J|A|C|S
COMMUNICATIONS

Published on Web 06/25/2008

Catalytic Scaffolding Ligands: An Efficient Strategy for Directing Reactions

Thomas E. Lightburn, Michael T. Dombrowski, and Kian L. Tan*

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

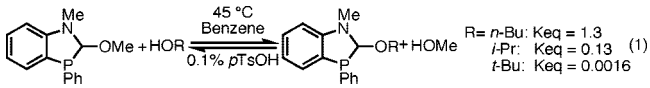
Received April 23, 2008; E-mail: kian.tan.1@bc.edu

In organic synthesis, directing groups are used to control selectivity in a range of reactions from asymmetric epoxidation to C−H activation.[1,2] Ideally, a directing group serves as an efficient ligand as well as a functional group handle for future synthetic steps.[3] The structural requirements for these two features are often at odds with each other and require chemical transformations to convert the "functional group" into a "directing group" and vice versa. Inspired by the work in the area of C−H functionalization,[4] we have designed a scaffolding ligand that simultaneously and reversibly binds alcohol substrates, as well as a metal-based catalyst (Scheme 1). *Consequently, the directed reaction can be performed with a catalytic amount of ligand, and we are able to tune the ligand for efficient catalysis without having to change the nature of the substrate*. Herein, we applied this strategy to the challenging problem of branch-selective hydroformylation.[3b,5] Using a catalytic quantity of a scaffolding ligand (20−25 mol %), we obtained excellent regioselectivity for disubstituted olefins (up to 98:2) and high branch selectivity (up to 88:12) for terminal olefins.

Current methods for performing branch-selective hydroformylation include modifying the olefin substrate electronically to favor C−C bond formation at the more substituted site of terminal alkenes.[6] Another approach is to use phosphorus-based auxiliary directing groups, which can deliver high regio-, diastereo-, and enantioselectivity.[3b,7] Most recently, supramolecular catalysts have been introduced to address this problem; however, this approach gives rise to only moderate levels of branch selectivity (branched:linear of 67:33).[8]

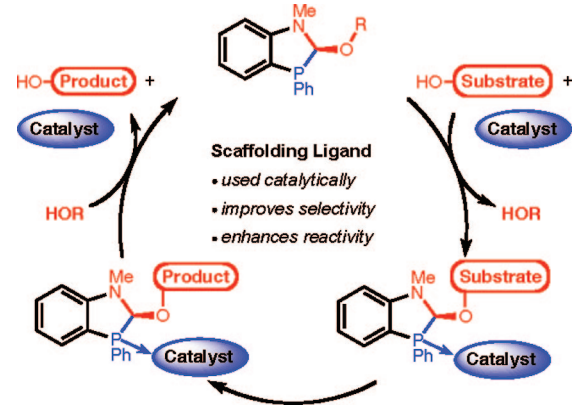
Our investigation began with the synthesis of scaffolding ligands **2a**−**c** (Scheme 2). Starting from *N*-methylaniline, ligand **2a** is synthesized in a three-step sequence that requires no column chromatography, making it amenable to large-scale synthesis.[9] The ligand is isolated as one major diastereomer (as judged by ^{1}H and ^{31}P NMR).[10] An X-ray crystal structure of **2b** confirmed that the stereochemistry of the ligand was *anti*.

Synthesis of **2b** and **2c** is achieved by mixing **2a** with the appropriate alcohol and 1 mol % of *p*-TsOH. The mild conditions under which this reaction occurs suggest that exchange of alcohols is facile. Equilibration occurs with primary, secondary, and even tertiary alcohols at 45 °C with catalytic acid (as monitored by ^{1}H and ^{31}P NMR spectroscopy, eq 1).[11] The K_{eq} depends largely on the sterics of the alcohol, with isopropanol showing a 10-fold decrease in binding to the ligand as compared to methanol, and *tert*-butanol exhibiting >100-fold change.[12]



Having established that the ligand reversibly exchanges with alcohols, we tested **2** as a ligand in the hydroformylation of terminal olefin **3**.[13] When reactions are performed with PPh_3 as a control ligand, 75:25 regioselectivity favoring lactone **6** is observed (Table 1, entry 1). Furthermore, the γ-lactone formed as the minor regioisomer is obtained as a mixture of diastereomers. Application of **2a** leads to a reversal in the regioselectivity and a significant enhancement of the diastereoselectivity (88:12) in favor of *anti*-**4** (Table 1, entry 2).[14] Use of **2b** improves the yield of the reaction (Table 1, entry 3); this is likely due to an increase in the concentration of the substrate-bound ligand since free isopropanol competes less effectively for binding to the ligand than methanol. Use of **2c** results in a decrease in yield (Table 1, entry 4). This result may be due in part to decreased stability of the

Scheme 1. Mechanism of Catalytic Scaffold-Directed Reactions



Scheme 2. Synthesis of Scaffolding Ligands **2a**−**c**

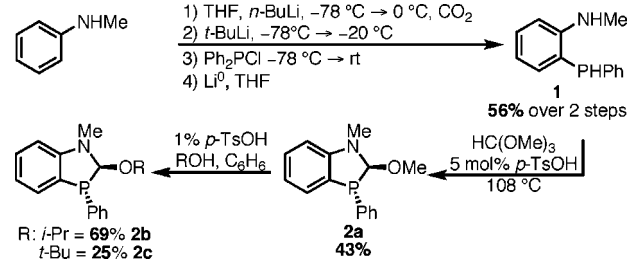
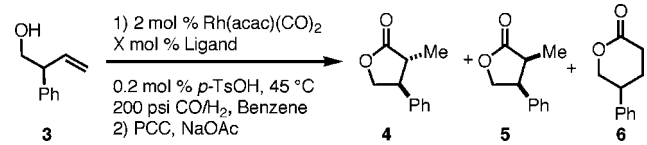


Table 1. Optimization of Branch-Selective Hydroformylation[a]

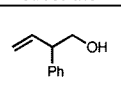
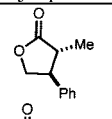
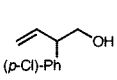
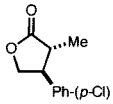
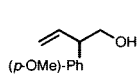
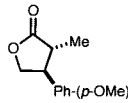
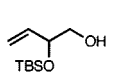
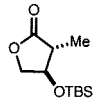
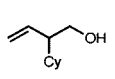
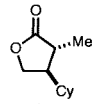
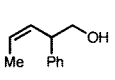
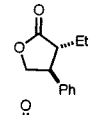
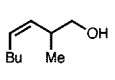
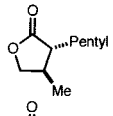
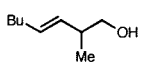
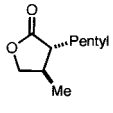


entry	ligand	rr[b]	dr (**4**:**5**)	yield (%)
1	4% PPh_3	25:75	42:58	>98
2[c]	20% **2a**	81:19	88:12	80
3[c]	20% **2b**	84:16	88:12	>98
4[c]	20% **2c**	84:16	88:12	92
5	5% **2b**	60:40	79:21	53
6	10% **2b**	77:23	85:15	71

[a] Yields and selectivities determined by GC using hexamethylbenzene as an internal standard; reaction time 16 h; see Supporting Information for experimental details. [b] rr = ratio of five- to six-membered ring lactones. [c] Yields and selectivities are an average of two runs.

10.1021/ja803011d CCC: $40.75

Table 2. Evaluation of Substrates in the Hydroformylation Reaction

entry	substrate	major product	yield[a]	rr[b]	dr[b]
1			94[c]	86:14 (25:75)[d]	89:11
2			>98[e]	82:18 (33:67)[d]	87:13
3			86[c]	84:16 (29:71)[d]	88:12
4			75[c]	88:12 (20:80)[d]	80:20
5			86[c]	65:35 (16:84)[d]	87:13
6			88[e,f]	98:2 (33:66)[g]	>98:2
7			70[c,f]	95:5 (38:62)[g]	92:8
8			69[e,f]	94:6 (40:60)[g]	78:22

[a] Unless otherwise noted, isolated yield of all lactone products. [b] Regio- (five- to six-membered lactones) and diastereoselectivities (*anti*:*syn*) were determined by GC of the crude reaction mixtures; reaction time 16 h. [c] With 2 mol % of $Rh(acac)(CO)_2$, benzene, 200 psi CO/H_2, 20 mol % of **2b**, 45 °C, 0.2 mol % of *p*-TSA; PCC, NaOAc, 3 Å sieves. [d] With 2 mol % of $Rh(acac)(CO)_2$, 4 mol % of PPh_3, benzene, 200 psi CO/H_2, 45 °C; PCC, NaOAc, 3 Å sieves. [e] With 6 mol % of $Rh(acac)(CO)_2$, benzene, 200 psi CO/H_2, 25 mol % of **2b**, 65 °C, 0.2 mol % of *p*-TSA; PCC, NaOAc, 3 Å sieves. [f] Isolated yield of only five-membered ring lactones. [g] With 6 mol % of $Rh(acac)(CO)_2$, benzene, 200 psi CO/H_2, 12 mol % of PPh_3, 65 °C; PCC, NaOAc, 3 Å sieves.

ligand. Lowering the ligand loading of **2b** to 10 mol % results in a decrease in selectivity and yield of the lactone products (Table 1, entry 6).

With the optimal conditions in hand, we investigated the substrate scope. Rh-catalyzed directed hydroformylation of alcohol substrates with an electron-rich and electron-deficient aromatic ring at the allylic position affords good regio- and diastereoselectivities (Table 2, entries 2 and 3). Subjection of a compound with a silyl ether at the allylic position results in improved regioselectivity (Table 2, entry 4). Substitution of the phenyl substituent with the more electron-rich cyclohexyl group provides lower regio- (65:35) and high diastereoselectivity (Table 2, entry 5). The latter finding suggests that the reaction is proceeding through a directed hydroformylation rather than an unselective background reaction. The lower regioselectivity reflects the difficulty in overcoming the significant preference for the linear aldehyde, which is evident by comparing the selectivity of the reaction with PPh_3 (b:l = 16:84; Table 2, entry 5).

The levels of diastereoselectivity in the hydroformylation reactions correlate well with the size of the substituent at the allylic position. The high *anti* selectivity in five-membered ring lactone formation can be rationalized based on minimization of $A^{1,3}$-strain.[1,15] To support this hypothesis, we investigated the reaction of a *Z*-disubstituted olefin. As shown in entry 6 of Table 2, this hydroformylation proceeds with excellent diastereoselectivity (>98:2) and regioselectivity (98:2). Concerned that these high selectivities may be unique to a substrate that bears an allylic phenyl group, the transformation in entry 7 of Table 2 was performed: even with the small methyl group, excellent regio- and diastereoselectivity is observed. Consistent with the importance of $A^{1,3}$-strain, there is diminished diastereoselectivity in the catalytic hydroformylation of the *E* olefin (Table 2, entry 8).

In summary, we have achieved branch-selective hydroformylation through the use of an appropriately designed scaffolding ligand. We are currently developing this concept to include other functional groups as well as synthesizing enantioenriched ligands for applications to asymmetric catalysis. We plan to implement this strategy toward the development of catalytic processes.

Acknowledgment. We thank Dr. Bo Li for determining the X-ray structure for **2b**. We thank Jillian Thayer for experimental assistance. We also thank Boston College for providing funding for this research project.

Supporting Information Available: Experimental details and compound characterization, cif file of **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a review on substrate-directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(2) For reviews on directed C−H functionalization, see: (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (c) Dick, A.; Sanford, M. *Tetrahedron* **2006**, *62*, 2439. (d) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.
(3) For examples of removable directing groups in late-metal-catalyzed reactions, see ref 1 and: (a) Breit, B.; Seiche, W. *Synthesis* **2001**, *1*, 1. (b) Itami, K.; Yoshida, J. *Synlett* **2006**, *2*, 157. (c) Oestreich, M. *Eur. J. Org. Chem.* **2005**, *5*, 783.
(4) For examples of catalytic directing groups in C−H functionalization reactions, see: (a) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728. (b) Park, Y. J.; Park, J. W.; Jun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222. (c) Jun, C.; Moon, C.; Lee, D. *Chem.—Eur. J.* **2002**, *8*, 2423. (d) Bedford, R. B.; Betham, M.; Caffyn, A.; Charmant, J.; Lewis-Alleyne, L.; Long, P.; Polo-Ceron, D.; Prashar, S. *Chem. Commun.* **2008**, 990. (e) Bedford, R.; Limmert, M. *J. Org. Chem.* **2003**, *68*, 8669. (f) Lewis, J.; Wu, J.; Bergman, R.; Ellman, J. *Organometallics* **2005**, *24*, 5737.
(5) For leading references on hydroformylation, see: (a) *Rhodium Catalyzed Hydroformylation*; Van Leeuwen, P. W. N. M., Claver, C., Eds.; Springer-Verlag: New York, 2002. (b) Frohning, C. D. Kohlpaintner, C. W. Bohnen, H. W. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; Wiley: Weinheim, Germany, 2002; Vol. 1, p 31.
(6) For reviews of branched hydroformylation in asymmetric catalysis, see: (a) Agbossou, F.; Carpentier, J.; Mortreaux, A. *Chem. Rev.* **1995**, *95*, 2485. (b) Diegeuz, M.; Pamies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113. (c) Claver, C.; Dieguez, M.; Pamies, O.; Castillon, S. *Top. Organomet. Chem.* **2006**, *18*, 35. (d) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251.
(7) (a) Krauss, I. J.; Wang, C. C. Y.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 11514. (b) Leighton, J. L.; O'Neil, D. N. *J. Am. Chem. Soc.* **1997**, *119*, 11118. (c) Breit, B. *Acc. Chem. Res.* **2003**, *36*, 264. (d) Breit, B.; Breuninger, D. *J. Am. Chem. Soc.* **2004**, *126*, 10244.
(8) (a) Smejkal, T.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 311. (b) Kuil, M.; Soltner, T.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *J. Am. Chem. Soc.* **2006**, *128*, 11344. (c) Slagt, V. F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *J. Am. Chem. Soc.* **2004**, *126*, 1526.
(9) In the Supporting Information, a more detailed discussion of the synthesis is presented.
(10) ^1H and ^{31}P NMR analysis showed a minor compound (~3%) which we have assigned as the minor *syn*-diastereomer. DFT calculations suggest that the *anti*-diastereomer is 2 kcal/mol more stable than the *syn*.
(11) K_{eq} values are an average of three runs; all values deviated by <15% of the average value. See Supporting Information for details.
(12) For all three alcohols, the time to reach half the equilibrium concentrations is less than 2 h, showing that the exchange is rapid. Without the acid catalyst, the exchange with isopropanol had a $t_{1/2}$ > 10 h.
(13) Hydroformylation of **3** leads to spontaneous formation of lactols under the reaction conditions. Because the lactols have an additional stereocenter, they are oxidized to the lactones for ease of analysis and isolation.
(14) Hydroformylation of the methyl ether of **3** with **2b** leads to a linear:branched ratio of 74:26, demonstrating the necessity of a free alcohol for branch selectivity. See Supporting Information for details.
(15) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

JA803011D