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# Alternative routes to tricyclic cyclohexenes with trinuclear palladium complexes

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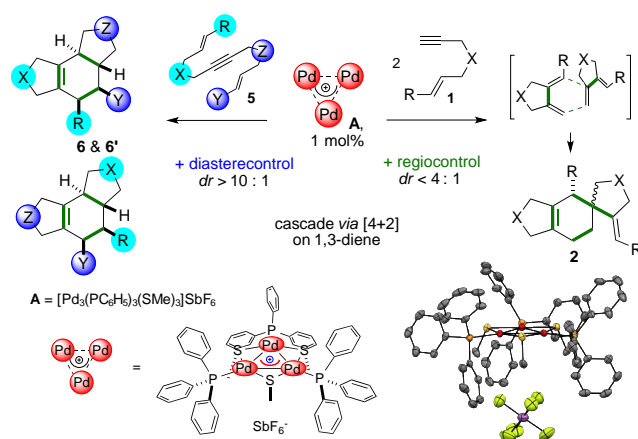
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**ABSTRACT:** Highly symmetric all-metal aromatic Pd<sub>3</sub><sup>+</sup> complexes can catalyze the cycloisomerization of terminal 1,6-enynes and internal dienynes under mild conditions. Modification of substrates dictates the mechanism and steers the reaction towards different polycyclic frameworks, enabling the development of complex cascades. The reactivity of Pd<sub>3</sub><sup>+</sup> complexes is complementary to that of mononuclear Pd(0) and Pd(II) ones. **KEYWORDS:** *alkynes, aromaticity, multinuclear catalysis, cascades, diastereoselectivity.*

All-metal aromatics are an intriguing class of cyclic molecules that parallel their prototypical carbon-based peers by presenting a similarly delocalized bonding network.<sup>1</sup> These structures have exotic metal-metal bonds. However, in most cases their limited stability prevented widespread experimental applications.<sup>2</sup> Taking advantage of a straightforward synthetic route<sup>3</sup> to a family of bench-stable Pd<sub>3</sub><sup>+</sup> complexes that are the noble-metal analogues of the cyclopropenyl cation,<sup>4</sup> we have been able to observe their spectacular ability to semi-reduce alkynes under transfer hydrogenation conditions.<sup>5</sup> In these reactions, terminal alkynes polymerize. This let us speculate that it could have been possible to develop selective C–C forming events too.

Cycloisomerization<sup>6</sup> are prototypical sustainable reactions that have been intensely studied exploiting mononuclear soft  $\pi$ -acidic noble metal complexes.<sup>7</sup> Upon pioneering work by Trost,<sup>8</sup> many elegant cascades of polyunsaturated reagents have been triggered by palladium.<sup>9</sup> Several complementary mechanisms have been studied in these sequences, involving each of the most common oxidation states of this metal (0, II and IV). To the best of our knowledge, no discrete palladium cluster has been able yet to induce the selective formation of C–C bonds from unsaturated reagents.

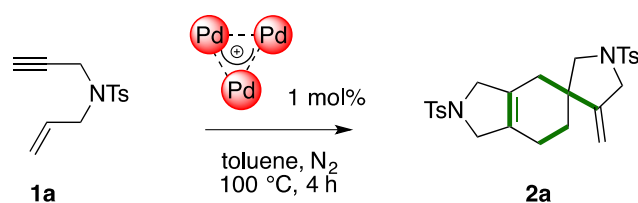


**Scheme 1.** C-C forming sequences to tricyclic cyclohexenes and the complex used in this study

We report herein the distinct reactivity of either terminal enynes or internal dienynes with all-metal aromatic  $\text{Pd}_3^+$  complexes (Scheme 1). Complex polycyclic architectures, namely tricycles with a central cyclohexene featuring a synthetically challenging tetrasubstituted double bond and up to four contiguous stereocenters could be readily obtained. Hints on the mechanism of these two different sequences suggest that they occur through pathways alternative to those observed with mononuclear complexes. In initial experiments, 1,6-enyne **1a** was mixed with 1 mol% of  $\text{Pd}_3^+$  complex **A** in a dry and degassed solvent. The solution was then warmed and samples were periodically taken to monitor the reaction by TLC. Upon screening a variety of conditions, we never observed the least trace of conversion. However, addition of triethylammonium formate (2 equiv.) gave a proof of principle of the feasibility of our

approach (Table 1, entry 1). Full conversion of **1a** was observed upon 6 hours. The main product was the linear diene coming from reduction of **1a** (35%) and broad  $^{13}\text{C}$  NMR peaks suggested that partial polymerization occurred despite a dilute mixture (0.06 M on **1a**). We were however intrigued by appearance of NMR resonances different from those of literature precedents.<sup>8</sup> Isolation and characterization of the product (**2a**, 21%) revealed that a formal enyne dimerization occurred, enabling the assembly of three fused cycles through the creation of four new C–C bonds. The central ring of **2** had a hindered tetra-substituted double bond and a spiro carbon.

TABLE 1. Dimerization of enyne 1a

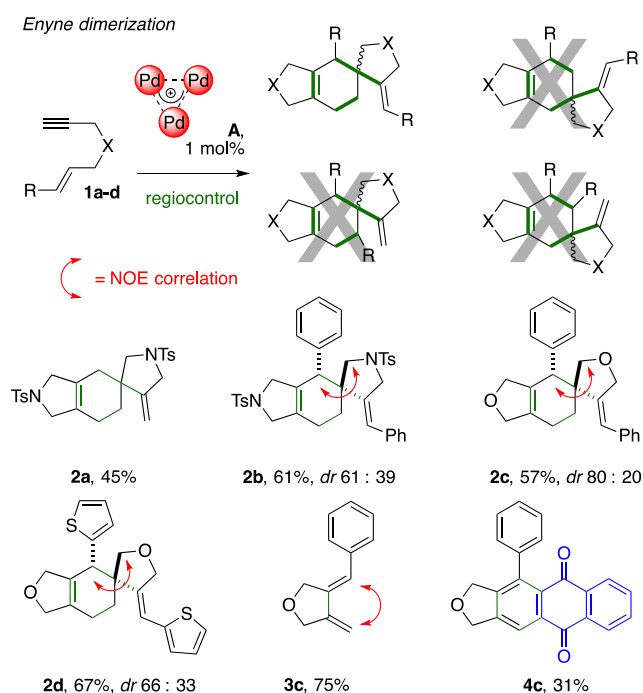


Entry <sup>[a]</sup>	Additive	Yield of <b>2a</b> (%) <sup>[b]</sup>	Entry <sup>[a]</sup>	Additive	Yield of <b>2a</b> (%) <sup>[b]</sup>
1	Et <sub>3</sub> NHCO <sub>2</sub> H <sup>[c]</sup>	21	6	C <sub>7</sub> H <sub>7</sub> SO <sub>3</sub> H	-
2	Et <sub>3</sub> NHCO <sub>2</sub> H	27	7	CH <sub>3</sub> CO <sub>2</sub> H	45
3	Et <sub>3</sub> N	-	8	C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> H	45
4	HCO <sub>2</sub> H	35	9	C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> H <sup>[d]</sup>	42
5	C <sub>6</sub> H <sub>5</sub> OH	24	10 <sup>[e]</sup>	C <sub>6</sub> H <sub>5</sub> CO <sub>2</sub> H	-

[a] Conditions: **1a** (0.3 mmol, 0.06 M), **A** (1 mol%), 1 equiv. of additive, N<sub>2</sub>, 6 h, 100 °C; [b] Isolated yields; [c] 2 equiv.; [d] 0.2 equiv., 36 h; [e] without **A**.

Use of 1 equiv. of triethylammonium formate gave a small improvement (27%, entry 2). No conversion was observed replacing ammonium formate with trimethylamine (entry 3), ruling out the requirement of the base. The yield slightly increased with formic acid (35%, entry 4). Phenol provided **2a** in 24% yield (entry 5). Extensive decomposition occurred with 1 equiv. of PTSA (entry 6). The best compromise to minimize side reactions was achieved with either acetic or benzoic acid (45% each, entries 7–8). The reaction is slower with 0.2 equiv. of acid (36 hours, entry 9). These results showed the requirement of a mild acid environment to trigger these reactions. Product **2a** did not form without **A** (entry 10). **2a** did not form under these conditions using either Pd(OAc)<sub>2</sub> or Pd(dba)<sub>2</sub> (5 mol% each). These data suggest that the formal enyne dimerization is a peculiar feature of the all-metal aromatic trinuclear complex. We thus checked the generality of this method (Figure 1).

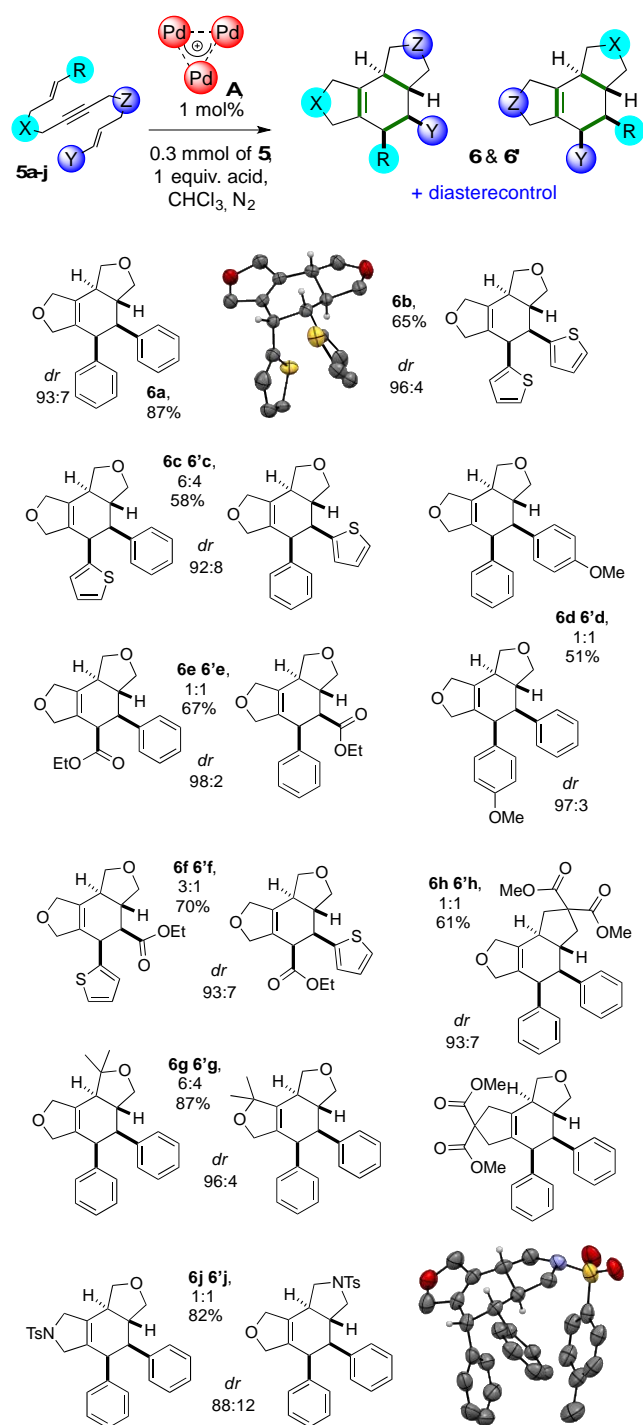
A substituted olefin proved beneficial and provided **2b** in 61% yield as a 61:39 mixture of diastereoisomers. Their relative configuration has been assigned through NMR correlation experiments (see SI). Replacement of the nitrogen tether with an oxygen one is tolerated (**2c**, 57%). The diastereoselection was slightly higher in this case (*dr* = 80:20). The phenyl substituent could be replaced by heterocycles, such as 2-thienyl units. This proved beneficial for yield (67%, *dr* = 66:33). No other isomers of **2** were observed, neither by NMR nor *via* MS analyses. We reasoned that this might have been due to a 4+2 cyclization between two monocyclic 1,3-dienes, which would favor formation of a single regioisomer thanks to secondary orbital interactions.<sup>10</sup>



**Figure 1. Dimerization of terminal enynes**

We performed the reaction on enyne **1c** at 45 °C to confirm this hypothesis. This enabled to isolate 1,3-diene **3c** in 75% yield, pointing towards a Diels-Alder cyclization at the root of the cascade leading to **2**. Pivoting on the electron rich nature of diene **3c**, we tried to quench it with an electron-poor dienophile. Addition of an oxygen balloon to favor rearomatization<sup>11</sup> of the intermediate cyclohexene enabled to recover fused tetracyclic quinone **4c** in 31% yield upon 36 hours at 45 °C. Try as we might, we were so far unable to improve this yield, although the multi-step assembly of decorated polycyclic anthraquinones is often much more worrisome.<sup>12</sup> Taken together, these results suggest that the Pd<sub>3</sub><sup>+</sup> catalyst **A** can trigger the formation of conjugated exocyclic dienes from terminal enynes and their sequential Diels-Alder cycloaddition forms tricycles **2**.

We then switched to internal triple bonds by preparing dienynes **5** (Figure 2). Optimization of conditions showed that best results are obtained in chloroform at 45 °C with either acetic or benzoic acid at a 0.6 M concentration of **5**. Alkynes disubstituted with identical fragments delivered the corresponding tricycles **6** with very high diastereocontrol (dr > 93:7) and good to excellent yields (**6a** and **6b**, 87% and 65% yields respectively). The relative configuration of the four contiguous stereocenters of the central cyclohexene ring was established *via* X-ray analyses on **6b**.



**Figure 2. Triple cyclization of internal dienes**

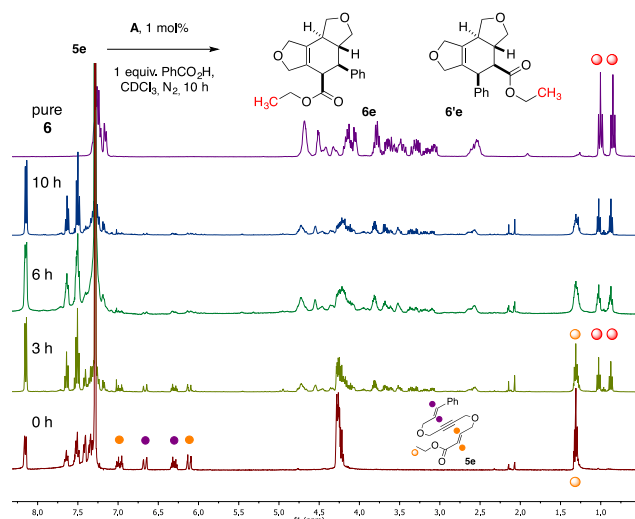
Unexpected results came varying alkene fragments. The diene with one phenyl and one thienyl ring delivered a 6:4 mixture of tricycles **6c** and **6'c**, in which the relative position of these two aromatics on the central ring is scrambled (58% combined yield). Both products formed with excellent diastereocontrol (92:8). The same trend was observed with a phenyl and an anisole fragment, **6d** and **6'd** forming in 1:1 ratio. They both displayed almost complete diastereoselection (97:3, 51% yield). We functionalized the diene with an aromatic and an ester unit to test electronic effects. The reaction afforded **6e** and **6'e** in 1:1 mixture (67% yield, *dr* = 98:2). A slight difference is observed with an ester combined with a thiophene, **6f** and **6'f** being recovered in a 3:1 mixture. The diastereomeric ratio of **6f** is 97:3 (minor isomer of **6'f** not detected). Remarkably, this trend is observed with a sterically demanding *gem*-dimethyl substituent alpha

to the triple bond. Products **6g** and **6'g** were retrieved in 6:4 ratio and 87% combined yield. Once again, diastereoselectivity was very high for both tricycles (94:6). A malonate tether followed suit, enabling one to access hidrindane motifs (**6h** and **6'h** in 1:1 ratio, *dr* = 93:7, 61% yield). The method allows the access to nitrogen heterocycles, as portrayed by **6j** and **6'j** that evenly formed in 82% combined yield (*dr* = 88:12). X-ray analysis on the latter paralleled the result of **6b**. Formation of **6g-j** required heating at 70 °C, no conversion of dienyne **5g-j** being observed at 45 °C. Products **c-g** were recovered in mixture (details in SI).

No interaction between **A** and benzoic acid was observed by <sup>1</sup>H and <sup>31</sup>P NMR at RT. According to DFT, formic acid can interact with the delocalized HOMO of the prototypical sub-nanometric metal surface ( $\Delta H = -11.5, -13.5$  and  $-14.1$  kcal/mol with  $\text{PMe}_3$ ,  $\text{PPh}_3$  and  $\text{P}(\text{tolyl})_3$  as ligands respectively). This suggests that the core of  $\text{Pd}_3^+$  complex **A** has basic character *despite* its positive charge.<sup>13</sup> Entropy factors disfavor ( $\Delta G = +2.7, -1.5$  and  $-1.4$  kcal/mol respectively), correlating with NMR observations. This fits with the effect of acid concentration on rate (Table 1) and suggests that actual concentration of acids-**A** adducts remains always tiny, contributing to the chemical stability of **A** itself. Analyses of the <sup>31</sup>P spectra showed indeed the diagnostic resonance of complex **A** throughout reactions.<sup>14</sup> Similar chemical stability are usually not observed with mononuclear Pd, Pt and Au complexes instead. This correlates with MS and UV-Vis analyses on alkyne semireductions<sup>5</sup> and suggests that the **A** is actually the catalyst. This is confirmed by modelling, formation of various Pd(*n*) mono- and dimeric complexes from  $\text{Pd}_3^+$  being highly endoergonic (by +42-74 kcal/mol in  $\Delta G$ , see SI).

Products **6** are complementary to reported polycyclization of dienyne.<sup>15</sup> In all cases presented in Figure 2 the diastereocontrol is very high. The relative configuration of the four contiguous stereocenters of **6** is always identical, regardless of either steric (**6g**) or electronic factors (**6e** and **6f**). This is at odds with an initial electrophilic alkyne activation<sup>7,9</sup> followed by nucleophilic olefin attack to form an intermediate 1,3-diene.<sup>16</sup> As alternative route, Brønsted acids can trigger formation of Pd(II) hydrides from the corresponding Pd(0) complexes.<sup>8-9</sup> This leads to alkyne hydrometalation followed by alkene insertion into the resulting Pd–C bond. Products are eventually released *via*  $\beta$ -hydride elimination. We performed the reaction with deuterated acetic acid to rule out this possibility. No deuterium incorporation in **6a** has been observed by <sup>1</sup>H and <sup>2</sup>H NMR and MS analyses. Taken together, these observations seem to exclude the involvement of Pd hydrides.<sup>8,17</sup> A complementary mechanism involves the oxidative cycloaddition of a linear enyne on Pd(II) to provide the corresponding bicyclic Pd(IV) metallacycle.<sup>8-9</sup> A diene can be released through sequential  $\beta$ -hydride and C–H reductive eliminations. A similar pathway seems the most likely, **6** and **6'** products stemming from alkene competition on the formation of an intermediate metallacycle.





**Figure 3. Reaction of 5e leading to 6e and 6'e (1:1 mixture) followed by NMR**

We then monitored the reaction of **5e** by NMR (Figure 3). The reagent (bottom line, reaction with  $C_6H_5CO_2H$  as NMR standard) converts directly to **6e** and **6'e**. No intermediate triene resonances are observed in the vinyl region throughout the reaction (5–7 ppm). On the contrary, traces of triene resonances are observed monitoring the reaction of **5a** (Figure S7 in SI), which did not have an electron poor alkene group. These findings suggest that formation of **6** is eventually due to a highly diastereoselective Diels-Alder cyclization, which became apparent increasing the HOMO-LUMO gap.

We introduced  $Pd_3^+$  complexes in the synthesis of highly decorated tricycles from linear unsaturated reagents. These reactions provided interesting structural architectures, casting a bright light for future applications of all-metal aromatics in C–C bond forming sequences.

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## ASSOCIATED CONTENT

**Supporting Information.** Synthesis and characterization of complexes, substrates and products; additional experiments, scope limitations, X-ray and modeling details.

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