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Highly Enantioselective Hydrogenative Desymmetrization of Bicyclic Imides Leading to Multiply Functionalized Chiral Cyclic Compounds

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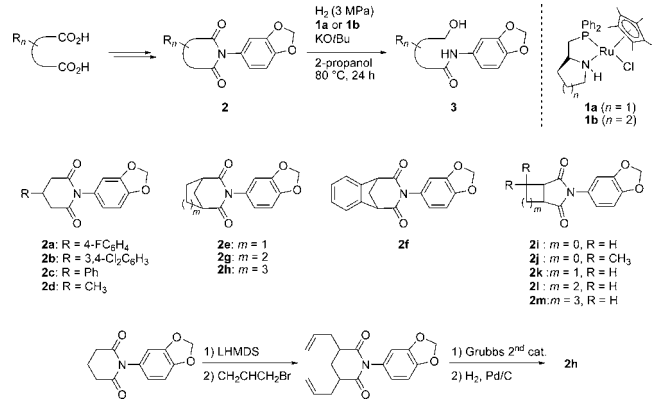
Abstract: Highly enantioselective hydrogenative desymmetrization of bicyclic imides has been developed with chiral Cp*Ru(PN) catalysts. The present hydrogenation directly provides stereochemically well-defined cyclic compounds with excellent enantiomeric exessses, which might otherwise require a detour to reach.

The development of synthetic methods remains a critical issue in chemistry, since there is still a distinct difference in the efficiency of the production of chemical substances between natural providence and art. In this regard, the development of a novel catalytic process that provides direct access to products is potentially beneficial, because it could possibly eliminate a conventional detour requiring sacrificial elements that are not embedded finally in the target molecules, thereby promoting effective utilization of resources and energy. One good example is Noyori's discovery of highly efficient molecular catalysts for direct hydrogenation of ketones,[1,2] which has recently rendered the hydrometalation of ketones unnecessary, at least in the stereoselective production of chiral secondary alcohols. Such a breakthrough can only be achieved through a deep understanding of the function of all elements making up the catalyst molecule in the catalytic cycle, which allows intensive structural modification of that catalyst molecule.

We have focused on the development of molecular catalysts for the straightforward hydrogenation of carboxylic acid derivatives,[3] which has been more challenging but much less studied until recently.[4] After careful tuning of the "Ru/NH bifunctionality" [5] as well as the reaction conditions, we have successfully developed the Cp*Ru(PN) catalyst system[6–8] for direct hydrogenation of imides,[6c] *N*-acylcarbamates,[6d] *N*-acylsulfonamides,[6d] and esters.[6d] In addition, we have demonstrated that chiral modification of the Cp*Ru(PN) complex allows an unprecedented enantioselective hydrogenation of prochiral cyclic imides to furnish chiral hydroxyamides.[6c] Encouraged by these results, we have further studied the asymmetric hydrogenation of a wide variety of prochiral imides with the *N*-(3,4-methylenedioxy)phenyl group, since the corresponding chiral products would serve as synthetically valuable building blocks. Consequently, we have found that chiral Cp*Ru(PN) catalysts **1a** and **1b**[8] promote highly enantioselective hydrogenation of symmetrically structured bicyclic imides in addition to monocyclic imides. Herein we describe this hydrogenative desymmetrization of bicyclic imides that provides multiply functionalized chiral cyclic hydroxyamides with excellent enantiomeric excesses (ee's).

Several new mono- (**2b**−**d**) and bicyclic imides (**2e**−**g**, **i**−**m**) have been readily prepared by the condensation of 3,4-(methylenedioxy)aniline and the corresponding dicarboxylic acid derivatives

Scheme 1. Chiral Cp*Ru((PN) Complexes (**1a**,**b**) and Prochiral *N*-(3,4-Methylenedioxy)phenyl Imides (**2**)



(Scheme 1; see the Supporting Information for details). On the other hand, the bicyclic imide with a [4.1.3] skeleton (**2h**) has been prepared differently from the parent *N*-(3,4-methylenedioxy)phenyl glutarimide, as illustrated in Scheme 1.[9,10] Notably, the aryl ring of the newly synthesized glutarimides seems to adopt an almost perpendicular orientation toward the imide group in the solid state, as determined by X-ray diffraction study (see the Supporting Information). For example, the mean values of four dihedral angles defined by $C_{C=O}-N-C_{ipso}-C_{ortho}$ are 67.9° (**2a**),[6c] 76.1° (**2e**), 69.6° (**2f**), 76.7° (**2g**), and 77.5° (**2h**), respectively.

The stereochemical outcome of the hydrogenation has proven to be delicately influenced by the structure of the chiral PN ligands in the catalyst. While the binary chiral catalyst system of **1a** and KO*t*-Bu caused highly enantioselective hydrogenation of not only monocylic *glutarimides* (**2a**−**d**, Table 1, entries 1−4) but also bicyclic ones (**2e**−**h**, entries 5−8) to give the corresponding hydroxyamides **3a**−**h** with excellent ee's, the enantioselectivity of the products derived from bicyclic *succinimides* (**2i**−**m**) decreased to the moderate range (52−63% ee) with the same chiral catalyst system. However, changing the chiral catalyst from **1a** to **1b** caused substantial improvement in the enantioselectivity, giving **3j**−**m** with up to 92% ee (entries 10−13). These results demonstrate that judicious choice of the chiral catalyst is crucial for determining the enantioselection of the prochiral two carbonyl groups in the substrates.

The present hydrogenation provides multiply functionalized chiral products, including 1,3- and 1,2-*cis*-disubstituted cyclic compounds which would be otherwise less accessible.[11] Moreover, the hydrogenation products are convertible to a variety of chiral cyclic compounds. For example, bromination of **3g** and subsequent base-induced cyclization of **4g** afforded the corresponding chiral bicyclic lactam (**5g**), which should serve as a good precursor of the dearylated[6c] lactam. Ring-opening polymerization of this stereochemically well-defined bicyclic lactam might generate heretofore

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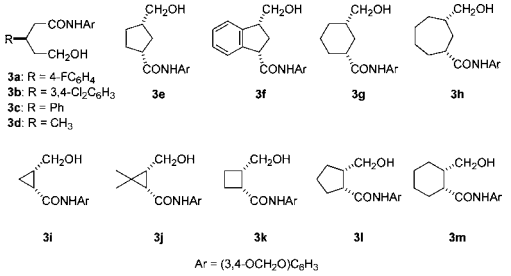
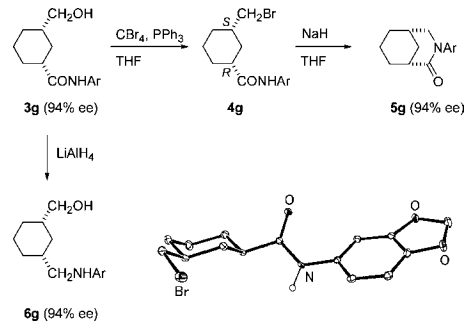
Table 1. Enantioselective Hydrogenation of **2a**−**m**[a]

entry	2	1	3	ee (%)[b]
1[c]	**2a**	**1a**	**3a**	98 (−)
2	**2b**	**1a**	**3b**	91 (−)
3	**2c**	**1a**	**3c**	96 (−)
4	**2d**	**1a**	**3d**	88 (+)
5	**2e**	**1a**	**3e**	94 (−)
6[d]	**2f**	**1a**	**3f**	97 (−)
7[e]	**2g**	**1a**	**3g**	94 (−)
8	**2h**	**1a**	**3h**	93 (−)
9	**2i**	**1a**	**3i**	62 (−)
10	**2j**	**1b**	**3j**	76 (−)
11	**2k**	**1b**	**3k**	91 (+)
12	**2l**	**1b**	**3l**	81 (−)
13	**2m**	**1b**	**3m**	92 (−)



[a] $P(H_2)$ = 3 MPa, 80 °C, imide:**1**:KO*t*Bu = 10:1:1, [imide] = 0.02−0.2 M in 2-propanol, >99% conversion. [b] HPLC analysis using a Daicel Chiralcel or Chiralpak column. The sign of rotation is indicated in parentheses. [c] Reference 6c. [d] 48 h. [e] The absolute configuration of **3g** was indicated to be 1*R*,3*S* on the basis of the absolute structure of **4g**, which was determined by X-ray diffraction study using the Flack absolute structure parameters (see the Supporting Information).

Scheme 2. Stereospecific Transformations of **3g** and an ORTEP Diagram of **4g**



unknown oligo- or poly(amides) with a rigid chiral cyclic skeleton in the repeat unit as new members of the δ-peptide or 5-nylon family,[12] which are anticipated to form ordered secondary structures.[13] Furthermore, reduction of **3g** with $LiAlH_4$ provided a chiral δ-aminoalcohol (**6g**, Scheme 2), which should enjoy widespread use as a platform for optically active ligands in catalytic asymmetric synthesis.[14] Therefore, our hydrogenative desymmetrization may constitute a viable method in asymmetric synthesis.

In summary, we have found that suitably designed chiral Cp*Ru(PN) catalyst systems promote hydrogenation of symmetrically structured bicyclic imides to provide a variety of new chiral cyclic hydroxyamides in a highly enantioselective manner. This work also unequivocally demonstrates that modular design of chiral molecular catalysts can provide direct access to stereochemically well-defined molecules, which might otherwise have required a detour to reach.

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Supporting Information Available: Experimental procedures and X-ray crystallographic data (CIF) for **2e**−**h** and **4g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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