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Regioselective Hydroformylation of Allylic Alcohols

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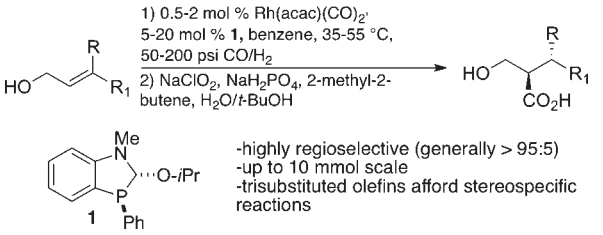
ABSTRACT



A highly regioselective hydroformylation of allylic alcohols is reported toward the synthesis of β-hydroxy-acid and aldehyde products. The selectivity is achieved through the use of a ligand that reversibly binds to alcohols in situ, allowing for a directed hydroformylation to occur. The application to trisubstituted olefins was also demonstrated, which yields a single diastereomer product consistent with a stereospecific addition of CO and hydrogen.

Hydroformylation is an efficient means of generating aldehyde products through the three-component coupling of CO, H_2, and an olefin. Hydroformylation is a commerical process used to synthesize millions of tons of aldehyde products per year.[1,2] The vast majority of these products are linear aldehydes due to their importance in commodity chemical synthesis. The more difficult formation of the aldehyde at a branched carbon can be achieved by using (1) a symmetrical olefin, (2) an electronically activated olefin, and/or (3) an olefin containing a directing group.[3] Although directing groups are highly effective at controlling regio- and stereoselectivity, this strategy is synthetically inefficient because the directing group, often phosphorus-based,[4] must be added and removed in two additional synthetic steps and generates a stoichiometric

(1) (a) *Rhodium Catalyzed Hydroformylation*; van Leeuwen, P. W. N. M., Claver, C., Eds.; Springer-Verlag: New York, 2002; Vol. 22. (b) Frohning, C. D.; Kohlpainter, C. W.; Gaub, A.; Seidel, A.; Torrence, P.; Heymanns, P.; Hohn, A.; Beller, M.; Knifton, J. F.; Klausener, A.; Jentsch, J. D.; Tafesh, A. M. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; Wiley: Weinheim, 2002; Vol. 1, Chapter 2.

(2) For recent examples of hydroformylation applications, see: (a) Dydio, P.; Dzik, W. I.; Lutz, M.; de Bruin, B.; Reek, J. N. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 396–400. (b) Vasylyev, M.; Alper, H. *Synthesis* **2010**, *17*, 2893–2900. (c) Takahashi, K.; Yamashita, M.; Ichihara, T.; Nakano, K.; Nozaki, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 4488–4490. (d) Simaan, S.; Marek, I. *J. Am. Chem. Soc.* **2010**, *132*, 4066–4067. (e) Gual, A.; Godard, C.; Castillon, S.; Claver, C. *Tetrahedron: Asymmetry* **2010**, *21*, 1135–1146. (f) Zhang, X.; Cao, B.; Yu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 4047–4050. (g) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027–14029. (h) Chercheja, S.; Nadakudity, S. K.; Eilbracht, P. *Adv. Synth. Catal.* **2010**, *352*, 637–643. (i) Noonan, G. M.; Newton, D.; Cobley, C. J.; Suarez, A.; Pizzano, A.; Clarke, M. L. *Adv. Synth. Catal.* **2010**, *352*, 1047–1054. (j) Sherrill, W. M.; Rubin, M. *J. Am. Chem. Soc.* **2008**, *130*, 13804–13809. (k) Eilbracht, P.; Schmidt, A. Catalytic Carbonylation Reactions. *Topics in Organometallic Chemistry*; Spinger-VERLAG: Berlin, 2006; Vol. 18, pp 65−95.

(3) (a) Breit, B.; Seiche, W. *Synthesis* **2001**, *1*, 1–36. (b) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450–2494.

(4) For selected examples of phosphorus-based directing groups in hydroformylation, see: (a) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1985**, *50*, 3420–3421. (b) Burke, S. D.; Cobb, J. E.; Takeuchi, K. *J. Org. Chem.* **1990**, *55*, 2138–2151. (c) Jackson, W. R.; Perlmutter, P.; Tasdelen, E. E. *J. Chem. Soc., Chem. Commun.* **1990**, *10*, 763–764. (d) Jackson, W. R.; Perlmutter, P.; Tasdelen, E. E. *Tetrahedron Lett.* **1990**, *31*, 2461–2462. (e) Breit, B. *Acc. Chem. Res.* **2003**, *36*, 264–275. (f) Breit, B.; Breuninger, D. *J. Am. Chem. Soc.* **2004**, *126*, 10244–10245. (g) Breit, B.; Breuninger, D. *Eur. J. Org. Chem.* **2005**, *18*, 3916–3929. (h) Breit, B.; Breuninger, D. *Eur. J. Org. Chem.* **2005**, *18*, 3930–3941. (i) Rein, C.; Demel, P.; Outten, R. A.; Netscher, T.; Breit, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 8670–8673. (j) Bruch, A.; Gebert, A.; Breit, B. *Synthesis* **2008**, *14*, 2169–2176. (k) Bigot, A.; Breuninger, D.; Breit, B. *Org. Lett.* **2008**, *10*, 5321–5324. (l) Breit, B.; Bigot, A. *Chem. Commun.* **2008**, *48*, 6498–6500. (m) Laemmerhold, K. M.; Breit, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 2367–2370. (n) Krauss, I. J.; Wang, C. C. Y.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 11514–11515.

(5) (a) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210–9211. (b) Worthy, A. D.; Gagnon, M. M.; Dombrowski, M. T.; Tan, K. L. *Org. Lett.* **2009**, *11*, 2764–2767. (c) Sun, X.; Frimpong, K.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 11841–11843. (d) Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757–14759.

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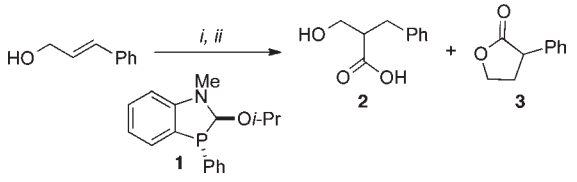
byproduct in the process. In Rh catalyzed hydroformylation we[5] and others[6] have reported a means of circumventing this problem by developing ligands that reversibly and covalently bind to organic substrates.[7] We have termed these compounds as scaffolding ligands due to their functional similarity to scaffolding proteins,[8] which are a class of proteins whose major role is to localize multiple proteins in a functional cluster. An important function of our scaffolding ligand is to bring together the substrate and catalyst. This induced intramolecularity allows for both acceleration of the reaction as well as control of regio- and stereochemistry.[9]

We recently reported that ligand **1** can be used in the hydroformylation of 1,1-disubstituted olefins with excellent regioselectivity for the quaternary aldehyde product.[5c] Herein we report the extension of the methodology to 1,2-di- and trisubstituted olefins as an alternative to the formaldehyde aldol process.

Table 1. Pressure Optimization[a]



entry	pressure (psi)	regioselectivity (**2**:**3**)	conversion (%)
1	50	96:4	85
2	100	95:5	90 (83)[b]
3	200	95:5	89
4	400	95:5	88

[a] (i) 10 mol % **1**, 1 mol % $Rh(acac)(CO)_2$, 45 °C, CO/H_2, 0.05 mol % *p*-TsOH benzene; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O/*t*-BuOH. [b] Isolated yield of **2**, and H_2O_2 used in place of 2-methyl-2-butene.

We initially investigated the hydroformylation of a cinnamyl alcohol. Similar to our observations in the hydroformylation of 1,1-disubstituted olefins, we found it necessary to oxidize the product in situ using Pinnick conditions because the β-hydroxy aldehyde was found to dimerize during hydroformylation.[10] During our optimization studies we found that variation of the CO/H_2 pressure shows little effect on the conversion or selectivity (Table 1). Using 1 mol % $Rh(acac)(CO)_2$ and 10 mol % **1** the expected β-hydroxyacid product is formed in 83% isolated yield and with excellent regioselectivity (rs = 95:5, Table 1, entry 2). The selectivity is in contrast to other reports of hydroformylation of cinnamyl alcohol yielding the aldehdye α to the aromatic ring.[11]

Both electron-donating and -withdrawing groups were tolerated in the reaction without affecting the regioselectivity (Table 2, entries 1 and 2). Ortho substitution on the aromatic ring led to excellent regioselectivity as well as an increase in the isolated yield of the desired carboxylic acid product (Table 2, entry 3). Both *E* and *Z* olefins substituted with alkyl groups afford the desired products with high regioselectivities (Table 2, entries 4–7). The hydroformylation of a substrate with a phthalimide group yields the γ-amino acid product. Phthalimides are known directing groups for Rh-catalyzed hydroformylation,[2f,g] so this result demonstrates that our scaffolding ligand can override internal substrate chelating groups even when employed in catalytic quantities. Hydroformylation of a monoprotected diol affords the desired product in good regioselectivity and yield (Table 2, entry 9). The TBDPS group was used to protect the alcohol because silyl migration was observed when a TBS group was used.

We also investigated the hydroformylation of 3-methylbut-2-en-1-ol, a less reactive trisubstituted olefin. Increasing the catalyst loading (2 mol % Rh and 20 mol % **1**) and temperature (55 °C) affords the desired product in good yield (85%, Scheme 1). Hydroformylation of trisubstituted olefins is generally a challenging reaction that requires more forcing conditions. Ligand **1** operates under relatively mild conditions for these types of substrates, albeit using higher Rh loadings, suggesting it is one of the more reactive hydroformylation catalyst systems.[12,13] Because the insertion of the Rh hydride into the olefin occurs through a *syn* addition, hydroformylation of trisubstituted olefins presents the opportunity for forming two stereocenters in a stereospecific fashion. This was

(6) (a) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7346–7349. (b) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 967–970. (c) Usui, I.; Nomura, K.; Breit, B. *Org. Lett.* **2011**, 612–615. (d) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450–2494.

(7) For examples of the use of reversible covalent interactions in other metal-catalyzed reactions, see: (a) Lewis, L. N. *Inorg. Chem.* **1985**, *24*, 4433–4435. (b) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728–2735. (c) Preston, S. A.; Cupertino, D. C.; Palma-Ramirez, P.; Cole-Hamilton, D. J. *J. Chem. Soc., Chem. Commun.* **1986**, 977–978. (d) Iraqi, A.; Fairfax, N. R.; Preston, S. A.; Cupertino, D. C.; Irvine, D. J.; Cole-Hamilton, D. J. *J. Chem. Soc., Dalton Trans.* **1991**, 1929–1935. (e) Park, Y. J.; Park, J. W.; Jun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222–234. (f) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112–114. (g) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669–8682. (h) Bedford, R. B.; Haddow, M. F.; Webster, R. L.; Mitchell, C. J. *Org. Biomol. Chem.* **2009**, *7*, 3119–3127. (i) Oi, S.; Watanabe, S. I.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665–8668. (j) Carrion, M. C.; Cole-Hamilton, D. J. *Chem. Commun.* **2006**, 4527–4529. (k) Lewis, J. C.; Wu, J.; Bergman, R. G.; Ellman, J. A. *Organometallics* **2005**, *24*, 5737–5746.

(8) (a) Sheng, M.; Sala, C. *Annu. Rev. Neurosci.* **2001**, *24*, 1–29. (b) Bhattacharyya, R. P.; Remenyi, A.; Yeh, B. J.; Lim, W. A. *Annu. Rev. Biochem.* **2006**, *75*, 655–680. (c) Mishra, P.; Socolich, M.; Wall, M. A.; Graves, J.; Wang, Z.; Ranganathan, R. *Cell* **2007**, *131*, 80–92.

(9) Pascal, R. *Eur. J. Org. Chem.* **2003**, 1813–1824.

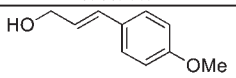
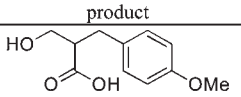
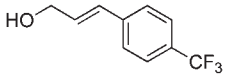
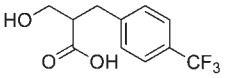
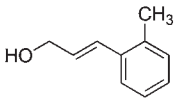
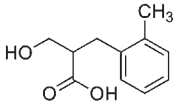
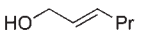
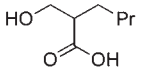
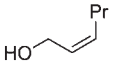
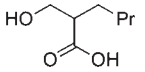
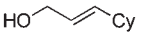
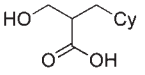
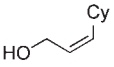
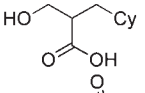
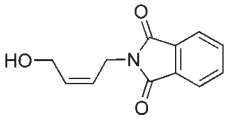
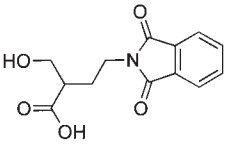
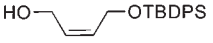
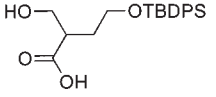
(10) Boeckman, R. K.; Miller, J. R. *Org. Lett.* **2009**, *11*, 4544–4547.

(11) Nozaki, K.; Li, W.; Horiuchi, T.; Takaya, H. *Tetrahedron Lett.* **1997**, *38*, 4611–4614. Also see ref 2g.

(12) For examples of hydroformylation of trisubstituted olefins, see: (a) da Silva, J. G.; Barros, H. J. V.; Balanta, A.; Bolanos, A.; Novoa, M. L.; Reyes, M.; Contreras, R.; Bayon, J. C.; Gusevskaya, E. V.; dos Santos, E. N. *Appl. Catal., A* **2007**, *326*, 219–226. (b) Clarke, M. L.; Roff, G. L. *Chem.—Eur. J.* **2006**, *12*, 7978–7986. (c) Breit, B.; Winde, R.; Mackewitz, T.; Paciello, R.; Harms, K. *Chem.—Eur. J.* **2001**, *7*, 3106–3121. (d) Siegel, H.; Himmele, W. *Angew. Chem., Int. Ed.* **1980**, *19*, 178–183. (e) Himmele, W.; Siegel, H. *Tetrahedron Lett.* **1976**, *17*, 907–910.

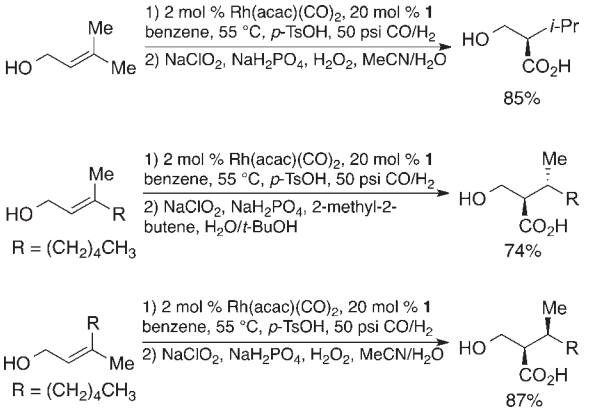
(13) For examples of hydroformylation of trisubstituted olefins using a stoichiometric phosphine directing group, see: Breit, B; Grüanger, C. U.; Abillard, O. *Eur. J. Org. Chem.* **2007**, *15*, 2497–2503.

Table 2. Regioselective Hydroformylation of Allylic Alcohols

entry	substrate	product	regioselectivity[g]	yield (%)
1[a]			>95:5	87
2[a]			>95:5	62
3[a]			94:6	93
4[b]			>95:5	81
5[b]			>95:5	92
6[c]			>95:5	72
7[d]			>95:5	82
8[e]			88:12	71
9[f]			85:15	84

[a] (i) 1 mol % $Rh(acac)(CO)_2$, 10 mol % **1**, 45 °C, 50 psi CO/H_2, 0.0125 mol % *p*-TsOH; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O/*t*-BuOH. [b] Reaction performed 2 mol % $Rh(acac)(CO)_2$, 20 mol % **1**, 0.025 mol % *p*-TsOH. [c] Reaction performed at 35 °C and 200 psi CO/H_2 [d] Reaction performed at 35 °C, 200 psi CO/H_2, 0.025 mol % *p*TsOH [e] Reaction performed at 45 °C, 100 psi CO/H_2, 0.025 mol % *p*-TsOH. [f] Reaction performed with 0.2 mol % *p*-TsOH, 100 psi CO/H_2. [g] Regioselectivities were determined by taking the crude ^1H NMR after oxidation. The authentic lactone products were independently synthesized and characterized by performing the hydroformylation with PPh_3 as the ligand.

Scheme 1. Hydroformylation of Trisubstituted Olefins



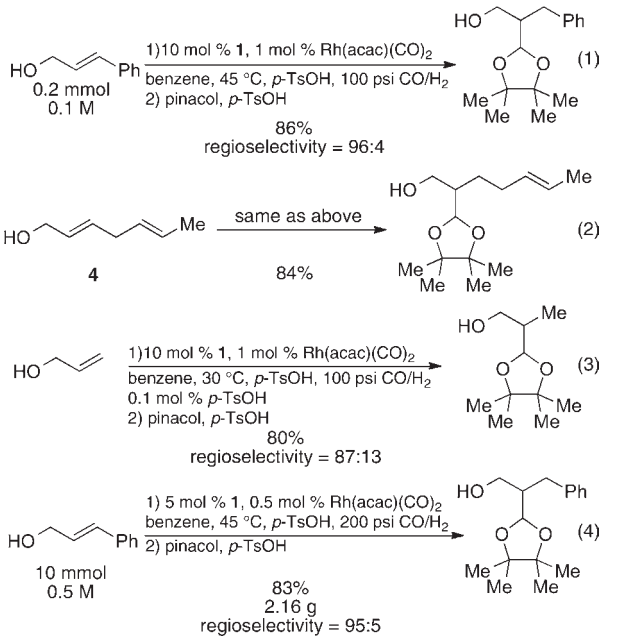
confirmed through the hydroformylation of both *E*- and *Z*-3-methyloct-2-en-1-ol which form single diastereomers as the sole products (Scheme 1).[14]

(14) The ^1H and ^{13}C NMR show that the products are nonidentical (see Supporting Information for details). Based on a *syn* addition of hydrogen and CO the *E*-olefin will form the *anti* product and the *Z*-olefin will form the *syn* product.

In order to extend the synthetic utility of the hydroformylation reaction we investigated methods of isolating the product in the aldehyde oxidation state. This is readily achieved by forming the acetal of the product immediately following hydroformylation. Reaction of cinnamyl alcohol and subsequent protection with pinacol affords the acetal in 86% yield, and the selectivity is consistent with the oxidation results (Scheme 2, eq 1). These modified conditions also allowed for the hydroformylation of diene **4**. Previous attempts to hydroformylate and oxidize **4** resulted in a complex mixture of products. Using the acetal protection conditions the olefin proximal to the alcohol reacts selectively affording the desired product in 84% yield (Scheme 2, eq 2). This procedure was also used in the hydroformylation of allyl alcohol, which formed the desired product in 80% yield (rs = 87:13, Scheme 2, eq 3).

An attractive feature of hydroformylation is that it is an atom economical reaction such that no byproducts are formed. In order to improve the synthetic utility of our method, we reoptimized the reaction conditions focusing on lowering the catalyst and ligand loadings as well as improving the volume efficiency. Under the optimal conditions the concentration of the reaction is increased from 0.1 to 0.5 M, while the rhodium

Scheme 2. Acetal Protection of Hydroformylation Products



loading is reduced to 0.5 mol % and the ligand loading to 5 mol %. Under the modified conditions the same regioselectivity is observed in the reaction with only a slight decrease in the isolated yield (83% vs 86%, Scheme 2, eq 4).

In summary we have demonstrated that our scaffolding strategy can be extended to the hydroformylation of 1,2-di- and trisubstituted olefins, providing an alternative disconnection to the formaldehyde aldol reaction. These reactions are performed under mild conditions and yield highly regioselective reactions. The extension to trisubstituted olefins under mild conditions allows the generation of two stereocenters in a stereospecific fashion. Furthermore, we have improved the practicality of the reaction by reducing the ligand and catalyst loading as well as increasing the concentration of the reaction. We are currently investigating enantioselective variants of this transformation and are continuing to develop ligands with increased reactivity and stability.

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Supporting Information Available. Experimental details, compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.