Acyl palladium species in synthesis: single-step synthesis of α,β-unsaturated ketones from acid chlorides†

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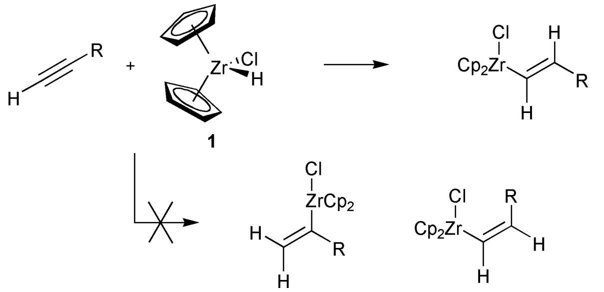
Conditions are reported for the facile, one-pot synthesis of α,β-unsaturated ketones *via* the palladium-catalysed cross-coupling of acyl chlorides with hydrozirconated acetylenes, and its use in the 2-step synthesis of D-5-*O*-benzyl deoxyxylulose.

The oxidative addition of palladium(0) complexes and acyl chlorides leads to the formation of acyl palladium chloride species.[1] These have been crystallised for X-ray structure elucidation,[2] but have found limited use in catalytic cross-coupling reactions. However, we,[3] and others,[4–7] have recently shown that acyl palladium complexes can be useful synthetic tools. For example, we have recently shown that acyl chlorides can be coupled with terminal acetylenes, in a palladium-dependent reaction, to form acetylenic ketones in a single step.[3]

Cross-coupling reactions using acyl chlorides provide useful products which are difficult to form by more traditional methods. For example, addition of classical nucleophiles such as Grignard or Reformatsky reagents to acyl chlorides usually leads to multiple additions. Cross-coupling reactions involving acyl chlorides, however, can be difficult to perform because of their incompatibility with base. This is especially relevant where the nucleophilic component is generated in a base-dependent reaction. We have encountered this drawback in modified Sonogashira reactions using acyl chloride substrates, and have previously reported conditions for improving yields through reducing the equivalents of triethylamine to a stoichiometric level.[3]

Compatibility of cross-coupling reactions toward acyl chloride electrophiles would be significantly improved if the nucleophilic component was generated by a base-free technique. Reductive hydrometallation is one such technique, and when applied to acetylenes generates nucleophilic vinyl–metal complexes. Of the hydrometallation techniques available, hydrozirconation using Schwartz reagent **1** (zirconocene chloride hydride) is reported to be the most chemo-, stereo- and regio-selective (Scheme 1).[8]

Vinyl zirconocene species have previously been reported as nucleophiles in cross-coupling reactions. For example, Negishi has demonstrated that vinyl zirconocene reagents react with aryl and vinyl halide electrophiles under palladium or nickel catalysis.[9,10] Direct cross-coupling is possible when using relatively less hindered vinyl groups. However, more hindered substrates react in low yield. Negishi showed that low yields can be overcome through transmetallation of the hindered vinyl zirconocene to zinc. The reaction then proceeds in high yield.[11]



Scheme 1 Regio- and stereo-selectivity observed in hydrozirconation.

The use of acyl halides in reactions with zirconium reagents has received less attention. It is known that catalysis is not required for the reaction of *alkyl* zirconocene complexes with acyl chlorides as long as steric bulk is minimal. Vinyl zirconocene complexes, however, fail to react under these conditions.[12] Wipf has shown that CuI·SMe$_2$ catalysis can improve the yield of products formed by the reaction of alkyl zirconium species with acyl chlorides. Wipf, and more recently Huang, have also reported the application of this catalyst to the reaction of vinyl zirconocenes with acyl chlorides, however few examples have been explored.[13] Both Negishi[10] and Lipshutz[14] have reported the transmetallation of vinyl zirconium species to aluminium, prior to coupling to acyl chlorides, but the reaction of vinyl zirconium reagents with acyl palladium reagents has not been reported.

We investigated the possibility of reacting vinyl zirconium species with acyl palladium species under catalytic conditions. An initial reaction was conducted by first generating the vinyl zirconocene complex **2**,[9] and then adding *p*-nitrobenzoyl chloride and 5 mol% Pd(PPh$_3$)$_2$Cl$_2$ (Scheme 2). The reaction yielded the desired product **3**, which was isolated as a single isomer in 79% yield. A control reaction lacking Pd(PPh$_3$)$_2$Cl$_2$ yielded no product, supporting our hypothesis that acyl palladium species are key intermediates.

Two byproducts were observed (Scheme 2). The first of these, diene **4**, presumably occurs as a byproduct of activation of the Pd(PPh$_3$)$_2$Cl$_2$ precatalyst. The palladium chloride ligands probably transmetallate with two equivalents of the vinyl zirconocene, and reductive elimination would then yield **4** and the active catalyst, Pd^0(PPh$_3$)$_2$ (Scheme 3). An additional 10 mol% of acetylene and Schwartz reagent were used in further reactions to compensate for this loss. The second byproduct **5** is the result of addition of vinyl zirconocene to the target enone. Formation of **5** reduced the overall reaction yield but not by a significant amount.

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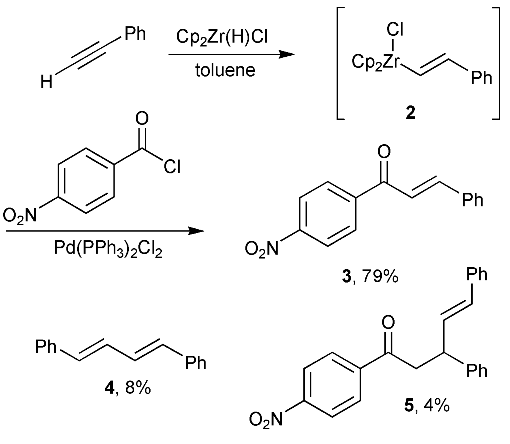
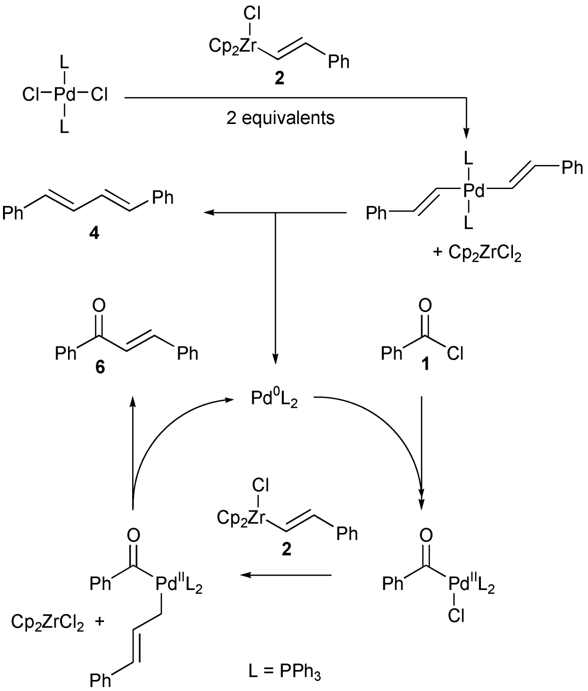
† Electronic supplementary information (ESI) available: Experimental procedures, data for all synthetic compounds, and crystal structure data for compound **22**. See DOI: 10.1039/b616582f

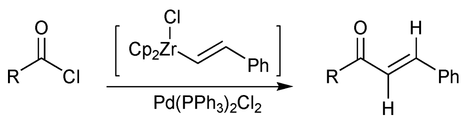


Scheme 2 Reaction between acyl chloride and vinyl zirconocene.



Scheme 3 Proposed activation of the precatalyst and catalytic cycle.

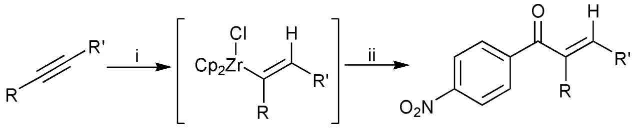
Table 1 Coupling reactions of phenylacetylene



Entry	R′	Product	Conditions[a]	Yield (%)[b]
1	*p*-NO_2Ph	**3**	a	79
2	Ph	**6**	a	79
3	*p*-BrPh	**7**	a	75
4	*p*-MeOPh	**8**	a	73
5	Cyclohexyl	**9**	a	91
6	^{t}Bu	**10**	b	90
7	^{n}Pr	**11**	a	88
8	Me	**12**	a	67

[a] *Reagents and conditions*: (a) i. phenylacetylene, zirconocene hydride chloride, toluene, 1 h, 40 °C; ii. 5 mol% $Pd(PPh_3)_2Cl_2$, acyl chloride, 3 h, r.t.; (b) same as (a), but with stage ii being conducted for 24 h at r.t. [b] Isolated purified yield.

Table 2 Coupling reactions of *p*-nitrobenzoyl chloride



Entry	R	R′	Product	Conditions[a]	Yield (%)[b]
1	H	$(CH_2)_3Me$	**13**	a	89
2	H	Cyclohexyl	**14**	a	71
3	H	^{t}Bu	**15**	a	14
4	H	^{t}Bu	**15**	b	63
5	H	$SiMe_3$	**16**	a	43
6	H	Bn	**17**	a	79
7	H	CH_2OBn	**18**	a	65
8	H	CH_2OAc	**19**	a	27
9	H	Ac	**20**	a	0
10	H	$CH_2N(Me)_2$	**21**	a	0
11	Et	Et	**22**	a	73
12	Me	^{n}Pr	**23**	a	40
13	Me	^{n}Pr	**23**	c	88
14	Me	Ph	**24**	c	16

[a] *Reagents and conditions*: (a) i. acetylene, zirconocene hydride chloride, toluene, 1 h, 40 °C; ii. 5 mol% $Pd(PPh_3)_2Cl_2$, *p*-nitrobenzoyl chloride, 3 h, r.t.; (b) same as (a), but using 15 mol% $Pd(PPh_3)_2Cl_2$; (c) same as (a), but with stage ii being conducted for 24 h at 40 °C. [b] Isolated purified yield.

Yields of the bis-addition product were reduced further in cases where the substrate lacked a *p*-nitro substituent.

The observation that no reaction occurs between the vinyl zirconium species and the acyl chlorides in the absence of palladium suggests that the reaction proceeds by the generally accepted catalytic mechanism of oxidative addition, transmetallation, and reductive elimination (Scheme 3). The stereochemistry achieved in the initial hydrozirconation of the acetylene appears to be carried through the catalytic cycle.

The reaction conditions were then applied to a wider range of starting materials (Table 1 and Table 2). Typical reaction conditions employed were addition of Schwartz reagent (1.12 eq.) to the acetylene (1.10 eq.) in anhydrous toluene, under nitrogen and protected from light. The mixture was warmed to 40 °C with stirring for 1 h. The reaction was cooled to room temperature, and then acyl chloride (1.0 eq.) and $Pd(PPh_3)_2Cl_2$ (5 mol%) were added. Completion of the reaction was often achieved within 3 h (TLC, ^{1}H NMR). The use of more hindered reagents required heating or extended reaction times. The completion of reaction was often, but not always, marked by the precipitation of zirconocene dichloride.

Substituted benzoyl chlorides (Table 1, entries 2–4), and alkanoyl chlorides (Table 1, entries 5–8) were successfully used as the electrophilic component. *p*-Bromobenzoyl chloride (Table 1, entry 3) reacted in good yield without any evidence of the aryl bromide taking part in cross-coupling. No significant difference was observed between strongly electron-donating (Table 1, entry 4) or electron-withdrawing (Table 1, entry 1) substituents on the benzoyl chloride in terms of yield or required reaction conditions.

The range of acetylenes tested included both terminal (Table 2, entries 1–10) and internal examples (Table 2, entries 11–14).

The linear aliphatic acetylene (Table 2, entry 1) and cyclohexyl acetylene (Table 2, entry 2) reacted in high yield under standard reaction conditions; however, the branched *tert*-butyl acetylene (Table 2, entry 3) reacted in low yield unless the catalyst loading was increased to 15 mol%. TMS acetylene (Table 2, entry 5) also reacted in lower yield.

The reaction of the benzyl ether (Table 2, entry 7) proceeded in high yield, but alternative oxygen functionalities reacted in lower yields. For example, reaction of the ester (Table 2, entry 8) gave a low yield, and reaction of the ketone (Table 2, entry 9) failed entirely. Reaction of the tertiary amine (Table 2, entry 10) also failed, which may indicate an incompatibility with base.

The reaction of 3-hexyne (Table 2, entry 11) gave the expected target material in high yield. However, the reaction of 2-hexyne proceeded in low yield, but allowing the second stage of the reaction to stir for a period of 24 h at 40 °C improved the yield significantly (Table 2, entry 13). Unfortunately, extended reaction times did not improve the yield of the phenyl methyl acetylene reaction (Table 2, entry 14).

Negishi observed that although hindered vinyl zirconocenes could be formed by the reaction of Schwartz reagent with substituted acetylenes, they appeared not to undergo transmetallation to the palladium(II) intermediates derived from aryl halides.[9] For example, the reaction of the vinyl zirconocene derived from 3-hexyne, in a palladium-catalysed cross-coupling reaction with phenyl iodide, did not proceed until a stoichiometric zinc species was introduced. This contrasts with our results, where the reaction of the vinyl zirconocene derived from 3-hexyne with the *p*-nitrobenzoyl chloride (Table 2, entry 11) proceeds in high yield without the requirement for a zinc mediator.

Analysis of the enone products from all reactions described in Tables 1 and 2 showed that only single isomers were obtained. ^{1}H-NMR confirmed the expected regiochemistry, and NOE studies suggested the correct stereochemistry. The stereochemistry of enone **22** was confirmed by X-ray crystallography (Fig. 1).

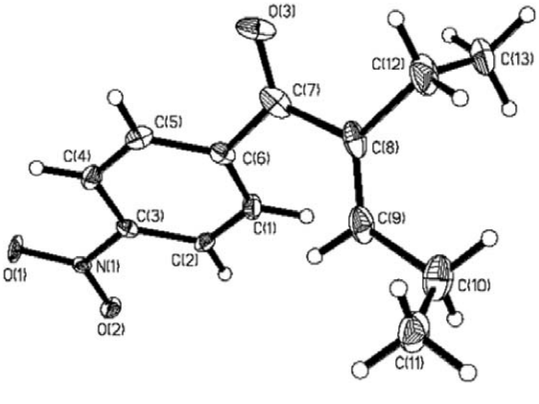
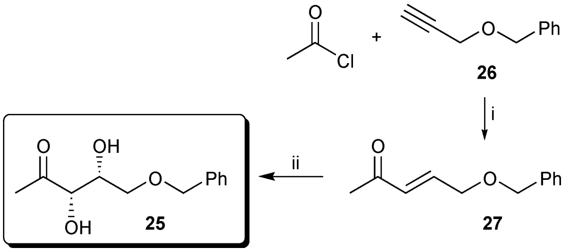


Fig. 1 X-Ray structure of enone **22** (ORTEP probability 50%).[15]

The ability to couple simple commercially available precursors, to form useful synthetic intermediates that are difficult to synthesise by other methods, is a key advantage of the reaction. We applied the reaction to the 2-step synthesis of protected deoxyxylulose **25**. Deoxyxylulose (DX), and its 5-*O*-phosphate (DXP), have formed the target for several syntheses because of the central position of DXP in the non-mevalonate biosynthetic pathway to terpenes and because of DXP's role as a biological precursor of pyridoxal phosphate and thiamine pyrophosphate.[16] For example, Welzel and co-workers have described a 5-step synthesis of **25** from ethyl bromoacetate,[17] while Fechter and co-workers have described an alternative 5-step synthesis from acrolein.[18] We recently described a 4-step sequence to the related protected DXP.[19] An important feature of all these routes is their ability to incorporate isotopic labels at strategic positions.

We reacted propargyl benzyl ether **26** with Schwartz reagent, and the reaction mixture was then treated with acetyl chloride and $Pd(PPh_3)_2Cl_2$ to yield the expected unsaturated ketone **27** in 72% yield. The olefin **27** was treated with stoichiometric OsO_4 in the presence of $(DHQD)_2PHAL$ to afford the *syn*-diol **25** in 59% yield and 93% ee (Scheme 4). These reactions are eminently suitable for the incorporation of isotopic labels. For example, acetyl chloride can be synthesised from acetic acid, which is available with all combinations of ^{13}C and ^{2}H labels. Propargyl benzyl ether can be simply deuterated at the acetylenic position by base treatment followed by D_2O quench, and deuterium could also be incorporated stereospecifically at C-4 of **25** by the use of deuterated Schwartz reagent. These reactions are currently underway in our laboratories, and the use of isotopically labelled deoxyxylulose as a probe to investigate the mechanism of non-mevalonate pathway enzymes will be reported in due course.



Scheme 4 Synthesis of D-5-*O*-benzyl deoxyxylulose. *Reagents and conditions*: i) Schwartz reagent, toluene, then acetyl chloride, $Pd(PPh_3)_2Cl_2$; ii) OsO_4, CH_2Cl_2, $(DHQD)_2PHAL$, then MeOH, HCl.

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15 Crystal structure data for compound **22**. $C_{13}H_{15}NO_3$, $M = 233.26$, triclinic, $a = 8.2761(17)$, $b = 10.042(2)$, $c = 15.189(3)$ Å, $\alpha = 74.44(3)$, $\beta = 81.70(3)$, $\gamma = 82.47(3)^\circ$, $U = 1197.7(5)$ Å^3, $T = 100(2)$ K, space group $P\bar{1}$, $Z = 4$, $\mu(\text{Mo-K}\alpha) = 0.092\ \text{mm}^{-1}$, 13 744 reflections measured, 5466 unique ($R_{\text{int}} = 0.0676$) which were used in all calculations. The final R_1 and wR_2 were 0.1222 and 0.2105 ($I > 2\sigma I$). CCDC reference number 622616. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b616582f.

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