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In situ tandem allylic acetate isomerisation-ring closing metathesis: 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium benzylidenes and palladium(0)–phosphine combinations

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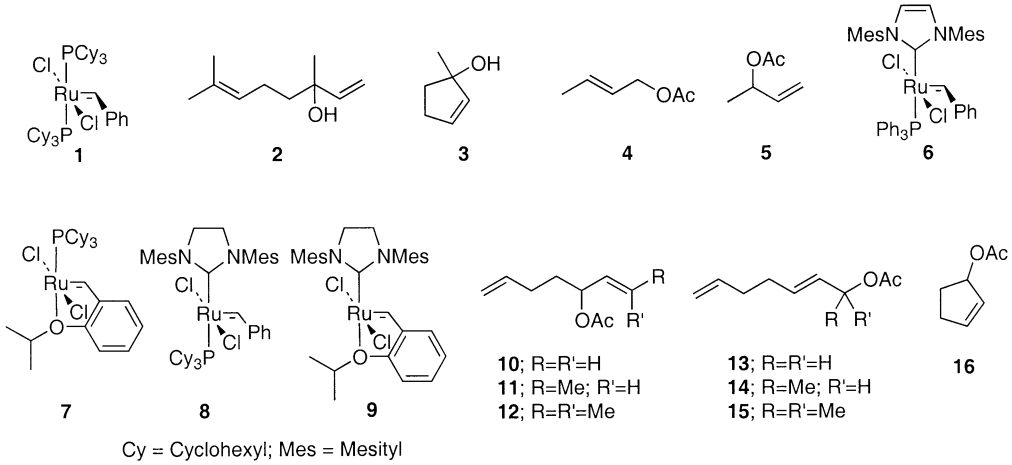
Abstract—The use of 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium benzylidenes as olefin metathesis pre-catalysts in conjunction with palladium(0)–phosphine combinations allows tandem in situ allylic acetate isomerisation–ring closing metathesis reactions to occur. The tandem reaction can either be performed on separate substrates in the same pot, or on substrates containing both allylic acetate and diene functionality. © 2002 Elsevier Science Ltd. All rights reserved.

Palladium(0) catalysed methods, exemplified by allylic acetate isomerisation,[1] and ring-closing metathesis using ruthenium benzylidene pre-catalysts[2] have developed into powerful synthetic tools in organic chemistry. We have recently reported on attempts to utilise bis(tricyclohexylphosphine)benzylidene ruthenium(II) dichloride (Grubbs' catalyst) **1**[3] and phosphine-modified palladium(0) as tandem catalysts for in situ allylic acetate isomerisation–ring closing metathesis.[4] Since allylic isomerisations proceed with high atom efficiency[5] and ring-closing metathesis typically greatly increases the molecular complexity of the product, 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. In the above study we chose to separate the putative allylic acetate and ring closing metathesis functionalities into separate substrates so that we could study the effect of added palladium(0) on the ring-closing capability, and the effect of added Grubbs' catalyst **1** on the ability of Pd(0) phosphine complexes to effect allylic isomerisation. In this context we explored the ring-closing metathesis of linalool **2** into pentenol **3**, and allylic acetate isomerisation of butenyl acetate **4** into **5**. Unfortunately, we found that the triphenylphosphine necessary (minimum 2 equiv./Pd atom) to activate palladium(0) for allylic isomerisation poisoned Grubbs' catalyst. Additionally it was found that the PCy_3 (Cy = cyclohexyl) that is necessarily liberated from Grubbs' catalyst in order to generate the de facto active 14e$^-$ ruthenium species[6] inhibited allylic isomerisation. Thus, while it was possible to catalyse



Cy = Cyclohexyl; Mes = Mesityl

Keywords: allylic isomerisation; palladium(0); ruthenium benzylidene; 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene; olefin metathesis.

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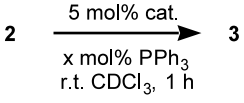
allylic acetate isomerisation of **4** into **5** (at moderate to high PPh_3 loadings) or to effect efficient ring-closing metathesis of **2** into **3** (at low PPh_3 loadings), it was not possible to do both using Grubbs' catalyst **1**/Pd(0) combinations. However, we were able to effect partially successful in situ tandem allylic acetate isomerisation (of **4**)–ring closing metathesis (of **2**) using the PCy_3-free catalyst **6** reported by Nolan.[7]

Based on these findings we have now examined a series of ruthenium catalysts with a view to identifying a phosphine-tolerant catalyst, which, ideally, is also PCy_3-free for in situ tandem allylic acetate isomerisation–ring closing metathesis. We selected ruthenium benzylidene complexes **7**–**9** as possible candidates. Specifically, we chose to study the Hoveyda-ligand modified Grubbs catalyst **7**[8] where the single PCy_3 ligand ostensibly remains bound during RCM turnover; the 'SIMes' catalyst **8**[9] reported by Grubbs where the *N*-heterocyclic carbene remains bound (but PCy_3 is released); and the Hoveyda-ligand modified SIMes ('HSIMes') catalyst **9**.[10] In this letter we report on the tolerance of catalysts **7**–**9** to added triphenylphosphine for the ring-closing metathesis of linalool (**2**→**3**); their competence for RCM of a series of acetoxydienes **10**–**12**; the relative effectiveness of these catalysts for in situ tandem allylic acetate isomerisation–ring closing metathesis using linalool **2** and butenyl acetate **4**; and their effectiveness for the in situ tandem allylic acetate isomerisation–ring closing metathesis of substrates **13**–**15** (via **10**–**12**) to **16** where the allylic acetate and olefin functionality are in the same substrate. The results show that the combination of the SIMes or HSIMes catalyst **8** or **9** and Pd(0)–PPh_3 combinations are effective for the in situ tandem allylic acetate isomerisation–ring closing metathesis reaction.

Catalysts **7**–**9** (5 mol%) were tested for their tolerance to added triphenylphosphine in the ring closing metathesis of diene **2** (Table 1). In our previous work,[4] Grubbs' catalyst **1** (5 mol%) had been shown to ring-close linalool **2** quantitatively to cyclopentene **3** at room temperature in 1 h, but to be shut down completely by the addition of just 10 mol% PPh_3. The Hoveyda modified catalyst **7** was found to be somewhat less active than Grubbs' catalyst **1** at room temperature and also sensitive to the addition of excess triphenylphosphine. Encouragingly, both the SIMes catalyst **8** and the HSIMes catalyst **9** were found to be much less sensitive to added triphenylphosphine. Even at 40 mol% of added PPh_3, HSIMes **9** was still moderately active (51% conversion) for the ring closing metathesis of linalool **2**. These results are in line with Grubbs' work, where it has been shown that phosphine re-binding to a SIMes-Ru 14e$^-$ centre is slow.[11,12]

Table 1. Effect of added PPh_3 on ring closing metathesis of linalool 2 using catalysts **1**, **7**–**9**[a]



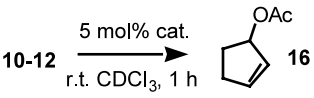
PPh_3 (mol%)	1	7	8	9
0	100	65	100	95
10	0	0	51	84
20	0	0	47	56
30	0	0	39	52
40	0	0	28	51

[a] All reactions were performed in $CDCl_3$ at rt for 1 h. The conversions were measured by ^1H NMR spectroscopy.

Catalysts **1**, **7**–**9** were also explored for their ring-closing competence for a series of acetoxydienes **10**–**12**[†]). The acetoxy dienes **10**–**12** were chosen since they are the corresponding 'internal' isomerisation partners of acetates **13**–**15**, and would be generated from the in situ allylic isomerisation ready for ring-closing metathesis. The substitution pattern was varied since this was expected to be a significant factor in the relative equilibria position in the allylic isomerisation (from **13**–**15**), and also to direct initial metathesis to the terminal olefin thus preventing any potential detrimental chelation with the acetate group.

It was found that all catalysts were competent for the RCM of acetoxy olefins **10** and **11** with essentially complete conversion. However, for the trisubstituted olefin **12**, whilst the SIMes-ligated ruthenium catalysts **8**, **9** gave excellent conversions, catalysts **1** and **7** were much less effective. This highlights the known superior activity for the SIMes-containing catalysts and their ability to turn-over 'difficult' substrates.[2]

Table 2. Ring closing metathesis of acetoxy dienes **10**–**12**[a]



Substrate	1	7	8	9
10	>95	>95	>95	88
11	>95	>95	>95	>95
12	46	12	95	>95

[a] All reactions were performed in $CDCl_3$ at rt for 1 h. The conversions were measured by ^1H NMR spectroscopy.

[†] The acetates **10**–**12** were prepared by acetylation of the corresponding alcohols, and the alcohols were prepared by addition of the Grignard reagent derived from 1-bromobut-3-ene to the corresponding aldehyde (i.e. acrolein, crotonaldehyde and 3-methyl-2-butenal). Selected data for acetates **10**–**12**: Acetate **10**: pale yellow oil; IR (thin film) 1744 cm^{-1}; δ_H ($CDCl_3$, 270 MHz) 5.76 (m, 2H), 5.19 (m, 2H), 4.97 (m, 3H), 2.07 (m, 2H), 2.05 (s, 3H), 1.70 (m, 2H); δ_C ($CDCl_3$, 68 MHz) 170.1, 137.5, 136.4, 74.1, 33.3, 29.3, 21.0. Acetate **11**: Pale yellow oil; IR (thin film) 1738 cm^{-1}; δ_H ($CDCl_3$, 270 MHz) 5.70 (m, 2H), 5.35 (m, 1H), 5.13 (q, 1H, J=5.9 Hz), 4.90 (m, 2H), 2.05 (m, 2H), 1.96 (s, 3H), 1.83–1.51 (m, 2H), 1.66 (d, 3H, J=4.8 Hz); δ_C ($CDCl_3$, 68 MHz) 170.4, 137.7, 129.4, 115.0, 74.5, 33.7, 29.7, 21.4, 17.8. Acetate **12**: IR (thin film) 1735 cm^{-1}; δ_H ($CDCl_3$, 270 MHz) 5.72 (ddt, 1H, J=16.8, 10.1, 6.4 Hz), 5.41 (dt, 1H, J=9.1, 6.9 Hz), 5.04–4.85 (m, 3H), 1.95 (m, 2H), 1.93 (s, 3H), 1.74–1.41 (m, 2H), 1.65 (br s, 6H); δ_C ($CDCl_3$, 68 MHz) 170.3, 137.7, 137.2, 123.6, 114.9, 71.1, 34.1, 29.4, 25.7, 21.3, 18.4.

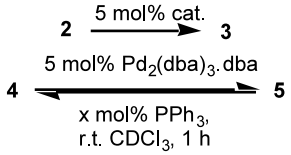
The in situ tandem allylic acetate isomerisation–ring closing metathesis of acetate **4** and linalool **2** using catalysts **7**–**9** (5 mol%) and $Pd_2(dba)_3$·dba (dba = dibenzylideneacetone) (5 mol%) was investigated as a function of phosphine loading (Table 3). The results from our previous work[4] using Grubbs' catalyst **1** are included for completeness. The equilibrium position for butenyl acetates **4** and **5** under Pd(0) catalysis had previously been established as 60:40, respectively, and at least 2 equiv. of added PPh_3/Pd atom were required for efficient catalysis.[4] As expected, in all cases (Table 3), 2 equiv. of added PPh_3 were generally required before isomerisation commenced (although in the case of catalyst **7** some isomerisation was observed at 10 mol% PPh_3 loading). In the case of added Grubbs' catalyst **1** the equilibrium position was not reached even at relatively high phosphine loadings, and this has been attributed to the effect of tricyclohexylphosphine.[4] For catalysts **7**–**9**, relatively fast isomerisation occurred (ca. 70:30, **4**:**5**) once sufficient triphenylphosphine had been added. While this was in line with our expectations for the presence of both PCy_3-free catalysts **7** and **9**, surprisingly, the presence of the PCy_3-containing catalyst **8** was not particularly detrimental.

The corresponding ring closing metathesis results for the in situ closure of linalool **2** were encouraging. We have previously shown that the presence of $Pd_2(bda)_3$·dba allowed Grubbs' catalyst **1** (5 mol%) to retain some metathesis activity up to 10 mol% of added PPh_3.[4] Presumably, the Pd(0) acts as a partial scavenger for the added phosphine.[4,6] However, the Hoveyda-modified catalyst **7** was found to be more sensitive to added phosphine and no ring closing metathesis was observed after addition of 10 mol% PPh_3. Pleasingly, both the SIMes catalyst **8** (5 mol%) and the 'HSIMes' catalyst **9** (5 mol%) retain some activity even up to 40 mol% added triphenylphosphine. There are three features of these latter results that require comment. The HSIMes catalyst **9** in general shows a higher activity than that of the SIMes catalyst **8** at a given phosphine loading. Secondly, the extent of ring closing metathesis is reduced relative to the addition of triphenylphosphine alone (c.f. Table 1). This may be a result of *N*-heterocyclic carbene exchange[‡,13] from Ru to Pd resulting in a less active olefin metathesis species (a control experiment with the addition of dba alone does not reduce RCM activity). Especially striking in this respect is the effect of addition of 10 mol% PPh_3 where the extent of ring closing metathesis using the HSIMes catalyst **9** drops from >95% (at 0 mol% PPh_3) to just 14%, before recovering again at higher phosphine loadings. With Ru to Pd *N*-heterocyclic carbene exchange in mind, we suggest that addition of a small quantity of phosphine (i.e. 10 mol%) sufficiently disrupts the dimeric structure[14] of $Pd_2(dba)_3$·dba to produce co-ordinatively unsaturated Pd(0) which has a high propensity to co-ordinate the SIMes ligand thus promoting the exchange. Amatore has extensively studied the use of '$Pd(dba)_2$'+$n$$PPh_3$ where $n \geq 2$,[15] but the PPh_3 regime at $n<2$ (i.e. in this system) has not previously been studied. At higher phosphine loadings the Pd(0) is essentially co-ordinatively saturated and the exchange may be slower. This effect is also seen for the SIMes catalyst **8**, but is less dramatic.

Having noted that catalyst **9** is tolerant to 40 mol% added PPh_3, we elected to employ $Pd(PPh_3)_4$ as the Pd(0) source rather than $Pd_2(dba)_3$·dba/$x$$PPh_3$, making the experimental protocol simpler. When linalool **2**, and butenyl acetate **4** were exposed to 5 mol% **9** and 5 mol% $Pd(PPh_3)_4$ for 1 h at rt in $CDCl_3$, the ratio of **4**:**5** was 65:35 and the extent of pentenol **3** formation was 32%. After 18 h, the ratio of acetates was unchanged and the ring closing metathesis had proceeded to 61%.

Finally we turned to the attempted in situ allylic isomerisation–ring closing metathesis of substrates **13**–**15**[§] to give **16**.[¶] It should be noted that **13**–**15** will not

Table 3. In situ allylic acetate isomerisation–ring closing metathesis of **2** and **4**[a]



PPh_3 (mol%)	Catalyst							
	1		**7**		**8**		**9**	
	3	**5**	**3**	**5**	**3**	**5**	**3**	**5**
0	98	0	60	0	79	0	95	0
10	40	0	0	18	18	0	14	0
20	0	18	0	29	25	23	31	32
30	0	25	0	27	18	21	25	33
40	0	17	0	32	18	24	29	31

[a] All reactions were performed in $CDCl_3$ at rt for 1 h. The conversions were measured by ^1H NMR spectroscopy.

[‡] Caddick and Cloke have recently shown that the *N*-heterocyclic carbene ligands are unexpectedly labile and readily exchange between two Pd(0) centres. See Ref. 13.

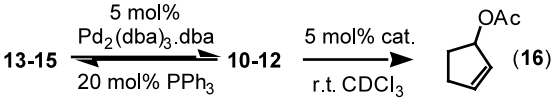
[§] Acetates **13**–**15** were prepared from pent-4-enal. Horner–Emmons homologation gave ester $H_2C{=}CHCH_2CH_2CH{=}CHCO_2Et$. DIBAL-H reduction followed by acetylation gave **13**. Alternatively, DIBAL-H reduction, PCC re-oxidation, addition of MeMgBr followed by acetylation gave **14**. Addition of excess MeMgBr to the α,β-unsaturated ester followed by acetylation gave **15**. Selected data for acetates **13**–**15**. Acetate **13**: colourless oil; IR (thin film) 1740 cm^{-1}; δ_H ($CDCl_3$, 270 MHz) 5.74 (m, 2H), 5.53 (dt, 1H, $J=15.2$, 6.2 Hz), 4.93 (m, 2H), 4.44 (d, 2H, $J=6.2$ Hz), 2.10 (m, 4H), 1.98 (s, 3H); δ_C ($CDCl_3$, 68 MHz) 170.7, 137.7, 135.5, 124.3, 115.0, 65.1, 33.0, 31.6, 21.0. Acetate **14**: pale yellow oil; IR (thin film) 1738 cm^{-1}; δ_H ($CDCl_3$, 270 MHz) 5.80–5.57 (m, 2H), 5.41 (dd, 1H, $J=15.4$, 6.7 Hz), 5.23 (app. quintet, 1H, $J=6.4$ Hz), 4.97–4.86 (m, 2H), 2.07 (m, 4H), 1.96 (s, 3H), 1.21 (d, 3H, $J=6.5$ Hz); δ_C ($CDCl_3$, 68 MHz) 170.2, 137.9, 132.3, 129.0, 114.9, 71.1, 33.1, 31.5, 21.4, 20.4. Acetate **15**: pale yellow oil; IR (thin film) 1750 cm^{-1}; δ_H ($CDCl_3$, 270 MHz) 5.85–5.70 (m, 2H), 5.61 (m, 1H), 4.95 (m, 2H), 2.11 (m, 4H), 1.95 (s, 3H), 1.47 (s, 6H).

[¶] Acetate **16**: colourless oil; IR (thin film) 1730 cm^{-1}; δ_H ($CDCl_3$, 270 MHz) 6.06 (m, 1H), 5.80 (m, 1H), 5.65 (m, 1H), 2.47 (m, 1H), 2.28 (m, 2H), 1.99 (s, 3H), 1.79 (m, 1H); δ_C ($CDCl_3$, 68 MHz) 171.0, 137.6, 129.3, 80.5, 31.1, 29.1, 20.5.

undergo ring closing metathesis directly since they would give the thermodynamically disfavoured cyclobutenes, and only their isomerised partners **10**–**12** will be subject to closure. The allylic acetates **13**–**15** were first exposed to either 5 mol% $Pd_2(dba)_3$·dba/20mol% PPh_3 or $Pd(PPh_3)_4$ in order to establish their equilbria positions under Pd(0) catalysis. As controls, the pure 'internal' isomers **10**–**12** were subjected to the same conditions in order to approach the equilibrium from the opposite direction. Acetates **10** and **12** behaved as expected, and gave rise to equilibria positions as dictated by their substitution patterns: **10**:**13** = 74:26; **12**:**14** = <5:95. However, acetate **11** (and its corresponding isomerisation partner **14**) proceeded only very slowly towards equilibrium under these conditions. For instance after 18 h starting from acetate **11** and employing catalytic $Pd(PPh_3)_4$, the ratio of **11**:**14** was 69:31, whereas starting from **14** the ratio of **11**:**14** was 32:68. This was unexpected, but may be the result of a relatively stable π-allyl complex with intramolecular η^2-alkene co-ordination.[16] Nevertheless, the slow rate of isomerisation for this substrate was likely to be detrimental in its in situ tandem allylic acetate isomerisation ring–closing metathesis reaction.

Exposure of acetates **13**–**15** to catalysts **1**, **7**–**9** (5 mol%) and $Pd_2(dba)_3$·dba (5 mol%)/PPh_3 (20 mol%) gave the following results (Table 4). As expected, no in situ tandem allylic acetate isomerisation ring-closing metathesis was observed with catalyst **1** with any of the substrates **13**–**15**, on account of its sensitivity to added triphenylphosphine. A similar effect was seen with Hoveyda catalyst **7** (although some success was achieved for substrate **13**). For substrate **14** no tandem isomerisation–RCM was observed, evidently due to the slow allylic isomerisation rate of linear acetate **14** into **11** (vide supra). However, we were pleased to find that SIMes catalyst **8** was moderately effective for both substrates **13** and **15**, and that the HSIMes catalyst **9** was effective for substrate **15** (but oddly not for acetate **13** under these conditions). Further optimisation with substrate **13** gave the following pleasing result. Using HSIMes catalyst **9** (40 mol%) and an equivalent loading of $Pd_2(dba)_3$·dba in the presence of 2 equiv. of triphenylphosphine per Pd atom gave essentially complete conversion to acetate **15** with only traces of the two allyl acetates **13** and **10** apparent.

Table 4. In situ tandem allylic acetate isomerisation–ring closing metathesis using acetates **13**–**15**[a]



Substrate	Cat.	% Isomerisation[b]	% **16**
13	**1**	20 (20)	0
13	**7**	30 (15)	15
13	**8**	40 (0)	40
13	**9**	5 (0)	5
14	**1**	0 (0)	0
14	**7**	0 (0)	0
14	**8**	<5 (0)	Trace
14	**9**	<5 (0)	Trace
15	**1**	60 (60)	0
15	**7**	60 (60)	0
15	**8**	57 (0)	57
15	**9**	56 (0)	56

[a] All reactions were performed in $CDCl_3$ at rt for 20 h. Conversions were measured by ^1H NMR spectroscopy.

[b] % Isomerisation refers to the consumption of substrate. The quantity of 'internal' acetate isomer remaining (i.e. **10**–**12** for substrates **13**–**15**, respectively) is given in parenthesis.

In conclusion we have demonstrated that SIMes-containing catalysts **8** and **9** can be used in conjunction with Pd(0)–phosphine combinations for in situ tandem allylic acetate isomerisation–ring closing metathesis reactions. The critical feature is that unlike Grubbs' catalyst **1**, or Hoveyda-modified catalyst **7**, these nucleophilic carbene-ligated systems are only moderately sensitive to added triphenylphosphine. An additional advantage of the use of catalyst **9**—as noted by Hoveyda[10]—is that this catalyst may be recovered after use by simple column chromatography. Further applications of in situ allylic isomerisation–olefin metathesis will be reported in due course.

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