Remarkable Ligand Effects in Regioselective Palladium-Catalysed Allylic Substitution Reactions

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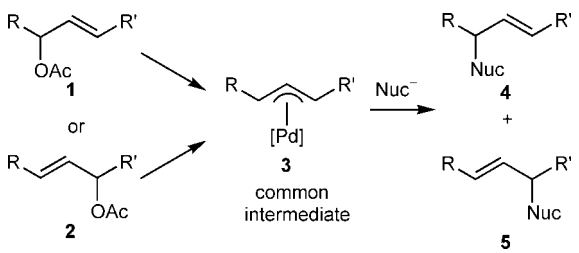
Introduction

The regiochemistry of palladium-catalysed allylic substitution reactions can be strongly influenced by the nature of the intermediate allylpalladium complex. For soft nucleophiles, the incoming nucleophile usually approaches from the less sterically hindered terminus of the allyl moiety.[1] This preference can be overturned when other transition metals are used, including molybdenum,[2] iridium,[3] or rhodium.[4] Differences in the electronic nature of the substituents of the allyl group can also exhibit a strong regiochemical bias in the palladium-catalysed reaction.[5] The nature of the ligands associated to the allylpalladium complex can also affect the regiochemistry of the nucleophilic attack.[6] However, it is generally expected that both regioisomers of an allyl acetate **1** and **2** will react via a common intermediate **3** to provide the same ratio of substitution products **4** and **5**. When the regioisomeric starting materials afford significantly differing ratios of products, this is known as a memory effect. Memory effects certainly have precedent in palladium-catalysed allylic substitution, but are not the typical outcome of such reactions.[7]



Scheme 1. Regioisomeric allyl acetates and products

Results and Discussion

We have previously reported that tricyclohexylphosphine (PCy_3) allows palladium-catalysed allylic substitution reactions to take place with good selectivity for a variety of substrates (for example, 12 : 1 in favour of the branched product **8** starting from the branched acetate **6**).[8] In this update we report that the memory effect can be enhanced by variation of the solvent, and that other nucleophiles and phosphine ligands can also be used. In particular, the branched acetate **6** undergoes palladium-catalysed allylic substitution with $NaCH(CO_2Me)_2$ to provide the branched substitution product **8** with up to 120 : 1 regiocontrol when dichloromethane is employed as the solvent. It is unclear why dichloromethane should provide higher regioselectivity than either THF or toluene, but the nucleophile is only sparingly soluble in this solvent. However, the corresponding linear acetate does not give the same ratio of product isomers, affording little regioselectivity, and also is a very sluggish reaction partner when dichloromethane is employed as the solvent (although in THF, the reaction goes to completion in 7 h with the same distribution of regioisomers). The low conversion of the linear acetate is notable, and encouraged us to perform a competition reaction between the linear and branched acetates. A 1 : 1 mixture of branched acetate **6** and linear acetate **7** was subjected to palladium-catalysed allylic substitution with $NaCH(CO_2Me)_2$ using tricyclohexylphosphine as the ligand. After 1 hour, analysis of the reaction mixture revealed that all of the branched acetate had been consumed, and the ratio of branched to linear substitution products was 44 : 1 (**8** : **9**). Even after 50 hours, only 10% of the linear acetate had reacted, demonstrating a very considerable preference for the branched substrate over the linear substrate. Interestingly, when triphenylphosphine is used as the ligand, the linear acetate reacts to completion in less than 1 hour. It seems reasonable to assume that the bulky palladium/tricyclohexylphosphine combination has a steric preference for the less substituted alkene.

t-Butyl malonate ester **10** afforded similar results to the methyl malonate ester used in Scheme 2. However, we sometimes (and frustratingly unpredictably)

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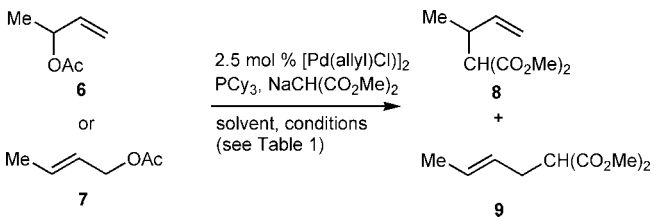
Table 1. Regiocontrol with dimethyl malonate

Substrate	Ligand[a]	Solvent/Conditions	Products **8** : **9**[b]
6	PPh_3 (2 : 1)	THF, r. t.	1 : 1
7	PPh_3 (2 : 1)	THF, r. t.	1 : 1.3
6	PCy_3 (2 : 1)	THF, r. t.	16 : 1
7	PCy_3 (2 : 1)	CH_2Cl_2, r. t.	1 : 1[c]
6	PCy_3 (1 : 1)	THF, r. t.	16 : 1
6	PCy_3 (2 : 1)	THF, 0 °C	22 : 1
6	PCy_3 (2 : 1)[d]	THF, r. t.	15 : 1
6	PCy_3 (2 : 1)	CH_2Cl_2, r. t.	120 : 1
6	PCy_3 (2 : 1)	Toluene, r. t.	40 : 1

[a] Ratio of phosphine to palladium in parentheses.
[b] Except in the case noted, reaction proceeded to 100% conversion in 1 h (75–80% yield).
[c] In this case the reaction proceeded to 10% conversion after 50 h.
[d] The corresponding benzoate was used as substrate.

observed small amounts of diallylation products with simple malonates. We were concerned that the linear products may be more reactive to diallylation than the branched isomers, thereby distorting the true ratio of products. In order to completely eliminate the possibility of diallylation, we also employed the mono-substituted malonate **11**. The results obtained with this bulky nucleophile show that good regioselectivity could now be obtained from both the branched acetate starting material **6** and also that the linear acetate **7** now proceeded with good memory to provide the linear product **13b** with good regioselectivity.



Scheme 2. Allylic substitution with dimethyl malonate

We intend to investigate the origin of the memory effect in more detail. However, it is interesting to note that the use of either one or two equivalents of tricyclohexylphosphine per palladium has essentially no impact on the reactivity or regiochemical outcome of the reaction. One avenue for investigation will be the possibility that only one equivalent of tricyclohexylphosphine is co-ordinated to the allylpalladium complex, and that acetate resides *cis* to the position that it left from in the allyl acetate.

In our previous report,[8] we had shown that a wide range of other phosphines (including bulky electron-rich arylphosphines and bulky bidentate aliphatic phosphines) did not exhibit the same memory effect as tricyclohexylphosphine. However, we have now discovered that other bulky aliphatic phosphines do

Table 2. Regiocontrol with other malonates

Substrate	Nucleophile	Ligand	Solvent	Products **12 a/b** : **13 a/b**[a]
6	Na-**10**	PPh_3	CH_2Cl_2	1 : 1
6	Na-**10**	PCy_3	CH_2Cl_2	35 : 1
6	Na-**10**	PCy_3	THF	58 : 1
7	Na-**10**	PCy_3	THF	1 : 1.6
6	Na-**11**	PPh_3	THF	1 : 3
6	Na-**11**	PCy_3	THF	14 : 1
6	Na-**11**	PCy_3	CH_2Cl_2	14 : 1
7	Na-**11**	PCy_3	THF	1 : 11
7	Na-**11**	PCy_3	CH_2Cl_2	1 : 7.4

[a] Reactions proceeded to 100% conversion in 2 h (up to 97% yield) except for the last two entries (75% and 95% conversion after 38 h).

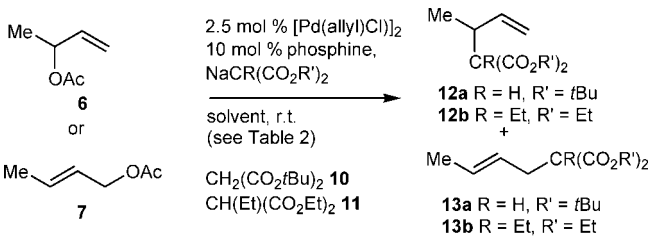
Table 3. Use of other bulky aliphatic phosphines

Substrate	Ligand	Products **8** : **9**[a]
6	PCy_3	16 : 1
6	$P(c\text{-}C_5H_9)_3$	24 : 1
6	$P(i\text{Pr})_3$	26 : 1
6	$P(t\text{Bu})_3$	43 : 1

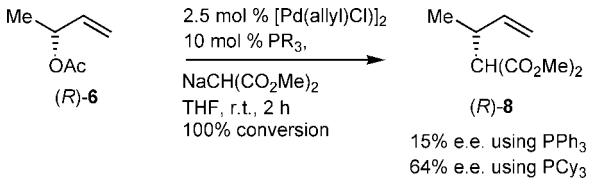
[a] Reactions performed in THF at r. t. with 2 equiv. phosphine to palladium.

have a strong preference for conversion of the branched acetate **6** into the branched substitution product **8**. Even using THF as the solvent, the ligands shown in Table 3 all provide somewhat higher regioselectivity than tricyclohexylphosphine itself and warrant further investigation.

Evans and Nelson have recently reported that enantiomerically pure branched acetate (*S*)-**6** undergoes substitution with malonate with retention of stereochemistry and regiochemistry using a rhodium based catalyst.[9] It is expected that with palladium catalysts the enantiomeric excess of the substrate will be severely eroded by a π–σ–π process during the reaction,[10] and indeed this is observed using a palladium catalyst in combination with triphenylphosphine (Scheme 4). However, the use of tricyclohexylphosphine/palladium catalyst with the substrate (*R*)-**6** allows the formation of the substitution product **(*R*)-8** with significantly greater retention of stereochemical integrity.



Scheme 3. Allylic substitution with other malonates



Scheme 4. Partial retention of stereochemistry using PCy_3

Conclusion

The use of tricyclohexylphosphine in palladium-catalysed allylic substitution reactions leads to a memory effect. Branched acetates afford branched substitution products preferentially. Linear acetates afford a mixture of branched and linear substitution products, although when a bulky nucleophile is used, the selectivity for the linear substitution product increases.

Experimental Section

General Remarks

Solvents were dried and distilled under appropriate conditions. Other substrates, ligands and the palladium catalyst were used as supplied from commercial sources. (*R*)-2-Acetoxybut-3-ene, (*R*)-**6**, was prepared by acetylation of the commercially available enantiomerically enriched alcohol. The malonate substitution products are literature compounds,[8,9] but a general procedure for the allylic substitution reaction is given below, along with GC data for the products.

General Procedure for Palladium-Catalysed Allyic Substitution

Into a flame-dried flask under N_2 were placed $[(C_3H_5)PdCl]_2$ (2.5 mol %, 0.008 g) and PCy_3 (10 mol %, 0.0245 g) and the mixture was stirred in THF (2 mL) for 30 min to ensure complete formation of catalyst. This solution was then added to $NaCH(CO_2Me)_2$ (1.5 eq, 1.31 mmol) in THF (16 mL) along with 2-acetoxybut-3-ene (**6**; 1 eq, 0.1 g, 0.876 mmol). The reaction was stirred at r. t. under an N_2 atmosphere. Once the reaction was complete, the mixture was diluted with CH_2Cl_2, washed with ammonium chloride, brine, and water. Column chromatography was performed on silica using Et_2O/petroleum ether as the eluent affording a mixture of products **8** and **9**. ^1H NMR data were consistent with literature values.[8,9] GC (Chiral BETA-DEX 120; fused silica capillary column; 60 m × 0.25 mm i. d.; 70 °C for 10 min then 10 °C/min until 150 °C): (**8**) 23 min, ((*E*)-**9**) 25.9 min, ((*Z*)-**9**) 26.3 min.

GC data for the other products using the same column and the same conditions were obtained as follows: (**12a**) 32.9 min, ((*E*)-**13a**) 36.3 min, ((*Z*)-**13a**) 38.8 min; (**12b**) 31.3 min, ((*E*)-**13b**) 36.9 min, ((*Z*)-**13b**) 37.8 min.

Enantiomeric purity of (*E*)-**8** was assessed by the use of the chiral shift reagent $Eu(hfc)_3$ (10 mg product, 1eq $Eu(hfc)_3$).

Acknowledgments

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