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Stereospecific co-crystallization of reactant and palladium complex in the resolution of stilbendiamine using N*-chiral *ortho*-palladated matrix

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Abstract

Resolution of racemic 1,2-diphenyl-1,2-ethanediamine was performed through recrystallization of its diastereomeric adducts **2a,b** with N*-chiral *ortho*-palladated complex (S_CR_N)-**1**. The structure and absolute configuration of the less soluble (S_CR_N,*SS*)-**2a** diastereomer was determined by X-ray diffraction. The complex has an unusual dimeric structure with a palladacycle:diamine ratio of 2:3; the association of **2a** with an additional diamine molecule of the same (*SS*) absolute configuration is achieved due to hydrogen bonds between the coordinated and solvate diamine. © 1998 Elsevier Science Ltd. All rights reserved.

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1. Introduction

During the last decade, homochiral *ortho*-palladated complexes have evolved into powerful tools for the resolution of diverse substrates.[1,2] As a rule, the resolution includes selective crystallization of one (or both) diastereomeric 1:1 adduct(s). However, several examples of a palladium:substrate ratio of 2:1 in the isolated diastereomer are also known.[3] In these instances the consumption of a rather expensive resolving agent is increased twofold. We present below some preliminary results of C_2-symmetric diamine resolution which may be performed via the dimeric association with a palladacycle:substrate=2:3 ratio.

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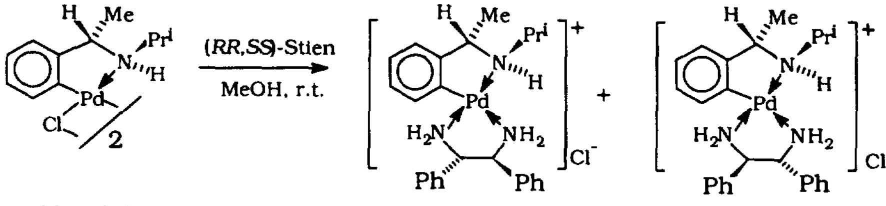
2. Results and discussion

For the resolution of racemic 1,2-diphenyl-1,2-ethanediamine (abbreviation Stien), we have chosen N*-chiral dimeric *ortho*-palladated complex (S_CR_N)-**1** as the resolving agent. In the reaction of dimer (S_CR_N)-**1** with two molar equivalents of racemic Stien, the formation of a 1:1 mixture of diastereomeric adducts (S_CR_N,SS)-**2a** and (S_CR_N,RR)-**2b** was detected by ^{1}H NMR spectroscopy. After recrystallization twice from MeCN, the less soluble diastereomer (S_CR_N,SS)-**2a** was obtained in a yield of 51% (25% with respect to the total Pd) and in 88% de.[4]



(S_CR_N)-**1**　(S_CR_N,SS)-**2a**　(S_CR_N,RR)-**2b**

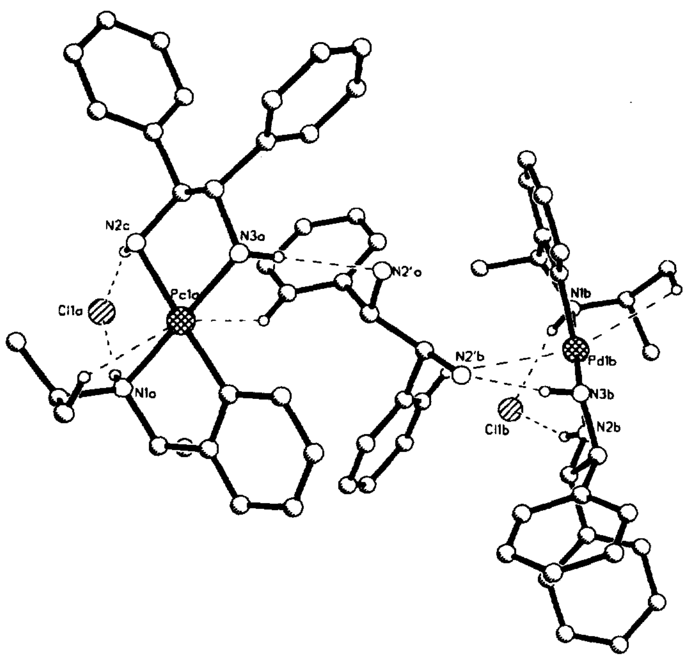
To increase the efficiency of the resolving agent utilization, further experiments were conducted with a Pd:Stien ratio of 1:2 so that the selective crystallization of one of the two diastereomers might be accomplished.[5] The less soluble diastereomer (S_CR_N,SS)-**2a** was isolated under these conditions after crystallization three times from methanol–ether in a yield of 44% (with respect to the total Pd) with >98% de. However, our attempts to obtain the complex (S_CR_N,SS)-**2a** in an analytically pure state failed: both the ^{1}H NMR spectra and elemental analysis data[7] indicated the inclusion of non-stoichiometric amounts of the free Stien molecules in the crystalline adduct. This problem was solved by X-ray single crystal analysis of this complex.

The molecular structure, numbering scheme and selected bond lengths and angles of the less soluble diastereomer (S_CR_N,SS)-**2a** are presented in Fig. 1. The most interesting feature of the structure is the association of two symmetry center related mononuclear complex molecules with one co-crystallization molecule of free diamine (SS)-Stien, [{(S_CR_N)-L}Pd{(SS)-Stien}Cl]$_2$·(SS)-Stien **3a** [L=2-{1-(N-isopropylamino)ethyl}phenyl-C,N]. The association of the three molecules is due mainly to the formation of the pair of hydrogen bonds N(3a)–H...N(2′a) and N(3b)–H...N(2′b) between NH groups of coordinated diamines and N atoms of bridged solvate diamine, 2.281 Å. The pair of very weak intermolecular agostic interactions Pd(1a)...H–C(2′a) and Pd(1b)...H–C(2′b), 3.05 Å, between the orthogonally oriented *ortho*-H of Ph-groups of bridged diamine and palladium might also be proposed as a factor of additional stabilization of this unusual structure.

The benzylaminate palladacycle has an envelope-like conformation with the bend along the Pd(1)...C(7) bond of 26.6° less puckered compared to the starting dimer (S_CR_N)-**1**; averaged intrachelate torsion angles are 16.0 and 19.8–22.3°[8] respectively. It retains the usual λ(S_CR_N)-stereochemistry with the pseudo-axially oriented α-Me and N-Pr^i substituents; the short ^{i}Pr...Pd contact at a distance of 2.858 Å should be noted.

The diamine metallacycle adopts a strongly twisted δ-conformation of the asymmetric envelope with equatorial C–Ph groups and axial α-CH groups; the α-HCCH-α torsion angle is 179.6°. The average intrachelate torsion angle is 32.2°. The chloride counterion forms two very strong hydrogen bonds with the equatorial N–H groups of the same complex cation; one of these groups belongs to the benzylaminate and another one to diamine chelate rings (Cl...H distances 2.447 and 2.477 Å, respectively).

The retention of the (λS_CR_N,δSS)-stereochemistry of the **2a** diastereomer in solution was confirmed by means of ^{1}H NMR spectroscopy including NOE techniques [Fig. 2(a,b)].



Selected bond lengths (A) and angles (deg.)

Pd(1)-C(1)	1.973(5)
Pd(1)-N(3)	2.058(4)
Pd(1)-N(1)	2.076(4)
Pd(1)-N(2)	2.152(4)
N(1)-C(9)	1.494(6)
N(1)-C(7)	1.505(6)
N(2)-C(12)	1.479(6)
N(3)-C(13)	1.499(6)
C(1)-Pd(1)-N(3)	96.8(2)
C(1)-Pd(1)-N(1)	82.6(2)
N(3)-Pd(1)-N(1)	179.2(2)
C(1)-Pd(1)-N(2)	175.4(2)
N(3)-Pd(1)-N(2)	81.9(2)
N(1)-Pd(1)-N(2)	98.6(2)

Fig. 1. X-Ray structure of adduct **3a**. $C_{32}H_{40}ClN_4Pd$, M 662.6, orthorhombic space group $P2_12_12$, a 15.350(4), b 23.348(9), c 8.396(1) Å, V 3009.1(14) Å^3, Z 4, d_{calc} 1.374 g cm^{-3}, Mo-K$_\alpha$ radiation, μ(Mo-K$_\alpha$) 0.721 cm^{-1}; 293 K; the final R and R_w values are 0.0317 and 0.0789, respectively, for 3868 independent reflections corrected for absorption by a Ψ-scan curve

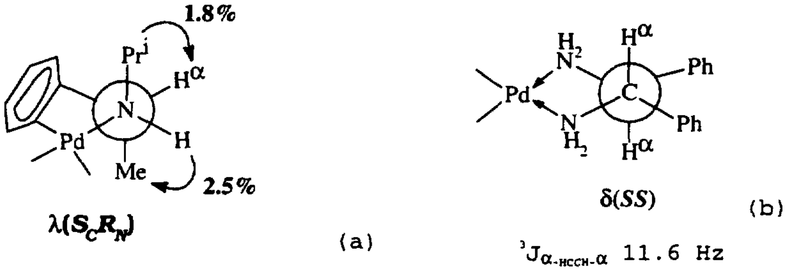


Fig. 2. Conformation of benzylaminate (a) and diamine (b) metallacycles

The identical (*SS*)-configuration of chelated and bridging Stien ligands[9] prompted us to use this for improvement of the preparative resolution procedure. In the reaction of dimeric complex (S_CR_N)-**1** with six molar equivalents of racemic diamine Stien under non-optimized conditions, the dimeric association of the diastereomer (S_CR_N,*SS*)-**2a** with (*SS*)-Stien **3a** with >98% de was obtained after its twofold recrystallization from MeCN in an analytically pure state in a yield of 66% (with respect to the Stien and the total Pd). Attempts to resolve the related C_2-symmetric aliphatic diamine using the most popular *ortho*-palladated complex (derived from 1-naphthylethylamine) have not been successful.[6]

The isolation of the free diamine (*SS*)-Stien from **3a** was performed by its protonation with dilute aqueous HCl in the two-phase system CH_2Cl_2/H_2O in a yield of 85%. The resolving agent (S_C,R_N)-**1** was recovered from the organic phase in essentially quantitative yield.

Although other routes to enantiopure Stien are also known (including resolution[10] and asymmetric synthesis[11]), the use of an *ortho*-palladated matrix for this purpose seems to be a very attractive approach. To the best of our knowledge this is the first case of a double enantiomer selection (in the inner and outer coordination spheres) during the selective crystallization of the diastereomeric *ortho*-palladated complexes and the first example of a structurally characterized palladium complex with stilbendiamine.

3. Experimental

3.1. Diastereomeric complex separation

A solution of racemic stilbendiamine (0.5904 g, 2.781 mM) in anhydrous MeOH (3 mL) was added to a suspension of dimer (S_CR_N)-**1** (0.282 g, 0.463 mM) in the same solvent (4 mL) under argon. After 1 h stirring at room temperature the reaction mixture was filtered and evaporated in vacuo; subsequent recrystallization (twice) of the oily residue from anhydrous MeCN afforded the solvated adduct (S_CR_N,*SS*)-**2a**·0.5(Stien) in a yield of 66% (0.382 g, 0.614 mM) and a diastereomeric purity (determined from ^{1}H NMR data) of >98% de: m.p. (dec) 201–203°C, $[\alpha]_D^{20}$ −39.4 (c 1.7, MeOH). Anal. calcd: C, 61.74; H, 6.48; N, 9.00 for $C_{32}H_{40}ClN_4Pd$. Found: C, 61.45; H, 6.51; N, 9.03. The ^{1}H NMR spectrum is the same as in the literature,[7] except for the intensity of the free diamine signals.

3.2. Diamine isolation

A suspension of the individual diastereomer (S_CR_N,*SS*)-**2a**·0.5(Stien) (0.212 g, 0.341 mM) in CH_2Cl_2 (10 mL) was treated with aqueous 1 N HCl (5 mL) under vigorous shaking for 5 min; the aqueous phase was extracted with CH_2Cl_2 (3×10 mL), concentrated in vacuo and treated with saturated KOH solution under cooling. The diamine was thoroughly extracted with benzene and the combined organic extracts were dried over KOH, concentrated in vacuo and treated with hexane. Diamine (*SS*)-Stien was isolated in a yield of 85% (0.0923 g, 0.435 mM) and an optical purity of 99% ee: $[\alpha]_D^{20}$ −106.2 (c 0.8, MeOH); lit. data: $[\alpha]_D^{20}$ −106.5 (c 1.09, MeOH).[12]

3.3. Resolving agent regeneration

The combined dichloromethane extracts from the diamine isolation (see Section 3.2) were washed with water, dried over Na_2SO_4, and concentrated in vacuo. After chromatographic purification using a short silica column, the starting dimer (S_CR_N)-**1** was recovered in 95% yield (0.0985 g, 0.162 mM).

Acknowledgements

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4. For (S_CR_N,SS)-**2a**: m.p. (dec) 204–206°C, $[\alpha]_D^{20}$ −34.3 (c 1.5, MeOH). Anal. calcd: C, 56.18; H, 6.41; N, 7.86 for $C_{25}H_{32}ClN_3Pd{\cdot}H_2O$. Found: C, 56.01; H, 6.14; N, 7.75. Diastereomeric purity (88% de) was determined by ^{1}H NMR using the integral intensity of the Me groups of the NPr^i substituent.
5. The ^{1}H NMR spectra of the starting mixture of dimer (S_CR_N)-**1** and racemic Stien in a 1:4 molar ratio contains two sets of signals from the two diastereomers **2a,b** in nearly a 1:1 ratio and the signals of free diamine. The absence of stereoselectivity in their complexation seems to be a result of the low efficiency of steric interactions between the benzylaminate palladacycle and the primary amino groups of the diamine (cf. findings of Leung et al.[6]); it is likely that the disruption of the agostic interaction *iso*-Pr...Pd in a polar medium may decrease the conformational stability and ability to chiral recognition of palladacycle as well.
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7. For (S_CR_N,SS)-**2a**·0.3(Stien): m.p. (dec) 204–206°C, $[\alpha]_D^{20}$ −50.0 (c 1.2, MeOH). Anal. calcd: C, 60.46; H, 6.39; N, 8.69 for $C_{29.2}H_{36.8}ClN_{3.6}Pd$. Found: C, 60.57; H, 6.37; N, 8.79. ^{1}H NMR (DMSO-d_6, 40°C; δ, ppm; J, Hz): 1.247 (d, $^3J_{HH}$ 6.4, 3H, CHMe_2), 1.254 (d, $^3J_{HH}$ 6.4, 3H, CHMe_2), 1.693 (d, $^3J_{HH}$ 6.6, 3H, α-Me), 3.058 (m, $^3J_{HH}$ 6.4, $^3J_{CH\text{-}NH}$ 4.4, 1H, CHMe$_2$), 3.934 (br.t, $^2J_{NH\text{-}NH}$ 12.1, $^3J_{NH\text{-}CH}$ 9.0, 1H, N^2H^{ax}), 4.119 (q, $^3J_{HH}$ 6.7, 1H, α-CH of palladacycle), 4.222 (m, 1H, α-CH, Stien), 5.147 (br.t, $^2J_{NH\text{-}NH}$ 9.0, $^3J_{NH\text{-}CH}$ 12.0, 1H, N^3H^{ax}), 5.225 (br.d, $^2J_{NH\text{-}NH}$ 12.1, 1H, N^2H^{eq}), 5.524 (br.d, $^2J_{NH\text{-}NH}$ 9.0, 1H, N^3H^{eq}), 6.051 (d, 1H, $^3J_{NH\text{-}CH}$ 4.4, N^1H of palladacycle), 7.15–7.40 (m, 13H, Ph, η^2- and free Stien); aromatic protons of palladacycle: 6.774 (dt, $^3J_{HH}$ 7.4, $^4J_{HH}$ 1.4, 1H, C^5H), 6.911 (dt, $^3J_{HH}$ 7.2, $^4J_{HH}$ 0.8, 1H, C^4H), 6.938 (dd, $^3J_{HH}$ 7.6, $^4J_{HH}$ 1.6, 1H, C^3H), 7.040 (d, $^3J_{HH}$ 7.2, 1H, C^6H); free Stien: 3.870 (br.s., 0.6H, α-CH).
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