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Functionalization of Heteroaromatic Substrates using Groups 9 and 10 Catalysts

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1.1 Introduction

A hydroarylation reaction is the formal addition of aromatic or heteroaromatic C—H bonds across an olefin C=C or an alkyne C≡C bond, as represented in Figure 1.1b,d, respectively. This C—C bond forming reaction, catalyzed by transition metals, is one of the most popular synthetic tools in metal-mediated organic synthesis to introduce alkyl or alkenyl groups at given positions of aromatic or heteroaromatic compounds. It combines a perfect atom economy, the use of simple, non-prefunctionalized reagents, and an environmentally benign design. From the point of view of the synthesis shown in Figure 1.1, it is evident that hydroarylation of olefins is an alternative route to the Friedel–Crafts alkylation (Figure 1.1a), while hydroarylation of alkynes can be considered complementary to the alkenylation of (hetero)aromatic rings (i.e., Heck and Fujiwara–Moritani reactions, Figure 1.1c). A quick comparison shows that Friedel–Crafts alkylation needs halogenated precursors, strongly acidic reagents, usually high temperatures and long reaction times, shows moderate to poor selectivity, and generates stoichiometric amounts of waste products, while Heck (or Suzuki, Sonogashira, and other couplings) also needs halogenated substrates and produces large amounts of residue. It is clear that hydroarylation provides additional simple and advantageous pathways to landmark C—C bond forming reactions.

The processes shown in Figure 1.1 are general examples of intermolecular couplings. The corresponding intramolecular versions, where the heteroaromatic ring and the olefin or the alkyne are linked by a tether, are also well known. Both processes, intra- and intermolecular, involving alkenes and alkynes, have been used as main synthetic tools for the synthesis and functionalization of a myriad of heterocycles, whose industrial and academic importance resides in the fact that they are basic scaffolds of products with biological and pharmacological activity, new optical materials, or important synthetic precursors and intermediates [1–3]. Due to the importance and the widespread use of these reactions, several reviews covering this area have been published along the years [4–28].

Catalytic Hydroarylation of Carbon-Carbon Multiple Bonds, First Edition.
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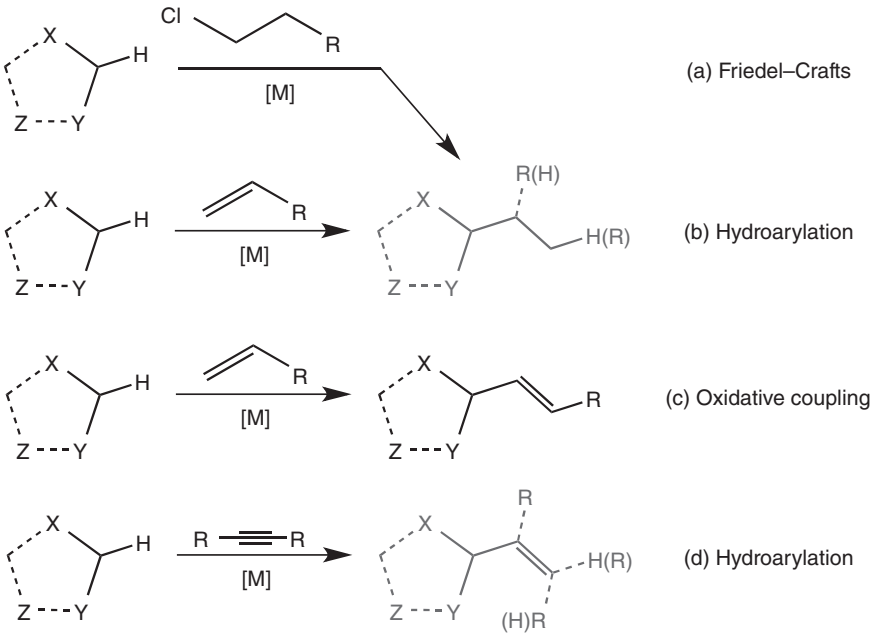


Figure 1.1 General intermolecular hydroarylation of C—C multiple bonds with (hetero)aromatic substrates and comparison to Friedel–Crafts alkylation.

An additional important aspect of the hydroarylation reaction is the selectivity of the reaction, which is closely related to the mechanism through which it takes place. Figure 1.2 exemplifies the most representative cases found for heteroarene–alkyne coupling, and a very similar mechanism scheme can be drawn for reactions involving olefins.

The reaction can take place either through alkyne activation or heteroarene activation. In the former case, vinylidene or π-complexes are formed as intermediates, and subsequent reaction with electron-rich arenes results in the formation of the vinylated derivatives, usually as a mixture of cis and trans stereoisomers. The reaction can also occur through metalation of the arene through C—H bond activation, either by oxidative addition or by concerted-metallation deprotonation. The resulting intermediates undergo migratory insertion of the alkyne into the M—C bond or the M—H bond, respectively. Protodemetalation or reductive elimination by C—C coupling afford selectively the *cis*-adducts.

The potential of this reaction was very clear from the first examples of hydroarylation of alkenes and alkynes, which were reported during 1978–1980 by Hong and Yamazaki [29–34]. In these works, the reaction of benzene (and other arenes) as solvents with $Ph_2C{=}C{=}O$ [29], ethylene [30, 34], or alkynes [31] under Rh catalysis and CO atmosphere afforded $Ph_2CHC(O)Ar$ ($Ar = C_6H_5$ in 68% yield based on ketene; other aryl groups in 53–57% yield), styrene (yields up to 9170% based on Rh atom), and stilbenes (around 45% yield based on alkyne), respectively, among other byproducts [33]. The processes are shown in Figure 1.3a–c. While the formation of the substituted acetophenone and

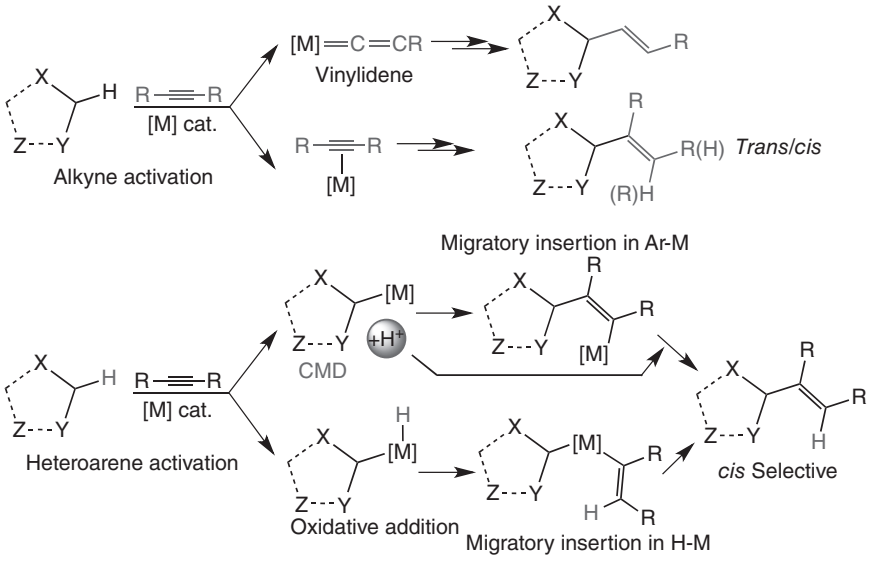


Figure 1.2 Hydroarylation of alkynes: mechanisms and selectivity of the resulting compounds.

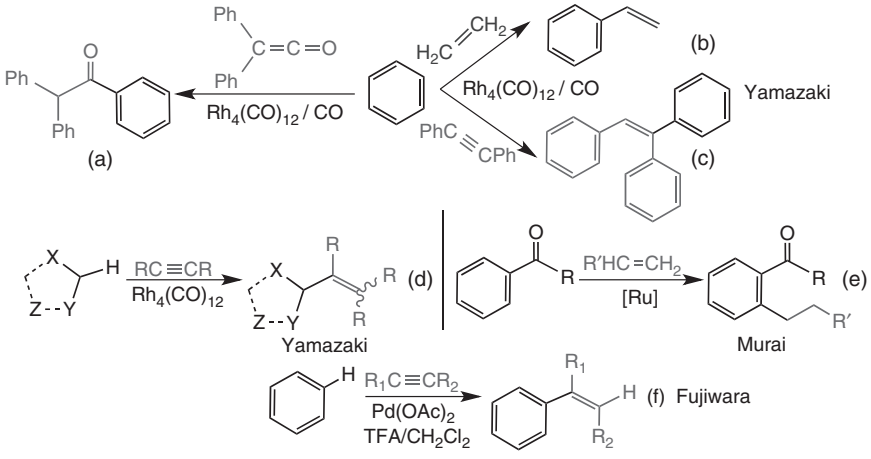


Figure 1.3 Examples of seminal hydroarylation reactions.

stilbenes are true hydroarylations, the production of styrene is formally a Fujiwara–Moritani oxidative coupling. The coupling with alkynes was extended to heteroarenes such as furan (80% yield; 41–86% for substituted furanes), thiophene (48%) and *N*-methylpyrrole (31%), as shown in Figure 1.3d [32]. In 1993, Murai and coworkers described the regioselective *ortho*-alkylation of acetophenones with different alkenes (Figure 1.3e), catalyzed by Ru-complexes, a milestone reaction considered a paradigm of atom- and step-economy [35]. This work was also one of the former examples of chelation-assisted functionalization, and paved the way for future research in the area. It is also worth mentioning the

work of Fujiwara and coworkers, who in 2000 reported a very efficient addition of simple arenes to alkynes catalyzed by Pd(II), Pt(II), or other electrophilic metals. The reaction takes place in a mixture of CF_3CO_2H (which increases the electrophilicity of the catalyst) and other solvents, and affords unusual *trans*-hydroarylated compounds under kinetic control (Figure 1.3f) [36].

This chapter aims to cover the most relevant literature on hydroarylation reactions, catalyzed by transition metals from groups 9 and 10, involving heteroaromatic substrates. In particular, only hydroarylation reactions involving challenging cleavage of heteroaryl C—H bonds will be considered, excluding most of those dealing with aryl halides and/or arylboronic acids. The chapter has been organized taking into account the nature of the heterocycle to be functionalized, since this type of classification gives to the reader an overview of how many different structural motifs are accesible starting from each individual ring; that is, the versatility of each substrate. Therefore, furans, thiophenes, indoles, pyrroles, pyridines, and other miscellaneous heterocycles will be described separately.

1.2 Thiophenes, furans, and Related Heterocycles

Hong *et al.* [32] reported in 1980 that under an atmosphere of CO the catalyst $Rh_4(CO)_{12}$ is able to achieve the activation of aromatic C—H bonds in five-membered heteroarenes and, in this way, promote the hydroarylation of alkynes. Both unsubstituted and 2-substituted furans react at the α-position (Figure 1.4a). When the reaction is performed with an unsymmetrical alkyne (1-phenylpropyne), the process is regioselective, obtaining the isomer with the phenyl group attached to the same C of the alkene as the furyl ring. The CO pressure must be higher than 10 kg/cm^2 in order to avoid cyclotrimerization of the alkynes, and furan is added in great excess (acting as the solvent). If both *α*-positions are occupied by substituents (2,5-dimethylfuran), then the functionalization takes place at the ß-position, although the yield (40%) is lower than that of mono-*α*-substituted furans. All these reactions yield vinyl derivatives as a mixture of *Z* and *E* isomers, enriched in the *Z* isomer in all cases. The authors propose that the *E* isomer is first formed, but after some time the *Z* isomer becomes predominant in the mixture since it is thermodynamically more stable. The same catalytic system was applied to thiophene to obtain the corresponding 2-vinylated heterocycle (Figure 1.4b). Competitive experiments were carried out in order to determine the relative reactivity of various heterocycles. Furan was found to be more reactive than thiophene, which in turn is more reactive than

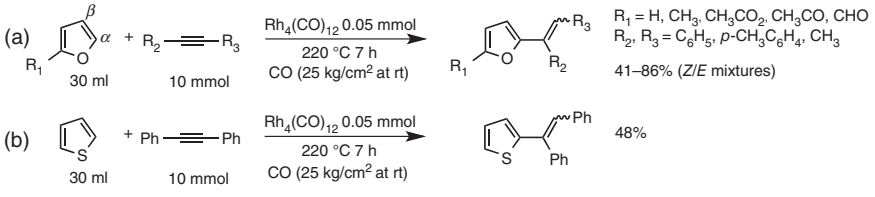


Figure 1.4 Hydroarylation of alkynes under Rh catalysis (yields are based on alkyne).

N-methylpyrrole. All of these heteroaromatic substrates are more reactive than benzene toward acetylenes [32].

As previously mentioned, the group of Fujiwara was pioneer in developing hydroarylation reactions using alkynes [36]. The year 2000 saw the publication of several seminal papers dealing with this topic, which describe the efficient hydroarylation of alkynes and alkenes with electron-rich aromatic substrates using catalytic amounts of Pd(II) or Pt(II) compounds, in solvent mixtures containing trifluoroacetic acid (HTFA), and both inter- and intramolecular transformations were reported [36, 37]. These reactions are proposed to proceed through alkyne-activation pathways by coordination to cationic and electrophilic complexes of the metals. In the same year the Fujiwara group dedicated another work to heterocycles, making use of the same catalytic process [38]. From a number of reports of detailed exploration of the reactivity of pyrrole and indole derivatives, a single example of the functionalization of a furan derivative is presented (Figure 1.5a): 2-methylfuran adds to an alkynoate at room temperature in the presence of catalytic $Pd(OAc)_2$ (5%) in acetic acid, affording exclusively the *Z*-heteroarylalkene. The addition of heteroaromatic compunds to alkynoates likely follows the mechanism outlined in Figure 1.5b. The formation of intermediate **A** proceeds through electrophilic metalation of the aromatic C—H bond with the cationic Pd(II) species $[PdOAc]^+$, and, after that, the coordination of the alkyne affords **B**. The *trans* insertion of the C—C triple bond to the σ-aryl-Pd

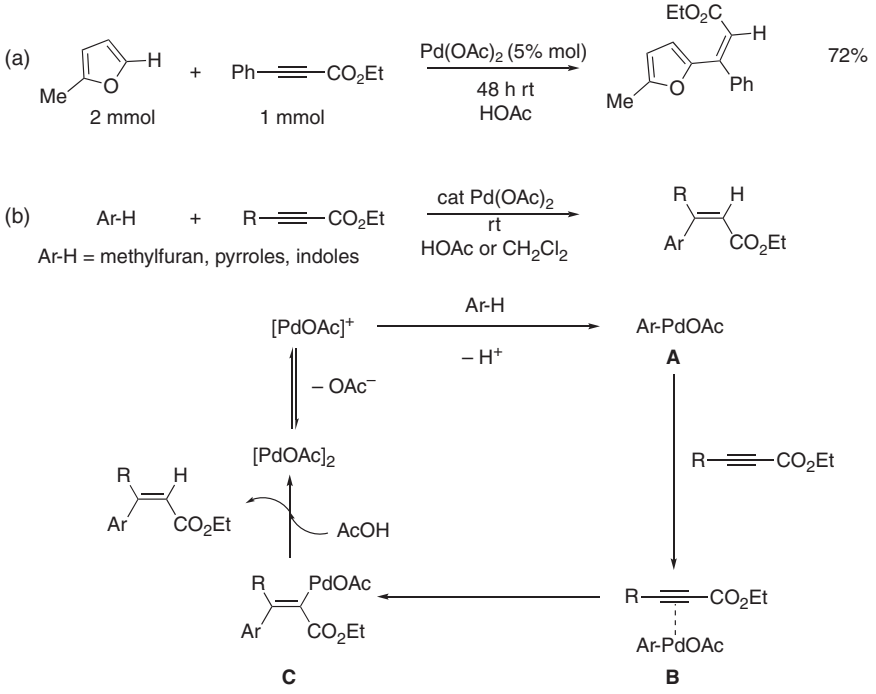


Figure 1.5 Hydroarylation of ethylphenylpropiolate with 2-methylfuran (a) and possible mechanism (b).

bond results in the vinyl complex **C**, which upon protonation by AcOH releases the *cis*-heteroarylalkenes.

Several years later Kitamura revisited the reactions between heteroarenes and propiolates, this time using a Pt(II) catalyst instead of Pd(II), following the assumption that Pt(II) was more active than Pd(II). Both thiophenes [39] and furans [40] react with ethyl propiolates or propiolic acids using K_2PtCl_4 and AgOTf under strong acidic conditions: the former in HTFA, and the later in acetic acid (AcOH). The reactions take place preferentially at C2, but when this position is already substituted the addition of the alkene occurs at C3. In contrast to the reaction catalyzed by $Pd(OAc)_2$ [38], in the reaction of 2-methylfuran with ethyl phenylpropiolate two molecules of furan are added to the triple bound by means of two consecutive hydroarylation transformations (Figure 1.6a). However, in the case of 2,5-dimethylfuran, the mono-adduct is obtained as an *E*/*Z* mixture (Figure 1.6b). When adding terminal ethyl propiolate to 2,5-dimethylfuran, only one hydroarylation takes place yielding the *Z* isomer. The second addition of the heterocycle to the double bond requires higher temperatures in order to take place (50 °C vs 30 °C) (Figure 1.6c).

In the reactions with thiophenes, the alkynes undergo a double hydroarylation (Figure 1.7a–c). The hydroarylation possibly follows an electrophilic aromatic substitution mechanism, as illustrated in Figure 1.7d. The process starts with the interaction between the alkyne and a cationic platinum species **A** (formed from the platinum precatalyst and AgOTf by ion exchange), which activates the alkyne (**B**). Then, the heteroarene attacks the triple C—C bond, forming a Wheland intermediate **C**. Proton release affords vinyl platinum complex **D**, which after protonation by TFA or HOAc produces the heteroarylacrylate **E**. A second hydroarylation can then take place by subsequent activation of the alkene fragment in **E**

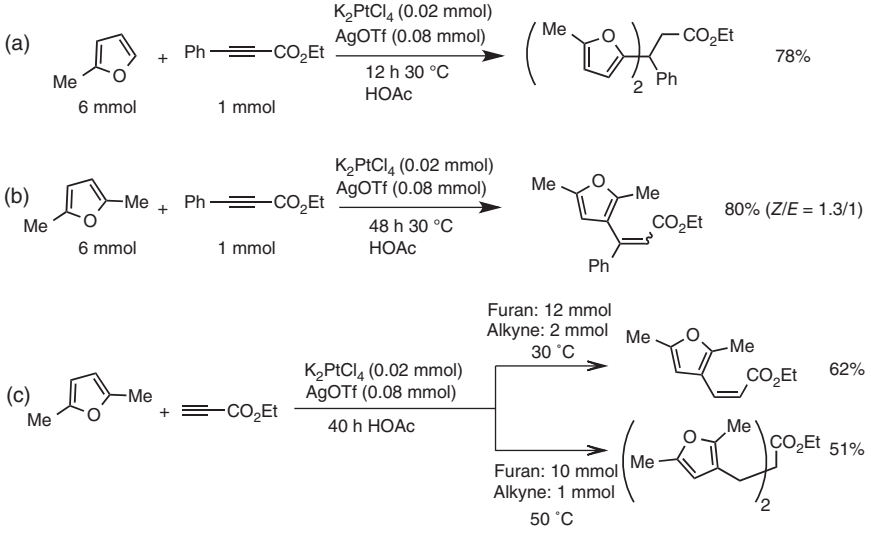


Figure 1.6 Reactions between ethylpropiolates and furans.

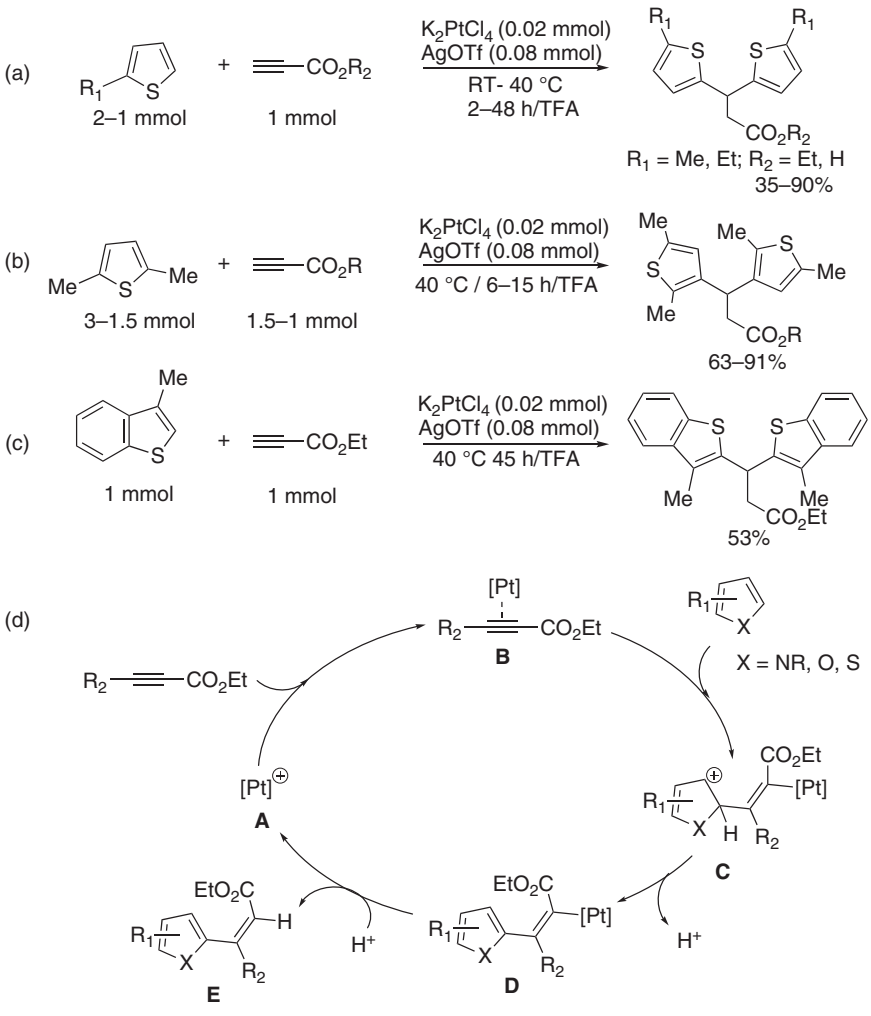


Figure 1.7 Reactions between ethylpropiolates and thiophenes, and mechanistic proposal.

by interaction with platinum cationic species, followed by heteroarene attack and protonation, yielding the final double-hydroarylation product.

As part of a study on hydroarylation reactions of ethyl phenylpropiolate with heterocycles, catalyzed by the chelating dicarbene Pd(II) complex shown in Figure 1.8 (**I** and $AgBF_4$ in HOAc), Biffis and coworkers [41] applied their optimized catalytic system to the same substrates explored by Fujiwara in order to compare the effectiveness of the two different catalytic systems. 2-Methylfuran reacted with the alkyne yielding a mixture of the *Z*-vinylated derivative and the diaddition product. Conversion of thiophene derivatives using the dicarbene Pd catalyst precursor **I** was not successful, showing that this system is clearly less effective than that reported by Fujiwara.

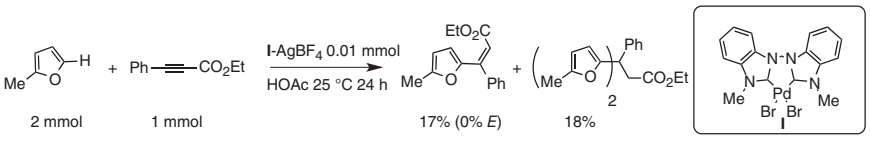


Figure 1.8 Hydroarylation of ethyl phenylpropiolate using a dicarbene Pd(II) complex.

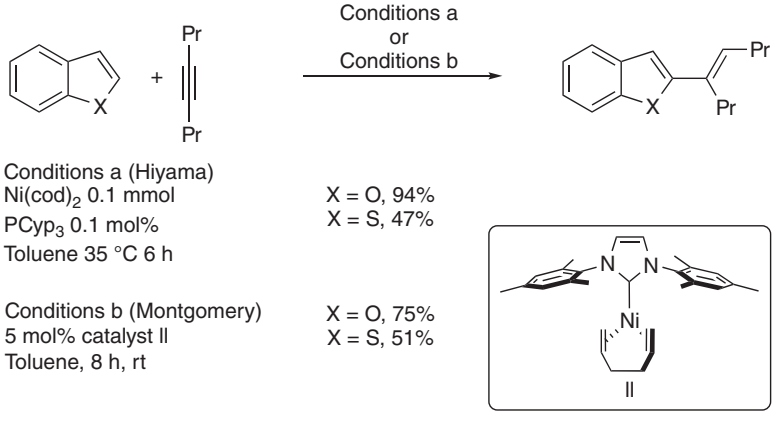


Figure 1.9 Ni-catalyzed hydroarylation of alkynes.

The group of Hiyama was interested in the development of nickel catalysts for hydroarylation reactions of unactivated alkynes under mild catalysis. In 2006, they reported the hydroarylation of 4-octyne with benzofuran and benzothiophene, which exclusively took place at the C2 position using $Ni(cod)_2$ and tricyclopentylphosphine ($PCyp_3$) as a ligand (Figure 1.9, conditions a) [42]. Later, in 2015, the group of Montgomery offered an alternative procedure using Ni(0)-NHC complexes as pre-catalysts (Figure 1.9, conditions b) [43].

The group of Yoshikai explored the use of a Co(II) catalyst in conjunction with a Grignard reagent, triarylphosphine ligand, and pyridine in order to achieve the hydroarylation of internal alkynes with heteroaromatic imines (Figure 1.10) [44]. Their strategy consisted in making use of an imine as a directing group for the C—H functionalization, improving its effectiveness by exploiting the chelation-assistance effect, and also allowing for the consecutive transformation of the initial product of hydroarylation. The alkenylation of a benzofuran derivative with 4-octyne afforded exclusively the *E* isomer, while the isomerization of

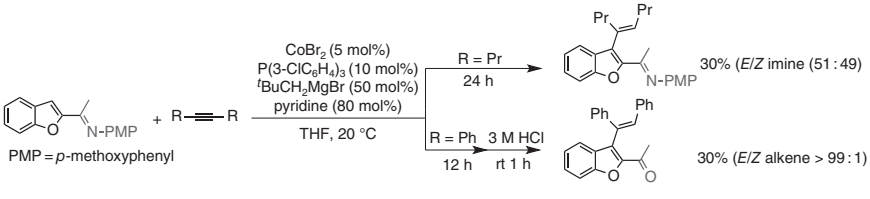


Figure 1.10 Imine as an effective directing group for the functionalization of benzofuran.

the imine moiety (E/Z 51 : 49) took place. The coupling with diphenylacetylene afforded the corresponding ketone by imine hydrolysis under acidic conditions, predominantly as the *E* isomer.

Thiophenes have also been subjected to hydroarylation reactions of unactivated internal alkynes, such as 3-hexyne and diphenylacetylene. Inoue reported in 2005 the use of a dinuclear palladium complex that enabled high stereo- and regioselectivities, producing *E*-2-alkenylthiophenes [45]. The catalyst of choice is $[Pd_2Me_2(\mu\text{-}OH)(\mu\text{-dpfam})]$ (dpfam = *N*,*N*′-bis[2-(diphenylphosphino)phenyl] formamidinate), shown in Figure 1.11. The procedure tolerates the presence of ketone and ester R_1 groups, but not of aldehyde.

Fujiwara suggested that intramolecular reactions could be more efficient than the corresponding intermolecular processes [36, 46]. The intramolecular hydroarylation of the triple bond of dibenzofurane alkynoates yielded selectively the kinetically favored six-membered rings by *endo*-cyclization (instead of the five-membered ones by *exo*-cyclization), as a mixture of regioisomers (Figure 1.12).

Sames and coworkers [47, 48] discovered that $PtCl_4$ was a better catalyst for intramolecular hydroarylation reactions of arene-alkyne (arene-yne) substrates than those previously described by Fujiwara using Pd(II) and Pt(II) [36, 46]. Alkynoate esters formed a fused furo-dihydropyran (the *exo*-cyclization product) in good yield (57% $Z/E = 1:1$) with $PtCl_4$ (Figure 1.13). $PtCl_2$ was ineffective and $PtCl_4$ was superior to $Pd(OAc_2)$ in HTFA/AcOH.

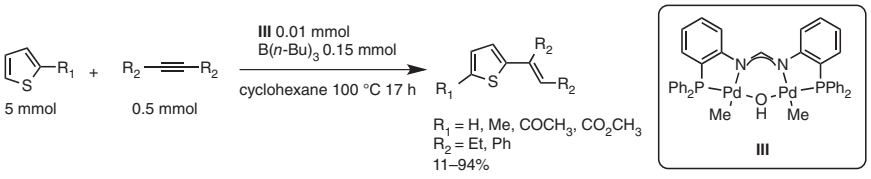


Figure 1.11 Hydroarylation of unactivated alkynes catalyzed by a Pd(II) complex.

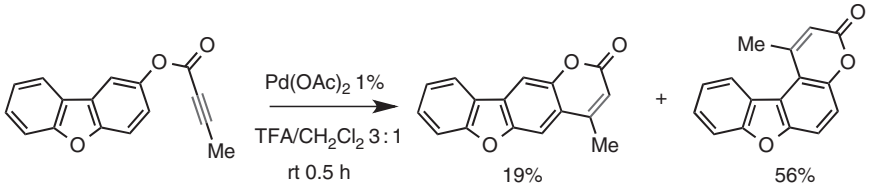


Figure 1.12 Intramolecular hydroarylation of alkynoates using $Pd(OAc)_2$ as the catalyst precursor.

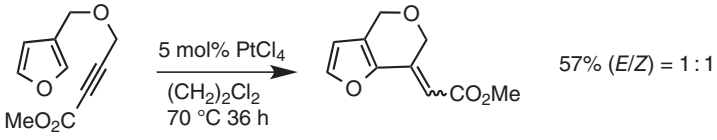


Figure 1.13 Intramolecular hydroarylation of a furan-yne substrate.

Kitamura and Otsubo applied this strategy to the functionalization of benzofurans in order to obtain angelicins, valuable materials for photobiological applications [49]. They reported the intramolecular hydroarylation of 4-benzofuranyl alkynoates containing different substituents R_1 in the presence of $Pd(OAc)_2$ in $HTFA/CH_2Cl_2$ (Figure 1.14). The angelicin derivatives were obtained in more than 70% yield, and HTFA was essential for the reaction to occur probably because it promotes the formation of highly reactive $[Pd(TFA)]^+$ species.

Unactivated terminal alkenes can also take part in intramolecular hydroarylations. In 2002, Fürstner and Mamane explored the formation of polycyclic structures by intramolecular hydroarylation catalyzed by $PtCl_2$ [50]. They reported the formation of naphthothiophene by 6-*endo*-dig cyclization of 2-(2-ethynylphenyl)thiophene (Figure 1.15a). In 2004, formation of the same structural core using other electrophilic metal salts as catalysts was explored [51]. Surprisingly, $GaCl_3$ and $InCl_3$ proved to be very effective and superior in their performance to $PtCl_2$ (Figure 1.15b). Lee's group reported the platinum-catalyzed synthesis of naphthalenes from 2-alkynyl cinnamates by 6-*endo* cyclization. Among them, 5-ethoxycarbonylbenzofuran was obtained from the hydroarylation of a terminal enyne (Figure 1.16) [52].

Furylalkynes are valuable starting materials that can sometimes exhibit divergent reactivity. The group of Echavarren has extensively studied this topic and the mechanisms involved in the formation of the different products. 5-(2-Furyl)-1-alkynes, containing either ether or malonate functionality, react in acetone and with $PtCl_2$ as a catalyst to afford mixtures of phenols (Figure 1.17a)

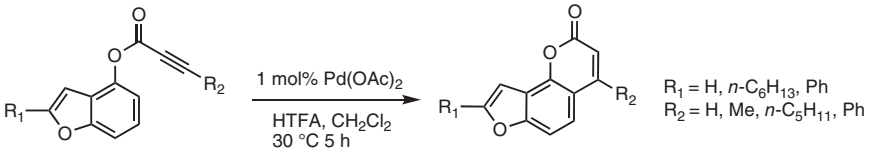


Figure 1.14 Synthesis of angelicin derivatives by intramolecular hydroarylation of benzofuran.

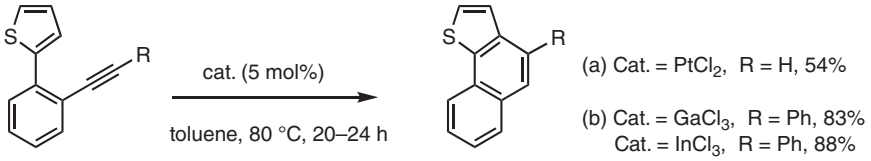


Figure 1.15 Intramolecular hydroarylation of 2-(2-ethynylphenyl)thiophene.

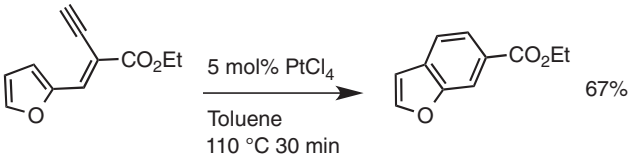


Figure 1.16 Intramolecular hydroarylation of terminal enynes catalyzed by $PtCl_4$.

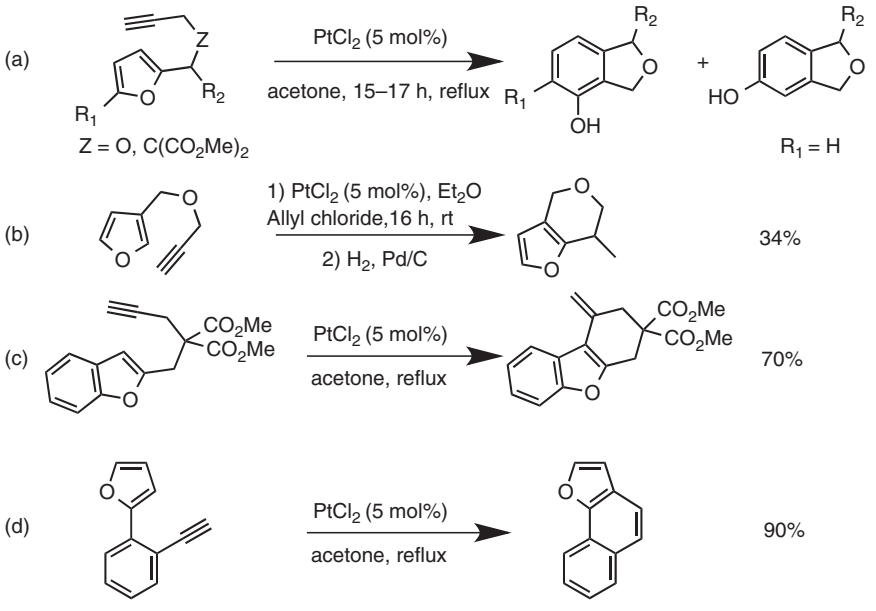


Figure 1.17 Intramolecular reactions of furylalkynes catalyzed by $PtCl_2$.

[53, 54]. These reactions involve intramolecular cyclization and further complex structural rearrangements, whereas 3-furylmethyl propargyl ether undergoes cyclization (Figure 1.17b). The product is hydrogenated to avoid polymerization. The role of the additive allyl chloride is not clear. A benzofuran malonate derivative also undergoes *exo*-cyclization (Figure 1.17c). Finally, the intramolecular cyclization of ethynylphenylfuran to yield naphthofuran was also reported (Figure 1.17d).

Gunnoe and coworkers reported in 2008 the hydroarylation of simple ethylene using a bipyridine Pt(II) complex (Figure 1.18), enabling the regioselective formation of 2-ethylfuran with 76 turnovers after 16 h [55]. Traces of 2,5-dialkylated products were also observed.

The hydroarylation of styrene and its derivatives has been reported. The group of Hiyama [56] made use, once again, of a Ni(0) catalyst precursor in combination with the NHC-ligand IMes (IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) to develop the hydroarylation of styrene with benzofuran (Figure 1.19a). Sigman and coworker reported the hydroheteroarylation of vinyl phenols catalyzed by Pd(0) with phosphines as ancillary ligands, and base and butyl

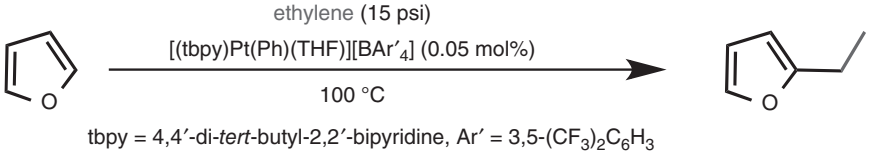


Figure 1.18 Hydroarylation of ethylene catalyzed by a bipyridine Pt(II) complex.

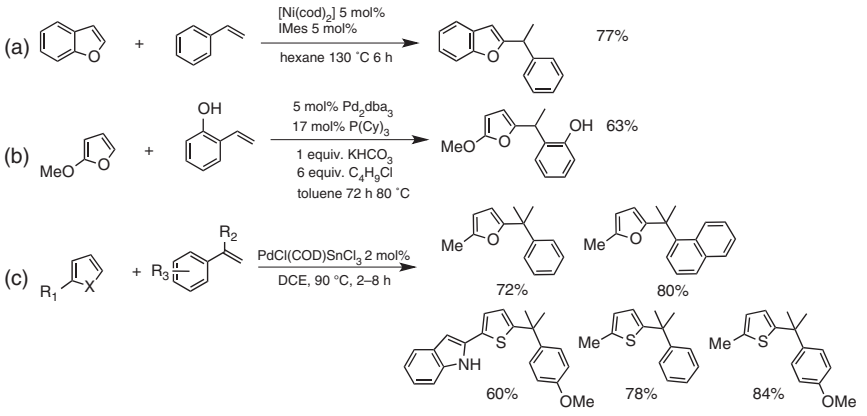


Figure 1.19 Examples of hydroarylation of styrene and styrene derivatives.

chloride as the H source (Figure 1.19b) [57]. The hydroarylation of α-methyl substituted aryl alkenes is challenging because they are prone to dimerize or polymerize in the presence of Lewis acids [58]. But, bimetallic catalysis successfully allowed the functionalization of heteroarenes with α-methyl substituted aryl alkenes using the catalyst $PdCl(SnCl_3)(COD)$ (COD = 1,5-cyclooctadiene), which is air- and moisture-stable (Figure 1.19c). This high catalytic performance is remarkable because, individually, Pd(II) and Sn(II) species were ineffective. However, no explanation was provided for this feature. In the case of 2-(thiophen-2-yl)-1*H*-indole, only alkylation on the thiophene ring was observed. All reactions shown in Figure 1.19 were regioselective: only Markovnikov products were obtained with selectivity at the C2 position of furan, benzofuran, and thiophene.

Hartwig and coworker developed an asymmetric Ir-catalyzed intermolecular hydroarylation of bicycloalkenes [59]. Furans and thiophenes with different substituents reacted with norbornene in the presence of $[IrCl(coe)_2]_2$ (coe = cyclooctene) and a chiral bisphosphine ligand in good yields (Figure 1.20). Reactions of thiophenes proceeded with high enantioselectivity, while the enantiomeric excess only reaches 78% in the case of furans. Under the same reaction conditions, couplings with norbornadiene afforded mixtures of products. Apart from the desired alkylated product, oxidative homocouplings as well as the reduction of the double bond of the incorporated fragment were detected. By increasing the concentration of the alkene (up to 2.5 equiv. instead of 1.2), the amount of product formed by homocoupling of the heteroarene was reduced, and thus the yields were increased (doubled for the benzothiophene), although no further explanations were provided about this fact.

Inspired by the hydroarylation of styrenes and benzofurans reported by Hiyama and coworkers [56], the group of Sames developed the catalytic intramolecular alkylation of benzofurans, aiming to obtain structural analogs to *Iboga* alkaloids, of important pharmaceutical activity [60]. Two examples, depicted in Figure 1.21, were successful, with isolated yields of 74% and 38%. The lower yield for the latter example may result from greater steric hindrance of the

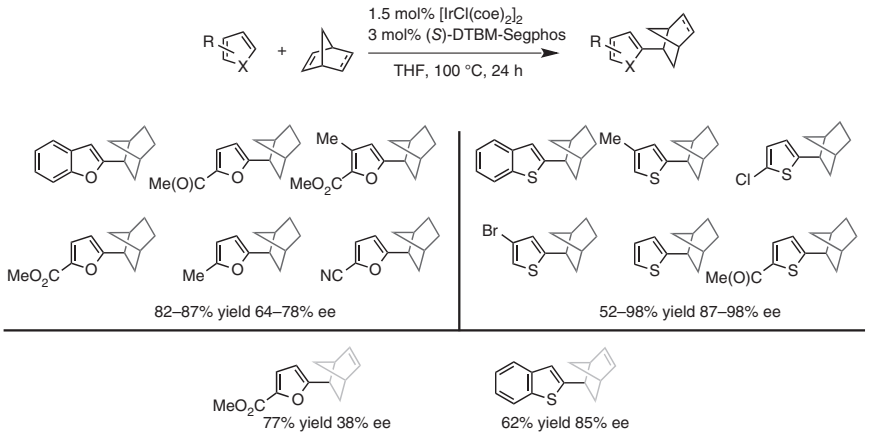


Figure 1.20 Enantioselective hydroarylation of bicycloalkenes with heteroarenes using an Ir catalyst.

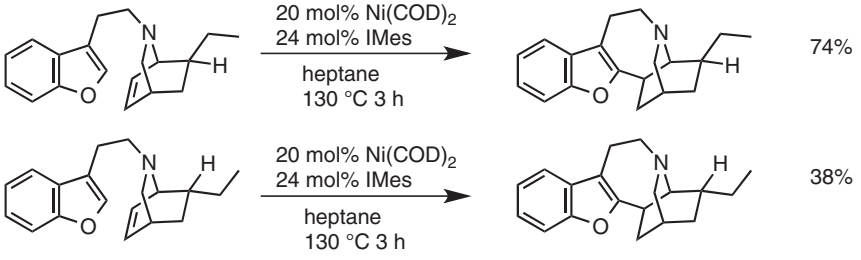


Figure 1.21 Intramolecular hydroarylations affording *Iboga* alkaloid benzofuran analogs using a Ni catalyst.

ethyl group toward the amine in the *exo*-epimer, thus preventing the amine from obstructing the catalytic cycle. Moreover, the ethyl group in the *exo*-epimer could favor the most suitable configuration of the N atom of the amine for the cyclization. The corresponding intermolecular alkylation does not take place under these conditions, which proves the suitability of this method.

The group of Hartwig explored the hydroarylation of unactivated terminal alkenes with heteroarenes, to afford the linear alkylation products, using the Ni-NHC catalytic system shown in Figure 1.22 (IPrMe = 4,5-dimethyl-*N*,*N*′-bis (2,6-diisopropylphenyl)imidazol-2-ylidene; IPrOMe = 4,5-dimethoxy-*N*,*N*′-bis (2,6-diisopropylphenyl)imidazol-2-ylidene) [61]. The production of linear products with non-functionalized olefins is uncommon. With benzofurans, the reaction was regioselective toward the C2 position. Furan afforded a 1 : 1 mixture of C2-mono- and C2,C5-dialkylation products. On the other hand, C2-substituted rings afforded selectively the C5-alkylated derivatives. The presence of potential directing groups (bearing a coordinating O atom) at C2 or C3 did not alter the regioselectivity. After fine-tuning the reaction time, temperature, and catalyst loading, substrates containing functional groups such as carbonyl groups, boronate esters, or siloxysilanes were efficiently functionalized.

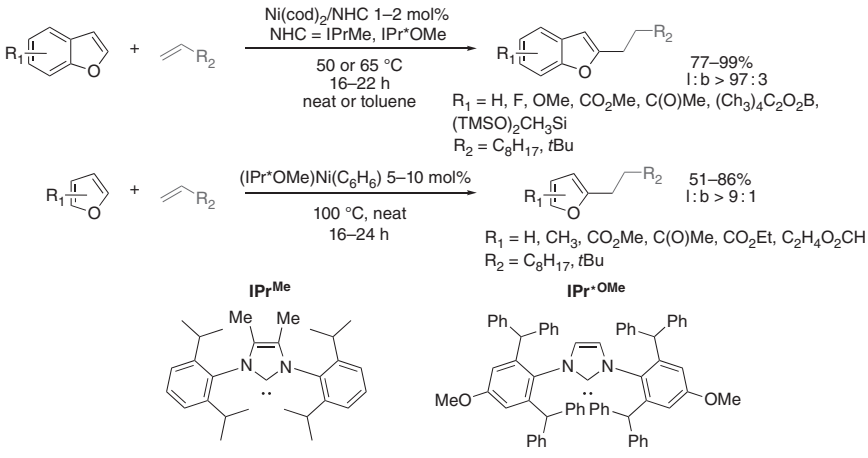


Figure 1.22 Hydroarylation of alkenes with furan and benzofuran derivatives.

When tolerated by the functional group, the addition of NaO^{t}Bu increases the yields because it prevents isomerization of the terminal alkene to the internal alkene.

The formation of branched alkylated products opens the door for the analysis of asymmetric hydroarylations. It was recently reported that a hydroxoiridium complex with a chiral diene ligand based on the tetrafluorobenzobarrelene (tfb) framework is able to catalyze the asymmetric hydroarylation of vinylethers with heteroarenes (Figure 1.23) [62]. Making use of a sulfonylamide as a directing group, branched alkylated furan and thiophene derivatives were obtained in good yield and excellent enantiomeric excess.

Chelation assistance has enabled the alkylation (using olefins) and alkenylation (using alkynes) of thiophenes at the C3 position. Several works in recent years make use of pyridine as a directing group, and thus describe the functionalization of 2-(thiophen-2-yl)pyridine (Figure 1.24). Yoshikai and coworkers reported the hydroarylation of 4-octyne with thiophene using a catalytic system comprising $CoBr_2$, $PMePh_2$, and the Grignard reagent MeMgCl, as shown in Figure 1.24a. The E/Z ratio was higher than 99 : 1 [63]. A better yield was achieved by the Chang group using the rollover cyclometalation strategy using $Rh(acac)_3$ in

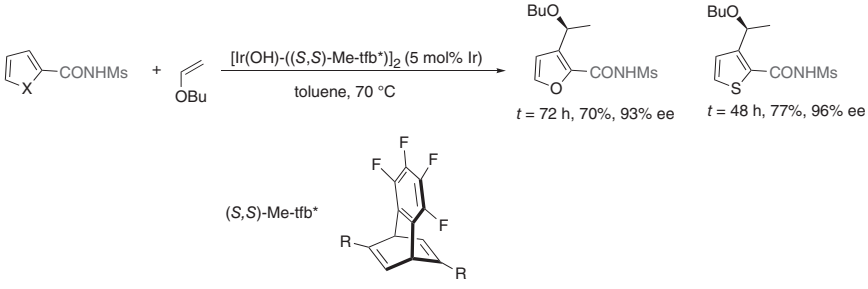


Figure 1.23 Asymmetric hydroarylation of vinyl ethers using an Ir catalyst precursor.

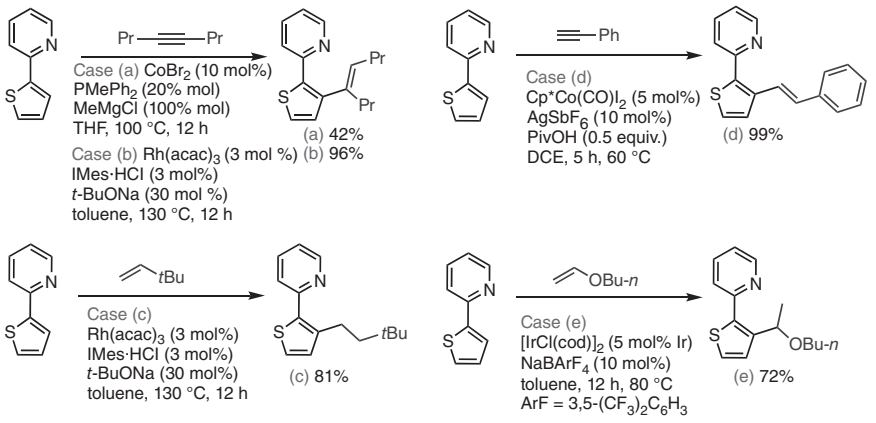


Figure 1.24 Hydroarylation reactions of alkenes and alkynes with 2-(thiophen-2-yl)pyridine.

combination with IMes·HCl ligand and *t*-BuONa (Figure 1.24b) [64]. The strong *trans*-effect exerted by the carbene ligand on the Rh center is proposed for the partial decoordination of the bidentate ligand, thus leading to cyclometalation and subsequent C—H activation selectively on the thiophene ring. The same system is effective for the reaction with alkenes (Figure 1.24c) [64]. 2-(Thiophen-2-yl)pyridine reacts almost quantitatively with phenylacetylene yielding exclusively the *E* isomer using a Cp*Co(III) catalyst under mild conditions (Figure 1.24d) [65]. Moreover, the Ir-catalyzed reaction with vinyl ethers takes place with high selectivity to the branched derivatives (Figure 1.24e) [66].

The group of Castarlenas explored the use of the Rh(III)-NHC complex $[Rh(\mu\text{-}Cl)(H)_2(IPr)]_2$ (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) as a catalyst for the hydroarylation of alkynes and alkenes with 2-(thiophen-2-yl) pyridine (Figure 1.25) [67]. This work included a detailed mechanistic study, involving the isolation and identification of intermediates as well as the study of their reactivity by NMR experiments and DFT calculations. The catalyst proved to be efficient for the hydroarylation of terminal alkenes, affording only linear products, and of internal alkynes, where only *E*-isomers were formed. However, terminal alkynes afforded homocoupling adducts [67].

The mechanistic study suggests that the $[Rh(\mu\text{-}Cl)(H)_2(IPr)]_2$ dimer is broken down upon coordination of thienylpyridine, and through loss of H_2 the active species **3** is generated (Figure 1.26a). The C—H bond on the thiophene ring is

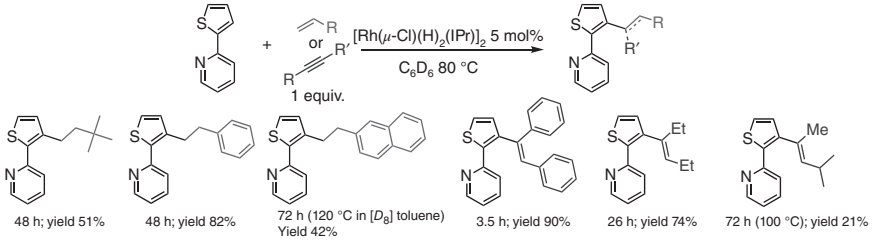


Figure 1.25 Rh-catalyzed functionalization of 2-(thiophen-2-yl)pyridine.

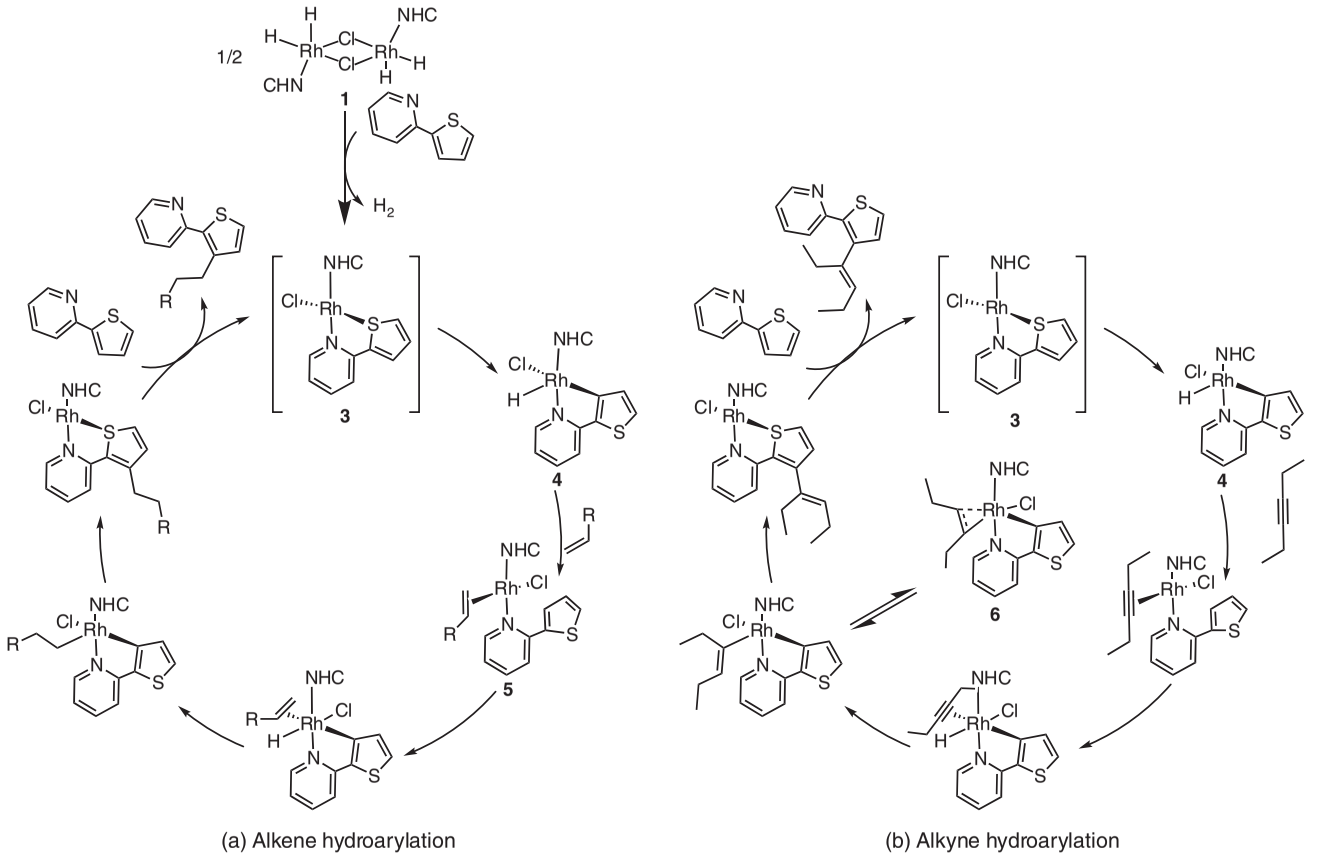


Figure 1.26 Mechanistic proposal for hydroarylation of alkynes and alkenes catalyzed by an NHC-Rh complex.

activated by oxidative addition, affording **4**. Complex **4** was prepared from the Rh dimer **1** by addition of two equivalents of 2-(2-thienyl)pyridine and was identified by NMR spectroscopy. The mode of C—H activation is also supported by DFT calculations, which show that σ-bond metathesis or concerted pathways have much higher activation barriers compared to the loss of H_2. The coordination of the olefin is followed by reductive elimination of the thiophene and the hydrido ligand to give intermediate [Rh(Cl)(IPr)(η^2-PhCH = CH_2)(*N*-PyTh)] (**5**), which was also characterized by NMR. The alkene coordinates at the free position *trans* to the H ligand, so the migratory insertion of the alkene into the Rh—H bond is discarded. Subsequently, the authors proposed a second cyclometalation of the thiophene ring, which affords a hydride *cis* to the alkene moiety and thus the insertion of the olefin into the C—H bond takes place. Eventually, reductive elimination liberates the functionalized product and the active species is regenerated by coordination of another molecule of 2-(thiophen-2-yl)pyridine. When 3-hexyne was added to complex **4**, intermediate **6** was obtained as the only reaction product. The structure of **6** was assigned by means of a detailed NMR study. The authors proposed an analogous catalytic cycle for the hydroarylation of alkynes to the one described for the reaction of alkenes. (Figure 1.26b). Complex **6** (a metallacyclopropene species) is in equilibrium with an alkenyl complex, which undergoes reductive elimination of the alkenyl ligand and the cyclometalated substrate to form the functionalized product.

1.3 Pyrroles, Indoles, Pyridines, and Imidazopyridines

There are a few examples of the hydroarylation using pyrroles with Pd and Pt complexes as catalysts. In most cases the pyrroles are protected, but cases of reactivity of free pyrroles are known. Early examples, published by Fujiwara and coworkers involve the use of $Pd(OAc)_2$ as catalyst in the hydroarylation of unprotected pyrroles and electron-poor internal alkynes, obtaining reactivity at position 2 and the *Z*-regioisomer in good yield (Figure 1.27a) [38]. Free pyrroles have also been functionalized in position 2 using a Pt catalyst by Kitamura and coworker [40], although a mixture of products functionalized in positions 2 and 3 can be obtained when electron-poor internal alkynes, such as ethyl phenylpropiolate, are used (Figure 1.27b). This contribution also reports a double pyrrole insertion into an alkyne to yield the bifunctionalized product (Figure 1.27c) [40]. A double insertion was also reported by Biffis and coworkers using a bis-NHC Pd catalyst (Figure 1.27d) [41].

There are two ways for the less active position 3 of a pyrrole to be selectively functionalized. The first, proposed by Tsukada, is by *N*-protection of the pyrrole with a bulky Boc group (Boc = *tert*-butyloxycarbonyl) using a Pd(II) catalyst (Figure 1.28a) [45]. This method allows the selective synthesis of modified pyrroles using electron-rich internal alkynes. The second is reported by the Fujiwara group and involves the protection of the positions 2 and 5 of free pyrroles in order to be functionalized at C3 by a more reactive ethyl phenylpropionate (Figure 1.28b) [68].

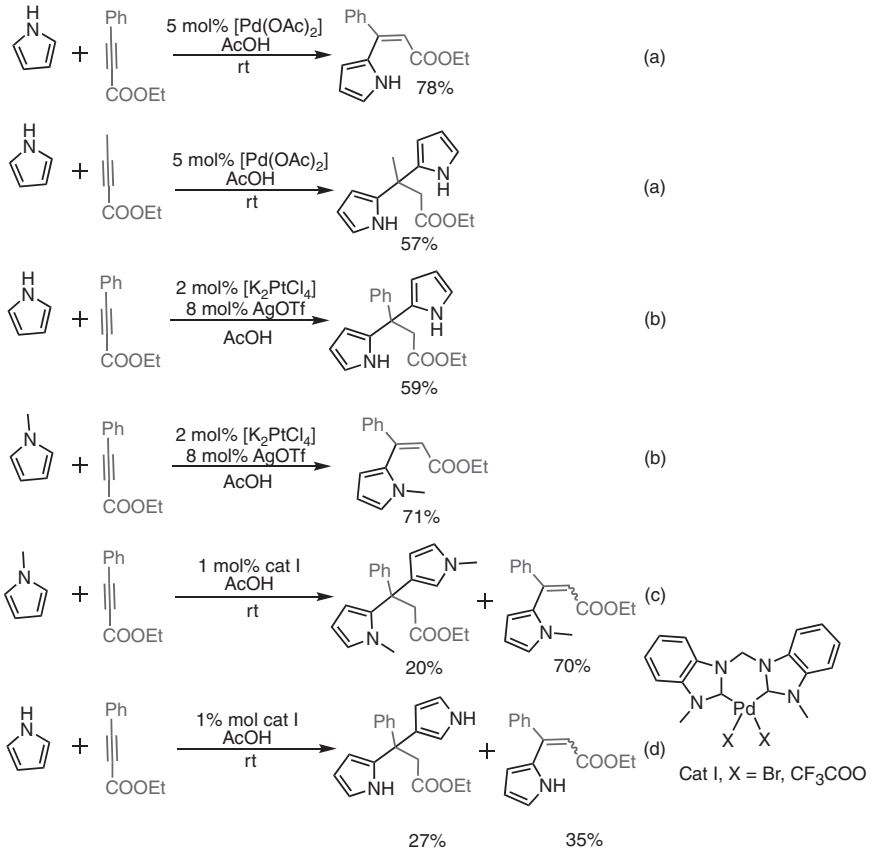


Figure 1.27 Hydroarylation of alkynes at the C2 position of a pyrrole using Pd or Pt catalysts.

Another interesting type of hydroarylation reaction is intramolecular benzannulation. One of the first examples was reported by Fürstner and Mamane [50]. In this case the coupling between a 2-phenylpyrrole and an alkyne catalyzed by $PtCl_2$ allowed the synthesis of 1*H*-benzo[*g*]indoles, while the coupling of *N*-phenylpyrrole gave the pyrrolo[1,2-*a*]quinoline (Figure 1.29a). Other metals such as Ga and In were also used as catalysts that gave very good yields as well [51]. The high electrophilic nature of $GaCl_3$ and $InCl_3$ and their behavior as soft Lewis acids (compared to B and Al) made the catalysts ideal candidates for this kind of chemistry. These heterocycles have shown their importance as anti-tumor agents in medicinal chemistry. The Sames group also proposed the benzannulation of *N*-substituted pyrroles to yield the corresponding dihydroindolizines using an electron-poor alkyne and $PtCl_4$ as catalyst (Figure 1.29b) [47].

Other interesting contributions from Beller and coworkers were the development of a method for the synthesis of pyrroloazepin-4-one via an internal cyclization of the corresponding pyrrolamide using Pt(IV) as catalyst (Figure 1.30a) [69, 70]. Interestingly, the major product was obtained after a rearrangement of the coupling product via a spiro intermediate. The group

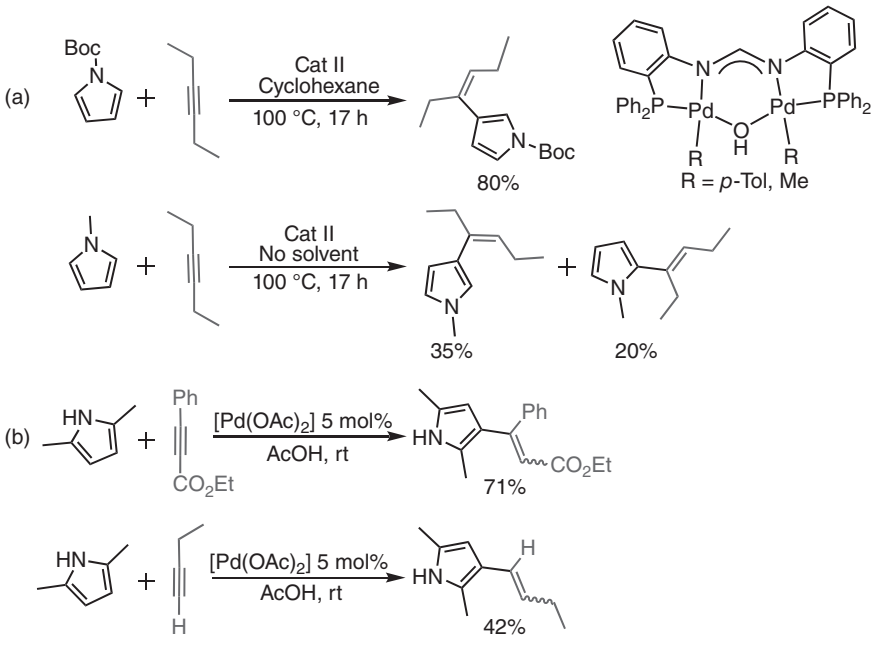


Figure 1.28 Hydroarylation of alkynes at the C3 position of pyrroles.

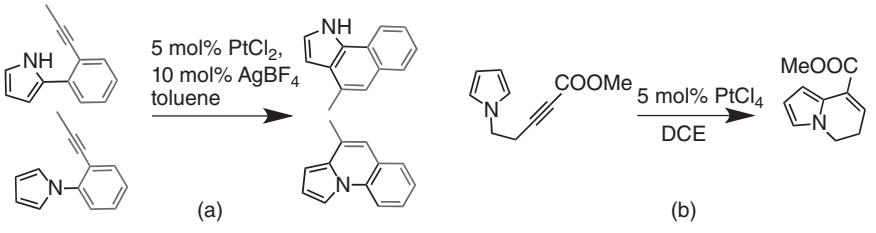


Figure 1.29 Intramolecular benzannulation at the C2 position of pyrroles using tethered alkynes.

of Van der Eycken also successfully attempted the intramolecular synthesis of pyrroloazepinones but by using a different alkyne (Figure 1.30b) [71]. The reaction works using Pt(II) instead of Pt(IV), and the expected product of the coupling was obtained. Finally, Waser and coworker developed a method for the synthesis of substituted indoles from pyrroles via a domino cyclization/alkynylation reaction (Figure 1.30c) [72]. The reaction achieved the 5-substituted indole as the sole product and no traces of other alkynylated positions were observed.

Functionalization of pyridines has been a difficult challenge due to the low reactivity of the pyridine ring using traditional methods such as the Friedel–Crafts alkylation, and therefore examples of this reactivity are scarce. In this context, the hydroarylation of internal alkynes at the C2 position of an *N*-pyridine oxide was developed by Hiyama using a Ni catalyst to obtain mainly the *E*-stereoisomer (Figure 1.31a) [73]. Using a related catalytic system, but with

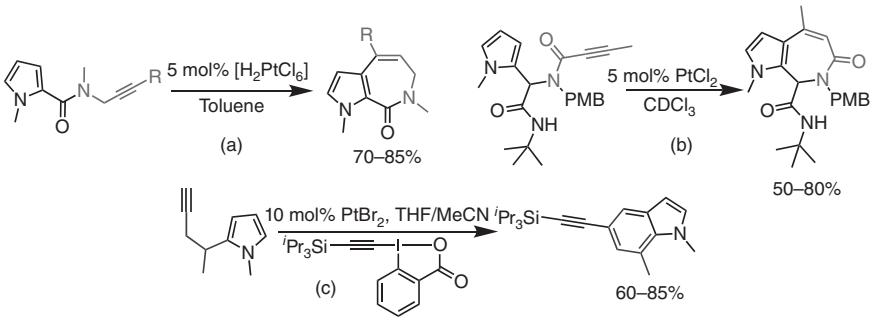


Figure 1.30 Benzannulation at the C3 position of pyrroles.

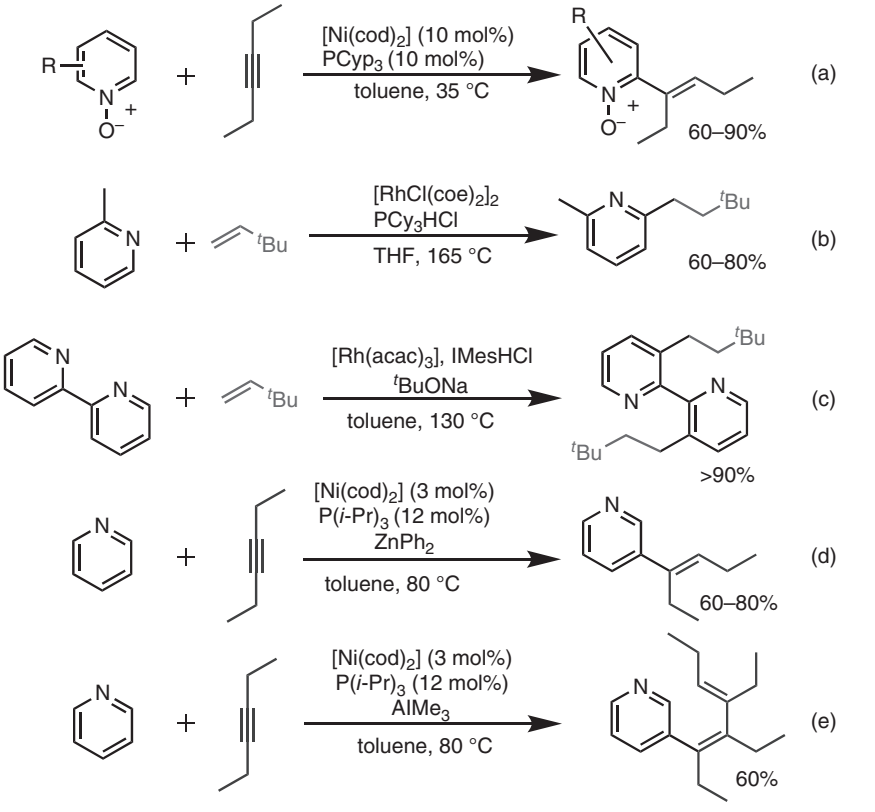


Figure 1.31 Hydroarylation of alkynes and alkenes at C2 and C3 positions of pyridines.

the assistance of $ZnPh_2$ or $AlMe_3$ as Lewis acids, even free pyridines could be successfully hydroarylated (Figures 1.31d and e) [74]. Bergman proposed that the hydroarylation of alkenes using a Rh(I) catalyst and a phosphine was able to functionalize pyridines and quinolines (Figure 1.31b) [75]. Finally, Chang and coworkers described the hydroarylation of alkenes using pyridines and bipyridines with a catalyst of Rh(III) with IMes.HCl as ligand (Figure 1.31c,

IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) [64]. Mono- and bis-inserted compounds were obtained for a wide range of bipyridines and biquinolines with a wide range of alkenes and internal alkynes.

Hiyama and coworkers also developed the hydroarylation of alkynes and alkenes with polifluoropyridines and pyridinones using $[Ni(COD)_2]$ as catalyst in combination with $PCyp_3$ (Cyp = cyclopentyl) as co-catalyst [76]. In the case of pyridinones, a Lewis acid such as $AlMe_3$ is needed to obtain optimized results. In the case of fluoropyridines, position 4 is functionalized (Figure 1.32a). However, in the case of pyridinones, position 2 is activated. Montgomery and coworkers studied the reaction mechanism [43]. The catalytic system in this case comprises $[Ni(COD)_2]$ and IMes as ligands and highlights the importance of the source of Ni(0) (Figure 1.32b). The use of directing groups such as amides has also been studied. Shi and coworkers performed the hydroarylation of alkynes (mostly diarylacetylenes) using amides as directing products in the *ortho*-position [77]. $[RhCp^*Cl_2]_2$ ($Cp^* = C_5Me_5$) as catalyst and $Cu(OAc)_2$ and $AgSbF_6$ as co-catalysts were used and, interestingly, although *E*-isomers are obtained for most pyridines, when picolinamide was used as substrate *Z*-isomers were obtained (Figure 1.32c). Carretero and coworkers used a similar catalytic system to yield phenyltetrasubstituted isoquinolines as a product of a double insertion of diphenylacetylene (Figure 1.32d) [78].

The same catalytic system used by Bergman in the alkylation of pyridines can be applied in the intramolecular cyclization of enol-tethered methylpyridines

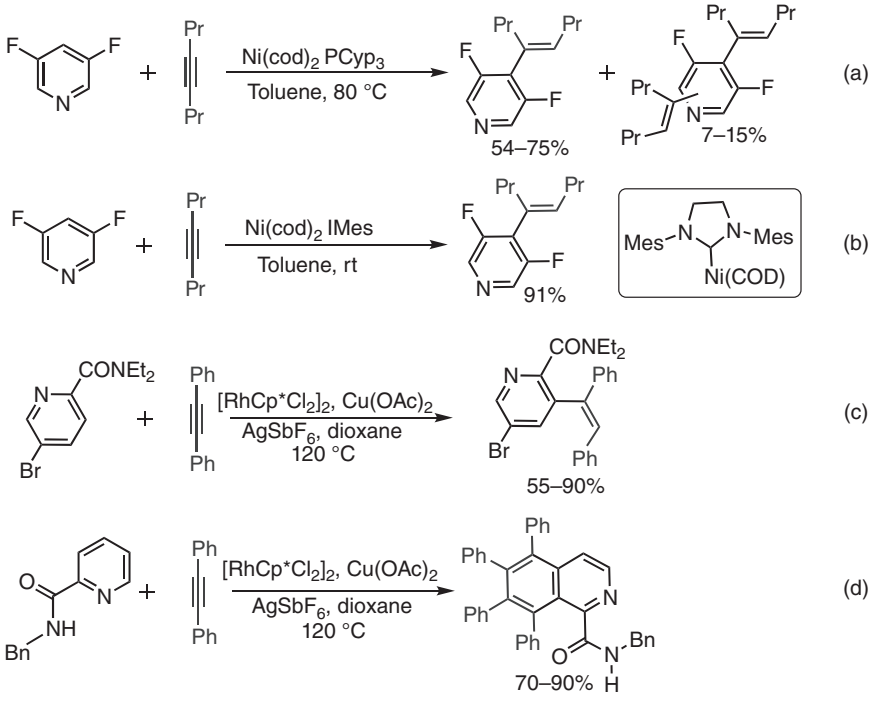


Figure 1.32 Hydroarylation of alkynes and alkenes using pyridines.

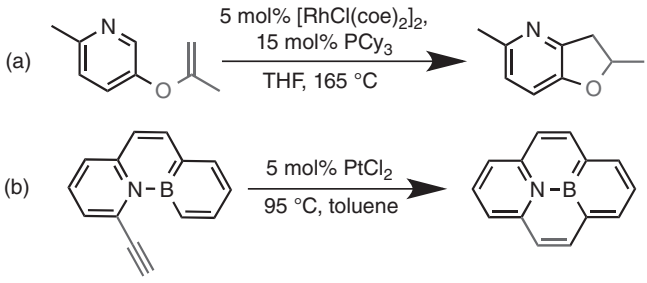


Figure 1.33 Cyclization of pyridines via intramolecular hydroarylation.

to yield the corresponding 2,3-dihydrofuro[3,2-*b*]pyridine (Figure 1.33a) [79]. As explained earlier, $[RhCl(coe)]_2$ and PCy_3 promote the internal cyclization in position 2 of pyridine. This technique was also used with other substrates such as quinolines. In addition, the internal cyclization of an azaboraphenanthrene to yield a 10*a*-aza-10*b*-borapyrene, using $PtCl_2$ as catalyst, was reported (Figure 1.33b). This product displays interesting fluorophore properties with potential applications in sensors and biochemical labeling studies [80].

Indoles are among the most commonly applied *N*-containing heterocyclic substrates in which the hydroarylation reaction has been tested with alkynes as a common coupling partner. One of the first examples was reported by the Hiyama group with a Ni-catalyzed hydroarylation using *N*-methylindoles along with 4-octyne as internal alkyne [42]. The C—H activation occurs at the C2 of the indole (Figure 1.34a). A wide range of indoles and other heterocycles are used under mild conditions to give good yields as it has been described in the preceding paragraphs (see Figure 1.9, conditions a). Yoshikai and coworker proposed the hydroarylation of *N*-pyrimidylindoles functionalizing the C2 position using a $CoBr_2$ catalyst, a phosphine, and a Grignard reagent as a reductant under very mild conditions (Figure 1.34b) [81]. The *syn*-isomer was achieved as reported by the Hiyama and the Yoshikai group. These results were further improved recently by Petit using $Co^0(PMe_3)_4$ as cobalt catalyst and an imine as a directing group in a microwave reactor without the need of a reductant (Figure 1.34c) [82]. The product obtained in this case is the *anti*-isomer.

Another interesting contribution was the work developed by the late K. Fagnou (Figure 1.34d); the directing group used in this case was *N*,*N*-dimethylcarbamoyl with a Rh catalyst obtaining good yields and selectivities [83]. Yu and coworkers attempted the rare hydroarylation of terminal alkynes with *N*-pyrimidylindoles using a Co(II) catalyst and, as in the case of Yoshikai, avoided the use of Grignard reagents (Figure 1.34e) [65]. The reaction gives regio- and stereoselectively the *E*-isomer.

Functionalization at the C3 position of indoles through hydroarylation of alkynes has also been developed using a Pt catalyst [84]. The group of Cheng developed the hydroarylation of alkynols over the C3 position of indoles using $PtCl_2$ as catalyst (Figure 1.35a). The first step is the cyclization of the alkynol (either by 5-*endo-dig* or 6-*endo-dig* or even 6-*exo-dig* pathways, as shown in Figure 1.35c) promoted by the Pt complex. Next, the most likely mechanism

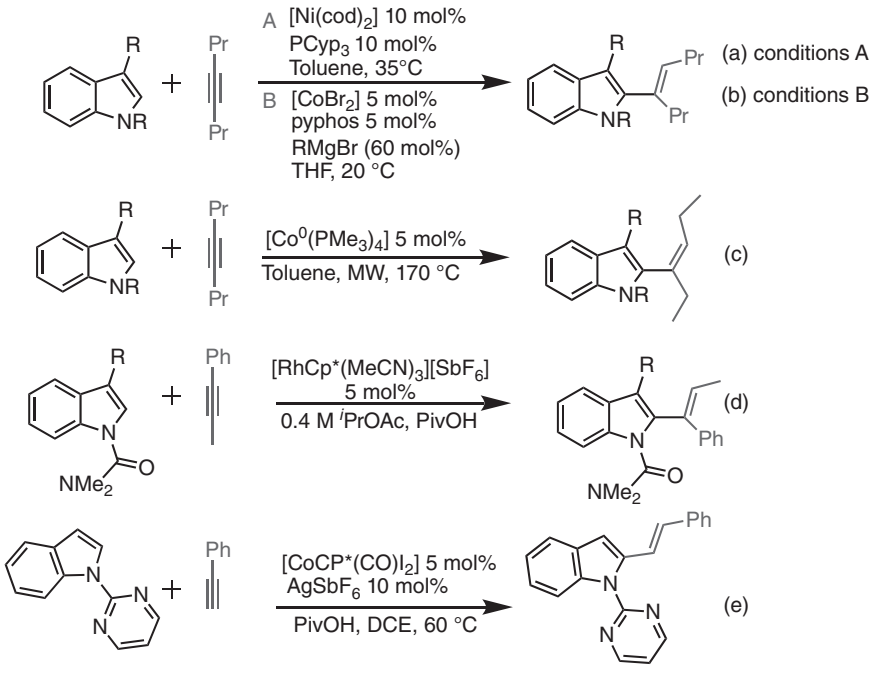
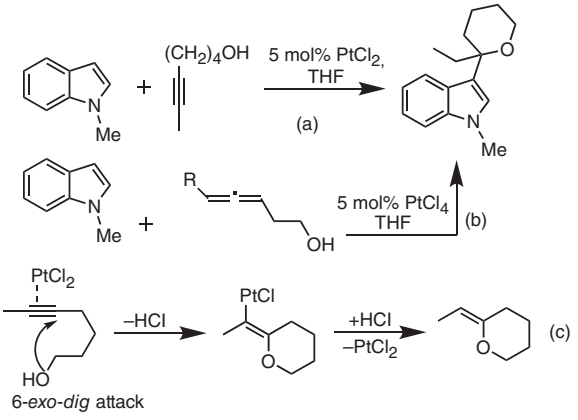


Figure 1.34 Hydroarylation of alkynes at the C2 position of indoles.

Figure 1.35 Hydroarylation of alkynes and allenes at the C3 position of indoles.



involves the electrophilic metallation of the indol, followed by insertion of the C=C double bond and protodemetallation. This product can also be obtained using allenes as reagents instead of alkynes using $PtCl_4$ as the catalyst precursor. In this case just the pyrane derivative is obtained, as Ma and coworkers demonstrated. In both cases, the selectivity is in the C3 position of the indole (Figure 1.35b) [85, 86].

Hydroarylation of alkenes with indoles has been widely studied. Both C2 and C3 positions of the indoles have been successfully and selectively functionalized using a wide variety of alkenes. There are many examples of functionalization

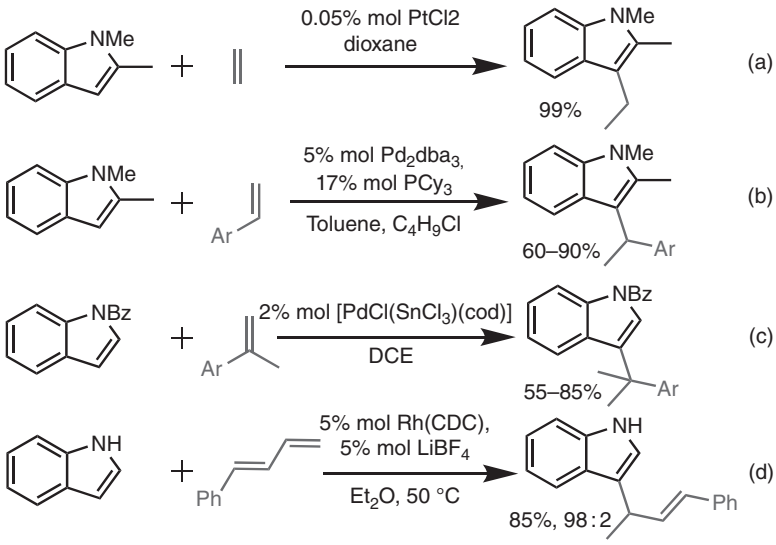


Figure 1.36 Hydroarylation of alkenes at the C3 position of indoles.

of the C3 position of indoles. One of the earliest examples was reported by Widenhoefer and coworkers using different alkenes, from ethylene to styrene, and $PtCl_2$ in dioxane as the catalytic system (Figure 1.36a) [87]. The use of styrene, however, resulted in a mixture that was between the branched and the linear products. A Pd catalyst shows activity for the hydroarylation of vinylphenols with indoles, both on its own and as a heterobimetallic Pd–Sn catalyst. In the first case, $Pd_2(dba)_3$ was used with PCy_3, while alkyl halides were used as a hydride source (Figure 1.36b) [57]. Interestingly, no alkylation of the phenol was observed. In the second case, Roy and coworkers designed a heterobimetallic catalyst to perform the reaction using substituted styrene as starting material [58]. Moderate to good yields were obtained for free and *N*-substituted indoles (Figure 1.36c). More recently, the group of Meek developed a method for the hydroarylation of α,β-unsaturated compounds catalyzed by Rh with CDC ligands (CDC = carbodicarbenes ligands). Good yields and excellent selectivities toward the γ-substituted product in the C3 of the indole were obtained (Figure 1.36d) [88].

There are also a good number of examples of hydroarylation of alkenes at the C2 position of indoles. Hiyama and coworkers studied the hydroarylation of several styrenes using *N*-methylindoles with C3 protected with an electron-withdrawing group (Figure 1.37a) [56]. The catalyst of choice was $[Ni(cod)_2]$ with the carbene IMes to yield the product with excellent yields in most cases (70–90%). Yoshikai and coworker also studied the hydroarylation of styrene using an imine as a directing group, which directed to C2 with $CoBr_2$ as catalyst, Ixyl as ligand (Ixyl = 1,3-bis(2,6-dimethylphenyl)imidazolium chloride), and a Grignard reagent as a reducing agent (Figure 1.37b) [89, 90]. The reaction worked well and just the branched product was obtained for *N*-methylindole (yields around 80–90%). The same author reported the testing of an array of phosphines that

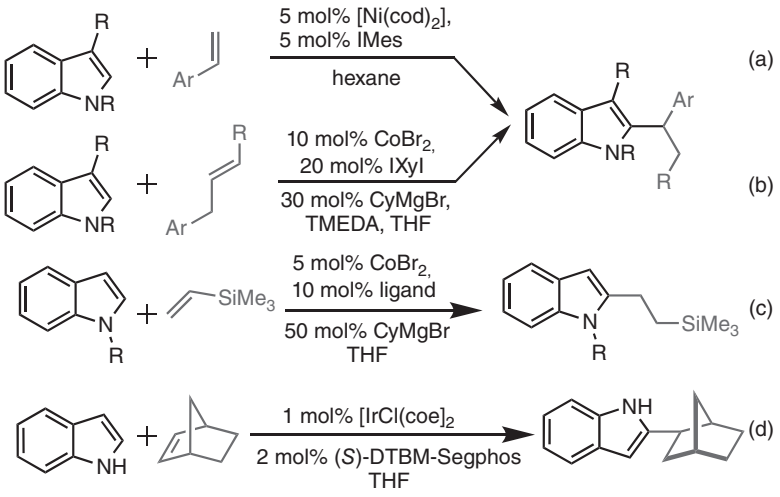


Figure 1.37 Hydroarylation of alkenes at the C2 position of indoles.

led to different results. If the phosphine of choice is triphenylphosphine, the product was predominantly branched with excellent yield (70–90%). However, the use of (dimethoxyphenyl)diphenylphosphine lowers yield (<10%), although overall a change in the selectivity was obtained and the linear product was dominant. More interestingly, use of an additive such as 2-methoxypyridine allowed the synthesis of both products. If the additive was used without a ligand the product was predominantly branched in good yields, and if the additive was used together with the phosphine the product was predominantly linear in good yields. A similar catalytic system was used by the same author but instead of an imine at C3, an *N*-pyrimidylindole was used as starting material with pyrimidyl as the *ortho*-directing group. Different vinylsilanes were hydroarylated. A phenanthroline derivative is the ligand of choice this time allowing the selective synthesis of the linear product (yields around 50–90%; Figure 1.37c) [91]. Finally, Hartwig and coworker developed the enantioselective insertion of indoles to norbornene (Figure 1.37d) [59]. The reaction is performed using an Ir(I) catalyst and a chiral ligand ((*S*)-DTBM-Segphos = (*S*)-(+)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole) which allows the functionalization at C2 of the indole with excellent yields (85–95%) and enantioselectivities (99% ee).

One of the first examples of internal cyclization on the C2 of alkenylindoles was developed by Bergman and coworkers [92]. *N*-substituted indoles were cyclized to yield the tricyclic compound using a Rh(I) precursor and a phosphoramidite ligand in toluene (Figure 1.38a). Because the hydroarylation incorporated a substituted alkene, a chiral center was created, and excellent yields and enantioselectivities were obtained. The selectivity to C2 is achieved by using an imine directing group at C3 of the indole. A similar strategy but a completely different catalytic system is used by Yoshikai and coworkers [93]. In this case $CoBr_2$ acted as catalytic precursor, a carbene as ligand and a Grignard as additive was used

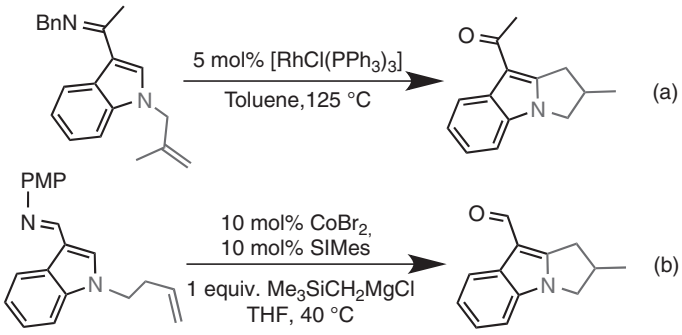


Figure 1.38 Benzannulation at the C2 position of indoles.

at 40 °C to promote cyclization at the C2. Interestingly, the choice of carbene determines the selectivity toward a five- or a six-member ring: SIMes·HCl (SIMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene) promoted the formation of a five-membered ring (Figure 1.38b) while IPr·HCl promoted the formation of a six-membered ring, this regioselectivity being dependent on the steric hindrance of the NHC ligand.

Intramolecular cyclization at the C3 of indoles has also been developed, although examples are limited. Widenhoefer and coworkers reported the intramolecular cyclization of 2-alkenyl indoles to yield tetrahydrocarbazoles using a Pt(II) complex in dioxane [94–96]. The reaction proceeded in good yields and selectivities, and both substituted and free indoles could be functionalized (Figure 1.39a). The same authors describe an asymmetric variant of this reaction using $PtCl_2$(P-P) (P-P = chiral diphosphine). Several diphosphines were screened ((*S*)-BINAP, (*S*)-tol-BINAP, and others), but the best results were obtained with (*S*)-3,5-*t*-Bu-4-MeOMeOBIPHEP, achieving excellent yields (56–96%) and enantioselectivities (up to 90% ee). Ma and coworkers also achieved the synthesis of carbazoles through internal cyclization (Figure 1.39b) [86]. In this case, a preformed allenol indole was used as starting material and $PtCl_2$ as the catalyst yielding the corresponding carbazole. Many substrates were tested with different

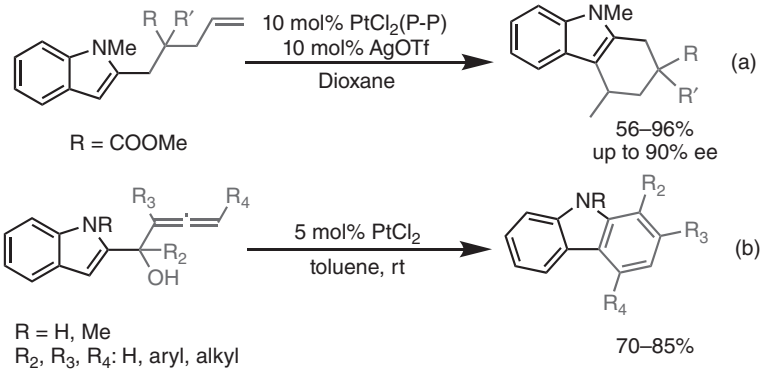


Figure 1.39 Benzannulation at the C3 position of indoles.

substituents in the indole or the allenol moieties obtaining good to excellent yields and demonstrating the versatility of the method.

1.4 Azoles and Other Miscellaneous Heterocycles

Interest in the synthesis of diverse *N*-heterocycles prompted Bergman and coworkers to initiate extensive research in catalytic hydroarylation using a large variety of *N*-heteroaromatic substrates. The first examples of this rich chemistry were related to the intramolecular cyclization of *N*-homoallyl benzimidazoles to give fused carbocycles, as shown in Figure 1.40 [97]. The reaction is fully regioselective, and only the C—H bond in *α* to both N atoms is activated. The reaction scope is quite general with respect to alkene substituents, because terminal and internal alkenes as well as trisubstituted alkenes were successfully cyclized with a high degree of regioselectivity to give new five- or six-membered rings. In general, terminal to internal alkene isomerization is observed before C—C coupling, giving five-membered rings. The authors suggest that either the internal geminal substitution or the allylic α,α-dibranching could be responsible for the formation of the larger six-membered rings. For instance, the internal geminal substitution could lead the formation of the six-membered ring because

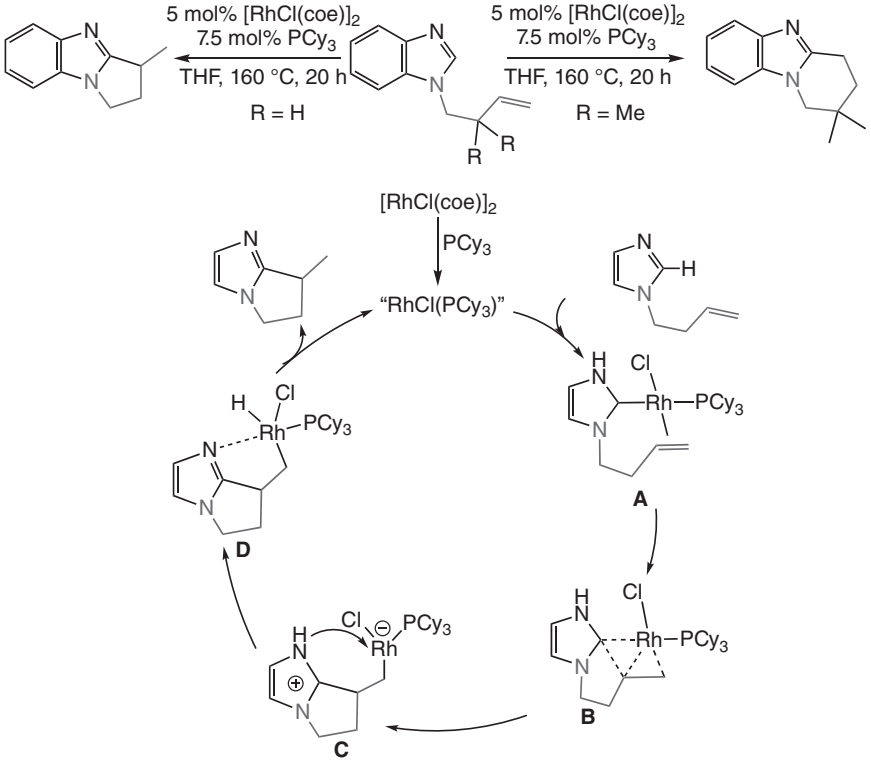


Figure 1.40 Intramolecular hydroarylation of homoallyl-benzimidazoles using a Rh catalyst.

of the difficulty to cyclize forming a quaternary center [8, 97]. In the same way, when the olefin cannot isomerize, the formation of the six-membered ring is favored. Mechanistic study by DFT methods of the reactions shown in Figure 1.40 revealed that the Rh(I) *N*-heterocyclic carbene complex **A** is the likely resting state [98]. This is surprising because a C—H bond activation using electron-rich Rh(I) complexes usually results in a Rh(III)-hydride species [8, 13]. From complex **A**, a transition state leading to insertion of the alkenyl group into the Rh-C(carbene) bond was proposed as the rate-determining step [98]. After alkene insertion the zwitterion **C** is formed, which evolves through intramolecular proton transfer to give hydride **D**. By C—H reductive elimination the final cyclized derivative is obtained and the catalyst is renewed.

Processes shown in Figure 1.40 were notably accelerated in the presence of Brønsted or, even more effectively, Lewis acids. Therefore, additives such as lutidinium chloride, YCl_3, or $MgBr_2$ have a dramatic impact on the reaction rate, although the authors have not provided a rationale for this fact. This acceleration allowed the expansion of this reaction to the first intermolecular hydroarylation of benzimidazole, benzothiazole, benzoxazole, dimethylthiazole, and purine (Figure 1.41) [99]. Optimization of the additive showed that lutidinium chloride provided the highest yields. The scope of the reaction is quite general, both for the heteroaromatics (some of them shown in Figure 1.41) and for the alkenes, activated and unactivated, regardless of being susceptible to possible isomerization. In all studied cases the hydroarylation reactions take place regioselectively to give the linear alkyl derivative. However, no reaction was observed with pyrimidine or indole, showing that the formation of a Rh-NHC intermediate is important. The range of substrates able to be functionalized using this method was notably expanded in a subsequent work by including aryl-substituted benzimidazoles [100]. The reaction conditions were also re-optimized, and the authors found that $[HPCy_3]Cl$, the phosphonium salt of PCy_3, is the best option as phosphine and additive (Lewis acid), which simplifies the experimental setup due to its stability. In this case the authors provide a tentative explanation, based on the formation of a Rh(III) hydride [100]. The reactions presented in

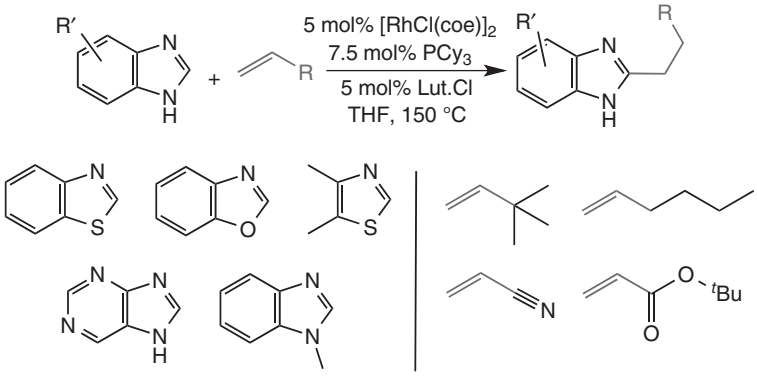


Figure 1.41 Intermolecular hydroarylation of benzimidazole and related heteroaromatic substrates using a Rh catalyst.

Figures 1.40 and 1.41 were reinvestigated using microwave radiation in place of conventional heating [101]. Under optimized conditions the reaction times can be reduced from 20 h to 6–12 min without erosion of the yield.

This powerful and versatile methodology was applied to the synthesis of more complex products. For instance, intramolecular alkene hydroarylation is a key step in the synthesis of a potent kinase inhibitor, more specifically the c-Jun N-Terminal Kinase (JNK3) inhibitor shown in Figure 1.42 [102]. The inclusion of this step in the total synthesis of JNK3 inhibitor reduces the number of synthetic steps from 14 to 11, and increases the total yield from less than 6% to 13%, representing an advance in synthetic methods.

Other heterocyclic substrates able to form *N*-heterocylic carbene (NHC) complexes with Rh have been studied. 4,4-Dimethyl-2-oxazoline reacted with a large variety of alkenes, including substrates with protected aldehyde, acid, alcohol, and amine functional groups, to give linear hydroarylated derivatives with excellent regioselectivity (Figure 1.43 left) [103]. Notably, the reaction temperature in these processes is substantially lower (45 °C, versus 150–180 °C typically used in other reactions). This surprising increase in catalyst activity correlates with observations in other NHC-based catalysts: a higher catalytic efficiency is observed when unsaturated NHC ligands are replaced by their saturated versions in the same complexes [103].

The synthetic possibilities of the dihydroquinazoline skeleton have also been investigated by Bergman and coworkers because of its presence in products with medicinal applications [104]. 3,4-Dihydroquinazoline reacts with alkenes under Rh-catalysis to give the corresponding 2-alkyl-3,4-dihydroquinazolines in good

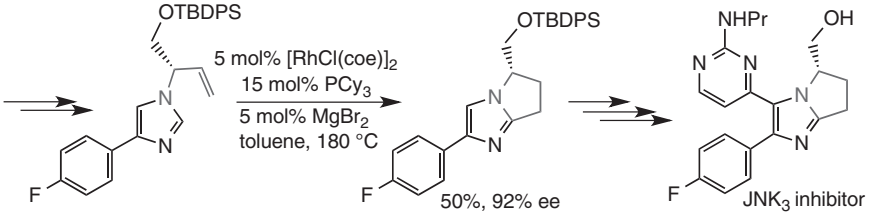


Figure 1.42 Application of intramolecular alkene hydroarylation to the synthesis of high value-added products.

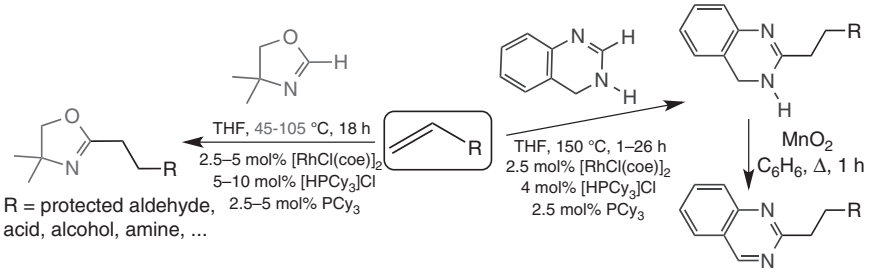


Figure 1.43 Oxazolines and dihydroquinazolines as substrates in hydroarylation reactions catalyzed by Rh complexes.

yields (Figure 1.43 right). Under prolonged heating a mixture with the corresponding aromatized quinazoline is obtained, because a Rh/PCy_3 system can also work as a transfer dehydrogenation catalyst. Another procedure for the production of quinazolines in two steps is described: (i) the controlled Rh-catalyzed hydroarylation of the olefin with the dihydroquinazoline and (ii) the oxidation of the reaction crude with MnO_2 (Figure 1.43) [104]. The intramolecular version of the hydroarylation has been applied to the total synthesis of Vasicoline, a representative of a family of products with biological activity (Figure 1.44) [104].

3-Methyl-3,4-dihydroquinazoline (**A** in Figure 1.45) has also been used as a model for interesting experimental and computational mechanistic studies [104, 105]. These studies were focused on the C—H bond activation of the dihydroquinazoline ligand promoted by $RhCl(PCy_3)_2$ and the concomitant formation of a Rh-NHC species **C**. The results show that complex **B**, where ligand **A** is N1-bonded to the Rh center, is an intermediate in the synthesis of the NHC-carbene derivative **C**. The kinetic analysis of the concentration changes of **A**, **B**, and **C** along the time at 37 °C clearly showed that **B** is a likely intermediate on the pathway to **C**. Based on this, the authors propose an intramolecular H transfer ongoing from **B** to **C** as the most plausible mechanism for C—H bond activation; that is, the H at carbon C2 is transferred to nitrogen N1 without exchange with any other H atom while it is being transferred [105]. All these facts were supported by isotopic labeling experiments.

All examples previously shown in this section shared a common feature, which is the regioselective insertion of the alkene in the C—H bond of the heterocycle to give the linear alkyl derivative. In the following sections the discussion is on

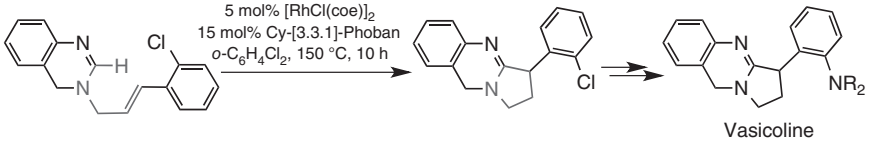


Figure 1.44 Intramolecular alkene hydroarylation as a key step in the synthesis of Vasicoline.

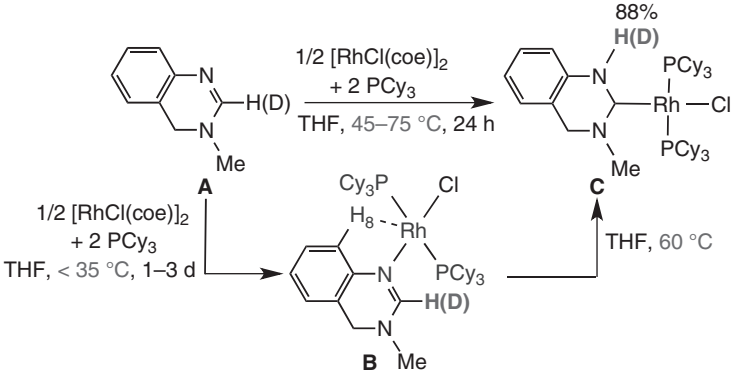


Figure 1.45 Intermediates in the C—H bond activation of 3,4-dihydroquinazolines using Rh catalysts.

Ni catalysts, in combination with Lewis acids, to afford control of the regioselectivity of the alkene insertion, affording either branched (1,1-disubstituted ethane or Markovnikov addition) or linear derivatives (1,2-disubstituted ethane or anti-Markovnikov addition) depending on the reaction conditions [56, 106–108]. Hiyama and coworkers have reported that the hydroarylation of substituted styrenes and other related alkenes with heterocycles, catalyzed by $Ni(cod)_2$ and a very bulky NHC as stabilizing ligand, affords the corresponding 1,1-diarylethanes, that is, the branched derivatives, as it is shown in left part of Figure 1.46 [56]. This method notably expanded the range of substrates able to undergo hydroarylation to give branched products with respect to previous methods. The scope is wide because styrenes with electron-donating and electron-withdrawing groups, and even indene, successfully give the branched 1,1-diarylderivatives. On the other hand, an aliphatic alkene such as 1-tridecene affords exclusively the linear derivative, probably due to the lack of functionalities with a π-system. In addition, heteroaromatics such as benzimidazole, benzoxazole, oxazole, and benzothiazole, among others, couple with styrene to also give the branched product. Mechanistic studies resulted in the proposal that the reaction starts with oxidative addition of the C—H bond to Ni(0) to give a Ni(II)-H species, followed by coordination of the alkene, hydronickelation by migratory insertion, and reductive elimination to regenerate the Ni(0) catalyst. No explanation about the observed selectivity was provided [56].

Following the seminal work of Hiyama, Ong and coworkers reported control of the regioselectivity of the insertion by choice of additives, as shown in central and left parts of Figure 1.46 [106]. When the reaction between benzimidazole and styrene is performed in the absence of additives the branched product, the 1,1-diarylsubstituted ethane, is formed [106]. The scope of both benzimidazoles and styrenes covers a wide range of substrates with yields of branched products comprised between 50–99%. However, when the reaction between benzimidazole and styrene is performed in the presence of an additional 10% of a Lewis acid, such as $AlMe_3$, the regioselectivity of the process switches completely, and the linear derivative is obtained with full regioselectivity and yields around 90% in almost all studied cases. As for the branched reaction, the scope of alkenes

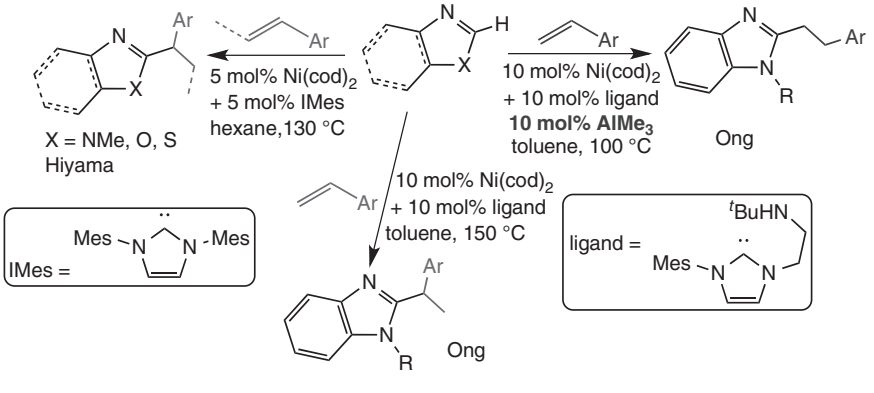


Figure 1.46 Hydroarylation of alkenes using Ni catalysts with control of the regioselectivity.

and azoles able to undergo hydroarylation is quite wide. Interestingly, the reaction conditions in the presence of a Lewis acid are milder (toluene, 100 °C) than in its absence (toluene, 150 °C), showing that the addition of the Lewis acid has an additional accelerating effect.

The switch in the regioselectivity of the hydroarylation processes shown in Figure 1.46 was combined with an isomerization reaction in a subsequent elegant work by Ong and coworkers [107]. As shown in Figure 1.47, branched or linear compounds can be obtained with full selectivity from azoles and allylarenes. In the left part of Figure 1.47, the reaction takes place in toluene at 130 °C to give the corresponding 1,1-diarylpropanes in good to excellent yields and with full regioselectivity. This means that allylbenzene undergoes a previous fast isomerization to *trans*-β-methyl-styrene (process also catalyzed by $Ni(cod)_2$/IMes), which takes place at 80 °C in only 1 h) and further reacts with the azole to give the 1,1-diarylpropane (Markovnikov addition) [107]. On the other hand, the reaction of azoles with allylarenes under the same catalytic conditions but in the presence of $AlMe_3$ gives the linear anti-Markovnikov 1,3-derivative (Figure 1.47 right) [107]. The effect of the addition of $AlMe_3$ as a critical game-changer is multiple: (i) it decreases the rate of the olefin isomerization, making this process slower than the hydroarylation reaction and (ii) switch the regioselectivity towards the linear product [106]. The origin of this outstanding selectivity seems to be related to the subtle balance of the steric versus electronic control of the insertion of the alkene into the Ni—H bond [106, 108].

Recent work of Filloux and Rovis has shown that the enantioselectivity of the hydroarylation can be controlled with careful design of the catalytic system [109]. The method reported the hydroarylation of α-substituted acrylates with different benzoxazoles, a process catalyzed by $[Rh(OAc)(COD)]_2$ in NCMe at 100 °C (Figure 1.48), which affords the corresponding linear C2-alkylated benzoxazoles. The system requires the presence of an enantiomerically pure diphosphine ligand, based on previous reports. Due to this mandatory requirement, other chiral ligands were not tested. The screening of different diphosphines showed that the bulky CTH-(*R*)-xylyl-P-Phos (Figure 1.48) was the best option. Under these conditions high yields (most of them higher than 60%) and enantioselectivities (range

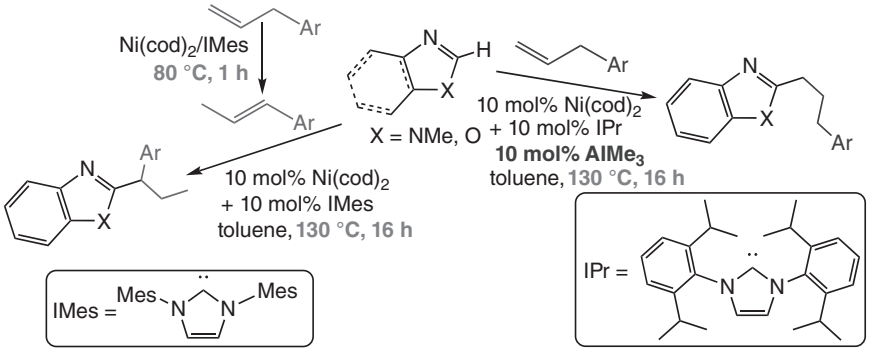


Figure 1.47 Tandem isomerization–hydroarylation using a Ni catalyst with control of regioselectivity.

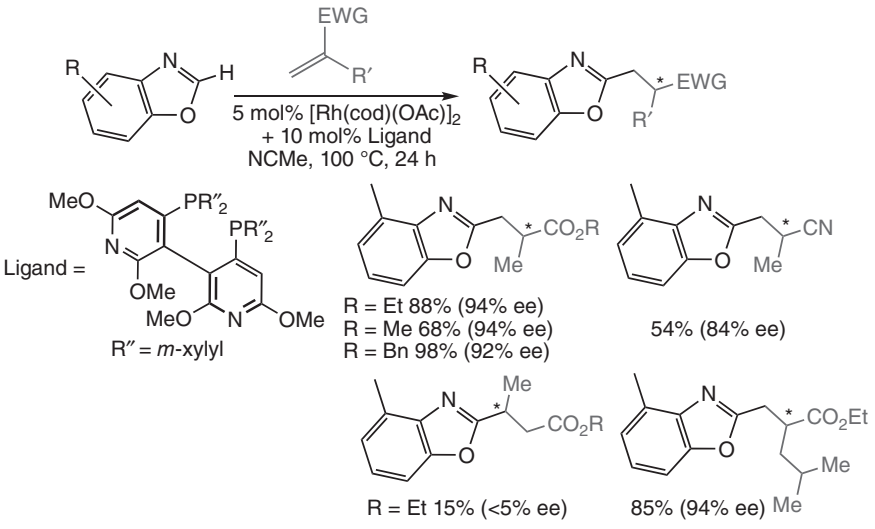


Figure 1.48 Enantioselective hydroarylation of electron-poor alkenes using a Rh catalyst.

68–96%, with most of them higher than 90%) were achieved. Following mechanistic studies that include isotope labeling, it seems that the enantiodeterminant step is the migratory insertion followed by a stereospecific isomerization that insulates the formed stereocenter from epimerization [109].

Cobalt complexes have recently been shown to achieve high activity and selectivity for the hydroarylation of alkynes with a large diversity of heterocycles [110]. Yoshikai and coworkers described chemo-, regio-, and stereoselective addition of substituted azoles to electron-rich internal alkynes catalyzed by $CoBr_2$ to give good yields of the C2-alkenylated derivatives (Figure 1.49) [110]. Under optimized conditions the reaction requires a diphosphine ligand in catalytic amounts (10%) and a Grignard reagent in substoichiometric amounts (50%). The reaction takes place at room temperature selectively with activation of the C2—H bond

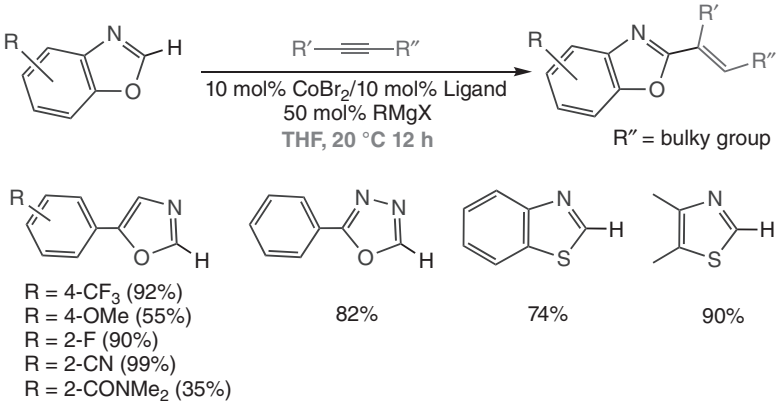


Figure 1.49 Cobalt-catalyzed hydroarylation of alkynes using azoles.

of the heterocycle, in spite of the presence of many other seemingly readily activated C—H bonds in the starting substrates. The reaction occurs with excellent (*E*)-stereoselectivity, since the *E*/*Z* ratio is higher than 99/1 in all cases. Moreover, full regioselectivity was observed in the insertion of asymmetrically substituted alkynes, forming the C—C bond at the less hindered carbon.

Nickel complexes, in combination with different Lewis acids, have shown a high versatility for the hydroarylation of alkenes, as presented in previous paragraphs in this section (Figures 1.46 and 1.47), and this is also true for the hydroarylation of alkynes. Hiyama and coworkers have reported the hydroarylation of alkynes with indoles [42]. In the same contribution a large number of azoles have shown to display the same reactivity, (shown in Figure 1.50a) using $Ni(cod)_2$ and $PCyp_3$ (Cyp = cyclopentyl) as the catalytic system. The reaction occurs at 35 °C and gives excellent levels of stereo- and regioselectivity. The same group has reported the hydroarylation using different imidazoles, represented in Figure 1.50b [111]. When the starting material has substituents at N1 and C4 but not at C2, the functionalization occurs by selective activation of the C2—H bond. The reaction affords in all cases the *E*-isomer, but further isomerization to the *Z*-isomer has been detected in alkynes containing aryl groups. On the other hand, when the starting imidazole contains substituents at N1, C2, and C4, the functionalization takes place selectively at C5 achieving, as expected, excellent

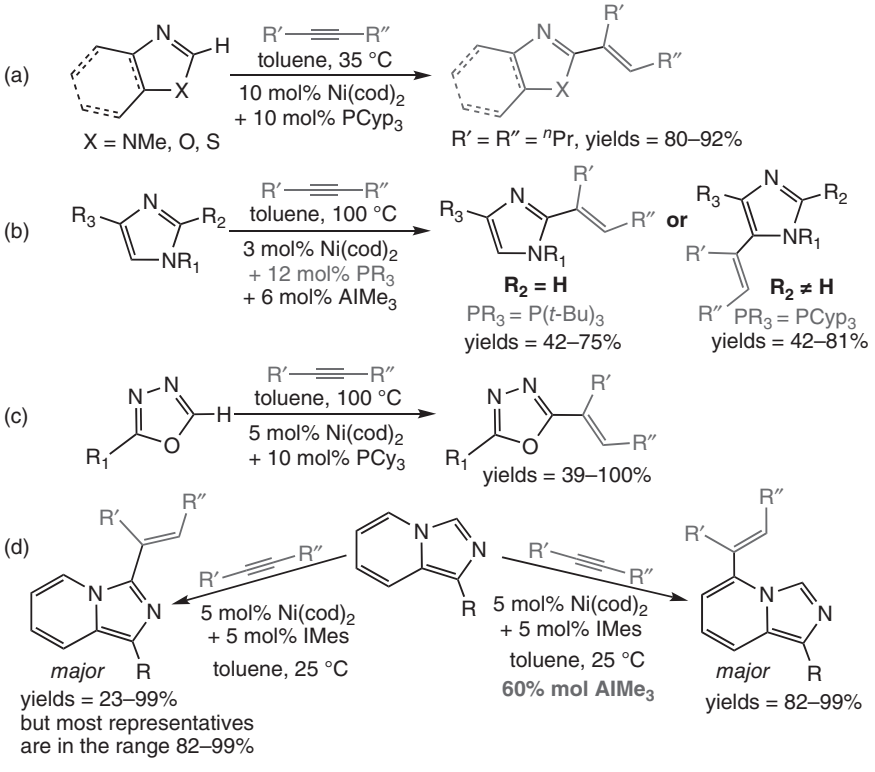


Figure 1.50 Summary of nickel-catalyzed hydroarylation of alkynes.

stereo- and regioselectivities in the final alkenylated derivatives (*E*-isomers with the bulkiest R″ group in *trans* to the imidazole ring) [111].

Miura and coworkers reported an efficient method for the synthesis of alkenylated oxadiazoles, as shown in Figure 1.50c [112]. The oxadiazole core is probably one of the most interesting in the agrochemical and pharmaceutical fields, and the development of efficient methods for their rapid synthesis is of considerable importance in organic synthesis. The reaction is selective at the five position of the oxadiazole ring and stereoselective for formation of the *E*-isomer for electron-rich internal alkynes. Unfortunately, only one example of terminal alkyne was reported, and other terminal alkynes did not show adequate reactivity. Imidazo[1,5-*a*]pyridines are another example of heteroarenes that show adequate control of the reactivity through fine-tuning of the additives. In this respect, recent results of the group of Ong are shown in Figure 1.50d [113]. The starting imidazo[1,5-*a*]pyridine has the C1 atom substituted; therefore, C3—H and C5—H are the bonds most plausible to be activated. When the reaction is performed at 25 °C using $Ni(cod)_2$ as catalyst and IMes as an optimal stabilizing ligand, the incorporation of the alkyne was observed at, mainly, the C3-position (C3/C5 = 5/1 to 7/1, left part) giving the *E*-alkene complete stereoselectivity [113]. The addition of a Lewis acid, such as $AlMe_3$, and its further bonding to the N2 atom, affords the C5-functionalized derivative as the main reaction product (Figure 1.50d, right part). The reaction gives in this case higher C5/C3 ratios (8/1 to 14/1) and complete *E*-selectivity.

From Figure 1.50, it is noteworthy that the same catalytic system, through fine-tuning and undergoing only small changes, is able to display high catalytic activity and remarkable selectivity for different heteroromatic substrates.

1.5 Summary

In summary, the hydroarylation of alkenes and alkynes with heteroarenes is a basic and fundamental tool for the formation of new C—C bonds in metal-catalyzed organic synthesis. The research performed until now has shown that the reaction seems to be unlimited, because it provides the expected coupling products for virtually all types of heteroarenes, both electron-rich (furanes, thiophenes, pyrroles, indoles) as well as electron-deficient (pyridines, quinolines), and also for a large variety of electronically and sterically different alkenes and alkynes. In addition, in most of the cases the coupling can be performed through metal-catalyzed C—H bond activation strategies, avoiding the prefunctionalization of the starting materials, then saving time, energy, and resources, and minimizing the amount of waste. In this chapter we have focused our interest in the transition metals of the 9 and 10 groups, but other metals can also be used. The reaction can be easily tuned by addition of diverse additives, and it is especially accelerated in the presence of Lewis acids. Despite its general character, the reaction can show very high levels of selectivity: stereoselectivity, when the (*Z*/*E*) geometry of the olefin formed by hydroarylation of an alkyne is considered; regioselectivity, with respect to the activated position in the starting

heteroarene, or when asymmetric alkenes or alkynes are considered; or even enantioselectivity, when new stereogenic centers are being formed.

Despite these impressive developments, there are still a number of challenges for the future. Further research on electron-deficient rings, clearly less developed than electron-rich ones, generalization of the use of C—H bond activation processes promoted by earth-abundant metals (Fe, Co, Ni), or a better control of the selectivity (mainly the enantioselectivity) are tasks for a close future.

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