

# Rhodium-Catalyzed and Zinc(II)-Triflate-Promoted Asymmetric Hydrogenation of Tetrasubstituted $\alpha,\beta$ -Unsaturated Ketones

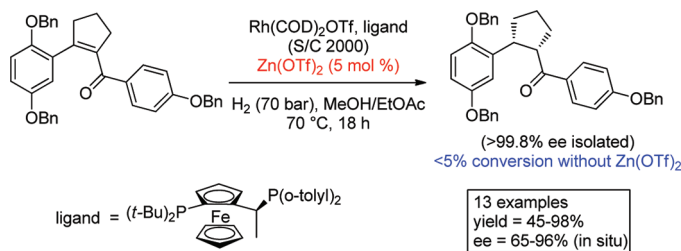
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Received December 20, 2011

## ABSTRACT



The asymmetric hydrogenation of tetrasubstituted  $\alpha,\beta$ -unsaturated ketones has been accomplished using an in situ formed rhodium-Josiphos catalyst. The reaction is enhanced by addition of catalytic zinc(II) triflate, which significantly improves turnover frequency while suppressing epimerization of the products.

Homogeneous asymmetric hydrogenation of olefins is a powerful tool for the synthesis of enantiopure chiral materials.<sup>1</sup> Numerous examples of this general methodology exist in the synthesis of molecules of pharmaceutical importance.<sup>2</sup> The selective reduction of  $\alpha,\beta$ -unsaturated ketones is an appealing approach to the synthesis of optically active ketone products.<sup>3</sup> The products of such

transformations may contain one or two new stereocenters depending upon the degree of substitution in the starting material. Unlike more widely studied systems such as  $\alpha,\beta$ -unsaturated acids and esters, enones require an additional degree of chemoselectivity such that the carbonyl functionality is not reduced in either the starting substrate or product.<sup>4</sup> Several research groups have independently reported the asymmetric reduction of trisubstituted enones with iridium<sup>5–7</sup> and ruthenium-based<sup>8</sup> catalysts.

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(1) A classic example of asymmetric alkene reduction is the synthesis of L-DOPA: Knowles, W. S.; Sabacky, M. J. *J. Chem. Soc., Chem. Commun.* **1968**, 1445. Also see Ager, D. J. Enantioselective Alkene Hydrogenation: Introduction and Historic Overview. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C., Eds.; Wiley-VCH: Weinheim, Germany, 2007; Vol 2, pp 745–772.

(2) See: *Asymmetric Catalysis on Industrial Scale*, 2nd ed.; Blaser, H.-U., Federsel, H.-J., Eds.; Wiley-VCH: Weinheim, Germany, 2006; Vol. 2.

(3) (a) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, 122, 6797. (b) Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. A. *Org. Lett.* **2004**, 6, 1273. (c) Ouellet, S. G.; Walji, A.; Macmillan, D. W. C. *Acc. Chem. Res.* **2007**, 40, 1327.

(4) For examples of chemo- and stereoselective reductions of enones to provide allylic alcohols, see: (a) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, 120, 13529. (b) Xie, J.-H.; Liu, X.-Y.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2011**, 50, 7329.

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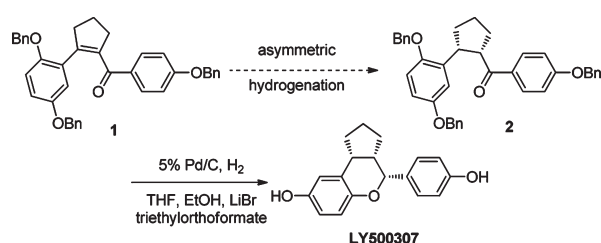
(6) Lu, W.-J.; Chen, Y.-W.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2008**, 47, 10133.

(7) Rageot, D.; Woodmansee, D. H.; Pugin, B.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2011**, 50, 9598.

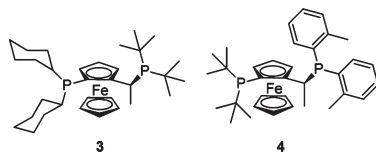
(8) (a) Massonneau, V.; Maux, P. L.; Simonneaux, G. *Tetrahedron Lett.* **1986**, 27, 5497. (b) Massonneau, V.; Maux, P. L.; Simonneaux, G. *J. Organomet. Chem.* **1987**, 327, 269.

However, examples of asymmetric reductions of the corresponding tetrasubstituted enones are rare.<sup>9–11</sup> In conjunction with the synthesis of ER $\beta$  agonist LY500307, we required the stereoselective reduction of enone **1** to saturated ketone **2** (Scheme 1). Attempts to reduce **1** under several known conditions failed, which highlighted the need to develop methodology that expanded the scope of this reaction type. We report herein the development of a highly chemo- and enantioselective rhodium-catalyzed asymmetric reduction of tetrasubstituted enones. A key feature of this method is the use of catalytic zinc triflate, which significantly improves turnover frequency and suppresses epimerization in the  $\alpha$ -position of the products.

**Scheme 1.** Synthesis of LY500307 via Asymmetric Hydrogenation of Enone **1**



Catalyst screening with enone **1** led to the identification of a rhodium complex with ligand **3** (Figure 1),<sup>12</sup> which provided high stereoselectivity (> 95% ee) and conversion (> 95%).<sup>13</sup> High throughput screening<sup>14</sup> led to the identification of the rhodium complex of ligand **4**, which was also highly stereoselective (95% ee) but superior to **3** with regard to chemoselectivity and stability across a wider range of reaction conditions. Efforts to further develop both leads were disappointing, however, as catalyst loadings were too high for practical development.<sup>15</sup>



**Figure 1.** Optimized ligands from screening.

(9) Asymmetric hydrogenation of unfunctionalized tetrasubstituted alkenes is known; see: Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402.

(10) Chemoselective reduction of tetrasubstituted enones has been reported using Rh/Al. See: Yamaguchi, M.; Nitta, A.; Reddy, R. S.; Hirama, M. *Synlett* **1997**, 177.

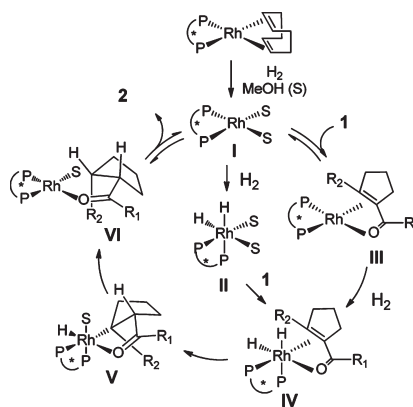
(11) An example of ruthenium-catalyzed asymmetric hydrogenation of endocyclic tetrasubstituted enones is the synthesis of Jasmine odorants. See: Saudan, L. A. *Acc. Chem. Res.* **2007**, *40*, 1309 and references therein. Similarly, Rh-catalyzed asymmetric reduction of trisubstituted endocyclic enones has also been reported. See: Ohshima, T.; Tadaoka, H.; Hori, K.; Sayo, N.; Mashima, K. *Chem.—Eur. J.* **2008**, *14*, 2060.

(12) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.

(13) See the Supporting Information for the full details of this screen.

The mechanistic landscape for rhodium-catalyzed asymmetric hydrogenation is dominated by studies associated with *N*-acyldehydroamino acids and derivatives thereof.<sup>16</sup> Applying this previous work, a catalytic cycle for enone **1** is shown in Scheme 2. Key dihydride complex **IV** can be formed from complex **III** or solvate dihydride **II**. Evidence supporting either the solvate dihydride (**II**)<sup>17</sup> or unsaturated solvate (**I**)<sup>18</sup> has not been studied for enone systems. We speculated that the combination of severe steric environments of both the ligand–metal complex and the substrate were contributing factors to slow substrate metal coordination to form complex **III** or **IV**.

**Scheme 2.** Plausible Catalytic Cycle for Enone Hydrogenation



A screen of additives revealed that several Lewis acids dramatically improved the rate of the reaction (Table 1). For example, 5 mol % Zn(OTf)<sub>2</sub> afforded full conversion at a catalyst loading of S/C 2000, while the control reaction did not proceed. Furthermore, when zinc triflate was added to a control experiment after 16 h (1–2% conversion), the reaction proceeded at an identical rate to that of a standard reaction where zinc triflate was present at the outset (Figure 2). This demonstrated that the catalyst was stable over long reaction times, but turnover frequency was low.<sup>19</sup>

We observed that Lewis acids derived from superacids such as triflic acid or tetrafluoroboric acid led to increased turnover, while others such as zinc chloride and

(14) This supplemental high throughput screening was conducted by Dr. Felix Spindler and Dr. Erhard Bappert at Solvias AG, Basel, Switzerland. This screen was designed to further examine the ferrocene-based scaffold that had been previously identified.

(15) Maximum S/C was 100 for **3** and 200 for **4**. While this may be of some utility for small scale material production, these loadings are easily an order of magnitude too high for practical process development.

(16) Dehydroaminoacids such as (*Z*)- $\beta$ -amidocinnamate (MAC) have a different substrate–metal binding relationship than that of  $\alpha,\beta$ -unsaturated ketones. This difference is manifested in a metalacycle **V**, which is bound to the  $\beta$ -carbon instead of the  $\alpha$ -carbon as in MAC.

(17) Gridnev, I. D.; Imamoto, T.; Hoge, G.; Kouchi, M.; Takahashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 2560.

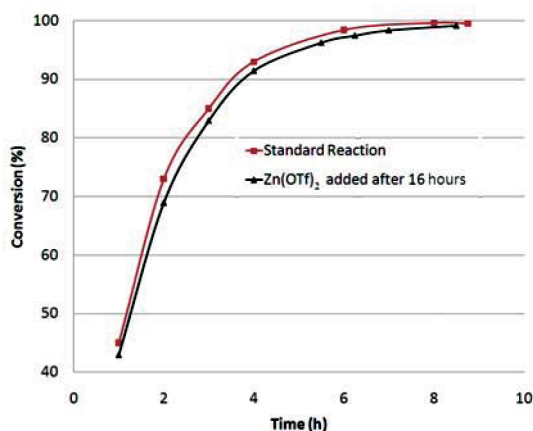
(18) There is still considerable question concerning the sequence of events involved in the formation of complex **IV**. For leading references, see: (a) Chan, A. S. C.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838. (b) Gridnev, I. D.; Imamoto, T. *Acc. Chem. Res.* **2004**, *37*, 633.

(19) At S/C 2000, the control experiment without Zn(OTf)<sub>2</sub> progressed to ~2% after 18 h, while the experiment with Zn(OTf)<sub>2</sub> was complete in 8 h. This represents a > 100 $\times$  increase in TOF.

**Table 1.** Study of Key Additives<sup>a</sup>

$  \begin{array}{c}  \text{Rh(COD)}_2\text{OTf, 4} \\  \text{S/C 2000} \\  \text{1} \xrightarrow[\text{additive}]{\text{MeOH / EtOAc, 18 h}} \text{2} + \text{5} \\  \text{70 }^\circ\text{C, H}_2 \text{ (1000 psi)}  \end{array}  $					
entry	additive	equiv	conv (%) <sup>b</sup>	5 (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	none		1	0	
2	Sc(OTf) <sub>3</sub>	0.20	100	40	95
3	ZnCl <sub>2</sub>	0.15	12	0	94
4	Zn(OAc) <sub>2</sub>	0.25	0	0	
5	Zn(BF <sub>4</sub> ) <sub>2</sub>	0.30	100	0	95
6	Zn(OTf) <sub>2</sub>	0.05	100	0	95
7	Zn(OTf) <sub>2</sub>	1.0	100	0	95
8	TfOH	0.01	100	6	95
9	TfOH	0.001	17	0	96

<sup>a</sup> All reactions were conducted on 100 mg of **1** in 1.1 mL of 30% MeOH/EtOAc. <sup>b</sup> Peak area % by reverse phase HPLC at 220 nm shown. <sup>c</sup> Reported on the basis of normal phase HPLC analysis with a chiral column (AD-H Chiral Pak) at 220 nm.

**Figure 2.** Overlay of a standard reaction with Zn(OTf)<sub>2</sub> with a reaction where Zn(OTf)<sub>2</sub> was added after 16 h.

zinc acetate did not provide similar results. This prompted us to determine if Brønsted acids were contributing to this acceleration. As shown in Table 1, triflic acid<sup>20</sup> is a potent cocatalyst (< 0.1 mol %);<sup>21</sup> however, these reactions were prone to epimerization of product to form *trans*-ketone **5**.

(20) Tetrafluoroboric acid was also examined, and similar results were observed. However, HBF<sub>4</sub> led to slightly lower ee and has the additional liability of generating HF. On the basis of this, we focused the work on triflic acid and salts thereof.

(21) For an example of cooperative metal–Brønsted acid catalysis, see: Li, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* **2009**, *131*, 6967.

(22) If TfOH was generated via Zn(OTf)<sub>2</sub> + MeOH, increasing the Zn(OTf)<sub>2</sub> concentration by 20× should result in higher TfOH concentration. This, in turn, should result in an increased amount of product epimerization. We would also expect the hydrolysis rate of zinc triflate to be negligible on the basis of literature precedent. See: Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169.

Other acids such as TFA, MSA, and nitric acid all failed to promote the reaction as well. When 1 equiv of zinc triflate was used (Table 1, entry 7), no epimerization was observed, which suggested that triflic acid was not the source of rate acceleration.<sup>22</sup> To further isolate the effect of zinc triflate, we examined the reaction rates between a standard reaction and one where 10 mol % 2,6-di-*tert*-butylpyridine was added as an acid scavenger.<sup>23</sup> After 8 h, the conversion was 96% with the acid scavenger, just slightly slower than the rate of the control reaction (> 99%). This data also suggested that both zinc triflate and triflic acid catalyze this reaction independently. As such, any mechanistic rationale must account for both possibilities.

The reduction of **1** could be accelerated further by increasing temperature<sup>24</sup> and pressure.<sup>25</sup> In both cases, these changes had almost no effect on enantioselectivity.<sup>26</sup> Other solvents were examined,<sup>27</sup> but the mixed system of methanol and ethyl acetate was superior from reaction rate, solubility, impurity profile, and environmental considerations.<sup>28</sup> Reduction of des-keto **1** failed, which showed the necessity of the directing group.<sup>29</sup> Experiments with D<sub>2</sub> showed equal 96%<sup>30</sup> incorporation at both the α and β positions of the enone, which is consistent with the pathway in Scheme 2. This result eliminated the possibility of alkene migration prior to reduction. When optimized conditions<sup>31</sup> were applied to substrate **1** (10 g scale), ketone **2** was obtained in 90% isolated yield (> 99.8% ee<sup>32</sup>) after crystallization.<sup>33</sup>

A possible mechanistic rationale for this rate acceleration is shown in Scheme 3. Mixed ketal (**VII**) could form in

(23) This could include residual TfOH in Zn(OTf)<sub>2</sub> or TfOH generated from reaction with residual water or methanol.

(24) A screen of temperature was conducted with ligand **5** (S/C 2000 and 4000) and 5 mol % Zn(OTf)<sub>2</sub>. Reaction profiles were clean at temperatures up to 90 °C, but above 90 °C, the reaction profiles showed increased impurities, notably epimerization in the α-position. A slight erosion of ee was also observed (94 vs 95% ee).

(25) A significant pressure effect was noted, where reactions conducted at S/C 4000 were easily driven to completion under 1000 psig of hydrogen.

(26) The lack of pressure effect on ee may suggest that the solvate dihydride is an important intermediate in the catalytic cycle.

(27) 1,2-DCE (with precatalyst formation in methanol) is an excellent solvent system in terms of rate. However, we see increased epimerization of product, and the use of this solvent is discouraged because of the environmental impact and toxicological liabilities. Other mixed solvent systems, MeOH/toluene and MeOH/THF, resulted in slower reaction rates.

(28) Alcohols are commonly used in asymmetric hydrogenations; however, compounds **1** and **2** are poorly soluble in alcohols, which prevents their use as the sole solvent. Ethyl acetate is added to maintain a homogeneous solution, but EtOAc is not a viable solvent alone and slows the reaction down at higher concentrations.

(29) The allylic alcohol derived from **1** was also made but was unstable under reaction conditions.

(30) The remaining 4% was equal H incorporation in the same positions. We believe this is due to exchange from the solvent catalyzed by zinc triflate. Reactions at high catalyst loading without zinc triflate showed 100% deuterium insertion.

(31) S/C 4000, 0.1 equiv of Zn(OTf)<sub>2</sub>, 1000 psig H<sub>2</sub>, 30% MeOH/EtOAc, 70 °C, 18 h.

(32) Crude ee was 94–95%, and upgrade to > 99.5% was obtained by crystallization. Complete details are available in the experimental section.

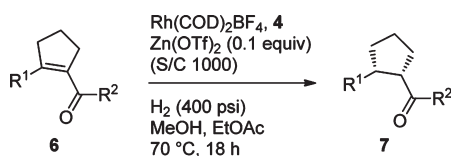
(33) See: May, S. A.; Johnson, M. D.; Braden, T. M.; Calvin, J. R.; Haeblerle, B. D.; Jines, A. R.; Miller, R. D.; Renner, G. A.; Richey, R. N.; Schmid, C. R.; Vaid, R. K.; Yu, H. *Org. Process Res. Dev.* (submitted) for a full account of the scale up to 140 kg (88% yield) using a continuous process in a plug flow reactor.

the presence of either Brønsted or Lewis acids, resulting in a more electron rich alkene as well as a better directing group in the hydroxyl group of the mixed ketal. The result may be an increase in the rate of substrate ligand complex formation to deliver **III** (Scheme 2). Additional work is underway to further examine the mechanism of this reaction.

**Scheme 3.** Possible Catalytic Function of Lewis or Brønsted Acid



**Table 2.** Expanded Scope of Rh-Catalyzed Asymmetric Reduction

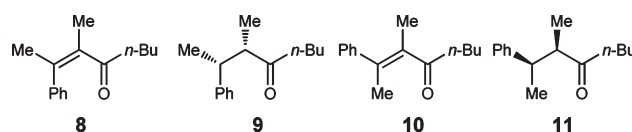


entry <sup>a</sup>	R <sup>1</sup>	R <sup>2</sup>	ee (%) <sup>b</sup>	yield (%) <sup>c,d</sup>
1 ( <b>6a</b> )	2,6-(BnO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Ph	95	90
2 ( <b>6b</b> )	2,6-(BnO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Me	90	45 <sup>e</sup>
3 ( <b>6c</b> )	2,6-(BnO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Et	92	91 <sup>e</sup>
4 ( <b>6d</b> )	2,6-(BnO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<i>i</i> Pr	96	95 <sup>e</sup>
5 ( <b>6e</b> )	C <sub>6</sub> H <sub>5</sub>	H	80	97
6 ( <b>6f</b> )	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	4-OMe	77	94
7 ( <b>6g</b> )	3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	3-OMe	82	94
8 ( <b>6h</b> )	2-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	2-OMe	95	98
9 ( <b>6i</b> )	2-EtOC <sub>6</sub> H <sub>4</sub>	2-OEt	95	95
10 ( <b>6j</b> )	2- <i>i</i> -PrOC <sub>6</sub> H <sub>4</sub>	2- <i>o</i> iPr	94	86

<sup>a</sup> All reactions were conducted on 200 mg of substrate. <sup>b</sup> ee is reported on crude reaction products. <sup>c</sup> Yields represented are isolated after purification. <sup>d</sup> Poor conversion was observed without Zn(OTf)<sub>2</sub> in all cases under otherwise identical conditions. <sup>e</sup> S/C 100 used in these cases to ensure reaction completion in 18 h.

Examination of alternative substrates established that the methodology has reasonably broad scope (Table 2).

(34) The addition of zinc triflate to ruthenium-based catalysts does improve turnover as well, but the effect is not as dramatic as in the rhodium case. For example, the reduction of **1** with a Ru-(**4**) complex (S/C 50) fails to give any conversion without zinc triflate, while the reaction with 0.2 equiv proceeds to 19% conversion with 60% ee. Results on related systems will be reported in due course.



**Figure 3.** Influence of olefin geometry on stereoinduction.

As the substitution about the ketone changes from phenyl to alkyl (Table 2, entries 1–4), higher catalyst loading was required, and there was slight erosion of ee as R<sup>2</sup> decreased in size. Varying substitution of the aryl ring in the β-position (Table 2, entries 5–10) showed that steric bulk does influence enantioselectivity.

Interestingly, in the case of acyclic substrates **8** and **10**, the alkene geometry influenced the stereochemical course of the reaction (Figure 3). *Z*-alkene **8** proceeded to the expected (2*R*,3*S*) product **9**, while the *E*-alkene **10** delivered opposite facial selectivity, the (2*R*,3*R*) product **11** under identical conditions.

In conclusion, a chemo- and enantioselective Rh-catalyzed reduction of tetrasubstituted α,β-unsaturated ketones has been developed. Catalyst turnover frequency is enhanced by the addition of catalytic zinc triflate, which allows for high S/C while suppressing epimerization in the α-position of the products. Further efforts are underway to expand the scope<sup>34,35</sup> and understand the mechanism of this transformation.

**Acknowledgment.** We wish to thank Professors Clark Landis, William Roush, Peter Wipf, Eric Carreira, and Dr. Joseph Martinelli for helpful discussions regarding this work. We also thank Jonas Y. Buser and David Foley for NMR work relating to the D<sub>2</sub> reactions. We also wish to acknowledge Chao Ye, You Chen, Ling Xia Jiang, Hui Liu, Anping Ren, Xiaoyang Wang, Weifeng Xi, Baitao Gao, Hui Lin, and Zhihua Liu for preparation and characterization of acrylic acids used in the preparation of substrates **6** in Table 2.<sup>36</sup>

**Supporting Information Available.** Detailed experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(35) Efforts on other tetrasubstituted substrates (tetrasubstituted *N*-acyl derivatives, for example) will be reported in due course.

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The authors declare no competing financial interest.