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Metal–Ligand Cooperation by Aromatization–Dearomatization: A New Paradigm in Bond Activation and "Green" Catalysis

CHIDAMBARAM GUNANATHAN AND DAVID MILSTEIN*

Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

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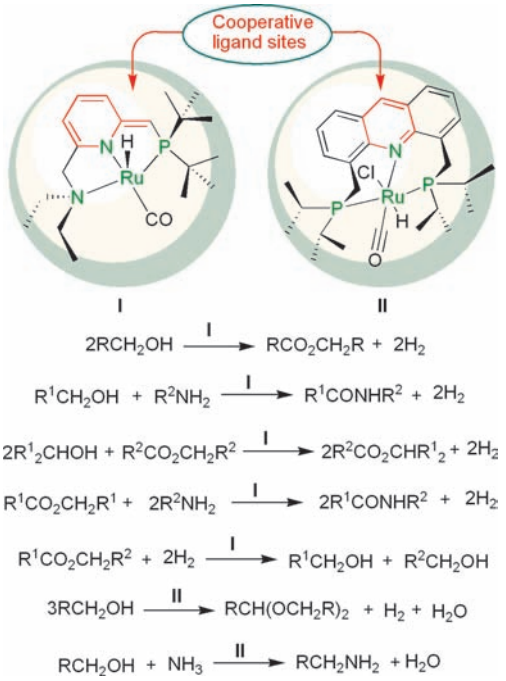
CONSPECTUS

In view of global concerns regarding the environment and sustainable energy resources, there is a strong need for the discovery of new, green catalytic reactions. For this purpose, fresh approaches to catalytic design are desirable. In recent years, complexes based on "cooperating" ligands have exhibited remarkable catalytic activity. These ligands cooperate with the metal center by undergoing reversible structural changes in the processes of substrate activation and product formation.

We have discovered a new mode of metal–ligand cooperation, involving aromatization–dearomatization of ligands. Pincer-type ligands based on pyridine or acridine exhibit such cooperation, leading to unusual bond activation processes and to novel, environmentally benign catalysis. Bond activation takes place with no formal change in the metal oxidation state, and so far the activation of H–H, C–H (sp^2 and sp^3), O–H, and N–H bonds has been demonstrated. Using this approach, we have demonstrated a unique water splitting process, which involves consecutive thermal liberation of H_2 and light-induced liberation of O_2, using no sacrificial reagents, promoted by a pyridine-based pincer ruthenium complex. An acridine pincer complex displays unique "long-range" metal–ligand cooperation in the activation of H_2 and in reaction with ammonia.



In this Account, we begin by providing an overview of the metal–ligand cooperation based on aromatization–dearomatization processes. We then describe a range of novel catalytic reactions that we developed guided by these new modes of metal–ligand cooperation. These reactions include the following: (1) acceptorless dehydrogenation of secondary alcohols to ketones, (2) acceptorless dehydrogenative coupling of alcohols to esters, (3) acylation of secondary alcohols by esters with dihydrogen liberation, (4) direct coupling of alcohols and amines to form amides and polyamides with liberation of dihydrogen, (5) coupling of esters and amines to form amides with H_2 liberation, (6) selective synthesis of imines from alcohols and amines, (6) facile catalytic hydrogenolysis of esters to alcohols, (7) hydrogenolysis of amides to alcohols and amines, (8) hydrogenation of ketones to secondary alcohols under mild hydrogen pressures, (9) direct conversion of alcohols to acetals and dihydrogen, and (10) selective synthesis of primary amines directly from alcohols and ammonia. These reactions are efficient, proceed under neutral conditions, and produce no waste, the only byproduct being molecular hydrogen and/or water, providing a foundation for new, highly atom economical, green synthetic processes.

Introduction

A major challenge of catalysis today is the replacement of traditional synthetic processes with environmentally benign, sustainable catalytic reactions, which use no toxic reagents and produce no waste. In most reactions catalyzed by metal complexes, the catalytic activity is metal-based,

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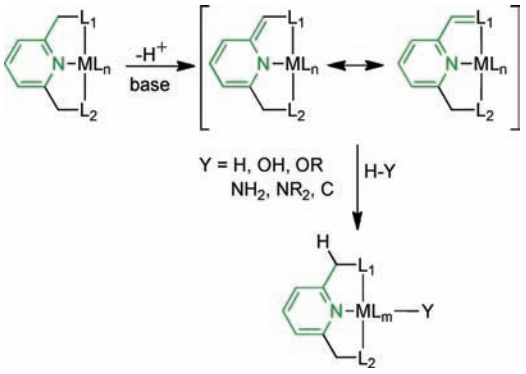


FIGURE 1

while the ligands, which can play crucial roles in affecting the properties of the metal center, do not undergo themselves bond making and breaking processes and do not actively participate in the catalytic cycle.[1] However, there are catalysts in which the ligands can cooperate with the metal center by undergoing themselves reversible structural changes in the processes of substrate activation and product formation, such as in the case of hydrogenation of polar bonds.[2]

Transition metal complexes of bulky, electron-rich "pincer" ligands have important applications in synthesis, bond activation, and catalysis.[3,4] Electron donating, pyridine-based PNP and PNN pincer ligands can stabilize coordinatively unsaturated metal complexes.[5] Recently, we have discovered new modes of metal–ligand cooperation involving aromatization–dearomatization processes of PNP and PNN pyridine-based pincer complexes,[6] leading to unusual bond activation processes and to novel, environmentally benign catalysis. Recently, we have also observed unusual "long-range" metal ligand cooperation with an acridine–pincer ruthenium complex, with reversible dearomatization of the middle acridine ring. These processes might be involved in catalysis by this complex. In this Account, we provide an overview of the metal–ligand cooperation based on aromatization–dearomatization processes. We first describe stoichiometric processes discovered in our laboratory and then the development of new catalytic reactions involving alcohols, esters, acetals, amines, imines, ketones, and amides.

Metal–Ligand Cooperation Based on Aromatization–Dearomatization of Pyridine-Based Pincer Systems

Pyridine-based pincer complexes can undergo deprotonation at the pyridinylmethylenic carbon, resulting in dearomatization of the pyridine moiety.[7–9] The dearomatized complex can then activate chemical bonds (H–Y; Y = H, OH, OR, NH_2, NR_2, C) by cooperation between the metal and the ligand, thereby regaining aromatization (Figure 1). Such processes occur with no formal change in the metal oxidation state.

Examples are shown in Schemes 1–3. ^{1}H NMR spectra of complexes **2**, **5**, **8**, **11**, **14**, and **15** indicate dearomatization as the pyridine protons are shifted to lower frequency. X-ray structure of complex **2** (Figure 2) shows that the C6–C7 bond (1.350 Å) is significantly shorter than C1–C2 (1.505 Å).[8] In complex **5**, C1–C2 (1.450 Å) is significantly shorter than C7–C6 (1.552 Å) whereas C1–P1 (1.803 Å) is shorter to a smaller extent than P2–C7 (1.843 Å), indicating that the dearomatized resonance structure of **5** contributes significantly more than the aromatized phosphor-ylide form (Figure 1).[9]

Reaction of the dearomatized **2** with benzene results in C–D activation with concomitant aromatization of the pyridine ring to form the Ir–Ph complex **3** (Scheme 1).[8] Interestingly, upon reaction with dihydrogen, the dearomatized ruthenium complexes **5**, **8**, and **11** undergo aromatization to quantitatively yield the *trans*-dihydride complexes **6**, **9**, and **12**, respectively (Scheme 2). Both complexes **6** and **12** slowly lose H_2 at room temperature to regenerate complexes **5** and **11**, respectively, while complex **9** is stable at room temperature.

Dearomatization of the cationic platinum complex **13** by treatment with base forms the neutral complex **14**. Interestingly, reaction of **14** with an equivalent of MeLi results in attack at the metal center with decoordination of the amine arm, rather than chloride substitution, to give the anionic, dearomatized Pt–Me complex **15**. This complex is relatively stable, although it bears no stabilizing π acceptors. Upon reaction of **15** with water, selective protonation–aromatization to give complex **16** takes place, with no protonation of the methyl group. Reaction of **16** with MeLi results in dearomatization, with no chloride substitution being observed (Scheme 3).[10]

sp^2 and sp^3 C–H Activation Based on Metal–Ligand Cooperation

Our studies indicate that an Ir(III) oxidative addition intermediate **18** is involved in the C–D activation of deuterated benzene by the dearomatized Ir(I) complex **2** (Schemes 1 and 4).[8] Complex **18** can be generated and fully characterized spectroscopically at −70 °C by deprotonation of the cationic **17**.[11,12] Upon warming up, proton transfer to the side arm takes place, with aromatization and concomitant reduction of the metal center to provide complex **3**.

Complex **2** reacts with acetone to yield the acetonyl Ir(I) complex **19**, by sp^3 C–H activation. Like benzene C–H activation, this reaction also proceeds via an Ir(III) intermediate **21**.

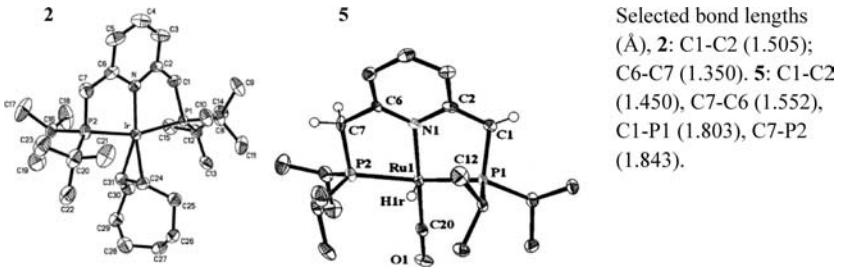
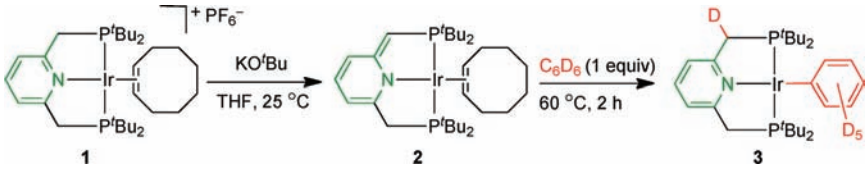
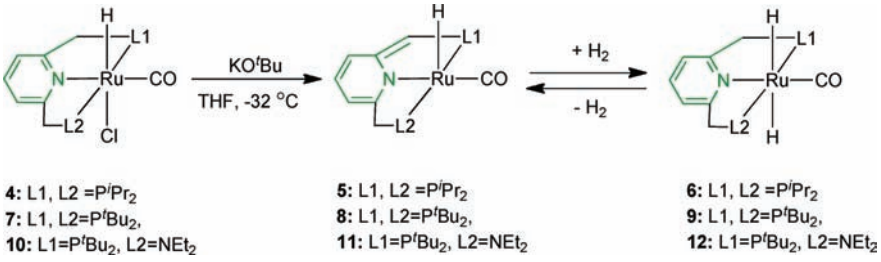


FIGURE 2. Single crystal X-ray structures of dearomatized PNP complexes **2** and **5**.

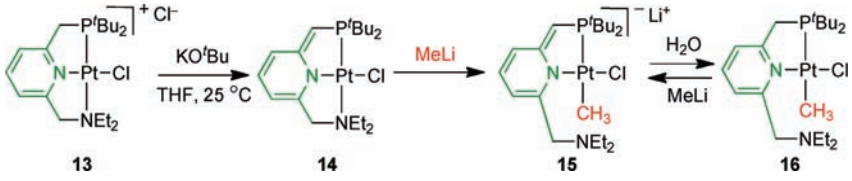
SCHEME 1



SCHEME 2



SCHEME 3



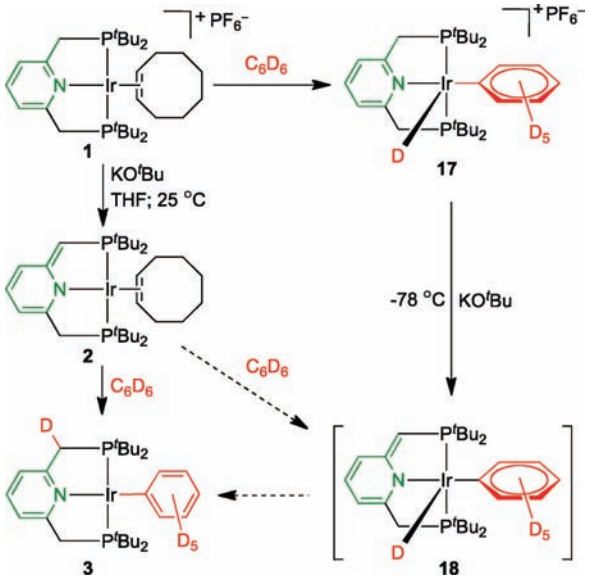
Upon substitution of the COE ligand by acetone, C–H bond cleavage of acetone forms intermediate **21** followed by proton migration to the side arm with concomitant aromatization to form the aromatic complex **19** (Scheme 5).[13]

Reaction of H_2 with (PNP)Ir(I): Activation of H_2 Is by a Dearomatized Ir(III) Intermediate

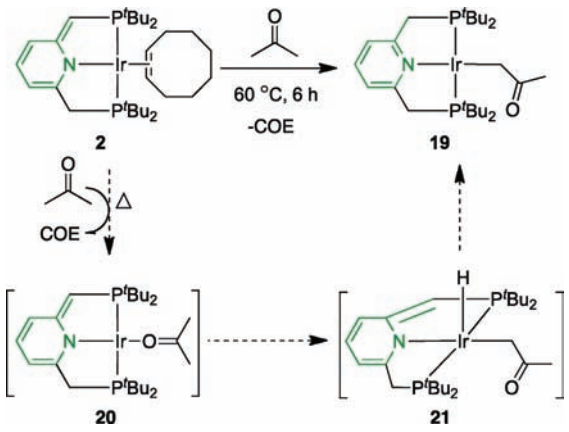
Interestingly, complex **3** reacts with H_2 to provide an Ir(III) *trans*-dihydride complex exclusively. Use of D_2 reveals, surprisingly, formation of the D–Ir–H complex **22** with one D atom attached to the pyridinylmethylenic carbon, suggesting that H_2 is actually activated by the dearomatized Ir(III) complex **23**, formed by proton migration from the side arm. Indeed, complex **23**, generated and fully characterized[8] at −70 °C by deprotonation of **3,** reacts with H_2 to form the *trans*-dihydride complex **22**. Thus, what seems to be H_2 oxidative addition to Ir(I) is actually H_2 activation by Ir(III) (Scheme 6). The Ir(III) intermediate can be trapped by treating the Ir(I) phenyl complex **3** with CO, forming complex **25**.

Involvement of the dearomatized Ir(III) intermediate **23** in the stereoselective activation of H_2 to exclusively form the *trans*-dihydride complex is supported by density functional theory (DFT) calculations,[14,15] which suggest that a catalytic amount (relative to **3**) of adventitious water assists the proton-transfer step by bridging the gap the proton has to travel (in **23′**, the hydrogen atom is 3.6 Å away from

SCHEME 4



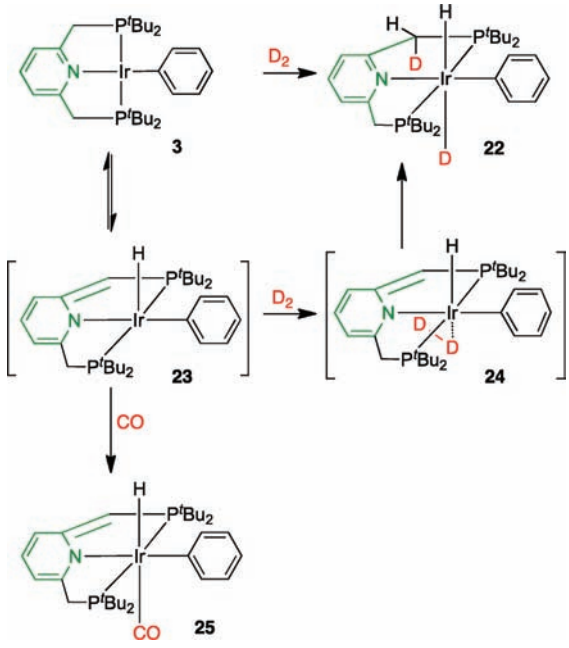
SCHEME 5



methylene carbon). Deprotonation of the arm methylene by Ir (**3′**–**23′**) is endergonic ($\Delta G_{298} = 11.1$ kcal mol^{-1}). Transition states involved in the direct deprotonation by Ir ($\Delta G^{\ddagger}_{298} =$ 35.9 kcal mol^{-1}) involving one water molecule ($\Delta G^{\ddagger}_{298} =$ 26.5 kcal mol^{-1}) and two water molecules ($\Delta G^{\ddagger}_{298} = 20.7$ kcal mol^{-1}) were identified as depicted in Figure 3. The smaller barrier involving two water molecules is reasonable for a room temperature reaction.

Like the Ir(I) phenyl complex **3**, the Ir(I) acetonyl complex **19** also reacts with H_2 (1 equiv) in benzene-d_6 to provide exclusively the *trans*-dihydride Ir(III) complex **26**, whose structure was corroborated by an X-ray diffraction study (Scheme 7).[13] Further, reaction of **19** with D_2 in benzene leads to formation of the *trans*-H–Ir–D complex **27**, with incorporation of one deuterium atom in the benzylic

SCHEME 6



position. Mechanistically, H_2 and D_2 activation proceed via intermediacy of the Ir(III) complex **21**. DFT studies reveal similar reactivity patterns of phenyl and acetonyl complexes **3** and **19**.

Cooperative H_2 activation and catalytic ammonia borane dehydrogenation by aliphatic pincer PNP-Ru complexes were recently reported.[16]

O–H and N–H Activation Based on Metal–Ligand Cooperation

a. Water Splitting. The dearomatized PNN complex **11** readily cleaves the O–H bond of water. Upon reaction with water at room temperature, aromatization takes place to quantitatively form the *trans*-hydrido–hydroxo complex **28** (Scheme 8).[17] This compound is probably formed by a mechanism involving water coordination at the vacant site trans to the hydride, followed by proton migration to the side arm, as indicated by DFT studies.[18]

Interestingly, further reaction of complex **28** with water at 100 °C releases H_2 and forms the *cis*-dihydroxo complex **29**. DFT studies, independently carried out by Yoshizawa et al.[18a] and Hall and Yang,[18b] indicate that this process involves H_2 liberation from **28** by coupling of the hydride ligand with a proton from the side arm, followed by addition of H_2O to the generated dearomatized intermediate. Significantly, irradiation of complex **29** in the 320–420 nm range results in O_2 liberation with regeneration of complex **28** (Scheme 8). Combining these separate stoichiometric

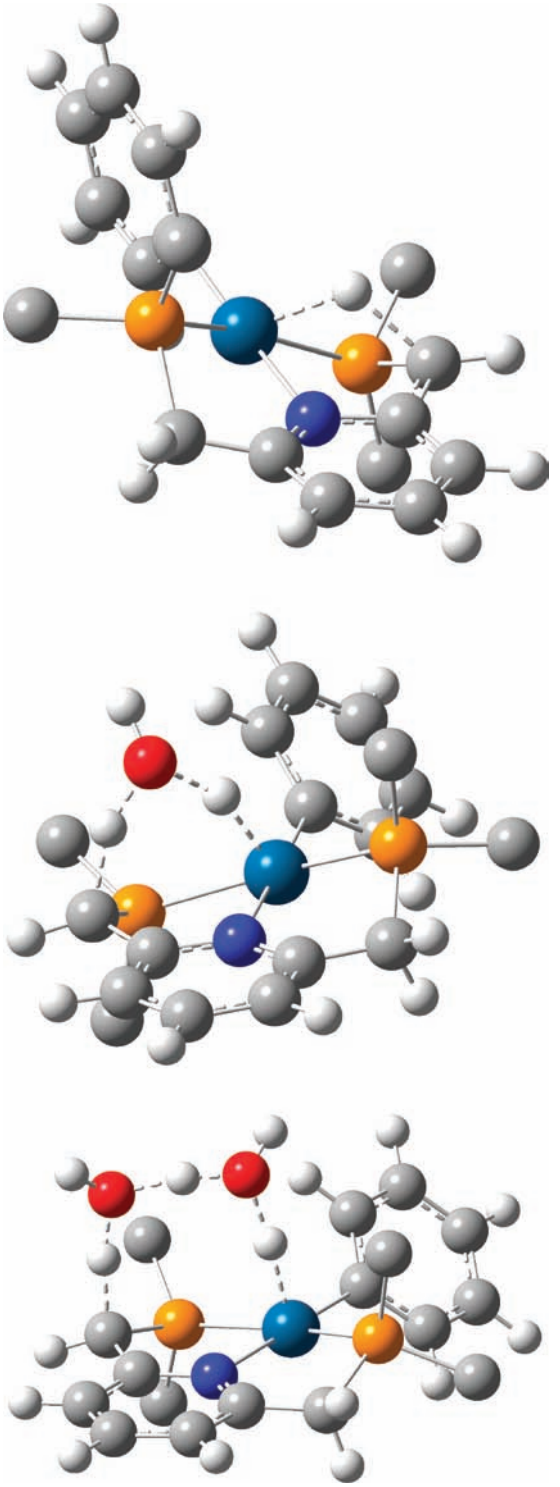
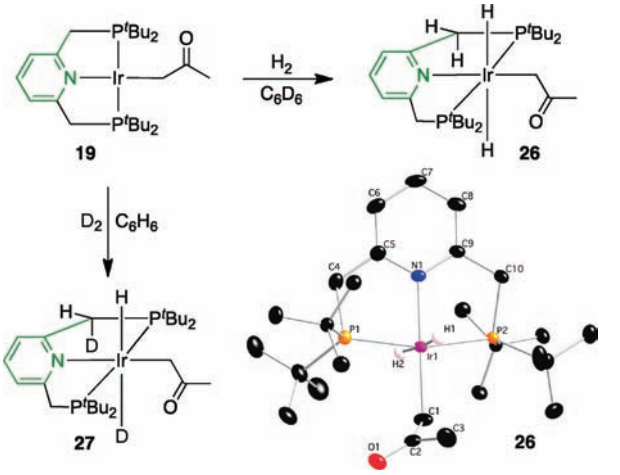
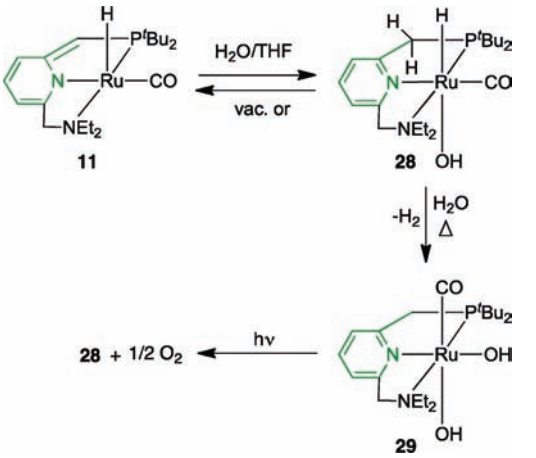


FIGURE 3. M06/SDD optimized structures of TS(**3′**–**23′**) + $n$$H_2O$ (from top to bottom: n = 0, 1, 2). Symbol (′) indicates the model complexes with PMe_2 ligands. H's on methyl groups are omitted for clarity. Structures modified from ref 14. Reproduced by permission of The Royal Society of Chemistry.

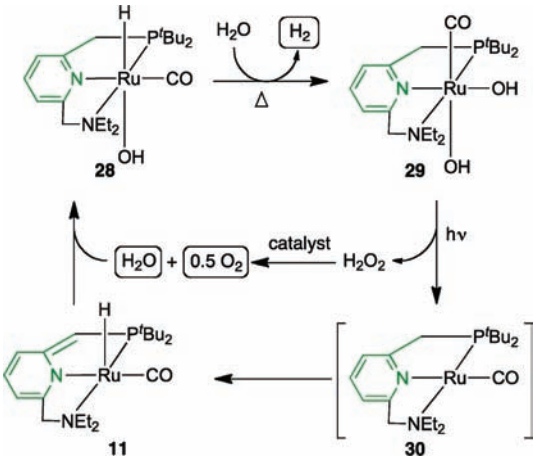
SCHEME 7



SCHEME 8



SCHEME 9



reactions, a stepwise cycle in which H_2 and O_2 are released in consecutive steps is attained (Scheme 9). Following the thermal reaction of complex **28** with water to liberate dihydrogen and give complex **29**, photolysis of **29** may release hydrogen peroxide by reductive elimination,

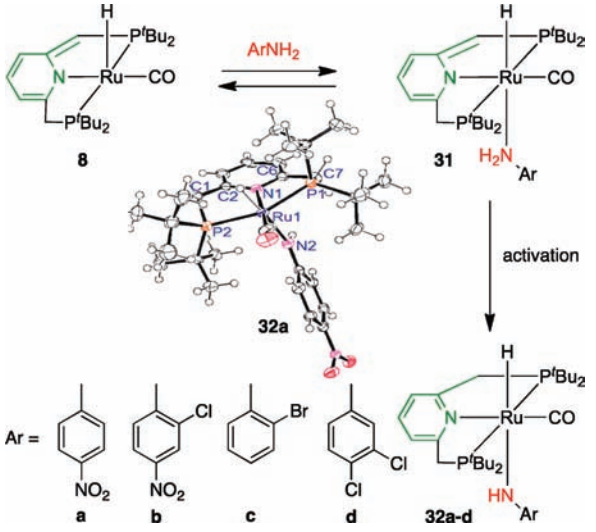
probably forming a Ru(0) intermediate **30**, which converts to complex **11** by proton migration from the methylene group of the phosphine arm to the ruthenium center. The liberated hydrogen peroxide is then rapidly catalytically decomposed (possibly by **11**, which is, as we have observed in a separate experiment, an excellent catalyst for H_2O_2 disproportionation) into dioxygen and water. This is a new approach toward a complete cycle for the generation of dihydrogen and dioxygen from water promoted by a soluble metal complex. In addition, isotopic labeling experiments using $H_2{}^{17}O$ and $H_2{}^{18}O$ demonstrate unequivocally that the process of oxygen–oxygen bond formation is intramolecular, establishing a fundamentally new mode of O–O bond formation, by photolytic coupling of OH groups. DFT calculations by Hall show that the photolytic reductive elimination of H_2O_2 can take place from a dissociative triplet state via a singlet–triplet crossing.[18b] Another DFT study by Fang concludes that a lower energy pathway for triplet O_2 formation, consistent with all experimental findings, involves a nonadiabatic two-step process in which concerted hydrogen transfer and dehydration involving two molecules of complex **29** take place. This O–O bond formation is intramolecular, and occurs along the T1 pathway, as a result of the S1 to T1 intersystem crossing being very efficient.[18c]

b. N–H Activation. N–H activation by metal–ligand cooperation involving ligand aromatization was demonstrated with the dearomatized complex **8**. When **8** was reacted with electron-poor anilines, N–H activation took place with proton transfer to the unsaturated ligand arm, leading to aromatization of the central pyridine ring (Scheme 10).[19] 4-Nitroaniline and 2-chloro-4-nitroaniline reacted at room temperature with **8** to provide the complexes **32a** and **32b**, respectively. Reactions of 2-bromoaniline and 3,4-dichloroaniline resulted in equilibria involving the activated aromatic complexes **32c** and **32d**, and the starting **8**, even in the presence of an excess of the halogenated anilines. The reversibility of N–H bond activation at room temperature in these complexes suggests that the barrier for this process is low and that potential catalytic cycles based on such systems could readily eliminate product amines.

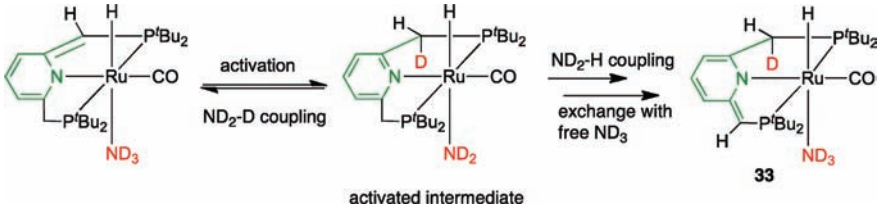
Thermodynamically, coordinated amine complexes of type **31** are the preferred forms for electron rich amines and ammonia. When ND_3 was reacted with complex **8**, formation of the deuterated complex **33** was observed after 5 min at room temperature, indicating N–D activation (Scheme 11). The reaction is highly stereospecific, and only one of the two CH_2 arm hydrogen signals in the ^1H NMR spectrum disappeared. No exchange of the vinylic hydrogen took place. Such dramatic selectivity suggests that the activation process occurs on only one face of the ligand in an intramolecular manner with one coordinated molecule of ND_3. The reverse reaction would affect only the (endo) hydrogen on the same face as the coordinated ND_3 moiety. This result also suggests that N–H activation, and perhaps O–H activation (see below) of other substrates, might occur in a stereoselective fashion.

Upon heating complex **8** with an excess of isopropylamine at 80 °C in a closed NMR tube, formation of the *trans*-dihydride **9** was observed. Presumably, after N–H activation, H_2 elimination involving the hydride ligand and an arm proton takes place, as suggested for complex **28**

SCHEME 10



SCHEME 11



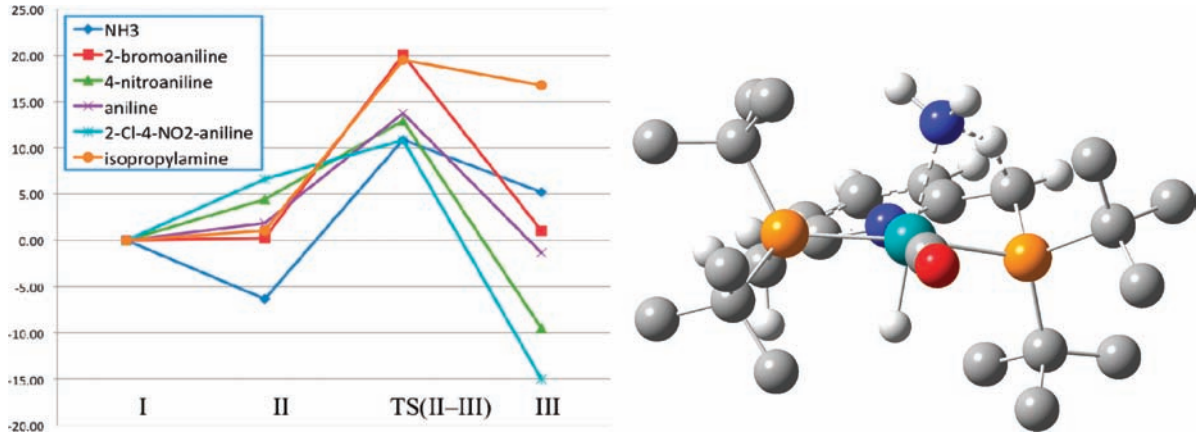
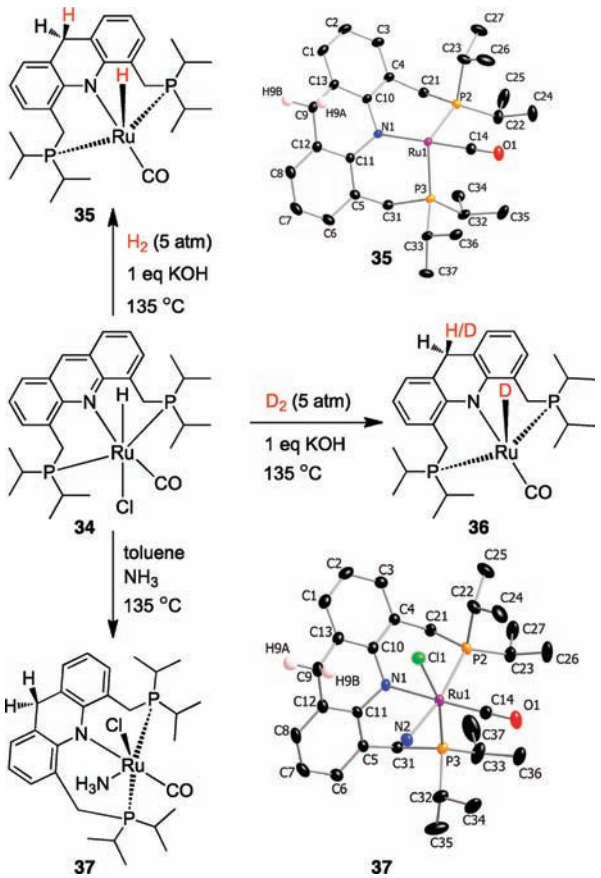


FIGURE 4. (left) Calculated free energies (ΔG_{298}, kcal mol^{-1}) for (I) the unbound starting materials and (II) coordinated and (III) NH-activated amine complexes. (right) Calculated structure of TS(II–III), the transition state for activation of NH_3 (H's on methyl groups are omitted for clarity). Figure adapted with permission from ref 19. Copyright 2010 American Chemical Society.

SCHEME 12



by DFT studies,[18] followed by β-H elimination and H_2 readdition.[19]

The trend observed in the experimental data of N–H activation reactions is also reflected in DFT studies (Figure 4). The barriers for the exchange between coordinated (II) and activated (III) states are low and accessible at room temperature.

Long-Range Metal–Ligand Cooperation

We have developed a unique, "long-range" mode of metal–ligand cooperativity involving an acridine-based pincer system.[20] The X-ray structure of the acridine PNP complex **34** exhibits an unusually long Ru–N bond (2.479 Å),[21] suggesting that N-coordination of the acridine ligand might be hemilabile. The acridine-PNP ligand affords a flexible ligand framework, as it forms six-membered rings (versus five membered rings of the pyridine-based complexes). Reaction of **34** with H_2/KOH is conceptually different from that of pyridine-based PNP complexes,[6] and it results in dearomatization of the central acridine ring in **34** as a result of heterolytic splitting of H_2 (Scheme 12).[22] A similar reaction with D_2 yields complex **36** with D_2 splitting. The ^{2}H and ^{1}H NMR spectra of **36** indicate the presence of a major amount of Ru–D (broad singlet at −20.75 ppm) and a very minor amount of Ru–H (triplet at −20.84 ppm), respectively. The ^{2}H NMR spectrum also exhibits a broad multiplet corresponding to the *C*D*H* group of the middle acridine ring (C9). These observations confirm the dearomatization as a result of D_2 splitting. Dearomatization in **35** is further corroborated by an X-ray structure, which exhibits a trigonal-bipyramidal geometry. The Ru–N bond (2.171 Å) is dramatically shorter (by 0.308 Å) than that in **34**. The central acridine ring has a boat-type conformation, and the acridine moiety is tilted toward the Ru center with a C(11)–N(1)–C(10)–Ru(1) torsion angle of 145.16°. DFT calculations indicate that this process involves formation of a Ru dihydride intermediate bearing a decoordinated, bent acridine ligand in which C9 is in close proximity to a hydride, followed by through-space hydride transfer.

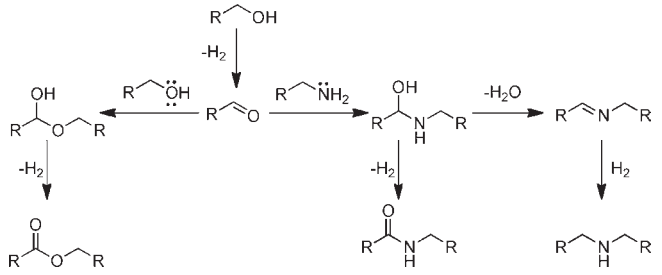
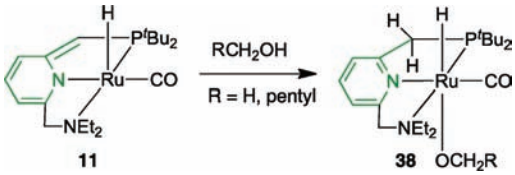


FIGURE 5

SCHEME 13



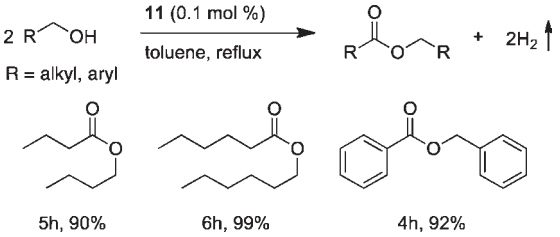
Interestingly, dearomatization of the central acridine ring was also observed upon reaction of **34** with ammonia, leading to complex **37** (Scheme 12). The X-ray structure of **37** shows an unusual *fac* configuration of the PNP ligand. Presumably, decoordination of the acridine nitrogen followed by NH_3 coordination places the bent acridine ring in a favorable position for hydride transfer to C9. The flexibility of the acridine PNP ligand enables formation of both *mer* (i.e., **34**–**36**) and *fac* (i.e., **37**) PNP complexes.

Facile Transformation of Alcohols into Esters, Amides, and Imines with Liberation of H_2

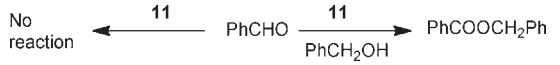
Esters, amides, imines, and amines are important fundamental building blocks in the chemical industry. Conventional syntheses of these compounds involve carboxylic acids and their derivatives, often using promoters or coupling reagents and leading to much waste.[23,24] Green processes for their production are highly desirable. Guided by our metal–ligand cooperation studies, we have developed catalytic processes for the syntheses of these products directly from alcohols with liberation of molecular H_2 (or H_2O) as the only byproduct, using no toxic reagents and producing no waste.

Reaction of the dearomatized complex **11** with alcohols results in O–H activation to provide the aromatic coordinatively saturated hydrido–alkoxy complex **38** (Scheme 13). This observation, together with the fact that dearomatized pincer complexes react with H_2 reversibly to form *trans*-dihydrides (Scheme 2), suggested to us the possibility of new catalytic reactions based on the dehydrogenation of alcohols[7] (Figure 5).

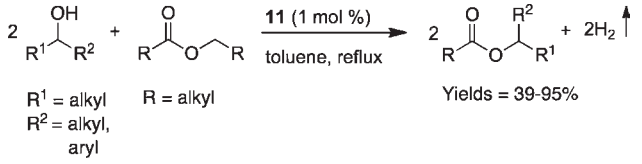
SCHEME 14



SCHEME 15



SCHEME 16



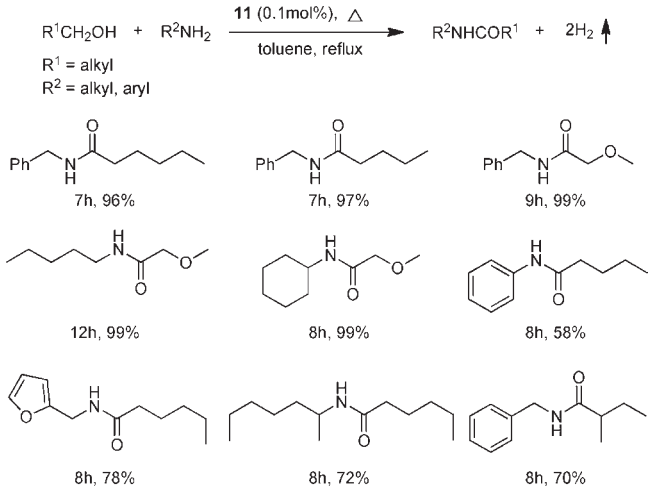
Refluxing a toluene solution of primary alcohols with complex **11** (0.1 mol %) as catalyst resulted in formation of the corresponding esters in excellent yields with liberation of H_2 (Scheme 14).[7] Ester yields of over 90% (TON > 900) were obtained under mild, neutral conditions. Only traces of aldehydes were formed. As opposed to the normal esterification of an acid and alcohol, in which an equilibrium mixture is generated, the evolved hydrogen shifts the equilibrium toward completion.

Mechanistically ester formation could occur by a Tischenko type condensation,[25] or hemiacetal formation followed by its dehydrogenation.[26] Our studies establish that the latter pathway is operative.[7] Thus, no ester is formed upon reaction of benzaldehyde with a catalytic amount of **11**, while reaction of equivalent amounts of benzaldehyde and benzyl alcohol results in quantitative formation of benzyl benzoate (Scheme 15).[7]

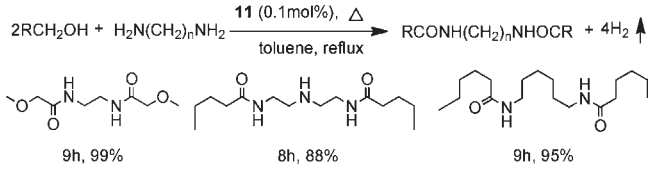
The dehydrogenative coupling of alcohols can be carried out using the air stable saturated complexes **4** or **10** as precatalysts in the presence of one equivalent of base (relative to these complexes).[7,27] Similarly, **7** catalyzes the acceptorless dehydrogenation of secondary alcohols to ketones.[28]

Furthermore, complex **11** catalyzes the acylation of secondary alcohols by nonactivated esters, such as ethyl acetate, with liberation of H_2 (Scheme 16).[29] When symmetrical esters are used as acylating substrates, both the acyl and

SCHEME 17



SCHEME 18

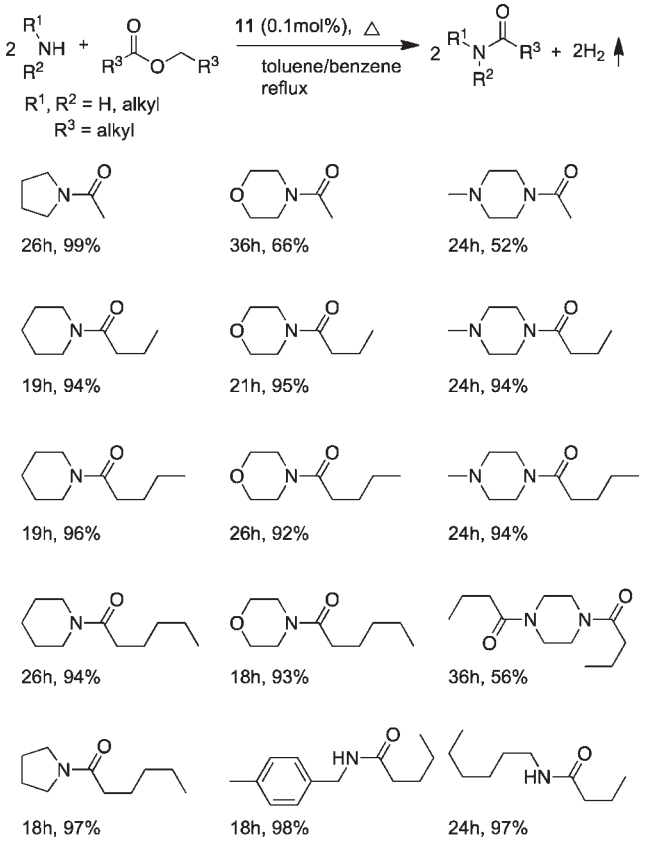


alkoxy parts of the reactant ester are incorporated in the product, presenting an atom economical and environmentally benign method for transesterification reactions.

Next, we investigated the reaction of primary alcohols with amines. In principle, three reactions can occur (Figure 5). Reaction of the intermediate aldehyde with the amine can form an intermediate hemiaminal, which can spontaneously eliminate water to form an imine, which can undergo hydrogenation with the liberated H_2 to yield a secondary amine.[30] Competing hemiacetal formation can provide an ester if nucleophilicity of the amine is low. We aimed at H_2 liberation from the presumed hemiaminal intermediate to form an amide. Indeed, amide formation occurs exclusively with liberation of hydrogen, with 0.1 mol % **11** as catalyst in the reaction of equivalent amounts of alcohols and amines in refluxing toluene (Scheme 17). This fundamentally new chemical reaction proceeds in high yields and high turnover numbers.[31]

While the yields are good to excellent in most cases, use of sterically hindered substrates results in lower yields of amides, as observed with 2-methyl-1-butanol and 2-methylhexamine. Also, as a result of the lower nucleophilicity of aniline, ester formation becomes competitive. The reactions are selective to the primary amine functionality, and secondary amines such as dibenzylamine do not react under

SCHEME 19

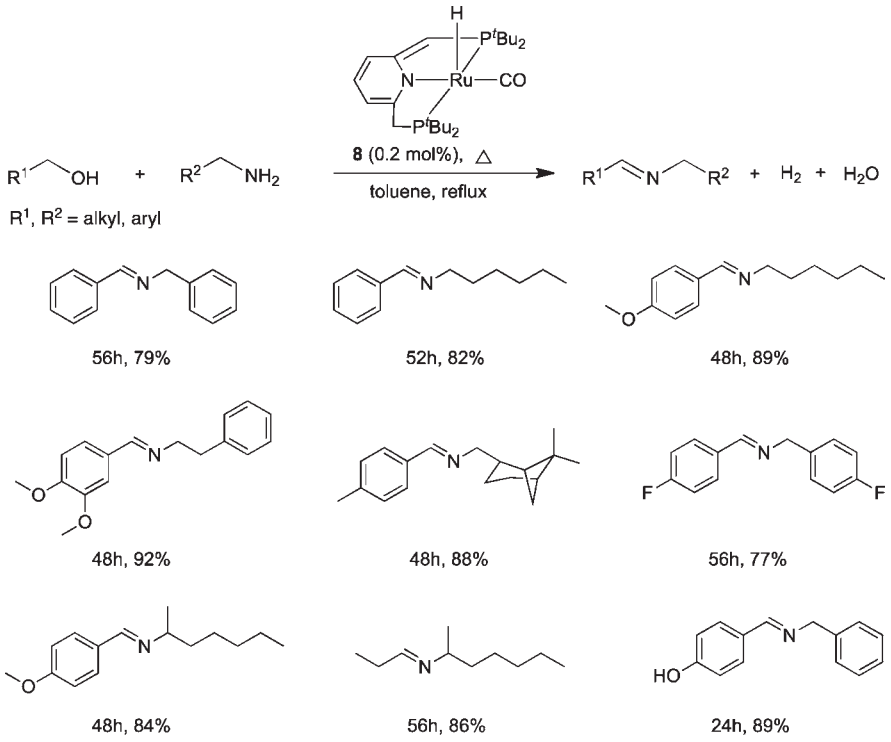


these conditions. Reactions with diamines give bis-amides (Scheme 18). Diethylenetriamine is chemoselectively acylated at the primary amine groups, requiring no protection of the secondary amine functionality. We have also used this reaction for the preparation of polyamides.[32] Subsequently, polymerization using complex **11** as catalyst was very recently reported.[33]

Efficient synthesis of amides by reaction of esters with amines with liberation of H_2 under neutral conditions catalyzed by complex **11** was reported very recently (Scheme 19).[34] Similar to the alcohol acylation process (Scheme 16), both acyl and alkoxo parts of the symmetrical esters are incorporated in the product. These reactions are possibly initiated by N–H activation of the amine by metal–ligand cooperation involving **11**. Ester coordination followed by intramolecular nucleophilic attack by the amido ligand at the acyl functionality is thought to be a key step.[34] Overall, in one catalytic cycle, two molecules of amide and of H_2 are formed.

Surprisingly, when the PNP complex **5** or **8** is employed in the coupling of alcohols and amines, a different course of reaction takes place, providing an efficient method for the synthesis of imines with liberation of dihydrogen,[35] with no

SCHEME 20



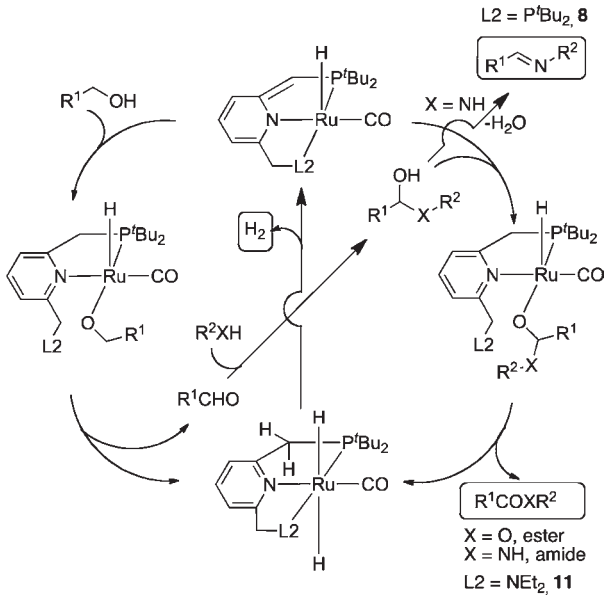


FIGURE 6. Proposed simplified catalytic cycle for the synthesis of esters, amides, and imines from alcohols, catalyzed by PNP and PNN ruthenium pincer complexes. Note that mechanisms not involving amine arm dissociation are also possible (see text).

imine hydrogenation taking place (Scheme 20). A range of alcohols and amines containing either electron-donating or -withdrawing substituents react to yield the corresponding imines in very good yields. Sterically hindered amines are also tolerated. This new catalytic reaction works very well in the challenging synthesis of unstable aliphatic imines. Convenient to practical applications, the reaction can be carried out in air.[35]

A common, simplified catalytic cycle for the direct esterification, amidation, and imination reactions based on alcohols with liberation of hydrogen is proposed in Figure 6. Upon reaction of dearomatized complexes (**5**, **8**, or **11**) with alcohols, facile O–H activation takes place to provide the saturated hydrido-alkoxy complexes. This is followed by β-hydride elimination, the mechanism of which is not clear at this stage. It may occur by arm opening to provide a cis coordination site, as depicted in Figure 6, but other mechanisms are also possible, including alkoxide dissociation from the saturated complex accompanied by hydride abstraction.[36] This step generates an intermediate aldehyde and the known *trans*-dihydride complexes (**6**, **9**, or **12**, respectively), which were demonstrated to liberate H_2 and regenerate the dearomatized complexes. The generated aldehyde is in equilibrium with the corresponding hemiacetal (X = O), which undergoes a similar catalytic cycle providing the ester.[7] In the presence of amines, the course of reaction differs based on L_2 (i.e., P^tBu_2 or NEt_2). With the PNN complex **11**, the intermediate hemiaminal (X = NH, but see next paragraph) undergoes dehydrogenation to provide amides,[31]

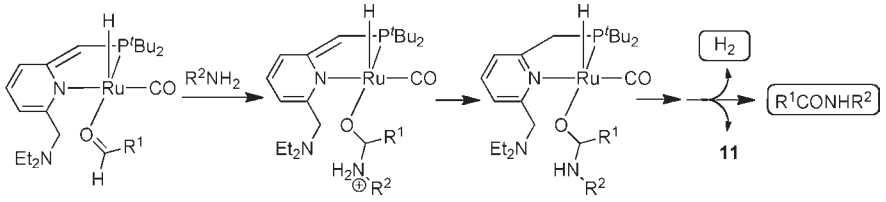
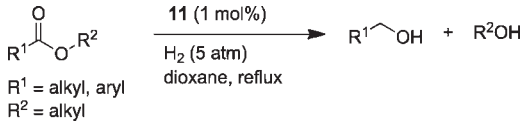
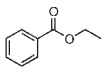
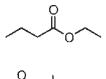
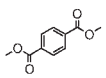
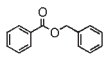
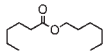


FIGURE 7

TABLE 1. Mild Hydrogenation of Esters to Alcohols Catalyzed by the PNN Pincer Complex **11**



Entry	Ester	Time (h)	Conv. (%)	Alcohols (Yields, %) RCH$_2$OH	Alcohols (Yields, %) R^{1}OH
1		4	100	 (97)	MeOH (100)
2		4	99.2	 (96)	EtOH (99)
3		4	100	 (98)	EtOH (98.6)
4		24	10.5	EtOH (10.5)	^{t}BuOH (10.5)
5		5	100	 (97)	MeOH (100)
6		7	98.5	 (98)	
7		5	82.2	 (82.2)	
8		12	86	EtOH (85.6)	

whereas with the PNP complex **8**, the anticipated water elimination takes place to provide imines.[35]

The striking difference in the catalytic activity of the PNN and PNP complexes can be rationalized as follows. In the case of the PNN complex, bearing the hemilabile amine arm, the coordinated aldehyde is attacked by the primary amine, forming a quaternary ammonium intermediate, followed by intramolecular proton transfer to the dearomatized phosphine arm (Figure 7), while in the case of the PNP complex attack of the aldehyde by the amine takes place after it is released into solution, generating a free hemiaminal intermediate which liberates water. A similar conclusion was reached in another study.[37d]

These direct transformations of alcohols to esters, amides, and imines proceed in high yields and high turnover numbers under neutral conditions with no generation of waste, the only byproduct being H_2, thus providing attractive "green" synthetic methods. Following our report, other reports on amide formation from alcohols and amines appeared.[37] Interestingly, the metal–ligand cooperation concept was applied in nonpincer complexes for the coupling of alcohols with water, alcohols and amines; however, sacrificial hydrogen acceptors were used.[38]

Catalytic Hydrogenation of Esters, Amides, and Ketones

Complex **11** also catalyzes the hydrogenolysis of esters to alcohols under 5 atm of H_2.[9] The reaction is general and not limited to activated esters (Table 1). It proceeds under relatively mild, neutral conditions, providing a "green", mild pathway for the synthesis of alcohols from esters. The reaction is sensitive to steric hindrance of the esters. Ester hydrogenation is still rare.[39]

A possible mechanism of the reaction is outlined in Figure 8. Addition of H_2 to the dearomatized PNN complex **11** leads to the *trans*-dihydride complex **12**, which can undergo decoordination of the amine "arm" to provide a site for ester coordination. Hydride transfer to the ester carbonyl and subsequent amine arm coordination and dearomatization of the pyridine core regenerates complex **11** and eliminates a hemiacetal, which is in equilibrium with the aldehyde in solution. The aldehyde is then hydrogenated to the corresponding alcohol via a similar cycle. Note that direct attack of the trans dihydride on the ester carbonyl group, without prior coordination, is also possible.

Under mild hydrogen pressure (10 atm), it is possible to catalyze the unprecedented selective hydrogenolysis of amides to the corresponding alcohols and amines, involving C–N cleavage. The bipyridine-based dearomatized PNN complex **39** shows higher activity than **11** (Scheme 21).[40]

Nozaki reported Ir(III)PNP pincer catalyzed efficient hydrogenation of CO_2 to formate salts, also suggested to involve dearomatization of the pincer ligand.[41]

Very recently, we have reported facile hydrogenation of ketones to the corresponding secondary alcohols under mild hydrogen pressure (4.1 atm) catalyzed by the iron complex **40**, that operates by metal–ligand cooperation via ligand dearomatization–aromatization (Scheme 22).[42a]

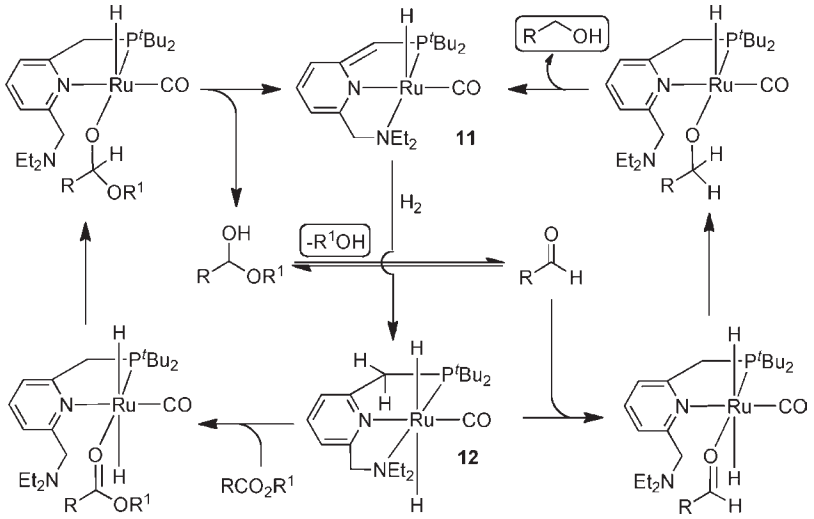
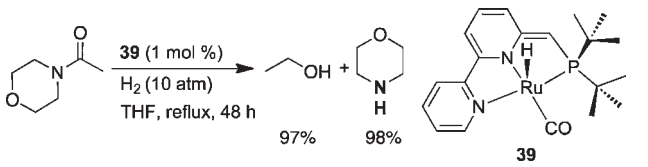
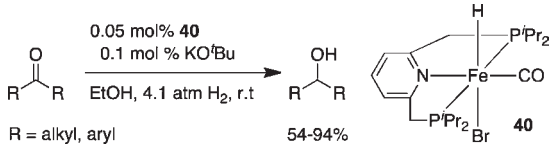


FIGURE 8

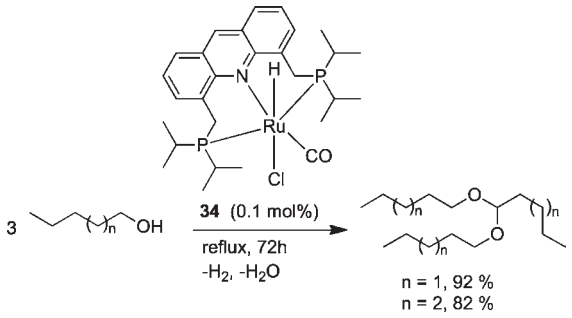
SCHEME 21



SCHEME 22



SCHEME 23



This process is the most efficient of the very few ketone hydrogenation reactions catalyzed by well-defined iron complexes.[42b,c]

Direct Conversion of Alcohols to Acetals and H_2

Unlike the pyridine-based complexes **4** and **10**, which do not react with alcohols in neutral media,[7] air-stable acridine-based complex **34** catalyzes the conversion of primary alcohols to acetals (Scheme 23).[21] Small amounts of esters and aldehydes are also formed. Acetal formation from alcohols was reported by Murahashi et al.[26]

Our studies indicate that the reaction proceeds via observable enolether intermediates, resulting from hemiacetals by water elimination. Thus, formation of the acetal likely takes place by addition of the alcohol to the C=C bond of the enolether (route (ii), Figure 9).

In the presence of 1 equiv of base (relative to Ru), complex **34** catalyzes alcohol dehydrogenation to esters (Scheme 24), as observed for pyridine based pincer complexes **4** and **10**. A Ru(0) intermediate, possibly formed by deprotonation of **34**, may be the actual catalyst. Further studies suggest that the reactions proceed via the hemiacetal intermediate[26] rather than by a Tischenko disproportionation[25] of an aldehyde intermediate.

Selective Synthesis of Primary Amines

The acridine-based **34** catalyzes the selective formation of primary amines directly from alcohols and ammonia (Scheme 25),[43] with no derivatives of alcohols (such as alkyl halides) being required. Selective formation of primary amines is a challenging task, since being more nucleophilic than ammonia they compete with it in reaction with electrophiles.[44] Minor amounts of secondary amines are observed in reactions of aliphatic alcohols. Our studies indicate that these might be formed in two pathways: (i) reaction of the product primary amine with an intermediate aldehyde (Figure 10, route a), or (ii) N–H activation of the initially formed primary amine followed by β-H elimination and nucleophilic attack by another

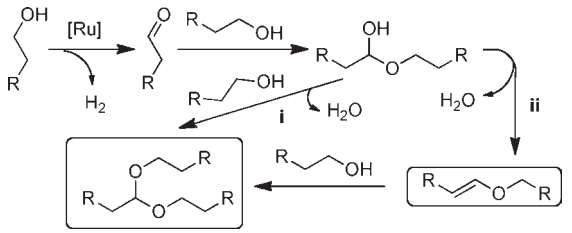
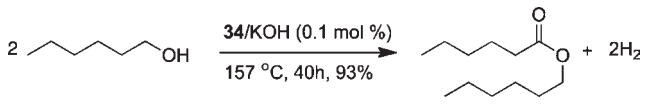
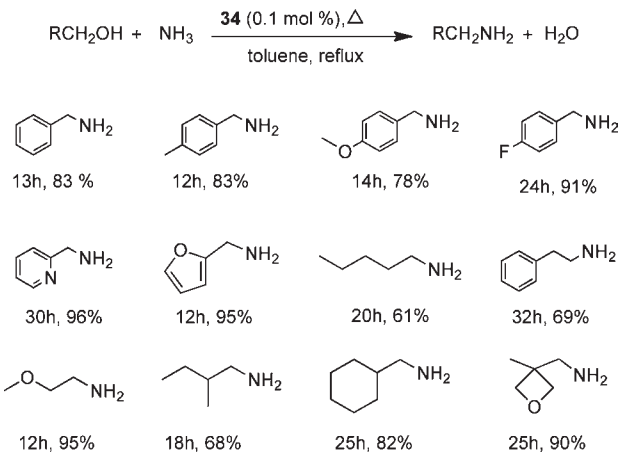


FIGURE 9

SCHEME 24



SCHEME 25



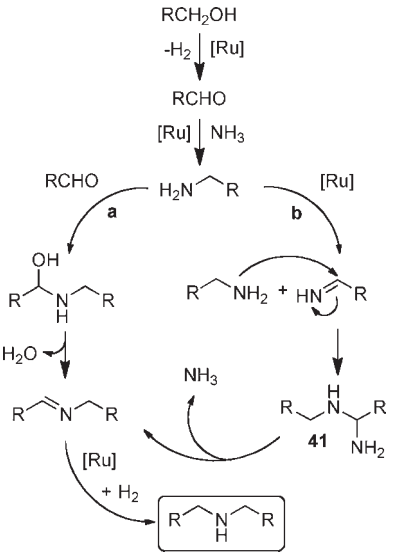
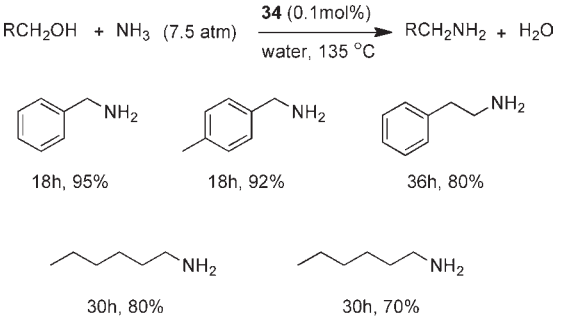


FIGURE 10

SCHEME 26



molecule of the primary amine on the imine. Elimination of ammonia from intermediates **41** (Figure 10, route b) and subsequent hydrogenation delivers secondary amines. Thus, it is important to stop the reaction as soon as the alcohol has been consumed in order to avoid self-coupling of primary amines.

An assortment of primary alcohols was directly converted to primary amines by reaction with ammonia (Scheme 25). The reaction takes place effectively also in neat alcohols, requiring no added solvent.

Interestingly, the reaction can proceed in water as reaction medium with excellent selectivity for primary amines (Scheme 26). Benzyl alcohols and phenethyl alcohol, which are insoluble in water at room temperature, form a homogeneous solution on heating while aliphatic alcohols such as 1-hexanol were not miscible with water even on heating and the reaction may take place "on water".[45]

While the mechanism of this new selective amination reaction is not clear at this stage, it may involve "long-range" metal–ligand cooperation with C9 of acridine as a cooperative site, involving dearomatization of the heteroaromatic acridine ring, as observed upon reaction of complex **34** with ammonia (Scheme 12).[20]

Concluding Remarks

In this Account, we have reviewed our work on new modes of metal–ligand cooperation, based on aromatization–dearomatization of the heteroaromatic core in pyridine- and acridine-based pincer complexes. In the pyridine-based complexes, these processes involve reversible deprotonation of the benzylic position, while with the acridine system "long range" metal–ligand cooperation takes place, involving the electrophilic C-9 position of the acridine moiety. In addition to the higher stability associated with pincer complexes, the relatively low resonance energy of heteroaromatics as compared with arenes, and stabilization of the dearomatized ligand by the

metal center, make the PNN and PNP ligands highly effective motifs for metal–ligand cooperation. These heteroaromatic pincer ligands act in concert with metal center in the activation of strong bonds, such as C–H, H–H, N–H, and O–H bonds, providing a new approach to bond activation and a basis for catalytic design. Guided by these modes of metal–ligand cooperation, novel, highly efficient atom economical, and environmentally benign methods were developed for a range of products directly from alcohols with the liberation of H_2, a significant departure from the conventional synthetic procedures. While we have disclosed cooperative catalysis by ruthenium and iron pincer complexes, catalytic studies involving pincer complexes of other transition metal complexes are currently in progress in our laboratories. In recent years, the research areas of cooperativity in catalysis by metal complexes, and the broad field of pincer complexes, have gained much interest. As shown in this Account, combining these two areas within the theme of pincer-complex cooperativity can lead to new bond activation modes and to unprecedented, green catalytic reactions.

We thank all our co-workers, whose names appear in the cited references, for their valuable contributions. This research was supported by the European Research Council under the FP7 framework (ERC No 246837), by the Israel Science Foundation, by the MINERVA Foundation, by the DIP Program for German-Israeli Cooperation, by the Kimmel Center for Molecular Design, and by the Peter J. Cohn Fund. D.M. is the holder of the Israel Matz Professorial Chair.

BIOGRAPHICAL INFORMATION

Chidambaram Gunanathan received his B.Sc (chemistry) and M.Sc (organic chemistry) from University of Madras, India. He was awarded a Ph.D in chemistry for his research work at Central Salt and Marine Chemicals Research Institute, Bhavnagar, India with Prof. S. Muthusamy. In 2005, he joined in the groups of Prof. David Milstein and Prof. Hadassa Degani at Weizmann Institute of Science, Israel for his postdoctoral stint, where he was also a Dean of Faculty Postdoctoral Fellow. He also worked with the group of Prof. Walter Leitner at RWTH Aachen University, Germany as an Alexander von Humboldt Research Fellow. In May 2011, he joined as Assistant Professor at the National Institute of Science Education and Research, Bhubaneswar, India. He is also a recipient of Ramanujan Fellowship from DST, New Delhi. His research interests are the design and catalytic application of pincer complexes and discovery of new reactions for atom economy.

David Milstein received his Ph.D degree at the Hebrew University of Jerusalem in 1976. He carried out postdoctoral studies at Colorado State University, where together with his advisor, John Stille, he discovered the Stille Reaction. In 1979 he joined the CR&D Department of the DuPont Company in the United States, where he became a Group Leader in the homogeneous catalysis area. In 1987 he accepted a professorial appointment at the Weizmann Institute of Science in Israel, where he became Head of the Department of Organic Chemistry in 1996 until 2005. In 2000 he became Head of the Kimmel Center for Molecular Design. He is the Israel Matz Professor of Organic Chemistry since 1996. His research interests focus on the development of fundamental organometallic chemistry and its application to the design of new sustainable processes catalyzed by transition metal complexes. Awards received include the Kolthoff Prize, the Israel Chemical Society Award, the ACS Award in Organometallic Chemistry, the RSC Sir Geoffrey Wilkinson Prize, and the Meitner Humboldt Research Award. He was elected to the German National Academy of Sciences-Leopoldina in 2006.

FOOTNOTES

*To whom correspondence should be addressed. E-mail: david.milstein@weizmann.ac.il.

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