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Enantioselective Palladium Catalysed Allylic Substitution with Sulfur-Containing Oxazoline Ligands

Christopher G Frost and Jonathan M J Williams*

Department of Chemistry, Loughborough University of Technology, Loughborough, Leicestershire, LE11 3TU, UK.

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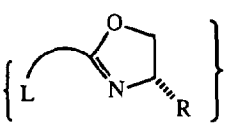
Abstract: Enantiomerically pure sulfur/nitrogen ligands have been prepared in one step from amino alcohols and 2-(methylthio)benzonitrile. We have successfully employed these ligands for enantioselective palladium catalysed allylic substitution, with asymmetric induction of up to 80% ee

In recent years, enantiomerically pure oxazoline ligands have been employed successfully to control the enantioselectivity of various metal catalysed processes.[1]

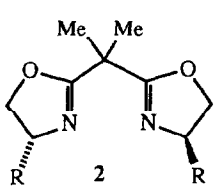
We are currently examining the preparation of ligands **1** which possess the homochiral oxazoline group and contain a tethered auxiliary donor ligand.[2] Such ligands are anticipated to control asymmetric induction in catalytic reactions by a combination of the asymmetric environment provided by the oxazoline and the electronic disparity of the donor atoms.

Auxiliary Donor Ligand  ***Chirality-Controlling Oxazoline Moiety***

1

Enantiocontrol using oxazoline ligands has been achieved in palladium catalysed allylic substitution[3] by ourselves[4] and by other groups[5] with the ligands **2-4**.

The enantioselectivity and rate of reaction for the palladium catalysed allylic substitution process are greatest for the P/N ligand **4**. Both the steric bulk and the π-accepting properties of the diphenylphosphinyl moiety may be important in controlling enantioselectivity. All of these ligands are synthetically accessible in a few steps from commercially available starting materials.



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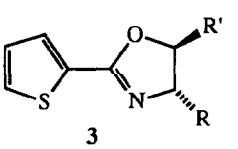

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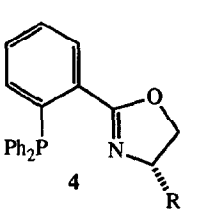
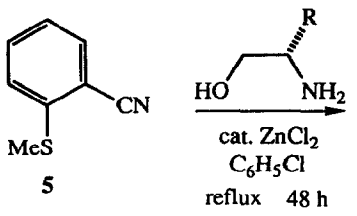


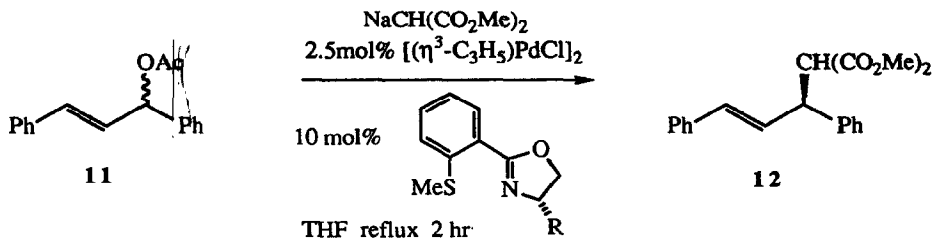
4

Herein we report the sulfur-containing analogues of ligand **4** which are prepared in one step from commercially available 2-(methylthio)benzonitrile[6] and enantiomerically pure amino alcohols. Thus, treatment of **5** with amino alcohols in the presence of catalytic amounts of anhydrous zinc chloride affords the *o*-thioanisyloxazolines **6-10** in reasonable yields.[7] These robust, air-stable ligands are readily purified by column chromatography.[8]



R = Me	**6**	60%
R = CH_2Ph	**7**	42%
R = iPr	**8**	56%
R = Ph	**9**	58%
R = tBu	**10**	53%

With the ligand synthesis in hand, we investigated the suitability of these ligands for asymmetric palladium catalysed allylic substitution. Thus, treatment of the allyl acetate **11** with a slight excess of the sodium salt of dimethylmalonate in refluxing THF in the presence of 2.5 mol% $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and 10 mol% of the ligand **6-10** afforded the substitution product **12** in good yields and with reasonable levels of asymmetric induction after 2 hours. In each case we obtained the S-(-)-enantiomer predominating, as illustrated.[9]

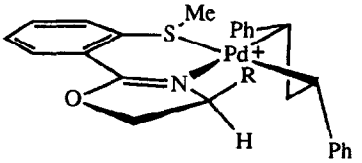


Ligand	*Isolated yield (%)*	*Enantiomeric excess (%)*
6	91	40
7	78	50
8	93	55
9	95	62
10	92	68

The rate of the allylic substitution reaction with these ligands is greater than for the thienyl ligands. The rate difference may be attributed to the π-acceptor ability of sulphur as a sulphide in the ligands **6-10**, whereas in the electron rich thiophene ring, the sulfur is not a π-acceptor.[10] Encouraged by the reactivity of these ligands, we found that the reaction still proceeded to completion within 12 hours at 20 °C, and that the process was more enantioselective at this lower temperature.

Ligand	*Isolated yield (%)*	*Enantiomeric excess (%)*
7	90	52
8	98	58
9	84	66
10	86	80

Palladium catalysed allylic substitution reactions are known to proceed *via* π-allyl complexes,[3] and so there are two possible diastereomeric intermediates **13** and **14** which may be considered for these ligands. We had originally assumed that nucleophilic addition would occur *trans* to the better π-acceptor (sulfur) in what would appear to be the more stable intermediate **13**, although this would lead to the R-(+)-enantiomer which we do not observe. However, as recently suggested by Reiser[11] for the analogous thienyl and phosphine ligands **3** and **4**, the reaction may proceed through the less stable (and perhaps more reactive) intermediate, in this case the intermediate **14**.



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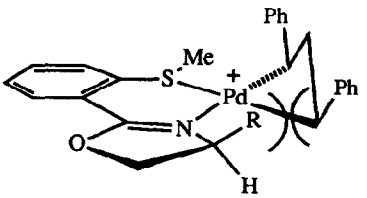

14

We considered that the rate at which equilibrium can occur may therefore have an effect on the enantioselectivity of the reaction. Palladium allyl complexes are able to equilibrate in the presence of acetate,[12] and we have found that addition of acetate to the reaction dramatically decreases the observed enantioselectivity of the product. This observation suggests that the equilibration of the possible diastereomeric intermediates may be of importance to the enantioselectivity of palladium catalysed allylic substitution in the presence of these ligands. We are currently trying to identify other factors which may increase or decrease levels of enantioselectivity for this process.

Added acetate	*Enantiomeric excess (%)*
None	58
1eq KOAc	48
10eq KOAc	30
10eq NaOAc	34

Conversion of **11** to **12** in the presence of acetate using ligand **8** at 20 °C[13]

Since acetate is produced during the course of the reaction, there will be one equivalent of acetate present by the end of the reaction. To remove acetate completely from the reaction, we investigated the possibility of employing an alternative leaving group. However, when diethylphosphate was employed as the leaving group, we found that the substitution product **12** was formed with only 26% ee, when using ligand **9** at 20 °C.

In summary, we have shown that *o*-thioanisyl oxazolines **6-10** are able to function as ligands for palladium catalysed allylic substitution. For the allyl acetate **12**, asymmetric inductions of 40-80% ee and yields of 78-98% have been achieved with the sodium salt of dimethyl malonate as the nucleophile. Further studies including modifications to ligand design and reaction conditions are in progress.

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5. (a) Ligand **2**: U. Leutenegger, G. Umbricht, C. Fahrni, P. von Matt and A. Pfaltz, *Tetrahedron*, 1992, **48**, 2143. (b) Ligand **4**: J. Sprinz and G. Helmchen, *Tetrahedron Lett.*, 1993, *34*, 1769. (c) Ligand **4**: P. von Matt and A. Pfaltz, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 566.
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9. The enantiomeric excess was assayed using 0.8 equivalents of the homochiral shift reagent Eu(hfc)$_3$, which gave baseline separation of one of the ^{1}H nmr signals due to a methyl ester. The absolute stereochemistry was determined by measurement of the optical rotation and comparison with literature values (ref 5a).
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12. For an example of epimerisation of π-allyl complexes with acetate, see; H. Greenberg, V. Langer and J. E. Bäckvall, *J. Chem. Soc., Chem. Commun.*, 1991, 1190.
13. In the presence of 0.5 equivalents of NaOAc, using ligand **10** at 20 °C, the enantiomeric excess fell from 80% to 72%.