

University of Texas Rio Grande Valley

ScholarWorks @ UTRGV

---

Chemistry Faculty Publications and  
Presentations

College of Sciences

---

12-30-2022

## Cooperative heterometallic platforms enabling selective C–H bond activation and functionalization of pyridines

Manar M. Shoshani

*The University of Texas Rio Grande Valley*

Follow this and additional works at: [https://scholarworks.utrgv.edu/chem\\_fac](https://scholarworks.utrgv.edu/chem_fac)

 Part of the [Chemistry Commons](#)

---

### Recommended Citation

Shoshani, Manar M. "Cooperative Heterometallic Platforms Enabling Selective C–H Bond Activation and Functionalization of Pyridines." *Cell Reports Physical Science*, Dec. 2022, p. 101213. ScienceDirect, <https://doi.org/10.1016/j.xcrp.2022.101213>.

This Article is brought to you for free and open access by the College of Sciences at ScholarWorks @ UTRGV. It has been accepted for inclusion in Chemistry Faculty Publications and Presentations by an authorized administrator of ScholarWorks @ UTRGV. For more information, please contact [justin.white@utrgv.edu](mailto:justin.white@utrgv.edu), [william.flores01@utrgv.edu](mailto:william.flores01@utrgv.edu).

## Perspective

# Cooperative heterometallic platforms enabling selective C–H bond activation and functionalization of pyridines

Manar M. Shoshani<sup>1,\*</sup>

## SUMMARY

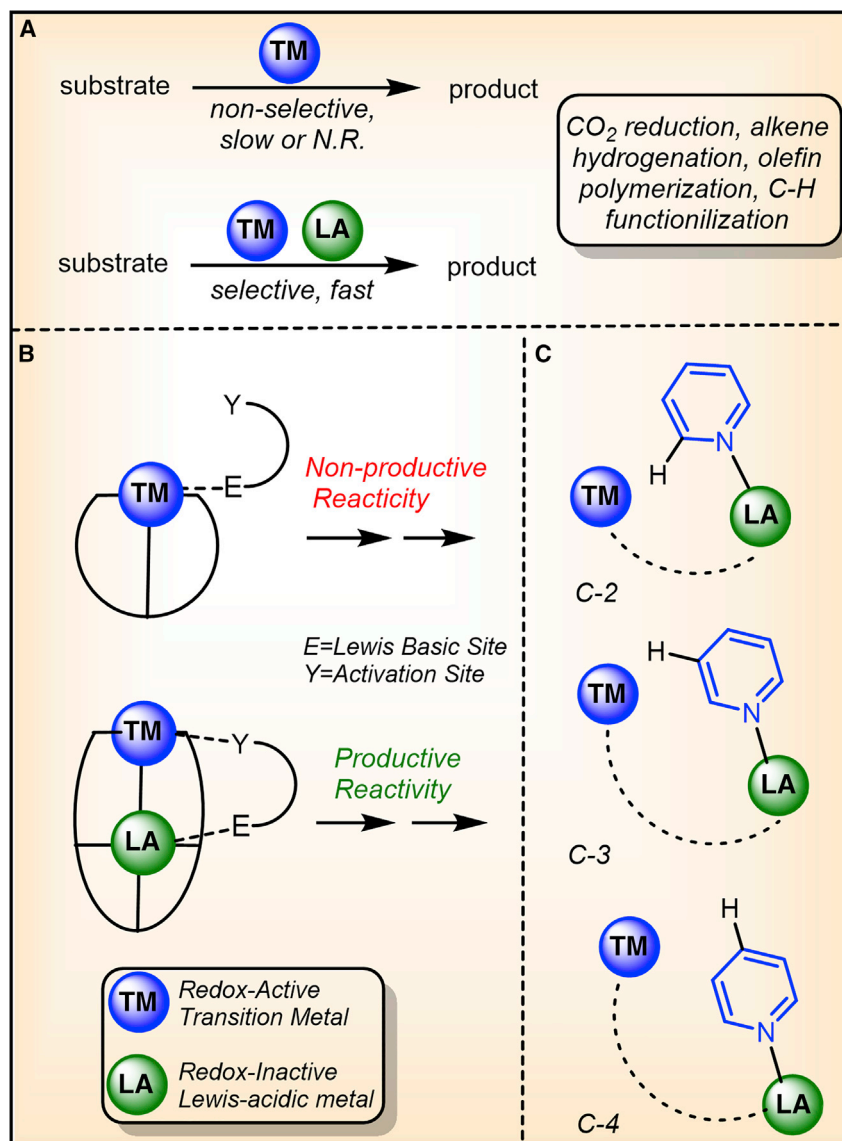
The development of methodologies for regioselective C–H functionalization of *N*-heterocycles has seen sustained growth over the last two decades. Cooperative reactivity stemming from the addition of Lewis-acidic metals to late-transition-metal complexes has enabled regioselective catalytic transformations. Progress in the design of ligands and Lewis-acidic metal precursors has led to development of *in situ* cooperative catalysts able to facilitate C–H functionalization of pyridine at C-2, C-3, and C-4 positions. Very recently, focused efforts toward well-defined heterometallic complexes facilitating C–H bond catalysis have been targeted. Transformations showcasing regioselective C-2 transformations have been achieved. This perspective examines select examples delineating the evolution of strategies to better facilitate cooperative reactivity between Lewis-acidic metals and late transition metals in regioselective C–H functionalization. Potential pathways to further evolve methods to access modular regiodivergence in pyridine C–H bond catalysis will be discussed.

## INTRODUCTION

Selective C–H activation and functionalization of *N*-heterocycles, such as pyridines, have garnered significant attention due to the prevalence of *N*-heterocyclic cores in biomolecular targets.<sup>1</sup> The azine family, specifically, are essential molecular motifs as one of the most heavily used classes of heterocycles in the pharmaceutical and agricultural industries.<sup>2,3</sup> Correspondingly, synthetic methodologies for the selective activation and functionalization of C–H bonds on pyridines have been popularized to bolster the atom-economic development of target species bearing a pyridine core.<sup>4</sup> Synthetic challenges have often precluded efficient transformations of the electron-deficient pyridine, including deactivation pathways as a result of the strong binding nature of the Lewis-basic *N*-atom of pyridine to transition metals. Various strategies to circumvent these challenges have been introduced including auxiliary directing groups<sup>5</sup> or sequestering the Lewis basicity of pyridine by forming pyridine *N*-oxides,<sup>6</sup> functionalizing these substrates, and subsequently deprotecting. Identifying efficient pathways to avoid the protection and deprotection steps presents a potentially step-economical process. Progress in the field has been achieved with select mononuclear transition-metal catalysts capable of C-2 functionalization of pyridines and pyridine derivatives.<sup>7–9</sup> More recently, selective C-2 borylation of a series of heterocycles, including pyridines, by tridentate Co PNP complexes, have been developed that display a wide substrate scope.<sup>10</sup> Furthermore, strong nucleophiles can react with pyridines at the C-2 position selectively to introduce a C-2 substituent.<sup>11</sup> Hence, identifying catalysts that expand upon C-2 selectivity has been of particular interest.

<sup>1</sup>Department of Chemistry, University of Texas Rio Grande Valley, Brownsville, TX 78520, USA

\*Correspondence: [manar.shoshani@utrgv.edu](mailto:manar.shoshani@utrgv.edu)  
<https://doi.org/10.1016/j.xcrp.2022.101213>



**Figure 1. Cooperativity between transition metals (TMs) and Lewis acids (LAs)**

(A) LA metal enhancement in catalysis.

(B) Productive reactivity by incorporating LA metals.

(C) Selectivity in C–H activation of pyridine by TM/LA complexes

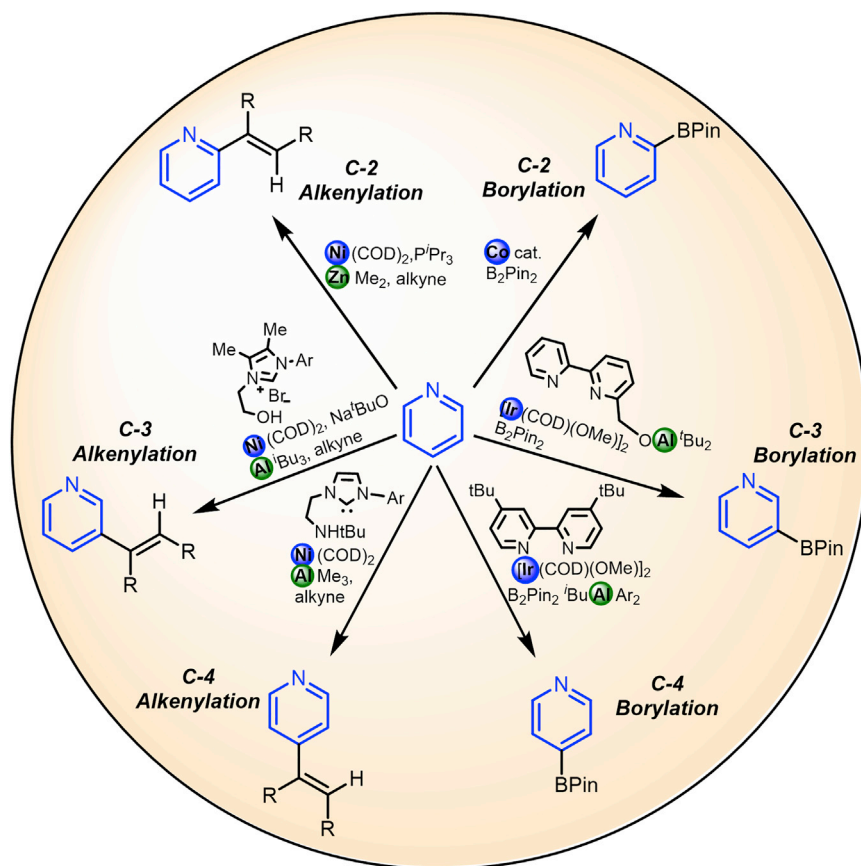
A wide array of literature showcases the substantial role that Lewis-acidic additives have played in enhancing and enabling reactivity. Transformations that have benefited from the addition of Lewis-acidic metals to transition-metal catalysts include CO<sub>2</sub> reduction,<sup>12,13</sup> C–H functionalization,<sup>14</sup> ethylene polymerization,<sup>15,16</sup> alk(yne/ene) hydrogenation,<sup>17,18</sup> and ethylene-CO<sub>2</sub> coupling,<sup>19,20</sup> among others (Figure 1A).<sup>21</sup> In addition to enabling or accelerating reactivity,<sup>22</sup> incorporation of Lewis-acidic metals has also demonstrated sharp changes in selectivity in catalytic transformation.<sup>23,24</sup> Given the role that Lewis-acidic metals play in catalytic activity, there have been focused efforts to design well-defined heterometallic species housing Lewis-acidic metals and redox-active base metals in a single, multidentate ligand scaffold.<sup>25–28</sup> Often, these ligands are designed to ligate base metals to strong neutral sigma donor such as phosphines or carbenes and ligate Lewis-acidic metals

such as Al, Y, Sc, and La to mono-, di-, or tri-anionic counterparts. It should be noted that boron has been often invoked in a series of cooperative transformations, and installing borane and boryl moieties in ligand scaffolds has also served as a promising strategy in bond activation.<sup>29–31</sup> For a recent perspective on boron in the secondary coordination sphere of transition-metal complexes, see the report by Drover et al.<sup>32</sup>

Generally, Lewis-acidic metals participate in cooperative reactivity by attenuating the electronic parameter of the redox-active metals; however, redox-active and Lewis-acidic metals may also cooperatively bind and/or cleave a bond of a substrate. The latter approach is a strategy increasingly invoked in the past two decades to facilitate the C–H activation and functionalization of substituted aromatics, as well as pyridines (Figure 1B).<sup>33</sup> Lewis-acidic metals have documented abilities in the enhancement of performance parameters in elementary steps of activation, including oxidative addition,<sup>34</sup> as well as reductive elimination.<sup>35</sup> In addition to the stoichiometric enhancement that Lewis acids impart, they also bear crucial roles in catalysis.<sup>14</sup> *In-situ*-generated or single-component heterometallic complexes cooperatively catalyze C–H functionalization of pyridines by the Lewis-acidic metal center serving as a “sacrificial” coordination site to the Lewis-basic N-atom (Figure 1B). This strategy, however, extends past enhancing the catalytic activity; the Lewis-acidic metal often directs intramolecular pyridine activation and functionalization, thus introducing high regioselectivity. Through this strategy, several reports incorporating late-transition metals and Lewis-acidic metals have tackled site-selective C–H activation and functionalization.<sup>33</sup> For a review on the broad utilization of secondary sphere and outer sphere interactions to achieve site selectivity in C–H functionalization, see the report by Yu et al.<sup>36</sup> This perspective focuses on select and recent examples of *in-situ*-generated and well-defined heterometallic species consisting of a redox-active metal and a redox-inactive Lewis-acidic metal, demonstrating regiodivergent methodologies to access selective and efficient C-2, C-3, and C-4 C–H bond activation and functionalization (Figure 1C).

### Recent progress for *in-situ*-generated transition metal (TM)/Lewis acid (LA) metal catalysts

Among some of the first examples, Nakao and co-workers demonstrated that simple Ni(0) precursors and triisopropylphosphine with trialkyl aluminum-based additives led to regioselective *ortho* (C-2) dialkenylation under mild conditions (50°C, 24 h).<sup>37</sup> They also showed that dialkyl zinc agents can serve as the LA to impart regioselectivity and, specifically, form the monoalkenylated product (Figure 2, top left). The Lewis-acidic Al and Zn centers are proposed to coordinate to pyridine, directing the catalytic C-2 functionalization. The role and the nature of the LA in the catalyst performance was interrogated; no reactivity was observed in the absence of LAs, and Lewis-acidic chloride-based additives showed complete catalyst deactivation. Separately, Chatani and co-workers demonstrated that similar catalyst combinations (Ni(COD)<sub>2</sub> and PCy<sub>3</sub>) in the presence of aryl zinc reagents led to regioselective C-2 arylation of a variety of *N*-heterocycles.<sup>38</sup> Further studies showcasing advances in C-2 functionalization using Ni-LA combinations have since been reported.<sup>39</sup> While impressive, C-2 C–H activation is achievable through isolated mononuclear TM complexes without the presence of a LA *vide supra*. For example, Chirik et al., among others, have demonstrated that well-defined mononuclear complexes are able to facilitate regioselective C–H borylation with a series of heterocycles including pyridines, thiophenes, and furans and have garnered a thorough mechanistic understanding (Figure 2, top right).<sup>10,40</sup> Though the initial Nakao report did not provide novel regioselectivity, the strategy for regiodivergence



**Figure 2.** Select examples of regioselective C-2, C-3, and C-4 C–H functionalization by TM and TM/Lewis-acidic metal catalysts

through the incorporation of Lewis-acidic metals provided a blueprint to future successes that are expanded upon below.

Para-selective (C-4) C–H functionalization of pyridine has also been developed by several groups, with the Ong group providing the initial report followed very shortly by the Nakao group, both using Ni/Al systems with NHC carbene ligands. The Nakao group report proposed that steric exclusion of C-2 and C-3 activation was at play when using bulky NHC ligands as well as bulky Lewis-acidic Al additives, which coordinate to Lewis-basic nitrogen, rendering the process C-4 selective for C–H alkylation.<sup>41</sup> The substrate scope reported good functional group tolerance with functionalities distant from the pyridine core, and the transformation required elevated temperatures (130°C) to proceed. The Ong group developed a different approach by invoking NHC ligands with a flanking amino arm proposed to coordinate to the Lewis-acidic Al center from the Al-based additives (Figure 2, bottom left).<sup>42</sup> Through this strategy, regioselective C-4 C–H bond alkylation of pyridines was achieved in the presence of  $\text{AlMe}_3$  and under fairly mild conditions (80°C, 16 h). Interestingly, for various substituted pyridines, competing C-3 functionalization is also observed. A crystal structure of an intermediate was obtained and features a precatalyst to activation; a trigonal Ni complex bound to two NHC ligands and bound  $\eta^2$  to the C-3–C-4 bond of a pyridine– $\text{AlMe}_3$  Lewis acid/Lewis base pair. The isolated complex is capable of stoichiometric and catalytic C–H alkylation and offered ample proof of concept to the base

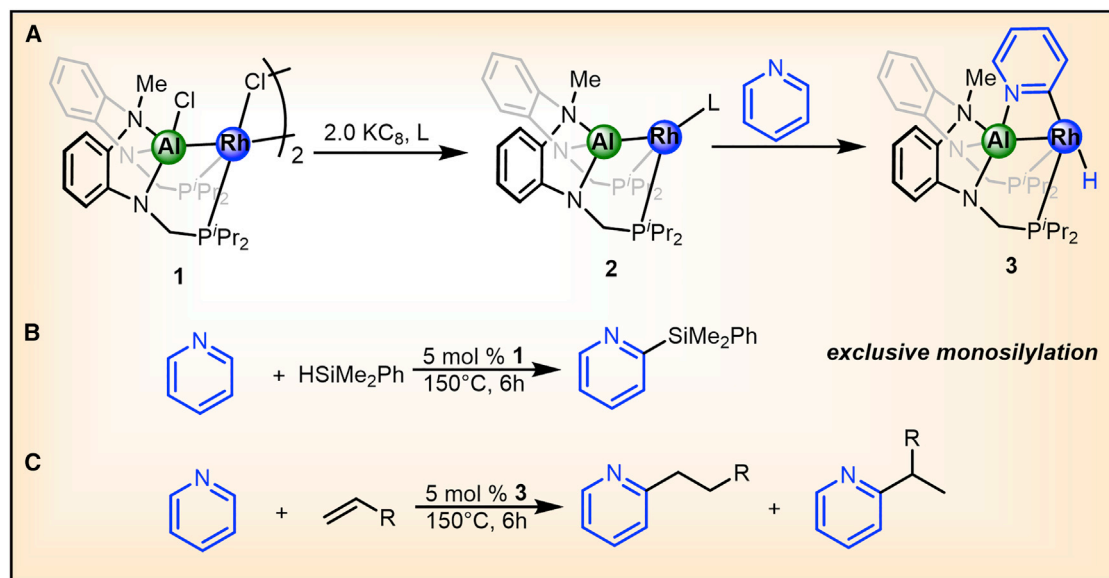
metal/LA hypothesis for regioselective C–H activation. This pivotal result uncovered direct evidence, from the solid state, of the successful implementation of the bimetallic strategy harnessing cooperativity between TMs and LA metal in regioselective C–H activation. C-4-selective activation of both pyridines and benzamides through Nakao's LA-assisted size-exclusion hypothesis was extended to Ir/LA complexes through C–H borylation. The catalyst mixture included Ir precursor, bipyridine ligands, and various LAs, including bulky Al-based LAs (Figure 2, bottom right).<sup>43</sup> The report outlines a fairly wide substrate scope with moderate to high yield, and catalysis is carried out at room temperature. The reports here outlined that using a combination of bulky ligands and/or precatalysts, or installing flanking arms for LA coordination, disfavors the more precedented C-2 bond activation. Further examples featuring a TM and an LA to achieve C-4 C–H functionalization of pyridines have also been reported.<sup>44,45</sup>

Meta-selective (C-3) C–H bond activation and functionalization has remained a long-standing challenge with very limited examples in pyridine C–H functionalization. Nakao et al. recently developed a system combining Ir and Lewis-acidic metals, this time to facilitate the C-3 C–H borylation of pyridines and benzamides.<sup>46</sup> The strategy extended upon earlier work with C-4 activation by modifying the ligands to introduce flanking sites to coordinate LAs on the substituted bipyridine ligands. Mono- and bisphenolic units were introduced at the 2 positions of the bipyridine ligands and was shown to drive selectivity toward C-3 borylation. More specifically, an alkoxy ditertbutyl aluminum moiety at the 2 position of bipyridine was used (Figure 2, middle right), and C-3 borylation was achieved under mild conditions (30°C, 18 h). Notably, competing C-4 C–H borylation was also observed with a survey of Al additives used in this study. A recent breakthrough in the field was reported that used Ni precatalysts with carbenes bearing flanking alkoxy subunits.<sup>47</sup> Using simple Lewis-acidic sources such as Al<sup>i</sup>Bu<sub>3</sub>, along with alkoxy-substituted carbene ligands and Ni(COD)<sub>2</sub>, near-exclusive C-3 C–H alkenylation is achieved with a wide survey of sterically and electronically differentiating pyridines and under relatively mild conditions (80°C for 0.5 h) (Figure 2, middle left). Stoichiometric studies conducted showcase complexation of the Al centers to the alkoxy fragment and to pyridine substrate.

Cumulatively, these results demonstrate that Lewis-acidic complexes can introduce regiodivergent properties and can toggle the selectivity in differing catalytic systems. Slight changes in the ligands used impart drastic changes in selectivity.

### Well-defined TM/LA metal platforms facilitating C–H activation

As highlighted above, there has been substantial efforts in identifying catalysts to impart differing selectivities in pyridine moieties. The ill-defined nature can limit the degree of mechanistic insight on potential active species in catalysis. For example, C–C-bond-forming reactions have been hypothesized, and later experimentally supported, to be facilitated by *in-situ*-generated multimetallic complexes capable of cooperative bond cleavages.<sup>48,49</sup> This is done despite using mononuclear Ni or Fe sources and presents as a motivation to use well-defined heterometallic complexes as catalysts for pyridine C–H activation and functionalization. Additionally, alkyl aluminums are able to result in oxidation state changes of redox-active metals, so one can imagine that the role of the Al centers may be multifaceted under certain conditions. Isolating structures of intermediates and undertaking stoichiometric and catalytic studies offer the opportunity to gain a more thorough mechanistic picture and ultimately better optimize catalysts, not only to impart exclusive regioselectivity but also to efficiently use Earth-abundant metals.

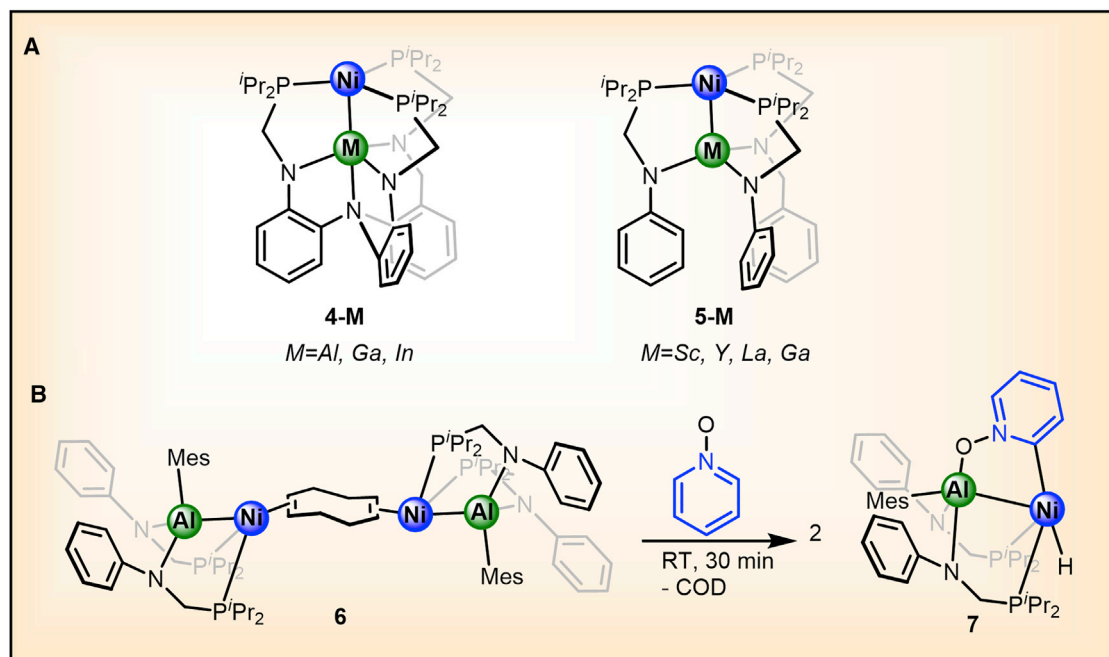


**Figure 3. Rh-Al well-defined catalyst for C–H functionalization**

- (A) Heterobimetallic Rh–Al complexes 1–3.  
 (B) Catalytic pyridine silylation by complex 1.  
 (C) C2-monoalkylation by complex 3 (L = norbornadiene).

Though this perspective focuses on Lewis-acidic metals, it is important to note that boron has been utilized in well-defined species including examples aiding in pyridine C–H bond activation. Ozerov et al. outlined an elegant method to impart C-2 selectivity of a pyridine unit with a Ir-boryl complex.<sup>50</sup> Though the system lacked catalytic activity, the stoichiometric activation outlined a method to gain crucial mechanistic insight for selective C–H activation and functionalization.

The Nakao group has reported a well-defined Rh–Al complex on a site-differentiated multidentate ligand scaffold.<sup>51</sup> Rhodium is bound to diarylalkylphosphine moieties, while Al is bound to two anilides and an amine unit (Figure 3A). The initial report showcased multiple species with both the Al center as a Z-type ligand (complex 1) and X-type alumanyl ligand (complex 2) to the Rh species. A Rh-alumanyl complex is also implicated as an intermediate in catalysis for C–H silylation.<sup>52</sup> Heterometallic complex 1 is used as a catalyst for C–H silylation of pyridine derivatives (Figure 3B) and shows an impressive scope, including sterically and electronically differentiating pyridines. Furthermore, 1 was interrogated in late-stage functionalization and showed selective C-2 silylation in good yield. The well-defined nature of the heterometallic complex 2 was utilized for the isolation of intermediates of C–H bond activation, forming complex 3. A crystal structure of 3 was isolated and shows that C-2 C–H bond activation is observed with the activated pyridine bridging between the Rh and Al center. The Al coordinating to the Lewis-basic N-atom and the Rh center bound to the aryl C-2 carbon and the resultant hydride. To examine a direct complex of C–H activation in catalysis, complex 3 was successfully used under catalytic conditions for the C-2 alkylation of pyridine (Figure 3C). These works showcased an impressive transformation by entirely well-defined species. Toward moving in the direction of sustainable catalytic transformations, identifying catalysts composed of more Earth-abundant catalysts serve as a potential promising advancement.



**Figure 4. Well-defined Ni-LA complexes and potential for C–H functionalization**

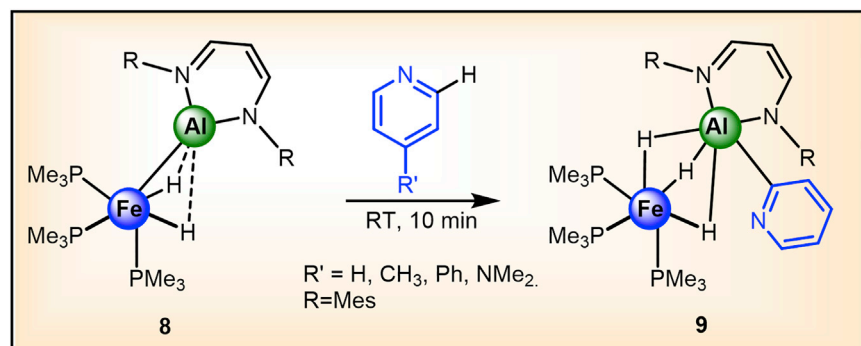
(A) Heterometallic Ni-Lewis-acidic complexes with Z-type ligand donation.

(B) Cooperative C-2 activation of pyridine N-oxide by heterobimetallic Ni-alane complex 6

The Lu group have been major contributors to the studies of well-defined TM/Lewis-acidic metals. They have designed heterometallic motifs consisting primarily of Lewis-acidic metals bound to a tris(amide) site and base metal bound to a trisphosphine site (Figure 4A, complexes 4-M and 5-M).<sup>17,18,53</sup> More recently, they expanded upon their studies, which include reactivity and electronic structure, to more sterically accessible redox-active and redox-inactive metals (Figure 4B). Specifically, they developed a site-differentiated ligand scaffold housing Ni at a bistralkylphosphine site and Al at a bis(amide)/amine site, leaving a mesityl group bound to the Al, complex 6.<sup>54</sup> Remarkably, complex 6 displays cooperative aryl group transfer of the mesityl group in the presence of donors such as THF. A series of reactivity studies were reported for this system, including C-2-selective C–H activation of pyridine N-oxide. The resultant product was isolated and, similar to Nakao's example, features the Lewis-basic atom bound to the Al center and the Ni center bound to the activated aryl moiety and resultant hydride ligand (complex 7). The intramolecular C–H activation represents a crucial advancement in using Earth-abundant metal centers to generate well-defined heterometallic species capable of regioselective C–H bond activation, especially ones often invoked in regioselective *in situ* catalytic transformations. Importantly, the Lu group reports that free pyridine binds  $\kappa$ -N to the Ni center of 6 rather than the Al center. Identifying pathways to extend these transformations to unactivated pyridines and observing catalytic turnovers are needed.

Very recently, the Crimin group reported a novel Fe-Al system (8) surprisingly capable of facile C–H activation of pyridine.<sup>55</sup> The system is unlike the previous two as complex 8 employs primarily monodentate donors on the redox-active metal such as trialkyl phosphines and is only bridged to the Al center via hydride ligands rather than through a multidentate ligand scaffold. Bond metrics and density





**Figure 5. Heterobimetallic C-2 activation by Fe-aluminylene complex 8**

functional theory (DFT) studies of the system suggest an aluminylene-type interaction to the iron center and that the Al is ligated by a  $\beta$ -diketiminato ligand. Complex 8 facilitates the C-2-selective C–H bond activation under remarkably mild conditions (room temperature [RT], 10 min). The scope of C–H bond activation is explored with varying substituents at the C-4 positions and bears surprising functional group tolerance given the wide array of reactivity reported with these and related systems. The pyridine C–H bond activation is one of the latest of impressive bond activations through cooperative heterometallic systems reported by Crimmin.<sup>56–58</sup> Importantly, this result is also unique as it uses a coordinatively saturated Fe center, and the resultant product features the aryl group bound exclusively to the Al center and the H-atom as a bridging hydride between the Fe and Al centers (Figure 5, complex 9). The reactivity is proposed to proceed through a novel cooperative mechanism in which a reductive deprotonation of the C–H bond is proposed as a key elementary step rather than the oxidative addition/reductive elimination pathway proposed for the examples above. Exploration into alkyl pyridines substituted at the C-2 and C-3 positions display more diverse metal-ligand cooperativity, including more facile addition of the activated pyridine moiety to the  $\beta$ -diketiminato ligand.<sup>59</sup> Identifying systems with robust and predictable activation pathways for a wide substrate scope of pyridines are needed for the development of the next generation of well-defined heterometallic catalysts for C–H functionalization.

## Conclusions

In summary, the past 10–15 years have demonstrated that incorporating Lewis-acidic metals in TM complexes has served as a transformational advancement for regioselective catalytic functionalization of heterocycles. Initial *in situ* methods showcased that adding simple Lewis-acidic metal precursors to spectator sigma donating ligands and redox-active metal precursors enables reactivity with high regioselectivity. Expanding on these results and applying a size-exclusion principle, regioselective C-4 transformations were observed with both Ni/Al and Ir/Al systems. Incorporating flanking anionic binding sites in the ancillary ligands helped to bridge the gap between ill-defined and well-defined systems, especially with reports providing structures of intermediates. These variants have allowed for the further advancement of C-4- as well as C-3-selective alkenylations and borylation.

Well-defined heterometallic complexes able to facilitate regioselective C–H functionalization are a highly encouraging route due to the potential of garnering substantial insight through deconvoluted studies of mechanism and lead to a more rational design of the next generation of catalysts. Regioselective C–H functionalization by well-defined heterometallics is still an emerging field with only a

handful of examples showcasing cooperative C–H activation and/or functionalization. Furthermore, only one class of well-defined heterometallic examples display catalytic activity toward C–H functionalization of pyridine, with all examples observing exclusive C-2 selectivity. The lack of suitable examples in C–H activation of heterocycles by well-defined complexes is, in part, a result of the limited number of single-component complexes featuring TMs and LAs. Synthetic methods for heterometallic complexes often rely on self-assembly of metal cations in multidentate ligand scaffolds; challenges in predictable and selective binding along with the propensity to form oligomeric species often complicate successful synthesis of target multimetallic species. In this vein, a successful strategy to circumvent some of these challenges has been to (1) design ligand scaffolds with site-differentiated binding sites and (2) saturate the metals' coordination sphere; however, a prerequisite of the hypothesis discussed *vide infra* is the successful binding of Lewis-basic N to the Lewis-acidic metals. Though the use of well-defined heterometallic complexes in C–H activation is still in its infancy, their continued study and development will inspire future catalyst design.

Several strategies in the advancements mentioned in this perspective show substantial potential for further growth. In the realm of *in-situ*-generated catalysts, a potential advancement may stem from the design of ligands with flanking donors to incorporate binding sites that allow for the modular implementation of Lewis-acidic metals, extending past Al and Zn, such as Mg, Y, La, and others. For well-defined species, one of the major continued challenges is striking the balance of steric accessibility of the Lewis-acidic metal while also preventing decomposition often generated by the lack of donors surrounding the LA. Only very recently have frameworks been developed that rationally house metal-alumanyl and metal-alane adducts with open coordination sites.<sup>60</sup> Continued development of well-defined heterometallic complexes may soon expand upon the number of species suitable for catalytic and regioselective C–H functionalization. For both *in situ* and well-defined systems, identifying pathways to access explicit regiodivergence in a single framework by modulating the LA presents a potential transformational innovation.

## ACKNOWLEDGMENTS

M.M.S. acknowledges the University of Texas Rio Grande Valley and the UT Science and Technology Acquisition and Retention Program (903-1162) and the Welch Foundation Departmental grant BX-0048.

## DECLARATION OF INTERESTS

The author declares no competing interests.

## REFERENCES

1. Basu, D., Kumar, S., Bandichhor, R., and Bandichhor, R. (2018). Transition metal catalyzed CH activation for the synthesis of medicinally relevant molecules: a Review. *J. Chem. Sci.* 130, 71–111.
2. Vitaku, E., Smith, D.T., and Njardarson, J.T. (2014). Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: miniperspective. *J. Med. Chem.* 57, 10257–10274.
3. Lamberth, C. (2013). Heterocyclic chemistry in crop protection. *Pest Manag. Sci.* 69, 1106–1114.
4. Kakiuchi, F., and Chatani, N. (2003). Catalytic methods for C–H bond functionalization: application in organic synthesis. *Adv. Synth. Catal.* 345, 1077–1101.
5. Grigg, R., and Savic, V. (1997). Transition metal catalyzed alkylation of pyridines and indoles. *Tetrahedron Lett.* 38, 5737–5740.
6. Campeau, L.-C., Rousseaux, S., and Fagnou, K. (2005). A solution to the 2-pyridyl organometallic cross-coupling problem: regioselective catalytic direct arylation of pyridine N-oxides. *J. Am. Chem. Soc.* 127, 18020–18021.
7. Berman, A.M., Lewis, J.C., Bergman, R.G., and Ellman, J.A. (2008). Rh (I)-catalyzed direct arylation of pyridines and quinolines. *J. Am. Chem. Soc.* 130, 14926–14927.
8. Li, M., and Hua, R. (2009). Gold (I)-catalyzed direct C–H arylation of pyrazine and pyridine with aryl bromides. *Tetrahedron Lett.* 50, 1478–1481.
9. Wen, J., Qin, S., Ma, L.-F., Dong, L., Zhang, J., Liu, S.-S., Duan, Y.-S., Chen, S.-Y., Hu, C.-W., and Yu, X.-Q. (2010). Iron-Mediated direct Suzuki–Miyaura reaction: a new method for the ortho-arylation of pyrrole and pyridine. *Org. Lett.* 12, 2694–2697.

10. Obligacion, J.V., Semproni, S.P., and Chirik, P.J. (2014). Cobalt-catalyzed C–H borylation. *J. Am. Chem. Soc.* *136*, 4133–4136.
11. Joule, J.A., Mills, K., and Smith, G.F. (2020). *Heterocyclic Chemistry* (CRC Press).
12. Hong, D., Kawanishi, T., Tsukakoshi, Y., Kotani, H., Ishizuka, T., and Kojima, T. (2019). Efficient photocatalytic CO<sub>2</sub> reduction by a Ni (II) complex having pyridine pendants through capturing a Mg<sup>2+</sup> ion as a Lewis-acid cocatalyst. *J. Am. Chem. Soc.* *141*, 20309–20317.
13. Krogman, J.P., Foxman, B.M., and Thomas, C.M. (2011). Activation of CO<sub>2</sub> by a heterobimetallic Zr/Co complex. *J. Am. Chem. Soc.* *133*, 14582–14585.
14. Guan, W., Zeng, G., Kameo, H., Nakao, Y., and Sakai, S. (2016). Cooperative catalysis of combined systems of transition-metal complexes with Lewis acids: theoretical understanding. *Chem. Rec.* *16*, 2405–2425.
15. Cai, Z., Xiao, D., and Do, L.H. (2015). Fine-tuning nickel phenoxyimine olefin polymerization catalysts: performance boosting by alkali cations. *J. Am. Chem. Soc.* *137*, 15501–15510.
16. Smith, A.J., Kalkman, E.D., Gilbert, Z.W., and Tonks, I.A. (2016). ZnCl<sub>2</sub> capture promotes ethylene polymerization by a salicylaldiminato Ni complex bearing a pendent 2',2'-bipyridine group. *Organometallics* *35*, 2429–2432.
17. Ramirez, B.L., and Lu, C.C. (2020). Rare-earth supported nickel catalysts for alkyne semihydrogenation: chemo- and regioselectivity impacted by the Lewis acidity and size of the support. *J. Am. Chem. Soc.* *142*, 5396–5407.
18. Cammarota, R.C., and Lu, C.C. (2015). Tuning nickel with Lewis acidic group 13 metalloligands for catalytic olefin hydrogenation. *J. Am. Chem. Soc.* *137*, 12486–12489.
19. Jin, D., Williard, P.G., Hazari, N., and Bernskoetter, W.H. (2014). Effect of sodium cation on metallacycle β-hydride elimination in CO<sub>2</sub>–ethylene coupling to acrylates. *Chemistry* *20*, 3205–3211.
20. Jin, D., Schmeier, T.J., Williard, P.G., Hazari, N., and Bernskoetter, W.H. (2013). Lewis acid induced β-elimination from a nickelalactone: efforts toward acrylate production from CO<sub>2</sub> and ethylene. *Organometallics* *32*, 2152–2159.
21. Fontaine, F.-G., and Zargarian, D. (2004). Me<sub>2</sub>AlCH<sub>2</sub>PMe<sub>2</sub>: a new, bifunctional cocatalyst for the Ni (II)-catalyzed oligomerization of PhSiH<sub>3</sub>. *J. Am. Chem. Soc.* *126*, 8786–8794.
22. Gregor, L.C., Grajeda, J., Kita, M.R., White, P.S., Vetter, A.J., and Miller, A.J.M. (2016). Modulating the elementary steps of methanol carbonylation by bridging the primary and secondary coordination spheres. *Organometallics* *35*, 3074–3086.
23. Camp, A.M., Kita, M.R., Blackburn, P.T., Dodge, H.M., Chen, C.-H., and Miller, A.J.M. (2021). Selecting double bond positions with a single cation-responsive iridium olefin isomerization catalyst. *J. Am. Chem. Soc.* *143*, 2792–2800.
24. Tahmouresilerd, B., Xiao, D., and Do, L.H. (2021). Rigidifying cation-tunable nickel catalysts increases activity and polar monomer incorporation in ethylene and methyl acrylate copolymerization. *Inorg. Chem.* *60*, 19035–19043.
25. Wang, Q., Brooks, S.H., Liu, T., and Tomson, N.C. (2021). Tuning metal–metal interactions for cooperative small molecule activation. *Chem. Commun.* *57*, 2839–2853.
26. Takaya, J., and Iwasawa, N. (2017). Synthesis, structure, and catalysis of palladium complexes bearing a group 13 metalloligand: remarkable effect of an aluminum-metalloligand in hydrosilylation of CO<sub>2</sub>. *J. Am. Chem. Soc.* *139*, 6074–6077.
27. Lai, Q., Cosio, M.N., and Ozerov, O.V. (2020). Ni complexes of an alane/tris (phosphine) ligand built around a strongly Lewis acidic tris (N-pyrrolyl) aluminum. *Chem. Commun.* *56*, 14845–14848.
28. Morisako, S., Watanabe, S., Ikemoto, S., Muratsugu, S., Tada, M., and Yamashita, M. (2019). Synthesis of A Pincer-IrIV complex with A base-free alumanyl ligand and its application toward the dehydrogenation of alkanes. *Angew. Chem., Int. Ed. Engl.* *58*, 15031–15035.
29. Lin, T.-P., and Peters, J.C. (2013). Boryl-mediated reversible H<sub>2</sub> activation at cobalt: catalytic hydrogenation, dehydrogenation, and transfer hydrogenation. *J. Am. Chem. Soc.* *135*, 15310–15313.
30. Zurakowski, J.A., Bhattacharyya, M., Spasyuk, D.M., and Drover, M.W. (2020). Octaboraneyl [Ni (H)(diphosphine) 2]<sup>+</sup> complexes: exploiting phosphine ligand lability for hydride transfer to an [NAD]<sup>+</sup> model. *Inorg. Chem.* *60*, 37–41.
31. Emslie, D.J.H., Blackwell, J.M., Britten, J.F., and Harrington, L.E. (2006). A zwitterionic palladium (II) η<sup>3</sup>-boratoxyphenyladienyl complex: cooperative activation of dibenzylideneacetone between palladium and a phosphine/thioether/borane ligand. *Organometallics* *25*, 2412–2414.
32. Zurakowski, J.A., Austen, B.J., and Drover, M.W. (2022). Exterior decorating: Lewis acid secondary coordination spheres for cooperative reactivity. *Trends in Chemistry* *4*, 331–346.
33. Luan, Y.-X., and Ye, M. (2022). Ligand-ligated Ni–Al bimetallic catalysis for C–H and C–C bond activation. *Chem. Commun.* *58*, 12260–12273.
34. Ghosh, I., and Jacobi, P.A. (2002). Lewis acid-promoted oxidative addition of thioimides to Pd (0). *J. Org. Chem.* *67*, 9304–9309.
35. Shen, Q., and Hartwig, J.F. (2007). Lewis acid acceleration of C–N bond-forming reductive elimination from heteroaryl palladium complexes and catalytic amidation of heteroaryl bromides. *J. Am. Chem. Soc.* *129*, 7734–7735.
36. Meng, G., Lam, N.Y.S., Lucas, E.L., Saint-Denis, T.G., Verma, P., Chekshin, N., and Yu, J.-Q. (2020). Achieving site-selectivity for C–H activation processes based on distance and geometry: a carpenter's approach. *J. Am. Chem. Soc.* *142*, 10571–10591.
37. Nakao, Y., Kanyiva, K.S., and Hiyama, T. (2008). A strategy for C–H activation of pyridines: direct C-2 selective alkenylation of pyridines by Nickel/Lewis Acid catalysis. *J. Am. Chem. Soc.* *130*, 2448–2449.
38. Tobisu, M., Hyodo, I., and Chatani, N. (2009). Nickel-Catalyzed reaction of arylzinc reagents with N-aromatic heterocycles: a straightforward approach to C–H bond arylation of electron-deficient heteroaromatic compounds. *J. Am. Chem. Soc.* *131*, 12070–12071.
39. Li, J.-F., Pan, D., Wang, H.-R., Zhang, T., Li, Y., Huang, G., and Ye, M. (2022). Enantioselective C2–H alkylation of pyridines with 1, 3-dienes via Ni–Al bimetallic catalysis. *J. Am. Chem. Soc.* *144*, 18810–18816. <https://doi.org/10.1021/jacs.2c09306>.
40. Schaefer, B.A., Margulieux, G.W., Small, B.L., and Chirik, P.J. (2015). Evaluation of cobalt complexes bearing tridentate pincer ligands for catalytic C–H borylation. *Organometallics* *34*, 1307–1320.
41. Nakao, Y., Yamada, Y., Kashihara, N., and Hiyama, T. (2010). Selective C-4 alkylation of pyridine by nickel/Lewis acid catalysis. *J. Am. Chem. Soc.* *132*, 13666–13668.
42. Tsai, C.-C., Shih, W.-C., Fang, C.-H., Li, C.-Y., Ong, T.-G., and Yap, G.P.A. (2010). Bimetallic nickel aluminum mediated para-selective alkenylation of pyridine: direct observation of η<sup>2</sup>, η<sup>1</sup>-pyridine Ni (0)–Al (III) intermediates prior to C–H bond activation. *J. Am. Chem. Soc.* *132*, 11887–11889.
43. Yang, L., Semba, K., and Nakao, Y. (2017). para-Selective C–H borylation of (hetero) arenes by cooperative iridium/aluminum catalysis. *Angew. Chem.* *129*, 4931–4935.
44. Lee, W.-C., Chen, C.-H., Liu, C.-Y., Yu, M.-S., Lin, Y.-H., and Ong, T.-G. (2015). Nickel-catalyzed para-CH activation of pyridine with switchable regioselective hydroheteroarylation of allylarenes. *Chem. Commun.* *51*, 17104–17107.
45. Andou, T., Saga, Y., Komai, H., Matsunaga, S., and Kanai, M. (2013). Cobalt-catalyzed C4-selective direct alkylation of pyridines. *Angew. Chem., Int. Ed. Engl.* *52*, 3213–3216.
46. Yang, L., Uemura, N., and Nakao, Y. (2019). meta-Selective C–H borylation of benzamides and pyridines by an iridium–Lewis acid bifunctional catalyst. *J. Am. Chem. Soc.* *141*, 7972–7979.
47. Zhang, T., Luan, Y.-X., Lam, N.Y.S., Li, J.-F., Li, Y., Ye, M., and Yu, J.-Q. (2021). A directive Ni catalyst overrides conventional site selectivity in pyridine C–H alkenylation. *Nat. Chem.* *13*, 1207–1213.
48. Neidig, M.L., Carpenter, S.H., Curran, D.J., DeMuth, J.C., Fleischauer, V.E., Iannuzzi, T.E., Neate, P.G.N., Sears, J.D., and Wolford, N.J. (2019). Development and evolution of mechanistic understanding in iron-catalyzed cross-coupling. *Acc. Chem. Res.* *52*, 140–150. <https://doi.org/10.1021/acs.accounts.8b00519>.
49. Wilke, G. (1979). Organo transition metal compounds as intermediates in homogeneous catalytic reactions. In *Organomet. Chem.*, Y.

- Ishii and N. Hagihara, eds. (Pergamon), pp. 677–690.
50. Shih, W.-C., and Ozerov, O.V. (2017). Selective ortho C–H activation of pyridines directed by Lewis acidic boron of PBP pincer iridium complexes. *J. Am. Chem. Soc.* **139**, 17297–17300.
51. Hara, N., Saito, T., Semba, K., Kuriakose, N., Zheng, H., Sakaki, S., and Nakao, Y. (2018). Rhodium complexes bearing PAIP pincer ligands. *J. Am. Chem. Soc.* **140**, 7070–7073.
52. Hara, N., Uemura, N., and Nakao, Y. (2021). C2-Selective silylation of pyridines by a rhodium–aluminum complex. *Chem. Commun.* **57**, 5957–5960.
53. Rudd, P.A., Liu, S., Gagliardi, L., Young, V.G., Jr., and Lu, C.C. (2011). Metal–alane adducts with zero-valent nickel, cobalt, and iron. *J. Am. Chem. Soc.* **133**, 20724–20727.
54. Graziano, B.J., Vollmer, M.V., and Lu, C.C. (2021). Cooperative bond activation and facile intramolecular aryl transfer of nickel–aluminum pincer-type complexes. *Angew. Chem.* **133**, 15214–15221.
55. Gorgas, N., White, A.J.P., and Crimmin, M.R. (2022). Cooperative C–H bond activation by a low-spin  $d^6$  iron–aluminum complex. *J. Am. Chem. Soc.* **144**, 8770–8777.
56. Garçon, M., Mun, N.W., White, A.J.P., and Crimmin, M.R. (2021). Palladium-Catalysed C–H bond zincation of arenes: scope, mechanism, and the role of heterometallic intermediates. *Angew. Chem.* **133**, 6210–6218.
57. Rekhroukh, F., Chen, W., Brown, R.K., White, A.J.P., and Crimmin, M.R. (2020). Palladium-catalysed C–F alkylation of fluorobenzenes: mechanistic diversity and origin of selectivity. *Chem. Sci.* **11**, 7842–7849.
58. Kong, R.Y., Batuecas, M., and Crimmin, M.R. (2021). Reactions of aluminium (I) with transition metal carbonyls: scope, mechanism and selectivity of CO homologation. *Chem. Sci.* **12**, 14845–14854.
59. Gorgas, N., White, A.J.P., and Crimmin, M.R. (2022). Diverse reactivity of an iron–aluminum complex with substituted pyridines. *Chem. Commun.* **58**, 10849–10852.
60. Hara, N., Semba, K., and Nakao, Y. (2022). X-type aluminyl ligands for transition-metal catalysis. *ACS Catal.* **12**, 1626–1638. <https://doi.org/10.1021/acscatal.1c04340>.