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EDGE ARTICLE

Palladium-catalyzed cascade reactions of 3-iodochromones with aryl iodides and norbornadiene leading to annulated xanthones†

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An efficient, palladium-catalyzed cascade reaction, which leads to formation of annulated xanthones, was devised. The process, which uses readily available 3-iodochromones, aryl iodides and norbornadiene as starting materials, takes place *via* a tandem Heck reaction/double C–H activation/retro-Diels–Alder pathway. The high chemoselectivity of the process is mechanistically unique and it serves as a new approach to achieve regioselective control of C–H activation in Pd/norbornene or norbornadiene systems. Its broad substrate scope, including heteroaryl coupling partners, enables access to diverse annulated xanthones.

Introduction

Among the important group of C–H activation/C–C bond forming processes, the Pd-catalyzed/norbornene-mediated reaction (Catellani reaction) is widely recognized as being a powerful method to form diversely functionalized aromatic compounds and condensed heterocycles. The Catellani reaction follows a cascade pathway in which C–C bonds and C–O or C–N bonds form sequentially.[1] Generally, the "*ortho* effect" of aryl iodides ensures that Csp^2–Csp^2 rather than Csp^2–Csp^3 coupling of Pd(IV) intermediates occurs regioselectively to generate biaryl linkages and an active Pd(II) species, which participates in a variety of coupling reactions.[2]

A large effort has been devoted to improving the efficiency and practicality of this Csp^2–Csp^2 coupling process.[3] In contrast, the development of techniques to selectively promote Csp^2–Csp^3 reductive elimination of the key aryl Pd intermediate in the reaction pathway still presents a distinct challenge. In an early report, Catellani suggested that it might be possible to facilitate aryl–norbornyl bond formation by Csp^2–Csp^3 coupling when an *ortho* group is absent.[4] Recently, Catellani and Malacria discovered that certain chelating functional groups on the second *ortho* substituent can guide alternate reactivity, thus offsetting the normal *ortho* effect.[5] In the study described below, we have uncovered a new, palladium-catalyzed cascade reaction of 3-iodochromones with aryl iodides and norbornadiene that forms annulated xanthones *via* a Heck coupling/double C–H activation/retro-Diels–Alder sequence and that involves an unexpected Csp^2–Csp^3 reductive elimination reaction of the key aryl Pd intermediate even though no *ortho* chelating functional groups are present.

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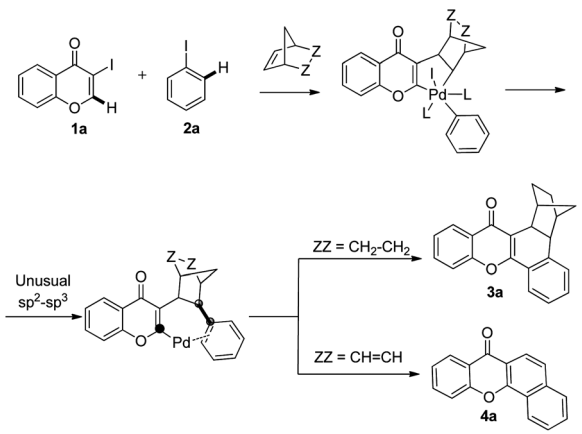
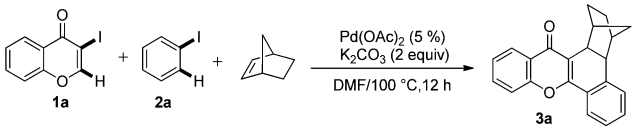
The chromone ring system is an important structural motif frequently found in natural products, pharmaceuticals and other important synthetic substances.[6] The results of recent investigations have shown that C–H functionalization reactions could occur at the C-2 and C-3 position of chromones.[7] In a continuation of an effort aimed at the development of strategies for the preparation of diverse natural-product-like scaffolds,[8] we speculated that regioselective C–H activation at the C-2 position of chromones might take place in the course of the Catellani reaction and that this pathway would serve as a facile method for forming flavones and/or xanthones (Scheme 1).

Results and discussion

Initial studies aimed at exploring this proposal focused on the Pd-catalyzed reaction of 3-iodochromone (**1a**) with iodobenzene

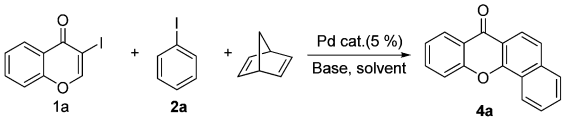


Scheme 1 A proposed sp^2–sp^3 coupling process in the palladium-catalyzed reaction of 3-iodochromone with iodobenzene and norbornadiene or norbornene.



Scheme 2 Pd-catalyzed tandem formation of compound **3a**.

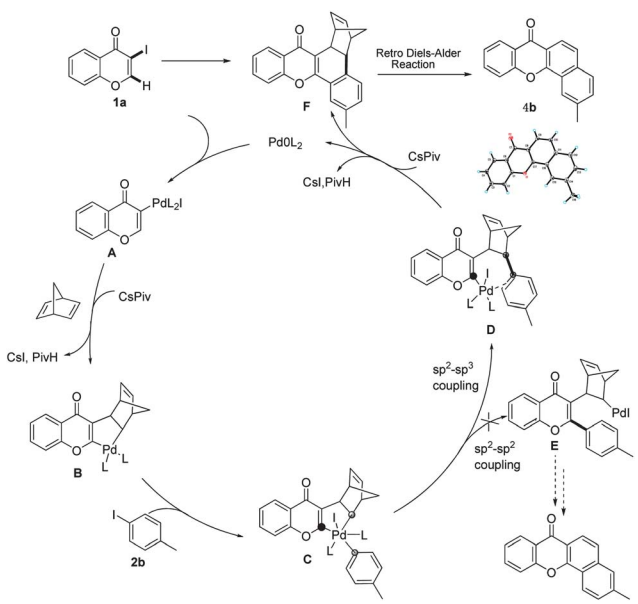
Table 1 Optimization of the cascade reaction



Entry	Solvent	Pd cat.	Base	*T*/°C	*t*/h	Yield[d] (%)
1[a]	DMF	$Pd(OAc)_2$	K_2CO_3	90	12	10
2[a]	DMF	$Pd(OAc)_2$	Cs_2CO_3	90	12	Messy
3[a]	DMF	$Pd(OAc)_2$	CsPiv	90	12	45
4[a]	DMA	$Pd(OAc)_2$	CsPiv	90	12	40
5[a]	DMSO	$Pd(OAc)_2$	CsPiv	90	12	31
6[a]	DMF[b]	$Pd(OAc)_2$	CsPiv	90	12	18
7[a]	DMF[c]	$Pd(OAc)_2$	CsPiv	90	12	50
8[a]	DMF[c]	$Pd(OAc)_2$	CsPiv	130	3	57
9[e]	DMF[c]	$Pd(OAc)_2$	CsPiv	130	3	78
10[e]	DMF[c]	$PdCl_2$	CsPiv	130	3	56
11[e]	DMF[c]	$Pd_2(dba)_3$	CsPiv	130	3	47
12[e]	DMF[c]	$PdCl_2(PPh_3)_2$	CsPiv	130	3	45
13[e]	DMF[c]	$Pd(PPh_3)_4$	CsPiv	130	3	38
14[e]	DMF[c]	$PdCl_2(PPh_3)_2$	CsPiv	130	3	33

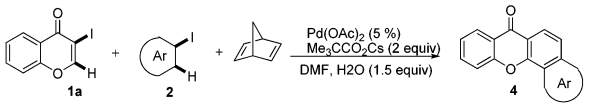
[a] All reactions were carried out using the following molar ratio of the reagents: **1a** : **2a** : norbornadiene = 1 : 1 : 2. [b] Freshly distilled DMF. [c] Freshly distilled DMF with 1.5 equiv. of water. [d] Isolated yield. [e] The reaction was run with molar ratio of the reagents: **1a** : **2a** : norbornadiene = 1 : 2 : 6.

(**2a**) in the presence of norbornene. Under the reaction conditions described by Catellani (see procedure A), the unexpected product **3a** is produced in 82% yield (Scheme 2). We hypothesized that this catalytic reaction proceeds *via* a pathway involving



Scheme 3 Proposed catalytic cycle.

Table 2 Scope of aryl iodides[a]



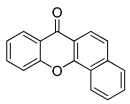
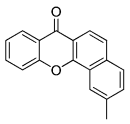
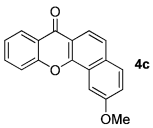
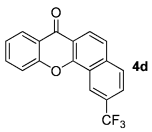
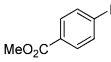
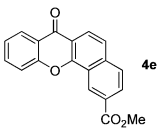
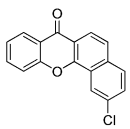
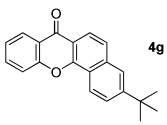
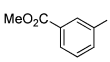
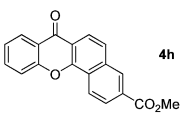
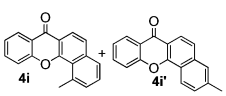
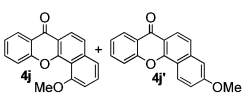
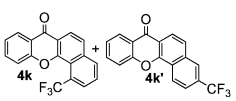
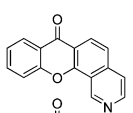
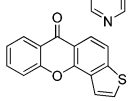
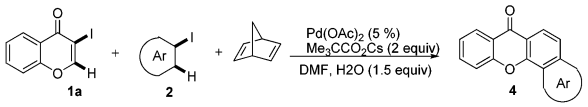
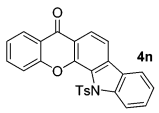
Entry	Substrate **2**	Product	Yield (%)
1	 **2a**	 **4a**	78
2	 **2b**	 **4b**	78
3	 **2c**	 **4c**	40
4	 **2d**	 **4d**	83
5	 **2e**	 **4e**	63
6	 **2f**	 **4f**	58
7[b]	 **2g**	 **4g**	67
8[b]	 **2h**	 **4h**	51
9[b]	 **2i**[c]	 **4i** **4i'**	44/22[c]
10[b]	 **2j**[c]	 **4j** **4j'**	39/21[c]
11[b]	 **2k**	 **4k** **4k'**	13/40[c]
12	 **2l**	 **4l**	62
13	 **2m**	 **4m**	65

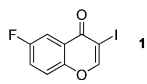
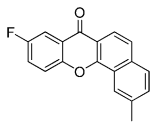
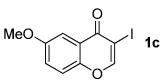
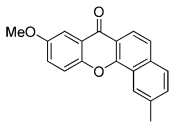
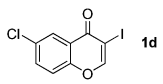
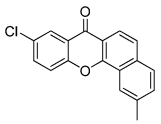
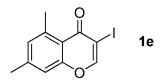
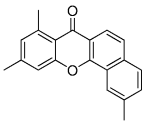
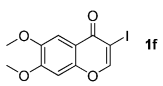
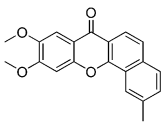
Table 2 (*Contd.*)



Entry	Substrate **2**	Product	Yield (%)
14	 **2n**	 **4n**	40

[a] All reactions were run under optimized conditions, unless otherwise noted. [b] Reactions were run at 90 °C for 12 h. [c] The ratios were determined by using ^{1}H NMR analysis.

Table 3 Iodochromone scope of the process

Entry	Substrate **1**	Product	Yield (%)
1	 **1b**	 **4o**	71
2	 **1c**	 **4p**	85
3	 **1d**	 **4q**	60
4	 **1e**	 **4r**	73
5	 **1f**	 **4s**	80

Csp^2–Csp^3 reductive elimination. Intrigued by this hypothesis, norbornadiene was utilized as a substrate in a reaction carried out under otherwise identical conditions. We believed that retro-Diels–Alder reaction would occur on the initially formed product to afford a benzoxanthone derivative. Importantly, substances in the benzoxanthone family display interesting bioactivities[9] and, as a result, various methods for their synthesis have been described.[10] However, the cascade process we envisioned would represent the most direct and functionally tolerant method for forming these targets (Table 1).

Indeed, reaction of **1a** and **2a** in the presence of norbornadiene, promoted by $Pd(OAc)_2$ in the presence of K_2CO_3 (see procedure A), was observed to generate the desired benzoxanthone **4a** in only 10% yield (entry 1). The low yield of the reaction might be a consequence of the high reactivity of norbornadiene.[5a,11] When the softer base Cs_2CO_3 was utilized (entry 2), this reaction produces an inseparable mixture of products. Since the use of pivalate anion as a ligand is known to improve the efficiency of many C–H activation processes.[12] Me_3CCO_2Cs (entry 3) was employed as a base in the reaction. Significantly, benzoxanthone **4a** is produced in 45% yield under these conditions. Moreover, other higher boiling solvents, such as DMSO and DMA, could also be used to facilitate the final retro-Diels–Alder step (entries 4–6). However, freshly distilled DMF (entry 6) was not an effective solvent, indicating that water is required to promote the reaction.[3g,k,13] The results of a brief examination showed that 1.5 equiv. of water is ideal. As expected, the reaction occurs more rapidly at higher temperatures (entry 8). Importantly, increasing the amounts of both iodobenzene and norbornadiene leads to a dramatically improved 78% yield (entry 9). Finally, although other common Pd sources can be utilized to promote this reaction, $Pd(OAc)_2$ is the most efficient catalyst (entries 10–14). The combined studies demonstrate that DMF containing 1.5 equiv. H_2O as the solvent at 130 °C, Me_3CCO_2Cs as the base, 5 mol% $Pd(OAc)_2$ as the catalyst, 2 equiv. of PhI, 6 equiv. of norbornadiene, and 3 h reaction time are the optimal conditions for the new reaction.

To gain insight into the mechanism of the process, reaction of **1a** with *para*-iodotoluene (**2b**) was carried out under the optimized conditions. This reaction generates the benzoxanthone **4b** in 78% yield. The structure of **4b** and in particular the position of the methyl group was assigned by using X-ray crystallographic analysis (ESI†). Importantly, the position of methyl group in **4b** is fully consistent with the proposed catalytic cycle, where Csp^2–Csp^3 rather than Csp^2–Csp^2 coupling takes place in the reductive elimination step (Scheme 3). The overall route could be initiated by oxidative addition of Pd(0) to **1a**, followed by norbornadiene insertion, and intramolecular sp^2 C–H activation at the 2-position of the chromone ring then forms the chromone fused palladacycle **B**. A second oxidative addition of the aryl iodide affords the Pd(IV) complex **C**, which then undergoes reductive elimination by either Csp^2–Csp^3 or Csp^2–Csp^2 coupling. The position of the methyl group in **4b** shows that Csp^2–Csp^3 reductive elimination regioselectively gives intermediate **D**, which undergoes the second sp^2 C–H activation to form **F** followed by release of the Pd(0) complex. The retro-Diels–Alder reaction of **F**, taking place at 130 °C leads to formation of the benzoxanthone product. An alternative mechanism may involve initial oxidative addition by ArI, which reacts with norbornadiene to generate a phenyl fused palladacycle and followed by a second oxidative addition of 3-iodochromone to give the same Pd(IV) complex **C**. Since 3-iodochromone with an electron-withdrawing group is more reactive than iodobenzene for the initial oxidative addition of Pd(0), the first possibility is favored. Also, we speculate that the selective operation of Csp^2–Csp^3 coupling is a consequence of stabilization of intermediate **D** by the electron-donating effect of the oxovinyl system.

Next, differently substituted aryl iodides were used to explore the scope of the new tandem reaction, conducted under optimized conditions. The results, summarized in Table 2, show that the electronic nature of *para*-substituents on the aryl iodide has a significant effect on the reaction (entries 2–5). Specifically, electron donating group substituted aryl iodides undergo inefficient reactions owing to a slow oxidative insertion step converting Pd(II) to Pd(IV) (entry 3). In addition, the steric bulk of *meta* aryl iodide substituents can be used to govern the regioselectivity of the C–H activation step. As demonstrated by reactions of the *meta*-*tert*-butyl and -methoxycarbonyl substituted aryl iodides **2g** and **2h** that yield the respective benzoxanthones **4g** and **4h**, the course of the process is guided by steric hindrance (entries 7 and 8). As expected, mixtures of two benzoxanthones, arising by C–H activation at either *ortho*-phenyl site, are generated in reactions of the aryl iodides **2i**, **2j** and **2k**, which contain smaller electron-donating or electron-withdrawing *meta*-groups (entries 9–11). It should be noted that reactions of aryl iodides bearing *ortho*-CH_3, -OMe and -CF_3 substituents are low yielding, perhaps because of steric effects that slow oxidative insertion in the Pd(II) intermediate **B**.

It is significant that the heteroaryl iodides, 2-iodothiophene, 4-iodopyridine and 3-iodoindole, undergo this reaction to give the desired products in moderate to good yields. In contrast, bromobenzene can not be used in place of its iodide counterpart as the coupling partner, presumably because it does not react with the palladium(II) metallacycle intermediate. Lastly, different 3-iodochromones containing both electron-withdrawing and -donating substituents on the chromone ring react with 4-iodotoluene (Table 3) to give the corresponding benzoxanthones in good yields.

Conclusions

In the investigation described above, we have developed a highly efficient cascade process that involves unique C–H activation of the 2-position of the chromone ring system. The compatibility of this novel reaction with aryl iodides allows for an efficient method to prepare benzoxanthones. The high selectivity of the novel Pd/norbornene catalytic system should be applicable to reactions that result in the construction of interesting fused ring systems. Moreover, observations made in this study suggest that slightly different catalysts might be needed for reactions of each substrate type and that the Pd/norbornene catalytic system may be more mechanistically complicated than previously believed. We anticipate that the novel reaction discovered in this investigation will be applicable to other substrates and that future studies in this area will lead to the development of more comprehensive catalytic systems.

Acknowledgements

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Notes and references

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