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An Improved Catalyst for Ring-Closing Alkyne Metathesis Based on Molybdenum Hexacarbonyl/2-Fluorophenol

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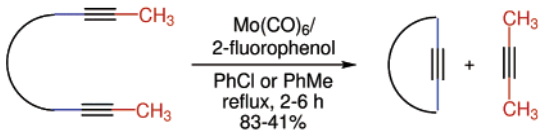
ABSTRACT

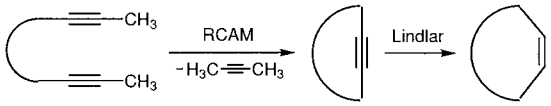


An improved "instant" catalyst for ring-closing alkyne metathesis reaction is described. Catalyst formed in situ from molybdenum hexacarbonyl and 2-fluorophenol can be used without exclusion of air and moisture and shows high activity in metathesis of functionalized diynes. This system allows cyclization of substrates which were incompatible with previously known $Mo(CO)_6$/phenol catalysts.

During recent years, olefin metathesis has gained a position of increasing significance. In particular, ring-closing olefin metathesis (RCM) of dienes provides good access to various carbo- and heterocycles of ring sizes ≥ 5.[1] Among the shortcomings that infringe upon the superb overall application profile of RCM in the synthesis of medium- and macrocyclic products, the lack of control over the stereochemistry of the newly formed double bond is most noteworthy. The products formed are usually obtained as mixtures of the (*E*)- and (*Z*)-isomer. This constitutes a significant drawback in target oriented synthesis, as can be seen from many examples reported in the literature.[2]

To circumvent this problem, Fürstner et al have recently proposed an indirect but stereoselective approach to macrocyclic (*Z*)-alkenes, which comprises a ring-closing metathesis reaction of diynes (RCAM) followed by semireduction of the resulting cycloalkyne product (Scheme 1).[3]

Scheme 1. Stereoselective Synthesis of (*Z*)-Cycloalkenes by Ring-Closing Alkyne Metathesis (RCAM) and Semireduction



Three different catalyst systems have been used so far for this purpose, including (a) a very effective catalyst formed from molybdenum amides $Mo[N(^tBu)(Ar)]_3$ and methylene chloride,[4a] (b) the tungsten alkylidyne complex $(^tBuO)_3W{\equiv}CMe_3$, developed by Schrock,[4b] and (c) a structurally unknown catalyst formed in situ from molybdenum hexacarbonyl and various phenols.[4c,d] Unfortunately, all those systems suffer from either significant instability (a), incompatibility with some functional groups (b), or very low reactivity (c).[5]

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(1) Pertinent reviews: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (d) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037−2056.

(2) This drawback can be clearly seen, for example, from the epothilone case; cf. discussion in refs 3c,g.

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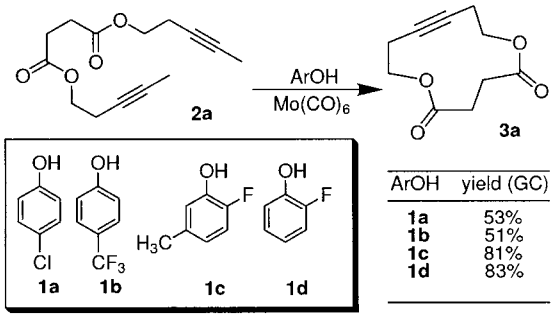
The $Mo(CO)_6$/phenol system has been known since 1974, when Mortreux used a catalyst formed in situ from $Mo(CO)_6$/resorcinol at 160 °C for the cross metathesis of simple disubstituted acetylenes.[4c,d] Later Mori utilized a similar reaction ($Mo(CO)_6$/4-chlorophenol) for the preparation of unsymmetrically substituted alkynes.[6] Bunz et al have shown that removing the alkyne with the lower boiling point (usually 2-butyne) by constant nitrogen purge and using more acidic 4-trifluoromethylphenol improved the reaction protocol.[7] These modified Bunz conditions allow access to high molecular weight poly(*p*-phenylacetylenes) used in light devices such as LEDs and polymer-based lasers.[7a] Although this "instant"[7] system gives satisfactory results in many cases, its scope is in general limited due to harsh conditions: high temperature (130−160 °C) and long reaction time (several hours). For example, the in situ catalyst system, employing $Mo(CO)_6$ and 4-chlorophenol additive, was totally unsuitable for application to the more sensitive substrates, such as prostanoids.[3d]

Even though the molybdenum/phenol-based system is significantly less active than the well-defined catalysts (a and b), it is still attractive because it can be formed in situ from stable off-the-shelf constituents in commercial grade solvents. Although considerable improvements of the $Mo(CO)_6$/phenol system in the cross-metathesis and polymerization of simple acetylenes have been made,[6−8] no one has further optimized this system for more challenging ring-closing alkyne metathesis reactions. Therefore we were prompted to refine this "user friendly" catalyst further in order to extend its scope and to enhance reactivity toward more elaborate and sensitive substrates. We considered that it is reasonable to search for additives having better activating properties than the best ones known: 4-chlorophenol (**1a**) and 4-trifluoromethylphenol (**1b**).

A test RCAM reaction of diyne **2a**, $Mo(CO)_6$ (10 mol %), and phenol (100 mol %) was performed under air, in refluxing reagent-grade chlorobenzene (6 h).[3b] Phenols **1a** and **1b** give moderate yields of the desired cycloalkyne **3a** under these conditions, serving thereby as the calibration point for this investigation (Scheme 2).

Scheme 2. Screening of the Catalytic Activity of Different Phenols in the Cyclization of Diyne **2a**



ArOH	yield (GC)
1a	53%
1b	51%
1c	81%
1d	83%

Our rather naïve assumption that simply increasing the phenol acidity will directly result in a better metathesis catalyst has proved wrong, as neither 2-nitro-4-trifluoromethylphenol nor 2,3,5,6-tetrafluorophenol, nor even perfluorophenol, was active in the test reaction. In line with these observations we have found that although 2- and 4-nitrophenol[8b] are completely inactive, phenols of lower acidity, such as 3-nitrophenol and 4-cyanophenol, form active metathesis catalysts.

In an attempt to understand the structure−activity relationship of an activator better we decided to screen a large library of alcohols, phenols, calixarenes, and chinon-type compounds. As a result we have selected a group of five phenols having better activation properties of $Mo(CO)_6$ than phenols **1a** and **1b**. Among them 2-fluorophenols **1c** and **1d** were the most active, giving a high yield of the cycloalkyne product **3a**.[9]

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(5) For short reviews on alkyne metathesis see ref 1b and: Bunz, U. H. F.; Kloppenburg, L. *Angew. Chem., Int. Ed.* **1999**, *38*, 478−481.

(6) (a) Kaneta, N.; Hirai, T.; Mori, M. *Chem. Lett.* **1995**, 627−628. (b) Kaneta, N.; Hikichi, K.; Asaka, S.; Uemura, M.; Mori, M. *Chem. Lett.* **1995**, 1055−1056.

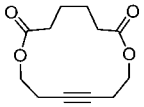
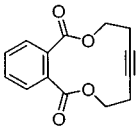
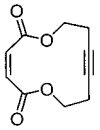
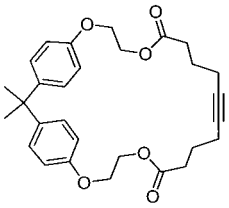
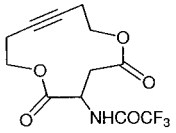
(7) (a) Kloppenburg, L.; Song, D.; Bunz, U. H. F. *J. Am. Chem. Soc.* **1998**, *120*, 7973−7974. (b) Pschirer, N. G.; Bunz, U. H. F. *Tetrahedron Lett.* **1999**, *40*, 2481−2484. (c) Brizius, G.; Pschirer, N. G.; Steffen, W.; Stitzer, K.; zur Loye, H. C.; Bunz, U. H. F. *J. Am. Chem. Soc.* **2000**, *122*, 12435−12440. (d) Bunz, U. H. F. *Acc. Chem. Res.* **2001**, *34*, 998−1010. For examples of RCAM with the Bunz "instant" catalyst, see: (e) Pschirer, N. G.; Fu, W.; Adams, R. D.; Bunz, U. H. F. *Chem. Commun.* **2000**, 87−88. (f) 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*, 3607−3610.

(8) (a) Villemin, D.; Cadiot, P. *Tetrahedron Lett.* **1982**, *23*, 5139−5140. (b) Devarajan, S.; Walton, D. R. M. *J. Organomet. Chem.* **1979**, *181*, 99−104. (c) For application of $Mo(CO)_6$-activator systems under microwave irradiation see: Villemin, D.; Héroux, M.; Blot, V. *Tetrahedron Lett.* **2001**, *42*, 3701−3703 and ref 3f. (d) du Plessis, J. A. K.; Vosloo, H. C. M. *J. Mol. Catal.* **1991**, *65*, 51−54. (e) Vosloo, H. C. M.; du Plessis, J. A. K. *J. Mol. Catal. A: Chem.* **1998**, *133*, 205−211. (f) During preparation of this manuscript another notable example of optimization of the $Mo(CO)_6$/4-chlorophenol system has been reported: Brizius, G.; Bunz, U. H. F. *Org. Lett.* **2002**, *4*, 2829−2831.

(9) The "instant" system formed from 2-fluorophenol catalyzes the RCAM transformation even in lower boiling solvents such as toluene (**3a**: 64% of yield, 6 h) and dichloroethane (26%). However, from the preparative point of view chlorobenzene was found to be superior with regard to higher conversions and shorter reaction times (cf. also Table 1, entry b). *Ring-closing alkyne metathesis*: A solution of diyne **2a**−**g** (0.4 mmol), $Mo(CO)_6$ (5−10 mg, 0.04−0.02 mmol, 5−10 mol %), and 2-fluorophenol (45 mg, 0.4 mmol) in chlorobenzene (20 mL) was refluxed for 2−6 h, using an electric heating mantle. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (*c*-hexane/ethyl acetate 4:1) to give alkyne **3a**−**g**. *Alkyne **3e***: colorless solid. MS (EI) *m*/*z* (rel intensity, %) 478 ([$M^{+\bullet}$], 28), 463 (28), 165 (9), 152 (11), 99 (100), 55 (9), 43 (17); IR (KBr, cm^{-1}) 2969 (m), 1726 (s), 1607 (m), 1511 (m), 1456

The "instant" catalyst formed from 2-fluorophenol was then tested for activity by using representative substrates for alkyne ring-closing metathesis (Table 1). Gratifyingly, our

Table 1. Comparison of the Catalyst Systems for RCAM[c]

entry	product **3**	yield; time[a]
b		**A**: 83%; 3 h (36%; 6 h)[b] **C**: 73%
c		**A**: 50%; 6 h **B**: 0%
d		**A**: 56%; 3 h **B**: 0%
e		**A**: 61%; 6 h
f		**A**: 41%; 6 h

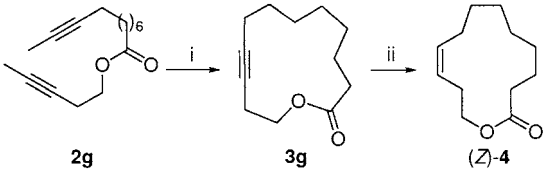
[a] Isolated yields after silica gel chromatography. [b] The reaction was carried out in refluxing benzene. [c] A = $Mo(CO)_6$ (5 mol %)/2-fluorophenol, PhCl, reflux, 3−6 h; B = $Mo(CO)_6$ (5 mol %)/4-chlorophenol, PhCl, reflux (ref 3b); and C = $(^tBuO)_3W{\equiv}CMe_3$, PhCl, 80 °C (ref 3b).

improved system turned out to catalyze the RCAM very efficiently, allowing us to prepare different cycloalkynes (**2b**−**g**) of ring sizes ≥12 in yields generally better than those previously reported for the 4-chlorophenol system.[3b] Moreover, catalyst formed from **1d** converts diynes previously *found to be incompatible* with $Mo(CO)_6$/phenol systems, such as **2c**, **2d** (Table 1, entries c and d), or secondary amides (entry f).[3b] We were also pleased to see that substrates possessing rather sensitive DIAN−ether linkages (entry e) and aspargic acid derivative (entry f) were cyclized successfully.

The facts that (i) the reactive catalyst can be formed from inexpensive 2-fluorophenol *in an open reaction flask under an atmosphere of air* by using commercially available reagent-grade chlorobenzene, (ii) during the course of metathesis reaction *no inert gas purging/bubbling is necessary*,[10] and (iii) in most cases the metathesis requires *shorter reaction times*, as compared with previously known $Mo(CO)_6$ systems constitute a particularly appealing facet of this improved system.

The higher reactivity of the 2-fluorophenol-based system can be clearly seen from the stereoselective synthesis of yuzu lactone **4**, the minty, camphor-like odored macrolide isolated from the flesh and peel of the Japanese citrus tree *Citrus junos* Tanaka (Yuzu).[11] It has been reported by Fürstner[3b] that the RCAM reaction of diyne **2g** and subsequent Lindlar reduction deliver this olfactory product in a highly stereoselective manner (Scheme 3). The cyclization with $Mo(CO)_6$/

Scheme 3. Optimized Synthesis of Yuzu Lactone **4**[a]



[a] Key: (i) $Mo(CO)_6$, 2-fluorophenol, PhCl, reflux, 2 h, 79% (or $Mo(CO)_6$, 4-chlorophenol, PhCl, reflux, overnight, 62%, ref 3b); (ii) Lindlar catalyst, quinoline, H_2 (1 atm), hexanes, 98% (ref 3b).

4-chlorophenol proceeds in good yield but requires prolonged reaction time (overnight, 62% of yield).[3b] As we checked, treatment of the same substrate with our 2-fluorophenol-based system provides the key intermediate **3g** in even better yield after significantly shorter reaction time (2 h, 79%).

In conclusion, we have shown that the "instant" catalyst for alkyne metathesis still can be significantly improved by careful selection of the activator. The application of 2-fluorophenol leads to catalyst that is not only easier to use but also more reactive. This system allows cyclization of substrates that were incompatible with previously known $Mo(CO)_6$/phenol catalysts. Experiments to fully determine the scope and limitations of this catalyst are under way.

Acknowledgment. This work was supported by the Volkswagen Foundation (Grant I/77 592). We wish to thank Dr. Andrzej Kwast for numerous GC measurements, which speeded up our work considerably, as well as Mr. Mariusz Tryznowski for preparation of diynes **2c**−**e**.

Supporting Information Available: Experimental procedures and characterization data for cycloalkynes **3a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(m), 1297 (s), 1246−1234 (s), 1060 (m); HRMS (EI) ($C_{29}H_{34}O_6$; $M^{+\bullet}$) calcd 478.2355, found 478.2368. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 156.6, 143.7, 127.4, 114.8, 79.5, 66.6, 63.3, 41.4, 33.0, 30.3,24.2, 18.0. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.63−1.71 (4H, m), 1.66 (6H, s), 2.05−2.09 (4H, m), 2.26 (4H, t, J = 7.1 Hz), 4.22−4.24 (4H, AA′XX′), 4.38−4.4 (4H, AA′XX′), 6.80−6.84 (4H, AA′XX′), 7.08−7.12 (4H, AA′XX′).

(10) Although it is known that the $Mo(CO)_6$-phenol systems are generally air stable, most authors routinely apply this chemistry under protective atmosphere of inert gas (for example cf. refs 3f, 3b, and 8f).

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