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Bimetallics in a Nutshell: Complexes Supported by Chelating Naphthyridine-Based Ligands

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Conspectus: Bimetallic motifs are a structural feature common to some of the most effective and synthetically useful catalysts known, including in the active sites of many metalloenzymes and on the surfaces of industrially relevant heterogeneous materials. However, the complexity of these systems often hampers detailed studies of their fundamental properties. To glean valuable mechanistic insight into how these catalysts function, this research group has prepared a family of dinucleating 1,8-naphthyridine ligands that bind two first-row transition metals in close proximity, originally designed to help mimic the proposed active site of metal oxide surfaces. Of the various bimetallic combinations examined, dicopper(I) is particularly versatile, as neutral bridging ligands adopt a variety of different binding modes depending on the configuration of frontier orbitals available to interact with the Cu centers. Organodicopper complexes are readily accessible, either through the traditional route of salt metathesis or *via* the activation of tetraarylborate anions through aryl group abstraction by a dicopper(I) unit. The resulting bridging aryl complexes engage in C–H bond activations, notably with terminal alkynes to afford bridging alkynyl species. The μ -hydrocarbyl complexes are surprisingly tolerant of water and elevated temperatures. This stability was leveraged to isolate a species that typically represents a fleeting intermediate in Cu-catalyzed azide-alkyne coupling (CuAAC); reaction of a bridging alkynyl complex with an organic azide afforded the first example of a well-defined, symmetrically bridged dicopper triazolide. This complex was shown to be an intermediate during CuAAC, providing support for a proposed bimetallic mechanism. These platforms are not limited to formally low oxidation states; chemical oxidation of the hydrocarbyl complexes cleanly results in formation of mixed-valent Cu^ICu^{II} complexes with varying degrees of distortion in both the bridging moiety and the dicopper core. Higher oxidation states, *i.e.* dicopper(II), are easily accessed *via* oxidation of a dicopper(I) compound with air to give a Cu^{II}₂(μ -OH)₂ complex. Reduction of this compound with silanes resulted in the unexpected formation of pentametallic copper(I) dihydride clusters or trimetallic monohydride complexes, depending on the nature of the silane. Finally, development of an unsymmetrical naphthyridine ligand with mixed donor side-arms enables selective synthesis of an isostructural series of six heterobimetallic complexes, demonstrating the power of ligand design in the preparation of heterometallic assemblies.

Key References

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- Nicolay, A.; Tilley, T. D. Selective Synthesis of a Series of Isostructural M^{II}Cu^I Heterobimetallic Complexes Spontaneously Assembled by an Unsymmetrical Naphthyridine-Based Ligand. *Chem. Eur. J.* **2018**, *24* (41), 10329–10333.³ *The Tilley group's first report of unsymmetrical naphthyridine-based ligands that are effective for the selective synthesis of heterobimetallic complexes.*
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Introduction

Bimetallic moieties have drawn significant attention from the synthetic chemistry community over the last few decades due to the range of possible reaction pathways that result from close metal-metal contacts. Compared to monometallic species, bimetallic complexes can enable multielectron transfer processes through redox cooperativity,^{5,6} as well as exhibit increased catalytic activity^{7,8} and unusual selectivity,^{9,10} making them compelling design elements in homogeneous catalysis. Indeed, nature employs dinuclear active sites in numerous catalytically active metalloenzymes. Notable examples of homobimetallic units include soluble methane monooxygenase (Fe-Fe),¹¹ catechol oxidase (Cu-Cu),¹² and arginase (Mn-Mn, Figure 1a);¹³ metalloenzymes with heterobimetallic active sites, such as purple acid phosphatase (Fe-Zn)¹⁴ or CO dehydrogenases (Ni-Fe or Cu-Mo),^{15,16} are also well known. Beyond enzymatic catalysis, cooperativity between metal centers at an active site has been identified in the surface chemistry of heteroge-

neous catalysts. For example, cobalt oxide (Co_3O_4) is an inexpensive and highly efficient material for water oxidation catalysis,¹⁷ and both spectroscopic¹⁸ and computational¹⁹ evidence point to dicobalt edge moieties as the dimensionally reduced active site. Similarly, the catalytic performance of other materials seems to stem from dinuclear fragments, like the $[\text{Cu}_2\text{O}]^{2+}$ core in the Cu-ZSM-5 zeolite (catalyzing methane oxidation to methanol, Figure 1b),²⁰ or metallic dimers supported on different oxides, such as Rh/ SiO_2 ²¹ or Ir/ $\alpha\text{-Fe}_2\text{O}_3$,²² which are active catalysts for hydroformylation and water oxidation, respectively. The latter example involves study of the heterogenization of a dinuclear iridium complex that robustly binds to metal oxide surfaces, improving the stability of the electrocatalyst; at the same time, higher catalytic activities are observed in comparison to the bulk material analogue, IrO_x .²³ Interestingly, depending on the identity of the metal oxide surface, either *side-on* (in Fe_2O_3) or *end-on* (in WO_3) binding modes of the dinuclear Ir fragment were accessed.²⁴

Strikingly, despite considerable efforts to understand the aforementioned catalysts, most of the mechanisms by which these reactions operate are far from being well understood, given the complex nature of the systems involved (*i.e.* biological or heterogeneous systems). Similarly, homogeneous catalysts that leverage metal-metal cooperativity, as in Pd-catalyzed cross-couplings (*e.g.* Stille or Sonogashira, where added Cu has a beneficial effect), are challenging to thoroughly study.^{25,26} Thus, better-defined bimetallic model systems are highly valuable for elucidating the fundamental steps involved in catalysis.^{27,28} Such models can stabilize proposed reactive intermediates²⁹ or serve as catalysts whose stereoelectronic properties can be easily tuned through ligand modification. This latter aspect is of paramount importance, since the metal-metal distance, coordination number, and resulting geometry are inherently controllable with appropriately designed dinucleating ligands.^{30–32}

From this perspective, 1,8-naphthyridine is an excellent scaffold, as it supports two metal atoms in close proximity due to the rigidity conferred by the fused pyridine rings, and may be functionalized at the 2- and 7- positions to produce chelating ligands (Figure 1c).^{30,33} These flanking side-arms provide thermodynamic stability and can be tuned to modify electronic properties or drive the selective formation of heterobimetallic derivatives (*vide infra*). While complexes of unfunctionalized or 2-functionalized 1,8-naphthyridines commonly feature coordination of more than one naphthyridine ligand,³³ several groups have taken advantage of 2,7-functionalized 1,8-naphthyridine-based scaffolds to drive the formation of dinuclear complexes containing a single naphthyridine ligand.

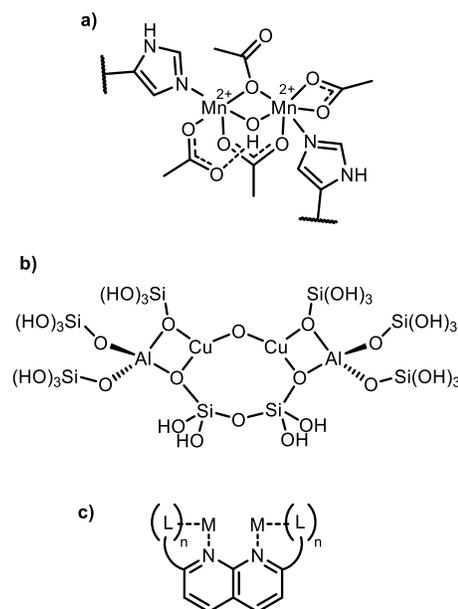


Figure 1. a) Active site of arginase. b) Active site of zeolite Cu-ZSM-5. c) General structure of 2,7-functionalized 1,8-naphthyridine.

Seminal work by Kaska and Ford in the 1980s demonstrated the formation of homobimetallic Cu^{II} and Rh^{III} complexes of bnpn (2,7-bis(2-pyridyl)-1,8-naphthyridine), the latter being a robust catalyst for the water gas shift reaction.³⁵ Subsequent work by Kaska and Sauvage on the dcnp²⁻ (2,7-dicarboxylate-1,8-naphthyridine) scaffold highlighted the importance of the bridging and dinucleating ligands in delocalizing electron density over two metals in mixed-valence $\text{Ru}^{\text{II}}/\text{Ru}^{\text{III}}$ complexes.³⁶ During the early 1990s, studying rigid-chain Mo-based polymers, Chisholm and co-workers employed 2,7-dioxo-1,8-naphthyridine (DON, Figure 2) to isolate a tetranuclear Mo complex featuring two Mo-Mo quadruple bonds as a soluble oligomer.^{37,38} In the early 2000s the Lippard group synthesized a library of 2,7-functionalized 1,8-naphthyridine ligands containing a variety of nitrogen-based side-arms (Figure 2),³⁹ which afforded a series of homobimetallic complexes mimicking active sites of different metalloenzymes and oxygen-activating proteins.^{40–42} For instance, a BPAN-containing dinuclear Zn complex was 6.4 times faster in performing transesterification of HPNP (2-hydroxypropyl-4-nitrophenyl phosphate, used as an RNA model) than the corresponding mononuclear reference.⁴⁰ More recently, Bera and co-workers have successfully utilized a range of substituted naphthyridine ligands to examine the reactivity of binuclear complexes of Cu ,^{43–45} Ru ,^{46–48} and Pd .⁴⁹ Naphthyridine-based ligands are also suitable for the synthesis of pentametallic string complexes of Ni ⁵⁰ and coordination polymers of Ag .⁵¹

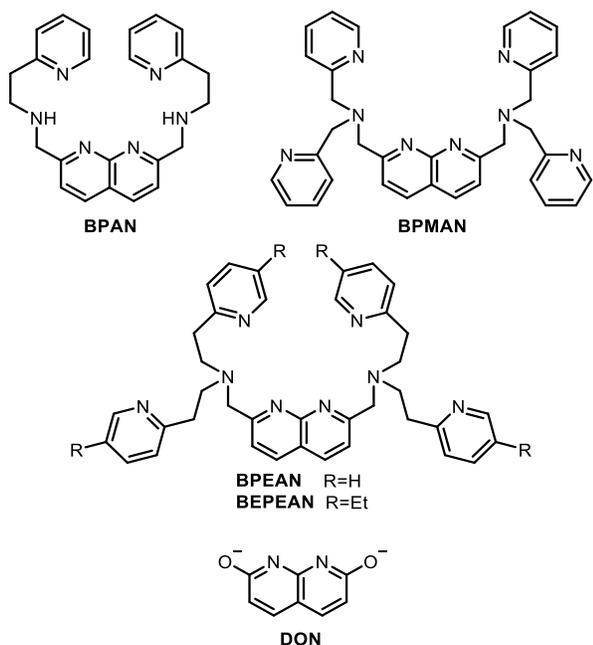


Figure 2. Representative examples of 2,7-functionalized 1,8-naphthyridine-based ligands.

These examples demonstrate the versatility of the 1,8-naphthyridine framework in different contexts for bimetallic coordination chemistry. While infrequently used in the past, this ligand platform gained popularity in the 2000s, especially following Bera *et al.*'s 2009 review that described bimetallic complexes of 1st, 2nd and 3rd row transition metals supported by this scaffold.³³ Over the last decade, our group and others have significantly advanced the chemistry of 2,7-functionalized 1,8-naphthyridine frameworks that are the focus of this Account.

Symmetrical naphthyridine ligand design

Our work on 1,8-naphthyridine scaffolds stemmed from interest in important small molecule transformations and, more specifically, the longstanding challenge of developing a model for heterogeneous water oxidation catalysts composed of inexpensive, earth-abundant metals. One such catalyst is cobalt oxide (CoO_x), for which the minimal proposed active site is comprised of two octahedral cobalt centers that are 2.82 Å apart and connected by two bridging oxo or hydroxy ligands (Figure 3).⁵² Furthermore, the key O–O bond forming step is thought to occur by coupling of coaxial oxygen species on the two metal centers. Thus, modeling these structural features seemed to require a dinucleating ligand that could support a $\text{Co}(\mu\text{-O})_2\text{Co}$ fragment while isolating variable, coaxial positions at octahedral Co centers. After considering various dinucleating ligand platforms, several based on 1,8-naphthyridine seemed most promising for enforcement of these structural parameters, as its two nitrogen atoms are 2.31 Å apart⁵³ and part of a rigid, relatively inflexible backbone.

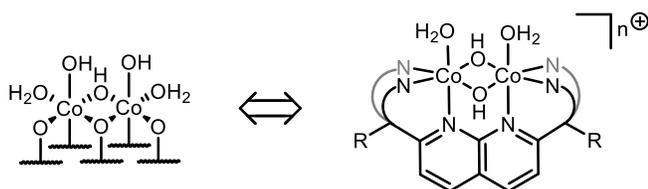


Figure 3. Schematic depiction of the proposed CoO_x dinuclear active site and its targeted dicobalt synthon

However, at the time no appropriate, naphthyridine-based ligand featuring chelating side-arms that would enforce $\sim 90^\circ$ angles between similarly strong donors, while isolating coaxial terminal coordination positions, had been reported. This led to the design and synthesis of a family of naphthyridine ligands functionalized at the 2- and 7-positions with dipyriddy moieties, DPMN, DPEN and DPFN (Figure 4).^{1,54}

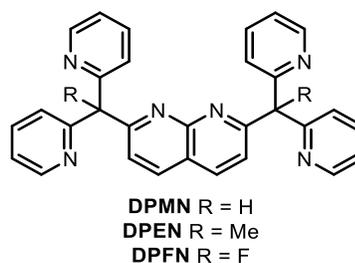


Figure 4. Dinucleating ligands with 2,7-dipyridyl chelating side-arms.

These three ligands enforce very similar coordination environments within the binding pocket but in the context of water oxidation it seemed that the fluorinated DPFN analogue, readily obtained by fluorination of DPMN with Selectfluor, would be most useful. Indeed, the DPFN ligand persists under harsh oxidizing conditions, exhibiting no oxidation event within the electrochemical window of 0.1 M ${}^t\text{Bu}_4\text{NPF}_6$ in DMF (1.7 V vs. NHE).⁵⁴ In addition, it forms dicobalt complex 1 upon treatment with cobalt nitrate under oxidizing conditions, which accurately reproduces the structural features of the layered oxy-hydroxide CoOOH edge site, with two octahedral cobalt centers 2.7826(5) Å apart, each bound to one terminal *aqua* ligand and two bridging hydroxides (Figures 5 and 6).

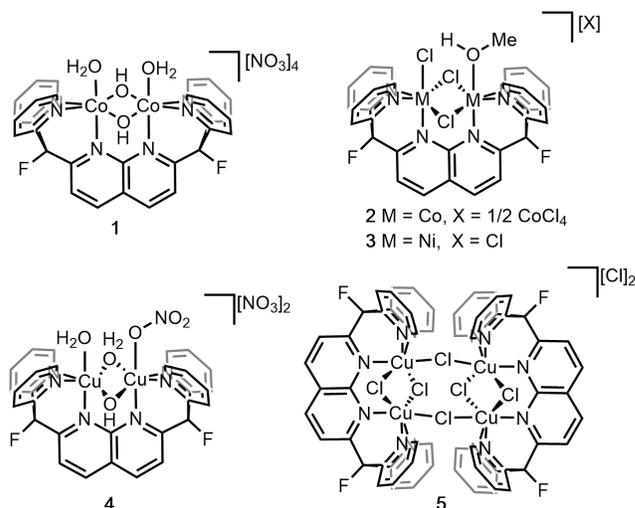


Figure 5. Early examples of complexes of DPFN with first-row transition metals.

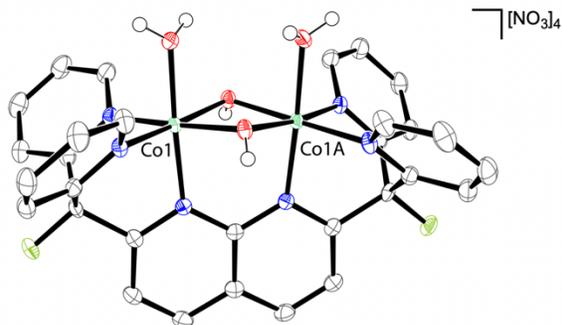


Figure 6. Solid-state structure of **1** determined by single crystal X-ray diffraction.

While electrolysis experiments at pH 9 revealed low catalytic activity for **1**, observed reactivity showed that phosphate (a commonly used buffer for electrocatalytic studies) coordinates to the dicobalt site as a bridging ligand to form a stable, phosphate-bridged tetranuclear Co complex.⁵⁴ The stability of this species suggests that commonly used buffers involving a potentially bridging anion (e.g., PO_4^{3-} , BF_4^- , ClO_4^-) could deactivate a catalytic reaction center involving a bimetallic diamonoid $\text{M}_2(\mu\text{-O})_2$ structure. Subsequently, a structurally similar DPEN-supported complex was prepared by Nocera and co-workers and also studied as a model system for cobalt oxide-catalyzed water oxidation.^{17,55} They also showed that the activity of $[\text{Co}_2(\mu\text{-OH})_2(\text{OH})_2(\text{DPEN})]^{2+}$ is indeed suppressed by higher borate concentrations.¹⁵

This ligand platform was designed to hold two cobalt centers in close proximity to mimic the edge sites of CoO_x , but concurrent studies showed that it also effectively binds a number of other divalent first-row transition metals to give bimetallic complexes such as **2–5** (Figure 5).⁵⁶ These results further highlighted the remarkable ability of these naphthyridine ligand frameworks to assemble two transition metals into a bimetallic core.¹⁷

Extension to dicopper(I) complexes

In probing the breadth of bimetallic assemblies that could be accessed with these naphthyridine-based platforms, structural aspects of dicopper(I)-DPEN complexes stood out.¹ Treatment of two equivalents of $[\text{Cu}(\text{NCMe})_4]\text{PF}_6$ with DPEN afforded the C_{2v} -symmetric complex $[\text{Cu}_2(\mu\text{-NCMe})(\text{DPEN})][\text{PF}_6]_2$ (**6**) which possesses an unusual MeCN binding mode, σ -bridging symmetrically between the two Cu centers (Figure 7). This binding mode was especially intriguing at the time, as it represented a rare example of a primarily σ -donor contributing both lone pair electrons to a 3-center, 2-electron bonding ($3c\text{-}2e$) interaction.⁵⁷

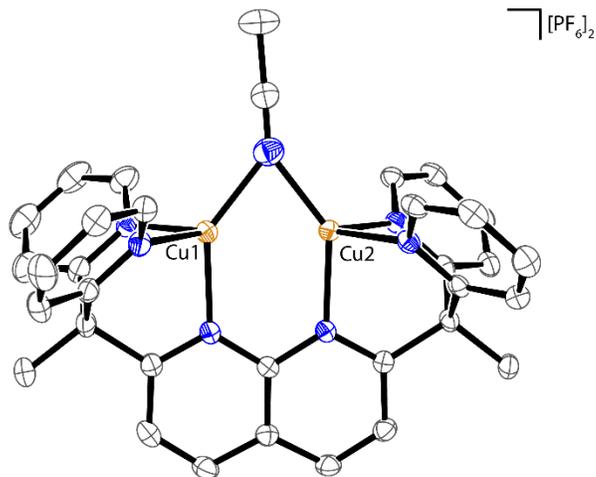


Figure 7. Solid-state structure of **6**.

Since the aforementioned report, it has become clear that this bonding mode represents a general feature of acetonitrile coordination to dicopper fragments supported by tetra(pyridyl)naphthyridine ligands. For example, DPFN forms the analogous complex $[\text{Cu}_2(\mu\text{-NCMe})(\text{DPFN})][\text{NTf}_2]_2$ (**7**).² This symmetrical binding can be rationalized by a simple MO diagram of the dicopper(I) core (Figure 8, left). As each Cu^I center possesses a full $3d^{10}$ outer electron shell, any interaction with an additional electron pair must involve the low-lying empty $4s$ orbitals. For the MeCN bridging ligand, vibrational analysis and DFT are consistent with a $3c\text{-}2e$ bond. An NBO analysis reveals that the $3c\text{-}2e$ bond involves contributions from the terminal, sp -hybridized lone pair of electrons on MeCN and, primarily the $4s$ orbitals on the Cu centers (see SI), while a quantum theory of atoms in molecules (QTAIM) analysis suggests a direct, cuprophilic interaction between the two Cu^I centers, as indicated by the presence of a bond critical point between both Cu atoms, and a ring critical point within the Cu–N–Cu three membered ring.⁵⁸ Moreover, NBO analysis highlights a weak π -backbonding interaction occurring *via* backdonation of the metals' $3d$ orbitals into the π^* orbitals on the MeCN fragment (see SI). Similar binding was observed for other strong field donors featuring a sp -hybridized terminal lone pair of electrons, such as CO or xlyl isocyanide, and in all 3 systems, IR spectroscopy reveals a moderately lower $\text{C}\equiv\text{X}$ stretching frequency consistent with weak π -backbonding.¹

Given the observed, strong tendency of ligands to symmetrically bind to both Cu centers in this system, it was of interest to investigate structures for a broader range of donor types. An intriguing target in this regard is the phosphalkyne MeCP, which is isoelectronic with MeCN but has never been observed to engage in analogous $3c\text{-}2e$ bonding. In collaboration with the Scheer group in Regensburg, $[\text{Cu}_2(\mu\text{-PCMe})(\text{DPFN})][\text{NTf}_2]_2$ (**8**, Scheme 1) was synthesized and found to exhibit a bridging ligand geometry where the $\text{C}\equiv\text{P}$ triple bond symmetrically coordinates to the Cu centers but is tilted away from the central position and to one side of the complex (Figure 9, top), both in the solid state and in solution (as determined by variable temperature ^1H NMR spectroscopy).⁵⁹ The observed binding geometry is consistent with the greater energy difference between electrons of the terminal lone pair and the π orbitals of MeCP compared to those of MeCN, stemming from reduced $2p_n\text{-}3p_n$ (vs. $2p_n\text{-}2p_n$) overlap.⁶⁰ As a result, phosphalkynes preferably bind *side-on*. Similar binding is observed for internal alkynes (Figure 9, bottom).^{38,40}

Interestingly, both phosphalkynes and alkynes adopt a geometry in which the bridging ligand tilts towards one side of the naphthyridine core. This tilted geometry is rationalized by the MO diagram in Figure 8. An NBO analysis of $[\text{Cu}_2(\text{MeCCMe})(\text{DPFN})][\text{NTf}_2]_2$ (**9**) shows that backdonation from the filled $3d^{10}$ orbitals on Cu^I into the π^* orbitals of the bridging ligand fragment is optimized in this tilted geometry. Bridging ligands that are relatively weak π -acceptors in a tilted geometry, like nitriles and CO, bind more symmetrically to maximize σ -donation, while ligands with a poorer σ -donation capability, which rely significantly on π -

backdonations such as internal alkynes and phosphalkynes, prefer the tilted binding mode. Interestingly, for phosphalkynes there are two observed, tilted geometries. With sterically small substituents, the preferred binding mode has the phosphorus atom in the naphthyridine-dicopper plane and the alkyl group to the side (Figure 9, top), while bulkier phosphalkyne substituents, as in ^tBuCP, favor *side-on* binding with the phosphorus atom to the side. For intermediate cases such as AdCP (Ad = adamantyl), these two geometries interconvert in solution, as shown by variable temperature ¹H NMR spectroscopy.⁵⁹

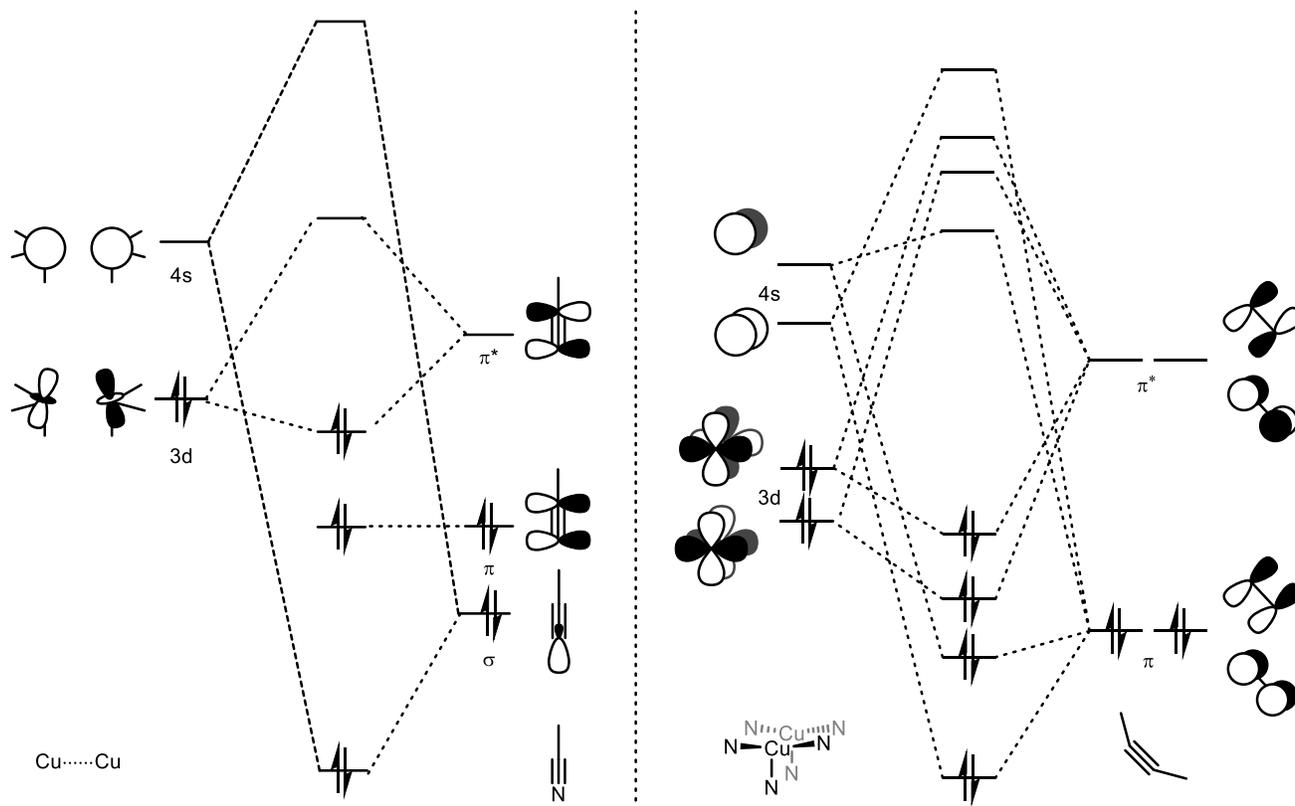
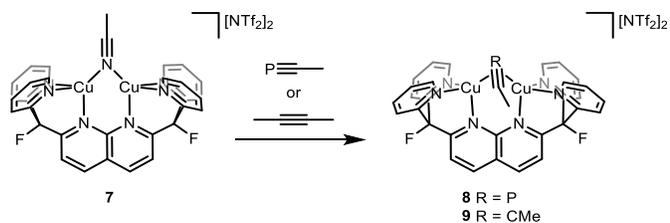


Figure 8. MO diagrams depicting an *end-on* interaction (left) and a *side-on* interaction (right) of an unsaturated bridging fragment with a naphthyridine-supported dicopper core.



Scheme 1. Synthesis of *side-on* bound complexes **8** and **9**.

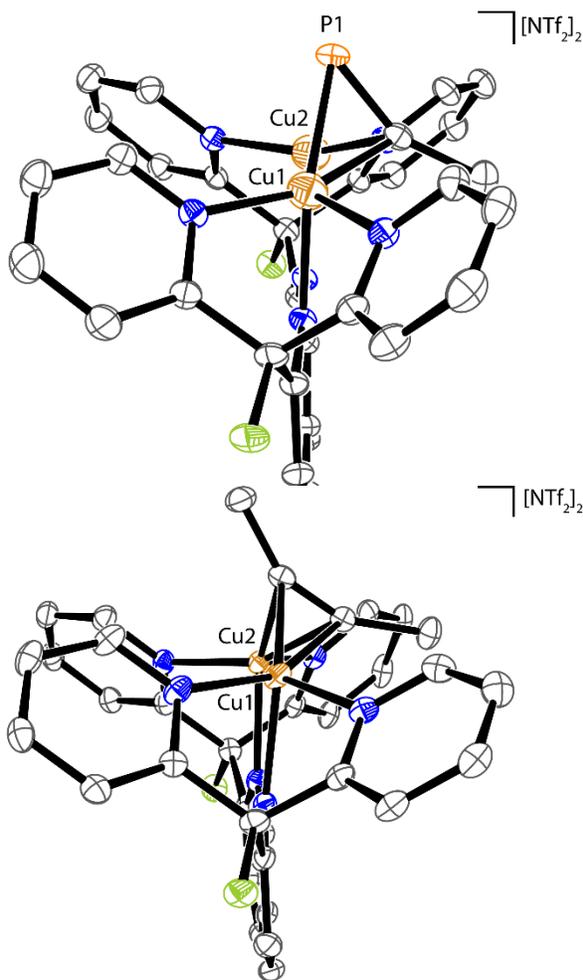
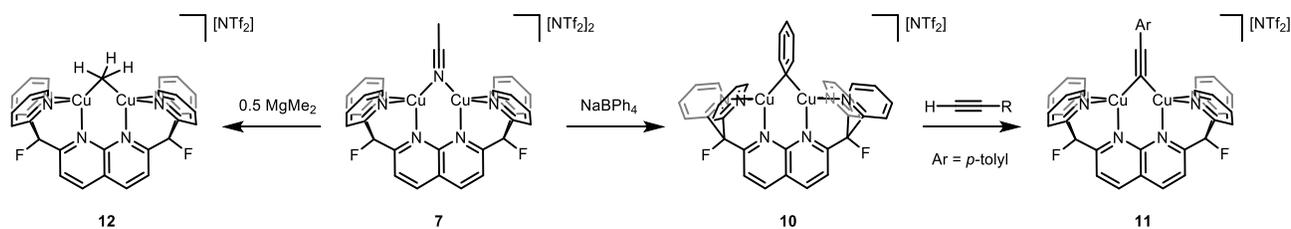


Figure 9. Solid-state structures (viewed along the Cu–Cu axis) of **8** (top) and **9** (bottom).

Synthesis of organocopper(I) complexes

Initial work on dicopper(I) highlighted the potential of DPEN and DPFN ligands to stabilize novel coordination geometries. However,

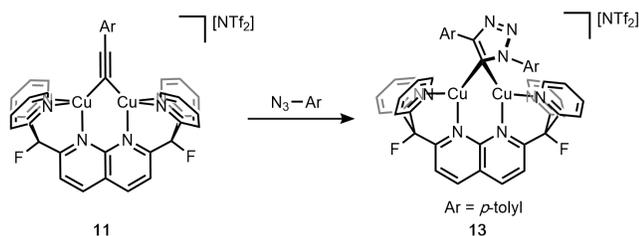
the $[\text{Cu}_2\text{L}(\text{naphthyridine})]^{2+}$ complexes used in these studies exhibited limited solubility in organic solvents. In an attempt to prepare more soluble complexes, we screened solubilizing counterions including the well-known family of tetraarylborate anions. This led to the serendipitous discovery that $[\text{Cu}_2(\mu\text{-NCMe})(\text{DPFN})]^{2+}$ abstracts an aryl group from these anions, including the notoriously difficult-to-activate $\text{B}(\text{C}_6\text{F}_5)_4^-$ anion, to afford μ -aryl complexes.² In particular, the activation of sodium tetraphenylborate occurred under mild conditions, reaching completion overnight at ambient temperature, providing the $[\text{Cu}_2(\mu\text{-Ph})(\text{DPFN})]^+$ cation as a convenient and versatile starting point for organodichlorocopper chemistry. Additional screening led us to select trifluoromethanesulfonimide (triflimide, NTf_2^-) as the weakly coordinating anion of choice. Although not commercially available, $[\text{Cu}(\text{NCMe})_4]\text{NTf}_2$ is easily prepared on decagram scale⁶¹ and exhibits chemical behavior analogous to that of the PF_6^- salt. The resulting complex, $[\text{Cu}_2(\mu\text{-NCMe})(\text{DPFN})][\text{NTf}_2]_2$ (**7**) exhibits a good balance between solubility and crystallinity⁶² and identical reactivity towards NaBPh_4 , providing $[\text{Cu}_2(\mu\text{-Ph})(\text{DPFN})]\text{NTf}_2$ (**10**, Scheme 2), which exhibits a symmetrically bridging phenyl ring between the two Cu^{I} centers and retains the C_{2v} symmetry observed for **6**. This convenient synthesis of an organocopper complex with an sp^2 -hybridized bridging carbanion led to a family of related complexes with bridging sp - and sp^3 -hybridized hydrocarbyl fragments.^{63,64} A bridging p -tolylalkynyl complex, $[\text{Cu}_2(\mu\text{-CC-}p\text{-MeC}_6\text{H}_4)(\text{DPFN})][\text{NTf}_2]$ (**11**), was conveniently prepared by treatment of **10** with p -tolylacetylene, while the synthesis of a bridging methyl complex (**12**) relied on displacement of MeCN in **7** by a Me^- fragment using Me_2Mg (Scheme 2). In all cases, the bridging organic moiety binds symmetrically between the two Cu centers. The symmetrical binding of the aryl and alkynyl ligands in **10** and **11** is interpreted as arising primarily from σ -type donation; as in nitriles and CO breaking of the C_{2v} -symmetry (*i.e.* tilting on one side of the naphthyridine plane or towards one Cu center) would weaken the σ -donation more than any additional stabilization that may come from greater involvement of the π -system. This is supported by DFT calculations on **10**, which show strong σ -donation from the aryl ligand and relatively weak π -type interactions (see SI).



Scheme 2. Synthesis of organocopper complexes **10–12**.

Reactivity and unusual stability of organocopper(I) complexes

One characteristic shared by these organocopper complexes is their surprising persistence. Their slow reaction rates with certain substrates was leveraged to isolate intermediates in Cu-catalyzed azide-alkyne cycloaddition (CuAAC) reactions mediated by **11**.⁶³ This bimetallic complex catalyzes the “click” reaction, and stoichiometric reaction with an organic azide cleanly affords the bridging triazolide complex **13** (Scheme 3 and Figure 10). Complex **13**, the first structurally characterized, symmetrically bridged dicopper triazolide, reacts with a terminal alkyne to regenerate the μ -alkynyl complex, and mechanistic studies confirmed the viability of a CuAAC mechanism involving cooperation of two copper(I) centers. This mechanism cycles between μ -alkynyl and μ -triazolide complexes as described above, with the bridging position serving as a coordination site. A dinuclear CuAAC mechanism had been somewhat controversial in the literature, but was suggested by computations⁶⁵ and isotopic labelling.⁶⁶ Interestingly, **13** exhibits a tilted geometry in the solid state that was attributed to steric interactions with the triazolide ligand. However, the similarity between this geometry and that observed for **8** and **9** suggests that electronic factors could contribute as well, since the triazolide can act as a π -acceptor ligand.



Scheme 3. Synthesis of triazolide complex **13**.

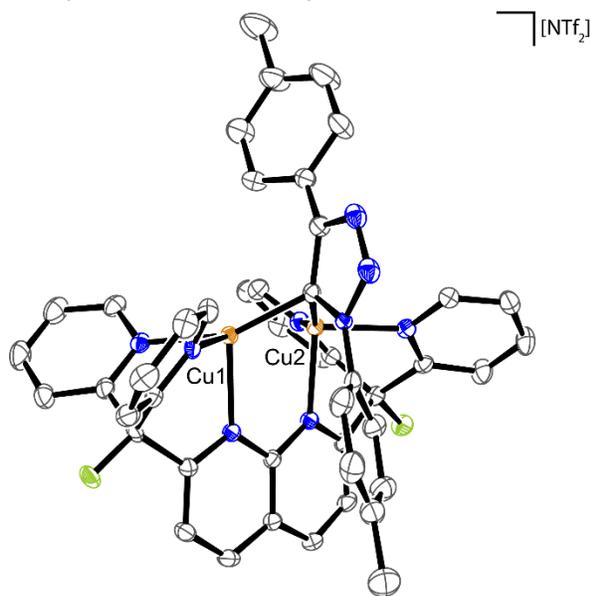


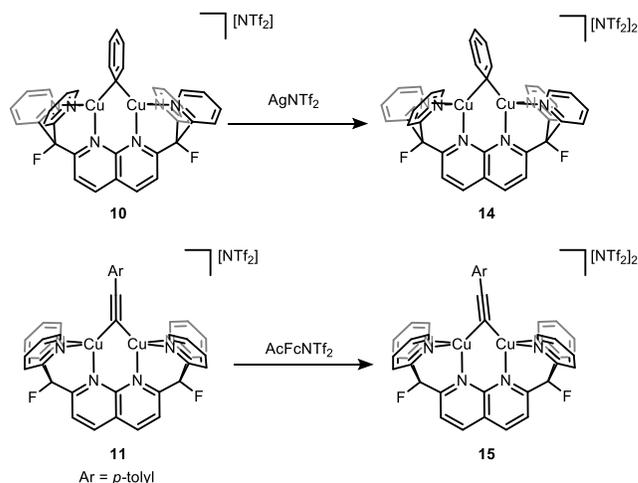
Figure 10. Solid-state structure of **13** determined by single-crystal X-ray diffraction.

The robustness of these complexes also manifests in their surprising stability toward water: complexes **10** and **12** react only slowly, the latter undergoing incomplete hydrolysis after 14 days in the presence of 170 equivalents of H₂O (in THF). This robustness is also reflected in a lack of reactivity toward element-hydrogen bonds. While **10** and **12** activate C–H bonds, this reactivity is associated with relatively acidic substrates such as terminal alkynes and

C₆F₅H, and the latter requires forcing conditions to produce the μ -C₆F₅ complex. Among several hydroxy-containing substrates, only C₆F₅OH was cleanly activated. Neither **10** nor **12** reacted with *tert*-butanol at ambient temperature, and upon heating only complex mixtures were produced (see SI).

Oxidized Cu^ICu^{II} and Cu^{II}Cu^{II} complexes

Well-defined organocopper(II) compounds are quite rare, and higher oxidation state copper species have been invoked as intermediates in a variety of important bond-forming processes.⁶⁷ It was therefore of interest to explore the electrochemical behavior of these dicopper complexes. Gratifyingly, cyclic voltammograms of **10** and **11** exhibited reversible oxidation features at modest potentials. Complex **10** was oxidized with AgNTf₂ to form paramagnetic, mixed-valence Cu^ICu^{II} species **14**. X-ray crystallography revealed that oxidation of the dicopper(I) core results in significant tilting of the bridging phenyl group toward one Cu center, concomitant with greater asymmetry in both the Cu–N and Cu–C(*ipso*) bond lengths. Similarly, the alkynyl complex **11** was oxidized with [AcFc]NTf₂ to form mixed-valence **15**. Unlike **14**, its dicopper core shows markedly smaller deviations from **11**, although the bridging alkynyl unit is canted slightly toward one Cu center (Scheme 4).



Scheme 4. Oxidation of **10** and **11** yields mixed-valent complexes **14** and **15**.

To probe the electronic structure of these unusual organocopper compounds, **14** and **15** were studied by EPR spectroscopy (Figure 11). Interestingly, at low temperatures (*i.e.* 4–100 K) **14** displayed a four-line pattern, which upon warming (*i.e.* between 150 and 278 K) collapses into a single resonance with a significant number of hyperfine peak splittings, indicating increased delocalization of the unpaired electron across both Cu centers. This temperature dependence is consistent with a Robin-Day Class II system,⁶⁸ where the unpaired electron is unequally delocalized over the two Cu centers. In contrast, EPR analysis of complex **15** exhibits a rhombic signal with at least seven peaks even at low temperatures (*i.e.* 30–130 K), which is best simulated by assuming coupling of the unpaired electron with two slightly inequivalent Cu centers. Overall, there is a greater extent of electron delocalization across both metals in alkynyl complex **15** relative to phenyl complex **14** despite both falling under the Class II umbrella, highlighting the pronounced influence of the bridging fragment on the electronic structure of the complex. The formal oxidation state of these dicopper complexes also has a dramatic effect on their reactivity; for instance, while dicopper(I) complex **11** is a competent catalyst for

CuAAC, mixed-valence **15** decomposed under identical catalytic conditions, while yielding only small amounts of triazole product.

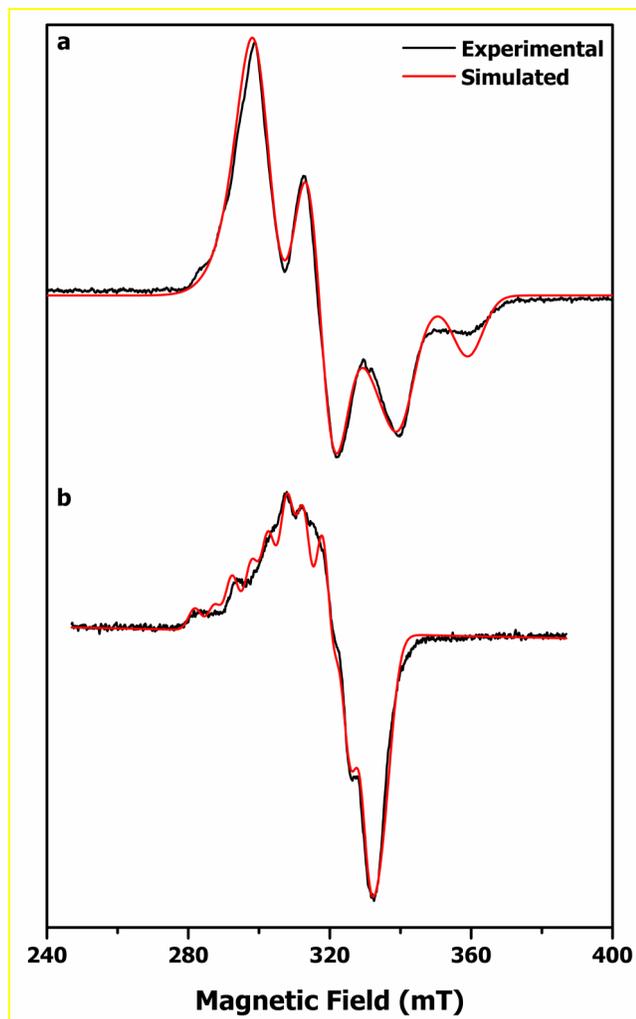


Figure 11. Experimental (black) and simulated (red) *cw* EPR spectra of (a) **14** in THF at 100K and (b) **15** in THF at 110 K.

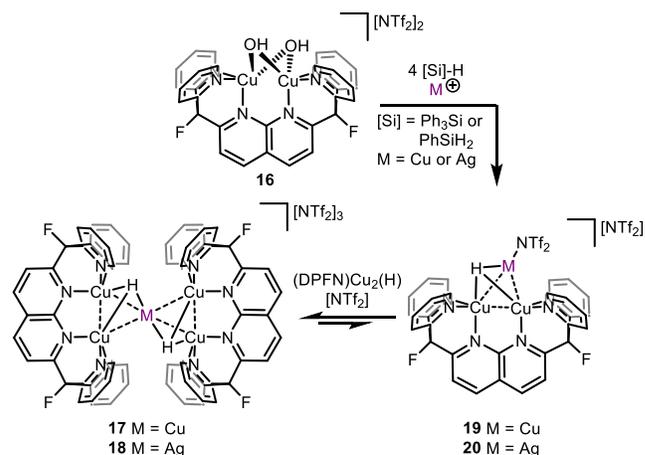
Concurrent with our studies on dicopper oxidation, Le Poul and Belle reported the synthesis of a stable dicopper(II) complex of DPFN (formed *via* simple coordination of the ligand to Cu^{II} salts)⁶⁹ which, upon oxidation to a mixed valence Cu^{II}/Cu^{III} complex, was competent for electrocatalytic C–H activation of toluene.⁷⁰ Similarly, DPFN-supported dicopper MeCN complex **7** in THF reacts cleanly under air to afford the dicopper(II) complex [Cu₂(μ-OH)₂(DPFN)][NTf₂]₂ **16** (see Scheme 5). The Evans method revealed an effective magnetic moment of μ_{eff} = 2.6 μ_B, consistent with two S = 1/2 metal centers with strong ferromagnetic coupling.⁶⁹ X-ray diffraction analysis shows that the product adopts a butterfly-type core, with the two hydroxide ligands symmetrically bridging both Cu centers.⁴

Silane reduction route to hydride clusters

Copper(I) hydride species are versatile catalysts for a range of transformations and can exhibit various structural and bonding motifs, often comprising multicopper clusters with high nuclearities.⁷¹ Attempts to synthesize [Cu₂(DPFN)]²⁺-supported hydride complexes were made by treatment of **7** with hydride sources such as LiHBEt₃ and KBH₄ but resulted only in formation of complex mixtures (see SI). Notably, an established, alternative route to copper hydride complexes involves reduction of Cu^{II} hydroxides or

alkoxides with hydric reagents (*e.g.*, silanes and boranes).^{72–74} To probe the feasibility of this synthetic route, complex **16** was exposed to PhSiH₃. Upon mild heating (1 h at 60 °C), a color change from blue to red-orange and effervescence of a gas were observed. Analysis of the reaction mixture by ¹H NMR spectroscopy revealed formation of a major diamagnetic, DPFN-containing product featuring one equivalent of a Cu-bound hydride ligand. Surprisingly, single-crystal X-ray diffraction analysis demonstrated that this species is not the expected dicopper monohydride complex, but rather a pentacopper dihydride cluster.⁴ The five Cu atoms lie in a plane, and adopt a “bow tie”-type configuration (**17**, Scheme 5). Although the hydrides could not be located from the Fourier difference map, density functional theory calculations identify them as tri-capping ligands on opposite faces of the bow tie plane. The central Cu atom appears to arise from a Cu^I source, since addition of a stoichiometric quantity of [Cu(OTf)]₂C₆H₆ allowed the reaction to take place at ambient temperature and in higher yield.

Changing the additional metal source to AgNTf₂ yielded the corresponding silver bow tie complex (**18**). In this case, the hydrides were located by X-ray crystallography (Figure 12), and determined to possess positions analogous to those calculated for the all-copper congener. Mechanistic experiments determined that both bow tie complexes were formed *via* trimetallic intermediates (**19–20**), which were independently prepared by treatment of **16** with the milder reductant Ph₃SiH. EXSY NMR spectroscopy revealed that these penta- and trimetallic hydride species are in equilibrium in solution. These unusual examples illustrate some of the limits of the [Cu₂(DPFN)]²⁺ platform. Although it supports a range of hydrocarbyl bridging ligands,^{2,63,64} hydrides require the presence of an additional Lewis acid for stabilization. The planar nature of these clusters indicates that they could serve as useful mimics for the active sites at copper surfaces during a number of catalytic and electrocatalytic processes, in particular hydrogenations and reductions.



Scheme 5. Reduction of dicopper(II) **16** with silanes yields trimetallic and pentametallic hydride complexes.⁷⁵

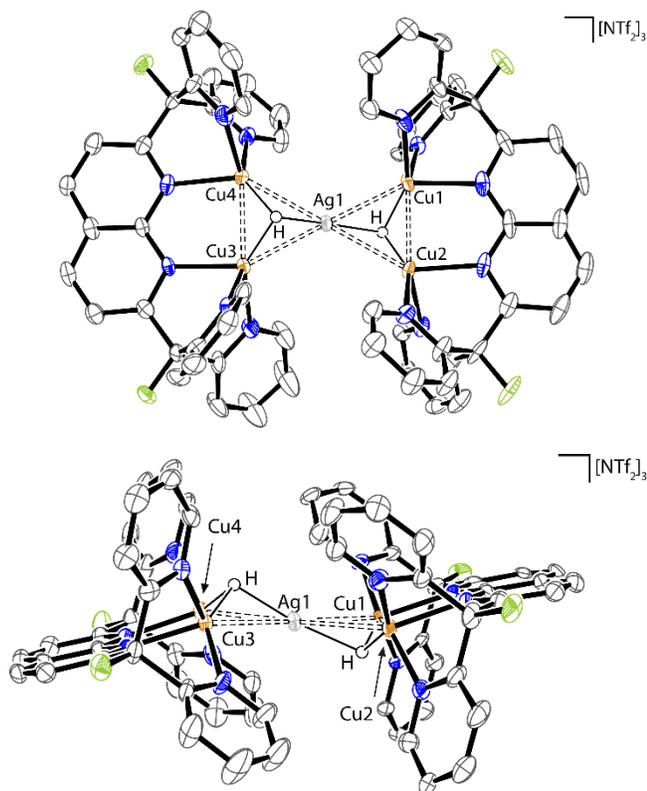
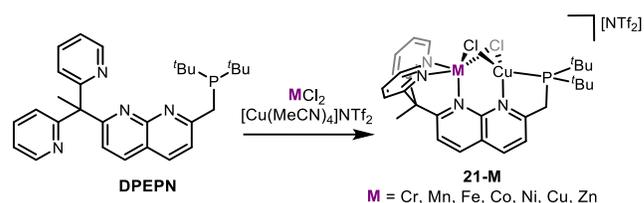


Figure 12. Top view (top) and side-view (bottom) of the solid-state structure of complex **18**.

Unsymmetrical ligands

The aforementioned studies clearly illustrate the utility of naphthyridine-based ligands for exploration of bimetallic units and properties resulting from metal-metal cooperativity. These studies have primarily focused on homobimetallic cores and C_{2v} -symmetric ligands. However, heterobimetallic assemblies might offer the greatest promise for accessing dramatically new properties and reactivity. Notably, nature utilizes heterobimetallic centers for certain difficult transformations. In principle, the synthesis of a heterobimetallic complex should be greatly facilitated by the use of an unsymmetrical, dinucleating ligand. Thus, to expand the breadth of this research to heterobimetallic complexes, naphthyridine ligands featuring distinctly different binding sites for two metals were designed and synthesized. This led to a dipyrindyl-phosphine ligand system (Scheme 6) that provides a harder set of three donors (N,N,N) on one side and a softer donor set (N,P) on the other. The two binding sites are therefore differentiated by geometry, steric properties, coordination number, as well as donor type. These characteristics of the DPEPN ligand lead to profoundly discriminating coordination pockets, such that combining DPEPN, $[\text{Cu}(\text{NCMe})_4]\text{NTf}_2$, and one equivalent of a first-row metal dichloride results in spontaneous formation of the heterobimetallic complex with Cu^{I} bound to the phosphine donor (Scheme 6).³



Scheme 6. Synthesis of a series of heterobimetallic complexes.

Interestingly, the series of complexes **21-M**, readily prepared with $M = \text{Cr-Zn}$ (see SI for details about the previously unreported Cr derivative), features only small structural variations, as evidenced by the overlay of their solid-state structures (Figure 13). This structure is consistent with selective coordination of the M^{II} ion in the harder, dipyrindyl-based pocket while the softer Cu^{I} center coordinates to the phosphine. To confirm the precision of this synthesis and the absence of scrambling in the bimetallic units, a combination of cyclic voltammetry, revealing a single electroactive species, and ESI-MS, verifying the heterobimetallic composition, was used. Anomalous X-ray diffraction unambiguously confirmed this characterization, showing that for $M = \text{Co, Ni, and Zn}$, the ion bound to the dipyrindyl side-arm strongly absorbs X-rays at the $M \text{ K}\alpha$ edge, while the ion bound to the phosphine donor absorbs $\text{Cu} \text{ K}\alpha$ radiation (Figure 14). Indeed, when the incoming X-rays' wavelength is tuned to an element's $\text{K}\alpha$ edge, the radiation is partially absorbed instead of diffracted and a reduced diffraction intensity is observed, which results in a smaller peak in the Fourier map at the spatial position occupied by the absorbing ion (Cu at the $\text{Cu} \text{ K}\alpha$ wavelength, and M at the $M \text{ K}\alpha$ wavelength).

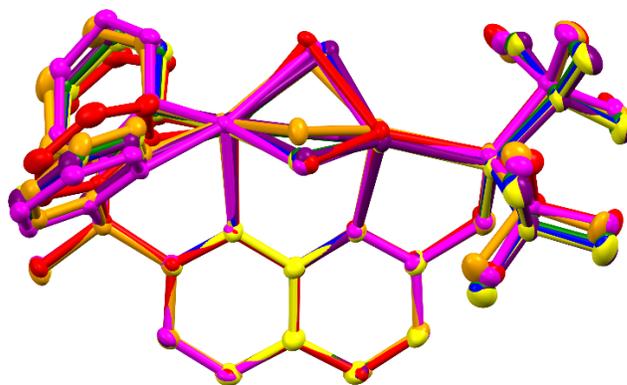


Figure 13. Overlay of the solid-state structures of **21-M** ($M = \text{Cr-Zn}$). One NTf_2^- anion and solvent omitted for clarity.

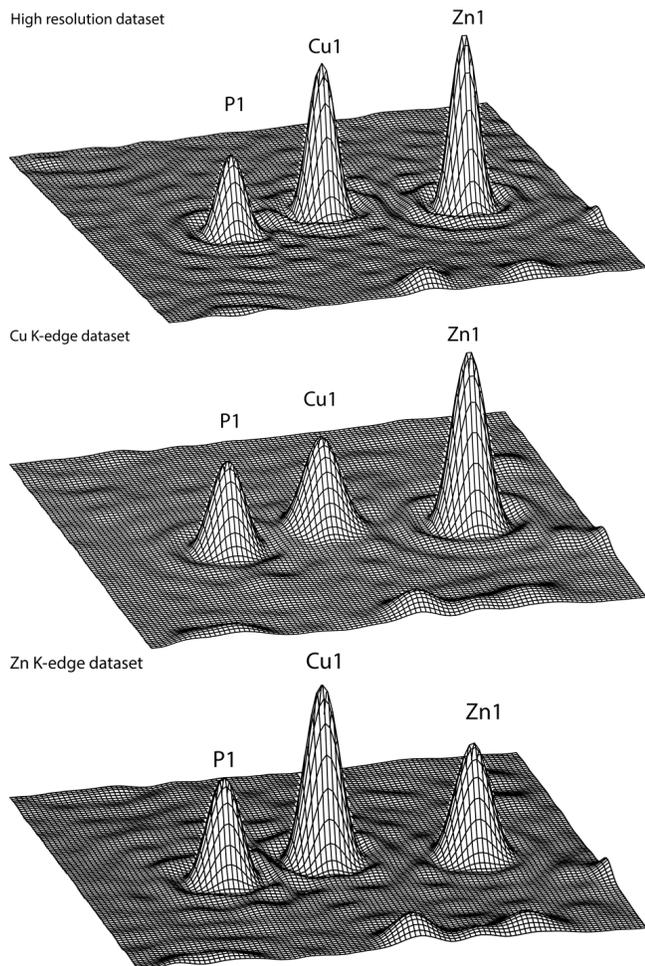
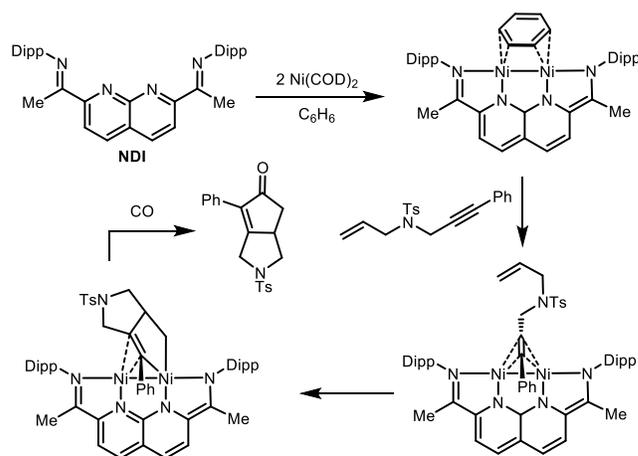


Figure 14. Fourier electron density maps determined by single crystal X-ray diffraction of $[\text{Zn}(\mu\text{-Cl})_2\text{Cu}(\text{DPEPN})]\text{NTf}_2$ in the Cu1-Zn1-P1 plane at 16 keV (top), Cu K-edge radiation (middle) or Zn K-edge radiation (bottom).

Recent studies of other naphthyridine-based systems

Since the initiation of the project described in this Account, dinucleating, naphthyridine-based ligands have gained popularity as platforms for studying reactivity and catalysis mediated by bimetallic centers. In addition to the studies conducted by the Belle, Le Poul, and Nocera groups (*vide supra*),^{17,55,69} of particular note is a dinickel complex supported by naphthyridine with diimine side-arms (NDI) reported by the Uyeda group in 2014.⁷⁶ Diimine side-arm groups in chelating ligands have recently come under intense focus for their electrochemical properties,⁷⁷ and in this case they allow the $\text{Ni}_2(\text{NDI})$ scaffold to access five different stable oxidation states. The $\text{Ni}_2(\text{C}_6\text{H}_6)(\text{NDI})$ complex is a versatile catalyst precursor for a wide variety of transformations, including hydrosilation,⁷⁸ alkyne trimerization,⁷⁹ and nitrene dimerization.⁸⁰ This dinickel system was also used to model several proposed steps in a Pauson-Khand reaction, such that a bound alkyne complex and a nickelacyclic product of oxidative cyclization (Scheme 7) were observed,⁸¹ accomplishing a long-standing goal in organometallic chemistry.⁸² Additionally, treatment of the nickelacycle with CO generated the desired cyclopentenone product in high yield. More recently, Uyeda and co-workers have reported a family of $\text{Ni}_2(\text{NDI})$ complexes that catalyze the formal [4+1] cyclization of 1,3-dienes with vinylidene equivalents,⁸³ a challenging transformation that is enabled by metal-metal interactions induced by the dinucleating naph-

thyridine ligand. Building on these findings, Braconi and Cramer have introduced chiral variants of these $\text{Ni}_2(\text{NDI})$ systems, able to affect cyclopropanation of alkenes with high yields and enantioselectivities.⁸⁴ Other groups have also reported chiral naphthyridine-based ligands featuring oxazoline moieties.⁸⁵



Scheme 7. Uyeda's modelling of the Pauson-Khand reaction with a dinickel complex.

Utilizing a related NDI ligand, Bera and co-workers have recently reported a dicopper(I) complex that is active for catalytic alcohol dehydrogenation.⁴⁴ Use of symmetrical diphosphino-substituted naphthyridine ligands has been explored by Broere and co-workers, who obtained dicopper(I) complexes that bind ligands in the bridging position,^{86,87} as was observed for the DPFN-supported compounds. In addition, in a manner similar to that the Milstein group explored with related PNP ligands,⁸⁸ Broere and co-workers reported deprotonations of the methylene-linked phosphine side-arms, which led to activation of H_2 and isolation of a bridging mesityl complex, analogous to our DPFN-based phenyl complex **10**.^{86,89} In 2015, Zhang and co-workers utilized the BPMAN ligand (Figure 2) and found that treatment with Cu^{II} gives $[\text{Cu}_2(\text{OH})(\text{BPMAN})][\text{OTf}]_3$, which is a precursor to an electrocatalyst for water oxidation under pH-neutral conditions.⁹⁰ Himmel and co-workers found that 2,7-bis(*N,N*-diisopropylguanidino)-1,8-naphthyridine supports complexes with three, four, or six Cu atoms in linear assemblies.⁹¹ Similarly, Khustnutdinova and coworkers employed related unsymmetrical naphthyridine-based ligands containing a BPMAN side-arm to support multinuclear Cu chains (2–4 Cu atoms) synthesized in a stepwise, selective, and reversible fashion, lengthening the chain by adding more equivalents of Cu^{I} or shortening it through chemical reduction.⁹² They also employed similar ligands to synthesize Cu-Pd multimetallic species as functional models for reaction intermediates in the Sonogashira reaction.⁹³ In addition, their use of an unsymmetrical diamine-OP Bu_2 naphthyridine ligand afforded a Cu-Pt heterobimetallic system that appears to exhibit metal-metal cooperativity in alkyne C–H activation and aryl abstraction from the BARf_2 anion, as was observed for **7** (Scheme 1).⁹⁴

Concluding remarks

This Account highlights the utility of dinucleating naphthyridine-based ligands for the controlled assembly of homo- and heterobimetallic complexes with accessible coordination sites and the two metals in close proximity. The study of these complexes can establish fundamental principles and mechanistic insights into the influence of metal-metal cooperativity on reactivity, and this infor-

mation should aid in catalyst design, and in advancing the understanding of known bimetallic reaction centers in biology and heterogeneous catalysis. The bimetallic complexes encountered in these studies have revealed new aspects of coordination chemistry; for example, dicopper complexes **14** and **15** illustrate how the nature of a bridging hydrocarbyl group can affect the metal-metal interaction and give either valence-trapped or delocalized electron structures. Dicopper systems have also been useful in establishing unusual binding modes for alkynes and phosphalkynes, and related, recently reported multimetallic hydride complexes appear to offer models for the activation of hydrogen on a copper surface. With respect to catalysis, dicopper complexes have been used to establish the viability of a bimetallic mechanism for alkyne-azide cycloaddition and to stabilize a previously elusive intermediate (the triazolide-bridged complex **13**). The dicobalt complex **1** provided a structural model for the bimetallic site of a heterogeneous electrocatalyst for water oxidation, and was used to probe anion complexation.

Recently, the diversity of side-arm functionalizations for naphthyridine-based ligands has dramatically increased, and unsymmetrical 2,7-disubstituted naphthyridines allow for the selective formation of heterobimetallic units. Complexes of the latter type afford interesting metal-metal combinations and future possibilities for providing unique reactivity patterns, as perhaps exemplified by bioinorganic systems. Both symmetrical and unsymmetrical naphthyridine-based ligands can support virtually isostructural species across different oxidation states, which provides a useful probe of electronic structure and its influence on reactivity. In summary, the studies described here help illustrate the importance of ligand design for creating bimetallic systems, and for providing synthetic control of reaction pathways for a bimetallic core.

BIOGRAPHIES

Addison N. Desnoyer received his B.Sc. (Hons.) degree from the University of British Columbia Okanagan in 2012 and his PhD from the University of British Columbia in 2017. After a postdoctoral stint at the University of Minnesota, he joined the Tilley group at UC Berkeley as an NSERC Postdoctoral Fellow, where his research focuses on bimetallic copper complexes.

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