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New chiral C_2-symmetric bis(oxazolinylpyridinyl)dioxolane ligands for asymmetric catalysis: palladium catalysed allylic substitution

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Abstract: New chiral C_2-symmetric bis(oxazolinylpyridinyl)dioxolane ligands were prepared and assessed in the enantioselective palladium catalysed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. Enantioselectivities up to >98% were obtained. © 1997 Elsevier Science Ltd

Our interest in the synthesis and application of chiral pyridine derivatives as ligands for metal complexes in enantioselective catalysis[1] has prompted us to design and synthesise a new class of chiral C_2-symmetric oxazolinylpyridine ligands.[2] In this communication we report the synthesis of (4*S*,5*S*)-2,2-dimethyl-4,5-bis[6-(4-substituted-2-oxazolinyl)pyridin-2-yl]-1,3-dioxolanes **3a–c** and the preliminary results obtained with these ligands in enantioselective palladium catalysed allylic substitutions.[3]

The design of these new ligands is such that it is possible to single out for them, on the basis of a molecular modelling study, two limiting conformations both maintaining C_2-symmetry: in the former case they could behave as bis-bidentate ligands (Scheme 1, left), whereas in the latter they could coordinate to a metal atom in a tetradentate fashion (Scheme 1, right). Moreover, by proper selection both of the configuration of the stereocentre and the bulkiness of the substituent on the oxazoline ring, the structures of ligands should be adjustable for the specific requirement of a particular metal-catalysed reaction.

The synthesis of ligands **3a–c** started from the (4*S*,5*S*)-2,2-dimethyl-4,5-bis(2-pyridinyl)-1,3-dioxolane **1** which was accessible from L-(+)-diethyltartrate following a literature procedure[4] (Scheme 1). Thus, the reaction of **1** with 3-chloroperbenzoic acid in CH_2Cl_2 at room temperature for two days[5] gave the corresponding dioxide, which, by treatment with dimethylcarbamyl chloride and trimethylsilylcyanide in CH_2Cl_2 at room temperature for 6 days[6] afforded the dinitrile **2** in 85% yield. Finally, the oxazolinylpyridines **3a–c**[7] were obtained in 68–73% yields by heating under reflux for 24 h a chlorobenzene solution of **2** with the appropriate aminoalcohol in the presence of catalytic amount of zinc chloride.[8]

To test the ability of new ligands to provide asymmetric induction in palladium-catalysed allylic substitutions, which can be designed in a variety of ways,[9] we chose to focus on reactions which proceed through a *meso* η^3-allyl intermediate. As a model study of this class of reactions we examined the alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. Allylic substitutions were carried out employing Trost's procedure which used $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as procatalyst and a mixture of dimethyl malonate, N,O-bis(trimethylsilyl)acetamide (BSA) and potassium acetate.[10] The reactions were carried out in methylene chloride at room temperature or at reflux.

Initially, we prepared and assessed in this catalytic process the oxazolinylpyridine **3a**. This ligand gave a moderately reactive catalytic species which required 78 h at room temperature to afford the dimethyl 1,3-diphenylprop-2-enylmalonate **5** in 78% yield and 67% enantiomeric excess with the (*S*)-enantiomer prevalent. When the reaction was carried out at reflux a shorter reaction time (6 h) was needed with only a small drop in enantioselectivity (62% ee) (Table 1).

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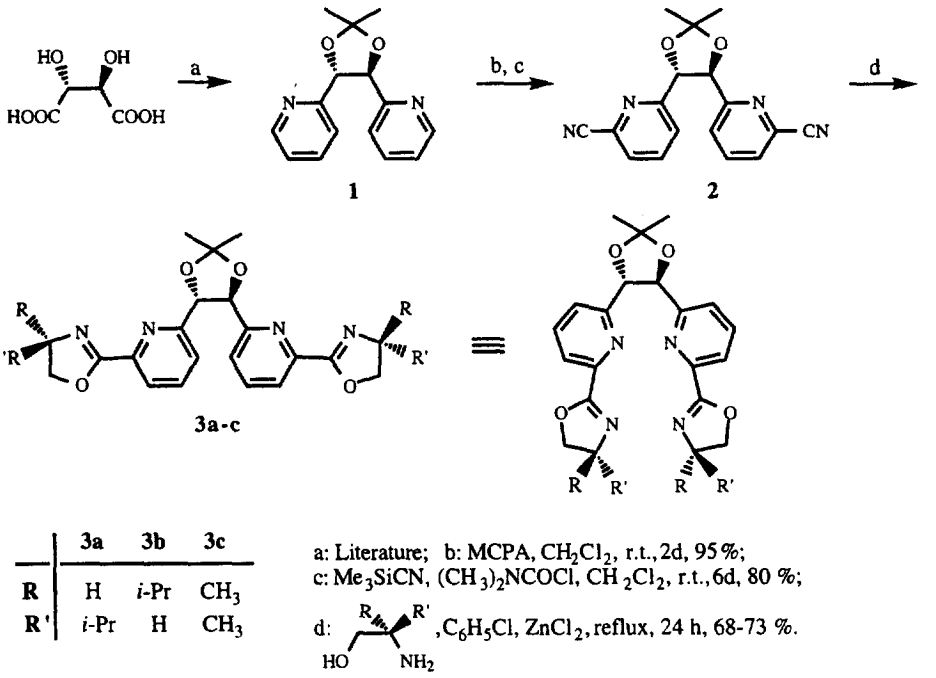

	3a	3b	3c
R	H	*i*-Pr	CH_3
R'	*i*-Pr	H	CH_3

Scheme 1.

Then, we prepared the ligand **3b** which differs from **3a** by the opposite configuration of the stereocentre on the oxazoline ring. Using **3b** the substitution allylic compound **5** was obtained enantiomerically pure (ee >98%) with the (*S*)-configuration.

The stereochemical outcome showed that the two ligands **3a** and **3b** derived from the two opposite enantiomers of the same aminoalcohol gave very different enantioselectivity but the same chiral sense of enantioselection. Therefore, the stereochemical course of the reaction was determined mainly by the chirality of the dioxolane ring. On this basis, we prepared the compound **3c** with no stereocentre on the oxazoline ring. Also in this case **5** was obtained as a single enantiomer (ee >98%) with the (*S*)-configuration. Therefore, with this class of ligands in the examined catalytic process the chirality of the dioxolane backbone is sufficient to give a very good stereoselectivity.

At present it is not possible to draw conclusions concerning the catalytic species involved in the mechanism. However, since the ligand **1** provided a very poor catalytic system regarding both catalytic activity and enantioselectivity (Table 1), it is reasonable to tentatively assume that the ligands **3** coordinate to the palladium in a bis-bidentate fashion.

In conclusion we have developed new C_2-symmetric chiral oxazolinylpyridines and demonstrated that they are very effective ligands in the palladium catalysed enantioselective alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate. A deeper investigation aimed at the determination of the catalytic species involved in the examined catalytic process and to the application of this kind of ligand in other palladium catalysed allylic substitutions is now in progress.

Acknowledgements

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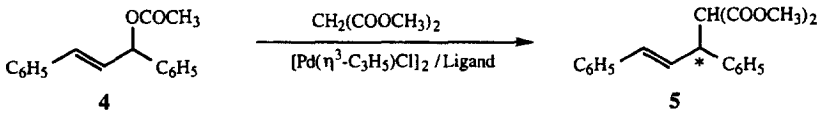
Table 1. Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[a]



4 5

Ligand	React. time, h	Temp. °C	Yield[b]	% Ee[c]	Conf.[d]
3a	78	r.t.	87	67	S
3a	6	reflux	82	62	S
3b	3	reflux	91	>98[e]	S
6c	18	r.t.	81	>98[e]	S
6c	5	reflux	77	93	S
1	48	reflux	56	16	S

[a]Typical procedure: A solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) and ligand (10 mol %) in CH_2Cl_2 (1 ml) was stirred at r.t. for 0.5 h. 1,3-Diphenylprop-2-enyl acetate (0.4 mmol) in CH_2Cl_2 (2 ml), dimethyl malonate (1.2 mmol), N,O-bis(trimethylsilyl) acetamide (BSA) (1.2 mmol) and potassium acetate (3 mol %) were added in sequence and stirring continued at room or reflux temperature until the conversion was complete as shown by TLC analysis [light petroleum:ether/3:1; R_f (product)=0.3]. The reaction mixture was diluted with ether (25 ml) and washed with ice-cold saturated NH_4Cl. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure and the residue purified by flash chromatography [light petroleum:ether/3:1] to give dimethyl 1,3-diphenylprop-2-enylmalonate.[b]Isolated yields. [c]Determined by ^{1}H-NMR using Eu(hfc)$_3$ as chiral shift reagent; splitting of the signal for one of the two methoxy groups was observed. [d]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. [e]No splitting of the signal for one of the two methoxy groups was dectected.

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7. All new compounds gave satisfactory analytical data. (4*S*,5*S*)-2,2-Dimethyl-4,5-bis{6-[4,5-dihydro-4-(*R*)-(1-methylethyl)oxazol-2-yl)pyridin-2-yl]}-1,3-dioxolane **3a**: mp 109–110°C; $[\alpha]_D^{25}$ + 105.6 (*c* 0.75, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.02 (d, 1H), 7.83–7.71 (m, 2H),

5.22 (s, 1H), 4.39 (m, 1H), 4.11 (m, 2H), 1.83 (m, 1H), 1.66 (s, 3H), 1.02 (d, 3H), 0.88 (d, 3H). (4*S*,5*S*)-2,2-Dimethyl-4,5-bis{6-[4,5-dihydro-4-(*S*)-(1-methylethyl)oxazol-2-yl)pyridin-2-yl]}-1,3-dioxo lane **3b**: mp 173–174°C; $[\alpha]_D^{25}$ −95.4 (*c* 0.95, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.02 (d, 1H), 7.82–7.68 (m, 2H), 5.30 (s, 1H), 4.41 (m, 1H), 4.08 (m, 2H), 1.83 (m, 1H), 1.65 (s, 3H), 1.02 (d, 3H), 0.84 (d, 3H). (4*S*,5*S*)-2,2-Dimethyl-4,5-bis{6-[(4,4-dimethyl-(5H)-oxazol-2-yl)]pyridin-2-yl}-1,3-dioxolane **3c**: mp 152°C; $[\alpha]_D^{25}$ + 5.65 (*c* 0.56, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 8.00 (d, 1H), 7.84–7.71 (m, 2H), 5.29 (s, 1H), 4.11 (s, 2H), 1.66 (s, 3H), 1.33 (s, 6H).

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