# Enediynes via Sequential Acetylide Reductive Coupling and Alkyne Metathesis: Easy Access to Well-Defined Molybdenum Initiators for Alkyne Metathesis

James M. Blackwell, Joshua S. Figueroa, Frances H. Stephens, and Christopher C. Cummins*

*Massachusetts Institute of Technology, Room 2-227, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139*

*Received March 3, 2003*

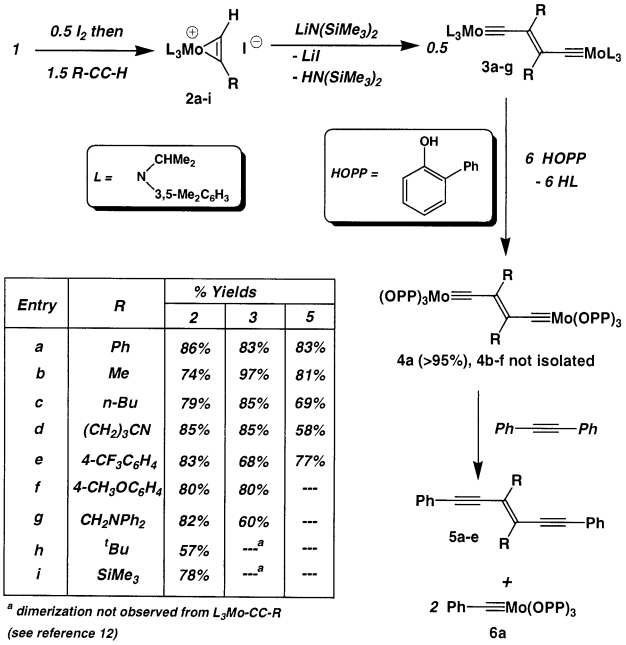
*Summary: A new synthetic route utilizes the reductive coupling of molybdenum(IV) acetylides toward the construction of both enediyne molecules and trialkoxymolybdenum alkylidynes, the latter being useful as alkyne metathesis initiators. The molybdaziridine hydride complex Mo(H)($\eta^2$-Me$_2$CNAr)(N[i-Pr]Ar)$_2$, **1**, readily prepared from MoCl$_3$(thf)$_3$, is elaborated in three generally high-yielding steps to enediynes and/or metathesis catalysts.*



Group 6 metal alkylidyne complexes are recognized as useful catalysts for the alkyne metathesis reaction.[1] Recently, various molybdenum-containing recipes have been devised that effect this important transformation without the benefit of a well-defined active catalyst; this is particularly so in exciting polymer synthesis applications[2] and in impressive ring-closing variants utilized in natural product synthesis.[3] On the other hand, despite the fact that structurally well-defined trialkoxymolybdenum alkylidyne complexes are known to function as efficient and functional-group-tolerant catalysts for alkyne metathesis,[4,5] they have not been widely adopted because of difficulties encountered in their synthesis. In this communication, we describe a convenient synthetic protocol for preparing such alkyne metathesis catalysts starting from Mo(H)($\eta^2$-Me$_2$CNAr)(N[i-Pr]Ar)$_2$, **1**.[6] This protocol can also be directed toward the synthesis of conjugated (*E*)- and (*Z*)-enediynes, molecules of great importance in materials[7] and biological chemistry[8−10] owing respectively to their remarkable electronic and antibiotic properties.

Molybdenum(VI) alkyne complexes **2a**−**g**, prepared from molybdaziridine hydride **1** in high yield (Scheme 1),[11] are converted to the dinuclear enedialkylidyne complexes **3a**−**g** upon deprotonation with Li[N(SiMe$_3$)$_2$].[12−14] Reaction times for these reductive coupling reactions

**Scheme 1**




| Entry | R | % Yields 2 | 3 | 5 |
|---|---|---|---|---|
| a | Ph | 86% | 83% | 83% |
| b | Me | 74% | 97% | 81% |
| c | n-Bu | 79% | 85% | 69% |
| d | $(CH_2)_3CN$ | 85% | 85% | 58% |
| e | 4-$CF_3C_6H_4$ | 83% | 68% | 77% |
| f | 4-$CH_3OC_6H_4$ | 80% | 80% | --- |
| g | $CH_2NPh_2$ | 82% | 60% | --- |
| h | $^t$Bu | 57% | ---[a] | --- |
| i | $SiMe_3$ | 78% | ---[a] | --- |

[a] dimerization not observed from L$_3$Mo-CC-R (see reference 12)

(1) Schrock, R. R. *Chem. Rev.* **2002**, *102*, 145, and references therein.
(2) (a) Brizius, G.; Bunz, U. H. F. *Org. Lett.* **2002**, *4*, 2829. (b) Bunz, U. H. F. *Acc. Chem. Res.* **2001**, *34*, 998. (c) Ge, P.-H.; Fu, W.; Herrmann, W. A.; Herdtweck, E.; Campana, C.; Adams, R. D.; Bunz, U. H. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3607.
(3) (a) Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem. Eur. J.* **2001**, *7*, 5299. (b) Fürstner, A.; Mathes, C. *Org. Lett.* **2001**, *3*, 221. (c) Grela, K.; Ignatowska, J. *Org. Lett.* **2002**, *21*, 3747.
(4) McCullough, L. C.; Schrock, R. R.; Dewan, J. C.; Murdzek, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 5987.
(5) Tsai, Y.-C.; Diaconescu, P. L.; Cummins, C. C. *Organometallics* **2000**, *19*, 5260.
(6) Tsai, Y.-C.; Johnson, M. J. A.; Mindiola, D. J.; Cummins, C. C.; Klooster, W. T.; Koetzle, T. F. *J. Am. Chem. Soc.* **1999**, *121*, 10426.
(7) (a) Martin, R. E.; Gubler, U.; Cornil, J.; Balakina, M.; Boudon, C.; Bosshard, C.; Gisselbrecht, J.-P.; Diederich, F.; Günter, P.; Gross, M.; Brédas, J.-L. *Chem. Eur. J.* **2000**, *6*, 3622. (b) Chow, S.-Y.; Palmer, G. J.; Bowles, D. M.; Anthony, J. E. *Org. Lett.* **2000**, *2*, 961.
(8) (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Danishefsky, S. J.; Shair, M. D. *J. Org. Chem.* **1996**, *61*, 16.
(9) (a) Nicolaou, K. C.; Ulven, T. M. T.; Baran, P. S.; Zhong, Y. L.; Sarabia, F. *J. Am. Chem. Soc.* **2002**, *124*, 5718. (b) Jones, G. B.; Wright, J. M.; Plourde, G. W., II; Hynd, G.; Huber, R. S.; Matthews, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 1937. (c) Shimizu, T.; Miyasaka, D.; Kamigata, N. *Org Lett.* **2000**, *2*, 1923. (d) Hayashi, M.; Saigo, K. *Tetrahedron Lett.* **1997**, *38*, 6241. (e) Kosinski, C.; Hirsch, A.; Heinemann, F. W.; Hampel, F. *Eur. J. Org. Chem.* **2001**, 3879.
(10) For a mechanistically distinct transition metal (Re, Mn) mediated synthesis of enediynes see: (a) Casey, C. P.; Kraft, S.; Powell, D. R. *J. Am. Chem. Soc.* **2002**, *124*, 2584. (b) Casey, C. P.; Dzwiniel, T. L. *INDR 371* presented at ACS Meeting, Boston, MA, Aug 2002.
(11) Typically, **1** is treated with 0.5 equiv of I$_2$ followed by 1.5 equiv of alkyne to provide complexes **2**; see Supporting Information for details.
(12) Deprotonation leads to formation of the corresponding triamidomolybdenum(IV) acetylide. The phenylacetylide complex formed from **2a** has been isolated and characterized by X-ray crystallography; its reactivity will be the subject of a forthcoming paper. See also: Shih, K.-Y.; Schrock, R. R.; Kempe, R. *J. Am. Chem. Soc.* **1994**, *116*, 8804.
(13) Group 6 enedialkylidynes have also been made via (a) the reaction of enediynes with ($^t$BuO)$_3$W≡CEt, see: Krouse, S. A.; Schrock, R. R. *J. Organomet. Chem.* **1988**, *355*, 257. (b) Via oxidation of dianionic vinylidene complexes (W and Mo), see: Woodworth, B. E.; White, P. S.; Templeton, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 828. (c) Via reaction of a Cr phenylacetylide complex and Na/K alloy, see: Ustynyuk, N. A.; Vinogradova, V. N.; Andrianov, V. G.; Struchkov, Y. T. *J. Organomet. Chem.* **1984**, *268*, 73.

10.1021/om0301482 CCC: $25.00 
Publication on Web 07/22/2003

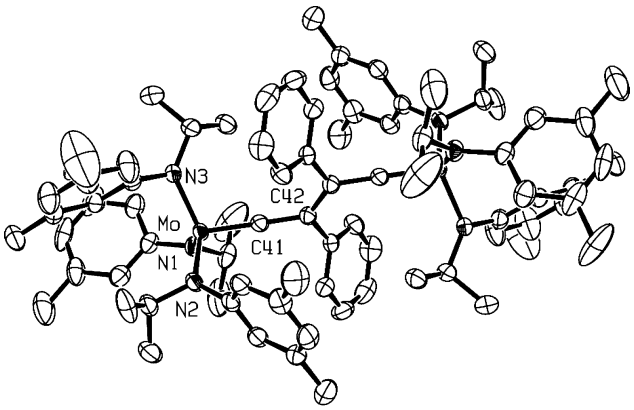


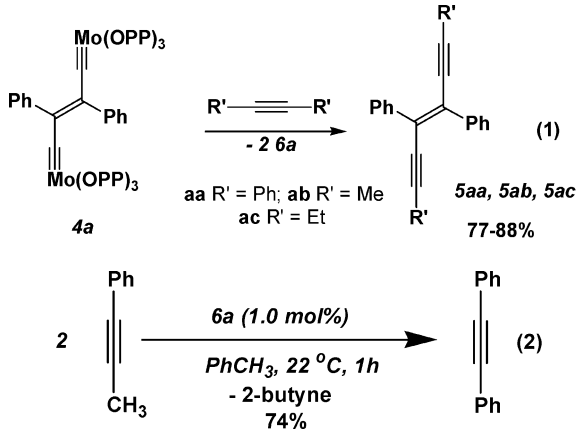

**Figure 1.** ORTEP diagram of enedialkylidyne **3a** showing thermal ellipsoids at the 50% probability level (symmetry equivalent atoms are not labeled). Selected bond lengths (Å): Mo−C41 = 1.758(3); C41−C42 = 1.443 (4); C42−C42A = 1.368(6). Selected angles (deg): Mo−C41−C42 = 175.3(3).



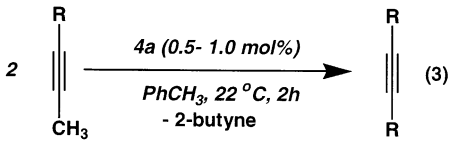
proceeding via molybdenum(IV) acetylides vary from 96 h (R = Ph) to less than 2 h (R = Me). The enedialkylidyne **3f** derived from 4-methoxyphenyl acetylene is formed in high yield in 12 h, demonstrating that the coupling reaction occurs more readily for electron-rich phenylacetylenes. However, complexes **2h** and **2i** derived from *tert*-butyl acetylene and trimethylsilyl acetylene do not provide dimeric enedialkylidynes under these reaction conditions; instead, the monomeric molybdenum(IV) acetylides so derived are isolable.[12] An X-ray crystal structure of **3a** established the *E*-disposition of the two alkylidyne fragments as shown in Figure 1. Both the Mo−C bond distance (1.758(3) Å) and the Mo−C−C bond angle (175.3(3)°) of the crystallographically identical alkylidyne units are parameters typical of other structurally characterized triamidomolybdenum alkylidyne compounds.[15] In all cases, characteristic resonances for the alkylidyne $C_\alpha$ carbons (293−302 ppm) were observed by $^{13}C$ NMR spectroscopy.

The enedialkylidynes **3a**−**e** are conveniently elaborated to the corresponding enediynes **5a**−**e** via a two-step, one-pot protocol involving replacement of the electron-rich amido ligands with 2-phenylphenoxy (OPP) ligands followed by treatment with diphenylacetylene.[16] This protocol takes advantage of the well-established reactivity of trialkoxymolybdenum alkylidynes with alkynes;[4,5] notably, the electronically saturated triamido derivatives, **3**, exhibit no reactivity with diphenylacetylene.

The aryloxy-substituted enedialkylidyne **4a** (R = Ph) is easy to isolate owing to its low solubility in diethyl ether. It is converted to enediynes **5aa**, **5ab**, and **5ac** when treated with the appropriate symmetrical alkyne as shown in eq 1. In the case of the **4a** to **5aa** conversion, the benzylidyne coproduct, **6a**, could be isolated in 45% yield and was demonstrated to exhibit alkyne metathesis activity. For instance **6a** catalyzes the conversion of 1-phenylpropyne to diphenylacetylene (and 2-butyne) at 24 °C as shown in eq 2.[17]




However, enedialkylidyne **4a** (isolated in >95% yield from **3a**) can itself serve as an efficient alkyne metathesis precatalyst as illustrated by the examples in eq 3. Hence, a robust and highly effective alkyne metathesis initiator, **4a**, is prepared in three high-yielding steps (68% overall) from the readily procured molybdaziridine hydride, **1**.[18] Enedialkylidyne **4a** and its two direct synthetic precursors **2a** and **3a** all are conveniently isolated as powders in high yields owing to their insolubility in pentane or diethyl ether.




*R = Ph (95%); R = 4-(NO$_2$)C$_6$H$_4$OCH$_2$CH$_2$- (60%);*
*R = 3-(Me$_2$N)C$_6$H$_4$OCH$_2$CH$_2$- (91%);*
*R = 3-(CF$_3$)C$_6$H$_4$OCH$_2$CH$_2$- (82%);*
*R = PhC(O)OCH$_2$CH$_2$- (87%).*

A powerful intramolecular reductive coupling protocol has been adapted from the above-described chemistry, providing conjugated cycloalkenedialkylidynes. The corresponding cycloalkenediynes (Scheme 2) can be obtained by using the combined alcoholysis/alkyne metathesis strategy described earlier. The pentane insoluble diyne complexes **7** are prepared in high yield and converted to the enedialkylidynes **8** by dropwise addition of a tetrahydrofuran (thf) solution of **7** to 2 equiv of Li[N(SiMe$_3$)$_2$] dissolved in thf. Intramolecular coupling occurs rapidly, and purification consists of removing the thf in vacuo, replacing with pentane, and filtering twice through Celite. The enedialkylidyne products are then redissolved in pentane with a few drops of thf and stored at −35 °C, leading to precipitation of a solid. After isolation by filtration, the enedialkylidyne is purified further by crystallization from a yellow-orange pentane/thf solution. Yields for the yellow crystalline solids range from 38% for **8c** to 68% for **8d**.

(14) See also: (a) Torraca, K. E.; McElwee-White, L. *Coord. Chem. Rev.* **2000**, *206*, 469, and references therein for related ligand-centered radical coupling reactions. (b) Beevor, R. G.; Freeman, M. J.; Green, M.; Morton, C. E.; Orpen, A. G. *J. Chem. Soc., Chem. Commun.* **1985**, 68. (c) Iyer, R. S.; Selegue, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 910.

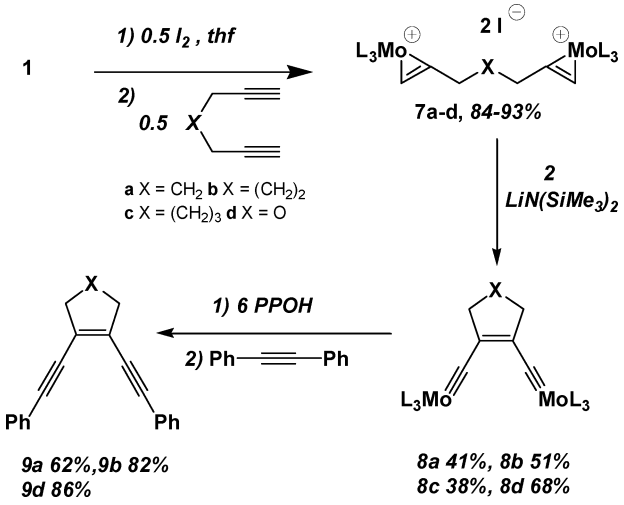
(15) Cochran, F. V.; Schrock, R. R. *Organometallics* **2001**, *20*, 2127.

(16) A similar procedure carried out on **3f** and **3g** failed to yield any enediyne product, possible reasons for which are currently being pursued.

(17) The protocol consists of mixing 1-phenylpropyne with catalytic alkylidyne (1−2 mol % Mo) in toluene and removing the solvent slowly (1−2 h) in vacuo (rough pump) with concomitant removal of 2-butyne.

(18) This source of a reactive triamidomolybdenum(III) synthetic equivalent is typically prepared in 10−20 g quantities as a crystalline solid ($Et_2O$) starting from $MoCl_3(thf)_3$, which is prepared from $MoCl_5$ via Poli's procedure, see: Stoffelbach, F.; Saurenz, D.; Poli, R. *Eur. J. Inorg. Chem.* **2001**, *10*, 2699.

**Scheme 2**




$^1$H NMR analysis of the crude reaction mixture for **8c** confirms that cyclization proceeds less cleanly than is observed for the other derivatives, likely reflective of the increased steric demands in placing two bulky alkylidyne fragments adjacent on a cycloheptene ring. $^{13}$C NMR spectroscopy shows one signal in each case that is typical for the $C_\alpha$ resonance of a molybdenum alkylidyne complex (290−302 ppm). The cycloalkenedialkylidyne complexes **8** were subsequently converted to enediynes **9** using the tandem alcoholysis/alkyne metathesis strategy delineated above.[19]

X-ray structure determinations of complexes **8c** (X = $(CH_2)_3$) and **8d** (X = O) illustrate the steric pressure inflicted on the two alkylidyne fragments vicinally disposed on a cycloalkene ring; see Figure 2 and Supporting Information. In the case of **8d**, accommodation of these two bulky groups is facilitated by distortion from linearity of both of the Mo−C−C angles (167.1(6)° and 173.6(6)°); no significant difference, however, is observed in the two Mo−C bond lengths (1.747(8) and 1.760(7) Å, respectively). For the cycloheptenedialkylidyne **8c**, steric pressure is expected to be even greater, and in the solid state, one of the Mo−C−C angles is significantly bent (161.2(5)°) while the other is only slightly kinked (176.0(5)°). Again, both Mo−C bond distances are comparable (1.754(7) and 1.752(7) Å, respectively).

In conclusion, we have developed a procedure for the synthesis of enediynes and well-defined alkyne metathesis initiators wherein two molybdenum centers conspire to form *eight new C−C bonds* from two terminal and two internal acetylenes. This redistribution of acetylenic bonds is instigated by the electron-rich triamidomolybdenum's passion to form Mo−C and other triple bonds[20] and is followed by the well-established metathesis reactivity of trialkoxymolybdenum alkylidyne complexes.[4,5] Further studies are being directed toward the preparation of functionally rich enediynes where the functionality can be introduced from the outset at the alkyne complexation step or at the final triple-bond metathesis step. We are also interested in further gauging the efficiency of enedialkylidynes such as **4a** in alkyne methathesis catalysis relative to the undefined active components popularized in other alkyne metathesis protocols.

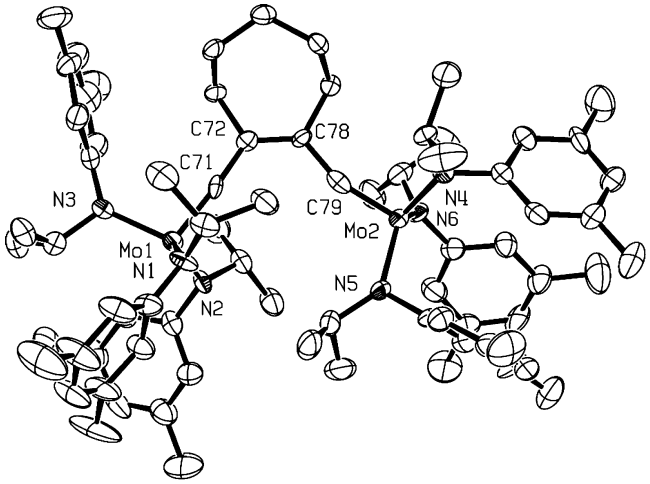



**Figure 2.** ORTEP diagram of enedialkylidyne **8c** showing thermal ellipsoids at the 50% probability level. Selected bond lengths (Å): Mo1−C71 = 1.752(7); Mo2−C79 = 1.754(7); C71−C72 = 1.433(9); C78−C79 = 1.461(9). Selected angles (deg): Mo1−C71−C72 = 176.0(5); Mo2−C79−C78 = 161.2(5).

**Acknowledgment.** For generous funding of this work, the authors thank the National Science Foundation (CHE-9988806). J.M.B. thanks NSERC (Canada) for a postdoctoral fellowship.

**Supporting Information Available:** Full preparative and spectroscopic details for all new compounds including X-ray structural data for complexes **3a**, **8c**, and **8d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM0301482

(19) No attempts in this case were made to isolate alkylidyne **6a**.

(20) Cummins, C. C. *Chem. Commun.* **1998**, 1777.