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Chiral Sulfoxides and Sulfides Tethered to Pyridines as Ligands for Enantioselective Catalysis: Palladium Catalyzed Allylic Substitution and Addition of Diethylzinc to Benzaldehyde

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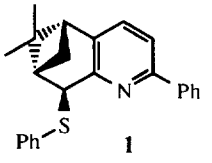
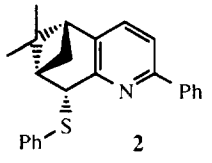
Abstract: Chiral 2-(1-*p*-tolylsulfinyl)alkylpyridines and the corresponding sulfide-pyridines were prepared and assessed in the enantioselective palladium catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate and addition of diethylzinc to benzaldehyde.

Recently, we have introduced the use of thioalkylpyridines as ligands for asymmetric reactions. Thus, we prepared and assessed in palladium catalyzed allylic substitutions the diastereomerically pure 8-phenylthio tetrahydroquinolines **1** and **2**, obtaining enantioselectivities up to 83 %.[1] This interesting result prompted us to undertake a study on the synthesis and application in asymmetric catalysis of heterotopic sulfur-containing pyridine ligands with general structure **3**.

Now, we report the preparation of diastereomerically pure 2-(1-*p*-tolylsulfinyl)alkylpyridines **5** and the corresponding homochiral thioalkylpyridines **6** (Scheme). Moreover, we examined the performance of these new ligands in two well known enantioselective catalytic model reactions which are frequently investigated to check scope and limitations of new catalysts, namely in palladium catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate and in addition of diethylzinc to benzaldehyde.



1



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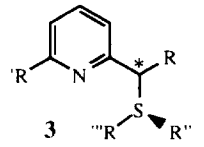
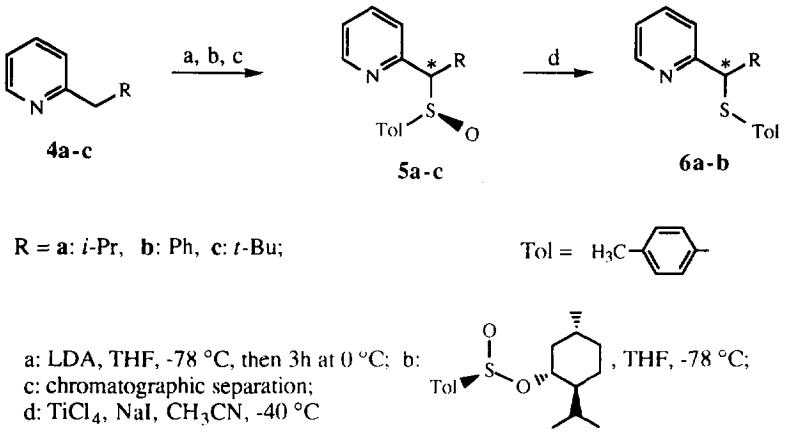


3

The sulfoxides **5** were readily accessible by quenching the red solution of lithiated **4**, obtained by treatment with lithium diisopropylamine at -78 °C and then 3 h at 0 °C, with (-)-(R)-menthyl (S)-*p*-tolylsulfinate[2] at -78 °C (Scheme). Good yields were obtained with **5a,b**, whereas only a very poor conversion was achieved with **5c**. In all cases a mixture of epimers at the carbon stereocentre of **5a-c** in an about 1:1 ratio for **5a,b** and 83/17 for **5c** was obtained. Single diastereomers of all sulfoxides were obtained in pure form through chromatography and their enantiomeric excess was determined to be about 100 % by ^{1}H NMR with Eu(tfc) as a shift reagent. The absolute configurations to the carbon stereocentre of sulfoxides could not be determined until now, however it does not appear essential to our study.

Tolylsulfinylpyridines **5a,b** (**5c** was not obtained in sufficient quantities for this step so far) were deoxygenated to the corresponding sulfides in good yields with the titanium(IV) chloride/sodium iodide reagent system[3] at -40 °C. Our initial attempts to deoxygenate the sulfoxide (-)-**5b** with other common reagents, as lithium aluminium hydride[2] or trifluoroacetic anhydride/sodium iodide,[4] gave the partial racemized sulfide **6b** (the enantiomeric excess was determined by ^{1}H NMR with Eu(tfc) as a shift reagent; the splitting of the signals of both the methyl groups was observed). In order to confirm that the deoxygenation process occurs without racemization, the two epimeric compounds **5b** were reduced to the corresponding sulfides (+)- and (-)-**6b**. As expected, they showed opposite sign and very similar value of the optical rotation.

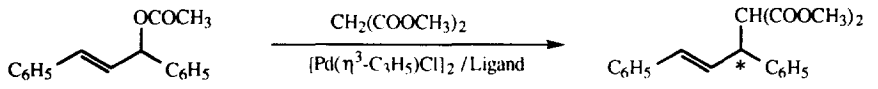
Scheme



The performance of new ligands was evaluated in the palladium catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[5] and the asymmetric addition of diethylzinc to benzaldehyde.[6]

Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate: Since not only nitrogen-sulfide but also nitrogen-sulfoxide heterotopic ligands[7] have been employed successfully to control the enantioselectivity in the palladium-catalyzed asymmetric allylic substitution,[8] we examined both 2-(1-*p*-tolylsulfinyl)alkylpyridines and the corresponding sulfide-pyridines in this catalytic process. 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 in methylene chloride at room temperature.[9] In some cases an alternative procedure involving the use of sodium dimethylmalonate in tetrahydrofuran at room or reflux temperature[10] was employed too. The results are reported in Table 1. Sulfoxides were not able to provide a reactive palladium catalyst and only (-)-**5a** afforded the substitution compound in 90 % yield and in 34 % enantiomeric excess. However, the reaction required 128 h to achieve a 50 % conversion. Moreover, when the reaction was carried out with sodium dimethylmalonate in tetrahydrofuran at reflux, a complete conversion was obtained after 24 h although with a lower enantioselectivity. On the other hand, sulfides gave effective palladium catalysts but low levels of asymmetric induction were achieved.

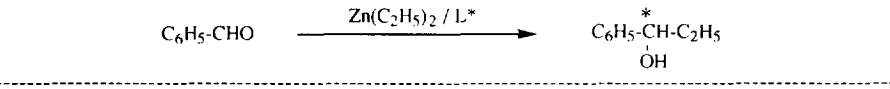
Table 1. Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate.



Ligand	Method[a]	React. time, h	Conv.[b]	Yield[c]	% Ee[d]	Conf.[e]
(-)-5a	A	168	50	90	34	S
(-)-5a	B[f]	24	100	91	6	-
(+)-5a	A	168	-	-	-	-
(+)-5b[g]	A	168	-	-	-	-
(+)-5b[h]	A	168	-	-	-	-
(-)-6a	A	24	100	95	20	S
(-)-6a	B	20	100	96	2	-
(+)-5b	A	48	40	92	4	-

[a]Method A: Reaction of the ligand (10 mol %) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %) with 1,3-diphenylprop-2-enyl acetate (0.4 mmol), $CH_2(COOMe)_2$ (1.2 mmol), N,O-bis(trimethyl silyl)acetamide (BSA) (1.2 mmol) and KOAc (3.5 % mol) in CH_2Cl_2 (2 ml) at r.t. Method B: This reaction was performed using $NaCH(COOMe)_2$ (0.6 mmol) in THF (2 ml) at r.t. [b]Based on recovered starting material. [c]Isolated yields based on converted starting material. [d]Determined by ^{1}H-NMR using $Eu(hfc)_3$ as chiral shift reagent. [e]The assignement is based on the sign of the optical rotation: Leutenegger, U.; Umbricht, G.; Fahrni, C.; Matt, P.V.; Pfaltz, A. *Tetrahedron*, **1992**, *48*, 2143. [f]Reaction carried out at reflux temperature. [g]Diastereomer having $[\alpha]^{25}_D$ +278.3. [h]Diastereomer having $[\alpha]^{25}_D$ +36.7

Table 2. Enantioselective Addition of Diethylzinc to Benzaldehyde[a]



Ligand	React. time, h	Yield[b] %	% Ee[c]	Conf.[d]
(-)-5a	12	87	13	S
(+)-5a	12	91	11	S
(+)-5b[e]	8	86	14	S
(+)-5b[f]	8	92	3	-
(-)-5c	24	85	19	S
(+)-5c	24	89	15	S

[a]Reaction carried out at room temperature in hexane/toluene with a molar ratio Et_2Zn/aldehyde/ligand= 2/1/0.06. [b]GLC yield of the crude products.[c]Determined by chiral GC (30 m Beta Dex-120 column, Supelco).[d]Determined from the specific rotation of (S)-1-phenylpropanol: $[\alpha]^{25}_D$ -47.6 ($CHCl_3$): Kitamura, M., Suga, S., Kawai, R., Noyori, R. *J. Am. Chem. Soc.*, **1986**, 108, 6071. [e]Diastereomer having $[\alpha]^{25}_D$ +278.3. [f]Diastereomer having $[\alpha]^{25}_D$+36.7

Asymmetric addition of diethylzinc to benzaldehyde: Chiral pyridine ligands, namely pyridyl alcohols and amines, have been used as effective ligands in the catalyzed enantioselective addition of alkylzinc compounds to aldehydes leading to a diverse array of secondary alcohols of high enantiomeric purity.[11] Since also β-

hydroxysulfoxides[12] were found effective ligands in this catalytic process, we decided to examine β-pyridylsulfoxides as ligands for the enantioselective addition of diethylzinc to benzaldehyde.

The reactions were carried out in hexane-toluene solution in the presence of 5 mol % of ligands at 25 °C. All catalysts gave l-phenyl-1-propanol in good yield but with low enantioselectivity (Table 2). An examination of the table indicates the enantiomeric excess and the configuration of the resulting carbinol are independent from both the substituent and the configuration at the carbon stereocentre. Therefore, this suggests that the stereochemical outcome of the reaction is determined by the stereochemistry of the sulfoxide unit.

In summary, the synthesis of chelating ligands of the desired type has been achieved and their catalytic activity in palladium catalyzed allylic substitution and addition of diethylzinc to benzaldehyde demonstrated as well. Further studies aimed at the synthesis of new sulfur-pyridine ligands are in progress.

EXPERIMENTAL SECTION

General. Boiling points are uncorrected. Melting points were determined on a Buchi 510 capillary apparatus and are uncorrected. The ^1H NMR (300 MHz) spectra were obtained with a Varian VXR-300 spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in a 1 dm tube. Elemental analyses were performed on a Perkin-Elmer 240 B analyzer. The allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[9,10] and the asymmetric addition of diethylzinc to benzaldehyde[8,11] were carried out according to reported procedures.

Materials. 2-Methylpyridine, 2-benzylpyridine and (-)-(R)-menthyl (S)-*p*-tolylsulfinate were purchased from Aldrich Chemical Co. Ltd. 2-(2-Methylpropyl)pyridine and 2-(2,2-dimethylpropyl)pyridine were prepared by CpCo(COD) catalyzed co-cyclotrimerization of 3-methylbutyronitrile and 3,3-dimethylbutyronitrile with acetylene.[13]

2-(1-*p*-Tolylsulfinylalkyl)pyridines: general procedure. A solution of the pyridine **4** (20 mmol) in anhydrous THF (10 ml) was added at -78 °C to a solution of lithium diisopropylamine (22 mmol) in anhydrous THF (100 ml). The resulting solution was stirred at -78 °C for 1 h and 3 h at 0 °C. Then a solution of (-)-(R)-menthyl (S)-*p*- tolylsulfinate (5.4 g, 20 mmol) in THF (20 ml) was added dropwise at -78 °C. After 1 h at -78 °C, the solution was allowed to reach slowly room temperature and then treated with H_2O. The organic phase was separated and the aqueous phase extracted twice with CH_2Cl_2. The combined organic phases were dried on anhydrous Na_2SO_4, the solvent evaporated and the residue purified by chromatography to give pure sulfoxides:

2-(2-Methyl-1-*p*-tolylsulfinylpropyl)pyridine, (-)-5a: This compound was isolated in 40 % yield after chromatography on neutral aluminium oxide (petroleum ether/ethyl acetate = 1/1): mp 72-73°C (ethyl acetate/isopropylether); $[\alpha]^{25}_D$ -130.1 (*c* 1.1, $CHCl_3$); ^1H NMR: δ 8.47 (d, 1H); 7.5 (dt, 1H); 7.14-7.00 (m, 5H); 6.88 (d, 1H); 3.78 (d, 1H); 2.88-2.74 (m, 1H) 2.28 (s, 3H); 1.16 (d, 3H); 1.09 (d, 3H). *Elem. Anal.*, found % (calcd. for $C_{16}H_{19}NOS$) C 71.14 (71.04); H, 7.46 (7.36); N, 4.75 (4.87).

(+)-2-(2-Methyl-1-*p*-tolylsulfinylpropyl)pyridine, (+)-5a: This compound was isolated in 33 % yield after chromatography on neutral aluminium oxide (petroleum ether/ ethyl acetate = 1/1): mp 85°-87°C (ethyl acetate/isopropyl ether); $[\alpha]^{25}_D$ +202.44 (*c* 0.86, $CHCl_3$); ^1H NMR: δ 8.15 (d, 1H); 7.60 (dt, 1H); 7.34 (d,

1H); 7.11-6.95 (m, 4H); 3.63 (d, 1H); 2.70-2.55 (m,1H); 2.29 (s, 3H); 1.5 (d, 3H); 0.85 (d, 3H). *Elem. Anal.*, found % (calcd. for $C_{16}H_{19}NOS$) C 71.22 (71.04); H, 7.26 (7.36); N, 4.65 (4.87).

(+)-2-(1-Phenyl-1-*p*-tolylsulfinylmethyl)pyridine, (+)-5b: This compound was isolated in 38 % yield after flash chromatography (benzene/acetone = 8/2): mp 140°C; $[\alpha]^{25}_D$ +278.3 (*c* 1.1, $CHCl_3$); ^1H NMR: δ 8.64 (d, 1H); 7.50 (dt, 1H); 7.45-7.37 (m, 2H); 7.34-7.24 (m, 3H); 7.20-7.13 (m, 3H); 7.13-7.00 (m, 3H); 4.89 (s, 1H); 2.30 (s, 3H). *Elem. Anal.*, found % (calcd. for $C_{19}H_{17}NOS$) C 74.11(74.24); H, 5.46 (5.57); N, 4.45 (4.56).

(+)-2-(1-Phenyl-1-*p*-tolylsulfinyltmethyl)pyridine, (+)-5b: This compound was isolated in 47 % yield after flash chromatography (benzene/acetone= 8/2) : mp 128 °C; $[\alpha]^{25}_D$ +36.7 (*c* 1.1, $CHCl_3$); ^1H NMR: δ 8.36 (d, 1M); 7.68 (dt, 1H); 7.2 (d, 1H); 7.30-7.13 (m, 8H); 7.07 (d, 2H); 4.93 (s, 1H); 2.34 (s, 3H). *Elem. Anal.*, found % (calcd. for $C_{19}H_{17}NOS$) C, 74.21 (74.24); H, 5.66 (5.57); N, 4.43 (4.56).

2-(2,2-Dimethyl-1-*p*-tolylsulfinylpropyl)pyridine, (-)-5c: This compound was isolated in 0.3 % yield after flash chromatography (petroleum ether/ethyl acetate= 6/4): mp 100°-102°C; $[\alpha]^{25}_D$ -209.2 (*c* 0.72, $CHCl_3$); ^1H NMR: δ 8.50 (d, 1H); 7.39 (t, 1H); 7.16 (d, 1H); 7.07-6.94 (m, 3H); 6.66 (d, 1H); 3.75 (s, 1H); 2.26 (s, 3H); 1.32 (s, 9H). *Elem. Anal.*, found % (calcd. for$C_{17}H_{21}NOS$) C, 71.14 (71.04); H, 7.46 (7.36); N, 4.75 (4.87).

(+)-2-(2,2-Dimethyl-1-p-tolylsulfinylpropyl)pyridine, (+)-5c: This compound was isolated in 1.7 % yield after chromatography (petroleum ether/ethyl acetate = 6/4): mp 113°-115°C; $[\alpha]^{25}_D$ +233.16 (*c* 0.38, $CHCl_3$); ^1H NMR: δ 8.22 (d, 1H); 7.64 (q, 1H); 7.15 (d, 2H); 7.06-6.94 (m, 4H); 3.52 (s, 1H); 2.28 (s, 3H); 1.30 (s, 9H). *Elem. Anal.*, found % (calcd. for $C_{17}H_{21}NOS$) C 71.18 (71.04); H, 7.47 (7.36); N, 4.75 (4.81).

2-(1-*p*-Tolylthioalkyl)pyridines: general procedure. $TiCl_4$ (8 mmol, 0.68 ml) and a solution of NaI (12 mmol) in CH_3CN (4 ml) were added in sequence to a cooled (-40 °C) solution of the sulfoxide **5** (2 mmol) in CH_3CN (6 ml). The mixture was stirred at -40 °C for 2 h and then a 10 % aqueous solution of NaOH (4 ml) was cautiously added at -40 °C. The reaction mixture was extracted with ether (25 mL) and the separed organic phase washed with a 10 % aqueous solution of $Na_2S_2O_3$ (20 ml) and H_2O (25 ml). The organic phase was dried on anhydrous Na_2SO_4, the solvent evaporated and the residue purified by flash chromatography (petroleum ether/ethyl acetate = 8/2) to give pure 2-(1-*p*-tolylthio)alkylpyridines:

2-(2-Methyl-1-*p*-tolylthiopropyl)pyridine, (-)-6a: This compound was isolated in 63 % yield by deoxygenation of (-)-2-(2-methyl-1-*p*-tolylsulfinylpropyl)pyridine: mp 45-6°C; $[\alpha]^{25}_D$ -261.3 (*c* 1.0, $CHCl_3$); ^1H NMR: δ 8.50 (d, 1H); 7.55 (td, 1H); 7.28 (d, 1H); 7.15-7.04 (m, 3H); 6.97 (d, 2H); 4.09 (d, 1H); 2.38-2.24 (m, 1H); 2.24 (s, 3H); 1.17 (d, 3H); 0.92 (d, 3H). *Elem. Anal.*, found % (calcd. for $C_{16}H_{19}NS$) C 74.54 (74.66); H, 7.46 (7.44); N, 5.35 (5.44).

(+)-2-(1-Phenyl-1-*p*-tolylthiomethyl)pyridine, (+)-5b: This compound was isolated in 65 % yield by deoxygenation of (+)-2-(1-phenyl-1-*p*-tolylsulfinylpropyl)pyridine ($[\alpha]^{25}_D$ +278.3): mp 66-8 °C; $[\alpha]^{25}_D$ +48.7 (*c* 1.0, $CHCl_3$); ^1H NMR: δ 8.57 (d, 1H); 7.62 (dt, 1H); 7.45 (t, 3H); 7.32-7.09 (m, 6H); 6.98 (d, 2H);

5.57 (s, 1H); 2.24 (s, 3H). ***Elem. Anal.***, found % (calcd. for $C_{19}H_{17}NS$) C 78.55 (78.31); H, 5.66 (5.88); N, 4.95 (4.81).

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