Summer Scholar Report

Regioselective Hydroformylation of Nosyl-Protected Homoallylic Sulfonamides

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Introduction: Hydroformylation, first discovered by Otto Roelen in 1938, involves the addition of carbon monoxide and hydrogen gas to an olefin to produce aldehydes. Nine million tons of aldehyde products are produced per year by rhodium-catalyzed hydroformylation on an industrial scale[i]. It is significant in commodity chemical synthesis because the aldehyde products are easily reduced to alcohols, which can then be converted to detergent or esterified to yield plasticizers. Rhodium–catalyzed hydroformylation is also applied to the synthesis of a key intermediate of vitamin A[ii]. Much effort has been put forth in studying hydroformylation due to its industrial significance.

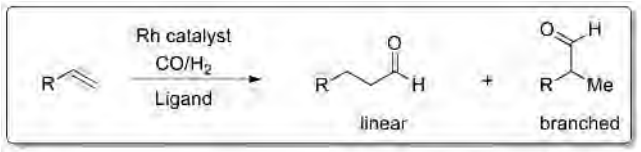


Figure 1: *Regiochemistry in Hydroformylation*

There are two primary challenges associated with regioselective hydroformylation. The first is the control of regioselectivity so that only the desired regioisomer is formed (linear or branched product). Given its industrial importance, academic and industrial efforts have been long focused in the development of catalysts for linear selective hydroformylation of terminal olefins.[iii] Branched- selective hydroformylation is often limited to activated substrates like styrene and vinyl acetate. The control of regioselectivity in hydroformylation is traditionally exerted via the use of stoichiometric phosphorus-based directing groups within the structure of the substrate. Although phosphorus-based directing groups are excellent ligands for the metal catalysts employed in hydroformylation, these functionalities have limited use in subsequent chemical transformations. Easily cleavable phosphorus-based directing groups have been developed to partially address this problem, but come with the inevitable shortcomings of additional synthetic steps and production of a stoichiometric amount of phosphorus-based byproducts[i]. The second challenge involves the optimization of the catalyst system to allow substituted olefins (often more sterically hindered) to be employed under mild reaction conditions

Our[iv] group and the Breit[iii] group simultaneously and independently developed different phosphorus-based ligands in 2008 to address the above challenges. The concept of utilizing reversible covalent bonds to induce an intramolecular reaction is central to the development of our scaffolding phosphorus ligand. Our scaffolding ligand has both a substrate binding domain and a metal binding domain (Figure 2). The substrate binding domain allows for the reversible covalent binding of various organic functionalities, including both the substrate and the product, which enables the catalytic usage of the ligand. The metal binding domain facilitates the coordination of the metal catalyst. The entropic cost in bringing together both the substrate and the metal catalyst is used to accelerate subsequent hydroformylation[v] (Figure 3). With the scaffolding ligand in hand, the Tan group was able to control regioselectivity (branched-selective) and enhance the reactivity such that less activated and trisubstituted olefins react under mild conditions[vi]. The Tan group has also modified their original racemic ligand and produced an enantioenriched ligand, which demonstrated good yield and enantioselectivity (up to 93% ee) in obtaining β-amino-alcohols from PMP protected allylic amines[i].

The application of the scaffolding ligand to regioselective hydroformylation of nosyl-protected homoallylic sulfonamides is discussed in this report.

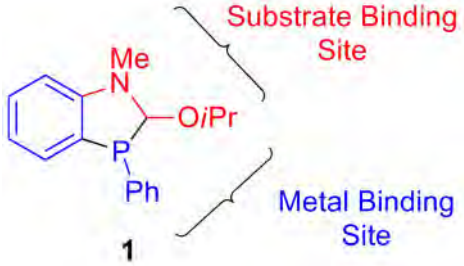


Figure 2: *Racemic Scaffolding Ligand*

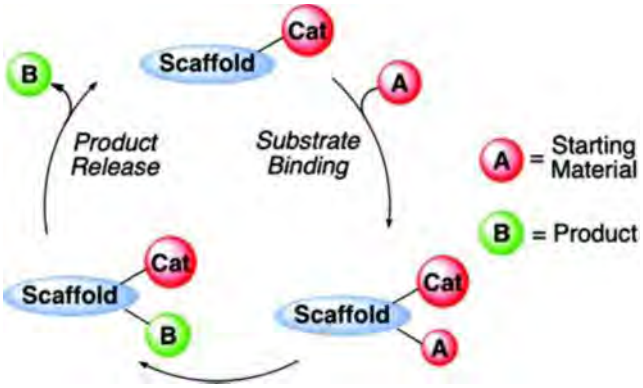


Figure 3: *Mechanism of the Scaffolding Ligand*

Results: Three substrates (**2**, **3**, and **4**) were synthesized by utilizing the two routes shown in Figure 4. Although the Mitsunobu reaction provides a one-step synthesis to the desired substrates, the yields are low. The second route is preferred because it gives a total yield of 79%, despite the fact that it involves two additional steps. Once the three substrates were prepared, the exchange of each of the three sub-

strates on to ligand **1** was studied. To our surprise, the sulfonamide exchange occurred rapidly with ligand **1**, with exchange between 72 % and 81% (Table 1) in two hours, under moderate heating at 65 °C in the presence of a catalytic amount of *p*-TsOH.

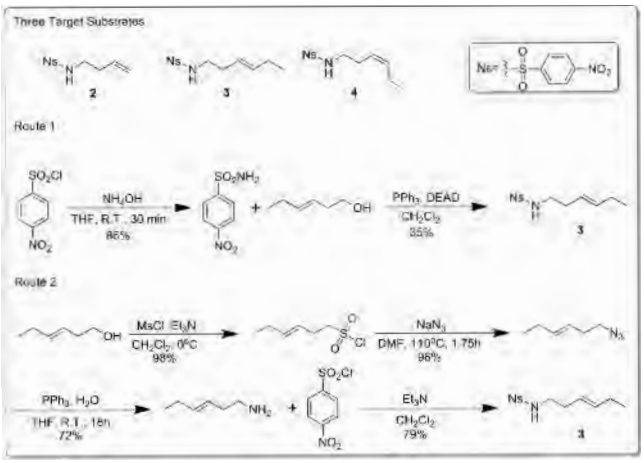
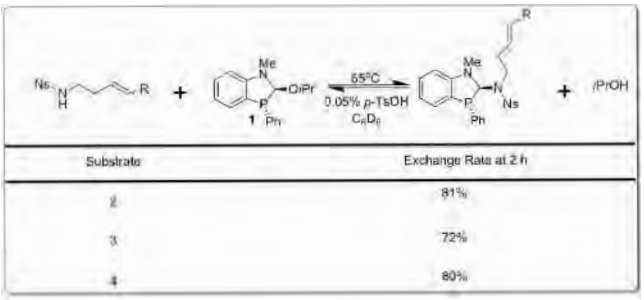


Figure 4: *Synthetic Routes for Substrates **2-4**: two different routes are shown for the synthesis of substrate **3***



Substrate	Exchange Rate at 2 h
2	81%
3	72%
4	80%

Table 1: *Exchange Data of Substrates **2, 3, and 4** with Scaffolding Ligand **1***

Hydroformylation reactions of substrates **2-4** were then investigated. As a control reaction, triphenylphosphine was used as the ligand, rather than ligand **1**. The mixture of aldehyde products after hydroformylation was oxidized and cyclized to the corresponding five-membered and the six-membered cyclic lactams.

Substrate **2** (Table 2, entry 1) shows strong preference for the formation of the linear product over the branched product (**B: L= 28:72**), given that the terminal carbon is much more active. Hydroformylation of substrates **3** and **4**(Table 2, entries 2 and 3) give almost **50:50** mixtures of the linear and the branched product, consistent with there being no discrimination between either disubstituted olefinic carbon by triphenylphosphine.

Hydroformylation of substrate **2** using ligand **1** shows a remarkable reversal in regioselectivity. Terminal olefin substrate **2** favors the formation of a linear product when triphenylphosphine serves as the ligand. (Table 2, entry 1) The scaffolding ligand is able to overturn the regioselectivity to **60:40** in the favor of the branched isomer.

A pressure screen was performed and the results are summarized in Table 3, entries 1-5. It was found that varying pressure does not produce any significant change to the conversion, regioselectivity, and yield of the reaction.

Hydroformylation of substrates **3** using ligand **1** shows excellent regioselectivity, good conversion and yield. The scaffolding ligand is able to direct the formation of branched isomer over the linear isomer with a **95:5** regioselectivity, compared to the almost **50:50** mixture exhibited by the triphenylphosphine control experiment (Table 2, entry 2).

A pressure screen was performed and the results are summarized in Table 2, entries 6-10. It was observed that varying pressure does not produce any significant change in the conversion, regioselectivity, and yield, consistent with the results of the pressure screen of substrate **2**.

An acid concentration screen (Table 3, entries 11-15) was also performed, which showed that altering the concentration of *p*-TsOH does not improve the results. In fact, at 0.25% *p*-TsOH, the conversion begins to drop, potentially due to accelerated ligand decomposition. Substrate **4** was used in the hydroformylation reactions in entries 16 and 17. It should be noted that substrate **3** (with the trans-olefin) and substrate **4** (with the cis-olefin) behave similarly in hydroformylation. An increase of rhodium catalyst loading from 2% to 4% (Table 3, entries 16-17) does not exhibit any significant change in the conversion, regioselectivity and yield.

Conclusion: In summary, this research has focused on achieving excellent regioselectivity in the hydroformylation of homoallylic sulfonamides by using a phosphine-based scaffolding ligand designed by the Tan group. A model system was chosen, and pressure, rhodium catalyst loading, and acid concentration were screened. It was found that good conversion (**>60%**) and excellent regioselectivities (**95:5**) were achieved under mild conditions for substrates which

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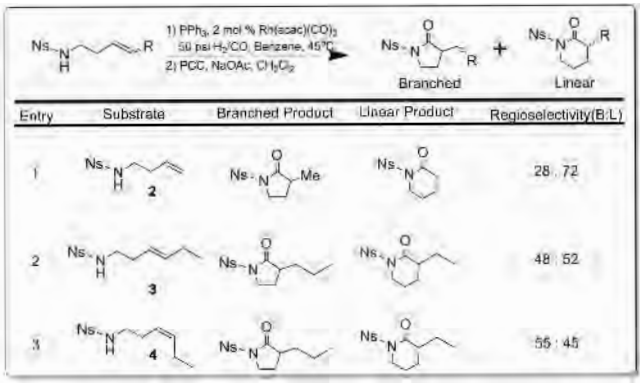
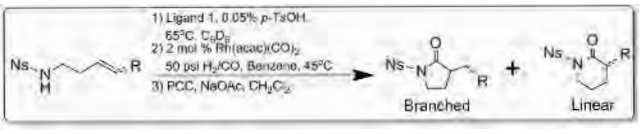


Table 2: *Control Experiments of Substrates **2, 3, and 4** with Triphenylphosphine. Regioselectivity determined by ^1H NMR.*



Scheme 1: *General Conditions of Hydroformylation Reactions in Table 3*

are typically unreactive. Present work is focusing on expanding the substrate scope, as well as the exploration of new enantioenriched ligands to achieve high levels of enantioselectivity.

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Entry	Substrate	Condition Altered	Conversion (%)	Regioselectivity (B:L)	Branched Product Yield (%)	Linear Product Yield (%)
1	2	50 psi H_2/CO	89	66 : 34	41	21
2	2	100 psi H_2/CO	84	64 : 36	42	24
3	2	200 psi H_2/CO	87	59 : 41	48	33
4	2	300 psi H_2/CO	89	65 : 35	43	23
5	2	400 psi H_2/CO	88	58 : 42	38	29
6	3	50 psi H_2/CO	65	96 : 4	48	2
7	3	100 psi H_2/CO	57	96 : 4	48	2
8	3	200 psi H_2/CO	62	95 : 5	49	2
9	3	300 psi H_2/CO	66	95 : 5	33	2
10	3	400 psi H_2/CO	68	94 : 6	41	2
11	3	0.05 % p-TsOH	56	94 : 6	35	2
12	3	0.10 % p-TsOH	66	94 : 6	40	2
13	3	0.15 % p-TsOH	63	95 : 5	55	3
14	3	0.20 % p-TsOH	63	95 : 5	43	2
15	3	0.25 % p-TsOH	54	96 : 4	38	2
16	4	2 % $Rh(acac)(CO)_2$	74	95 : 5	51	3
17	4	4 % $Rh(acac)(CO)_2$	69	90 : 10	49	5

Table 3: *Optimization of Homoallylic Sulfonamide Hydroformylation. Substrates **2**, **3**, and **4** were exchanged with ligand **1** at 65°C prior to hydroformylation. Gen- eral conditions of the hydroformylation reactions in entries 1-17 follow the ones given in scheme 1, except for the altered condition. Conversion, regioselectivity, and product yield were determined by ^1H NMR.*

References

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