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# Palladium-catalyzed Cocyclotrimerization of Arynes with a Pyramidalized Alkene†

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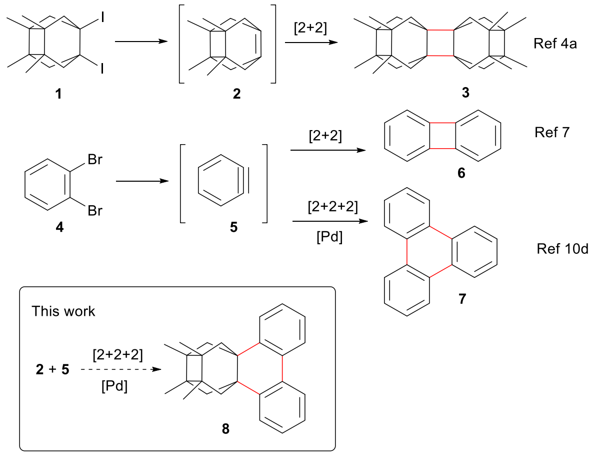
**The metal-catalyzed [2+2+2] cocycloaddition of arynes with pyramidalized alkenes is presented. The generation of a highly reactive pyramidalized alkene in the presence of a large excess of in situ-produced arynes, led to the corresponding cocyclotrimerization (1:2)-adducts in good yields, establishing the first example of a palladium-based reaction of a pyramidalized alkene.**

Pyramidalized alkenes are considered a special case of highly reactive molecules due to their distorted geometry. In these systems, one or both of the $sp^2$ carbon atoms do not lie in the same plane as the attached ones.[1] This peculiarity confers these alkenes a particular chemical behavior, high reactivity and therefore, short life time.[2] Since Weinshenker and Greene reported the synthesis of the first pyramidalized alkene,[3] many contributions have been published regarding both characterization and reactivity. Nevertheless, pyramidalized alkene chemistry has been mainly focused on Diels-Alder cycloadditions, dimerizations, or cross-coupling reactions between two different alkene moieties.[4] To the best of our knowledge, the chemistry of these systems with transition metals has been only limited to the use of platinum, describing several attempts of trapping pyramidalized alkenes as metal complexes.[5]

Arynes can be considered a special kind of highly reactive alkynes, presenting a deformation of the sp hybridation linear geometry imposed by the strain of the six-membered ring.[6] Similarly to pyramidalized alkenes, arynes can undergo dimerization,[7] and stabilization by complexation to metal fragments is also reported.[8] Due in part to the introduction of milder methods of aryne generation,[9] transition metal catalyzed [2+2+2] cycloadditions have lately focused renewed attention.[10] Nevertheless, cocyclotrimerization reactions of arynes and alkenes remain almost unexplored. Cheng and co-workers reported the first example using bicyclic alkenes and palladium catalysts, yielding dihydrophenanthrene derivatives.[11] In a later work, some of us described the cocyclotrimerization of arynes with electrophilic monosubstituted alkenes through palladium catalysis, and the use of nickel complexes to improve the efficiency when disubstituted alkenes were employed.[12] More recently, Sato's research group has extended the cotrimerization methodology to inactivated alkenes through nickel catalysis,[13] but the process is still limited to a few different alkenes.

Following the purpose of our research group of exploring in deep the chemistry of arynes,[14] we envisioned an unreported palladium-catalyzed cocyclotrimerization of arynes with pyramidalized alkenes. Both intermediates are known to be involved in homodimerization reactions and can be stabilized by coordination with transition metals. Herein we describe the generation of both intermediates in the same reaction mixture, in the presence of a catalytic amount of a transition metal complex to obtain cocyclotrimerization products (e.g. **8**, Scheme 1).



**Scheme 1**. Pyramidalized alkene and aryne cycloadditions.

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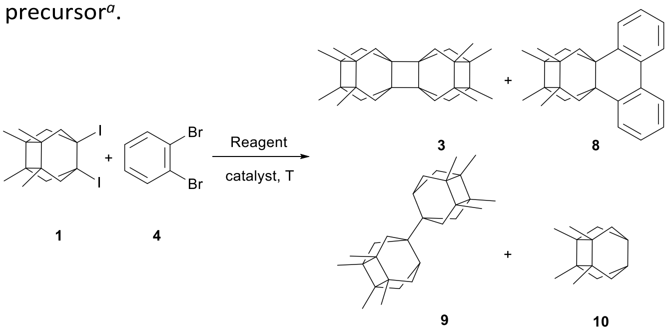
A highly reactive alkene, **2**, presenting a cyclobutane ring, two cyclohexane rings in boat conformation, and a pyramidalized angle of $\Phi = 47.5°$, was selected to start the study.[4a] One of the most common methods to generate this kind of pyramidalized alkenes is the treatment of the corresponding diiodo precursors, such as **1**, with *n*BuLi or a large excess of sodium.[4] On the other hand, benzyne **5** was selected as the most simple aryne moiety, readily accessible from 1,2-dibromobenzene (**4**, Scheme 1).[15]

Thus, reaction of **1** with excess of **4** and the equivalent amount of Na/Hg amalgam at room temperature, led to a complex mixture where triphenylene (**7**) and dimers **3** and **9** were the sole identified compounds (Table 1, entry 1). The same experiment in the presence of catalytic amount of $Pd(PPh_3)_4$ or $Pd_2(dba)_2$ slightly changed the ratio of the observed dimers, however no co-cyclization product **8** was detected (entries 2 and 3). Compounds **9** and **10** have been previously reported as common byproducts in reactions of diiodoalkane **1** under the mentioned conditions.[4a]

Then, reaction of **1** with excess of 1,2-dibromobenzene (**4**) and the equivalent amount of *n*-BuLi solution at -78°C, dramatically increased the selectivity towards dimer **3**, but no traces of the expected cocyclization product **8** were observed (Table 1, entry 4). To our delight, when the same experiment was carried out in the presence of catalytic amount of $Pd(PPh_3)_4$, cocyclization product **8** was isolated in a 13% yield from a very complex reaction mixture. Interestingly, no traces of products **3**, **9** or **10** were observed (Table 1, entry 5). NMR and MS analysis showed the incorporation of two benzynes, **5**, and one alkene, **2**, into the final adduct **8**.

**Table 1**. Reaction of **1** as alkene precursor and **4** as benzyne precursor[a].



| Entry | Reagent | T (°C) | Catalyst | $3^b$ | $8^c$ | $9^b$ | $10^b$ |
|---|---|---|---|---|---|---|---|
| 1 | Na/Hg | RT | - | 49% | - | 5% | - |
| 2 | Na/Hg | RT | $Pd(PPh_3)_4$ | 23% | - | 8% | 2% |
| 3 | Na/Hg | RT | $Pd_2(dba)_3$ | 19% | - | 6% | 1% |
| 4 | *n*-BuLi | -78 | - | 89% | - | 7% | - |
| 5 | *n*-BuLi | -78 | $Pd(PPh_3)_4$ | - | 13% | - | - |

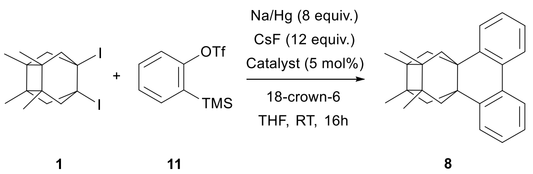
[a] Reaction conditions, for entries 1-3: **1** (1 equiv.), **4** (3 equiv.), Na/Hg (12 equiv.), catalyst (5 mol%), THF, RT, 16h. Entries 4-5: **1** (1 equiv.), **4** (3 equiv.), *n*-BuLi (4 equiv.), catalyst (5 mol%), THF, -78°C-RT, 16h.

[b] Determined by GC/MS analysis of reaction mixtures.

[c] Isolated yield after column chromatography.

Due to the excess of 1,2-dibromobenzene **4**, triphenylene (**7**) was observed as byproduct in all the experiments.

**Table 2**. Catalyst and stoichiometry screening for reaction of **1** and **11** as aryne precursor.



| Entry | 11 (equiv.) | Catalyst | 8 |
|---|---|---|---|
| 1 | 3 | $Pd(PPh_3)_4$ | 62%[a] |
| 2 | 6 | $Pd(PPh_3)_4$ | 79%[a] |
| 3 | 0.5 | $Pd(PPh_3)_4$ | -[a,c] |
| 4 | 6 | $Pd_2(dba)_3$ | -[a] |
| 5 | 6 | $Pt(PPh_3)_4$ | -[a,b] |
| 6 | 6 | $AuClPPh_3$ | -[a] |
| 7 | 6 | $Ni(PPh_3)_4$ | -[a] |

[a] Triphenylene (**7**) was obtained as byproduct in all the experiments. [b] Traces of dimers **3** and **9** were detected by GC/MS analysis of reaction mixture. [c] Products **3** and **9** were obtained in similar yields as entry 2 in Table 1.

In order to improve the yield of the observed transformation, a combined strategy where pyramidalized alkene and aryne were generated employing different reagents, was also considered. Simultaneous slow addition of *n*-BuLi, and TBAF solution as fluoride source, to a mixture of diiodoalkane **1** and Kobayashi's aryne precursor **11**,[9] gave only a complex reaction mixture, both in the presence or in absence of a metal catalyst. Surprisingly, when Na/Hg amalgam was combined with CsF in THF at room temperature and in the presence of $Pd(PPh_3)_4$ as catalyst, a 62% yield of the previously described adduct **8** was isolated (Table 2, entry 1). This yield was improved up to 79% by increasing the excess of aryne precursor (Table 2, entry 2). Other catalysts such as $Pt(PPh_3)_4$, $AuClPPh_3$ or $Ni(PPh_3)_4$ led to complex reaction mixtures where triphenylene (**7**) and dimers **3** and **9** were detected in minor amounts.

An inverse stoichiometry was also tested, finding that an excess of diiodoalkane **1** with one equivalent of aryne precursor **11** did not yield the corresponding adduct with the expected inverse ratio, leading only to a mixture of the alkene dimers (Table 2, entry 3). This finding is in agreement with the precedents of cotrimerization reactions of arynes with conventional alkenes.[11-13]

Two blank experiments were performed in order to confirm that both benzyne and the pyramidalized alkene were successfully generated in this complex reaction media, and therefore they are intermediates in the co-cyclization reaction. Independent reaction of aryne precursor **11** in the detailed reaction conditions, yielded expected triphenylene (**7**), product of aryne cyclotrimerization (Scheme 2, reaction *a*). In addition, reaction of **1** under the same conditions led to the previously described mixture of compounds **3**, **9** and **10** (Scheme 2, reaction *b*).

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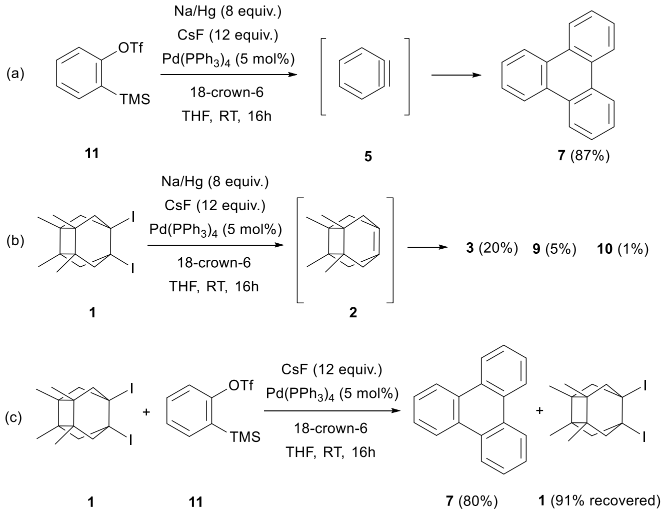
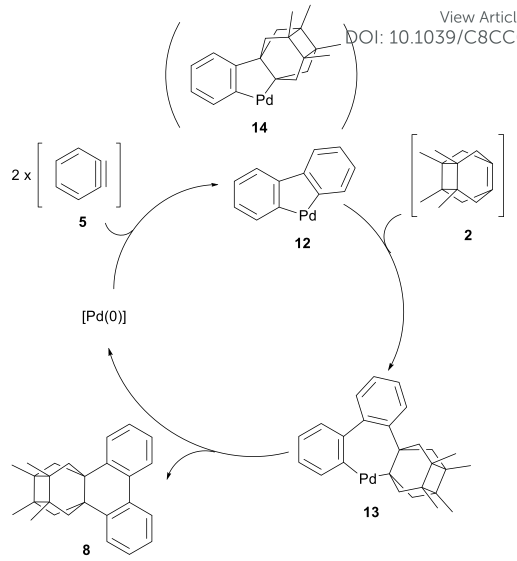


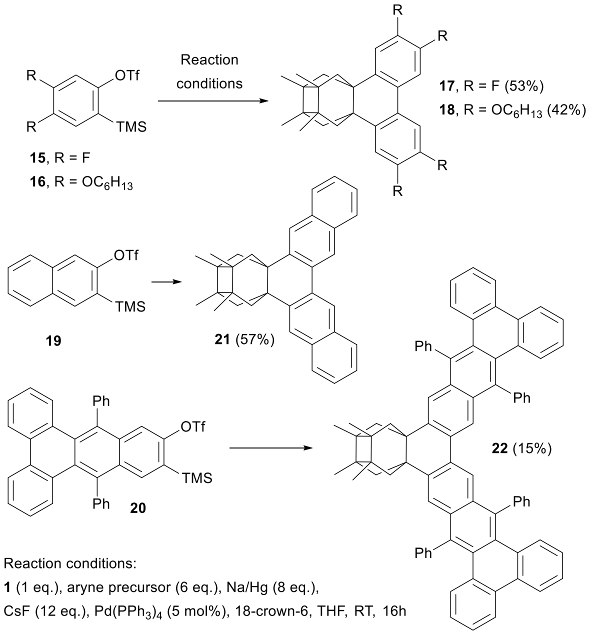
**Scheme 2**. Control experiments to confirm the presence of both benzyne (**5**) and pyramidalized alkene **2** in the reaction media. Yield of trimer **7** in experiment *c* was referred to aryne precursor **11**.



**Scheme 3**. Proposed reaction mechanism for cocyclotrimerization of pyramidalized alkene **2** and benzyne (**5**).

To discard an oxidative addition of palladium into C-I bond as a possible first step in the reaction mechanism for this process, one additional experiment in the absence of base was tested. Thus, reaction of precursors **1** and **11** in the absence of Na/Hg amalgam, only yielded triphenylene (**7**) as final product, while starting material **1** was mainly recovered (Scheme 2, reaction *c*). A plausible mechanism for this reaction could be closely related to the ones previously reported for the cotrimerization of arynes and alkenes.[16] A first coordination of the metal complex to two benzyne units, **5**, followed by an oxidative coupling, would furnish metallacycle **12** (Scheme 3). Then, insertion of pyramidalyzed alkene **2** into a carbon-metal bond would afford metallacycloheptadiene **13**, which could evolve through reductive elimination to produce the observed adduct **8**, and returning the active catalytic specie to the catalytic cycle. A similar mechanistic pathway through metallacycle **14** could not be ruled out, as the isolation of triphenylene (**7**) as by-product is easily explained due to the high excess of benzyne in the reaction media.

In a first attempt to extend the methodology to different arynes beyond benzyne, we performed the reaction of alkene precursor **1** with substituted aryne precursors **15**,[17a] and **16**,[17b] to see if it was compatible with acceptor and donor substituents on the aryne, respectively. To our delight, the use of the optimized reaction conditions led to the corresponding adducts **17** and **18** in good yield (Scheme 4). Additionally, we decided to explore the cocyclotrimerization reaction using polycyclic aryne precursors **19**,[17c] and **20**.[17d] The reaction with naphthalyne precursor **19** afforded adduct **21** in 57% yield, while the use of triflate **20** led to isolation of compound **22**, a large polycyclic hydrocarbon with molecular formula $C_{82}H_{60}$. The fact that five different arynes successfully react with pyramidalized alkene **2** confirms the generality of the reaction.[18]



**Scheme 4**. Reaction of diiodo derivative **1** with aryne precursors **15, 16, 19** and **20**.

Adducts **8** and **21** were crystalized by slow evaporation of hexanes and hexanes/chloroform. Further X-Ray diffraction analysis of the resulting crystals confirmed unambiguously the proposed structures (Scheme 5).[19]

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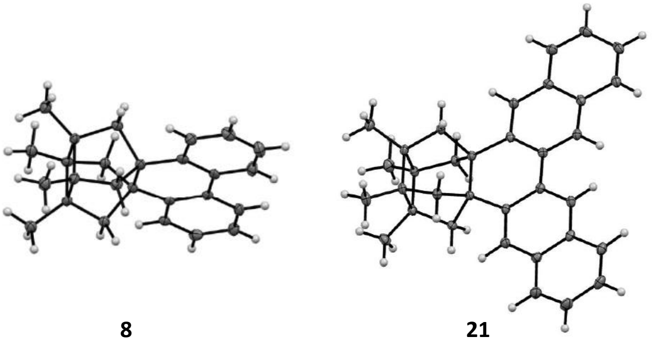
The X-ray diffraction structures of adducts **8** and **21** showed that, for both compounds, the distances between the flagpole hydrogen atoms (2.027 Å and 2.077 Å in **8** and **21**, respectively) and the flagpole carbon atoms (2.620 Å and 2.615 Å in **8** and **21**, respectively) are smaller than the sum of the van der Waals radius of the involved atoms (1.1–1.2 Å and 1.7–1.8 Å, respectively). Thus, severe steric congestion should be expected from the inability of the boat cyclohexane rings to relieve the H–H and C–C flagpoles interactions. Notwithstanding, both structures showed a high stability, remaining unaltered for months at room temperature under air.



**8**

**21**

**Scheme 5**. X-Ray diffraction structures for adducts **8** and **21**.

In summary, a new cocyclotrimerization of arynes with a pyramidalized alkene has been reported. Different conditions and metal catalysts have been tested, finding that simultaneous and parallel generation of arynes and pyramidalized alkenes in the presence of Pd(PPh$_3$)$_4$, yielded the adducts resulting from the reaction of two arynes with one alkene in good yields. Notably, five different substituted or polycyclic arynes successfully react with the pyramidalized alkene. This reaction constitutes a first example of pyramidalized alkene reactivity through palladium catalysis.

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18 For preliminary attempts using two additional pyramidalized alkenes see supporting information.

19 CCDC 1554197 (for compound **8**), 1554198 (for compound **21**).

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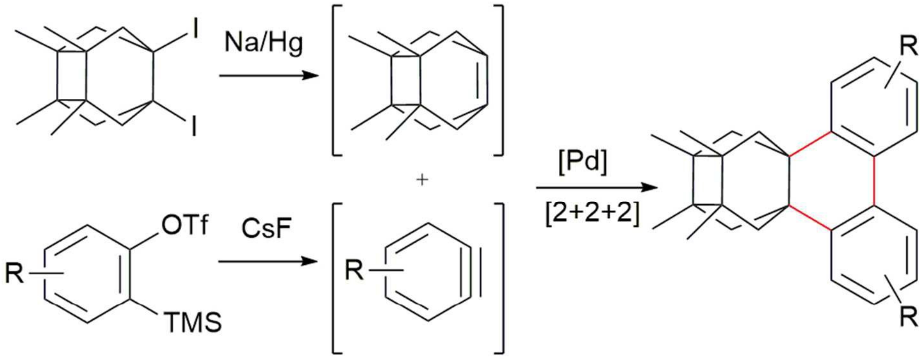

A pyramidalised alkene and diverse arynes are generated in the presence of a Pd-catalyst to afford [2+2+2] cocycloaddition products

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