A number of books have been published describing different facets of the fast growing field of palladium chemistry and its applications to organic synthesis [1–5]. Also found in the literature are several review articles and book chapters summarizing the development of palladium chemistry involving heterocycles [6–11]. In this chapter, we will highlight some important name reactions involving catalytic palladium (throughout this monograph, all palladium involved is catalytic unless specified otherwise) and their mechanisms in the context of heterocyclic chemistry.

Palladium chemistry involving heterocycles has its unique characteristics stemming from the heterocycles’ inherently different structural and electronic properties in comparison to the corresponding carbocyclic aryl compounds. One example illustrating the striking difference in reactivity between a heteroarene and a carbocyclic arene is the “heteroaryl Heck reaction” (vide infra, see Section 1.4). We define a “heteroaryl Heck reaction” as an intermolecular or an intramolecular Heck reaction occurring onto a heteroaryl recipient. Intermolecular Heck reactions of carbocyclic arenes as the recipients are rare [12a–d], whereas heterocycles including thiophenes, furans, thiazoles, oxazoles, imidazoles, pyrroles and indoles, etc. are excellent substrates. For instance, the heteroaryl Heck reaction of 2-chloro-3,6-diethylpyrazine (1) and benzoxazole occurred at the C(2) position of benzoxazole to elaborate pyrazinylbenzoxazole 2 [12e].

While intermolecular Heck reaction of a carbocyclic arene as the recipient is reluctant to occur, intramolecular Heck reaction of carbocyclic arenes has been well-precedented as illustrated by the following two examples [13].
1.2.4 The Stille–Kelly coupling

The Stille–Kelly reaction is the Pd-catalyzed intramolecular aryl dihalide cyclization using ditin [44]. In 1990, en route to the total synthesis of pradimicinone, Kelly et al. synthesized tricyclic 34 by treating dibromide 32 with hexamethylditin in the presence of Pd(Ph3P)4. The intermediacy of monostannane 33 was confirmed by three experiments. (1), Pd(Ph3P)4 alone does not promote the cyclization of 32 to 34; (2), under the agency of Pd(Ph3P)4 catalysis, independently prepared 33 was converted to 34 in the absence of Me3Sn—SnMe3; (3), workup of the Me3Sn—SnMe3-mediated cyclization in the middle of the reaction reveals the presence of the monostannane 33. When the dibromide was replaced with diiodide or ditriflate, the cyclization worked as well. The Stille–Kelly reaction offers a means for predetermining the regiochemical outcome of the cyclization of unsymmetrical stilbenes, such control is not always available in photosynthesis or oxidative cyclization.

In Grigg’s approach to hippadine (37), he established the connection between the two phenyl rings via the Stille–Kelly reaction [45]. When diiodide 35 was submitted to the Pd(0)/ditin catalyst system, the intramolecular cyclization was realized to establish the C—C bond in lactam 36. Oxidation of the indoline moiety in 36 using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) then delivered hippadine (37). Analogously, the intramolecular Stille coupling of dibromide 38 led directly to hippadine (37) [46].
we define a “heteroaryl Heck reaction” as an intermolecular or an intramolecular Heck reaction that occurs onto a heteroaryl recipient. Such heteroaryl Heck reactions may be exemplified by the Pd-catalyzed reaction between iodobenzene and thiazole to assemble 5-phenylthiazole [73]. The addition occurs regioselectively at the electron-rich position C(5) of the thiazole ring.

![Chemical Reaction](image)

In one possible mechanism, oxidative addition of iodobenzene to Pd(0) gives Pd(II) intermediate 74, which subsequently inserts into thiazole regioselectively at the C(5) position to form the σ-adduct of arylpalladium(II) 75. The order of reactivity is similar to the electrophilic substitution, which is known to be C(5) > C(4) > C(2) [74]. Treatment of the insertion adduct 75 with a base regains the aromaticity after deprotonation, giving rise to 73 along with Pd(0) for the next catalytic cycle.

![Mechanism Diagram](image)

An intramolecular heteroaryl Heck was the pivotal step in the synthesis of 5-butyl-1-methyl-1H-imidazo[4,5-c]quinolin-4(5H)-one (76), a potent antiasthmatic agent [75]. The optimum yield was obtained under Jeffery’s “ligand-free” conditions.

![Synthetic Reaction](image)

Normally, the oxidative addition of an aryl chloride to Pd(0) is reluctant to take place. But such a process is greatly accelerated in the presence of sterically hindered, electron-rich phosphine
Grigg extended this alkyne cyclization to trapping with stannanes to give 3-exo-dienes [347], alkynes to afford tetracycles [338, 348], and alkenes leading to cyclopropanes [349], an example of which is illustrated. In his studies Grigg and co-workers have found that thallium and silver salts suppress direct capture of these palladium intermediates prior to capture [350].

Overman’s exhaustive study of the Pd-catalyzed cyclization of o-halo-N-acryloylanilines leading to spirooxindoles and related compounds has paid great dividends in advancing the art of organic synthesis [351–360]. Overman and his co-workers have developed this chemistry for the asymmetric synthesis of spirooxindoles leading to either enantiomer of physostigmine (293) [355, 359] and physovenine [359], for gelsemine studies [352, 353], and, via a spectacular bis-Pd-catalyzed cyclization, to total syntheses of chimonanthine and calycanthine [355], as summarized in the transformation of 294 to 295. Hiemstra, Speckamp and co-workers have pursued similar studies of Pd-catalyzed cyclizations to spirooxindoles, culminating in total syntheses of (±)-gelsemine and (±)-21-oxogelsemine [361].
In addition, ortho-lithiation of halopyridines with bulky bases such as LDA was followed by reaction with \( R_3 SnCl \) to produce the desired halostannylpyridines as bifunctional building blocks [54, 55].

![Chemical Reaction](attachment:image.png)

The second procedure for preparing pyridylstannanes is halogen-metal exchange of a halopyridine using \( BuLi \) followed by quenching the resulting lithiopyridine with \( Bu_3 SnCl \). Interestingly, halogen-metal exchange of 2,5-dibromopyridine occurred \textit{regiospecifically at C(5)}, giving rise to 2-bromo-5-lithiopyridine, which upon treatment with \( Bu_3 SnCl \) afforded 2-bromo-5-(tributylstannyl)pyridine (69) [56].

![Chemical Reaction](attachment:image.png)

The third methodology in pyridylstannane synthesis is unique to 2,6-dihalopyridines whose synthesis using the conventional lithiation method is low-yielding (17% yield) [57]. Schubert \textit{et al.} prepared 2,6-bis(trimethyltin)pyridine (70) \textit{via} an \( S_N Ar \) displacement of 2,6-dichloropyridine with sodium trimethylstannane, derived \textit{in situ} from trimethyltin chloride [58–60].

![Chemical Reaction](attachment:image.png)

The fourth approach involves the Pd-catalyzed reaction between a halopyridine (or a triflate) with hexaalkylstannite. This protocol is especially applicable to substrates with base-sensitive moieties. Pyridylstannane 72 was synthesized from the Pd-catalyzed cross-coupling of bromopyridine 71 and hexamethyldistannane [61].
give the corresponding cross-coupled product 75 in moderate yield in the presence of catalytic Pd(Ph₃P)₄ and 3 equivalents of TBAF [65]. In this case, more than one equivalent of fluoride ion was needed to form a pentacoordinated silicate. On the other hand, alkyltrifluorosilane 74 was prepared by hydrosilylation of the corresponding terminal olefin with trichlorosilane followed by fluorination with CuF₂. This method provides a facile protocol for the synthesis of alkyl-substituted aromatic compounds.

\[
\begin{align*}
\text{MeO}_2C\text{O} & + \text{F}_3\text{SiO} \xrightarrow{\text{Pd(Ph}_3\text{P)}_4, \text{TBAF}} \text{MeO}_2C\text{O} \\
73 & \quad 74 \quad \text{THF, 36\%} \\
\end{align*}
\]

6.4 Sonogashira reaction

Alkynylfurans are readily prepared via the Sonogashira reactions of halofurans [66, 67]. Due to activation of the α-positions, regioselective Sonogashira reaction can be achieved at C(2) rather than C(3) [35, 68].

\[
\begin{align*}
\text{OHC}&\text{-Br} \quad + \quad \equiv \quad \xrightarrow{\text{PdCl}_2(\text{Ph}_3\text{P})_2, \text{CuI, Et}_3\text{N}} \quad \text{OHC} \\
\text{Br} & \quad \equiv \quad \text{OHC} \\
\end{align*}
\]

Applying a strategy akin to Yanaka’s furopyrimidine synthesis [24], a Merck process group synthesized functionalized furo[2,3-b]pyridine 78 [69]. Pd-catalyzed coupling of iodopyridone 76 and trimethylsilylacetylene led to alkynyl pyridone 77 using n-BuNH₂ as the base, whereas Et₃N, i-Pr₂NEt, and K₂CO₃ were inferior. Subsequent cyclization of 77 provided an expeditious entry to furo[2,3-b]pyridine 78. Analogously, nucleoside analogs with an unusual bicyclic base 81 were prepared from alkyne 80, the Sonogashira adduct of iodouracil 79 [70].

\[
\begin{align*}
\text{EtO}_2\text{C} & + \equiv\text{TMS} \xrightarrow{1\% \text{Pd(OAc)}_2, 2\% \text{Ph}_3\text{P}, 2\% \text{CuI, 2 eq. BuNH}_2} \text{EtO}_2\text{C} \\
\text{I} & \quad \equiv \quad \text{TMS} \\
\text{76} & \quad 77 \\
\text{THF, 38 \degree C, 18 h, 81\%} \\
\end{align*}
\]