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Palladium mediated bis- and tris-biaryl Heck coupling for the synthesis of heterocycles

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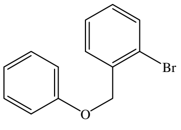
Abstract

A simple and straightforward palladium mediated ligand free bis- and tris-biaryl coupling on an unactivated phenylbenzyl ether system to produce hitherto unreported heterocyclic compound is described.

Keywords: Biaryl-coupling; Heck cyclization; Palladium acetate; 2-Bromobenzyl bromide

Recognizing the need for efficient routes to biaryl compounds, organic chemists have developed an arsenal of catalytic methods including the Suzuki–Miyaura, Negishi, Kumada–Corriu, and Hiyama couplings.[1,2] The direct arylation of electron rich, heteroaromatic rings has begun to replace these more traditional techniques in specific case.[3–6] In contrast to these advances, the direct arylation of simple aromatic rings remains a significant challenge.[7–11] The aryl–aryl linkage is found in a wide range of compounds, from natural products such as vancomycin[12] and aporphine alkaloids[13] to important synthetic compounds such as 1,1′-bi-2-naphthol[14] and BINAP.[15] Intramolecular aryl–aryl coupling reactions involving a palladium reagent have been used to synthesize many condensed aromatic compounds.[16–20] Recently, we reported the synthesis of condensed heteroaromatic compounds using biaryl-coupling reactions with palladium reagents.[21–23] Phenolates have been shown to exhibit enhanced reactivity in intramolecular arylation reactions.[24] On the other hand, ethers such as **1**, that lack a phenolate-activating group react poorly and give mainly the debrominated product.[25]



1

Fagnou et al. improved[26] the yield of the cyclized product by using Pearlman's catalyst $Pd(OH)_2/C$. Though this is a heterogeneous system, the actual catalytically active species is believed to be a soluble Pd derivative. But in this case, the reaction took sufficiently long time for completion. They were also able to achieve much better yield of the cyclized product (above 90%) by using N-heterocyclic carbene[27] and 2-(diphenylphosphino)-2-(*N*,*N*-dimethylamino)biphenyl[28] as a ligand with $Pd(OAc)_2$ as a catalyst. Here we report a simple, expedient, and straightforward ligand free Heck coupling process for bis- and tris-biaryl coupling.

The Heck precursors **4a–d** required for our present study were synthesized in 80–90% yields by refluxing resorcinol **2**, *m*-aminophenol **5**, and 2,7-dihydroxynaphthalene **6** with either 2-bromobenzyl bromide **3a** or 2-bromo-3-methoxybenzyl bromide **3b** in dry acetone in the presence of anhydrous potassium carbonate and a small amount of sodium iodide (Finkelstein conditions) (Scheme 1).

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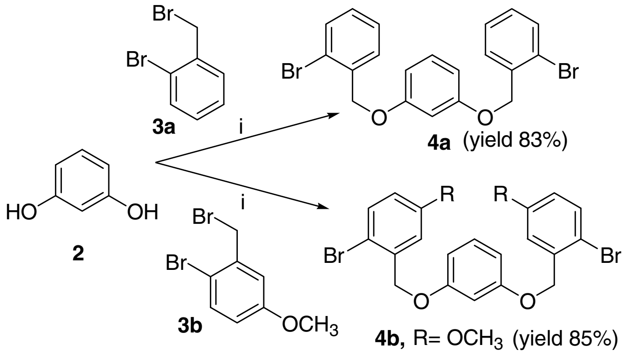
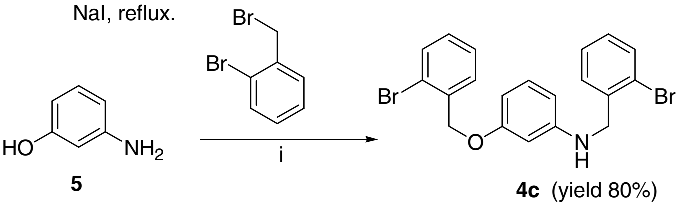
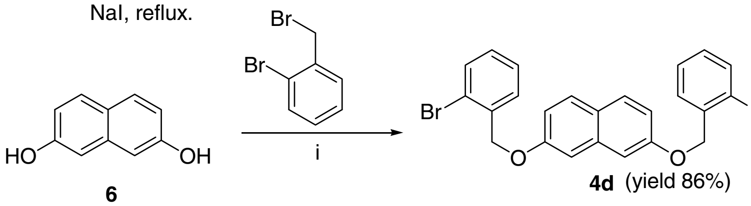


Reagents and condition: i. dry acetone, anhydrous K_2CO_3, NaI, reflux.



Reagents and condition: i. dry acetone, anhydrous K_2CO_3, NaI, reflux.



Reagents and condition: i. dry acetone, anhydrous K_2CO_3, NaI, reflux.

Scheme 1.

Precursor **4a**, when subjected to intramolecular Heck reaction in the presence of 10 mol % of $Pd(OAc)_2$ as catalyst KOAc as base and tetrabutylammonium bromide as promoter in DMF at about 100 °C, afforded linearly fused bis-cyclized product **8a** (Table 1) in 75% yield along with 10% of the monocyclized product. Increasing, the reaction

Table 1
Results are summarized below

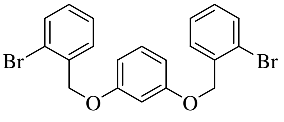
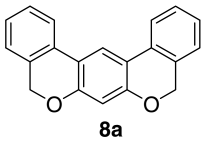
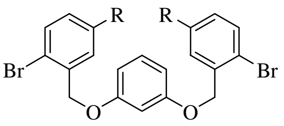
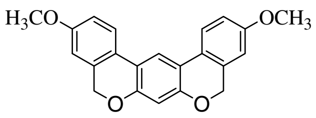
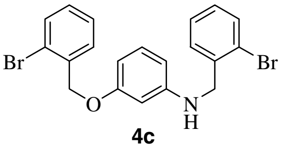
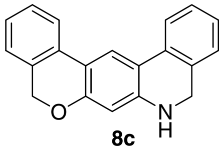
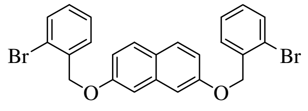
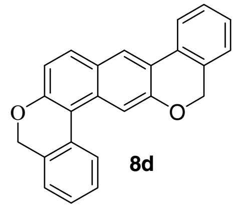
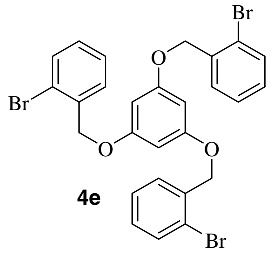
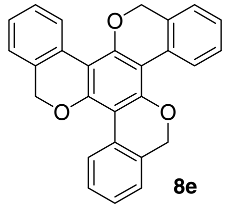
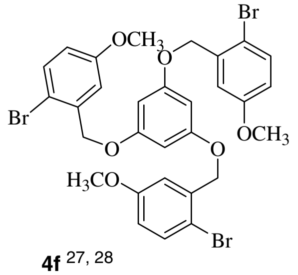
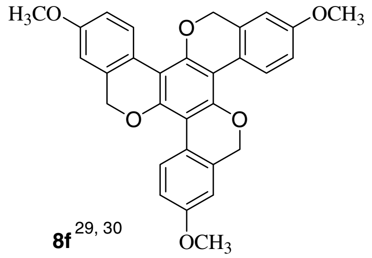
Entry	Precursor	Time (h)	Product	Yield (%)
1	 **4a**	4	 **8a**	75
2	 **4b,** R= OCH_3	5	 **8b**	80
3	 **4c**	3.6	 **8c**	77

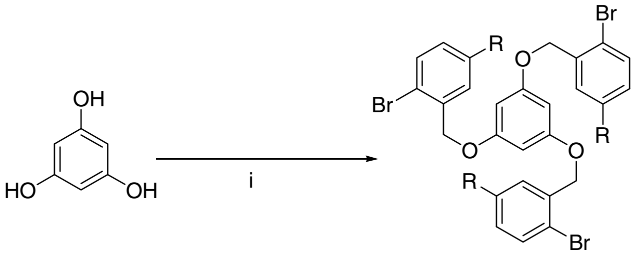
Table 1 (*continued*)

Entry	Precursor	Time (h)	Product	Yield (%)
4	 **4d**	4	 **8d**	70
5	 **4e**	4.2	 **8e**	75
6	 **4f**[27,28]	4	 **8f**[29,30]	85

temperature did not improve the yield of the bis-cyclized product. The use of $Pd(PPh_3)_2Cl_2$ or $PdCl_2$ as catalyst did not improve the yield of the bis-cyclized product. Among several aprotic polar solvents examined DMF gave the highest yield of the product, while DMSO and CH_3CN were found to give lower yields of the products. The effect of the base was also examined and KOAc was found to be superior to NEt_3 and Cs_2CO_3. Substrates **4b** and **4c**, under the similar conditions gave the corresponding bis-cyclized product. However, substrate **4d**, under similar conditions gave the bis-cyclized **8d**.

Phloroglucinol (1,3,5-trihydroxybenzene), on reaction with 2-bromobenzyl bromide or 2-bromo-3-methoxybenzyl bromide in the presence of acetone, K_2CO_3, and NaI gave the 1,3,5-tribenzylated products **4e** and **4f** (Scheme 2).

Tribenzylated **4e**, when subjected to intramolecular Heck reaction with 10 mol % of $Pd(OAc)_2$ as catalyst KOAc as base and TBAB as promoter in DMF at 120 °C gave the tris-cyclized product **8e** (Table 1) in 75% yield in about 4 h. The use of the low boiling solvent CH_3CN did not lead to any tris-cyclized product, instead the corresponding monocyclized product was obtained. The reaction temperature plays an important role in the formation of the tris-cyclized product, on decreasing the temperature, the yield of tris-cyclized product decreases. Substrate **4f**[29,30] gave the corresponding tris-cyclized product **8f**[31,32] under similar conditions (Table 1). Usually, ligand such as PPh_3, $(o\text{-tolyl})_3P$ is necessary[33–36] for carrying out this type of palladium mediated biaryl Heck Coupling. However, no ligand was needed for the reactions reported here.



4e, R = H (yield 84%)
4f, R = OCH_3 (yield 90%)

Scheme 2. Reagents and condition: (i) 2-bromobenzyl bromide or 2-bromo-5-methoxybenzyl bromide, dry acetone, anhydrous K_2CO_3, NaI, reflux.

In conclusion, we have developed a ligand free Heck based approach for bis- and tris-biary coupling of unactivated phenylaryl ethers for the regioselective synthesis of heterocyclic compounds.

Acknowledgments

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29. A mixture of 1,3,5-trihydroxybenzene (1 mmol), 2-bromo-3-methoxybenzyl bromide (3.2 mmol), anhydrous K_2CO_3 (1 g), and NaI (cat. amount) was refluxed in dry acetone (75 mL) for 16 h. The reaction mixture was cooled, filtered, and the solvent was removed. The residual mass was extracted with CH_2Cl_2 (3 × 25 mL). The CH_2Cl_2 extract was washed with water (3 × 10 mL) and dried (Na_2SO_4). The solvent was removed and the residual mass was purified by column chromatography over silica gel using petroleum ether–ethyl acetate (9:1) as eluent to afford compound **4f**.
30. Compound **4f**: White solid, mp 121–122 °C, yield 90%. IR (KBr): $\nu_{max} = 1617, 1596\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 3.8$ (s, 9H), 5.05 (s, 6H), 6.31 (s, 3H), 6.74 (dd, 3H, $J = 2.9$ Hz, 8.72 Hz), 7.11 (d, 3H, $J = 2.9$ Hz), 7.45 (d, 3H, $J = 8.72$) ppm. MS (m/z) = 720 (M^+), 722 (M^++2), 724 (M^++4). Anal. Calcd for $C_{30}H_{27}Br_3O_6$; C, 49.82; H, 3.76. Found C, 50.00; H, 3.82.
31. A mixture of **4f** (100 mg, 0.138 mmol), TBAB (112 mg, 0.34 mmol), KOAc (20 mg, 0.21 mmol), $Pd(OAc)_2$ (3.1 mg, 1.4×10^{-2} mmol) in dry DMF (5 mL) was heated at 100 °C for 4 h. After completion, the reaction mixture was poured into water (25 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The CH_2Cl_2 extract was washed with water (3 × 10 mL) and dried (Na_2SO_4). The solvent was removed and the residual mass was purified by column chromatography over silica gel using petroleum ether–ethyl acetate as eluent (9:1) to afford compound **8f**.
32. Compound **8f**: White solid, mp 171–172 °C yield 85%. IR (KBr): $\nu_{max} = 2833, 1612\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): 3.85 (s, 9H), 5.07 (s, 6H), 6.75 (d, 3H, $J = 2.6$ Hz), 6.91 (dd, 3H, $J = 2.7$ Hz, 8.8 Hz), 8.19 (d, 3H, $J = 8.8$ Hz), ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 158.69, 152.47, 133.18, 128.56, 122.13, 113.78, 110.27, 108.50, 69.46, 55.78. HRMS: m/z calcd for $C_{30}H_{24}O_6$ $[M+H]^+$: 481.1646; found: 481.1641. Anal. Calcd for $C_{30}H_{24}O_6$; C, 74.99; H, 5.03. Found: C, 75.09; H, 5.08.
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