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Palladium-catalyzed cascade allylation/carbopalladation/cross coupling: a novel three-component reaction for the synthesis of 3,3-disubstituted-2,3-dihydrobenzofurans

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Abstract—A novel one-pot palladium-catalyzed cascade between 2-iodophenol, methyl bromomethylacrylate and an arylboronic acid provides an efficient access to heterocycles possessing the 3,3-disubstituted-2,3-dihydrobenzofuran skeleton via allylation/carbopalladation/Suzuki cross-coupling.

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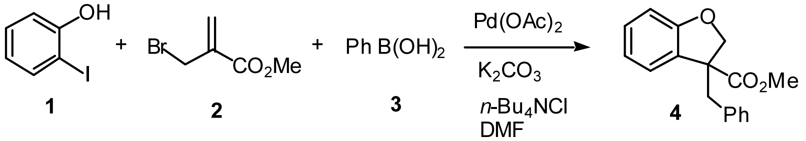
The search for new methods for the construction of organic molecules from simple starting materials is an ongoing challenge for the organic chemist. Domino reactions are an attractive area since in one operation many bonds can be successively created.[1] Exploited in their intermolecular version, these multi-component reactions (MCR) are powerful methods for the efficient synthesis of new compounds.[2]

Palladium-catalyzed processes have come to the foreground of transition metal-promoted multi-component reactions because of the wide variety of processes which can be mediated by this metal.[3] Recently we have published a new Pd-catalyzed multi-component reaction involving a Pd-catalyzed allylation of methyl bromomethylacrylate **2** followed by a Heck reaction on the substituted acrylate, demonstrating that **2** could participate in a one-pot substitution/carbopalladation reaction.[4] We now report a new three-component reaction involving **2** and providing new molecules with a dihydrobenzofuran skeleton. The reaction is described in Eq. (1).

When 2-iodophenol **1**, methyl bromomethylacrylate **2** and phenylboronic acid **3** were reacted together in the presence of $Pd(OAc)_2$, K_2CO_3 and n-Bu_4NCl in DMF at 80°C, 3,3-disubstituted 2,3-dihydro benzofuran **4** was obtained as the sole product in good yield (74% NMR yield, 45% isolated).[5]

This reaction proceeded via allylic alkylation of 2-iodophenol **1** followed by *exo-trig* cyclization via carbopalladation of the acrylate and then Suzuki cross-coupling of the resulting alkylpalladium. Conditions had to be adapted in order to design one catalytic system which could catalyze the different processes. Indeed most catalytic systems include the presence of phosphines to perform a cyclization/Suzuki-coupling.[6] In our case the reaction rate was dramatically reduced when triphenylphosphine was used as a ligand.[7] Furthermore an aqueous medium, which is considered as a standard condition for the Suzuki cross-coupling of arylboronic acids,[6] had to be avoided due to the potential hydrolysis of the methyl ester. We were finally pleased to find out that a phosphine-free system but in



(1)

Keywords: palladium; catalysis; cyclization; multicomponent reactions; oxygen heterocycles.

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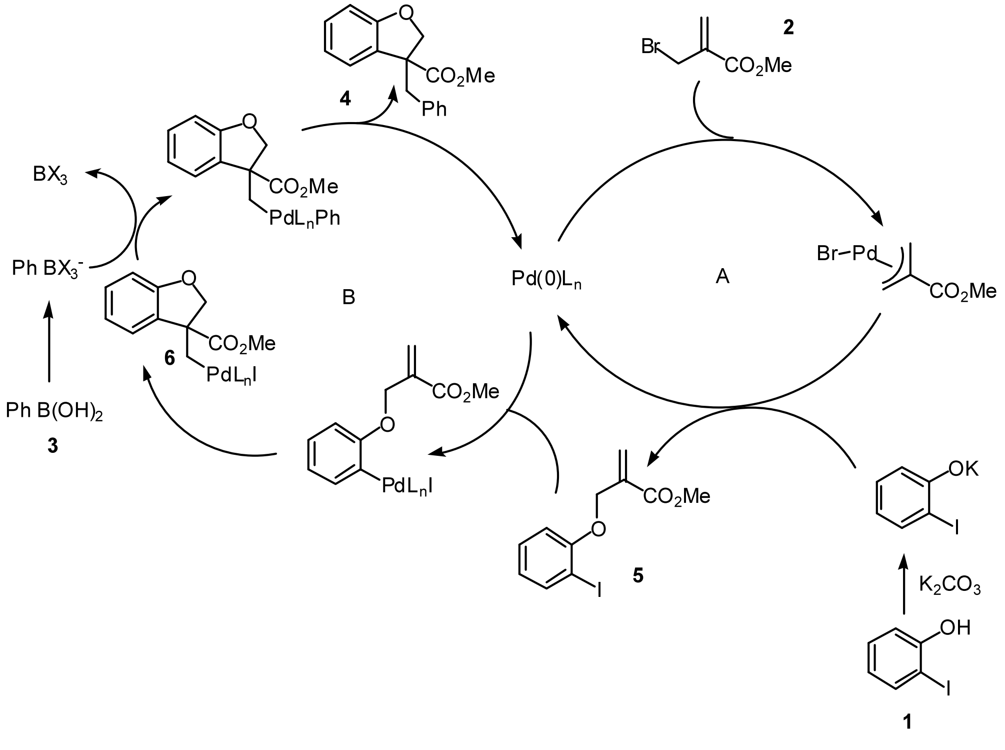
the presence of a tetraalkylammonium salt was efficient in this reaction. This system has been previously reported for the Heck reaction[8] and for the Suzuki coupling.[9] It has been shown that the combination of $Pd(OAc)_2$ with n-Bu_4NCl in the presence of a base generated colloidal palladium nanoparticles which are involved in the catalytic cycle.[9] In the case described herein the Pd particles also catalyzed the allylation of phenol **1**. While the alkylation does occur in the absence of palladium, the reaction is much faster in the presence of the catalyst.

Tsuji–Trost allylation[10] and cyclisation–anion capture[11] are well documented as separate processes. To the best of our knowledge, we present herein the first example of a palladium-catalyzed allylation/carbopalladation/Suzuki-cross coupling MCR reaction. The palladium participates in two different catalytic cycles (Scheme 1). Initial reduction of $Pd(OAc)_2$ with n-Bu_4NCl in the presence of K_2CO_3 generates the active Pd(0) species denoted as $Pd(0)L_n$ in Scheme 1. It is likely that the reaction proceeds firstly via palladium activation of the allylic bromide **2** followed by alkylation of the phenoxide,[12] providing **5** and regenerating Pd(0) (catalytic cycle A). The palladium complex is also expected to participate in catalytic cycle B: oxidative addition of **5** to Pd(0) followed by cyclic carbopalladation of the olefin provides alkylpalladium **6**. Transmetallation with phenylboronate (from reaction of phenylboronic acid **3** with the base and/or anions present in the reaction medium) followed by reductive elimination generates the final product **4** and recycles Pd(0).

To our knowledge, only a few examples of Pd-catalyzed allylations combined with another Pd-catalyzed process making use of a unique catalytic system are known in the literature.[4,13] The process has been categorized as Pd-catalyzed pseudo-domino reaction (Pd-PDOM).[13d] Recently allenes[14] have been involved in a Pd-catalyzed MCR complementary to the one described here: these reactions require either sequential addition of the reactant and/or do not give access to the structures described herein.

Table 1 reports the yields of 3,3-disubstituted 2,3-dihydrobenzofurans obtained from five different arylboronic acids $ArB(OH)_2$. Electron donating and withdrawing substituents can be present on the aromatic ring. However, substitution at the *ortho* position led to lower yields.

In summary, we have described a novel three-component reaction which gave access to new dihydrobenzofuran structures. Further development of this reaction and related processes are underway in our laboratory.



Scheme 1.

Table 1. Palladium-catalyzed synthesis of dihydrobenzofurans

Ar-	Ph-	4-MeO-C_6H_4-	3-NO_2-C_6H_4-	2-Me-C_6H_4-	4-Ph-C_6H_4-
Isolated yield (%)	45	50	40	28	57

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5. To a solution of methyl-2-bromomethacrylate (48.9 mg, 0.274 mmol) in DMF (3 mL) were added K_2CO_3 (110.15 mg, 0.955 mmol), 2-iodophenol (50.2 mg, 0.228 mmol), *n*-Bu_4NCl (76 mg, 0.274 mmol), a solution of $Pd(OAc)_2$ (5.12 mg, 0.0273 mmol) in DMF (1 mL) and $PhB(OH)_2$ (30.54 mg, 0.25 mmol). The resulting mixture was stirred for 15 h at 80°C, cooled to room temperature, filtered over Celite and concentrated. Column chromatography (silica gel, hexane/CH_2Cl_2: 1/1) afforded 27.5 mg (45%) of the title compound. IR (neat) 3030 (w), 2953 (m), 2923 (m), 1733 (s), 1480 (s), 1226 (s), 1022 (m), 701 (m) cm^{-1}; ^1H NMR (Me_4Si, $CDCl_3$, 250 MHz) δ 3.12 (d, 1H, $J=13.7$ Hz), 3.50 (d, 1H, $J=13.7$ Hz), 3.76 (s, 3H, OMe), 4.53 (d, 1H, $J=9.5$ Hz), 4.91 (d, 1H, $J=9.5$ Hz), 6.81 (d, 1H, $J=8$ Hz), 6.94 (td, 1H, $J=7.5$ Hz, $J=0.9$ Hz, H), 7.03–7.07 (m, 2H), 7.19–7.30 (m, 4H), 7.41 (dd, 1H, $J=7.5$ Hz, $J=1.2$ Hz); ^{13}C NMR (Me_4Si, $CDCl_3$, 100 MHz) δ 44.46, 52.93, 58.10, 77.01, 110.48, 121.09, 125.52, 127.51, 128.84, 129.99, 130.01, 136.59, 159.94, 173.28; HRMS calculated for $C_{17}H_{16}O_3$ (M^+) 268.1099, observed 268.1081.
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