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Regioselective Hydroformylation of Sulfonamides using a Scaffolding Ligand

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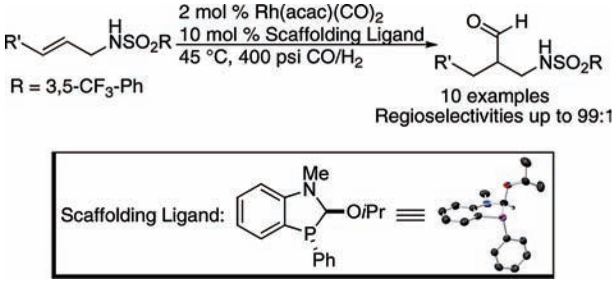
ABSTRACT



A highly regioselective hydroformylation of allylic sulfonamides has been developed by employing a catalytic directing group. The reaction tolerates a wide range of electronically and sterically modified olefins, and only 10% of the scaffolding ligand is required to effectively control the regioselectivity.

The control of regio- and stereoselectivity is a paramount goal in organic synthesis. Though many strategies have been employed for this task, one of the most reliable and predictable has been the application of directing groups.[1] In metal-based catalysis, directing groups are functionalities within the organic substrate that can serve as a ligand for the catalyst. The intimate association of the metal with the substrate allows for enhanced control of the selectivity of the transformation. A potential liability for the directing group process is that often the ideal ligand for the metal is not necessarily a useful functional group handle for future synthetic transformations. This conundrum is most apparent in hydroformylation where phosphorus-based ligands are the ideal ligands for the reaction, yet this functionality has limited application in organic synthesis.[2] To circumvent this problem, several groups have devised phosphorus-based directing groups that can be cleaved easily in a subsequent step.[3] Though this strategy is useful, it inherently generates a stoichiometric amount of phosphorus-based byproduct and requires additional synthetic steps.

Most recently our group[4] as well as the Breit group[5] reported catalytic directing groups[6] in the regioselective hydroformylation of homoallylic alcohols. Both groups used the concept of reversible covalent modifications to a phosphorus-based ligand to allow for transient attachment of the substrate to the ligand. The rate acceleration provided by

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(1) (a) Hoveyda, A.; Evans, D.; Fu, G. *Chem. Rev.* **1993**, *93*, 1307. (b) Itami, K.; Yoshida, J. *Synlett* **2006**, *2*, 157. (c) Oestreich, M. *Eur. J. Org. Chem.* **2005**, *5*, 783. (d) Kakiuchi, F.; Chatani, N. *Adv. Syn. Catal.* **2003**, *345*, 1077. (e) Dick, A.; Sanford, M. *Tetrahedron* **2006**, *62*, 2439.

(2) Breit, B. *Synthesis* **2001**, *1*, 1.

(3) (a) Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237. (b) Jackson, W. R.; Perlmutter, P.; Tasdelen, E. E. *Tetrahedron Lett.* **1990**, *31*, 2461. (c) Jackson, W. R.; Perlmutter, P.; Tasdelen, E. E. *J. Chem. Soc., Chem. Commun.* **1990**, *10*, 763. (d) Breit, B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2835. (e) Breit, B.; Zahn, S. K. *J. Org. Chem.* **2001**, *66*, 4870. (f) Breit, B.; Demel, P.; Gebert, A. *Chem. Commun.* **2004**, *1*, 114. (g) Breit, B. *Liebigs Ann. Chem.* **1997**, 1841. (h) Breit, B.; Dauber, M.; Harms, K. *Chem.—Eur. J.* **1999**, *5*, 2819. (i) Krauss, I. J.; Wang, C. C. Y.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 11514.

(4) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210.

(5) (a) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7346. (b) Smejkal, T.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 311.

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the directing group allows branched selective hydroformylation to proceed using only a catalytic amount of ligand. Our bifunctional ligand incorporates two independent binding domains: a substrate binding site and metal binding site (Figure 1). A unique substrate binding site provides the possibility of bonding to a variety of organic functionalities without substantially interfering with the metal binding domain. We have set out to expand the substrate scope so that the most common and useful organic functional groups can be used in the directed hydroformylation. In this report, we discuss the application of scaffolding ligand **1** in the synthesis of β-amino-aldehydes (Mannich product[7]) through a highly regioselective hydroformylation of protected amines.

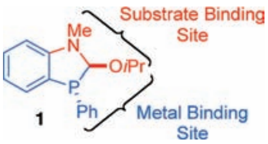
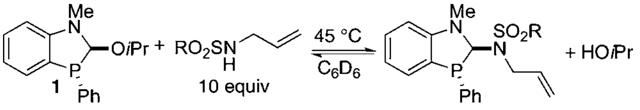


Figure 1. Design of scaffolding ligand.

As a prerequisite to the success of our strategy, we attempted to establish whether protected amines would exchange rapidly with ligand **1**. Preliminary studies showed that while carbamates and amides did not exchange with **1**, sulfonamides were incorporated on to the ligand readily (Table 1). We believe that the success of sulfonamides is related to the similarity in pK_a to alcohols. Indeed, we found that as the pK_a of the substrate decreased, an increase in the rate of exchange was observed (Table 1). Though the initial exchange with ligand **1** is important, efficient catalysis cannot be achieved without also establishing that exchange of sulfonamide bound ligand **4** and free sulfonamide substrate occurs. To test this important aspect, we exchanged substrate **2** onto ligand **1** then in a subsequent step added sulfonamide **3** (Scheme 1). To our surprise, we discovered that exchange is very rapid with a 53:47 mixture of **4** and **5** forming in 1 h at 25 °C.[8]

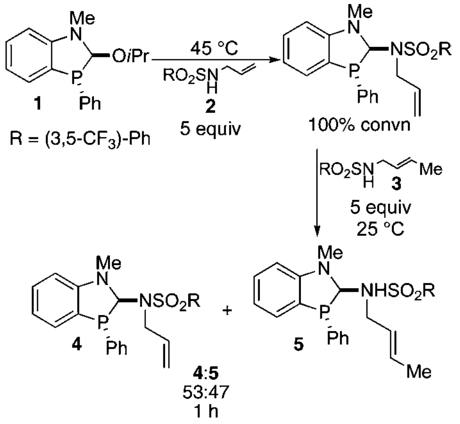
Table 1. Relative Rates of Exchange with Sulfonamides



R	conversion at 6 h
p-OMe-Ph	0
p-Me-Ph	0
p-NO_2–Ph	23%[a]
(3,5-CF_3)-Ph	69%[b]

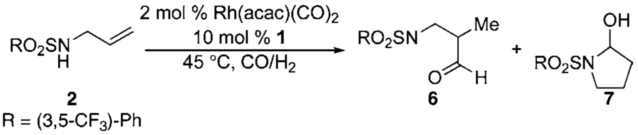
[a] >95% conversion reached in 6 days. [b] >95% conversion reached in 13 h.

Scheme 1. Exchange Reaction with Sufonamides



Having demonstrated that the exchange reaction occurs, we investigated the regioselective hydroformylation of **2** (Table 2). As a control reaction, the hydroformylation was performed with triphenylphosphine as the ligand. The reaction yields a 50:50 mixture of the linear and branched products with complete conversion (Table 2, entry 1). Similar terminal substrates have been shown to favor linear products, suggesting that in our case there is a moderate directing group

Table 2. Optimization of Sulfonamide Hydroformylation



entry	pressure (psi)	regioselectivity (6: 7)	conversion (%)[b]
1[a]	200	50:50	>95
2	200	60:40	>95
3[c]	200	90:10	86
4[c]	100	88:12	83
5[c]	300	95:5	>95
6[c]	400	97:3	>95

[a] Reaction run with 4% PPh_3 as the ligand. [b] Conversion determined by ^1H NMR. [c] **2** and **1** were exchanged at 55 °C prior to hydroformylation.

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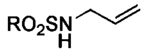
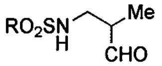
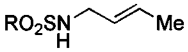
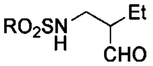
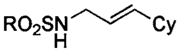
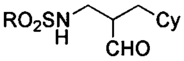
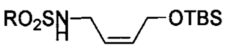
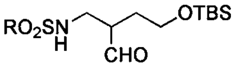
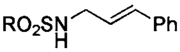
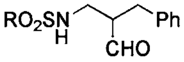
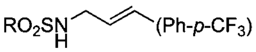
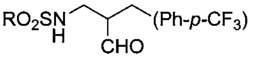
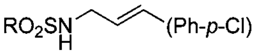
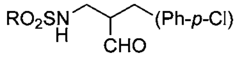
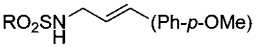
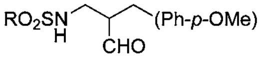
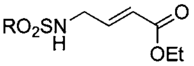
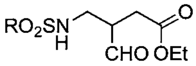
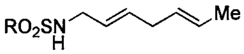
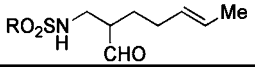
(6) For examples of catalytic directing group strategies in other metal catalyzed reactions, see: (a) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728. (b) Park, Y. J.; Park, J. W.; Jun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222. (c) Jun, C.; Moon, C. W.; Lee, D. *Chem.—Eur. J.* **2002**, *8*, 2423. (d) Bedford, R. B.; Betham, M.; Caffyn, A. J. M.; Charmant, J.; Lewis-Alleyne, L.; Long, P.; Polo-Ceron, D.; Prashar, S. *Chem. Commun.* **2008**, 990. (e) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669. (f) Lewis, J. C.; Wu, J.; Bergman, R. G.; Ellman, J. A. *Organometallics* **2005**, *24*, 5737.

(7) (a) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797. (b) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (c) Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899.

(8) At equilibrium the ratio of **4**:**5** is 43:57, which is expected based on the similarity between the allyl and crotyl sulfonamides.

Table 3. Evaluation of Substrate Scope[a]

entry	substrate	product	regioselectivity[b]	yield (%)[j]
1			96:4 (57:43)[c]	80
2			99:1 (71:29)[c]	85
3			99:1 (85:15)[c]	84
4			94:6[d] (54:46)[c]	83
5			99:1 (65:35)[c]	86
6			98:2[e] (12:82)[c,e]	92
7			99:1[e] (13:87)[c,e]	69
8			97:3[f] (22:78)[g]	87
9			87:4:9[h] (<1:45:55)[c,h]	79
10			>95:5[i]	75

[a] Conditions: (a) Substrate, 10 mol % **1,** 55 °C, benzene, 6 h. (b) 2 mol % Rh(acac)$(CO)_2$, 400 psi CO/H_2, 45 °C. [b] Regioselectivity of aldehyde: hemiaminal determined by SFC analysis. [c] Regioselectivity for reactions run with 4% PPh_3 instead of **1.** [d] Hydroformylation performed at 40 °C. [e] Hydroformylation performed in 5% THF/benzene. [f] Hydroformylation performed in 10% THF/benzene with 3 mol % Rh(acac)$(CO)_2$ at 55 °C. [g] Hydroformylation performed in 10% THF/benzene with 3 mol % Rh(acac)$(CO)_2$ and 6 mol % PPh_3 at 55 °C. [h] Ratio of aldehyde:hemiaminal:hydrogenated product. [i] Selectivity determined by analysis of crude ^{1}H NMR. [j] Isolated yields of the mixture of regioisomers.

effect from the sulfonamide functionality.[9] Hydroformylation of **2** in the presence of **1** affords complete conversion and a regioselectivity of 60:40 in favor of the branched isomer (Table 2, entry 2). Because of our earlier observation that the initial exchange between **1** and **2** is slow as compared to hydroformylation, we decided to repeat the reaction after preforming **4**. Under the modified conditions, a significant increase in the b:l selectivity to 90:10 is observed (Table 2, entry 3). Optimization of the CO/H_2 pressure to 400 psi further enhances the regioselectivity to 97:3 (b:l) (Table 2, entry 6). We believe the increased CO pressure inhibits the background hydroformylation reaction by inhibiting olefin coordination allowing for the directed reaction to compete more effectively.[10] Increased CO pressure may also facilitate ligand exchange on the metal, which is important in the turnover of the substrate.

Optimized reaction conditions in hand, we evaluated the reaction with regards to functional group tolerance. Application to a disubstituted olefin yields the desired regioisomer in comparable yield to the terminal olefin with an increase in regioselectivity to >99:1 (Table 3, entry 2). Furthermore, a more sterically hindered cyclohexyl substituted olefin provides good yield and selectivity for the desired regioisomer (Table 2, entry 3). A *Z*-substituted olefin shows enhanced reactivity, allowing the hydroformylation to be performed under milder reaction conditions while maintaining high yields and selectivities (Table 3, entry 4). A variety of styrene derived substrates afford the aldehyde β to the aromatic ring (Table 3, entry 5−8). These results highlight the utility of this strategy, since hydroformylation of styrenes usually favors the aldehyde at the α-position. Hydroformylation of an α,β-unsaturated ester using PPh_3 as the ligand provides very high regioselectivity for the hemiaminal product, presumably due to direction from the ester functionality (Table 3, entry 9). Also a significant amount of hydrogenation of the double bond occurs. When scaffolding ligand **1** is employed, the regioselectivity is reversed with minimal hydrogenation being observed (Table 3, entry 9). To further highlight the excellent chemoselectivity of the directed hydroformylation, reaction with a skip diene substrate yields only one aldehyde product and leaves the distal olefin unaffected (Table 3, entry 10).

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(9) For examples of amide directed hydroformylation see: (a) Ojima, I.; Zhang, Z. *J. Org. Chem.* **1988**, *53*, 4422. (b) Ojima, I.; Zhang, Z. *J. Organomet. Chem.* **1991**, *417*, 253. (c) Campi, E. M.; Chong, J. M.; Jackson, W. R.; Van Der Schoot, M. *Tetrahedron* **1994**, *50*, 2533. (d) Dickson, R. S.; Bowen, J.; Campi, E. M.; Jackson, W. R.; Jonasson, C. A. M.; McGrath, F. J.; Paslow, D. J.; Polas, A.; Renton, P.; Gladiali, S. *J. Mol. Cat. A.* **1999**, *150*, 133.

(10) van Leeuwen, P. W. N. M.; Casey, C. P.; Whiteker, G. T. *Rhodium Catalyzed Hydroformylation*; Leeuwen, P. W. N. M., Claver, C., Eds.; Kluwer Academic Publishers: Norwell, MA, 2001; Chapter 4, pp 63−106.

In conclusion, we have demonstrated that sulfonamides bind to scaffolding ligand **1**, and can be used in the highly regioselective hydroformylation for the synthesis of β-amino-aldehydes. We are currently developing enantiopure scaffolding ligands so that we can perform this reaction enantioselectively. Furthermore, we believe this new ligand class will be useful in other metal catalyzed reactions.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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