

ARTICLE

Tuning Metal-Metal Interactions for Cooperative Small Molecule Activation

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Cluster complexes have attracted interest for decades due to their promise of drawing analogies to metallic surfaces and metalloenzyme active sites, but only recently have chemists started to develop ligand scaffolds that are specifically designed to support multinuclear transition metal cores. Such ligands not only hold multiple metal centers in close proximity but also allow for fine-tuning of their electronic structures and surrounding steric environments. This Feature Article highlights ligand designs that allow for cooperative small molecule activation at cluster complexes, with a particular focus on complexes that contain metal-metal bonds. Two useful ligand-design elements have emerged from this work: a degree of geometric flexibility, which allows for novel small molecule activation modes, and the use of redox-active ligands to provide electronic flexibility to the cluster core. The authors have incorporated these factors into a unique class of dinucleating macrocycles (ⁿPDI₂). Redox-active fragments in ⁿPDI₂ mimic the weak-overlap covalent bonding that is characteristic of M–M interactions, and aliphatic linkers in the ligand backbone provide geometric flexibility, allowing for interconversion between a range of geometries as the dinuclear core responds to the requirements of various small molecule substrates. The union of these design elements appears to be a powerful combination for analogizing critical aspects of heterogeneous and metalloenzyme catalysts.

Introduction

The catalytic transformation of small molecules into value-added products has motivated decades of research in molecular transition metal chemistry. A majority of the work in this area has been devoted to the development of mononuclear catalysts, and enormous gains in catalytic performance have been realized by fine-tuning the steric and electronic profiles of supporting ligand environments.^{1–6} Such efforts led to the emergence of a variety of molecular catalysts that are used in industrial processes, like the Grubbs catalysts for catalytic olefin metathesis reactions, various cross-coupling catalysts for use in the synthesis of pharmaceuticals, and Ziegler-Natta catalysts for olefin polymerization.

Other areas of industry are replete with heterogeneous catalysts, including many that operate over promoter-modified metallic surfaces. These catalysts find use in a range of applications, including steam reforming of methane, ammonia synthesis, and catalytic converters. In these processes, the activation of small molecules is generally understood to occur between multiple metal centers,^{7–10} *i.e. metal atoms work cooperatively to activate small molecule substrates*. This multinuclear approach to small molecule activation is also used in biological systems, which are able to leverage amino acid side chains and inorganic ligands to create multinuclear clusters that

are able to mediate multi-electron and multi-proton transformations. Examples include the multicopper oxidases,^{11, 12} which activate dioxygen across three copper centers at a metalloenzyme active site, and the Fe-S clusters of the nitrogenase enzymes that mediate the catalytic reduction of N₂ to NH₃ under ambient conditions.^{13, 14}

With an interest in modelling these multimetallic activation processes and discovering novel catalysts inspired by industrial/biocatalytic systems, chemists have sought to design molecular complexes that are able to activate small molecules across multiple metal centers.^{15, 16} This field has its origins in Muetterties' study of the cluster-surface analogy, which sought to create low-valent, often late-metal, cluster compounds that would mimic the properties of a metallic surface.^{17–19} Many of the compounds studied at the time made use of simple carbonyl, hydride, and phosphine ligands.^{19–23} Since then, a variety of metallic complexes supported by σ -donating and π -accepting ligands have been reported and studied for small molecule activation chemistry.^{24–34} Examples include Bergman's sulfur-atom abstraction reactions by a heterobimetallic Cp₂Zr(μ -N^tBu)IrCp* complex (Cp* = pentamethylcyclopentadienyl),²⁵ Mankad's bimetallic (^{Dipp}NHC)Cu–FeCp(CO)₂ complexes (^{Dipp}NHC = *N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) that perform catalytic photochemical C–H borylation reactions,³¹ and Johnson's pentanuclear nickel cluster that abstracts a carbon atom from alkenes.³² All make use of ligands that are common to mononuclear transition metal chemistry to construct multinuclear complexes with unique reactivity profiles.

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Building on the success of these unsupported M–M bonded complexes, the field has recently turned its considerable capacity for ligand design to the development of scaffolds capable of housing multiple metal centers within close proximity of one another. Ligand design plays a crucial role in the assembly of multimetallic clusters, as both the electronic and the steric properties may impact cluster aggregation and substrate accessibility.^{35, 36} We have categorized these ligand design strategies into two primary classes (Fig. 1). The first involves the design of ligands that support the use of an ancillary metal (M_A) as a ligand on an active site metal (M_B).^{37–43} In this case, the coordination environment about M_A is saturated, such that the chemistry performed by the bimetallic complex is localized at M_B . This approach has led to an enormous amount of fascinating chemistry, starting with some of the earliest examples of M–M multiple bonds,^{27, 42} through the broad use of dirhodium carbenes in organometallic chemistry,^{43–46} and on to later work that has provided more rational control over the identities and coordination environments of both M_A and M_B .^{37, 47, 48}

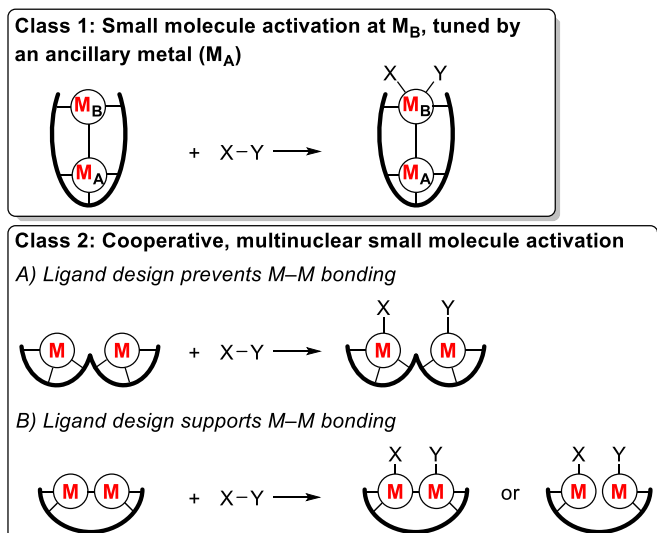


Fig. 1 Categories of ligand design classes aimed at generating multinuclear complexes capable of undergoing small molecule activation chemistry.

The other primary class deals with the design of ligands that allow multiple metal centers to cooperatively bind and activate small molecule substrates. This second approach may be subdivided into systems that hold the metal centers beyond their M–M bonding range (Class 2A) and those that support well-defined M–M bonding (Class 2B). While the former leads to larger binding pockets and typically draws comparisons with bioinorganic active sites, the latter yields high state-densities and is better discussed in the context of both atom-precise clusters and active sites on heterogeneous catalysts. The distinction is important when designing new ligands, since the presence of a M–M bond can be incompatible with many common mononucleating ligands.

This Feature Article is intended to highlight ligand design for multinuclear complexes that appear to undergo cooperative small molecule activation. Following the initial description of a

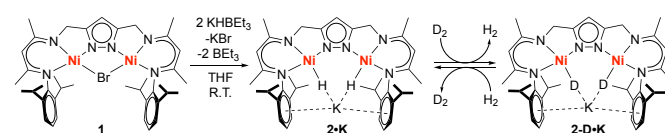
pair of illustrative examples of recent work that falls within Class 2A, the bulk of the text will describe the burgeoning field of ligand design for multinuclear complexes that bear M–M bonds (Class 2B), with a particular focus on the two ligand design criteria that have been critical to our research: i) *limited* geometric flexibility that provides for structural adjustments during small molecule activation and ii) electronic flexibility, which may be used to store and release electron density as needed by the cluster core. Following a survey of past developments in these respective areas, an overview will be presented of our use of a ligand system that merges these concepts to create a system that is able to mimic aspects of metallic surfaces.

Ligand Design for Multinuclear Complexes that Activate Small Molecules

A Case Study in Ligand Design for Class 2A

The scope of chemistry that falls under the heading of Class 2A is too broad to survey here,^{49–57} so we will simply illustrate two recent examples of ligand designs that appear to provide a kinetic advantage for small molecule activation by pre-organizing the metal centers with respect to one another. Both examples make use of the classical β -diketiminate (BDI) scaffold, underscoring the breadth of chemistry that is available when even such a well-studied ligand is creatively incorporated into multinucleating platforms.

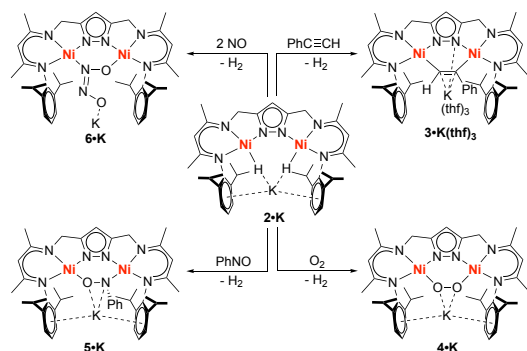
In the first example, the Meyer group reported a pyrazolate-derived ligand that incorporated BDI groups on the 3- and 5-positions of the pyrazole ring. Deprotonation of this ligand, followed by transmetalation with $\text{NiBr}_2(\text{DME})$ led to the formation of the dinickel- μ -bromide species **1**. The pyrazolate “linker” between the two metal-ligating BDI units resulted in a long metal-metal distance (3.781(1) Å) and ensured minimal, if any, metal-metal interaction. Upon treatment of **1** with KHBET_3 , a dinickel dihydride species **2•K** was formed (Scheme 1).⁵⁸ It was found that two aryl rings of the diisopropylphenyl (Dipp) substituents held the K^+ ion through cation- π interactions. The K^+ ion was also found to be coplanar with the pyrazolate-bridged dinickel dihydride core and formed $\text{K}^+\cdots\text{hydride}$ interactions [$d(\text{K}^+\cdots\text{H}) = 2.45(3)–2.53(3)$ Å]. Treatment of **2•K** with D_2 revealed the reversible formation of **2-D•K** and H_2 exclusively, without any sign of H/D scrambling. Additional studies indicated that the two Ni–H bonds are formed synchronously.



Scheme 1 Reversible transformation between **2•K** and **2-D•K**.

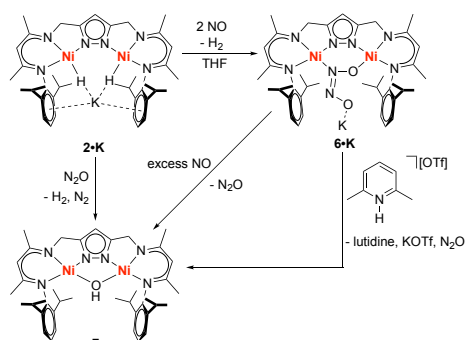
Further studies on the **2•K** complex revealed its ability to behave as a dinickel(I) synthon for reductive binding to small molecule substrates. When treated with small molecules (e.g. alkynes, O_2 , $\text{RN}=\text{O}$, NO), **2•K** was able to lose one molecule of

H₂ and bind the incoming substrate in a μ - η^1 : η^1 fashion. In this transformation, the substrate was reduced, and as a result, the corresponding [RC=CR]²⁻,⁵⁸ [O₂]²⁻,⁵⁹ [RNO]²⁻,⁶⁰ and [N₂O₂]²⁻ moieties⁶¹ were generated (Scheme 2). The reduced substrates are then able to undergo further electron- or proton-transfer reactions. The treatment of **2•K** with NO is particularly interesting in that it was proposed to generate an initial transient species with a [Ni₂(NO)] core. It was speculated that the bridging NO unit may bind in an unusual μ - κ^1 N: κ^1 O-geometry with respect to the Ni centers – similar to the peroxide ligand in **4•K** – before binding an additional equivalent of NO to generate the *cis*-hyponitrite species **6•K**.



Scheme 2 Selected chemical transformations reported with **2•K**.

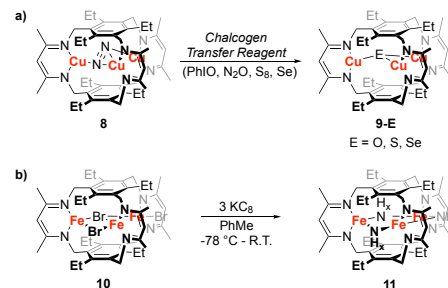
It was found that **6•K** would further react with excess NO to form N₂O, with the concomitant formation of the μ -hydroxide complex **7**. Direct treatment of **2•K** with N₂O also led to H₂ loss and the formation of **7**, likely via N₂ release and formation of a basic μ -oxo species that quickly captured a proton from the medium. Treatment of **6•K** with acid generated **7** and N₂O in good yields (Scheme 3). This reactivity is reminiscent of a proposed N₂O formation step from a *cis*-hyponitrite intermediate bound within the flavodiiron nitric oxide reductases (FNORs).^{62, 63} The dinucleating ligand scaffold in **6•K** enforces the unique μ - κ^1 N: κ^1 O *cis*-hyponitrite binding mode, a geometry that appears to be disfavored in related mononuclear systems but may be important to the mechanism of N₂O formation.⁶⁴



Scheme 3 FNOR-related reactivity enabled by **2•K**.

Recently, Murray and co-workers demonstrated a new design of a cyclophane-based ligand that binds Zn, Cu, Co, Fe, or Mn salts to afford the corresponding trimetallic clusters.^{65–68}

Within the cavity, the metals are oriented toward each other, each bound by a BDI fragment with no significant metal-metal interactions. The orientation of the three metal centers suggests feasible small molecule activation within the cavity of this cyclophane-based ligand. Deprotonative metallation of this ligand with [Cu(OTf)]₂·C₆H₆ afforded the first molecular copper(I) dinitrogen complex, **8**, confirming the accessibility of small molecules to the cavity of the cyclophane.⁶⁹ Facile displacement of N₂ was achieved in chalcogen (O, S, Se) atom transfer reactions (**9-E**, E = O, S, Se; Scheme 4a).^{70, 71} The μ_3 -O product **9-O** was also observed upon activation of O₂ by **8**, which exhibited multicopper oxidase-type reactivity.⁷²



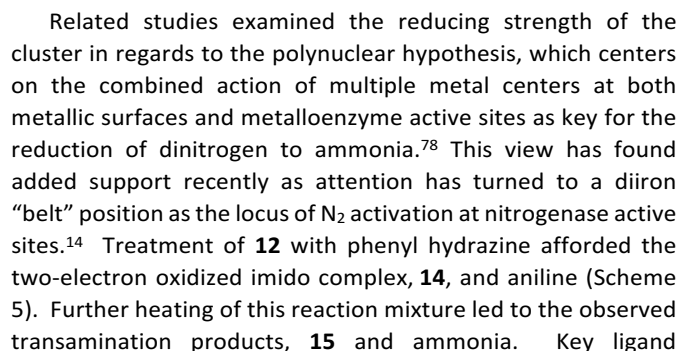
Scheme 4 (a) Chalcogen transfer reactions to the tricopper dinitrogen complex **8**. (b) N₂ activation by the triiron cluster **10** under reducing conditions.

Murray and co-workers also noted the advantage of N₂ accessibility to the cavity through N₂ reduction studies. The triiron cluster, **10** was found to activate N₂ under reducing conditions (Scheme 4b). The formation of triiron amido/imido products were observed, and isotopic labelling experiments confirmed that dinitrogen was being activated.⁷³ The same bromide cluster was found to be competent for catalytic N₂ silylation (0.2 mol%), affording 50% N(SiMe₃)₃ over 96 hours.⁷⁴ This chemistry is particularly interesting to consider in light of the Holland group's remarkable demonstration that mononuclear (BDI)Fe complexes are competent for performing the reductive cleavage of N₂ to form a tetrairon dinitride.⁷⁵ The inability to isolate a comparable species in the Murray system during N₂ reduction raises the possibility that reaction site tuning offered by the multinucleating cyclophane ligand hinders stabilization of a transient triiron dinitride, but details of the reaction mechanism are still under investigation.⁷⁶

Class 2B: The Importance of Geometric Flexibility

The design of ligands that bind multinuclear complexes and allow for reactivity at a M–M bond presents unique challenges with no clear precedent in traditional and bioinorganic coordination chemistry. The ligands must provide suitable steric protection to the M–M bond, while placing donors in atypical geometries for many organic molecules. In addition, the changes in coordination environments and electronic structures brought by small molecule activation reactions often induce structural rearrangements at the multinuclear core. Several successful examples of ligand design for cluster complexes have leveraged some degree of geometric flexibility in the ligand architecture to promote intermolecular chemistry. The following examples highlight recent work to gain control

The Thomas group has also designed less coordinatively saturated systems. Like their 3-fold symmetric congeners, the heterobimetallic complexes **25**⁸⁸ and **PR³27** (PR₃ = PMe₃, PMePh₂)⁸⁹ were found to exhibit strong metal-metal interactions through the d_{z2} σ-bonding interaction and d_{xz}/d_{yz} π-bonds (Fig. 2). The TiCo heterobimetallic complex **25** highlighted the importance of available coordination sites, as the complex was able to promote the reductive coupling of ketones to form alkenes, as aided by the cleavage of the C–O bond across the Ti≡Co bond.⁸⁸ Concomitant metal-oxo cluster (**26**) formation was observed in the presence of NaI, a necessary stoichiometric additive used to obtain the alkene product in good yields over short reaction times (Scheme 6c).



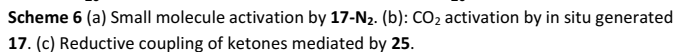
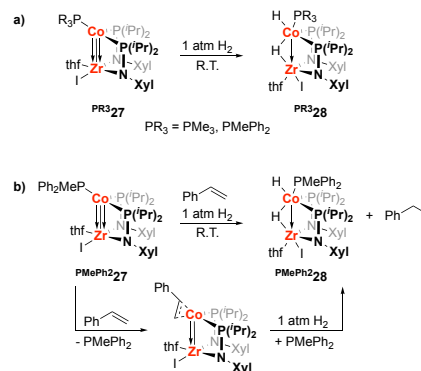


Fig. 2 Representative example of the molecular frontier orbital diagram of **25**.

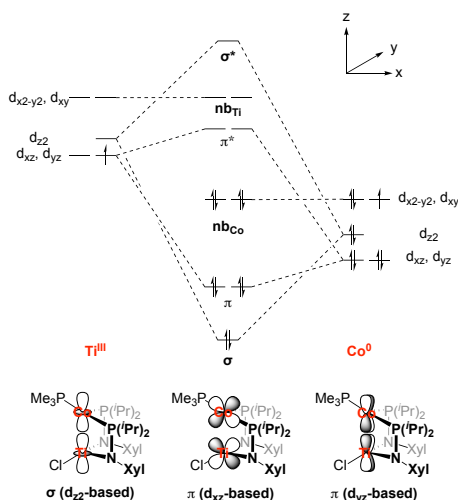
bond (Scheme 7a).⁸⁹ This stoichiometric reactivity prompted catalytic hydrogenation studies. The treatment of **PR₃27** with styrene and H₂ afforded ethylbenzene.⁸⁹ The lability of the bound PR₃ group is important, as the alkene must first displace the phosphine before hydrogenation takes place. Thus, the PMePh₂-coordinated complex **PMe₂Ph27** was found to be a more active catalyst due to its greater lability (Scheme 7b).



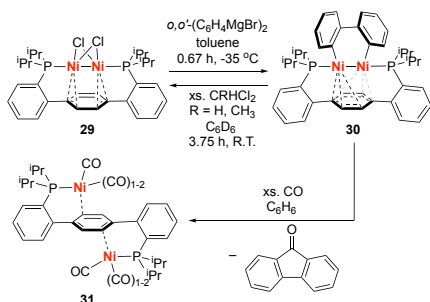
Scheme 7 (a) Activation of H₂ across the Co–Zr multiple bond in **PR³27**. (b) Hydrogenation reaction of styrene mediated by **PMePh₂27**.

In the past decade, redox-active ligands have been shown to play important roles in various catalytic reactions.^{90, 91} The valence orbitals of redox-active ligands lie close in energy to the metal d-manifold, but the two are only able to form weak-overlap covalent bonds. This increases the density of states available to the system and decreases the interelectron repulsion between the electrons that occupy these covalent orbitals. As a result, redox events at complexes that bear such ligands allow for significant contributions from the ligand when undergoing redox processes that would traditionally occur at a metal center. This allows redox-active ligands to work as reservoirs of electrons/holes for a variety of catalytic reactions, thus mimicking the electron delocalization that occurs as a result of M–M bond. In this way, redox-active ligands can be thought to extend the nuclearity of a cluster complex. This section will highlight the use of known redox-active ligands to support multinuclear complexes with close M–M distances.

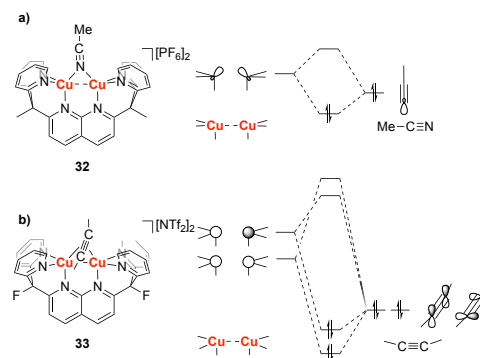
Metal-arene interactions have been found to afford stabilization of low-valent intermediates in catalytic processes,^{92, 93} and the observation that multiple metal centers can coordinate to a single arene scaffold has spurred interest in ligand design to support M–M bonded clusters. The Agapie group has reported the synthesis of a *p*-terphenyl diphosphine ligand. Treatment of this ligand with 1.0 equiv. of Ni(COD)₂ and 1.0 equiv. of NiCl₂(dme) resulted in a comproportionation reaction, affording a dinuclear Ni^I complex, **29** (Scheme 8).⁹⁴ Crystallographic analysis revealed significant bonding interactions between the two nickel centers ($d_{\text{Ni-Ni}} = 2.36580(16)$ Å) and the central aryl ring of the terphenyl unit ($d_{\text{Ni-Ct(C2)}} = 1.952$ Å and 1.953 Å, respectively; Ct = centroid). In one application of this system, it was found that treatment of **29** with the di-Grignard reagent *o,o'*-biphenyldiyl magnesium bromide afforded the corresponding biphenyldiyl complex **30**.

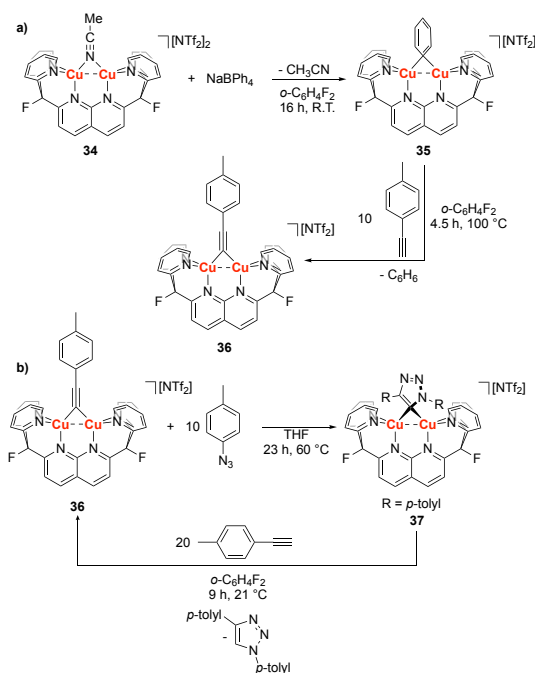


It is interesting to note that each of the nickel centers in **30** is coordinated in an η^3 fashion with the central ligand phenyl ring. This phenyl ring is found to be significantly distorted towards a boat conformation, which was not observed in the precursor **29**. The distortion of the arene ring may be an indication of the redox noninnocence between the dinickel core and the π^* system of the arene,⁹⁵ as has been described in more detail by Agapie in related work on mononuclear Mo chemistry.⁹⁶⁻⁹⁸ This concept of ligand-based redox activity will return in several examples described below.



two copper centers interact cooperatively with the donor orbital on the central ligand to form 3-center, 2-electron (3c,2e) bonds (Fig. 3a). Further studies on this system revealed that the DPFN ligand can support a Cu_2 center that is capable of binding $\text{C}\equiv\text{P}$ and $\text{C}\equiv\text{C}$ bonds in a $\mu\text{-}\eta_2\text{:}\eta_2$ -fashion, where the substrate $\rightarrow\text{Cu}_2$ interaction mainly involves donation from the occupied π -orbitals of the triple bond to the empty $4s$ orbital on each copper center (Fig. 3b).¹¹¹

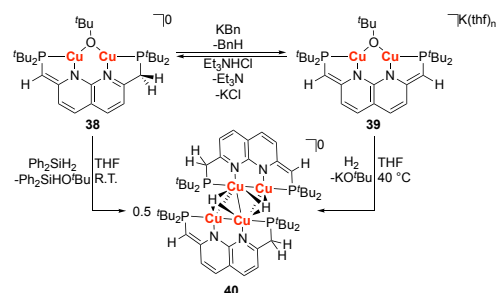




Scheme 9 (a) Aryl transfer reactions to **34** to form **35** and subsequent C–H activation to form **36**. (b) Alkyne-azide cycloaddition reaction mediated by **36**.

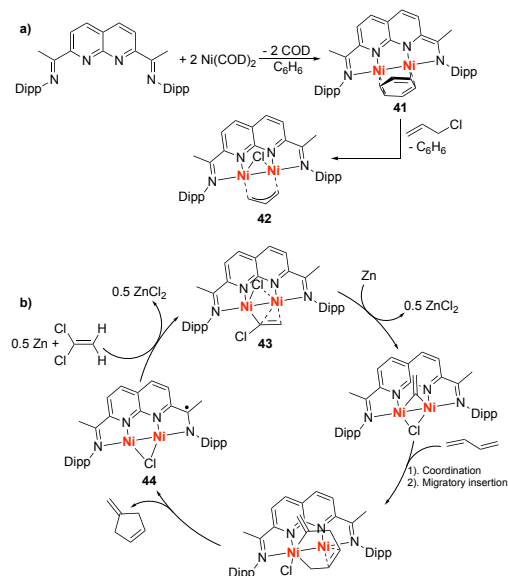
Another example of a dicopper system supported by a naphthyridine framework was reported by the Broere group, who used an “expanded pincer” ligand, $(\text{tBuPNNP})\text{H}_2$ that was formed by installation of $-\text{CH}_2\text{P}^t\text{Bu}_2$ groups at the 2- and 7-positions of the naphthyridine ring.¹¹³ This ligand was shown to undergo two stepwise, reversible deprotonation processes accompanied by naphthyridine dearomatization to form $[(\text{tBuPNNP})\text{H}]^-$ (mono-deprotonated) and $[(\text{tBuPNNP})]^{2-}$ (doubly deprotonated).

Dinuclear Cu^{I} species were produced by treatment of $(\text{tBuPNNP})\text{H}_2$ with 2.0 equiv. of Cu^{I} salts. When mesitylcopper was used as the Cu^{I} source, a dicopper bridging mesityl complex could be formed. The protonation state of the ligand was shown to affect the bonding of the μ -mesityl group in the $[\text{Cu}_2(\mu\text{-mesityl})]$ core in this complex.¹¹⁴ In particular, the ligand’s transition from one protonation state to the other could be used to activate hydrogen-containing species. Upon treatment of the bridging *tert*-butoxide species **39** with H_2 , dihydrogen was cooperatively activated by the dicopper center and the $[(\text{tBuPNNP})]^{2-}$ ligand to form **40** with a “butterfly-shaped” $[\text{Cu}_4(\mu_3\text{-H})_2]$ core supported by two $[(\text{tBuPNNP})\text{H}]^-$ ligands (Scheme 10).¹¹³ The cooperativity between the bimetallic core and the ligand was supported by isotopic labelling experiments, in which the use of D_2 instead of H_2 resulted in deuterium incorporation into both the $\mu_3\text{-H}$ position as well as the ligand $\text{CH}_2\text{P}^t\text{Bu}_2$ and CHP^tBu_2 backbone. However, treatment of **40** with D_2 at 40°C , with or without KO^tBu present, did not lead to such deuterium incorporation reactivity, indicating that H_2 activation across the dicopper core and the ligand is reversible and occurs before the formation of **40**.



Scheme 10 H_2 activation by **39**.

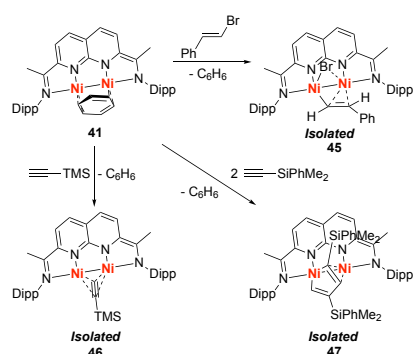
The Uyeda group was first to report the use of the redox-activity of the naphthyridinediimine (NDI) ligand. The complexation of the neutral ligand with two equivalents of Ni^0 caused the NDI ligand to be reduced by two electrons, while the two Ni^0 centers were oxidized. The two Ni^{I} centers formed a Ni – Ni bond and bound benzene to generate product **41** (Scheme 11a).¹¹⁵ The $[(\text{NDI})\text{Ni}]_2$ moiety in **41** was shown to traverse 5 different charge states by cyclic voltammetry. Isolation, characterization, and computational studies on the corresponding complexes support that the ligand exists in oxidation states of -2 , -1 and 0 , while the $[\text{Ni}]_2$ core adopts charges of $+1$ to $+3$. Treatment of **41** with allyl chloride resulted in a dinuclear oxidative addition reaction to afford a dinickel allyl complex **42**, in which the allyl anion forms a symmetric $\eta^2\text{-1,3-}\kappa^2$ -interaction with the dinickel core (Scheme 11a).¹¹⁶ Computational studies suggest that the Ni centers retain $+1$ oxidation states in this reaction, which indicates that the NDI ligand provides the electron density needed for the activation of allyl chloride.



Scheme 11 (a) Formation of the dinickel complex **41** and its allyl chloride activation. (b) Proposed catalytic cycle of the $[4+1]$ cycloaddition reaction catalyzed by $[(\text{NDI})\text{Ni}]_2$ -based complexes

Complex **41** has also been used to activate CH_2Cl_2 and mediate catalytic reductive cyclopropanation reactions.¹¹⁷ Mono-nickel complexes with structurally similar chelating ligands do not show similar catalytic performance. These

control reactions illustrate the crucial role of the dinickel core in the catalytic performance. Later studies revealed that NDI-bound dinickel complexes are also capable of activating vinylidene chlorides *en route* to the catalytic reductive vinylidene transfer to C=C bonds. This chemistry forms either methylene cyclopropane derivatives¹¹⁸ or, when 1,3-dienes are used as substrates, [4+1] cycloaddition products (Scheme 11b).^{119, 120} An important intermediate in the catalytic cycle is proposed to be a $[(\text{NDI})\text{Ni}_2(\eta^2\text{-ClC=CH}_2)(\mu\text{-Cl})]$ species (**43**) that is formed by oxidative addition of vinylidene chlorides on the bridging chloride species **44**, followed by reduction and halide abstraction by 0.5 equiv. of Zn. The presence of this complex is supported by the isolation of **45**, which was formed from the oxidative addition of BrCH=CHPh to **41** (Scheme 12). The lack of a second halide prohibited further C–X activation of the substrate.¹¹⁸



Scheme 12 Formation of important intermediates in catalytic organic transformations catalyzed by NDI-bound dinickel complexes.

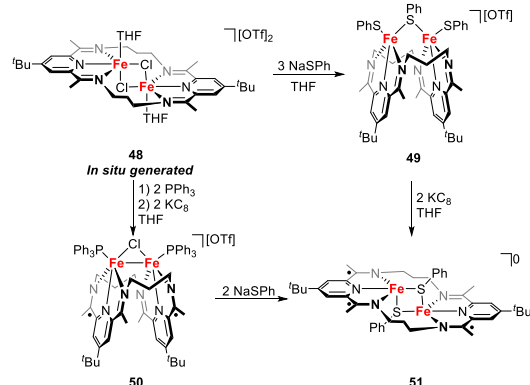
Aside from the dinuclear oxidative addition of C–Cl bonds, the $(\text{NDI})\text{Ni}_2$ moiety was also found to mediate a wide variety of chemical transformations^{121–128} and, in particular, coordinate and activate unsaturated C–C bonds as parts of catalytic ring formation/rearrangement reactions.^{129, 130} **41** was reported as an effective catalyst towards alkyne cyclotrimerization reactions with 1,2,4-trisubstituted benzenes as the major products, while structurally similar mono-nickel complexes showed poorer reactivity.¹³⁰ The key intermediates in this dinickel-facilitated ring-formation reaction were identified by the isolation of **46** and **47** by using trimethylsilylacetylene and phenyldimethylsilylacetylene as the substrates, respectively (Scheme 12). The former compound can be viewed as the first species formed *en route* to the alkyne cyclotrimerized product. The substrate in this complex is coordinated to the dinickel center in a $(\mu\text{-}\eta^2\text{:}\eta^2)$ fashion, and a significant elongation of the $\text{C}\equiv\text{C}$ bond was observed. **47** represents the active metallocyclic species formed when a second equivalent of alkyne enters the catalytic cycle. Only one Ni is included in the five-membered metallocycle, while the other Ni provides stabilization to the metallacyclopentadiene system via a dihapic π -interaction with one of the double bonds. This dinuclear stabilization is similar to those proposed in $\text{Co}_2(\text{CO})_8$ -catalyzed Pauson-Khand reactions.^{131, 132}

Combining Redox-Active Fragments with Geometric Flexibility

Our group has been working with a series of dinucleating macrocyclic ligands that offer two primary points of interest with respect to small molecule activation chemistry. One is the inclusion of redox-active elements as a way to expand the electronic flexibility of the cluster core. This is achieved by use of two pyridinediimine (PDI) units, which are well-known redox-active ligands for mononuclear coordination complexes.^{133, 134} The second is an element of geometric flexibility, included in this present case by way of catenated methylene linkers that join the PDI imino nitrogens. Both elements find precedent in the examples highlighted above. The electronic flexibility of Uyeda's complexes, for instance, provides access to rich redox chemistry at a robust dinickel core, and the comparison between the Murray and Holland complexes (see above) illustrates the potential impact of altering control over the positions of the metals. This latter point also finds support from the field of heterogeneous catalysis. Metallic surfaces are known to undergo restructuring during substrate binding, activation, and transformation into the products.¹³⁵ It is thought that this *limited* mobility of the metal atoms at the surface is important both for providing stabilization to the range of surface species that develop through the course of the reaction and for avoiding entry into thermodynamic sinks.

Drew, Nelson, Nelson, and co-workers first reported a series of bimetallic first-row transition metal complexes supported by a series of macrocyclic ligands that contain two 2,6-diiminopyridine (PDI) units, linked at their imino nitrogens by catenated methylene linkers (e.g. $-\text{CH}_2\text{CH}_2\text{CH}_2-$).^{136–140} However, reactivity studies of these complexes were limited due to poor solubility in common organic solvents.¹³⁷ We recently revisited this ligand and found that upon installation of *tert*-butyl groups at the 4-positions of the PDI moieties, the solubility profiles of the resulting complexes increased significantly. This minor synthetic modification provided access to a range of reduction chemistry, allowing for further study into the electronic structures of these complexes and their reactivity toward small molecules. This modified ligand is noted as $^n\text{PDI}_2$ in the following text, where *n* is the number of catenated CH_2 units between the two PDI groups.

Recently we reported a series of diiron complexes in which we observed the interconversion of two different conformations of the ligand – “stair-step” and “folded”.¹⁴¹ The THF-soluble diiron complex **48** rests in the stair-step conformation (Scheme 13), in which the $\text{Fe}_2(\mu\text{-Cl})_2$ core constitutes an edge-sharing connection between two octahedral metal centers. The planes of the PDI units in **48** are roughly parallel to one another, with the pyridyl nitrogens facing in opposite directions. Upon either anion metathesis to form **49** or reduction to form **50**, the ligand was found to adopt a folded conformation, in which the planes of the PDI units were again found to be roughly parallel but the pyridyl nitrogens pointed in the same direction. Reduction of **49** or salt metathesis of **50** with NaSPh both led to the ligand reverting to a stair-step conformation on formation of a $[\text{Fe}_2(\mu\text{-SPh})_2]$ core.



Scheme 13 Ligand conformation change in the series of diiron complexes. Adapted with permission from reference 141. Copyright 2019 American Chemical Society.

We also observed that the ligand's geometric flexibility extends to an ability to hold the metal centers in a wide range of M–M distances. X-ray crystallographic studies revealed an Fe–Fe distance of 3.3262(5) Å in **48** and 2.7320(11) Å in **51**. Both display the stair-step ligand geometry but exhibit a ~0.6 Å difference in Fe–Fe distances. More recently, we reported the synthesis and characterization of a series of bimetallic iron, cobalt and nickel complexes **52** – **57** that are isostructural to the folded-ligand complex **50** (Fig. 4).¹⁴² Inspection of their crystallographic data also revealed a wide range of metal–metal distances (Fig. 4) that again spanned nearly 0.6 Å, from 2.63–3.22 Å.

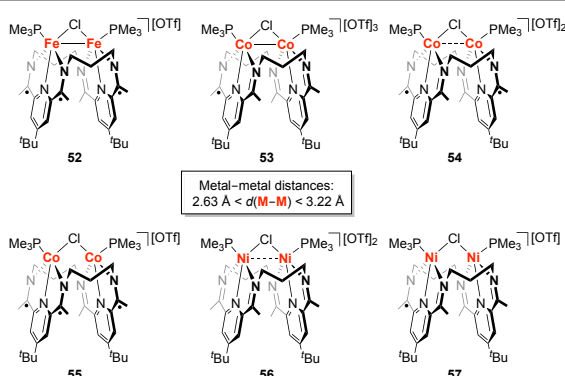


Fig. 4 Molecular structures of bimetallic iron, cobalt and nickel complexes **52** – **57** supported by the 3PDI₂ ligand.

In addition to exploring the variety of geometric structures supported by the 3PDI₂ ligand, we have been interested in determining the electronic structures of these complexes as a way of guiding our understanding of the small molecule activation chemistry described below. In the folded complex **49**, variable temperature XRD studies revealed that the ligand maintains the [Fe₂(SPh)₃] core in a folded conformation despite the increase in Fe–Fe distances from 3.1726(5) Å at 100 K to 3.2344(8) Å at 250 K (Fig. 5).¹⁴¹ These data were correlated through SQUID magnetometry and DFT studies to the presence of a wide range of thermally accessible spin states, ranging from the diamagnetic ground state up through an S = 8 state. The magnetic states were found to result from population of Fe–Fe

antibonding orbitals, leading to the cleavage of the Fe–Fe bonding interaction on warming.

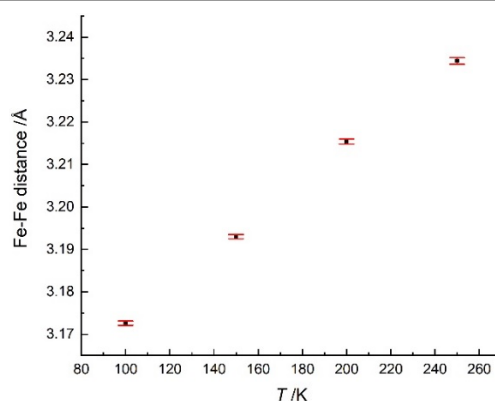


Fig. 5 Fe–Fe distances in **49** at different temperatures. Error is depicted as red bars. Reprinted with permission from reference 141. Copyright 2019 American Chemical Society.

Complexes **52** – **57** constituted a *pseudo*-electron transfer series that allowed for an in-depth investigation into the interdependence of the M–M bonding and the extent of ligand reduction.¹⁴² Two metrics in particular have been useful for delineating the trends in the experimental data. One is the imputed M–M bond orders as determined by their formal shortness ratios (FSRs),¹⁴³ which are equal to the intermetallic distance divided by the sum of the single bond covalent radii of the metal centers.¹⁴⁴ The other is the physical oxidation state of the ligand (Δ_{avg} , average Δ value¹³⁴ for the two PDI moieties on the ligand; Table 1). The Δ value represents the difference between the average C–N and C_{im}–C_{py} distances on the ligand backbone. These FSR and Δ_{avg} data for the bimetallic complexes are given in Table 2, and the combination of these values with computational studies suggested significant mixing of ligand π^* character and M–M bonding/antibonding character in the valence region of these compounds (Fig. 6). When these valence orbitals are populated, electron density will be transferred to both the M–M σ -(anti)bonding and ligand π^* manifolds. As such, the population of electrons in these orbitals affects both M–M bond orders and the ligand oxidation states. As will be described below, the covalency in the M–PDI interactions was also calculated to play a role in the electronic structure of an N₂-bound diiron species.

Table 1 Δ_{avg} values of $^3\text{PDI}_2$ ligands in different oxidation states. Adapted with permission from reference 142 (<https://pubs.acs.org/doi/10.1021/acs.inorgchem.9b02339>). Copyright 2020 American Chemical Society. Further permissions related to the material excerpted should be directed to the ACS.

$^3\text{PDI}_2$ oxidation state	$\Delta_{\text{avg}}/\text{\AA}$
$(^3\text{PDI}_2)^0$	0.171
$(^3\text{PDI}_2)^{-}$	0.138
$(^3\text{PDI}_2)^{2-}$	0.104
$(^3\text{PDI}_2)^{3-}$	0.080
$(^3\text{PDI}_2)^{4-}$	0.056

Table 2 FSR values and Δ_{avg} values of complexes **52** – **57**. Adapted with permission from reference 142 (<https://pubs.acs.org/doi/10.1021/acs.inorgchem.9b02339>). Copyright 2020 American Chemical Society. Further permissions related to the material excerpted should be directed to the ACS.

	52	53	54	55	56	57
$\Delta_{\text{avg}}/\text{\AA}$	0.086	0.134	0.119	0.085	0.163	0.138
FSR	1.138	1.138	1.207	1.349	1.181	1.397

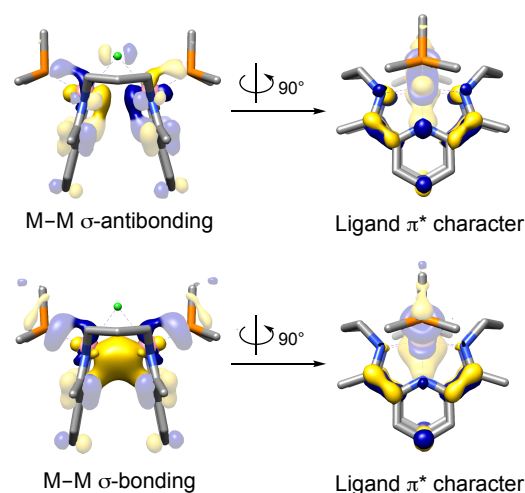
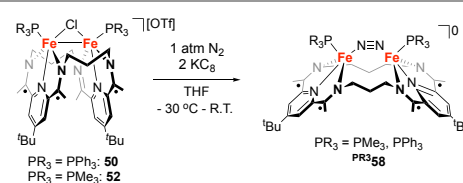


Fig. 6. Selected example showing mixing of M–M bonding/antibonding character with ligand π^* character in selected molecular orbitals of complexes **52** – **57**.

Further reactivity studies on $^n\text{PDI}_2$ -supported bimetallic complexes revealed their ability to activate substrates in a bimetallic fashion. Reduction of **50** or **52** with 2.0 equiv. of KC_8 resulted in the formation of diiron- $\mu\text{-N}_2$ complexes $\text{PR}^3\text{58}$ ($\text{PR}_3 = \text{PMe}_3, \text{PPh}_3$) with unusual $\text{Fe-Ct}_{\text{N}_2}\text{-Fe}$ angles of ca. 150° (Ct_{N_2} = centroid of N_2 ; Scheme 14, Fig. 7a).¹⁴⁵ These $\text{Fe-N}_2\text{-Fe}$ geometries are highly unusual for molecular $\mu\text{-N}_2$ complexes,^{146, 147} as most form linear bridges that maximize π -backbonding from the traditional d_π orbitals into the N_2 π^* -manifold. The geometry is reminiscent, however, of the $\alpha\text{-N}_2$ binding mode on $\text{Fe}(111)$ surfaces¹⁴⁸ – a critical binding mode that precedes N_2 cleavage during the catalytic reduction of N_2 to NH_3 in the Haber-Bosch Process. The bridging N_2 units in $\text{PR}^3\text{58}$ are mildly activated ($\text{N-N} = 1.135(3)$ for $\text{PR}_3 = \text{PMe}_3$ and $1.139(3)$ $\text{\AA}$ for $\text{PR}_3 = \text{PPh}_3$), consistent with the spectroscopically observed N-N stretching frequencies of 2003 and 1959 cm^{-1} , respectively.



Scheme 14. Synthesis of the bridging N_2 complex $\text{PR}^3\text{58}$ from **50** and **52**.

The unusual N_2 binding geometries in $\text{PR}^3\text{58}$ appear to result from the constraints imposed by the macrocycle, as the ligand is unable to unfurl far enough to support a linear $\text{Fe-N}_2\text{-Fe}$ geometry. This may be compared to the other known examples of similar $\text{Fe-N}_2\text{-Fe}$ geometries, which feature alkali metal ions in proximity to the $\mu\text{-N}_2$ units. Holland reported the example of $\text{Fe}_3(\mu\text{-N}_2)_x(\mu\text{-Cl})_{3-x}$ rings ($x = 2, 3$) capped by alkali metal ions,¹⁴⁶ and Mendiola reported the use of two meridionally coordinated Fe centers linked through K -arene interactions in addition to the $\mu\text{-N}_2$ unit.¹⁴⁷ It is unclear in these systems whether the alkali metals are ancillary counterions, necessary components for generating constrained geometry macrocycles, or partners in tuning electronically driven geometric features. But given the structures the $\alpha\text{-N}_2$ binding mode on $\text{Fe}(111)$ and the discovery of related $\mu\text{-}\kappa^1\text{N}:\kappa^1\text{N}$ geometries at the active-site belt positions of a reductant-depleted nitrogenase,^{14, 148} we were interested to determine the electronic structure changes that result from this unusual binding geometry.

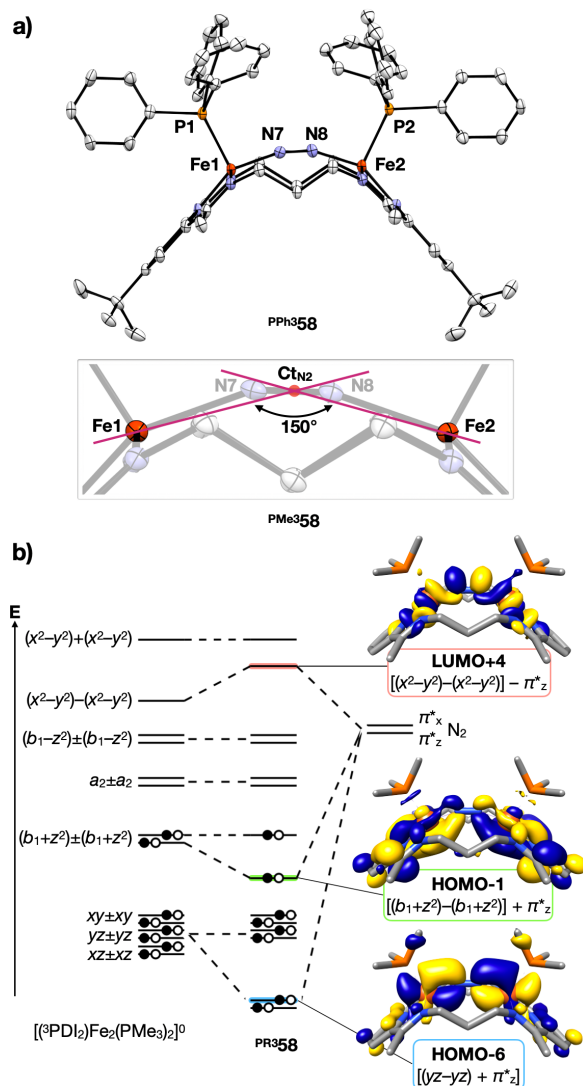
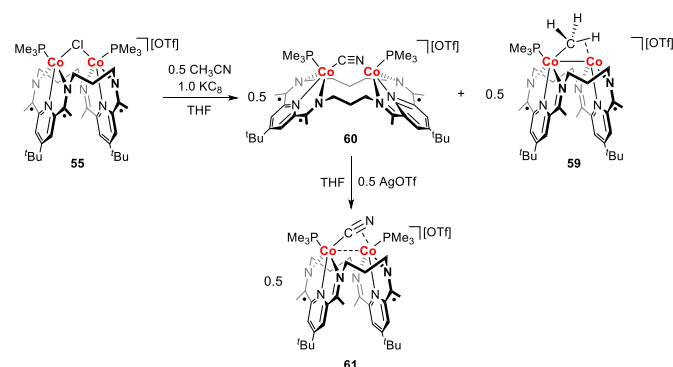


Fig. 7. Crystal structure (a) and electronic structure (b) of **PR358**. Adapted with permission from reference 145. Copyright 2020 American Chemical Society.

Despite the modest activation of N_2 in **PR358**, computational studies revealed interesting orbital interactions that may be of use to the field. In addition to the traditional π -backbonding interactions (e.g. HOMO-6), HOMO-1 was found to result from admixture of 3PDI_2 π^* character into the N_2 π^* manifold, as mediated by the Fe d_{z^2} orbitals. To higher energies, the LUMO+4 was identified as resulting from backbonding of Fe $d_{x^2-y^2}$ – a d_σ orbital – into the N_2 π^* system (Fig. 7b). This unusual π -backbonding interaction has implications for the mode of N_2 activation at other constrained geometry binding sites, especially those with high-spin electron configurations at Fe.

Small molecule activation was also discovered for a 3PDI_2 -bound dicobalt system. Reduction of the **55** by 1.0 equiv of KC_8 in the presence of 0.5 equiv of MeCN led to C–C bond activation of MeCN and the formation of equimolar amounts of a bridging methyl complex **59** and bridging cyanide complex **60** (Scheme 15).¹⁴⁹ The former complex is the first structurally characterized example of a bridging methyl group on Co. An agostic interaction was apparent from the 1H NMR spectrum, which revealed inequivalence (2H:1H) of the methyl hydrogens

at low temperatures with the 1H signal displaying an upfield signal (–12.7 ppm) with a small C–H coupling constant ($^1J_{CH} = 74.5$ Hz). In the latter complex, **60**, the $[C\equiv N]^-$ unit bridges between the Co centers in a $\mu-CN-\kappa^1C:\kappa^1N$ fashion, reminiscent of the N_2 binding mode in the isoelectronic **PR358** species. Upon one-electron oxidation of this complex, a weak Co–Co bond is formed, and as a result, the binding mode of the $[C\equiv N]^-$ unit changed to a $\mu-CN-\kappa^1C:\eta^2-CN$ fashion (Scheme 15). This is an atypical, semi-bridging configuration that has not been reported previously for Co. Notably, the ligand geometry changed from arched to folded to allow for closer contact between cobalt atoms, highlighting both the geometric flexibility of the ligand scaffold to enable the cleavage and reformation of M–M bonds and the access to unique small molecule binding modes as a result of the macrocyclic framework.

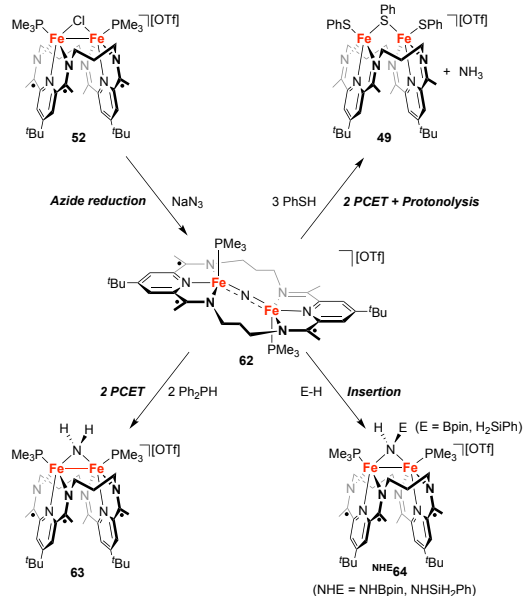


Scheme 15 MeCN activation and C≡N binding mode change on the $[^3PDI_2-Co_2]$ platform.

Aside from reduction of the bridging chloride complexes, interesting reactivity was also observed on substitution of the bridging chloride with an azide. Treatment of **52** with NaN_3 resulted in the formation of a diiron bridging nitride species **62** (Scheme 16).¹⁵⁰ Crystallographic studies revealed a change in the 3PDI_2 ligand conformation from folded to stair-step to accommodate the linear Fe–N–Fe moiety. The Fe– N_μ bond distances of 1.677(3) and 1.673(3) Å indicate multiple bond character similar to what has been reported for Fe imido complexes,^{151, 152} and the Δ_{avg} value of 0.073 Å is indicative of a $(^3PDI_2)^{3-}$ ligand.

Considering that bridging iron nitrides serve as key intermediates in catalytic ammonia synthesis, we are delighted to find that **62** presents a diverse profile of N–H bond formation chemistry. Treatment of **62** with Ph_2PH led to the clean formation of a diamagnetic bridging amide species **63**, concomitant with the formation of an equivalent of Ph_2P-PPh_2 , suggesting two PCET reactions from the phosphine to the nitride center (Scheme 16). During this reaction, the ligand was found to have folded to support the change from an sp -hybridized $\mu-N$ to an sp^3 -hybridized $\mu-NH_2$ unit. Moreover, **62** was also found to react with $PhSiH_3$ and $HBpin$ (pin = pinacolate) to generate the E–H insertion products, **NHE64** (NHE = $NHBPi$, $NHSiH_2Ph$). Finally, treating **62** with 3.0 equiv. of $PhSH$ was found to completely remove the $\mu-N$ moiety and form NH_3 in 71% yield. The product from this reaction, **49**, reveals oxidation

of the $(^3\text{PDI}_2)^{3-}$ in **62** to $(^3\text{PDI}_2)^0$ in **49**, consistent with an intramolecular electron transfer in addition to N–H bond formation.



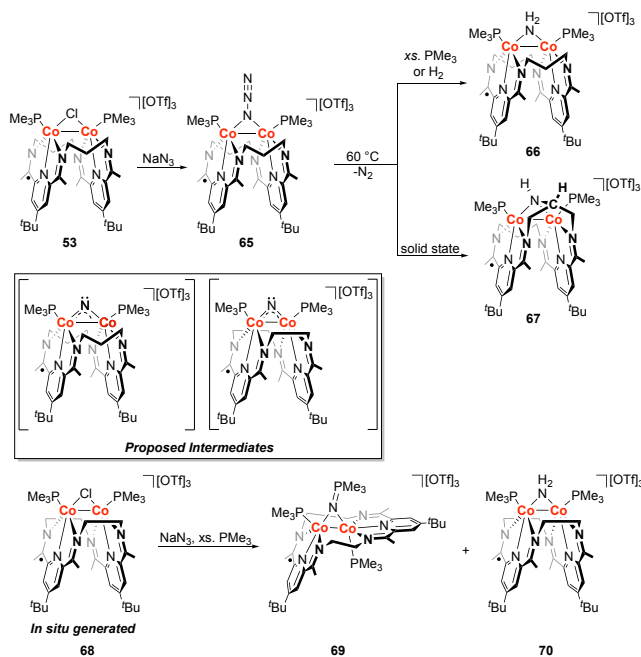
Scheme 16 Chemical transformations mediated by **62**.

We were unable to isolate a bridging azide species by salt metathesis of **52** with NaN_3 . However, treatment of its isoelectronic dicobalt congener **53** with NaN_3 led to the isolation of a dicobalt bridging azide species **65** (Scheme 17).¹⁵³ The complex displayed a folded ligand geometry with unusually short Co–N distances of *ca.* 1.94 Å. Despite the Co(II) physical oxidation state of each Co ion, the phosphines were found via NMR spectroscopy (EXSY) to be inert with respect to exchange, presumably as a result of the Co–Co bonding interaction (2.5819(4) Å) *trans* to the phosphine.

Thermolysis of **65** resulted in the isolation of products that are consistent with the transient formation of a dicobalt nitride – a moiety that was unknown to the field at the time.¹⁵⁴ Heating **65** at 60 °C in MeCN led to the formation of an amide species **66** in low, albeit reliable, yields. This result was consistent with an initial thermolysis of the azide, followed by the abstraction of two hydrogen atoms from an unknown source. The yield of **66** was increased by heating the complex under 1 atm of H_2 (Scheme 17). However, performing the same reaction with D_2 resulted in deuterium incorporation on the ligand CH_2 linkers, with no detectable D-incorporation at the amido group. This isotopic labelling experiment indicated that activation of the aliphatic C–H bonds of the linker by the putative nitride provided the source of the N–H bonds in **66**. This hypothesis was further supported by the isolation of a ligand C–H activation product, **67**, following thermolysis of **65** in the solid state at 60 °C. This product results from the net insertion of a nitrogen atom into a C–H bond on the central methylene group of the alkyl linker.

The reactivity of the putative dicobalt bridging nitride appeared to be altered when a macrocycle with a shorter alkyl linker was employed. Use of the two-carbon bridged ligand

$^2\text{PDI}_2$ led to the formation of two isolable products following azide decomposition: a $\mu\text{-NH}_2$ species, **70**, and a product with a bridging phosphinimide unit, **69** (Scheme 17). P–N bond formation via attack of a phosphine on an electrophilic nitride is a well-known reaction in late-metal, terminal nitride chemistry,¹⁵⁵ but it had not previously been demonstrated at a bridging nitride. Differing product distributions and reaction dependencies (e.g. on the concentration of added PMe_3) between the $^2\text{PDI}_2$ - and $^3\text{PDI}_2$ -supported nitrides indicate that the geometric constraints of the macrocycle are imparting reaction selectivity that may be exploited in more well-behaved systems.



Scheme 17 Difference in reactivity of the putative nitride formed with the $^3\text{PDI}_2$ ligand and $^2\text{PDI}_2$ ligand.

Conclusions

The examples covered in the Feature Article were intended to demonstrate how judicious ligand design can be used to facilitate *cooperative* small molecule activation by multimetallic complexes. By creating ligand frameworks specifically designed to house multiple metal centers, entirely new methods for small molecule activation and catalysis are being discovered. From dinuclear oxidative addition and reductive elimination to cooperative cycloaddition chemistry, traditional inorganic and organometallic reactivity is being cast in a new light as chemists gain control over the coordination environment of multinuclear metal complexes.

It is clear from the wide variety of ligands designed to support multimetallic centers that control of the intermetallic distance plays a significant role in the mode of multinuclear small molecule activation. When the intermetallic distances are short, substrates tend to bind in a $\mu\text{-}\eta^1\text{:}\eta^1$, $\mu\text{-}\eta^1\text{:}\eta^2$, or less commonly, $\mu\text{-}\eta^2\text{:}\eta^2$ fashion that allows for retention of the M–M bonds. With larger intermetallic distances, substrates more commonly access M–X–Y–M moieties ($\mu\text{-}\kappa^1\text{:}\kappa^1$) with no M–M

bonding interaction. This comparison highlights how even minor changes to the ligand architecture can have an outsized impact on the system's mode of reactivity. Other design considerations naturally include the donor choice and the geometry of the primary coordination sphere about each metal center, but an additional element that has arisen in several of these early ligand designs is the inclusion of redox-active ligands within the multimetallic support. The interplay of these elements with the compact valence manifold of M–M bonded cores is highly system dependent but offers a way to increase the electronic flexibility in a way that should be useful for catalytic applications.

Work in our group has taken into consideration both this ligand redox-activity and tunable intermetallic distances when pursuing bimetallic chemistry. The $^{\text{PDI}}\text{I}_2$ ligand scaffold is able to hold bimetallic cores within a range of intermetallic distances, owing, in part, to the unique ability of the $^{\text{PDI}}\text{I}_2$ class of ligands to adopt various geometries (stair-step, folded, arched) and oxidation states in response to the requirements of the cluster core. The constrained geometry imparted by the macrocycle appears, however, to prevent access to thermodynamic sinks, as evidenced by the various small molecule binding motifs described above that are unique to the $^{\text{PDI}}\text{I}_2$ -supported complexes. For example, the stair-step ligand geometry was able to stabilize the $\mu\text{-N}$ in **62**, but the ligand folded to accommodate the formation of sp^3 -hybridized bridging amides following PCET and E–H insertion reactions. Similarly, the arched ligand geometries in **PR358** and **60** lead to unique $\mu\text{-N}_2$ and $\mu\text{-CN}$ geometries that promote mixing of the metal's d_{σ} manifold with the substrate's π^* system. This strategy of introducing limited geometric flexibility appears to add a new dimension to the development of ligands that are capable of supporting multinuclear complexes for small molecule activation chemistry.

In conclusion, ligand design to support multimetallic complexes that undergo cooperative, small molecule activation is a robust and active field of research. The reaction pathways available to these systems are highly dependent on intermetallic distances, the redox activity of the ligand, and the coordination environment of the metal centers. Despite these developments, the use of ligands that contain redox-active elements is underexplored, and the use of those with limited geometrical flexibility is virtually unknown. However, our results indicate that the combination of these features offers a new horizon in the discovery of novel reaction pathways and catalysts. Future work will need to be done to improve the connections between these variables and the multinuclear sites of metalloenzymes and metallic surfaces. In particular, the effects of geometric constraints on the electronic structures and reactivity profiles of small molecules will be of interest. We further anticipate that future challenges in this field will include both the rational design of supported complexes that feature heterometallic centers and designs that enable precise control over the geometries of the complexes that are formed.

Conflicts of interest

There are no conflicts to declare.

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