JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Distal-Selective Hydroformylation using Scaffolding Catalysis

Candice L. Joe, Thomas P. Blaisdell, Allison F. Geoghan, and Kian L. Tan*,†

Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, United States

Supporting Information

ABSTRACT: In hydroformylation, phosphorus-based directing groups have been consistently successful at placing the aldehyde on the carbon proximal to the directing group. The design and synthesis of a novel catalytic directing group are reported that promotes aldehyde formation on the carbon distal relative to the directing functionality. This scaffolding ligand, which operates through a reversible covalent bond to the substrate, has been applied to the diastereoselective hydroformylation of homoallylic alcohols to afford δ-lactones selectively. Altering the distance between the alcohol and the olefin revealed that homoallylic alcohols gives the distal lactone with the highest levels of regioselectivity.

The functionalization of carbon−carbon double bonds serves as a bedrock for synthetic chemistry. The ease of synthesis, ubiquity, and low cost of olefins makes them ideal building blocks for organic synthesis. A critical challenge in olefin functionalization reactions is the control of regioselectivity. Often reactions have an inherent regio-preference that can be exploited or amplified; however, in these cases, accessing the inherently less favorable product is challenging. Olefins, such as 1,2-disubstituted olefins, pose an alternative problem in that there is often no electronic or steric differentiation of the olefinic carbons; this presents the onerous task of synthesizing either isomer of product selectively. To fully realize the potential of olefin functionalization reactions, our goal is to develop a general strategy that can overcome innate substrate bias and, in the case of unbiased substrates, is able to predictably synthesize either structural isomer of the product.

Hydroformylation is a classic example of an olefin functionalization reaction where the control of regioselectivity is the preeminent challenge. The hydroformylation of olefins generally prefers to form the aldehyde on the least hindered carbon.[1] Over the last several decades, branch selective hydroformylation has been developed in the context of enantioselective hydroformylation by exploiting substrates that have an electronic bias to form the more hindered aldehyde.[2] Landis[3] and Zhang[4] have shown that substrates bearing weakly Lewis basic functional groups can produce

Scheme 1. Scaffold Controlled Regioselective Hydroformylation

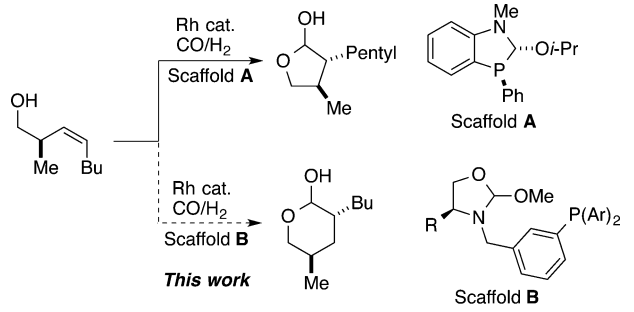
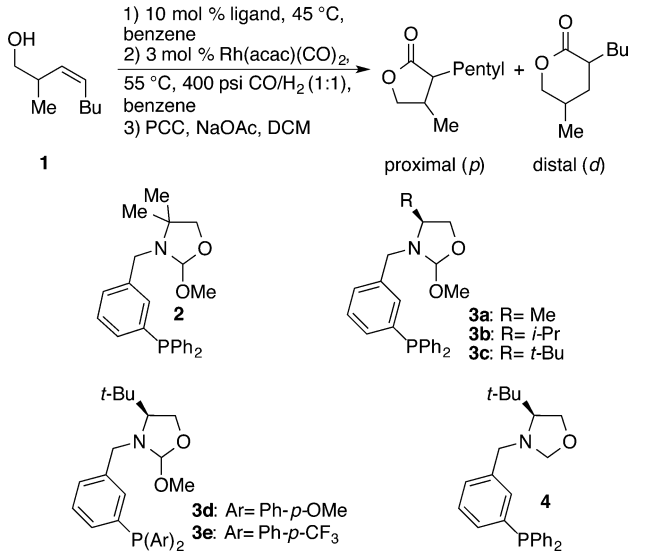


Table 1. Optimization of Ligand Structure



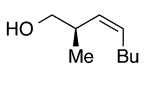
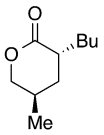
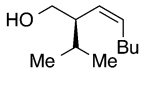
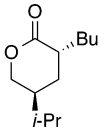
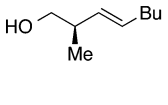
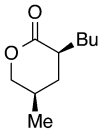
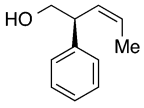
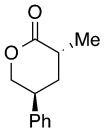
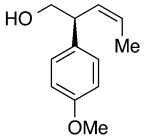
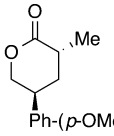
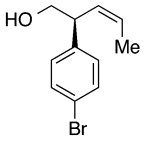
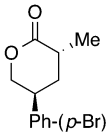
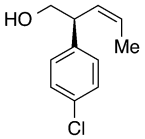
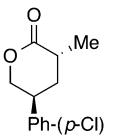
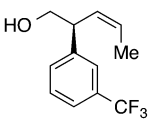
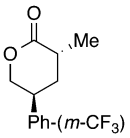
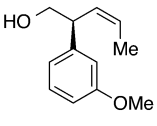
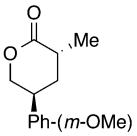
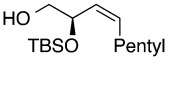
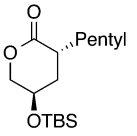
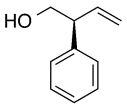
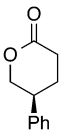
entry	substrate	ligand	% conv[a]	rs[b] (p:d)	dr[c] (a:s)
1	rac-**1**	PPh_3	30	46:54	53:47
2	rac-**1**	**2**	60	19:81	76:24
3	(*S*)-**1**	3b	65	28:72	67:33
4	(*R*)-**1**	3b	87	9:91	88:12
5	(*R*)-**1**	3a	55	24:76	74:26
6	(*R*)-**1**	3c	92	9:91	87:13
7	(*R*)-**1**	3d	63	14:86	84:16
8	(*R*)-**1**	3e	88	10:90	85:15
9	(*R*)-**1**	4	44	44:56	58:42
10[d]	(*R*)-**1**	3c	95	9:91	87:13

[a]Determined by ^{1}H NMR of the crude hydroformylation mixture using mesitylene as an internal standard. [b]Regioselectivity (proximal:distal) determined by gas chromatography of the crude reaction mixture after PCC oxidation. [c]Diastereomer ratio (*anti:syn*) as determined by ^{1}H NMR (CD_3OD) of the reaction mixture after PCC oxidation. [d]Reaction run using 0.10 mol % *p*-TsOH.

Received: April 28, 2014

   dx.doi.org/10.1021/ja504247g | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 2. Substrate Scope

entry	substrate	major product	rs[a] (p:d)	dr[a] (a:s)	% yield[b]
1[c]			9:91	87:13	78%
2[d]			5:95	91:9	53%
3[c]			20:80	32:68	52%
4[e]			12:88	83:17	66%
5[e]			7:93	88:12	72%
6[e]			13:87	89:11	62%
7[e]			12:88	87:13	68%
8[e]			9:91	91:9	73%
9[e]			9:91	86:14	77%
10[e]			15:85	89:11	50%
11[f]			16:84	----	80%

[a]Regioselectivities (proximal:distal) and diastereomer ratio (*anti*:*syn*) were determined by GC or ^{1}H NMR of the crude reaction mixtures after PCC oxidation. [b]Isolated yield of combined distal lactone products. [c](i) 10 mol % **3c**, 0.10 mol % *p*-TsOH, 45 °C, benzene; (ii) 3 mol % Rh(acac)(CO)$_2$, 55 °C, 400 psi H_2/CO, benzene; (iii) PCC, NaOAc, 3 Å sieves, DCM. [d]Standard conditions except 20 mol % **3c** and 6 mol % Rh(acac)(CO)$_2$ were used. [e]Standard conditions except 12 mol % **3c** and 4 mol % Rh(acac)(CO)$_2$ were used. [f]Standard conditions except the hydroformylation was run at 35 °C using 5 mol % **3c** and 2 mol % Rh(acac)(CO)$_2$.

branched aldehydes with practical levels of regio- and enantioselectivity. In a pioneering report, Clarke reported significant branched and enantioselectivity for unactivated terminal olefins (e.g., 1-hexene) using ligand control.[5] In an alternative strategy, Reek et al. demonstrated control of regio- and enantioselectivity in unactivated disubstituted olefins using supramolecular catalysis.[6]

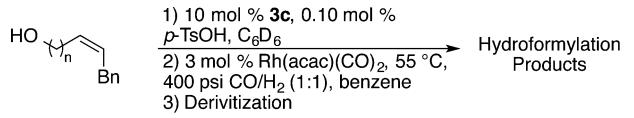
Stoichiometric phosphorus-based directing groups are effective at accessing the branched isomer for terminal alkenes[7] as well as favoring aldehyde formation on the carbon proximal to the directing group for more highly substituted olefins.[8] Improving upon the overall atom efficiency of this strategy, the Breit group[9] and our group[10] reported the first catalytic phosphorus-based directing groups in 2008.[11] Although a reliable strategy, the use of directing groups has been limited to placing the aldehyde in the proximal position relative to the directing functionality.[12] Recently, this deficiency has been partially addressed by using ligands that can hydrogen bond to olefin substrates bearing a carboxylic acid functional group, enabling the aldehyde to be formed on the carbon distal to the directing functionality.[13] Here, we report a novel scaffolding ligand that utilizes reversible covalent bonding to perform distal and diastereoselective hydroformylation of homoallylic alcohols toward the synthesis of δ-lactones (Scheme 1).

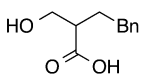
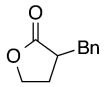
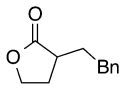
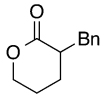
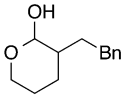
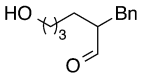
Combining the design elements from the Breit supramolecular catalyst[13a] and our original azaphosphole ligand (scaffold A),[10a] we targeted a small collection of ligands with the substructure of scaffold B. The critical features for these ligands are an oxazolidine group that our group has previously shown to bind to alcohols[14] and a triaryl phosphine, which serves as the metal binding site. This overall series has a modular synthesis allowing for both the tuning of the steric and electronic properties of the phosphine as well as the positioning of the substrate and metal-binding sites.

We initially tested the new ligands in the hydroformylation of homoallylic alcohols bearing an allylic substituent (Table 1). Using PPh_3 as a control ligand, a slight preference exists for the formation of the distal product with minimal levels of diastereocontrol and low conversion (Table 1, entry 1); these results highlight the dual challenge of achieving high levels of reactivity and selectivity for disubstituted olefins in hydroformylation. Employing scaffolding ligand **2** (entry 2) results in a significant increase in conversion and regio- and diastereoselectivity. Next, chiral scaffolding ligand **3b**, which is derived

dx.doi.org/10.1021/ja504247g | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 3. Importance of Substrate Tether



entry	n	proximal	distal	% conv[a]	rs[b] (p:d)
1[c]	n = 1			> 99% (> 99%)	58:42 (67:33)
2[d]	n = 2			84% (40%)	21:79 (57:43)
3[e]	n = 3			89% (36%)	46:54 (59:41)

[a]Conversion based on remaining starting material after the hydroformylation reaction using mesitylene as an internal standard. [b]Regioselectivities (proximal:distal) were determined by ^{1}H NMR. [c]Crude hydroformylation reaction was subjected to Pinnick oxidation (see Supporting Information for experimental details). [d]Crude hydroformylation reaction was subjected to PCC oxidation (see Supporting Information for details). [e]No derivatization of the crude hydroformylation reaction was carried out. [f]Results in parentheses run under identical conditions, except PPh_3 was used rather than ligand **3c**.

from L-valine, was synthesized. A matched/mis-matched relationship is observed when employing enantiopure variants of the substrate (entries 3 and 4), with the (*R*)-isomer being matched. Reducing the size of the substituent on the oxazolidine backbone to a methyl group (entry 5) results in lower conversion and selectivities; however, ligand **3c** bearing an oxazolidine backbone derived from L-*tert*-leucine affords high levels of regio- and diastereoselectivity (entry 6). Ligand **3c** is also the most active, giving 92% conversion in the hydroformylation reaction. With the *tert*-leucine backbone in hand, the electronics on the phosphine were perturbed. Both electron-rich (ligand **3d**) and electron-deficient (ligand **3e**) phosphines gave inferior results when compared to electron neutral ligand **3c**. In particular, both the conversion and diastereoselectivity during the hydroformylation reaction suffered (entries 7 and 8). Using ligand **4**, which contains no substrate-binding site, the reaction proceeds sluggishly; moreover, both the regio- and diastereoselectivities are comparable to the results utilizing PPh_3 as ligand (entry 9). This demonstrates the importance of the substrate-binding site for both achieving high levels of selectivity and obtaining rate acceleration in the reaction. Employing a catalytic amount of *p*-TsOH during the reaction afforded nearly identical results (entry 10) but proved to be a necessary additive to obtain reproducible conversions and selectivities.

The selective formation of the *anti* diastereomer of the *δ*-lactone (Table 2, entry 1) is attributed to the minimization of $A^{1,3}$-strain in the hydrometalation step of the reaction.[15] In support of this hypothesis, the diastereoselectivity is amplified in favor of the *anti* diastereomer (91:9 dr) when a larger isopropyl substituent is placed in the allylic position (Table 2, entry 2).[16] To further demonstrate the effect of $A^{1,3}$-strain on diastereoselectivity, an *E*-configured olefin substrate was examined (Table 2, entry 3). While the *δ*-lactone is still formed selectively (20:80 rs), the *syn*-isomer is observed as the major stereoisomer. Notably, the magnitude of diastereoselection for the *E*-olefin in favor of the *syn* product (32:68) is lower than that of the corresponding *Z*-olefin substrate for the formation of the *anti* isomer (87:13). This result is consistent with decreased $A^{1,3}$-strain between the respective hydrogen and butyl substituents interacting with the allylic methyl group.

A substrate bearing a phenyl substituent at the allylic position underwent the directed hydroformylation efficiently in high levels of selectivity (entry 4). Various electron-deficient and electron-rich *para*-substituted (entries 5−7) and *meta*-substituted (entries 8,9) aromatic substituents were well tolerated and afforded the *δ*-lactones in a regio- and diastereoselective fashion. Highlighting the functional group tolerance of the reaction, a substrate bearing a silyl ether substituent at the allylic position gave the *anti δ*-lactone product in a selective fashion (entry 10).[17] Employing a terminal olefin substrate (entry 11), the inherent regiochemical preference can be amplified, in comparison to a control reaction where PPh_3 is used as ligand, to afford the six-membered lactone as the major product.[18]

A critical question for this new ligand class is where the regioselectivity in the hydroformylation reaction originates from. In part, we hypothesize that the preference for the *δ*-lactone vs the *γ*-lactone is the formation of a less strained, larger metallacycle during the catalytic cycle. This is analogous to carbocycles that exhibit a significant drop in ring strain moving from 11- to 12-membered rings. To probe this question, we investigated the hydroformylation of allylic, homoallylic, and bis-homoallylic alcohols (Table 3). Allylic alcohols undergo hydroformylation with a slight preference for the proximal product in the presence of ligand **3c**, which is similar to the regiochemical preference employing PPh_3 as ligand (Table 3, entry 1). Relative to the control reaction with PPh_3, homoallylic alcohols show a significant preference for the *δ*-lactone product (entry 2). Interestingly, under these conditions a low level of enantioselectivity (19% ee) is observed. Decreasing the pressure to 100 psi H_2/CO increases the enantioselectivity to 37% ee with similar levels of regioselectivity for the *δ*-lactone.[19] Notably, the reaction with PPh_3 is sluggish (40% conversion), which highlights the rate accelerating affect in the presence of ligand **3c**. Minimal levels of regiocontrol for the distal product are observed in the case of a bis-homoallylic alcohol substrate (entry 3), but enhanced conversion is observed. These results are most consistent with a directed reaction that is nonselective, but an undirected reaction cannot be ruled out at this time. Overall these results demonstrate that the regiochemical outcome of the reaction is highly dependent on the appropriate choice of tether length between the olefin and the phosphine on the ligand. This is in contrast to proximal selective directing groups, which generally are more promiscuous with respect to substrate class.

In the context of hydroformylation of 1,2-disubstituted olefins, the challenge of directing to the carbon distal to the directing group has gone relatively unaddressed. We have developed a highly tunable catalytic directing group, which can carry out the distal and diastereoselective hydroformylation of homoallylic alcohols. Together with previous examples of proximal-selective hydroformylation, these results begin to more fully address the challenge of generally controlling regioselectivity in olefin functionalization reactions.

dx.doi.org/10.1021/ja504247g | J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

Ligand syntheses, experimental details, compound characterization, and determination of absolute configurations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

kian.tan@novartis.com

Present Address

[†]Novartis, 250 Massachusetts Ave., Cambridge, MA 02138.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Alfred P. Sloan Foundation (K.L.T.), the John LaMattina Graduate Fellowship (C.L.J.), and the NIGMS (RO1GM087581) for funding this project. Mass spectrometry instrumentation at Boston College is supported by funding from the NSF (DBI-0619576).

■ REFERENCES

(1) Franke, R.; Selent, D.; Börner, A. *Chem. Rev.* **2012**, *112*, 5675.

(2) (a) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251. (b) Gual, A.; Godard, C.; Castillón, S.; Claver, C. *Tetrahedron: Asymmetry* **2010**, *21*, 1135. (c) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113. (d) Agbossou, F.; Carpentier, J. F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485. (e) Claver, C.; Diéguez, M.; Pàmies, O.; Castillón, S. *Top. Organomet. Chem.* **2006**, *18*, 35. (f) Jouffroy, M.; Gramage-Doria, R.; Armspach, D.; Sémeril, D.; Oberhauser, W.; Matt, D.; Toupet, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3937.

(3) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027.

(4) Zhang, X.; Cao, B.; Yu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 4047.

(5) Noonan, G. M.; Fuentes, J. A.; Cobley, C. J.; Clarke, M. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2477.

(6) (a) Kuil, M.; Soltner, T.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *J. Am. Chem. Soc.* **2006**, *128*, 11344. (b) Gadzikwa, T.; Bellini, R.; Dekker, H. L.; Reek, J. N. H. *J. Am. Chem. Soc.* **2012**, *134*, 2860. (c) Bellini, R.; Reek, J. N. H. *Chem.—Eur. J.* **2012**, *18*, 7091.

(7) (a) Jackson, W. R.; Perlmutter, P.; Suh, G.-H. *J. Chem. Soc. Chem. Commun.* **1987**, *21*, 724. (b) Krauss, I. J.; Wang, C. C.-Y.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 11514.

(8) Breit, B.; Grünanger, C. U.; Abillard, O. *Eur. J. Org. Chem.* **2007**, *15*, 2497.

(9) (a) Breit, B.; Demel, P.; Gebert, A. *Chem. Commun.* **2004**, *24*, 114. (b) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7346. (c) Usui, I.; Nomura, K.; Breit, B. *Org. Lett.* **2011**, *13*, 612. (d) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 967. (e) Ueki, Y.; Ito, H.; Usui, I.; Breit, B. *Chem.—Eur. J.* **2011**, *17*, 8555.

(10) (a) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210. (b) Worthy, A. D.; Gagnon, M. M.; Dombrowski, M. T.; Tan, K. L. *Org. Lett.* **2009**, *11*, 2764. (c) Sun, X.; Frimpong, K.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 11841. (d) Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757. (e) Joe, C. L.; Tan, K. L. *J. Org. Chem.* **2011**, *76*, 7590. (f) Lightburn, T. E.; De Paolis, O. A.; Cheng, K. H.; Tan, K. L. *Org. Lett.* **2011**, *13*, 2686.

(11) Examples of reversible covalent bonding in other metal-catalyzed reactions: (a) Lewis, L. N. *Inorg. Chem.* **1985**, *24*, 4433. (b) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728. (c) Preston, S. A.; Cupertino, D. C.; Palma-Ramirez, P.; Cole-Hamilton, D. J. *J. Chem. Soc., Chem. Commun.* **1986**, 977. (d) Park, Y. J.; Park, J. W.; Jun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222. (e) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112. (f) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669. (g) Oi, S.; Watanabe, S. I.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665. (h) Carrión, M. C.; Cole-Hamilton, D. J. *Chem. Commun.* **2006**, 4527. (i) Lewis, J. C.; Wu, J.; Bergman, R. G.; Ellman, J. A. *Organometallics* **2005**, *24*, 5737.

(12) A notable example of distal selective hydroformylation using a stoichiometric phosphorus-based directing group was reported by Burke et al. in the total synthesis of (+)-phyllanthocin: Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237.

(13) (a) Šmejkal, T.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 311. (b) Dydio, P.; Reek, J. N. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 3878. (c) Šmejkal, T.; Gribkov, D.; Geier, J.; Keller, M.; Breit, B. *Chem.—Eur. J.* **2010**, *16*, 2470. (d) Dydio, P.; Dzik, W. I.; Lutz, M.; de Bruin, B.; Reek, J. N. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 396.

(14) (a) Sun, X.; Worthy, A. D.; Tan, K. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8167. (b) Worthy, A. D.; Sun, X.; Tan, K. L. *J. Am. Chem. Soc.* **2012**, *134*, 7321. (c) Giustra, Z. X.; Tan, K. L. *Chem. Commun.* **2013**, *49*, 4370. (d) Sun, X.; Lee, H.; Lee, S.; Tan, K. L. *Nat. Chem.* **2013**, *5*, 790. (e) Blaisdell, T. P.; Lee, S.; Kasaplar, P.; Sun, X.; Tan, K. L. *Org. Lett.* **2013**, *15*, 4710.

(15) Absolute configuration of the major δ-lactone product was further confirmed by 1D NOE experiments. See Supporting Information for details.

(16) The low isolated yield can be attributed to incomplete converson (72%) during the hydroformylation reaction. In the presence of 12 mol % PPh_3, 6 mol % $Rh(acac)(CO)_2$, 75 °C, 400 psi H_2/CO, benzene no appreciable conversion was observed.

(17) The low isolated yield can be attributed to incomplete conversion (75%) during the course of the hydroformylation reaction.

(18) In the presence of PPh_3 under identical conditions, 28:72 rs (prox:dist) is obtained.

(19) Landis has also seen a similar pressure effect on enantioselectivity in the asymmetric hydroformylation of styrene: Watkins, A. L.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14352. See Supporting Information for further details on pressure effects on the enantioselectivity.