J|A|C|S COMMUNICATIONS

Published on Web 09/30/2010

Application of a Chiral Scaffolding Ligand in Catalytic Enantioselective Hydroformylation

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Abstract: The synthesis of β-amino-aldehydes has been achieved through enantioselective hydroformylation of PMP-protected allylic amines. The reaction is accomplished by using a scalemic scaffolding ligand that covalently and reversibly binds to the substrate. These ligands behave like chiral auxiliaries because they are covalently attached to the substrate during hydroformylation; however, similar to traditional asymmetric ligands, they can be used in catalytic quantities. The directed hydroformylation of disubstituted olefins occurs under mild conditions (35 °C and 50 psi CO/H_2), and *Z*-olefins afford excellent enantioselectivities (up to 93% ee).

Hydroformylation is an efficient method for synthesizing aldehyde products from olefins. The practicality of this method is evident with 9 million tons of aldehyde products being produced per year by hydroformylation.[1] The vast majority of these products are achiral commodity chemicals. The efficiency and utility of hydroformylation have led many researchers to pursue enantioselective variants.[2] Beyond inducing enantioselectivity, there are two main challenges faced in performing enantioselective hydroformylation: (1) controlling regioselectivity such that a chiral product is formed; (2) improving the reactivity of the catalyst system so that substituted olefins can be employed under mild conditions. Over the past 20 years there has been significant progress toward overcoming these obstacles. In 1993 Takaya and co-workers[3] as well as Whiteker and Babin[4] demonstrated the first practical enantioselective hydroformylation of activated olefins such as styrene and vinyl acetate. The reaction occurs with both high regioselectivity (due to electronic preferences or chelation) and high enantioselectivity. Since this ground-breaking work, efforts in enantioselective hydroformylation have focused on substrates that possess an inherent preference to form branched products or that are symmetrical such that only one regioisomer can be formed.[5] Recently, Zhang and co-workers reported the enantioselective hydroformylation of terminal alkenes that bear nitrogen-based directing groups (for example Boc and phthalimide) with good regioselectivities (b/l = 66:34 to 86:14).[6] Our group[7] and the Breit group[8] have developed a strategy that employs a catalytic directing group that controls the regioselectivity in hydroformylation. This strategy employs a metal-binding ligand (such as **2**, Figure 1) that can covalently and reversibly bind an organic substrate. These ligands not only control the regioselectivity of the reaction but also enhance the reactivity such that disubstituted olefins react under mild conditions. In this publication we extend this concept to enantioselective catalysis by designing and implementing an enantioenriched scaffolding ligand. Using 15 mol % of chiral scaffolding ligand **1** we obtain β-amino-aldehyde products with good yield and enantioselectivity (up to 93% ee).

† These authors contributed equally.

Our investigation began by developing an enantiomerically enriched scaffolding ligand. In our initial studies on the regio- and diastereoselective hydroformylation of homoallylic alcohols,[7a] we developed a ligand (**2**) that contains two stereogenic centers (Figure 1). Preliminary experiments with racemic ligand **2** suggested that the phosphorus stereocenter was not configurationally stable under the substrate exchange conditions;[9] therefore, we designed ligand **1**, which contains an additional stereocenter that is readily incorporated into the ligand synthesis via an enantioselective asymmetric hydrogenation of 2-isopropylquinoline. By incorporating the stereocenter on the tetrahydroquinoline ring, thermodynamic gearing controls the conformation of the other two stereocenters even under the exchange conditions. Computational studies suggested that the isopropyl group and C−O bond would have an *anti* relationship in order to minimize any *syn*-pentane-like interactions (Figure 1). Upon synthesis of (^{i}PrO)-**1**, we confirmed that the absolute and relative configuration of the ligand was the expected *anti*−*anti* configuration by obtaining an X-ray structure of the Rh((^{i}PrO)-**1**)$_2$(CO)Cl complex (Figure 2).

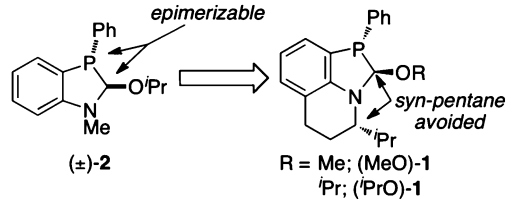


Figure 1. Chiral ligand design.

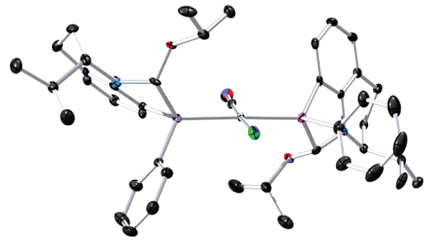
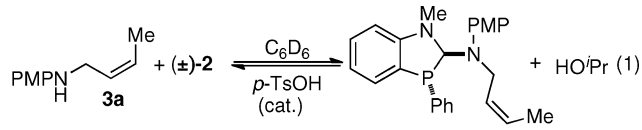


Figure 2. ORTEP structure of Rh(**1**)$_2$(CO)Cl.

With our enantioenriched ligand in hand we began our studies of the hydroformylation of amine-based substrates.[7b] As a first step, we investigated the ability of **3** to covalently bind to (±)-**2** and found that exchange occurs with a K_{eq} of 3.8 ± 0.5 (eq 1). Prior to hydroformylation **3a** was exchanged onto (±)-**2** and the free alcohol was removed *in vacuo*. Hydroformylation of **3a** followed by immediate reduction[10] afforded the β-amino-alcohol product in 39% yield by ^{1}H NMR (37% isolated) with 54% of **3a** remaining (eq 2).[11] Though the conversion is modest we were encouraged that the regioselectivity was high. With chiral ligand (^{i}PrO)-**1** or (MeO)-**1**,[12] the yield is significantly increased and excellent enantioselec-

tivity (92% ee) is observed (eq 2).[13] As a testament to the benefit of using directing groups the optimized conditions are very mild for the hydroformylation of a disubstituted olefin, only 35 °C and 50 psi of CO/H_2 (eq 2) are required.



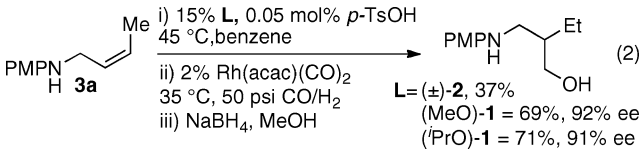
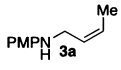
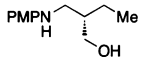
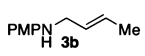
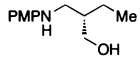
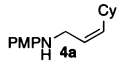
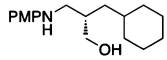
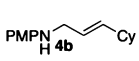
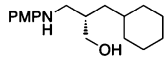
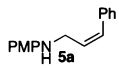
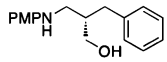
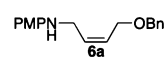
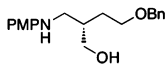
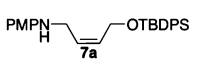
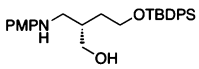
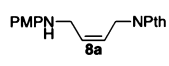
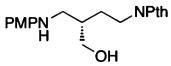
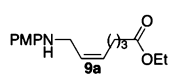
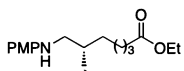
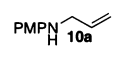
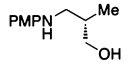


Table 1. Substrate Scope for Enantioselective Hydroformylation

entry	substrate	product	yield (%)	ee (%)
1[a]			69 (61)[e]	92 (92)[e]
2[a]			74	80
3[a]			75	86
4[a]			62	76
5[a]			45	79
6[b]			70	92
7[c]			66	90
8[d]			55	93
9[c]			68	90
10[c]			64	73

[a] (i)15 mol % (MeO)-**1**, 0.05 mol % *p*-TsOH, 45 °C, benzene; (ii) 2 mol % $Rh(acac)(CO)_2$, 35 °C, 50 psi of CO/H_2, (iii) $NaBH_4$, MeOH. [b] Standard conditions except 1.75 mol % $Rh(acac)(CO)_2$ and 0.03 mol % *p*-TsOH were used. [c] Standard conditions except 1.5 mol % $Rh(acac)(CO)_2$ was used. [d] Standard conditions except 1.75 mol % $Rh(acac)(CO)_2$ was used. [e] Reaction performed with 500 mg (2.8 mmol) of **3a**.

Having optimized the reaction parameters we investigated the substrate scope. As stated previously (*Z*)-**3a** yields the desired product in excellent enantioselectivity (Table 1, entry 1). When (*E*)-**3b** is hydroformylated the product is formed with good enantioselectivity (80% ee) and with the same absolute sense of enantioinduction (Table 1, entry 2). When the olefin is substituted with a more sterically demanding cyclohexyl group, the high enantioselectivity is maintained at 86% ee for the *Z*-olefin but a decrease in ee to 76% ee is observed for (*E*)-**4b** (Table 1, entries 3 and 4). Phenyl substituted **5a** affords the product with good enantioselectivity though with a modest yield (Table 1, entry 5). In this case 44% of **5a** remains at the end of the reaction demonstrating that the aldehyde is added selectively β to the aromatic ring, rather than the electronically preferred α-position. Entries 6−9 indicate a variety of functional groups are tolerated under the reaction conditions. For example substrates with either benzyl or silyl protected alcohols afford the desired product with high yields and enantioselectivities (Table 1, entries 6 and 7, respectively). A phthalamide and ester group are also compatible and maintain high enantioselectivities (Table 1, entries 8 and 9). Hydroformylation of a terminal olefin provides the product in 73% ee similar to the selectivities of the *E*-olefins, emphasizing the importance of a *cis* substituent to obtain excellent enantioselectivities.

We have demonstrated that asymmetric hydroformylation can be performed with good yield and high enantioselectivity by using an enantioenriched scaffolding ligand. The scaffolding ligand induces asymmetry more like a chiral auxiliary rather than a traditional chiral ligand for asymmetric catalysis in that the substrate is covalently bound to the group generating the stereoselectivity. Given the robustness and reliability of chiral auxiliaries to induce asymmetry, we believe scaffolding ligands will be able to afford high enantioselectivity in a broad range of reactions.

Acknowledgment. We thank Dr. Bo Li for determining the X-ray structure in Figure 2. We thank the Kingsbury and Hoveyda groups for use of their SFC and HPLC, respectively. We thank the ACS-PRF (DNI-5001400) and NIGMS (RO1GM087581) for funding this project. Mass spectrometry instrumentation at Boston College is supported by funding from the NSF (DBI-0619576).

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

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(9) The configurational instability of the phosphorous is unusual given the mild exchange conditions. We believe the instability arises from the fact that an iminium ion is a likely intermediate under the acidic exchange conditions. Rehybridization of the phosphorous to sp^2 would generate an aromatic heterocycle significantly lowering the barrier to inversion. Alternatively, the heterocycle may be ring opening to the secondary phosphine, which epimerizes and then ring closes to reform the heterocycle.

(10) Attempts to isolate the aldehyde directly resulted in poor recovery. Hayashi and co-workers had similar isolation problems: Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677–3680.

(11) The regioselectivities cannot be determined, because the product of hydroformylation of the carbon distal from the aniline functionality is not stable under the reaction conditions. This product likely forms a cyclic hemi-aminal that decomposes under the acidic conditions. Estimates of the regioselectivities are provided in the Supporting Information.

(12) Ligand (MeO)-**1** is a mixture of four diastereomers; see Supporting Information for further discussion. The pre-equilibration with **3** prior to hydroformylation forms a single diastereomer of substrate bound ligand. We prefer to use (MeO)-**1** over (^{i}PrO)-**1** because it can be synthesized in greater yield and affords comparable results to (^{i}PrO)-**1** (see eq 2).

(13) At the request of a reviewer we performed the reaction without pre-exchanging the substrate onto (MeO)-**4**. A comparable result is achieved with a marginally lower yield (67%) and ee (91%).

JA107433H