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Formation of bi-aryls via a domino palladium catalysis

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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 among the 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–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.

Herein, we present an interesting domino palladium-catalyzed reaction for the synthesis of bi-aryls. In this Letter, we present an interesting observation that the alkyl group of 1-(2-bromophenyl)-2-methylpropan-1-ones/(2-bromophenyl)(cyclohexyl)methanones **3a–h**/**6a–h** plays an important role, wherein the isopropyl/cyclohexyl ketone moiety in the presence of a Pd-catalyst enters 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. For example, (+)-isoschizandrin,[9] which is a lignin from *Schizandra chinesis*, has been used in Chinese traditional medicines as an antitussive. Another naturally occurring compound, steganone,[10] was found to inhibit tubulin polymerization both in vitro and in vivo. The derivatives of valoneaic acid[11] like ellagitannins, which are widely distributed in many kinds of higher plants, possess interesting biological activities like antioxidant and anti tumor properties (Fig. 1).

The 1-(2-bromophenyl)-2-methylpropan-1-one precursors **3a–h** required for this study have been accessed from the corresponding *ortho*-bromobenzaldehydes **1a–h** using isopropyl Grignard addition and oxidation of the resulted secondary alcohols **2a–h** (for details, see: Supporting information). Having obtained the requisite 1-(2-bromophenyl)-2-methylpropan-1-ones **3a–h**, 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 a 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). The selective formation of **4a** is justified on the basis that the mild base K_2CO_3 would not be strong enough to deprotonate the α-hydrogen of isopropyl ketone **3a**, therefore, the assumed simple sp^3 C–H activation would be triggered by the initially formed aryl Pd(II) species, for the formation of five-membered palladacycle. This cyclic

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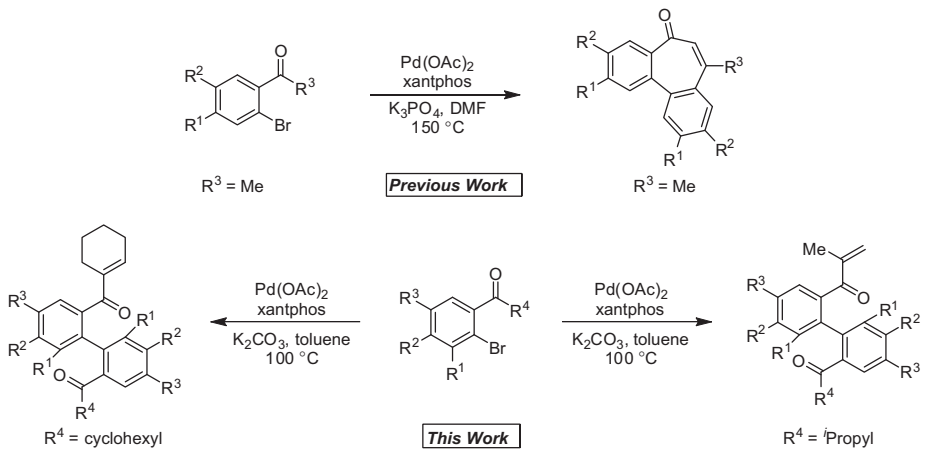


Scheme 1. Illustration of the influence of an alkyl group on the out-come of Pd-catalysis.

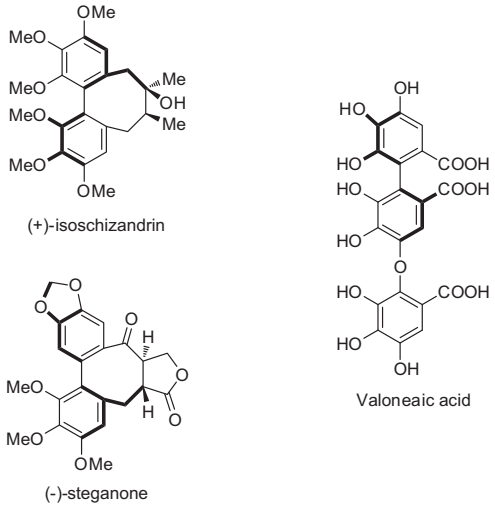
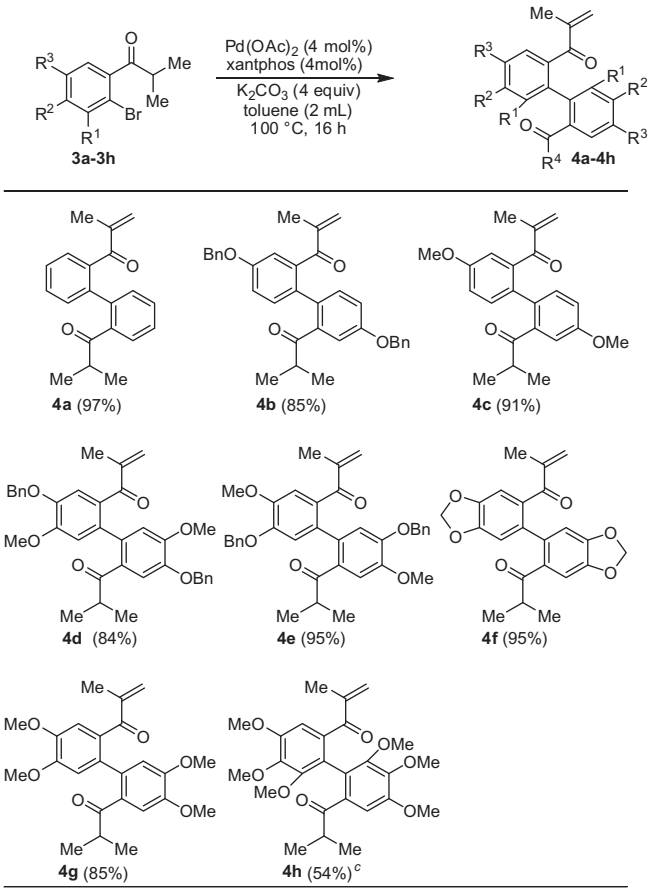


Figure 1. Naturally occurring bi-aryl compounds.

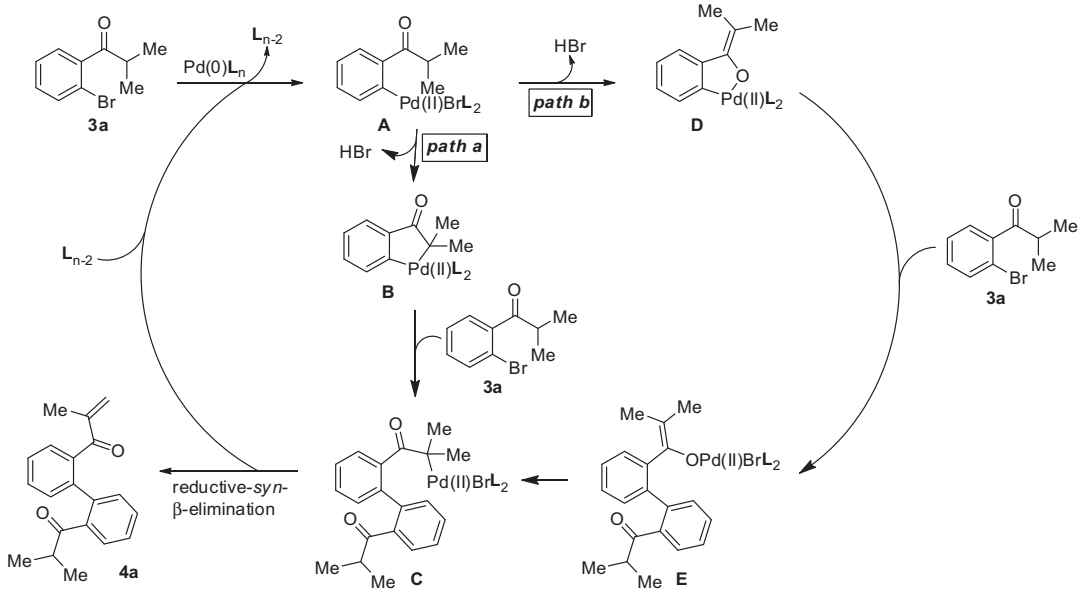
Pd(II) species would in turn couple with the second molecule of **3a** to establish the bi-aryl bond and finally would undergo fast reductive *syn*-β-elimination (due to the availability of β-hdrogens) than the intramolecular aldol reaction (for details, see; Scheme 2). In the case of 2-bromoacetophenones possessing comparatively more acidic hydrogens than that of the isopropyl ketone **3a**, relatively strong base K_3PO_4 was found to be successful. This base is reasonably strong enough to pick-up easily the α-hydrogen(s) as proton(s), facilitate the formation of five membered palladacycle followed by bi-aryl coupling and undergo exclusively intramolecular aldol condensation (due to non-availability of β-hydrogens) to furnish the 7-methyl-5*H*-dibenzo[*a*,*c*][7]annulen-5-ones.[8g] 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**–**h**. Agreeably, it was observed that the optimized conditions are amenable to the other 1-(2-bromophenyl)-2-methylpropan-1-ones **3b**–**h** and furnished the bi-aryl products **4b**–**h** 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**.

In addition to the spectroscopic structural elucidation of the bi-aryls **4**, the skeletal structure of **4a** has been further unambigu-

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



[a] Reaction conditions: **4a**–**h** (100 mg, 0.27–0.44 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.



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

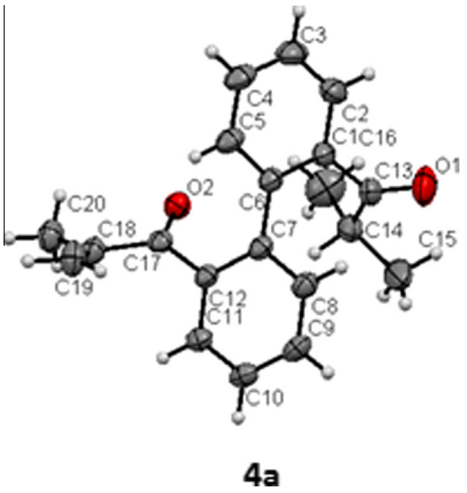


Figure 2. X-ray crystal structure of **4a**. Thermal ellipsoids are drawn at 50% probability level.

ously confirmed by the single crystal X-ray diffraction analysis (Fig. 2).[12]

After the accomplishment of bi-aryls **4a**–**h**, we have turned our focus to extend the scope and limitations of the method (the requisite precursor ketones **6a**–**h** were prepared using standard cyclohexyl Grignard reagent addition to the 2-bromobenzaldehydes **1** and oxidation of the resulted secondary alcohol **5**, see: Supporting information). Therefore, Pd-catalysis on (2-bromophenyl)(cyclohexyl)methanones **6a**–**h**, was attempted for the formation of the expected bi-aryls. Interestingly, the method was also quite successful and gave **7a**–**h** 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.

The plausible mechanistic paths (paths a and b) for the formation of **4a** are described in Scheme 2. Initially, an oxidative insertion of Pd(0)-catalyst (i.e., via path a) leads to aryl-palladium(II) species A,[13] which on intramolecular activation of sp^3 C–H bond [in this present case, the mild base K_2CO_3 would not be strong enough to deprotonate α-hydrogen of isopropyl ketone, therefore, simple sp^3 C–H activation would be triggered by Pd(II) species of intermediate A is assumed] of the ketone and concomitant elimination of HBr, might lead to a five-membered palladacycle B. Now the key palladacycle B combines with a second molecule of **3a** via oxidative C–Br bond insertion and simultaneous bi-aryl bond formation would yield Pd(II)[13] complex C. Finally, expulsion of a Pd-species via reductive *syn*-β-elimination might furnish the bi-aryl product **4a**. Alternatively, chelation of aryl Pd(II)-species of **A** (i.e., via path b) would chelate with the oxygen of ketone and generate the five membered palladacycle D. Coupling of palladacycle D with a second molecule of **3a** would furnish the bi-aryl intermediate E, which upon isomerization could meet the intermediate C that has been formed via path a.

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 functionalization on the aromatic moieties.

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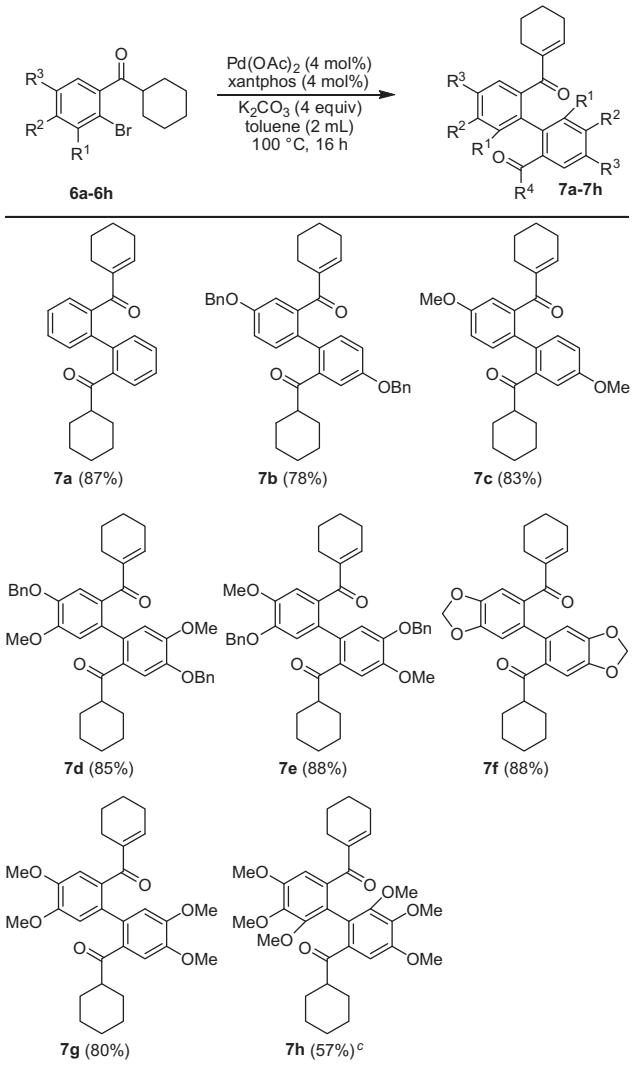
Supplementary data

Supplementary data (spectral data and copies of ^1H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.030.

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



[a] Reaction conditions: **7a**–**h** (100 mg, 0.25–0.37 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.

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