Catalytic Terminal C–H Bond Functionalization of Linear Alkanes: Recent Advances

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Alkanes present a unique challenge to synthetic chemists. They are abundant in nature and relatively inexpensive, and thus have the potential to be a viable source of chemical feedstock; at the same time, they are among the most unreactive chemicals in nature.[1,2,3] Industrially, alkanes are processed via heterogeneous catalysis which require extreme conditions such as high temperature and pressure, and undergo reactions which show poor or poorly-understood selectivity.[3] The quest for a catalytic method which functionalizes alkanes selectively, especially at the terminal positions, has been a goal of the chemical community for the past few decades.

Efforts have been made in both heterogeneous and homogeneous catalytic fields to find a system that catalytically functionalizes the terminal position of linear alkanes. One such approach is based on the high selectivity achieved by natural enzymes, which depends on shape-selective recognition to bind substrates and activate them: Herron and Tolman utilized the pore sizes of a zeolite to selectively functionalize *n*-octanes,[4] and Suslick and coworkers directed the steric hindrance of porphyrin systems to hydroxylate preferentially the terminal positions of linear alkanes.[5]

Other approaches, notably in homogeneous catalysis, have included steps to generate a sufficiently reactive transition metal intermediate to oxidatively add the highly stable C-H bond. The alkyl component of the complex is then converted to a more thermodynamically stable product. Examples of such include iridium and rhodium complexes which are either photolyzed or reacted with hydrogen acceptors to yield reactive intermediates, which then oxidatively add the alkanes and produce either olefins[6,7,8] or aldehydes[8] as the final product. However, some problems exist for the methods cited such as catalyst deactivation[4,6] and isomerization of the terminal products into internal isomers.[6,7]

Recent methods for terminal C-H functionalization of linear alkanes utilize similar approaches as mentioned above. Thomas and coworkers rationally designed molecular sieve catalysts to shape-selectively oxidize terminal positions of linear alkanes.[9,10,11] Using various aluminophosphate (AlPO) molecular sieves, whose Al(III) ions had been replaced by redox active Co(III) or Mn(III) ions in few atom percents, they obtained high selectivity for terminally functionalized alcohols, aldehydes, and acids for *n*-hexane and *n*-octane substrates.[9] CoAlPO-18 and MnAlPO-18 were particularly effective, yielding 61.3% and 65.5% terminal-functionalized alkanes respectively.[9] CoAlPO catalysts were also used to oxidize *n*-hexane to hexanoic and adipic acids effectively.[10] Iron substituted aluminophosphates were also shown to catalyze the synthesis of adipic acid in one step synthesis from cyclohexane, in an improvement to the industrially utilized two-step synthesis.[12] The reaction mechanism for these catalysts is reasoned to be via a free-radical pathway.[9]

In another approach, it was discovered that alkanes could stoichiometrically be functionalized to yield organoboranes in reaction with [$Cp^*W(CO)_3Bcat'$] (Cp^* = pentamethylcyclopentadienyl; cat' = 1,2-$O_2C_6H_2$-3,5-$(CH_3)_2$).[13] Using the thermodynamic uniqueness of this system, Hartwig and coworkers catalytically functionalized linear alkanes via two methods: 1) photochemical activation of [(Cp*)Re(CO)$_3$] (Figure **1A**) and 4,4,4',4'5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (B$_2$pin$_2$) under CO;[14] and 2) thermal activation of [(Cp*)Rh(h^2-C$_2$H$_4$)$_2$] (Figure **1B**) and [(Cp*)Rh(h^4-C$_6$Me$_6$)] (Figure **1C**) with B$_2$pin$_2$[15] to form organoboranes, which may ultimately be converted facilely into other functionalized forms without the loss of regiochemistry.[13] In both cases, the terminally borylated alkanes were obtained in high yields: 95% from *n*-pentane using the rhenium catalyst (2.4%, 56 hours)[14], and 88% from *n*-octane using the rhodium catalyst (5.0%, 25 hours).[15]

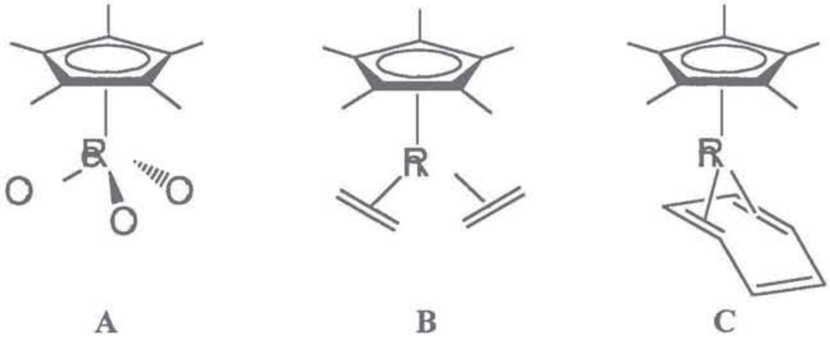

Figure 1

Thomas' molecular sieve catalysts give a commercially viable selectivity for primary C-H bond functionalization, and yield industrially significant products such as adipic acid (used in nylon production)[16]. Despite the high product selectivity, however, the conversion of substrates is necessarily low (~7%) so as to prevent the leaching of transition metals by polar products.[9] Hartwig's rhenium and rhodium systems are highly effective at terminal functionalization, but the borane reagents are costly, and the commercialization of such a process to a large-scale industrial one is not viable. Further progress in the field of alkane activation is anticipated in the coming years.

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