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Bis-N-heterocyclic Carbene Aminopincer Ligands Enable High Activity in Ru-Catalyzed Ester Hydrogenation

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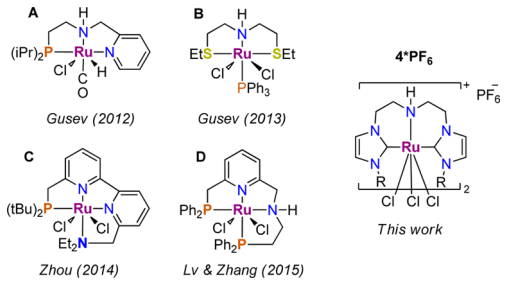
Supporting Information

ABSTRACT: Bis-N-heterocyclic carbene (NHC) aminopincer ligands were successfully applied for the first time in the catalytic hydrogenation of esters. We have isolated and characterized a well-defined catalyst precursor as a dimeric $[Ru_2(L)_2Cl_3]PF_6$ complex and studied its reactivity and catalytic performance. Remarkable initial activities up to 283 000 h^{-1} were achieved in the hydrogenation of ethyl hexanoate at only 12.5 ppm Ru loading. A wide range of aliphatic and aromatic esters can be converted with this catalyst to corresponding alcohols in near quantitative yields. The described synthetic protocol makes use of air-stable reagents available in multigram quantities, rendering the bis-NHC ligands an attractive alternative to the conventional phosphine-based systems.

Reduction of organic compounds with molecular hydrogen is a powerful synthetic tool. A key factor for putting this reaction in practice is the availability of a potent catalyst that drives the hydrogenation reaction. One of the reactions where the active catalyst is desired is the reduction of carboxylic acid esters to alcohols. It currently relies on the conventional approaches utilizing stoichiometric amounts of inorganic hydrides and producing vast amounts of waste. Therefore, catalytic reduction of esters with H_2 is viewed as a green alternative for conventional reduction protocols. Early examples of such catalytic processes[1] required very harsh reactions conditions (ca. 85 bar H_2, T > 100 °C). Tremendous progress in the field was made by the groups at Firmenich[2] and Takasago[3] and the group of Milstein,[4] who described several bifunctional ester hydrogenation catalysts that operated under significantly milder conditions. Following these reports, the field of ester hydrogenation witnessed a rapid development with catalyst performances steadily improving. Progress was mainly associated with the introduction of tri- and tetradentate aminopincer ligands.[1c,5] Recently, Gusev and co-workers[6] reported a family of Ru and Os-PNN pyridine aminophosphine pincer catalysts, with which turnover numbers (TONs) of ≈18 000 were reached in the hydrogenation of methyl benzoate at 100 °C and 50 bar H_2 (Scheme 1, **A**). The same group also disclosed a Ru-SNS pincer complex producing ≈60 000 turnovers in ethyl acetate hydrogenation at only 40 °C and 50 bar H_2 (Scheme 1, **B**).[7] Recent

Scheme 1. Selected Examples of Active Catalysts for Ester Hydrogenation



reports by Zhou[8] and Zhang[9] feature tetradentate phosphine-based Ru catalysts (Scheme 1, **C** and **D**), which are currently the most active catalysts in terms of the productivity (turnover frequency, TOF) and stability (TON). These Ru-PNNX (X = P,N) catalysts are efficient at very low Ru loadings of 10−100 ppm with respect to the ester substrate. For example, TON up to 80 000 and estimated TOF of >10 000 h^{-1} are obtained with Ru-PNNP catalyst **D** (Scheme 1) at 80 °C and 50 bar H_2.

With the exception of Ru-SNS (Scheme 1, **B**), the most potent ester hydrogenation catalysts rely on phosphine ligands that are prepared from often expensive and air- or moisture-sensitive organophosphorus reagents. On the contrary, N-heterocyclic carbene ligands (NHCs) are air-stable and can be prepared from abundant building blocks.[10] Ru-NHC complexes have already found widespread catalytic application, for example, in metathesis reactions[11] and various hydrogenation processes.[12] However, their application in the catalytic hydrogenation of esters is scarce, and the performance of the Ru-NHCs[13] is still inferior to that of the phosphine-based catalysts. In this work, we demonstrate that the use of bis-NHC aminopincer ligands for Ru-catalyzed hydrogenation of esters can lead to remarkable activity that rivals that of the phosphine-based catalysts.

Bis-NHC aminopincer ligand precursors[14] are prepared via a simple reaction of the corresponding imidazoles with nitrogen mustard derivatives (Scheme 2). While the ligand **L1H** is prepared in a one-step reaction, synthesis of **L2H**−**L5H** requires a three-step procedure that involves the protection/deprotection

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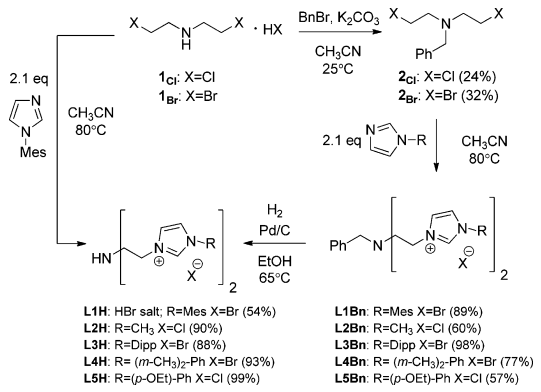
Scheme 2. Structure and Synthesis of Bis-NHC Aminopincer Ligands[a]

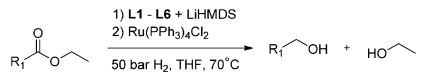


[a]Mes = 2,4,6-trimethylphenyl; Dipp = 2,6-diisopropylphenyl.

of the amine site with the benzyl group to avoid the degradation of **1**. Following these methods, we obtained a ligand library containing 10 bis-NHC ligands with different substituents at the amine site and imidazolium ring.

We performed hydrogenation of ethyl hexanoate and ethyl benzoate at 70 °C and 50 bar H_2 using Ru catalysts with different bis-NHC ligands to identify the most competent one. The catalysts were generated in situ by treating a suspension of the imidazolium salts in THF with LiHMDS (lithium hexamethyldisilazide) followed by the addition of the metal precursor—$Ru(PPh_3)_4Cl_2$. Use of a strong base was necessary to deprotonate the imidazolium ligand precursors and form the free NHCs capable of coordination.[14a] The results of the catalytic tests are summarized in Table 1.

Table 1. Results of the Ligand Screening in Hydrogenation of Ethyl Hexanoate and Ethyl Benzoate[a]



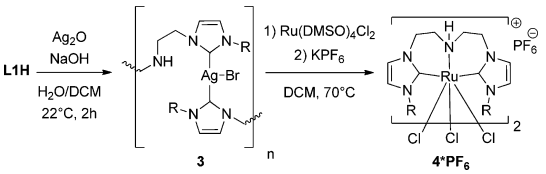
entry	ligand	ester R_1	S/Ru	Y_{alc} (%)	TON
1	**L1Bn**			0	0
2	**L2Bn**	n-C_5H_{11}	15000	0	0
3	**L4Bn**			0	0
4	**L1H**	n-C_5H_{11}	15000	95	**14250**
5		Ph	5000	83	**4150**
6	**L2H**	n-C_5H_{11}	15000	1	150
7		Ph	5000	0	0
8	**L3H**	n-C_5H_{11}	15000	100	**15000**
9		Ph	5000	65	**3250**
10	**L4H**	n-C_5H_{11}	15000	40	6000
11		Ph	5000	50	2500
12	**L5H**	n-C_5H_{11}	15000	2	300
13		Ph	5000	37	1850

[a]Conditions: 5 mmol ester, 2 mol % of KO^{t}Bu, 2 mL of THF, 70 °C, 50 bar H_2, 16 h, S/Ru = substrate-to-ruthenium molar ratio.

The structure of the ligand had a strong influence on the activity of in situ generated Ru catalysts (Table 1). In line with the observations made by Gusev and co-workers,[7] substitution (i.e., benzylation) at the NH site of the ligand yields inactive catalysts (entries 1−3, Table 1). Substituents at the NHC groups were also found to have an impact on the performance. The best catalysts were formed from mesityl-substituted (**L1H**, entries 4 and 5) and diisopropylphenyl-substituted (**L3H**, entries 8 and 9) ligands. The remaining ligands with *meta*- and *para*-substituted phenyl groups (**L4H** and **L5H**) or methyl substituents (**L2H**) on the imidazolium rings resulted in no to moderate activity. Inferior performance of **L2H**, **L4H**, and **L5H** may be explained by the lower stability of free NHCs derived from these ligands with reduced bulk around the carbene center.[10a] Alternatively, one can expect a reactivity of **L4H** and **L5H** toward cyclometalation by Ru that is notorious for its negative impact on the activity in a metathesis reaction.[15] The type of the Ru precursor employed for the in situ catalysis also had an impact on catalytic performance, with $RuHCl(CO)(PPh_3)_3$ being significantly less active than the $Ru(PPh_3)_4Cl_2$ discussed above (see Table S1 in Supporting Information (SI)).

Inspired by the promising performance of precatalysts formed form **L1H**/$Ru(PPh_3)_4Cl_2$, we sought to isolate the corresponding well-defined Ru-CNC complex. Because the reaction of the free NHCs derived from **L1H** with $Ru(PPh_3)_4Cl_2$ led to complex mixtures, we employed an alternative synthetic strategy involving transmetalation from the Ag-NHC complex with **L1H** to the Ru center (Scheme 3). The corresponding Ag-NHC complex **3**

Scheme 3. Synthesis of 4*PF_6



(Scheme 3) was previously reported by Edworthy et al.[14b] The original procedure involved the reaction of **L1H** with Ag_2O in dry CH_2Cl_2 in the presence of molecular sieves (4 Å) over several days. We have greatly simplified the preparation of **3** using the approach originally described for preparing Ag benzimidazol-2-ylidene complexes by Lin and co-workers.[16] When imidazolium salt **L1H** is reacted with Ag_2O in the presence of NaOH in a biphasic CH_2Cl_2/H_2O medium, **3** is generated within 2 h in 82% yield without exclusion of air.

NHC transfer from **3** to $Ru(PPh_3)_4Cl_2$ at 70 °C in dichloromethane led to a single new Ru complex. Electrospray ionization mass spectrometry (ESI-MS) shows a signal at 1193 amu corresponding to the dimeric $[Ru_2(\mathbf{L1H})_2Cl_3]^+$ species $\mathbf{4}^+$. Use of the phosphine-containing $Ru(PPh_3)_4Cl_2$ precursor is undesired because it leads to the formation of $Ag(PPh_3)_n$ byproducts that could not be separated from the target compound.[17] Preparation and isolation of $\mathbf{4}^+$ was further attempted using an air-stable phosphine-free precursor $Ru(DMSO)_4Cl_2$ instead.

Reaction of $Ru(DMSO)_4Cl_2$ with **3** in CH_2Cl_2 or THF yields the same cationic $\mathbf{4}^+$ as evidenced by NMR and ESI-MS. Initially, $\mathbf{4}^+$ was obtained as a cationic dimer $[Ru_2(\mathbf{L1H})_2Cl_3]^+$ with a dibromoargenate $[AgBr_2]^-$ counterion that could be observed in the negative-mode ESI-MS. To avoid the potential light sensitivity induced by the dibromoargenate anion, the crude product was further treated with excess KPF_6 to obtain the pure complex **4*PF_6** as a crystalline solid (Scheme 3).

Two CNC ligand units in **4*PF_6** appear equivalent in the ^{1}H NMR spectrum (see Figure S2 in SI). However, symmetry within the CNC ligand is not retained upon complexation. Imidazole backbone protons appear as four separate doublets with $^3J_{HH} = 2$ Hz, and aromatic protons of the mesityl substituents give four

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singlets. In addition, eight ethylene linker protons appear separately, indicating that geminal protons within the CH_2 groups of the linkers are not equivalent. Accurate assignment of these resonances can be done using selective excitation NMR measurements (double pulsed field gradient spin echo NOESY). Using this approach, one can also reveal the broad resonance of the N*H* proton at δ 3 ppm that otherwise is overlapped by other resonances in the spectrum.

X-ray crystal structure analysis of **4*PF$_6$** (Figure 1) reveals the bistrigonal antiprism geometry of the complex. Two ligand units

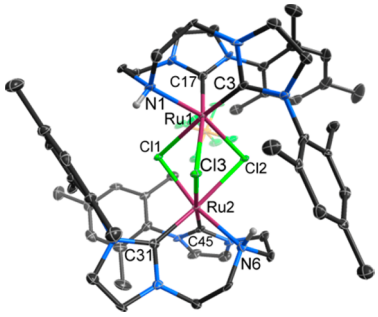


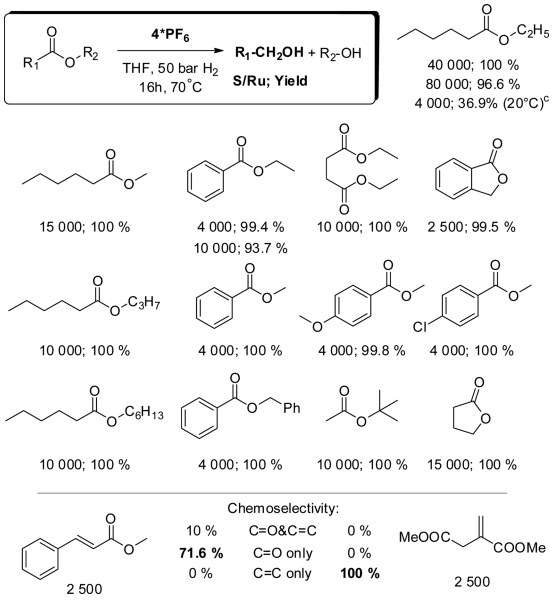
Figure 1. Molecular structure of **4*PF$_6$** in the crystal. Displacement ellipsoids are shown at the 50% probability level. All hydrogens except the N*H* group are omitted for clarity. Selected bond lengths (Å): Ru1−C3 1.969, Ru1−C17 1.987, Ru1−N1 2.145, Ru2−N6 2.160, Ru2−C31 1.973, Ru2−C45 1.988.

occupy the opposite faces of the octahedrally coordinated Ru, which is consistent with their apparent equivalence in solution as follows from ^{1}H NMR spectroscopy. The formation of $L_2Ru_2(\mu\text{-}Cl)_3$ units is well-known for Ru complexes with tridentate ligands that prefer facial coordination, such as TriPhos.[18]

4*PF$_6$ is an active ester hydrogenation catalyst. Under 50 bar H_2 at 70 °C, it can convert a wide range of aliphatic and aromatic esters to their corresponding alcohols in quantitative yields (Scheme 4). Full conversions of hexanoic acid esters were obtained at a substrate-to-ruthenium (S/Ru) ratio of 10 000. Aromatic esters, including rather challenging phthalide and benzyl benzoate substrates, can also be fully converted at S/Ru = 2500−4000. A very high TON of 79 680 was obtained with ethyl hexanoate, which is nearly identical to the value reported by Zhang et al. for hydrogenation of ethyl acetate at a slightly higher temperature and a longer reaction time (80 °C, 50 bar H_2, 30 h) with the tetradentate Ru-PNNP catalyst.[9] Diethylsuccinate and γ-butyrolactone are converted to 1,4-butanediol in quantitative yields at S/Ru = 10 000−15 000. Hydrogenation of dimethyl itaconate was fully chemoselective for the reduction of the C═C bond and yielded no alcohol product. Hydrogenation of methyl cinnamate yields a mixture of the saturated and the unsaturated alcohol with up to 70% of cinnamyl alcohol, indicating that our hydrogenation catalyst exhibits a certain selectivity favoring the ester group reduction. Apart from esters, **4*PF$_6$** is also active in hydrogenating aldehydes and ketones to corresponding alcohols. This reaction is more facile than the ester reduction and proceeds readily at room temperature (see section 3 of the SI).

To obtain insight into the nature of the catalytically active species, we investigated the transformations of the precatalyst **4*PF$_6$** during hydrogenation of ethyl acetate using NMR spectroscopy combined with ESI-MS. The reaction was carried out in an NMR tube at 3 bar H_2 in THF-d_8 in the presence of KO^{t}Bu base (10 equiv per Ru). No notable color change occurred upon the addition of the catalyst to the reaction

Scheme 4. Results of Ester Hydrogenation with 4*PF$_6$[a] (S/Ru Ratio and Alcohol Yields[b])



[a]Conditions: 5 mmol ester, 2 mL of THF, 70 °C, 50 bar H_2, 2 mol % of KO^{t}Bu, 16 h. [b]Yields are given for alcohols derived from the acyl group of the ester; lactone and diester reduction provided diol products. [c]Reaction at 20 °C: 38/62% selectivity to hexanol/hexyl hexanoate at 97% conversion.

mixture. Interestingly, although ≈25% conversion of ethyl acetate was reached at room temperature, no products of the transformations of the initial dimeric complex could be observed within the detection limit of NMR (see Figure S8 in SI). Heating of the reaction mixture to 70 °C led to further conversion of ethyl acetate to 61%,[19] accompanied by partial transformation of the initial Ru complex to a new species. Mass spectrometry allows for identifying the newly formed species as the monomeric Ru complex bearing a 1-ethoxyethanolate ligand (**I-1**, Figure 2a) that is similar to the intermediates observed earlier by Gusev[20] and Bergens[21] for related reactions. Species **I-1** rapidly disappears

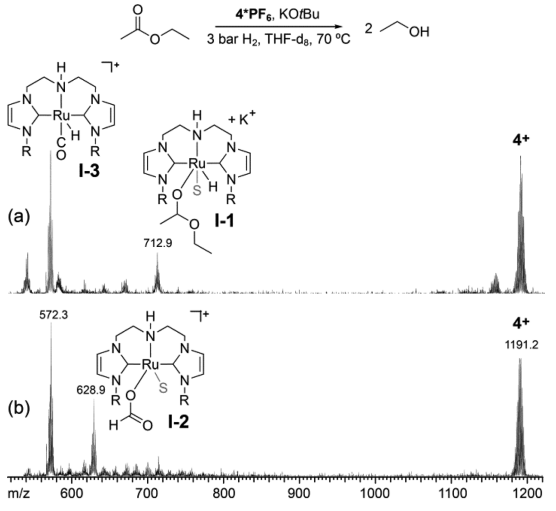


Figure 2. ESI-MS spectra of the reaction mixture of NMR scale ethyl acetate hydrogenation (3 bar H_2, THF-d_8, 10 equiv of KO^{t}Bu per Ru, S/Ru = 500): untreated (a) and quenched with HCOOH (b); S = CH_3CN.

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when the reaction mixture is quenched with 0.1% HCOOH in acetonitrile, producing a monomeric Ru-formate complex **I-2** (Figure 2b). This is consistent with **I-1** containing the alkoxide ligand that is rapidly protonated in the presence of the acid. Ru-carbonyl complex **I-3** was also observed in the catalytic mixture. Carbonylation of the metal center was previously proposed to be the main source of catalyst deactivation.[2,3] Intermediate formation of the aldehyde product during ester hydrogenation may be responsible for the carbonylation of the metal center. Formation of benzaldehyde could be observed during the methyl benzoate hydrogenation with **4*PF$_6$** (see Table S2 in SI). Although these results do not constitute a definite proof for the nature of the active catalyst, they suggest that the dimeric structure of the initial Ru complex is not retained under the catalytic conditions and that the Ru species formed in the catalytic reaction are monomeric.

To further investigate the catalytic activity of **4*PF$_6$**, we performed a series of kinetic measurements with ethyl hexanoate as a substrate on a 100 mmol scale. At S/Ru = 10 000, very high initial TOF^0 values up to 78 600 h^{-1} were observed (Figure 3).

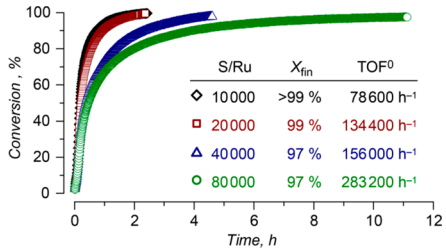

Figure 3. Kinetic traces of ethyl hexanoate hydrogenation with **4*PF$_6$**. Conditions: 40 bar H_2, 70 °C, 100 mmol ester, 2 mol % of KO^{t}Bu, S/Ru indicated on the graph. X_{fin}, final conversion, TOF^0, initial rate.

Ester conversion was >99% with a selectivity of 99.7% to 1-hexanol. No straightforward reaction order with respect to catalyst concentration could be derived from these experiments, indicating a complex behavior associated with the formation of the active species. Consistent with the proposed monomeric nature of the active species, the initial TOF substantially increases upon decreasing the precatalyst concentration. At S/Ru of 80 000, an initial TOF^0 of 283 200 h^{-1} and a TON of 53 900 in 1 h were obtained, confirming the remarkable productivity of **4*PF$_6$**.

To summarize, we report the first well-defined Ru catalyst based on bis-NHC pincer ligands that is highly active for the hydrogenation of esters. After performing a ligand screening using in situ generated catalysts, we isolated a dimeric catalyst precursor **4*PF$_6$** that is extremely active under basic conditions. According to our preliminary studies, the active state of the catalyst is a monometallic species. Catalytic performance of **4*PF$_6$** ranks it among the most active ester hydrogenation catalysts to date, bringing this methodology a step closer toward its implementation on an industrial scale.

■ ASSOCIATED CONTENT

Supporting Information

Synthesis and characterization details and hydrogenation procedures. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04237.

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Notes

The authors declare no competing financial interest.

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(19) Incomplete conversion of ethyl acetate was due to lower reactivity of the catalyst under mild conditions of the NMR experiment, which is not associated with preactivation of **4*PF$_6$** as the latter has no significant effect on the activity (see Table S3 in the SI).

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