

## Intercepting Palladacycles Derived by C–H Insertion. A Mechanism-Driven Entry to Heterocyclic Tetraphenylenes

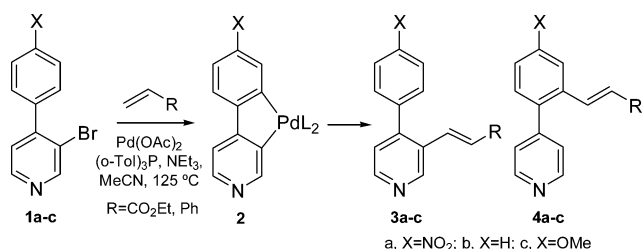
David Masselot, Jonathan P. H. Charmant, and Timothy Gallagher\*

School of Chemistry and Structural Chemistry Laboratory, University of Bristol, Bristol BS8 1TS, United Kingdom

Received October 12, 2005; E-mail: t.gallagher@bristol.ac.uk

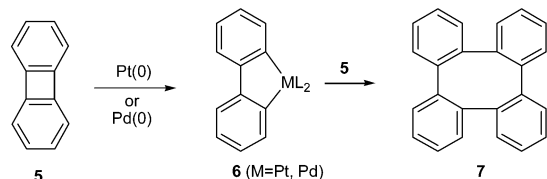
We recently described the efficient Heck reactions of pyridyl-based biaryl halides **1a–c**, which lead to the formation of the expected adducts **3** as well as the more unusual isomeric “crossover” products **4** (Scheme 1).<sup>1,2</sup> This “crossover Heck” process is mechanistically significant, involving as it does a C–H cleavage step, with palladacycle **2** as a plausible intermediate. A role for **2**, however, raises a number of issues. For example, **1a** (X = NO<sub>2</sub>) leads to a higher proportion of crossover adduct than **1c** (X = OMe): **3a:4a** = 3:1 versus **3c:4c** = 10:1. These substituent effects are not consistent with palladacycle formation via electrophilic aromatic substitution (EAS), that is, more crossover is observed with the more electron-deficient substrate.<sup>3–5</sup>

**Scheme 1.** “Crossover Heck” Reaction



The mechanism<sup>5</sup> associated with the formation and reaction of the postulated palladacycle **2** is still under study, but to date, we have been unable to isolate or observe directly this intermediate.<sup>6</sup> An alternative approach is to gain indirect support for the involvement of **2**, and this paper focuses on methods aimed at intercepting this palladacycle. This would provide a mechanistic insight into the process outlined in Scheme 1, but also offers an unusual synthetic entry to novel polyarene variants.

Of particular relevance to this objective is the elegant work of Jones, who showed that Pd(0) or Pt(0) will catalyze the dimerization of biphenylene **5** to give tetraphenylene **7**.<sup>7</sup> This occurs via sequential C–C insertion reactions, and the intermediacy of a metallacycle **6** (M = Pt or Pd) was demonstrated.

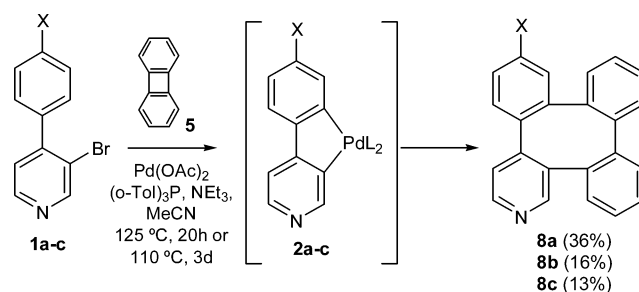


This observation raises the possibility that palladacycle **2** (derived from biaryls **1**, Scheme 1) could also be intercepted by biphenylene **5**.<sup>8</sup> This would not only provide valuable evidence and support for the intermediacy of **2**, but should generate a novel synthetic entry to “mixed” (i.e., unsymmetrical) tetraphenylene derivatives. Substituted tetraphenylenes are of significant interest given the unusual electronic properties associated with these systems.<sup>9,10</sup> However, access to either unsymmetrical or heterocyclic tetraphenylene

variants<sup>11</sup> is not straightforward, so new synthetic approaches to such systems merit investigation.

We focused initially on the 4-nitrophenyl derivative **1a**, given that this substrate showed the highest propensity to undergo C–H insertion (as judged by the level of crossover adduct **4a** observed). Using conditions similar to those employed in Scheme 1 with 1 equiv of biphenylene **5**, the desired tetracycle **8a** was observed in addition to 4-(4′-nitrophenyl)pyridine **9**, the product of C–Br reduction. This reaction was slow (which may account for formation of significant amounts of **9**), so this process was subjected to further optimization.<sup>12a</sup> Our current conditions (**5** (1000 mol %), Pd(OAc)<sub>2</sub> (10 mol %), (o-Tol)<sub>3</sub>P (20 mol %), NEt<sub>3</sub> (1000 mol %), MeCN, sealed tube, at either 125 °C for 20 h or 110 °C for 3 days) gave the target tetraphenylene **8a** in 36% isolated yield after chromatography (Scheme 2).

**Scheme 2**



Given the novel nature of this process, the structure of tetraphenylene **8a** was also established by single-crystal X-ray crystallographic analysis (Figure 1).

Interestingly, we did not observe formation of tetraphenylene **7** in any appreciable amounts under these conditions, but dimerization of **5** to give **7** is reported to be slow.<sup>7</sup> A number of important control experiments were carried out, with a major mechanistic issue concerning the timing of the individual steps. Does **1a** undergo oxidative addition faster than biphenylene **5**; that is, does the formation of **8a** involve **2a** or **6**? Also, is evidence available for the second step being the formation of palladacycle **2a** followed by reaction of this species with biphenylene **5**? First, the process shown in Scheme 2 does require palladium, and tetraphenylene **8a** was not observed in the absence of catalyst. Second, and in order to identify which component (**1a** vs **5**) was undergoing oxidative addition more rapidly, we ran a competition between **1a** and **5** under Heck conditions.<sup>12b</sup> Only Heck adducts derived from **1a** (i.e., **3a** and **4a**) were observed, and no Heck adducts<sup>7</sup> derived from **5** were detected.<sup>12c</sup> This demonstrates clearly that aryl bromide **1a** undergoes selective (faster) oxidative addition in preference to biphenylene **5**. Third, we observed no reaction between 3-bromopyridine and biphenylene **5** under the conditions shown in Scheme 2. This indicates that formation of tetraphenylene **8a** requires an aryl ring ortho to the site of oxidative addition (i.e., a role for palladacycle

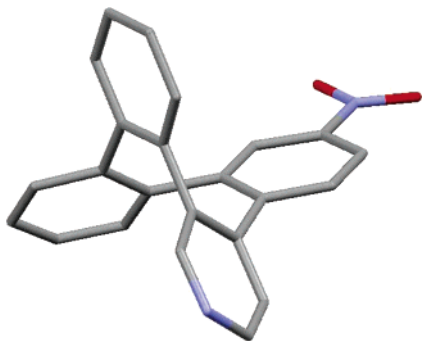


Figure 1. Structure of tetraphenylene **8a**.

**2a**) and excludes the direct interaction of the oxidative addition  $\eta^1$  complex (i.e.,  $\text{ArPdBrL}_2$ ) with biphenylene **5**.

Taken together with these control experiments, the formation of tetraphenylene **8a** indicates the selective formation of a reactive palladacycle **2a** from **1a**, which arises via C–Br oxidative addition followed by C–H insertion into the adjacent aryl ring prior to reaction with biphenylene **5**.<sup>12d</sup>

To extend the scope of tetraphenylenes available, two other 4-aryl-3-bromopyridines **1b**<sup>1</sup> and **1c**<sup>1</sup> have been examined. Using similar conditions, tetraphenylenes **8b** and **8c** were isolated in 16 and 13% yields, respectively.<sup>13</sup> Our earlier work<sup>1</sup> had indicated a similar trend, that is, both **1b** and **1c** were less effective than **1a** with respect to the formation of crossover Heck adducts **4**, and this moderated level of reactivity is apparent in their reactions with **5**. This observation—an effect associated with the 4'-X substituent—taken together with the control experiments mentioned earlier provides additional support for the intermediacy of a palladacycle **2** in both Schemes 1 and 2.

In summary, we have provided new evidence to support the conclusion that palladacycle **2** is implicated in the process illustrated in Scheme 1. This assertion is based on an ability to intercept **2** with biphenylene **5**, which, in turn, demonstrates a novel strategy for the construction of heterocyclic tetraphenylene derivatives **8**. The latter are preliminary synthetic results but importantly serve to validate the basic concept involved, and improved mechanistic understanding will be a factor in making this an effective synthetic process. The mechanism associated with conversion of **1** to **2** (and **3/4**) does remain open to debate, but our results show that a Pd(II) species needs to be considered in the catalytic cycle. A Pd(IV) hydride intermediate or EAS both appear less plausible, and the electronic effects observed with **1a–c** endorse recent computational studies.<sup>5</sup> Further, given the role of **2** and the feasibility of a Heck reaction involving this species, ring opening of **2** (or migration of palladium) is not required to explain the formation of crossover adducts **4**.

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**Supporting Information Available:** Experimental procedures, product characterization, and Heck-based control experiment between **1a** and **5**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (a) An excess of **5** is important to limit C–Br reduction. With **1a**, the mass balance is made up of **8a** (36%) and **9** (55%). (b) Jones<sup>7</sup> has shown that **6** derived from **5** participates in Heck reactions, and our control experiment indicates that **1a** undergoes oxidative addition more rapidly than **5**. (c) We did not observe **7**, **8a**, or **9** under these Heck conditions, and increasing the concentration of **5** made no impact. This control reaction (see Supporting Information) also shows an induction period prior to consumption of **1a**, and addition of liquid mercury to this Heck process very significantly reduced the rate of reaction of **1a**. The implications of this are not clear; the active catalyst is not immediately present, and mercury is either preventing the formation of or removing the catalytically competent Pd species. For a related application of a catalytic species derived from Pd black, see: Campeau, L.-C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, *7*, 1857–1860. (d) A more open-ended question relates to how the Pd insertion into biphenylene might be accelerated. This has implications for the efficiency of formation of tetraphenylenes **8**.
- Tetraphenylene **8b** was characterized by X-ray crystallography (see Supporting Information) and was obtained in a similar (12%) yield using 3-bromo-4-(4'-pyridyl)benzene<sup>1</sup> (the regioisomer of **1b**). While this establishes an alternative entry to a common palladacycle (**2b**), these isomeric halides are synthetically less readily accessible than **1**.

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