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Introduction

Polyyynes 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** (ref. 2) and ichthyothereol **2** (ref. 3)) represent the major part of this class of compounds that can be isolated from plants, fungi or bacteria (Fig. 1a). 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-catalysed cross-coupling between **3** and various terminal alkynes that lead to the desired triynes **4** (Fig. 1b).⁷

Despite the mentioned advances in this field, the development of versatile and efficient methodologies is still necessary. Several well-defined W- and Mo-based catalysts (e.g. **Cat-1** and **Cat-2**, Fig. 2) can promote metathesis reactions of alkynes, allowing for the formation of new carbon–carbon triple bonds.⁸ Logically, extension of this methodology to triyne 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** (Fig. 2a). The anticipated conjugated triynes could not be isolated.⁹ In 2013, the authors extended the methodology to diyne cross-metathesis (DYCM) (Fig. 2b)^{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** (Fig. 2c), a key intermediate in the total synthesis of ivorenolide B **1** (Fig. 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 regioselectivity¹³ of diyne metathesis reactions favouring the triyne products over the diyne products as previously reported (Fig. 2d).^{9–12} We would like now to report on a methodology that allows for the unprecedented selective formation of

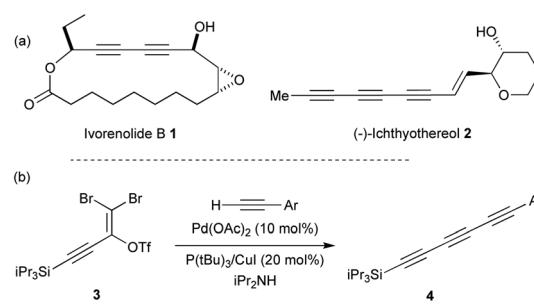


Fig. 1 (a) Examples of natural products containing diynes and triynes. (b) Synthesis of triynes as reported by Tykwinski and co-workers.

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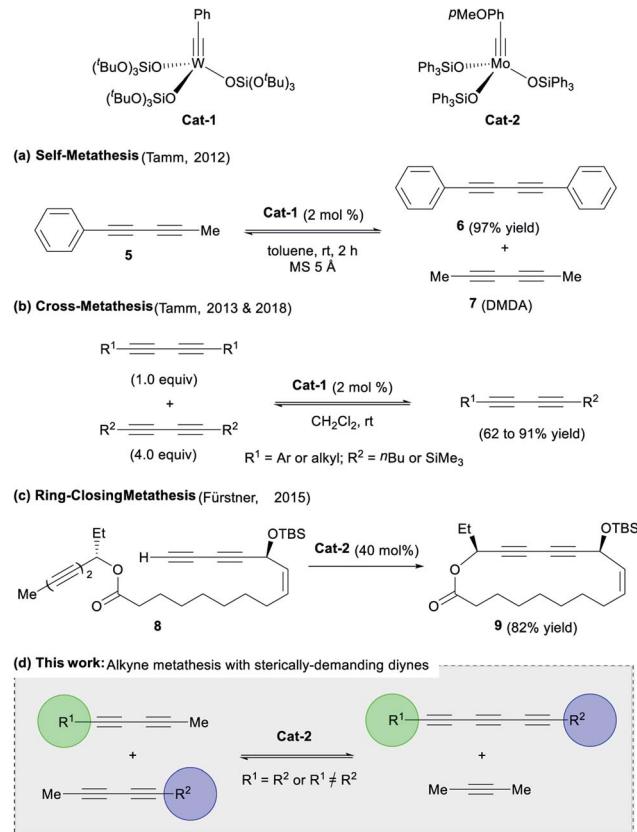


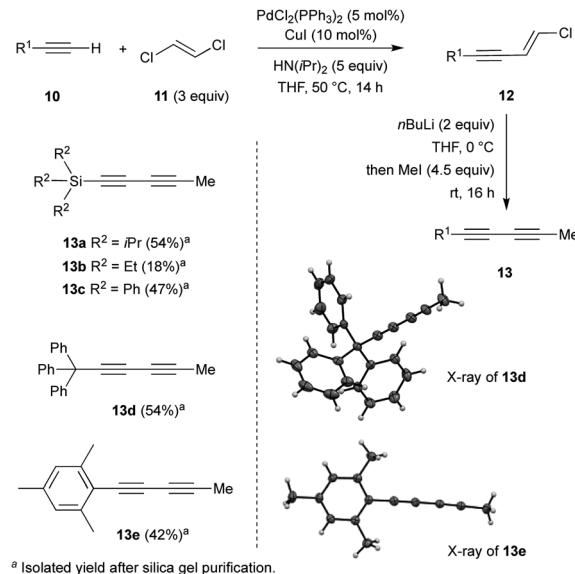
Fig. 2 (a–c) Previous works on diynes metathesis catalysed by Mo- or W-catalysts and (d) the proposed concept for the access of conjugated triynes (This work).

symmetrical and dissymmetrical conjugated triynes from alkyne metathesis.

Results and discussion

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-catalysed 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). The reactivity and behaviour of these more or less sterically-demanding diynes were then assessed in alkyne self- and cross-metathesis. 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). Inspired by the work of Fürstner and co-workers,^{12c} the addition of 4 and 5 Å molecular sieves (MS) in the reaction media to trap 2-butyne could not only increase the



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

conversion up to 96% but also allow for the formation of the desired symmetrical (*TIPS*)₂tryne **14a** in excellent 86% GC yield (Table 1, entry 2). Nevertheless, symmetrical (*TIPS*)₂diyne **15a** was also obtained in a respective triyne/diyne ratio of 86 : 14 (see ESI,† 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.

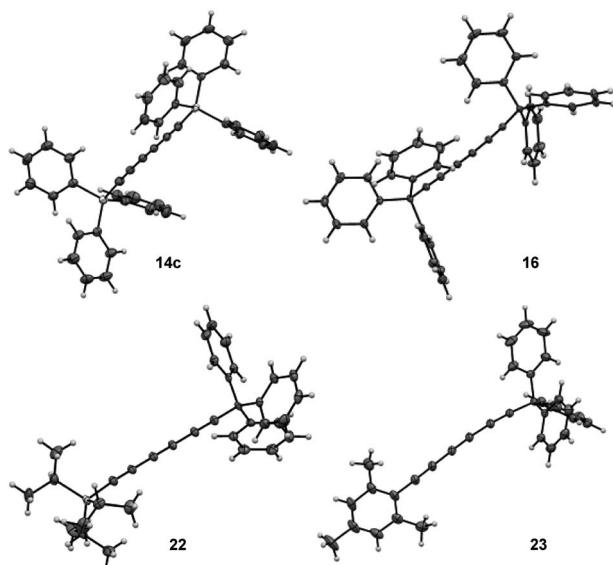
More importantly, the selectivity increased up to 95 : 5 with the lowest catalyst loading, although the GC yield dropped to 59% for triyne **14a** (entry 5). By increasing the scale of the reaction, it was possible to isolate **14a** in good 63% isolated yield after silica gel purification (entry 6). 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).¹⁵ Mo-based complex **Cat-2** appeared quite productive, although symmetrical (TMS)₂diyne **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 behaviour was also observed with TES-diyne **13b** (ratio **14b** : **15b** = 2 : 98) that led to symmetrical (TES)₂diyne **15b** in a moderate 56% GC yield (entry 8). Regarding diyne **13c** featuring a bulkier Ph₃Si group, the expected symmetrical (TPS)₂tryne **14c** was formed more significantly but (TPS)₂diyne **15c** remained predominant (ratio **14c** : **15c** = 40 : 60, entry 9).¹⁶ Moreover, X-ray diffraction analysis could be done allowing to confirm the solid-state structure of desired triyne **14c** that exhibited usual geometrical features for this kind of compounds^{6b} (Fig. 3).



Table 1 Self-metathesis of silylated diynes **13a–c,f** catalysed by Mo-complex **Cat-2**^a

| Entry | Diyne | Cat-2 (mol%) | Conv. ^b (%) | Ratio 14 : 15 ^c | Yield 14 ^b | | Yield 15 ^b | |
|----------------|------------|-----------------|------------------------|--|------------------------------|------------------------------|------------------------------|------------------------------|
| | | | | | Yield 14 ^b | Yield 15 ^b | 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 4 Å/5 Å (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 4 Å/5 Å. ^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 ¹³C NMR spectroscopy. ^l Estimated yield from an isolated mixture of **14c** + **15c**.

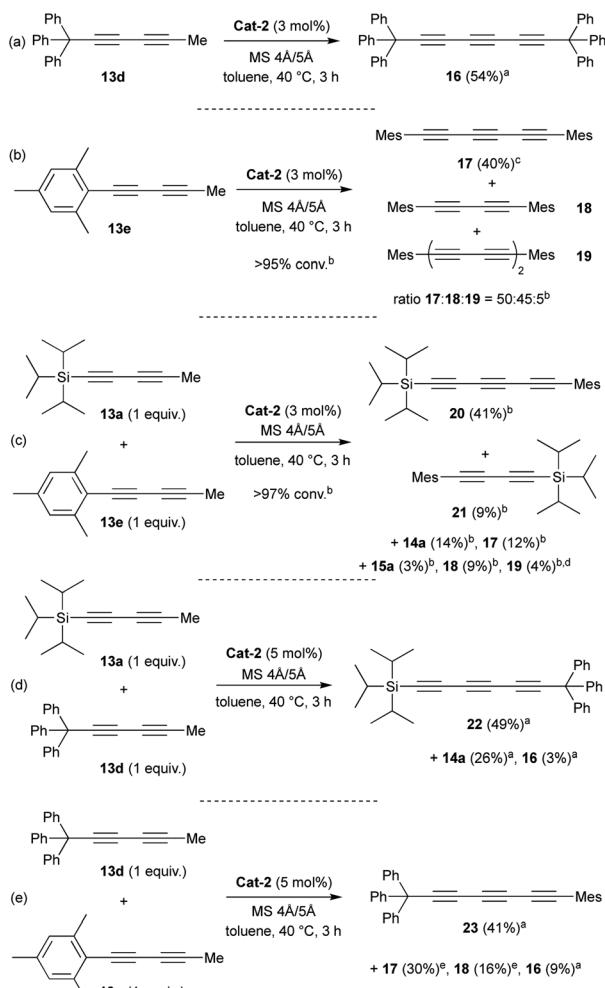
Fig. 3 Solid-state structures of symmetrical triynes **14c** and **16** and dissymmetrical triynes **22** and **23** from single crystal X-ray diffraction.

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 2a).

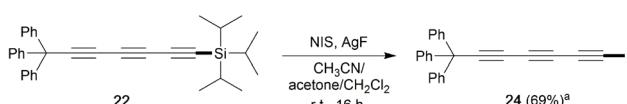
Furthermore, X-ray diffraction analysis unambiguously confirmed the structure of trityl-substituted triyne **16** (Fig. 3). Additionally, the stability of trityl-triyne **16** toward the Mo-benzylidene catalyst was evaluated, as the competitive conversion of triyne to higher polyynes was suspected. Triyne **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 behaviour was also observed with a mixture of triyne/diyne **14a/15a** (81/19 ratio) without any alteration of the triyne/diyne ratio (see ESI for details†). Those additional experiments highlighted the remarkable stability of the triynes into the reactive media. Mo-benzylidene catalyst was also efficient toward mesityl-substituted diyne **13e** affording the expected symmetrical triyne **17** in moderate 40% GC-MS yield (Scheme 2b). 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).¹⁷ The steric hindrance of the mesityl group appeared thus less suitable to promote the selective formation of the triyne metathesis product. The more challenging cross-metathesis reaction was then studied. First, by reacting TIPS- and Mes-diyne **13a** and **13e**, the formation of the highly desirable dissymmetrical triyne **20** as the major product was observed, reaching 41% GC yield (Scheme 2c). 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





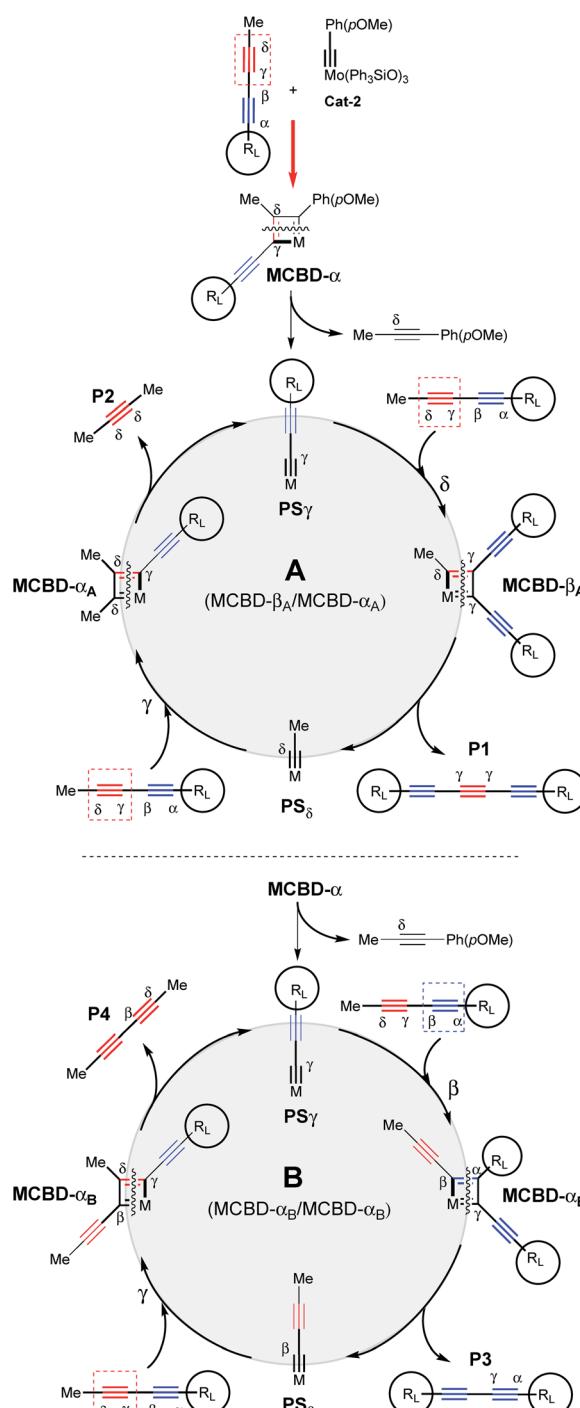
Scheme 2 Scope of self- and cross-metathesis catalysed by Mo-complex **Cat-2**. ^aIsolated yield after silica gel chromatography. ^bDetermined by GC-MS analysis. ^cYield determined by GC-MS analysis with *n*-dodecane as the internal standard. ^d(TIPS)₂tetrayne and TIPS/Mes-tetrayne were also detected (1–3%). ^eYield from an inseparable isolated mixture of **17** + **18** (ratio = 55/45).

15 and **18** (3 and 9%, resp.). Of note, few traces (1–4%) of symmetrical/dissymmetrical tetrynes were also detected (see ESI 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 2d and 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 (Fig. 3).



Scheme 3 Post-functionalization of dissymmetrical triyne **22** (^a isolated yield after silica gel purification).

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*-



Scheme 4 Proposed mechanism for the self-metathesis of sterically-hindered diynes catalysed by Mo-complex **Cat-2** leading to conjugated triynes (cycle A) or diynes (cycle B). Reversibility is expected for each step. Only productive metathesis steps are represented.

iodosuccinimide (NIS). The expected 7-iodohepta-2,4,6-triyne-1-trityl **24** was isolated in good 69% isolated yield. 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,^{9–11,18} a catalytic cycle could be proposed. 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 **MCBD- α** leading to propagating species **PS γ** . The latter is then engaged through the catalytic cycle **A** by reacting again towards the less hindered $\equiv\text{C}$ triple bond to produce the valuable symmetrical (γ,γ)-triyne **P1**. In opposition, if **PS γ** reacts with the more hindered internal α,β -alkyne, a catalytic cycle **B** already described by Tamm and co-workers is involved and explains the formation of the undesired diyne product **P3**.¹¹

Conclusions

In conclusion, it was demonstrated herein that the utilization of sterically-hindered diynes can modify the selectivity of alkyne metathesis to favour the formation of the desired triynes. Therefore, for the first time, the synthesis of symmetrical and dissymmetrical conjugated triynes by self- and cross-metathesis was successfully achieved. By involving an efficient molybdenum benzylidene complex,¹⁹ 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 demonstrating higher selectivity and productivity.²⁰

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- For a recent review, see: A. L. K. Shi Shun and R. R. Tykwienski, *Angew. Chem., Int. Ed.*, 2006, **45**, 1034.
- Y. Wang, Q.-F. Liu, J.-J. Xue, Y. Zhou, H.-C. Yu, S.-P. Yang, B. Zhang, J.-P. Zuo, Y. Li and J.-M. Yue, *Org. Lett.*, 2014, **16**, 2062.

- S. C. Cascon, W. B. Mors, B. M. Tursch, R. T. Aplin and L. J. Durham, *J. Am. Chem. Soc.*, 1965, **87**, 5237.
- For a recent review, see: W. Shi and A. Lei, *Tetrahedron Lett.*, 2014, **55**, 2763.
- For a recent review, see: M. Jevric and M. B. Nielsen, *Asian J. Org. Chem.*, 2015, **4**, 286.
- (a) E. Jahnke and R. R. Tykwienski, *Chem. Commun.*, 2010, **46**, 3235; (b) W. A. Chalifoux and R. R. Tykwienski, *Nat. Chem.*, 2010, **2**, 967; (c) E. Métay, Q. Hu and E. Negishi, *Org. Lett.*, 2006, **8**, 5773; (d) R. Decicco, A. Black, L. Li and N. S. Goroff, *Eur. J. Org. Chem.*, 2012, 4699.
- K. Azyat, E. Jahnke, T. Rankin and R. R. Tykwienski, *Chem. Commun.*, 2009, 433.
- For recent reviews, see: (a) A. Fürstner, *Angew. Chem., Int. Ed.*, 2013, **52**, 2794; (b) H. Ehrhorn and M. Tamm, *Chem.-Eur. J.*, 2019, **25**, 3190; (c) A. Fürstner, *Handbook of Metathesis*, ed. R. R. Grubbs, A. G. Wenzel, D. J. O'Leary and E. Khosravi, 2nd edn, Wiley-VCH, Weinheim, Germany, 2015, ch. 6.
- S. Lysenko, J. Volbeda, P. G. Jones and M. Tamm, *Angew. Chem., Int. Ed.*, 2012, **51**, 6757.
- S. T. Li, T. Schnabel, S. Lysenko, K. Brandhorst and M. Tamm, *Chem. Commun.*, 2013, **49**, 7189.
- T. M. Schnabel, D. Melcher, K. Brandhorst, D. Bockfeld and M. Tamm, *Chem.-Eur. J.*, 2018, **24**, 9022.
- (a) F. Ungeheuer and A. Fürstner, *Chem.-Eur. J.*, 2015, **21**, 11387; (b) S. Schaubach, K. Gebauer, F. Ungeheuer, L. Hoffmeister, M. K. Ilg, C. Wirtz and A. Fürstner, *Chem.-Eur. J.*, 2016, **22**, 8494 For pioneer development of Mo-alkylidene **Cat-2**, see: (c) J. Heppekausen, R. Stade, R. Goddard and A. Fürstner, *J. Am. Chem. Soc.*, 2010, **132**, 11045; (d) J. Heppekausen, R. Stade, A. Kondoh, G. Seidel, R. Goddard and A. Fürstner, *Chem.-Eur. J.*, 2012, **18**, 10281.
- We previously reported that sterically-hindered alkynes could promote high regioselectivity in asymmetric conjugate addition of enynones, see: M. Tissot, D. Poggiali, H. Hénon, D. Müller, L. Guénée, M. Mauduit and A. Alexakis, *Chem.-Eur. J.*, 2012, **18**, 8731.
- N. Kerisit, R. Ligny, E. S. Gauthier, J.-P. Guegan, L. Toupet, J.-C. Guillemin and Y. Trolez, *Helv. Chim. Acta*, 2019, **102**, e1800232.
- V. Fiandanese, D. Bottalico, G. Marchese and A. Punzi, *Tetrahedron*, 2006, **62**, 5126.
- Due to their higher molecular weight, all metathesis reactions with **13d** were monitored by quantitative ^{13}C -NMR spectroscopy.
- Tetryne **19** resulted from the self-metathesis of triyne **17**.
- T. J. Katz and J. McGinnis, *J. Am. Chem. Soc.*, 1975, **97**, 1592.
- (a) W. Zhang, S. Kraft and J. S. Moore, *J. Am. Chem. Soc.*, 2004, **126**, 329; (b) D. E. Gross and J. S. Moore, *Macromolecules*, 2011, **44**, 3685; (c) P. Persich, J. Llaveria, R. Lhermet, T. de Haro, R. Stade, A. Kondoh and A. Fürstner, *Chem.-Eur. J.*, 2013, **19**, 13047.
- (a) M. Koy, I. Elser, J. Meisner, W. Frey, K. Wurst, J. Kästner and M. R. Buchmeiser, *Chem.-Eur. J.*, 2017, **23**, 15484; (b) J. Hillenbrand, M. Leutzsch and A. Fürstner, *Angew. Chem., Int. Ed.*, 2019, **58**, 15690.

