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Catalytic Hydrogenation of Carboxamides and Esters by Well-Defined Cp*Ru Complexes Bearing a Protic Amine Ligand

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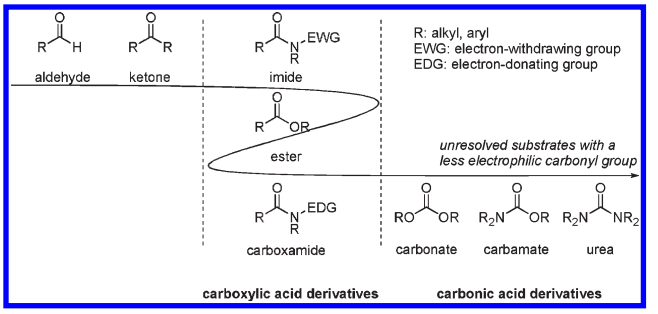
Supporting Information

ABSTRACT: A novel catalytic method for the straightforward hydrogenation of carboxamides and esters to primary alcohols has been developed. Chiral modification in the ligand sphere of the well-defined Cp*Ru catalyst molecule opens up a new possibility for the development of an enantioselective hydrogenation of racemic substrates via dynamic kinetic resolution.

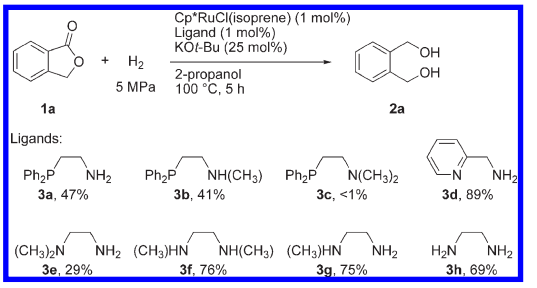
Since molecular hydrogen (H_2) is currently receiving increasing attention as a major secondary fuel and energy carrier,[1] tremendous efforts have been devoted to the review of conventional methods for manufacturing H_2 from various points of view.[1b−e] Apart from fuel development, however, there still remain a variety of possible applications of this potentially useful clean resource that should lead to the reduction of environmental impact. In this respect, catalysts have played pivotal roles in synthetic chemistry and are continuing to expand the utilization of H_2.[2] Unfortunately, however, only a limited number of catalytic methods have emerged as powerful tools for the direct hydrogenation of carboxylic acid derivatives,[3] with a few notable exceptions focusing on the hydrogenation of carboxylic esters catalyzed by Ru-based molecular catalysts.[4] In fact, there still remain several C═O bonds in carboxylic acid derivatives[5] and more in carbonic acid derivatives that are not readily reduced by molecular hydrogen (Scheme 1); hence, their reductive transformations still rely heavily on the stoichiometric use of metal hydride reagents, which possibly causes an overall increase in environmental impact.

We recently demonstrated that bifunctional Cp*Ru(PN) catalysts[6,7] promote highly selective hydrogenations of various carboxylic acid derivatives, including imides,[6b,d] *N*-acylcarbamates,[6c] and *N*-acylsulfonamides.[6c] During the course of those studies, we unexpectedly found that in addition to the *N*-acyl groups, a carboxylic ester functionality in several *N*-acylcarbamate derivatives is also susceptible to hydrogenation, giving an alcohol.[6c] Intrigued by these results, we revisited the optimal conditions for the hydrogenation and found that the coexistence of *a substoichiometric amount of inorganic base* in the reaction medium[8] dramatically broadens the scope of reducible functionalities with Cp*Ru(LN) catalysts (LN = chelating protic amine ligand). Consequently, not only carboxylic esters[6e] but several *N*-arylcarboxamides[6f] with a considerably less electrophilic carbonyl group have now entered the range of substrates amenable

Scheme 1. Challenge Levels in Catalytic Hydrogenation



Scheme 2. Ligand Acceleration in the Hydrogenation of 1a



to straightforward hydrogenation with a well-defined molecular catalyst. Herein we disclose the scope of our catalytic method and its application to an enantioselective hydrogenation via dynamic kinetic resolution (DKR) aided by the coexistence of the inorganic base.

Initially, the acceleration effect of the ligand structure on the hydrogenation of carboxylic esters was examined using phthalide (**1a**) as a model substrate. The hydrogenation of **1a** was conducted in 2-propanol containing Cp*RuCl(isoprene), various amine ligands, and KO*t*-Bu under 5 MPa H_2 at 100 °C for 5 h, and the results are summarized in Scheme 2. While the PN ligands **3a** and **3b** smoothly effected the hydrogenation to give 1,2-benzenedimethanol (**2a**) as the sole product in 47 and 41% yield, respectively, the use of aprotic congener **3c** resulted in no formation of **2a**, indicating the importance of the Ru/NH bifunctionality. Of particular note is that the ligands **3d**

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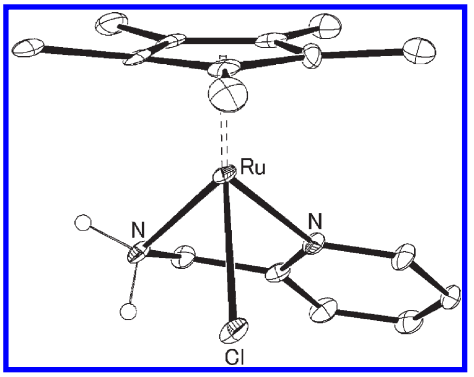


Figure 1. Molecular structure of **4d.** H atoms except those on the protic amino group have been omitted for clarity.

and **3e**, in which the tertiary phosphine moiety in **3a** is replaced with a pyridine or a tertiary amine, promoted the hydrogenation of **1a** under otherwise identical conditions, whereas these catalyst systems hardly promoted the hydrogenation of carboxylic acid derivatives (including imides or *N*-acylcarbamates) as long as they were activated by an equivalent amount of inorganic base.[3,6] It is also noteworthy that protic 1,2-diamine ligands (**3f**−**h**) bearing NH groups at both ends proved to be more effective in terms of catalytic activity than **3e** bearing an NH group at one end. The change of the alkaline metal or the alkoxide moiety in KO*t*-Bu as the base did not cause any significant difference in the rate acceleration unless their initial amount was reduced to 25 mol % or less, although their dose-dependent role is still unclear.[8,9]

Encouraged by the marked catalytic performance with the ligand **3d**, Cp*RuCl(2-$C_5H_4NCH_2NH_2$) (**4d**) was newly prepared by the reaction of Cp*RuCl(isoprene) and **3d**[7a,10] and structurally characterized (Figure 1). This complex was then used as a catalyst precursor to explore the scope and limitation of the hydrogenation at 100 °C under 5 MPa H_2 in 2-propanol containing 25 mol % KO*t*-Bu.

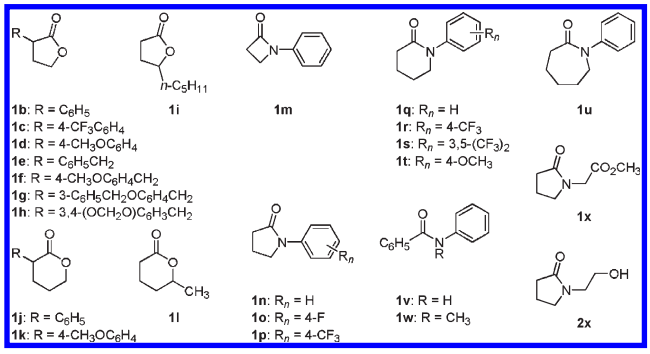
Various lactones with different ring sizes or substitution patterns (**1b**−**l**) were smoothly hydrogenated in 2-propanol containing 1 mol % **4d** within 18 h to give the corresponding diols (**2b**−**l**) in good yields, as listed in entries 1−11 of Table 1. In contrast, the substrate scope of carboxamides with a less electrophilic carbonyl was delicately influenced by the electronic nature of the substituent on the nitrogen. For example, *N*-phenylpyrrolidinone (**1n**) was smoothly hydrogenated in 2-propanol containing 10 mol % **4d** to give 4-(phenylamino)butan-1-ol (**2n**) in 73% yield (entry 13), although *N*-benzylpyrrolidinone was reluctant under similar conditions. Nevertheless, a wide variety of carboxamides were susceptible to the present hydrogenation as long as they had an aryl group on their nitrogen, as listed in entries 12−22 of Table 1. The inertness of carboxamides lacking any aryl group allowed a selective hydrogenation of a certain type of amide ester such as **1x**, which cleanly afforded **2x** under similar conditions (entry 23).

The coexistent substoichiometric amount of base in the present hydrogenation may cause a reversible deprotonation in the substrates having a relatively acidic C−H bond, which possibly leads to racemization of chiral nonracemic substrates with a tertiary stereogenic center at the α carbon.[4e] In fact, the hydrogenation of (*R*)-**1b** with 55% ee using 2 mol % **4d** at 80 °C for 48 h under conditions otherwise identical to those listed in Table 1 afforded completely racemic (±)-**2b** quantitatively.

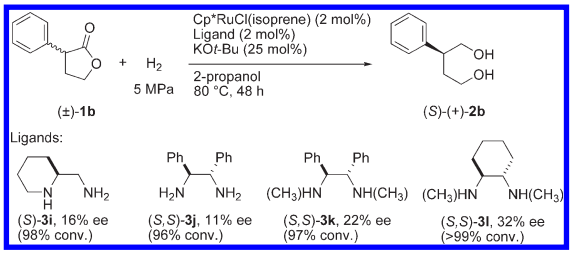
Table 1. Hydrogenation with 4d[a]

entry	substrate	product	time (h)	conv. (%)	yield (%)[b]
1	**1b**	**2b**	6	>99	82
2	**1c**	**2c**	12	>99	81
3	**1d**	**2d**	18	>99	80
4	**1e**	**2e**	15	>99	74
5	**1f**	**2f**	12	>99	83
6	**1g**	**2g**	15	>99	90
7	**1h**	**2h**	12	>99	86
8	**1i**	**2i**	14	>99	73
9	**1j**	**2j**	12	>99	87
10	**1k**	**2k**	12.5	>99	81
11	**1l**	**2l**	15	>99	81
12	**1m**	**2m**	24	>99	83
13	**1n**	**2n**	24	84	73
14	**1o**	**2o**	24	87	75
15	**1p**	**2p**	24	>99	88
16	**1q**	**2q**	24	>99	96
17	**1r**	**2r**	24	>99	90
18	**1s**	**2s**	24	>99	93
19	**1t**	**2t**	24	88	78
20	**1u**	**2u**	72	60	60[c]
21	**1v**	$C_6H_5CH_2OH$	48	88	64[c]
22	**1w**	$C_6H_5CH_2OH$	24	>99	73
23[d]	**1x**	**2x**	23	>99	85

[a] Conditions: $P(H_2)$ = 5 MPa, 100 °C, [**1**] = 1.0 M in 2-propanol, **1**:KO*t*-Bu = 100:25, unless otherwise noted. **1**:**4d** = 100:1 for entries 1−11 and 10:1 for entries 12−22. [b] Isolated yield. [c] Product yield determined by ^{1}H NMR spectroscopy using triphenylmethane as an internal standard. [d] [**1**] = 1.0 M in THF, **1**:$NaOCH_3$ = 100:25, **1**:**4d** = 100:1.



Scheme 3. Hydrogenative DKR of (±)-1b



Accordingly, we next examined the enantioselective hydrogenation of (±)-**1b** in the presence of a chiral catalyst system via DKR and found that a range of optically active 1,2-diamine ligands (**3i**−**l**) did promote the asymmetric hydrogenation to give optically active (*S*)-(+)-**2b** with appreciable enantioselectivity as illustrated in Scheme 3. Although the enantioselectivity was

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still moderate, this result indicates *for the first time* that a suitable design of chiral catalyst system can provide direct access to chiral nonracemic diols from racemic esters.

In conclusion, we have developed a new catalytic method for the straightforward hydrogenation of carboxamides and esters. Our method using chiral ligands will be particularly useful when stereochemically well-defined 2-substituted alcohols are required despite the lack of any convenient access to stereochemically well-defined 2-substituted esters. Exploration of suitable chiral catalyst systems that meet this purpose is now in progress in our laboratories.

■ ASSOCIATED CONTENT

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

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