Table I

| storage time, day | storage temp, °C | $[\alpha]^{24}_D$, deg | L/D (HPLC) |
|---|---|---|---|
| 0 | | +18.2 | 100/0 |
| 1 | -30 | +17.9 | 99/1 |
| 9 | -30 | +17.4 | 99/1 |
| 9 | 24 | +6.9 | 70/30 |

M sodium bicarbonate buffer, pH 9.0, was treated with 100 μL of a 0.02 M solution of 5-(dimethylamino)naphthalene-1-sulfonyl chloride in acetone.[12] The mixture was stirred at 37 °C for 30 min and quenched with 0.1 mL of formic acid. The mixture was evaporated to dryness under a stream of nitrogen and the residue dissolved in methanol (0.5 mL). The solution (10 μL) was analyzed by HPLC, using as the mobile phase a solution of arginine (5 mM), copper sulfate pentahydrate (2.5 mM), and ammonium acetate (5 mM) in glass distilled water, adjusted to pH 7.8 with $NH_4OH$.[13] Fluorescence at 520 nm was monitored with excitation at 340 nm. Samples were run in duplicate, and authentic samples of D- and L-leucine were used as controls. The observed L to D ratios along with measured optical rotations of the leucine hydrochloride samples are summarized in Table I.

**Ethyl (3*R*,4*S*)- and (3*S*,4*S*)-Boc-4-amino-3-hydroxy-6-methylheptanoate 1 (R = Et, R′ = Boc).** To diisopropylamine (23.2 g, 0.23 mol) in dry tetrahydrofuran (77 mL) cooled to -20 °C under an $N_2$ atmosphere was added dropwise *n*-butyllithium in hexane (1.46 M, 157.2 mL, 0.23 mol). The solution was stirred 15 min, the temperature lowered to -78 °C, and dry ethyl acetate (20.2 g, 0.23 mol) added dropwise while the temperature was maintained below -75 °C. The solution was stirred 10 min and a precooled (-78 °C) tetrahydrofuran solution (114 mL) of Boc-L-leucinal **3** (R′ = Boc; 33 g, 0.153 mol) was added while the temperature was maintained below -75 °C. After 12 min, 2 M HCl (117 mL) was added while the temperature was held below -65 °C. The mixture was warmed to 10 °C, treated with 2 M HCl to pH 2.5, and extracted with ether (3 × 400 mL). The ethereal extracts were combined, washed with saturated NaCl (2 × 200 mL), dried over $MgSO_4$, and filtered. Evaporation of the filtrate in vacuo gave 42.5 g of a light-purple oil. Chromatography of the crude oil on silica gel (2 kg) by the procedure of Still et al.,[15] eluting with 20% ethyl acetate in hexane, afforded 17.6 g (38%) of Boc-Sta-OEt [(3*S*,4*S*)-1 R = Et, R′ = Boc; $R_f$ 0.32, >99% by GC]: $^1$H NMR ($CDCl_3$) δ 0.93 (d, 6 H, $(CH_3)_2$, *J* = 6 Hz), 1.27 (t, 3 H, $CH_2CH_3$, *J* = 6 Hz), 1.3-1.75 (m, 3 H, *i*-Pr$CH_2$CH), 1.44 (s, 9 H, $(CH_3)_3$), 2.50 (m, 2 H, $CH_2C$=O), 3.35 (s, 1 H, OH), 3.63 (br m, 1 H, 1 H, CHNH), 4.03 (br m, 1 H, CHOH), 4.18 (q, 2 H, $CH_2CH_3$, *J* = 6 Hz), 4.75 (br d, 1 H, NH).

Also isolated were 16.2 g of predominantly (3*R*,4*S*)-1 (R = Et, R′ = Boc; 95% 3*R*,4*S*; 5% 3*S*,4*S*), and 0.8 g of Boc-leucinal **3** (R′ = Boc).

**(3*S*,4*S*)-Boc-4-amino-3-hydroxy-6-methylheptanoic Acid [Boc-statine (1, R = H, R′ = Boc)].** Boc-Sta-OEt [(3*S*,4*S*)-1, R = Et, R′ = Boc; 5 g, 16.5 mmol] was dissolved in dioxane (25 mL) and diluted with water (25 mL). Monitored with a meter standardized with 1:1 dioxane/pH 10 buffer, the turbid solution was treated at room temperature with 1 M NaOH(aq) to maintain the pH of the mixture between 12.0 and 12.2. After 1 h, TLC (20% EtOAc/80% hexane) of the clear solution indicated the disappearance of the ester. The pH of the solution was adjusted to 6.5 with 1 M HCl and the dioxane was removed in vacuo. The remaining aqueous solution was acidified to pH 2.5 with 10% citric acid and extracted with ether (3 times). The combined ethereal extracts were washed with saturated NaCl, dried over $MgSO_4$, and filtered. Evaporation of the filtrate gave an oil which upon treatment with ether and dilution with hexane gave Boc-statine [(3*S*,4*S*-1, R = H, R′ = Boc] as a white solid (3.9 g, 86% yield): mp 118-120 °C (lit.[8] mp 117-118 °C); $[\alpha]^{24}_D$ -39.5° (*c* 0.12, $CH_3OH$) [lit.[8] $[\alpha]^{24}_D$ -39.6° (*c* 0.31, $CH_3OH$)]; $^1$H NMR ($CDCl_3$) δ 0.94 (d, 6 H, $(CH_3)_2$, *J* = 6 Hz), 1.30-1.73 (m, 3 H, *i*-Pr$CH_2$CH), 1.45 (s, 9 H, $(CH_3)_3$), 2.55 (m, 2 H, $CH_2C$=O), 3.59 (br m, 1 H, CHNH), 4.03 (br m, 1 H, CHOH), 4.79 (br d, 1 H, NH, exchanged with $D_2O$).

Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.70; H, 9.08; N, 5.09. Found: C, 56.75; H, 9.38; N, 5.23.

Table II

| *SS/RR* by weight[a] | *SS/RR* by HPLC |
|---|---|
| 3*S*,4*S* | 99.6/0.4 |
| 95.1/4.9 | 95.5/4.5 |
| 96.7/3.3 | 97.7/2.3 |
| 84.3/15.7 | 84.7/15.3 |
| 49.4/50.6 | 54.6/45.4 |
| 3*R*,4*R* | 2.3/97.7 |

[a] Weighed samples of (3*R*,4*R*)- and (3*S*,4*S*)-1 (R = H, R′ = Boc) corrected for the observed contamination of each with the other.

**(3*R*,4*R*)-Boc-4-amino-3-hydroxy-6-methylheptanoic Acid (1, R = H, R′ = Boc).** The synthetic sequence of Scheme II, described above, was repeated with Boc-D-leucine hydrate in place of the Boc-L-leucine hydrate. The product obtained had physical properties identical with those described above except for $[\alpha]^{24}_D$ +39.1° (*c* 0.12, $CH_3OH$).

**Chiral Integrity Studies of Boc-4-amino-3-hydroxy-6-methylheptanoic Acid (1, R = H, R′ = Boc).** Boc-amino acid 1 (R = H, R′ = Boc; 400 mg, 1.45 mmol) was dissolved in ethyl acetate (3 mL) and cooled to 0 °C. The solution was saturated with HCl(g), stirred 15 min, and then saturated with nitrogen for 15 min. Evaporation of the solvent in vacuo gave an oil, which was repeatedly treated with ethyl acetate and evaporated in vacuo. The residue was dried at room temperature under high vacuum for 16 h to give the free amino acid hydrochloride as a sticky solid.

1·HCl (R = R′ = H) (20 μmol) was dissolved in pH 10 borate buffer (2 mL) and cooled to 0 °C. L-Glutamic acid *N*-carboxyanhydride was added,[16] and the solution was vortexed for 2 min and then quenched with 1 M HCl (1 mL). The derivatized samples were assayed by HPLC, using a gradient of phosphate buffer (8.7 mM phosphoric acid adjusted to pH 3.2 with 25% aqueous trimethylamine) with acetonitrile (100/0 → 90/10 over 30 min) on a Waters Associates C-18 column (30 × 0.39 cm). The sample derived from (3*S*,4*S*)-1 (R = H, R′ = Boc) showed a single major component ($t_R$ 11 min) as did that derived from the 3*R*,4*R* material ($t_R$ 20 min). Mixtures of weighed quantities of (3*R*,4*R*) and (3*S*,4*S*)-1 (R = H, R′ = Boc) were assayed by the same procedure. All the results are summarized in Table II.

**Acknowledgment.** We are grateful to the following people for assistance in recording and interpreting spectral and analytical data: Dr. David Cochran for NMR spectra, Mr. K. B. Streeter and Mr. John Moreau for microanalyses, and Mr. Robert Strachan for amino acid derivatization. We are also indebted to Professor Jeremy Knowles and to Drs. Jack Baldwin, Mark Bock, Joshua Boger, and Daniel Veber for many valuable discussions.

**Registry No.** (3*R*,4*S*)-1 (R = Et, R′ = Boc), 67010-44-0; (3*S*,4*S*)-1 (R = Et; R′ = Boc), 67010-43-9; (3*S*,4*S*)-1 (R = H; R′ = Boc), 58521-49-6; (3*R*,4*R*)-1 (R = H; R′ Boc), 82010-28-4; (3*S*,4*S*)-1·HCl (R = R′ = H), 82010-29-5; 3*R*,4*R*-1·HCl (R = R′ = H), 82010-30-8; L-**2** (R = H; R′ = Boc), 13139-15-6; L-**3** (R′ = Boc), 58521-45-2; **4**, 82010-31-9; H-Leu-OH·HCl, 760-84-9; Boc-D-Leu-OH, 16937-99-8.

## Reduction of Aromatic Nitro Compounds by Secondary Alcohols Using Rhodium Complexes as Catalysts

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Both ketones and aromatic amines have been industrially important chemicals. Most of the ketones are made by oxidizing or dehydrogenating the corresponding secondary alcohols, while aromatic amines are manufactured

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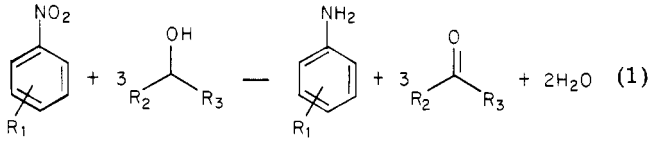
Table I. Results of Nitrobenzene Reduction by Cyclohexanol Catalyzed by Various Rhodium Complexes

| expt[a] | catalyst | base | aniline produced, % | av rate,[b] cycles $Rh^{-1}$ $h^{-1}$ |
|---|---|---|---|---|
| 1 | $RhCl(CO)(PPh_3)_2$ | KOAc | 74.2 | 39.9 |
| 2 | $RhH(CO)(PPh_3)_3$ | KOAc | 54.8 | 29.3 |
| 3 | $RhCl_3 + PPh_3$ | KOAc | 61.5 | 33.0 |
| 4 | $RhCl_3 + P(OPh)_3$ | KOAc | 67.8 | 36.3 |
| 5 | $RhCl_3$ | KOAc | 51.6 | 27.6 |
| 6 | $RhCl_3 + Ph_2PCH_2CH_2PPh_2$ | KOAc | 41.2 | 22.0 |
| 7 | $Rh_2Cl_2(CO)_4$ | KOAc | 80.0 | 41.9 |
| 8 | $RhCl_3 + PPh_3$ | KOAc | 60.2 | 32.3 |
| 9 | $RhCl(CO)(PPh_3)_2$ | KOH | 43.0 | 23.1 |
| 10 | $RhCl_3 + PPh_3$ | KOH | 41.6 | 22.3 |
| 11 | $RhCl(CO)(PPh_3)_2$[c] | $Et_3N$ | 51.8[d] | 6.4 |

[a] Except if otherwise mentioned, all experiments were run for 7 h at 150 °C in a 50-mL flask containing $4.0 \times 10^{-5}$ mol of Rh, $2.0 \times 10^{-3}$ mol of KOAc, $5.0 \times 10^{-3}$ mol of nitrobenzene, and 6.2 mL of cyclohexanol. [b] Based on cyclohexanone produced. [c] The amount of catalyst is $8.0 \times 10^{-5}$ mol. [d] The reaction time is 11 h.

by reducing the aromatic nitro compounds using hydrogen as the reductant.[1] A transfer hydrogenation reaction between a secondary alcohol and a nitro compound with the alcohol serving as the reductant and the nitro compound as the oxidant to produce the corresponding ketone and aniline in one reaction might be of great value to their manufacturing methods. In addition, although the hydrogen-transfer reaction from alcohol to ketone or olefin has been extensively investigated,[2-9] the homogeneous hydrogen transfer from alcohol to nitro compound has never been carefully explored. To date, only one report has appeared on the catalytic coupling reaction between isopropyl alcohol and nitrobenzene to give aniline in poor yield by using a $RhCl(PPh_3)_3/KOH$ system.[10] We herein report the results of our efforts in search of the more effective catalyst systems that can promote a very general coupling reaction between a secondary alcohol and an aromatic nitro compound (eq 1).



(1)

The high catalytic activities of rhodium complexes in the transfer hydrogenation from alcohol to ketone or olefin led us to examine the effectiveness of rhodium complexes in the homogeneous catalysis of eq 1. Most rhodium complexes investigated were thus found to be active catalysts, and an effective catalyst system was obtained, consisting of a rhodium complex and a base in a mixture of aromatic nitro compound and secondary alcohol. All the reactions were conducted under nitrogen or in vacuo at a temperature of 120–150 °C. The solutions turned to dark brown quickly and remained the same color to the end of the reaction. The products were identified by comparing their NMR, IR, and GC spectra with those of the authentic samples. The relative ratios of ketones, aromatic nitro compounds, and amines were determined either by NMR or GC integration methods.

Table I summarizes the activities in the coupling between nitrobenzene and cyclohexanol of various catalyst systems prepared from different rhodium complexes and bases. Of these systems, $[Rh(CO)_2Cl]_2$ and $RhCl(CO)(PPh_3)_2$ with potassium acetate as base are the two most active ones with an average rate of 42 and 40 turnovers $h^{-1}$ $Rh^{-1}$, respectively, at 150 °C based on the cyclohexanone produced. Surprisingly, the data show that, in contrast to the results of many transfer hydrogenations, the most effective base is KOAc, not the strong base KOH. When KOH was used, precipitation was found in the catalytic solution, indicating a possible decomposition of the rhodium species. To test whether the activity of the rhodium complex using KOAc as the base was decreasing, in one experiment using $RhCl_3/PPh_3$ we vacuum distilled the catalyst solution at the end of the reaction and recharged the residue with nitrobenzene and cyclohexanol. The solution was then heated at 150 °C for 7 h, and within the experimental error, no loss in the catalytic activity was observed (Table I, expt 8).

To probe the requirements of the catalyst systems, we performed two control experiments leading to the following observations: (i) in the absence of rhodium complex and with KOAc as the base, no product formation was detected;[11] (ii) the omission of the base results in only a trace of products. It thus appears that rhodium complex is a necessary component for the catalysis to proceed, and the base is a cocatalyst that can promote the catalytic activity.

In addition to cyclohexanol, other secondary alcohols, 2-propanol, 2-butanol, 2-hexanol, and 2-octanol, can also couple with nitrobenzene with various rates to form aniline and the corresponding ketones. The results are shown in Table II. As indicated in eq 1, the reduction of each molecule of mononitro compound requires the oxidation of three molecules of alcohol. The stoichiometry is clearly established from the results in Table II with potassium acetate as the base. However, when triethylamine is used instead, the ratio of ketone to amine is only ca. 2.0, indicating that a direct participitation of triethylamine in the

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(11) According to ref 10, in the absence of rhodium complex, KOH catalyzed $PhNO_2$ reduction to azoxybenzene and azobenzene.

Table II. Results of the Nitrobenzene Reduction by Various Secondary Alcohols Using the $RhCl(CO)(PPh_3)_2$/KOAc System

| expt[a] | alcohol | temp, °C | reaction time, h | aniline produced, % | av rate,[b] cycles $Rh^{-1}$ $h^{-1}$ | ketone/ aniline ratio |
|---|---|---|---|---|---|---|
| 1 | 2-octanol | 150 | 11 | 44.6 | 15.3 | 3.2 |
| 2 | cyclohexanol | 150 | 7 | 74.2 | 39.9 | 3.0 |
| 3 | 2-butanol[c] | 150 | 7 | 53.5 | 28.8 | 3.0 |
| 4 | 2-propanol[c] | 150 | 7 | 100 | 57.0 | 2.9 |
| 5 | 2-butanol[c] | 120 | 10 | 14.1 | 5.4 | 3.1 |
| 6 | 2-propanol[c] | 120 | 10 | 19.4 | 7.2 | 3.0 |

[a] The catalyst solution in each experiment contains $4.0 \times 10^{-5}$ mol of $RhCl(CO)(PPh_3)_2$, $2.0 \times 10^{-3}$ mol of nitrobenzene, and 6.2 mL of alcohol. [b] Based on the ketone produced. [c] The reaction was conducted in a sealed tube.

Table III. Results of the Reductions of Various Substituted Nitro Compounds by Cyclohexanol Using $RhCl(CO)(PPh_3)_2$ as the Catalyst

| expt[a] | nitro compd | base | time, h | % substituted aniline |
|---|---|---|---|---|
| 1 | *o*-nitrotoluene | $Et_3N$ | 11 | ~0 |
| 2 | *m*-nitrotoluene | $Et_3N$ | 11 | 23.2 |
| 3 | *p*-nitrotoluene | $Et_3N$ | 11 | 25.4 |
| 4 | *o*-nitrotoluene | $CH_3COOK$ | 5 | 80.2 |
| 5 | *m*-nitrotoluene | $CH_3COOK$ | 5 | ~100 |
| 6 | *p*-nitrotoluene | $CH_3COOK$ | 5 | ~100 |
| 7 | *o*-chloronitrobenzene | $CH_3COOK$ | 5 | ~100 |
| 8 | *p*-chloronitrobenzene | $CH_3COOK$ | 5 | 63.8 |
| 9 | *p*-nitrophenol | $CH_3COOK$ | 5 | 36.6 |

[a] The solution in each experiment contains $8.0 \times 10^{-5}$ mol of $RhCl(CO)(PPh_3)_2$, $5.0 \times 10^{-3}$ mol of nitro compound, $2.0 \times 10^{-3}$ mol of base, and 6.2 mL of cyclohexanol. Each run was conducted at 150 °C.

reduction of nitro compounds is involved. Investigation of this subject is now underway.

The results of the couplings between other aromatic mononitro compounds and cyclohexyl alcohol catalyzed by rhodium complexes are listed in Table III. Nitrotoluenes, chloronitrobenzenes, and nitrophenol all were found to react with cyclohexanol to form the corresponding substituted anilines and cyclohexanone. no other detectable product was observed. It is interesting to note that, under the same catalytic conditions, *p*-nitrotoluene is reduced faster than *o*-nitrotoluene, while the reverse is true for the corresponding chloro compounds. More surprisingly, the dinitro aromatic compounds, 2,4-dinitrotoluene, 2,4-dinitroaniline, and 2,4-dinitrochlorobenzene, cannot be reduced under the same conditions. Furthermore, the presence of the dinitro compound totally inhibits the reduction of mononitro compound by the secondary alcohol.

The studies of the dependence of the catalytic activity on ligand concentrations on using $RhCl_3/PPh_3$/KOAc system show that the chloride concentration does not affect the catalytic activity. However, the $PPh_3$/Rh ratio in the solution has a marked influence on the catalytic rate. A maximum activity was obtained at a $PPh_3$/Rh ratio of 1 (Figure 1), indicating that the most active species in the solution probably has one triphenylphosphine attached to the Rh metal center. Excess triphenylphosphine in the catalyst solution inhibits the activity and was found to be oxidized to triphenylphosphine oxide at the end of the reactin.[12] The observation that the catalyst stystem with 1 mol of 1,2-bis(diphenylphosphino)ethane, a bidentate ligand, present per mole of Rh has a much lower activity than that with a $PPh_3$/Rh ratio of 1 also supports the idea that the most active species has a phosphine/Rh ratio of less than 2. However, the fact that $RhCl_3$ in the absence of $PPh_3$ is still an active catalyst, albeit with less activity,

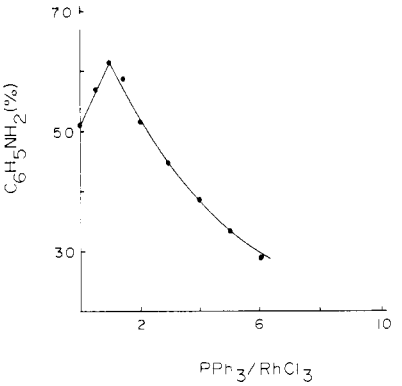


**Figure 1.** Effect of the $PPh_3$/Rh ratio on the catalytic reaction rate. Except for the amount of $PPh_3$, the reaction conditions are the same as those that in Table I, expt 3.

indicates that $PPh_3$ enhances the rate but is not an essential component. Attempts to isolate the catalyticly active species from the $RhCl_3/PPh_3$/KOAc system resulted in a black precipitate whose IR spectrum has revealed the incorporation of acetate and triphenylphosphine on the metal.[13]

## Experimental Section

$^1H$ NMR spectra were measured on JEOL FX-100 and JEOL C-60 HL NMR spectrometers, and infrared spectra were recorded on a JASCO A-100 spectrometer. Gas chromatographic analyses were performed on a Varian Model 1440-10 gas chromatograph using a Versamide 900 column.

Rhodium trichloride hydrate, cyclohexanol, triphenylphosphine, triphenyl phosphite, isopropyl alcohol, 2-butanol, *o*-nitrotoluene, *m*-nitrotoluene, *p*-nitrotoluene, nitrobenzene, *m*-chloronitro-

(12) The triphenylphosphine oxide may be obtained by distilling off the organic compounds in the catalyst solution followed by *n*-hexane extraction.

(13) The black precipitate was isolated by the following method. The volatile organic compounds in the catalytic solution were removed by vacuum diatillation. The residue, after being washed by water and *n*-hexane, was recrystallized twice from THF–*n*-hexane to afford the precipitate. The IR spectrum of the precipitate shows the characteristic peak of acetate at 1590 $cm^{-1}$ (s) and the peaks of triphenylphosphine at 750 (s) and 700 $cm^{-1}$ (s).

benzene, *p*-chloronitrobenzene, *o*-nitrophenol, potassium acetate (Wako), bis(1,2-diphenylphosphino)ethane (Stream), and 2-octanol (Fluka) were used as purchased. $RhCl(CO)(PPh_3)_2$,[14] $PhH(CO)(PPh_3)_3$,[15] and $Rh_2Cl_2(CO)_4$[16] were prepared according to the methods reported previously.

**Catalytic Reduction of Aromatic Nitro Compounds by Secondary Alcohols. Example I.** To a solution containing 0.196 g ($2.0 \times 10^{-3}$ mol) of KOAc, 0.5 mL ($5.0 \times 10^{-3}$ mol) of nitrobenzene, and 6.2 mL of cyclohexanol in a side-arm flask was added 0.0276 g ($4.0 \times 10^{-5}$ mol) of $RhCl(CO)(PPh_3)_2$. The system was then heated under a nitrogen atmosphere at 150 °C for 7 h. A $^1H$ NMR and an infrared spectrum of the solution were recorded. The solution after a bulb-to-bulb distillation was analyzed on the above gas chromatograph with toluene as the internal standard. The products, cyclohexanone, and aniline were identified by comparing the NMR, IR, and GC spectra with those of the authentic samples. The yield (Table I) and the product ratio (Table II) were calculated from the relative peak areas in the NMR spectra or in the gas chromatograms. The same method was used in the reduction of other nitro compounds by cyclohexanol.

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**Example II.** To a solution containing 0.196 g ($2.0 \times 10^{-3}$ mol) of KOAc, 0.50 mL ($5.0 \times 10^{-3}$ mol) of nitrobenzene, and 6.2 mL of isopropyl alcohol in an ampule was added 0.0276 g ($4.0 \times 10^{-5}$ mol) of $RhCl(CO)(PPh_3)_2$, and the ampule was then evacuated, sealed, and heated at 150 °C for 7 h. The products were analyzed by the same method as in example I. The yield of aniline was 100%. When 2-butanol was used to reduce nitrobenzene, this technique was also employed.

**Acknowledgment.** We thank the National Science Council of the Republic of China for support of this research.

**Registry No.** $RhCl(CO)(PPh_3)_2$, 15318-33-9; $RhH(CO)(PPh_3)_3$, 17185-29-4; $RhCl_3$, 10049-07-7; $PPh_3$, 603-35-0; $P(OPh)_3$, 101-02-0; $Ph_2PCH_2CH_2PPh_2$, 1663-45-2; $Rh_2Cl_2(CO)_4$, 14404-25-2; nitrobenzene, 98-95-3; cyclohexanol, 108-93-0; 2-octanol, 123-96-6; 2-butanol, 78-92-2; 2-propanol, 67-63-0; aniline, 62-53-3; *o*-nitrotoluene, 88-72-2; *m*-nitrotoluene, 99-08-1; *p*-nitrotoluene, 99-99-0; *o*-chloronitrobenzene, 88-73-3; *p*-chloronitrobenzene, 100-00-5; *p*-nitrophenol, 100-02-7; 3-methylbenzenamine, 108-44-1; 4-methylbenzenamine, 106-49-0; 2-methylbenzenamine, 95-53-4; 2-chlorobenzenamine, 95-51-2; 4-chlorobenzenamine, 106-47-8; 4-aminophenol, 123-30-8; 2,4-dinitrotoluene, 121-14-2; 2,4-dinitroaniline, 97-02-9; 2,4-dinitrochlorobenzene, 97-00-7.

# *Communications*

## Strategy for the Generation of $^{13}C$ Subspectra. Application to the Analysis of the $^{13}C$ Spectrum of the Antibiotic Ristocetin

*Summary:* Three heteronuclear multipulse methods, combined to routinely generate accurate $^{13}C$ subspectra of differing $^1H$ multiplicity, are applied as a test of the strategy to the antibiotic ristocetin.

*Sir:* Elucidation of the structure of an organic compound is facilitated by determination of the number of protons directly attached to each carbon atom. A popular method, SFORD $^{13}C$ spectroscopy[1] is of limited use for large molecules because of overlapping multiplets and poor signal-to-noise. A more attractive alternative is to generate individual methine (CH), methylene ($CH_2$), methyl ($CH_3$), and quaternary (q) $^{13}C$ subspectra. A degree of such spectral editing has been achieved with the INEPT pulse sequence,[2,3] but this is too sensitive to variations in $^1J_{^{13}C-^1H}$ for confident application to unknown compounds,[4] especially large complex molecules like ristocetin.

We have generated $CH/CH_3$ and $CH_2/q$ subspectra by spin-echo sequences utilizing the proton-flip method[4] (sequences A and B are the gated-decoupled equivalents[5]), $CH_2/q$ subspectra at one-third and full intensity, respectively using sequence C,[6] and CH subspectra using the EPT sequence D,[7] and in each case we demonstrated a relative insensitivity to variations in $^1J_{^{13}C-^1H}$ values. Here we combine these three methods (sequences A to D) to provide accurate subspectra generation and as a stringent test we apply the strategy to ristocetin.

$$^{13}C\ \ \frac{\pi}{2}-\frac{1}{J}\cdots\pi-\frac{1}{J}-\text{acquire and decouple } ^1H \qquad \text{(A)}$$

$$^{13}C\ \ \frac{\pi}{2}-\frac{1}{J}-\pi-\frac{1}{J}-\text{acquire}$$
$$^1H\ \ \text{decouple} \qquad \text{(B)}$$

$$^{13}C\ \ \frac{\pi}{2}-\frac{1}{2J}-\left|-\frac{1}{2J}-\pi-\frac{1}{2J}-\right|-\frac{1}{2J}-\left|\text{acquire}\right.$$
$$^1H\ \ \left|\text{decouple for }\frac{1}{J}\right|\qquad\qquad\left|\text{decouple}\right. \qquad \text{(C)}$$

$$^{13}C\ \ \left|\frac{\pi}{2}\right|\qquad\left|\pi\right|\qquad\left|\text{acquire}\right.$$
$$^1H\ \ \frac{\pi}{2}[x]-\frac{1}{2J}-\pi-\frac{1}{2J}-\frac{\pi}{2}[\pm y]-\frac{1}{2J}-\left|\text{decouple}\right. \qquad \text{(D)}$$

The alternative gated-decoupling method (sequences A and B) was used for two reasons. Proton refocusing pulses are not used and are not a source of error. Secondly, and

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(5) Le Cocq, C.; Lallemand, J.-Y. *J. Chem. Soc., Chem. Commun.* **1981**, 150. Cookson, D. J.; Smith, B. E. *Org. Magn. Reson.* **1981**, *16*, 111.
(6) Pegg, D. T.; Bendall, M. R.; Doddrell, D. M. *J. Magn. Reson.* **1982**, *49*, 32. Note that the decoupling irradiation used for the burst in sequence C must provide randomization of the $^1H$ spins over three dimensions, unlike normal decoupling irradiation. This can be achieved by changing the 180° random phase changes of normal decoupling irradiation to 90° random phase changes.

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