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Palladium-catalyzed and KO^{t}Bu-promoted C_{aryl}–$O_{alcoholic}$ coupling: an efficient one-pot synthesis of oxygen containing fused rings

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ABSTRACT

An efficient one-pot synthetic method has been developed for the synthesis of oxygen containing fused rings from 2′-bromo-biaryl-2-carbaldehyde via tandem reduction followed by palladium-catalyzed and KO^{t}Bu-promoted C_{aryl}–$O_{alcoholic}$ coupling.

6*H*-Benzo[*c*]chromenes are one of the most important heterocycles because they have been found in several natural products.[1] Some important bioactive molecules with these moieties are presented in Figure 1.[2] Now, 6*H*-benzo[*c*]chromene on PCC oxidation will lead to the formation of benzopyranone[3] which is a basic unit of pharmacologically active natural products such as gilvocarcin V, alternariol, coumestrol, and lamellarin D etc (Fig. 2).[4] So it has drawn our attention to develop a synthetic route for these compounds, starting from simple materials.

During the last decade, development of methods for carbon–heteroatom bond formations by various transition metal catalyzed cross-coupling has drawn the attention of researchers greatly.[5] Among those most are associated with C–N bond formation processes, however methods for aromatic C–O bond formations are also developed.[6–8] Aryl alkyl ethers can be synthesized by copper-mediated classical Ullmann reaction.[9,10] Buchwald has developed a methodology for C_{aryl}–O bond formation using modified Ullmann reaction.[11] 6*H*-Benzo[*c*]chromenes have been synthesized by many research groups.[12–14] Fagnou and co-workers have reported the synthesis via direct arylation[12] while Shen's synthesis involves the use of palladium-catalyzed intramolecular decarboxylative coupling of arene carboxylic acids/esters with aryl bromides.[13] Shi and co-workers used transition metal catalyzed direct functionalization of aromatic C–H bonds.[14]

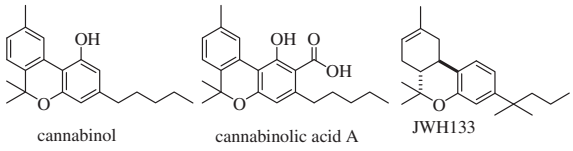

Figure 1. Bioactive molecules containing 6*H*-benzo[*c*]chromene moieties.

Herein, we report a new efficient one-pot synthesis of 6*H*-benzo[*c*]chromenes. Our strategy is based on Pd(0)-catalyzed and KO^{t}Bu-mediated intramolecular C_{aryl}–$O_{alcoholic}$ coupling of reduced product of 2′-bromo-biaryl-2-carbaldehyde in which the reduction of carbaldehyde and coupling were performed in one-pot. This methodology is more demanding over other existing methodologies, including low toxicity of boronic acid derivatives, high yields, short reaction times, and simple materials.

The starting materials **3a–3g** for the tandem reactions were prepared by Suzuki–Miyaura cross-coupling[15] by the treatment of 2-bromocarboxaldehydes **1a–1g** with 2-bromophenylboronic acid **2** in the presence of Pd-catalyst, base, ligand, dry DMF, and heating conditions (Scheme 1). To determine an optimal condition for the cross-coupling reaction, 2-bromo-benzaldehyde was taken as the standard substance. Then a thorough screening was performed with different combinations of Pd-catalysts and bases (Table 1). We got an optimal condition when substrate **1a** (1 mmol) and **2** (1.2 mmol) were heated at 80 °C in the presence of $Pd(OAc)_2$ (10 mol %), NaOAc (1.5 mmol), and PPh_3 (0.25 mmol) in dry DMF

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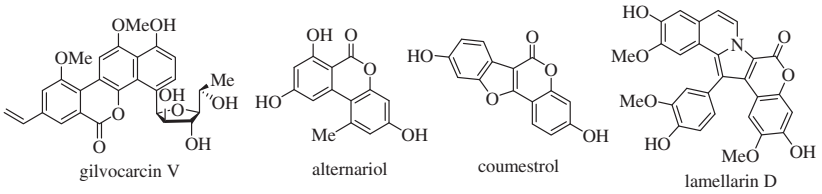
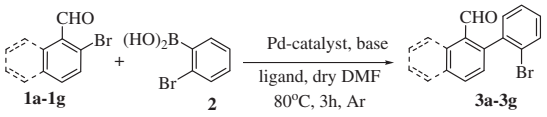
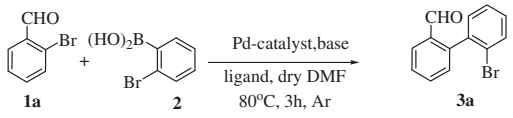


Figure 2. Pharmacologically active natural products containing benzopyranone moieties.



Scheme 1. Synthesis of 2′-bromo-biaryl-2-carbaldehydes.

Table 1
Optimal condition determination[a,b] for Suzuki–Miyaura cross-coupling



Entry	Catalyst	Ligand	Base	Yield[c] (%)
1	$Pd(PPh_3)_4$	—	Et_3N	78
2	$Pd(OAc)_2$	PPh_3	Et_3N	75
3	**$Pd(OAc)_2$**	**PPh_3**	**NaOAc**	**80**
4	$Pd(OAc)_2$	PPh_3	Na_2CO_3	72
5	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	75
6	$Pd(OAc)_2$	PPh_3	K_2CO_3	55
7	$Pd(PPh_3)_4$	—	NaOAc	72
8	$PdCl_2$	PPh_3	NaOAc	68

[a] Reagents and conditions: **1a** (1 mmol), 2-bromophenylboronic acid (1.2 mmol), Pd-catalyst (10 mol %), base (1.5 mmol), PPh_3 (0.25 mmol), and dry DMF (6 mL) heated at 80 °C for 3 h.
[b] Two-necked round-bottomed flask fitted with condenser was used for reaction.
[c] Yields refer to the isolated yields after purification through column chromatography.

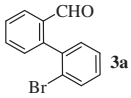
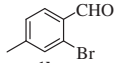
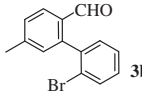
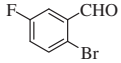
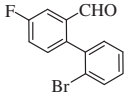
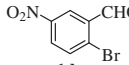
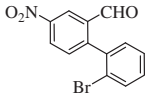
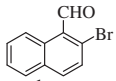
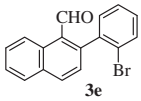
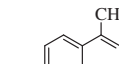
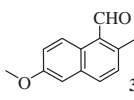
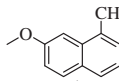
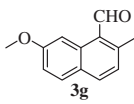
(6 mL) for 3 h with 80% isolated yield through column chromatography.

Now with this optimal condition in our hand we performed cross-couplings with various 2-bromocarbaldehydes **1a–1g** to get **3a–3g** (Table 2). *ortho*-Bromonaphthalenecarboxaldehydes **1e–1g** were synthesized from β-tetralones in excellent yields through Vilsmeier–Haack type reaction followed by DDQ oxidation.[16]

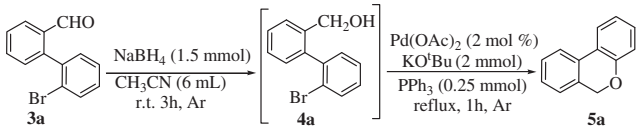
Compound **3a** was taken as the standard substance for one-pot synthesis of oxygen containing fused rings. At first, it was reduced with $NaBH_4$ (1.5 mmol) in dry CH_3CN (6 mL) at room temperature for 3 h under Ar atmosphere. Then the reaction mixture was allowed to undergo coupling reaction without isolation of intermediate alcohol by the addition of KO^{t}Bu (2 mmol), $Pd(OAc)_2$ (2 mol %), and PPh_3 (0.25 mmol) and then refluxed for 1 h (Scheme 2). A thorough screening was performed after reduction with different combinations of Pd-catalysts and bases (Table 3) and we got optimal condition when the reduced product of **3a** (1 mmol) was refluxed for 1 h in the presence of $Pd(PPh_3)_2Cl_2$ (2 mol %), and KO^{t}Bu (2 mmol) with 90% isolated yield through column chromatography.

Substrates **3a–3g** were subjected to one-pot synthesis of fused rings via tandem reduction followed by palladium-catalyzed and KO^{t}Bu-promoted C_{aryl}–$O_{alcoholic}$ coupling under above optimal condition (Table 4). It has been observed that when the substituent was –NO_2 group, yield of the fused ring compound was dramatically decreased.

Table 2
Synthesis of various 2′-bromo-biaryl-2-carbaldehydes through Suzuki–Miyaura cross-coupling[a]

Entry	Substrate	Product	Yield (%)
1	 1a	 3a	80
2	 1b	 3b	78
3	 1c	 3c	80
4	 1d	 3d	76
5	 1e	 3e	79
6	 1f	 3f	74
7	 1g	 3g	75

[a] Reagents and conditions: All the reactions were carried out under the following conditions: **1a–1g** (1 mmol), 2-bromophenylboronic acid (1.2 mmol), $Pd(OAc)_2$ (10 mol %), NaOAc (1.5 mmol), PPh_3 (0.25 mmol), and dry DMF (6 mL) heated at 80 °C for 3 h.

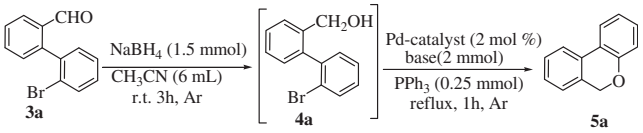


Scheme 2. Synthesis of oxygen containing fused rings in one-pot.

From the above observations it can be concluded that the reduced products were unable to undergo coupling reactions with different types of weak bases and various Pd-catalysts. Again, only a trace amount of coupling product was obtained in the absence of Pd-catalyst. The proposed mechanistic pathway for this type of transformation is as per the literature report.[17]

6*H*-Benzo[*c*]chromene on PCC oxidation will lead to the formation of benzopyranone (Scheme 3).[3]

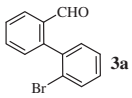
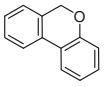
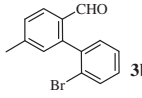
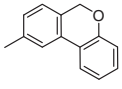
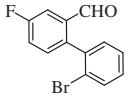
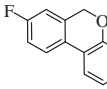
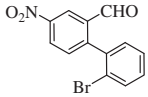
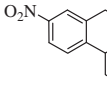
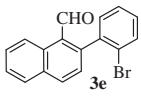
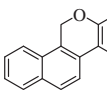
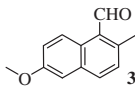
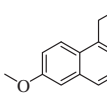
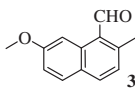
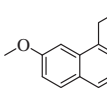
Table 3
Optimal condition determination for one-pot cyclization after reduction[a,b]



Entry	Catalyst	Ligand	Base	Yield[c] (%)
1	$Pd(OAc)_2$	PPh_3	KO^{t}Bu	88
2	$PdCl_2$	PPh_3	KO^{t}Bu	85
3	$Pd(OAc)_2$	PPh_3	NaO^{t}Bu	87
4	$PdCl_2$	PPh_3	NaO^{t}Bu	82
5	**$Pd(PPh_3)_2Cl_2$**	—	**KO^{t}Bu**	**90**
6	$Pd(PPh_3)_2Cl_2$	—	NaO^{t}Bu	88
7	$Pd(PPh_3)_4$	—	KO^{t}Bu	82
8	$Pd(PPh_3)_4$	—	NaO^{t}Bu	80
9	$Pd(PPh_3)_2Cl_2$	—	K_3PO_4	Nil
10	$Pd(PPh_3)_2Cl_2$	—	Na_2CO_3	Nil
11	$Pd(PPh_3)_2Cl_2$	—	Cs_2CO_3	Nil
12	$Pd(PPh_3)_2Cl_2$	—	K_2CO_3	Nil
13	$Pd(PPh_3)_2Cl_2$	—	Et_3N	Nil
14	$Pd(OAc)_2$	PPh_3	Na_2CO_3	Nil
15	$Pd(OAc)_2$	PPh_3	K_2CO_3	Nil
16	—	—	KO^{t}Bu	Trace

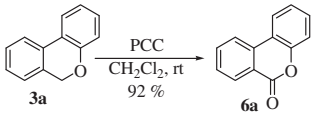
[a] Reagents and conditions: (a) **3a** (1 mmol), $NaBH_4$ (1.5 mmol), CH_3CN (6 mL), rt reaction for 3 h under Ar. (b) Pd-catalyst (2 mol %), base (2 mmol), PPh_3 (0.25 mmol) and refluxed for 1 h under Ar.
[b] Two-necked round-bottomed flask fitted with condenser was used for reactions.
[c] Yields refer to the isolated yields after purification through column chromatography.

Table 4
One-pot synthesis of oxygen containing fused rings[a]

Entry	Substrate	Product	Yield (%)
1	 **3a**	 **5a**	90
2	 **3b**	 **5b**	88
3	 **3c**	 **5c**	89
4	 **3d**	 **5d**	62
5	 **3e**	 **5e**	89
6	 **3f**	 **5f**	84
7	 **3g**	 **5g**	85

[a] Reagents and conditions: (a) **3a**–**3g** (1 mmol), $NaBH_4$ (1.5 mmol), CH_3CN (6 mL), rt reaction for 3 h under Ar. (b) $Pd(PPh_3)_2Cl_2$ (2 mol %), KO^{t}Bu (2 mmol) and refluxed for 1 h under Ar.

In conclusion, we have developed a general methodology for the synthesis of 6*H*-benzo[*c*]chromenes and 5*H*-6-oxa-chrysens via tandem reduction followed by palladium-catalyzed and KO^{t}Bu-promoted C_{aryl}–$O_{alcoholic}$ coupling [18,19] which upon further PCC oxidation will lead to benzopyranones. Thus this methodology can also be used for the synthesis of various types of chromene, chrysene, and benzopyranone based natural products.



Scheme 3. PCC oxidation of 6*H*-benzo[*c*]chromene.

Acknowledgments

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Supplementary data

Supplementary data (detailed experimental procedures and spectral data for the compounds **3a**, **4a** and **5a**–**5g**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.01.062.

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18. *General procedure for the synthesis of oxygen containing fused rings:* Substrates **3a**–**3h** (1 mmol) and $NaBH_4$ (1.5 mmol) were placed in a two-necked round-bottomed flask fitted with condenser. After the addition of 6 mL CH_3CN the reaction mixture was allowed to react at rt for 3 h under Ar. Then the reaction mixture was allowed to undergo coupling reaction without isolation of intermediate alcohol by the addition of KO^{t}Bu (2 mmol), and $Pd(PPh_3)_2Cl_2$ (2 mol %) and then refluxed for 1 h under Ar. It was allowed to cool to rt and extracted with EtOAc (3 × 20 mL). Then the organic part was washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave crude product which was then purified through column chromatography by using silica gel (60–120 mesh) and pet ether/EtOAc (100:1) as eluent.

19. *Spectral data of representative compounds, 6H-benzo[c]chromene (***5a***):* From **3a** (0.08 g, 1 mmol), $NaBH_4$ (0.017 g, 1.5 mmol), KO^tBu (2 mmol), and $Pd(PPh_3)_2Cl_2$ (2 mol %) in CH_3CN (6 mL) at rt to refluxing condition under Ar, product **5a** was obtained as colorless oil in 90% isolated yield (0.05 g) by column chromatography. R_f = 0.4 (pet. ether/EtOAc = 100:1); ^1H NMR ($CDCl_3$, 200 MHz) δ = 4.98 (2H, s), 6.86–7.02 (3H, m), 7.07–7.24 (3H, m), 7.54–7.62 (2H, m). ^{13}C NMR (50 MHz in $CDCl_3$) δ = 68.6, 117.6, 122.2, 122.3, 123.1, 123.5, 124.8, 127.8, 128.6, 129.6, 130.3, 131.6, 155.0; Elemental analysis: found C, 85.60; H, 5.66. $C_{13}H_{10}$ requires C, 85.69; H, 5.53.