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α-Amino Ester Derivatives as Nucleophiles in Stereoselective Palladium Catalysed Allylic Substitution Reactions

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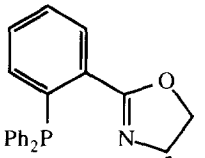
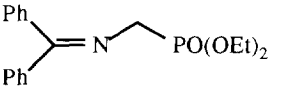
Abstract: The stereoselective palladium catalysed reaction between allyl acetates and imino esters is reported. For suitable substrates, diastereoselectivities are good (up to 84:16), and in the presence of enantiomerically pure phosphorus-containing oxazoline ligands, the enantioselectivities (up to 97% ee) are very high.

This group[1] and others[2] have examined the use of phosphorus containing oxazolines **1** and **2** as ligands for asymmetric palladium catalysed allylic substitution reactions.[3] Recently, we have used phosphonate **3** as a nucleophile in diastereoselective and enantioselective palladium catalysed allylic substitution reactions to generate α aminophosphonate derivatives with good diastereoselectivity and excellent enantioselectivity.[4]

Genêt *et al* have reported the use of imino esters **4** and **5** as nucleophiles in palladium catalysed allylic alkylation reactions.[5] Furthermore, the same research group has demonstrated the use of these nucleophiles in the preparation of enantiomerically enriched α-amino esters.[6]



1 R = ^{i}Pr
2 R = ^{t}Bu



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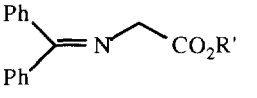

4 R' = Me
5 R' = Et
6 R' = ^{t}Bu

Herein we report the use of imino esters **4** and **6** in diastereoselective and enantioselective palladium catalysed allylic substitution reactions. Firstly, we examined the diastereoselectivity in the formation of the allylic substitution products **9** - **11** using an achiral palladium catalyst. Thus, treatment of allyl acetates **7** and **8** with 2.7 mol% $[Pd(allyl)Cl]_2$ and 20 mol% PPh_3 in the presence of imino ester nucleophiles and base[7] afforded the substitution products **9** - **11** with the isolated yields and diastereoselectivities reported in Table 1.

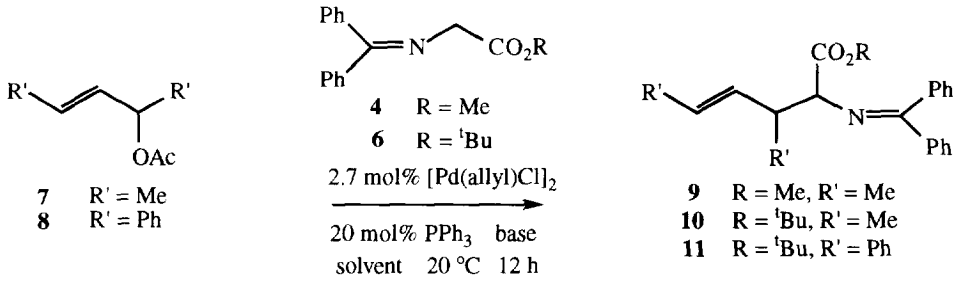

Table 1: Palladium catalysed formation of **9** - **11** and the diastereomer ratios observed

Substrate	*Nucleophile*	*Solvent*	*Base*	*Product*	*Diastereomer ratio*	*Yield*
7	**4**	THF	BSA/KOAc	**9**	56 : 44[a]	74
7	**4**	THF	BSA/CsOAc	**9**	61 : 39	90
7	**6**	THF	BSA/CsOAc	**10**	69 : 31[a]	68
8	**6**	THF	BSA/KOAc	**11**	84 : 16[b]	95
8	**6**	THF	BSA/CsOAc	**11**	82 : 18	96
8	**6**	DMF	BSA/KOAc	**11**	78 : 22	85
8	**6**	DMF	BSA/CsOAc	**11**	78 : 22	88
8	**6**	THF	LDA	**11**	77 : 23	91
8	**6**	DMF	LDA	**11**	81 : 19	80

[a] Diastereomer ratio determined by ^{1}H NMR [b] Diastereomer ratio determined by ^{1}H NMR and HPLC (Microsorb Si-80-125-C5 column, hexane/isopropanol 99.75/0.25). BSA = N,O-bis(trimethylsilylacetamide)

Having established good levels of simple diastereocontrol (with allyl acetate **8** as the substrate), we turned our attention to the control of absolute stereochemistry. We chose to investigate the use of allyl acetate **12** as the substrate with the imino esters **6** and **13**, since the substitution products **14** and **15** contain only one stereogenic centre. However, in the presence of ligands **1** or **2**, only modest levels of enantioselectivity were observed in the products **14** and **15**, as indicated in Table 2. The low level of asymmetric induction indicates that the enantiomerically pure palladium catalyst is unable to control the orientation of the incoming nucleophile effectively.

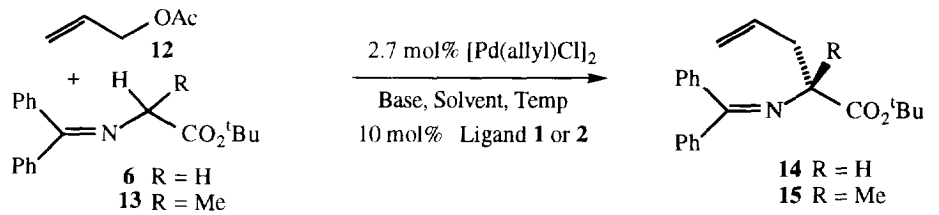

Table 2: Palladium catalysed formation of **14** and **15** and the enantioselectivities observed.

Solvent	*Base*	*Ligand*	*Temperature*	*Product*	*Yield*	*Ee* [a]
DMF	BSA/CsOAc	**1**	20°C	**14**	80 %	10 %
DMF	BSA/KOAc	**1**	20°C	**14**	67 %	10 %
THF	LDA	**1**	-78°C	**14**	66 %	13 %
THF	BSA/CsOAc	**2**	20°C	**14**	75 %	5 %
DMF	BSA/CsOAc	**2**	20°C	**14**	51 %	17 %
THF	LDA	**2**	20°C	**15**	80%	10%

[a] Enantiomeric excess was determined using HPLC (Chiralcel OD column, hexane/isopropanol 99.5/0.5)

Higher levels of enantioselectivity were observed in the reaction of imino ester **6** with the phenyl-substituted allyl acetate **8** (up to 97% ee) This level of enantioselectivity is similar to that observed in related reactions between substrate **8** and other nucleophiles such as dimethyl malonate[1,2] and imino phosphonates.[4] The sense of asymmetric induction in the formation of **11** is assumed to be the same as that observed with other nucleophiles and the relative stereochemistry to be the same as when imino phosphonates **3** are employed as the nucleophile.[8] When the methyl-substituted nucleophile **13** was reacted with acetate **8**, the diastereomer ratio of the corresponding product was sensitive to the ligand employed (65:35 ratio with triphenylphosphine, but 82:18 with ligand **2**).

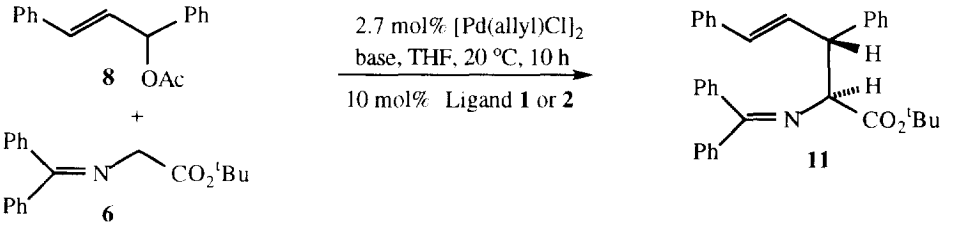

Table 3: Enantioselective palladium catalysed formation of **11**

Base	*Ligand*	*Diastereomer ratio* [a]	*ee of major* [b]	*ee of minor* [b]	*Yield*
LDA	**1**	80 : 20	77 %	64 %	80 %
BSA/CsOAc	**1**	71 : 29	97 %	96 %	82 %
BSA/CsOAc	**2**	78 : 22	97 %	97 %	89 %

[a] Diastereomer ratio determined by HPLC (Microsorb Si-80-120-C5 column hexane/propanol 99.75/0.25)

[b] Enantiomeric excess determined by HPLC (Chiralcel OD column hexane/propanol 99.75/0.25)

In summary, we have demonstrated that palladium catalysed allylic substitution reactions between an imino ester and an achiral palladium allyl intermediate can take place with good diastereoselectivity. In the presence of an enantiomerically pure ligand **1** or **2**, this reaction provides imino esters with excellent enantioselectivity. This route to enantiomerically enriched imino esters is complimentary to the asymmetric alkylation of imino esters achieved in the presence of chiral phase transfer catalysts.[9] We are currently examining our methodology for the synthesis of enantiomerically enriched non-proteinogenic amino acids.

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