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Direct formation of 1-vinyl-1*H*-isochromene derivatives *via* a palladium-catalysed coupling reaction

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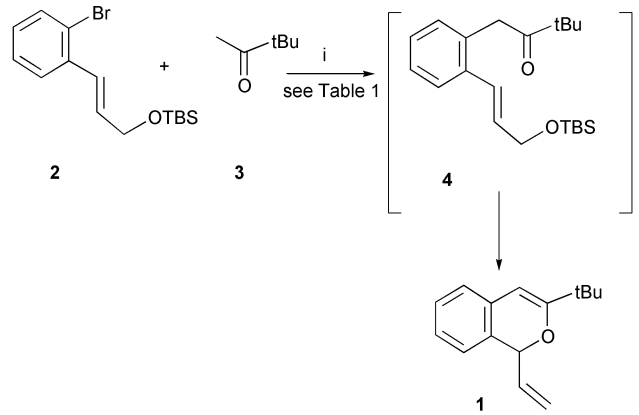
The palladium-catalysed reaction of the *tert*-butyldimethylsilyl ether of a 3-(*o*-bromophenyl)allylic alcohol with a methyl ketone leads directly to a 1-vinyl-1*H*-isochromene *via* a tandem ketone arylation–allylic cyclisation reaction.

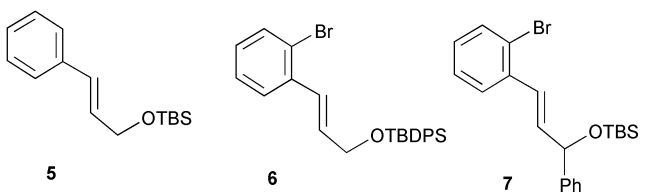
As a part of a wider project concerned with the synthesis of biologically active molecules, we wished to prepare 1-vinyl-1*H*-isochromenes **1**. We felt that we could achieve this end in two stages. The first stage (for the example shown in Scheme 1) would require the coupling reaction of an appropriate aryl



Scheme 1 Intramolecular cyclisation reaction to form 1-vinyl-1*H*-isochromenes. *Reagents and conditions*: (i) ligand, base, solvent, $[Pd_2(dba)_3]$, 85 °C (See Table 1).

bromide **2** with a ketone **3** to give **4**.[1] The second stage would involve replacement of the TBS with an acetyl group and subsequent cyclisation of the ketone enolate onto the allylic system. For the first step, we were confident that a palladium-catalysed ketone arylation reaction would be effective. The reason for the choice of a non-activating silyl group in **2** was simply to prevent the allylic substitution from outpacing the aryl coupling at the high reaction temperatures required (> 80 °C). Allylic acetates, for example, are known to react with ketones under palladium-catalysed reactions at rt.[2]

We first examined the coupling of the *tert*-butyldimethylsilyl-protected allylic alcohol substrate **2** with pinacolone (Scheme 1). Starting material **2** was prepared from readily available 2-bromobenzaldehyde in three steps in 90% overall yield following a literature procedure to the alcohol which was then silyated.[3] Initial attempts to couple **2** to pinacolone following the procedure of Hartwig *et al*.[1] (NaO*t*-Bu, Pd/DPPF, toluene, 100 °C) led mainly to the debrominated cinnamyl ether **5**; no coupling product was observed. Investigation of several



bases (NaO*t*-Bu, Na_2CO_3, Cs_2CO_3 LHMDS) gave none of the expected product **4**. In the case of LiHMDS, however, the 1*H*-isochromene **1**‡ was formed as the major product. Subsequent optimisation of this tandem arylation–allylic substitution reaction improved the yield of this product to 71%.§ As far as we are aware, this represents the first observation of such a tandem enolate arylation–allylic cyclisation reaction. Notable in this process is the involvement of a silyloxy leaving group, which would normally not be considered to be a suitable group for allylic activation. Presumably this reacts because of the high reaction temperature. Related intramolecular reactions of β-keto ester enolates and diketones have been reported to form five-membered rings in palladium-catalysed intramolecular cyclisations.[4]

During this work it appeared that a lithium base and a co-ordinating solvent must be employed to make the reaction work. Trost has reported a similar requirement for a lithium base in an allylic alkylation reaction.[2d] A series of phosphine ligands and ketones were also investigated (Table 1) and it was found that a

Table 1 Palladium-catalysed ketone arylation–allylic cyclisation reactions

Aryl bromide	Ketone	Solvent	Ligand	Product	Yield (%)
2	**3**	Toluene/THF	dppf	**1**	67
2	**3**	Dioxane/THF	dppf	**1**	71
2	**3**	Toluene	dppf	—	0
6	**3**	Toluene/THF	dppf	**1**	54
7	**3**	Toluene/THF	dppf	—	0
2	**3**	Dioxane	L-S-ESPHOS	**1**	15[a]
2	**3**	Toluene/THF	$(o\text{-Tol})_3P$	**1**	61
2	**3**	Toluene/THF	$(t\text{-Bu})_3P$	**1**	27[b]
2	Acetophenone	Toluene/THF	dppf	**8**	28
2	Propiophenone	Toluene/THF	dppf	**9**	36[c]

[a] Side-products: **4**; 21%, **5**: 6% [b] Side-products; **4**: 30%, **5**: 6%. [c] Side-product; **10** 6%.

substantial amount of the intermediate **4** could be isolated when either tri-*tert*-butylphosphine or the bis(diazaphospholidine) ligand semi-ESPHOS[5] were used. This intermediate, **4**, was then exposed to the reaction conditions in the absence of palladium and ligands. No cyclisation occurred after several hours, indicating that the cyclisation step was also palladium catalysed. Tri-*o*-tolylphosphine also proved to be a good ligand for isochromene formation. The isolation of **4** from certain experiments suggests that it may be possible to 'tune' the reaction conditions towards the formation of either cyclic or acyclic products. We are currently investigating this issue.

Changing the protecting group on the bromide in **2** from TBS- to the TBDPS- (*i.e.* **6**) did not effect the tandem reaction. Substitution at the allylic ether carbon with a phenyl group (*i.e.* **7**) led to an unreactive substrate. Aromatic ketones such as acetophenone and propiophenone also proved compatible with the reaction conditions. In each case the desired cyclic products **8** and **9** respectively were formed, although the non-optimised yields were low to moderate in both cases. In the case of propiophenone a small amount (6%) of non-cyclised material **10** was also formed.

We wished to confirm that the choice of a trialkylsilyloxy-allylic substrate was essential for a successful reaction. This was achieved through the attempted reaction of acetate **11** with both

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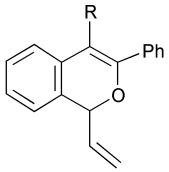
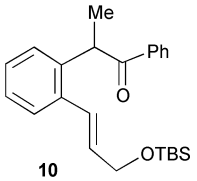


8 R = H
9 R = Me



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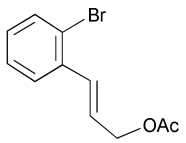
pinacolone and acetophenone under our reaction conditions for cyclisation. In the former case the result was a complex mixture, in the latter case the deacetylated alcohol was the major product of the reaction, together with a small amount of ketone **12**. The latter result serves to confirm the ability of the silyloxy group to delay the allylic reaction conveniently until after the arylation process has been completed.



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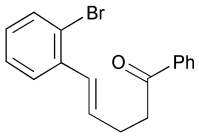

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In conclusion, we have demonstrated that, through the careful choice of ether protecting group, a tandem enolate-arylation–allylic cyclisation process may be 'fine-tuned' in order for the steps to take place in a desired order. The overall result is a convenient and rapid synthesis of vinyl-1*H*-isochromenes, which represent valuable synthetic building blocks for further reactions. The results of our studies on these products, together with further details of the coupling–cyclisation process, will be reported in full in due course.

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Notes and references

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‡ *Characterisation data* for 1-vinyl-3-*tert*-butyl-1*H*-isochromene 1. ν_{max}(NaCl)/cm^{-1} 2954, 1638, 1085, 914, 750; δ_H(300 MHz, $CDCl_3$) 1.16 (9H, s, C(C*H*$_3$)$_3$), 5.16 (1H, dt, *J* 17.1 and 1.3, CH=C*H*$_2$), 5.23 (1H, dt, *J* 10.4 and 1.3, CH=C*H*$_2$), 5.46 (1H, d, *J* 6.6, ArC*H*(OR)CH=CH$_2$), 5.67 (1H, s, ArC*H*=C(OR)), 6.15 (1H, ddd, *J* 17.1, 10.4 and 6.6, CH(OR)C*H*=CH$_2$), 6.90–7.30 (4H, m, Ar*H*); δ_C(75 MHz, $CDCl_3$) 28.3, 35.5, 79.3, 97.7, 118.2, 123.8, 124.9, 126.2, 128.5, 129.4, 132.0, 136.7, 164.2; *m/z* (EI) 214 [M]$^+$, 187, 129 (Found: [M]$^+$, 214.136173. $C_{15}H_{18}O$ requires *m/z*, 214.135765).

§ General experimental procedure for the synthesis of 1-vinyl-3-*tert*-butyl-1*H*-isochromene 1. To a solution of LiHMDS (1 M in THF, 3 eq.) was slowly added a solution of the pinacolone (2 eq.) in solvent at 5 °C. A solution of $Pd_2(dba)_3$ (5% mol) and ligand (10% mol) in solvent was added at room temperature, followed by a solution of *tert*-butyldimethyl [3-(2-bromophenyl)allyloxy]silane **2** (1 eq.). The reaction mixture was heated to 100 °C overnight, allowed to cool and then quenched with 1 M HCl solution at room temperature. The mixture was twice extracted with dichloromethane and the combined organic layers were dried and the solvent was evaporated under reduced pressure yielding the crude product. The crude product was purified by flash chromatography.

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