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Copper(I)–N-Heterocyclic Carbene Complexes as Efficient Catalysts for the Synthesis of 1,4-Disubstituted 1,2,3-Sulfonyltriazoles in Air

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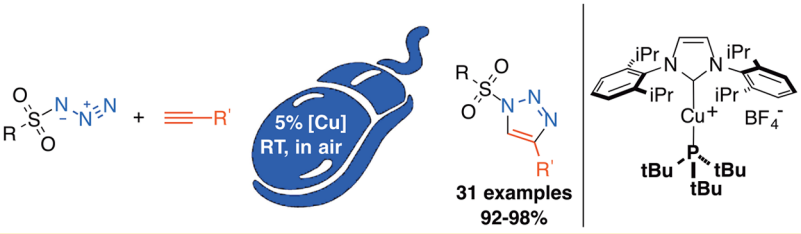
Supporting Information

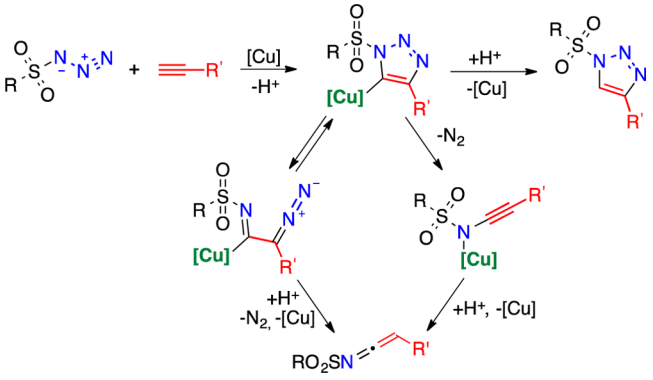


ABSTRACT: Bis-NHC and mixed NHC/PR_3 copper(I) complexes (NHC = N-heterocyclic carbene) were found to be efficient catalysts enabling the azide–alkyne cycloaddition reaction leading to the formation of 1,2,3-sulfonyltriazoles under Click conditions. The mechanism of this transformation was probed and decoordination of the NHC ligand (even in the NHC/PR_3 mixed ligand systems) during the catalytic transformation was observed.

INTRODUCTION

Heterocycles are important compounds that can be found in a multitude of applications ranging from important motifs in agrochemicals and pharmaceutical compounds to their prominent role as fragments in natural products. Among heterocycles, triazoles are of particular interest as they are stable in acidic and basic media.[1,2] One of the most versatile and efficient route leading to the formation of 1,4-disubstituted 1,2,3-triazoles is the copper-catalyzed azide–alkyne [3+2] cycloaddition (Scheme 1).[2] The success story of this process is due to the simple assembly of heterocycles via "Click chemistry",[3] using a catalytic or thermally mediated reaction (Huisgen reaction).[4] Despite the versatility of this route, sulfonyl-substituted triazoles are difficult to access due to the ring-opening side-reaction which occurs once the triazolyl-Cu intermediate is formed (Scheme 1).[2] While this ring-opening provides access to amidines and amides,[5] it also impedes the synthesis of a library of *N*-sulfonyl triazoles through azide–alkyne [3+2] cycloaddition. Such functionalized triazoles are very convenient precursors for azavinyl carbenes in metal-catalyzed transannulation, yet only a few procedures for their synthesis have been reported.[6]

Scheme 1. [3+2] Cycloaddition vs N_2-elimination



This unwelcome ring-opening reaction explains why only a handful of systems have been reported for the synthesis of such compounds through cycloaddition (Table 1).[7] Fokin and Chang reported a synthetic protocol combining a copper salt (CuI 10 mol%), 2,6-lutidine and a strong base, in chloroform, at low temperature (0 °C) to yield these compounds.[7a] In 2008, the Zhao group developed an aqueous media process using CuBr and PhSMe (10 mol%).[7b] More recently, Pérez and co-workers described well-defined copper(I) complexes bearing a tridentate ligand for such transformations.[7c] However, an inert atmosphere was required for the reaction to proceed. In parallel, a heterogeneous version was reported based on a carboxylate copper(I) complex.[7d] All previously reported studies highlight the same crucial points concerning sulfonyl triazole, namely, its inherent poor stability under synthetic reaction conditions and propensity to ring-open during its synthesis leading to unwanted side-products. Recently, we have shown that synergistic effects are present when using heteroleptic NHC/NHC′ (NHC = N-heterocyclic carbene) and mixed NHC/phosphine copper complexes in catalysis.[8]

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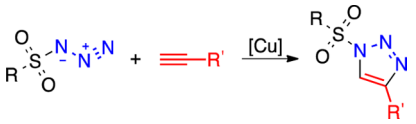
Table 1. Sulfonyl Triazoles from [3+2] Cycloaddition: The State of the Art



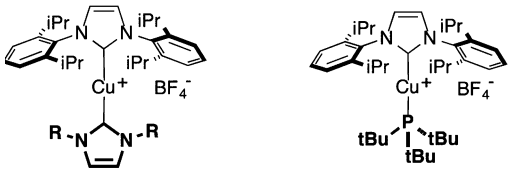
catalytic system[a]	loading (mol%)	solvent	temp (°C)	time (h)
CuI/2,6-lutidine[7a]	10/120	$CHCl_3$	0	12
CuBr/PhSMe[7b]	10/20	H_2O	RT	16
$[Tpm^{Br}Cu(NCMe)]BF_4$[7c]	5	$CHCl_3$	40	24
CuTC[7d,h]	10	toluene	0-RT	4−18
Cu_2O[7f]	10	H_2O	RT	4
$Cu(OAc)_2{\cdot}H_2O$/2-amino phenol[7g]	10/5	MeCN	RT	1

[a]Abbreviations: Tpm^{Br} = trispyrazolylbromomethane, TC = thiophene-2-carboxylate.

These complexes have shown interesting catalytic activity in 1,3-cycloadditions leading to the formation of 1,4-disubstituted 1,2,3-triazole derivatives. These successful results encouraged us to investigate the particularly challenging reaction that is the synthesis of 1,4-disubstituted 1,2,3-sulfonyltriazoles. Herein, we report what represents, to the best of our knowledge, the first application of copper(I)−NHC complexes in the preparation of *N*-sulfonyl-1,2,3-triazoles, in air and in the absence of base or additive.

RESULTS AND DISCUSSION

In order to probe the ability of heteroleptic biscarbene complexes of the type $[(Cu)(IPr)(NHC')]{\cdot}BF_4$ (IPr = *N,N'*-bis{2,6-(diisopropyl)phenyl}imidazol-2-ylidene; NHC′ is I^tBu = *N,N'*-di-*tert*-butylimidazol-2-ylidene, ICy = *N,N'*-dicyclohexylimidazol-2-ylidene, and IMes = *N,N'*-bis{2,4,6-(trimethyl)phenyl}imidazol-2-ylidene) and $[Cu(IPr)(PR_3)]{\cdot}BF_4$ for the preparation of *N*-sulfonyl-1,2,3-triazoles, tosyl azide and phenylacetylene were selected as model substrates (Figure 1 and Table 2).



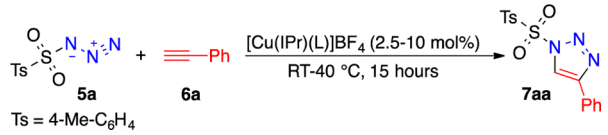
1 R = 2,4,6-$Me_3C_6H_2$
2 R = tBu
3 R = Cy

4

Figure 1. Complexes used in this study.[8]

Comparison of the reactivity of complexes **1**−**4** at room temperature in various solvents (see Supporting Information) proved the undisputed superiority of the mixed phosphine−NHC ligand system **4** (see Table 2, entries 1−12 for selected examples). This is consistent with our previous observations made when investigating the formation of 1,4-disubstituted 1,2,3-triazoles.[8] Indeed, complexes bearing *N*-aryl-substituted carbenes were shown to be less efficient in the formation of 1,2,3-triazoles than *N*-alkyl or PR_3/NHC copper(I) complexes, presumably due to an encapsulation of the metal center by the aryl groups.[8] Increasing the temperature to 40 °C has various

Table 2. Optimization of the Reaction Conditions[a,b]



entry	complex (L)	solvent	temp (°C)	cat. amount (mol%)	conv [c] (%)
1	**1** (IMes)	toluene	RT/40	10	10/8
2	**1** (IMes)	H_2O	RT/40	10	20/25
3	**1** (IMes)	–	RT/40	10	13/15
4	**2** (ItBu)	toluene	RT/40	10	30/90
5	**2** (ItBu)	H_2O	RT/40	10	50/70
6	**2** (ItBu)	–	RT/40	10	25/90
7	**3** (ICy)	toluene	RT/40	10	30/50
8	**3** (ICy)	H_2O	RT/40	10	30/50
9	**3** (ICy)	–	RT/40	10	32/40
10	**4** ($PtBu_3$)	toluene	RT/40	10	>99/80
11	**4** ($PtBu_3$)	H_2O	RT/40	10	80/>99
12	**4** ($PtBu_3$)	–	RT/40	10	>99/80
13	**4** ($PtBu_3$)	toluene	RT/40	5	>99/50
14	**4** ($PtBu_3$)	H_2O	RT	5	40
15	**4** ($PtBu_3$)	–	RT	5	40
16	**4** ($PtBu_3$)	toluene	RT	2.5	65

[a]Reaction conditions: tosyl azide (1.00 mmol), phenylacetylene (1.05 mmol), solvent (0.5 mL), catalyst, RT−40 °C, 15 h. [b]See Supporting Information for complete optimization. [c]Conversion determined by ^1H NMR based on azide, average of at least two reactions.

effects. In general, the catalytic efficiency of **1** is not affected by the temperature change, while with complexes **2** and **3**, an increase in catalyst activity is observed. Interestingly, with complex **4**, increasing the temperature is detrimental to the catalyst performance, except when the reaction is carried out in water or in ethyl acetate (see Table 2, entries 1−12, and Supporting Information). Of note, the fact that quantitative conversion is reached in the absence of solvent as well as in water, providing that the catalyst loading is 10 mol%. We must also mention that when reactions are carried out in water, no amide formation was observed, which is in contrast with other catalyst systems.[7a] Decreasing the catalyst loading showed the optimal conditions to be toluene as solvent at room temperature with 5 mol% Cu. The scope of the reaction was examined using these optimized conditions (Scheme 2). A large panel of substrates was investigated. The overall study shows the selectivity of the catalyst for the formation of the triazole, without formation of the rearrangement product. Alkyl-/aryl-substituted and functionalized azides and alkynes reacted successfully, leading to 1,4-disubstituted 1,2,3-sulfonyltriazoles in high yields (31 examples). A wide range of functionalities was tolerated including methoxy, fluoro, methyl and trifluoromethyl groups. For instance, using tosyl azide as model substrate, different alkyl/aryl alkynes reacted successfully, leading to the formation of sulfonyl triazoles **7aa**−**7ai**. The presence of electron-withdrawing groups (**7ab** and **7ag**) or electron-donating groups (**7ad**, **7af**, **7ah**, and **7ai**) in *ortho*, *meta*, or *para* positions of the aryl ring present on the alkyne is well tolerated as essentially quantitative conversion to the desired product was observed, with excellent isolated yields (93−98%). Similar observations were made when using methoxyphenylsulfonyl azide as substrate (**7ba**−**7bj**). Alkyne substrates bearing a heterocycle or an alkyl group were also

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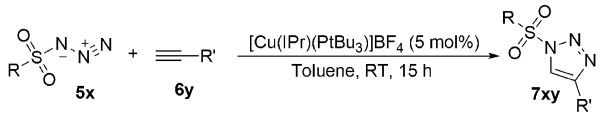
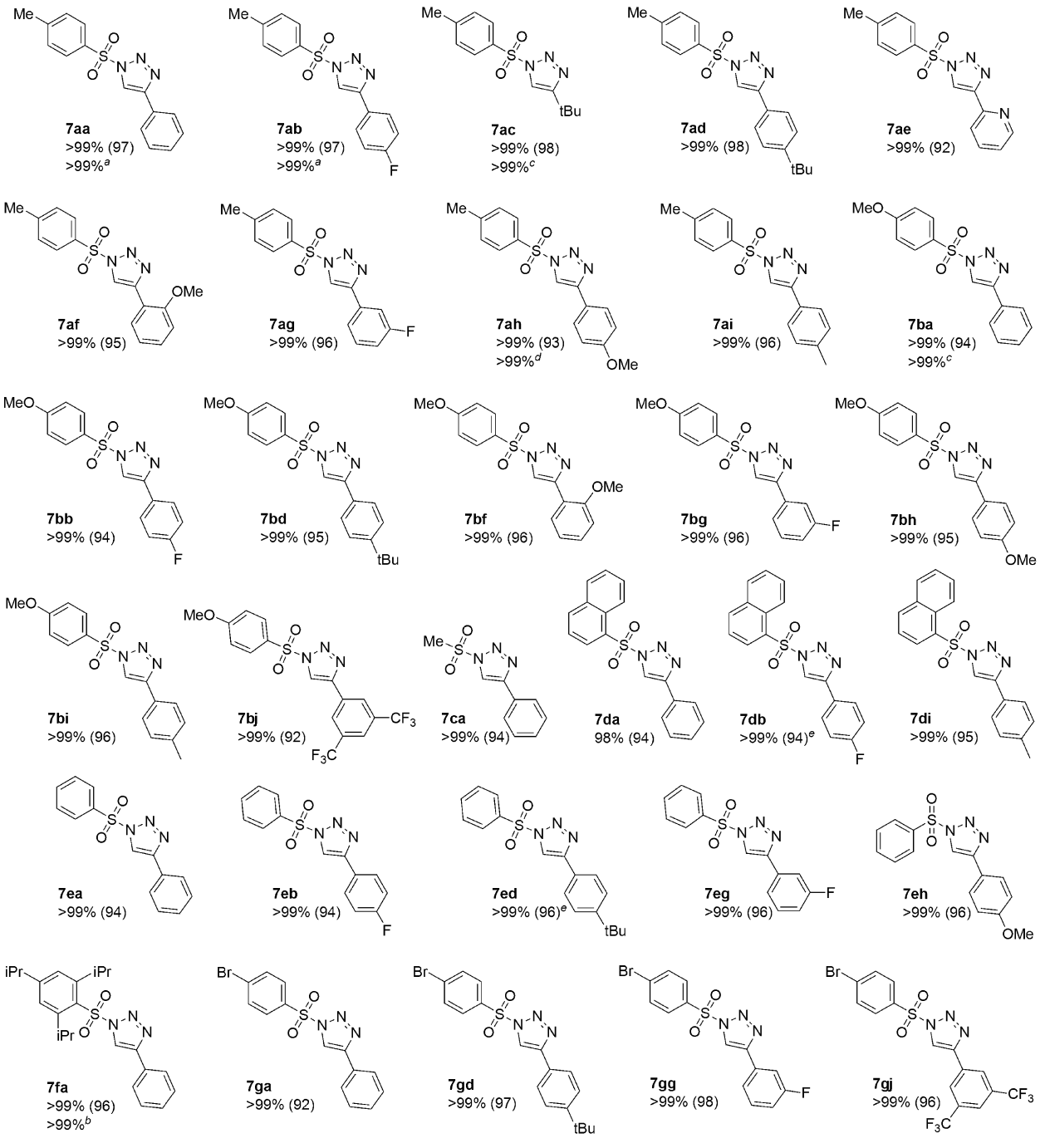
Scheme 2. Scope of the Reaction





Reaction conditions: azide (1.00 mmol), alkyne (1.05 mmol), catalyst (5 mol%), toluene (0.5 mL); Conversion determined by ^{1}H NMR based on the azide; Isolated yield in parentheses (average of 2 reactions). [a] 8 h. [b] 7 h. [c] 6 h. [d] 5 h. [e] 10 mol% [Cu]

shown to be suitable for this reaction (**7ae** and **7ac**). Further variations of the tosyl substrates were well tolerated, including when sterically hindered groups were used. For instance, naphthyl derivatives **7da**, **7db**, and **7di** were successfully obtained, as well as **7fa**, which shows that a sterically congested substrate such as 2,4,6-triisopropylphenylsulfonyl azide can efficiently undergo [3+2] cycloaddition. While the reaction time was set to 15 h for convenience, monitoring some reactions showed that much shorter reaction times (5−8 h) were enough to reach completion (see Scheme 2, **7aa**, **7ab**, **7ac**,

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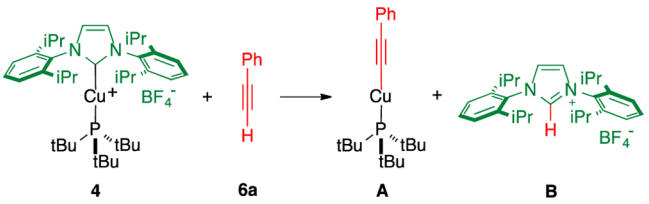
7ba, **7ah**, **7fa**). We next paid particular attention to the workup protocol. We found that impurities could be easily removed by filtration through Celite, and that addition of hexane or diethyl ether to the filtrate leads to precipitation of the product, which can be collected by simple filtration.

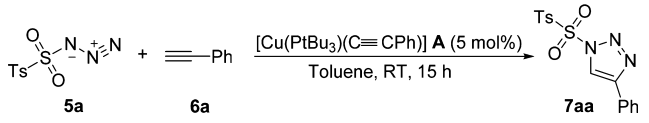
In order to probe the mechanism of this transformation, $[Cu(IPr)(PtBu_3)]\cdot BF_4$ **4** was mixed with a stoichiometric amount of phenylacetylene. This results in the loss of the NHC ligand with concomitant formation of the corresponding imidazolium salt and of the acetylide complex $[Cu(PtBu_3)(C{\equiv}CPh)]$, with the phosphine ligand remaining coordinated to Cu (Scheme 3). This somehow counterintuitive reactivity points out the basicity of the leaving ligand, which is key in such reactions.

Scheme 3. Reaction of 4 with Phenylacetylene



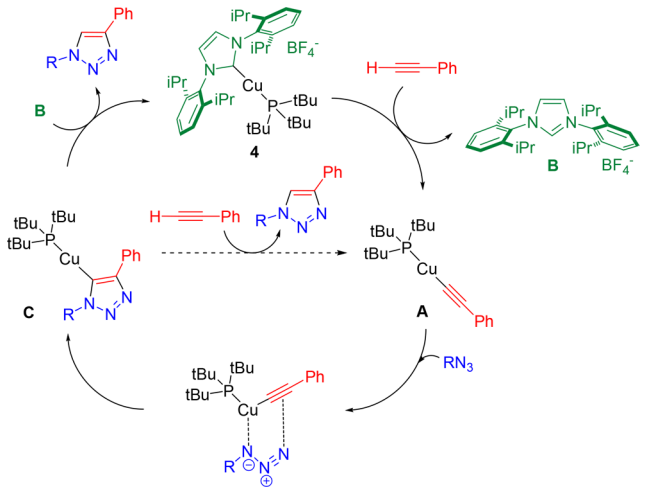
The acetylide complex $[Cu(PtBu_3)(C{\equiv}CPh)]$ **A** was shown catalytically relevant, as illustrated by the addition of **5a** to **6a** using the optimized reaction conditions described above (Scheme 4).

Scheme 4. Catalytic Activity of Phosphine Copper Acetylide Complex A



A catalytic cycle for this transformation is proposed in Scheme 5, highlighting the non-innocent role of the NHC ligand, which acts as a built-in base to activate the alkyne. This leads to the formation of an acetylide derivative, which subsequently interacts with the azide substrate[9] leading to the formation of the putative copper−triazolyl intermediate **C**. At this point, the proton which was captured by the carbene ligand in the initiation of the catalytic cycle is transferred to the triazole fragment, hence liberating the product and regenerating the active catalyst. There is also a possibility that the regeneration of **4** is bypassed by reaction of **C** with the alkyne, hence directly generating **A**. However, considering the difference in acidity between phenylacetylene and $IPr\cdot HBF_4$ (ca. 10 pK_a units),[10] we suspect the main pathway involves proton transfer from the imidazolium salt.

Scheme 5. Proposed Catalytic Cycle



CONCLUSION

The first application of copper(I)−NHC complexes leading to the formation of 1,2,3-sulfonyltriazoles has been reported. This new system proceeds in air and in the absence of additive. Catalytic studies highlight the high activity and versatility of the mixed NHC/PR_3 Cu catalyst. In addition, the catalytic system is fully selective as no side product is observed. The carbene ligand is not innocent and plays a built-in base role to catch and then release the proton from the alkyne substrate.

EXPERIMENTAL SECTION

General Procedure for the Preparation of *N*-Sulfonyltriazoles. A vial was charged with the azide (1.00 mmol), the alkyne (1.05 mmol), and the copper(I) catalyst (5 mol%). Toluene (0.5 mL) was then added. The mixture was stirred at room temperature for 15 h. Ethyl acetate (1 mL) was then added, and the mixture was filtered through a plug of Celite. The solution was concentrated to half its volume, and hexane or diethyl ether was added. The product was collected by filtration, washed with hexane or diethyl ether (2 × 3 mL), and dried under vacuum. The conversion was monitored and evaluated by ^1H NMR spectroscopy.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.7b00506.

Procedures and NMR spectra for complexes and organic compounds (PDF)

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Notes

The authors declare no competing financial interest.

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