**Viper Learning Object: In-Class Activity**

**Distinguishing Between Metal Catalysts for Inner- and Outer-Sphere C-H Bond Functionalization**

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**Background (to be read by students before class):**

 Homogeneous transition metal catalysts have proven useful in catalyzing C-H bond functionalization and in preventing over-oxidation.[[1]](#endnote--1),[[2]](#endnote-0),[[3]](#endnote-1) Transition metal catalyzed C-H bond functionalization can be divided into two general categories, systems that involve an outer-sphere, or coordination chemistry, mechanism (scheme 1) and systems that involve an inner-sphere, or organometallic, mechanism (scheme 2).2,[[4]](#endnote-2) Outer-sphere C-H bond functionalization does not actually involve the C-H bond directly interacting with the metal-center; instead, the C-H bond reacts with a ligand coordinated to the metal-center.2,4 The active ligand either inserts directly into the C-H bond, or it abstracts a hydrogen atom and recombines with the organic radical. Outer-sphere C-H bond functionalization typically occurs for metals in high oxidation states with reactive oxo, imido, or carbene ligands.2 The rate of these reactions is typically determined by C-H bond strength, similar to autoxidation reactions; therefore, selectivity favors the reaction of weaker C-H bonds such as those that are tertiary, benzylic, allylic, or alpha to heteroatoms, and over-oxidation can be a problem due to weaker C-H bonds in the oxidized products.2,4



**Scheme 1.** Outer-sphere C-H bond functionalization pathways.



**Scheme 2.** Inner-sphere C-H bond functionalization pathway.

Inner-sphere C-H bond functionalization involves initial reaction of the C-H bond with the transition metal center to form a metal-alkyl or -aryl.2,4 This is followed by a functionalization step in which the coordinated alkyl or aryl reacts either with a ligand bound to the metal center or with an external reagent. The selectivity of inner-sphere C-H bond functionalization is typically related to the propensity of the metal center to bind a particular C-H bond.2,4 Because inner-sphere C-H bond functionalization is less dependent on C-H bond strength than outer-sphere functionalization, inner-sphere catalysts are often utilized for the functionalization of strong C-H bonds as they have the potential to prevent overoxidation. Also in contrast to outer-sphere pathways, inner-sphere pathways are favored by diamagnetic complexes that perform two-electron chemistry, avoiding one-electron changes in oxidation state and radical pathways.4

1. Kalyani, D.; Sanford, M. S. *Top. Organomet. Chem.* **2007**, *24*, 85-116. [↑](#endnote-ref--1)
2. Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439-2463. [↑](#endnote-ref-0)
3. Labinger, J. A.; Bercaw, J. E. *Nature*, **2002**, *417*, 507-514. [↑](#endnote-ref-1)
4. Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437-2450. [↑](#endnote-ref-2)