Alkyne Metathesis

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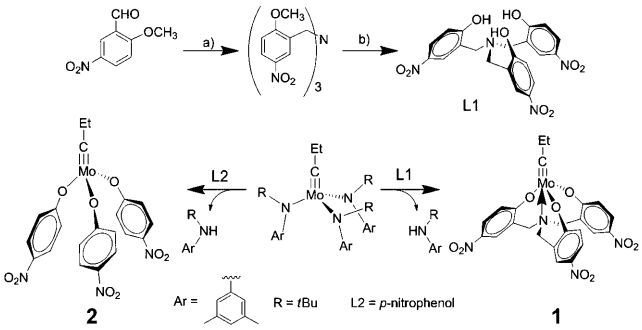
Introducing A Podand Motif to Alkyne Metathesis Catalyst Design: A Highly Active Multidentate Molybdenum(VI) Catalyst that Resists Alkyne Polymerization**

*Kuthanapillil Jyothish and Wei Zhang**

There has been significantly growing interest in recent years in the transition-metal-catalyzed metathesis of alkenes and alkynes.[1] The synthetic potential of alkyne metathesis, however, is much less explored though they have shown enormous potential in the preparation arylene ethynylene polymers,[2] macrocycles,[3] and in natural product synthesis.[1c,4] Typically, the metal alkylidyne catalysts for alkyne metathesis contain a tungsten or molybdenum–carbon triple bond and alkoxide/amide ligands,[1–5] and their catalytic activity can be tuned by judicious ligand design.[1–9]

Coordination of small molecules, and in particular 2-butyne (a common metathesis byproduct), to the hexavalent molybdenum alkylidyne complex is known to be an interfering reaction and leads to undesired alkyne polymerization (through the ring-expansion mechanism, which requires two open substrate-binding sites) as well as nonproductive reaction pathways.[10] Polyhedral oligomeric silsesquioxane (POSS) and silica are the only reported ligands to date that can overcome this long-standing problem.[9a,11] However, the siloxane-based approach lacks tunability in the catalyst structure, thus making it difficult to study the structure–activity relationship of the catalyst and tune its activity. Our present study is aimed at the design of a multidentate organic ligand that can block one substrate-binding site of the molybdenum center to inhibit the undesired alkyne polymerization while also keeping the structural tunability for introducing customizable electron-withdrawing substituents to improve both the metathesis activity and functional group tolerance.

Taking advantage of the favorable trigonal pyramid geometry of trisubstituted amines,[12] we designed the triphenolamine ligand L1 (Scheme 1) that would allow the effective coordination of the three phenol moieties to molybdenum, with the three methylene units blocking one substrate-binding site of the metal center. The synthesis of the multidentate triphenolamine ligand (L1) was achieved in good yield starting from the corresponding methyl-protected salicylaldehyde followed by reductive amination and deprotection (Scheme 1). A crystal of the complex **1** was obtained from a 1:1 mixture of the molybdenum(VI) propylidyne precursor and L1 using a solvent system comprising nitrobenzene and carbon tetrachloride.[13] The single-crystal X-ray structure analysis showed a phenoxide-bridged dimer of complex **1** with an octahedral coordination geometry around each metal center (Figure 1). Interestingly, the trigonal-pyramidal geometry of the triphenolamine ligand enables the coordination of the central nitrogen to molybdenum, thus efficiently blocking one open binding site of the complex. These interesting features are anticipated to make the catalyst **1** resistant to the interfering alkyne polymerization, and the strong chelating effect of the multidentate ligand should significantly enhance the catalyst stability and its activity.



Scheme 1. Synthesis of the multidentate ligand L1 and the generation of the alkyne metathesis catalysts [L1Mo(≡CEt)] (**1**) and [$(L2)_3$Mo(≡CEt)] (**2**) from the molybdenum(VI) precursor [$(3,5\text{-}C_6H_3(t\text{Bu})N)_3$Mo(≡CEt)]. Conditions: a) $NaBH(OAc)_3$, NH_4OAc, THF, RT, 69%; b) LiI, quinoline, 170°C, 87%.

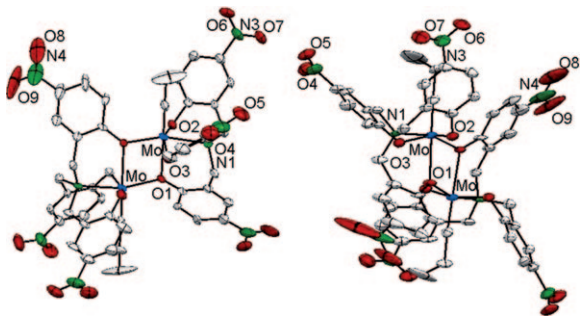


Figure 1. Crystal structure of the dimeric complex [{L1Mo≡CEt}$_2$] shown in two different orientations. Ellipsoids set at 50% probability; hydrogen atoms omitted for clarity.

[*] Dr. K. Jyothish, Prof. Dr. W. Zhang
Department of Chemistry and Biochemistry, University of Colorado
Boulder, CO 80309 (USA)
Fax: (+1) 303-492-5894
E-mail: wei.zhang@colorado.edu

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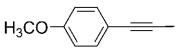
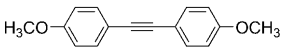
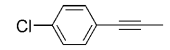
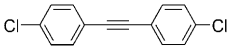
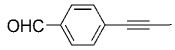
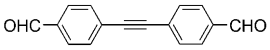
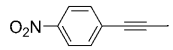
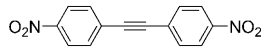
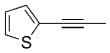
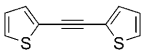
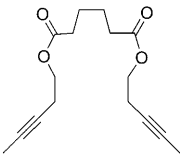
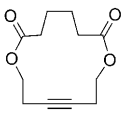
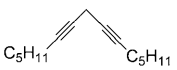
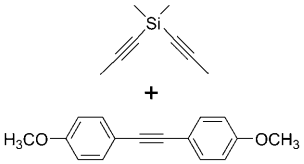
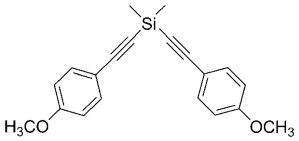
The solvent compatibility of **1** was tested with 4-propynylanisole as the substrate in a series of solvents (carbon tetrachloride, chloroform, toluene, chlorobenzene, 1,2-dichlorobenzene, 1,2,4-trichlorobenzene, and THF, in a closed system). The catalyst is metathesis-active in all of the above solvents (52–70% conversion), and the highest conversion is observed in carbon tetrachloride. ^{1}H NMR spectroscopy experiments using 1,4-dimethoxybenzene as an internal standard showed the quantitative displacement of the precursor ligands (Supporting Information, Figure S2) with L1 and the in situ generation of **1** in the solution phase. Furthermore, the ^{13}C NMR analysis of the trisamido molybdenum(VI) propylidyne precursor before and after mixing with L1 showed a significant deshielding effect; the chemical shift of the carbyne carbon bonded to the metal moved from $\delta = 302.6$ ppm[14] to $\delta = 322.6$ ppm, further indicating the displacement of anilide ligands on the molybdenum(VI) propylidyne precursor with L1 (Supporting Information, Figure S3, S4). Furthermore, ^{15}N NMR experiments by using a ^{15}N-labeled sample of L1 gave insight into the coordination behavior of the central nitrogen atom to molybdenum. The signal observed at $\delta = 44.8$ ppm for the nitrogen in the free ligand L1 shifted significantly to $\delta = 69.0$ ppm upon mixing with the catalyst precursor, which indicates the coordination of the L1 nitrogen to the metal center to form the multidentate metal complex (Supporting Information, Figure S3, S4).

Table 1 summarizes some model experiments that use the catalyst system **1** generated in situ and with carbon tetrachloride as the solvent. The scope of the metathesis activity was probed with various substrates: 1) containing electron donating/withdrawing substituents; 2) heterocyclic molecules; 3) the ring-closing alkyne metathesis (RCAM) of diynes to cycloalkyne; and 4) 1,4-diynes that are generally considered as difficult substrates, presumably owing to the formation of undesired stable metal–diyne chelates.[15] Interestingly, **1** was found to be compatible with all the different substrates tested, and even challenging examples containing nitro and aldehyde functional groups that are known to shut down the activity of some highly active alkyne metathesis catalysts.[7a,b,16,17] All the metathesis products were obtained in good to excellent yields under ambient conditions.[18] In particular, catalyst **1** gave the highest yield to date[6a,17] for the metathesis of *p*-nitro-substituted propynyl benzene, thus substantiating the high catalytic activity of **1**. Half-lives of less than 1 hour were generally observed for these model reactions, even with catalyst loadings of as low as 3 mol% (based on Mo). Successful metathesis of 1,4-diynes opens many new possibilities for preparing cross-conjugated polymeric or cyclic molecules.

Given the high functional group tolerance and metathesis activity of **1**, the idea of utilizing the multidentate structural feature to inhibit small alkyne polymerization was tested with 2-butyne, the metathesis byproduct of propynyl substrates. Indeed, as hypothesized, even in the presence of a large excess of 2-butyne (> 100 equiv), use of **1** did not lead to any polymerization (Supporting Information, Figure S5) even after 24 h. However, the catalyst generated from the corresponding monodentate analogue 4-nitrophenol (**2**), showed a broad peak around $\delta = 1.7$–2.0 ppm (Supporting Information, Figure S5) within 1 h after exposure to 2-butyne, thus indicating significant polymerization had occurred (Table 2, entry 1).

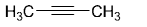
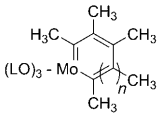
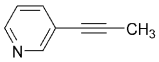
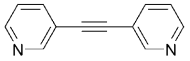
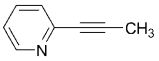
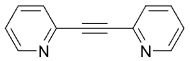
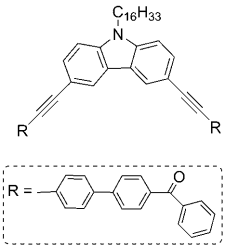
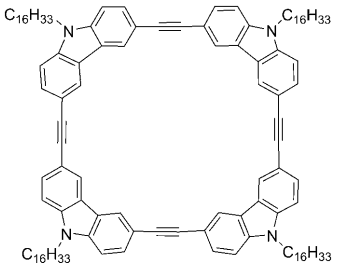
Previously, the high catalytic activity of **2** was reported, and it has been successfully employed in the synthesis of conjugated polymers and shape-persistent macrocycles with high efficiency.[1d,2b,3a–c] A comparison of the metathesis activity of **1** versus **2** showed that our newly designed multidentate molybdenum catalyst has even higher catalytic activity and broader substrate scope. In particular, the metathesis of substrates containing donor moieties, such as pyridine substrates (Table 2, entries 2,3), failed when **2** was

Table 1: Homodimerization, ring-closing alkyne metathesis, and cross-metathesis reactions of propynyl substrates and 1,4-diynes.[a]

Entry	Substrate	*T* [°C]	*t* [h]	Product	Yield [%]
1		RT	4		87[b]
2		RT	4		80[b]
3		40	7		71[b]
4		40	12		55[b]
5		40	4		74[b]
6		40	4		93[b]
7		40	4		60[c]
8		40	7		44 (45)[b,d]

[a] 3 Mol% catalyst loading for all entries. [b] In a closed system (solvent CCl_4), and the solution exposed to vacuum 4–5 times during the reaction to remove the metathesis byproduct 2-butyne. [c] No removal of the byproduct alkyne, equilibrium conditions. [d] The number in parenthesis indicates the isolated monoanisole silane.

Table 2: Comparison of the metathesis activity of **1** versus **2**.[a]

Entry	Substrate	*T* [°C]	*t* [h]	Product	Yield of **1** [%][b]	Yield of **2** [%][b]
1		RT	24		–	40
2		70	3		61	–
3		70	3		20	–
4		30	2/22[c]		95	84

[a] 3 Mol% catalyst loading for entries 1, 2, 4; 7 mol% for entry 3. [b] Yields in a closed system (solvent: CCl_4); – no reaction. [c] Reaction times: **1**: 2 h, **2**: 22 h.

In summary, compared to alkyne metathesis catalysts with monodentate ligands, the high catalytic activity and robustness of **1** can be attributed to two major factors: 1) stronger complexation offered by the multidentate ligand (entropy-favored) in comparison to a monodentate ligand, making the catalyst more robust and elongating its life time; and 2) spatial blocking of one substrate-binding site of the molybdenum alkylidyne complex, completely inhibiting undesired alkyne polymerization, and also greatly minimizing non-productive substrate binding, thus enabling the efficient metathesis of heterocycles that contain donor moieties. The high functional group tolerance, fast reaction rate, and high stability are three great advantages of catalyst **1**. More importantly, the strategy of utilizing multidentate ligands opens many new possibilities for the design of highly efficient, robust alkyne metathesis catalysts. Currently, the structure–activity relationship of this novel class of catalysts and their synthetic applications toward well-defined molecular architectures are being investigated in our laboratories and will be reported in due course.

used, even with high catalyst loadings (10–15 mol%). In contrast, the same substrates were successfully metathesized by **1** (Supporting Information, Figure S8). To the best of our knowledge, *o*-propynylpyridine is a very tough substrate, and its homodimerization by alkyne metathesis has not yet been reported. Using **1**, catalytic metathesis (Table 2, entry 3) was accomplished, thus further indicating the superior activity of catalyst **1**. The precipitation-driven cyclooligomerization[3c] of diyne monomer (Table 2, entry 4) by alkyne metathesis further substantiated the high activity of **1**; even with 3 mol% catalyst loading, the reaction is complete within 2 h at 30°C with a yield of 95% (Supporting Information, Figure S9). In contrast, for **2**, with 10 mol% catalyst loading, the same transformation took 22 h to give a yield of 84%.[3c] It was also observed that reducing the catalyst loading to 3 mol% significantly lowered the reaction conversion when **2** was used (Supporting Information, Figure S10).

The multidentate catalyst **1** is also much more stable than **2**. The metathesis activity of these two catalysts at different time intervals after their in situ generation (in the absence of substrates) was compared, with 4-chloropropynylbenzene as the substrate. Complex **1** showed a comparable activity (<10% decrease) even after 24 h and retained appreciable catalytic activity for several days, whereas **2** showed activity only within the first few hours. It was also observed that adding the substrate in the very beginning to the pre-generated catalyst solution for **2** led to longer catalyst lifetimes. This result indicates an intermolecular decomposition pathway[19] for **2**, either through ligand loss by cleavage of the labile Mo–O bond or by catalyst dimerization. The presence of substrates likely minimizes the bimolecular reaction of the catalyst itself, thus extending its lifetime. For **1**, the multidentate ligand is anticipated to bind more strongly to the molybdenum center owing to the chelate effect, and this favorable structural feature extends its lifetime.

Experimental Section

General procedure for metathesis experiments: The ligand and the precursor were premixed in dry carbon tetrachloride for 20 min to generate the catalyst in situ. The substrate was then added and the stirring was continued with regular monitoring of the reaction by NMR spectroscopy. During the reaction, the solution was exposed to vacuum (about 4 or 5 times, 20 s each time) to remove the metathesis byproduct 2-butyne. Loss of solvent during the application of vacuum was compensated by adding fresh solvent each time. For purification of the metathesis reaction products (Table 1, entries 1–6, 8; Table 2, entries 2 and 3), the solvent was removed with a rotary evaporator and the residue obtained was subjected to column chromatography over silica gel. For entry 4, the reaction mixture was filtered before the filtrate was concentrated and subjected to column chromatography over silica gel. For full details, see the Supporting Information.

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[1] a) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18; b) R. R. Schrock, C. Czekelius, *Adv. Synth. Catal.* **2007**, *349*, 55; c) A. Fürstner, P. W. Davies, *Chem. Commun.* **2005**, 2307; d) W. Zhang, J. S. Moore, *Adv. Synth. Catal.* **2007**, *349*, 93; e) M. Mori, *Adv. Synth. Catal.* **2007**, *349*, 121; f) D. Astruc, *New J. Chem.* **2005**, *29*, 42.

[2] a) U. H. F. Bunz, *Acc. Chem. Res.* **2001**, *34*, 998; b) W. Zhang, J. S. Moore, *Macromolecules* **2004**, *37*, 3973; c) F. R. Fischer, C. Nuckolls, *Angew. Chem.* **2010**, *122*, 7415; *Angew. Chem. Int. Ed.* **2010**, *49*, 7257.

[3] a) W. Zhang, J. S. Moore, *Angew. Chem.* **2006**, *118*, 4524; *Angew. Chem. Int. Ed.* **2006**, *45*, 4416; b) W. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **2005**, *127*, 11863; c) W. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **2004**, *126*, 12796; d) P.-H. Ge, W. Fu, W. A. Herrmann, E. Herdtweck, C. Campana, R. D. Adams, U. H. F. Bunz, *Angew. Chem.* **2000**, *112*, 3753; *Angew. Chem. Int. Ed.* **2000**, *39*, 3607; e) C. A. Johnson II, Y. Lu, M. Haley, *Org. Lett.* **2007**, *9*, 3725; f) J. Jiang, G. N. Tew, *Org. Lett.* **2008**, *10*, 4393.

[4] a) A. Fürstner, K. Grela, *Angew. Chem.* **2000**, *112*, 1292; *Angew. Chem. Int. Ed.* **2000**, *39*, 1234; b) K. Micoine, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 14064; c) A. Fürstner, O. Larionov, S. Flügge, *Angew. Chem.* **2007**, *119*, 5641; *Angew. Chem. Int. Ed.* **2007**, *46*, 5545.

[5] R. R. Schrock, *Chem. Rev.* **2002**, *102*, 145.

[6] a) B. Haberlag, X. Wu, K. Brandhorst, J. Grunenberg, C. G. Daniliuc, P. G. Jones, M. Tamm, *Chem. Eur. J.* **2010**, *16*, 8868; b) S. Beer, C. G. Hrib, P. G. Jones, K. Brandhorst, J. Grunenberg, M. Tamm, *Angew. Chem.* **2007**, *119*, 9047; *Angew. Chem. Int. Ed.* **2007**, *46*, 8890; c) J. M. Blackwell, J. S. Figueroa, F. H. Stephens, C. C. Cummins, *Organometallics* **2003**, *22*, 3351; d) O. Coutelier, A. Mortreux, *Adv. Synth. Catal.* **2006**, *348*, 2038.

[7] Nitride-based alkyne metathesis catalysts have also been reported; see: a) J. Heppekausen, R. Stade, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2010**, *132*, 11045; b) M. Bindl, R. Stade, E. K. Heilmann, A. Picot, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2009**, *131*, 9468; c) A. M. Geyer, E. S. Wiedner, J. B. Gary, R. L. Gdula, N. C. Kuhlmann, M. J. A. Johnson, B. D. Dunietz, J. W. Kampf, *J. Am. Chem. Soc.* **2008**, *130*, 8984.

[8] Use of alkyne metathesis catalysts generated in situ from $Mo(CO)_6$ has also been reported; see: a) A. Mortreux, M. Blanchard, *J. Chem. Soc. Chem. Commun.* **1974**, 786; b) V. Sashuk, J. Ignatowska, K. Grela, *J. Org. Chem.* **2004**, *69*, 7748; c) G. Brizius, N. G. Pschirer, W. Steffen, K. Stitzer, H. Zur Loye, U. H. F. Bunz, *J. Am. Chem. Soc.* **2000**, *122*, 12435.

[9] For solid-phase-based alkyne metathesis catalysts, see: a) H. Weissman, K. N. Plunkett, J. S. Moore, *Angew. Chem.* **2006**, *118*, 599; *Angew. Chem. Int. Ed.* **2006**, *45*, 585; b) N. Merle, M. Taoufik, M. Nayer, A. Baudouin, E. Le Roux, R. M. Gauvin, F. Lefebvre, J. Thivolle-Cazat, J.-M. Basset, *J. Organomet. Chem.* **2008**, *693*, 1733.

[10] a) H. Strutz, J. C. Dewan, R. R. Schrock, *J. Am. Chem. Soc.* **1985**, *107*, 5999; b) W. Zhang, S. Kraft, J. S. Moore, *J. Am. Chem. Soc.* **2004**, *126*, 329.

[11] a) H. M. Cho, H. Weissman, S. R. Wilson, J. S. Moore, *J. Am. Chem. Soc.* **2006**, *128*, 14742; b) R. M. Gauvin, O. Coutelier, E. Berrier, A. Mortreux, L. Delevoye, J.-F. Paul, A.-S. Mamede, E. Payen, *Dalton Trans.* **2007**, 3127.

[12] R. R. Schrock, *Acc. Chem. Res.* **1997**, *30*, 9.

[13] The crystal was obtained from the solvent mixure after the solution containing the complex was left in the freezer for over two weeks. Owing to the extremely poor solubility of the crystal in CCl_4, its catalytic activity could not be tested. In nitrobenzene, the catalyst has much better solubility, but no metathesis reaction was observed.

[14] W. Zhang, S. Kraft, J. S. Moore, *Chem. Commun.* **2003**, 832.

[15] V. Huc, R. Weihofen, I. Martin-Jimenez, P. Oulie, C. Lepetit, G. Lavigne, R. Chauvin, *New J. Chem.* **2003**, *27*, 1412.

[16] Some tungsten alkylidynes react with carbonyl groups, see J. H. Freudenberger, R. R. Schrock, *Organometallics* **1986**, *5*, 398.

[17] N. G. Pschirer, U. H. F. Bunz, *Tetrahedron Lett.* **1999**, *40*, 2481.

[18] Presumably applying continuous vacuum to the reaction would further enhance the yields; however, given the low boiling point of CCl_4, continuous vacuum conditions were not tested.

[19] R. R. Schrock, *Chem. Commun.* **2005**, 2773.

