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Sequential Unsymmetrical Aryl Coupling of *o*-Substituted Aryl Iodides with *o*-Bromophenols and Reaction with Olefins: Palladium-Catalyzed Synthesis of 6*H*-Dibenzopyran Derivatives

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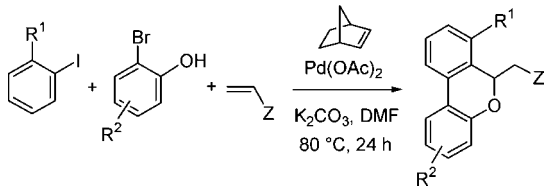
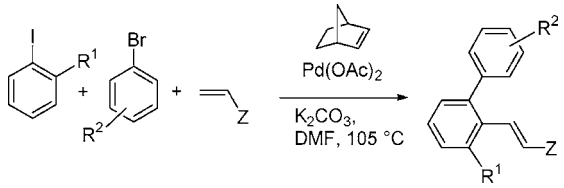
ABSTRACT



Dibenzopyran derivatives are prepared by palladium- and norbornene-catalyzed reaction of aryl iodides, *o*-substituted with electron-releasing substituents, *o*-bromophenols, and activated alkenes.

During the past decades, palladium catalyzed reactions have attracted the interest of several groups.[1] We recently reported a new mode for the arylation of aryl iodides with different aryl bromides (Scheme 1).[2] The criterion to achieve this reaction relies substantially on the presence of ortho electron-releasing substitutents in the aryl iodides and electron-withdrawing groups in the aryl bromides. The unsymmetrical aryl coupling was followed by alkene insertion into the biphenylylpalladium bond thus formed. The different reactivity of aryl iodides and bromides in the first oxidative addition leading to palladium(II) complexes and in the subsequent reaction with palladacycle species, respectively, accounts for the satisfactory selectivity observed.

Scheme 1



We have now investigated the unusual behavior of *o*-bromophenols, which despite the absence of electron-withdraw-

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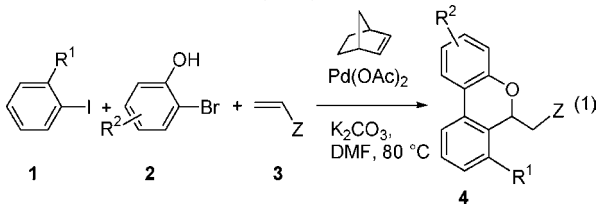
ing groups undergo a satisfactory unsymmetrical aryl coupling followed by alkene insertion and subsequent ring closure to 6*H*-dibenzopyran derivatives.[2a] Thus, the reaction of *o*-iodotoluene (**1**, R^1 = Me; 1.0 equiv), *o*-bromophenol (**2**, R^2 = H; 1.0 equiv), and methyl acrylate (**3**, Z = CO_2Me; 3.2 equiv) in the presence of $Pd(OAc)_2$ (0.04 equiv) and norbornene (0.8 equiv) as catalysts and K_2CO_3 (3.2 equiv) as a base in DMF at 80 °C for 24 h under nitrogen leads to the formation of the dibenzopyran derivative **4** (R^1 = Me; R^2 = H; Z = CO_2Me) (eq 1).

The results reported in Table 1 provide a hint to understanding the role exerted by substituents R^1 and R^2 in the course of the reaction.

Table 1. Synthesis of the 6*H*-Dibenzopyran Derivative **4** by Reaction of an *o*-Substituted Aryl Iodide, an *o*-Bromophenol, and an Electron-Deficient Terminal Alkene in the Presence of K_2CO_3, Norbornene, and $Pd(OAc)_2$[a]

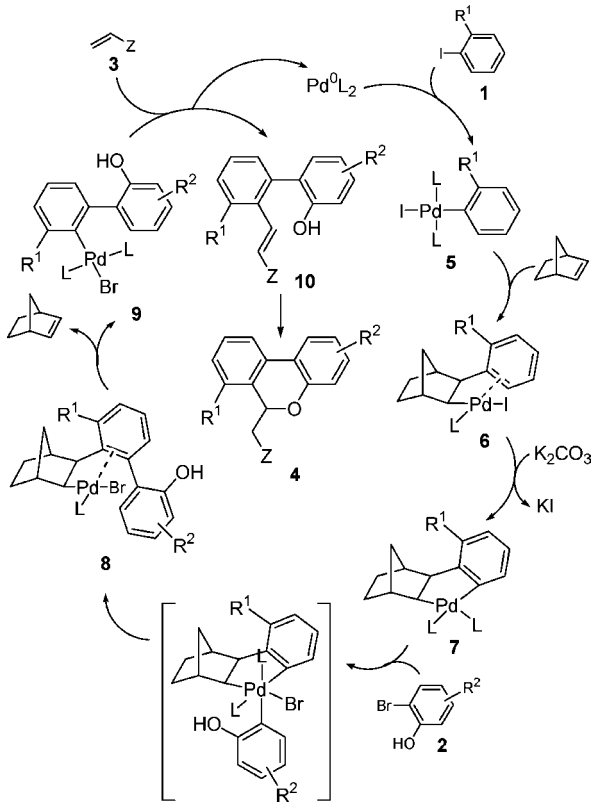


entry	R^1 in **1**	R^2 in **2**	Z in **3**	**4** yield (%)[b]
1	Me	H	CO_2Me	**4a** 83
2	Et	H	CO_2Me	**4b** 64 (89)[c]
3	$-(CH)_4-$[d]	H	CO_2Me	**4c** 69 (91)
4	CF_3	H	CO_2Me	**4d** 92
5	2,4-Me	H	CO_2Me	**4e** 88 (99)
6	Me	4-Me	CO_2Me	**4f** 46 (60)
7	Me	5-Me	CO_2Me	**4g** 52 (62)
8	Me	4-CO_2Me	CO_2Me	**4h** 40 (55)
9	Me	5-CO_2Me	CO_2Me	**4i** 72 (97)
10	Me	4-NO_2	CO_2Me	**4j** 58 (85)[e]
11	Me	5-NO_2	CO_2Me	**4k** 83 (91)
12	Me	4-NO_2,6-Br	CO_2Me	**4l** 86 (92)
13	Me	H	CO_2t-Bu	**4m** 80 (96)
14	Me	H	COMe	**4n** 93 (100)
15	Me	H	CN	**4o** 73 (87)

[a] Molar ratio of the reagents in the order reported in the title: 25:25:80:80:20:1; 80 °C, 24 h; DMF as solvent, under nitrogen; 2×10^{-3} mmol $Pd(OAc)_2$/mL DMF. [b] Isolated yield based on the employed aryl halide. Unless otherwise indicated, conversion of the aryl iodide was over 92%. [c] In parentheses isolated yield based on converted aryl bromide **2**. [d] Stands for a condensed ring. [e] The open precursor **10j** (Scheme 2) was also isolated in 13% yield.

The mechanistic rationalization of these transformations is depicted in Scheme 2. The reaction proceeds as previously shown for the unsymmetrical aryl−aryl coupling.[2] The catalytic cycle starts with the oxidative addition of the aryl iodide **1** to palladium(0) leading to the arylpalladium iodide species **5**.[3] Stereoselective norbornene insertion gives the *cis*,*exo*-arylnorbornylpalladium iodide complex **6**,[4] in which

Scheme 2. Mechanistic Rationalization of the Formation of 6*H*-Dibenzopyran Derivatives **4**



a double bond of the aromatic ring occupies a coordination site.[5]

This weak interaction favors formation of palladacycle **7**,[6] which occurs by C−H activation.[7] At this stage the *o*-bromophenol derivative **2** selectively reacts at the aromatic site of the palladium(II) metallacycle **7**, possibly through a palladium(IV) intermediate[8] shown in parentheses, to form complex **8**. Likely owing to steric effects, norbornene deinsertion takes place giving the biphenylylpalladium complex **9**,[9] which reacts with the terminal alkene according

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to a Heck process.[10] The resulting vinylbiphenyl derivative **10** undergoes an intramolecular Michael-type reaction by attack of the ortho hydroxyl group, originally belonging to the aryl bromide, onto the vinyl group to yield the benzopyran derivative **4**.[11] Its formation must occur easily since the uncyclized precursor **10** has never been isolated except for the case of 4-nitro-2-bromophenol (entry 10, Table 1).

It is noteworthy that norbornene behaves as a catalyst. As shown in Scheme 2, the molecule of norbornene inserted into the arylpalladium bond of complex **5** is deinserted from intermediate **8**, thus becoming available for a new catalytic cycle. The amount of norbornene is very important for the success of the reaction since a high concentration favors its own insertion and in the same time prevents the competing insertion of the terminal alkene. On the other side norbornene deinsertion is thus made more difficult and byproducts, containing the norbornane structure, are formed.[12] The amount of norbornene must be therefore accurately balanced to obtain the best result.

As previously mentioned, the most striking feature of this reaction is the ability of *o*-bromophenol to react with the palladium(II) complex **7** faster than the aryl iodide despite the presence of an electron-donating substituent which should make it less reactive. This peculiar behavior most likely has to be ascribed to a beneficial chelating effect[13] of the *o*-hydroxy group, since *p*-bromophenol as well as *o*- and *p*-bromoanisole, did not react at all. The Michael reaction appears to be catalyzed by the basic medium and not by palladium.

As shown in Table 1, the reaction is strongly influenced by the substituents present on both aryl halides. When the ortho R^1 group on the aryl iodides is a methyl, the desired products, resulting from the reaction with *o*-bromophenol and methyl acrylate, are isolated in 83 and 88% yield, respectively (entries 1 and 5). *o*-Ethyliodobenzene (R^1 = Et) and 1-iodonaphthalene ($R^1 = -(CH)_4-$) still give satisfactory results (64 and 69%, respectively; entries 2 and 3), while *o*-*i*-propyliodobenzene (R^1 = *i*-Pr) and *o*-iodoanisole (R^1 = OMe) completely inhibit the formation of compound **4** (data not reported in Table 1). For reasons to be still ascertained, these groups offset the beneficial effect of *o*-bromophenol, yet allow the coupling of two molecules of the aryl iodide to give the symmetrically substituted vinylbiphenyl derivative of Scheme 1 (R^1, *o*-R^2 = *i*-Pr, Z = CO_2Me, 78% yield; R^1, *o*-R^2 = OMe, Z = CO_2Me, 65% yield) as the main product.

As previously reported,[2] aryl iodides bearing electron-withdrawing groups are not suitable for the nonsymmetrical coupling because they react with palladacycle **7** faster than the aryl bromides. An anomalous behavior was observed with 2-trifluoromethyl-1-iodobenzene, which in combination with *o*-bromophenol and methyl acrylate, leads to the corresponding dibenzopyran **4d** (R^1 = CF_3, R^2 = H, Z = CO_2Me) in very high yield (92%, entry 4). This result is in agreement with the previously observed poor reactivity shown by 2-trifluoromethyl-1-iodobenzene in the symmetrical aryl−aryl coupling process[12] as well as by the corresponding bromo derivative (2-trifluoromethyl-1-bromobenzene) as partner of an aryl iodide in the unsymmetrical aryl−aryl coupling (Scheme 1).[2a] The low reactivity shown by these derivatives[2a,12] suggests that a strong interaction of the *ortho*-CF_3 group with palladium(II) could be at work at the stage of metallacycle **7**, thus preventing aryl coupling.

Variation of R^2 on the *o*-bromophenol appears to be crucial. The presence of electron-withdrawing groups is expected to favor the reaction of the *o*-bromophenol derivative with **7** but to negatively affect the final ring closure to **4**. Satisfactory results were obtained using electron-withdrawing groups, such as CO_2Me and NO_2, para to the C−Br bond (entries 9 and 11), whereas bromides with these groups in meta gave the desired products in lower yield (entries 8 and 10). As is well-known, a CO_2Me group meta to the C−Br bond is less electron-withdrawing than in ortho and para and as a consequence causes a lower reactivity, as previously observed in our coupling experiments,[2] toward complex **7**. Moreover, the CO_2Me group, being para to the OH group, appears to negatively influence the ring closure. The result is a 40% yield of the desired product **4h** which compares very poorly with the 83% of **4a** obtained from the unsubstituted *o*-bromophenol (entry 1). The *m*-NO_2 substituent (entry 10) still is able to favor the reaction of the aryl bromide but, being para to hydroxyl group, it strongly retards the final ring closure. Compound **4j** and its open precursor **10j** (*E* isomer) were isolated in 58 and 13% yield, respectively, the latter being obtained only with this bromophenol derivative. Curiously, no uncyclized precursor was found when using *o*-dibromo-*m*-nitrophenol (entry 12), despite the NO_2 group being para to the C−OH bond (meta to the C−Br bond). Beside acrylates only electron-deficient alkenes entries (14 and 15), give good results.

In conclusion we have achieved an efficient catalytic process for the synthesis of 6*H*-dibenzopyran derivatives starting from easily available reagents. The reaction proceeds along a rather complex pathway but is very simple from the experimental point of view and allows the formation of two new C−C bonds and one C−O bond in a single operation. 6*H*-Dibenzopyrans belong to an important class of biologically active compounds,[14] being the basic structure of cannabinols.[15]

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The new catalytic method has also allowed a better understanding of substituent and chelating effects in nonsymmetrical and symmetrical aryl coupling.

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Supporting Information Available: Experimental procedures and characterization for compounds **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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