Ligand-Substrate Interactions for Preorganization in Transition-Metal Catalysis

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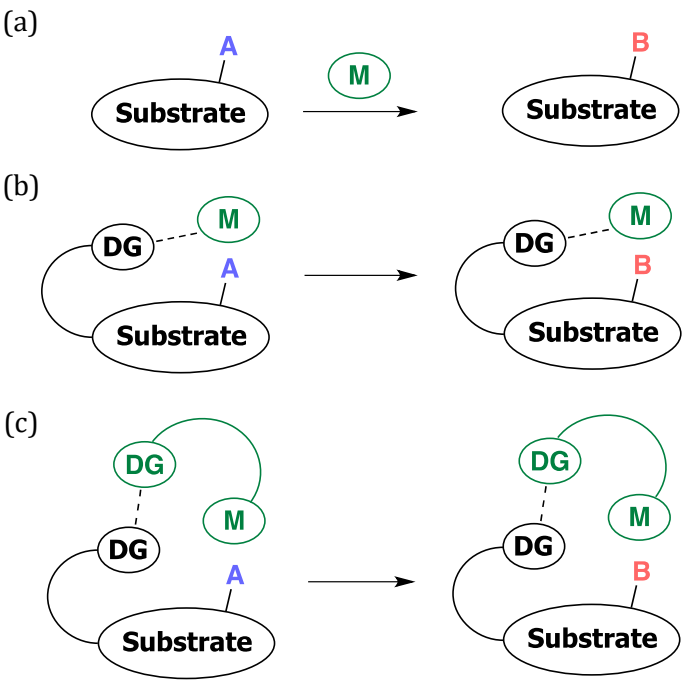
Introduction:

Non-covalent interactions govern most chemical changes in biology and chemistry. Weak interactions – between 1 and 10 kcal/mol – are used to alter the native reactivity of countless systems, stabilizing transition states to achieve site-, regio-, and stereoselective chemical change. These include ion pairs and hydrogen bonding interactions.[1,2] Nature is particularly gifted at using this approach, and enzymes employ a number of such non-covalent interactions to preorganize a substrate within an active site. These principles have been thoroughly applied in organic synthesis.[3] In contrast, in order to alter the innate reactivity of transition-metal catalysts, directing groups that bind *covalently* to the metal center are often used (Scheme 1b). This approach has been explored extensively with a variety of catalysts and systems.[4] More recently, methods have emerged that use functional groups in the secondary coordination sphere of transition-metal catalysts to preorganize substrates and control selectivity (Scheme 1c).



Scheme 1: Strategies in Transition-Metal Catalysis; (a) Metal-Catalyzed Transformations; (b) Traditional Directing Group Approach; (c) Non-Covalent Directing Group Approach

Outline:

There are three principle advantages to using non-coordinating preorganization for controlling reactivity in transition-metal catalysis: **(1)** breaking covalent coordination of a directing group to a metal center generally requires harsh conditions while *relatively mild conditions* can be used to disrupt non-covalent interactions and turn over the catalyst;[5] **(2)** a covalent

directing group approach often requires some strongly Lewis basic functionality while a variety of functional groups can direct in a non-covalent fashion; **(3)** preorganization involving ligand-substrate interactions does not require a coordination site at the active transition-metal center and does not change the inherent reactivity of the catalyst.

The groups of Breslow and Campbell developed a platform for a *site-selective* metal-oxo catalyzed oxidation of $C_{(sp^3)}$–H bonds using cyclodextrins to induce selectivity.[6] This work set the groundwork for Crabtree and Brudvig to develop a strategy of using non-coordinating interactions to selectively oxidize the benzylic C–H bonds of Ibuprofen using a manganese catalyst.[7] A number of groups have also reported on the use of non-coordinating interactions in transition-metal catalysis to induce *regioselectivity*,[1] defined as the reaction at one site over the other within a single functional group. Many of these are arene iridium-catalyzed C–H borylations or rhodium-catalyzed alkene hydrofunctionalizations. More recently this strategy has been invoked as an explanation for enhancing *enantioselectivity* in various transformations, including transition-metal catalyzed reductions and oxidations.[8]

There are reports highlighting four different ligand-substrate interactions to induce selectivity: **(1)** coordination either through a Lewis base/acid adduct between substrate and ligand or involving two Lewis basic sites mediated by a cation; **(2)** hydrophobic interactions between a catalyst's cyclodextrin rings and a substrate's non-polar groups; **(3)** electrostatic interactions involving full or partial charges between substrate and ligand; **(4)** hydrogen bonding, involving either one or two point binding modes. Many groups are currently focused on developing methods that employ weaker, less-strongly bonding interactions to control selectivity in transition-metal catalysis.

References:

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