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Synthesis of unsymmetrical 1,3-diynes *via* alkyne cross-metathesis†

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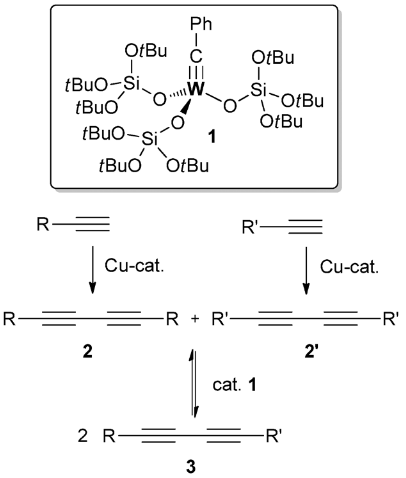
The tungsten benzylidyne complex $[\mathrm{PhC{\equiv}W\{OSi(O}t\mathrm{Bu)_3\}_3}]$ (1) efficiently catalyses the metathetic conversion between symmetrical and unsymmetrical 1,3-diynes, which provides the opportunity to prepare the latter species directly from terminal alkynes by a combination of copper-catalysed homocoupling and catalytic alkyne cross-metathesis (ACM).

Recent years have clearly seen "alkyne metathesis on the rise"[1] with the development of a substantial number of novel well-defined molybdenum and tungsten alkylidyne complexes,[2,3] which are able to efficiently promote the catalytic metathesis of internal and recently even terminal alkynes.[4] One of these (pre-)catalysts, the siloxy-supported tungsten benzylidyne complex **1** (Scheme 1), did not only metathesize methyl-capped alkynes ($\mathrm{RC{\equiv}CMe}$),[5] but also proved to be active in the catalytic metathesis of conjugated diynes of type $\mathrm{RC{\equiv}C{-}C{\equiv}CMe}$ (R = aryl, alkyl).[6] Surprisingly, this method did not yield the anticipated triynes $\mathrm{RC{\equiv}C{-}C{\equiv}C{-}C{\equiv}CR}$ together with 2-butyne ($\mathrm{MeC{\equiv}CMe}$), but selectively produced stoichiometric amounts of the symmetrical diynes $\mathrm{RC{\equiv}C{-}C{\equiv}CR}$ and $\mathrm{MeC{\equiv}C{-}C{\equiv}CMe}$ (dimethyldiacetylene, DMDA). These equilibrium reactions are driven to completion in the presence of powdered molecular sieves (5 Å), which adsorb DMDA in a similar fashion as it acts as a 2-butyne scavenger in the molecular-sieve-promoted alkyne metathesis protocol developed by Fürstner *et al.*[7]

In view of the established methods for the synthesis of symmetrical 1,3-diynes such as copper(I)- or copper(II)-catalysed Glaser, Eglington, and Hay homocoupling of terminal alkynes,[8] the usefulness and applicability of this diyne metathesis reaction might be questioned with good reason, in particular, since the stoichiometric loss of the C_6-building block DMDA results in a poor, if not dreadful, atom economy.[9] It should be noted, however, that C–C bond formation in the copper-mediated transformations proceeds irreversibly, whereas the fully reversible making and breaking of carbon–carbon triple-bonds during the alkyne metathesis steps offers full thermodynamic control, which was successfully exploited for the synthesis of macrocyclic diynes by ring-closing diyne metathesis (RCDM).[6]



Scheme 1 Synthesis of unsymmetrical 1,3-diynes by a combination of copper-catalysed homocoupling of terminal alkynes and diyne cross-metathesis (DYCM).

Furthermore, the reversibility of this transformation should also allow establishment of an equilibrium between two symmetrical 1,3-diynes **2** and **2′** and their unsymmetrical counterpart **3**, allowing us in principle to combine copper-catalysed homocoupling of terminal alkynes with subsequent diyne cross-metathesis (DYCM)[10] of the resulting symmetrical 1,3-diynes (Scheme 1). A somewhat related approach had already been pursued by Gross and Moore, who polymerised a diethynylcarbazole under Hay conditions and subjected the resulting diyne polymer to standard alkyne metathesis conditions by use of the catalyst system $[\mathrm{EtC{\equiv}W\{N(Ar)(}t\mathrm{Bu)\}_3}]$–$\mathrm{Ph_3SiOH}$ (11/18 wt%). In contrast to **1**, however, the generated catalyst did not exhibit selectivity towards diyne formation, and the resulting tetrameric macrocycles showed a statistical distribution of yne (C_2) and diyne (C_4) bridges.[11]

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† Electronic supplementary information (ESI) available: Full details of all experimental procedures involving copper-catalysed homocoupling of terminal alkynes and diyne cross-metathesis (DYCM); selected ^{1}H and ^{13}C NMR spectra; details of the electronic structure calculations and X-ray crystal structure determination. CCDC 935939. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc43108h

Considering the importance of conjugated diynes as building blocks in natural products and materials science,[12–14] the route outlined in Scheme 1 offers an alternative to classical methods for constructing unsymmetrical diynes such as the Cadiot–Chodkiewicz coupling and its variants.[8] However, the preparation of alkynyl halides by halogenation of terminal alkynes is required, which is clearly less economical and environmentally benign than a method directly coupling two different terminal alkynes. Accordingly, direct cross-coupling of two different terminal alkynes has been reported several times,[15,16] and, for instance, unsymmetrical 1,3-diynes were obtained in modest to good yields by Ni/Cu- or Fe/Cu-catalysed aerobic oxidative coupling reactions in the presence of a 5- or 6-fold excess of one of the alkynes, respectively.[16a–c]

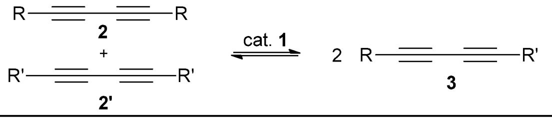
In contrast to these examples, where the irreversibility of the C–C bond forming steps affords statistical diyne mixtures, it is safe to assume that alkyne metathesis catalysed by **1** is under thermodynamic control with an equilibrium constant $K = [\mathbf{3}]^2/([\mathbf{2}][\mathbf{2}'])$. To test the feasibility of the proposed DYCM protocol, several symmetrical 1,4-diaryl- and 1,4-dialkyl-1,3-butadiynes **2** and **2′** were synthesised by CuCl-catalysed alkyne homocoupling in dimethylsulfoxide at 90 °C (Scheme 1, see also Table 2).[17] Preliminary NMR experiments were carried out in CD_2Cl_2 for the equilibrium reaction between 1,4-bis(*p*-anisyl)-1,3-butadiyne (R = *p*-MeOC$_6$H$_4$) and 5,7-dodecadiyne (R′ = *n*-Bu), revealing that an equilibrium is established within four hours at room temperature in the presence of 1.7 mol% of catalyst **1**. Integration of the sufficiently well separated ^{1}H NMR signals for the OCH_3 groups in **2** (6H, $\delta \approx 3.75$ ppm) and **3** (3H, $\delta \approx 3.73$ ppm) allows us to determine their relative equilibrium concentrations and the resulting equilibrium constant *K*. These measurements were performed for various ratios of the starting concentrations $[\mathbf{2}']_0:[\mathbf{2}]_0$, and the results are summarised in Table 1. In agreement with Le Chatelier's principle, increasing the excess of **2′** over **2** from 1 : 1 to 4 : 1 shifts the equilibrium towards **3** with an increasing [**3**] : [**2**] ratio. For all four experiments, *K* is satisfactorily well reproduced with an average $\bar{K} = 5.83$. The resulting Gibbs free energy ($\overline{\Delta G_{298\mathrm{K}}} = -4.4\ \mathrm{kJ\ mol^{-1}}$) indicates that the formation of the unsymmetrical 1,3-diyne is slightly exergonic, and theoretical values of $\Delta G_{298\mathrm{K}}$ derived by DFT calculations for this and other diyne combinations are of the same order of magnitude (see ESI†).

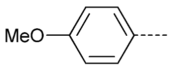
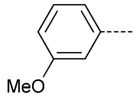
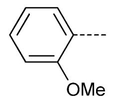
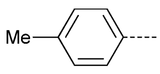
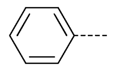
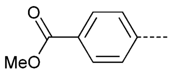
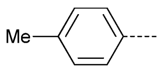
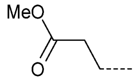
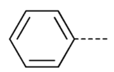
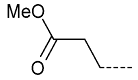
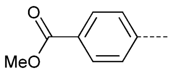
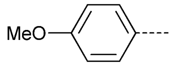
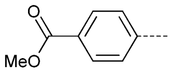
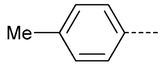
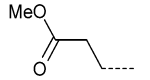
Table 1 NMR study of the equilibrium reaction between 1,4-bis(*p*-anisyl)-1,3-butadiyne (**2**, R = *p*-MeOC$_6$H$_4$) and 5,7-dodecadiyne (**2′**, R′ = *n*Bu) affording 1-*p*-anisyl-1,3-octadiyne (see also Table 2, entry 1)[a]

$[\mathbf{2}']_0:[\mathbf{2}]_0$[b]	$[\mathbf{3}]:[\mathbf{2}]$[c]	K[d]	$\Delta G_{298\mathrm{K}}$[e] [kJ mol^{-1}]	Yield[f] [%]
1 : 1	2.36	5.57	−4.3	54
2 : 1	5.31	6.06	−4.5	73
3 : 1	7.98	5.80	−4.4	80
4 : 1	10.97	5.88	−4.4	85

[a] NMR samples were prepared by mixing the appropriate aliquots from 0.1 M standard solutions of **2** and **2′** in CD_2Cl_2 (total volume = 0.6 mL), followed by addition of 0.1 mL of a 0.01 M solution of **1** in CD_2Cl_2 (total sample volume = 0.7 mL, total alkyne concentration = 0.086 M, catalyst loading = 1.7 mol%); see ESI for full details. [b] Ratio of the starting concentrations. [c] Ratio of equilibrium concentrations determined by integration of the OCH_3 ^{1}H NMR signals in **3** (3H) and **2** (6H). [d] $K = [\mathbf{3}]^2/([\mathbf{2}][\mathbf{2}']) = [\mathbf{3}]^2/[([\mathbf{2}]_0 - [\mathbf{3}]/2)(X[\mathbf{2}]_0 - [\mathbf{3}]/2)] = 2Y^2/(X(2 + Y) - Y)$ with $X = [\mathbf{2}']_0/[\mathbf{2}]_0$ and $Y = [\mathbf{3}]/[\mathbf{2}]$. [e] $\Delta G_{298\mathrm{K}} = -RT\ln K$ with $R = 8.314\ \mathrm{J\ K^{-1}\ mol^{-1}}$ and $T = 298$ K. [f] Yield based on the conversion of **2**; yield = $Y/(Y + 2)$ with $Y = [\mathbf{3}]/[\mathbf{2}]$.

Table 2 Diyne cross-metathesis of symmetrical to unsymmetrical 1,3-diynes catalysed by **1** using a **1** : 4 ratio of **2** and **2′**[a]



Entry	R	R′	Yield[b] [%]	Time
1		*n*Bu-----	76	4 h
2		*n*Bu-----	83	5 h
3		*n*Bu-----	65	11 h
4		*n*Bu-----	75	4 h
5		*n*Bu-----	62	6 h
6		*n*Bu-----	76	8 min
7			81	5 h
8			79	5 h
9			87	13 min
10			85	8 min
11		*n*Bu-----	84	8 h

[a] Conditions: substrate **2** (0.025 M), substrate **2′** (0.1 M), catalyst **1** (2 mol%), CH_2Cl_2, room temperature; see ESI for full details. [b] Yield of product **3** isolated after filtration through alumina and purification by column chromatography; the yields are based on the conversion of the minor diyne **2**.

Preparative DYCM was then carried out at room temperature for all diyne combinations listed in Table 2 (entries 1–11). The conversion was followed by gas chromatography and, after equilibration, the reaction mixtures were filtered through alumina, followed by separation of the diynes by column chromatography. The isolated yields of **3** are based on the conversion of the minor diyne component **2** and range from 62% (entry 5) to 87% (entry 9). In most cases, the starting materials can be recovered in excellent to quantitative yield, depending on the separability of the 1,3-diyne substrates (see ESI† for full details).

It should also be noted that it cannot be unequivocally deduced at this stage whether the range of yields could be ascribed to differences in $\Delta G_{298\mathrm{K}}$ for the various DYCM systems or is merely a result of the specific work-up and separation process during each

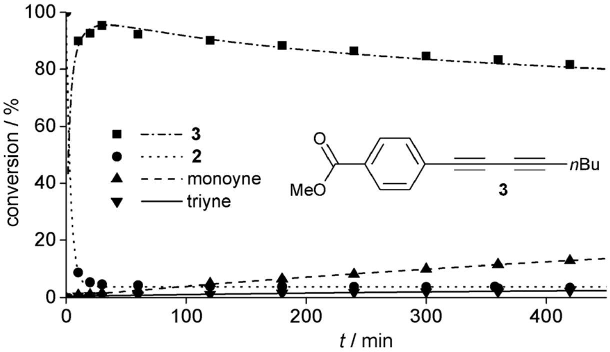


Fig. 1 Conversion–time diagram for the diyne cross-metathesis (DYCM) between **2** (R = p-C_6H_4COOMe) and **2′** (R′ = nBu), see Table 2, entry 6.

experiment. Clearly, steric and electronic properties have a marked impact on the metathesis rate, as shown for instance by the significantly longer equilibration time found for the reaction of 5,7-dodecadiyne with 1,4-bis(*o*-anisyl)-1,3-butadiyne (11 h, entry 3) in comparison to those observed for its *para*- and *meta*-substituted isomers (4 and 5 h, entries 1 and 2). Whereas several other diyne combinations require similar reaction times (entries 4,‡ 5, 7 and 8), the use of the symmetrical butadiyne with methyl benzoate 1,4-substituents leads to rapid equilibration and very short reaction times, irrespective of whether the other diyne is aliphatic (8 min, entry 6) or aromatic (8 and 10 min, entries 9 and 10). Finally, aliphatic 1,3-diynes can also be cross-metathesized, albeit at a rather slow rate (8 h, entry 11).

It should be emphasized that it is crucial to establish the appropriate reaction time for each diyne combination, since degradation of the products is observed upon stirring the equilibrated reaction mixtures for prolonged periods. This is exemplified by the conversion–time diagram shown in Fig. 1 for one of the fastest DYCM reactions (Table 2, entry 6), indicating slow and continuous consumption of the unsymmetrical diyne **3**. In other cases, where longer reaction times are required, the degradation is also significantly slower, and consequently, the yields are hardly affected by this secondary process (see ESI† for other conversion–time diagrams). For all $RC{\equiv}C{-}C{\equiv}CR'$ systems studied so far, the corresponding alkynes $RC{\equiv}CR'$ and triynes $RC{\equiv}C{-}C{\equiv}C{-}C{\equiv}CR'$ (and over time also tetraynes) are identified as secondary reaction products by GC/MS analysis (Fig. 1), suggesting that disproportionation of diynes into monoynes and triynes (and subsequently into polyynes)[14c] takes place, but favourably at a significantly slower rate than the desired DYCM reaction. Apparently, this disproportionation can be faster with other alkylidyne catalyst systems, which might explain the observation made by Gross and Moore upon isolation of tetrameric macrocycles with yne (C_2) and diyne (C_4) moieties from a diyne polymer under alkyne metathesis conditions (*vide supra*).[11] The reasons as to why disproportionation with catalyst **1** is relatively slow remain unclear at the moment, and this needs to be further addressed by means of theoretical calculations concerning possible competing reaction mechanisms.[6]

In conclusion, the recent observation that the tungsten alkylidyne complex **1** is able to promote the metathesis of 1,3-diynes in a surprisingly selective and efficient manner[5] was exploited for the preparation of unsymmetrical 1,3-diynes by cross-metathesis of their symmetrical counterparts, which are conveniently accessible by copper-catalysed homocoupling of terminal alkynes. It should be emphasized again that copper-catalysed routes alone are not competitive with the DYCM reaction, since the irreversibility of the C–C bond forming step affords the symmetrical diynes **2** and **2′** as side products, which have to be discarded, if only the unsymmetrical diyne **3** was of further use. In contrast, the combination of copper catalysis and alkyne metathesis allows recycling of the symmetrical diynes and feeding them back into a (potentially continuous) DYCM process. Ideally, full exploitation and optimisation of this new method would be achieved by constantly removing the product **3** from the reaction mixture, *e.g.* by precipitation or evaporation, in order to drive the equilibrium reaction to completion with regard to full conversion of **2** and **2′** into **3**. Further work in this direction is currently in progress in our group.

Notes and references

‡ The molecular structure of the product 1-(*p*-methylphenyl)-1,3-octadiyne (Table 2, entry 4) was determined by X-ray diffraction analysis; see ESI† for the representation.

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