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On the use of tandem allylic acetate isomerisation and ring-closing metathesis with palladium(0) phosphine complexes and ruthenium benzylidenes as orthogonal catalysts

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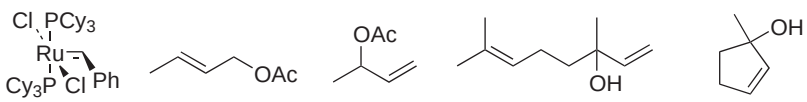
Abstract—Attempted tandem allylic acetate isomerisation and ring-closing metathesis using combinations of palladium(0)/Grubbs' catalyst/PPh_3 led to either allylic isomerisation or ring-closing metathesis but not both in tandem. The effect was traced to deactivation of Grubbs' catalyst by added PPh_3 and poisoning of the Pd(0) by the necessarily released PCy_3 (Cy = cyclohexyl) from Grubbs' catalyst. Successful tandem isomerisation/ring-closing metathesis was achieved by the use of palladium(0)/PPh_3 systems in conjunction with a PCy_3 free olefin metathesis catalyst. © 2001 Elsevier Science Ltd. All rights reserved.

Ring-closing alkene metathesis using ruthenium benzylidene pre-catalysts[1] and palladium(0) catalysed methods, exemplified by allylic acetate isomerisation,[2] have developed into powerful synthetic tools in organic chemistry. Since ring-closing metathesis typically greatly increases the molecular complexity of the product, and allylic isomerisations proceed with high atom efficiency,[3] it is not inappropriate to ask if the two catalyst systems can be combined, without detriment, to provide high-value products in a single operation. We have therefore initiated a research programme aimed at the tandem use of ruthenium benzylidenes and palladium(0) phosphine complexes. In this context it is germane to note that Grigg has reported a successful one-pot Heck coupling/ring-closing metathesis (and vice versa) using Pd(0)/Grubbs' catalyst combinations.[4,5] In this Letter, we report on the severe negative consequences of attempted combination of phosphine-bearing palladium(0) and Grubbs' catalyst **1**[6] for tandem allylic acetate isomerisation/ring-closing metathesis and report a modified palladium–ruthenium system which partially overcomes these problems.

At the outset we were hoping for a general synergistic interaction between the palladium and ruthenium centres. Tricyclohexylphosphine dissociation from the ruthenium centre is necessary to generate the de facto active catalyst,[7] and thus any free Pd(0) should facilitate this, simultaneously activating itself for allylic acetate isomerisation. In this respect we were aware that any excess phosphine in the system would severely retard ring-closing metathesis[8] and it was therefore clear that the nature and quantity of any added phosphine would be a critical factor that would require investigation.

For this investigation we chose to separate the putative allylic acetate and ring closing metathesis functionalities into separate substrates such that we could study the effect of added palladium(0) phosphine complexes on the ring-closing capability of Grubbs' catalyst, and the effect of added Grubbs' catalyst on the ability of Pd(0) phosphine complexes to effect allylic acetate isomerisation. 1-But-2-enyl acetate **2** and 2-but-3-enyl acetate **3**



1 **2** **3** **4** **5**

Keywords: Grubbs' catalyst; palladium(0); tricyclohexylphosphine; metathesis; allylic isomerisation.

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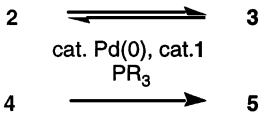
were selected as the corresponding pair of allylic acetate isomerisation substrates and linalool **4** as the ring-closing metathesis substrate.‡

Treatment of either of the pure acetates **2** or **3** with 5 mol% $Pd(PPh_3)_4$ in $CDCl_3$ led to an equilibrium ratio (as determined by ^1H NMR) of 58:42, in favour of the linear isomer, within 1 h. $Pd_2(dba)_3$.dba was selected as a phosphine-free palladium(0) source to study the effect of added triphenylphosphine on the allylic acetate isomerisation: acetate **2** was treated with 5 mol% $Pd_2(dba)_3$·dba (i.e. 10 mol% Pd atom) in the presence of increasing quantities of triphenylphosphine (Table 1, entries 1–6). Inspection of the table reveals that efficient isomerisation (i.e. essentially reaching equilibrium) only occurs once 20 mol% of PPh_3 has been added (i.e. 2:1 P:Pd) (entry 3) and that increasing quantities of triphenylphosphine does not have a deleterious effect on the isomerisation (entries 4–6).

Grubbs' catalyst **1** (5 mol%) quantitatively converts linalool into 1-methylcyclopent-2-enol **5**[9] in $CDCl_3$ or CH_2Cl_2 in 1 h (Table 1, entry 7). In line with the observation of Grubbs,[8] attempted ring-closure of linalool **4** in the presence of just 5 mol% PPh_3 severely retards the rate of ring-closing metathesis (entry 8) and at 10 mol% PPh_3 loading no ring-closed adduct was observed (entry 9). Encouragingly, $Pd_2(dba)_3$.dba alone

Table 1. Effect of added phosphine on the tandem ring-closing metathesis of **4** into **5** and/or allylic isomerisation of **2** into **3**



Entry[a]	Mol% **2**	Mol% Pd(0)	Mol% **4**	Mol% **1**	Mol% PR_3	**2**:**3**[b]	%**5**[b]
1	100	5[c]	–	–	0[e]	100:0	–
2	100	5[c]	–	–	10[e]	95:5	–
3	100	5[c]	–	–	20[e]	60:40	–
4	100	5[c]	–	–	30[e]	59:41	–
5	100	5[c]	–	–	40[e]	59:41	–
6	100	5[c]	–	–	200[e]	61:39	–
7	–	–	100	5	–	–	100
8	–	–	100	5	5[e]	–	14
9	–	–	100	5	10	–	0
10	–	5[c]	100	5	–	–	100
11	–	5[c]	100	5	5[e]	–	100
12	–	5[c]	100	5	10[e]	–	100
13	–	5[c]	100	5	15[e]	–	100
14	–	5[c]	100	5	20[e]	–	5
15	–	5[c]	100	5	40[e]	–	5
16	–	5[c]	100	5	80[e]	–	0
17	100	5[c]	–	5	–	100:0	–
18	100	5[c]	–	5	10[e]	94:6	–
19	100	5[c]	–	5	20[e]	70:30	–
20	100	5[c]	–	5	30[e]	75:25	–
21	100	5[c]	–	5	40[e]	80:20	–
22	100	5[c]	–	5	80[e]	72:28	–
23	100	5[c]	–	5	200[e]	65:35	–
24	100	5[c]	100	5	5[e]	100:0	80
25	100	5[c]	100	5	10[e]	99:1	40
26	100	5[c]	100	5	15[e]	94:6	0
27	100	5[c]	100	5	20[e]	90:10	0
28	100	5[c]	100	5	30[e]	88:12	0
29	100	5[c]	100	5	40[e]	84:16	0
30	100	5[c]	100	5	80[e]	77:23	0
31	100	5[c]	100	5	200[e]	68:32	0
32	100	5[d]	–	–	5[f]	59:41	–
33	100	5[d]	–	–	10[f]	98:2	–
34	100	5[d]	–	–	15[f]	100:0	–

[a] All runs perfomed in $CDCl_3$ (1 mL) at rt for 1 h using 0.24 mmol of substrate under N_2.
[b] As determined by ^1H NMR.
[c] $Pd_2(dba)_3$.dba.
[d] $Pd(PPh_3)_4$.
[e] R = Ph.
[f] R = Cy.

‡ All the compounds described in this letter are known and their spectral data matches that previously reported.

(5 mol% i.e. 1:2 Ru:Pd) does not prevent quantitative ring-closure (entry 10) and its presence allows the addition of up to 15 mol% PPh_3 before the Grubbs' catalyst is deactivated (entries 11–13). Grubbs has demonstrated the ability of Cu(I) salts to sequester phosphines[8] allowing metathesis to turn over in what would otherwise be prohibitively high phosphine concentrations. It is reasonable to assume, that in this system Pd(0) is playing a similar role. At higher PPh_3 loadings (entries 14–16) where presumably there is insufficient Pd(0) to sequester all the excess phosphine, ring-closing metathesis is completely inhibited.

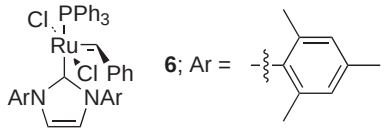
Isomerisation of acetate **2** in the presence of Grubbs' catalyst **1** with added triphenylphosphine was then examined. As previously observed at least two equivalents of PPh_3 per Pd was required to effect isomerisation (Table 1, entries 17–19). However, at this phosphine loading equilibrium is not reached within 1 h. Peculiarly, increasing quantities of added phosphine lead to less efficient isomerisation (entries 20–22) until the phosphine is in large excess where the equilibrium position of acetates **2**:**3** is approached within 1 h (entry 23).

Having shown that isomerisation can proceed in the presence of Grubbs' catalyst **1** (at high phosphine loadings), and that ring-closing metathesis occurs effectively in the presence of Pd(0) (albeit at relatively low phosphine levels) we sought to determine if a ring-closing metathesis and an allylic acetate isomerisation could be induced in the same vessel: a 1:1 mixture of diene **4** and acetate **2** were exposed to 5 mol% each of $Pd_2(dba)_3$·dba and Grubbs' catalyst **1** in the presence of increasing quantities of PPh_3. Unsurprisingly, ring-closing metathesis was successful at low loadings of added PPh_3 (Table 1, entries 24–25) but with markedly sharper inhibition. This effect is ascribed to the presence of acetate **2** where presumably palladium π-allyl formation is also occurring with the consequence that the Pd(0) centre is less able to sequester excess triphenylphosphine. Unfortunately, very little isomerisation was observed at these low phosphine loadings and large quantities of PPh_3 were required before rapid isomerisation occurred (entries 26–31).

The above results can be rationalised by noting that excess PPh_3 inhibits ring-closing metathesis, and by postulating that PCy_3 inhibits Pd(0) catalysed allylic acetate isomerisation. Thus, as one PCy_3 ligand necessarily dissociates from the ruthenium centre to generate the de facto active catalytic species[7] for metathesis it becomes available in solution to ligate Pd(0). This notion was confirmed by treating acetate **2** with 5 mol% $Pd(PPh_3)_4$ in the presence of added tricyclohexylphosphine (Table 1, entries 32–35). The isomerisation proceeded to the equilibrium position until 10 mol% PCy_3 had been added whereupon complete inhibition was observed. This result also suggests that PCy_3 has a greater affinity for Pd(0) than does PPh_3. Similarly, Grubbs' catalyst **1** can be prepared by quantitative displacement of PPh_3 from $Cl_2Ru(PPh_3)_2$=CHPh by PCy_3[6] demonstrating the relative affinities of the two phosphines for the ruthenium metal centre. This is quantified by the high pK_a value of the conjugate acid of PCy_3 ($pK_a = 9.70$) compared to that of PPh_3 ($pK_a = 2.73$). The other issue here is the relative preference for PCy_3 to ligate Pd(0) or to the ruthenium centre. On the basis of the attempted isomerisations in the presence of catalyst **1** (Table 1, entries 17–31) it would seem there is a preference for Pd(0). Accordingly, an explanation now exists for the counter-intuitive decrease in isomerisation of acetate **2** encountered at PPh_3 loadings between 20–80 mol% in the presence of Grubbs' catalyst **1** and for the poor rates of isomerisation in the attempted tandem one-pot ring-closing metathesis/allylic acetate isomerisation. Increasing the triphenylphosphine loading raises the effective concentration of PCy_3 in solution by competitive recombination with the ruthenium centre resulting in increased inhibition of isomerisation as the PCy_3 ligates Pd(0). This effect is negated when moving to 200 mol% PPh_3 as the relative concentration of PCy_3 diminishes.

The exact mechanism of allylic acetate isomerisation inhibition by PCy_3 is not known, but it is thought that a memory effect may be involved, where the acetate returns to its original position in the π-allyl complex.[10] The reasoning may be steric or electronic in origin but the large Tolman cone angle of PCy_3 ($\theta = 170°$) compared to PPh_3 ($\theta = 145°$)[11] cannot be ruled out as a major factor. In any event, it became apparent that for a successful tandem allylic acetate isomerisation/ring-closing metathesis Pd/Ru catalyst system the PCy_3 ligand should be excluded.

Our attention then turned to the recently described family of ruthenium catalysts incorporating *N*,*N*-di(2,4,6-trimethylphenyl)imidazol-2-ylidene ('IMes') ligands as phosphine mimics developed independently by Nolan,[12] Herrmann[13] and Grubbs.[14] A mixed PPh_3/IMes complex **6** had been reported by Nolan[12] and this seemed ideally suited to our purpose. In this complex it is the PPh_3 that dissociates from the ruthenium centre to initiate metathesis rather than the carbene fragment since the *N*-heterocyclic carbenes are stronger σ-donors and much less labile than phosphines.[12]



In the control experiment catalyst **6** (5 mol%) quantitatively converted linalool **4** into pentenol **5** at room temperature in $CDCl_3$ in 1 h. This catalyst was then employed in tandem with $Pd_2(dba)_3$·dba for the attempted isomerisation/ring-closing metathesis. It was found that an optimised mixture of 10 mol% **6**, 5 mol% $Pd_2(dba)_3$·dba and 20 mol% PPh_3 in $CDCl_3$ gave a 75:25 mixture of **2**:**3** and a 75% conversion of **4** into ring-closed adduct **5** in 1 h at room temperature. This result clearly demonstrates that excluding PCy_3 from the system allows both isomerisation and ring-closing to proceed in tandem. However, the equilibrium isomerisation position is not reached nor does ring-closing metathesis proceed quantitatively as it does in the sepa-

rate control experiments. Since the *N*-hererocyclic carbenes can be categorised as 'phosphine mimics'[15] it is not unreasonable to propose that the IMes ligand also inhibits the isomerisation process by ruthenium–palladium exchange. However, the success of this system over and above the use of catalyst **1** can be attributed to only slow IMes/PPh_3 exchange relative to PCy_3/PPh_3 exchange, respectively.

Application of this modified system to tandem allylic isomerisation and ring-closing metathesis in the same substrate will be reported in due course.

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