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Alternative routes to tricyclic cyclohexenes with trinuclear palladium complexes

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ABSTRACT: Highly symmetric all-metal aromatic Pd$_3^+$ 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(IV/III) 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. These structures have exotic metal-metal bonds. However, in most cases their limited stability prevented widespread experimental applications. Taking advantage of a straightforward synthetic route to a family of bench-stable Pd$_3^+$ complexes that are the noble-metal analogues of the cyclopropenyl cation, we have been able to observe their spectacular ability to semi-reduce alkynes under transfer hydrogenation conditions. 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 are prototypical sustainable reactions that have been intensely studied exploiting mononuclear soft π-acidic noble metal complexes. Upon pioneering work by Trost, many elegant cascades of polyunsaturated reagents have been triggered by palladium. 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.
We report herein the distinct reactivity of either terminal enynes or internal dienynes with all-metal aromatic 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 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 $^{13}$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. 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.
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)$_2$ or Pd(dba)$_2$ (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.  

<table>
<thead>
<tr>
<th>Entry$^{[a]}$</th>
<th>Additive</th>
<th>Yield of 2a (%)$^{[b]}$</th>
<th>Entry$^{[c]}$</th>
<th>Additive</th>
<th>Yield of 2a (%)$^{[d]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_3$NHCO$_2$H$^{[c]}$</td>
<td>21</td>
<td>6</td>
<td>C$_7$H$_5$SO$_3$H</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Et$_3$NHCO$_2$H</td>
<td>27</td>
<td>7</td>
<td>CH$_3$CO$_2$H</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>Et$_3$N</td>
<td>-</td>
<td>8</td>
<td>C$_6$H$_5$CO$_2$H</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>HCO$_2$H</td>
<td>35</td>
<td>9</td>
<td>C$_6$H$_5$CO$<em>2$H$</em>{[d]}$</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>C$_6$H$_5$OH</td>
<td>24 ($^{[e]}$)</td>
<td>10$^{[e]}$</td>
<td>C$_6$H$_5$CO$_2$H</td>
<td>-</td>
</tr>
</tbody>
</table>

[a] Conditions: 1a (0.3 mmol, 0.06 M), A (1 mol%), 1 equiv. of additive, N$_2$, 6 h, 100 °C; [b] Isolated yields; [c] 2 equiv.; [d] 0.2 equiv., 36 h; [e] without A.
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 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. Taken together, these results suggest that the Pd^3+ 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 diastereoccontrol (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.
Unexpected results came varying alkene fragments. The dienyne 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 dienyne 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.

Figure 2. Triple cyclization of internal dienynes
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 = 93:7, 61% yield). X-ray analysis on the latter paralleled the result of 6b. Formation of 6g-j required heating at 70 °C, no conversion of dienyines 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 1H and 31P NMR at RT. According to DFT, formic acid can interact with the delocalized HOMO of the prototypical sub-nanometric metal surface (ΔH = -11.5, -13.5 and -14.1 kcal/mol with PMe3, PPh3 and P(tolyl)3 as ligands respectively). This suggests that the core of Pd3+ complex A has basic character despite its positive charge.13 Entropy factors disfavor (ΔG = +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 31P spectra showed indeed the diagnostic resonance of complex A throughout reactions.14 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 semireductions5 and suggests that the A is actually the catalyst. This is confirmed by modelling, formation of various Pd(n) mono- and dimeric complexes from Pd3+ being highly endoergic (by +42-74 kcal/mol in ΔG, see SI).

Products 6 are complementary to reported polycyclization of dienynes.15 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 activation7,9 followed by nucleophilic olefin attack to form an intermediate 1,3-diene.16 As alternative route, Brønsted acids can trigger formation of Pd(II) hydrides from the corresponding Pd(0) complexes.8-9 This leads to alkyne hydrometalation followed by alkene insertion into the resulting Pd–C bond. Products are eventually released via β-hydride elimination. We performed the reaction with deuterated acetic acid to rule out this possibility. No deuterium incorporation in 6a has been observed by 1H and 2H NMR and MS analyses. Taken together, these observations seem to exclude the involvement of Pd hydrides.5,17 A complementary mechanism involves the oxidative cycloaddition of a linear enyne on Pd(II) to provide the corresponding bicyclic Pd(IV) metallacycle.5,9 A diene can be released through sequential β-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.
We then monitored the reaction of 5e by NMR (Figure 3). The reagent (bottom line, reaction with C₆H₅CO₂H 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 Pd₃⁺ 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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REFERENCES


(14) Partial decomposition of A occurs at 70 °C when the concentration of 5 fades; operating at 45 °C, it is possible to retrieve the complex by chromatography (around 70% recovery).


(16) The 3:1 ratio of 6f and 6f′ could suggest a partial electrophilic pathway for this dienyne that has a strongly donating 2-thienyl unit and a withdrawing ester one on its alkynes.