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Enantiomerically pure 1-(2-methoxy-1-naphthyl) and 1-(2-methylthio-1-naphthyl)isoquinoline: two new axially chiral N-O and N-S ligands for asymmetric catalysis

Giorgio Chelucci,[a]* Alessia Bacchi,[b] Davide Fabbri,[c] Antonio Saba[a] and Fausta Ulgheri[a]

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

[b]Dipartimento di Chimica Generale, Università di Parma, Viale delle Scienze, I-43100 Parma, Italy.

[c]Istituto A.T.C.A.P.A., C.N.R., via Vienna 2, I-07100 Sassari, Italy.

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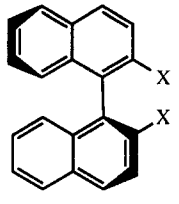
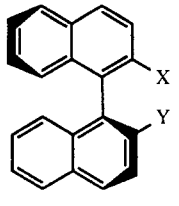
Abstract: The synthesis and resolution of 1-(2-methoxy-1-naphthyl)isoquinoline and 1-(2-methylthio-1-naphthyl)isoquinoline is reported. These ligands were assessed in the enantioselective palladium catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate. Enantioselectivity up to 68 % was obtained.

Now that symmetrical 2,2'-disubstituted 1,1'-binaphthyls, such as BINOL **1a**, BINAP **1b**, BINAPO **1c** and their congeners are established ligands in asymmetric catalysis,[1] there are an increasing interest on the synthesis and application of their unsymmetrical analogues such as MOP **2a**[2] and NOBIN **2b**.[3] This class of compounds[4] can be roughly related to the 1-(2-substituted-1-naphthyl)isoquinolines in which a nitrogen atom replaces one of the two substituents on the 2,2'-positions of the binaphthyl backbone. The 1-(2-diphenylphosphino-1-naphthyl)isoquinoline **3c** (QUINAP)[5] and the 1-(2-hydroxymethyl-1-naphthyl)isoquinoline **3d**[6] are the two enantiopure naphthylisoquinolines which have been so far reported.

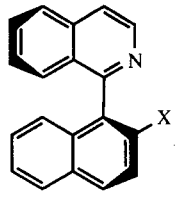
In this communication, we report the synthesis and resolution of two N-O and N-S chelating ligands of this type, namely the 1-(2-methoxy-1-naphthyl)isoquinoline **3a** and 1-(2-methylthio-1-naphthyl)isoquinoline **3b**. The preliminary results in palladium catalysed allylic substitution are reported as well.



1a: x= OH ; **1b**: x= PPh_2
1c x= $OPPh_2$



2a: x= OCH_3, Y= PPh_2
2b: x= OH, Y= NH_2



3a: x= OCH_3 ; **3b**: x= SCH_3
3c x= PPh_2 ; **3d**: x= CH_2OH

Alcock *et al.*[5] reported the preparation of the racemic ligand **3a** as an intermediate in the synthesis of QUINAP. Their procedure was successfully adapted to the synthesis of **3b** (Scheme 1). Thus, arylboronic acid

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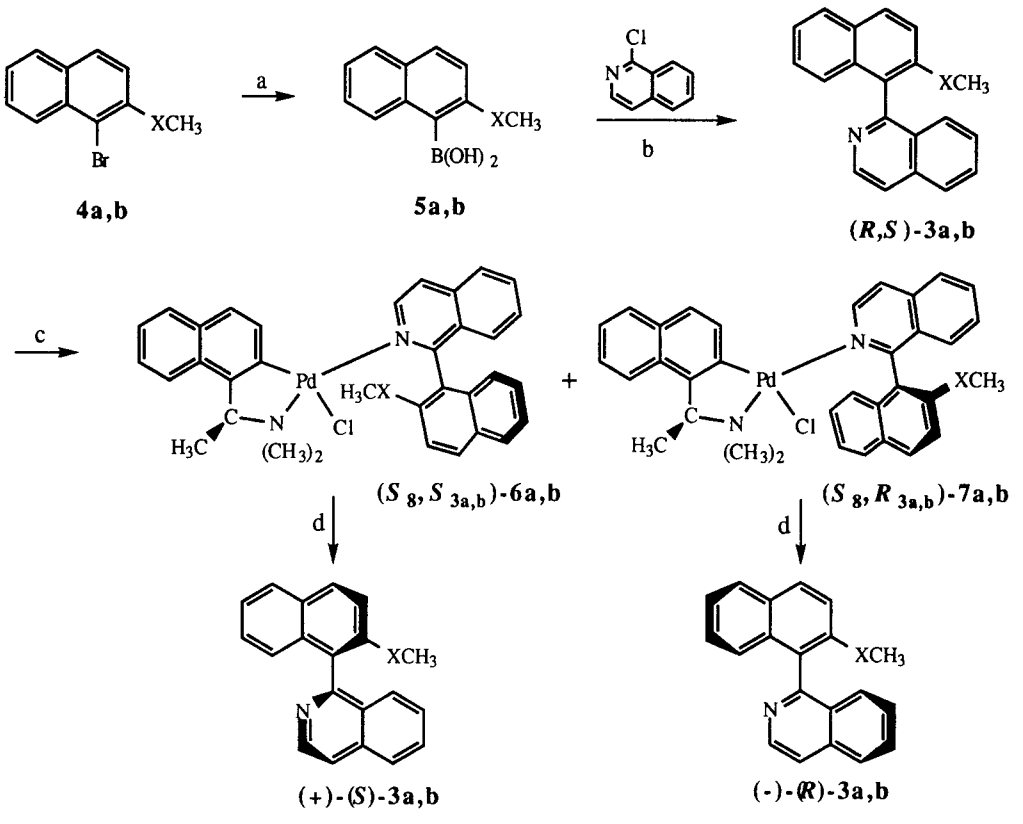
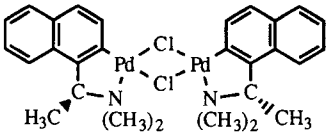
5b, prepared by reacting the Grignard reagent from 1-bromo-2-methylthionaphthalene **4b** with trimethylborate in THF at -60 °C, was cross-coupled with 2-chloroisoquinoline in the presence of 3% $Pd(PPh_3)_4$ and Na_2CO_3 in dimethoxyethane at reflux temperature to give the ligand **3b**[7] in satisfactory yield (71 %).

Scheme 1



a: X=O ; **b**: X=S

a: Mg, THF then B $(OCH_3)_3$, -60 °C then H_2O;
b: $Pd(PPh_3)_4$, Na_2CO_3, DME reflux;
c: (S)-**8**, CH_2Cl_2 then chromatographic separation
d: 1,2-bis(diphenylphosphino)ethane, CH_2Cl_2.



(*S*)-**8**

For the resolution of racemic **3a,b**, a method used for the separation of enantiomers of chelating ligands was followed.[8] The reaction of **3a,b** and (-)-di-μ-chlorobis[(*S*)-dimethyl(1-(1-naphthyl)ethyl)aminato-C^2,N]dipalladium(II) (*S*)-**8**[9] in CH_2Cl_2 produced the pair of diastereomeric complexes (S_8,$S_{3a,b}$)-**6** and (S_8,$R_{3a,b}$)-**7** in equal amounts, as shown in the ^1H NMR spectrum by the two doublets at δ 0.48 and 0.66 ppm for the benzylic methyls of the two diastereomers derived from **3a** and δ 0.51 and 0.67 ppm from those derived from **3b**. The structure of these complexes which are mononuclear Pd complexes (determined from the integration of the ^1H NMR spectrum) can be confidently formulated as **6** and **7** since in these Pd-complexes the softer donor is expected to take up the position *trans* to the NMe_2 group. Separations of these diastereomers was achieved by flash chromatography (eluents: benzene/ethyl acetate= 2/1 for the **6a-7a** mixture and petroleum ether/ethyl acetate = 1/1 for the **6b-7b** mixture). Finally, the free ligands (+)-(*S*)-**3a**

($[\alpha]_D^{20}$ +92.5 (*c* 1.15, $CHCl_3$), **(+)-(*S*)-3b** ($[\alpha]_D^{20}$ +59.5 (*c* 1.63, $CHCl_3$)), **(-)-(*R*)-3a** ($[\alpha]_D^{20}$ -93.6 (*c* 1.05, $CHCl_3$)) and **(-)-(*R*)-3b** ($[\alpha]_D^{20}$ -60.3 (*c* 1.56, $CHCl_3$)) were regenerated from the palladium complexes by treatment with 1,2-bis(diphenylphosphino)ethane in CH_2Cl_2. Crystals of the compound **(-)-3a** were grown from a CH_2Cl_2/petroleum ether mixture and their structure was determined by X-ray diffraction. The molecular structure found for compound **(-)-3a** (Figure 1) shows that the molecule has ***R*** absolute configuration.[10] The molecule can be described on the basis of two planar moieties, comprising, respectively, atoms from C1 to C9 and N (isoquinoline) and from C10 to C20 and O (2-methoxy-naphthyl). Both the systems are planar within 0.07 Å and their two average planes form a dihedral angle of 69°. The rotation around the C5-C10 bond (C5-C10=1.496(3) Å) is hindered by the repulsive intramolecular contacts N···C16=3.226(3) Å and O···C6=3.155(3) Å, fixing the torsion angle N-C5-C10-C15=71.9(3)°.

Since, the ^1H NMR spectra of the palladium complexes **7a** and **7b** (derived from ligands **(-)-3a** and **(-)-3b**) shows very similar chemical shifts for the benzylic methyls (δ 0.48 and δ 0.51 ppm, respectively) it is reasonable to attribute to **(-)-3b** the same ***R*** absolute configuration assigned to **(-)-3a**. To determine if there had been a loss of enantiomeric purity during the generation of the ligands from the corresponding palladium complexes, the ligands **(-)-3a,b** were allowed to react in a NMR tube with an excess of **(*S*)-8**. Only the signals related to complexes **7a,b** were detected in the ^1H NMR spectra (the spectra were recorded again after one week), indicating that the recovered ligands were enantiomerically pure. Stirring the resolved ligands **(+)-3a** and **(+)-3b** in a chloroform solution at 25 °C for two weeks and at 50 °C for 24 h did not result in any detectable racemisation.

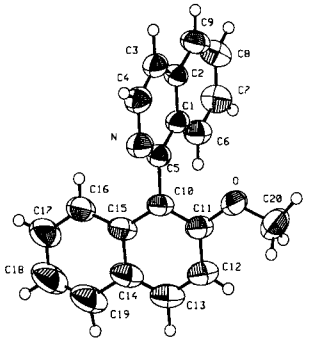


Figure 1. ORTEP view of **(-)-(*R*)-3a**. Thermal ellipsoids are drawn at 50% probability level. Crystal data: C20H15N O, M=285.34, orthorhombic, space group $P2_12_12_1$, a=23.284(5)Å, b=8.107(2)Å, c=7.950(2)Å, V=1500.7(6)Å3, Z=4, Dc=1.263 g cm-3, CuKα radiation, λ=1.54178Å, μ(CuKα)=6.09 cm-1; final R1 and wR2 are 0.047 and 0.141, for 2366 observed reflections (I>2σ(I)) and 2843 unique data respectively.

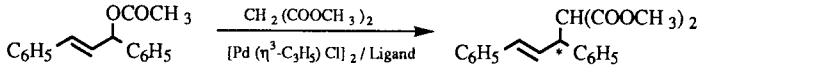
To test the ability of new ligands to provide asymmetric induction in the palladium-catalysed allylic substitutions which proceed through a meso η^3-allyl intermediate we examined the alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate which serves a model substrate to compare the outcome with different ligands.[11] Allylic substitutions were carried out using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as procatalyst and a mixture of dimethyl malonate, N,O-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in methylene chloride at room temperature.[12] The results of the catalytic reaction are reported in Table 1.

Ligands **3a,b** were not able to provide reactive palladium catalysts; even though total conversion of the starting material was achieved in about two weeks, good yields of dimethyl 1,3-diphenylprop-2-enylmalonate **10** were obtained. Moreover, a moderate enantioselectivity (68 % ee) was achieved with **3a** whereas with **3b** the reaction was not enantioselective (2 % ee).

Out of the many new ligands used to control the enantioselectivity in palladium catalysed allylic substitution there are few examples of atropisomeric chiral ligands, all contain phosphorous as donor atom (for instance: BINAP, 90 % ee[13]; BINAPO, 79 % ee[11a]; QUINAP, 79 % ee[14]). In the model reaction studied, the ligand **3a** generates, to our knowledge, the highest reported asymmetric induction for a ligand based on the 1,1'-binaphthyl backbone not containing phosphorous as donor atom.

We are currently investigating further applications of **3a** and **3b** to asymmetric synthesis.

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



9 **10**

Entry	Ligand	Temperature	React. time, d[b]	Yield[c]	% Ee[d]	Conf.[e]
1	**(+)-3a**	r.t.	14	83	68	R
2	**(+)-3b**	r.t.	11	75	2	R

[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(trimethylsilyl)acetamide (BSA) (1.2 mmol) and KOAc (3.5 % mol) in CH_2Cl_2 (2 ml) at room or reflux temperature. [b]Determined by TLC analysis (SiO_2; light petroleum:ether:3/1; R_f **9** = 0.42; R_f **10** = 0.30. [c]Isolated yields. [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.

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References

1. For reviews on binaphthyls, see: Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley & Sons: New York, **1994**. Rosini, C.; Franzini, L; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. Narasaka, K. *Synthesis* **1991**, 1. Tomioka, K. *Synthesis* 1990, 541.
2. Hayashi, T. *Acta Chim. Scand.* **1996**, *50*, 259 and references therein.
3. Smrcina, M.; Vyskocil, S.; Polivkova, J.; Sejbal, J.; Hanus, V.; Polasek, M.; Verrier; Kocovsky, P. *Tetrahedron: Asymmetry* **1997**, *7*, 537 and references therein.
4. For further examples of unsymmetrical 1,1'-binaphthyls, see: Gladiali, S.; Pulacchini, S.; Fabbri, D.; Manassero, M.; Sansoni, M. *Tetrahedron: Asymmetry* **1998**, *9*, 391. Fukuda, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 197. Backer, R. W.; Sargent, M.V. *Pure Appl. Chem.* **1994**, 66, 2143. Gladiali, S.; Dore, A; Fabbri, D. *Tetrahedron: Asymmetry* **1994**, *5*, 1143. Singer, R.A; Sasaki, H.; Irie, R.; Katsuki, T. *Synlett* **1993**, 300.
5. Alcock, E.W.; Brown, J.M.; Hulmes, D.I. *Tetrahedron: Asymmetry* **1993**, *4*, 743.
6. Baker, R.W.; Rea, S.O.; Sargent, M.V.; Schenkelaars, E.M.C.; Skelton, B.W.; White, A.H. *Tetrahedron: Asymmetry* **1994**, *4*, 45.
7. All compounds showed satisfactory spectroscopic and analytical data. Compound **3b**: mp 108-110 °C; ^{1}H-NMR ($CDCl_3$): δ 8.75 (d, 1H, 5.4 Hz), 7.97 (d, 1H, 8.4 Hz), 7.93 (d, 1H, 8.1 Hz), 7.87 (d, 1H, 8.1 Hz), 7.78 (d, 1H, 5.7 Hz), 7.64 (ddd, 1H, 8.1, 6.3, 2.1 Hz), 7.60 (d, 1H, 8.7 Hz), 7.42-7.33 (m, 3H), 7.24 (ddd, 1H, 8.4, 1.2 Hz), 6.97 (dd, 1H, 8.4, 1.2 Hz), 2.38 (s, 3H).
8. Alcock, E.W.; Hulmes, D.I.; Brown, J.M. *J. Chem Soc., Chem. Comm.* **1995**, 395.
9. Allen, D.G.; McLaughlin, G.M.; Robertson, G.B.; Steffen, W.L.; Salem, G.; Wild, S.B. *Inorg. Chem.* **1982**, *21*, 1007.
10. The absolute configuration was determined by refining Flack's parameter according to SHELXL 97 protocol (G. Sheldrick, University of Goettingen, Germany, 1997).
11. (a) Trost, B.M.; Van Vranken, D.L. *Chem. Rev.*, **1996**, 96, 395. (b) Reiser, O. *Angew. Chem.*, **1993**, *105*, 576; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547. Hayashi, T., in *Catalytic Asymmetric Synthesis Ed.* Ojima, I.,VCH, Weinheim, **1993**. Frost, C.G.; Howarth, J.; Williams, J.M.J. *Tetrahedron: Asymmetry* **1992**, 3, 1089.
12. Trost, B.M.; Murphy, D.J. *Organometallics* **1985**, *4*, 1143.
13. Yamaguchi, M.; Shima, T.; Yamagishi, T.; Hida, M.; *Tetrahedron Lett.* **1990**, *31*, 5049.
14. Brown, J.M.; Hulmes, D.I.; Guiry, P.J. *Tetrahedron* **1994**, *50*, 4493.