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Stereoselective Intramolecular 1,3-Dipolar Cycloaddition of Chiral Chromium Tricarbonyl Complexed Nitrone

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Abstract: The new tricarbonyl(2-allyloxybenzaldehyde)chromium(0) complex (**4a**) has been prepared in both a racemic and an enantiomerically pure form. The thermal intramolecular 1,3-dipolar cycloaddition of the corresponding (1*R*)-N-methyl nitrone (**5a**) afforded, after decomplexation. *cis*-(3a*S*,9b*R*)-1,3a,4,9b-tetrahydro-1-methyl-3H-[1]benzopyrano[4,3-c]isoxazole (**7**) with complete enantioselection.

[3+2] Cycloaddition reactions are of general application for the synthesis of five-member heterocycles.[1] Nitrones are widely used as 1,3-dipoles in such reactions in both bimolecular and intramolecular addition to olefines in order to give isoxazolidine derivatives,[2-4] and the stereochemical outcome of such reactions has been largely elucidated.[5]

The isoxazolidine ring is a versatile heterocycle because the N-O bond cleavage provides an easy entry to a variety of interesting 1,3-difunctional derivatives[6], such as 1,3-aminoalcohols, and control of the absolute stereochemistry in cycloaddition processes to produce optically active isoxazolidine is an important research target. The planar chirality of tricarbonyl(η^6arene)chromium complexes[7] offers a unique opportunity of reaching these goals. Chiral chromium complexed nitrones have recently been used in intermolecular 1,3-dipolar cycloaddition to electron-rich olefins, leading to isoxazolidine derivatives with a high degree of stereo- and regioselection.[8]

Oppolzer has published an intramolecular version of nitrone-alkene cycloaddition involving aromatic systems such as A[9], to give tricyclic isoxazolidine derivative B.(Scheme 1) The *N*-methyl nitrone of 2-allyloxybenzaldehyde seemed to us a very interesting substrate, since the corresponding Cr(CO)$_3$ complex is chiral and could be used in a stereoselective intramolecular cycloaddition.

Scheme 1
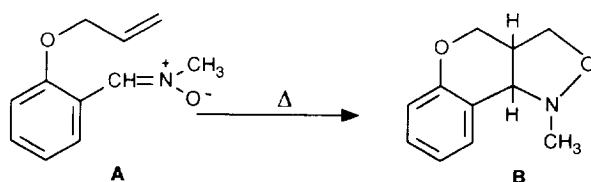
Results and Discussion.

We first prepared the new racemic tricarbonylchromium complex of 2-allyloxybenzaldehyde **4a** through nucleophilic substitution of the diethyl acetal of 2-fluoro or 2-chlorobenzaldehyde tricarbonylchromium **1** or **2**[10] with sodium allyl alcoholate in dimethoxyethane and in the presence of tetrabutyl ammonium bromide as phase transfer catalyst. The fluoro derivative **1** reacts at room temperature, whereas **2** needs 50 °C for 5 h. After acidic hydrolysis of the acetal function, the complexed aldehyde **4a** was recovered in approximately 75% overall yield. The complexed nitrone **5a** was obtained after the reaction of **4a** with *N*-methyl hydroxylamine in dioxane solution at room temperature for 12 h. (Scheme 2)

Scheme 2
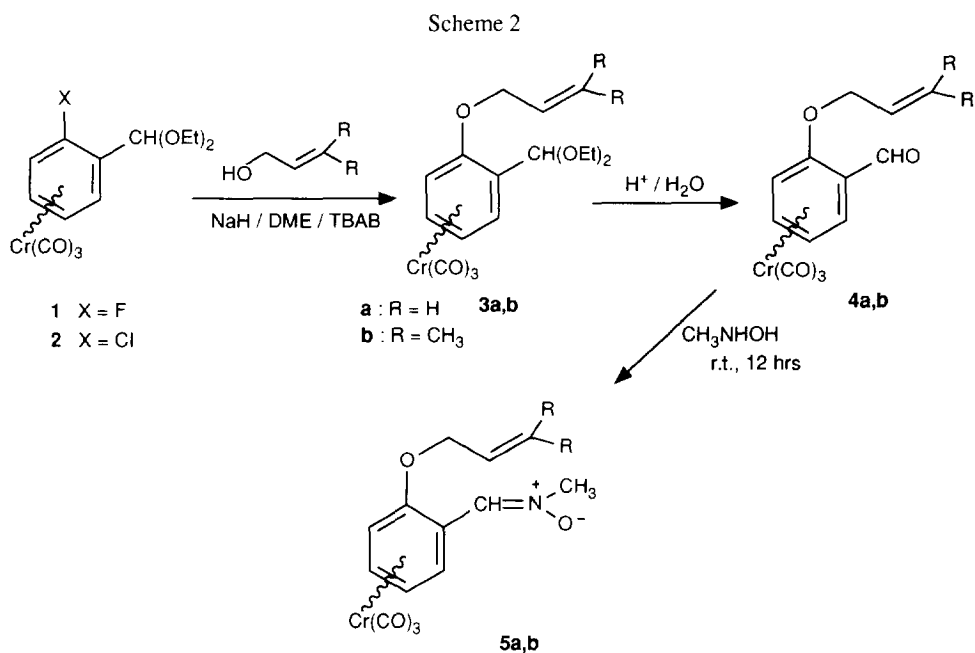
A toluene solution of racemic **5a** was then heated at 80 °C for 8 h to give the $Cr(CO)_3$ complex of 1,3a,4,9b-tetrahydro-1-methyl-3H-[1]benzopyrano[4,3-c]isoxazole **6**, which was quantitatively decomplexed by air and sunlight to the corresponding cycloadduct **7** (Scheme 3). ^{1}H NMR analysis revealed that **7** was a single diastereoisomer and that the ring junction was *cis* as demonstrated by the *J*= 7.37 Hz between H_a and H_b.[9]

Scheme 3
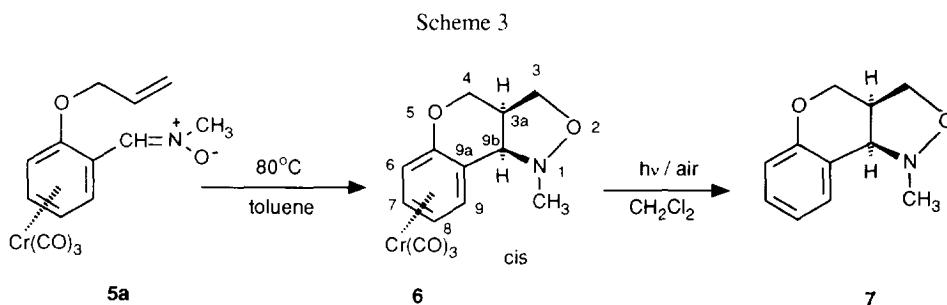
In order to confirm the high degree of stereoselectivity observed in the intramolecular cycloaddition of **5a**, and with the aim of obtaining the corresponding optically active heterocycle, we then decided to prepare the homochiral nitrone **5a**. In this case, acetal (+)-(1R)-**3a** was obtained by treating (-)-(1R)-tricarbonyl(2-chlorobenzaldehyde)chromium ($[\alpha]_D$= -1120)[10] with an excess of triethyl orthoformate and a catalytic amount of 96% H_2SO_4. Following the procedure described above for the racemic substrate, we obtained the enantiomerically pure complexed aldehyde (1R)-**4a** ($[\alpha]_D$=-1007), which was transformed into nitrone (1R)-**5a** ($[\alpha]_D$= -2203). After heating (-)-**5a** at 80 °C in toluene solution for 7 h, we isolated the complexed cycloadduct **6** ($[\alpha]_D$=-245) which, after decomplexation (hv, air), gave the target compound (+)-**7** with complete enantioselection. Enantiomeric excess was determined by ^{1}H NMR, using Eu(hfc)$_3$ as chiral shift reagent in C_6D_6 .[11]

The absolute configuration of the benzopyranoisozaxole derivative (+)-**7** was determined on the basis of an X-Ray analysis of the racemic complexed cycloadduct **6**.(Fig 1).
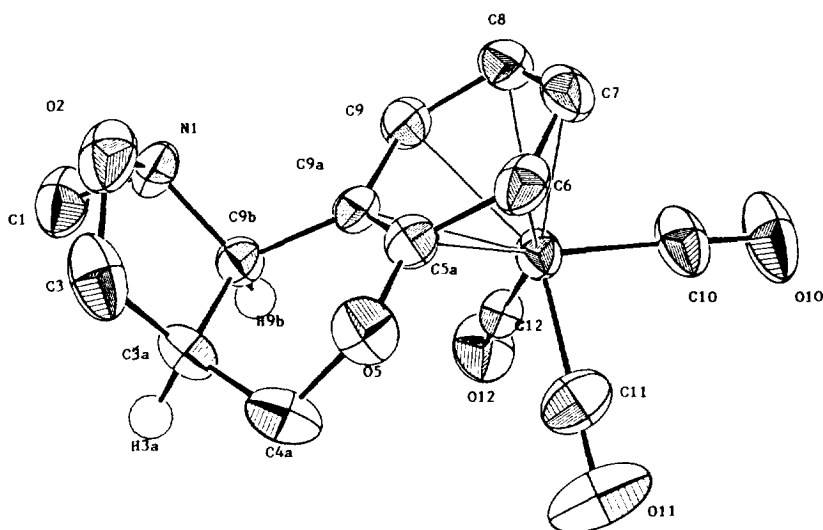
Fig. 1: *ORTEP drawing of compound 6. Anisotropic displacement elipsoids are drawn at 50% probability. Only the two hydrogen atoms (with arbitrary radii) definining the stereochemistry of C3a and C9b carbons are shown.*

The X-Ray structure[12] revealed a 3aS*,9aR*,9bR* configuration at the stereogenic centers and, on this basis, the absolute stereochemistry of cis-(+)-**7** was established to be 3aS, 9bR, because the absolute configuration of the starting (-)-(1R)-tricarbonyl(2-chlorobenzaldehyde)chromium has already been unambiguously determined.[10]

The stereochemistry of complex **6** is in agreement with the accepted stereochemical model explaining the high degree of stereoselectivity found in the reactions of these chiral chromium complexes. Moreover, the stereochemical outcome of the above intramolecular cycloaddition is the same as that reported by Japanese authors for an intermolecular nitrone-alkene cycloaddition.[8] According to this model, the double bond approaches the favorite Re face of nitrone (1R)-**5a** (having Z geometry) from the side opposite that bearing

the $Cr(CO)_3$ group and, through a transition state A, leads to the cycloadduct **6** in the assigned configuration. (Fig. 2)
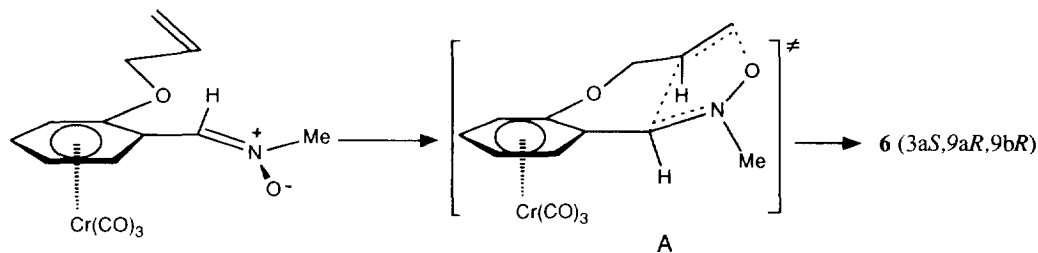

Fig. 2

Finally, in order to extend the above intramolecular cycloaddition reaction, the racemic nitrone **5b** was synthesized following the procedure described above from (±)-tricarbonyl(2-fluoro-1-diethoxymethyl benzene)chromium, using 3-methyl-2-buten-1-ol as nucleophile. Nitrone **5b** was then heated at 80 °C and also at 110 °C. In both cases, the complexed nitrone completely disappeared after 6 h but no cycloadduct was detected in the reaction mixture and the only recovered compound was complex **4b** along with some decomplexed products. This is probably due to increased steric hindrance at the double bound.

In conclusion, we would like to emphasize that the intramolecular 1,3-dipolar nitrone-olefin cycloaddition occurs on the $Cr(CO)_3$ complexed structure **5a** with complete stereoselection even at a reaction temperature of 80 °C. A number of structures bearing both the dipole and the dipolarophile as substituents of the same arene ring can in principle be complexed with $Cr(CO)_3$ and obtained as chiral substrate precursors of a wide range of optically active policyclic heterocycles.

Experimental:

All of the reactions were performed under nitrogen. Thermolyses with hexacarbonylchromium(0) were carried out in the dark in a round-bottomed flask, equipped with a Liebig air condenser and a water condenser on top. All of the chemicals were used as obtained from commercial sources. Column chromatography and TLC were carried out using respectively silica gel 60 and silica gel 60 F_{254} pre-coated plates. The melting points were measured using a Büchi apparatus and are uncorrected. The IR spectra were recorded using a 1725X FTIR spectrometer. NMR spectra were recorded in $CDCl_3$ (unless stated otherwise) using a Varian XL 300 spectrometer. The optical rotations were measured using a Perkin-Elmer 241 Polarimeter, with a 1 dm pathlength at 25 °C.

The racemic complexed acetals **1** and **2** were prepared by direct complexation of the corresponding free ligand as previously reported[10].

(-)-(1R)-Tricarbonyl(2-chloro-1-diethoxymethylbenzene)chromium(0) **2**. H_2SO_4 (96%, 0.01 ml) was slowly added to a stirred solution of (-)1-*R*- tricarbonyl(2-chlorobenzaldehyde)chromium ($[α]_D= -1120$)[10] (0.3 g, 1.1 mmol) in absolute ethanol (3 ml) and diethyl orthoformate (0.83 ml, 5 mmol). After stirring for 20 min at 30 °C (TLC: Et_2O), the mixture was neutralized by adding TEA, diluted with water (15 ml)

and extracted with Et_2O (3x15 ml). After the evaporation of the solvent the yellow oily residue was dissolved in petroleum ether and passed over a pad of neutral aluminium oxide. The concentration of the filtrate under reduced pressure yielded the complexed acetal **2** (0.36 g, 92 %), m.p. 55 °C (petroleum ether). (Found C, 48.00; H, 4.35%. $C_{14}H_{15}ClCrO_5$ requires C, 47.93; H, 4.32%), $[\alpha]_D= -15$ ($c= 0.2$, $CHCl_3$). ^{1}H NMR: δ, 1.24 (t, 3H, OCH_2CH_3); 1.35 (t, 3H, OCH_2CH_3); 3.66 (q, 2H, OCH_2CH_3); 3.71-3.92 (m, 2H, OCH_2CH_3); 5.03 (t, 1H, arom., J_o=6.3 Hz); 5.37-5.45 (m, 3H, arom., CH); 5.93 (d, 1H arom., J_o=6.3 Hz).

(+)-(1R)-Tricarbonyl(2-allyloxy-1-diethoxymethylbenzene)chromium(0) **3a**. Allyl alcohol (0.15 g, 2.58 mmol) was added at 0 °C to a stirred suspension of NaH (60% in oil, 0.12 g, 3 mmol,) and TBAB (0.04 g, 0.13 mmol) in anhydrous DME (7 ml). The slurry was stirred at 40 °C for 30 min, then a solution of **2a** (0.3 g, 0.86 mmol) in DME (3 ml) was added slowly. The mixture was heated at 50 °C for 3 h, TLC (Et_2O:petroleum ether, 1:1). After evaporation of the solvent, the mixture was diluted with water (20 ml) and extracted with Et_2O (3x20 ml).The organic layer, dried over Na_2SO_4, was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography using petroleum ether: diethyl ether (3:1) as eluent to give **3a** (0.29 g, 90 %) as a yellow oil.$[\alpha]_D= + 151$ ($c= 0.2$ $CHCl_3$) ^{1}H NMR, δ: 1.19 (t, 3H, OCH_2CH_3); 1.35 (t, 3H, OCH_2CH_3); 3.60-3.80 (m, 4H, OCH_2CH_3); 4.45 (d, 2H, OCH_2, J=5.04 Hz); 4.84 (t, 1H, arom., J_o=6.22 Hz); 4.89(d, 1H, arom., J_o=6.50 Hz); 5-28-5.48 (m, 3H, CH, =CH_2); 5.51 (t, 1H, arom., J_o=6.50 Hz); 5.91-6.08 (m, 2H, 1H arom.,=CH).

(-)-(1R)-Tricarbonyl(2-allyloxybenzaldehyde)chromium(0) **4a**. A stirred solution of acetal **3a** (0.25 g, 0.67 mmol) in dioxane (5 ml) was treated with aqueous HCl (2 N, 0.2 ml), following the disappearence of starting product by TLC (Et_2O:Petroleum ether, 1:2). The mixture was then diluted with aqueous $NaHCO_3$ (10 ml) and extracted with Et_2O (3x10 ml). Evaporation of the solvent gave a red oil that was purified by silica gel chromatography using petroleum ether: diethyl ether (3:1) as eluent to give **4a** (0.19 g, 94 %), m.p. 109 °C (petroleum ether). (Found C, 52.01; H, 3.40%. $C_{13}H_{10}CrO_5$ requires C, 52.35; H, 3.39%) $[\alpha]_D= -1007$ ($c= 0.2$ $CHCl_3$). IR (nujol) 1980, 2000 br (CO) and 1677 cm^{-1} (HC=O). ^{1}H NMR δ 4.52 (d, 2H, OCH_2, J=5.49Hz); 4.97 (t, 1H, arom. J_o=6.4Hz); 5.04 (d, 1H, arom., J_o=6.9Hz); 5.35-5.48 (m, 2H, =CH_2); 5.79 (dt, 1H,arom. J_o=6.9Hz, J_m=1.3Hz); 5.95-6.1 (m, 1H, CH=); 6.22 (dd, 1H, arom., J_o=6.4Hz, J_m=1.3Hz); 10.05 (s, 1H, HCO).

(-)-(1R)-Tricarbonyl[N-(2-allyoxybenzyliden)methylamine-N-oxide]chromium(0) **5a**. Triethylamine (0.22 ml, 1.6 mmol) was added at room temperature to a stirred solution of **4a** (0.15 g, 0.5 mmol) and N-methylhydroxylamine hydrochloride (0.12 g, 1.5 mmol) in dioxane (6 ml). The solution was stirred overnight at room temperature, then diluted with water (15 ml) and extracted with CH_2Cl_2 (3x10 ml). After evaporation of the solvent, the residue was purified by silica gel chromatography using petroleum ether: diethyl ether (1:1) as eluant to give **5a** (0.14 g, 85%). $[\alpha]_D= -2203$ (c=0.2 $CHCl_3$). IR (nujol) 1800,2000 (CO) and 1530 cm^{-1} (NO). (Found C, 51.42; H, 3.98; N, 4.30%. $C_{14}H_{13}CrNO_5$ requires C, 51.38; H, 4.01; N, 4.28%). ^{1}H NMR δ 3.83 (s, 3H, CH_3N); 4.49 (d, 2H, OCH_2, J=5.56Hz); 4.94 (t, 1H, arom. J_o=6.5Hz); 5.05 (d, 1H, arom. J_o=6.8Hz); 5.28-5.47 (m, 2H, =CH_2); 5.62 (t, 1H, arom. J_o=6.8Hz); 5.94-6.10 (m, 1H, CH=); 7.45 (s, 1H, CH=N); 7.78 (d, 1H, arom., J_o=6.5Hz).

(-)-(9aR,9bR,3aS)-Tricarbonyl(1,3a,4,9b-tetrahydro-1-methyl-3H-[1]benzopirano[4,3-c]isoxazole)chro

mium(0) **6.** A solution of nitrone **5a** (0.1 g, 0.3 mmol) in toluene (5 ml) was heated at 80 °C for 7 h. After evaporation of the solvent the residue was purified by silica gel chromatography using petroleum ether: diethyl ether (1:1) as eluant to give **6** (0.07 g, 70%), besides 20 % of starting complexed benzaldehyde **4a**. M.p. 108 °C (isopropanol). (Found C, 51.35; H, 3.98; N, 4.26%. $C_{14}H_{13}CrNO_5$ requires C, 51.38; H, 4.01; N, 4.28%). $[\alpha]_D$= -245 (*c*=0.2 CHCl₃). IR (nujol) 1871, 1963 cm⁻¹(CO). ¹H NMR δ 2.80 (s, 3H, CH₃N); 3.18-3.28 (m, 1H, CH); 3.78 (d, 1H, CH, J_{cis}=7.37Hz); 3.84 (dd, 1H, CH₂, J_{gem}=8.20Hz, J_{cis}=5.58Hz); 4.19 (2H, AB part of ABX syst., CH₂); 4.30 (t-like, 1H, CH₂, J_{gem}=8.20Hz, J_{trans}=8.70Hz); 5.01 (t, 1H, arom. J_o=6.30Hz); 5.28 (d, 1H, arom. J_o=6.50Hz); 5.43 (t, 1H, arom. J_o=6.50Hz); 5.60 (d, 1H, J_o=6.30Hz).

(+)-(9bR,3aS)-1,3a,4,9b-tetrahydro-1-methyl-3H-[1]benzopirano[4,3-c]iso xazole **7**. A solution of **5** (0.15 g, mmol) in CH₂Cl₂ (30 ml) was exposed to air and sunlight for about 2 h TLC (petroleum ether: diethyl ether, 1:1) . After evaporation of the solvent, the residue was taken up with diethyl ether and filtered over a pad of celite to give the essentially pure **7** (oil). $[\alpha]_D$= +18 (*c*=0.5 CHCl₃). ¹H NMR (C₆D₆) δ, 2.40-2.54 (m, 1H, CH); 2.94 (s, 3H, CH₃N); 3.30 (d, 1H, CH, J_{cis}=5.62Hz); 3.50 (dd, 1H, CH₂, J_{gem}=8.06Hz, J_{cis}=4.10HZ); 3.90 (dd, 1H, J_{gem}=10.65Hz, J_{cis}=5.13Hz CH₂); 3.94 (t, 1H, CH₂, J_{gem}=8.06Hz, J_{trans}=7.9Hz); 4.17 (t, 1H, CH₂, J_{gem}=10.65Hz, J_{trans}=10.50Hz); 6.93-7.22 (m, 4H, arom.).

(±)-Tricarbonyl[2-(2-methyl-2-butenyloxy)-1-diethoxymethylbenzene]chromium(0) **3b**. Yellow oil, (85%). IR (neat) 1966,1877 cm⁻¹(CO). ¹H NMR δ 1.20 (t, 3H, OCH₂CH₃, J=7.06Hz); 1.32 (t, 3H, OCH₂CH₃, J=7.06Hz); 1.72 (s, 3H, =CCH₃); 1.80 (s, 3H, =CCH₃); 3.60-3.76 (m, 2H, OCH₂CH₃); 3.81 (dq, 2H, OCH₂CH₃, J=7.06Hz); 4.41 (t, 2H, OCH₂, J=5.75Hz); 4.88(t, 1H, arom., J=6.26Hz); 4.95 (d, 1H, arom., J=6.58Hz); 5.39 (t, 1H, CH=, J=5.75Hz); 5.41 (s, 1H, CH); 5.50 (t, 1H, arom., J=6.58Hz); 6.02(d, 1H, arom., J= 6.26Hz).

(±)-Tricarbonyl[2-(2-methyl-2-butenyloxy)benzaldehyde]chromium(0) **4b**. M.p. 90-91 °C (petroleum ether). (Found C, 55.14; H, 4.32; $C_{15}H_{14}CrO_5$ requires C, 55.21; H, 4.29. IR (nujol) 1980,1885 (CO) and 1677 (HC=O) cm⁻¹. ¹H NMR δ, 1.78 (s, 3H, =CCH₃); 1.82 (s, 3H, =CCH₃); 4.52(d, 2H, CH₂, J=6.87Hz); 4.96(t, 1H, arom., J=6.28Hz); 5.05 (d, 1H, arom., J= 6.8Hz); 5.42 (t, 1H, CH=, J=6.87Hz); 5.80 (dt, 1H, arom., J_o=6.8Hz, J_m=1.3Hz); 6.21 (dd, 1H, arom., J_o=6.28Hz, J_m=1.41Hz); 10.1 (s, 1H, CHO).

(±)-Tricarbonyl[N-[2-(2-methyl-2-butenyloxy)benzyliden]methylamine N-oxide]chromium(0) **5b**. M.p. 119-120 °C (diisopropyl ether). (Found C, 54.15; H, 4.90; N, 3.92; $C_{16}H_{17}NO_5Cr$ requires C, 54.07; H, 4.83; N, 3.94. ¹H NMR δ 1.75 (s, 3H, =CCH₃); 1.80 (s, 3H, =CCH₃); 3.82 (s, 3H, N-CH₃); 4.46 (d, 2H, CH₂, J= 6.96Hz); 4.94 (t, 1H, arom., J=6.40Hz); 5.07 (d, 1H, arom., J=6.80Hz); 5.42 (t, 1H, CH=, J=6.96Hz); 5.64 (t, 1H, arom., J=6.80Hz); 7.42 (s, 1H, CH=N); 7.81 (d, 1H, arom., J=6.40Hz).

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11 The use of $CDCl_3$ as solvent did not allow any separation of the peaks due to the antipodes, even changing the chiral shift reagent.

12 Crystal data for **6**. $C_{14}H_{13}CrNO_5$, Mw= 327.26, Triclinic, Space Group P-1, a= 9.8147(8), b= 11.947(2), c= 13,186(4) Å, α= 74.300(2)°, β= 71.240(2)°, γ= 82.340(1)°, V=1407.6(7) Å^3, Z= 4, D_c=1.544 g.cm^3, MoKα radiation, λ= 0.71069 Å, μ (MoKα)= 8.111 cm^{-1}. Data were collected on a Nonius CAD4 diffractometer and corrected for the Lorentz-polarization effect. No absorption correction was deemed necessary. Of the 3655 collected reflections, 2938 [F>3.0σ(F)] were considered as observed and used for the solution and refinement of the structure. The structure was refined by full-matrix least squares using anisotropic displacement parameters for all atoms; the contribution of the hydrogen atoms, in calculated positions, was taken into account but not refined. The final R value was 0.036.