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Chemoselective Hydrogenation of Imides Catalyzed by Cp*Ru(PN) Complexes and Its Application to the Asymmetric Synthesis of Paroxetine

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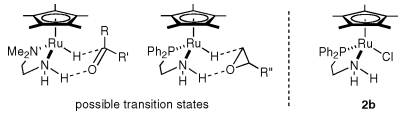
We have been engaged in the development of transition-metal/NH bifunctional molecular catalysts[1] including Cp*Ru(II) complexes bearing protic amine ligands.[2] A ternary system of Cp*RuCl(cod), $Me_2N(CH_2)_2NH_2$ (**1a**), and a base (Cp* = η^5-C_5Me_5, cod = 1,5-cyclooctadiene) provides excellent catalytic activity for the chemoselective hydrogenation of ketones.[2a] On the other hand, the analogous system with $Ph_2P(CH_2)_2NH_2$ (**1b**) serves as an effective catalyst not only for the hydrogenation of ketones but also for the hydrogenolysis of epoxides.[2b] The difference in their reactivity may be attributable to the electronic factor of tertiary amino and phosphino groups in the ligands. We postulated that the Brønsted acidity of the NH_2 group in the possibly active species, Cp*RuH[$L(CH_2)_2NH_2$-κ^2-*L*,*N*] (L = NMe_2 or PPh_2) is responsible for the range of reducible polar bonds (Scheme 1). Then, to test the hypothesis, we examined the reactivity of both catalyst systems for the reduction of imides. We found that the binary catalyst system of Cp*RuCl[$Ph_2P(CH_2)_2NH_2$-κ^2-*P*,*N*] (**2b**) and a base effects an efficient hydrogenation of imides leading to amides and primary alcohols. Furthermore, the chiral modification of **2b** successfully leads to the development of the highly enantioselective hydrogenation of prochiral imides via desymmetrization, which is applicable to the concise synthesis of the antidepressant (−)-paroxetine.

Initial experiments focused on the ligand acceleration effect in the hydrogenation of *N*-benzylphthalimide (**3a**) as a model reaction. We found that the hydrogenation (P_{H_2} = 1 MPa) proceeds smoothly in the presence of Cp*RuCl(cod), **1b**, and KO*t*-Bu (**3a**/Ru/**1b**/KO*t*-Bu = 100:1:1:1, [**3a**] = 0.33 M in 2-propanol) at 80 °C to give *N*-benzyl 2-hydroxymethylbenzamide (**4a**) selectively in >99% yield after 2 h. In sharp contrast, the use of the diamine **1a** resulted in the complete recovery of the starting material under the same conditions. Structurally analogous PN ligands with an NH group (**1c**−**e**) also accelerate the reaction (21%, 64%, and 67% yields after 2 h, respectively), whereas the tertiary amine variant $Ph_2P(CH_2)_2$-NMe_2 was completely ineffective. These results strongly present the crucial importance of the NH group in the ligand, which may exert suitable Brønsted acidity in the transition state. It should be noted that the binary system of **2b** and a base exhibited almost equal catalytic activity.

As we have reported separately, another notable feature of the system of **2b** and a base is its excellent catalytic activity for the intramolecular transfer hydrogenation of *sec*-alcohols, which has led to our recent development of the racemization of chiral nonracemic *sec*-alcohols[2c] as well as the isomerization of allylic alcohols.[2d] Accordingly, it was of interest to clarify the role of 2-propanol used in the hydrogenation of **3a**. Although **3a** was also convertible to **4a** in 2-propanol containing the same catalyst system in the absence of H_2, its rate was considerably slower (9% yield, 2 h) and the pressurization of H_2 dramatically accelerated the reaction. Furthermore, the reaction also proceeded in non-alcoholic solvents such as THF or toluene in the presence of H_2 albeit less efficiently.

Scheme 1. Possible Transition States for the Reductive Cleavage of C−O Bonds in Ketone or Epoxide



Scheme 2. Cp*Ru(PN)−Catalyzed Hydrogenation of **3a**

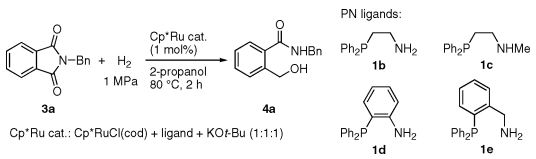
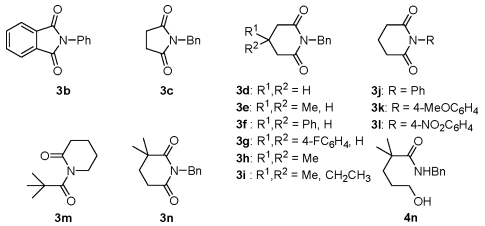


Table 1. Hydrogenation of Various Imides[a]

entry	3	time (h)	yield (%)	entry	3	time (h)	yield (%)
1	**3b**	18	>99	8[b]	**3i**	18	49
2	**3c**	18	>99	9[b]	**3j**	18	88
3	**3d**	18	>99	10[b]	**3k**	18	>99
4	**3e**	18	>99	11[b]	**3l**	18	>99
5	**3f**	18	>99	12[b,c]	**3m**	2	>99[d]
6	**3g**	18	>99	13[b]	**3n**	18	>99[e]
7[b]	**3h**	18	>99				

[a] Conditions: P_{H_2} = 3 MPa, 80 °C, [**3**] = 0.20 M in 2-propanol, **3**/**2b**/KO*t*-Bu = 100:1:1 (1 mol %) unless otherwise noted. [b] Reaction run using 5 mol %. [c] [**3m**] = 0.04 M in 2-propanol. [d] The depivaloylated amide was obtained exclusively. [e] **4n** was obtained exclusively.



These results led us to conclude that 2-propanol mainly promotes the reaction by participating in the heterolytic cleavage of H_2 possibly through a hydrogen-bonding network as we previously proposed,[2a,b] and it hardly serves as a hydrogen source in the present reaction conditions.

Next, the scope of the hydrogenation with **2b** (P_{H_2} = 3 MPa) was examined using various imides (Table 1). A variety of symmetrical cyclic imides (entries 1−11) gave ω-hydroxycarboxamides exclusively. Neither of the substituents on the ring system (entries 4−8) or on the nitrogen (entry 3 vs entries 9−11) interferes with the catalytic activity. The product distribution in the case of unsymmetrical imides (entries 12, 13) was delicately influenced by steric and electronic factors. While the pivaloyl group in **3m** was selectively hydrogenated to give the corresponding amide, the

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Scheme 3. A New Method for the Deprotection of *N*-Phthaloyl Amino Acid Derivative

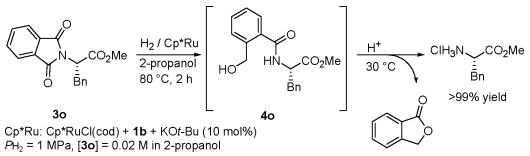
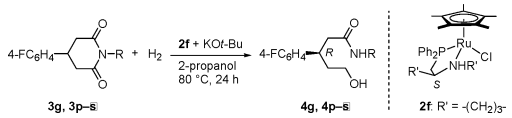


Table 2. Enantioselective Hydrogenation of Prochiral Glutarimides[a]



entry	**3**	R	yield (%)	ee (%)	confign
1	**3g**	Bn	>99	64[b]	(+)[c]
2	**3p**	CH_2(1-naphthyl)	>99	75[d]	(−)[c]
3	**3q**	Ph[e]	78	85[f]	(−)[c]
4	**3r**	4-$MeOC_6H_4$	90	91[d]	(−)[c]
5	**3s**	(3,4-OCH_2O)C_6H_3	>99	98[g]	*R*-(−)[h]

[a] Conditions: imide/**2f**/KO*t*-Bu = 10:1:1, [imide] = 0.20 M in 2-propanol unless otherwise noted. [b] HPLC analysis using a Daicel Chiralcel OD-H column. [c] Not determined. The sign of rotation of the isolated product in parenthesis. [d] HPLC analysis using a Daicel Chiralcel OD column. [e] THF was used as a cosolvent (2-propanol/THF = 1:5.6 (v/v)) owing to the low solubility of **3q**. [f] HPLC analysis using a Daicel Chiralpak AS column. [g] HPLC analysis using a Daicel Chiralpak AD column. [h] See ref 5.

less substituted acyl group in **3n** was exclusively hydrogenated to give **4n**. Although there is no clear explanation for these selectivities at present, we believe that the orientation of the two carbonyl groups plays a key role in the selectivity.[3]

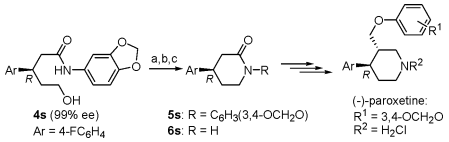
The present catalysis can be applied for the deprotection of the primary amine from *N*-phthalimides.[4] For instance, *N*-(o-hydroxymethylbenzoyl)-L-Phe methyl ester (**4o**), which was cleanly formed in situ by the hydrogenation of *N*-phthaloyl-L-Phe methyl ester underwent acid-promoted cyclization by adding HCl solution in dioxane at 30 °C for 1 h to produce the HCl salt of L-Phe methyl ester with concomitant formation of phthalide in high yields (Scheme 3). Notably, no measurable loss of optical purity of the corresponding amino acid derivative was observed in this protocol.

Encouraged by the marked catalytic performance of the Cp*Ru catalyst with **1b** in the hydrogenation of imides, we next examined asymmetric hydrogenation of prochiral glutarimides with a well-defined chiral catalyst precursor Cp*RuCl[(*S*)-$Ph_2PCH_2CHR'NHR'$-κ^2-*P*,*N*] (R′ = −$(CH_2)_3$−, **2f**). The screening tests of substituents on nitrogen in 4-(4-fluorophenyl)glutarimides (Table 2) has revealed that *N*-aryl compounds exhibit better enantioselectivities than *N*-alkyl compounds (entries 1, 2 vs entries 3−5).

Lowering the reaction temperature to 60 °C resulted in increased enantioselectivity and that of **4s** reached as high as 99% ee.[5,6] As illustrated in Scheme 4, its further synthetic elaboration including bromination of OH group, base-induced cyclization, and CAN-mediated dearylation (Supporting Information) gave the chiral piperidinone (*R*)-**6s**, which constitutes an important synthetic intermediate for the preparation of the antidepressant (−)-paroxetine.[7]

In summary, we have found that the Cp*Ru(PN) system is an effective catalyst for hydrogenation of imides. This work presents the first catalytic chemoselective and stereoselective hydrogenation

Scheme 4. Preparation of (−)-Paroxetine[a]



[a] Reaction conditions: (a) CBr_4, PPh_3, (b) NaH, (c) CAN.

of imides into amides and primary alcohols.[8] Our system may provide an alternative method for stoichiometric metal-hydride reduction because of its unique chemoselectivity and stereoselectivity.

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Supporting Information Available: Full experimental details including spectral data and determination of ee's. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) For a related example using $NaBH_4$: Osby, J. O.; Martin, M. G.; Ganem, B. *Tetrahedron Lett* **1984**, *25*, 2093−2096.

(5) X-ray crystal structures of **3s** and **5s** (See Supporting Information) provide an insight for the differentiation of two enantiotopic carbonyl groups in **3s** by **2f**. The chiral environment around the H−N−Ru−H moiety in the hydride complex derived from **2f** should form a pericyclic transition state with the pro-*R* carbonyl group preferentially.

(6) *N*-(3,4-methylenedioxy)phenyl-3-phenylglutarimide also undergoes enantioselective hydrogenation to give the product in 96% ee. Details will be published elsewhere.

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