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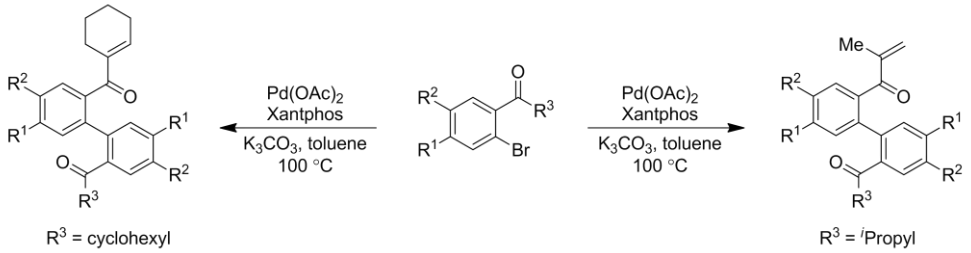
Formation of Bi-aryls via a Domino Palladium-Catalysis

J. Krishna, A. Gopi Krishna Reddy, and G. Satyanarayana*



R^3 = cyclohexyl

R^3 = ^{i}Propyl

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J. Krishna, A. Gopi Krishna Reddy, and G. Satyanarayana*

[a] Department of Chemistry, Indian Institute of Technology (IIT) Hyderabad, Ordnance Factory Estate Campus, Yeddumailaram – 502 205, Medak District, Andhra Pradesh, India.

Fax: +91(40) 2301 6032

E-mail: gvsatya@iith.ac.in

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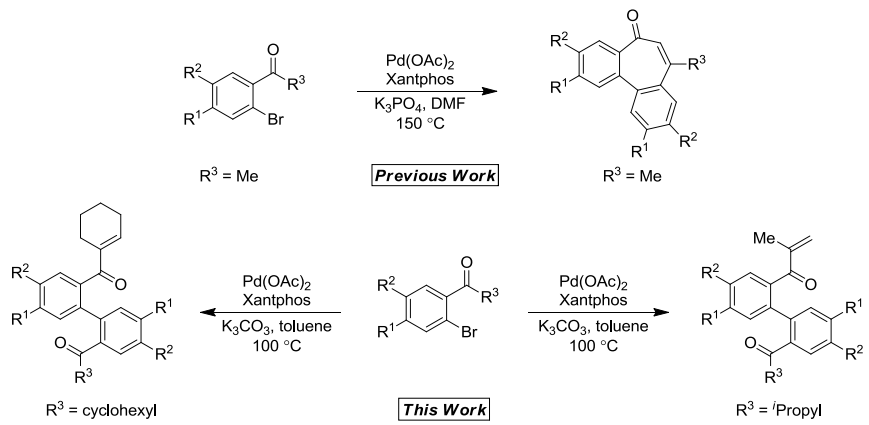
ABSTRACT

Synthesis of bi-aryls via a domino Pd-catalyzed reaction of 1-(2-bromophenyl)-2-methylpropan-1-ones/(2-bromophenyl)(cyclohexyl)methanones is presented. The mechanism of the reaction is believed to proceed through a five membered palladacycle that combines with a second molecule of halo-arene to yield the bi-aryls. This method is quite successful to deliver highly sterically crowded bi-aryls with dense functionalities on the aromatic rings.

The development of sustainable synthetic methods is a significant task in synthetic organic chemistry. In this regard; transition-metal catalysis is identified as a potent tool for constructing C–C bonds most efficiently. In this context, palladium is recognized as being amongst most used metals suitable for a wide variety of reactions, namely, coupling reactions such as Heck,[1] Stille,[2] Suzuki,[3] Sonogashira[4] and Buchwald-Hartwig.[5] In particular, C–H activation reactions through organo-palladium intermediate species have also become popular in the field of organic synthesis.[6,7]

In continuation of our ongoing research interest on transition-metal catalysis,[8] particularly on domino one-pot[8f,g,h] and sequential domino one-pot[8d,e] processes, very recently, we have reported a novel domino Pd-catalysis for the synthesis of novel 7-methyl-5*H*-dibenzo[*a*,*c*][7]annulen-5-ones,[8g] a carbon core structure of colchicinoid natural products.



Scheme 1. Illustration of the influence of an alkyl group on the out-come of Pd-catalysis.

Herein, we present an interesting domino palladium- catalysed for the synthesis of bi-aryls. In this paper, we present an interesting observation that the alkyl group of 1-(2-bromophenyl)-2-methylpropan-1-ones/(2-bromophenyl)(cyclohexyl)methanones **3a-3h/6a-6h** plays an important role, wherein the isopropyl/cyclohexyl ketone moiety in the presence of a Pd-catalyst enter into a different mechanistic path and diverts the reaction after bi-aryl coupling unlike the previous report on 1-(2-bromphenyl)ethanones (Scheme 1).[8g]

The bi-aryl is an important structural core present in some biologically active natural products.[9] For example, mastigophorene (A) exhibits nerve-growth stimulating activity,[10,11] korupensamine A, shows good antimalarial activity in vitro and in vivo,[12] whereas binaphthalene gossypol,[13] possessed proposed antispermatogenic,[14] antitumor,[15] and antimalarial[16] activities (Figure 1).

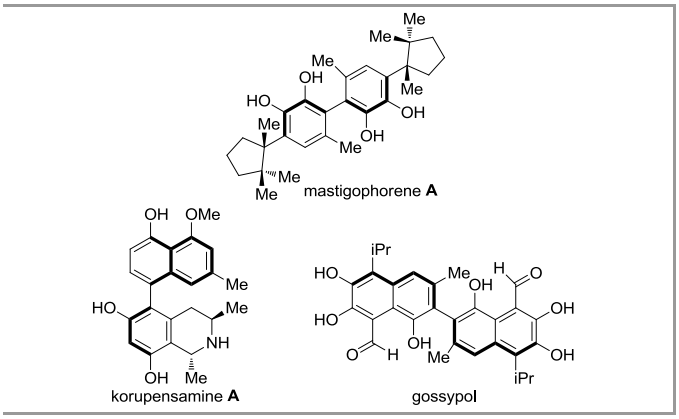
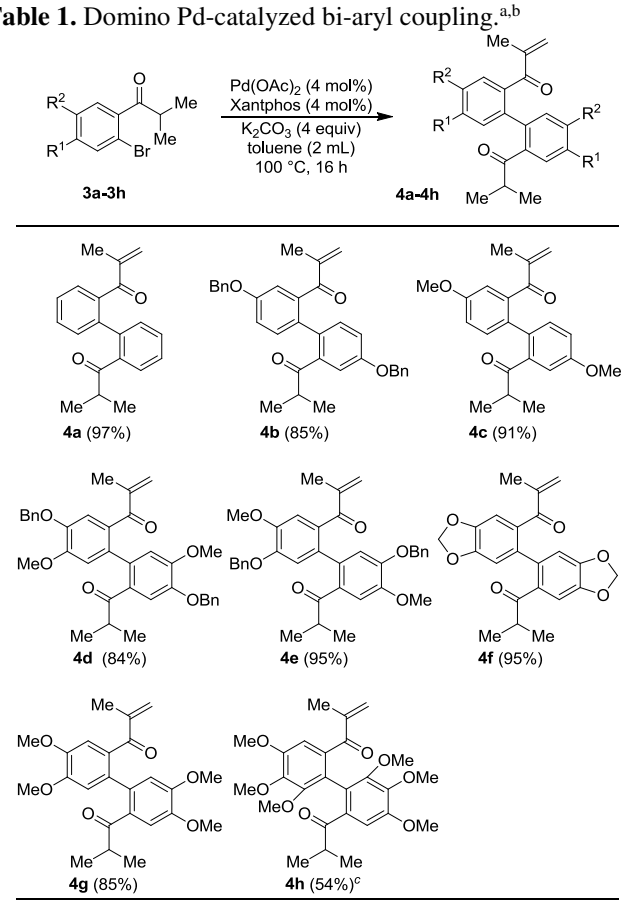


Figure 1 Naturally occurring bi-aryl compounds.

The 1-(2-bromophenyl)-2-methylpropan-1-one precursors **3a**–**3h** required for this study have been accessed from the corresponding *ortho*-bromobenzaldehydes **1a**–**1h** using isopropyl Grignard addition and an oxidation protocol (for details, see: supporting information). Having obtained the requisite 1-(2-bromophenyl)-2-methylpropan-1-ones **3a**–**3h**, the Pd-catalysis for bi-aryl formation was explored. However, the reaction was unsuccessful under the optimized conditions that were established in the case of 1-(2-bromophenyl)ethanones.[8g] Surprisingly, with slight modification of the reaction conditions (i. e. with base K_2CO_3 and solvent toluene), the reaction progressed well in a very controlled fashion and furnished only the bi-aryl product **4a** in excellent yield (Table 1). After the accomplishment of **4a**, to check the scope and limitations of the present method, these optimized conditions were applied to the other systems of 1-(2-bromophenyl)-2-methylpropan-1-ones **3b**–**3h**. Agreeably, it was observed that the optimized conditions are amenable to the other 1-(2-bromophenyl)-2-methylpropan-1-ones **3b**–**3h** and furnished the bi-aryl products **4b**–**4h** in very good to excellent yields (Table 1). However, in case of **4h**, the reaction was found to be slower and took a longer time when compared to other systems, therefore, furnished the product **4h** in moderate yield (Table 1). This can be justified because of steric hindrance of the di-*ortho*-substituents on either aromatic rings of the bi-aryl product **4h**.

Table 1. Domino Pd-catalyzed bi-aryl coupling.[a,b]



[a] Reaction conditions: **4a**–**4h** (100 mg, 0.27 to 0.44 mmol), 0.14–0.22 M in toluene.

[b] Yields in the parentheses are isolated yields of chromatographically pure products.

[c] Isolated yield of chromatographically pure product based on the starting material recovery.

In addition to the spectroscopic structural elucidation of the bi-aryls **4**, the skeletal structure of **4a** has been further unambiguously confirmed by the single crystal X-ray diffraction analysis (Figure 2).[17]

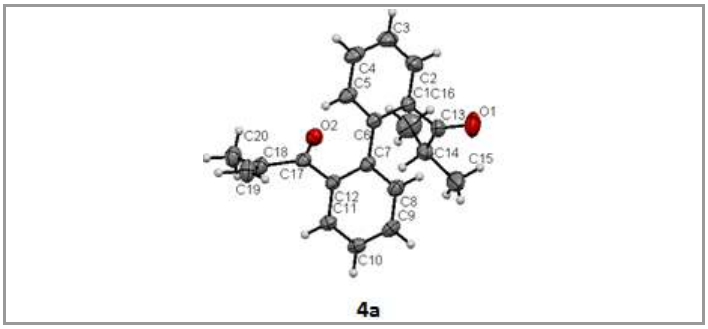
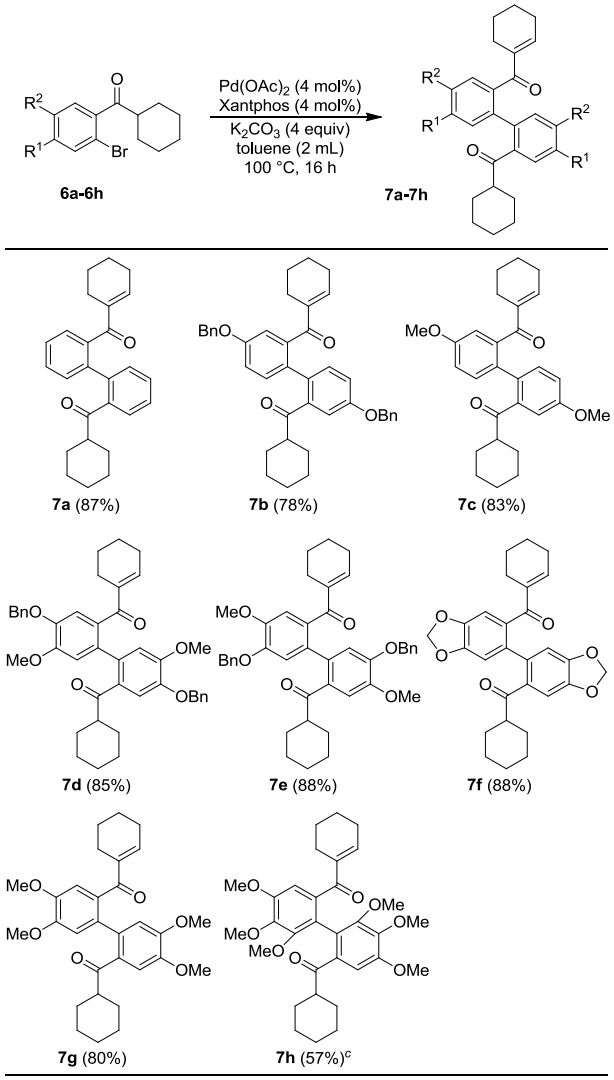


Figure 2 X-ray crystal structure of **4a**. Thermal ellipsoids are drawn at 50% probability level.

After the accomplishment of bi-aryls **4a-4h**, we have turned our focus to extend the scope and limitations of the method (the requisite precursors **6a-6h** were prepared using standard cyclohexyl Grignard reagent addition and an oxidation protocol, see: supporting information). Therefore, Pd-catalysis on (2-bromophenyl)(cyclohexyl)methanones **6a-6h**, was attempted for the formation of the expected bi-aryls. Interestingly, the method was also quite successful and gave **7a-7h** in very good yields as shown in Table 2. Once again, the effectiveness of substrate **7h**

was lowered when compared to the other starting materials applied.

Table 2. Domino Pd-catalyzed bi-aryl coupling.[a,b]

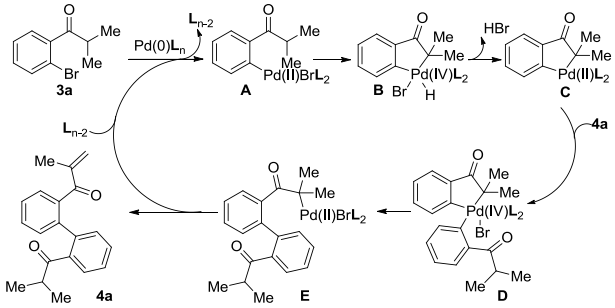


[a] Reaction conditions: **7a**–**7h** (100 mg, 0.25 to 0.37 mmol), 0.12–0.18 M in toluene.

[b] Yields in the parentheses are isolated yields of chromatographically pure products.

[c] Isolated yield of chromatographically pure product based on the starting material recovery.

The plausible mechanism for the formation of **4a** is as described in Scheme **2**. Initially, an oxidative insertion of Pd(0)-catalyst leads to aryl-palladium(II) species **A**, which on intramolecular activation of sp^3 C-H bond of the ketone might lead to a five membered palladacycle **B.** Elimination of HBr from Pd(IV)[17] cyclic intermediate **B** might generate Pd(II) species **C**. The key palladacycle **C** combines with a second molecule of **4a** via oxidative C-Br bond insertion and would yield Pd(IV)[17] complex **D**. Finally, bi-aryl coupling leads to the Pd(II) intermediate **E**, which on expulsion of a Pd-species via β-elimination might furnish the bi-aryl product **4a**. This can be justified based on the availability of β-hydrogen, which may facilitate the rapid reductive *syn*-elimination (Scheme 2). It is worth mentioning that the possible formation of higher oxidation state Pd(IV) intermediates **B** and **D** are justified based on previous reports.[18]



Scheme 2. Plausible catalytic cycle for the formation of **4**

In summary, we have developed a domino Pd-catalysis for the synthesis of bi-aryls via homo-coupling, a carbon core structure present in biologically active bi-aryl natural products. The method is efficient to deliver the bi-aryls with dense functionalisation on the aromatic moieties.

Acknowledgments

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Supplementary Material

Spectral data and Copies of ^{1}H and ^{13}C NMR spectra related to this article can be found online at.

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