Designing New Ligands for the Palladium-Catalyzed Oxidative Kinetic Resolution of Chiral Alcohols

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We have sought a synthetic replacement for the natural product (–)-sparteine to perform palladium-catalyzed oxidative kinetic resolutions of chiral alcohol. The key interactions responsible for the success of ((–)-sparteine)PdX₂ complexes (X = chloride, acetate) in enantioselective oxidations have been elucidated using quantum mechanics (B3LYP DFT with the PBF polarizable continuum solvent model). The enantioselectivities observed under base-rich reaction conditions follow directly from calculated energies of diastereomeric β-hydride elimination transition states incorporating (R) and (S) substrates. This relationship reveals an important role of the anion, namely to communicate the steric interaction of the ligand on one side of the PdII square plane and the substrate on the other side.

A variety of bispidinones and bispidines were proposed as mimics of (–)-sparteine. For these, enantioselectivities in the oxidation of 1-phenylethanol were predicted, as well as activation barriers and ligand stabilities. The candidates with high calculated selectivity were predicted to be less stable than (–)-sparteine, and this was confirmed experimentally, as the synthesized ligands failed to form isolable complexes with PdIII and showed no oxidation activity.

We then sought to duplicate the function of the (–)-sparteine catalyst not by imitating the ligand’s structure directly, but by engineering enantiodiscrimination into a catalyst already known to oxidize secondary alcohols with no selectivity. For this purpose the rate-limiting step in oxidations by palladium dicarboxylate complexes of an N-heterocyclic carbene was determined. A mechanism for the C-Hβ activation step which does not involve traditional β-hydride elimination is consistent with the experimental measurements (activation parameters, kinetics, kinetic isotope effect). Using the geometry of this step, hypothesized carbenes containing stereocenters were computationally screened for selectivity, activity and stability. This process revealed motifs which foster selectivity without spoiling the activity and stability of the proven catalyst. Large, rigid moieties (anthracenyl, substituted aryl) project the chirality of nearby stereocenters over a large volume of space, while flexible structures accommodate both antipodes of the substrate. Despite the distance from the metal center, meta-substituents on N-aryl groups promote selectivity in the oxidation of 1-phenylethanol.

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\begin{align*}
\text{Aerobic oxidation of alcohols by Pd}^{\text{II}} \text{ complexes} \\
\text{[((–)-sparteine)PdCl}_2 \quad & \quad ((R,R)-\text{bispidine})\text{PdCl}_2 \quad & \quad (\text{N-heterocyclic carbene})\text{Pd(OAc)}_2(\text{H}_2\text{O})
\end{align*}
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