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A Fine-Tuned Molybdenum Hexacarbonyl/Phenol Initiator for Alkyne Metathesis

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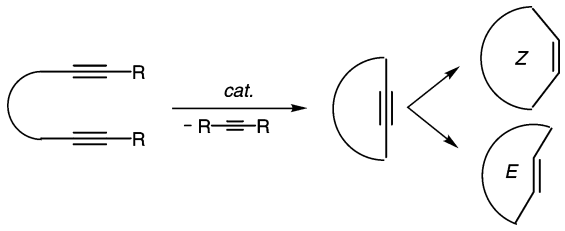
Abstract: A new, highly potent activator for molybdenum hexacarbonyl and 2-fluorophenol is described. An "instant" catalyst formed in situ from molybdenum hexacarbonyl and 2-fluorophenol shows high activity for cross- and ring-closing alkyne metathesis reaction. The use of 2-fluorophenol can be combined with other activation methods to allow alkyne metathesis at relatively low temperature (80 °C).

One of the most intensively studied and applied transformations in organic chemistry of the past decade is the transition-metal-catalyzed olefin metathesis. Several reviews covering this area of research have been published recently.[1] However, one disadvantage of *alkene metathesis* is that mixtures of (*E*)- and (*Z*)-C=C isomers are typically obtained. This constitutes a significant drawback in target oriented synthesis, as can be seen from many examples reported in the literature.[2] For this and other reasons, increasing attention is being focused on the sister reaction: *alkyne metathesis*.[3] Fürstner et al.[4] have recently shown that this transformation can serve as an indirect but fully stereoselective solution to this problem, since, the resulting C≡C bond can be stereoselectively reduced to either the (*E*)- or the (*Z*)-isomer (Scheme 1)[5] or transformed to the other functionality.[6]

Although some applications of this transformation in the synthesis of organic[7] and organometallic compounds[8] and in materials science[9] are very promising, alkyne metathesis in general is still in its infancy as compared with alkene metathesis. The envisaged extension of this methodology requires developing improved, more stable, and active catalysts.

SCHEME 1. Stereoselective Synthesis of (*E*) and (*Z*)-C=C Isomers by Alkyne Metathesis and Semireduction



Four different catalysts systems have been used so far for this purpose, including (a) a structurally unknown catalyst formed in situ from molybdenum hexacarbonyl and various phenols (Mortreux[10] or "instant"[9] catalyst); (b) the tungsten alkylidyne complex (*t*-BuO)$_3$W≡C-*t*-Bu, developed by Schrock;[11] (c) highly active species prepared by Fürstner[12] from Cummins' molybdenum amides[13] [Ar(ᵗBu)N]$_3$Mo and methylene chloride; (d) molybdenum-(VI) alkylidynes RC≡Mo(OAr)$_3$ synthesized recently by Moore[14] and Cummins.[15]

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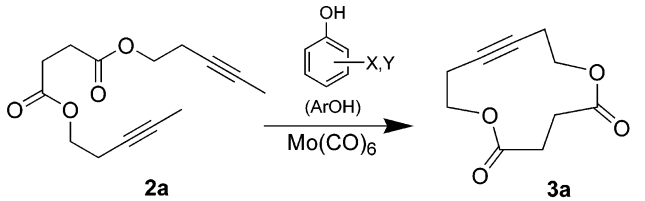
Even though the ill-defined molybdenum/phenol-based system (a) is significantly less active than the well-defined catalysts (b−d), it is still attractive because it can be formed in situ from stable and cheap off-the-shelf constituents and used in commercially grade solvents. Therefore, we were prompted to refine this "user-friendly" catalyst further in order to extend its scope and to enhance reactivity toward more elaborate and sensitive substrates. In a preliminary communication, we reported the use of the $Mo(CO)_6$/2-fluorophenol system as a catalysts for ring-closing alkyne metathesis (RCAM).[16] In this paper, systematic studies on the preparation and application of this "instant" catalyst in several alkyne cross-metathesis (ACM), homometathesis (HM), and ring-closing (RACM) reactions are reported.

The $Mo(CO)_6$/phenol system has been known since 1974, when Mortreux used catalyst formed in situ from $Mo(CO)_6$/resorcinol at 160 °C for the cross-metathesis of simple disubstituted acetylenes.[10] Later, Mori utilized a similar reaction ($Mo(CO)_6$/4-chlorophenol) for the preparation of unsymmetrically substituted alkynes.[17] 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 catalyst significantly.[9c−f] Although these subsequently refined[18] systems give satisfactory results in many cases, its scope is in general limited due to harsh conditions: high temperature (130−160 °C) and long reaction time. 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.[7b]

During the course of the present work, further important improvement has been published by Brizius and Bunz.[19] In this method, preheated mixture of $Mo(CO)_6$/4-chlorophenol/3-hexyne was used as a catalyst at 130 °C, allowing transformations that were not possible with classical Mortreux system. Similar preactivation principle, consisting of the separation of the reaction into two consecutive steps, namely (i) precatalyst generation at high temperature and (ii) metathesis reaction at low temperature, has been recently introduced by Lavigne et al.[20] Using this new catalyst, generated by heating of a mixture of $Mo(CO)_6$/4-chlorophenol/1,2-diphenoxyethane at 135 °C, it was possible to lower the metathesis temperature to 50 °C. Although such considerable improvements of the $Mo(CO)_6$/phenol system have been made,[17,19,20] we considered that it is still reasonable to search for phenolic additives having better activating properties than the best ones known: 4-trifluoromethylphenol and 4-chlorophenol.

SCHEME 2. Screening of the Catalytic Activity of Selected Phenols in the Cyclization of Diyne 2a[a]



ArOH[b]				
1a (4.08)	**1b** (5.23)	**1c** (5.45)	**1d** (5.50)	**1e** (6.25)
2,3,5,6-F_4-4-CF_3	2-NO_2-4-CF_3	2,3,5,6-F_4	2,3,4,5,6-F_5	4-$SO_2C_4F_9$
0 (0)	dec. (0)	0 (0)	0 (0)	dec. (0)
1f (6.92)	**1g** (7.14)	**1h** (7.22)	**1i** (7.96)	**1j** (8.04)
2,6-Br_2-4-F	2-NO_2	4-NO_2	3,5-$(CF_3)_2$	2,4-Cl_2
dec. (0)	0 (0)	0 (0)	30 (25)	45 (33)
1k (8.31)	**1l** (8.33)	**1m** (8.50)	**1n** (8.51)	**1o** (8.55)
4-CO_2CH_3	3-NO_2	2-Cl	4-CF_3	3,4-Cl_2
45 (13)	45 (23)	64 (28)	80 (51)	90 (69)
1p (8.71)	**1q** (8.82)	**1r** (9.47)	**1s** (9.92)	**1t** (10.65)
2-F	2-F-5-CH_3	4-Cl	4-F	2,6-$(CH_3)_2$
95 (83)	94 (81)	83 (53)	60 (15)	0 (0)

[a] Key: (a) $Mo(CO)_6$ (10 mol %), ArOH, PhCl, reflux, 6 h; (b) phenol (calculated pK_a),[21] X, Y, GC conversion, % (GC yield, %).

Test RCAM reaction of diyne **2a**, $Mo(CO)_6$ (10 mol %), and phenolic activators (100 mol %) was performed under air, in refluxing reagent-grade chlorobenzene (6 h). 4-Chloro- and 4-trifluoromethylphenol give under these conditions moderate yields of the desired cycloalkyne **3a**, serving thereby as the calibration point for this investigation (Scheme 2). After screening various alcohols, phenols, calixarenes, and chinon-type compounds, we selected a library of 10 phenols that gives conversions ≥30% in the model transformation (Scheme 2). Our rather naive assumption that simply increasing the phenol acidity will directly result in a better metathesis catalyst has proved wrong, as neither 4-trifluoro-3,4,5,6-tetrafluorophenol (**1a**), 2-nitro-4-trifluoromethylphenol (**1b**), 2,3,5,6-tetrafluorophenol (**1c**), nor even pentafluorophenol (**1d**) were active in the test reaction. In line with these observations, we have found that although 2- and 4-nitrophenols (calculated[21] pK_a ≤ 7.22) are completely inactive, phenols of lower acidity, such as 3-nitrophenol (**1l**, pK_a 8.33) and **1k** (pK_a 8.31), form active metathesis catalyst. On the other end of the scale, resorcinol, 2,5-dimethyl- or 2,5-di-*tert*-butylphenol, calix[4]- and calix[6]arenes, and alcohols (*t*-BuOH, $(CF_3)_2C(Me)OH$ and $(CF_3)_2C(Ph)OH$) failed completely to activate for alkyne metathesis.[18b]

This indicates that the optimal phenol acidity is one of the most crucial factors for a catalyst activity. The calculated pK_a values of the best seven phenols (**1k**−**q**) selected by us were in the range of 8−9, fitting well with the calculated pK_a of the known best activators (**1n**, pK_a 8.51 and **1r**, 9.47). The 2-fluorophenols **1p** (pK_a 8.71) and

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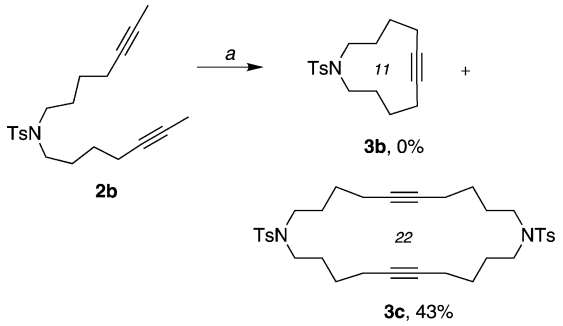
(21) All acid−base ionization constants (pK_a values) calculations were performed using ACD/pK_a program for 25 °C and zero ionic strength in aqueous solutions (Advanced Chemistry Development, Inc., 90 Adelaide Street West, Suite 600 Toronto, Ontario M5H 3V9, Canada).

SCHEME 3. Cyclization of Diyne 2b[a]



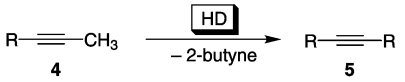
[a] Isolated yield. Conditions: (a) $Mo(CO)_6$ (10 mol %), 2-fluorophenol, PhCl, reflux, 2 h.

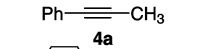
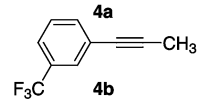
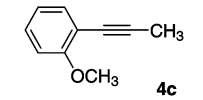
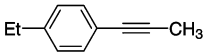
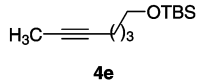
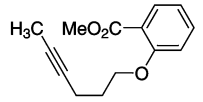
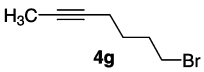
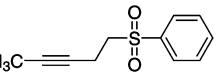
1q (8.82) were the most active, as witnessed by the high conversion and the yield of the cycloalkyne product **3a**.[22] It has been proposed by Bunz[9c] and Schrock[23] that the active species in the Mortreux system are molybdenum(VI) alkylidyne complexes ($RC{\equiv}Mo(OAr)_3$), formed in situ via phenol-induced decarbonylation and oxidation of $Mo(CO)_6$. Therefore, the spectacular enhancement of the catalytic performance observed in the case of **1p** and **1q** could be rationalized in terms of reducing the decarbonylation time of $Mo(CO)_6$. An interaction of the fluoride atom of **1p** with the coordination sphere of molybdenum, proposed by Lavigne,[20] constitutes another reasonable explanation.

Ring-Closing Alkyne Metathesis. The application of the "instant" catalyst formed from 2-fluorophenol has been published previously.[16] Gratifyingly, our improved system turned out to catalyze the RCAM very efficiently, allowing us to prepare different cycloalkynes of ring sizes ≥12 in yields generally better than those previously reported for 4-chlorophenol system.[16] However, cyclization of diyne **2b**, a model precursor in the synthesis of the keramaphidin C and related alkaloids[25] afforded exclusively only the cyclodimeric product **3c**. This result can be explained in view of the high ring strain of the 11-membered cycloalkyne **3b** (Scheme 3).[26]

Metathesis Homodimerization. The scope and compatibility of the new procedure were tested using an alkyne homodimerization reaction (Table 1). Whereas the traditional protocol for alkyne metathesis using $Mo(CO)_6$/4-chlorophenol performed rather poorly or even failed completely (Table 2, entries b and c; catalyst E)[27] our 2-fluorophenol-based system was able to convert various 2-propyne derivatives into the desired products in good yields in all but one case. More importantly, we have found that the activating effects of the newly developed protocols[16,19,20] are fully additive: the catalyst B prepared by mixing $Mo(CO)_6$, 2-fluorophenol (1 equiv), and sacrificial 3-hexyne[19] shows higher activity than the parent $Mo(CO)_6$/2-fluorophenol system (Table 2, entries b, c; catalyst B). Similarly, addition of a chelating 1,2-diphenoxyethane[20] to that system amplifies its catalytic potential even higher (Table 2, entries f, g; catalyst C). It should be noted that in these cases no separate preheating in a high-pressure tube[19] is required, and catalysts B and C can be conveniently prepared in situ by mixing the required components ($Mo(CO)_6$, 2-fluorophenol, 3-hexyne, and 1,2-diphenoxyethane) in the presence of substrate(s).

TABLE 1. Comparison of Homodimerization (HD) Reactions of Substituted Acetylene Derivatives Promoted by Different Catalyst Systems[a]



entry	substrate **4**	catalyst; yield (%); time[a]
a	 **4a**	**A**; 69 (89); 15 min
b	 **4b**	**A**; 43; 1 h **B**; 54; 1 h [**D**; 59, **E**; 14][b]
c	 **4c**	**A**; 71 (75); 1 h **B**; (96); 1 h [**D**; 68, **E**; 0][b]
d	 **4d**	**B**; 51; 30 min
e	 **4e**	**A**; (82); 1 h
f	 **4f**	**A**; 45; 3 h **B**; 48; 3 h **C**; 63; 3 h
g	 **4g**	**A**; 0; 3 h **C**; 74 (78); 1 h
h	 **4h**	**A**; 0; 3 h **C**; 0; 3 h

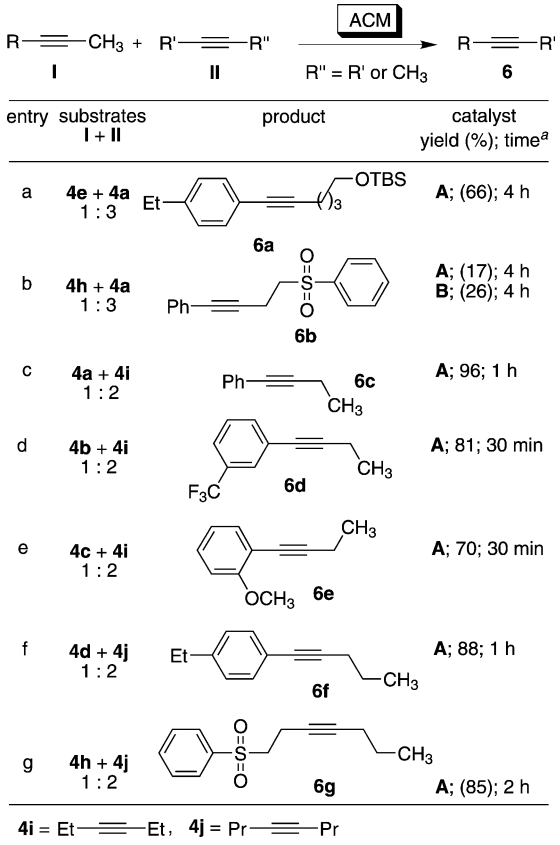
[a] Isolated yields after silica gel chromatography. GC conversions are shown in parentheses. Catalysts: A = $Mo(CO)_6$ (5 mol %), 2-fluorophenol (1 equiv), PhCl, reflux; B = $Mo(CO)_6$ (5 mol %), 2-fluorophenol (1 equiv), 3-hexyne (5 mol %), PhCl, reflux; C = $Mo(CO)_6$ (5 mol %), 2-fluorophenol (1 equiv), 3-hexyne (5 mol %), 1,2-diphenoxyethane (5 mol %), PhCl, reflux; D = Mo[N(*t*-Bu)(3,5-dimethylphenyl)]$_3$ (5 mol %), CH_2Cl_2, toluene, 80 °C; E = $Mo(CO)_6$ (5 mol %), 4-chlorophenol (0.3 equiv), 1,2-dichlorobenzene, 140 °C. [b] Reference 27.

Alkyne Cross-Metathesis (ACM). A set of substrates (**I**) was then subjected to alkyne cross-metathesis (Table 3). The unsymmetrical (entries a, b) or symmetrical (entries c−g) cross-metathesis partners (**II**) were used in an excess (2−3 equiv) to secure good selectivity for cross metathesis over homodimerization of **I** and good yields of the products **6a**,**c**−**g**.

Next, we decided to check if terminal or C-silylated alkynes are compatible with our catalytic system. The successful ACM reactions of C-silylated substrates, such as **4k** have been described recently.[19,27] Therefore, we

(22) See the Supporting Information for experimental details.
(23) Listemann, M. L.; Schrock, R. R. *Organometallics* **1985**, *4*, 74−83.
(24) Rodefeld, L.; Tochtermann, W. *Tetrahedron* **1998**, *54*, 5893−5896.
(25) (a) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *54*, 6201−6258. (b) Note that approach for keramaphidin C and manzamine C based on conventional diene RCM, though efficient in chemical terms, mainly afforded the unnatural (*E*)-isomer, see: Arisawa, M.; Kato, C.; Kaneko, H.; Nishida, A.; Nakagawa, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1873−1876.
(26) For a similar example, see ref 7f.
(27) Fürstner, A.; Mathes, C. *Org. Lett.* **2001**, *3*, 221−223.

TABLE 2. ACM of Substrates 4a−h with Symmetrical and Unsymmetrical Alkynes



entry	substrates I + II	product	catalyst yield (%); time[a]
a	**4e** + **4a** 1 : 3	**6a**	**A**; (66); 4 h
b	**4h** + **4a** 1 : 3	**6b**	**A**; (17); 4 h **B**; (26); 4 h
c	**4a** + **4i** 1 : 2	**6c**	**A**; 96; 1 h
d	**4b** + **4i** 1 : 2	**6d**	**A**; 81; 30 min
e	**4c** + **4i** 1 : 2	**6e**	**A**; 70; 30 min
f	**4d** + **4j** 1 : 2	**6f**	**A**; 88; 1 h
g	**4h** + **4j** 1 : 2	**6g**	**A**; (85); 2 h

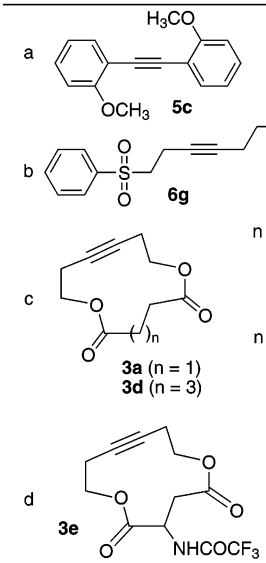
[a] Isolated yields after silica gel chromatography. GC conversions are shown in parentheses. Catalysts: A = $Mo(CO)_6$ (5 mol %), 2-fluorophenol (1 equiv), PhCl, reflux; B = $Mo(CO)_6$ (5 mol %), 2-fluorophenol (1 equiv), 3-hexyne (5 mol %), PhCl, reflux.

were not surprised to find that **4k** undergoes ACM with 3-hexyne to afford the desired cross-metathesis product **6c** (Scheme 4). To the best of our knowledge, terminal alkynes are not amenable to productive metathesis with any of so far known catalysts;[3] in fact, compound **4l** did not undergo metathesis at all on exposure to $Mo(CO)_6$/2-fluorophenol. The only products isolated under these conditions were 1,2,4- and 1,3,5-triphenylbenzenes **7** (Scheme 4).

Finally, some ACM and RCAM reactions were conduced in various solvents at lower temperatures (110−80 °C). We have found that while in the case of the catalyst system A the lowering of the temperature has visibly negative effect on reaction conversions, the catalyst C, prepared by mixing $Mo(CO)_6$, 2-fluorophenol (1 equiv), sacrificial 3-hexyne,[19] and 1,2-diphenoxyethane[20] performs well even at lower temperature (80 °C, Table 3). However, this highly active four-component system was not effective at room temperature (20 °C).

In conclusion, we have shown that the "instant" catalyst for alkyne metathesis can be still significantly improved by careful selection of an activator. The use of 2-fluorophenol can be combined with other activation methods to allow alkyne metathesis at relatively low temperature (80 °C). Applications of this catalyst in target-oriented syntheses are underway.

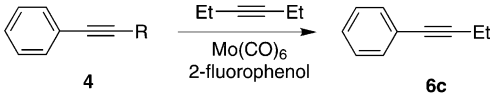
TABLE 3. ACM and RCAM Reactions at Lower Temperatures



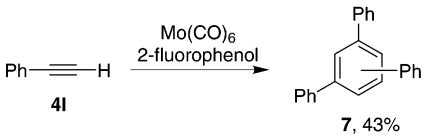
entry	product	catalyst, temp. (°C) (solvent); time	yield (%)[a]
a	**5c**	**C**, 135 (PhCl); 1 h	(88)
		C, 110 (PhMe); 1.5 h	(99)
		C, 84 (DCE); 2 h	(67)
		C, 84 (DCE); 7 h	(92)
b	**6g**	**A**, 135 (PhCl); 2 h	(85)
		C, 84 (DCE); 8 h	73
c	**3a** (n = 1) **3d** (n = 3)	n = 1 **A**, 135 (PhCl); 3 h	(83)
		A, 111 (PhMe); 6 h	(64)
		A, 84 (DCE); 6 h	(26)
		n = 3 **A**, 135 (PhCl); 3 h	83
		A, 84 (C_6H_6); 6 h	(36)
		C, 84 (DCE); 16 h	82
d	**3e**	**A**, 135 (PhCl); 6 h	41
		C, 84 (DCE); 20 h	49

[a] Isolated yields after silica gel chromatography. GC conversions are shown in parentheses. Catalysts: A = $Mo(CO)_6$ (5 mol %), 2-fluorophenol (1 equiv); C = $Mo(CO)_6$ (5 mol %), 2-fluorophenol (1 equiv), 3-hexyne (5 mol %), 1,2-diphenoxyethane (5 mol %).

SCHEME 4. Metathesis of C-Methylated, C-Silylated, and Terminal Alkynes Catalyzed by $Mo(CO)_6$/2-Fluorophenol[a]



entry	**4**, R	yield (%); time[a]
a	**4a**, CH_3	96; 1 h
b	**4k**, $SiMe_3$	(68); 2 h



[a] Isolated yields after silica gel chromatography. GC conversions are shown in parentheses. ACM conditions: 3-hexyne (2 equiv), $Mo(CO)_6$ (5 mol %), 2-fluorophenol (1 equiv), PhCl, reflux. HD conditions: $Mo(CO)_6$ (5 mol %), 2-fluorophenol (1 equiv), PhCl, reflux, 6 h.

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Supporting Information Available: Full experimental procedures, NMR spectra, and characterization data for cycloalkynes **3** and alkynes **5** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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