ORGANIC LETTERS

2000
Vol. 2, No. 13
1795−1798

$[PtCl_3(C_2H_4)]^-[(S,S)\text{-}(PhMeCH)_2NH_2]^+$: A New and Versatile Ionic Organometallic Chiral Derivatizing Agent for the Determination of the Enantiomeric Composition of Chiral Unsaturated Compounds by ^{195}Pt NMR Spectroscopy

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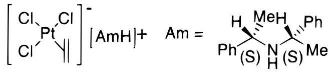
Received March 8, 2000

ABSTRACT



CDA

chiral substrates = unsaturated ethers, olefins, allenes

The ionic complex $[PtCl_3(C_2H_4)]^-[(S,S)\text{-}(PhMeCH)_2NH_2]^+$ containing a chiral secondary amine is a new and versatile chiral derivatizing agent (CDA) for the determination of the enantiomeric composition of several unsaturated compounds including simple olefins: the diastereoisomeric mixtures arising from the exchange of ethylene by the unsaturated analytes are easily detected by ^{195}Pt NMR spectroscopy.

Chiral derivatizing agents (CDAs)[1] for NMR spectroscopy represent one of the most effective answers to the great demand of rapid and reliable direct methods for the determination of the enantiomeric composition of chiral substrates. Their use involves the derivatization reaction between an enantiomerically pure chiral auxiliary and the substrates to be analyzed to obtain diastereoisomeric pairs having anisochronous absorptions in their NMR spectra. Since the first applications by Mislow and Raban,[2] a great number of CDAs have been developed based mainly on low molecular weight organic compounds, endowed with polar functionalities essential for the derivatization process and hence devoted to the analyses of polar chiral compounds.[1] Organometallic CDAs[3] have the interesting feature that the derivatization process can involve the coordination to the metal center by π-moieties in the chiral analytes and hence they open interesting perspectives to the analyses of apolar chiral substrates, such as aromatic or unsaturated ones. It is noteworthy that, in particular cases, the metal nuclei are also observable by NMR and hence offer the additional important opportunity of making the analysis of the diastereoisomeric products possible by detection of the metal nuclei resonances, producing simple NMR spectra not complicated by extensive scalar couplings.

About 10 years ago we proposed the square planar *cis*- or *trans*-dichloro[(*S*)-α-methylbenzylamine](ethylene)platinum(II) complexes as CDAs for the analyses by ^{195}Pt NMR spectroscopy of unsaturated ethereal[3f] compounds and trisub-

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(1) (a) Parker, D. *Chem. Rev.* **1991**, *91*, 1441−1457. (b) Yamaguchi, S. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 1, pp 125−149. (c) Hulst, R.; Kellogg, R. M.; Feringa, B. L. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 115−138. (d) Wu, R.; Hernandez, G.; Odom, J. D.; Dunlap, R. B.; Silks, L. A. *Chem. Commun.* **1996**, 1125−1126. (e) Kim, H. C.; Choi, S.; Kim, H.; Ahu, K.-H.; Koh, J. H.; Park, J. *Tetrahedron Lett.* **1997**, *38*, 3959−3962. (f) Anaya de Parrodi, C.; Moreno, G. E.; Quintero, L.; Juaristi, E. *Tetrahedron: Asymmetry* **1998**, *9*, 2093−2099. (g) Parve, O.; Aidnik, M.; Lille, U.; Martin, I.; Vallikivi, I.; Vares, L.; Pehk, T. *Tetrahedron: Asymmetry* **1998**, *9*, 885−896.

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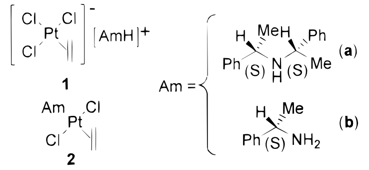
10.1021/ol0000509 CCC: $19.00

stituted allenes,[3g,h] respectively. The above complexes are both covalent and contain a primary amine. However, the preparation of *cis* complexes[4] is quite laborious and limited to primary amines and the applications reported for *trans* ones are rather limited. Furthermore, none of them is applicable to unfunctionalized olefins.

In the present paper we report the synthesis and use of the new ionic organometallic CDA $[PtCl_3(C_2H_4)]^-[AmH]^+$ (**1a**) (Scheme 1) where Am is the chiral secondary amine (*S*,*S*)-bis(α-methylbenzyl)amine. This new CDA can be prepared very easily from Zeise's salt and exhibits widespread applicability for ^{195}Pt NMR analyses of several classes of unsaturated chiral compounds including simple olefins. The enhanced versatility of **1a** is demonstrated here by comparing its performances to those of the analogous ionic complex **1b** containing (*S*)-α-methylbenzylamine and of the covalent complexes *trans*-dichloro[amine](ethylene)platinum(II) containing the same secondary (**2a**) and primary (**2b**) amines (Scheme 1).

Scheme 1



Ionic complexes **1** were prepared according to the following procedure: Zeise's salt $[PtCl_3(C_2H_4)]^-K^+$, suspended in any organic solvent (chloroform, acetone or benzene), was treated with an equimolar amount of the amine hydrochloride. Rapid exchange of the two cations (Scheme 2) occurred, evidenced by solubilization of the yellow solid and formation of a white fine powder of KCl. By filtration of the reaction mixture and evaporation of the solvent, the complexes were isolated as yellow solids. Covalent complexes **2** were obtained by a simple modification of the procedure described in the literature,[5] by treating Zeise's salt, dissolved in methanol/H_2O (1:2), with a methanol solution of an equimolar amount of the amine as a free base: the products precipitated as pale yellow solids. Secondary amine (*S*,*S*)-bis(α-methylbenzyl)amine was prepared, as reported in the literature procedure,[6] by condensation of (*S*)-α-methylbenzylamine with acetophenone followed by catalytic (Pd/C) hydrogenation of the imines; purification of the hydrogenation product gave a mixture (90:10) of the two diastereoisomeric amines from which the major isomer (*S*,*S*) was selectively isolated by crystallization of the HCl salts in water. The new ionic complexes were characterized by elemental analysis and ^{1}H NMR spectroscopy: the ^{1}H NMR spectrum of **1a** (Figure 1a) clearly showed the presence of the NH_2^+ group at 8.80 ppm and the complexed ethylene at 4.72 ppm, well distinguishable from the NH (5.30 ppm) and ethylene (4.25 ppm) protons of the corresponding *trans* covalent complex **2a** (Figure 1b). In addition, the two methyl

Scheme 2

$$K^+[PtCl_3(C_2H_4)]^- + [AmH]^+ \xrightarrow[25\ °C]{CHCl_3} [AmH]^+[PtCl_3(C_2H_4)]^- + KCl\downarrow$$

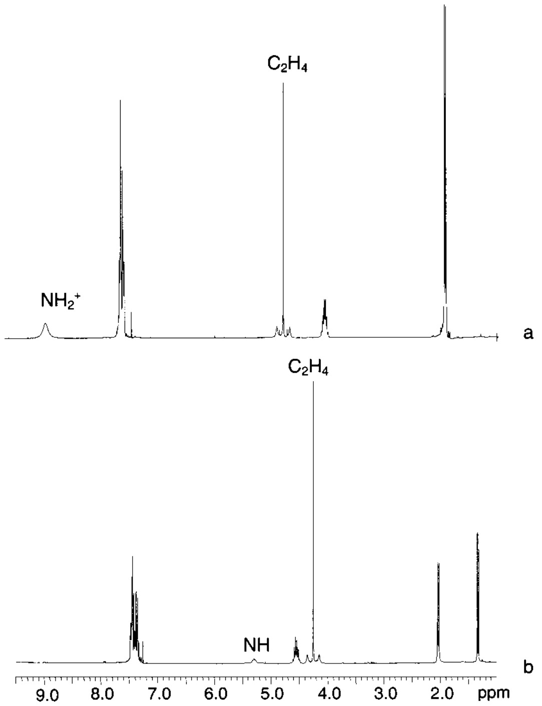


Figure 1. ^{1}H NMR (300 MHz, $CDCl_3$, ppm referred to TMS as external standard) of the complexes containing the secondary amine: (a) ionic **1a**, (b) covalent **2a**.

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[3] (a) Parker, D.; Taylor, R. J. *Tetrahedron* **1988**, *44*, 2241−2248. (b) Parker, D.; Taylor, R. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1781−1783. (c) Wiesauer, C.; Kratky, C.; Weissensteiner, W. *Tetrahedron: Asymmetry* **1996**, *7*, 397−398. (d) Chooi, S. Y. M.; Leung, P.-H.; Lim, C. C.; Mok, K. F.; Quek, G. H.; Sim, K. Y.; Tan, M. K. *Tetrahedron: Asymmetry* **1992**, *3*, 529−532. (e) Buriak, J. M.; Osborn, J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 689−690. (f) Salvadori, P.; Uccello-Barretta, G.; Bertozzi, S.; Settambolo, R.; Lazzaroni, R. *J. Org. Chem.* **1988**, *53*, 5768−5770. (g) Salvadori, P.; Uccello-Barretta, G.; Lazzaroni, R.; Caporusso, A. M. *J. Chem. Soc., Chem. Commun.* **1990**, 1121−1123. (h) Uccello-Barretta, G.; Balzano, F.; Salvadori, P.; Lazzaroni, R.; Caporusso, A. M.; Menicagli, R. *Enantiomer* **1996**, *1*, 365−375. (i) Dunina, V. V.; Kuz′mina, L. G.; Kazakova, M. Yu.; Grishin, Yu. K.; Veits, Yu. A.; Kazakova, E. I. *Tetrahedron: Asymmetry* **1997**, *8*, 2537−2545. (j) Canet, J.-L.; Canet, I.; Gelas, J.; Ripoche, I.; Troin, Y. *Tetrahedron: Asymmetry* **1997**, *8*, 2447−2451. (k) Staubach, B.; Buddrus, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1344−1346. (l) Albert, J.; Granell, J.; Muller, G.; Sainz, D.; Font-Bardia, M.; Solans, X. *Tetrahedron: Asymmetry* **1995**, *6*, 325−328. (m) Klein, J.; Neels, S.; Borsdorf, R. *J. Chem. Soc., Perkin Trans 2* **1994**, 2523−2524. (n) Chelucci, G.; Bacchi, A.; Fabbri, D.; Saba, A.; Ulgheri, F. *Tetrahedron Lett.* **1999**, *40*, 553−556. (o) Alcock, N. W.; Hulmes, D. I.; Brown, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 395−397.

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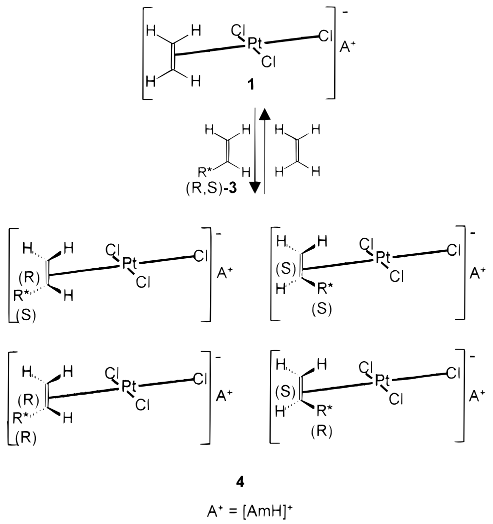
groups of the amine are anisochronous (2.04 ppm; 1.33 ppm) in **2a** and equivalent (1.93 ppm) in **1a**.

Use of complexes **1** as CDAs simply involves exchange of their coordinated ethylenes by unsaturated compounds **3** to produce complexes **4** (Scheme 3). Coordination of the two prochiral faces of the double bond of each enantiomer produces two diastereoisomers whose ratio reflects the diastereoselectivity in the complexation. Therefore, complexes **4** are composed of a maximum of four diastereoisomers in solution. By using a very small excess of the CDA with respect to **3** (CDA:**3** = 1:0.8), the fast formation of the diastereoisomeric mixtures is quantitative and kinetic resolution phenomena are avoided (see below). As each diastereoisomer can give rise to a single ^{195}Pt resonance, ^{195}Pt NMR spectroscopy is an easy way of their detection method using short instrumental times (ranging between 30 min and 1 h) for solutions containg 50−100 mg of substances in 0.5 mL of deuterated solvent. Therefore, the enantiomeric composition determination can be performed by comparing the areas of the signals arising from each enantiomer. The signals from the small excess of the CDAs are never superimposed on those of the diastereoisomeric mixtures as the former are always low-frequency shifted by 50−300 ppm relative to the resonances of the diastereoisomeric mixtures.

Scheme 3



The efficiency of **1a** as a CDA was tested for several classes of unsaturated racemic compounds (Scheme 4) by recording the ^{195}Pt NMR spectra in benzene of the corresponding complexes **4** and determining the nonequivalences given as differences between the chemical shifts of the more ($\Delta\Delta\delta_1$) and less ($\Delta\Delta\delta_2$) abundant diastereoisomers formed by the two enantiomers. The results are summarized in Table 1. These values have been compared to those obtained by using as CDA the corresponding *trans* covalent complex **2a** or the ionic complex **1b** and the covalent complex, **2b**, containing the corresponding primary amine, (*S*)-α-methylbenzylamine.

Scheme 4

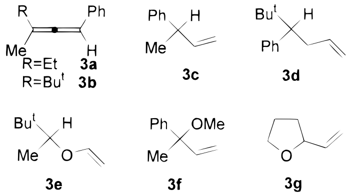


Table 1. ^{195}Pt NMR (64.3 MHz, C_6D_6, 25 °C) Nonequivalences (Hz) Measured by Using **1a** as CDA, Given as Differences between the Chemical Shifts of the More ($\Delta\Delta\delta_1$) and Less ($\Delta\Delta\delta_2$) Abundant Diastereoisomers in the Complexes **4**

complex	$\Delta\Delta\delta_1$	$\Delta\Delta\delta_2$
4a	420	372
4b	376	
4c	120	196
4d	114	0
4e	118	148
4f	0	249
4g	131	667

By using complex **1a**, relevant nonequivalences were measured for all compounds indicated in Scheme 4. As an example, the complexation of trisubstitued allene **3a** produced four diastereoisomers, each giving a distinct ^{195}Pt NMR absorption, and for the major and minor diastereoisomers, remarkable nonequivalences of about of 400 Hz were measured (Figure 2a). Comparable nonequivalences were obtained by using as CDA the corresponding covalent

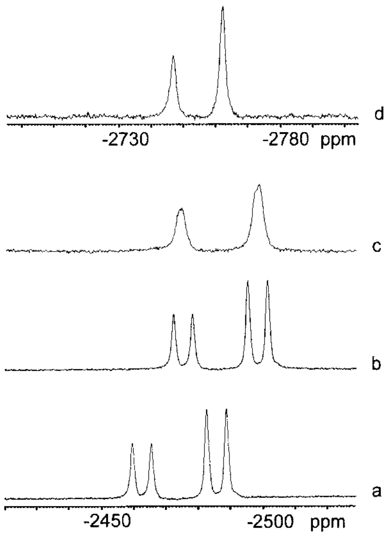


Figure 2. ^{195}Pt NMR spectra (64.3 MHz, C_6D_6, 25 °C, Na_2PtCl_6 external standard) of diastereoisomeric mixtures containing (*R*)(*S*)-**3a** formed from CDA: (a) **1a**, (b) **2a**, (c) **1b**, (d) **2b**.

complex **2a** (Figure 2b); however this is the only case in which the two CDAs **1a** and **2a** showed similar efficiencies: for the other substrates indicated in Scheme 4, only the ionic complex **1a** was effective as CDA and it had remarkable efficiency. When the two complexes containing the primary amine, ionic **1b** and covalent **2b**, were used as CDAs, no nonequivalences were detected for any diastereoisomeric mixture arising from the complexation of the substrates **3a**−**3g** (Figure 2c,d).

The reliability of the enantiomeric purity determinations by integration of the ^{195}Pt resonances of the diastereoisomeric mixtures has been checked by using CDA **1a** and samples of substrate **3b** having a known enantiomeric composition (determined by gas chromatographic analyses on CYDEX-B) ranging from 36% (Figure 3b) to 64% (Figure 3c,d) or the racemate (Figure 3a): the values obtained by integration were always in good agreement with the known enantiomeric purity values (±5%). This result confirms also that a very small excess of the CDA (CDA:substrate = 1:0.8) is sufficient to avoid the phenomena of kinetic resolution.

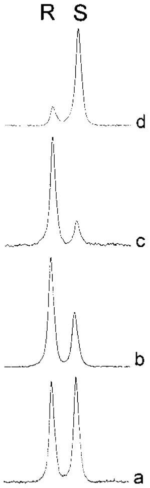


Figure 3. ^{195}Pt NMR (64.3 MHz, C_6D_6, 25 °C, Na_2PtCl_6 external standard) analyses of the diastereoisomeric mixtures formed from CDA **1a** and racemic (a) or enantiomerically enriched **3b**, having known enantiomeric purities (determined by gas chromatography on CYDEX-B): (b) 36%, (c) 64%, (d) 64% ($\delta_S = -2417$ ppm and $\delta_R = -2411$ ppm).

It is noteworthy that the nature of the solvent employed in the measurements does not affect remarkably the magnitude of the nonequivalences measured for **2a**, whereas it seems to be fundamental for the success of the determinations in the case of **1a**, where, for several cases, the use of $CDCl_3$ as solvent instead of benzene did not allow us to detect enantiodiscrimination in solution.

The new ionic CDA $[PtCl_3(C_2H_4)]^-[(S,S)\text{-}(PhMeCH)_2NH_2]^+$ (**1a**) shows a versatility markedly superior to those of previously reported organometallic CDAs;[3] in fact, it can be applied to the analyses of several classes of chiral unsaturated analytes, such as vinyl ethers, acyclic and cyclic allyl ethers having both tertiary and quaternary chiral carbon atoms, simple olefins having the chiral carbon atom in the α or *β* position to the double bond, and allenes. This is an important finding because there is a great paucity of NMR methods for the determination of the enantiomeric composition of unsaturated compounds with particular reference to simple olefins.

Furthermore, we must take into account that the preparation and use of this new ionic CDA are really simple: the CDA is prepared in a few minutes and the exchange of its coordinated ethylene by the enantiomeric mixture to be analyzed can be performed directly in the NMR tube.

Finally we must also give due consideration to the fact that the results presented here open the way for the development of a new class of organometallic CDAs whose efficiency and versatility can be suitably modulated by means of the nature of its amine conterion.

Acknowledgment. This work was supported by the Ministero della Ricerca Scientifica e Tecnologica (MURST) and CNR, Italy.

Supporting Information Available: NMR characterization data of CDAs and amine hydrochloride **a**. Elemental analyses. Experimental procedure for ee determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0000509