Characterization and application of catalytic regioselective hydroformylation with a cationic bis(dioxaphospholane)rhodium catalyst precursor

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Characterization and Application of Catalytic Regioselective Hydroformylation with a Cationic Bis(dioxaphospholane)rhodium Catalyst Precursor

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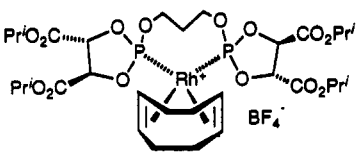
A cationic rhodium complex containing a bis(dioxaphospholane) ligand is very effective in regioselective hydroformylation. Aryl olefin substrates are hydroformylated with very high rates (>3000 turnovers per Rh per hour) and high regioselectivity (>92:8 for branched products). With smaller substrate:catalyst ratios higher regioselectivity (higher than 97:3) is found, and control and mass balance experiments indicate this is caused by selective decomposition of the linear aldehyde product. Very good regioselectivity is also found with methyl acrylate. Modest regioselectivity is obtained with terminal alkyl olefins. The efficient hydroformylation of 2,6-dimethylstyrene is consistent with the absence of π-benzyl intermediates in this catalyst system. The application of regioselective hydroformylation in organic synthesis is developed to give a new route to a racemic intermediate to α-cuparenone. The efficient synthesis of 3-methylindole from *o*-vinylaniline by hydroformylation/dehydration is described, along with a similar annulation of *o*-vinylacetophenone.

Introduction

We recently developed general and efficient routes to cationic rhodium complexes of bis(dioxaphospholane) ligands, as in **1**, and shown that these complexes are competent as precursors for the hydrogenation of olefins and the hydroformylation of styrene.[2] In this paper we discuss how the latter reaction can be made remarkably selective and active for the synthesis of branched aldehydes from aryl olefins and methyl acrylates. We also present some novel applications of catalytic hydroformylation in organic synthesis and discuss inferences about catalytic intermediates based on our results.



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Regioselective Hydroformylation of Styrene. Hydroformylation is best known in the context of the synthesis of linear alkyl aldehydes and alcohols from alkyl olefins, and this is appropriate because of the high commercial value of the products.[3] The use of hydroformylation in organic synthesis is also important, especially in the context of the synthesis of branched products that can form the basis for natural product and pharmaceutical synthesis.[4]

Styrene is a very important substrate for the study of branched-selective hydroformylation.[5] Several different catalyst systems have been employed in the hydroformylation of styrene. Relatively few systems operate at very high activity ($Rh_4(CO)_{12}$[7] and a Union Carbide mono(phosphite) type system at elevated temperatures and pressures[8]), and in these cases the regioselectivity is relatively modest or poor. Conversely, catalytic activity is often low with catalysts that provide high regioselectivity, especially with cationic rhodium catalysts.[9] Finally, while platinum/tin catalysts offer great promise in asymmetric hydroformylation,[10] they are typically very slow and never offer extremely high regioselection or, for that matter, chemoselection; linear aldehydes and hydrocarbons from simple hydrogenation are major side products.[11]

The recent report by Consiglio and Rama[12] of 100% selectivity for the branched isomer from styrene with "Et$_4$-Diop" illustrates several relevant factors. Significant pressures and temperatures—comparable to those that we routinely employ—are used, but conversions are modest. In addition, a phosphine ligand, especially an alkylated phosphine, is very basic; it may promote aldol-type chemistry that could dramatically alter the product mixture (vide infra). Lastly, the phosphorus–carbon bonds of phosphines can be difficult to make economically and they are subject to hydrogenolysis, both disadvantages for practical catalysis.[13] In all of these instances, phosphite

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(5) The only alkyl olefin substrate that can in principle yield an economically important branched aldehyde on a large scale is butene, which would give 2-methylbutanal, a potential precursor to isoprene.[6]

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ligands may have a distinct advantage over corresponding phosphines.

Phosphite Ligands in Hydroformylation. Most early studies of catalytic hydroformylation focused on trialkylphosphines (e.g., $Co_2(CO)_8/PBu_3$[3]) and triarylphosphines (as in Wilkinson's catalyst[14]). Recently, however, hydroformylation catalysts incorporating aryl phosphites have also become important components of catalyst mixtures. Formulations of the type Rh(I)/triaryl phosphite are the basis of several patents concerning the hydroformylation of terminal alkyl olefins,[15] vinyl acetate and related substrates,[16] and internal olefins that give only branched aldehydes because the catalyst does not also catalyze olefin isomerization.[17] Similar increases in selectivity were noted in platinum/tin catalysts.[18] Bulky phosphites are known to increase the rate of hydroformylation of both mono-[19] and disubstituted alkyl olefins[20] and of cyclic vinyl ethers[21] compared to triarylphosphine-based systems. Part of the reason for this may be the combination of bulk and electron deficiency of the ligand, which seem to restrict the Rh:P ratio of the detectable metal complex under catalytic conditions to 1:1.[22]

Cyclic monodentate phosphorus–oxygen heterocycles (which can be considered trivially as cyclic mono(phosphites)) are the key component in several patents for the hydroformylation of α-olefins to linear aldehydes[23] and for internal olefins to mostly or exclusively branched aldehydes.[8] These reports include very effective biaryl-based bis(phosphite) ligands.[24] A recent report indicates that ligands of this class, with a chiral binaphthol backbone, may be useful in asymmetric hydroformylation, at least with vinyl acetate as the substrate.[25]

There are several reasons why ligands containing P–O bonds may be desirable additives in catalytic hydroformylation. On the one hand, the phosphorus–oxygen bond should be less labile to oxidative-cleavage reactions that compromise the catalyst.[13] Of course, the P–O bond is subject to cleavage by hydroxylic reagents. However, we have shown that dioxaphospholanes, *when complexed to a metal*, are considerably more resistant to decomposition, even by strong acid at elevated temperatures (HBF_4/Et_2O, 60 °C, 16 h).[26] Similar observations have been made concerning chelating aryl-based bis(phosphite) type ligands for nickel-catalyzed hydrocyanation[27a] and, in a recent patent, rhodium-catalyzed hydroformylation of alkyl olefins.[27b] In addition, phosphite ligands are much less basic than phosphines, which is useful in preventing base-catalyzed side reactions.[28] Finally, phosphites are an excellent environment to exploit the many chiral diols available by asymmetric synthesis and from the chrial pool, offering the promise of facile access to new asymmetric catalysts.[25,29]

Results

Catalytic Hydroformylation of Styrene and Other Olefins. Hydroformylation of styrene under 25 atm of 1:1 CO/H_2 with catalyst precursor 1 proceeds with 75:25 selectivity for 2-phenylpropanal compared to 3-phenylpropanal.[2] Much higher selectivity, over 97.5:2.5, and higher rates are achieved if the pressure of the reaction is raised to greater than 50 atm (eq 1). Excellent selectivity

$$PhCH{=}CH_2 + CO + H_2 \rightarrow PhCH(CHO)CH_3 + PhCH_2CH_2CHO \quad (1)$$

is also seen with most styrene derivatives (Table I). The only case where the preferred product does not have a formyl α to the aryl group is with α-methylstyrene, and then the reaction is also at least 1 order of magnitude slower than for substrates with no α branching. In addition, we found that the actual catalyst can be recycled by removing product in vacuo and reintroducing the residue into a new reaction. Comparable regioselectivity is observed.

Very good selectivity is also found with the internal aryl olefins β-methylstyrene and indene. The former case, we think, is particularly important because it demonstrates that the catalyst is truly selective for a position α to an aryl group and can therefore be employed in the synthesis of longer α-aryl aldehydes. Regioselective hydroformylation of β-methylstyrene has been examined by others, though the selectivity for α-hydroformylation was never greater than 88% of the aldehyde products.[30] Indene is also a little-studied substrate, though Consiglio and Nefkens reported >95% selectivity for the α-aldehyde using a platinum/tin catalyst.[31]

The bis(dioxaphospholane) catalyst system is, in comparison with other hydroformylation catalysts, unusually active given its high selectivity. We regularly performed preparative-scale reactions in 24 h with 5 g of 4-methylstyrene in a 450:1 substrate:Rh ratio to give 96% selectivity for branched aldehyde in quantitative isolated yield for use in the preparation of intermediates to α-cuparenone (vide infra). This corresponds to a turnover frequency of at least 23 turnovers h^{-1}. Partial conversion experiments with styrene (70 °C, 100 atm) show that a 60% conversion occurs in 2 h at a substrate:catalyst ratio of 10 000:1 (6 g:5 mg), corresponding to ca. 3000 turnovers h^{-1}. However, in these cases the selectivity decreases to 92:8 for the branched aldehyde 2-phenylpropanal.

These basic results are consistent with the hypothesis that the system rapidly catalyzes the hydroformylation of

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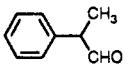
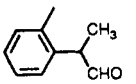
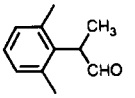
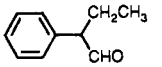
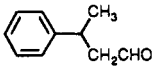
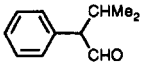
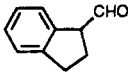
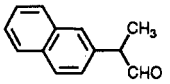
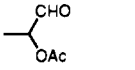
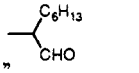
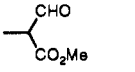
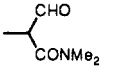
Table I. Hydroformylation with Precatalyst 1[a]

entry no.	substrate	pressure (atm) CO	pressure (atm) H_2	major aldehyde product (%)		notes
1	styrene	5	5		50	
2	"	12	12	"	75	
3	"	28	28	"	98	
4	"	50	50	"	97.5	
5	"	50	50	"	95	1743:1 styrene:Rh ratio
6	"	50	50	"	95	5454:1 styrene:Rh ratio
7	"	50	50	"	97.5	1 equiv of C_5H_5N/Rh added
8	"	50	50	"	92	10 000:1 styrene:Rh ratio; 60% conversion; 2 h; 3000 turnovers h^{-1}
9	"	50	50	"	91	4 equiv of extra ligands; 10 000:1 styrene:Rh ratio; 38% conversion; 3 h; 1267 turnovers h^{-1}
10	2-methylstyrene	50	50		97	
11	2,6-dimethylstyrene	50	50		97	
12	(*E*)-1-phenylpropene (β-methylstyrene)	24	24		75	
13	"	50	50	"	94	
14	2-phenylpropene (α-methylstyrene)	50	50		>99	50% conversion; <2.5 turnovers h^{-1}
15	2-methyl-1-phenylpropene (β,β-dimethylstyrene)	50	50		100	10% conversion; 0.3 turnovers h^{-1}
16	indene	50	50		93	
17	2-vinylnaphthalene	50	50		98	
18	vinyl acetate	50	50		>99	
19	1-heptene	24	24		55	
20	"	50	50	"	60	
21	methyl acrylate	50	50		>99	
22	dimethylacrylamide	50	59		>99	50% hydrogenated
23	methyl vinyl ketone	50	50	none		100% hydrogenated
24	(*E*)-cinnamic acid	50	50	none		100% hydrogenated

[a] All reactions were run with a substrate:catalyst ratio of 50:1 for 16 h while the reactor was immersed in a 70 °C oil bath. Complete conversion of substrate occurred except where noted. In cases where a substrate:catalyst ratio greater than 50 was used, the pressure was periodically returned to 1500 psi of total pressure by adding more synthesis gas.

aryl olefins with high (>90%) selectivity and that then the linear aldehyde either selectively decomposes or isomerizes[32] to give a higher percentage of the branched product. A control experiment shows that the catalyst probably does not isomerize the aldehyde, however. Addition of 3-phenylpropanal (a linear aldehyde) to a mixture for the hydroformylation of 2-vinylnaphthalene shows that, while the vinylnaphthalene is hydroformylated with the expected selectivity, no 2-phenylpropanal is formed. More important, GC analysis of the product distributions (with naphthalene as a nonvolatile internal standard) indicates that the change in selectivity with contact time results from loss of the linear aldehyde at a much higher rate than for branched aldehyde.

The origin of the selectivity in this and other systems can be ascribed to either an innate preference for a branched alkyl intermediate[33] or, as has been suggested,[34] an η^3-benzyl complex, as in **2a**. Such benzyl complexes are known with rhodium[35,36] or related[37] metals. However, an η^3-benzyl intermediate derived from 2,6-dimethylsty-

(32) There are unfortunately no experimental or calculational data that can be used to predict *K* for the 2-phenylpropanal = 3-phenylpropanal equilibrium. Note, however, that in alkyl aldehydes α-branching is more favored than in simple alkyls. The standard free enthalpy of the reaction *n*-butryaldehyde = isobutyraldehyde is −2.7 kcal mol^{-1}: Tjebbes, J. *Acta Chem. Scand.* **1962**, *16*, 953.

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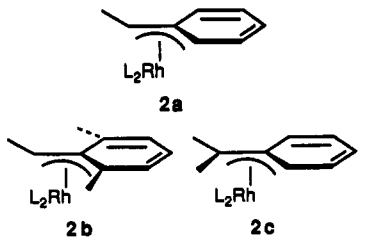


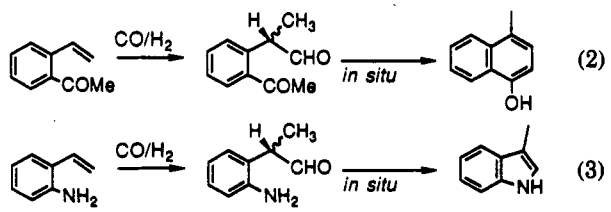
rene, **2b**, must have a methyl group *Z* with respect to the allylic system. The same would be true of the η^3-benzyl intermediate derived from α-methylstyrene, **2c**. Yet the selectivity for 2,6-dimethylstyrene is very similar to that for simple styrene while, as noted before, the selectivity for α-methylstyrene is completely opposite that for all other aryl olefins we studied. The best explanation for these trends is steric crowding in a simple alkyl intermediate, and we conclude that the η^3-benzyl intermediate is not important in this system.[38]

The cationic bis(dioxaphospholane)rhodium compound **1** is also an effective precursor for the hydroformylation of alkyl olefins, though it is not nearly as active as well-known neutral compounds. The selectivity, at sufficiently high pressures, is slightly for the branched aldehyde. With an internal alkyl olefin, 2-heptene, only two aldehydes are formed. Neither of them is 1-octanal, strongly suggesting that the catalyst does not catalyze olefin isomerization prior to aldehyde production. (A similar inference can be made from the results with β-methylstyrene, which only gives internal olefins.) The catalytic reaction is also kinetically faster for the terminal olefin; in experiments at partial conversion, only 1-heptene is consumed in competition with 2-heptene. These results are similar to those obtained by Pittman and Hirao using triarylphosphine-modified homogeneous and heterogeneous catalysts.[40]

No hydrogenation is observed for any hydrocarbon substrate, but the chemoselectivity is compromised when there is a carbonyl group α to the olefin. Methyl acrylate undergoes hydroformylation exclusively to just the branched product, as is known in other systems.[41] Dimethylacylamide yields equal amounts of hydroformylation and hydrogenation products, and the aldehyde that is formed is, apparently, only the branched isomer. Methyl vinyl ketone shows no hydroformylation at all, again in keeping with the results in the literature.[42]

Application of Regioselective Hydroformylation to the Synthesis of Organic Intermediates. The importance of regioselective hydroformylation in organic synthesis has been recognized for some time.[4] It has the potential to form important intermediates with extensive branching α to an aryl or a keto group. Understandably, there is emphasis on the problem of asymmetric hydroformylation,[10] but there are a great number of applications of branched aldehydes where it is not important to have the aldehyde as a single enantiomer. There are two reasons for this. First, several reactions are selective for one or another branched aldehyde enantiomer.[44] Second, the aldehyde in many cases is converted into an achiral enol or enolate. Two examples of this latter case are shown here, resulting in annulation of the aldehyde group with an ortho-disposed nucleophile and alkylation of the α-position to give a quaternary carbon.

The insensitivity of the catalyst to ortho substituents (as with 2,6-dimethylstyrene) means that the 2-arylpropanal group can be generated in the presence of groups that will react in situ to give a further product. The hydroformylation of 2-vinylacetophenone to give 4-methyl-1-naphthol is one such case (eq 2). This hydroformylation/



cyclization reaction is reminiscent of the chelation-controlled amide-directed hydroformylation of butenamides and related substrates by Ojima and co-workers,[45] though of course our reaction probably does not rely on chelation control with the acetyl group. In practice, the yields of the naphthol are poor, we believe because of competing oligomerization reactions. Much better results, including near-quantitative yields, are obtained in the synthesis of 3-methylindole from *o*-vinylaniline (eq 3).

We are aware of only one report of direct synthesis of an indole through hydroformylation/cyclization in a one-pot reaction.[46] Ucciani and Bonfand showed that *o*-nitrostyrene is a good substrate for regioselective hydroformylation using simple catalyst precursors and that the product aldehyde could be chemically reduced to an indole.[47] The lack of similar work from others is remarkable, given the importance of the indole group in natural product and pharmaceutical synthesis and the known utility of transition-metal reagents in the synthesis and functionalization of indoles.[48] In another report, Ojima and co-workers reported the use of a branched aldehyde, formed by hydroformylation of pentafluorostyrene, in the synthesis of a tetrafluoroindole through *subsequent* conversion of the aldehyde to an aldimine, lithiation, and intramolecular nucleophilic aromatic substitution.[49]

(35) (a) Werner, H.; Feser, R. *J. Organomet. Chem.* **1982**, *232*, 351. (b) Stöhler, H.-O.; Pickardt, J. *Z. Naturforsch., B* **1981**, *36*, 315. (c) Stille, J. K.; Fries, R. W. *J. Am. Chem. Soc.* **1974**, *96*, 1514. (d) Clement, D. A.; Nixon, J. F.; Poland, J. S. *J. Organomet. Chem.* **1974**, *76*, 117.

(36) Slough, G. A.; Bergman, R. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1989**, *111*, 938.

(37) Crascall, L. E.; Litster, S. A.; Redhouse, A. D.; Spencer, J. L. *J. Organomet. Chem.* **1990**, *394*, C35.

(38) This is the first experiment, to our knowledge, to test for an η^3-benzyl intermediate. Such intermediates, may, of course, be present in other catalytic systems, and we note in particular the close connection between the η^3-benzyl complexes synthesized by Spencer and co-workers[37] and the hydroformylation conditions employed by Botteghi and Paganelli.[39]

(39) Botteghi, C.; Paganelli, S. *J. Organomet. Chem.* **1991**, *417*, C41.

(40) Pittman, C. U., Jr.; Hirao, A. *J. Org. Chem.* **1978**, *43*, 640.

(41) For a leading reference, see: Consiglio, G.; Kollár, L.; Kölliker, R. *J. Organomet. Chem.* **1990**, *396*, 375.

(42) (a) Goetz, R. W.; Orchin, M. *J. Am. Chem. Soc.* **1963**, *85*, 2782. (b) Murata, K.; Matsuda, A.; Masuda, T. *J. Mol. Catal.* **1984**, *23*, 121. This included a careful examination of the NMR spectrum for any enol derivatives that might form.[43]

(43) Noi, R. S.; Ershov., B. A.; Kol'tsov, A. I. *Zh. Org. Khim.* **1973**, *9*, 426.

(44) For examples, see: (a) Niwa, S.; Hatanaka, T.; Soai, K. *J. Chem. Soc., Perkin Trans.* **1991**, 2025. (b) Hayashi, M.; Miwata, H.; Oguni, N. *Chem. Lett.* **1989**, 1969. (c) Marron, B. E.; Schlicksupp, L.; Natale, N. R. *J. Heterocycl. Chem.* **1988**, *25*, 1067. (d) Tomo, Y.; Yamamoto, K. *Tetrahedron Lett.* **1985**, *26*, 1061.

(45) Ojima, I.; Korda, A.; Shay, W. R. *J. Org. Chem.* **1991**, *56*, 2024.

(46) A recent report describes the palladium-catalyzed reaction of *o*-nitrostyrenes to give indoles using CO as a simple oxygen atom acceptor: Akazome, M.; Kondo, T.; Watanabe, Y. *Chem. Lett.* **1992**, 769.

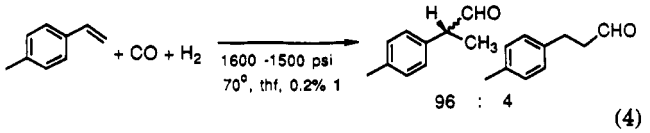
(47) Ucciani, E.; Bonfand, A. *J. Chem. Soc., Chem. Commun.* **1981**, 82.

(48) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113.

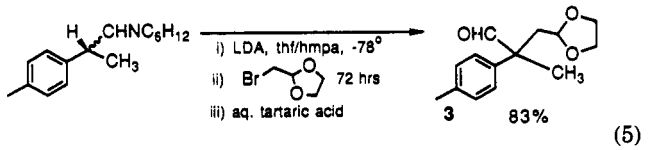
(49) Ojima, I.; Kato, K.; Nakahashi, K.; Fuchikami, T.; Fujita, M. *J. Org. Chem.* **1989**, *54*, 4511.

A branched α-aryl aldehyde can also serve as the locus for the generation of benzylic quaternary carbon centers, if the precursor can be obtained efficiently and the benzylic position is reactive enough with the available electrophiles. An example of this is the synthesis of a quaternary precursor to α-cuparenone.

A preparative-scale reaction with 4-methylstyrene utilizing a 500:1 substrate:catalyst ratio gives a 96:4 ratio of branched to linear product (eq 4) in quantitative isolated yield.[50] The alkylation of this aldehyde by a butyllithium/



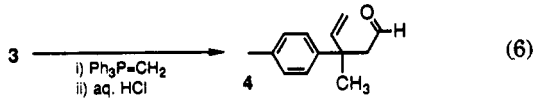
(4)



(5)

allyl bromide combination proceeds smoothly. However, less reactive electrophiles, such as α-haloacetals, fail to alkylate the intermediate enolate in useful yields. Therefore, the aldehyde was converted to the corresponding cyclohexylaldimine.[51] Lithiation of this compound and alkylation with 2-(bromomethyl)-1,3-dioxolane (eq 5) gives the aldehyde acetal **3** in quantitative yield.

The acetal aldehyde **3** functions as a selectively protected 1,4-dialdehyde.[52] Conversion of the free aldehyde into an olefin by a Wittig reaction followed in one pot by hydrolysis gives the olefin aldehyde **4** (eq 6). Kametani et al. showed that this compound can be converted into α-cuparenone in five steps.[53]



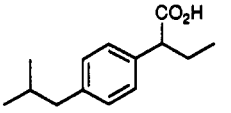
(6)

Discussion

Our results, and others in the literature, permit us to make several inferences as to the factors important in regioselective hydroformylation. First, the paradigm that the stability of the alkyl intermediate is most important in selectivity is strengthened by our control experiments to rule out an η^3-benzyl intermediate. Second, cationic catalyst precursors are very promising in regioselective hydroformylation, perhaps because they accentuate the polarization of the metal–alkyl bond to make the presence of a electron-withdrawing phenyl group at the α-position more important.[54] Third, the effect of phosphite-type ligands, amply documented for alkyl olefins and vinyl ethers by other groups,[8,15–24] holds true here, perhaps for the same reasons of increased polarization of the metal–alkyl bond. Finally, we cannot with our results evaluate the importance of a relatively large chelate ring on efficiency or selectivity, but certainly the ligand we employ is compatible with a large variety of metal geometries.[55]

The observed changes in selectivity lead to another particularly important point. Control experiments (potassium carbonate, room temperature, overnight) confirm literature results[56] that the linear aldehyde, 3-phenylpropanal, is very susceptible to base-catalyzed decomposition. This provides a plausible explanation for cases where the product ratio in a hydroformylation reaction changes with time, at least within the accuracy of either NMR or GC integrals. Also, we feel it provides an important caveat for other workers to observe when interpreting their results, especially under conditions that may catalyze the enolization of aldehydes.

Finally, these results include additional examples of the utility of hydroformylation in synthesis. Note that these results will presumably carry over to internal aryl olefins also. There is a well-recognized connection between the 2-arylpropanals made by hydroformylation of styrene derivatives and the 2-arylpropanoic acid class of nonsteroidal antiinflammatory drugs.[57] However, longer chains may be important also, as in the case of butibufen (**5**),[58] which is the butanoic acid related to ibuprofen. Access to these, though, will require catalyst precursors, such as **1**, that are effective with β-methylstyrene, not just styrene.



5

Experimental Section

General Considerations. All solvents for hydroformylation and organic synthetic reactions were dried over appropriate drying agents and distilled under nitrogen before use. Cyclohexylamine (Fisher), (*E*)-1-phenylpropene (Pflalz and Bauer), indene (ICN Phamaceuticals), and 2,6-dimethylstyrene (Chem Service Co.) were used as supplied. Synthesis gas (1:1 $CO:H_2$) was obtained from Linde and used as supplied. Methyl acrylate, dimethylacrylamide, methyl vinyl ketone, (*E*)-cinnamic acid, vinyl acetate, 1-heptene, 2-heptene, 2-phenylpropene, 2-vinylnaphthalene, 4-methylstyrene, 2-(bromomethyl)-1,3-dioxolane, *n*-butyllithium (1.6 M in hexanes), and silica gel (230–400 mesh) were all obtained from Aldrich and used as supplied.

The rhodium catalyst precursor was prepared as previously described,[2] and it was handled under an inert atmosphere with standard Schlenk or glovebox techniques prior to use. The inhibitor in styrene poisons the catalyst. Therefore, styrene (Fisher) was purified by stirring over 10% NaOH for 24 h and then dried with $MgSO_4$ prior to distillation from CaH_2. It was

(50) This aldehyde itself is an intermediate in a different synthesis of racemic α-cuparenone: Wenkert, E.; Buckwalter, B. L.; Craveiro, A. A.; Sanchez, E. L.; Sathe, S. S. *J. Am. Chem. Soc.* **1978**, *100*, 1267.

(51) Furniss, B. S.; Hannaford, A. J.; Smith, A. R.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific Technical: Essex, U.K., 1989; pp 782–783.

(52) Le Bourgne, J. F.; Cuvigny, Th.; Larchevêque, M.; Normant, H. *Tetrahedron Lett.* **1976**, *17*, 1379.

(53) Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *Chem. Pharm. Bull.* **1985**, *33*, 4821.

(54) We are well aware that a cationic catalyst precursor may convert to a neutral catalyst by deprotonation of a cationic hydride intermediate. However, we note that the formulation we usually employ (THF solvent, BF_4^- counterion) seems incompatible with deprotonation and added base does not improve the reaction.

(55) The importance of a long, flexible backbone in hydroformylation has been discussed in detail in several papers: (a) Alper, H.; Zhou, J.-Q. *J. Org. Chem.* **1992**, *57*, 3729. (b) Casey, C. P.; Whiteker, G. T. *Isr. J. Chem.* **1990**, *30*, 299. (c) Casey, C. P.; Whiteker, G. T. *J. Org. Chem.* **1990**, *55*, 1394. (d) Miyazawa, M.; Momose, S.; Yamamoto, K. *Synlett* **1990**, *1*, 711.

(56) (a) Cerveau, G.; Chuit, C.; Corriu, R. J. P.; Reye, C. *J. Organomet. Chem.* **1987**, *328*, C17. (b) Chuit, C.; Corriu, R. J. P.; Reye, C. *Synthesis* **1983**, 294.

(57) (a) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kukanni, D. G. *Tetrahedron: Asymmetry* **1992**, *4*, 163. (b) Todd, P. A.; Clissold, S. P. *Drugs* **1990**, *40*, 91. (c) Brune, K.; Lanz, R. In *The Pharmacology of Inflammation*; Bonta, I. L., Bray, M. A., Parnham, M. J., Eds.; Elsevier: Amsterdam, 1985; Chapter 21. (d) Brogden, R. N. *Drugs* **1986**, *32* (Suppl. 4), 27.

(58) Castell, J. V.; Larrauri, A.; Gómez-Lechón, M. J. *Xenobiotica* **1988**, *18*, 737 and references therein.

stored in a freezer prior to use. 2-Vinylacetophenone was prepared by coupling 2-bromoacetophenone and tributylvinylstannane.[11]

Ratios of aldehyde products were typically obtained by accurate integration of the NMR spectrum in the region 9–10 ppm. Where information about mass recovery was also important, GC analysis was used to corroborate the NMR results. Naphthalene was added to the reactants before the hydroformylation reaction, as a nonvolatile, nonreactive internal standard.

Hydroformylation Procedure. A typical analytical-scale hydroformylation procedure was conducted as follows. In the glovebox 0.12 g (1.1 mmol) of styrene, 0.020 g of 1 (0.022 mmol), and 6 mL of THF were mixed thoroughly to generate a clear light orange solution, which was then poured into a glass sleeve containing a magnetic stirbar. The sleeve was inserted into the bomb (71 mL total volume, Parr), and the fittings were made hand-tight. The bomb was tightly sealed mechanically and then was charged with the appropriate pressure of synthesis gas. The bomb was placed in an oil bath heated to 70 °C. The reaction was conducted for 16 h with external stirring. At the conclusion of the reaction the bomb was removed from the oil bath and, after 15 min to reach room temperature, the excess synthesis gas was vented. The bomb was disassembled and the reaction mixture, after the removal of most of the THF by a stream of N_2 gas, was analyzed by ^1H NMR in $CDCl_3$. For reactions in which a significant drop in pressure might occur (i.e. with more than 5 mmol of substrate) the pressure was periodically increased to maintain a nearly constant value.

Partial Conversion Experiments. These were conducted to ascertain the rate of the catalytic reaction over a set period of time (the results do not take into account any initiation time). The substrate (styrene, 6.00 g, 58 mmol), complex 1 (5 mg, 0.0058 mmol), and solvent (THF, 9 mL) were combined, and the apparatus was set up as before. The total pressure was kept at 100–105 atm. Results were determined by NMR and GC analysis.

Preparative-Scale Hydroformylation of *o*-Vinylacetophenone. A solution of 2-vinylacetophenone (0.70 g, 4.8 mmol) and complex 1 (0.028 g, 0.032 mmol) in 10 mL of THF was placed in a glass liner in an autoclave. The system was charged with 100 atm of synthesis gas and externally heated to 70 °C for 16 h. The resulting deep red solution was treated with 30 mL of ether and extracted with two 20-mL portions of 10% aqueous NaOH. The aqueous layer was treated with concentrated HCl to make it acid. Then the aqueous layer was extracted with ether. The ether extracts were concentrated to give 0.38 g of spectroscopically pure 4-methylnaphthol (51%).

Preparative-Scale Hydroformylation of *o*-Vinylaniline. A solution of 2-vinylaniline (0.19 g, 1.6 mmol) and catalyst precursor 1 (24 mg, 0.027 mmol) in 7 mL of THF was placed in a glass liner in an autoclave. The system was charged with 100 atm of synthesis gas and externally heated to 70 °C for 16 h. The reaction mixture was cooled to room temperature, and excess synthesis gas was vented. The solution was removed from the autoclave, and the solvent was removed under vacuum to yield a red oil. This residue was redissolved in ether, and the solution was filtered through a bed of silica, which was washed with excess ether. The solvent was removed to give a quantitative yield (0.21 g) of spectroscopically pure 3-methylindole.

Preparative-Scale Hydroformylation of 4-Methylstyrene. A 71-mL Parr pressure bomb equipped with a glass liner and a stirbar was charged with 5.0 g (42.4 mmol) of 4-methylstyrene, 9 mL of THF, and 20 mg of 1. The system was pressurized with 110 atm of 1:1 CO/H_2 and then heated to 70 °C; the reaction mixture was stirred magnetically. More synthesis gas was added periodically to ensure that the pressure remained above 110 atm. A yield of 6.25 g of the aldehyde mixture (100%) was obtained after solvent was removed; only product was detected by ^1H NMR. The aldehyde was used directly in the next step.

Synthesis of Aldehyde Acetal 3, α-Methyl-α-(4-methylphenyl)-1,3-dioxolane-2-propanal. A mixture of the aldehydes was converted into the corresponding aldimines in 85% yield by reaction with neat cyclohexylamine and treatment with BaO, which removes any coloration due to traces of Rh metal complex. The aldimine (2.1 g, 9.0 mmol) and THF/HMPA (25 mL/3.0 g) were added to a suspension of LDA in THF in a bath at −70 °C. After 2 h, a solution of the bromodioxolane in THF (1.5 g/9.0 mmol/5 mL) was added. The solution was warmed to room temperature overnight and then was stirred for 72 h. Workup was accomplished by overnight treatment with 5% aqueous tartaric acid to give, after extraction and concentration, 2.2 g (83%) of spectroscopically pure acetal aldehyde **3**. Material for elemental analysis was prepared by column chromatography (SiO_2, 5:1 hexanes:acetone). Pertinent spectroscopic data: ^1H NMR (ppm relative to $CHCl_3$) 9.45 (s, C*H*O), 7.18 (4 H br, RC_6H_4R'), 4.78 (1 H, m, C*H*(OCH_2CH_2O)), 3.95, 3.77 (4 H, m, $CH(OCH_2CH_2O)$), 2.40–2.24 (2 H, m, CH_2), 2.34 (3 H, s, Ar–CH_3), 1.54 (3 H, s, α-CH_3); ^{13}C NMR (ppm) 200.9 (*C*HO), 136.9, 136.3 (ipso C), 129.5, 126.8 (*o*, *m* C), 102.1 ($CH(OCH_2CH_2O)$), 64.8, 64.4 (OCH_2CH_2O), 51.4 (quaternary C), 40.0 (CH_2), 20.8, 19.63 (CH_3's). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.75. Found (Galbraith): C, 71.77; H, 7.79.

Synthesis of Aldehyde 4, β-Ethenyl-β,4-dimethylbenzenepropanal. A solution of the acetal aldehyde (0.35 g, 1.9 mmol) in 5 mL of Et_2O was treated with a solution of the methylenetriphenylphosphorane, generated by deprotonation of methyltriphenylphosphonium bromide with *n*-BuLi, in 10 mL of ether. A white precipitate, presumably $Ph_3P{=}O$, appeared under a yellow solution. The reaction was continued overnight and then opened to air and quenched with 15 mL of 2.0 M HCl and 15 mL of THF. The homogeneous solution was stirred 2 h to complete hydrolysis of the acetal. The product was recovered by extraction with excess ether, drying, and evaporation of solvent to give a quantitative yield of Kametani's intermediate olefin aldehyde **4**,[54] as judged by NMR and mass spectroscopic studies.

Acknowledgment. We are very grateful to Professors Marc Walters and David Schuster of this department for the loan of high-pressure apparatus. Partial financial support came from Biomedical Research Support Grant RR07062, Division of Research Resources, National Institutes of Health, administered by the Research Challenge Fund of New York University, and through a loan of rhodium salts from Platina Laboratories.

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