Asking Ligands to Lend a Hand

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https://doi.org/10.51167/acm00039

In classical transition-metal-catalysts, the ligand is a spectator, while all key transformations such as oxidative addition, β-hydride elimination and reductive elimination occur at the metal center. Herein, the ligand plays no direct role in the catalytic cycle and its function is limited to stabilizing the metal center and tuning its coordination environment. In recent years, participating ligands, which play an active role during the course of reaction, have received greater attention (**Scheme 1**). The use of such ligands has allowed for the development of more active/selective catalysts and opened up new reaction pathways. There are many ways in which a ligand can influence the metal center to accelerate the catalytic transformation. For example, hemilabile ligands allow reversible dissociation of a donor unit to adapt to the stereoelectronic requirements of the reaction intermediates.[1] Redox-non-innocent ligands participate in transferring electrons to/from the metal.[2] There is a class of ligands that directly participate in bond making/breaking and undergo reversible chemical transformation during the catalytic cycle.[3,4] These modes of ligand cooperativity have been discussed in many excellent reviews including those by Caulton,[1] Milstein[3] and Grützmacher[4]. Herein, we aim to address two distinct strategies to achieve 'ligand-driven-chemistry' – the use of (a) electronically asymmetric ligand, and (b) protic ligands. A brief discussion on the role of ligands in water activation for functionalization of organic compounds is given at the end.

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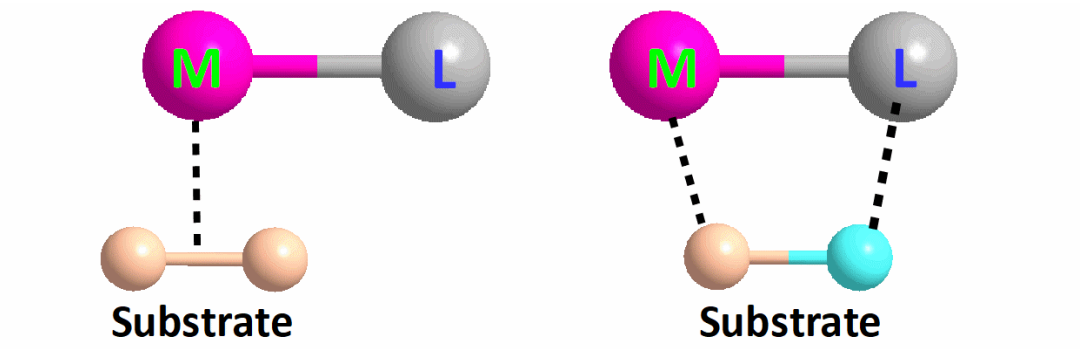
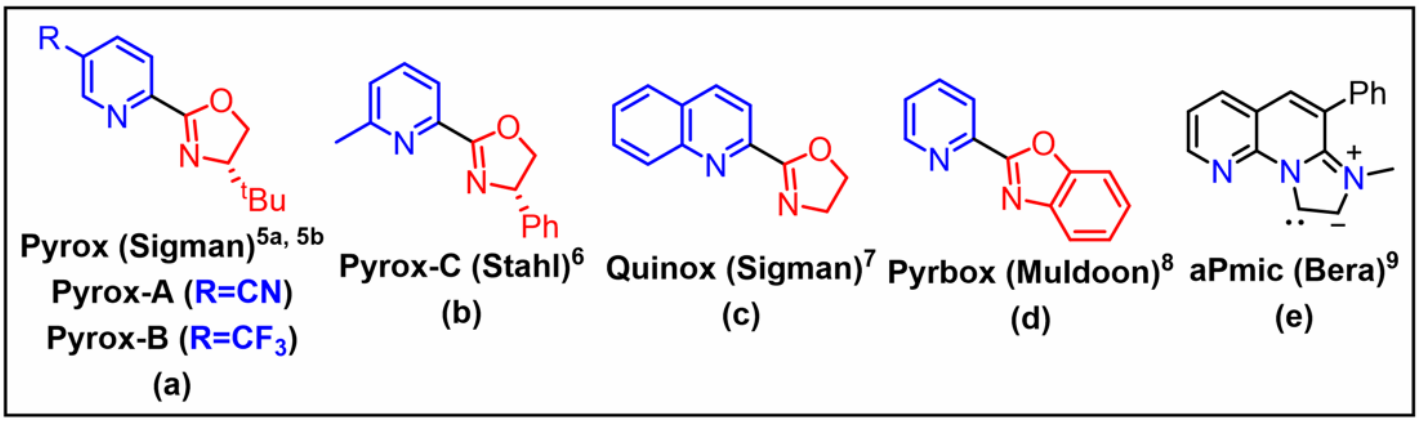


Scheme 1. Conventional metal catalysis vs ligand driven catalysis.

A. Electronically asymmetric ligands

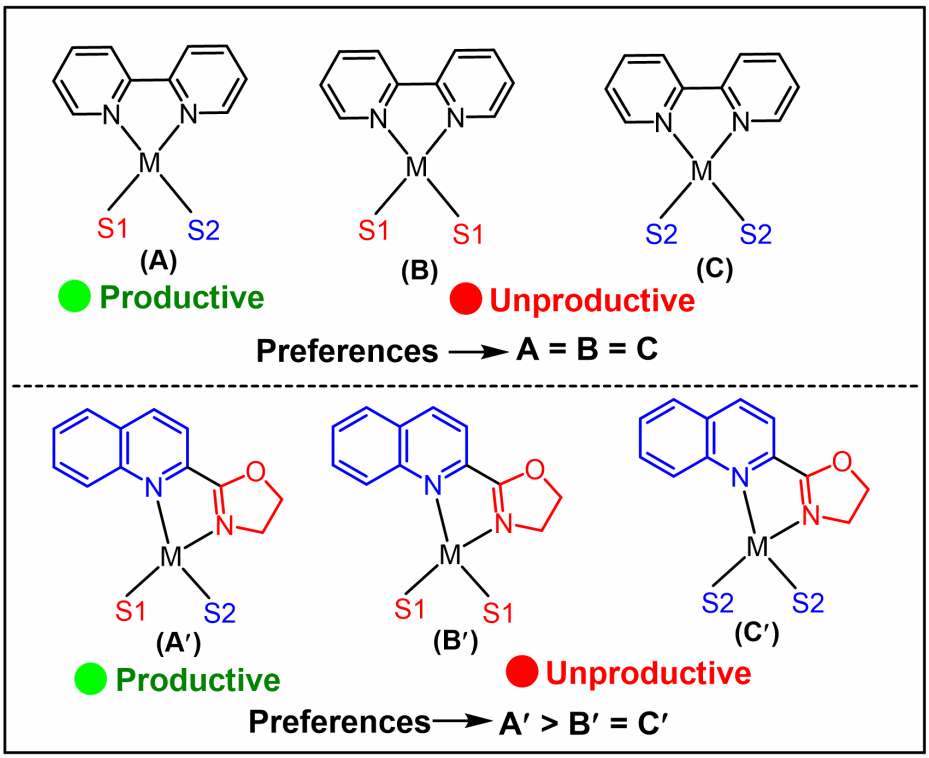
Electronically asymmetric ligands have donor components differing in their electronic characteristics (**Scheme 2**).[5-9] These ligands are particularly useful for catalytic transformations involving two electronically different reactants. The difference in the electronic characteristics of the donor components enables the two electronically different reactants to bind the metal center in a specific arrangement. This has a major consequence on the subsequent reactions occurring at the metal center. For example, as shown in **Scheme 3**, there is no preference for the productive arrangement (arrangement **A**) involving two electronically distinct reactants (S1 and S2) on the metal center over the unproductive arrangements (**B** and **C**) employing an electronically symmetric ligand. In contrast, an



Scheme 2. Representative examples of electronically asymmetric ligands. Reprinted (adapted) with permission from Ref 10. Copyright (2020) American Chemical Society.

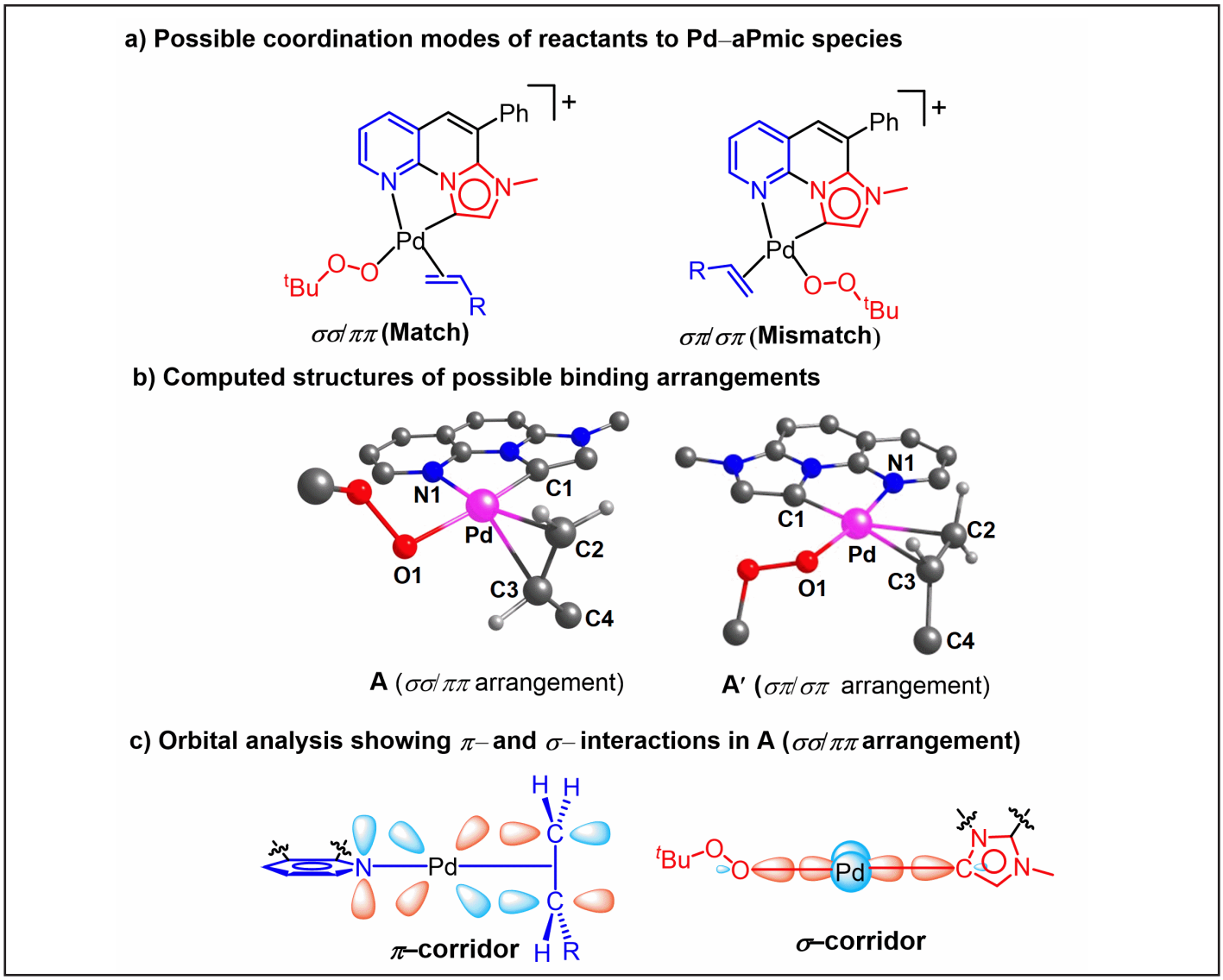
electronically asymmetric ligand, such as quinoline-2-oxazoline (Quinox) (**Scheme 2c**), can favor the productive arrangement (arrangement **A′**) of S1 and S2 on the metal center as compared to unproductive arrangements (**B′** and **C′**). Quinox features two electronically distinct donor modules — an electron-rich oxazoline ring and an electron-deficient quinoline ring.

One such transformation is the catalyst-controlled Wacker-type oxidation, which involves the coordination of an olefin and a *t*butylperoxide anion to a Pd center. An electronically asymmetric ligand favors the metal to bind these two reactants in a specific arrangement. Therefore, the binding of two olefins or two *t*butylperoxide anions to the Pd center, which give catalytically inactive species, is prevented. For example, Sigman proposed that Quinox ligand prefers an arrangement in which *t*butylperoxide anion binds Pd center *trans* to the oxazoline ring (electron-rich moiety), whereas alkene binds *trans* to the quinoline ring (electron-deficient moiety).[7] This hypothesis was supported by Hammett analysis of a series of substituted Quinox ligands and electronically diverse substrates. The specific arrangement of the precursors on the Pd center plays a key role in the excellent activity and selectivity of Pd–Quinox complex for Wacker type oxidations. In contrast, the electronically symmetric ligand 2,2-bipyridine was ineffective in the catalytic oxidation of allylic acetate and related catalytic reactions.



Scheme 3. Role of electronic asymmetry of ligand to favor a productive arrangement of reactants on a metal center relative to unproductive arrangements.

We revealed the electronic asymmetry of an annelated pyridyl-mesoionic carbene ligand (aPmic) (**Scheme 2e**).[10] The two coordinating modules of this ligand differ in their relative ability for *σ*-donation/*π*-bonding, which plays a key role in the excellent activity and selectivity of Pd–aPmic species for Wacker-type oxidations. The carbene moiety is a strong *σ*-donor, whereas the pyridyl unit has a *π*-bonding character besides acting as *σ*-donor. This electronic dissymmetry of the two modules of aPmic enables the binding of olefin and $^{t}BuOO^{-}$ to Pd (of Pd–aPmic species) in a specific arrangement. The favorable arrangement is where the π-acid ligand olefin binds *trans* to the pyridyl unit and the *σ*-donor $^{t}BuOO^{-}$ binds *trans* to the carbene carbon, which is also a *σ*-donor (**Scheme 4a**). Evaluation of the computed structures of matching arrangement **A** (also indicated by *σσ*/*ππ* arrangement) and mismatching arrangement **A′** (*σπ*/*σπ* arrangement) disclosed interesting features (**Scheme 4b**). The olefin is perpendicular to the Pd(aPmic) plane in **A**, similar to well-known Zeise's salt $K[PtCl_3(C_2H_4)]$.[11] However, olefin lies in the Pd(aPmic) plane in **A′**. The comparison of metrical parameters revealed stronger Pd–N1 and Pd–C2/C3 interactions in **A** as compared **A′**. Natural bond orbital analysis indicated that these differences primarily arise as the matching arrangement (**A**) has significant *π*-type interactions between p*π* of N1, d*π* of Pd, and *π** of olefin (which is perpendicular to the Pd(aPmic) plane) (**Scheme 4c**). In contrast, the pyridyl and olefin are not mutually *trans* in **A′** and the *π*-type interactions are absent. Hence, a perpendicular disposition of olefin is not necessitated in **A′**. Overall, it is the pyridine module that guides the orientation of the olefin in **A**. The Pd–O1 and Pd–C1



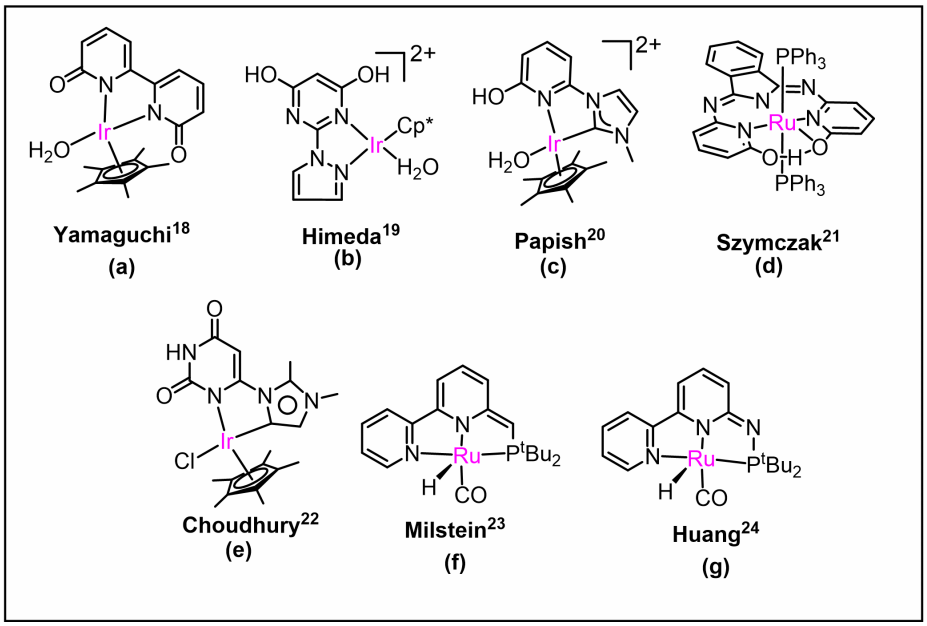
Scheme 4. Role of electronic asymmetry of aPmic to enable a specific arrangement of reactants on Pd–aPmic species.

distances are similar irrespective of their *trans* partners in **A** and **A′**, indicating similar interactions of *t*butylperoxide anion with the metal.

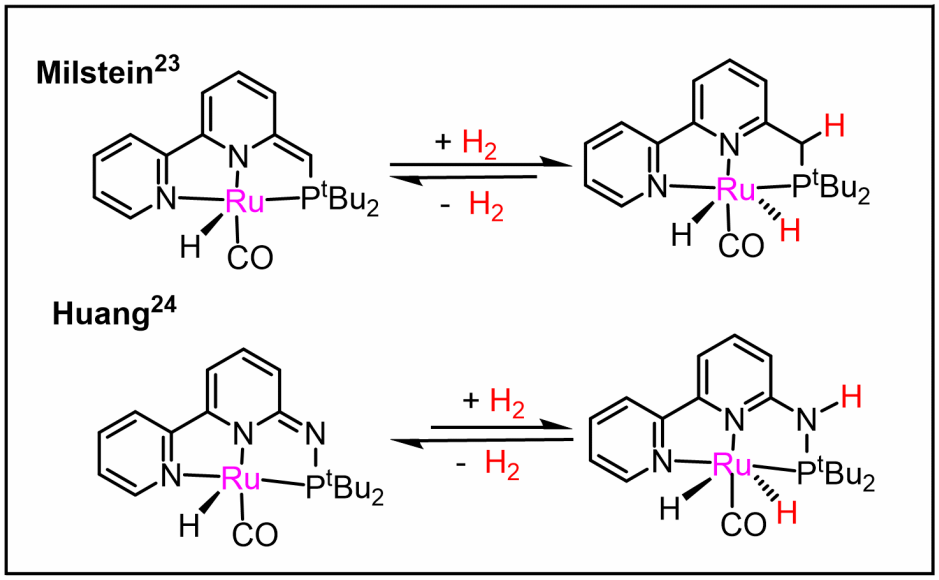
In the example above, we examined how an electronically asymmetric ligand controls the substrate assembly on the metal center. Now we disclose the role of protic ligands to regulate proton/hydride management at the metal and thus influence the (de)hydrogenation related chemistry.

B. Protic catalysts

Protic ligands can reversibly interconvert between two electronically distinct states on gaining or losing a proton (**Scheme 5**).[2,12-24]. A H_2 molecule (or its equivalents) is activated through metal–ligand cooperative action to generate the hydrogenated form of the catalyst with a nucleophilic hydride at the metal centre and a proton on the ligand, which are then transferred



Scheme 5. Representative examples of protic catalysts.

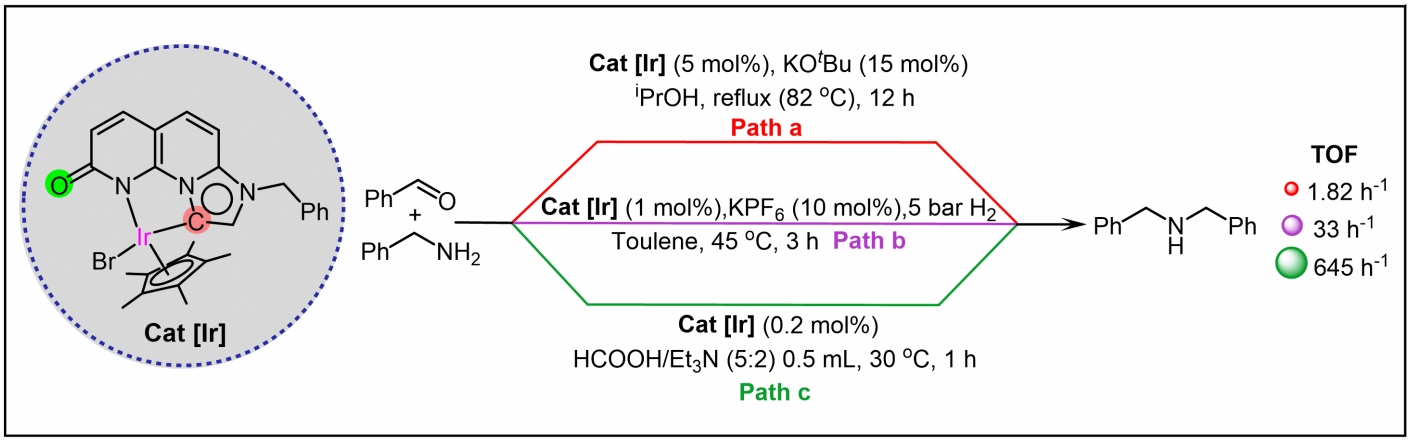


Scheme 6. Activation of H_2 through MLC involving ligand protonation /deprotonation.

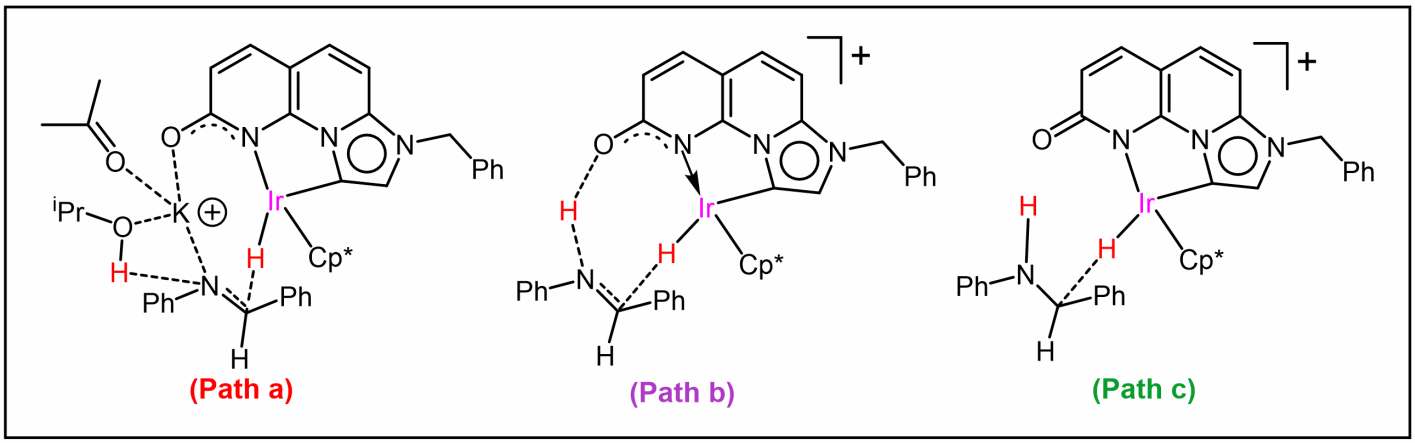
to a suitable substrate (**Scheme 6**).[23,24] The catalysts bearing these ligands efficiently mediate the reactions that involve hydride and proton management, such as (de)hydrogenation and borrowing-hydrogenation. Important considerations to develop efficient protic catalysts include the nature (acid/base properties) of the proton responsive unit (PRU), spatial position/orientation of the PRU and the metal hydricity. Milstein utilized metal-ligand cooperativity (MLC) involving dearomatization–aromatization of the central pyridine of pyridine-based pincer complexes to catalyze a series of (de)hydrogenation type reactions (**Scheme 6**). Huang and coworkers studied analogous systems, where the CH_2 arm(s) were replaced with one or two NH groups.

pH dependent mechanism

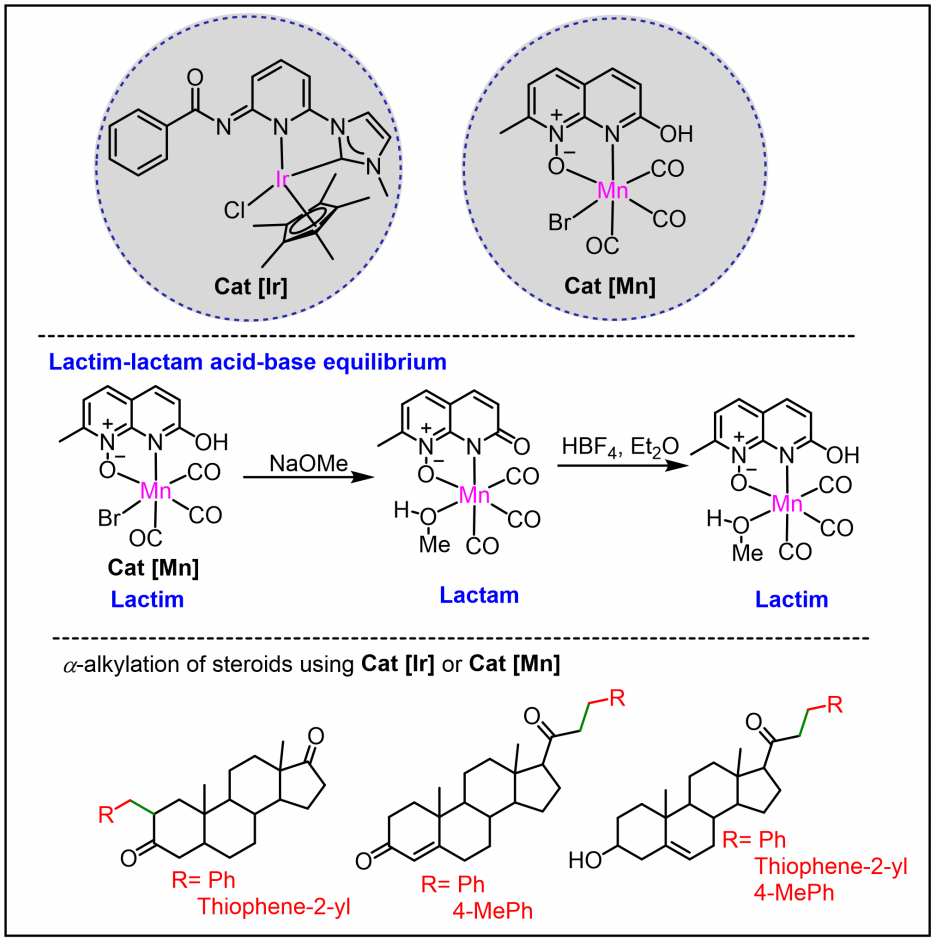
Our group incorporated a proton-responsive hydroxy unit on an annulated imidazo[1,2-*a*][1,8]naphthyridine based mesoionic carbene (MIC) platform (**Scheme 7**).[25] A Cp*Ir(III) bearing this ligand in anionic lactam form was isolated and the acid–base equilibrium between the lactam-lactim tautomers on the ligand scaffold was examined by ^{1}H NMR and UV–vis spectra. This protic catalyst was employed to activate H_2, ^{i}PrOH/KO^{t}Bu, and HCOOH/Et_3N (5:2) and subsequent delivery of a proton and hydride to an imine. Each of the three reduction systems behaves mechanistically differently, determined by the acid–base properties of the ligand framework (**Scheme 8**). Under basic conditions (^{i}PrOH/KO^{t}Bu), the anionic lactam form of the ligand dominates the reaction pathway. The HCOOH/Et_3N (5:2) medium is not acidic enough to protonate the ligand lactam oxygen. Instead, a hydride transfer *via* ion-pair decarboxylation from the formate takes place to afford an Ir–H species,



Scheme 7. A Cp*Ir(III) protic catalyst for the reductive amination of aldehydes using three different hydrogen sources.



Scheme 8. Proposed transition states using three different hydrogen sources.



Scheme 9. Cp*Ir(III) protic catalyst bearing a pyridyl(benzamide)-functionalized NHC ligand, and Mn(I) protic catalyst based on a naphthyridine-*N*-oxide scaffold for the alkylation of ketones.

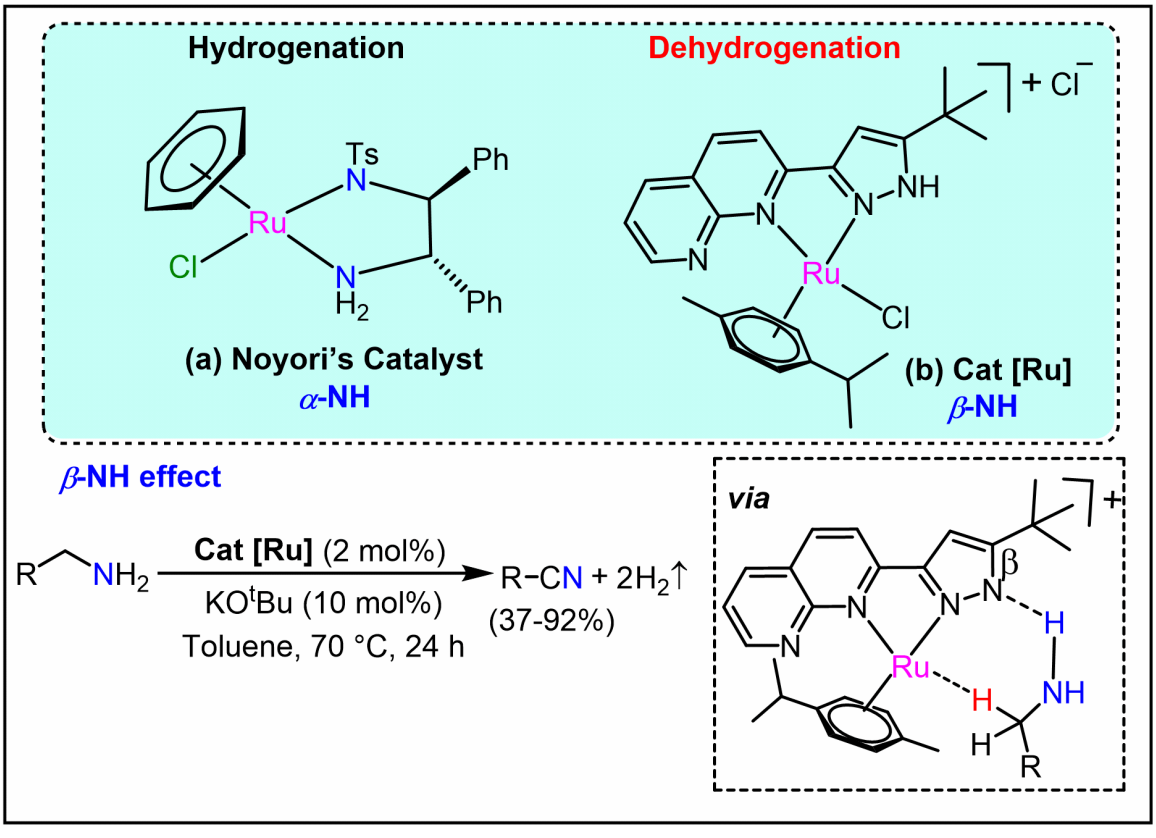
whereas the lactam form of the ligand remains unaltered. The anionic lactam ligand facilitates a hydride transfer to the protonated imine. The direct hydrogenation in a neutral medium involves the lactam/lactim tautomerization of the ligand scaffold.

Subsequently, we designed protic ligands based on different molecular scaffolds. Two such examples are highlighted below.

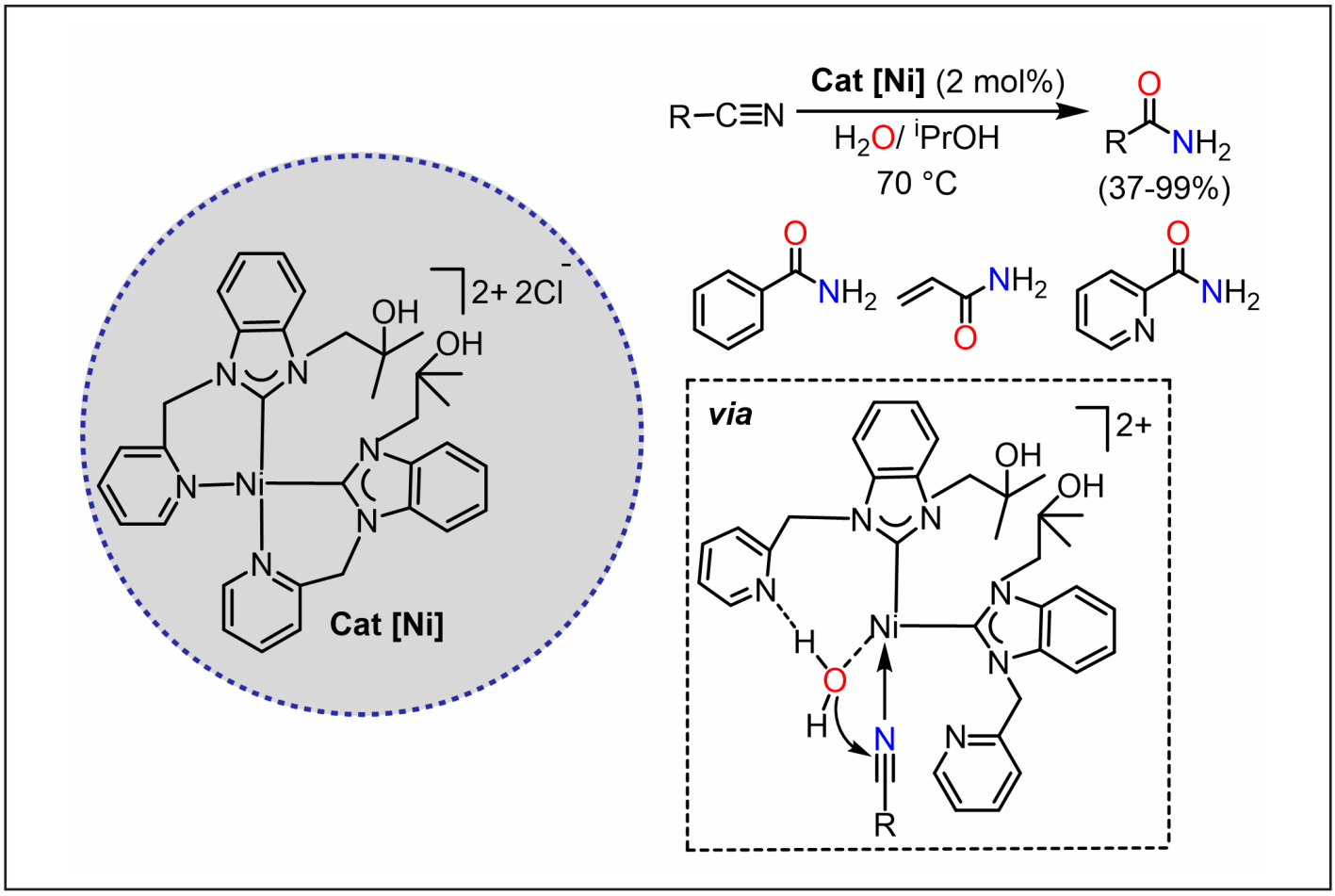
Different molecular scaffolds for protic ligands

We designed a Cp*Ir(III) protic catalyst bearing a pyridyl(benzamide)-functionalized NHC ligand, and both the protonated and deprotonated forms were isolated (**Scheme 9**).[26]. This protic complex is an excellent catalyst for the alkylation of ketones and secondary alcohols with primary alcohols. Mechanistic studies confirmed the involvement of PRU in the catalytic process. Initially, the hydrogenated form of the catalyst with a proton at PRU and hydride at Ir center is generated by the dehydrogenation of alcohol. Subsequently, both the proton and hydride are transferred to the *in-situ* generated ***α,β***-usaturated carbonyl intermediate.

Recently, we introduced a Mn(I) complex containing a proton responsive hydroxy unit on 1,8-naphthyridine-***N***-oxide scaffold that showed excellent catalytic efficacy towards



Scheme 10. Examples of catalysts exploiting NH effect (above) and application for acceptorless dehydrogenation of amines



Scheme 11. A Ni(II) catalyst for base-free hydration of nitriles to amides.

α-alkylation of ketones with primary alcohols (**Scheme 9**).[27] The reaction mechanism is similar to **Cat [Ir]** as described above and involves (de)protonation at PRU. Both **Cat [Ir]** and **Cat [Mn]** were successfully utilized for the *α*-alkylation of bioactive steroids (**Scheme 9**).

The 'NH effect'

The remarkable catalytic activity of some transition metal-based catalysts is attributed to the presence of NH group(s) in the ligand, also known as 'NH effect'.[28] The NH group is either directly coordinated to the metal center (**Scheme 10a**)[29] or remotely positioned (**Scheme 10b**)[30]. The NH/N$^-$ functionality can facilitate the catalysis by acting as a proton donor (or acceptor). This amino/amido moiety can also stabilize rate-determining transition state through non-covalent interactions.[31] A Ru(II) complex bearing a naphthyridine-functionalized pyrazole ligand was employed for catalyzing the oxidant free and acceptorless selective double dehydrogenation of primary amines to nitriles (**Scheme 10**).[30] The role of the PRU on the ligand scaffold was demonstrated by control experiments, including the use of a N-methylated pyrazole analogue. DFT calculations revealed intricate hydride and proton transfers to achieve the overall elimination of 2 equiv of H_2.

C. Ligand-promoted water activation

Use of water as a reactant for oxygenation and reduction of organic compounds has been an important objective in our group.[32-35] Towards this efforts, we reported a Ni(II) complex bearing pyridyl- and hydroxyl-functionalized NHCs and showed its catalytic activity towards the hydration of organonitriles to corresponding amides (**Scheme 11**).[36] Mechanistic investigation revealed that the hemilabile pyridyl moiety interacts with a water molecule through hydrogen bonding thereby enhancing its nucleophilicity (**Scheme 11**). Subsequently, the nucleophilic water molecule attacks the Ni(II)-bound nitrile to afford iminol intermediate which is rapidly tautomerized to corresponding amide derivatives. Based on the Hammett studies, it was concluded that nucleophilic attack of H_2O is more facile over the attack of OH^-. Further, the pK_a values show that the pyridyl unit is not adequately basic to deprotonate the H_2O molecule.

Moving Forward

A brief overview of the ligand-driven reactions using electronically asymmetric ligands and protic ligands is presented. Ligand-driven catalysis enables improved or new reactivity as compared to systems in which ligands play only a spectator role. This has led to the development of many sustainable and green catalytic processes, which are important in synthetic chemistry and establishing renewable energy resources. Ligands have also been employed for water activation at the metal. It is reasonable to assume that the scope of participating ligands will continue to widen and new strategies for ligand-driven catalysis will be developed. This article is a précis of our recent efforts on 'ligand-driven chemistry' and hope it would persuade others to join hands.

References

1. Caulton, K. G. (2012). Systematics and future projections concerning redox-noninnocent amide/imine ligands. *Eur. J. Inorg. Chem.* **2012**, 435-443.
2. Luca, O. R. and Crabtree, R. H. (2013). Redox-active ligands in catalysis. *Chem. Soc. Rev.* **42**, 1440-1459.
3. Khusnutdinova, J. R. and Milstein, D. (2015). Metal-Ligand Cooperation. *Angew. Chem. Int. Ed.* **54**, 12236-12273.
4. Grützmacher, H. (2008). Cooperating ligands in catalysis. *Angew. Chem. Int. Ed.* **47**, 1814-1818.
5. (a) Hickey, D. P., Sandford, C., Rhodes, Z., Gensch, T., Fries, L. R., Sigman, M. S. and Minteer, S. D. (2019). Investigating the role of ligand electronics on stabilizing electrocatalytically relevant low-valent Co(I) intermediates. *J. Am. Chem. Soc.* **141**, 1382-1392. (b) McCammant, M. S. and Sigman, M. S. (2015**).** Development and investigation of a site selective palladium-catalyzed 1, 4-difunctionalization of isoprene using pyridine-oxazoline ligands. *Chem. Sci.* **6**, 1355-1361.
6. McDonald, R. I., White, P. B., Weinstein, A. B., Tam, C. P. and Stahl, S. S. (2011**).** Enantioselective Pd(II)-catalyzed aerobic oxidative amidation of alkenes and insights into the role of electronic asymmetry in pyridine-oxazoline ligands. *Org. Lett.* **13**, 2830-2833.
7. Michel, B. W., Camelio, A. M., Cornell, C. N. and Sigman, M. S. (2009**).** A General and Efficient catalyst system for a Wacker-type oxidation using TBHP as the terminal oxidant: Application to classically challenging substrates. *J. Am. Chem. Soc.* **131**, 6076-6077.
8. Chai, H., Cao, Q., Dornan, L. M., Hughes, N. L., Brown, C. L., Nockemann, P., Li, J. and Muldoon, M. J. (2017**).** Cationic palladium(II) complexes for catalytic Wacker-type oxidation of styrenes to ketones using O_2 as the sole oxidant. *Eur. J. Inorg. Chem.* **2017**, 5604-5608.
9. Daw, P., Petakamsetty, R., Sarbajna, A., Laha, S., Ramapanicker, R. and Bera, J. K. (2014). A highly efficient catalyst for selective oxidative scission of olefins to aldehydes: Abnormal-NHC-Ru(II) complex in oxidation chemistry. *J. Am. Chem. Soc.* **136**, 13987-13990.
10. Saha, S., Yadav, S., Reshi, N. U. D., Dutta, I., Kunnikuruvan, S. and Bera, J. K. (2020). Electronic asymmetry of an annelated pyridyl-mesoionic carbene scaffold: application in Pd(II)-catalyzed Wacker-type oxidation of olefins. *ACS Catal.* **10**, 11385-11393.
11. Kauffman, G., Ed. (1976). Classics in Coordination Chemistry: Part 2; Dover: New York, 21-37.
12. Kuwata, S. and Ikariya, T. (2014). Metal-ligand bifunctional reactivity and catalysis of protic N-heterocyclic carbene and pyrazole complexes featuring β-NH units. *Chem. Commun.* **50**, 14290-14300.
13. Wang, L., Kanega, R., Kawanami, H. and Himeda, Y. (2017). Development of proton-responsive catalysts. *Chem. Rec.* **17**, 1071-1094.
14. Onishi, N., Iguchi, M., Yang, X., Kanega, R., Kawanami, H., Xu, Q. and Himeda, Y. (2019). Development of effective catalysts for hydrogen storage technology using formic acid. *Adv. Energy Mater.* **9**, 1801275.
15. Li, H., Gonçalves, T. P., Lupp, D. and Huang, K. W. (2019). $PN^3(P)$-Pincer complexes: Cooperative catalysis and beyond. *ACS Catal.* **9**, 1619-1629.
16. Fujita, K. (2019). Development and application of new iridium catalysts for efficient dehydrogenative reactions of organic molecules. *Bull. Chem. Soc. Jpn.* **92**, 344-351.
17. Kuwata, S. and Ikariya, T. (2011). β-Protic pyrazole and N-heterocyclic carbene complexes: Synthesis, properties, and metal-ligand cooperative bifunctional catalysis. *Chem. Eur. J.* **17**, 3542-3556.
18. Kawahara, R., Fujita, K. and Yamaguchi, R. (2012). Cooperative catalysis by iridium complexes with a bipyridonate ligand: Versatile dehydrogenative oxidation of alcohols and reversible dehydrogenation-hydrogenation between 2-propanol and acetone. *Angew. Chem. Int. Ed.* **51**, 12790-12794.
19. Wang, W.-H., Ertem, M. Z., Xu, S., Onishi, N., Manaka, Y., Suna, Y., Kambayashi, H., Muckerman, J. T., Fujita, E. and Himeda, Y. (2015). Highly robust hydrogen generation by bioinspired Ir complexes for dehydrogenation of formic acid in water: Experimental and theoretical mechanistic investigations at different pH. *ACS Catal.* **5**, 5496-5504.
20. Siek, S., Burks, D. B., Gerlach, D. L., Liang, G., Tesh, J. M., Thompson, C. R., Qu, F., Shankwitz, J. E., Vasquez, R. M., Chambers, N., Szulczewski, G. J., Grotjahn, D. B., Webster, C. E. and Papish, E. T. (2017). Iridium and ruthenium complexes of N-heterocyclic carbene- and pyridinol-derived chelates as catalysts for aqueous carbon dioxide hydrogenation and formic acid dehydrogenation: The role of the alkali metal. *Organometallics* **36**, 1091-1106.
21. Geri, J. B. and Szymczak, N. K. (2015). A proton-switchable bifunctional ruthenium complex that catalyzes nitrile hydroboration. *J. Am. Chem. Soc.* **137**, 12808-12814.
22. Maji B. and Choudhury J. (2019). Switchable hydrogenation with a betaine-derived bifunctional Ir–NHC catalyst. *Chem. Commun.* **55**, 4574-4577.
23. Zhang, J., Balaraman, E., Leitus, G. and Milstein, D. (2011). Electron-rich PNP- and PNN-type ruthenium(II) hydrido borohydride pincer complexes. synthesis, structure, and catalytic dehydrogenation of alcohols and hydrogenation of esters. *Organometallics* **30**, 5716-5724.
24. Gonçalves, T. P., Dutta, I. and Huang, K.-W. (2021). Aromaticity in catalysis: metal ligand cooperation via ligand dearomatization and rearomatization. *Chem. Commun.* **57**, 3070-3082.
25. Pandey, P., Daw, P., Reshi, N. U. D., Ehmann, K. R., Hölscher, M., Leitner, W. and Bera, J. K. (2020). A proton-responsive annulated mesoionic carbene (MIC) scaffold on Ir complex for proton/hydride shuttle: An experimental and computational investigation on reductive amination of aldehyde. *Organometallics* **39**, 3849-3863.
26. Kaur, M., Reshi, N. U. D., Patra, K., Bhattacherya, A., Kunnikuruvan, S., and Bera, J. K. (2021). A proton-responsive pyridyl(benzamide)-functionalized NHC ligand on Ir complex for alkylation of ketones and secondary alcohols. *Chem. Eur. J.* **27**, 10737-10748.
27. Patra, K., Laskar, R. A., Nath, A. and Bera, J. K. (2022). A protic Mn(I) complex based on a naphthyridine-N-oxide scaffold:Protonation/deprotonation studies and catalytic applications for alkylation of ketones. *Organometallics* **41**, 1836-1846.
28. Dub, P. A. and Gordon, J. C. (2017). Metal-ligand bifunctional catalysis: The "accepted" mechanism, the issue of concertedness, and the function of the ligand in catalytic cycles involving hydrogen atoms. *ACS Catal.* **7**, 6635-6655.
29. Noyori, R. and Hashiguchi, S. (1997). Asymmetric transfer hydrogenation catalyzed by chiral ruthenium complexes. *Acc. Chem. Res.* 30, 97-102.
30. Dutta, I., Yadav, S., Sarbajna, A., De, S., Hölscher, M., Leitner, W. and Bera, J. K. (2018). Double dehydrogenation of primary amines to nitriles by a ruthenium complex featuring pyrazole functionality. *J. Am. Chem. Soc.***140**, 8662-8666.
31. Dub, P. A. and Gordon, J. C. (2018). The role of the metal-bound N–H functionality in Noyori-type molecular catalysts. *Nat. Rev. Chem.* **2**, 396-408.
32. Ghatak, T., Sarkar, M., Dinda, S., Dutta, I., Rahaman, S. M. W. and Bera, J. K. (2015). Olefin oxygenation by water on an iridium center. *J. Am. Chem. Soc.* **137**, 6168-6171.
33. Sarbajna, A., Dutta, I., Daw, P., Dinda, S., Rahaman, S. M. W., Sarkar, A. and. Bera, J. K. (2017). Catalytic conversion of alcohols to carboxylic acid salts and hydrogen with alkaline water. *ACS Catal.* **7**, 2786-2790.
34. Daw, P., Sinha, A., Rahaman, S. M. W., Dinda, S. and Bera, J. K. (2012). Bifunctional water activation for catalytic hydration of organonitriles. *Organometallics* **31**, 3790–3797.
35. Singh, K., Pal, N. K., Guha, C. and Bera, J. K. (2019). Hydrative syntheses of amides from alkynes catalyzed by an Au(I) complex containing pyridyl-functionalized NHC ligand. *J. Organomet. Chem.* **886**, 1-8.
36. Singh, K., Sarbajna, A., Dutta, I., Pandey, P. and Bera, J. K. (2017). Hemilability-driven water activation: A Ni^{II} catalyst for base-free hydration of nitriles to amides. *Chem. Eur. J.* **23**, 7761-7771.