INTRODUCING FUNCTIONALITY THROUGH C-H BOND ACTIVATIONS

Reported by Rachel S. Hector September 24, 2001

INTRODUCTION

Carbon-hydrogen (C-H) bond activation reactions, those that replace hydrogen in a carbon-hydrogen bond with another atom, have received considerable attention in recent years.[1] The direct functionalization of carbon atoms traditionally regarded to be "unreactive" has often been referred to as a "Holy Grail"[1a] of synthetic chemistry, since control of the reactivity of these atoms would allow organic chemists to make use of hydrocarbons previously unusable in synthesis. C-H activation provides attractive methods for introducing functionality at carbon-hydrogen bonds without requiring prior functionalization of the hydrocarbon substrates. The development of catalytic variants of these processes allows for efficient and straightforward syntheses of many types of organic molecules. The breadth of the ever-growing field of C-H activation is such that an attempt to cover all of its aspects would be impractical; therefore, this work will present an overview of recent reports on C-H bond activation resulting in the formation of carbon-heteroatom bonds.

Scope of the Field

The term "C-H activation" is used loosely in the current literature. Authors often refer to C-H activation as a process that functionalizes "unreactive" carbon atoms. However, the term "unreactive" is used to refer to carbon atoms that are not adjacent to an electron-withdrawing group, which may include allylic, benzylic, and even sp^2 carbons, which are clearly activated. While some view the classical activation as one assisted by metal complexes, many authors label as "C-H activation" any process that accomplishes the removal of a hydrogen atom by methods other than deprotonation. In an attempt to impose some order on this lack of standardized vocabulary, this author has classified C-H activation reactions as belonging to one of three categories: allylic and benzylic functionalizations, remote functionalizations, and functionalization of untethered alkanes. Within these categories, activation mechanisms range from insertion of a metal complex into the C-H bond to hydrogen abstraction by a radical or other species.

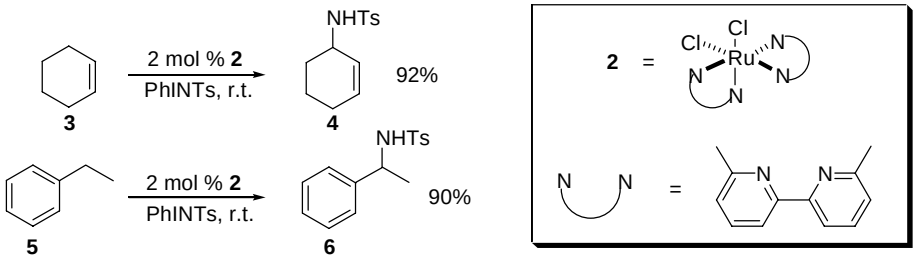
ALLYLIC AND BENZYLIC C-H BOND ACTIVATIONS

Reactions at allylic and benzylic positions are well-known chemical transformations. They represent the most questionable form of what is termed C-H activation; these positions are not unfunctionalized in the strictest sense because of resonance interaction with the neighboring pi system.

As such, C-H activation reactions performed on allylic and benzylic substrates often proceed with faster rates and higher yields than their unfunctionalized alkane counterparts.

Several examples of metal-catalyzed aminations and hydroxylations of allylic and benzylic hydrocarbons exist. One recent effort by Che and co-workers makes use of ruthenium catalysts and the nitrogen transfer agent PhINTs (**1**) to give aminated products in high yields (Scheme 1).[2] Studies have suggested that a metal-imido species is the most likely reactive intermediate in metal-catalyzed reactions with N-tosylimidoiodosobenzene the imidoiodobenzene **1** as the nitrogen source.[3] Competition experiments by Che and co-workers show that the rate of amidation is enhanced by both electron-withdrawing and electron-donating groups. Plotting $\log(k_{rel})$ against a carboradical parameter TE, a measure of the bond-dissociation energy of C-H bonds, gives a linear plot, indicating that little or no charge develops in the transition state. The authors also determined that C-H bond cleavage occurs in the rate-determining step, based on kinetic isotope effect studies that gave a k_H/k_D value of 6.5. From this information, the authors conclude that the activation occurs by abstraction of hydrogen by the reactive species to give an allylic or benzylic radical, which then reacts with the metal-amino complex to give an alkyl amine.

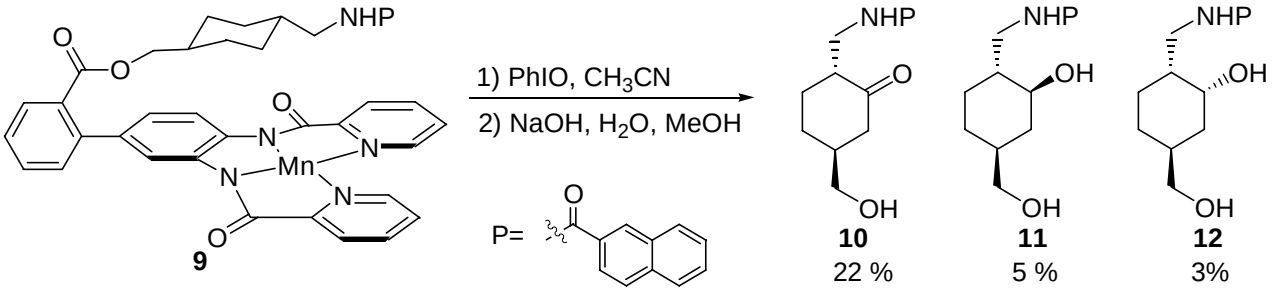
Scheme 1. Amidation of Allylic and Benzylic Hydrocarbons.



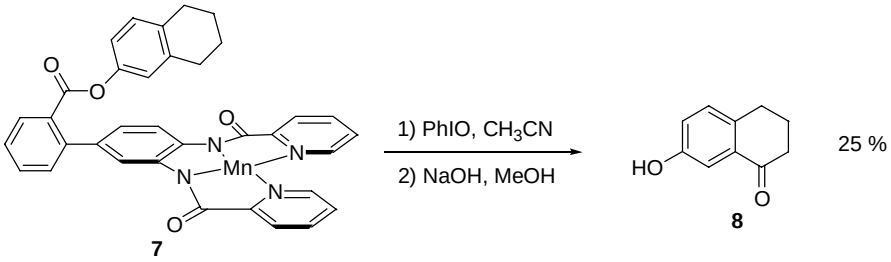
Many methods for oxygenation of unfunctionalized hydrocarbons have been developed over the years.[1b] These systems are often used to model biological oxygenation reactions, such as those catalyzed by cytochrome P-450. A recent study combined metal catalysis and molecular recognition to functionalize benzylic C-H bonds.[4] Sames and co-workers have tethered substrates to a catalytic center to achieve C-H bond activation using iodosyl benzene as the oxidant (Scheme 2). A manganese-oxo compound formed from the iodosyl benzene may abstract a hydrogen held above the reaction center by the tether, activating that carbon for oxidation. Reacting the untethered benzylic substrate with the catalyst produces a mixture of products resulting from oxidation of both benzylic positions, illustrating the function of the tether in the determination of the stereochemistry. Attempts to use this system to oxidize unreactive hydrocarbons by attaching a cyclohexylmethanol derivative to the tethering moiety **9** gave a 22% yield of ketone **10**, as well as 8% of a mixture of diastereomeric alcohols (Scheme 3). The

functionalization of the cyclohexylmethanol derivative was attempted without tethering the substrate; the result was re-isolation of 90% of the starting material along with an inseparable mixture of side products.

Scheme 2. Tethered C-H Activation of a Benzylic Substrate.

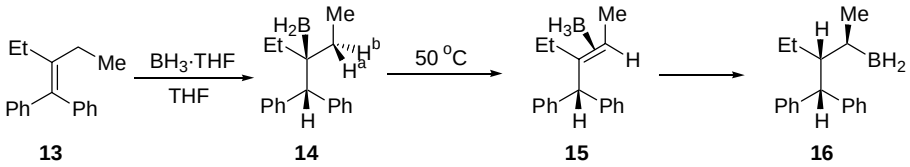


Scheme 3. Tethered C-H Activation of a Cyclohexyl Substrate.



While many C-H activations require the use of metal catalysts, a method recently developed by Knochel and co-workers uses a thermal migration of boranes[5] to effect formal allylic C-H bond activations, furnishing three contiguous stereocenters.[6] The reaction proceeds with the hydroboration of tetrasubstituted alkene **13** to provide tertiary alkylborane **14** (Scheme 4). Upon heating, this species undergoes a proposed dehydroboration to give the isomeric alkene-borane complex followed by another hydroboration to give secondary alkylborane **16**. The dehydroboration step is highly selective, giving only products resulting from the removal of H^a. The alkylborane product can be converted into a wide range of products, including alcohols, amines, and alkylating agents.

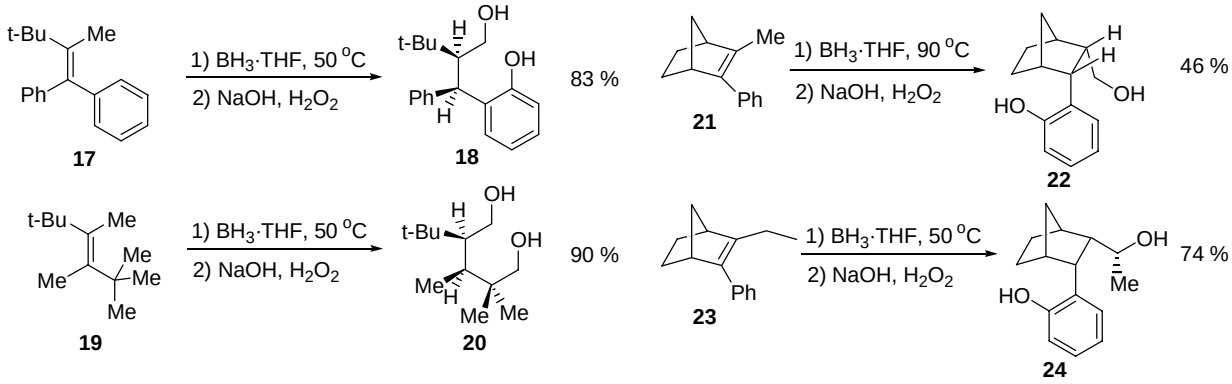
Scheme 4. Thermal Migration of Alkylboranes.



DIRECTED FUNCTIONALIZATION

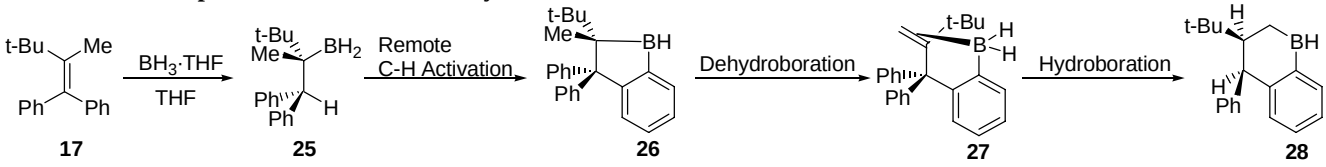
In general terms, remote functionalization occurs when a functional group reacts with a C-H bond in a non-activated portion of the molecule, i.e. a C-H bond that is not allylic, benzylic, or adjacent to another functional group. This may be facilitated by the use of intramolecular directing strategies, which have been widely used in recent C-H activation literature. Knochel and co-workers exploit a side reaction of their hydroboration of alkenes, seen above, to functionalize remote C-H bonds (Scheme 5).[7] The conversion of olefins **17** and **19** to the corresponding diols commences with hydroboration of the alkene as in the previous example. Oxidation with H_2O_2 and NaOH gives diol products **18** and **20** in good yields and as one diastereomer.

Scheme 5. Remote functionalization of selected substrates.



The researchers have learned that the remote functionalization can occur only when the alkene contains bulky tertiary alkyl substituents. Upon heating, diastereoselective insertion into an appropriately located C-H bond forms a six-membered ring. Recent mechanistic studies of this rearrangement have shown that the reaction proceeds through a pathway in which C-H activation occurs first to give five-membered boracycle **26** which can then undergo a 1,2-migration through a borane-olefin complex to give the 6-membered boracycle **28** (Scheme 6).[8]

Scheme 6. Proposed Mechanistic Pathway.

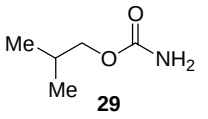
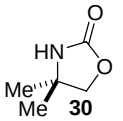
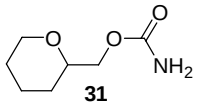
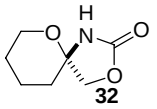
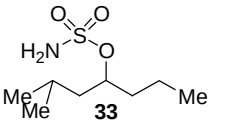
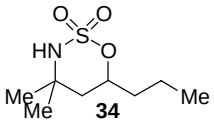
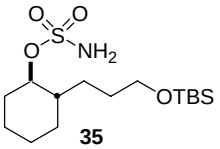
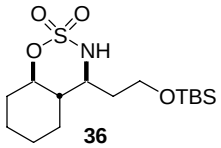


The authors have also determined that the reaction proceeds well with bicyclic substrates (Scheme 5). The geometric rigidity of these systems does not allow activation of the phenyl C-H before

migration because the borane is fixed trans with respect to the phenyl ring. Thus, migration of the borane must occur before C-H activation in these bicyclic systems.

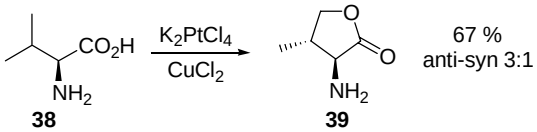
Du Bois has recently developed another example of directed functionalization in which carbamates or sulfamate esters undergo oxidative cyclization to give oxazolidinones or oxathiazines, respectively.[9] Using dirhodium catalysts and iodophenyldiacetate as the stoichiometric oxidant, the researchers obtain cyclized products in good yields with stereospecific C-H activation (Table 1). Free nitrene species are not thought to be the reactive intermediates in these reactions, because of the high stereospecificity of the insertion. Instead, the insertion is proposed to involve the intermediacy of the rhodium catalysts, possibly as a metal nitrenoid.[10]

Table 1. Oxidative Cyclization Products.

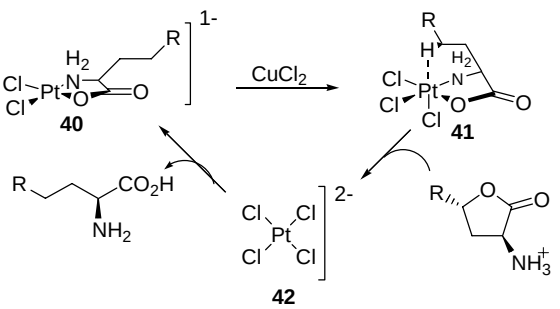
Substrate	Product	Catalyst	Yield
 **29**	 **30**	$[Rh_2(OAc)_4]$	83
 **31**	 **32**	$[Rh_2(tpa)_4]$	84
 **33**	 **34**	$[Rh_2(OAc)_4]$	90
 **35**	 **36**	$[Rh_2(oct)_4]$	75

The functionalization of L-amino acids to produce lactones has been shown in another example of catalytic remote functionalization (Scheme 7).[11] The substrates are treated with potassium platinum(II) chloride and a stoichiometric amount of copper chloride to give products with moderate *anti*/*syn* selectivity. The proposed catalytic cycle is shown in Scheme 8. The substrate is thought to displace two chlorine ligands to chelate to the metal, giving complex **40**. Oxidation of this complex by copper chloride leads to a Pt(IV) species **41**, which accomplishes C-H activation, followed by reductive elimination to give the lactone. Despite showing initial promise for functionalization of amino acids, the reaction suffers from low recovered yields (15-35%) and from a competing reaction leading to L-proline derivatives.

Scheme 7. Catalytic Amino Acid Functionalization.



Scheme 8. Proposed Catalytic Cycle.

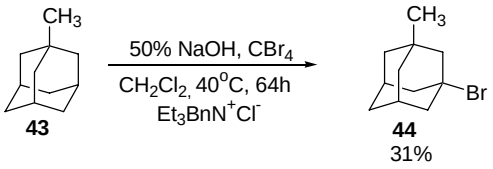


FUNCTIONALIZATION OF ALKANES

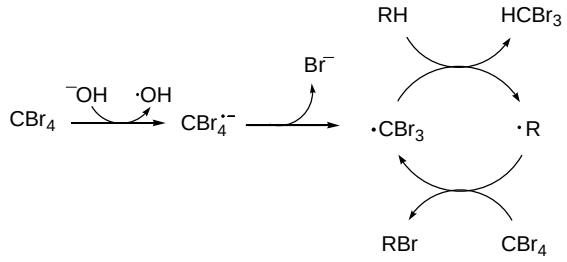
Few examples exist in the current literature in which an alkane is functionalized to give a C-X bond by C-H activation at a position that is not allylic or benzylic, and without a tethered functionality to assist in the reaction. One reason for this dearth of examples is that selectivity is difficult to control in an intermolecular system consisting of only sp^3-hybridized carbons. Control over selectivity can be established through the use of sterically hindered reagents or by relying on radical stability to control regioselectivity.

Examples of radical activation include the selective halogenation of unfunctionalized hydrocarbons. Fokin and co-workers have found that in solutions of carbon tetrabromide and 50% NaOH under phase-transfer conditions, substrates are selectively brominated at tertiary positions (Scheme 9).[12] The researchers chose adamantanes as models for tertiary hydrocarbons, but the reaction also proceeds in moderate yields with acyclic systems and is highly selective for tertiary positions in all cases. The authors have proposed that the bromination is accomplished by single-electron oxidation of hydroxide ion by CBr_4, followed by the formation of carbontribromide radical that abstracts a hydrogen from a tertiary position to initiate the radical chain reaction (Scheme 10). The authors state that this mechanism may account for some of the observed selectivities, because the increased stablility of tertiary radicals relative to secondary favors abstraction of the hydrogen at the tertiary position.

Scheme 9. Phase-Transfer Bromination.

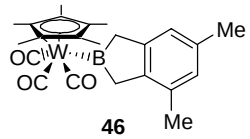


Scheme 10. Catalytic Cycle of Radical Bromination.



As previously mentioned, organoboranes are important synthetic intermediates. Consequently, a method for the generation of these species from simple alkanes is of great interest. Hartwig and co-workers have developed a number of methods for these transformations that give alkanes activated at primary carbons. The researchers found that complexes such as $Cp^*W(CO)_3Bcat'$ 46 stoichiometrically activate alkanes such as pentane, 1-ethylcyclohexane and 2-methylbutane at the primary position whereas reaction with cyclohexane showed that secondary positions can be functionalized, albeit in significantly lower yields.(Table 2)[13].

Table 2. Stoichiometric Borylation.



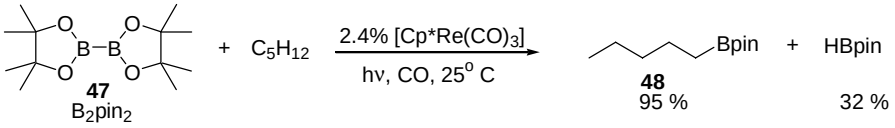
46

RH $\xrightarrow[h\nu]{}$ R−Bcat'

Entry	RH	Yield (%)
1	pentane	85
2	ethylcyclobutane	74
3	2-methylbutane	55
4	cylcohexane	22

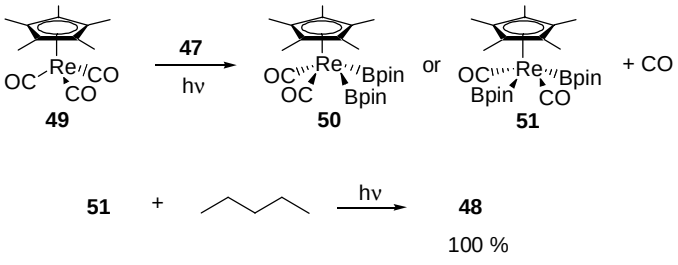
The reaction has been made catalytic by irradiating pinacol diborane in the presence of a rhenium catalyst under a carbon monoxide atmosphere to afford alkyl boronates such as **48** (Scheme 11)[14]. The reaction has been proposed to proceed with photolytically assisted oxidative addition of the diborane reagent to the metal center (Scheme 12). Upon generation of this reactive species, C-H activation and borylation of the hydrocarbon can occur. These findings are corroborated by the reaction of metalloborane **51** with pentane (Scheme 12). The reaction gives the same observed products as the catalytic process, implying that **51** is an intermediate in the reaction pathway.

Scheme 11. Catalytic Regiospecific Borylation.

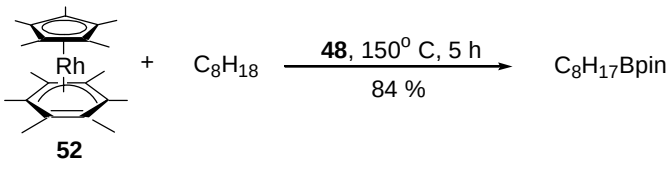


This catalytic borylation has also been extended to proceed under thermal conditions. In this system, the catalyst is Cp*Rh(η^4-C_6Me_6), which upon reaction with octane and pinacol diborane gives regiospecifically borylated product in 72% yield after 80 hours using 1 mol% catalyst 52 at 150° C (Scheme 13)[15]. It was noted that HBpin produced in the reaction could also borylate octane in the presence of the catalyst, thus eliminating the need for diborane reagents in the catalytic cycle. The alkyl boranes produced by these methods can easily be converted into alcohols, amines, ketones, and olefins, making these products very versatile synthetic intermediates.

Scheme 12. Mechanistic Studies of Borylation.



Scheme 13. Borylation Under Thermal Conditions.



FUTURE DEVELOPMENTS

It is clear from the work presented here that the field of C-H activation holds great promise for expanding the scope of useful organic reactions in synthesis. The areas of remote functionalization and alkane functionalization are yielding intriguing results and inspiring new questions. Organic chemists are now able to create carbon-heteroatom bonds selectively at tertiary and primary carbons, and to readily functionalize allylic and benzylic carbons in many diverse compounds. One logical next step in these activation reactions is to investigate the methods for stereoselective insertion reactions. The study of the mechanisms of C-H activation reactions should lead to more efficient reactions and better control over reactivity. The ultimate goal of this research is the ability to functionalize any carbon in a molecule, without relying on previously introduced functionality. While this goal is not yet in sight, the major steps toward it continue to provide impetus for future investigations.

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