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A facile route to flavone and neoflavone backbones *via* a regioselective palladium catalyzed oxidative Heck reaction†

Mehdi Khoobi,[a] Masoumeh Alipour,[b] Samaneh Zarei,[b] Farnaz Jafarpour*[b] and Abbas Shafiee*[a]

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A straightforward and atom-economical base-free palladium-catalyzed regioselective direct arylation of coumarins and chromenones is devised. This protocol is compatible with a wide variety of electron-donating and -withdrawing substituents and allows construction of various biologically important flavone and neoflavone backbones.

Chromenone derivatives such as flavones (2-aryl-4*H*-4-chromenones) and neoflavones (4-arylcoumarins) have attracted considerable attention as a result of their interesting biological and pharmacological activities and their presence in a variety of natural products. Depending on the substitution pattern of neoflavones, their antiprotozoal,[1] anticancer,[2–4] anti-HIV,[5] antimalarial,[6,7] antibacterial,[8] and cytotoxic properties[9] have been recognized. Moreover several polyoxygenated 4-arylcoumarins have been evaluated as neoflavonoid analogues of combretastatin A-4, an anti-tubulin agent that targets the colchicine site.[2] Furthermore, 2-aryl-4*H*-4-chromenones are very interesting structural scaffolds with various biological and pharmaceutical activities and have been assigned as privileged structures in drug development.[10] Hence several methods for the construction of these privileged motifs have been pursued during the past years.

Construction of 4-arylcoumarins is based on two conventional strategies. First is the reactions in which benzopyranone rings are closed *via* Pechmann, Perkin, Ponndorf, Houben-Hoesch reactions[11a] and very recently catalytic hydroarylation of alkynes as the key synthetic steps,[11b,c] and second is the reactions in which coumarin frameworks activated at the 4-position are arylated *via* transition-metal catalyzed cross-coupling reactions. Compared with classical procedures, transition-metal mediated cross-couplings result in various types of coumarin derivatives in a divergent manner which is a highly promising tool for drug discovery and development. In this regard, several research groups are focused on the use of transition metals in the synthesis of 4-arylated coumarins, and metal catalyzed coupling of bromo,[12] triflate,[13] tosylate,[14] phosphonate[15] and carbonate[16] derivatives of coumarins with organoboron, -tin, -zinc, -bismuth and -indium organometallic reagents has been developed. An alternative procedure includes cross-coupling reaction of aryl halides and 4-coumarinylzinc bromide, prepared from bromocoumarin.[17]

Despite significant progress in this area, synthesis of 4-arylcoumarins *via* direct-arylation of unactivated coumarins remains an unsolved problem. Although transition-metal catalyzed installment of aryl groups on the pyranone ring is wider in scope than older procedures, however, its application requires the prior selective functionalization of the C-4 position of the coumarin with a halogen or hydroxyl group which is not always trivial. Direct functionalization of the desired scaffold through regioselective C–H bond activation provides an efficient cost-effective and atom-economical entry to these compounds as it eliminates the need for introducing protecting groups and reactive functionalities prior to C–C formation. One might therefore expect that the development of general, atom-economical and regioselective arylation methods merits further consideration.

On the other hand, organoboron-mediated Heck-type reaction is one of the most attractive metal-catalyzed reactions which constitute a useful synthetic C–C bond-forming method. The commercial availability of boron reagents, broad functional group tolerance, low toxicity and general applicability of the reaction contributed to its increasing importance in academic and industrial research.[18]

As part of our continuing efforts in metal-catalyzed C–H bond functionalization of heterocycles,[19] herein, we set out to explore a cost-effective and atom-economical regioselective direct arylation of chromenones *via* palladium-catalyzed oxidative boron Heck-type reaction. This protocol should give economically viable and environmentally attractive access to C2 and C4 arylated chromenones.

To begin, coumarin **1a** was chosen as the test substrate in the oxidative Heck reaction with phenylboronic acid. The feasibility of the reaction was tested by treating the substrates under various reaction conditions (Table 1). Due to previous reports which suggested a base-assisted β-elimination process for the Heck type reaction with cyclic systems,[18b] we initiated an investigation of base-mediated reaction. In this regard, coumarin was treated with phenylboronic acid under oxygen-promoted Pd(II)-catalyzed coupling reaction in the presence of

[a] *Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, 14176, Tehran, Iran. E-mail: ashafiee@ams.ac.ir*
[b] *School of Chemistry, College of Science, University of Tehran, P.O. Box 14155-6455, Tehran, Iran. E-mail: jafarpur@khayam.ut.ac.ir*

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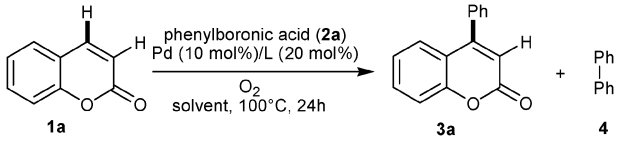
Table 1 Screening of reaction conditions for the intermolecular oxidative Heck-reaction of coumarin and phenylboronic acid[a]

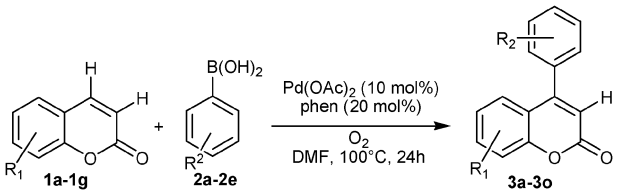


Entry	Catalyst	Ligand	Base	Solvent	Yield[b] (%) 3a	4
1	$Pd(OAc)_2$	—	Na_2CO_3	DMF	0	94
2	$Pd(OAc)_2$	phen	Na_2CO_3	DMF	0	80
3	$Pd(OAc)_2$	phen	K_2CO_3	DMF	5	85
4	$Pd(OAc)_2$	phen	KOAc	DMF	5	90
5	$Pd(OAc)_2$	phen	K_2HPO_4	DMF	5	90
6	$Pd(OAc)_2$	bpy	—	DMF	62	30
7	$Pd(OAc)_2$	dmap	—	DMF	40	20
8	$Pd(OAc)_2$	dmphen	—	DMF	15	70
9	$Pd(OAc)_2$	phen	—	DMF	**85**	10
10	$Pd(OAc)_2$	phen	—	Dioxane	68	15
11	$Pd(OAc)_2$	phen	—	ACN	14	0
12	$Pd(OAc)_2$	phen	—	Toluene	0	0
13	$PdCl_2$	phen	—	DMF	35	10
14	$Pd(acac)_2$	phen	—	DMF	78	20
15	$Pd(dppf)_2Cl_2$	phen	—	DMF	35	25
16[c]	$Pd(dba)_2$	phen	—	DMF	5	15

[a] All reactions were run under the following conditions: coumarin **1a** (2 equiv.), phenylboronic acid **2a** (0.1 mmol), Pd catalyst (10 mol%), ligand (20 mol%), O_2 (balloon pressure) in the corresponding solvent (0.4 M) were heated in a sealed tube at 100 °C for 24 h. [b] Isolated yields. [c] 30% of 3-arylated derivative **5** was also formed.

$Pd(OAc)_2$ (10 mol%), Na_2CO_3 (2 equiv.) in DMF at 100 °C for 24 h. However we found that the reaction was not successful with Na_2CO_3 as the base, and **4**, the boronic acid homo-coupled product, was obtained solely (entry 1). Addition of a ligand and screening of the bases also did not give any satisfactory results (entries 2–5). The results revealed that inorganic bases were incompatible with the proposed system. On the basis of these results, we screened the reaction conditions to determine optimal base-free conditions. In this regard some nitrogen ligands which are supposed to work as not only a palladium ligand but also a base participating in the β-elimination step were screened. We were pleased to see that in the presence of 20 mol% of bipyridine, 4-phenylcoumarin **3a** was obtained in 62% yield accompanied with 30% of the homo-coupling product **4** (entry 6). While *N*,*N*-dimethyl-4-aminopyridine and 2,9-dimethyl-1,10-phenanthroline resulted in only moderate to low yields of the desired product and large amounts of biphenyl (entries 7 and 8), in the presence of phenanthroline as a ligand, the desired 4-arylcoumarin was constructed in 85% yield (entry 9). The 3-arylated product was not detected at all and the reaction proceeded with minimal biphenyl formation. A screening of solvents was then performed. Replacing DMF with other solvents such as 1,4-dioxane and acetonitrile resulted in lower yields (entries 10 and 11). In toluene, the reaction did not proceed at all (entry 12). Subsequently, we sought optimal conditions by screening various palladium sources. While with $PdCl_2$ and $Pd(dppf)_2Cl_2$ the conversions were unsatisfactorily low (entries 13 and 15), $Pd(acac)_2$ provided **3a** in 78% yield (entry 14). With $Pd(dba)_2$ as the catalyst, only traces of the desired product **3a** along with 30% of 3-arylated coumarin **5** and low amounts of biphenyl **4** were obtained (entry 16). A screening of oxidants such as $Na_2S_2O_8$, BQ and $Cu(OAc)_2$ was also conducted, but provided no improvements (see ESI†).

Table 2 Scope of the regioselective arylation of coumarins[a]

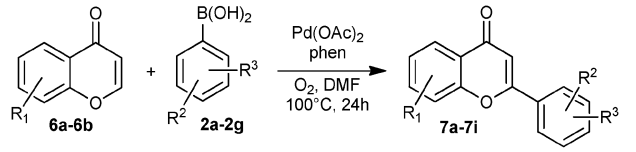


Entry	R^1	R^2	Product	Yield[b] (%)
1	H **1a**	H **2a**	**3a**	85
2	6-CH_3 **1b**	H **2a**	**3b**	88
3	6-NO_2 **1c**	H **2a**	**3c**	72
4	7-OH **1d**	H **2a**	**3d**	68
5	7-OCH_3 **1e**	H **2a**	**3e**	71
6	7-OCH_2CH_3 **1f**	H **2a**	**3f**	74
7	H **1a**	4-CH_3 **2b**	**3g**	73
8	H **1a**	4-CH_2CH_3 **2c**	**3h**	76
9	6-NO_2 **1c**	4-CH_2CH_3 **2c**	**3i**	68
10	6-NO_2 **1c**	4-CH_3 **2b**	**3j**	77
11	6-CH_3 **1b**	4-CH_2CH_3 **2c**	**3k**	84
12	7-Cl **1g**	4-CH_3 **2b**	**3l**	82
13	6-CH_3 **1b**	4-Br **2d**	**3m**	80
14	7-OH **1d**	4-CH_2CH_3 **2c**	**3n**	68
15	H **1a**	3-NO_2 **2e**	**3o**	0

[a] All reactions were run under the following conditions: coumarin **1** (2 equiv.), arylboronic acid **2** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), 1,10-phenanthroline (20 mol%), O_2 (balloon pressure) in DMF (0.4 M) were heated in a sealed tube at 100 °C for 24 h. [b] Isolated yields.

Using the optimized conditions, various electron-rich and electron-poor coumarins were tested in their reaction with phenylboronic acid (Table 2, entries 1–6). The results indicated that the scope of the reaction was quite broad given that alkyl, alkoxy, nitro, halo and hydroxyl substituents were tolerated. The desired products were obtained in high yields and the reactions were highly regioselective, with no 3-arylated coumarin detected. The highest yield was obtained with methylcoumarin **1b** but also methoxy, ethoxy and nitro substituted coumarins resulted in the corresponding 4-arylcoumarins in yields exceeding 70%. Furthermore, the tolerance of an unprotected hydroxyl group on coumarin was noteworthy. Hydroxycoumarin **1d** reacted with phenylboronic acid to afford the desired product with no requirement of hydroxyl protection. This feature is ubiquitous in hydroxycoumarin based biologically active products, which eliminates the requirement of protection and deprotection of hydroxyl groups. Furthermore, we studied the scope and limitations of the oxidative Heck arylation of coumarins with various aryl boronic acids. The cross-coupling reaction of alkyl substituted arylboronic acids and coumarins with various electron releasing and withdrawing groups also proceeded smoothly under the same optimized reaction conditions to give the corresponding 4-arylcoumarins in moderate to high yields (entries 7–14). However, 3-nitrophenylboronic acid did not react under the optimized reaction conditions (entry 15). Furthermore, both halo-substituted partners were tolerated under the reaction conditions. 7-Chloro coumarin **1g** arylated at the C-4 position in 82% yield and the 7-arylated adduct was not observed at all (entry 12). 4-Bromophenylboronic acid **2d** also showed

Table 3 Scope of the regioselective arylation of chromenones[a]



Entry	R^1	R^2, R^3	Product	Yield[b] (%)
1	H **6a**	H, H **2a**	**7a**	86
2	H **6a**	4-OCH_3, H **2f**	**7b**	80
3	H **6a**	2-OCH_3, 4-OCH_3 **2g**	**7c**	88
4	H **6a**	4-CH_2CH_3, H **2c**	**7d**	92
5	H **6a**	4-CH_3, H **2b**	**7e**	90
6	H **6a**	4-Br, H **2d**	**7f**	85
7	7-OCH_3 **6b**	2-OCH_3, 4-OCH_3 **2g**	**7g**	91
8	7-OCH_3 **6b**	H, H **2a**	**7h**	81
9	7-OCH_3 **6b**	4-CH_2CH_3, H **2c**	**7i**	77
10	H **6a**	3-NO_2, H **2e**	**7j**	0

[a] All reactions were run under the optimized conditions. [b] Isolated yields.

compatibility with the reaction conditions and resulted in the halogenated coumarin **3m**, a good partner for further functionalizations, in high yield (80%, entry 13).

Motivated by these results, we next sought to expand the scope of our system to regioselective arylation of a more challenging substrate such as 4*H*-chromen-4-one. Like cyclohexenone, chromenone is a typical example of a substrate where mixtures are commonly noticed.

We were pleased to see that under our optimized reaction conditions, the reaction of chromenone **6a** and phenylboronic acid **2a** proceeded with high regioselectivity to afford the desired C-2 arylated adduct **7a** in 86% yield (Table 3, entry 1). Furthermore, methoxy substituted arylboronic acids **2f** and **2g** provided the desired products **7b** and **7c** in 80% and 88% yields, respectively (entries 2 and 3). 4-Alkyl substituted arylboronic acids **2c** and **2b** also reacted with high efficiency and selectivity, resulting in the desired products **7d** and **7e** in 92% and 90% yields, respectively (entries 4 and 5). 4′-Brominated flavone **7f** was also obtained in high yield (entry 6).

Next it was desirable to extend the scope of this regioselective arylation reaction to construct methoxy flavones as a superior cancer chemopreventive flavonoid subclass with high hepatic metabolic stability.[20] In this regard, 7-methoxy chromenone **6b** was reacted with 2,4-dimethoxyphenylboronic acid **2g** and the result was gratifying (91% yield, entry 7). Also the cross-coupling of **6b** with unsubstituted and alkyl substituted arylboronic acids proceeded successfully, affording the desired products **7h** and **7i** in 81% and 77% yields, respectively (entries 8 and 9). The reaction of chromenone with nitro substituted boronic acid was not successful (entry 10).

In summary, we have developed a versatile, regioselective and atom economical arylation of chromenones. This protocol provides a straightforward route to biologically interesting flavone or neoflavone backbones. It takes advantages of the regioselective heteroarene functionalization precluding its prefunctionalization, the no base requirements and the compatibility with a wide range of substituents including OH and halo functionalities. Investigation on broadening the scope of the reaction toward the synthesis of biological active targets is currently underway.

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