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Synthetic Applications with Use of a Silica-Supported Alkyne Metathesis Catalyst

Hyeon Mo Cho, Haim Weissman, and Jeffrey S. Moore*

Roger Adams Laboratory, Departments of Chemistry and Materials Science & Engineering, University of Illinois at Urbana−Champaign, Urbana, Illinois 61801

jsmoore@uiuc.edu

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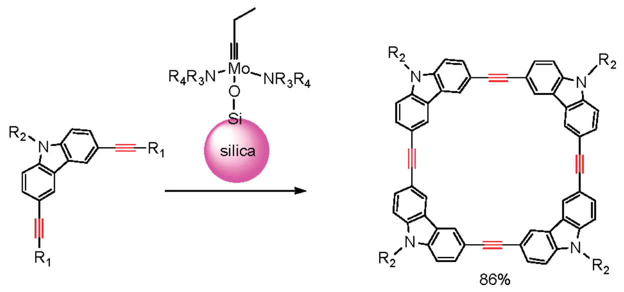
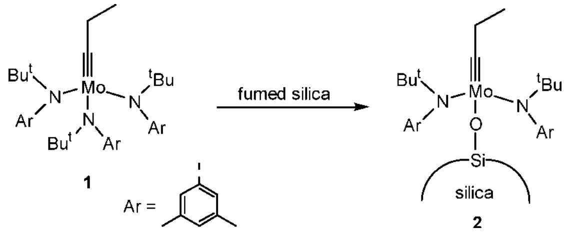
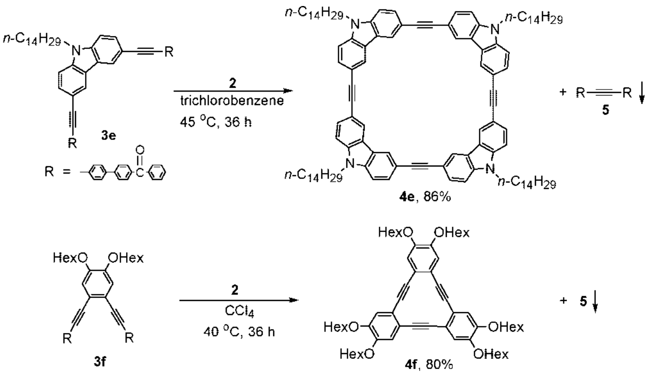


A highly active and durable fumed silica-supported heterogeneous molybdenum(VI) catalyst was applied to ring closing alkyne metathesis and cyclooligomerization reactions to give high yields of metathesis products near room temperature conditions.

We recently reported phenol-free, silica-supported molybdenum catalysts for alkyne metathesis that are active at ambient temperature and produce almost no unwanted alkyne polymerization products.[1] Here we describe the application of this system in RCAM (ring closing alkyne metathesis) and in the synthesis of shape-persistent macrocycles by cyclooligomerization. High yields of metathesis products are obtained with near room temperature conditions; product workup and isolation are streamlined by the absence of phenol ligands enabling catalyst removal by simple filtration.[2,3]

RCAM provides medium-ring macrocyclic products and its combination with a Lindlar reduction or hydrosilation−desilylation offers a stereocontrolled route to (*Z*)- or (*E*)-alkenes,[4] a shortcoming of ring-closing alkene metathesis. Heterogeneous Mo catalyst **2** was applied to known RCAM substrates. The alkyne metatheses were performed at room temperature in 1,2,4-trichlorobenzene under vacuum-driven conditions to remove 3-hexyne. After stirring a mixture of 5 mol % trisamido molybdenum(VI) complex **1** and fumed silica (7 × weight of Mo complex) for 5 min in trichlorobenzene, a solution of the RCAM substrate was added to the suspension and the pressure was reduced to 1 mmHg. RCAM of diyne **3a** gave the corresponding cyclic compound **4a** in 67% isolated yield. Fürstner and co-workers reported that **4a** was obtained in 68% yield by RCAM using a homogeneous tungsten alkylidyne complex at 80 °C.[5] Also Grela and Ignatowska found that a homogeneous system, Mo(CO)$_6$ with 2-fluorophenol, gave **3a** at 132 °C in 50% yield.[6] This comparison shows that the heterogeneous Mo catalyst **2** is sufficiently active even at room temperature to catalyze RCAM reactions. Using a similar procedure, RCAM products **4b−d** were obtained in moderate yields using room temperature, vacuum-driven metathesis conditions (Table 1). Compounds **4a−d** were easily isolated after removing the phenol-free catalyst by simple filtration and purified by silica gel chromatography. Trace metal impurity anlaysis by Inductively Coupled Plasma (ICP) revealed that Mo metal was present at less than 0.1 wt % (i.e., below the ICP detection limit).





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[1] Weissman, H.; Plunkett, K. N.; Moore, J. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 585.

[2] For alkyne metathesis with a heterogeneous system see: (a) Chabanas, M.; Baudouin, A.; Copéret, C.; Basset, J.-M. *J. Am. Chem. Soc.* **2001**, *123*, 2062. (b) Mortreux, A.; Delgrange, J. C.; Blanchard, M.; Lubochinsky, B. *J. Mol. Catal.* **1977**, *2*, 73. (c) Mortreux, A.; Petit, F.; Blanchard, M. *J. Mol. Catal.* **1980**, *8*, 97.

[3] For alkene metathesis with a heterogeneous system see: (a) Nguyen, S. T.; Grubbs, R. H. *J. Organomet. Chem.* **1995**, *497*, 195. (b) Ahmed, M.; Barrett, A. G. M.; Braddock, D. C.; Cramp, S. M.; Procopiou, P. A. *Tetrahedron Lett.* **1999**, *40*, 8657. (c) Yao, Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 3896. (d) Jafarpour, L.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 4075. (e) Kingsbury, J. S.; Garber, S. B.; Giftos, J. M.; Gray, B. L.; Okamoto, M. M.; Farrer, R. A.; Fourkas, J. T.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4251. (f) Dowden, J.; Savović, J. *Chem. Commun.* **2001**, 37. (g) Copéret, C.; Chabanas, M.; Saint-Arroman, R. P.; Basset, J.-M. *Angew. Chem., Int. Ed.* **2003**, *42*, 156. (h) Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4510.

[4] (a) Fürstner, A.; Radkowski, K. *Chem. Commun.* **2002**, 2182. (b) Lacombe, F.; Radkowski, K.; Seidel, G.; Fürstner, A. *Tetrahedron* **2004**, *60*, 7315. (c) Fürstner, A.; Seidel, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 1734. (d) Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem. Eur. J.* **2001**, *7*, 5299. (e) Fürstner, A.; Davies, P. W. *Chem. Commun.* **2005**, 2307. (f) Bunz, U. H. F.; Kloppenburg, L. *Angew. Chem., Int. Ed.* **1999**, *38*, 478.

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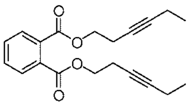
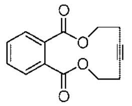
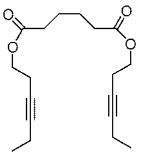
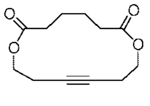
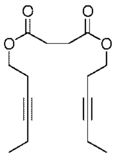
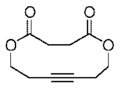
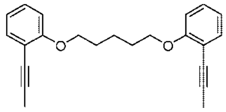
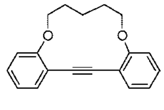
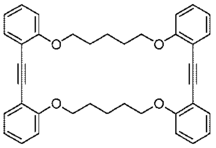
10.1021/jo8003919 CCC: $40.75

TABLE 1. RCAM with Heterogeneous Catalyst 2

entry	substrate	product^a	yield^b
1	 **3a**	 **4a**	62%
2	 **3b**	 **4b**[5,7]	65%
3	 **3c**	 **4c**[5,7]	67%
4	 **3d**	 **4d-M**	65%
		 **4d-D**	5%

^{a} Reaction condition: trichlorobenzene solvent, room temperature, 1 mmHg, overnight. ^{b} Isolated yields after silica gel chromatography.

The RCAM product from **3d** gave a mixture of monomeric macrocycle **4d-M** and dimeric macrocycle **4d-D**, similar to the finding of Brizius and Bunz.[8] Interestingly single-crystal X-ray analysis of **4d-D** showed that all sp, sp^2, sp^3 carbon, and oxygen atoms are on the same rectangular plane (Figure 1).

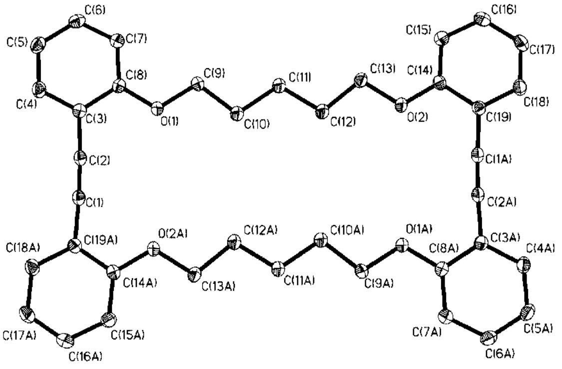


FIGURE 1. ORTEP drawing of **4d-D**, shown with 35% thermal ellipsoids. H atoms are omitted for clarity. Torsion angles of C(4)−C(3)−C(8)−O(1),C(2)−C(3)−C(8)−O(1),O(1)−C(9)−C(10)−C(11), C(9)−C(10)−C(11)−C(12), and C(10)−C(9)−O(1)−C(8) are almost 0 or 180°. The C1−C2A and C11−C11A distance are 11.896(2) and 5.514(2) Å, respectively. The distance between two parallel molecular planes stacked closest in the unit cell is around 3.6 Å (see the Supporting Information). Selected bond lengths (Å) and angle (deg): C(1)−C(2) 1.196(2); C(2)−C(3) 1.432(1); C(8)−O(1) 1.357(1); C(9)−O(1) 1.432(1); C(8)−O(1)−C(9) 116.62(8).

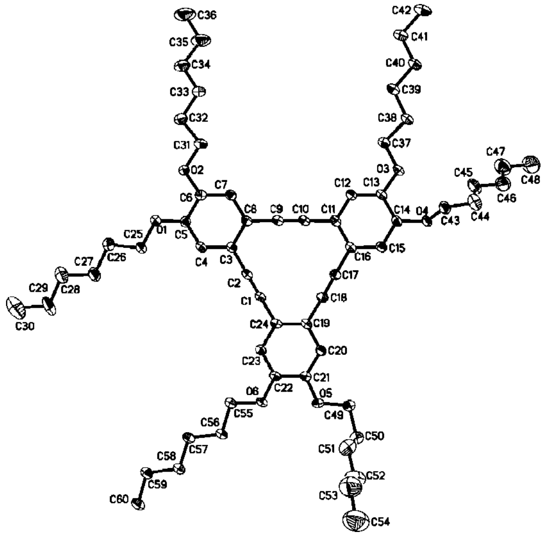


FIGURE 2. ORTEP drawing of **4f**, shown with 35% thermal ellipsoids. H atoms are omitted for clarity.

We also applied heterogeneous catalyst **2** to the cyclooligomerization of arylene ethynylene macrocycles,[9] reactions that proceed best with highly active and durable catalysts. Cyclooligomerizations were carried out near room temperature under precipitation-driven conditions to remove bis(benzoylbiphenyl)-ethyne (**5**) as a poorly soluble byproduct. Multiple alkyne metatheses from substrates **3e** and **3f** using 10 mol % of **2** gave tetrameric macrocycle **4e**[10] and trimeric macrocycle **4f**,[11] respectively, in high isolated yields. The products were obtained in nearly pure form simply by filtering off the insoluble byproduct **5** and the supported catalyst **2**. Mo metal in the products observed by ICP was found to be less than 0.1 wt % after purification by silica gel chromatography. Single-crystal analysis of **4f** showed a planar triangular core (Figure 2).

In summary, the high activity and durability of the fumed silica-supported Mo(VI) **2** has been demonstrated in preparative

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[7] (a) Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 9453. (b) Sashuk, V.; Ignatowska, J.; Grela, K. *J. Org. Chem.* **2004**, *69*, 7748.

[8] Brizius and Bunz obtained a mixture of **4d-M** in 79% yield and **4d-D** in 2% yield, see: Brizius, G.; Bunz, U. H. F. *Org. Lett.* **2002**, *4*, 2829.

[9] (a) Klyatskaya, S.; Dingenouts, N.; Rosenauer, C.; Müller, B.; Höger, S. *J. Am. Chem. Soc.* **2006**, *128*, 3150. (b) Ziegler, A.; Mamdouh, W.; Ver Heyen, A.; Surin, M.; Uji-i, H.; Abdel-Mottaleb, M. M. S.; De Schryver, F. C.; De Feyter, S.; Lazzaroni, R.; Höger, S. *Chem. Mater.* **2005**, *17*, 5670. (c) Höger, S. *Chem. Eur. J.* **2004**, *10*, 1320. (d) Zhao, D.; Moore, J. S. *Chem. Commun.* **2003**, 807. (e) Yamaguchi, Y.; Yoshida, Z. *Chem. Eur. J.* **2003**, *9*, 5430. (f) Grave, C.; Schluter, A. D. *Eur. J. Org. Chem.* **2002**, 3075. (g) Höger, S. *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 2685. (h) Prautzsch, V.; Ibach, S.; Vogtle, F. J. *Inclusion Phenom. Macrocycl. Chem.* **1999**, *33*, 427. (i) Seo, S. H.; Jones, T. V.; Seyler, H.; Peters, J. O.; Kim, T. H.; Chang, J. Y.; Tew, G. N. *J. Am. Chem. Soc.* **2006**, *128*, 9264. (j) Eickmeier, C.; Junga, H.; Matzger, A. J.; Scherhag, F.; Shim, M.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2103. (k) Ferrara, J. D.; Tessier-Youngs, C.; Youngs, W. J. *J. Am. Chem. Soc.* **1985**, *107*, 6719. (l) Ferrara, J. D.; Djebli, A.; Tessier-Youngs, C.; Youngs, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 647.

[10] Zhang, W.; Moore, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 12796.

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scale RCAM and cyclooligomerization reactions at room temperature. The cyclic products could be isolated with ease due to the absence of phenol ligands and the insolublity of the heterogeneous catalyst. These procedures are more mild and easier to perform compared to other alkyne metathesis reactions.

Experimental Section

Typical Procedure for 4a by Vacuum-Driven Alkyne Metathesis. In an argon-filled glovebox, a two-necked flask connected to a vacuum manifold was sequentially charged with trisamidomolybdenum(VI) propylidyne **1** (12.2 mg, 0.0184 mmol), fumed silica (85.4 mg, Silica M5 pretreated at 400 °C under dry oxygen), and 1,2,4-trichlorobenzene (7.0 mL). The resulting mixture was stirred for 5 min and **3a** (120 mg, 0.368 mmol) in 1,2,4-trichlorobenzene (11 mL) was added to the stirred catalyst. The pressure was reduced to 1 mmHg by dynamic vacuum. The resulting suspension was stirred at room temperature for 16 h. EtOAc (5 mL) was added to the reaction mixture and the fumed silica was removed by suction filtration. The filtrate was concentrated in vacuo and the crude product was further purified by column chromatography (EtOAc:*n*-Hex = 1:4) to give **4a** as a white solid (60 mg, 67%). ^{1}H NMR and FD MS of **4a** are in agreement with those published in the literature.[5,6]

Typical Procedure for 4e by Precipitation-Driven Alkyne Methathesis. A one-necked flask was sequentially charged with trisamidomolybdenum(VI) propylidyne **1** (18.0 mg, 0.0270 mmol), fumed silica (126 mg), and 1,2,4-trichlorobenzene (7.0 mL) in the glovebox. The resulting mixture was stirred for 5 min and monomer **3e** (250 mg, 0.270 mmol) in 1,2,4-trichlorobenzene (8 mL) was added to the stirred catalyst mixture. After the flask was sealed, the resulting mixture was stirred at 45 °C for 36 h during which time a light yellow precipitate formed. CH_2Cl_2 (5 mL) was added to the reaction mixture and the solids were removed by suction filtration. The filtrate was concentrated in vacuo and the crude product was further purified by column chromatography ($CHCl_3$:*n*-Hex = 1:1 to $CHCl_3$) to give macrocyclic product **4e** as a yellow solid (89 mg, 86%). ^{1}H NMR and MALDI MS of **4e** are in agreement with those previously reported.[10]

Crystal Data for 4d-D and 4f. Suitable single crystals, **4d-D** and **4f** for the X-ray diffraction study were grown from THF and Et_2O, respectively. **4d-D**: $C_{38}H_{36}O_4$, $M = 556.69$, $T = 193(2)$ K, monoclinic, $P2_1/n$, $a = 13.5686(5)$ Å, $b = 7.0838(3)$ Å, $c = 16.6718(6)$ Å, $\alpha = 90°$, $\beta = 103.212(2)°$, $\gamma = 90°$, $V = 1560.03(10)$ Å^3, $Z = 2$, $D_c = 1.185$ Mg/m^3, $\mu = 0.076$ mm^{-1}, 16221 reflections measured, 3442 unique ($R_{int} = 0.0245$). Final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0354$, $wR_2 = 0.0930$, GOF = 1.053. CCDC 604087. **4f**: $C_{60}H_{84}O_6$, $M = 901.31$, $T = 193(2)$ K, triclinic, $P\bar{1}$, $a = 8.4210(9)$ Å, $b = 23.793(3)$ Å, $c = 28.702(3)$ Å, $\alpha = 104.861(3)°$, $\beta = 97.562(3)°$, $\gamma = 97.425(3)°$, $V = 5429.8(11)$ Å^3, $Z = 4$, $D_c = 1.103$ Mg/m^3, $\mu = 0.069$ mm^{-1}, 69902 reflections measured, 20705 unique ($R_{int} = 0.0658$). Final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0685$, $wR_2 = 0.1960$, GOF = 1.005. CCDC 604088.

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Supporting Information Available: Crystallographic data for **4d-D** and **4f**, and ^{1}H NMR spectra and elemental analysis data for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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