Ketone Enolates as Nucleophiles in Palladium-catalysed Allylic Alkylation

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Summary Lithium enolates from pentan-3-one, cyclohexanone, acetophenone, and mesityl oxide react with some representative (acyclic and cyclic) allylic acetates in a palladium-catalysed alkylation in good yields and under mild conditions; the substitution is shown to proceed with retention of configuration.

THE palladium-catalysed alkylation reaction, involving stabilised anions (from conjugate acids of pK_a *ca.* 10—20) has been widely developed.[1] Among the conjugated bases from organic acids of $pK_a > 20$, the enolate of acetophenone was the only anion reported to alkylate allyl acetate, successfully, although in an uncontrolled way (mono- and di-alkylation).[2]

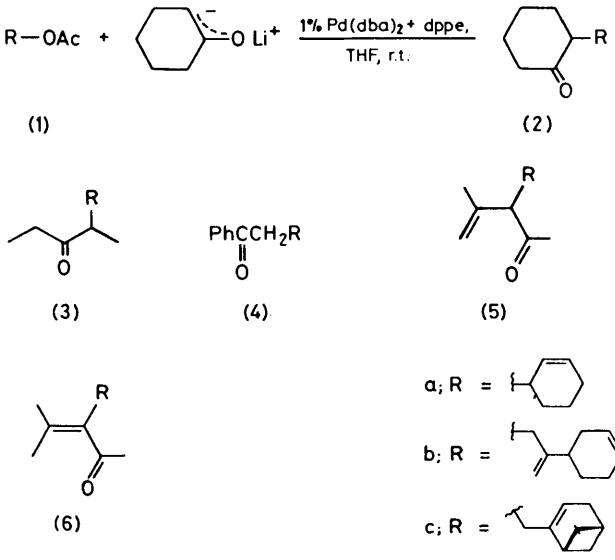
We have previously described the use of a catalytic system [1% bis(dibenzylideneacetonato)palladium + 1,2-bis(diphenylphosphino)ethane, $Pd(dba)_2$–dppe] which allows the alkylation of allylic acetates by stabilised malonate and cyclopentadienide anions under mild conditions (room temperature) and in good yields.[3] We now report that ketone enolates are efficient nucleophiles under the reaction conditions described;[3] lithium enolates from pentan-3-one, cyclohexanone, acetophenone, and mesityl oxide react with many allylic acetates in a reaction catalysed by $Pd(dba)_2$–dppe in fair to good yields.

TABLE. Reaction of lithium ketone enolates with allylic acetates.

Ketone	Allylic substrate	Product	Isolated yield/%[a]	B.p./°C (p/mmHg)[b]
Cyclohexanone	(**1a**)	(**2a**)	55	80 (0·3)
"	(**1c**)	(**2c**)	48	90 (0·2)
"	(**1c**)[c]	(**2c**)	64	"
Pentan-3-one	(**1a**)	(**3a**)	83	70 (0·1)
"	(**1b**)	(**3b**)	63	130 (0·1)
Acetophenone	(**1a**)	(**4a**)	57	120 (0·1)
Mesityl oxide	(**1a**)	(**5a**)	47	70 (0·2)
"	(**1b**)	(**6b**)	41	120 (0·2)

[a] Satisfactory elemental analyses and ^1H n.m.r. spectra were obtained for all compounds. [b] Pot-temperature of the kugelrohr apparatus. [c] As the pivalate.

In a typical procedure cyclohex-2-enyl acetate (**1a**) (3·6 mmol), $Pd(dba)_2$ (36 μmol) and dppe (36 μmol) in 3 ml of dry tetrahydrofuran (THF) under N_2 were stirred for 10 min. This solution was injected into a solution of 4·0 mmol of the lithium salt of cyclohexanone† in 10 ml of THF at −78 °C and stirred for 48 h at room temperature. Conventional work-up left an oil, kugelrohr distillation of which gave 352 mg (55%) of the pure (g.l.c.) substitution product (**2a**), b.p. 106 °C at 0·3 mmHg (Table). The reaction is regioselective with myrtenyl acetate (**1c**), giving the less substituted product.



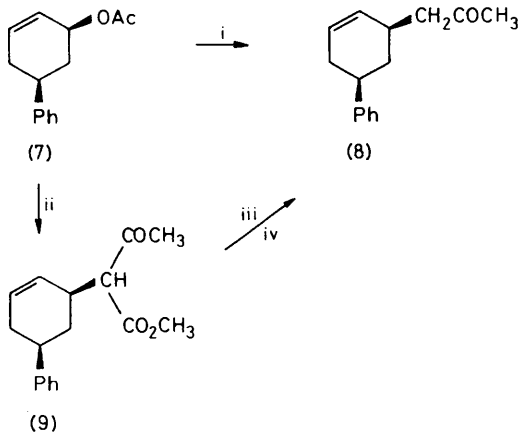
The dienolate from mesityl oxide is exclusively alkylated at the α-position to produce, depending on the starting acetate (**1a**) or (**1b**), the β,γ-olefinic ketone (**5a**), or the isomerised α,β-unsaturated ketone (**6b**), respectively.

Among the side-products was the alcohol ROH, arising from nucleophilic attack of the enolate on the acetate group

† Generated by addition of the ketone to one equivalent of lithium di-isopropylamide (LDA) in THF at −78 °C.

of (**1**). The use of allylic pivalates in some cases reduced the extent of the side-reaction.

The stereochemistry of the reaction of the lithium enolate of acetone with 5-phenylcyclohex-2-enyl acetate (**7**)‡ has been determined by comparison of the product with that obtained through the Pd-catalysed alkylation of (**7**) with the sodium salt of methyl acetoacetate isolated after saponification and decarboxylation of the intermediate (**9**) (Scheme). Both products are identical (t.l.c., g.l.c., n.m.r.). On the basis of the known stereochemistry of the Pd-catalysed alkylation of allylic acetates by stabilised anions,[4] the stereochemistry of (**8**) is *cis*. The overall retention of configuration shown for the substitution suggests that the enolate attacks the π-allylic ligand *trans* to the Pd in the complex, as has been shown previously for enol stannanes.[2]



SCHEME. *Reagents and conditions:* i, $Li^+ {}^-CH_2C(:O)Me$, $Pd(dba)_2$, dppe, THF, −78 to 20 °C; ii, $Na^+ MeC(:O)^-CHCO_2Me$, $Pd(dba)_2$, dppe, THF, room temp.; iii, KOH, MeOH; iv, H^+, $-CO_2$.

The reactivity of ketone enolates as nucleophiles in the palladium-catalysed alkylation to give α-substituted ketones in good, non-optimised yields widens the scope of this reaction, and is under further investigation for use in natural product synthesis.

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‡ Compound (**7**) was obtained by acetylation of the corresponding alcohol, prepared according to E. Dunkelblum, R. Levene, and J. Klein, *Tetrahedron*, 1972, **28**, 1009.

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