

Breaking Selectivity Barriers in Oxidative Phenol Coupling with Hydroxo Multicopper(II) Clusters

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Metal-catalyzed oxidative phenol coupling offers a direct route to biphenols and diaryl ethers from simple phenolic precursors. Although substantial progress has been made in controlling chemoselectivity (cross-coupling vs. homocoupling and C–C coupling vs. C–O coupling) and stereoselectivity (axial chirality), other aspects of selectivity remain largely unexplored.

In nature, the biosynthesis of glycopeptide antibiotics, including vancomycin, and other biologically active macrocyclic peptides, relies on enzymatic oxidative phenol macrocyclizations of linear precursors to form biaryl and diaryl ether-linked macrocyclopeptides. Despite their synthetic importance, biomimetic and step-economical chemical counterparts of these transformations remain underdeveloped.

A major limitation of oxidative phenol coupling is its narrow substrate scope: the reaction is typically restricted to phenols having multiple electron-donating substituents that block reactive positions, or to 2-naphthol derivatives. As a result, unsubstituted phenols and ortho- or meta-monosubstituted phenols that are expected to yield a mixture of biphenol isomers have largely remained inaccessible.

To address these long-standing challenges, we have developed hydroxo multicopper(II) clusters, such as $\text{Cu}_2(\text{tmeda})_2(\mu\text{-OH})_2(\mu\text{-OTf})(\text{OTf})$ (tmeda and $[\text{Cu}_4(\text{pmbma})_4(\mu^3\text{-OH})_4](\text{OTf})_4$ (pmbma = *N*-(2-pyridinylmethylene)benzenemethanamine) that, in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), enable the oxidative macrocyclization of linear peptides and mediate the oxidative coupling of simple unsubstituted as well as mono- and polysubstituted phenols with complete ortho–ortho selectivity.

In this talk, I will highlight the unique reactivity and selectivity of hydroxo multicopper(II) clusters and discuss key mechanistic features that enable them to promote redox transformations inaccessible to conventional, mononuclear metal catalysts.

References:

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- (2) Bera, R.; Shaashua, O.; Libman, A.; Derks, M. T.G.M.; Yuan, B.; Pereverzev, A. Y.; Kapanaiyah, R.; Ben Lulu, M.; Kertzman, L.; Vainer, Y.; Torubaev, Y. V.; Roithová, J.; Pappo, D. Ortho-Ortho Selective Oxidative Coupling of Phenols by Hydroxo Multicopper(II) Clusters, *J. Am. Chem. Soc.* **2025**, ASAP.