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HYDROFORMYLATION CATALYSED BY RHODIUM COMPLEXES OF TREHALOSE-DERIVED LIGANDS aa and ββ-TREDIP; A HIGHLY REGIOSELECTIVE ROUTE TO α-METHYLARYLPROPIONALDEHYDES

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Abstract: Rhodium complexes of the ligand αα-TREDIP give 62:1 iso-regioselectivity in the hydroformylation of styrene under ambient conditions without excess phosphine, higher than any previously reported value. The results are compared with those obtained with other ligands, and extended to the preparation of 2-(6-methoxy-2-naphthyl)-propanal, a precursor of the anti-inflammatory drug naproxen.

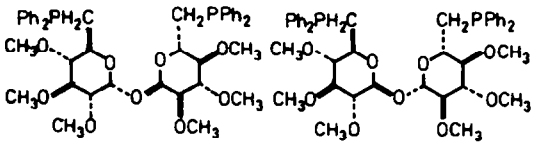
It has been known for over fifteen years that rhodium phosphine complexes catalyse the hydroformylation of olefins under very mild conditions in a highly selective manner.[1] Thus terminal aliphatic olefins are converted into linear aldehydes and vinylarenes into branched aldehydes; the former process is of considerable commercial significance.[2] Despite this, the usage of hydroformylation in organic synthesis is rather rare[3] although it occasionally has unusual scope.[4] This may reflect a general reluctance among organic chemists to work with synthesis gas, and inhibitions against working at higher than atmospheric pressure, essential if large quantities of substrate and modest amounts of catalyst are involved.

The rationale behind this work has been the preparation of biphosphine ligands with sufficient flexibility in the backbone to permit cis-chelation (bite angle 90-120°) and also trans-chelation (bite angle 180°). The major selective catalytic pathway in hydroformylation involves two phosphines coordinated to rhodium, and with PPh_3 they may be mutually cis or trans at different stages in the catalytic cycle.[5] The selectivity increases with increasing phosphine: rhodium ratio [6] for PPh_3 and other monophosphines, because competitive ligation by CO lowers the selectivity. A chelating biphosphine should alleviate this problem if cocomplexation of its donor atoms has a sufficiently high effective molarity.

Hydroformylation of styrene

Reactions were carried out with αα- and ββ-TREDIP, 1 and 2, with the cis chelating biphosphine DIOP 3, and with the L-iditol derived biphosphine 4. Rather than prepare a number of precursor rhodium complexes, a standard method was sought for conducting hydroformylation with a 1:1 complex formed in situ. Crabtree and Morris have already provided the basis of one such method starting from the bicyclo[2,2,1]heptadienerhodium bisphosphine cation and an equivalent of base,[7] since this latter complex may be prepared directly from $(C_7H_8)_2Rh^+$ and the phosphine. An alternative approach was to react the ligand with an equivalent of tris(allyl)rhodium[8] under CO/H_2 (1:1 or 1:2) in dichloromethane in the presence of substrate, whereupon a deep red solution was obtained and hydroformylation proceeded smoothly.

Results obtained are recorded in Table 1. The reaction mixture was normally stirred for 20 h. (occasionally up to 45 h. if reaction was incomplete at that stage) at 20° and then worked up and analysed by g.l.c.



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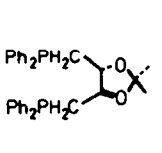

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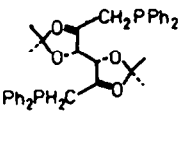

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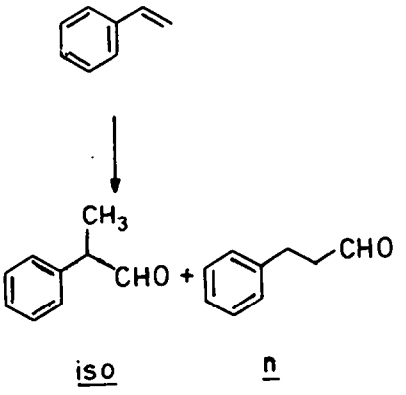
TABLE 1 Hydroformylation of styrene

Run	Ligand	Precursor[a]	H_2/CO	% Aldehydes[b]	iso/n
1	2 PPh_3	A	1:1	99.5	14.8[a]
2	3	A	1:1	71	4.0[c]
3	3	B	1:1	99	2.1[c]
4	4	A	1:1	100	11.2
5	1	A	1:1	70	19.4
6	1	A	2:1	90	17.5
7	1	B	1:1	100	61.5
8	1	B	2:1	80	42.4
9	2	A	1:1	100	13.2
10	2	A	2:1	93	11.5
11	2	B	1:1	69	11.2
12	2	B	2:1	85	15.9



[a] Precursor A is tris(allyl)rhodium and precursor B is bis(bicyclo[2,2,1]heptadiene)rhodium tetrafluoroborate plus two equivalents of NEt_3. In each case the precursor (0.018 mmol) and biphosphine (0.018 mmol) were dissolved in CH_2Cl_2 (1 ml.) and degassed under argon. Styrene (0.44 mmol) was added, argon replaced by CO/Hz and uptake of gas monitored by burette. The reaction mixture was passed through a short column of silica gel and analysed directly by g.l.c (3% Carbowax, 120°).
[b] Recovered starting material and reduced product were not distinguished in this analysis.
[c] Single runs, otherwise experiments conducted at least in duplicate.

The most interesting feature of these experiments is the reproducibly high regioselectivity observed with αα TREDIP 1 and precursor B, this being more selective than any case reported in the literature. In Wilkinson's early work, it was reported that $HRhCO(PPh_3)_3$ effected iso/n selectivity of 8:1 in the hydroformylation of styrene.[1] Subsequent work with chiral monophosphines gave selectivities up to 49:1 for which it was necessary to employ a substantial excess(>4:1) of phosphine.[9] Other cases where a reasonably high selectivity in favour of the branched-chain isomer has been recorded include chelating derivatives of dibenzophosphole,[10] giving up to 10:1, and CHIRAPHOS complexes,[11] giving 16:1. With polymer-supported analogues of Wilkinsons catalyst, a ratio of 12.9:1 was achieved.[13] In a comparison of the reactivity of p-substituted styrenes towards hydroformylation catalysed by $HRh(PPh_3)_4$ it was demonstrated that electron-withdrawing groups increased both the rate and the regioselectivity,[12] the best case being p-NO_2 with an iso:n ratio of 25:1. The high selectivity observed in the case of 1 a suggests that some special feature may be involved. It has been shown that rhodium complexes of the ligand may be cis or trans-chelated, and in the latter case oxygen-coordination is possible.[14] The inherent flexibility of the backbone indicates that interconversion between the two geometries should occur with a low intrinsic energy barrier. This is a very favourable state of affairs for hydroformylation since the chelate may remain bound to rhodium throughout the catalytic cycle, as indicated in Figure 1. The ββ isomer 2 favours cis-coordination more and trans-coordination rather less than does the αα-isomer 1, and it is notably less effective as a regioselective hydroformylation catalyst.

The hydroformylation of styrene to 2-phenylpropanal introduces a new chiral centre, and much effort has been devoted to asymmetric catalysis. With rhodium complexes the results are uniformly moderate.[15] $PtCl_2$ complexes in the presence of $SnCl_2$ give much better enantiomer excesses (up to 75%)[16] but the reaction must be run at high pressure and the selectivity, both towards the branched-chain isomer and over hydrogenation, is rather weak. In the present case the optical purity of product was examined by N.m.r. chiral shift analysis using Eu(hfc)$_3$ and shown to be vanishingly small, as might be expected for a ligand with a high degree of backbone flexibility.

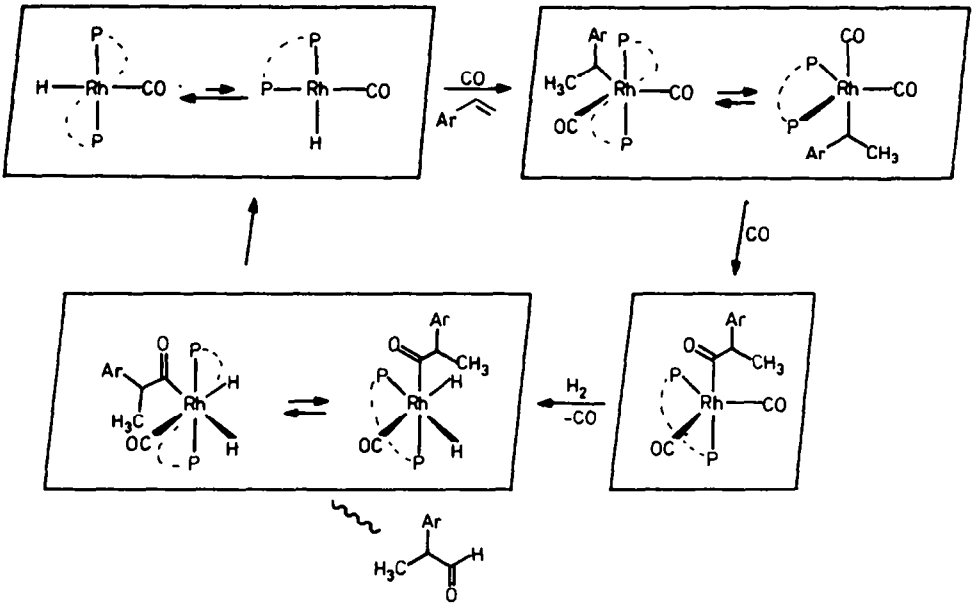
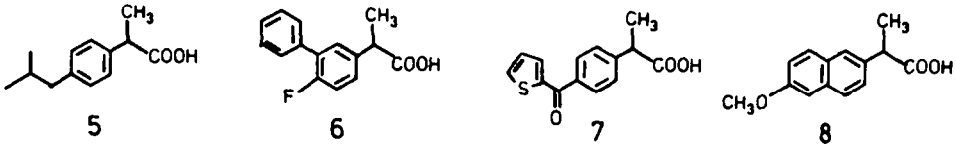


Figure 1

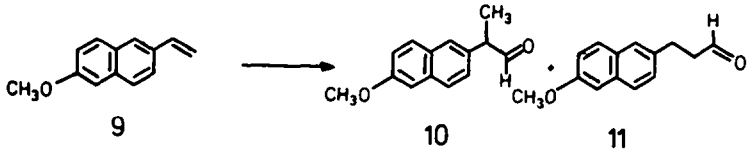
A hydroformylation route to Naproxen

2-Arylpropionic acids are an important class of antiinflammatory agents,[17] including the clinically viable drugs Brufen 5, Froben 6, Suprofen 7 and Naproxen 8. The generality of selective hydroformylation by aa-TREDIP rhodium complexes was examined by application to a Naproxen analogue. Present routes to the compound involve straightforward aromatic chemistry[18] or nickel-catalysed cross-coupling between 2-(bromomagnesio)-6-methoxynaphthalene and the magnesium salt of ethyl 2-bromopropionate.[19]



5 6 7 8

Synthesis of 6-ethenyl-2-methoxynaphthalene 9 was effected by cross-coupling vinylmagnesium bromide with 2-iodo-6-methoxynaphthalene in the presence of a catalytic amount of $Pd(PPh_3)_4$,[20] which gave the desired product in 69% yield. Hydroformylation was carried out according to procedure A, and gave a mixture of the two aldehydes 10 and 11 in ratio 20:1, in 94.5% isolated yield. Although the catalyst is optically active, the reaction product 10 is effectively racemic, judged on the basis of its ^1H N.m.r. spectrum in the presence of $Eu(hfc)_3$. Enzymatic resolution of racemic naproxen esters using the lipase from Candida cylindracea has recently been reported.[21]



9 10 11

Two further results should be recorded. Firstly the selectivity in hydroformylation of oct-1-ene, where n-nonanal predominates, is lower when αα-TREDIP is employed in procedure A, since 28% of the branched-chain isomer was observed, compared with around 10% when PPh_3-based catalysts are used.[1] Further the hydroformylation of phenyl vinyl sulphoxide gives 97% of the branched-chain aldehyde 12 with αα-TREDIP as catalyst. One diastereomer appears to predominate in the ^1H N.m.r. spectrum of crude product but this may reflect thermodynamic control since the α-proton will be rather acidic, and facilitate keto enol interconversion. The reaction is very slow, however, and only a few turnovers were achieved in 48 h. under ambient conditions.

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Experimental

Tris(allyl)rhodium,[9] bis(bicyclo[2,2,1]heptadiene)rhodium tetrafluoroborate[22] and tetrakis(triphenylphosphine)palladium[23] were prepared by published procedures. All reactions involving organometallic complexes were conducted under an inert atmosphere using vacuum line and Schlenk techniques as previously described.

2-Iodo-6-methoxynaphthalene

2-Methyl-2-propyllithium in pentane (1.4 M, 70 ml, 98 mmol) was added to a solution of 2-bromo-6-methoxynaphthalene[24] (10.01 g, 42.2 mmol) in tetrahydrofuran (90 ml) at -78°. The mixture was stirred at -78° for 1h, a solution of iodine (16.85 g, 66.4 mmol) in tetrahydrofuran (70ml) was added, and the mixture was then stirred at room temperature for 72h. The solvent was removed in vacuo, dichloromethane (250 ml) was added and the solution was washed with water (100 ml), saturated sodium thiosulphate solution (4 x 100 ml), water (100 ml) and saturated sodium chloride solution (100 ml) and then dried (anhydrous magnesium sulphate). The solvent was removed in vacuo and the residue recrystallized from dichloromethane/methanol to give 2-iodo-6-methoxynaphthalene (10.03 gm, 35.3 mmol, 83.7%) as yellow plates; m.p. 143-4°; ^1H-N.m.r.: δ (300 MHz, $CDCl_3$) 3.9 (3H, s, OMe), 7.05-7.7 (5H, m, arom), 8.15 (1H, m, arom, ortho-H); found: C, 46.50; H, 3.28; $C_{11}H_9IO$ requires: C, 46.50; H, 3.19%.

6-Ethenyl-2-methoxynaphthalene

Tetrakis(triphenylphosphine)palladium (0) (171) (0.100 g, 0.087 mmol) was added to a mixture of 2-iodo-6-methoxynaphthalene (0.99 g, 3.48 mmol) in tetrahydrofuran (15 ml) and vinylmagnesium bromide (0.8 M, 12 ml, 9.6 mmol) in tetrahydrofuran at -78°. The solution was stirred under argon at room temperature for 5d, during which time it became brown and a white precipitate was formed. Hydrochloric acid (3 M, 4 ml, 12 mmol) was added, the solvent was removed in vacuo, dichloromethane (50 ml) and water (50 ml) were added, and the aqueous layer was extracted with dichloromethane (50 ml). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (50 ml), water (2 x 50 ml) and saturated sodium chloride solution. The solution was dried (anhydrous magnesium sulphate) and the solvent removed in vacuo to give an orange residue which was sublimed (100°) as a white solid, examination of which by ^1H-NMr showed a mixture of 6-ethenyl-2-methoxynaphthalene (88%) and 2-methoxynaphthalene (12%). Recrystallization from ethanol/water gave pure 6-ethenyl-2-methoxynaphthalene (0.440 g, 2.39 mmol, 68.6%); m.p. 92-3° (lit.[19a] 93-4°); ^1H-NMr δ (300 MHz, $CDCl_3$) 3.95 (3H, s, OMe), 5.3 (1H, d, J 10.5 Hz, $=CH_AH_B$), 5.85 (1H, d, J 17 Hz, $=CH_AH_B$), 6.85 (1H, dd, J_{HH} 10.5 Hz, J_{HH} 17 Hz, $CH=CH_AH_B$), 7.15 (2H, m, arom), 7.6-7.75 (4H, m, arom).

2'(2-methoxy-6-naphthyl)-propanal

6-Ethenyl-2-methoxynaphthalene (166) (100 mg, 0.543 mmol) was added to a degassed solution of the biphosphine αα-TREDIP (28 mg, 0.037 mmol) and tris(allyl)rhodium (8 mg, 0.035 mmol) in dichloromethane (2 ml). The solution was stirred under hydrogen/carbon monoxide (1:1 ratio) for 48h., and then passed through a column of silica gel to remove the rhodium salts. The solvent was removed in vacuo and examination of the crude product (^1H-NMR) indicated the presence of 2'(2-methoxy-6-naphthyl)-propanal (95%) and 3-(6-methoxy-2-naphthyl-propanal (5%). There was no trace of starting material. Sublimation of the product gave a white solid (110 mg, 0.513 mmol, 94.5%), showing the same ratio of aldehydic products of 95:5; mainly 2'(2-methoxy-6-naphthyl) propanal; ^1H-NMr δ (300 MHz, $CDCl_3$) 1.55 (3H, d, J 7 Hz, CH_3), 3.8 (1H, q, J 6 Hz, CH), 3.95 (3H, s, OCH_3), 7.15 (2H, m, Ar), 7.3 (2H, m, Ar), 7.75 (2H, m, Ar), 9.75 (1H, d, J 1 Hz, CHO); m.p. 59.5-61.5° (lit [18] 52-7°).

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