Enantioselective Hydrogenation of 2-Methylquinoxaline to (−)-(2*S*)-2-Methyl-1,2,3,4-tetrahydroquinoxaline by Iridium Catalysis

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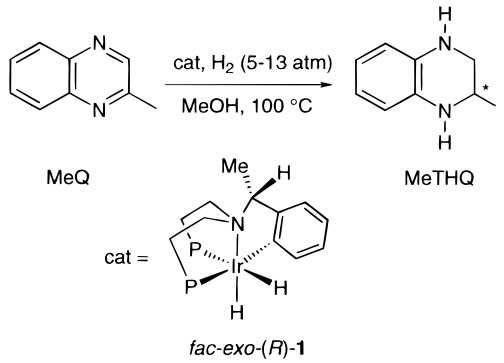
The orthometalated dihydride complex *fac-exo*-(*R*)-[$IrH_2\{C_6H_4C^*H(Me)N(CH_2CH_2PPh_2)_2\}$] is an effective catalyst precursor for the enantioselective hydrogenation of 2-methylquinoxaline (MeQ) to 2-methyl-1,2,3,4-tetrahydroquinoxaline (MeTHQ) with ee's up to 90% (5 bar of H_2, MeOH, 100 °C). In-situ high-pressure NMR spectroscopy in catalytic conditions shows that the catalytically active species is generated by deorthometalation rather than by H_2 reductive elimination. ^1H NMR spectroscopy also suggests that the two C═N groups in MeQ are hydrogenated at comparable rates.

Introduction

Optically pure tetrahydroquinoxalines are compounds of great biological interest but of difficult access via stereoselective organic synthesis.[1] An alternative, high-yield method for the preparation of chiral tetrahydroquinoxalines would be the enantioselective hydrogenation of the corresponding 2-substituted quinoxalines by transition-metal catalysis,[2] as recently reported for other prochiral nitrogen heterocycles.[3] None of the current enantioselective metal catalysts, however, is apparently capable of performing the enantioselective hydrogenation of 2-susbstituted quinoxalines with attractive optical yields.[2] Indeed, the only example of such a reaction was reported by Murata et al. for 2-methylquinoxaline (MeQ) which was converted to 2-methyl-1,2,3,4-tetrahydroquinoxaline (MeTHQ) by [(+)-(DIOP)RhH] catalysis with an ee of 3%.[4]

In this work, we show that the hydrogenation of MeQ to MeTHQ can be accomplished with quite satisfactory ee (up to 90%) using the orthometalated dihydride complex *fac-exo*-(*R*)-[$IrH_2\{C_6H_4C^*H(Me)N(CH_2CH_2PPh_2)_2\}$] (*fac-exo*-(*R*)-**1**) as the catalyst precursor (eq 1).[5a]



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Experimental Section

General Information. All manipulations, except as stated otherwise, were performed under a pure argon or nitrogen atmosphere. Freshly distilled, dry solvents were used throughout. The complex *fac-exo*-(*R*)-[$IrH_2\{C_6H_4C^*H(Me)N(CH_2CH_2PPh_2)_2\}$] (*fac-exo*-(*R*)-**1**) was synthesized as previously described.[5a] 2-Methylquinoxaline (MeQ) was obtained from Aldrich and was distilled under reduced pressure prior to use. ^1H (200.13 MHz) and ^{31}P (81.01 MHz) NMR spectra were obtained on a Bruker ACP 200 spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane, referenced to the chemical shifts of residual solvent resonances (^1H) or 80% H_3PO_4 (^{31}P), with downfield values reported as positive. The high-pressure NMR experiments were performed with a titanium high-pressure charging head constructed at the

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(1) (a) Butera, J. A.; Spinelli, W.; Anantharaman, V.; Marcopulos, N.; Parsons, R. W.; Moubarak, I. F.; Cullinan, C.; Bagli, J. F. *J. Med. Chem.* **1991**, *34*, 3212. (b) Aguilera, R.; Duplant, J.-C.; Nofre, C. *Bull. Soc. Chim. Fr.* **1968**, *11*, 4491. (c) Armarego, W. L. F.; Waring, P.; Paal, B. *Aust. J. Chem.* **1982**, *35*, 785. (d) Fisher, G. H.; Schultz, H. P. *J. Org. Chem.* **1974**, *39*, 635. (e) Battistini, M.; Erba, E.; Pocar, D. *J. Chem. Soc., Perkin Trans.* **1993**, 339. (f) Matsuura, S.; Sugimoto, T.; Haegawa, H.; Imaizumi, S.; Ichiyama, A. *J. Biochem. (Tokyo)* **1980**, *87*, 951.

(2) (a) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; p 31. (b) James, B. R. *Catal. Today* **1997**, *37*, 209.

(3) (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (b) Brunner, H.; Huber, C. *Chem. Ber.* **1992**, *125*, 2085. (c) Schnider, P.; Koch, G.; Prétôt, R.; Wang, G.; Bohnen, F. M.; Krüger, C.; Pfaltz, A. *Chem. Eur. J.* **1997**, *3*, 887.

(4) Murata, S.; Sugimoto, T.; Matsuura, S. *Heterocycles* **1987**, *26*, 763.

(5) (a) Bianchini, C.; Farnetti, E.; Glendenning, L.; Graziani, M.; Nardin, G.; Peruzzini, M.; Rocchini, E.; Zanobini, F. *Organometallics* **1995**, *14*, 1489. (b) Bianchini, C.; Glendenning, L.; Peruzzini, M.; Purches, G.; Zanobini, F.; Farnetti, E.; Graziani, M.; Nardin, G. *Organometallics* **1997**, *16*, 4414. (c) Bianchini, C.; Glendenning, L.; Zanobini, F.; Farnetti, E.; Graziani, M.; Nagy, E. *J. Mol. Catal. A: Chem.* **1998**, *132*, 13.

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ISSECC-CNR (Firenze, Italy),[6] while the 10 mm sapphire NMR tube was purchased from Saphikon, Milford, NH. *Note*: *Since high gas pressures are involved, safety precautions must be taken at all stages of studies involving high-pressure NMR tubes.* Merck silica gel 60, 230−400 mesh ASTM, was used for column chromatography. Reactions under a controlled pressure of hydrogen were performed with a stainless steel autoclave (100 mL internal volume) constructed at ISSECC-CNR (Firenze, Italy) and equipped with a magnetic stirrer, a glass inset, and a pressure controller. The temperature control was achieved by an oil bath thermostat accurate to ±0.2 °C. GC analyses were performed on a Shimadzu GC-14A gas chromatograph equipped with a flame ionization detector and a 30 m (0.25 mm ID, 0.25 mm FT) SPB-1 Supelco fused silica capillary column coupled with a C-R6A Chromatopac operating in the corrected area method. GC/MS analyses were performed on a Shimadzu QP 2000 apparatus equipped with a column identical to that used for GC analyses. HPLC analyses were performed with a Shimadzu LC-8A liquid chromatograph coupled with a Shimadzu SPD-M6A photodiode array UV−vis detector operating in the 200−350 nm wavelength range and equipped with a Daicel Chiralcel OD-H 0.46 × 25 cm column. Optical rotations were measured with a Perkin-Elmer 341 polarimeter using 10 cm cells.

Catalytic Reactions. A suspension of *fac-exo*-(*R*)-**1** (0.02 mmol) in the appropriate solvent (20 mL) was strirred at 40 °C under argon until the complete dissolution of the starting complex occurred (ca. 30 min). MeQ (2.00 mmol) was added at room temperature, and the resulting solution was transferred via a Teflon capillary into a 100 mL autoclave under argon. Argon was then replaced by hydrogen with 3 cycles of 5 bar/normal pressure. The autoclave was finally charged with the desired pressure of H_2 and then heated using a thermostated oil bath with magnetic stirring. After the desired time, the reactor was cooled to room temperature and a sample of the reaction mixture was analyzed by GC. The rest of the solution was concentrated in vacuo to ca. 3 mL and chromatographed over silica using a mixture of *n*-hexane:*i*-PrOH:Et_3N = 60:39:1 (v:v:v) as the eluent. The organic products obtained were identified through their GC/MS spectra. The ee of the diamine 2-methyl-1,2,3,4-tetrahydroquinoxaline (MeTHQ) product was determined by HPLC analysis (eluent *n*-hexane:*i*-PrOH:Et_2NH = 60:40:0.1; flow = 0.5 mL/min; λ_{max} = 228, 256, 315 nm; ret. times 13.6 [(+)-(2*R*)] and 16.0 [(−)-(2*S*)] min. The absolute configuration of the MeTHQ was assigned by comparison of the optical rotation value to that of an authentic specimen.[1c,d]

In Situ HPNMR Studies. In a typical experiment, a 10 mm sapphire HPNMR tube was charged with a solution of *fac-exo*-(*R*)-**1** (30 mg, 0.04 mmol) and a 30-fold excess of MeQ (157 μL, 1.2 mmol) in toluene-d_8 (2 mL) under nitrogen. The tube was pressurized with hydrogen to 20 bar at room temperature and then placed into a NMR probe at 20 °C. The reaction was followed by variable-temperature $^{31}P\{^1H\}$ and ^1H NMR spectroscopy in the temperature range from 20 to 100 °C for an overall time of ca. 2 h. After 1 h at 70 °C, *fac-exo*-(*R*)-**1** partially converted to the geometric isomer *fac-endo*-(*R*)-[$IrH_2\{C_6H_4C^*H(Me)N(CH_2CH_2PPh_2)_2\}$][5a] (*fac-endo*-(*R*)-**1**) and the deorthometalated trihydride (*R*)-[$IrH_3\{C_6H_5C^*H(Me)N(CH_2CH_2PPh_2)_2\}$][5b,c] ((*R*)-**2**) (product ratio = *fac-exo*-(*R*)-**1**:*fac-endo*-(*R*)-**1**:(*R*)-**2** = 100:10:15, based on ^1H NMR integration). The product ratio did not appreciably change when the probe-head of the spectrometer was heated to 100 °C for 1 h. ^1H NMR spectroscopy showed the selective conversion (15%, 100 °C, 1 h) of MeQ to (−)-(2*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline ((−)-(2*S*)-MeTHQ). After the catalytic reaction was quenched by cooling to room temperature, the solvent was removed under reduced pressure and the residue was worked out as described above for the product identification and ee determination.

Table 1. Hydrogenation of MeQ to MeTHQ Catalyzed by *fac-exo*-(*R*)-1[a]

entry	solvent	temp (°C)	H_2 (bar)	time (h)	yield[b] (5)	ee[c] (%)
1	MeOH	100	5	24	53.7	90.0
2	MeOH	100	13	24	85.3	74.6
3	*i*-PrOH	100	5	24	96.5	73.0
4	*i*-PrOH	100	13	24	91.9	72.2
5	*i*-PrOH	70	13	24	34.2	60.5
6	toluene	100	13	24	81.4	1.8
7	*i*-PrOH	100	0	24	0.0	

[a] Reaction conditions: catalyst precursor 0.02 mmol; substrate 2.00 mmol; solvent 20 mL. [b] GC, reaction mixture. [c] HPLC, isolated product. (*S*) configuration in all cases.

Monitoring the hydrogenation of MeQ in the presence of *fac-exo*-(*R*)-**1** by ^{31}P NMR spectroscopy in either toluene-d_8 or MeOH-d_4 in the temperature and pressure ranges from 70 to 100 °C and from 5 to 20 bar of H_2, respectively, did not show the formation of other species than (*fac-endo*-(*R*)-**1**) and ((*R*)-**2**). This latter complex was only formed above 15 bar due to its instability with respect to the elimination of H_2.[5b,c] In the same range of experimental conditions, ^1H NMR spectroscopy showed that MeQ (diagnostic singlet at δ 2.62 for the methyl group in the 2-position in toluene-d_8) is straighforwardly converted to MeTHQ (diagnostic doublet at δ 1.14 for the same methyl group) with no detectable intermediate.

(*R*)-[$IrH_3\{C_6H_5C^*H(Me)N(CH_2CH_2PPh_2)_2\}$] ((*R*)-2). ^1H NMR (toluene-d_8, 296 K, 200.13 MHz): δ −22.90 (dddd, $^2J_{H_a,P_{cis}}$ = 13.3 Hz, $^2J_{H_a,P_{cis}}$ = 13.3 Hz, $^2J_{H_a,H_m}$ = 6.1 Hz, $^2J_{H_a,H_m}$ = 6.1 Hz, $1H_{apical}$), −9.20 (dddd, $^2J_{H_m,P_{trans}}$ = 138.4 Hz, $^2J_{H_m,H_a}$ = 52.7 Hz, $^2J_{H_m,P_{cis}}$ = 24.5 Hz, $^2J_{H_m,H_a}$ = 6.1 Hz, $2H_{meridional}$). $^{31}P\{^1H\}$ NMR (toluene-d_8, 296 K, 81.01 MHz): δ 25.6 (d, $^2J_{PP}$ = 8.7 Hz, 1P), 25.1 (d, $^2J_{PP}$ = 8.7 Hz, 1P).

The NMR characteristics of *fac-exo*-(*R*)-**1** and *fac-endo*-(*R*)-**1** in toluene-d_8 have been given elsewhere.[5a]

Results and Discussion

The hydrogenation of MeQ has been accomplished in MeOH, *i*-PrOH, or toluene using the orthometalated dihydride complex *fac-exo*-(*R*)-**1** as the catalyst precursor. Selected results are summarized in Table 1.

Though the reduction of the substrate via hydrogen transfer can be ruled out (entry 7), the conversions and, particularly, the optical yields in (−)-(2*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline[1b−d] ((−)-(2*S*)-MeTHQ) increase remarkably in alcohol solvents (entries 1−5 vs 6) as compared to toluene or benzene. In line with the large majority of asymmetric hydrogenation of imines,[2] MeOH is better than any other solvent for the asymmetric induction. In MeOH, the ee increases, decreasing the H_2 pressure, whereas the conversion decreases (entries 1 and 2).

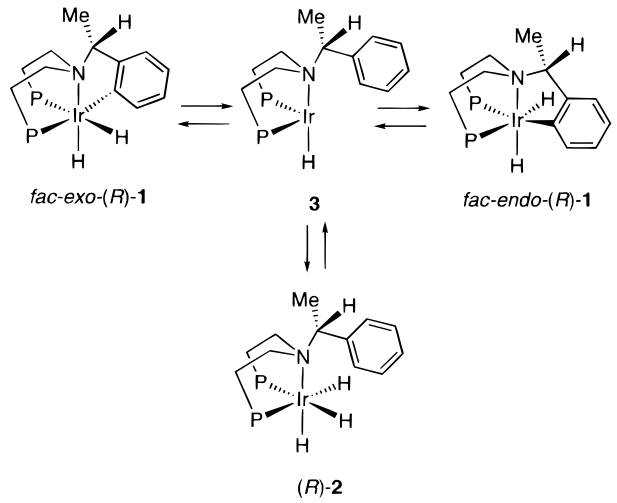
Catalytic hydrogenation reactions of imines,[8a] ketones,[5a,c] or alkenes[8b] based on orthometalated complexes have some precedents in the literature. Depending on the complex structure, a free coordination site for the incoming unsaturated substrate may be generated by deorthometalation, reductive elimination of dihydrogen, or ligand displacement.[5,7,8] To determine

(6) (a) Bianchini, C.; Meli, A.; Patinec, V.; Sernau, V.; Vizza, F. *J. Am. Chem. Soc.* **1997**, *119*, 4945. (b) Bianchini, C.; Meli, A.; Traversi, A. IT, FI97 A000025 1997.

(7) (a) Bacalski, A. G.; Cullen, W. R.; Fryzuk, M. D.; James, B. R.; Kang, G.-J.; Rettig, S. *Inorg. Chem.* **1991**, *30*, 5002. (b) Spindler, F.; Pugin, B.; Blaser, H.-U. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 558.

(8) (a) Bedford, R. B.; Castillòn, S.; Chaloner, P. A.; Claver, C.; Fernandez, E.; Hitchcock, P. B.; Ruiz, A. *Organometallics* **1996**, *15*, 3990. (b) Lewis, L. N. *J. Am. Chem. Soc.* **1986**, *108*, 743.

Scheme 1



which of these paths is actually followed by the catalyst precursor *fac-exo*-(*R*)-**1**, high-pressure NMR (HPNMR) studies using sapphire tubes sealed with Ti-alloy valves have been carried out.[6] Under catalytic conditions in either toluene-d_8 or MeOH-d_4, $^{31}P\{^1H\}$ and ^1H NMR spectroscopies unambiguously show that *fac-exo*-(*R*)-**1** is in equilibrium with both its *fac-endo*-(*R*) isomer[5a] and the deorthometalated trihydride (*R*)-[$IrH_3\{C_6H_5C^*H(Me)N(CH_2CH_2PPh_2)_2\}$] ((*R*)-**2**) (Scheme 1).[5b,c]

Besides providing evidence for the occurrence of the deorthometalation path, ^1H HPNMR spectroscopy also shows that the hydrogenation of MeQ selectively yields MeTHQ with no detectable intermediate on the NMR time scale over the range of pressures and temperatures investigated (70−100 °C; 5−20 bar of H_2) (Figure 1).

The NMR diagram thus suggests that the two C=N groups in MeQ are hydrogenated at comparable rates, which is consistent with the nonsterically demanding catalyst (*R*)-[$IrH\{C_6H_5C^*H(Me)N(CH_2CH_2PPh_2)_2\}$] (**3**). This 16e$^-$ fragment has already been proposed to be the catalytically active species in the enantioselective hydrogen-tranfer reduction of α,β-unsaturated and asymmetrical ketones.[5a,c] The NMR evidence cannot discriminate between two-stage and one-stage processes, however.

According to the general mechanism proposed for imine hydrogenation by early[9] or late transition metal catalysis,[2,10] **3** is an excellent candidate for the reduction of MeQ to MeTHQ via the usual steps of substrate coordination, hydride migration to give amide species, H_2 oxidative addition, and reductive elimination of the amine to complete the cycle.[11]

Current studies from this laboratory show that the substitution of *fac-exo*-(*S*)-**1**[5a] for *fac-exo*-(*R*)-**1** gives MeTHQ with the opposite absolute configuration, i.e., (+)-(*2R*)-2-methyl-1,2,3,4-tetrahydroquinoxaline, in comparable yields and ee.

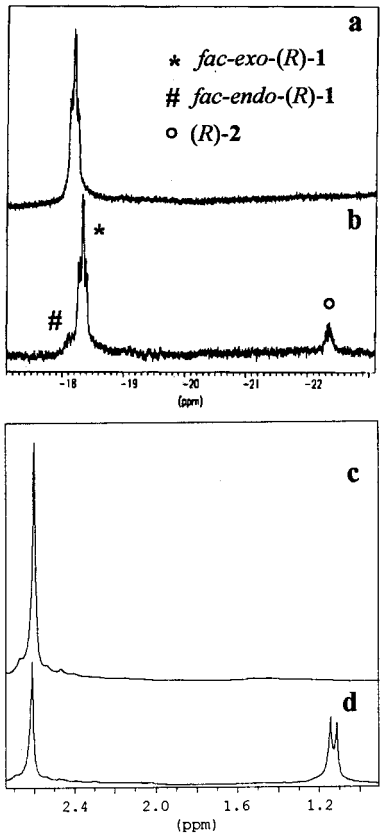


Figure 1. ^1H NMR spectra (sapphire tube, toluene-d_8, 200.13 MHz) acquired during the hydrogenation (20 bar of H_2) of MeQ in the presence of *fac-exo*-(*R*)-**1** (substrate-to-catalyst ratio = 30). (a) Spectra in the region of the terminal hydride ligand trans to the N donor atom at 20 °C and (b) after the NMR probe was heated to 70 °C for 1 h. A similar spectrum was observed after 1 h heating at 100 °C. Spectra in the region of the 2-methyl group in MeQ (singlet at δ 2.62) and MeTHQ (doublet at δ 1.14) (c) at 20 °C and (d) after the NMR probe was heated to 70 °C for 1 h.

In conclusion, we have described here the first example of effective enantioselective hydrogenation of a 2-substituted quinoxaline by chiral metal catalysis as well as the usefulness of HPNMR spectroscopy to study asymmetric catalysis.

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(9) Willoughby, C. A.; Buchwald, S. I. *J. Am. Chem. Soc.* **1994**, *116*, 8952.

(10) (a) Ng Cheong Chan, Y.; Osborn, J. A. *J. Chem. Soc., Chem. Commun.* **1990**, 869. (b) Ng Cheong Chan, Y.; Osborn, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 9400.

(11) A referee has suggested that an alternative mechanism involving the reaction of the trihydride (*R*)-**2** with the substrate also be considered. This mechanism can be ruled out as the trihydride is a labile species that readily converts to the orthometalated complex via H_2 elimination, followed by orthometalation.[5b,c] At room temperature, a dihydrogen pressure higher than 7 bar is necessary to induce the formation of an equilibrium concentration of (*R*)-**2**, while a pressure of 20 bar is required at the catalytic temperature (70−100 °C).