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Cross-Metathesis

Cross-Metathesis of Terminal Alkynes

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Abstract: Terminal acetylenes are amongst the most problematic substrates for alkyne metathesis because they tend to undergo rapid polymerization on contact with a metal alkylidyne. The molybdenum complex **3** endowed with triphenylsilanolate ligands, however, is capable of inducing surprisingly effective cross-metathesis reactions of terminal alkyl acetylenes with propynyl(trimethyl)silane to give products of type R^1–C≡CSiMe . This unconventional way of introducing a silyl substituent onto an alkyne terminus complements the conventional tactics of deprotonation/silylation and excels as an orthogonal way of alkyne protecting group chemistry for substrates bearing base-sensitive functionalities. Moreover, it is shown that even terminal aryl acetylenes can be cross-metathesized with internal alkyne partners. These unprecedented transformations are compatible with various functional groups. The need to suppress acetylene formation, which seems to be a particularly effective catalyst poison, is also discussed.

Introduction

The great strides in alkyne metathesis during the last decade were powered by a new generation of catalysts that combine high activity with an excellent chemoselectivity profile.[1,2] Adequate post-metathetic transformations allow the resulting functionalized alkyne products to be converted into a host of structural motifs.[1–3] With regard to the substrate scope, however, the reaction remains largely confined to the use of internal acetylene derivatives, whereas applications to terminal alkynes are exceedingly rare. As such substrates are often more readily accessible, however, attempts at changing this situation are deemed relevant from the synthetic vantage point.

The initial forays to do so go back to the pioneering studies of Schrock and co-workers on the chemical behavior and metathesis activity of well-defined high-valent metal alkylidynes of tungsten and molybdenum.[4,5] There authors clearly delineated the many pitfalls for the productive conversion of terminal alkynes. As in every metathesis of unsymmetrical substrates, the two possible orientations of the reactants in the first [2+2] cycloaddition open two competing pathways **I** and **II** which are interconnected by virtue of the fact that this initial step is reversible (Scheme 1). In case of a terminal alkyne, however, channel **I** is not just degenerate but potentially destructive. Specifically, it was shown that a metallacyclobutadiene of type **B** is prone to transannular C–H activation with concomitant loss of one of the ancillary ligands X that picks up the proton and hence formally acts as a base; this pathway is particularly favorable in the presence of external donor ligands L. Although X-ray data show that the ligand in the resulting deprotiometallacycle **C** is η^3-bound in the solid state,[4–8] a hapticity change suffices to reveal an alkynyl–alkylidene motif (**D**), which can trigger rapid substrate polymerization.[9,10]

The productive channel **II** is not free of serious complications either. Cycloreversion of **E** forms the desired product RC≡CR and leads to the metal methylidyne **F**, which then reacts with a terminal alkyne substrate RC≡CH via metallacycle **H** to regenerate the loaded complex **A**, as necessary for sustained metathesis; at the same time, however, acetylene is produced which is well soluble in most organic media, despite its low boiling point. For its small size and good donor properties, HC≡CH starts to outcompete the actual substrate and hence to deplete the loaded catalyst **A**. An increasing concentration of the methylidyne **F**, favors the dimerization of this fairly unstable species[11] with formation of dimetallatetrahedranes **G** (Scheme 1).[12,13] Such μ-bridging acetylene complexes, in turn, are able to first insert additional HC≡CH and thence progressively will add further substrate, thus opening yet another polymerization channel. In any case, the available evidence suggests that accumulating acetylene is a veritable catalyst poison.[14]

Early preparative attempts supported the notion that productive metathesis of terminal alkynes is difficult, if not impossible. Thus, Schrock and co-workers had already noticed that phenylacetylene is polymerized on contact with (*t*BuO)$_3$W≡CR (**1a**, R = Ph).[4,10] Likewise, the Mortreux group found that treatment of various terminal alkynes with complex **1b** (R = *t*Bu) resulted only in a short initial phase of metathesis, which was then quickly superseded by polymerization.[15] In a courageous endeavor, these authors tried to empirically optimize the system such that metathesis would endure.[16] Using quinuclidine as an additive, they actually managed to accomplish a first successful self-metathesis reaction, by which 1-heptyne

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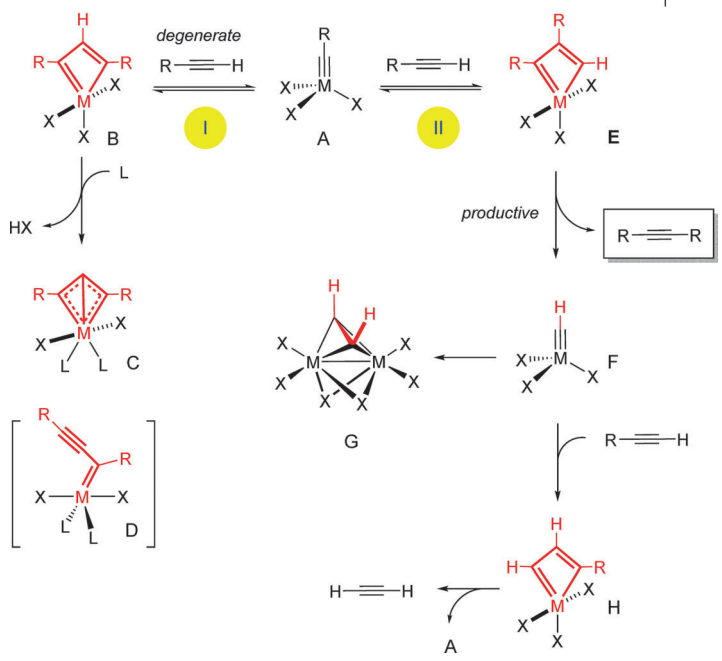
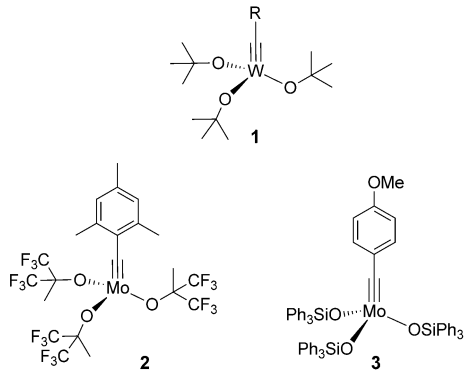


Scheme 1. Basic scenarios relevant in attempted metathesis reactions of terminal alkynes; L = neutral ligand; M = Mo, W; X = anionic ligand.



was transformed into 6-dodecyne in 70% (80% GC) yield with up to 88% selectivity for metathesis over polymerization. Notably, however, attempted extension of this procedure to aryl alkynes met with failure.[16]

The next step was taken by Tamm and co-workers who described the metathesis of terminal alkynes ("TAM") using the molybdenum alkylidyne **2** endowed with hexafluoro-*tert*-butoxy ligands.[17] It is somewhat ironic that complexes of this type had already been described by Schrock in 1984 as powerful alkyne metathesis catalysts,[18] but their ability to accept these problematic substrates had gone unrecognized for decades. It is tempting to speculate that the poorly basic alkoxides in **2** disfavor the formal deprotonation of the metallacyclobutadiene intermediates of type **C** and hence retard the detrimental deprotiometallacycle formation to the extent that productive metathesis can persist. Yet, once again only terminal acetylenes with an aliphatic substituent could be used, whereas aryl alkynes underwent instantaneous polymerization.

Under the premise that a weakly basic ancillary ligand might be key to success, complex **3** and relatives endowed with triarylsilanolate substituents might also qualify as catalysts.[7,19] Commercial **3** is highly active, exhibits a remarkable tolerance toward a myriad of functional groups, and has already stood the test of total synthesis in many challenging cases.[20,21] In fact, this particular alkylidyne provides a window of opportunity for the productive metathesis of terminal alkynes, as previously communicated.[22,23] Outlined below is a more systematic study into the hitherto largely unknown cross-metathesis of terminal acetylene derivatives. It is shown—for the first time ever—that even terminal *aryl* alkynes can be engaged with surprising ease and without noticeable polymerization interfering.

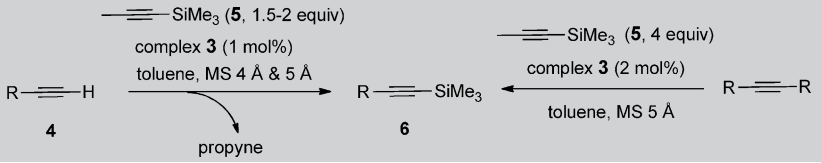
Results and Discussion

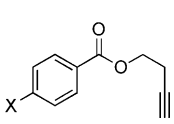
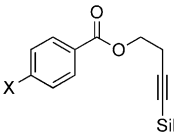
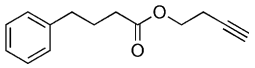
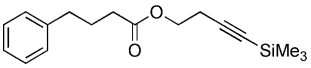
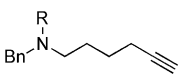
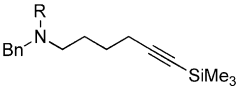
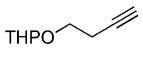
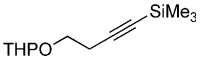
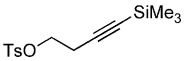
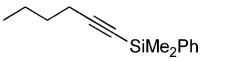
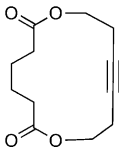
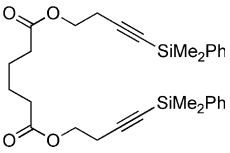
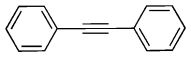
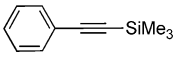
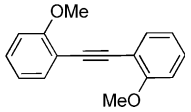
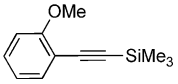
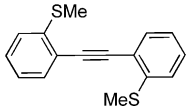
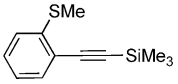
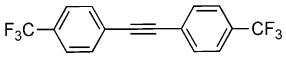
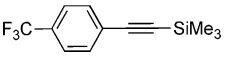
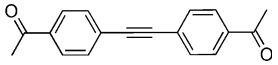
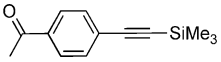
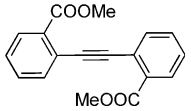
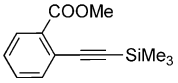
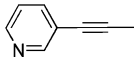
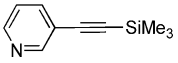
Alkyne cross-metathesis (ACM) as an alternative to conventional protecting group chemistry

Because of an arguably larger preparative relevance, we deliberately focused our investigations on the previously unexplored cross-metathesis of terminal alkynes rather than on the somewhat dreary formation of symmetric "dimers" by self-metathesis.[1,24,25] As every cross-metathesis, however, ACM can a priori lead to statistical product mixtures.[26] To avoid this complication, propynyl(trimethyl)silane (**5**) was chosen as partner for its reluctance to react with itself even in the presence of complex **3** as one of the most active and selective alkyne metathesis catalysts presently available.[7, 19] Moreover, the envisaged transformation **4** → **6** (Table 1) seemed interesting as it allows one to attach a TMS group onto the alkyne terminus under essentially neutral conditions; if so, the method is complementary to conventional alkyne protecting group chemistry that relies on the deprotonation of an alkyne C–H bond with a strong base or an organometallic reagent (KH, KHMDS, LDA, BuLi, MeMgX etc.), followed by trapping of the resulting polar acetylide anion with a proper silyl electrophile R SiX.[27] Although widely practiced, this tactic obviously precludes any substituent from being present in the substrate that is base-sensitive and/or susceptible to nucleophilic attack.

Gratifyingly, ACM of an assortment of terminal alkyl alkynes **4** with silane **5** worked well in the presence of esters, carbamates, sulfonamides, an aryl chloride or an acetal moiety (Table 1, entries 1–6). The chosen catalyst **3** is obviously neither basic- nor nucleophilic-at-carbon, nor is it strongly Lewis-acidic even though it formally comprises a Mo^{VI} center. All reactions proceeded at ambient temperature in the presence of powdered molecular sieves (4 and 5 Å) to sequester the released propyne. At the same time, these additives keep the medium dry and hence retard catalyst decomposition.[7] Since **5** is not undergoing self-metathesis to any significant extent under the chosen conditions, a small excess is usually sufficient to reach full conversion (≤2 equiv). In contrast to the smooth transfor-

Table 1. Preparation of silylated acetylene derivatives by alkyne cross-metathesis (ACM).



Entry	Substrate	Product	Yield [%]
1			96 (X = OMe)
2			94 (X = Cl)
3			67
4			91 (R = Ts)
5			93 (R = Boc)
6			88
7			95
8	5-decyne		71[a]
9			77[b]
10			79
11			94
12			91
13			97
14			98
15			66
16			68[c]

[a] Using propynyl(dimethylphenyl)silane as the reagent in toluene at RT. [b] Using 10 mol% of **3** and propynyl(dimethylphenyl)silane as the reagent in toluene at 60 °C. [c] Using 3 mol% of **3** and 6 equiv of **5**; Bn = benzyl; THP = tetrahydropyran-2-yl; Ts = *p*-toluenesulfonyl.

mation of terminal alkyl alkynes, however, the less reactive terminal aryl alkynes (see below) do not cross well with **5** under the same conditions.

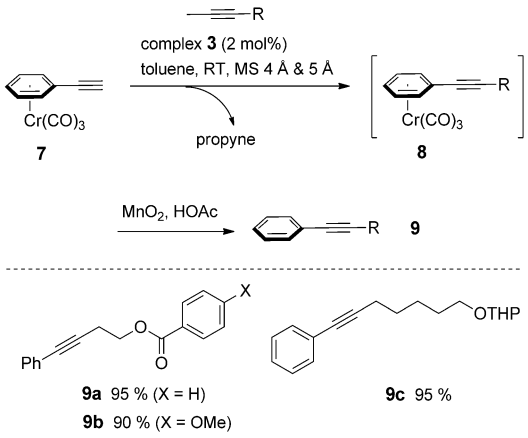
It is worth noting that silyl-capped products can also be accessed starting from internal alkynes; in this case it does not matter whether the substituents on the triple bond are aliphatic or aromatic. As expected, the reaction is tolerant of various polar substituents and heteroatom donor sites (entries 7–16), and can even be run in a ring-opening mode (entry 9). It is also possible to transfer a phenyl(dimethyl)silyl group (entries 8, 9), whereas attempted ACM of 5-decyne with propynyl(triisopropyl)silane was unsuccessful. This failure is tentatively attributed to steric factors that disfavor binding of such a bulky substrate to the operative molybdenum alkylidyne unit in **3** which is surrounded by three sizeable Ph_3SiO ligands.[7] Despite this limitation, the new ACM-based methodology constitutes a potentially valuable alternative for the introduction of silyl protecting groups onto an alkyne terminus, especially when working with functionalized compounds.

Alkyne cross-metathesis of terminal aryl acetylene derivatives

As mentioned above, cross-metathesis reactions of any sort deliver statistical product mixtures whenever the partners exhibit comparable electronic and/or steric properties.[26] The reluctance of propynyl(trimethyl)silane (**5**) to react with itself helps to avoid such a situation, while this compound is sufficiently activated to engage into crossing with regular (internal or terminal) alkynes. In a quest for other substrates with a similar reactivity profile, electron deficient *terminal* aryl alkynes were found to qualify. This observation was surprising, as it stands in marked contrast to all previous attempts to engage such compounds into alkyne metathesis reactions, all of which had failed because of rapid polymerization.[4,9,10,15–17] If seen against this backdrop, the results reported below constitute a significant advance over prior art.

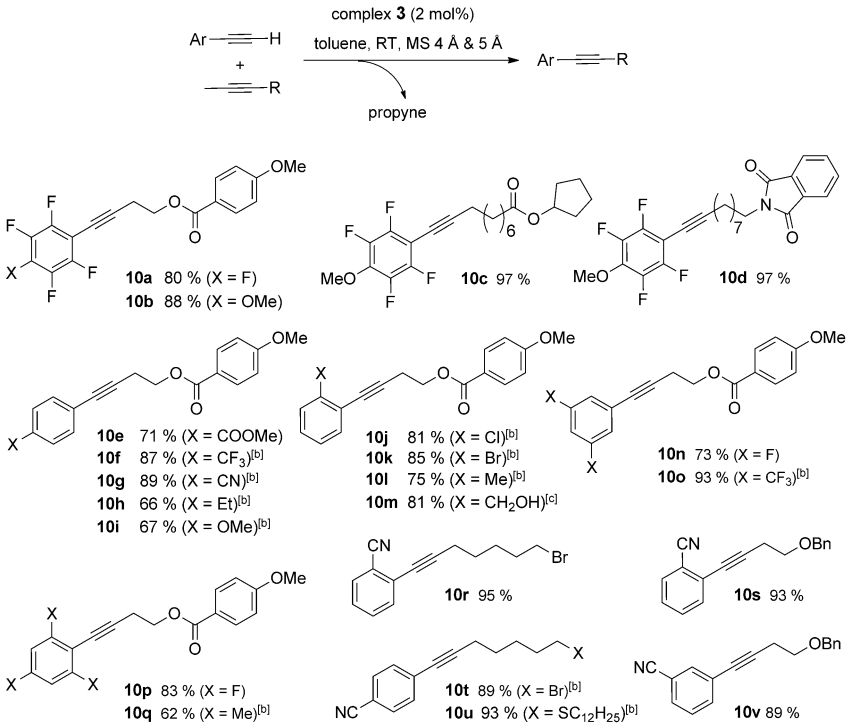
We started our screening exercise somewhat conservatively using the Cr(CO) -complex **7**[28] as an aryl alkyne partner of utmost electron deficiency (Scheme 2). When reacted with an

adequate internal alkyne RC≡CMe (2 equiv) in the presence of the alkylidyne **3** (2 mol%) at ambient temperature, the desired cross-metathesis product **9** was isolated in excellent yield after oxidative decomplexation of the chromium unit from intermediate **8** primarily formed; the remainder of RC≡CMe got dimerized. Following up on this lead finding, it was quickly recognized that complexation to a [Cr(CO)] fragment is by no means compulsory; actually, an array of ordinary aryl alkynes gave similarly favorable outcomes. However, it is necessary to add a fairly large amount of activated molecular sieves to the reaction mixture in order to keep the medium dry and to sequester the released propyne, which seems to poison the catalyst otherwise. A combination of MS 4 Å/5 Å in a 1:2 ratio was found optimal (see the Experimental Section).



Scheme 2. Exploratory study on the cross-metathesis of a terminal aryl alkyne, rendered electron deficient by coordination to a [Cr(CO)] fragment.

Encouraged by these results, an assortment of terminal aryl acetylenes was subjected to ACM with different partners (Scheme 3). The reactions were surprisingly fast and productive, provided that the chosen aryl alkyne contained one or more electron-withdrawing groups such as –F, –Cl, –Br, –CF , –CN, –COOR. Under this condition, the outcome was largely independent of whether the substituent was located *para*, *meta* or *ortho* to the triple bond. The success stems from the reluctance of these substrates to undergo any self-metathesis when exposed to complex **3** in toluene. Specifically, a control experiment with (4-methoxy-2,3,5,6-tetrafluorophenyl)acetylene gave no indication for the formation of the corresponding tolane derivative; importantly, no polymerization of this particular substrate was observed either.

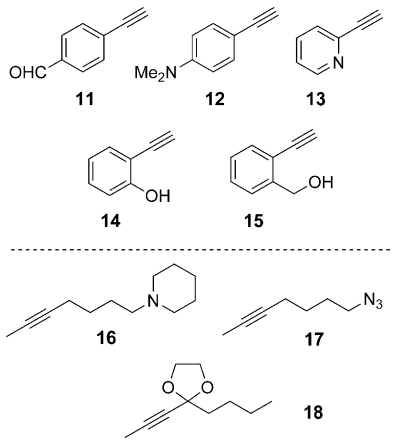


Scheme 3. Alkyne cross-metathesis of terminal aryl acetylenes and products. [a] Unless stated otherwise, the reactions were carried out with **3** (2 mol%) in toluene (≈0.02 M) at ambient temperature in the presence of MS 4 and 5 Å, using 2 equivalents of RC≡CMe. [b] With 4 equivalents of RC≡CMe. [c] In the substrate, the primary –OH was TBS-protected; this group was cleaved during work-up; Bn = benzyl; TBS = *tert*-butyl(dimethyl)silyl.

It is of note, however, that this situation is different for less electron-deficient aryl acetylenes. Thus, addition of a catalytic amount of complex **3** to a solution of (4-ethylphenyl)acetylene in toluene resulted in rapid and essentially quantitative polymer formation. Nevertheless, respectable results in the cross-metathesis reactions of this and related substrates could be attained, provided that a larger excess (4 equiv) of the respective internal reaction partner RC≡CMe was used (see compounds **10h**, **10i**, **10l**, **10m**, **10q**).

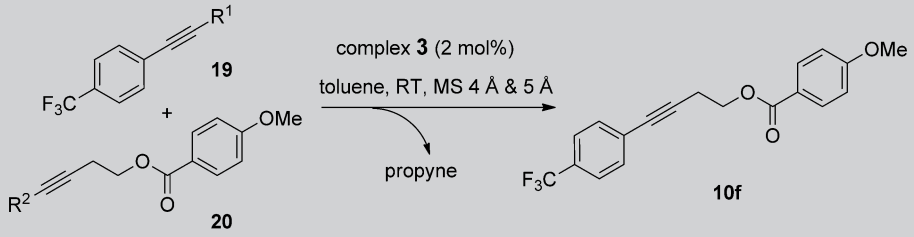
Limitations were encountered with the substrates shown in Chart 2, which were either unreactive (**13**, **15**) or led to intractable mixtures (**11**, **12**, **14**). With regard to the crossing partners, the internal alkynes **16**–**18** were found unsuitable, although the reasons for their failure are not clear at this point; the functional groups presented by these compounds are—per se—compatible with the chosen catalyst.[29]

The data compiled in Table 2 are also informative. Thus, the outcome of the ACM reaction was invariant to the permutation of the substituents R^1 and R^2 on the termini of the partners, as long as at least one of them is an internal alkyne (entries 1–3). In contrast, extensive polymerization was observed when *both* substrates were terminal (entry 4). This is the only combination in which acetylene is necessarily formed; therefore it is reason-



able to assume that this by-product sets the current limits for the methodology described herein. While our data show that catalyst **3** is obviously able to cope with most terminal alkynes, it seems to derail when acetylene starts to accumulate in the mixture. Under this premise, entry 4 also implies that acetylene is not sequestered by the added molecular sieves as effectively as its larger homologues propyne or 2-butyne.[30] One may hence conclude that further progress in terminal alkyne metathesis might not only result from an even better catalyst design but also from the development of more effective acetylene traps.

Table 2. The outcome of ACM as a function of the termini of the two reaction partners.[a]



Entry	R^1	R^2	Yield [%][b]
1	Me	Me	86
2	H	Me	87
3	Me	H	87
4	H	H	5[c]

[a] All reactions were carried in toluene (0.024 M) at ambient temperature with 0.25 mmol of the respective aryl alkyne and 1 mmol of the corresponding reaction partner in the presence of MS 4 Å (1 g) and MS 5 Å (2 g). [b] isolated product, unless stated otherwise. [c] GC yield; the crude mixture contained unreacted **19**, the homodimer of **20**, as well as substantial amounts of polymeric material.

Conclusion

Although terminal acetylenes traditionally belong to the most problematic substrates for alkyne metathesis, this situation is currently about to change.[17,22,23,25] In this report we describe two successful new developments that allow such substrates to be engaged in preparatively useful and largely unprecedented manners. Specifically, the molybdenum alkylidyne complex **3** enables the efficient cross-metathesis of terminal alkynes of the type R^1–C≡CH (R^1 = alkyl) with propynyl(trimethyl)silane. This unconventional way of introducing a silyl group onto an alkyne terminus complements the traditional tactics of deprotonation/silylation; it is particularly useful whenever substrates bearing base-sensitive functionalities need to be protected. Furthermore, the very first examples of productive metathesis reactions of *aryl* alkynes Ar–C≡CH are presented, which were previously beyond reach because of exceedingly facile competing polymerization. Overall, the observed reactivity patterns suggest that the alkylidyne complex **3** endowed with only weakly basic triphenylsilanolates ligands obviates destructive formation of deprotio-metallacycles of type **C** when operated at ambient temperature.[13] A yet limiting factor, however, seems to be its inability to cope with any free acetylene in solution, which likely poisons the catalyst and, in so doing, engenders competitive substrate polymerization.

Experimental Section

All experimental details can be found in the Supporting Information. The material includes compound characterization and copies of spectra of new compounds.

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Keywords: alkynes · alkylidynes · cross-metathesis · molybdenum · protecting groups

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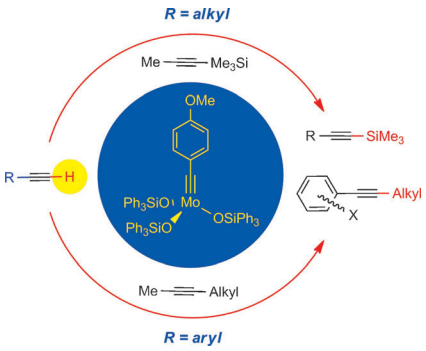
FULL PAPER

Asking for trouble? Attempted metathesis of terminal acetylenes has usually ended in rapid polymerization. With the help of a molybdenum alkylidyne catalyst endowed with silanolate ligands, however, it is possible to cross-metathesize either terminal alkyl alkynes with propynyl(trimethyl)silane or terminal aryl acetylenes with internal aliphatic alkynes. These unprecedented transformations are compatible with various functional groups.



Cross-Metathesis

*R. Lhermet, A. Fürstner**

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Cross-Metathesis of Terminal Alkynes