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Click Chemistry |*Hot Paper*|

Instantaneous Click Chemistry by a Copper-Containing Polymeric-Membrane-Installed Microflow Catalytic Reactor

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Abstract: The copper(I)-catalyzed Huisgen cycloaddition (azide–alkyne cycloaddition) is an important reaction in click chemistry that ideally proceeds instantaneously. An instantaneous Huisgen cycloaddition has been developed that uses a novel catalytic dinuclear copper complex-containing polymeric membrane-installed microflow device. A polymeric membranous copper catalyst was prepared from poly(4-vinylpyridine), copper(II) sulfate, sodium chloride, and sodium ascorbate at the interface of two laminar flows inside microchannels. Elucidation of the structure by XANES, EXAFS, and elemental analysis, as well as second-order Møller–Plesset perturbation theory (MP2) calculations and density functional theory (DFT) calculations assigned the local structure near Cu as a μ-chloro dinuclear Cu^{I} complex. The microflow device promotes the instantaneous click reaction of a variety of alkynes and organic azides to afford the corresponding triazoles in quantitative yield.

Introduction

Instantaneous production of organic materials is important for quick supply of lead compounds for pharmaceutical, biochemical, and material science as well as effective positron emission tomography (PET) for nuclear medical imaging.[1] The click reaction is one of the most promising means. The copper-catalyzed Huisgen 1,3-dipolar cycloaddition of organic azides and terminal alkynes (copper(I)-catalyzed azide–alkyne cycloaddition) is a typical click reaction for the preparation of bioactive compounds, pharmaceutical lead compounds, bio-probes, and functional soft materials, as well as for bioconjugation.[2] In particular, development of immobilized copper catalysts for this purpose with high catalytic activity and reusability without leaching of metal species is important.[3] In 2006, Lipshutz reported a pioneering work in heterogeneous click chemistry by using Cu/C.[4] Recently, some researchers have reported excellent heterogeneous Cu catalysts for this reaction with high turnover numbers (up to 1000).[5] Our group developed a highly active, insoluble, amphiphilic polymeric imidazole–Cu catalyst, which, with 4.5×10^{-4}–4.5×10^{-3} mol% Cu, catalyzed the Huisgen 1,3-dipolar cycloaddition of alkynes and organic azides.[6] Recently, Astruc and co-workers reported a dendrimer-encapsulated micellar Cu catalyst for the cycloaddition with a catalytic turnover number of 510 000.[7]

We envisioned that, by installing highly active heterogeneous catalysts inside a microchannel, the click reaction could be instantaneously accomplished. Accordingly, we attempted to develop a microflow reactor system in which an insoluble membranous catalyst was installed at the interface of two laminar flows by using our previously reported molecular convolution methodology.[8] Microflow reactor systems provide many fundamental and practical advantages and have been developed as novel devices for rapid organic transformations.[9] Microflow Huisgen cycloaddition using immobilized copper catalysts is a promising application for which the efficiency of various catalytic reactions has been found to increase due to the vast interfacial area and the short distance of the molecular diffusion path within the narrow space of the microflow reactor.[10] Herein, we report the development of the first polymeric membranous copper catalyst-installed microflow reactor, and its applicability to Huisgen cycloaddition of alkenes and organic azides. A variety of triazoles were quantitatively produced within a residence time of a few seconds by using the membranous copper catalyst-installed microflow reactor.

Results and Discussion

Four different polymeric membranous copper catalysts (**A**–**D**) were installed within microflow devices. The polymeric Cu membranes were formed with a glass microchannel reactor bearing a Y-junction and a channel pattern 100 μm wide, 40 μm deep, and 40 mm long (Figure 1). Poly(4-vinylpyridine) (PVPy, **1**) in ethyl acetate/methanol (3:1 v/v; 5.0 mM in pyridine; flow rate = 50 μL min^{-1}; from inlet A1), aqueous copper(II) sulfate solution (4.0 mM; flow rate = 25 μL min^{-1}; from inlet B1), and an aqueous solution of sodium ascorbate (NaAsc; 0.80 M)

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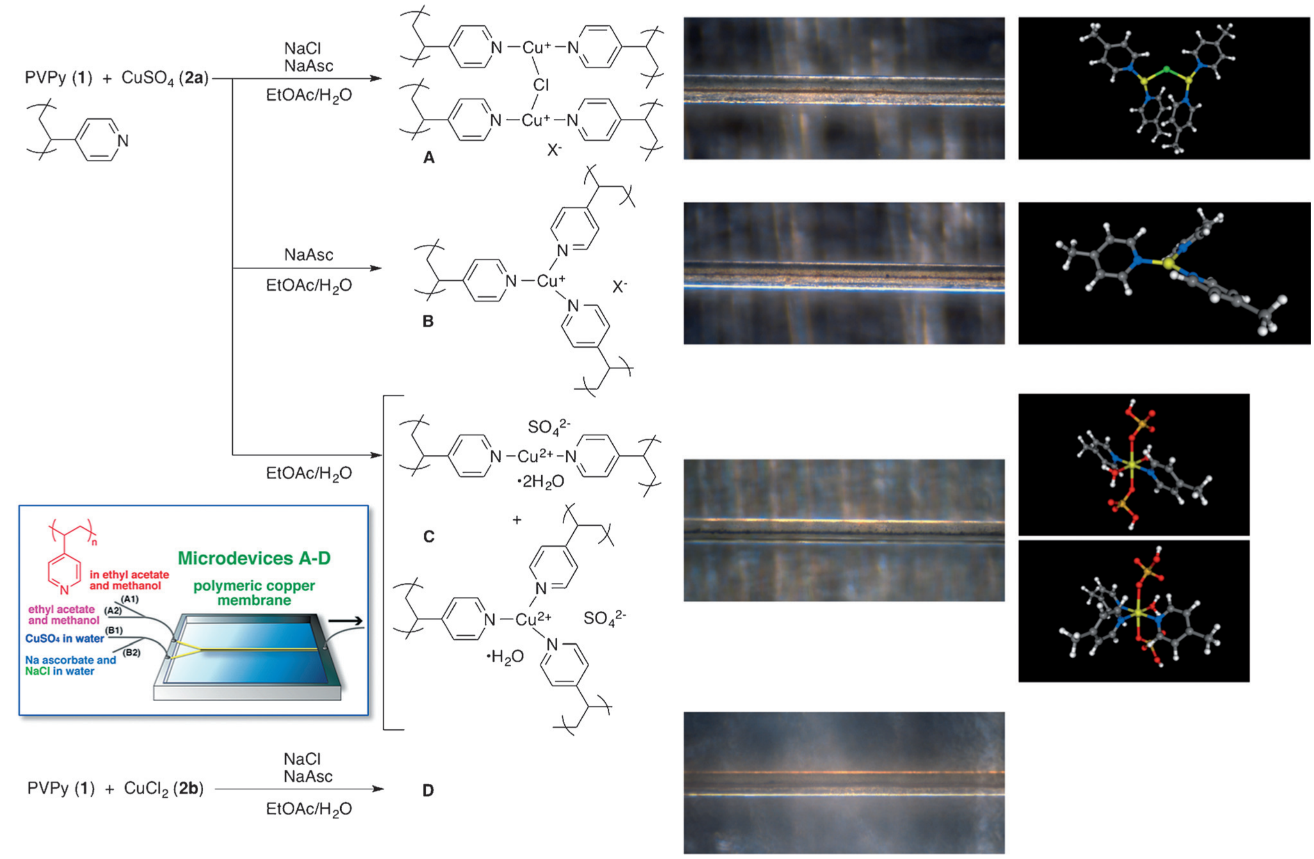


Figure 1. Preparation of copper-containing polymeric membrane-installed microdevices **A**-**D**.

and sodium chloride (20 mM; flow rate = 25 μL min^{-1}; from inlet B2) were installed in the microchannel at 25 °C for 60 s, and then 2% methanolic ethyl acetate (flow rate = 1 μL min^{-1}; from inlet A2) and an aqueous solution of NaAsc (0.80 M) and NaCl (20 mM) (flow rate = 1 μL min^{-1}; from inlet B2) were installed at 50 °C for 10 min. Instantaneously, a two-phase parallel laminar flow formed under the flowing conditions and a polymeric copper membrane **A** of approximately 10 μm thickness precipitated out at the interface of the laminar flows. Analysis by energy-dispersive X-ray spectroscopy (EDX) and scanning electron microscopy (SEM) showed that Cu and Cl species were dispersed uniformly throughout the membrane and S species were not detected (Figure 2). X-ray absorption near-edge structure (XANES) and extended X-ray absorption fine structure (EXAFS) spectroscopies and elemental analysis, as well as second-order Møller–Plesset perturbation theory (MP2) and density functional theory (DFT) calculations suggested that the local structure near the Cu complex is a μ-chloro dinuclear copper complex $[Cu^{I}_2(\mu\text{-}Cl)(py)_4]^+$ (py = pyridine unit in PVPy **1**; for details, see the Supporting Information, Figures S1–S8 and Table S1). When a catalytic Cu membrane was prepared without NaCl, a polymeric Cu membrane **B** readily formed, the local structure of which near the Cu^{I} complex is a mononuclear copper complex $[Cu^{I}(py)_3]^+$ (Figure 1). Similar complexation without NaCl and NaAsc afforded the membranous Cu^{II} complex **C**, for which the local structure near Cu was composed of a mixture of $[Cu^{II}(py)_2(OH_2)_2]^{2+}$ and $[Cu^{II}(py)_3(OH_2)]^{2+}$ (for the determination of these structures, see the Supporting Information, Figures S1–S8). The polymeric membrane **D** was also prepared from $CuCl_2$ **2b** (in place of $CuSO_4$ **2a**), PVPy **1**, NaCl and NaAsc.

With the copper-containing polymeric membrane-installed microflow devices **A**–**D** in hand, the Huisgen cycloaddition of an organic azide and an alkyne, that is, the click reaction, was conducted under microflow conditions inside these microflow devices (Scheme 1). When an acetone/water solution of benzyl azide (**3a**), phenylacetylene (**4a**), and NaAsc was injected from one inlet, and an acetone/water solution was installed from the other inlet at 50 °C, we were pleased to find that the reaction with the microflow device **A** smoothly proceeded in 8 s to give 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (**5a**) with 99% yield, and leaching of Cu species was found by inductively coupled plasma mass spectrometry (ICP-MS) to be less than 50 ppb. Microscopic snapshots of the microdevice **A** before and after use (0 h vs. 24 h) exhibited the stability of the catalytic membrane during the reaction (Figure 3). The reaction with the microdevice **B** under similar conditions gave **5a** with 86% yield, whereas that with the microdevices **C** and **D** afforded **5a** with 26% and 48% yield, respectively.

Since microdevice **A** provided the fastest transformation in the click reaction, the reaction of a variety of substituted benzylic azides **3** and alkynes **4** was carried out (Table 1). The cycloaddition of an electron-deficient 4-nitrobenzyl azide (**3b**) and **4a** proceeded smoothly to give the triazole **5b** in 99%

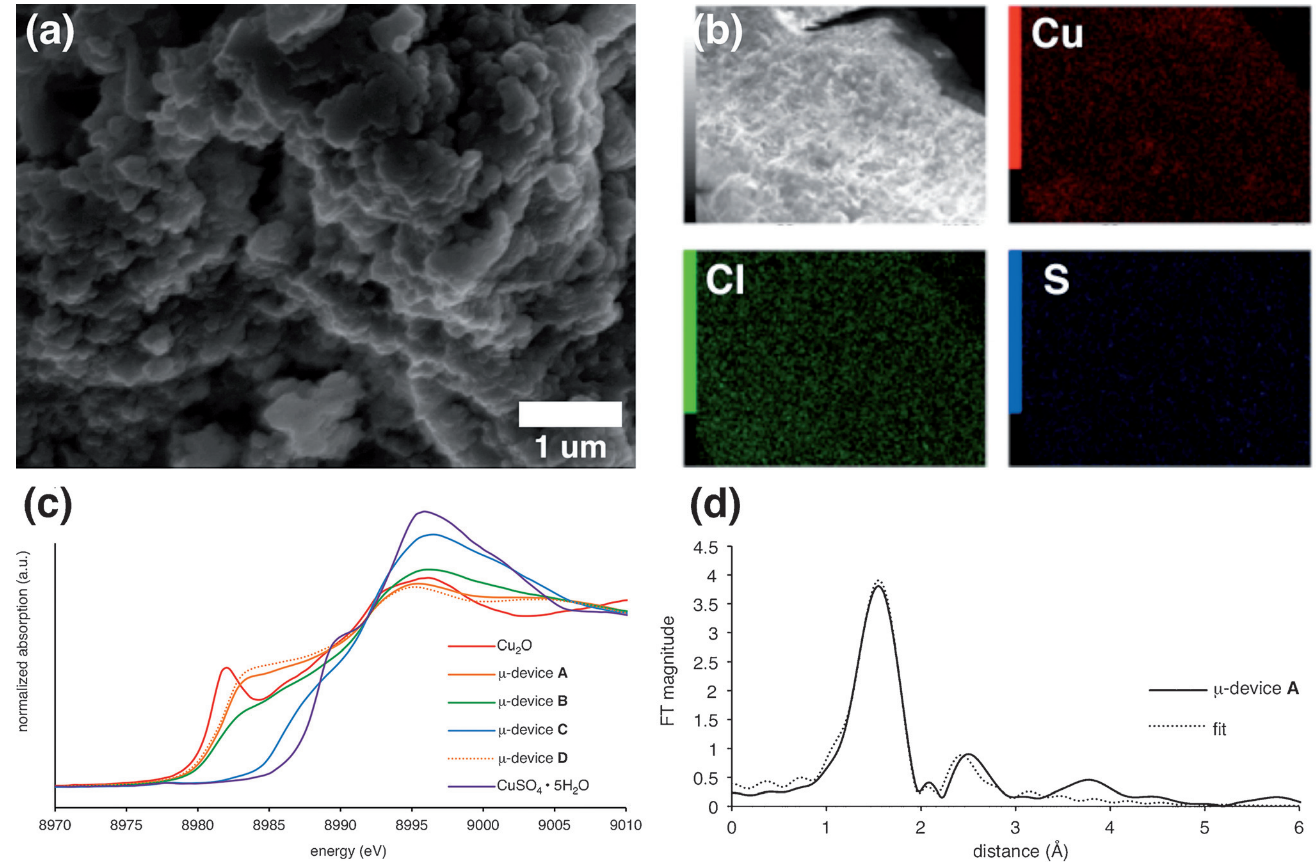
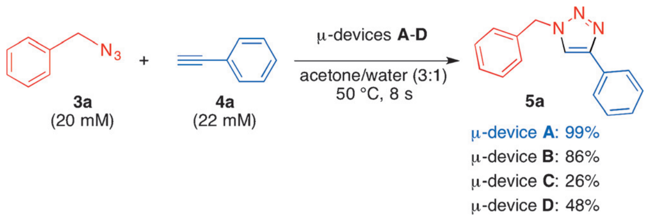


Figure 2. a) SEM image of **A**; b) EDX/SEM images of **A** (SEM, Cu, Cl and S); c) XANES spectra of **A**–**D**, Cu_2O, and $CuSO_4{\cdot}5\,H_2O$; d) k^3-weighted FT-EXAFS of microdevice **A** and the best fit



Scheme 1. Huisgen cycloaddition of **3a** and **4a** promoted by microdevices **A**–**D**.

yield in 13 s (entry 2). A fluoro compound, 4-fluorobenzyl azide (**3c**), was readily converted under similar conditions to afford the triazole **5c** in 99% yield in 13 s (entry 3). The more electron-rich 4-methylbenzyl azide (**3d**) and 4-methoxybenzyl azide (**3e**) led to efficient conversion, giving the corresponding triazoles **5d** and **5e** in 94% and 86% yield in 19 s (entries 4 and 5). The reaction of a naphthyl substrate, 2-naphthylmethyl azide (**3f**), for 13 s gave the triazole **5f** in 92% yield (entry 6). The reaction of **3a** with less reactive electron-rich alkynes, *p*-tolylacetylene (**4b**) and *p*-anisylacetylene (**4c**), was also performed, affording the corresponding triazoles **5g** and **5h** in 98% and 90% yield, respectively (entries 7 and 8). The microdevice was also applied to the cycloaddition of less reactive aliphatic azides and alkynes: the reaction of 1-azidodecane (**3g**) with **4a** in 2-propanol took 38 s, affording 1-decyl-4-phenyl-1*H*-1,2,3-triazole (**5i**) in 83% yield (entry 9). An aliphatic alkyne, 1-heptyne (**4d**), readily reacted with **3a** within 13 s, giving the triazole **5j** in 91% yield (entry 10). An alkynol, 5-hexyn-1-ol

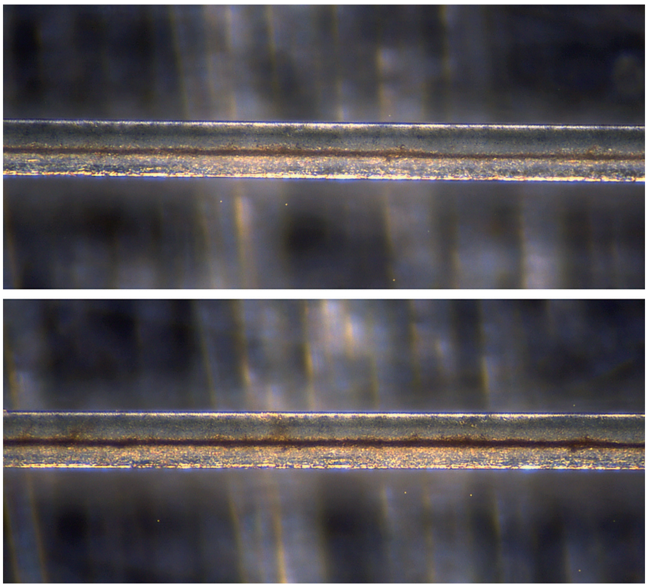
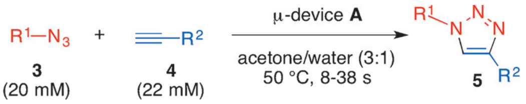


Figure 3. Snapshots of microdevice **A** in the reaction of **3a** with **4a** (top: 0 h, bottom: 24 h).

Table 1. Huisgen cycloaddition of organic azides **3** and alkynes **4** mediated by microdevice **A** to give triazoles **5**.[a]

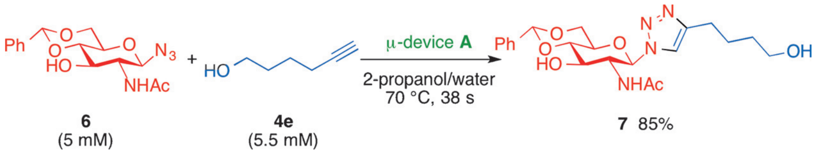


Entry	**3** (R^1)	**4** (R^2)	**5**	Yield [%]
1	**3a** ($PhCH_2$)	**4a** (Ph)	**5a**	99
2	**3b** ($4\text{-}NO_2C_6H_4CH_2$)	**4a**	**5b**	99
3	**3c** ($4\text{-}FC_6H_4CH_2$)	**4a**	**5c**	99
4	**3d** ($4\text{-}CH_3C_6H_4CH_2$)	**4a**	**5d**	94
5	**3e** ($4\text{-}OMeC_6H_4CH_2$)	**4a**	**5e**	86
6	**3f** ($2\text{-}C_{10}H_7CH_2$)	**4a**	**5f**	92
7	**3a**	**4b** ($4\text{-}CH_3C_6H_4$)	**5g**	98
8	**3a**	**4c** ($4\text{-}OMeC_6H_4$)	**5h**	90
9[b]	**3g** ($C_{10}H_{21}$)	**4a**	**5i**	83
10	**3a**	**4d** (C_5H_{11})	**5j**	91
11	**3a**	**4e** ($CH_2(OH)(CH_2)_3$)	**5k**	99
12[b]	**3g**	**4e**	**5l**	98

[a] Conditions: [Inlet A] organic azide **3** (20 mM), alkyne **4** (22 mM) and NaAsc (20 mM) in acetone/water (3:1 v/v); [Inlet B] acetone/water (1:1 v/v); flow rate = 0.1–0.5 μL min^{-1}, residence time = 8–38 s, 50 °C; [b] conditions: [Inlet A] organic azide **3** (10 mM), alkyne **4** (11 mM) and NaAsc (20 mM) in 2-propanol/water (3:1 v/v); [Inlet B] 2-propanol/water (1:1 v/v); flow rate = 0.1 μL min^{-1}, residence time = 38 s, 70 °C.

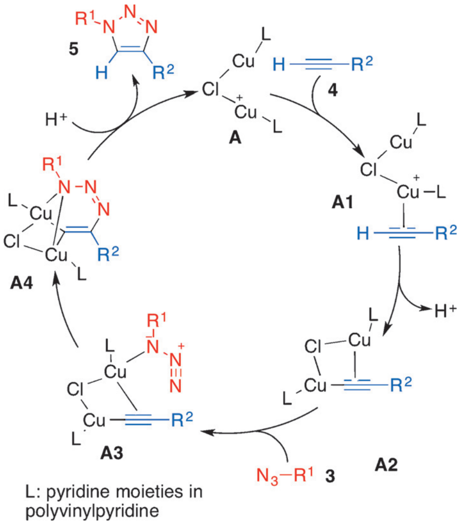
(**4e**), underwent cycloaddition with **3a** in 38 sec to afford **5k** in 99% yield (entry 11). The reaction of the aliphatic azide **3g** and the aliphatic alkyne **4e** afforded 4-(1-decyl-1*H*-1,2,3-triazol-4-yl)butan-1-ol (**5l**) in 98% yield (entry 12).

To apply the catalytic microdevice for the preparation of conjugated materials, the Huisgen cycloaddition of a sugar derivative was investigated (Scheme 2). When an *N*-acetyl-D-glucosamine (GlcNAc) derivative **6**, bearing amide and acetal moieties, was connected with the alkyne **4e** bearing a terminal alcohol, a plausible connector to a variety of proteins and sugars, by using the copper-containing polymeric membrane-installed microflow reactor **A** at 70 °C in 38 s, the desired triazole carbohydrate **7** was readily obtained in 85% yield.



Scheme 2. Conjugation of *N*-acetyl-D-glucosamine (GlcNAc) derivative and a linear alcohol.

As shown in Scheme 1, the microdevice **A**, incorporating a dinuclear Cu complex (Figure 1), afforded the triazole **5a** in a higher yield than the microdevices **B**–**D**. To rationalize the superiority of the dinuclear Cu catalyst-installed microdevice **A**, a proposed reaction mechanism is shown in Scheme 3, which is based on the report by Fokin and co-workers on a homogeneous dinuclear copper catalyzed azide–alkyne cycloaddition.[11] Thus, coordination of alkyne **4** to the dinuclear copper catalyst **A**, followed by deprotonation gives the copper acetylide **A2**. Coordination of organic azide **3** to **A2** followed by intramolecular cycloaddition affords dinuclear copper intermediate **A4**. Protonation of **A4** results in the formation of the triazole **5** and regeneration of the catalyst **A**. We are still not certain why catalytic microdevice **A** was the best for the instantaneous cycloaddition. However, it is worth noting that the addition of NaCl provided complex **A** as a μ-chloro dinuclear Cu species, whereas **B** and **C** were mononuclear Cu complexes (Figure 1). Based on Fokin's report,[11,12] **A** could act as a cooperative catalyst, in which a dinuclear Cu species activated both an organic azide **3** and an alkyne **4** synergistically, promoting the instantaneous click reaction (Scheme 3). Moreover, **D**, prepared from $CuCl_2$ (**2b**), **1**, NaAsc, and NaCl, gave the triazole **5a** in 48% yield. This result suggested that addition of NaCl to $CuSO_4$ (**2a**) was important for the formation of an active dinuclear copper complex membrane.



Scheme 3. Proposed reaction mechanism of the **A**-promoted Huisgen cycloaddition.

Conclusion

In conclusion, we have developed the first polymeric membranous copper catalyst-installed microflow device. The microdevice was applied to the Huisgen cycloaddition, affording the corresponding triazoles with quantitative yield within 8–38 s. Our microdevice system will be useful for bioconjugation, positron emission tomography for nuclear medical imaging, and high-throughput screening of pharmaceutical, biochemical, and material compounds.

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Keywords: click chemistry · copper · cycloaddition · microreactors · polymeric membranes

[1] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004 – 2021; *Angew. Chem.* **2001**, *113*, 2056 – 2075.

[2] a) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057 – 3064; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596 – 2599; *Angew. Chem.* **2002**, *114*, 2708 – 2711; c) R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565 – 598; *Angew. Chem.* **1963**, *75*, 604 – 637; d) V. D. Bock, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2006**, 51 – 68; e) J.-F. Lutz, *Angew. Chem. Int. Ed.* **2007**, *46*, 1018 – 1025; *Angew. Chem.* **2007**, *119*, 1036 – 1043; f) J. Xiao, T. J. Tolbert, *Org. Lett.* **2009**, *11*, 4144 – 4147; g) D. K. Mohapatra, P. K. Maity, M. Shabab, M. I. Khan, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5241 – 5245; h) D. Pearson, A. J. Downard, A. Muscroft-Taylor, A. D. Abell, *J. Am. Chem. Soc.* **2007**, *129*, 14862 – 14863; i) V. Aragão-Leoneti, V. L. Campo, A. S. Gomes, R. A. Field, I. Carvalho, *Tetrahedron* **2010**, *66*, 9475 – 9492; j) R. K. Iha, K. L. Wooley, A. M. Nyström, D. J. Burke, M. J. Kade, C. J. Hawker, *Chem. Rev.* **2009**, *109*, 5620 – 5686; k) Y. Xia, W. Li, F. Qu, Z. Fan, X. Liu, C. Berro, E. Rauzy, L. Peng, *Org. Biomol. Chem.* **2007**, *5*, 1695 – 1701; l) A. Brik, C. Y. Wu, C. H. Wong, *Org. Biomol. Chem.* **2006**, *4*, 1446 – 1457; m) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128 – 1137; n) S. M. Lee, H. Chen, T. V. O'Halloran, S. T. Nguyen, *J. Am. Chem. Soc.* **2009**, *131*, 9311 – 9320; o) A. Chernykh, T. Agag, H. Ishida, *Polymer* **2009**, *50*, 382 – 390; p) B. L. Li, Z. T. Liu, Y. M. He, J. Pan, Q. H. Fan, *Polymer* **2008**, *49*, 1527 – 1537; q) M. R. Whittaker, C. N. Urbani, M. J. Monteiro, *J. Am. Chem. Soc.* **2006**, *128*, 11360 – 11361; r) S. Sommer, N. D. Weikart, A. Brockmeyer, P. Janning, H. D. Mootz, *Angew. Chem. Int. Ed.* **2011**, *50*, 9888 – 9892; *Angew. Chem.* **2011**, *123*, 10062 – 10066; s) E. Lallana, R. Riguera, E. Fernandez-Megia, *Angew. Chem. Int. Ed.* **2011**, *50*, 8794 – 8804; *Angew. Chem.* **2011**, *123*, 8956 – 8966; t) G. Clavé, S. Campidelli, *Chem. Sci.* **2011**, *2*, 1887 – 1896; u) W. H. Binder, R. Sachsenhofer, *Macromol. Rapid Commun.* **2007**, *28*, 15 – 54.

[3] a) C. Girard, E. Önen, M. Aufort, S. Beauviére, E. Samson, J. Herscovici, *Org. Lett.* **2006**, *8*, 1689 – 1692; b) S. Chassaing, M. Kumarraja, A. S. S. Sido, P. Pale, J. Sommer, *Org. Lett.* **2007**, *9*, 883 – 886; c) I. S. Park, M. S. Kwon, Y. Kim, J. S. Lee, J. Park, *Org. Lett.* **2008**, *10*, 497 – 500; d) S. Chassaing, A. S. S. Sido, A. Alix, M. Kumarraja, P. Pale, J. Sommer, *Chem. Eur. J.* **2008**, *14*, 6713 – 6721; e) K. Namitharan, M. Kumarraja, K. Pitchumani, *Chem. Eur. J.* **2009**, *15*, 2755 – 2758; f) A. Coelho, P. Diz, O. Caamaño, E. Sotelo, *Adv. Synth. Catal.* **2010**, *352*, 1179 – 1192; g) M. Liu, O. Reiser, *Org. Lett.* **2011**, *13*, 1102 – 1105; h) Y. Wang, J. Liu, C. Xia, *Adv. Synth. Catal.* **2011**, *353*, 1534 – 1542; i) T. Osako, Y. Uozumi, *Org. Lett.* **2014**, *16*, 5866 – 5869; j) A. Shaygan Nia, S. Rana, D. Döhler, X. Noirfalise, A. Belfiore, W. H. Binder, *Chem. Commun.* **2014**, *50*, 15374 – 15377; k) H. Nulwala, K. Takizawa, A. Odukale, A. Khan, R. J. Thibault, B. R. Taft, B. H. Lipshutz, C. J. Hawker, *Macromolecules* **2009**, *42*, 6068 – 6074; l) U. Sirion, Y. J. Bae, B. S. Lee, D. Y. Chi, *Synlett* **2008**, 2326 – 2330; m) T. R. Chan, V. V. Fokin, *QSAR Comb. Sci.* **2007**, *26*, 1274 – 1279; n) T. Suzuka, K. Ooshiro, K. Kina, *Heterocycles* **2010**, *81*, 601 – 610; o) Y. Kitamura, K. Taniguchi, T. Maegawa, Y. Monguchi, Y. Kitade, H. Sajiki, *Heterocycles* **2009**, *77*, 521 – 532; p) L. Bonami, W. Van Camp, D. Van Rijckegem, F. E. Du Prez, *Macromol. Rapid Commun.* **2009**, *30*, 34 – 38; q) I. Luz, F. X. Llabrés i Xamena, A. Corma, *J. Catal.* **2010**, *276*, 134 – 140; r) L. Liang, J. Ruiz, D. Astruc, *Adv. Synth. Catal.* **2011**, *353*, 3434 – 3450; s) X. Xiong, H. Chen, Z. Tang, Y. Jiang, *RSC Adv.* **2014**, *4*, 9830 – 9837; t) B. Dervaux, F. E. Du Prez, *Chem. Sci.* **2012**, *3*, 959 – 966 (Minireview)and references cited therein.

[4] B. H. Lipshutz, B. R. Taft, *Angew. Chem. Int. Ed.* **2006**, *45*, 8235 – 8238; *Angew. Chem.* **2006**, *118*, 8415 – 8418.

[5] a) K. Yamaguchi, T. Oishi, T. Katayama, N. Mizuno, *Chem. Eur. J.* **2009**, *15*, 10464 – 10472; b) F. Alonso, Y. Moglie, G. Radivoy, M. Yus, *Adv. Synth. Catal.* **2010**, *352*, 3208 – 3214; c) A. Megia-Fernandez, M. Ortega-Muñoz, J. Lopez-Jaramillo, F. Hernandez-Mateo, F. Santoyo-Gonzalez, *Adv. Synth. Catal.* **2010**, *352*, 3306 – 3320; d) T. Jin, M. Yan, Menggenbateer, T. Minato, M. Bao, Y. Yamamoto, *Adv. Synth. Catal.* **2011**, *353*, 3095 – 3100.

[6] Y. M. A. Yamada, S. M. Sarkar, Y. Uozumi, *J. Am. Chem. Soc.* **2012**, *134*, 9285 – 9290.

[7] C. Deraedt, N. Pinaud, D. Astruc, *J. Am. Chem. Soc.* **2014**, *136*, 12092 – 12098.

[8] a) Y. Uozumi, Y. M. A. Yamada, T. Beppu, N. Fukuyama, M. Ueno, T. Kitamori, *J. Am. Chem. Soc.* **2006**, *128*, 15994 – 15995; b) Y. M. A. Yamada, T. Watanabe, K. Torii, Y. Uozumi, *Chem. Commun.* **2009**, 5594 – 5596; c) Y. M. A. Yamada, T. Watanabe, T. Beppu, N. Fukuyama, K. Torii, Y. Uozumi, *Chem. Eur. J.* **2010**, *16*, 11311 – 11319; d) Y. M. A. Yamada, T. Watanabe, A. Ohno, Y. Uozumi, *ChemSusChem* **2012**, *5*, 293 – 299; e) M. Minakawa, Y. M. A. Yamada, Y. Uozumi, *RSC Adv.* **2014**, *4*, 36864 – 36867.

[9] a) S. J. Haswell, R. J. Middleton, B. O'Sullivan, V. Skelton, P. Watts, P. Styring, *Chem. Commun.* **2001**, 391 – 398; b) P. D. I. Fletcher, S. J. Haswell, E. Pombo-Villar, B. H. Warrington, P. Watts, S. Y. F. Wong, X. Zhang, *Tetrahedron* **2002**, *58*, 4735 – 4757; c) H. Pennemann, V. Hessel, H. Löwe, *Chem. Eng. Sci.* **2004**, *59*, 4789 – 4794; d) K. Jähnisch, V. Hessel, H. Löwe, M. Baerns, *Angew. Chem. Int. Ed.* **2004**, *43*, 406 – 446; *Angew. Chem.* **2004**, *116*, 410 – 451; e) J. Kobayashi, Y. Mori, S. Kobayashi, *Chem. Asian J.* **2006**, *1 – 2*, 22 – 35; f) C. Wiles, P. Watts, *Eur. J. Org. Chem.* **2008**, 1655 – 1671; g) J.-I. Yoshida, A. Nagaki, T. Yamada, *Chem. Eur. J.* **2008**, *14*, 7450 – 7459; h) J.-I. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* **2011**, *4*, 331 – 340.

[10] a) A. R. Bogdan, N. W. Sach, *Adv. Synth. Catal.* **2009**, *351*, 849 – 854; b) L. Kupracz, J. Hartwig, J. Wegner, S. Ceylan, A. Kirschning, *Beilstein J. Org. Chem.* **2011**, *7*, 1441 – 1448; c) N. P. Tu, J. E. Hochlowski, S. W. Djuric, *Mol. Diversity* **2012**, *16*, 53 – 58; d) S. B. Ötvös, Á. Georgiádes, I. M. Mándity, L. Kiss, F. Fülöp, *Beilstein J. Org. Chem.* **2013**, *9*, 1508 – 1516; e) J. Bao, G. K. Tranmer, *Chem. Commun.* **2015**, *51*, 3037 – 3044; f) M. Fuchs, W. Goessler, C. Pilger, C. O. Kappe, *Adv. Synth. Catal.* **2010**, *352*, 323 – 328; g) I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem. Int. Ed.* **2009**, *48*, 4017 – 4021; *Angew. Chem.* **2009**, *121*, 4077 – 4081; h) R. P. Jumde, C. Evangelisti, A. Mandoli, N. Scotti, R. Psaro, *J. Catal.* **2015**, *324*, 25 – 31.

[11] B. T. Worrell, J. A. Malik, V. V. Fokin, *Science* **2013**, *340*, 457 – 460.

[12] Although Fokin's report is based on homogeneous Cu catalysis, this catalytic cycle could also fit our heterogeneous dinuclear Cu catalytic pathway.

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