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α-Aminophosphonate Derivatives as Nucleophiles in Diastereoselective and Enantioselective Palladium Catalysed Allylic Substitution Reactions

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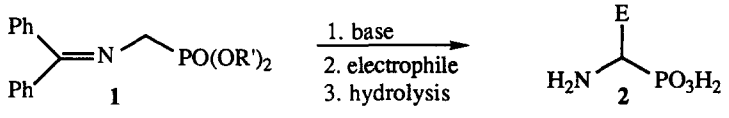
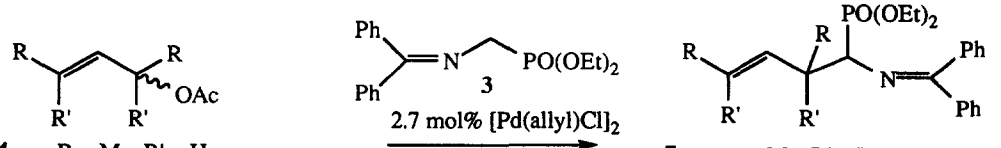
Abstract: The palladium catalysed reaction between allyl acetates and Schiff base derivatives of α-aminophosphonates is reported. For suitable substrates, the observed diastereoselectivities (up to 87:13) and enantioselectivities (>96% ee) are high.

α-Aminophosphonic acids and their derivatives exhibit a wide range of biological properties,[1] and are able to function as α-aminocarboxylic acid surrogates. Our interest lay in the stereocontrolled synthesis of α-aminophosphonate derivatives by asymmetric catalysis.

Genêt *et al* have previously reported the use of the phosphonate **1** as a nucleophile, and also as a precursor to α-aminophosphonates **2** after hydrolysis.[2] Furthermore, the same group has demonstrated the use of such compounds as nucleophiles in palladium catalysed allylic substitution reactions.[3]



Based on Genêt's results, we have examined the use of phosphonate **3** in diastereoselective palladium catalysed allylic substitution reactions. The reaction between the phosphonate **3** with allyl acetates **4** - **6** afforded the corresponding substitution products **7** - **9** when subjected to palladium catalysis under the conditions indicated in Table 1.[4]



4 R = Me, R' = H
5 R = H, R' = -$CH_2CH_2CH_2$-
6 R = Ph, R' = H

7 R = Me, R' = H
8 R = H, R' = -$CH_2CH_2CH_2$-
9 R = Ph, R' = H

In the case of the allyl acetate **6**, good levels of diastereoselectivity were observed in the product **9** (up to 87:13 ratio of diastereomers).[5] However, for substrates **4** and **5**, a mixture of diastereomers was observed in the products **7** and **8**.[5] Whilst we were unable to separate any of the diastereomers by column chromatography, in the case of the product **9**, the diastereomers were separable by semi-preparative hplc.[6]

As shown in Table 1, the yield and diastereoselectivity are dependent upon the choice of solvent and base. However, from a practical stand-point, the use of BSA (bistrimethylsilylacetamide)[7] in conjunction with either potassium acetate or caesium acetate is considered to be easier, since prior deprotonation of the phosphonate **3** is not required.

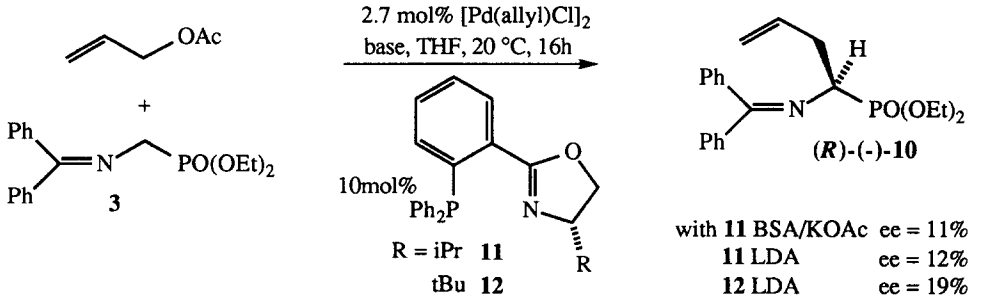
Table 1: Palladium catalysed formation of **7** - **9** and the diastereomer ratios observed

Substrate	*Solvent*	*Base*	*Product*	*Diastereomer ratio*	*Yield*
4	THF	KHMDS	**7**	53 : 47	63
5	THF	KH	**8**	52 : 48	54
5	THF	BSA/KOAc	**8**	---	9
5	DMF	LDA	**8**	50 : 50	60
5	DMF	KH	**8**	52 : 48	67
6	THF	LDA	**9**	81 : 19	55
6	THF	KH	**9**	87 : 13	71
6	THF	BSA/KOAc	**9**	87 : 13	76
6	THF	BSA/CsOAc	**9**	87 : 13	80
6	DMF	KH	**9**	82 : 18	69
6	DMF	BSA/KOAc	**9**	83 : 17	88
6	PhMe	KH	**9**	87 : 13	80
6	PhMe	BSA/KOAc	**9**	62 : 38	18
6	Et_2O	KH	**9**	75 : 25	70
6	Et_2O	BSA/KOAc	**9**	87 : 13	17

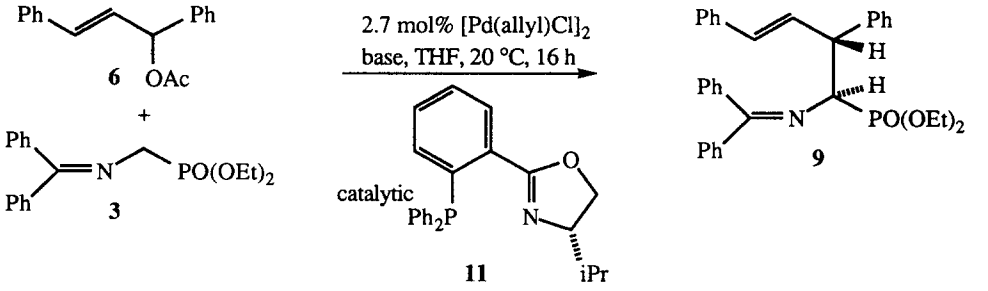
Recently, we and others have examined the use of phosphorus[8] and sulfur[9]-containing oxazolines as ligands for asymmetric palladium catalysed allylic substitution reactions. Herein we report the use of either ligand **11** or **12** to control the enantioselectivity of palladium catalysed reactions involving the phosphonate **3** as the nucleophile.

When propenyl acetate is reacted with the nucleophile **3**, the substitution product (S)-(+)-**10** contains only one chirality centre. The orientation of the nucleophile in the approach to the putative π-allylpalladium intermediate is important for the control of asymmetric induction in the formation of **10**,[10] and from the modest levels of enantioselectivity observed,[11] we assume that the nucleophile approaches in an essentially

stereorandom manner. The sense of asymmetric induction was established by hydrolysis of the imine to the amine and comparison with the literature rotation of the allyl substituted diethylaminophosphonate.[12]



However, higher levels of enantioselectivity were observed in the reaction of phosphonate **3** with the allyl acetate **6** in the formation of the substitution product **9**.[13] This result is consistent with the high enantioselectivity found with these ligands when the incoming nucleophile is dimethylmalonate[8,9] or a nitrogen nucleophile.[14] The sense of asymmetric induction is assumed to be the same as for the dimethylmalonate cases. The relative configuration has been determined from an X-ray crystallographic study.[15]



We found that the highest yield, diastereoselectivity and enantioselectivity were obtained by using a high ligand loading (20 mol%), and employing BSA/KOAc as the base, as shown in Table 2.

Table 2: Enantioselective palladium catalysed formation of **9**

Base	*11*	*Diastereomer ratio*	*ee of major*	*ee of minor*	*Yield*
KHMDS	10 mol%	84 : 16	48	50	83
BSA/KOAc	10 mol%	85 : 15	>96	93	65
BSA/KOAc	20 mol%	87 : 13	>96	93	98
LDA	10 mol%	84 : 16	85	82	84

In summary, we have demonstrated that palladium catalysed allylic substitution reactions between two achiral partners (phosphonate and achiral palladium allyl intermediate) can take place diastereoselectively. In the presence of an enantiomerically pure ligand, these reactions are able to produce enantiomerically enriched products. Efforts to establish the sense of diastereocontrol and rationalise the observed results are currently under way.

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3. J. P. Genêt, J. Uziel and S. Juge, *Tetrahedron Lett.*, 1988, **29**, 4559.
4. The use of an imine derived from benzaldehyde and diethylaminophosphonate afforded reduced diastereoselectivity in the palladium catalysed allylic alkylation reaction of **6**. The use of a ditertbutyl phosphonate ester afforded similar yields and diastereoselectivities to the diethylphosphonate ester **3**.
5. Diastereoselectivities were determined by hplc analysis (Microsorb Si-80-125-C5 column, hexane/ethanol 97/3), and confirmed by ^{31}P nmr spectroscopy.
6. Compound **9** was separated into diastereomers using a Microsorb Si-80-120-C5 semi-preparative column.
7. B. M. Trost and J. Vercauteren, *Tetrahedron Lett.*, 1985, **26**, 131. For the reactions reported in this communication, we employed 3 equivalents of BSA, and 5 mol% of KOAc.
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10. For a review on stereocontrol in palladium catalysed allylic substitution, see; C. G. Frost, J. Howarth and J. M. J. Williams, *Tetrahedron: Asymmetry*, 1992, **3**, 1089.
11. The enantioselectivity was determined by chiral hplc, using a Chiralpak AD column (hexane/ethanol 95/5)
12. (R)-(-)-**10**, $[\alpha]_D^{25}$ = -1.08 (c 3.7, $CHCl_3$) (19%ee by hplc), compared with the literature value for (*S*)-(+)-**10**; $[\alpha]_D^{25}$ = +4.17 (c 1.6, $CHCl_3$) (92-97%ee); M. Ferrari, G. Jommi, G. Miglierini, R. Paglarin and M. Sisti, *Synth. Commun.*, 1992, **22**, 107.
13. The major and minor diastereomers were separated (see ref 6), and the enantioselectivity of each diastereomer was then determined by chiral hplc with an Apex Chiral PK column
14. (a) Unpublished results, R. Jumnah, A. C. Williams and J. M. J. Williams. (b) see ref 8(e)
15. I. C. Baldwin, A. M. Z. Slawin and J. M.J. Williams, full details will be published elsewhere in due couse.

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