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

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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 under certain external stimulus such as heating or photoirradiation.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; hydrosilylation⁴ and metathesis⁵ 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-triazoles⁶ is the most popular Huisgen 1,3-dipolar cycloaddition.⁷ The recent discovery of copper(I) as efficient and regiospecific catalyst for this process⁸ has rendered it the best Click reaction⁹ to date. Since mild and neutral condition 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 catalyst 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)imidazolin-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).[‡] 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

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.

is 1.51(2) Å, compared with the double bond length of 1.37(2) Å in the corresponding [(IPr)CuCl].¹³

Reaction of benzyl azide and phenylacetylene under standard

Table 1 Solvent Screening

1a + 2a		[(SIPr)CuCl] (2 mol %) Solvent, RT	
entry	solvent	conv (t = 3 days) ^a	conv (t = 1 week) ^a
1	water/ <i>t</i> -BuOH (1:1)	6%	6%
2	THF	46%	96%
3	<i>i</i> -PrOH	42%	63%
4	water	21%	26%
5	DMF	6%	16%
6	acetone	0%	0%
7	DMSO	0%	0%

^a ¹H NMR Conversion

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

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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

	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

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 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 Additionally, 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 ¹H 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 blank 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 untouched after 24 h of heating. Furthermore, as expected, a mixture of regioisomers was formed in a 60/40 ratio of 1,4 to 1,5 product. Finally, the reaction did not reach completion even after seven days.¹⁶

Next, we investigated the scope of this catalytic system. 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 metal copper was never observed. Alkynes with various electronic and steric properties could be used. However, highly activated alkynes, such as ethyl propiolate, had to be avoided since reactions took place even at room temperature.¹⁸ Benzylic or alkyl azides differently functionalized 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, not only sulfonyl triazoles,¹⁹ but also *N*-acylsulfonamides,²⁰ or azetidines²¹ can be prepared. In our case, **3l** was the only product

Table 2 Latent-[(SIPr)CuCl]-Catalyzed Formation of Triazoles **3**^a

$\text{R}^1\text{--N}_3 + \text{---R}^2 \xrightarrow[2) \text{ Water, 60}^\circ\text{C, t}]{1) [(SIPr)CuCl] (2 \text{ mol } \%), \text{ DMSO, RT, 1 week}} \text{R}^1\text{--N--N--N--R}^2$				
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 mixture DMSO/water at 60°C without latent period. ^c 10% of the starting azide was also recovered. ^d Reaction in MeCN, ¹H NMR conversion.

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 reached comparable yields. These results clearly illustrate the stability of the catalyst in solution.

All the precedent reactions were carried out on a 1-mmol-scale and required 1 mL of each solvent. In view of a plausible future 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 ratio DMSO : water = 1 : 0.6 was found optimal¹⁸ 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**.

Scheme 3 Large-Scale Synthesis 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

- † Synthesis of [(SIPr)CuCl]: In a vial, copper(I) chloride (0.171 g, 1.5 mmol), SIPr-HCl (0.586 g, 1.37 mmol) and potassium methoxide (0.132 g, 1.88 mmol) were loaded inside a glovebox and stirred in dry toluene (4 mL) overnight at room temperature outside the glovebox. After filtration of the reaction mixture through a plug of celite (DCM), the filtrate was mixed with pentane to form a precipitate. A second filtration afforded the title complex as a white solid (0.588 g, 80%). Spectroscopic data were in accordance with reported values, see ref 12.
- § Crystal structure data for [(SIPr)CuCl], C₂₇H₃₈ClCuN₂·2CH₂Cl₂, *M* = 659.44, monoclinic, *a* = 9.5227(11) Å, *b* = 16.4203(19) Å, *c* = 11.0548(13) Å, β = 103.810(2)°, *V* = 1678.6(3) Å³, *T* = 150(2) K, space group *P*2₁/m, *Z* = 2, absorption coefficient = 1.069 mm⁻¹. Intensities were measured to a maximum 2θ of 52°, but measurements above 2θ = 45° were not significantly above background due to solvent disorder. Of 13663 reflections collected in the 2θ range 2.4°–45°, 2289 were unique reflections (*R*_{int} = 0.0506) and were used in all calculations. Two solvent molecules were observed to both be disordered about the crystallographic mirror plane, and were refined with geometrical constraints and 50% occupancy. An attempt to refine the structure in space group *P*2₁ also yielded disordered solvent molecules and did not significantly improve the refinement. Hydrogen atom positions were from a constrained refinement using a riding model. The final agreement factors were wR2(all data) = 0.0801, R1(all data) = 0.0379, R1(observed data) = 0.0321. CCDC 649761. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x.

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- 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 ¹H NMR.

See the Electronic Supplementary Information for details.

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