Synthesis of Conjugated Triynes via Alkyne Metathesis

Idriss Curbet,[†⊥] Sophie Colombel-Rouen,[†⊥] Romane Manguin,[†⊥] Anthony Clermont,[†] Alexandre Quelhas,[†] Daniel S. Müller,[†] Thierry Roisnel,[†] Olivier Baslé,[‡†] Yann Trolez*[†] and Marc Mauduit*[†]

[†] Univ Rennes, Ecole Nationale Supérieure de Chimie de Rennes, CNRS, ISCR UMR 6226, F-35000 Rennes, France

Supporting Information Placeholder

ABSTRACT: *The synthesis of conjugated triynes by molybdenum-catalyzed alkyne metathesis is reported. Strategic to the success of this approach is the utilization of sterically-hindered diynes that allowed for the site-selective alkyne metathesis to produce the desired conjugated triyne products. The steric hindrance of alkyne moiety was found to be crucial in preventing the formation of diyne byproducts. This novel synthetic strategy was amenable to self- and cross-metathesis providing straightforward access to the corresponding symmetrical and dissymmetrical triynes with high selectivity.*

Polyynes are an important class of natural products which display a broad array of biological activities such as antibacterial, antimicrobial, antitumor and anticancer properties.[1] Conjugated diynes and triynes (e.g. ivorenolide B **1**[2] and ichthyothereol **2**[3]) represent the major part of this class of compounds that can be isolated from plants, fungi or bacteria (Figure 1, a). While the diyne core is easily accessible,[4] the triyne moiety appears more difficult to access and represents a synthetic challenge.[5] Several methods have been developed to access symmetrical and unsymmetrical triynes.[6] For instance, Tykwinski and co-workers recently reported an elegant synthetic strategy involving a Pd-catalyzed cross-coupling between **3** and various terminal alkynes that lead to the desired triynes **4** (Figure 1, b).[7] Despite the mentioned advances in this field, the development of versatile and efficient methodologies is still necessary.

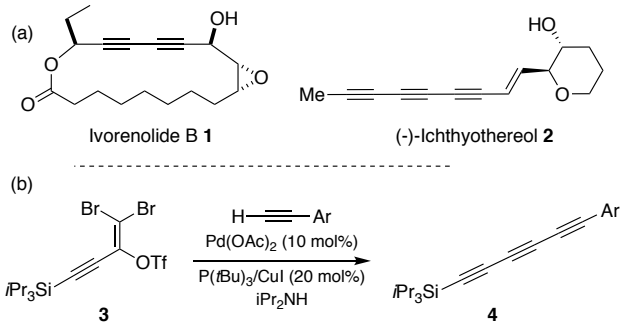
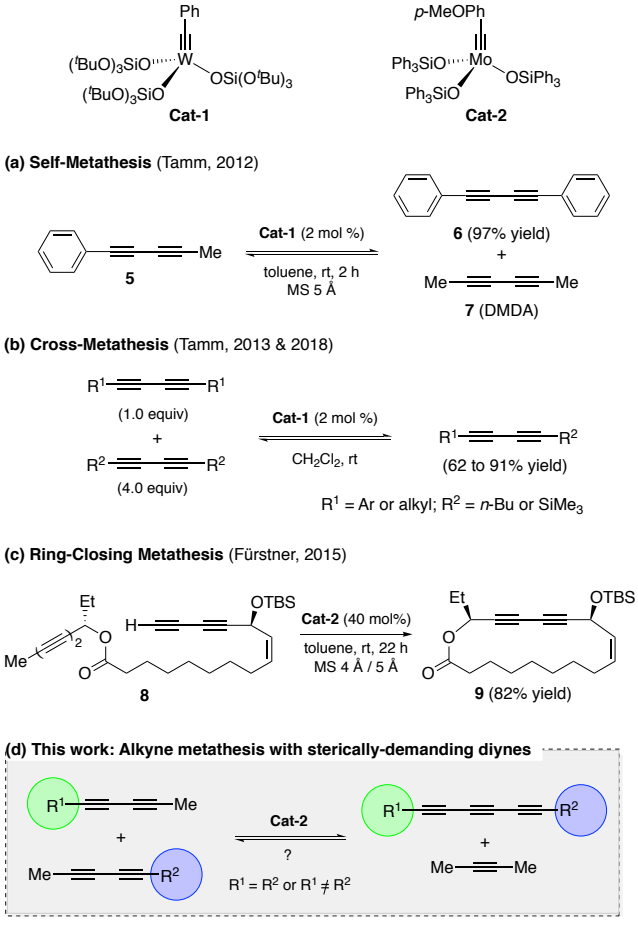


Figure 1. (a) Examples of natural products containing diynes and triynes. (b) Synthesis of triynes as reported by Tykwinski and co-workers.

Several well-defined W- and Mo-based catalysts (e.g. **Cat-1** and **Cat-2**, Figure 2) can promote metathesis reactions of alkynes, allowing for the formation of new carbon-carbon triple bonds.[8] Logically, extension of this methodology to diyne substrates would represent a promising and straightforward way to synthesize the highly desirable 1,3,5-hexatriyne core. This strategy was recently attempted by Tamm and co-workers using a tungsten-alkyne complex **Cat-1**, which unexpectedly led to the exclusive formation of symmetrical diynes (e.g. **5**) and related dimethyldiacetylene **7** (Figure 2, a).

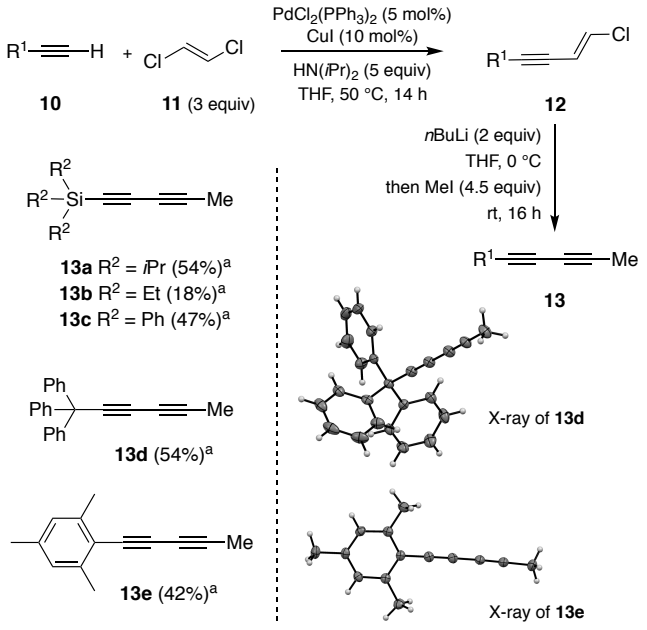
Figure 2. Previous works on diynes metathesis catalyzed by Mo- or W-catalysts and the proposed concept for the access of conjugated triynes (**this work**)



The anticipated conjugated triynes could not be isolated.[9] In 2013, the authors extended the methodology to diyne cross-metathesis (DYCM) (Figure 2, b)[10,11] resulting in unsymmetrical diynes products along with traces of the triyne products upon prolonged reaction time. In line with these pioneering works, Fürstner and coworkers also observed a similar reactivity in the catalytic ring-closing metathesis (RCM) of a bis-diyne **8** with molybdenum-alkyne complex **Cat-2** that produced the corresponding cyclized diyne **9** (Figure 2, c), a key intermediate in the total synthesis of Ivorenolide B **1** (Figure 1).[12] In order to enforce the appropriate C≡C triple bond to react, it was hypothesized that the introduction of bulky groups would influence the regioselectivity[13] of diyne metathesis reactions favoring the triyne products over the diyne products as previously reported (Figure 2, d).[9-12] We would like now to report on a methodology that allows for the unprecedented selective formation of symmetrical and dissymmetrical conjugated triynes from alkyne metathesis.

Investigations began with the synthesis of diynes **13a-e** bearing various substituents following a robust methodology from the literature (Scheme 1).[14] Starting from terminal alkynes **10**, the Pd-catalyzed Sonogashira coupling with (*E*)-1,2-dichloroethylene **11** resulted in the corresponding chloro-enynes **12**. The latter was then reacted with *n*-Buli and iodomethane to produce the expected diynes **13a-e** in moderate to good overall yields (Scheme 1). Additionally, structures of diynes **13d** and **13e** were confirmed by single crystal X-ray diffraction studies (Scheme 1).[15] The reactivity and behavior of these more or less sterically-demanding diynes were then assessed in alkyne self- and cross-metathesis.

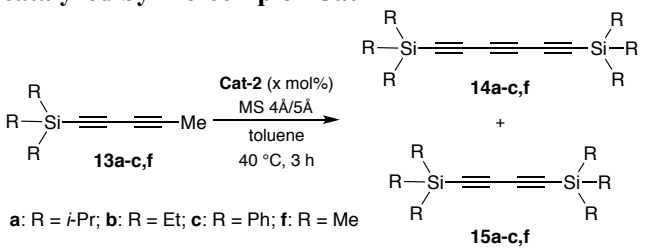
Scheme 1. Synthetic access of sterically-demanding dienes 13a-e.



[a] Isolated yield after silica gel purification.

First, we investigated the self-metathesis of silylated diynes **13a-c,f** (Table 1). Triisopropylsilylpentadiyne **13a** was exposed to alkyne metathesis catalyst **Cat-2** (3 mol%) at 40 °C over three hours. While a 50% conversion was observed, only traces of desired triyne **14a** (1%) were detected by GC analysis (entry 1). Since no other side-products were detected in the crude mixture, it was suspected that the loss of material was due to the competitive formation of higher molecular weight polyynes[16] enhanced by the presence of 2-butyne co-product.[17] Inspired by the work of Fürstner and coworkers,[12c] the addition of 4 and 5 Å molecular sieves (MS) in the reaction media to trap 2-butyne could not only increase the conversion up to 96% but also allow for the formation of the desired symmetrical $(TIPS)_2$triyne **14a** with excellent 86% GC yield (Table 1, entry 2). Nevertheless, symmetrical $(TIPS)_2$diyne **15a** was also obtained in a respective triyne/diyne ratio of 86:14 (see Supplementary Information, SI for details). Interestingly, at lower catalyst loading (2 and 1 mol%, entries 3 and 5) as well as at ambient temperature (entry 4), **Cat-2** remained quite productive reaching respectively 80, 59 and 74% GC yields. More importantly, the selectivity increased up to 95:5 with the lowest catalyst loading, although the GC yield dropped to 59% for triyne **14a** (entry 5).

Table 1. Self-metathesis of silylated diynes 13a-c,f catalyzed by Mo-complex Cat-2[a]



entry	diynes	**Cat-2** (mol%)	Conv (%)[b]	Ratio **14**:**15**[c]	Yield **14** (%)[b]	Yield **15** (%)[b]
1[d]	**13a**	3	50	nd	1	-
2	**13a**	3	96	86:14	86	-
3	**13a**	2	91	90:10	80	-
4[e]	**13a**	2	89	90:10	74	-
5	**13a**	1	75	95:5	59	-
6[f]	**13a**	3	96	81:19	63[g]	-
7[h]	**13f**	3	91	0:100	-	48
8	**13b**	3	>98	2:98	-	56
9[i]	**13c**	3	95[j]	40:60[k]	12[k,l]	19[k,l]

[a]Reaction conditions: diyne (0.04 mmol), catalyst (3 mol%), MS 4Å/5Å (40 mg), toluene (0.35 mL), 40 °C, 3 h, under Ar. [b]Determined by GC-analysis with acetophenone as internal standard.[c]Determined by GC-analysis. [d]Performed without MS 4Å/5Å. [e]Performed at 20 °C. [f]Performed at 0.55 mmol-scale. [g]Isolated yield after silica gel chromatography. [h]Performed at 20 °C over 1 h. [i]Performed at 0.26 mmol-scale. [j]Based on the recovered starting material. [k]Determined by quantitative ^{13}C NMR spectroscopy. [l]Estimated yield from an isolated mixture of **14c** + **15c**.

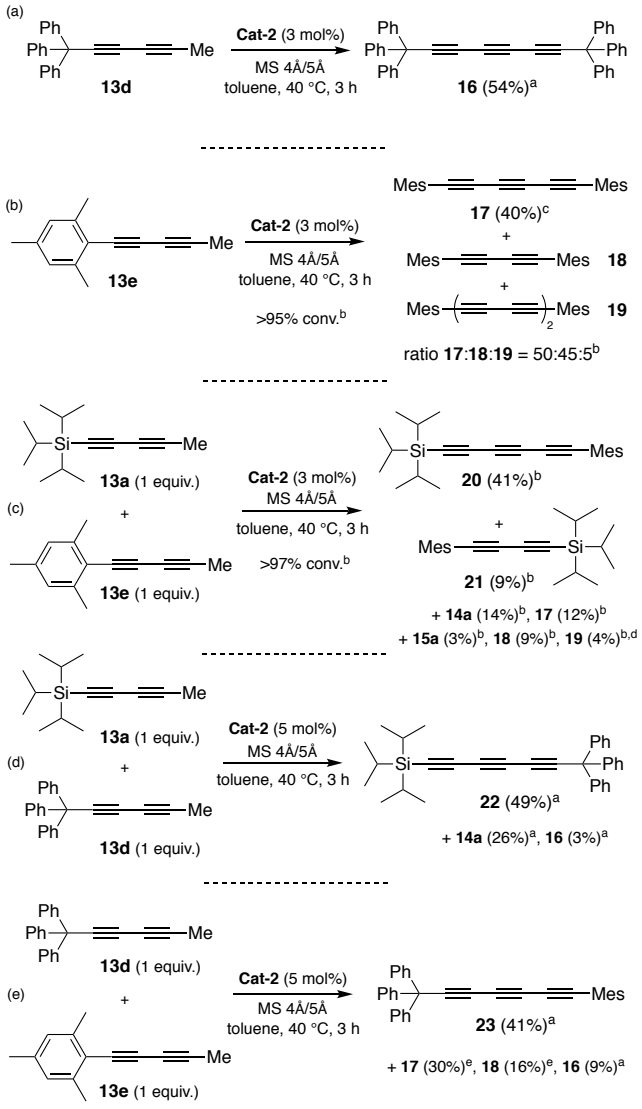
By increasing the scale of the reaction, it was possible to isolate **14a** in good 63% isolated yield after silica gel purification (entry 6).

After demonstrating that the presence of a bulky triisopropylsilyl (TIPS) group allowed for the formation of the triyne as the major metathesis product, it was investigated whether less sterically-hindered Si-substituent such as trimethylsilyl (TMS), triethylsilyl (TES) or triphenylsilyl (TPS) groups would give preferentially rise to the symmetrical diyne or the triyne product. Hence, TMS-diyne **13f** was synthesized according to a protocol from the literature and exposed to the aforementioned conditions (3 mol%, 40 °C, 3 h).[18] Mo-based complex **Cat-2** appeared quite productive, although symmetrical $(TMS)_2$diyne **15f** was exclusively formed (ratio **14f**:**15f** = 0:100) in 48% GC yield (Table 1, entry 7), which is consistent with previous observations from the Tamm group (Scheme 1b).[11] A similar behavior was also observed with TES-diyne **13b** (ratio **14b**:**15b** = 2:98) that led to symmetrical $(TES)_2$diyne **15b** in a moderate 56% GC yield (entry 8). Regarding diyne **13c** featuring a bulkier Ph_3Si group, the expected symmetrical $(TPS)_2$triyne **14c** was formed more significantly but $(TPS)_2$diyne **15c** remained predominant (ratio **14c**:**15c** = 40:60, entry 9).[19] Moreover, X-ray diffraction analysis could be done allowing to confirm the solid-state structure of desired triyne **14c**[15] that exhibited usual geometrical features for this kind of compounds[6b] (Figure 3).

Encouraged by the promising good result reached with TIPS substituent, we decided to investigate other substituents such as triphenylmethyl (trityl) or mesityl (Mes) groups (Scheme 2). To our delight, as seen with the TIPS-substrate **13a**, **Cat-2** demonstrated efficient catalytic activity in the self-metathesis of the trityl-substituted diyne **13d** resulting in the desired symmetrical triyne product **16** in 54% isolated yield (Scheme 2, a). Furthermore, X-ray diffraction analysis unambiguously confirmed the structure of trityl-substituted triyne **16**.[15] Additionally, the stability of trityl-triyne **16** toward the Mo-benzylidyne catalyst was evaluated, as the competitive conversion of triyne to higher polyynes was suspected. Triyne **16** was thus exposed to Mo-**cat 2** (3 mol%) at 40 °C over 3 hours. Interestingly, 96% of the starting material were recovered. It is worth to notice that a similar behavior was also observed with a mixture of triyne/diyne **14a**/**15a** (81/19 ratio) without any alteration of the triyne/diyne ratio (see SI for details). Those additional experiments highlighted the remarkable stability of the triynes into the reactive media.

Mo-benzylidyne catalyst was also efficient toward mesityl-substituted diyne **13e** affording the expected symmetrical triyne **17** with moderate 40% GC-MS yield (Scheme 2,b). However, GC-MS analysis evidenced a significant formation of symmetrical diyne **18** but also some traces of tetrayne **19** (ratio **17**:**18**:**19** =50:45:5).[20] The steric hindrance of the mesityl group appeared thus less suitable to promote the selective formation of the triyne metathesis product.

Scheme 2. Scope of self- and cross-metathesis catalyzed by Mo-complex Cat-2.



[a]Isolated yield after silica gel chromatography. [b]Determined by GC-MS analysis [c]Yield determined by GC-MS analysis with *n*dodecane as the internal standard. [d]$(TIPS)_2$tetrayne and TIPS/Mes-tetrayne were also detected (1-3%). [e]Yield from an inseparable isolated mixture of **17** + **18** (ratio = 55/45).

The more challenging cross-metathesis reaction was then studied. First, by reacting TIPS- and Mes-diynes **13a** and **13e**, the formation of the highly desirable dissymmetrical triyne **20** as the major product was observed, reaching 41% GC yield (Scheme 2,c). Unsurprisingly, some amounts of symmetrical triynes **14a** and **17** were also observed (14 and 12%, resp.), as well as the dissymmetrical diyne **21** (9%) and its symmetrical congeners **15** and **18** (3 and 9%, resp.). Of note, few traces (1-4%) of symmetrical/dissymmetrical tetraynes were also detected (see SI for details). Secondly, with trityl-diyne **13d** as a partner, TIPS-diyne **13a** led to the expected dissymmetrical triyne **22** in 49% isolated yield while Mes-diyne **13e** produced the corresponding dissymmetrical triyne **23** in 41% isolated yield (Scheme 2,

d,e). Again, some amounts of symmetrical triynes/diynes were also formed. Furthermore, solid-state structures of these challenging dissymmetrical triynes **22** and **23** were also confirmed by X-ray diffraction analysis (Figure 3).[15]

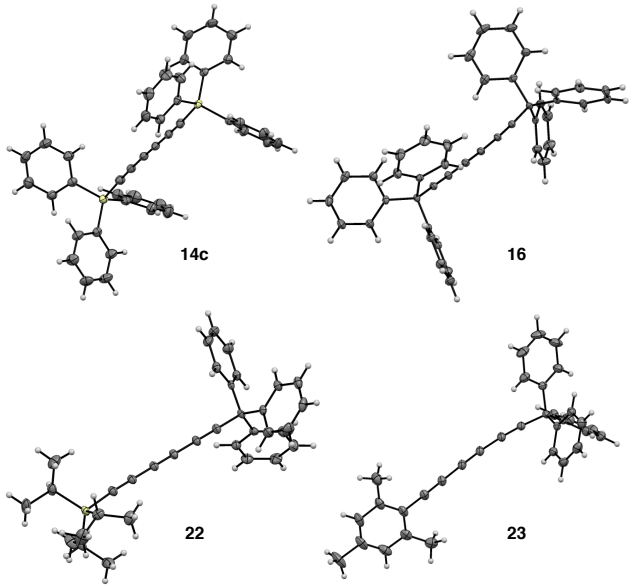
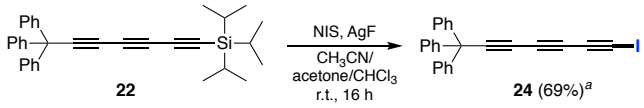


Figure 3. Solid-state structures of symmetrical triynes **14c** and **16** and dissymmetrical triynes **22** and **23** from single crystal X-ray diffraction.

In order to show the synthetic potential of this methodology to furnish valuable triyne building-blocks, the post-transformation of dissymmetrical triyne **22** was then explored. As depicted in Scheme 3, the TIPS fragment was successfully removed using silver fluorine followed by direct iodination of the resulting deprotected alkyne in the presence of *N*-iodosuccinimide (NIS). The expected 7-iodohepta-2,4,6-triyne-1-trityl **24** was isolated in good 69% isolated yield.

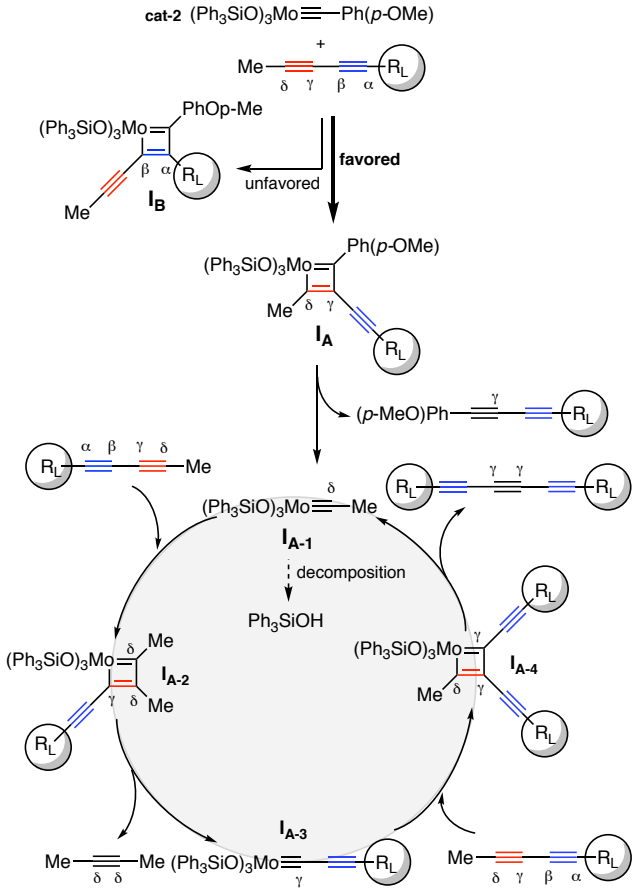
Scheme 3. Post-functionalization of dissymmetrical triyne 23.



[a] Isolated yield after silica gel purification.

Considering the aforementioned experimental results, a plausible reaction pathway for the self-metathesis of sterically-hindered diynes is suggested in Scheme 4. Depending on the steric hindrance brought by the R_L-substituent of the diyne, and according to the established mechanism of the alkyne metathesis,[21,9-11] a catalytic cycle could be envisioned. If R_L is large enough, Mo-based complex **Cat-2** reacts preferably with the less hindered δ,γ-CC triple bond to form the metallacyclobutadiene $\mathbf{I_A}$ leading to active species $\mathbf{I_{A\text{-}1}}$. The latter is then engaged through the catalytic cycle of Scheme 4 to produce the valuable symmetrical (γ,γ)-triyne. In opposition, if the Mo-catalyst reacts with the more hindered α,β-alkyne, a catalytic cycle already described by Tamm and co-workers is involved and explains the formation of the diyne product.[11]

Scheme 4. Proposed mechanisms for the self-metathesis of sterically-hindered diynes catalyzed by Mo-complex Cat-2 leading to conjugated triynes.[a]



[a] Reversibility is expected for each step. Only productive metathesis steps are represented.

In conclusion, it was demonstrated herein that the utilization of sterically-hindered diynes can modify the selectivity of alkyne metathesis to favor the formation of the desired triynes. Therefore, the first synthesis of symmetrical and dissymmetrical conjugated triynes by self- and cross-metathesis was successfully achieved. By involving an efficient molybdenum benzylidyne complex, remarkable triyne:diyne ratios were reached (up to >95:5) affording expected triynes in moderate to good yields (up to 86%). These pioneer results pave the way to further developments with the quest for more efficient alkyne-metathesis complexes with higher productivity. Notably, the synthesis of more sophisticated (highly functionalized) triyne frameworks that are ubiquitous in a wide range of natural products will be targeted in the future as well as tetraynes or higher polyynes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
NMR spectra of products, GC analyses, experimental procedures and single crystal X-ray crystallographic (PDF)
X-ray crystallographic data (CIF)

AUTHOR INFORMATION

Corresponding Author

* E-mail: yann.trolez@ensc-rennes.fr; marc.mauduit@ensc-rennes.fr
⊥These authors contributed equally to this work

ORCID

Olivier Baslé: 0000-0002-4551-473X
Yann Trolez: 0000-0002-5421-9556
Marc Mauduit : 0000-0002-7080-9708

Present Address

‡ LCC-CNRS, Université de Toulouse, CNRS, Toulouse, France

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We are grateful to the CNRS, the Ecole Nationale Supérieure de Chimie de Rennes (grant to RM and AC) and the Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation (grant to RM and AQ). This work was also supported by the region Bretagne (SAD 2016 N° 9639 – RZSELECT; grant to DSM) and the FASO (grant to IC and DSM). Prof. A. Fürstner is acknowledged for the generous gift of molybdenum benzylidyne complex. We are grateful to Elsa Caytan and the PRISM core facility (Biogenouest©, UMS, Biosit, Université de Rennes 1) for quantitative ^{13}C NMR experiences.

REFERENCES

(1) For a recent review, see: Shi Shun, A. L. K.; Tykwinski, R. R. Synthesis of Naturally Occurring Polyynes. *Angew. Chem. Int. Ed.* **2006**, *45*, 1034–1057.

(2) Wang, Y.; Liu, Q.-F.; Xue, J.-J.; Zhou, Y.; Yu, H.-C.; Yang, S.-P.; Zhang, B.; Zuo, J.-P.; Li, Y.; Yue, J.-M. Ivorenolide B, an Immunosuppressive 17-Membered Macrolide from *Khaya Ivorensis*: Structural Determination and Total Synthesis. *Org. Lett.* **2014**, *16*, 2062–2065.

(3) Cascon, S. C.; Mors, W. B.; Tursch, B. M.; Aplin, R. T.; Durham, L. J. Ichthyothereol and Its Acetate, the Active Polyacetylene Constituents of Ichthyothere terminalis (Spreng.) Malme, a Fish Poison from the Lower Amazon. *J. Am. Chem. Soc.* **1965**, *87*, 5237–5241

(4) For a recent review, see: Shi, W.; Lei, A. 1,3-Diyne Chemistry: Synthesis and Derivations. *Tetrahedron Lett.* **2014**, *55*, 2763–2772.

(5) For a recent review, see: Jevric, M.; Nielsen, M. B. Synthetic Strategies for Oligoynes. *Asian J. Org. Chem.* **2015**, *4*, 286–295.

(6) (a) Jahnke, E.; Tykwinski, R. R. The Fritsch–Buttenberg–Wiechell Rearrangement: Modern Applications for an Old Reaction. *Chem. Commun.* **2010**, *46*, 3235–3249; (b) Chalifoux, W. A.; Tykwinski, R. R. Synthesis of Polyynes to Model the *sp*-Carbon Allotrope Carbyne. *Nat. Chem.* **2010**, *2*, 967–971; (c) Métay, E.; Hu, Q.; Negishi, E. Highly Efficient and Selective Synthesis of Conjugated Triynes and Higher Oligoynes of Biological and Materials Chemical Interest via Palladium-Catalyzed Alkynyl−Alkenyl Coupling. *Org. Lett.* **2006**, *8*, 5773–5776; (d) Decicco, R.; Black, A.; Li, L.; Goroff, N. S. An Iterative Method for the Synthesis of Symmetric Polyynes. *Eur. J. Org. Chem*. **2012**, 4699–4704.

(7) Azyat, K.; Jahnke, E.; Rankin, T.; Tykwinski, R. R. Synthesis of Tri- and Tetraynes Using a Butadiynyl Synthon. *Chem. Commun.* **2009**, 433–435.

(8) (a) Fürstner, A. Alkyne Metathesis on the Rise. *Angew. Chem. Int. Ed.* **2013**, *52*, 2794–2819; (b) Ehrhorn, H.; Tamm, M. Well-Defined Alkyne Metathesis Catalysts: Developments and Recent Applications. *Chem. Eur. J.* **2019**, *25*, 3190–3208.

(9) Lysenko, S.; Volbeda, J.; Jones, P. G.; Tamm, M. Catalytic Metathesis of Conjugated Diynes. *Angew. Chem. Int. Ed.* **2012**, *51*, 6757–6761.

(10) Li, S. T.; Schnabel, T.; Lysenko, S.; Brandhorst, K.; Tamm, M. Synthesis of Unsymmetrical 1,3-Diynes via Alkyne Cross-Metathesis. *Chem. Commun.* **2013**, *49*, 7189–7191.

(11) Schnabel, T. M.; Melcher, D.; Brandhorst, K.; Bockfeld, D.; Tamm, M. Unraveling the Mechanism of 1,3-Diyne Cross-Metathesis Catalyzed by Silanolate-Supported Tungsten Alkylidyne Complexes. *Chem. Eur. J.* **2018**, *24*, 9022–9032.

(12) (a) Ungeheuer, F.; Fürstner, A. Concise Total Synthesis of Ivorenolide B. *Chem. Eur. J.* **2015**, *21*, 11387–11392; (b) Schaubach, S.; Gebauer, K.; Ungeheuer, F.; Hoffmeister, L.; Ilg, M. K.; Wirtz, C.; Fürstner, A. A Two-Component Alkyne Metathesis Catalyst System with an Improved Substrate Scope and Functional Group Tolerance: Development and Applications to Natural Product Synthesis. *Chem. Eur. J.* **2016**, *22*, 8494–8507. For pioneer development of Mo-alkylidyne **Cat-2**, see: c) Heppekausen, J.; Stade, R.; Goddard, R.; Fürstner, A. Practical New Silyloxy-Based Alkyne Metathesis Catalysts with Optimized Activity and Selectivity Profiles. *J. Am. Chem. Soc.* **2010**, *132*, 11045–11057 d) Heppekausen, J.; Stade, R.; Kondoh, A.; Seidel, G.; Goddard, R.; Fürstner, A. Optimized Synthesis, Structural Investigations, Ligand Tuning and Synthetic Evaluation of Silyloxy-Based Alkyne Metathesis Catalysts. *Chem. Eur. J.* **2012**, *18*, 10281–10299.

(13) We previously reported that sterically-hindered alkynes could promote high regioselectivity in asymmetric conjugate addition of enynones, see: Tissot, M.; Poggiali, D.; Hénon, H.; Müller, D.; Guénée, L.; Mauduit, M.; Alexakis, A. Formation of Quaternary Stereogenic Centers by NHC-Cu-Catalyzed Asymmetric Conjugate Addition Reactions with Grignard Reagents on Polyconjugated Cyclic Enones. *Chem. Eur. J.* **2012***, 18, 8731–8747.*

(14) Kerisit, N.; Ligny, R.; Gauthier, E. S.; Guegan, J.-P.; Toupet, L.; Guillemin, J.-C.; Trolez, Y. Synthesis and Reactivity of 5-Bromopenta-2,4-diynenitrile (BrC_5N) an Access to π-Conjugated Scaffolds. *Helv. Chim. Acta. **2019**, 102*, e1800232.

(15) CCDC-1908076 (diyne **13d**), CCDC-1908077 (diyne **13e**), CCDC-1966970 (triyne **14c**), CCDC-1908075 (triyne **16**), CCDC-1915266 (triyne **22**) and CCDC-1920652 (triyne **23**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via: www.ccdc.cam. ac.uk/data_request/cif.

(16) The generation of higher polyynes by metathesis was previously reported, see ref. 10. Macrocyclic polyynes were also reported, see: Gross, D. E.; Moore, J. S. Arylene–Ethynylene Macrocycles via Depolymerization–Macrocyclization. *Macromolecules* **2011**, *44*, 3685–3687.

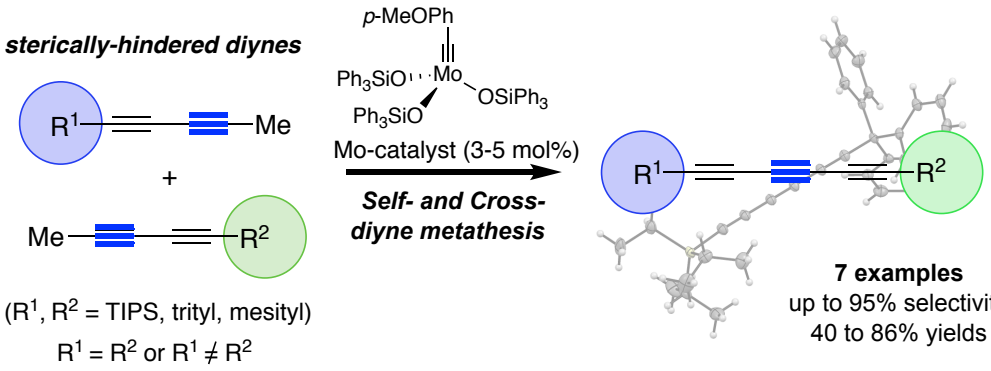
(17) Zhang, W.; Kraft, S.; Moore, J. S. Highly Active Trialkoxymolybdenum(VI) Alkylidyne Catalysts Synthesized by a Reductive Recycle Strategy. *J. Am. Chem. Soc.* **2004**, 126, 329–335.

(18) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. Synthesis of Naturally Occurring Polyacetylenes via a Bis-Silylated Diyne. *Tetrahedron* **2006**, *62*, 5126–5132.

(19) Due to their higher molecular weight, all metathesis reactions with **13d** were monitored by quantitative ^{13}C-NMR spectroscopy.

(20) Tetrayne **19** resulted from the self-metathesis of triyne **17**.

(21) Katz, T. J.; McGinnis, J. Mechanism of the Olefin Metathesis Reaction. *J. Am. Chem. Soc.* **1975**, *97*, 1592–1594.


sterically-hindered diynes
R1
Me
+
Me
R2
(R1, R2 = TIPS, trityl, mesityl)
R1 = R2 or R1 ≠ R2
p-MeOPh
Ph3SiO
Mo
OSiPh3
Ph3SiO
Mo-catalyst (3-5 mol%)
Self- and Cross-diyne metathesis
R1
R2
7 examples
up to 95% selectivity
40 to 86% yields