Hydrogenolysis of Imides and *N*-acylcarbamates Catalyzed by (η^5-$C_5(CH_3)_5$)Ru Complexes Bearing a 2-Diphenylphosphinoethylamine Ligand

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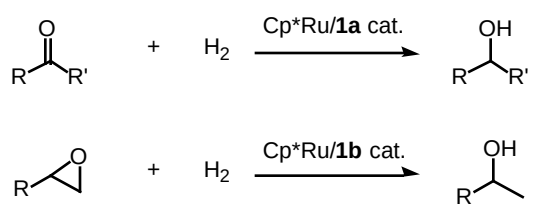
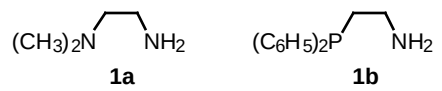
Abstract: Hydrogenolysis of imides and *N*-acylcarbamates is accomplished by the ternary catalyst system of Cp*RuCl(cod)–2-diphenylphosphinoethylamine ligand–KO*t*-Bu (Cp* = η^5-$C_5(CH_3)_5$, cod = 1,5-cyclooctadiene) under mild conditions. Both tertiary phosphine and primary amine functionalities in the ligand are indispensable in realizing efficient reaction rates.

Recently we have been engaged in the development of catalytic reactions with Cp*Ru(II) complex bearing primary amine ligands.[1] The ternary catalyst system of Cp*RuCl(cod), *N*,*N*-dimethylaminoethylamine (NN) ligand (**1a**), and KOH provides an excellent catalytic activity for the hydrogenation of ketones.[1a] On the other hand, an analogous system with a 2-diphenylphosphinoethylamine (PN) ligand (**1b**) serves as an effective catalyst for the hydrogenolysis of epoxides[1b] as well as for the hydrogenation of ketones (Scheme 1).

Scheme 1



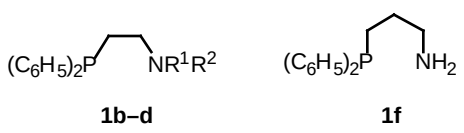
Cp*Ru/**1** cat. : Cp*RuCl(cod)/**1**/KOH



1a **1b**

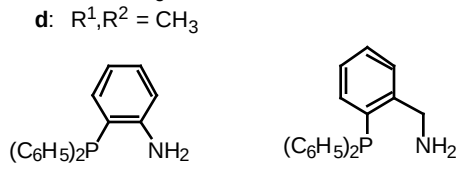
The difference in the reactivity between **1a** and **1b** may be attributable to the electronic difference between the tertiary amino group and the tertiary phosphino group of the ligand. We postulated that the Brønsted acidity of the NH_2 group in its catalytically active species, Cp*RuH[$L(CH_2)_2NH_2$] (L = $N(CH_3)_2$ or $P(C_6H_5)_2$) is responsible for the range of reducible polar bonds. To verify the hypothesis, we have examined the reactivity of both the **1a** and **1b** catalyst systems for the reduction of imides.[2,3] Recently, we found that the catalyst with **1b** is an efficient catalyst for hydrogenolysis of imides and *N*-acylcarbamates (**2**) to the corresponding amides or carbamates (**3**) and primary alcohols (Scheme 2).

PN Ligands:



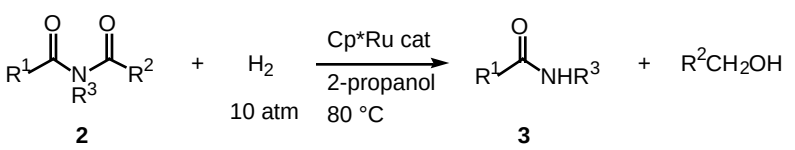
1b–d **1f**

b: R^1,R^2 = H
c: R^1 = CH_3, R^2 = H
d: R^1,R^2 = CH_3



1e **1g**

Scheme 2



2 **3**

Cp*Ru cat: Cp*RuCl(cod) / **1b** / KO*t*-Bu

2 and **3**

a: R^1,R^2 = *o*-C_6H_4, R^3 = $CH_2C_6H_5$
b: R^1,R^2 = -$(CH_2)_2$-, R^3 = $CH_2C_6H_5$
c: R^1,R^2 = -$(CH_2)_2$-, R^3 = CH_3
d: R^1,R^2 = CH_3, R^3 = $CH_2C_6H_5$
e: R^1= CH_3, R^2 = *t*-C_4H_9, R^3 = $CH_2C_6H_5$
f: R^1= C_6H_5, R^2 = CH_3, R^3 = $CH_2C_6H_5$
g: R^1,R^3 = -$(CH_2)_3$-, R^2 = CH_3
h: R^1= CH_3O, R^2 = CH_3, R^3 = $CH_2C_6H_5$
i: R^1,R^3 = -$O(CH_2)_2$-, R^2 = CH_3

The hydrogenolysis of *N*-benzylphthalimide (**2a**) in the presence of Cp*RuCl(cod), **1b**, and KO*t*-Bu (H_2 = 10 atm, imide:Ru:**1b**:KO*t*-Bu = 100:1:1:1) proceeds smoothly in 2-propanol at 80 °C to give *N*-benzyl2-hydroxymethylbenzamide (**3a**) selectively in >99% yield after 2 h. On the other hand, the use of **1a** instead of **1b** resulted in the complete recovery of the starting material under the same conditions. While a secondary amine variant **1c** was also an effective ligand to give **3a** as a sole product, albeit in low yield under identical conditions (21% yield), the tertiary amine variant **1d** 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 is noted that other PN ligands like **1e**–**g** were less effective than **1b**.

While **2a** was slowly converted into **3a** even in the absence of H_2 in 2-propanol containing the catalyst system with **1b**, the pressurization of H_2 dramatically accelerates the rate. This result may indicate that hydrogen transfer from 2-propanol to **2a**, producing acetone and the product, does occur in the presence of the catalyst with **1b**. On the other hand, molecular hydrogen may suppress reverse hydrogen transfer, which may take place with the accumulation of acetone, by regenerating 2-propanol from acetone. However, it is worth pointing out that the molecular hydrogen itself may contribute directly to the reduction of **2a**, since the hydrogenolysis does proceed in THF, which cannot serve as a hydrogen source, albeit in much slower rate.

The effectiveness of the catalyst system with **1b** was demonstrated by the successful hydrogenolysis of various imides and *N*-acylcarbamates (Table 1). The reaction was carried out at 80 °C in 2-propanol containing Cp*RuCl(cod), **1b**, and KO*t*-Bu under 10 atm of H_2 and the representative results are listed in Table 1.

Table 1 Hydrogenolysis of imides or *N*-acyl carbamates in the presence of Cp*Ru/**1b** catalyst system.[a]

entry	substrate	cat, mol%	time, h	conv.[b], %	product	yield[b], %
1	**2a**	1	2	>99	**3a**	>99
2	**2b**	1	8	93	**3b**	93
3	**2c**	1	2	94	**3c**	94
4	**2d**	10	2	>99	**3d**	>99
5	**2e**	10	2	>99	**3e**(=**3d**)	>99
6	**2f**	10	2	>99	**3f**	61[c]
7	**2g**	1	8	>99	**3g**	83[d]
8	**2h**	10	2	>99	**3h**	>99
9	**2i**	1	2	91	**3i**	91

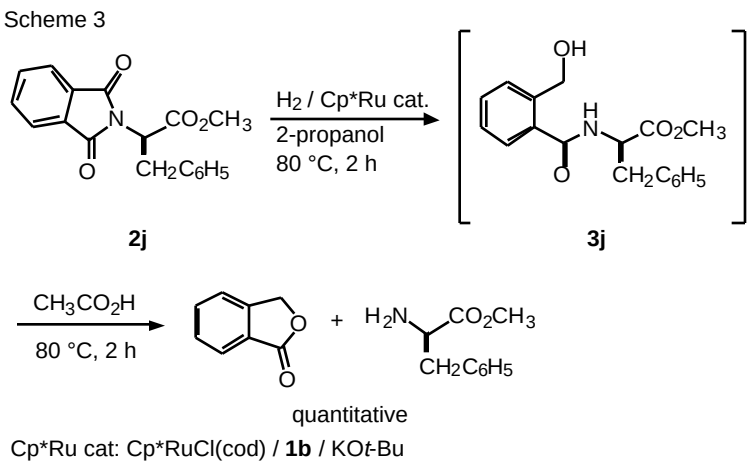
[a] Conditions; cat. = Cp*RuCl(cod) + **1b** + KO*t*-Bu (1:1:1), [substrate] = 0.33 M in 2-propanol, P_{H_2} = 10 atm. [b] Determined by ^{1}H NMR. [c] *N*-acetylbenzylamine(**3d**) was formed in 38 % yield. [d] *N*-acetyl-4-amino-1-butanol was formed in 16% yield.

Symmetric cyclic imides with two carbonyl groups in the ring system (**2a–c**) undergo hydrogenolysis to give ω-hydroxycarboxamides selectively in good yields (entry 1–3). One of the two N–C bonds in symmetric acyclic imide **2d** is reductively cleaved to give the corresponding amide **3d** and the primary alcohol in good yields (entry 4). On the other hand, the product distribution in the case of unsymmetric imides (**2e**–**g**) is delicately influenced by steric and electronic factors (entry 5–7). The hydrogenolysis of **2e** occurs exclusively at the sterically more congested pivaloyl group to give *N*-acetylbenzylamine(**3e**) in excellent yield (entry 5). However, the selectivity between the acetyl and benzoyl groups was only modest (ca. 3 : 2) in the hydrogenolysis for **2f** (entry 6). The preferential formation of pyrrolidone by the hydrogenolysis of **2g** (entry 7) may indicate that the present catalyst system favors the exo acyl group over the endo acyl group. Although there is no clear explanation for these selectivities at present, we believe that the orientation of the two carbonyl groups in unsymmetrical imides should play a key role for the selectivities. *N*-Acylcarbamates (**2h**–**i**) are selectively hydrogenolyzed at the *N*–acyl side exclusively to give the corresponding carbamates in good yields (entry 8,9).

The present catalysis can be successfully applied to the deprotection of *N*-phthaloyl amino acid derivatives. For instance, *N*-(*o*-hydroxymethyl benzoyl)-L-Phe methyl ester (**3j**), cleanly formed *in situ* by the hydrogenolysis of *N*-phthaloyl-L-Phe methyl ester (imide:Ru:**1b**:KO*t*-Bu = 10:1:1:1, P_{H_2} = 10 atm, [**2j**] = 0.33 M in 2-propanol, 80 °C, 2 h), underwent acid-promoted cyclization by adding acetic acid to the reaction mixture after ventilation of H_2 and heating at 80 °C for 2 h, to produce L-Phe methyl ester with concomitant formation of phthalide quantitatively.[4] It should be noted that no measurable loss of optical purity of the corresponding amino acid derivative was observed in this protocol (Scheme 3).

In conclusion, we have found that the Cp*RuCl(cod)–**1b**–KO*t*-Bu combined system is an effective catalyst for hydrogenolysis of imides and *N*-acylcarbamates. Our system might provide a new catalytic altenative for stoichiometric metal hydride reduction[2,5] because of its unique chemoselectivity and regioselectivity. Desymmetrization of *meso*-imides by the hydrogenolysis using chiral PN ligands will be reported in due course.

Scheme 3



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References and Notes.

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