Click Chemistry

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A Mechanochemically Triggered "Click" Catalyst

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Abstract: *"Click" chemistry represents one of the most powerful approaches for linking molecules in chemistry and materials science. Triggering this reaction by mechanical force would enable site- and stress-specific "click" reactions—a hitherto unreported observation. We introduce the design and realization of a homogeneous Cu catalyst able to activate through mechanical force when attached to suitable polymer chains, acting as a lever to transmit the force to the central catalytic system. Activation of the subsequent copper-catalyzed "click" reaction (CuAAC) is achieved either by ultrasonication or mechanical pressing of a polymeric material, using a fluorogenic dye to detect the activation of the catalyst. Based on an N-heterocyclic copper(I) carbene with attached polymeric chains of different flexibility, the force is transmitted to the central catalyst, thereby activating a CuAAC in solution and in the solid state.*

With the discovery of the copper-catalyzed "click" chemistry (CuAAC) by the research groups of Meldal[1] and Sharpless,[2] the efficiency and quality of this reaction has been truly probed and proven in many areas of chemistry.[3] Not only the fields of polymer,[4] biological sciences,[5] and drug discovery[6] have profited, but materials and surface science have also taken significant advantage from the overall valuable properties of this reaction. Thus, for example, cross-linking reactions (such as network formation),[7] surface-modification methods (such as self-assembled monolayers[8] or polymeric surfaces),[9] or the generation of self-healing materials[10] have been enabled as a consequence of its high substrate tolerance as well as its solvent insensitivity usually under low temperatures. Besides the known large number of homogeneous and heterogeneous Cu^I-based catalysts, especially latent catalytic "click" systems have been designed, for example, those which can be triggered by a specific stimulus. Thus, a site-specific activation of the "click" reaction by triggers such as light,[11] pressure,[8a,12] or a simple heterogeneous ball-milling procedure[13] have been achieved. However, a homogeneous mechanochemical "click" system has not yet been developed to the best of our knowledge (Figure 1).

The design of our mechanochemical "click" catalyst starts with two principal considerations based on considerations generally accepted in the mechanochemical world:[14] first

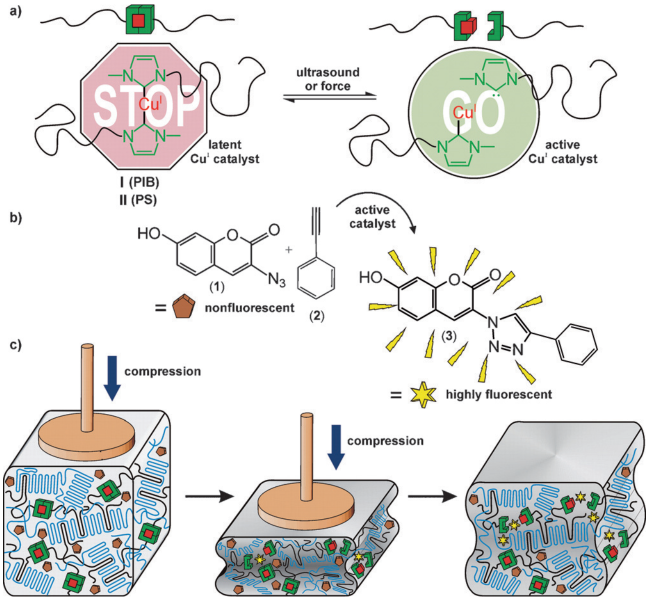

Figure 1. a) Mechanochemical activation of latent copper(I) N-heterocyclic carbene (NHC) catalysts (**I**, **II**) by ultrasound or compression. b) Fluorogenic "click" reaction of nonfluorescent coumarin dye **1** with **2** catalyzed by the activated mechanocatalysts **I** or **II**, which result in the formation of the highly fluorescent dye **3**. c) Mechanochemical activation of the latent polymeric NHC-copper(I) catalysts (**I**, **II**) within the crystalline poly(tetrahydrofuran) (PTHF) matrix by compression.

a Cu^I-based catalytic system is needed, which is not active under ambient conditions, but can solely be activated by mechanical force. Second, a catalytic system able to transmit mechanical force to the mechanochemical labile bond through affixed polymer chains is required. To fulfill both criteria, we designed an N-heterocyclic carbene (NHC) complex[15] bearing attached polymer chains on the NHC ligands. This system is projected to be not catalytically active for the "click" reaction at room temperature.[16] Thus, the catalytic systems **I** and **II** were designed, where the "click" activity was known to be poor or absent[16,17] in the bis(NHC)-Cu^I complexes, but present in the corresponding mono-(NHC)-Cu^IX complexes. Attaching polymer chains of different flexibility which are able to act as a lever to transmit the mechanical force onto the central Cu^I complex leads to the initial formation of biscarbene $[Cu(polymer\text{-}NHC)_2]X$ complexes **I** and **II** (Figure 2). The selected polymers are poly(isobutylene) (PIB), which displays a low glass-transition temperature (T_g ca. −80 °C) and is highly flexible at RT, and the rigid poly(styrene) (PS; T_g ca. 100 °C). The subsequently mechanically activated catalysis is detected through a fluorogenic "click" reaction of 3-azido-7-hydroxycoumarin (**1**) with phenylacetylene (**2**) that is able to detect traces of a fluorescently active dye generated by the "click" reaction.

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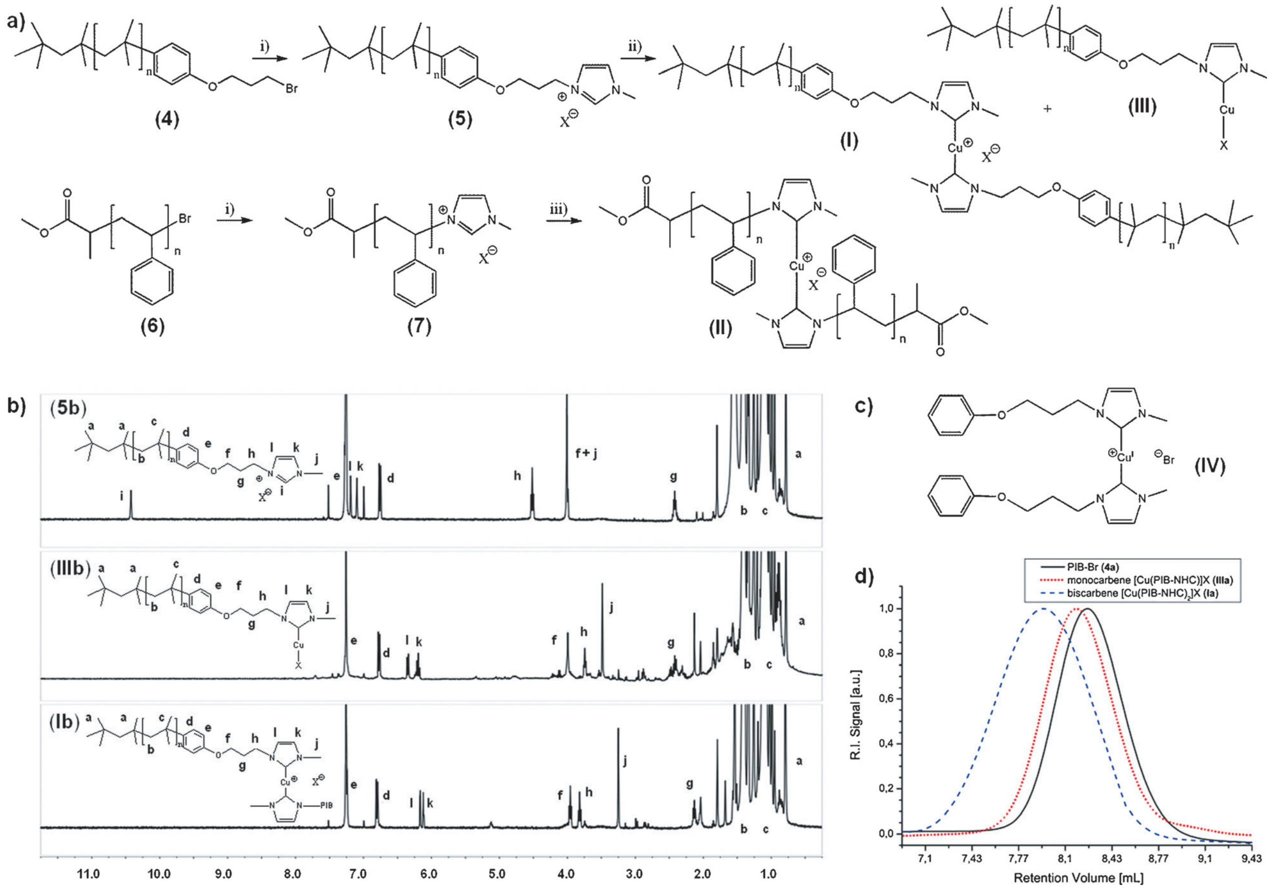


Figure 2. a) Synthetic route to the biscarbene complexes [Cu(PIB-NHC$_2$)]X (**I**) and [Cu(PS-NHC$_2$)]X (**II**), and the monocarbene complex [Cu(PIB-NHC)]X (**III**) (X = Br$^-$; I$^-$; PF$_6$$^-$). i) *N*-methylimidazolium telechelic polymers **5** and **7** generated by a quaternization reaction using NaI/15-crown-5-ether and *N*-methylimidazole. Transformation to the bis- (**I**, **II**) and monocarbene (**III**) complexes for PIB by ii) reaction of **5** with KHMDS (**11**) and [Cu(CH$_3$CN)$_4$]PF$_6$ (**10**); for PS by iii) reaction of **7** with NaO*t*Bu (**12**) and **10** (for synthetic details see the Supporting Information). b) ^{1}H NMR spectra of *N*-methylimidazolium-telechelic PIB (**5b**) and the corresponding mono- and biscarbene copper(I) complexes (**Ib**, **IIIb**). c) Structure of model complex [Cu(NHC)$_2$]X (**IV**). d) GPC traces for PIB-Br (**4a**, $M_{n(GPC)} = 2200$ g mol^{-1}), **IIIa** ($M_{n(GPC)} = 2900$ g mol^{-1}), and **Ia** ($M_{n(GPC)} = 4750$ g mol^{-1}) indicating the doubling of the molecular weight.

As known for various mechanochemically triggered systems (e.g. mechanochemically triggered Ru-NHC complexes[18] or cyclobutane-1,3-diones)[19] the positioning of the “weak link” in the middle of the polymer chains leads to significantly better transmittance of force—therefore, our mechanochemical Cu^{I}-NHC complex is placed within two polymer chains of equal chain length, thereby allowing either the chain length of the polymers (from $M_n = 4750$ g mol^{-1} to 17200 g mol^{-1}) or its rigidity (PIB versus PS) to be tuned.

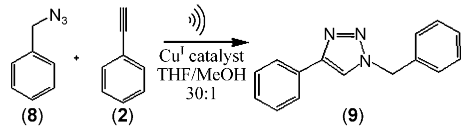
The synthesis of the catalysts **I** and **II** (Figure 2a) starts either from the appropriately bromo-telechelic PIB (**4**), prepared by living carbocationic polymerization (LCCP)[20] or from the bromo-telechelic PS (**6**) synthesized by atom-transfer radical polymerization (ATRP).[21] In both cases, the *N*-methylimidazolium-functionalized polymers (**5** and **7**) were synthesized by in situ transformation through nucleophilic substitution to the iodo-telechelic moieties using sodium iodide/15-crown-5-ether. Quaternization reactions with *N*-methylimidazole results in the formation of the *N*-methylimidazolium telechelic polymers (**5**, **7**), which are now able to act as macroligands for catalysts **I** and **II**. The ^{1}H NMR spectra as well as MALDI-TOF-MS spectra prove the attachment of the *N*-methylimidazolium moiety (for synthetic details as well as analytical data see the Supporting Information). The final bis(*N*-methylimidazol-2-ylidene-telechelic polymer) complexes [Cu(polymer-NHC)$_2$]X **I** and **II** were obtained by reaction of **5** with tetrakis(acetonitrile)copper(I) hexafluorophosphate ([Cu(CH$_3$CN)$_4$]PF$_6$; **10**) in the presence of potassium hexamethyldisilazide (KHMDS; **11**), or of **7** with **10** and NaO*t*Bu (**12**; see the Supporting Information). Additionally, the pure PIB monocarbene ([Cu(PIB-NHC)]X complex (**III**) was obtained cleanly by column chromatography (see the Supporting Information) as a mechanochemical system with only one polymer handle attached to the copper complex.

Structural proof of the synthesized complexes **I**, **II**, and **III** was accomplished by ^{1}H NMR spectroscopy as well as MALDI-TOF-MS analysis. Comparing the ^{1}H NMR spectra of the biscarbene [Cu(PIB-NHC)$_2$]X (**I**) as well as the monocarbene [Cu(PIB-NHC)]X complex (**III**) to that of the initial *N*-methylimidazolium-telechelic PIB (**5**) clearly shows the disappearance of the imidazolium proton H$_i$ at $\delta =$

10.42 ppm and the shift of the signals corresponding to the CH groups of the respective NHC moieties (see Figure 2 b). MALDI-TOF mass spectra of the mechanocatalyst **I** also proves the prospected structure, fitting well with its calculated isotope patterns (e.g. **Ia**, $C_{130}H_{242}Cu_1N_4O_2$, $[M]^+$: simulated 1956.829 g mol^{-1}, found: 1956.846 g mol^{-1}; for detailed information see the Supporting Information). Moreover, the increase in the molecular weight upon formation of the biscarbene [Cu(PIB-NHC)$_2$]X (**I**) complex was proven by comparing the molecular weights by gel-permeation chromatography (GPC; see Figure 2 d as well as the Supporting Information). A doubling of the molecular weight in the case of the biscarbene complex **Ia** (4750 g mol^{-1}) compared to the starting polymer **4 a** (2200 g mol^{-1}) and to the monocarbene complex **IIIa** (2900 g mol^{-1}) clearly indicated the desired chemical structures (see Table S1 in the Supporting Information). Similar observations were made for the [Cu(PS-NHC)$_2$]X (**II**) complex, thereby proving the final biscarbene complex structure (see the Supporting Information).

The reactivity of the catalysts towards "click" reactions was probed first in solution (see Table 1) by using a conventional "click" reaction of phenylaceylene (**2**) and benzylazide (**8**), monitored by ^{1}H NMR spectroscopy. The native catalysts **I** and **II** are inactive at room temperature (see Table 1 entries 2 and 8), irrespective of the molecular weight of the attached polymer chain, thereby proving that the initial biscarbene [Cu(polymer-NHC)$_2$]X complexes **I** and **II** are inactive in their "latent" state. Even heating the catalysts **Ia** or **II** to a temperature of 60 °C (see Table 1, entries 3 and 9) induces only a poor activity (less than 3 % conversion as determined by ^{1}H NMR spectroscopy). However, triggering the reaction by ultrasound, which is a generally accepted tool for applying mechanochemical force in solution,[18,22] leads to a significant catalytic activity (Table 1, entries 5—7, and 10. In accordance with different mechanochemical systems,[18] an increase in the chain length of the attached polymers, acting as a mechanical handle, from M_n (GPC) = 4750 g mol^{-1} (**Ia**) to 17 200 g mol^{-1} (**Ic**)) leads to an increase in the catalytic activity from 10 to 27 % in the conversion of the "click" reaction, congruent to an increased mechanical activation through the applied ultrasound. Moreover, a model [Cu(NHC)$_2$]X catalyst (**IV**; see Figure 2 c) without attached polymer chains shows only a poor catalytic activity for the "click" reaction after 24 h at room temperature (Table 1 entry 11). As a consequence of the expected higher rigidity of the poly(styrene)-based catalyst **II**, its catalytic activity after activation by ultrasound is 44 % (Table 1 entry 10) and thus higher than those of catalyst **Ic**, which contains PIB with an even higher molecular weight (Table 1 entry 7). Furthermore, the PIB-based monocarbene complex (**IIIa**) is active, even without applied ultrasound, as no shielding second ligand blocks the catalytic active site of the copper center.

Table 1: Ultrasound triggered "click" reaction of phenylacetylene (**2**) and benzylazide (**8**) using mechanocatalysts [Cu(PIB-NHC)$_2$]X (**I**) or [Cu(PS-NHC)$_2$]X (**II**) in solution.[a]



(**8**) (**2**) (**9**)

	Ultra-sound[b]	T	t [h]	Cu^I catalyst	M_n (GPC)[c] [g mol^{-1}]	Conversion[d] [%]
1	on	RT	72	without	–	0
2	off	RT	168	**Ia**	4750	0
3	off	60 °C	72	**Ia**	4750	< 2
4	off	RT	24	**IIIa**[e]	2900	11
5	on	RT	24	**Ia**	4750	10
6	on	RT	24	**Ib**	8900	17
7	on	RT	24	**Ic**	17 200	27
8	off	RT	144	**II**	13 100	0
9	off	60 °C	72	**II**	13 100	< 3
10	on	RT	24	**II**	13 100	44
11	off	RT	24	**IV**	–	0

[a] For all reactions 1 equiv azide **8**, 1 equiv alkyne **2**, and 0.01 equiv of the Cu^I catalyst (0.75 mM; **I**, **II**, **III**) were used in 30:1 THF/MeOH. All experiments were repeated at least twice and display the same results with maximum deviation of ± 1 %. [b] 90 min pulsing at 20 kHz with 30 % of maximal amplitude of 125 μm with a pulse sequence of 5 s pulse, 10 s break, 60 min without pulsing, repeated three times. [c] For **I** and **III** a PIB standard and for **II** a PS standard were used. [d] In [D$_8$]THF, detected through the increasing triazole resonance at $\delta = 8.12$ ppm as well as the shift of the CH$_2$ resonance from $\delta = 4.34$ to 5.58 ppm. [e] 1.1 equiv Na/ascorbate were additionally used for reaction of **IIIa**.

Finally, and most importantly, the mechanochemical activation was probed within a real solid polymer matrix, devoid of any solvent. As it is known that an optimal transmittance of mechanochemical force is achieved when the structural polymer contains crystalline regions, high-molecular-weight poly(tetrahydrofurane) (PTHF)[23] (M_n(GPC) = 112 000 g mol^{-1}; crystallinity 68 %) was chosen as the structural polymer, into which the mechanocatalyst **I** was embedded to check the pressure-induced activation. Critical for the detection of the so-generated, mechanically induced catalytic activity is a reliable detection system for monitoring the progress of the "click" reaction directly within a solid polymer matrix. Based on previous knowledge of the fluorogenic "click" reaction,[24] the fluorogenic 7-hydroxy-3-(4-phenyl-1*H*-[1,2,3]triazole-1-yl)-coumarin dye (**3**)[25] ($\lambda_{em} = 427$ nm, $\lambda_{ex} = 260$ nm as well as 360 nm) was used to probe and quantify the catalyst activity in the solid state.

The biscarbene [Cu(PIB-NHC)$_2$]X complex **Ic** (concentration 5.17×10^{-6} mmol$_{Cu}$ mg$_{sample}$$^{-1}$) was embedded into the PTHF matrix (65 % crystallinity after embedding; determined by DSC), together with the two reactive components phenylacetylene (**2**) and the initial nonfluorescent 3-azido-7-hydroxycoumarin dye (**1**; 1.56×10^{-4} mmol$_{dye}$ mg$_{sample}$$^{-1}$). Application of 10 tons pressure by a hydraulic press (3 × 30 min) causes a clear induction of the catalytic activity as detected by the increased fluorescence at 427 nm ($\lambda_{ex} = 360$ nm) of the transformed fluorogenic dye **3**, thus proving the mechanochemical activation of the latent copper catalyst by compression (see Figure 3 b, B and C). The measured fluorescence after compression corresponds to a dye concentration of about 6.66×10^{-6} mmol$_{dye}$ mg$_{sample}$$^{-1}$ and correlates to a conversion of approximately (4.3 ± 1) % of the "click" reaction (see the Supporting Information), thereby proving that no significant fluorescence is observed before compression (Figure 3 a). Control experiments were conducted to exclude the

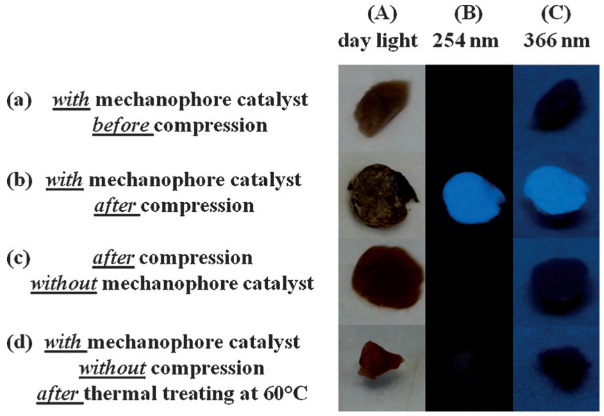


Figure 3. Mechanochemical activation of latent mechanocatalysts within the bulk material. a,b) Images of embedded nonfluorescent coumarin dye **1** and **2** within a high-molecular-weight PTHF matrix ($c = 1.56\times10^{-4}$ $\text{mmol}_{\text{dye}}\,\text{mg}_{\text{sample}}^{-1}$) together with latent mechanocatalyst **Ic** [Cu(PIB-NHC)$_2$]X ($M_{n(\text{GPC})} = 17\,200$ g mol^{-1}, 5.17×10^{-6} $\text{mmol}_{\text{cat}}\,\text{mg}_{\text{sample}}^{-1}$). Sample (a) reveals no fluorescence before compression, but shows strongly increased fluorescence (b) after compression with 10 tons by a press, thus indicating the activation of the latent mechanocatalyst which triggers the fluorogenic "click" reaction. c,d) Double-blind experiments: c) pressing of **1** and **2** within the PTHF matrix without mechanocatalysts, with no fluorescence and thus no "click" reaction; d) thermally treated sample of **1** and **2** within the PTHF matrix and with mechanocatalyst at 60 °C without compression also showing no fluorescence.

influence of the compression event itself (Figure 3 c) as well as a potential thermal impact on the fluorogenic "click" reaction (Figure 3 d). In the first control experiment, no mechanocatalyst was added to the mixture of **1** and **2** in the PTHF matrix, and the sample was subjected to a compression experiment (Figure 3 c). The second control experiment was conducted to exclude a potential thermal acceleration by compression of the "click" reaction of **1** with **2**. Thus, a mixture of **Ic**, **1**, and **2** with the high-molecular-weight PTHF was subjected to a thermal treatment of 60 °C for 72 h: in both cases no significant fluorescence could be observed, thus proving the mechanochemical activation of the latent copper(I) catalyst by compression into a solid polymer matrix.

In summary, for the first time we report on a mechanochemical "click" catalyst, based on biscarbene [Cu(polymer-NHC)$_2$]X complexes **I** and **II**, either in solution or embedded into a PTFH matrix. The biscarbene [Cu(polymer-NHC)$_2$]X complexes (**I**, **II**) display no catalytic activity towards a standard "click" system (consisting of benzylazide (**8**) and phenylacetylene (**2**)) until ultrasound activates the complex, which clearly indicates activity in solution, also depending on the molecular weight of the used polymers. Blending of complex **Ic** inside a PTHF matrix leads to pressure-sensitive activation of the catalysts, as quantified by a fluorogenic "click" reaction. The so-generated mechanochemical catalysts are highly attractive components for a spatially and mechanochemically triggered "click" reaction, with self-healing of stress-reporting materials as the closest application.

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