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Transition metal catalyzed oxidative functionalization of carbon–hydrogen bonds

Allison R. Dick and Melanie S. Sanford*

Department of Chemistry, University of Michigan, 930 N. University Ave, Ann Arbor, MI 48109, USA

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* Corresponding author. Tel.: +1 734 615 0451; fax: +1 734 647 4865; e-mail: mssanfor@umich.edu

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1. Introduction

The development of mild, general, and selective transition metal catalyzed methods for the functionalization of carbon–hydrogen bonds represents a significant current challenge in organic chemistry. Although this field is currently in its infancy, such transformations have the potential to fundamentally change retrosynthetic approaches to complex molecule synthesis. In addition, they could serve as powerful tools for the rapid and direct synthesis of diverse functionalized products for structure–activity relationship (SAR) studies in medicinal and materials chemistry.

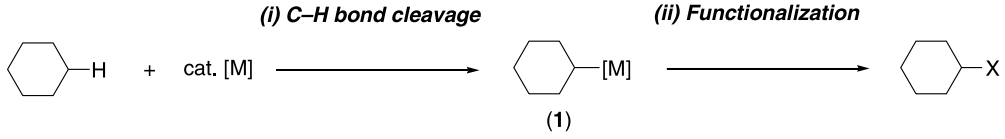
The vast majority of transition metal catalyzed C–H activation/functionalization reactions of complex organic molecules have focused on the transformation of C–H bonds into C–C bonds. These powerful methods have found recent application in the elegant syntheses of a variety of biologically active molecules[1–9] and have been the subject of numerous review articles.[10–18] In contrast, metal catalyzed C–H activation/oxidation reactions—which allow the selective installation of valuable functional groups such as carbon–oxygen, carbon–halogen, carbon–nitrogen, or carbon–boron bonds—have been less thoroughly reviewed in the literature. The latter transformations are the subject of the current article, which will focus on the background, recent exciting progress, and the potential for future developments in this area.

2. General mechanisms for transition metal catalyzed C–H bond functionalization

A variety of transition metal catalysts have been developed for the oxidative functionalization of carbon–hydrogen bonds to produce alcohol, amine, alkyl/aryl halide, and alkyl/aryl borane products. Although all of these catalysts promote the same general transformations (C–H→C–X), they can operate within two very different mechanistic manifolds. These two mechanisms, which are referred to as 'inner-sphere' and 'outer-sphere' throughout this review, are described in detail below. Notably, alternative terminology, introduced by Crabtree, labels these mechanisms 'organometallic' and 'coordination,' respectively.[19]

2.1. Inner-sphere mechanism

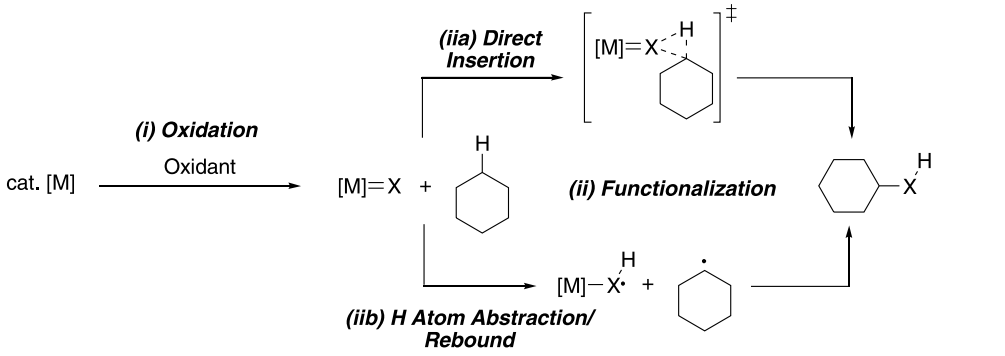
The 'inner-sphere' C–H bond functionalization mechanism involves two discrete steps: (i) cleavage of a carbon–hydrogen bond to afford a transition metal alkyl/aryl species (**1**) and (ii) functionalization of **1** by reaction with either an external reagent or at the metal center (Eq. 1). The key distinguishing feature of this mechanism is the formation of a discrete organometallic intermediate (**1**), and the structural and electronic requirements of this intermediate dictate the regio- and stereoselectivity of functionalization. These transformations often proceed with high selectivity for the less sterically hindered C–H bonds of a molecule; however, other factors, including the ligand environment at the metal center and the mechanism of the C–H bond cleavage step, can also influence selectivity in these systems.



(1)

2.2. Outer-sphere mechanism

The 'outer-sphere' mechanism for C–H bond functionalization mimics biological oxidation reactions catalyzed by enzymes such as cytochrome P450 and methane monooxygenase (MMO). These processes proceed via (i) formation of a high oxidation state metal complex containing an activated ligand X (typically a metal oxo-, imido- or carbene species) followed by (ii) reaction of ligand X with a C–H bond (Eq. 2). This latter step can proceed by either direct insertion (Eq. 2, iia) or H-atom abstraction/radical rebound (Eq. 2, iib). The key distinguishing feature of the outer-sphere mechanism is that the alkane/arene substrate does not interact directly with the transition metal center but instead reacts with a coordinated ligand. As shown in Eq. 2, these transformations involve build up of radical and/or cationic character at carbon, and therefore typically show high selectivity for weaker C–H bonds (e.g., those that are benzylic, allylic, 3°, or α to heteroatoms).



(2)

It is also important to note that there are a number of non-transition metal catalyzed reactions for the oxidative functionalization of carbon–hydrogen bonds.[20–22] These include electrophilic aromatic substitution, directed *ortho*-lithiation/electrophilic addition,[23] reactions of dioxiranes,[24–26] and free radical halogenation, hydroxylation, and/or amination.[20,21] Many of these reactions are widely used in synthetic organic chemistry, and often exhibit complementary levels of reactivity, functional group tolerance, and selectivity to the transition metal catalyzed reactions discussed throughout this review.

3. General challenges for transition metal catalyzed C–H bond functionalization

The four major challenges associated with the catalytic oxidative functionalization of C–H bonds within the context of complex organic molecules are (a) reactivity, (b) chemoselectivity, (c) regioselectivity, and (d) stereoselectivity. A short description of each challenge along with general strategies that have been used to address it is detailed below.

3.1. Reactivity

The strength of typical carbon–hydrogen bonds (which have bond dissociation energies between 85 and 105 kcal/mol) presents a first and very significant challenge in this area. While most oxidation reactions are thermodynamically downhill, there is generally a large kinetic barrier associated with the C–H bond cleavage event required prior to/during functionalization. As described throughout this review, transition metal catalysts serve to increase the rates of reactions of C–H bonds by many orders of magnitude.

3.2. Chemoselectivity

The ability to stop functionalization at the required oxidation state represents a second major challenge, as the over-oxidation of functionalized products is often highly thermodynamically downhill. A number of strategies have been used to address this important issue, including: (i) running reactions to low conversion, (ii) utilizing large excesses of substrate relative to oxidant, (iii) carrying out intra- rather than intermolecular functionalization reactions, (iv) kinetically blocking over-oxidation through the installation of deactivating functional groups, and (v) catalyst design and selection.

3.3. Regioselectivity

Most organic molecules contain many different types of carbon–hydrogen bonds; therefore, developing transformations that regioselectively functionalize a single C–H bond within a complex structure remains a third critical challenge in this field. A number of approaches have been used to address this problem, including: (i) the use of substrates containing weaker or activated C–H bonds (e.g., 3° or benzylic/allylic systems), (ii) the use of coordinating ligands within a substrate as directing groups, (iii) carrying out intramolecular functionalization reactions via favorable five- or six-membered transition states, (iv) the use of supramolecular chemistry to position a specific C–H bond near the catalyst active site, and (v) the use of the transition metal catalysts/ligands to control selectivity.

3.4. Stereoselectivity

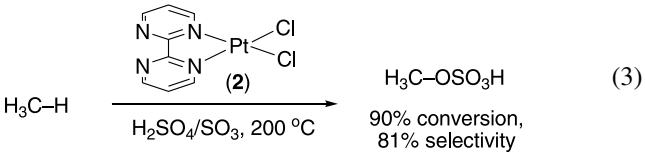
The functionalization of carbon–hydrogen bonds to generate new stereogenic centers in a highly diastereoselective and/or enantioselective fashion represents a fourth challenge in this field. While this issue has been the least well explored to date, both substrate-based approaches (involving the use of substrates containing pre-installed stereocenters or chiral auxiliaries) as well as catalyst-based approaches (involving the use of chiral transition metal complexes to control the enantioselectivity of functionalization) have been developed. Notably, the stereospecific oxidative functionalization of C–H bonds at existing stereocenters represents another attractive method for the construction of chiral molecules, and has also found a number of applications.

4. C–H bond oxygenation

The direct oxygenation of carbon–hydrogen bonds represents a powerful approach to alcohol products, which find widespread application as synthetic intermediates and as products in the commodity chemical, fine chemical, and pharmaceutical industries. As outlined below, efforts to develop methods for metal catalyzed C–H bond oxygenation have focused on both the inner-sphere and outer-sphere mechanisms.

4.1. Inner-sphere catalysts

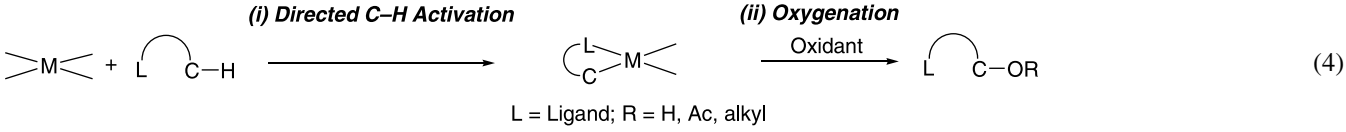
Applications of inner-sphere catalysts in C–H bond oxygenation have primarily focused on the transformation of methane to methanol, a process of great potential utility for the conversion of natural gas into a more readily transportable liquid fuel. A variety of catalysts (including Pt,[27] Pd,[28,29] and Au[30] complexes) and terminal oxidants (such as K_2PtCl_6,[27] $K_2S_2O_8$,[29] $CuCl_2$,[28] and O_2[31]) have been used, and the area has been extensively reviewed.[19,32–37] Platinum complex **2** is the most efficient and selective homogeneous catalyst reported to date, and converts CH_4 to CH_3OSO_3H in 90% conversion with 81% selectivity, with SO_3 as the terminal oxidant (Eq. 3).[38] The excellent chemoselectivity is due to the installation of an electron-withdrawing sulfonic acid group, which deactivates the product toward further oxidation. However, the high temperature (200 °C) and acidic medium (concentrated H_2SO_4) render this system untenable for the selective oxygenation of more complex organic molecules. Efforts to apply related Pt catalysts to the oxygenation of *n*-alkanes and simple substituted hydrocarbons have resulted in low TON's and only modest levels of regio- and chemoselectivity.[39–42]



(3)

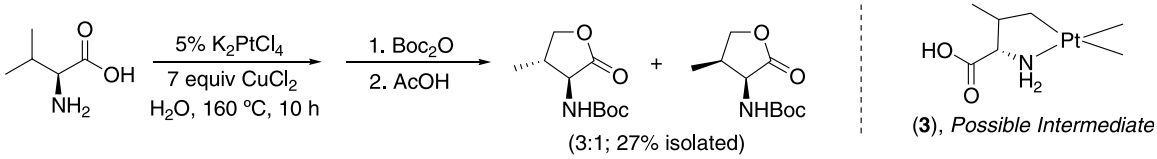
Homogeneous catalysts that operate under far milder conditions have been developed for the oxygenation of benzene C–H bonds.[43,44] In particular, palladium-based catalysts (typically $Pd(OAc)_2$) in conjunction with a variety of oxidants (for example, O_2/polyoxometallates,[45,46] dichromate,[47] peroxydisulfate,[48] and $PhI(OAc)_2$[49]) have been utilized for the transformation of benzene to phenol or an ester derivative at moderate temperatures (~100 °C) in acetic acid. However, the application of these transformations to substituted aromatic compounds (e.g., toluene, anisole, or naphthalene) generally results in the formation of undesirable mixtures of regioisomeric products.[49]

Several strategies have been successfully used to achieve regioselective C–H bond oxygenation via the inner-sphere mechanism. One approach involves the use of substrates containing coordinating functional groups, which can bind to the catalyst and direct C–H activation and subsequent functionalization to a specific C–H bond within the molecule (Eq. 4).[10,50–52]



(4)

Early work demonstrated the viability of this strategy in the K_2PtCl_4-catalyzed oxygenation of propionic acid with Pt^{IV} as a stoichiometric oxidant. While this transformation proceeded with <3 turnovers, it showed good regioselectivity for the β-position, which was rationalized based the formation of a chelated intermediate.[53,54] A related Pt-catalyzed method (using 5 mol% K_2PtCl_4 and 7 equiv $CuCl_2$ as a stoichiometric oxidant at 160 °C) has been used for the β-oxygenation of several amino acid derivatives (Eq. 5).[55] For example, valine underwent β-oxygenation with excellent regioselectivity and moderate diastereoselectivity (*anti*/*syn*=3:1), presumably due to the formation of metalacyclic intermediate **3**.[55]



(5)

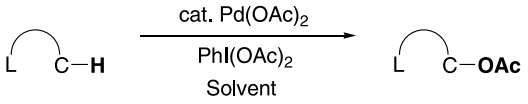
More recently, $Pd(OAc)_2$ has been used as the catalyst for ligand-directed C–H bond acetoxylation using $PhI(OAc)_2$ as a stoichiometric oxidant.[56–58] These Pd-catalyzed reactions typically proceed under significantly milder conditions (≤100 °C), with higher TON (often ≥50), and with broader substrate scope than those with Pt catalysts. As summarized in Table 1, a wide variety of directing groups, including pyridine, azo, amide, imine, oxime ether, and pyrazole derivatives, can be utilized, and this methodology is efficient for the regioselective oxygenation of both arene (sp^2) and alkane (sp^3) C–H bonds. Significantly, the oxidation of 3-methyl-2-pentanone *O*-methyl oxime (entry 8), which contains six different types of C–H bonds, selectively affords a single product in good (76%) yield. The observed selectivity for C–H activation/oxygenation at the less sterically encumbered 1° C–H bond relative to the 2° C–H bond in this substrate is a hallmark of the inner-sphere mechanism. Interestingly, C–H bonds can also be replaced with ether functionality (OR) through the use of alcohol-based solvents in these transformations (e.g., see entry 7).[58a,b] Notably, these reactions are believed to proceed via a $Pd^{II/IV}$ mechanism in which the key bond-forming step involves C–O reductive elimination from unusual Pd^{IV} intermediates.[49,58c]

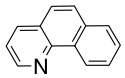
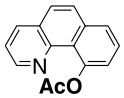
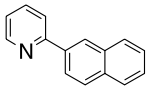
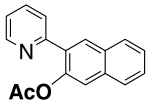
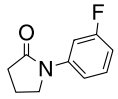
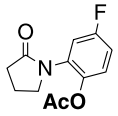
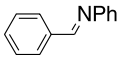
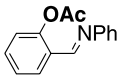
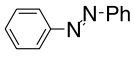
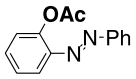
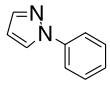
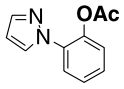
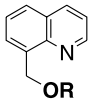
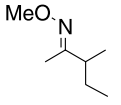
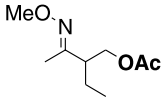
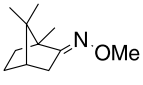
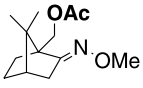
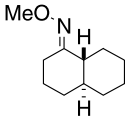
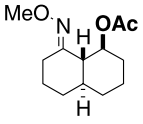
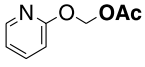
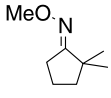
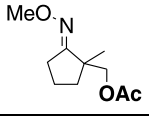
A second successful approach to regioselective C–H bond oxygenation with inner-sphere catalysts has involved the use of activated allylic substrates. Palladium trifluoroacetate has been shown to stoichiometrically cleave weak allylic C–H bonds to produce Pd-allyl intermediates,[59] and catalytic oxygenation of these species can be achieved in acetic acid using benzoquinone (BQ), duroquinone (DQ), or MnO_2 as a terminal oxidant.[60,61] Pd-catalyzed allylic acetoxylation has been applied to a variety of cyclic and acyclic substrates; furthermore, subtle modification of reaction conditions can be used to control the regioselectivity of oxygenation, providing efficient routes to both linear and branched allylic acetate products (Table 2, entries 3 and 4).[62,63] This methodology has been applied to the efficient construction of early intermediates in the syntheses of isoretronecanol and miyakolide (Table 2, entries 5 and 6, respectively).[64] Interestingly, when *tert*-butylhydroperoxide is used as a stoichiometric oxidant in related reactions, a peroxy moiety can be incorporated at the allylic position.[65]

4.2. Outer-sphere catalysts

The outer-sphere approach to C–H bond hydroxylation has been the subject of numerous reviews;[19,66–71] therefore, this section aims to summarize general features and the synthetic scope of these reactions, rather than providing a comprehensive treatment. The most active and most widely used outer-sphere catalysts are Mn, Fe, or Ru porphyrins of general structure **4** containing electron-withdrawing

Table 1. $Pd(OAc)_2$-catalyzed oxygenation of C–H bonds with $PhI(OAc)_2$



Entry	Starting material	Major product	Yield (%)
1[a]			86
2[a]			72
3[b]			88
4[a]			47
5[a]			62
6[a]			54
7[a]			R=Ac; 88, R=Me; 77[c]
8[d]			78
9[d]			75
10[d]			81
11[d]			66
12[d]			61

[a] Ref.58a.
[b] Ref.56.
[c] Reaction conducted in MeOH.
[d] Ref.57.

substituents (e.g., Ar=C_6F_5, C_6Cl_5, or 2,6-$C_6H_3Cl_2$; X=H, F, Cl, Br; Fig. 1).[72] These catalysts are utilized in conjunction with a stoichiometric oxidant (most commonly PhI=O, pyridine *N*-oxide, or peroxides), and their activity is often enhanced by the addition of an axial ligand such as imidazole.[73] Hydroxylation reactions catalyzed by **4** have been applied to a variety of substrates (Fig. 1) and typically show high selectivity for weak benzylic or 3° C–H bonds. The current limitations of this methodology from the perspective of a synthetic chemist are (i) the general requirement for large excesses of substrate relative to oxidant, (ii) modest levels of chemoselectivity (over-oxidation to ketones is a common side reaction), (iii) the general requirement for an 'activated' C–H bond within the molecule, (iv) modest levels of regioselectivity in substrates containing multiple weak C–H bonds, and (v) the inherent difficulties associated with synthesis and modification of porphyrin ligands.

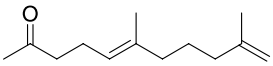
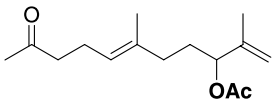
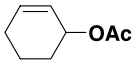
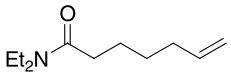
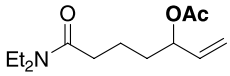
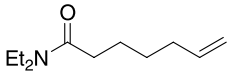
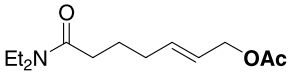
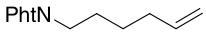
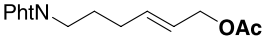
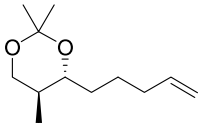
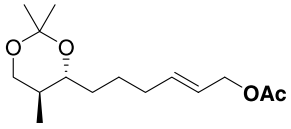
Recent work has made progress toward addressing a number of these limitations; for example, **4** (with M=Ru(CO), Ar = C_6F_5 or C_6H_5; X=H) has been shown to be a highly active catalyst for alkane hydroxylation without the requirement for large excesses of substrate relative to oxidant.[74,75] In these systems, a 1:1 ratio of alkane substrate (which can include adamantane, cyclohexane, methylcyclohexane, or decalin) to stoichiometric oxidant (2,6-dichloropyridine *N*-oxide) provides hydroxylated products in good yield (generally 70–90%) at low temperature (25–60 °C) with TON up to 120,000.

Significant recent efforts have also aimed to control the regioselectivity of oxygenation in substrates containing multiple C–H bonds of similar strengths. These methods typically rely on either substrate shape[76] or supramolecular interactions between catalyst and substrate[77–80] to geometrically bias oxygenation to a specific C–H bond. For example, cyclodextrin-substituted porphyrin **5** was used to orient steroid substrate **6**, facilitating highly regioselective hydroxylation at C_6, even in the presence of more activated 3° and benzylic C–H bonds (Fig. 2).[77] Interestingly, this transformation also proceeds with high levels of chemoselectivity (no ketone products were observed) and diastereoselectivity (only the equatorial C_6–H bond was hydroxylated) due to the strict geometric requirements of the catalyst active site (Fig. 2).

The enantioselective hydroxylation of alkanes using chiral metalloporphyrins and related outer-sphere catalysts has also been explored. Pioneering work by Groves demonstrated the asymmetric oxygenation of ethylbenzene and indan derivatives in 40–72% ee using a vaulted binaphthyl linked Fe porphyrin catalyst (**7**) (Fig. 3).[81,82] More recently, chiral Mn salen catalyst **8**[83] and chiral Ru porphyrin **9**[84] have been used to achieve slightly higher %ee values (generally ranging from 65–90%) for benzylic oxidations of a series of similar substrates (Table 3). The yields and substrate scope of all of these transformations remain modest, but they represent important precedent for the asymmetric oxygenation of hydrocarbon substrates.

Non-heme outer-sphere catalysts for alkane hydroxylation have also been developed, with Cr-[85,86] and Fe-based[87–91] complexes being the most common. These typically show comparable substrate scope and regioselectivity to the porphyrin systems (Fig. 1), but are often less robust.[92] Notably, the mechanism of hydroxylation reactions catalyzed by non-heme outer-sphere catalysts remains the subject of debate,[87,88,90,91,93–95] and some are likely to

Table 2. Palladium-catalyzed allylic oxygenation reactions

Entry	Conditions	Starting material	Major product	Yield (%) (linear: branched)
1[a]	5% $Pd(TFA)_2$, 20% PPh_3 1 equiv DQ, AcOH			31 (1:22)
2[b]	0.5% $Pd(OAc)_2$ 10% BQ, 1 equiv MnO_2, AcOH			77
3[c]	20% $Pd(OAc)_2$, 20% VS 2 equiv BQ, 4 equiv AcOH in dioxane			56 (1:18)
4[d]	10% $Pd(OAc)_2$, 10% VS 2 equiv BQ, 4 Å MS, 1:1 DMSO:AcOH			62 (23:1)
5[e]	10% $Pd(OAc)_2$, 2 equiv BQ, 4 Å MS 1:1.4 DMSO:AcOH			71 (17:1)
6[e]	10% $Pd(OAc)_2$, 2 equiv BQ, 4 Å MS 1:1.4 DMSO:AcOH			53 (19:1)

Abbreviations: DQ=duroquinone; BQ=benzoquinone; VS=vinylsulfoxide.
[a] Ref.61.
[b] Ref.60.
[c] Ref.62.
[d] Ref.63.
[e] Ref.64.

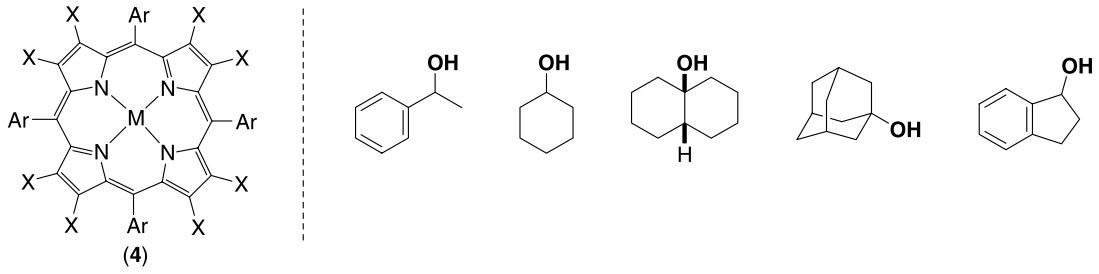


Figure 1. Porphyrin-based coordination catalyst **4** and representative alcohol products from C–H bond oxygenation reactions.

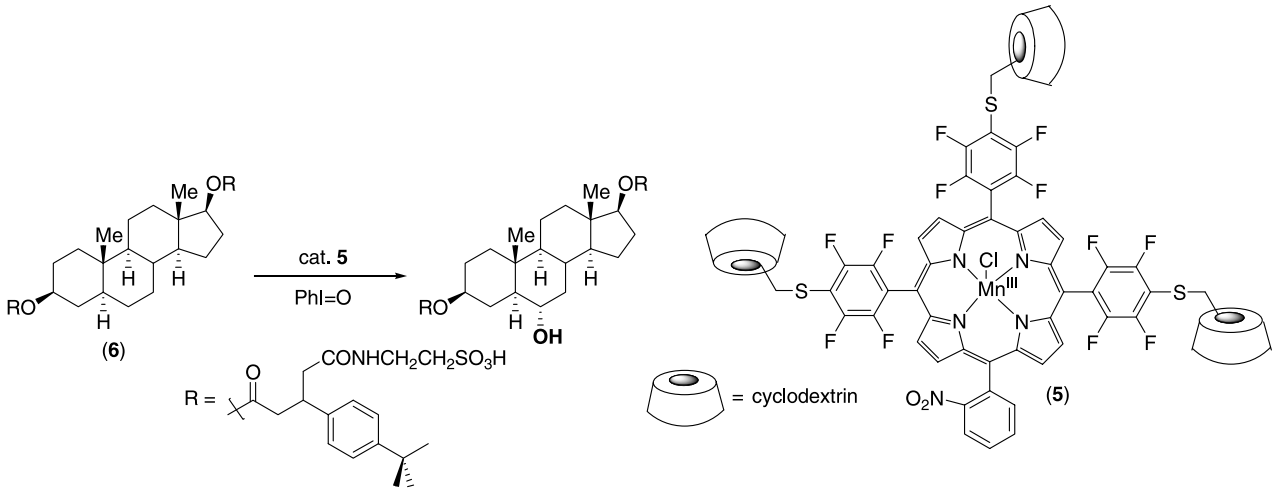


Figure 2. Regioselective oxidation with cyclodextrin substituted porphyrin **5**.

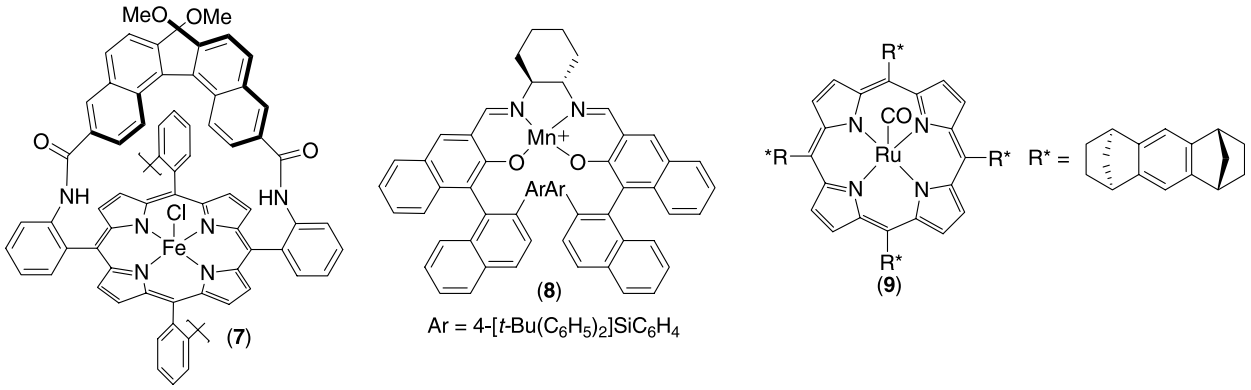
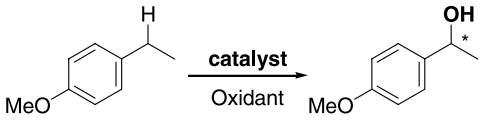


Figure 3. Chiral catalysts for asymmetric C–H bond hydroxylation.

Table 3. Asymmetric hydroxylation of *p*-methoxyethylbenzene



Catalyst	Oxidant	Yield (%)	ee (%)
7[a]	Ph-I=O	20	66 (*R*)
8[b]	Ph-I=O	13	87 (*R*)
9[c]	Cl_2pyNO	65[d]	62 (*S*)

[a] Ref. 81.
[b] Ref. 83.
[c] Ref. 84.
[d] Yield at 15% conversion.

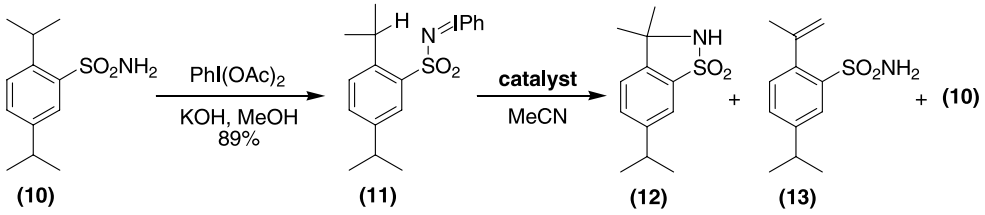
involve transition metal catalyzed generation of HO· followed by H-atom abstraction/propagation rather than a true outer-sphere mechanism.

In summary, significant progress has been made in the development of both inner-sphere and outer-sphere catalysts for the selective oxygenation of alkane and arene C–H bonds. In many cases, these two classes of catalysts exhibit highly complementary selectivities, and both have been used in a variety of synthetic applications. Future work in this area will likely include the application of these methods in the context of biologically active targets, the development and refinement of asymmetric catalysts for these transformations, and the continued pursuit of active transition metal catalysts for non-directed oxygenation of unactivated C–H bonds.

5. C–H bond amination

Amines are ubiquitous functional groups in organic synthesis and serve as critical components of a large number of biologically active molecules. Typical methods for the introduction of amino groups involve nucleophilic displacement, catalytic amination of aryl or vinyl halides,[96] nitration of an aromatic group followed by reduction, or addition of a nucleophile to an imine. These methods offer the disadvantages that they require pre-installation of reactive functional groups and often proceed under relatively harsh conditions. As such, methodology that allowed the regioselective formation of C–N bonds directly from carbon–hydrogen bonds would be of great potential synthetic utility.

In a seminal experiment in 1982, Breslow and Gellman reported the use of Mn or Fe porphyrin catalysts for the amination of cyclohexane using PhI=NTs as a stoichiometric oxidant.[97] While this reaction proceeded in low (~7%) yield, subsequent work demonstrated that intramolecular variants of this transformation are far more efficient.[98] For example, treatment of tosylamine **10** with $PhI(OAc)_2$/KOH in MeOH (which forms iodonium ylide **11** in situ) followed by the addition of a catalyst results in clean intramolecular C–H bond amination to afford **12** (Eq. 6). A survey of metal catalysts revealed that $Rh_2(OAc)_4$ is particularly effective, producing **12** in 86% yield. This key transformation demonstrated the first uses of both the oxidant ($PhI(OAc)_2$) and catalyst system (rhodium carboxylates) that have subsequently been widely applied in C–H bond amination reactions. Importantly, these transformations (and the related reactions described herein) are generally believed to proceed via the outer-sphere mechanism,[99] involving reactive metal–nitrene or metal–imido intermediates.[100–110]



(6)

Subsequent to this important work, a number of groups have recognized the potential synthetic utility of this transformation and have begun to develop its scope. In addition, such oxidative amination products have been observed as major side-products in catalytic aziridination reactions.[111–113] Due to heightened interest in this methodology, several reviews have recently appeared,[114–116] often in conjunction with their aziridination counterparts.[117,118]

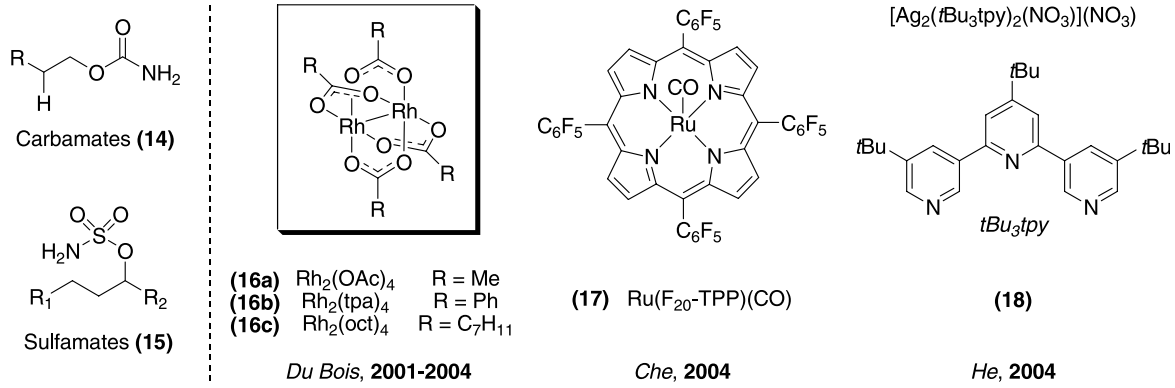


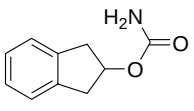
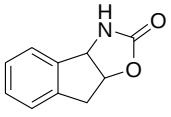
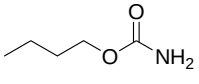
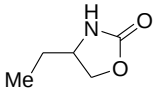
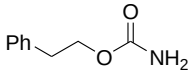
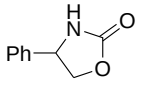
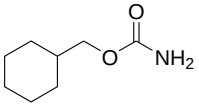
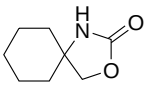
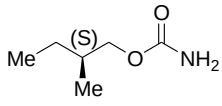
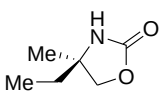
Figure 4. Common substrate classes and catalysts for intramolecular C–H amination.

5.1. Intramolecular C–H amination

The most synthetically useful recent developments in this field have involved intramolecular C–H insertion reactions. Early studies by Espino and Du Bois focused on carbamate-based substrates of general structure **14** (Fig. 4), which are readily synthesized from primary alcohols by treatment with $Cl_3CC(O)NCO$ followed by K_2CO_3/MeOH.[119] These substrates undergo facile $Rh_2(OAc)_4$-catalyzed intramolecular C–H bond amination to produce oxazolidinones in a mild one-pot procedure (5 mol% catalyst, 1.4 equiv $PhI(OAc)_2$, 2.3 equiv MgO, 40 °C, 12 h).

As summarized in Table 4, this methodology allows the intramolecular amination of a wide variety of 2°, 3° and benzylic C–H bonds to afford diverse 1,2 aminooxygenated products. Importantly, reactions of the chiral substrate shown in entry 5 proceed with complete retention of stereochemistry at the asymmetric carbon center, thereby providing a potential route to synthetically valuable α,α-disubstituted alkyl amines and quaternary α-amino acids. More recent work has demonstrated that other catalysts, including **16b**[119] and **18**[120] (Fig. 4) are also very effective for these transformations under only slightly more vigorous conditions (Table 4).

Table 4. Synthesis of oxazolidinones via intramolecular C–H amination

Entry	Substrate	Product	Catalyst	Yield (%)
1			**16a**	86
			18	89
2			**16b**	44
			18	58
3			**16b**	74
			18	81
4			**16a**	77
			16b	79
			18	85
5			**16**	nd
			18	73

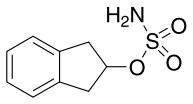
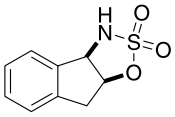
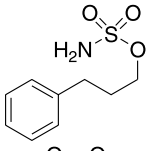
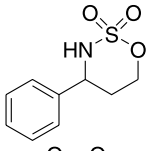
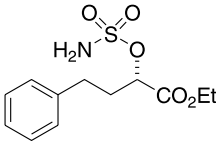
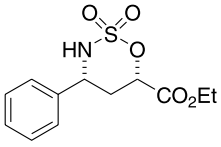
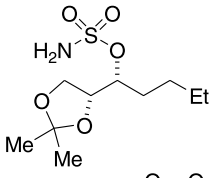
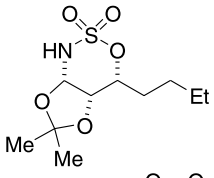
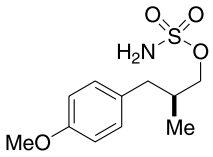
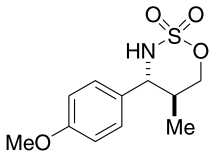
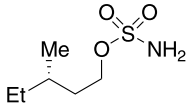
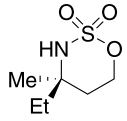
Reaction conditions: for catalysts **16a** and **16b**: 5% catalyst, 1.4 equiv $PhI(OAc)_2$, 2.3 equiv MgO, CH_2Cl_2, 40 °C, 12 h. (Ref. 119); for catalyst **18**: 4% $AgNO_3$, 4% tBu$_3$tpy, 2.0 equiv $PhI(OAc)_2$, MeCN, 82 °C (Ref. 120).

Sulfamate esters, which are readily available via condensation of $ClSO_2NH_2$ with primary and secondary alcohols, are also useful precursors for intramolecular C–H bond amination reactions.[120–125] Seminal early work by Du Bois and co-workers demonstrated that these substrates undergo intramolecular nitrogen insertion into 2°, 3° and benzylic C–H bonds[125] as well as α to oxygen substituents[121,123] under mild conditions (2–5% catalyst **16a** or **16c**, 1.1 equiv $PhI(OAc)_2$, 2.3 equiv MgO, CH_2Cl_2). Interestingly, the sulfamates show a strong preference for cyclization to form six-membered rings, in striking contrast to their carbamate counterparts. This allows access to synthetically useful 1,3-aminooxygenated products (Table 5). Notably, more recent work has demonstrated that **17**[122] and **18**[120] are also effective catalysts for cyclizations to afford these oxathiazinane products (Table 5, entries 1 and 2).

Like the carbamate cyclization reactions, sulfamate C–H insertion reactions proceed stereospecifically; for example, the $Rh_2(OAc)_4$-catalyzed cyclization of the chiral substrate shown in Table 5, entry 6 affords the product as a single enantiomer. In addition, these transformations proceed with high levels of diastereocontrol (typically >10:1) in substrates with both α-branching (Table 5, entries 1, 3 and 4) and β-branching (Table 5, entries 4 and 5). The diastereoselectivity of cyclization has been rationalized based on a chair-like transition state in which the metallonitrene inserts into an equatorial C–H bond.[124]

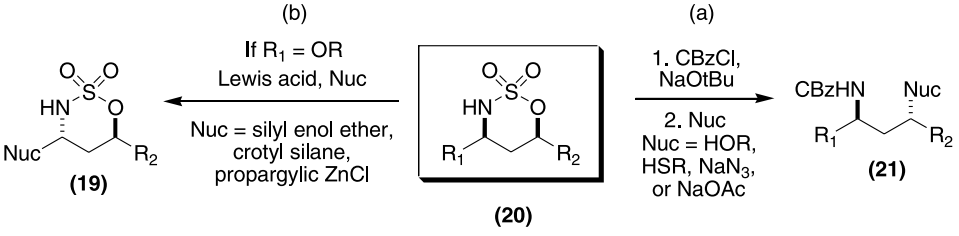
These cyclic oxathiazinane products are extremely synthetically useful intermediates, and a simple sequence of (a) *N*-CBz protection followed by (b) addition of an N-, O-, or S-based nucleophile (e.g., amines, thiols, alcohols, H_2O, N_3^-, AcO^-) results in nucleophilic ring opening to afford diverse 1,3-amino functionalized products (Eq. 7, a).[125] In addition, the N,O acetal products generated from C–N insertion α to oxygen serve as valuable precursors to iminium ions (via treatment with Lewis acids), which can then undergo highly

Table 5. Intramolecular amination of sulfamate esters

Entry	Substrate	Product	Catalyst	Yield (%)
1			**16a**[a] **17**[b] **18**[c]	60 66 65
2			**17**[b] **18**[c]	77 87
3			**16c**[d]	91 (dr=15:1)
4			**16b**[e]	91
5			**16c**[d]	85 (dr=20:1)
6			**16a**[a]	91

[a] Ref.125.
[b] Ref.126.
[c] Ref.120.
[d] Ref.124.
[e] Ref.123.

diastereoselective couplings with alkynyl zinc reagents,[123] allyl silanes,[121] and silyl enol ethers[121] (Eq. 7, b).



(7)

Very recent efforts have focused on the development of asymmetric catalysts for both carbamate and sulfamate cyclization reactions, and chiral Ru porphyrin **22**,[126] Rh dimer **23**,[127] and Mn salen complex **24**[128] have all been examined for these transformations (Fig. 5). The results obtained with these catalysts are typified by the reactions of substrate **25** shown in Table 6. In general, the Ru catalyst is the most selective, affording cyclized products in 70–86% ee, while the more readily accessible **24** provides moderate 23–71% ee for similar cyclizations. The Rh catalyst **23** gave poor results for sulfamate ester **25** (with a maximum of 30% ee); however, up to 66% ee was obtained with **23** using aliphatic sulfonamide-based substrates. In general, this problem is far from solved, and future work will aim to prepare more readily accessible catalysts that display increasing selectivity, higher reactivity, and greater substrate scope for these asymmetric transformations.

5.2. Intermolecular C–H amination

Intermolecular transition metal catalyzed C–H amination reactions are inherently more challenging, and they have been investigated far more extensively than their intramolecular analogues. A wide variety of catalysts have been developed for these transformations, including rhodium,[106–108,129,130] copper,[104,131–133] manganese,[100,103,109,110,134–136] and ruthenium[100–103,105,136–138] complexes (Fig. 6).

Despite significant work in this area, the scope of intermolecular C–H amination reactions generally remains limited to the functionalization of highly activated 2° benzylic or allylic C–H bonds to form

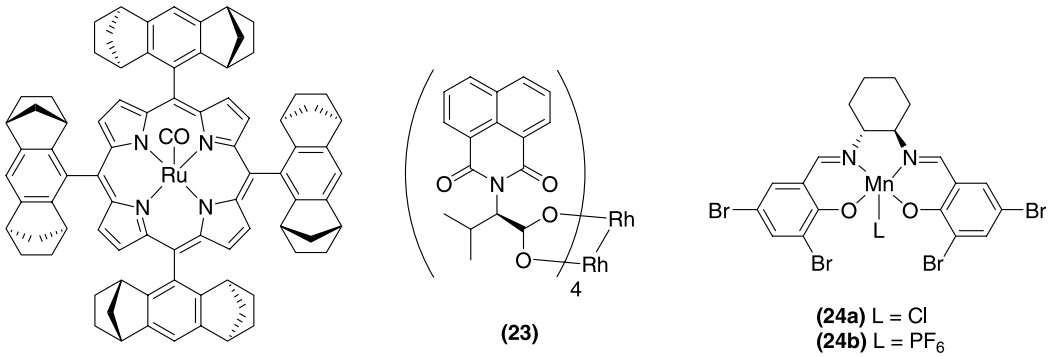
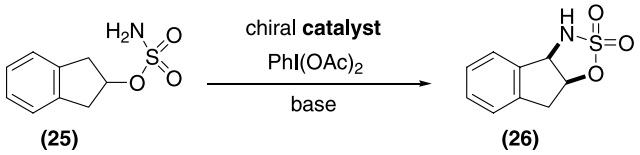


Figure 5. Chiral catalysts for intramolecular C–H amination.

Table 6. Asymmetric intramolecular C–H amination



Catalyst	Yield (%)	ee (%)
22[a]	53	81
23[b]	52	30
24a[c]	48	52

[a] Ref.126.
[b] Ref.127.
[c] Ref.128.

products such as those shown in Figure 7. In addition, the majority of current intermolecular amination reactions require large excesses of substrate (typically 5- to 5000-fold) relative to oxidant to achieve reasonable yields. These features clearly limit the broad utility of this methodology, and, as such, recent efforts in the area have focused on addressing these challenges.

An important recent advance was made by Che and co-workers, who reported that porphyrin catalyst **29** (with M=Mn and R=C_6F_5) is highly active for intermolecular alkane amination with PhI=NTs as a stoichiometric oxidant.[136] With this catalyst system, the amination of indan proceeds with TON's up to 2600; furthermore, a diverse set of activated substrates, including adamantane, tetrahydrofuran, *trans*-3-hexene, ethylbenzene and cyclohexene, are aminated efficiently without the requirement for an excess of organic substrate relative to oxidant.

Peréz and co-workers have developed a copper based catalyst **27** (Fig. 6) that has significantly expanded the substrate scope of C–H bond amination reactions. For example, **27** efficiently catalyzes the amination of 1° benzylic C–H bonds of toluene and mesitylene, unactivated 2° C–H bonds of cyclohexane,

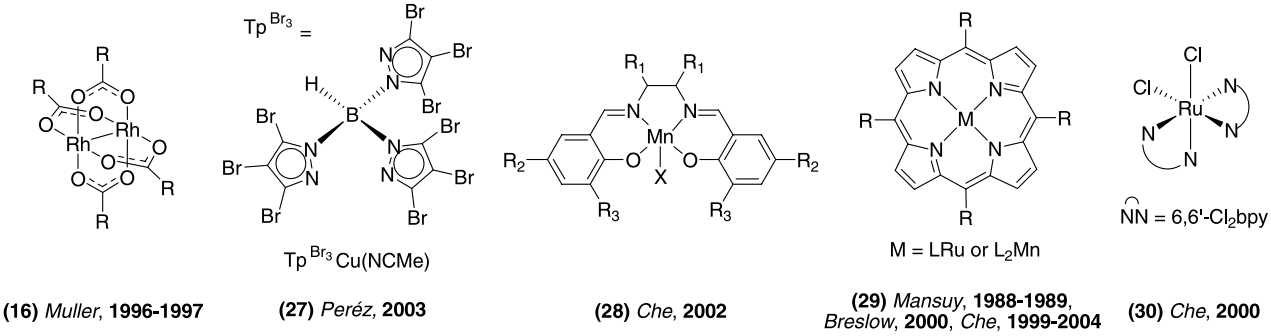


Figure 6. Catalysts for intermolecular C–H amination.

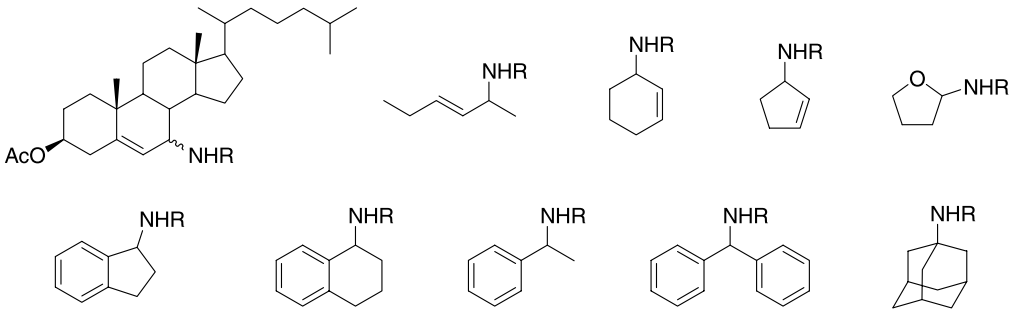


Figure 7. Typical products of intermolecular C–H amination (R=Ns or Ts).

and aromatic C–H bonds of benzene (Fig. 8).[132] The notable limitation of this system is that large excesses of substrate relative to stoichiometric oxidant (PhI=NTs) are required in order to achieve good yields.

Another class of substrates that has been recently explored for intermolecular C–H bond amination is aromatic heterocycles (Fig. 8). Che and co-workers have demonstrated that the amination of furan, pyrrole, and thiophene derivatives can occur in good yields at 40 °C with catalyst **29** (M=Ru-CO, R=*p*-$C_6H_4CH_3$, Fig. 6).[137] Again, however, a 10-fold excess of substrate relative to oxidant is required for optimal conversions. Notably, these transformations could proceed via either direct nitrene insertion into the activated C–H bond, or by initial aziridination followed by rearomatization, and further studies are required to distinguish these two mechanistic pathways.

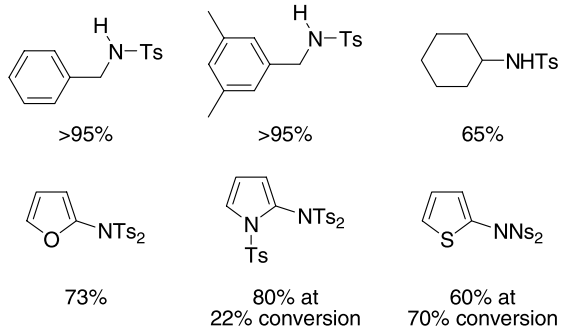
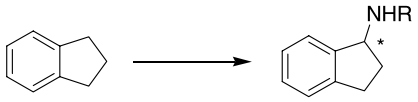


Figure 8. Expansion of substrate scope by Peréz and Che.

Very recent efforts by Du Bois and co-workers have made progress in addressing both the challenges of substrate scope and stoichiometry through the systematic design of a new Rh catalyst–$Rh_2(esp)_2$[139] (Fig. 9). The high stability of the catalyst incorporating the esp ligand (**31**) allows the intermolecular amination of *p*-methoxyethylbezene and cyclooctane with $H_2NSO_3CH_2CCl_3$/$PhI(OAc)_2$ to afford good yields (71 and 84% respectively) of **32** and **33** using ≤5-fold excess of substrate relative to oxidant.

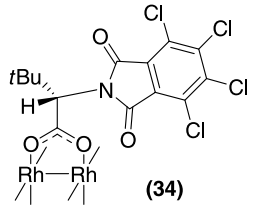
Significant efforts have also focused on the development of asymmetric catalysts for intermolecular C–H amination reactions, and Table 7 highlights the best results obtained

Table 7. Asymmetric intermolecular C–H amination



Entry	Catalyst	R	Yield (%)	ee (%)
1[a]	**22**	Ts	47	31 (*S*)
2[b]	**24b**	Ts	63	66 (*S*)
3[c]	**34**	Ns	82	70 (*R*)

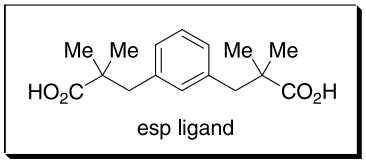
[a] Ref.103.
[b] Ref.134.
[c] Ref.130.



with catalysts **22**, **24b** (Fig. 5), and **34** in the amination of indan.[100,103,134] The chiral Rh dimer **34** is generally the best catalyst developed thus far for these transformations (providing 19–84% ee for a variety of substrates); however, further advancements will be necessary to render this methodology competitive with more mature asymmetric transformations.

5.3. Intramolecular C–H amination in natural product synthesis

Perhaps the greatest test of any synthetic methodology is its ability to be applied to the construction of highly complex molecules—in particular natural products. Although general methods for intramolecular C–H bond amination are relatively new, they have already found application in the preparation of a variety of natural product targets. The simplest example involves the synthesis of the glycon of L-vancosamine derivatives.[140] In the key transformation, carbamate **35** was converted to oxazolidinone **36** in 86% yield with $PhI(OAc)_2$ and 10% $Rh_2(OAc)_4$ (Eq. 8). This fragment can then be elaborated to many derivatives of vancosamine, which is a key component of the potent antibiotic vancomycin.



(31)

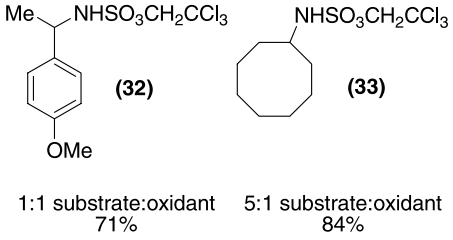
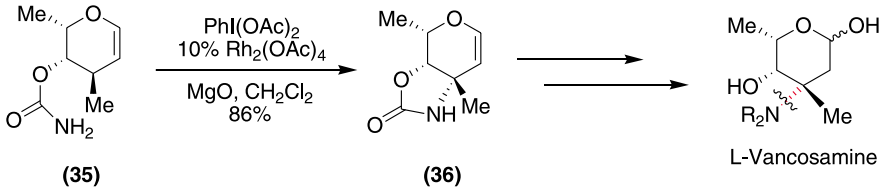


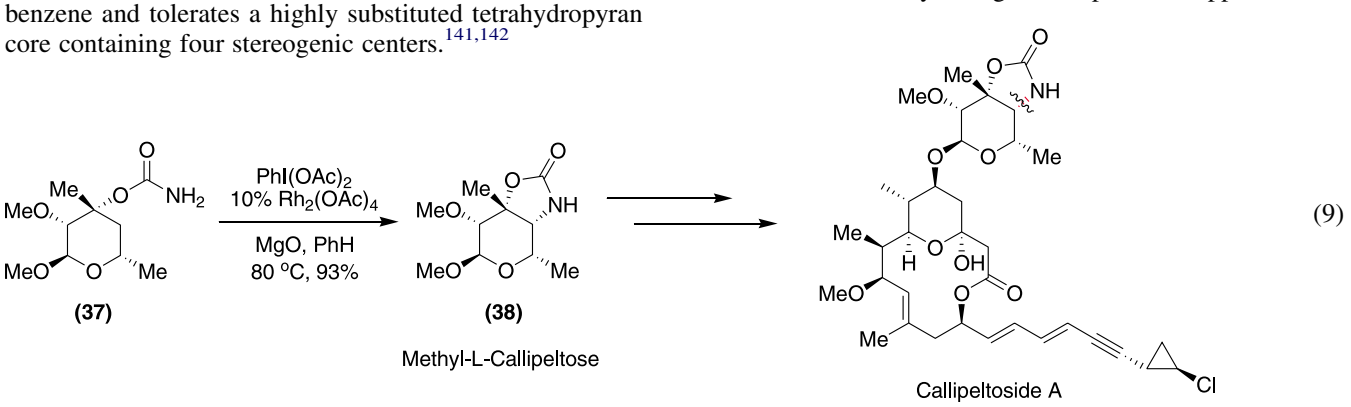
Figure 9. Expansion of substrate scope with $Rh_2(esp)_2$.



(35) (36)

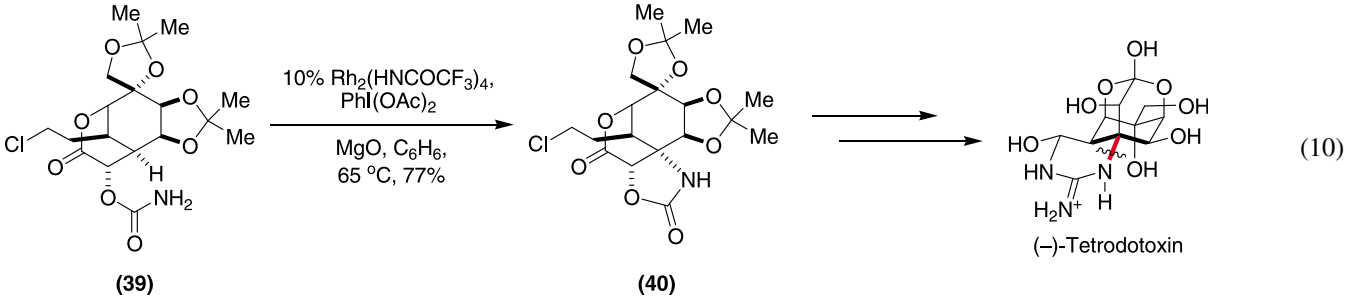
(8)

A carbamate C–H bond amination reaction has also been applied to the synthesis of methyl-L-callipeltose, a fragment of the antitumor natural product callipeltoside A. As summarized in Eq. 9, this transformation proceeds in good yield with $PhI(OAc)_2$ and 10% $Rh_2(OAc)_2$ in refluxing benzene and tolerates a highly substituted tetrahydropyran core containing four stereogenic centers.[141,142]



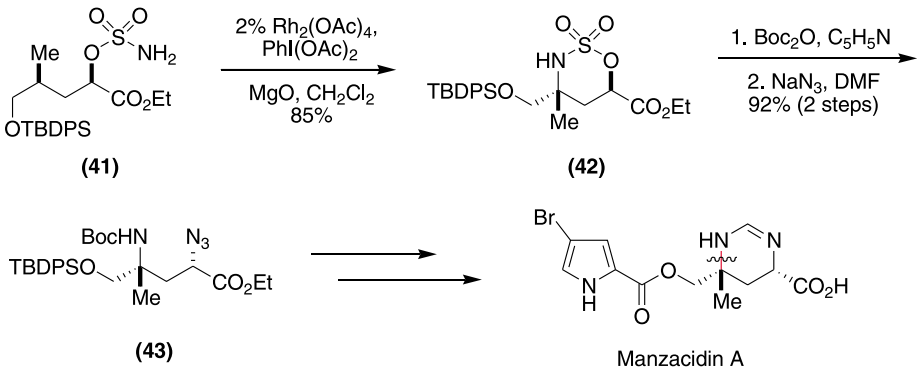
(9)

Intramolecular oxazolidinone formation was also utilized at a late stage in the synthesis of the guanidinium poison (−)-tetrodotoxin.[143] In the key step, Hinman and DuBois converted intermediate **39** to **40** in 77% yield using $PhI(OAc)_2$ and 10% $Rh_2(HNCOCF_3)_4$ in benzene (Eq. 10). This transformation is particularly remarkable because of the structural complexity of the substrate.



(10)

Finally, sulfamate esters were used for intramolecular amination in the synthesis of the bromopyrrole alkaloids manzacidins A and C.[144] Intermediate **41** was smoothly converted to **42** in 85% yield with $PhI(OAc)_2$ and only 2% $Rh_2(OAc)_4$ (Eq. 11), ultimately leading to manzacidin A. Manzacidin C was prepared in an identical manner from a different stereoisomer of the starting material. This is an elegant example of the versatility of oxathiazinane rings for elaboration to 1,3-difunctionalized products via a simple nucleophilic ring-opening event.

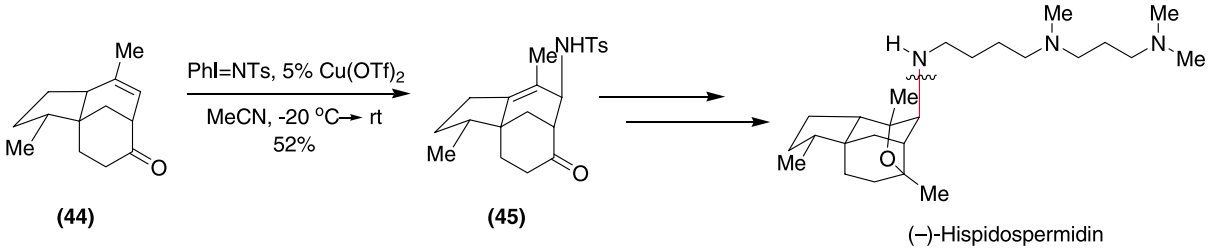


(11)

5.4. Intermolecular C–H amination in natural product synthesis

Due to the greater challenges inherent in intermolecular C–H amination, only a single example of its application in total synthesis has been reported: the construction of tetracyclic spermidine alkaloid hispidospermidin.[145] In what amounts to a formal 'ene' process, amination of intermediate **44** to produce **45** was accomplished in 52% yield using PhI=NTs and 5 mol% $Cu(OTf)_2$ in MeCN (Eq. 12). This is a remarkable example of allylic amination occurring without significant formation of aziridine byproduct. Additionally, this transformation involves a novel

double-bond migration that cleanly yields a single regioisomeric product.



(44) (45) (−)-Hispidospermidin (12)

In summary, catalytic C–H bond amination is a synthetically useful transformation that often proceeds with high levels of regio- and diastereoselectivity. As such, it has found application in the synthesis of a variety of different organic structures with increasing degrees of complexity. Future investigations should focus on expanding the substrate scope, especially of the intermolecular reactions, and developing more highly enantioselective catalysts for these transformations. The development of inner sphere catalysts for C–H bond amination represents another important future direction in this area, and a very recent report by Buchwald has demonstrated the potential viability of this approach.[99]

6. C–H bond halogenation

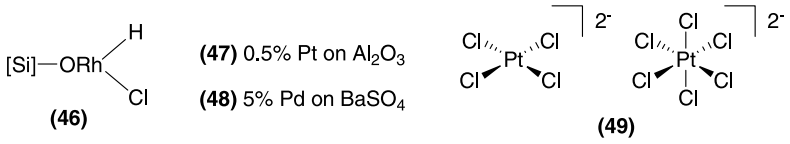
Halogenated hydrocarbons are incredibly versatile synthons for organic chemists. Classically, they have found use as substrates for nucleophilic substitution reactions,[146] benzyne formation,[147] and as precursors to a variety of main group organometallic reagents, including organolithium[148] and Grignard reagents.[149] Since the advent of transition metal cross coupling reactions, they have also become the substrates of choice for the formation of new carbon–carbon bonds.[150,151] Additionally, many natural products and pharmaceuticals contain halogen atoms in positions that are critical for their biological activity.

The construction of carbon–halogen (C–X) bonds from C–H bonds has been largely limited to classical organic reactions involving either electrophilic (X^+) or free radical ($X\cdot$) halogenating reagents.[20,21,23] Significant work has also aimed to develop transition metal catalysts that mimic the haloperoxidase enzymes;[152–156] however, the role of the metal in these systems is merely to generate X^+, which then acts as a classical electrophilic halogenating reagent. In contrast, metal-based catalyst systems that directly transform C–H to C–X bonds via inner-sphere mechanisms remain rare.

6.1. Chlorination of methane

Early studies of inner-sphere C–H bond halogenation focused on the reaction of methane with Cl_2.[157–159] A variety of heterogeneous and homogeneous complexes, including silica-supported Rh complexes,[159] Pt on Al_2O_3,[158] Pd on $BaSO_4$,[158] and aqueous mixtures of Na_2PtCl_4 and Na_2PtCl_6,[157] have been developed as catalysts for this transformation (Fig. 10).

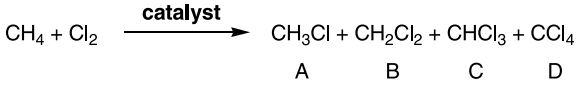
As summarized in Table 8, these reactions all proceed with high selectivity for the formation of monochlorinated CH_3Cl, and are proposed to proceed via metal-alkyl



Schwartz, **1984** *Olah*, **1985** *Horváth*, **1993**

Figure 10. Catalysts for the chlorination of methane.

Table 8. Transition metal catalyzed chlorination of methane



Entry	Catalyst	Conditions	Ratio A:B:C:D	Notes
1[a]	**46**	2% catalyst, 1:3.3 CH_4:Cl_2, 100 °C	92:8:trace:trace	13.7% conversion based on CH_4
2[b]	**47**	3:1 CH_4:Cl_2, 250 °C	99:1:0:0	36% conversion based on Cl_2
3[b]	**48**	2:1 CH_4:Cl_2, 200 °C	99:1:0:0	30% conversion based on Cl_2
4[c]	**49**	Pt^{IV}:Pt^{II}=7.5:1, w/Cl_2, 100 °C	Not reported, but A dominates	CH_3OH is major byproduct

[a] Ref.159.
[b] Ref.158.
[c] Ref.157.

intermediates. However, they remain limited by (i) moderate TON and/or high reaction temperatures, (ii) the requirement for corrosive Cl_2 (and in some cases super-stoichiometric Pt^{IV}) as the terminal oxidant, and (iii) limited applicability to the selective halogenation of more complex hydrocarbon substrates.[160,161]

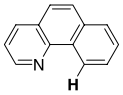
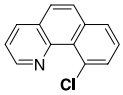
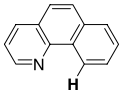
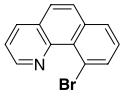
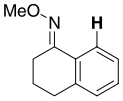
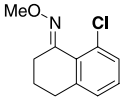
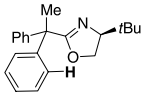
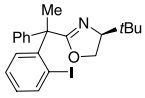
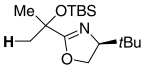
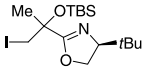
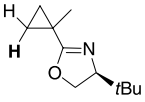
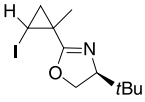
6.2. Selective halogenation of organic substrates

More recent work has revealed that highly regioselective palladium(II)-catalyzed C–H bond halogenation can be accomplished in complex organic substrates that contain appropriate chelate directing groups. For example, $Pd(OAc)_2$ serves as an efficient catalyst for the nitrogen-directed chlorination or bromination of benzo-[*h*]quinoline using *N*-chloro or *N*-bromosuccinimide as mild stoichiometric oxidants (Table 9, entries 1 and 2).[58a] These transformations proceed in excellent (>90%) yield with catalyst loadings as low as 1 mol% and show extremely high levels of regioselectivity for functionalization at C_{10}. Interestingly, directed Pd-catalyzed C–H bond halogenation proceeds rapidly and can effectively out-compete uncatalyzed reactions between the substrate and oxidant. For example, α-tetralone *O*-methyl oxime undergoes exclusive aromatic chlorination with *N*-chlorosuccinimide/catalytic $Pd(OAc)_2$ (Table 9, entry 3), while only benzylic oxidation is observed in the absence of palladium.[162] These reactions, like the related $Pd(OAc)_2$-catalyzed oxygenations, are also believed to proceed via a $Pd^{II/IV}$ mechanism, and the key product release step presumably involves C–X bond-forming reductive elimination from Pd^{IV} intermediates.[58c]

Palladium(II)-catalyzed directed C–H activation/halogenation reactions have also been expanded to the introduction of iodine substituents through the use of I_2 as a terminal oxidant in conjunction with $PhI(OAc)_2$ as an acetate source (which serves to regenerate the $Pd(OAc)_2$ catalyst after each turnover).[163] This system is effective for the regioselective oxazoline-directed iodination of both aromatic and aliphatic C–H bonds (Table 9, entries 4–6). The use of chiral oxazoline directing groups results in modest to excellent levels of diastereoselectivity in substrates containing diastereotopic phenyl groups, methyl groups, or C–H bonds (Table 9, entries 4, 5 and 6, respectively). Notably, the oxazoline auxiliary is readily removed by hydrolysis; therefore this transformation provides an unusual and potentially useful route to chiral carboxylic acid derivatives.

In general, transition metal catalyzed halogenation reactions are the least studied of all of the topics covered in this review. This leaves the door open for further advances in catalyst design, selectivity, functional group compatibility, and asymmetric transformations.

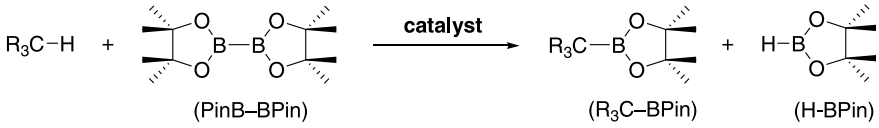
Table 9. Selective C–H activation/halogenation catalyzed by $Pd(OAc)_2$

Entry	Substrate	Product	Yield (%)
1[a,b]			95
2[a,b]			93
3[a,c]			86
4[d]			98 (dr=99:1)
5[d]			62 (dr=93:7)
6[d]			65 (dr=99:1)

[a] $Pd(OAc)_2$ (1%), 1.1 equiv *N*-halosuccinimide, MeCN, 100°.
[b] Ref.58a.
[c] Ref.162.

7. C–H bond borylation

Organoboron compounds are synthetically valuable intermediates that are readily transformed into alcohols and also find widespread application in cross-coupling reactions.[164,165] The direct transition metal catalyzed borylation of alkane or arene C–H bonds represents an attractive and atom economical approach to access these important compounds (Eq. 13). Experimental and computational studies have established that alkane/arene borylation is thermoneutral or thermodynamically downhill depending on the organic substrate, making this an ideal target for catalysis.[166,167]



(13)

A variety of transition metal catalysts have been developed for C–H activation/borylation (e.g., see **50**–**56** in Fig. 11), and these reactions generally proceed via inner-sphere mechanisms involving metal–aryl or metal–alkyl intermediates.[168–174] This section aims to summarize synthetically useful aspects of these reactions, including reactivity, regioselectivity, substrate scope, and functional group tolerance.

7.1. Aromatic C–H bond borylation

Iverson and Smith reported the first example of catalytic C–H activation/borylation using **50** as a catalyst for the borylation of benzene.[175] While this reaction was slow, required benzene as the solvent, and proceeded with only ~3 turnovers, it provided critical early precedent for the feasibility of this catalytic transformation. Based on prior work in C–H activation/silylation of arenes using similar

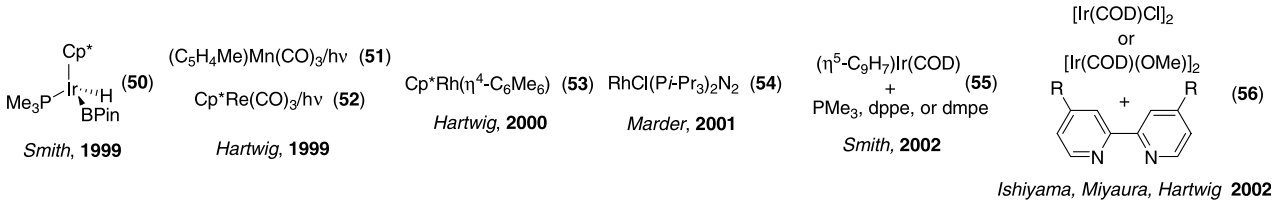
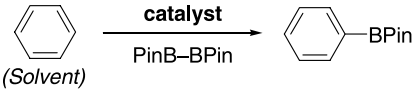


Figure 11. Precatalysts for C–H activation/borylation reactions.

catalysts,[176] Hartwig subsequently demonstrated that **51** and **53** are efficient catalysts for the photochemical (**51**)[177] and thermal (**53**)[178] borylation of benzene (Table 10). The activity of **53** (TON=328) was particularly remarkable at the time, as it was an order of magnitude greater than previously reported catalysts.[178] Later studies showed that catalysts **54**–**56** exhibit comparable (TON=222 for **54**) or significantly higher (TON=4500 for **55**; TON=8000 for **56**) activity for benzene borylation.[179–181]

Table 10. Catalytic borylation of benzene



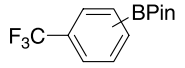
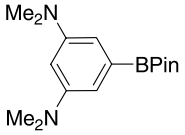
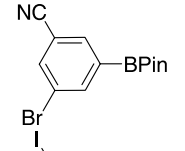
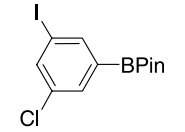
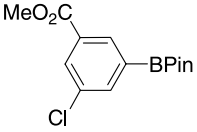
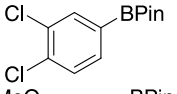
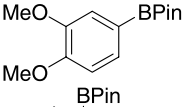
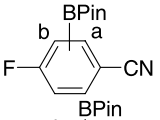
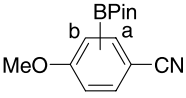
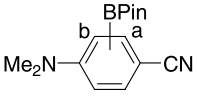
Catalyst	Conditions	TON
50[a]	150 °C, 120 h	3.1
51[b]	2 atm CO, 25 °C, 36 h	7.6
53[c]	150 °C, 45 h	328
54[d]	H–BPin, 140 °C, 104 h	222
55[e]	L=dmpe, 150 °C, 61 h	4500
56[f]	100 °C, 16 h	8000

[a] Ref.175.
[b] Ref.177.
[c] Ref.178.
[d] Ref.181.
[e] Ref.179.
[f] Ref.180.

More recent work has demonstrated the application of C–H activation/borylation to a wide variety of substituted aromatic substrates (Table 11).[179,182–185] In general, **53**, **55** and **56** are the most active, versatile, and general catalysts for these transformations, with overall activity following the trend **56**>**55**>**53**≫**50**. Remarkably, many reactions using catalyst **56** take place at room temperature![180,183,186] As a result of these highly active catalysts, most arene borylation reactions can now be carried out with only minimal (typically 1.1–4-fold) excess of arene substrate (Table 11, entries 2–10). This advance has dramatically expanded the synthetic utility of these transformations, and they can now be applied to valuable advanced intermediates.

As summarized in Table 11, C–H activation/borylation reactions catalyzed by **55** and **56** tolerate a wide variety of functionalities, including CN, CF_3, F, Cl, Br, I, OMe, NMe_2, and CO_2Me groups.[175,179,184,185] (Notably, **53** is somewhat less functional group tolerant and leads to partial reduction of nitriles and aryl halide derivatives.)[184] Catalyst **56** also generally shows low reactivity toward benzylic C–H bonds;[183,187] however, facile and selective benzylic C–H activation/borylation can be achieved using **54**[181] or Pd/C[187]

Table 11. Catalytic borylation of aromatic substrates

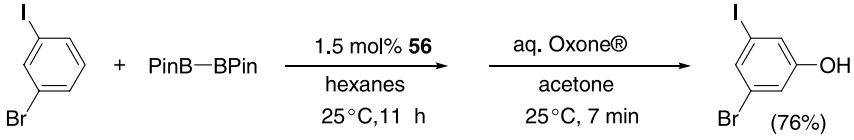
Entry	Product	Catalyst	Yield (%)
1		**53** **56**	84 (*m*:*p*=2:1)[a] 80 (*m*:*p*=2.3:1)[b]
2		**53**	69[c]
3		**56**	83[d]
4		**56**	82[d]
5		**55** **56**	95[e] 80[d]
6		**56**	82[d]
7		**55**	62[e]
8		**56**	71 (*a*:*b*=1:12)[f]
9		**56**	65 (*a*:*b*=2:1)[f]
10		**56**	58 (*a*:*b*=99:1)[f]

[a] Ref.185.
[b] Ref.180.
[c] Ref.184.
[d] Ref.183.
[e] Ref.179.
[f] Ref.182.

as catalysts. Although the origin of this selectivity is not well understood, these catalysts serve as useful complements to **56** in this context.

Arene borylation catalyzed by **53**, **55** and **56** proceeds with very high selectivity for functionalization of the least sterically hindered C–H bond of the substrate.[179,182–185] This remarkable selectivity (which is

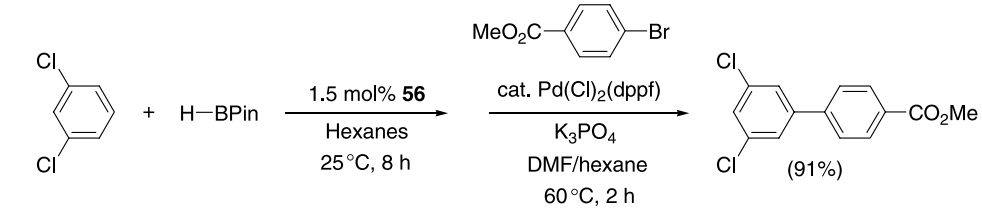
characteristic of inner-sphere catalysis) is typically independent of the electronic nature of the aromatic ring substituents, and often leads to substituted products that would not be accessible by either classical electrophilic aromatic substitution or directed *ortho*-lithiation reactions. For example, the borylation of 1,3 disubstituted substrates occurs exclusively at the sterically accessible *meta*-position regardless of the electronic nature of the substituents (Table 11, entries 2–5). High selectivity for functionalization at the 4-position is observed in diverse 1,2 disubstituted derivatives (entries 6 and 7). Furthermore, in 1,4 disubstituted systems containing a CN group, the regioselectivity of borylation



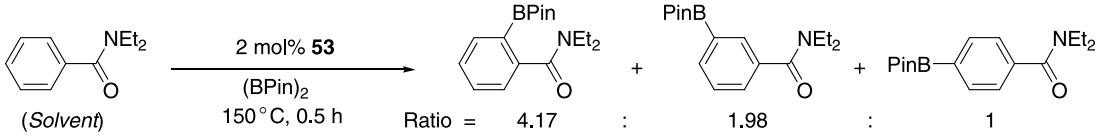
(15)

is exquisitely sensitive to the size of the second arene substituent. With small substituents such as F, substitution adjacent to the F is preferred (entry 8), while when the size increases to NMe_2 (entry 10), borylation occurs exclusively next to CN.[182]

In most mono-substituted arene substrates (Table 11, entry 1), a statistical (~2:1) mixture of *meta* and *para* substituted products is formed, and this ratio is largely independent of the transition metal catalyst.[180,185] When a good chelating group (e.g., an amide derivative) is placed on the arene ring, a significant amount of the *ortho*-borylated product is obtained (Eq. 14). This is believed to be due to competing coordination of the amide to the catalyst, resulting in ligand-directed *ortho*-functionalization.[185]



(16)



(14)

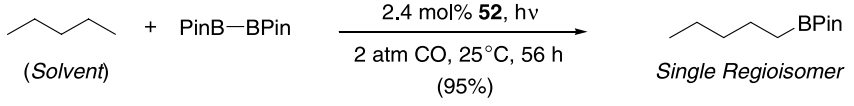
As summarized in Table 12, aromatic heterocycles are also excellent substrates for C–H activation/borylation catalyzed by **55** and **56**.[179,188–190] In general, high selectivity is observed for borylation at the 2-position of furans, thiophenes, pyrroles, and indoles (entries 1–3, 5, and 6). However, the regioselectivity of pyrrole or indole borylation can be shifted exclusively to the 3-position by protecting the nitrogen with a sterically bulky TIPS group (entry 4).[184,190] Again, this change in selectivity reflects a preference for reaction at the least sterically hindered C–H bonds.

Arylboronic esters are valuable precursors to phenol derivatives, and a convenient one pot synthesis of phenols via (i) catalytic arene C–H activation/borylation followed by (ii) oxidation with Oxone® has recently been reported (Eq. 15).[191] These reactions generally proceed in good to excellent yields, and a wide range of arene substituents (Cl, Br, F, NMe_2, CO_2Me, CH_3, CF_3) are tolerated without over-oxidation to quinones, *N*-oxides or benzylic oxidation products.

Several one-pot routes to biaryl compounds via catalytic C–H activation/borylation followed by Pd-catalyzed Suzuki–Miyaura cross-coupling have also been reported (Eq. 16),[179,186] and C–C coupled products are typically obtained in excellent (80–90%) yield over the two steps. Notably, the reaction shown in Eq. 16 offers the added advantages that C–H activation/borylation can be conducted at room temperature and that inexpensive and more readily available H–BPin rather than $(BPin)_2$ can be used as the boron source.

7.2. Alkane C–H bond borylation

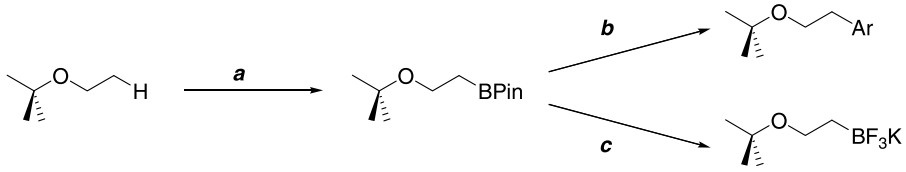
Chen and Hartwig reported the first example of catalytic alkane borylation using **52** as a catalyst for the borylation of *n*-pentane (Eq. 17).[177] This photochemical reaction proceeded at room temperature in neat *n*-pentane to afford 95% of the mono-borylated product. Importantly, functionalization occurs exclusively at the least sterically hindered terminal position. Control experiments (using an independently synthesized sample of the 2-borylated product) showed no isomerization under the catalytic conditions, indicating that the observed selectivity is kinetic in nature.



(17)

A key advance in this area involved the development of catalyst **53**, which promotes alkane borylation under convenient thermal conditions, and, to date, **53** remains the catalyst of choice for this transformation.[178] Simple hydrocarbons such as *n*-octane and methylcyclohexane undergo facile borylation catalyzed by **53**, and a variety of functional groups including ethers, acetals, 3° amines, and alkyl fluorides are well-tolerated.[178,192] As summarized in Figure 12, borylation proceeds with extremely high levels of regioselectively at the least sterically hindered 1° C–H bonds of most substrates. Notably, high selectivity (typically >20:1) for the 1° position is observed even in molecules containing relatively weak or acidic C–H bonds. Furthermore, comparable yields and selectivities are obtained when these reactions are conducted with alkane as the limiting reagent (albeit with approximately double catalyst loading). These features suggest that alkane borylation has significant potential for the selective functionalization of many more complex organic substrates.

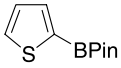
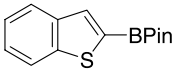
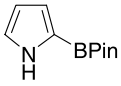
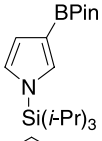
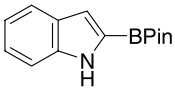
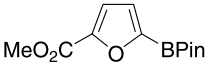
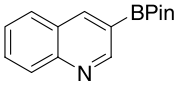
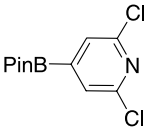
As shown in Eq. 18, Hartwig and co-workers also demonstrated the one pot conversion of alkanes to alcohols (using H_2O_2/KOH), alkyl arenes (using catalytic Pd^0 and an aryl bromide), and to alkyl trifluoroborates (using KHF_2).[192]



(18)

a. 5 mol% **53**, B_2Pin_2; ***b***. 10 mol% Pd_2dba_3, 10% $Fc(P\textit{i}\text{-}Pr_2)_2$, 2 equiv Ar–Br, 4 equiv CsOH; ***c***. KHF_2 in MeOH

Table 12. Catalytic borylation of heterocyclic substrates

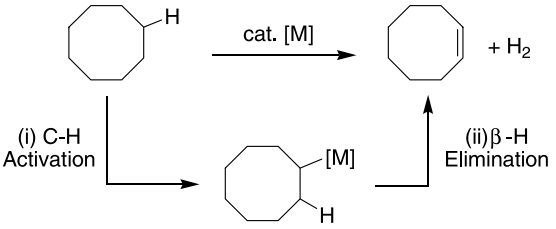
Entry	Product	Catalyst	Yield (%)
1		**56**	83[a]
2		**56**	89[a]
3		**56**	67[a]
4		**56**	79[a]
5		**56**	92[a]
6		**56**	80[b]
7		**56**	84[a]
8		**55**	69[c]

[a] Ref.190.
[b] Ref.189.
[c] Ref.179.

In conclusion, the past decade has seen impressive progress in the development of transition metal catalysts for the borylation of unactivated arene and alkane C–H bonds. Future investigations in this area will likely focus on further explorations of substrate scope and, in particular, the application of this methodology to complex biologically active target structures.

8. C–H bond dehydrogenation

The dehydrogenation of saturated carbon–hydrogen bonds (Eq. 19) represents an attractive approach to oxidatively transform alkanes into valuable alkene functionality. Unlike the other transformations discussed in this review, dehydrogenation involves a net removal of two C–H bonds rather than replacement of a C–H bond with a C–X bond. Typically, inner-sphere catalysts are used to effect this transformation via a general mechanism involving (i) C–H activation to generate a metal alkyl intermediate followed by (ii) β-hydride elimination to afford the alkene product (Eq. 19).[193]



(19)

A variety of Rh,[194–209] Ir,[194,195,210–226] Re,[220,227] and Pt[228–231] catalyst systems have been developed for this reaction (Fig. 13), with the most widely used being Rh complex **60**[199,200,203–209] and Ir complex **62**.[195,211,213–219]

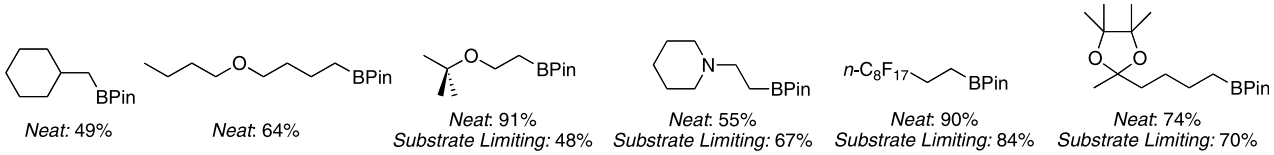


Figure 12. Scope of products obtained from alkane borylations catalyzed by **53**.

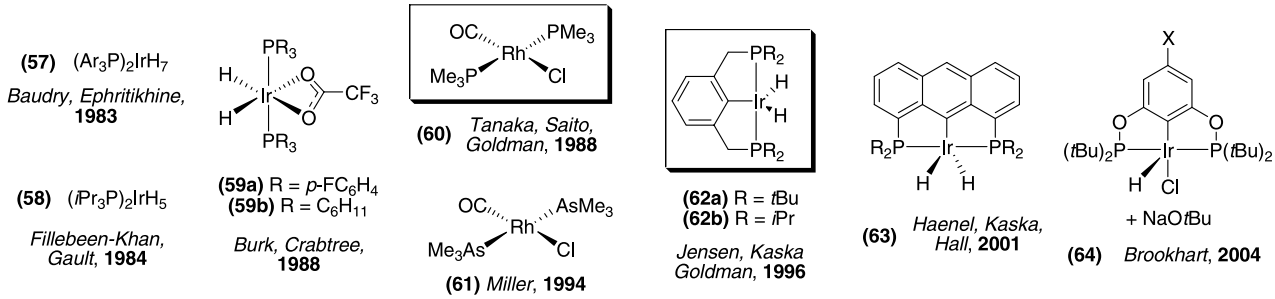
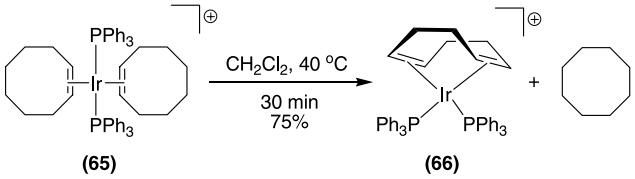


Figure 13. Commonly used organometallic catalysts for alkane dehydrogenation.

While catalysts can lower the kinetic barrier to the two C–H bond cleavage events, they cannot alter the thermodynamics of these transformations. Dehydrogenation reactions are typically endothermic (e.g., $\Delta H = +33$ kcal/mol for the conversion of ethane to ethylene and hydrogen), but are entropically favorable, as they release 1 equiv of H_2 gas.[232] High reaction temperatures (>500 °C) can be utilized to render dehydrogenative processes thermodynamically downhill;[232] however, such extreme conditions are generally not amenable to selective functionalization of more complex organic molecules. As such, recent work has focused on strategies to render these reactions thermodynamically favorable at lower temperatures. These include: (i) coupling the desired dehydrogenation reaction to the hydrogenation of a sacrificial olefin, (ii) utilizing photochemical rather than thermal energy to supply the necessary driving force, or (iii) removal of H_2 from the reaction mixture (via reflux or an inert gas purge) to drive the equilibrium to the right.

8.1. Transfer dehydrogenation

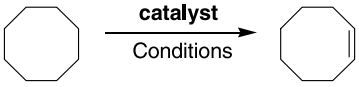
The most widely used approach to low temperature catalytic alkane dehydrogenation involves net hydrogen transfer from an alkane to a reactive sacrificial olefin (SO). This transformation was initially discovered by Crabtree, who reported that thermolysis of Ir complex **65** leads to clean stoichiometric transfer dehydrogenation to afford Ir cyclooctadiene product **66** along with free cyclooctane (Eq. 20).[233]



(65) (66) (20)

Subsequent to this initial discovery, a wide variety of catalysts, including **57**–**64** (Fig. 13), have been developed for transfer dehydrogenation processes, typically in conjunction with *tert*-butylethylene (tbe), norbornene, cyclohexene, or ethylene as sacrificial olefins. The conversion of cyclooctane to cyclooctene is commonly used as a test reaction because of the unusually low enthalpy of dehydrogenation of this reaction (23.3 kcal/mol, nearly 5 kcal/mol lower than cyclohexane).[204] The results of cyclooctane transfer dehydrogenation with a variety of different catalysts are summarized in Table 13, entries 1–5. In general, Rh-based catalysts are more efficient than their Ir counterparts, although iridium complexes containing terdentate P–C–P phosphine or phosphinite ligands have proven particularly active and robust. Interestingly, in some cases it was found that conducting the reaction under an atmosphere of H_2 actually promoted the reaction (Table 13, entries 2 and 5).[194,197,199,200]

Table 13. Catalytic dehydrogenation of cyclooctane



Entry	Catalyst	TON	Conditions
1[a]	**58**	70	150 °C, w/tbe, 5 days
2[b]	**60**	106	60 °C, w/cyclohexene, 1000 psi H_2, 100 min
3[c]	**62a**	>1000	150 °C, w/tbe added incrementally
4[d]	**64**	806–2210	200 °C, w/tbe, 8 min–2 weeks
5[e]	**61**	2460	100 °C, w/ethylene, 500 psi H_2, 4 h
6[f]	**60**	667	96 °C, *hν*, 6 h
7[g]	**60**	930	rt, *hν*, 68.5 h
8[h]	**60**	up to 5000	50 °C, *hν*, time not specified

[a] Ref.226.
[b] Ref.200.
[c] Ref.195.
[d] Ref.210.
[e] Ref.197.
[f] Ref.206.
[g] Ref.209.
[h] Ref.204.

8.2. 'Acceptorless' dehydrogenation

The synthetic utility of transfer dehydrogenation is limited by the requirement for a sacrificial olefin; as such, significant efforts have aimed to develop alternative driving forces for these transformations. Early work revealed that the dehydrogenation of cyclooctane catalyzed by **59b** can take place in the absence of an H_2 acceptor when conducted under photochemical conditions.[222] The efficacy of this process is attributed to the ability of photochemical energy to provide a thermodynamic driving force for these reactions.[222] These photochemical processes can be extremely efficient; for example, the photochemical dehydrogenation of cyclooctane with **60** proceeds with up to 5000 turnovers (Table 13, entry 8).[204]

Pioneering work by Fujii and Saito revealed that derivatives of **60** with varying phosphine ligands catalyze the

acceptorless dehydrogenation of cyclooctane under thermal conditions when the H_2 by-product is removed under reflux.[202] More recently, similar H_2-removal procedures have been successfully developed for the dehydrogenation of cycloalkanes with catalysts **59**, **62**, and others[198,211,214,219,220] with TON up to 987 for cyclodecane.[215] Importantly, these transformations proceed at comparable temperatures to the transfer dehydrogenation reactions described above (~150 °C).

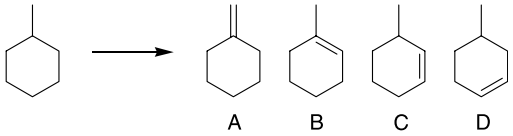
8.3. Substrate scope and selectivity

Because cyclooctane and other cyclic alkanes are symmetrical substrates, they yield no information about the regioselectivity of the dehydrogenation process. To address this, the dehydrogenation of methylcyclohexane[214,217,221,224,227] (Table 14) and *n*-hexane[203,206,208,209,221] (Table 15) have been studied.

Although the selectivity is somewhat catalyst dependent, the results in Tables 14 and 15 illustrate the general trend—under irreversible photochemical conditions at low conversions (kinetic control), these transformations proceed with modest selectivity for the functionalization of 1° C–H bonds to afford terminal olefins. In the case of catalyst **60**, this selectivity is further enhanced by addition of excess phosphine ligand (but at the expense of catalyst activity) (Table 15, entries 3–5). At longer reaction times or higher temperatures, however, equilibration to thermodynamically favored internal olefins is observed, presumably due to isomerization reactions unrelated to the inherent selectivity of the C–H activation event.

Dehydrogenations of isopropylcyclohexane,[199,204] ethylcyclohexane,[218] decalin,[214,217] and other *n*-alkanes[205,216,221] have also been examined for selectivity, producing similar

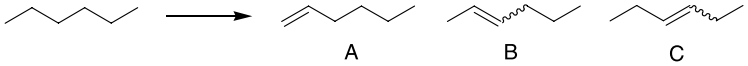
Table 14. Selectivity of dehydrogenation of methylcyclohexane



Entry	Catalyst	Cond	Ratio A:B:C:D (%)	TON
1[a]	**62b**	100 °C, 5 min	71:6:9:15	2.2
2[a]	**62b**	100 °C, 1 h	55:15:12:18	3.6
3[a]	**62b**	150 °C, 65 h	1:62:13:24	10
4[b]	**59a**	Δ	10:58:14:18	4.5
5[b]	**59a**	*hν*	39:31:12:18	7.1

[a] Ref.224.
[b] Ref.221.

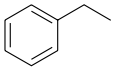
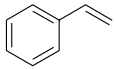
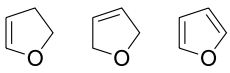
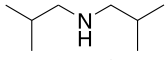
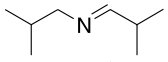
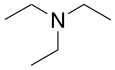
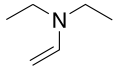
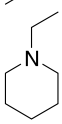
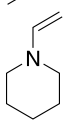
Table 15. Selectivity of dehydrogenation of *n*-hexane



Entry	Catalyst	Cond	Ratio A:B:C (%)	TON
1[a]	**59a**	Δ	4:74:22	5.1
2[a]	**59a**	*hν*	24:61:15	4.9
3[b]	**60**	*hν*, PMe_3:Rh=2:1	7:77:15	5.4
4[b]	**60**	*hν*, PMe_3:Rh=5:1	70:24:6	4.0
5[b]	**60**	*hν*, PMe_3:Rh=10:1	86:12:3	0.6

[a] Ref.221.
[b] Ref.208.

Table 16. Selected substrates for dehydrogenation reactions

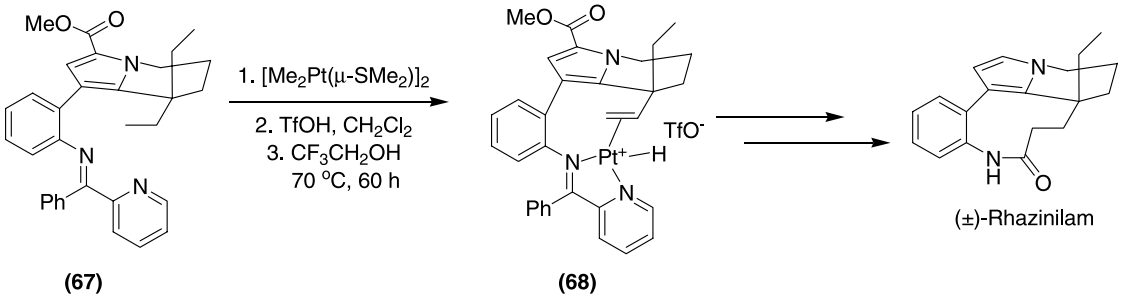
Entry	Substrate	Product(s)	Catalyst(s)
1			**62a**[a,b]
2			**60**[c,d] **62a**[a,b]
3			**62a**[e]
4			**62a**[f]
5			**62a**[f]

[a] Ref.214.
[b] Ref.218.
[c] Ref.199.
[d] Ref.200.
[e] Ref.234.
[f] Ref.235.

product mixtures. Also, it has been shown that cyclohexane can be dehydrogenated either to cyclohexene or benzene, depending on reaction conditions.[223,225] These dehydrogenation reactions also show some functional group tolerance; for example, tetrahydrofuran has been successfully dehydrogenated to give mixtures of dihydrofurans and furan (Table 16, entry 2),[199,200,214,218] and 2° and 3° amine substrates yield either imine[234] or enamine[235] products, respectively (Table 16, entries 3–5).

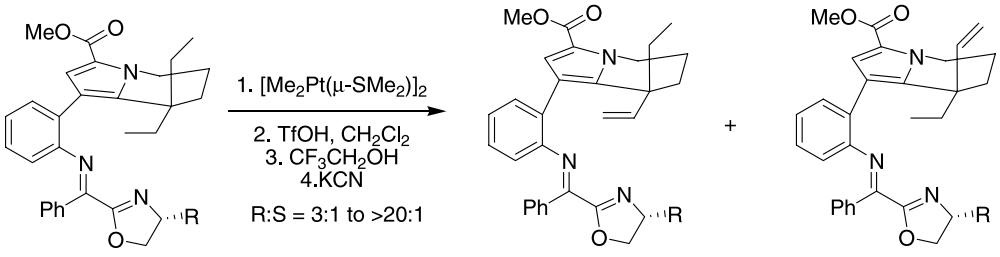
8.4. Application in natural product synthesis

The potential utility of efficient and selective alkane dehydrogenation reactions is illustrated in Sames' elegant construction of the antimitotic natural product rhazinilam.[236] The key transformation in this total synthesis involved imine/pyridine-directed dehydrogenation of an ethyl group of intermediate **67** at Pt^{II} to afford **68** in 79% yield over three steps (Eq. 21). This Pt product was then readily transformed into the natural product in eight straightforward steps.



(67) (68) (21)

Importantly, this route was also amenable to the asymmetric total synthesis of rhazinilam.[237] Substitution of the imine in **67** with a chiral oxazoline auxiliary led to stereoselective C–H activation/dehydrogenation, and diastereomeric ratios of up to 20:1 were obtained when R was large (e.g., *t*-Bu) and when the reaction temperature was lowered to 60 °C (Eq. 22).



(69) (R)-(70) (S)-(70) (22)

This work clearly demonstrates the potential of selective catalytic dehydrogenation, yet its requirement for stoichiometric Pt highlights the need for further advancements in catalyst reactivity, selectivity, and functional group tolerance.

In conclusion, alkane dehydrogenation represents a synthetically powerful approach to the oxidative functionalization of alkanes under mild conditions. In order to fully exploit this transformation, future work will require the development of catalysts that operate with high levels of regioselectivity in the context of more complex organic molecules. Additionally, new approaches to control competing olefin isomerization reactions will also be required to selectively isolate valuable terminal olefinic products.

9. Future challenges

While significant progress has been made in the development of efficient and highly selective transition metal catalysts for C–H bond oxidation, this field remains largely in its infancy, and a wide variety of exciting challenges remain. Future work will strive to develop more highly active transition metal catalysts that operate efficiently at milder temperatures and lower catalyst loadings. Such catalysts will likely find increased application in the chemical and pharmaceutical industries and should lead to enhanced kinetic control over the regio- and stereoselectivity of C–H bond oxidation. The development of catalysts that promote the selective intermolecular oxidation of unactivated C–H bonds without the requirement for activating or directing groups also remains an important ongoing goal. The borylation chemistry detailed in Section 7 represents an elegant example of the potential attainability and synthetic utility of such transformations. The development of new methods for the oxidative transformation of C–H bonds into other important functional groups, including carbon–fluorine, carbon–sulfur, and carbon–phosphorus bonds, remains an important frontier in this field. Finally, these new methods and catalysts will increasingly find application in the construction and functionalization of complex chemical systems and biologically active molecules.

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Biographical sketch

Allison R. Dick was born in Ames, Iowa, and received her BS in chemistry from Wheaton College (IL) in 2002, where she also minored in music. During that time, she completed an NSF-sponsored REU program at University of Pittsburgh in the laboratory of Professor David Waldeck. She began her graduate career at University of Michigan in August 2002, and is currently a fourth year graduate student working with Professor Melanie Sanford. Her research has focused on synthetic and mechanistic studies of palladium-catalyzed C–H bond oxidation reactions. Allison was the recipient of an Eli Lilly Graduate Fellowship in Organic Chemistry.

Melanie S. Sanford was born in New Bedford, MA and grew up in Providence, RI. She received her BS and MS degrees in chemistry at Yale University in 1996 where she carried out undergraduate research under the direction of Professor Robert Crabtree. She earned her PhD from California Institute of Technology in 2001, where she studied the mechanism of ruthenium-catalyzed olefin metathesis reactions under the direction of Professor Robert Grubbs. After 2 years as a National Institutes of Health post-doctoral fellow in the laboratories of Professor John Groves, she joined the faculty at the University of Michigan where she is currently an assistant professor of chemistry. Professor Sanford's research interests encompass the development and mechanistic study of new transition metal catalyzed reactions for applications in organic synthesis. She has been the recipient of a Camille and Henry Dreyfus New Faculty Award and an Arnold and Mabel Beckman Young Investigator Award as well as young investigator awards from Boehringer Ingelheim, Amgen, and Eli Lilly.