

Enantioselective Palladium Catalyzed Allylic Substitution with Sulfur-Containing Pyridine Ligands

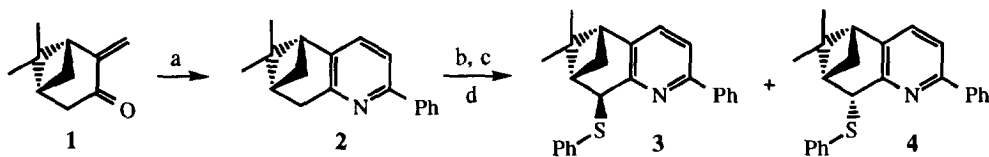
Giorgio Chelucci* and M. Antonietta Cabras.

Dipartimento di Chimica, Università di Sassari, via Vienna 2, I-07100 Sassari, Italy.

Abstract: Diastereomerically pure (5*R*,7*R*,8*S*)- and (5*R*,7*R*,8*R*)-5,6,7,8-tetrahydro-6,6-dimethyl-2-phenyl-8-phenylthio-5,7-methanoquinoline were prepared and assessed in the enantioselective palladium catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate. Enantioselectivities up to 83 % were obtained. Copyright © 1996 Elsevier Science Ltd

Enantioselective reactions based on palladium catalyzed allylic substitutions are currently an actively pursued research area.¹ In this context, heterotopic sulfur-nitrogen ligands such as sulfur-containing oxazolines are now reaching high levels of stereocontrol.² As a part of work aimed at the synthesis and application in asymmetric catalysis of chiral pyridine ligands³ which are gaining an important role in homogeneous catalytic asymmetric synthesis,⁴ we are now devoting our interest to sulfur-containing pyridine ligands. In this communication we report the preparation of diastereomerically pure (5*R*,7*R*,8*S*)- and (5*R*,7*R*,8*R*)-5,6,7,8-tetrahydro-6,6-dimethyl-2-phenyl-8-phenylthio-5,7-methanoquinoline (**3** and **4**) and their application in the enantioselective palladium catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate.

Scheme



a: Phenacylpyridinium iodide, AcOH, AcONH₄, 120°C, 4h, 82%; b: BuLi, THF, 1h at -78 °C then 1h at 0 °C; c: PhSO₂SPh, THF, -78 °C then slowly r.t., 70%; d: chromatography: SiO₂, toluene/petroleum ether = 1/1

The ligands **3** and **4** were readily accessible in a two step procedure⁵ (Scheme). The reaction of (+)-pinocarvone **1**, obtained by SeO₂ oxidation⁶ of β-pinene (92 % ee)⁷, with 1-phenacylpyridinium iodide⁸ gave the pyridine **2** in 82 % yield.⁹ The red solution of lithiated **2**, obtained by treatment with *n*-butyllithium at -78 °C for 1 h and then 1 h at 0 °C, was quenched with *S*-phenyl benzenethiosulphate at -78 °C to give a 3:1 mixture of **3** and **4** which were separated by chromatography on silica gel (toluene/petroleum ether = 1/1).¹⁰

The ability of new ligands to provide asymmetric induction in palladium catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate was examined. Allylic substitutions were carried out employing Trost's procedure, which used [Pd(η³-C₃H₅)Cl]₂ as precatalyst, and a mixture of dimethyl malonate, *N,O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in methylene chloride at room

temperature.¹¹ In both cases chemical yields were excellent and good levels of asymmetric induction were obtained. It should be noted that both epimers **3** and **4** which differ only in the C₈ carbon configuration, gave a similar level of stereodifferentiation but opposite configuration of dimethyl 1,3-diphenylprop-2-enylmalonate. This result indicates that the steric course of the reaction depends on the stereogenic centre bonded to the sulfur (C₈) and it is surprisingly insensitive to the other stereocentres.

In conclusion, we have shown that sulfur-pyridine compounds are able to function as ligands for palladium catalyzed allylic substitutions and that two epimeric ligands, generated from the same intermediate, behave as pseudoenantiomers. Further studies including modifications to ligand design and reaction conditions are in progress.

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

Ligand	React. time, h	Yield, ^b %	% Ee ^c	Conf.
3	38	90	83	R
4	48	85	78	S

^aTypical procedure: A solution of $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$ (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 (1 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 r.t. 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.^bIsolated yields. ^cDetermined by $^1\text{H-NMR}$ using $\text{Eu}(\text{hfc})_3$ as chiral shift reagent.

References and Notes

- Reiser, O. *Angew. Chem.*, **1993**, *105*, 576; *Angew. Chem. Int. Ed. Engl.*, **1993**, *32*, 547; Hayashi, T., in *Catalytic Asymmetric Synthesis*, Ed. Ojima, VCH, Weinheim, **1993**; Frost, C.G., Howarth, J., Williams, J.M.J. *Tetrahedron: Asymmetry*, **1992**, *3*, 1089. Dawson, G.J., Williams, J.M.J., Coote, S.J. *Tetrahedron: Asymmetry*, **1995**, 2535, and references therein.
- Allen, J.V., Coote, S.J., Dawson, G.J., Frost, C.G., Martin, C.J., Williams, J.M.J., *J. Chem. Soc., Perkin Trans.1*, **1994**, 2065. Sprinz, J., Kiefer, M., Helmchen, G., Reggelin, M., Huttner, G., Walter, O., Zsolnai, L. *Tetrahedron Letters*, **1994**, 1523.
- Basoli, C. Botteghi, C., Cabras, M.A., Chelucci, G., Marchetti, M. *J. Organometal. Chem.*, **1995**, 488, C20-C22; Chelucci, G., Cabras, M.A., Saba, A. *J. Mol. Catalysis*, **1995**, *95*, L7-L10; Chelucci, G., Cabras, M.A., Botteghi, C., Marchetti, M. *Tetrahedron: Asymmetry*, **1994**, *5*, 299.
- For a review: Chelucci, G. *Gazz. Chim. Ital.* **1992**, *122*, 89.
- During the drafting of this paper an analogue strategy in the synthesis of 2-(1-hydroxyalkyl)pyridines was reported: Collomb, P., von Zelewsky, A. *Tetrahedron: Asymmetry*, **1995**, 2903.
- Birch, A.J., Raverty, W.D., Stephenfon, G.R., *Organometallics*, **1984**, *3*, 1075.
- (1S)-(-)- β -Pinene [$[\alpha]_D^{20}$ -21 (neat), 92% ee] was purchased from Aldrich Chemical Co. Ltd.
- King, L.C. *J. Am. Chem. Soc.*, **1944**, *66*, 894.
- Krohnke, F. *Synthesis*, **1976**, 1.
- These compounds were isolated as oils. **3**: $[\alpha]_D^{22}$ -80.2 (c 2.3, CHCl_3); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 7.93 (d, 2H), 7.66 (d, 2H), 7.47-7.09 (m, 8H), 4.87 (d, 1H), 2.79 (m, 1H), 2.58 (m, 1H), 2.46 (m, 1H), 1.67 (d, 1H), 1.34 (s, 3H), 0.64 (s, 3H). **4**: $[\alpha]_D^{20}$ +118.1 (c 1.2, CHCl_3); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ : 8.01 (d, 2H), 7.84 (d, 2H), 7.52-7.19 (m, 8H), 4.83 (s, 1H), 2.74 (m, 3H), 1.41 (s, 3H), 1.39 (overlapping, 1H), 0.88 (s, 3H).
- Trost, B.M., Murphy, D.J. *Organometallics*, **1985**, *4*, 1143.