[8] The number of nitromethane molecules and perchlorate anions per unit cell in the tetragonal [Ag(hat)ClO$_4$]·2CH$_3$NO$_2$ crystal indicated by the crystallography showed excellent agreement with the number calculated with the PLATON Program[6] on the basis of the electron density in the framework voids. This agreement affords confidence in the number of water molecules (4H$_2$O per [Ag(hat)]ClO$_4$) present in the cubic hydrated crystal calculated in the same way by using the PLATON program, which in addition accorded well with the 3.5H$_2$O indicated by elemental analysis.

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

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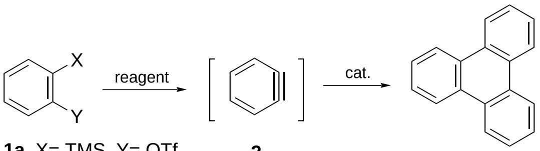
Over the last 15 years much effort has been devoted to the preparation and characterization of transition metal complexes of arynes.[1] Parallel studies on the reactivity of these complexes—particularly those of Ti, Zr,[2] and Ni[3]—have shown that characteristic reactions involve insertion of molecules containing multiple bonds (e.g. alkenes, alkynes, CO) into the metal–aryne bond, which in a way is reminiscent of the chemistry of alkyne complexes. However, while alkynes participate in a number of synthetically useful metal-catalyzed transformations,[4] 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[5] and have therefore been the target of many synthetic studies.[6]

There are many precedents of triphenylene formation under conditions that lead to arynes, especially when arynes are generated from an organometallic system.[7] For example, triphenylene was obtained in 85% yield from the decomposition of 2-fluorophenylmagnesium bromide in THF.[8] Closer to our results, triphenylene was isolated in 30% yield during attempts at obtaining a platinum complex of benzyne (1,2-didehydrobenzene).[9] An example of the formation of triphenylene as side product of a palladium-catalyzed domino reaction has also been reported.[10] 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[11] 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 Me$_3$Si and TfO groups (Tf = trifluoromethanesulfonyl), which proceeds at room temperature.[12]

Early in our study we found that when 2-trimethylsilylphenyl trifluoromethanesulfonate (**1a**) was treated with CsF and a catalytic amount (3 mol%) of [Pd(PPh$_3$)$_4$] in acetonitrile, the only low-polarity product detected was triphenylene (**3**), which was isolated in 52% yield [Eq. (1)]. To optimize the reaction conditions, exhaustive experimentation was carried out; some significant results are given in Table 1. The best results were obtained using 10 mol% of [Pd(PPh$_3$)$_4$][13] and 2 equivalents of anhydrous CsF in acetonitrile at room temperature (entry 1), which afforded triphenylene in 83% yield. Use of other sources of Pd^0 (entries 2 and 3) or fluoride (entry 4) gave slightly lower yields. Likewise, alternative methods to generate benzyne, such as reaction of 1,2-dibromobenzene (**1b**) with *n*BuLi, in the presence of [Pd(PPh$_3$)$_4$] (entry 5) also gave poorer results. It is noteworthy that triphenylene was not detected in the reaction mixture when **1a** was treated with CsF in the absence of a Pd catalyst (entry 6), and that when **1a** was treated with [Pd(PPh$_3$)$_4$] in the absence of fluoride, the starting material was untouched (entry 7). In our opinion, these two control experiments provide good evidence of the intermediacy of benzyne as the



(1)

1a, X= TMS, Y= OTf
1b, X=Y=Br

2

3

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

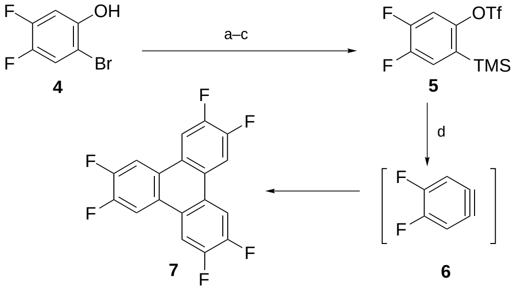
Entry	Starting material	Reagent	Catalyst (0.1 equiv)	Additives	Yield [%][b]
1	**1a**	CsF	[Pd(PPh$_3$)$_4$]	–	83
2	**1a**	CsF	[Pd$_2$(dba)$_3$]	dppe	70
3	**1a**	CsF	[Pd$_2$(dba)$_3$]	P(*o*-tol)$_3$	60
4	**1a**	Bu$_4$NF	[Pd(PPh$_3$)$_4$]	–	71
5	**1b**	BuLi	[Pd(PPh$_3$)$_4$]	–	40
6	**1a**	CsF	–	–	–
7	**1a**	–	[Pd(PPh$_3$)$_4$]	–	–

[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. dba = *trans,trans*-dibenzylideneacetone, dppe = 1,2-bis(diphenylphosphanyl)ethane, tol = C_6H_4Me.

reactive species, and suggest that the metal promotes the reaction by acting as a template.

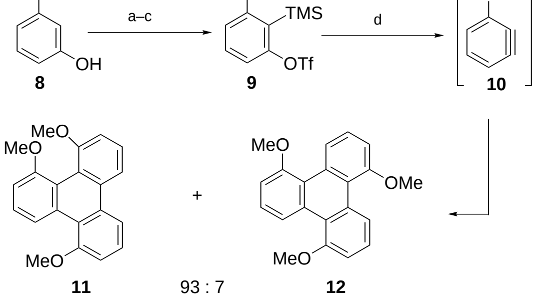
Next, we applied the optimized cyclotrimerization procedure developed for benzyne to the substituted arynes **6** and **10**, to see if it was compatible with donor and acceptor substituents on the aryne and to determine the regiochemistry of the reaction. Furthermore, we were interested to know if the reaction is of general utility for the synthesis of functionalized triphenylenes.

The precursor of 4,5-difluorobenzyne (**6**) was 4,5-difluoro-2-trimethylsilylphenyl triflate (**5**), which was prepared from commercially available 2-bromo-4,5-difluorophenol (**4**) in three steps. Treatment of **5** with CsF in the presence of 10 mol% of [Pd(PPh$_3$)$_4$] afforded 2,3,6,7,10,11-hexafluorotriphenylene (**7**) in 52% yield (Scheme 1).



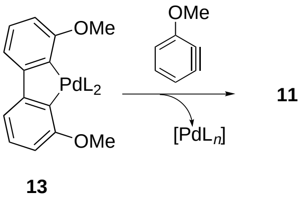
Scheme 1. Synthesis of **7** via intermediate **6**. a) HMDS. b) 1. *n*BuLi; 2. TMSCl, THF, −78°C. c) 1. *n*BuLi; 2. Tf$_2$O, 0°C. d) [Pd(PPh$_3$)$_4$] (0.1 equiv), CsF, CH$_3$CN, RT. HMDS = 1,1,1,3,3,3-hexamethyldisilazane, TMS = trimethylsilyl.

Generation of 3-methoxybenzyne (**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 2. Synthesis of **11** and **12** via intermediate **10**. a) HMDS. b) 1. LDA; 2. TMSCl. c) 1. *n*BuLi; 2. Tf$_2$O. d) [Pd(PPh$_3$)$_4$] (0.1 equiv), CsF, CH$_3$CN, RT. LDA = lithium diisopropylamide.

Similarly high regioselectivity has been reported in metal-catalyzed alkyne cyclotrimerizations,[14] 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 preparation of 1,12-substituted triphenylenes, which are currently of interest owing to their potential application as chiral cores for liquid crystals.[15]



(2)

Experimental Section

A solution of the aryne precursor (**1**, **5**, or **9**; 1 mmol) in CH$_3$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$_3$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.[16]

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[16] Triphenylene and the substituted derivatives gave correct analytical and spectroscopic data. **3**: M.p. 194 °C (literature value[6a] 198 °C). **7**: ^{1}H NMR ([D$_8$]THF) $\delta = 8.42$ (t, $J = 10.3$ Hz, 6H); MS: m/z (%): 336 (100), 168 (16); HR-MS: calcd for $C_{18}H_6F_6$: 336.0374, found: 336.0364. **11**: M.p. 188 °C; ^{1}H NMR (CDCl$_3$) $\delta = 9.04$ (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); ^{13}C NMR (CDCl$_3$) $\delta = 158.2$, 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, 56.1, 55.8, 55.7; MS: m/z (%): 318 (100), 303 (25), 288 (15); HR-MS: calcd for $C_{21}H_{18}O_3$: 318.1256, found: 318.1268. **12**: ^{1}H NMR (CDCl$_3$) $\delta = 9.00$ (dd, $J = 8.5$, 1.2 Hz, 3H), 7.48 (t, $J = 8.2$ Hz, 3H), 7.14 (dd, $J = 8.1$, 1.0 Hz, 3H), 4.02 (s, 9H); MS: m/z (%): 318 (100), 303 (22), 288 (30).

Investigations into the Manzamine Alkaloid Biosynthetic Hypothesis**

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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 (**1**, Figure 1), was isolated in 1986 by Higa et al.[3] and recently synthesized.[12] 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]

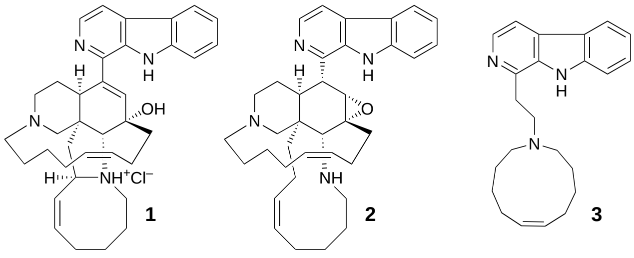

Figure 1. Manzamine A (**1**), B (**2**), and C (**3**).

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: ammonia, a C_{10} unit (a symmetrical dialdehyde), tryptophan, and a C_3 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,[6e] 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). Hydroxyphosphonium 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)propanal in 83 % yield. Acid-mediated deprotection gave the alcohol **11** (94 %), which was treated with *p*-toluenesulfonyl chloride to give **12** (95 %). A one-pot Finkelstein reaction, dimerization and macrocyclization was effected by the slow addition of **12** into a mixture of NaI in 2-butanone 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 (*m*CPBA) furnished diastereomeric N-oxides (98 %), which could be treated with trifluoroacetic anhydride to give bis-dihydropyridine **7** (100 %).

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