Catalytic Hydrogenation

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Hydrogenation of *N*-Acylcarbamates and *N*-Acylsulfonamides Catalyzed by a Bifunctional [Cp*Ru(PN)] Complex**

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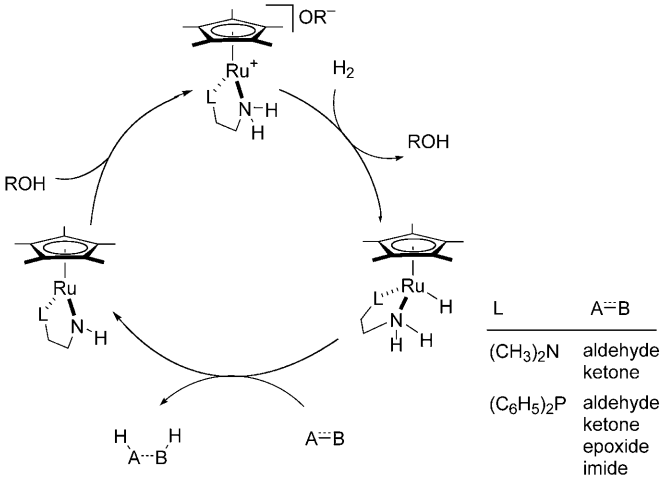
The development of well-designed molecular catalysts for the hydrogenation of polar organic functionalities continues to be an important challenge, because it would provide a solution to reducing the energy required and waste generated for such a reactions. It would also provide direct access to stereochemically well-defined molecules through a structural modification of the catalyst molecule.[1] The difficulty with this issue is the discovery of an appropriate catalyst which can generate a more hydridic species from molecular dihydrogen (H_2) with concomitant release of a more protic product by a formal heterolytic H_2 cleavage. Over a decade ago, an intriguing clue was offered by a Noyori's bifunctional catalyst, consisting of [$RuCl_2$(diphosphane)(diamine)] and a base, for the hydrogenation of ketones, which promotes this energetically disfavored process with an aid of alcoholic solvents.[2,3] We also successfully developed new bifunctional catalyst systems comprised of [Cp*RuCl{$L(CH_2)_2NH_2$-κ^2-*L*,*N*}] complexes and a base for the highly efficient hydrogenation of polar organic functionalities (Cp* = η^5-$C_5(CH_3)_5$; L = $(CH_3)_2N$, or $(C_6H_5)_2P$).[4] The nucleophilicity of the RuH moiety as well as the electrophilicity of the NH moiety in the catalytically active [Cp*RuH{$L(CH_2)_2NH_2$-κ^2-*L*,*N*}] complexes are suitably controlled by the electronic nature of L in the ligand (Scheme 1).

For example, both [Cp*Ru(NN)] (N = tertiary amine) and [Cp*Ru(PN)] (P = tertiary phosphane) catalysts are capable of heterolytic H–H bond cleavage, wherein the increased π-accepting property of the tertiary phosphane enhances the Brønsted acidity of the ligated NH group to facilitate the activation of polar functional groups. Accordingly, [Cp*Ru(NN)] favorably promotes the hydrogenation of ketones,[4a] whereas [Cp*Ru(PN)] effects the hydrogenation of epoxides[4b] and imides[4c] as well as ketones. This successful expansion of the Ru/NH bifunctionality[5] has led us to additionally examine the catalytic performance of



Scheme 1. A possible catalytic cycle for the hydrogenation of polar functionalities with [Cp*Ru(LN)] catalysts.

[Cp*Ru(PN)] in the hydrogenation of polar organic functionalities and we found the unprecedented hydrogenation of *N*-acylcarbamates and *N*-acylsulfonamides. Herein, we disclose the details of the reactions and their synthetic applications.

Initial experiments focused on the effect of alcoholic solvents upon the chemoselectivity in the hydrogenation of *N*-Boc-pyrrolidinone (**2a**; Boc = CO_2tBu) as a model substrate. The reaction was carried out at 80 °C under 3 MPa of H_2 in an alcoholic solvent containing **2a**, [Cp*RuCl{$(C_6H_5)_2P$-$(CH_2)_2NH_2$-κ^2-*P*,*N*}] (**1**), and KO*t*Bu (**2a**/Ru/KO*t*Bu = 100:1:1, [**2a**] = 0.2 M). Substrate **2a** was smoothly consumed in a variety of alcoholic solvents, but the reaction course was delicately influenced by the sterics of the alcohol employed. In fact, the use of methanol or 2-propanol significantly caused alcoholysis in addition to the hydrogenation of **2a** to result in the formation of a mixture of $BocNH(CH_2)_4OH$ (**2ax**) and $BocNH(CH_2)_3CO_2R$ (**2ay**: R = CH_3, **2az**: R = $CH(CH_3)_2$) in ratios of 66:34 in methanol and 82:18 in 2-propanol, respectively. However, the use of *tert*-butyl alcohol suppressed the undesired alcoholysis to give **2ax** as a sole product. The effect of the base turned out to be negligible since the use of other bases such as nBu$_4$NOH and KOH instead of KO*t*Bu gave the similar results (Scheme 2).

Next, the scope of the present hydrogenation with a binary catalyst system of **1** and KO*t*Bu was examined in *tert*-butyl alcohol using a variety of *N*-acylcarbamates and *N*-acylsulfonamides. Table 1 lists the selected examples. In addition to the Boc group (**2a**), a range of electron-withdrawing groups on the nitrogen atom of the pyrrolidinone

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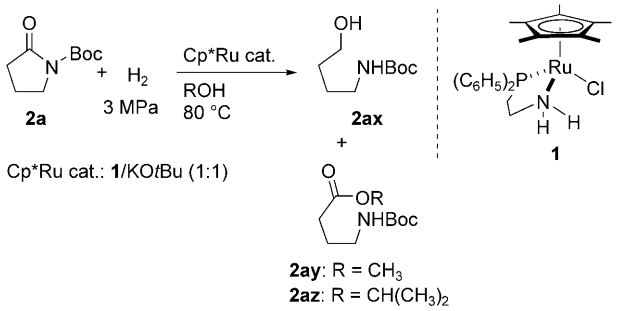
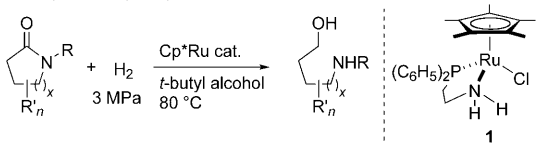
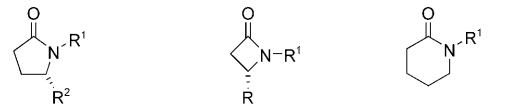


Scheme 2. Hydrogenation of **2a** with [Cp*Ru(PN)] in various alcoholic solvents.

Table 1: Hydrogenation of *N*-acylcarbamates and *N*-acylsulfonamides catalyzed by a catalyst system of **1** and KO*t*Bu.[a]

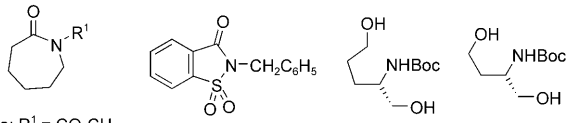




2a: R^1 = Boc, R^2 = H
2b: R^1 = CO_2CH_3, R^2 = H
2c: R^1 = Cbz, R^2 = H
2d: R^1 = Ms, R^2 = H
2e: R^1 = Ts, R^2 = H
2g: R^1 = Boc, R^2 = $CO_2C_2H_5$

3a: R^1 = CO_2CH_3, R = H
3b: R^1 = Boc, R = H
3c: R^1 = Boc, R = $CO_2CH_2C_6H_5$

4a: R^1 = CO_2CH_3
4b: R^1 = Boc
4c: R^1 = Ts



5a: R^1 = CO_2CH_3
5b: R^1 = Boc
5c: R^1 = Ts

2f **6** **7**

Entry	Substrate	Ca. [mol%]	*t* [h]	Yield [%]
1	**2a**	2	36	>99
2	**2b**	1	24	>99
3	**2c**	5	24	92
4	**2d**	1	2	>99
5	**2e**	5	24	>99
6	**2f**	10	48	>99
7	**2g**	5	24	82[b]
8	**3a**	2	24	>99
9	**3b**	5	24	>99
10	**3c**	5	24	>99[c]
11	**4a**	2	24	>99
12	**4b**	5	24	>99
13	**4c**	2	24	>99
14	**5a**	10	24	>99
15	**5b**	10	48	>99
16	**5c**	10	48	>99

[a] Reaction conditions: P_{H_2} = 3 MPa, 80 °C, **1**/KO*t*Bu = 1:1, [substrate] = 0.2 M in *tert*-butyl alcohol. [b] **2g** was consumed completely. **6** was obtained in 18% yield as a by-product. [c] Yield of **7**.

(**2b–e**) allowed the selective hydrogenation of the endocyclic carbonyl group to afford the corresponding acyclic hydroxy compounds in high yields (entries 1–5). Separate experiments for the comparison of the initial reaction rate for these substrates revealed that the reactivity increases in the following order according to the group on the nitrogen center: Cbz < Boc ≈ Ts < CO_2CH_3 < Ms (Cbz = $CO_2CH_2C_6H_5$, Ts = $SO_2C_6H_4pCH_3$, Ms = SO_2CH_3).[6] A wide variety of carboxamides having activating groups on their nitrogen center (**2f**, **2g**, **3a–c**, **4a–c**, **5a–c**) were subjected to reduction at the acyl side to afford the corresponding compounds (entries 6–16). Notably, the ring structure of the lactam significantly influenced the rate of the hydrogenation. For example, the hydrogenation of *N*-Boc-ε-lactam **5b** proceeds very sluggishly compared to the *N*-Boc lactams **2a**, **3b**, and **4b**, each having a different ring size (compare entries 1, 9, 12, and 15). Similarly, the rate of the hydrogenation for *N*-Ts-ε-lactam **5c** is exceptionally slower than the *N*-Ts lactams **2e** or **4c** (compare entries 5, 13, and 16). Nevertheless, the carbonyl groups in N-substituted seven-membered lactams displayed similar $^{13}C\{^1H\}$ NMR and IR spectra as those in the other congeners (see the Supporting Information). The X-ray crystal structural analysis[7a] has confirmed that neither **5c** nor **2e** or **4c** display any significant pyramidalization around their nitrogen atom[7b,c] (Figure 1). Therefore, we believe that

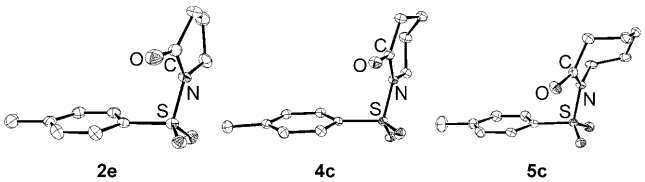


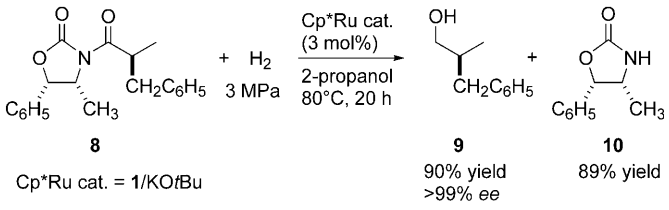
Figure 1. Molecular structures of **2e**, **4c**, and **5c**. Hydrogen atoms are omitted for clarity.

the seven-membered ring structure specifically generates the sterically less accessible environment around the reducible carbonyl group, although additional studies are required to clarify this structural dependence on the reactivity.

In contrast to the reaction over the heterogeneous catalysts,[8] **2c** underwent the selective hydrogenation to give the *N*-Cbz-4-amino-1-butanol without the formation of any by-products arising from hydrogenolysis of the *N*-benzyl group (entry 3). Furthermore, no measurable loss of optical purity was observed in the hydrogenation of chiral substrate **2g,** having greater than 99% *ee*, despite the basic reaction conditions (entry 7). Notably, the ester group in both **2g** and **3c** was also hydrogenated after a prolonged reaction time, leading to the formation of (*S*)-*N*-Boc-2-amino-1,5-pentanediol (**6**) and (*S*)-*N*-Boc-2-amino-1,4-butanediol (**7**), respectively (entries 7 and 10).[9]

The present hydrogenation was applicable to the reductive transformation of chiral *N*-acyloxazolidiones, which are useful synthetic intermediates in the asymmetric synthesis developed by Evans et al.[10] For example, the *N*-acyloxazolidinone **8** underwent selective hydrogenation, in the presence of **1** and KO*t*Bu, to furnish the corresponding chiral alcohol **9**

without any loss in the *ee* value, along with the original chiral auxiliary **10** in high yields. Interestingly, this reaction could be performed in 2-propanol without any undesired alcoholysis (Scheme 3). Our method may constitute an environmentally benign catalytic alternative to the method using $LiAlH_4$, which sometimes causes difficulty in the recovery of the chiral auxiliaries.



Scheme 3. Catalytic hydrogenation of **8** with **1** and KO*t*Bu.

As we reported previously, the catalyst system including [Cp*RuCl{L(CH$_2$)$_2$NH$_2$-κ^2-*L*,*N*}] and a base readily activates H_2 in a protic solvent through the formation of a hydrogen-bonding network to generate [Cp*RuH{L(CH$_2$)$_2$NH$_2$-κ^2-*L*,*N*}].[4a,d] Therefore, this study clearly showed that the bifunctional [Cp*RuH(PN)] complex exerts sufficient reactivity to facilitate the interaction with *N*-acylcarbamates[11a–c] or *N*-acylsulfonamides[11d] which bear a less electrophilic carbon atom in comparison to those in ketones, epoxides, and imides. We believe that the π-accepting nature of the phosphane unit in the PN ligand and the relatively strong Brønsted acidity of the ligated NH group in the [Cp*Ru(PN)] system significantly contributes to the expansion of the range of reducible polarized C=O bonds.[1a,4b]

In summary, we have developed the straightforward catalytic hydrogenation of *N*-acylcarbamates and *N*-acylsulfonamides using the bifunctional [Cp*RuCl(PN)] complex **1**. The present hydrogenative transformations are characterized by the simple and efficient procedure under mild conditions and by the unique chemoselctivity. Additional studies to explore the scope in the hydrogenation of polar functionalities along this line are underway in our laboratories.[9,12]

Experimental Section

General procedure: A degassed solution of **2a** (185.2 mg, 1.0 mmol) in *tert*-butyl alcohol (5 mL) was transferred to a 50 mL stainless autoclave containing a mixture of **1** (10.0 mg, 0.02 mmol) and KO*t*Bu (2.2 mg, 0.02 mmol). After the argon present in the autoclave was replaced by H_2, H_2 (3 MPa) was introduced into the autoclave. The mixture was stirred vigorously at 80 °C for 36 h. After carefully venting H_2, the mixture was filtered through a plug of silica gel (Fuji Silysia FL100D neutral) eluting with ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified by bulb-to-bulb distillation to give **2ax** (189.3 mg, > 99 % yield). Spectral data for the hydrogenated products are provided in the Supporting Information.

Hydrogenation of **8** leading to **9** and **10**: The hydrogenation of **8** (259.7 mg, 0.81 mmol) in 2-propanol (5.6 mL) containing **1** (12.3 mg, 0.025 mmol) and KO*t*Bu (2.8 mg, 0.025 mmol) was performed at 80 °C for 20 h under 3 MPa of H_2. Purification of the crude product by silica gel column chromatography (Fuji Silysia FL100D neutral) provided **9** (108.8 mg, 90 % yield) and **10** (127.2 mg, 89 % yield), respectively. Spectral data for the products are provided in the Supporting Information.

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[7] a) Crystal data for **2e**: $C_{11}H_{13}NO_3S$, *monoclinic*, $P2_1/n$, $a = 8.1846(16)$, $b = 13.7397(19)$, $c = 10.632(2)$ Å, $\beta = 107.947(7)°$, $V = 1137.5(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.397$ g cm^{-3}, $F_{000} = 504.00$, $\mu = 2.754$ cm^{-1}, transmission factors: 0.871–0.921, reflections measured 11658, independent reflections 2509, $R1 = 0.0429$ [$I > 2\sigma(I)$], $wR2 = 0.1325$ (all data), residual electron density 0.34/−0.39 e Å^{-3}. For **4c**: $C_{12}H_{15}NO_3S$, *monoclinic*, $P2_1/c$, $a = 8.301(3)$, $b = 14.313(4)$, $c = 11.191(4)$ Å, $\beta = 114.328(3)°$, $V = 1211.6(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.389$ g cm^{-3}, $F_{000} = 536.00$, $\mu =$

2.628 cm^{-1}, transmission factors: 0.872–0.949, reflections measured 8930, independent reflections 2705, $R1 = 0.0348$ [$I > 2\sigma(I)$], $wR2 = 0.1083$ (all data), residual electron density 0.27/−0.33 e $Å^{-3}$. For **5c**: $C_{13}H_{17}NO_3S$, *orthorhombic*, $P2_12_12_1$, $a =$ 8,289(3), $b = 10.605(4)$, $c = 15.237(6)$ Å, $V = 1339.3(9)$ $Å^3$, $Z = 4$, $\rho_{calcd} = 1.326$ g cm^{-3}, $F_{000} = 568.00$, $\mu = 2.415$ cm^{-1}, transmission factors: 0.812–0.930, reflections measured 10632, independent reflections 3045, $R1 = 0.0339$ [$I > 2\sigma(I)$], $wR2 = 0.0992$ (all data), residual electron density 0.35/−0.39 e $Å^{-3}$. Data were collected at 193 K using a Rigaku Saturn CCD area detector with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.7107$ Å) to a maximum 2θ value of 55°. Intensity data were corrected for Lorentz-polarization effects and for absorption. Structure solution and refinements were performed with the CrystalStructure program package.[13] The structures were refined against F^2 with anisotropic temperature factors for all non-hydrogen atoms. All hydrogen atoms were added geometrically and refined by using a riding model. CCDC 705015 (**2e**), 705016 (**4c**), and 705017 (**5c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif; b) K. Kondo, T. Iida, H. Fujita, T. Suzuki, K. Yamagichi, Y. Murakami, *Tetrahedron* **2000**, *56*, 8883 – 8891; c) J. D. Dunitz, F. K. Winkler, *Acta Crystallogr. Sect. B* **1975**, *31*, 251 – 263.

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