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Alkyne Cross Metathesis Reactions of Extended Scope

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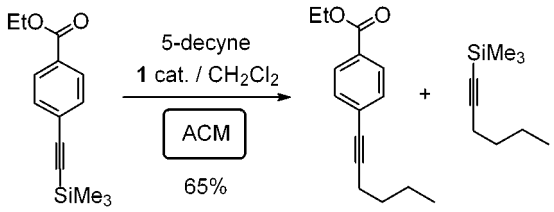
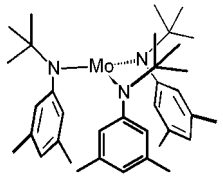
ABSTRACT



A catalyst formed in situ from Mo[N(*t*-Bu)(Ar)]$_3$ 1 (Ar = 3,5-dimethylphenyl) and CH_2Cl_2 in toluene effects cross metathesis reactions of functionalized alkynes that are beyond reach of more traditional promotors. An application to the synthesis of prostaglandin E_2 (PGE_2) 19 and the acetylated PGE derivative 18b shows the compatibility of this method with sensitive substrates.

As compared with the metathesis of alkenes that has seen a prolific growth during the past decade,[1] metathesis of alkynes is still in its infancy. Only recently it has been shown that this transformation holds great promise for advanced organic synthesis and polymer chemistry. In particular, various applications to ring-closing alkyne metathesis,[2−4] alkyne homodimerization,[5] cyclooligomerization,[6] or polymerization reactions[7] display a remarkably wide scope. A largely unexplored field of application, however, is alkyne cross metathesis (ACM). The very limited number of successful examples reported in the literature[8] rely on a structurally unknown catalyst formed in situ from $Mo(CO)_6$ and phenol additives; though optimized by Bunz,[9d] this system requires rather harsh conditions (130−140 °C)[9] that preclude applications to elaborate and highly functionalized substrates.

Therefore we were prompted to investigate if more efficient catalysts upgrade the profile of this particular transformation. Most promising is the molybdenum complex Mo[N(*t*-Bu)(Ar)]$_3$ **1** (Ar = 3,5-dimethylphenyl) activated in situ by CH_2Cl_2,[3,10] because this reagent combination performs particularly well in macrocyclization reactions.[3,4]



1

The superiority of **1**/CH_2Cl_2 is evident from the homodimerization and prototype cross metathesis reactions compiled in Table 1. It is remarkable that substrates bearing electron-donating or electron-withdrawing substitutents are converted with similar ease. Note that alkynes **3**−**8** es-

(1) Recent reviews: (a) Fürstner, A. *Angew. Chem.* **2000**, *112*, 3140; *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (d) Fürstner, A. *Top. Catal.* **1997**, *4*, 285.

(2) Fürstner, A.; Seidel, G. *Angew. Chem.* **1998**, *110*, 1758; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1734.

(3) Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 9453.

(4) (a) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108. (b) Fürstner, A.; Grela, K. *Angew. Chem.* **2000**, *112*, 1292; *Angew. Chem., Int. Ed.* **2000**, *39*, 1234. (c) Fürstner, A.; Rumbo, A. *J. Org. Chem.* **2000**, *65*, 2608. (d) Fürstner, A.; Seidel, G. *J. Organomet. Chem.* **2000**, *606*, 75. (e) Fürstner, A.; Radkowski, K.; Grabowski, J.; Wirtz, C.; Mynott, R. *J. Org. Chem.* **2000**, *65*, 8758.

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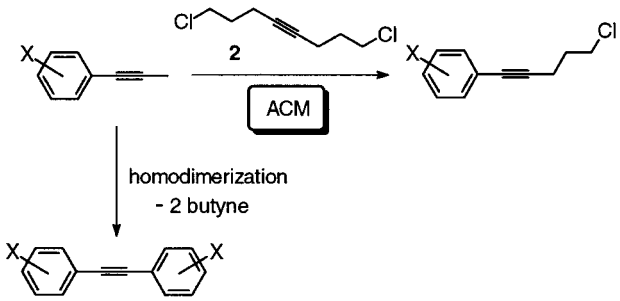
Table 1. Comparison of Homodimerization and Alkyne Cross Metathesis Reactions of Substituted Propynyl Benzene Derivatives Promoted by Two Different Catalyst Systems



substrate		homodimerization		ACM
		1[a]	$Mo(CO)_6$[b]	1[a]
F_3C	**3**	59	14	70
NC	**4**	58	15	70
OMe	**5**	68	0	67
COOMe	**6**	76	0	62
O, H	**7**	46	0	47
S	**8**	0	0	55

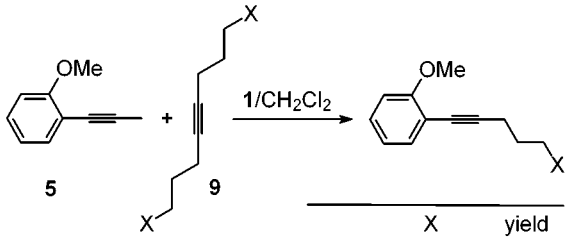
[a] Activated in situ with CH_2Cl_2 in toluene at 80°C; [b] Activated in situ with p-chlorophenol (30 mol%) in 1,2-dichlorobenzene at 140°C, *cf.* ref. 9d.

sentially fail to react or decompose in the presence of the traditional promotor system $Mo(CO)_6$/*p*-chlorophenol.[9d]

The generality of ACM catalyzed by **1**/CH_2Cl_2 is further illustrated by Scheme 1 compiling reactions of substrate **5** with differently functionalized symmetrical alkynes **9a**−**d**. The yields obtained and the selectivity for cross metathesis over homodimerization of **5** are excellent in all cases. ACM even remains the largely preferred pathway if a 1:1 mixture of propynyl benzene **11** and the nonsymmetrical alkyne **12** is exposed to **1**/CH_2Cl_2 (Scheme 2); homodimerization of the individual substrates does not seriously compete under these conditions (only 9% of tolane derived from **11** are formed).

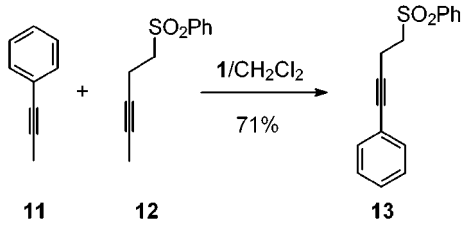
The ACM reactions compiled in Scheme 3 deserve particular mention. Terminal alkynes or C-silylated alkynes are not amenable to productive metathesis so far; in fact, compound **14a** (X = H) does not homodimerize at all on exposure to **1**/CH_2Cl_2 under standard reaction conditions.

Scheme 1. ACM of Substrate **5** with a Set of Symmetrical Alkynes **9a**−**d** (1.5 equiv) Catalyzed by **1** (10 mol %)/CH_2Cl_2 in Toluene at 80 °C

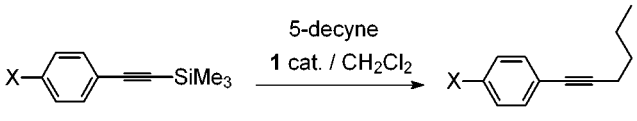


	X	yield
10a	Me	72%
b	Cl	67%
c	CN	82%
d	CH_2OTHP	68%

Scheme 2. ACM of Two Non-Symmetrical Alkynes (1 equiv each) Catalyzed by **1** (10 mol %)/CH_2Cl_2 in Toluene at 80 °C



Scheme 3. ACM of C-Silylated Alkynes with 5-Decyne (1.5 equiv) Catalyzed by **1** (10 mol %)/CH_2Cl_2 in Toluene at 80 °C



	X	yield
15a	H	55%
b	OMe	60%
c	COOEt	65%

(8) A few prototype ACM reactions of simple substrates catalyzed by $Mo(CO)_6$ in the presence of phenol additives have been reported: (a) Mortreux, A.; Delgrange, J. C.; Blanchard, M.; Lubochinsky, B. *J. Mol. Catal*. **1977**, *2*, 73. (b) Kaneta, N.; Hikichi, K.; Asaka, S.−I.; Uemura, M.; Mori, M. *Chem. Lett*. **1995**, 1055. (c) A single example of an ACM reaction using a defined tungsten alkylidyne catalyst was described by Schrock et al. without specifying the yield obtained; cf.: Sancho, J.; Schrock, R. R. *J. Mol. Catal*. **1982**, *15*, 75.

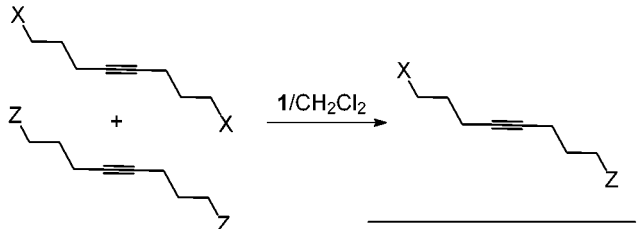
(9) (a) Mortreux, A.; Blanchard, M. *J. Chem. Soc., Chem. Commun*. **1974**, 786. (b) Villemin, D.; Cadiot, P. *Tetrahedron Lett*. **1982**, *23*, 5139. (c) Kaneta, N.; Hirai, T.; Mori, M. *Chem. Lett*. **1995**, 627. (d) Pschirer, N. G.; Bunz, U. H. F. *Tetrahedron Lett*. **1999**, *40*, 2481.

(10) (a) For an excellent review on the preparation of **1** and its reactions with small inorganic molecules, see: Cummins, C. C. *Chem. Commun*. **1998**, 1777. (b) Laplaza, C. E.; Odom, A. L.; Davis, W. M.; Cummins, C. C.; Protasiewicz, J. D. *J. Am. Chem. Soc*. **1995**, *117*, 4999 and literature cited therein.

Therefore we were surprised to find that this and related substrates undergo smooth ACM with 5-decyne to afford the desired cross metathesis products **15a**−**c** in respectable yields. To the best of our knowledge, these are the first examples of metathesis reactions involving C-silylated starting materials.

ACM of alkynes bearing only alkyl substitutents on the triple bond can also be carried out, although they were found to be slightly less efficient. This is evident from the "scrambling" processes depicted in Scheme 4.[11] They are,

Scheme 4. Scrambling of Functionalized Alkynes Catalyzed by **1** (5 mol %)/CH_2Cl_2 in Toluene at 80 °C[11]

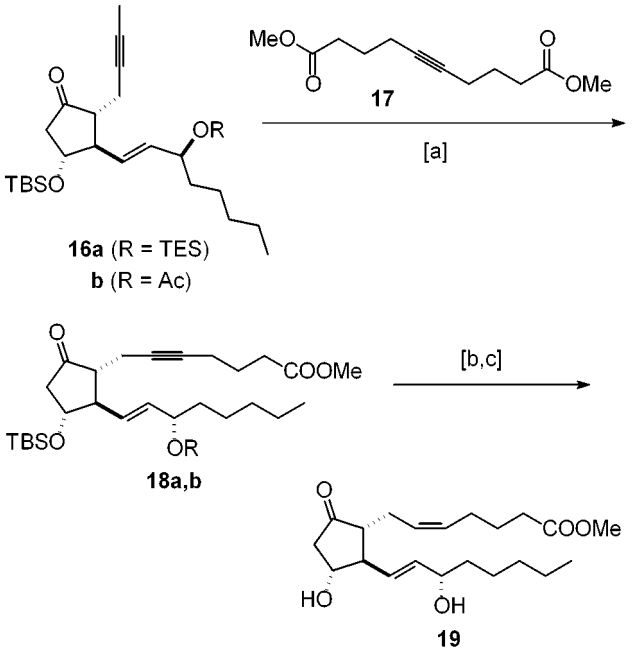


X	Z	yield
CN	CH_2OTHP	55%
Cl	CN	48%

however, synthetically useful if one of the reaction partners is readily available and can be used in slight excess.

This possibility is illustrated by an application to the synthesis of prostaglandin E_2 **19** and the 15-*O*-acetylated PGE_2 derivative **18b** (R = Ac) (Scheme 5). Thus, reaction of compound **16a** (R = TES) bearing a 2-butynyl group as a truncated α-side chain[12] with an excess of alkyne **17** (2 equiv) affords the cross metathesis product **18a** in 51% yield; homodimerization of **16a** is not observed at all under these conditions. Subsequent Lindlar reduction of **18a** followed by deprotection of the silyl groups with aqueous HF in THF delivers PGE_2 methyl ester **19**. The synthesis of the acetylated analogue **18b** (R = Ac) from **16b** proceeds in a similar fashion. These examples attest to the mildness of the method as well as to the exceptional tolerance of the catalyst, which preserves the labile aldol unit of these prostanoids and does not epimerize the chiral center α to the ketone to any appreciable extent. It is also noteworthy that the catalyst

Scheme 5[a]



[a] [a] **1** (10 mol %), CH_2Cl_2/toluene, 80 °C, 51% (**18a**), 44% (**18b**); [b] H_2 (1 atm), Lindlar catalyst, CH_2Cl_2, 87%; [c] aq HF, THF, 88%.

rigorously distinguishes between the reactive alkyne unit and the inert alkene entity of **16**.

In summary, it has been shown that ACM is a highly selective and efficient transformation if the recently disclosed catalyst system **1**/CH_2Cl_2 is employed. This particular reagent combination allows extension of the scope of this transformation to C-silylated alkynes and tolerates polar functionalities as diverse as ether, ester, nitrile, trifluoromethyl, aldehyde, acetal, alkyl chloride, sulfone, ketone, silyl ether, and pre-exisiting alkene groups. Further studies on alkyne metathesis effected by this and related catalysts will be disclosed in due course.

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Supporting Information Available: Representative procedure for ACM, as well as full spectroscopic characterization of all homodimerization and cross metathesis products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The scramblings depicted in Scheme 4 are carried out with a 1:1 mixture of the symmetrical starting materials; the yields indicated refer to the CM product.

(12) The preparation of **16** by a "three component coupling" reaction is described in detail in a more comprehensive study on the synthesis of prostanoids by ring-closing alkyne metathesis and ACM: Fürstner, A.; Grela, K.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **2000**, *122*, 11799.