

The α -arylation of α -bromo- and α -chloroenones using palladium-catalysed cross-coupling

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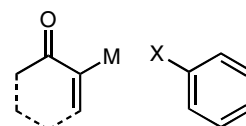
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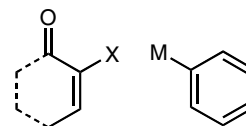
Abstract—The palladium-catalysed cross-coupling reaction of various arylboronic acids with α -bromo-enones and α -chloroenones offers an operationally simple approach to the synthesis of both cyclic and acyclic α -arylenones.

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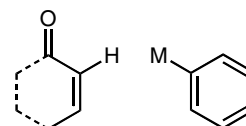
The catalytic α -functionalisation of *enones* with sp^2 carbon groups such as aryl and alkenyl is a desirable but challenging prospect. Although there is no general method for this useful transformation, approaches involving metal catalysed cross-coupling show considerable potential as described by Negishi in an excellent review.¹ In this context, palladium or nickel complexes have been studied in the catalytic synthesis of α -aryl- α,β -unsaturated carbonyl compounds by the cross-coupling of α -organometallics with aryl halides or the complementary combination of α -halocarbonyl compound and sp^2 carbon derived organometallics (Fig. 1). Of the many possible permutations, the most success has been realised with α -iodoenones and organozinc derivatives, although requiring strictly anhydrous reaction conditions, yields are generally high and the loading of palladium catalyst (typically $\text{PdCl}_2(\text{PPh}_3)_2$) are acceptably low (5–10 mol %).² An elegant solution avoiding transition metal catalysis has recently been reported by Koech and Krische.³ The regioselective α -arylation of simple enones is achieved by nucleophilic (phosphine) catalysis. This elegant methodology employs triarylbismuth(V) dichlorides as aryl transfer reagents and tolerates a wide-range of aryl substitution with the exception of strong π -donating groups in the *para* position (e.g., *p*-OMe). In this letter, we report an effective method for the synthesis of α -arylenones using a palladium catalysed cross-coupling of arylboronic acids and either α -bromo- or α -chloroenones.⁴ This



Cross-coupling of an α -organometallic and aryl halide (M=Zn, Sn; X=I)



Cross-coupling of an α -halocarbonyl and aryl organometallic (M=Zn, Sn, B; X=I, OTf)



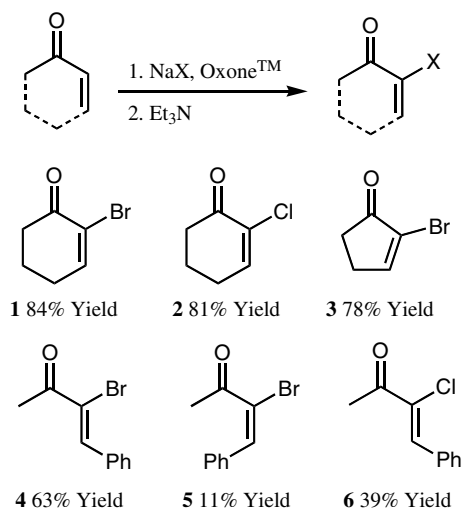
Enolate arylation *via* nucleophilic catalysis (M = hypervalent Bi)

Figure 1. Catalytic approaches to the synthesis of α -aryl- α,β -unsaturated carbonyl compounds.

study complements the recent excellent work of Felpin involving additions to α -iodoenones using a heterogeneous Pd(0)/C catalyst system.⁵

The substrates **1–6** were conveniently prepared from a mixture of oxone™ and either sodium bromide or sodium chloride as described by Dieter et al.

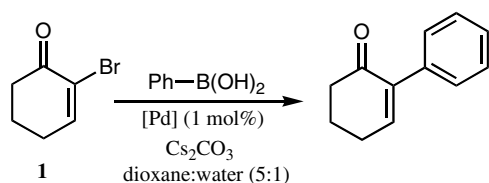
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Scheme 1. The preparation of α -haloenones.

(Scheme 1).⁶ The α -bromination of *trans*-4-phenyl-3-buten-2-one afforded **4** as the major product along with a low yield of **5** due to σ -bond rotation prior to elimination.

As a representative example, the reaction of α -bromocyclohexenone **1** with phenylboronic acid was investigated in aqueous solvent in the presence of various palladium complexes.⁷ In all cases, **1** was completely consumed affording the α -arylated product in varying isolated yields, as indicated (Scheme 2, entries 1–5). The substrate was found to undergo extensive decomposition on prolonged heating and the isolated yields of product reflects the relative activity or the longevity of



Entry	[Pd] (1 mol%)	Isolated yield (%)
1	Pd(PPh ₃) ₄	7
2	Pd(PPh ₃) ₂ Cl ₂	37
3	Pd(PCy ₃) ₂ Cl ₂	77
4	Pd(PToI ₃) ₂ Cl ₂	41
5	Pd(P ^t Bu ₃) ₂ Cl ₂	44

Reaction conditions: A mixture of cesium carbonate (2 mmol), palladium complex, (0.01 mmol), arylboronic acid (2 mmol) and the α -haloenone (1 mmol) in 1,4-dioxane (5 ml) and water (1 ml) were stirred at reflux for 24 h. The mixture was poured into water (50 ml), extracted with EtOAc (3 x 20 ml), dried over MgSO₄, evaporated under reduced pressure and purified by flash column chromatography (SiO₂, petroleum ether:EtOAc, 90:1) to afford the product.

Scheme 2. The reaction of α -bromocyclohexenone with phenylboronic acid.

the different palladium complexes under the reaction conditions. Interestingly, Felpin notes the complete failure of α -bromocyclohexenone to undergo Suzuki–Miyaura coupling employing the Pd(0)/C catalyst system, an observation attributed to substrate decomposition.⁵ In our hands, the most active complex was identified as the electron-rich PdCl₂(PCy₃)₂ and this was employed in subsequent reactions.

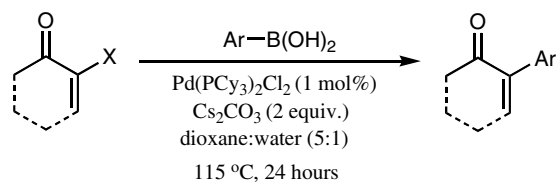
The protocol demonstrated useful scope with respect to the boronic acid employed, the isolated yields were higher with activated boronic acids than with electron-poor boronic acids (Scheme 3, entries 1–6). The lower yield of isolated product with *p*-chlorophenylboronic acid (Scheme 3, entry 3) was due to a competitive polymerisation process. The less reactive *m*-nitrophenylboronic acid did not afford any desired product, only evidence of protodeboronation was found. Given the potential of this approach, a number of alternative α -haloenones (**2–6**) were examined with the aim of achieving a unique cross-coupling of arylboronic acids and α -chloroenones. Although advances in catalyst design and screening have revealed a number of palladium-based systems for the efficient coupling reactions of aryl chlorides, the corresponding reactions of vinyl chlorides have received much less attention.⁸ The reaction of α -chlorocyclohexenone **2** with phenylboronic acid was successful affording a 45% yield of product. Unfortunately much lower isolated yields were obtained with the α -bromocyclopentenone **3** (Scheme 3, entries 8–10). Despite the low yields of products, no starting material was recovered from these reactions suggesting that the inherent instability of this substrate on heating is a limiting factor. Gratifyingly, the acyclic substrates (**4** and **5**) proved to be competent substrates affording good isolated yields of product at just 1 mol % catalyst loading (Scheme 3, entries 11–17). Although **4** and **5** are less reactive than α -bromocyclohexenone **1**, these acyclic substrates proved to be stable to heating and very little degradation was observed.

We were pleased to note that good yields of product were also obtained in the cross-coupling of electron-rich and electron-poor boronic acids with the acyclic α -chloroenone **6** (Scheme 3, entries 18–20). Again, the lower reactivity of this substrate towards oxidative addition was offset by the enhanced thermal stability resulting in a useful coupling process.

In conclusion, cyclic and acyclic α -arylenones can be prepared using a palladium-catalysed cross-coupling protocol involving α -bromo- or α -chloroenones and commercially available boronic acids. The acyclic α -haloenones offer the best scope as a consequence of their increased stability.

Acknowledgements

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Entry	Substrate	Ar	Isolated yield (%)	Entry	Substrate	Ar	Isolated yield (%)
1	1		77	11	4		52
2	1		70	12	4		64
3	1		39	13	4		98
4	1		70	14	4		59
5	1		--	15	4		--
6	1		21	16	5		50
7	2		45	17	5		66
8	3		18	18	6		64
9	3		15	19	6		78
10	3		15	20	6		51

Scheme 3. The scope of the palladium-catalysed coupling.

Supplementary data

Experimental procedures and compound characterisation data are available. Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2006.02.134](https://doi.org/10.1016/j.tetlet.2006.02.134).

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