

Atmospheric Hydrogenation of Esters Catalyzed by PNP-Ruthenium Complexes with an *N*-Heterocyclic Carbene Ligand

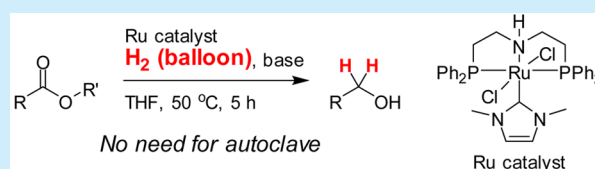
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S Supporting Information

ABSTRACT: New pincer ruthenium complexes bearing a monodentate *N*-heterocyclic carbene ligand were synthesized and demonstrated as powerful hydrogenation catalysts. With an atmospheric pressure of hydrogen gas, aromatic, heteroaromatic, and aliphatic esters as well as lactones were converted into the corresponding alcohols at 50 °C. This reaction protocol offers reliable access to alcohols using an easy operational setup.



The reduction of esters to alcohols, which is one of the most fundamental transformations in organic synthesis, has been generally performed by using a stoichiometric amount of metal hydride such as lithium aluminum hydride or sodium borohydride.¹ Although these protocols are reliable in laboratory-scale activities, the inevitable workup procedures, which include a hazardous quench step, filtration, and repeated extraction, and the resulting formation of undesirable wastes are problematic, especially on a manufacturing scale. Catalytic hydrogenation is an ideal reaction that can contribute environmentally benign approaches to overcome these issues; however, harsh pressure and temperature conditions are required to transform hardly reducible esters, particularly for heterogeneous catalysts.²

Since the striking example of a pyridine-based Ru-PNN system utilized for the ester hydrogenation was reported by Milstein et al. in 2006,³ more than 10 metal complexes with a range of pincer-type ligands have rendered effective homogeneous catalysts^{4,5} based on the metal/ligand bifunctionality, as typified by the examples shown in Figure 1. In connection with extensive efforts on the structural modification of the cooperative ligands, the catalyst performance has been

improved in terms of its productivity and catalyst robustness. Our group reported a Ru-MACHO complex bearing a tridentate bis[2-(diphenylphosphino)ethyl]amine (PNP) ligand effective for hydrogenation of esters, in which a multiton scale application was demonstrated at 30 °C, while minimizing the loss in optical purity of the substrate, methyl (*R*)-lactate.^{5a} Although significant advances have been made for a series of bifunctional catalysts that display high turnover numbers and turnover frequencies, there remains an operational concern regarding the use of specialized equipment in the pressurized reaction that will be an obstacle for adopting the protocol.⁶ In this study, we reported the first atmospheric hydrogenation of esters using a new Ru complex.

In most of the reported Ru-MACHO derivatives, π -back bonding contribution of coordinating carbon monoxide (CO) increases robustness of the Ru complex, but the nucleophilicity of the hydride intermediates is presumably depressed. We envisioned that the catalytic performance of the Ru-PNP system could be enhanced by replacing the CO with electron donating ligands. In light of the strong σ -donating property of *N*-heterocyclic carbene (NHC) ligands,⁷ the Ru-NHC system has been conceived to bring a positive influence to the hydrogenation.^{5c,d,h,o} Recently, Pidko and co-workers disclosed that bis(NHC)-amino pincer ligands are highly effective for the ester hydrogenation achieving a TOF of up to 283 200 h⁻¹ though under 40 bar of H₂.^{5h}

The initial hydrogenation experiments were performed using methyl benzoate as a benchmark substrate, mixed with 0.05 mol % of [RuCl₂(PNP)]₂ (1; ester/Ru = 1000)⁸ and 10 mol % of KO^tBu at 1.0 MPa of hydrogen pressure and 80 °C in toluene. As listed in Table 1, a small amount (4%) of benzyl alcohols was formed after 5 h (entry 1). Although the addition of PPh₃

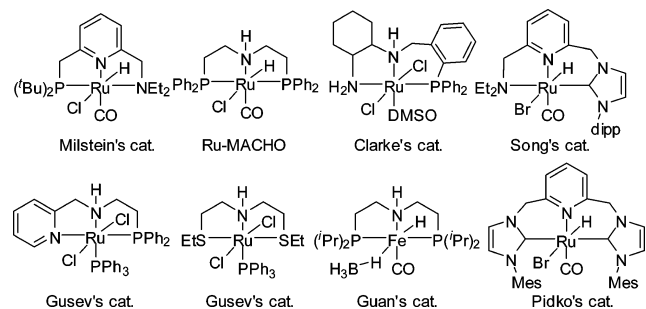
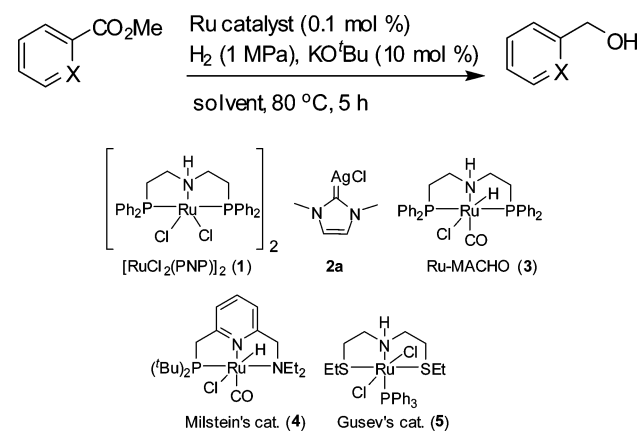


Figure 1. Pincer catalysts for hydrogenation of esters.

Received: June 30, 2016

Table 1. Comparison of the Catalytic Activity in Hydrogenation of Methyl Benzoate or Methyl Picolinate^a


entry	catalyst	X	solvent	% yield ^b
1	1 ^c	CH	toluene	4
2	1 + PPh ₃ ^d	CH	toluene	6
3	1 + 2a ^e	CH	toluene	93
4	1 + 2a ^e	CH	THF	63
5	1 + 2a ^e	CH	MeOH	<1
6 ^f	1 + 2a ^e	N	toluene	100
7	3	CH	toluene	49
8	4	CH	toluene	64
9	5	CH	toluene	82
10 ^f	5	N	toluene	3

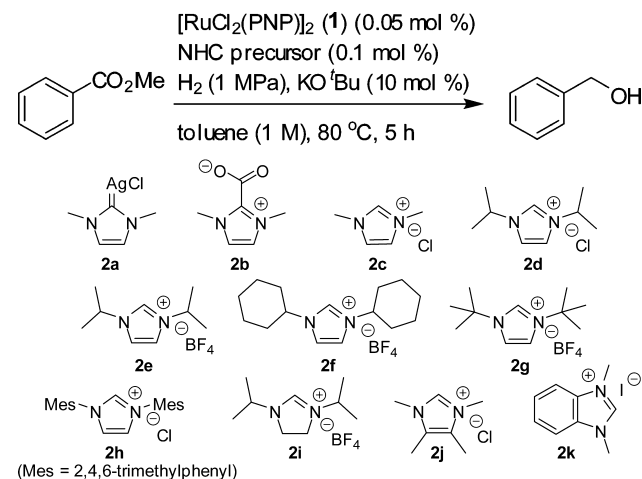
^aReaction conditions: substrate (10.0 mmol), Ru catalyst (0.1 mol %), H₂ (1 MPa), KO^tBu (1.0 mmol), solvent (10 mL), 80 °C for 5 h.

^bYield was determined by GC. ^c0.05 mol %. ^dThe catalyst was prepared *in situ* from 1 (0.05 mol %) and PPh₃ (0.1 mol %). ^eThe catalyst was prepared *in situ* from 1 (0.05 mol %) and 2a (0.1 mol %).

^fSubstrate = 2.5 mmol.

made little impact on the reaction outcome, a catalyst prepared *in situ* from 1 and a silver(I) complex of 1,3-dimethylimidazol-2-ylidene (2a)⁹ underwent smooth hydrogenation in 93% yield (entries 2 and 3). Changing the solvent to THF or methanol deteriorated the catalytic activity (entries 4 and 5). Methyl picolinate was also converted into the corresponding alcohol quantitatively (entry 6). Ru-MACHO and Milstein's catalyst³ gave moderate yields of 49% and 64% for the hydrogenation of methyl benzoate (entries 7 and 8). Gusev's catalyst^{5f} showed good catalytic performance in the hydrogenation of methyl benzoate, whereas methyl picolinate was mostly unreacted under identical conditions (entries 9 and 10). These results support the important role of the NHC ligand in the catalytic ester hydrogenation.

Screening the NHC precursors in the hydrogenation of methyl benzoate revealed that the substituents on the nitrogen atoms delicately influence the catalytic activity (Table 2). As shown in Table 2, an NHC ligand with methyl groups (2a–c)^{9,10} gave high yields, regardless of the precursor forms (entries 1–3). Although ^tPr-substituted imidazolium salts (2d–e) also promoted the hydrogenation in 70% and 83% yields, more sterically congested NHCs (2f–h) lowered the yield of benzyl alcohols in the order Cy > ^tBu > Mes (entries 4–8). NHCs (2i and 2j) from 4,5-dihydroimidazole and 1,3,4,5-tetramethylimidazole exhibited limited activity for the hydrogenation (entries 9–10). An NHC ligand derived from benzimidazole (2k)¹¹ gave the hydrogenation product in a reasonable yield of 69%.

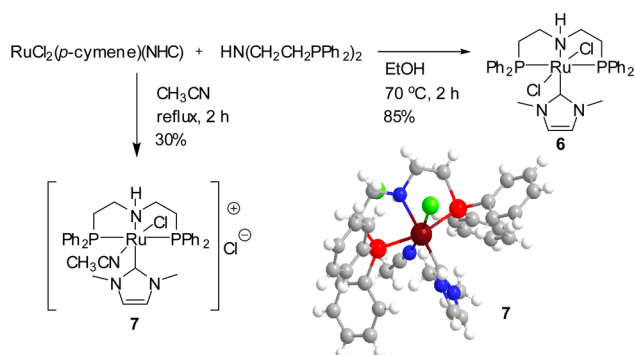
Table 2. NHC Ligand Effect on the Catalytic Activity^a


entry	NHC precursor	% yield ^b
1	2a	93
2	2b	86
3	2c	85
4	2d	70
5	2e	83
6	2f	42
7	2g	11
8	2h	5
9	2i	8
10	2j	39
11	2k	69

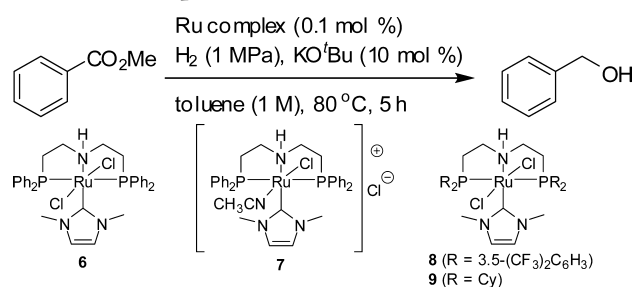
^aReaction conditions: substrate (10.0 mmol), 1 (0.05 mol %), NHC precursor (0.1 mol %), H₂ (1 MPa), KO^tBu (1.0 mmol), toluene (10 mL), 80 °C for 5 h. ^bYield was determined by GC.

Attempts to prepare the NHC-coordinated PNP–ruthenium complex by treatment of the catalyst precursor 1a with an equimolar amount of 2a in acetonitrile at 80 °C for 1 h were unsuccessful. Performing the reaction under 0.1 MPa of hydrogen gas in the presence of KO^tBu afforded a complex mixture. As an alternative synthetic approach, we examined the coordination of the PNP pincer to RuCl₂(*p*-cymene)(NHC),¹² which can be prepared from [RuCl₂(*p*-cymene)]₂ and 1,3-dimethylimidazolium-2-carboxylate (2b). When RuCl₂(*p*-cymene)(NHC) was treated with an equimolar amount of PNP in ethanol at 70 °C for 2 h, a neutral dichlororuthenium complex RuCl₂(NHC)(PNP) (6) was obtained as a pale yellow powder in 85% yield. Interestingly, the use of CH₃CN as the solvent provided a cationic acetonitrile-coordinated complex, [RuCl(CH₃CN)(NHC)(PNP)]Cl (7), which was isolated as a yellow crystalline precipitate in 30% yield after cooling the reaction mixture. The crystal structure of 7 shows that the amino-diphosphine ligand coordinates to the ruthenium center in a meridional position with the NHC ligand located at a site *trans* to the protic amine moiety (Scheme 1). In contrast, the PNP–ruthenium complexes were not formed at all in THF, implying that the coordination of the PNP ligand occurs via the dissociation of the chloro ligand in RuCl₂(*p*-cymene)(NHC), aided by polar solvents having sufficient coordinating ability. The related PNP ligands having a cyclohexyl and 3,5-bis(trifluoromethyl)phenyl group at the phosphorus atom also provided the corresponding neutral NHC–Ru analogues (8 and 9) in ethanol solution (see Supporting Information).

Scheme 1. Synthesis of NHC-Coordinated PNP–Ru Complexes



The isolated neutral complex **6** is an effective hydrogenation catalyst. As shown in entry 1 of Table 3, **6** gave a comparable

Table 3. Hydrogenation of Esters Using NHC-Coordinated Ruthenium Complexes^a

entry	Ru complex	% yield ^b
1	6	94
2	7	57
3	8	95
4	9	45

^aReaction conditions: substrate (10.0 mmol), Ru complex (0.1 mol %), H_2 (1 MPa), KO^tBu (1.0 mmol), toluene (10 mL), 80 °C for 5 h. ^bYield was determined by GC.

yield of the product (94%) to that obtained by the *in situ* formed catalyst. The cationic complex **7** proved to possess a slightly lower activity than that of **6**, possibly due to the strong coordination of CH_3CN to the Ru center (entry 2). The modified complex **8** with 3,5-bis(trifluoromethyl)phenyl groups on the phosphorus atom also proved comparable to **6** (95%), although the complex **9** with dicyclohexylphosphino groups led to a lower yield (45%, entries 3 and 4).

Encouraged by these positive results, we anticipated that the NHC–Ru catalyst would prove instrumental to the atmospheric hydrogenation of esters (Table 4).¹³ As shown in Table 4, methyl benzoate is mostly converted with 1.0 mol % of **6** in the presence of KO^tBu (10 mol %) under a hydrogen atmosphere in toluene at 80 °C to give benzyl alcohol in 40% yield along with benzyl benzoate in 23% yield (entry 1). The byproduct was possibly formed via the dehydrogenative condensation of the major product, benzyl alcohol, under an atmospheric pressure of H_2 or transesterification of the substrate with benzyl alcohol. The product selectivity was increased by lowering the temperature to 50 °C and using THF as the solvent (entries 2 and 3). A higher catalyst loading to 2.0 mol % was required to reach almost full conversion and a 93% yield (entry 4).

Table 4. Atmospheric Hydrogenation of Methyl Benzoate Catalyzed by **6**^a

Reaction scheme showing the atmospheric hydrogenation of methyl benzoate ($\text{C}_6\text{H}_5\text{CO}_2\text{Me}$) to benzyl alcohol ($\text{C}_6\text{H}_5\text{CH}_2\text{OH}$) using **6** (1.0 mol %) in THF (1.0 M) for 5 h. The reaction conditions are H_2 (balloon) and KO^tBu (10 mol %).

entry	cat. loading, mol %	temp, °C	solvent	% conv ^b (% yield)
1	1.0	80	toluene	94 (40)
2	1.0	50	toluene	85 (55)
3	1.0	50	THF	92 (74)
4 ^c	2.0	50	THF	99 (93)

^aReaction conditions: substrate (1.0 mmol), **6** (1.0 or 2.0 mol %), H_2 (balloon), KO^tBu (0.1 mmol), solvent (1.0 mL) for 5 h. ^bConversion and yield were determined by GC. ^cTHF (2.0 mL).

The complex **6** served as a competent catalyst for the hydrogenation of a variety of esters under atmospheric pressure in THF at 50 °C (Table 5). Methyl picolinate and methyl

Table 5. Atmospheric Hydrogenation of Esters and Lactone^a

Reaction scheme showing the atmospheric hydrogenation of various esters to alcohols using **6** (2.0 mol %) in THF (0.5 M) for 5 h. The reaction conditions are H_2 (balloon) and base (20 mol %).

entry	substrate	alcohol	base	% conv ^b (% yield)
1	$\text{C}_6\text{H}_5\text{CO}_2\text{Me}$	$\text{C}_6\text{H}_5\text{CH}_2\text{OH}$	KO^tBu^c	99 (90) ^e
2	$\text{C}_5\text{H}_4\text{NCO}_2\text{Me}$	$\text{C}_5\text{H}_4\text{NCH}_2\text{OH}$	KO^tBu^c	>99 (98) ^e
3	$\text{C}_5\text{H}_3\text{N}_2\text{CO}_2\text{Me}$	$\text{C}_5\text{H}_3\text{N}_2\text{CH}_2\text{OH}$	KO^tBu	>99 (90)
4	$\text{PhCH=CHCO}_2\text{Me}$	$\text{PhCH}_2\text{CH}_2\text{OH}$	NaOMe^d	>99 (89)
5	$\text{C}_6\text{H}_4(\text{Br})\text{CO}_2\text{Me}$	$\text{C}_6\text{H}_4(\text{Br})\text{CH}_2\text{OH}$	KO^tBu	>99 (94)
6	$\text{C}_6\text{H}_3(\text{Br})_2\text{CO}_2\text{Me}$	$\text{C}_6\text{H}_3(\text{Br})_2\text{CH}_2\text{OH}$	KO^tBu	>99 (94)
7	$\text{C}_6\text{H}_5\text{CO}_2\text{Et}$	$\text{C}_6\text{H}_5\text{CH}_2\text{OH}$	KO^tBu	>99 (90)
8	$\text{C}_6\text{H}_5\text{CO}_2^t\text{Bu}$	$\text{C}_6\text{H}_5\text{CH}_2\text{OH}$	KO^tBu	>99 (91)
9	$\text{CH}_2=\text{CHCO}_2\text{Me}$	$\text{CH}_2\text{CH}_2\text{OH}$	KO^tBu^c	99 (94)
10	$\text{C}_5\text{H}_7\text{O}_2$	$\text{C}_5\text{H}_9\text{O}_2$	NaOMe^d	92 (73)

^aReaction conditions: substrate (1.0 mmol), **6** (2.0 mol %) base (0.2 mmol), H_2 (balloon), THF (2.0 mL), 50 °C for 5 h. ^bConversion and yield were determined by GC. ^c0.1 mmol ^d0.5 mmol. ^eIsolate yield.

nicotinate were transformed into the corresponding alcohols while keeping the pyridine moiety intact in excellent yields (entries 2 and 3). Ethyl cinnamate, having a C–C double bond, was fully hydrogenated to 3-phenyl-1-propanol (entry 4). The catalysts hydrogenate bromo-substituted benzoates, affording benzylic alcohols in 94% yield without dehalogenation (entries

5 and 6). The hydrogenation of more sterically congested ethyl and *tert*-butyl esters also furnished benzyl alcohol as the alcohol as well (entries 7 and 8). The substrates need not be aromatic for the hydrogenation to be successful—methyl heptanoate was completely reduced to 1-heptanol in 94% yield (entry 9). In the case of γ -butyrolactone, although hydrolysis proceeded competitively, the desired 1,4-diol was obtained in 73% yield (entry 10).

In summary, the incorporation of NHC ligands into the bifunctional PNP–ruthenium complex results in an outstanding ester hydrogenation catalyst, compared to the catalyst systems based on the well-defined Ru-pincer complexes that have emerged to date. The atmospheric hydrogenation of esters was achieved by the isolable NHC-coordinated PNP–ruthenium complex in THF at a nonsevere temperature of 50 °C. The hydrogenation can be conducted using glassware reactors such as a Schlenk flask equipped with a balloon containing H₂ and thus provides a practical protocol for reduction of esters. Further studies are in progress to evaluate the utility of this catalyst in other challenging hydrogenations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b01900](https://doi.org/10.1021/acs.orglett.6b01900).

Experimental section, characterization data, X-ray data for 7 (PDF)

Crystallographic data for 7 (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This study was financially supported by JSPS KAKENHI Grant Numbers 24350079 and 26621043. The authors thank our analytical technology research team for ¹³C NMR and mass spectroscopic data.

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(13) The results of the hydrogenation conducted at 0.4 MPa of hydrogen pressure are summarized in the Supporting Information.