Directing Abilities of Alcohol-Derived Functional Groups in the Hydroformylation of Olefins

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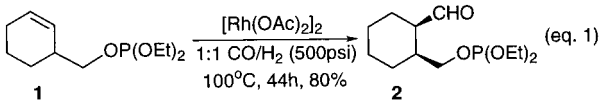
The hydroformylation of allylic and homoallylic alcohols and their derivatives using cationic and neutral rhodium complexes has been examined. The highest diastereoselectivity (87:13) was observed in the reaction of 1-methoxymethoxy-2-methylenecyclohexane. Higher yields and similar selectivities were obtained in the reaction of the TBDMS-protected alcohol. The major diastereomer results from hydroformylation syn to the functional group, which would suggest a directing effect. However, hydroformylation of 3-methylene-1-cyclohexanol derivatives occurs on the face opposite to the directing group in the major isomer. These data, in addition to the results of hydroformylation of 1-methyl-2-methylenecyclohexane, suggest that inherent conformational preferences are of significant importance in determining the product distribution and that the directing power of simple alcohols and their derivatives is moderate at best under the conditions examined in this study.

Introduction

Stereochemical control is a major concern in organic chemistry. In the subset of organic reactions catalyzed by transition-metal complexes, the hydrogenation of olefins stands out as the most remarkable, general example of stereocontrolled synthesis.[1] Using carefully designed catalysts, extremely high diastereo- and enantiofacial control can be achieved. In the wide majority of these cases, functionality in the substrate is used to direct the reduction.[1,2] In the case of enantioselective hydrogenations, chelation of the substrate via the olefin and a second functional group such as a hydroxyl, amido, ester, carboxylic acid, etc., is crucial to achieve high selectivity.[1,3] Similar functional groups have also been used successfully in *diastereoselective* hydrogenations.[2] In these cases, binding of the functional group is used to direct the reduction relative to existing stereochemistry in the substrate.

Our interest in stereocontrolled C−C bond-forming reactions prompted us to study the substrate-directed hydroformylation reaction. Contrary to the intensive investigation of methods for *enantioselective* hydroformylation,[4] diastereoselective hydroformylations using existing functionality in the substrate have been largely neglected.[5] This is presumably due to the necessary presence of CO in the reaction mixture, which is a particularly good ligand for late transition metals, and may hinder or even prevent the coordination of internal directing groups. Most approaches to directed hydroformylation reactions have, therefore, required the presence of strong catalyst directing groups such as phosphines or phosphites within the substrates. In 1986, Burke reported an intramolecular phosphine-directed hydroformylation that was used in the total synthesis of (+)-phyllanthocin.[6] Jackson has shown that phosphites are also very effective directing groups (eq 1).[7] The hydroformylation of **1** proceeds to give an 80% yield of a single stereo- and regioisomer out of four possible hydroformylation products.



More recently, Breit[8] showed that the phosphine-containing group, *o*-(PPh_2)C_6H_4CO−, can be used to control the stereochemistry of the hydroformylation in acyclic systems (eq 2). When a simple alcohol was employed (**3**, R = H), no diastereoselectivity was observed. However, when the phosphine-containing substrate was hydroformylated, the directed product (**4**) was obtained in a 92:8 ratio with the isomeric aldehyde **5**.

In terms of simple, non-phosphorus-containing directing groups, very few successful reports have appeared.

(1) (a) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH Publishers: New York, 1993. (b) Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; John Wiley & Sons: New York, 1994.

(2) Diastereoselective hydrogenations: (a) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. (b) Crabtree, R. *Acc. Chem. Res.* **1979**, *12*, 331. (c) Schultz, A. G.; McCloskey, P. J. *J. Org. Chem.* **1985**, *50*, 5905. (d) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348. (e) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190.

(3) For a remarkable exception in which simple trisubstituted styrene derivatives can be hydrogenated with very high enantioselectivity see: Blankenstein, J.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 4445 and references therein. See also: (b) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878.

(4) (a) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033. (b) Agbossou, F.; Carpentier, J. F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485. 54. (c) Francio, G.; Faraone, F.; Leitner, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 1428. (d) Breeden, S.; Hamilton-Cole, D. J.; Foster, D. F.; Schwarz, G. J.; Willis, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 4106.

(5) See however, the elegant work of Leighton et al. in the hydroformylation of enol ethers: (a) Sarraf, S. T.; Leighton, J. L. *Tetrahedron Lett.* **1998**, *39*, 6423. (b) Leighton, J. L.; O'Neil, D. N. *J. Am. Chem. Soc.* **1997**, *119*, 11118.

(6) Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237

(7) Jackson, W. R.; Perlmutter, P.; Tasdelen, E. E. *J. Chem. Soc., Chem. Commun.* **1990**, 763.

(8) (a) Breit, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2835. (b) Breit, B. *Chem. Commun.* **1997**, 591. (c) Breit, B. *Liebigs Ann./Rec.* **1997**, 1841.

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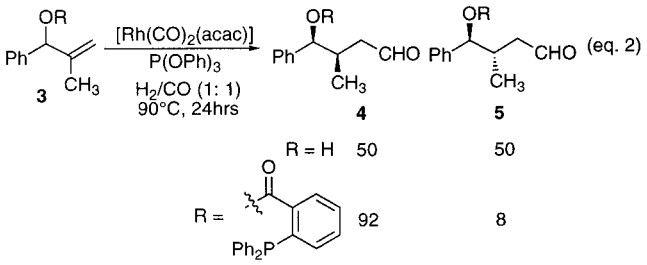
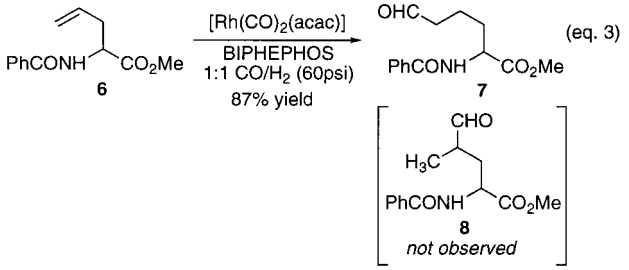


Ojima has shown that an amide can be used to direct the regioselectivity in hydroformylations of alicyclic alkenes (eq 3).[9] In this case, the directed product is the one that arises from placement of the aldehyde at the terminal carbon of the alkene (**7**), and the branched isomer **8** is not observed.[9b] Krafft has also shown that amines can be used as directing groups, although the hydroformylation requires stoichiometric amounts of Rh in this case.[9e] Finally, in an intriguing study, Yamamoto has postulated that stereoelectronic effects can be used to explain results obtained in the hydroformylation of axially substituted exocyclic olefins.[10]

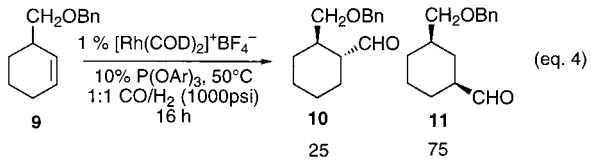


Somewhat surprisingly, the use of cationic catalysts in directed hydroformylations has not been reported, even though cationic Rh and Ir catalysts are known to be the most effective catalysts in directed hydrogenation studies.[2,11] High diastereoselectivity was also observed in directed hydroborations using cationic complexes.[12] The positive charge on Rh should increase its Lewis acidity and decrease its ability to back-bond to carbon monoxide, which may mean that internal directing groups can bind more effectively to Rh. Thus, it is conceivable that cationic catalysts would more effectively control the regioselectivity and stereoselectivity of the hydroformylation reaction using commonplace functional groups such as alcohols and their derivatives.

Results and Discussion

The first system that we chose to study was the benzyl-protected allylic alcohol **9**, which is a non-phosphorus-containing analogue of Jackson's substrate **1**.[13] Four possible aldehydes could be produced, resulting from hydroformylation proximal or distal and syn or anti to the CH_2OBn group. Of these four possible isomers, **10** and **11** were the major products, accounting for 70−90% of the aldehydes produced.[14]

Aldehydes **10** and **11** were usually observed in approximately equal amounts, except when the catalyst was modified by an extremely bulky phosphite ligand, tris-(2,4-di-*tert*-butylphenyl) phosphite.[15] In this case, a 25:75 ratio of **10** to **11** was observed (eq 4). To avoid complications due to the low regiocontrol of the hydroformylation of **9**, we turned our attention to the 1,1-disubstituted alkene **12**.



As expected by Keulemans' rule,[16] the hydroformylation of **12a**−**h** gives only the primary aldehyde in all cases. The cationic catalyst ($[Rh(COD)_2]^+BF_4^-$) is more reactive than $[Rh(COD)Cl]_2$. Under identical conditions ($CO/H_2 = 500:500$, room temperature, 20 h), the conversion of **12a** to **13a** was 94% using $[Rh(COD)_2]^+BF_4^-$ and 61% using $[Rh(COD)Cl]_2$ (see Table 1). Similarly, the pivaloyl derivative **12b** gave 100% conversion after 47 h in the presence of the cationic catalyst, compared with only 40% conversion after 43 h using $[Rh(COD)Cl]_2$. The non-chlorine-containing neutral catalyst $[Rh(CO)_2(acac)]$ gave 100% conversion after 47 h.[17] Interestingly, all three complexes gave approximately the same selectivities (70:30 in favor of the trans product). The addition of phosphites did not change the diastereoselectivity. Increasing the reaction temperature to 50 °C gave a slightly lower diastereoselectivity, and changing the H_2/CO pressure from 1:1 to 3:1 or 1:3 had little effect.

Acetyl, pivaloyl,[17] and benzyl derivatives **12a**−**c** reacted with only moderate selectivity for the trans isomer, but significantly better selectivities were obtained with the MOM-protected alcohol **12d** (87:13).[18] Although these results could be explained by the ability of the MOM protecting group to bind to Rh in a bidentate fashion, enhancing its effectiveness as a directing group, several of the data in Table 1 are inconsistent with this interpretation. The MEM-protected alcohol **12e** reacts with lower selectivity, and the TBS derivative (**12f**) was almost as selective as the MOM substrate, despite the fact that

(9) (a) Ojima, I.; Korda, A.; Shay, W. R. *J. Org. Chem.* **1991**, *56*, 2024. (b) Ojima, I.; Tzamarioudaki, M.; Eguchi, M. *J. Org. Chem.* **1995**, *60*, 7078. (c) Ojima, I.; Vidal, E. *J. Org. Chem.* **1998**, *63*, 7999. (d) Ojima, I.; Iula, D. M.; Tzamarioudaki, M. *Tetrahedron Lett.* **1998**, *39*, 4599. (e) Krafft, M. *Tetrahedron Lett.* **1989**, *30*, 539.

(10) Doi, T.; Komatsu, H.; Yamamoto, K. *Tetrahedron Lett.* **1996**, *37*, 6877.

(11) (a) Evans, D. A.; Morrissey, M. M.; Dow. R. L. *Tetrahedron Lett.* **1985**, *26*, 6005. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(12) (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671. (b) For an alternative strategy in which coordinative unsaturation is achieved by indenyl ring slippage see: Brinkman, J. A.; Nguyen, T. T.; Sowa, J. R., Jr. *Org. Lett.* **2000**, *2*, 981.

(13) The hydroformylation of the parent alcohol was first attempted, but only decomposition was observed.

(14) The two major diastereomers (**10-*trans*** and **11-*cis***) could be identified, but the minor isomers could not be isolated. Because of this, we are not currently able to determine the exact diastereoselectivity for the proximal and distal hydroformylation.

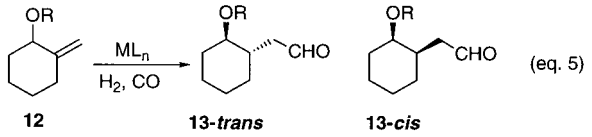
(15) van Leeuwen, P. W. N. M.; Roobeek, L. F. *J. Organomet. Chem.* **1987**, *40*, 129.

(16) (a) Keulemans, A. J. M.; Kwantes, A.; Van Bavel, T. *Rec. Trav. Chim. Pays-Bas.* **1948**, *67*, 298. (b) Lazzaroni, R.; Settambolo, R.; Uccello-Barretta, G.; Caiazzo, A.; Scamuzzi, S. *J. Mol. Catal. A: Chem.* **1999**, *143*, 123.

(17) Our results with pivaloyl derivative **12b** are similar to those obtained with *cis*-2-acyloxyl-4-^{t}Bu-methylenecyclohexane studied by Yamamoto.

(18) In this case, and in the case of MEM derivative **12e**, the diastereomeric aldehydes decomposed rapidly and at different rates, so it was necessary to run the reaction to low conversion in order to obtain an accurate assessment of the diastereoselectivity. For all other aldehydes, the dr was the same at various conversions.

Table 1. Diastereoselectivity in the Hydroformylation of 12[a]



12 **13-*trans*** **13-*cis***

substrate	R	catalyst	convn[b] (%)	yield[c] (%)	trans/cis
12a	Ac	$[Rh(COD)_2]^+BF_4^-$	94	62	63:37
12a	Ac	$[Rh(COD)Cl]_2$	61	40	63:37
12b	Piv	$[Rh(COD)_2]^+BF_4^-$	100	100	70:30
12b	Piv	$[Rh(COD)Cl]_2$	40	38	70:30
12b	Piv	$[Rh(CO)_2(acac)]$	100	100	70:30
12c	Bn	$[Rh(COD)_2]^+BF_4^-$	100	85	69:31
12c	Bn	$[Rh(COD)Cl]_2$	100	100	67:33
12d	MOM	$[Rh(COD)_2]^+BF_4^-$	32[d]	26	87:13
12d	MOM	$[Rh(COD)Cl]_2$	46[d]	29	85:15
12e	MEM	$[Rh(COD)_2]^+BF_4^-$	42[d]	41	73:27
12e	MEM	$[Rh(COD)Cl]_2$	15[d]	15	68:32
12f	TBS	$[Rh(COD)_2]^+BF_4^-$	100	84[e]	80:20
12f	TBS	$[Rh(COD)Cl]_2$	100	81	80:20
12g	TIPS	$[Rh(COD)_2]^+BF_4^-$	100	80	71:29
12g	TIPS	$[Rh(COD)Cl]_2$	92	87	71:29
12h	H	$[Rh(CO)_2(acac)]$	100	96	48:52[f]

[a] Reaction conditions: 500 psi H_2, 500 psi CO, room temperature, 0.2 M in benzene (dry and distilled), reaction time ca. 20−60 h, except for compounds **12c** and **12g**, which required 90−100 h (see the Experimental Section). [b] Conversion, determined by NMR analysis of the crude reaction mixture. [c] NMR yield. [d] Reactions with the MOM and MEM substrates were run to lower conversion ($t = 6-24$ h) since the aldehyde products were sensitive to decomposition. For other substrates there is no change in diastereoselectivity at lower conversion. [e] Isolated yield after silica gel chromatography. [f] Determined by oxidation to the known lactones.[20]

silicon is usually considered to decrease the coordinating ability of oxygen atoms to which it is attached.[19] Furthermore, virtually identical diastereoselectivities were observed for the cationic and neutral catalysts.

Unprotected alcohol **12h** was also examined. Although only decomposition products were observed when $[Rh(COD)Cl]_2$ or $[Rh(COD)_2]^+BF_4^-$ was used as the catalyst, $[Rh(CO)_2(acac)]$ did catalyze the hydroformylation leading to the corresponding hemiketals in a 52:48 ratio, determined after oxidation to the corresponding lactones.[20]

Thus, in all cases except for R = H, the major aldehyde isomer was the 1,2-trans product, as determined by spectroscopic and chemical means. Coupling constants typical of adjacent diaxial protons (≥10 Hz) were observed for the protons on the two substituted positions of the cyclohexane ring. NOE difference experiments also supported the assignment of trans stereochemistry to the major isomer. Finally, **13f-*trans***, the major product from hydroformylation of **12f**, was converted to the corresponding acid, followed by deprotection and cyclization to give a product whose spectral characteristics were identical to the known[20] trans lactone **15** (Scheme 1).

With the assignment of stereochemistry confirmed and reaction conditions optimized, we examined the substrate that gave the best results in Brown's directed hydrogenation studies, 3-methylenecyclohexanol (**16c**).[21] In the

Scheme 1

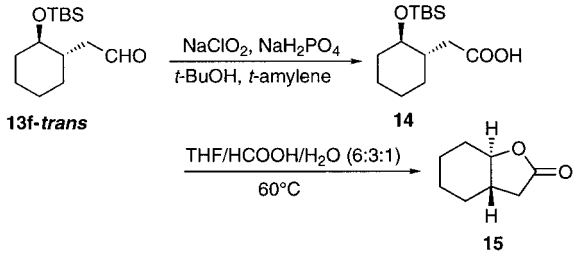
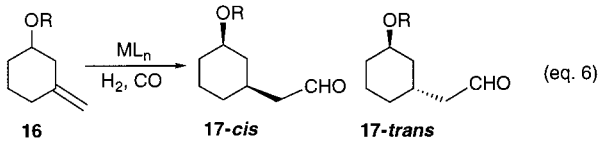


Table 2. Diastereoselectivity in the Hydroformylation of 16[a]



16 **17-*cis*** **17-*trans***

substrate	R	catalyst	convn[b] (%)	yield[c] (%)	trans/cis
16a	TBS	$[Rh(COD)_2]^+BF_4^-$	100	100	33:67
16a	TBS	$[Rh(COD)Cl]_2$	100	81	32:68
16b	MOM	$[Rh(COD)_2]^+BF_4^-$	100[d]	92[e]	40:60
16b	MOM	$[Rh(COD)_2]^+BF_4^-$ + DPPB (1:1)	22[d]	22	45:55
16b	MOM	$[Rh(COD)Cl]_2$	100[d]	70	42:58
16c	H	$[Rh(CO)_2(acac)]$	100[f]	96	42:58

[a] Reaction conditions: 500 psi H_2, 500 psi CO, room temperature, 0.2 M in benzene (dry and distilled), reaction time ca. 48−64 h (see the Experimental Section). [b] Conversion, determined by NMR analysis of the crude reaction mixture. [c] NMR yield. [d] Note that for this substrate, the MOM-protected derivative does not decompose so reactions can be run to 100% conversion. [e] Isolated yield after reduced pressure distillation. [f] Reaction was carried out at 80 °C for 24 h.

presence of cationic rhodium complexes, the *hydrogenation* of **16c** proceeded with >95% selectivity, favoring the trans isomer.[21] Subjection of **16a** and **b** to CO/H_2 in the presence of cationic or neutral catalysts gave a mixture of **17-*cis*** and **-*trans***, in which the cis isomer predominated (Table 2, eq 6).

Although the selectivity was moderate, the major isomer observed was the cis isomer, which would NOT be expected based on a directed reaction. Again, no significant selectivity difference was observed between the hydroformylation of the MOM and TBS protected derivatives or between the cationic and neutral catalysts. The addition of DPPB[22] to the cationic catalyst greatly decreased its reactivity (22% conversion after 48 h) compared with the unmodified cationic catalyst (100% conversion after 40 h) but no improvement in selectivity was observed. Again the presence of a free hydroxyl group interfered with the hydroformylation using $[Rh(COD)Cl]_2$ or $[Rh(COD)_2]^+BF_4^-$ as the catalysts, but $[Rh(CO)_2(acac)]$ was able to catalyze the hydroformylation of **16c** when the reaction was run at 80 °C. No reaction was observed at lower temperatures. The diastereoselectivity in this case was the same as that observed for the MOM-protected substrate **16b** with $[Rh(COD)Cl]_2$.

With the inclusion of the results for substrate **16**, a unified picture of the controlling elements in the hydroformylation of **9**, **12**, and **16** began to coalesce. With all three substrates, the major products observed were those

(19) Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 697. Although note that McKittrick and Ganem reported that OTBS groups can direct the epoxidation when trifluoroacetic acid was used. McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4895.

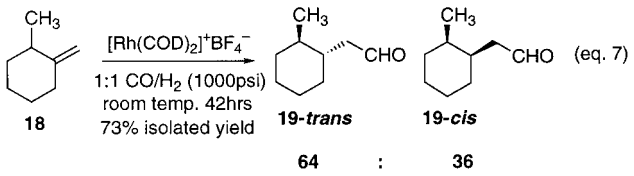
(20) (a) Brunner, M.; Alper, H. *J. Org. Chem.* **1997**, *62*, 7565. (b) Herz, W.; Glick, L. A. *J. Org. Chem.* **1963**, *28*, 2970.

(21) Brown, J. M.; Hall, S. A. *Tetrahedron Lett.* **1984**, *25*, 1393.

(22) DPPB (1,4-bis(diphenylphosphino)butane) complexes with cationic Rh provided the best selectivity in Brown's system.

that had both substituents in equatorial positions on the cyclohexane ring. To determine whether the overall reaction was reversible,[23] a mixture of the cis and trans diastereomers of **13f** enriched in the ***minor*** *cis* product (64% cis) was resubjected to the reaction conditions. The aldehydes were then reisolated from the reaction mixture and the cis/trans ratio was determined to be unchanged. No enrichment in the major, trans isomer was observed. This ruled out the possibility that the overall reaction was reversible, but the observed product mixture could still be governed by a reversible metal hydride addition to the olefin or by an irreversible metal hydride addition with a product-like transition state. [24]

As a final test of the directing abilities of allylic substituents in methylenecyclohexyl substrates, compound **18** was prepared. By replacing the oxygen substituent with a methyl group, we can be assured that any selectivity observed is not due to directing effects. Hydroformylation of **18** led to a 64:36 mixture of aldehydes favoring the trans isomer (eq 7).[25] Since the selectivities obtained are similar to those obtained using allylic alcohol derivatives **12a**−**g**, it is likely that, under the conditions we have examined, the directing abilities of simple protected alcohols are modest at best.



In conclusion, we have demonstrated that exocyclic allylic alcohol derivatives such as **12** undergo a diastereoselective hydroformylation reaction, yielding the trans aldehyde in up to 87:13 selectivity. Higher yields and similar selectivities are obtained in the reaction of the TBDMS protected alcohol. The results obtained with the 1,3-substituted system suggest that the reaction proceeds either by a reversible metal hydride addition or by an irreversible metal hydride addition with a late transition state. Studies are underway to determine the mechanism of the hydroformylation of these substrates and to examine the hydroformylation of systems without inherent conformational preferences. These results will be reported in due course.

Experimental Section

General Procedures. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Unity 400 MHz Varian NMR spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Infrared spectra were obtained as thin films on NaCl disks. High-resolution mass spectra were recorded on a double-focusing mass spectrometer with 8 kV accelerating and 70 eV ionizing voltages. Column chromatography was carried out with flash grade silica gel (230−400 mesh) using Still's method.[30]

Benzene was dried over sodium metal and distilled under a nitrogen atmosphere. $Rh(COD)_2BF_4$[31] and $[Rh(COD)Cl]_2$[32] were synthesized according to the literature.

General Procedure for Hydroformylation. In an oven-dried liner, 122 mg of 2-methylene-1-benzylcyclohexanol (**12c**) (0.6 mmol and 3.7 mg of $[Rh(COD)Cl]_2$ (0.0075 mmol, 1.2 mol %) were dissolved in 3.0 mL of benzene (dried over Na). An additional 5.0 mL of benzene was added between the liner and the steel autoclave. The gauge and gauge block assembly were attached, and the system was pressurized with 500 psi H_2 and 500 psi CO and then stirred at room temperature for 108 h. The solvent was evaporated, and an internal NMR standard (*p*-nitrotoluene) was added to measure the conversion (100%) and NMR yield (100%). The diastereoselectivity was determined to be 33:67 in favor of the trans isomer by analyzing the crude mixture using 400 ^{1}H NMR. The cis and trans isomers could be separated by careful column chromatography eluting with 30:1 hexane/EtOAc. They were independently characterized as the aldehyde or, in some cases, as the more stable acid derivatives after oxidation as described below. Isolation of the aldehydes as a mixture of diastereomers could be accomplished in most cases by Kugelrohr distillation at reduced pressure.

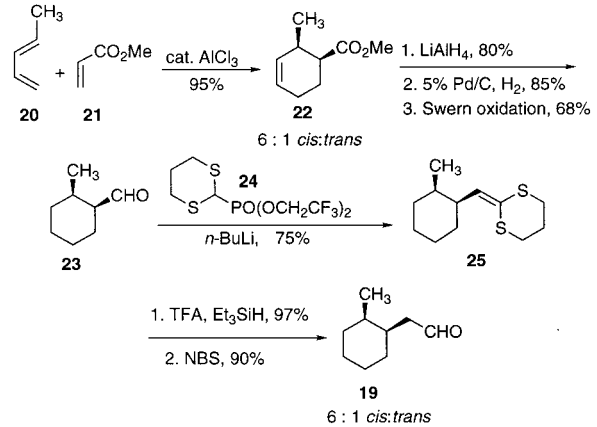
General Procedure for Oxidation. In a 100 mL round-bottomed flask was dissolved 151 mg of *trans*-(2-benzyloxy)-cyclohexylacetaldehyde (**13c-*trans***) (0.65 mmol) in 10 mL of *t*-BuOH. A 3.43 mL portion of *tert*-amylene was added. A solution of 0.58 g of $NaClO_2$ and 0.95 g of KH_2PO_4 in 5.84 mL of water was added slowly. The reaction mixture was left at room temperature overnight. The solvent was removed in vacuo, and the residue was quenched with 10 mL of water. The aqueous layer was extracted three times with ether, and the combined organic layers were dried over $MgSO_4$. Filtration and removal of the volatiles in vacuo gave the crude acid. The pure acid can be obtained by column chromatography, eluting with 4:1 hexane/EtOAc

***cis*-(2-Benzyloxy)cyclohexylacetaldehyde (13c-*cis*):** IR (neat) 1720 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 9.75 (t, J = 2.0 Hz, 1H), 7.38−7.28 (m, 5H), 4.59 (d, J = 12.0 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 3.56 (dt, J = 2.8, 5.6 Hz, 1H), 2.65 (ddd, J = 2.0, 6.4, 16.8 Hz, 1H), 2.39 (ddd, J = 2.0, 6.4, 16.8 Hz, 1H), 2.28−2.24 (m, 1H), 1.94−1.90 (m, 1H), 1.66−1.56 (m, 3H), 1.50−1.34 (m, 4H); ^{13}C {^{1}H} NMR (100 MHz) ($CDCl_3$) δ 202.84,

(23) Brookhart has demonstrated that *n*-butyraldehyde and *iso*-butyraldehyde can be interconverted by a cobalt catalyst: Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965.

(24) Garland postulates that hydrogenolysis of the metal acyl complex is rate determining when $Rh_4(CO)_{12}$ is used. (a) Garland, M.; Feng, J. *Organometallics* **1999**, *18*, 417. (b) Garland, M.; Pino, P. *Organometallics* **1991**, *10*, 1693. On the other hand, Casey has shown that the metal hydride addition is rate determining when bis phosphine Rh complexes are used for the hydroformylation of 1-hexene: Casey, C. P.; Petrovich, L. M. *J. Am. Chem. Soc.* **1995**, *117*, 6007. Studies are currently underway to determine the mechanism under our conditions.

(25) To confirm the stereochemistry of the observed product, the following synthetic scheme was carried out. An endo selective Diels−Alder reaction was performed to produce **22**. This reaction is known to provide the cis isomer as the major product.[26] Reduction of the ester and then the alkene, followed by oxidation of the primary alcohol generated aldehyde **23**. Treatment of this aldehyde with the lithium anion of dithiane-substituted phosphonate **24**, a reagent designed to prevent deprotonation of sensitive aldehydes, yielded **25**.[27] Compound **25** was deprotected[28,29] to reveal aldehyde **19**, as a 6/1 cis/trans mixture. Comparison of the spectral data of this material with that of the aldehyde produced by hydroformylation indicated that the major product in the hydroformylation was the trans isomer.



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138.95, 128.29, 127.53, 127.40, 76.28, 70.10, 45.95, 35.49, 28.09, 27.66, 24.29, 21.06.

The aldehyde is not stable enough to be characterized by elemental analysis or HRMS. The analysis was carried out on the corresponding acid. ***cis*-(2-Benzyloxy)cyclohexylacetic acid:** IR (neat) 3030, 1700 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 10.62 (brs, 1H), 7.35−7.27 (m, 5H), 4.60 (d, J = 12.0 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 3.62 (dt, J = 2.8, 5.6 Hz, 1H), 2.59 (dd, J = 7.2, 16.0 Hz, 1H), 2.33 (dd, J = 6.8, 15.6 Hz, 1H), 2.16−2.06 (m, 1H), 1.98−1.88 (m, 1H), 1.66−1.30 (m, 7H); ^{13}C {^1H} NMR (100-MHz) ($CDCl_3$) δ 177.85, 138.76, 128.31, 127.58, 127.45, 76.22, 70.21, 37.35, 36.32, 28.04, 27.39, 24.35, 20.85; HRMS (EI, 70 eV) calcd for M^+ 248.1412, found 248.1393.

***trans*-(2-Benzyloxy)cyclohexylacetaldehyde (13c-*trans*):** IR (neat) 1724 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 9.71 (dd, J = 2.0, 3.2 Hz, 1H), 7.38−7.28 (m, 5H), 4.59 (d, J = 11.2 Hz, 1H), 4.39 (d, J = 11.2 Hz, 1H), 3.01 (ddd, J = 4.0, 9.6 Hz, 9.6 Hz, 1H), 2.60 (ddd, J = 3.6, 7.2, 16.0 Hz, 1H), 2.25−2.19 (m, 2H), 2.09−2.04 (m, 1H), 1.83−1.77 (m, 2H), 1.72−1.65 (m, 1H), 1.32−1.20 (m, 3H), 1.16−1.04 (m, 1H); ^{13}C {^1H} NMR (100 MHz) ($CDCl_3$) δ 202.54, 138.36, 128.37, 127.99, 127.60, 81.65, 70.40, 48.52, 39.39, 37.92, 31.06, 25.43, 24.66.

The aldehyde is not stable enough to be characterized by elemental analysis or HRMS, the analysis was carried out on the corresponding acid. ***trans*-(2-Benzyloxy)cyclohexylacetic acid:** IR (neat) 3036, 1708 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 10.82 (brs, 1H), 7.36−7.28 (m, 5H), 4.68 (d, J = 11.6 Hz, 1H), 4.45 (d, J = 11.2 Hz, 1H), 3.08 (ddd J = 4.4, 10.0, 10.0 Hz, 1H), 2.70 (dd, J = 5.6, 15.6 Hz, 1H), 2.26−2.14 (m, 2H), 1.98−1.80 (m, 3H), 1.70−1.62 (m, 1H), 1.30−1.22 (m, 3H), 1.15−1.02 (m, 1H); ^{13}C {^1H} NMR (100 MHz) ($CDCl_3$) δ 177.52, 138.22, 128.38, 127.87, 127.64, 81.73, 70.44, 40.31, 38.66, 31.60, 30.87, 25.34, 24.59; HRMS (EI, 70 eV) calcd for M^+ 248.1412, found 248.1396.

2-Methoxyethoxymethoxycyclohexylacetaldehyde (13e). Hydroformylation of 2-methylene-1-methoxyethoxymethoxycyclohexanol (**12e**) (96.6 mg, 0.482 mmol) was carried out in the presence of $Rh(COD)_2BF_4$ (2.4 mg, 0.0059 mmol) at room temperature for 6 h in a fashion analogous to that used for 2-methylene-1-benzylcyclohexanol (**12c**). An internal NMR standard (*p*-nitrotoluene) was added to measure the conversion (42%) and NMR yield (41%). The diastereoselectivity was determined to be 27:73 in favor of the trans isomer by analyzing crude mixture using 400 ^1H NMR. The cis and trans isomers could be separated by column chromatography eluting with 85:15 hexane/EtOAc.

***trans*-(2-Methoxyethoxymethoxy)cyclohexylacetaldehyde (13e-*trans*):** IR (neat) 1724 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 9.73 (dd, J = 1.6, J = 3.2 Hz, 1H), 4.81 (d, J = 7.2 Hz, 1H), 4.64 (d, J = 7.2 Hz, 1H), 3.70−3.67 (m, 2H), 3.58−3.55 (m, 2H), 3.41 (s, 3H), 3.22 (dt, J = 4.0, 10.0 Hz, 1H), 2.59 (ddd, J = 3.2, 6.8, J = 16.0 Hz, 1H), 2.26−2.15 (m, 2H), 2.07−1.96 (m, 1H), 1.85−1.76 (m, 2H), 1.71−1.64 (m, 1H), 1.32−1.06 (m, 4H); ^{13}C {^1H} NMR (100 MHz) ($CDCl_3$) δ 202.60, 93.93, 80.22, 71.73, 67.25, 59.01, 48.32, 39.07, 31.99, 31.87, 25.32, 24.57; HRMS (EI, 70 ev) calcd for $M^+ - C_2H_3O$ 187.1334, found 187.1324.

***cis*-(2-Methoxyethoxymethoxy)cyclohexylacetaldehyde (13e-*cis*):** IR (neat) 1724 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 9.80 (t, J = 2.0 Hz, 1H), 4.77 (d, J = 7.2 Hz, 1H), 4.70 (d, J = 7.2 Hz, 1H), 3.76 (dt, J = 3.2, 6.0 Hz, 1H), 3.73−3.70 (m, 2H), 3.56 (t, J = 4.4 Hz, 2H), 3.41 (s, 3H), 2.63 (ddd, J = 1.6, 6.4, 16.8 Hz, 1H), 2.36 (ddd, J = 2.4, 7.2, 16.8 Hz, 1H), 2.29−2.21 (m, 1H), 1.87−1.78 (m, 1H), 1.62−1.32 (m, 7H); ^{13}C {^1H} NMR (100 MHz) ($CDCl_3$) δ 202.72, 93.88, 75.04, 71.77, 67.13, 59.05, 45.82, 35.32, 29.04, 27.66, 24.01, 21.23; HRMS (EI, 70 eV) calcd for M^+ 230.1524, found 230.1518.

3-*tert*-Butyldimethylsiloxycyclohexylacetaldehyde (17a). Hydroformylation of 3-methylene-1-*tert*-butyldimethylsiloxylcyclohexanol (**16a**) (626.0 mg, 2.77 mmol) was carried out in the presence of $Rh(COD)_2BF_4$ (12.5 mg, 0.031 mmol) at room temperature for 64 h in a fashion analogous to that used for 2-methylene-1-benzylcyclohexanol (**12c**). An internal NMR standard (*p*-nitrotoluene) was added to measure the conversion (100%) and NMR yield (100%). The diastereoselectivity was determined to be 32:68 in favor of the cis isomer by analyzing crude mixture using (^1H NMR). The cis and trans isomers could be separated by column chromatography eluting with 49:1 hexane/EtOAc.

***cis*-(3-*tert*-Butyldimethylsiloxy)cyclohexylacetaldehyde (17a-*cis*):** IR (neat) 1724 cm^{-1}; ^1H NMR (400-MHz) ($CDCl_3$) δ 9.78 (t, J = 2.4 Hz, 1H), 3.59 (tt, J = 4.0, 10.4 Hz, 1H), 2.36 (dd, J = 2.0, 6.8 Hz, 2H), 2.01−1.83 (m, 3H), 1.80−1.71 (m, 1H), 1.70−1.63 (m, 1H), 1.37−1.14 (m, 2H), 1.12−1.02 (m, 1H), 0.91−0.88 (m, 10H); 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C {^1H} NMR (100 MHz) ($CDCl_3$) δ 202.29, 70.88, 50.87, 42.64, 35.65, 31.95, 31.26, 25.86, 23.81, 18.16, −4.59, −4.64; HRMS (EI, 70 eV) calcd for $M^+ - C_4H_9$ 199.1154, found 199.1164.

***trans*-(3-*tert*-Butyldimethylsiloxy)cyclohexylacetaldehyde (17a-*trans*):** IR (neat) 1724 cm^{-1}; ^1H NMR (400 MHz) δ 9.74 (t, J = 2.8 Hz, 1H), 4.04 (m, 1H), 2.47−2.35 (m, 1H), 2.27−2.24 (m, 2H), 1.84−1.56 (m, 4H), 1.50−1.42 (m, 1H), 1.40−1.31 (m, 1H), 1.24−1.16 (m, 1H), 1.07−0.95 (m, 1H), 0.90 (s, 9H); 0.05 (s, 6H); ^{13}C {^1H} NMR (100 MHz) ($CDCl_3$) δ 202.96, 66.62, 50.82, 40.29, 33.26, 32.55, 26.83, 25.79, 19.88, 18.05, −4.89, −4.92; HRMS (EI, 70 eV) calcd for $M^+ - C_4H_9$ 199.1154, found 199.1151.

3-Methoxymethoxycyclohexylacetaldehyde (17b). Hydroformylation of 3-methylene-1-methoxymethoxycyclohexanol (**16b**) (507 mg, 3.25 mmol) was carried out in the presence of $[Rh(COD)Cl]_2$ (15.5 mg, 0.031 mmol) at room temperature for 64 h in a fashion analogous to that used for 2-methylene-1-benzylcyclohexanol (**12c**). An internal NMR standard (*p*-nitrotoluene) was added to measure the conversion (100%) and NMR yield (70%). The diastereoselectivity was determined to be 42:58 in favor of the cis isomer by analyzing crude mixture (^1H NMR). The cis and trans isomers could be separated by column chromatography eluting with 9:1 hexane/EtOAc.

***cis*-(3-Methoxymethoxy)cyclohexylacetaldehyde (17b-*cis*):** IR (neat) 1728 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 9.77 (t, J = 2.0 Hz, 1H), 4.68 (s, 2H), 3.54 (tt, J = 4.4, 10.8 Hz, 1H), 3.37 (s, 3H), 2.37 (dd, J = 2.0, 6.4 Hz, 2H), 2.08−1.90 (m, 3H), 1.84−1.77 (dp, J = 3.6, 13.6 Hz, 1H), 1.73−1.65 (m, 1H), 1.39−1.27 (tq, J = 3.6, 13.2 Hz, 1H), 1.24−1.12 (m, 1H), 1.08−0.99 (q, J = 12.0 Hz, 1H); 0.97−0.87 (dq, J = 3.6, 12.0 Hz, 1H); ^{13}C {^1H} NMR (100 MHz) ($CDCl_3$) δ 201.99, 94.52, 75.13, 55.16, 50.86, 39.50, 32.49, 32.07, 31.24, 23.80; HRMS (EI, 70 eV) calcd for $M^+ - C_2H_5O$ 141.0915, found 141.0918.

***trans*-(3-Methoxymethoxy)cyclohexylacetaldehyde (17b-*trans*):** IR (neat) 1726 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 9.76 (t, J = 2.4 Hz, 1H), 4.68(d, J = 0.8 Hz, 2H), 3.90 (m, 1H), 3.39 (s, 3H), 2.42−2.28 (m, 3H), 1.92−1.64 (m, 4H), 1.58−1.50 (m, 1H), 1.45−1.36 (m, 1H), 1.29−1.20 (m, 1H), 1.12−1.00 (m, 1H); ^{13}C {^1H} NMR (100 MHz) ($CDCl_3$) δ 202.53, 94.68, 71.33, 55.23, 50.69, 37.23, 32.24, 30.20, 27.19, 20.26; HRMS (EI, 70 eV) calcd for $M^+ - C_2H_5O$ 141.0915, found 141.0913.

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Supporting Information Available: Tables containing yields and diastereomeric ratios for optimization of reaction conditions in the hydroformylation of **9** and **12c**. The effect of parameters such as temperature, pressure, type and equivalents of phosphine additives, CO/H_2 ratios, and total pressure are included. Spectroscopic data are included for *trans*-(2-acetoxy)cyclohexylacetaldehyde **(13a-*trans*)**, *trans*-(2-methoxymethoxy)cyclohexylacetic acid (from **13d-*trans***), *cis*-(2-*tert*-butyldimethylsiloxy)cyclohexylacetic acid (from **13f-*cis***), and *trans*-(2-*tert*-butyldimethylsiloxy)cyclohexylacetic acid (from **13f-*trans***). This material is available free of charge via the Internet at http://pubs.acs.org.

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