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Synthesis of Saturated Heterocycles via Metal-Catalyzed Alkene Diamination, Aminoalkoxylation, or Dialkoxylation Reactions

Sherry R. Chemler and David A. Copeland

Abstract The development of metal-catalyzed additions of nitrogen and oxygen moieties across alkenes to form saturated nitrogen and oxygen heterocycles is described herein. This chapter covers the most recent advances in osmium and palladium-catalyzed alkene oxidation and amination reactions and also summarizes the emerging areas of copper, iron, and gold-catalyzed alkene oxidations and aminations. In most examples, moderate to excellent levels of diastereoselectivity, either by stereospecific addition across the alkene or substrate-directed diastereocontrol, have been achieved. This enables the synthesis of nitrogen and oxygen-containing heterocycles with predictable control of stereogenic centers. In a few cases, asymmetric catalysis has been achieved, allowing for the synthesis of chiral nitrogen and oxygen-containing heterocycles from achiral substrates. In many of these oxidation reactions, use of pre-oxidized substrates or stoichiometric amounts of added oxidants are required to achieve the catalytic cycles, which frequently involve higher oxidation states of the metal catalysts.

Keywords Alkenes · Aminohydroxylation · Asymmetric catalysis · Copper · Diamination · Dihydroxylation · Gold · Indolines · Iron · Osmium · Palladium · Pyrolidines · Saturated heterocycles · Tetrahydrofurans

Contents

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1 Alkene Diamination

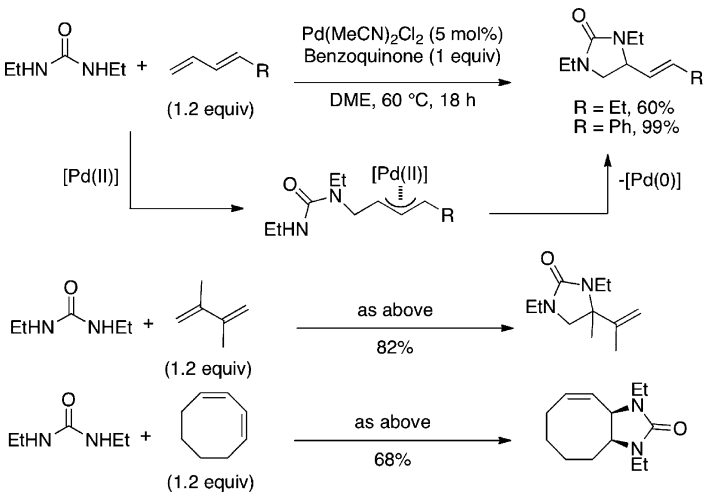
The synthesis of a saturated nitrogen heterocycle and concomitant introduction of two nitrogen functionalities across an alkene can be enabled in a very direct and efficient manner using transition metal catalysis. Alkene diamination, initially explored in the 1970s with stoichiometric metal promoters, has experienced a resurgence of effort in the last decade [1–4]. Transition metals employed to catalyze olefin diamination reactions for the synthesis of saturated heterocyclic compounds include palladium, copper, nickel, and gold (vide infra). Methods for alkene diamination that do not use metals have also been recently developed [5–13], but these reactions fall out of the scope of which will be covered in this chapter. This review will focus on contributions made in the last decade, with emphasis on stereoselective metal-catalyzed alkene diamination protocols.

1.1 Palladium-Catalyzed Alkene Diaminations

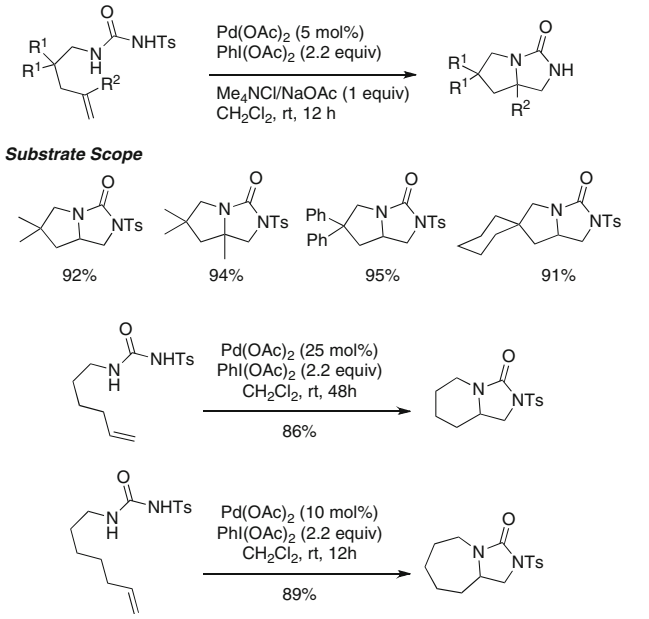
The first Pd-catalyzed alkene diamination was reported in 2005 and enabled the regio- and diasteroselective synthesis of cyclic ureas from conjugated dienes (Scheme 1) [14]. The regioselectivity is thought to result from the required formation of a π-allyl palladium intermediate (Scheme 1). Displacement of [Pd(0)] with the second amine generates the product and oxidation of [Pd(0)] with benzoquinone regenerates the [Pd(II)] catalyst.

That same year, a Pd-catalyzed intramolecular diamination of unactivated, isolated alkenes was reported to occur in the presence of stoichiometric $PhI(OAc)_2$ (2.2 equiv.) [15]. This reaction generated fused 5,5-, 6,5-, and 7,5-bicyclic ureas in high yields from unsaturated *N*-tosylureas (Scheme 2).

A mechanism involving a [Pd(II)]/[Pd(IV)] catalytic cycle was proposed (Scheme 3) [15, 16]. The authors proposed a sequence involving *syn*-aminopalladation, oxidation of [Pd(II)] to [Pd(IV)], N–Pd disassociation and C–N bond formation via S_N2 substitution at carbon. An alternative mechanism that would give the same

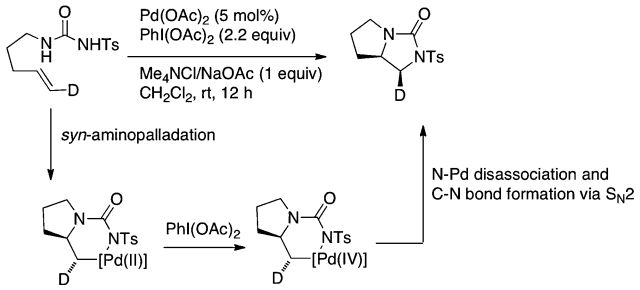


Scheme 1 Pd-catalyzed diamination of conjugated dienes [14]

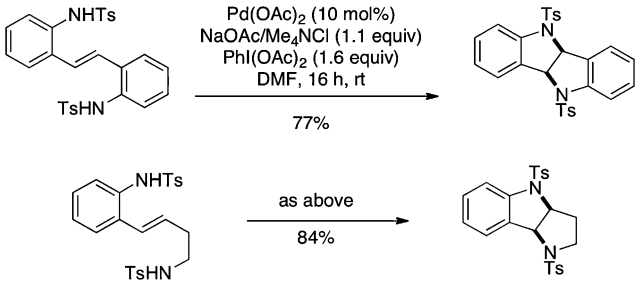


Scheme 2 Pd-catalyzed diamination of isolated alkenes [15]

stereochemical result has been supported by density functional theory (DFT) calculations and entails anti-aminopalladation, N–Pd association, oxidation to Pd(IV) and reductive elimination to give the N–C bond [17].



Scheme 3 Proposed Pd-catalyzed diamination mechanism [15, 16]

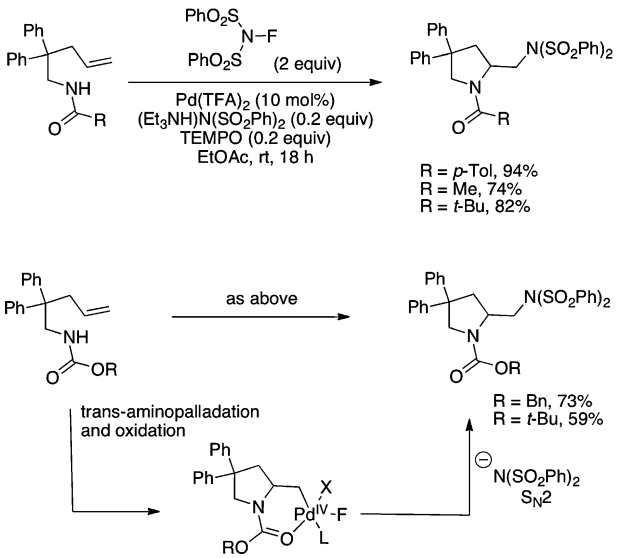


Scheme 4 Diamination of internal alkenes [18]

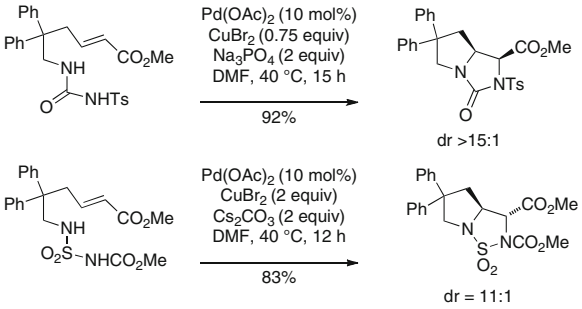
Using a similar protocol, bis-amination of internal alkenes for the synthesis of bisindoles was also achieved (Scheme 4) [18]. It is noteworthy that a metal-free alkene diamination has been reported to occur with similar substrates and reagents to give largely identical products, but in the absence of a palladium catalyst [8].

Other oxidants were subsequently explored to enable the intramolecular Pd-catalyzed alkene diamination. In 2009, a Pd-catalyzed intra/intermolecular diamination that used *N*-fluorobenzenesulfonamide (NFBS) as both the oxidant and external amine source was reported [19]. Both γ-unsaturated amides and carbamates underwent the *exo*-selective reaction in good to excellent yield. A Pd(II)/Pd(IV) catalytic cycle involving *trans*-aminopalladation and C–N formation via S_N2 substitution was also proposed for this alkene diamination sequence (Scheme 5) [19, 20].

Copper(II) bromide has also been used as the stoichiometric oxidant for the Pd-catalyzed diamination of internal acrylates (Scheme 6) [21–23]. Complementary diastereoselectivities were obtained based upon the substrate structure: ureas gave *cis*-substituted cyclic urea products from *trans*-acrylates [23] and sulfamides gave *trans*-substituted cyclic sulfamide products from *trans*-acrylates [22]. In the urea substrate case, the proposed mechanism is *cis*-aminopalladation followed by S_N2 displacement of [Pd], activated by $CuBr_2$. In the sulfamide case, the proposed



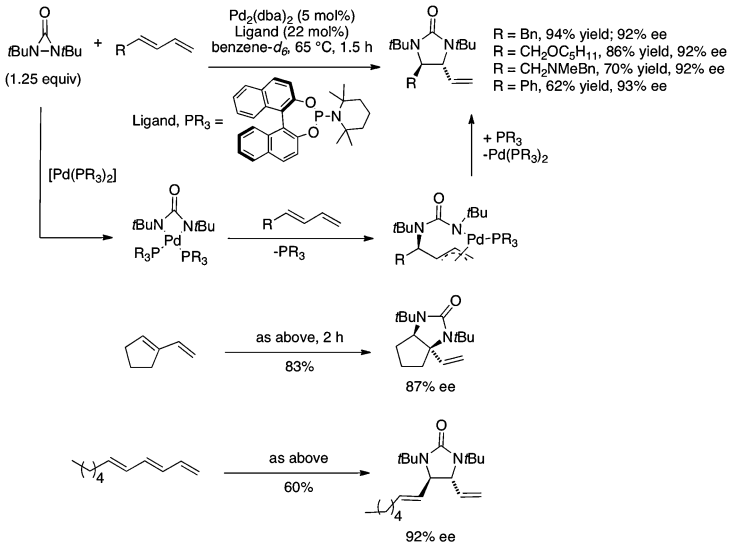
Scheme 5 Pd-catalyzed diamination with NFBS as oxidant [19, 20]



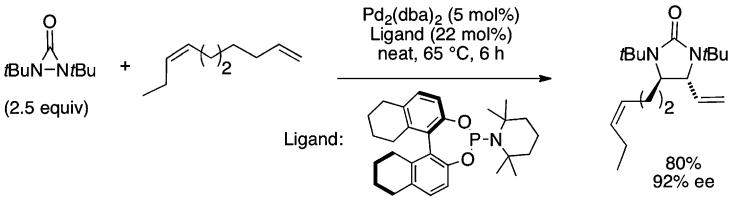
Scheme 6 Pd-catalyzed diamination of acrylates [22, 23]

mechanism is *cis*-aminopalladation, displacement of [Pd] with bromide and subsequent C–N bond formation via bromide displacement.

The catalytic asymmetric alkene diamination has been a long sought-after goal in asymmetric catalysis. The first catalytic enantioselective diamination was reported in 2007. This reaction forms cyclic ureas via Pd-catalyzed intermolecular diamination of conjugated dienes using di-*tert*-butyldiaziridinone as a pre-oxidized diamine source [24]. The reaction is general for alkyl and aryl-substituted dienes and was regioselective for diamination at the more substituted, internal alkene of the diene (Scheme 7). Yields were good to excellent and enantioselectivity levels were generally high. Chiral phosphoramidite ligands proved superior in imparting enantioselectivity to the products. The mechanism involves oxidative addition of



Scheme 7 Pd-catalyzed enantioselective diamination of dienes [24, 25]



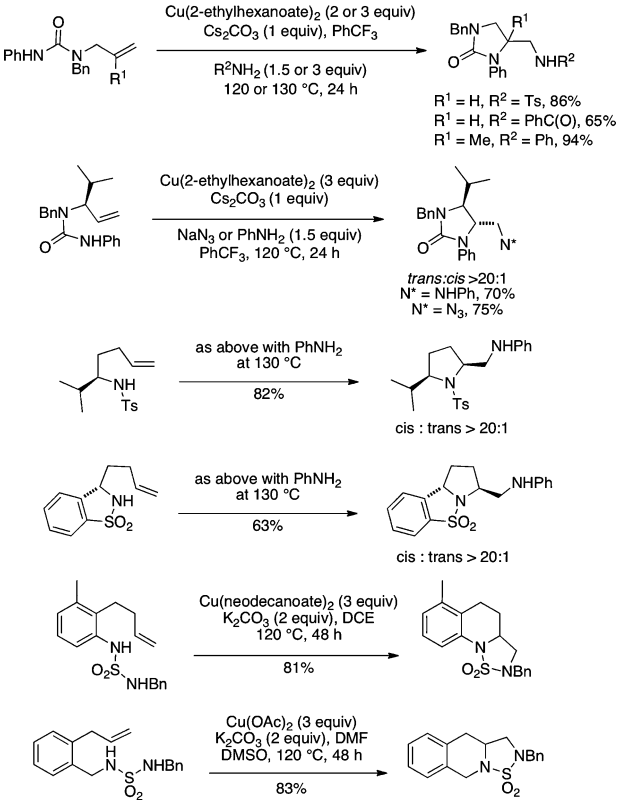
Scheme 8 Catalytic enantioselective C–H diamination [26]

Pd(0) into the N–N bond of the diaziridinone, addition of the N–Pd(II) complex to the internal alkene of the diene and concomitant π-allyl Pd formation and finally C–N bond formation via Pd(0) displacement (Scheme 7) [25].

This method was further advanced by the demonstration that the diene could be formed in situ from terminal alkenes (Scheme 8) [26]. This C–H diamination reaction could be performed neat and provided similar products to those shown in Scheme 7 (vide supra).

1.2 Copper-Catalyzed Alkene Diaminations

Since 2005, the diamination of alkenes has been similarly pursued using less expensive copper complexes as reaction promoters and catalysts [27]. Highly diastereoselective intra/intramolecular and intra/intermolecular copper(II)-promoted alkene diaminations have enabled the synthesis of pyrrolidines and indolines from



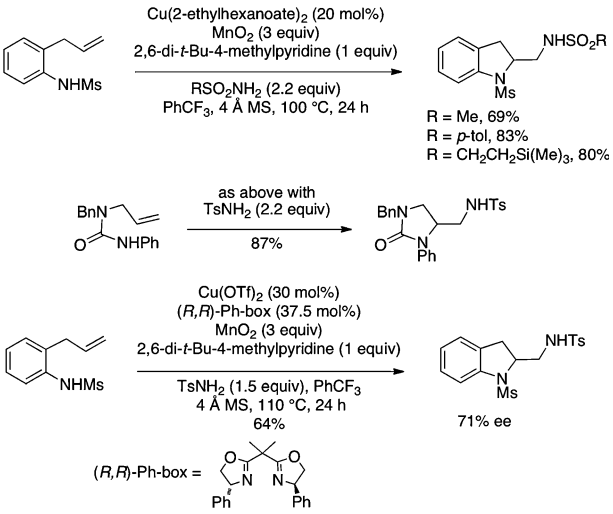
Scheme 9 Copper(II)-promoted alkene diaminations [27–29]

unsaturated sulfamides, sulfonamides, amides, and ureas (Scheme 9) [27–29]. Some examples of tetrahydroisoquinoline-forming diaminations have also been reported (Scheme 9). The reactions were performed with $Cu(OAc)_2$ [27], $Cu(neodecanoate)_2$ [28], and $Cu(2\text{-ethylhexanoate})_2$ [29] as reaction promoter. Reactions with $Cu(2\text{-ethylhexanoate})_2$ in $PhCF_3$ generally proved most efficient [29].

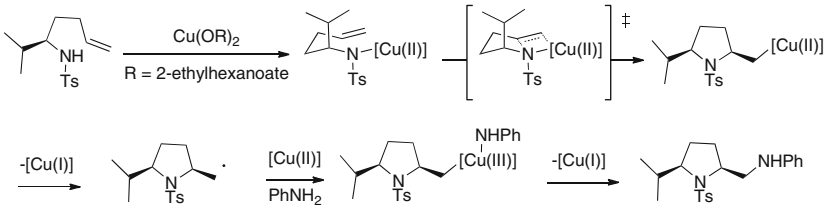
The intra/intermolecular alkene diamination was rendered catalytic in [Cu(II)] with sulfonamides as the intermolecular amine component and MnO_2 (3 equiv.) as the stoichiometric oxidant (Scheme 10) [29]. A promising catalytic enantioselective intra/intermolecular alkene diamination using [Cu((*R*,*R*)-Ph-box)]$(OTf)_2$ as the catalyst was also reported (Scheme 10).

The reaction mechanism, based on reaction diastereoselectivity and isotopic labeling studies [29], is thought to involve *cis*-aminocupration, homolysis of the resulting C–[Cu(II)] bond, addition of the resulting carbon radical to [Cu(II)], amine coordination and reductive elimination of the [Cu(III)] intermediate to form the new C–N bond and [Cu(I)] (Scheme 11). In the catalytic reactions, MnO_2 is thought to oxidize the extruded [Cu(I)] back to [Cu(II)] [29].

In 2012, more electron-rich unsaturated amidine substrates were shown to undergo copper-catalyzed intramolecular alkene diamination to form bi- and



Scheme 10 Cu(II)-catalyzed intra/intermolecular diamination [29]



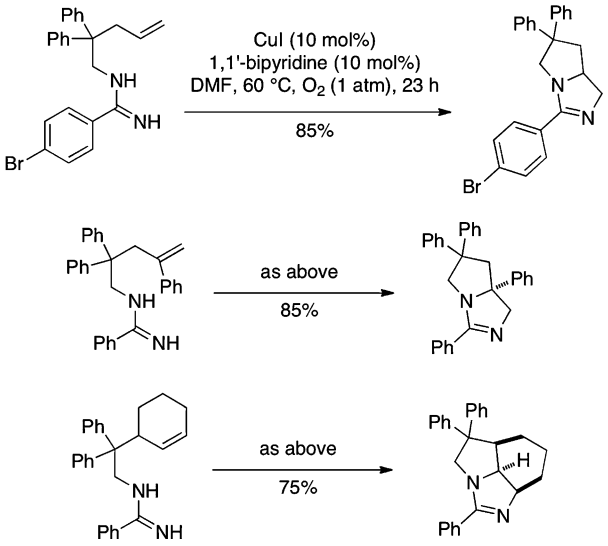
Scheme 11 Proposed mechanism of the Cu(II)-promoted alkene diamination [29]

tricyclic amidines (Scheme 12) [30]. Both terminal and internal alkenes underwent the reaction efficiently.

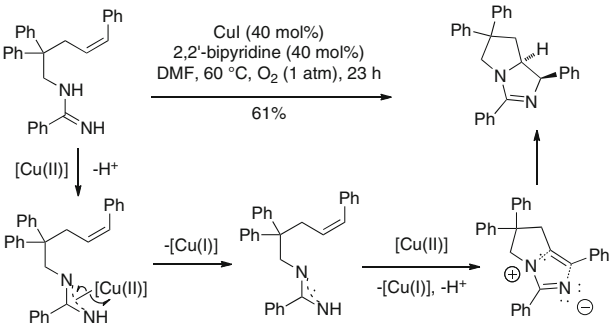
The proposed mechanism, consistent with product diastereoselectivity, involves two-electron oxidation of the amidine followed by a concerted [3+2]-type annulation (Scheme 13) [30].

The copper-catalyzed intermolecular diamination of terminal alkenes and conjugated dienes has been reported for the synthesis of cyclic ureas, sulfamides, and guanidines, where diaziridinones, thiadiaziridines, and (cyanimino)-diaziridines, respectively, were used as both diamine source and oxidant (Scheme 14) [31–34]. A catalytic, enantioselective diamination (up to 74% ee) of the terminal alkene of conjugated dienes was achieved [35, 36], making the method complementary to analogous Pd-catalyzed diene diaminations (vide supra, Sect. 1.1).

It was further found that depending upon the substrate and catalyst structure, the regioselectivity in the diamination of conjugated dienes can be tuned for either the internal or terminal alkene of the diene (compare Schemes 14 and 15) [33, 38]. Mechanistically, it was determined that the diamination can occur via a more



Scheme 12 Cu-catalyzed diamination of unsaturated amidines [30]

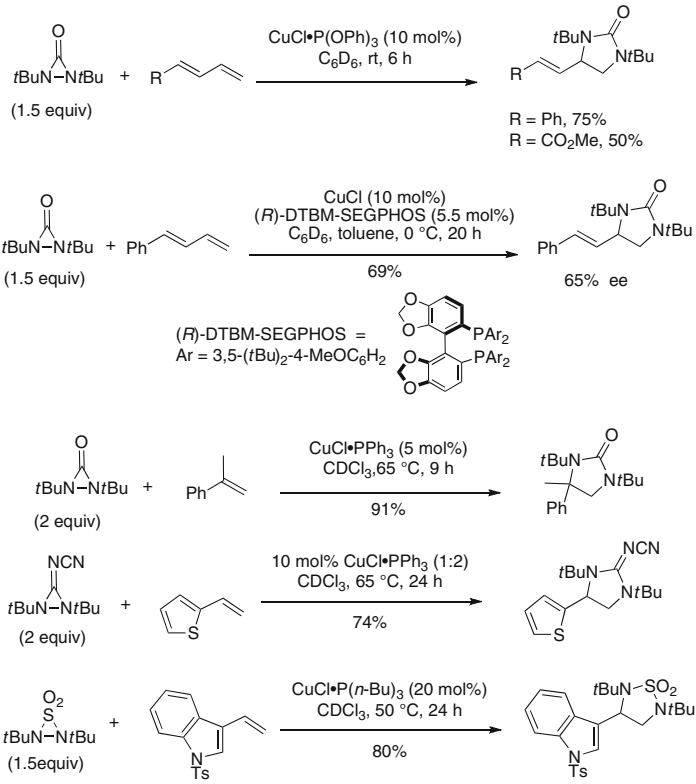


Scheme 13 Proposed mechanism for the unsaturated amidine diamination [30]

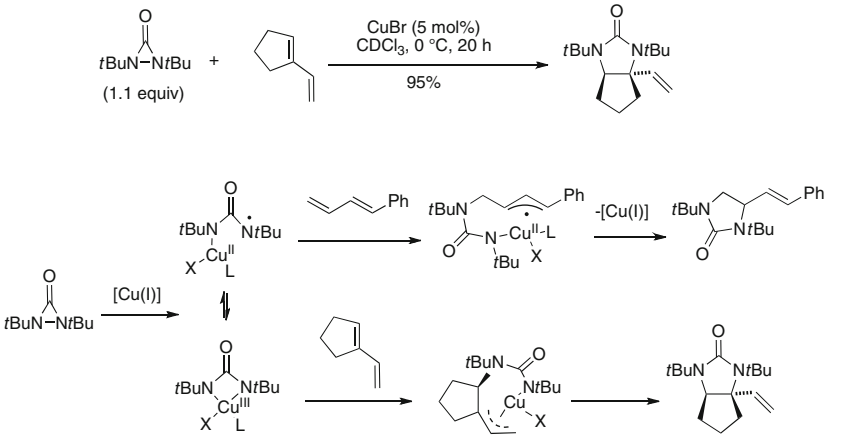
radical-type mechanism, selective for the terminal alkene, or via a more electrophilic, Cu(III)-type mechanism, selective for the internal alkene (Scheme 15) [33].

1.3 Nickel-Catalyzed Alkene Diaminations

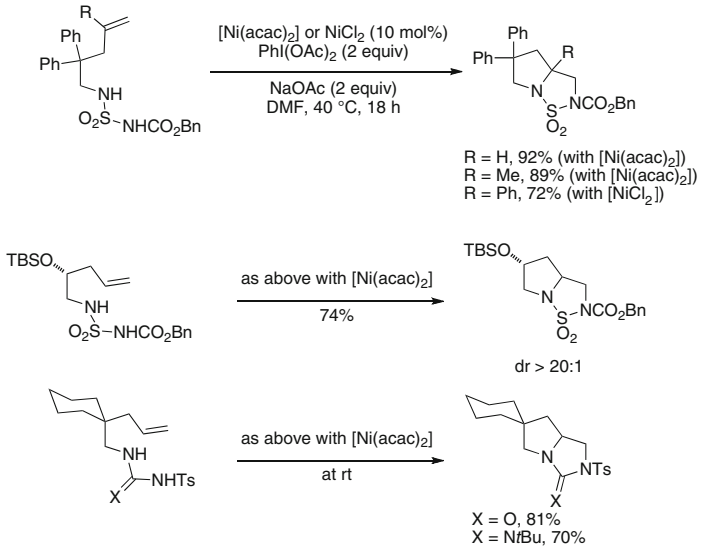
Nickel complexes have been used to catalyze the intramolecular diamination of unsaturated sulfamides, ureas, and guanidines (Scheme 16) [4, 39]. Terminal and 1,1-disubstituted alkenes underwent the reaction with good efficiency, and $PhI(OAc)_2$ was used as the stoichiometric oxidant.



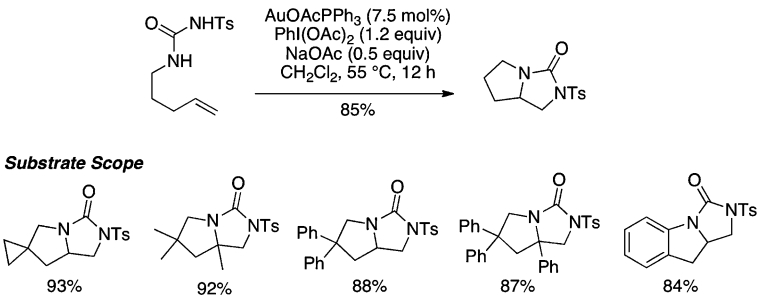
Scheme 14 Copper-catalyzed diamination of alkenes and dienes [31, 32, 34, 35, 37]



Scheme 15 Regioselectivity and mechanism of the copper-catalyzed diamination of dienes [33, 38]



Scheme 16 Nickel-catalyzed intramolecular alkene diamination [4, 39]

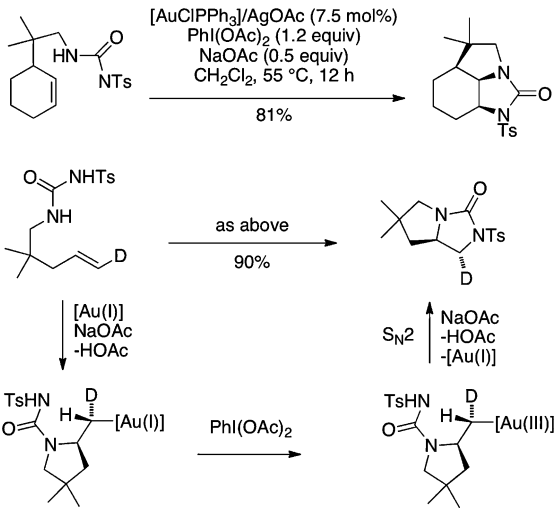


Scheme 17 First Au-catalyzed alkene diamination [40]

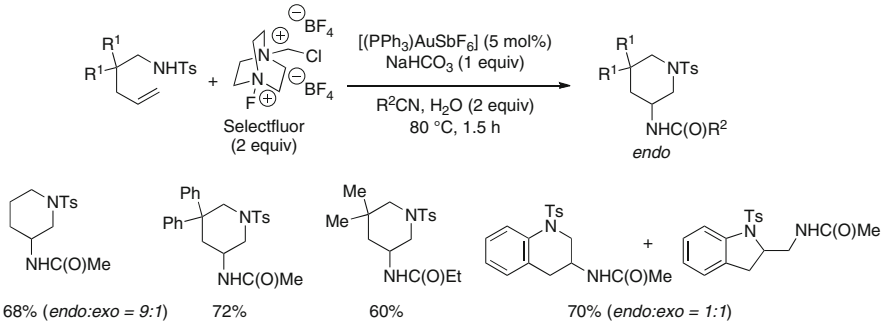
1.4 Gold-Catalyzed Alkene Diaminations

Gold-catalyzed alkene diamination was first reported in 2009 [40]. This *exo*-selective reaction provided 5,5-fused bicyclic ureas from terminal and 1,1-disubstituted γ-alkenyl-*N*-tosylureas in high yields (Scheme 17).

One example of a net *cis*-diamination of an internal alkene was also presented (Scheme 18). These reactions require $PhI(OAc)_2$ (1.2 equiv.) as stoichiometric oxidant and an Au(I)/Au(III) catalytic cycle was proposed (Scheme 18). The product stereochemistry is consistent with *trans*-aminoauration followed by S_N2 displacement of [Au(III)] by the second amine moiety.



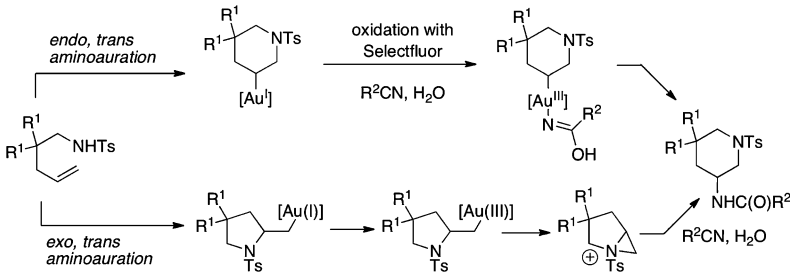
Scheme 18 Proposed Au-catalyzed diamination mechanism [40]



Scheme 19 *Endo*-selective Au-catalyzed diamination [41]

A complementary, largely *endo*-selective Au-catalyzed alkene diamination reaction was reported in 2011 (Scheme 19) [41]. In this reaction, Selectfluor (2 equiv.) was used as the stoichiometric oxidant to enable the Au(I)/Au(III) catalytic cycle. Nitriles served as the source of the second (external) amine nucleophile, providing amide-functionalized piperidine products.

Two possible mechanistic scenarios were proposed (Scheme 20). In the first, *endo*-selective *trans*-aminoauration followed by Au(I)/Au(III) oxidation, nitrile complexation, hydration and reductive elimination provide the piperidine product. In the second, *exo*-selective (or possible *endo*-selective) *trans*-aminoauration followed by Au(I)/Au(III) oxidation and intramolecular S_N2 displacement provide



Scheme 20 Mechanistic alternatives for the *endo*-selective Au-catalyzed diamination [41]

an aziridinium ion intermediate that can undergo S_N2 attack by the nitrile via a Ritter-type mechanism [41].

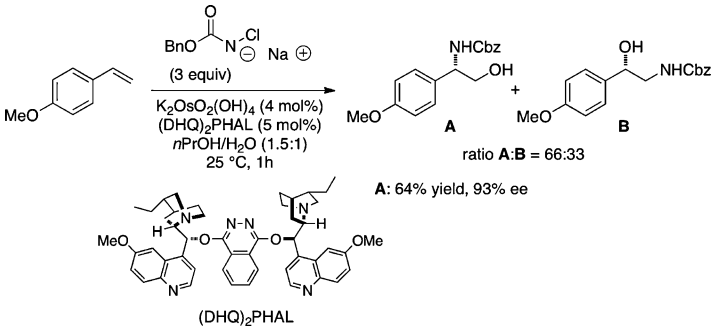
2 Alkene Aminoalkoxylation

Metal-catalyzed alkene aminoalkoxylation reactions furnish various nitrogen and oxygen-containing heterocycles directly and oftentimes stereoselectively. The development of a number of aminoalkoxylation methods has been reviewed [42–45]. While numerous diastereoselective metal-catalyzed ring-forming alkene aminoalkoxylations have been reported (vide infra), catalytic enantioselective alkene aminoalkoxylations are more rare. The synthesis of chiral nitrogen heterocycles with good to excellent levels of enantiomeric excess from achiral alkene substrates is an active and growing topic of asymmetric catalysis (vide infra). It should be noted that a number of aminoalkoxylation reactions promoted by hypervalent iodine species and other non-metal containing compounds have also been reported recently but are outside the scope of this review [6, 46–52].

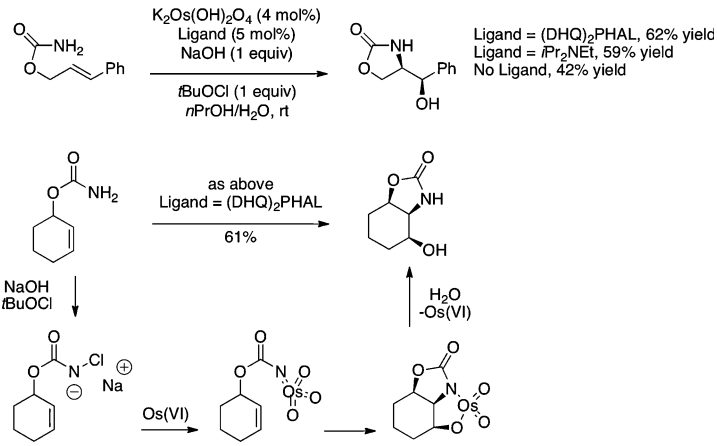
2.1 Osmium-Catalyzed Alkene Aminoalkoxylation

Perhaps the most developed diastereoselective ring-forming alkene aminoalkoxylation method is the osmium-catalyzed tethered aminohydroxylation [43, 53]. In these reactions, both high cyclic and acyclic diastereocontrol has been achieved (vide infra). The tethered alkene aminohydroxylation reaction was introduced in response to a perceived need to better control the regioselectivity of an intermolecular Os-catalyzed alkene aminohydroxylation process (Scheme 21) [44, 54].

The tethered aminohydroxylation reaction involves regiospecific, diastereoselective intramolecular addition of an amine to a pendant olefin and concomitant introduction of an alcohol from an exogenous hydroxyl source, e.g. H_2O. It was initially introduced in 2001 and involved the cyclization/aminohydroxylation of



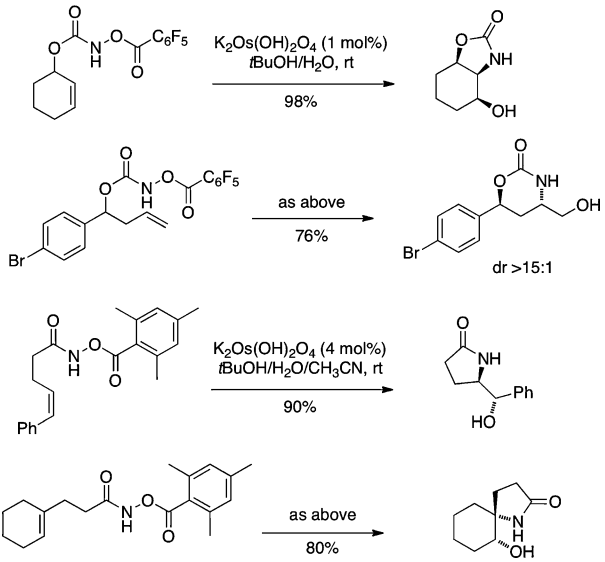
Scheme 21 Intermolecular catalytic enantioselective aminohydroxylation [54]



Scheme 22 Tethered aminohydroxylation range and mechanism [55, 56, 58]

allylic carbamates (Scheme 22) [55, 56]. The use of a chiral $(DHQ)_2PHAL$ ligand improved the reaction yield with some substrates but, unlike in the intermolecular aminohydroxylation shown in Scheme 21, did not render the reactions enantioselective. The reoxidant for this reaction is the *N*-chlorocarbamate salt, formed in situ from reaction of *t*-BuOCl and the primary carbamate in the presence of NaOH. The mechanism is thought to involve formation of Os(VIII) from Os(VI) and intramolecular [3+2] cycloaddition followed by osmate ester hydrolysis (Scheme 22). Under these reaction conditions, chlorination of the alkene could become a competing process and the lifetime of the chlorocarbamate could be short, requiring excess of the carbamate and reagents to be used at times [57].

To address the drawbacks presented by the chlorocarbamate intermediate, improvements were made to the reaction. The first improvement involved the use of hydroxycarbamate derivatives that eliminated the need for additional oxidant (Scheme 23) [57, 59]. External ligand was also no longer required in these



Scheme 23 Pre-oxidized substrates in the tethered aminohydroxylation [57, 59, 60]

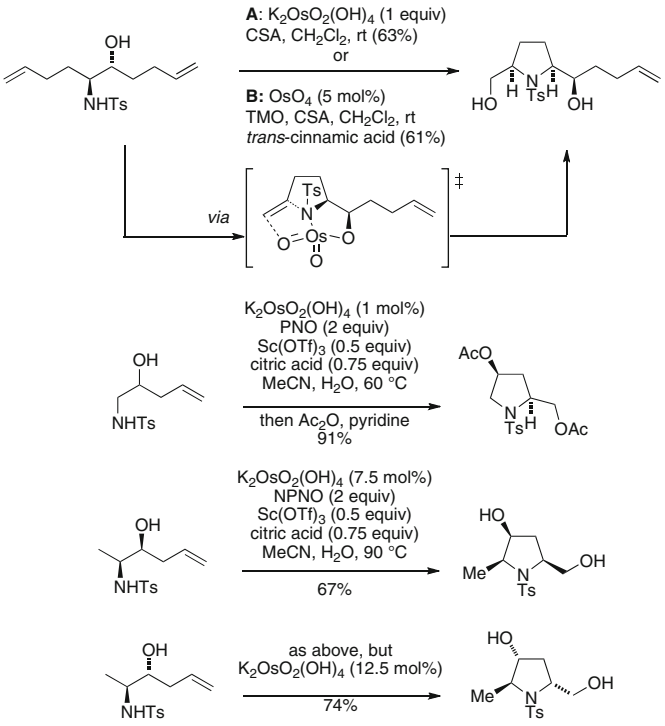
reactions, and different hydroxylamine groups were optimal for different kinds of substrates, e.g. carbamates vs amides (Scheme 23).

Subsequently, an experiment using stoichiometric Os(VI) in a tethered alkene aminohydroxylation revealed that the Os(VI) oxidation state is capable of promoting the reaction (Scheme 24) [61]. This enabled the development of a second process improvement involving the use of vicinal hydroxyl-functionalized secondary carbamate and sulfonamide substrates that could employ dual chelation to Os(VI) and the use of more mild oxidants, trimethylamine *N*-oxide (TMO), pyridine *N*-oxide (PNO), and *p*-nitropyridine *N*-oxide (NPNO), used in the presence of Bronsted and Lewis acid catalysts, to enable the reoxidation of Os(IV) to Os(VI) [61–63].

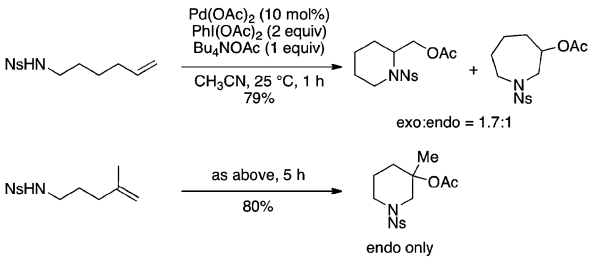
2.2 Palladium-Catalyzed Alkene Aminoalkoxylation

A number of Pd-catalyzed alkene aminoalkoxylation reactions that result in the formation of nitrogen and oxygen heterocycles, e.g., pyrrolidines and tetrahydrofurans, were reported from 2005 to 2010 [64–67]. Higher oxidation state organopalladium intermediates were invoked in the majority of the proposed reaction mechanisms (vide infra). In these examples added oxidant was essential to enabling cycles catalytic in Pd(II), and ones that avoided potentially competing β-hydride elimination pathways.

Two novel methods for intramolecular palladium-catalyzed alkene aminoalkoxylation were independently reported in 2005 [64, 65]. The first method involved

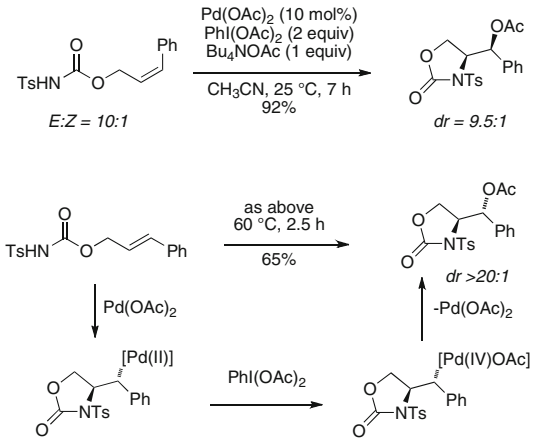


Scheme 24 Diastereoselective pyrrolidine synthesis [61–63]

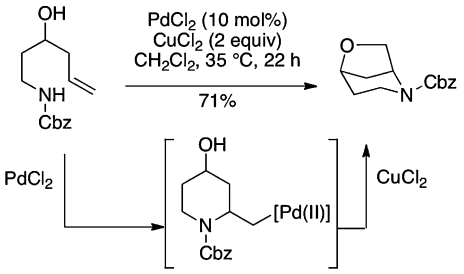


Scheme 25 Regioselectivity of Pd-catalyzed aminoacetoxylation [64]

the use of $PhI(OAc)_2$ (2 equiv.) as the stoichiometric oxidant and the reaction was performed at rt in CH_3CN using catalytic $Pd(OAc)_2$ [64]. Regioselectivity (*exo* vs *endo*) in the cyclization reaction was largely dependent upon the substrate's structure; *N*-tosylamides and *N*-tosylcarbamates cyclized onto pendant alkenes with high *exo*-selectivity, while an *N*-sulfonylalkyl-enes cyclized with poor regioselectivity in the case of monosubstituted alkenes and with *endo* selectivity in the case of 1,1-disubstituted alkenes (Scheme 25).



Scheme 26 Diastereoselectivity and mechanism [64]

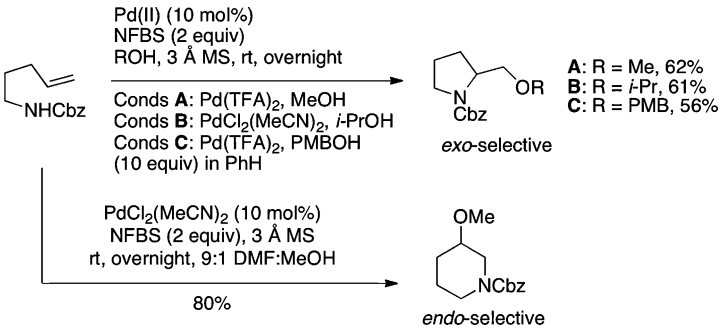


Scheme 27 Doubly intramolecular aminoalkoxylation [65]

E- and *Z*-phenyl-substituted internal alkenes underwent highly *exo*-selective Pd-catalyzed aminoacetoxylations; these reactions also occurred with high stereospecificity (Scheme 26). Based on the observed diastereoselectivity, a catalytic cycle involving *trans*-aminopalladation, oxidation of Pd(II) to Pd(IV) with $PhI(OAc)_2$ and subsequent reductive elimination was proposed (Scheme 26). In 2006, an entirely intermolecular alkene aminoacetoxylation was subsequently reported to occur under similar reaction conditions [68].

A second Pd-catalyzed aminoalkoxylation published in 2005 involved *exo* cyclization of a 3-hydroxy-5-hexenylcarbamate at 35°C in CH_2Cl_2 in the presence of catalytic $PdCl_2$ and $CuCl_2$ (2 equiv.) as the stoichiometric oxidant (Scheme 27) [65]. This aminoalkoxylation is doubly intramolecular since the substrate's hydroxyl group serves as the oxygen source for the terminal alkene carbon. The mechanism is thought to involve aminopalladation followed by $CuCl_2$-assisted oxidative C–O bond formation.

An intra/intermolecular Pd-catalyzed alkene aminoalkoxylation using alcohol solvents as the oxygen source and *N*-fluorobenzenesulfonamide (NFBS) as the oxidant



Scheme 28 Complementary regioselective aminoalkoxylations [66]

(2 equiv.) was reported in 2010 [66]. This reaction gave excellent *exo*-selectivity and moderate yields of ether-substituted pyrrolidines using $Pd(TFA)_2$ or $PdCl_2(MeCN)_2$ as catalyst, depending upon the nucleophilic alcohol (Scheme 28). Interestingly, the selectivity could be switched in favor of the *endo* regioisomer when the reaction was performed with $PdCl_2(MeCN)_2$ as catalyst in the polar solvent DMF (Scheme 28).

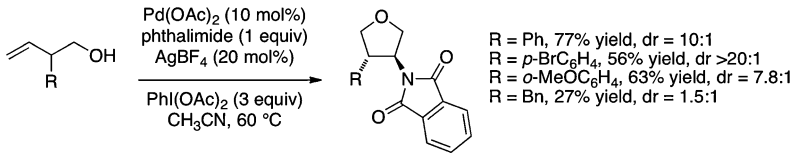
The authors proposed *exo*-selective aminopalladation, oxidation of the resulting organopalladium(II) intermediate to a Pd(IV) species and subsequent nucleophilic displacement with external alcohol to be the operating mechanism [66]. In the case of the *endo*-selective reactions, the authors speculated an intermediate aziridinium ion is formed by intramolecular displacement (neighboring group participation) of Pd(IV). Preferential attack at the more substituted carbon then provides the piperidine product [66].

A more unusual, tetrahydrofuran-forming inter/intramolecular Pd-catalyzed aminoalkoxylation of homoallylic alcohols was reported in 2007 [67]. In this reaction, $Pd(OAc)_2$ (10 mol%) served as catalyst, $PhI(OAc)_2$ (3 equiv.) was the oxidant and $AgBF_4$ (20 mol%) as additive improved the reaction efficiency. The reaction was generally diastereoselective, favoring formation of 3,4-anti-disubstituted tetrahydrofurans (Scheme 29). The reaction was more efficient with aryl rather than alkyl substituents at the substrate's allylic position.

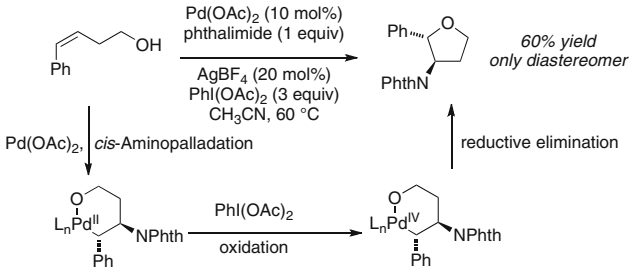
The proposed reaction mechanism, based upon observed product stereochemistry, involves *cis*-aminopalladation to give a tethered organopalladium(II) intermediate, Pd(II) to Pd(IV) oxidation with $PhI(OAc)_2$, and subsequent reductive elimination to form the C–O bond (Scheme 30).

2.3 Gold-Catalyzed Aminoalkoxylation

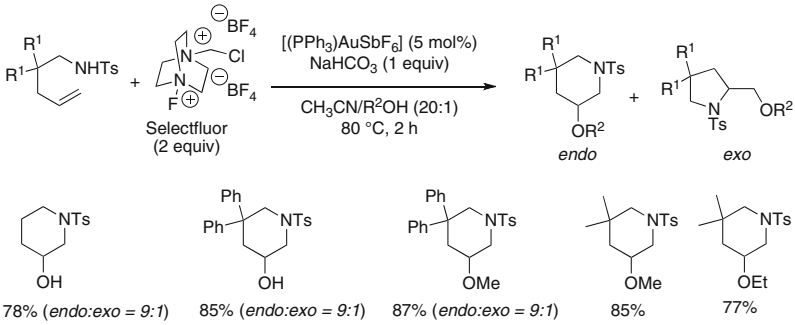
The regioselective synthesis of piperidines from 4-pentenylsulfonamides via gold-catalyzed aminoalkoxylation in the presence of Selectfluor as stoichiometric oxidant was reported in 2011 [41]. The reaction occurred with high *endo* regioselectivity and was most efficient for terminal alkenes. Both alcohols and ethers were formed, depending on the reaction solvent (Scheme 31).



Scheme 29 Tetrahydrofuran-forming aminoalkoxylation [67]



Scheme 30 Proposed mechanism of the Pd-catalyzed aminoalkoxylation [67]

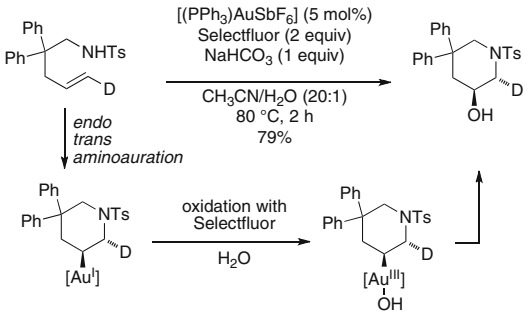


Scheme 31 Au-catalyzed aminoalkoxylation scope [41]

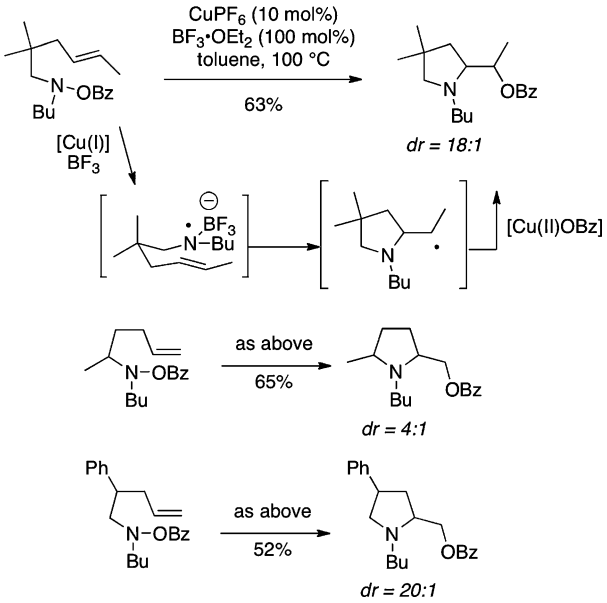
The mechanism, supported by isotopic labeling studies, is thought to involve *endo*-selective anti-aminoauration followed by oxidation of the organo-Au(I) intermediate to an organo-Au(III) intermediate and reductive elimination to secure the C–O bond (Scheme 32).

2.4 Copper-Catalyzed Ring-Forming Alkene Aminoalkoxylation

A number of copper-catalyzed alkene aminoalkoxylations have been reported. A range of reaction mechanisms and copper oxidation states have been invoked in these diverse transformations where the substrate structure, reagents, and copper catalysts largely dictate the reaction pathway.



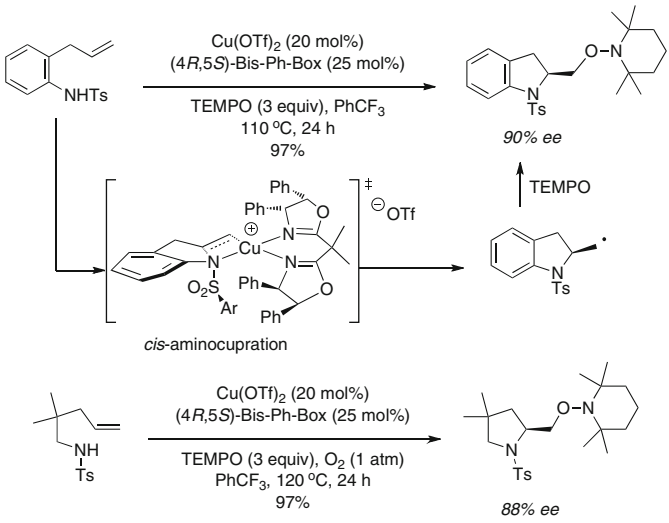
Scheme 32 Proposed mechanism involves an Au(I)/Au(III) cycle [41]



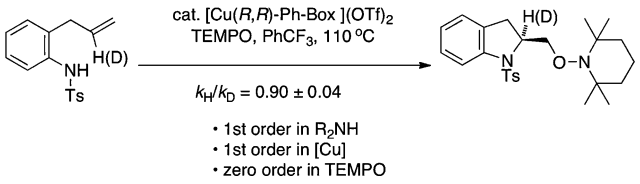
Scheme 33 Regioselective and diastereoselective alkene oxyamination [69]

The first copper-catalyzed alkene aminoalkoxylation for the synthesis of pyrrolidines from 4-pentenyl-*O*-benzoyl-hydroxylamines was reported in 2002 (Scheme 33) [69]. The reaction was largely regioselective (*endo* vs *exo* cyclization) and diastereoselective. A mechanism involving Cu(I)-catalyzed nitrogen radical formation, addition to the alkene and subsequent Cu(II)-assisted benzoylation of the resulting carbon radical was proposed.

The first catalytic enantioselective intramolecular alkene aminoalkoxylation was reported in 2008 [70]. Chiral indolines and pyrrolidines were synthesized from γ-alkenylsulfonamides using catalytic [Cu((4*R*,5*S*)-di-Ph-Box)]$(OTf)_2$ in the presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) as alkoxyl source and O_2 (1 atm, balloon) as oxidant (Scheme 34) [70]. Removal of the *N*-sulfonyl group



Scheme 34 Enantioselective copper(II)-catalyzed aminoalkoxylation [70]



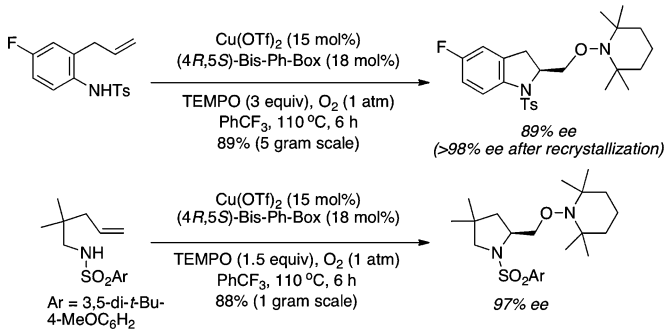
Scheme 35 Kinetic analysis of the enantioselective aminoalkoxylation [71]

and either N–O reduction to the corresponding alcohol or N–O oxidation to the corresponding aldehyde was demonstrated. A mechanism involving *cis*-aminocupration [Cu(II) oxidation state] across the alkene via a chair-like transition state, subsequent C–[Cu(II)] homolysis and direct quenching of the resulting carbon radical with TEMPO was proposed [70, 71].

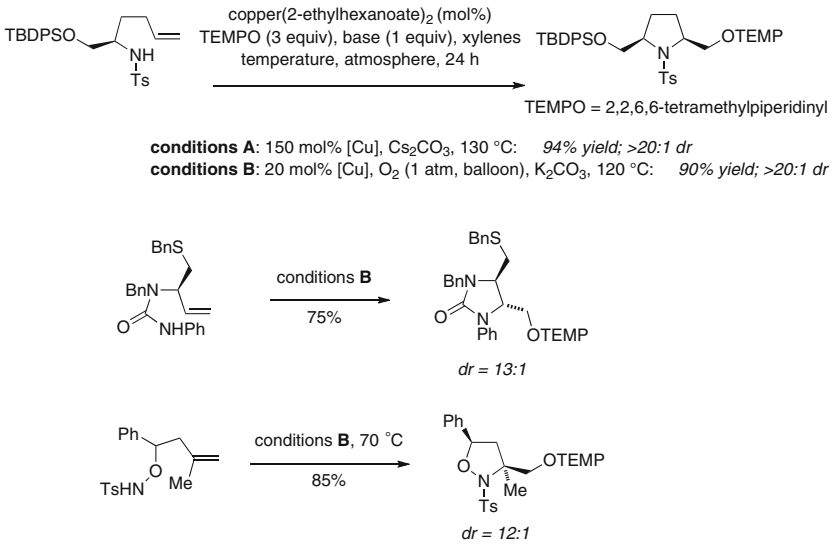
The copper-catalyzed enantioselective aminooxygenation reaction mechanism was further probed using kinetics and isotope effect studies [71]. The reaction was found to be first order in [Cu], first order in amine substrate and zero order in TEMPO. These data, along with an inverse secondary kinetic isotope effect (see Scheme 35), supported the alkene addition as the rate-determining step of the reaction.

The enantioselective aminoalkoxylation was subsequently optimized for catalyst loading, time and enantioselectivity, and was demonstrated on a multigram scale (Scheme 36) [71, 72].

The copper(II) 2-ethylhexanoate-catalyzed and promoted diastereoselective synthesis of disubstituted pyrrolidines [73], cyclic ureas [74], and isoxazolidines



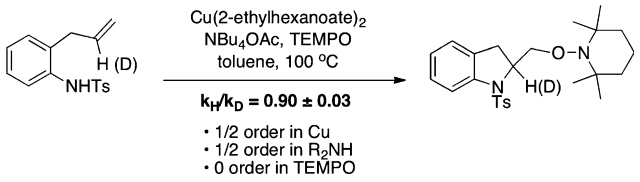
Scheme 36 Multigram scale optimized aminooxygenation reactions [71, 72]



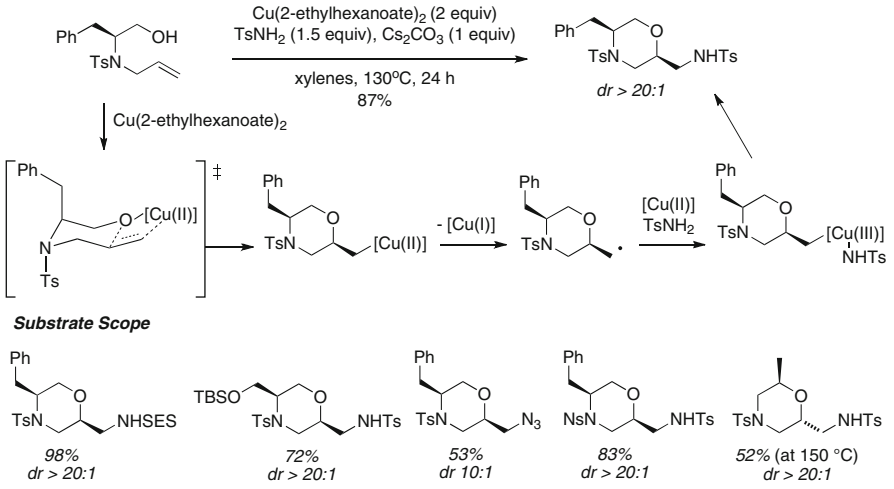
Scheme 37 Diastereoselective copper(II)-catalyzed aminoalkoxylations [73–75]

[75] via alkene aminoalkoxylation has also been reported. The copper(II) acetate-promoted aminoxygenation of alkenylimines and amidines has also been described [76]. Representative examples are shown in Scheme 37.

An in-depth mechanistic analysis of the indoline-forming copper(II) 2-ethylhexanoate-promoted aminooxygenation revealed the reaction is 1/2 order in [Cu], 1/2 order in sulfonamide substrate, and zero order in TEMPO (Scheme 38) [77]. The kinetics are consistent with involvement of a pre-equilibrium step wherein the copper(II) carboxylate dimer is converted to a monomeric species upon complexation with the sulfonamide. An inverse secondary KIE was observed in the alkene addition step, supporting its role as the rate-determining step of the reaction. The existence and viability of an R_2N–[Cu(II)] intermediate along the reaction pathway was supported by reaction kinetics and EPR spectroscopy.



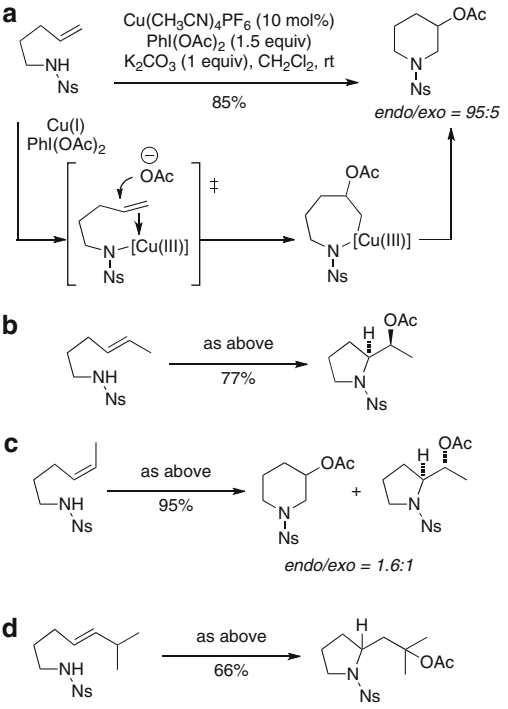
Scheme 38 Kinetic analysis of the copper(II)-promoted aminoalkoxylation [77]



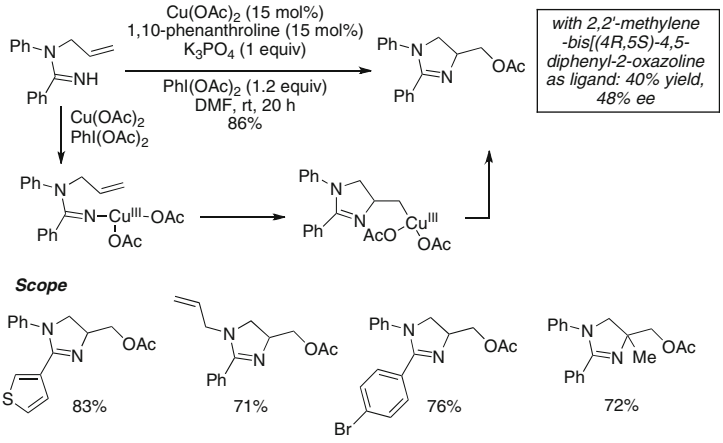
Scheme 39 Morpholine-forming aminoalkoxylation mechanism and scope [78]

The diastereoselective synthesis of morpholines via a copper(2-ethylhexanoate)$_2$-promoted alkene oxyamination was reported in 2012 (Scheme 39) [78]. The oxyamination is a less common transformation; it is thought to initiate with *cis*-oxycupration across the alkene in analogy with a recently reported alkene carboetherication reaction [78, 79]. Homolysis of the carbon–copper(II) bond followed by recombination of the carbon radical with copper(II) in the presence of a primary sulfonamide provides a transient organocopper(III) intermediate that, upon reductive elimination, provides the C–N bond. The reaction was general for a number of alkenol substrates and external amine sources [$TsNH_2$, $MsNH_2$, 2-trimethylsilylethyl-sulfonamide ($SESNH_2$), benzamide and NaN_3].

Copper-catalyzed intramolecular alkene aminoalkoxylation reactions can also be conducted if $PhI(OAc)_2$ is used as the stoichiometric oxidant [80, 81]. These reactions tend to occur at room temperature and oxidation of copper(I)/copper(II) to copper(III) is thought to occur prior to alkene aminocupration. In 2010, 4-pentenyl-sulfonamides were shown to undergo both *endo* and *exo* cyclization pathways where terminal alkenes favored the former and internal alkenes favored the latter pathway (Scheme 40) [80]. Carbocation formation and hydride shift appeared to have occurred in one instance (Scheme 40, Eq. d).

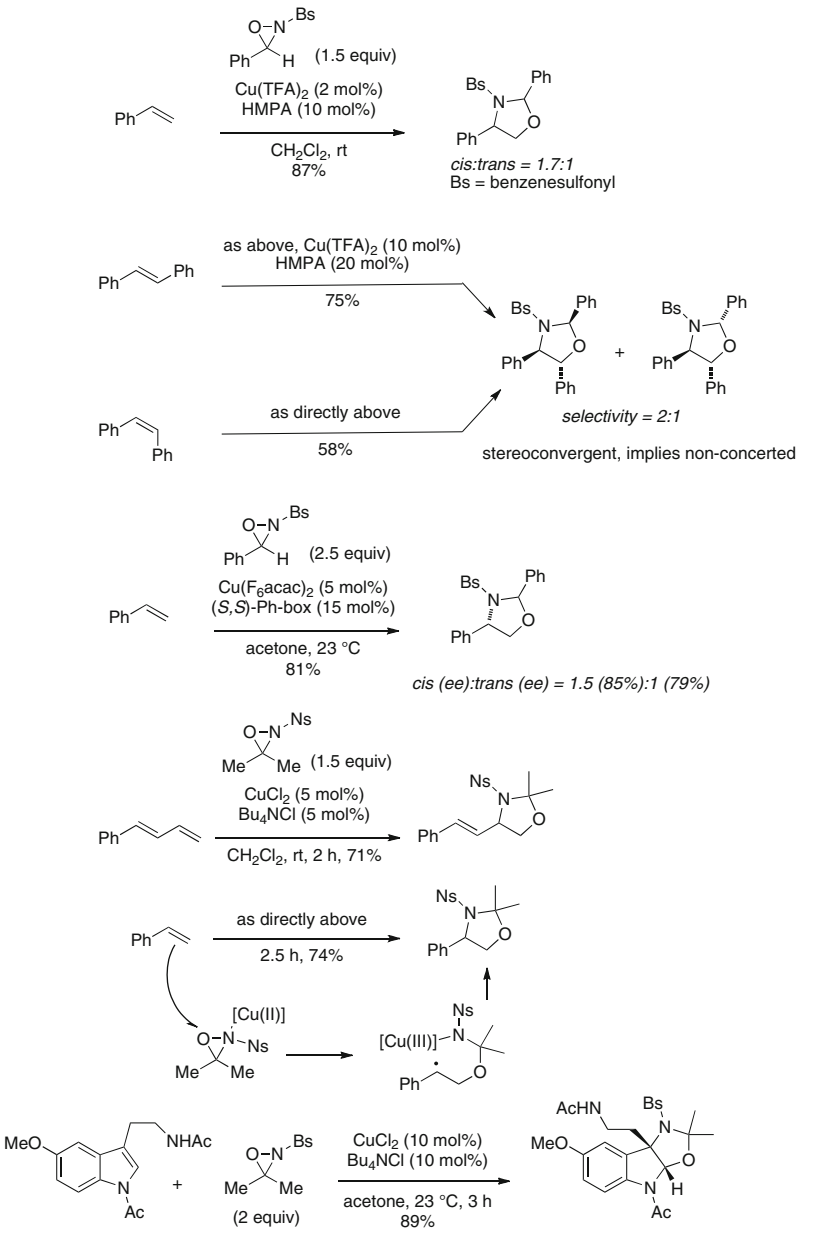


Scheme 40 Aminooxygenation via Cu(III) [80]



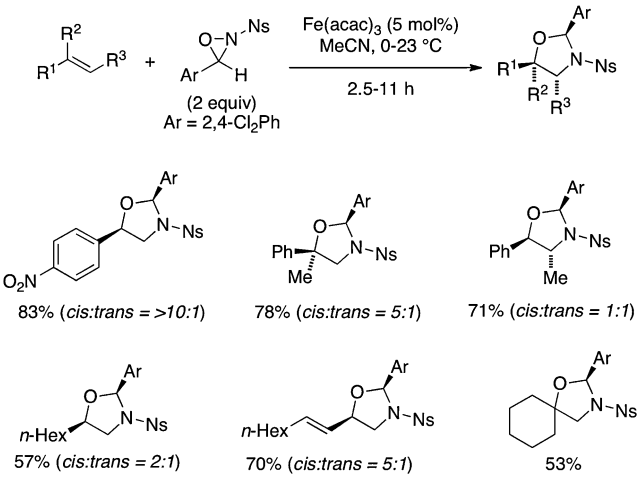
Scheme 41 Aminoacetoxylation of *N*-allylamidines [81]

N-Allylamidines also undergo intramolecular copper-catalyzed aminoacetoxylation in the presence of $PhI(OAc)_2$ as oxidant [81]. Terminal and 1,1-disubstituted alkenes underwent the aminoacetoxylation reaction efficiently (Scheme 41).



Scheme 42 Copper(II)-catalyzed aminoalkoxylations using oxaziridines [82–84, 86]

Conversion of the cyclic adducts to acyclic diaminoalcohols was demonstrated. The proposed mechanism (Scheme 41) involves copper-amine complexation and copper oxidation with $PhI(OAc)_2$ to give an R_2N–copper(III) intermediate.



Scheme 43 Iron-catalyzed alkene aminoalkoxylation [87]

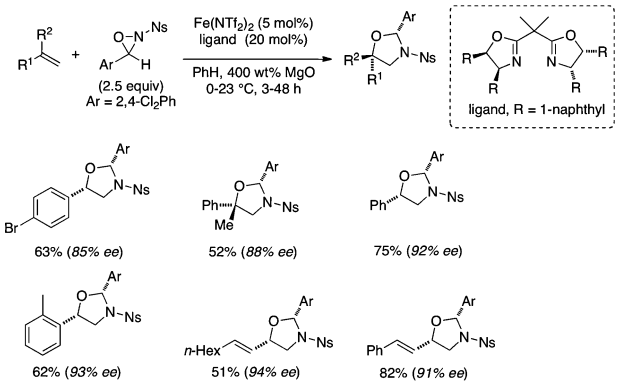
Aminocupration and subsequent reductive elimination then secures the C–O bond. When a chiral bis(oxazoline) ligand was used, a promising 48% ee was obtained. The ligand-based asymmetric induction is a strong indication that an aminocupration step is involved in the reaction mechanism.

The intermolecular copper(II)-catalyzed aminoalkoxylation of alkenes via activation of *N*-sulfonyl oxaziridines was first reported in 2006 (Scheme 42) [82]. Styrenes had the highest reactivity and a range of cyclic aminals were synthesized in good yields [82–85]. Hydrolysis of the aminal and removal of the sulfonyl group could be achieved to reveal the respective aminoalcohols with amine-bearing stereocenters. The catalytic enantioselective aminoalkoxylation of styrenes was achieved with moderate enantioselectivities [86]. A non-concerted mechanism involving generation of a benzylic radical was proposed based on stereochemical trends and radical trapping experiments [83].

2.5 Iron-Catalyzed Alkene Aminoalkoxylation

An Fe-catalyzed oxyamination of alkenes with *N*-sulfonyloxaziridine was reported in 2010 [87]. This reaction gives complementary regioselectivity to the analogous copper-catalyzed aminooxygenation reaction summarized above in that the reaction generates an oxygen-bearing stereocenter. Both terminal and internal styrenes were reactive and dienes and alkyl-substituted terminal alkenes also underwent oxyamination (Scheme 43). As in the analogous copper-catalyzed reaction (vide supra), mixtures of diastereomers epimeric at the aminal carbon were obtained.

The Fe-catalyzed reaction was rendered enantioselective in 2012 (Scheme 44) [88]. For the enantioselective reaction, styrenes and 1,1-disubstituted styrenes and 1-substituted dienes were the best substrates while internal alkenes proved unreactive. These reactions occurred with excellent enantioselectivity and significant preference



Scheme 44 Enantioselective iron-catalyzed aminoalkoxylation [88]

for the *cis* aminal diastereomer was observed. A mechanism for the oxyamination reaction has not yet been proposed.

3 Alkene Dialkoxylation

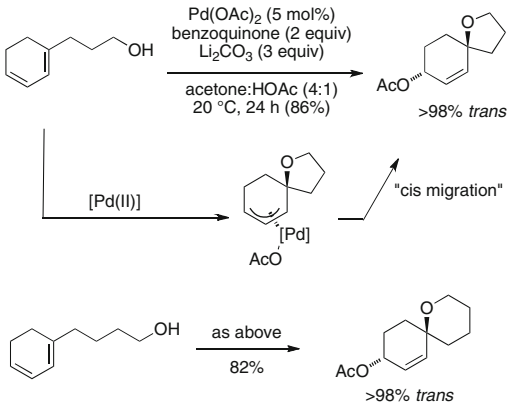
Metal-catalyzed alkene dialkoxylation has been used in the synthesis of tetrahydrofurans, lactones, tetrahydropyrans, dioxanes, and morpholines. Some of these methods have been reviewed previously [89, 90].

3.1 Palladium and Copper-Catalyzed Alkene Dialkoxylation Reactions

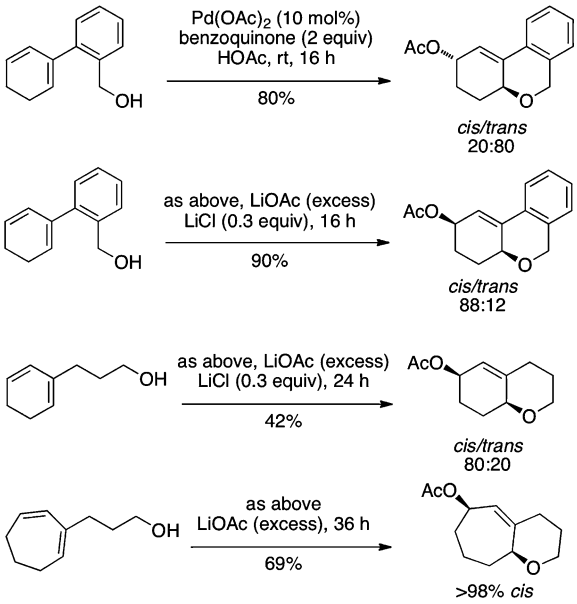
The palladium(II)-catalyzed intramolecular 1,4-alkoxyacetoxylation of dienes for the synthesis of spirocyclic tetrahydrofurans and tetrahydropyrans was first reported in 1991 (Scheme 45) [91, 92]. The mechanism is thought to involve *trans*-oxypalladation to form a π-allyl intermediate. In the absence of excess nucleophiles, the intermediate palladium(II) acetoxy complex is thought to undergo a *cis* migration (reductive elimination) to yield the major 1,4-*trans* diastereomer.

The analogous synthesis of fused-ring tetrahydropyrans was reported in 2004 [93]. Both the 1,4-*trans* and 1,4-*cis* diastereomers can be obtained selectively in several cases (Scheme 46). While the 1,4-*trans* diastereomer forms in the absence of external nucleophile, in the presence of LiOAc and catalytic LiCl, the 1,4-*cis* diastereomer is favored, presumably due to S_N2-type attack of the π-allylpalladium intermediate with acetate ion.

The synthesis of chiral tetrahydrofurans and a tetrahydropyran via an enantioselective palladium(II)-catalyzed intramolecular alkene dioxygenation

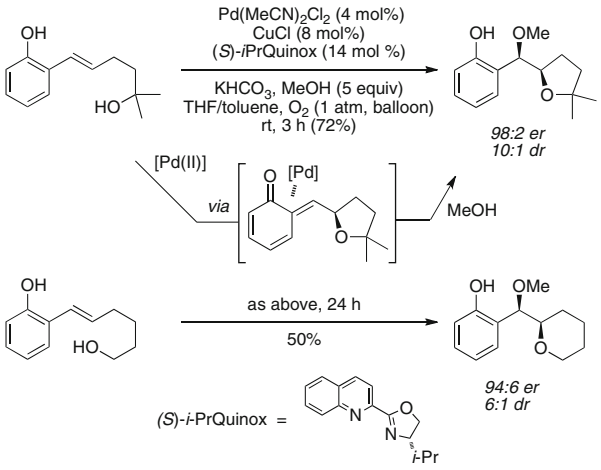


Scheme 45 Palladium-catalyzed 1,4-alkoxyacetoxylation of dienes [91, 92]



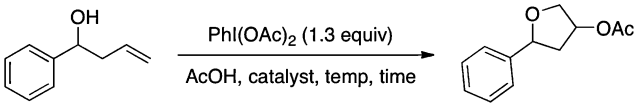
Scheme 46 *Cis*- and *trans*-selective diene 1,4-alkoxyacetoxylation [93]

using molecular O_2 as the terminal oxidant was reported in 2009 (Scheme 47) [94]. The reaction mechanism is thought to involve in situ formation of an *ortho*-quinone methide followed by subsequent addition of an exogenous nucleophile, e.g., MeOH [95]. In this reaction, CuCl was included as a rate-accelerating additive but is not thought to be the primary catalyst.



Scheme 47 Enantioselective Pd-catalyzed dialkoxylation [94]

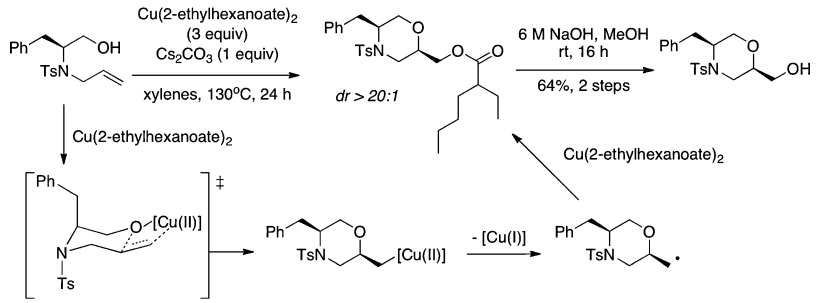
Table 1 Intramolecular *endo*-selective alkene dialkoxylations [96–99]



Entry	Catalyst	Conditions	Yield (%)	dr
1	$[Pd(dppp)(H_2O)_2](OTf)_2$ (2 mol%)	H_2O, rt, 72 h	78	1.1:1
2	$[Bis(NHC)Pd(H_2O)_2](OTf)_2$ (4 mol%)	H_2O, rt, 60 h	60	1.5:1
3	$Cu(OTf)_2$ (10 mol%)	80°C, 16 h	80	1.3:1
4	HOTf (5 mol%)	50°C, 72 h	72	1.2:1

In 2008 and 2010, two independent research groups reported Pd(II)-catalyzed intramolecular alkene dialkoxylation reactions for the synthesis of tetrahydrofurans and lactones using $PhI(OAc)_2$ as the terminal oxidant in the presence of HOAc (Table 1, entries 1 and 2) [96, 97]. Both groups hypothesized that the Pd(II)/Pd(IV) catalytic cycle was involved in the reaction mechanism. An analogous, copper(II)-catalyzed intramolecular alkene dialkoxylation using $PhI(OAc)_2$ was also reported in 2010, where a Cu(III) intermediate was invoked in the catalytic mechanism (Table 1, entry 3) [98]. A subsequent report in 2011 indicated that $PhI(OAc)_2$ under acidic conditions can provide similar product distributions (Table 1, entry 4), thereby calling into question the role of the Pd(II) and Cu(II) species in reactions that employ $PhI(OAc)_2$ under acidic conditions [99].

A copper(II) 2-ethylhexanoate-promoted alkene dialkoxylation was subsequently reported to occur under basic conditions (Scheme 48) [78]. The role of the copper species in promoting this reaction is less ambiguous given the absence of



Scheme 48 Copper(II)-promoted alkene dialkoxylation [78]

additional reactive species [78]. The reaction was highly diastereoselective, and alkene addition was proposed to occur via a *cis*-oxycupration mechanism in analogy with an alkene carboetherification reaction proposed to occur via a similar reaction mechanism under related reaction conditions [79].

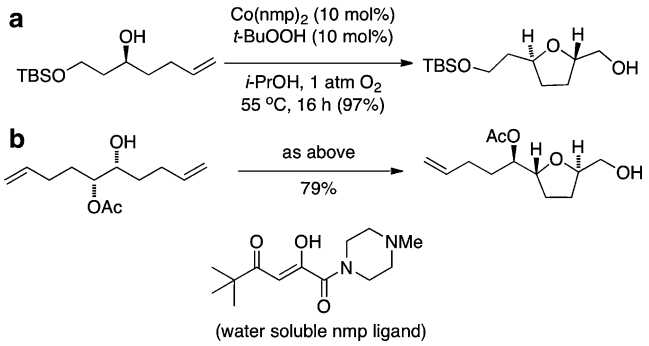
3.2 Cobalt-Catalyzed Alkene Dialkoxylation Reactions

2,5-*Trans*-disubstituted tetrahydrofurans can be synthesized from 4-pentenols using catalytic amounts of Co(II) complexes in the presence of *t*-butyl peroxide in the presence of O_2 (1 atm) [100, 101]. The method has been optimized for ease of catalyst/ligand removal by use of the water soluble *N*-methylpiperazine (3,5,5-dimethyl-1-(4-methylpiperazine-1-yl)hexane-1,2,4-trione (nmp) ligand (Scheme 49) [101]. The reaction mechanism is thought to involve a carbon radical intermediate which adds to O_2 to form the final C–O bond [102].

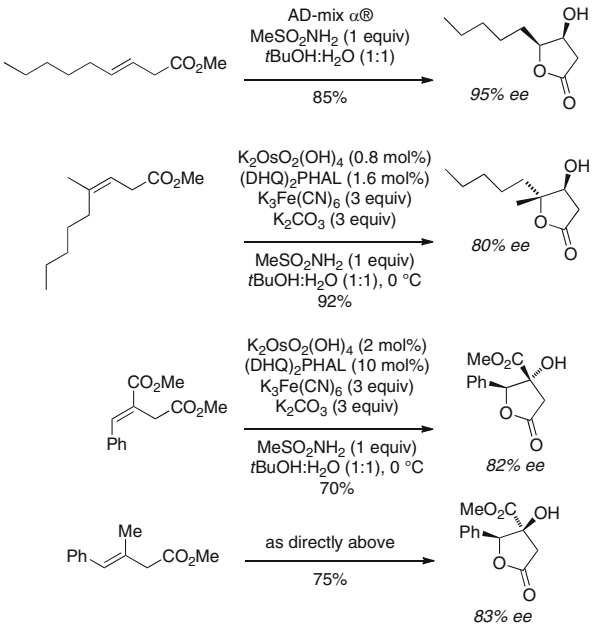
3.3 Osmium-Catalyzed Alkene and Diene Dialkoxylations

Variants of osmium-catalyzed alkene dihydroxylation [103] have been reported for the synthesis of lactones [104–106]. Examples of lactone synthesis proceeding via enantioselective alkene dihydroxylation and in situ lactonization are shown below (Scheme 50) [105, 106].

Osmium has also been used to catalyze the stereoselective synthesis of 2,5-*cis*-tetrahydrofurans from 1,5-dienes (Scheme 51) [107]. Initial intermolecular alkene dihydroxylation then facilitates a tethered, intramolecular dihydroxylation process [63].



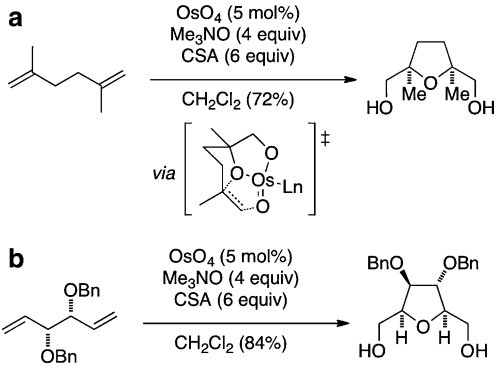
Scheme 49 Mukaiyama aerobic oxidative cyclization [101]



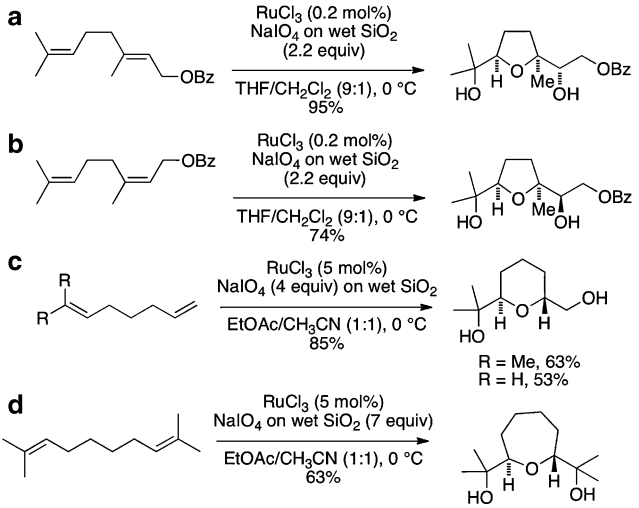
Scheme 50 Lactones via enantioselective Os-catalyzed dihydroxylation [105, 106]

3.4 Ruthenium-Catalyzed Diene Dialkoxylations

RuO_4 (derived from $RuCl_3$) has been used to promote and catalyze the oxidation of 1,5-, 1,6-, and 1,7-dienes to the corresponding tetrahydrofurans, tetrahydropyrans, and oxepanes [108]. Some examples are shown below (Scheme 52).



Scheme 51 Osmium-catalyzed dialkoxylation of alkenes [107]



Scheme 52 Ruthenium-catalyzed oxidation of dienes [108]

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