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Palladium-Catalysed Cyclisation and Functionalisation of 1,1-Diacetoxy-2,7-diene and 1,1-Diacetoxy-2-en-7-yne Derivatives

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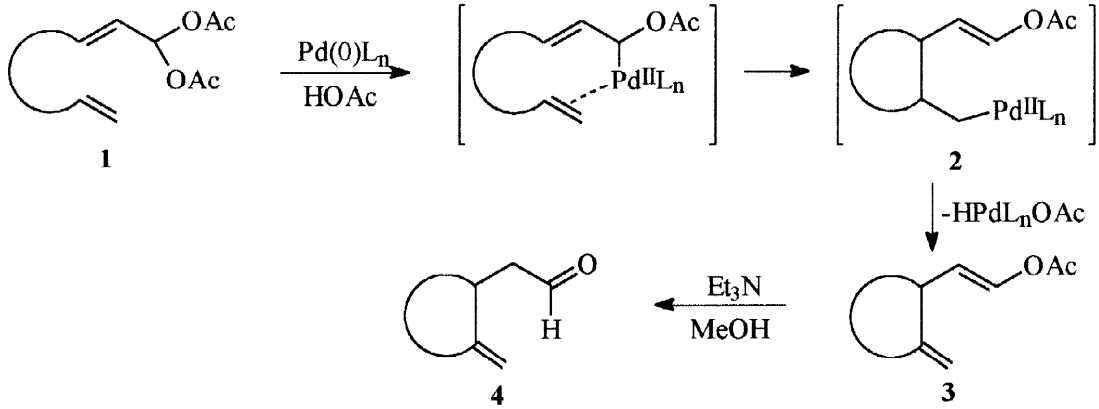
Abstract: The palladium-catalysed 'metallo-ene' cyclisation, cyclisation/carbonylation, -vinylstannane coupling, and Pd(II)-catalysed chloropalladation/carbocyclisation of 1,1-diacetoxy-2,7-diene and 1,1-diacetoxy-2-en-7-yne derivatives are described. The cyclic enolacetate products could readily be converted into the corresponding aldehydes that are amenable to further transformation.

The palladium(0)-catalysed 'metallo-ene' cyclisation of acetoxy-2,7-dienes and -2-en-7-ynes, pioneered by Oppolzer and co-workers,[1] has proven to be a synthetically powerful means of producing a variety of functionalised five-membered ring systems. In an attempt to introduce differentiated additional functionality into the cyclised product, we explored the feasibility of allylic *geminal*-diacetate starting materials for these 'metallo-ene' reactions. Assuming a similar reaction mechanism (Scheme 1) for the cyclisation of 1,1-diacetoxy-2,7-dienes (**1**), the products (**3**) would, in addition to an exocyclic methylene, contain an enolacetate moiety. The latter is readily converted into the corresponding aldehyde (**4**) on treatment with mild base.



1 2 3 4

Scheme 1

The allylic *gem* diacetate starting materials were readily prepared (Scheme 2) from the corresponding monoacetates[1,2] (**5**) by deacetylation, reaction with the Dess-Martin periodinane (DMP) oxidising agent[3] to furnish the allyl aldehyde (**6**), and diacetate (**7**) formation on treatment with iodine (catalytic) in acetic anhydride.[4]

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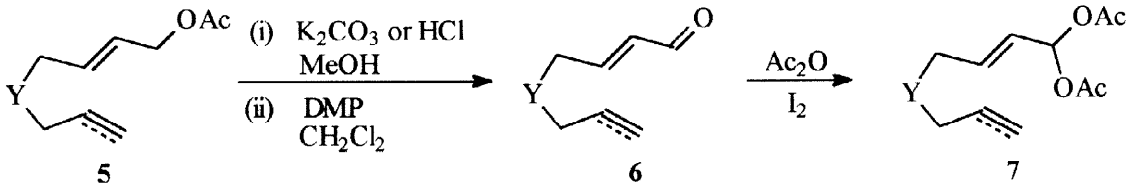
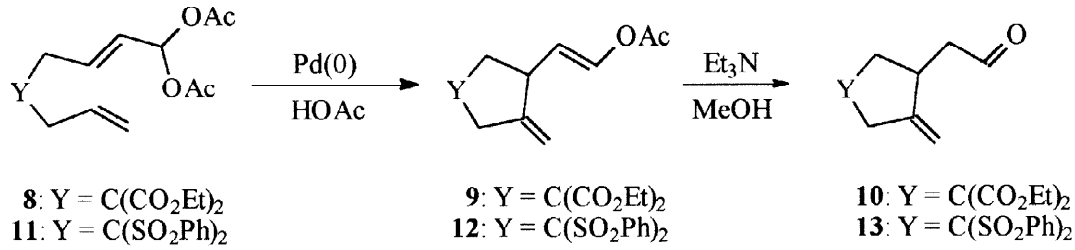


Scheme 2

'Metallo-ene' cyclisation of the *gem* diacetates **8** and **11** in acetic acid[5] in the presence of a Pd(0) catalyst (0.1 mol equiv) at 75-80 °C proceeded at a faster rate than the reactions of the corresponding monoacetates (**5**) to afford the cyclic enolacetate products[6] **9** and **12**, respectively (Scheme 3). These were quantitatively converted into the corresponding aldehydes **10** and **13**, respectively, upon treatment with triethylamine in methanol at room temperature for 10 minutes.



Scheme 3

A variety of palladium(0) catalysts were exploited (Table 1). The combination of $Pd_2(dba)_3.CHCl_3$/tri-*o*-tolylphosphine (TOTP) was superior to the other catalysts with regard to reaction rates and product yields. $Pd_2(dba)_3.CHCl_3$/1,3-bis(diphenylphosphino)propane was ineffective and no conversion of **8** into **9** was observed after 6 h in acetic acid at 80 °C.

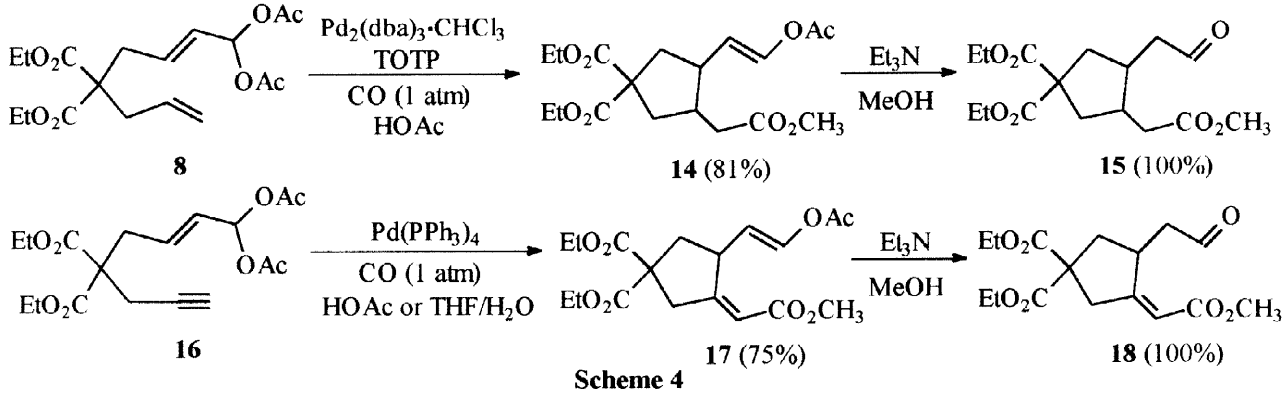
Table 1. Transformation of **8** → **9**[a]

Entry	Catalyst	Time (h)	Yield[b] (%)
1	$Pd(PPh_3)_4$	4	80
2	$Pd_2(dba)_3.CHCl_3$/tri-*o*-tolylphosphine	0.1	98
3	$Pd(OAc)_2$/triispropylphosphite	3	91
4	$Pd(OAc)_2$/tributylphosphine	3	90
5	$Pd_2(dba)_3.CHCl_3$/1,3-bis(diphenylphosphino)propane	6	0

[a]Substrate (1 mol equiv), palladium (0.1 mol equiv) and ligand (0.4-0.6 mol equiv) stirred in acetic acid at 80 °C. [b]Isolated yield.

When these reactions were conducted in the presence of carbon monoxide the intermediate cyclised σ-alkylpalladium intermediate (**2**) was intercepted by CO to form the corresponding σ-acylpalladium species that was converted into the corresponding cyclic carboxylic acid. Again, the use of a protic solvent was essential for the transformation of **8** and **16** into **14** and **17**, respectively (Scheme 4), isolated as their methyl carboxylate

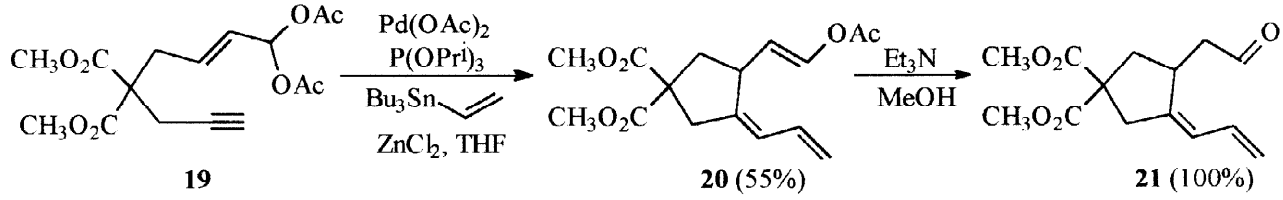
derivatives[7] after methylation with an etherial solution of diazomethane. The aldehydes **15** and **18** were obtained in quantitative yields from **14** and **17**, respectively, by treatment with basic methanol.



Scheme 4

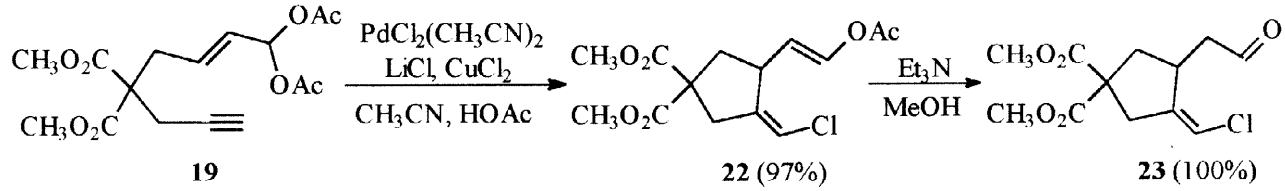
The cyclisation/carbonylation of **16** proceeded equally well when it was carried out in aqueous THF.[8]

In another type of bimolecular C-C coupling process, the intermediate σ-alkylpalladium intermediate (**2**) was intercepted by vinyltributyltin[2] in a transmetallation step (Scheme 5). Reaction of *gem* diacetate **19** with vinyltributyltin (2 mol equiv) and $ZnCl_2$ (2 mol equiv) in the presence of $Pd(OAc)_2$ (0.1 mol equiv) and triisopropylphosphite (0.6 mol equiv) in THF under reflux for 10 minutes furnished the cyclic triene **20** in fair yield.



Scheme 5

Exposure[9] of *gem* diacetate **19** (Scheme 6) to Wacker-like conditions, i.e. $PdCl_2(CH_3CN)_2$ (0.1 mol equiv), $CuCl_2$ (5 mol equiv) and a large excess of LiCl in acetic acid/acetonitrile at room temperature for 30 minutes effected the smooth conversion into the chloroproduct **22** (97% isolated yield). A probable reaction



Scheme 6

mechanism[10] involves coordination of the substrate to palladium/copper to form a metal-alkyne complex, chloropalladation of the alkyne moiety followed by intramolecular carbopalladation and termination by the reductive elimination of a palladium acetate species.

Acknowledgements The authors thank AECI (Ltd) and the Rand Afrikaans University for financial support.

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6. Spectroscopic and analytical data for **9** (colourless syrup); NMR: δ_H (300 MHz; $CDCl_3$) 1.21 (t, 3H, *J* 7.1 Hz), 1.22 (t, 3H, *J* 7.1 Hz), 1.94 (dd, 1H, *J* 13.0 Hz, *J* 11.0 Hz), 2.09 (s, 3H), 2.55 (dd, 1H, *J* 13.0 Hz, *J* 1.2 Hz), 2.90 (dddd, 1H, *J* 17.1Hz, *J*, *J*, *J* 2.1 Hz), 3.06 (dm, 1H, *J* 17.1 Hz), 3.04-3.20 (m, 1H), 4.15 (q, 2H, *J* 7.1 Hz), 4.17 (q, 2H, *J* 7.1 Hz), 4.79 (ddd, 1H, *J*, *J*, *J* 2.1 Hz), 5.24 (dd, 1H, *J* 12.4 Hz, *J* 9.2 Hz), 7.11 (dd, 1H, *J* 12.4 Hz, *J* 0.7 Hz); δ_C (75 MHz; $CDCl_3$) 13.98, 20.62, 39.99, 40.67, 41.87, 58.50, 61.53, 61.57, 108.26, 115.54, 136.59, 150.47, 167.99, 171.37, 171.53; *m/z* (%): 310 (M^+, 8), 268 (84), 223 (66), 195 (53), 194 (94); HRMS calcd for $C_{16}H_{22}O_6$: 310.1416 (M^+), found 310.1411.
7. Spectroscopic and analytical data for **14** (colourless syrup); NMR: δ_H (300 MHz; $CDCl_3$) 1.23 (t, 6H, *J* 7.2 Hz), 1.89-2.21 (m, 5H), 2.10 (s, 3H), 2.42-2.50 (m, 2H), 2.60 (dd, 1H, *J* 13.5 Hz, *J* 6.9 Hz), 3.63 (s, 3H), 4.17 (2q, 4H, *J* 7.2 Hz), 5.22 (dd, 1H, *J* 12.6 Hz, *J* 9.3 Hz), 7.10 (d, 1H, *J* 12.6 Hz); δ_C (75 MHz; $CDCl_3$) 13.91, 20.55, 37.34, 39.51, 40.57, 41.75, 44.10, 51.51, 58.30, 61.53, 61.57, 115.39, 136.43, 168.05, 172.16, 172.35, 172.95; *m/z* (%): 370 (M^+, 2), 297 (31), 255 (39), 237 (40), 181 (34); HRMS calcd for $C_{18}H_{26}O_8$: 370.1628 (M^+), found 370.1632.
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