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Mechanistic Studies on the Cu-Catalyzed Three-Component Reactions of Sulfonyl Azides, 1-Alkynes and Amines, Alcohols, or Water: Dichotomy via a Common Pathway

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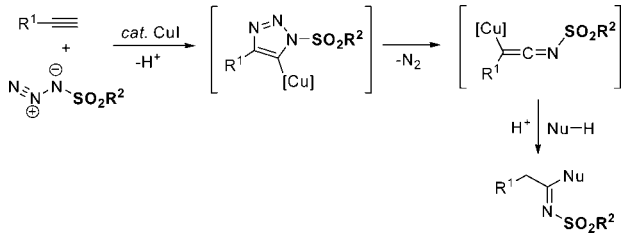

Combined analyses of experimental and computational studies on the Cu-catalyzed three-component reactions of sulfonyl azides, terminal alkynes and amines, alcohols, or water are described. A range of experimental data including product distribution ratio and trapping of key intermediates support the validity of a common pathway in the reaction of 1-alkynes and two distinct types of azides substituted with sulfonyl and aryl(alkyl) groups. The proposal that bimolecular cycloaddition reactions take place initially between triple bonds and sulfonyl azides to give *N*-sulfonyl triazolyl copper intermediates was verified by a trapping experiment. The main reason for the different outcome from reactions between sulfonyl and aryl(alkyl) azides is attributed to the lability of the *N*-sulfonyl triazolyl copper intermediates. These species are readily rearranged to another key intermediate, ketenimine, into which various nucleophiles such as amines, alcohols, or water add to afford the three-component coupled products: amidines, imidates, or amides, respectively. In addition, the proposed mechanistic framework is in good agreement with the obtained kinetics and competition studies. A computational study (B3LYP/LACV3P*+) was also performed confirming the proposed mechanistic pathway that the triazolyl copper intermediate plays as a branching point to dictate the product distribution.

Introduction

Tandem reactions,[1] performed with a cascade, domino, or zipper type, can link a series of reaction steps together in a single operation. In general, an initial step generates a reactive intermediate that undergoes further transformations with either strategically positioned reactive centers in the same molecule or other compounds in the reaction mixture. Over the past decades, tandem reactions have gained a wide interest since they can offer extremely high efficiency and selectivity without relying on a series of elaborate separate operations. However, the fact that only a few practically useful catalytic tandem reactions are available to date[2] may be attributed to a poor compatibility of catalysts with reacting functional groups in the subsequent steps.

Copper-catalyzed azide−alkyne cycloaddition (CuAAC),[3] which is the best known click reaction,[4] is an efficient way to produce 1,4-disubstituted 1,2,3-triazoles. The scope of the reaction is very broad with respect to both components.[3]

[†] Korea Advanced Institute of Science and Technology.
[‡] The Scripps Research Institute.
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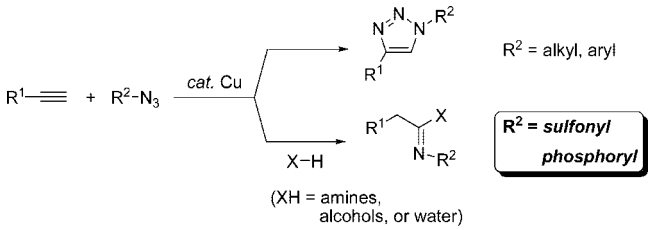
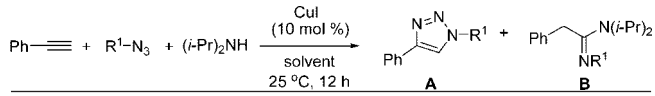
SCHEME 1



However, when acyl, sulfonyl, or phosphoryl azides are employed, the corresponding triazoles are obtained in poor yield under the standard CuAAC conditions (vide infra). In fact, in the presence of primary or secondary amines, sulfonyl azides produce amidines in excellent yield at room temperature.[5a,c] The scope of this mild three-component reaction is extremely broad with regard to all three components, and phosphoryl azides also served as a high-yielding type of azide to give the corresponding *N*-phosphoryl amidines.[5b] Likewise, the copper-catalyzed reaction of sulfonyl azides, 1-alkynes, and alcohols readily takes place to afford imidates under similar conditions.[6] Additionally, a novel nonconventional approach for the formation of acyl sulfonamides has been developed by using the same procedure, employing water as the third reactant in this case (Scheme 1).[7,22]

The synthetic utility of generated molecules from the Cu-catalyzed three-component couplings has been extensively investigated in various areas. For example, amidine derivatives are utilized as potent pharmacophores[8] as well as efficient organocatalysts.[9] Imidates are used as key intermediates for the conversion to useful synthetic building blocks,[10] and acyl sulfonamides are well-known to have interesting bioactivities.[11] Moreover, this catalytic approach has been readily applied to the preparation of other types of synthetically interesting compounds such as azetidinimines,[12] iminocoumarins,[13] and indoline derivatives.[14] Recently, CuAAC with sulfonyl azides was also employed for the synthesis of macrocycles.[15] While appreciation of the Cu-catalyzed three-component reaction as a tool for the synthesis of high utility continues to expand, a more detailed mechanistic description is required to further synthetic developments. Herein, we report our results of detailed mechanistic investigations of the Cu-catalyzed three-component reaction based on the product distribution, intermediate trapping experiments, kinetic parameters, and computational studies.

TABLE 1. Reactivity of Different Azides in the Presence of Amines[a]



entry	R^1	solvent	conv (%)[b]	**A**/**B**[b]	yield (%)[c]
1	$PhCH_2$	CH_3CN	>99	>99:1	88 (**A**)
2	$PhCH_2$	*t*-BuOH/H_2O[d]	>99	>99:1	92 (**A**)
3	$PhCH_2$	THF	>99	>99:1	90 (**A**)
4	Ph	THF	95	>99:1	82 (**A**)
5	PhCO	THF	27	1:>99	9 (**B**)
6[e]	$(4\text{-}NO_2)C_6H_4CO$	THF	>99	1:>99	41 (**B**)
7[e]	$(PhO)_2PO$	THF	81	1:>99	58 (**B**)
8	$PhSO_2$	THF	>99	2:98	93 (**B**)
9	$(4\text{-}Me)C_6H_4SO_2$	THF	>99	1:>99	89 (**B**)
10	$MeSO_2$	THF	>99	1:>99	82 (**B**)

[a] Conditions: phenylacetylene (0.5 mmol), azide (1.2 equiv), diisopropylamine (1.2 equiv), CuI (10 mol %) in the indicated solvent. [b] Determined by ^1H NMR relative to an internal standard, 1,3-benzodioxane. [c] Isolated yield. [d] *t*-BuOH/H_2O = 3:1. [e] Decomposition of azides occurred simultaneously and no detectable side products resulting from reaction with phenylacetylene were observed.

Results and Discussion

Product Distribution in the Cu-Catalyzed Three-Component Reactions. While CuAAC between aryl- or alkyl azides and 1-alkynes readily provides 1,4-disubstituted 1,2,3-triazoles, it was observed that sulfonyl azides predominantly yield amidines when the reaction is carried out in the presence of primary or secondary amines.[5a] We were, therefore, interested in the reactivity of similarly electron-deficient azides and the effects of their substitution on the outcome of the reaction (i.e., triazole to amidine product ratio). As Table 1 illustrates, both yields and chemoselectivity of these reactions are indeed strongly dependent on the nature of the participating azides.

As expected, both benzyl and phenyl azides readily participated in the cycloaddition reaction, and no incorporation of the diisopropylamine in the product was observed (Table 1, entries 1−4). In sharp contrast, when benzoyl azide was employed, an amidine species (**B**, R^1 = PhCO) was exclusively observed with much lower efficiency (entry 5). Introduction of an electron-withdrawing group on the benzoyl azide reactants significantly accelerated the reaction, leading to the corresponding amidine in better yield (41%), still with excellent selectivity (entry 6). Phosphoryl azide was similarly reactive, producing the corresponding amidine species exclusively (entry 7). Unsurprisingly, sulfonyl azides were the most reactive in this reaction, providing amidines in highest yields, regardless of their electronic properties (entries 8−10).

A similar trend on the azide reactivity was also observed when alcohols were used as nucleophiles (Table 2). It should be noted that a tertiary amine additive, representatively triethylamine, was required to obtain satisfactory yields. As expected, reaction of phenylacetylene with benzyl azide afforded the corresponding triazole (**A**, R^1 = $PhCH_2$) as a major product even in the presence of benzyl alcohol (entry 1). Reaction of sulfonyl azides, in sharp contrast, resulted in almost exclusive formation of

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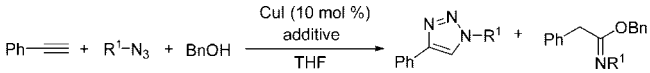
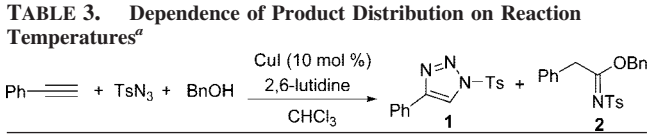
TABLE 2. Ratio of Product Distribution in the Formation of Imidates[a]



entry	R^1	additive	pK_a (THF)[b]	A/C[c]	yield (%)[d]
1	$PhCH_2$	Et_3N	12.5	>99:1	94
2	$(4\text{-Me})C_6H_4SO_2$	Et_3N	12.5	1:>99	63
3[e]	$(4\text{-Me})C_6H_4SO_2$	Et_3N	12.5	1:>99	86
4	$(4\text{-Me})C_6H_4SO_2$	2,6-lutidine	7.2	1:3.2	93
5	$(4\text{-Me})C_6H_4SO_2$	pyridine	5.5	1:2.7	54
6	$(4\text{-Me})C_6H_4SO_2$	$(2\text{-MeO})C_5H_4N$	2.6	4.7:1	64

[a] Conditions: phenylacetylene (0.5 mmol), azide (1.2 equiv), benzyl alcohol (1.2 equiv), additive (1.2 equiv), CuI (0.05 mmol). Conversion of all reactions was over 99%. [b] pK_a of conjugate acid of amine additives employed (ref 16). [c] Determined by ^{1}H NMR based on an internal standard, 1,3-benzodioxane. [d] Isolated yield of the combined products. [e] Chloroform was used as a solvent.

TABLE 3. Dependence of Product Distribution on Reaction Temperatures[a]



entry	temp (°C)	time (h)	conv (%)[b]	**1/2**[b]
1	−25	12	32	>99:1
2	0	9	>99	9.3:1
3	25	2	>99	1:3.2
4	50	0.5	>99	1:5.9

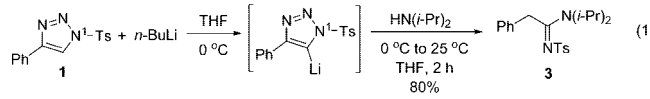
[a] Conditions: phenylacetylene (0.5 mmol), *p*-toluenesulfonyl azide (1.2 equiv), benzyl alcohol (1.2 equiv), 2,6-lutidine (1.2 equiv) and CuI (0.05 mmol). [b] Determined by ^{1}H NMR relative to an internal standard (1,4-dimethoxybenzene).

imidate species (**C**, $R^1 = (4\text{-Me})C_6H_4SO_2$) (entry 2). Confirming our earlier observation,[6] the imidate yield was noticeably increased when chloroform was used as a solvent (entry 3). It is noteworthy that chemoselectivity was dependent on the nature of amine additives even under otherwise identical conditions. For example, while an imidate (**C**, $R^1 = (4\text{-Me})C_6H_4SO_2$) was obtained exclusively when Et_3N additive was used (entry 2), the selectivity was significantly decreased in the presence of 2,6-lutidine (entry 4). It seems that the acidity of the employed base's conjugated acid has a great influence on the observed selectivity: more acidic conjugated acids favor formation of the triazole. The use of 2-methoxypyridine (pK_a = 2.6 in THF) led to the preferential formation of triazole species (entry 6). However, the possibility that the influence of the steric effects and the nature of the basic nitrogen atom (sp^2 vs sp^3) may also play a role in determining selectivity cannot be ruled out.

Performing the reaction at different temperatures provided a further mechanistic insight. In fact, the product distribution proved to be highly sensitive to the temperature variation, as shown in Table 3.

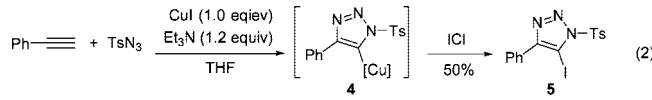
When phenylacetylene, *p*-toluenesulfonyl azide, and benzyl alcohol were allowed to react at −25 °C in the presence of CuI and 2,6-lutidine, triazole **1** was produced almost exclusively, albeit very slowly (Table 3, entry 1). However, as the temperature was increased, the imidate pathway took over and the yield of imidate **2** was gradually increased. For example, the amount of triazole was substantially decreased at 0 °C, although it was still the major product (entry 2). The ratio was reversed at room temperature, providing the corresponding imidate as a major product (entry 3). When the reaction was carried out at 50 °C, the tendency for the formation of imidate was further increased (entry 4).

Triazole Intermediacy in the Three-Component Reactions. The observed dependence of product ratio on the reaction conditions strongly implicates a triazole intermediate in the copper-catalyzed three-component reactions involving sulfonyl and phosphoryl azides. However, since the isolated triazoles bearing *N*-sulfonyl or *N*-phosphoryl groups are stable under the reaction conditions we employed, they cannot be intermediates in the reaction pathway. In addition, the ratio of the product mixtures remained constant throughout the course of the reaction,[17] confirming again that *neutral triazole is not the precursor for the formation of reactive intermediates under the reaction conditions*.[18] On the other hand, when an isolated *N*-sulfonyl triazole (**1**) was treated with a strong base such as *n*-BuLi,[19] the corresponding amidine (**3**) was isolated in high yield in the presence of diisopropylamine (eq 1).



(1)

This result reveals that while the parent triazoles are stable, the deprotonated triazole species is readily converted to a reactive intermediate that can subsequently react with nucleophiles (e.g., amines, alcohols, or water). Therefore, in analogy to the reaction intermediate in the CuAAC of aryl or alkyl azides, the *N*-sulfonyl triazolyl copper species seems also to be a key intermediate in the route to amidines (imidates or amides).[20] In support of this hypothesis, we attempted to trap the proposed triazolyl copper intermediates. When phenylacetylene and *p*-toluenesulfonyl azide were allowed to react with iodine monochloride (ICl) in the presence of triethylamine and CuI (1.0 equiv), 5-iodo-1-sulfonyltriazole (**5**) could be isolated with up to 50% yield (eq 2).[21] *This chemical trapping experiment supports the intermediacy of a σ-copper triazolyl species such as* **4**.



(2)

Likewise, intermediate **4** can be captured with electrophiles other than ICl. For instance, with 10 equiv of allyl iodide in anhydrous acetonitrile, 5-allyl-1-sulfonyltriazole (**6**) is isolated in 51% yield (eq 3).[22] Under neutral to slightly acidic pH, the trap of intermediate **4** by proton generates *N*-sulfonyl triazoles albeit in low yield. For example, performing the reaction between 4-acetamidobenzenesulfonyl azide and phenylacetylene in *t*-BuOH/H_2O (1:1, 0.1 M) in the presence of 2 mol % of

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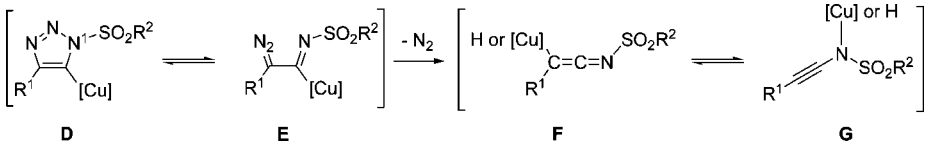
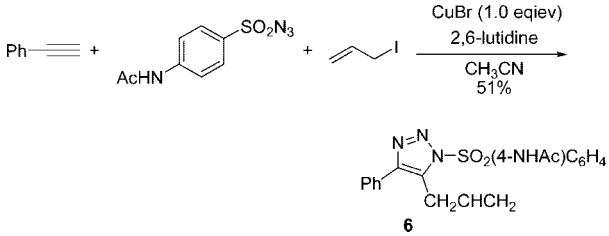
SCHEME 2. Ring–Chain Isomerization of *N*-Sulfonyl Triazolyl Copper Intermediate

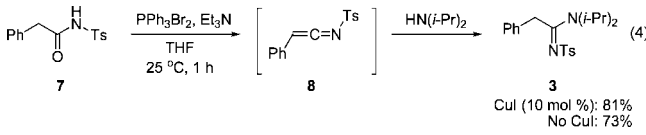


$CuSO_4$ and Na-ascorbate/ascorbic acid (10 mol % each) results in the formation of 1-sulfonyltriazole product (42%).



(3)

Validity of Ketenimine as a Key Intermediate. On the basis of previously reported synthetic procedures,[23] amidine compounds could be prepared starting from *N*-sulfonamides via ketenimine species (eq 4).[24] It is also well-known that alcohols or water readily participate in the reaction with ketenimine leading to imidates[25] or amides.[26] In fact, when (*N*-tosyl)phenylacetamide (**7**) was treated with PPh_3Br_2 in the presence of Et_3N, an in situ generated ketenimine species (**8**) was reacted with diisopropylamine to provide the corresponding amidine (**3**) in good yield. It was also revealed that the efficiency of the hydroamination step was not significantly influenced by the presence of a copper catalyst.



(4)

Therefore, it is reasonable to assume that ketenimine species are involved in our three-component coupling reactions upon release of a nitrogen molecule from the labile *N*-sulfonyl triazolyl copper intermediates (Scheme 2). We recently reported that *N*-sulfonyl triazolyl copper species (**D**) have much higher propensity for the ring-opening process comparing to *N*-aryl or alkyl triazolyl intermediates.[27] This proposal is also supported by the computational studies which revealed that the activation energy of the ring-opening process of *N*-methanesulfonyl triazolyl complex is 84 kJ mol^{-1} lower than that of the corresponding *N*-methyl species. One of the most plausible ring-opening routes from the *N*-sulfonyl triazolyl copper species (**D**) to ketenimines (**F**) could be envisioned as the well-known Dimroth rearrangement[28] via the α-diazoimino species (**E**). The Dimroth rearrangement, also called an amidine rearrangement, is a ring−chain isomerization process whereby the heterocyclic ring is broken. Release of molecular nitrogen from **E** followed by the hetero-Wolff rearrangement[29] provides the key ketenimine intermediate (**F**), which is in equilibrium with ynamides species (**G**). It is highly plausible to assume that the in situ generated ketenimine species (**F**)[19] reacts readily with amines, alcohol, or water to give the three-component coupled products. In this route, concurrent release of N_2 might be a main driving force for the transformation of the triazolyl copper species (**D**) to the key ketenimine intermediate (**F**).

On the basis of the above depicted mechanistic pathways, the observed dependence of product distribution on the base additives (Table 2) and reaction temperatures (Table 3) can be subsequently explained.[30] Since the protonation process of the triazolyl copper species (**D**, Scheme 2) is expected to take place more readily in the presence of more acidic proton donors, the corresponding *N*-sulfonyl triazole compounds can be more efficiently trapped when 2,6-lutidine additives are present compared to Et_3N base. Taking advantage of the concomitant entropic contribution, release of a dinitrogen molecule from the *N*-sulfonyl triazolyl copper species (**D**) would be accelerated at higher temperatures.

Intermediacy of the ketenimine was further supported by additional trapping experiments. As already reported, when an isolated 1-benzenesulfonyl-4-phenyltriazole was treated with *n*-BuLi followed by *N*-benzylideneaniline, an azetidinimine product could be obtained albeit in low yield.[12a] Since the product azetidinimine is generated by the nucleophilic attack of the *N*-benzylideneaniline at the in situ generated ketenimine, this result again strongly indicates the ketenimine intermediacy in the ring-opening process of triazole species. More importantly, the same type of azetidinimines were also obtained in high yields from the Cu-catalyzed reaction of *p*-toluenesulfonyl azides and 1-alkynes in the presence of imines.[12a]

Kinetics. The kinetic profile of the Cu-catalyzed three-component reactions was examined by competition studies under the amidine-generating conditions. Measurement of the relative rates of reactions of para-substituted phenylacetylene derivatives revealed that electron-withdrawing substituents slightly accelerated the reaction (Figure 1a). Hammett plotting of $\log(k_{rel})$ versus σ_p^- shows the ρ value of ca. 0.5 ($r = 0.99$), implying that there is buildup of negative charge in the rate-limiting transition stage. As shown Figure 1b, the reaction was also sensitive to the electronic variation of benzenesulfonyl azides ($\rho = 0.3$, $r = 0.99$), indicating that electron-withdrawing group on the azide accelerates the reaction more readily.

Further insightful data were acquired by determining pseudo-first-order rates from the reaction of phenylacetylene, *p*-

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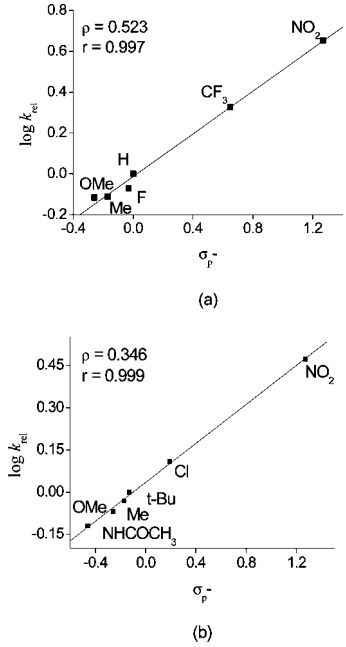

FIGURE 1. Hammett plotting in the Cu-catalyzed three-component reactions with (a) para-substituted phenylacetylenes and (b) para-substituted benzenesulfonyl azide derivatives.

toluenesulfonyl azide, and diisopropylamine in the presence of CuI. Initial rates were measured at different concentrations of each reactant as well as of the catalyst. NMR analysis of aliquots taken from the reaction mixture at regular intervals revealed the rate dependence of each reacting species on the concentrations of reactants ranging from 2.8 to 233 mM (Figure 2).[17]

Overall, in the amidine-forming reactions, the following rate law was obtained under CuI-catalytic conditions:

$$\text{rate} = k[\text{CuI}]^{1.4}[\text{TsN}_3]^{0.7}[\text{PhC}{\equiv}\text{CH}]^{0.3}[\text{HN}(i\text{-Pr})_2]^{0.0} \quad (5)$$

That is, the reaction is close to second order in the [CuI], first order in sulfonyl azide, and half-order in alkyne if we use normalization. In the previous kinetic studies of the reactions of benzyl azides with phenylacetylenes, the reaction was also second in copper pointing to the involvement of dinuclear copper intermediated in the rate-determining step.[20b] Importantly, *the reaction rate was completely independent of the amine concentration*. Although a precise description of the kinetic behavior of each reacting component is not tried at the present, this result clearly suggests that the addition of amine to the ketenimine intermediate is not involved in the rate-determining stages.

Mechanistic Proposal for the Cu-Catalyzed Three-Component Reactions. Although several mechanistic possibilities were surmised after finding the Cu-catalyzed three-component coupling reactions, some experimental data obtained thereafter clarified most of those pathways. First, a route through hydroamination between alkynes and amines as the first step was envisioned (Scheme 3, path a).[31] In fact, several examples of the thermal cycloaddition between resultant enamines with sulfonyl azides have been known affording triazoline moieties, which subsequently undergo cycloreversion upon the loss of nitrogen to amidine products.[32] Alternatively, aziridination of enamine with copper nitrenoids,[33] which may be derived from the copper-mediated decomposition of sulfonyl azides, also can be proposed. However, the hydroamination route (path a) is not compatible with the reaction sequence especially when water is involved as a reagent. Moreover, since the three-component reactions are applicable only to terminal alkynes, validity of this path a cannot be sustained. Another possibility involving the ynamide intermediate is also readily ruled out on the basis of similar reasoning (Scheme 3, path b).[34]

The possibility of direct nucleophilic attack of the terminal nitrogen of sulfonyl azide by copper acetylide can be envisioned. However, even though copper acetylide may be sufficiently nucleophilic,[35] no previous examples of such reaction between copper acetylides and azides are known, and the likely product of this pathway, 1,5-disubstituted triazole, has not been observed.[36]

In Scheme 4, we offer a plausible mechanistic pathway and intermediates involved in the Cu-catalyzed three-component reactions based on the experimental data and considerations described above. We propose that the initial steps of the reaction between terminal alkynes and sulfonyl azides are similar to the previously proposed pathway for the reactions involving aryl and alkyl azides.[20] Although it is likely that more than one copper atom is involved in the catalysis (vide supra),[20b,39] only species containing single copper are shown. The cupracycle formation proceeds via the reaction of copper acetylide with sulfonyl azide. In fact, *an amidine compound was produced from the reaction of preformed copper acetylide with sulfonyl azide and amine*. Coordination of the sulfonyl azide to the copper of the acetylide is followed by stepwise triazole ring formation. Once the *N*-sulfonyl triazolyl copper species (**D**) is formed, it can undergo ring−chain isomerization leading to a ketenimine intermediate (**F**) upon release of dinitrogen molecule. Subsequent addition of certain nucleophilic reagents, such as amines, alcohols, or water, to the ketenimine intermediates takes place as the last step affording the final products, amidines, imidates, or amides.

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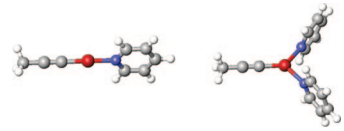
(37) Since copper(I) species often form tricoordinate complexes, the bis-pyridine acetylide complex was modeled (**X2**), which was found to be close to isoenergetic with **X1**. When the anionic ligand is a worse σ donor, e.g., chloride, the tricoordinate species is more favored. In a recent computational study by Ahlquist and Fokin,[39] it was illustrated how a second copper atom could stabilize the cycloaddition transition state as well as the following intermediate, explaining the observed second order dependence of copper on the rate. In the current study we will mainly discuss mononuclear copper acetylides, since the interest is to compare the reactivity of *N*-sulfonyl azides to the *N*-alkyl analogues



X1 **X2**

(38) It is possible that a second nitrogen ligand (pyridine) can bind to the copper in the triazolyl intermediate **X10** to form a complex **X10(Py)**, although this step was calculated to be slightly endothermic (10 kJ mol^{-1}). This further shows that stronger σ-donors favor dicoordinate copper(I) centers.

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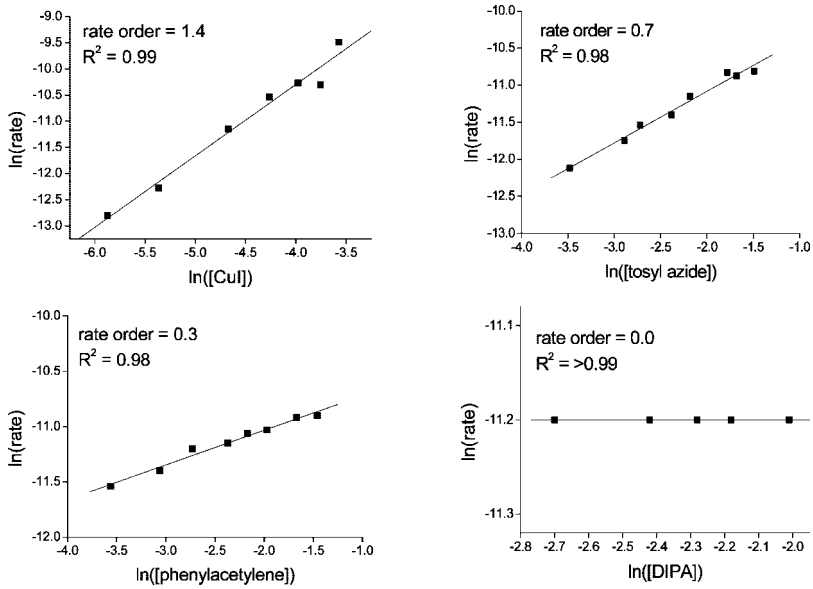
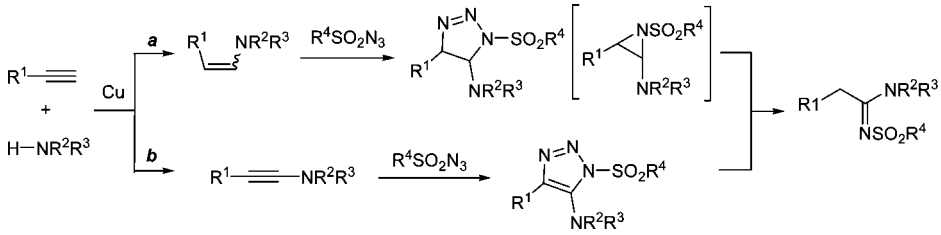
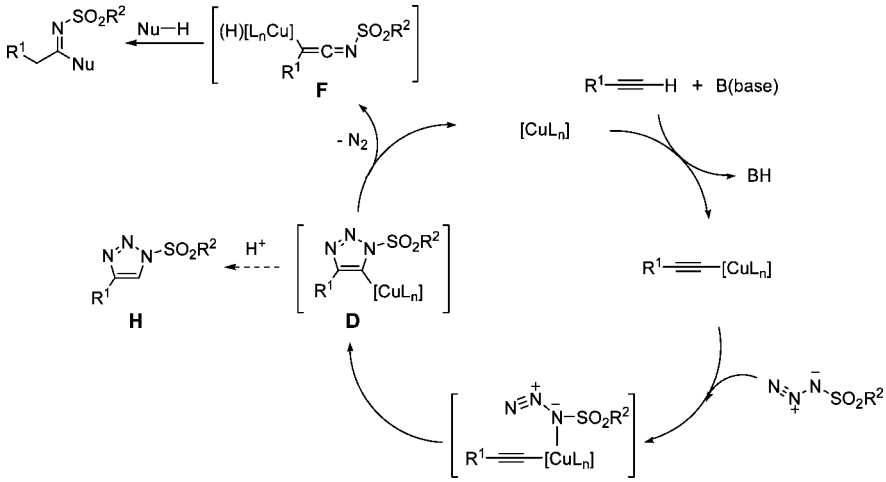


FIGURE 2. Initial rate measurement with the four reacting species in the CuI-catalyzed amidine synthesis: (a) CuI, (b) TsN_3, (c) phenylacetylene, and (d) diisopropylamine.

SCHEME 3



SCHEME 4. Proposed Mechanistic Pathways for the Cu-Catalyzed Three-Component Reactions



It should be noted that the cuprated triazole species plays the key role in determining the outcome of the reaction. That is, ketenimine compounds can be generated via the ring-opening rearrangement from the cuprated triazole. Otherwise, the copper triazole may be trapped upon protonation as triazole compound. Although the three-component coupled products are provided with excellent selectivity under the developed reaction conditions, the trapping conditions were also previously developed by us to deliver *N*-sulfonyl triazole compounds (**H**).[27] In fact, as can be seen above, the choice of suitable base additives and reaction temperatures are the most important key factors in controlling the product distribution.

Computational Studies. The experimental evidence for the formation of a triazolyl intermediate prompted us to determine the mechanistic parameters for its formation and breakdown using computational methods, performed at the density functional theory (DFT) B3LYP/LACV3P*+ level. The corresponding formation of an *N*-alkyl or aryl triazolyl copper species has been previously investigated.[20] Therefore, the present study focuses on the reactivity of sulfonyl azides. A mononuclear copper acetylide with one pyridine spectator ligand on copper was chosen as a stating point (**X1**, Figure 3).[37] The first intermediate is the cupracycle **X7** formed after the proximal nitrogen of the azide coordinates to the copper atom. The

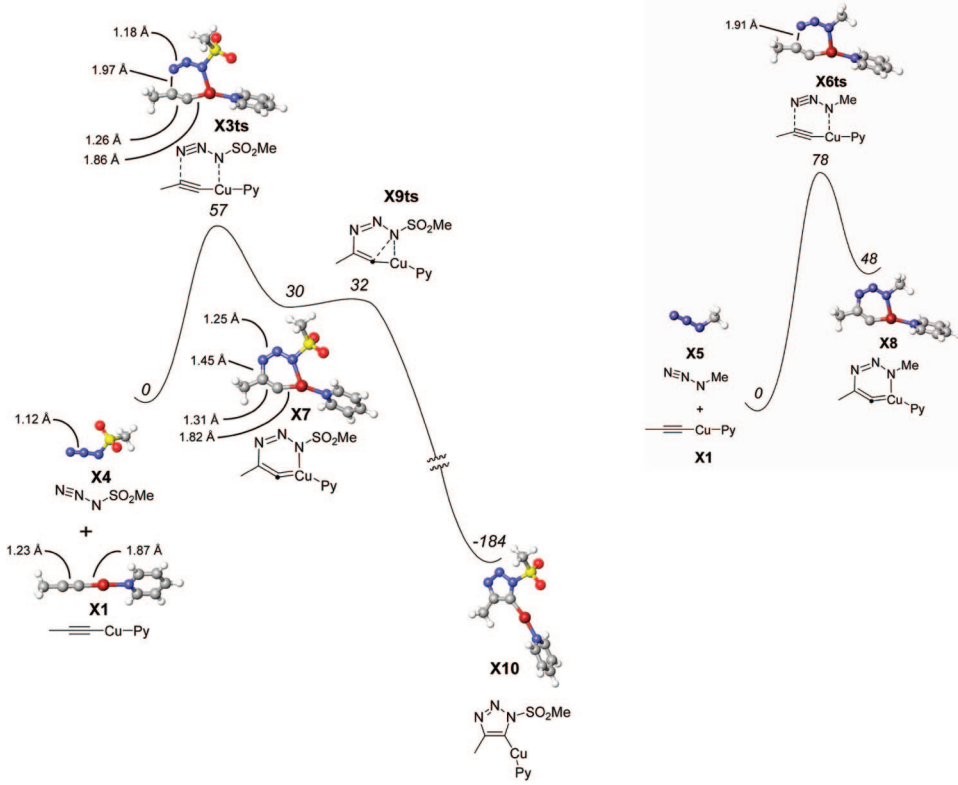


FIGURE 3. Reaction coordinates for the stepwise cycloaddition of two types of azides to a copper acetylide, which yield a triazolyl copper intermediate. Numbers in italics are the relative energies (in kJ mol^{-1}).

transition state for this step was located (**X3ts**), in which the C^2-N^3 distance was calculated at 1.97 Å. Attempts to locate a prereactive complex with the azide coordinated to the copper failed. Instead the result was a structure where the azide and the copper acetylide were only interacting by weak intermolecular interactions. The explanation for the failure to locate a complex with the azide coordinated is likely that the calculations were performed including the implicit Poisson−Boltzmann solvent model throughout the optimizations. The barrier was therefore calculated from the separated reactants.

For methanesulfonyl azide (**X4**) used in this study, the overall metallacycle formation barrier (**X3ts**) was calculated at 57 kJ mol^{-1}. To compare this to the more frequently utilized alkyl azides, the overall cycloaddition barrier for methyl azide (**X5**) to the copper acetylide (**X1**) was calculated. This barrier was found to be substantially higher (**X6ts**), 78 kJ mol^{-1}, thus indicating that sulfonyl azides react even more readily with copper acetylides than alkyl azides. In the methyl azide reaction, the C^2-N^3 distance was found to be 1.91 Å (**X6ts**), which is slightly shorter than in the methanesulfonyl azide transition state (**X3ts**, 1.97 Å), thus implying a later transition state in the methyl azide case.

The reaction between **X1** and **X4** results in the formation of the cupracycle intermediate **X7**. This reaction step was calculated to be endothermic by 30 kJ mol^{-1}, which is again substantially more favorable for the methansulfonyl azide than the methyl azide for which an endothermicity of 48 kJ mol^{-1} was calculated (**X8**). As expected, the subsequent formation of the second C−N bond takes place via transition state **X9ts** with a very low barrier of merely 2 kJ mol^{-1}, leading to the triazolyl copper intermediate (**X10**), in line with the experimental observations. The reaction of the separated reactants **X1** and **X4** to the triazolyl species (**X10**) was calculated to be highly exothermic (−184 kJ mol^{-1}).

The triazolyl intermediate then becomes a branching point of the two subsequent reactions: (i) direct protonation yields the *N*-sulfonyl triazole or (ii) N_2 extrusion leads to the ketenimine intermediate. For the latter, a stepwise mechanism was characterized that involves a ring-opening process giving an α-diazoimine intermediate with subsequent N_2 release. The ring-opening step was shown to be significantly accelerated by the presence of the sulfonyl group, explaining the experimental observation that aryl and alkyl azides *do not* give amidines (imidates or amides) via the ring-opening rearrangement process. Breaking of the C−N bond in the diazoimine species was found to be relatively facile, and a comparison between the Cu^I substituted versus the protonated diazoimine showed that the presence of the copper center has a favorable influence on the N_2 elimination.[27]

Herein the reaction step has been remodeled with the pyridine ligand (Figure 4).[38] Ring-opening of **X10** takes place via transition state **X12ts** with a calculated activation barrier of 52 kJ mol^{-1}. In the transition state (**X12ts**), the scissile N^1-N^2 bond is elongated to 2.27 Å, while the bond between the other two nitrogen atoms (N^2-N^3) is significantly shortened to 1.15 Å. The species resulting from the ring-opening process is a diazoiminyl copper complex **X13**, where the N−N−C angle in the diazo moiety is practically linear (175°). The transformation from **X10** to **X13** was calculated to be endothermic by 28 kJ mol^{-1}.

The dissociation of the dinitrogen molecule can now take place, and this conversion proceeds via a transition state **X14ts** where the breaking C−N bond was elongated to 1.71 Å and the N_2 fragment was bent, with an N−N−C angle of 133°. The

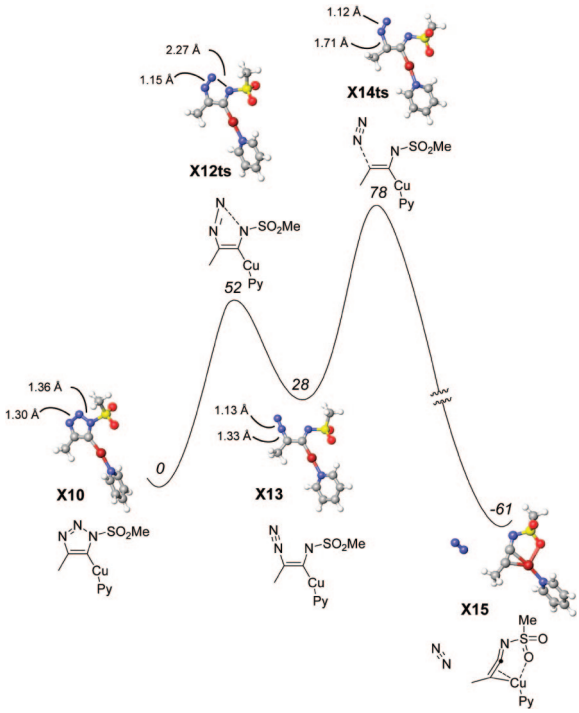


FIGURE 4. Reaction pathway for the proposed stepwise N_2 dissociation from the triazolyl copper intermediate **X10**. Numbers in italics are relative energies (in kJ mol^{-1}).

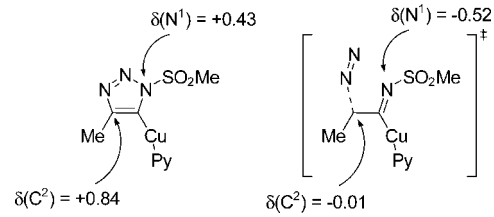


FIGURE 5. Change of Mulliken charges in triazolyl intermediate **X10** and transition state **X12ts**.

activation energy relative to the diazoiminyl complex **X13** was calculated to be 50 kJ mol^{-1}. Since **X13** is higher in energy than the triazolyl intermediate **X10**, the reaction has an effective barrier of 78 kJ mol^{-1}. This activation barrier is low enough for it to take place easily at ambient temperatures, yet it is not too low to be uncontrollable. We showed that under the right conditions the triazolyl intermediate could be trapped and formed selectively by simply using the right acidity and reacting at lower temperature (0 °C).[27] Resulting from the dissociation of the dinitrogen fragment is the keteneiminyl complex **X15**, which was located by simply optimizing a slightly distorted geometry of the transition state **X14ts**.

In addition, the above calculation results suggest that N_2 dissociation might be the rate-determining step (RDS). Shown in Figure 5 is the Mulliken charge in the triazolyl intermediate **X10** and transition state **X12ts**, which was related to the RDS. It revealed that the Mulliken charge on the C^2-carbon of the acetylenes went from +0.84 in **X10** to −0.01 in **X12ts**. The partial charge on the N^1-nitrogen was more negative in the transition state **X12ts** than in the triazolyl intermediate **X10**. These results might distinctly corroborate the experimentally obtained positive ρ-values of the Hammett plot with substituted acetylene and sulfonyl azides (Figure 1). In fact, the experimental observation that the reaction is favored by electron-deficient aryl acetylene and accelerated by the electron-withdrawing group substituted aryl sulfonyl azide may fit this computational result.

Conclusions

The experimental results obtained from the product distribution, intermediate trapping studies, and kinetic profiling offer key insights into the mechanistic pathways of the copper-catalyzed three-component reactions of sulfonyl azides, 1-alkynes and amines, alcohols, or water. 1-Sulfonyl triazolyl copper species, formed via a stepwise cycloaddition of copper acetylide and sulfonyl azide, are a crucial branching point that controls the subsequent steps: protonation leading to (*N*-sulfonyl)triazoles or ring-opening producing ketenimine species. Computational studies reveal that the triazolyl copper species having an N^1-sulfonyl group has much lower activation energy for the hypothetical ring-opening step compared to that of the N^1-alkyl substituents. This consideration may explain why the Dimroth-type rearrangement occurs so readily with 5-cuprated 1-sulfonyl triazoles. Better mechanistic understanding of these three-component catalytic reactions is offered by the present study, providing additional opportunities for developing new and useful synthetic methodologies.

Experimental Section

Procedure for the Product Distribution Experiment on the Type of Azides (Table 1). To a stirred mixture of phenylacetylene (51.2 mg, 0.5 mmol), indicated azide (0.6 mmol), and CuI (9.5 mg, 0.05 mmol) in solvent (1.0 mL) was slowly added diisopropylamine (0.085 mL, 0.6 mmol) at 25 °C. After the reaction mixture was stirred for 12 h at room temperature, it was diluted with CH_2Cl_2 (2 mL) and then quenched with saturated NH_4Cl aqueous solution (3 mL). The mixture was stirred for an additional 30 min at room temperature and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Conversion and ratio were determined by ^{1}H NMR relative to an internal standard, 1,3-benzodioxane. The crude residue was purified by flash column chromatography to give the major product, triazoles or amidines, as a white solid.

Procedure for the Trapping Experiment of Triazolyl Intermediate (Eq 2). To a stirred solution of phenylacetylene (**1**, 204.3 mg, 2.0 mmol), *p*-toluenesulfonyl azide (473.3 mg, 2.4 mmol), ICl (2.4 mL of 1.0 M solution, 2.4 mmol), and CuI (380.9 mg, 2.0 mmol) in THF (8 mL) was added Et_3N (0.335 mL, 2.4 mmol) under an N_2 atmosphere at 0 °C. After the reaction mixture was stirred at 0 °C for 12 h, it was diluted with CH_2Cl_2 (5 mL) and then quenched with saturated NH_4Cl aqueous solution (10 mL). After the separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatograph (EtOAc/*n*-hexane, 1:3) to afford the desired product as a yellowish liquid, 1-(4-methylbenzenesulfonyl)-4-phenyl-5-iodo-1,2,3-triazole (**5**, 420.6 mg, 49.5%).

1-(4-Methylbenzenesulfonyl)-4-phenyl-5-iodo-1,2,3-triazole (5). Yellowish liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 7.43−7.38 (m, 5H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 133.1, 130.4, 129.3, 129.2, 128.9, 128.5, 128.3, 21.9; IR (KBr) ν 3064, 1609, 1494, 1456, 1124, 1034, 978 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{15}H_{12}IN_3O_2S$ [M + H]$^+$ 425.9773, found 425.9757.

Procedure for the Transformation of Amide to Amidine via Ketenimine (Eq 4). A solution of 4-methyl-*N*-phenylacetylbenzenesulfonamide (**7**, 72.0 mg, 0.25 mmol), PPh_3Br_2 (220.0 mg, 0.5 mmol), CuI (10 mol %, 4.8 mg), and Et_3N (0.070 mL, 0.5

mmol) in THF (2 mL) was stirred under an N_2 atmosphere at 25 °C. After the reaction mixture was stirred for 1 h, diisopropylamine (0.175 mL, 1.25 mmol) was added, and then the mixture was stirred for 2 h at room temperature. It was then diluted with CH_2Cl_2 (2 mL) and quenched with saturated NH_4Cl aqueous solution (3 mL). The mixture was stirred for an additional 30 min and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatograph (EtOAc/*n*-hexane, 1:1) to afford the desired product as a white solid, N^1,N^1-diisopropyl-N^2-(4-methylbenzensulfonyl)-2-phenylacetamidine (**3**, 75.4 mg, 81.0%).

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Supporting Information Available: Experimental details of the product distribution, trapping studies, kinetic studies, characterization, copies of ^{1}H and ^{13}C NMR spectra of the newly obtained products (**5**) in the present studies, *X*,*Y*,*Z* coordinates for the calculated compounds/transition states, and energies of the respective geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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