Microwave enhanced palladium catalysed coupling reactions: A diversity-oriented synthesis approach to functionalised flavones†

Richard J. Fitzmaurice,[a] Zac C. Etheridge,[a] Emelie Jumel,[a] Derek N. Woolfson[b] and Stephen Caddick*[a]

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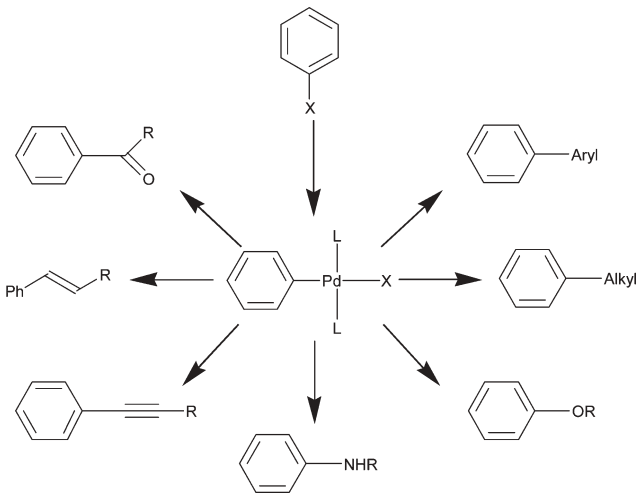
Microwave enhanced diversity-oriented synthesis (MEDOS) using palladium catalysed protocols is introduced as a powerful new strategy for the synthesis of systematically modified small molecules and is highlighted by application to functionalised flavones.

Diversity-oriented synthesis (DOS) has become accepted as an important strategy for chemical biology and has been exploited in a number of important chemical and biological problems.[1] Underpinning the DOS approach is a requirement for generic synthetic methods that enable the elaboration of a functional group into a variety of different molecular structures. Palladium catalysed organic transformations offer a platform for DOS, because of the wide range of transformations mediated by palladium.[2] Thus, an aryl halide can act as a 'chemical code' for a variety of valuable functional groups, including pharmacophores, recognition motifs *etc.* Judicious choice of catalyst and coupling agent are required to convert the aryl halide into the target structure (Scheme 1).

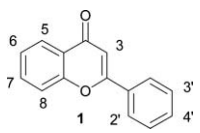
A further advantage of basing a DOS approach on palladium chemistry is that such reactions are known to be significantly enhanced by microwave heating.[3] Therefore microwave-enhanced diversity oriented synthesis approach (MEDOS) based on palladium chemistry may be particularly useful. The present paper describes this strategy and demonstrates its applicability to a biologically relevant class of small-molecule structures.

In selecting a small-molecule template to illustrate the potential of the strategy, we wished to identify a class of molecule of widespread importance in biology, but which had not been extensively elaborated using palladium catalysis. We chose the flavones, a key class of flavonoids that occur naturally in a wide range of sources and exhibit a plethora advantageous biological effects.[4–9] Recently, the flavone motif has been incorporated into a number of synthetic constructs with resulting interesting biological properties.[10–12] In our own programme we have identified flavones as an entirely new class of ligand for the protein apo-Neocarzinostatin.[13]

Although a range of synthetic strategies are available for the synthesis and modification of flavones **1**, relatively scant attention has been given to the elaboration of functionalised flavones using palladium mediated cross-couplings.[7,14,–21] We concluded, therefore, that the biological importance of this class of compounds made them an ideal candidate for development of the MEDOS approach using palladium catalysis. Here, we describe the realisation of the strategy and its applicability to functionalised flavones.



Scheme 1 Palladium chemistry as a platform for diversity.



Many routes have been described for the *de novo* synthesis of flavones.[7,10,12,16,22–26] Our own initial investigations toward the synthesis of haloflavones have been conducted using protocols based upon the classical Baker–Ventakaraman *O*-acylation approach.[22,25] However, reactions proved to be relatively low yielding and slow to perform. Application of a *C*-acylation methodology described by Cushman[23] for the synthesis of hydroxylated flavones is more successful and results in generally good yields of flavones **2–10** (Scheme 2). The 5-Br and 7-Br flavones were restricted due to lack of availability of the corresponding brominated acetophenones. In order to study palladium-based elaborations at all positions, triflates **11** and **13** were readily accessed *via* microwave-assisted triflation with Tf_2NPh of the corresponding alcohols **6** and **12** in excellent yields (Scheme 3).[27] It is noteworthy that reaction of **11** under thermal conditions with Tf_2O in NEt_3–DCM or pyridine provided disappointing yields, 20–25%.

[a]*Department of Chemistry, University College London, Christopher Ingold Laboratories, 20 Gordon Street, London, UK WC1H 0AJ. E-mail: s.caddick@ucl.ac.uk*
[b]*School of Chemistry, University of Bristol, Cantock's Close, Bristol, UK BS8 1TS and Department of Biochemistry, School of Medical Sciences, University Walk, Bristol, UK BS8 1TD*
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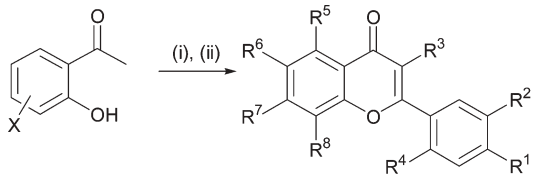


2, R^1 = Br, 89% **5**, R^4 = Br, 79% **8**, R^8 = Br, 75%
3, R^2 = Br, 78% **6**, R^5 = OH, 57%‡ **9**, R^1 = Cl, R^6 = Br, 94%
4, R^3 = Br, 61%† **7**, R^6 = Br, 75% **10**, R^2 = Br, R^4 = Cl, R^6 = Me, 61%

Reagents and Conditions: (i) 4 eq. LHMDS, THF, -78 ºC to –20 ºC then XArCOCl, THF, -78 ºC to RT; (ii) cH_2SO_4, AcOH, 120 ºC, 5 min.
† from flavone via treatment with Br_2/AcOH, ‡ 5 eq. LHMDS.

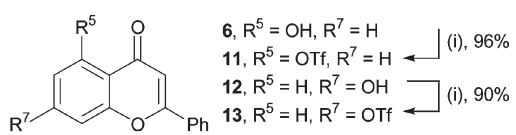
Scheme 2 Synthesis of functionalised flavones.

Initial investigations in the Suzuki–Miyuara reaction on flavone **2** identified Li's[28] POPd catalyst with CsF as optimum and furnished the desired arylated flavone in 83% yield *via* conventional heating at 85 °C for 5 h. Use of microwave heating at 85 °C reduced the reaction time to 15 min and improved the yield to 98%.

Application of the optimised POPd based protocol to the range of flavone bromides and triflates is described in Table 1. Reactions generally proceeded smoothly across the substrate range with the best yields obtained for the most electron poor bromides **2**, **3**, and **9**. Reactions with both triflated flavone substrates **11** and **13** also proceeded smoothly in high yield. As expected, reactions with relatively electron rich bromide **7** were less successful with both electron-rich and electron-poor boronic acids. Reaction of bromoflavone **5** afforded only a low yield of the desired arylated flavone on reaction with phenylboronic acid. This can in part be attributed to the hindered nature of the bromide substrate and in part to difficulty in separating the desired arylated compound from the simple reduction product. Use of the more electron poor 3-nitrophenyl boronic acid afforded a crystalline product to aid purification.

Arylation of flavone **4** was wholly unsuccessful using POPd–CsF catalyst regime. However, use of $Pd(PPh_3)_4$–K_3PO_4 with microwave heating afforded the arylated product in 86% yield. Attempts to selectively mono arylate bishaloflavones **9** and **10** using POPd–CsF protocol were unsuccessful and provided inseparable mixtures of monoarylated, *via* displacement of both bromine and chlorine, and bis arylated products.

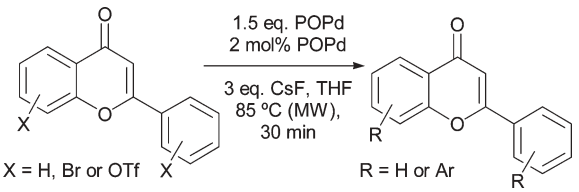
Imidazolium salts have been successfully used as ligands in a wide range of Buchwald–Hartwig amination reactions on aryl halides. However, use of a $Pd_2(dba)_3$–SIMES.HCl catalyst regime on flavone **2** required high temperature microwave heating, 165 °C, to achieve reasonable reaction rates and gave only moderate yields, 51%.[29] Application of Buchwald's $Pd_2(dba)_3$–BINAP–NaO^tBu catalyst was considerably more effective at lower temperatures (Table 2).[30] Employing these conditions with microwave heating afforded a range of functionalised flavones in good to moderate yield. Reaction of sterically hindered flavone **5** did not generate any of the required aminated product with only direct haloflavone reduction observed. Attempts to aminate triflate **13** were low yielding compared to the bromides and the catalyst mixture was completely inactive towards triflate **11**. Attempts to apply POPd as an amination catalyst were unsuccessful with both POPd–CsF and POPd–Cs_2CO_3 proving completely inactive as catalysts for amination of **2** with hexylamine. Monoamination of bromochloroflavones **9** and **10** was achieved readily using only one equivalent of amine, with $Pd_2(dba)_3$–BINAP–NaO^tBu

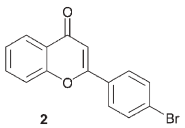
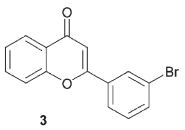
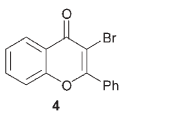
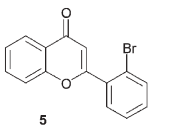
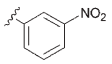
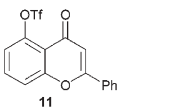
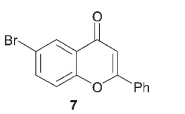
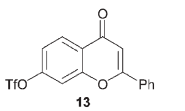
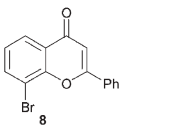


Reagents and Conditions: (i) Tf_2NPh, K_2CO_3, THF, 10 min, 120 ºC (MW).

Scheme 3 Triflation of hydroxylated flavones.

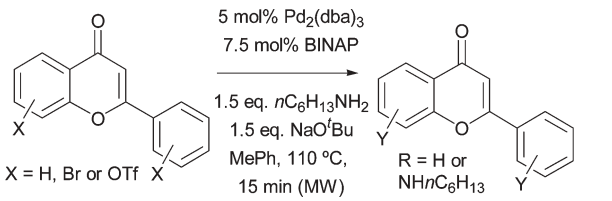
Table 1 Suzuki–Miyaura reactions with POPd–CsF

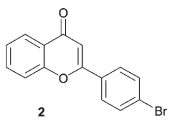
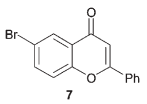
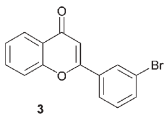
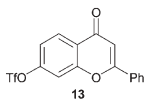
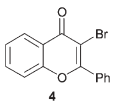
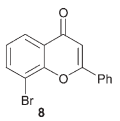
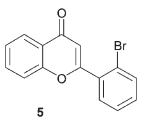
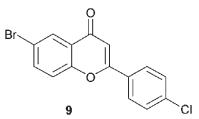
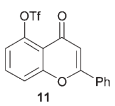
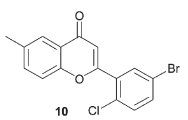


Substrate	=Ar	Yield (%)
 **2**	–Ph	98[a]
 **3**	–Ph	89
 **4**	–Ph 	0 0
 **5**	–Ph 	44 64
 **11**	–Ph	89
 **7**	–Ph 	60[b] 53
 **13**	–Ph	82
 **8**	–Ph 	84[c] 57

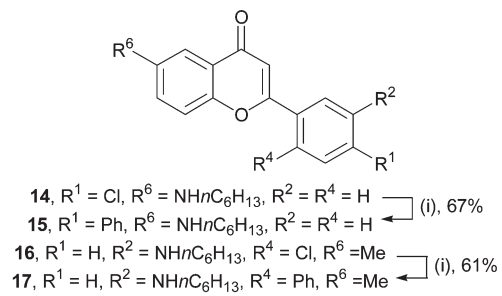
[a] 83% yield with 5 h conventional heating [b] 2 × 30 min [c] 3 × 30 min.

Table 2 Buchwald–Hartwig aminations on bromoflavones



Substrate	Yield (%)	Substrate	Yield (%)
	83		42
	64		35[b]
	33[a]		77
	0		37[c]
	0[b]		57[c]

[a] $Pd(OAc)_2$ instead of $Pd_2(dba)_3$. [b] 2 eq. amine, 3 mol% $Pd_2(dba)_3$, 4.5 mol% BINAP, 1.4 eq. Cs_2CO_3. [c] 1 eq. *n*-hexylamine, 80 °C (MW), 1 h.



Reagents and Conditions: (i) 1.5 eq. $PhB(OH)_2$, 2 mol% POPd, 3 eq. CsF, THF, 120 °C, 1 h..

Scheme 4 Arylation of chloroflavones.

catalyst regime, with a small amount of bis amination observed, 7%, in the case of **10**. Yields for this mono amination of bromochloroflavone **9** and **10** compared well with the analogous reactions on monobrominated substrates **2** and **6**. The use of $Pd(OAc)_2$ as palladium source furnished the desired hydrolytically unstable aminated flavone without further purification in the case of bromoflavone **4**.

Arylation of chloroflavones **14** and **16** with POPd–CsF at 120 °C (MW) afforded the desired products **15** and **17** in moderate yields. Aminated arylated flavones **15** and **17** can be generated directly from the corresponding bromochloroflavones without intermediate purification, save filtration, with no loss of overall yield.

In summary, we have successfully demonstrated the power of the MEDOS strategy by application to a variety of systematically modified and functionalised flavones, We anticipate this approach finding widespread applicability in small molecule synthesis and the development of small molecules as tools for chemical biology.

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