[*n*-Bu$_4$N][Δ-TRISPHAT] Salt, an Efficient NMR Chiral Shift Reagent for Neutral Planar Chiral Tricarbonylchromium Complexes

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Summary: The determination of the enantiomeric purity of planar chiral Cr(CO)$_3$ complexes of substituted benzaldehydes and nitrones has been conveniently carried out by ^{1}H NMR analysis using a TRISPHAT salt as a diamagnetic chiral shift reagent.

Introduction

Planar chiral tricarbonylchromium complexes are widely used in organic synthesis.[1] The *o*-substituted benzaldehyde derivatives, in particular, are versatile building blocks for natural product synthesis.[2] The preparation of these compounds in enantioenriched form can be achieved either by resolution of racemic mixtures[3] or by diastereoselective[3c,4] or enantioselective synthesis.[5] The determination of their enantiomeric purity is then crucial and is usually carried out by optical rotation measurements, chiral HPLC analysis,[6] or ^{1}H NMR, using chiral derivatizing agents[3c] or lanthanide shift reagents.[7,8] Recently, it has been shown that the easily prepared and resolved tris(tetrachlorobenzenediolato)phosphate(V) anion (**1**; TRISPHAT) is configurationally stable in solution as an ammonium salt, e.g. [*n*-Bu$_4$N][Δ-**1**].[9] This anion is a useful diamagnetic NMR chiral shift reagent for cationic transition-metal complexes[10] and phosphonium salts.[11] The efficiency of the reagent has been explained by the formation of diastereomeric contact ion pairs between anions **1** and the chiral cations. The resulting short-range intermolecular discriminating interactions lead to a magnetic nonequivalence for the enantiomers of the cations. It was then debatable whether an anion such as **1** could behave as a NMR chiral shift reagent for neutral molecules. While favorable Coulombic interactions are absent with chiral neutral molecules, charge−dipole interactions could be sufficiently strong to allow a differentiation of the two enantiomers. This is indeed the case, and we report here that the enantiomeric purity of arene Cr(CO)$_3$ complexes bearing an electron-deficient functional group (aldehyde or nitrone) can be determined using a TRISPHAT salt.

Results and Discussion

A number of racemic tricarbonylchromium benzaldehyde complexes, **2a**−**9a** (Figure 1), were studied in combination with the shift reagent (Table 1). In an NMR tube, the [*n*-Bu$_4$N][Δ-**1**] salt was added as a solid to a solution of the complex until a satisfactory separation of some of the signals of the enantiomers ($\Delta\delta$) was observed.[12] Usually, it was necessary to add 2−5 equiv of the reagent. For aldehydes **2a**−**6a**, a sufficiently large split was obtained, and the enantiomeric purity was measured by direct integration of the separated signals (Table 1). In most cases, the proton leading to the largest difference in chemical shifts ($\Delta\delta_{max}$) was one of the aromatic hydrogen atoms. When an enantioenriched sample of benzaldehyde complex **5a** was used, an enantiomeric excess (ee) of 87% was measured—a difference of <0.5% from the result obtained by chiral HPLC analysis (Figure 2).[13]

For aldehydes **7a**−**9a**, baseline separations could not be realized. To favor the interactions between the arene Cr(CO)$_3$ complexes and anion **1**, and possibly obtain larger splits, we decided to increase the dipolar moment of the complexes.[14] This was realized by the in situ

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(12) As no hydrogen atom is present on the anion, a rather large ^{1}H NMR spectral window (δ >3.0 ppm) is available for the analyses with [*n*-Bu$_4$N][Δ-**1**].

(13) HPLC (Chiracel OD-H, *n*-hexane/*i*-PrOH 98/2, 1 mL/min). Retention times 15.2 and 21.1 min.

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Table 1. Largest Differences of Chemical Shift ($\Delta\delta_{max}$, ^{1}H NMR, 400 MHz) Observed for the Enantiomers of Arene Cr(CO)$_3$ Complexes with [*n*-Bu$_4$N][Δ-1]

aldehyde			nitrone		
complex	amt of **1**, equiv	$\Delta\delta_{max}$[a]	complex	amt of **1**, equiv	$\Delta\delta_{max}$[a]
2a	3.0	0.057	**2c**	2.6	0.058
3a	2.7	0.018	**3b**	2.8	0.036
4a	4.6	0.028			
5a	2.3	0.026			
6a	3.1	0.031			
7a	1.8	*b*	**7b**	3.6	0.050
8a	2.8	*b*	**8b**	2.2	0.110
9a	1.6	*b*	**9b**	1.7	0.040

[a] In ppm. [b] Insufficient separation.

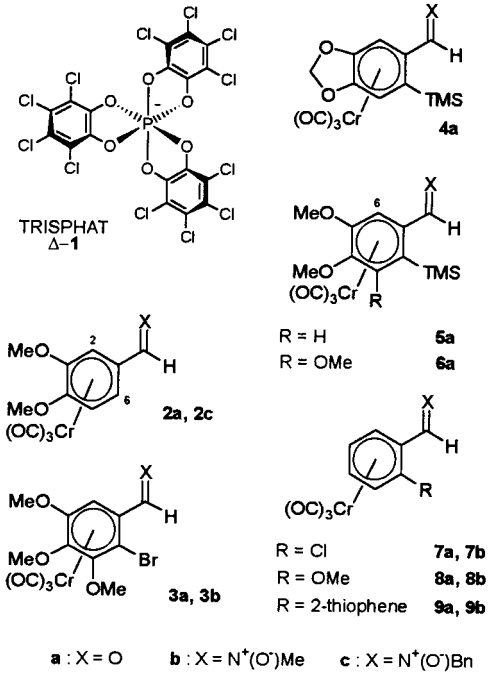

Figure 1. TRISPHAT anion (**1**) and arene Cr(CO)$_3$ complexes (**2**−**9**).

conversion of the aldehydes into nitrone derivatives **3b** and **7b**−**9b** (with *N*-methylhydroxylamine) and **2c** (with *N*-benzylhydroxylamine) (Figure 1).[15] Nitrones showed better separations of the signals in all cases (Table 1, Figure 3). It was thus possible to measure the enantiomeric purity of aldehydes **7a**−**9a** by their in situ transformation into nitrones **7b**−**9b**.

We also observe that this method could be applied to planar Cr(CO)$_3$ complexes with *meta* substituents (e.g. **2a**,**c**). As expected, the larger the number of equivalents of [*n*-Bu$_4$N][Δ-**1**] added, the better the separation of the signals (Figure 4). Improved results were obtained with concentrated solutions of Cr(CO)$_3$ complexes (Figure 5). Finally, the salt [*n*-Bu$_4$N][Δ-**1**] can be easily recovered from the NMR tubes and reused as an NMR chiral shift reagent.

In conclusion, we have shown that determination of the enantiomeric purity of planar chiral arene Cr(CO)$_3$−substituted-benzaldehyde complexes can be done using the TRISPHAT salt as an NMR chiral shift reagent. When necessary, an in situ transformation of the aldehyde into a nitrone was easily performed, leading to higher splits of the signals. This expands the use of diamagnetic anionic chiral shift reagents to neutral molecules.

(15) Planar chiral nitrone complexes have been used in asymmetric reactions: (a) Mukai, C.; Kim, I. J.; Cho, W. J.; Kido, M.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2495. (b) Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A.; Albinati, A. *Tetrahedron: Asymmetry* **1995**, *6*, 1711.

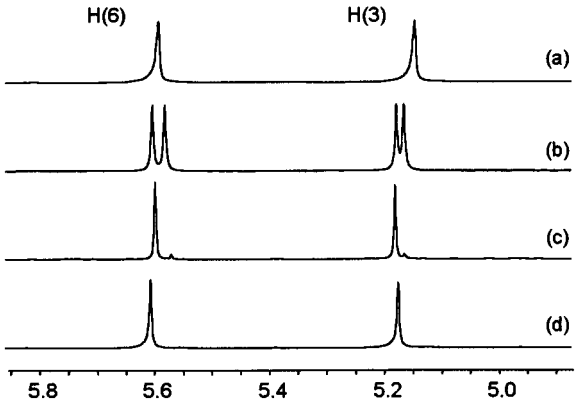

Figure 2. ^{1}H NMR spectra (partial, 400 MHz, C_6D_6/2% DMSO-d_6) of (a) *rac*-**5a**, (b) *rac*-**5a** + 2.3 equiv of [*n*-Bu$_4$N]-[Δ-**1**], (c) (+)-(1*S*)-**5a** (87% ee) + 3.7 equiv of [*n*-Bu$_4$N]-[Δ-**1**], and (d) (+)-(1*S*)-**5a** (>99% ee) + 2.3 equiv of [*n*-Bu$_4$N]-[Δ-**1**].

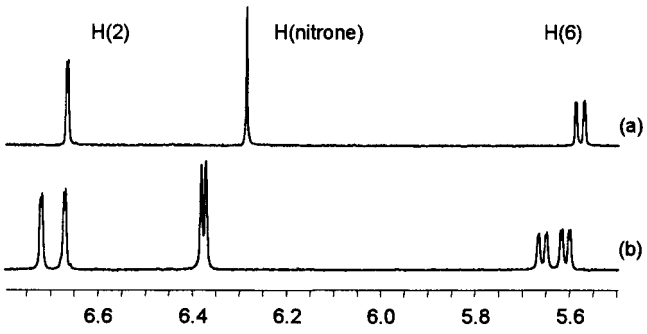

Figure 3. ^{1}H NMR spectra (partial, 400 MHz, C_6D_6/2% DMSO-d_6) of *rac*-**2c** with (a) 0 equiv and (b) 2.8 equiv of [*n*-Bu$_4$N][Δ-**1**].

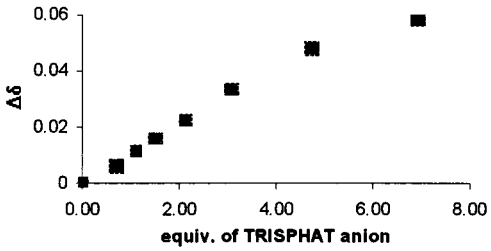

Figure 4. $\Delta\delta_{max}$ (H methyl) as a function of the number of equivalents of TRISPHAT anion for nitrone **7b** (concentration 9.3 mM).

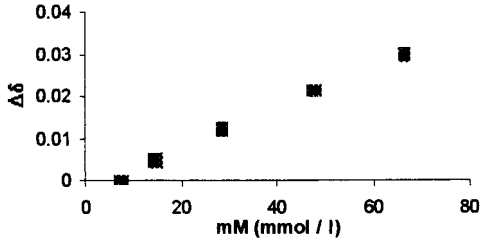

Figure 5. $\Delta\delta_{max}$ (H methyl) as function of the concentration of nitrone **7b** (with 1.1 equiv of [*n*-Bu$_4$N][Δ-**1**]).

Experimental Section

Preparation of Arene $Cr(CO)_3$ Complexes. Arene $Cr(CO)_3$ complexes were prepared by the previously described procedures.[1,2]

Preparation of the [*n*-Bu_4N][Δ-1] Salt. To a solution of [cinchonidinium][Δ-**1**][9] dissolved in a minimum of EtOH was added [*n*-Bu_4N][OH] (2 equiv) in MeOH (Fluka), and H_2O (∼2%) was added to complete the precipitation. Filtration of the solid, redissolution in acetone, and concentration in vacuo afforded the [*n*-Bu_4N][Δ-**1**] salt (100%). ^1H NMR ($CDCl_3$, 400 MHz): δ 3.20 (m, 8H, NCH_2-), 1.67 (m, 8H, $N-CH_2CH_2-$), 1.31 (m, 8H, $-CH_2CH_3$), 0.90 (t, 12H, $J = 7.3$ Hz, $-CH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.7 (d, $J_{C-P} = 6.6$ Hz), 122.6, 113.7 (d, $J_{C-P} = 19.8$ Hz), 59.2, 23.8, 19.7, 13.4. ^{31}P NMR ($CDCl_3$, 162 MHz): δ −79.2. $[\alpha]_D^{20} = -368$, $[\alpha]_{578}^{20} = -380$, $[\alpha]_{546}^{20} = -437$, $[\alpha]_{436}^{20} = -820$, $[\alpha]_{365}^{20} = -1506$, $c = 0.10$, EtOH. MS-ES: (+) *m*/*z* 242.3 ($[Bu_4N]^+$); (−) *m*/*z* 768.5 ($TRISPHAT^-$).

Typical Procedure for the NMR Chiral Shift Experiment with Benzaldehyde Derivatives. A 3−4 mg amount of the arylaldehyde $Cr(CO)_3$ complex was dissolved in 500 μL of a mixture of C_6D_6 and 2% DMSO-d_6, and 2−5 equiv of the [*n*-Bu_4N][Δ-**1**] salt was added.

Typical Procedure for the NMR Chiral Shift Experiment using Derivatization of the Aldehydes into Nitrones. The preparation of the nitrones was effected directly in the NMR tubes by the addition of triethylamine (1.6 equiv) and *N*-benzyl- or *N*-methylhydroxylamine hydrochloride (1.5 equiv) to solutions of 3−4 mg of the arylaldehyde $Cr(CO)_3$ complexes in 500 μL of C_6D_6. The solutions were stirred overnight to give complete conversion to the corresponding nitrones. After addition of 2% of DMSO-d_6, the NMR experiments were continued as described above.

Recovery of [*n*-Bu_4N][Δ-1]. Chromatography over silica gel of the mixture obtained after the NMR chiral shift experiment using CH_2Cl_2 as eluent allowed the recovery of the [*n*-Bu_4N][Δ-**1**] salt (yield >90%).

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