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Molybdenum Nitride Complexes with Ph_3SiO Ligands Are Exceedingly Practical and Tolerant Precatalysts for Alkyne Metathesis and Efficient Nitrogen Transfer Agents

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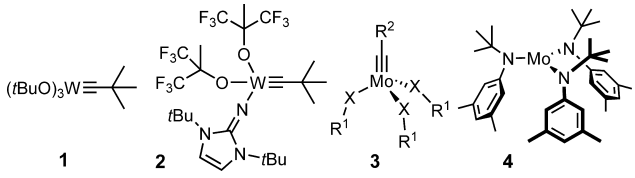
The first recorded examples of alkyne metathesis relied on the use of unidentified catalysts generated in situ from simple ingredients following empirically optimized recipes.[1] Although these procedures are operationally simple, they require harsh conditions and are therefore of limited preparative value. It was only after the advent of structurally defined high-valent metal alkylidyne complexes that the full potential of this transformation could be exploited,[2,3] for example, in applications to the total synthesis of complex natural products and materials science.[4−6]

Chart 1. Some Established (Pre)Catalysts for Alkyne Metathesis

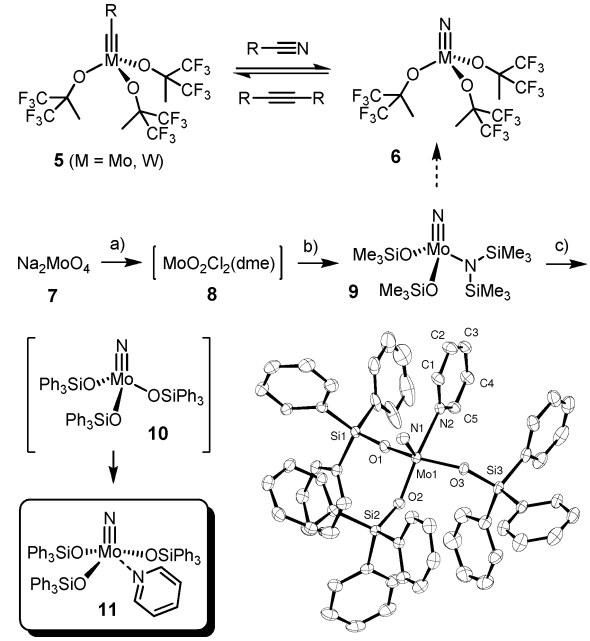


Among the various Schrock alkylidynes that qualify as catalysts,[2] tungsten neopentylidyne **1** has found the broadest use (Chart 1).[7] This air- and moisture-sensitive complex (and variants thereof, such as **2**[8]) effects certain alkyne metathesis reactions even at room temperature.[3b,8,9] Because of their appreciable Lewis acidity, however, these complexes are incompatible with substrates containing donor sites such as nitrogen heterocycles, divalent sulfur, or polyether chains.[10] Superior tolerance is exhibited by some molybdenum alkylidynes of type **3** (X = O, NR^3),[11] which can even be generated in situ by activation of the tris(amido)molybdenum species **4**.[12,13] Despite its outstanding application profile, however, **4** requires careful handling under rigorously inert conditions in an argon atmosphere, as this complex is capable of activating many small molecules, including N_2.[14]

In an attempt to further alkyne metathesis in all its variants, we have aimed at the development of new catalysts that combine the user-friendliness of the original "black-box" recipes with the far superior activity and functional group tolerance of defined metal alkylidynes. Outlined below is such a system, which significantly upgrades the practicality of the method without compromising its application profile.

Inspiration was provided by the discovery that nitride complexes endowed with fluorinated alkoxide ligands, such as **6**, upon treatment with sacrificial alkynes, equilibrate with the corresponding metal alkylidynes **5** (Scheme 1).[15] However, as the preparation of **6** requires the use of azides as well as the manipulation of air-sensitive intermediates, a more convenient starting material was sought. Alcoholysis of complex **9** might provide such an alternative entry point. **9** is safely and conveniently obtained in multigram quantities by heating of cheap sodium molybdate (**7**) with TMSCl in DME and treatment of the resulting crude dioxo species **8** with commercial LiHMDS.[16]

Scheme 1[a]



[a] (top) Known equilibration between metal nitride **6** and alkylidyne **5** (ref 15). (middle and bottom-left) Preparation of the new metathesis precatalysts. Conditions: (a) TMSCl, 1,2-dimethoxyethane (DME), reflux; (b) LiHMDS, hexane, 64% (for two steps); (c) Ph_3SiOH (3 equiv), toluene, 80 °C, then pyridine (5 equiv), 81%. (bottom-right) Structure of complex **11** in the solid state.

Initial attempts to use **9** as a catalyst, however, were unsuccessful. This complex was found to be totally inactive in the model ring-closing alkyne metathesis (RCAM)[17] reaction of **12**, and addition of different fluorinated alcohols to the mixture led to no improvement. Gratifyingly, however, screening of other additives revealed that cheap Ph_3SiOH is uniquely qualified as an ancillary ligand. It provides much better yields of cycloalkyne **13** than any of the other tested silanols,[18,19] phenols, or fluorinated alcohols (for the full list, see the Supporting Information). Whereas a minimum of 1.5 equiv of Ph_3SiOH relative to **9** was necessary to ensure appreciable activity, the use of an excess was uncritical (Table 1).

NMR inspection showed that the $-N(SiMe_3)_2$ unit in **9** is protonated off by the first equivalent of Ph_3SiOH. The exact composition of the mixture upon addition of further equivalents, however, could not be deduced from the spectra because of considerable line broadening caused by rapid ligand-exchange processes. Complex **11** is the only defined species that could be crystallized from such mixtures upon addition of excess pyridine, independent of whether 2 equiv or more of Ph_3SiOH was used.[20] The structure of **11** in the solid state shows the distorted square-pyramidal coordination geometry of this monomeric five-coordinate

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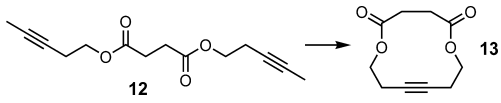
Mo(6+) complex. The Mo≡N bond [1.653(2) Å] is somewhat longer than comparable distances in the less bulky tris(trimethylsilyl) analogue (two independent molecules, 1.615 and 1.638 Å)[21] and near the longer end of reported Mo≡N distances (1.563[22] to 1.688 Å[23]). One of the Mo−O−Si bond angles in **11** is surprisingly obtuse (170.5°), which may be caused by the crowded ligand environment.

Table 1. Optimization of the RCAM Reaction of Diyne **12**[a]

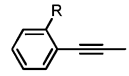
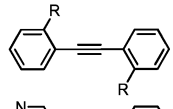
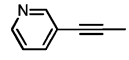
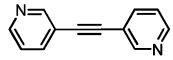
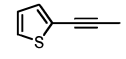
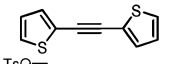
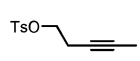
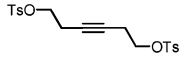


Entry	[Mo]	Additive	Time (h)	Yield[b]
1	**9** (20%)	Ph_3SiOH (80%)	1.2	83%
2	**9** (20%)	Ph_3SiOH (30%)	1.2	81%
3	**9** (20%)	Ph_3SiOH (20%)	1.2	<10%
4	**11** (20%)	−	2	79%
5	**11** (5%)	−	18	74%
6	**11** (2%)	−	65	74%

[a] All reactions were carried out in toluene at 80 °C; small amounts (<5%) of the acyclic and cyclic dimers derived from **12** were also detected in the crude mixtures. [b] Isolated yield.

It is remarkable that the pyridine adduct **11** retains appreciable catalytic activity, comparable to that of the in situ **9**/Ph_3SiOH mixture (Table 1, entries 2 and 4), yet has the advantage of being sufficiently robust to be weighed in air and still provide active catalyst solutions, which is inconceivable with all of the other structurally defined alkyne metathesis precatalysts known to date. Entry 6 shows that 2 mol % of **11** suffice to effect RCAM in good yield, although long reaction times are necessary at this loading. While this result indicates that the pyridine ligand tempers the activity, it also demonstrates a previously unknown long-term stability, which clearly surpasses that of all catalysts previously assayed in our laboratory.

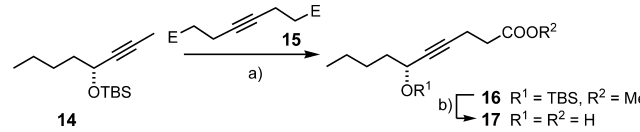
Table 2. Intermolecular Alkyne Metathesis Reactions[a]

Entry	Substrate	Product	Yield
1			R = H (84%/76%[b])
2			R = COOMe (70%)[c]
3			R = OMe (59%)
4			R = SMe (67%)
5			68%[c]
6			61%
7			81%[c]

[a] Unless stated otherwise, all reactions were performed using complex **11** (20 mol %) in toluene at 80 °C. [b] Using 2 mol % **11**. [c] At reflux.

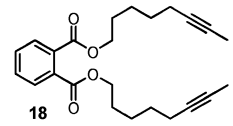
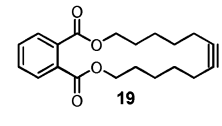
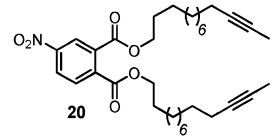
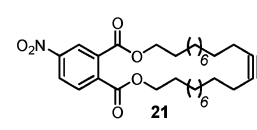
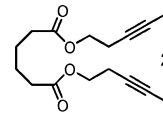
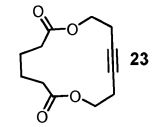
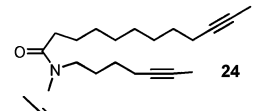
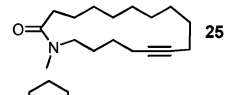
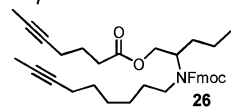
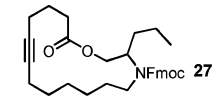
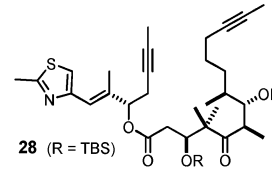
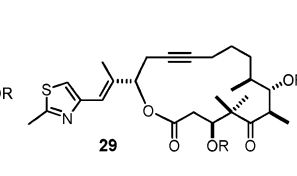
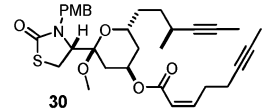
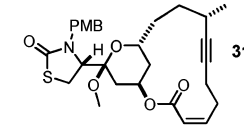
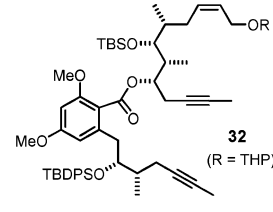
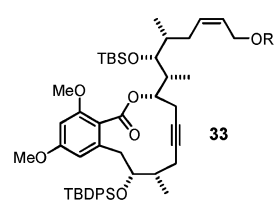
Equally rewarding is the fact that a variety of challenging substrates could successfully be metathesized with this complex (Table 2). The reaction of propynyl benzene was again possible with only 2 mol % **11**. Moreover, this transformation could even be performed in dry air without compromising the yield, although higher loadings were necessary (68 and 79% yield at 10 and 20% loading, respectively); it should be noted that reactions in air are unfeasible when **1**−**4** are used. Complex **11** also enabled the formation of compounds bearing donor sites at the ortho position (entries 2−4), a pyridine derivative (entry 5), the elimination-prone primary sulfonate shown in entry 7, and even sulfur-containing products (entries 4 and 6), which are beyond the reach of the established catalysts **1** and **4**/CH_2Cl_2.[24] Moreover, properly protected secondary propargylic alcohols could be used, though these are also unsuitable for the tungsten catalysts **1** and **2**. This paved the way for the first total synthesis [by alkyne cross-metathesis (ACM)[25]] of gallicynoic acid I (**17**), a secondary metabolite recently isolated from *Coriolopsis gallica* (Scheme 2).[26] Our approach established the previously unknown 6*R* configuration of this compound and proved that propargylic stereocenters are not racemized under the reaction conditions.

Scheme 2[a]



[a] Synthesis of gallicynoic acid I (**17**) by ACM. Conditions: (a) **9** (20 mol %)/Ph_3SiOH (40 mol %), toluene, 80 °C, 76%; (b) (*i*) LiOH, MeOH(aq)/1,4-dioxane; (*ii*) TBAF, THF, 61%. E = COOMe.

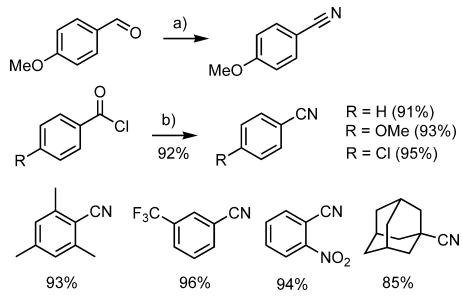
Table 3. RCAM Reactions[a]

Substrate	Product	Yield
		79%
		82%
		87%[b]
		54%[b]
		79%
		61%
		42%
		81% 87%[c] ---[d]

[a] Unless stated otherwise, all reactions were performed using **9** (20 mol %)/Ph_3SiOH (40 mol %) in toluene at 80 °C. [b] Using **11** (20 mol %). [c] Using **4** (10 mol %), toluene/CH_2Cl_2. [d] Using **1** (10 mol %); only −OTHP cleavage was observed (see the text).

A set of RCAM reactions (Table 3) further substantiated the tolerance of the new catalyst system against various functionalities, including the sensitive nitro group. Its performance is best illustrated by several applications to polyfunctional substrates previously used in this laboratory for the total synthesis of bioactive natural products. Specifically, **27** constitutes a precursor for the insect repellent azamacrolide homoepilachnene,[10] whereas Lindlar hydrogenation of **29** paves a stereoselective way to the anticancer agent epothilone A.[12b,27] Notably, the somewhat lower yield (42%) obtained in the cyclization of **30** en route to a fully synthetic latrunculin A analogue corresponds well to the result previously obtained with complex **4** (41%) and likely reflects the ring strain inherent in the resulting meta-bridged bicycle **31**.[28] The most instructive case is the cyclization of diyne **32**, which provides access to the F-ATPase inhibitor cruentaren A.[29] Whereas attempted ring closure with the aid of tungsten alkylidyne **1** resulted only in cleavage of the −OTHP group because of the Lewis acidity of this complex, the established tris(amido)molybdenum precatalyst **4** and the much more convenient new system described herein afforded almost the same yield of the 12-membered cycloalkyne **33**. We therefore conclude that complex **11**, or alternatively, a **9**/2Ph_3SiOH combination, represent cheap, practical, safe, scalable, and exceedingly tolerant precatalysts for all kinds of alkyne metathesis reactions known to date.

Scheme 3[a]



[a] Nitrogen transfer reactions. Conditions: (a) **9**, TMSCl, DABCO (1.1 equiv each), MeCN, microwave, 160 °C, 2 h, 73%; (b) **9** (1 equiv), MeCN, room temperature.

Only a few functional groups have been found to be incompatible. Whereas the fate of epoxides remains unclear, it was noticed that aromatic aldehydes react with **11** and even with its precursor **9** to give the corresponding nitriles (Scheme 3). Although this reaction is stoichiometric, it constitutes a striking example of a formal "redox metathesis" event, wherein the aldehyde is oxidized during the mutual exchange of the multiple-bonded entities.[30] The mechanism of this transformation is currently unknown and the subject of further investigations. Less surprising but highly useful, given the ready availability of **9** from on-sale precursors, is the fact that this complex effectively transforms acid chorides into the corresponding nitriles (rather than amides) at ambient temperature (Scheme 3).[31,32] Further investigations into the scope and limitations of these and related nitrogen transfer processes will be reported in due course.

Acknowledgment. Financial support by the MPG and the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: Large-scale preparation of the catalysts, ligand screening, a table providing a comparison of the different alkyne metathesis catalysts, experimental procedures, spectral data for all compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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