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Sulfur–imine mixed donor chelate ligands for asymmetric catalysis: enantioselective allylic alkylation

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Abstract

A new series of sulfur–imine mixed donor chiral ligands, prepared in only two steps from commercially available (*S*)-valinol, have been shown to give up to 94% enantiomeric excess in a palladium-catalysed allylic substitution reaction.

We have developed a new series of sulfur–imine mixed donor chiral ligands **1** prepared in only two steps from a commercially available amino alcohol. In this preliminary study we have demonstrated them to be good ligands for the palladium-catalysed substitution of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. Sulfur–nitrogen ligands have been used for enantioselective allylic substitution reactions[1] and recently a report has appeared using a phosphorus-containing chiral amidine ligand.[2] Due to the similar structure and reasoning behind the development of these ligand systems, we wish to report our preliminary studies in this communication.

The successful use of metal complexes for enantioselective catalysis is largely dependent upon the structure and electronic properties of chiral ligands. We set out to develop a series of new chiral *N,S*-chelates, derived from amino acids, where the chirality inherent to the backbone of the amino acid could be transmitted closer towards the reaction centre by the correct choice of donor groups and substituents. We have tackled this idea by preparing ligands **1**, **2** and **3** (Fig. 1) that all possess a ligating sulfur atom in place of the hydroxyl group derived from the amino acid. We hoped we could obtain good catalytic activity, as sulfur would have a high affinity towards most metals useful in catalytic reactions, have less tendency to diminish the Lewis acidity of the metal compared to metal alcoholates[3] and continue to render the ligands heterodentate. Our first efforts in this area involved the synthesis of amino thiols **2**. These were found to be poor ligands in asymmetric cuprate reagents, but more fruitful in the asymmetric addition of diethylzinc to aromatic aldehydes.[4] To assay the effectiveness of ligand systems **3** in palladium catalysis we chose the popular test reaction involving the substitution of 1,3-diphenyl-2-propenyl acetate **4** with the nucleophile derived from the reaction of dimethyl malonate, *N,O*-bis(trimethylsilyl)acetamide (BSA)

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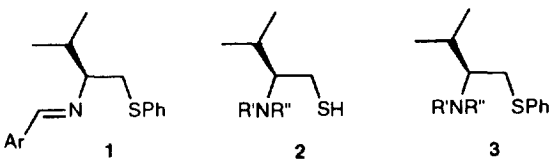
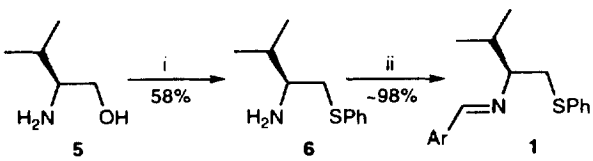


Fig. 1.

and potassium acetate as catalyst. The palladium catalyst (5 mol%) was preformed by refluxing the allyl palladium chloride dimer with 2 molar equivalents of the chiral ligand in dichloromethane for 2 hours. Sulfides **3**, closely related to ligands **2**, were inactive,[5] but transformation of the amine function into an imine produced ligands which made good chiral catalysts with palladium. This was not surprising as amine ligands afford palladium complexes of low reactivity compared to ligands containing donor groups that are π-acceptors.[1a] We believe the unsaturated nitrogen atom may offer greater stabilisation to low oxidation state electron-rich transition metals, such as palladium, due to the low lying N=C π* orbital. This has important implications in the rationalisation of a transition state model to explain the enantioselection in our ligand system.

Ligands **1** are prepared in only two steps from commercially available (*S*)-valinol **5** (Scheme 1).[6] Exchange of the hydroxyl group was achieved by heating in a sealed tube with diphenyldisulfide and tri-*n*-butylphosphine to give the aminosulfide **6** in 58% yield.[7] Formation of the imine was readily achieved in near quantitative yield by treatment with an aromatic aldehyde in dichloromethane at room temperature, employing anhydrous magnesium sulfate as desiccant. A range of imines **1** were prepared in order to investigate the steric and electronic influences of these ligands. This short and high yielding synthesis could be used to synthesise a wide range of structurally and electronically modified ligands.

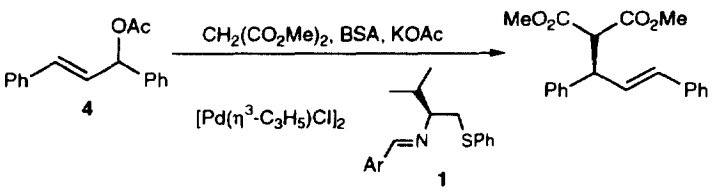


Scheme 1. (i) 3 equiv. PhSSPh, 4 equiv. Bu_3P, THF, 76°C, 72 h; (ii) 1.0 equiv. ArCHO, CH_2Cl_2, rt, 16 h

Our initial experiments in this simple system for palladium-catalysed asymmetric allylic substitutions are promising, as summarised in Table 1, and show enantiomeric excesses of up to 94% (entry 6). The sense of enantioinduction was confirmed by specific rotation of the product methyl-2-carbomethoxy-3,5-diphenylpent-4-enoate[1] and was found to be *R* for all cases. The electronic and steric properties of the imine aromatic group have been briefly investigated. It would appear that electron-withdrawing substituents give a lower enantiomeric excess (compare entry 1 to entry 2), whereas an electron-donating substituent has little effect (compare entry 1 to entry 3). Sterically demanding groups in the *ortho* position seem to be deleterious (entries 4 and 5). However a chloro substituent in the *ortho* position gives us, at present, our best enantiomeric excess (entry 6, 94%). The lone pairs of halogens are known to overlap with aromatic π-systems, but at the same time halogens deactivate the aromatic nucleus. The chloro substituent in this ligand system has a complex mixture of steric and electronic properties and further studies are underway to understand them.

In Fig. 2, only possible intermediates **7** to **10** that could lead to the observed enantiomer of the product with our ligand systems are depicted. The origin of chirality in palladium-catalysed allylations using chiral mixed donor ligands is widely accepted to be due to the nucleophile attacking the π-allyl complex *trans* to the better π-acceptor.[1a,c,8] In our ligand system we believe that the imine group is the better π-acceptor as thioethers are considered poor π-acceptors[9] and the amine ligands **3** (secondary and tertiary)

Table 1
Allylic alkylation of (±)-(*E*)-diphenyl-2-propenyl acetate catalysed by palladium–**1** complex



entry	Ar	yield (%)[a]	ee (%)[b]
1	C_6H_5	86	89
2	*p*-$O_2NC_6H_4$	77	82
3	*p*-$MeOC_6H_4$	85	88
4	2,4,6-$Me_3C_6H_2$	90	84
5	9-anthryl	77	83
6	*o*-ClC_6H_4	87	94
7	*p*-ClC_6H_4	78	89

a Isolated yield. *b* Determined by ^1H NMR using the chiral shift reagent Eu(hfc)$_3$

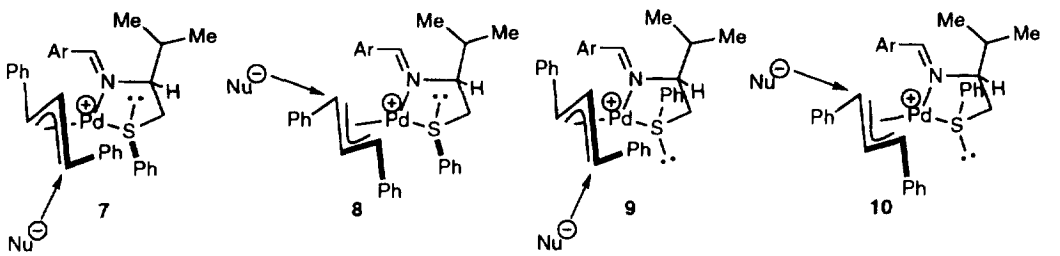


Fig. 2. Possible intermediate π-allyl complexes

produced unreactive complexes.[5] This effectively rules out intermediates **8** and **10** (Fig. 2) as possibilities to account for the sense of enantioselection. In any case, these intermediates both possess destabilising steric interactions: **8** has an interaction between the allyl phenyl and the sulfide phenyl and **10** has a 1,3-interaction between the sulfide phenyl and the *iso*-propyl on the backbone of the chelate ligand. The intermediates shown in Fig. 2 all illustrate the principle of our ligands transmitting the chirality inherent to the backbone of the amino acid closer to the reaction centre. We believe the *iso*-propyl group on the backbone of the chelate ring can dictate the chirality at the sulfur centre upon coordination. Thioethers have been shown to be tetrahedral when bound to transition metals.[10] The extent to which the *iso*-propyl stereogenic centre affects the planarity of the imine awaits the results of further investigations. Of the two intermediates where the trajectory of the nucleophile is *trans* to the donor group which we believe is the better π-acceptor, we anticipate that **7** would be more stable. A combination of both of the steric interactions that destabilise intermediates **8** and **10** is present in **9**. If it is not unreasonable to assume that palladium-catalysed allylations proceed through the intermediate which is the major diastereoisomer at equilibrium[8a] then intermediate **7** could account for the sense of enantioselection recorded for these ligands.

In summary, we have developed a new mixed donor ligand for the enantioselective palladium-catalysed allylic substitution reaction. The ligands are available in only two steps from commercial amino alcohols. The ligand system described corroborates our principles of ligand architecture and the

concept of transmitting the chirality inherent to a chiral ligand closer to the reaction centre for maximum effect. Further reaction variables such as solvent, catalyst loading and substituent effects are being fully investigated to further support our transition state model and will be reported in due course.

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