SOS Science of Synthesis

Catalytic Transformations via C—H Activation 2

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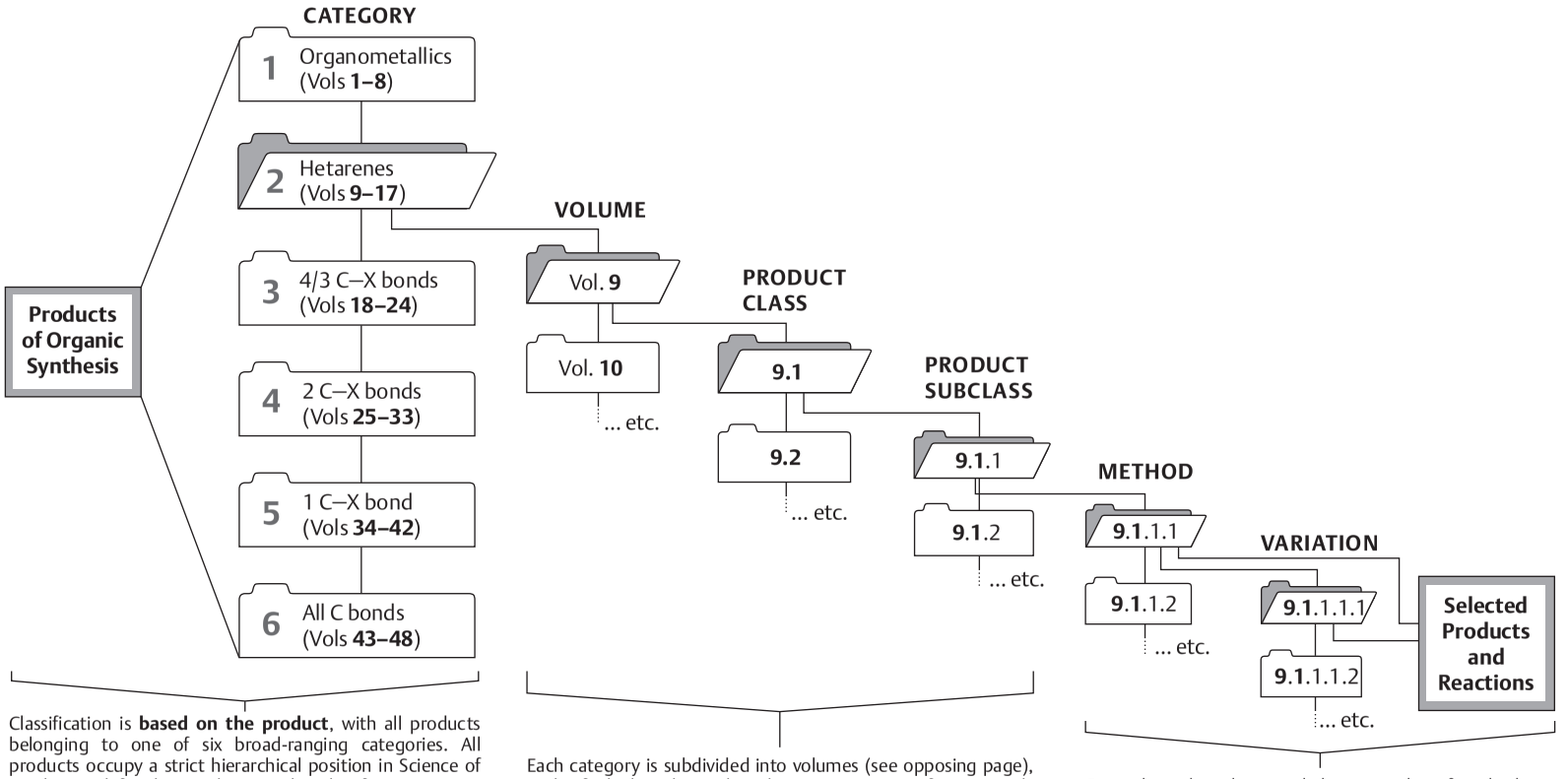

Classification is **based on the product**, with all products belonging to one of six broad-ranging categories. All products occupy a strict hierarchical position in Science of Synthesis, defined according to the classification principles*. Products in Categories 3–6 are organized according to oxidation state, with products containing the greatest number of carbon–heteroatom (C—X) or C—C π-bonds to a single carbon occupying the highest positions (e.g., carboxylates, enolates, and alcoholates are covered in Categories 3, 4, and 5, respectively).

Each category is subdivided into volumes (see opposing page), each of which is devoted to discrete groupings of compounds called **product classes** (e.g., "Thiophenes" is Product Class 10 of Volume 9). Product classes may be further subdivided into **product subclasses**, (e.g., "Thiophene 1,1-Dioxides" is Product Subclass 3 of Product Class 10 of Volume 9). Consequently, the relationship between heading name and heading number varies below product class level within individual volumes.

For each product class or subclass, a number of methods are described for synthesizing the general product type. Often there are variations on a method given. Both methods and variations contain experimental procedures with relevant background information and literature references. **Selected products and reactions** display the scope and limitations of the methods.

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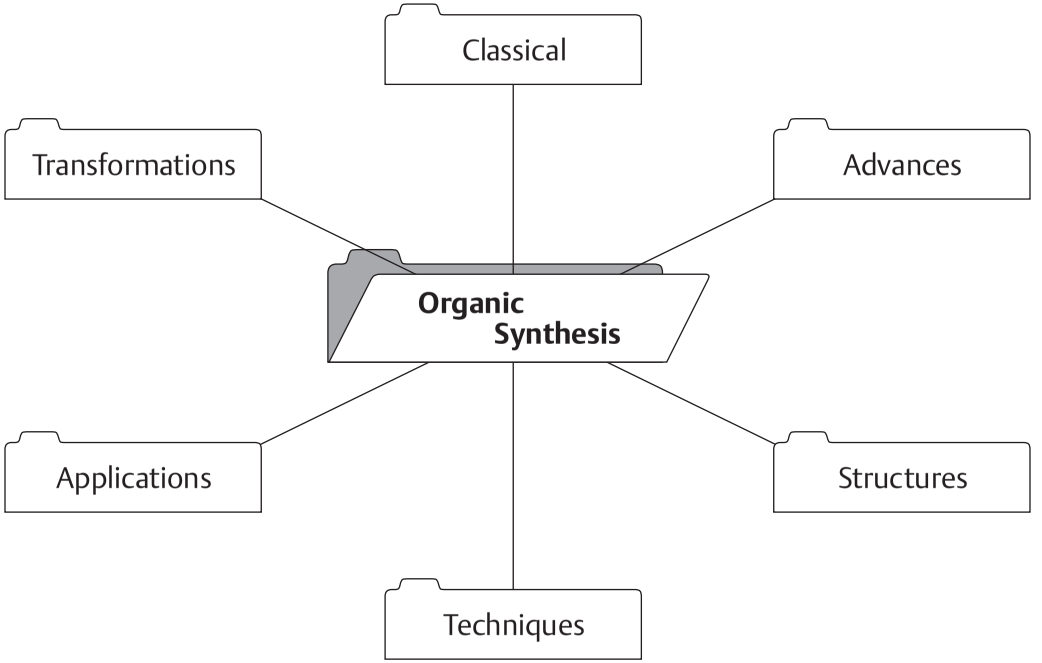
The **Science of Synthesis Reference Library** comprises volumes covering special topics of organic chemistry in a modular fashion, with six main classifications: (1) Classical, (2) Advances, (3) Transformations, (4) Applications, (5) Structures, and (6) Techniques. Volumes in the **Science of Synthesis Reference Library** focus on subjects of particular current interest with content that is evaluated by experts in their field. **Science of Synthesis**, including the **Knowledge Updates** and the **Reference Library**, is the complete information source for the modern synthetic chemist.



Science of Synthesis

Science of Synthesis is the authoritative and comprehensive reference work for the entire field of organic and organometallic synthesis.

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- Methods critically evaluated by leading scientists
- Background information and detailed experimental procedures
- Schemes and tables which illustrate the reaction scope

Science of Synthesis

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Preface

As the pace and breadth of research intensifies, organic synthesis is playing an increasingly central role in the discovery process within all imaginable areas of science: from pharmaceuticals, agrochemicals, and materials science to areas of biology and physics, the most impactful investigations are becoming more and more molecular. As an enabling science, synthetic organic chemistry is uniquely poised to provide access to compounds with exciting and valuable new properties. Organic molecules of extreme complexity can, given expert knowledge, be prepared with exquisite efficiency and selectivity, allowing virtually any phenomenon to be probed at levels never before imagined. With ready access to materials of remarkable structural diversity, critical studies can be conducted that reveal the intimate workings of chemical, biological, or physical processes with stunning detail.

The sheer variety of chemical structural space required for these investigations and the design elements necessary to assemble molecular targets of increasing intricacy place extraordinary demands on the individual synthetic methods used. They must be robust and provide reliably high yields on both small and large scales, have broad applicability, and exhibit high selectivity. Increasingly, synthetic approaches to organic molecules must take into account environmental sustainability. Thus, atom economy and the overall environmental impact of the transformations are taking on increased importance.

The need to provide a dependable source of information on evaluated synthetic methods in organic chemistry embracing these characteristics was first acknowledged over 100 years ago, when the highly regarded reference source **Houben–Weyl Methoden der Organischen Chemie** was first introduced. Recognizing the necessity to provide a modernized, comprehensive, and critical assessment of synthetic organic chemistry, in 2000 Thieme launched **Science of Synthesis, Houben–Weyl Methods of Molecular Transformations**. This effort, assembled by almost 1000 leading experts from both industry and academia, provides a balanced and critical analysis of the entire literature from the early 1800s until the year of publication. The accompanying online version of **Science of Synthesis** provides text, structure, substructure, and reaction searching capabilities by a powerful, yet easy-to-use, intuitive interface.

From 2010 onward, **Science of Synthesis** is being updated quarterly with high-quality content via **Science of Synthesis Knowledge Updates**. The goal of the **Science of Synthesis Knowledge Updates** is to provide a continuous review of the field of synthetic organic chemistry, with an eye toward evaluating and analyzing significant new developments in synthetic methods. A list of stringent criteria for inclusion of each synthetic transformation ensures that only the best and most reliable synthetic methods are incorporated. These efforts guarantee that **Science of Synthesis** will continue to be the most up-to-date electronic database available for the documentation of validated synthetic methods.

Also from 2010, **Science of Synthesis** includes the **Science of Synthesis Reference Library**, comprising volumes covering special topics of organic chemistry in a modular fashion, with six main classifications: (1) Classical, (2) Advances, (3) Transformations, (4) Applications, (5) Structures, and (6) Techniques. Titles will include *Stereoselective Synthesis*, *Water in Organic Synthesis*, and *Asymmetric Organocatalysis*, among others. With expert-evaluated content focusing on subjects of particular current interest, the **Science of Synthesis Reference Library** complements the **Science of Synthesis Knowledge Updates**, to make **Science of Synthesis** the complete information source for the modern synthetic chemist.

The overarching goal of the **Science of Synthesis** Editorial Board is to make the suite of **Science of Synthesis** resources the first and foremost focal point for critically evaluated information on chemical transformations for those individuals involved in the design and construction of organic molecules.

Throughout the years, the chemical community has benefited tremendously from the outstanding contribution of hundreds of highly dedicated expert authors who have devoted their energies and intellectual capital to these projects. We thank all of these individuals for the heroic efforts they have made throughout the entire publication process to make **Science of Synthesis** a reference work of the highest integrity and quality.

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Cross Coupling and Heck-Type Reactions (3 Vols.)
Water in Organic Synthesis
Asymmetric Organocatalysis (2 Vols.)
Stereoselective Synthesis (3 Vols.)

Abstracts

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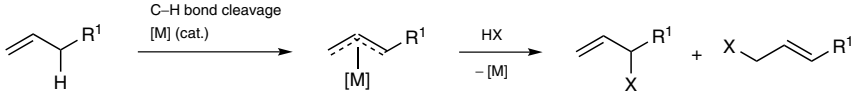
2.1 C—C and C—X Bond Formation by Allylic C—H Activation

G. Liu and P. Chen

This chapter documents recent studies into allylic functionalization via C—H activation processes catalyzed by metals such as palladium, rhodium, ruthenium, copper, and iron. The focus is on the formation of C—C, C—N, and C—O bonds reported in the last two decades, but more recent developments involving the formation of other C—X bonds, such as C—F and C—Si are also highlighted.



[M] = Pd, Rh, Ru, Cu, Fe, etc.; X = C, N, O, Si, F, etc.

Keywords: allylic C—H activation · alkenes · palladium · rhodium · ruthenium · copper · iron · allylic amines · allylic acetates

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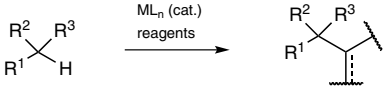
2.2 C—C Bond Formation by Alkyl C—H Activation

O. Baudoin

In comparison to the wealth of methods recently developed for the catalytic functionalization of the C(sp^2)—H bonds of arenes and hetarenes, relatively little work has focused on the functionalization of the unactivated C(sp^3)—H bonds of alkyl fragments. This chapter highlights selected examples of the fast-growing literature on the catalytic functionalization of unactivated C(sp^3)—H bonds through organometallic C—H activation, with an emphasis on the most synthetically useful methods. It covers heteroatom-directed C(sp^3)—H activation with regard to cross coupling with alkenes, alkynes, and carbon monoxide, organoboron reagents, diaryliodonium salts, and organic halides. Also included is C(sp^3)—H activation/intramolecular C—C coupling induced by oxidative addition and nondirected intermolecular C(sp^3)—H arylation.



Keywords: C(sp^3)—H bond activation · carbon—carbon coupling · transition metals · palladium catalysis · ruthenium catalysis · alkylation

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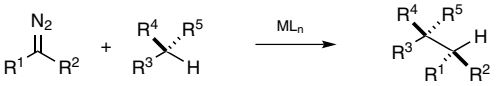
2.3 C—C Bond Formation Using Carbenes

X. Cui and X. P. Zhang

Transition-metal-catalyzed carbene C—H insertion has been developed as one of the most direct and effective methods for the construction of C—C bonds from C—H bonds. During the past two decades, a number of transition-metal-based catalytic systems have been established for asymmetric C—H functionalization via carbene insertion. Synthetically use-

ful systems have been developed to functionalize C—H bonds in both intermolecular and intramolecular fashions. In this chapter, highly selective and practical catalytic systems for stereoselective C—H functionalization via catalytic carbene transfer are summarized. Literature reports are classified and discussed according to the type of C—H bond. This review focuses mainly on the issue of stereoselectivity, particularly on enantioselectivity.



Keywords: asymmetric synthesis · C—H functionalization · transition-metal catalysis · diazo reagents · metal carbenes · dirhodium(II) complexes

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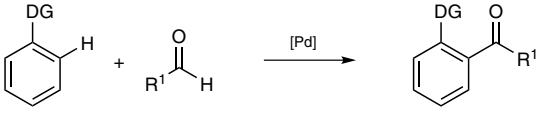
2.4 C—C Bond Formation Using Radicals

W.-W. Chan and W.-Y. Yu

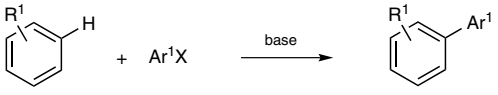
Direct C—H carbo-functionalization of (hetero)aromatic rings, as an atom-efficient route for regioselective C—C bond formation, is receiving current attention. In this review, radical coupling of unfunctionalized (het)arenes for C—C bond formation is described. Recent progress on the palladium-catalyzed regioselective C—H acylation of arenes with acyl radicals, as well as the transition-metal-free C—H arylation using aryl radicals, are presented. Some remarkable advances in the Minisci-type radical C—H alkylation of heterocycles are also discussed.

palladium-catalyzed radical acylation



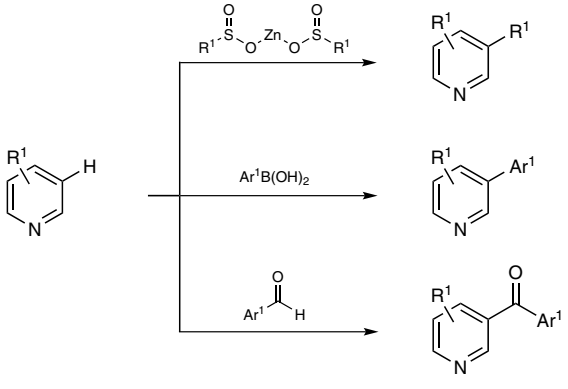
DG = oxime, amide, amine, azo; R^1 = aryl, alkyl, hetaryl

metal-free radical arylation



X = Br, I

Minisci-type radical coupling



Keywords: C—H functionalization · organocatalysis · palladium · cross coupling · radicals · heterocycles

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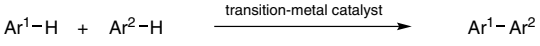
2.5 C—C Bond Formation by Double C—H Activation

J.-B. Xia and S.-L. You

This chapter focuses on transition-metal-catalyzed aryl—aryl bond-forming reactions via double C—H activation. Biaryl scaffolds have received much attention as a privileged structure broadly found in biologically active natural products, pharmaceuticals, agrochemicals, and functional molecules in material sciences, etc. Transition-metal-catalyzed cross-coupling reactions are the most general and efficient methods to synthesize biaryls, but both coupling partners need to be preactivated in transition-metal-catalyzed cross-coupling reactions when compared with simple arenes. Over the past decade, significant advances have been made in transition-metal-catalyzed biaryl synthesis using simple arenes as substrates via C—H activation. This chapter summarizes representative examples of transition-metal-catalyzed biaryl synthesis using two simple arenes as substrates via double C—H activation.



Keywords: transition-metal catalysis · double C—H activation · biaryl synthesis · directing groups

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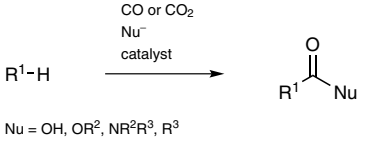
2.6 C—C Bond Formation by C—H Carboxylation or Carbonylation

H. Zhang, C. Liu, and A. Lei

The direct C—H carbonylation or carboxylation involving carbon monoxide is an ideal and environmentally friendly method toward the synthesis of carboxylic acids and derivatives. Within this emerging area, a number of significant examples have been reported, which are summarized in this chapter. Additionally, the recent progress on C—H carboxylation utilizing carbon dioxide is included in this review.



Keywords: C—H carbonylation · C—H carboxylation · carbon monoxide · carbon dioxide · directing groups · transition-metal catalysis · carboxylic acids · carboxylic esters · carboxylic amides · carbonyl compounds

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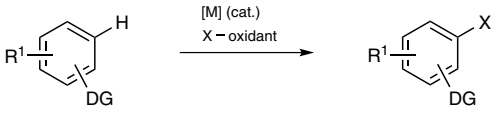
2.7 C—Hal Bond Formation by Arene C—H Activation

M. S. Sanford and A. Cook

C_{aryl}—H bonds are transformed into C_{aryl}—halogen bonds via transition-metal-catalyzed C—H activation. Fluorination, chlorination, bromination, and iodination are discussed and a wide variety of arenes bearing various directing groups are competent substrates.



DG = directing group; X = F, Cl, Br, I

Keywords: halogens · carbon—halogen bonds · carbon—hydrogen bonds · regioselectivity · arenes · transition metals · pyridines · amides · quinoxalines · oximes · benzothiazoles · esters · benzonitriles · ketones · carboxylic acids

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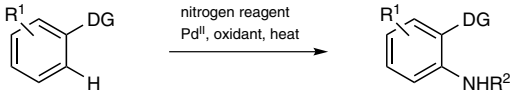
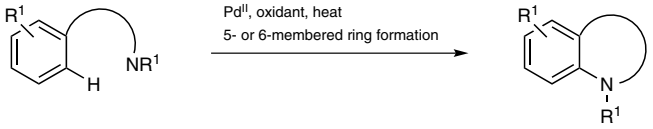
The search for methodologies allowing C(sp^2)—N bond formation is of utmost interest as the arylamine motif is ubiquitous in nature and life and material sciences. This chapter focuses on palladium-catalyzed arene C—H activation for the direct amination of C(sp^2)—H bonds, generally under oxidizing conditions. These processes mainly allow the efficient introduction of carboxamides and sulfonamides, but the insertion of an amino group is also possible. Intramolecular transformations lead to the formation of either five-membered rings, such as carbazoles, indole derivatives, and benzo-fused nitrogen heterocycles, or six-membered rings, such as quinolinones and phenanthridinones. On the other hand, intermolecular reactions occur with complete regioselectivity, generally *ortho* to an appropriate directing group, which can be an oxime, a ketone, a carboxylic acid, or an amide.



DG = *ortho*-directing group



Keywords: palladium · arylamines · amination · intramolecular · intermolecular · regioselectivity · chemoselectivity · directing groups · carboxamides · sulfonamides · oxidants · heterocycles · carbazoles · indoles · dihydroindoles · oxindoles · benzimidazoles · benzotriazoles · quinolinones · phenanthridinones

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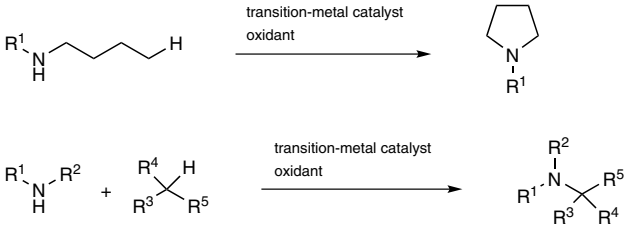
New routes for the formation of C—N bonds are important due to the prevalence of these bonds in complex natural products and molecules of pharmaceutical interest. Metallonitrene amination requires pre-oxidation of an amine, using precursors such as azides, *N*-(tosyloxy)carbamates, and iminoiodinanes. Binding of a transition-metal catalyst to the nitrene source gives the metallonitrene, which is capable of inserting into C—H bonds. Insertion may be made enantioselective in some systems by the use of a chiral metal complex. Most early examples of metallonitrene C—H amination focused on insertion into

benzylic C—H bonds, but recently the substrate scope has been expanded to include aryl, vinyl, and even unactivated tertiary, secondary, and primary bonds.



Keywords: amination · nitrenes · C—N bonds · enantioselectivity · rhodium catalysts · ruthenium catalysts · iridium catalysts · cobalt catalysts · iron catalysts

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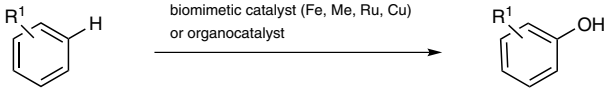
2.10 C—O Bond Formation by Arene C—H Activation via Biomimetic and Organocatalytic Oxidation

Y. Hitomi and K. Arakawa

This chapter is a summary of selected reactions for C—O bond formation via arene C—H bond activation by biomimetic and organocatalytic oxidation catalysts, which include manganese, iron, copper, and vanadium complexes as well as photocatalysts.



Keywords: arene complexes · arenes · hydroxylation · oxidation · oxygenation · quinones · phenols · porphyrins · iron catalysts · iron complexes · manganese catalysts · manganese complexes · ruthenium catalysts · ruthenium complexes · hydroperoxides · hydroquinones · copper catalysts · copper complexes

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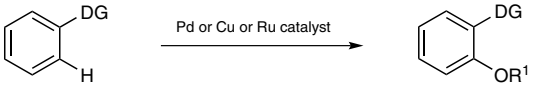
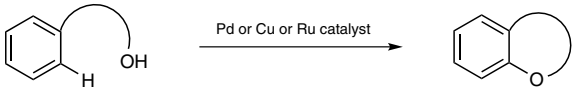
2.11 C—O Bond Formation by Arene C—H Activation via Metal-Catalyzed Oxidation

D.-D. Li and G.-W. Wang

This chapter highlights significant achievements in metal-catalyzed selective oxidation processes of arene C—H bonds to construct C—O bonds. A directing group is usually required to achieve high *ortho*-regioselectivity. Various functional groups have been fruitfully exploited as the directing groups for the acyloxylation, alkoxylation, hydroxylation, and intramolecular C—O cyclization of arenes by the palladium-, copper-, and ruthenium-catalyzed C—H activation. These transition-metal-catalyzed C—H/C—O processes can be efficiently achieved by utilizing either a monodentate or bidentate directing group.



DG = directing group; R^1 = Ac, CO*t*-Bu, H, alkyl, etc.



Keywords: arene C—H bond activation · C—O bond formation · palladium catalysis · copper catalysis · ruthenium catalysis · acyloxylation · alkoxylation · hydroxylation · intramolecular C—O cyclization

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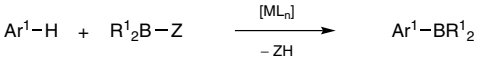
2.12 C—B Bond Formation by Arene C—H Activation

A. Ros, R. Fernández, and J. M. Lassaletta

This chapter provides a survey of the most useful available methodologies for the direct borylation of arenes and hetarenes, which proceed in all cases via a C—H activation event mediated by transition metals such as rhodium, iridium, or palladium. The borylation reactions have been organized into two main groups: (1) direct borylations with regioselectivity mainly controlled by steric factors, and (2) site-selective borylation, with regioselectivity driven by directing effects.



Keywords: C—H activation · organoboron compounds · borylation · arenes · hetarenes · synthetic methods · rhodium · iridium · palladium · directing groups

Catalytic Transformations via C—H Activation 2

Table of Contents

2.1 C–C and C–X Bond Formation by Allylic C–H Activation

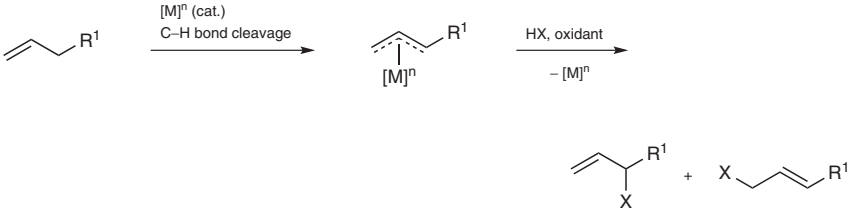
G. Liu and P. Chen

General Introduction

Transition-metal-catalyzed C—H bond cleavage and functionalization are attractive processes because of the demands of green chemistry, including atom economy and step economy.[1–4] Over the past half century, massive efforts have been made to activate specific "inert" C—H bonds, and these efforts have combined mechanistic studies and synthetic applications.[5–8] Among these studies, the activation of allylic C—H bonds with the assistance of an alkenyl group has received much attention, as alkenyl groups can efficiently coordinate with transition metals. Many transition metals have been discovered to participate in this process. Palladium, arguably the most powerful transition metal in organic synthesis,[9] has been found to be capable of catalyzing various C—H bond activation reactions, including activation of allylic C—H bonds.[10] Other metals such as rhodium, ruthenium, copper, and iron are also used for allylic C—H bond functionalization.

Although various transition metals can be used to catalyze the functionalization of allylic C—H bonds, the reactions operate under only three different mechanistic scenarios. The first scenario (Scheme 1) involves cleavage of a C—H bond with the assistance of a metal to afford an allylic metal species. This is followed by two possible processes: (1) attack by either an external or internal nucleophile at the carbon center to give the linear or branched product, with $[M]^n$ regenerated in the presence of an oxidant; or (2) attack at the metal center in the presence of an oxidant, followed by reductive elimination to give the allylic product and regenerate $[M]^n$. Most palladium-catalyzed allylic C—H functionalization reactions and ruthenium-catalyzed allylic C—C bond-forming reactions follow these pathways.

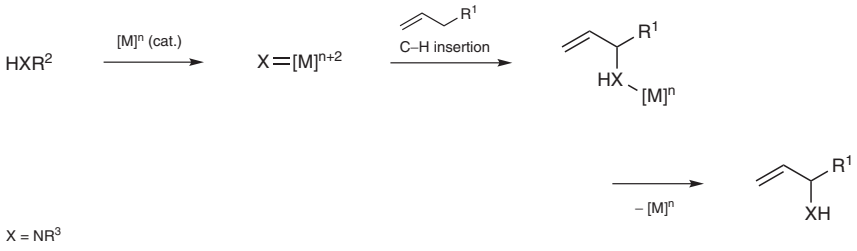
Scheme 1 Typical Mechanism for Transition-Metal-Catalyzed Allylic C–H Activation



The second scenario (Scheme 2) involves the initial formation of a nitrene or carbene metal complex (X═M; X = CR^3R^4, NR^3, etc.), and this is followed by insertion of the nitrene or carbene species into the allylic C—H bond to give the product.

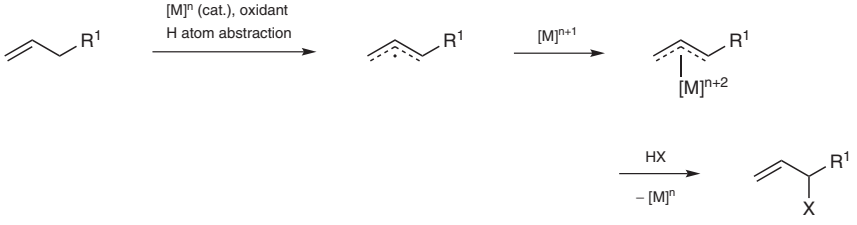
for references see p 34

Scheme 2 Typical Mechanism for Transition-Metal-Catalyzed C–H Insertion of a Metal Nitrenoid



The third scenario (Scheme 3) involves hydrogen abstraction by a radical species to form an allylic radical, which is either oxidized by a metal to give an allylic cation or directly bound to a metal, followed by nucleophilic attack to provide the coupling product.

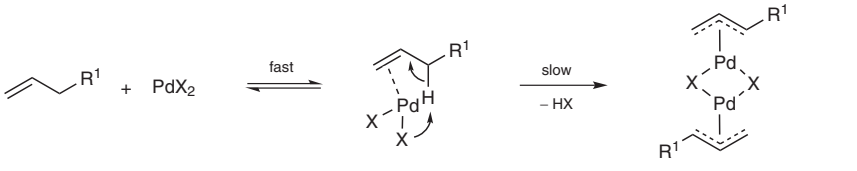
Scheme 3 Typical Mechanism for Transition-Metal-Catalyzed Radical Allylic Abstraction



In this chapter, the first two scenarios will be discussed. For the third scenario, related studies on allylic oxidation reactions are well documented in reviews,[11,12] and only recent progress on asymmetric versions of this reaction will be summarized herein.

As mentioned above, allylic C—H activation by a palladium catalyst has been extensively studied from both methodological and mechanistic aspects. The earliest example of the generation of a π-allylpalladium complex through allylic C—H activation was reported by Hüttel and Christ from a mixture of palladium(II) chloride and 2-methylbut-1-ene.[13] Generally, the formation of π-allylpalladium complexes proceeds through fast, reversible π-coordination of the palladium catalyst to the alkene, and this is followed by a rate-determining allylic hydrogen abstraction step (Scheme 4).[14] Early kinetic results for the reaction of methylenecyclohexane and palladium(II) chloride in acetic acid ruled out the possibility of proton abstraction by an external base, and a kinetic isotopic effect study gave an isotope effect of 3.5, which is consistent with the calculated value for proton abstraction by an internal base.[15,16] Recent mechanistic investigations by Fristrup and co-workers have also corroborated this latter mechanism involving removal of an allylic hydrogen atom by an internal base.[17]

Scheme 4 Proposed Mechanism for the Formation of a π-Allylpalladium Complex[15–17]



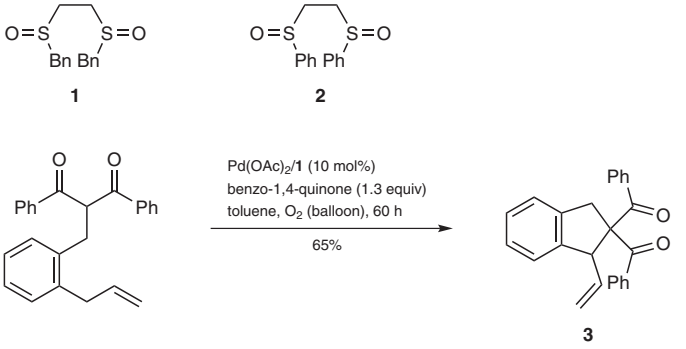
2.1.1 C–C Bond Formation by Allylic C–H Activation

The forging of C—C bonds by transition-metal catalysis is widely used in synthetic chemistry. One of the most important named reactions for the construction of allylic C—C bonds is the Tsuji–Trost reaction.[18,19] A broad range of nucleophiles and allylic substrates bearing various leaving groups are transformed into allylation products. In the presence of chiral ligands, high levels of regioselectivity and stereoselectivity can be achieved; however, prefunctionalization (i.e., the presence of a halogen, acetate, or carbonate) at the allylic position is required for the formation of the allylic palladium species in the Tsuji–Trost reaction. In contrast, the direct functionalization of alkenes through allylic C—H activation would be more attractive in terms of green and sustainable chemistry.

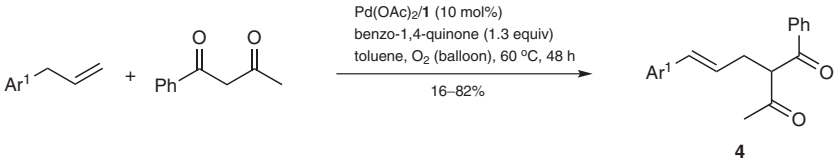
2.1.1.1 Reaction Using a Palladium Catalyst

Pioneering work by Trost and co-workers indicated that allylic alkylation could be realized by C—H activation in two steps with a stoichiometric amount of a palladium species.[20–22] However, the catalytic version of this reaction was not achieved for a long time, owing to the lack of suitable ligands and oxidants. In 2008, inspired by allylic C—N and C—O bond formation through palladium(II)-catalyzed C—H activation (see Sections 2.1.2.1 and 2.1.3.1), Shi and co-workers utilized a catalyst system comprising bis(sulfoxide) **1**, palladium, and benzo-1,4-quinone to realize the first catalytic allylic alkylation reactions (Scheme 5).[23] Both intra- and intermolecular allylic alkylation products (e.g., compounds **3** and **4**) can be obtained in moderate yields from an allylic C—H bond and a 1,3-diketone. Notably, only linear *E* products **4** are formed in the intermolecular reaction and no branched or *Z*-alkene products are observed by GC analysis. Simultaneously, White and co-workers demonstrated the allylic alkylation of alkenes with methyl nitroacetate as the carbon nucleophile in a method employing bis(sulfoxide) **2**.[24] 2,6-Dimethylbenzo-1,4-quinone is the most effective oxidant in this reaction. Both electron-donating and electron-withdrawing substituents on the aryl rings are tolerated to give linear products **5**, generally in good yields. However, the regioselectivity of the reaction is influenced by the substituents on the aryl ring; electron-withdrawing groups on the aryl ring significantly increase the yield of linear products (linear/branched ratio). Later, the same group developed the first intermolecular allylic C—H alkylation reaction of unactivated terminal alkenes, which is also suitable for activated terminal alkenes.[25]

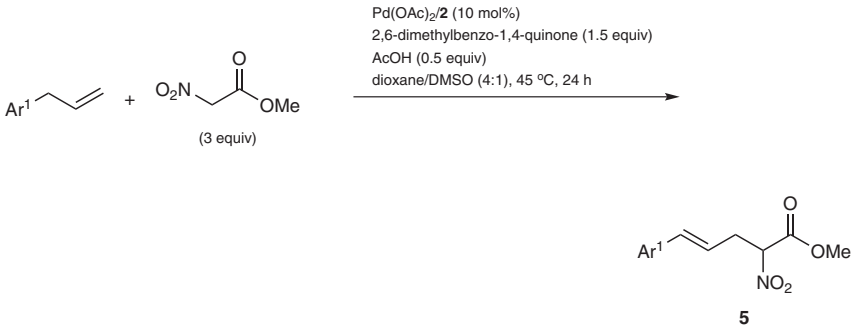
Scheme 5 Palladium-Catalyzed Direct Allylic Alkylation[23,24]



for references see p 34



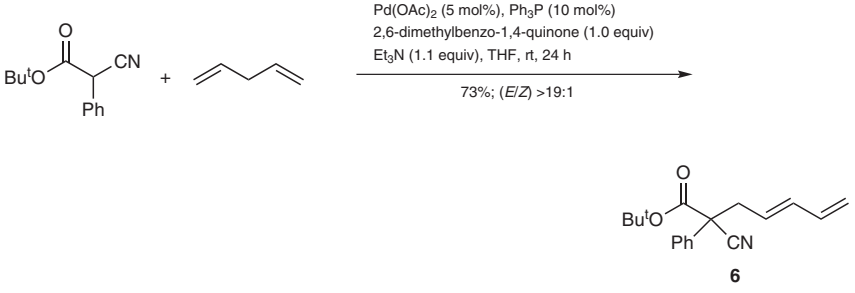
Ar^1 = Ph, 4-$MeOC_6H_4$, 4-Tol, 3-Tol, 4-PhC_6H_4, 4-ClC_6H_4, C_6F_5



Ar^1	Ratio (linear/branched)	Yield (%)	Ref
4-$MeOC_6H_4$	1.7:1	50	[24]
4-Tol	3:1	61	[24]
Ph	4:1	62	[24]
4-AcC_6H_4	10:1	66	[24]
4-$F_3CC_6H_4$	10:1	56	[24]
2-$F_3CC_6H_4$	>20:1	59	[24]

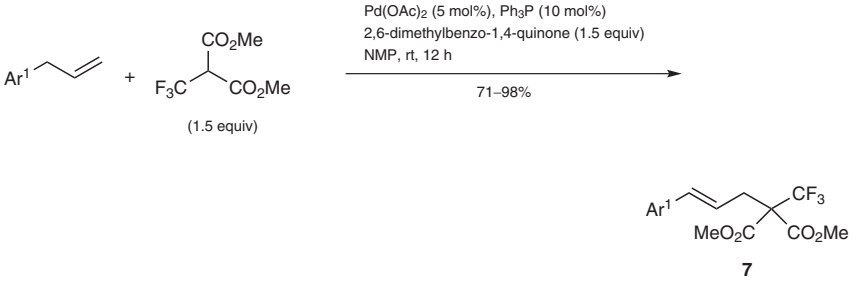
Recently, Trost and co-workers reported the first example of the palladium-catalyzed alkylation of 1,4-dienes for which a sulfoxide ligand is not required (Scheme 6). Triphenylphosphine is used as the ligand instead of a sulfoxide. The reaction gives 1,3-diene-containing product **6** with good regioselectivity and *E*-selectivity.[26]

Scheme 6 Palladium-Catalyzed Alkylation of a 1,4-Diene[26]



A similar reaction system has been applied to the allylic C—H alkylation of allylarenes by using a trifluoromethyl-containing nucleophile (Scheme 7).[27] This reaction provides a host of aromatic products **7**, bearing trifluoromethylated all-carbon quaternary centers, in remarkably high yields. Such products are interesting structural motifs for drug design.

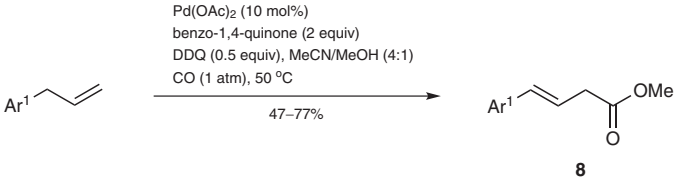
Scheme 7 Palladium-Catalyzed Alkylation with a Trifluoromethyl-Containing Nucleophile[27]



Ar^1 = Ph, 4-Tol, 4-ClC_6H_4, 4-$MeOC_6H_4$, 4-$F_3COC_6H_4$, 2,4-$(MeO)_2C_6H_3$, 1-naphthyl, 2-thienyl, 3,4,5-$F_3C_6H_2$

By employing carbon monoxide as a π-acid to react with the allylpalladium species, β,γ-unsaturated esters **8** can be successfully synthesized directly from allylarenes (Scheme 8).[28] Not only do allylarenes work well in the reaction, but propen-2-ylbenzene (α-methylstyrene) and its derivatives also efficiently give methyl 3-arylbut-3-enoates in good yields.

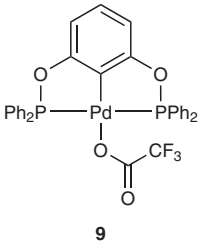
Scheme 8 Palladium-Catalyzed Oxidative Carbonylation[28]



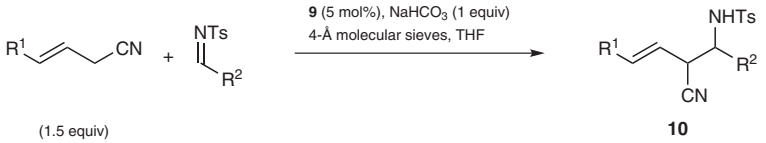
Ar^1 = Ph, 4-$F_3CC_6H_4$, 3,5-$Me_2C_6H_3$, 2-Tol, 4-$MeOC_6H_4$, 4-FC_6H_4, 2-naphthyl

Aydin and Szabó have used palladium–phosphine pincer complex **9** to catalyze the allylation of *N*-tosylimines under nonoxidative conditions (Scheme 9).[29] The reaction affords homoallylic amine derivatives **10** with high regioselectivity.

Scheme 9 Palladium-Catalyzed Nonoxidative Allylic Alkylation[29]



for references see p 34

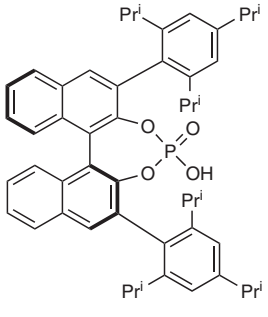


R^1	R^2	Temp (°C)	Time (h)	dr	Yield (%)	Ref
H	Ph	20	5	3:2	90	[29]
H	4-FC_6H_4	20	1	3:2	91	[29]
H	2-naphthyl	20	2	1:1	87	[29]
Me	Ph	40	14	1:1	98	[29]
Me	4-FC_6H_4	20	3	1:1	98	[29]
CH_2CN	Ph	20	4	1:1	97	[29]

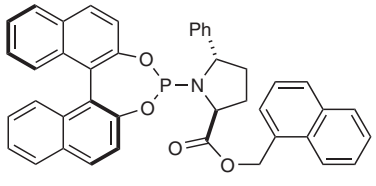
Recently, enantioselective allylic C—H alkylation reactions have also attracted much attention. In 2012, Chai and Rainey developed a palladium-catalyzed migratory ring-expansion reaction for the synthesis of chiral spirocyclic indenes; the reaction is initiated by enantioselective allylic C—H activation (Scheme 10).[30] 1,1′-Bi-2-naphthol-derived Brønsted acid **11** was shown to be the best chiral catalyst to give chiral spirocyclic indene **13** with good enantioselectivity. No reaction occurs in the absence of either palladium(II) acetate or Brønsted acid **11**.

Trost and co-workers have described a palladium-catalyzed enantioselective allylic alkylation reaction (Scheme 10).[31] Ligand screening revealed that chiral phosphoramidite **12** gives the best conversion in the reaction, with moderate to good levels of enantioselectivity. Highly electron-rich allylarenes, such as 1-allyl-4-methoxybenzene, are disfavored in the C—H activation process, whereas moderately electron-rich and electron-deficient substrates undergo this reaction to give products **14** with good enantioselectivities. For example, 1-allyl-3-methoxybenzene gives a quite good ee value, because the strong *para*-donating nature of the methoxy group is overwhelmed by its σ-withdrawing ability.

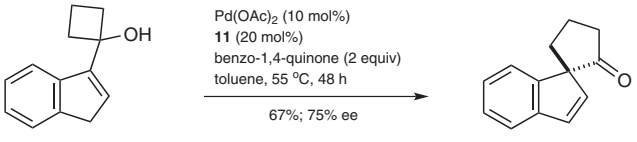
Scheme 10 Palladium-Catalyzed Enantioselective Allylic Alkylation[30,31]



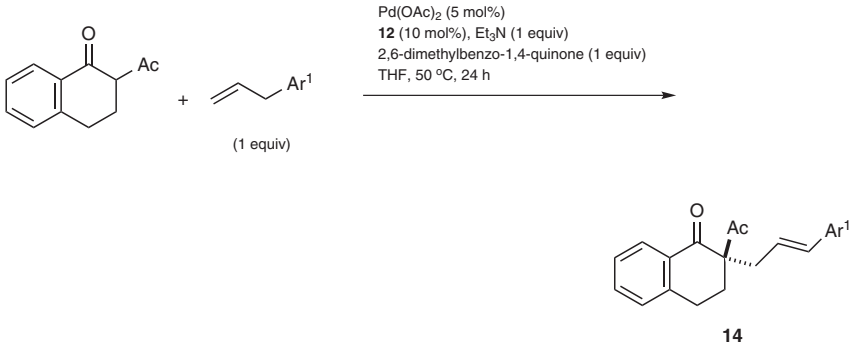
11



12



13



Ar^1	ee (%)	Yield (%)	Ref
Ph	85	89	[31]
4-Tol	79	59	[31]
4-$OHCC_6H_4$	71	84	[31]
3-$MeOC_6H_4$	79	63	[31]

1-Phenyl-2-(3-phenylprop-2-enyl)butane-1,3-dione (4, Ar^1 = Ph); Typical Procedure:[23]
A 25-mL Schlenk tube was charged with 1-phenylbutane-1,3-dione (113.5 mg, 0.7 mmol), 1,2-bis(benzylsulfinyl)ethane-supported $Pd(OAc)_2$ (11.1 mg, 0.05 mmol), and benzo-1,4-quinone (70.2 mg, 0.65 mmol), followed by toluene (2.5 mL) and allylbenzene (66.4 μL, 0.5 mmol). The mixture was stirred at 60 °C under an atmosphere of O_2 (1 atm, balloon pressure) for 48 h. After cooling, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel) to give the title compound; yield: 113.9 mg (82%).

***tert*-Butyl (*E*)-2-Cyano-2-phenylhepta-4,6-dienoate (6); Typical Procedure:**[26]
An oven-dried reaction vial equipped with an oven-dried stirrer bar was charged with 2,6-dimethylbenzo-1,4-quinone (27.2 mg, 0.20 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), and Ph_3P (5.2 mg, 0.02 mmol). The vial was sealed with a septum and then evacuated and filled with argon (3 ×). THF (0.6 mL) was added, and the mixture was stirred for about 1 min until a yellow soln was obtained. Penta-1,4-diene (23.0 μL, 0.22 mmol) was then added by syringe, followed by *tert*-butyl 2-cyano-2-phenylacetate (43.5 mg, 0.20 mmol), Et_3N (30.5 μL, 0.22 mmol), and THF (0.4 mL). The mixture was stirred at rt for 24 h. After concentration under reduced pressure, the residue was purified by column chromatography (silica gel, hexanes/EtOAc 95:5) to give the title compound as a colorless oil; yield: 41.4 mg (73%); ratio (*E*/*Z*) >19:1.

***N*-(2-Cyano-1-phenylbut-3-enyl)-4-toluenesulfonamide (10, R^1 = H; R^2 = Ph); Typical Procedure:**[29]
A mixture of *N*-tosyl benzaldehyde imine (51.8 mg, 0.2 mmol), but-3-enenitrile (20.1 mg, 0.3 mmol), $NaHCO_3$ (16.8 mg, 0.2 mmol), 4-Å molecular sieves (40 mg), and catalyst **9** (6.97 mg, 0.01 mmol) in THF (0.3 mL) was stirred at 20 °C for 5 h. Then, the mixture was filtered through a thin pad of silica gel, which was washed with $CHCl_3$, and the combined filtrate was concentrated. The residue was purified by column chromatography (silica gel, CH_2Cl_2/Et_2O 20:1) to give the title compound; yield: 58.7 mg (90%); dr 3:2.

for references see p 34

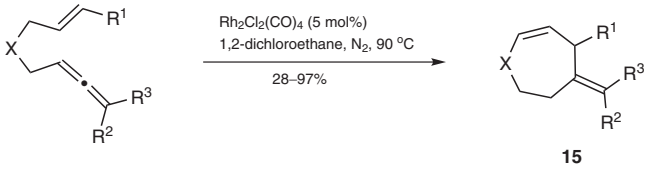
(2*S*)-2-Acetyl-2-[(*E*)-3-(4-tolyl)prop-2-enyl]-3,4-dihydronaphthalen-1(2*H*)-one (14, Ar[1] = 4-Tol); Typical Procedure:[31]

A reaction vial equipped with a stirrer bar was charged with 2-acetyl-3,4-dihydronaphthalen-1(2*H*)-one (188 mg, 1.00 mmol), 2,6-dimethylbenzo-1,4-quinone (136 mg, 1.00 mmol), $Pd(OAc)_2$ (5.6 mg, 0.03 mmol), and phosphoramidite **12** (32.3 mg, 0.05 mmol) under an atmosphere of argon. THF (2.44 mL) was added, followed by Et_3N (0.139 mL, 1.00 mmol) and 4-allyltoluene (0.132 mL, 1.00 mmol). The yellow soln was heated to 50 °C for 3 h, at which point a soln of $Pd(OAc)_2$ (5.6 mg, 0.03 mmol) and **12** (32.3 mg, 0.05 mmol) in THF (2.44 mL) was added by cannula. The mixture was stirred at 50 °C for an additional 21 h. After cooling to rt, the soln was concentrated, and the residue was purified by column chromatography (silica gel, CH_2Cl_2/Et_2O 9:1) to give the title compound as a colorless oil; yield: 194 mg (59%, as reported); 79% ee.

2.1.1.2 Reaction Using Rhodium and Ruthenium Catalysts

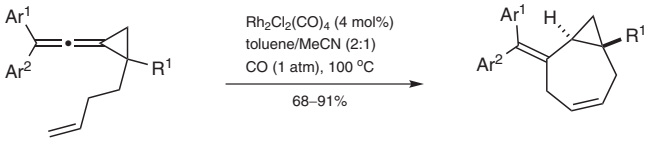
Cycloisomerization of enynes is an efficient strategy that can be used to construct C—C bonds.[32,33] Usually, a metallacyclopentene species is involved as the intermediate. However, in some cases the reactions are initiated by allylic C—H activation to form a π-allylmetal species. Brummond and co-workers have found that ene–allenes undergo carbocyclization with a rhodium(I) catalyst (Scheme 11).[34] Seven-membered heterocyclic compounds **15**, such as azepines and oxepines, can be prepared from ene–allenes in moderate to high yields. A similar reaction with (diarylvinylidene)cyclopropanes has been reported by Shi and co-workers.[35] Bicyclo[5.1.0]octene derivatives **16** can be synthesized in good to excellent yields; the presence of acetonitrile is necessary for the formation of the bicyclo[5.1.0]octene derivatives. Li and Yu have developed a conjugated diene assisted rhodium(I) activation of allylic C—H bonds (Scheme 11).[36,37] This reaction affords multisubstituted cyclic compounds **17**, such as tetrahydropyrroles, tetrahydrofurans, and cyclopentanes, with high chemoselectivity and diastereoselectivity. An asymmetric version of this reaction has been successfully developed to synthesize two adjacent sp^3-carbon centers.[38]

Scheme 11 Rhodium(I)-Catalyzed Cycloaddition by C–H Activation[34–36]



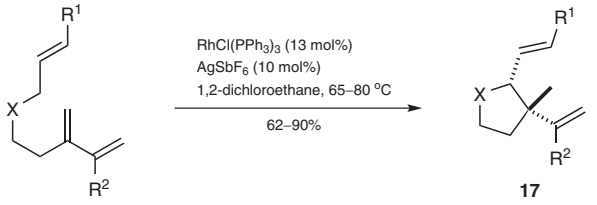
15

R^1 = H, Me, Ph, $SiMe_2Bn$, $SiMe_3$; R^2 = H, Me, *t*-Bu, $(CH_2)_5Me$; R^3 = H, Me; X = NTs, NBz, NCbz, O



16

Ar^1 = Ar^2 = Ph, 4-Tol, 4-$MeOC_6H_4$, 4-ClC_6H_4; R^1 = Ph, 4-Tol, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, Me

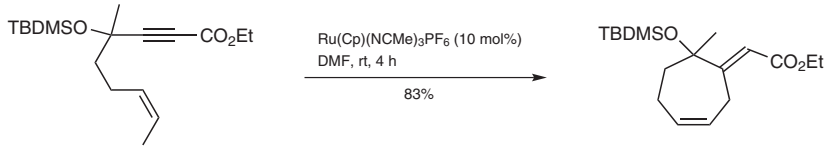


17

R^1 = H, Me, Ph; R^2 = H, Me, Bu, Ph; X = NTs, O, $C(CO_2Me)_2$

Trost and Toste have studied a similar cycloisomerization of 1,n-enynes with a ruthenium catalyst.[39,40] For example, 1,6-enyne **18** smoothly undergoes cycloisomerization to give product **19** (Scheme 12).[39–42] This reaction provides seven-membered product **19** instead of the normally obtained cyclopentane product. Octacarbonyldicobalt(0) can also serve as an effective catalyst for this reaction.[43]

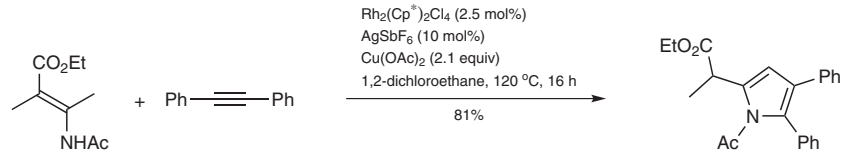
Scheme 12 Ruthenium-Catalyzed Cycloisomerization by C–H Activation[39]



18 **19**

Multisubstituted pyrroles can be synthesized from the intermolecular reaction of enamines and unactivated alkynes by rhodium-catalyzed allylic C–H activation (Scheme 13).[44] For substrate **20**, with an ester group on the double bond, allylic C–H activation of the enamine takes place first, which is followed by cyclization with the alkyne to give pyrrole **21**.

Scheme 13 Rhodium(III)-Catalyzed Oxidative Pyrrole Synthesis[44]



20 (1.3 equiv) **21**

3-Methyl-3-(prop-1-en-2-yl)-1-tosyl-2-vinylpyrrolidine (17, R^1 = H; R^2 = Me; X = NTs); Typical Procedure:[36]

A mixture of $RhCl(PPh_3)_3$ (9.0 mg, 9.7 μmol) and $AgSbF_6$ (4.3 mg, 12.6 μmol) in anhyd 1,2-dichloroethane (1.0 mL) was stirred at rt under an atmosphere of argon for 10 min, which resulted in the formation of a brown suspension. A soln of the sulfonamide (29.6 mg, 97 μmol) in 1,2-dichloroethane (1.2 mL) was then added dropwise. The reaction tube was immersed in an oil bath (65 °C). Upon completion of the reaction, as indicated by TLC, the mixture was cooled to rt, filtered, and then the filter was washed with eluent (petroleum ether/EtOAc 5:1). The combined filtrate was concentrated, and the residue was purified by column chromatography (silica gel) to afford the product as a colorless oil; yield: 26.7 mg (90%).

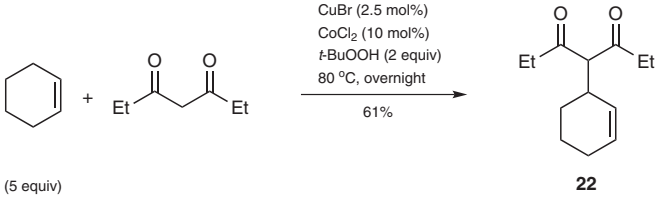
for references see p 34

Ethyl 2-(1-Acetyl-4,5-diphenyl-1*H*-pyrrol-2-yl)propanoate (21); Typical Procedure:[44]
A dried sealed tube with a J. Young Teflon valve was charged with $Rh_2(Cp^*)_2Cl_4$ (15.5 mg, 0.025 mmol), $AgSbF_6$ (34.3 mg, 0.10 mmol), and anhyd $Cu(OAc)_2$ (381.0 mg, 2.1 mmol) in a glovebox. Ethyl (*E*)-3-acetamido-2-methylbut-2-enoate (240.5 mg, 1.3 mmol), diphenylacetylene (178.2 mg, 1.0 mmol), and anhyd 1,2-dichloroethane (5.0 mL) were then added under an atmosphere of argon. The mixture was stirred at 120 °C for 16 h. After cooling to rt, the mixture was diluted with EtOAc (15 mL) and filtered through a short pad of silica gel. The combined filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, pentane/EtOAc 97:3) to provide the title compound as a yellow solid; yield: 292.0 mg (81%); R_f 0.20 (pentane/EtOAc 95:5).

2.1.1.3 Reaction Using Copper, Iron, and Cobalt Catalysts

As mentioned in the General Introduction (Scheme 3), allylic C—H bonds can be activated by hydrogen-atom abstraction to form an allylic radical in the presence of a metal and an oxidant. Copper-, iron-, and cobalt-catalyzed allylic alkylations mostly follow this pathway. Oxidative cross-dehydrogenative coupling is an efficient strategy that can be used to construct C—C bonds by using two different C—H bonds.[45,46] Among these coupling reactions, those with allylic C(sp^3)—H bonds are fairly rare. Li and Li demonstrated the first copper-catalyzed allylic alkylation reaction through the cross-dehydrogenative coupling of allylic C(sp^3)—H and methylene C(sp^3)—H bonds (Scheme 14).[47] An excess of cyclohexene is required to furnish the desired alkylated product **22** owing to competing oxidation to its corresponding allylic alcohol and ketone. Cobalt(II) chloride is used as the cocatalyst and the ratio of copper(I) bromide to cobalt(II) chloride is important for this reaction.

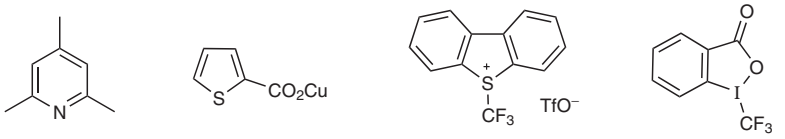
Scheme 14 Allylic Alkylation by a Cross-Dehydrogenative Coupling Reaction[47]



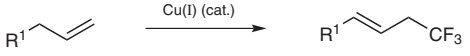
The Liu,[48] Buchwald,[49] and Wang[50] groups independently demonstrated the copper-catalyzed allylic trifluoromethylation of alkenes using electrophilic trifluoromethylation reagents (Scheme 15). Allylic trifluoromethylation products **27** can be obtained in good yields by using the Umemoto reagent (**25**) in the presence of copper thiophene-2-carboxylate (**24**) and ligand **23**.[48] By using the Togni reagent II (**26**), the reaction gives only products **27** under catalysis by copper salts.[49,50] With regard to the mechanism, Liu has proposed a Heck-type four-membered-ring transition state based on the experimental results and theoretical calculations. In contrast, Wang has suggested a copper-assisted single-electron-transfer oxidation pathway involving an allylic radical intermediate. However, details of the C—CF_3 bond-forming step are not clear at this stage.

Chu and Qing have disclosed the copper-catalyzed direct allylic C—H oxidative trifluoromethylation of alkenes with the less expensive Ruppert–Prakash reagent ($TMSCF_3$).[51] Only terminal alkenes are suitable for this reaction, which gives allylic trifluoromethylation products **27** with moderate *E*/*Z* selectivity.

Scheme 15 Copper-Catalyzed Allylic Trifluoromethylation[48–51]



23 **24** **25** **26**



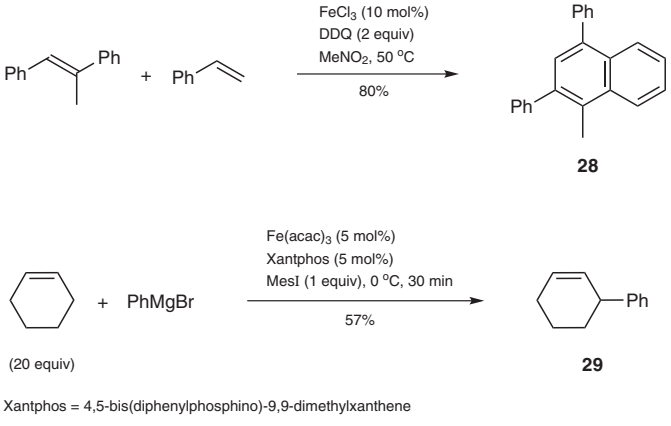
27

R^1	Conditions	Ratio[a] (*E*/*Z*)	Yield (%)	Ref
$(CH_2)_3OTs$	**23** (2 equiv), **24** (20 mol%), **25** (1.2 equiv), DMA, 40 °C	n.d.	76	[48]
$(CH_2)_7Br$	$[Cu(NCMe)_4]PF_6$ (15 mol%), **26** (1 equiv), MeOH, 0 °C to rt	96:4	78	[49]
$(CH_2)_{11}Me$	CuCl (20 mol%), **26** (2 equiv), MeOH, 70 °C	n.d.	93	[50]
Bn	**24** (30 mol%), $TMSCF_3$ (4 equiv), K_2CO_3 (4 equiv), $PhI(OAc)_2$ (2 equiv), NMP, 80 °C	10.7:1	76	[51]

[a] n.d. = not determined.

Recently, Deng and co-workers reported the iron-catalyzed tandem cross-dehydrogenative coupling of 1,2-diarylprop-1-enes and styrene (Scheme 16).[52] The reaction is initiated by the generation of an allylic radical. The radical then adds to styrene, and this is followed by benzannulation to afford multisubstituted naphthalenes of type **28**. Nakamura and co-workers have developed the iron-catalyzed allylic arylation of alkenes by using an aryl Grignard reagent (Scheme 16).[53] (Cyclohex-2-enyl)benzene (**29**) is synthesized from cyclohexene and phenylmagnesium bromide in moderate yield.

Scheme 16 Iron-Catalyzed Allylic Arylation[52,53]



Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

4-(Cyclohex-2-enyl)heptane-3,5-dione (22); Typical Procedure:[47]

A ~5.5 M soln of *t*-BuOOH in decane (2.0 mmol) was added to a mixture of CuBr (3.6 mg, 0.025 mmol), $CoCl_2$ (13.0 mg, 0.1 mmol), cyclohexene (5.0 mmol), and heptane-3,5-dione

for references see p 34

(128.1 mg, 1.0 mmol) under an atmosphere of N_2 at rt. The mixture was stirred at 80 °C overnight. The resulting mixture was purified by column chromatography (silica gel, hexane/Et_2O 10:1) to give the title compound; yield: 127.1 mg (61%).

(*E*)-7,7,7-Trifluorohept-4-en-1-yl 4-Toluenesulfonate [27, $R^1 = (CH_2)_3OTs$]; Typical Procedure:[48]

In a glovebox, copper thiophene-2-carboxylate (**24**; 7.6 mg, 0.04 mmol) was added to a reaction tube. Hex-5-enyl 4-toluenesulfonate (50.9 mg, 0.2 mmol), 2,4,6-collidine (**23**; 48.5 mg, 0.4 mmol), the Umemoto reagent (**25**; 96.6 mg, 0.24 mmol), and DMA (0.5 mL) were added under an atmosphere of argon. After the mixture had been stirred at 40 °C for 24 h, H_2O was added at rt, and the resulting mixture was extracted with EtOAc. The combined organic phase was washed with H_2O and brine and then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, petroleum ether/EtOAc) to give the title compound as a yellow oil; yield: 50 mg (76%, as reported).

(Cyclohex-2-enyl)benzene (29); Typical Procedure:[53]

A flame-dried flask was charged with cyclohexene (0.61 mL, 6 mmol), $Fe(acac)_3$ (5.3 mg, 0.015 mmol), Xantphos (8.7 mg, 0.015 mmol), and MesI (73.8 mg, 0.3 mmol). The mixture was carefully degassed by three freeze–pump–thaw cycles and then stirred for 30 min at rt to give a clear red soln. A 1.0 M soln of PhMgBr in THF (0.3 mL, 0.3 mmol) was then added at 0 °C. The mixture was stirred for an additional 20 min at 0 °C and then quenched with sat. aq NH_4Cl. After extraction with Et_2O, the combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude mixture was purified by column chromatography (silica gel, hexane) to afford the title compound as a colorless oil; yield: 27.1 mg (57%).

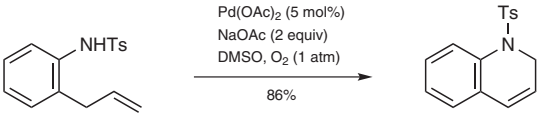
2.1.2 C–N Bond Formation by Allylic C–H Activation

Direct C—H amination reactions are highly appealing in the context of streamlining the syntheses of nitrogen-containing compounds.[2] Early results in C—H amination involve the Hofmann–Löffler–Freytag reaction with haloamines[54] and C—H insertion reactions of nitrenes (generated mostly from azides),[55] which suffer from low yields and poor selectivities. However, the efficiency and selectivity are clearly improved under catalysis by a transition metal. Rhodium, copper, iron, and ruthenium catalysts are widely used in this transformation, including rare cases of allylic C—H aminations. Very recently, high chemoselectivity and regioselectivity in palladium-catalyzed allylic C—H amination reactions have been described, and this area of research has attracted much attention.

2.1.2.1 Reaction Using a Palladium Catalyst

Palladium(II)-catalyzed oxidative allylic amination of alkenes usually proceeds via aminopalladation and subsequent palladium hydride elimination. Allylic amination through C—H activation is suppressed by aminopalladation owing to the strong nucleophilicity and coordination ability of amines and amides. To avoid this problem, a two-step sequence can be performed with the use of a stoichiometric amount of palladium.[56,57] In 1996, Larock and co-workers reported the palladium-catalyzed oxidative allylic C—H amination of alkene-containing 4-toluenesulfonamides (Scheme 17).[58] *N*-(2-Allylphenyl)-4-toluenesulfonamide undergoes closure of a six-membered ring under catalysis by palladium(II) acetate to give 1,2-dihydroquinoline **30**. On the basis of the regioselectivity, the mechanism of this process is proposed to be direct cyclization via a π-allylpalladium intermediate.

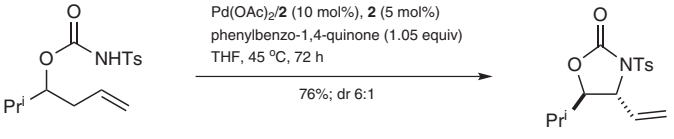
Scheme 17 Palladium-Catalyzed Cyclization of a 4-Toluenesulfonamide[58]



30

In 2007, White and co-workers demonstrated the palladium-catalyzed intramolecular allylic amination with weak nitrogen nucleophiles (*N*-tosylcarbamates) as the key factor to avoid the competitive aminopalladation step (Scheme 18).[59,60] The system comprising palladium(II) acetate and bis(sulfoxide) **2** is efficient for this process. *anti*-Oxazolidinone product **32** is formed from unsaturated carbamate **31** with good diastereoselectivity and this compound can be rapidly transformed into a useful *syn*-1,2-amino alcohol moiety in a few steps. Similar routes to access *syn*-1,3-amino alcohols and *syn*-1,2-amino alcohols have been developed, for which more electron-deficient *N*-[(4-nitrophenyl)sulfonyl]carbamates and ureas are used as nucleophiles, respectively.[61,62]

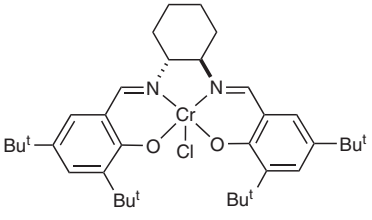
Scheme 18 Intramolecular Palladium-Catalyzed Allylic Amination with Phenylbenzo-1,4-quinone as Oxidant[59]



31 **32**

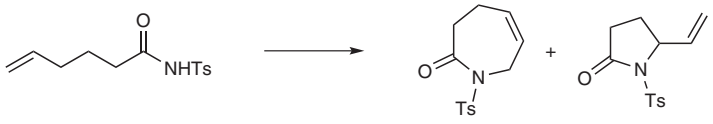
More interestingly, Liu and co-workers have found that a Brønsted base can modulate the regioselectivity of palladium-catalyzed intramolecular aerobic oxidative allylic amination reactions (Scheme 19).[63] In the presence of a Brønsted base (sodium benzoate), seven-membered lactam **34** is obtained predominantly, whereas five-membered lactam **35** is favored in the absence of a base; Lewis acid **33** only increases the yield and does not have any effect on the regioselectivity of the reaction. This observation indicates that the reaction proceeds through a rate-determining allylic C—H activation/irreversible reductive elimination pathway to form the C—N bond.

Scheme 19 Brønsted Base Modulated Allylic Amination[63]



33 Cr(salen)Cl

for references see p 34

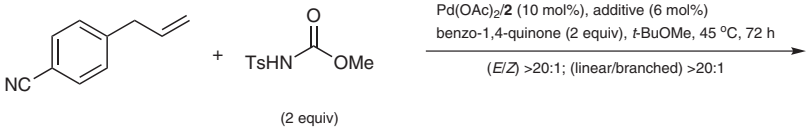


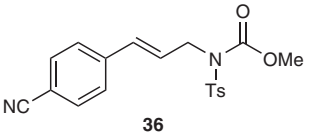
34 **35**

Conditions	Ratio (**34**/**35**)	Yield (%)	Ref
$Pd(OAc)_2$ (10 mol%), NaOBz (1 equiv), maleic anhydride (0.4 equiv), 4-Å molecular sieves, DMA, O_2 (1 atm), 70 °C	86:14	88	[63]
$Pd(OAc)_2$ (10 mol%), **33** (10 mol%), DMA, O_2 (1 atm), 50 °C	<3:97	61	[63]

In 2008, White and co-workers extended the intramolecular allylic C—H amination reaction to an intermolecular version (Scheme 20).[64,65] Two general strategies can be applied to increase the rate of the C—N bond-forming step. One strategy involves the use of a Lewis acid (e.g., compound **33**) as a cocatalyst to activate the electrophilic π-allylpalladium intermediate towards nucleophilic attack through reaction with benzo-1,4-quinone.[64] The other strategy involves the addition of a catalytic amount of an exogenous Brønsted base (e.g., *N*,*N*-diisopropylethylamine) to increase the concentration of the deprotonated nitrogen nucleophile in solution.[65] Linear (*E*)-allylamine products (e.g., **36**) are obtained with high regioselectivity and stereoselectivity through the use of either strategy.

Scheme 20 Palladium-Catalyzed Intermolecular Allylic Amination with Benzo-1,4-quinone as Oxidant[65]





36

Additive	Yield (%)	Ref
iPr_2NEt	79	[65]
33	59	[65]

A benzo-1,4-quinone-free aerobic system for allylic C—H amination without a cocatalyst has been disclosed by Liu and co-workers (Scheme 21).[66] Linear allylic amines (e.g., **37**) are generated from terminal alkenes and methyl tosylcarbamate (or saccharin) with high regioselectivities, together with small amounts of non-allylic isomers. The addition of maleic anhydride increases the reaction yield, which indicates that maleic anhydride plays a role similar to that of benzo-1,4-quinone in promoting nucleophilic attack. If the strong oxidant [bis(pivaloyloxy)iodo]benzene is used instead of dioxygen, the isomerization reaction is suppressed, as isomerization is possibly catalyzed by palladium black or palladium(0) nanoparticles.[67] [Bis(pivaloyloxy)iodo]benzene successfully oxidizes the π-allylpalladium(II) species directly to a π-allylpalladium(IV) intermediate that undergoes

reductive elimination to regenerate palladium(II) without the formation of palladium(0). In this reaction, naphtho-1,4-quinone is used instead of benzo-1,4-quinone. Molybdovanadophosphate is another efficient oxidant that can be used in aerobic oxidative allylic C—H amination reactions.[68]

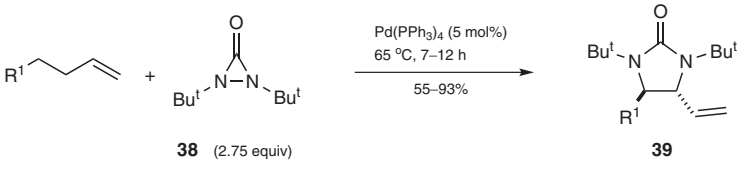
Scheme 21 Palladium-Catalyzed Intermolecular Allylic Amination[66,67]

37

Conditions	Ratio (allylic/homoallylic)	Yield (%)	Ref
$Pd(OAc)_2$ (10 mol%), NaOAc (0.25 equiv), maleic anhydride (0.4 equiv), 4-Å molecular sieves, DMA, O_2 (6 atm), 35 °C	70:30	87	[66]
$Pd(OAc)_2$ (5 mol%), naphtho-1,4-quinone (20 mol%), $PhI(O_2Ct\text{-}Bu)_2$ (1.5 equiv), Bu_4NOAc (1 equiv), NMP, 40 °C	91:9	83	[67]

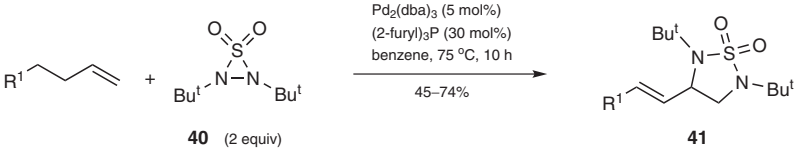
Shi and co-workers have demonstrated that the dehydrogenative diamination of terminal alkenes can be achieved with di-*tert*-butyldiaziridinone (**38**) or *N*,*N*-di-*tert*-butylthiadiaziridine 1,1-dioxide (**40**) in the presence of a palladium(0) catalyst (Scheme 22).[69–71] The authors have proposed that both reactions are initiated by allylic C—H activation of the terminal alkene by a four-membered-ring palladium(II) species, generated from insertion of palladium(0) into the N—N bond, to give intermediate **42**. If **38** is used as the nitrogen source, intermediate **42** undergoes β-hydride elimination to give a diene that in turn gives internal diamination product **39** in good yield with high stereoselectivity. The regioselectivity can be changed to the terminal carbon position by using **40** as the nitrogen source. In this case, a linear allyl sulfonamide is formed from intermediate **42** through reductive elimination, and this is accompanied by regeneration of the palladium(0) catalyst. Then, intramolecular cyclization of the alkene and β-hydride elimination gives final product **41** in moderate yield.

Scheme 22 Palladium-Catalyzed Dehydrogenative Diamination[69,71]



38 (2.75 equiv) **39**

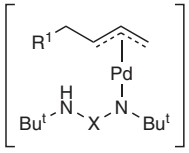
$R^1 = (CH_2)_5Me$, Et, Ph, CH_2OBn, $CH{=}CH_2$



40 (2 equiv) **41**

$R^1 = (CH_2)_4Me$, Bn, Ph, OBn

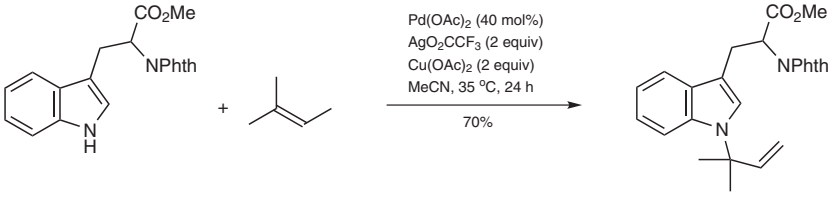
for references see p 34



42 X = CO, SO_2

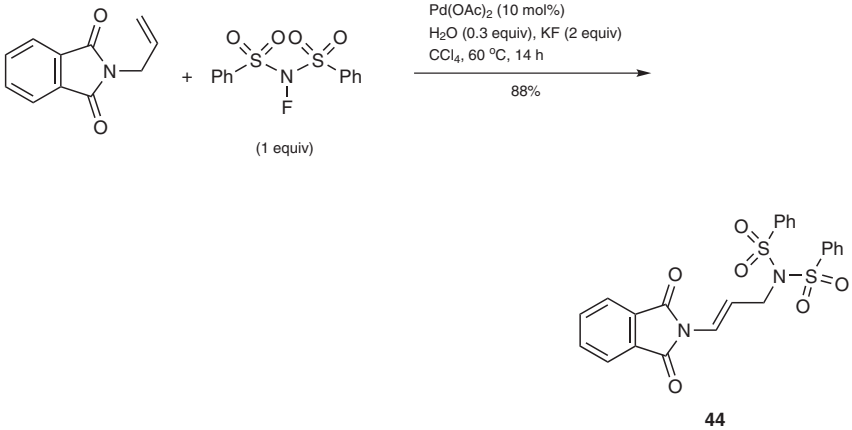
Baran and co-workers have found that indole alkaloids can be prenylated regioselectively by using 2-methylbut-2-ene (Scheme 23).[72] The *N*-*tert*-prenylation reaction of indoles occurs exclusively to give products such as **43**, without observation of C2-prenylated products. The reaction proceeds through C—H activation of 2-methylbut-2-ene to give a π-allylpalladium species; then, either direct coordination with the indole nitrogen atom or palladation of the indole at C3 followed by metallo-Claisen rearrangement gives product **43**.

Scheme 23 Palladium-Catalyzed Prenylation of an Indole[72]



Zhang and co-workers have disclosed the palladium/water-catalyzed allylic C—H amination of alkenes by using *N*-fluorobenzenesulfonimide as the nitrogen source (Scheme 24).[73] This reaction gives linear allylic amine **44** with high regioselectivity. In addition, with this protocol, Selectfluor-mediated allylic amination of allylbenzene with methyl tosylcarbamate can be successfully realized at room temperature in water.

Scheme 24 Palladium-Catalyzed Allylic Amination with *N*-Fluorobenzenesulfonimide[73]



1-Tosyl-1,2-dihydroquinoline (30); Typical Procedure:[58]
A mixture of *N*-(2-allylphenyl)-4-toluenesulfonamide (71.3 mg, 0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), and NaOAc (41.0 mg, 0.5 mmol) in DMSO (5 mL) was stirred under an atmosphere of O_2 (balloon) at 80 °C for 72 h. The mixture was then cooled to rt, diluted

with Et_2O and THF, and extracted with Et_2O. The combined organic layer was washed with sat. aq NaCl and dried ($MgSO_4$). After concentration, the residue was purified by column chromatography (silica gel) to afford the title compound; yield: 61.3 mg (86%); mp 85–86 °C.

***anti*-5-Isopropyl-3-tosyl-4-vinyloxazolidin-2-one (32); Typical Procedure:**[59]
$Pd(OAc)_2$/1,2-bis(phenylsulfinyl)ethane complex (15.1 mg, 0.03 mmol), an additional amount of 1,2-bis(phenylsulfinyl)ethane (**2**; 4.2 mg, 0.015 mmol), and phenylbenzo-1,4-quinone (58.0 mg, 0.32 mmol) were added to a soln of 2-methylhex-5-en-3-yl tosylcarbamate (**31**; 93.4 mg, 0.30 mmol) in THF (0.45 mL). The mixture was stirred at 45 °C for 72 h. The mixture was diluted with CH_2Cl_2 (25 mL) and then sat. aq NH_4Cl (5 mL) and brine (5 mL) were added. After separation, the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc 17:3) to afford the title compound as a mixture of *anti*/*syn* products; yield: 70.8 mg (76%); dr 6:1.

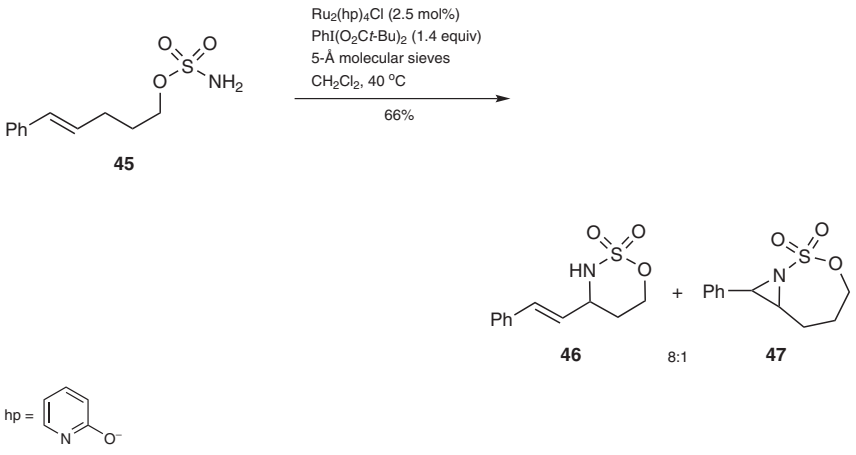
Methyl (*E*)-Tosyl(undec-2-enyl)carbamate (37); Typical Procedure:[66]
A mixture of undec-1-ene (92.6 mg, 0.6 mmol), methyl tosylcarbamate (45.9 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), maleic anhydride (7.8 mg, 0.08 mmol), NaOAc (4.1 mg, 0.05 mmol), and 4-Å molecular sieves (50 mg) in DMA (0.8 mL) was stirred under an atmosphere of O_2 (6 atm) at 35 °C for 36 h. Upon completion of the reaction, the mixture was concentrated under reduced pressure, and the crude residue was purified by column chromatography (silica gel) to afford the title compound; yield: 66.4 mg (87%); regioisomer ratio 70:30.

2.1.2.2 Reaction Using Rhodium and Ruthenium Catalysts

Metal nitrenoid based C—H aminations have been widely used in organic synthesis.[74–76] The reaction occurs preferentially at electron-rich C—H bonds, and alkene aziridination takes place over allylic C—H amination for alkenyl substrates. Catalytic systems based on rhodium have been studied in depth for this reaction. Du Bois and co-workers have extensively studied rhodium-catalyzed C—H amination reactions of benzylic, secondary, and tertiary C—H bonds.[77] Examples of rhodium-catalyzed intramolecular allylic amination through C(sp^3)—H activation are rare.[78–83] However, the chemoselectivity of this reaction is optimized by using tetrakis(2-oxypyridinato)diruthenium(II,III) chloride [$Ru_2(hp)_4Cl$] as the catalyst (Scheme 25).[84] The amination reaction of sulfamate **45** gives allylic sulfonamide product **46** as the major product rather than aziridine product **47**.

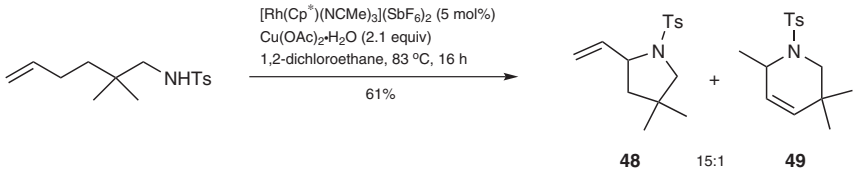
for references see p 34

Scheme 25 Ruthenium-Catalyzed Intramolecular Allylic Amination[84]



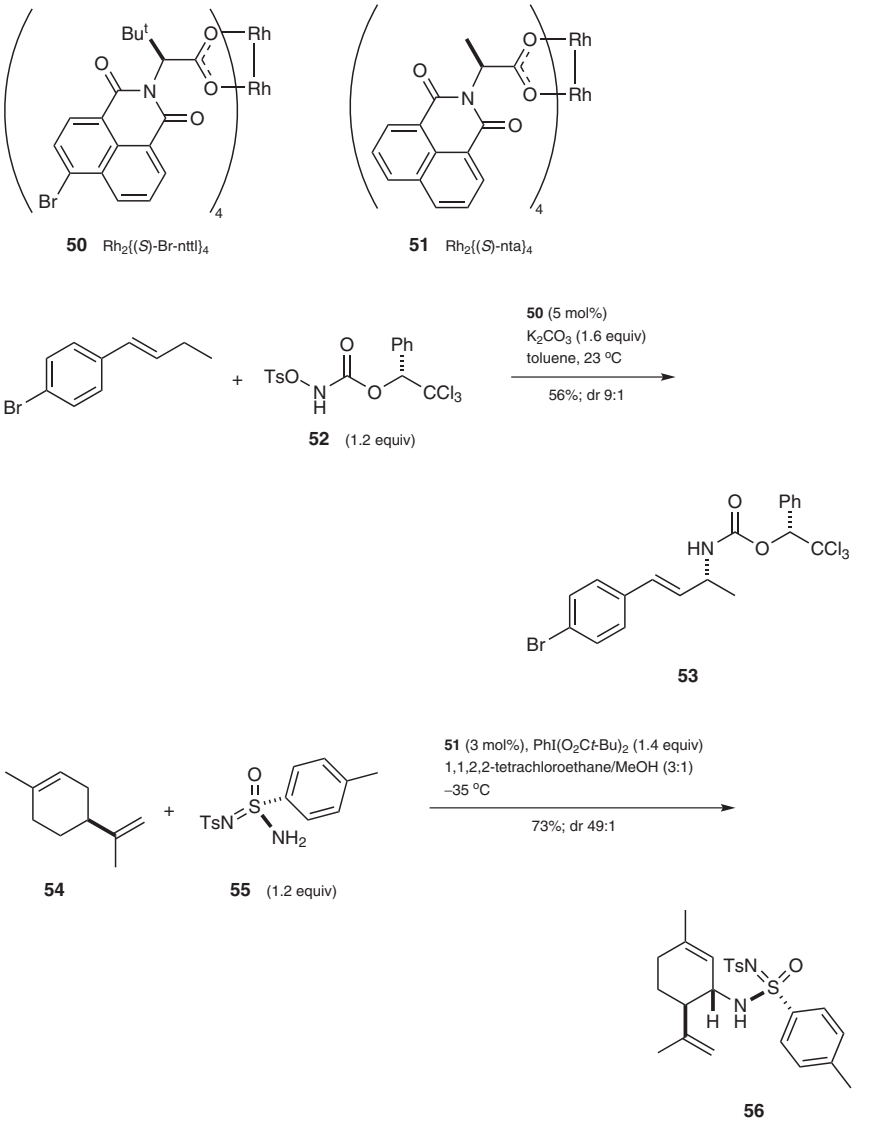
Cossy and co-workers have reported rhodium(III)-catalyzed intramolecular allylic amination using tosylated amines as the nitrogen source (Scheme 26).[85] Cyclic amines such as pyrrolidine **48** can be accessed with high regioselectivity. Mechanistic studies show that a π-allylrhodium complex is formed by allylic C—H activation, and N-metalation occurs to produce a six-membered metallacycle, which leads to pyrrolidine **48** after reductive elimination. Minor product **49** is also formed from allylic C—H amination of the nonterminal alkene carbon atom.

Scheme 26 Rhodium(III)-Catalyzed Allylic Amination[85]



Lebel and co-workers have reported the first stereoselective rhodium-catalyzed intermolecular C—H amination of alkenes to produce chiral allylic amines (Scheme 27).[86] For terminal styrenes, aziridination is the major reaction, whereas for β-substituted styrenes, allylic amination becomes a competitive pathway. In the presence of chiral rhodium catalyst **50** [Rh_2{(*S*)-Br-nttl}$_4$], β-substituted styrenes are aminated with (*R*)-2,2,2-trichloro-1-phenylethyl [(4-toluenesulfonyl)oxy]carbamate (**52**) to give chiral allylic amines such as **53** with high diastereoselectivity. By using sulfonimidamide **55** as the chiral aminating reagent, Dauban and co-workers have demonstrated that (*S*)-limonene (**54**) can be selectively aminated in the presence of chiral catalyst **51** [Rh_2{(*S*)-nta}$_4$] to give product **56** regiospecifically.[87,88] This reaction also affords allylic C—H amination products of terpenes and enol ethers with high regioselectivities, chemoselectivities, and diastereoselectivities.

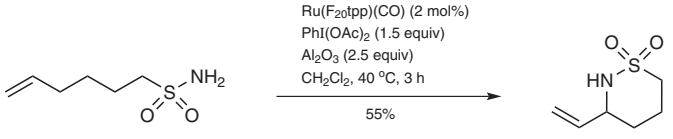
Scheme 27 Rhodium-Catalyzed Intermolecular Allylic Amination[86,88]



With reactivity similar to that of rhodium catalysts, ruthenium catalysts favor the aziridination of alkenes over allylic C—H amination. Che and co-workers have found that hex-5-ene-1-sulfonamide can be intramolecularly amidated to give six-membered cyclic sulfonamide **57** without the formation of any aziridination product (Scheme 28).[89] Similar results have been shown in copper- and dirhodium-catalyzed reactions.[79,90,91]

for references see p 34

Scheme 28 Ruthenium-Catalyzed Allylic Amination[89]

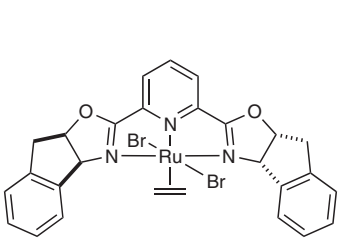


57

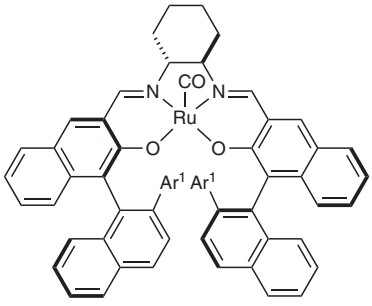
F_{20}tpp = 5,10,15,20-tetrakis(pentafluorophenyl)porphyrinato dianion

Blakey and co-workers have demonstrated two examples of enantioselective allylic C—H bond amination with ruthenium–PyBOX complex **58** as the catalyst (Scheme 29).[92] The allylic amination reaction proceeds with complete selectivity to produce C—H insertion product **60** with excellent enantioselectivity. Katsuki and co-workers have also found that the intermolecular allylic C—H amination reaction can be achieved with chiral ruthenium–salen complex **59** to give allylic [2-(trimethylsilyl)ethyl]sulfonyl-protected amine **61** with excellent enantioselectivity.[93] However, amination at the allylic position is limited to ethyl, methyl, and cyclic methylene groups.

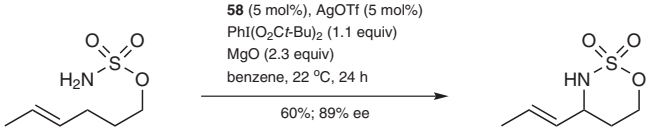
Scheme 29 Ruthenium-Catalyzed Enantioselective Allylic Amination[92,93]



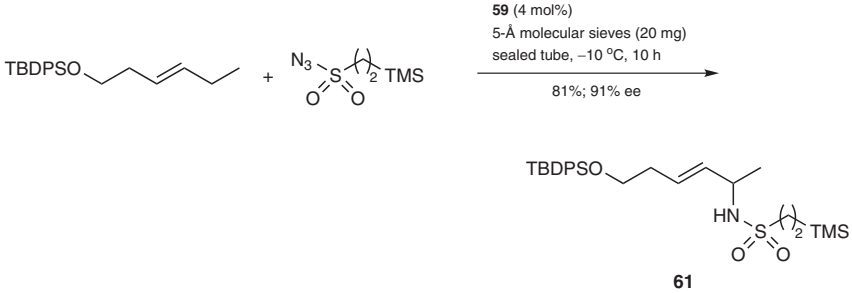
58



59 $Ar^1 = 2,6\text{-}F_2C_6H_3$



60



61

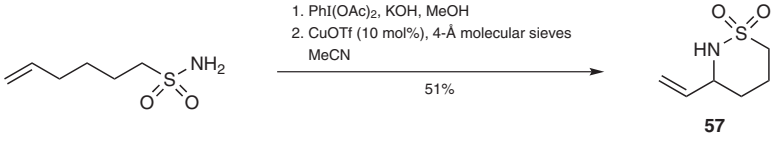
(*E*)-4-(2-Phenylvinyl)-1,2,3-oxathiazinane 2,2-Dioxide (46); Typical Procedure:[84]
A mixture of sulfamate **45** (40.7 mg, 0.17 mmol), powdered 5-Å molecular sieves (60 mg), and $Ru_2(hp)_4Cl$ (2.4 mg, 4.0 μmol) in CH_2Cl_2 (3.5 mL) was stirred for 15 min; then, $PhI(O_2Ct\text{-}Bu)_2$ (97.5 mg, 0.24 mmol) was added in one portion. The deep-red suspension was stirred at 40 °C for 24 h. The mixture was cooled to rt, and the brown suspension was filtered through a short column containing basic alumina layered on top of Celite, eluting with EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, CH_2Cl_2/hexane/EtOAc 15:25:2) to give the title compound as a white solid; yield: 26.9 mg (66%); R_f 0.3 (hexane/EtOAc 3:1).

2.1.2.3 Reaction Using Copper and Iron Catalysts

Copper, iron, and cobalt sometimes show similar properties in catalysis. For example, C—H amination can be achieved with their corresponding nitrenoid complexes.[74] However, for alkene substrates, aziridination reactions dominate over allylic C—H amination reactions, and this reactivity is similar to that observed with rhodium nitrenoids.

Copper-catalyzed allylic C—H amination reactions are rare. Early examples of allylic C—H amination of cyclohexene always occurred in competition with aziridination, and other byproducts were also found.[94–96] Dauban and Dodd have reported the copper-catalyzed aziridination of unsaturated sulfonamides, but only one example of an allylic C—H amination has been demonstrated (Scheme 30).[90,91] Hex-5-ene-1-sulfonamide is intermolecularly amidated to give six-membered cyclic product **57** in 51% yield.

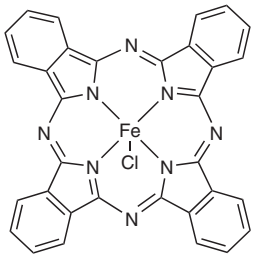
Scheme 30 Allylic Amination with a Copper Nitrenoid[90]



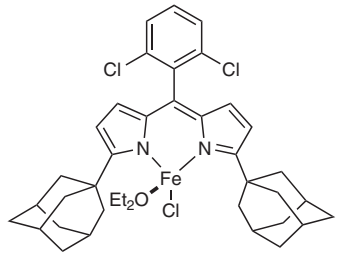
57

Similar reactions with iron complexes have only recently been reported. Paradine and White described the first iron-catalyzed selective C—H amination reaction in which allylic C—H amination is strongly preferred over aziridination of the alkene by using catalyst **62** (Scheme 31).[97] The allylic C—H bond is more reactive than other types of C—H bonds, such as benzylic and alkyl C—H bonds, and this results in the formation of allylic amination product **64** rather than alkyl amination product **65**. Hennessy and Betley have developed an iron-catalyzed direct C—H amination route without the use of an oxidant.[98] Cyclic amine products **66** are formed in moderate to good yields, albeit with low diastereoselectivity, upon exposure of alkyl azides to iron dipyrrinato catalyst **63**.

Scheme 31 Iron-Catalyzed Allylic Amination[97,98]

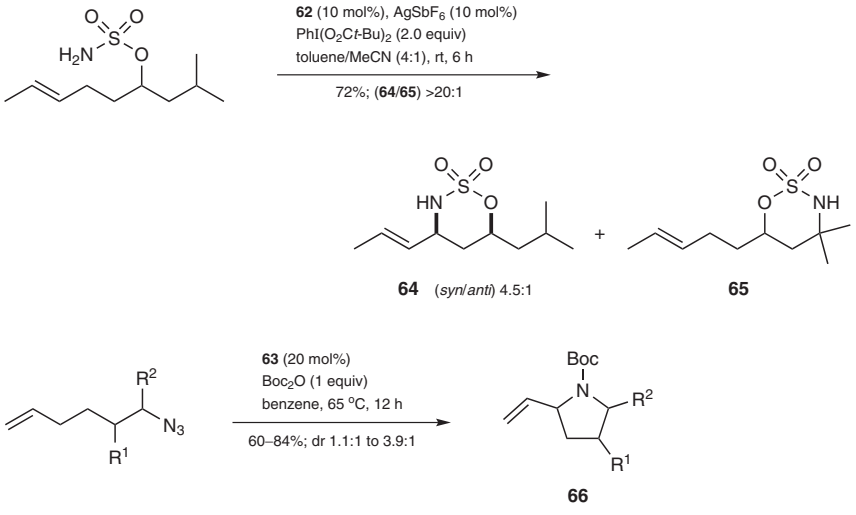


62



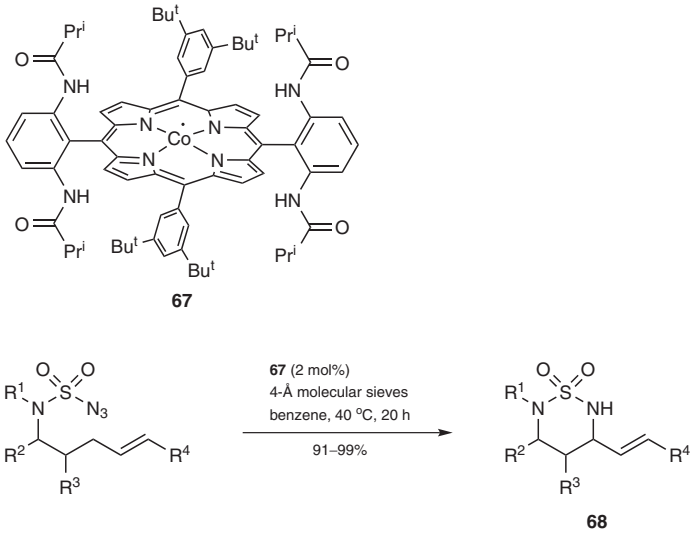
63

for references see p 34



Zhang and co-workers have reported a cobalt-catalyzed intramolecular allylic C—H amination reaction (Scheme 32).[99] With the proper choice of cobalt–porphyrin complex **67**, sulfamoyl azides intramolecularly aminate allylic C—H bonds to produce the corresponding six-membered cyclic sulfamides **68** in excellent yields. Owing to the neutral and nonoxidizing reaction conditions, this reaction tolerates substrates with various functional groups.

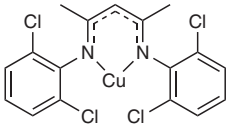
Scheme 32 Cobalt-Catalyzed Allylic Amination[99]



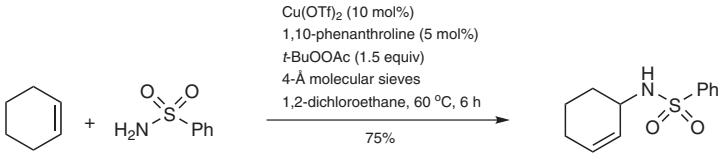
Aza-Kharasch–Sosnovsky-type amination is another intriguing method for allylic amination. Katsuki and Clark, respectively, reported the copper-catalyzed racemic and asymmetric allylic amination of cyclohexene and cyclopentene with *tert*-butyl *N*-(4-toluenesulfonyl)peroxycarbamate, albeit in low yield.[100,101] Because of the modest thermal stability of peroxycarbamates, the acidic *N*-sulfonylamide saccharin can be used in combination

with *tert*-butyl hydroperoxide.[102] Primary and secondary sulfonamides have also been employed for allylic and benzylic amination by Pelletier and Powell (Scheme 33).[103] A benzylic acetate intermediate was isolated, and this was converted into the product under the copper-catalyzed conditions. This observation indicates that allylic amination product **70** is possibly obtained from an allylic acetate, which is generated by copper-promoted allylic oxidation. However, direct amination from the C—H bond cannot be excluded. Warren and co-workers have investigated a series of anilines without strong electron-withdrawing groups on the nitrogen atom for the allylic C—H amination of cyclohexene using catalyst **69**.[104] Electron-poor anilines are favored in the reaction to give products **71** in good to excellent yields.

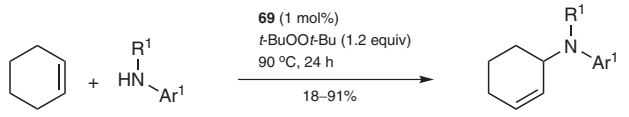
Scheme 33 Copper-Catalyzed Allylic Amination[103,104]



69



(3 equiv) **70**



(10 equiv) **71**

R^1 = H, Me, Et; Ar^1 = Ph, 2-pyridyl, Mes, 4-NCC_6H_4, 4-ClC_6H_4, 2-Tol

A special C(sp^3)—H transformation of allylarenes and alkenes to alkenenitriles has been demonstrated by Jiao and Qin (Scheme 34).[105] Alkenenitriles **74** can be synthesized in moderate to good yields directly from alkenes through cleavage of three C—H bonds. An allylic radical is generated by oxidation by 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone under the assistance of an iron catalyst and is further oxidized to an allylic cation; this is followed by substitution to give allyl azide **72**, which is further oxidized by 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone to give azide-substituted allylic cation **73**. Schmidt-type rearrangement then gives the final products **74**.

for references see p 34