Alkyne Metathesis

DOI: 10.1002/ange.201300758

Alcohol-Promoted Ring-Opening Alkyne Metathesis Polymerization**

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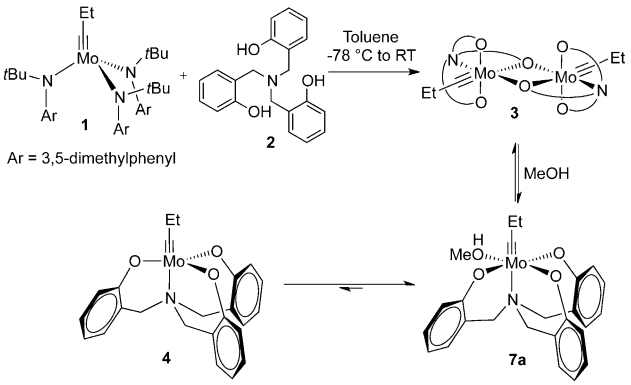
In contrast to the widespread adoption of olefin ring-opening metathesis polymerization, there are few reported examples of ring-opening alkyne metathesis polymerization (ROAMP).[1,2] This is due in part to a comparative shortage of catalysts for alkyne metathesis,[3] and particularly a shortage of well-defined catalysts that can initiate controlled metathesis polymerizations. An effective ROAMP initiator must react with strained monomers but not catalyze cross-metathesis scrambling of the resulting polymer chains. Furthermore, current applications of ROAMP are limited because existing catalysts require rigorously anhydrous conditions and because hydroxylic solvents and substrates are not tolerated.[4] Here we describe a bench-stable[5] molybdenum alkylidyne complex that reacts with methanol to produce a well-defined initiator for the metathesis polymerization of cyclooctynes. The reaction tolerates alcohols, water, phenolic substrates and in situ photochemical unmasking of alkynes. This is the first example of an effective and well-characterized catalytic system for ROAMP.

The genesis of the catalyst described here was a report by Jyothish and Zhang,[6] in which a trinitrated podand ligand was used in combination with the well-known tris-amido molybdenum alkylidyne complex **1**[7] (Scheme 1) to create a highly active catalyst for alkyne cross-metathesis. This system has only been applied as an uncharacterized mixture generated by in situ activation of **1**; further purification gave a dimeric product with no catalytic activity.

To gain insight into the nature of these systems we investigated the activation of **1** with unsubstituted podand ligand **2** (tris(2-hydroxybenzyl)amine; THBA).[8] We obtained mixtures with variable levels of metathesis activity. An unpurified precipitate from the reaction mixture is highly active toward ROAMP and cross-metathesis,[9] but further purification of this precipitate leads to lower activity. Silica gel chromatography and recrystallization from THF yielded complex **3**, an air-stable dimer with very low activity under typical (aprotic) reaction conditions.



Scheme 1. Synthesis of EtCMo(thba) dimer and activation by methanol.

Figure 1 displays the crystal structure of **3**, which features a phenoxide-bridged Mo_2O_2 motif with distorted octahedral geometry at molybdenum. This structure is analogous to the one previously reported for the trinitro version of this catalyst.[6] In the NMR spectra, recorded in toluene (Figure 2) or THF, the presence of six inequivalent benzylic protons indicates that the dimeric structure remains stable in solution.

We studied the reactivity of dimer **3** with cyclooctyne **5a**, a highly reactive ROAMP monomer,[2a] as our model substrate (Table 1). At room temperature, **3** does not react with **5a** in either [D_8]toluene or [D_8]THF (entry 1). Thermal cleavage of **3** at 100 °C in the presence of **5a** results in slow metathesis polymerization, reaching 16% conversion after 1 hour (entry 2). This exceptionally low reactivity highlights the stability of the aryloxide-bridged Mo_2O_2 dimer.

Remarkably, the metathesis activity of dimer **3** is much higher under protic conditions. A solution of **3** in CD_3OD/[D_8]toluene (4:1) reacts immediately with alkyne **5a** to give insoluble poly-**5a**. The polymerization of 5 equivalents of **5a** is complete within 2 hours at room temperature (Table 1, entry 3). Poly-**5a** is obtained with a M_n of 5200 and a PDI of 1.6.[10] The higher-than-theoretical molecular weight and moderately high PDI indicate that initiation of new chains is somewhat slower than propagation.[11] The reaction is not inhibited by air or water (entries 4 and 5). Chain growth continues to proceed for at least 8 hours if additional portions

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[**] Primary support for this project was provided by the Chemical Sciences, Geosciences and Biosciences Division, Office of Basic Energy Sciences, US Department of Energy (DOE) under award number DE-FG02-01ER15264. We thank Yi Rong and Aaron Sattler for X-ray crystallographic studies of compound **3** and the National Science Foundation (CHE-0619638) for the X-ray diffractometer. D.W.P. thanks Wesley Sattler for insightful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201300758.

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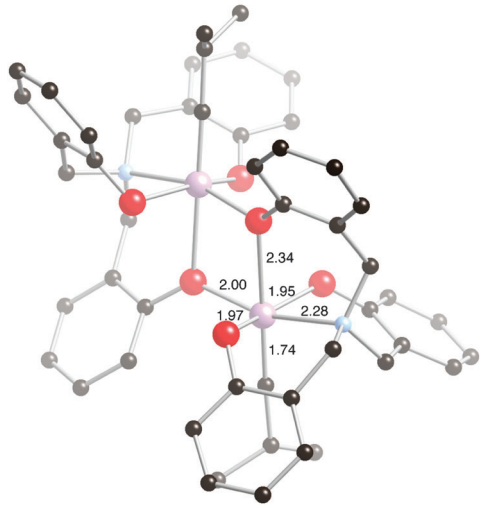


Figure 1. Crystal structure of compound **3**. Bond lengths are indicated in angstroms. The propylidyne methyl groups are disordered over two positions. Hydrogen atoms have been removed for clarity. O red, C black, N blue, Mo lavender. Crystallographic data and a thermal ellipsoid plot are provided in the Supporting Information, Table S1 and Figure S12.[14]

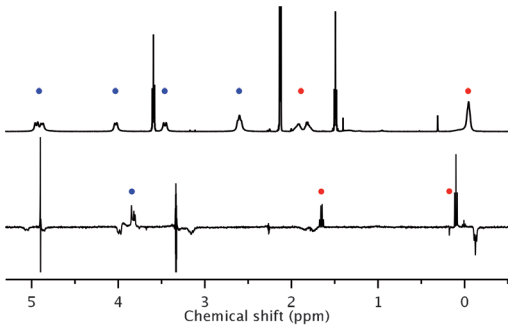


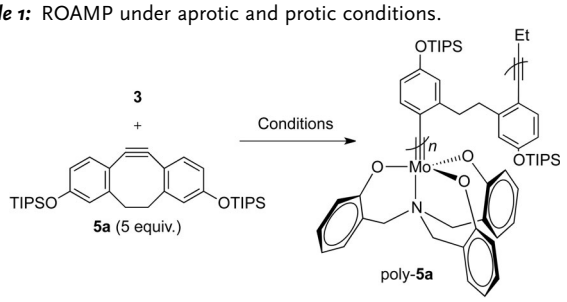
Figure 2. Partial ^{1}H NMR spectra of **3** (top) and **7a** (bottom). Blue dots indicate benzylic protons on thba ligand; red dots indicate propylidyne CH_2 and CH_3. The spectrum of **7a** was obtained by difference spectroscopy.

of **5a** are added to the reaction mixture, thus indicating that termination of growing chains is slow (Figure 3). This is the first example of a ROAMP reaction that proceeds in and is promoted by protic solvent.

We directly compared ligand **2** with Zhang's trinitro ligand **6**[6] by activating trisamide **1** in situ and adding methanol and alkyne **5a** to the resulting mixture (Scheme 2). The catalyst derived from **6** is active toward ROAMP in the presence of methanol, but its high activity results in runaway chain growth as indicated by the high M_n and PDI of the resulting polymer. In contrast, the in situ activation of **1** with **2** results in a polymer with close to theoretical values of M_n and PDI.

To investigate the reactivity of **3** in the presence of methanol, we recorded NMR spectra of **3** in mixtures of 20–80% CD_3OD/[D_8]toluene. We obtained equilibrium mixtures containing **3** and three new species, as indicated by methyl triplets at $\delta = 0.10$, 0.01, and −0.53 in the ^{1}H NMR spectrum

Table 1: ROAMP under aprotic and protic conditions.



Entry	Solvent	Temperature	Time [h]	Yield [%]	M_n	PDI
1	[D_8]THF	RT	1	0[a]	n.d.	n.d.
2	[D_8]toluene	100 °C	1	16[a]	n.d.	n.d.
3	CD_3OD[b]	RT	2	>90[a]	5200	1.6
4	MeOH[b,c]	RT	2	47[d]	4000	1.3
5	MeOH/H_2O[e]	RT	2	53[d]	4500	1.3

[a] Conversion measured by ^{1}H NMR spectroscopy. [b] 20% toluene added for solubility. [c] Under air in non-dry solvent. [d] Yield of the isolated product. [e] Methanol with 20% toluene and 5% water. n.d. = not determined, TIPS = triisopropylsilyl.

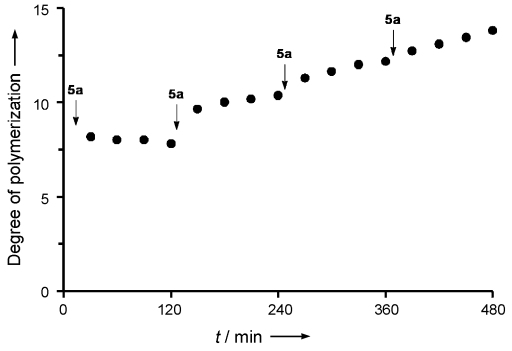
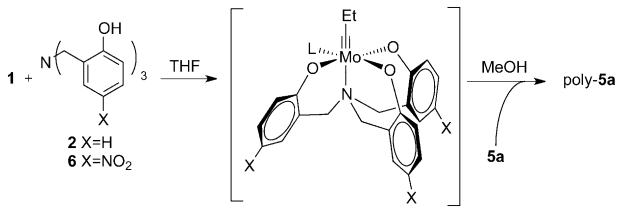


Figure 3. Time-resolved polymerization of **5a** initiated by **3** in THF/methanol under air. Arrows denote the addition of 5 equivalents of **5a**.



Scheme 2. Comparison of ligands **2** and **6**. Activation with **2**: yield 60%, M_n 3200, PDI 1.2. Activation with **6**: yield 57%, M_n 6300, PDI 2.4. L = ligand.

(see the Supporting Information, Figure S18). We refer to these species respectively as **7a**, **7b**, and **7c** and collectively as **7**. At equilibrium under typical reaction conditions, the proportions of **7a**, **7b**, **7c**, and unreacted **3** are 24, 4, 1, and 69%, respectively. We propose that **7a** is the mononuclear, octahedral methanol adduct depicted in Scheme 1. Plausible assignments of **7b** and **7c** include propylidene tautomers of **7a**, a Mo_3O_3 trimer, or pentacoordinate **4**, but our investigation of these species is hampered by their low concentration at equilibrium. ^{1}H NMR difference spectroscopy

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(Figure 2 and Figure S20 in the Supporting Information) reveals that **7a** has higher symmetry than **3**, with well-resolved aryl, benzylic and propylidyne peaks. When the mixture of **3** and **7** is concentrated to dryness and the residue is dissolved in [D_8]toluene, the dimer **3** is recovered in 96% yield (see the Supporting Information, Figure S19).

The following observations support our assignment of **7a**: At different total concentrations of molybdenum, a plot of $[\mathbf{7a}]^2$ versus [**3**] is linear, as expected for an equilibrium between a dimeric and a monomeric species (Figure 4 and

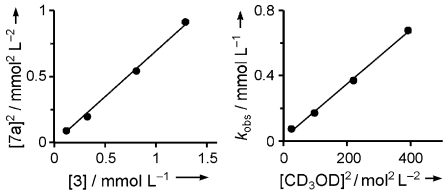


Figure 4. Effects of total molybdenum concentration (left) and methanol concentration (right) on the **3**/**7a** equilibrium. K_{obs} is defined as $[\mathbf{7a}]^2/[\mathbf{3}]$.

Figure S21 in the Supporting Information). The observed equilibrium constant ($K_{obs} = [\mathbf{7a}]^2/[\mathbf{3}]$) varies linearly with $[CD_3OD]^2$, thus implying that **7a** contains a methanol ligand (Figure 4 and Figure S22 in the Supporting Information). When a ^{1}H NMR spectrum of **3**/**7** is obtained in CD_3OH with solvent suppression (excitation sculpting[12] with 180° flipback pulse; see the Supporting Information, Figure S24), the methylene signal for the propylidyne ligand is still a quartet, thus ruling out α-protonated (propylidene) tautomers. Finally, DFT calculations (see the Supporting Information, Figures S30 and S31) predict that the *trans* stereoisomer of **7a** (as shown) is more stable than the *cis* isomer by approximately 17 kcal mol^{-1}.

Kinetic investigations of the polymerization of methanol-soluble cyclooctyne **5b** (Figure 5a) implicate methanol adduct **7a** as an important intermediate in the metathesis of alkynes with the **3**/MeOH system. When we dissolved dimer **3** in CD_3OD/[D_8]toluene (4:1), equilibrium was established between **3** and **7a**. After 1 hour, we added 5 equivalents of PEG-solubilized **5b** to the mixture. Within 5 minutes we observed the nearly total disappearance of intermediate **7a** and the appearance of polymer chain ends, which were quantified by integration of their methyl signal at $\delta = 1.16$. As the reaction proceeded, the signal for chain ends continued to increase while the corresponding signal for **3** decreased.

From these observations we infer (Figure 5b) that dimer **3** reacts slowly with methanol to form monomeric **7a**. This process requires a protic environment, not simply the presence of a two-electron donor, as demonstrated by the attempted polymerization of **5a** by **3** in THF (Table 1, entry 1). Complex **7a** loses methanol to generate a small equilibrium concentration of the active species **4**, which is trapped by strained alkyne **5b** to give ring-opened polymers. These two steps occur rapidly and **7a** is consumed almost quantitatively within 5 minutes. After cyclooctyne **5b** is

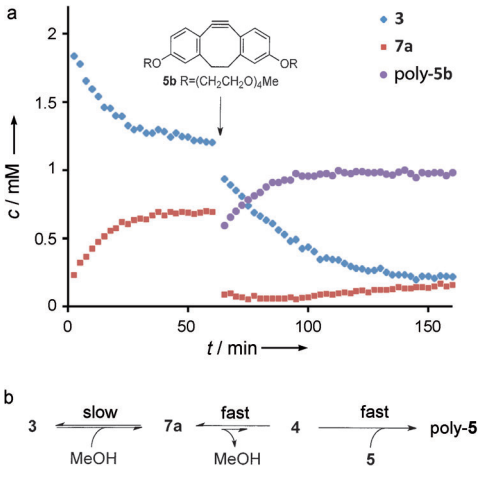
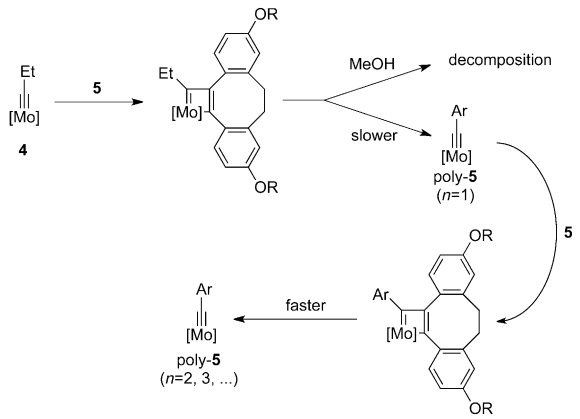


Figure 5. a) Structure of **5b** and polymerization initiated by **3**/CD_3OD. Poly-**5b** denotes initiated chain ends. **3** is counted as total [Mo] so that all concentrations are directly comparable. **7b** and **7c** are omitted. b) Kinetics of polymerization shown in a.

consumed (in approximately 100 minutes; see the Supporting Information, Figure S25), the equilibrium between **3** and **7a** is re-established.

As the reaction with alkyne **5b** proceeds, the conversion of molybdenum propylidynes into polymer chain ends occurs in 55% yield. We hypothesize (Scheme 3) that the remaining 45% comprise side products arising from metallacyclic metathesis intermediates,[13] as the initiator is stable toward methanol in the absence of alkynes. Side reactions evidently occur more often in the initial reaction of **5b** with propylidyne **4**. If every ring-opening event proceeded with 55% efficiency, less than 1% of chains would reach the observed average molecular weight of 10 units. We surmise that the metallacycle formed by the addition of **5b** to poly-**5b** is short-lived because of the steric interactions of its three aryl substituents. Rapid fragmentation of this intermediate leads to well-behaved propagation of the metathesis polymerization. In contrast, the ethyl-substituted metallacycle formed by the initial addition of **5b** to propylidyne **4** is less crowded. This longer-lived intermediate is susceptible to side reactions with methanol to give products that we have not yet characterized.



Scheme 3. Degradation of initially formed molybdenacyclobutadiene intermediate.

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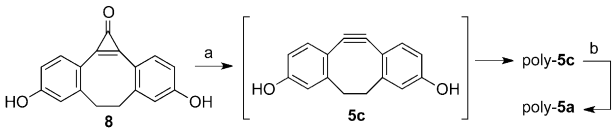
We have attempted cross-metathesis reactions of unstrained alkynes with dimer **3** or Zhang's **1**/**6** system in the presence of methanol, but this leads to the disappearance of the catalyst with no detectable formation of metathesis products. As described above, catalyst death apparently occurs by degradation of metallacyclic metathesis intermediates. The problem is worse for unstrained alkynes because there is no ring strain promoting the fragmentation of metallacyclobutadiene into alkyne and metal alkylidyne. To achieve acyclic cross-metathesis under protic conditions, it will be necessary to adjust the energetics of the metallacycle/alkyne equilibrium so that the metallacyclic intermediate is accessible but very short lived.

As an extension, we demonstrate (Scheme 4) that this catalytic system is able to initiate ROAMP in the presence of acidic functional groups such as phenols. We developed



Scheme 4. Tandem decarbonylation and polymerization of cyclopropenone **8**. a) *hν*, **3** (20 mol%), THF/MeOH (3:7); not isolated. b) $(i\text{Pr})_3\text{SiCl}$, Et_3N, DMF; 72% (2 steps), M_n 6300, PDI 1.3.

a tandem photolysis/polymerization of masked alkyne **8** because pure phenol **5c** is difficult to isolate. A THF/MeOH (3:7) suspension of **8** with 20 mol% of dimer **3** was photolyzed for 2 hours, then concentrated and treated with TIPSCl/Et_3N in DMF to solubilize the resulting polymer for characterization. Poly-**5a** was obtained in 72% yield with a M_n of 6300 and a PDI of 1.3.

This study introduces a new approach to catalyst design for ROAMP. The podand ligand motif resists ligand exchange and thereby reveals a new reactivity manifold for alkyne metathesis in the presence of alcohols and water. The extremely stable dimeric structure of **3** permits convenient handling and is readily converted into metathesis-active monomeric species by treatment with methanol. These design principles bring expanded scope and improved convenience to alkyne metathesis chemistry.

Received: January 28, 2013
Published online: March 12, 2013

Keywords: alkylidynes · metathesis · homogeneous catalysis · podand ligands · polymerization

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[14] CCDC 907844 (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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