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Use of Tricyclohexylphosphine To Control Regiochemistry in Palladium-Catalyzed Allylic Alkylation

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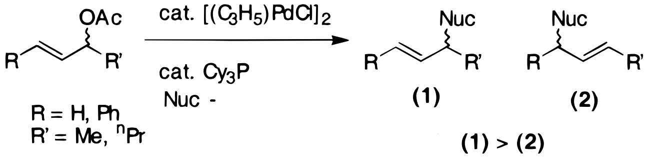
ABSTRACT



Tricyclohexylphosphine, Cy_3P, in conjuction with $[(C_3H_5)PdCl]_2$ catalyzes allylic alkylation of terminal allylic acetates with high regioselectivity toward branched products, which is in contrast to most other palladium catalysts. Other ligands, even those of similar basicity or bulkiness, did not show the same regioselectivity. Alkylation of 1,4-diacetoxy-2-butene gave predominantly branched products which had not been observed previously.

Transition metal catalyzed allylic substitution is an important process for organic synthesis.[1] One of the most challenging problems in allylic substitution reactions is to control the regioselectivity when the reaction proceeds through an unsymmetrical intermediate. For instance, when a mono-substituted allylic acetate is used as substrate, palladium catalysts generally give a mixture of isomers with a strong tendency to form the linear product, although a few ligands have been shown to reverse this regiochemistry for certain substrates.[2,3]

Attempts to obtain branched products have focused on the use of alternative metals as catalysts, and Ir,[4] Mo,[5] Ru,[6] Rh,[7] W,[8] and Pt[9−11] catalysts have all been shown to give a higher proportion of branched products than palladium. We have recently been interested in platinum-catalyzed allylic alkylation.[11,12] One of the striking findings from our study was the discovery that if the combination $[(C_3H_5)PtCl]_4/Cy_3P$ was used as catalyst, excellent regioselectivity toward branched products was obtained in the alkylation of but-2-enyl (B/L = 15:1) and hex-2-enyl (B/L = 10:1) acetates. A Pd catalyst

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Table 1. Effect of Ligand on Regioselectivity of Allylic Alkylation of But-2-enyl Acetate (**1**) with Sodium Dimethylmalonate

ligand[a]	**2/3**[b]	*E/Z* for **3**[c]
Cy_3P[d]	11.5:1	N/D[f]
$Cy_3P[(C_3H_5)PtCl]_4$ cat.[d]	15.4:1	N/D[f]
Ph_3P[e]	1:2.0	N/D[f]
$Ph_3P(Ph_3P)_2Pt{-}$stilbene cat.[d]	2.1:1	4.6:1
$[2,4,6\text{-}(CH_3O)_3C_6H_2]_3P$	1:3.9	5.5:1
tri-*o*-tolylphosphine	1:1.5	5.5:1
$(p\text{-}CH_3O\text{-}C_6H_4)_3P$	1:1.2	5.7:1
$(p\text{-}FC_6H_4)_3P$	1:1.3	5.1:1
$Cy_2PCH_2CH_2PCy_2$	1:1.1	4.7:1
dppe	1:1.4	6.4:1

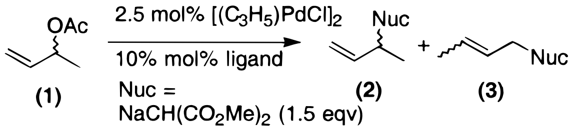
[a] All reaction run using 2.5 mol % of $[(C_3H_5)PdCl]_2$ catalyst, 1.5 equiv of $NaCH(CO_2Me)_2$ nucleophile, THF solvent at 20 °C unless stated. In all cases conversion was 100%, as determined by GC. [b] Determined by GC and checked by ^1H NMR. [c] Determined by GC. [d] Taken from ref 11. [e] Taken from ref 9. [f] N/D = not determined.

in combination with this ligand was tested for comparison and to our surprise also gave good regioselectivity.

As palladium is generally the preferred choice of metal for allylic alkylation, we thought it important to study this ligand effect further. In this Letter we show how we have attempted to understand the nature of the ligand effect and utilized it in the preparation of compounds in isomerically pure form.

The first point we needed to address was whether any other ligands would show this effect. Toward this end, ligand effects on regiochemistry in the alkylation of but-2-enyl acetate (**1**) with sodium dimethylmalonate were studied (selected results are shown in Table 1 and Scheme 1).

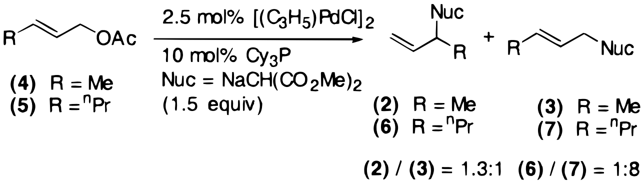
Scheme 1



Tricyclohexylphosphine is a bulky and strongly electron donating phopshine. This is quantified by its large cone angle ($\theta = 170°$)[13] and the high pK_a value of its conjugate acid (pK_a = 9.70). This can be compared with PPh_3 ($\theta = 145°$, pK_a = 2.73).[14] The ligands in Table 1 were chosen because they share some characteristics with Cy_3P and can therefore be used to ascertain whether the regioselectivity observed is a property of a general class of ligands. Tri (2,4,6-trimethoxyphenyl)phosphine[15] is both more bulky and basic ($\theta = 184°$, pK_a = 11.02) than Cy_3P but gives regioselectivity opposite to that of the Cy_3P/Pd-catalyzed reactions. Tri-*o*-tolylphosphine is one of the most bulky phosphines ($\theta = 194°$, pK_a = 3.08) and also gives predominantly linear products, again in contrast to the tricyclohexylphosphine system. Tris(4-methoxyphenyl)- and tris(4-fluorophenyl)phosphines are informative as they have a similar cone angle ($\theta = 145°$) but different basicities (pK_a's = 4.57 and 1.97, respectively.[14] It can be concluded that there is no direct trend between basicity or cone angle and the proportion of branched products observed for this particular reaction. The formation of predominantly linear products with a wide range of ligands has been observed for other substrates by other workers.[16]

It was suggested to us that the results obtained may be due to a strong "memory effect"[17] when Cy_3P was used as ligand (the product is the same regioisomer as the starting material). To test this theory, the regioisomeric allylic acetates (**4** and **5**) were tested (Scheme 2). The regioselectivity was altered (from 11.5:1 to 1.3:1 for **4** and from 3.1:1 to 1:8.8 for **5**), and much greater proportions of linear products (from linear starting material) were observed. This is good evidence that a memory effect is associated with this ligand.

Scheme 2. Tricyclohexylphosphine/Palladium Catalysts Give Mainly Linear Products When Linear Allylic Acetates Are Employed



We have also looked at the effect of Cy_3P on Pd-catalyzed allylic alkylation on commercially available *cis*-1,4-diacetoxy-2-butene (**8**). Allylic substitution on derivatives of diacetate **8** have previously yielded linear isomers.[18] When compound **8** is alkylated with 1.02 equiv of sodium dimethylmalonate using triphenylphosphine as ligand (Table 2), predominantly linear products are observed (in addition to small amounts of byproducts).

Switching the ligand to Cy_3P gives a dramatic reversal of regiochemistry (B/L = 3.4:1). The branched isomer can be isolated pure by column chromatography albeit in only 39% yield due to the similar R_f of branched and linear products. Because the starting material was linear, this result does not fit in with the memory effect explanation.

When **11** is alkylated using palladium catalysts, a mixture of inseparable isomers (**12** and **13**) is produced with a strong

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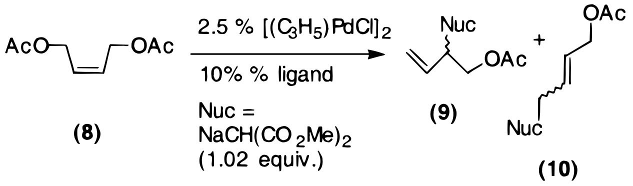
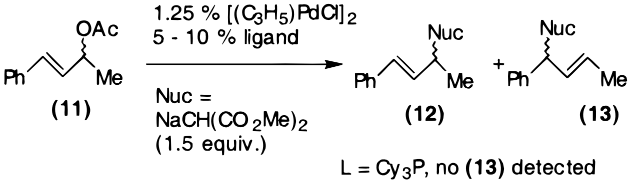
Table 2. Effect of Ligand on Regioselectivity in Allylic Alkylation of Acetate **8**



ligand	**9**/**10**	*E*/*Z* for **10**
Ph_3P	8/92	1.8:1
Cy_3P	77/23	2.2:1

preference for **12** (for most ligands **12**/**13** = ca. 10:1).[11,19,20] When Cy_3P is used as ligand, product **12** was obtained as a single regioisomer (Scheme 3).

Scheme 3



Tricyclohexylphosphine, which was unique among the ligands we screened, gives unusual regiochemistry in Pd-catalyzed allylic alkylations that proceed through unsymmetrical intermediates. Most of the results we have obtained suggest that the intermediate allyl complexes formed direct the nucleophile to the allylic carbon atom which was previously substituted by the acetate leaving group. While we have no definitive explanantion for this, the work of Mealli and Musco and their co-workers may be significant.[21] They described the NMR spectroscopic properties of $[(PPh_3)_2Pt(allyl)]X$ ($X = {}^-BF_4$, ${}^-OAc$) as being identical (at low temperature where static η^3-allyl complexes are present). For the compounds $[(Cy_3P)_2Pt(allyl)]X$ ($X = {}^-BF_4$, ${}^-OAc$), they observed significantly different spectral properties, on changing the counterion. This was proposed to be evidence that the acetate leaving group was still intimately involved with the cationic palladium allyl complex. It seems feasable that the reactions described here proceed through similar allyl complexes in which the acetate ion is not a simple "spectator" leaving group. The use of a chloride-free catalyst, $[(Cy_3P)_2Pd(allyl)]BF_4$, affords results very similar to those identified in Table 1, affording a 14:1 ratio of **2**:**3**. Thus, the presence of chloride is not solely responsible for the effects that we have observed.

In conclusion, allylic alkylation using tricyclohexylphosphine as ligand could give insight on the mechanism of palladium-catalyzed allylic substitution, which has recently been shown to be more complex than first thought a few years ago. Furthermore, the use of this cheap and commercially available ligand may allow retention of the regiochemistry of allylic acetates in the nucleophilic substitution products and should be of synthetic use.

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Supporting Information Available: Representative procedures and analytical data for compounds **2**, **9**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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