New Synthetic Route to Pharmacologically Active 1-(*N*,*N*-dialkylamino)-3,3-diarylpropanes *via* Rhodium-Catalyzed Hydroformylation of 1,1-Diarylethenes

Carlo Botteghi,*,† Lamberto Cazzolato,† Mauro Marchetti,‡ and Stefano Paganelli†

Dipartimento di Chimica, Università di Venezia, Calle Larga Santa Marta 2137, I-30123 Venezia, Italy, and Istituto per l'Applicazione delle Tecniche Chimiche Avanzate ai Problemi Agrobiologici - C.N.R., Via Vienna 2, I-07100 Sassari, Italy

Received February 15, 1995

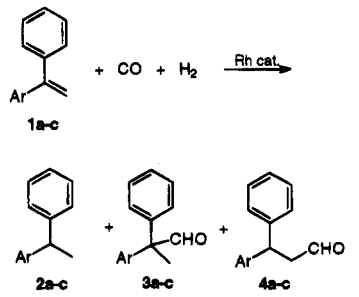
The rhodium-catalyzed hydroformylation of olefins containing various functions is a useful tool for the preparation of numerous compounds having biological activity.[1-6] However, there are several problems connected with the use of nonconventional olefin substrates; in particular, the lack of sufficiently high chemo- and regioselectivity represents in several instances a strong limitation to make hydroformylation attractive for industrial application.[7]

In a recent paper,[8] we reported that the hydroformylation of 1,1-diarylethenes **1a–c**, in which an aryl group has a 2-pyridyl structure, generally occurs with unsatisfactory chemoselectivity due to the concomitant reduction of the olefin double bond (formation of **2a**) and to very high regioselectivity toward the formation of the more branched aldehyde **3a** (Scheme 1). These outcomes are disappointing, because the target of this catalytic reaction was the achievement of the linear isomeric product **4a** (the 3,3-diarylpropanal) in a yield as high as possible, this aldehyde representing a valuable intermediate for the preparation of the antiallergic agent pheniramine.[6]

Electronic effects connected with the presence in the substrate of the pyridine nitrogen atom are responsible for this rather unusual practically regiospecific formation of the aldehyde **3a**, in which the formyl function is bound to a quaternary carbon atom.[8] As a matter of fact, substitution in **1a** of the 2-pyridyl with the phenyl group causes the steric effect to prevail, forcing the formyl group to attack the less sterically hindered terminal carbon atom.[8]

The breadth of pharmacological activity of the easily available 1-(*N*,*N*-dialkylamino)-3,3-diarylpropanes derived from aldehydes **4b,c**, spanning from choleretic to spasmolitic, antihistaminic, and antipruritic activity, has

Scheme 1



a, Ar = 2-pyridyl; b, Ar = phenyl; c, Ar = *p*-tolyl.

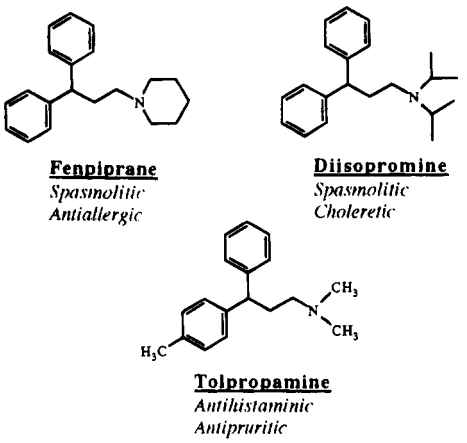


Figure 1.

stimulated our interest in optimizing the key hydroformylation step and the subsequent transformation of the *oxo* aldehydes **4b,c** into the therapeutic agents shown in Figure 1.[9,10]

These compounds are currently prepared by conventional reaction schemes not involving transition metal catalysis.[11,12]

The hydroformylation of 1,1-diphenylethene catalyzed by rhodium and cobalt complexes was reported some years ago by Orchin and Matsui:[13] under rather drastic reaction conditions (120–180 °C, 100–200 atm CO/H_2 = 1) only rhodium catalysts afforded good yields (up to 85%) of aldehydes, 1,1-diphenylethane (hydrogenation) being the only byproduct. The aldehyde produced in all experiments was exclusively the straight chain aldehyde, 3,3-diphenylpropanal.[13]

The commercially available 1,1-diphenylethene was subjected to a set of hydroformylation experiments under milder reaction conditions and using different catalytically active rhodium carbonyl complexes. These catalytic precursors were chosen from the known family of rhodium derivatives, keeping in mind that they must be structurally simple, readily accessible, and inexpensive for potential industrial application.

(1) Botteghi, C.; Paganelli, S.; Schionato, A.; Marchetti M. *Chirality* **1991**, *3*, 355.
(2) Stille, J. K.; Su, Heng; Brechot, Ph.; Parrinello, G.; Hegedus, L. S. *Organometallics* **1991**, *10*, 1183.
(3) Ojima, I.; Kato, K.; Nakahashi, K. *J. Org. Chem.* **1989**, *54*, 4511.
(4) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033.
(5) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1994**, 395.
(6) Botteghi, C.; Chelucci, G.; Del Ponte, G.; Marchetti, M.; Paganelli, S. *J. Org. Chem.* **1994**, *59*, 7125.
(7) Botteghi, C.; Ganzerla, R.; Lenarda, M.; Moretti, G. *J. Mol. Catal.* **1987**, *40*, 129.
(8) Botteghi, C.; Paganelli, S.; Bigini, L.; Marchetti, M. *J. Mol. Catal.* **1994**, *93*, 279.
(9) Kleemann, A.; Engel, J. *Pharmazeutische Wirkstoffe*; George Thieme Verlag: Stuttgart 1987.
(10) Elks, J.; Ganellin, G. R. *Dictionary of Drugs;* Chapman Hall: London, 1990.
(11) Klosa, J. *J. Prakt. Chem.* **1966**, *34*, 312.
(12) Ind. and Lab. Pharm. C. Janssen Brit. Pat. 808 158, 1959; *Chem. Abstr.* **1959**, *53*, 17972i.
(13) Matsui, Y.; Orchin, M. *J. Organometal. Chem.* **1983**, *246*, 57.

0022-3263/95/1960-6612$09.00/0

Table 1. Hydroformylation of 1,1-Diphenylethene by Rhodium Complexes[a]

entry	catalytic precursor (Rh/ligand molar ratio)	reaction time, h	temp, °C	convn, %	hydrogenation yield,[b] %	hydroformylation yield,[b] %	3,3-diphenylpropanal, % of total aldehydes
1	$HRh(CO)(PPh_3)_3$	48	80	81.7	<1	81.0	96.0
2	$HRh(CO)(PPh_3)_3$	48	120	>99	48.6	51.2	>99
3	$HRh(PPh_3)_4$	48	80	57.4	3.8	52.6[c]	99.0
4	$HRh(PPh_3)_4$	114	90	>99	19.5	80.5	98.0
5	$[Rh(CO)_2Cl]_2$	24	80	50.8	2.3	48.5	>99
6	$[Rh(CO)_2Cl]_2$	48	80	75.2	>1	74.8	>99
7[d]	$[Rh(CO)_2Cl]_2$	48	80	61.2	3.5	57.1[c]	>99
8	$[Rh(CO)_2Cl]_2/PPh_3$ (1/50)	48	80	<1			
9	$Rh(CO)_2(acac)$[e]	24	80	46.4	3.4	43.0	99.0
10	$Rh(CO)_2(acac)$/PYDIPHOS[f] (1/1.5)	24	80	47.0	19.0	28.0	99.0
11	$Rh(CO)_2(acac)$/PYDIPHOS P-oxide[f] (1/1.5)	70	80	57.0	~1	56.0	99.0
12	$Rh(CO)_2(acac)/P(OPh)_3$ (1/2.5)[g]	48	80	38.0		38.0	>99
13	$Rh(CO)_2(acac)/C_{60}H_{36}P_2O_6$[h] (**5**) (1/1.5)	48	80	23.0	2.0	18.0	>99

[a] Substrate 5.6 mmol; benzene 10 mL; $p(CO) = p(H_2) = 50$ atm; substrate to catalyst molar ratio 270:1. [b] Determined by GLC analysis. [c] High boiling byproducts were detected in the reaction mixture in <1% amount. [d] Experiment carried out at $p(CO) = 75$ atm and $p(H_2) = 25$ atm. [e] acacH = 1,3-pentanedione. [f] See reference 14 (Figure 2). [g] See reference 15. [h] See reference 16 (Figure 2).

Table 2. Hydroformylation of 1-Phenyl-1-(*p*-tolyl)ethene by Rhodium Complexes[a]

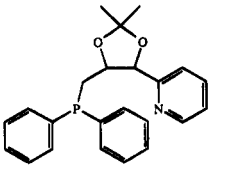
entry	catalytic precursor	reaction time, h	temp, °C	convn, %	hydrogenation yield,[b] %	hydroformylation yield,[b] %	3-phenyl-3-(*p*-tolyl)propanal, % of total aldehydes
1	$HRh(CO)(PPh_3)_3$	48	90	72.1	8.1	64.0	>99
2	$HRh(PPh_3)_4$	72	90	40.0	5.0	35.0	>99
3	$HRh(PPh_3)_4$	66	120	>99	4.0	66.0[c]	97.0
4	$[Rh(CO)_2Cl]_2$	24	90	95.0	7.0	88.0	>99
5	$[Rh(CO)_2Cl]_2$	24	100	>99	53.0	46.0[d]	>99
6	$Rh(CO)_2(acac)$	48	80	14.0	3.0	11.0	98.0
7	$Rh(CO)_2(acac)$	24	90	70.0	3.0	67.0	98.0

[a] Substrate 6.2 mmol; benzene 10 mL; $p(CO) = p(H_2) = 50$ atm; substrate to catalyst molar ratio 270:1. [b] Determined by GLC analysis. [c] About 30% of 3-phenyl-3-(*p*-tolyl)propan-1-ol were found in the reaction mixture. [d] ≥1% 3-phenyl-3-(*p*-tolyl)propan-1-ol were found in the reaction mixture.

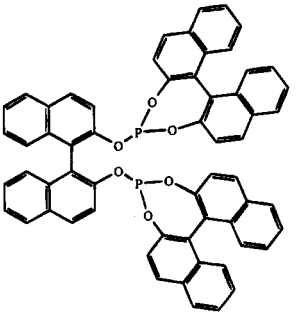
The experimental conditions and the results of the hydroformylation of 1,1-diphenylethene are reported in Table 1.

From the data obtained in the hydroformylation of 1,1-diphenylethene the following considerations can be made: (1) almost quantitative chemoselectivity was achieved with $HRh(CO)(PPh_3)_3$ (entry 1) and with $[Rh(CO)_2Cl]_2$ (entry 6), the substrate hydrogenation being in several cases the only side reaction as previously found by Orchin and Matsui;[13] (2) the regioselectivity for the formation of **4b** is always very high (96–99%); (3) the use of a 3:1 CO/H_2 mixture to prevent the undesired hydrogenation reaction produces a decrease of the hydroformylation rate as the only effect; (4) the use of added phosphine ligand is detrimental both for the reaction rate (entry 8) and the chemoselectivity (entries 10, 11), and the rhodium complex formed with PYDIPHOS *P*-oxide (entry 11 and Figure 2) seems to display a lower catalytic activity but to give a better chemoselectivity with respect to its pyridylphosphine analogue (entry 10);[14] (5) the use of added phosphite ligands seems to reduce the reaction rate, but increases the chemoselectivity (entries 12 and 13).

The behavior of 1-phenyl-1-(*p*-tolyl)ethene under hydroformylation conditions is rather similar to that of 1,1-diphenylethene; however, the reaction rate was lower, and hence, it advisable to increase the reaction temperature to 90–100 °C. The results are listed in the Table 2.



PYDIPHOS



Tri-binaphthyldiphosphite **5**

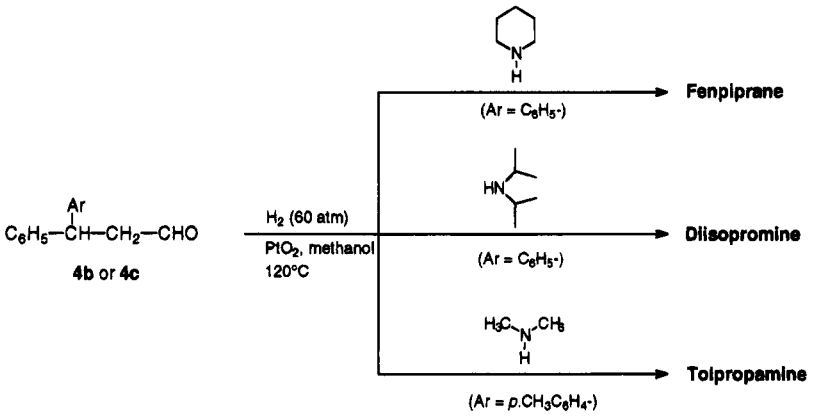
Figure 2.

The highest yields in aldehyde **4c** were achieved with $[Rh(CO)_2Cl]_2$ (entry 4). The chemoselectivity strongly decreases at higher temperatures (entries 3 and 5) due both to the substrate hydrogenation and/or to the reduction of the *oxo* aldehyde to the corresponding alcohol. Also, with this olefinic substrate the regioselectivity for the formation of 3-phenyl-3-(*p*-tolyl)propanal was very high (98–99%).

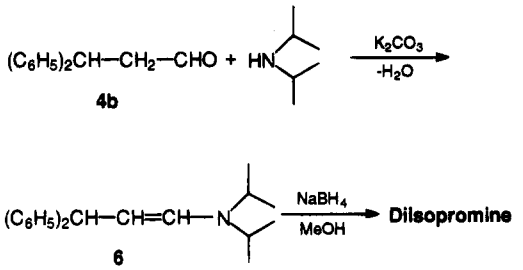
The linear aldehyde **4b**, isolated from the reaction mixture by flash cromatography, was converted to fenpiprane and diisopromine by treatment with piperidine

(14) Basoli, C.; Botteghi, C.; Cabras, M. A.; Chelucci, G.; Marchetti, M. *J. Organomet. Chem.* **1995**, *488*, C20.
(15) Trzeciak, A. M.; Ziolkowski, J. J. *J. Mol. Catal.* **1988**, *48*, 319.
(16) Baker, M. J.; Pringle, P. G. *J. Chem. Soc., Chem. Commun.* **1991**, 1292.

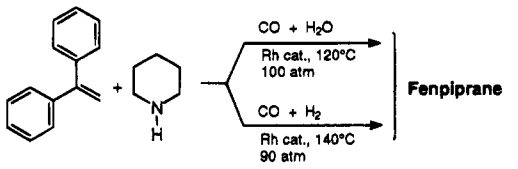
Scheme 2



Scheme 3



Scheme 4



and diisopropylamine, respectively, under reductive amination conditions according to literature procedures.[17] Thus, 3,3-diphenylpropanal was allowed to react with an excess of the appropriate amine (1:6 molar ratio) and hydrogen (60 atm) in methanol in the presence of platinum catalyst at 120 °C. Very high aldehyde conversion and almost complete chemoselectivity were obtained: fenpiprane and diisopromine were isolated by flash chromatography from the reaction mixture in 80–85% yield (Scheme 2).

Analogous results were obtained in the reductive amination under the same conditions of the aldehyde **4c** to tolpropamine (Scheme 2).

Optionally, a two step reductive amination involving the formation of an enamine[18] followed by the double bond reduction with sodium borohydride[19] can be carried out (Scheme 3). Diisopromine was obtained in this way in 70% overall yield.

Then we attempted to convert 1,1-diphenylethene to the desired therapeutically active amines in a one-step aminomethylation reaction[20,21] (Scheme 4). In this process an olefin is allowed to react with carbon monoxide and water[20] or molecular hydrogen[21] in the presence of an amine under reaction conditions very close to those employed for the *oxo* process. Accordingly, we subjected 1,1-diphenylethene to an aminomethylation reaction using piperidine and water as a hydrogen source at 140 °C and 100 atm of CO in the presence of a catalytic amount of $Rh_6(CO)_{16}$ or $RhCl_3(pyridine)_3$.[20] The desired fenpiprane was obtained in only about 20% yield. 1,1-Diphenylethane derived from the substrate hydrogenation was the main product of this reaction. The aminomethylation of diphenylethene was repeated using hydrogen instead of water and $[Rh(CO)_2Cl]_2$ as the catalyst at 120 °C and 100 atm ($CO/H_2 = 1$). In this case the only reaction observed was the substrate hydrogenation. We believe that the increased tendency of rhodium carbonyl complexes toward hydrogenation when modified with amines and the higher temperature required for the aminomethylation process are responsible for the low chemoselectivity observed.[22]

An attempt to carry out a one-pot conversion of 1,1-diarylethenes into the corresponding pharmacologically active 1-(*N*,*N*-dialkylamino)-3,3-diarylpropanes under the hydroformylation conditions adopted by us gave disappointing results; reaction of 1,1-diphenylethene with synthesis gas (100 atm, $CO/H_2 = 1$) at 80 °C catalyzed by $[Rh(CO)_2Cl]_2$ took place with 20% conversion affording almost exclusively 1,1-diphenylethane. On the contrary, if preformed 3,3-diphenylpropanal is allowed to react with excess of piperidine under the above hydroformylation conditions fenpiprane is formed in 80% yield.

Finally, on the basis of this last result we succeeded in performing a one-pot transformation of 1,1-diphenylethene into fenpiprane in high yield. We subjected the olefin to the hydroformylation using the reaction conditions reported in Table 1 (entry 1); after 48 h about 80% of the substrate was converted. At this point we injected into the reaction vessel under pressure a benzene solution of piperidine. After additional 24 h reaction fenpiprane was obtained in 78% yield based on the starting 1,1-diphenylethene.

In conclusion, the rhodium-catalyzed hydroformylation of 1,1-diarylethenes represents a very convenient reaction for a new competitive synthetic route to pharmacologically active 1-(*N*,*N*-dialkyl)-3,3-diaylpropanes.

Work is currently in progress in our laboratory to extend these new synthetic approaches to other structurally related biologically active compounds and to apply this methodology to semiindustrial scale preparations, paying attention to an efficient catalyst recovery.

(17) Kiyooka, S.; Suzuki, K.; *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2081.
(18) Azzena, U.; Chelucci, G.; Delogu, G.; Gladiali, S.; Marchetti, M.; Soccolini, S.; Botteghi, C. *Gazz. Chim. Ital.* **1986**, *116*, 307.
(19) Carlsson, S.; Lawesson, S.-O. *Tetrahedron* **1982**, *38*, 413.
(20) Jachimowicz, F.; Raksi, J. W. *J. Org. Chem.* **1982**, *47*, 445.
(21) Jones, M. D. *J. Organomet. Chem.* **1989**, *366*, 403.
(22) Paulik, F. E. *Catal. Rev.* **1972**, *6*, 49.

Experimental Section

Materials. $HRh(CO)(PPh_3)_3$,[23] $HRh(PPh_3)_4$,[24] and $RhCl_3(Py)_3$[25] were prepared following well-known procedures. The rhodium complexes $[Rh(CO)_2Cl]_2$, $Rh(CO)_2(acac)$, and PtO_2 were Aldrich products.

PYDIPHOS,[14] PYDIPHOS *P*-oxide,[14] and tribinaphthyl diphosphite[16] (**5**) were prepared following the literature procedures. Triphenylphosphine and triphenyl phosphite were Aldrich products.

1,1-Diphenylethene was purchased from Janssen Chimica. 1-Phenyl-1-(*p*-tolyl)ethene was prepared (82% yield) by Wittig reaction on 4-methylbenzophenone (Aldrich) with a ready-to-use mixture of methyltriphenylphosphonium bromide and sodium amide (Fluka AG)[26] and purified by distillation on $LiAlH_4$ (bp 71 °C at 0.05 mmHg). *N,N*-Dimethylamine, *N,N*-diisopropylamine, and piperidine were Aldrich products.

Analytical and spectral data were obtained as reported in ref 6.

General Procedure for the Hydroformylation of Substrates 1b and 1c. A 150 mL stainless steel reaction vessel was charged under nitrogen purge with 5.6 mmol of olefin, 0.021 mmol of rhodium catalyst, and 10 mL of anhydrous benzene. The reactor was then pressurized to 100 atm with synthesis gas ($CO/H_2 = 1$) and heated at 80−120 °C for the desired time (see Tables 1 and 2). From the reaction mixture the aldehydes **4b** and **4c** were recovered by flash chromatography on silica gel with a 9:1 hexane/ether mixture.

Compounds **4b** and **4c** gave satisfactory analytical data, and ^1H NMR patterns were in agreement with their structures.

Compound **4b**:[27] mp 50−51 °C; IR 1719 (vs) cm^{-1}. Anal. Calcd for $(C_6H_5)_2CHCH_2CHO$: C, 85.68; H, 6.71. Found: C, 85.43; H, 6.58.

Compound **4c**: mp 38−39 °C; IR 1724 (vs) cm^{-1}. Anal. Calcd for $C_6H_5(CH_3C_6H_4)CHCH_2CHO$: C, 85.68; H, 7.19. Found: C, 85.38; H, 6.96.

General Procedure for the Reductive Amination of the Aldehydes 4b and 4c: Fenpiprane, Diisopromine, and Tolpropamine. Aldehydes **4b** and **4c** were transformed into the corresponding *N,N*-dialkylamino derivatives following a literature procedure.[17]

A mixture of the aldehyde (2.4 mmol), the desired secondary amine (14.3 mmol) and PtO_2 (0.12 mmol), in methanol (3 mL) was introduced into a 150 mL stainless steel reaction vessel and pressurized to 60 atm with H_2. After 24 h at 120 °C the reactor was cooled to rt, the residual gas released, and the reaction mixture analyzed by GLC to determine the conversion degree of the substrate. The pure tertiary amines were obtained by flash chromatography on silica gel with a 7:3 hexane/ether mixture (80−85% yield) and gave physical constants and analytical data in agreement with those reported in the literature.[12,28]

Fenpiprane: IR 1351 (m) cm^{-1}; *m/z* 279 $(M)^+$. **Diisopromine:** IR 1360 (m) cm^{-1}; *m/z* 295 $(M)^+$. **Tolpropamine:** IR 1380 (m) cm^{-1}; *m/z* 253 $(M)^+$.

Synthesis of Diisopromine by Reduction of 1-(*N,N*-Diisopropyl)-3,3-diphenyl-1-propene (6). (a) Synthesis of the Enamine 6. The enamine **6** was prepared according to a known procedure.[18] To a mixture of 1.92 g (19 mmol) of *N,N*-diisopropylamine and 0.370 g (2.7 mmol) of anhydrous K_2CO_3 was added, under nitrogen, 1 g (4.7 mmol) of the aldehyde **4b**. The reaction mixture was stirred at rt for 24 h and then filtered and the solution analyzed by GLC to determine the conversion (75% yield). Compound **6** was not isolated but was identified by GC mass spectrometry: *m/z* 293 $(M)^+$, 278 $(M - CH_3)^+$, 167 $[(C_6H_5)_2CH]^+$, 126 $[CH{=}CH\text{-}N(iPr)_2]^+$.

(b) Reduction of the Enamine 6 to Diisopromine. According to the literature,[19] the enamine **6** (*ca.* 36 mmol) was added to 0.54 g (14 mmol) of $NaBH_4$ suspended in 12 mL of anhydrous methanol. The reaction mixture was stirred under nitrogen at rt for 16 h and then decomposed by adding 3 mL of 1% solution of NaOH and extracted with ether. Pure diisopromine (93% yield) was obtained by flash chromatography on silica gel using a 7:3 hexane/ether mixture as eluent.

Synthesis of Fenpiprane by Aminomethylation of 1b. The aminomethylation reaction was carried out following a known procedure.[20] A solution of 1 g (5,5 mmol) of 1,1-diphenylethene, 0.94 g (11 mmol) of piperidine, 0.2 g (11 mmol) of water, 1.1 mL of *N*-methylpyrrolidine, and 0.0058 g (0.013 mmol) of $RhCl_3(Py)_3$ was placed in a stainless steel reaction vessel, pressurized to 90 atm with CO, and maintained at 140 °C for 16 h. The reactor was then cooled to rt, the residual gas vented, and the reaction mixture analyzed by GLC to determine the conversion (20% yield). Fenpiprane was isolated in pure form from the reaction mixture by flash chromatography on silica gel using a 8:2 hexane/ether mixture as eluent.

Synthesis of Fenpiprane by Reductive Amination of 3,3-Diphenylpropanal with Piperidine under Hydroformylation Conditions. A mixture of 0.5 g (2.4 mmol) of the aldehyde **4b**, 0.41 g (4.8 mmol) of piperidine, 0.0038 g (0.0096 mmol) of $[Rh(CO)_2Cl]_2$, and 5 mL of benzene was introduced into a 150 mL stainless steel reaction vessel and pressurized to 80 atm with CO/H_2 (1:1). After 24 h at 80 °C the reactor was cooled to rt, the residual gas released, and the reaction mixture analyzed by GLC. Pure fenpiprane was obtained by flash chromatography on silica gel using a 8:2 hexane/ether mixture as eluent (80% yield).

One-Pot Preparation of Fenpiprane from 1,1-Diphenylethene. A 150 mL stainless steel reaction vessel was charged under nitrogen purge with 1 g (5.5 mmol) of olefin, 0.019 g (0.021 mmol) of $HRh(CO)(PPh_3)_3$, and 10 mL of anhydrous benzene. The reactor was then pressurized to 50 atm with synthesis gas ($CO/H_2 = 1$) and heated at 80 °C for 48 h. A sample of the reaction product was then taken and analyzed by GLC: about 81% substrate conversion was observed. At this point 12 mL of a 1 M solution of piperidine (12 mmol) in anhydrous benzene was introduced under pressure into the reactor. After additional 24 h reaction at 80 °C the autoclave was cooled to rt, the residual gas released and the reaction mixture analyzed by GLC. Fenpiprane was isolated in pure form by usual working up in 78% overall yield.

Acknowledgment. This work was financial supported by the EEC, Contract No. CI 1-CT92-0008.

Supporting Information Available: ^1H NMR peak assignments and copies of the spectra of all compounds (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO950295C

(23) Ahmad, N.; Levison, J. J.; Robinson, S. D.; Uttley, M. F. *Inorg. Synth.* **1974**, *15*, 45.
(24) Scrivanti, A.; Campostrini, R.; Carturan, G. *Inorg. Chim. Acta* **1988**, *142*, 187.
(25) Collmann, J. P.; Holtzclaw, H. F., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 2054.
(26) Schlosser, M.; Schaub, B. *Chimia* **1982**, *36*, 396.
(27) Kuznetsov, S. G.; Libman, N. M. *Zh. Org. Khim.* **1965**, *1*, 1399; *Chem. Abstr.* **1966**, *64*, 618h.
(28) Buczkowski, Z.; Gryff-Keller, A.; Zajaczkowska, E. *Rocz. Chem.* **1972**, *46*, 1047; *Chem. Abstr.* **1972**, *77*, 163730s.