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Resolution of a Cyclopalladated Complex Containing an Asymmetric Metallated Carbon Atom

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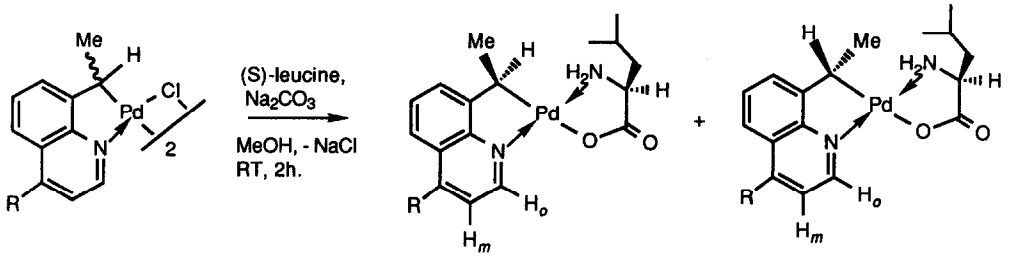
Abstract : *Enantiomerically enriched cyclopalladated 8-ethylquinoline derivatives containing a stereogenic centre directly linked to palladium have been obtained by a resolution technique using (S)-leucine as chiral auxiliary.*

Optically active organopalladium compounds, especially those derived from metallated tertiary amines, are currently attracting much interest. For example, it has recently been shown that cyclopalladated complexes containing the (*R*)- or (*S*)- forms of dimethyl(1-(1-naphthyl)ethyl)amine or dimethyl(1-phenylethyl)amine are useful for the resolution and ^{1}H NMR studies of various chelating ligands.[1] From a synthetic point of view, prostaglandin precursors have been formed from an aminomethylferrocenyl palladium complex, obtained by an impressive asymmetric C-H activation process.[2]

As part of a project aimed at studying the potential of our palladium mediated formation of heterocycles[3] for stereoselective synthesis, we required a complex containing an asymmetric metallated carbon atom. Such compounds are rare and their resolution is a far from trivial process.[4] Useful candidates for this study were the racemic complexes **1**, obtained by the C-H activation of 8-ethylquinoline derivatives.[5] **1a** has already been prepared in enantiomerically enriched form, although the methods used often suffer from reproductibility problems [5(ii)] or involve transmetallation reactions using organomercurials.[6]

Enantiomerically pure, readily available (*S*)-amino acids were chosen for the attempted resolution of **1**. Reaction of the latter with a slight excess of amino acid and Na_2CO_3 gave **2a-b** as solids after CH_2Cl_2 extraction, in 88% and 78% yields respectively. The ^{1}H NMR spectra of **2a-b** are rather complicated[7], with each discernable proton being duplicated due to the formation of a 1:1 mixture of diastereomers.

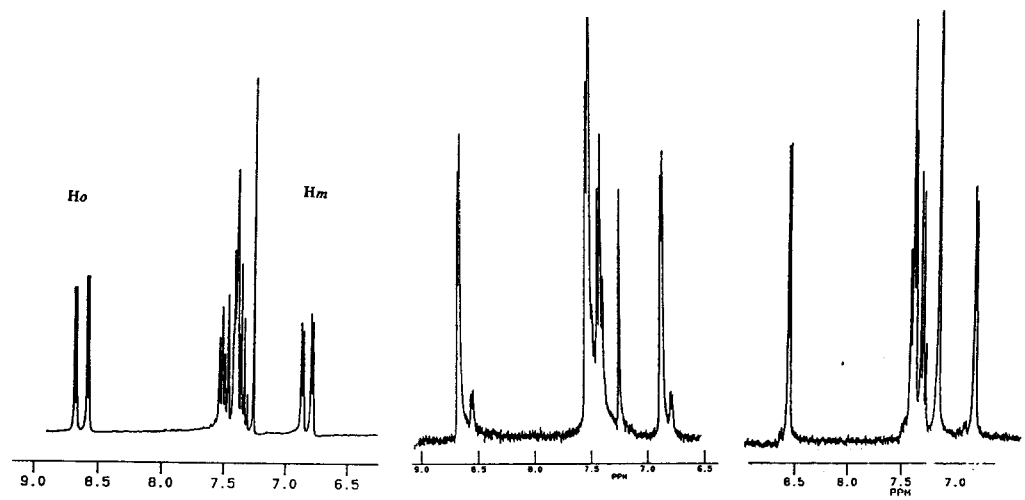


1a : R = H
1b : R = Me

(*R,S*)-**2a**, R = H
(*R,S*)-**2b**, R = Me

(*S,S*)-**2a**, R = H
(*S,S*)-**2b**, R = Me

Attempted chromatographic and fractional crystallisation techniques for the resolution of **2a** and **2b** were unsuccessful (e.g. when (*R,S*), (*S,S*)- **2b** was left to crystallise in CH_2Cl_2/hexane at -20°C overnight both the precipitate and filtrate had a diastereomeric excess (d.e.) = 0%). We found that **2b** could be resolved by a quick precipitation method and that this method was most efficient for this particular complex using (*S*) -leucine as the chiral auxiliary.[8] When a hexane layered (10 ml) solution of (*R,S*) (*S,S*)- **2b** (ca. 500 mg) in warm CH_2Cl_2 (30 ml) was refrigerated at -20°C for 10 min, a precipitate (185 mg, (*S,S*)-**2b**, d.e. = 26%) and filtrate ((*R,S*)-**2b**, d.e. =16%) were recovered. Several repetitions of this procedure for the separate fractions enabled the separation of the two diastereomeric forms of **2b** with d.e.' s of ca. 90%, in ca. 50 mg quantities. This procedure could also be employed for **2a** and similar results were obtained. ^1H NMR was used to measure the d.e.' s of the complexes obtained. The aromatic region of the ^1H NMR spectrum of **2b** obtained directly from **1b** and (*S*)-leucine is presented in **Figure 1** (i); H_o and H_m are of equal intensity indicating the presence of a 1:1 mixture of diastereomers. In (ii), (*S,S*)- **2b** is in large excess; in (iii), (*R,S*)-**2b** predominates.



(i) (*R,S*)(*S,S*)-**2b** (d.e. = 0%) (ii) (*S,S*)-**2b** (d.e. ca. 80%) (iii) (*R,S*)-**2b** (d.e. > 90%)

Figure 1: 300 MHz ^1H NMR of **2b** at different d.e.' s. ($CDCl_3$, δ given in ppm on x-axis).

A single crystal X-ray structure determination was carried out to find out the absolute configuration of the carbon linked to palladium in **2b**. Crystals were grown of a sample corresponding to **Figure 1** (ii) by slow hexane diffusion into a $CHCl_3$ solution of **2b**[9]. The ORTEP diagram (**Figure 2**) shows clearly the *anti* arrangement of the methyl of the metallated ethyl group ((*S*)-configuration) and the alkyl chain of the (*S*)-leucine part.

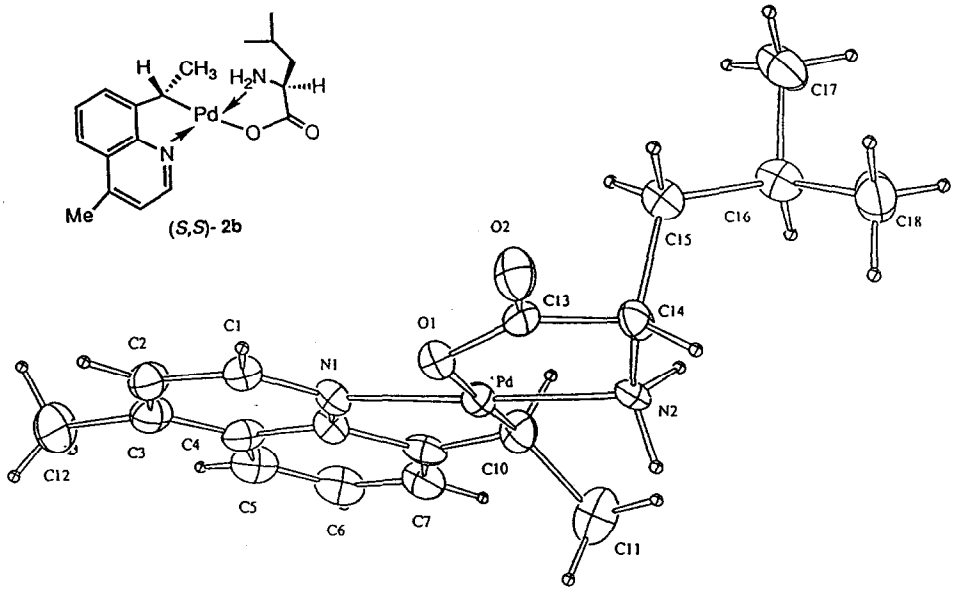
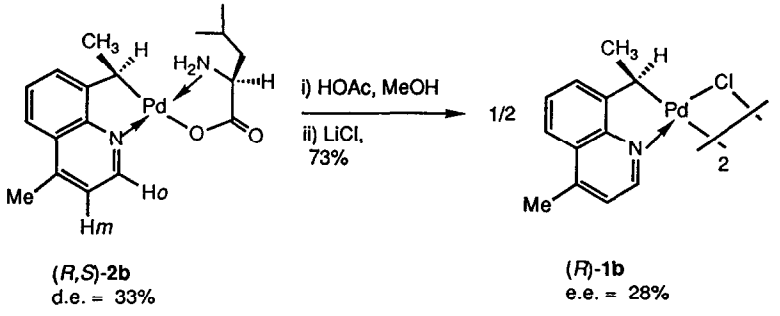


Figure 2: ORTEP diagram of (*S,S*)-**2b**.

($C_{18}H_{24}N_2O_2Pd$. M = 406.8. Orthorhombic crystals. Space group $P2_12_12_1$. CuKα radiation on a Phillips PW 1100/16 diffractometer at -100 °C. a = 22.506 (7); b = 9.523 (3); c = 7.882 (3). 1144 data were collected (1083 with I> 3σ). R(F) = .024).

We now required **1b** in optically active form. Treatment of a diastereomerically enriched sample of (*R,S*)-**2b** (d.e. = 33%) with dilute HCl in MeOH (RT, overnight) led to **1b**. A portion of the latter sample was converted into its leucinate **2b** which by ^{1}H NMR had a d.e. = 0%. Under these conditions acidolysis of the Pd-C bond may occur, finally yielding racemic **1b**. However, with dilute acetic acid (MeOH, RT, overnight, followed by LiCl/acetone) the same **2b** sample was converted into **1b** with the same absolute configuration at carbon and virtually the same enantiomeric enrichment (e.e. = ca. 28% by ^{1}H NMR of leucinate). By this method both antipodes of **1b** could be obtained in enantiomerically enriched form in ca. 100 mg quantities.



(*R,S*)-**2b**
d.e. = 33%

(*R*)-**1b**
e.e. = 28%

A reasonably efficient, reproducible method has been developed enabling the preparation of enantiomerically enriched cyclopalladated 8-ethylquinoline derivatives. A study of the reactivity of **1a** and **1b** in carbon-carbon bond forming reactions is currently underway.

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5) (i) 8-Ethylquinoline derivatives were synthesised according to K.N. Campbell and I. J. Schaffner, *J. Am. Chem. Soc.* **1945**, 67, 86; (ii) **1a** and **1b** were synthesised according to V. I. Sokolov, T. A. Sorokina, L. L. Troitskaya, L. I. Solovieva and O.A. Reutov, *J. Organomet. Chem.* **1972**, 36, 389 and (iii) M. Pfeffer, *Inorg. Synth.* **1989**, 26, 213.
6) V. I. Sokolov, V. V. Bashilov, A. A. Musaev and O. A. Reutov, *J. Organomet. Chem.* **1982**, 225, 57.
7) Key data: ^{1}H NMR (δ in ppm, $CDCl_3$, 293 K, **2a** on a Bruker AC 200 MHz, **2b** on an AX 300 MHz).
(*R,S*)-**2a** (d.e. > 95 %); 0.96 & 1.00 (2d, 6H, $^3J_{HH}$ = 6.5 Hz, $(CH_3)_2$ CH) ; 1.21 (d, 3H, CH_3CHPd) ; 1.70 (m, 1H, $CH(CH_3)_2$); 1.91 & 2.00 (2m, 2H, CH_2); 2.09 (m, 1H, NH); 3.75 (m, 2H, PdCHMe & CHN); 4.42 (m, 1H, NH); 7.04 (dd, 1H, $^3J_{HmHp}$= 4.9 Hz, $^3J_{HmHo}$= 8.4 Hz, H*m*); 7.34-7.45 (m, 3H, Harom); 7.87 (dd, 1H, H*p*); 8.77 (dd, 1H, $^4J_{HoHp}$= 1.2 Hz, H*o*).
(*S,S*)-**2a** (d.e. > 80%); 0.98 & 1.02 (2d, 6H, $^3J_{HH}$ = 6.5 Hz, $(CH_3)_2$ CH) ; 1.26 (d, 3H, CH_3CHPd) ; 1.77 (m, 1H, $CH(CH_3)_2$); 1.96-2.07 (2m, 2H, CH_2); 2.55 (m, 1H, NH); 3.58 & 3.72 (2m, 2H, CHN & NH); 3.98 (q, 1H, PdCHMe); 7.14 (dd, 1H, $^3J_{HmHp}$= 4.9 Hz, H*m*); 7.43-7.60 (m, 3H, Harom); 8.02 (dd, 1H, $^4J_{HoHp}$= 1.2 Hz, H*p*); 8.82 (dd, 1H, $^3J_{HoHm}$= 8.4 Hz, H*o*).
(*R,S*)- **2b** (d.e.= ca. 95 %, α_{589}^{25} = -13.8°, $CHCl_3$, *c* = 2.1 mg/ml); 0.98 & 1.02 (2d, 6H, *J* = 6.5 Hz, $(CH_3)_2CH$); 1.23 (d, 3H, *J* = 7.3 Hz, PdCHCH_3); 1.74 (m, 1H, $CHMe_2$) ; 1.93 & 2.06 (2m, 2H, CH_2); 2.11 (m, 1H, NH); 2.42 (s, 3H, *p*-Me); 3.75 (m, 2H, PdCHCH$_3$ & CHN); 4.30 (bs, 1H, NH); 6.92 (d, 1H, H*m*); 7.34-7.52 (m, 3H, H arom); 8.64 (d, 1H, $^3J_{HoHm}$= 5.1 Hz, H*o*).
(*S,S*)- **2b** (d.e.= ca. 80 %); 0.96 & 1.02 (2d, 6H, *J* = 6.5 Hz, $(CH_3)_2CH$); 1.27 (d, 3H, ^3J = 7.3 Hz, PdCHCH_3); 1.80 (m, 1H, $CHMe_2$); 1.91 & 2.07 (2m, 2H, CH_2); 2.48 (s, 3H, *p*-Me); 2.56 (m, 1H, NH); 3.74 (m, 1H, CHN); 3.95 (q, 1H, PdCHCH$_3$); 4.6 (bs, 1H, NH); 6.90 (d, 1H, H*m*); 7.4-7.6 (m, 3H, H arom); 8.69 (d, 1H, $^3J_{HoHm}$= 5.1 Hz, H*o*).
Correct C, H, N, analyses were obtained for all new compounds.
8) Curiously, although a whole host of similar complexes (with other amino acids and amino alcohols) of **1a** and **1b** are known, leucine derivatives give the best results for the resolution process (J. Dupont, R. Konrath, M. Pfeffer, J. Spencer, unpublished observations). However, other more conventional resolution techniques (such as tartaric acid derivatives etc) have not yet been attempted.
9) Better crystals were obtained using $CHCl_3$ than with CH_2Cl_2 as solvent, **2b** being slightly more soluble in the former.

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