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Edited by Lutz Ackermann, T. Brent Gunnoe
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Introduction and Preface

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Whether the target is a biologically active compound or a chemical feedstock, the ability to selectively install alkyl or alkenyl groups at a position of an aromatic or heteroaromatic compound is of central importance to synthetic chemistry. Friedel–Crafts catalysis and transition metal-catalyzed carbon–carbon bond coupling using aryl halides and organometallic reagents (e.g., Suzuki, Stille, and Sonogashira reactions) have been developed over time to install C—C bonds into aromatic substrates. These reactions are powerful tools for synthetic chemists, yet they are often hampered by one or more issues including harsh reaction conditions, lack of regioselectivity and/or stereoselectivity, use of toxic organometallic reagents, and the use of halogenated substrates. The direct addition of aromatic C—H bonds to unsaturated substrates (e.g., olefins or alkynes) provides an atom-economical strategy that is complementary to Friedel–Crafts and traditional C—C coupling reactions. Thus, it is not surprising that after the first published reports of hydroarylation of olefins and alkynes, the number of groups interested in the synthetic and mechanistic aspects of transition metal-mediated addition of C—H bonds across C—C double and triple bonds has steadily grown.

To our knowledge, the first review article to include olefin or alkyne hydroarylation chemistry was published in 1990 [1], the first focused review appeared in 2002 [2], and the first book was published in 2009 [3]. The extensive advancements in catalytic addition of C—H bonds across C—C multiple bonds and their rising impact on the methods used in synthetic organic chemistry warrants a comprehensive textbook that can be a single source providing a broad overview of the state of the art in the field. Skilled chemists may look to utilize the chemistry in synthetic applications while graduate students and novices to the field may discover fundamentally interesting chemistry. The authors of each chapter have presented a detailed review of their topic supplementing areas not covered with references for the interested reader, including both experimental and theoretical data. The book provides an overview of what has been accomplished, and also includes commentary on existing challenges and opportunities.

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In Chapter 1, Villuendas, Ruiz, and Urriolabeitia detail the use of group 9 and 10 catalysts to functionalize heteroarenes. Hydroarylation reactions with aryl halides or arylboronic acids are not covered as emphasis is placed on the cleavage of heteroaryl C—H bonds. The synthetic utility and versatility of these reactions is conveyed by organizing the sections by type of heterocycle (thiophene, furan, indoles, etc.) rather than by type of catalyst. Future challenges and directions in the field are discussed in the summary.

Chapter 2 includes the alkylation of functionalized arene and heteroaromatic substrates utilizing ruthenium catalysts as detailed by Burns, Kozhushkov, and Ackermann. Electrophilic alkyl halides are omitted as chelation-assisted *ortho*-C—H activation is the focus. The sections of the chapter are organized based on the mechanistic modes of C—H cyclometalation via C—H bond cleavage, C—H oxidative addition, and carboxylate-assisted C—H activation. The summary highlights the broad applicability of the reactivity for a variety of chemical industries while identifying the need for further improvements to develop milder reaction conditions and asymmetric C—H bond functionalizations.

Chapters 3 and 4 examine olefin hydroarylation as organized by catalyst identity. In Chapter 3, McKeown, Habgood, Cundari, and Gunnoe examine d^6 transition metal catalysts for the alkylation of arenes without chelation assistance while in Chapter 4 Suslick and Tilley detail the use of d^8 transition metal catalysts. The industrial relevance of the reactions is emphasized as alkyl benzenes are precursors to large-scale chemicals such as polymer precursors and surfactants. The synergistic use of experimental and theoretical experiments for mechanistic information to further catalyst development is highlighted.

Nakao focuses on nickel-catalyzed hydroarylation of carbon–carbon multiple bonds in Chapter 5, which is an area that has experienced dramatic advancement in recent years. The characteristic features of nickel catalysis that are highlighted include reactivity with electron-deficient arenes including heteroarenes. This chapter is organized by reactions of alkenes and alkynes with fluorobenzenes, five-membered heteroarenes, and azines.

While ruthenium, rhodium, and iridium complexes are the most prevalent for directing group-assisted hydroarylation reactions, there is a growing body of work demonstrating the utility of catalysts from the first row transition metals. In Chapter 6, Yoshikai builds on the nickel catalysis discussed in Chapter 5 by examining the hydroarylation of alkynes and alkenes catalyzed by first row transition metals in groups 7–9. The majority of the chapter consists of hydroarylation reactions of alkynes and alkenes utilizing both high- and low-valent cobalt catalysts. Examples of iron complexes for the hydroarylation of alkenes and alkynes, as well as the use of a Lewis acidic iron salt for the hydroarylation of alkenes, are included. Notable at the end is a discussion on low-valent manganese complexes for the hydroarylation of alkynes.

In Chapter 7 Kirillova, Miloserdov, and Echavarren review copper, silver, and gold catalysts utilized for alkyne hydroarylation. The content is organized by the reactivity, selectivity, and mechanistic aspects of intra- and intermolecular reactions with emphasis on electron-rich heterarenes and unactivated arenes. Alkyne hydroarylation using arylboron, aryl halide, and related congeners are

reviewed by Yamamoto in Chapter 8. The organization of the sections is first by substrate, and then by catalyst identity. Alkyne hydroarylations as both singular reactions and as part of sequential processes are discussed. Both Chapters 7 and 8 feature the inclusion of synthetic applications to biologically active compounds.

In the final chapter, Chapter 9, Widenhoefer reviews the hydroarylation of allenes. In comparison with the hydroarylations of alkenes and alkynes, which often involve directed C—H bond activation, allenes undergo a π-activation followed by an arene outer-sphere addition. Organized by nucleophile with emphasis on electron-rich arenes and heteroaromatics, both intramolecular and intermolecular reactions are presented with discussion on the mechanistic details related to the modes of ring closure.

Whether read in its entirety or as a specific chapter, the reader is provided with the historical development of catalytic olefin and alkyne hydroarylation chemistry including scope, mechanistic details, and areas for future development. Examples of industrial relevance and synthetic targets are included where appropriate. It is our hope that the readers find the information useful for their endeavors in the laboratory.

References

1 Cacchi, S. (1990) The palladium-catalyzed hydroarylation and hydrovinylation of carbon-carbon multiple bonds: new perspectives in organic synthesis. *Pure Appl. Chem.*, **62**, 713–722.

2 Kakiuchi, F. and Murai, S. (2002) Catalytic C-H/olefin coupling. *Acc. Chem. Res.*, **35**, 826–834.

3 Bandini, M. and Umani-Ronchi, A. (eds) (2009) *Catalytic Asymmetric Friedel-Crafts Alkylations*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany.

1

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].

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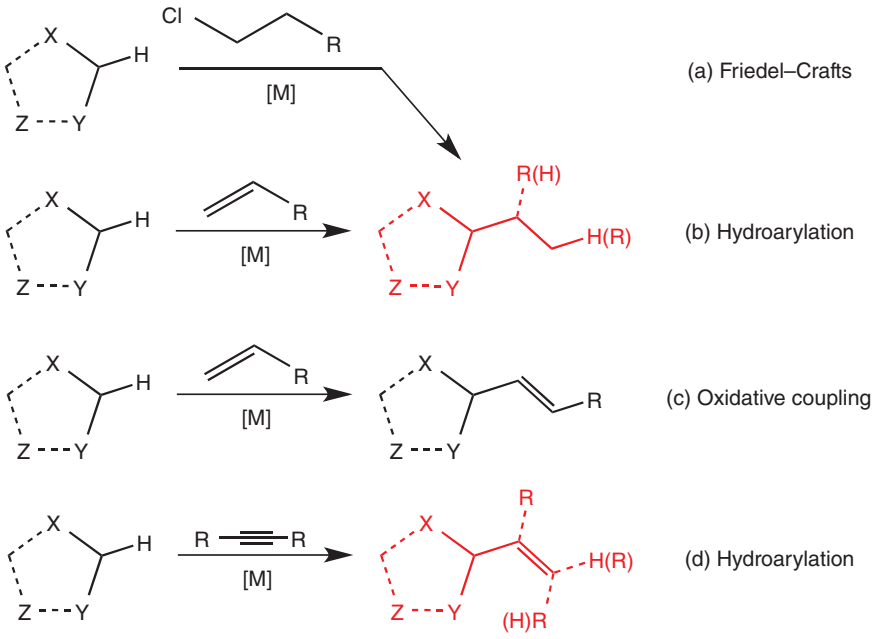

Figure 1.1 General intermolecular hydroarylation of C—C multiple bonds with (hetero)aromatic substrates and comparison to Friedel–Crafts alkylation.

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

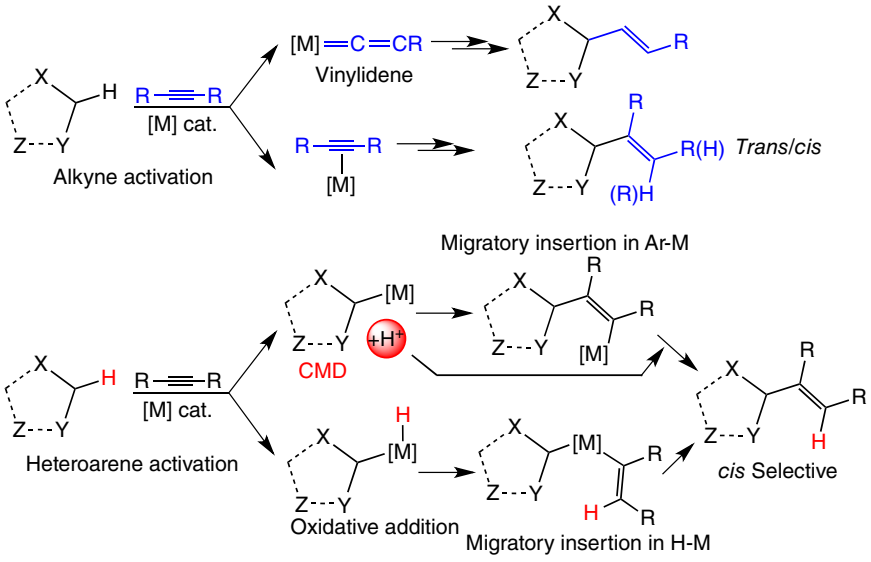

Figure 1.2 Hydroarylation of alkynes: mechanisms and selectivity of the resulting compounds.

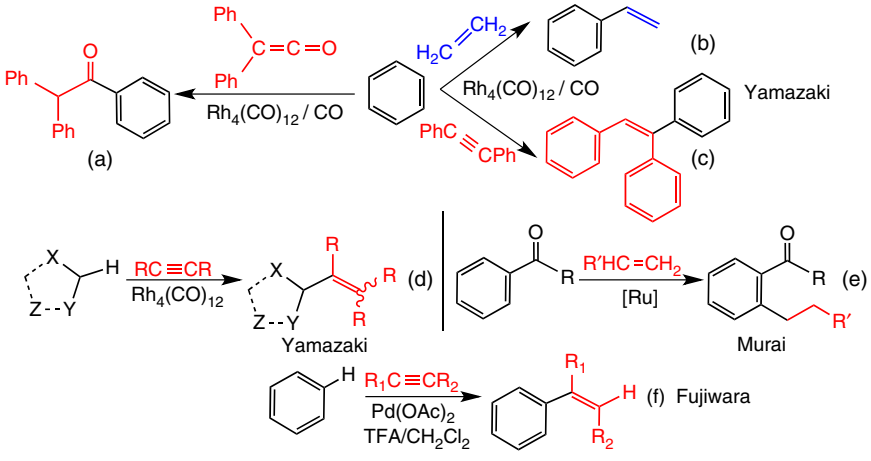

Figure 1.3 Examples of seminal hydroarylation reactions.

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

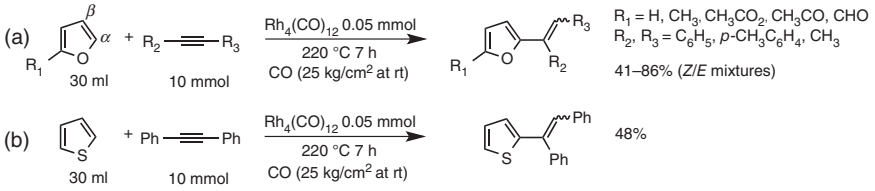

Figure 1.4 Hydroarylation of alkynes under Rh catalysis (yields are based on alkyne).

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

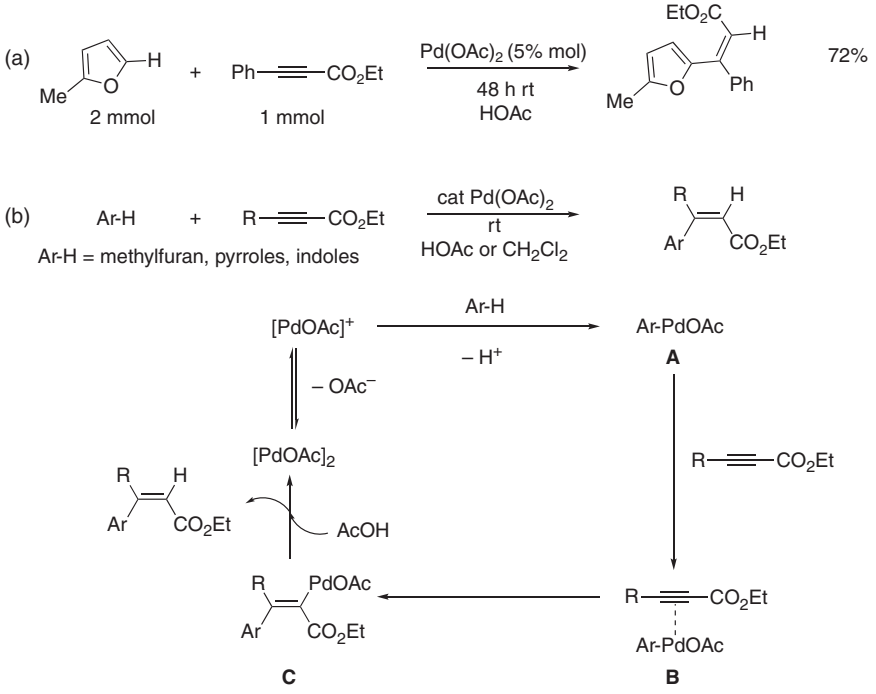

Figure 1.5 Hydroarylation of ethylphenylpropiolate with 2-methylfuran (a) and possible mechanism (b).

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**

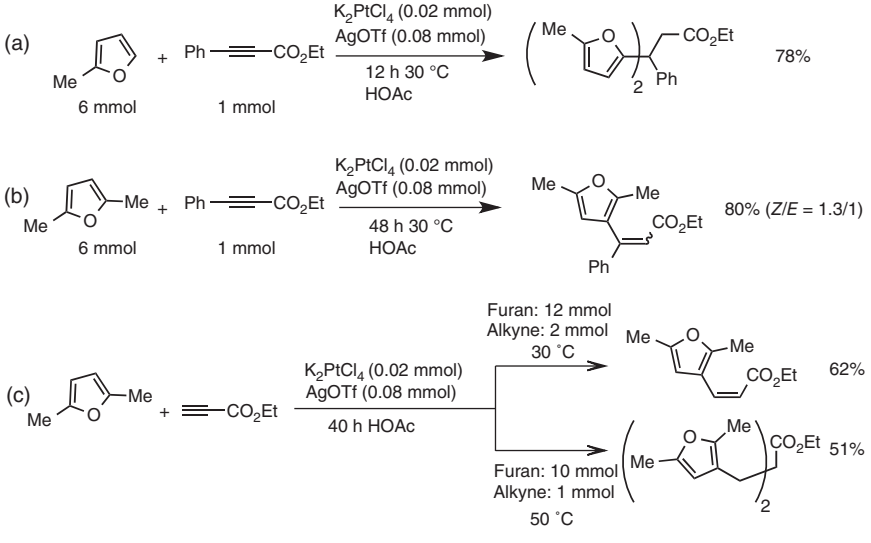

Figure 1.6 Reactions between ethylpropiolates and furans.

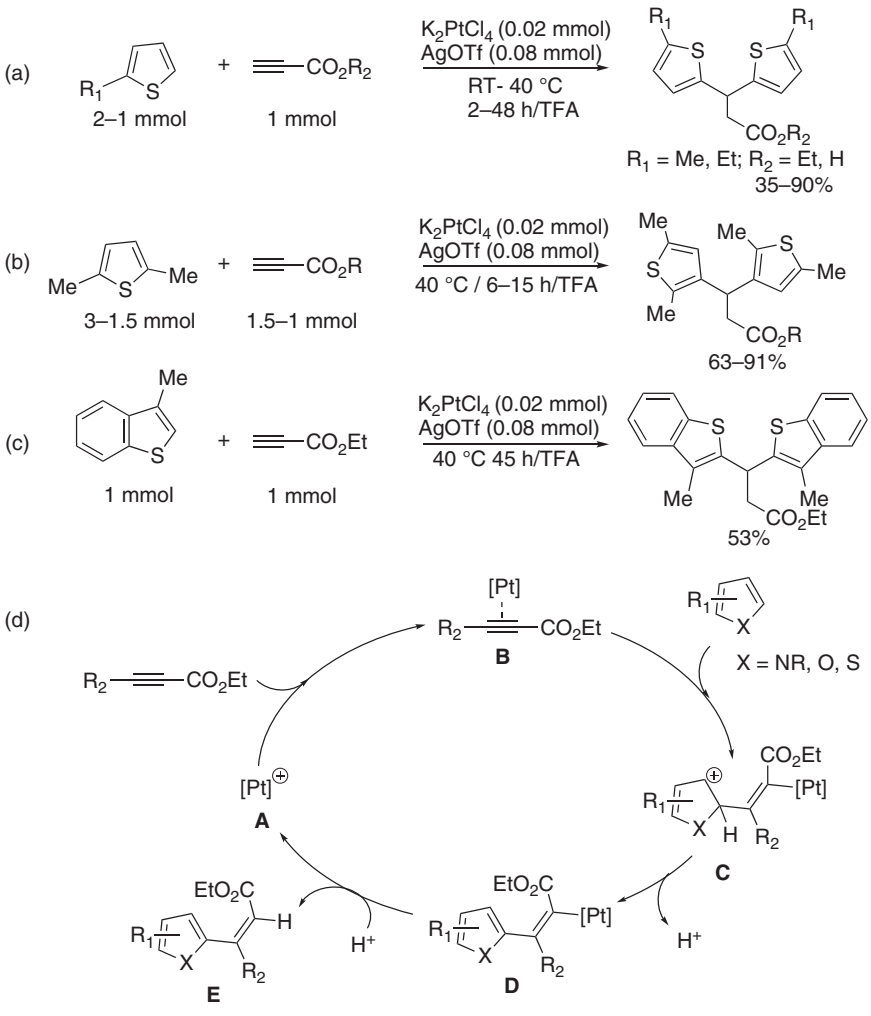

Figure 1.7 Reactions between ethylpropiolates and thiophenes, and mechanistic proposal.

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.

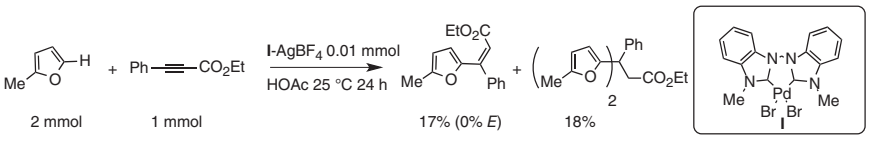

Figure 1.8 Hydroarylation of ethyl phenylpropiolate using a dicarbene Pd(II) complex.

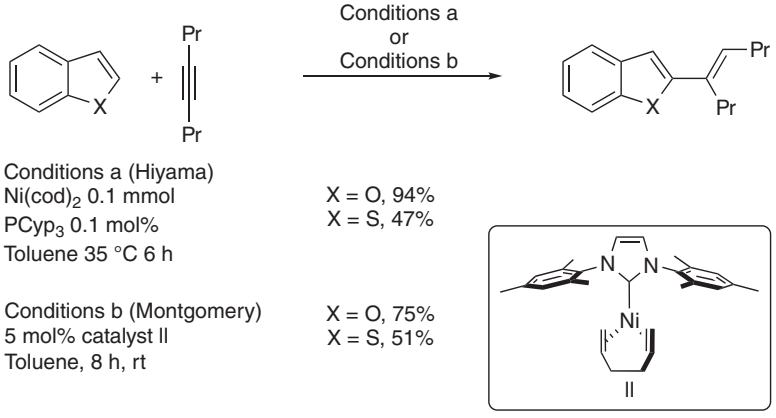

Figure 1.9 Ni-catalyzed hydroarylation of alkynes.

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

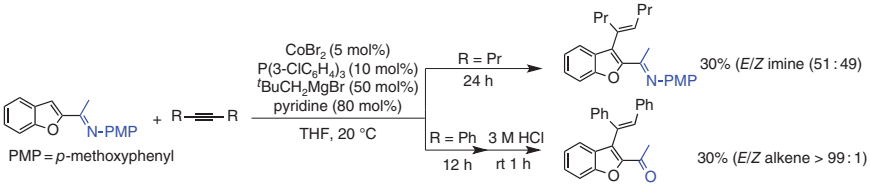

Figure 1.10 Imine as an effective directing group for the functionalization of benzofuran.

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(μ-OH)(μ-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.

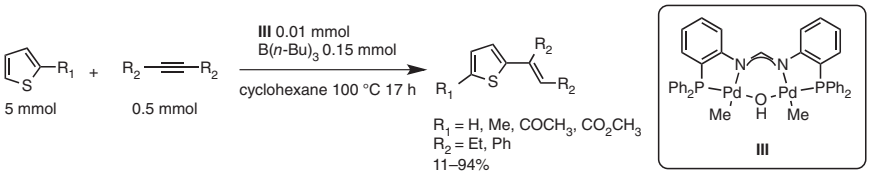

Figure 1.11 Hydroarylation of unactivated alkynes catalyzed by a Pd(II) complex.

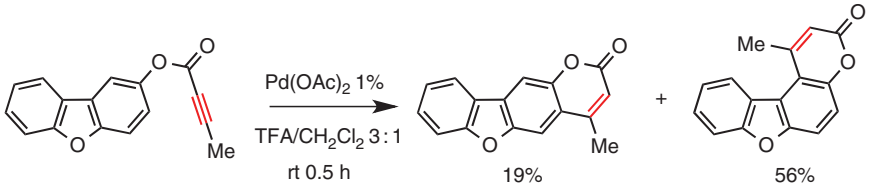

Figure 1.12 Intramolecular hydroarylation of alkynoates using $Pd(OAc)_2$ as the catalyst precursor.

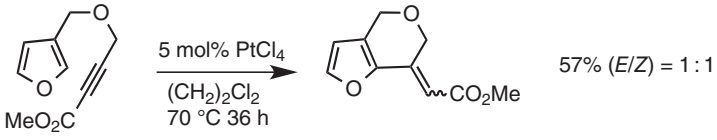

Figure 1.13 Intramolecular hydroarylation of a furan-yne substrate.

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)

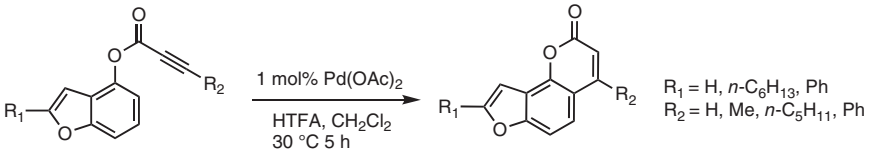

Figure 1.14 Synthesis of angelicin derivatives by intramolecular hydroarylation of benzofuran.

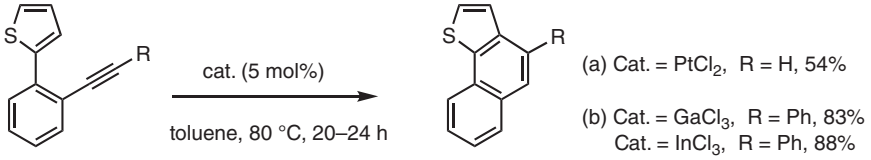

Figure 1.15 Intramolecular hydroarylation of 2-(2-ethynylphenyl)thiophene.

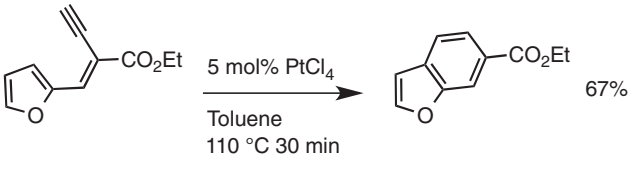

Figure 1.16 Intramolecular hydroarylation of terminal enynes catalyzed by $PtCl_4$.

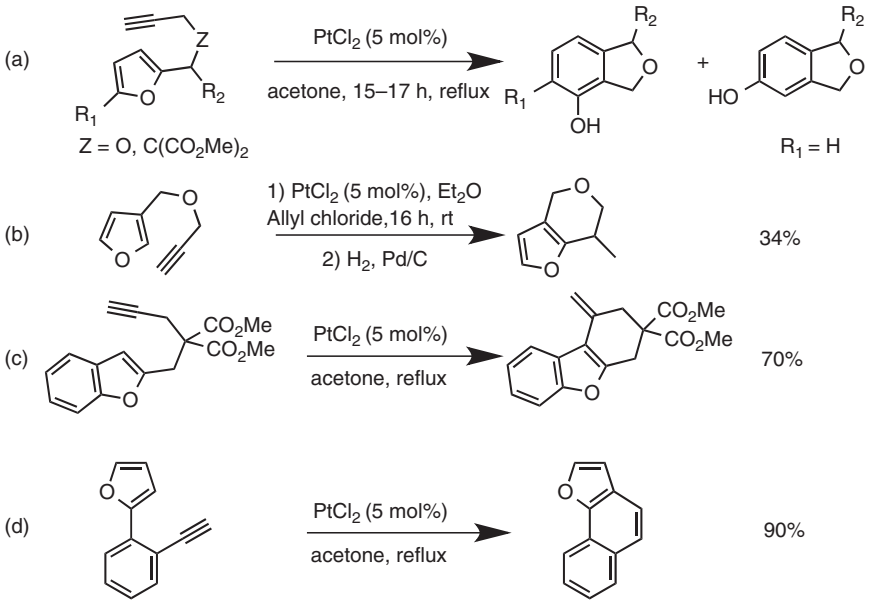

Figure 1.17 Intramolecular reactions of furylalkynes catalyzed by $PtCl_2$.

[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

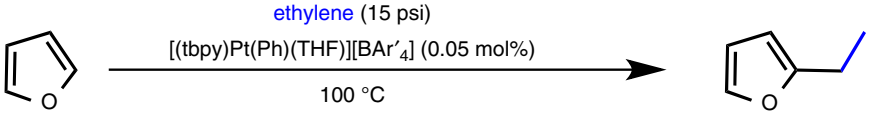

Figure 1.18 Hydroarylation of ethylene catalyzed by a bipyridine Pt(II) complex.

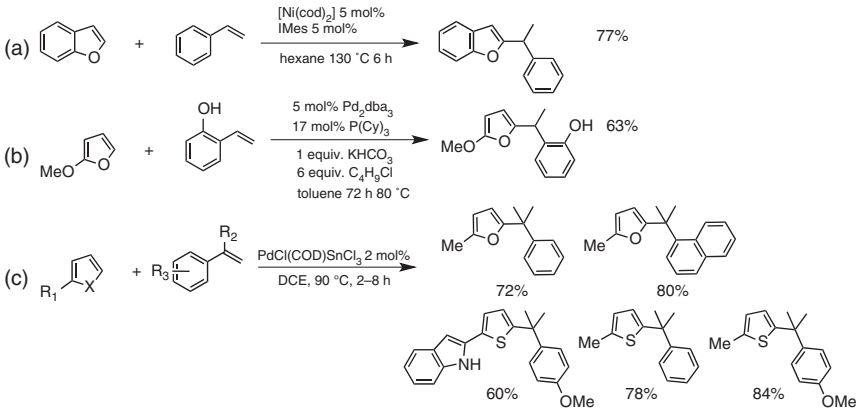

Figure 1.19 Examples of hydroarylation of styrene and styrene derivatives.

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

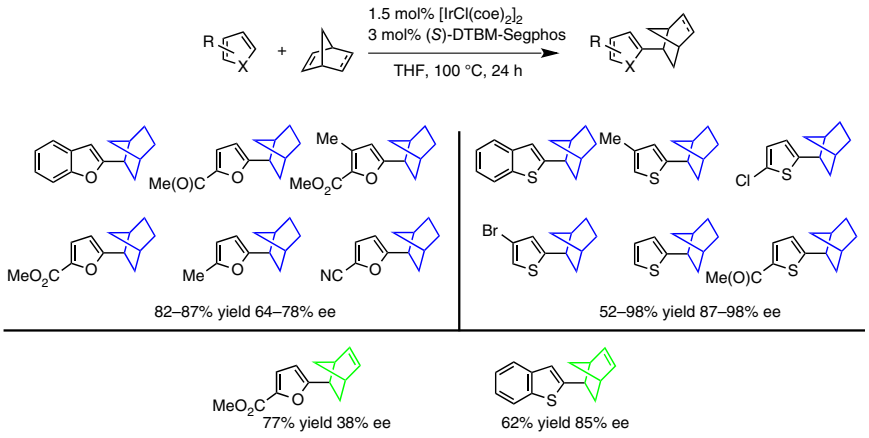

Figure 1.20 Enantioselective hydroarylation of bicycloalkenes with heteroarenes using an Ir catalyst.

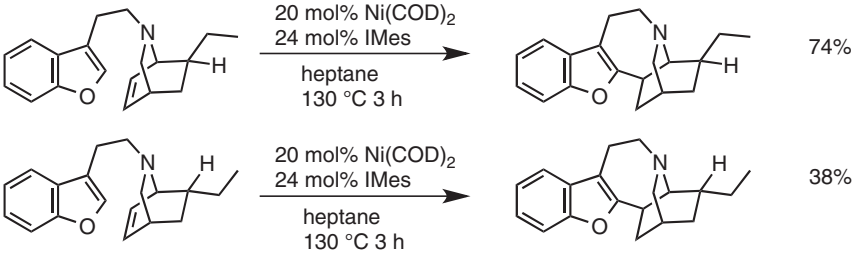

Figure 1.21 Intramolecular hydroarylations affording *Iboga* alkaloid benzofuran analogs using a Ni catalyst.

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.

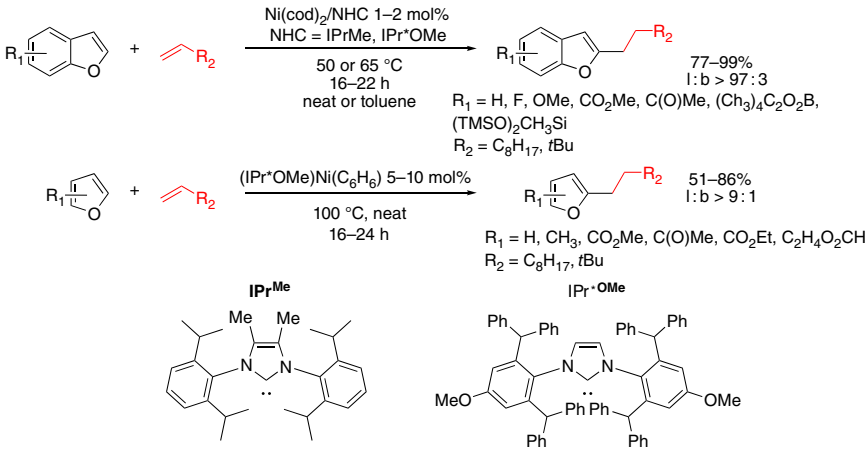

Figure 1.22 Hydroarylation of alkenes with furan and benzofuran derivatives.

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

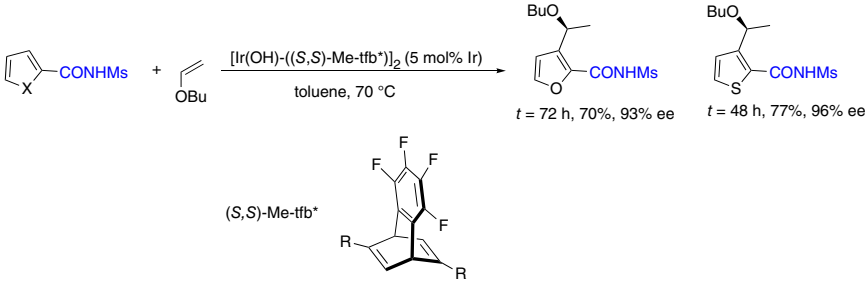

Figure 1.23 Asymmetric hydroarylation of vinyl ethers using an Ir catalyst precursor.