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Highly Selective Asymmetric Hydrogenation Using a Three Hindered Quadrant Bisphosphine Rhodium Catalyst

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An academic quest for new and unique chiral phosphine ligands with properties superior to their predecessors is being driven by a pharmaceutical industry that is demanding increasingly efficient catalysts and better enantioselectivities for the manufacture of an array of chiral products.[1] However, many recent advances have evolved by the manipulation of phosphine ligand structures whose parent structures have been known for some time.[2] Many historically successful ligands are C_2-symmetrical; therefore, C_2-symmetry has remained a popular design for contemporary ligands. One of the better-known concepts of ligand design is the "quadrant diagram" of ligand−metal complexes (Figure 1). It has become generally accepted that chiral C_2-symmetrical bisphosphine ligands whose rhodium catalysts contain two nonadjacent hindered quadrants, such as Bis-P*,[3] **1**, is a "good" design for potentially high enantioselectivity for the asymmetric hydrogenation of certain substrates. This trend may have delayed the widespread development of useful C_1-symmetrical bisphosphine ligands and their corresponding hydrogenation catalysts.[4]

We report the synthesis of ligand **2** and the three hindered quadrant diagram of its rhodium complex (Figure 1).[5,6] A rhodium complex of **2** is reported to provide high enantioselectivity in catalyzed asymmetric hydrogenation of α-acetamido dehydroamino acids as well as a substrate precursor to the pharmaceutical candidate pregabalin. Advantages are described for the use of the rhodium complex to catalyze the large-scale hydrogenation of the pregabalin substrate.

The facile synthesis of both enantiomers of **2** and their corresponding rhodium complexes, **5**, is highlighted in Scheme 1. Synthesis of borane complex **4** was achieved in one step via the treatment of **3** with s-BuLi to form the methyllithium anion followed by the addition of di-*tert*-butylchlorophosphine. Coordination of the intermediate with borane provided racemic **4** in 55% yield. Separation via chiral preparatory HPLC produced each enantiomer of ligand **4** in 90% mass recovery.[7]

After separation, either enantiomer of ligand **2** could be generated from **4** via borane deprotection with DABCO in toluene at 80 °C. However, ligand **2** is sensitive to oxidation via air exposure. Upon formation, it was convenient to immediately synthesize its rhodium complex, **5**, by reaction with $[Rh(COD)_2]^+$ BF_4^-. Catalyst precursor **5** is stable in air for several hours. The absolute configuration of **5a** was determined by X-ray crystallography.[8]

High enantioselectivities have been achieved using many different chiral ligands in the rhodium-catalyzed asymmetric hydrogenation of α-acetamido dehydroamino acids. However, use of new chiral catalysts for the hydrogenation of this class of substrates provides the appropriate data for the comparison of catalyst selectivity with established benchmarks. Hydrogenation of substrates **6a**−**e** with **5a** provided products **7a**−**e** with near-perfect selectivity (Table 1). Imamoto et al. previously reported the synthesis of a similar ligand, 1-((1-adamantyl)methylphosphino)-2-(dicyclohexylphosphino)ethane.[4b] However, the observed highest enantiomeric excess (ee) for this ligand in rhodium-catalyzed asymmetric hydrogenation of α-acetamido dehydroamino acids was 71%.

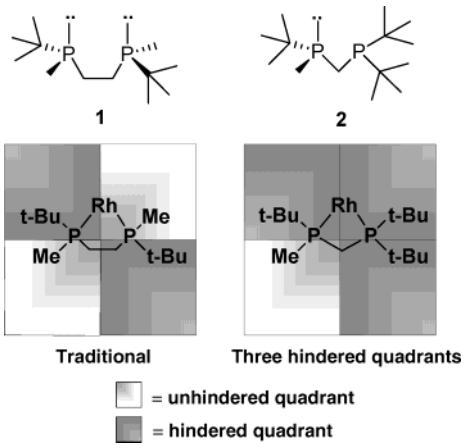
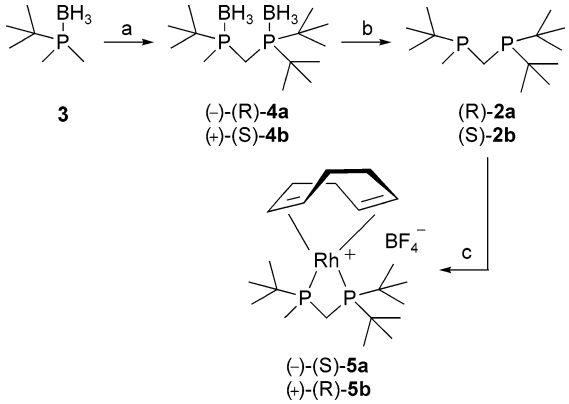


Figure 1. Quadrant diagram of Rh-**1** and Rh-**2**.

Scheme 1. Synthesis of Ligand **2** and Rhodium Complex **5**[a]



[a] Reagents and Conditions: (a) (1) s-BuLi, THF, −78 °C; (2) di-*tert*-butylchlorophosphine; (3) borane methyl sulfide complex (63% from **3**); (4) chiral preparatory HPLC separation (90% mass recovery); (b) DABCO, 80 °C, 4 h (81%); (c) $[Rh(COD)_2]^+$ BF_4^-, MeOH (64%).

The practical application of **5a** to the asymmetric hydrogenation of **8** to form **9** is demonstrated in Table 2. Compound **9** can be converted to pregabalin, a pharmaceutical used to treat epilepsy and pain, as described previously.[9] Using mild conditions (1 mol % **5a**, 45 psi H_2), the transformation provided **9** as the sole product of the hydrogenation in 99% ee (entry 1). Results have been reported for the use of (*R*,*R*)-Rh-Me-DuPhos to catalyze this transformation.[9,10] Entry 2 shows that (*R*,*R*)-Rh-Me-DuPhos is capable of similarly high enantioselectivities under mild conditions.

Selectivity is an important factor that is considered in large-scale asymmetric hydrogenation process research. However, many other factors contribute to the final decision to apply a particular catalyst in large-scale production. We examined two variables for

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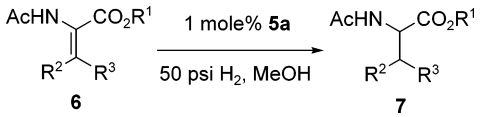
Table 1. Asymmetric Hydrogenation of α-Acetamido Dehydroamino Acids Using **5a** as Catalyst

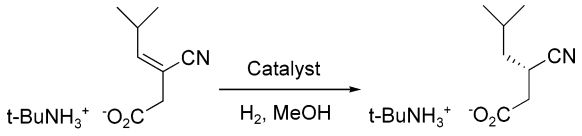


6 **7**

entry[a]	substrate	R^1	R^2	R^3	ee[b] (%)	config.
1	**6a**	H	H	H	>99	R
2	**6b**	H	Ph	H	>99	R
3	**6c**	Me	H	H	>99	R
4	**6d**	Me	Ph	H	>99	R
5	**6e**	Me	$R^2,R^3 = -C_5H_{10}-$		99	R

[a] Reactions were performed on 1 mmol substrate at room temperature with a substrate concentration of 0.2 M. Each was complete within 5 min. [b] Enantiomeric excesses were determined via chiral HPLC or GC as described in the Supporting Information.

Table 2. Asymmetric Hydrogenation of **8**: **5a** vs (*R,R*)-Rh-Me-DuPhos



8: E/Z (1:5.7) **9**

entry[a]	catalyst	substrate conc[b] (%)	S/C[c]	psi H_2	time[d]	ee[e] (%)
1	**5a**	6	100	45	<15 min	99
2	(*R,R*)-Rh-Me-DuPhos	6	100	90	<15 min	95
3	(*R,R*)-Rh-Me-DuPhos	10	2700	45	4 h	97
4	**5a**	20	27000	50	40 h	98

[a] (*R,R*)-Rh-Me-DuPhos reactions were performed at 55 °C, while **5a** reactions were performed at room temperature. [b] Substrate concentration in MeOH (w/w %). [c] Substrate:catalyst molar ratio. [d] Time at which gas uptake had ceased. All entries afforded >98% conversions at this time. [e] Enantiomeric excesses were determined via chiral GC as described in the Supporting Information. All experiments afforded the S configuration.

the hydrogenation of **8** to contrast the properties of **5a** and (*R,R*)-Rh-Me-DuPhos: substrate concentration[11] and catalyst loading. The results utilizing catalyst precursor **5a** were superior to those reported for (*R,R*)-Rh-Me-DuPhos (entry 3)[9] in both respects. Catalyst precursor **5a** is capable of producing **9** in 98% ee (100-g scale) using two times more concentrated reaction solutions and one-tenth of the reported catalyst loading (entry 4). Exploitation of these factors could have a profound impact on the cost of goods for producing a pharmaceutical on a scale that is appropriate for worldwide consumption.

In conclusion, a facile synthetic route to both enantiomers of ligand **2** and rhodium complex **5** was presented. Results reported for the use of **5** in the asymmetric hydrogenation of α-acetamido dehydroamino acids as well as a pregabalin substrate precursor provide support for association of high enantiomeric excesses with the three hindered quadrant motif exhibited by the catalyst.[12] Although this communication does not contain a catalytic cycle study, our report may also have implications for the mechanistic understanding of asymmetric hydrogenation selectivity. Applications of **5** to the gamut of asymmetric hydrogenation substrate classes are currently under investigation.

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Supporting Information Available: Materials and methods, synthetic procedures for **2**−**5**, and the chiral preparatory HPLC separation method for the enantiomers of **4**. X-ray crystallographic data for **5a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Reviews: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley−VCH: New York, 2000; pp 1−110. (c) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. I, pp 121−182.

(2) An excellent example is the development of an extraordinary number of phospholane ligands, all of which are based on the DuPhos structure. For a discussion on this topic, see: Hoge, G. *J. Am. Chem. Soc.* **2003**, *125*, 10219.

(3) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635.

(4) There have been reports of useful ligands that break the C_2-symmetry mold; however, cohesive models remain elusive for C_1-symmetrical ligands with respect to steric environments of the ligands and their corresponding catalysts that translate to high enantioselectivity during hydrogenation. See: (a) Blaser, H.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A. *Top. Catal.* **2002**, *19*, 3. (b) Ohashi, A.; Kikuchi, S.; Yasutake, M.; Imamoto, T. *Eur. J. Org. Chem.* **2002**, *15*, 2535. (c) Matsumura, K.; Shimizu, H.; Saito, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2003**, *345*, 180.

(5) Ligand **2** is referred to as "Trichickenfootphos" in Pfizer laboratories. This name is derived from visual inspection of the ligand and the association of *tert*-butyl groups with chicken feet.

(6) We have also succeeded in synthesizing 1-(*tert*-butylmethylphosphino)-2-(di-*tert*-butylphosphino)ethane. This ligand produces enantioselectivities similar to those of **2** in the rhodium-catalyzed asymmetric hydrogenation of α-acetamido dehydroamino acids.

(7) Despite the stigma associated with chiral preparatory HPLC separations, this type of separation is becoming increasingly important to the pharmaceutical industry. That **4** contains one chiral center makes it ideal for a chiral separation-based synthesis as well as a strong candidate for production-scale separation via simulated moving bed (SMB) chromatography. See: Welch, W. M.; Ewing, F. E.; Huang, J.; Menniti, F. S.; Pagnozzi, M. J.; Kelly, K.; Seymour, P. A.; Guanowsky, V.; Guhan, S.; Guinn, M. R.; Critchett, D.; Lazzaro, J.; Ganong, A. H.; DeVries, K. M.; Staigers, T. L.; Chenard, B. L. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 177.

(8) Interestingly, Imamoto's methylene-bridged MiniPHOS ligand can only be synthesized in bischelate form. No bischelate complex was observed during the synthesis of **5**. See: Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988.

(9) Burk, M. J.; De Koning, P. D.; Grote, T. M.; Hoekstra, M. S.; Hoge, G.; Jennings, R. A.; Kissel, W. S.; Le, T. V.; Lennon, I. C.; Mulhern, T. A.; Ramsden, J. A.; Wade, R. A. *J. Org. Chem.* **2003**, *68*, 5731.

(10) (*R,R*)-Rh-Me-DuPhos = (−)-1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)-benzene(cyclooctadiene)rhodium (I) tetrafluoroborate.

(11) Concentration is an important factor in large-scale hydrogenation because it determines the amount of product that can be produced in a finite reactor volume.

(12) No commentary on the mechanism of asymmetric hydrogenation using this catalyst is being presented at this time; however, we feel that it is prudent to associate the ligand and its design, the three hindered quadrant motif, with high enantioselectivity for the demonstrated substrate classes.

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