Tetrahedron Letters, Vol. 34, No. 48, pp. 7793-7796, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Sulfides Tethered to Oxazolines: Ligands for Enantioselective Catalysis

Graham J. Dawson, Christopher G. Frost, Christopher J. Martin and Jonathan M. J. Williams*

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

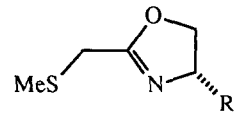
Steven J. Coote

Glaxo Group Research Ltd., Ware, Herts, SG12 0DP, UK.

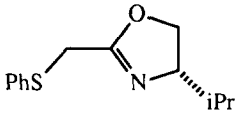
Abstract: Sulfides tethered to oxazolines function as effective ligands for palladium catalysed allylic substitution, affording good to excellent levels of enantioselectivity (56 to >96% ee). Both the tether length between the nitrogen and sulfur atoms and also the nature of the sulfide have been shown to affect the performance of these ligands.

Palladium catalysed allylic substitution has been exploited in terms of chemo-, regio-, diastereo-, and enantioselectivity.[1] Recently, the use of enantiomerically pure phosphorus-containing oxazoline ligands has been successfully exploited both by this group[2] and by others[3,4] for asymmetric palladium catalysed allylic substitution. Furthermore, we have previously reported the preparation of enantiomerically pure oxazolines tethered to thiophenes[5] and to aryl sulfides.[6]

The combination of an oxazoline group with an auxiliary donor atom provides a bidentate ligand which creates an electronic bias in the metal catalyst. However, the precise nature of the auxiliary donor atom will have an influence on the electronic and steric environment around the metal. In order to examine such influences, we have prepared new ligands **1** - **8** containing both the oxazoline moiety and an auxiliary sulfide donor.



R = Ph **1**
R = iPr **2**
R = tBu **3**



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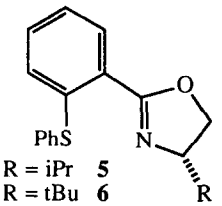
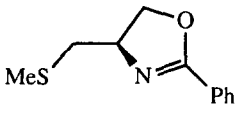


R = iPr **5**
R = tBu **6**



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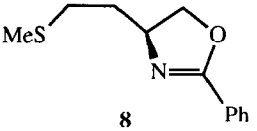

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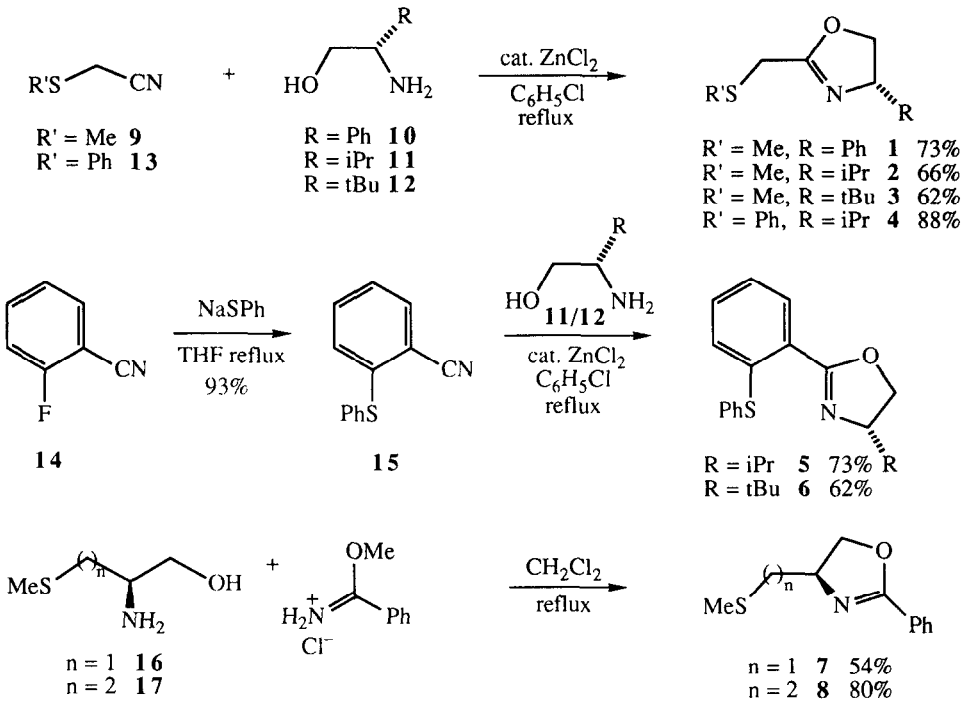
Ligand syntheses were readily achieved as follows: Treatment of methylthioacetonitrile **9** with enantiomerically pure amino alcohols **10** - **12** and catalytic amounts of zinc chloride in chlorobenzene at reflux for 48 hours afforded the corresponding oxazolines **1** - **3** in good yields.[7] Similarly, treatment of

phenylthioacetonitrile **13** under the same conditions with valinol **11** afforded oxazoline **4**. The reaction of *o*-fluorobenzonitrile **14** with sodium phenylthiolate afforded the diarylsulfide **15**.[8] Subsequent reaction of **15** with amino alcohols **11** and **12** afforded the oxazolines **5** and **6**. Oxazolines **7** and **8**[9] were prepared from methioninol **16** and methyl cysteinol **17** in 54% and 80% yields respectively, on treatment with methylbenzimidate hydrochloride in dichloromethane at reflux for 18 hours. All of these ligands were purified by flash chromatography, and satisfactorily characterised by high field NMR, IR and HRMS.



The oxazolines **1** - **8** were employed as ligands for enantioselective palladium catalysed allylic substitution. Thus, treatment of 1,3-diphenylprop-2-enyl-1-acetate **18** with the sodium salt of dimethylmalonate **19** in the presence of palladium catalyst and catalytic ligand **1** - **8** afforded the substitution product **20** with good to excellent levels of enantioselectivity. The experimental conditions are provided in the Table. The enantiomeric excess was determined from examination of the ^{1}H nmr spectrum of **20** in the presence of the shift reagent Eu(hfc)$_3$, and the absolute stereochemistry of the product was determined by comparison of the optical rotation with literature values.[10]

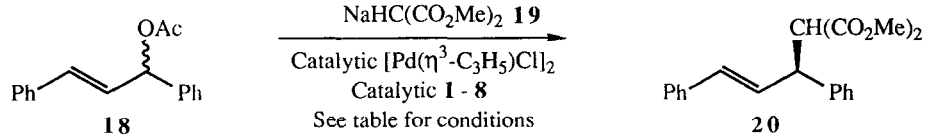


Table: Conversion of **18** into **20** with palladium catalyst and enantiomerically pure ligands.

Ligand	*Catalyst*[b]	*Conditions*	*Yield (%)*	*ee (%)*	*Enantiomer*
1	2mol% Pd; 4mol% L*	THF, reflux, 24hr	67	60	(S)-(-)
2	2mol% Pd; 4mol% L*	THF, reflux, 24hr	74	70	(S)-(-)
3	2mol% Pd; 4mol% L*	THF, reflux, 24hr	69	75	(S)-(-)
3	2mol% Pd; 4mol% L*	THF, 20°C, 48hr	76	74	(S)-(-)
4	2mol% Pd; 4mol% L*	CH_2Cl_2, reflux, 48hr[a]	52	76	(S)-(-)
5	5mol% Pd; 10mol% L*	THF, 20°C, 36hr[a]	91	78	(S)-(-)
5	5mol% Pd; 10mol% L*	CH_2Cl_2, 20°C, 36hr[a]	96	90	(S)-(-)
6	5mol% Pd; 10mol% L*	CH_2Cl_2, 20°C, 48hr[a]	67	>96	(S)-(-)
6	5mol% Pd; 10mol% L*	CH_2Cl_2, 20°C, 96hr[a]	92	>96	(S)-(-)
7	5mol% Pd; 20mol% L*	THF, 20°C, 48hr	86	56	(R)-(+)
8	5mol% Pd; 20mol% L*	THF, 20°C, 48hr	79	88	(R)-(+)

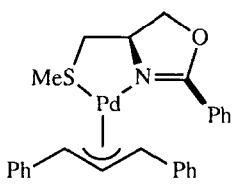
[a] These reactions were run using $MeO_2CCH_2CO_2Me$ and BSA (bis-trimethylsilyl acetamide) with catalytic KOAc (3mol%) in place of $NaCH(CO_2Me)_2$ as the nucleophilic component (ref 3 and 4).
[b] $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was used as the palladium source (5mol% Pd = 2.5mol% dimeric catalyst)

Interestingly, oxazolines **1-6** afford an excess of the (S)-(-)-enantiomer of **20**, whereas oxazolines **7** and **8** afford an excess of the (R)-(+)-enantiomer of **20**, even though all of the ligands were prepared from the same relative configuration of amino acid. Comparison of the isomeric ligands **1** and **7** reveals that, in terms of their topology, these ligands are quasi-enantiomeric.

The results indicate that aryl sulfides provide higher levels of enantioselectivity than do alkyl sulfides, since ligand **4** affords the substitution product with 76% ee, whereas ligand **2** affords 70% ee, and the diaryl ligands **5** and **6** provide the highest levels of selectivity.[11] The superior asymmetric induction achieved with the aryl sulfides may be rationalised in terms of steric effects or electronic effects (aromatic sulfides are better π-acceptors than aliphatic sulfides)[6]

Trost has reported that as the length of the tether in bidentate ligands is increased, so the bite angle of the ligand can be increased.[12] This in turn places the chiral environment of the ligand closer to the allyl unit, and thereby can produce greater levels of asymmetric induction. In complex **22** the ligand is forced into closer proximity with the allyl moiety than for complex **21**, and hence greater enantioselectivity should be provided by ligand **8** which proceeds *via* complex **22** than for ligand **7**, which proceeds *via* complex **21**.

This is confirmed by experiment, where ligand **8** affords the product **20** with 88% ee, whereas ligand **7** affords only 56% ee.



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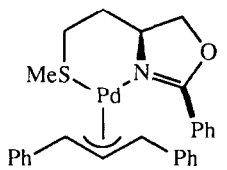

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In a previous study, we have demonstrated that the enantioselectivity of the palladium catalysed allylic substitution process may be affected by the presence of acetate.[6] With the ligands described herein, we have observed that the use of stoichiometric amounts of $Pd(dba)_2$ [bis(dibenylideneacetone)palladium] results in a lowering of enantioselectivity. Thus, treatment of $Pd(dba)_2$ with one equivalent of ligand **2** and 1,3-diphenylprop-2-enyl-1-acetate **18**, stirring for 12 hours, followed by addition of excess **19** afforded the substitution product **20** with only 32% ee, as opposed to the catalytic reaction which afforded 70% ee.

Palladium catalysed allylic substitution reactions proceed *via* π-allyl complexes and equilibration between π-allyl complexes has been reported to be promoted by the presence of Pd(0).[13] We speculate that it may be the rate of equilibration between the possible π-allyl complexes which affects the enantioselectivity of the reaction.

In summary, we have prepared several novel ligands containing oxazoline groups tethered to sulfides. These ligands have been effective for asymmetric palladium catalysed allylic substitution. The steric or electronic properties of the sulfide and the tether length of these bidentate ligands are important in determining the success of these ligands for palladium catalysed allylic substitution.

Further studies regarding the scope of this reaction, and addressing more detailed mechanistic issues will be reported in due course.

Acknowledgements. We thank Glaxo Group Research for a studentship (to GJD) and the SERC for a QUOTA studentship (to CGF). We are grateful to Johnson Matthey for the loan of palladium salts.

References and Notes

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(Received in UK 27 August 1993; accepted 24 September 1993)