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### Introduction

Polyynes are an important class of natural products which display a broad array of biological activities such as antibacterial, antimicrobial, antitumor and anticancer properties.<sup>1</sup> 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,<sup>4</sup> the triyne moiety appears more difficult to access and represents a synthetic challenge.<sup>5</sup> Several methods have been developed to access symmetrical and unsymmetrical triynes.<sup>6</sup> 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).<sup>7</sup>

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.<sup>8</sup> 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.

# Expedient synthesis of conjugated triynes via alkyne metathesis†

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The first synthesis of conjugated triynes by molybdenum-catalysed 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 the 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.

This strategy was recently attempted by Tamm and coworkers 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 trivnes could not be isolated.9 In 2013, the authors extended the methodology to divne cross-metathesis (DYCM) (Fig. 2b)<sup>10,11</sup> resulting in unsymmetrical divnes 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 ringclosing metathesis (RCM) of a bis-diyne 8 with molybdenumalkyne 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 regioselectivity<sup>13</sup> of diyne metathesis reactions favouring the trivne products over the divne 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).<sup>14</sup> Starting from terminal alkynes 10, the Pd-catalysed Sonogashira coupling with (*E*)-1,2-dichloro-ethylene 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 coworkers,<sup>12e</sup> 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)<sub>2</sub>triyne **14a** in excellent 86% GC yield (Table 1, entry 2). Nevertheless, symmetrical (TIPS)<sub>2</sub>diyne **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 trivne as the major metathesis product, it was investigated whether less sterically-hindered Sisubstituent such as trimethylsilyl (TMS), triethylsilyl (TES) or triphenylsilyl (TPS) groups would give preferentially rise to the symmetrical divne or the trivne product. Hence, TMS-divne 13f was synthesized according to a protocol from the literature and exposed to the aforementioned conditions (3 mol%, 40 °C, 3 h).<sup>15</sup> Mo-based complex Cat-2 appeared quite productive, although symmetrical (TMS)<sub>2</sub>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 behaviour was also observed with TES-divne 13b (ratio 14b: 15b = 2:98) that led to symmetrical (TES)<sub>2</sub>diyne 15b in a moderate 56% GC yield (entry 8). Regarding diyne 13c featuring a bulkier Ph<sub>3</sub>Si group, the expected symmetrical (TPS)2triyne 14c was formed more significantly but (TPS)<sub>2</sub>diyne 15c remained predominant (ratio 14c: 15c = 40: 60, entry 9).<sup>16</sup> 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<sup>6b</sup> (Fig. 3).

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



Entry	Diynes	<b>Cat-2</b> (mol%)	$\operatorname{Conv.}^{b}(\%)$	Ratio <b>14 : 15</b> <sup><i>c</i></sup>	Yield <b>14</b> <sup>b</sup>	Yield $15^b$
1 <sup><i>d</i></sup>	139	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 <sup><i>f</i></sup>	13a	3	96	81:19	63 <sup>g</sup>	_
7 <sup>h</sup>	13f	3	91	0:100	_	48
8	13b	3	>98	2:98	_	56
$9^i$	13c	3	95 <sup>j</sup>	$40:60^{k}$	$12^{k \ l}$	$19^{k l}$

<sup>*a*</sup> 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. <sup>*b*</sup> Determined by GCanalysis with acetophenone as internal standard. <sup>*c*</sup> Determined by GC-analysis. <sup>*d*</sup> Performed without MS 4 Å/5 Å. <sup>*e*</sup> Performed at 20 °C. <sup>*f*</sup> Performed at 0.55 mmol-scale. <sup>*g*</sup> Isolated yield after silica gel chromatography. <sup>*h*</sup> Performed at 20 °C over 1 h. <sup>*i*</sup> Performed at 0.26 mmol-scale. <sup>*j*</sup> Based on the recovered starting material. <sup>*k*</sup> Determined by quantitative <sup>13</sup>C NMR spectroscopy. <sup>*l*</sup> 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 Mobenzylidyne catalyst was evaluated, as the competitive conversion of trivne to higher polyvnes was suspected. Trivne 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 trivne/divne ratio (see ESI for details<sup>†</sup>). Those additional experiments highlighted the remarkable stability of the triynes into the reactive media. Mo-benzylidyne catalyst was also efficient toward mesitylsubstituted diyne 13e affording the expected symmetrical trivne 17 in moderate 40% GC-MS yield (Scheme 2b). However, GC-MS analysis evidenced a significant formation of symmetrical divne 18 but also some traces of tetravne 19 (ratio 17: 18: 19 = 50: 45: 5.<sup>17</sup> The steric hindrance of the mesityl group appeared thus less suitable to promote the selective formation of the trivne metathesis product. 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 trivne 20 as the major product was observed, reaching 41% GC yield (Scheme 2c). Unsurprisingly, some amounts of symmetrical trivnes 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 Mocomplex Cat-2. <sup>a</sup>Isolated yield after silica gel chromatography. <sup>b</sup>Determined by GC-MS analysis. <sup>c</sup>Yield determined by GC-MS analysis with *n*-dodecane as the internal standard. <sup>d</sup>(TIPS)<sub>2</sub>tetrayne and TIPS/ Mes-tetrayne were also detected (1–3%). <sup>e</sup>Yield 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 tetraynes were also detected (see ESI for details<sup>†</sup>). 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 (<sup>a</sup> isolated yield after silica gel purification).

In order to show the synthetic potential of this methodology to furnish valuable triyne building-blocks, the posttransformation 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*-

-Ph

18

19



Scheme 4 Proposed mechanism for the self-metathesis of stericallyhindered 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-1trityl 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<sub>L</sub>-substituent of the divne, and according to the established mechanism of the alkyne metathesis,9-11,18 a catalytic cycle could be proposed. If R<sub>L</sub> is large enough, Mo-based complex Cat-2 reacts preferably with the less hindered  $\delta$ ,  $\gamma$ -CC triple bond to form the metallacyclobutadiene MCBD-α leading to propagating species  $PS\gamma$ . The latter is then engaged through the catalytic cycle A by reacting again towards the less hindered C=C triple bond to produce the valuable symmetrical  $(\gamma, \gamma)$ triyne P1. In opposition, if  $PS\gamma$  reacts with the more hindered internal  $\alpha,\beta$ -alkyne, a catalytic cycle **B** already described by Tamm and co-workers is involved and explains the formation of the undesired divne 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 molyb-denum benzylidyne complex,<sup>19</sup> 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.<sup>20</sup>

## Conflicts of interest

There are no conflicts to declare.

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