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Graphical Abstract

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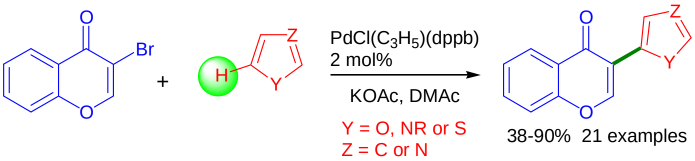

Pd-catalysed heteroarylations of 3-bromochromen-4-one via C-H bond activation of heteroarenes

Fatma Belkessam,[a,b] Fazia Derridj,[a,c] Liqin Zhao,[a] Abdelhamid Elias,[b] Mohand Aidene,[b] Saffia Djebbar,[c] Henri Doucet,[a*]

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[b]*Département de chimie, Tizi Ouzou University, BP 17 RP 15000 Tizi-Ouzou, Algeria.*
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Abstract

The palladium-catalysed direct coupling of 3-bromochromen-4-one with heteroaromatics was found to proceed in moderate to high yields. A wide variety of heteroaromatics can be coupled with this chomenone derivative using 2 mol% $PdCl(C_3H_5)(dppb)$ catalyst and KOAc as the base. Moreover, the reaction tolerates a range of useful functional groups on the heteroarene.

Several flavones and chromen-4-one derivatives containing an (hetero)aryl substituent, such as Pranlukast, Cromitrile, Puerarin, Hesperetin or Naringinine have been found to a display useful bioactivities; Eriodictyol is a natural product which has taste-modifying properties (Fig 1). Therefore, the discovery of simple procedures for the preparation of a variety of (hetero)arylated chromen-4-ones would provide powerful tools for pharmaceutical researchers.

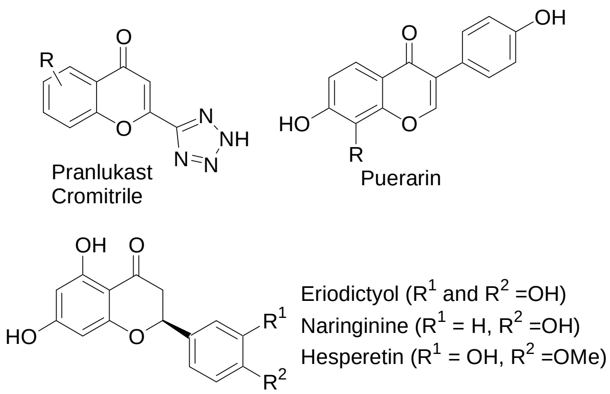

Figure 1 Examples of bioactive chromen-4-one derivatives

A classical method to prepare 3-(hetero)arylated chromen-4-one derivatives is to employ a 3-halochromen-4-one with a (hetero)aryl boronic acid derivative using a palladium catalyst (Scheme 1, top).[1,2] However, these reactions require the preliminary preparation of $HetArB(OR)_2$, which might be tricky in several cases due to the poor stability of some of these heteroarylboronic acids. Moreover, these couplings provide a boron salt as by-product.

In recent years, the palladium-catalysed direct coupling of heteroaromatics with *aryl*-halides or *vinyl*-halides proved to be an extremely powerful method for the synthesis of arylated or vinylated heteroaromatics.[3-6] On the other hand, to our knowledge, palladium-catalysed direct heteroarylations using 3-halochromen-4-ones has not been reported (Scheme 1, bottom).[7] The use of such reactants, which are commercially available, would allow to prepare a wide variety of 3-heteroarylchromen-4-ones in only one step. Moreover, their asymmetric reduction should allow the synthesis of useful chiral chromanones.[8]

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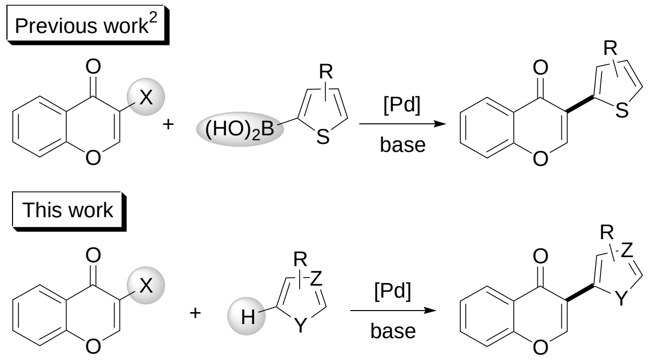
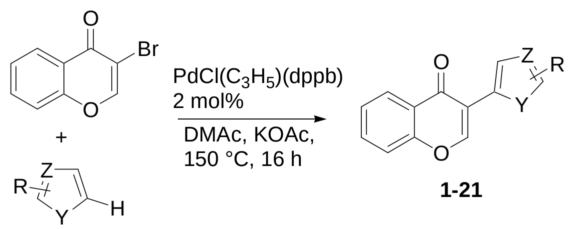


Scheme 1

Here, we wish to report (i) on influence of the conditions for palladium-catalysed direct coupling of 3-bromochromen-4-one with 2-*i*butylthiazole, and (ii) show the scope of this coupling using a set of heteroaromatics.

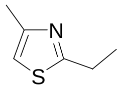
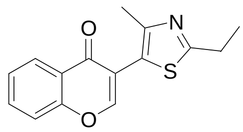
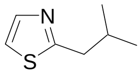
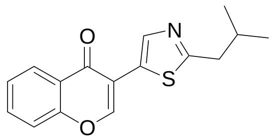
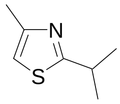
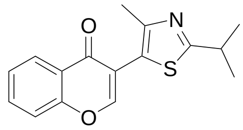
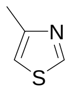
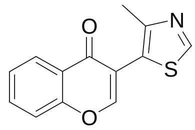
First, we examined the reactivity of 3-bromochromen-4-one for the palladium-catalysed direct coupling with 2-ethyl-4-methylthiazole using 2 mol% $PdCl(C_3H_5)$(dppb) as the catalyst, DMAc as the solvent and KOAc as the base (Scheme 2, table 1, entry 1). These conditions had been previously found operative for similar reactions.[5a] Using these conditions, a complete conversion of this bromide derivative was observed, and the desired coupling product **1** was isolated in 83% yield (Table 1, entry 1). In the presence of only 0.5 mol% $PdCl(C_3H_5)$(dppb) a conversion of 96% of 3-bromochromen-4-one was observed to give **1** in 78%; whereas, a lower conversion of 90% was obtained with 2 mol% of ligand-free $Pd(OAc)_2$ catalyst (Table 1, entries 2 and 3). A moderate yield in **1** was formed for the reaction performed in greener solvent diethyl carbonate (Table 1, entry 4).

Then, we extended the scope of the heteroarylation of 3-bromochromen-4-one to a variety of thiazole derivatives (Table 1). From 2-*i*butylthiazole or 4-methyl-2-*i*propylthiazole, the desired products **2** and **3** were also obtained in very good yields of 89% and 88% (Table 1, entries 5 and 6). We also examined the reactivity of 4-methylthiazole.



Scheme 2

Table 1. Palladium-catalysed direct coupling of thiazoles with 3-bromochromen-4-one (Scheme 2).[11]

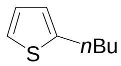
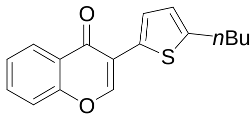
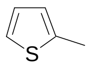
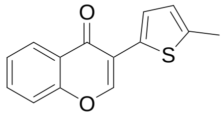
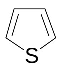
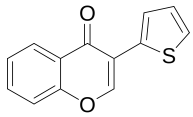
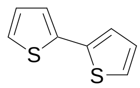
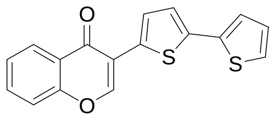
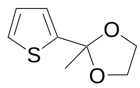
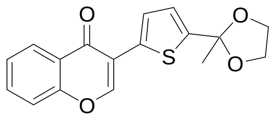
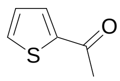
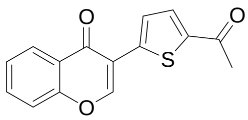
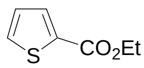
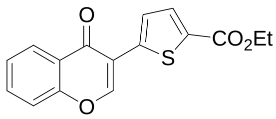
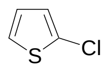
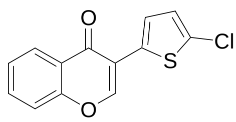
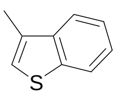
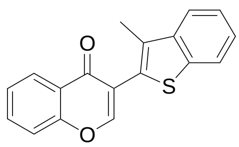
Entry	Heteroarene	Product	Yield (%)
1		 **1**	83
2			78[a]
3			72[b]
4			43[c]
5		 **2**	89
6		 **3**	88
7		 **4**	81

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), 3-bromochromen-4-one (1 mmol), thiazole derivative (2 mmol), KOAc (2 mmol), DMAc, 16 h, 150 °C, isolated yields. [a] $PdCl(C_3H_5)(dppb)$ (0.005 mmol). [b] $Pd(OAc)_2$ (0.02 mmol). [c] diethylcarbonate as the solvent.

With this thiazole derivative, we might have observed the formation of both the C2 and C5 arylated thiazoles, as in the presence of Cs_2CO_3, a selective arylation at C2, which proceed via a non-concerted metalation-deprotonation, followed by an arylation at C5, has been reported.[9,10] However, in the presence of KOAc as the base/ligand, a high yield of **4**, due to a completely regioselective arylation at C5, was obtained (Table 1, entry 7). This high regioselectivity can be explained by the nature of the base (KOAc) which favours a concerted-metallation-deprotonation mechanism (CMD).[9]

We then examined the reactivity of several thiophene derivatives for the coupling with 3-bromochromen-4-one (Table 2). From 2-*n*-butylthiophene, **5** was obtained in 72% yield due to a partial conversion the 3-bromochromen-4-one (Table 2, entry 1). As expected a similar yield was obtained using 2-methylthiophene (Table 2, entry 2). The reaction of unsubstituted thiophene also proceeds to give the desired coupling product **7** in 69% yield (Table 2, entry 3).

Table 2. Palladium-catalysed direct coupling of thiophenes with 3-bromochromen-4-one (Scheme 2).[11]

Entry	Heteroarene	Product	Yield (%)
1		 **5**	72
2		 **6**	75
3		 **7**	69[a]
4		 **8**	67
5		 **9**	70
6		 **10**	59
7		 **11**	38
8		 **12**	68
9		 **13**	67

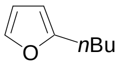
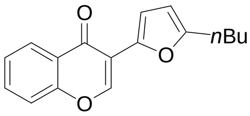
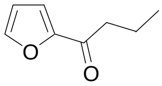
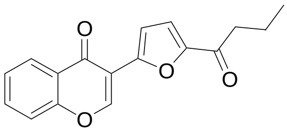
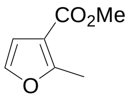
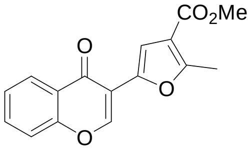
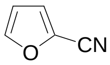
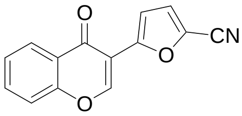
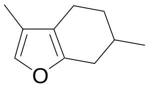
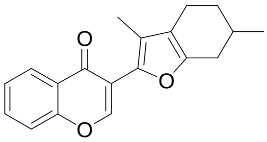
Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), 3-bromochromen-4-one (1 mmol), thiophene derivative (2 mmol), KOAc (2 mmol), DMAc, 16 h, 150 °C, isolated yields. [a] thiophene: 4 mmol.

For this reaction, 4 equiv. of thiophene were employed in order to avoid the formation of 2,5-disubstituted thiophene. With [2,2']bithiophenyl, the desired product **8** was also obtained in good yield (Table 2, entry 4). We also examined the reactivity of thiophenes bearing functional groups. From protected or non-protected 2-acetylthiophenes, **9** and **10** were obtained in 70% and 59% yields, respectively (Table 2, entries 5 and 6). A moderate yield in **11** was obtained with ethyl thiophene-2-carboxylate due to an important formation of unidentified side-products (Table 2, entry 7). This might be due to partial decarboxylation of this thiophene derivative. On the other hand, from 2-chlorothiophene, the desired product **12** was produced in high yield (Table 2, entry 8). It should be noted that no cleavage of the C-Cl bond of this thiophene derivative was observed allowing further transformations. Finally, 3-methylbenzothiophene was successfully employed to give the C2-substituted benzothiophene **13** in 67% yield (Table 2, entry 9).

Several furan derivatives were also employed successfully to provide 3-furanylchromene-4-ones (Table 3). For example, in the presence of 2-*n*-butylfuran, **14** was produced in 60% yield (Table 3, entry 1). 2-Butyrylfuran and methyl 2-methylfuran-3-carboxylate also reacted quite nicely the give **15** and **16** in 56% and 67% yields, respectively (Table 3, entries 2 and 3). A moderate yield of 46% in **17** was obtained from furan-2-carbonitrile due to some formation of the homo-coupling product of 3-bromochromen-4-one (Table

3, entry 4). Finally, we examined the reactivity of menthofuran. This 2,3,4-trisubstituted furan, which is naturally present in mint oil, was also found to be reactive for the direct coupling with 3-bromochromen-4-one (Table 3, entry 5). The desired product **18** was obtained in 78% yield.

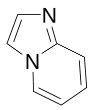
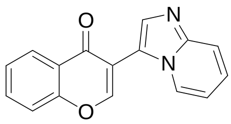
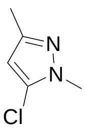
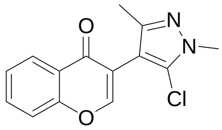
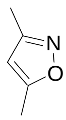
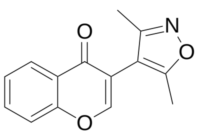
Table 3. Palladium-catalysed direct coupling of furans with 3-bromochromen-4-one (Scheme 2).[11]

Entry	Heteroarene	Product	Yield (%)
1		 **14**	60
2		 **15**	56
3		 **16**	67
4		 **17**	46
5		 **18**	78

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), 3-bromochromen-4-one (1 mmol), furan derivative (2 mmol), KOAc (2 mmol), DMAc, 16 h, 150 °C, isolated yields.

Finally, the reactivity of imidazo[1,2-a]pyridine, 5-chloro-1,3-dimethylpyrazole and 3,5-dimethylisoxazole was examined (Table 4). Activation of C-H bond at C3 of imidazo[1,2-a]pyridine provides **19** in 90% yield. Lower yields of 57% and 66% in **20** and **21** were obtained for the coupling at C4 of 5-chloro-1,3-dimethylpyrazole or 3,5-dimethylisoxazole due to partial conversions of the 3-bromochromeneone.

Table 4. Palladium-catalysed direct coupling of various heteroarenes with 3-bromochromen-4-one (Scheme 2).[11]

Entry	Heteroarene	Product	Yield (%)
1		 **19**	90
2		 **20**	57
3		 **21**	66

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 mmol), 3-bromochromen-4-one (1 mmol), heteroarene (2 mmol), KOAc (2 mmol), DMAc, 16 h, 150 °C, isolated yields.

In summary, we have demonstrated that 3-bromochromen-4-one can be heteroarylated with a variety of heteroarenes via palladium-catalysed C-H bond activation using an air-stable palladium catalyst. Functional groups such as chloro, acetyl, nitrile or ester on the heteroarene are tolerated. This procedure is economically attractive as both 3-bromochromen-4-one and a wide variety of hereroarenes are commercially available and as this procedure employ a moderate loading of palladium catalyst and an inexpensive base. Another advantage is the reduction of number of steps to prepare these heteroarylated chromenones compared to Suzuki coupling reactions.

Acknowledgments

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References and notes

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11. Typical experiment for the synthesis of products **1-21**: The reaction of the 3-bromochromen-4-one (0.225 g, 1 mmol), heteroarene (2 mmol) and KOAc (0.196 g, 2 mmol) at 150 °C during 16 h in DMAc (4 mL) with $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol), under argon affords the coupling product after evaporation of the solvent and purification on silica gel. **3-(2-Ethyl-4-methylthiazol-5-yl)-chromen-4-one (1)** ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 7.8 Hz, 1H), 7.99 (s, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 2.96 (q, J = 7.6 Hz, 2H), 2.38 (s, 1H), 1.34 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 172.6, 156.1, 154.3, 149.7, 134.0, 126.4, 125.6, 123.8, 119.3, 118.1, 117.9, 26.9, 16.4, 14.2. elemental analysis: calcd (%) for $C_{15}H_{13}NO_2S$ (271.34): C 66.40, H 4.83; found: C 66.25, H 4.98.