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Enantioselective Palladium Catalysed Allylic Substitution. Electronic and Steric Effects of the Ligand.

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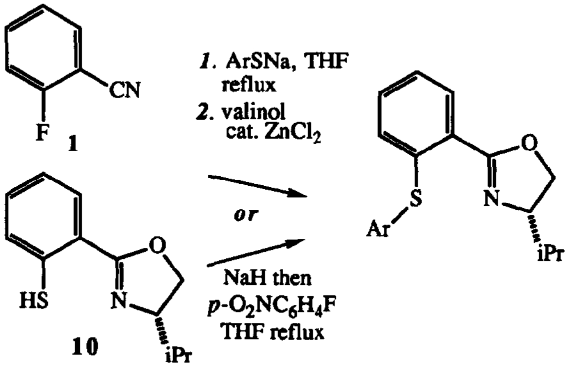
Abstract: Ligands containing an enantiomerically pure oxazoline and a sulfur-containing tether have been examined for their ability to provide asymmetric induction in palladium catalysed allylic substitution reaction. The enantioselectivity obtained was found to be highly dependent upon the stereochemistry at sulfur (for sulfoxides), and also somewhat dependent upon the nature of the aryl group attached to the sulfur.

Recently, this group and others have examined the use of phosphorus[1] and sulfur[2]-containing oxazolines as ligands for asymmetric palladium catalysed allylic substitution reactions. Ligands containing two different donor atoms are able to impart an electronic distortion upon the allyl moiety in an intermediate palladium allyl complex, and nucleophilic addition to the complexed allyl is predicted to occur *trans* to the better π-acceptor.[3]

Herein, we report our findings with regard to variation in the nature of the aryl group attached to the sulfide ligands, and also of the importance of the stereochemistry at the sulfur atom.

Ligands **2-8** were prepared by the reaction of *o*-fluorobenzonitrile **1** with an appropriate thiolate,[4] followed by oxazoline formation upon treatment with valinol and catalytic zinc chloride.[5] Ligand **9** was prepared from the oxazoline containing thiol **10**[6] by deprotonation and reaction with *p*-fluoronitrobenzene.



	Ar	*1*	*2*
2	Ph	82%	41%
3	o-MeC$_6$H$_4$-	74%	57%
4	p-MeC$_6$H$_4$-	75%	88%
5	o-MeOC$_6$H$_4$-	80%	59%
6	p-MeOC$_6$H$_4$-	86%	54%
7	o-NCC$_6$H$_4$-	48%	53%
8	p-Me$_2$NC$_6$H$_4$-	60%	80%
9	p-O$_2$NC$_6$H$_4$-	(66% from **10**)	

These ligands were examined for their ability to introduce asymmetric induction in a palladium catalysed allylic substitution reaction.[7] Thus, treatment of 1,3-diphenylpropenyl acetate **11** with three equivalents of dimethyl malonate and BSA (bistrimethylsilylacetamide) and catalytic amounts of ligand, potassium acetate and allylpalladium chloride dimer in dichloromethane at 20°C for 48 hours afforded the substitution product **12**. The enantioselectivity of the reaction was determined from integration of the signals in the NMR spectrum due to one of the methoxy groups in the presence of the chiral shift reagent Eu(hfc)$_3$. The results of these reactions are given in Table 1 (at [**11**] = 0.08M) and in Table 2 (at [**11**] = 0.4M).

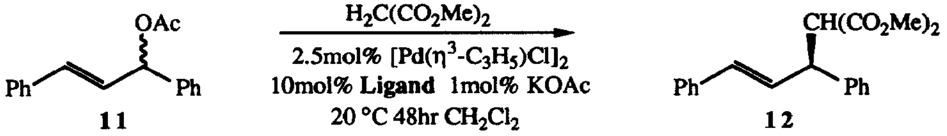


Table 1: Palladium catalysed conversion of **11** (at 0.08M) into the substitution product **12**

Ligand	*Aryl group*	*E.e. (%)*	*Conversion (%)*
2	Ph	89	36
3	*o*-MeC_6H_4-	88	41
4	*p*-MeC_6H_4-	93	69
7	*o*-NCC_6H_4-	81	10
8	*p*-$Me_2NC_6H_4$-	92	39
9	*p*-$O_2NC_6H_4$-	87	16

The low conversions observed in Table 1 were remedied by concentration of the reaction mixture from a starting concentration of **11** from 0.08M to 0.4M, and the latter results are given in Table 2.

Table 2: Palladium catalysed conversion of **11** (at 0.4M) into the substitution product **12**

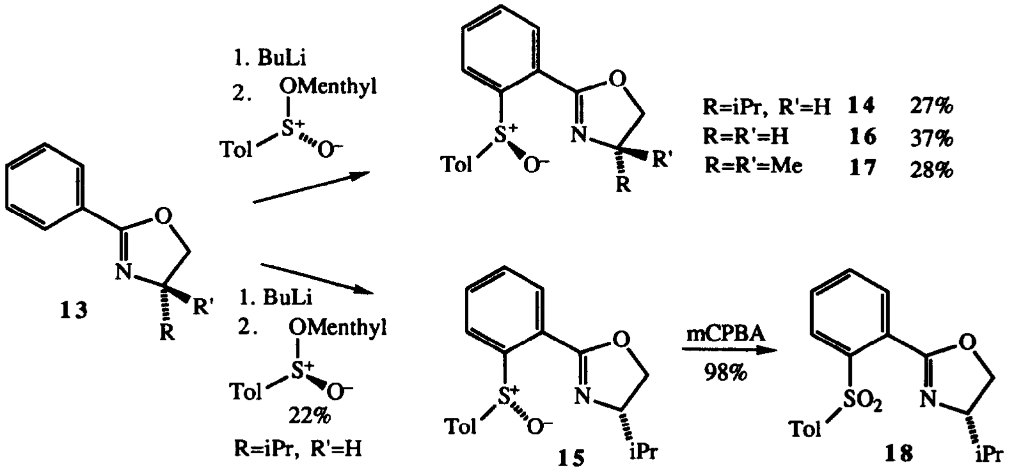
Ligand	*Aryl group*	*E.e. (%)*	*Conversion (%)*
2	Ph	92	100
3	*o*-MeC_6H_4-	91	100
4	*p*-MeC_6H_4-	92	100
5	*o*-$MeOC_6H_4$-	90	81
6	*p*-$MeOC_6H_4$-	88	100
7	*o*-NCC_6H_4-	85	100
8	*p*-$Me_2NC_6H_4$-	92	96
9	*p*-$O_2NC_6H_4$-	87	60

The results in the Tables 1 and 2 indicate relatively small changes in the enantioselectivity provided by the ligands despite changes in the nature of the aryl group (from 81-93%ee). The lowest level of enantioselectivity was provided by the ligand containing an *ortho*-cyano group, and the detrimental effect on enantioselectivity may be caused by either the change in sterics or electronics. However, comparison of the enantioselectivity provided by ligands containing differing *para*-substituents suggests that any effects would be caused by electronic effects.

However, considering reactions at the same concentration, there is only a small effect on enantioselectivity (compare ligands **8** and **9** which afford 92 and 87% ee respectively). At lower concentration, the extent of conversion was lower in all cases. However, it seems that ligands which contain an aryl group possessing an electron withdrawing group afford a lower yield in the palladium substitution reaction (ligands **7** and **9** affording 10 and 16% conversions respectively at the lower concentration).

We have already reported that replacement of the isopropyl group in ligand **2** with a t-butyl group affords a ligand which provides very high enantioselectivity (>96%ee).[2] However, we chose not to examine further analogues of a t-butyl containing ligand, since any variations caused by the electronic nature of the ligand would be difficult to detect.

Oxazolines tethered to sulfoxides were prepared in modest (unoptimised) yield by ortho-lithiation of the parent 2-phenyloxazoline **13** with BuLi[8] and addition of either (*S*)- or (*R*)-p-tolylmenthylsulfinate.[9] Both diastereomeric isomers **14** and **15** were prepared in this manner.[10] Additionally, ligands **16** and **17** in which the oxazolinyl moiety is achiral, and the asymmetry of the ligand is simply a consequence of the sulfoxide stereochemistry were prepared in an analogous manner. The sulfone **18** was prepared by treatment of the sulfoxide oxazoline **15** with mCPBA.



The sulfoxide and sulfone ligands were also examined in the palladium catalysed allylic substitution process. The substitution product **12** was obtained with the yields and enantioselectivities indicated in Table 3.

Table 3: Pd catalysed conversion of **11** (at 0.06M) to the substitution product **12** using sulfoxide and sulfone ligands

Ligand	*E.e. (%)*	*Yield (%)*
14	88	96
15	55	42
16	56	92
17	49	60
18	-	0

Ligand **14** provides both a much greater enantioselectivity and also yield in the palladium catalysed reaction than does the diastereomeric ligand **15**. This suggests that the stereochemistry of the sulfur centre is important in determining the stereochemical outcome of the reaction. Since the sulfide ligands afford similar levels of enantioselectivity to the better diastereomeric sulfoxide ligand **14**, we assume that the stereochemistry of the sulfides can switch readily to the preferred configuration upon binding to the palladium. The sulfone ligand **18**, which is not able to bind to palladium through sulfur did not provide a reactive palladium catalyst, suggesting that coordination through the oxygen of the sulfone is unfavourable. Furthermore, this suggests that the sulfoxide ligand is more likely to bind through the sulfur atom than the oxygen.[11]

Also of interest is the reasonable level of enantioselectivity provided by the ligands **16** and **17**. Here the enantiocontrol in the palladium catalysed reaction is being controlled entirely by the stereochemistry of the sulfoxide unit. Sulfoxides have been used as ligands in other reactions,[12] although this is the first example of sulfoxides as ligands controlling the enantioselectivity of palladium catalysed allylic substitution. Future efforts will consider ligands in which a sulfoxide is tethered to other donor ligands.

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