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Highly Enantioselective Asymmetric Hydrogenation of β-Acetamido Dehydroamino Acid Derivatives Using a Three-Hindered Quadrant Rhodium Catalyst

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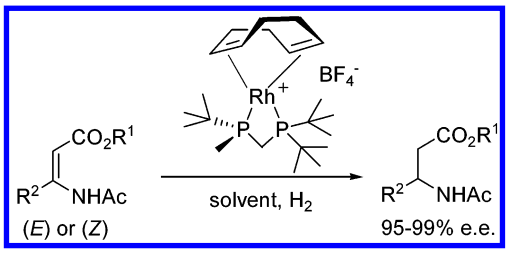
ABSTRACT



A previously reported three-hindered quadrant chiral ligand and its corresponding rhodium complex provide high enantioselectivity for the asymmetric hydrogenation of β-acetamido dehydroamino acid substrates. Both (*E*)- and (*Z*)-substrates are hydrogenated with high enantioselectivity in all of the reported examples. Asymmetric hydrogenation of a cyclic β-acetamido dehydroamino acid substrate in 85% ee is also reported.

The continuing importance of chiral β-amino acids to medicinal chemistry is highlighted by the number of recent reports and reviews that detail convenient chiral methodologies to access them.[1] Although asymmetric hydrogenation of β-acetamido dehydroamino acids with chiral homogeneous catalysts is a methodology that offers promise for the synthesis of β-amino acids, a stumbling block for this approach has been poor selectivity during the hydrogenation of mixtures of the configurational isomers of the substrates. While (*E*)-substrates can be hydrogenated in high enantiomeric excess using a variety of known catalysts, only a few catalysts can hydrogenate (*Z*)-substrates with synthetically practical selectivity.[2] To exacerbate this issue, the synthesis of an exclusively (*E*)-isomer substrate has not been realized via current methodologies. In fact, the (*Z*)-isomer is often the major product produced via these synthetic protocols.[2] Therefore, there is a need for efficient catalysts that can hydrogenate both (*E*)- and (*Z*)-β-acetamido dehydroamino acids in high enantiomeric excess.

We recently reported the synthesis of both enantiomers of ligand **1** featuring an HPLC chiral separation crux (Figure 1).[3] Resolved rhodium complexes of the ligand, **2**, were demonstrated to provide very high enantioselectivity for a

(1) (a) Ikemoto, N.; Tellers, D. M.; Dreher, S. D.; Liu, J.; Huang, A.; Rivera, N. R.; Njolito, E.; Hsiao, Y.; McWilliams, J. C.; Williams, J. M.; Armstrong, J. D., III; Sun, Y.; Mathre, D. J.; Grabowski, E. J. J.; Tillyer, R. D. *J. Am. Chem. Soc.* **2004**, *126*, 3048−3049. (b) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290−4299. (c) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035. (d) Gademann, K.; Hintermann, T.; Schreiber, J. V. *Curr. Med. Chem.* **1999**, *6*, 905. (e) *Enantioselective Synthesis of β-Amino* Acids; Juaristi, E., Ed.; Wiley-VCH: New York, 1996.

(2) (a) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907−6910. (b) Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Börner, A. *J. Org. Chem.* **2003**, *68*, 1701−1707. (c) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509−3511. (d) Lee, S.-g.; Zhang, Y. J. *Org. Lett.* **2002**, *4*, 2429−2431. (e) Peña, D.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 14552−14553. (f) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *23*, 4159−4161. (g) Yasutake, M.; Gridnev, I. D.; Higashi, N.; Imamoto, T. *Org. Lett.* **2001**, *11*, 1701−1704.

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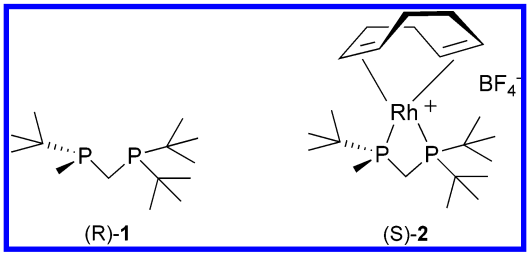
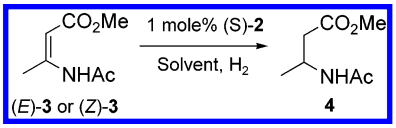


Figure 1. Structure of ligand (*R*)-**1** and catalyst (*S*)-**2**.

variety of classic substrates, α-acetamido dehydroamino acids, during catalyzed asymmetric hydrogenation. We also reported the practical synthetic utility of the rhodium complex in the asymmetric hydrogenation of a substrate precursor to the pharmaceutical candidate, pregabalin.[4] Associations were drawn between the observed high enantioselectivity and the structure of ligand **1** that features three bulky *tert*-butyl groups located in the vicinity of the rhodium catalysis center. To further highlight the utility of the design of ligand **1** and its corresponding rhodium catalysts, we report the highly enantioselective hydrogenation of both (*E*)- and (*Z*)-*β*-acetamido dehydroamino acids.

Table 1 depicts an initial screen for the application of catalyst (*S*)-**2** to the asymmetric hydrogenation of (*E*)- and

Table 1. Asymmetric Hydrogenation of (*E*)- and (*Z*)-Methyl-3-acetamido-2-butenoate Using (*S*)-**2** as a Catalyst[a]



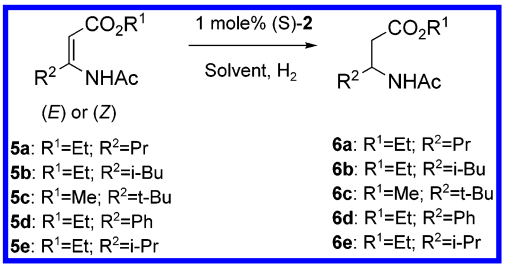
entry	substrate	solvent	psi H_2	ee (%)[b]
1	(*E*)-**3**	MeOH	20	99 (*R*)
2	(*E*)-**3**	THF	20	99 (*R*)
3	(*E*)-**3**	EtOAc	20	99 (*R*)
4	(*E*)-**3**	CH_2Cl_2	20	99 (*R*)
5	(*Z*)-**3**	MeOH	20	96 (*R*)
6	(*Z*)-**3**	THF	20	96 (*R*)
7	(*Z*)-**3**	EtOAc	20	98 (*R*)
8	(*Z*)-**3**	CH_2Cl_2	20	97 (*R*)
9	(*Z*)-**3**	THF	50	94 (*R*)
10	(*Z*)-**3**	THF	6	99 (*R*)
11	(*E*)-**3**/(*Z*)-**3** (1:1)	THF	20	98 (*R*)

[a] Reactions were performed on 1 mmol of substrate at room temperature with a substrate concentration of 0.2 M. Each was complete within 15 min. [b] Enantiomeric excesses were determined via chiral GC as described in Supporting Information.

(*Z*)-methyl-3-acetamido-2-butenoate, **3**. Four solvents (MeOH, THF, EtOAc, and CH_2Cl_2) were examined at 20 psi H_2 for the hydrogenation of (*E*)-**3** in entries 1−4. Each produced 99% ee with complete conversion in fast reaction times (complete in less than 15 min). Entries 5−8 depict results for the identical solvent screen on substrate (*Z*)-**3**. All entries afforded 96% ee or greater with reaction times similar to those observed for (*E*)-**3**. For reactions performed in THF we observed subtle pressure effects. The initial screen at 20 psi (entry 6) provided 96% ee with complete conversion to product. However, when the initial applied pressure over the reaction solution was increased to 50 psi, the enantiomeric excess of the reaction decreased to 94% (entry 9). Performing the reaction at 6 psi produced the highest enantiomeric excess (99%) for THF (entry 10). Entry 11 depicts asymmetric hydrogenation of a 1:1 mixture of (*E*)- and (*Z*)-**3** in THF solvent and 20 psi H_2. These conditions produced 98% ee product.

A broader screen of *β*-acetamido dehydroamino acid derivatives was then undertaken to examine the efficacy of this catalyst system for this substrate class (Table 2). Entries

Table 2. Asymmetric Hydrogenation of *β*-Acetamido Dehydroamino Acid Derivatives, **5a**−**e**, Using (*S*)-**2** as a Catalyst[a]



entry	substrate	olefin configuration	solvent	psi H_2	ee (%)[b]
1	**5a**	(*E*)	THF	20	99 (*R*)
2	**5a**	(*Z*)	THF	20	96 (*R*)
3	**5b**	(*E*)	THF	20	98 (*R*)
4	**5b**	(*Z*)	THF	20	98 (*R*)
5	**5c**	(*E*)	THF	20	99 (*S*)
6	**5d**	(*Z*)	THF	20	96 (*S*)
7	**5e**	(*E*)	THF	20	99 (*S*)
8	**5e**	(*Z*)	THF	20	78 (*S*)
9	**5e**	(*Z*)	MeOH	20	69 (*S*)
10	**5e**	(*Z*)	EtOAc	20	84 (*S*)
11	**5e**	(*Z*)	EtOAc	50	66 (*S*)
12	**5e**	(*Z*)	EtOAc	6	92 (*S*)

[a] Reactions were performed on 1 mmol of substrate at room temperature with a substrate concentration of 0.2 M. Each was complete within 15 min. [b] Enantiomeric excesses were determined via chiral GC as described in Supporting Information.

1−4 depict the results of hydrogenation of both (*E*)- and (*Z*)-**5a** (R = propyl) and **5b** (R = isobutyl). High enantiomeric excesses of **6a** and **6b** (>96%) were obtained for each case. Identical conditions for the case of (*E*)-**5c** (R = *tert*-butyl, entry 5) provided **6c** in 99% ee. The (*Z*) isomer of **5c** was not observed during the synthesis of the substrate; therefore, this isomer was not tested. Entry 6 depicts the

(3) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966−5967.
(4) (a) Lauria-Horner, B. A.; Pohl, R. B. *Expert Opin. Investig. Drugs* **2003**, *12*, 663. (b) Selak, I. *Curr. Opin. Investig. Drugs* **2001**, *2*, 828.

result for substrate (*Z*)-**5d** (R = phenyl). Only two catalysts have been reported to provide high enantiomeric excess for phenyl and substituted phenyl β-acetamido dehydroamino acid derivatives.[2c−d] Catalyst (*S*)-**2** provided product **6d** in 96% ee.

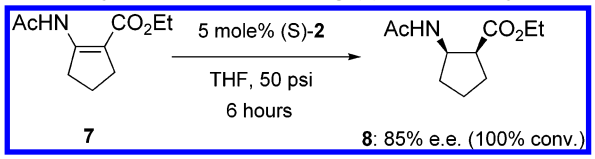
Entry 7 depicts the result of the hydrogenation of substrate **5e**. The (*E*)-isomer was hydrogenated in 99% ee at 20 psi H_2 in THF. However, the hydrogenation of (*Z*)-**5e** provided **6e** in only 78% ee under the same conditions (entry 8). We found a solvent influence on the degree of enantioselectivity for this substrate. When the reaction was run in MeOH (entry 9), the enantiomeric excess of **6e** was 69% under essentially the same reaction conditions as those described for entry 8. However, when the reaction was performed in EtOAc, the enantiomeric excess of **6e** increased to 84% ee (entry 10).

Similar to results reported in Table 1, we found more dramatic pressure effects for the hydrogenation of (*Z*)-**5e**. Using EtOAc as a solvent, increasing the hydrogen pressure over the reaction to 50 psi produced 66% ee (entry 11). However, in entry 12 the pressure of the reaction was reduced to 6 psi. These conditions provided **6e** in 92% ee.

Finally, a recently published Communication describes highly enantioselective hydrogenation of cyclic β-acetamido amino acid substrates using bisphosphine ruthenium complexes.[5] However, it was mentioned that the electron-rich Rh−(*S*,*S*,*R*,*R*)-Tangphos complex provided no reactivity for the transformation under 50 psi H_2. Scheme 1 depicts the asymmetric hydrogenation of cyclic β-acetamido dehydroamino acid **7** using (*S*)-**2** as a catalyst. The result of 85% ee shows potential for the application of rhodium catalysts to this substrate class.

In conclusion, more evidence has been presented in this Communication that the three-hindered quadrant motif of rhodium catalysts derived from ligand **1** can provide enantioselectivities equal to the current state-of-the-art with

Scheme 1. Asymmetric Hydrogenation of Cyclic β-Acetamido Dehydroamino Acid **7** Using (*S*)-**2** as a Catalyst



C_2-symmetrical ligands during asymmetric hydrogenation. Provided the few catalysts that have been reported to provide high enantioselectivity for the hydrogenation of (*Z*)-isomers of β-acetamido dehydroamino acids, this report continues to challenge the need for C_2-symmetry in asymmetric hydrogenation ligand design. Broader applications of this catalyst to a variety of substrate types will unveil the true potential of the ligand.

The design of ligand **1** may also have impact in other areas of asymmetric catalysis. Bisphosphine transition metal catalysts have been shown to provide high enantiomeric excess for a variety of catalytic transformations other than asymmetric hydrogenation.[6] It remains to be seen if ligand **1** can successfully be applied to these transformations as well.

Acknowledgment. Pfizer, Inc., is acknowledged for continuing support of this research.

Supporting Information Available: Materials and methods, synthetic procedures for the synthesis of substrates **3** and **5**, and methods for the evaluation of enantiomeric excesses of **4**, **6**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Tang, W.; Wu, S.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 9570−9571.
(6) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363−372.