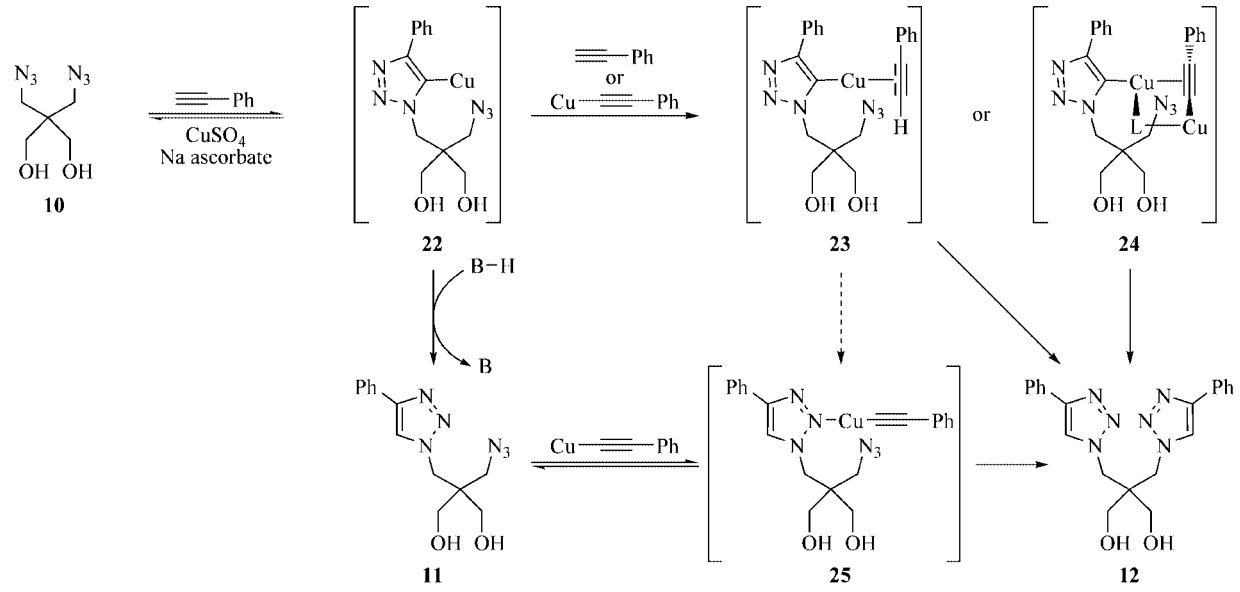


Scheme 5. Cu-catalyzed cyclization of dialkyne **19**.

that the formation of the first triazole catalyzes the subsequent cycloaddition to give the ditriazole. Cu^{I}-catalyzed alkyne–azide cycloaddition of the independently-prepared monotriazole **11** proceeded at a higher rate than cycloaddition of the diazide **10**, but the rate acceleration was not sufficient to explain the overwhelming preference for ditriazole **12**. Based on these findings and results indicating that the conversion of diazide **10** into ditriazole **12** occurs via some intermediate other than monotriazole **11**, Finn and co-workers propose a mechanism based on capture of intermediate **22** before protonation that would yield free ditriazole **12** (Scheme 6).[23]

Initial cycloaddition yields the copper triazole intermediate **22**, via the same mechanism outlined for the formation of the copper triazoles **6** and **7** (Scheme 3). This intermediate can either undergo protonation to afford monotriazole **11** or can associate with another terminal alkyne[30] or a copper acetylide species[30a,31] to give intermediates **23** and **24**, respectively. Due to the favorable conformation that holds the alkyne and azide functionalities in close proximity in both intermediates **23** and **24**, rapid intramolecular triazole formation is expected from either intermediate.[23] Based on kinetic results indicating the presence of two copper ions in the active copper acetylide species, however, the reaction more likely proceeds via copper dimer **24**. Intermediate copper monotriazole **22** is a simplification of the actual complex, which most likely contains two copper ions and perhaps a bound acetylene (see triazole **6**, Scheme 3). Ligand dissociation could facilely lead to copper dimer **24**, which is not only properly positioned for rapid intramolecular cyclization, but also has an activating π-interaction between the triazole-bound copper ion and the acetylene. Additionally, formation of triazole-copper complex **25** explains the rate enhancement of monotriazole **11** over diazide **10** by directing the Cu^{I} acetylide to the azide. As a side-note, these results also suggest that copper–triazole intermediates **6** or **7** (Scheme 3) may have significant lifetimes, even in aqueous solution, since capture by an alkyne or copper acetylide species seems to occur more quickly than protonation.[32]

Overall, kinetic and mechanistic studies have established the presence of two copper ions, one or two acetylenes, and one azide in the active complex. π complexation of a copper acetylide species to another copper ion may help position substrates appropriately for cycloaddition and activate the acetylene for attack by the azide. Further studies into the



Scheme 6. Proposed mechanism to account for diazide reactivity.

mechanism of Cu^{I}-catalyzed alkyne–azide coupling should reveal more of the character of the active copper acetylide species, but to date, its exact nature remains unknown.

3. Analysis of Results Reported for Cu^{I}-Catalyzed Alkyne–Azide Cycloaddition

3.1 Solution-Phase Results

Since the independent discovery of Cu^{I}-catalyzed alkyne–azide coupling by two different groups in 2002,[5,10] reported conditions have varied widely, with catalyst generation a particular source of contention. Meldal and co-workers initially described the use of Cu^{I} salts on the solid phase,[5] while Sharpless and co-workers reported solution-phase in-situ reduction of Cu^{II} salts or comproportionation of Cu^{0} and Cu^{II}.[10] No comprehensive studies on the ideal conditions for Cu^{I}-catalyzed alkyne–azide coupling have been completed to date, but results over the past two years suggest that alkyne–azide coupling affords most triazoles in high yield under a variety of conditions, underscoring the robustness of this reaction.

3.1.1 Formation of Cu^{I} Catalyst by Reduction of Cu^{II} Salts

In-situ generation of Cu^{I} from Cu^{II} salts, usually Cu^{II} sulfate pentahydrate, can occur by comproportionation with copper metal or by reduction and has the advantage of not requiring inert atmospheres despite the instability of the Cu^{I} oxidation state in the presence of oxygen.[33,34] Although both reduction and comproportionation have a wide scope and tolerate many organic functional groups, copper–metal comproportionation is generally limited to special applications, such as biological systems, that preclude the use of most reducing agents.[35] This preference for reduction likely results from a combination of the longer reaction times required for comproportionation and the simpler workup of the reduction method. In traditional solution chemistry with copper sulfate (Table 1, Table 2),[5,23,36] sodium ascorbate[37] at a three- to ten-fold excess over the copper catalyst is the favored reducing agent, though the use of tris(2-carboxyethyl)phosphane hydrochloride (TCEP)[38] has been reported in biological systems.[35c,39]

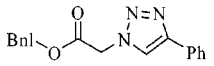
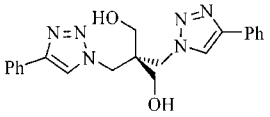
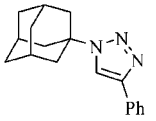
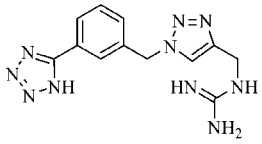
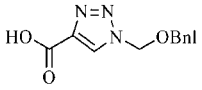
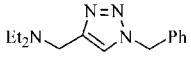
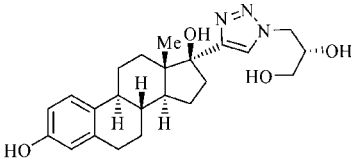
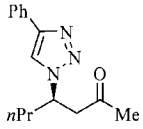
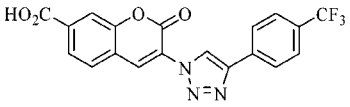
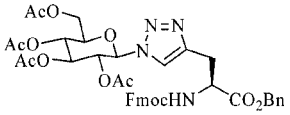
Current examples in literature demonstrate the scope of this click reaction and the variety of conditions that have proven successful. Alkyne–azide cycloaddition tolerates a wide range of functional groups, including unprotected alcohols, carboxylic acids, and amines, and shows little sensitivity to steric factors, as even tertiary azides undergo coupling in high yield (see Table 1, Table 2). Most commonly, the reaction is performed in a water/alcohol mixture, which facilitates solvation of lipophilic reactants while still retaining the advantages of water, such as faster reaction times and preclusion of the need for an added base. Mixtures of water and organic cosolvents such as DMSO seem to produce equally good results.[36c] Catalyst loading can be quite low, though molecules with solubility problems in water/alcohol mixtures, such as calixarene **26**, may require a higher loading to obtain a good yield (Table 2).

As expected for a reaction classified as "click chemistry," triazoles are generated for the most part with high yields and almost no workup. Workup for most reactions involves little more than filtration to collect a pure precipitate; even the aqueous extraction required for non-solid product triazoles necessitates only the most basic techniques.[23,36a–36b]

3.1.2 Formation of Cu^{I} Catalyst by Oxidation of Cu Metal

Oxidation of copper metal provides another method for generating the Cu^{I} catalyst for triazole formation. Addition of excess copper turnings to azides and alkynes in water/alcohol mixtures affords the corresponding triazoles in good yield (Table 3).[21c] Since reactions with copper turnings require longer running times and more copper than

Table 1. Representative results of solution-phase triazole formation by $CuSO_4$ reduction. All reactions were carried at room temperature and were complete in 12 to 24 hours.

Entry	Product Triazole	Alkyne	Azide	Cu^{II} Salt[a]	Na Ascorbate	Solvent	Yield[b]
1[c]		1 eq	1 eq	0.01 eq	0.1 eq	1:1 H_2O:*t*BuOH	92%
2[c]		1 eq[d]	1 eq	0.01 eq	0.1 eq	1:1 H_2O:*t*BuOH	93%
3[c]		1 eq	1 eq	0.01 eq	0.1 eq	1:1 H_2O:*t*BuOH	84%
4[c]		1 eq	1 eq	0.01 eq	0.1 eq	1:1 H_2O:*t*BuOH	88%
5[c]		1 eq	1 eq	0.01 eq	0.1 eq	1:1 H_2O:*t*BuOH	88%
6[c]		1 eq	1 eq	0.01 eq	0.1 eq	1:1 H_2O:*t*BuOH	90%
7[c]		1 eq	1 eq	0.01 eq	0.1 eq	1:1 H_2O:*t*BuOH	94%
8[e]		2 eq	1 eq	0.01 eq	0.1 eq	1:1 H_2O:EtOH	89%
9[f]		1 eq	1 eq	0.05 eq	0.2 eq	1:1 H_2O:EtOH	86%
10[g]		1 eq	1 eq	0.2 eq $Cu(OAc)_2$	0.4 eq	1:1 H_2O:*t*BuOH	70%

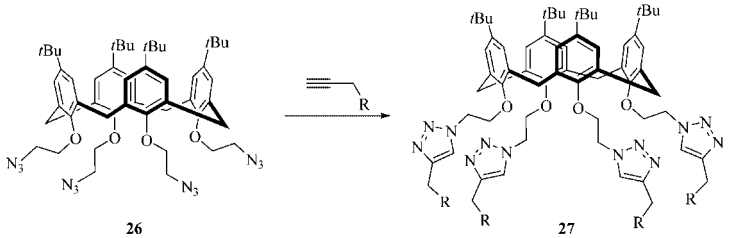
[a] Cu^{II} salt is $CuSO_4$ unless otherwise noted. [b] Isolated yield. [c] Ref.[5] [d] Equivalents per azide unit. [e] Ref.[36b] [f] Ref.[36d]. [g] Ref.[36i]

other protocols, nanosize Cu^0 provides an alternative method of catalyst generation comparable to the efficiency of other protocols.[40] Oxidative dissolution of Cu^0 nanosize activated powder into Cu^I by an amine hydrochloride salt[41] yields the desired triazole in good yield (Scheme 7). This protocol shows high tolerance to a variety of functional groups but requires the presence of an amine salt, either added (as in Scheme 7) or incorporated into alkyne or azide.[40a] Presumably, amine hydrochloride salt mediates dissolution of Cu^0 into Cu^I. Subsequent coordination of a nitrogen-based ligand to the Cu^I species then occurs, followed by displacement by an alkyne to give the active copper acetylide species. Cu^I can then either undergo disproportionation[42] to Cu^{II} and Cu^0 or further oxidation to Cu^{II}; oxidation to Cu^{II} apparently prevails, indicated by the blue color that forms upon completion of the reaction.[40a]

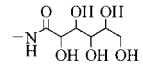
Cu^0 nanosize clusters also effectively catalyze alkyne–azide cycloaddition, though without the need for an amine hydrochloride salt (Scheme 8).[40b] Evidence indicates that the reaction takes place on the surface of the nanoclusters rather than in solution, but Cu^I is most likely still the active oxidation state in this reaction.[43]

Reactions with nanosize Cu^0 appear to have the same wide scope and high yields as expected in click chemistry, though the main disadvantages will likely limit future implementation. Solvation of Cu^0 nanosize particles requires

Table 2. Results of solution-phase triazole formation by $CuSO_4$ reduction on calixarenes (data taken from ref.[36h]). All reactions were carried at under N_2 at 60 °C and were complete 24 hours.

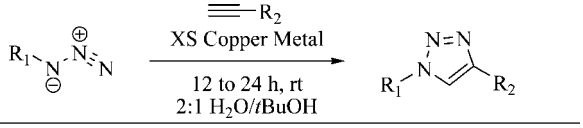


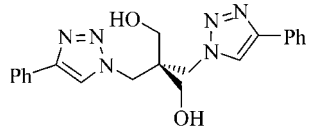
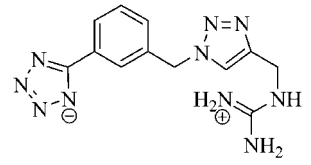
26 **27**

Entry	Alkyne Substituent	Alkyne	$CuSO_4$	Azide	Na Ascorbate	Solvent	Yield[a]
1	R = 	1.25 eq[b]	0.2 eq	1 eq	1.25 eq	1:2:2 THF:H_2O:EtOH	51%
2	R = $-SO_3Na$	1.05 eq[b]	0.4 eq	1 eq	4.5 eq	1:2:2 THF:H_2O:EtOH	79%
3	R = $-NMe_3Br$	1.05 eq[b]	0.4 eq	1 eq	4.5 eq	1:2:2 THF:H_2O:EtOH	78%

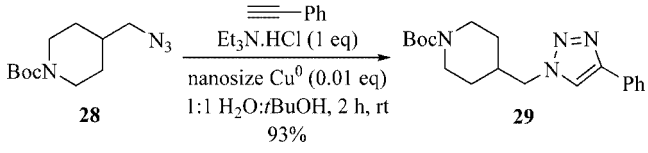
[a] Isolated yield. [b] Equivalents per azide unit.

Table 3. Results of solution-phase triazole synthesis with Cu metal (data taken from ref.[21c]).



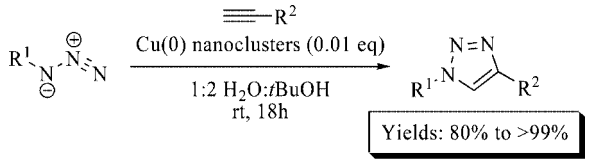
Entry	Product Triazole	Alkyne	Azide	Yield
1		1 eq[a]	1 eq	98%
2		1 eq	1 eq	88%

[a] Equivalents per azide unit.



28 **29**

Scheme 7. Typical example of solution-phase triazole synthesis with nanosize Cu^0.



$R^1 = C_6H_5$; $C_6H_5CH_2$–
$R^2 = C_6H_5$; $C_6H_5(OH)CH$–; $CH_2(OH)$–

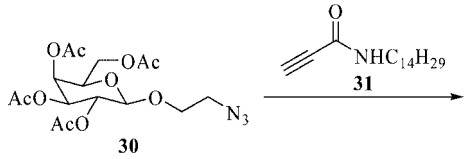
Scheme 8. Triazole formation catalyzed by Cu^0 nanoclusters.

a slightly acidic environment, approximately pH 5, implying that acid-sensitive functional groups that easily withstand other protocols require protection prior to cyclization. Further, Cu^0 nanosize clusters are not commercially available, and Cu^0 nanosize powder costs more than seven times as much as other copper sources utilized in Cu^I-catalyzed alkyne–azide coupling,[44] greatly limiting the applicability of these protocols in research and industry.

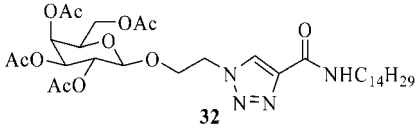
3.1.3 Formation of Cu^I Catalyst by Addition of a Cu^I Salt

Initial solution-phase Cu^I-catalyzed alkyne–azide coupling reactions lacked the apparent robustness observed with copper sulfate reduction or Cu^0 oxidation, due to complicating side reactions.[10,45] An early study by Wong and co-

Table 4. Results of cycloaddition of the azide **30** and alkyne **31** (data taken from ref.[46]).



30 **31**



32

Entry	Alkyne	Base (1 eq)	CuI	Solvent	*T* [°C]	Time	Yield[a]
1	5 eq	None	None	None	80	24 h	89%[b]
2	1 eq	Et_3N	2 eq	MeCN	rt	18 h	trace
3	1 eq	DIPEA	2 eq	MeCN	rt	18 h	38%
4	1 eq	Et_3N	0.1 eq	toluene	rt	18 h	65%
5	1 eq	DIPEA	0.1 eq	toluene	rt	18 h	85%
6	1 eq	None	0.1 eq	toluene	rt	3 days	52%
7	1 eq	None	0.1 eq	toluene	rt	7 days	61%

[a] Isolated yields. [b] 4:1 Mixture of 1,4- and 1,5-regioisomers.

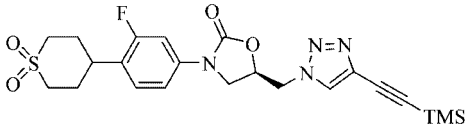
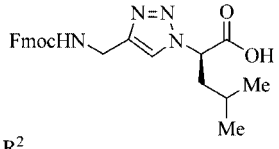
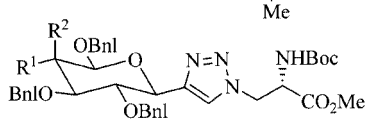
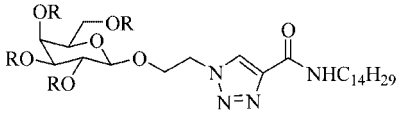
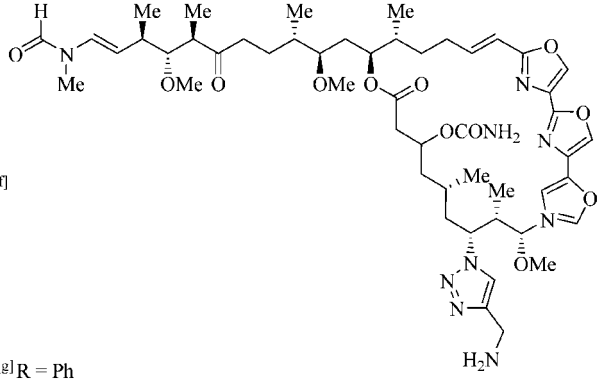
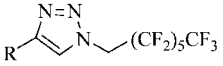
workers demonstrated this extreme sensitivity to reaction conditions (Table 4): Triethylamine in acetonitrile afforded no product, whereas use of DIPEA for the base produced the triazole **32** in 38% yield.[46] With no base added (Table 4, Entries 6, 7), reactions proceeded much more slowly, most likely due to difficulties forming the active copper acetylide complex. As discussed above, deprotonation of the π complex **2** to form the copper acetylide **4** (Scheme 3) can occur without the addition of a base in water, but in organic solvents, the formation of **4** is unfavorable and a base is required for deprotonation.[21c]

In practice, bases such as DIPEA and 2,6-lutidine improve results in Cu^I-catalyzed alkyne–azide coupling by minimizing side-product formation,[5,12,45] but the absence of thorough studies comparing conditions makes comprehensive analysis difficult (Table 5).[47] Excess base appears to give particularly high yields (Table 5, Entry 2), perhaps by stabilizing the Cu^I oxidation state. Nitrogen-type donors, including bases and certain solvents such as acetonitrile,[48] help to prevent degradation of Cu^I by oxidation or disproportionation, which greatly increases reaction rates, especially due to the second-order dependence on Cu^I concentration.

In general, a variety of triazole products are obtained in good yield through a range of conditions. Fluoro-substituted triazoles, however, prove more difficult to synthesize (Table 5, Entry 6),[47f] likely due to their highly electron-deficient nature. Binding to the copper–acetylene complex may be less favorable, enabling more side-product formation to occur.[45] Other factors may be involved, however, as unprotected alcohols interfere with cycloaddition of fluoro-substituted azides,[47f] a problem not observed with other systems.[49]

Cu^I salts therefore represent a reliable means of catalyzing alkyne–azide cycloaddition, particularly in the presence of excess base. Optimal solvent and base conditions may

Table 5. Results of solution-phase triazole formation by Cu^I salt addition. All reactions were carried at room temperature.

Entry	Product Triazole	Alkyne	Azide	Cu Salt	Base	Solvent	Time	Yield[a]
1[b]		1.6 eq	1 eq	0.1 eq CuI	1.1 eq 2,6-lutidine	MeCN	12 h	80%
2[c]		1 eq	1 eq	0.1 eq CuI	2 eq (each) 2,6-lutidine DIPEA	MeCN	3 h	97%
3a[d] R^1 = H, R^2 = OBnl		1 eq	1 eq	0.1 eq CuI	1 eq DIPEA	toluene	15 h	80%
3b[d] R^1 = OBnl, R^2 = H								82%
4a[e] R = H		1 eq	1 eq	0.1 eq CuI	1 eq DIPEA	toluene	18 h	85%
4b[e] R = Ac								80%
5[f]		1.5 eq	1 eq	0.13 eq CuI	2 eq Et_3N	1:1 H_2O/MeOH	1 h	63%
6a[g] R = Ph								66%
6b[g] R = C_6H_{13}		1.1 eq	1 eq	0.01 eq CuI	1.1 eq Et_3N	2:1 H_2O/MeCN	20 h	77%
6c[g] R = CO_2Me								37%

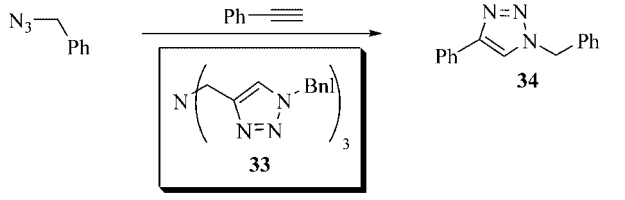
[a] Isolated yield. [b] Ref.[47a], dry conditions. [c] Ref.[12a], dry conditions, inert atmosphere. [d] Ref.[47b] [e] Ref.[46] [f] Ref.[47d] [g] Ref.[47f]

depend on the substrate, but in general, this reaction shows good results under varying conditions.

3.1.4 Ligand-Assisted Cu[I]-Catalyzed Alkyne–Azide Coupling

Although alkyne–azide cycloaddition is effectively catalyzed under "ligand-free" conditions in which only solvent molecules or bases serve as ligands to the metal, the addition of certain heterocyclic chelates further accelerates the reaction, likely by shielding the Cu^{I} ion from interactions leading to degradation.[22] As a result of this, ligands such as amine triazole **33** dramatically reduce the minimum catalyst loading as much as tenfold without requiring longer reaction times (Table 6). Further, addition of ligand **33** precludes the need for base even in organic solvents, as the tertiary nitrogen center functions both as a donor to Cu^{I} and a proton acceptor (Table 6, Entry 1).

Table 6. Ligand-assisted Cu^{I}-catalyzed cycloaddition.

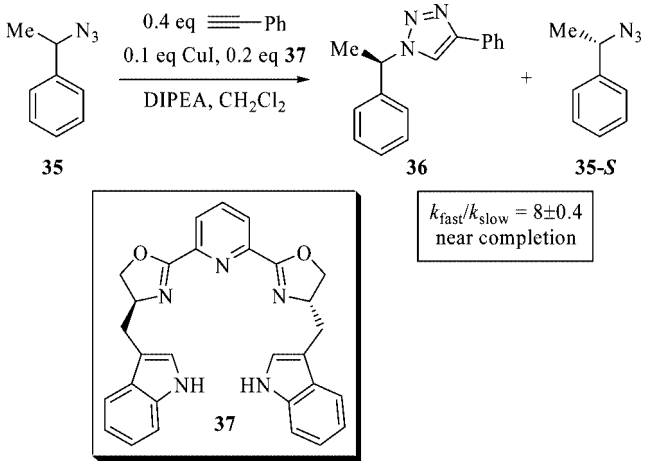


Entry	Conditions	Yield
1[a]	$Cu(MeCN)_4PF_6$ (0.01 eq), ligand **33** (0.01 eq) 2:1 *t*BuOH/H_2O, rt, 24 h	84%
2[b]	Na ascorbate (0.05 eq), $CuSO_4$ (0.0025 eq) ligand **33** (0.005 eq), 1:1 EtOH/H_2O, 4 h, rt	> 85%

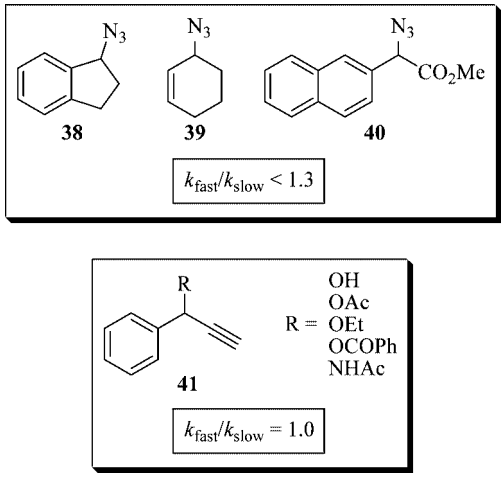
[a] Ref.[22]. [b] Ref.[50].

In contrast to the limited research into ligand effects in traditional solution-phase chemistry, the numerous examples of ligand rate acceleration in bioconjugation provide additional evidence of the stabilizing properties of ligand **33**.[35,39,50] In fact, one study investigating in-vivo proteome labeling observed that Cu^{II} sulfate and ligand **33** efficiently catalyzed triazole formation, even in the absence of a reducing agent.[39a] Interestingly, however, copper catalysis lacking both a reducing agent and ligand **33** afforded significantly reduced levels of labeled product, suggesting that the endogenous reductant produces only a low concentration of Cu^{I} that requires ligand stabilization to efficiently produce labeled product. Of the research currently available, only a study utilizing alkyne–azide cycloaddition to couple dyes onto protein observed no rate enhancement or improvement of any sort through addition of ligand **33**.[35a]

While amine triazole **33** was first reported as the most efficient ligand for cycloaddition catalysis,[22] various other ligands, including chiral pybox ligands such as pybox ligand **37** (Scheme 9), effectively accelerate cycloaddition as well.[51] These chiral ligands also add enantioselectivity to click chemistry: Fokin, Finn, and co-workers reported modest levels of selectivity in the kinetic resolution of racemic azide **35**, with a 2:1 ratio of CuI/**37** proving most effective. Attempted kinetic resolution of azides **38** to **40** proved unsuccessful, with only low rates of selectivity observed,[52] and benzyl acetylenes analogous to azide **35** reacted with no enantioselectivity (Scheme 10).[51]



Scheme 9. Kinetic resolution of azide **35**.



Scheme 10. Results of kinetic resolution on other racemic substrates.

These results suggest that in the acetylene–azide copper intermediate (dimer **9**, L_2 = **37**; Scheme 3), only the azide substituents experience a chiral environment, likely due to proximity to the chiral ligand.[51] As the binding mode of dimer **9** suggests (Scheme 3), the azide substituents lie closer to the Cu^{I}–ligand complex than the acetylene substituents, resulting in better enantioselectivity for the kinetic resolution of azides. As the precise nature and binding modes of intermediates such as dimer **9** and copper–acetylide intermediates **4** and **5** remains to date unknown (Scheme 3), other factors such as counterion association or complex binding modes may also influence reactivity.

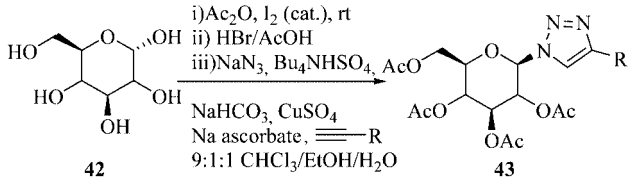
Overall, ligand-accelerated cycloaddition seems to suit bioconjugation studies particularly well, especially in-vivo experiments that may limit the use of other bases or means of improving reaction results. Kinetic resolution is also an interesting application, particularly with respect to mechanistic aspects of alkyne–azide cycloaddition, but for tradi-

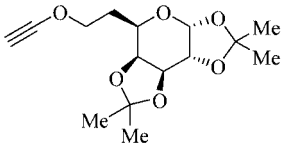
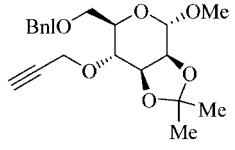
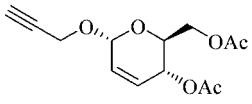
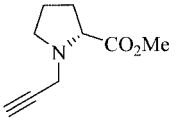
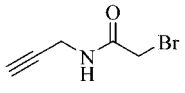
tional chemistry, especially on the scale done in most academic laboratories, the necessity of removing the ligand from the subsequent products complicates the simple workup and purification that make this click chemistry so attractive to chemists. While addition of ligands such as **33** or **37** may improve certain aspects of the cycloaddition, other methods, such as use of excess base, may in some cases produce the same results and preclude the need for additional purification.

3.1.5 One-Pot Multi-Step Reactions involving Cu^I-Catalyzed Alkyne–Azide Coupling

Given the unfavorable reputation of azides among organic chemists, in-situ generation of azides without isolation can further expand the applications of copper catalyzed click chemistry. Such one-pot procedures can help to expand the efficiency and further broaden the scope of this reaction, particularly if the wide scope and reliability of alkyne–azide coupling is maintained. Gratifyingly, the newly-reported one-pot procedures involving click chemistry show the same level of success as expected from traditional alkyne–azide coupling reactions.

Table 7. One-pot synthesis of triazolylglycosides by click chemistry (data taken from ref.[53]). Reactions with glucose and galactose were conducted at room temp. and run overnight; reactions with mannose were conducted at 80 °C and run overnight.

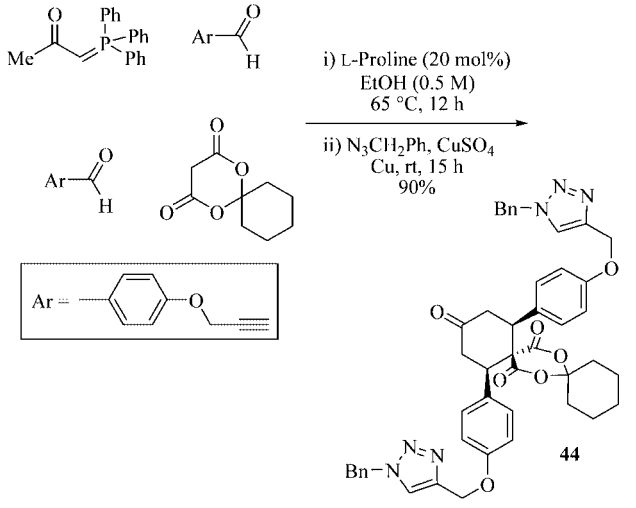


Entry	Sugar Moiety	Alkyne	Yield[a]
1a	D-Glucose		95%
1b	D-Galactose		71%
2	D-Glucose		81%
3	D-Glucose		77%
4	D-Glucose		71%
5	D-Glucose		72%
6a	D-Galactose		71%
6b	D-Mannose		98%
7	D-Mannose		71%

[a] Isolated yield.

One-pot synthesis of triazole-substituted glycoconjugates from unprotected monosaccharides utilizes click chemistry to rapidly link complex monomers.[53] In one pot, acetate protection, brominolysis, and subsequent azide generation in the presence of an acetylide yields the expected triazole product in good yield over the four transformations (Table 7). Alkyne–azide coupling on protected D-glucose and D-galactose proceeds smoothly overnight at room temperature, but steric interference from the β-substituent on the three position of D-mannose reduces the reaction rate such that elevated temperatures are required to obtain the desired triazole (Table 7, Entries 6b, 7).[54] Wang and coworkers also demonstrate success with in-situ azide generation and subsequent Cu^I-catalyzed alkyne–azide cycloaddition on saccharides; their methods afford even polyvalent glycoconjugates in fair yield, demonstrating the efficiency of their methodology.[53]

Combining multiple reactions in a single pot requires specific selectivity and minimal side-product formation; the inertness of alkyne and azide functional groups makes alkyne–azide coupling ideal for this purpose. Researchers have recently developed a protocol for a one-pot reaction involving four transformations (Scheme 11): the Wittig olefination, the Knoevenagel condensation, the Diels–Alder cyclization, and Cu^I-catalyzed alkyne–azide cycloaddition.[55] This reaction works with a variety of organic azides and provides high yields over the four transformations.



Scheme 11. One-pot Wittig Knoevenagel Diels–Alder click cycloaddition.

3.1.6 Microwave-Assisted Cu^I-Catalyzed Alkyne–Azide Coupling

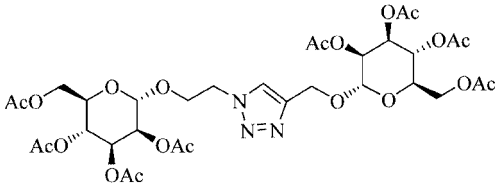
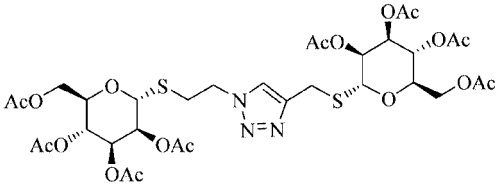
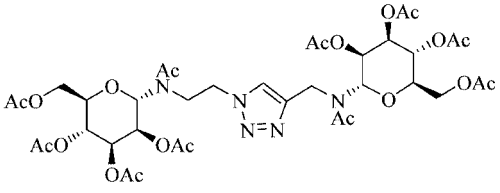
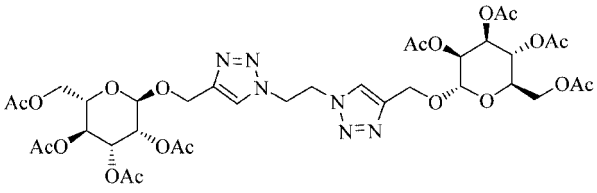
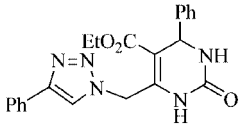
Since the first reports in 1986,[56] microwave-assisted organic synthesis has generated considerable attention by producing products in cleaner, higher-yielding reactions than

traditional methodology and by reducing reaction times to minutes and seconds, rather than days and hours.[57] Since the energy of the microwave photons in all current dedicated microwave reactors is too low to break chemical bonds,[58] the enhancement observed in microwave chemistry may result from efficient dielectric heating that creates an inverted temperature gradient relative to traditional heating methodologies.[58c]

Although Cu[I]-catalyzed alkyne–azide coupling often requires no additional heating, microwave chemistry can dramatically reduce reactions times in many cases from over twelve hours (see Table 5) to less than one hour (Table 8).[36a,59] Yields for these reactions show no considerable gain over traditional methodology,[60] suggesting that microwave heating increases the rate of the desired reaction and any undesired side reactions equally.[45]

Alkyne substituent effects, similar to those observed for cycloaddition reactions conducted at room temperature, dramatically affect the success of the microwave-assisted reaction. As previously noted for traditional methodologies,[10,26] electron-deficient alkynes react most quickly, likely due to facile formation of the Cu[I] acetylide species and increased rate of electrophilic attack by the bound azide (Scheme 3). For reactions utilizing $(Ph_3P)_3CuBr$/DIPEA, this effect seems particularly pronounced: Electron-rich alkyne reactants yield no product (Table 8, Entries 2a and 3a) in contrast to the high yield obtained for the more electron-poor oxygen-substituted alkyne (Table 8, Entry 1).[59a] Remarkably, addition of copper iodide to the $(Ph_3P)_3CuBr$/DIPEA system (Table 8, Entry 3b) or use of $(EtO)_3PCuI$ for $(Ph_3P)_3CuBr$ (Table 8, Entry 2) dramatically improves the results. Use of DBU, a stronger base than

Table 8. Representative microwave-assisted Cu[I]-catalyzed triazole formation. All reactions were carried in a microwave oven.

Entry	Product Triazole	Alkyne	Azide	Cu Source	Base or Reducing Agent	Solvent	Time	Yield[a]
1[b]		1.1 eq	1 eq	0.1 eq $(Ph_3P)_3CuBr$	3 eq DIPEA	toluene	34 min	86%
2a[b]		1.1 eq	1 eq	0.1 eq $(Ph_3P)_3CuBr$	3 eq DIPEA	toluene	[c]	0%
2b[b]		1.1 eq	1 eq	0.1 eq $(EtO)_3PCuI$	3 eq DIPEA	toluene	15 min	99%
3a[b]		1.1 eq	1 eq	0.1 eq $(Ph_3P)_3CuBr$	3 eq DIPEA	toluene	[c]	0%
3b[b]		1.1 eq	1 eq	0.1 eq $(Ph_3P)_3CuBr$	3 eq DBU	toluene	46 min	51%
3c[b]		1.1 eq	1 eq	0.1 eq CuI and 0.1 eq $(Ph_3P)_3CuBr$	3 eq DIPEA	toluene	26 min	96%
4[b]		1.1 eq[d]	1 eq	0.1 eq $(Ph_3P)_3CuBr$	3 eq DIPEA	toluene	11 min	93%
5[e]		1 eq	1 eq	0.02 eq $CuSO_4$	0.2 eq Na ascorbate	DMF	10 min	73%

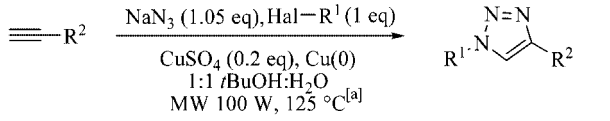
[a] Isolated yield. [b] Ref.[59a], 850 W, no *T* reported. [c] No time reported. [d] Equivalents of alkyne per azide functionality. [e] Ref.[59b], 90 °C, no microwave wattage reported.

DIPEA, also offers some improvement over the $(Ph_3P)_3$-CuBr/DIPEA system for electron-rich alkynes (Table 8, Entry 3a), but the yield remains rather disappointing. DBU likely increases the rate of copper acetylide formation by favoring deprotonation of the π-complexed alkyne (Scheme 3), but the stronger base may also favor side-product formation,[45] resulting in a low yield.

Furthermore, by dramatically increasing reaction rate, microwave-assisted alkyne–azide cycloaddition provides a possible means of overcoming some of the difficulties with aqueous solvents observed with other protocols. For products insoluble in water/alcohol mixtures or too soluble and thus difficult to extract by aqueous workup, microwave-assisted reactions enable rapid product formation in anhydrous organic solvents with extremely low catalyst loadings (Table 8, Entry 5).

Microwave chemistry even facilitates one-pot reactions, generating a variety of triazoles directly from the alkyl halide in under 15 minutes (Table 9).[11] Since this procedure utilizes potentially unstable or volatile organic azides without isolation, novel triazoles inaccessible by the traditional protocol become available (Table 9, Entry 3).

Table 9. One-pot synthesis of selected triazoles by microwave-assisted click chemistry (data taken from ref.[11]).



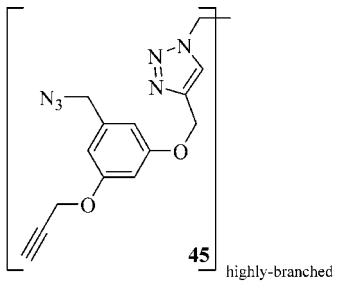
Entry	Halide	Alkyne	Time	Yield
1a Hal = Br	Ph–Hal	Ph–	10 min	93%
1b Hal = Cl			10 min	91%
2	Ph–Br	Ph–	10 min	88%
3	MeI	Ph–	10 min	88%
4a R = $(CH_2)_2OH$			10 min	81%
4b R = $C(OH)Me_2$			10 min	84%
4c R = $CH(OH)C_5H_{13}$	Ph–Br	R–	10 min	89%
4d R = CO_2Et			15 min	83%
4e R = TMS			15 min	88%

[a] Entries 4d and 4e were conducted at 75 °C.

In general, microwave-assisted Cu^I-catalyzed alkyne–azide cycloaddition shares the same wide scope and inertness to functional groups with room-temperature protocols. Nearly all substrates tolerated the high temperatures, which ranged from 75 to 140 °C; for cycloaddition involving ethyl propiolate and (trimethylsilyl)acetylene (Table 9, Entries 4d, 4e), temperatures of 125 °C reduced yields, but the desired products were obtained in good yield at 75 °C without significantly increasing reaction time.[11] These preliminary results suggest that microwave chemistry can dramatically accelerate cycloaddition without affecting yield or ease of product purification,[11,36a,59] further adding to the advantages of Cu^I-catalyzed alkyne–azide coupling.

3.1.7 Cu^I-Catalyzed Alkyne–Azide Coupling in the Solution-Phase Synthesis of Dendritic and Polymeric Materials

Due to the reliability of Cu^I-catalyzed click chemistry, a wide range of complex dendrimers and polymeric materials can be obtained with incredible efficiency, paving the way for applications in nanotechnology and homogeneous catalysis.[36a,36e,61] Interesting highly-branched polymers (**45**)[61a] and novel conjugated polymers (**46**)[61b] (Figure 1) form facilely from the corresponding monomers, under $CuSO_4$/Na ascorbate and $Cu(OAc)_2/Cu^0$ conditions, respectively. Coupling of terminal azide-functionalized polystyrene with alkynes also proved successful under conditions of CuBr/(pentamethyl)diethylenetriamine (PMDETA) in THF at 35 °C.[62]



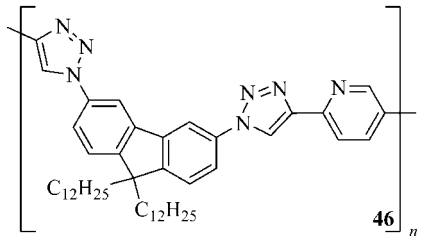


Figure 1. Polymers accessible by click chemistry.

Cycloaddition reactions to form a variety of dendrimers, including fourth-generation dendrimer **47** (Figure 2), utilized $CuSO_4$/Na ascorbate conditions and gave poly-triazole products in yields over 90%: even the final click reaction to yield dendrimer **47** proceeded in 92% yield.[36a] Dendronized linear polymers, potential new materials for nanoscale applications, are also rapidly accessible via click chemistry (Scheme 12).[36e] Dendrimers as large as third generation underwent facile cycloaddition to poly(vinylacetylene) under $CuSO_4$/Na ascorbate conditions, but reaction with fourth generation dendritic azides afforded only starting material, likely due to difficulties with azide binding to the copper–acetylide complex.

3.2 Solid-Phase Cu^I-Catalyzed Alkyne–Azide Coupling

Although solution-phase click chemistry has demonstrated the power of this transformation, success on the solid phase makes this cycloaddition an essential tool in drug discovery, which relies on solid-phase combinatorial chemistry to generate new libraries of compounds for biological testing.[2b] Such success transitioning from solution-phase

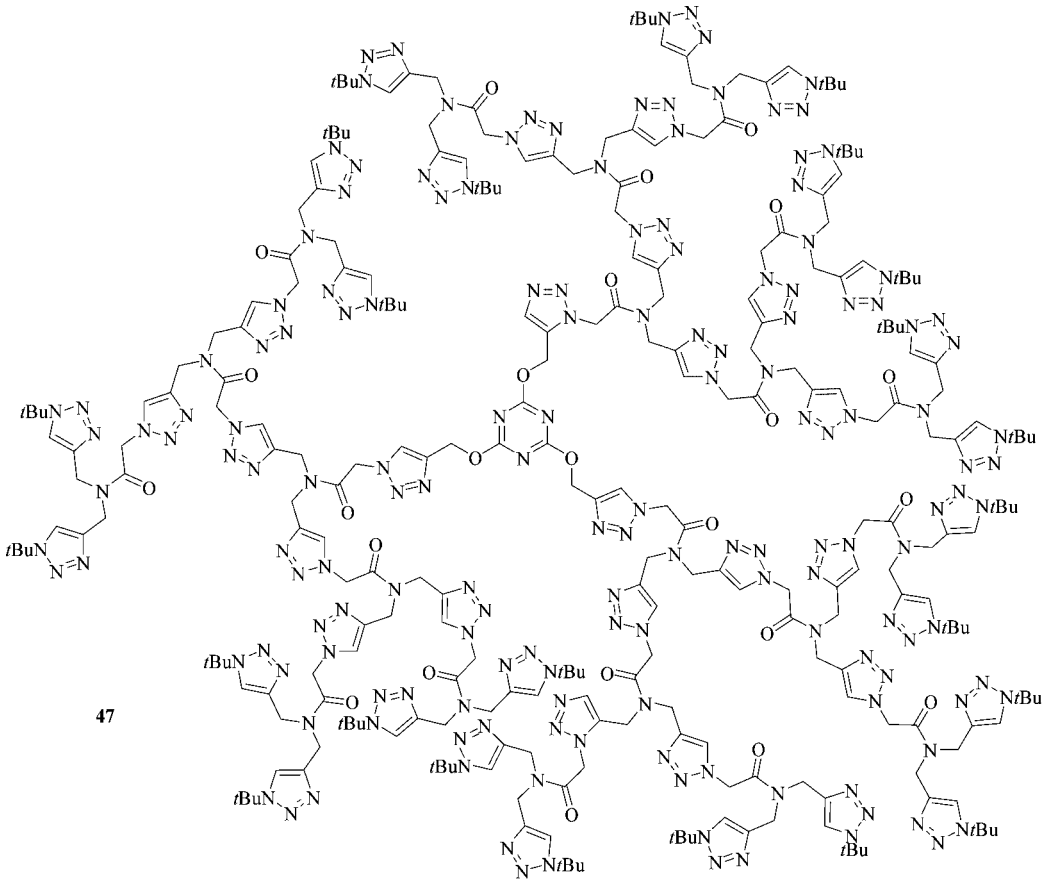
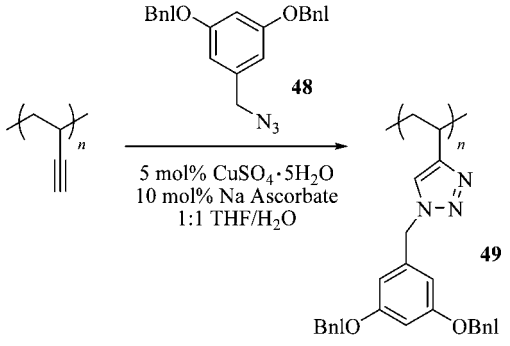


Figure 2. Fourth-generation dendrimer **47**.



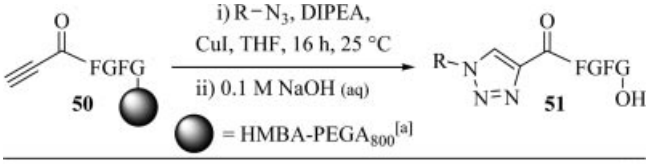
Scheme 12. Synthesis of first-generation-dendronized linear polymers by click chemistry.

to solid-phase chemistry has made possible further applications of solid-phase cycloaddition, outside the synthesis of biologically interesting compounds; triazoles can serve as linkers to bind other functionalities to solid-phase resins[63] and can functionalize metal surfaces to change their properties[26b] and induce adhesion.[21b]

According to preliminary research results, solid-phase Cu[I]-catalyzed alkyne–azide coupling shows little sensitivity to conditions, resin type, or subsequent transformations, though alkyne homocoupling may prove problematic.[45] Both Cu[I] salts and in-situ Cu[II] salt reduction effectively catalyze the reaction[64] in various organic solvents, including THF,[20c,63] DMF,[10] and acetonitrile/DMSO (4:1).[29] Triazole formation on different resins, including polar matrices, such as PEGA, and apolar supports, such as polystyrene, further demonstrates the robustness of solid-phase click chemistry. Thus far, only homocoupling appears to limit the reliability of this chemistry: Meldal and coworkers originally reported difficulty with coupling alkynes onto an azide-substituted resin, due to excessive alkyne homocoupling.[10] More recently, however, triazole formation on azide-substituted resins has proceeded in high yield, even at alkyne concentrations of up to 1.25 M,[63] but for resins with more sterically hindered azide functionalities, alkyne homocoupling may dominate and dramatically reduce yields.

Despite this possible limitation, solid-phase alkyne–azide coupling has potential to generate numerous molecules of diverse functionality (Table 10,[10] Scheme 13[63a]). In general, cycloaddition proceeds facilely on the solid phase but may show more sensitivity to steric issues than solution-phase work (Table 10, Entry 1b). Incorporation of a triazole into a peptide as an amide bond mimic occurs without problem[20c] in the solid phase (Table 10, Entry 2), a particular advantage considering the success of modern peptide synthesis on the solid phase. In addition to triazole-containing products, use of the triazole functionality as a linker to attach substrates to the resin enables the synthesis of any number of functionalities, including non-triazole containing amides (Scheme 13).

Table 10. Purity[b] of selected triazole products formed from resin **50** (data taken from ref.[10]).



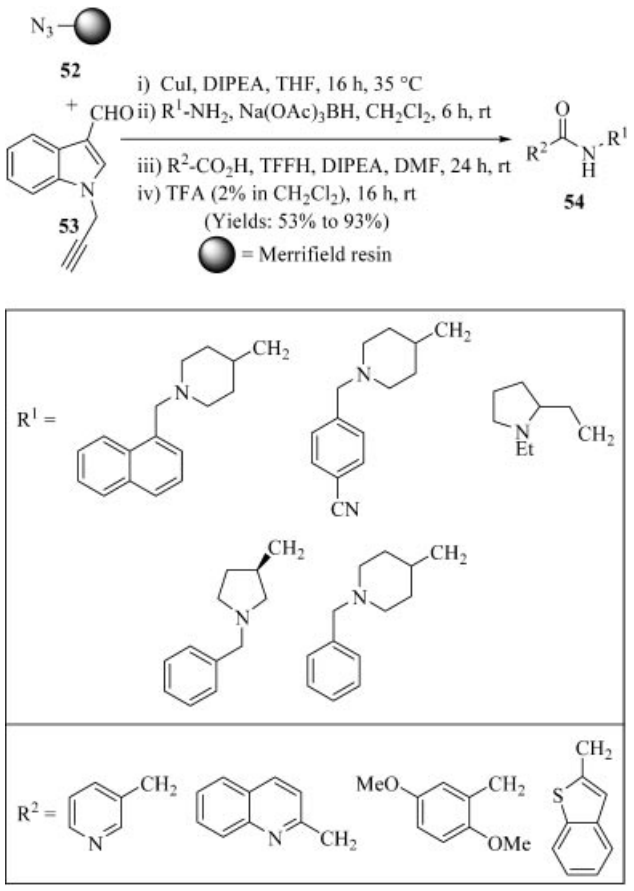
Entry	R	Purity[b]
1a	$R^1 = R^2 = Me$	>95%
1b	$R^1 = R^2 = Ph$	0%
1c	$R^1 = R^2 = H$	>95%
1d	$R^1 = R^2 = nC_{14}H_{29}$	91%
1e	$R^1 = Ph$, $R^2 = H$	>95%
2a[c]	R = H	90%
2b[c]	$R = CH_2CH_2SMe$	84%
3		>95%
4		>95%

[a] HMBA-PEGA$_{800}$: Dimethyl acrylamide and mono-2-acrylamidoprop-1-yl[2-aminoprop-1-yl] polyethylene glycol cross-linked with bis(2-acrylamidoprop-1-yl) polyethyleneglycol (PEGA resin) derivatized with 4-(hydroxymethyl)benzoic acid (HMBA) linker. [b] Conversion was >95% for all reactions except Entry 1b. [c] Fmoc group on primary amine removed after cyclization prior to analysis.

Solid-phase click chemistry is clearly just beginning to develop, but given its reliability and robustness, the potential applications in combinatorial chemistry and materials science will likely increase rapidly.

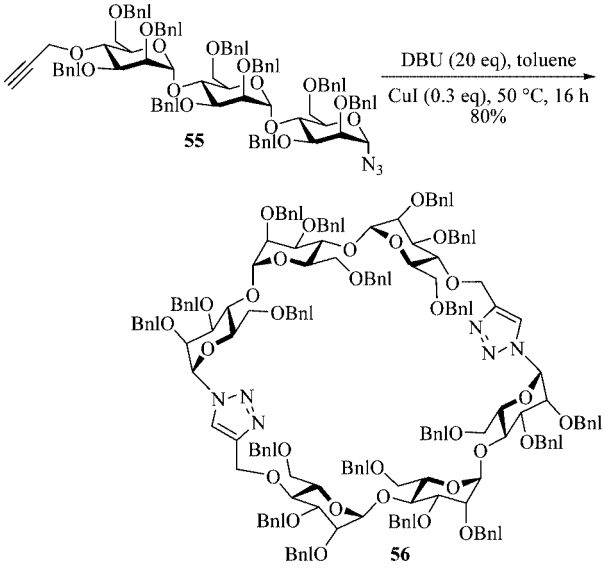
3.3 Intramolecular Cu^I-Catalyzed Alkyne–Azide Coupling

Despite biological significance of the triazole and the success of intermolecular triazole formation, intramolecular alkyne–azide coupling remains surprisingly limited. On a macromolecular scale, intramolecular triazole formation can occur on specially synthesized DNA molecules,[65] by cyclodimerization of solid-phase-bound suitably functionalized peptides,[29] or on copper surfaces to induce adhesion,[21b] but more traditional examples are rare. Solution-phase chemistry has, to date, only one reported intramolecular triazole cyclization: Successful dimerization followed by intramolecular Cu^I-catalyzed cycloaddition yielded macrocycle **56** in 80% yield (Scheme 14).[66] Interestingly, copper iodide and DBU in toluene proved most efficient of the various copper sources, additives, and solvents explored for this reaction; DBU even gave higher



Scheme 13. Amides synthesized by reactions on a triazole-linked resin.

yields than reactions including triazole ligand **33** (Table 6), indicating as before that amide bases may serve to stabilize the Cu^I oxidation state similarly to heterocyclic ligands **33** and **37**. Clearly, these conditions succeed in favoring macrocycle **56** over byproduct formation[45] and oligimerization,



Scheme 14. Dimerization of the trisaccharide **55**.

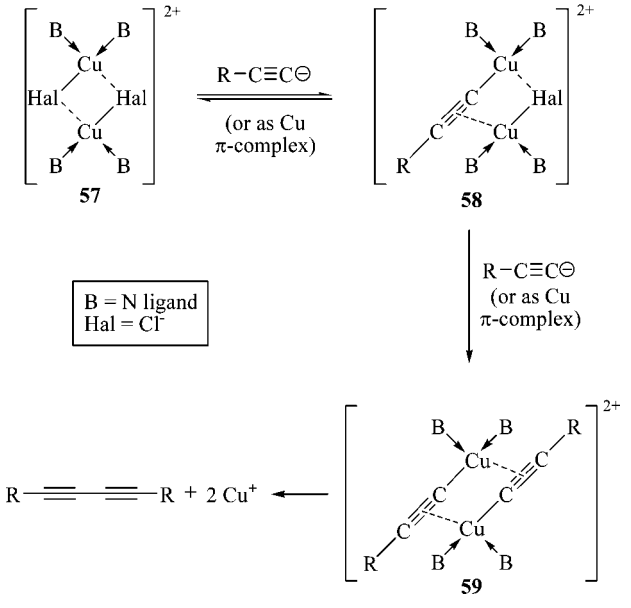
but precisely why remains unclear. Additional examples might distinguish between whether these conditions in general mediate successful intramolecular triazole formation or effects specific to the substrate dominate in determining optimal conditions.

3.4 Problematic Alkyne–Azide Cycloadditions: When Click Reactions Fail to "Click"

Overall, Cu[I]-catalyzed alkyne–azide cycloaddition generates triazoles with outstanding reliability and efficiency, but as with any reaction, some problems do exist. In a few cases, various researchers have reported byproduct formation due to alkyne homocoupling, a process which copper also catalyzes.[10,36h] Further, azide binding may prove problematic for highly electron-deficient azides[47f] or for polyalkyne substrates that have the flexibility to coordinatively saturate Cu[I].[36h]

3.4.1 Alkyne Homocoupling

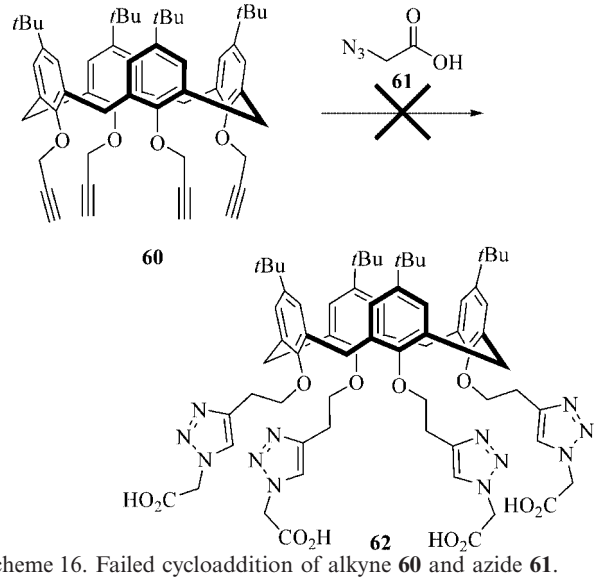
As the numerous reactions delineated above indicate, click chemistry nearly always proceeds in high yield with no byproduct formation. In the unusual case of a low-yielding reaction, Cu-catalyzed acetylenic homocoupling is the most likely culprit (Scheme 15).[67] Since small, unhindered amines, such as pyridine and TMEDA, mediate this conversion through stabilization of intermediates **58** and **59**,[68] low yields reported by Wong and co-workers for alkyne–azide cycloaddition under conditions of CuI/Et_3N (Table 4, Entry 2) likely result from increased alkyne homocoupling. Increasing the steric bulk in a base reduces its ligand donor properties, implying that sterically hindered bases should stabilize copper acetylide intermediates **58** and **59** to a lesser degree and slow this side reaction.



Scheme 15. Proposed mechanism for Cu-catalyzed acetylenic coupling.

3.4.2 Cu[I] Saturation

As described above, Cu[I]-catalyzed alkyne–azide cycloaddition requires labile ligands around the Cu[I] to enable competitive azide binding. For flexible polyalkynes such as tetraalkyne **60**, the proximity of the alkynes may in effect coordinatively saturate the Cu[I] atom through chelation (Scheme 16).[36h] Although Zhao and co-workers successfully synthesized triazole-functionalized calixarene **27** from calixarene azide **26** (Table 2), they were unable to effect conversion of calixarene alkyne **60**, even at elevated temperatures. Presumably, formation of a copper–acetylide species on one of the alkyne chains positioned the Cu[I] ion in the vicinity of the neighboring alkyne units, which subsequently formed complexes with the Cu[I] and precluded the binding of azide **61**. Complex mixtures were obtained from reactions at elevated temperatures, most likely resulting from alkyne homocoupling.[36h]



Scheme 16. Failed cycloaddition of alkyne **60** and azide **61**.

Conclusions

Considering its impressive scope, yields, and reliability, Cu[I]-catalyzed alkyne–azide coupling deserves to be designated "click chemistry." Perhaps in part due to this robustness, a variety of conditions affords the desired product with comparable catalyst loading, reaction time, product purity, and yield. Factors such as solubility, the need for an inert atmosphere, or particular substrate effects may weigh more heavily on the success of a reaction than any general set of conditions. On the whole, catalyst generation through Cu[I] salt addition with excess of a hindered base seems to give the best results for traditional solution-phase chemistry, but other methods clearly work well also, particularly for biological systems.

Although the scope of this reaction is indeed remarkable, not every azide or alkyne gives good results. Highly electron-deficient fluorine-substituted azides react sluggishly with low yields in general (Table 5, Entry 6), and sulfonyl-

substituted azides in the presence of Cu^{I}, acetylenes, and amines give *N*-sulfonylamines, and no triazole product,[69] indicating that alkyne–azide coupling requires a more electron-rich azide. In contrast, electron-poor alkynes actually accelerate the reaction by facilitating the formation of the metallocycle **8** (Scheme 3).[10,26] Steric constraints, particularly on the solid phase (Table 10, Entry 1b), may also limit the success of this reaction, but only in extreme cases. Otherwise, alkyne and azides for the most part "click" together, just as expected.

With such a powerful reaction, applications in combinatorial chemistry, organic synthesis, bioconjugation, and other fields are just beginning to be explored. As continued mechanistic studies reveal more about important copper intermediates, optimal conditions may be easier to predict, leading to even greater reliability and further application. Since the discovery of Cu^{I}-catalyzed click chemistry in 2002, interest and applications of triazoles has increased dramatically, with no sign of slowing down.

[1] R. S. Bohacek, C. McMartin, W. C. Guida, *Med. Res. Rev.* **1996**, *16*, 3–50.

[2] For reviews of click chemistry, see: a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; b) H. C. Kolb, K. B. Sharpless, *Drug Discov. Today* **2003**, *8*, 1128–1137.

[3] R. Huisgen, in *1,3-Dipolar Cycloadditional Chemistry* (Ed.: A. Padwa), Wiley, New York, **1984**.

[4] a) E. Saxon, C. R. Bertozzi, *Science* **2000**, *287*, 2007–2010; b) K. L. Kiick, E. Saxon, D. A. Tirrel, C. R. Bertozzi, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 19–24.

[5] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599.

[6] Azides, however, can decompose exothermically with loss of N_2 and should be treated with due care. Although aliphatic azides have a particularly high kinetic stability relative to other azides, the presence of other energetic functional groups in the molecule, such as alkynes, increases the hazard. Further, certain transition metal complexes, especially Fe and Co triads, can catalyze decomposition. Despite these potential hazards, a number of groups report that azides can be prepared, stored and used with minimal risk. See: M. Peer, *Spec. Chem. Mag.* **1998**, *18*, 256–263; ref.[2a].

[7] a) For a review of asymmetric 1,3-dipolar cycloaddition reactions, see: K. V. Gothelf, K. A. Jorgensen, *Chem. Rev.* **1998**, *98*, 863–909; b) For a review of synthetic applications, see: J. Mulzer, *Org. Synth. Highlights* **1991**, 77–95.

[8] For examples of uncatalyzed 1,3-cycloaddition reactions between azides and alkynes, see: a) A. R. Katritzky, S. K. Singh, *J. Org. Chem.* **2002**, *67*, 9077–9079; b) Z.-X. Wang, H.-L. Qin, *Chem. Commun.* **2003**, 2450–2451; c) K. Harju, M. Vahermo, I. Mutikainen, J. Yli-Kauhaluoma, *J. Comb. Chem.* **2003**, *5*, 826–833; d) G. Molteni, A. Ponti, *Chem. Eur. J.* **2003**, *9*, 2770–2774; e) I. Akritopoulou-Zanze, V. Gracias, S. W. Djuric, *Tetrahedron Lett.* **2004**, *45*, 8439–8441.

[9] a) J. Bastide, O. Henri-Rousseau, *Bull. Soc. Chim. Fr.* **1973**, 2294–2296; b) N. P. Stepanova, N. A. Orlova, V. A. Galishev, E. S. Turbanova, A. A. Petrov, *Zh. Org. Khim.* **1985**, *21*, 979–983; c) N. P. Stepanova, V. A. Galishev, E. S. Turbanova, A. V. Maleev, K. A. Potekhin, E. N. Kurtkutova, Y. T. Struchov, A. A. Petrov, *Zh. Org. Khim.* **1989**, *25*, 1613–1618; d) D. Clarke, R. W. Mares, H. McNab, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1799–1804.

[10] C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064.

[11] P. Appukkuttan, W. Dehaen, V. V. Fokin, E. van der Eycken, *Org. Lett.* **2004**, *6*, 4223–4225.

[12] a) W. S. Horne, C. D. Stout, M. R. Ghadiri, *J. Am. Chem. Soc.* **2003**, *125*, 9372–9376; b) W. S. Horne, M. K. Yadav, C. D. Stout, M. R. Ghadiri, *J. Am. Chem. Soc.* **2004**, *126*, 15366–15367.

[13] W. P. Purcell, J. A. Singer, *J. Phys. Chem.* **1967**, *71*, 4316–4319.

[14] M. H. Palmer, R. H. Findlay, A. J. Gaskell, *J. Chem. Soc. Perkins Trans. 2* **1974**, *4*, 420–428.

[15] a) R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M. J. Carmarasa, *J. Med. Chem.* **1994**, *37*, 4185–4194; b) S. Velaquez, R. Alvarez, C. Perez, F. Gago, C. De, J. Balzarini, M. J. Camarasa, *Antiviral Chem. Chemother.* **1998**, *9*, 481–489.

[16] L. L. Brockunier, E. R. Parmee, H. O. Ok, M. R. Candelore, M. A. Cascieri, L. F. Colwell, L. Deng, W. P. Feeney, M. J. Forrest, G. J. Hom, D. E. MacIntyre, L. Tota, M. J. Wyvratt, M. H. Fisher, A. E. Weber, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2111–2114.

[17] M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, K. C. Grega, J. B. Hester, D. K. Hutchinson, J. Morris, R. J. Reischer, C. W. Ford, G. E. Zurenko, J. C. Hamel, R. D. Schaadt, D. Stapert, B. H. Yagi, *J. Med. Chem.* **2000**, *43*, 953–970.

[18] a) D. R. Buckle, C. J. M. Rockell, *J. Chem. Soc. Perkin Trans. 1* **1982**, 627–630; b) D. R. Buckle, D. J. Outred, C. J. M. Rockell, H. Smith, B. A. Spicer, *J. Med. Chem.* **1983**, *26*, 251–254; c) D. R. Buckle, C. J. M. Rockell, H. Smith, B. A. Spicer, *J. Med. Chem.* **1986**, *29*, 2262–2267.

[19] For triazole cytokine inhibition, see: a) J. S. Tullis, J. C. VanRens, M. G. Natchus, M. P. Clark, B. De, L. C. Hsieh, M. J. Janusz, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1665–1668; b) D.-K. Kim, J. Kim, H.-J. Park, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2401–2405.

[20] a) For triazole *anti*-platelet activity, see: A. C. Cunha, J. M. Figueiredo, J. L. M. Tributino, A. L. P. Miranda, H. C. Castro, R. B. Zingali, C. A. M. Fraga, M. C. B. V. de Souza, V. F. Ferreira, E. J. Barreiro, *Bioorg. Med. Chem.* **2003**, *11*, 2051–2059; b) For triazole inhibition activity against tuberculosis, see: K. Dabak, Ö. Sezer, A. Akar, O. Anaç, *Eur. J. Med. Chem.* **2003**, *38*, 215–218; c) For triazole protozoan protease inhibition, see: C. W. Tornøe, S. J. Sanderson, J. C. Mottram, G. H. Coombs, M. Meldal, *J. Comb. Chem.* **2004**, *6*, 312–324.

[21] a) Q. Wang, T. R. Chan, R. Hilgraf, V. V. Fokin, K. B. Sharpless, M. G. Finn, *J. Am. Chem. Soc.* **2003**, *125*, 3192–3193; b) D. D. Díaz, S. Punna, P. Holzer, A. K. McPherson, K. B. Sharpless, V. V. Fokin, M. G. Finn, *J. Pol. Sci. A: Pol. Chem.* **2004**, *42*, 4392–4403; c) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210–216.

[22] T. R. Chan, R. Hilgraf, K. B. Sharpless, V. V. Fokin, *Org. Lett.* **2004**, *6*, 2853–2855.

[23] V. O. Rodinov, V. V. Fokin, M. G. Finn, *Angew. Chem. Int. Ed.* **2005**, *44*, 2210–2215.

[24] a) For a review of transition metal-catalyzed acetylenic coupling, see: P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632–2657; b) For a common example, see: K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

[25] B. M. Mykhalichko, O. N. Temkin, M. G. Mys'kiv, *Russ. Chem. Rev.* **2001**, *69*, 957–984.

[26] a) J. Bastide, O. Henri-Rousseau, in *Chemistry of the Carbon−Carbon Triple Bond* (Ed.: S. Patai), Interscience Publishers, London, **1978**, p. 447–552; b) J. P. Collman, N. K. Devaraj, C. E. D. Chidsey, *Langmuir* **2004**, *20*, 1051–1053.

[27] J. Diez, M. P. Gamasa, J. Gimeno, E. Lastra, A. Aguirre, S. García-Granda, *Organometallics* **1993**, *12*, 2213–2220.

[28] a) For examples of known eight-membered ring metallocycles containing copper, see: D. J. Darensbourg, W.-Z. Lee, M. J. Adams, J. C. Yarbrough, *Eur. J. Inorg. Chem.* **2001**, 2811–2822; b)

For syntheses and characterizations of other eight-membered ring metallocycles, see: M. Green, J. Z. Nyathi, C. Scott, F. Stone, A. Gordon, A. J. Welch, P. Woodward, *J. Chem. Soc. Dalton Trans. Inorg. Chem.* **1978**, *9*, 1067–1080.

[29] S. Punna, J. Kuzelka, Q. Wang, M. G. Finn, *Angew. Chem. Int. Ed.* **2005**, *44*, 2215–2220.

[30] a) F. Olbrich, U. Behrens, E. Weiss, *J. Organomet. Chem.* **1994**, *472*, 365–370; b) W. Frosch, S. Back, K. Rheinwald, K. Köhler, H. Pritzkow, H. Lang, *Organometallics* **2000**, *19*, 4016–4024; c) K. Köhler, H. Pritzkow, H. Lang, *J. Organomet. Chem.* **1998**, *553*, 31–38.

[31] V. W.-W. Yam, S. W.-K. Choi, C.-L. Chan, K.-K. Cheung, *Chem. Commun.* **1996**, 2067–2068.

[32] For examples of stable Cu[I] complexes with an sp^2 carbon atom ligand, see: a) G. Pampaloni, R. Peloso, C. Graiff, A. Tiripicchio, *Organometallics* **2005**, *24*, 819–825; b) X. Yang, P. Knochel, *Synlett* **2004**, *13*, 2303–2306; c) R. R. Conry, A. A. Tipton, W. S. Striejewske, E. Erkizia, M. A. Malwitz, A. Caffaratti, J. A. Natkin, *Organometallics* **2004**, *23*, 5210–5218; d) J. M. Kok, B. W. Skelton, A. H. White, *J. Cluster Sci.* **2004**, *15*, 365–376.

[33] For a review on the complexes of Cu[I] and dioxygen, see: S. Schindler, *Eur. J. Inorg. Chem.* **2000**, 2311–2326.

[34] Unpublished results reported by Fokin and co-workers indicate that when Cu[I] is quenched by air-oxidation, it can be regenerated by the reducing agent, thus maintaining a low, steady state concentration of Cu[I] of 200 to 700 μM for reactions in H_2O/*t*BuOH; see ref.[21b]

[35] a) A. Deiters, T. A. Cropp, M. Mukerji, J. W. Chin, J. C. Anderson, P. G. Schultz, *J. Am. Chem. Soc.* **2003**, *125*, 11782–11783; b) L. V. Lee, M. L. Mitchell, S.-J. Huang, V. V. Fokin, K. B. Sharpless, C.-H. Wong, *J. Am. Chem. Soc.* **2003**, *125*, 9588–9589; c) W.-h. Zhan, H. N. Barnhill, K. Sivakumar, H. Tian, Q. Wang, *Tetrahedron Lett.* **2005**, *46* 1691–1695.

[36] a) P. Wu, A. K. Feldman, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Fréchet, K. B. Sharpless, V. V. Fokin, *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 3928–3932; b) M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 1313–1317; c) W. G. Lewis, F. G. Magallon, V. V. Fokin, M. G. Finn, *J. Am. Chem. Soc.* **2004**, *126*, 9152–9153; d) K. Sivakumar, F. Xie, B. M. Cash, S. Long, H. N. Barnhill, Q. Wang, *Org. Lett.* **2004**, *6*, 4603–4606; e) B. Helms, J. L. Mynar, C. J. Hawker, J. M. J. Fréchet, *J. Am. Chem. Soc.* **2004**, *126*, 15020–15021; f) P. L. Suarez, Z. Gándara, G. Gómez, Y. Fall, *Tetrahedron Lett.* **2004**, *45*, 4619–4621; g) B.-C. Suh, H. Jeon, G. H. Posner, S. M. Silverman, *Tetrahedron Lett.* **2004**, *45*, 4623–4625; h) E.-H. Ryu, Y. Zhao, *Org. Lett.* **2005**, *7*, 1035–1037; i) B. H. M. Kuijpers, S. Groothuys, A. R. Keereweer, P. J. L. M. Quaedflieg, R. H. Blaauw, F. L. Van Delft, F. P. J. T. Rutjes, *Org. Lett.* **2004**, *6*, 3123–3126.

[37] a) M. B. Davies, *Polyhedron* **1992**, *11*, 285–321; b) C. Creutz, *Inorg. Chem.* **1981**, *20*, 4449–4452.

[38] a) J. A. Burns, J. C. Butler, J. Moran, G. M. Whitesides, *J. Org. Chem.* **1991**, *56*, 2648–2650; b) T. L. Kirley, *Anal. Biochem.* **1989**, *180*, 231–236; c) W. H. Fischer, J. E. Rivier, A. G. Craig, *Rapid Commun. Mass Spectrom.* **1993**, *7*, 225–228; d) E. B. Getz, M. Xiao, T. Chakrabarty, R. Cooke, P. R. Selvin, *Anal. Biochem.* **1999**, 73–80.

[39] a) A. E. Speers, G. C. Adam, B. F. Cravatt, *J. Am. Chem. Soc.* **2003**, *125*, 4686–4687; b) Q. Wang, T. R. Chan, R. Hilgraf, V. V. Fokin, K. B. Sharpless, M. G. Finn, *J. Am. Chem. Soc.* **2003**, *125*, 3192–3193; c) A. E. Speers, B. F. Cravaat, *Chem. Bio.* **2004**, *11*, 535–546.

[40] a) H. A. Orgueira, D. Fokas, Y. Isome, P. C.-M. Chane, C. M. Baldino, *Tetrahedron Lett.* **2005**, *46*, 2911–2914; b) L. D. Pachón, J. H. van Maarseveen, G. Rothenberg, *Adv. Synth. Catal.* **2005**, *347*, 811–815.

[41] Absence of an amine hydrochloride salt gave only trace products or recovered starting material after two hours; see ref.[40a]. For information on the dissolution of copper in aqueous systems and facilitation by amine hydrochloride salts, see: a) J. S. Thayer, *Adv. Organomet. Chem.* **1995**, *38*, 71–74; b) P. L. Timms, T. W. Turney, *Adv. Organomet. Chem.* **1977**, *15* 84–87; c) A. E. Jukes, *Adv. Organomet. Chem.* **1974**, *12*, 228–229.

[42] I. G. Crivelli, C. Andrade, M. A. Francois, D. Boys, A. Haberland, R. Segura, A. M. Leiva, B. Loeb, *Polyhedron* **2000**, *19*, 2289–2295.

[43] These Cu nanoclusters have been shown previously to form Cu[I]–alkyne intermediates; see: M. B. Thathagar, J. Beckers, G. Rothenberg, *Green Chem.* **2004**, *6*, 215.

[44] From Sigma–Aldrich, 25 g of Cu^0 nanopowder costs € 92.40, compared to € 12.40 for 25 g of copper sulfate pentahydrate and € 7.10 for 25 g of reagent grade Cu[I] iodide.

[45] Alkyne homocoupling may result in lower yields in some substrates; see below, section 3.4.1.

[46] F. Fazio, M. C. Bryan, O. Blixt, J. C. Paulson, C.-H. Wong, *J. Am. Chem. Soc.* **2002**, *124*, 14397–14402.

[47] a) F. Reck, F. Zhou, M. Girardot, G. Kern, C. J. Eyermann, N. J. Hales, R. R. Ramsey, M. B. Gravestock, *J. Med. Chem.* **2005**, *48*, 499–506; b) A. Dondoni, P. P. Giovannini, A. Massi, *Org. Lett.* **2004**, *6*, 2929–2932; c) Z. Li, T. S. Seo, J. Ju, *Tetrahedron Lett.* **2004**, *45*, 3143–3146; d) C. Petchprayoon, K. Suwanborirux, R. Miller, T. Sakata, G. Marriott, *J. Nat. Prod.* **2005**, *68*, 157–161; e) Z. Zhou, C. J. Fahrni, *J. Am. Chem. Soc.* **2004**, *126*, 8862–8863; f) Y.-M. Wu, J. Deng, X. Fang, Q.-Y. Chen, *J. Fluorine Chem.* **2004**, *125*, 1415–1423.

[48] I. M. Kolthoff, J. Coetzeem, *J. Am. Chem. Soc.* **1957**, *79*, 1852.

[49] For examples of unprotected alcohols that undergo click reactions without problem, see Table 1, Entries 2 and 3, and Table 5, Entry 4.

[50] J. A. Link, D. A. Tirrell, *J. Am. Chem. Soc.* **2003**, *125*, 11164–11164.

[51] J.-c. Meng, V. V. Fokin, M. G. Finn, *Tetrahedron Lett.* **2005**, *46*, 4543–4546.

[52] The poor enantioselectivity observed for azide **39** may result from suprafacial [3,3] sigmatropic migration of the azido group, which would lead to racemization of the unconverted enantiomer.

[53] S. Chittaboina, F. Xie, Q. Wang, *Tetrahedron Lett.* **2005**, *46*, 2331–2336.

[54] This steric effect has been noted elsewhere; see: ref.[10].

[55] D. B. Ramachary, C. F. Barbas III, *Chem. Eur. J.* **2004**, *10*, 5323–5331.

[56] a) R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, J. Rousell, *Tetrahedron Lett.* **1986**, *27*, 279–282; b) R. J. Giuere, T. L. Bray, S. M. Duncan, G. Majetich, *Tetrahedron Lett.* **1986**, *27*, 4945–4958.

[57] For a recent review of microwave use in synthetic and combinatorial chemistry, see: C. O. Kappe, *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284.

[58] a) D. Stuerga, M. Delmotte, in *Microwaves in Organic Synthesis* (Ed.: A. Loupy), Wiley-VCH, Weinheim, **2002**, p. 1–34; b) M. D. P. Mingos, in *Microwave-Assisted Organic Synthesis* (Eds.: P. Lidström, J. P. Tierney), Blackwell, Oxford, **2004**, Ch. 1; c) D. R. Baghurst, D. P. M. Mingos, *Chem. Soc. Rev.* **1991**, *20*, 1–47; d) C. Gabriel, S. Gabriel, E. H. Grant, B. S. Halstead, D. M. P. Mingos, *Chem. Soc. Rev.* **1998**, *27*, 213–223.

[59] a) F. Pérez-Balderas, M. Ortega-Muñoz, J. Morales-Sanfrutos, F. Hernández-Mateo, F. G. Calvo-Flores, J. A. Calvo-Azín, J. Isac-García, F. Santoyo-González, *Org. Lett.* **2003**, *5*, 1951–1954; b) B. Khanetskyy, D. Dallinger, C. O. Kappe, *J. Comb. Chem.* **2004**, *6*, 884–892.

[60] See ref.[59a]; two reactions conducted under both microwave conditions and at room temperature afforded the desired product in almost identical yields, with microwave conditions only reducing reaction times.

[61] a) A. J. Scheel, H. Komber, B. I. Voit, *Macromol. Rapid Commun.* **2004**, *25*, 1175–1180; b) D. J. V. C. van Steenis, O. R. P.

David, G. P. F. van Strijdonck, J. H. van Maarseveen, J. N. H. Reek, *Chem. Commun.* **2005**, 4333–4335.
[62] A. J. Dirks, S. S. van Berkel, N. S. Hatzakis, J. A. Opsteen, F. L. van Delft, J. J. L. M. Cornelissen, A. E. Rowan, J. C. M. van Hest, F. P. J. T. Rutjes, R. J. M. Nolte, *Chem. Commun.* **2005**, *33*, 4172–4174.
[63] a) S. Löber, P. Rodriguez-Loaiza, P. Gmeiner, *Org. Lett.* **2003**, *5*, 1753–1755; b) S. Löber, P. Gmeiner, *Tetrahedron* **2004**, *60*, 8699–8702; c) L. Bettinetti, S. Löber, H. Hübner, P. Gmeiner, *J. Comb. Chem.* **2005**, *7*, 309–316.
[64] Only one example of Cu^{II} sulfate reduction to catalyze triazole formation on the solid phase has been reported (see ref.[26b]).
[65] Z. J. Gartner, R. Grubina, C. T. Calderone, D. R. Liu, *Angew. Chem. Int. Ed.* **2003**, *42*, 1370–1375.
[66] K. D. Bodine, D. Y. Gin, M. S. Gin, *J. Am. Chem. Soc.* **2004**, *126*, 1638–1639.
[67] a) M. D. Cameron, G. E. Bennett, *J. Org. Chem.* **1957**, *22*, 557–558; b) P. Cadiot, W. Chodkiewicz, in *Chemistry of Acetylenes* (Ed: G. G. Viehe), Marcel Dekker, New York, **1969**, p. 597–648; c) For a recent review of acetylenic couplings, see: P. Siemsem, R. C. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632–2657.
[68] F. Bohlmann, H. Schönowsky, E. Inhoffen, G. Grau, *Chem. Ber.* **1964**, *97*, 794–800.
[69] I. Bae, H. Han, S. Chang, *J. Am. Chem. Soc.* **2005**, *127*, 2038–2039.

Received: June 29, 2005
Published Online: October 25, 2005

