Articles

Synthesis of 2-Arylpropionaldehydes through Hydroformylation

Denis Neibecker* and Régis Réau

Laboratoire de Chimie de Coordination du CNRS, Unité No. 8241, liée par conventions à l'Université Paul Sabatier et à l'Institut National Polytechnique, 205 route de Narbonne, 31077 Toulouse Cedex, France

Serge Lecolier

Centre de Recherches du Bouchet, SNPE, Le Bouchet, 91710 Vert le Petit, France

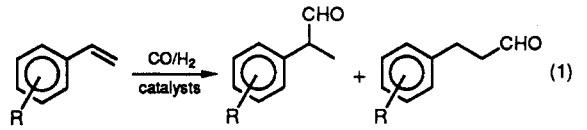
Received February 14, 1989

The rhodium–phospholes and rhodium–phosphanorbornadienes-catalyzed hydroformylation of the readily available vinylarenes **1–3** gives rise to arylpropionaldehydes **4–6** in good yields.

Introduction

Now that 2-arylpropionic acids are commonly used as antiinflammatory drugs,[1] there is much interest in their simple and economic synthesis.[2] Recently, Riley and co-workers[3] reported an efficient method based on the oxidation of the corresponding 2-arylpropionaldehydes using manganese stearate as oxidizing agent and *m*-chloroperoxybenzoic acid as catalyst initiator. The major preparations reported for these aldehydes start from aryl olefins[4] or aryl methyl ketones.[5] However, their drawbacks include being multistep processes or requiring expensive reagents.

A nice and simple way to synthesize 2-arylpropionaldehydes (**4–6**) is the hydroformylation of the easily available[2h,4c,6,8b] corresponding vinylarenes (**1–3**) (eq 1).



(1)

R = H	**1**	**4**	**7**
R = *p*-iBu	**2**	**5**	**8**
R = *m*-PhO	**3**	**6**	**9**

This reaction has been attempted by using ruthenium,[4c] cobalt,[7] rhodium,[7a,8] iridium,[4c] and platinum[9] catalysts, but high activities and selectivities to the branched aldehydes **4–6** were achieved with rhodium–phosphane systems only. For example, the rhodium–triphenylphosphine-catalyzed hydroformylation of styrene **1** proceeds under mild conditions (25 °C, 1 bar), and hydratropaldehyde **4** selectivities up to 94% can be achieved.[10]

We previously reported that phospholes **10**[11] and phosphanorbornadienes **11**[12] are efficient ligands for the rhodium-catalyzed hydroformylation of 1-hexene under mild conditions.[13] We therefore attempted to synthesize 2-arylpropionaldehydes **4–6** (eq 1) by the use of these new catalytic systems.

Results and Discussion

We first performed the hydroformylation of styrene (**i**) to prepare hydratropaldehyde **4**, an important starting material for cosmetics, polymers, or pharmaceuticals,[14] and

(1) Jordano, C.; Casteldi, G.; Uggeri, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 413.

(2) (a) Shimasaki, T.; Otsuka, Y.; Kondo, H. Jpn. Kokai 79 123 336, 1979. (b) Fujimory, Y. Jpn. Kokai 78 82 740, 1978. (c) Kiyoura, T. Jpn. Kokai 79 132 547, 1979. (d) Takeuchi, K.; Sugi, Y.; Matsuzaki, T. *Chem. Ind.* **1985**, 446. (e) Alper, H.; Hashem, K.; Heveling, J. *Organometallics* **1982**, *1*, 775. (f) Miekus, M.; Joo, F.; Alper, H. *Organometallics* **1987**, *6*, 1591. (g) Arzoumanian, H.; Buono, G.; Choukrad, M'B.; Petrignani, J.-F. *Organometallics* **1988**, *7*, 59. (h) Nugent, W. A.; Mc Kinney, R. J. *J. Org. Chem.* **1985**, *50*, 5370.

(3) (a) Riley, D. P.; Getman, D. P.; Beck, G. R.; Heintz, R. M. *J. Org. Chem.* **1987**, *52*, 287. (b) Getman, D. P.; Beck, G. R.; Riley, D. P. Eur. Pat. Appl. 226 566, 1987.

(4) (a) Wuts, P. G. M. Eur. Pat. Appl. 263 205, 1988. (b) Wuts, P. G. M. PCT Int. Appl. 87 519, 1987. (c) Shimizu, I.; Hirano, R.; Matsumura, Y.; Nomura, H.; Uchida, S.; Sato, A. Eur. Pat. Appl. 170 147, 1986. (d) Nisshin Chemicals, Jpn. Kokai 84 137 438, 1984. (e) Kikuchi, H.; Kogure, K.; Toyoda, M. *Chem. Lett.* **1984**, 341. (f) Kutsuma, T.; Takano, S.; Nagayama, I.; Ogasahara, K. Jpn. Kokai 76 127 030, 1976. (g) Owaki, S.; Kitamura, S. Jpn. Kokai 76 122 034, 1976. (h) Izuka, Y.; Sawa, Y.; Kawashima, T.; Miura, S. Jpn. Kokai 76 101 949, 1976.

(5) (a) Torres, E.; Josep, M.; Cuixart, G.; Jesus, M. Span. Pat. 551 355, 1987. (b) Maeda, S.; Shinoo, Y.; Takenaka, S.; Arashida, S.; Shimizu, I. Eur. Pat. Appl. 220 792, 1987. (c) Beu, D. L.; Kevorkian, M.; Jugrestan, F.; Farcasanu, I.; Bora, G.; Breazu, D.; Russu, J.; Geomolean, H. Rom. Pat. 86 370, 1985. (d) Palecek, J.; Svoboda, J.; Lutisanova, M.; Dedek, V.; Mostecky, J. Czech. Pat. 218 511, 1985. (e) Ohta Pharmaceutical Jpn. Kokai 81 154 428, 1981. (f) Vila Pahi, F. J. Span. Pat. 462 396, 1978. (g) Nagayama, I.; Okazaki, T.; Sakamoto, T.; Kutsuma, T. Jpn. Kokai 78 18 535, 1978. (h) Tsukuma, T.; Nagayama, I.; Okazaki, T.; Sakamoto, T.; Sugai, S.; Hasegawa, Y. Jpn. Kokai 78 31 637, 1978. (i) Sabatini, M. Jpn. Kokai 77 131 553, 1977. (j) Bruzzi, G.; Vila Pahi, F. J. Ger. Offen. 2 724 702, 1977. (k) Yoshimura, S.; Takahashi, S.; Ichino, M.; Nakamura, T. Jpn. Kokai 77 46 034, 1977. (l) Kutsuma, T.; Nagayama, I.; Okazaki, T.; Matsuoka, K.; Takano, S.; Ogasahara, K. Jpn. Kokai 76 128 933, 1976. (m) Kawashima, T.; Miyake, M.; Iizuka, Y.; Sawa, Y. Jpn. Kokai 76 100 040, 1976. (n) Omiya, T.; Sabakini, M. M. Jpn. Kokai 76 65 730, 1976. (o) Kogure, K.; Nagakawa, K.; Fukawa, H. *Agric. Biol. Chem.* **1976**, *40*, 291. (p) Cassebaum, H.; Hilger, H. Ger. Pat. (East) 113 889, 1975. (q) Dytham R. A. Fr. Pat. 1 545 270, 1968.

(6) (a) Shimizu, I.; Hirano, R.; Matsumara, Y.; Nomura, H.; Uchida, K.; Sato, A. Eur. Pat. Appl. 168 803, 1986. (b) Shimizu, I.; Hirano, R.; Matsumara, Y.; Nomura, H.; Uchida, K.; Sato, A. Eur. Pat. Appl. 168 802, 1986.

(7) (a) Laï, R.; Ucciani, E. *J. Mol. Catal.* **1978**, *4*, 401. Fujimoto, M.; Nakayama, S. Jpn. Kokai 77 62 233, 1977.

(8) (a) Takesada M.; Wakamatsu Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2192. (b) Takeda, M.; Mori, S.; Taniyama, E.; Iwane, H. Jpn. Kokai 79 24 843, 1979. (c) Arakawa, M. Jpn. Kokai 77 97 930, 1977.

(9) Parrinello, G.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 7122.

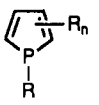
(10) Cerriotti, A.; Goulaschelli, L.; Longoni, G.; Malatesta, M. C.; Strumolo, O. *J. Mol. Catal.* **1984**, *24*, 309.

(11) Mathey, F. *Chem. Rev.* **1988**, *88*, 429.

(12) Mathey, F.; Mercier, F.; Charrier, C. *J. Am. Chem. Soc.* **1981**, *103*, 4595.

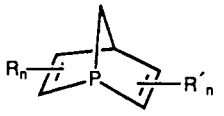
(13) (a) Neibecker, D.; Réau, R. *J. Mol. Catal.* **1989**, *53*, 219. (b) Neibecker, D.; Réau, R. *Angew. Chem.* **1989**, *101*, 479.

0022-3263/89/1954-5208$01.50/0 © 1989 American Chemical Society



10

1,2,5-triphenylphospholе, TPP
1-*o*-tolyl-2,5-diphenylphospholе, *o*-TDPP
1-*tert*-butyl-3,4-dimethylphospholе, *t*-BDMP
1,2,3,4,5-pentaphenylphospholе, PPP



11

3,4-dimethyl-2,5,6-triphenyl-1-phosphanorbornadiene, DMTPPN
2,3,6,7,7′-pentaphenyl-1-phosphanorbornadiene, PPPN

(ii) to select the phospholes and the phosphanorbornadienes to be used for the hydroformylation of substituted styrenes, **2** and **3**. The phospholes and the phosphanorbornadienes were evaluated by comparison with triphenylphosphine, which is the best ligand described so far for the rhodium-catalyzed hydroformylation of vinylarenes[10,15] (Table I, entries 1–8).

As may be seen, the phosphanorbornadienes are as selective as triphenylphosphine (entries 3 and 6 vs entry 2); no hydrogenation of styrene occurs, but a good activity is attained with PPPN only. Except for *t*-BDMP, which gives rise to a catalytically inactive system,[13] the phospholes lead to hydratropaldehyde selectivies below 90%. Furthermore, with *o*-TDPP, 16% of the styrene consumed is hydrogenated (entry 4). As observed with 1-hexene,[13] the highest activity is obtained with TPP. However, since the conversion reaches 100%, the catalytic activity, as measured by TOF (Table I), could have been underestimated. Runs performed in 3 h revealed that TPP is actually 2 times more active than triphenylphosphine (Table I entry 9 vs entry 10).

These results show that only TPP and PPPN are of interest for the rhodium-catalyzed hydroformylation of styrene (entries 3 and 9). Since one of the main goals in fine chemical synthesis is to tend toward mild reaction conditions, these two phosphanes were used at 25 °C for the hydroformylation of styrene **1**, *p*-isobutylstyrene **2**, and *m*-phenoxystyrene **3** (Table I, entries 11 to 19).

Decreasing the temperature influences the styrene hydroformylation rate, especially with the triphenylphosphine system. At 25 °C, TPP is much more active but less selective than triphenylphosphine (entry 11 vs entry 13). Among the phosphanes studied, the most efficient ligand is PPPN which exhibits a good activity (4 times more active than triphenylphosphine) and a high selectivity to hydratropaldehyde (91%) (entry 12). Under these mild conditions neither hydrogenation of the substrate nor side reactions of the aldehydes occur.

The hydroformylation of *p*-isobutylstyrene **2** (entries 14–16) leads to the same results as that of styrene. Compared to triphenylphosphine, the Rh–TPP system exhibits a high activity but a modest selectivity to the desired branched aldehyde (entry 14 vs entry 16). PPPN is the most efficient ligand for the synthesis of the aldehyde **5**, which is a direct precursor of 2-(*p*-isobutylphenyl)-propanoic acid known as Ibuprofen.[2h] This system is 2 times more active than the triphenylphosphine-based one and yields only aldehydes and selectively the desired branched isomer **5** (entry 15).

The *m*-phenoxy group dramatically influences the behavior of the Rh–TPP system. The activity is higher than that observed with styrene and *p*-isobutylstyrene (entry 17 vs entries 11 and 14), and for the first time the branched aldehyde selectivity reaches that obtained with triphenylphosphine. The Rh–PPPN system is also convenient for *m*-phenoxystyrene hydroformylation; it is as selective and 7 times more active than the triphenylphosphine-based one (entry 18).

Under these mild reaction conditions, the Rh–TPP system is the most efficient for the synthesis of aldehyde **6**, a precursor of 2-(*m*-phenoxyphenyl)propanoic acid known as Phenoprofen. These results, together with the property of the Rh–TPP system to reach its optimum activity and selectivity for a phosphorus to rhodium ratio of 2,[16] show its high potential in hydroformylation reactions.

In conclusion, the use of phospholes and phosphanorbornadienes as ligands in the rhodium-catalyzed hydroformylation of vinylarenes leads to very efficient catalytic systems. Aldehydes **4–6**, precursors of 2-arylpropionic acids of pharmaceutical interest, can be easily prepared from readily available starting materials[6,9] thanks to Rh–PPPN or Rh–TPP systems. No side reaction such as hydrogenation of the substrate occurs, and it can be anticipated that the desired branched aldehyde selectivity may be increased by tailoring the reaction parameters, especially the hydrogen/carbon monoxide ratio.[13]

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded at 90 MHz on a Bruker WH 90 spectrometer in $CDCl_3$ using tetramethylsilane as internal standard. Infrared spectra were measured with a Perkin-Elmer 597 spectrometer. GC analyses were performed on an Intersmat IGC 120 flame ionization detector gas chromatograph. All solvents were carefully dried, distilled, and stored according to literature procedures.[17] Similarly, all reagents were stored under argon after distillation or recrystallization.

Starting Materials. All the gases were high quality gases (argon U, carbon monoxide N20, and hydrogen U) from L'Air Liquide. Triphenylphosphine (Janssen Chimica, 98%) was recrystallized from methanol. Phospholes and phosphanorbornadienes were kindly supplied by Dr. F. Mathey and synthesized according to published procedures.[11,12] Triethylamine (Janssen Chimica, 99%) was distilled from potassium hydroxide just before use. The catalyst precursor $[Rh(CO)_2Cl]_2$ was prepared according to the procedure of Mc Cleverty and Wilkinson.[18]

The starting vinylarenes (1–3) and authentic samples of the aldehydes (4–6) were either commercially available (styrene 1 and hydratropaldehyde 4 from Fluka) or prepared as follows.

***p*-Isobutylstyrene (2).** A mixture of 1-(*p*-isobutylphenyl)-1-chloroethane (18.0 g, 91.5 mmol), tetrabutylammonium bromide (2.95 g, 9.15 mmol), potassium hydroxide (5.13 g, 91.6 mmol), and 3-*tert*-butyl catechol (0.2 g) was heated at 120 °C for 1 h. Distillation of the reaction mixture afforded 7.94 g (54%) of *p*-isobutylstyrene, bp 45 °C (0.5 Torr), whose spectral data (^{1}H NMR, IR) are in agreement with reported values.[9]

2-(*p*-Isobutylphenyl)propanol. A solution of Ibuprofen (2.28 g, 11 mmol) in diethyl ether (30 mL) was slowly added to a stirred solution of $LiAlH_4$ (0.720 g, 19 mmol) in diethyl ether (30 mL) at 10 °C. After the mixture was stirred for 4 h, water (100 mL) was added dropwise to decompose excess hydride; 10% sulfuric acid (30 mL) was then added, affording a clear solution. The mixture was extracted with diethyl ether, washed successively with 10% sulfuric acid, 5% aqueous sodium hydrogen carbonate,

(14) (a) Siegel, H.; Himmele, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 178. (b) Cornils, V. B.; Payer, R. *Chem. Zeit.* **1974**, *98*, 596.
(15) (a) Pittman, C. U.; Lin, C. C. *J. Org. Chem.* **1978**, *43*, 4928. (b) Hayashi, T.; Tanaka, M.; Ogata, I. *J. Mol. Catal.* **1979**, *6*, 1.
(16) Bergounhou, C.; Neibecker, D.; Réau, R. *J. Chem. Soc., Chem. Commun.* **1988**, 1370.
(17) Perrin, D. D.; Armarengo, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: New York, 1988.
(18) Mc Cleverty, J. A.; Wilkinson, G. *Inorg. Synth.* **1966**, *8*, 211.

Table I. Hydroformylation of Vinylarenes 1–3 Catalyzed by Rhodium–Phosphole and Rhodium–Phosphanorbornadiene Systems[a]

entry	R	phosphane	temp, °C	time, h	conversion, %	aldehyde[b] (%)	branched aldehyde[c] (%)	TOF,[d] h^{-1}
1	H	TPP	40	6.0	100 (90)[e]	4 + 7 (100)	4 (84)	40
2	H	PPh_3	40	6.0	87	4 + 7 (99)	4 (94)	32
3	H	PPPN	40	6.0	82	4 + 7 (99)	4 (91)	30
4	H	*o*-TDPP	40	6.0	75	4 + 7 (84)	4 (80)	29
5	H	PPP	40	6.0	49	4 + 7 (100)	4 (87)	19
6	H	DMTPPN	40	6.0	32	4 + 7 (100)	4 (94)	13
7	H	*t*-BDMP	40	6.0	0	4 + 7 (0)	4 (0)	0
8	H	none	40	6.0	0	4 + 7 (0)	4 (0)	0
9	H	TPP	40	3.0	87	4 + 7 (100)	4 (83)	67
10	H	PPh_3	40	3.0	35	4 + 7 (100)	4 (93)	28
11	H	TPP	25	6.0	64	4 + 7 (100)	4 (85)	24
12	H	PPPN	25	6.0	46	4 + 7 (100)	4 (91)	17
13	H	PPh_3	25	6.0	10	4 + 7 (100)	4 (95)	4
14	*p*-iBu	TPP	25	6.0	79	5 + 8 (100)	5 (83)	27
15	*p*-iBu	PPPN	25	6.0	58	5 + 8 (100)	5 (90)	22
16	*p*-iBu	PPh_3	25	6.0	29	5 + 8 (100)	5 (94)	10
17	*m*-PhO	TPP	25	6.0	95	6 + 9 (100)	6 (91)	35
18	*m*-PhO	PPPN	25	6.0	64	6 + 9 (100)	6 (93)	24
19	*m*-PhO	PPh_3	25	6.0	9	6 + 9 (100)	6 (93)	3.3

[a] $[Rh(CO)_2Cl]_2$ = 0.02 mmol, vinylarene/Rh = 220–240, phosphorus/Rh = 5, 20 bar, CO/H_2 = 1/1, Et_3N/Rh = 10, toluene 8 mL. [b] Defined as moles of linear and branched aldehydes formed per mole of vinylarene consumed, as determined by GC. [c] As determined by GC and ^1H NMR (integration of the aldehydic protons). [d] Turnover frequency defined as moles of substrate hydroformylated per mole of catalyst per hour. [e] Isolated yield (see Experimental Section).

and water, and dried over magnesium sulfate. Removal of the solvent gave 1.98 g (94% yield) of 2-(*p*-isobutylphenyl)propanol whose spectral data (^1H NMR, IR) are in agreement with reported values.[19]

2-(*p*-Isobutylphenyl)propanal (5). A solution of dry dimethyl sulfoxide (0.9 mL, 12.7 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a cold (−78 °C) solution of oxalyl chloride (0.5 mL, 5.8 mmol) in CH_2Cl_2 (5 mL) over 6 min. After 10 min, a solution of 2-(*p*-isobutylphenyl)propanol (1.01 g, 5.25 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 1 h, triethylamine (3.7 mL, 26.4 mmol) was added, and the reaction mixture was allowed to warm to room temperature. After addition of water (20 mL) the mixture was extracted with dichloromethane. The solvent was removed, and ether was added to the residue to separate triethylamine hydrochloride, which was removed by filtration. The filtrate was dried over magnesium sulfate and evaporated to give an oil, which was purified by column chromatography on silica gel, eluting with 10% diethyl ether in hexane, to give **5** (0.451 g, 54%) as a colorless oil, which presented spectral data in agreement with published values.[4e]

p-Phenoxystyrene (**3**) and 2-(*m*-phenoxyphenyl)propanal (**6**) were prepared by the same procedures starting from 1-(*m*-phenoxyphenyl)-1-chloroethane and Phenoprofen, respectively.

Hydroformylation Experiments. The hydroformylation of vinylarenes was performed in an home-made 100-mL Teflon-coated stainless steel autoclave magnetically stirred and equipped with a safety valve, a ball valve for the introduction of liquids, a manometer, and an argon/gas inlet–outlet valve. In a typical run, $[Rh(CO)_2Cl]_2$ and a phosphane was weighed and introduced in the autoclave, which then was closed. The atmosphere was replaced by argon, and a toluene solution containing the required quantity of substrate and triethylamine was introduced through the ball valve. This valve was closed, and the autoclave was pressurized with CO and H_2 and heated to the desired temperature in about 5 min. After the reaction times quoted in the table, the autoclave was cooled to −40 °C and vented in ca. 1 h in a well-ventilated hood. The reaction products were collected under argon into a Schlenk tube with toluene and analyzed by GC [Styrene: 3 m × $^1/_8$ in. column 10% carbowax 20M on chromosorb 80–100 mesh working at 180 °C and N_2 as carrier gas (flow rate 1.8 L h^{-1}) with hexadecane as internal standard for the aldehyde analysis, working at 80 °C, 0.8 L h^{-1} flow rate of N_2 for the ethylbenzene analyses. *p*-Isobutylstyrene: 2 m × $^1/_8$ in. column 10% SE 30 on gas chrom Q 80–100 mesh working at 140 °C, 0.7 L h^{-1} flow rate of N_2 with ethyl hydrocinnamate as internal standard. *m*-Phenoxystyrene: 2 m × $^1/_8$ in. column 10% SE 30 on gas chrom Q 80–100 mesh working at 160 °C, 0.7 L h^{-1} flow rate of N_2 with ethyl hydrocinnamate as internal standard]. The toluene and excess triethylamine were removed under reduced pressure, and an aliquot was analyzed by ^1H NMR spectroscopy.

A preparative run was performed under conditions of entry 1 by starting from 9.8 g (94 mmol) of styrene and 78 mg (0.2 mmol) of $[Rh(CO)_2Cl]_2$ in toluene (80 mL) and treated as mentioned above until no toluene remained. Trap-to-trap distillation (0.02 Torr) afforded 11.4 g (90%) of a mixture of aldehydes 4 + 7.

Acknowledgment. We wish to thank the Centre National de la Recherche Scientifique (CNRS) for financial support and the Société Nationale des Poudres et Explosifs (SNPE) for financial support, for a fellowship to R.R., for permission to publish this paper, and for providing samples of 1-(*p*-isobutylphenyl)-1-chloroethane, 1-(*m*-phenoxyphenyl)-1-chloroethane, Ibuprofen, and Phenoprofen. We are also grateful to Dr. F. Mathey and Dr. A. Breque from the Ecole Polytechnique at Palaiseau (France) for providing the phospholes and the phosphanorbornadienes. Helpful discussions with Dr. I. Tkatchenko (CNRS) are also gratefully acknowledged.

Registry No. 1, 100-42-5; 2, 63444-56-4; 3, 63444-54-2; 4, 93-53-8; 5, 51407-46-6; 6, 59908-87-1; 7, 104-53-0; 8, 40764-03-2; 9, 122801-83-6; *o*-TDPP, 122801-82-5; *p*-*i*-$BuC_6H_4CHClCH_3$, 62049-65-4; *m*-$PhOC_6H_4CHClCH_3$, 80379-89-1; ibuprofen, 15687-27-1; 2-(4-isobutylphenyl)propanol, 36039-36-8; 2-(*m*-phenoxyphenyl)propanoic acid, 29679-58-1.

(19) Takano, S.; Ogasawara, K.; Nagayama, I.; Kutsuma, T. *Synth. Commun.* **1976**, 349.