

## A highly chemo-, regio-, and stereoselective metallacycle-mediated annulation between a conjugated enyne and an ene-diyne

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In honor our friend and colleague, Professor Gordon Gribble

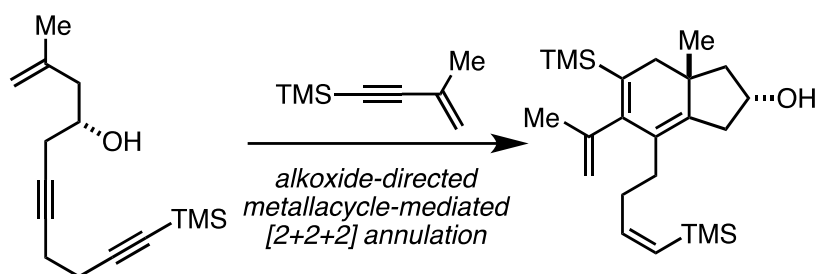
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### Abstract

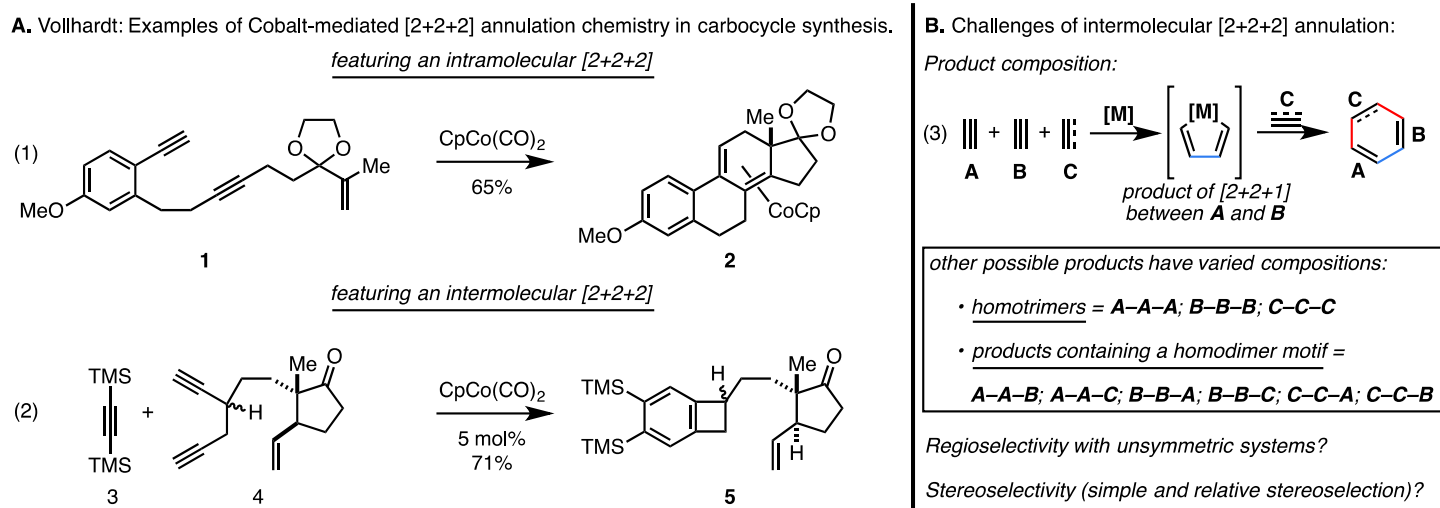
Alkoxide-directed metal-centered intermolecular [2+2+2] annulation is shown to chemo-, regio-, and stereoselectively engage two polyunsaturated substrates in productive cyclization chemistry. This annulation process is unique in the field, revealing that it is possible to selectively engage three of five  $\pi$ -systems residing in the coupling partners in initial [2+2+2] reaction, and demonstrating that one of the two remaining  $\pi$ -systems (the TMS-alkyne) can ultimately serve to simply generate a new metallacyclopentene of great potential value in additional metallacycle-mediated coupling chemistry.



**Keywords:** Metallacycle-mediated cross-coupling, titanium, chemoselective, directed C–C bond-formation, tandem reaction.

## Introduction

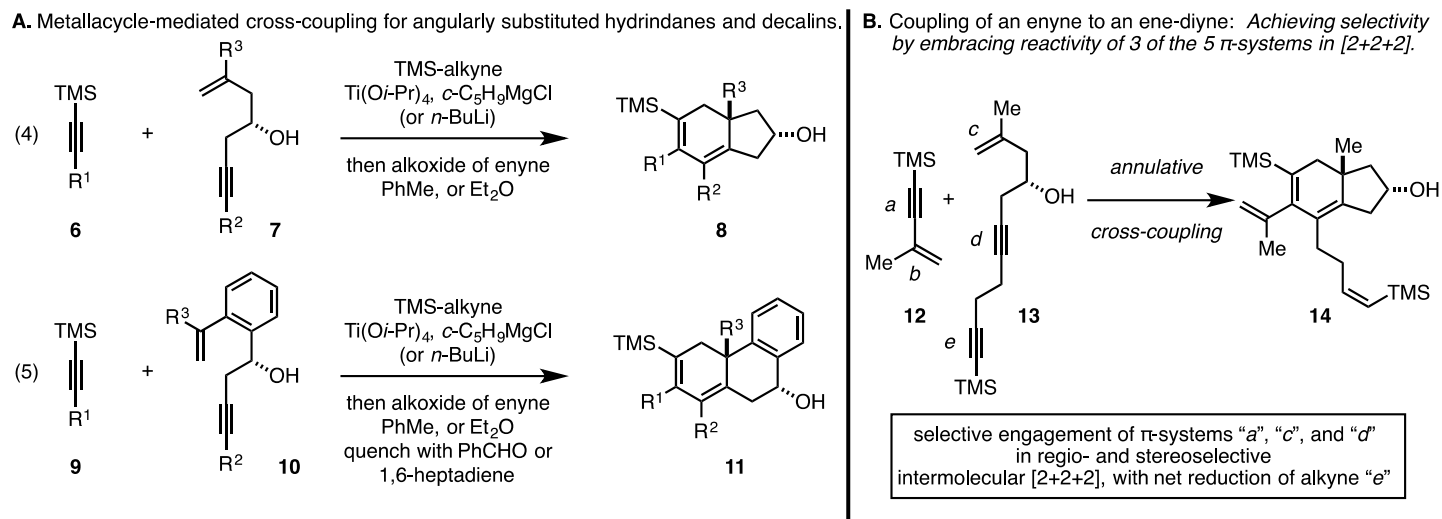
Since the pioneering work of Professor Vollhardt that revealed the great value of metal-centered [2+2+2] annulation chemistry for accessing stereodefined carbo- and heterocyclic targets, this area of organometallic chemistry has grown to occupy a unique role in organic synthesis (Figure 1A).<sup>1-5</sup> These reactions that may be considered to be inspired by the foundation of chemistry first established by Reppe,<sup>6</sup> and later developed by luminaries in the field, often embrace organometallic intermediates of relevance for [2+2+2] annulation as a means to realize a large swathe of complex and diverse bond-forming reactions.<sup>7-13</sup> While many of these advances have been demonstrated to be of great value in complex molecule or natural product synthesis,<sup>14</sup> it is typically the case that intermolecular versions of this type of organometallic chemistry are rather restricted in scope, and therefore of limited value in stereoselective synthesis, including natural product synthesis.<sup>14</sup> As illustrated in Figure 1B, controlling intermolecular reactivity in metallacycle-mediated coupling chemistry is challenging due to the possibility of generating products of varied composition, in addition to the clear issues of selectivity that surface when employing: (a) unsymmetrical systems (regioselectivity), (b) alkenes as one of the three reactive  $\pi$ -systems ( $\pi$ -facial selectivity), and/or (c) polyunsaturated substrates where issues of chemoselectivity surface.



**Figure 1.** Introduction to metal-centered [2+2+2] annulation chemistry.

For over ten years, we have been interested in establishing principles that ultimately result in avoiding the common dependence on intramolecularity and/or use of symmetrical substrates in this rather broad area of chemistry. To date, we have reported over thirty distinct and highly selective coupling reactions between a variety of unsymmetrically substituted unsaturated systems, and have demonstrated the utility of these reactions in total synthesis and function-oriented synthesis<sup>15</sup> of representative members of diverse families of natural products (alkaloids, terpenoids, and polyketides).<sup>16-27</sup> These reactions, termed metallacycle-mediated cross-coupling processes, have recently grown to include [2+2+2] annulation reactions between alkynes and 1,6- and 1,7-enynes as a means to prepare angularly substituted hydrindanes and decalins (Figure 2A).<sup>28-32</sup> Here, in efforts that aimed to explore the question of whether it is possible to chemoselectively engage two polyunsaturated substrates in metallacycle-mediated annulative cross-coupling, we have elucidated the first organometallic transformation of its kind, where four of five resident  $\pi$ -unsaturations in the overall reaction are embraced as sites of reactivity in a highly selective annulation reaction (Figure 2B).

## Results and Discussion

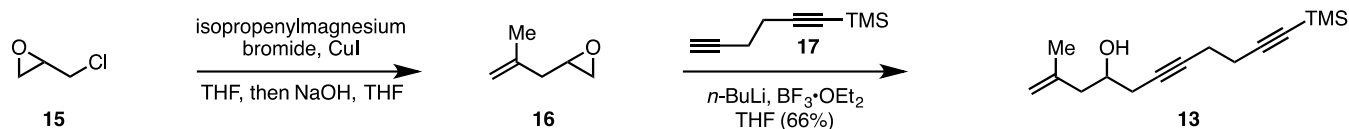
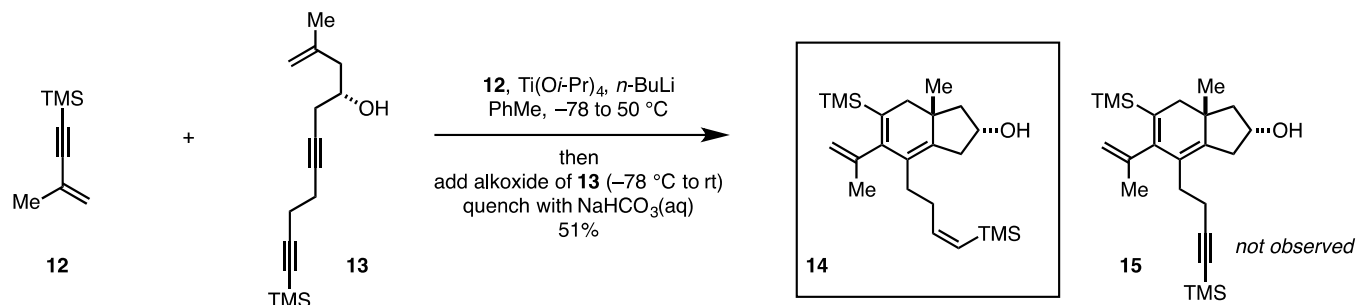


**Figure 2.** Alkoxide-directed metallacycle-mediated annulative cross-coupling and selective engagement of a subset of  $\pi$ -systems resident in polyunsaturated substrates.

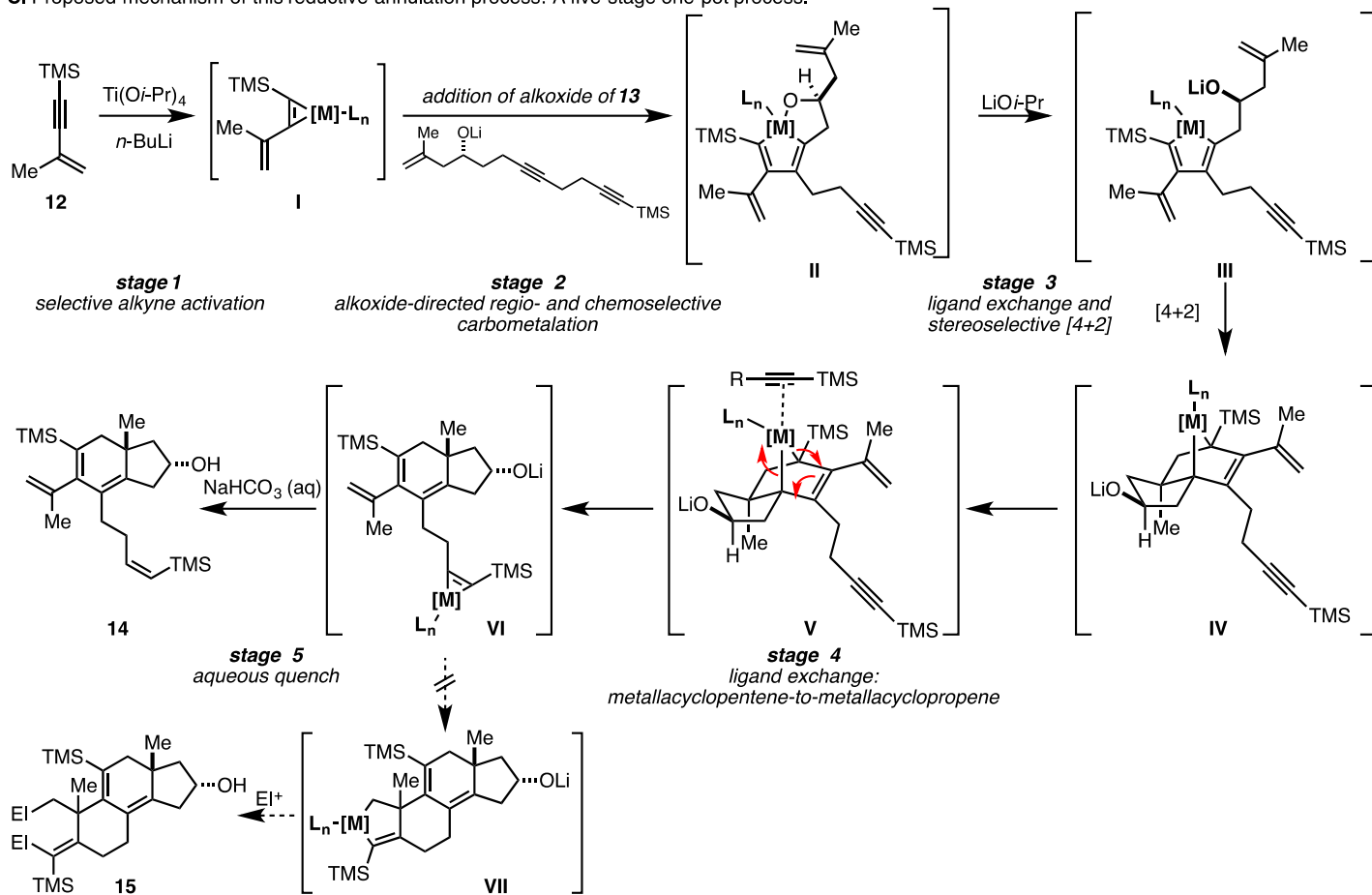
To explore the coupling reaction depicted in Figure 2B, efforts were first directed toward the synthesis of the desired ene-diyne **13**. As illustrated in Figure 3A, epichlorohydrin was easily advanced to the desired ene-diyne **13** by initial reaction with isopropenylmagnesium bromide and CuI, followed by treatment with base to generate the low molecular weight alkenyl epoxide **16**.<sup>33</sup> With this intermediate in hand, regioselective opening of the epoxide with the Li-acetylide of diyne **17**, promoted by the action of  $\text{BF}_3 \cdot \text{OEt}_2$ , delivered the desired coupling partner **13** in 66% yield.

Ti-mediated annulation was then pursued as depicted in Figure 3B. Initial chemoselective activation of the commercially available enyne **12** by the action of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and *n*-BuLi, followed by addition of the lithium alkoxide of ene-diyne **13** as a solution in PhMe, and quenching of the reaction with aqueous  $\text{NaHCO}_3$ , resulted in the formation of the cross-conjugated triene-containing hydrindane **14**, isolated in 51% yield as a single regio- and stereoisomer – no evidence was found for the formation of any other isomer of this coupled product, nor was evidence found for the presence of the TMS-alkyne containing product **15**.<sup>32</sup>

As depicted in Figure 3C, a mechanistic rationale for the formation of **14** is based on initial alkoxide-directed reaction between the preformed Ti-alkyne complex of **12** (I) with the internal alkyne of ene-diyne **13** that is proximal to the hydroxy group. The resulting fully substituted metallacyclopentadiene (III) can then participate in stereoselective intramolecular [4+2] to deliver the bridged bicyclic metallacyclopentene intermediate IV. We currently believe that this intermediate serves as the source of Ti for ligand transfer to the third reactive alkyne of this substrate combination (the TMS-alkyne of the ene-diyne coupling partner **13**), resulting in the intermediacy of a new titanacyclopropene intermediate (VI). Interestingly, this intermediate organometallic does not appear competent to engage the 1,1-disubstituted alkene in carbometalation chemistry *en route* to the generation of a new carbocyclic system (VI  $\rightarrow$  VII  $\rightarrow$  **15**).<sup>34</sup> Rather, aqueous quenching of this reaction delivers the tricyclic product **14** that contains a pendent (Z)-vinylsilane.

A. Synthesis of the ene-diyne coupling partner **13**.B. Coupling of enyne **12** with ene-diyne **13** deliver a reduced product of annulation.

## C. Proposed mechanism of this reductive annulation process: A five-stage one-pot process.

Figure 3. Synthesis of ene-diyne **13**, and exploration in metallacycle-mediated annulative cross-coupling.

## Conclusions

A unique and highly selective intermolecular [2+2+2] annulation reaction of polyunsaturated substrates has been described. The reaction is believed to be possible due to the power of alkoxide-direction as a force

to control the regio- and stereochemical course of metallacycle-mediated coupling reactions. Observations made in the course of this study have led to the hypothesis that a pendent alkyne on the enyne substrate has the potential to engage the bridged bicyclic organometallic intermediate generated in the course of [2+2+2] annulation in a simple ligand exchange reaction, and defines a unique sequence of chemical transformations of potential value in more complex multi-component coupling chemistry. We look forward to exploring the value of this new sequence for addressing challenging problems associated with the synthesis of terpenoid and terpenoid-inspired targets.

## Experimental Section

**Synthesis of (3*R*,4*R*)-4-((*tert*-butyldimethylsilyloxy)-4-(furan-2-yl-3-methylbutan-1-ol (14).** To a solution of 2-methyl-4-trimethylsilyl-1-butene (**12**, 1.288 mL, 7.24 mmol) in anhydrous toluene (45 mL) was added Ti(*O-i*-Pr)<sub>4</sub> (2.145 mL, 7.24 mmol) at rt. The mixture was cooled to –78 °C and *n*-BuLi (2.46 M in hexanes, 5.87 mL, 14.46 mmol) was added dropwise via syringe. The reaction flask was removed from the cooling bath and the mixture was warmed to rt before heating to 50 °C (without a reflux condenser) for 1 h. After this period, the reaction solution was cooled to rt and then placed in a –78 °C cooling bath.

Simultaneously, ene-diyne **13** (0.600 g, 2.41 mmol) was dissolved in anhydrous toluene (15 mL) and treated with *n*-BuLi (2.46 M in hexanes, 0.981 mL, 2.41 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 15 minutes, and then warmed to rt over 5 minutes. The alkoxide solution was added dropwise, via cannula, to the Ti-alkyne complex and then gradually warmed to rt overnight (13 h). The reaction mixture was quenched with saturated aq NaHCO<sub>3</sub> (40 mL), and the organic and aqueous phases were separated. The aqueous layer was extracted with EtOAc (× 3), and the combined organic phases were dried over anhydrous MgSO<sub>4</sub>. The supernatant was removed from the drying agent by vacuum filtration through a glass fritted funnel, and the solvents were removed *in vacuo* to afford the crude product, which was purified by flash column chromatography with 89:11 hexanes–EtOAc to afford **14** (475 mg, 51%) as a clear, colorless, amorphous solid.

**Analytical Data for 14.** TLC (SiO<sub>2</sub>) R<sub>f</sub> = 0.30 (hexanes–ethyl acetate, 87:13); <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 6.26 (dt, *J* = 14.0, 7.0 Hz, 1H), 5.46 (d, *J* 14.2 Hz, 1H), 4.99 (app s, 1H), 4.80 (br s, 1H), 4.48 (app quintet, *J* 6.9 Hz, 1H), 2.83 (dd, *J* 17.7, 7.4 Hz, 1H), 2.36 (dd, *J* 17.7, 6.3 Hz, 1H), 2.22 (d, *J* 15.4 Hz, 1H), 2.17–2.02 (m, 5H), 2.01 (d, *J* 15.4 Hz, 1H), 1.77 (br s, 3H), 1.50 (dd, *J* 12.3, 7.8 Hz, 1H), 0.84 (s, 3H), 0.10 (s, 9H), 0.09 (s, 9H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 149.9, 149.2, 146.2, 145.3, 129.1, 128.5, 128.0, 115.8, 72.2, 51.1, 40.7, 39.6, 38.8, 33.7, 29.8, 24.6, 21.0, 0.4; IR (neat) 3315, 2953, 2924, 1606, 1246, 850, 836 cm<sup>-1</sup>; HRMS (ES-TOF) *m/z* [M + H]: calcd for C<sub>23</sub>H<sub>41</sub>OSi<sub>2</sub> 389.2696; found 389.2701.

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## Supplementary Material

Supplemental material includes  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for all new compounds.

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