

## Chiral oxazolinylpyridines as ligands for enantioselective palladium catalysed allylic substitution

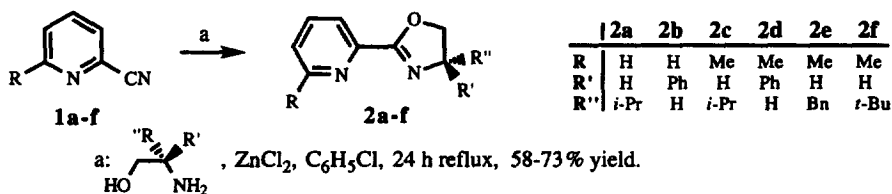
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**Abstract:** Chiral oxazolinylpyridines were prepared and assessed in the enantioselective palladium catalysed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. Enantioselectivity up to 91% was obtained. © 1997 Elsevier Science Ltd

Our interest in the synthesis and application of chiral pyridine derivatives as ligands for metal complexes in enantioselective catalysis<sup>1</sup> has prompted us, on the basis of our very recent report,<sup>2</sup> to prepare new chiral oxazolinylpyridines and to assess these ligands in enantioselective palladium catalysed allylic substitutions.<sup>3</sup>

Oxazolinylpyridines **2a–f**<sup>4</sup> were readily obtained in 58–73% yields by heating under reflux for 24 h a chlorobenzene solution of **1a–f** with the appropriate aminoalcohol in the presence of a catalytic amount of zinc chloride<sup>5</sup> (Scheme 1).



Scheme 1.

As a model study of palladium catalysed allylic substitutions we examined the alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate.<sup>6</sup> Initially, we prepared the oxazolinylpyridines **2a** and **b** which were assessed in this catalytic process following the usual protocol (see Table 1).<sup>7</sup> Both ligands gave a reactive catalytic species which afforded the dimethyl 1,3-diphenylprop-2-enylmalonate **4** in good yield and in 24 and 55% enantiomeric excess,<sup>8</sup> respectively (Table 1). This promising result prompted us to continue this investigation modifying the ligand design. The accepted mechanism for palladium catalysed allylic substitutions which proceed through a meso  $\eta^3$ -allyl intermediate, foresees that the nucleophile attacks the allylic termini of two alternative diastereomeric  $\pi$ -allyl palladium complexes (for instance **5** and **6** for ligand **2c**). The regioselectivity and stereoselectivity of the nucleophilic attack is determined by steric and electronic properties of the ligand.<sup>9</sup> Taking into account steric factors, we thought that a bulkier substituent than hydrogen on the 6-position of the pyridine ring could increase the stabilization of the sterically favoured diastereomeric transition state and in addition could further destabilize the more disfavoured one (**5** and **6**, respectively for ligand **2c**). In other words this substituent which is directed towards the substrate should assist the substituent on the stereocentre of the oxazoline ring to improve the stereodifferentiating ability of the ligand.

As expected, the 6-methylpyridines **2c** and **2d** gave a much higher enantioselectivity (70 and 74% ee, respectively) than the related 6-unsubstituted pyridines **2a** and **2b**. Finally, a further increase of enantioselectivity (91% ee) was achieved with the ligand **2f** bearing the very bulky *t*-butyl group on the oxazoline ring. The stereochemical outcome indicates that the nucleophilic attack is predominantly

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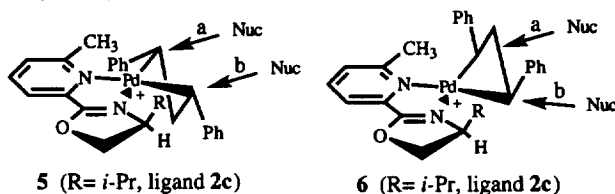
**Table 1.** Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate<sup>a</sup>

Ligand	React. time, h	Yield <sup>b</sup>	% Ee <sup>c</sup>	Conf. <sup>d</sup>
<b>2a</b>	1	84	24	S
<b>2b</b>	2.5	86	55	R
<b>2c</b>	2	93	70	S
<b>2d</b>	4.5	81	74	R
<b>2e</b>	7.5	88	62	S
<b>2f</b>	2.3	92	91	S

<sup>a</sup>Reaction of the ligand (10 mol %) and  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  (2.5 mol %) with 1,3-diphenylprop-2-enyl acetate (0.4 mmol),  $\text{CH}_2(\text{COOMe})_2$  (1.2 mmol), N,O-bis(trimethylsilyl)acetamide (BSA) (1.2 mmol) and KOAc (3.5 % mol) in  $\text{CH}_2\text{Cl}_2$  (2 ml) at r.t.

<sup>b</sup>Isolated yields. <sup>c</sup>Determined by  $^1\text{H-NMR}$  using  $\text{Eu}(\text{hfc})_3$  as chiral shift reagent. <sup>d</sup>The assignment is based on the sign of the specific rotation: Leutenegger, U.; Umbricht, G.; Fahrni, C.; Matt, P.V.; Pfaltz, A. *Tetrahedron*, **1992**, *48*, 2143.

to the allylic terminus *trans* to the oxazoline nitrogen in the more stable conformation (a in **5**) or *cis* in the more reactive one (b in **6**)<sup>10</sup>

**5** (R = *i*-Pr, ligand **2c**)**6** (R = *i*-Pr, ligand **2c**)

In summary we have shown that simple chiral oxazolinylpyridines are very effective ligands for palladium catalysed allylic substitutions. Further studies aimed at the application of these ligands in other palladium catalysed allylic substitutions are now in progress.

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