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# Desymmetrization of *meso*-Cyclic Imides via Enantioselective Monohydrogenation

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***Abstract:*** *meso*-Cyclic imides are monohydrogenated to form the corresponding hydroxy lactams in 88−97% ee using *trans*-[Ru((*R*)-BINAP)(H)$_2$((*R*,*R*)-dpen)] and related compounds as catalysts with base in THF. The hydrogenation proceeds with high enantiogroup- and chemoselectivity, and it is a desymmetrization reaction, forming up to five stereogenic centers in one reaction. Conversion of a hydroxy lactam into the corresponding iminium ion followed by addition of indene extended the number of stereogenic centers from 5 to 7.

We report the first enantioselective desymmetrization of *meso*-cyclic imides by monohydrogenation to form hydroxy lactams. Hydroxy lactams and their derivatives are versatile building blocks that have been used to prepare numerous heterocyclic compounds,[1] including vitamins, antibiotics, ACE inhibitors, and anticancer drugs such as (+)-biotin,[2] loracarbef,[3] (−)-A58365A,[4] and swainsonine.[5] Hydroxy lactams are readily converted into the corresponding lactones or lactams,[6] and they are precursors to *N*-acyliminium ions.[1] *N*-Acyliminium ions undergo a myriad of C−C bond-forming reactions.[1] Recent reports include organocatalytic enantioselective Morita−Baylis−Hillman-type reactions[7] and Pictet−Spengler-type cyclizations.[8]

Desymmetrization is an efficient method for multiplying the enantioselectivity of a catalytic reaction.[9] Multiple stereogenic centers are formed simultaneously and in identical ee in one reaction from simple substrates. Desymmetrizations are typically enantiogroup-selective reactions, with relatively few examples among catalytic hydrogenations.[9d] Of these, most are dihydrogenations of *meso*-cyclic anhydrides to form the corresponding lactones.[2e,10] There exists only one report of the enantioselective desymmetrization of *meso*-cyclic imides by catalytic hydrogenation: Ikariya and co-workers[11] showed that certain *meso*-cyclic imides were dihydrogenated (30 atm $H_2$, 80 °C, 24 h, 10 mol % Ru catalyst, and 10 mol % KO*t*-Bu in 2-PrOH) to form the ring-opened alcohol−amides in 64−98% ee. Dihydrogenation presumably occurred via hydrogenation of the more reactive aldehyde−amide tautomer of the hydroxy lactam. Although enantioselective monoreductions of *meso*-cyclic imides with chiral B−H or Al−H reagents that trap the hydroxy lactam are known,[2c,d,12] there are no reports of enantioselective monohydrogenations.[13] We hypothesized that monohydrogenation should occur when the catalyst is sufficiently active to reduce the imide under mild conditions that disfavor the tautomerization.

We recently reported the low-temperature preparation and study of the Noyori ketone hydrogenation catalyst *trans*-[Ru((*R*)-BINAP)(H)$_2$((*R*,*R*)-dpen)] (**1c**) (Scheme 1).[14] The dihydride **1c** is a remarkably active carbonyl reducing agent in THF. For example, we showed that **1c** rapidly adds acetophenone at −80 °C to form *trans*-[Ru((*R*)-BINAP)(H)(OCH(CH$_3$)(Ph))((*R*,*R*)-dpen)].[14c] **1c** also catalyzes the hydrogenation of esters in THF to give the alcohol products under mild conditions, and it stoichiometrically adds lactones at −80 °C to form the corresponding Ru hemiacetoxides.[15] This unexpectedly high reactivity in THF led us to explore the enantioselective monohydrogenation of *meso*-cyclic imides using **1c** and related complexes as catalysts under mild conditions.

We prepared solutions containing **1c** and related catalysts for this study by reacting mixtures of *trans*-[Ru((*R*)-BINAP)(H)(L)((*R*,*R*)-dpen)](BF$_4$) (**2**, L = $\eta^2$-H$_2$ or THF), KO*t*-Bu, and $H_2$ (∼2 atm) at −78 °C in THF.[14a] As 1 equiv of base is consumed to prepare **1**, the amount of base quoted in this text is that remaining after **1** is prepared. Catalysts containing other diamine ligands (Scheme 1) were prepared similarly. The common catalyst precursor *trans*-[Ru((*R*)-BINAP)(Cl)$_2$((*R*,*R*)-dpen)][16] was inactive toward this imide hydrogenation.

***Scheme 1.*** Structures of Catalysts and Cyclic Imides

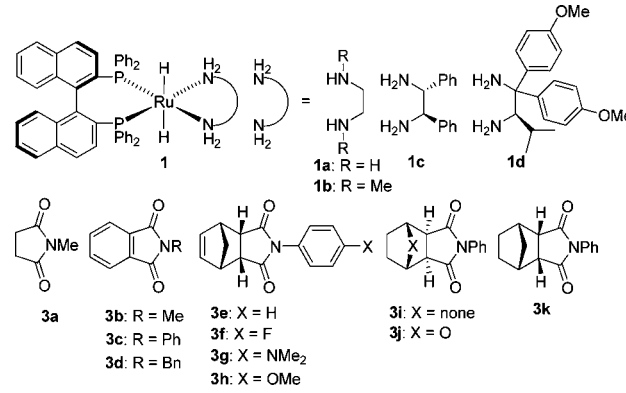
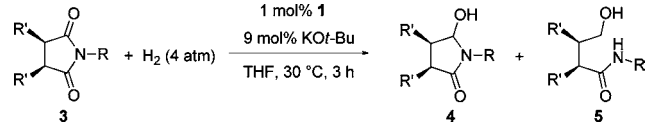



***Table 1.*** Achiral Hydrogenation of Imides[a]




| entry | catalyst | imide | **3** (%)[b] | **4** (%)[b] | **5** (%)[b] |
|---|---|---|---|---|---|
| 1 | **1a** | **3a** | 0 | 0 | 100 |
| 2 | **1b** | **3a** | 100 | 0 | 0 |
| 3[c] | **1a** | **3a** | 100 | 0 | 0 |
| 4 | **1a** | **3b** | 30 | 70 | 0 |
| 5[d] | **1a** | **3c** | 24 | 76 | 0 |
| 6 | **1a** | **3d** | 34 | 66 | 0 |
| 7 | **1c** | **3b** | 45 | 55 | 0 |
| 8[e] | **1c** | **3b** | 50 | 30 | 20 |

[a] [Imide] = 0.33 M, unless otherwise noted. [b] Determined by $^1$H NMR. [c] Imide/**1a**/KO*t*-Bu = 200:1:9, [imide] = 0.5 M in 3:1 THF/2-PrOH. [d] [Imide] = 0.11 M in 2:1 THF/$CH_2Cl_2$ because of the solubility of **3c**. [e] At 60 °C.

Table 1 summarizes our results for achiral hydrogenations in THF at 30 °C. *N*-Methylsuccinimide (**3a**) was exclusively dihy-



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drogenated to the alcohol−amide product (entry 1). The N-substituted phthalimides (**3b**−**d**) were monohydrogenated under moderate conditions to yield the corresponding hydroxy lactams (entries 4−6). Increasing the reaction temperature resulted in partial dihydrogenation (entry 8). Thus, monohydrogenation occurs at lower temperatures when the imide structure disfavors ring-opening tautomerization. Use of 2-PrOH (entry 3) and secondary diamine ligands (entry 2 vs entries 4 and 7) disabled the catalyst system.

Table 2 summarizes our results for enantioselective hydrogenations using mainly **1c** as catalyst. We chose imide **3e** (Scheme 1) to evaluate the extent of hydrogenation (mono/di), and the chemo- (C═C/C═O), diastereo- (cis/trans), and enantiogroup selectivity of the hydrogenation. Also, the product hydroxy lactam **4e** (Figure 1) contains five stereogenic centers.

***Table 2.*** Enantioselective Hydrogenation of *meso*-Cyclic Imides[a]

| entry | imide | *T* (°C) | time (h) | **4** (%)[b] | **5** (%)[b] | d.r. of **4**[b] | ee of **4** (%)[c] |
|---|---|---|---|---|---|---|---|
| 1[d] | **3e** | 22 | 3 | 70 | 12 | >99:1 | 83 |
| 2[e] | **3e** | 0 | 17 | 98 | 0 | >99:1 | 96 |
| 3 | **3f** | 0 | 17 | 99 | 0 | >99:1 | 97 |
| 4 | **3g** | 0 | 17 | 92 | 0 | >99:1 | 97 |
| 5 | **3h** | 0 | 17 | 98 | 0 | >99:1 | 95 |
| 6[f] | **3i** | 0 | 57 | 90 | trace | 97:3 | 88 |
| 7[g] | **3j** | 0 | 6 | 97 | trace | 93:7 | 92 |
| 8 | **3k** | 0 | 17 | 44 | 0 | >99:1 | 92 |

[a] Imide/**1c**/KO*t*-Bu = 500:1:9, [imide] = 0.625 M, 50 atm $H_2$ in THF, unless otherwise noted. [b] Determined by $^1$H NMR spectroscopy; d.r. = diastereomeric ratio. [c] Determined by HPLC analysis using a Daicel CHIRALPAK IB column. [d] Imide/**1c**/KO*t*-Bu = 100:1:4, [imide] = 0.125 M. [e] Imide/**1c**/KO*t*-Bu = 1000:1:9, [imide] = 1.25 M. [f] Imide/**1c**/KO*t*-Bu = 1000:1:99, [imide] = 0.25 M. [g] Imide/**1d**/KO*t*-Bu = 100:1:4, [imide] = 0.125 M.

Hydrogenation (50 atm) of **3e** at 22 °C formed a mixture of mono- and dihydrogenation products in a ~6:1 ratio with 83% ee for hydroxy lactam **4e** and without olefin hydrogenation[16] (entry 1). At 0 °C, **3e** reacted to yield only **4e** in 98% yield with 96% ee using 0.1% catalyst (entry 2). One recrystallization increased the ee to >99%. The *p*-F, -$NMe_2$, and -OMe variants **3f**−**h** reacted in 92−99% yield with 95−97% ee using 0.2% **1c** as the catalyst (entries 3−5). The *meso*-cyclohexane imide **3i** reacted in 90% yield with 88% ee (entry 6), and the O-bridging imide **3j** reacted with catalyst **1d** in 97% yield with 92% ee (entry 7). The norbornane imide **3k** reacted in 44% yield with 92% ee (entry 8). This imide is also relatively unreactive toward Al−H reduction,[6] most likely as a result of steric hindrance by the norbornane backbone.[17] The stereochemistry at the hydroxy carbon of the hydroxy lactam products was almost exclusively trans (see the Supporting Information for the solid-state structure of **4e**). Control experiments with the cis isomer of **4e**[6] showed that cis−trans isomerization is catalyzed by base under the conditions of these hydrogenations. Thus, the enantiogroup selectivity is preserved under the conditions of these hydrogenations, but the cis/trans selectivity at the hydroxy carbon is not.

To demonstrate the utility of this hydrogenation, we converted hydroxy lactam **4e** into the corresponding iminium ion by treatment with $BF_3$·$OEt_2$ at 22 °C in toluene. Either *cis*- or *trans*-**4e** would form this iminium ion. Reaction with indene formed polycyclic lactam **6** containing seven stereogenic centers in a 91:9 diastereomeric ratio (d.r.). One recrystallization increased the d.r. to >99%. Figure 1 shows the solid-state structure of the major diastereomer of **6**. This reaction occurred by addition of indene to the convex face of the iminium ion to form the benzylic carbocation, followed by intramolecular cyclization with the *N*-phenyl ring and rearomatization.[18] Analogues of **4e** were also used in the literature to prepare indolizidine and pyrrolizidine alkaloids.[19]

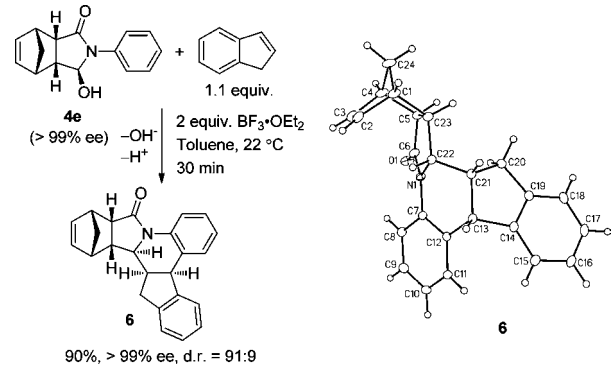


***Figure 1.*** Addition reaction between **4e** and indene and an ORTEP drawing of **6** with 20% probability ellipsoids. The absolute configuration was not determined.

This paper has presented the first chemo-, diastereo-, and enantiogroup-selective monohydrogenations of *meso*-cyclic imides. These desymmetrization reactions formed up to five stereogenic centers in high ee with one hydrogenation. *N*-Acyliminium ion chemistry readily increases the number of stereogenic centers. The cis/trans selectivity at the hydroxy carbon was not preserved during the hydrogenation, and the trans isomer is strongly favored by thermodynamics. The scope of these hydrogenations, the origins of the enantioselectivity, and the cis/trans selectivity of these catalyst systems are under study in our laboratory.

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**Supporting Information Available:** Experimental procedures, characterization of compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (c) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311. (d) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339.
(2) (a) Corey, E. J.; Mehrotra, M. M. *Tetrahedron Lett.* **1988**, *29*, 57. (b) Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H.; Poetsch, E.; Casutt, M. *Angew. Chem., Int. Ed.* **1995**, *34*, 2391. (c) Shimizu, M.; Nishigaki, Y.; Wakabayashi, A. *Tetrahedron Lett.* **1999**, *40*, 8873. (d) Chen, F. E.; Dai, H. F.; Kuang, Y. Y.; Jia, H. Q. *Tetrahedron: Asymmetry* **2003**, *14*, 3667. (e) Bonrath, W.; Karge, R.; Netscher, T.; Roessler, F.; Spindler, F. *Chimia* **2009**, *63*, 265.
(3) Metais, E.; Overman, L. E.; Rodriguez, M. I.; Stearns, B. A. *J. Org. Chem.* **1997**, *62*, 9210.
(4) Lee, P.; Moeller, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 11434.
(5) Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 8100.
(6) Matuki, K.; Inoue, H.; Ishida, A.; Takeda, M.; Nakagawa, M.; Hino, T. *Chem. Pharm. Bull.* **1994**, *42*, 9.
(7) Myers, E. L.; de Vries, J. G.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1893.
(8) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404.
(9) (a) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1. (b) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. (c) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313. (d) Atodiresei, L.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683.
(10) Osakada, K.; Obana, M.; Ikariya, T. *Tetrahedron Lett.* **1981**, *22*, 4297.
(11) Ito, M.; Sakaguchi, A.; Kobayashi, C.; Ikariya, T. *J. Am. Chem. Soc.* **2007**, *129*, 290.
(12) (a) Kang, J.; Lee, J. W.; Kim, J. I.; Pyun, C. *Tetrahedron Lett.* **1995**, *36*, 4265. (b) Ostendorf, M.; Romagnoli, R.; Pereiro, I. C.; Roos, E. C.; Moolenaar, M. J.; Speckamp, W. N.; Hiemstra, H. *Tetrahedron: Asymmetry*

**1997**, *8*, 1773. (c) Dixon, R. A.; Jones, S. *Tetrahedron: Asymmetry* **2002**, *13*, 1115. (d) Oba, M.; Koguchi, S.; Nishiyama, K. *Tetrahedron* **2004**, *60*, 8089.
(13) For an early report of monohydrogenation over Pd/C, see: McAlees, A. J.; McCrindle, R. *J. Chem. Soc. C* **1969**, 2425.
(14) (a) Hamilton, R. J.; Leong, C. G.; Bigam, G.; Miskolzie, M.; Bergens, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 4152. (b) Hamilton, R. J.; Bergens, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 13700. (c) Hamilton, R. J.; Bergens, S. H. *J. Am. Chem. Soc.* **2008**, *130*, 11979.
(15) Takebayashi, S.; Bergens, S. H. *Organometallics* **2009**, *28*, 2349.
(16) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 41.
(17) Brown, H. C.; Kawakami, J. H. *J. Am. Chem. Soc.* **1970**, *92*, 1990.
(18) Zhang, W.; Zheng, A.; Liu, Z.; Yang, L.; Liu, Z. *Tetrahedron Lett.* **2005**, *46*, 5691.
(19) Arai, Y.; Kontani, T.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 15.

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