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# A novel palladium-catalyzed homocoupling reaction initiated by transmetallation of palladium enolates

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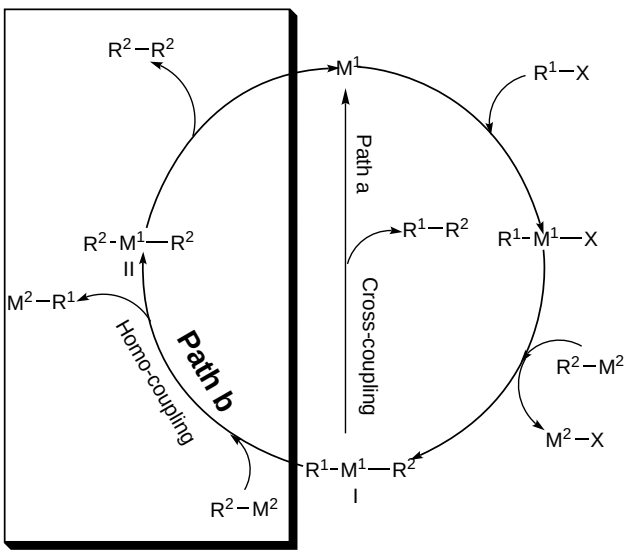
**Abstract**—Palladium-catalyzed homocoupling reaction of aryl boronic acids has been developed using a protocol similar to the well-documented crosscoupling reaction. α-Halocarbonyl compounds are applied to initiate the reaction via oxidative addition to a palladium(0) species. The resulting palladium enolate halide can promote the double transmetallation. Reductive elimination generates the desire homocoupling product. © 2002 Elsevier Science Ltd. All rights reserved.

Biaryls form the central core in a large number of natural products and is an important pharmacophore in a variety of biologically active compounds.[1] Pd- and Ni-catalyzed crosscoupling reactions have been developed to construct the biaryl compounds.[2] Compared with the enormous literature on crosscoupling reactions, there have been fewer studies carried out on Pd-catalyzed homocoupling reactions.[3–5] Generally, crosscoupling reactions are initiated by oxidative addition, followed by transmetallation, and reductive elimination to give the coupling products (Scheme 1, path a).[2b] If a homocoupling reaction is expected to proceed in a similar manner, a second transmetallation between $R^2$–$M^2$ and intermediate **I** for forming intermediate **II** is required (Scheme 1, path b). To our knowledge, there are no reports that the intermediate $R^1$–M–X generated by oxidative addition of $R^1X$ to $M^1$ can undergo double transmetallation to form intermediate **II**, which can produce the homocoupling product via reductive elimination. In the course of studying asymmetric α-arylation of ketones or esters, we serendipitously found that α-halocarbonyl compounds can serve as this type of reagent. The α-halocarbonyl compounds can undergo oxidative addition with a palladium(0) species and mediate the aforementioned double transmetallation. Homocoupling products are generated in this process. Herein, we would like to present our results in this area.




**Scheme 1.**

The α-arylation of ketones has been explored by the Hartwig and Buchwald groups,[6] and its asymmetric version has also been achieved by Buchwald et al.[7] However, because the strong basic conditions are necessary for the formation of palladium enolate, the reaction is limited to the formation of chiral quaternary carbon centers. Racemization of tertiary carbon centers adjacent to a carbonyl can occur under the strong basic conditions. In order to overcome this difficulty, we envision that α-halocarbonyl compounds can undergo oxidative addition to a palladium(0) species and a palladium enolate can be formed without use of a base. Transmetallation of the palladium enolate with an organometallic compound and reductive elimination can produce the α-arylation product. Under this design, we examined a palladium-catalyzed reaction between methyl α-bromophenylacetate **1** and 3,5-dimethyl

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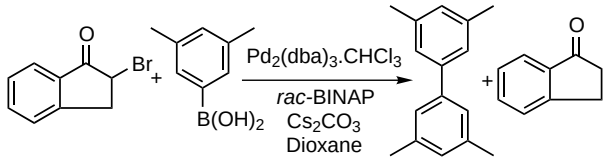
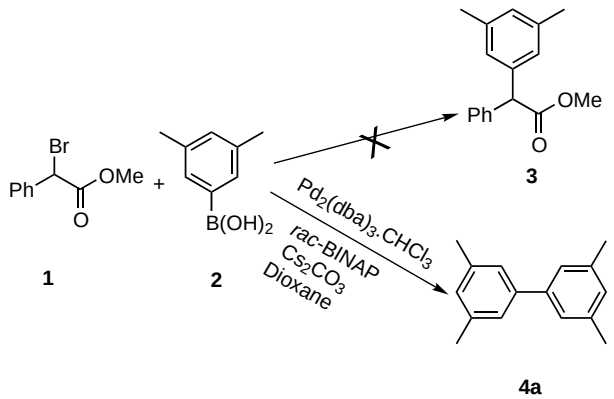
phenyl boronic acid **2**.[8] Surprisingly, the expected crosscoupling product **3** was not formed while the homocoupling compound **4a** was produced as the exclusive product. This unexpected result led us to pursue the mechanism for the formation of **4a** and to investigate the role of α-bromophenyl acetate **1** (Scheme 2).

Using this reaction protocol, we have examined the reaction with a different α-bromo carbonyl compound **5** and found that the homocoupling product **4a** was obtained along with compound **6**, which is the reduction product of **5** (Eq. (1)). In the absence of the α-bromo ester, no coupling product could be obtained. Therefore, we believe that the α-bromo carbonyl compound plays an important role in this reaction.



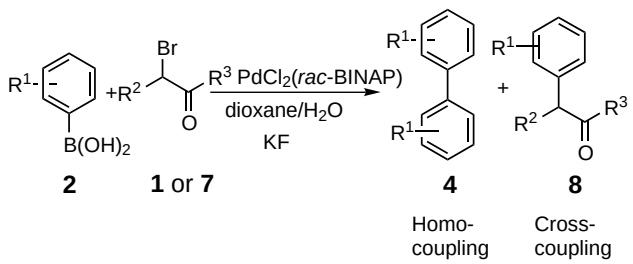

(1)

Under the palladium-catalyzed homocoupling condition, we have investigated the reaction of a variety of aryl boronic substrates and readily available ethyl α-bromo acetate **7**.[9] A competition between homocoupling and crosscoupling reactions was observed (Table 1, entries 1, 3–5, 7, 9 and 12). We found that the substitution at the α-position of the bromoester would favor the homocoupling reaction and hinder the crosscoupling reaction (Table 1, entries 3 and 5). In addition, water plays a dramatic role in controlling the selectivity between homocoupling and crosscoupling reactions. When water was added, the ratio of homo- and crosscoupling products switched from 30:70 to




**Scheme 2.**

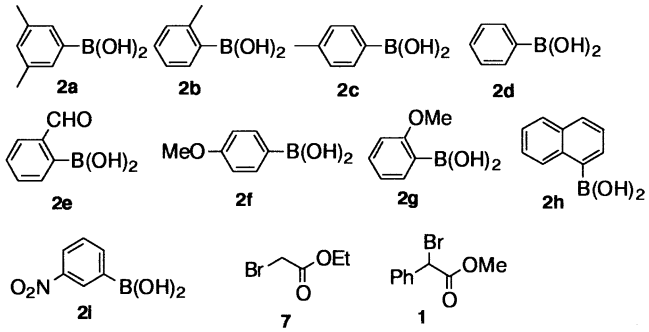
**Table 1.** Palladium-catalyzed coupling reaction of aryl boronic acids[a]




| Entry | | Substrates | Solvent | Yields (%) | Products[b] | |
|---|---|---|---|---|---|---|
| | | | | | Homo- | Cross- |
| 1 | **2a** | **7** | Dioxane | 89 | 50 | 50 |
| 2 | **2a** | **1** | Dioxane/$H_2O$ | 95 | 100 | 0 |
| 3 | **2b** | **7** | Dioxane | 82 | 30 | 70 |
| 4 | **2b** | **7** | Dioxane/$H_2O$ | 89 | 70 | 30 |
| 5 | **2b** | **1** | Dioxane | 88 | 94 | 6 |
| 6 | **2b** | **1** | Dioxane/$H_2O$ | 85 | 100 | 0 |
| 7 | **2c** | **7** | Dioxane | 92 | 50 | 50 |
| 8 | **2c** | **1** | Dioxane/$H_2O$ | 91 | 100 | 0 |
| 9 | **2d** | **7** | Dioxane | 92 | 50 | 50 |
| 10 | **2d** | **1** | Dioxane/$H_2O$ | 94 | 100 | 0 |
| 11 | **2e** | **1** | Dioxane/$H_2O$ | 93 | 100 | 0 |
| 12 | **2f** | **7** | Dioxane | 94 | 60 | 40 |
| 13 | **2f** | **1** | Dioxane/$H_2O$ | 92 | 100 | 0 |
| 14 | **2g** | **7** | Dioxane | 89 | 100 | 0 |
| 15 | **2g** | **1** | Dioxane/$H_2O$ | 95 | 100 | 0 |
| 16 | **2h** | **1** | Dioxane/$H_2O$ | 89 | 100 | 0 |
| 17 | **2l** | **1** | Dioxane/$H_2O$ | 90 | 100 | 0 |

[a] All reactions were performed using 2.5 mol% $PdCl_2$ (*rac*-BINAP) and 300 mol% KF. The reactions were done at 100°C for 2–24 h and progress of the reaction was monitored by TLC.

[b] Isolated yields were reported, and the ratio of homocoupling product versus crosscoupling product was determined by NMR.

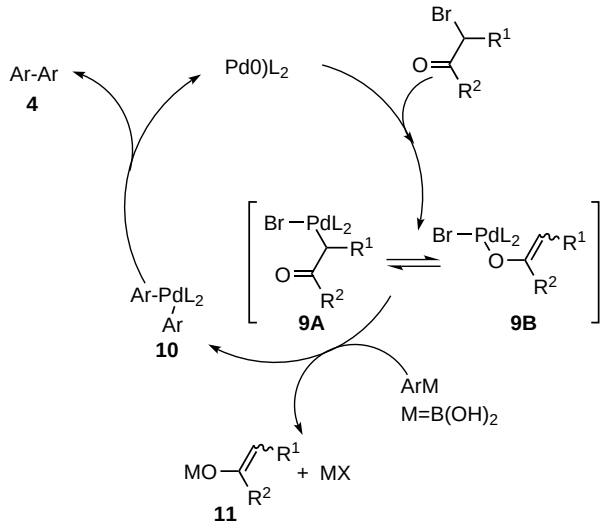



70:30 in the reaction of *ortho*-methyl phenyl boronic acid and ethyl α-bromoacetate (Table 1, entries 3 and 4). Significantly, we obtained 100% homocoupling selectivity when methyl α-bromo phenylacetate **1** was used in the presence of water (Table 1, entries 2, 6, 8, 10, 11 and 13–17). It is noteworthy that the present homocoupling protocol can not only be carried out in an aqueous condition, but also can tolerate a wide variety of functional groups. Aldehyde, methoxy, and nitro groups are compatible in the reaction (Table 1, entries 11, 12, 14, 16, 17). Another interesting phenomenon is the role of *ortho*-methoxy group. The reaction of ethyl α-bromo acetate surprisingly gave exclusive homocoupling product over the crosscoupling product (Table 1, entry 14). However, if the methoxy group was not present at the *ortho* position, the high selectivity for homocoupling disappeared (Table 1, entry 12).

Compared with the extensive study and application of crosscoupling reaction catalyzed by transition metal complexes (Scheme 1, path a), the homocoupling reaction has received little attention. Because of this scant coverage in the literature, we feel that our discovery of this homocoupling via a traditional crosscoupling approach will invigorate work in this area.

In the proposed mechanism of our homocoupling reaction, a palladium enolate was hypothesized as the key intermediate. Recently, the chemistry of palladium enolate has received intensive attention.[6,7,10] Three proposed structures are Pd–carbon ($\eta^1$), Pd–oxygen ($\eta^1$) and Pd–oxo π-allyl ($\eta^3$) enolates.[10f,11] Many organic transformations with palladium enolates such as protonolysis,[10a–e] arylation of carbonyl compounds,[6,7] Mannich-type reaction,[10f] and aldol reaction[10g–j] have been reported. Scheme 3 illustrates a proposed mechanism for the homocoupling reaction. First, the reaction is initiated by oxidative addition of an α-halocarbonyl compound to Pd(0).[12] Double transmetallation of **9** generates the intermediate **10** and reductive elimination of **10** yields the homocoupling product.

The oxidative addition of α-halocarbonyl compounds as the initial step is well documented.[11] A *C*-bound Pd enolate **9A** formed by oxidative addition to a palladium(0) species can tautomerize to an *O*-bound Pd enolate **9B**. Double transmetallation of the Pd enolate is the key step for this new coupling reaction. Compared with transmetallation between an aryl organometallic reagent and a halide anion at a palladium center, there




**Scheme 3.**

is little known about the transmetallation between aryl organometallic reagents and enolate anion at a palladium center. In our study, we found several controlling factors for the chemoselectivity between homocoupling and crosscoupling reactions: (1) The increased yield of homocoupling product in aqueous medium suggests that homocoupling reaction is preferred. It is reasonable that the intermediate **11** is hydrolyzed in the presence of water and this process facilitates the formation of the intermediate **10**. (2) When methyl α-bromophenylacetate (**1**) was employed in this reaction, the high homocoupling selectivity may be derived from the fast tautomerization from a *C*-bound palladium enolate to an *O*-bound palladium enolate. (3) The dramatic homocoupling selectivity of an *ortho*-methoxy group may be the result of coordination of the methoxy group to a palladium center. This coordination can weaken the *O*-bound palladium enolate bond and make it a better leaving group, which facilitates the second transmetallation.

In summary, we have developed a novel palladium-catalyzed homocoupling reaction using a protocol similar to the well-documented crosscoupling reaction. Further investigation of the scope, synthetic applications, as well as development of the asymmetric version of this palladium-catalyzed homocoupling reaction to make chiral biaryl compounds will be reported in due course.

## Acknowledgements

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9. **General procedure for the homocoupling of aryl boronic acid catalyzed by palladium.** To a Schlenk tube were added $PdCl_2$(*rac*-BINAP) (0.01 mmol), KF (3.0 mmol), 1 mmol aryl boronic acid and solvent [dioxane (5 mL) or dioxane (4 mL) and $H_2O$ (1 mL)]. Under nitrogen, an α-bromo carbonyl compound [ethyl bromoacetate ester (0.6 mmol) or methyl α-bromophenylacetate ester (0.6 mmol)] was added and then the reaction mixture was stirred at 100°C for 24 h. After the reaction was completed, 5 mL of ethyl acetate and ca. 3–5 g silica gel were added to the reaction mixture. The solvent was removed under reduced pressure and the residue was loaded on a silica gel column for purification. **3,5,3′,5′-Tetramethylbiphenyl (4a):** $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.54 (s, 4H), 7.31 (s, 2H), 2.71 (s, 12H).

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