Ester Hydrogenation with Bifunctional Metal–NHC Catalysts: Recent Advances

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ABSTRACT: Hydrogenation of ester to alcohol is an essential reaction in organic chemistry due to its importance in the production of a wide range of bulk and fine chemicals. There are a number of homogeneous and heterogeneous catalyst systems reported in the literature for this useful reaction. Mostly, phosphine-based bifunctional catalysts, owing to their ability to show metal–ligand cooperation during catalytic reactions, are extensively used in these reactions. However, phosphine-based catalysts are difficult to synthesize and are also highly air- and moisture-sensitive, restricting broad applications. In contrast, N-heterocyclic carbenes (NHCs) can be easily synthesized, and their steric and electronic attributes can be fine-tuned easily. In recent times, many phosphine ligands have been replaced by potent σ-donor NHCs, and the resulting bifunctional metal–ligand systems are proven to be very efficient in several important catalytic reactions. This mini-review focuses the recent advances mainly on bifunctional metal–NHC complexes utilized as (pre)catalysts in ester hydrogenation reactions.

INTRODUCTION
Hydrogenation of esters to corresponding alcohols is among the most vital processes in organic chemistry owing to its application in the synthesis of useful chemicals. Unlike traditional methods, where stoichiometric amounts of LiAlH₄ (lithium aluminium hydride) or DiBAIH (diisobutyl aluminium hydride) are required,¹ catalytic hydrogenation is an environment-friendly process.² Since most of the homogeneous catalysts need harsh reaction conditions, such as very high temperature and pressure (>200 °C, >200 bar),³ the development of homogeneous catalysts for ester hydrogenation under mild conditions has drawn recent attention.⁴ Homogeneous transition metal catalysts mainly derived from phosphate-based bifunctional ligands are used in ester hydrogenations.⁵ In 2006, Milstein and co-workers described catalytic ester hydrogenation reactions with PNN—Ru-based homogeneous catalysts (Chart 1, I) under mild reaction conditions.⁶ Using catalyst I (1 mol %, 115 °C, and 5.3 bar H₂), aromatic and aliphatic esters were effectively hydrogenated to the corresponding alcohols. The proposed catalytic cycle involves an unusual aromatization/dearomatization sequence for the heterolytic cleavage of H₂, which might be the reason for the high activity of I in ester hydrogenation. This type of unusual ligand-assisted heterolytic activation of H₂ is an essential step in the hydrogenation reaction. Such ligand systems, owing to their ability to show unusual metal–ligand cooperation during catalytic reactions, are extensively studied in the catalytic hydrogenation of polar bonds.⁷ Since then, several phosphine-based homogeneous catalysts have been reported for ester hydrogenation (Chart 1).⁸,⁹ Gusev and co-workers have reported a Ru pincer catalyst (II)⁸a for ester hydrogenation, which offered higher turnover numbers (TONs) of ≈18 000 for methyl benzoate hydrogenation at 100 °C and 50 bar H₂. From the same group, a phosphine-free SNS–Ru complex (III)⁸b was reported, which offered ≈60 000 TONs for the hydrogenation of ethyl acetate at 40 °C and 50 bar H₂ (Chart 1). Zhou and Zhang described highly active Ru complexes IVc and Ve for the tetradentate phosphate-based ligands for ester hydrogenation reactions. Recently, efforts are being made to replace noble metals with cost-effective and environment-friendly sustainable base metals. Milstein and co-workers reported the first PNP–Fe catalyst (VI)⁸d for the hydrogenation of activated esters; since then, a number of metal catalysts of non-noble metals based on Fe, Co, and Mn have been described for ester hydrogenation reactions (Chart 1, VI–XII).⁸e–j,m Moreover, most of the reported metal catalysts for ester hydrogenation involve air- and moisture-sensitive phosphate ligands, which are generally challenging to prepare, limiting a broad application. Therefore, development of phosphine-free ester hydrogenation catalysts that can be easily prepared and the electronic and steric attributes can be easily tuned is highly desirable.

N-Heterocyclic carbenes have gradually replaced the phosphate ligands, owing to their easy synthetic methods and
Chart 1. Selected Ester Hydrogenation Catalysts Reported in the Literature

Chart 2. NHCs Stabilized Metal Catalysts for Hydrogenation of Esters
strong σ-donor and relatively weak π-acceptor properties. The NHC ligands, owing to their strong σ-donating nature, form robust complexes with metal ions in different oxidation states, and this favors important catalyst attributes like enhanced catalyst lifetime and activity by significantly decreasing metal leaching during catalysis. Moreover, the modulation of its N-substituents can also fine-tune the steric and electronic properties of the NHCs. As a result, the transition metal complexes of NHCs have been extensively studied in homogeneous catalysis. Along this line, catalytic ester hydrogenation processes using well-defined metal–NHC complexes have started evolving in recent times. Mostly RuII complexes of NHCs have been used in the ester hydrogenation reactions (Chart 2). These complexes exhibit prominent enhancements in catalytic activity using either metal–ligand cooperation based on the “N–H” group or the “aromatization/dearomatization effect”. Herein, we present an overview of the recent developments in catalytic hydrogenations of esters, using NHC-based bifunctional catalyst systems. The reviews on hydrogenations of esters, using phosphine-based systems, are already accessible. This review will discuss only those systems which are derived from NHC scaffolds and will also offer the ligand effect on catalytic ester hydrogenation reactions.

**ESTER HYDROGENATION USING METAL–NHC CATALYSTS**

Song and co-workers developed a CNN analogue of the PNN pincer ligand described by Milstein and co-workers. The authors replaced the phosphine of the PNN system with electron-rich NHCs and synthesized their corresponding RuII complexes (Scheme 1). The CNN–NHC ligand having electron-rich imidazoyl NHC and diethylamino groups as side-arms were synthesized starting from 2,6-bis-(bromomethyl)pyridine via nucleophilic substitutions with appropriate imidazole and diethylamine in good yields. The free carbene (CNN-1) generated in situ from the reaction of imidazolium salts with LiHMDS (lithium bis(trimethylsilyl)amide), on treatment with [RuHCl(CO)(PPh3)] in the presence of LiBr, afforded ruthenium hydride complex 1 (Scheme 1).

To get insight into the mechanistic pathway, the authors have done stoichiometric studies. Complex 1 on treatment with 1 equiv of KHMS (potassium bis(trimethylsilyl)amide) afforded the dearomatized complex 2, as confirmed by NMR spectroscopic studies. Further, the reactivity of 2 toward dihydrogen was studied, too. The reaction of 2 with H2 (∼3.8 atm) yielded ruthenium dihydride complex 3 via aromatization of the pyridine ring in the ligand backbone (Scheme 1). The 1H NMR spectrum of 3 in CD2Cl2 showed a singlet at ∼4.35 ppm, indicating a trans-dihydride complex. Interestingly, the reaction of 2 with D2 suggests that both the methylene arms of the Ru–CNN pincer (1) can participate in the H2 activation and releasing processes (Scheme 1). This suggests that the hydrogenation reactions are operating through the aromatization/dearomatization mechanism, similar to the Ru–PNN system (Scheme 1, I). The Ru–CNN pincer catalyst 1 in the presence of a base (KOtBu or KHMS) catalyzes the hydrogenation of unactivated esters under mild reaction conditions (105 °C and 5.3 bar H2) (Scheme 2). The
bulky ester tert-butyl acetate was also converted into the corresponding alcohol in good yield with a 100-fold increase in TOF (turnover frequency) under mild conditions, which could not be efficiently hydrogenated by the Milstein catalyst (Chart 1, I).

The RuII complex 1 shows excellent efficiency and high TONs for the hydrogenation for several aromatic and aliphatic esters (yields ≥92%) under the standard conditions as 1 mol % of complex 1, 8 mol % of KO'Bu, 2 mL of toluene, 105 °C, and 5.3 bar H2 (Scheme 2).

In the same year, Milstein and co-workers described a novel bipyridine-based CNN−NHC ligand (CNN-2) and its RuII pincer complexes for the hydrogenation of esters (Scheme 3).12b The authors have judiciously substituted the phosphine of the PNN system, reported earlier from the same group,13 with NHCs to examine the effect of more electron-donating NHCs in hydrogenation reactions. The reaction of 6-(chloromethyl)-2,2′-bipyridine with 1-mesityl-1H-imidazole in dry acetonitrile under reflux conditions afforded the desired ligand CNN-2 in good yield (Scheme 3). The ligand (CNN-2) was fully characterized using spectroscopic methods, and single-crystal X-ray diffraction studies confirmed the molecular structure. The ligand (CNN-2) on treatment with LiHMDS followed by reaction with [RuHCl(CO)(PPh3)3] afforded ruthenium hydride complex 4. Complex 4 in the presence of 1 equiv of KO'Bu (relative to Ru) found to be the active catalyst for the hydrogenation of non-activated esters to alcohols under mild conditions (4 and KO'Bu both 1 mol %, 135 °C, 5.4 bar H2, and 2 h), as shown in Scheme 3. Under optimized reaction conditions, the hydrogenation of ethyl benzoate afforded benzyl alcohol in 97 % yield in 2 h with a TON of 97. However, when the reaction was prolonged for 12 h with 50 bar H2 pressure, at 110 °C, 0.025 mol % of complex 4, and 0.025 mol % of KO'Bu, a TON of 2840 was afforded. The reaction of 4 with KHMDS afforded dearomatized pincer complex 4a. Complex 4a is slightly unstable and is very likely to be an intermediate in the catalytic cycle. The ester hydrogenation protocol using complex 4 is an attractive alternative for the mild synthesis of primary alcohols from non-activated esters.

Later on, Morris and co-workers utilized the concept of heterolytic cleavage of dihydrogen across a transition metal−amido bond. The heterolytic cleavage of dihydrogen affords bifunctional metal−hydride and protic amine sites for reduction of polar bonds to produce valuable chemicals.14 The authors have synthesized a RuII complex 5 derived from a chelating N-heterocyclic carbene having a pendant NH2 donor group (C−
The RuII complex 5 was an active catalyst for the hydrogenation of esters in basic solution at 50 °C and 25 bar of H2 pressure (Scheme 4). Maximum TOF of 1510 h⁻¹ was obtained for the hydrogenation of phthalide in 4 h.

The authors proposed an outer-sphere bifunctional mechanism based on the DFT calculations for ester hydrogenation catalyzed by complex 5. The reaction of precatalyst 5 with KOtBu might afford RuII-amido complex 5a as the active catalyst. The catalytic cycle (Scheme 5) consists of mainly four steps: (1) H2 activation by the RuII-amido complex 5a affords complex 5b (step 1); (2) outer-sphere transfer of the Ru−H/N−H pair from the complex 5b to an ester via a six-membered cyclic transition state, forming a hemiacetal molecule (step 2); (3) C=O bond cleavage of the hemiacetal coupled with proton transfer from the hydroxyl oxygen to the amido nitrogen via a six-membered cyclic transition state (step 3); (4) regeneration of complex 5a and the reduction of the corresponding aldehyde to alcohol via similar outer-sphere mechanism (step 4).

Pidko and co-workers described the synthesis of bis-NHC analogues of the Ru−PNP pincer complex (Chart 1, I) and their RuII complexes for the catalytic ester hydrogenation reactions. The bis-imidazolium ligand (CNC-1 and CNC-2) treated with the base 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), followed by the reaction with [RuHCl(CO)(PPh3)3] in the presence of LiBr in THF, afforded ruthenium hydride complexes 6 and 7 (Scheme 6). In contrast, a similar reaction in the presence of acetonitrile as a solvent provided acetonitrile adducts 8 and 9. Since the lutidine-derived PNP pincer complexes are known to undergo dearomatization upon treatment with a strong base and...
generate five-coordinate active species for catalytic reactions. The reactivity of 6 with strong bases was probed by NMR spectroscopy. The reaction of 6 with strong bases such as KHMDS or KO'Bu at room temperature afforded a mixture of products containing de aromatized complex 8a together with some unidentified products, as confirmed by NMR spectroscopy. In contrast, the de aromatized complex 8a was synthesized directly from 8 by a reaction with KO'Bu in quantitative yield (Scheme 6). Similar to the Ru−PNP analogue, 8a reacts with H2 to form the dihydride complex 8b together with the rearomatization of the pyridine ring. The relatively unstable complex 8b was in situ characterized by NMR spectroscopy. The Ru−CNC complexes 6–9 hydrogenate a wide range of esters to the corresponding alcohols. The Ru−CNC catalyst 6 effectively hydrogenates aromatic esters, aliphatic esters, and lactones (Scheme 7). The Ru−CNC complexes show typical metal−ligand cooperation in reactions with strong bases (8a) and hydrogen (8b) that might be the reason for the better activity of these complexes in ester hydrogenation reactions. Pidko and co-workers also described the synthesis of bis-NHC analogue of PNP amino pincer ligands and their RuII complexes for the catalytic ester hydrogenation reactions. Bis-NHC amino pincer ligands were prepared from the reactions of the corresponding imidazoles with nitrogen mustard derivatives. The authors have generated several bis-NHC ligands and scrutinized them in an ester hydrogenation reaction with the [Ru(PPh3)4Cl2] precursor in the presence of a base (Scheme 8).

The active catalysts were in situ synthesized by treating the imidazolium salts with LiHMDS, followed by treatments with [Ru(PPh3)3Cl2]. The structure of the ligand had a strong influence on the activity of in situ generated Ru catalysts. The benzyl-substituted NHCs were inactive in the catalysis. The mesityl and 2,6-diisopropylphenyl-substituted NHCs were found to be the best catalysts. The ligands having meta- and para-substituted phenyl groups or methyl substituents on the imidazolium “N” resulted in no to moderate activity. The lower stability of the free NHCs may explain the inferior performance of these due to reduced bulk around the carbene center.

Inspired by the exciting results of precatalysts, the authors wanted to isolate the well-defined Ru−CNC complexes (Scheme 9). The reaction of imidazolium salt L1H with AgO in the presence of NaOH in a CH2Cl2/H2O medium afforded the Ag−NHC complex within 2 h in good yield. Further, the Ag−NHC complex when treated with [Ru(DMSO)4Cl2] in CH2Cl2 or THF afforded cationic complex [Ru3(L1H),Cl2]−[AgBr2], as proven by NMR and ESI-MS data. The anion exchange reaction of [Ru3(L1H),Cl2][AgBr2] with PF6 anion afforded highly stable complex [Ru3(L1H),Cl2][PF6] (10). The dibromomargentate [AgBr2]− counterion was exchanged with PF6 anion to avoid the light-induced sensitivity of cationic dimer [Ru3(L1H),Cl2][AgBr2].

Ru6 complex 10 was found to be the highly active catalyst for the hydrogenation of esters (Scheme 10). Under optimized reaction conditions (50 bar H2 and 70 °C), a wide range of aliphatic and aromatic esters were hydrogenated in nearly quantitative yields. Challenging esters, phthalide, and benzyl benzoate were converted to the corresponding alcohols at S/C = 2500–4000. Complex 10 also afforded a very high TON of 79 680 for ethyl hexanoate reduction, with nearly identical values reported by Zhang et al. for the hydrogenation of ethyl acetate with the tetradentate Ru−PNP at a slightly higher temperature and a longer reaction time (80 °C, 50 bar H2, 30 h).

The Ru−PNN system reported by Milstein et al. in 2006 (Chart 1, I) and the Ru−MACHO15 complex derived from a pincer-type ligand have been found to be effective homogeneous catalysts for ester hydrogenation reactions, based on the metal/ligand bifunctionality. In both of the reported Ru−PNN complexes, π-back-bonding contribution from the ruthenium center to the carbon monoxide (CO) increases the robustness of the Ru complex. As a result, the nucleophilicity of the hydride intermediates is presumably decreased. The authors envisioned that the catalytic activity of the Ru−PNP system could be

Scheme 7. Ester Hydrogenation Catalyzed by Lutidine-Derived Ru−CNC Complex 6

| Complex 6 | KOMe, 50 bar H2, 70 °C, 4 h | Product | Yield % |
|-----------|-----------------------------|---------|---------|
| Ph        | n-pentyl                      | 97 %    |
| Ph        | 100 %                        |
| X = Cl    | 86 %                         |
| X = OMe  | 60 %                         |

a = % yield of corresponding alcohols

Scheme 8. Bis-NHC Amino Pincer Ligands and Their Performance in the Ester Hydrogenation

![Scheme 8](image-url)
enhanced by replacing the CO with electron-donating ligands. Because of the strong σ-donating ability of NHC ligands, the authors have substituted the CO of the bifunctional Ru–MACHO system with NHCs to check the effect of more electron-donating NHC ligand on the ester hydrogenation reaction. In order to prepare the NHC-coordinated PNP–ruthenium complexes, the authors have taken an alternative route. The reaction of [RuCl2(η6-p-cymene)]2 with the desired NHC provided [RuCl2(η6-p-cymene)(NHC)], which, when treated with an equimolar amount of PNP in ethanol at 70 °C for 2 h, afforded a neutral dichlororuthenium complex [RuCl2(NHC)(PNP)] (11) as a pale-yellow powder in 85% yield (Scheme 11). A similar reaction in CH3CN afforded a cationic acetonitrile-coordinated complex, [RuCl(CH3CN)(NHC)(PNP)]Cl (12), as a yellow crystalline precipitate in 30% yield. Interestingly, NHC-coordinated bifunctional PNP–ruthenium complex 12 was found to be an excellent ester hydrogenation catalyst. With this catalyst, aromatic, heteroaromatic, and aliphatic esters, as well as lactones were converted into the corresponding alcohols in nearly quantitative yields under an atmospheric pressure of hydrogen gas at 50 °C (Scheme 12).

Inspired from the exciting results obtained in ester hydrogenations using CNN–NHC-based multidentate ligands (CNN-1 and CNN-2), Chianese and co-workers synthesized two new CNN pincer ligands (CNN-3 and CNN-4) and their RuII complexes 13 and 14 for the hydrogenation of esters (Schemes 13 and 14). Most general and successful methods known in the literature for the complexation of multidentate NHC ligands are (i) transmetalation from the Ag−NHC complex and (ii) complexation of free carbenes generated in situ by the reaction with strong bases. The authors used the first method to synthesize the RuII complexes of multidentate CNN pincer ligands. The CNN pincer ligands CNN-3 and CNN-4, upon treatment with Ag2O in the presence of molecular sieves followed by treatment with [RuHCl(CO)(PPh3)]2, afforded CNN–Ru pincer complexes 13 and 14, as monitored by 1H NMR spectroscopy (Scheme 13).

Further, both of the complexes were tested in ester hydrogenation reactions under mild reaction conditions (105 °C, 6 bar H2). The catalytic activity was found to be
The dimethylamino-substituted CNN$^{-}$Ru complex 13 was an inactive catalyst, whereas a diethylamino-substituted CNN$^{-}$Ru complex afforded 980 turnovers for the benzyl benzoate hydrogenation. Various esters such as ethyl, hexyl, and benzyl esters are perfectly suitable in the hydrogenation process with complex 14 (Scheme 14). However, methyl esters were found to be unsuitable in this methodology, probably due to the poisoning effect of the byproduct methanol to the Ru catalyst. This result with methyl esters was in line with a similar poisoning effect observed for a "Co(PNP)" catalyst, which was poisoned by the CO ligand generated from the decarbonylation reaction of the byproduct methanol.16

The subtle modification of the catalyst structure, such as changing an NMe$_2$ group to a NEt$_2$ group, resulted in a dramatic increase in catalytic activity. The same authors synthesized new CNN ligands with variable N-substituents on both NHC and NR$_2$ ends to check the overall effect on the catalytic activity (Scheme 15).12h Six new ruthenium complexes of CNN pincer ligands (Scheme 15, complexes 15a−15f) were synthesized by a similar method used earlier to prepare complexes 13 and 14. The ruthenium complex of 2,6-diisopropylphenyl-substituted NHC ligand (15b) was the most active catalyst in this series, which suggests that increased steric bulk on the NHC "N" might be the reason for better activity. For the (NR$_2$) group, catalysts substituted with isopropyl or ethyl groups were the most active, whereas catalysts substituted with methyl groups were significantly less active. The CNN$^{-}$Ru complex 15b was found to be the active catalyst for hydrogenation of a range of esters with catalyst loadings of 0.05−0.2 mol % (Scheme 15).

In recent years, methodologies that developed the phosphine-free base metal-catalyzed hydrogenation of esters to alcohols have been benchmarked. Liu and co-workers reported the first non-noble metal bis-NHC-based catalyst that permits effective hydrogenation of esters to alcohols.12i Since a number of homogenous catalysts have demonstrated substantial improvements in catalytic activity using metal−ligand cooperation functionality based on the "N−H effect", the authors designed
their ligand backbone comprising an N−H moiety. Initially, the catalytic investigation was started with an in situ generated Co complex by mixing the NHC ligands (Chart 3), CoCl₂, and tBuOK in THF according to the following appropriate reaction conditions: 2 mol % of CoCl₂, 2 mol % of ligand, 10 mol % of KO₄Bu, and 30 bar H₂ at 100 °C. The highest performance was obtained with L₃, carrying a mesityl substituent (Mes). In contrast, the other ligands having methyl (L₁), phenyl (L₂), or 2,6-disopropylphenyl (L₄) substituents showed almost no reactivity (Chart 3). Under optimized reaction conditions, a range of esters having electron-donating and electron-withdrawing groups were reduced to alcohols in good to excellent yields (Scheme 18).

This methodology worked well for substrates having methoxyl, amino, methylthio, fluoro, chloro, trifluoromethyl, and alkenyl functional groups. However, using this methodology, nitro- and amide-substituted substrates could not be reduced. A series of aliphatic esters, lactones, and polyesters were all efficiently reduced in high yields (Scheme 18).

For cyclic esters, the hydrogenation was found to be chemoselective, and the internal C−C double bond very much endured. To additionally explore the synthetic utility of this technique, it was employed in the hydrogenation of pharmaceutical molecules, as well. Encouraged by the excellent performance of the in situ generated catalysts, the authors synthesized the corresponding well-defined NHC−Co complex. The reaction of L₃ with [Co{N(SiMe₃)₂}(THF)] having [N(SiMe₃)₂]⁻ as an internal base afforded the desired NHC−CoII complex 18 in 42% isolated yield (Chart 3).

To understand the reaction mechanism, the hydrogenation of benzyl benzoate was carried out using NHC precursor L₅ as the ligand (Chart 3). With L₅ as the ligand, a very low yield of benzyl alcohol was obtained. In contrast, ligand L₃ containing an N−H group afforded an excellent yield under similar reaction conditions. This suggests that metal−ligand cooperation based on the "N−H effect" might be the reason for better activity of "N−H"-containing ligand L₃ in the cobalt-catalyzed ester hydrogenation reactions. The authors proposed a possible mechanism based on the experimental observation and results from the literature, as shown in Scheme 19.

The reaction of 18 with KO₄Bu might afford the CoII−amido complex 19, which when further reacts with H₂ affords CoI−hydride complex 20. The CoI−hydride complex 20 upon oxidative addition with H₂ might lead to the formation of CoIII−trihydride complex 21. The PNP pincer CoIII complexes have shown similar reactivity with KO₄Bu and H₂, as has been reported in the literature, supporting the proposed activation process. Further, CoIII−trihydride complex 21 might reduce benzyl benzoate via concerted hydride and proton transfer from the cobalt center and amino group, respectively, in complex 21 to generate the hemiacetal and the CoII−amido dihydride complex 22. The hemiacetal produced might afford benzyl alcohol and benzaldehyde, whereas complex 21 is regenerated from 22 by addition of H₂ to complete the catalytic cycle. Finally, the benzaldehyde could also be hydrogenated to benzyl alcohol in the same fashion (Scheme 19).
It is important to note that most of the NHC−Ru(II) complexes discussed in this mini-review showed good to excellent activity in the ester hydrogenation reaction (Table 1), performing similar or sometimes better to their phosphine counterparts. The comparison of catalytic activity among the different catalysts is not straightforward due to variable reaction conditions employed for measuring the performance parameters such as conversion (%), yield (%), TON, and TOF at different stages of the reaction. The NHC−Ru(II) complexes (6 and 10) of biscarbene ligands and NHC-coordinated PNP−Ru complex 12 showed good activity in the ester hydrogenations (Table 1, entries 4−6). Complex 10 is a remarkably active catalyst for ester hydrogenation and affords quantitative conversion to corresponding alcohols with high TOF values. The highest TOF so far reported is obtained with complex 10 (TOF = 283 200 h\(^{-1}\)) in 1 h. Another elegant example is NHC-coordinated bifunctional PNP−ruthenium complex 12, where the authors replaced the CO with electron-donating NHC ligands to make the metal center electron-rich for better catalytic activity. The high activity of NHC−Ru(II) complexes 6, 10, and 12 in the ester hydrogenation suggests that, by applying strong electron-donor ligands in the metal coordination sphere, one can fine-tune the catalytic activity of complexes thus formed.

### SUMMARY AND OUTLOOK

In summary, we depicted an overview on homogeneous catalysts derived from NHC-based complexes for ester hydrogenation reactions. Significant progress has been made in the last decade using phosphine-based bifunctional catalysts utilizing the metal−ligand cooperation effects. Recently, NHCs owing to strong σ-donor ability, easy synthetic methods, and relatively

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**Table 1. Various Catalysts and Reaction Conditions for Hydrogenation of Esters**

| entry | ester | catalyst | catalyst concentration\(^a\) | base (mol %)\(^b\) | solvent | temp (°C) | \(p(H_2)\) (bar) | yield (%) | ref |
|-------|-------|----------|-------------------------------|-------------------|---------|-----------|--------------|----------|-----|
| 1     | aliphatic/aromatic | 1 | 1 mol % | KO\(\text{Bu}\) (8) | toluene | 105 | 5.3 | 92−99 | 12a |
| 2     | aliphatic/aromatic | 4 | 1 mol % | KO\(\text{Bu}\) (1) | toluene | 135 | 5.4 | 89−96 | 12b |
| 3     | aliphatic/aromatic | 5 | S/C = 1500 | KO\(\text{Bu}\) (8) | THF | 50 | 25 | up to 98 | 12c |
| 4     | aliphatic/aromatic and lactones | 6 | S/C = 200 | KO\(\text{Me}\) (10) | THF | 70 | 50 | 60−100 | 12d |
| 5     | aliphatic/aromatic and lactones | 10 | S/C = 2500−40000 | KO\(\text{Bu}\) (2) | THF | 70 | 50 | 93−100 | 12e |
| 6     | aliphatic/aromatic lactones | 12 | 2 mol % | KO\(\text{Bu}\) (20) | THF | 50 | balloon | 73−98 | 12f |
| 7     | aliphatic/aromatic | 14 | S/C = 125–1000 | NaO\(\text{Bu}\)\(^d\) | toluene | 105 | 6 | 5−99 | 12g |
| 8     | aliphatic/aromatic | 15b | S/C = 500−2000 | NaO\(\text{Bu}\)\(^d\) | toluene | 105 | 6 | 82−99 | 12h |
| 9     | aliphatic/aromatic | 16 | 0.05−0.8 mol % | toluene | 105 | 30 | 81−99 | 12i |
| 10    | aliphatic/aromatic | Co\(\text{Cl}_2/\text{L3}\) both 2 mol % | KO\(\text{Bu}\) (10) | THF | 100 | 30 | 66−99 | 12j |

\(^a\)The catalyst concentration was expressed either in mol % with respect to the substrate (ester) or in the form of S/C where S = substrate concentration and C = catalyst concentration.\(^b\)Base concentration was expressed in mol % with respect to substrate.\(^c\)The base concentration (B) was used in the ratio of B/C = 8.\(^d\)NaO\(\text{Bu}/[\text{Ru}]\) was 6:1.
higher stability toward air and moisture have replaced the phosphines as ligands in metal-complex-catalyzed ester hydrogenations as has been discussed with several examples. Bis-NHC-stabilized RuII complexes developed by Pidko and co-workers are elegant catalysts for ester hydrogenation reactions, signifying the importance of bis-NHC ligands as an attractive alternative to the conventional phosphine-based systems. However, most of the NHC-based catalysts are based on costly metal Ru and require relatively harsh reaction conditions in terms of the temperature and pressure. Only recently a Co–NHC-based system was utilized in ester hydrogenation, but it still requires relatively high temperature and high hydrogen pressure (100 °C and 30 bar H2) together with an excess of base for effective transformation. Therefore, rational design of new NHC ligands is important to explore unprecedented catalytic activity of base metal complexes in these important catalytic reactions. We believe that the next generation of base metal complexes of suitably designed NHC-based ligands will open a new arena for reduction chemistry using H2 gas.

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**Notes**
The authors declare no competing financial interest.

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Joyanta Choudhury is an Associate Professor at IISER Bhopal, India. He obtained Ph.D. in 2006 from IIT Kharagpur, India, working under Professor Sujit Roy. He then moved to The Scripps Research Institute (TSRI), Florida, USA, as postdoctoral fellow to work on CH4-to-CH3OH conversion chemistry with Professor Roy A. Periana. In 2008, he received the Marie Curie International Incoming Fellowship (IFIF) from the European Union (EU) and joined the Weizmann Institute of Science, Israel, for his second postdoctoral stint to work with Professor Milko E. van der Boom on materials chemistry. His research focusses on (a) addressing renewable energy related problems and (b) developing smart functional materials for electrochromic and related applications, wastewater treatment, etc. His research works on “switchable catalysis” and “CO2-conversion chemistry” have been covered as News in ChemistryWorld magazine (published by Royal Society of Chemistry) in 2017 and 2019, respectively.

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**REFERENCES**

1. (a) Gribble, G. W. Sodium borohydride in carboxylic acid media: a phenomenal reduction system. *Chem. Soc. Rev.* 1998, 27, 395–404. (b) Seyden-Penne, J. Reductions by the Alumino- and Borohydrides in Organic Synthesis, 2nd ed.; Wiley-VCH: New York, 1997; p. 224.
2. Clarke, M. L. Recent developments in the homogeneous hydrogenation of carboxylic acid esters. *Catal. Sci. Technol.* 2012, 2, 2418–2423.
3. Pritchard, J.; Filonenko, G. A.; van Putten, R.; Hensen, E. J. M.; Pidko, E. A. Heterogeneous and homogeneous catalysis for the hydrogenation of carboxylic acid derivatives: history, advances and future directions. *Chem. Soc. Rev.* 2015, 44, 3808–3833.
4. Dub, P. A.; Ikariya, T. Catalytic Reductive Transformations of Carboxylic and Carbonic Acid Derivatives Using Molecular Hydrogen. *ACS Catal.* 2012, 2, 1718–1741.
5. Werkmeister, S.; Junge, K.; Beller, M. Catalytic Hydrogenation of Carboxylic Acid Esters, Amides, and Nitriles with Homogeneous Catalysts. *Org. Process Res. Dev.* 2014, 18, 289–302.
6. Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. Efficient Homogeneous Catalytic Hydrogenation of Esters to Alcohols. *Angew. Chem., Int. Ed.* 2006, 45, 1113–1115.
7. Khusnutdinova, J. R.; Milstein, D. Metal–Ligand Cooperation. *Angew. Chem., Int. Ed.* 2015, 54, 12236–12273.
8. (a) Spasyuk, D.; Smith, S.; Gusev, D. G. From Esters to Alcohols and Back with Ruthenium and Osmium Catalysts. *Angew. Chem., Int. Ed.* 2012, 51, 2772–2775. (b) Spasyuk, D.; Smith, S.; Gusev, D. G.
Replacing Phosphorus with Sulfur for the Efficient Hydrogenation of Esters. Angew. Chem., Int. Ed. 2013, 52, 2538–2542. (4.) Li, W.; Xie, J.-H.; Yuan, M.-L.; Zhou, Q.-L. Ruthenium complexes of tetradeutate bipyridine ligands: highly efficient catalysts for the hydrogenation of carboxylic esters and lactones. Green Chem. 2014, 16, 4081–4085. (d) Zell, T.; Ben-David, Y.; Milstein, D. Unprecedented Iron-Catalyzed Ester Hydrogenation. Mild, Selective, and Efficient Hydrogenation of Trifluorooxocetate Esters to Alcohols Catalyzed by an Iron Pincer Complex. Angew. Chem., Int. Ed. 2014, 53, 4685–4689. (e) Tan, X.; Wang, Y.; Liu, Y.; Wang, F.; Shi, L.; Lee, K.-H.; Lin, Z.; Lv, H.; Zhang, X. Highly Efficient Tetradeutate Ruthenium Catalyst for Ester Reduction: Especially for Hydrogenation of Fatty Acid Esters. Org. Lett. 2015, 17, 454–457. (f) Srimani, D.; Mukherjee, A.; Goldberg, A. F. G.; Leitus, G.; Diskin-Posner, Y.; Shimon, L. J. W.; Ben-David, Y.; Milstein, D. Cobalt-Catalyzed Hydrogenation of Esters to Alcohols: Unexpected Reactivity Trend Indicates Ester Enolate Intermediacy. Angew. Chem., Int. Ed. 2015, 54, 12357–12360. (g) Werkmeister, S.; Junge, K.; Wendt, B.; Albertio, E.; Jiao, H.; Baumann, W.; Junge, H.; Gallou, F.; Beller, M. Hydrogenation of Esters to Alcohols with a Well-Defined Iron Complex. Angew. Chem., Int. Ed. 2014, 53, 8722–8726. (h) Korstanje, T. J.; Ivar van der Vlugt, J.; Elsevier, C. J.; de Bruijn, B. Hydrogenation of carboxylic acids with a homogeneous cobalt catalyst. Science 2015, 350, 298. (i) Elangovan, S.; Garbe, M.; Jiao, H.; Spannenberg, A.; Junge, K.; Beller, M. Hydrogenation of Esters to Alcohols Catalyzed by Defined Manganese Pincer Complexes. Angew. Chem., Int. Ed. 2016, 55, 15364–15368. (j) Espinosa-Jalapa, N. A.; Nerush, A.; Shimon, L. J. W.; Leitus, G.; Avram, L.; Ben-David, Y.; Milstein, D. Manganese-Catalyzed Hydrogenation of Esters to Alcohols. Chem. - Eur. J. 2017, 23, 5934–5938. (k) van Putten, R.; Uslamin, E. A.; Garbe, M.; Liu, C.; Gonzalez-de-Castro, A.; Lutz, M.; Junge, K.; Hensel, E. J. M.; Beller, M.; Lefort, L.; Pikko, E. A. Non-Pincer-Type Manganese Complexes as Efficient Catalysts for the Hydrogenation of Esters. Angew. Chem., Int. Ed. 2017, 56, 7531–7534. (l) Junge, K.; Wendt, B.; Cingolani, A.; Spannenberg, A.; Wei, Z.; Jiao, H.; Beller, M. Cobalt Pincer Complexes for Catalytic Reduction of Carboxylic Acid Esters. Chem. - Eur. J. 2018, 24, 1046–1052. (m) van Putten, R.; Uslamin, E. A.; Garbe, M.; Liu, C.; Gonzalez-de-Castro, A.; Lutz, M.; Junge, K.; Hensel, E. J. M.; Beller, M.; Lefort, L.; Pikko, E. A. Non-Pincer-Type Manganese Complexes as Efficient Catalysts for the Hydrogenation of Esters. Angew. Chem., Int. Ed. 2017, 56, 7531–7534. (9) (a) Vivancos, A.; Segarra, C.; Albrecht, M. Mesomeric and Related Lewis Heterato-Stabilized N-Heterocyclic Carbenes: Synthesis, Catalysis, and Other Applications. Chem. Rev. 2018, 118, 9493–9586. (b) Crudden, C. M.; Horton, J. H.; Ebralidze, I. I.; Zenkina, O. V.; McLean, A. B.; Drevniok, B.; Leitus, G.; Kraatz, H.-B.; Thenenakandiyil, R.; Choudhury, J. Small “Yaw” Angles, Large “Bite” Angles and an Electron-Rich Metal: Revealing a Stereoelectronic Synergy To Enhance Hydrogenation Activity. Chem. - Eur. J. 2017, 23, 13051–13057. (b) Kumar, A.; Semwal, S.; Choudhury, J. Catalytic Conversion of CO2 to Formate with Renewable Hydrogen Donors: An Ambient-PHase and H2-Independent Strategy. ACS Catal. 2019, 9, 2164–2168. (i) Semwal, S.; Kumar, A.; Choudhury, J. Aridium—NHC-based catalyst for ambient pressure storage and low temperature release of H2 via the CO2/H2O couple. Catal. Sci. Technol. 2018, 8, 6137–6142. (10) (a) Sun, Y.; Koehler, C.; Tan, R.; Annibale, V. T.; Song, D. Ester hydrogenation catalyzed by Ru-CNN pincer complexes. Chem. Commun. 2011, 47, 8349–8351. (b) Fogler, E.; Balaraman, E.; Ben-David, Y.; Leitus, G.; Shimon, L. J. W.; Milstein, D. New CNN-type Ruthenium NHC Complexes. Mild, Efficient Catalytic Hydrogenation of Esters. Organometallics 2011, 30, 3826–3833. (c) O, W. W.; Norris, R. H. Ester Hydrogenation Catalyzed by a Ruthenium(II) Complex Bearing an N-Heterocyclic Carbene Tethered with an “NH,” Group and a DFT Study of the Proposed Bifunctional Mechanism. ACS Catal. 2013, 3, 32–40. (d) Filonenko, G. A.; Cosimi, E.; Lefort, L.; Conley, M. P.; Copéret, C.; Lutz, M.; Hensen, E. J. M.; Pikko, E. A. Lutidine-Derived Ru-CNC Hydrogenation Pincer Catalysts Versatile Coordination Properties. ACS Catal. 2014, 4, 2667–2671. (e) Filonenko, G. A.; Aguila, M. J. B.; Schuler, C.; Puten, R.; Wiecko, J.; Müller, C.; Lefort, L.; Hensen, E. J. M.; Pikko, E. A. Bis-N-heterocyclic Carbene Aminopincer Ligands Enable High Activity in Ru-Catalyzed Ester Hydrogenation. J. Am. Chem. Soc. 2015, 137, 7620–7623. (f) Ogata, O.; Nakayama, Y.; Nara, H.; Fujiihara, M.; Kayaki, Y. Atmospheric Hydrogenation of Esters Catalyzed by PNP-Ruthenium Complexes with an N-Heterocyclic Carbene Ligand. Org. Lett. 2016, 18, 3894–3897. (g) Kim, D.; Le, L.; Drance, M. J.; Jensen, K. H.; Bogdanovski, K.; Cervarich, T. N.; Barnard, M. G.; Padalov, N. J.; Knapp, S. M. M.; Chianese, A. R. Ester Hydrogenation Catalyzed by CNN-Pincer Complexes of Ruthenium. Organometallics 2016, 35, 982–989. (h) Le, L.; Liu, J.; He, T.; Kim, D.; Lindley, E. J.; Cervarich, T. N.; Malek, J. C.; Pham, J.; Buck, M. R.; Chianese, A. R. Structure–Function Relationship in Ester Hydrogenation Catalyzed by Ruthenium CNN-Pincer Complexes. Organometallics 2018, 37, 3286–3297. (i) Le, L.; Liu, J.; He, T.; Malek, J. C.; Cervarich, T. N.; Buttner, J. C.; Pham, J.; Keith, J. M.; Chianese, A. R. Unexpected CNNN-to-CC Ligand Rearrangement in Pincer–Ruthenium Precatalysts Leads to a Base-Free Catalyst for Ester Hydrogenation. Organometallics 2019, 38, 3311–3321. (j) Shao, Z.; Zhong, R.; Ferraccioli, R.; Li, Y.; Liu, Q. General and Phosphine-Free Cobalt-Catalyzed Hydrogenation of Esters to Alcohols. Chem. J. Chem. 2019, 37, 1125–1130. (13) Balaraman, E.; Gnanaprakasam, B.; Shimon, L. J. W.; Milstein, D. Direct Hydrogenation of Amides to Alcohols and Amines under Mild Conditions. J. Am. Chem. Soc. 2010, 132, 16756–16758. (14) Ikariya, T.; Murata, K.; Noyori, R. Bifunctional transition metal-based molecular catalysts for asymmetric syntheses. Org. Biomol. Chem. 2006, 4, 393–406. (15) Kuriyama, W.; Matsutomo, T.; Ogata, O.; Ino, Y.; Aoki, K.; Tanaka, S.; Ishida, K.; Kobayashi, T.; Sayo, N.; Saito, T. Catalytic Hydrogenation of Esters. Development of an Efficient Catalyst and Processes for Synthesizing (R)-2-Propanol and (l)-Menthol (l-Menthyl)-ethanol. Org. Process Res. Dev. 2012, 16, 166–171. (16) Yuwen, J.; Chakraborty, S.; Brennessel, W. W.; Jones, W. D. Additive-Free Cobalt-Catalyzed Hydrogenation of Esters to Alcohols. ACS Catal. 2017, 7, 3735–3740. (17) (a) Rozenez, S. S.; Padilla, R.; Camp, C.; Arnold, J. Unusual activation of H2 by reduced cobalt complexes supported by a PNP pincer ligand. Chem. Commun. 2014, 50, 2612–2614. (b) Lagaditis, P. O.; Schlusaß, B.; Demeshko, S.; Württele, C.; Schneider, S. Square-Planar Cobalt(III) Pincer Complex. Inorg. Chem. 2016, 55, 4529–4536.