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Preface

The most essential step in the catalytic cycle in a variety of transition metal catalyzed reactions is the formation of carbon-metal bonds. Among possible isomers, the generation of a single isomer of the organometallic compound, in which the metal is stereo- and regioselectively attached to the carbon of interest, necessarily leads to the selective formation of organic products. In many cases, the stereo- and regioselectivities are controlled mainly by steric and/or electronic factors. Chelation is also a reliable method for controlling stereo- and regiochemistry. Cyclometalation using Li, Mg, Mn, and Pd has traditionally been relied upon in ortho C–H bond functionalization. Directed hydrometalation and carbometalation, using Li, Al, Mg, and Zn, have also been utilized for the regio- and stereoselective generation of organometallic species. Despite the obvious strength of these approaches in stoichiometric systems, they are rarely applied to catalytic reactions. Recently, a chelation-assisted catalytic transformation has been recognized as one of the most useful methodologies, not only for controlling regio- and stereoselectivity of reactions, but also for accelerating reactions. In particular, the chelation methodology has been used as a new activation method, in which a carbon-metal bond is generated directly from a C–H bond, a reaction rarely achieved using conventional methods.

Although this monograph cannot possibly provide a comprehensive review of all transition metal catalyzed reactions involving directed metalation, a critical summary is given, which illustrates the power of this methodology in a rapidly developing field. For example, C–H bond activation reactions are some of the most extensively studied reactions that rely heavily on the development of chelation methodology. A wide variety of C–H bond functionalization reactions have been developed recently and are highlighted in this monograph. This methodology is now being applied to the activation of other unreactive bonds, such as C–C, C–F, C–O, and C–N. Other metalation reactions such as the hydroformylation of alkenes are described. Although this reaction is one of the largest volume industrial applications of homogeneous catalysis, it has not been widely used as a synthetic transformation on a laboratory scale. However, a unique stereo- and regioselective process has been developed through the utilization of directed hydrometalation. The regioselective Mizoroki–Heck reaction is another example in which directed carbometalation can be used to achieve a high regioselectivity.

This book will be a useful resource for researchers, teachers, and students, both expert and novice, who are interested in learning more about how this innovative methodology can contribute to different fields of chemistry. Finally, as editor I would like to thank all contributors for their participation in this project and for their patience throughout the entire process.

Osaka, Japan, August 2007 Naoto Chatani

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Catalytic Addition of C – H Bonds to C – C Multiple Bonds

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Abstract During the last decade, catalytic functionalization of C – H bonds has become one of the most attractive research areas in modern organic synthesis. To date, many efficient catalytic reactions have been reported. In almost all of these reactions, heteroatom-directed C – H bond cleavage and/or C – C bond formation are quite important for attaining high regioselectivity and efficiency. In this chapter, several representative results concerning transition metal-catalyzed alkylation of C – H bonds with olefins, alkenylation with acetylenes, and carbonylation with olefins and carbon monoxides will be briefly reviewed.

Keywords Alkenylation · Alkylation · Carbonylation · C – H bond cleavage · Conversion of C – H to C – C

Abbreviations

dcypb	1,4-Bis(dicyclohexylphosphino)butane
coe	1,5-Cyclooctadiene
thf	Tetrahydrofuran
DMA	*N*,*N*-Dimethylacetamide
(*R*),(*S*)-PPFOMe	(*R*)-1-[(*S*)-2-(Diphenylphosphino)ferrocenyl]ethyl methyl ether
$PCyp_3$	Tricyclopentylphosphine
(*R*)-(*S*)-$PPFPPh_2$	(*R*)-1-[(*S*)-2-(Diphenylphosphino)ferrocenyl]ethyldiphenylphosphine)

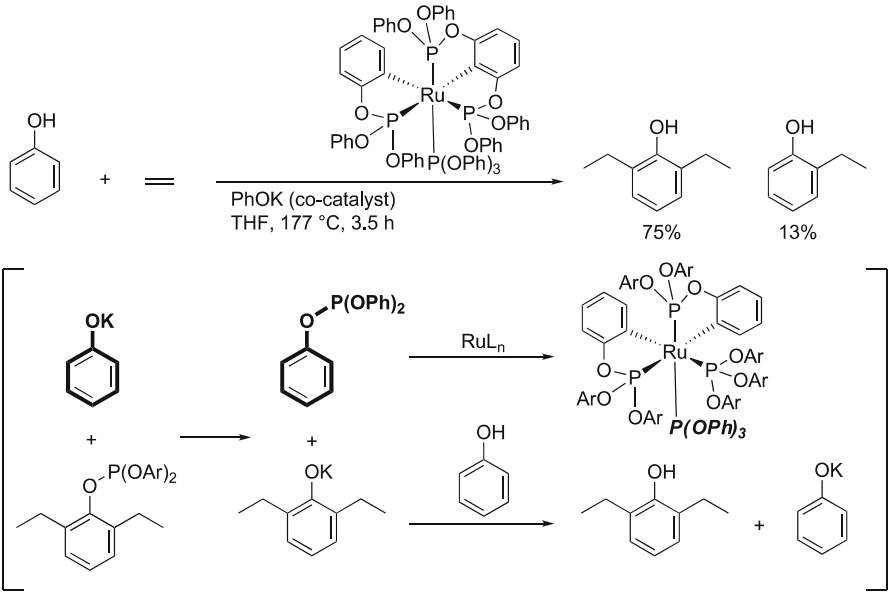
1 Introduction

When organic chemists plan to synthesize their target molecules, they usually propose synthetic routes to them by disconnecting carbon–carbon and/or carbon–heteroatom bonds on the basis of retro-synthesis analysis. To date, a large number of efficient, selective reactions have been developed. Among these, transition metal-catalyzed reactions are highly useful and reliable for constructing carbon–carbon and carbon–heteroatom bonds [1–3]. In these cases, the reactions involve cleavage of reactive bonds such as carbon–halogen and carbon–pseudohalogen bonds with transition metal complexes. For example, palladium-catalyzed cross-couplings using arylhalides and organometallic reagents are indispensable, mature synthetic methods in modern synthetic organic chemistry [4, 5]. In addition to these well-documented synthetic protocols, recently, catalytic functionalizations of otherwise unreactive carbon–hydrogen bonds leading to carbon–carbon and carbon–heteroatom bond formation have been widely studied [6–18] because this type of reactions usually does not sacrifice any functional groups in the starting materials.

A pioneering work of catalytic functionalization of C – H bonds was reported by Yamazaki and coworkers. They found that the dehydrogenative alkenylation of toluene with alkenes using a rhodium catalyst afforded a regioisomeric mixture of alkenylation products [19, 20]. This type of catalytic functionalizations of C – H bonds is indisputably highly important in organic synthesis. Unfortunately, however, in the cases of the reactions of substituted arenes without a directing functionality, a mixture of possible regioisomers is formed. From the point of view of organic synthesis, uncontrollable product selectivity is the most serious drawback of this reaction. Thus, controls of regioselectivity for C – H functionalization are very important issues for its use as a synthetic tool in organic synthesis.

The pioneering study of the transition metal-catalyzed regioselective C – H transformation was reported by Lewis and Smith [21]. The *ortho*-selective ethylation of phenols with ethylene was attained with the aid of the ruthenium(II) phosphite catalyst. This reaction proceeded through the coordination of phosphorous atom to the ruthenium and this coordination controlled the regioselectivity (Scheme 1). This pioneering result suggests that a coordination of a heteroatom to a metal has several merits for attaining selective functionalization of C – H bonds. One of these merits is that a coordination of a heteroatom facilitates an approach of a metal to *ortho* C – H bonds. Another one is stabilization of a C – M – H species, which is formed via an oxidative addition of a C – H bond to a metal. The C – M – H species are usually thermally unstable and easily return to the corresponding low-valent metal and the C – H bond via a reductive elimination.

Murai et al. adequately applied these merits to the catalytic alkylation of *ortho* C – H bonds of aromatic ketones using olefins. In 1993, they reported



Scheme 1 Chelation-assistance via exchange between KOPh and triarylphosphite

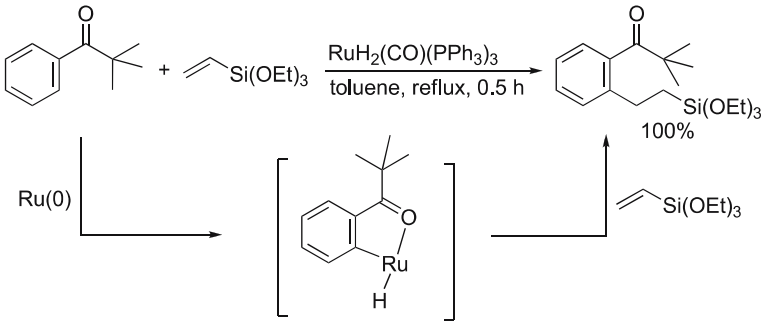
the first example of the highly efficient, regioselective functionalization of C – H bonds in aromatic ketones with olefins using a ruthenium complex as a catalyst [22]. In this case, the coordination of the ketone carbonyl group to the ruthenium is important for achieving high selectivity and efficiency. This result suggests that the use of a coordination of a heteroatom to a metal, called chelation-assistance, is a highly useful, reliable protocol in the catalytic functionalization of C – H bonds. After their pioneering works, a variety of studies on the selective functionalization of C – H bonds have been developed [6–18].

This review article will broadly survey the literature dealing with the transition metal-catalyzed addition of C – H bonds to carbon–carbon multiple bonds in organic synthesis up to late 2006. The catalytic functionalization of C – H bonds are categorized by directing functionalities such as oxygen and nitrogen atoms. Only limited numbers of examples involving unusual significance, originality, or complexity will be presented in an equation form. Several areas, e.g., reactions involving electrophilic substitution of aromatic compounds with transition metal salts, transition metal-carbenoids, transition metal-vinylidenes, oxidations of C – H bonds, and acetylenes will not be dealt with in this chapter.

2
Reactions via Coordination of a Carbonyl Oxygen Atom

2.1
Carbonyl Oxygen-Directed Addition of C – H Bonds to C – C Double Bonds

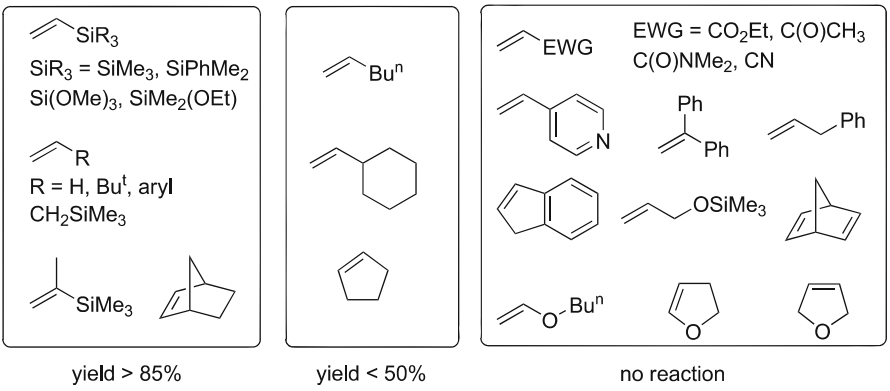
Catalytic additions of the sp^2 C – H bonds in arenes to olefins are highly useful reactions because they permit the alkylation of an aromatic ring without sacrificing functional group, such as a halogen or triflate. At the end of 1993, Murai et al. reported on the first example of a highly efficient, selective alkylation of aromatic ketones with olefins using $RuH_2(CO)(PPh_3)_3$ as catalyst (Eq. 1) [22]. The coordination of the ketone oxygen to the ruthenium is proposed to facilitate the approach of the ruthenium to an *ortho* C – H bond and to stabilize the ruthenacycle intermediate, which should be formed by oxidative addition of the *ortho* C – H bond to the ruthenium.



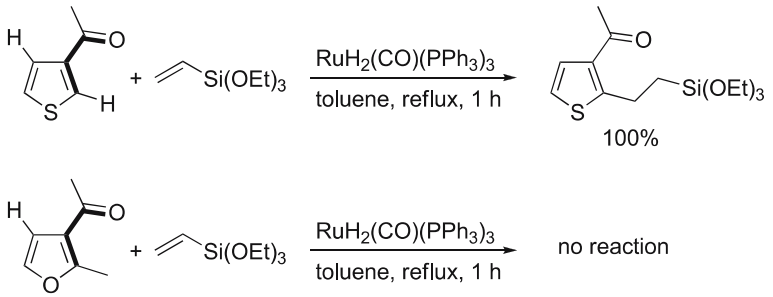
Equation 1

For alkylation of aromatic ketones with olefins, several ruthenium complexes such as $RuH_2(CO)(PPh_3)_3$, $Ru(CO)_2(PPh_3)_3$, $Ru(CO)_3(PPh_3)_2$, and $RuH_2(PPh_3)_4$ show good to excellent catalytic activities [15, 22–25]. Among these complexes, $RuH_2(CO)(PPh_3)_3$ is the most effective catalyst. Terminal olefins such as ethylene, vinylsilanes, *tert*-butylethylene, and styrenes are reactive for the reaction of aromatic ketones. Some strained internal olefins such as cyclopentene and norbornene can be used for this coupling, but olefins having electron-withdrawing groups, vinyl ethers, or internal olefins are ineffective (Scheme 2) [23].

The alkylation of 3-acetylthiophene takes place exclusively at the 2-position, but the alkylation of 2-methyl-3-acetylfuran did not proceed (Scheme 3). These results suggest that the α,β-conjugate enone framework appears to be important for accomplishing this alkylation reaction [23]. Murai and coworkers proposed a new reaction pathway involving a nucleophilic attack of ruthenium to the *ortho* carbon followed by migration of the *ortho* hydrogen

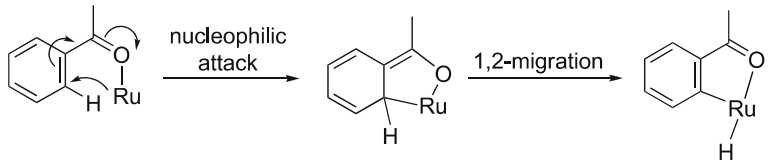


Scheme 2 Applicability of olefins



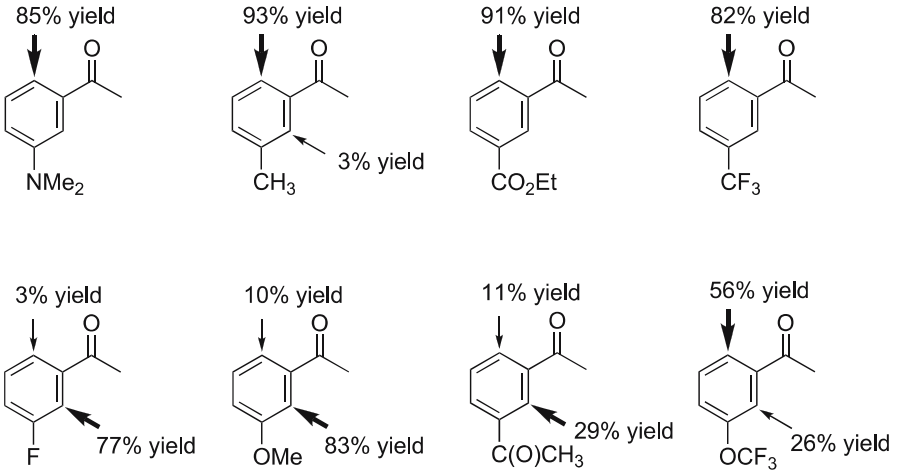
Scheme 3

onto the ruthenium, leading to an *ortho* ruthenated complex (Scheme 4) [24, 25]. The ab initio theoretical calculation on the ruthenium-catalyzed reaction of benzaldehyde with ethylene strongly supports this stepwise oxidative addition pathway. The α,β-conjugate enone framework appears to be essential for achieving this nucleophilic addition step (Scheme 4) [26, 27].



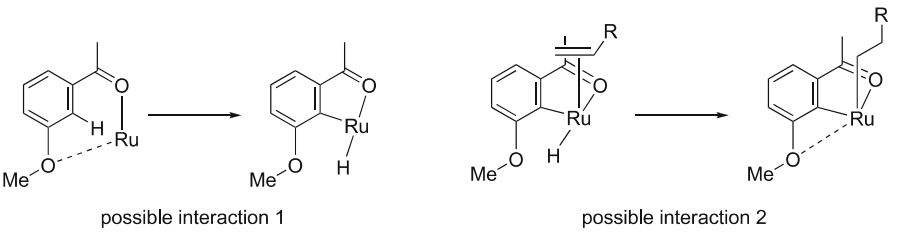
Scheme 4

The substituents on the aromatic ring influenced the regioselectivity of the C – C bond formation. The C – C bond formation basically occurs at the less congested *ortho* position (Scheme 5) [24, 25]. Interestingly, however, in



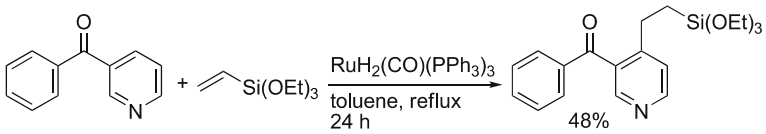
Scheme 5 Effect of substituent on the regioselectivity

the cases of the reaction of some *m*-substituted acetophenones, the C – C bond formation took place at the more congested *ortho* position (2-position). A heteroatom such as a fluorine or oxygen atom in the substituent may support bringing a ruthenium to the congested *ortho* position or may stabilize the intermediate prior to the C – C bond formation (Scheme 6). This unusual regioselectivity appears to be derived from weak interaction between the lone pair electrons on the heteroatom and the ruthenium center because, in the case of the reaction of 3′-trifluoromethoxyacetophenone, the regioselectivity was largely decreased compared to that in the case of 3′-methoxyacetophenone (Scheme 5) [24, 25]. Thus, the lone pair electrons of the oxygen and fluorine atoms participate in the regioselectivity-determining step.



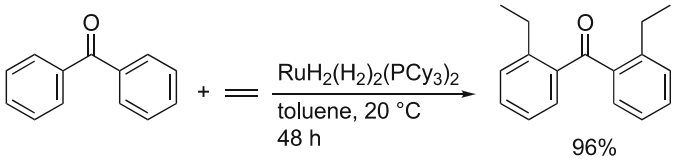
Scheme 6 Possible interactions between the oxygen atom and the ruthenium center

When phenyl 3-pyridyl ketone was used in the C – H/olefin coupling, the alkylation proceeded exclusively at the pyridine ring (Eq. 2) [28]. This result indicates that C – C bond formation takes place preferentially at the electron-deficient aromatic ring.

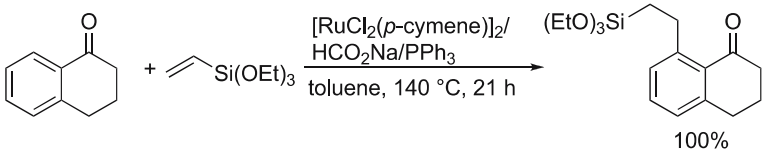


Equation 2

Other catalyst systems have also been reported. The groups of Chaudret [29] and Leitner [30, 31] independently reported that $RuH_2(H_2)(CO)(PCy_3)_2$-catalyzed alkylation of aromatic ketones with ethylene took place at room temperature to give the corresponding 1 : 2 coupling product in 96% yield (Eq. 3). Very recently, a new entry of an alkylation of aromatic ketones with olefins using a $[RuCl_2(p\text{-cymene})]_2/HCO_2Na/PPh_3$ catalyst system has been developed (Eq. 4) [32]. It was proposed that the ruthenium(II) complex was reduced to ruthenium(0) by the reaction of sodium formate.

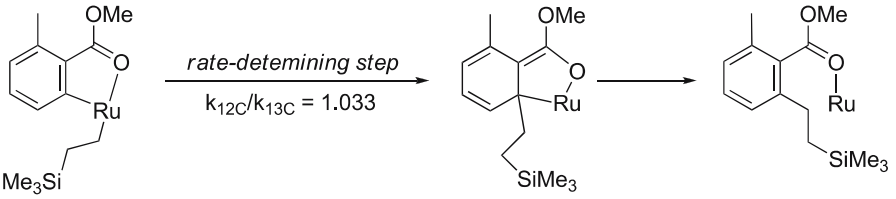


Equation 3



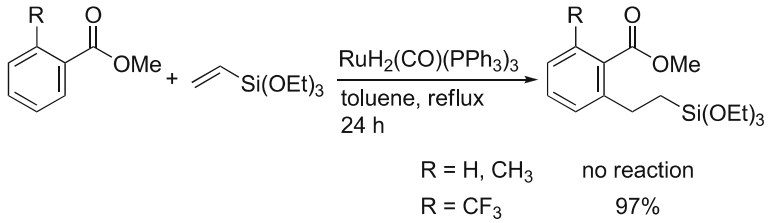
Equation 4

The carbonyl group in aromatic esters [33, 34], aldehydes [35], and amides [36] can also function as a directing group. In the studies of alkylations of these aromatic compounds, several important features of the catalytic alkylation of C – H bonds have been revealed. Murai and coworkers investigated the reaction mechanism by means of deuterium-labeling experiments and the ^{13}C kinetic isotope effect at natural abundance [34]. They revealed that there is a rapid equilibrium between the intermediates prior to the C – C bond formation step, i.e., a reductive elimination step, and that the C – C bond formation is rate-determining in the catalytic cycle (Scheme 7). This is one of the most important features of the $RuH_2(CO)(PPh_3)_3$-catalyzed alkylation of aromatic C – H bonds. The effect of substituents on the aromatic ring strongly affected the reactivity of the aromatic esters. Usually, a reductive



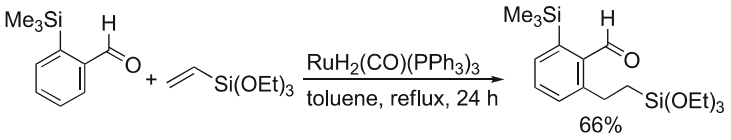
Scheme 7

elimination, which proceeds via a concerted reaction pathway, is facilitated by an electron-donating substituent, but in the Murai's case, an electron-withdrawing group (such as CF_3, CN, and CO_2Et) improves the reactivity of aromatic esters (Eq. 5) [33, 34]. They proposed that the C – C bond formation proceeds through a stepwise nucleophilic migration of the alkyl group on the ruthenium center to the *ipso*-carbon bound to the ruthenium (Scheme 7). The electron-withdrawing substituents stabilize the negative charge generated on the aromatic ring. The possibility of this stepwise-migration pathway was supported by ab initio theoretical calculation [26, 27]. This information on the reaction pathway provides an important working hypothesis for developing new catalytic reactions involving C – H bond cleavage via an oxidative addition to a transition metal complex.

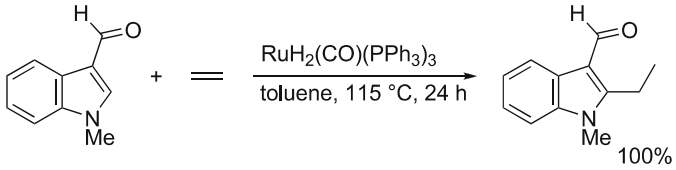


Equation 5

A formyl group is prone to attack by a low-valent transition metal complex [37, 38]. To prevent the oxidative addition of the formyl C – H bond to the metal, the following two protocols have been devised, one being steric and the other electronic in nature. The reaction of benzaldehyde having a trimethylsilyl or a *tert*-butyl group at the *ortho* position, which hindered the approach of the metal to the formyl group, provided the corresponding *ortho* alkylation product in high yield in each case [35] (Eq. 6). To block the formyl group from attack by the metal, the introduction of a heteroatom such as oxygen, sulfur, or nitrogen at the β carbon of the enal moiety was also effective. In the case of the reaction of 1-methylindole-3-carboxaldehyde with ethylene, the ethylation product is also obtained in quantitative yield (Eq. 7). From these



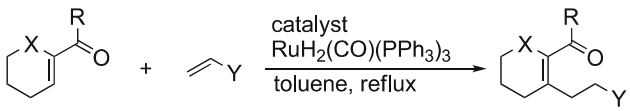
Equation 6



Equation 7

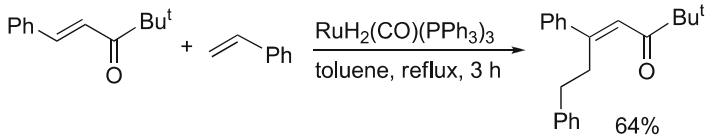
results, the steric and electronic devices appeared to be valid in the case of aldehyde-directed C – H/olefin coupling reactions.

Olefinic compounds having an α,β-unsaturated carbonyl framework can also be applied to the catalytic C – H/olefin coupling. Alkylation of α,β-unsaturated ketones [39, 40], aldehydes [35], esters [41], and amides [41] with olefins proceed with the aid of $RuH_2(CO)(PPh_3)_3$ as a catalyst. Treatment of cyclic substrates with olefins using $RuH_2(CO)(PPh_3)_3$ catalyst gave the corresponding β-alkylation products in high yields (Eq. 8) [39, 41]. In contrast, in the case of acyclic enone derivatives, control of the regio- and/or stereoselectivities is difficult. The structure of the conjugate enone moiety appears to affect the reaction pathway. The coupling reaction of (*E*)-4,4-dimethyl-1-phenylpent-1-en-3-one with styrene afforded the expected linear alkylation product (Eq. 9) [40]. However, in the case of the reaction of (*E*)-2,2-dimethylhex-4-en-3-one, an unusual branched isomer was formed as a sole product (Eq. 10). For these reactions, two different reaction pathways were proposed: the former involves an oxidative addition of the C – H bond by the utilization of chelation, and the latter involves hydroruthenation of styrene followed by carboruthenation of the enone (Scheme 8).

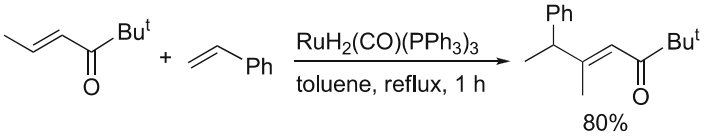


X = CH_2	R = ^{t}Bu	Y = $Si(OEt)_3$	0.5 h	96%
X = O	R = ^{t}Bu	Y = c-C_6H_{11}	12 h	98%
X = CH_2	R = OMe	Y = $Si(OEt)_3$	18 h	97%

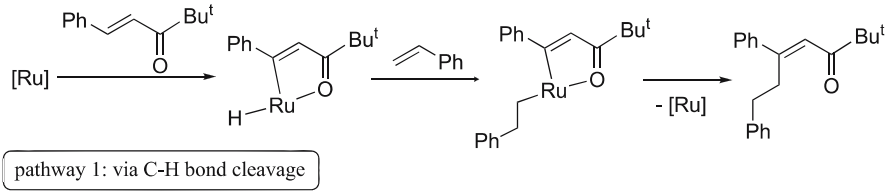
Equation 8

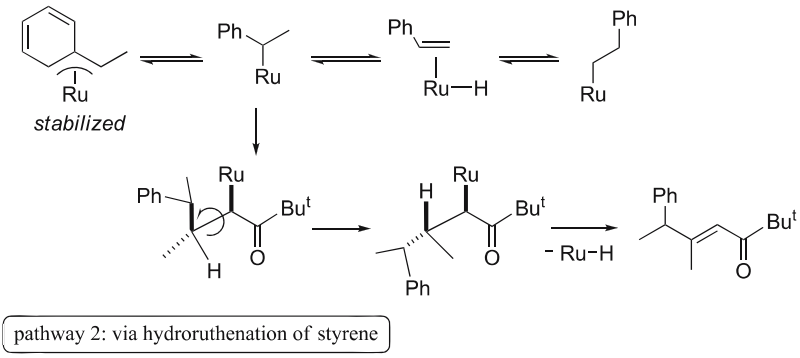


Equation 9



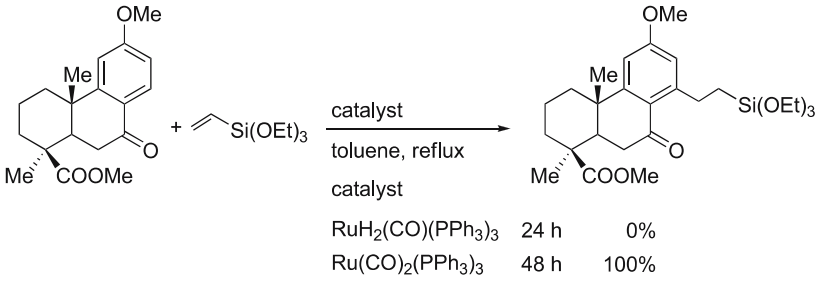
Equation 10





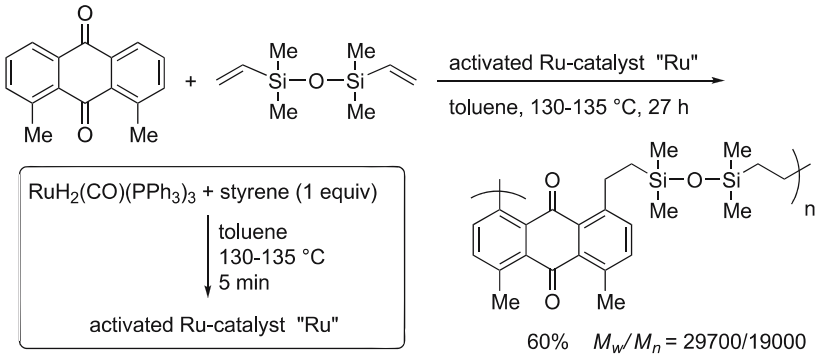
Scheme 8 Two distinct reaction pathways for reactions of acyclic enones with olefins

This catalytic alkylation of C – H bonds in aromatic ketones has been used for functionalization of diterpenoid [42–44]. In this case, $Ru(CO)_2(PPh_3)_3$ showed higher catalytic activity than $RuH_2(CO)(PPh_3)_3$. When the reaction was carried out using $Ru(CO)_2(PPh_3)_3$, the alkylation product was obtained in quantitative yield and the substituent in the diterpenoid remained intact (Eq. 11). As another application of this ruthenium-catalyzed alkylation of C – H bonds, polymerization of aromatic ketones with α,ω-dienes such as



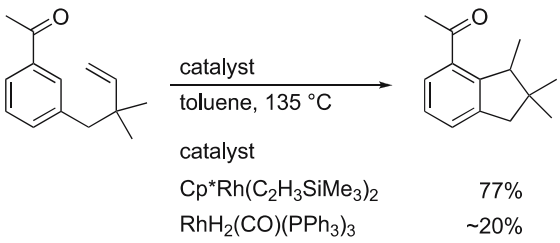
Equation 11

1,1,3,3-tetramethyl-1,3-divinyldisiloxane has been reported (Eq. 12) [45–47]. The use of a pre-activated ruthenium complex, which had been generated by reaction of $RuH_2(CO)(PPh_3)_3$ with styrene, resulted in high yields of the polymers.



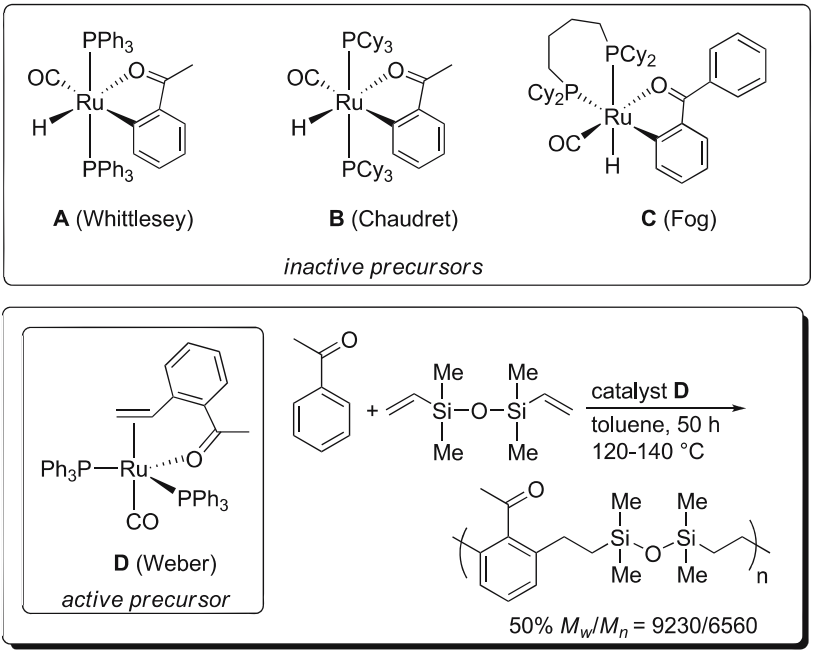
Equation 12

Intramolecular cyclization of aromatic ketones with an olefin tether at the *meta* position took place with the aid of $C_5Me_5Rh(C_2H_3SiMe_3)_2$ as a catalyst. This is the first entry for ketone carbonyl-directed intramolecular C – H/olefin coupling (Eq. 13) [48].



Equation 13

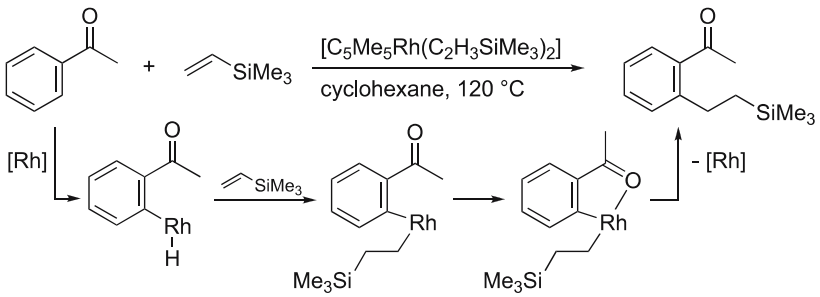
Several attempts have been made to synthesize more reactive catalysts and to elucidate the structure of the catalyst active species. In the case of the reaction using $RuH_2(CO)(PPh_3)_3$ as a catalyst precursor, two PPh_3 ligands and one CO ligand are present in the *ortho*-ruthenated acetophenone complex [49, 50]. Whittlesey and coworkers synthesized the highly plausible *ortho*-ruthenated acetophenone complex, $RuH(o\text{-}C_6H_4C(O)CH_3)(CO)(PPh_3)_2$ (**A**) (Scheme 9) [51]. Chaudret and coworkers prepared a similar *ortho* metalated $RuH(o\text{-}C_6H_4C(O)CH_3)(CO)(PCy_3)_2$ (**B**), which is a PCy_3 analogue of **A** [29]. A diphosphine version of **A**, $RuH(o\text{-}C_6H_4C(O)Ph)(CO)(dcypb)$ (**C**) (dcypb = $Cy_2P(CH_2)_4PCy_2$), was prepared by Fogg and coworkers [52]. These complexes appeared to be plausible as a catalyst active species, but all were found to be ineffective for the C – H/olefin coupling. Weber synthesized a unique zero-valent ruthenium complex **D** and examined the catalytic activity. This complex was effective for the alkylation of aromatic ketones [53]. The NMR studies with respect to catalyst active species done by Hiraki's group revealed that there were several ruthenium species during the catalytic reaction, and that complex **A** was an unreactive isomer but the regioisomer of **A** functioned as an active catalyst species [49, 50].



Scheme 9

All of the catalytic reactions mentioned above were proposed to take place via coordination of the carbonyl oxygen to the metal prior to the C – H bond

cleavage. Lenges and Brookhart reported a very important alternative mechanism for catalytic C – H/olefin coupling [54]. In this case, the C – H bond cleavage of the aromatic ketone with $C_5Me_5Rh(C_2H_3SiMe_3)_2$ occurred without coordination of the ketone carbonyl group and the coordination of the carbonyl group participated in the reductive elimination step (Scheme 10). Once the ketone carbonyl coordinates to the rhodium center, the C – C bond formation takes place irreversibly.

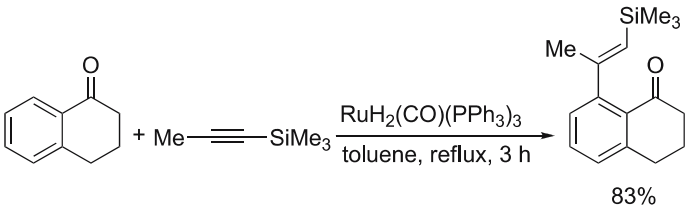


Scheme 10 Coordination of carbonyl group prior to the reductive elimination

In the case of the *ortho*-selective alkylation of C – H bonds, there are two types of chelation-assistance mode: one involves coordination of a hetero atom to a metal prior to C – H bond cleavage, and the other involves non-chelation-assisted C – H bond cleavage followed by chelation-assisted C – C bond formation. Therefore, a role of the hetero atom in the catalytic cycle cannot be predicted by means of product analysis. The competitive deuterium-labeling protocol established by Jones [55, 56] is a highly reliable tool for elucidating the coordination of the hetero atom to the metal prior to the C – H bond cleavage. Kakiuchi and coworkers have used the Jones protocol for revealing the coordination of the ketone carbonyl group to the ruthenium prior to C – H bond cleavage in the $RuH_2(CO)(PPh_3)_3$-catalyzed arylation of aromatic ketones with arylboronates [57].

2.2
Carbonyl Oxygen-Directed Addition of C – H Bonds to C – C Triple Bonds

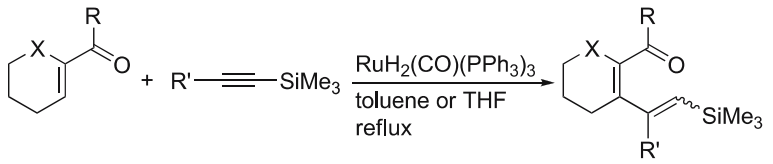
Simple change of the acceptor of C – H bonds from olefins to acetylenes leads to regioselective alkenylation of C – H bonds. The reaction of aromatic ketones such as α-tetralone with internal acetylenes gives the corresponding *ortho* alkylation product (Eq. 14) [58]. Highly regioselective C – C bond formation takes place when silylacetylene derivatives are used for this reaction. The stereochemistry around the double bonds is sensitive to the size of the substituent on the acetylene carbon. Thus, the reaction with 1-trimethylsilyloctyne gave a mixture of *E*- and *Z*-isomers of the alkenylation prod-



Equation 14

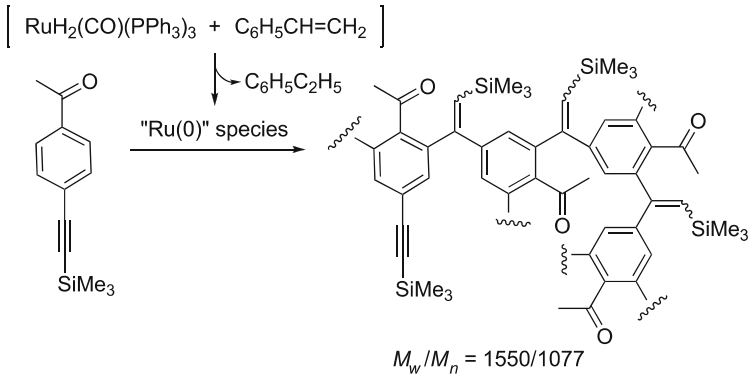
ucts, but the reaction with 1-trimethylsilylpropyne afforded the *E*-isomer as sole product. In the case of unsymmetrically substituted alkynes such as 1-phenylbutyne, four possible isomers were obtained. Control of stereo- and regiochemistry around the double bonds is an important issue in the future studies.

The C – H/acetylene coupling is also applicable to α,β-unsaturated carbonyl compounds and affords conjugate dienones. Trost et al. reported an alkenylation reaction of α,β-conjugate esters [41]. Subsequently, Murai and coworkers found the alkenylation of α,β-conjugate enones [59]. Cyclohexene and dihydropyran derivatives are effective for this coupling reaction. When the reaction of 1-(5,6-dihydro-4*H*-pyran-2-yl)-2,2-dimethylpropan-1-one with phenyl(trimethylsilyl)acetylene was carried out in the presence of $RuH_2(CO)(PPh_3)_3$ as a catalyst, the β-alkenylation product was obtained in 96% yield (Eq. 15). This olefinic C – H/acetylene coupling reaction provides a new entry for synthesis of highly congested conjugate dienones.



Equation 15

Woodgate applied the C – H/acetylene coupling reaction to fused aromatic ketones having a terpene framework. Alkenylation proceeded exclusively at the position *ortho* to the ketone carbonyl group [60]. The combination of acetophenone and diynes provides a new entry route to copolymerization of aromatic ketones with acetylenes. Weber extensively studied these reactions with respect to the step growth copolymerization of aromatic ketones and acetylenes [61]. In the case of the reaction using 4-[(trimethylsilyl)ethyl]acetophenone, hyperbranched poly[4-



Equation 16

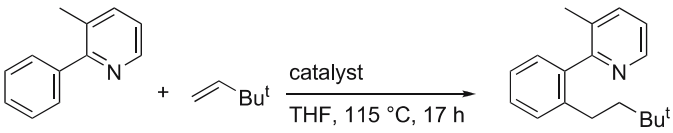
{(trimethylsilyl)ethyl}acetophenone] (M_w/M_n = 1550/1077) was obtained (Eq. 16).

3
Reactions via Coordination of a Nitrogen Atom

3.1
sp^2 Nitrogen-Directed Addition of C – H Bonds to C – C Double Bonds

A nitrogen functionality, such as pyridyl, oxazolyl, and imino groups, can also function as a directing group. The chelation-assisted alkylation of C – H bonds with olefin can be applied to aromatic and heteroaromatic compounds having an sp^2 nitrogen atom as a directing group.

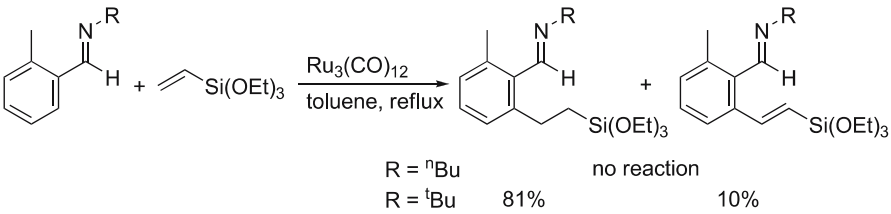
The reaction of arylpyridines with olefins using $[RhCl(coe)_2]_2/PCy_3$ as a catalyst afforded the *ortho*-selective alkylation product efficiently (Eq. 17) [62, 63]. The use of phosphine having a large cone angle improved the activity of the catalyst (Eq. 17).



catalyst	cone angle	yield
$[RhCl(coe)_2]/PCy_3$	170 °	92%
$[RhCl(coe)_2]/PPh_3$	145 °	80%
$[RhCl(coe)_2]/PBu_3$	132 °	40%
$[RhCl(coe)_2]/PMe_3$	118 °	21%

Equation 17

A variety of aromatic imines derived from the corresponding aldehydes and ketones can be used for this reaction [64, 65]. The combination of the catalyst and the substrate is important for attaining high efficiency. The $Ru_3(CO)_{12}$ complex showed higher catalyst activity than $RuH_2(CO)(PPh_3)_3$. In the case of ruthenium-catalyzed alkylation of aromatic imines, reactivities of the substrates are highly sensitive to the substituents in the imino groups. Aromatic imines having a *n*-butyl group on the imino nitrogen showed poor reactivity, but, interestingly, aromatic imines derived from *tert*-butylamine showed high reactivity (Eq. 18) [64]. Significant differences with respect to product selectivity between aldimines and ketimines were observed in the ruthenium- and rhodium-catalyzed C – H/olefin couplings. When the reaction of aromatic aldimines with olefins was carried out using a ruthenium catalyst, a mixture of alkylation and alkenylation products was obtained [64]. Interestingly, the reaction of acetophenone ketimine afforded the corresponding mono-alkylation product, exclusively. Thus, the substituent on the imino carbon atom largely affects the product selectivity.

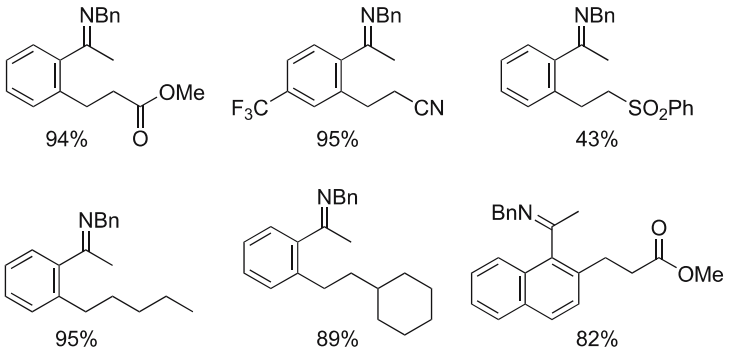


Equation 18

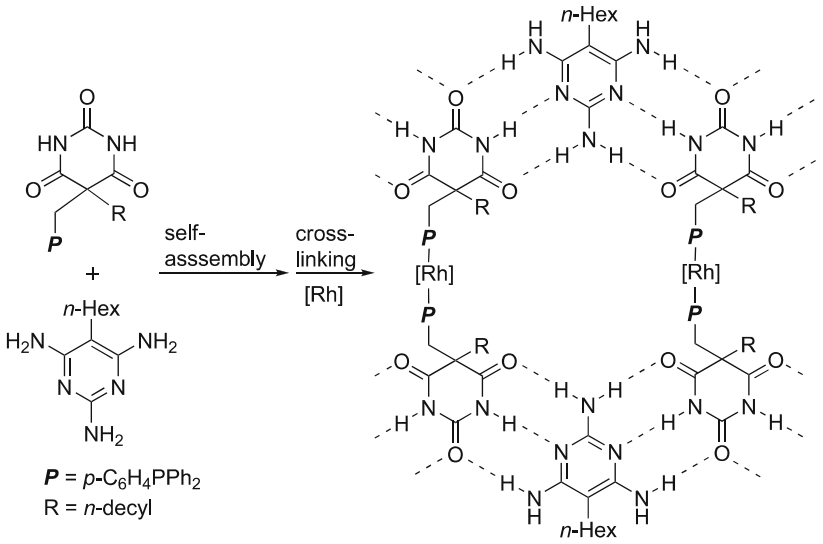
In the case of the $RhCl(PPh_3)_3$-catalyzed coupling of aromatic ketimines, applicability of olefins is wide. A variety of functionalized olefins such as methyl acrylates, *N*,*N*-dimethylacrylamide, phenyl vinyl sulfone, and α,ω-dienes, which are ineffective olefins in the ruthenium-catalyzed alkylation of aromatic imines, are applicable to the rhodium-catalyzed coupling (Scheme 11) [66, 67].

Recently, Jun and coworkers reported a new, unique recyclable self-assembly supported rhodium-catalyzed system (Scheme 12) [68]. This self-assembling catalyst system uses barbiturate with a triarylphosphine moiety that coordinates to the rhodium center and 2,4,6-triaminopyrimidine. The catalyst system is heterogeneous at room temperature due to formation of a hydrogen-bonding network. At higher reaction temperatures, the reaction mixture becomes homogeneous due to the loss of the hydrogen-bonding network. They used this recyclable catalyst for the alkylation of aromatic imines, and examined the reusability of the catalyst.

Very recently, a unique tandem reaction involving C – H bond cleavage was reported. The reaction of aromatic ketimines (generated in situ by re-



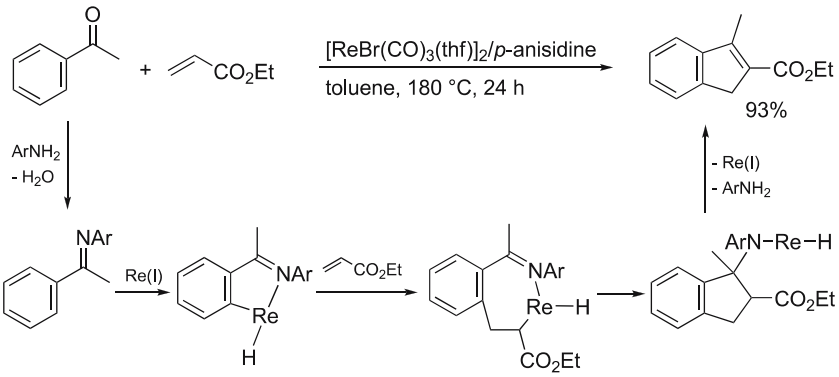
Scheme 11



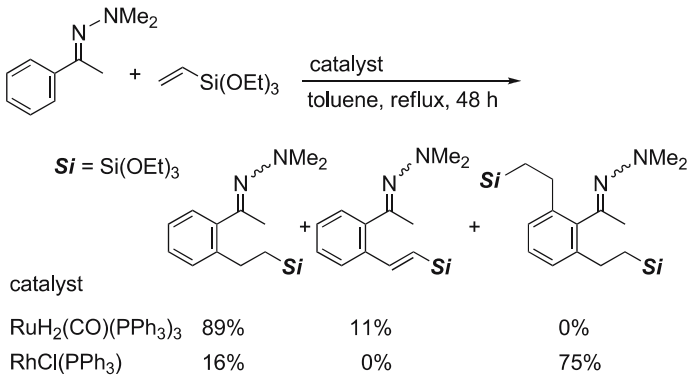
Scheme 12

action of aromatic ketones with *p*-anisidine) with acrylic acid esters, using $[ReBr(CO)_3(thf)]_2$ as a catalyst, gave indene derivatives [69]. These products were formed via C – H bond cleavage, followed by carbometalation of the acrylate, nucleophilic attack to the imino group, and elimination of *p*-anisidine (Scheme 13).

Hydrazone groups can also function as a directing group. In this case, $RuH_2(CO)(PPh_3)_3$, $Ru_3(CO)_{12}$, and $RhCl(PPh_3)_3$ complexes show high catalytic activity (Eq. 19) [70]. The ruthenium-catalyzed reaction of aromatic hydrazones with olefins gave a mixture of the alkylation and the alkenylation products. Interestingly, predominant formation of the alkylation product was observed in the $RhCl(PPh_3)_3$-catalyzed reaction. The choice of catalyst



Scheme 13

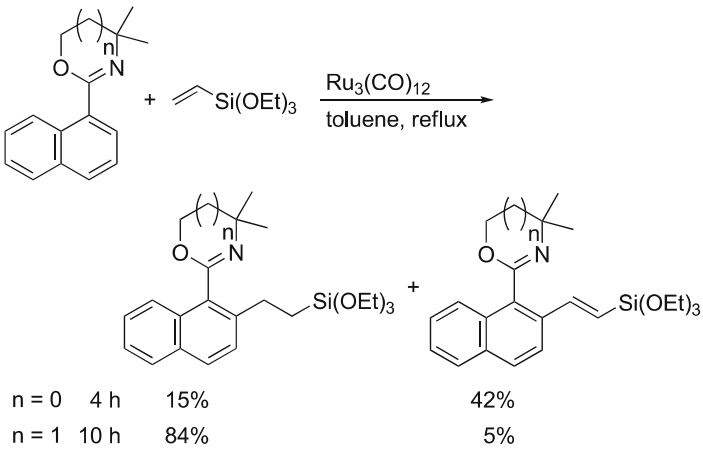


Equation 19

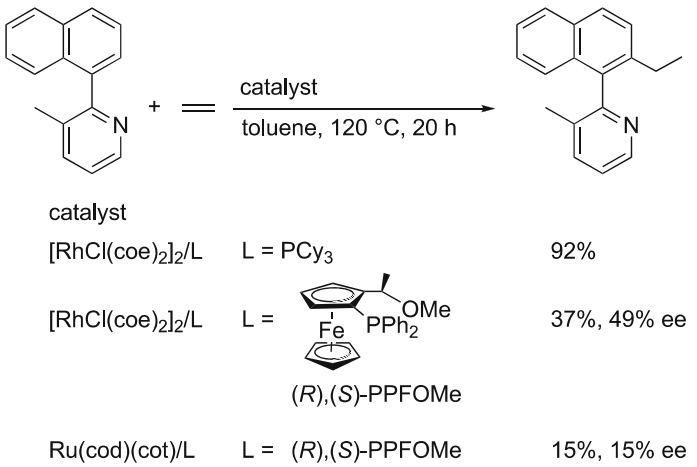
is important for the nitrogen-directed functionalization of C – H bonds in aromatic compounds with olefins.

Aromatic compounds having sp^2 nitrogen-containing heterocycles such as aryloxazolines (five-membered *N*,*O*-heterocycle) and aryloxazines (six-membered *N*,*O*-heterocycle) are also applicable for the coupling reaction with olefins [71]. The ring size of the *N*,*O*-heterocycles affects the product selectivity with respect to the alkylation and the dehydrogenative alkenylation products. The reaction of aryloxazolines provides the dehydrogenative alkenylation products as the major isomer, but in the case of aryloxazines, the usual 1 : 1 coupling product is formed as the major isomer (Eq. 20).

The C – H/olefin coupling of arylpyridines was extended to an atropselective alkylation of arylpyridines using $[RhCl(coe)_2]_2$ or Ru(cod)(cot) and a chiral phosphine ligand (Eq. 21) [72]. The chemical and optical yields are inadequate, but this result suggests that the atropselective alkylation of biaryl compounds can be attained by means of C – H/olefin coupling.

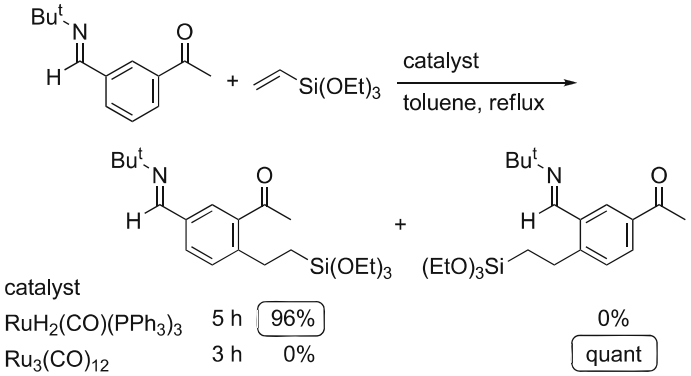


Equation 20



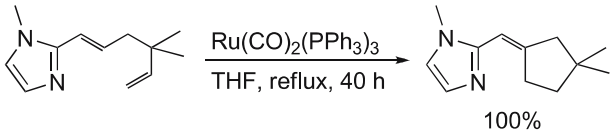
Equation 21

By taking advantage of the different catalytic activities between $RuH_2(CO)(PPh_3)_3$, which shows a high activity for aromatic ketones, and $Ru_3(CO)_{12}$, which is effective for aromatic imine, catalyst-specific C – C bond formation can be attained. In the case of coupling of 1-[3-(*tert*-butyliminomethyl)-phenyl]ethanone with triethoxyvinylsilane, the $RuH_2(CO)(PPh_3)_3$-catalyzed C – H/olefin coupling took place exclusively at the *ortho* position of the acetyl group, but the use of $Ru_3(CO)_{12}$ as a catalyst resulted in predominant C – C bond formation at the imino group side (Eq. 22) [73]. This catalyst-specific reaction can also be applied in the corresponding intermolecular version of catalyst-specific alkylation.



Equation 22

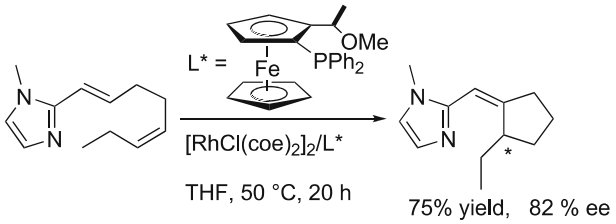
An intramolecular variant of chelation-assisted C – H/olefin coupling of heterocyclic compounds having an olefin moiety leads to the carbocyclic compounds. In 1996, the first development of the intramolecular C – H/olefin coupling reaction was reported by Murai and coworkers (Eq. 23) [74, 75]. They found that, for the carbocyclization via C – H/olefin coupling, $RhCl(PPh_3)_3$, $[RhCl(coe)_2]_2/PR_3$, $Ru(CO)_2(PPh_3)_3$, and $RuH_2(CO)(PPh_3)_3$ catalyst systems showed high catalyst activity. Rhodium complexes such as $RhCl(PPh_3)_3$, $[RhCl(coe)_2]_2/PR_3$, and $(\eta^5\text{-}C_5Me_5)Rh(C_2H_3SiMe_3)_2$ are usually more effective catalysts than ruthenium ones such as $RuH_2(CO)(PPh_3)_3$ and $Ru(CO)_2(PPh_3)_3$.



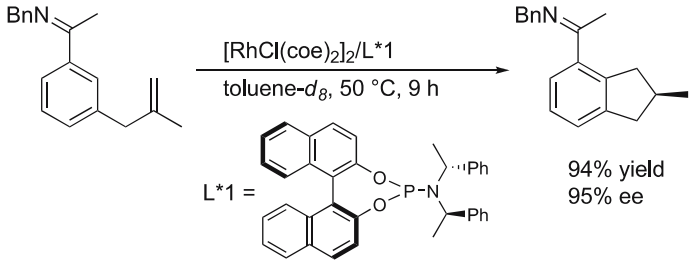
Equation 23

Their intramolecular cyclization via C – H/olefin coupling can be extended to enantioselective reactions. Chiral ferrocenylphosphine (*R*),(*S*)-PPFOMe was the suitable ligand for rhodium-catalyzed asymmetric carbocyclization via sp^2 nitrogen-directed C – H bond cleavage (Eq. 24) [76]. In these reactions, rhodium complexes showed the highest catalytic activity and the highest enantioselectivity but ruthenium catalysts showed moderate activity.

Highly efficient and enantioselective intramolecular cyclization of aromatic imines providing functionalized bicyclic ring systems were reported by Ellman and Bergman (Eq. 25) [77, 78]. Several aromatic imines having a 1,1-disubstituted olefin moiety can be used in this enantioselective cyclization. Chiral phosphoramidate and phosphite ligands gave impressive enantiose-

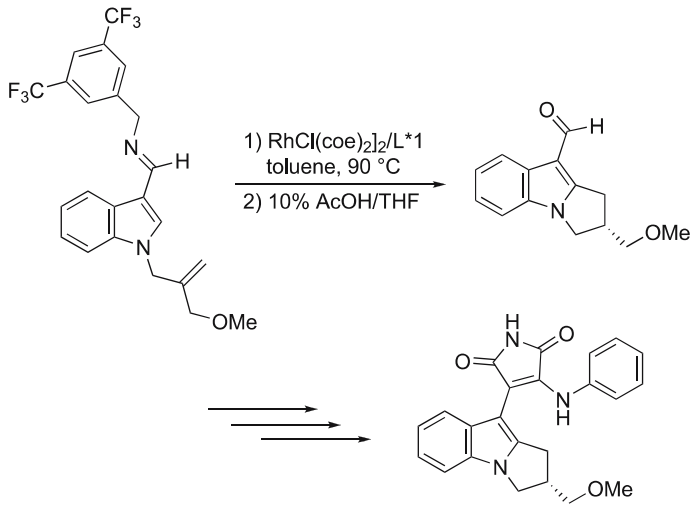


Equation 24



Equation 25

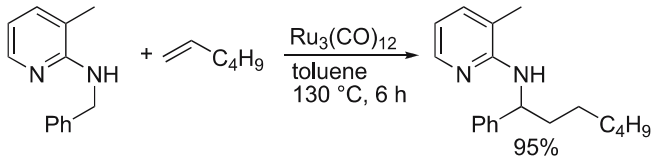
lectivities and conversions. This enantioselective cyclization reaction of aromatic imines giving bi- or tricyclic aromatic imines was applied to efficient and enantioselective synthesis of bioactive compounds. They synthesized biologically active dihydropyrrols or dihydroindoles by means of enantiolselective intramolecular cyclization using 1-allyl-3-imidazole derivatives (Eq. 26).



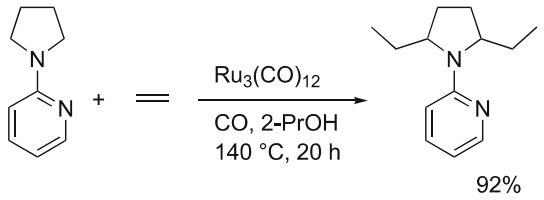
Equation 26

The intramolecular cyclization via C – H/olefin coupling allows a highly useful way for the synthesis of functionalized carbocycles.

The chelation-assisted aryl and olefinic C – H/olefin couplings can be extended to alkylation of sp^3 C – H bonds. The efficient alkylation of an sp^3 C – H bond α to the nitrogen atom in benzyl-(3-methylpyridin-2-yl)amine was reported by Jun et al. (Eq. 27) [79]. They proposed that the formation of a five-membered ruthenacycle was an important factor for carrying out this alkylation reaction. Murai and coworkers also reported on the ruthenium-catalyzed coupling of 2-*N*-pyridyldialkylamines (Eq. 28) [80]. The use of 2-propanol as a solvent dramatically improves the yield of the product and expands the applicable scope of the reaction.



Equation 27

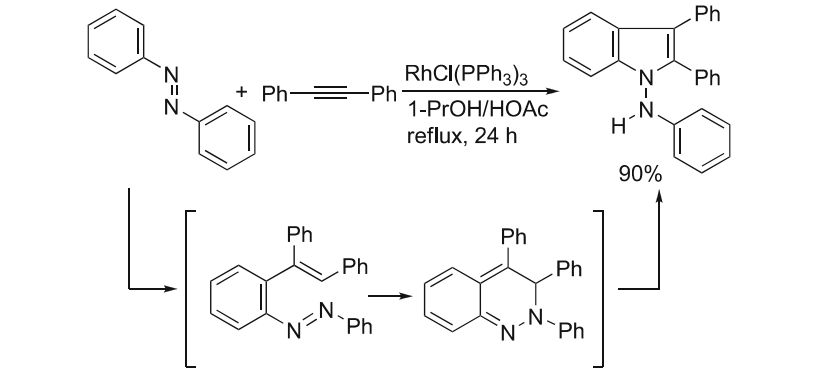


Equation 28

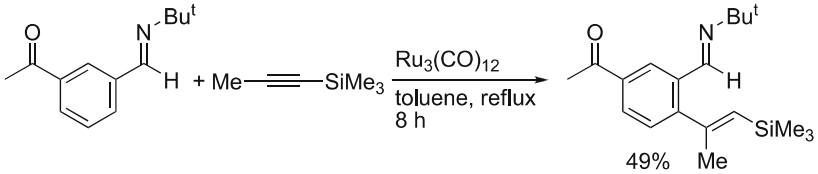
3.2 sp^2 Nitrogen-Directed Addition of C – H Bonds to C – C Triple Bonds

The rhodium-catalyzed coupling reaction of azobenzenes with acetylenes provided indole derivatives, which were formed via a C – H/acetylene coupling followed by a cyclization and rearrangement (Scheme 14) [81–83].

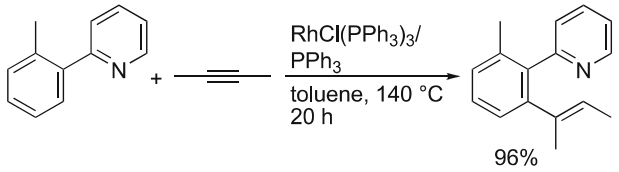
Several studies of transition metal-catalyzed *ortho*-selective alkenylation of C – H bonds in aromatic imines with acetylenes have been reported. The reaction of 3′-iminoacetophenone with internal acetylenes using $Ru_3(CO)_{12}$ as a catalyst resulted in alkenylation at the *ortho* position of the imino group (4′-position) (Eq. 29) [73]. Rhodium(I) complexes also functioned as a catalyst for the alkenylation of C – H bonds in arylpyridines and aromatic imines [84, 85]. The corresponding *ortho* alkenylation products were obtained in high yields (Eq. 30) [84]. The role of an additional PPh_3 ligand was proposed to



Scheme 14

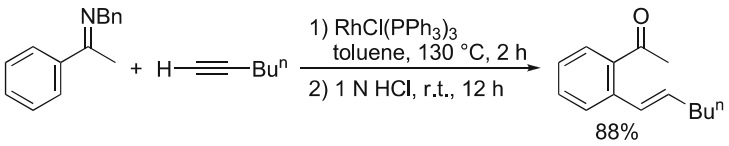


Equation 29



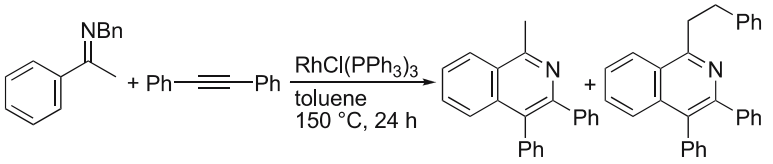
Equation 30

be the regeneration of reactive catalyst by the exchange with the phosphine oxide. The stereochemistry around the double bonds in the alkenylation products indicated that addition of the C – H bonds across the triple bonds took place in *syn* fashion. Terminal acetylenes are applicable in the case of the $RhCl(PPh_3)_3$-catalyzed alkenylation of ketimines (Eq. 31) [85].



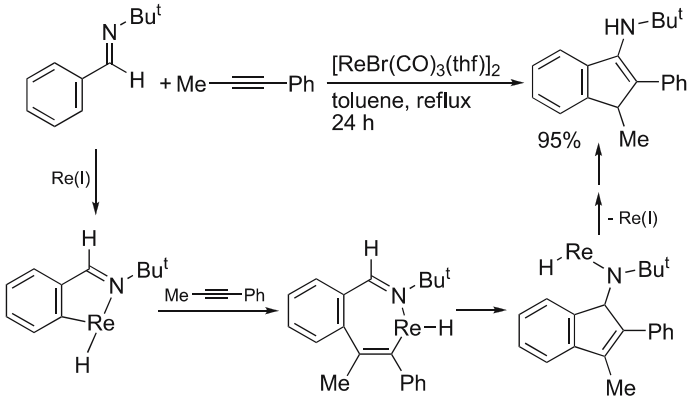
Equation 31

The coupling of aromatic ketimines with internal acetylenes using RhCl-$(PPh_3)_3$ catalyst afforded isoquinoline derivatives (Eq. 32). The reaction pathway is not clarified, but two molecules of the alkenylation product participated in the unusual tandem coupling reaction involving C – H bond cleavage and electrophilic reactions [85].



Equation 32

When $[ReBr(CO)_3(thf)]_2$ was used as catalyst for the reaction of aromatic aldimines with internal acetylene, indene derivatives were obtained in high yields (Scheme 15) [86–88]. They proposed that these products were formed through the reaction pathway shown in Scheme 15. The rhenium–carbon bonds have high nuclephilicity. The use of polar unsaturated molecules such as isocyanates and aldehydes led to formations of phthalimidines and isobenzofurans, respectively [89].

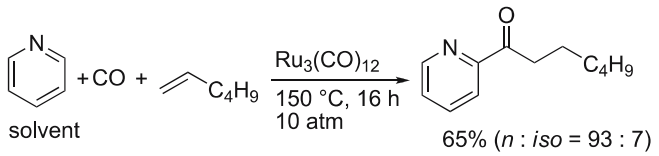


Scheme 15

3.3 sp^2 Nitrogen-Directed Carbonylation of C – H Bonds Using Olefins and Carbon Monoxide

Chelation-assisted acylation of C – H bonds with carbon monoxide is useful way for introduction of a carbonyl group on the benzene ring in a regioselective manner. In the case of Friedel–Crafts acylation of aromatic com-

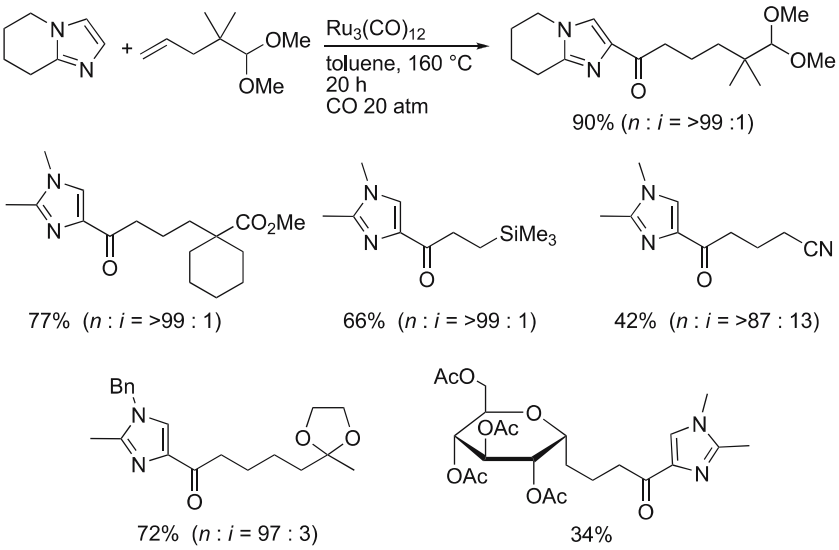
pounds, usually, a stoichiometric amount of Lewis acid should be required and a mixture of possible regioisomers are formed. The pioneering work of the catalytic C – H/CO/olefin coupling (carbonylation) was reported by Moore (Eq. 33) [90, 91]. For this reaction, $Ru_3(CO)_{12}$ complex showed the highest activity. Kinetic studies indicated that the rate of carbonylation displays a first order dependence upon both the catalyst concentration and the pyridine concentration, and a zero order dependence upon both the alkene concentration and the CO pressure. The reaction of internal alkenes, such as 2-hexene, gave the same liner/branched ratio as 1-hexene.



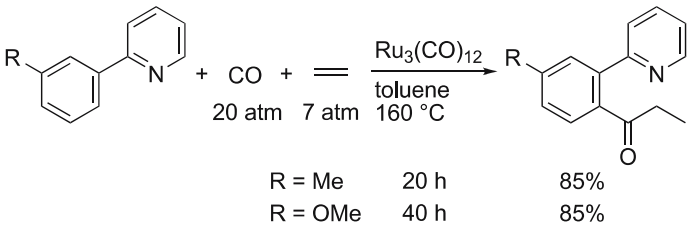
Equation 33

Extensive studies by Murai and Chatani found that various types of three-component coupling reactions of C – H/CO/alkenes can be catalyzed by $Ru_3(CO)_{12}$. In all cases, the coordination of sp^2 nitrogen was proposed to be essential for attaining the carbonylation reactions. Several five-membered nitrogen-containing heteroaromatic compounds can be used in the $Ru_3(CO)_{12}$-catalyzed acylation of C – H bonds. In these reactions, the C – C bond formation took place exclusively at the α position of the sp^2 nitrogen [92, 93]. Functional group compatibility of this carbonylation reaction is wide. A variety of functional groups, such as ketone, ester, cyano, acetal, *N*,*O*-acetal, ketal, and silyl groups, were tolerated under the reaction conditions (Scheme 16). The basicities of the sp^2 nitrogen in the heteroaromatic compounds largely affected the yields of the carbonylation products. Increasing the pK_a values of the sp^2 nitrogen in these heteroaromatic compounds, the yields of the products were increased as follows: imidazole (88%, pK_a 7.85) > thiazole (8%, pK_a 3.37) > oxazoles (5%, pK_a 2.91) > pyrazole (trace, pK_a 2.09) [93]. These results indicates that the coordination of the sp^2 nitrogen of these compounds participated in this C – H/CO/olefin coupling.

Drastic change of the regioselectivity from α to γ to the pyridine nitrogen was observed when the carbonylation was examined using 2-phenylpyridine as a substrate. Carbonylation did not take place at C – H bonds in the pyridine ring nor at the *m*- and *p*-positions of the benzene ring. The substituent on the aromatic ring largely affected the regioselectivity. In the case of *m*-substituted arenes with two different reaction sites, the C – C bond formation occurred at the less congested position exclusively (Eq. 34) [94, 95]. Several catalytic systems for the carbonylation of arylpyridines with carbon monoxide and ethylene have been studied. Combination of the catalyst and the solvent is important for attaining high yield. In the case of the rhodium carbonyl complex,



Scheme 16

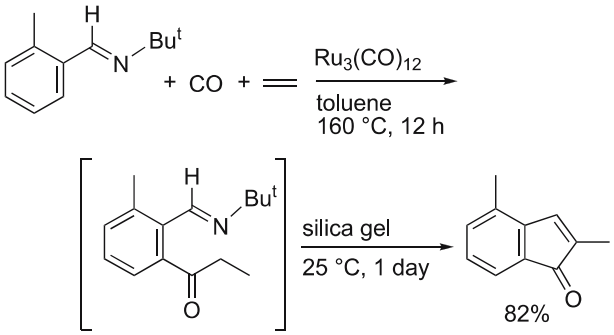


Equation 34

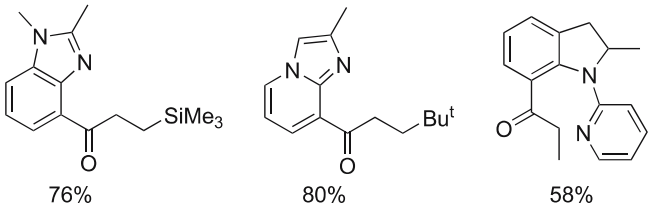
$Rh_4(CO)_{12}$, and ruthenium on carbon (Ru/C), the use of DMA as a solvent improved the yields of the *ortho* acylated arylpyridines [96]. The regioselectivity and the compatibility of the functional groups were not largely affected by these reaction parameters.

An oxazoline ring, which can be converted to a variety of functional groups such as carboxylic acid and nitrile groups, also functions as an effective directing group for the carbonylation at the *ortho* C – H bonds [97]. The reaction of aromatic aldimine gives indenones via carbonylation reaction at the *ortho* C – H bond followed by intramolecular aldol-type condensation (Eq. 35) [98].

The $Ru_3(CO)_{12}$-catalyzed carbonylation of C – H bonds in other aromatic compounds such as benzimidazoles [99, 100], imidazo[1,2-a]pyridines [99, 100], and *N*-pyridylindolines [101, 102] also gave the regioselective carbonylation products in good yields (Scheme 17).

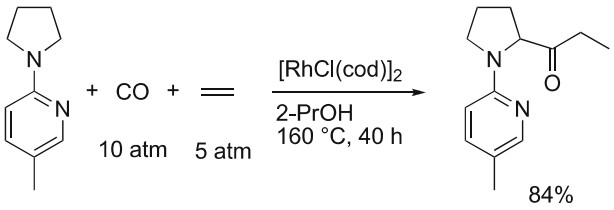


Equation 35



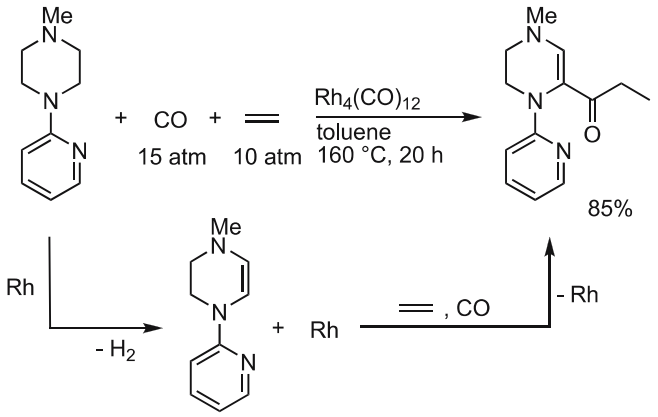
Scheme 17

The carbonylation of the sp^3 C – H bond adjacent to a nitrogen atom can be attained with the aid of $[RhCl(CO)_2]_2$ catalyst, and 2-propanol is the solvent of choice (Eq. 36) [103]. While cyclic amines exhibit a high reactivity (up to 84%), acyclic amines show relatively low reactivity (18%). Although the scope of this reaction is limited, this carbonylation protocol expands the scope of these reactions.



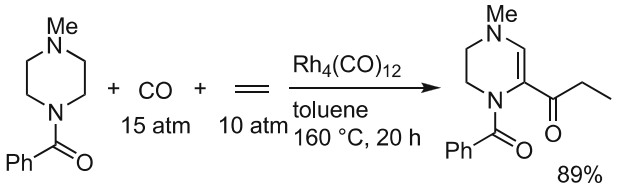
Equation 36

The reaction of *N*-(2-pyridinyl)piperazines with CO and ethylene in the presence of $Rh_4(CO)_{12}$ catalyst resulted in a novel type of carbonylation reaction (Scheme 18) [104]. The substitution of both an electron-donating group on the 4-nitrogen and an electron-withdrawing group (e.g., 5-COOMe, 4-COOMe, and 5-CF_3) on the pyridine ring causes a significant increase in reactivity. This carbonylation reaction proceeds through two discrete reac-



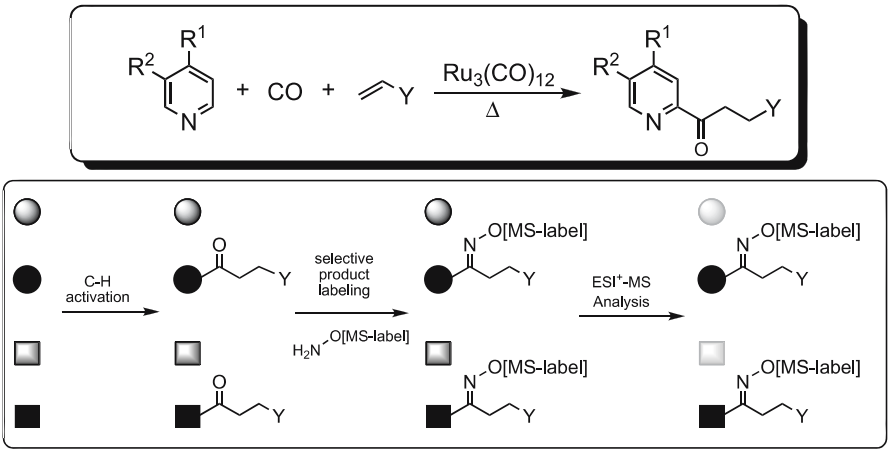
Scheme 18

tions: one is dehydrogenation of the piperazine ring and the other involves the carbonylation of the olefinic C – H bond [105]. In place of the pyridyl group, an acyl group can also serve as a directing group for carbonylation at an α C – H bond (Eq. 37) [106]. This is the first example of a carbonylation at a C – H bond that is directed by a functional group other than a C = N moiety.



Equation 37

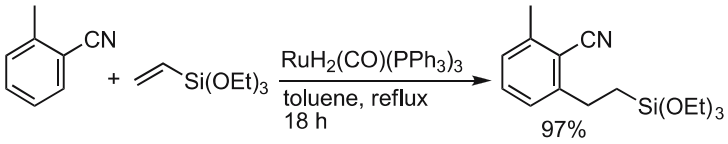
Several high-throughput protocols have recently been reported for determining optimal reaction conditions and applicable substrates and these protocols are frequently used to optimize the reaction conditions in transition metal-catalyzed reactions. Electrospray ionization mass spectrometry (ESI-MS) has drawn increasing attention for the analysis of combinatorial libraries. Ellman and Bergman applied this method to exploit $Ru_3(CO)_{12}$-catalyzed carbonylation at C – H bonds in *N*-heterocycles [107]. The high-throughput strategy for optimizing of the carbonylation and the discovery of new products are shown in Scheme 19.



Scheme 19

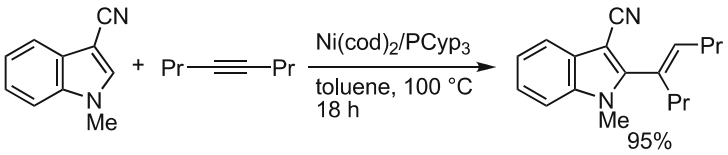
4
Other Functional Group-Directed Functionalization of C – H Bonds

Several other functional groups can be used as a directing group. In 1999, Murai and coworkers reported that the ruthenium-catalyzed alkylation of benzonitriles with triethoxyvinylsilane proceeded predominantly at the *ortho* position (Eq. 38) [108]. This regioselectivity indicates the possibility of π-coordination of the CN group to the ruthenium in the catalytic cycle.



Equation 38

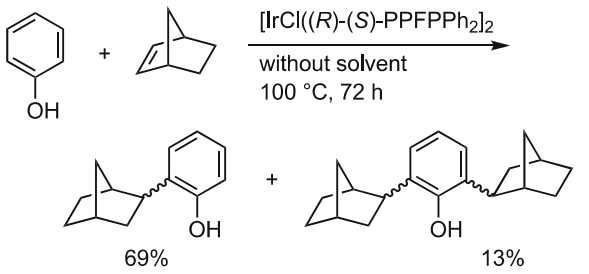
Alkenylation of C – H bonds in heteroarenes such as indols, benzimidazoles, and thiazoles with acetylenes takes place with the aid of $Ni(cod)_2/PCyp_3$ catalyst (Eq. 39) [109]. In these cases, the C – H bonds α to



Equation 39

the heteroatom add to the C – C triple bonds in *syn* fashion. The role of the directing group such as nitrile and ester groups in this catalytic reaction is a matter of some dispute, but this regio- and stereoselective alkenylation of heteroaromatic compounds provides a new protocol for functionalization of unreactive C – H bonds.

In the reaction of phenols with norbornenes using $[IrCl((R)\text{-}(S)\text{-}PPFPPh_2)]_2$, a phenolic hydroxy group can function as a directing group. The corresponding *ortho* alkylation products were obtained in good chemical yields, but the optical yields of these products were low (less than 5% ee) (Eq. 40) [110]. These results are very preliminary, but suggest the possibility of an asymmetric intermolecular alkylation of C – H bonds with olefins.



Equation 40

5 Concluding Remarks

In the 1970s and the 1980s, transition metal-catalyzed coupling reactions using organohalides and organometallic reagents were highly attractive research subjects in organic synthesis and a large number of reactions have been developed. In these cases, cleavage of carbon–halogen or carbon–pseudohalogen bonds with a low-valent transition metal is important for attaining these catalytic reactions. In the 1990s, double bonds in olefins became one of the most significant functional groups because ruthenium- and molybdenum-catalyzed olefin metathesis reactions were widely studied as one of the most exciting research topics. During the last decade, catalytic reactions involving C – H bond cleavage were paid attention by organic and organometallic chemists because otherwise-unreactive C – H bonds such as aromatic and aliphatic C – H bonds can be used as a functional group for constructing C – C bonds in organic synthesis. In particular, the C – H bond cleavage by means of chelation-assistance (i.e., directed metalation) was the most important breakthrough for developing highly efficient, selective catalytic reactions involving C – H bond cleavage. The catalytic reactions involving C – H bond cleavage via chelation-assistance have opened a new research field.

This chapter has described several studies of catalytic functionalization of unreactive C – H bonds, especially additions of C – H bonds to olefins and acetylenes, and carbonylation using olefins and carbon monoxide. These reactions are highly important and attractive because of 100% atom efficiency procedures for C – C bond formation. To date, a variety of functional groups, such as ketones, esters, aldehydes, amides, imines, imidates, nitrile, amines, and heterocylic compounds having sp^2 nitrogen, can be used as the directing group for the regioselective transformation of C – H bonds to C – C bonds.

The scope and limitations of these types of coupling reactions have been explored and several important features of these transformations have been uncovered. In the coming decade, it is likely that complex molecules involving natural products, pharmaceuticals, organic electronic devices, and so on will be synthesized using C – H bonds. So, the importance of the catalytic functionalization of C – H bonds by means of chelation-assistance will continue to increase.

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Chelation-Assisted Arylation via C–H Bond Cleavage

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Abstract Regioselectivity was achieved in transition-metal-catalyzed arylation reactions via C–H bond cleavage through the use of chelation-assistance. Palladium, rhodium, and ruthenium complexes proved useful for the development of broadly applicable methodologies for intermolecular direct arylation reactions. These include protocols for direct arylation reactions using aryl chlorides and tosylates as well as transformations that proceed through the cleavage of unactivated C(sp^3)–H bonds.

Keywords Arylation · Chelation · Palladium · Rhodium · Ruthenium

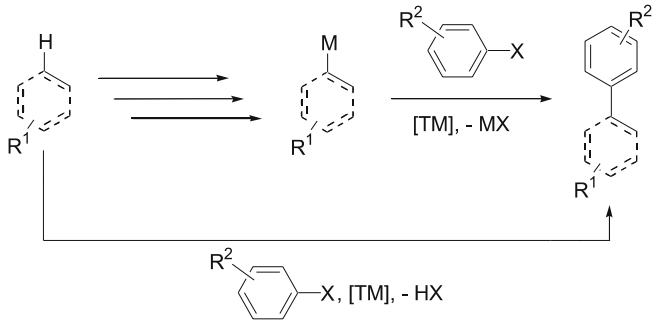
Abbreviations

Acac	acetylacetonate
Ac	acetyl
Ad	adamantyl
Ar	aryl
BQ	benzoquinone
cod	1,5-cyclooctadiene
cat	catalytic
DG	directing group
DMA	*N*,*N*-dimethylacetamide

DMF *N*,*N*-dimethylformamide
HMPT hexamethylphosphortriamide
M metal
NMP *N*-methylpyrrolidinone
TM transition-metal
TON turn over number
Ts 4-toluenesulfonyl

1 Introduction

Methodologies for regioselective arylation reactions largely employ transition-metal-catalyzed cross-coupling reactions between organic (pseudo)halides and organometallic reagents [1, 2]. The organometallic compounds are often not commercially available or are expensive, and their use gives rise to the formation of undesired by-products. Accordingly, focus has shifted to direct arylation reactions via cross-couplings of C – H bonds as an ecologically benign and economical alternative (Eq. 1) [3–9].



Equation 1

In contrast to more traditional cross-coupling reactions with organometallic reagents, pronucleophilic substrates for direct C – H bond arylation reactions do not display a single reactive functional group. Therefore, the regioselective arylation of a specific C – H bond in a given molecule constitutes a major objective for the development of preparatively useful direct arylation methodologies [10][1].

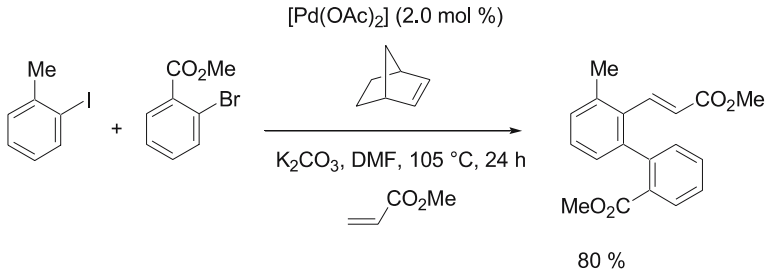
One approach for achieving selectivity in overall intermolecular arylation reactions is represented by the installment of a temporary linkage. Thereby, an intramolecular C – H bond arylation can be performed, which usually proceeds with excellent regioselectivity (for selected examples, see [11–17]). The

[1] For example unsatisfactory selectivities are obtained in iridium-catalyzed C–H bond arylation reactions of simple arenes

scope of this approach is inherently limited, and additional reaction steps are required, rendering the overall process economically less attractive for intermolecular transformations.

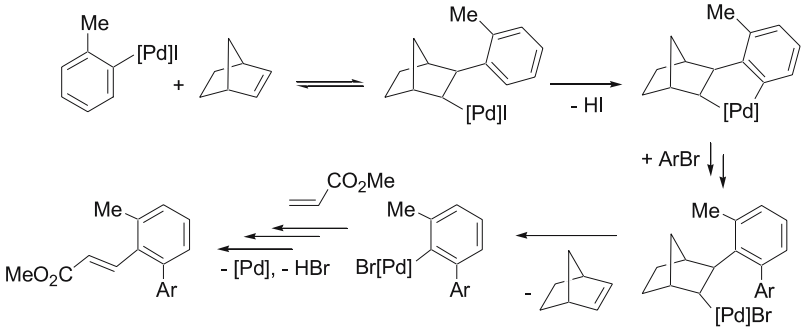
Useful intermolecular direct arylation reactions can be performed regioselectively, when electronic effects dominate the reactivity of a given substrate. Thus far, this approach proved mainly preparatively valuable for palladium- (selected examples [18–30] and references cited therein) [31, 32] or rhodium-catalyzed [33–37] arylation reactions of heterocyclic substrates.

Regioselective intermolecular *ortho*-alkylation and -arylation reactions of carbocyclic halides were developed based on elegant studies by Catellani and Chiusoli [38, 39]. The key to success was the use of palladium catalysts modified with norbornene as additive. In a beautiful recently reported transformation, chemo- and regioselective arylations of *ortho*-C – H bonds in aryl iodides were achieved using aryl bromides as electrophiles (Eq. 2) [40]. In this three-component reaction, an intermolecular Heck-reaction served as the final event of the catalytic cycle.



Equation 2

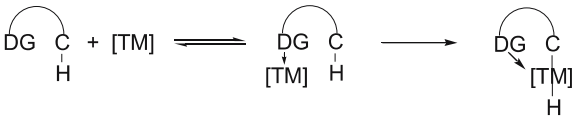
The mechanism of these regioselective arylations involves the oxidative addition of the aryl iodide to a palladium(0) species, and an insertion of norbornene into the formed palladium-carbon bond. This sets the stage for the selective activation of a specific *ortho*-C – H bond (Eq. 3). Recent computa-



Equation 3

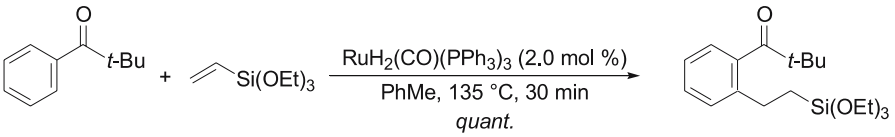
tional studies suggest that the subsequent arylation with the bromide takes place without the intermediacy of Pd(IV) species [41].

These early examples of selective C – H bond arylation through the use of a temporary covalent linker [42–45] highlight the potential of performing intermolecular direct arylations in an intramolecular fashion. A related, but more general strategy makes use of coordinating groups, which enable a chelation-aided functionalization of specific C – H bonds. The coordination of directing groups (DG) delivers the transition metals in close proximity to specific C – H bonds, and leads to cyclometalated products via entropically favorable intramolecular C – H bond activation processes (Eq. 4) [46, 47][2].



Equation 4

Early contributions demonstrated the utility of the coordination-assistance concept for regioselective catalytic *alkylation* reactions of arenes [48–51][3]. A seminal study was reported by Murai and coworkers, disclosing selective ruthenium-catalyzed alkylation reactions of aromatic ketones (Eq. 5) [50, 51].



Equation 5

Herein, a survey of the literature up to fall 2006 is provided, covering catalytic [52, 53][4] arylation reactions of C – H bonds, which proceed regioselectively due to the presence of a coordinating moiety. Chelation-assisted two-step arylation processes, such as directed *ortho*-metallation/cross-coupling sequences [54], will not be summarized in this review, but are discussed separately by Prof. Sniekus (in this volume). Only selected examples of vinylations of C – H bonds will be discussed in more detail in this work, although further transformations were reported, which are mechanistically related to chelation-assisted arylation reactions [55].

[2] It is noteworthy, that some of these transformations do not necessarily proceed through precoordination of the functional group to the transition metal, but might be the result of thermodynamic reaction control, as shown in a stoichiometric experiment employing an iridium complex [47]

[3] For a recent report on similar rhodium-catalyzed alkylations, see [49]

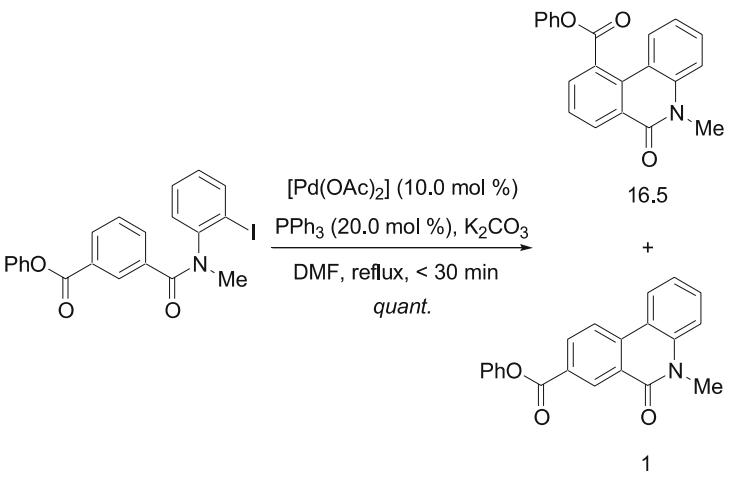
[4] For the early use of copper salts for regioselective stoichiometric direct arylation rections, see [52, 53]

2
Palladium-Catalyzed Arylations

2.1
Intramolecular Arylations

Cyclopalladation is a very facile process, which was observed as early as 1965 in the reaction between diazobenzene and palladium chloride [56]. Accordingly, palladium complexes [57][5] are arguably the most widely used transition metal catalysts for direct C – H bond arylation reactions [31].

The regioselectivity of palladium-catalyzed intramolecular direct arylation reactions [16, 58][6] can be influenced by coordinating groups in the substrate. Hence, Harayama and coworkers showed recently that direct arylation reactions of benzanilide substrates yield predominantly the sterically more hindered tri-*ortho*-substituted biaryls, when a phenoxycarbonyl substituent is present in *ortho*-position to the C – H bond (Eq. 6) [59]. The excellent catalytic performance is illustrated by a remarkably short reaction time.



Equation 6

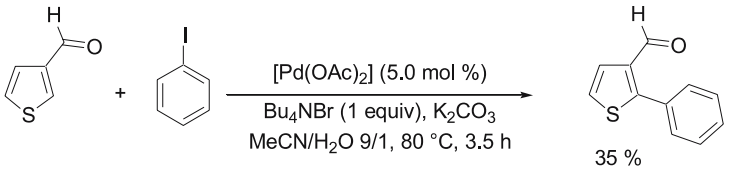
2.2
Intermolecular Arylations of Heterocycles

Heterocycles are ubiquitous in compounds with activity of relevance to biology. Intermolecular palladium-catalyzed arylation reactions of heterocyclic

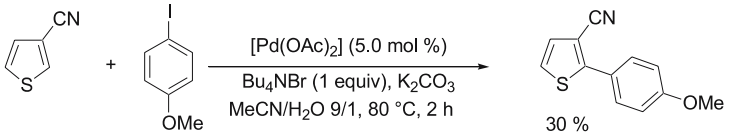
[5] For the stoichiometric arylation of the ligand in a cyclopalladated complex derived from tri(*o*-tolyl)phosphine, see [57]

[6] For mechanistic studies on palladium-catalyzed intramolecular direct arylation reactions, see [58] and references cited therein

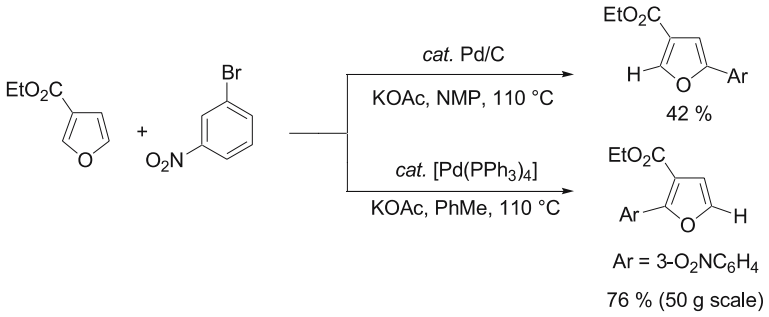
starting materials proved highly valuable and versatile [31, 32]. The regioselectivity of these transformations can be influenced by potentially coordinating functionalities. Lemaire and coworkers found that palladium-catalyzed direct arylations of thiophenes with electron-withdrawing substituents in the 3 position yielded selectively the more sterically hindered product. Particularly useful transformations were achieved under Jeffrey's reaction conditions. Importantly, the corresponding 5-arylated products were not observed, indicating chelation-assistance (Eqs. 7 and 8) [17, 60–62][7].



Equation 7



Equation 8



Equation 9

Interestingly, the catalytic system proved efficient in aqueous media. However, rather low yields of isolated products were generally obtained.

Careful choice of reaction conditions allowed Sharp and coworkers to develop regioselective direct arylations of 3-carbalkoxy furan and thiophene [63]. While a ligandless palladium catalyst yielded in NMP predominantly less sterically congested 5-arylated products, a palladium phosphine complex delivered, likely because of chelation-assistance, in an apolar solvent the more hindered 2-arylated heterocycles (Eq. 9).

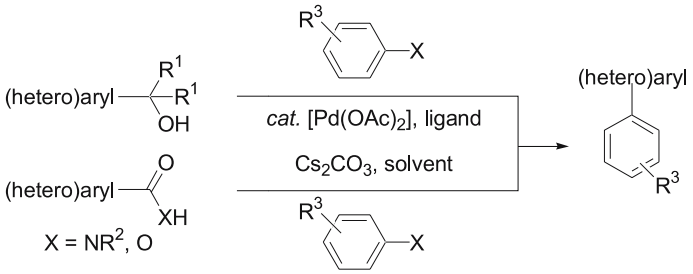
[7] For regioselective direct arylations of an electron-rich thiophene, see [62]

Further examples for regioselective chelation-aided direct arylation reactions of heterocyclic substrates were reported by Miura and coworkers [64], and are discussed separately by M. Miura (in this volume).

2.3
Intermolecular Arylations of Carbocycles and Acyclic Substrates

Seminal studies on palladium-catalyzed chelation-assisted intermolecular arylation reactions of carbocyclic substrates were disclosed by Miura and coworkers [31, 65–67]. Arylation reactions were achieved regioselectively employing for example alcohols [65, 68], amides [69], ketones [70, 71], or aldehydes [70] as directing groups. An extension of these methodologies to benzaldehyde derivatives and chlorides was recently reported by Özdemir and Çetinkaya [72, 73].

Regioselective arylations proved just as viable through the use of arylmethanols [74–76] or carboxylic acids and their derivatives as pronucleophiles (Eq. 10) [64] (see also [77, 78]).



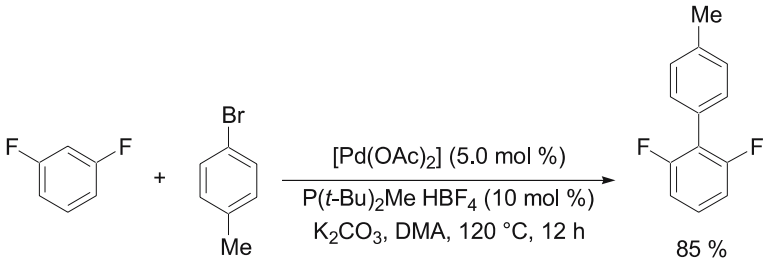
Equation 10

Some of these elegant transformations include not only a C – C bond cleavage [79], but also a direct arylation. A detailed discussion of these methodologies is provided separately by M. Miura (in this volume).

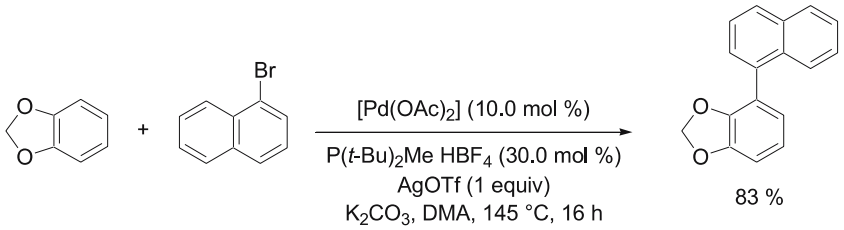
On the basis of intramolecular transformations, Fagnou and coworkers elaborated reaction conditions for regioselective palladium-catalyzed direct arylation reactions of benzene derivatives [16]. Particularly, the use of an electron-rich ligand along with K_2CO_3 as base allowed for highly regioselective direct arylation reactions of fluoroarenes (Eq. 11) [80, 81].

Computational studies indicated that the observed selectivities are rather a result of the C – H acidity [58] and not due to a stabilizing interaction between palladium and a fluorine substituent [80].

On the contrary, a directing group effect was proposed to account for the exclusive formation of single regioisomers in direct arylation reactions of electron-rich 1,3-benzodioxole (Eq. 12) [16, 82].



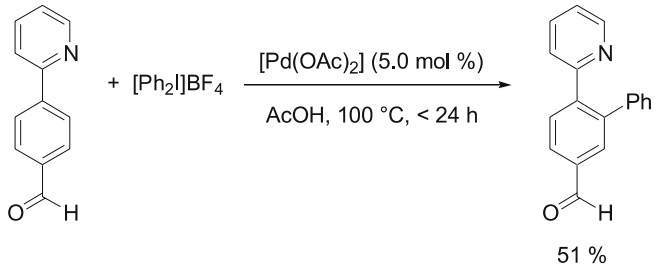
Equation 11



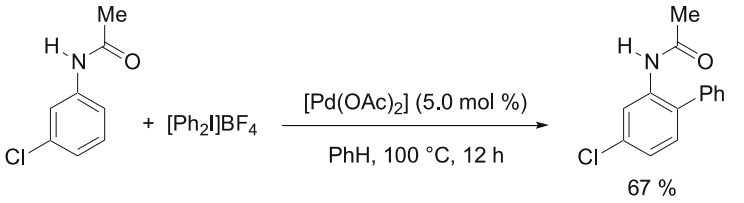
Equation 12

It is noteworthy that a less basic ether acts here as the directing group, and that easily accessible aryl chlorides proved suitable electrophiles.

Although in depth mechanistic insight into palladium-catalyzed direct arylation reactions is still lacking, the above summarized palladium-catalyzed arylation reactions likely proceed through Pd(0)/(II) catalytic cycles [58]. A different approach was reported for chelation-controlled arylation reactions with aryliodonium salts [83]. On the basis of reaction conditions elaborated for regioselective oxidation reactions of C – H bonds [84–88], Sanford disclosed palladium-catalyzed arylation reactions, which probably proceed through a Pd(II)/(IV) [89] regime [83]. From a practical viewpoint, it is noteworthy that the protocol tolerated a wide variety of valuable functionalities, such as halides, amides, enolizable ketones, or aldehydes as well as moisture and air (Eq. 13).



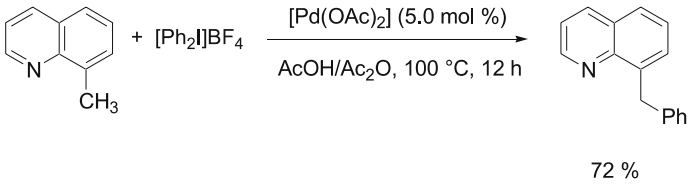
Equation 13



Equation 14

Further, a number of directing groups, including pyridines, pyrrolidinones, oxazolidinones, and anilides [90–93][8] were shown to enable highly selective arylation reactions [83] (Eq. 14).

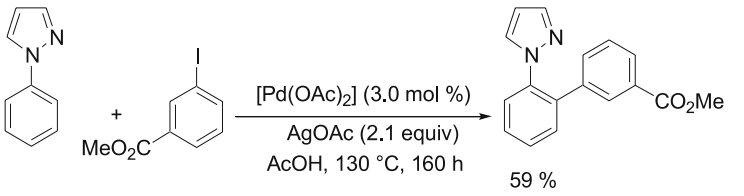
Also the more demanding intermolecular arylation of benzylic C – H bonds proceeded with high efficacy (Eq. 15) [83].



Equation 15

The scope of this protocol is somewhat limited due to the use of comparably expensive aryliodonium salts, of which only the benzene derivative is (thus far) commercially available.

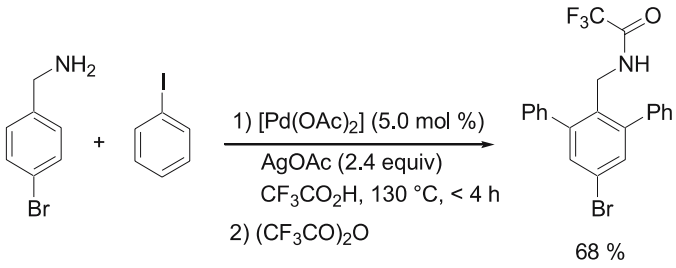
An extension to more easily accessible aryl iodides was accomplished by Daugulis and Zaitsev [94, 95]. Through the use of stoichiometric amounts of AgOAc, anilide [55, 90–93][8], and pyridine derivatives as well as a pyrazole were arylated employing electron-rich and moderately electron-poor aryl iodides [96] (Eq. 16). However, when using strongly electron-poor iodides, the reactions became slow and proceeded only with the most reactive pronucleophiles.



Equation 16

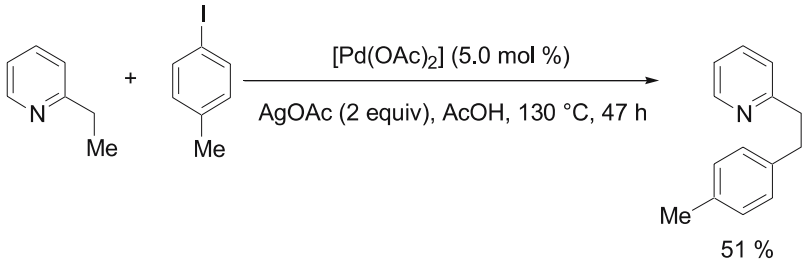
[8] For relevant stoichiometric transformations, see [90, 91]; for related palladium-catalyzed alkenylation and methylation reactions, see [55] and [92, 93]

Benzylamines and *N*-methylbenzylamines can be arylated in *ortho*-position with catalytic amounts of palladium acetate and aryl iodides [97]. Under the reaction conditions, the desired products are partially converted into the corresponding amides. Therefore, amine products were generally protected as amides prior to isolation (Eq. 17). Notably, bromo-substituents were tolerated by the catalytic system, which allows for further elaboration of the products. Unfortunately, amines displaying a β-hydrogen did not lead to C – H bond arylation.



Equation 17

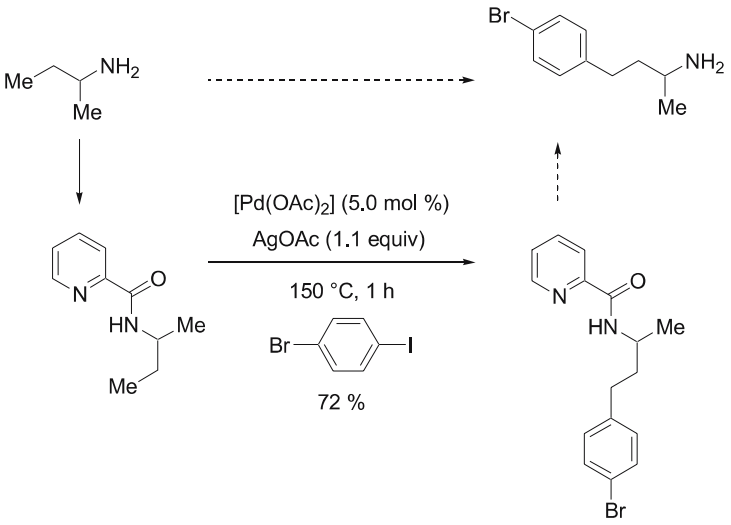
Notably, the catalytic system allowed for the selective arylation of more challenging substrates, namely an unactivated C(sp^3) – H [98, 99][9] bond in 2-ethyl pyridine (Eq. 18) [96].



Equation 18

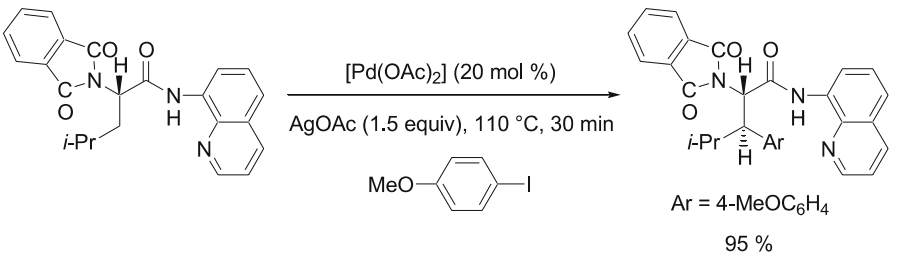
If an additional pyridine or quinoline coordinating group is present, C(sp^3) – H bonds can be more efficiently arylated. An application of this chemistry was disclosed by Daugulis and coworkers with the use of 8-amino-quinoline, or 2-picolinic acid as auxiliary directing groups. Thereby, selective C(sp^3) – H bond arylation reactions of carboxylic acids and amine derivatives, respectively, proved viable (Scheme 1) [100]. The chemo- and regioselective arylation of a specific C – H bond is a strong testament of the chelation-assistance concept.

[9] For the use of stoichiometric amounts of palladium for arylation reactions of C(sp^3)–H bonds, see [99]



Scheme 1 Regioselective arylation via cleavage of a C(sp^3) – H bond

Corey and coworkers showed that *N*-phthaloyl-α-amino acid amides of 8-aminoquinoline can be selectively arylated at the β-position (Eq. 19). The results reported by these authors are also generally supportive of a Pd(II)/Pd(IV) catalytic cycle [101].

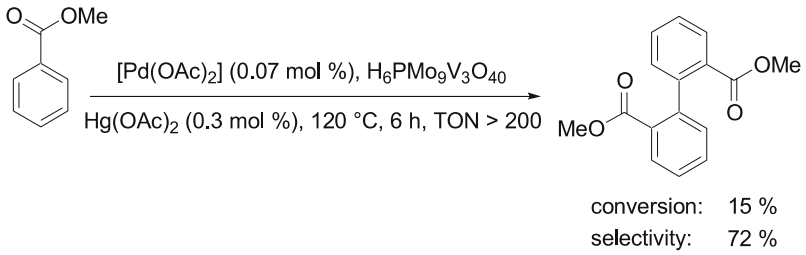


Equation 19

2.4 Oxidative Arylation Reactions

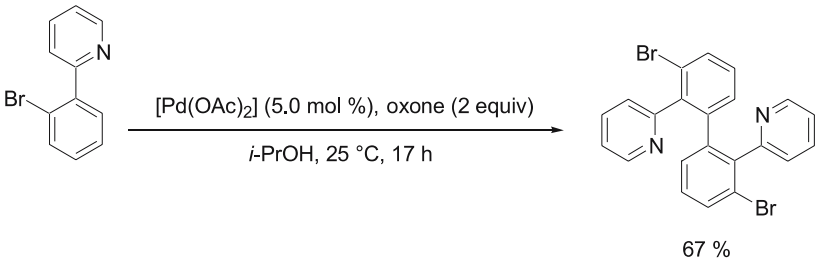
Regioselective direct arylation reactions of C – H bonds offer the advantages of enhanced efficiency and decreased by-product formation. With respect to starting material availability and atom economy, an even more attractive approach to biaryls is represented by the oxidative coupling of two unfunctionalized arenes. A variety of different reagents have been developed for oxidative aryl–aryl-coupling reactions [102–104].

An example for an oxidative coupling, which proceeded regioselectively through chelation-assistance, was reported by Lee and coworkers (Eq. 20) [105]. The reported conversion was comparably low, which was due to the low catalyst loading. Hence, an impressive turn over number (TON) of > 200 with respect to palladium was accomplished. The addition of catalytic amounts of mercury acetate enhanced the catalytic efficacy significantly.

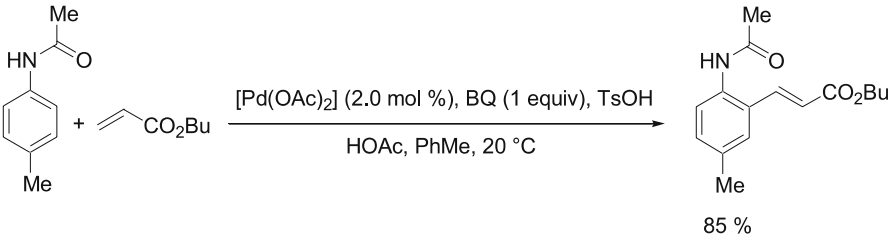


Equation 20

More recently, Sanford and coworkers reported on palladium-catalyzed regioselective oxidative coupling reactions of phenyl pyridine derivatives [106]. The use of oxone as terminal oxidant in *i*-PrOH as solvent allowed for very mild reaction conditions (25 °C). Thereby, a variety of important functional groups was tolerated, such as a bromide or a thienyl-substituent (Eq. 21).



Equation 21



Equation 22

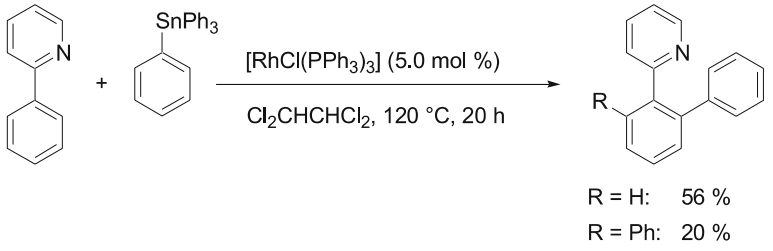
Interestingly, evidence was provided that suggests a mechanism, involving two sequential C – H bond activation reactions at Pd(II) and Pd(IV) with dramatically different selectivities.

A related chelation-assisted oxidative vinylation [107] of C – H bonds was previously achieved with a palladium catalyst in acidic medium, employing benzoquinone (BQ) as terminal oxidant (Eq. 22) [108, 109]. The transformation also takes place under remarkably mild reaction conditions (20 °C).

3
Rhodium-Catalyzed Arylation Reactions

3.1
Arylations with Aromatic Organometallic Reagents

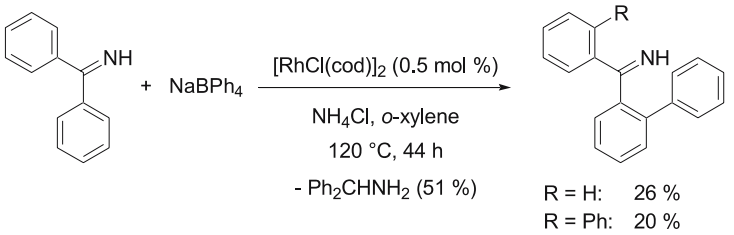
A rhodium-catalyzed chelation-assisted arylation of a C – H bond was reported in 1998 [110]. Arylstannanes allowed for rhodium-catalyzed regioselective functionalization reactions of 2-aryl pyridines (Eq. 23). More generally speaking, this study constitutes the first arylation of a C – H bond with organometallic compounds as arylating agents. Unfortunately, the mechanism of this remarkable transformation was not studied in more detail. It is, however, noteworthy that $Cl_2CHCHCl_2$ was necessary as solvent. Further, the formation of $Cl_2C = CHCl$ was observed, which was found essential for catalytic turnover [111, 112][10].



Equation 23

While studying a rhodium-catalyzed Suzuki–Miyaura-type cross-coupling with aryl halides [113], Miura and coworkers reported on a novel arylation reaction of an imine employing less toxic tetraphenylborate (Eq. 24) [114]. Unfortunately, rather low yields of mono- and di-arylated products were isolated. This is due to a reduction of the starting material via a sequence

[10] It is interesting to speculate whether catalytic turnover is achieved through hydro-dehalogenation of a chloroalkene. For a recent related study, see [112]

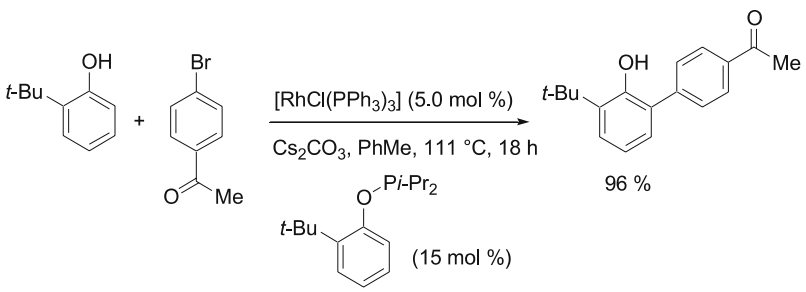


Equation 24

consisting of a rhodium hydride addition and subsequent protonation. The reduction of the imine is mandatory for the regeneration of a rhodium chloride species, and thereby for catalytic turnover. Note that the use of sacrificial pinacolone proved useful in ruthenium-catalyzed arylation reactions with aromatic organometallic species [115, 116] (Sect. 4.1).

3.2 Arylations with Aryl Halides

A rhodium-catalyzed arylation with organic halides was accomplished employing Wilkinson's catalyst along with a phosphinite additive. Thereby, a novel chelation-assisted arylation of phenols was achieved by Bedford and coworkers (Eq. 25) [117].

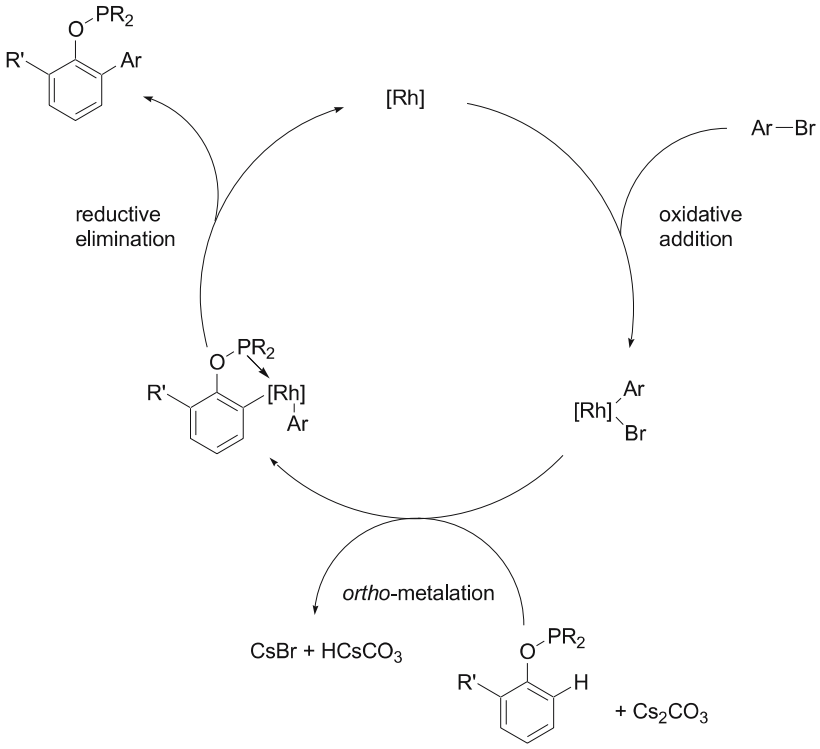


Equation 25

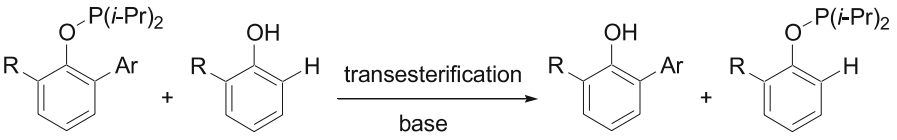
Notably, the methodology allows for the use of substrates displaying a variety of valuable functional groups, including heteroaromatic electrophiles. However, only *ortho*-substituted phenols were efficiently converted following this protocol.

The mechanism of the transformation is based on an *ortho*-metallation and arylation of the corresponding phosphinite as depicted in Scheme 2 [117].

Therefore, a transesterification of the phosphinite derived from the desired product by the phenol starting material is essential for the overall transformation (Eq. 26).



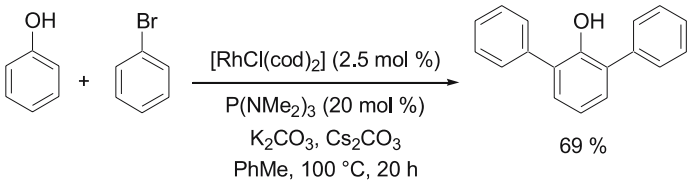
Scheme 2 Proposed mechanism for rhodium-catalyzed arylation of phenols



Equation 26

Accordingly, the phosphinite co-catalyst for each individual substrate needs to be prepared prior to catalysis from the corresponding phenol in order to avoid the formation of undesired and difficult to separate by-products. Conceptually, this rhodium-catalyzed transesterification-based *ortho*-functionalization of phenols is reminiscent of Lewis' ruthenium-catalyzed *ortho*-alkylation [48].

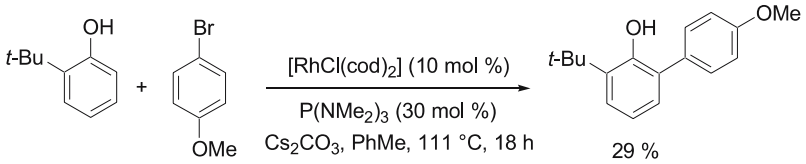
A solution to the problem was disclosed independently by Oi, Inoue and coworkers [118] as well as Bedford [119] with the use of economical, but toxic $P(NMe_2)_3$ (HMPT) as additive. A catalyst comprising $[RhCl(cod)_2]$ and HMPT proved complementary to the phosphinite-derived system, al-



Equation 27

lowing for an efficient conversion of phenol substrates displaying no *ortho*-substituents (Eq. 27).

However, sterically demanding substituents in *ortho*-position of the hydroxyl-group led to significantly reduced catalytic activity when compared to the one observed for phosphinite-based catalysts (Eq. 28).



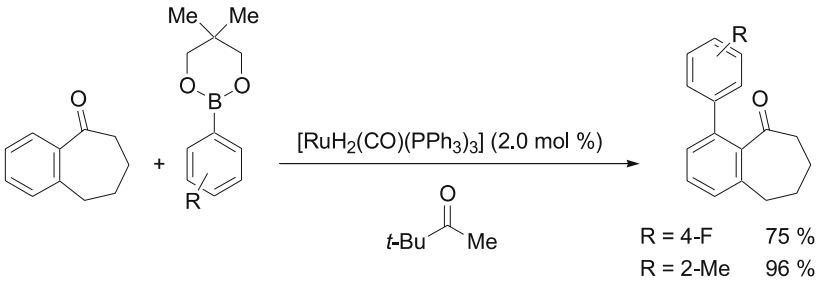
Equation 28

4
Ruthenium-Catalyzed Arylation Reactions

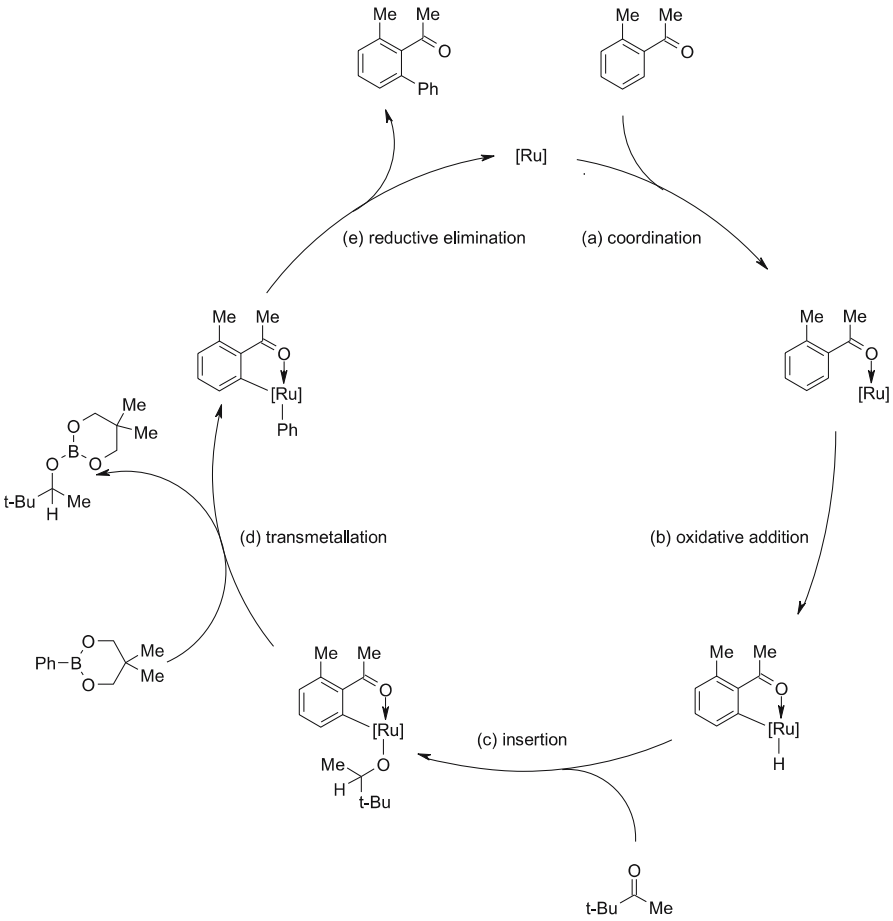
4.1
Arylations with Aromatic Organometallic Reagents

A ruthenium-catalyzed [120, 121] chelation-assisted approach was developed based on arylboronates as arylating agents [115, 116]. Thereby, a regioselective ruthenium-catalyzed arylation employing substrates with an oxygen-containing directing group was viable. A variety of aromatic ketones and boronates with both electron-donating as well as -withdrawing substituents were efficiently converted in pinacolone (Eq. 29).

Mechanistic studies showed that pinacolone acts here not only as solvent, but formally also as an oxidizing agent. Additionally, inter- and intramolecular competition experiments with D-labeled ketones provided evidence for a precoordination of the ruthenium catalyst by the oxygen of the aryl ketone [116]. Thus, a proposed mechanism was elaborated consisting of (a) coordination of the substrate, (b) oxidative addition to yield an *ortho*-metallated ruthenacycle, (c) insertion of pinacolone into the [Ru] – H bond, (d) transmetallation, and finally (e) reductive elimination (Scheme 3).



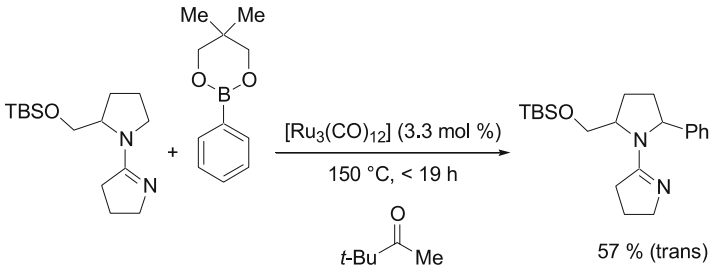
Equation 29



Scheme 3 Proposed mechanism for ruthenium-catalyzed arylations of ketones

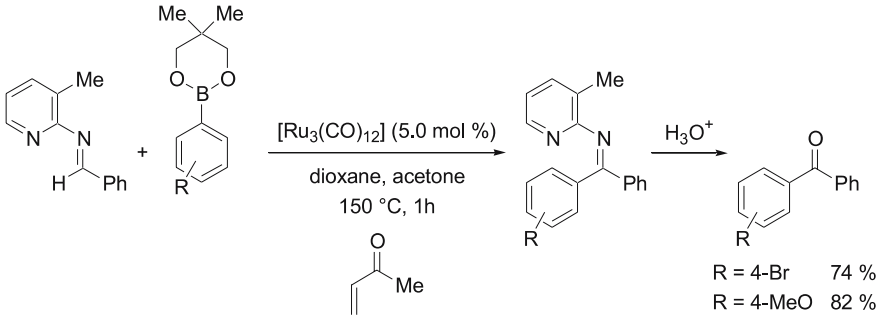
The use of easily available functionalized boron-based arylating reagents should prove highly valuable for further applications to organic synthesis.

Recently, an extension of this approach to the regioselective arylation of $C(sp^3)-H$ bonds was reported. Hence, the ruthenium-catalyzed α-arylation of pyrrolidines and piperidines was accomplished using arylboronates and pinacolone [122] (Eq. 30).



Equation 30

Jun used also a related approach for a ruthenium-catalyzed arylation of aldimines [123]. Here, a pyridyl-substituent allowed for the selective arylation employing arylboronates. Methyl vinyl ketone as additive led to high isolated yields for the corresponding ketones (Eq. 31).

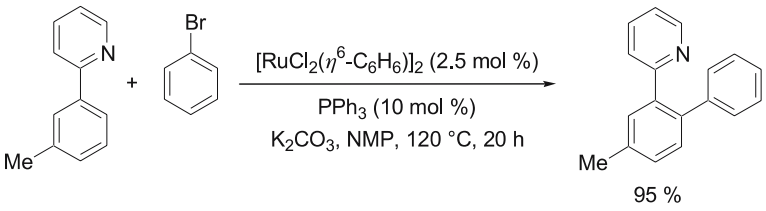


Equation 31

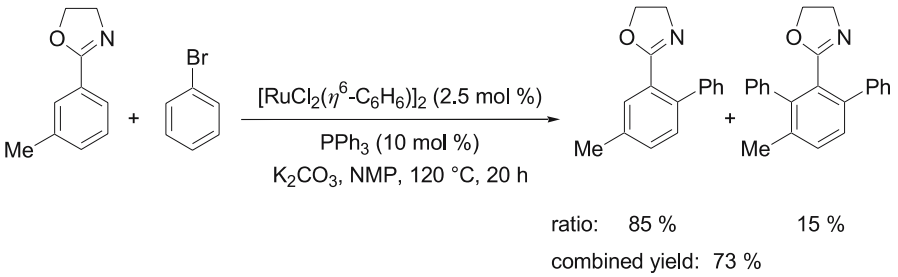
4.2 Arylations with Aryl Halides

A catalytic system comprising $[RuCl_2(\eta^6-C_6H_6)]_2$ and PPh_3 enabled regioselective arylation reactions of pyridines [124] and imines [125] employing aryl bromides (Eq. 32).

Subsequently, the same protocol proved applicable to chelation-assisted arylation reactions of aryl-substituted oxazolines (Eq. 33) [126]. The trans-



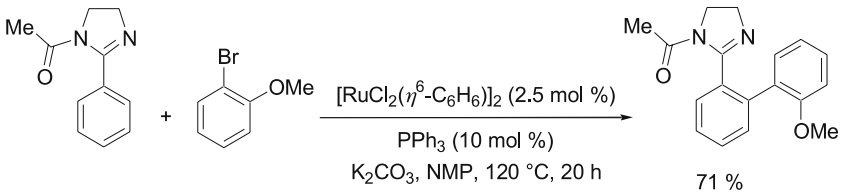
Equation 32



Equation 33

formation should prove valuable for organic synthesis, because 2-oxazolinyl substituents can be easily converted into valuable functionalities, such as the corresponding carboxylic acids [127].

Also imidazolines can be efficiently converted with aryl bromides, even when bearing an *ortho*-substituent (Eq. 34) [126].

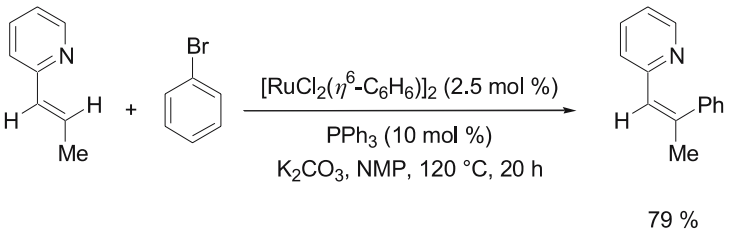


Equation 34

Also vinylic C – H bonds can be directly arylated with aryl bromides using this ruthenium catalyst [128]. Thereby, olefins are functionalized with regioselectivities, which are complementary to the ones obtained in palladium-catalyzed Heck reactions (Eq. 35).

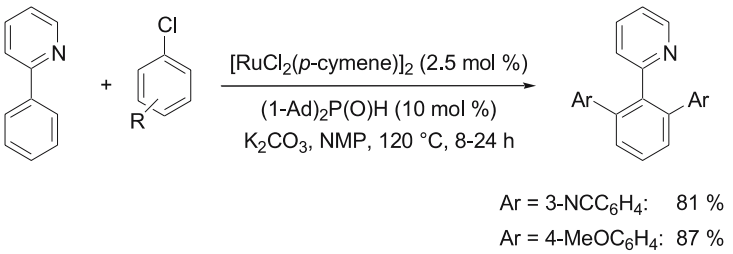
Unfortunately, studies directed towards elucidation of the catalysts working mode have not been reported.

For traditional cross-coupling reactions of organometallic species the development of electron-rich stabilizing ligands allowed for the use of readily available, inexpensive aryl chlorides as electrophiles [129]. On the contrary,



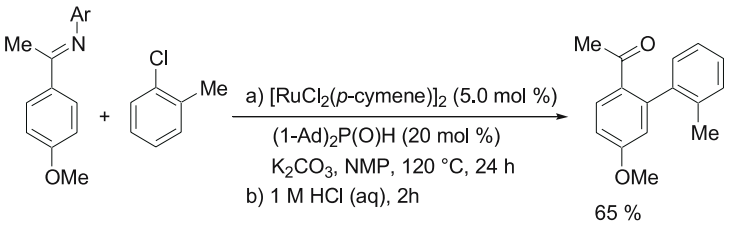
Equation 35

generally applicable methods for regioselective direct arylation reactions employing aryl chlorides were only reported for intramolecular palladium-catalyzed direct arylation reactions [31, 130–132][11]. Therefore, the author's research group set out to study transition-metal-catalyzed direct C – H bond arylation reactions employing aryl chlorides as readily available electrophiles. A direct C – H bond functionalization of substituted pyridines and imine was achieved with a ruthenium complex derived from secondary phosphine oxide $(1\text{-Ad})_2P(O)H$. The protocol proved applicable to a variety of differently substituted aryl chlorides, including electron-rich as well as functionalized electron-poor derivatives (Eq. 36) [133].



Equation 36

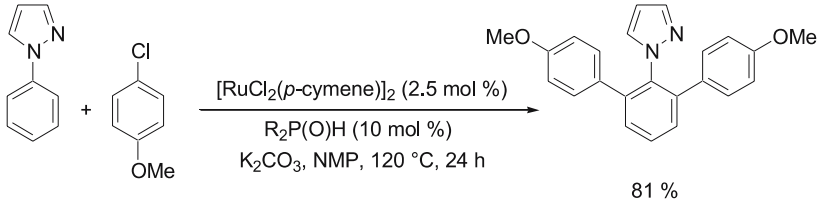
Also *ortho*-substituted aryl chlorides could be used, which should be valuable for further functionalization reactions of the products (Eq. 37) [133].



Equation 37

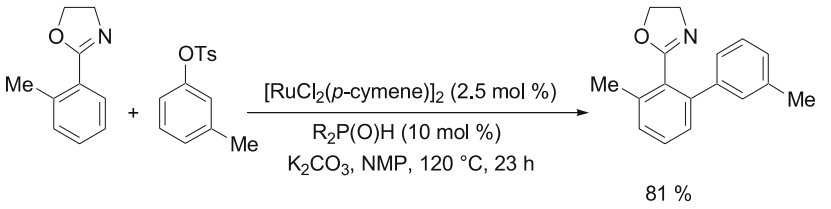
[11] For an intramolecular alkylation with chlorides, see [131] and references cited therein

Ruthenium-catalyzed regioselective C – H bond arylations of pyrazole derivatives were accomplished as well. Again, for an oxidative addition electronically deactivated, that is electron-rich, aryl chlorides could be used (Eq. 38) [134].



Equation 38

The possibility of using tosylates as electrophiles in cross-coupling chemistry is attractive, since they can be prepared from readily available phenols or ketones with reagents that are less expensive than those used to prepare the corresponding triflates. Further, tosylates are more convenient to use, because they are more stable to water than triflates and are highly crystalline. However, this greater stability makes tosylates less reactive in transition-metal-catalyzed processes. Recently, methods for traditional cross-coupling reactions between aryl tosylates and organometallic complexes have been developed (selected examples [135–139]). In contrast, catalytic, direct arylation reactions through C – H bond activation using tosylates have not been reported until recently. A ruthenium catalyst was used for previously unprecedented direct arylation reactions with tosylates [134]. The protocol proved applicable to highly functionalized and electron-rich aryl tosylates (Eq. 39).

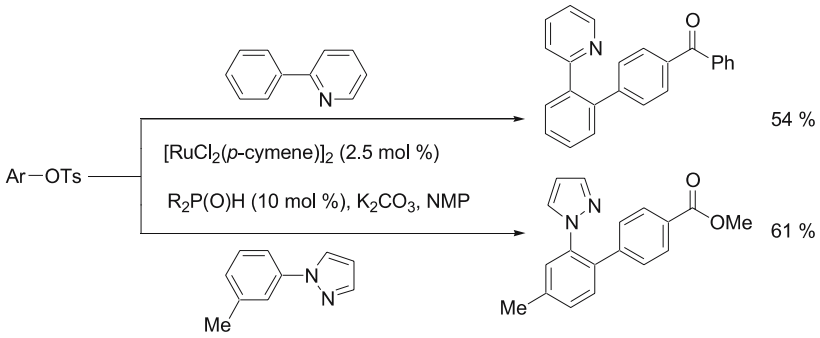


Equation 39

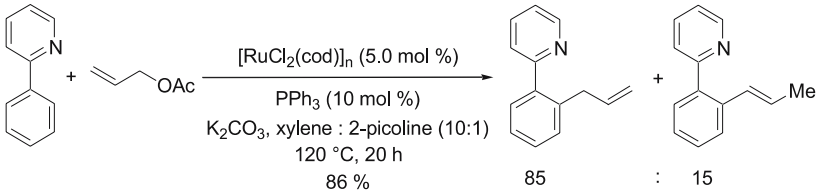
Additionally, the functionalization of C – H bonds in pyridines and pyrazoles employing aryl tosylates was reported (Eq. 40).

Oi, Inoue and coworkers developed recently a regioselective ruthenium-catalyzed allylation of 2-pyridylarenes using allyl acetates. A partial isomerization of the double bond was observed (Eq. 41) [140].

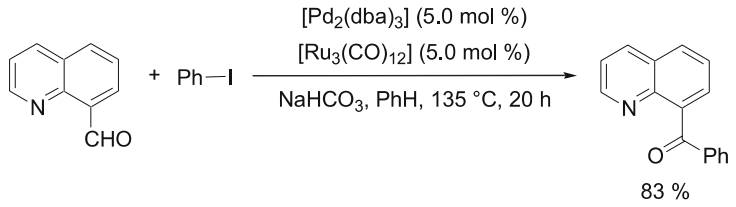
A ruthenium complex, in combination with a palladium catalyst, allowed for chelation-assisted coupling of an aldehyde with iodoarenes (Eq. 42) [141].



Equation 40



Equation 41



Equation 42

Interestingly, this cooperative catalysis [142] proved also applicable to regioselective arylation reactions of the same aldehyde with organostannanes [141].

5 Summary and Conclusion

A variety of methodologies for catalytic arylation reactions via C – H bond cleavage were developed in recent years. Preparatively useful protocols for intermolecular transformations, which proceed with high regioselectivities, were achieved through chelation-assistance. Predominantly, palladium, rhodium, and ruthenium complexes were employed and allowed for the use of either organometallic compounds or organic (pseudo)halides as arylating

agents. Importantly, these protocols proved applicable to a wide variety of substrates, bearing valuable functionalities as directing groups, such as alcohols, amines, ketones, imines, esters, or oxazolines. Additionally, the broad scope of these catalysts enabled the establishment of processes with more challenging substrate combinations. Hence, the regioselective arylation of $C(sp^3)-H$ bonds was recently accomplished with both palladium and ruthenium catalysts. The outstanding activity of ruthenium complexes enabled general direct arylation reactions, which are applicable to easily available and inexpensive aryl chlorides and tosylates. Given the importance of environmentally benign and economical processes, additional exciting developments are to be expected in this rapidly evolving research area.

Acknowledgements Support by the DFG through the Emmy Noether-Programm is gratefully acknowledged.

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Catalytic Arylation and Vinylation Reactions Directed by Anionic Oxygen Functions via Cleavage of C – H and C – C Bonds

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Abstract Aromatic compounds having oxygen-containing substituents such as phenols, phenyl ketones, benzyl alcohols, and benzoic acids undergo regioselective arylation and vinylation via C – H bond cleavage in the presence of transition-metal catalysts. The latter two substrates are also arylated and vinylated via C – C bond cleavage accompanied by liberation of ketones and CO_2, respectively. Coordination of their anionic oxygen to the metal center is the key to activate the inert bonds effectively and regioselectively. The recent progress of these oxygen-directed reactions is summarized herein.

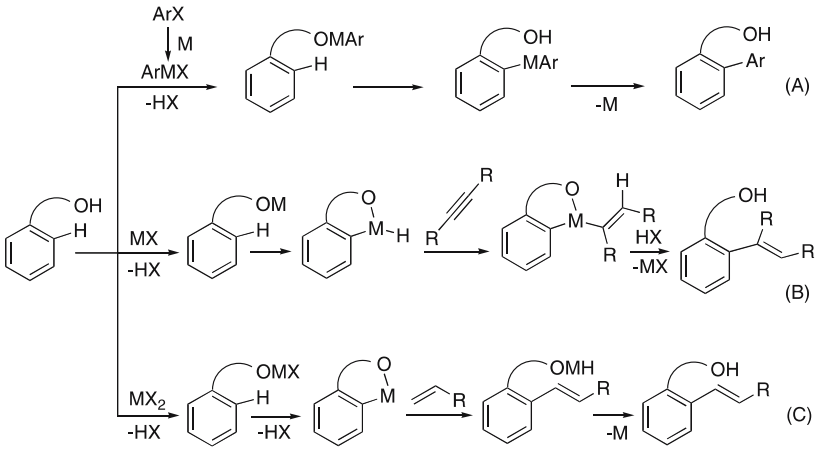
Keywords Arylation · C – C bond cleavage · C – H bond cleavage · Palladium · Vinylation

Abbreviations

BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
cod	1,5-Cyclooctadiene
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
MS3A	Molecular sieves (3 Å)
MS4A	Molecular sieves (4 Å)
μW	Microwave
NMP	*N*-Methyl-2-pyrrolidone

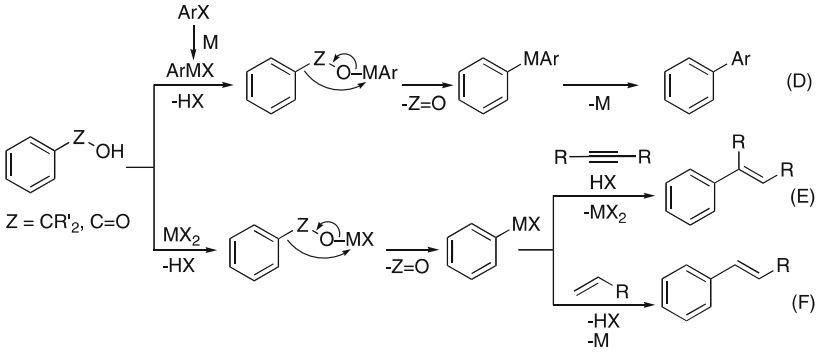
1 Introduction

Transition metal-catalyzed organic reactions via cleavage of C – H [1–10] and C – C bonds [10–20] have attracted much attention from atom-economic and chemoselective points of view, and various catalytic processes involving different modes to activate the relatively inert bonds have been investigated. Among the most promising activation strategies is to utilize the proximate effect by coordination of a functional group in a given substrate to the metal center of a catalyst. Since Murai et al. reported the pioneering work in this area (the ruthenium-catalyzed *ortho*-alkylation of aromatic ketones with alkenes [21]), various catalytic alkylation, vinylation, and arylation reactions of aromatic compounds bearing carbonyl or nitrogen-containing groups through C – H activation have been successfully developed [1–10]. Besides the functional groups containing a neutral hetereoatom, hydroxyl and carboxyl groups can also act as good anionic anchors to exhibit the proximate effect. The oxygenated substrates are capable of coupling with aryl halides and alkynes as well as alkenes under suitable conditions. Thus, coordination of the oxygen of such functional groups to ArMX (generated from M + ArX), MX, and MX_2 species, substituting their X^-, affords the corresponding oxymetal intermediates. Then, the C – H bond of the *ortho*-position is cleaved regioselectively to lead to introduction of aryl or vinyl groups (Scheme 1).



Scheme 1

Meanwhile, in the reaction of *tert*-benzyl alcohols and benzoic acids, it has been found that the proximal C – C bonds can also be cleaved in the oxymetal species to generate arylmetal intermediates with release of ketones or CO_2, which leads to the coupling at their *ipso*-positions (Scheme 2).

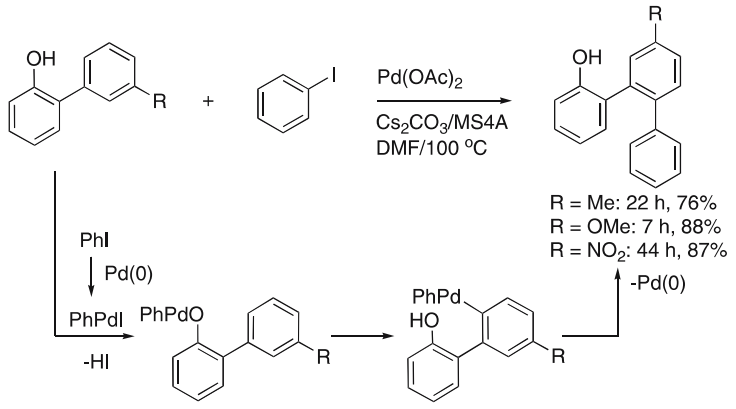


Scheme 2

This review focuses on the regioselective arylation and vinylation reactions of phenols, ketones, alcohols, and carboxylic acids involving C – H and C – C bond cleavages directed by their oxygen. The reactions of enolizable ketones are included in this chapter, while related transformations utilizing their carbonyl oxygen as a neutral anchor are treated in other chapters in this volume.

2 Phenols

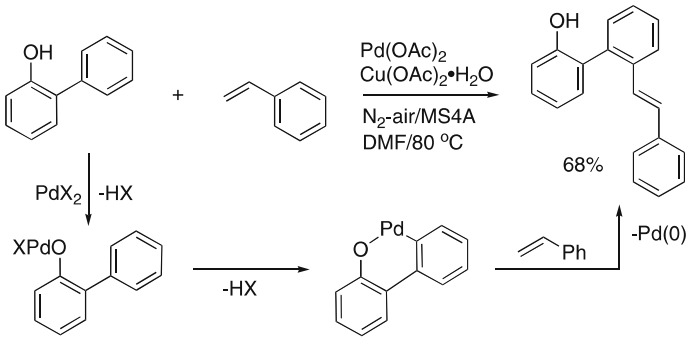
The palladium-catalyzed arylation of biphenyl-2-ols with aryl iodides is one of the first examples that proceeds by sequence A in Scheme 1. Treatment of biphenyl-2-ols with iodobenzene using Cs_2CO_3 as a base in the presence of a catalytic amount of $Pd(OAc)_2$ and MS4A in DMF affords the corresponding monophenylated products, 1,1′ : 2′,1″-terphenyl-2-ols (Eq. 1) [22, 23]. The



Equation 1

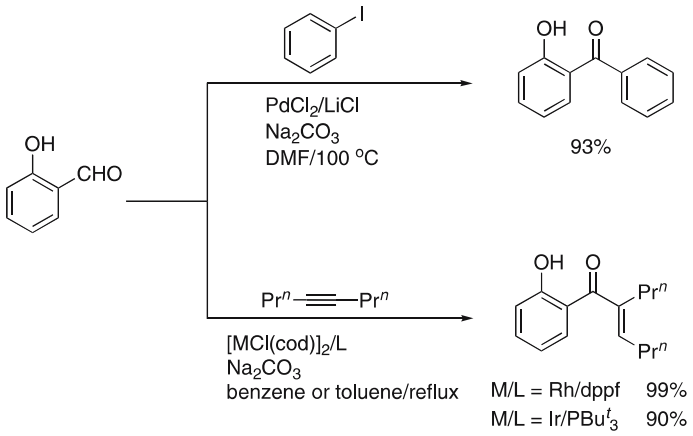
reaction proceeds via (1) oxidative addition of iodobenzene to Pd^0 to give PhPdI, (2) coordination of the phenolic oxygen to Pd as a trigger for the effective, regioselective C – H bond activation, (3) palladation at the 2′-position to form a diarylpalladium intermediate, and (4) reductive elimination of the product. The identity of base used is an important factor determining the reaction efficiency. The base Cs_2CO_3, which has relatively high solubility in DMF, may enhance the 2′-palladation step by assisting the deprotonation [24, 25]. Another role of the base may be to remove the iodide ion from the reaction medium, so that the coordination of phenolic oxygen to the arylpalladium intermediate is enhanced; CsI is known to be relatively insoluble in DMF [26]. Generally, the C – H bond cleavage step is considered to involve an electrophilic character. The fact that the reaction of biphenyl-2-ols bearing an electron-donating substituent at the 5′-position proceeds smoothly is consistent with the mechanism. However, the strongly electron-withdrawing nitro group does not inhibit the reaction. Thus, other mechanisms of the C – H palladation including σ-bond methathesis cannot be ruled out [25, 27].

Biphenyl-2-ol also undergoes vinylation at the 2′-position under palladium catalysis. As shown in Eq. 2, treatment of the substrate with styrene in the presence of a catalyst system of $Pd(OAc)_2/Cu(OAc)_2H_2O$ and MS4A under N_2–air (ca. 5 : 1, 1 atm) in DMF gives 2′-(2-phenylethenyl)-[1,1′-biphenyl]-2-ol as the oxidative coupling product [28]. The reaction may involve coordination of the phenolic oxygen to PdX_2 and subsequent palladation at the 2′-position to form a palladacycle intermediate. Then, insertion of styrene and β-hydride elimination occur to form the vinylated product with release of Pd^0 as in sequence C of Scheme 1. The reduced Pd^0 species can be reoxidized in the presence of the copper co-catalyst and air to allow the regeneration of PdX_2.



Equation 2

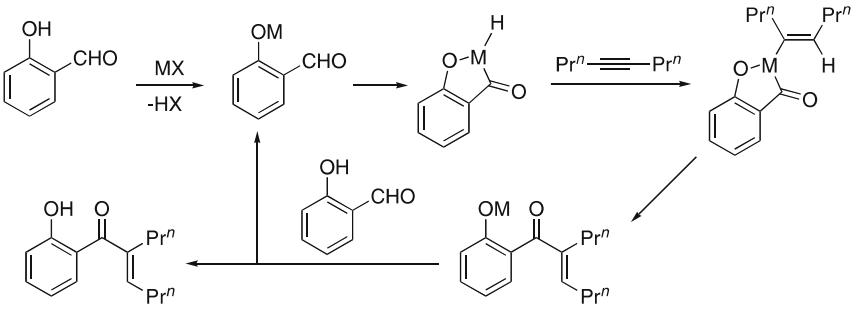
Salicylaldehyde also undergoes arylation and vinylation via cleavage of the aldehyde C – H bond (Eq. 3). Thus, the reaction with iodobenzene in the presence of $PdCl_2$/LiCl and Na_2CO_3 as a catalyst system and a base, respec-



Equation 3

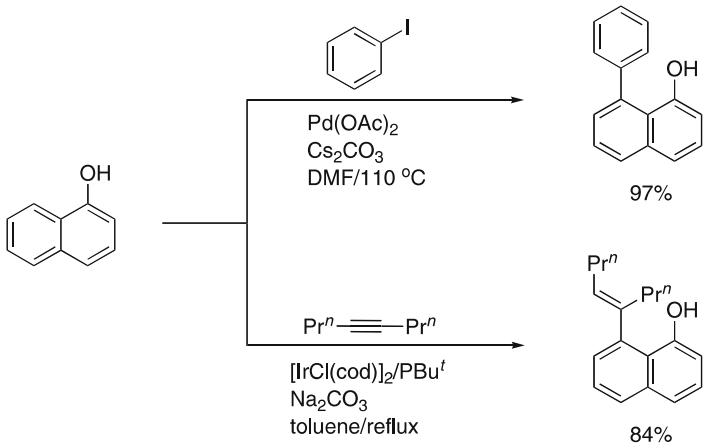
tively, affords 2-hydroxybenzophenone [29]. The stoichiometric activation of the aldehyde C – H bond has been realized in palladium- [30], platinum- [30], and nickel complexes [31]. On the other hand, treatment of the aldehyde with 4-octyne using a catalyst system of $[RhCl(cod)]_2$/dppf/Na_2CO_3 gives rise to the corresponding vinylated product quantitatively [32, 33]. An iridium-based catalyst system of $[IrCl(cod)]_2/PBu^t_3/Na_2CO_3$ can also be employed for the vinylation in place of the rhodium system [34].

The vinylation proceeds as in sequence B of Scheme 1 via (1) substitution on MX by the phenolic oxygen, (2) oxidative addition of the aldehyde C – H bond to form a hydrido–metalacycle intermediate, (3) insertion of the alkyne into the H–M bond, and (4) reductive elimination. The vinylated product is released via ligand exchange with another substrate molecule (Scheme 3).



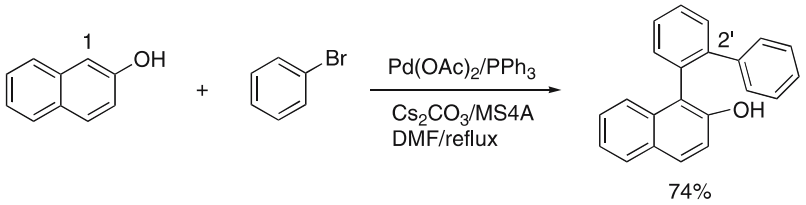
Scheme 3

Similarly, 1-naphthol is arylated and vinylated at the 8-position regioselectively by treatment with iodobenzene and 4-octyne in the presence of palladium- [22, 23] and iridium-based catalysts [34, 35], respectively (Eq. 4).



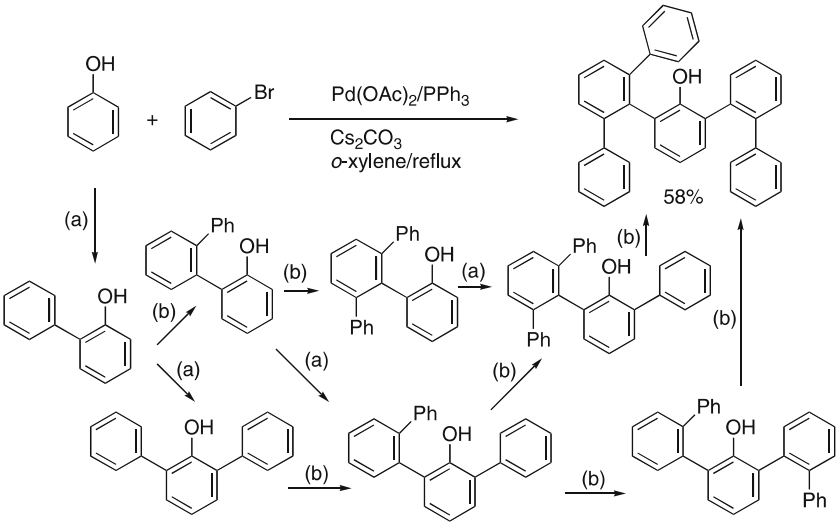
Equation 4

Treatment of 2-naphthol with bromobenzene in the presence of $Pd(OAc)_2$/PPh_3 and Cs_2CO_3 leads to phenylation on the 1-position. Under these conditions, further phenylation on the 2′-position of 1-phenyl-2-naphthol once formed occurs to give 1-(biphenyl-2-yl)-2-naphthol predominantly (Eq. 5) [22, 23]. The first phenylation may involve nucleophilic attack of the corresponding naphtholate on a phenylpalladium species generated in situ [36]. The second phenylation may take place as in the reaction of biphenyl-2-ols (Eq. 1).



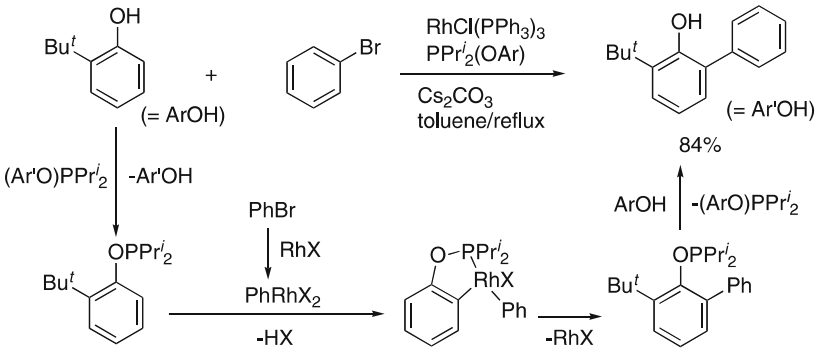
Equation 5

It is notable that this type of sequential multiple phenylation also takes place around the oxygen of phenol itself under suitable conditions. As shown in Eq. 6, treatment of phenol with excess bromobenzene affords a pentaphenylated product, 2-biphenyl-6-terphenylphenol, as the single major product [37]. As for the diphenylation of 2-naphthols, this reaction is considered to involve two mechanistic patterns: the reactions of the phenylpalladium intermediate with (a) phenolates at the *ortho*- (2- or 6-) position and (b) thus formed biphenyl-2-ols at the 2′- or 6′-position. The absence of the possible hexaphenylated product may be attributed to steric reasons.

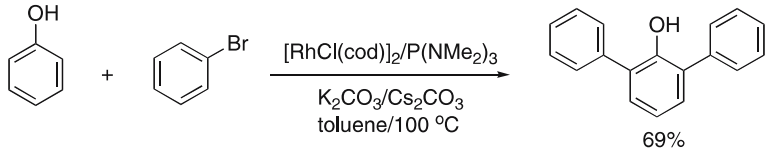


Equation 6

The directed arylation reactions of phenols at the 2-position with aryl halides using rhodium catalysts have also been reported by the groups of Bedford (Eq. 7) [38, 39] and of Oi and Inoue (Eq. 8) [40], independently, although these are not assisted by the direct coordination of phenolic oxygen to the metal. The key to the effective reactions is to employ phosphinites or phosphites as ligands. For example, the former reaction is considered to proceed via coordination of the phosphorus atom of a phosphinite to Ph-Rh^{III} generated by oxidative addition of bromobenzene, cyclometalation, and reductive elimination [39]. The arylated phosphinite then undergoes transesterification with the starting phenol to give the product. In this reaction, a phosphinite having the same aryloxy group with the starting phenol substrate has to be



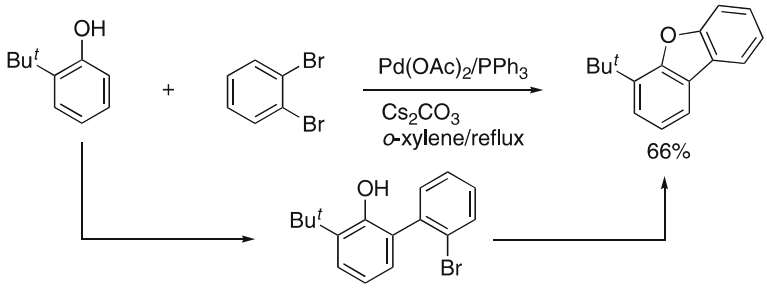
Equation 7



Equation 8

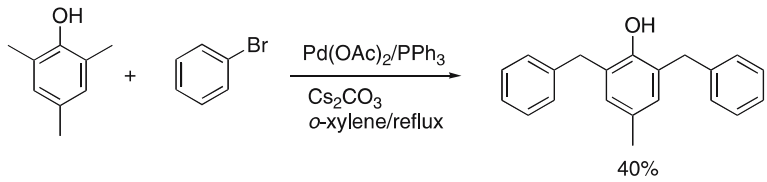
pre-prepared. This can, however, be avoided by using $P(NMe_2)_3$, which reacts with phenols in situ to give the corresponding phosphites [40]. Under the rhodium-catalyzed conditions, arylation at the 2′-position is sluggish to give mono- or diarylated phenols preferentially, rather than perarylated ones that are produced readily under palladium catalysis.

Even under palladium catalysis, the reaction of *o*-*tert*-butylphenol with *o*-dibromobenzene gives monoarylated product as shown in Eq. 9. After the first arylation at the 2-position, the formation of the C – O bond takes place intramolecularly, in place of the intermolecular 2′-arylation, to afford the corresponding benzofuran derivative [41].



Equation 9

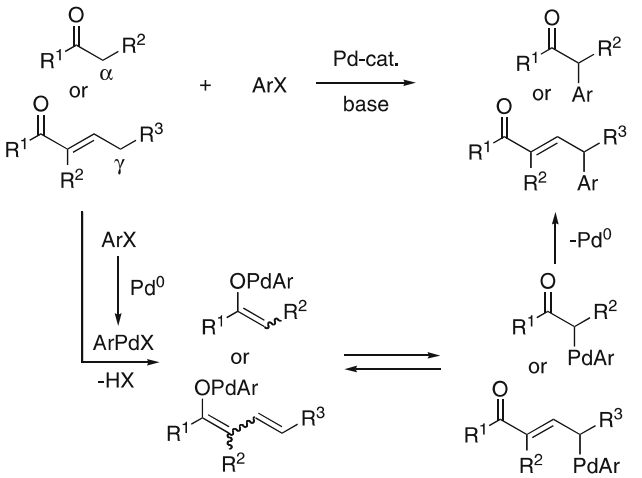
Around the phenolic oxygen, not only sp^2 C – H but also sp^3 C – H bonds can be arylated. Thus, treatment of 2,4,6-trimethylphenol with bromobenzene using $Pd(OAc)_2/PPh_3$ and Cs_2CO_3 leads to diphenylation at its benzyl positions selectively (Eq. 10) [37].



Equation 10

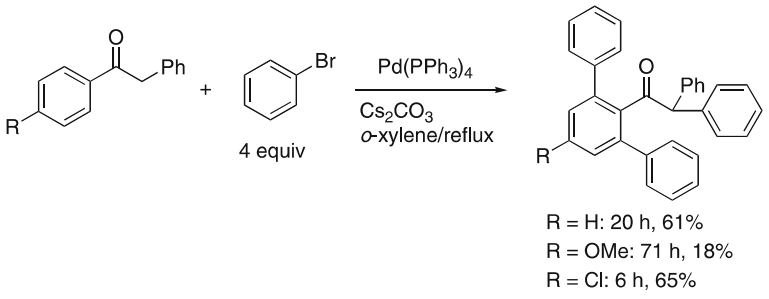
3
Ketones

In 1997, our group [22, 23] and others [42–44] reported the palladium-catalyzed intermolecular α-arylation of simple ketones. We also demonstrated the regioselective γ-arylation of α,β-unsaturated carbonyl compounds [45]. These reactions are considered to involve the coupling of enolates and dienolates, respectively, with the arylpalladium species generated in situ (Scheme 4).



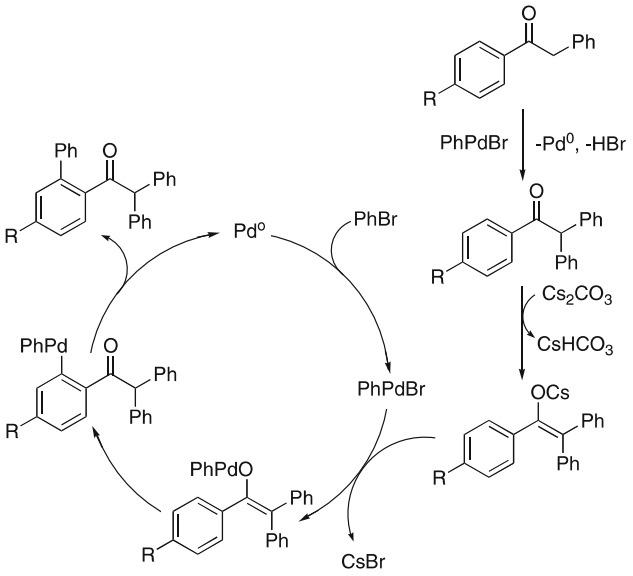
Scheme 4

Later, it was observed that treatment of acetophenones and benzyl phenyl ketones with excess aryl bromides leads to multiple arylation, not only at the α-position but also at the two *ortho*-positions. For example, the reaction of benzyl phenyl ketones with four equivalents of bromobenzene and Cs_2CO_3 in the presence of $Pd(PPh_3)_4$ as a catalyst affords the corresponding triphenylated products (Eq. 11) [46, 47].



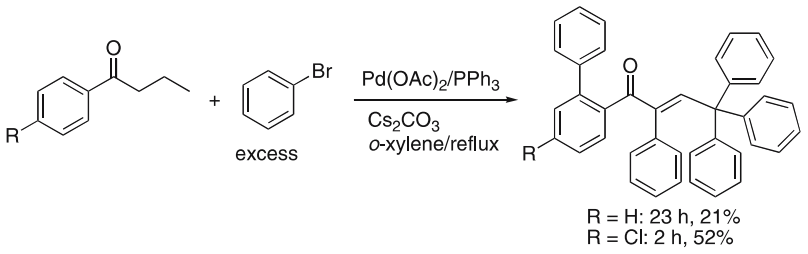
Equation 11

A plausible mechanism for the multiple phenylation is shown in Scheme 5. The ketones undergo α-phenylation prior to aromatic *ortho*-phenylation. The latter phenylation may proceed via coordination of enolic oxygen of the resulting diphenylmethyl aryl ketones to an intermediary arylpalladium species followed by *ortho*-palladation that induces C – H bond cleavage at the 2-position and successive reductive elimination. It should be noted that benzyl 4-chlorophenyl ketone undergoes triarylation considerably faster than the unsubstituted phenyl ketone, whereas the 4-methoxy derivative is consumed very slowly. These facts suggest that an electron-withdrawing substituent on the phenyl ketone enhances *ortho*-phenylation, possibly by promoting enolate formation.



Scheme 5

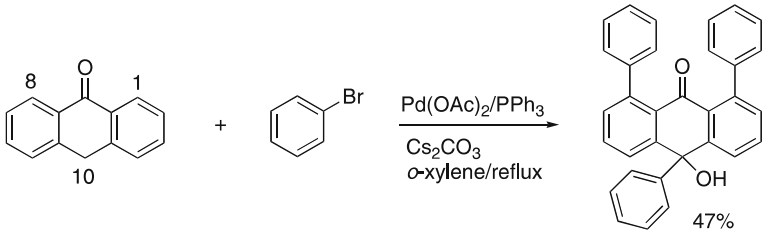
Treatment of butyrophenones with excess bromobenzene in the presence of $Pd(OAc)_2/PPh_3$ gives the corresponding pentaphenylated compounds (Eq. 12) [47, 48]. The reaction appears to involve (a) α-phenylation, (b) ox-



Equation 12

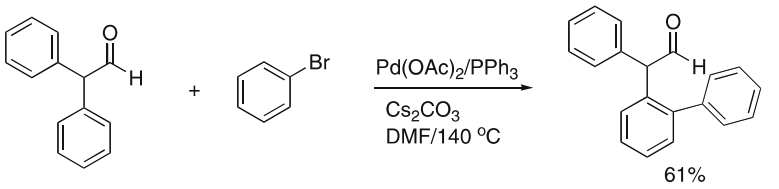
idative unsaturation of the propyl moiety, (c) three times γ-phenylation, and (d) *ortho*-phenylation of the benzoyl moiety. The *ortho*-phenylation seems to occur prior to the third γ-phenylation that precludes the dienolate formation.

A cyclic ketone, anthrone, which is a structural relative of benzyl phenyl ketone, also reacts with bromobenzene (Eq. 13) [48]. The ketone undergoes triphenylation at the 1-, 8-, and 10-positions, which parallels the reaction of benzyl phenyl ketone. However, the 10-position is unexpectedly hydroxylated. The hydroxy group may come from the base or adventitious water, but the mode of its addition is not clear.



Equation 13

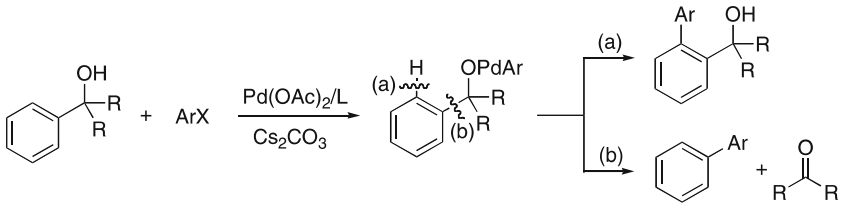
A structurally isomeric aldehyde, diphenylacetaldehyde, undergoes *ortho*-phenylation [48]. As shown in Eq. 14, *ortho*-monophenylated product can be obtained selectively by using 1.5 equivalents of bromobenzene [49].



Equation 14

4 Alcohols

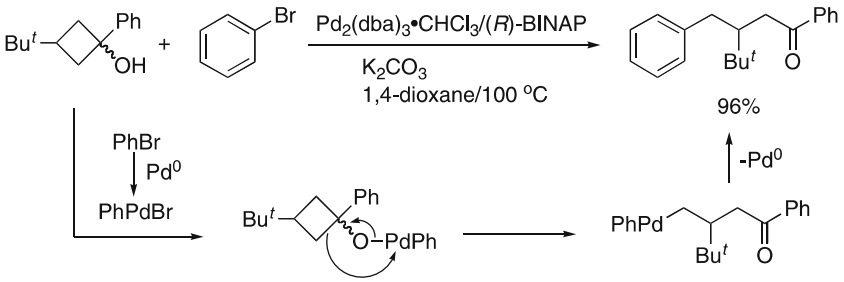
As shown in Eqs. 1 and 4, biphenyl-2-ols and 1-naphthols undergo regioselective phenylation at the spatially neighboring 2′- and 8-positions, respectively, via cleavage of the aromatic C – H bonds, in which coordination of the phenolic oxygen to the phenylpalladium intermediate is the key. We have also found that the alcoholic oxygen of *tert*-benzyl alcohols, too, is capable of acting as an effective coordinating group to lead to similar directed arylation (path a in Eq. 15, sequence A in Scheme 1). An additional important finding is that the



Equation 15

alcoholic substrates competitively undergo another unique aryl–aryl coupling via C – C bond cleavage (path b in Eq. 15, sequence D in Scheme 2) [50, 51]. The sp^2–sp^3 C – C bond fission with liberation of a ketone can be regarded as a β-carbon elimination process. The stoichiometric version of the β-carbon elimination in a rhodium alkoxide complex has been reported [52].

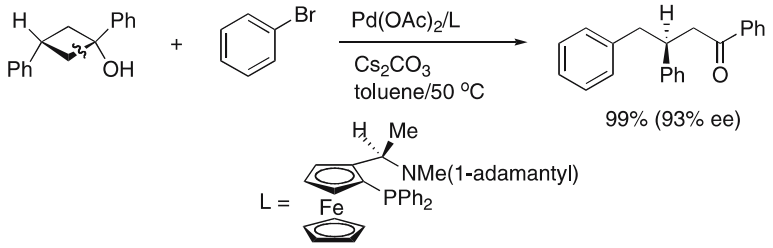
There is an important precedent for the catalytic arylation of alcohols via β-carbon elimination in strained four-membered ring systems [53–56]. An example is shown in Eq. 16. Treatment of a 1,3-disubstituted *tert*-cyclobutanol with bromobenzene in the presence of a catalyst system of $Pd_2(dba)_3CHCl_3$/(*R*)-BINAP and K_2CO_3 affords the corresponding ring-opened and phenylated product. The reaction is considered to involve an in situ-generated phenylpalladium species that can readily interact with the alcohol affording a phenylpalladium alkoxide intermediate. Then, β-carbon elimination and subsequent reductive elimination occur to give a γ-phenylated ketone with the regeneration of Pd^0 species.



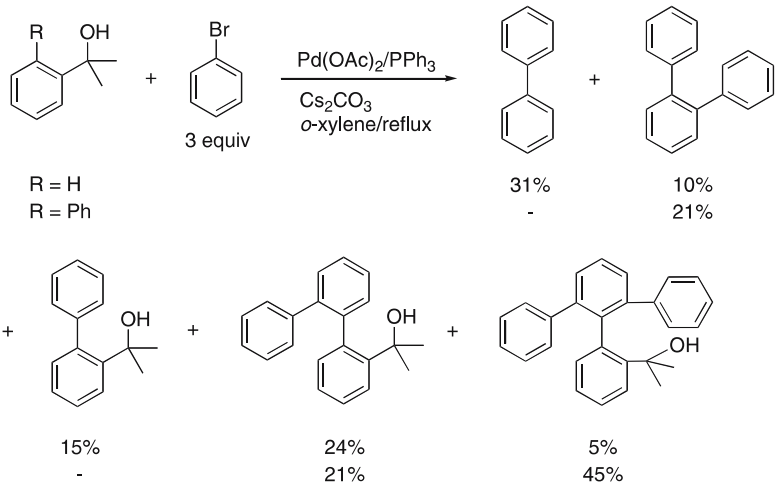
Equation 16

In the ring-opening arylation of 3-substituted cyclobutanols, enantioselective cleavage of the C – C bond can be achieved by using a palladium catalyst with a chiral ligand [53–56]. In particular, the use of a chiral ferrocene-containing *P*,*N*-bidentate ligand shown in Eq. 17 allows excellent enantioselectivity.

Recently, it was also found that the arylation of acyclic benzyl alcohols via C – C bond cleavage can be conducted under appropriate conditions (path b in Eq. 15) [50, 51]. As shown in Eq. 18, the reaction of a simple *tert*-benzyl



Equation 17

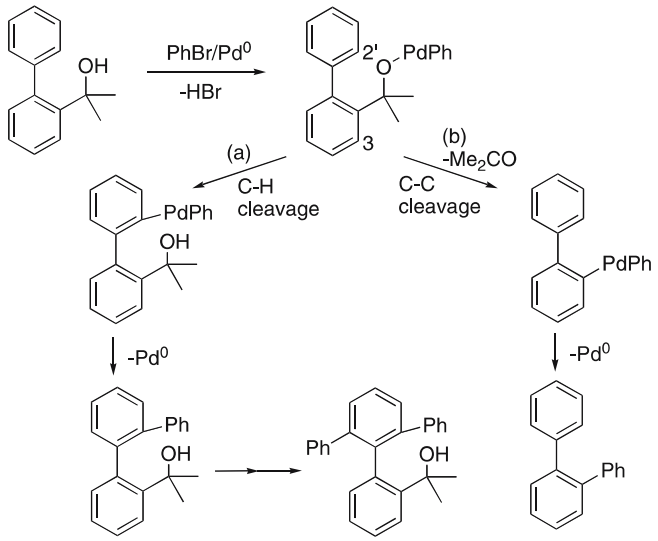


Equation 18

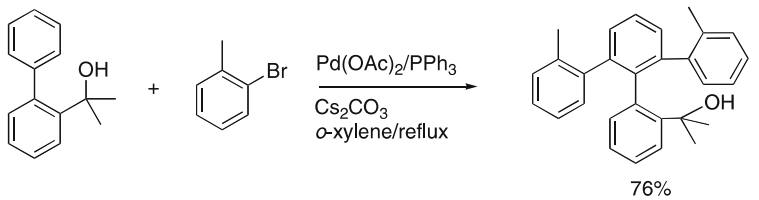
alcohol, 2-phenyl-2-propanol (R = H), with three equivalents of bromobenzene and Cs_2CO_3 in the presence of $Pd(OAc)_2/PPh_3$ as a catalyst system gives mono-, di-, and triphenylated products via successive C – H bond cleavage, together with biphenyl and *o*-terphenyl. The latter products are considered to be formed by the phenylative C – C bond cleavage of the starting alcohol and the monophenylated product, 2-(biphenyl-2-yl)-2-propanol, respectively (path b in Eq. 15 and Scheme 6).

The reaction started with 2-(biphenyl-2-yl)-2-propanol affords the 1,2,3-triphenylbenzene derivative with an enhanced yield (45%) (Eq. 18, R = Ph). The fact that the phenylation via C – H bond cleavage only takes place at the 2′-position and not at all at the 3-position suggests that the former is more preferable in this case (Scheme 6), although the latter occurs in the reaction of 2-phenyl-2-propanol (Eq. 18, R = H).

Interestingly, the reaction of 2-(biphenyl-2-yl)-2-propanol with *ortho*-substituted bromobenzenes proceeds more selectively via C – H bond cleavage. An example is shown in Eq. 19 using 2-bromotoluene, effectively affording a more sterically crowded 1,2,3-triphenylbenzene derivative.

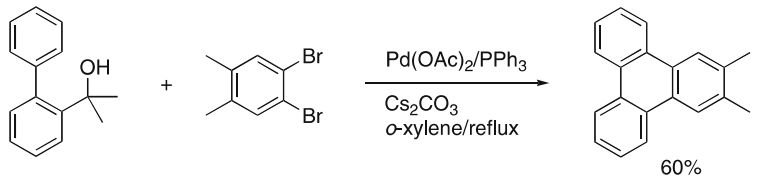


Scheme 6



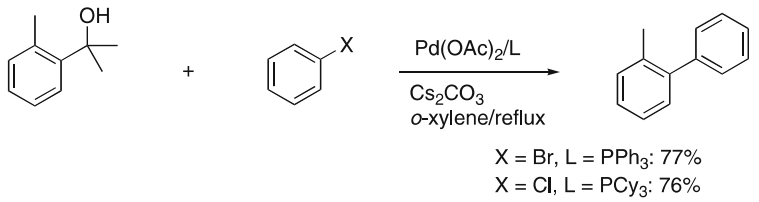
Equation 19

The reaction of 2-(biphenyl-2-yl)-2-propanol with *o*-dibromobenzenes affords the corresponding triphenylenes via cleavage of both C – H and C – C bonds (Eq. 20).



Equation 20

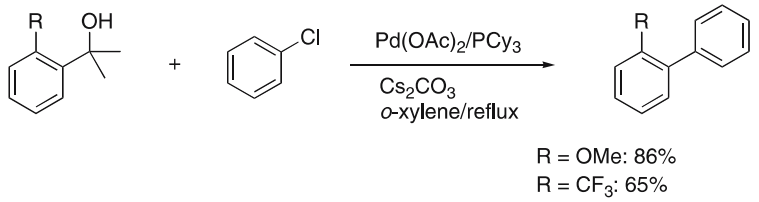
In sharp contrast to the reaction in Eq. 18, that of 2-(2-methylphenyl)-2-propanol with bromobenzene under similar conditions proceeds selectively via C – C bond cleavage to give 2-methylbiphenyl as the single major product (Eq. 21). Notably, use of PCy_3 in place of PPh_3 as a ligand allows the use of



Equation 21

inexpensive chlorobenzene. The predominant formation of 2-methylbiphenyl indicates that an appropriate *ortho*-substituent on 2-phenyl-2-propanol can selectively induce β-carbon elimination. The lack of products via β-carbon elimination with one of the methyl groups is attributable to the fact that such a reaction with an sp^3 carbon is energetically unfavorable. It should be noted that in a 2-methyl-2-phenyl-1-propylpalladium complex, selective β-phenyl elimination has been reported to occur [57].

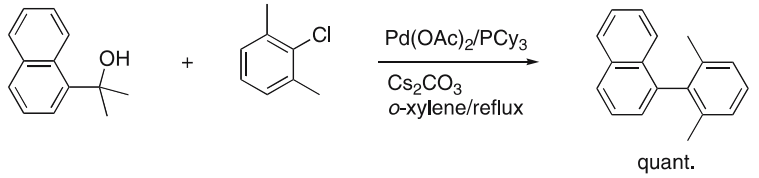
As expected, other *ortho*-substituted 2-phenyl-2-propanols undergo coupling with chlorobenzene accompanied by selective C – C bond cleavage to afford the corresponding biaryls (Eq. 22).



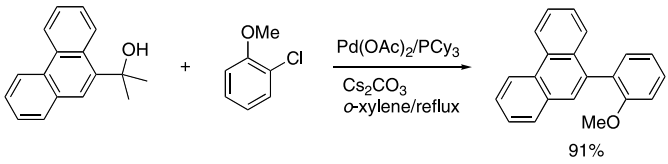
Equation 22

2-(1-Naphthyl)- and 2-(9-phenanthryl)-2-propanols as equivalents of *ortho*-substituted 2-phenyl-2-propanols are suitable substrates for the aryl–aryl coupling. Even using *ortho*-substituted aryl chlorides, the reactions occur efficiently (Eqs. 23 and 24).

It is of particularly mechanistic interest that *ortho*-substituted aryl groups even in aryldiphenylmethanols are eliminated selectively. Thus, the

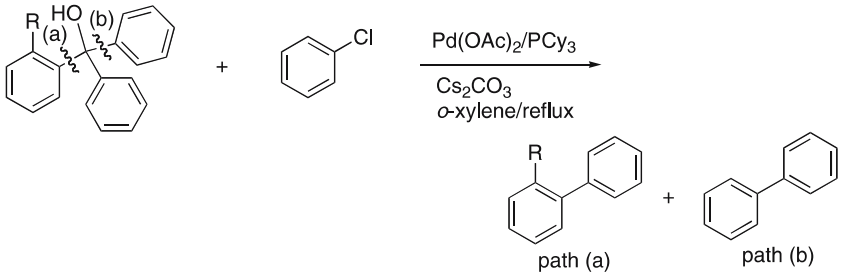


Equation 23



Equation 24

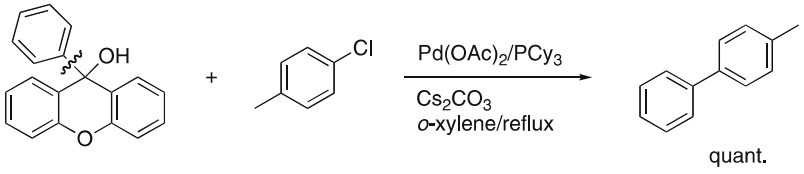
reaction of (2-methylphenyl)diphenylmethanol with chlorobenzene gives 2-methylbiphenyl along with benzophenone in more than 90% selectivity (Eq. 25). The reactions of (2-methoxyphenyl)- and (2-trifluoromethylphenyl)-diphenylmethanols produce the corresponding 2-substituted biphenyls almost exclusively with high yields. The selectivities appear to be determined by steric factors in the β-carbon elimination step. The transition state that leads to 2-substituted biphenyls should be more energetically favorable than that leading to unsubstituted biphenyl.



R = Me	86%	8%
R = OMe	>99%	<1%
R = CF_3	97%	2%

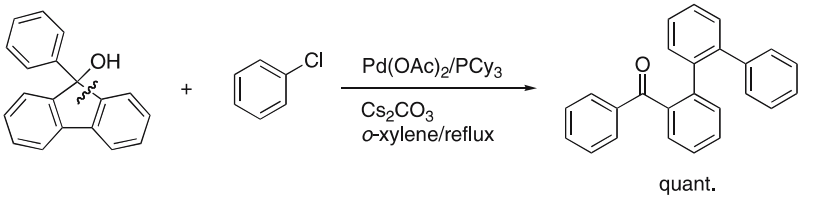
Equation 25

There are some significant factors other than the substituent steric effect that lead to selective elimination: (a) The reaction of 9-phenylxanthen-9-ol with 4-chlorotoluene cleanly proceeds to give 4-methylbiphenyl quantitatively along with xanthone (Eq. 26). The alcohol seems to be configurationally

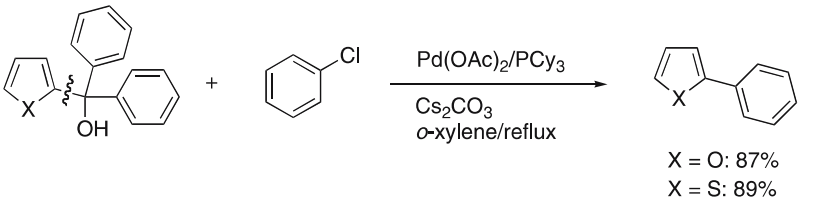


Equation 26

suitable for the selective elimination. (b) In contrast, 9-phenylfluoren-9-ol reacts via ring-opening β-carbon elimination (Eq. 27). This may be attributed to ring-strain. (c) (2-Thienyl)- and (2-furyl)diphenylmethanols are reactive, and the reactions with chlorobenzene are completed in relatively short periods of time to give 2-phenylthiophene and 2-phenylfuran, selectively, formation of biphenyl being negligible (Eq. 28). High reactivity of the heteroaryl groups may be due to the coordination ability of the internal heteroatoms.

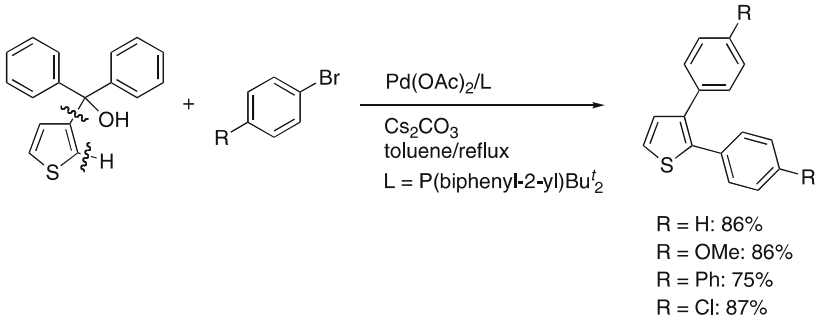


Equation 27



Equation 28

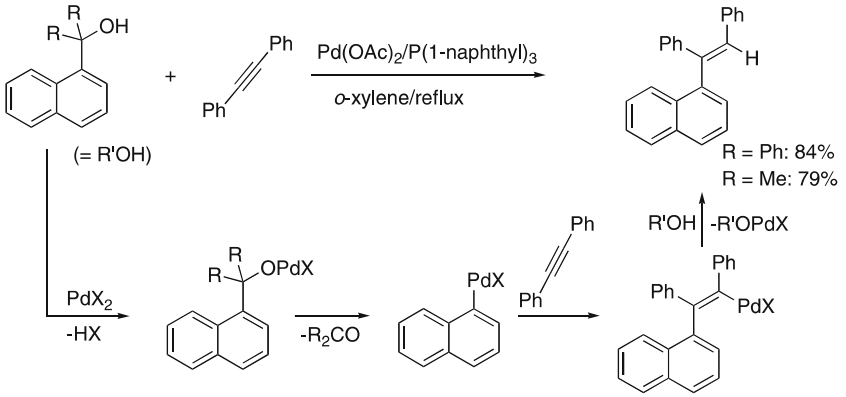
In contrast to the reaction of the (2-thienyl)methanol, (3-thienyl)diphenylmethanol undergoes diarylation via C – H and C – C bond cleavage successively (Eq. 29) [58].



Equation 29

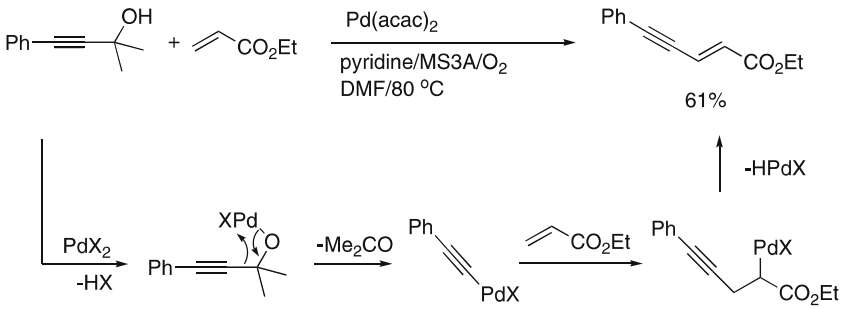
tert-Benzyl alcohols may also undergo vinylation via C – C bond cleavage (sequence E in Scheme 2). Thus, treatment of (1-naphthyl)methanols with

diphenylacetylene using a catalyst system of $Pd(OAc)_2$/P(1-naphthyl)$_3$ affords (*E*)-1-(1-naphthyl)-1,2-diphenylethene in good yields (Eq. 30) [59]. The use of the bulky aromatic phosphine, P(1-naphthyl)$_3$, is essential for the reaction to proceed effectively. The vinylation seems to proceed via coordination of the alcoholic oxygen to PdX_2, selective β-carbon elimination of the relatively bulky 1-naphthyl group, insertion of the alkyne into the naphthyl–palladium bond, and protonolysis of the resulting vinyl–palladium bond to afford the product, with the regeneration of a palladium alkoxide species.



Equation 30

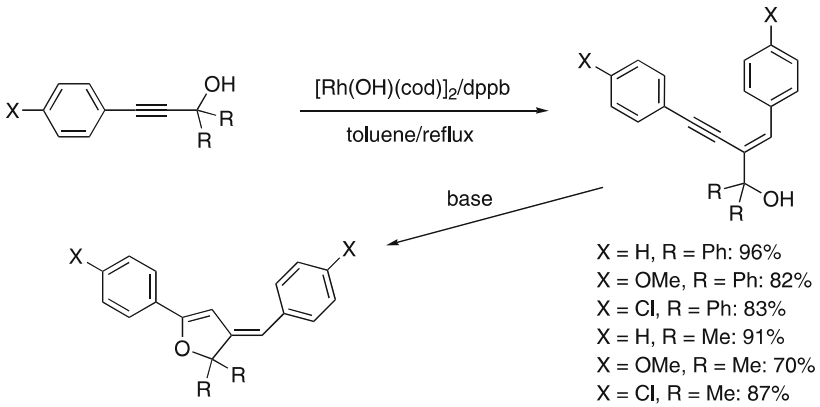
Alkynyl groups in tertiary alcohols are also detachable, as are aryl groups. Thus, as represented by Eq. 31, β-carbon elimination accompanied by cleavage of the sp–sp^3 C – C bond in the reaction of a *tert*-propargyl alcohol followed by oxidative coupling with an alkene under an oxygen atmosphere gives an enyne product [60].



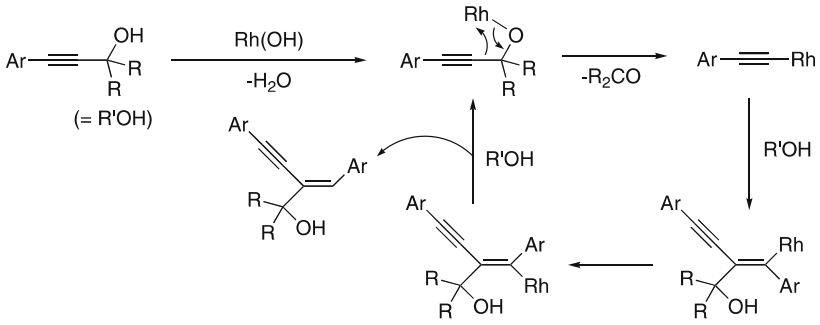
Equation 31

tert-Propargyl alcohols also undergo homocoupling via cleavage of the same C – C bond in the presence of a catalyst system of [Rh(OH)(cod)]$_2$/

dppb to afford 2-hydroxymethyl-(*E*)-enynes (Eq. 32) [61]. In this reaction, β-carbon elimination in a rhodium alkoxide species followed by insertion of another molecule of the alkyne, geometrical isomerization, and protonolysis occurs to form the homocoupling product (Scheme 7). The products are readily capable of cyclizing in the presence of a base to form dihydrofuran derivatives, which exhibit relatively strong fluorescence in the solid state.

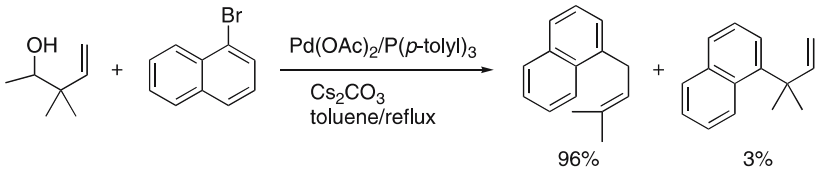


Equation 32



Scheme 7

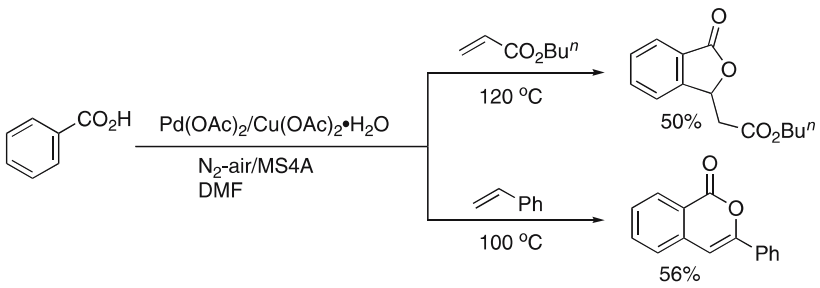
The sp^3–sp^3 C – C bond of homoallyl alcohols is also cleavable on a palladium catalyst. Thus, the alcohols undergo arylative C – C bond cleavage in the presence of $Pd(OAc)_2/P(p\text{-tolyl})_3$ and Cs_2CO_3, as shown in Eq. 33 [62].



Equation 33

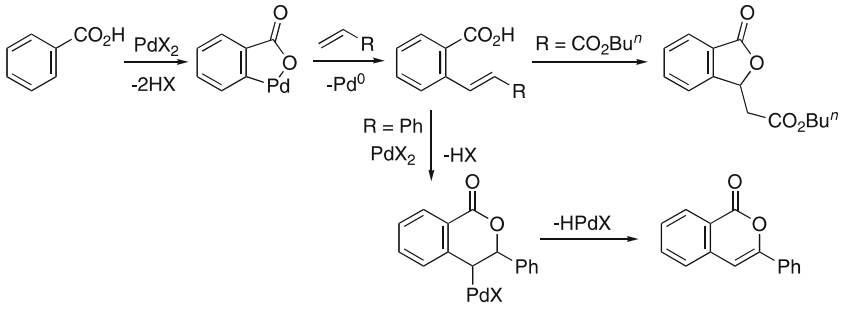
5
Carboxylic Acids

Benzoic acids undergo vinylation via C – H bond cleavage upon treatment with alkenes under similar conditions to those for the reaction of biphenyl-2-ols (Eq. 2). As shown in Eq. 34, the reactions with butyl acrylate and styrene afford five- and six-membered lactones, respectively [63].



Equation 34

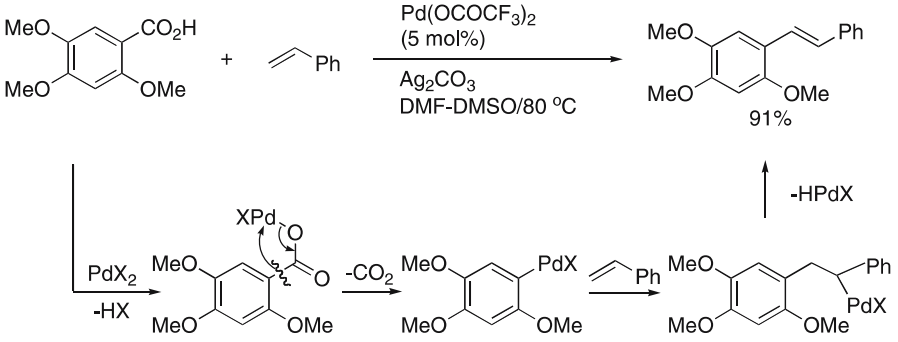
The vinylation appears to be initiated by coordination of the carboxylate oxygen to PdX_2 to yield a palladium benzoate species, which undergoes *ortho*-palladation to form a palladacycle intermediate (Scheme 8). The stoichiometric *ortho*-metalation of benzoic acid has been observed in rhodium, iridium, and osmium complexes [64]. Then, subsequent insertion of alkenes and β-hydride elimination occur to give 2-vinylated benzoic acids. The vinylation may be followed by nucleophilic cyclization (R = CO_2Bu^n) or Wacker-type oxidative cyclization (R = Ph) to produce phthalide and isocoumarin derivatives.



Scheme 8

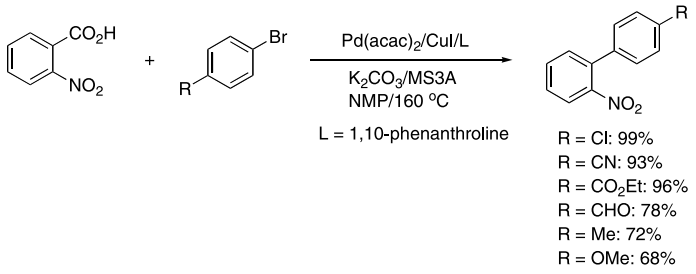
When sterically hindered benzoic acids, possessing at least one *ortho*-substituent, are used under appropriate conditions, not the *ortho* C – H viny-

lation but *ipso* decarboxylative vinylation occurs to give Mizoroki–Heck type products (Eq. 35, sequence F in Scheme 2) [65–67]. In the reaction, the palladium benzoate intermediate undergoes decarboxylation rather than *ortho*-palladation to form an ArPdX species, which is a common intermediate in the Mizoroki–Heck reaction.



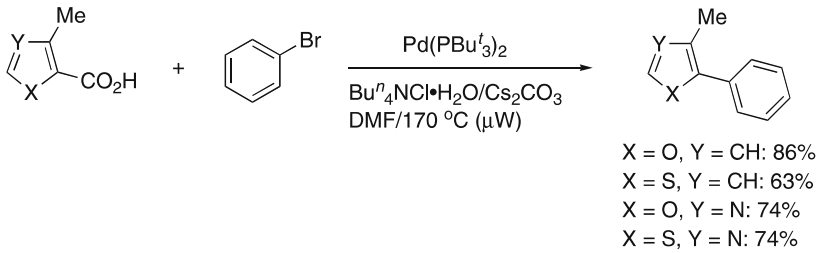
Equation 35

The decarboxylative arylation of benzoic acids has also been found to occur by treatment with aryl bromides under Pd/Cu catalysis (Eq. 36) [68]. In particular, benzoic acids having a coordinating functional group such as nitro group at the *ortho*-position react smoothly.



Equation 36

Heteroaromatic carboxylic acids are also decarboxylatively coupled with bromobenzene in the presence of $Pd(PBu^t{}_3)_2$, Cs_2CO_3, and tetrabutylammonium chloride as a catalyst, base, and promoter, respectively, under microwave heating conditions to give the corresponding phenylated heteroarenes (Eq. 37) [69]. It has been proposed that similar decarboxylative arylation may be involved in multiple arylation of thiophenecarboxamides [70].



Equation 37

6 Conclusion

The methods for transition metal-catalyzed arylation and vinylation reactions via coordination-assisted C – H or C – C bond cleavage have been developed significantly in recent years. In addition to carbonyl and nitrogen-containing groups, hydroxyl groups of phenols, enols, and alcohols and carboxyl group can also act as effective anionic anchors to direct metalation via cleavage of the relatively inert bonds. These new methods for introducing aryl and vinyl moieties into the functionalized substrates regioselectively provide useful alternatives in preparing various π-conjugated molecules. Further effort will be made continuously to improve catalytic efficiency and to develop new types of directed coupling.

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Chelate-Directed Oxidative Functionalization of Carbon–Hydrogen Bonds: Synthetic Applications and Mechanistic Insights

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Abstract This chapter describes advances over the past four decades in Pd-mediated and Pd-catalyzed reactions for the highly regioselective oxidative functionalization of C – H bonds. The synthetic utility and the key mechanistic features of both stoichiometric and catalytic C – X (X = O, Cl, Br, I, F, N) bond-forming reactions are presented. The intermediacy of high oxidation state Pd^{IV} species in many of these transformations has allowed for bond constructions that were not previously possible through traditional Pd^{0}/Pd^{II} couples.

Keywords C – H bond cleavage · Chelation · Carbon–heteroatom · Palladium · Palladium(IV)

1 Introduction

The development of regioselective, chemoselective, and functional group tolerant methods for the oxidative conversion of C – H bonds into C – X (X = O, N, F, Cl, Br, I) bonds remains a critical challenge in modern synthetic organic chemistry. Such reactions would offer a highly attractive approach to the assembly and/or modification of complex organic molecules *without the requirement for highly functionalized starting materials*. In order to develop synthetically useful transformations for the oxidative functionalization of alkanes and arenes, several critical challenges must be addressed. These include: (1) the inherently low reactivity of the starting C – H bonds, (2) the greater susceptibility of the products toward oxidation relative to the reactants, and (3) the incompatibility of most transition metal catalysts with the strong oxidants required for these transformations. However, the most formidable challenge in this area is the difficulty of achieving regioselective C – H functionalization in complex molecules that contain many different C – H bonds of comparable strength and reactivity.

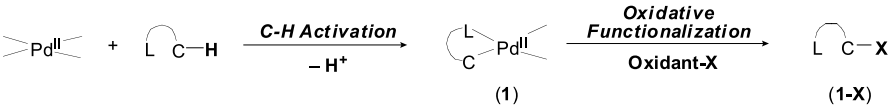
This chapter describes advances over the past four decades in Pd-mediated and Pd-catalyzed reactions for the highly regioselective oxidative functionalization of C – H bonds. In particular, we focus on transformations in which Pd^{II} salts promote the cleavage (or "activation") of C – H bonds, and strong oxidants subsequently convert the resulting C – Pd bond into a new functional group. Extremely high levels of regioselectivity have been achieved in these reactions through the use of substrates containing coordinating functional groups, which can bind the Pd catalyst and direct C – H activation and subsequent oxidative functionalization to an adjacent C – H bond.

The chapter is divided into three main sections. The first describes the general strategy for the chelate-directed oxidation of C – H bonds. The second details early studies involving the stoichiometric conversion of C – Pd bonds of cyclopalladated complexes to carbon–oxygen, carbon–chlorine, carbon–iodine, and carbon–nitrogen bonds. Finally, the last section summarizes recent advances in the rapidly emerging area of palladium-catalyzed ligand-directed carbon–heteroatom bond-forming reactions.

2 Directed C – H Activation/Oxidative Functionalization: General Strategy

The cyclopalladation of organic substrates bearing chelating functional groups was first discovered by Cope and Siekman in 1965 [1]. In this report, azobenzene was shown to react with Pd^{II} salts to afford a palladacyclic product in which a nitrogen atom was datively bound to the Pd and the C – H bond

ortho to the azo linkage was replaced with a C – Pd bond. A wide variety of aromatic substrates have subsequently been shown to undergo analogous regioselective *ortho* metalations at Pd^{II} centers [2–4]. These reactions have also been extended to the cyclopalladation of unactivated sp^3 C – H bonds [5–8], although such transformations remain significantly rarer (and often require harsher conditions) than those with arene substrates. In all cases, these transformations are believed to proceed via coordination of the azo linkage (or an alternative coordinating ligand, L) to the Pd center, followed by electrophilic C – H activation proximal to the chelating group to form a product of general structure **1** (Scheme 1).



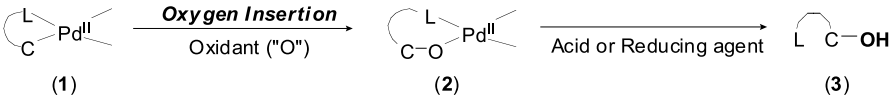
Scheme 1 General strategy for chelate-directed C – H bond oxidation reactions

Over the 40 years following Cope's initial discovery of the stoichiometric cyclopalladation of azobenzene, organic chemists have recognized and begun to exploit this type of transformation in organic synthesis. Complex **1** and its analogues undergo reactions with a variety of electrophilic oxidants, which transform the C – Pd bond into diverse new functional groups. The sections below review both the mechanisms and the synthetic utility of stoichiometric (Sect. 3) and catalytic (Sect. 4) reactions involving the chelate-directed oxidative conversion of C – H bonds into carbon–heteroatom bonds.

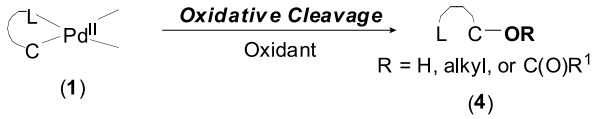
3
Chelate-Directed Carbon–Heteroatom Bond Formation: Stoichiometric Reactions

3.1
Carbon–Oxygen Bond Formation

Reactions of cyclometalated Pd^{II} complexes with electrophilic oxygenating reagents have been studied extensively, and two general approaches have been developed for the conversion of C – Pd bonds to C – O bonds. The first involves the two-step sequence of: (1) insertion of an oxygen atom ("O") into the C – Pd bond of **1** to afford **2**, followed by (2) reaction of **2** with acids or reducing agents to release the oxygenated organic product **3** (Scheme 2). The second approach (Scheme 3) involves direct oxidative cleavage of the C – Pd bond to afford the oxygenated organic product **4** without formation of isolable intermediates. Each of these types of stoichiometric oxygenation reactions is discussed in detail below.



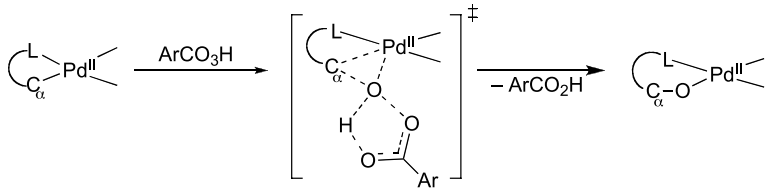
Scheme 2 Oxygen atom insertion into a C – Pd bond



Scheme 3 Direct oxygenation of a C – Pd bond

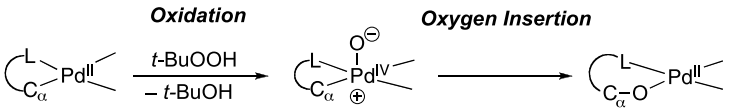
3.1.1 Carbon–Oxygen Bond Formation via Oxygen Insertion

A variety of reagents, including *m*-chloroperoxybenzoic acid (*m*-CPBA), *tert*-butylhydroperoxide (TBHP), H_2O_2, and iodosylbenzene (PhI = O), have been utilized for insertion of "O" into a C – Pd bond, and these "O" insertion reactions can proceed via two distinct mechanistic manifolds. Mechanism I involves direct reaction of the oxidant with the C – Pd bond via a concerted transition state that does not involve a change in oxidation state at the Pd^{II} center. This mechanism is exemplified in Scheme 4 for the reaction of a cyclometalated Pd^{II} complex with *m*-CPBA. Reactions that proceed by mechanism I are generally accelerated with increased nucleophilicity of C_α (the carbon that undergoes reaction with the electrophilic oxidant). In addition, because pre-coordination of the oxidant to Pd^{II} is typically essential for these transformations, they are also accelerated as the Pd center becomes more electrophilic [9–13].



Scheme 4 Example of oxygen insertion into a C – Pd bond via mechanism I

In contrast, mechanism II involves initial reaction of the nucleophilic Pd^{II} complex with the oxidant to afford a Pd^{IV} oxo intermediate, which then undergoes intramolecular insertion into the C – Pd bond to yield the product. This two-step mechanism is illustrated in Scheme 5 for the reaction of a cyclometalated Pd^{II} complex with TBHP. Importantly, the first step of this transformation (which is generally rate determining) is accelerated by

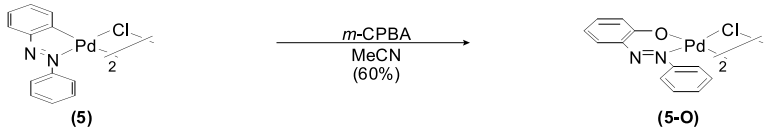


Scheme 5 Example of oxygen insertion into a C – Pd bond via mechanism II

electron-donating ligands that increase the nucleophilicity of the Pd^{II} center [14, 15]. In contrast, the second step proceeds faster as the electron density at C_α is decreased, since it involves reaction of a nucleophilic Pd–oxo with the electrophilic C_α [14–16]. As discussed below, both mechanisms I and II have been implicated in these "O" insertion reactions, depending on the nature of the oxidant and the reaction conditions employed.

3.1.1.1
Carbon–Oxygen Bond Formation via Oxygen Insertion: Mechanism I

The first reported example of "O" insertion into a C – Pd bond involved the reaction of cyclopalladated azobenzene complex **5** with *m*-CPBA to afford **5-O** in 60% yield (Eq. 1) [17].



Equation 1

Following this report, analogous reactions were applied to palladated *o*-hydroxyazobenzenes, *o*-(alkylthio)azobenzenes, 2-(alkylsulfinylazobenzenes, and (η^5-cyclopentadienyl)(1-(phenylazo)naphthylC(2),N) to afford **6-O**, **7-O**, **8-O**, and **9-O**, respectively (Fig. 1) [9–13, 17]. Interestingly, the thioether moiety in **7-O** remained unperturbed in this reaction, even in the presence of excess *m*-CPBA.

Mechanistic studies [9–13] on the reactions that form **6-O**, **7-O**, **8-O**, and **9-O** showed that the rate of oxygen atom insertion increased with increasing electron density on the arene ring being functionalized, with increasing elec-

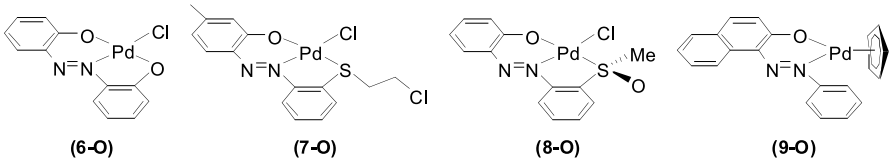
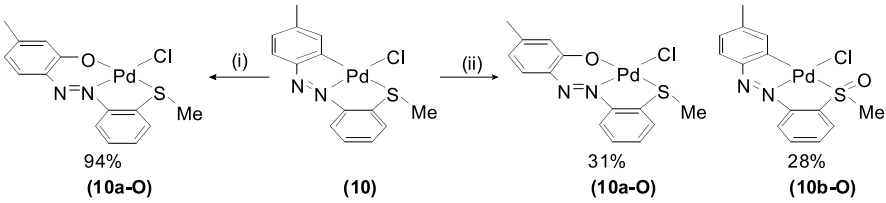


Fig. 1 "O" insertion products from reactions of cyclopalladated complexes with *m*-CPBA

trophilicity of the Pd^{II} center, and with improved leaving group ability of the peroxy acid. In addition, Eyring plots showed small positive values of $\Delta H^{\ddagger}$ and large negative values of $\Delta S^{\ddagger}$ for these transformations. Based on these data, the authors proposed that these "O" insertions proceed by mechanism I (Scheme 4).

More recently, the reaction of cyclopalladated *m*-(alkylthio)azobenzene **10** with *m*-CPBA in the presence of an iron porphyrin catalyst, iron(III) tetrakis(pentafluorophenyl)porphyrin chloride ($F_{20}TPPFe^{III}Cl$), was studied in detail [18]. As shown in Eq. 2, this transformation cleanly afforded "O" insertion product **10a-O** when conducted in toluene. However, interestingly, when the same reaction was carried out in CH_2Cl_2–MeOH (4 : 1), product **10b-O** (arising from the oxidation of the thioether moiety) was formed in comparable yield to **10a-O**. The authors proposed that **10a-O** was formed by concerted "O" insertion into the C – Pd bond (mechanism I), while **10b-O** was generated via oxidation of the thioether by an Fe(IV) oxo species (formed from the reaction of *m*-CPBA with $F_{20}TPPFe^{III}Cl$). These results demonstrate that slight modifications of reaction conditions can lead to oxidation of distinctly different sites of a palladacyclic molecule.

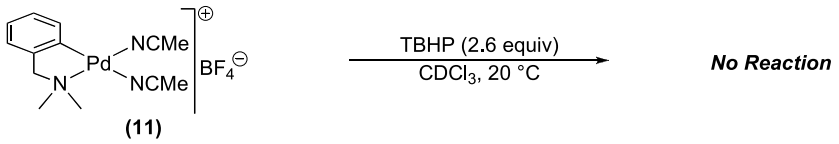


(i) $F_{20}TPPFe^{III}Cl$, *m*-CPBA, Toluene, 33 °C; (ii) $F_{20}TPPFe^{III}Cl$, *m*-CPBA, CH_2Cl_2-MeOH (4:1), 33 °C

Equation 2

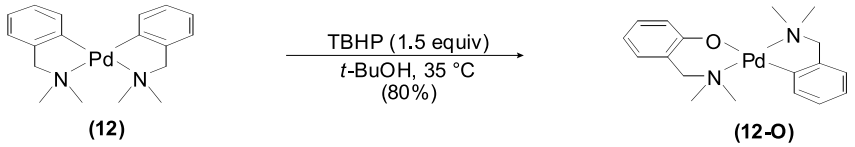
3.1.1.2 Carbon–Oxygen Bond Formation by "O" Insertion: Mechanism II

The oxygenation of cyclopalladated *N*,*N*-dimethylbenzylamine complexes using TBHP as the oxygen donor has also been investigated extensively [14–16, 19]. The efficacy of these transformations was found to be greatly en-



Equation 3

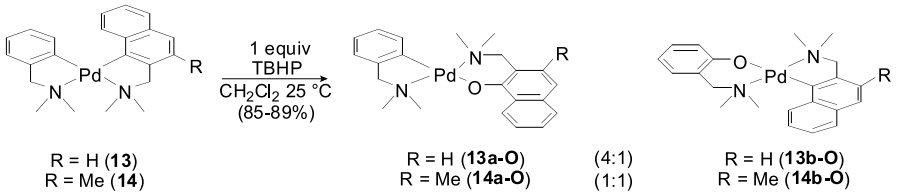
hanced with increasing electron density at the Pd^{II} center. For example, while cationic complex **11** was completely inert toward TBHP (Eq. 3), the electron-rich complex **12** reacted to afford **12-O** in 80% isolated yield (Eq. 4) [14, 15].



(12) **(12-O)**

Equation 4

These reactions were also more facile with decreasing electron density on the arene ring being oxygenated. For example, the major product from the reaction of heteroleptic Pd^{II} complex **13** was **13a-O** (arising from preferential oxidation of the naphthyl ring). However, **14** (which contains an electron-donating methyl substituent on the naphthyl ring) produced substantially decreased quantities of **14a-O** (Eq. 5) [16]. Based on these electronic effects, the authors hypothesized that mechanism II (Scheme 5) was operating.



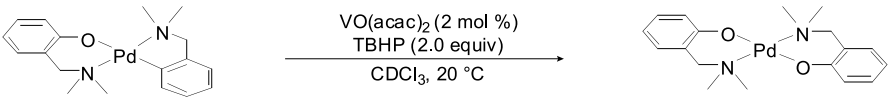
R = H (**13**)
R = Me (**14**)

R = H (**13a-O**)
R = Me (**14a-O**) (4:1) (1:1)

R = H (**13b-O**)
R = Me (**14b-O**)

Equation 5

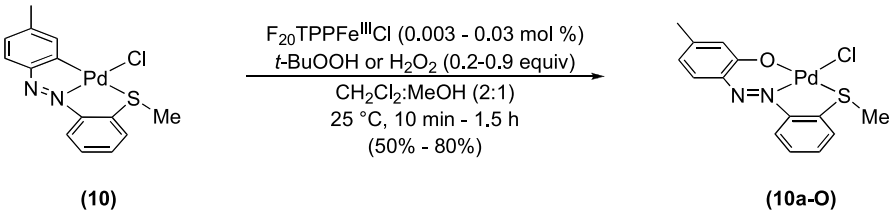
Catalytic quantities of $VO(acac)_2$ were shown to dramatically accelerate TBHP-mediated "O" insertion [14–16]. For example, while the uncatalyzed oxidation of **12-O** with TBHP occurred slowly over the course of several days, the addition of 2 mol % $VO(acac)_2$ produced the oxygenated product **12-O_2** in quantitative yield within 1.5 h at 20 °C (Eq. 6). In this system, a vanadium *t*-butyl peroxide (generated by reaction of $VO(acac)_2$ with TBHP) was proposed as the key oxygen atom transfer reagent. The greater electrophilicity of the vanadium *t*-butyl peroxide relative to TBHP was presumed to be responsible for the enhanced efficiencies.



(12-O) **(12-O_2)**

Equation 6

Oxygen insertions with TBHP and H_2O_2 were also accelerated by iron porphyrin catalysts [19, 20]. For example, the reaction of cyclopalladated alkylsulfinylazobenzene complex **10** with TBHP or H_2O_2 in the presence of catalytic $F_{20}TPPFe^{III}Cl$ in CH_2Cl_2–MeOH (2 : 1) resulted in selective oxidation of the C – Pd bond to afford **10a-O** within 1.5 h (Eq. 7).

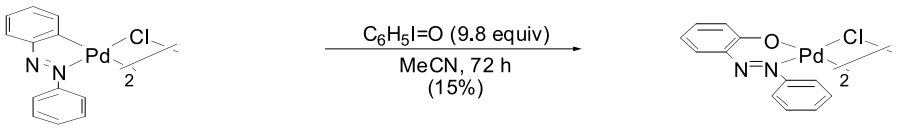


(10) **(10a-O)**

Equation 7

These iron porphyrin-catalyzed transformations have also been proposed to proceed via mechanism II. The key difference between the Fe- and the V-catalyzed reactions is the structure of the species that transfers "O" to the Pd^{II} center. While vanadium alkyl peroxides are believed to serve as the oxygen atom donors in the V-catalyzed systems, a free alkyl peroxide radical (generated by the reaction of the oxidant with the Fe porphyrin) is proposed to be the source of electrophilic oxygen in the Fe-catalyzed reactions. This hypothesis is predicated on the fact that while **10** did not exhibit appreciable reactivity with hydroperoxides alone, it underwent facile "O" insertion with ROO radicals that were generated by other means.

Finally, iodosylbenzene (PhI = O) and derivatives thereof have also been used as oxidants for "O" insertion into C – Pd bonds of cyclometalated complexes [19–21]. For example, azobenzene complex **5** reacted with PhI = O to afford the oxygenated complex **5-O** in 15% isolated yield (Eq. 8). Based on the large negative value of $\Delta S^{\ddagger}$ as well as similar results to the TBHP reactions, this and related transformations have also been proposed to proceed via mechanism II.

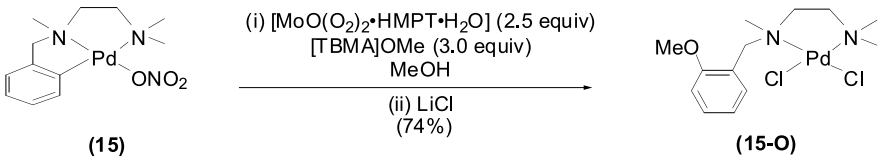


(5) **(5-O)**

Equation 8

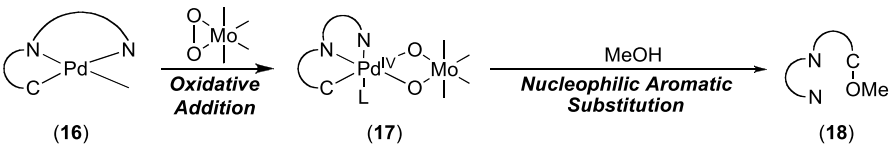
3.1.2
Direct Carbon–Oxygen Bond Formation

The stoichiometric oxygenation reactions discussed thus far lead to the insertion of an oxygen atom into a C – Pd bond to afford a new O – Pd bond. The functionalized organic ligand can then be released from the metal center in a second, subsequent step by treatment with acid or reducing reagents (Scheme 2). In contrast, several groups have developed alternative methods for the direct conversion of cyclopalladated complexes to oxygenated organic products, *without the intermediacy of a new palladacycle*. An early example involved the reaction of **15** with a molybdenum peroxide [$MoO(O_2)_2 \cdot HMPT \cdot H_2O$] in MeOH in the presence of (trimethyl)(benzyl)ammonium methoxide [(TBMA)OMe] to afford the corresponding methyl ether **15-O** in 74% isolated yield (Eq. 9). Notably, this transformation could also be carried out as part of a one-pot procedure involving initial cyclopalladation followed by in situ addition of the oxidant to afford the ether product in 68% overall yield [22, 23].



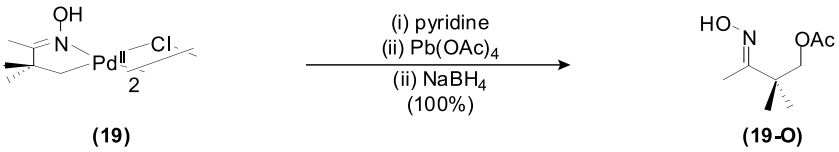
Equation 9

The mechanism of this reaction was proposed to involve oxidative addition of the molybdenum peroxide to the cyclopalladated complex to afford Pd^{IV} molybdate **17** (Scheme 6). This transient intermediate was then hypothesized to react with MeOH to generate product **18** via nucleophilic aromatic substitution [22, 23].



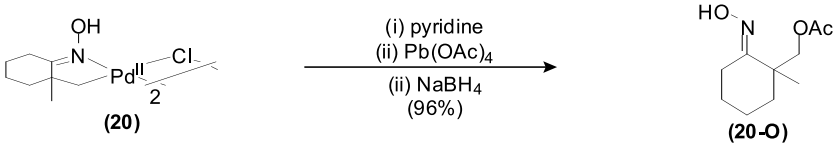
Scheme 6 General mechanism for oxygenations using molybdenum peroxide

This successive cyclopalladation/oxygenation sequence has also been applied to the functionalization of unactivated sp^3 C – H bonds. In an early example, Baldwin demonstrated that the cyclopalladation of pinacolone oxime could be followed by oxidative cleavage with $Pb(OAc)_4$ to form monoacetoxy product **19-O** in quantitative yield (Eq. 10) [7, 8]. Similarly, the reaction of cyclopalladated *E*-2,2-dimethylcyclohexanone oxime **20** with $Pb(OAc)_4$ afforded



Equation 10

20-O in 96% yield (Eq. 11) [7, 8]. These $Pb(OAc)_4$-mediated oxidative cleavage reactions have been proposed to proceed via the oxidation of Pd^{II} to Pd^{IV} followed by C – O bond-forming reductive elimination [24, 25].



Equation 11

Similar sp^3 C – H bond oxygenation reactions were applied to several other substrates (e.g., ethyl *t*-butyl ketooxime and phenyl *t*-butyl ketooxime). In contrast, they could not be used for the acetoxylation of compounds such as **21**–**24** (Fig. 2). The limited scope of these reactions was proposed to stem from three challenges associated with the synthesis of sp^3 palladacycles: (1) the requirement for achieving coplanarity between the target C – H bond and the oxime in order for cyclopalladation to take place (a challenge with substrates such as **21**), (2) the slow rates of cyclopalladation with substrates that are not highly branched at the α-position (e.g., oximes **22**, **23**, and **24**), and (3) the modest stability of palladacycles that contain β-hydrogens (such as those derived from **22**–**24**) [5, 6].

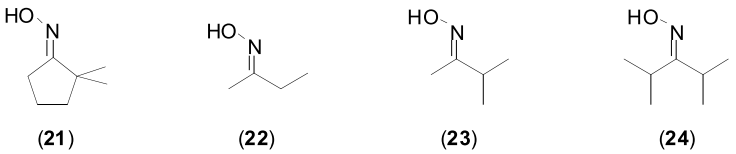
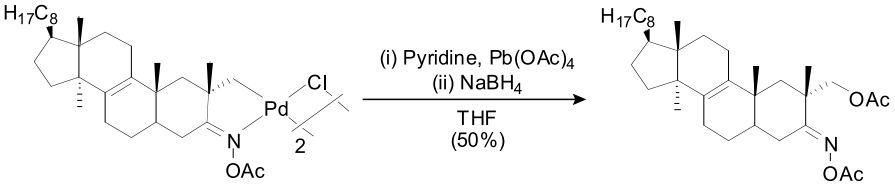


Fig. 2 Substrates that did not undergo stoichiometric cyclopalladation/acetoxylation

The potential synthetic utility of these stoichiometric chelate-directed sp^3 C – H activation/acetoxylation reactions was demonstrated by Sutherland in the biomimetic conversion of lanesterol to cholesterol [26, 27]. A key step in this synthesis involved C – H activation to form palladacycle **25**, followed by reaction with $Pb(OAc)_4$ to afford **25-O** in 50% isolated yield (Eq. 12).

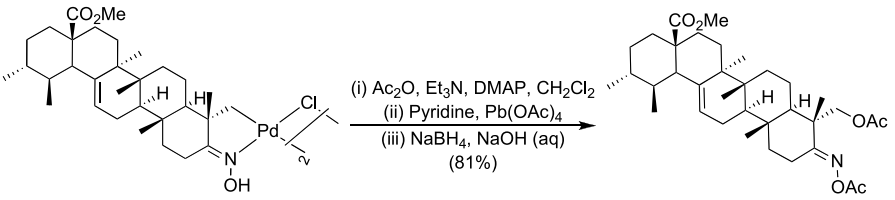
Subsequently, Gribble and coworkers employed the strategy of oxime-directed oxidation of unactivated methyl groups in the context of the syn-



(25) (25-O)

Equation 12

thesis of a derivative of the naturally occurring terpene 3α-hydroxyurs-12-ene-23,28-dioic acid [28]. In this system, the reaction of cyclopalladated dimer **26** with $Pb(OAc)_4$ afforded the diacetate product **26-O**, a key intermediate in the synthesis of the terpene (Eq. 13). More recently, analogous cyclopalladation/acetoxylation sequences have been applied to the formation of intermediates in the synthesis of rostratone, aphidicolin, and pyripyropene A [29, 30].

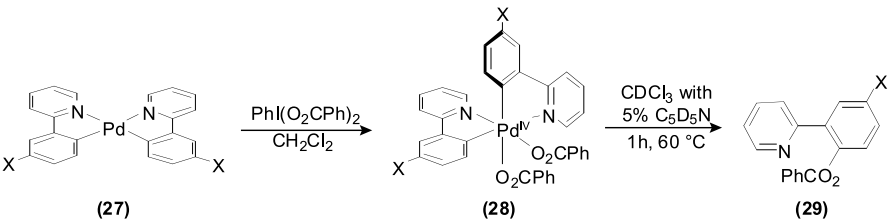


(26) (26-O)

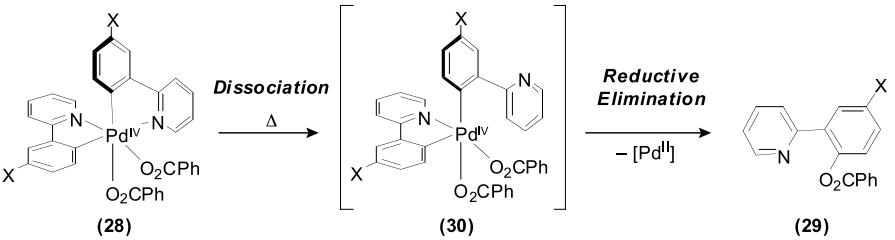
Equation 13

As discussed above, the vast majority of stoichiometric C – H bond oxygenation reactions of cyclopalladated complexes have been proposed to proceed via transient Pd^{IV} intermediates. While significant circumstantial evidence supported the intermediacy of such high oxidation state complexes, the direct observation of Pd^{IV} intermediates in these transformations remained elusive for more than 20 years. However, very recently, our group demonstrated that the oxidation of $(Arpy)_2Pd$ (**27**) (Arpy = 2-arylpyridine) with $PhI(O_2CPh)_2$ afforded the isolable Pd^{IV} bis-carboxylate complex **28** [31]. Furthermore, upon thermolysis, **28** underwent clean C – O bond-forming reductive elimination to produce *ortho*-oxygenated arylpyridine product **29** (Eq. 14).

Mechanistic investigations [including Erying analysis, Hammett analysis (with diverse substituted carboxylates), and solvent effects] provided evidence that C – O reductive elimination from **28** proceeded by initial dissociation of a pyridyl arm of one cyclometalated ligand to afford **30** (Scheme 7). While the exact nature of the subsequent C – O coupling step has not yet been definitively elucidated, investigations of this reaction with diverse sub-



Equation 14

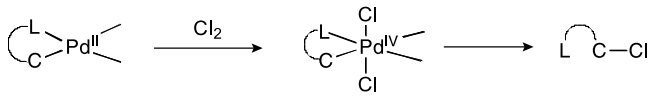


Scheme 7 Proposed mechanism of C – O reductive elimination from Pd^{IV} complex **28**

stituents X showed that there was only a modest electronic effect (Hammett $\rho \sim +2$) (Dick AR, Sanford MS (2006), unpublished results). The magnitude of this effect is not sufficiently large to be consistent with a nucleophilic aromatic substitution mechanism (with a fully delocalized negative charge) as proposed for the oxygenation reactions with $MoO(O_2)_2 \cdot HMPT \cdot H_2O$ discussed above [22, 23].

3.2 Carbon–Halogen (Halogen = Cl, I) Bond Formation

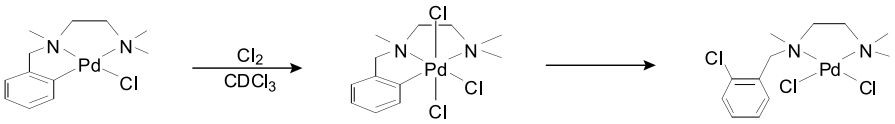
Cyclopalladation followed by oxidative halogenation of the resulting C – Pd bond has been developed as a method for the regioselective conversion of C – H bonds to carbon–halogen bonds. These stoichiometric halogenation reactions are believed to proceed via reaction of the cyclopalladated Pd^{II} complex with an electrophilic halogenating reagent (e.g., Cl_2 in Scheme 8) to form a Pd^{IV} intermediate. This Pd^{IV} complex then undergoes carbon–halogen bond-forming reductive elimination (by either internal or external attack of a halide anion) to afford the *ortho*-halogenated product.



Scheme 8 General mechanism for the chlorination of a C – Pd bond with Cl_2

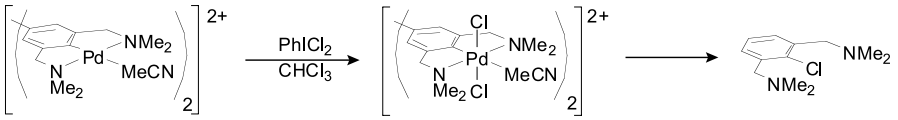
3.2.1
Carbon–Chlorine Bond Formation

Early work in this area demonstrated the stoichiometric chlorination of Pd^{II} complexes **31** and **34** (Eqs. 15 and 16). These complexes were shown to react with Cl_2 or $PhICl_2$, respectively, to afford moderately stable Pd^{IV} intermediates, which could be characterized by ^1H NMR spectroscopy at room temperature. Both complexes then decomposed to afford halogenated organic products, presumably via C – Cl bond-forming reductive elimination. However, the mechanism of reductive elimination in these systems was not investigated in detail [32, 33].



(31) (32) (33)

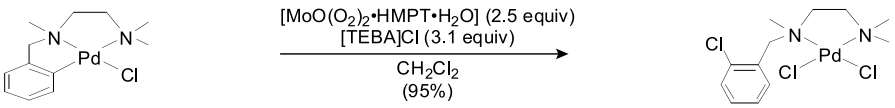
Equation 15



(34) (35) (36)

Equation 16

Complex **31** was also shown to undergo clean oxidative chlorination to afford **33** in the presence of $MoO(O_2)_2{\cdot}HMPT{\cdot}H_2O$ (Eq. 17) [23]. The yield of **33** in this reaction increased with the addition of chloride ion sources such as (triethyl)(benzyl)ammonium chloride ([TEBA]Cl). This result is consistent with a mechanism analogous to the ether-forming reaction discussed above (Eq. 9), involving oxidation to Pd^{IV} followed by external nucleophilic attack by Cl^- on the Pd^{IV} aryl species. Notably, overchlorination was not observed in this transformation; as a result, these mild conditions serve as an attractive



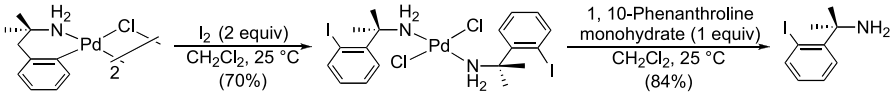
(31) (33)

Equation 17

alternative to the use of Cl_2 as an oxidant, which typically results in significant quantities of polychlorinated products.

3.2.2
Carbon–Iodine Bond Formation

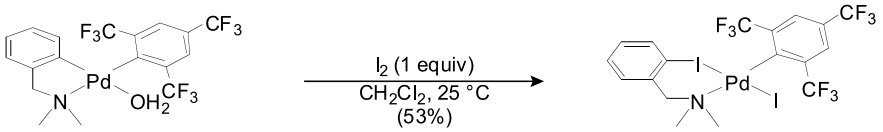
Recent work has shown that the stoichiometric reaction of cyclopalladated complex **37** with iodine affords the symmetrical product **38** in 70% yield. Further reaction of **38** with 1,10-phenanthroline monohydrate released the monoiodinated organic product **39** in 84% yield (Eq. 18) [34].



(37) (38) (39)

Equation 18

Espinet and coworkers have also demonstrated that the reaction of the cyclopalladated complex **40** with iodine led to replacement of the C – Pd bond by a C – I bond affording **40-I** in 53% isolated yield (Eq. 19). Notably, unlike the other halogenation reactions described above, this reaction is not believed to proceed via a Pd^{IV} intermediate [35]. Instead the authors propose that the palladated carbon undergoes direct electrophilic substitution to afford the product.

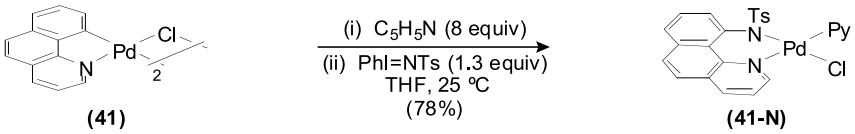


(40) (40-I)

Equation 19

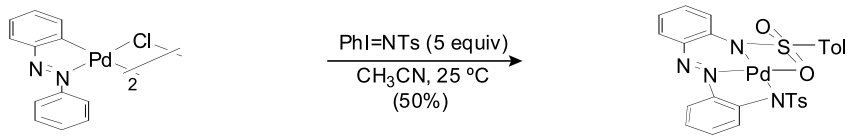
3.3
Carbon–Nitrogen Bond Formation

Very recently, our group has begun to explore *N*-tosyliminophenyliodinane (PhI = NTs) as an oxidant for the stoichiometric amination of C – Pd bonds in palladacycles [36]. For example, we have demonstrated that reaction of the cyclopalladated benzoquinoline dimer **41** with PhI = NTs in the presence of pyridine affords complex **41-N** in 78% isolated yield (Eq. 20). Interestingly, the analogous reaction of the palladated azobenzene dimer **5** led to the diamination product **5-N_2** (Eq. 21). While detailed mechanistic investigations



(41) (41-N)

Equation 20



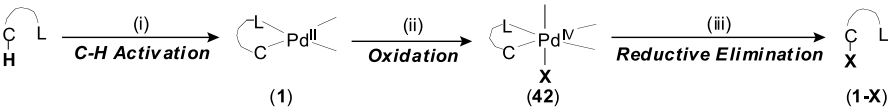
(5) (5-N_2)

Equation 21

of these transformations remain to be carried out, the close similarities between PhI = NTs and PhI = O [19–21] suggest the possibility of Pd^{IV} imido intermediates in these systems.

4 Chelate-Directed Carbon–Heteroatom Bond Formation: Catalytic Reactions

Palladium-catalyzed chelate-directed C – H activation/oxidation reactions can be viewed as an extension of the stoichiometric transformations described in Sect. 3, but with two key differences: (1) only a catalytic amount of Pd^{II} is used, and (2) the desired organic product is liberated from the metal in the final step of the catalytic cycle. The mechanisms of the vast majority of the reactions described in this section are believed to involve: (1) Pd^{II}-mediated C – H activation to afford a cyclopalladated adduct of general structure **1**, (2) oxidation of Pd^{II} to Pd^{IV} to produce transient intermediate **42**, and, finally, (3) carbon–heteroatom bond-forming reductive elimination from **42** to generate the desired functionalized product **1-X** (Scheme 9). The high regioselectivity observed in these transformations provides strong evidence in support of the chelate-directed C – H activation step of the catalytic cycle. Studies of stoichiometric reactions of Pd^{IV} complexes (vide supra) [23, 29, 32, 33], along with further mechanistic investigations



(1) (42) (1-X)

Scheme 9 General mechanism for Pd-catalyzed chelate-directed oxidation of C – H bonds

(detailed in the sections below), have provided support for the second and third steps of the proposed catalytic cycle.

Because these catalytic C – H activation/oxidative functionalization reactions proceed via high oxidation state Pd intermediates, they are often highly complementary to transformations that involve the more typical Pd^0/Pd^{II} couple. First, they do not require the exclusion of air or moisture. Second, they are tolerant toward functional groups such as aryl halides, which are often reactive in the presence of Pd^0 sources. Finally, as discussed in detail below, they can allow bond constructions that are challenging to achieve via traditional Pd^0/Pd^{II} reaction mechanisms. This section provides a detailed description of the recent advancements in this area [37–39].

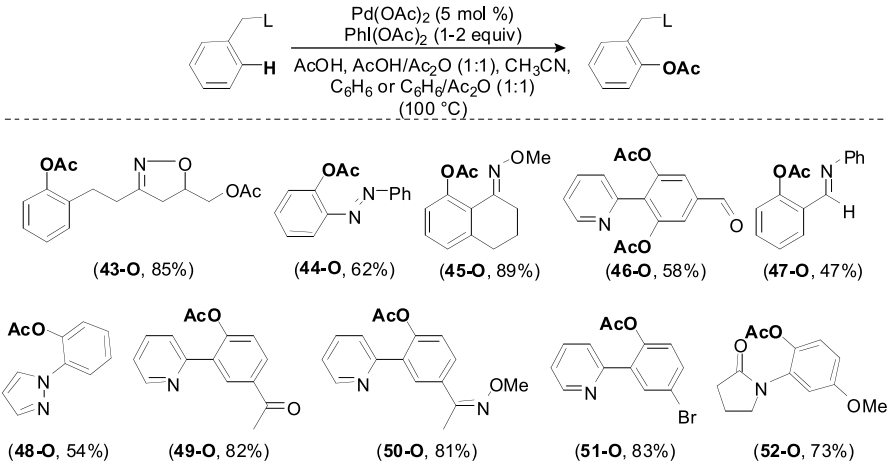
4.1 Carbon–Oxygen Bond Formation

The palladium-catalyzed oxygenation of aromatic C – H bonds using terminal oxidants such as dichromate [40, 41] and peroxydisulfate [42–44] has been known for over three decades. However, for many years, the synthetic utility of these methods was limited by their low yields as well as by poor levels of regio- and chemoselectivity. In 1996, Crabtree reported a new method for the palladium-catalyzed acetoxylation of benzene using $PhI(OAc)_2$ as the terminal oxidant [45]. This reaction afforded *significantly* enhanced yields and turnover numbers; however, its widespread applicability to diverse substituted arenes was still relatively modest, due to the formation of complex mixtures of regioisomeric products.

4.1.1 Carbon–Oxygen Bond Formation Using Hypervalent Iodine Reagents

Our group first demonstrated that $Pd(OAc)_2$ in conjunction with $PhI(OAc)_2$ could be used for the highly regioselective conversion of sp^2 C – H bonds to C – OAc bonds when applied to substrates that contained chelate-directing groups (Scheme 10) [46]. This transformation was proposed to proceed by a $Pd^{II/IV}$ catalytic cycle analogous to that shown in Scheme 9. Consistent with this mechanism, weaker oxidants that typically mediate $Pd^{0/II}$ cycles (e.g., benzoquinone, $Cu(OAc)_2$) were ineffective at promoting the acetoxylation reaction. Additionally, mechanistic studies (vide supra) demonstrated the ability of $PhI(OCOR)_2$ to oxidize Pd^{II} to Pd^{IV} in model complexes, as well as the feasibility of C – O bond-forming reductive elimination from Pd^{IV} centers to form C – OCOR bonds [31].

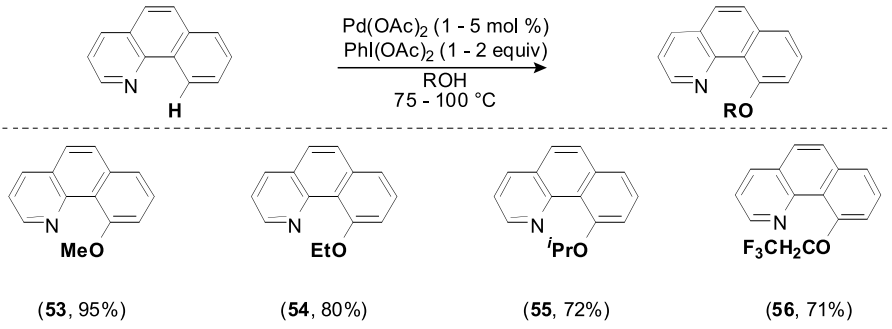
A wide variety of oxygen and nitrogen directing groups have been used in this transformation, and directed sp^2 C – H activation/oxygenation has been shown to proceed efficiently via five-, six-, and seven-membered palladacycles (Scheme 10). In addition, both acidic and basic functional groups such as



Scheme 10 Pd-catalyzed arene C – H activation/acetoxylation with $PhI(OAc)_2$

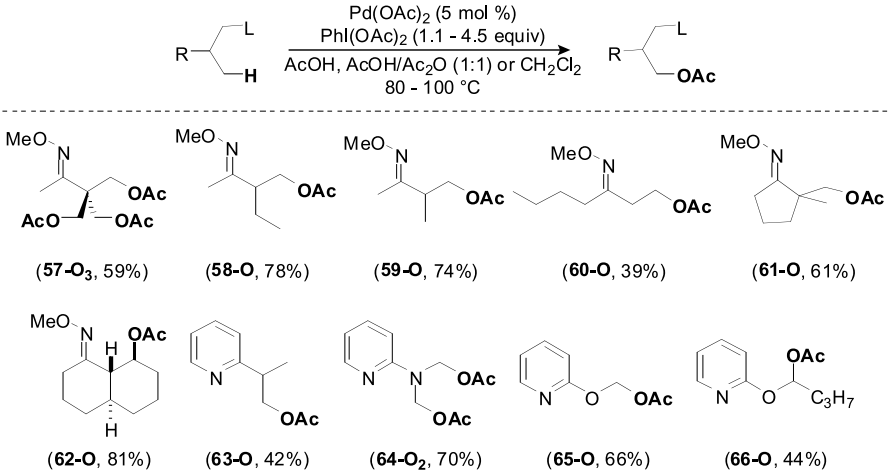
enolizable protons and ether moieties (Scheme 10), as well as oxidizable functionalities such as aromatic aldehydes and benzylic C – H bonds, were well tolerated under the reaction conditions. In these reactions, *meta*-substituted arene substrates generally reacted to afford *ortho*-acetoxylated products with > 20 : 1 selectivity for functionalization of the less sterically hindered C – H bond [47].

As shown in Scheme 11, changing the solvent from AcOH or MeCN to an alcohol (ROH) resulted in formation of the corresponding aryl ether products in excellent yields [46, 48]. These reactions are believed to proceed by in situ formation of $PhI(OR)_2$ (via the reaction of $PhI(OAc)_2$ with the alcohol solvent) [49], which can then serve as both the oxidant and the source of the ether functionality in the final products.



Scheme 11 Pd-catalyzed C – H activation/formation of aromatic ethers

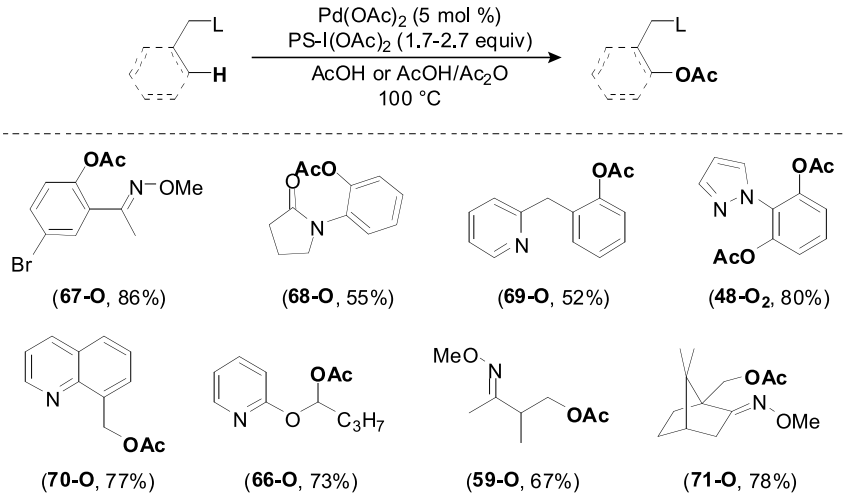
Palladium-catalyzed directed C – H activation/functionalization reactions with $PhI(OAc)_2$ were also applied to the regioselective oxygenation of sp^3 C – H bonds [50, 51]. As shown in Scheme 12, both oxime ethers and pyridines were effective directing groups for these transformations [50]. Importantly, the β-acetoxylated oxime ether products serve as precursors to valuable synthetic building blocks such as β-hydroxy ketones [52] (after deprotection of the acetate and oxime) and β-amino alcohols [53] (following acetate deprotection and reduction).



Scheme 12 Pd-catalyzed sp^3 C – H activation/acetoxylation with $PhI(OAc)_2$

In contrast to the stoichiometric sp^3 C – H bond oxygenation reactions discussed in Sect. 3 above, these catalytic reactions were *not* restricted to highly α-branched substrates, and products such as **59-O** and **60-O** could be obtained in modest to good yields. Importantly, these transformations proceeded with selectivity for the oxidation of 1° C – H bonds over 2° and 3° C – H bonds (for examples, see products **58-O** and **60-O**), and therefore complement C – H bond functionalizations that proceed by either radical or cationic mechanisms [38]. In fact, the acetoxylation of 2° C – H bonds was generally challenging in these systems, and only proceeded in good yields with substrates that were highly rigid (e.g., to form the decalone product **62-O**) or contained an activating heteroatom group adjacent to the target 2° C – H bond (e.g., to form 2-butoxypyridine product **66-O**).

We subsequently demonstrated that these palladium-catalyzed sp^2 and sp^3 C – H bond acetoxylation reactions could also be carried out using the polymer immobilized iodine(III) reagent poly-4-(diacetoxyiodo)styrene [PS – $I(OAc)_2$] (Scheme 13) [54]. The yields of products obtained in this protocol were comparable to reactions with soluble $PhI(OAc)_2$. Importantly, PS-$I(OAc)_2$ serves

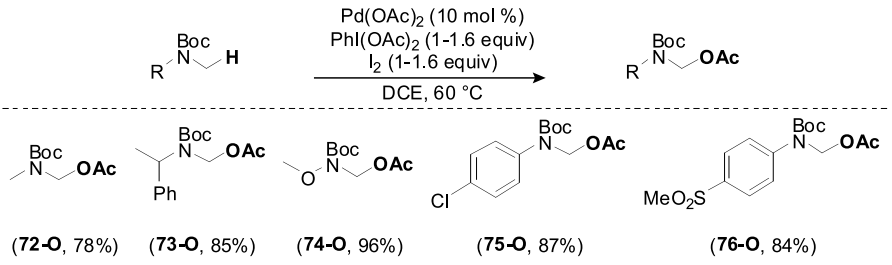


Scheme 13 Pd-catalyzed C – H activation/acetoxylation with PS-I$(OAc)_2$

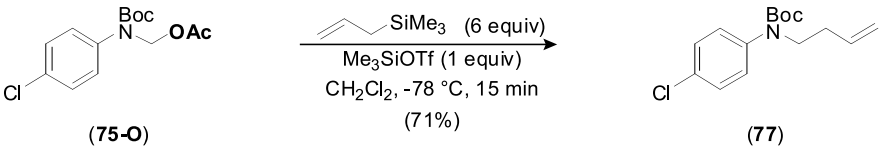
as a recyclable alternative to $PhI(OAc)_2$, since the PS-I by-product of these reactions can be recovered and used to regenerate the oxidant.

Recently, Pd-catalyzed sp^3 C – H bond acetoxylation reactions were expanded to amide-directed functionalization adjacent to activating nitrogen groups (Scheme 14) [55]. These transformations used $Pd(OAc)_2$ as a catalyst and a combination of I_2 and $PhI(OAc)_2$ as the terminal oxidants. Interestingly, neither I_2 nor $PhI(OAc)_2$ alone afforded any of the desired products, leading the authors to speculate that in situ generated IOAc served as the oxidant and the acetate source. As depicted in Scheme 14, this methodology was applied to a range of Boc-protected aryl amines and electron-deficient aniline derivatives. However, reactions of electron-rich Boc-protected aryl amines resulted in aromatic iodination rather than providing the desired oxygenated products.

The synthetic applicability of the Boc-protected acetoxylated products obtained via this methodology was demonstrated by the allylation of product **75-O** to afford the amide **77** in 71% isolated yield (Eq. 22).



Scheme 14 Pd-catalyzed amide-directed C – H activation/acetoxylation with $PhI(OAc)_2/I_2$

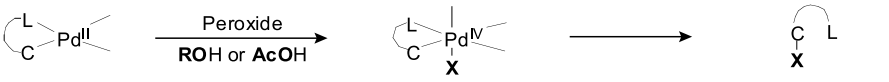


(**75-O**) (**77**)

Equation 22

4.1.2 Carbon–Oxygen Bond Formation Using Peroxides

As discussed above, Pd-catalyzed chelate-directed C – H activation/oxidation with $PhI(OAc)_2$ allows the regioselective oxygenation of a diverse set of sp^2 and sp^3 C – H bonds. However, these transformations remain limited by the fact that $PhI(OAc)_2$ is expensive ($\sim$ US \$1/g) and that it generates a stoichiometric amount of a toxic by-product (PhI) with each catalytic turnover. Hence, there has been considerable interest in developing methodologies for directed C – H bond oxygenation that use alternative, more environmentally benign oxidants. As summarized in Scheme 15, the general strategy to achieve this goal has involved the use of strong oxidants (that are capable of oxidizing Pd^{II} to Pd^{IV}) in conjunction with a coordinating solvent, which can bind to the Pd^{IV} intermediate and serve as the ultimate source of functionality in the final product.

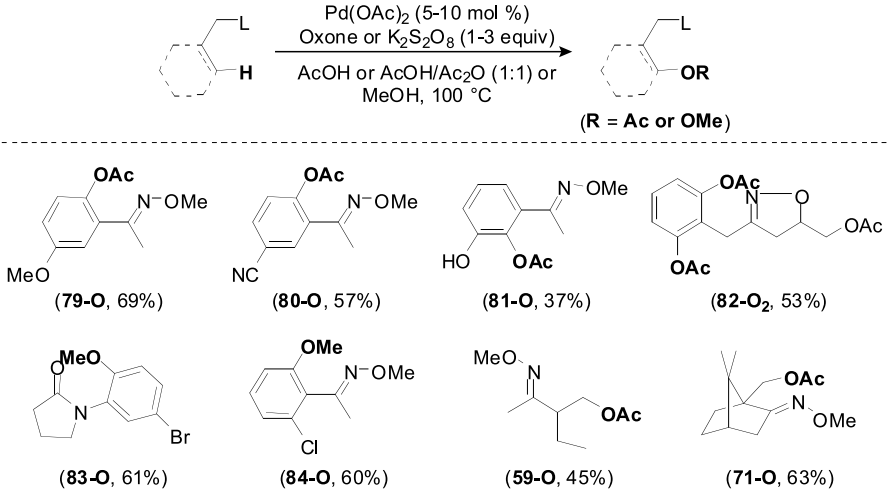


(**X** = **OAc** or **OR**) (**X** = **OAc** or **OR**)

(**78**)

Scheme 15 General mechanism for Pd-catalyzed C – H activation/C – O bond formation with peroxides as oxidants

Based on this approach, our group demonstrated the $Pd(OAc)_2$-catalyzed acetoxylation of sp^2 and sp^3 C – H bonds using inexpensive and readily available Oxone and $K_2S_2O_8$ as terminal oxidants. These reactions were conducted in AcOH or $AcOH/Ac_2O$, which served as both a solvent and a source of the acetate functionality in the ultimate products [56]. As shown in Scheme 16, these transformations generally exhibited comparable (or in some cases better) substrate scope and functional group tolerance to that of reactions with $PhI(OAc)_2$. In addition, the use of alcoholic solvents such as methanol in place of acetic acid allowed the facile construction of methyl ethers via intermediates such as **78** (Scheme 15). The ease, safety, cost-effectiveness, and general practicality of these reactions should make them amenable to large-scale processes.

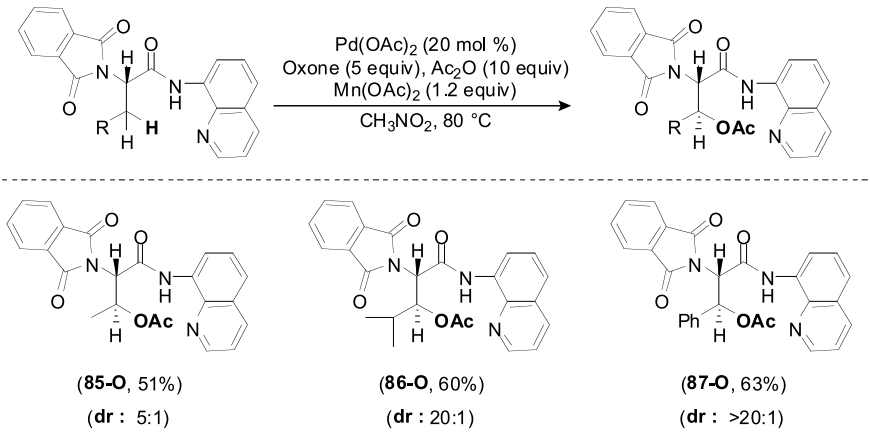


Scheme 16 Pd-catalyzed C – H activation/oxygenation with Oxone or $K_2S_2O_8$ in ROH (R = Ac or Me)

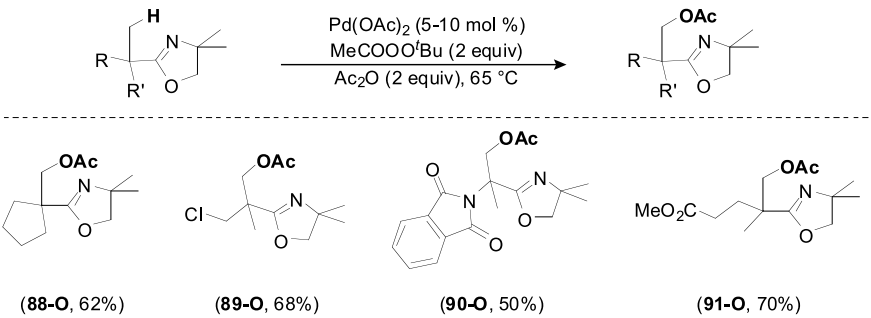
Corey recently demonstrated that quinoline-substituted carboxamides also serve as effective directing groups for Pd-catalyzed oxygenation reactions with Oxone as the terminal oxidant [57]. In these systems, stoichiometric $Mn(OAc)_2$ was used as a co-oxidant, and significantly diminished yields were obtained in the absence of this additive. The $Mn(OAc)_2$ was proposed to undergo oxidation to $Mn_3O(OAc)_7$ under the reaction conditions, and this complex was then believed to function as a Lewis acid, coordinating to Pd and lowering the barrier for C – H activation.

This carboxamide-directed oxygenation reaction was applied to 8-aminoquinoline derivatives of alanine, leucine, and phenylalanine, affording **85-O**, **86-O**, and **87-O**, respectively (Scheme 17). Importantly, the β-acetoxylated products could be hydrolyzed to the corresponding β-hydroxy amino acids, which are important constituents of a variety of bioactive natural compounds. These reactions are particularly notable because unactivated 2° C – H bonds (which are typically challenging to functionalize via Pd catalysis) underwent acetoxylation in high yields. This unusual reactivity profile may be due to: (1) enhanced reactivity of the Pd^{II} center based on interactions with the Lewis acidic $Mn_3O(OAc)_7$ and/or (2) dual chelation of the quinoline and the amide groups of these substrates to the Pd center, thereby accelerating 2° C – H bond activation.

Peroxyesters have also been used as terminal oxidants for Pd-catalyzed directed C – H bond acetoxylation [58]. In these transformations, the reaction of oxazoline substrates with $Pd(OAc)_2$ (5 mol %) and MeCOO*t*Bu (2 equiv) in Ac_2O afforded acetate products such as **88-O** to **91-O** in good yields (Scheme 18). Mechanistic studies of these transformations suggested multi-



Scheme 17 Pd-catalyzed amide-directed 2° sp^3 C – H activation/acetoxylation with Oxone, Ac_2O, and $Mn(OAc)_2$

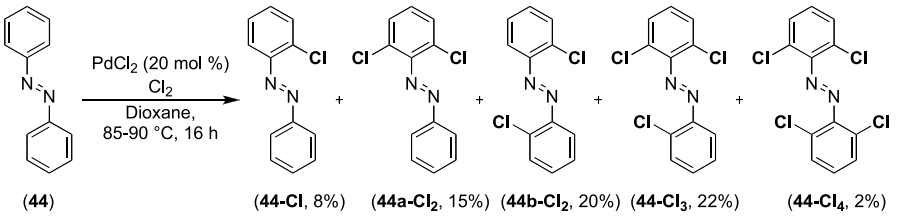


Scheme 18 Pd-catalyzed oxazoline-directed sp^3 C – H activation/acetoxylation with peroxyesters and Ac_2O

ple roles for the acetic anhydride. In addition to acting as the solvent, it was proposed to serve as the source of OAc in the final products as well as to be responsible for regenerating the catalyst and facilitating turnover.

4.2 Carbon–Halogen (Halogen = Cl, Br, I) Bond Formation

The first example of palladium-catalyzed chelate-directed C – H activation/halogenation involved the *ortho* chlorination of azobenzene with catalytic $PdCl_2$ and stoichiometric amounts of Cl_2 (Eq. 23) [59, 60]. The monochlorinated product **44-Cl** was obtained in modest yield (8%) along with the corresponding di-, tri-, and tetrachlorinated compounds. However, this early discovery was not extended to the chlorination of other substrates or to the

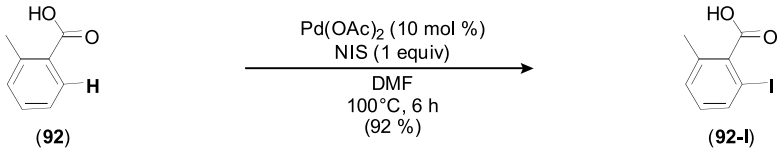


Equation 23

palladium-catalyzed formation of C – Br and C – I bonds. Further, the use of toxic Cl_2 gas greatly limited the practical applicability of this reaction.

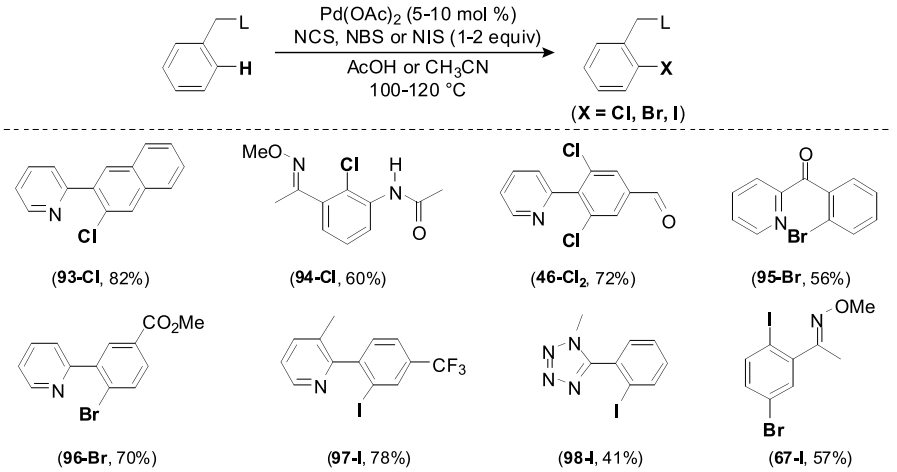
Several recent reports have revealed that other sources of electrophilic halogen (e.g., *N*-halosuccinimides, $CuCl_2$, and/or I_2/PhI(OAc)$_2$) can be applied in related transformations [61]. The key product-forming step of these reactions is proposed to involve reductive elimination to form a carbon–halogen bond from a transient Pd^{IV} intermediate (Scheme 9). Notably, the corresponding carbon–halogen bond-forming reductive elimination reactions within Pd^0/Pd^{II} manifolds have been shown to be slow and thermodynamically unfavorable [62]. This highlights one of the advantages of utilizing $Pd^{II/IV}$ catalysis: carbon–halogen bond formation is typically fast and highly thermodynamically downhill, which facilitates rapid catalytic turnover in these transformations.

In 2001, Kodama et al. reported a palladium-catalyzed method for the carboxylic acid directed *ortho* halogenation of benzoic acid derivatives using electrophilic halogenating reagents as the terminal oxidant. A representative example of this reaction is shown below (Eq. 24) [63].



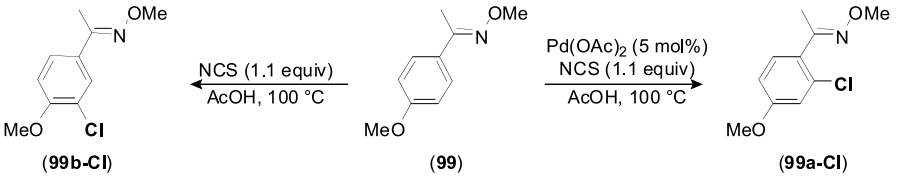
Equation 24

Subsequently, our group has reported a general procedure for the chelate-directed C – H activation/halogenation of arene substrates using catalytic Pd(OAc)$_2$ and a stoichiometric amount of an electrophilic halogenating reagent [46, 64, 65]. Although significant quantities of the desired *ortho*-halogenated products were observed with a variety of "X^+" sources (X = Cl, Br, I), the best results were obtained using *N*-halosuccinimides. As summarized in Scheme 19, these reactions exhibited a scope of directing group and functional group tolerance comparable to the sp^2 C – H activation/oxygenation reactions discussed in Sect. 4.1.



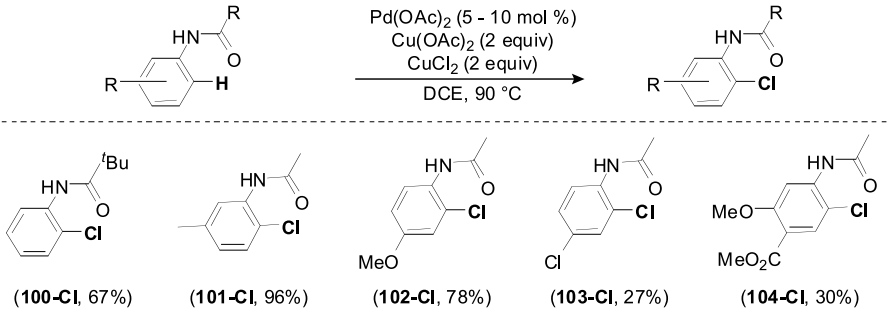
Scheme 19 Pd-catalyzed C – H activation/halogenation with *N*-halosuccinimides

A common feature of the reactions depicted in Scheme 19 is that the starting substrates are not activated toward electrophilic aromatic substitution; as such, they did not react with *N*-halosuccinimides to form halogenated products in the absence of the Pd catalyst. In contrast, the reaction of the oxime ether **99** (which bears an electron-donating methyl ether substituent on the arene ring) with *N*-chlorosuccinimide in the absence of Pd catalyst led to product **99b-Cl** via classical electrophilic aromatic substitution (Eq. 25). However, under otherwise identical conditions, the addition of catalytic $Pd(OAc)_2$ resulted in exclusive formation of the chelate-directed product **99a-Cl** (Eq. 25). This example demonstrates that Pd-catalyzed directed halogenation can outcompete uncatalyzed processes to afford complementary products.



Equation 25

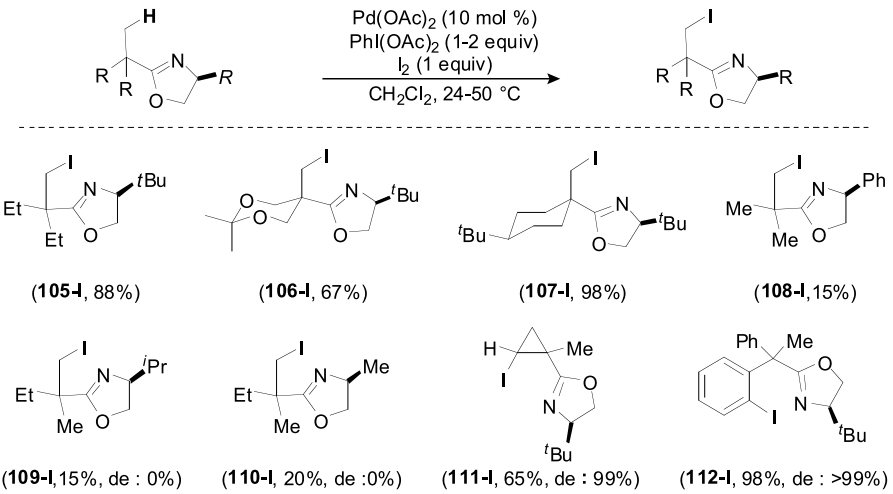
Shi and coworkers subsequently extended these directed arene chlorination reactions to acetanilide substrates using $CuCl_2$ as a terminal oxidant [66]. In these systems, appropriate choice of nitrogen protecting group (R in Scheme 20) was essential to obtaining significant quantities of the desired chlorinated compounds. Only the *N*-acetyl, *N*-pivolyl, and *N*-(3′-phenylpropionyl) amides afforded *ortho*-chlorinated products in modest to



Scheme 20 Pd-catalyzed acetanilide-directed C – H activation/chlorination with $CuCl_2$

good yields, while formyl, benzoyl, tosyl, and trifluoroacetyl amides exhibited low reactivity. The yields of these reactions were generally higher with arenes bearing an electron-donor substituent on the aromatic ring. Electron-withdrawing substituents such as chloro and ester groups led to significantly diminished yields of the chlorinated products **103-Cl** and **104-Cl**, respectively.

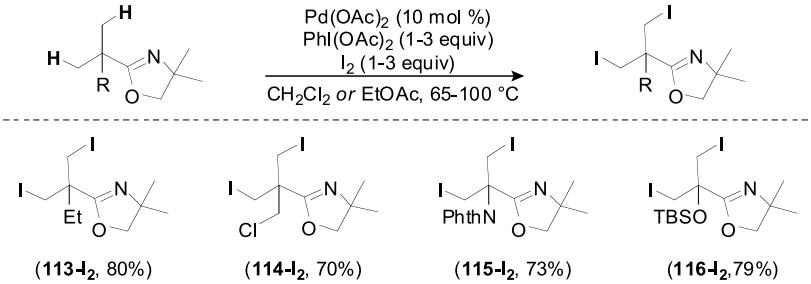
A Pd-catalyzed method for the selective chelate-directed iodination of sp^2 and sp^3 C – H bonds has also been recently reported [67, 68]. These transformations used I_2 as a terminal oxidant in conjunction with stoichiometric quantities of $PhI(OAc)_2$, which was proposed to serve as the acetate source for regenerating the $Pd(OAc)_2$ catalyst. These reactions are highly sensitive to the substituent at the 4-position of the oxazoline moiety. For example, the yields of these transformations decreased significantly when the *t*-Bu substituent was replaced with smaller Ph, *i*-Pr, or Me groups (Scheme 21). The reactions



Scheme 21 Pd-catalyzed oxazoline-directed C – H activation/iodination with $I_2/PhI(OAc)_2$

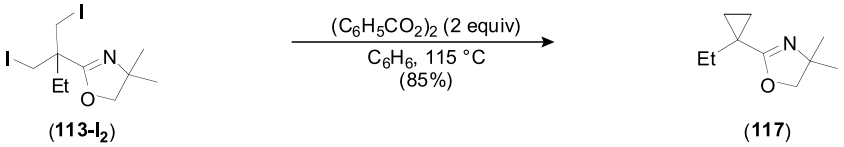
were generally selective for the functionalization of 1° C – H bonds relative to 2° C – H bonds, similar to the acetoxylation reactions described above. A notable exception was the reaction of the cyclopropyl substrate, which afforded product **111-I** via the iodination of the cyclopropyl 2° C – H bond in the presence of an adjacent methyl group. Interestingly, the reactions of prochiral substrates bearing significant steric bulk at the α-carbon led to the formation of products such as **112-I** with good levels of diastereoselectivity.

Yu and coworkers have subsequently expanded this methodology to the diiodination of 2-(1,1-dimethylalkyl)dimethyloxazoline substrates (Scheme 22) [69]. Analogous to the monoiodination reactions described above, these transformations were also sensitive to the substituent on the oxazoline group, and the reactions were most efficient with the dimethyloxazoline.



Scheme 22 Pd-catalyzed oxazoline-directed diiodination reaction

The 1,3-diiodide products obtained via this methodology were shown to serve as precursors to cyclopropane building blocks (Eq. 26) [69].



Equation 26

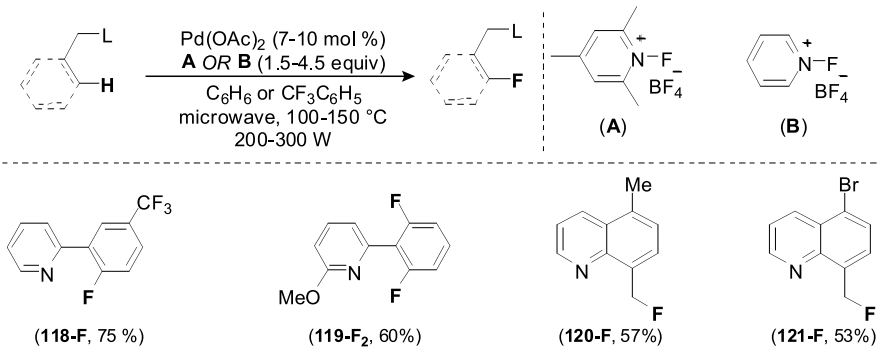
4.3 Carbon–Fluorine Bond Formation

Despite the important implications and widespread applicability of fluorine-containing compounds, synthetic methods (and particularly transition metal-catalyzed approaches) for the formation of carbon–fluorine bonds remain very limited. The modest scope and the harsh conditions required for classical electrophilic fluorination reactions have recently spurred efforts toward new, mild, chemoselective, regioselective, and environmentally friendly

approaches for C – F bond construction [70, 71]. As a result, the development of methods for the direct conversion of C – H bonds to C – F bonds under mild conditions would constitute a particularly notable advancement in the growing field of the transition metal-catalyzed functionalization of C – H bonds.

Recently, our group has demonstrated the first metal-catalyzed conversion of aromatic and benzylic C – H bonds to C – F bonds using $Pd(OAc)_2$ as the catalyst and *N*-fluoropyridinium salts as stoichiometric electrophilic fluorinating reagents [72]. The key step leading to the desired *ortho*-fluorinated products is proposed to involve C – F bond-forming reductive elimination from the putative Pd^{IV} intermediate **42** (Scheme 9). This is notable because attempts to develop Pd^0/Pd^{II} catalytic cycles for the conversion of C – X (X = halogen or H) bonds to C – F bonds have been unsuccessful due to the failure to achieve C – F bond-forming reductive elimination from Pd^{II} [73]. This exemplifies the fact that a Pd^{II}/Pd^{IV} manifold can facilitate bond constructions that are currently inaccessible within Pd^0/Pd^{II} reaction mechanisms.

As shown in Scheme 23, this reaction has been applied to the pyridine- and quinoline-directed fluorination of both aromatic and benzylic C – H bonds. The fluorinated products were obtained in modest to good yields with both electron-donating and electron-withdrawing substituents on the arene rings being functionalized. Current efforts are aimed toward delineating further mechanistic details and expanding the scope of these transformations.

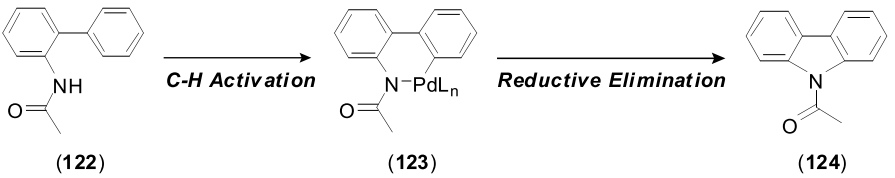


Scheme 23 Pd-catalyzed C – H activation/fluorination with *N*-fluoropyridinium salts

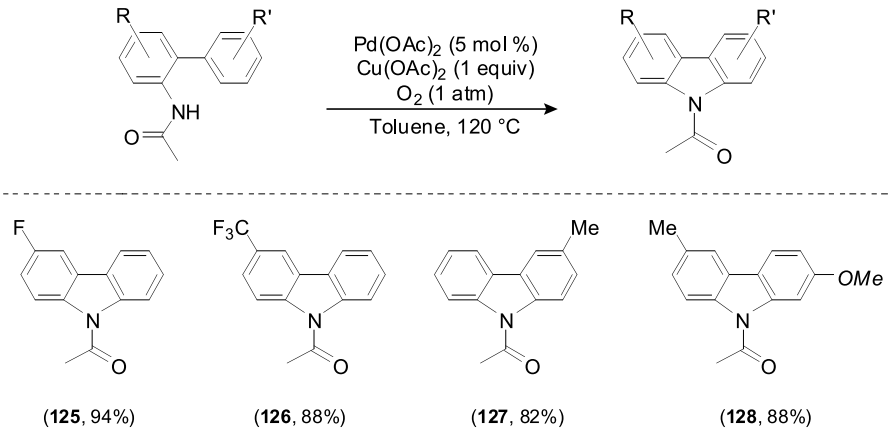
4.4 Carbon–Nitrogen Bond Formation

A final critical bond construction is the carbon–nitrogen linkage, which serves as an important component of many biological and pharmaceutical agents. The first reported example of a Pd-catalyzed directed C – H

activation/C – N coupling reaction involved the cyclization of 2-arylacetanilide derivatives to afford carbazole products using $Cu(OAc)_2$ and O_2 as terminal oxidants (Scheme 25) [74, 75]. This is the only catalytic transformation discussed in this chapter that is believed to proceed by a $Pd^{II/0}$ catalytic cycle. As summarized in Scheme 24, amide-directed arene C – H activation is proposed to form the palladacyclic intermediate **123**, which can then undergo C – N bond-forming reductive elimination to release the carbazole product **124** along with a Pd^0 species. From there, Pd^0 can be oxidized by $Cu(OAc)_2$ and/or O_2 to regenerate the Pd^{II} catalyst and complete the cycle. The widespread prevalence of palladium-catalyzed aryl halide amination reactions demonstrates the feasibility of this $Pd^{II/0}$ cycle for C – N coupling [76, 77].



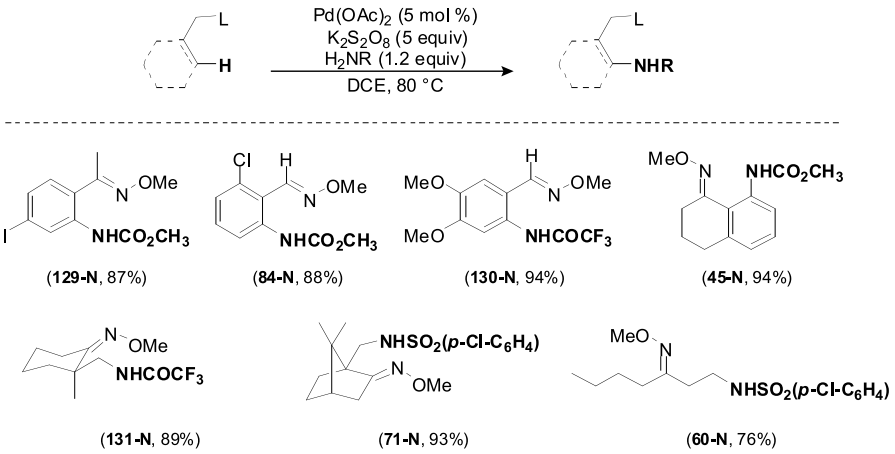
Scheme 24 Mechanism for Pd-catalyzed cyclization of 2-arylacetanilides



Scheme 25 Pd-catalyzed amide-directed C – H activation/intramolecular amination

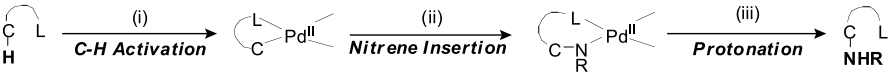
As summarized in Scheme 25, this transformation allowed the construction of a variety of carbazole products. Both electron-donating and electron-withdrawing groups were tolerated on the biphenyl moiety, and substrates containing *meta*-arene substituents afforded products such as **127** with excellent selectivity for amination of the less sterically congested C – H bond.

A new Pd-catalyzed chelate-directed C – H bond amination reaction has recently been reported that can be extended to a wide range of substrates [78]. This new transformation utilizes $Pd(OAc)_2$ as the catalyst with $K_2S_2O_8$ and NH_2R (R = CO_2Me, SO_2(p-Cl-C_6H_4)) as the terminal oxidant and functionalizing reagent, respectively, for the amination of pyridine, quinoline, and oxime ether derivatives (Scheme 26).



Scheme 26 Pd-catalyzed C – H activation/amination with $K_2S_2O_8/NH_2R$

The mechanism of these transformations has been proposed to involve (1) chelate-directed cyclopalladation followed by (2) insertion of a nitrene into the C – Pd bond, and finally (3) protonation of the Pd – N bond to release the product (Scheme 27). Further mechanistic studies are needed to elucidate the exact nature of the nitrene species (free versus metal-bound) involved in these reactions.



Scheme 27 Proposed mechanism for Pd-catalyzed directed C – H activation/amination reactions

5 Summary and Future Outlook

In summary, there have been remarkable recent advancements in the development of both palladium-mediated and palladium-catalyzed reactions for the highly regioselective chelate-directed conversion of C – H bonds to carbon–heteroatom bonds. These new transformations have the potential to

dramatically change retrosynthetic strategies for the synthesis of complex molecules. In addition, they should expedite the process of structure–activity relationship (SAR) studies in the pharmaceutical industry by allowing for the rapid and diverse functionalization of C – H bonds at the late stages of the synthesis of complex molecules. We anticipate that significant future endeavors in this area will focus on the applications of chelate-directed C – H bond oxidation reactions.

Another key aspect of this chemistry is that the involvement of unusual Pd^{IV} intermediates has allowed for bond constructions that were not realized prior to the discovery of these reactions. Future studies in this area are expected to further probe the reactivity and mechanisms available to Pd^{IV} intermediates in order to utilize this oxidation state for novel C – H bond functionalization reactions. In addition, the exploration of new Pd-catalyzed transformations (beyond directed C – H bond oxidation) that exploit the $Pd^{II/IV}$ couple is likely to emerge as a result of this chemistry.

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Directed C – C Bond Activation by Transition Metal Complexes

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Abstract Directed metallation of organic molecules is an important tool for the C – C bond activation since this strategy solves the accessibility problem occurring between a metal and a C – C bond that is to be cleaved. Stability of the five-membered metallacyclic complexes derived from the coordinating substrate and transition metal complexes are a driving force for undergoing the C – C bond activation. In this reaction, nitrogen, oxygen, and phosphorus are the most commonly used heteroatoms for directing functionality. Depending on the heteroatom in the substrate, different types of C – C bond activations can be observed.

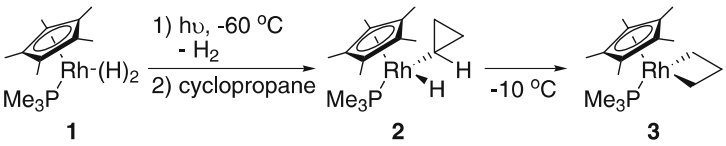
Keywords C – C bond cleavage · Chelation-assistance · Heteroatom coordination · Palladium · Rhodium

Abbreviations

BHT	2,6-di(*t*-butyl)-4-methylphenol
BINAP	2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl
Cy	cyclohexyl
dba	dibenzylidineacetone
TON	turnover number

1 Introduction

The activation of carbon–carbon bond is one of the most challenging subjects in organometallic chemistry as it can provide new synthetic routes which are hard to achieve via the traditional bond making processes [1–4]. For instance, although much of organic transformations known to date largely depend on the formation of carbon–carbon bond, the utilization of the activation (cleavage) process of carbon–carbon bond still remains relatively unexplored. However, if cleaving a certain carbon–carbon bond in an organic molecule and connecting the two carbon termini with another atom or organic molecule are both possible, completely new synthetic protocols (one backbone with various substituents) different from the conventional build-up approach (from small molecules to larger ones) could be devised. For these reasons, many chemists have devoted their efforts finding new strategies for carbon–carbon (C – C) bond activation and significant progress has been made in this field over the past few decades. There are several strategies known for cleaving carbon–carbon bonds, categorized by the factors facilitating the carbon–carbon bond cleavage. The first example of carbon–carbon bond activation is the ring expansion reaction of cyclopropane and cyclobutane derivatives using the strained energy of the three or four-membered cyclic hydrocarbons. For example, ultraviolet irradiation of the rhodium dihydride complex **1** generated the coordinatively unsaturated 16 electron species with the liberation of H_2, which reacted with liquid cyclopropane to give the hydridocyclopropylrhodium(III) complex **2** through C – H bond activation. Upon heating, rearrangement of **2** occurred, leading to a thermodynamically more stable C – C bond cleaved four-membered metallacyclic complex **3** (Eq. 1) [5].

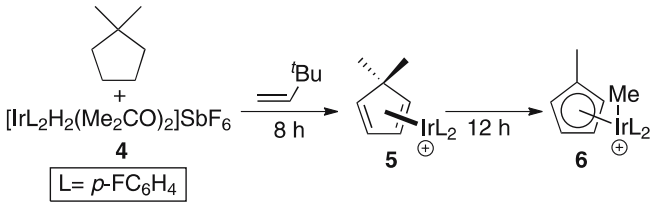


Equation 1

The ring-strain strategy has been widely studied for the carbon–carbon bond cleavage of cyclopropane or cyclobutane derivatives [6–9] because the relief of ring-strained energy of cyclopropane or cyclobutane is a very effective way of cleaving the carbon–carbon bond of the cyclic molecules.

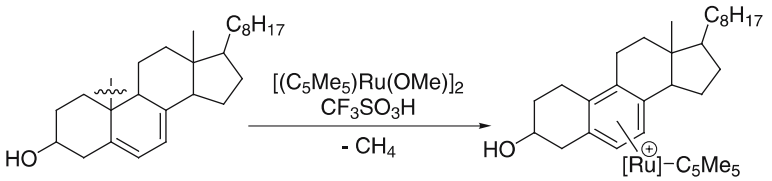
The second carbon–carbon bond activation strategy utilizes the aromatic stabilization energy gained by converting non-aromatic compounds into aromatic ones during the carbon–carbon bond cleavage step. For example, Crabtree et al. reported the aromatization reaction of 5,5-dialkylcyclopentadiene

involving alkyl group migration by iridium complexes **4**, in which the *endo*-alkyl group of 5,5-dialkylcyclopentadieneiridium complex **5** is cleaved by the metal center to form a cyclopentadienyl metal complex **6** (Eq. 2) [10].



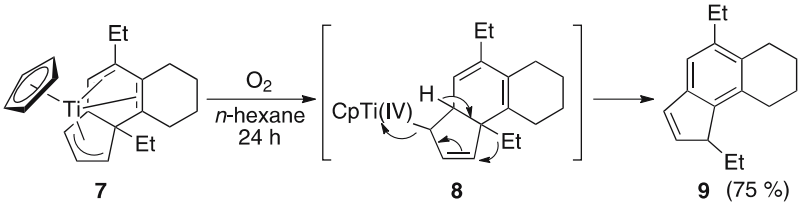
Equation 2

Chaudret et al. also applied this strategy to the synthesis of steroid derivatives, as shown in Eq. 3 [11]. However, the catalytic version of this reaction was not successful.



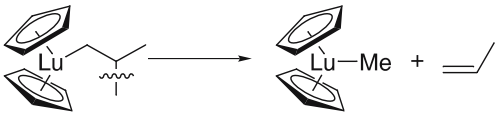
Equation 3

Recently, Takahashi et al. reported an interesting example of the aromatization strategy in the synthesis of indene derivatives from bis(cyclopentadienyl)titanacyclopentadiene complexes [12] in the course of studying carbon–carbon bond cleavage of cyclopentadienyl ligands [13]. When the Ti complex **7** was treated with molecular oxygen for 24 h, the indene compound **9** was obtained in a good yield accompanying the ethyl group migration in **7** to the nearby carbon and the benzene ring formation. During the reaction, titanium(II) is oxidized to titanium(IV) by O_2 with the generation of the intermediate **8**. The aromatization of the central six membered ring moiety in **8** takes place by the migration of an ethyl group to the allylic position of allyltitanium to form **9** (Eq. 4).



Equation 4

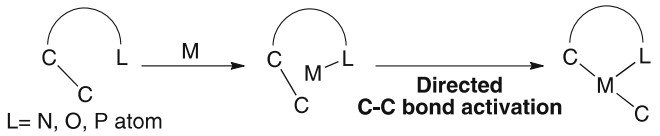
The third strategy for the carbon–carbon bond activation utilizes the formation of a strong metal–carbon bond which could make the final species more stable than the initial one. Though the β-hydrogen elimination is another competing process, Watson et al. observed the formation of the lutetium methyl complex **11** from the decomposition of the lutetium isobutyl complex **10** through β-alkyl elimination (Eq. 5) [14].



10 **11**

Equation 5

The fourth strategy, the chelation-assistant strategy, is distinct from the previously mentioned strategies which mainly depend on the thermodynamical consideration. The chelation-assistant strategy is based on the kinetic approach which forces a carbon–carbon bond to be placed near the metal center by the proper position of the coordination site of the substrate. Numerous examples of organometallic chelation compounds having a metal–carbon bond stabilized by the heteroatom coordination also support this strategy [15]. There are several types of coordinating atoms such as nitrogen, phosphorus, and oxygen. Generally, the chelation-assistant strategy, by the control of the initial substrate coordination geometry to the metal center, enables all the targeted bonds as well as carbon–carbon bonds to be in close proximity to the metal center. Indeed, the chelation-assistant strategy has exhibited interesting efficacy in the fields of carbon-hydrogen bond activation [16–21] and carbon-oxygen bond activation reactions [22–24]. In this chapter, various (catalytic and stoichiometric) carbon–carbon bond activation reactions mediated by transition metal complexes using the chelation-assistant (directed) strategy will mainly be discussed, as shown in Eq. 6.

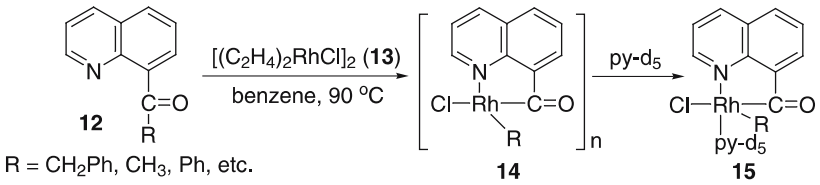


Equation 6

2
Nitrogen Atom-Directed C – C Bond Activation

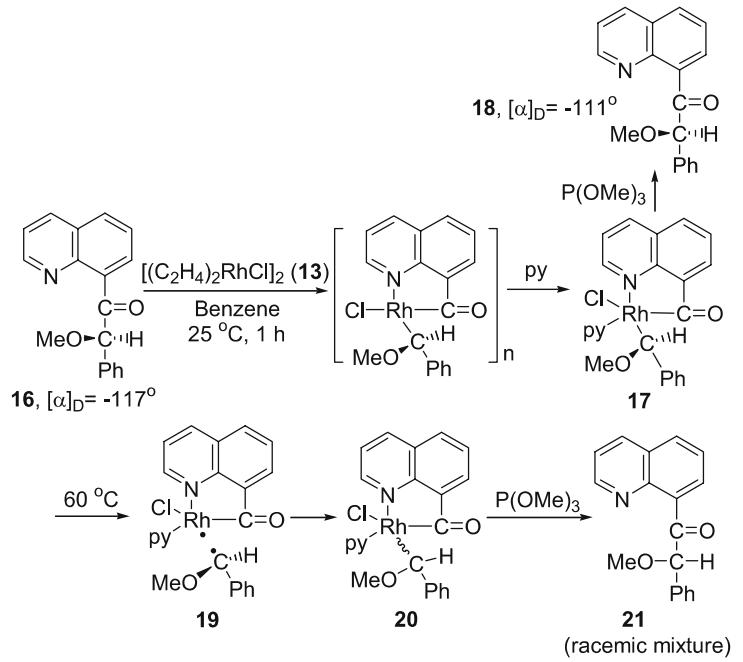
2.1
C – C Bond Activation of Ketones Containing Nitrogen Atom

The most common coordinating atom for the direct carbon–carbon bond activation is nitrogen. One of the early substrates in this category is the 8-acylquinoline system. Suggs devised 8-quinolinyl alkyl ketone for the carbon–carbon bond activation [25, 26]. When the reaction of 8-quinolinyl alkyl ketone **12** with chlorobis(ethylene)rhodium(I) dimer (**13**) was carried out, the acylrhodium(III) alkyl complex **14** was obtained as an insoluble chlorine-bridged polymer. This complex was solubilized in $CDCl_3$ by the addition of pyridine-d_5 to make a monomeric form **15** which could be characterized by spectroscopic and X-ray crystallographic analysis. Since the stable 5-membered metallacyclic complex is formed from the 8-acylquinoline **12** and the rhodium(I) complex **13**, the undesired decarbonylation can be successfully suppressed throughout the reaction (Eq. 7).



Equation 7

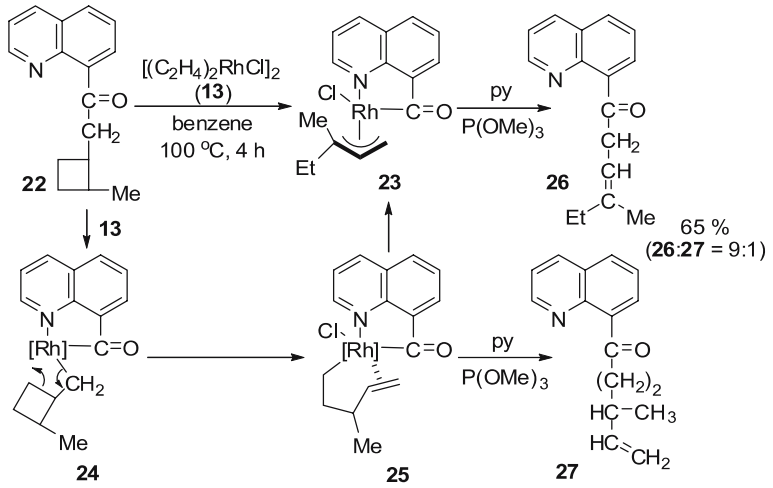
The chiral version of the nitrogen-directed carbon–carbon bond activation was also accomplished by the reaction of chiral alkyl ketone **16** and **13** at room temperature [27]. The stereochemistry of the chiral acylrhodium(III) species **17** could be presumed by the optical rotation analysis of the demetallated compound **18**, which was obtained by the ligand-promoted reductive elimination of **17** with $P(OMe)_3$. The optical rotation of **18** turned out to be similar to that of **16**. This result implies that both the α-carbon–carbon bond cleavage of ketone in **16** by Rh complex and the ligand-promoted reductive elimination proceeds with retention of the stereochemistry. However, when the complex **17** was heated, the racemized product **21** could be obtained, probably due to the thermal homolysis of the Rh-carbon bond in **17**, which was accompanied by the generation of two sp^2 carbon radicals as in **19** and the successive recombination/reductive elimination steps as in **20**, leading to the racemization. As the heating periods of **17** were extended, the degree of racemization of **21** also increased. Based on the kinetic study for the degree of racemization, the Rh-carbon bond strength was measured as 31 kcal/mol (Scheme 1).



Scheme 1

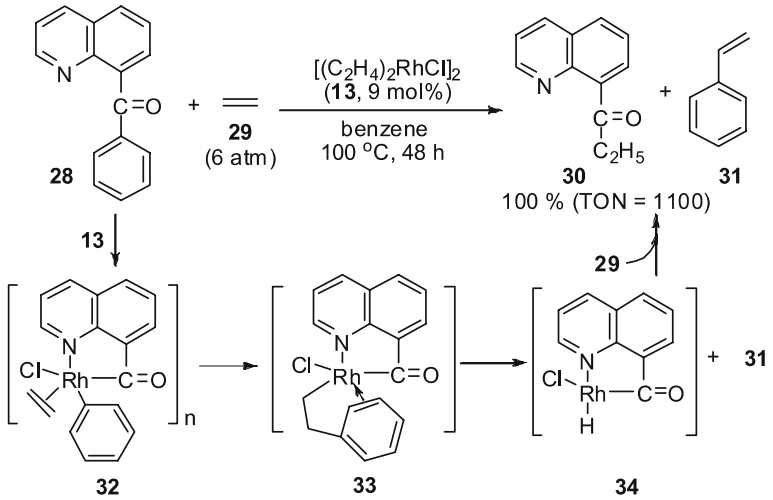
The cyclobutyl substituted 8-quinolinyl derivative **22** is an interesting substrate since the reaction of **22** with the Rh(I) dimer **13** leads to the consecutive double carbon–carbon bond activation [28]. The reaction of 8-quinolinyl-2′-methylcyclobutylmethyl ketone **22** with the rhodium(I) complex **13** yielded the acylrhodium(III) allyl complex **23**. The β,γ-unsaturated ketone **26** could be dominantly obtained after the ligand-promoted reductive elimination of the complex **23**. In this reaction mechanism, the initial C – C bond activation of 8-quinolinyl cyclobutylmethyl ketone **22** by Rh(I) generates the intermediate acylrhodium(III) cyclobutylmethyl complex **24**, and the subsequent second carbon–carbon bond cleavage of the cyclobutylmethyl group in **24** gives the acylrhodium(III) 3-methyl-4-pentenyl complex **25**. The olefin-isomerization of **25** leads to the stable acylrhodium(III) π-allyl complex **23**. The ligand-promoted reductive elimination of **23** and **25** by $P(OMe)_3$ produces β,γ-unsaturated ketone **26** and δ,ϵ-unsaturated ketone **27**, respectively, in a ratio of 9 : 1 (Scheme 2).

The carbon–carbon bond cleavage of the 8-quinolinyl alkyl ketone by rhodium(I) complex could be adapted for a catalytic reaction [29]. For example, when the reaction of 8-quinolinyl phenyl ketone (**28**) and ethylene (**29**, 6 atm) was carried out in the presence of the rhodium(I) complex **13**, a mixture of 8-quinolinyl ethyl ketone (**30**) and styrene (**31**) was obtained. The first step is a carbon–carbon bond cleavage of **28** by **13** to form the complex **32**,



Scheme 2

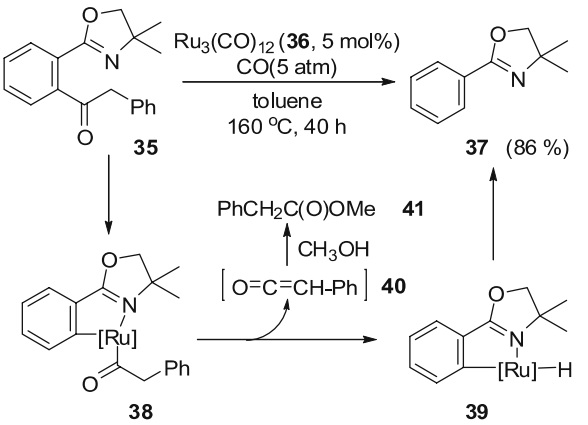
followed by insertion of **29** into the rhodium(III) phenyl complex to give the acylrhodium(III) phenethyl complex **33.** A β-hydrogen elimination in complex **33** produces **31** and acylrhodium(III) hydride **34,** which reacts with **29** to produce 8-quinolinyl ethyl ketone **30** with regeneration of the rhodium(I) complex **13** (Scheme 3).



Scheme 3

Chatani et al. studied the ruthenium-catalyzed decarbonylative cleavage of carbon–carbon bond of alkyl phenyl ketone [30]. The carbon–carbon bond of

alkyl phenyl ketone **35** bearing an oxazoline ligand was catalytically cleaved by $Ru_3(CO)_{12}$ (**36**) to give the deacylated compound **37**. The carbon–carbon bond of the phenylacetyl group in **35** is cleaved by **36** to generate acyl-ruthenium(II) complex **38** as an intermediate. A β-hydrogen elimination in **38** leads to the formation of phenyl ketene **40** and ruthenium(II) hydride complex **39**, which is reductively eliminated to yield **37**. In this reaction mechanism, the involvement of ketene **40** could be evidenced by the production of the ester **41** when methanol was used as a solvent, since **40** could be trapped by MeOH to form **41** (Scheme 4).



Scheme 4

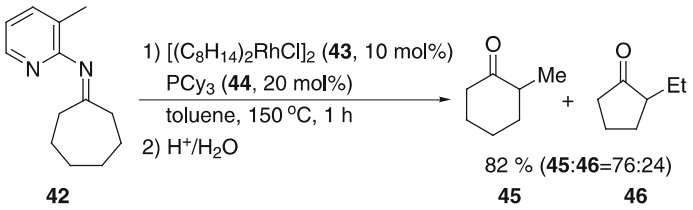
2.2
C – C Bond Activation of Ketimine

2.2.1
From Ketimine

As previously described, the chelation-assistant strategy is a powerful method to achieve the carbon–carbon bond activation by facilitating a close contact between metal and the carbon–carbon bond to be cleaved. However, somewhat paradoxically, the essential requirement of the coordinating group in a substrate is an inherent limitation of this protocol, and prohibits its practical application toward general non- or weak-coordinating substrates. An alternative approach to overcome this limitation is a temporary installation of a strong coordinating function into substrates such as imine, which can be easily removed from the product by hydrolysis. For example, ketimines prepared from the condensation of simple ketones and 2-aminopyridine derivatives can serve as chelating substrates through the coordination of pyridine

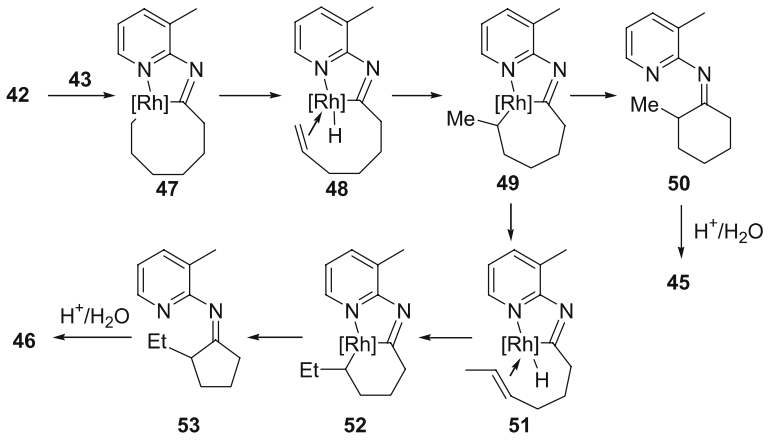
moiety, and after the reaction, the 2-aminopyridine group in the ketimine is readily hydrolyzed to yield the ketone products.

This approach was successfully applied to the C – C bond activation of cycloheptanone by the rhodium(I) complex [31]. The skeletal rearrangement of ketimine **42** by the carbon–carbon bond activation was observed at high temperature in the presence of a catalytic amount of chlorobis(cyclooctene)rhodium(I) dimer (**43**) and tricyclohexylphosphane (**44**). A mixture of 2-methylcyclohexanone (**45**) and 2-ethylcyclopentanone (**46**) was obtained in a ratio of 76 : 24 after hydrolysis of the resulting ketimines (Eq. 8).



Equation 8

The mechanism of this skeletal rearrangement is as follows. Initially, the oxidative addition of the α-carbon–carbon bond of the ketimine **42** to the rhodium(I) complex **43** produces a 5-membered metallacyclic complex **47**. A β-hydrogen elimination in **47** proceeds to generate the (iminoacyl)rhodium(III) hydride complex **48**. An intramolecular hydride insertion in **48** generates the branched alkyl complex **49**. With complex **49**, two reactions proceed: (i) reductive elimination to produce ketimine **50**. (ii) a β-hydrogen

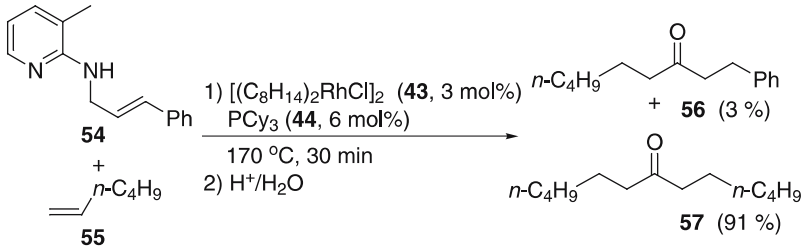


Scheme 5

elimination to form **51** and subsequent intramolecular hydride insertion in **51**, leading to the formation of complex **52**, which is reductively eliminated to give ketimine **53** (Scheme 5).

2.2.2 From Allylamine

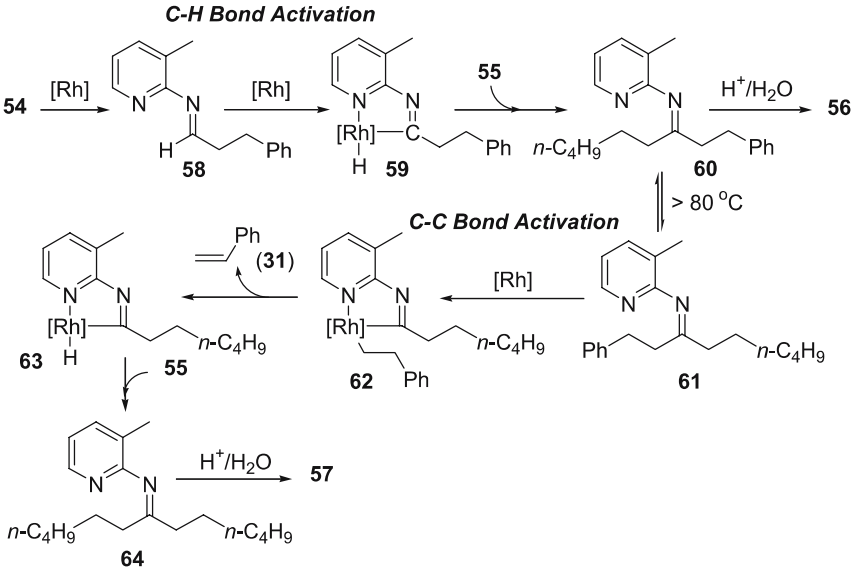
Allylamine is an interesting substrate for C – C bond activation since transition metals can readily transform the allylamine to the corresponding aldimine, the in situ-generated substrates for the carbon–carbon bond activation as well as the carbon-hydrogen bond activation. For instance, when allylamine **54** reacted with 1-hexene (**55**) in the presence of the rhodium(I) complex **43** and phosphane ligand **44**, a mixture of ketones **56** and **57** could be obtained after hydrolysis of the resulting ketimines (Eq. 9) [32].



Equation 9

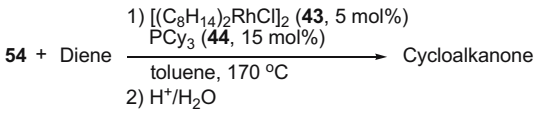
The rhodium(I)-catalyzed double bond isomerization of allylamine **54** takes place to give aldimine **58**, which reacts with the rhodium(I) complex **43** to give an (iminoacyl)rhodium(III) hydride complex **59** through the carbon-hydrogen bond activation. A hydride insertion of **59** into 1-hexene (**55**) and the subsequent reductive elimination produces ketimine **60**, which undergoes facile *syn-anti* isomerization, leading to ketimine **61** upon heating (above 80 °C). Chelation-assisted carbon–carbon bond activation of ketimine **61** by the rhodium(I) complex **43** leads to the formation of (iminoacyl)rhodium(III) phenethyl complex **62**, followed by β-hydrogen elimination, giving styrene (**31**) and the rhodium(III) hydride complex **63**. Subsequent hydride insertion of **63** into **55** and reductive elimination gives a symmetric dialkyl ketimine **64**. Hydrolysis of ketimine **60** and **64** yields ketone **56** and **57** as final products, respectively (Scheme 6).

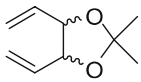
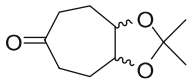
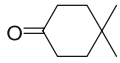
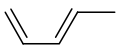
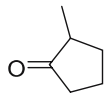
In this protocol, the allylamine **54** is a masked form of formaldehyde since it can yield the symmetric dialkyl ketones, as expected in the case of double hydroacylation of formaldehyde. However, with formaldehyde itself as a substrate, no reaction occurred. The allylamine approach could be applied to the synthesis of cycloalkanones from allylamine **54** and α,ω-dienes through the catalytic C – H and C – C bond activation (Table 1) [33].



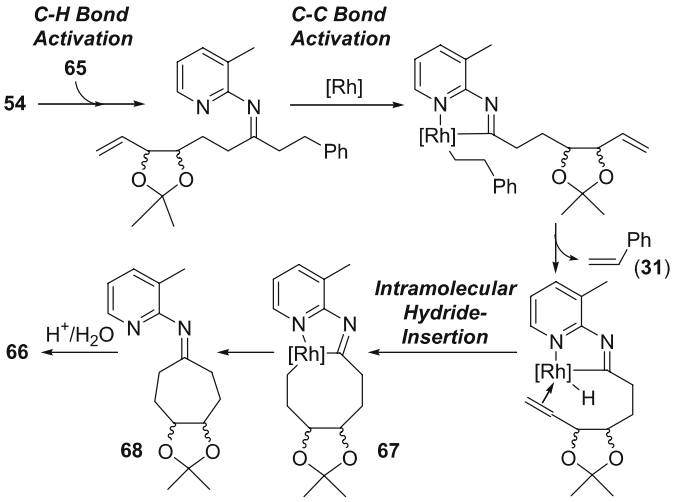
Scheme 6

Table 1 Cyclization of dienes with **54**



Entry	Diene	Reaction time (h)	Cycloalkanone	Isolated yield (GC yield)
1	 (**65**)	2	 (**66**)	86% (100%)
2		5		77% (100%)
3		18		(77%)

For example, when allylamine **54** was allowed to react with 1,5-hexadiene (**65**) in the presence of the rhodium(I) catalyst **43** and phosphane ligand **44**, cycloheptanone derivatives **66** could be obtained after hydrolysis of the resulting ketimine. The reaction mechanism is thought to be similar to that of the previous synthesis of symmetric dialkyl ketone. In this cyclization re-

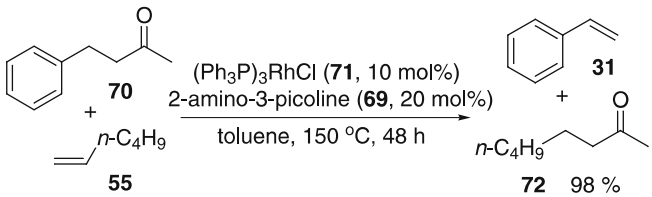


Scheme 7

action, a hydride-insertion proceeds intramolecularly to give metallacyclic complex **67**, which is reductively eliminated to form the ketimine of cycloheptanone derivative **68** (Scheme 7). The reaction of allylamine **54** with several α,ω-dienes gave five to seven-membered cycloalkanone derivatives.

2.3
C – C Bond Activation of Ketone (through in-situ Generated Ketimine)

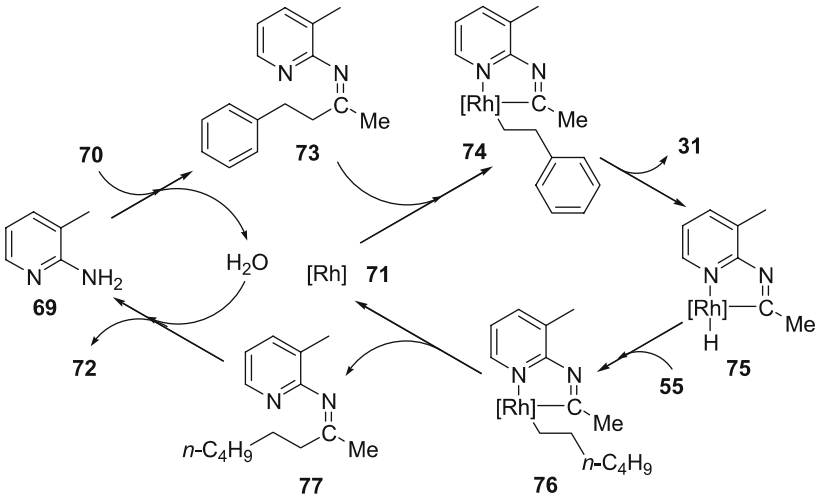
The facile catalytic C – C bond activation of unstrained ketone was successfully achieved through the chelation-assistance of 2-amino-3-picoline (**69**) by a rhodium(I) complex. For example, when the reaction of benzylacetone (**70**) and 1-hexene (**55**) was carried out in the presence of the rhodium(I) complex **71** and **69**, 2-octanone (**72**) was isolated in a high yield (Eq. 10) [34].



Equation 10

The ketimine **73** is initially formed by condensation of **70** and **69** with generation of H_2O. The α-carbon–carbon bond to the imine group in **73** is cleaved by Rh(I) in **71** to give an (iminoacyl)rhodium(III) phenethyl complex

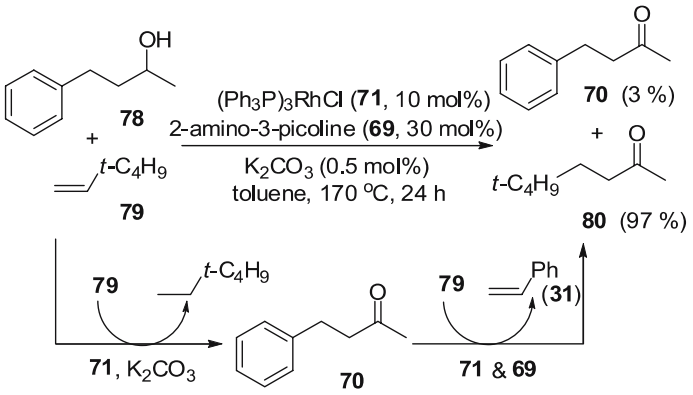
74. A β-hydrogen elimination of the phenethyl group in **74** provides (iminoacyl)rhodium(III) hydride complex **75** and **31.** A hydride insertion of **75** into **55** and reductive elimination of the resulting (iminoacyl)rhodium(III) hexyl complex **76** produces ketimine **77** with the regeneration of rhodium(I) catalyst **71.** Hydrolysis of ketimine **77** by H_2O previously generated from condensation of **70** and **69** yields ketone **72.** To identify the involvement of the ketimine **73** during the C – C bond cleavage step, separately prepared ketimine **73** was allowed to react with **55** in the presence of **71**, and a mixture of ketimine **77** and **31** was observed as evidence (Scheme 8).



Scheme 8

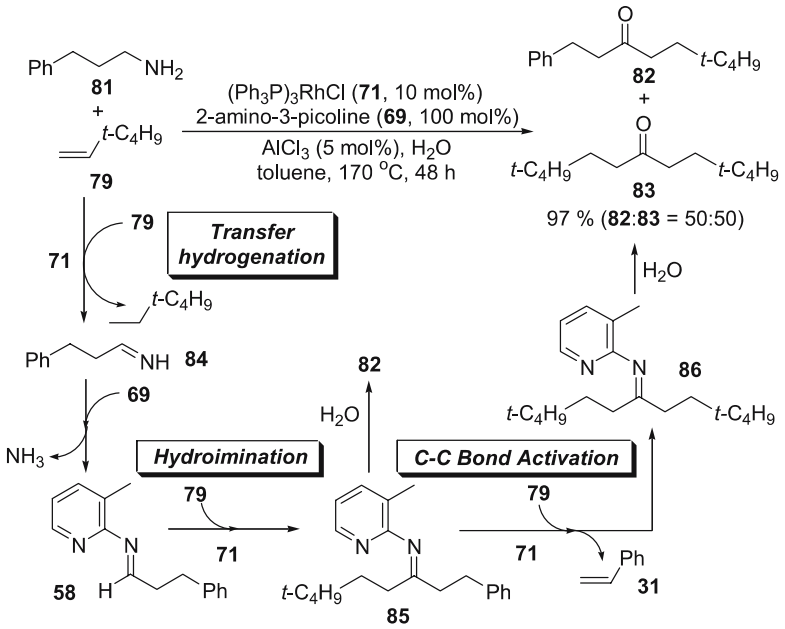
Secondary alcohols can also be used as substrates for the C – C bond activation [35]. The reaction of 4-phenyl-2-butanol (**78**) and 3,3-dimethyl-1-butene (**79**) was performed in the presence of K_2CO_3, rhodium(I) complex **71** and 2-amino-3-picoline (**69**) to yield the C – C bond cleaved product, 5,5-dimethyl-2-hexanone (**80**), as well as a small amount of benzylacetone (**70**). The reaction consisted of two consecutive reactions, transfer hydrogenation of alcohol **78** and chelation-assisted C – C bond activation of the resulting ketone **70**. For the facile oxidation of secondary alcohol, a small amount of K_2CO_3 is required to maintain sufficient reactivity of the C – C bond activation (Scheme 9).

As found in the rhodium(I)-catalyzed dehydrogenation of alcohol, primary amines can also be dehydrogenated in the presence of a Rh(I) catalyst (**71**), and the resulting imines can be applied for the C – C bond activation in situ [36]. When the reaction of 3-phenylpropylamine (**81**) and alkene **79** was performed in H_2O and $AlCl_3$ under a catalytic system of **71** and **69**, ketone **83** from the C – C bond cleavage of **85** as well as ketone **82** from the C – H bond



Scheme 9

cleavage of **58** were isolated in a ratio of 50 : 50. A dehydrogenated imine **84** is initially formed from **81** and **79** through the rhodium(I)-catalyzed transfer hydrogenation, and a transimination of the imine **84** with **69** generates aldimine **58** and ammonia. Chelation-assisted hydroimination of **79** with **58** produces ketimine **85**, followed by C – C bond activation of ketimine **85** to give symmetric dialkyl ketimine **86**. Hydrolysis of ketimine **85** and **86** yields ketone **82** and **83**, respectively (Scheme 10).



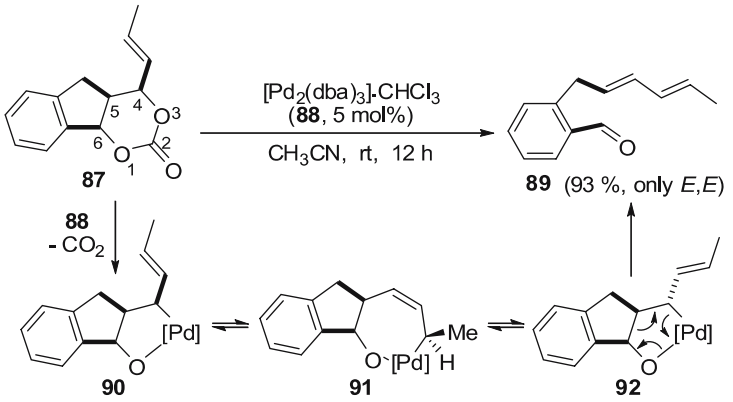
Scheme 10

3
Oxygen-Directed C – C Bond Activation

3.1
C – C Bond Activation Associated with Unstrained Organic Molecules

In this chapter, various reactions of recently developed oxygen-directed C – C bond activation will be discussed. Most of the reactions proceed through a β-carbon elimination of alkoxy metal complexes which are generated from alcohol and metal complexes.

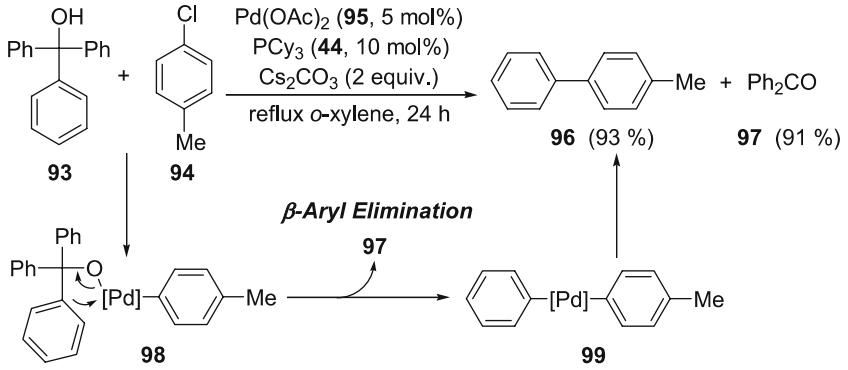
Tamaru et al. reported useful reactions for the synthesis of dienal using β-decarbopalladation [37, 38]. In the presence of palladium(0) complex **88**, vinyl cyclocarbonate **87** could be stereoselectively transformed into *E*,*E*-dienal **89**. The reaction proceeds via oxidative addition of the $O_3 - C_4$ bond of **87** to Pd(0) in **88** to form the oxypalladacyclic complex **90** with extrusion of CO_2. Complex **90** is isomerized to the more preferred conformation **92** through intermediate **91**. The ring-opening of the oxapalladacycle **92** yields *E*,*E*-dienal **89** (Scheme 11). Recently, it was reported that Ni complexes also promoted a similar type of decarboxylative ring opening reaction [39].



Scheme 11

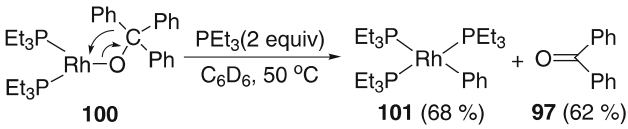
The palladium-catalyzed arylation of triphenylmethanol **93** with aryl halide **94** produced the corresponding diaryl compound **96**. The formation of an arylpalladium(II) triphenylmethanolate intermediate **98** might be the first step. A subsequent β-aryl elimination in **98** produces diarylpalladium(II) complex **99** with the liberation of benzophenone (**97**). Reductive elimination of **99** leads to the formation of the corresponding diaryl compound **96** (Scheme 12) [40].

Recently, Hartwig et al. reported that the β-carbon elimination was directly observed from the isolated triphenylmethoxyrhodium(I) complex **100**,



Scheme 12

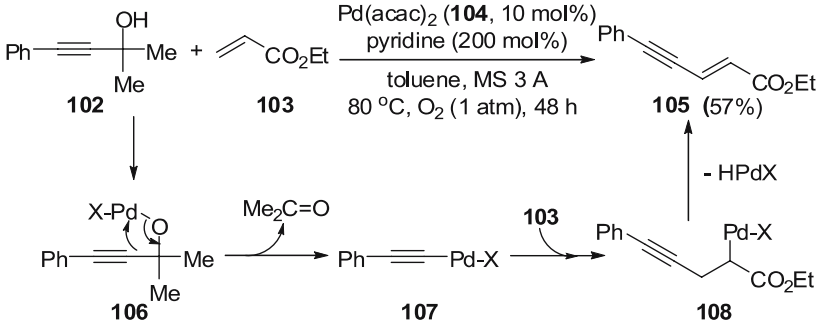
the hypothetical intermediate **98** in the above example [41]. Heating complex **100** with 2 equivalents of PEt_3 at 50 °C gives phenylrhodium(III) complex **101** and benzophenone (**97**), in which the former must be originated from the β-phenyl elimination (Eq. 11).



Equation 11

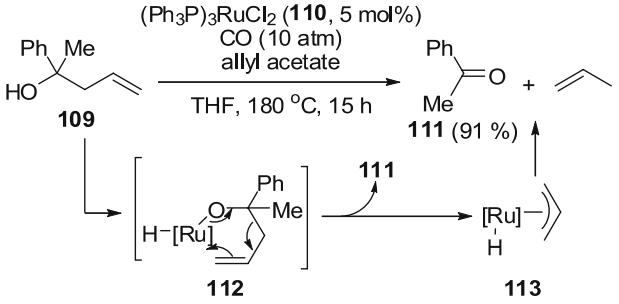
One of applicable substrates for the carbon–carbon bond activation is *tert*-propargyl alcohol, which reacts with alkene to yield enyne compounds [42]. For example, when the reaction of *tert*-propargyl alcohol **102** with acrylate **103** was carried out in the presence of palladium(II) acetylacetonate (**104**), pyridine and molecular sieve 3 Å under oxygen atmosphere, the enyne **105** was obtained. In this reaction, the palladium(II) alcoholate **106** undergoes β-carbon elimination, giving a palladium(II) acetylide complex **107** with extrusion of acetone. A Heck-type coupling reaction of **107** with **103** yields enyne **105** through the intermediate **108.** A driving force for the β-carbon elimination in **106** would be the formation of strong metal–carbon bond, as in **107** (Scheme 13).

When tertiary homoallyl alcohol **109** was heated in the presence of the ruthenium(II) complex **110**, CO, and allyl acetate, acetophenone (**111**) was isolated in a high yield along with the formation of propene [43]. The proposed mechanism of this deallylation reaction is the oxidative addition of the O – H bond in homoallyl alcohol **109** to the ruthenium(0) complex, generating the (homoallyloxy)ruthenium(II) hydride complex **112** and subsequent β-allyl elimination in **112**, leading to the formation of **111** and the

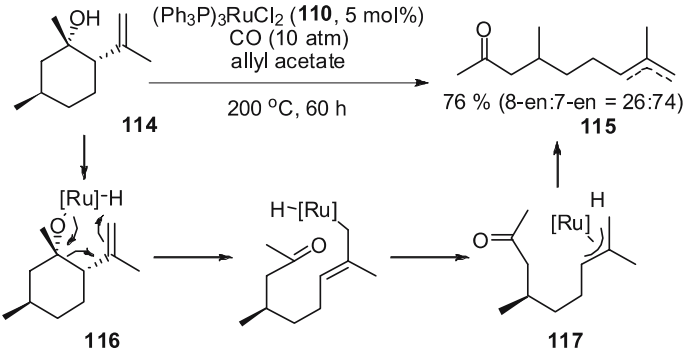


Scheme 13

π-allylruthenium(II) hydride complex **113**. This type of deallylation mechanism in (homoallyloxy)metal complex was recently confirmed by the fact that heating of the isolated (homoallyloxy)rhodium(I) complexes resulted in a β-allyl elimination, giving the rhodium(III) π-allyl complex and corresponding ketone [44]. Tertiary alcohols bearing a homoallyl group were required to perform this deallylation reaction. A driving force in this deal-



Scheme 14



Scheme 15

lylation reaction seems to be the formation of a stable π-allylruthenium(II) hydride complex (Scheme 14).

An intramolecular version of deallylation reaction can be done with cyclic homoallyl alcohol **114**. Under similar reaction conditions to the intermolecular case, cyclic *tert*-homoallyl alcohol **114** could be transformed into the unsaturated ketone **115**. Intramolecular β-deallylation of the alkoxyruthenium(II) hydride complex **116** leads to the formation of π-allylruthenium(II) hydride complex **117**. Complex **117** undergoes reductive elimination to produce a mixture of olefinic isomer **115** (Scheme 15).

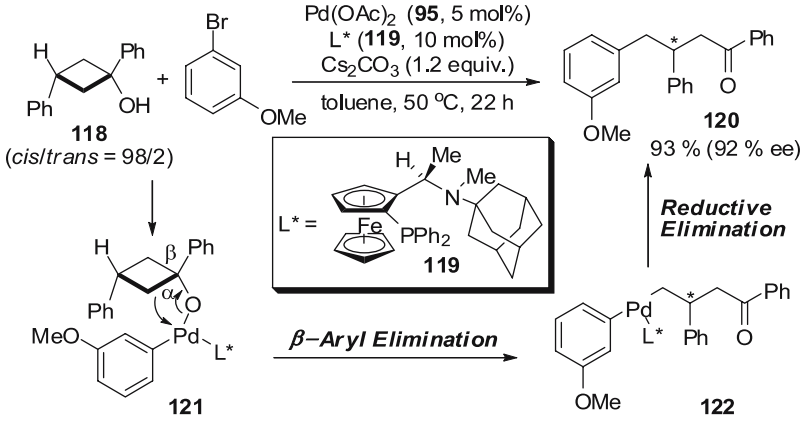
3.2
C – C Bond Activation Associated with Strained Ring Molecule

As discussed in the previous section, the main driving force of β-carbon elimination seems to be the formation of a stable metal–carbon bond such as metal π-allyl, metal-acetylide, or metal–phenyl bonds. In this section, the oxygen-directed carbon–carbon bond cleavage of strained ring molecules will be discussed using the ring-strained energy of the cyclobutyl group as a driving force.

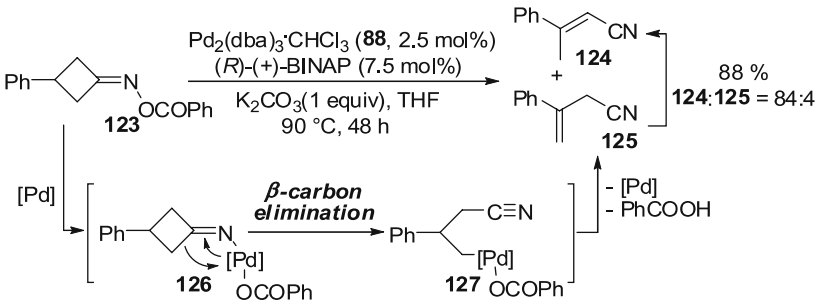
The reaction of cyclobutanol **118** with aryl bromide in the presence of a catalytic system of $Pd(OAc)_2$ (**95**) and $CsCO_3$ with chiral phosphane ligand (L^*) **119** could yield chiral ketone **120** with high enantioselectivity [45–47]. The first step is the formation of arylpalladium(II) cyclobutoxy intermediate **121**. A β-carbon elimination of **121** produces arylpalladium(II) alkyl complex **122** and the successive reductive elimination of **122** yields γ-arylated ketone **120** with high enantiomeric excess (ee). Because the stereochemical outcome of **120** is dependent on which of the α or β bonds in intermediate **121** can be cleaved, the role of the chiral phosphane ligand L^* is important at the bond cleavage step. Among various chiral ligands, the chiral N,P-ligand **119** exhibited the best stereoselectivity and reactivity towards the chiral γ-arylated ketones. As previously noted, the driving force would be a relief of the ring strained energy of the cyclobutyl group in **121** (Scheme 16).

O-benzoyloxime **123** can undergo the similar oxygen-directed C – C bond cleavage of the cyclobutyl group in **123**. It is noteworthy that the nitrile compound is the final product in this case. The key intermediate is a nitrogen-palladium complex **126** generated from the reaction of palladium complex and benzoyloxime **123**. A β-carbon-elimination of the complex **126** produces γ-cyanopropylpalladium(II) complex **127**. A subsequent β-hydrogen elimination in **127** and olefin-isomerization produces a mixture of alkenonitrile **124** and **125** (Scheme 17) [48].

Selective carbon–carbon bond cleavage of cyclobutanone can be achieved using a hydroxy group as a directing function. Murakami et al. used the β-carbon elimination for constructing a new carbon–carbon bond framework. For example, when *ortho*-hydroxyphenyl cyclobutanone **128** was heated in

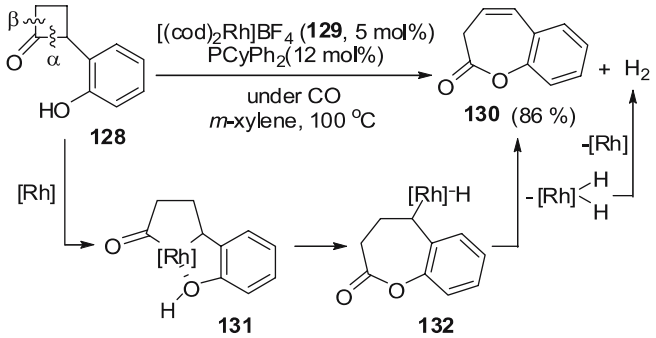


Scheme 16



Scheme 17

the presence of the cationic Rh(I) complex **129** and the phosphane ligand, a medium-sized lactone **130** was isolated in a high yield [49]. The reaction proceeds via the coordination of the phenolic hydroxy group of **128** to Rh(I), which allows a selective oxidative addition of the α-bond of cyclobutanone to

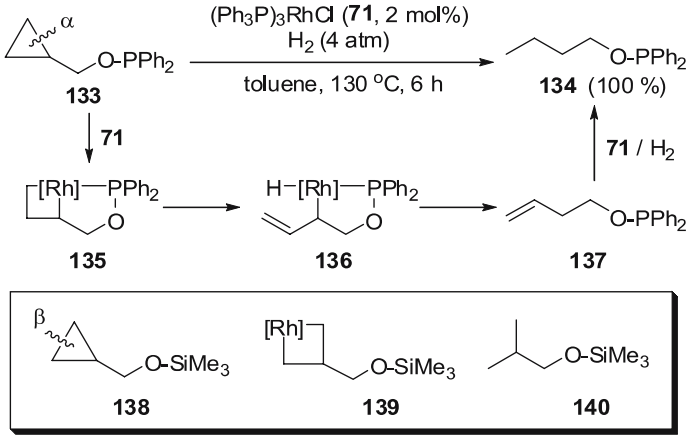


Scheme 18

Rh(I), as in **131**. Intramolecular addition of a hydroxy group into the acylrhodium(III) complex in **131** and a subsequent β-hydrogen elimination in lactone **132** yields **130** and hydrogen gas from the resulting rhodium(III) dihydride complex (Scheme 18).

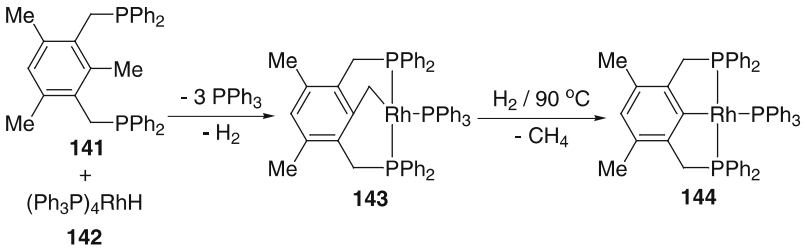
4 Phosphorus-Directed C – C Bond Activation

In general, since the phosphane ligands strongly coordinate to transition metals, they can be applied as a directing group in carbon–carbon bond activation. For example, the cyclopropylmethyl group in compound **133** can be selectively cleaved by a transition metal through the phosphorus directed carbon–carbon bond activation [50]. When compound **133**, having a phosphanyl ligand, was heated in the presence of the rhodium(I) complex **71** under H_2 (4 atm) at 130 °C, a linear alkyl compound **134** was exclusively obtained. In this reaction, the phosphanyl ligand induces a rhodium metal to cleave the α-bond of **133** to form the intermediate **135**. A β-hydrogen elimination in **135** and the reductive elimination of the intermediate **136** produces a linear alkenyl compound **137**, which undergoes rhodium(I)-catalyzed hydrogenation to yield **134**. On the contrary, when cyclopropylmethyl trimethylsilyl ether **138** was applied in this reaction under identical reaction conditions, the branched alkyl trimethylsilyl ether **140** was isolated. Because of the rather weak coordinating ability of the oxygen in **138** and the additional steric effect of the $SiMe_3$ moiety, the least hindered β-bond of the cyclopropyl group in **138** was cleaved by the rhodium(I) complex **71**, giving an intermediate **139**, which led to the formation of **140** as a final product (Scheme 19).



Scheme 19

Many examples of the phosphorus-directed carbon–carbon activation have been reported by Milstein et al. using the pincer type ligands, PCX (X = P, N, O). An early example of carbon–carbon bond activation using a phosphane-directing ligand is the reaction of rhodium(I) complex with a PCP pincer ligand **141** [51]. When the reaction of **141** and tetrakis(triphenylphosphane)-Rh(I) hydride (**142**) was carried out at an ambient temperature, the carbon-hydrogen bond activated complex **143** was observed along with the evolution of hydrogen gas. However, heating the complex **143** at 90 °C in hydrogen atmosphere resulted in the formation of the carbon–carbon cleaved complex **144** with liberation of methane (Eq. 12). The reaction tendencies of C – H and C – C bond activations can be explained such that the C – H bond activation is kinetically favored, whereas the C – C bond activation is thermodynamically favored because of the formation of stronger Rh-C_{Ph} bond in **144**.

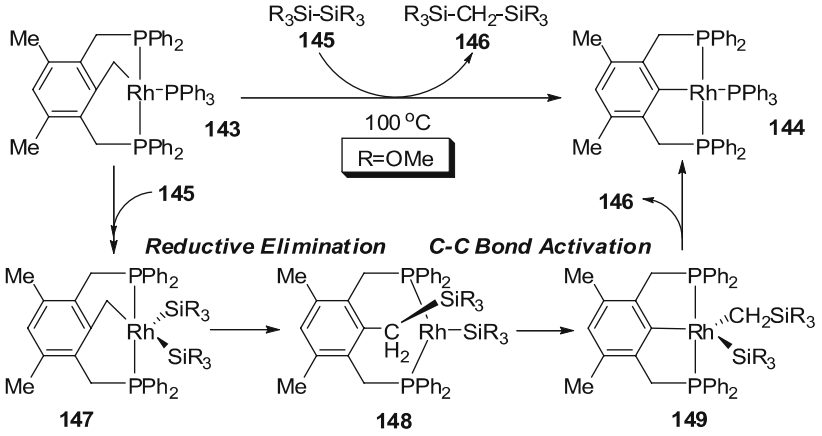


Equation 12

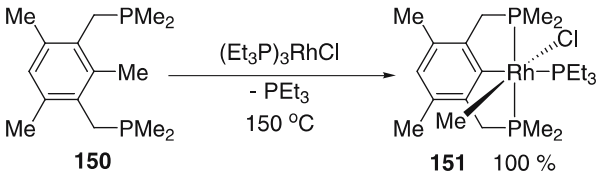
This C – H and C – C bond activation can be applied to the methylene transfer reaction [52]. For example, heating the complex **143** with $(MeO)_3Si$-$Si(OMe)_3$ (**145**) at 100 °C resulted in the cleavage of the CH_2 group from complex **143** and its insertion into the Si-Si bond of **145** to give $(MeO)_3Si$-CH_2-$Si(OMe)_3$ (**146**). A plausible mechanism for this reaction is as follows. Oxidative addition of the Si – Si bond in **145** to the rhodium complex **143** leads to the formation of complex **147**, and subsequent C – Si reductive elimination in **147** yields complex **148**. The carbon–carbon bond activation in **148** generates complex **149**, followed by reductive elimination to give product **146** (Scheme 20).

Notably, the C – C bond activation product was directly observed in the case of the more basic Me-PCP ligand **150** [53]. The reaction of $(Et_3P)_3RhCl$ with **150** at high temperature resulted in a quantitative yield of the C – C bond cleaved rhodium(III) complex **151** without observing the C – H bond cleavage complex (Eq. 13).

It was also reported that even the strong C_{Ph}-C_{CF_3} bond of the *t*-Bu-PCP ligand could be cleaved by the Rh(I) complex [54]. In this reaction, it was demonstrated that the C – C bond activation of the PCP ligand system proceeded via an intermediate complex coordinated simultaneously by both phosphorus atoms in the ligand. This coordination compound was prepared



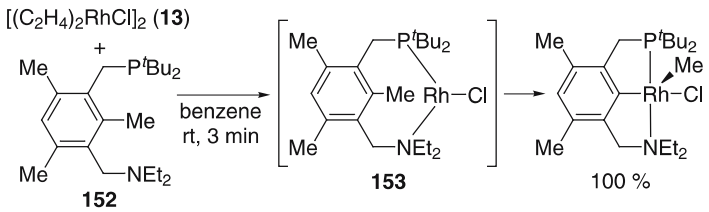
Scheme 20



Equation 13

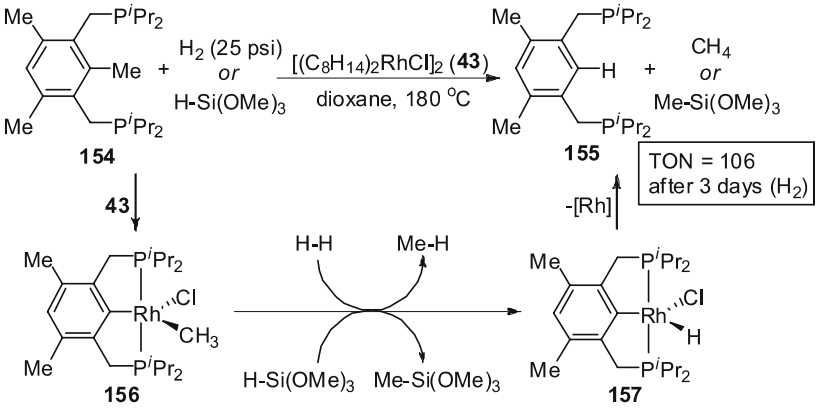
and characterized by ^{1}H NMR for proving single step insertion of a metal to the C – C bond [55], bringing the metal center into the proximity of the C – C bond to be cleaved.

Another PCN-Rh system **152** showed a unique preference for C – C bond activation [56]. At the intermediate **153**, the rhodium(I) metal is precoordinated by both phosphane and amine groups in PCN ligand. The rhodium metal center is nonsymmetrically positioned, which makes the distance between Rh and the C – C bond shorter and the coordination sphere of Rh less crowded. These factors render the Rh center to be placed near the C_{Ar}-C_{Me} bond and the activation barrier of C – C bond activation to be lowered (Eq. 14).



Equation 14

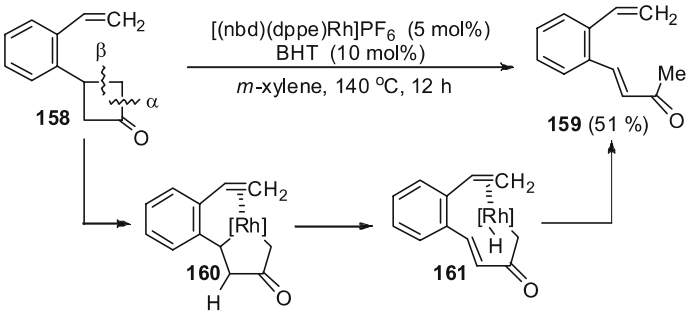
Although catalytic carbon–carbon bond activation using a pincer type compound is very rare, some noticeable examples of hydrogenolysis and hydrosilyation have been reported [57]. In those cases, when the reaction of ^{i}Pr-PCP substrate **154** with hydrogen gas or H-Si(OMe)$_3$ was carried out at high temperature in the presence of catalytic amounts of chlorobis(cyclooctene)rhodium(I) dimer (**43**), the C_{Ph}-C_{Me} bond-cleaved PCP ligand **155** along with methane or CH_3-Si(OMe)$_3$ was obtained. The proposed reaction mechanism can be explained considering the initial carbon–carbon bond cleaved rhodium(III) complex **156** undergoes hydrogenolysis to give methane and a rhodium(III) hydride complex **157**. Reductive elimination of complex **157** yields the C – C bond cleaved PCP compound **155**. By a similar reaction mechanism, complex **156** reacts with H-Si(OMe)$_3$ to give CH_3-Si(OMe)$_3$ and **157** (Scheme 21).



Scheme 21

5 Miscellaneous Reactions

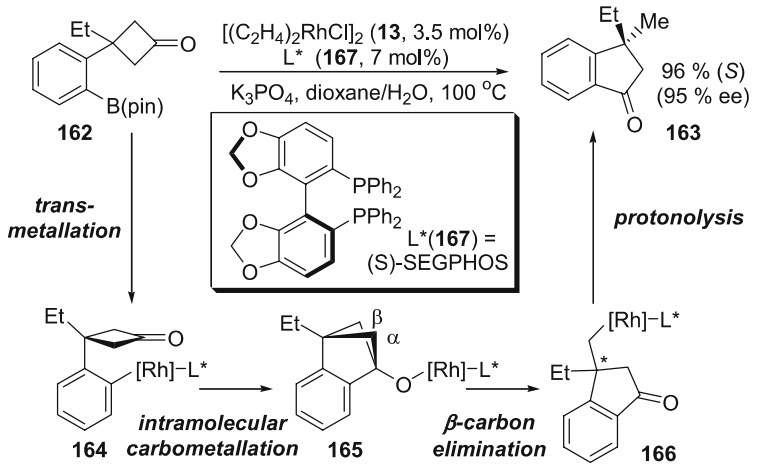
Similar to the case of coordinating heteroatoms, alkenyl groups can also be utilized as a metal-directing group through a η^2-coordination mode. For instance, the ring-cleavage reaction of 3-(*ortho*-styrylphenyl)cyclobutanone (**158**) in the presence of the rhodium(I) catalyst with bidentate phosphane ligand gave a ring-opening compound **159** through carbon–carbon bond activation [58]. While a common ring-cleavage of cyclobutanone by transition metal occurs at the α-bond in **158**, the oxidative addition by the rhodium complex occurs at the β-bond with the assistance of *o*-vinyl group directing functionality. The β-bond cleavage of the cyclobutanone group in **158** leads to the formation of complex **160**, followed by β-hydrogen elimination giv-



Scheme 22

ing complex **161**. Reductive elimination of complex **161** yields product **159** (Scheme 22).

Recently, it was reported that a chiral cyclopentanone **163** could be prepared enantioselectively from *ortho*-boronylphenyl cyclobutanone **162** through the rhodium(I)-catalyzed carbon–carbon bond activation with a chiral ligand **167** [59]. In this reaction, metal-directing could be achieved by transmetallation of boron in **162** with a rhodium catalyst to generate complex **164**. The intramolecular carbometallation of phenylrhodium(I) complex **164** to the carbonyl group and subsequent β-carbon elimination of the complex **165** leads to the formation of complex **166**. Protonolysis of **166** produces compound **163**. In this reaction, the enantioselective discrimination step is the β-carbon elimination in **165**. Depending on the chirality of L*, α or β-carbon bonds could be cleaved selectively to generate a chiral quaternary carbon center in **166** (Scheme 23). This protocol could be applied to the synthesis of (–)-herbertenol.



Scheme 23

6 Conclusion

In spite of the inertness of the carbon–carbon bond in traditional organic transformations, interest in the transition-metal mediated carbon–carbon bond activation has steadily increased. To date, several requirements have been identified and investigated in order to more practically achieve carbon–carbon bond activation. As a result, the product or intermediate organometallic complexes should be more thermodynamically stable than the starting molecules in terms of thermodynamic consideration. Based on these criteria, one method to achieve this goal is to use a high energy organic species such as strained ring molecules. Ring-opening of these strained ring molecules by carbon–carbon bond activation relieves the strained energy, making the process exothermic. The other option is to form 5-membered metallacyclic complexes, π-allyl transition metal complexes, complexes possessing strong metal–carbon bonds and others which strongly stabilize the intermediate organometallic species through the heteroatom-chelation strategy. The stabilization of intermediate complexes would lower the activation enthalpy of C – C bond activation. In this chapter, we mainly dealt with the heteroatom-directed carbon–carbon bond activations based on intermediate stabilization. By this strategy, the metal complexes can be located at the proper position, facilitating the carbon–carbon bond activation. Depending on the nature of coordinating heteroatoms and the types of coordination, different types of carbon–carbon bond activation reactions are shown. Although there are still many limitations to overcome in the present carbon–carbon bond activations by transition metal complexes, it is obvious that research of carbon–carbon bond activation is on the threshold of revealing new strategies for organic synthesis.

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Directed Rhodium-Catalyzed Hydroformylation of Alkenes

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Abstract Installation of substrate-bound catalyst-directing phosphine groups allows for efficient substrate control of all aspects of reaction selectivity in the course of the industrially important hydroformylation reaction. In particular, the *ortho*-diphenylphosphanylbenzoyl (*o*-DPPB) group has proved to be a highly efficient and practical directing group for controlling regioselectivity and diastereoselectivity of a range allylic and homoallylic alcohol derivatives. A chiral variant, the *o*-DPPF directing group, enables a desymmetrizing hydroformylation of prochiral dialkenyl- and diallylcarbinols to give substrates with two stereocenters in enantiomerically pure form. Incorporation of the hydroformylation as part of sequential processes is possible and has led to the development of synthetically appealing multiple carbon–carbon and carbon–heteroatom bond formations.

Keywords Desymmetrization · Hydroformylation · Sequential transformations · Substrate-directable reactions · Rhodium

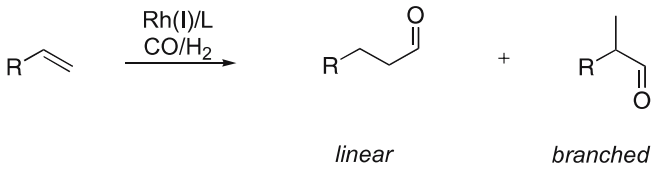
Abbreviations

BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
CDG	Catalyst-directing group
Cy	Cyclohexyl
DCC	Dicyclohexylcarbodiimide
DIBAL	Diisobutylaluminiumhydride
DMAP	4-*N*,*N*-Dimethylaminopyridine
o-DPPB	*ortho*-Diphenylphosphanylbenzoate
o-DPPF	*ortho*-Diphenylphosphanylferrocenoate
LDBB	Lithium 4,4′-ditertbutylbiphenylide

MOM	Methoxymethyl
Piv	Pivaloyl
TBS	*tert*-Butyldimethylsilyl
TOF	Turnover frequency
Tr	Trityl

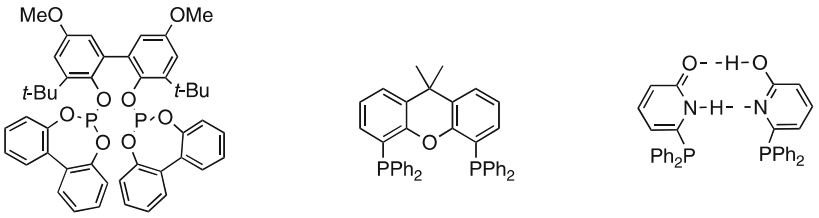
1 Introduction

In 1938 Otto Roelen discovered the hydroformylation of alkenes (Eq. 1), which is the addition of carbon monoxide and hydrogen across the π-bond of the alkene to give saturated C1-chain-elongated aldehydes [1, 2]. Today the reaction has become one of the most important applications of homogeneous catalysis in industry, with approximately 9 million tons of oxo products produced per year [3]. First generation catalysts, which to some extent are still in industrial use, were based on cobalt. However, the introduction of phosphine-modified rhodium complexes as extremely active and selective hydroformylation catalysts by Wilkinson et al. has been a milestone in this area [4]. As a consequence, modern hydroformylation research focuses primarily on rhodium systems [5, 6].



Equation 1

Hydroformylation is a catalytic addition reaction that fulfills all criteria of atom economy [7, 8]. Additionally, the synthetically valuable aldehyde function is formed, which renders hydroformylation products as ideal precursors for subsequent carbon–carbon and carbon–heteroatom bond formation. Hence, hydroformylation should be an interesting reaction for application in modern organic synthesis. Conversely, for a long time, application of this attractive carbon–carbon bond forming reaction in organic synthesis has remained scarce [6]. This is certainly due to the difficulty in controlling all aspects of reaction selectivity simultaneously. Today, solutions exist for linear-regioselective hydroformylation of alkyl-substituted terminal alkenes. Rhodium catalysts based on tailor-made ligands such as BIPHEPHOS (**1**) and XANTPHOS (**2**), as well as new self-assembly type ligands such as 6-DPPon (**3**), have proved particularly effective (Scheme 1) [9–13]. Conditions for linear-selective hydroformylation at room temperature and ambient pres-

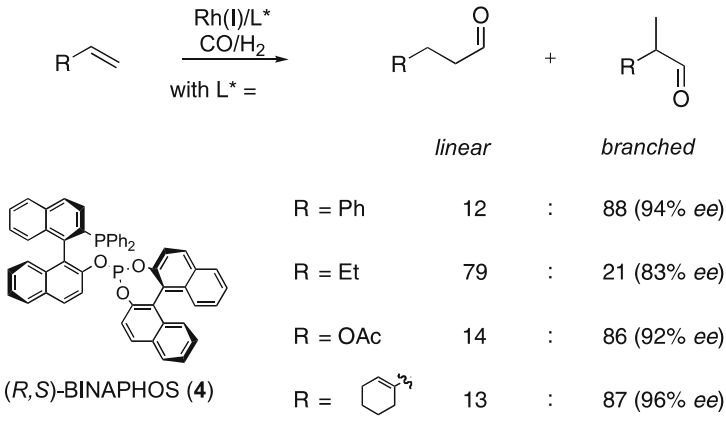


BIPHEPHOS (**1**) XANTPHOS (**2**) 6-DPPon (**3**)

Scheme 1 Ligands for linear regioselective hydroformylation of terminal alkenes

sure have been developed [14]. However, there is still no catalyst known to enable a branched-selective hydroformylation of an aliphatic terminal alkene. An even greater problem is the regioselective hydroformylation of a unsymmetrically 1,2-substituted aliphatic alkene.

Many chiral diphosphine ligands have been evaluated for inducing enantioselectivity in the course of the hydroformylation reaction [15, 16]. However, a real breakthrough only occurred in 1993 with the discovery of the BINAPHOS (**4**) ligand by Takaya and Nozaki (Scheme 2) [17].

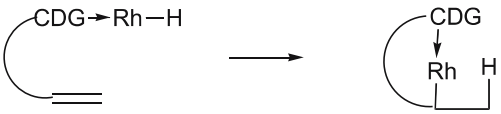


Scheme 2 Useful chiral ligands for enantioselective hydroformylation

This discovery provided the first efficient and rather general catalyst for enantioselective hydroformylation of several classes of alkenes such as arylalkenes, 1-heteroatom functionalized alkenes and substituted 1,3-dienes. Today modified versions of BINAPHOS as well as ligands based on diphosphites and diphospholane structures have shown to be equally or more effective [18–20]. But still, the most difficult problem with these enantioselective hydroformylations is the simultaneous control of both enantio- and regiose-

lectivity, which limits the structural variety of suitable alkenes for enantioselective hydroformylation significantly [6].

An alternative approach to a regio- and stereoselective hydroformylation might arise via substrate control. This approach should be particularly effective if attractive interactions between catalyst and substrate are employed in order to discriminate competing transition states leading to isomeric products (Scheme 3) [21]. During the last 10 years this approach has in fact proved to be reliable and useful for control of regio-, diastereo- and enantioselectivity in the course of the hydroformylation reaction [22]. This review summarizes the most important developments in directed hydroformylation with a focus on synthetically useful transformations. Additionally, applications of stereoselective hydroformylation as part of domino-type processes are included.

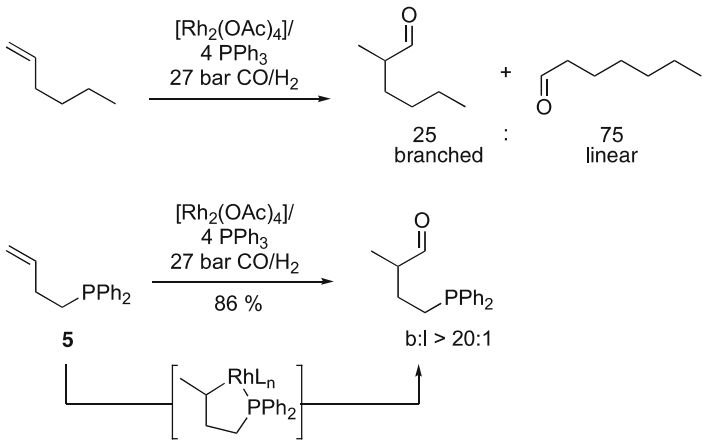


Scheme 3 Directed hydrometalation step of the hydroformylation of alkenes employing substrate-bound catalyst-directing groups (CDG)

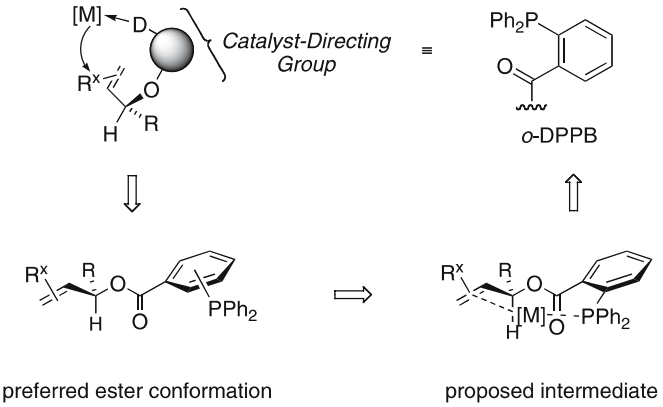
2 Directed Regioselective Hydroformylation

Hydroformylation of an aliphatic terminal alkene employing a standard triphenylphosphine rhodium catalyst furnishes, in general, a mixture of the linear and branched aldehyde with a preference for the linear isomer. Conversely, hydroformylation of 4-diphenylphosphanyl-but-1-ene (**5**) employing the same catalyst gave the branched aldehyde exclusively (Scheme 4) [23]. Hence, an appropriately positioned directing group is capable of overruling the intrinsic regiochemistry of the hydroformylation reaction.

A major disadvantage of this carbon-bound phosphine-directing group is the difficulty of its synthesis and its removal from the substrate. A solution to this problem provides a temporary substrate-bound catalyst-directing group [22, 24]. Such a group may be attached easily to e.g. an alcohol function which is present in many organic substrates. In this regard the *ortho*-diphenylphosphanyl benzoate (*o*-DPPB) function has proved to be particularly efficient for hydroformylation (Scheme 5). The following conceptual reflections were the basis for the successful development of this function. Thus, in order to allow for efficient and reversible binding of the rhodium catalyst under hydroformylation conditions (CO is an excellent and competing ligand present in large excess) a phosphine donor was selected. Further-



Scheme 4 Regioselectivity of the hydroformylation of terminal aliphatic alkenes: non-directed versus directed reaction

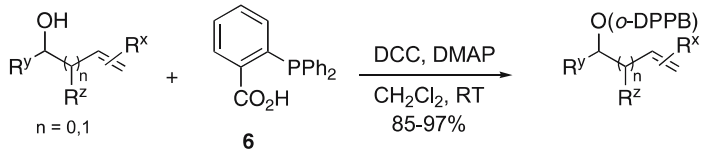


Scheme 5 Development of the catalyst-directing *o*-DPPB group

more, an ester linkage was chosen in order to allow a facile introduction into the substrate and removal from the product. Additionally, an ester connection sets limitations to the conformational space available for the substrate, and is therefore expected to limit the number of competing transition states (Scheme 5). Finally, geometry of this group has been specifically selected in order to allow for reversible transition metal binding and subsequent metal delivery into the allylic position of a corresponding allyl-*o*-DPPB ester substrate.

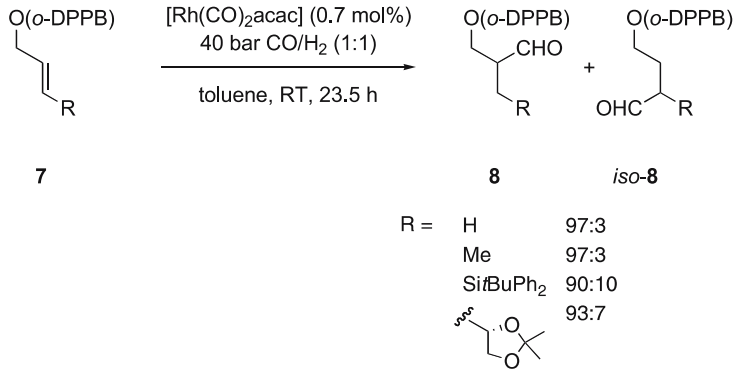
The required *ortho*-diphenylphosphanyl benzoic acid (**6**) is commercially available. Alternatively, it may be obtained in multigram scale in a one-pot operation starting from *ortho*-chlorobenzoic acid upon reaction with sodium

diphenylphosphide generated under Birch conditions from triphenylphosphine [25]. The corresponding *o*-DPPB esters are readily obtained through esterification employing standard protocols (Scheme 6).



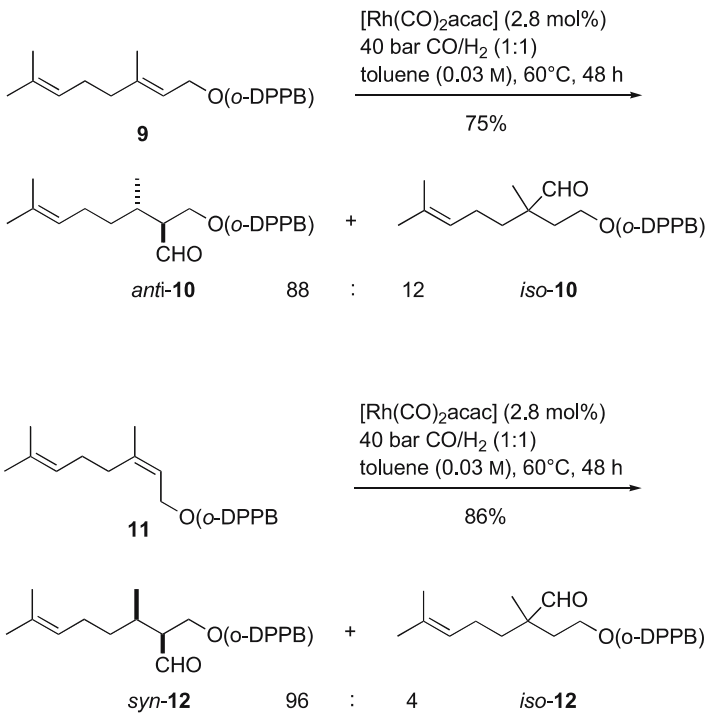
Scheme 6 Preparation of *o*-DPPB esters

Hydroformylation of allylic *o*-DPPB esters **7** proceeds in good to excellent levels of regioselectivity with the branched aldehyde **8** as the major regioisomer (Scheme 7) [26].



Scheme 7 Directed hydroformylation of allyl *o*-DPPB esters **7** with mono- and disubstituted alkene functions

Generally, trisubstituted alkenes are considered to be tough substrates for hydroformylation because the reaction rate of hydroformylation decreases exponentially with the number of substituents at the alkene function. On the other hand, one could expect that the intramolecular pathway for a directed hydroformylation should provide significant rate acceleration due to a reduction of activation entropy. In fact, employing the *o*-DPPB-directing group, efficient hydroformylation of even trisubstituted alkene functions in allylic position is possible. The rate-accelerating effect exerted by the internal metal delivery through the directing function is shown on hydroformylation of geranyl- and neryl-*o*-DPPB esters. A position-, regio- and stereoselective hydroformylation of the trisubstituted allylic alkene function of the geranyl and neryl *o*-DPPB esters **9** and **11** occurs in the presence of a remote trisubstituted alkene function (Scheme 8) [26].

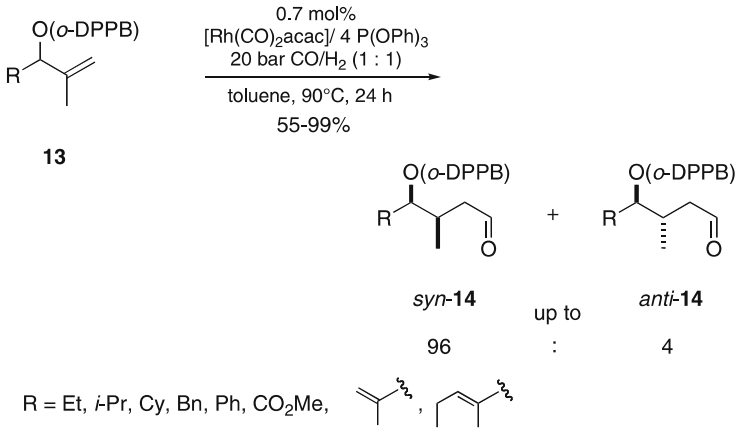


Scheme 8 *o*-DPPB-directed position-, regio-, and diastereoselective hydroformylation of geranyl and neryl *o*-DPPB esters **9** and **11**, respectively

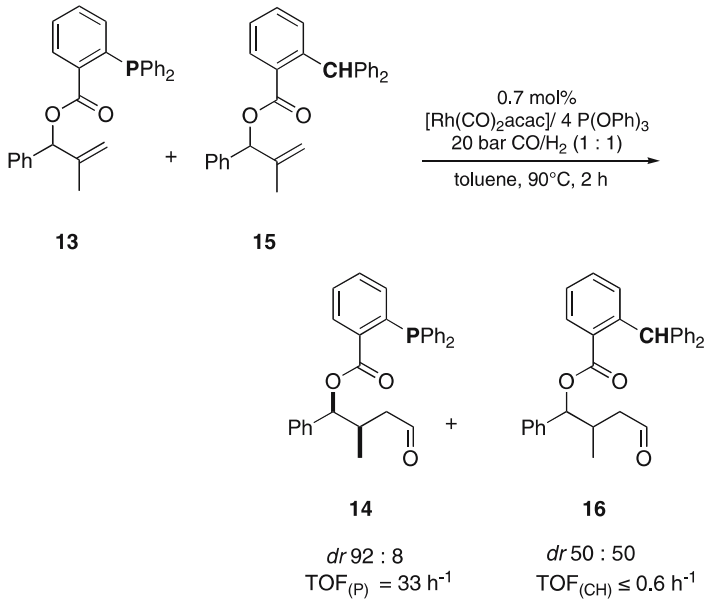
3 Directed Diastereoselective Hydroformylation

Hydroformylation of methallylic *o*-DPPB esters **13** should proceed with formation of the linear aldehyde exclusively. This is the result of Keuleman's rule, which states that formation of quarternary carbon centers is avoided. Hence, the only selectivity issue that remains to be controlled is that of diastereoselectivity. Thus, hydroformylation of *o*-DPPB esters **13** proceeded with high levels of acyclic stereocontrol to furnish the *syn*-aldehydes **14** as the major diastereomers (Scheme 9) [27, 28].

A competition experiment using *o*-DPPB substrate **13** (R = Ph) with the phosphine-free benzoate **15** provides evidence for the role of the *o*-DPPB substituent as a catalyst-directing group in the course of the hydroformylation (Scheme 10). Thus, exchanging the phosphorus of the *o*-DPPB group with a CH moiety, itself not able to coordinate to the catalytically active rhodium center, caused a complete loss of stereoselectivity in the hydroformylation reaction [28]. Also here, the significant rate-acceleration effected by the presence of the *o*-DPPB group is indicative of an intramolecular reaction pathway.



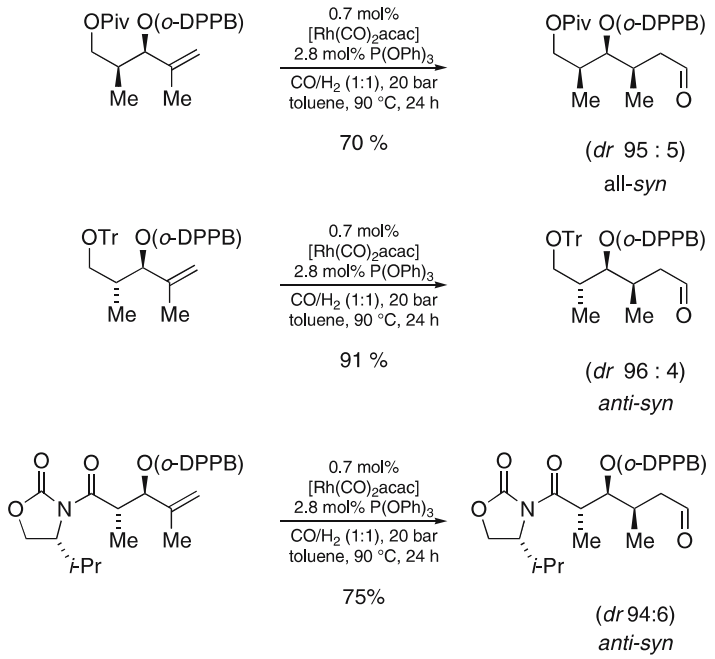
Scheme 9 Diastereoselective hydroformylation of methallylic *o*-DPPB esters **13**



Scheme 10 Probing the role of the *o*-DPPB group [TOF = mol(substrate) × mol(catalyst)$^{-1}$ × h^{-1}]

The methodology has been applied successfully for the construction of all-*syn* and *anti-syn* stereotriads, which are major building blocks for polypropionate synthesis (Scheme 11) [29, 30].

In further studies it was observed that diastereoselectivity is a function of the steric demand of both the substituent at the controlling stereocenter R^1,



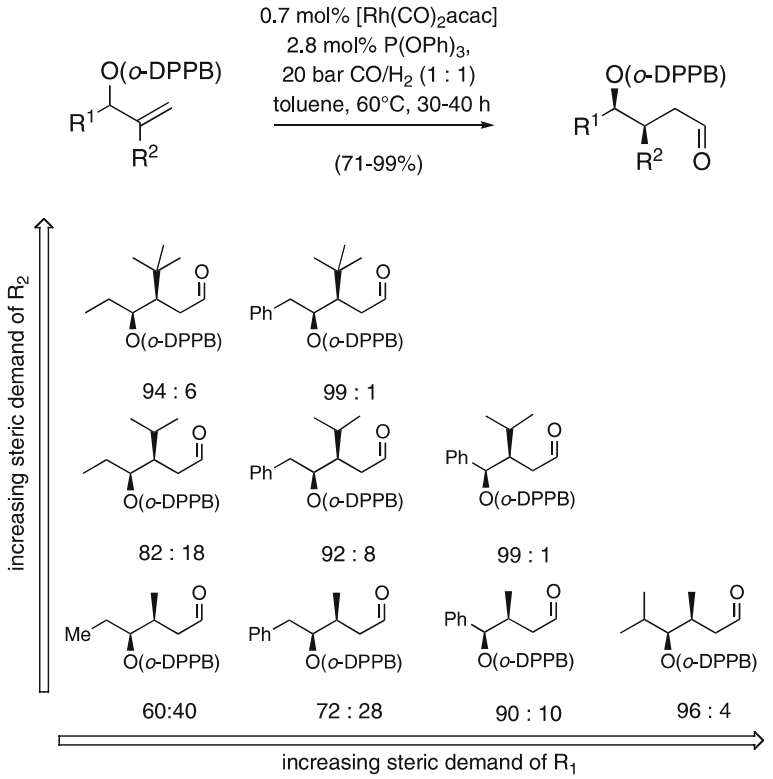
Scheme 11 Stereotriad construction employing the *o*-DPPB-directed diastereoselective hydroformylation

and the substituent at the 2-position of the allylic alcohol system R^2. Increasing the size of both increases diastereoselectivity (Scheme 12) [31].

With the hydrometalation step as the accepted selectivity-determining step in the hydroformylation reaction, a simple model can rationalize the experimentally observed diastereoselectivities (Scheme 13). As the hydrometalation step is known to be exothermic, the starting diastereomeric alkene complexes **I** and **II** should serve as good models for the corresponding competing diastereomorphic transition states for hydrometalation. A repulsive interaction between substituents R^1 and R^2 within complex **II** and the corresponding transition state favors the pathway via intermediate complex **I** ($A^{1,2}$ strain minimized) to give the *syn*-diastereomer as the major product.

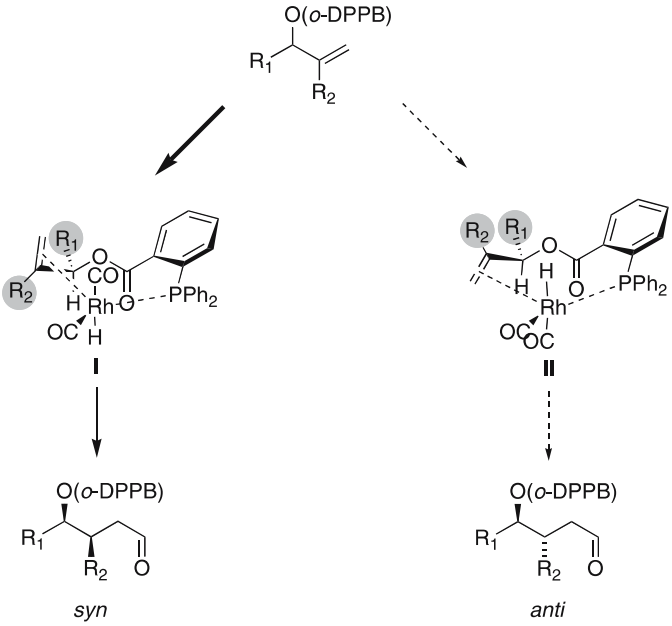
Interestingly, not only 1,2- but also 1,3-asymmetric induction can be effected employing the catalyst-directing *o*-DPPB group. Thus, hydroformylation of homomethallylic *o*-DPPB esters **17** furnishes the *anti*-aldehydes **18** in good yields and diastereoselectivities [32, 33] (Scheme 14). Control experiments showed that the *o*-DPPB group controls diastereoselectivity and, simultaneously, accelerates the rate of the hydroformylation reaction [33].

A model has been proposed in order to explain the *anti*-selectivity of this reaction (Scheme 15) [33]. Since the selectivity-determining hydrometalation step is exothermic, conformational preferences in the starting material

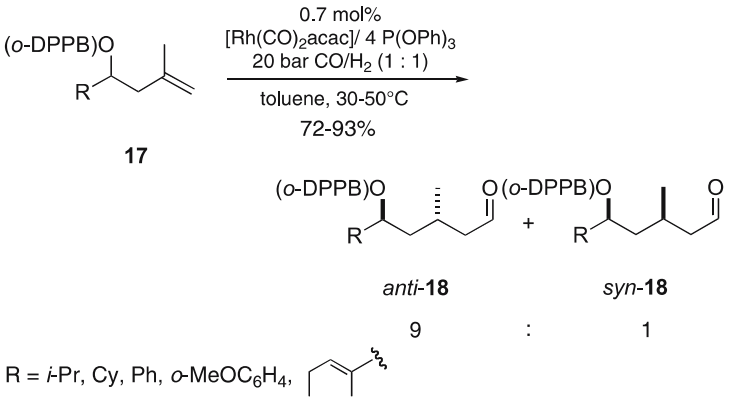


Scheme 12 Influence of steric demand of substituents R^1 and R^2 on the diastereoselectivity of the hydroformylation of 2-substituted allylic *o*-DPPB esteres

may be reflected in the transition state for hydrometalation. According to experimental and theoretical conformational analysis, homomethallylic *o*-DPPB ester **17** possess the preferred conformation **A**. Delivery of the rhodium catalyst via the catalyst-directing *o*-DPPB group provides the experimentally observed major *anti*-diastereomer, *anti*-**18**. The alternative conformation **B**, suffering from an additional *syn*-pentane interaction, should give the minor *syn*-diastereomer, *syn*-**18**. In order to probe this model, the influence of an additional tertiary stereocenter in allylic position has been explored. Exchanging H_b with a methyl substituent would disfavour conformation **B** since additional $A^{1,3}$ strain would arise (Scheme 15). Thus, the conformational equilibrium would be shifted towards conformation **A**, which should result in a more diastereoselective reaction. In accord with this prediction, the hydroformylation of the *anti*-derivative **19** furnished the *anti*-aldehyde **20** in a significantly increased diastereoselectivity of 96 : 4 (Scheme 16). However, when H_a is exchanged with a methyl substituent, both conformations **A** and **B** suffer from repulsive interactions. Thus, neither formation of the *anti*- nor



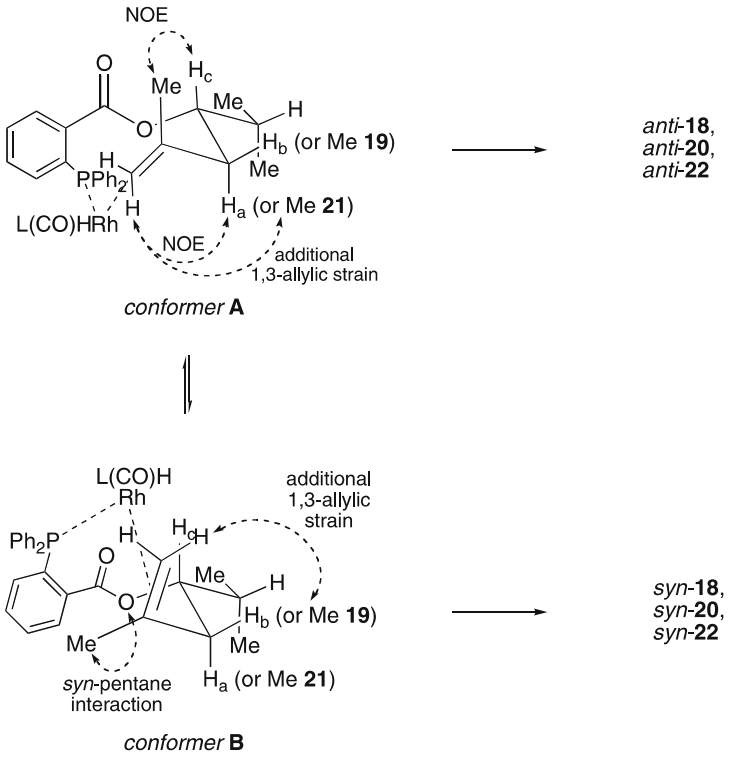
Scheme 13 Proposed model for the origin of 1,2-asymmetric induction



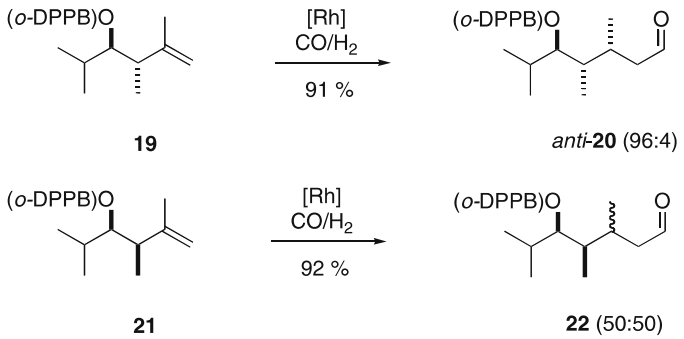
Scheme 14 Directed diastereoselective hydroformylation of homomethallylic *o*-DPPB esters **17**

the *syn*-diastereomer should be favored (Scheme 15). This prediction is again congruent with the hydroformylation experiment of *syn*-derivative **21**, which occurred in a completely stereorandom fashion (Scheme 16) [33].

A more difficult problem is the hydroformylation of allylic alcohol derivatives with a terminal alkene function. In this case, a simultaneous control of regio- and diastereoselectivity would be required. Most interesting would be

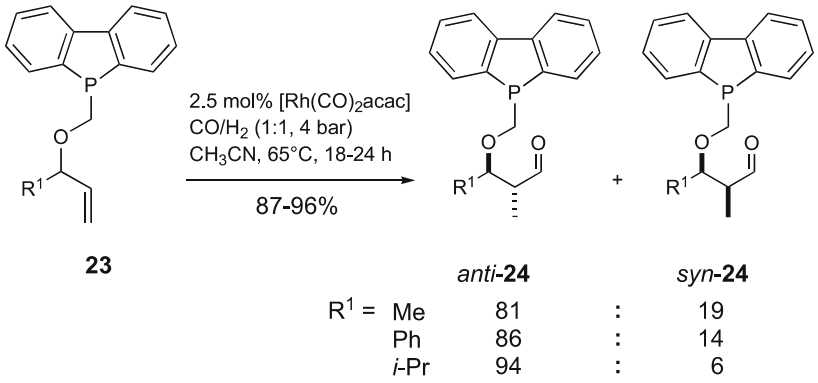


Scheme 15 Model for the origin of 1,3-asymmetric induction

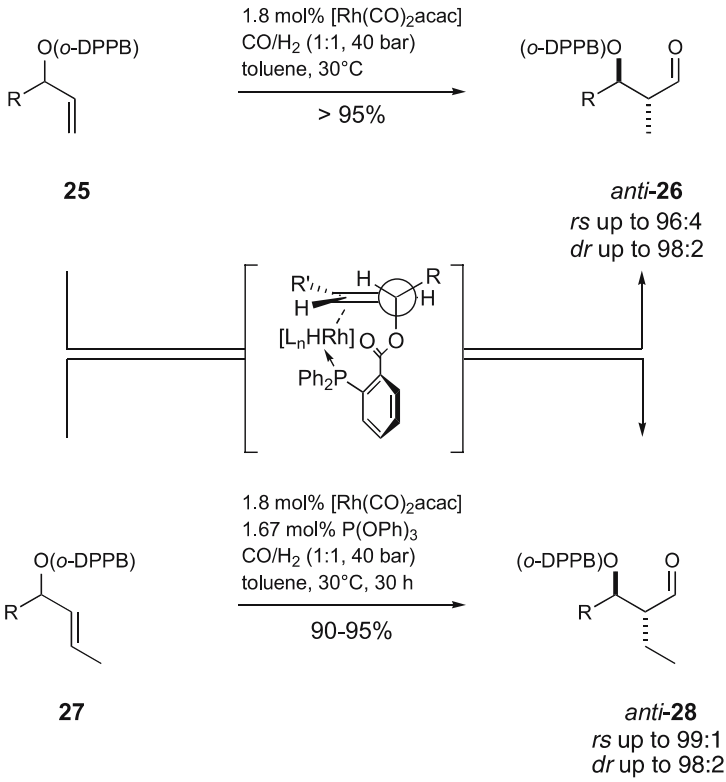


Scheme 16

a branched-selective hydroformylation since propionate aldol-type products would be formed. In fact, employing a dibenzophosphol-1-ylmethyl function as the catalyst-directing group, which is attached as a methyl ether to allylic alcohol substrates **23**, allows a regio- and stereoselective hydroformylation to give the *anti*-aldol propionates **24** in good yields (Scheme 17) [34].



Scheme 17 Dibenzophosphol-1-ylmethyl substituent as a catalyst-directing group for regio- and diastereoselective hydroformylation of allylic alcohol derivatives **17**



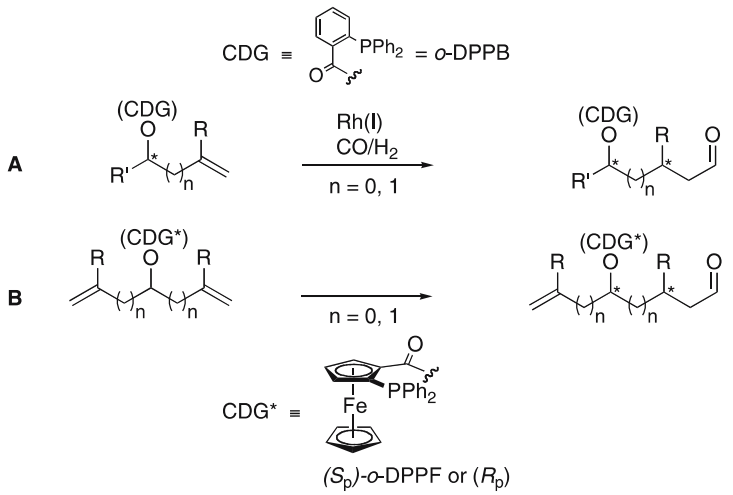
Scheme 18 *o*-DPPB-directed regio- and diastereoselective hydroformylation of allylic *o*-DPPB esters with mono- and 1,2-dialkyl-substituted alkene functions

Diastereoselectivity is best when R^1 is a secondary alkyl substituent. The catalyst-directing group is installed starting from the corresponding MOM-ether of the allylic alcohol by successive treatment with Me_2BBr and lithio dibenzophospholide. Removal of the directing group requires rather harsh reducing conditions such as treatment with LDBB or alternatively with $LiAlH_4$ in dioxane at 150 °C.

Even better selectivities can be obtained when the *o*-DPPB group is employed as the catalyst-directing function (Scheme 18) [35]. In these cases, optimal results are obtained, in the absence of a coligand [36]. Thus, starting with **25**, *anti*-propionate type aldols **26** are readily obtained, which are rather difficult to prepare by traditional aldol or allyl metal addition methodologies. Likewise, allylic alcohols with a 1,2-*trans*-disubstituted alkene function **27** could be hydroformylated to give similar *anti*-aldols **28** in good regio- and diastereoselectivities (Scheme 18). Minimization of $A^{1,3}$ strain in the course of the selectivity-determining hydrometalation step accounts for the observed diastereoselectivity [36].

4
Directed Desymmetrizing Hydroformylation

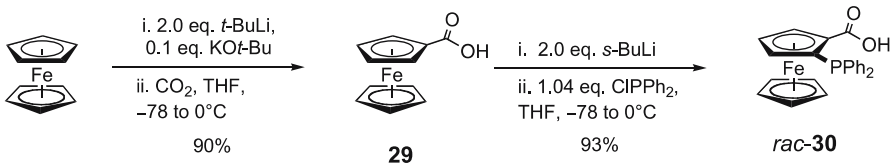
In all previous cases, stereochemical information for directed diastereoselective hydroformylation was provided by the substrate (**A** in Scheme 19). However, in the case of prochiral substrates the chiral information has to reside in the catalyst-directing group. As a planar chiral variant of the achiral



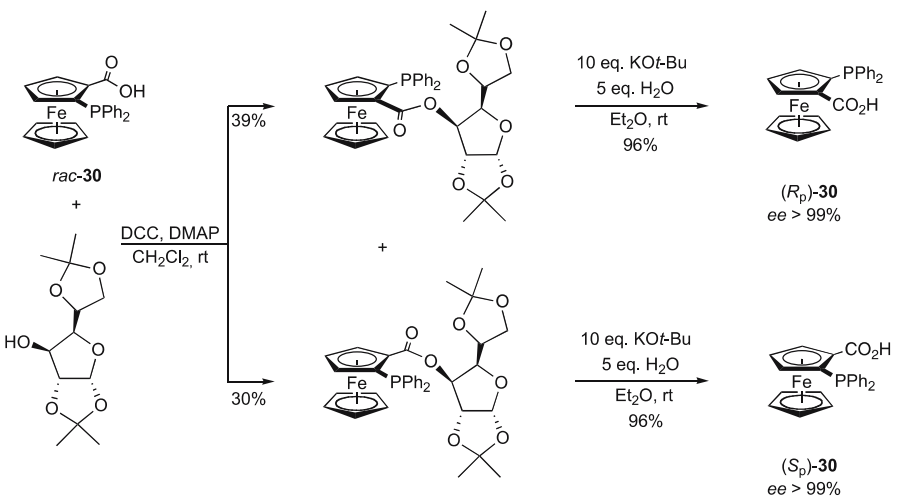
Scheme 19

o-DPPB group, the *ortho*-diphenylphosphanyl ferrocene carboxylate system (*o*-DPPF) was selected [37]. As prochiral substrates, symmetrical dialkenylcarbinols ($n = 0$) and diallylcarbinols ($n = 1$) were studied (**B** in Scheme 19). Interestingly, a stereoselective monohydroformylation could set two stereogenic centers simultaneously to give potentially interesting chiral building blocks for polyketide synthesis. However, stereoselective hydroformylation of these substrates is particularly challenging since diastereotopic alkene group discrimination and diastereotopic alkene face discrimination have to be managed simultaneously.

Synthesis of the corresponding carboxylic acid *rac*-**30** commences from ferrocene (Scheme 20) [38]. Metalation with Schlosser base and trapping with carbon dioxide gave ferrocene carboxylic acid (**29**). Directed *ortho*-metalation with two equivalents of *s*-BuLi furnished the corresponding *ortho*-lithio species, which was trapped with chlorodiphenylphosphine. Resolution has been achieved by chromatographic separation of the corresponding ester of glucose bisacetonide (Scheme 21) [21]. Final saponification liberates both optical antipodes of **30** in enantiomerically pure form [38].

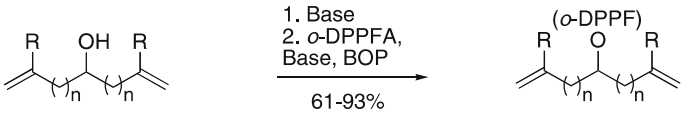


Scheme 20 Preparation of *rac*-**30**



Scheme 21 Resolution of *rac*-**30**

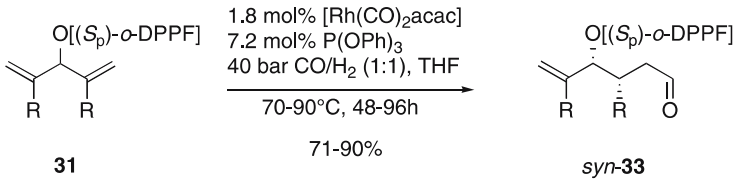
Esterification with dialkenyl and diallyl carbinols required a double activation strategy. Thus, acid **30** was activated with BOP and the alcohol coupling partner as the sodium or lithium alkoxide (Scheme 22) [37, 39, 40].



n=0, R = Me, Et, *i*-Pr, *t*-Bu, CH_2TMS **31**
n=1, R = Me, Et, *i*-Pr, Ph, CH_2OTMS **32**

Scheme 22

Subjection of bisalkenyl carbinol *o*-DPPF-esters **31** to hydroformylation conditions (Scheme 23) furnished the *syn*-aldehydes **33** as the major product in good to excellent diastereoselectivity and in enantiomerically pure form [37, 39]. Thus, of the four possible diastereomeric monoaldehydes only *syn*-**33** is formed with high selectivity.

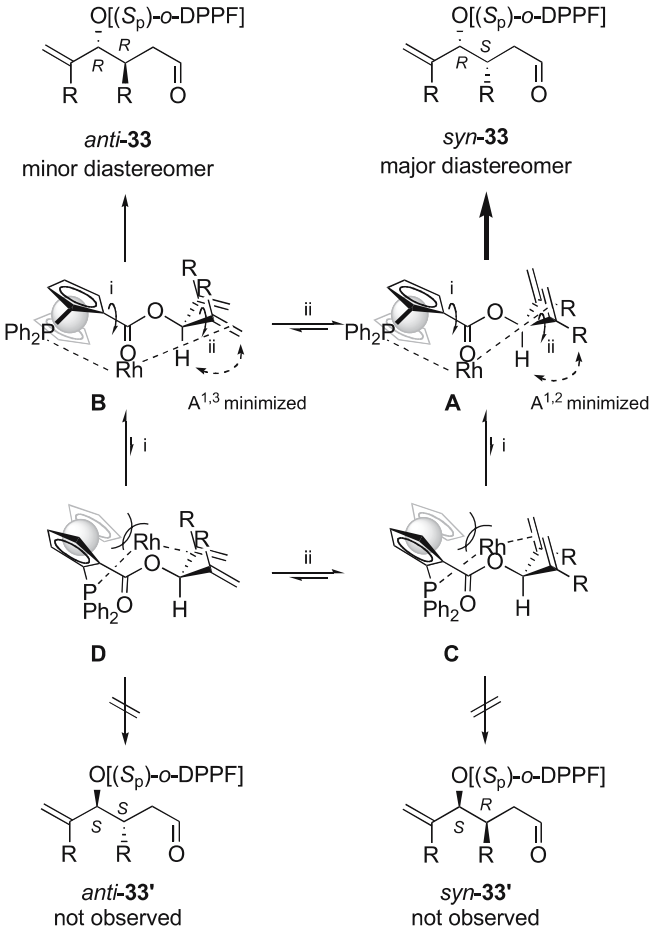


31 *syn*-**33**

R = Me, Et, *i*-Pr, *t*-Bu, CH_2TMS *dr* 88:12 to >99:1

Scheme 23 Desymmetrizing hydroformylation of dialkenyl carbinol *o*-DPPF esters **31**

From the absolute and relative configuration of monoaldehydes **33** it follows that the hydroformylation of dialkenylcarbinol *o*-DPPF esters **31** occurs with good diastereotopic face discrimination and perfect diastereotopic group discrimination. Diastereotopic face discrimination increases with the size of the R substituent at the alkene, which parallels the observations made in the course of the *o*-DPPB-directed hydroformylation of chiral 2-substituted allylic alcohols (Scheme 12), for which a stereochemical model has been proposed (Scheme 13) [31]. A similar model, modified by exchanging *o*-DPPB with the planar chiral *o*-DPPF group, allows rationalization of the stereochemical outcome of the directed desymmetrizing hydroformylation (Scheme 24) [39]. Comparison of the relative stability of the chelating rhodium alkene complexes **A–D**, which serve as models for the competing rate- and selectivity-determining hydrometalation transition states, allows for prediction of the stereochemistry of the directed hydroformylation [6]. Thus, for (S_p)-*o*-DPPF-esters **31** the relative stabilities of the two diastereomeric



Scheme 24 Stereochemical rational for desymmetrizing hydroformylation of *o*-DPPF esters **31**

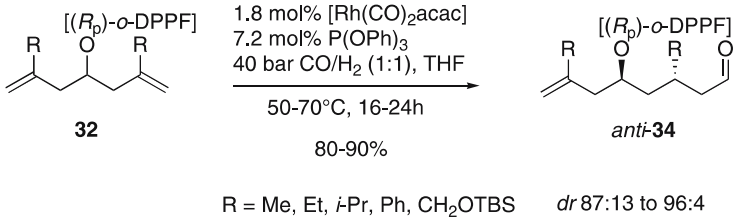
complexes **A** and **B** and the corresponding transition states for hydrometalation decide the alkene face diastereoselection of the reaction. Minimization of $A^{1,2}$ strain in the alkenic moiety leads via **A** to the major diastereomer *syn*-**33**. The reaction via chelation mode **B**, in which the alkene conformation minimizes $A^{1,3}$ strain, leads to the minor diastereomer *anti*-**33**. Since $A^{1,2}$ strain is a function of the steric demand of the R-substituent it is obvious that face diastereoselectivity increases with increasing size of R [31].

Group diastereoselectivity is determined by the relative stabilities of hydrometalation transition states resulting from chelation complexes **C** and **D** vs. **A** and **B**. Thus, coordination of the opposite diastereotopic alkene group requires a bond rotation process (i in Scheme 24). However, such a chelating bonding mode is prohibited because of severe steric hindrance between

the ferrocene nucleus and the rhodium metal center. This explains the perfect alkenic group diastereoselection observed experimentally [39].

Although this model provides a concise stereochemical rational, it may oversimplify the overall kinetics of the hydroformylation.

Diallyl carbinol-*o*-DPPF esters **32** are further excellent substrates for the desymmetrizing *o*-DPPF-directed hydroformylation. The *anti*-aldehydes **34** were obtained in good yield, excellent diastereoselectivity and in enantiomerically pure form (Scheme 25) [37, 40].

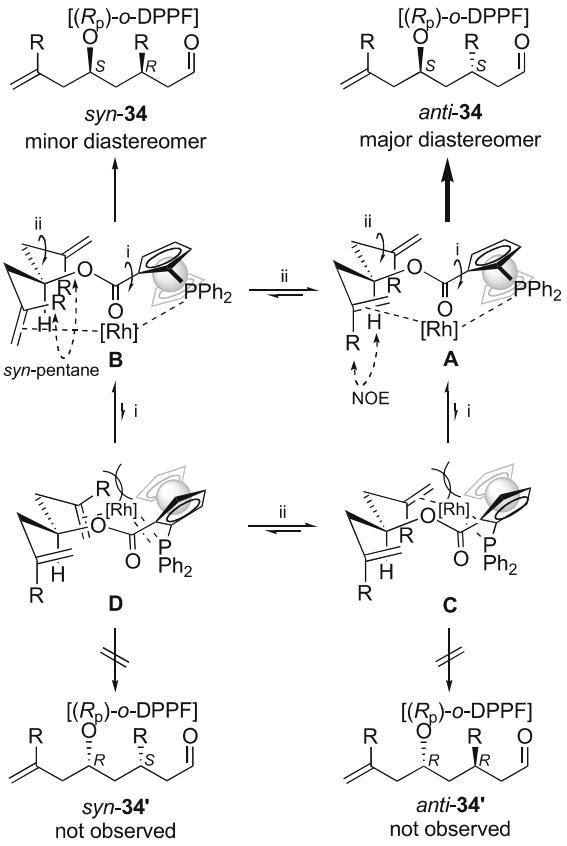


Scheme 25 Desymmetrizing hydroformylation of diallylcarbinol *o*-DPPF-esters **32**

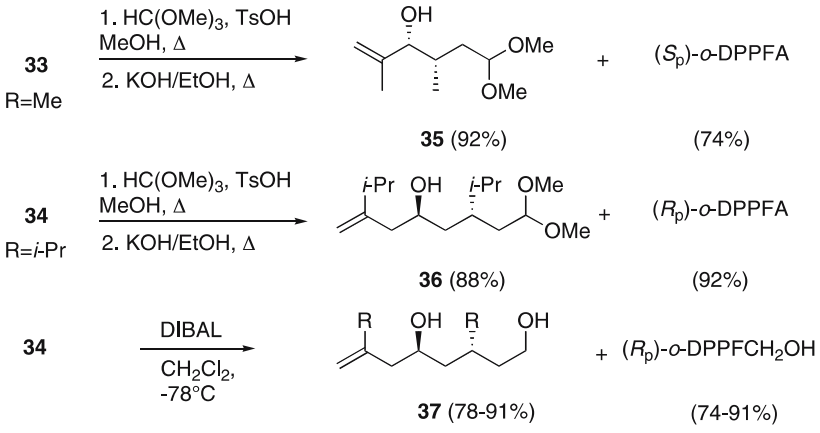
Also here, a rational for the stereochemical course of the *o*-DPPF-directed hydroformylation of diallylcarbinols was suggested based on comparison of the relative stabilities of the four diastereomorphic chelating rhodium alkene complexes **A**–**D** (Scheme 26) [40]. The alkene complexes serve as models for the competing rate- and selectivity-determining hydrometalation transition states of the directed hydroformylation. Thus, for (R_p)-*o*-DPPF-esters **32** the relative stabilities of the two diastereomeric complexes **A** and **B** and the corresponding transition states for hydrometalation decide the alkene face diastereoselection of the reaction. Minimization of the *syn*-pentane interaction in analogy to the related homomethallylic *o*-DPPB esters (Schemes 14 and 15) should lead via **A** to the major diastereomer *anti*-**34**. The reaction via chelation mode **B** presumably furnishes the minor diastereomer *syn*-**34**. NOESY experiments as well as X-ray studies show that conformation **A** is adopted in solution as well as in the solid state [40].

Group diastereoselectivity is determined by the relative stabilities of hydrometalation transition states resulting from chelation complexes **C** and **D** vs. **A** and **B**. Thus, coordination of the opposite diastereotopic alkene group requires a bond rotation process (i in Scheme 26). Such a chelating binding mode is prohibited because of severe steric hindrance between the ferrocene nucleus and the rhodium metal center, which results in a perfect alkenic group diastereoselection. Thus, neither diastereomer *syn*-**34′** nor *anti*-**34′** were formed [40].

Removal of the substrate-bound catalyst-directing *o*-DPPF group can be achieved through saponification after protection of the aldehydes as a dimethylacetal (Scheme 27). The alcohols **35** and **36** were obtained in good



Scheme 26 Stereochemical rational for desymmetrizing hydroformylation of *o*-DPPF esters **32**



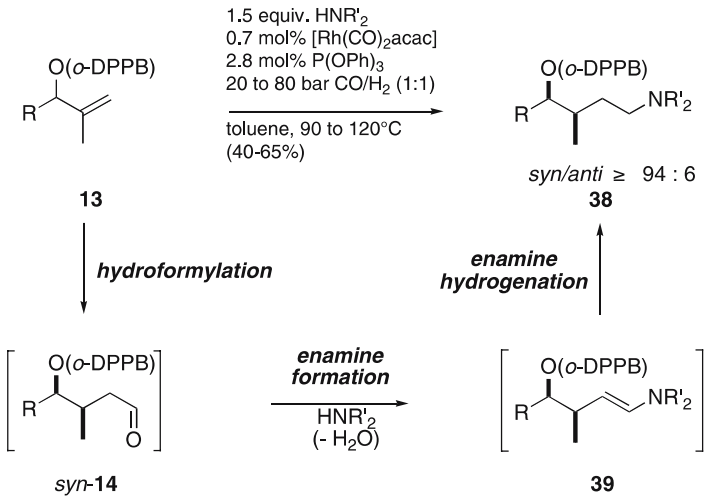
Scheme 27 Removal and recovery of the catalyst-directing *o*-DPPF group

yields and the *o*-DPPFA could be recovered. Alternatively, clean reductive removal of the *o*-DPPF group is achieved upon DIBAL reduction to furnish 1,5-diols **37** (Scheme 27) [37, 39, 40].

5
Directed Hydroformylation as a Key Step in Sequential Transformations

One may improve efficiency of an *o*-DPPB-directed hydroformylation by incorporating this reaction into sequential transformations [41, 42]. The hydroformylation itself is ideal for this purpose since the reaction provides under fairly mild reaction conditions access to the synthetically valuable aldehyde functionality. The aldehyde in turn is an ideal starting point to enable further skeleton-expanding reactions [43].

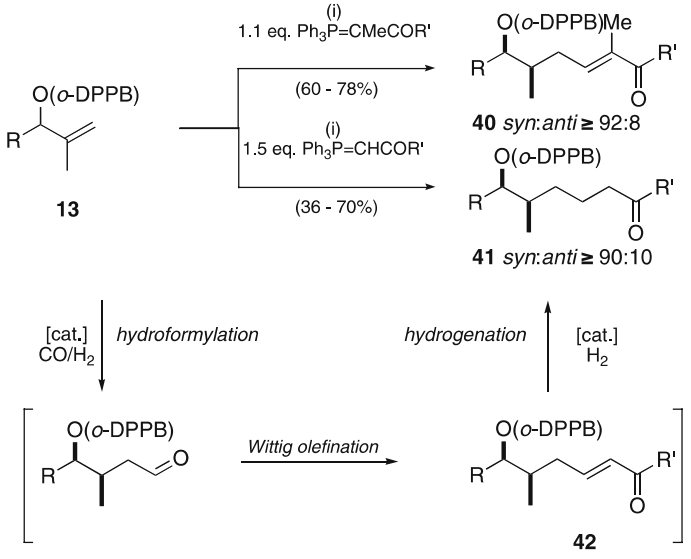
One type of sequential transformation employing the hydroformylation reaction as a key step is the hydroaminomethylation of olefins originally discovered by Reppe [44]. However, efficient control of diastereoselectivity in the course of this hydroaminomethylation reaction was unknown. Subjection of methallylic *o*-DPPB esters **13** to hydroformylation conditions in the presence of a secondary or primary amine resulted in the formation of the corresponding hydroaminomethylation products, the amines **38**, in diastereoselectivities of greater than 94 : 6 (Scheme 28) [45]. Hence, this process allows, in one step, the formation of a C – C bond, a C – N bond, introduction of the ubiquitous amine functionality, and additionally generates a new stereogenic center with high levels of acyclic stereocontrol. The mechanism of this sequential transform-



Scheme 28 *o*-DPPB-directed hydroaminomethylation

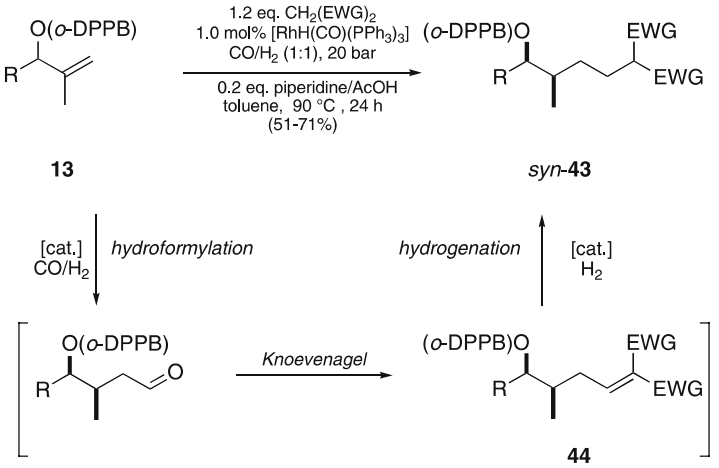
ation presumably involves three steps. First, *o*-DPPB-directed stereoselective hydroformylation of the methallylic *o*-DPPB esters **13** provides the aldehyde *syn*-**14**. Next comes enamine/iminium ion formation with the amine (secondary or primary) present. Subsequent rhodium-catalyzed hydrogenation finishes the sequence of reactions and affords the saturated amines **38**.

If other nucleophiles (e.g., carbon nucleophiles) are offered in the course of the hydroformylation reaction, other sequential transformations employing the hydroformylation as the key step should be possible. When performing an *o*-DPPB-directed hydroformylation of methallylic *o*-DPPB esters in the presence of stabilized Wittig ylides, the corresponding domino hydroformylation products, **41** and **42**, were obtained in good yields and diastereoselectivities (Scheme 29) [46, 47]. Stereocontrol was provided by the catalyst-directing *o*-DPPB group relying on 1,2-asymmetric induction. Reactions employing disubstituted, stabilized Wittig ylides stopped at the stage of the trisubstituted alkenes **40**. When monosubstituted ylides were used, the respective α,β-unsaturated carbonyl derivatives **42** experienced further hydrogenation to give saturated derivatives **41**. Hence, the same rhodium catalyst that catalyzed the hydroformylation of alkenes **13** acted upon acceptor-substituted alkenes **42** as a hydrogenation catalyst. Overall two new carbon–carbon single bonds and a new stereogenic center with high levels of acyclic stereocontrol were formed in one step. Since the hydroformylation is intrinsically tolerant to a large set of functional groups, this domino process may be suited to function as a fragment coupling step in the context of a convergent synthetic strategy.



Scheme 29 Domino hydroformylation–Wittig olefination–hydrogenation reaction. Reagents and conditions: (i) 0.7 mol % $[RhH(CO)(PPh_3)_3]$, 20 bar CO/H_2 (1 : 1), toluene, 90 °C, 48 h

Although the hydroformylation represents an atom-economic reaction, the Wittig olefination as part of the domino hydroformylation–Wittig olefination sequence is the reverse. In this regard a more appealing olefination reaction is the Knoevenagel condensation with water being the only by-product. Thus, subjection of methallylic *o*-DPPB derivatives **13** to hydroformylation conditions in the presence of stoichiometric amounts of a methylene-active derivative and catalytic amounts of piperidinium acetate furnished derivatives *syn*-**43** in good yields and stereoselectivities (Scheme 30) [48]. Hence, these products are the result of a sequential hydroformylation, Knoevenagel condensation, and a final rhodium-catalyzed hydrogenation of the electron-acceptor substituted alkenic function in **44**. Thus, again the same catalyst that catalyzes the hydroformylation step serves as a hydrogenation catalyst during the final step of this domino process. Malonates, β-ketoesters as well as β-diketones could serve as the methylene-active component. This sequential transformation allows in a single operation the formation of two carbon–carbon single bonds, with concomitant generation of a new stereogenic center with high levels of regio- and acyclic stereocontrol. Additionally, a synthetically useful β-dicarbonyl function is introduced.



Scheme 30 Domino hydroformylation–Knoevenagel hydrogenation reaction (*EWG* electron withdrawing group)

6 Summary and Conclusions

With the aid of substrate-bound catalyst-directing groups, efficient substrate control of all aspects of reaction selectivity in the course of the industrially important hydroformylation reaction can be achieved. In particular, the

o-DPPB group has proved to be a highly efficient and practical directing group for controlling regioselectivity and diastereoselectivity of a range of allylic and homoallylic alcohol derivatives. A chiral variant, the *o*-DPPF directing group, enables even a desymmetrizing hydroformylation of prochiral dialkenyl- and diallylcarbinols to give substrates with two stereocenters in enantiomerically pure form. Incorporation of the hydroformylation as part of sequential processes is possible and has led to the development of synthetically appealing transformations. Today, it is clear that the directing ability of the *o*-DPPB and *o*-DPPF group is not restricted to rhodium catalysis but can also be applied to palladium catalysis and copper-mediated processes. The multiple use of one directing group for sequences of directed reactions should be an interesting area to pursue in the future.

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Directed Mizoroki–Heck Reactions

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Abstract The Mizoroki–Heck reaction is one of the key C – C bond-forming processes in organic synthesis. A prominent variant, which has found broadest application in targeted complex molecule synthesis, is the asymmetric intramolecular Mizoroki–Heck reaction. This methodology has outshone another powerful facet of Mizoroki–Heck chemistry, which has been prospering in recent years, namely directed Mizoroki–Heck reactions. Initially designed to achieve high regiocontrol in intermolecular reactions, this technique has recently been extended to highly diastereoselective and even enantioselective substrate-directed inter- as well as intramolecular Mizoroki–Heck reactions. This summary delineates the evolution of this chemistry from regio- to diastereo- and finally, enantioselective transformations.

Keywords Diastereoselectivity · Enantioselectivity · Mizoroki–Heck reaction · Palladium · Regioselectivity

Abbreviations

dba	dibenzylideneacetone
DMA	*N*,*N*-dimethylacetamide
dppb	1,4-bis(diphenylphosphanyl)butane
dppf	1,1′-bis(diphenylphosphanyl)ferrocene
dppp	1,3-bis(diphenylphosphanyl)propane
dr	diastereomeric ratio
er	enantiomeric ratio

1 Introduction

A short survey of neighboring-group effects in Mizoroki–Heck reactions was published a couple of years ago [1]. The present article is based on the former yet providing additional (less obvious) examples of Mizoroki–Heck processes involving interaction of σ- as well as π-donors with electrophilic palladium(II) centers. Among the transition metal-catalyzed transformations that had conquered organic and organometallic chemistry by the end of the last century [2–4], the Mizoroki–Heck reaction had been a *sleeping beauty* for more than a decade since its initial appearance in the literature [4, 5]. As a C – C bond-forming process, this arylation/vinylation of an alkene inherently holds exciting synthetic potential if regio- and stereoselectivity are controllable elements in this reaction. However, both regio- (α or β) and diastereoselectivity (*E* or *Z*) emerged as notoriously difficult to control in intermolecular Mizoroki–Heck reactions [7, 8] of **1** and **2** (Fig. 1), which is clearly detrimental to synthetic applications. Conversely, an intramolecular reaction [9, 10] enables control of the regiochemistry, which is usually discriminated by the length of the tether in the cyclization precursor **3** (Fig. 1). Depending on the mode of the ring closure (*endo* or *exo*), there is occasional lack of stereocontrol in the newly formed exocyclic alkene moiety.

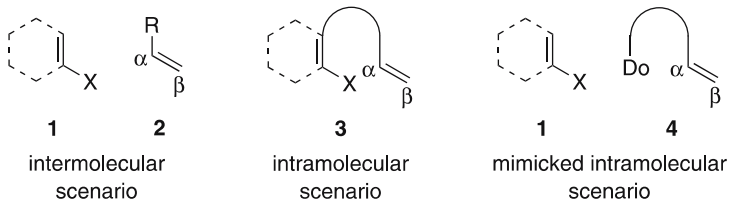


Fig. 1 Three different scenarios for Mizoroki–Heck reactions

Additionally, this variant is endowed with an important advantage. Whereas intermolecular Mizoroki–Heck reactions are generally limited to mono- and disubstituted alkenes, the substrate scope of intramolecular Mizoroki–Heck reactions also includes tri- and tetrasubstituted double bonds. C – C bond

formation at these highly substituted alkenes establishes an entry into the construction of sterically congested tertiary and all-carbon quaternary centers.

Its true value was put into perspective when Shibasaki and Overman simultaneously disclosed the enantioselective formation of tertiary and quaternary stereogenic carbons by means of catalytic asymmetric intramolecular Mizoroki–Heck reactions [11, 12]. The need for the construction of such stereocenters in the course of total synthesis inspired this development. Today, it still is the prominent, if not indispensable, tool for this synthetic challenge [13–16] as reflected by numerous beautiful applications to the synthesis of structurally intriguing natural products [17, 18].

Shortly after the advent of asymmetric Mizoroki–Heck cyclizations, Hayashi reported the first enantioselective intermolecular Mizoroki–Heck reaction of 2,3-dihydrofuran [19]. This substrate was carefully selected since the high α-regioselectivity of its arylation is steered electronically and there is no issue of diastereoselectivity (*E* or *Z*). With only a few exceptions, this asymmetric Mizoroki–Heck reaction is restricted to this substrate and there have been hardly any synthetic applications so far. Instead, this reaction has served as a sharpening stone for the development of novel chiral ligands in asymmetric catalysis [20].

These Mizoroki–Heck reactions have been extensively reviewed with particular focus on synthetic [9, 10, 13–18] as well as mechanistic aspects [7, 8, 21, 22] and are beyond the scope of this article. With regard to synthetic usefulness, the intramolecular Mizoroki–Heck reaction has undoubtedly outshone many other efforts in the wide-ranging area of Mizoroki–Heck chemistry. One of these underappreciated areas, which has recently been going through a second childhood, was systematically introduced by Hallberg several years ago [23–26]. In order to control the regioselectivity of an intermolecular Mizoroki–Heck reaction, Hallberg designed an alternative to intramolecular Mizoroki–Heck processes by installation of a suitable donor Do in the alkene fragment **2** (**2** $\Rightarrow$ **4**, Fig. 1), which is capable of coordinating the palladium catalyst. This then allows for intramolecular delivery of the aryl/vinyl fragment **1** thereby mimicking an intramolecular Mizoroki–Heck reaction, a scenario that has been coined by Hallberg as a *chelation-controlled* Mizoroki–Heck reaction [23–26]. This review will summarize the evolution of this concept from achieving the initial objective of controlling regioselectivity to recent diastereoselective and even enantioselective directed Mizoroki–Heck reactions.

2
Concept of Chelation Control

Controlling regio- and stereoselectivity with the aid of attractive interactions between substrate and reagent/catalyst is a continuing challenge in organic

synthesis. Although the literature is interspersed with numerous examples including the contributions by Hallberg, the generality of the concept itself was realized and summarized by Evans a little more than a decade ago [27]. The targeted development of such *substrate-directable chemical reactions* has flourished since then.

For achieving high regioselectivity in an intermolecular Mizoroki–Heck reaction, Hallberg modified an alkene **2**—considered as the substrate—by the introduction of a pending donor group Do (**2** ⇒ **4**, Fig. 1). The donor Do coordinates to an aryl- or vinylpalladium(II) intermediate—considered as the reagent—providing the alkene-palladium complex **5** (Fig. 2). Delivery of the aryl/vinyl group onto the alkene moiety will now proceed intramolecularly, thus reshaping a bimolecular into a unimolecular process. An intermediate such as **5** nicely reproduces the scenario of an intramolecular reaction **6** (Fig. 2). These donor groups have been illustratively described as *reagent-* or *catalyst-directing groups* [28].

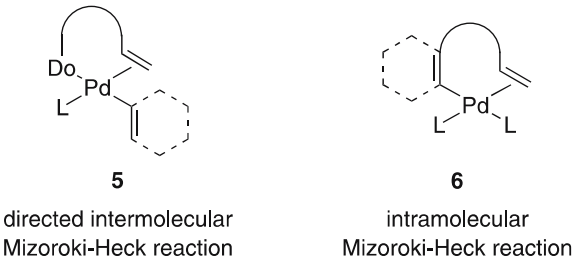


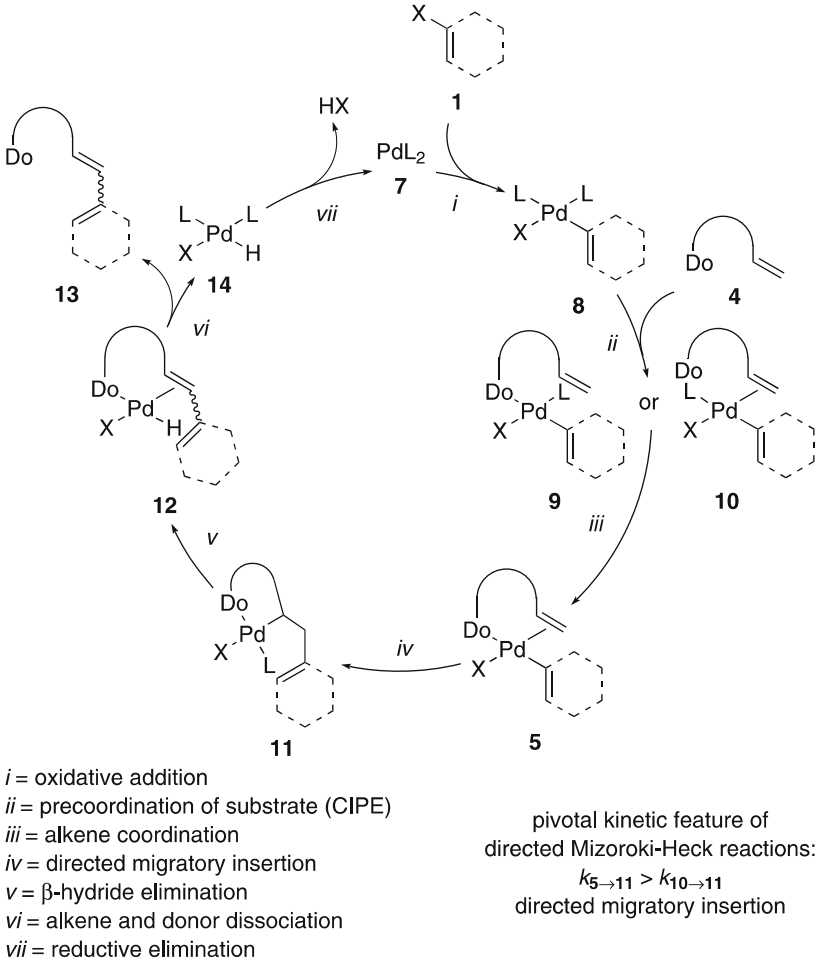
Fig. 2 Concept of chelation control [1, 27–33]

Although chelation is the essential feature in these Mizoroki–Heck reactions, it must be noted that the descriptive expression *chelation control* is somewhat ambiguous. As already mentioned, the intermolecular substrate-controlled Mizoroki–Heck reaction is a (pseudo-)unimolecular process, as is the corresponding intramolecular reaction, whereas chelation control is associated with bimolecular transformations, as in addition of nucleophiles to carbonyl compounds. In this context, chelation and non-chelation control are usually discussed [29, 30]. Therefore, these Mizoroki–Heck reactions are part of the family of substrate-directed reactions.

3
Catalytic Cycle and Mechanistic Considerations

The textbook mechanism of the Mizoroki–Heck reaction is still widely accepted even though detailed mechanistic investigations have led to a more refined understanding in recent years [7, 8]. However, many of these mecha-

nistic subtleties [21, 22] only apply to specific reaction conditions. In particular, palladium precatalysts, ligands and additives have a profound influence on the reaction mechanism [21, 22]. Scheme 1 shows a general catalytic cycle, which is adjusted to the presentation of the principles needed in directed Mizoroki–Heck reactions.



Scheme 1 Catalytic cycle of a substrate-directed Mizoroki–Heck reaction [1]

The catalytic cycle begins with the oxidative addition of a coordinatively unsaturated palladium(0) catalyst **7** into the C(sp^2) – X bond of **1** (step *i*, **7** → **8**). The resulting σ-arylpalladium(II) complex **8** is usually more Lewis acidic (or electrophilic) than **7**. Intermediate **8** will initially coordinate to one of the two Lewis basic sites available in substrate **4** (step *ii*). Precoordination of **8** to the donor group Do in **4** followed by alkene coordination is only fa-

vored (steps *ii* and *iii*, **8** → **9** → **5**) if the tether creates an ideal vicinity of both Lewis basic moieties. This desired order of coordination events is called the complex-induced proximity effect (CIPE) [31–33], in which the donor Do provides a temporary residence site prior to subsequent processes. Conversely, if the tethered donor in **9** is unable to deliver the palladium center to the alkene, the chelate **5** will not be formed. Hence, **9** might dissociate and directly coordinate with the alkene fragment (**8** → **10**). The unwanted intermediate **10** will proceed in the catalytic cycle without any substrate direction as in a standard bimolecular intermolecular Mizoroki–Heck reaction.

Both σ-arylpalladium(II) complexes **10** and **5** might undergo the migratory insertion (step *iv*), which will occur at different reaction rates k with $k_{5\rightarrow 11}$ being substantially larger than $k_{10\rightarrow 11}$. An enhanced reaction rate is oftentimes a reliable indicator of the presence of a substrate-directing effect [27]. Given an optimal array of ligands at palladium in **5**, the alkene insertion will afford σ-alkylpalladium(II) intermediate **11** highly regioselectively. After the C – C bond formation, **11** readily undergoes β-hydride elimination (step *v*, **11** → **12**), often without control of the double bond geometry, to release the product **13** (**12** → **14**). Importantly, both the alkene and the donor have to dissociate from the palladium(II) center in order to avoid product inhibition (step *vi*). Therefore, choosing a suitable donor group must be well-balanced for reversible binding. Reductive elimination of HX from the hydridopalladium(II) species **14** completes the catalytic cycle (step *vii*, **14** → **7**).

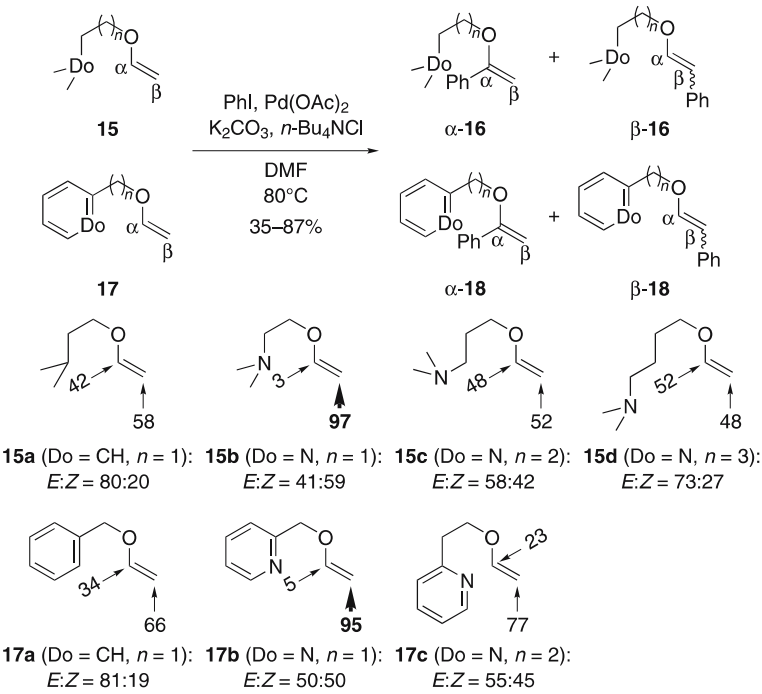
Apart from enhanced reaction rates and control of regioselectivity, the presence of a reagent-directing donor offers another advantage of eminent synthetic potential. These intermolecular Mizoroki–Heck reactions are now applicable to trisubstituted alkenes, which otherwise would react sluggishly.

4
Intermolecular C – C Bond Formation

4.1
Control of Regioselectivity in Intermolecular Mizoroki–Heck Reactions

4.1.1
Nitrogen as a Directing Group

In his seminal investigations, Hallberg nicely delineated the essential demands for achieving excellent regiocontrol in an intermolecular Mizoroki–Heck reaction [23, 24]. A series of vinyl ethers **15** and **17** was arylated under so-called Jeffery conditions [34] (**15** → **16** and **17** → **18**, Scheme 2). Substrates **15a** (n = 1) and **17a** (n = 1) devoid of a coordinating group (Do = CH) were chosen as reference systems since their electronically controlled [35] aryla-

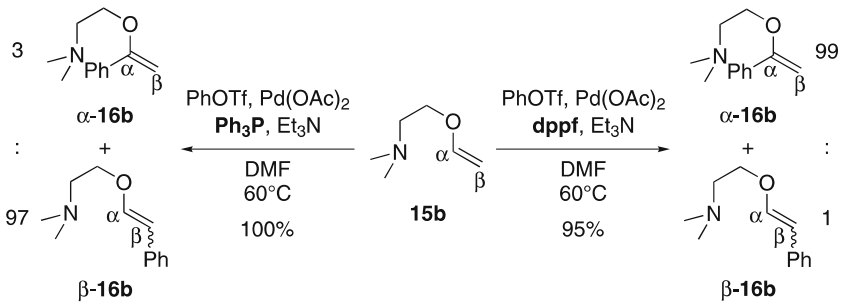


Scheme 2 Amino- and pyridyl-directed, regioselective Mizoroki–Heck reactions by Hallberg [23–26]

tion provides a mixture of regioisomers. This poor regioselectivity improved dramatically with the installation of an sp^3- [36] or sp^2-hybridized [37] nitrogen as in **15b** (Do = N, $n = 1$) or as part of a pyridyl moiety in **17b** (Do = N, $n = 1$). The selection of these donors was certainly inspired by literature precedence of the coordinating effect of these groups adjacent to C – C double bonds [36, 37]. Both substrates displayed a pronounced preference for β- rather than α-arylation. However, the mere presence of such a coordinating amino functionality is not sufficient; Mizoroki–Heck reactions of **15c** (Do = N, $n = 2$) and **15d** (Do = N, $n = 3$) as well as **17c** (Do = N, $n = 2$) with stepwise elongated tethers furnished the disubstituted alkenes **16c**/**16d** and **18c** in α-/β-selectivities comparable to those of **16a** and **18a** lacking the donor (Do = CH). This comparative investigation [24] verified the assumption that a directing amino group located in an ideal vicinity to the C – C double bond in **15** and **17**, respectively is the controlling element for the regiochemistry.

A separate experiment provided further evidence [24]: The directing effect of the tertiary amine in **15b** is almost completely overridden ($\alpha : \beta = 3 : 97$ versus $\alpha : \beta = 33 : 67$) when performing the Mizoroki–Heck reaction in the presence of an external (strong) donor such as pyridine (1.0 equiv.).

In the course of this systematic study, Hallberg discovered a remarkable peculiarity in the arylation of the standard workhorse **15b** (Scheme 3) [24]. As for the previously described Jeffery conditions (**15b** → β-**16b**, Scheme 2), high regioselectivities were also obtained with the usual Mizoroki–Heck protocol for cationic reaction conditions (**15b** → β-**16b**, Scheme 3). Interestingly, replacing the monodentate Ph_3P by a bidentate phosphane such as dppf resulted in a complete reversal of the regioselectivity (**15b** → α-**16b**, Scheme 3). Careful analysis of this puzzling observation led to an interdependence of the bite angle (P-Pd-P) of the bidentate phosphane ligand and the regioselectivity (Fig. 3). Whereas the β-selectivity remained untouched in the presence of dppm, all other bidentate phosphanes screened favored the formation of the α-product. Though only a bite angle of approximately 90°, as in dppp and dppf, ensures optimal α-selectivity, slightly deviating angles, as in dppe (< 90°) or dppb (> 90°), are less selective due to diminished stability of the diphosphanepalladium chelates.



Scheme 3 A regiochemical switch [24]

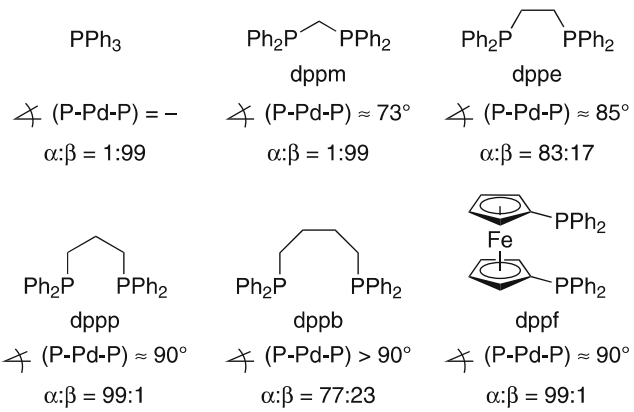
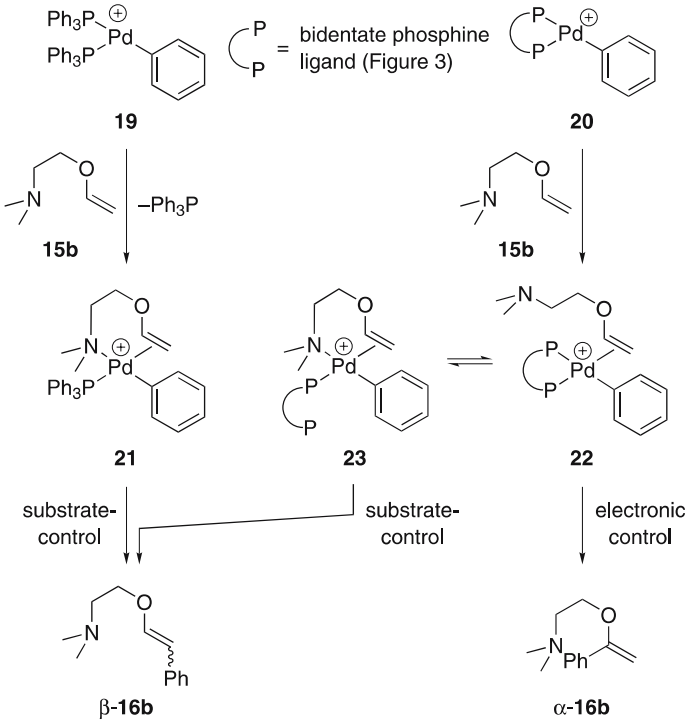


Fig. 3 Influence of the bite angle [24]

A mechanistic rationale is depicted in Scheme 4. With a monodentate phosphane ligand present, oxidative addition of a palladium(0) precatalyst into the aryl triflate generates the cationic σ-arylpalladium(II) intermediate **19**; the triflate counter ion is considered a particularly weak ligand and, therefore, is not coordinated to the electrophilic palladium(II) center. Following a reaction sequence of precoordination of the amino group and the alkene (**8** → **5**, Scheme 1), the tetracoordinate alkene-palladium complex **21** is formed (**19** → **21**, Scheme 4). Directed migratory insertion and subsequent steps liberate β-regioisomer β-**16b**.

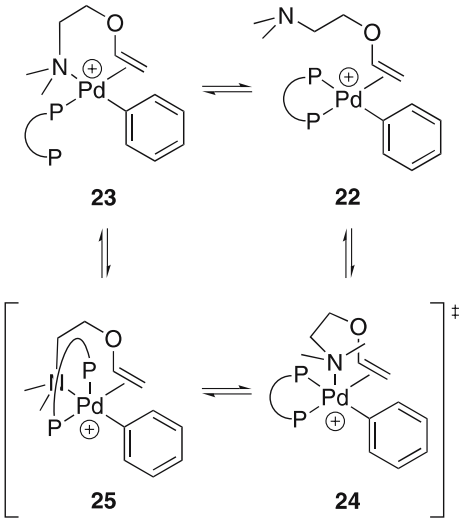


Scheme 4 Mechanistic rationale for inverted regioselectivity [24]

A different scenario applies with palladium complexed by a bidentate (chelating) phosphane. The C – C double bond of **15b** is coordinated by the cationic palladium reagent (**20** → **22**, Scheme 4); alternative precoordination of the tertiary amine by **20** is omitted for the sake of clarity. Without the amine donor coordinated to the palladium catalyst, the regioselectivity of alkene insertion is controlled by electronic (and steric) factors as in a usual intermolecular Mizoroki–Heck reaction favoring regioisomer α-**16b** [23–26]. The palladium complex **22** is in equilibrium with another tetracoordinate complex **23**, in which one of the phosphanyl groups of the bidentate diphos-

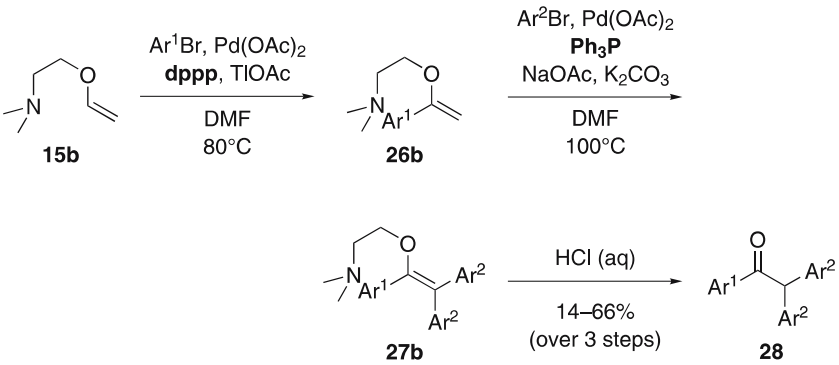
phane is substituted by the intramolecularly available amino group. Depending on the bite angle of the diphosphane and, hence, the stability of the P-Pd-P chelate, this displacement is a more- or less-facile process (bite angle $\neq 90°$) shifting the equilibrium to the left side (Scheme 4).

The current understanding suggests that the equilibrium of the square-planar complexes **22** and **23** might proceed via the pentacoordinate complex **24** by axial association of the tertiary amine. This hypothetical intermediate, in turn, is equilibrating with **25** by pseudorotational processes (Scheme 5), which is supported by literature precedence [38]. It should be noted that migratory insertion involving pentacoordinate palladium complexes such as **24** or **25** is rather unlikely [39, 40].



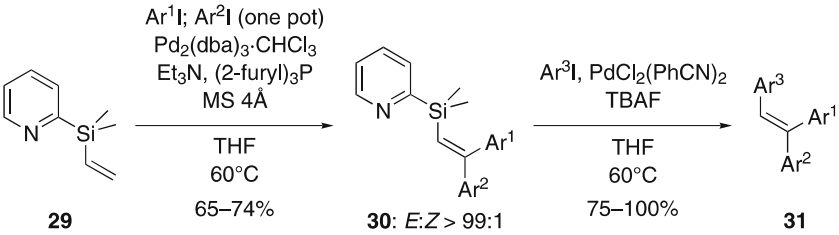
Scheme 5 Substitution at a square planar palladium complex [38–40]

This regiochemical switch found a noteworthy synthetic application [41]. Hallberg employed the simple platform **15b** for the practical two-step synthesis of triarylated vinyl ethers **27b** (Scheme 6), which furnish β,β-diarylated acetophenone derivatives **28** upon hydrolysis (**27b** → **28**). In the first step, the regiochemical controller is switched "off" by the bidentate diphosphane dppp, which ensures high α-regioselection (**15b** → **26b**). Replacing dppp by monodentate Ph_3P switches the regiocontroller "on" and allows for selective two-fold β-arylation. It proved advantageous performing α- prior to β-arylation; highly regioselective α,β- (38–70%) as well as β,β-diarylations (36–65% without hydrolysis) work equally well [41]. This reaction sequence is an impressive example of the benefits of a removable directing group enabling the three-fold arylation of a C – C double bond; these are known to be extremely sluggish in the absence of a donor.



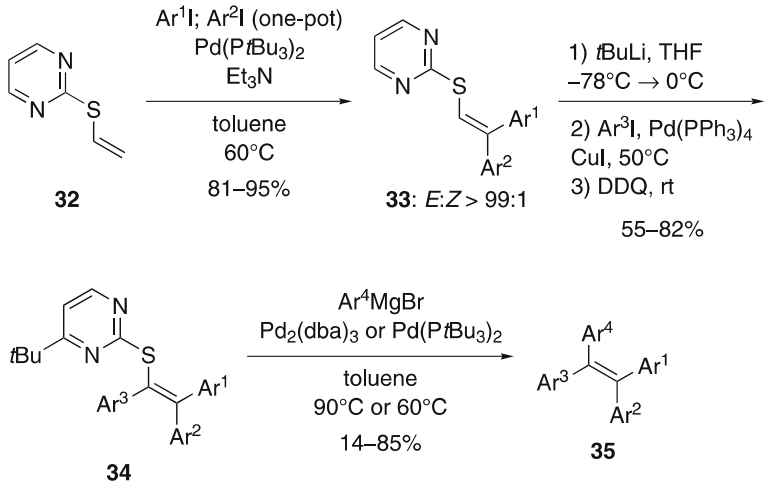
Scheme 6 Sequential amino-directed, regioselective Mizoroki–Heck arylations by Hallberg [41]

During the quest for such useful platforms, Itami and Yoshida [41–44] independently developed the two versatile starting materials **29** (Scheme 7) [45, 46] and **32** (Scheme 8) [47]. Both the 2-pyridyl and the 2-pyrimidyl group are excellent directing groups but, more importantly, these authors smartly connected these groups to the C – C double bond employing synthetically useful tethers. The silicon tether of the vinylsilane **29** is a simple placeholder for hydrogen (protodesilylation) or a useful functional group for subsequent Hiyama cross-coupling reactions [45, 46, 48]. Similarly, the C – S linkage in **32** cross-couples with Grignard reagents under palladium catalysis [47].



Scheme 7 Multisubstituted alkenes using an amino-directed Mizoroki–Heck arylation (part 1) [45, 46]

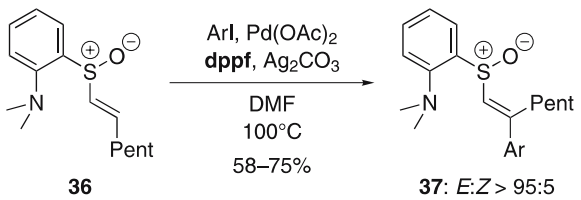
A representative reaction sequence is depicted in Scheme 7 [45, 46]. Platform **29** is subjected to a one-pot double Mizoroki–Heck arylation with two different aryl iodides, which are successively added (**29** → **30**); the β,β-diaryl vinyl silanes **30** are formed with high regio- and diastereoselectivity. Notably, cleavage of the C – Si bond, commonly observed in Mizoroki–Heck reactions of vinylsilanes, was not detected. A third aryl group is introduced by Hiyama cross-coupling of the integrated silicon group [48]. This flexible methodology



Scheme 8 Multisubstituted alkenes using an amino-directed Mizoroki–Heck arylation (part 2) [47]

offers an approach to the straightforward preparation of a library of triarylated alkenes **31** with defined double bond geometry.

Using platform **32**, Itami and Yoshida even accomplished a stereoselective route to tetraarylated alkenes **35** (Scheme 8) [47]. Again, the initial step is a one-pot double Mizoroki–Heck arylation furnishing the β,β-diaryl vinyl thioether **33** with high diastereoselection (**32** → **33**). Cleverly, the pyrimidyl moiety is employed in a directed α-lithiation of **33** forming a five-membered chelate. A second equivalent of *t*BuLi is consumed by the pyrimidyl group, which is prone to nucleophilic attack; this flaw is ironed out by final re-oxidation using DDQ. The intermediate vinyllithium is cross-coupled with a third aryl iodide under combined copper and palladium catalysis (**33** → **34**). Finally, the fourth aryl substituent is introduced by the before-mentioned palladium-catalyzed cross-coupling of the vinyl sulfide moiety and a Grignard reagent (**34** → **35**). This constitutes a modular and diastereoselective synthesis of the difficult-to-obtain class of tetraarylalkenes.

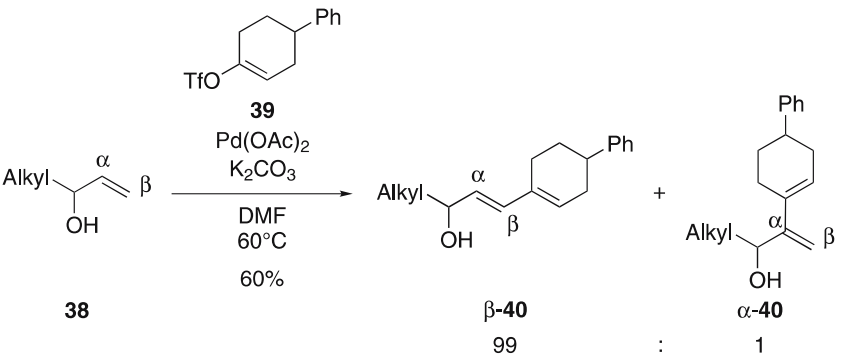


Scheme 9 Amino-directed, regioselective Mizoroki–Heck reaction by Carretero [49]

Carretero has designed the sulfoxide tether bearing a 2-anilido group as the catalyst-directing donor [49]. The otherwise capricious arylation of α,β-unsaturated sulfoxides is facilitated by the coordinating amino group and C – C bond formation occurs selectively in the β-position (**36** → **37**, Scheme 9). Nota bene: The observation by Hallberg that mono-/bidentate phosphanes are influencing reaction rate and regioselectivity (Scheme 3) [24], is not transferable to the work of Carretero.

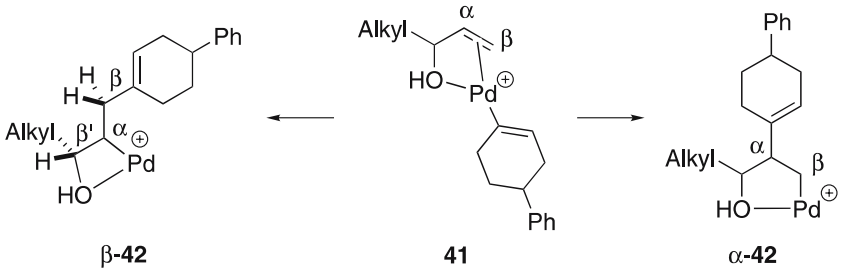
4.1.2 Oxygen as a Directing Group

Apart from this targeted design of nitrogen-based directing groups [23–26, 41–49], suitably positioned hydroxy groups, as in allylic alcohols, have always been suspected to influence the regiochemical outcome of intermolecular Mizoroki–Heck reactions [50–54]. Heck himself was the first to propose coordination of a hydroxy oxygen to a palladium(II) atom, well aware of the relatively weak oxophilicity of palladium(II) [50]. Cacchi and Ortar later reported the regioselective, hydroxy-directed vinylation of several allylic alcohols thereby producing linear conjugated dienes (Scheme 10) [51]. For example, C – C bond formation between **38** and **39** occurred with high preference for the β- rather than α-position in **38** (**38** → β-**40**). These findings were corroborated by Kang [52] and Sarpong [53]; Santelli also exploited the directing effect of a hydroxy group using an ethyleneglycol vinylether [54].



Scheme 10 Hydroxy-directed, regioselective Mizoroki–Heck reaction by Cacchi and Ortar [51]

A conclusive experiment by Cacchi and Ortar provided further evidence for their mechanistic proposal (Scheme 11) [51]. Highest β-/α-ratios were obtained in the absence of any of the conventional electron-donating additives, amines and phosphanes. Under these ligand-free conditions, it might only be the hydroxy group and, possibly, the solvent, DMF, stabilizing any

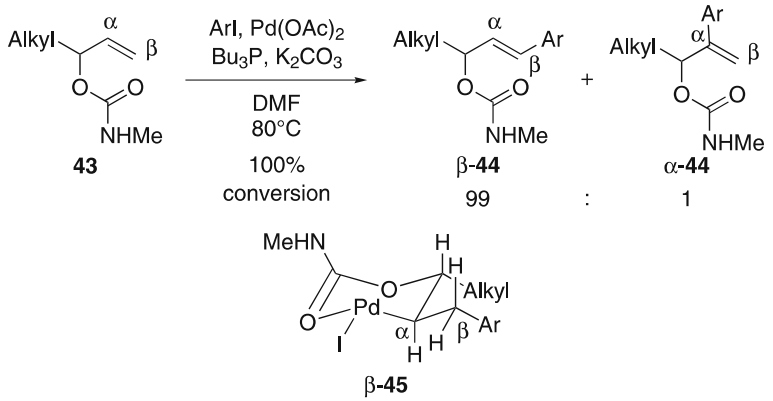


Scheme 11 Proposed directing effect of a hydroxy group [51]

palladium(II) intermediates. The rigid, hydroxy-stabilized alkene-palladium complex **41** will then undergo directed migratory insertion to afford *β*-**42** and not *α*-**42** [51].

The intermediacy of chelate *β*-**42** is also supported by the selective formation of *β*-**40**. For *σ*-alkylpalladium(II) complex *β*-**42**, there are two reaction pathways, *β*- and *β*′-hydride elimination, conceivable: formation of the conjugated diene (*β*-**42** → *β*-**40**) or the deconjugated enol (not shown). These eliminations usually require a synperiplanar orientation of the $C_{\beta} - H$ or $C_{\beta'} - H$ bond and the $C_{\alpha} - Pd$ bond. This conformation is thwarted in the former case by coordination of the synperiplanar oxygen donor ($C_{\beta'} - O$) to palladium(II) thereby hampering $C_{\alpha} - C_{\beta'}$ bond rotation; the latter scenario is, however, facile as a freely rotating $C_{\alpha} - C_{\beta}$ single bond makes two *β*-hydrogen available [52].

Temporary coordination of *N*-monosubstituted carbamates to electrophilic palladium(II) was also seen in Mizoroki–Heck reactions [55, 56]. Both *O*- (**43** → *β*-**44**, Scheme 12) [55] as well as *N*-allylated [56] carbamates were arylated with excellent regiocontrol. Tamaru proposed the six-membered chelate *β*-**45**, which is believed to result from a directed migratory insertion [55]. It remains

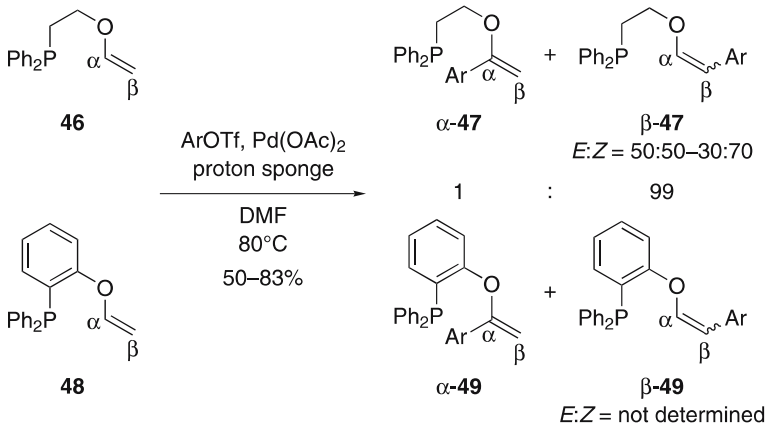


Scheme 12 Carbamate-directed, regioselective Mizoroki–Heck reaction by Tamaru [55]

unclear whether it is the oxygen (shown) or the nitrogen (not shown) functioning as the donor under the basic reaction conditions. Overman isolated stable σ-alkylpalladium(II) complexes, which are stabilized by the nitrogen of a deprotonated *N*-monosubstituted amide functionality [57–59].

4.1.3
Phosphorus as a Directing Group

In an extension of the work of Hallberg (Scheme 2) [23–26], Badone introduced the diphenylphosphanyl group to directed Mizoroki–Heck chemistry (Scheme 13) [60]. Replacing the dimethylamino group (cf. **15b**) with the phosphorus donor (cf. **46**) had the same directing effect. The arylated vinyl ethers were produced in excellent regioselectivities (**46** → β-**47**), control of the double bond geometry was again poor. The related precursor **48** gave a similar result (**48** → β-**49**) but was significantly less reactive than **46**.



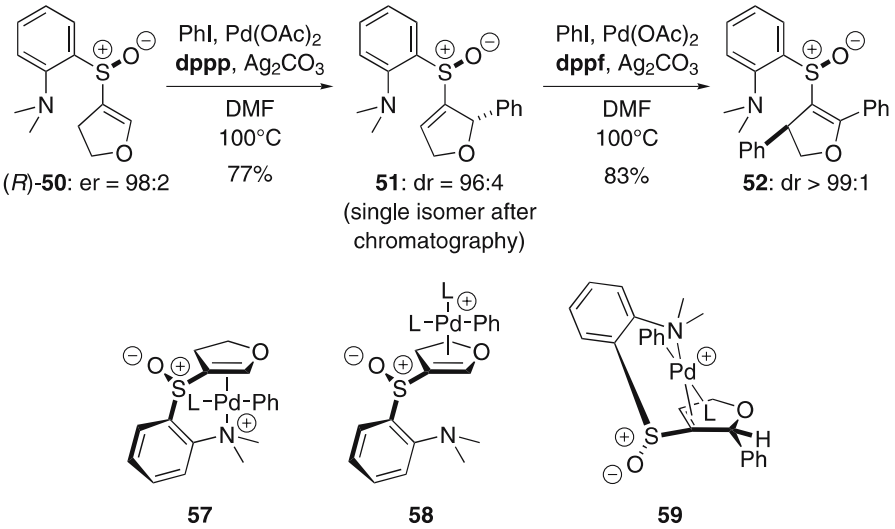
Scheme 13 Phosphanyl-directed, regioselective Mizoroki–Heck reaction by Badone [60]

4.2
Control of Diastereoselectivity in Intermolecular Mizoroki–Heck Reactions

4.2.1
Nitrogen as a Directing Group

The first to realize that these neighboring group effects in Mizoroki–Heck reactions are potential handles for controlling diastereoselectivity was Carretero [61–63]. Exploitation of the inherent chirality of the sulfoxide tether as a stereochemical controller led to the enantioenriched 2,3-dihydrofuran

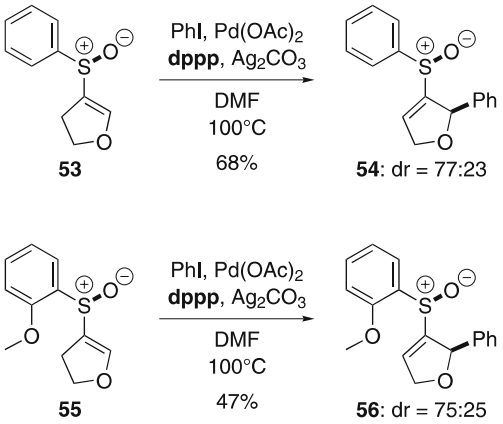
derivative (*R*)-**50**, which is decorated with an asymmetrically substituted sulfoxide tying together the furan backbone and the coordinating 2-anilido group (Scheme 14) [61]. Indeed, intermolecular Mizoroki–Heck arylation of (*R*)-**50** yields **51** with excellent diastereoselectivity.



Scheme 14 Sequential amino-directed, diastereoselective Mizoroki–Heck reaction by Carretero [61, 63]

The substrate control was unambiguously secured by Mizoroki–Heck reaction of the requisite precursor **53** devoid of the *N*,*N*-dimethylamino donor; arylation under identical reaction conditions clearly favored the opposite diastereomer with poor stereocontrol (**53** → **54**, Scheme 15). Weakening the σ-donor strength of the directing group by using oxygen (cf. **55**) instead of nitrogen (cf. **50**) also resulted in inverted diastereofacial selectivity (**55** → **56**, Scheme 15).

The high stereoselection is conceivable by means of the two diastereomeric alkene-palladium complexes **57** and **58**, respectively [61, 63]. With substrate-control operating, the C – C double bond is attacked from the *Si*-face (**57**, Scheme 14); steric control in turn would result in *Re*-face attack (**58**, Scheme 14). As already discussed, the migratory insertion is believed to involve tetra- rather than pentacoordinate alkene-palladium complexes. The complexes depicted in Scheme 14 are only to be understood as a simplified presentation since the ligand L is in reality a bidentate diphosphane. Therefore, formation of **57** might follow the pathways delineated in Scheme 5. However, other reaction pathways cannot be ruled out at this stage. One might hypothesize that coordination of the amino group is only preorganizing the

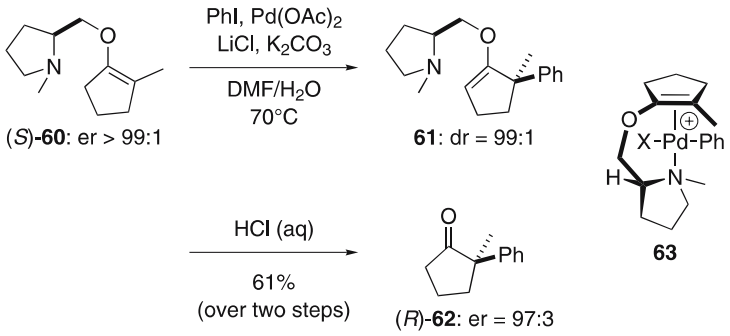


Scheme 15 Inverted diastereoselectivity for precursors devoid of a directing nitrogen [61, 63]

palladium-substrate complex followed by displacement of the directing group by the alkene itself leaving the chelating diphosphane untouched.

Carretero extended this chemistry by subjecting **51** to a second Mizoroki–Heck arylation, which shows perfect diastereoselectivity (**51** → **52**, Scheme 14) [61–63]. The complex **59** proposed by the authors is a reasonable explanation for the observed top-face attack (Scheme 14). Later, the same methodology was used for the related cyclopentene derivative [62].

Hallberg had already substantiated experimentally in his early work [23] that, if the nitrogen of the platform **15b** was incorporated into a six-membered cycle, regiocontrol was still very high. Amazingly, the modified proline-derived system (*S*)-**60** was only reported very recently (Scheme 16) [64]. The intermolecular arylation of its tetrasubstituted alkene generates a stereogenic quaternary carbon center with superb diastereose-



Scheme 16 Amino-directed, diastereoselective Mizoroki–Heck reaction by Hallberg [64]

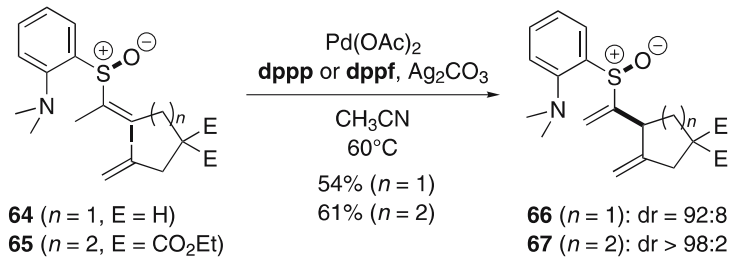
lectivity ((*S*)-**60** → **61**) and, after hydrolysis, with excellent enantioselectivity (**61** → (*R*)-**62**). This result is rationalized by the intermediacy of **63** (Scheme 16).

5
Intramolecular C – C Bond Formation

5.1
Control of Diastereoselectivity in Intramolecular Mizoroki–Heck Reactions

5.1.1
Nitrogen as a Directing Group

Carretero also succeeded in applying his auxiliary to an intramolecular Mizoroki–Heck reaction [65]. Vinyl iodides **64** ($n = 1$) and **65** ($n = 2$) cyclize in moderate yield yet with good to excellent diastereoselectivity (**64** → **66** and **65** → **67**, Scheme 17). The origin of diastereoselection still remains unclear. At least, control experiments have identified unequivocally the directing group as the decisive feature in these ring closures. As in the intermolecular variant, the diastereoselectivity decreases substantially (dr = 54 : 46) in the absence of the nitrogen donor.

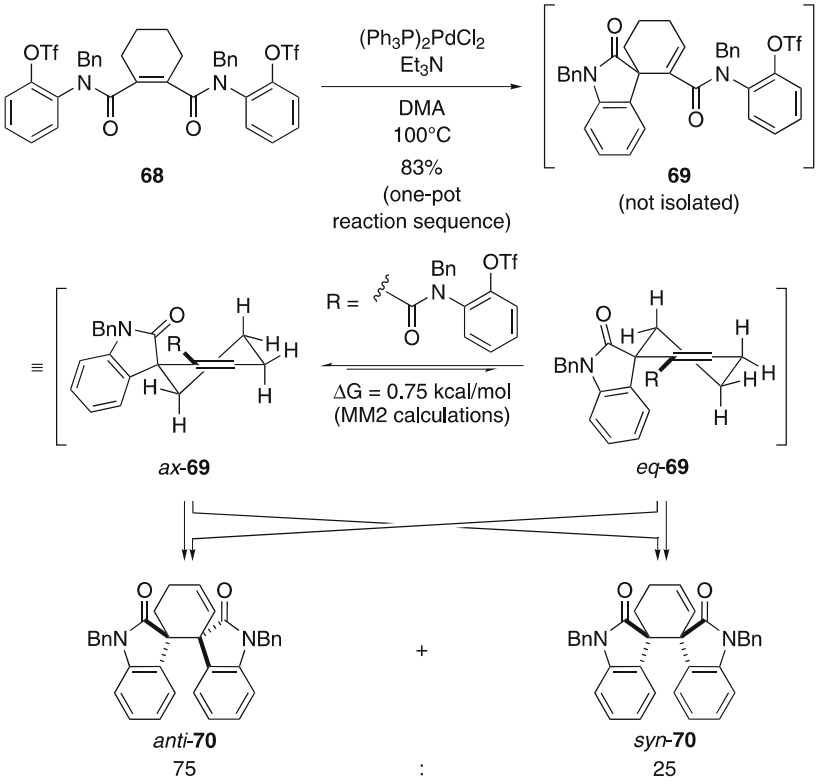


Scheme 17 Amino-directed, diastereoselective Mizoroki–Heck cyclization by Carretero [65]

5.1.2
Oxygen as a Directing Group

A less obvious case of an oxygen-directed intramolecular Mizoroki–Heck reaction was recently disclosed by Overman in the course of a mechanistic examination [66]. In order to identify the origins of diastereoselection in double Mizoroki–Heck cyclizations, several model systems were investi-

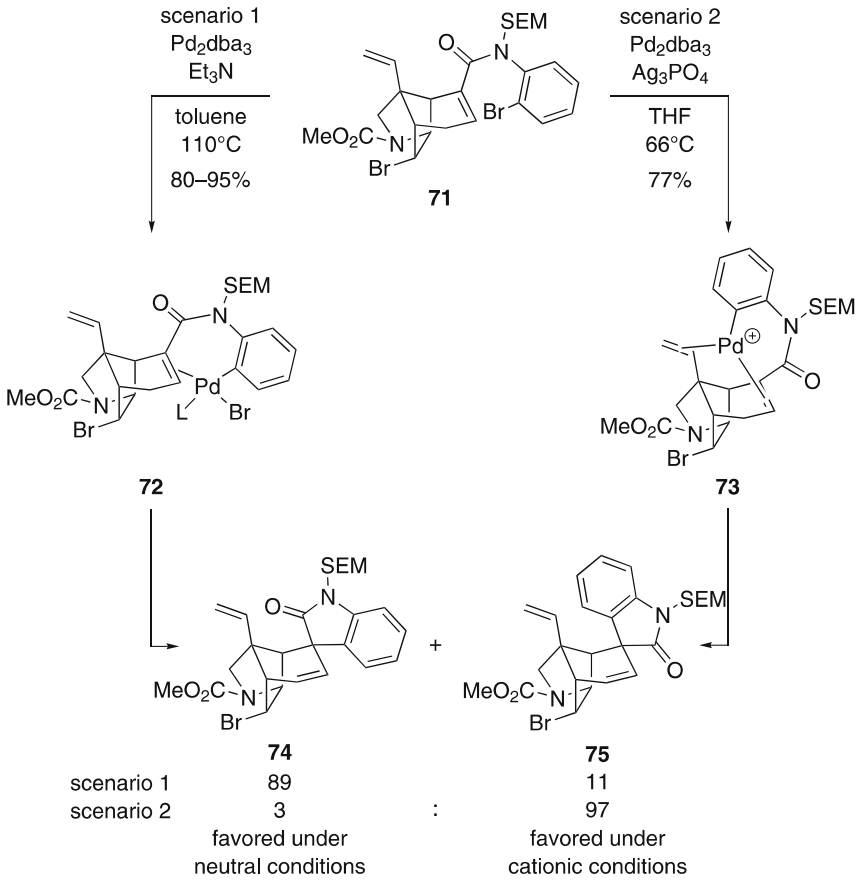
gated. For example, precursor **68** formed the diastereomeric dispirooxindoles *anti*-**70** and *syn*-**70** (dr = 75 : 25) with low stereoselection (Scheme 18). The diastereoselectivity-determining second ring closure emanates from the half-chair conformers *ax*-**69** and *eq*-**69**; top face attack (→ *anti*-**70**) is slightly preferred over bottom face attack (→ *syn*-**70**). Overman speculated that the small preference for top face attack originates from coordination of the Lewis basic carbonyl oxygen of the spirooxindole in **69** to the cationic [67] palladium atom.



Scheme 18 Double Mizoroki–Heck cyclization by Overman [66]

5.1.3
Alkene as a Directing Group

The directing structural elements discussed so far have all been σ-donors. In the context of a synthetic endeavor, Overman reported an intriguing case of a π-donor discriminating facial selectivity in an intramolecular Mizoroki–Heck reaction (Scheme 19) [68, 69]. The configuration at the oxindole quaternary carbon of gelsemine (not shown) set in this cyclization was found to be



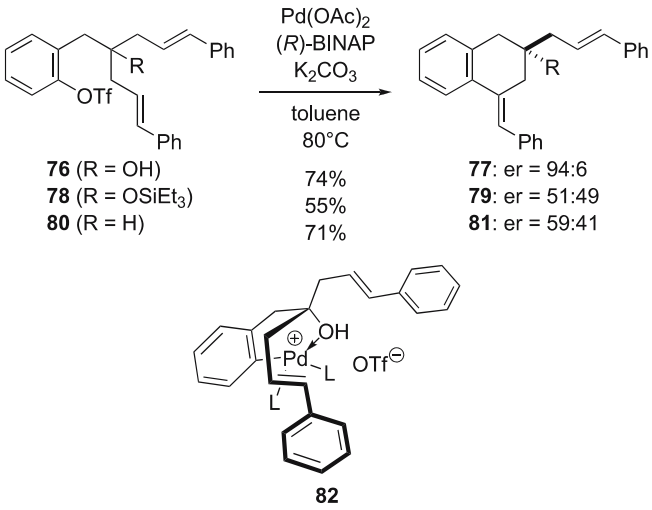
Scheme 19 Alkene-directed, diastereoselective Mizoroki–Heck cyclization by Overman [68, 69]

dependent on the presence of a halide ligand coordinated to the palladium catalyst. Under ligandless reaction conditions (in the absence of phosphane ligands, scenario 1), aryl bromide **71** was preferentially cyclized to **74** (dr = 89 : 11) with good diastereoselectivity (**71** → **74**). This stereochemical outcome is rationalized by the intermediacy of neutral [67] alkene-palladium complex **72** with a bromide ligand. Conversely, quantitative removal of the bromide ligand with a silver salt (scenario 2) generates the cationic [67] alkene-palladium complex **73**, in which the vacant coordination site is occupied by the pendant terminal alkene. This arrangement of donors resulted in a completely reversed stereoselectivity producing **75** (dr = 3 : 97) as the major diastereomer (**71** → **75**). Consistent with this proposal, no diastereoselection was seen (dr = 50 : 50) when the alkene donor was "defused" by hydrogenation prior to cyclization.

5.2
Control of Enantioselectivity in Intramolecular Mizoroki–Heck Reactions

A discovery by Oestreich indicates that a hydroxy group in a prochiral substrate is capable of controlling the level of enantioselectivity in a catalytic asymmetric Mizoroki–Heck cyclization [70–72] [also Machotta and Oestreich (2005), unpublished results]. The desymmetrizing intramolecular Mizoroki–Heck reaction [11, 14–16] of acyclic **76** provided **77** (er = 94 : 6) in an excellent enantiomeric ratio (**76** → **77**, Scheme 20). Whereas even higher enantiocontrol was seen for the corresponding methyl ether (er = 99 : 1) [Machotta and Oestreich (2005), unpublished results], hardly any was detected when subjecting the related silyl ether **78** (er = 51 : 49) to identical reaction conditions (**78** → **79**). These initial findings led to the assumption that, as proposed by Heck [50] as well as Cacchi and Orther [51], stereocontrol is governed by the hydroxy group in **76**. Further evidence was available from the cyclization of the deoxygenated substrate **80**, which produced **81** (er = 59 : 41) in almost racemic form (**80** → **81**).

On the basis of these experimental observations, Oestreich proposed a mechanism [70, 71], in which the cationic [67] σ-arylpalladium species is reversibly coordinated by the tertiary hydroxy group forming a six-membered chelate (**82**, Scheme 20). The fate of key intermediate **82** is in question since direct migratory alkene insertion involving pentacoordinate palladium is not to be expected [73]. As for many of the other alkene-



Reduce Drawings to 75%

Scheme 20 Hydroxy-directed, desymmetrizing Mizoroki–Heck cyclization by Oestreich [70, 71] and Machotta AB, Oestreich M (2005) unpublished results

palladium complexes presented in this article, the understanding of this process is vague. However, a modified scenario might be likely: coordination of the hydroxy group in **82** generates a highly ordered transition state, which allows for efficient differentiation of the formerly enantiotopic branches of **76**. Thus, a dissociative pathway seems more plausible than an associative migratory insertion. The high enantioselectivity observed for **76** could stem from the ideal vicinity of the hydroxy group and the palladium center.

6 Conclusion

Starting from the systematic work by Hallberg [24], heteroatom-directed Mizoroki–Heck reactions have been developed into a many-facetted area in synthetic organic chemistry. Several removable directing groups have been developed for the regioselective intermolecular arylation of alkenes [23–26, 41, 45, 46, 49]. Apart from achieving excellent regiocontrol, the actual advantage might be that tri- and tetrasubstituted C – C double bonds are now introduced to intermolecular Mizoroki–Heck chemistry. The synthetic potential has been demonstrated by Hallberg as well as Itami and Yoshida with a modular approach to tri- and tetrasubstituted alkenes with a defined configuration [41, 45, 46].

A further significant advancement has been accomplished by Carretero, who reported the first diastereoselective substrate-controlled Mizoroki–Heck reaction with the aid of a directing group [61–63, 65]. The same concept has been successfully applied by Hallberg to the first construction of asymmetrically substituted quaternary carbons using an intermolecular Mizoroki–Heck reaction [64].

It is known from publications by Heck [50] and others [51, 52] that an unprotected hydroxy group interferes with the palladium center in a Mizoroki–Heck reaction. Oestreich showed that such an interaction is the enantiocontrolling element in a catalytic asymmetric Mizoroki–Heck cyclization of an achiral precursor [70, 71]. This first evident example of a substrate-controlled enantioselective reaction illustrates that enantioselection is sometimes discriminated not only by the chiral catalyst but also by a suitably located donor.

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