A [(NHC)CuCl] complex as a latent Click catalyst†

Silvia Díez-González,*[a] Edwin D. Stevens[b] and Steven P. Nolan*[a]

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A latent catalyst for the [3 + 2] cycloaddition reaction of azides and alkynes has been developed in accordance with the principles of Click chemistry.

A catalyst can be defined as latent when it is inert under normal conditions such as ambient temperature and light, but active when an external stimulus such as heat or irradiation is applied.[1] These catalysts are valuable tools for controlling the initiation step in polymerization or curing processes.[2] Furthermore, storage and handling stabilities are usually enhanced. As a consequence of this inherent property of latency, such catalysts are widely utilized in industrial applications such as adhesives, paintings, coatings, inks and photoresists.[3] The current scope of this chemistry is not reduced to polyadditions; hydrosilylation[4] and metathesis[5] reactions have also been studied. The concept of latent catalysis can be seen as switching *on* and *off* a chemical transformation. This approach can also be of great interest for biological applications.

The reaction of azides and alkynes yielding 1,2,3-triazoles[6] is the most popular Huisgen 1,3-dipolar cycloaddition.[7] The recent discovery of copper(I) as efficient and regiospecific catalyst for this process[8] has rendered it the best Click reaction[9] to date. Since mild and neutral conditions are required and the reaction proceeds in high efficiency, this reaction has found a myriad of applications in both biology and material science.[10] We recently reported that [(NHC)CuX] complexes (NHC = N-heterocyclic carbene; X = Cl or Br) are highly efficient catalysts for the Huisgen [3 + 2] cycloaddition of azides and alkynes.[11] Naturally, we were interested in combining both concepts for the development of a latent catalyst for the Huisgen cycloaddition. While screening different complexes, we observed that [(SIPr)CuCl][12] (SIPr = *N*,*N*-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene) was the least reactive catalyst, and we envisaged that we could take advantage of such a low reactivity for the development of a latent catalyst for this transformation.

The catalyst synthesis was achieved in high yield by the reaction of the *in situ* generated NHC and CuCl in toluene at room temperature (Scheme 1, see ESI†). Suitable single crystals for X-ray diffraction were obtained by slow diffusion of hexane into a concentrated DCM solution of the catalyst. A representation of the X-ray structure of [(SIPr)CuCl] is shown in Fig. 1.‡ Bond distances and angles in this complex are similar to known copper(I)–N-heterocyclic carbene complexes.[13] The backbone single bond length is 1.51(2) Å, compared with the double bond length of 1.37(2) Å in the corresponding [(IPr)CuCl].[13]

$$\text{SIPr·HCl} + \text{CuCl} \xrightarrow[\text{Toluene}]{\text{KOMe}} [(\text{SIPr})\text{CuCl}] \quad 80\%$$

Scheme 1 Synthesis of [(SIPr)CuCl].

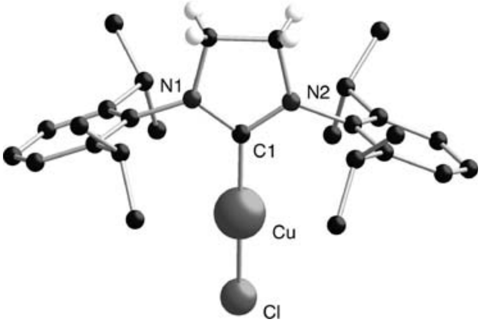

Fig. 1 Ball-and-stick drawing for [(SIPr)CuCl]. Selected bond lengths (Å): C(1)–Cu = 1.896(7), Cu–Cl = 2.114(2). Selected bond angle (deg): C(1)–Cu–Cl = 174.4(2). Most hydrogen atoms are omitted for clarity.

Reaction of benzyl azide and phenylacetylene under standard cycloaddition conditions led to 6% conversion (Table 1, entry 1). A number of 'Click-suitable' solvents were then tested. While high conversions were reached with THF or *i*-PrOH, water and DMF were less efficient solvents, and no conversion was detected after one week of stirring in acetone or DMSO.

At this point of our study, we had in hand a catalytic system that would not react under ambient conditions, even after prolonged reaction times. The next step would require activating such a system. First attempts in DMSO showed a conversion of 83% after heating at 60 °C for 8 h. Only 9% of **3a** was formed in acetone under these conditions (Scheme 2). Higher temperatures were not tested to avoid undesired thermal processes. It is well recognized that cycloaddition reactions can be greatly accelerated in water,[14] and accordingly, faster conversions were reached after the addition of water to the reaction mixture before starting heating (organic solvent/water = 1 : 1). As an added advantage, the use of water leads to the precipitation of the formed triazoles, facilitating the isolation step. It is important to note that both parameters, heating and addition of water, are essential for

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[a] *Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain. E-mail: sdiez@iciq.es; E-mail: snolan@iciq.es; Fax: (+34) 977-920-244; Tel: (+34) 977-920-224*
[b] *University of New Orleans, Department of Chemistry, New Orleans, LA 70148, USA*

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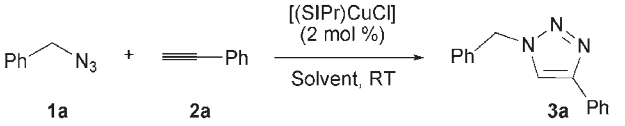
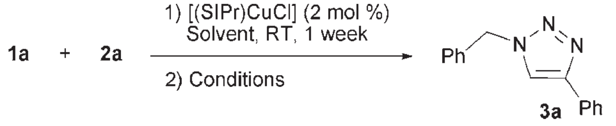
Table 1 Solvent screening



Entry	Solvent	Conversion (%)[a] After $t = 3$ days	Conversion (%)[a] After $t = 1$ week
1	Water/*t*-BuOH (1 : 1)	6	6
2	THF	46	96
3	*i*-PrOH	42	63
4	Water	21	26
5	DMF	6	16
6	Acetone	0	0
7	DMSO	0	0

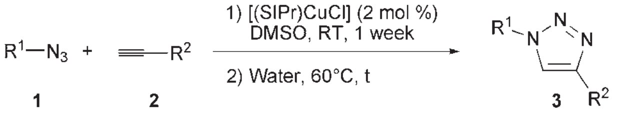
[a] ^{1}H NMR conversion.

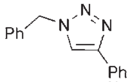
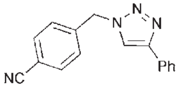
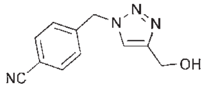
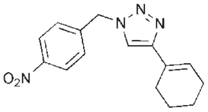
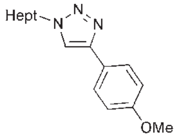
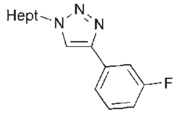
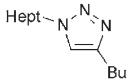
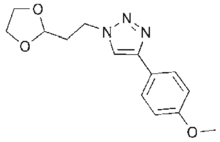
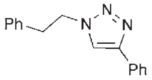
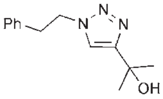
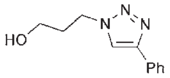
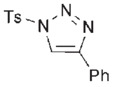


	Acetone	DMSO
2) 60°C, t = 8 h	9%	83%
2) Water, 60°C, t = 1 h	20%	99%
2) 60°C, t = 1 h	–	21%
2) Water, RT, t = 1 h	–	›5%

Scheme 2 Activation of the catalyst.

Table 2 Latent-[(SIPr)CuCl]-catalyzed formation of triazoles **3**[a]



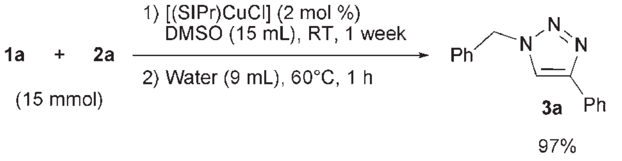
Entry	Triazole	3	Time/h	Yield (%)
1		**3a**	1	98
2		**3b**	2.5 0.5	90 93[b]
3		**3c**	16	78
4		**3d**	16 16	98 92[b]
5		**3e**	2 1	96 93[b]
6		**3f**	0.6 0.5	94 91[b]
7		**3g**	1 0.5	83 97[b]
8		**3h**	2	93
9		**3i**	1.5 1.5	93 96[b]
10		**3j**	3 2	97 92[b]
11		**3k**	16	83[c]
12		**3l**	18	20[d]

[a] Isolated yields are the average of two runs. [b] Reaction carried out in a DMSO/water mixture at 60 °C without a latent period. [c] 10% of the starting azide was also recovered. [d] Reaction in MeCN, ^{1}H NMR conversion.

obtaining optimized results. As shown in Scheme 2, only 21% of **3a** was formed in DMSO at 60 °C after 1 h, and no reaction was observed at room temperature 1 h after the water addition.[15] Moreover, during the latency period in DMSO as well as in the filtrate recovered at the end of the reactions, only the signals due to [(SIPr)CuCl] were observed by ^{1}H NMR. All these observations point towards a combination of classical aqueous and thermal activations of the catalyst towards the cycloaddition reaction.

Of note, similar results were obtained using 1 mol % of catalyst, although a longer reaction time of 2 h was required. A control experiment was also performed. When the model reaction was carried out under the optimized conditions in the absence of copper catalyst, 46% of **1a** remained unaltered after 24 h of heating, and the reaction did not reach completion even after seven days.[16] Furthermore, as expected, a mixture of 1,4- and 1,5-regioisomers was formed in a 60 : 40 ratio.

Next, we investigated the scope of this catalytic system The results are presented in Table 2.[17] Whereas no reaction was detected after at least 1 week of latency, most reactions proceeded smoothly after activation of the catalyst. Triazoles **3** were then isolated in high purity after extraction or filtration. In no case were precautions to exclude oxygen taken, and copper disproportionation with precipitation of copper metal was never observed. Alkynes with various electronic and steric properties can be used. However, highly activated alkynes, such as ethyl propiolate, had to be avoided since reactions took place even at room temperature (see ESI† for details). Differently functionalized benzylic or alkyl azides were used. Interestingly, tosyl azide moderately converted into the corresponding triazole (Table 2, entry 12). Sulfonyl azides have been reported to have an appealing reactivity in the presence of copper(I) acetylides, and depending on the reaction conditions,



Scheme 3 Large-scale synthesis of **3a**.

not only sulfonyl triazoles,[18] but also *N*-acylsulfonamides[19] or azetidimines[20] can be prepared. In our case, **3l** was the only product formed, but no further optimization for this specific example was carried out.

For the sake of comparison, some of the entries in Table 2 were also performed without passing through the latent period. Similar or slightly shorter reaction times were required in those cases, and comparable yields were reached. These results clearly illustrate the stability of the catalyst in solution.

All the preceding reactions were carried out on a 1 mmol scale and required 1 mL of each solvent. In view of the potential application of this catalytic system to large-scale synthesis, we took a closer look at the quantity of water required to efficiently activate the catalyst. A DMSO/water ratio of 1 : 0.6 was found optimal (see ESI† for details) in the reaction of benzyl azide and phenylacetylene, and it was successfully applied to a 15 mmol scale synthesis (Scheme 3), allowing for the isolation of 3.4 g of **3a**.

In conclusion, a robust and highly effective [(NHC)Cu^I]-based catalytic system for latent Huisgen cycloaddition reactions has been developed. While no reaction was observed under ambient conditions, triazoles were efficiently prepared by gentle heating upon addition of water. This novel approach to this reaction should open new and exciting applications, notably in material science, where for instance, a mixture of polymer precursors and the catalyst could be stored for a long time (or even be commercially available) under ambient conditions but transformed when desired upon heating.

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Notes and references

‡ Crystal structure data for [(SIPr)CuCl], details can be found in the Supporting information.

1 F. Sandа and T. Endo, *Macromol. Symp.*, 1996, **107**, 237–242; W. J. Muizebelt, *J. Coat. Technol.*, 1985, **57**, 43–49; S. P. Pappas and L. W. Hill, *J. Coat. Technol.*, 1981, **53**, 43–51.
2 For selected examples see: F. F. Wong, K.-L. Chen, C. M. Lin and M.-Y. Yeh, *J. Appl. Polym. Sci.*, 2007, **104**, 3292–3300; O. Coulembier, B. G. G. Lohmeijer, A. P. Dove, R. C. Pratt, L. Mespouille, D. A. Culkin, S. J. Benight, P. Dubois, R. M. Waymouth and J. L. Hedrick, *Macromolecules*, 2006, **39**, 5617–5628; O. Coulembier, A. P. Dove, R. C. Pratt, A. C. Sentman, D. A. Culkin, L. Mespouille, P. Dubois, R. M. Waymouth and J. L. Hedrick, *Angew. Chem., Int. Ed.*, 2005, **44**, 4964–4968; Y.-S. Chiu, Y.-L. Liu, W.-L. Wei and W.-Y. Chen, *J. Polym. Sci., Part A: Polym. Chem.*, 2003, **41**, 432–440; M. Kobayashi, F. Sanda and T. Endo, *Macromolecules*, 1999, **32**, 4751–4756; Y. Yagci and A. Önen, *J. Polym. Sci., Part A: Polym. Chem.*, 1994, **34**, 3621–3624.
3 J. V. Crivello, *J. Polym. Sci., Part A: Polym. Chem.*, 1999, **37**, 4241–4254 and references therein.
4 For selected examples, see: K. Kishi, T. Ishimaru, M. Ozono, I. Tomita and T. Endo, *J. Polym. Sci., Part A: Polym. Chem.*, 2000, **38**, 804–809; K. Kishi, T. Ishimaru, M. Ozono, I. Tomita and T. Endo, *J. Polym. Sci., Part A: Polym. Chem.*, 2000, **38**, 35–42; K. Kishi, T. Ishimaru and M. Ozono, *Macromolecules*, 1998, **31**, 9392–9394.
5 For selected examples, see: A. Ben-Asuly, E. Tzur, C. E. Diesendruck, M. Sigalov, I. Goldberg and G. Lemcoff, *Organometallics*, 2008, **27**, 811–813; A. Heijl, M. W. Day and R. H. Grubbs, *Organometallics*, 2006, **25**, 6149–6154; C. Slugovc, D. Burtscher, F. Stelzer and K. Mereiter, *Organometallics*, 2005, **24**, 2255–2258; L. Delaude, A. Demonceau and A. F. Noels, *Chem. Commun.*, 2001, 986–987.
6 R. Huisgen, *Pure Appl. Chem.*, 1989, **61**, 613–628; R. Huisgen, G. Szeimies and L. Moebius, *Chem. Ber.*, 1967, **100**, 2494–2507.
7 A. Padwa, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon, Oxford, 1991, vol. 4, pp. 1069–1109; R. Huisgen, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984, pp. 1–176.
8 C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057–3064; V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596–2599.
9 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021.
10 For reviews, see: J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, 526–539; A. Dondoni, *Chem.–Asian J.*, 2007, **2**, 700–708; J.-F. Lutz, *Angew. Chem., Int. Ed.*, 2007, **46**, 1018–1025. Special issue on Click chemistry: J.-F. Lutz, *QSAR Comb. Sci.*, 2007, **26**, 1110–1323.
11 S. Díez-González, A. Correa, L. Cavallo and S. P. Nolan, *Chem.–Eur. J.*, 2006, **12**, 7558–7564; J. Broggi, S. Díez-González, J. L. Petersen, S. Berteina-Raboin, S. P. Nolan and L. A. Agrofoglio, *Synthesis*, 2008, 141–148.
12 L. A. Goj, E. D. Blue, S. A. Delp, T. B. Gunnoe, T. R. Cundari, A. W. Pierpont, J. L. Petersen and P. D. Boyle, *Inorg. Chem.*, 2006, **45**, 9032–9045.
13 S. Díez-González, H. Kaur, F. K. Zinn, E. D. Stevens and S. P. Nolan, *J. Org. Chem.*, 2005, **70**, 4784–4796; N. P. Mankad, T. G. Gray, D. S. Laitar and J. P. Sadighi, *Organometallics*, 2004, **23**, 1191–1193; N. P. Mankad, D. S. Laitar and J. P. Sadighi, *Organometallics*, 2004, **23**, 3369–3371; H. Kaur, F. K. Zinn, E. D. Stevens and S. P. Nolan, *Organometallics*, 2004, **23**, 1157–1160; P. L. Arnold, A. C. Scarisbrick, A. J. Blake and C. Wilson, *Chem. Commun.*, 2001, 2340–2341. See also ref. 12.
14 For reviews, see: C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095–3166; R. Breslow, *Acc. Chem. Res.*, 2004, **37**, 471–478; F. Fringuelli, O. Piermatti, F. Pizzo and L. Vaccaro, *Eur. J. Org. Chem.*, 2001, 439–455.
15 When the reaction mixture was heated for 5 min after the addition of water and stirred at room temperature for 1 h, a similar conversion was obtained.
16 GC results after 7 days of reaction: **1a** (9%), **3a** (66%), 1,5-regioisomer of **3a** (25%).
17 General procedure for the latent [3 + 2] cycloaddition of azides and terminal alkynes: In a vial fitted with a screw cap, azide **1** (1.0 mmol), alkyne **2** (1.0 mmol), [(SIPr)CuCl] (10 mg, 2 mol%) and technical grade DMSO (1 mL) were loaded. The solution was stirred at room temperature for at least one week and controlled by GC to ensure the absence of reaction. Then, water (1 mL) was added and the reaction mixture was heated at 60 °C. After total consumption of the starting azide or no further conversion, the corresponding triazole was collected by filtration and washed with water and pentane. Alternatively, **3** could be also recovered after extraction with EtOAc. In all examples, the crude products were estimated to be greater than 95% pure by ^{1}H NMR.
18 E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless and S. Chang, *Angew. Chem., Int. Ed.*, 2007, **46**, 1730–1733.
19 S. H. Cho and S. Chang, *Angew. Chem., Int. Ed.*, 2007, **46**, 1897–1900; M. P. Cassidy, J. Raushel and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2006, **45**, 3154–3157.
20 M. Whiting and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2006, **45**, 3157–3161.