1,3-Dipolar Cycloaddition

DOI: 10.1002/ange.200803289

[(NHC)$_2$Cu]X Complexes as Efficient Catalysts for Azide–Alkyne Click Chemistry at Low Catalyst Loadings**

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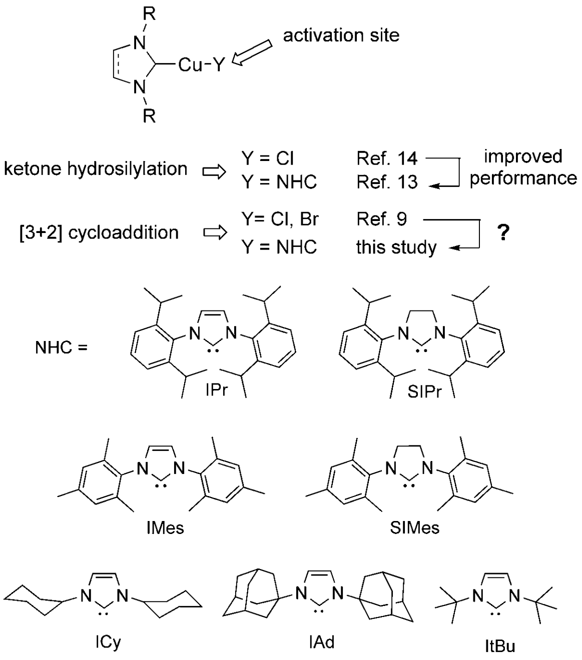
Dedicated to Professor Carl D. Hoff on the occasion of his 60th birthday

In 2001, Sharpless and co-workers defined the concept of "click chemistry" and the criteria for a transformation to be considered a "click" reaction.[1] Since then, the copper-catalyzed reaction of azides with alkynes to produce 1,2,3-triazoles regioselectively[2] (the 1,3-dipolar Huisgen cycloaddition[3]) has become the most widely used click reaction. As a result of its mild conditions and high efficiency, this reaction has found a myriad of applications in biology and materials science.[4] Less attention has been focused on the development of novel copper(I)-based well-defined catalytic systems[5–7] and on decreasing the amount of copper used.[5b,8] This last point is extremely important for future industrial applications and might be one of the last challenges to overcome for this transformation.

We recently reported the remarkable activity of [(NHC)CuX] complexes (NHC = N-heterocyclic carbene; X = Cl, Br) in the Huisgen cycloaddition.[9] Such catalytic systems have already been applied to the preparation of triazole-containing carbanucleosides,[10] porphyrins,[11] and platinum-based anticancer drugs,[12] as well as to the development of a latent catalyst for this transformation.[13]

We also studied a family of cationic NHC-containing complexes of the general formula [(NHC)$_2$Cu]X (X = PF$_6$, BF$_4$).[14] During the examination of their activity in the hydrosilylation of ketones, we observed enhanced reactivity of these complexes relative to that of their neutral analogues [(NHC)CuCl].[15] This improved activity was rationalized in terms of a more efficient pathway for the activation of the cationic precatalyst. Specifically, the second NHC ligand was postulated to have an active role in the catalytic cycle. Under hydrosilylation conditions, one NHC ligand is displaced by the base in the reaction mixture. We wondered if an alkyne could play a similar role to produce an active copper acetylide from [(NHC)$_2$Cu]X species (Scheme 1).



Scheme 1. Catalyst design.

We investigated the activity of [(NHC)$_2$Cu]X complexes **1**–**7** in the Huisgen cycloaddition with benzyl azide and phenylacetylene as model substrates (Table 1). The reactions were conducted on water with 2 mol% of the copper catalyst. The SIMes-containing complexes **4a** and **4b** displayed poor activity under these conditions, in contrast to the results of our previous studies with [(NHC)CuX] complexes.[9] This lack of reactivity can not simply be correlated with the medium steric bulk of the SIMes ligand, as complexes **7a** and **7b** with very bulky ItBu ligands were also ineffective.[16] [(ICy)$_2$Cu]PF$_6$ (**5a**) provided the best result: The cycloaddition reached completion within 90 min. No general trend in reactivity was found for this reaction with respect to the counterion of the metal complex. Further optimization with complex **5a** showed that acetonitrile, instead of water, was the most suitable solvent for this transformation.[17] Moreover, the reaction was found to proceed smoothly under neat conditions with a significantly decreased catalytic loading.

The scope of the reaction was examined with **5a** (0.5 mol%) under neat conditions at room temperature (Scheme 2). All reactions proceeded smoothly to completion

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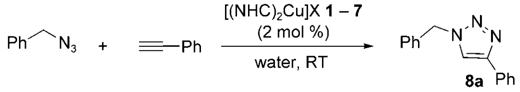
[**] The ICIQ Foundation and the Spanish Ministerio de Educación y Ciencia are gratefully acknowledged for financial support. S.D.G. thanks the MEC for financial support through the Torres Quevedo program. S.P.N. is an ICREA Research Professor. We thank Dr. Nicolas "La Click, c'est chic" Marion for insightful reading of this manuscript. NHC = N-heterocyclic carbene.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200803289.

Table 1: Catalyst screening.



[(NHC)$_2$Cu]PF$_6$		t [h]	Conv. [%][a]	[(NHC)$_2$Cu]BF$_4$		t [h]	Conv. [%][a]
[(IPr)$_2$Cu]PF$_6$	**1a**	18	71	[(IPr)$_2$Cu]BF$_4$	**1b**	8	100
[(SIPr)$_2$Cu]PF$_6$	**2a**	5	100	[(SIPr)$_2$Cu]BF$_4$	**2b**	5	100
[(IMes)$_2$Cu]PF$_6$	**3a**	6	100	[(IMes)$_2$Cu]BF$_4$	**3b**	6	100
[(SIMes)$_2$Cu]PF$_6$	**4a**	18	5	[(SIMes)$_2$Cu]BF$_4$	**4b**	18	13
[(ICy)$_2$Cu]PF$_6$	**5a**	1.5	99	[(ICy)$_2$Cu]BF$_4$	**5b**	5	95
[(IAd)$_2$Cu]PF$_6$	**6a**	5	100	[(IAd)$_2$Cu]BF$_4$	**6b**	3	100
[(ItBu)$_2$Cu]PF$_6$	**7a**	18	76	[(ItBu)$_2$Cu]BF$_4$	**7b**	18	35

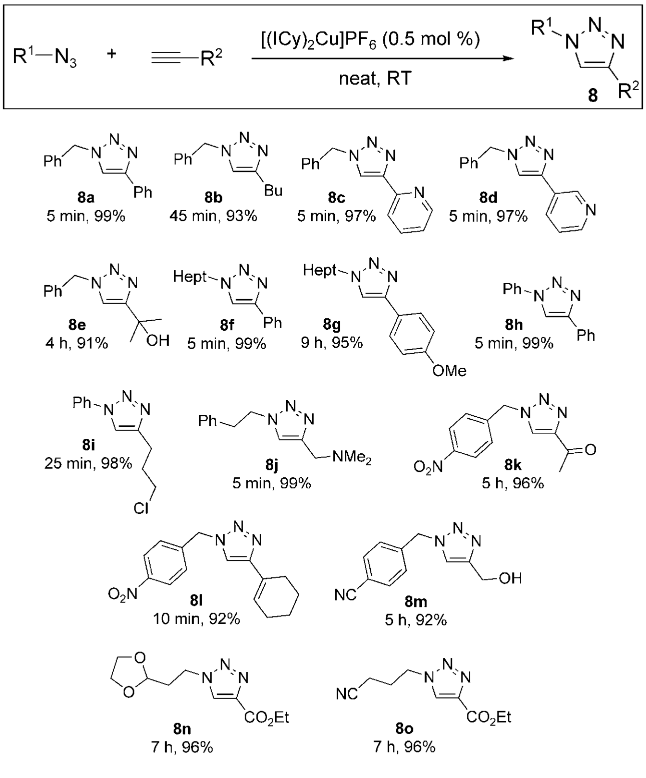
[a] The conversion (determined by ^{1}H NMR spectroscopy) is an average of the values for at least two independent experiments.

in short reaction times (from minutes to 9 h), and triazoles **8** were isolated in excellent yields and high purity after simple filtration or evaporation. According to the "click laws", no precautions to exclude oxygen or moisture were taken in any of these reactions. Neither copper disproportionation with the precipitation of metallic copper nor copper oxidation was observed under the optimized reaction conditions, which shows, once more, the high ability of NHCs to stabilize copper(I) species.[18]

Electron-rich, electron-poor, and hindered alkynes were found to be suitable cycloaddition partners, as well as enynes. Benzyl, alkyl, and aryl azides were successfully employed. A number of functional groups were tolerated, such as alcohol, ketone, ester, amine, pyridine, nitrile, and halogen functionalities. No direct correlation can be drawn between the electronic nature of the reactants and the outcome of the reaction. As we had observed previously,[9] the physical state of the reaction product is critical: Longer reaction times were required for the formation of oily or low-melting-point triazoles. In these cases, the results were improved simply by increasing the reaction temperature to 40 °C.[19]

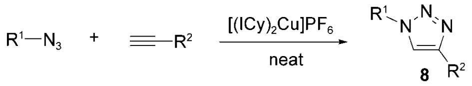
The high activity of this catalytic system naturally led us to examine the possibility of further decreasing the amount of metal used in this transformation. Again with benzyl azide and phenylacetylene as model substrates, we tested different catalyst loadings at various temperatures under neat conditions. In this particular case, reactions at 40 or 50 °C were faster than those at room temperature and could be carried out with the lowest catalyst loadings.[20] However, minor formation of the 1,5-disubstituted triazole regioisomeric to **8a** was observed consistently by GC and ^{1}H NMR spectroscopy after prolonged reaction times (8 h at 40 °C and 5 h at 50 °C). Thus, extreme caution is required to avoid undesired thermal processes. Results for the formation of a number of triazoles are presented in Table 2.

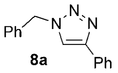
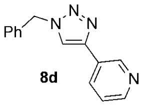
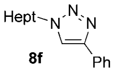
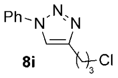
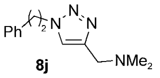
In all cases, the loading of **5a** could be lowered at least to 300 ppm at room temperature or 100 ppm at 40 °C. Under these conditions, good conversion was still attained after short to reasonable reaction times. The best results were observed for the synthesis of triazole **8a**: A copper loading as low as 40 ppm led to a remarkable turnover number (TON) above 20 000 and a turnover frequency above 5000 h^{-1}.[21] It is important to note that, under these reaction conditions, the



Scheme 2. [(ICy)$_2$Cu]PF$_6$-catalyzed formation of triazoles.

Table 2: [(ICy)$_2$Cu]PF$_6$-catalyzed synthesis of triazoles at low catalyst loadings.



8	T [°C]	[Cu] [ppm]	t [h]	Conv. [%][a]	TON
 8a	RT 40 50	50 50 40	48 8 4	80 89 81	16 000 17 800 20 250
 8d	RT	75	6	91	12 133
 8f	RT	200	20	72	3600
 8i	RT 40	300 100	43 18	85 70	2833 7000
 8j	RT 40	300 100	40 18	45 71	1500 7100

[a] The conversion (determined by GC) is an average of the values for at least two independent experiments.

use of our previous catalyst [(SIMes)CuBr] led to no conversion after 24 h.

To gain some insight into the activation pathway of the precatalyst, we next carried out a number of stoichiometric experiments. Whereas no interaction was observed between benzyl azide and **5a** in CD_3CN, the same copper complex was completely consumed in minutes in the presence of phenylacetylene. The equimolar formation of two new species was evidenced by ^1H NMR spectroscopy (Figure 1). One of them was identified unequivocally as ICy·HPF_6 (**B**) by comparison with a pure sample.[22] The second species was also isolated cleanly and identified as the mononuclear copper(I) acetylide **A** by NMR spectroscopy. To determine the identity of **A** unambiguously, we carried out the same reaction with the IPr-containing complex **1a**. In this case, no reaction was observed at room temperature. However, when the reaction mixture was heated overnight at 80 °C, the formation of two new species was observed, as well as remaining starting material. The new products were separated and identified as the known complex [(IPr)Cu$-$C$\equiv$CPh][23] and IPr·HPF_6. The lower reactivity of **1a** relative to that of **5a** can be correlated directly to its moderate catalytic activity (Table 1). Thus, it appears that one of the NHC ligands on the copper center can act as a base, deprotonating the alkyne, to initiate the catalytic cycle.

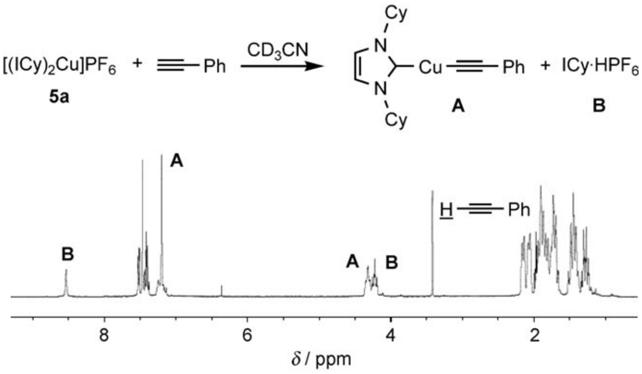
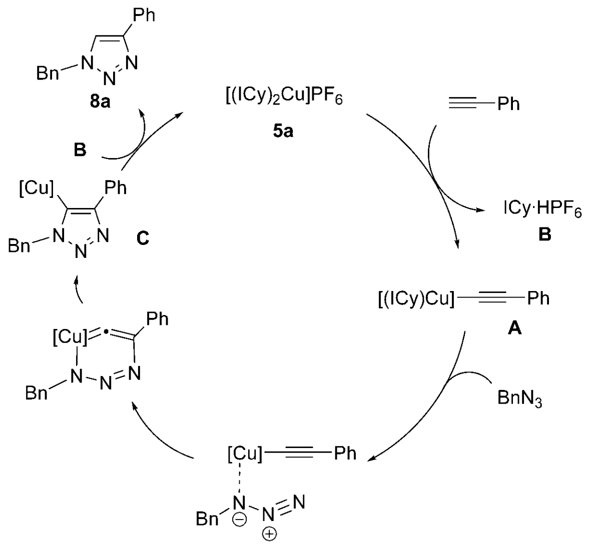


Figure 1. ^1H NMR spectrum for the reaction of **5a** with phenylacetylene. Cy = cyclohexyl.

A proposed mechanism for this transformation is depicted in Scheme 3. The bis(NHC) complex **5a** would be transformed into an acetylide **A** and an azolium salt **B** by reaction with the alkyne. Upon the interaction of **A** with the azide, the reaction would follow the pathway commonly accepted for this transformation[24] to form a triazolide intermediate **C**, the reaction of which with the azolium salt **B** would lead to the formation of the expected triazole **8a** and the regeneration of the catalyst. However, a binuclear mechanism can not be ruled out at this time.[25] We are currently carrying out theoretical calculations to clarify this point.

In an attempt to isolate intermediate **C**, we treated isolated complex **A** with benzyl azide in CD_3CN. However, we observed the formation of a complex mixture of unknown products as well as considerable precipitation, presumably of copper salts. We attribute this result to the extreme instability of **C** in the absence of a proton source. In contrast, when a mixture of **A** and **B** was treated with the azide, clean formation of triazole **8a** was observed, along with the regeneration of $[(ICy)_2Cu]PF_6$.



Scheme 3. Postulated mechanism. Bn = benzyl.

Further experiments to isolate the triazolide intermediate **C** met with limited success. The treatment of **5a** with an equimolar amount of phenylacetylene and a slight excess of benzyl azide in acetonitrile led either to the decomposition of the reaction mixture or to the direct formation of triazole **8a**. Nevertheless, we were able to observe by ^1H NMR spectroscopy the consumption of the starting materials and the formation of a new compound. The spectrum of the new species was attributed to **C**;[20] however, the formation of this intermediate as a minor component of the mixture and its high instability precluded its full characterization. Moreover, upon acidic hydrolysis this crude mixture rapidly evolved to triazole **8a** and ICy·HPF_6. These findings are in line with a report by Straub and co-workers, who recently isolated a NHC triazolide complex in which the environment around the copper center was highly encumbered, probably stabilizing the complex.[26]

In conclusion, we have developed a new catalytic system, $[(ICy)_2Cu]PF_6$ (**5a**) without a solvent, for the [3+2] cycloaddition of azides and alkynes under click conditions. This system has been shown to be broad in scope and highly efficient (TOFs up to 5000 h^{-1}) even at very low catalyst loadings (down to 40 ppm). Furthermore, preliminary mechanistic studies have shown the ability of the NHC ligand on the copper center to act as a base and deprotonate the starting alkyne to initiate the catalytic cycle. Further applications of this catalyst system, especially with a low catalyst loading, are currently under investigation in our laboratory.

Received: July 7, 2008
Revised: August 14, 2008

Keywords: alkynes · azides · click chemistry · copper · N-heterocyclic carbenes

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[19] For example, triazole **8g** was produced quantitatively at 40 °C in 3 h instead of 9 h. For triazoles **8n** and **8o**, a reaction time of only 1.5 h was required at 40 °C.

[20] For further details, see the Supporting Information.

[21] Vincent and co-workers recently reported a copper(I)–tren catalyst (tren = tris(2-aminoethylamine)) that promoted the Huisgen cycloaddition with high turnover numbers (TONs). TON values of up to 54000 were observed for the preparation of **8a** at 60 °C in 24 h in the absence of a solvent.[8] However, during our studies, even for the formation of the same triazole, we observed the non-negligible formation of the 1,5-regioisomer at 50 °C after only 5 h.

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