Efficient Palladium-Catalyzed Cyclotrimerization of Arynes: Synthesis of Triphenylenes**

Diego Peña, Sonia Escudero, Dolores Pérez,* Enrique Guitián,* and Luis Castedo

Over the last 15 years much effort has been devoted to the preparation and characterization of transition metal complexes of arynes.** Parallel studies on the reactivity of these complexes—particularly those of Ti, Zr,** and Ni**—have shown that characteristic reactions involve insertion of molecules containing multiple bonds (e.g. alkenes, alkynes, CO) into the metal–aryne bond, which in a way is reminiscent of the chemistry of alkylene complexes. However, while alkynes participate in a number of synthetically useful metal-catalyzed transformations, the synthetic applications of metal–aryne complexes are limited owing to the lack of a general and mild method for their generation and the need for stoichiometric amounts of metal in their reactions.

As part of a project aimed at the development of new reactions of arynes promoted by metal complexes, here we report on the metal-mediated cyclotrimerization of arynes.

These preliminary results show that the reaction proceeds in the presence of catalytic amounts of metal and that it has great potential for the preparation of triphenylenes, which are found at the core of many discotic liquid crystals** and have therefore been the target of many synthetic studies.**

There are many precedents of triphenylene formation under conditions that lead to arynes, especially when arynes are generated from an organometallic system.** For example, triphenylene was obtained in 85% yield from the decomposition of 2-fluorophenylmagnesium bromide in THF.* Closer to our results, triphenylene was isolated in 30% yield during attempts at obtaining a platinum complex of benzene (1,2-dihydrobenzene).** An example of the formation of triphenylene as side product of a palladium-catalyzed domino reaction has also been reported.* However, to the best of our knowledge, efficient preparation of triphenylenes by metal-catalyzed reaction of arynes is without precedent.

Development of a catalytic procedure for the trimerization of arynes requires careful selection of the catalyst and the method for generation of the aryne. The catalyst was chosen from among the various metal systems used for trimerization of alkynes; suitable candidates contained metals such as Ni, Co, Pd, and Pt. We decided to carry out the first trials with palladium complexes because they are easy to handle and in general stable. Among the many procedures available for the generation of arynes** we sought one that could be used under mild reaction conditions and did not involve strong bases or oxidants. The method of choice was the fluoride-induced elimination of Me₃Si and TfO groups (TfO⁻) from an organometallic system.** For example, triphenylene was isolated in 30% yield during attempts at obtaining a platinum complex of benzene.

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Similarly high regioselectivity has been reported in metal-catalyzed alkyne cyclotrimerizations, suggesting that alkyne and aryne cyclotrimerizations have similar mechanisms. If this is the case, isolation of the asymmetrically substituted isomer 11 as major product is explained by selective formation of the metallacyclic intermediate 13 as a result of C–C bond formation between the carbon atoms with less steric hindrance [Eq. (2)]. Our approach thus allows efficient prepara-

tion of 1,1,2-substituted triphenylenes, which are currently of interest owing to their potential application as chiral cores for liquid crystals.

**Experimental Section**

A solution of the aryne precursor (1.5, or 9, 1 mmol) in CH$_2$CN (2 mL) was added to a suspension of finely powdered anhydrous CsF (2 mmol) and [Pd(PPh$_3$)$_4$] (0.1 mmol) in CH$_2$CN (1 mL), and the mixture was stirred under argon at room temperature for 12 h. The solvent was evaporated, and the residue was purified by column chromatography (silica gel) to isolate the trimers.

**Keywords:** arynes · cyclotrimerizations · palladium · triphenylenes

**References**


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**Table 1. Metal-catalyzed synthesis of triphenylene [3, see Eq. (1)].**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Reagent</th>
<th>Catalyst (0.1 equiv)</th>
<th>Additives</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 a</td>
<td>CsF</td>
<td>[Pd(PPh$_3$)$_4$]</td>
<td>–</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>2 a</td>
<td>CsF</td>
<td>[Pd$_2$(dbta)$_4$]</td>
<td>dppe</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>3 a</td>
<td>CsF</td>
<td>[Pd$_2$(dbta)$_4$]</td>
<td>P(o-tol)$_3$</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>4 a</td>
<td>Bu$_2$NF</td>
<td>[Pd(PPh$_3$)$_4$]</td>
<td>–</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>5 b</td>
<td>BuLi</td>
<td>[Pd(PPh$_3$)$_4$]</td>
<td>–</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>1 a</td>
<td>CsF</td>
<td>[Pd(PPh$_3$)$_4$]</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>7 a</td>
<td>–</td>
<td>[Pd(PPh$_3$)$_4$]</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction conditions: MeCN, RT, 12 h (entries 1–3, 6, 7); THF, 0 °C, 12 h (entries 4, 5). [b] Yield of isolated product. dbta = trans-disubstituted bistrimethylsilylated acetylene, dppe = 1,2-bis(diphenylphosphoryl)ethane, tol = C$_6$H$_5$Me.

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Generation of 3-methoxybenzene (10) from triflate 9 under the same conditions afforded a mixture of 1,5,12- and 1,5,9-trimethoxytriphenylenes (11 and 12, respectively) in 93:7 ratio and 81% overall yield (Scheme 2).

**Scheme 1.** Synthesis of 7 via intermediate 6. a) HMDS. b) 1) nBuLi; 2) TMSI, THF, –78 °C. c) 1) nBuLi; 2) Ti(O-TMS)$_2$, 0 °C. d) [Pd(PPh$_3$)$_4$] (0.1 equiv), CsF, CH$_3$CN, RT. HMDS = 1,1,1,3,3,3-hexamethyldisilazane, TMS = trimethylsilyl.

**Scheme 2.** Synthesis of 11 and 12 via intermediate 10. a) HMDS. b) 1) LDA; 2) TMSI. c) 1) nBuLi; 2) Ti(O-TMS)$_2$. d) [Pd(PPh$_3$)$_4$] (0.1 equiv), CsF, CH$_3$CN, RT. LDA = lithium disopropylamide.
COMMUNICATIONS

Investigations into the Manzamine Alkaloid Biosynthetic Hypothesis


Over the past decade there has been an upsurge in the discovery of biologically active natural products from marine sponges.[1] In comparison to terrestrial plant and microbial systems, little is known about the biosynthesis of sponge metabolites.[2] One class of cytotoxic sponge metabolites which have recently fascinated organic chemists are the manzamine alkaloids. The first member of this class, manzamine A (Figure 1), was isolated in 1986 by Higa et al.[3]

and recently synthesized.[13] The unprecedented structure led the authors to the conclusion that “no obvious biogenetic path” could be envisaged leading to 1. Manzamines B (2) and C (3) were subsequently isolated from the same sponge.[4]

In 1992, we put forward a biogenetic hypothesis for the formation of the manzamines.[5] We proposed that each structure could be reduced into four building blocks: ammomia, a C10 unit (a symmetrical dialdehyde), tryptophan, and a C3 unit (an acrolein equivalent), shown in Scheme 1 for manzamine B (2). The key step in the proposal is the intramolecular endo Diels–Alder cycloaddition of the bis-dihydropyridine 4.[6] To date it is not known whether a “Diels–Alderase” exists.[7]

Since the publication of the hypothesis a large number of manzamine and related alkaloids have been isolated from various species of sponge worldwide.[8] Despite the lack of experimental evidence, the proposal has been applied repeatedly to explain the biogenetic origin of the manzamine and related alkaloids. One related alkaloid is keramaphidin B (5, Scheme 1), which was isolated independently by both the Kobayashi and Andersen groups.[9] Structurally 5 is simply the reduced form of the proposed cycloadduct 6 (Scheme 1). Herein, we report the biomimetic synthesis of 5, the first in vitro chemical evidence for this proposal.

The synthesis of 7 was first communicated in 1996,[9] but we found the route unsatisfactory because of moderate yields (7% overall) and the instability of one intermediate. Since then we have modified the synthesis (Scheme 2) with significant improvements (37% overall yield). Hydroxypophosphonium salt 8 was masked as its tetrahydropyranyl (THP) derivative 9 (93%). Olefin 10 was obtained from the ylide generated from 9 and 3-(3-pyridyl)propenal in 83% yield. Acid-mediated deprotection gave the alcoholic 11 (94%), which was treated with p-toluene sulfonyl chloride to give 12 (95%). A one-pot Finkelstein reaction, demethylation and macrocyclization was effected by the slow addition of 12 into a mixture of NaI in 2-butanol under reflux. The crude product was reduced to give bis-tetrahydropyridine 13 in 56% yield over the two steps. Oxidation of 13 with 3-chloroperbenzoic acid (mCPBA) furnished diastereomeric N-oxides (98%), which could be treated with trifluoroacetic anhydride to give bis-dihydropyridine 7 (100%).

Figure 1. Manzamine A (1), B (2), and C (3).

[16] Triphenylene and the substituted derivatives gave correct analytical and spectroscopic data. 3: M.p. 194°C (literature value 198°C), 7: 1H NMR (DMSO-d6) δ = 8.42 (t, J = 10.3 Hz, 6H), MS: m/z (%): 336 (100), 168 (16); HR-MS: calcd for C18H6F6O6: 336.0374, found: 336.0364. 11: M.p. 188°C; 1H NMR (CDCl3) δ = 0.04 (dd, J = 8.5, 0.8 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.48 (m, 3H), 4.04 (s, 3H), 3.97 (s, 6H); HR-MS: calcd for C21H11NO3: 374.0712, found: 374.0713. 12: 1H NMR (CDCl3) δ = 0.00 (dd, J = 8.5, 12.2 Hz, 3H), 7.48 (m, 3H), 4.02 (s, 9H); MS: m/z (%): 318 (100), 158.2, 157.9, 157.0, 133.0, 132.6, 131.9, 127.3, 127.0, 126.8, 121.1, 118.8, 118.4, 118.1, 115.9, 115.0, 110.4, 108.7, 108.5, 86.1, 55.8, 55.7: MS: m/z (%): 318 (100), 303 (25), 288 (15); HR-MS: calcd for C18H11NO3: 318.0856, found: 318.0862. 13: M.p. 194°C; 1H NMR (CDCl3) δ = 8.10 (d, J = 8.1 Hz, 1H), 7.48 (m, 3H), 4.02 (s, 9H); MS: m/z (%): 318 (100), 303 (22), 288 (30).

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