REVIEW
ARTICLE

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An Introductory Overview of C–H Bond Activation/ Functionalization Chemistry with Focus on Catalytic C(sp^3)–H Bond Borylation

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ABSTRACT

The direct and selective functionalization of C–H bonds provides novel disconnections and innovative strategies to streamline the synthesis of molecules with diverse complexities. However, despite the significant advances in the elaboration of techniques for C–H activation, the utilization of unactivated C(sp^3)–H bonds remains challenging. In particular, asymmetric transformation of C(sp^3)–H bonds is underdeveloped owing to the lack of catalytic systems that can competently discriminate among ubiquitous C–H bonds in organic molecules. This short review aims to outline the challenges and strategies for the catalytic functionalization of C(sp^3)–H bonds giving a general and non-exhaustive explanatory approach. Current strategies on the basis of the substrates and reaction mechanisms are summarized in Section 1. Examples of enantioselective C–H bond transformations are then given in Section 2. Finally, in Section 3, an outline of current methodologies towards the direct borylation of C(sp^3)–H bonds is described to showcase the importance of developing techniques for catalytic C–H bond chemistry. While we try to cover all excellent reports available in the literature on this topic, any omissions are unintentional, taking note of the most representative examples available.

Keywords: *C–H Bond Activation; Organometallic Catalysis; Organic Synthesis; Borylation*

C–H BOND FUNCTIONALIZATION STRATEGIES

Transformative synthetic methodologies have evolved from the traditional approach of functional group interconversion to the direct activation and functionalization of strong C–H bonds via transition metal catalysis, Figure 1 (Corey and Cheng, 1989; Hudlicky and Reed, 2007; Corey and Kürti, 2010). However, problem on site-selectivity resulting from the omnipresence of C–H bonds in organic compounds has become a long-standing challenge in synthesis. The

utilization of C(sp^2)–H bonds has matured into a successful field with the development of methodologies that circumvent challenges such as selectivity given the many possible chemical environments for these transformations (Arndtsen et al., 1995; Yamaguchi et al., 2012; Gutekunst and Baran, 2011; Davies and Morton, 2016).

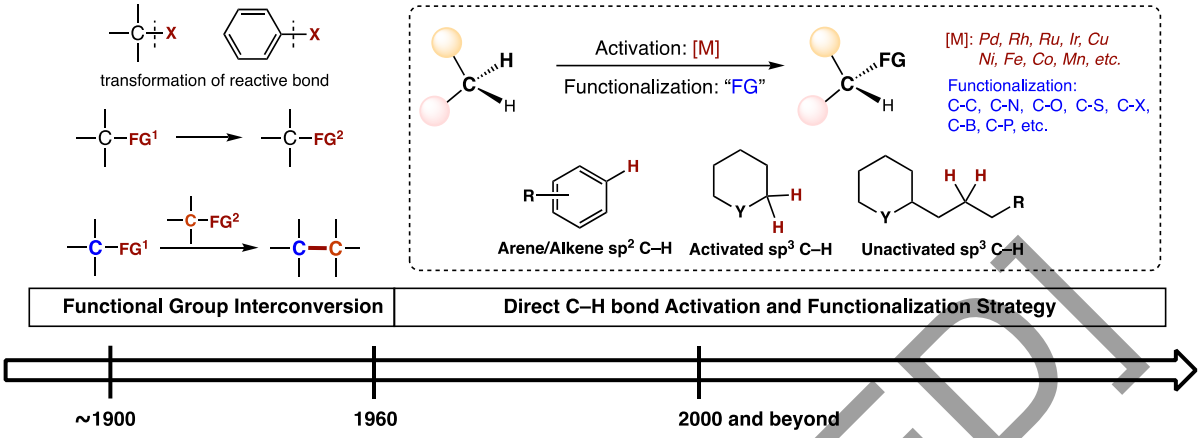
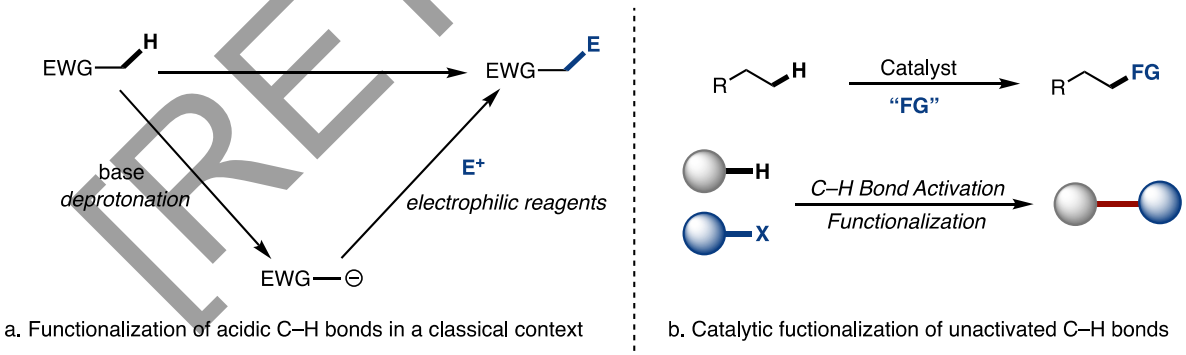


Figure 1. A simplified timeline on the evolution of methodologies from the traditional functional group (FG) interconversion to the direct utilization of inert C–H bonds.

Classical techniques introduce functionality at certain positions within a molecule that inherently possess many other functional moieties. This replacement or installation of new organic moieties has been in a strict sense an enabling process to convert readily available raw materials to higher-value, more complex chemical feedstocks (Godula and Sames, 2006; Wencel-Delord and Glorius, 2013; Labinger and Bercaw, 2002). Traditional functionalization relied on the acidity of C–H bonds as a consequence of other nearby groups and therefore processes based on deprotonation followed by electrophilic quenching of the intermediate nucleophiles have become a known methodology for molecular transformation (Figure 2a). The other end of the spectrum encompasses the direct functionalization of C–H bonds that are not influenced or activated by the reactivity of nearby existing functional moieties by catalytic processes (Figure 2b). The latter has an enormous advantage over the former in the context of scope, compatibility, and method diversification to open avenues for more efficient transformations.



a. Functionalization of acidic C–H bonds in a classical context

b. Catalytic fuctionalization of unactivated C–H bonds

Figure 2. Comparison between (a) classical and (b) catalytic C–H bond functionalization.

Several challenges should be addressed to enable the direct utilization of C–H bonds to be a versatile disconnection methodology in creating molecular complexity and in generating stereocenters that will greatly impact the landscape of synthesis not just in the chemical sciences but to other fields such as pharmaceutical, medical, agrochemical, and industrial sciences. Impediments to achieving C–H functionalization include but is not limited to the (1) intrinsic low reactivity, large kinetic barrier to cleave C–H bonds (Figure 3), (2) chemoselectivity, arising from the possibility that functionalized products may be more reactive than the starting material, (3) regioselectivity due to the ubiquity of both sp^2 and sp^3 C–H bonds, and (4) stereoselectivity in

generating chiral centers. In a striking contrast to C(sp^2)–H bond functionalization, the high dissociation energy (Roudesly et al., 2017), geometrical constraints, and the absence of desirable π-orbitals limit the exploitation and manipulation of C(sp^3)–H bonds (Wang et al., 2021).

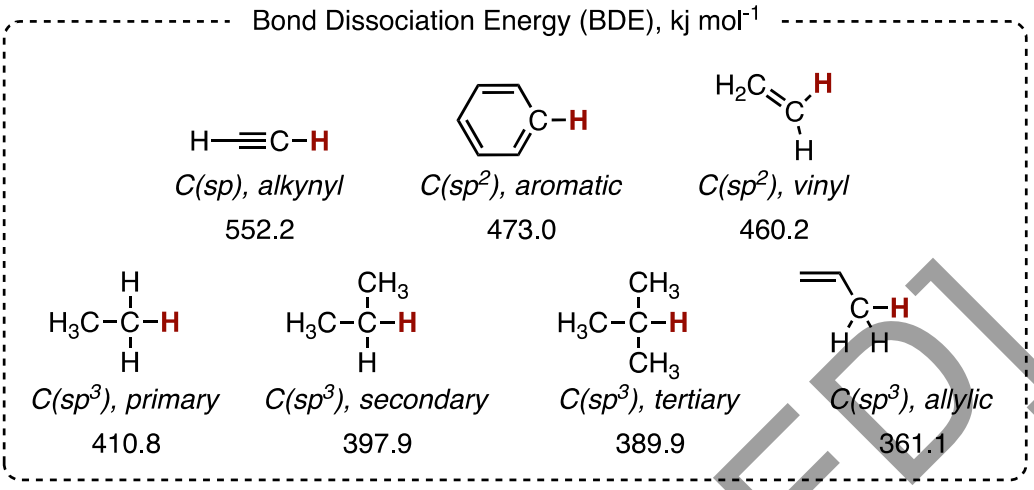


Figure 3. Bond dissociation energies of selected hydrocarbon C–H bonds.

Directed and Undirected C–H Bond Functionalization. Overcoming the challenge of site-selectivity due to the ubiquitous nature of C–H bonds is at the forefront of C–H bond activation chemistry. Undirected C–H bond functionalization reactions (see Figure 2b) are generally less developed than strategic functionalization methods that utilize a directing or anchoring group (Hartwig and Larsen, 2016). More often than not, a mixture of products is expected in the case of undirected functionalization especially in linear alkanes where the inherent chemical reactivity of one C–H bond can be similar to the reactivity of other C–H bonds within the chain (Figure 3). For example, secondary C–H bonds in alkanes have comparable reactivity and are less sterically accessible while tertiary C–H bonds are weaker and are more reactive towards radical abstraction. The strong primary C–H bonds in linear systems are known to be less susceptible towards functionalization. Unfortunately, these terminal primary C–H bonds are desired positions for molecular transformation especially in the production of many important classes of compounds (Falbe et al., 2003). Likewise, C–H bonds in aryl systems can have equal reactivity. However, depending on the type of catalyst, reagent, or specific reaction conditions these C–H bonds can be harnessed towards a regioselective transformation in addition to some advantageous characteristics of aryl or heteroaryl systems including the presence of π-conjugation and the greater acidity of their C–H bonds (Whisler et al., 2004).

Directed C–H bond functionalization has the advantage of installing a functional group at a targeted position of the substrate. In the presence of the directing group (DG), usually a Lewis basic functional moiety (Figure 4) possessing a non-bonding lone pair of electrons, C–H bond cleavage is facilitated by induction of a pre-association between the metal and the substrate (Engle et al., 2012). This interaction brings positivistic control of site selectivity as the directing group binds to the metal center delivering the catalyst to a proximal C–H bond to form a complex intermediate via cyclometallation.

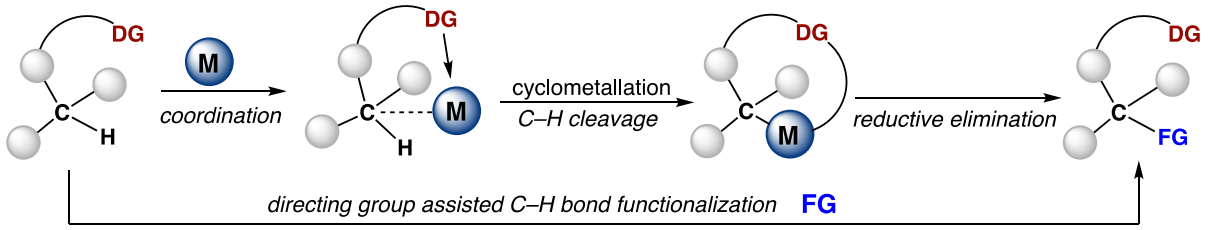


Figure 4. Directed C–H bond functionalization. DG = directing group

A groundbreaking report in 1993 by Chatani and co-workers on C–H alkylation reaction involving a Ru(0) catalyst system that coordinates to a ketone directing group (Figure 5) enabled the activation of the *ortho* C–H bond in aromatic ketone substrates (Murai et al., 1993). Since this precedent, directed C–H bond functionalization has tremendously progressed with the development of novel catalytic reactions. A key disadvantage often cited against the directed functionalization of C–H bonds is the need for the installation of the directing groups and the subsequent removal of these moieties after the reaction. This typically add more steps required for the functionalization and a careful tuning of the directing group for a specific reaction is almost always required. In this context, the exploration of weakly coordinating directing groups (Engle and Yu, 20124) has become common and in a more comprehensible manner the utilization of traceless or transient directing groups have also become a common theme (Gandeepan and Ackerman, 2018).

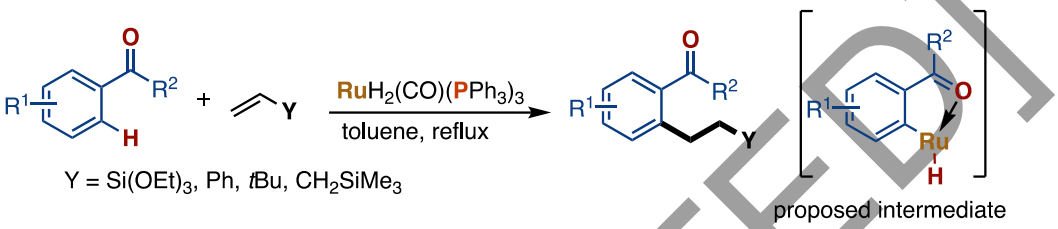


Figure 5. Utilization of a directing group (ketone) to make use of chelation control (Murai reaction).

Inner- and Outer-sphere Mechanisms of C–H Cleavage. Regardless of the strategy for C–H bond functionalization, directed or undirected, the propensity of C–H bonds to be cleaved and subsequently functionalized depends on the type of mechanisms on which these C–H bonds are activated and cleaved. Catalytic systems enabling the access to unreactive C–H bonds are implicitly understood on the basis of their mechanisms. Two general mechanisms are recognized for their competency to bring efficient C–H bond activation (Figure 6). These two classes vary in the way the metal catalysts interact with the targeted C–H bonds.

Known as the organometallic mechanism, inner-sphere C–H bond functionalization proceeds initially by the reaction of the C–H bond with the transition metal forming a metal-alkyl or metal-aryl (C–M) species (Dick and Sanford, 2006; Crabtree, 2001). This is subsequently followed by the functionalization step involving the reaction of the coordinated alkyl or aryl group with either a ligand bound to the metal center or with an external reagent (Figure 6a). The defining factor for the inner-sphere mechanism is the competency for the formation of the organometallic C–M species. Mechanistically, this process is less dependent on C–H bond strengths and are often advantageous for the functionalization of relatively strong C–H bonds as they have the potential to prevent over-oxidation. The C–M species governs all other discrete follow-up reactions with respect to the desirable characteristics of the reaction such as the resulting regio- and stereoselectivity in the products. Less hindered C–H bonds are preferred and diamagnetic complexes that perform two-electron chemistry are highly favorable to avoid one-electron changes in the oxidation state and radical pathways given that C–M species are oxidation labile.

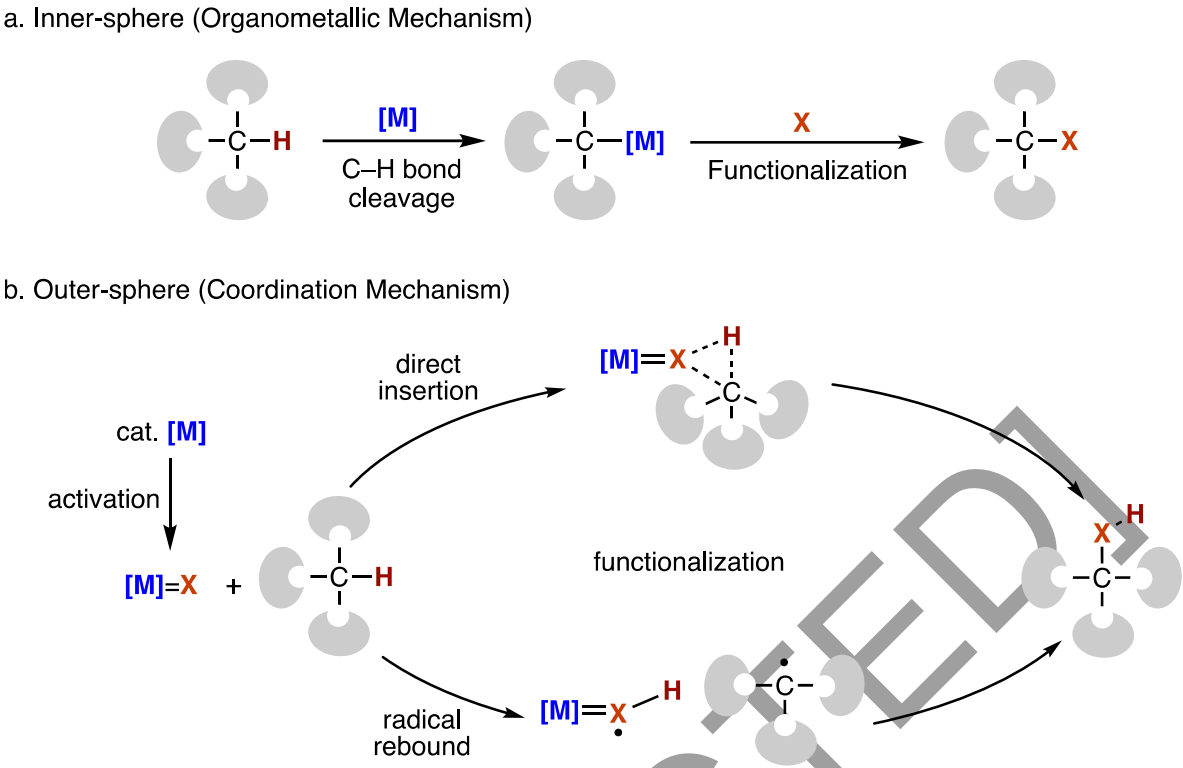


Figure 6. Schematic representation of (a) inner-sphere (organometallic), and (b) outer-sphere (coordination) mechanisms for C–H cleavage.

Operating when the metal center does not directly interact with the C–H bond, the outer-sphere or coordination mechanism involves the interaction of an activated and coordinated ligand to the C–H bond. The ligand either inserts directly into the C–H bond or it abstracts a hydrogen atom and recombines with the organic radical (Figure 6b) (Dick and Sanford, 2006; Crabtree, 2001). The reaction is initiated by the formation of a high oxidation state metal complex with activated ligands typically reactive oxo-, nitrene, or carbene species. In direct contrast to the inner-sphere mechanism, no distinct organometallic species are generated and the rate of the transformation is determined by the relative C–H bond strength, therefore selectivity favors the weaker C–H bonds such as those that are tertiary, benzylic, allylic, or alpha-to-heteroatoms (i.e., N, O, etc.). Potential problem arises from over-oxidation due to the weaker nature of C–H bonds in the oxidized product.

In the most general case, accompanying these two classes of mechanistic pathways are different intermediate pathways (Figure 7) known for the catalytic functionalization of unactivated C–H bonds as: (1) stepwise generation of M–C bond, (2) insertion of carbene/nitrene/oxene into C–H bonds, and (3) concerted formation of M–C bond either via an oxidative addition or via a concerted metalation-deprotonation (CMD) process. Cleavage of C–H bonds by hydrogen atom abstraction generates a carbon-centered (alkyl) radical, typically for oxidation reactions, and the recombination of this radical species with a metal complex or a variety of reagents can deliver desired functional groups to the alkyl radical (Figure 7a). Weaker C–H bonds react faster in this fashion since the C–H bond cleavage happens in a homolytic process giving intrinsic preference to relatively weaker C–H bonds in the alkyl chain (Salamone and Bietti, 2015). Site selectivity of the reaction can also be controlled by steric factors influencing the position of hydrogen atom abstraction. Bulky and/or hindered reagents have been utilized to shift the preference of H-atom abstraction to a secondary C–H bond over a tertiary C–H bond (Schmidt et al., 2014).

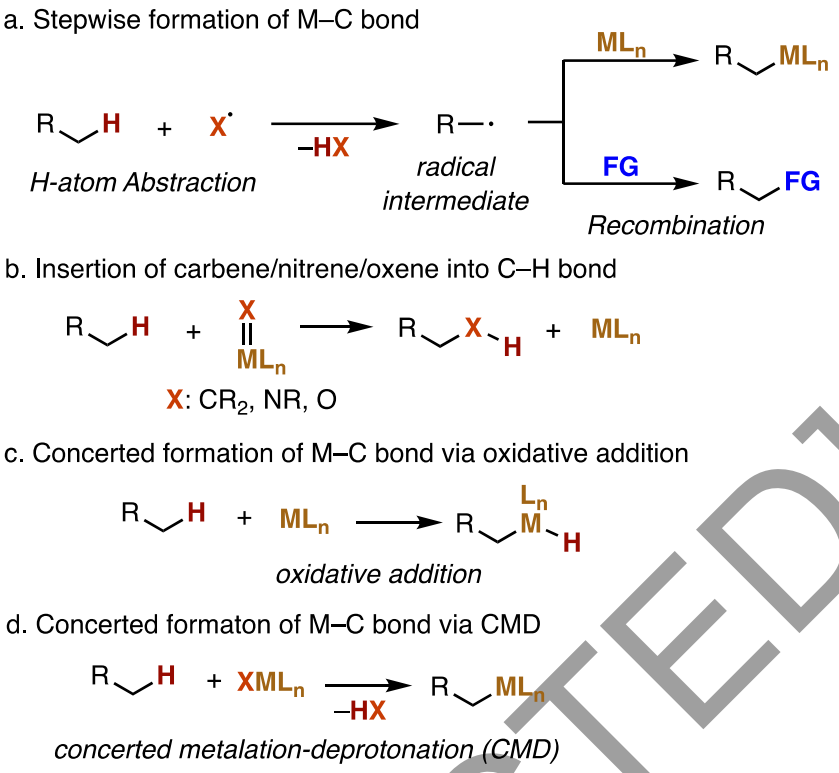


Figure 7. Intermediate pathways in the catalytic cleavage of C–H.

Catalytic reactions of carbene, nitrene, or oxene precursors with alkyl C–H bonds via a concerted insertion (Figure 7b) without the formation of any metal-alkyl intermediates has a preference over electron-rich weak C–H bonds (Doyle et al., 2010). The selectivity of reactions that proceed via the formation of metal–carbon (M–C) bonds depends on the relative strengths of the M–C bond in the resulting organometallic intermediates. Such is the case of C–H bond cleavage taking place either by means of oxidative addition (Figure 7c) or via a concerted metalation-deprotonation (CMD) process (Figure 7d) with significantly observed selectivity that runs counterintuitive to the selectivity of the aforementioned types of C–H functionalization. Reactions occurring via the formation of a M–C bond often have reactivity preference to aryl over alkyl C–H bonds, and primary over secondary or tertiary C–H bonds.

C(sp^3)–H Bond Functionalization via C–H Activation. While C(sp^3)–H bond functionalization has been less studied because of the thermodynamic and geometrical attributes of the tetrahedral carbon center, myriad strategic techniques have surfaced to evade the chemical inertness of C(sp^3)–H bonds. In 2008, Yu and co-workers reported the first example of cross-coupling C(sp^3)–H bonds with boronic acids (Figure 8) under Pd(II)/Pd(0) catalysis (Wang et al., 2008). *O*-Methyl hydroxamic acids, readily available from carboxylic acids, as directing groups were utilized for the formation of C–C bond via direct C–H activation exploiting the reactivity of hydroxamic acids towards β-C–H activation. Oxygen or air was shown to be a feasible terminal oxidant while both sp^2 and sp^3 boronic acids can be utilized as coupling partners. The products can easily be converted to esters, amides or alkanes making the reaction likely to find broad synthetic utility.

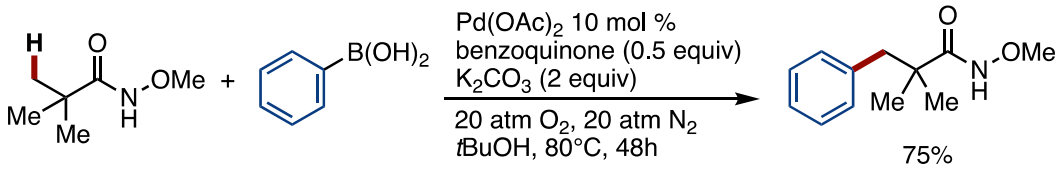


Figure 8. Hydroxamic acid-directed C(sp^3)–H coupling with boronic acids.

This has been immediately followed by a report on the amide-directed Pd(0)-catalyzed intermolecular arylation of C(sp^3)–H bonds (Figure 9) achieved using PR_3/ArI combination (Wasa et al., 2009). The protocol efficiently led to the arylation of a variety of aliphatic carboxylic acid derivatives including some important class of bioactive drug molecules. The use of fluorinated aryl iodides also has the advantage for introducing fluorine in different target molecules. The method does not utilize any external oxidant.

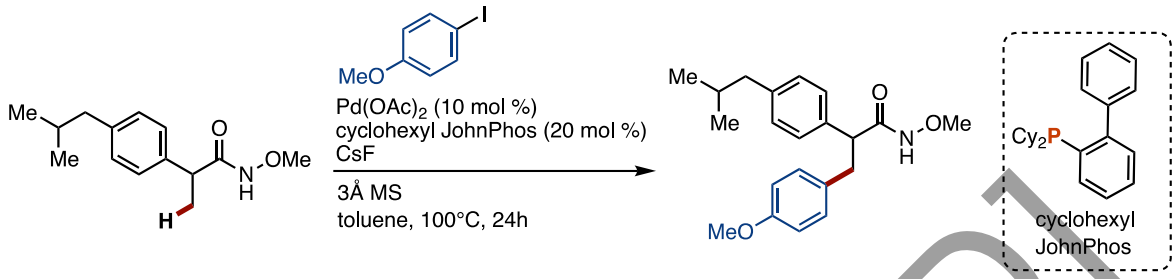


Figure 9. Pd-catalyzed intermolecular arylation of C(sp^3)–H bonds.

Baran in 2011 reported the first example of catalytic transition metal-mediated C–H activation on a cyclobutane ring (Figure 10) and accordingly the first example of sequential C(sp^3)–H arylation reactions in the synthesis of natural products (Gutekunst and Baran, 2011). Suitably, 2-aminothioanisole was used to direct the construction of unsymmetrical cyclobutanes in the synthesis of piperarborenine B featuring a divergent approach to the controlled *cis* or *trans* installation of two distinct aryl moieties.

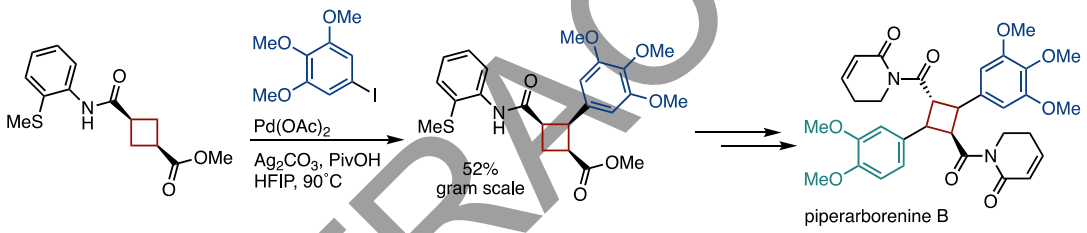


Figure 10. First example of transition metal-mediated C–H activation on a cyclobutane ring.

Chatani and Murai succeeded in the development of a catalytic carbonylation reaction at sp^3 C–H bond adjacent to nitrogen atom in alkylamines in the presence of a rhodium catalyst (Chatani et al., 2000). Various *N*-2-pyridylpyrolidine and piperidine derivatives underwent carbonylation without any observed formation of regioisomeric products (Figure 11a). The regioselective carbonylation was also demonstrated at benzylic position while the carbonylation of acyclic amine derivatives proceeded with low efficiency. Mechanistically, the reaction may have involved a conventional direct oxidative addition (Jun, 1998), which leads to the formation of an alkyl Rh complex followed by the corresponding insertion of ethylene and CO giving an acyl Rh complex, which upon reductive elimination provides the product.

Sames and co-workers have demonstrated the direct oxidative cross-coupling of C(sp^3)–H bonds and alkenes via a tandem C(sp^3)–H activation, Figure 11b, at the position adjacent to the amide nitrogen of the directing group and C–C bond formation accomplished under neutral catalytic conditions (DeBoef et al., 2004). Key mechanistic advancement of this methodology was the ability of the catalyst to facilitate C–H activation and alkene insertion in tandem and by preferring β-hydride elimination unlocking new possibilities for the diversification of proline derivatives under C(sp^3)–H activation followed by a Heck-type reaction and isomerization.

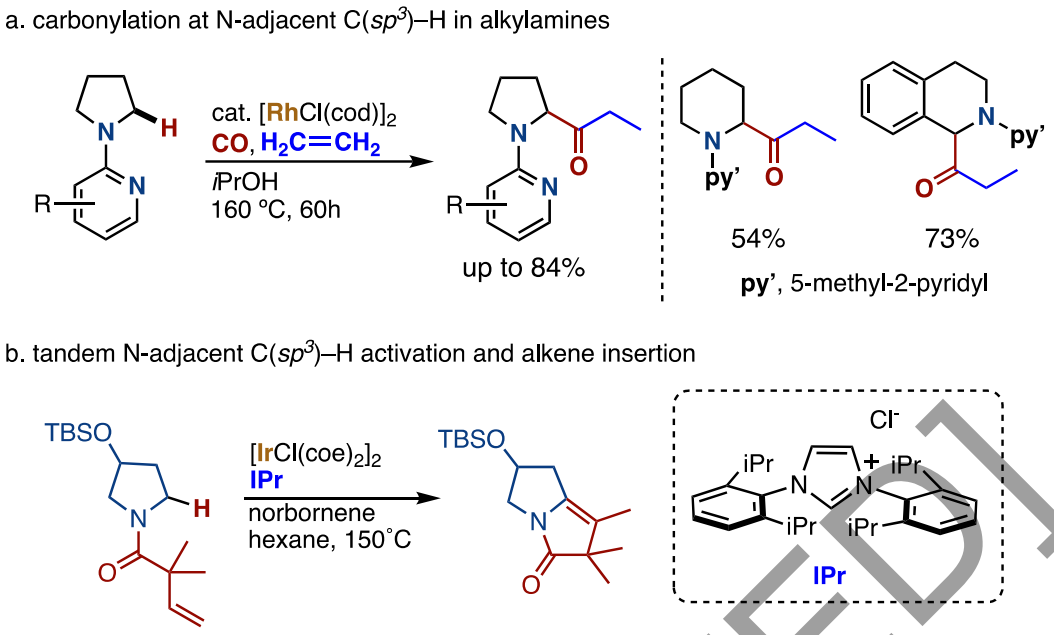


Figure 11. Carbonylation (a) and tandem C–H activation/alkene insertion (b) in sp^3 C–H bonds adjacent to nitrogen atom.

Reactions that proceed by C–H insertion involves the interaction of an electron-deficient species such as a carbene or nitrene or likewise by a metal-carbenoid or nitrenoid that inserts between the C and H atom of the targeted C–H bond for functionalization. While many metals (Ru, Ag, Cu, etc.) are known to form and stabilize carbenes, rhodium and dirhodium species are the most studied and utilized precursors given their high reactivity and versatility. Doyle reported the synthesis of a $GABA_B$ receptor agonist (*R*)-(–)-baclofen (Figure 12) using *p*-chlorophenethyl alcohol as starting material involving a catalytic C–H insertion reaction of a chiral dirhodium (II) carboxamidate with diazoacetate (Doyle and Hu, 2002). The intermediate γ-lactone resulting from the efficient C–H insertion was then subsequently converted to the corresponding receptor agonist.

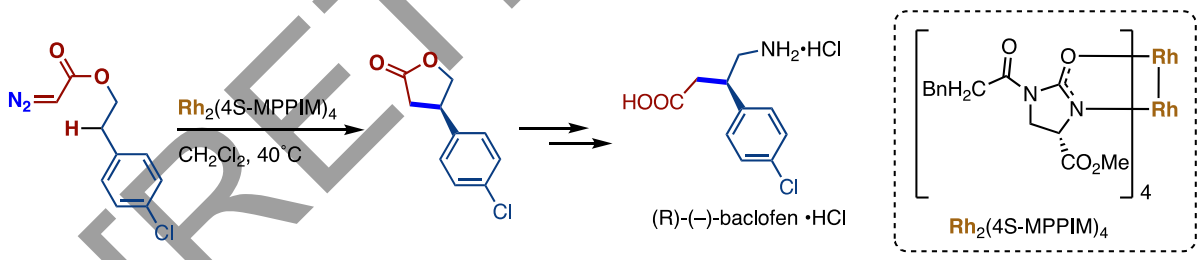


Figure 12. Synthesis of a receptor agonist via C(sp^3)–H insertion to a dirhodium carboxamidate.

Chemoselective functionalization via C–H insertion is primarily controlled by both steric and electronic factors. In general, carbenoid species have a preferential reactivity to functionalize C–H bonds in which the carbon atom can stabilize the build-up of positive charge due to the partial characteristic of C–H insertion reaction towards hydride abstraction. Modulation of the reactivity is usually accomplished by the utilization of bulky ligands on the metal species. For example, Davies demonstrated that intermolecular C–H insertions can be achieved with high chemo-, diastereo-, and enantioselectivity using a bulky dirhodium catalyst in the reaction of *N*-Boc-protected amines with aryldiazoacetate for the synthesis and elaboration of chiral amines (Davies et al., 1999). Their work exhibited that the selectivity of the carbenoid species is towards C–H insertion into methylene groups adjacent to the amide nitrogen (Figure 13).

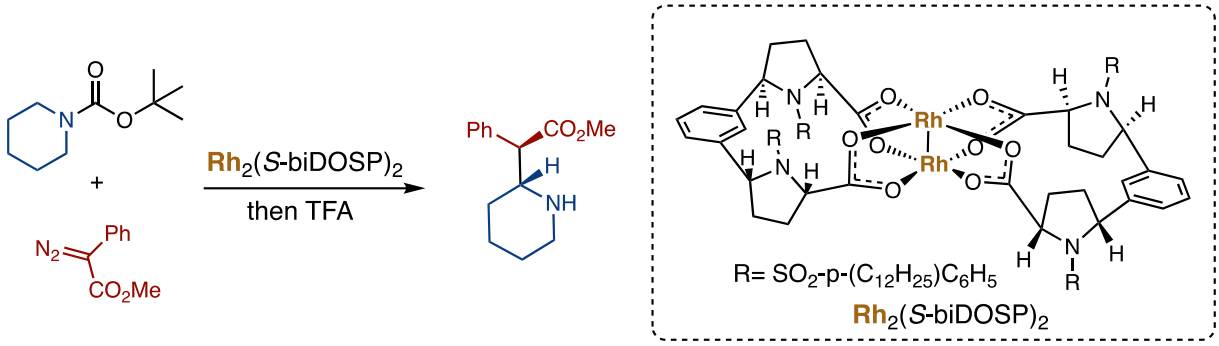


Figure 13. Intermolecular C–H insertion using bulky dirhodium catalyst.

Moreover, the insertion into tertiary C–H bonds are preferred over secondary C–H bonds as observed by Davies and co-workers. Insertions into primary C–H bonds are rather scarce. In these cases, the insertion proceeds with the retention of the configuration. Davies has shown, for example, that in the C–H activation of silyl ethers using rhodium carbenoid-induced C–H insertion the preferred site is on a methylene group (Davies et al., 2003). The reactivity is controlled by the balance between steric and electronic effects and a critical requirement for the observed chemoselectivity is the use of donor/acceptor-substituted carbenoids (Figure 14).

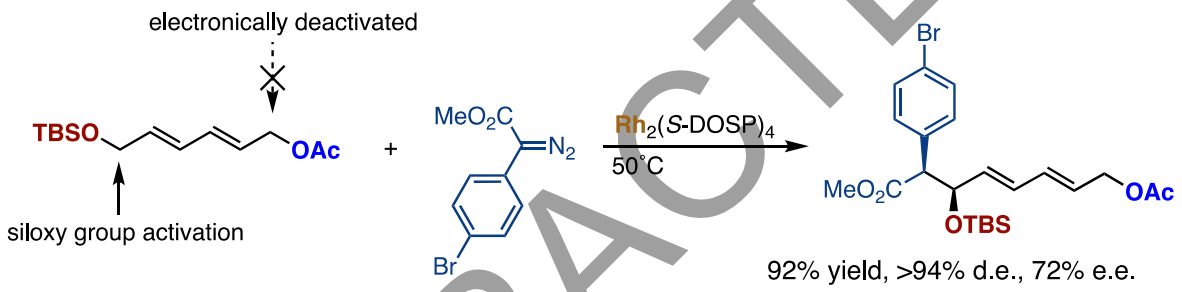


Figure 14. Activation of C–H bond α to oxygen atom as a surrogate to aldol reaction.

ENANTIOSELECTIVE C(sp^3)–H BOND FUNCTIONALIZATION

The chemical inertness of C(sp^3)–H bonds relative to C(sp^2)–H bonds has been the primary reason for the slow progress in the development of efficient catalytic systems that can harness the potential of C–H bonds for the direct conversion into new functionalities. In addition to the issues on chemical reactivity, a hindrance to the use of C–H bonds is the challenge of selective activation due to the omnipresence of C–H bonds in organic molecules. Enantioselective C(sp^3)–H bond functionalization is an attractive synthetic strategy for molecular diversification. However, the difficulty in stabilizing stereocenters or discriminating between C–H bonds make this methodology exceptionally strenuous and rare. To date, several approaches have surfaced to directly utilize C(sp^3)–H bonds in synthesis. Approaches based on biomimetic and enzymatic reactivities (Lewis et al., 2011; Li et al., 2019; Wang et al., 2020) were developed to enantioselectively modify C–H bonds. Representative examples include the biomimetic oxidation reactions mimicking the functions of cytochrome P450 (Murahashi, 2011) and flavoenzymes in an environmentally benign protocol (Freakley et al., 2019). Groves and Viski described the stereochemical course of the hydroxylation of ethylbenzene using a chiral iron porphyrin catalyst. As with enzymatic processes, it has been shown that the excellent stereospecificity results from the fit of the substrate to the catalyst and that a step-wise free-radical reaction proceeds with the retention of the configuration at the chiral center (Groves and Viski, 1989).

Metallonitrene and Metallocarbene Insertions. The prevalence of nitrogen in biologically active molecules has been the driving force for the development of reactions that directly utilize C–H bonds for the selective formation of carbon–nitrogen bonds (Roizen et al., 2012). Research efforts using metallonitrene intermediates have contributed significantly on the area of oxidative amination despite the fact that the use of metallonitrenes is far less developed than their metallocarbene counterparts. A remarkable example for this system was reported by Du Bois by using a valerolactam-derived dirhodium complex that affords excellent asymmetric control in the cyclization reactions of sulfamate esters (Zalatan and Du Bois, 2008). The influence of the ligand on chemoselectivity indicated the concerted asynchronous nitrene pathway generating the products at excellent enantioselectivities (Figure 15).

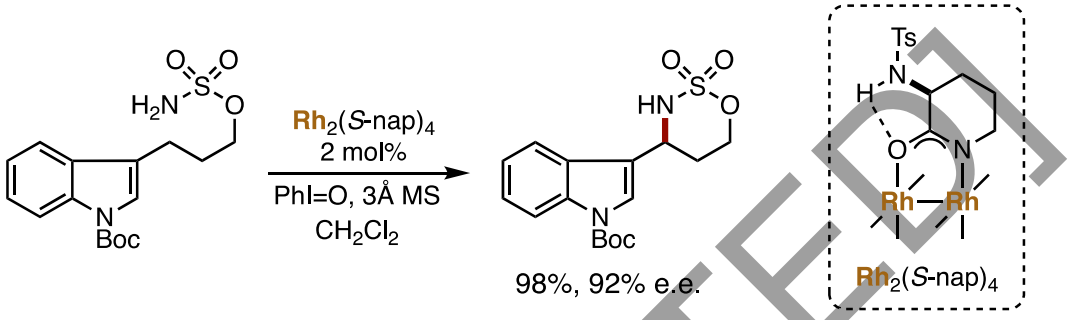


Figure 15. Enantioselective cyclization of sulfamate esters.

Similarly, Hashimoto disclosed a new synthetic route for the synthesis of the (*R*)-(–)-rolipam, an important phosphodiesterase type IV inhibitor, via an enantioselective intramolecular C–H insertion of *N*-alkyl-*N*-4-nitrophenyl-α-methoxycarbonyl-α-diazoacetamide (Figure 16) by chiral dirhodium (II) complex (Anada et al., 1999).

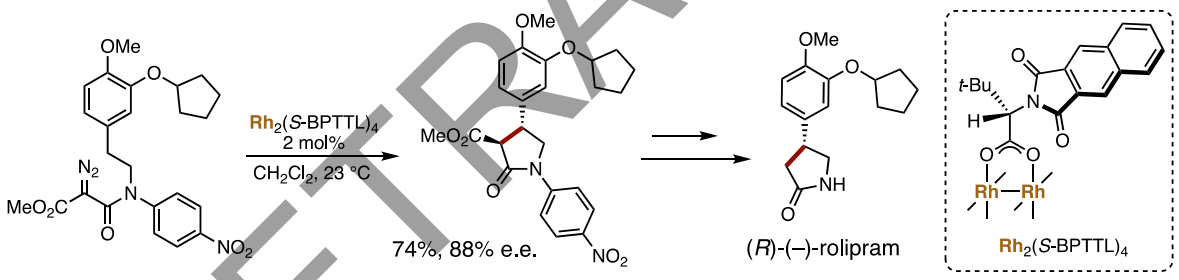


Figure 16. Enantioselective synthesis of (*R*)-(–)-rolipam.

More recently Davies and co-workers described the use of a dirhodium catalyst to achieve exceptional site-, diastereo-, and enantioselective C–H functionalization involving *n*-alkanes and terminally substituted *n*-alkyl compounds via an intermolecular carbene insertion (Liao et al., 2016). Remarkably, the reaction showed functional group compatibility including otherwise reactive groups such as halides, silanes, and esters. Also, the enantioselective functionalization is possible without the need for a directing group or any anchoring group present in the molecule (Figure 17).

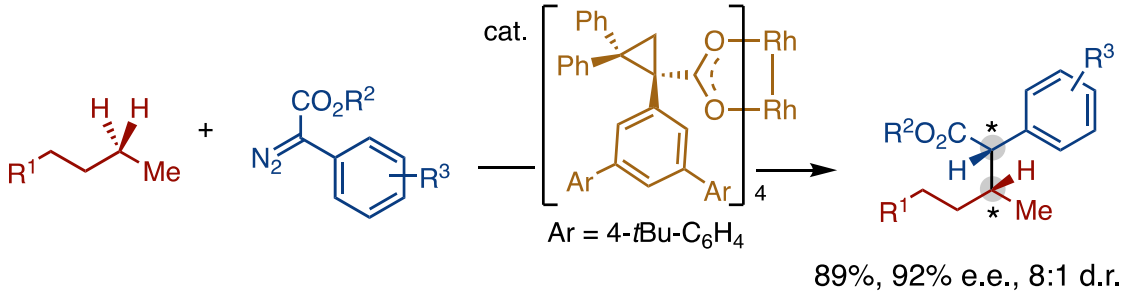


Figure 17. Metallocarbene insertion into C–H bond in *n*-alkanes.

The work by Davies also emphasized the importance of the structural features of the catalyst for enantiocontrol. The isolation of chiral reaction pocket in the highly enantioselective metallocarbene C–H insertion is pivotal to their results. Thus, this implies broad possibilities for future research on selective C–H functionalization incorporating a mechanistic outer sphere process.

Stereochemistry-Generating C(sp^3)–H Activation. Access to molecules with central chirality has been achieved by strategic stereochemistry-generating activation of C(sp^3)–H bonds. Processes that install chirality in this manner fall into two categories: (1) generation of chirality through desymmetrization of enantiotopic carbons (Figure 18a) and (2) generation of chirality through discrimination of enantiotopic C–H bonds, (Figure 18b). In both categories, the reaction can take place in an inter- or intramolecular fashion (Newton et al., 2017). A striking difference between these two categories is that in the case of desymmetrizing enantiotopic carbons functionalization takes place at two distinct carbon centers while in the process of discriminating enantiotopic protons the target C(sp^3)–H bond lies in the same carbon center – thus, this strategy is sometimes referred to as point desymmetrization. In comparison, the desymmetrization of enantiotopic carbons has received much more considerable attention than the point desymmetrization of enantiotopic protons. This disparity between the two methodologies can be attributed to the lack and difficulty of chiral catalyst design that can efficiently discriminate among C(sp^3)–H bonds in different chemical environments.

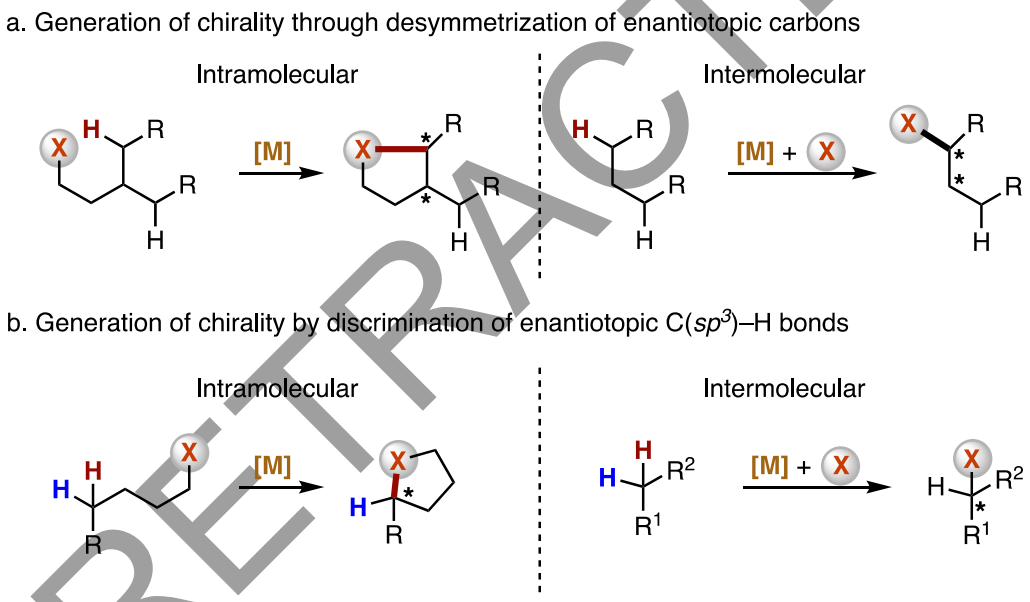


Figure 18. Stereochemistry-generating C(sp^3)–H bond activation strategies.

Desymmetrization of Enantiotopic Carbons. Yu and co-workers in 2008 reported a transition metal-catalyzed enantioselective C(sp^3)–H functionalization (Shi et al., 2008). Their work exploited the coordinating and directing properties of pyridine in order to direct palladation of both C(sp^2)–H and C(sp^3)–H bonds as well as chiral carboxylates to induce asymmetric palladation. The directed C(sp^3)–H butylation of 2-isopropylpyridine was demonstrated by employing a mono-*N*-protected amino acid (MPAA) ligand under Pd(II)/Pd(0) catalysis (Figure 19) albeit the low yield and enantioselectivity. A probable reason for this inefficient enantioinduction is the poor catalyst differentiation between a methyl group and a hydrogen atom, which are relatively close in size. Also, the presence of background reaction was revealed as the pyridine-directed C–H activation persisted in the absence of the chiral ligand causing a detrimental effect to the enantioselectivity of the reaction.

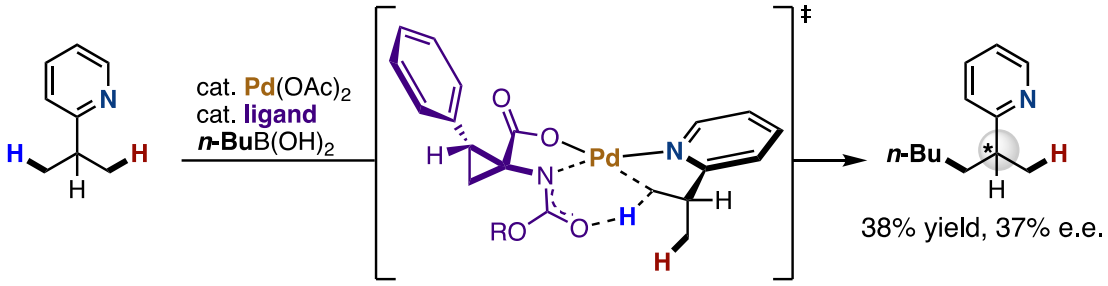


Figure 19. Discrimination between terminal methyl groups in 2-isopropylpyridine.

In 2011, several reports began to appear in the literatures detailing efforts to develop highly enantioselective C(sp^3)–H functionalizations. Excelling in this area of research, the Yu group have disclosed the enantioselective C–H functionalization involving the amide-directed intermolecular arylation, alkenylation, and alkylation of cyclopropanes with organoboron reagents giving excellent enantiocontrol by the utilization of a mono-*N*-protected amino acid as ligand (Wasa et al., 2011). It has been demonstrated that a diverse range of organoboron reagents can participate as coupling partners. Moreover, primary or secondary alkyl substitution at the α-position of the cyclopropane ring is well tolerated (Figure 20).

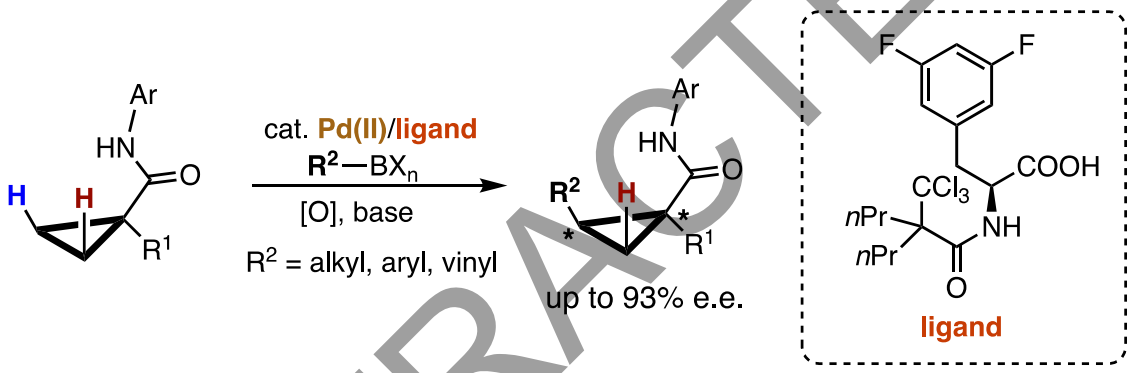


Figure 20. Enantioselective C(sp^3)–H bond functionalization of cyclopropanes.

This work was immediately followed by a report on the arylation of cyclobutyl C(sp^3)–H bonds by systematic tuning of the chiral ligand that led to the desymmetrization of enantiotopic carbons in cyclobutyl derivatives (Xiao et al., 2014). Excellent enantiocontrol on the cross-coupling of methylene β-C(sp^3)–H bonds in cyclobutanecarboxylic acid derivatives with arylboron reagents was achieved through the development of chiral mono-*N*-protected α-amino-O-methylhydroxamic acid ligands, which form a chiral complex with the Pd(II) center (Figure 21). This methodology gives access to cyclobutanecarboxylates having α-chiral quaternary stereocenters. The proposed stereomodels based on computational studies suggest that the side chain of the ligand is orthogonal to the square planar Pd(II) center brought by repulsive interactions between the *N*-protecting group and the large side chain of the ligand to prevent unfavorable steric clashing. These findings point out the significant role of ligand systems in the stereochemical outcomes of desymmetrization reactions and their propensity to promote the catalytic transformation.

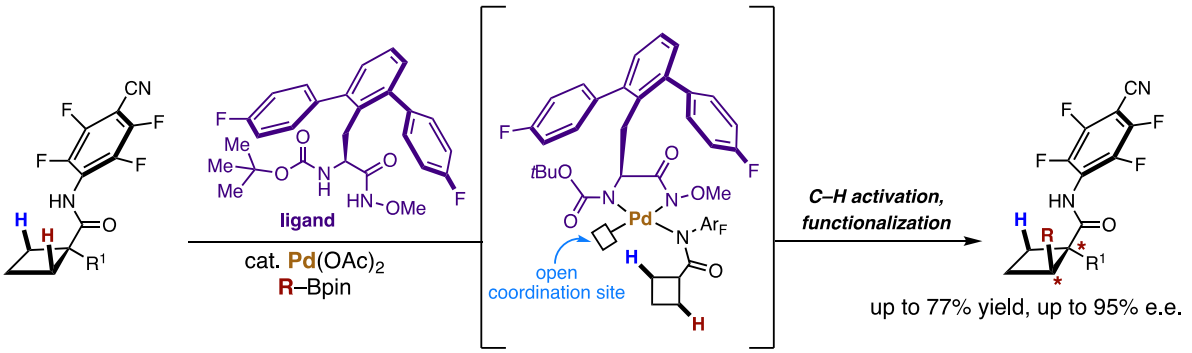


Figure 21. Desymmetrization of enantiotopic carbons in cyclobutyl derivatives.

Following this development Yu and co-workers also demonstrated an enantioselective desymmetrization in acyclic systems (Xiao et al., 2014), involving the functionalization of terminal methyl C(sp^3)–H bonds in amide using a chiral hydroxamic acid ligand (Figure 22).

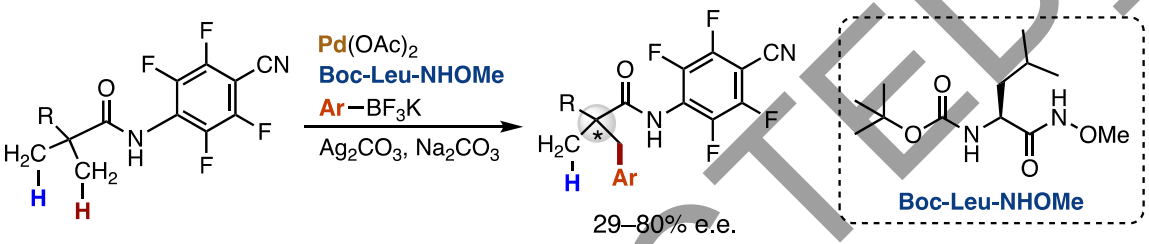


Figure 22. Pd-catalyzed enantioselective β-C(sp^3)–H activation of acylic amides.

A complimentary approach was reported by Hartwig using Rh(I)/Rh(III) desymmetrization of enantiotopic carbons in cyclopropylmethyl alcohols using bidentate C_2-symmetric ligands (Lee and Hartwig, 2016). In this notable functionalization, hydrosilyl ethers generated *in situ* via a dehydrogenative silylation of cyclopropylmethanols using diethylsilane have shown to undergo an asymmetric, intramolecular silylation involving cyclopropyl C–H bonds (Figure 23). This work represents the first example of a catalytic, enantioselective desymmetrization of enantiotopic carbons by silylation and the first example of a highly enantioselective functionalization of C–H bond in cyclopropane to generate a carbon–heteroatom bond.

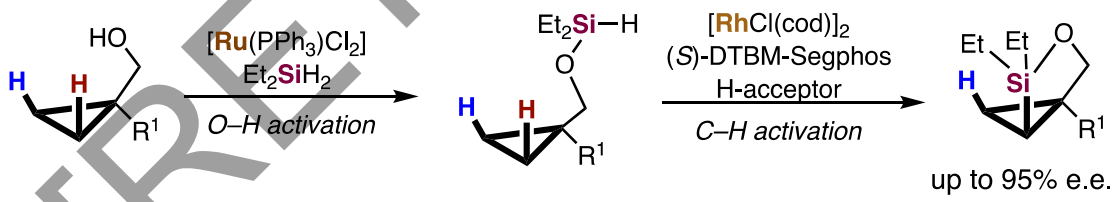


Figure 23. Rh-catalyzed enantioselective silylation of cyclopropyl C–H bonds.

Hartwig also disclosed a similar strategy for the enantioselective intramolecular silylations of unactivated primary C(sp^3)–H bond in dihydrobenzosiloles resulting to the desymmetrization of enantiotopic carbons in acylic system (Su and Hartwig, 2017). This approach entails the use of a chiral *N*,*N*-bidentate ligand under Ir-catalysis presenting a rare example of the desymmetrization of an isopropyl group by a transition-metal-catalyzed C–H bond functionalization (Figure 24).

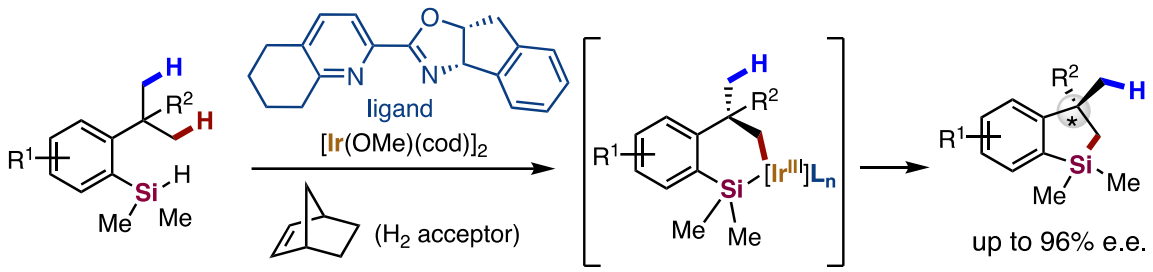


Figure 24. Ir-catalyzed enantioselective, intramolecular silylation of methyl C–H bonds.

Enantioselective Discrimination of Enantiotopic Methylene C(sp^3)–H Bonds. The activation of enantiotopic methylene C(sp^3)–H bonds remains one of the most difficult synthetic challenges to date. This difficulty arises from both kinetic and thermodynamic considerations. Secondary C–H bonds are in general less stereo-electronically prone to either C–H cleavage or C–H insertion compared to primary C–H bonds making them less sterically accessible in the viewpoint of kinetics. Moreover, methylene C–H bonds are characterized by a high heterolytic bond dissociation energy making their transformation thermodynamically uphill (Saint-Denis et al., 2018). The desymmetrization of enantiotopic C–H bonds in cyclic systems, as outlined in the previous sections, proceeded efficiently as C–H bonds in cyclic systems like those of cyclopropanes and cyclobutanes have electronic properties that are reminiscent with those of aromatic C–H bonds, therefore more reactive and prone to cleavage. In the case of methylene C–H bonds the catalytic system should be carefully designed to enable the discrimination between two enantiotopic C–H bonds on a single carbon center. Presently, despite these challenges several approaches have been reported with a myriad transformation involving predominantly the C–H functionalization of benzylic C–H bonds and activated C–H bonds α-to-heteroatom, while there are very few reports on the direct utilization of unbiased and unactivated methylene C(sp^3)–H bonds (Figure 25). These substrate categories have been the subject of research in methylene C–H activation chemistry due to their potential in streamlining the synthesis of important compounds that are significant in many industries.

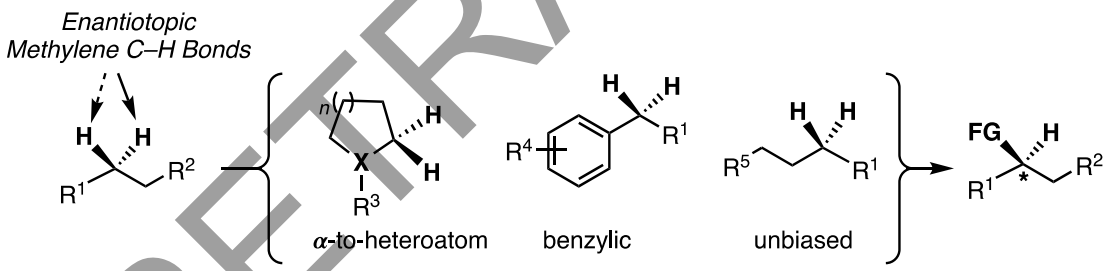


Figure 25. Substrate Categories involving Methylene C(sp^3)–H Bonds

Enantioselective benzylic methylene C–H activation has been done straightforward, notwithstanding several challenges, by two different catalytic approaches: (1) the utilization of chiral auxiliary towards a proximity-driven metalation, and (2) utilization of strong chiral bidentate directing groups (i.e., chiral C_2-symmetric ligands). Yu and co-workers have developed a chiral auxiliary approach using an amino acid reagent that reversibly reacts with aldehydes and ketones via the *in situ* formation of an imine. This serves preponderantly as a transient directing group effecting the enantioselective arylation of benzylic C–H bonds in aromatic aldehydes and ketones (Zhang et al., 2016). This methodology relied on the ligation of the transient aldehyde-imine intermediates to a Pd(II) center using an amino acid-derived ligand (Figure 26). The stereomodel for this arylation reaction is based on diastereoselection where the steric repulsion between the bulky *t*-butyl group of the amino acid ligand and the corresponding *R*-groups of the substrates force them to adopt a more feasible *trans*-conformation in the transition state to give the major product with excellent enantiocontrol. On the other hand, if the intermediate species adopt a *cis*-conformation a highly disfavored transition state featuring repulsive interactions will result to the generation of the minor product.

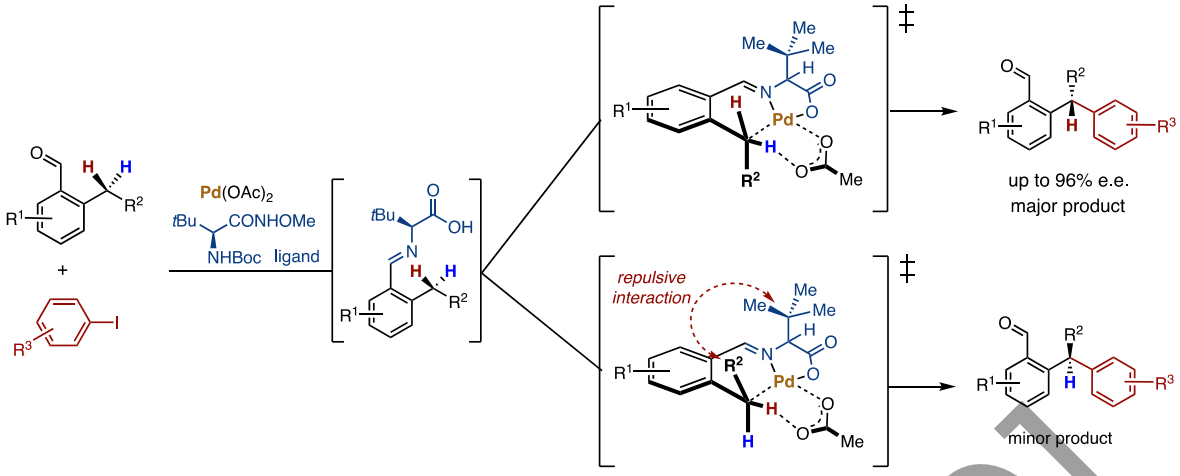


Figure 26. Enantioselective benzylic methylene C–H arylation via the formation of an aldehyde-imine intermediate.

Strategic benzylic methylene C–H activation methodologies based on strong bidentate directing groups were reported independently by Duan and Chen. Duan disclosed the use of chiral phosphoric amides in the enantioselective arylation of secondary C(sp^3)–H bonds of 8-aminoquinoline amides giving an array of β,β-diaryl carboxylic derivatives in moderate to good enantiomeric ratios (Yan et al., 2015). This report marks the first time for the utilization of a chiral phosphoric amide to control the stereoselectivity at the C–H bond cleavage step during the C–H activation reaction (Figure 27).

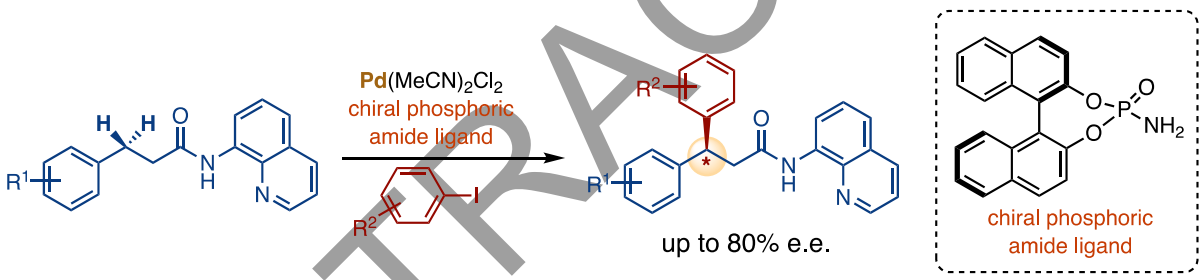


Figure 27. Enantioselective bidentate auxiliary directed Pd-catalyzed benzylic C–H arylation enabled by a chiral phosphoric acid ligand.

Complementary to Duan's work, Chen disclosed a similar Pd(II)-catalyzed benzylic arylation of amines enabled by a picolinamide directing group (Wang et al., 2016). The use of chiral BINOL phosphoric acid ligand in a solvent-free conditions enabled the differentiation of benzylic C–H bonds providing the first example of an enantioselective γ-C–H arylation of picolinamide-derivatized alkyl amines with enantioselectivities higher than those reported previously by Duan (up to 97% e.e.).

The functionalization of methylene C–H bonds adjacent to a heteroatom has been explored thoroughly by various groups. Excellent work on this area includes several methodologies reported by the Shibata group. On separate disclosures, the first example of an enantioselective cationic iridium(I)-catalyzed alkylation of 2–(alkylamino)pyridines with terminal alkenes (Pan et al., 2011) and alkynes (Pan et al., 2012) giving chiral amine derivatives were reported. Pyridine and 2-quinoline were identified as suitable directing groups for this transformation that activate and functionalize the methylene C–H bonds α-to-*N* atom of the amino moiety of the substrates (Figure 28). Mechanistically, the oxidative addition of the targeted methylene C–H bond to the Ir(I) catalyst coordinated to the chiral binaphthyl-based ligand is followed by insertion into olefins or alkynes to generate the alkylated or alkenylated products. This strategy was further utilized for the C(sp^3)–H alkylation of butyrolactam (Figure 29) to generate enantioenriched

γ-lactams that are inherently important in natural products (Tahara et al., 2015). As an example, the alkylated product from acrylate was transformed into the key intermediate in the synthesis of pyrrolam A.

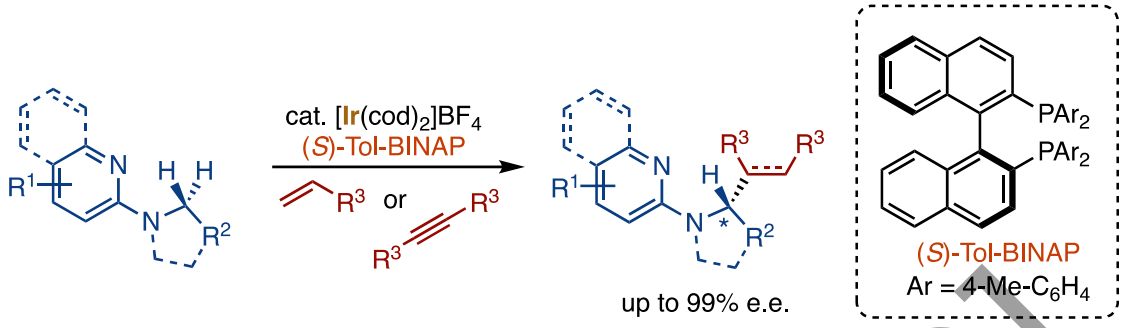


Figure 28. Ir-catalyzed enantioselective alkylation and alkenylation of C–H bonds adjacent to the N-atom in 2-(alkylamino)pyridines.

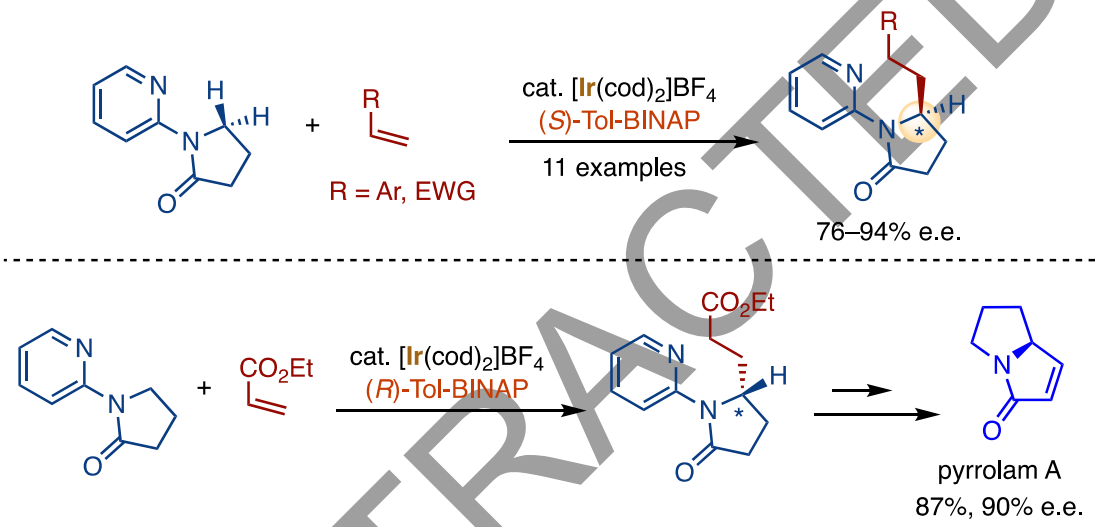


Figure 29. Enantioselective synthesis of pyrrolam A via C(sp^3)–H activation of N-adjacent C–H.

Along this line, Yu disclosed a Pd(II)/Pd(0)-catalyzed enantioselective functionalization of thioamines with boronic acids via the activation of C–H bonds in the substrate adjacent to the *N*-atom (Jain et al., 2016). This functionalization allowed the synthesis of essential motifs containing ethyl amines, azetidines, pyrrolidines, piperidines, azepanes, indolines, and tetrahydroisoquinolines. The use of chiral phosphoric acid ligand demonstrated efficient coupling of activated methylene C–H bonds leading to their differentiation in a chiral environment (Figure 30).

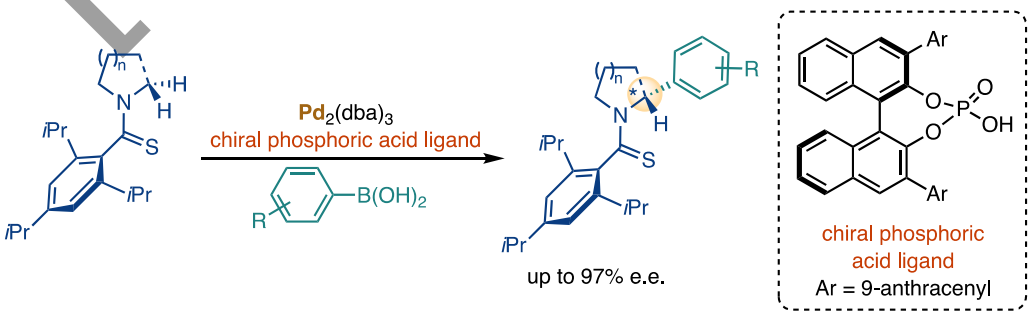


Figure 30. Enantioselective α-C(sp^3)–H functionalization of thioamines.

Arguably, among the substrate categories for C–H bond functionalization outlined in Figure 25, unbiased or unactivated C–H bonds in acylic substrates remain the most challenging target for C–H activation. The chemical inertness of these C–H bonds is well known and methods to directly utilized them will enable the synthesis of molecules with diverse complexities. One exceptional strategy towards this goal involved the use of chiral bidentate ligands that tolerate enantioselective methylene C–H activation. Houk, Yu, and co-workers reported the arylation of β-methylene C(sp^3)–H bonds in amide derivatives (Figure 31) by the utilization of a chiral aminoethyl quinoline ligand (Chen et al., 2016). Crucial to this work is the extensive ligand design that effectively discriminate between the methylene C–H bonds enabling the Pd(II)-catalyzed C–H arylation using a weak directing group affording the product with high enantioselectivity. Following the excellent enantiocontrol in this reaction, the stereochemical induction imparted by the bidentate ligand featuring a six-membered chelation to the Pd center was evaluated by computational studies (Yang et al., 2017). The favorable transition state has the quinoline portion of the ligand perpendicular to the square planar Pd(II) center, which forces the bulky *R*-group of the substrate to orient itself *trans* to the quinoline moiety. This orthogonal arrangement is a direct consequence of the presence of bulky *t*-butylphenyl groups in the ligand system as well as the bulky directing group of the substrate. In the transition state leading to the minor product, the perpendicular arrangement of the quinoline moiety of the ligand system induces an intense steric interaction with the *cis*-situated *R*-group of the substrate.

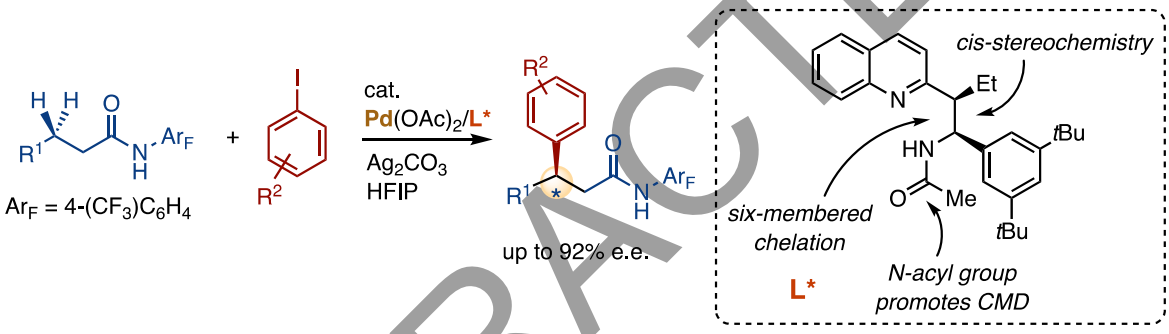


Figure 31. Monodentate directing group/bidentate ligand for enantioselective unactivated methylene C–H bond functionalization.

Overall, intricate ligand design is crucial to enable the differentiation of unactivated methylene C–H bonds. The development of novel classes of ligands will be valuable in dealing with this synthetic challenge and the possibility of extending these reactions to more complex system that can streamline the synthesis of organic compounds. Point desymmetrization is no doubt a powerful and attractive strategy that can be extremely helpful for the realization of more efficient catalytic diversification of molecules from simple precursors.

C–H ACTIVATION FOR THE CONSTRUCTION OF C–B BONDS

A more recently developed class of catalytic C–H bond functionalization, the transformation of C–H to C–B bonds has received considerable interest in the last two decades (Mkhalid et al., 2010; Jiang et al., 2018). Significant work on transition-metal boryl complexes have advanced our understanding on the broad synthetic utility of boron-containing moieties (Fyfe and Watson, 2017). As compared with other C–H bond functionalization strategies such as those of C–O, C–N, and C–C bond formation, the transformation of C–H bond to C–B bond is a thermoneutral or a thermodynamically favorable process. Bond energies for methylboronates and dioxoborolanes for the borylation of a primary C–H bond of methane forming an alkylboronate is thermodynamically downhill (Figure 32). Likewise, the formation of an alkylboronate ester is nearly thermoneutral (Rablen and Hartwig, 1996; Sakaki and Kikuno, 1997). These observed accessible barriers for C–H bond cleavage and the subsequent formation of a C–B bond can be

attributed to the strong σ-donor properties of the boryl group along with the presence of an unoccupied p_z-orbital on boron in a boryl complex. The existence of a low-energy LUMO (lowest unoccupied molecular orbital) on the boryl ligand plays crucial role in the stabilization of the transition state for C–H bond cleavage.

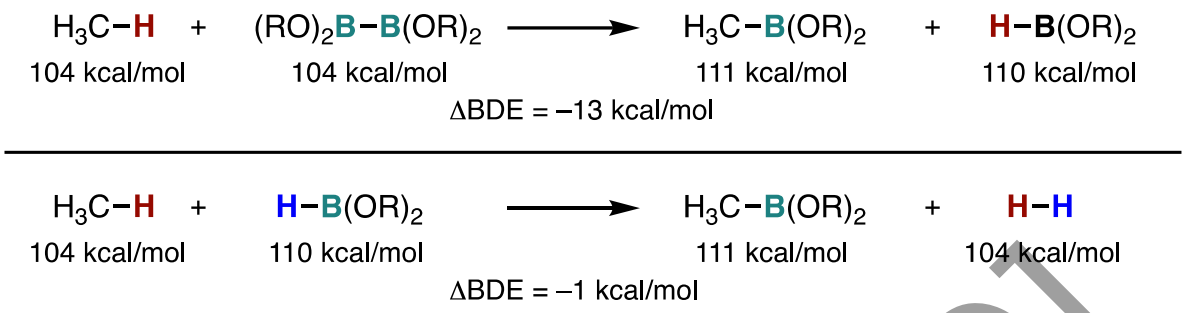


Figure 32. Thermodynamic barrier in the borylation of methane.

Catalytic C–H Bond Borylation. In 1999, Smith reported the first example of a catalytic C–H activation towards the formation of a C–B bond (Iverson and Smith, 1999). In this work a description of B–C bond forming chemistry was given with the demonstration of the catalytic viability of the reaction outlined in Figure 33. In this seminal work, the rate of reaction is fundamentally slow, with benzene as both the substrate and solvent, and the catalytic turnover number (TON) was only 3. However, despite these shortcomings, this work provided the first important precedent for the feasibility of this catalytic transformation that has seen significant progress in the next few years since after.

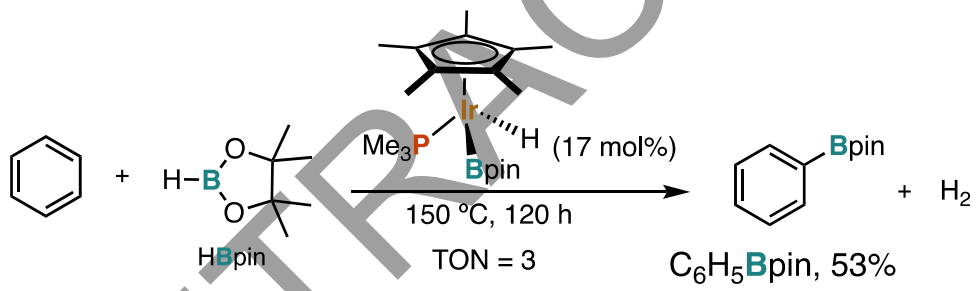


Figure 33. Catalytic borylative C–H bond functionalization.

Following the report of Smith on the possibility of a catalytic borylation, Hartwig disclosed the formation of a single product resulting from the terminal functionalization of linear alkanes mediated by the rhodium complex Cp*Rh(η^4-C_6Me_6) that efficiently catalyzes the formation of linear alkylboranes from readily available borane reagents under thermal conditions (Chen et al., 2000). This thermal, catalytic, regiospecific functionalization of alkanes (Figure 34) could potentially deliver more important classes of compounds like alcohols, amines, and alkenes as boron compounds are extremely important precursors to these classes of molecules. Likewise, the borylation of trialkylamines, ketones, and fluoroalkanes were demonstrated to occur regiospecifically at the methyl group that is least sterically hindered. This led to the conclusion that in the case of alkane borylation the preferred site is on the methyl group that is most electron-deficient (Lawrence et al., 2004).

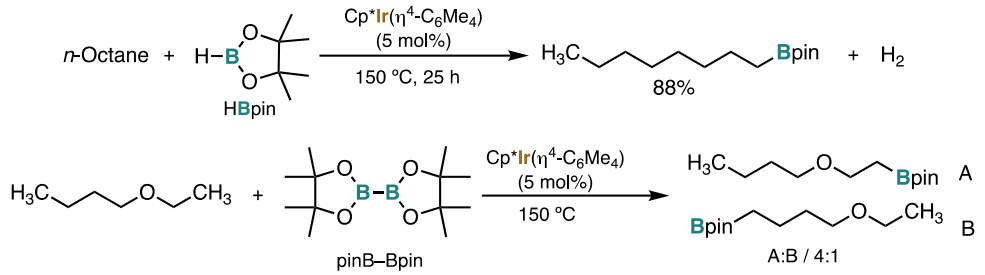


Figure 34. Thermal, catalytic, and regiospecific borylation of alkanes.

Along these lines, significant advancements were made in the realm of aromatic C–H bond borylation. Among the many catalytic systems that transpired into the last decade, phosphine- or nitrogen-based ligands were found to be the most suitable giving enhanced reactivity towards the borylation of aromatic C–H bonds including those of heteroaromatics even at ambient reaction conditions. Ishiyama, Hartwig, and Miyaura reported a stoichiometric aromatic C–H borylation catalyzed by an iridium(I)/2,2'-bipyridine catalytic system at room temperature using bis(pinacolato)diboron (Ishiyama et al., 2002). This protocol gave access to arylboronates in high yields and has become a practical tool for the preparation of arylboronate derivatives (Figure 35).

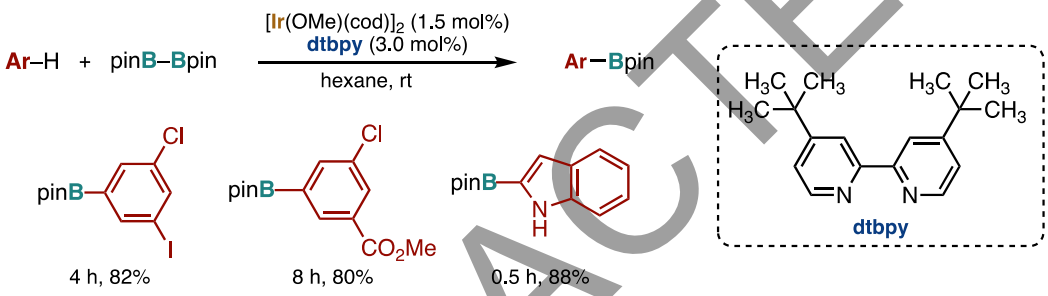


Figure 35. Aromatic C–H borylation by Ir/dtbpy catalytic system.

Recognizing the importance of arylboron intermediates in chemical synthesis, Hartwig reported a hydrosilane directed iridium-catalyzed *ortho*-borylation of arenes (Boebel and Hartwig, 2008). This strategy presented a new approach totally different from the addition of organolithium or magnesium species to borates. The transformation was successful towards the regioselective functionalization of benzylic silanes, phenols, and anilines (Figure 36).

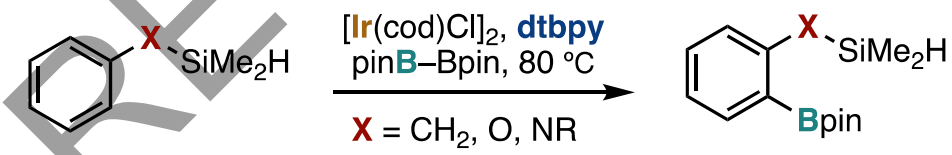


Figure 36. Silyl-directed Ortho-borylation of Arenes

Extensive mechanistic studies on the mild functionalization of arenes by diboron reagents (Figure 37) catalyzed by 4,4′-di-*tert*-butylbipyridine (dtbpy) and olefin-ligated iridium halide or alkoxide complexes were performed (Boller et al., 2005). Mechanistically, the intermediacy of a trisboryl complex [Ir(dtbpy)(coe)(Bpin)$_3$] (coe = cyclooctene) as the catalyst resting state was determined. Kinetic analysis showed that the trisboryl complex reacts with the arene after the reversible dissociation of coe. Furthermore, the resulting intermediate [Ir(dtbpy)(Bpin)$_3$] cleaves the arene C–H bond. As such, the C–H bond cleavage was identified as the turnover-limiting step.

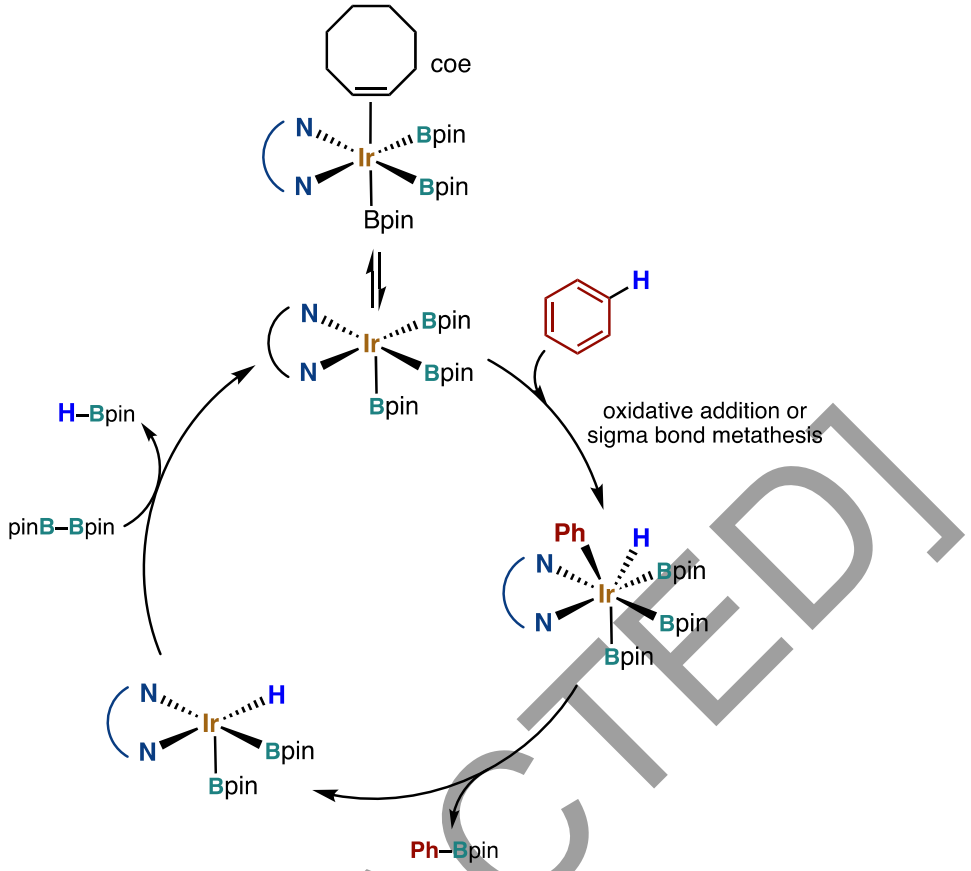


Figure 37. Proposed mechanism for the Ir-catalyzed borylation of arenes.

In a ravishing contrast to the catalytic borylation of C(sp^2)–H bonds in alkenes, arenes, or heteroarene systems the catalytic borylation of C(sp^3)–H bonds has contracted less progress. Catalytic borylation of C–H bonds with high efficiency has been a subject of many fundamental research efforts. For example, Suginome and co-workers described the Ir-catalyzed C(sp^3)–H borylation at the methyl groups of methylchlorosilanes giving the corresponding (borylmethyl)chlorosilanes (Ohmura et al., 2012). Remarkably, the catalytic functionalization is selective to the methyl groups on the silicon atom with the chlorine atom acting as the directing group and is left untouched after the reaction (Figure 38). A variety of chlorosilanes were amenable to this borylation reaction but subsequent conversion to the corresponding isopropoxysilanes was necessary because of the intrinsic air sensitivity of chlorosilanes.

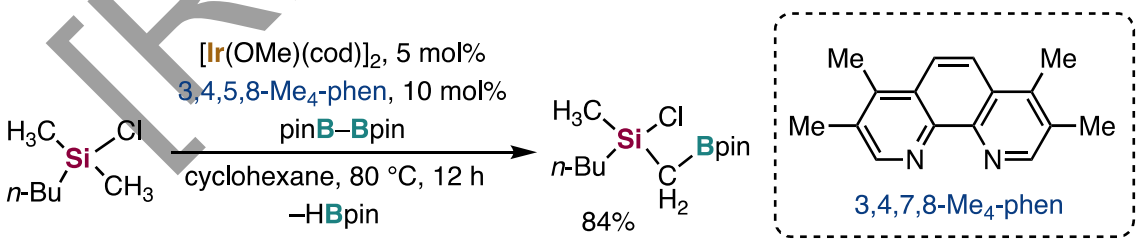


Figure 38. Iridium-catalyzed C(sp^3)–H borylation of methylchlorosilanes.

The efficient borylation at the methyl group in alkylchlorosilanes opened an opportunity to extend this protocol to C(sp^3)–H bonds at sterically hindered position. As a follow up to this report, Suginome later reported the borylation of C(sp^3)–H bonds on methyl groups (Ohmura et al., 2014) on an isopropyl moiety of substrates that do not bear any directing groups (Figure 39). In this work, a remarkable rate acceleration was observed in the presence of catalytic amount of *t*BuOK. The results indicated the possibility of diboron reagent activation by the additive although a clear and thorough mechanistic evaluation was not described.

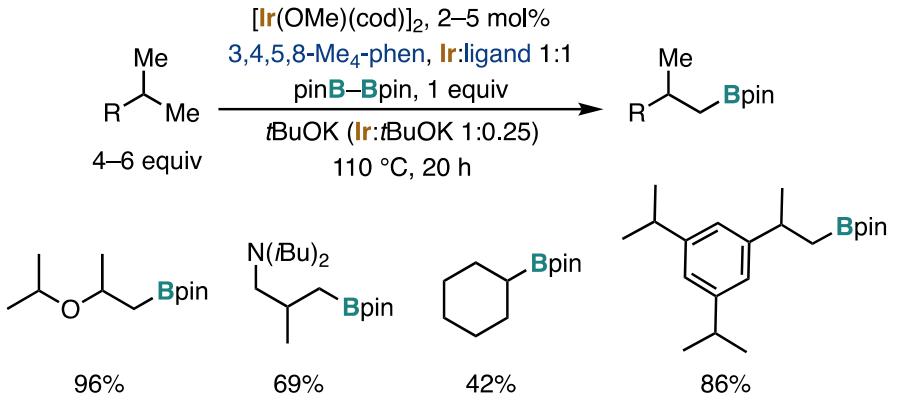


Figure 39. Iridium-catalyzed C(sp^3)–H Borylation Accelerated by *t*-BuOK

Directed C–H bond functionalization has also become a common theme in borylation reactions to address the problem of site-selectivity (Ros et al., 2014; Fyfe and Watson, 2017). *N*-Heterocycles are collectively one of the most utilized directing groups often requiring mild reaction conditions. A simple Pd-based system that catalyzes the conversion of primary C(sp^3)–H bonds in a variety of functionalized complex organic molecules into alkylboronate esters was reported by Shi and co-workers (Zhang et al., 2014). In this protocol, amino acids, amino alcohols, alkylamines, and bioactive molecules have been shown to undergo the borylation reaction with the use of readily available additives and reagents with oxygen as the terminal oxidant (Figure 40). A disadvantage of this protocol, however, is the need for a relatively high catalyst loading (utilization of 20 mol% of the Pd-catalyst) and the need for stoichiometric amount of the ligand.

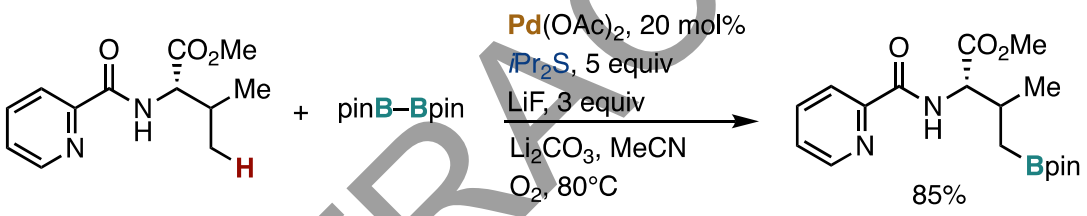


Figure 40. Pd-catalyzed primary C(sp^3)–H borylation of valine derivative.

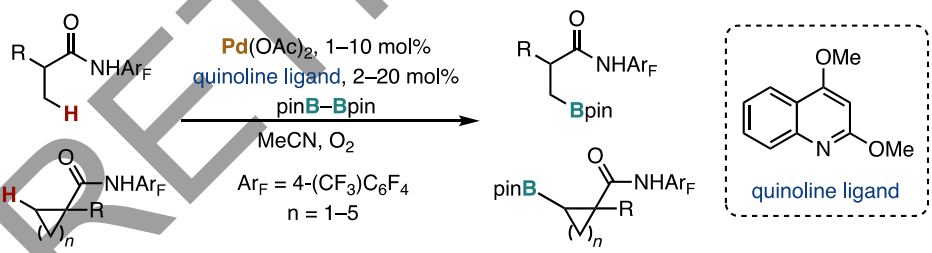


Figure 41. Pd-catalyzed directed borylation of C(sp^3)–H bonds.

Another Pd-based system was reported by Yu and co-workers that features the efficient borylation of carboxylic acid derived amides through ligand acceleration (He et al., 2016). In this work, quinoline-based ligands were shown to promote the C(sp^3)–H borylation of methyl C–H bonds as well as methylene C–H bonds in a broad range of cyclic amide substrates including cycloalkane derivatives (Figure 41). This borylation reaction presents a complimentary approach to the wide array of rhodium- or iridium-catalyzed borylation reactions and may emerge as an important protocol towards the development of more efficient systems aimed at C(sp^3)–H bond functionalization.

In the case of iridium-catalyzed borylation, it was envisaged that a five-coordinate Ir(III) trisboryl complex is directly involved in the catalytic cycle. This complex has only one vacant site required for C–H activation. As such, no vacant site is available for the coordination of the substrate

through a dative interaction. Various strategies were developed for the directed borylation under iridium catalysis to allow for an additional vacant coordination site. This paved way for methodologies that rely on catalytic C–H borylation directed by a dative interaction between the substrate and the metal-catalyst.

Sawamura, in 2009, succeeded in the development of an iridium-catalyzed directed borylation of aryl C–H bonds *ortho* to ester, amide, sulfonate, methoxy, and chloro directing groups using a novel heterogeneous silica-supported monophosphine ligand (Kawamorita et al., 2009). In the heterogeneous systems (Figure 42), it is most unlikely that more than one phosphine is ligated to the Ir as a consequence of immobilization. Thus, this leaves an additional coordination site to the Ir-center that will be available for the dative interaction of the substrate.

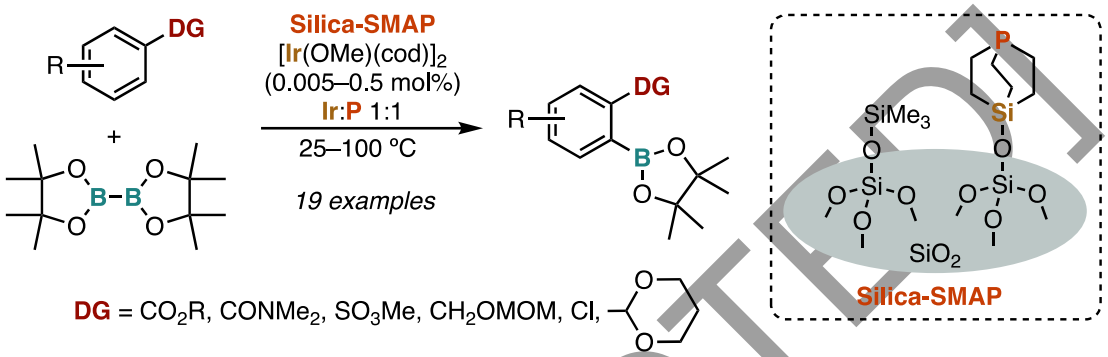


Figure 42. Heterogenous silica-supported compact phosphine-iridium catalyzed directed ortho borylation of arenes.

Following the report on aryl C–H bond borylation, Sawamura and co-workers reported the direct C(sp^3)–H borylation of amides, ureas, and 2-aminopyridine derivatives. The borylation reaction occurred site-selectively at the position α to the nitrogen atom of the directing group (Kawamorita et al., 2012). This protocol gives access to the synthesis of *α*-aminoalkylboronates in excellent yield (Figure 43). The catalytic system features a rhodium catalyst based on a heterogeneous silica-supported triarylphosphine ligand (Silica-TRIP) that is consists of an immobilized triptycene-type cage structure with a bridgehead P atom. Commendably, all the reactions occur under mild conditions (25–100 °C), and at a low catalyst loading (0.1– 0.5 mol % Rh).

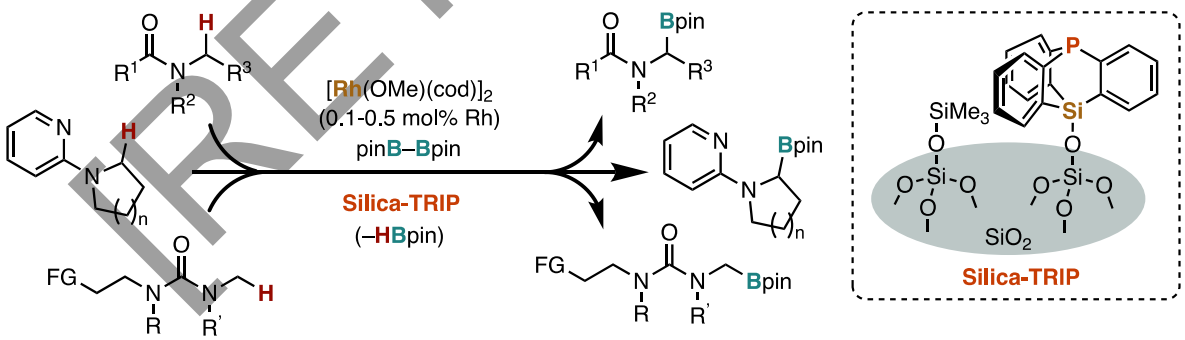


Figure 43. Rh-catalyzed borylation of N-adjacent C(sp^3)–H bonds using Silica-TRIP.

The use of heterogeneous ligand system proved to be versatile as Sawamura and co-workers disclosed the synthesis of primary and secondary alkylboronates through a site-selective C(sp^3)–H borylation of 2-alkylpyridine derivatives using the silica-supported monophosphine-Ir catalyst, Silica-SMAP (Kawamorita et al., 2013). The reaction occurs site-selectively at internal C–H bonds *γ* to the pyridine nitrogen atom (Figure 44). The results point out to the importance of proximity effects arising from the N-to-Ir coordination and the 1:1 metal:phosphine ligation. This reactivity suggests that the Silica-SMAP ligand is effective in creating a favorable environment for the formation of highly active species that promote the dative interaction of the substrate to the catalyst.

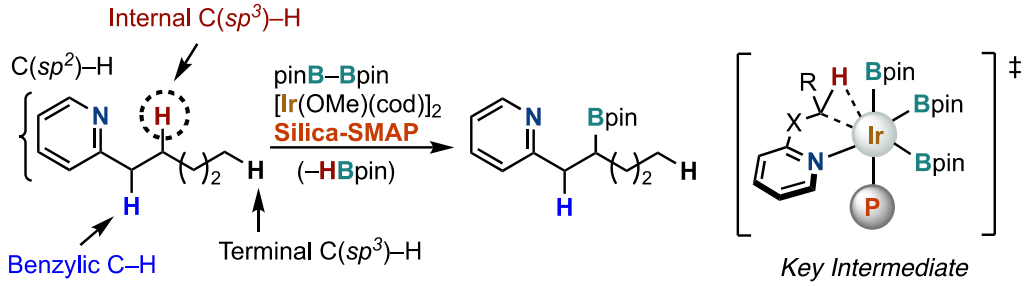


Figure 44. Ir-catalyzed site-selective borylation of C(sp^3)–H bonds using Silica-SMAP.

Sawamura likewise disclosed the heteroatom-directed C–H borylation of cyclopropanes and cyclobutanes using the heterogeneous system (Murakami et al., 2014). As with the previous work, the borylation targets the C–H bond γ to the N or O atoms of the directing group with an exceptional *cis* stereoselectivity (Figure 45). The protocol was shown to be applicable to N-heteroarenes, oximes, imines, and amides. Moreover, both secondary and tertiary C–H bonds were amenable towards the borylation reaction showcasing the versatility of the catalytic system.

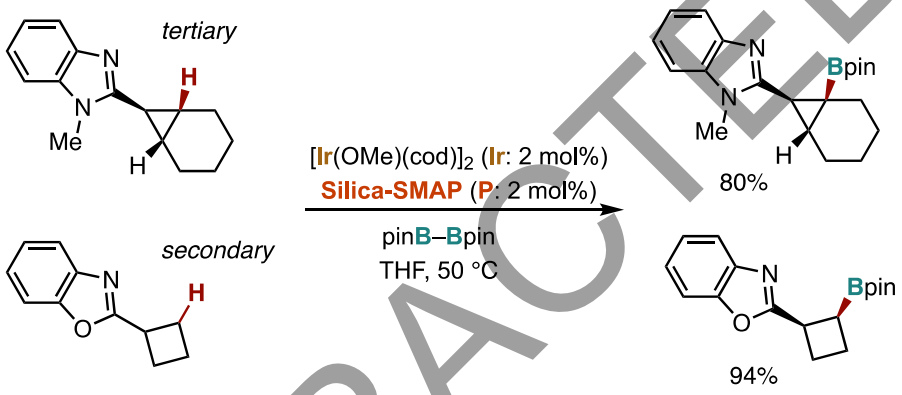


Figure 45. Stereoselective C–H borylation of small ring carbocycles.

Sawamura and co-workers were able to demonstrate the utilization of the heterogeneous ligand system towards the site-selective and stereoselective C(sp^3)–H borylation (Murakami et al., 2016) of the alkyl side chains of 1,3-azoles under mild reaction conditions (2 mol% Ir, 50– 90 °C), giving both primary and secondary alkylboronate derivatives (Figure 46). The reaction tolerates a variety of 1,3-(benzo)azoles including thiazoles, oxazoles, and imidazoles.

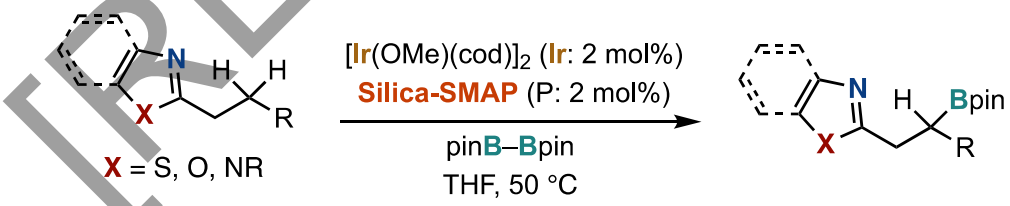


Figure 46. Site- and stereoselective C(sp^3)–H borylation of alkyl side chains of 1,3-azoles.

Collectively, the synthetic utility of the borylation reactions reported by Sawamura has been demonstrated by the transformation of the boronates to other functionalities (Figure 47). Thus, the Suzuki-Miyaura type cross coupling reaction of the corresponding borylated amide derivative with 2-bromoanisole proceeded smoothly giving the functionalized amide. A homologation-oxidation protocol was also demonstrated in the benzoimidazolyl-borylated-cyclobutane product to give the alcohol derivative in a considerable yield. Finally, the products were also amenable to the copper catalyzed amination procedure as demonstrated by the amination of the 2-ethylbenzothiazole borylated compound. Taking note of the numerous applications for the silica-supported monophosphine ligands developed by the Sawamura group, these systems represent the most versatile heterogeneous catalysts for directed borylation.

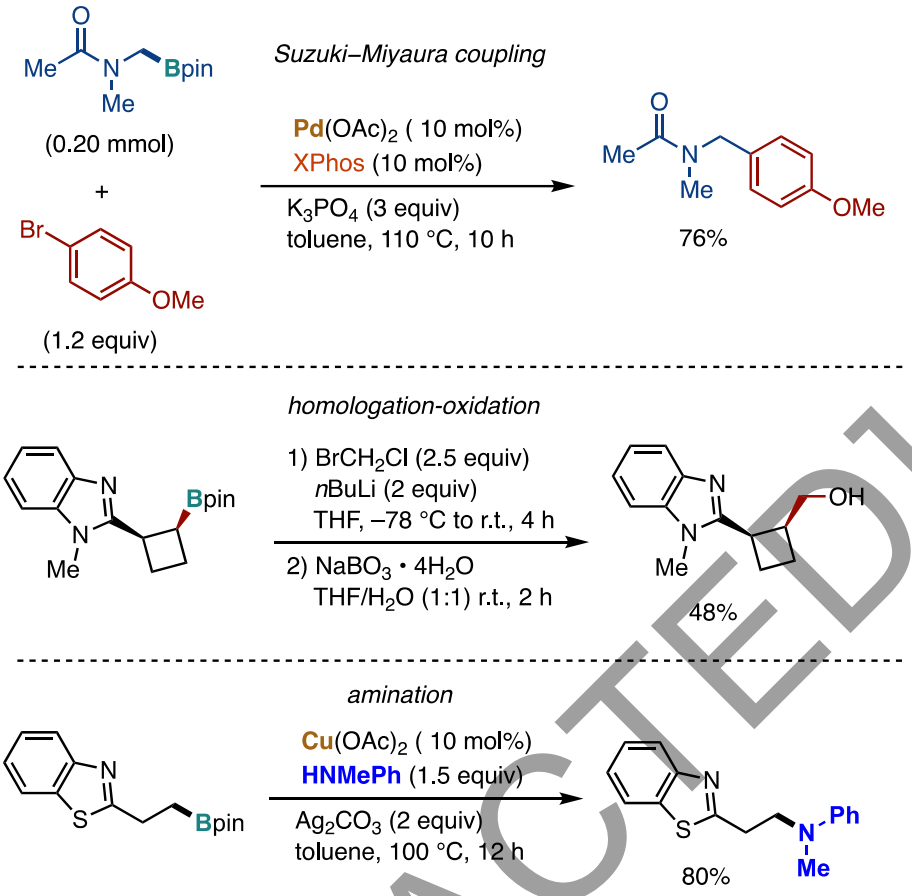


Figure 47. Synthetic utility of alkylboronates.

More recently, an alternative C(sp^3)–H borylation using a hydrogen atom transfer (HAT) strategy was reported by the Aggarwal group (Shu et al., 2020). Instead of utilizing a metal catalyst for C–H bond cleavage, intermolecular reaction with a heteroatom-centered radical followed by homolytic substitution of a diboron reagent facilitated the formation of the C–B bond (Figure 48a). The regioselectivity was determined by the bond dissociation energy (BDE) of the C–H bond thereby demonstrated high selectivity towards the borylation of alkyl groups. Norbornane and bis(catecholato)diboron, for example, upon irradiation in the presence of B-chlorocatecholborane and an alkoxyphthalimide in acetonitrile gave the corresponding pinacol boronic ester after in situ transesterification of the initially generated catechol boronic ester (Figure 48b). Such methodology complements the selectivities of existing methods as described in the previous sections.

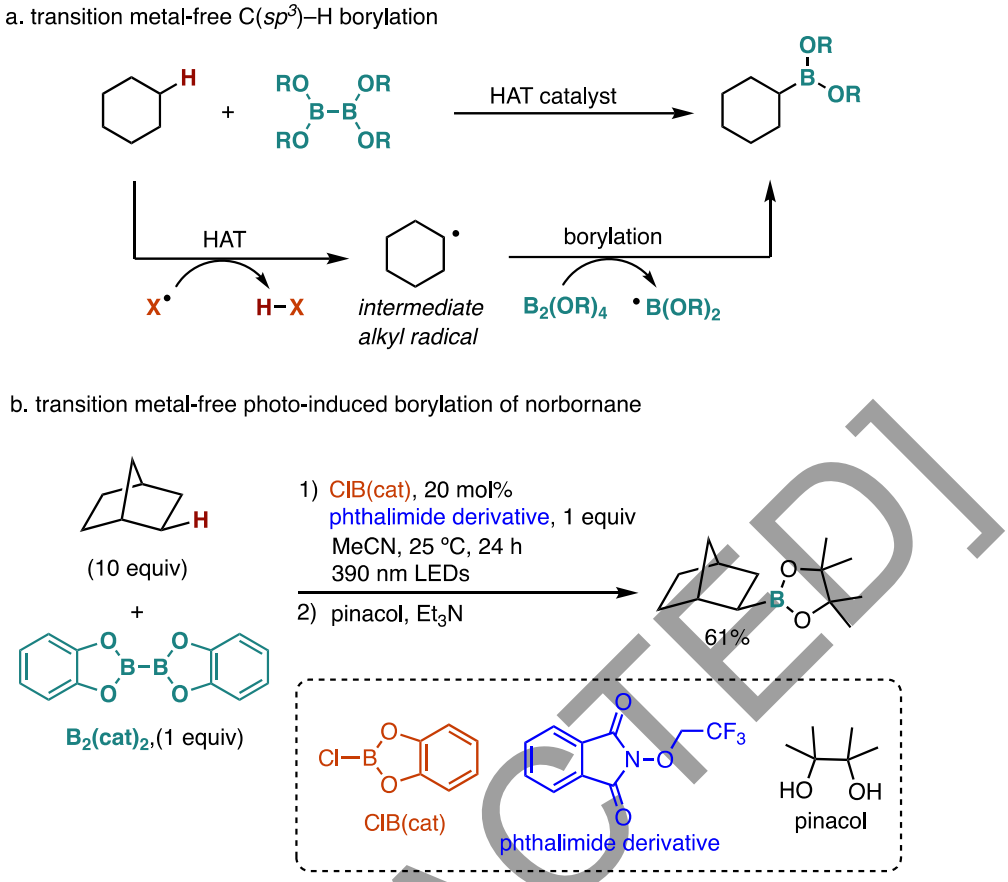


Figure 48. Photo-induced HAT strategy for the borylation of unactivated alkyl C–H bonds.

Asymmetric Borylation of C(sp³)–H Bonds. Despite the strategies that were developed for the borylation of C(sp^3)–H bonds, enantioselective C(sp^3)–H borylation remains unprogressive. Crucial to this goal is the competency of catalytic systems to differentiate between the chemically inert C–H bonds. Yu and co-workers initially attempted the elaboration of a Pd-catalyzed enantioselective borylation relying from their previous work on the borylation of methylene C–H bonds using quinoline ligands. The use of chiral acetyl-protected aminoethyl quinoline ligand which they utilized previously for β-C–H arylation reactions (see Figure 31) did not provide any desired borylated product under similar reaction conditions to the racemic reaction (He et al., 2017). They reason out that this chiral bidentate ligand may not be compatible with the transmetalation or the corresponding C(sp^3)–B reductive elimination step. Replacing the quinoline ligand with a chiral acetyl-protected aminomethyl oxazoline (APAO) ligand led to the desired reactivity (Figure 49). The protocol successfully enabled the asymmetric borylation of C(sp^3)–H bonds in cyclic amides, including cyclopropanes, cyclobutanes, and cyclohexanes with high levels of enantioselectivity. In this catalytic system, however, a high catalyst loading is necessary (10 mol% Pd, 30 mol% ligand) to accomplished the observed reactivity and enantioselectivity. Nonetheless, this system provides the first enantioselective Pd-catalyzed direct borylation of C(sp^3)–H bonds.

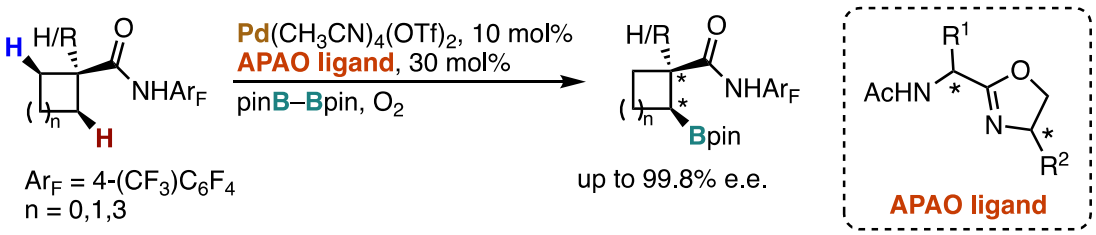


Figure 49. Pd-catalyzed enantioselective C(sp^3)–H borylation of cyclic amide derivatives.

Following the reported heteroatom-directed borylation of C(sp^3)–H bonds with Rh- and Ir-catalyst systems based on heterogeneous immobilized silica-supported bridgehead monophosphine, Silica-SMAP and Silica-TRIP, by Sawamura and co-workers (see Figures 42–46) several homogeneous monophosphines were observed to also promote the challenging C(sp^3)–H borylation. For example, the borylation of 2-aminopyridine derivatives with bis(pinacolatodiboron) under rhodium catalysis gave the corresponding secondary α-aminoboronate with the sterically hindered P(*o*-tol)$_3$ and P(*t*Bu)$_3$ identified to be the most effective ligands (Reyes, Harada, et al., 2017). These results open a synthetic opportunity to extend the reaction protocol to a catalytic asymmetric technique to directly synthesize enantioenriched alkylboronates from functionalized alkanes. Indeed, after broad screening of chiral homogeneous monophosphine ligands in the reaction shown in Figure 50, it was established that commercially available BINOL-based phosphoramidite, (*S*,*S*,*S*)-**L1**, induced good catalytic activity, albeit the moderate enantioselectivity (95% yield, 31% ee). Chiral phosphoramidites bearing SPINOL or TADDOL backbones were less effective for asymmetric induction.

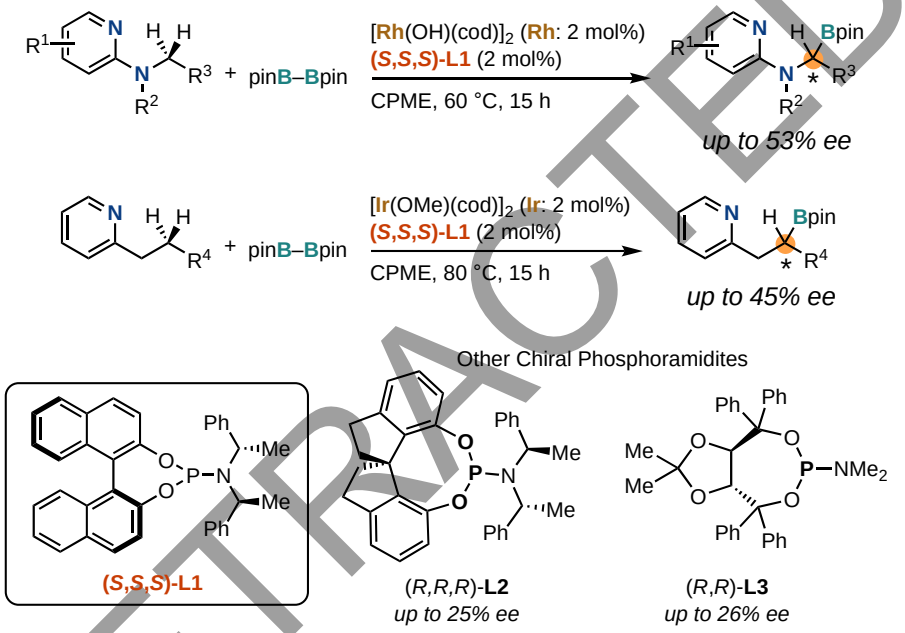


Figure 50. Rh- and Ir-catalyzed C(sp^3)–H borylation of using homogeneous phosphoramidite ligands.

Continuing along these lines and realizing the importance of stereochemistry-generating C–H activation approaches, Sawamura and co-workers reported the development of an innovative chiral catalyst system enabling the asymmetric differentiation of enantiotopic methylene C(sp^3)–H bonds (Reyes et al., 2019). Accordingly, the iridium-catalyzed asymmetric borylation of internal methylene C–H bonds in 2-alkylpyridine and 2-alkyl-1,3-azole derivatives (Figure 51), proceeded with excellent enantioselectivity delivering α-chirogenic alkylboronates using a triisopropylsilyloxy(TIPS)-modified BINOL-based monophosphite ligand (*R*,*R*)-L* (Reyes and Sawamura, 2020). Quantum chemical calculations using the artificial force induced reaction (AFIR) methods (Maeda et al., 2013) combined with DFT methods indicated that C(sp^3)–H bond cleavage of **L***-Ir(Bpin)$_3$-substrate proceeds via concerted oxidative addition of a C–H bond to the Ir(III) center. In the transition state leading to the major enantiomer product, the **L***-Ir(Bpin)$_3$ forms a narrow chiral reaction pocket where the alkylpyridine substrate is accommodated not just by the Ir–N coordination but also by the assembly of weak attractive interactions contributing to the overall stabilization of the transition state (Figure 51). These crucial secondary interactions include π-stacking, CH–π, and C–H···O noncovalent bonding between the substrate and the catalyst.

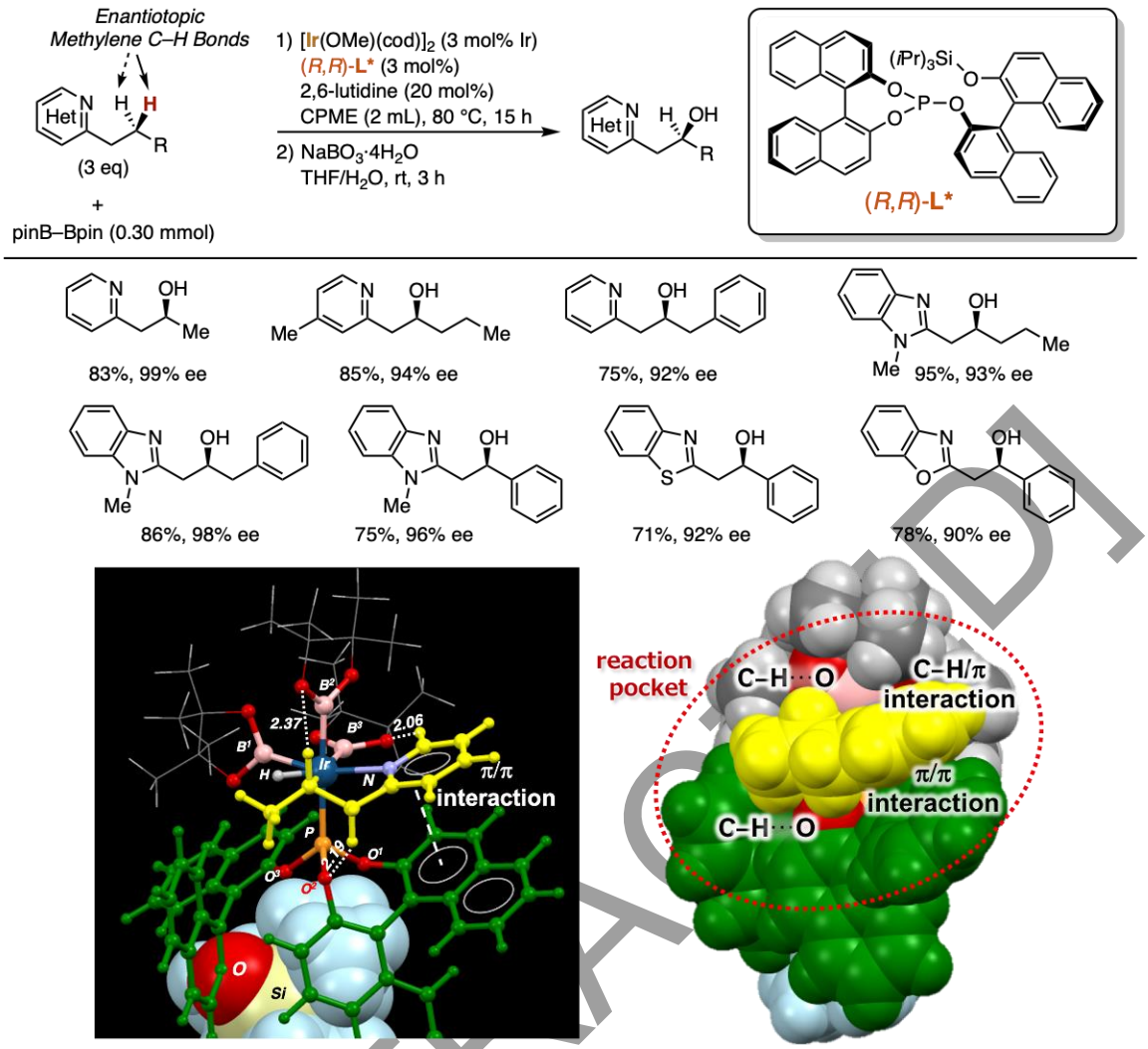


Figure 51. Ir-catalyzed C(sp^3)–H borylation of unactivated enantiotopic methylene C–H bonds. 3-D representations with geometrical features of the transition state leading to the major enantiomer is shown. In the ball-and-stick model (left) and the space-filling model (right), the binaphthyl moieties of (*R*,*R*)-L* are shown in green, the TIPS group in pale blue (*i*Pr) and pale yellow (Si), and the substrate in yellow. All atomic distances are given in Å. The calculations were done at the M06-L+D3/SDD&6-31G(d) level of theory.

Sawamura and co-workers then reported their findings that a rhodium catalyst system with the identical chiral phosphite ligand (*R*,*R*)-**L*** enabled a highly enantioselective borylation of *N*-adjacent C(sp^3)–H bonds (Figure 52) allowing the direct asymmetric synthesis of α-aminoboronates for a range of substrate classes including 2-(*N*-alkylamino)heteroaryls and *N*-alkanoyl or aroyl-based secondary or tertiary amides (Reyes et al., 2020). Various stereospecific transformations of the enantioenriched α-aminoboronates including Suzuki–Miyaura coupling with aryl halides and the reaction with an isocyanate derivative affording a new peptide chain elongation method have been demonstrated. The borylation protocol was successfully applied to the catalyst-controlled site- and stereoselective C(sp^3)–H borylation of an unprotected dipeptidic compound allowing remarkably streamlined synthesis of the anti-cancer drug molecule bortezomib.

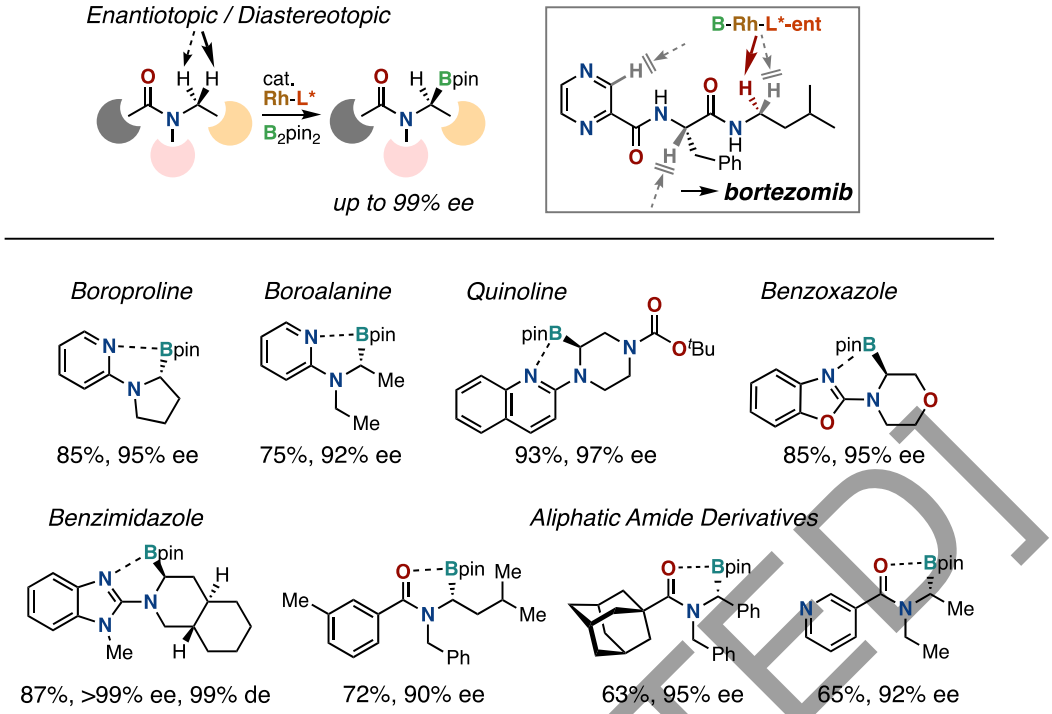


Figure 52. Rh-catalyzed asymmetric synthesis of α-aminoboronates via C–H bond borylation.

Shortly after, Xu and co-workers have also reported a series of enantioselective C–H bond borylation methodologies (Figure 53). In their work, the careful selection of iridium precursors and chiral bidentate boryl ligands (CBL) proved crucial in allowing a variety of C–H bond borylation encompassing different but complementary substrate classes to that reported by Yu and Sawamura. For example, the strategy can target C(sp^3)–H bonds in cyclopropanes (Shi et al., 2019) and cyclobutanes (Chen, Chen, et al., 2020), α-C(sp^3)–H bonds of azacycles (Chen, Yang et al., 2020), and unbiased methylene C–H bonds of acyclic amides (Yang et al., 2021) giving the corresponding boronates with excellent enantioselectivities.

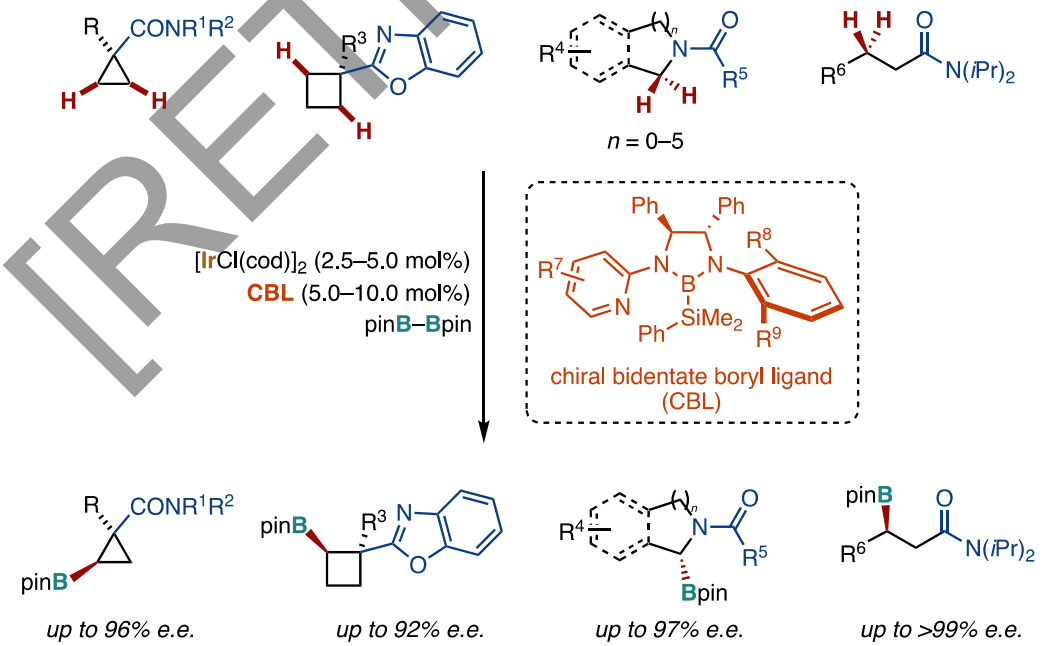


Figure 53. Asymmetric C–H bond borylation using chiral bidentate boryl ligands.

Remote C(sp^3)–H bond functionalization chemistry (Qiu and Wu, 2015; Sharma, 2018) has progressed slowly compared to the activation and subsequent transformation of remote C(sp^2)–H bonds (see: Ali and Siddiqui, 2021; Genov et al., 2020; Lu et al., 2019; Kuninobu et al., 2015). In particular, asymmetric functionalization of remote C(sp^3)–H bonds in easily accessible organic molecules remains underdeveloped, presumably due to the entropic penalty for the formation of larger-membered metallacycles via C–H metalation (Zhang and Shi, 2021). In this context, the functionalization was limited to specific substrates that do not have the conventional accessible C–H bonds to effect remote directing. However, the utility of linear aliphatic hydrocarbons has been traditionally difficult and scarce.

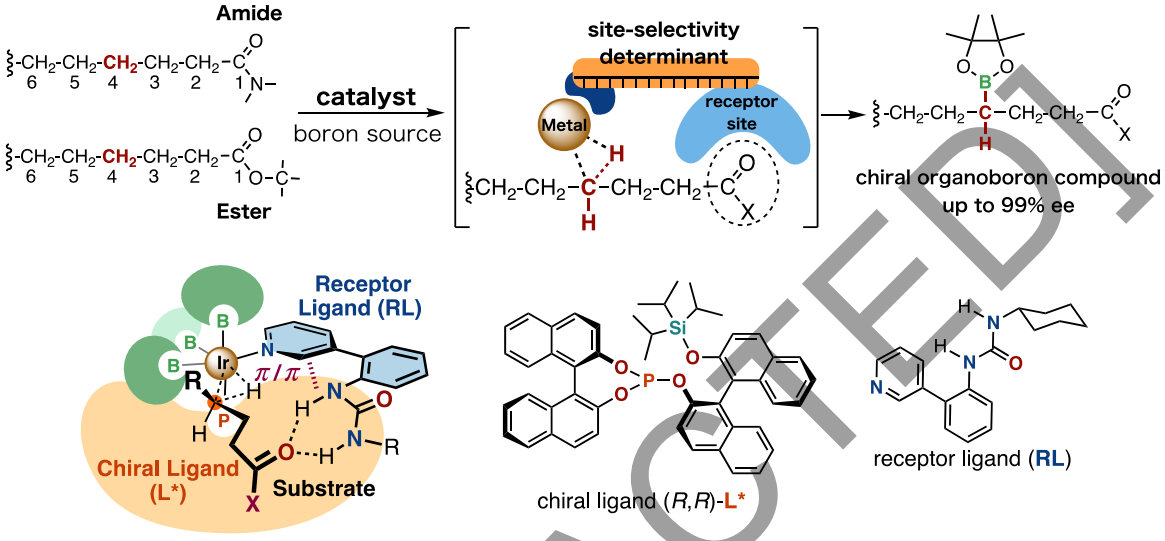
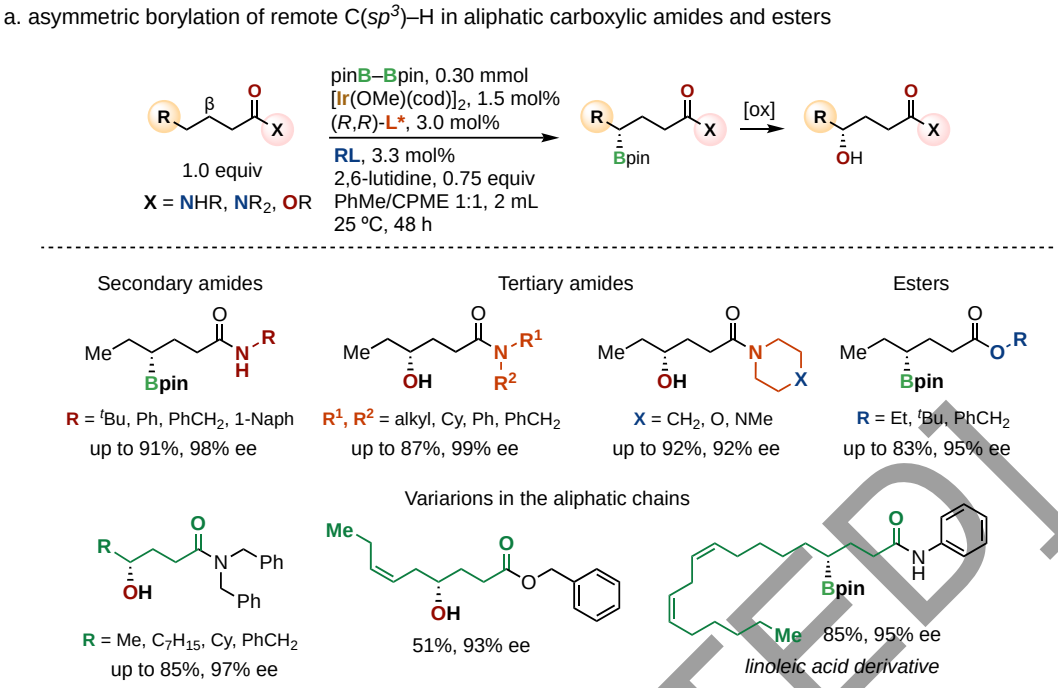


Figure 54. Strategy towards the asymmetric borylation of remote C–H bonds in aliphatic amides and esters.

The prevalence of aliphatic carboxylic acids and their derivatives as common feedstock chemicals has resulted to the upsurge of methodologies for the direct activation of C–H bonds within their hydrocarbon framework. However, compared to the functionalization of proximal C–H bonds, remote C(sp^3)–H bonds in these compounds is far less developed. Recently, Sawamura and co-workers disclosed a highly enantio- and site-selective catalytic borylation of remote C(sp^3)–H bonds γ to the carbonyl group in aliphatic carboxylic acid derivatives (Reyes et al., 2020). A chiral C–H activation catalyst was modularly assembled from an iridium center, a chiral monophosphite ligand, an achiral urea-pyridine receptor ligand, and pinacolatoboryl groups, Figure 54.



b. calculated transtion state for the asymmetric remote C–H borylation

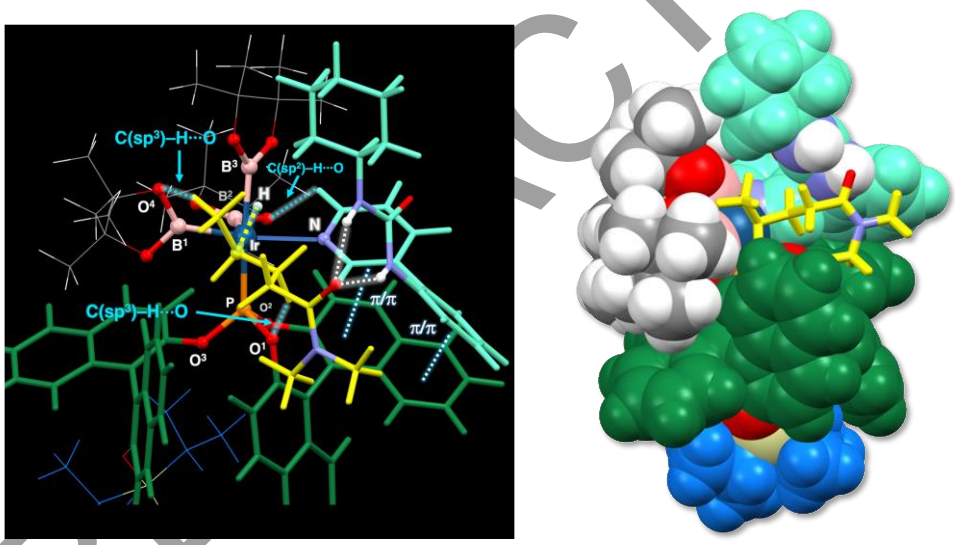


Figure 55. Substrate scope (a) of the catalytic asymmetric borylation of remote C–H bonds in aliphatic amides and esters and the corresponding calculated transition state (b) leading to the major enantiomer. The models showed a chiral reaction pocket (see space filling model) for substrate (yellow) binding formed by the [Ir(Bpin)$_3$], binaphthyl frameworks of the chiral monophosphite ligand (green), the isopropyl (iPr) groups in the triisopropylsilyl (TIPS) moiety of the ligand (blue) and the urea-pyridine receptor ligand (cyan). The calculations were done at the M06-L+D3/SDD&6-31G(d) level of theory.

Tolerating a wide range of substrates, aliphatic secondary and tertiary carboxamides, as well as ester derivatives were amenable for the asymmetric borylation (Figure 55a). The utilization of longer chain carboxylic acid derivatives were also suitable substrates even allowing variations not just in the chain length but also to the terminal functionalities of the hydrocarbon framework. An impressive tolerance towards unsaturation on the chain makes fatty acid-derived substrates including the amide derivative of linoleic acid, the doubly unsaturated essential omega-6 fatty acid, amenable to the asymmetric borylation. Linoleic acid was recently implicated in studies involving binding pockets in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

spike proteins (Toelzer et al., 2020), thus the developed protocol will find excellent applications in creating methodologies for introducing molecular complexity and chemical modification in fatty acids. Furthermore, versatile synthetic utility of the enantioenriched γ-borylcarboxylic acid derivatives was demonstrated paving the opportunity for developing strategic synthetic tools for building structural diversity from readily available raw materials. Quantum chemical calculations for the remote C–H borylation support an enzyme-like structural cavity formed by the catalyst components, which binds the substrate through multiple noncovalent interactions as shown in the three-dimensional representation (3D) in Figure 55b. One of the naphthalene rings of the monophosphite ligand (*R*,*R*)-L* has π/π interactions not only with the pyridine moiety but also with the *ortho*-phenylene linker of the receptor ligand, while the substrate is bound in the cavity not only through hydrogen bonding with the urea moiety, but also through C(sp^3)–H···O interactions and London dispersion interactions overall contributing to the substrate binding in the catalytic cavity. These features compliment those of natural enzymes that have intricate active sites for substrate binding. The interactions within this pocket effectively position the substrate bringing the targeted site in close proximity to the catalytic center.

OUTLOOK AND FUTURE PERSPECTIVE

It is without doubt that C–H bond activation chemistry has reached new heights in the advent of the new century. Researchers around the globe have devoted significant resources in advancing the field especially in the context of sustainable synthesis (Dalton et al., 2021; Samanta et al., 2020; Tzouras et al., 2017). There has been a surge in method development encompassing diverse techniques that would allow the rather difficult task of selectively activating C–H bonds in many different substrate classes and install new functionalities. Given this drive, it is expected that the field of C–H activation and functionalization will continue to mature to cope up with the increasing demands to produce new materials, pharmaceuticals, drugs, and innovative compounds. Collaborations from different fields also start to emerge as a useful strategy in circumventing the challenges in C–H activation chemistry. For example, inputs from theoretical and information scientists greatly help experimental scientists in their quest for efficient catalyst design. Advances in modern biological sciences have also prompted the creation of synthetic biomimetic systems that functionally perform chemical reactivities exhibited by natural enzymes (Chen and Arnold, 2020; Thompson and Cowan, 2020; Perez-Rizquez et al., 2019; Reyes and Tanaka, 2017). Only now that we begin to have a complete understanding that even synthetic catalysts in most parts mimic the mechanistic attributes of natural enzymes including the involvement of non-covalent interactions (Fanourakis et al., 2020) to stabilize the transition states associated with C–H bond functionalization within a generated catalytic pocket. These advances led to the creation of catalytic systems that adapt to the need to functionalize a specific C–H bond within the substrate scaffold.

The transformation of C–H bonds to C–B bonds presents not only an atom-economical and viable reaction but is also a frontier example of an enabling process in introducing molecular complexities given the versatility of organoboron reagents. These compounds are integral to many of the fundamental methodologies in the organic chemistry toolbox (i.e., cross-coupling reactions). Recent advances for the installation of boron functional groups have proven the importance of these compounds in many industries. Synthetically inaccessible molecules have been synthesized via the corresponding transformation of C–B bonds to various functionalities. Thus, strategies that will directly provide chiral organoboronates through asymmetric C–H borylation will find diverse applications in an array of industries, processes, and different field of studies. Given the enormous amounts of organic compounds that are suitable substrates we can only expect the continued growth of this chemistry in the future and it is without hesitation that C–H bond functionalization will take its role as the holy grail of chemistry.

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