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Asymmetric Palladium Catalysed Allylic Substitution Using Phosphorus Containing Oxazoline Ligands[1]

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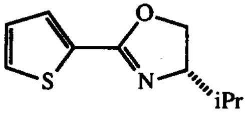
Abstract: A series of new phosphorus-containing oxazoline ligands has been developed. The use of these ligands for asymmetric palladium catalysed allylic substitution of 1,3-diphenylprop-2-enyl-1-acetate **12** with the sodium salt of dimethylmalonate has been achieved with 90 - 94% ee and 88 - 99% yield.

The control of enantioselectivity for palladium catalysed allylic substitution reactions has recently been demonstrated by several groups.[2] Pfaltz has shown that bis-oxazolines are effective ligands,[3] and we have previously shown that the use of thienyl oxazoline **1** as a ligand affords good levels of asymmetric induction in the palladium catalysed allylic substitution process.[4] We now wish to report our results based on the phosphorus containing oxazoline ligands **2** - **6**.



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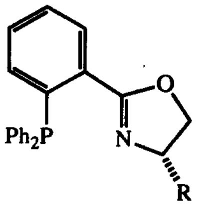
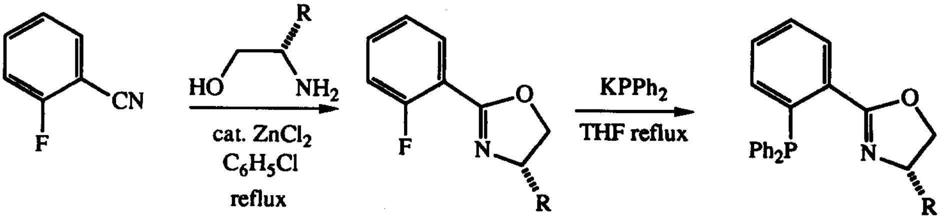


R = Me	**2**
R = CH$_2$Ph	**3**
R = iPr	**4**
R = Ph	**5**
R = tBu	**6**

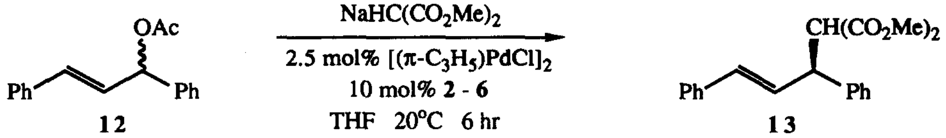
The ligands **2** - **6** are readily accessible in a two step procedure; the reaction of *o*-fluorobenzonitrile with homochiral amino alcohols[5] in the presence of catalytic amounts of zinc chloride[6] affords the 2-(*o*-fluorophenyl)oxazolines **7** - **11**, which are converted to the 2-(*o*-diphenylphosphinophenyl)oxazolines **2** - **6** on treatment with potassium diphenylphosphide in refluxing THF.[7]



R = Me	**7**	47%
R = CH$_2$Ph	**8**	48%
R = iPr	**9**	46%
R = Ph	**10**	49%
R = tBu	**11**	56%

R = Me	**2**	80%
R = CH$_2$Ph	**3**	76%
R = iPr	**4**	76%
R = Ph	**5**	84%
R = tBu	**6**	92%

The reaction of the allyl acetate **12** with the sodium salt of dimethyl malonate in the presence of catalytic $[(\pi-C_3H_5)PdCl]_2$ and the ligands **2** - **6** affords the allyl substituted product **13** in good yield with high enantioselectivity. The reactions were conducted at 20 °C, and were complete within 6 hours. The reaction is considerably faster than the corresponding reaction with the thienyl oxazoline **1**, which takes 48 hours at reflux to reach completion.[8]



The results are summarised in the table for each of the ligands. The enantiomeric excess was determined from analysis of the ^1H nmr spectrum in the presence of the homochiral lanthanide shift reagent $Eu(hfc)_3$, and the absolute stereochemistry of the product was determined as the (S)-(-)-enantiomer by comparison of the optical rotation with literature values.[3,4]

Ligand	***R***	***Isolated yield (%)***	***Enantiomeric excess (%)***
2	Me	88	90
3	$PhCH_2$	96	92
4	^iPr	92	94
5	Ph	96	92
6	^tBu	99	90

The thienyl ligand **1** and the phosphorus ligands **2** - **6** afford the same enantiomer of product in the palladium catalysed allylic substitution. The same relative sense of asymmetric induction is also obtained with the symmetrical bis-oxazolines employed by Pfaltz.[3] We are currently undertaking further studies to try to understand the origin of enantioselection in terms of the steric and electronic factors provided by the ligands.

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References and Notes

1. Reported in part as a poster presentation at the University of Bristol, Transition Metals in Organic Synthesis (2nd International Symposium), 22 - 24 September 1992.
2. For some recent reviews on palladium catalysed allylic substitution see; (a) C. G. Frost, J. Howarth and J. M. J. Williams, *Tetrahedron: Asymmetry*, 1992, 3, 1089. (b) G. Consiglio and R. Waymouth, *Chem. Rev.*, 1989, **89**, 257. (c) B. M. Trost, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 1173.
3. U. Leutenegger, G. Umbricht, C. Fahrni, P-V. Matt and A. Pfaltz, *Tetrahedron*, 1992, **48**, 2143.
4. C. G. Frost and J. M. J. Williams, *Tetrahedron Lett.*, in the press.
5. Homochiral amino alcohols were either commercially available, or prepared by the reduction of the corresponding amino acid, A. Giannis and K. Sandhoff, *Angew. Chem. Int. Ed. Engl.*, 1989, **28**, 218.
6. (a) H. Witte and W. Seeliger, *Justus Liebigs Ann. Chem.*, 1974, **68**, 996. (b) C. Bolm, K. Weickherdt, M. Zehnder and T. Ranff, *Chem. Ber.*, 1991, **124**, 1173.
7. The stereochemical integrity of the ligands was confirmed by measurement of the optical rotation of the amino alcohols obtained upon hydrolysis. All of the ligands and their precursors have been satisfactorily characterised by ^1H nmr and HRMS, and full experimental details will be published shortly.
8. For palladium catalysed allylic substitution reactions, the greater the π-accepting properties of the ligand, the faster the reaction rate. This is described in the literature; B. Åkermark, K. Zetterberg, S. Hansson, B. Krakenberger, A. Vitagliano, *J. Organometallic Chem.*, 1987, **335**, 133.

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