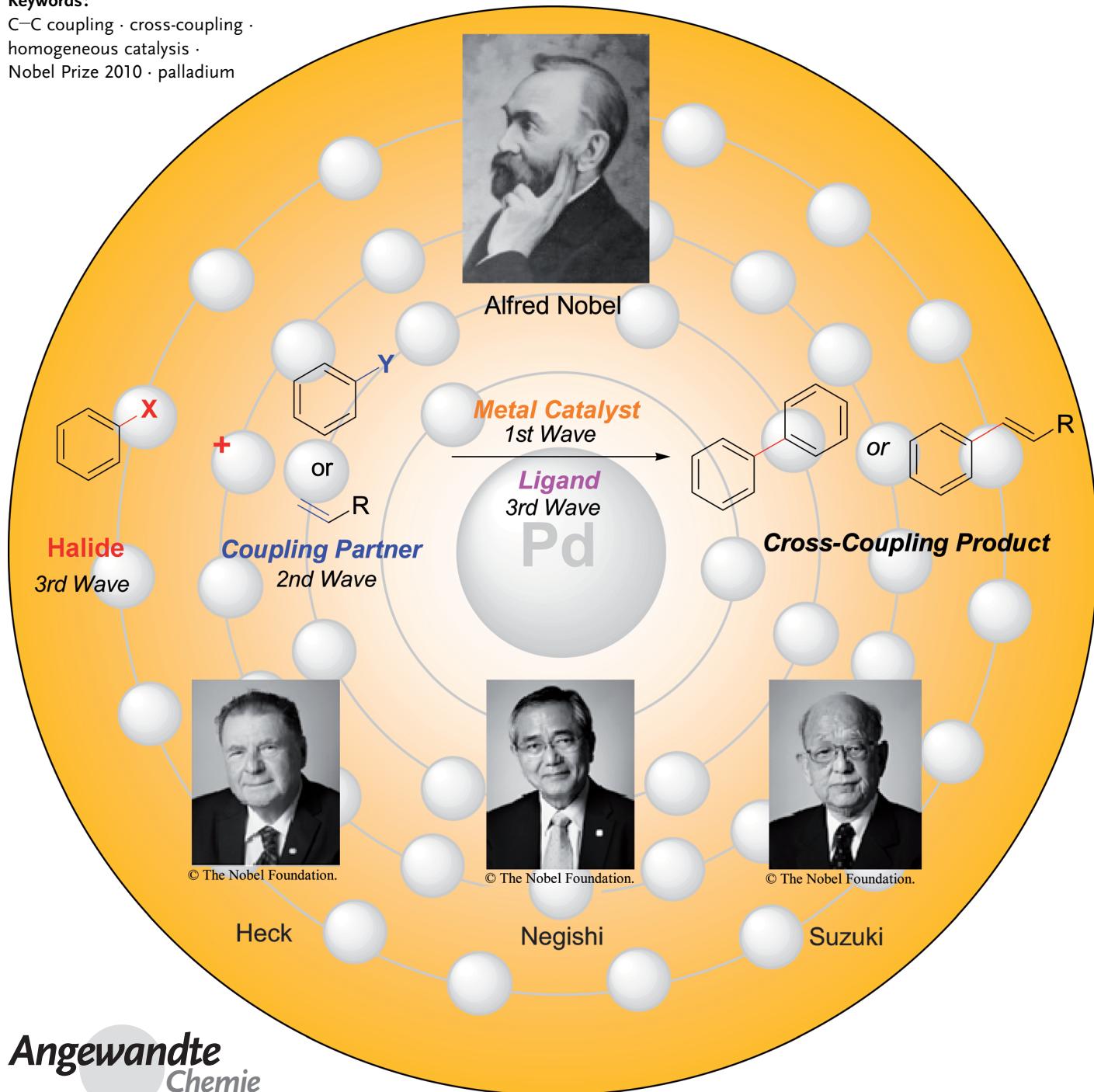


Palladium-Catalyzed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize

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C–C coupling · cross-coupling · homogeneous catalysis · Nobel Prize 2010 · palladium



In 2010, Richard Heck, Ei-ichi Negishi, and Akira Suzuki joined the prestigious circle of Nobel Laureate chemists for their roles in discovering and developing highly practical methodologies for C–C bond construction. From their original contributions in the early 1970s the landscape of the strategies and methods of organic synthesis irreversibly changed for the modern chemist, both in academia and in industry. In this Review, we attempt to trace the historical origin of these powerful reactions, and outline the developments from the seminal discoveries leading to their eminent position as appreciated and applied today.

1. Introduction

The award of the 2010 Nobel Prize in Chemistry to Richard Heck (Figure 1a), Ei-ichi Negishi^[2] (Figure 1b), and Akira Suzuki^[3] (Figure 1c) was a monumental event that was applauded by chemists worldwide. Prior to the event, wherever and whenever chemists met, these names, of course among select others, were frequently overheard as potential candidates since their discoveries laid the foundations of the field of palladium-catalyzed cross-coupling reactions. Their observations revolutionized the way chemists conceptualized and constructed molecules whilst simultaneously providing methods for previously impossible, yet highly significant, C–C bond forming processes. With time, these discoveries served to inspire chemists to develop a wide-range of additional cross-coupling reactions such as carbon–heteroatom coupling, α -arylation, direct arylation by C–H activation, and decarboxylative coupling, to name but a few terms. Researchers worldwide strove to extend, apply, and discover new variants of these powerful chemistries and, indeed, such efforts continue at an ever increasing pace today. As depicted in Figure 2, substantial growth in this area has taken place during the last decade in terms of publications and patents^[4] with the Suzuki–Miyaura cross-coupling proving by far the most popular, followed by the Heck and Sonogashira coupling reactions. Nonetheless, all of the palladium-mediated transformations continue to enjoy avid attention from the academic and industrial communities.

The generally accepted mechanisms for these palladium-catalyzed cross-coupling reactions are depicted in Scheme 1.^[5] Common to both types of coupling reaction is the oxidative addition of the aryl halide (or pseudohalide) to the catalytically active L_nPd^0 species which initiates the catalytic cycle. At this stage the processes diverge. In the Mizoroki–Heck coupling,^[6] the reaction progresses by co-ordination of an alkene to the Pd^{II} species, followed by its *syn* migratory insertion. The regioselectivity of this insertion depends on the nature of the alkene, the catalyst, and the reaction conditions employed. The newly generated organopalladium species then undergoes *syn* β -hydride elimination to form the alkene product. Subsequently, base-assisted elimination of H–X from $[L_nPd(H)(X)]$ occurs to regenerate the L_nPd^0 catalyst ($n=2$ typically).^[7] Alternatively, in the Negishi and Suzuki–

Miyaura reactions (and the related Corriu–Kumada, Stille, and Hiyama coupling processes), the oxidative addition is followed by transmetalation of an organometallic species to generate a Pd^{II} intermediate bearing the two organic coupling partner fragments. Subsequent reductive elimination results in C–C bond formation with the regeneration of Pd^0 species to re-enter into the catalytic cycle.

These cross-coupling processes have a rich and intriguing history commencing in the 19th century. The earlier discoveries of the conceptually related metal-mediated homocoupling processes, for example, Ullmann and Kharasch to name two, perhaps originally inspired chemists to ponder over the possibility of forming a C–C bond selectively between two different, rather than two identical, structural fragments. The issue of selectivity in cross-coupling reactions is of decisive significance, since a number of possible side reactions (e.g. homocoupling, isomerization, β -hydride elimination, and functional group interferences) must be avoided to develop a generally practical method for use in organic synthesis. The 1970s was ripe with innovation in the field of transition-metal catalysis with important contributions from Beletskaya, Corriu, Kumada, Kochi, Murahashi, Sonogashira, Stille, Trost, Tsuji, and Akio Yamamoto. These contributions, among which stand the defining work by Heck, Negishi, and Suzuki, demonstrated that carbon atoms in all hybridization states (dominated by sp^2 carbon) undergo C–C bond forming

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Figure 1. a) Prof. Heck during a 2006 sabbatical stay at Queen's University, Canada with Prof. Snieckus. b) Prof. Negishi delivering his 2010 Nobel lecture. c) Prof. Suzuki (center) in front of a photograph of Victor Grignard (Lyon University, France). As Grignard memorably quoted “Chacun de nous a son étoile. Suivons-la en nous félicitant de la voir chaque jour un peu plus loin”^[1] with Prof. Tamao and Prof. Fu (left) and Dr. Colacot and Prof. Hiyama (right) in 2007.

reactions under palladium catalysis. This work ushered in a new era in organic chemistry, which stimulated dedicated research efforts worldwide towards broadening the scope of all of these reactions. As a consequence, coupling reactions under milder conditions with lower Pd loadings were developed, using more efficient catalytic systems by incorporating a plethora of ligands with different steric and electronic properties. These powerful ligands ultimately led to the discovery of new cross-coupling reactions generating other bonds (e.g. C–N, C–O, C–P, C–S, C–B).

In a broad sense, the development of coupling chemistry outlined above may be contemplated to occur over three periods or waves after the discovery of cross-coupling as a concept:

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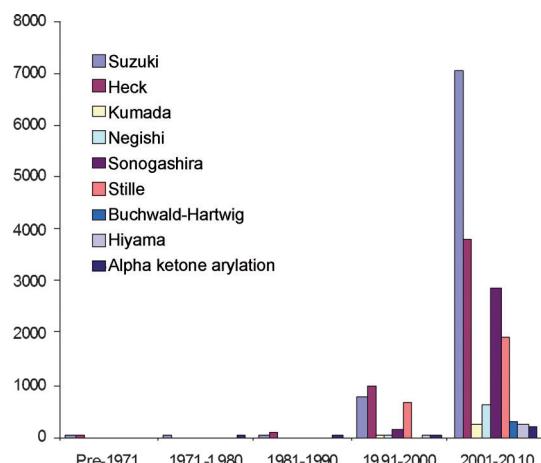
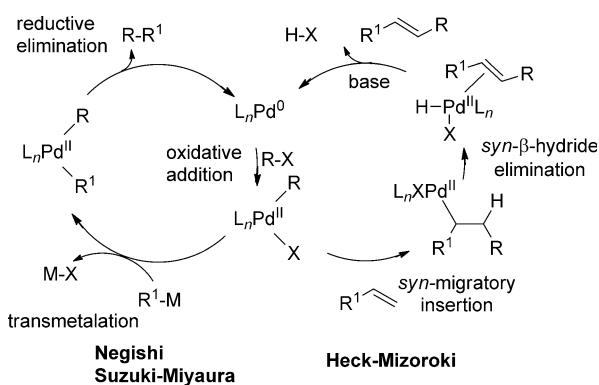
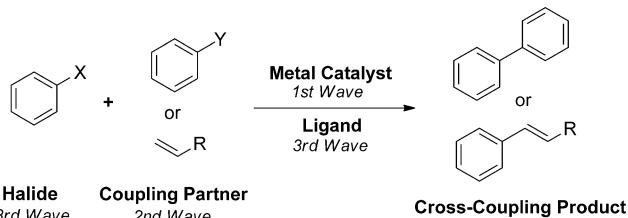


Figure 2. Growth in the number of publications and patents on named metal-catalyzed cross-coupling reactions.



Scheme 1. General catalytic cycles for Mizoroki–Heck, Negishi, and Suzuki–Miyaura reactions.

1st wave: investigation of the metal catalysts capable of promoting these transformations in a selective fashion, 2nd wave: expansion of coupling partner scope, and 3rd wave: the continuous improvement and extension of each reaction type through ligand variation, accommodating wider substrate scope, by reaction optimization and fine tuning (Scheme 2).



Scheme 2. The three waves of coupling chemistry as defined by reaction component.

Herein, we attempt to trace the origin of these chemistry household-name reactions and chart their evolution throughout the last century using these waves to frame our discussion (Figure 3), whilst guiding the reader to the original reports and key developments of coupling processes from the earliest examples to the 21st century.^[8] Given the nature of this task, the treatment of each reaction type must be brief, and any omissions are unintentional. Since the 2010 Nobel Prize was awarded for contributions specifically to the field of palladium-catalyzed cross-coupling reactions, our focus will be on the use of this metal although, in some discussions, other metals will be mentioned to give a more complete historical perspective. Owing to space limitation, we are unable to cover all the latest developments in detail, although the important findings are highlighted.

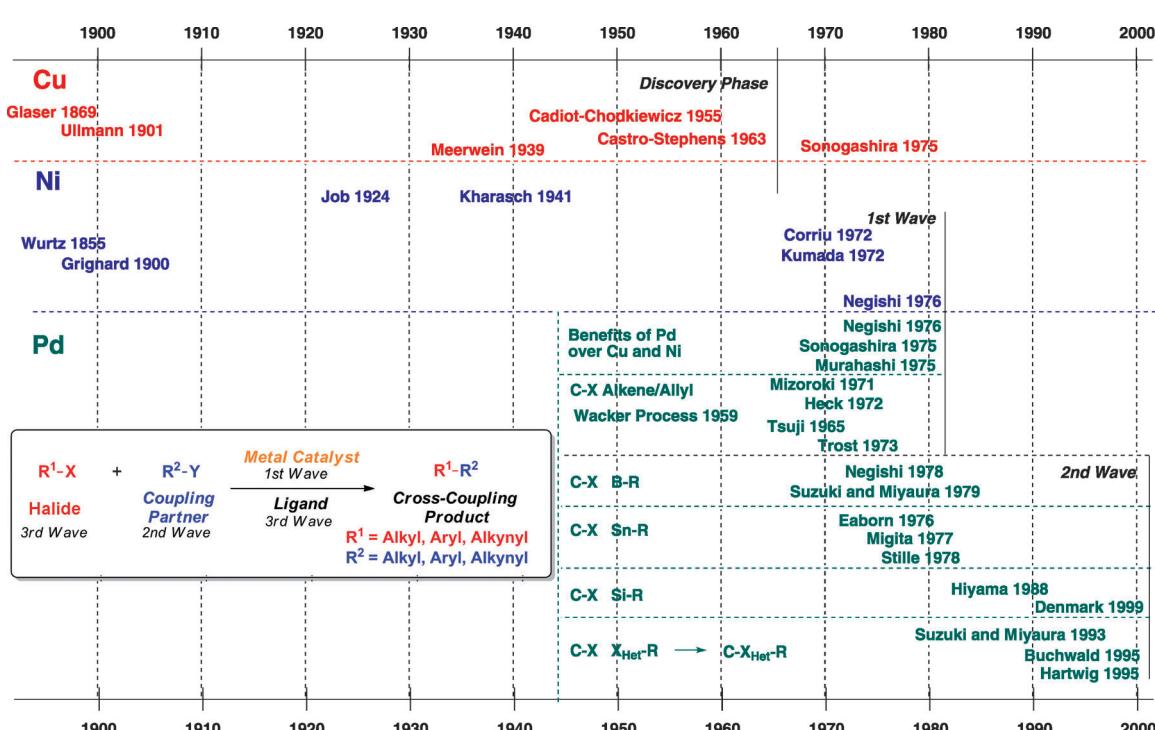


Figure 3. Timeline of the discovery and development of metal-catalyzed cross-coupling reactions.

2. The Origins of Cross-Coupling Reactions

2.1. Discovery (1869–1963): Functionalization of Alkyl and Aryl Halides by Metal Catalysis

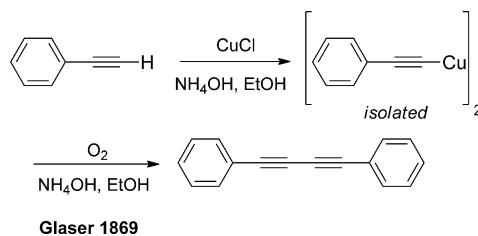
2.1.1. Stoichiometric Cross- and Homocoupling Processes

The development of metal-catalyzed cross-coupling reactions begins with some of the oldest known transformations in organic chemistry—stoichiometric metal-promoted homocouplings. Thus, the first examples of coupling—the use of metals to assemble carbon–carbon bonds between appropriately functionalized sp, sp², or sp³ centers—are found in the 150-year old literature. Without delving into a comprehensive review of transformations during this period, a discussion of the origins of cross-coupling is incomplete without a description of the initial stoichiometric processes that set the foundation for the later discoveries. With this knowledge, the modern chemist will appreciate the problems faced in the achievement of the original results and more clearly understand and respect the progress throughout the development of cross-coupling reactions.^[9]

The initial discoveries in the field of coupling chemistry came to light largely in two areas: organocopper and alkali/alkali-earth organometallic chemistry.

2.1.1.1. Copper-Mediated Process

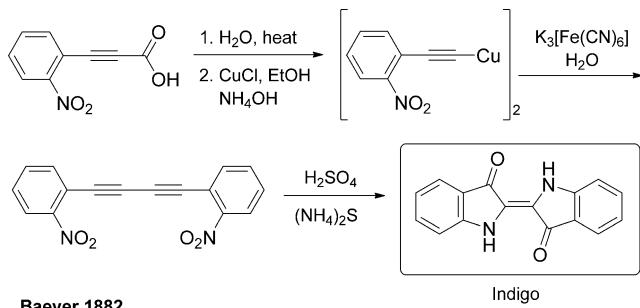
Historically, copper-promoted coupling began in 1869 when Glaser reported the homocoupling of metallic acetylide (Scheme 3).^[10,11] In these seminal studies, Glaser de-



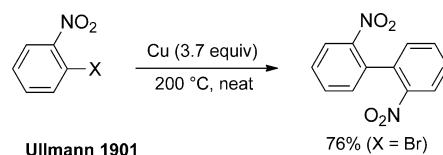
Scheme 3. The Glaser coupling.^[11]

scribed the oxidative dimerization of both copper and silver phenylacetylide to give diphenyldiacetylene in an open flask. Although the initial method involved the isolation of the potentially explosive^[12] copper acetylene intermediate, the advantages of this new sp-sp bond forming reaction were appreciated by the synthetic community during the following decades, for the construction of various acetylenic compounds. An impressive example of the use of the Glaser coupling for the synthesis of indigo by Baeyer (Scheme 4) in 1882^[13] is clearly a forerunner of the modern combined transition-metal-catalyzed Sonogashira–heteroannulation strategies for indoles and related heterocycles.

Following the development of C(sp)–C(sp) homocoupling, the copper method was extended to C(sp²)–C(sp²) bond formation. In 1901, Ullmann reported the dimerization of 2-bromo- and 2-chloronitrobenzene promoted by the use of superstoichiometric copper sources (Scheme 5).^[14,15] As is typical of the early copper-mediated reactions, the trans-



Scheme 4. Baeyer's synthesis of indigo.^[13]

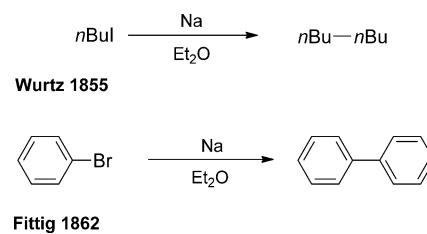


Scheme 5. The Ullmann reaction.^[14]

formation required fairly forcing conditions.^[16] The Ullmann dimerization, although linked to the Glaser-type process that preceded it, differed in one fundamental regard: *the dimerization occurs between carbons bearing halogens rather than between simple unfunctionalized carbon systems.*^[14,15] This theme of using carbon atoms bearing halogens for coupling chemistry was concurrently being developed in the areas of organomagnesium (Grignard) and organosodium (Wurtz–Fittig) chemistry.

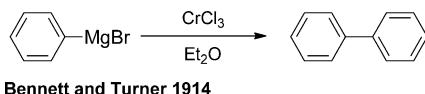
2.1.1.2. Organomagnesium and Organosodium Reagents in Coupling Processes

Alongside the fledgling developments in copper-mediated processes, advances were being made in the arena of organo-alkali-metal reagents. Studies on the generation of organosodium and organopotassium species had already revealed their pyrophoric character and high reactivity.^[17] As early as 1855,^[18] Wurtz reported the homodimerization of alkyl halides in the presence of metallic sodium and by 1862 Fittig extended this work to include the homodimerization of aryl halides^[19] in addition to his work with Tollens on the reaction of alkyl halides under similar conditions (Scheme 6).^[20] Undoubtedly, the ferocious reactivity of Na and K reagents limited the application of these reagents and led to the investigation and development of the milder



Scheme 6. Sodium-mediated dimerization of alkyl and aryl halides.^[18,19]

nucleophilic Grignard reagents^[21] in the early part of the 20th century. However, the reactivity with alkyl and aryl halide derivatives of even these softer reagents was limited and subject to numerous side reactions. The formation of C(sp²)–C(sp²) bonds using Grignard reagents was, to our knowledge, unknown until the report of Bennett and Turner in 1914^[22] who described the dimerization of phenylmagnesium bromide through the use of stoichiometric quantities of chromium(III) chloride (Scheme 7). A few years later, Krizewsky and Turner also reported a CuCl₂ promoted homocoupling reaction.^[23]



Scheme 7. Chromium chloride promoted dimerization of Grignard reagents.^[22]

Despite these remarkable achievements, the early metal-promoted reactions were limited in two key ways: 1) the use of poorly soluble, *stoichiometric or superstoichiometric metal reagents* and 2) issues of *selectivity* for coupling plagued these early procedures. The transformations were limited to homocoupling and often led to various side reactions and unwanted byproducts. The first glimpses of a solution to both these issues appeared during the first half of the 20th century, opening the door to new possibilities and, ultimately, to the powerful selective catalytic methods that we know and value today.

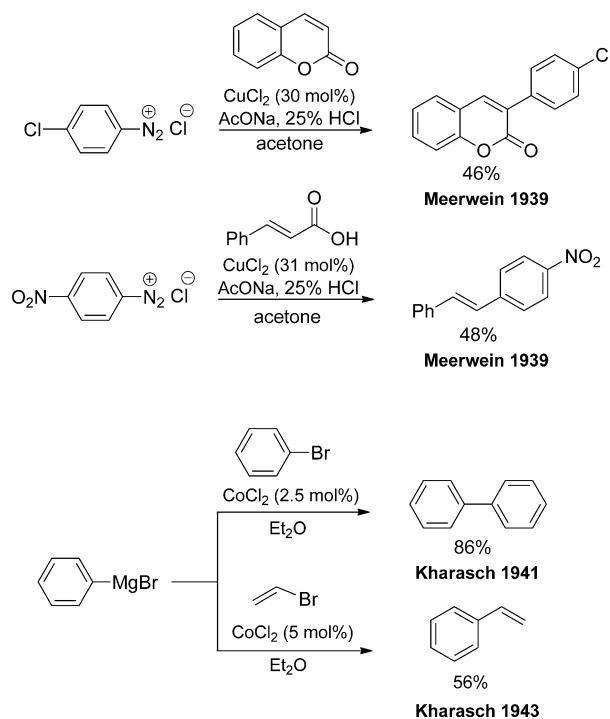
2.1.2. The Advent of Catalysis: Meerwein Arylations (1939) and Grignard-Based Kharasch Couplings (1941)

Although catalytic quantities of copper had been shown to promote the C–O coupling reaction of phenols with aryl halides as early as 1905 by Ullmann,^[24] the use of catalytic metals for the formation of C–C bonds somehow remained an elusive concept during the first part of the 20th century. The origin of catalysis for the construction of C–C bonds is shrouded by the fog of World War I. Corriu^[25] has drawn attention to the unnoticed work of Job, a French chemist working in the interwar period, who discovered as early as 1923 the action of NiCl₂ on phenylmagnesium bromide in the presence of ethylene, carbon monoxide, hydrogen and other gases—work which would be extended into the catalytic realm a year later.^[26] In his 1924 paper, Job attempted to draw the scientific community's attention to the importance of these observations with an inviting statement:

“Bref, nous croyons réaliser un progrès en introduisant la catalyse dans le domaine des organométalliques.”—“Briefly, we believe that we have made progress by introducing catalysis into the field of organometallics.”^[27]

Job's insightful observations have been largely forgotten and not cited by succeeding researchers. A similar story unfolded for other early observations (Scheme 8). In 1939, Meerwein reported the effects of catalytic copper(II) salts on the coupling of aryldiazonium salts with substituted

alkenes.^[28] Although the reactions described were limited to coumarins and cinnamic acids, and would themselves be expanded in later years, the significance of Meerwein's observations in the field of cross-coupling, especially decarboxylative coupling, appear to have been lost. The first systematic investigation of transition-metal-catalyzed C(sp²)–C(sp²) coupling is found in a 1941 publication by Kharasch^[29] concerning the observation of homocoupling of Grignard reagents, a reaction further described in general terms in his monumental book on Grignard reagents.^[30] In 1943,^[31] and in subsequent studies during the 1940s, this work was extended to the cross-coupling of vinyl bromide with aryl organomagnesium species using cobalt chloride. These studies represent the earliest reports of a *cross-coupling product*—the use of metals to connect two *different coupling partners* (Scheme 8) and, in contrast to that of Job, appears to have influenced, in time, the succeeding chemistry community. Thus, only in the 1970s Kochi would go on to investigate the mechanism of these processes and also to demonstrate Ag,^[32] Cu,^[33] and Fe^[34] salt catalysis under similar conditions. Kochi's careful and insightful work is of paramount significance to the current understanding of the mechanistic aspects of these reactions.^[35,36]



Scheme 8. The first examples of catalysis in couplings for C–C bond formation: Meerwein and Kharasch couplings.^[28, 29, 31]

Although the early Meerwein- and Kharasch-type couplings were extremely limited in substrate scope and functional-group compatibility, they had demonstrated a fundamental premise that would serve as the foundation for all of the coupling chemistry to follow: *Transition metals could be used in catalytic quantities to form carbon–carbon bonds.* Unfortunately, the limitations noted above rendered these

conditions unsuitable for broad application in synthesis. In particular, a fundamental problem of selectivity lay at the core of the cobalt- and nickel-promoted couplings, namely the ratio of the homo-coupling to cross-coupling product observed was highly substrate specific, producing uncontrollably variable yields. Thus, advances in the field awaited discovery of conditions which increased selectivity in favor of the cross-coupling product.

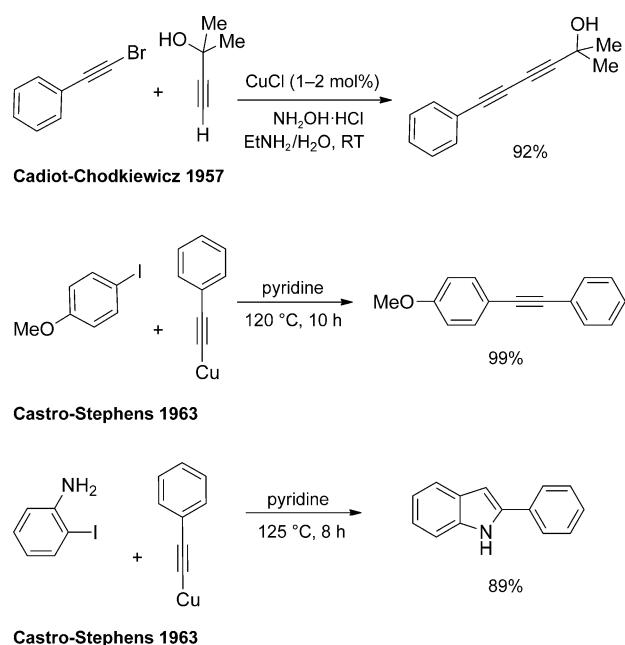
2.1.3. The First Selective Cross-Couplings: Cadiot–Chodkiewicz Coupling (1955) and Castro–Stephens Coupling (1963)

In 1955, the copper-catalyzed coupling of alkynes with bromoalkynes ($C(sp)-C(sp)$ coupling) was communicated by Cadiot and Chodkiewicz,^[37] followed swiftly by a full report by Chodkiewicz in 1957 (Scheme 9).^[38] In 1963, Castro and

selective $C-C$ bond formation between sp and sp carbon centers (Cadiot–Chodkiewicz) or sp and sp^2 carbon centers (Castro–Stephens), the framework of the cross-coupling concept began to emerge.

Moreover, by this point in the history of coupling chemistry, a set of standard requirements for coupling processes became apparent. In the broadest sense, any coupling procedure required three components to achieve a selective cross-coupling event: 1) an *organohalide*, usually aryl or alkynyl, as a coupling partner; 2) a *stoichiometric organometallic partner*, either prepared separately (Kharasch coupling) or *in situ* (Cadiot–Chodkiewicz coupling) to prevent homocoupling of the halide coupling component; 3) a *transition metal*, in stoichiometric or catalytic quantities, to effect the $C-C$ bond forming event. These components would prove to be the guiding principle in coupling chemistry throughout the next 50 years.

Organic chemists are experimental scientists, thus the next aim, of controlling the reactivity and selectivity of a coupling reaction, was approached in a systematic empirical fashion. In the initial studies, considerable variation of both the nature of the catalyst and organometallic coupling reagent were tested to expand the substrate scope by including various sp^2 and sp^3 coupling partners. However, in the course of these early days, industrial activity at Wacker and Hoechst, coupled with discussion between two chemists at Hercules, would provide a fertile ground for serendipity in discovery and the basis of a monumental surprise.



Scheme 9. The Cadiot–Chodkiewicz and the Castro–Stephens reactions.^[38,39]

Stephens reported the $C(sp)-C(sp^2)$ coupling involving aryl or vinyl halides with alkynes derivatized as copper salts.^[39] As now well appreciated, Castro and Stephens found that when the aryl iodide bore a nucleophilic heteroatom in the *ortho* position, the intermediate acetylene underwent cyclization giving indole or benzofuran products. Although the Cadiot–Chodkiewicz coupling proceeds under mild conditions, the Castro–Stephens method demanded elevated temperatures and employed the poorly soluble copper(I) phenylacetylide. These solubility problems—leading to batch to batch irreproducibility in yields—are an often cited drawback of these procedures.^[40]

Notwithstanding the practical issues, the work by these pioneering chemists represented a breakthrough achievement. For the first time, a robust solution to the selectivity problem had been found. With these first examples of truly

2.2. The First Wave (1968–1976): Investigation of The Metal Catalyst—The Rise of Palladium

2.2.1. Prologue: The Wacker Process (1957–1959)—The Potential of Palladium is Realized

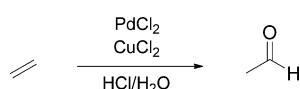
Following Wollaston's discovery of palladium in 1802 (Figure 4), later reported in 1805,^[41] his attempts to reap financial benefit were categorically futile.^[42] Without a useful function, his new element remained a mere chemical curiosity and, on his death, 97% of the palladium he had extracted remained unsold.^[42] Although Wollaston could not find a market for his stocks of palladium, during his time the



Figure 4. Samples of palladium (left) and rhodium (right) isolated by Wollaston, preserved at the Science Museum in London.

metallurgist Percival Norton Johnson, (founder of Johnson Matthey) established a gold refining company, advertised palladium for use in chemistry, medical instruments, and as a substitute for steel.^[43] For the next hundred years, the chemistry of palladium would be dwarfed by its more active cousins, platinum and nickel, as researchers investigated these metals reactivity in oxidations, reductions, and hydrogenations of unsaturated hydrocarbons.^[44] Catalysts would be developed which tuned and modulated this activity—generating the familiar palladium on charcoal^[45] and Lindlar^[46] catalysts, to name two that are common place in the laboratory and production setting today. Nevertheless, this work both on palladium and the other platinum group metals established the affinity and activity of palladium for double and triple bonds. In the 1950s, this affinity would be put to use by the industrial chemical powerhouses of Europe.

Post-World War II Europe was being rebuilt—and to rebuild required materials. The economic boom was accompanied by surging demand for cheap sources of plastics and precursor fine chemicals.^[47,48] As part of this effort, chemists at Wacker Chemie's central research institute, led by Walter Hafner, began on a quest to synthesize ethylene oxide from ethylene. On exposure of a stream of ethylene and oxygen to a bed of palladium on charcoal, however, the distinctive pungent smell generated suggested the production of acetaldehyde! This fruitful observation and its eventual refinement into a commercial process—now known as the Wacker process (Scheme 10)—established the importance of palladium as a metal for the synthesis of organic compounds.



Wacker Chemie GmbH 1959

Scheme 10. The Wacker Process.^[47]

Indeed, during these efforts Hafner would be the first to isolate and characterize a palladium π -allyl complex.^[49] The chemistry of these complexes would be developed alongside that of the more conventional coupling chemistry, beginning with Tsuji's observations in 1965 that carbon nucleophiles undergo reaction with palladium π -allyls (see Section 4.1).^[50] However, the initial Wacker Chemie research would serve as the inspiration for one of the most important discoveries in organic synthesis during the 20th century.

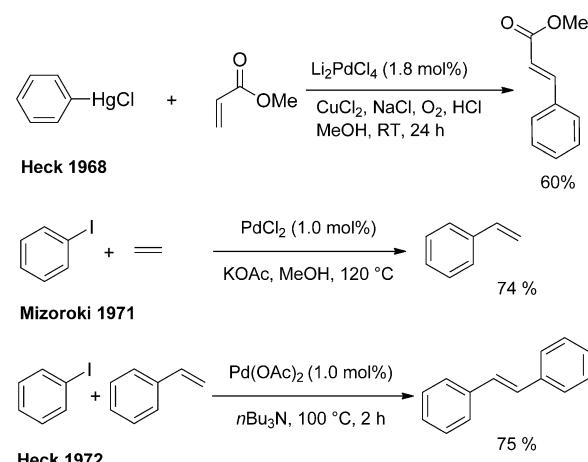
2.2.2. The Heck Reaction (1968–1973): Palladium Complexes as Cross-Coupling Catalysts—A New Type of Reactivity

Meanwhile, in the arena of coupling chemistry, further interesting developments were afoot. Although in these years there were a number of emerging reports on the direct activation of C–H bonds without the need for pre-functionalized coupling partners (see Section 4.4), it appears that for reasons of expediency and achieving selectivity, the attention of researchers was drawn towards the investigation of pre-functionalized coupling partners.

Entry of Richard Heck: Following post-doctoral studies, Heck accepted a position at Hercules Powder Co where he was afforded freedom that is seldom experienced by the modern industrial chemist. Briefed with the task of “doing something with transition metals,”^[51] Heck investigated the chemistry of cobalt carbonyl complexes. Although this work generated many interesting observations, finding profitable applications for his research proved difficult. Inspired by his colleague Pat Henry's work on the Wacker oxidation,^[52] Heck's attention turned in the direction of arylpalladium chemistry.

“In the laboratory across the hall from me ... worked ... Pat Henry. He had been studying the mechanism of the commercially important ‘Wacker Process’... Pat proposed that an intermediate β -hydroxyethylpalladium chloride species decomposed by the elimination of dichloropalladium hydride anion ... forming acetaldehyde. ... There was the widespread belief at this time that transition–metal–carbon bonds were quite weak and easily decomposed by homolytic cleavage. This belief arose because attempts to prepare compounds such as dimethylpalladium, dimethylnickel, methylcobalt, or trimethyliron all failed. Henry's proposal ... raised the doubt in my mind that maybe the metal–carbon bond wasn't so weak but that decomposition may occur preferably by other mechanisms. I decided to try an experiment to see what would happen if an organopalladium compound without β -hydrogens was prepared in the presence of something else ... *The first experiment I tried was to add phenylmercuric acetate to a stirred solution of lithium tetrachloropalladate in acetonitrile at 0°C under an atmosphere of ethylene. An immediate reaction occurred.*^[51]”

The result of this observation culminated, in 1968, with seven, single-author back-to-back Communications on the reaction of organomercurial compounds with alkenes in the presence of catalytic amounts of $\text{Li}_2[\text{PdCl}_4]$ (Scheme 11).^[53] Owing to the high toxicity of the organomercury reagents, alternative procedures were desired and these interesting results represented merely harbingers of subsequent, more prominent, reports by Heck. In 1968, Fitton and co-workers found a possible solution to the problem of obligatory organomercury compounds when they characterized the



Scheme 11. The first palladium(II)-catalyzed coupling reactions.^[53,55,56]

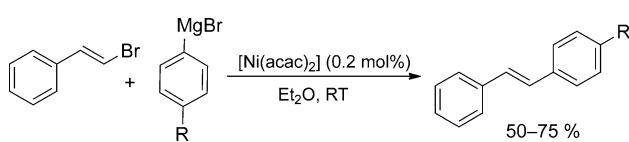
first oxidative addition product from the reaction of a $[\text{Pd}^0(\text{PPh}_3)_4]$ catalyst with an aryl halide substrate.^[54] In rapid succession, the independent and almost concurrent discoveries by Mizoroki^[55] and Heck^[56,53a] (Scheme 11) demonstrated the coupling reactions of aryl, benzyl, and styryl halides with alkenes employing palladium(II) catalysis, and set the stage for the evolution of the now named Mizoroki–Heck reaction.^[6] Over the following decades, a vast number of groups would demonstrate the high functional-group tolerance and wide applicability of this reaction system. Equally significant, powerful intramolecular variants^[57] appeared from numerous laboratories, especially in natural-product synthesis, which has been perhaps most decisively demonstrated by Overman.^[57] In addition, the construction of quaternary stereocenters in an intramolecular fashion,^[58] coupled with the development of asymmetric versions,^[59] would afford the Mizoroki–Heck reaction a unique place in the arsenal of methods available to synthetic chemists.^[7c]

With this work, Mizoroki and Heck had achieved something beautiful. Heck's ability to spot the potential synergy between the two disparate fields of palladium chemistry and the fledgling field of coupling chemistry gave birth to a new reaction scheme, opening up the future of palladium as an important metal for catalysis. Mechanistically, the Mizoroki–Heck reaction differs from most of the previously reported cross-coupling reactions on one crucial point: *the lack of an obligatory preformed organometallic species as one of the coupling partners*. The copper-catalyzed Cadiot–Chodkiewicz reaction also involves an analogous formal coupling of an unfunctionalized alkyne (Scheme 9); however, this reaction is suggested to proceed by the *in situ* generation of the organometallic cuprous acetylide. Although subsequently discovered reactions, such as the copper-free Sonogashira coupling would prove to be additional exceptions,^[60] at this point in the history of coupling, only the Heck reaction imparted freedom from the requirement of a transmetalation step. Conceptually therefore, the Mizoroki–Heck reaction may be classified as a formal vinylic C–H activation process.

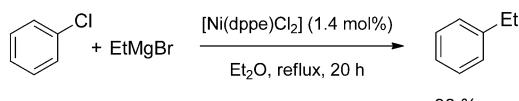
2.2.3. The Corriu–Kumada Reaction: The Birth of the Nickel-Catalyzed Selective Aryl Coupling

Alongside the discoveries of Heck and Mizoroki, the work of Kharasch was not forgotten in certain segments of the organic community, and work continued to improve and extend Grignard-based couplings to allow selective aryl–aryl bond formation. Perhaps the first solution to the selectivity problem came in the form of nickel-promoted reactions. As early as 1963, Wilke investigated the nickel-promoted cyclo-oligomerization of butadiene.^[61] By 1966, formation of butane from the thermal decomposition of $[\text{Et}_2\text{Ni}(\text{bipy})]$ ($\text{bipy} = 2,2'$ -bipyridine) had been observed by Yamamoto.^[62] Furthermore, in 1970, Yamamoto isolated and characterized the first nickel–aryl chloride oxidative addition product.^[63] In 1971, Semmelhack would take advantage of these earlier reports, and disclosed the homodimerization of aryl halides using stoichiometric quantities of $[\text{Ni}(\text{cod})_2]$ ($\text{cod} = 1,5\text{-cyclooctadiene}$).^[64] On the heels of these observations, Corriu^[65] and Kumada^[66] independently reported on the nickel-catalyzed

cross-coupling reactions of aryl and alkenyl halides with Grignard reagents (Scheme 12). This constituted a major breakthrough since it promised finding a solution to the selectivity problems associated with Kharasch couplings in which homodimerization byproducts prevailed. Significantly, Kumada introduced the use of phosphine ligands to modulate the reactivity of the metal, a result which would initiate a continuing and powerful trend in future cross-coupling research.



R = 4-MeOC₆H₄, 4-MeC₆H₄, 3-MeC₆H₄, 4-BrC₆H₄, 2,4-Me₂C₆H₃
Corriu 1972



Kumada 1972

Scheme 12. The Corriu–Kumada reaction.^[65,66]

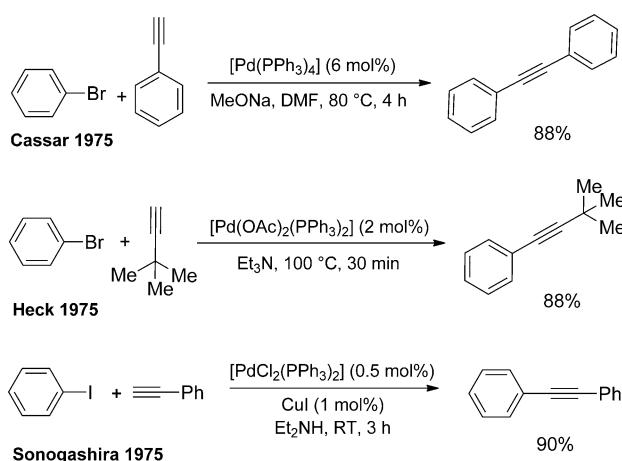
2.2.4. The Ascent of Palladium

Until the mid-1970s, the three metals that had proven to be most useful in coupling chemistry—copper, nickel, and palladium—appeared to show unique strengths. Copper dominated the landscape of acetylene chemistry, nickel had proven a robust solution to the problems of Grignard coupling selectivity, and palladium seemed to be confined to the role of an “alkenophile”—happy to hydrogenate a double bond or to catalyze the mechanistically distinct Mizoroki–Heck reaction. Over the next five years, the scope of palladium catalysis in coupling reactions would grow, demonstrating palladium as a “jack of all trades” and often offering improved selectivity over the other two metals of the triumvirate.^[5b]

2.2.4.1. The Sonogashira Reaction (1975): The Copper Process Evolves into a Palladium–Copper Cocatalyzed Reaction

As noted above, until the mid-1970s, the field of acetylene coupling was dominated by the use of copper salts as catalysts. However, in 1975 the palladium-catalyzed coupling of acetylenes with aryl or vinyl halides was concurrently disclosed by three independent groups: Sonogashira,^[67] Cassar,^[68] and Heck.^[69] The coupling conditions reported by Sonogashira, employing copper cocatalysis, made the reaction conditions exceedingly mild when compared to the non-cocatalyzed Cassar and Heck conditions (Scheme 13).

The noteworthy differences between the Sonogashira and the Castro–Stephens coupling reactions are self-evident: the Sonogashira coupling requires only catalytic quantities of transition metals and may be carried out at room temperature whereas the Castro–Stephens uses stoichiometric amounts of copper incorporated into the cuprous acetylide and requires elevated temperature (refluxing pyridine), leading to com-



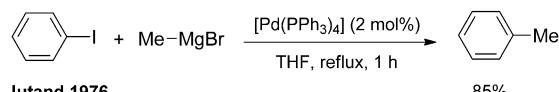
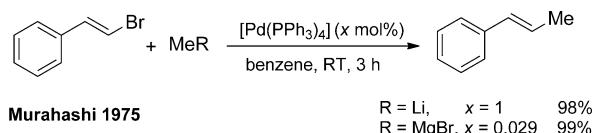
Scheme 13. The Sonogashira reaction.^[67–69]

peting homocoupling (Glaser coupling, see Section 2.1.1.1) byproduct formation. The combination of the detrimental effects of the Castro–Stephens coupling combined with the high functional-group tolerance of the Sonogashira method places the latter reaction in a premium position as a late-stage coupling strategy in the synthesis of complex molecules, for example, sensitive enyne-based natural products.^[70]

2.2.4.2. The Palladium-Catalyzed Corriu–Kumada Reaction (1975): Nickel Catalysis Evolves into Palladium Catalysis

The disclosure of the palladium-catalyzed Sonogashira reaction opened a new vista for dependable C(sp²)–C(sp) coupling. The advantageous effects of palladium catalysis became increasingly recognized and the promise of similar benefits through its use in the previously established nickel-catalyzed processes became an alluring prospect.

At the time, the nickel-catalyzed process was specific to the coupling of Grignard reagents. However, the activity of a number of palladium complexes were independently investigated over the 1975–1979 period by several groups (Scheme 14) in efforts to broaden the substrate scope of the Corriu–Kumada reaction. The contributions of Murahashi in 1975^[71] demonstrated, for the first time, coupling of Grignard reagents under palladium catalysis. In this context, noteworthy are also the contributions of Fauvarque and Jutand,^[72] Sekiya,^[73] Dang,^[74] and Negishi.^[75] Moreover, Murahashi demonstrated, although not catalytically, the use of the resourceful organolithium species as a coupling partner—a transformation previously impossible under nickel catalysis.



Scheme 14. The palladium-catalyzed Corriu–Kumada cross-coupling reaction.^[71,72]

Murahashi would subsequently develop this observation into a catalytic variant of the reaction 1979.^[71a]

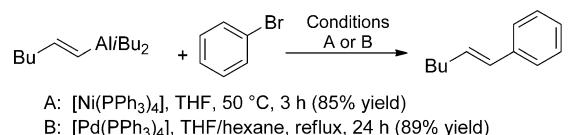
Similar to the palladium-catalyzed Sonogashira reaction, studies on the Corriu–Kumada coupling, catalyzed by palladium rather than by nickel, revealed some striking improvements. The palladium-catalyzed Corriu–Kumada coupling showed increased stereofidelity and broader substrate scope of the organometallic coupling partner. However, this selectivity came at a cost—the palladium-catalyzed procedures only allowed the coupling of the more reactive aryl bromides and iodides, whereas aryl chlorides proved to be inert. Thus, nickel remained the brutish older brother to palladium, able to affect the coupling of a wider range of halide (and later pseudohalide) partners for which palladium failed. However, repeatedly over the coming years, palladium would usurp nickel because its reactivity could be modulated through the use of ligands whilst still retaining its improved selectivity. As discussed below, nowhere is this observation clearer than in the efforts of Negishi to broaden the scope of the organometallic coupling partner.

2.3. The Second Wave (1976–1995): Exploration of the Organometallic Coupling Partner

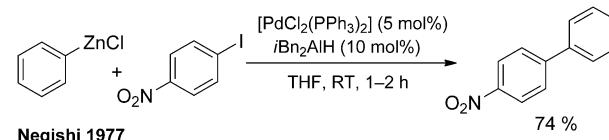
A common limitation of both organomagnesium and organolithium coupling methods was the inherent intolerance of sensitive functional groups to the reactive nature of these anionic organometallic species. Thus, in the years surrounding the Mizoroki–Heck discoveries, chemists sought to find less-reactive anionic organometallic reagents.

2.3.1. The Negishi Reaction (1976): Organoaluminum and Organozinc as Coupling Partners

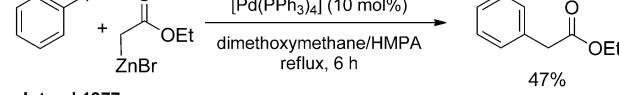
In 1976, Negishi reported on the cross-coupling of organoaluminum reagents, employing nickel catalysts (Scheme 15).^[76] However, in the synthesis of conjugated dienes with organoaluminum reagents, a significant deterioration of stereospecificity was observed in several cases. On



Negishi 1976



Negishi 1977



Jutand 1977

Scheme 15. The Negishi cross-coupling reaction.^[76–78]

substituting the nickel catalysts by palladium complexes, this drawback was eliminated. Subsequently, Negishi^[77] and Fauvarque and Jutand^[78] reported the use of zinc reagents in cross-coupling reactions (Scheme 15). Most significantly, the discoveries that organoaluminum intermediates and zinc reagents serve as coupling partners showed that magnesium and lithium could be replaced with other metals that were capable of participating in the proposed transmetalation step. Somewhat anticipatory of the future, Negishi and co-workers carried out metal-screening regimens to identify other possible organometallic reagents as coupling partners.^[79] As a result, the $[\text{PdCl}_2(\text{PPh}_3)_2]$ -catalyzed coupling of an aryl iodide with zinc-, boron-, and tin-based acetylene organometallic species to give the alkyne products was successfully achieved (Table 1).

Table 1: Coupling reactions of zinc, boron, and tin acetylates with an aryl iodide.^[80]

Metal	T [°C]	t [h]	Product	Yield [%] ^[a]	Starting material
Li	25	1	trace	88	
Li	25	24	3	80	
MgBr	25	24	49	33	
ZnCl	25	1	91	8	
HgCl	25	1	trace	92	
HgCl	reflux	6	trace	88	
BBu ₃ Li	25	3	10	76	
BBu₃Li	reflux	1	92	5	
AliBu ₂	25	3	49	46	
AlBu ₃ Li	25	3	4	80	
AlBu ₃ Li	reflux	1	38	10	
SiMe ₃	reflux	1	trace	94	
SnBu ₃	25	1	75	14	
SnBu₃	25	6	83	6	
ZrCp ₂ Cl	25	1	0	91	
ZrCp ₂ Cl	reflux	3	0	80	

[a] Conditions giving best yields are highlighted.

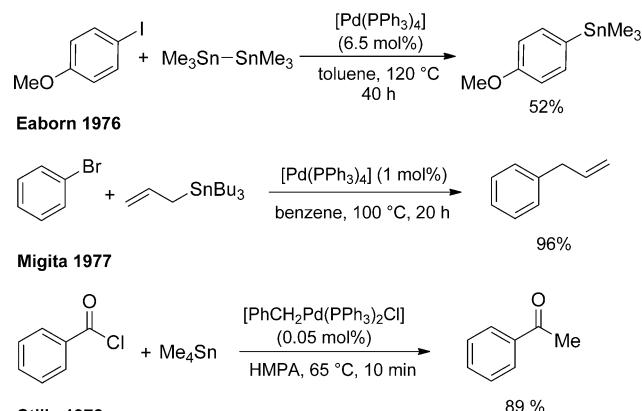
In the hands of Negishi and his students, the field of palladium- and nickel-catalyzed coupling reactions of unsaturated organic halides with organozinc reagents evolved into a general reaction which now stands out as a mild route with impressive functional-group compatibility.^[77b] With the demonstration of the reactivity of alternative organometallic derivatives, Negishi significantly broadened the concept of the cross-coupling approach and set the stage for the uncovering of milder, less electropositive-metal coupling species.

2.3.2. The Stille Reaction (1976–1978): Organostannane Coupling Partners

In 1973, Atwell and Bokermen demonstrated that the reaction of allyl halides with a disilane under palladium catalysis furnished the corresponding organosilane derivatives.^[81] Subsequently, Matsumoto showed that aryl bromides underwent the analogous reaction with hexamethyldisilane.^[82] However, these organosilanes were not observed to undergo

further coupling under the reaction conditions, and the next breakthrough would come from the use of organotin reagents. In a seminal report in 1976, Eaborn disclosed the first palladium-catalyzed cross-coupling of organodistannane reagents with aryl iodides (Scheme 16). In this report an important side reaction was noted—dimerization of the aryl halide component.^[83] Shortly thereafter, Migita reported on the palladium-catalyzed cross-couplings of organotin reagents with aryl bromides.^[84]

Following the initial reports of Eaborn and Migita, Stille and Milstein unveiled, in 1978, the synthesis of ketones^[85] by the coupling of aryl chlorides with organostannanes (Scheme 16) under significantly milder reaction conditions than those reported by Migita and Kosugi. In the early 1980s, Stille further explored and improved this reaction, developing

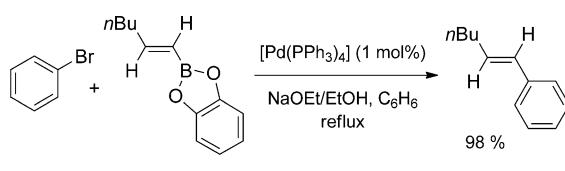


Scheme 16. The seminal stannane cross-coupling discoveries.^[83–85]

it into a highly versatile methodology displaying remarkably broad functional-group compatibility and, by demonstrating its utility in total syntheses, changed the ways that chemists thought about C–C bond construction.^[86] In this context, Beletskaya's contributions to palladium-catalyzed cross-coupling reactions using aryl tin reagents have not received sufficient recognition owing to their initial publication in the Russian literature.^[87] Without argument, the main disadvantage of the Migita–Stille reaction is the toxicity of the organostannanes. However, despite the toxicity issue, this reaction enjoys fourth place in terms of publications and patents in the last decade (Figure 2).^[88] To address the problems of toxicity, the range of organometallic coupling partners would need to be expanded further.

2.3.3. The Suzuki–Miyaura Reaction (1979): Activated Organoboranes as Coupling Partners

In 1979 Suzuki, having recently returned to Japan from his postdoctoral studies with H. C. Brown, pursued the remaining element of the three identified by Negishi (zinc, boron, and tin) and reported the palladium-catalyzed cross-coupling between 1-alkenylboranes and aryl halides (Scheme 17).^[89] Interestingly, Heck had observed in 1975 that boronic acids are competent cross-coupling partners when stoichiometric quantities of palladium are employed.^[90] However, it would be Suzuki's demonstration that this chemistry could be moved



Suzuki and Miyaura 1979

Scheme 17. The Suzuki–Miyaura cross-coupling reaction.^[89]

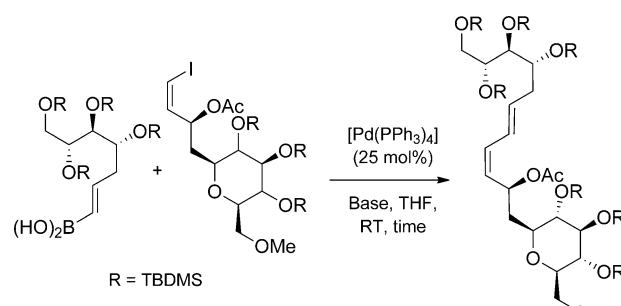
into the catalytic realm, now known as the Suzuki–Miyaura coupling (see Figure 2).

In a vast understatement, we note that the Suzuki–Miyaura reaction has developed into an extremely powerful and general method for the formation of C–C bonds,^[91] displaying a number of advantageous features: 1) easily handled and usually air- and moisture-stable organoboron starting materials; 2) mild and convenient reaction conditions and 3) the facile removal of less-toxic inorganic byproducts. These aspects make the Suzuki–Miyaura coupling reaction especially useful for industrial applications.

In later years, modification of the organoboron reagent has led to the development of milder and more selective Suzuki–Miyaura couplings, among which the Genêt/Molander BF₃K salts^[92,93] and the Burke MIDA (*N*-methyl-iminodiacetic acid) boronates^[94] are the most prominent. Recently Knochel introduced magnesium di(hetero)arylboronates and magnesium di(alkenyl)boronates as a new class of Suzuki reagent by treating the organic halides with B(OBu)₃ with Mg in the presence of LiCl.^[95] Often the exact nature of the organoboron species can have profound effects on the efficacy of a given transformation. Indeed, the mixed aqueous/organic solvent systems normally employed in Suzuki–Miyaura reactions may lead, not only to protodeboronation as a function of electronic and steric nature of the substrate, but can affect the nature of the boron reagent itself (boronic acid, half-acid ester, boroxine, borinic acid). The associated purity issue is often an unknown factor since its characterization is not usually carried out, and may cause difficulty in interpreting failed Suzuki–Miyaura coupling reactions, especially when boronates are employed.

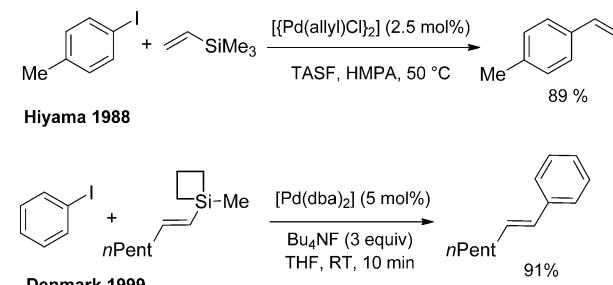
An important consideration in the Suzuki–Miyaura reaction is the base employed. Perhaps the earliest, most distinguished, example originates from Kishi's investigation of the effect of base in a reaction en route to the total synthesis of Palytoxin (Scheme 18).^[96] In this work, the use of thallium hydroxide as base makes the reaction complete, essentially on mixing of the reagents. Although effects may not be as dramatic as this on a routine basis, such examples have elegantly shown the importance of base source as well as the synthetic power of the Suzuki–Miyaura reaction.

A hallmark of the Suzuki discovery was the demonstration that “activation” of the organometallic component as the boronate (sometimes referred to as the “ate” complex) would allow the coupling of organometallic reagents unable to undergo transmetalation under standard conditions. This discovery pointed to the possibility of uncovering coupling reactions of other organometallics with lower electronegativity differences between the metal and the organic moiety.^[97] It would be a decade before such reactivity was revealed in a new class of organoelement compounds.

**Scheme 18.** Kishi's studies on the importance of base in the Suzuki–Miyaura coupling.^[96]

2.3.4. The Hiyama Reaction (1988–1994): Organosilicon Coupling Partners

In 1982, Kumada reported the use of organopentafluorosilicates in palladium-catalyzed cross-coupling reactions.^[98] In the same year, Hallberg disclosed the coupling of vinyltrimethylsilane.^[99] Building on these reports, in 1988 Hiyama and co-workers described the palladium- and nickel-catalyzed coupling of organosilanes with aryl halides and triflates activated by the inclusion of a fluoride source in the reaction mixture (Scheme 19).^[100,101] Thus tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)^[100] or CsF^[102] was shown to be required to activate the organosilane towards transmetalation by the formation of silicate intermediates. The Hiyama coupling provided a more environmentally friendly and safe option than the organoboron, organozinc, and organostannane reagents. This discovery has been pursued on other silicon derivatives, for example, siloxanes by Denmark^[103] and DeShong,^[104] among others, which anticipates the promise of greater prominence of the Hiyama coupling reaction in the near future.

**Scheme 19.** The Hiyama cross-coupling reaction.^[100,103]

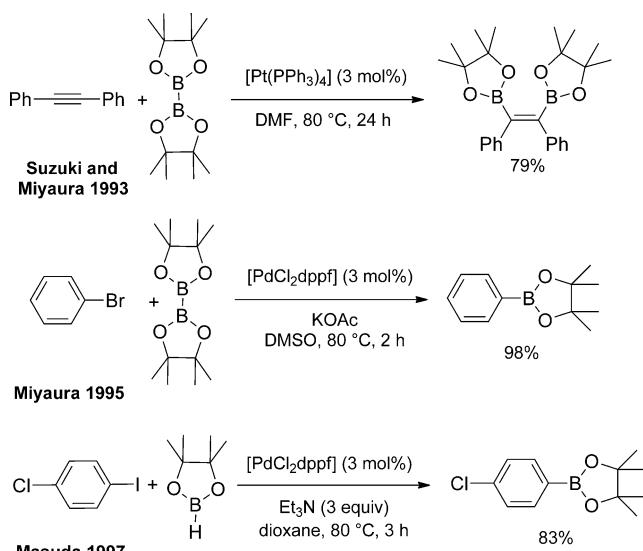
2.4. Carbon–Heteroatom Coupling Reactions

Up to this point in the historical development of cross-coupling, a stoichiometric organometallic partner had generally been required to achieve efficient cross-coupling, the exception being the Mizoroki–Heck reaction. Other functional partners, with a few exceptions, (e.g. R₃Si–SiR₃, R₃Sn–SnR₃) were unsuitable for functionalization of organic sub-

strates. The 1990s witnessed the evolution of non-carbon-based nucleophiles participating in a cross-coupling process, thus adding new dimensions for palladium-catalyzed processes.

2.4.1. The Miyaura Borylation (1993): C–B bond Formation

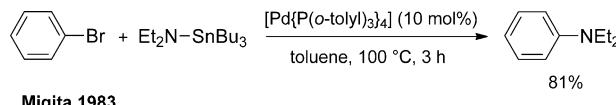
Between 1970–1990, although dimeric organometalloys, such as hexamethyldisilane^[105] and hexamethyldistannane,^[83] had been demonstrated as suitable coupling partners, the corresponding use of boron compounds containing a B–B bond was unknown. In 1993, Miyaura and Suzuki announced the addition of a boron ester across a triple bond using a platinum catalyst employing a diborane as a coupling partner (Scheme 20).^[106] Shortly after, Miyaura disclosed that the same, now famous, $B_2(\text{pin})_2$ reagent ($B_2(\text{pin})_2 = \text{bis}(\text{pinacolato})\text{diboron}$), undergoes coupling with aryl halides to form arylboronates using a preformed palladium catalyst, $[\text{PdCl}_2\text{dppf}]$ ($\text{dppf} = 1,1'\text{-bis}(\text{diphenylphosphino})\text{ferrocene}$).^[107] Importantly, the use of KOAc base proved to be essential in preventing consumption of the product by the competing Suzuki–Miyaura reaction. In 1997, Masuda reported an important modification of this procedure by using HB(pin)/triethylamine conditions,^[108] further reducing waste in the construction of C–B bonds. These boron-based couplings would set the stage for the evolution of a series of catalytic carbon–heteroatom bond forming processes.



Scheme 20. The Miyaura borylation reaction.^[106–108]

2.4.2. The Buchwald–Hartwig Coupling (1995): C–N Bond Formation

In 1983, Migita and co-workers disclosed the first palladium-catalyzed formation of C–N bonds, albeit this method required the use of stoichiometric amounts of heat- and moisture-sensitive tributyltin amide reagents (Scheme 21).^[109] These issues coupled with considerations of cost, toxicity, and hence lack of potential utility, prompted

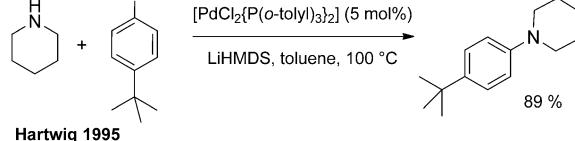
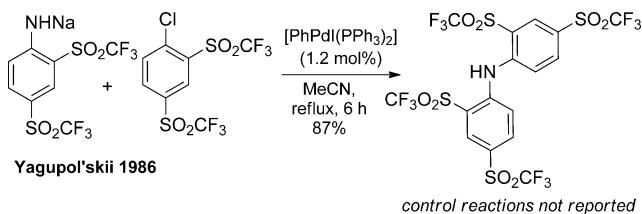


Migita 1983

Scheme 21. The Migita amidostannane coupling reaction.^[109]

efforts to develop conditions which allowed coupling of the free amine.

The earliest hint of the possibility that a free NH amine could be a suitable coupling partner is found in a report by Yagupol'skii (Scheme 22).^[110] This work was published in a Russian journal and therefore remains widely unknown, and



Scheme 22. The Buchwald–Hartwig C–N cross-coupling reactions.^[110,111]

lacked control experiments to exclude the possibility of alternative S_NAr reaction to rationalize the result. In 1995, Buchwald and Hartwig independently replaced the Migita amidotin reagent (Scheme 21) with a free amine when a strong base such as LiHMDS (HMDS = 1,1,1,3,3-hexamethyldisilazane) or NaOtBu was employed, and thereby called noteworthy attention to the C–N cross-coupling reaction.^[111] Rapidly, conditions were developed which extended these first practical C–N coupling results and led to the establishment of the C–O bond forming cross-coupling processes, placing the Ullmann reaction in a modern light.^[112] In the ensuing years, these reactions together with, to a lesser extent, C–S and C–P coupling processes, have entered routine use in synthetic chemistry.^[113]

3. The Third Wave: The Continuous Fine-Tuning of Cross-Coupling Reactions

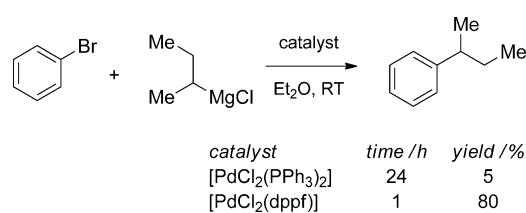
In the 2nd wave, we were spectators to the narratives of cross-coupling reactions with conceptually new reactivity. Alongside these discoveries, continuous efforts were also directed towards the modification of the reported named

reactions, with the aim of increasing functional-group compatibility and broadening the substrate scope. The importance of these modifications and manipulations cannot be underestimated, since they made it possible to begin employing cross-coupling chemistry in the synthesis of biologically important molecules, particularly on large scale. We will not be concerned with details of the modifications of these reactions, which we call fine-tuning, rather, a brief account of the historical order of events is given.^[114]

3.1. The Importance of Ligand Properties

During the early years in the development of cross-coupling reactions, the readily available PPh_3 was the ligand of choice. As the possibilities of improving reaction conditions and increasing substrate scope by changing the organometallic reagent progressed, the nature of the ligand employed became recognized as the most important variable for detailed investigation. Gradually, researchers started to map the effects of the choice of ligand upon the steps in the catalytic cycle (oxidative addition, transmetalation, and reductive elimination).

Kumada noted, as early as 1979, the beneficial effects of the bidentate ligand dppf in the palladium-catalyzed coupling reaction of Grignard reagents with organic halides (Scheme 23).^[115] It is now well appreciated that the use of bidentate ligands accelerates the reductive-elimination step in the catalytic cycle, thereby increasing the overall rate of the reaction. Achieving a faster and more favorable reductive-elimination step also means less competition from the β -hydride-elimination side-product formation.^[116]



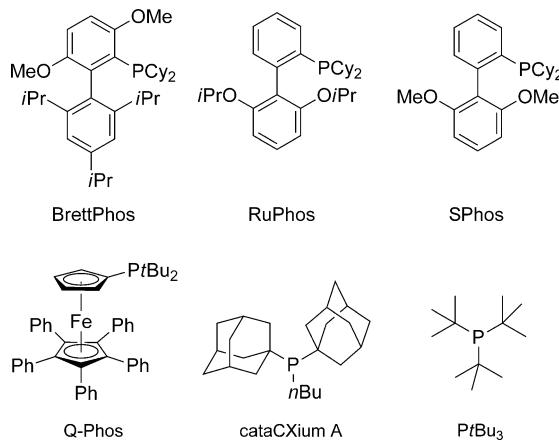
Scheme 23. Ligand effects in the Corriu–Kumada reaction with alkyl Grignard reagents.^[115]

In the following years, the profound effect of choice of ligand, in not only the Corriu–Kumada reaction, but also the other named cross-coupling processes was repeatedly noted. Since then, many sophisticated and effective bidentate ligands (P–P, P–N, P–C, P–O) have been developed. The geometric parameter “cone angle” was formulated by Tolman,^[117] and the concept of “bite angle”^[118] was introduced in relation to bidentate ligands. Initially, only the *steric properties* of the mainly aryl-derived ligands were investigated. In the early 1980s, Heck recognized that the palladium complex derived from the tri-*o*-tolylphosphine ligand, which is sterically more encumbered than triphenylphosphine, had increased activity compared to $[\text{Pd}(\text{PPh}_3)_4]$.^[119] A year later, Spencer reported that the combination of $\text{Pd}(\text{OAc})_2$ and $\text{P}(o\text{-tol})_3$ achieved particularly high turnover numbers in cross-coupling reac-

tions, and suggested that this could not simply be attributed to the bulk of the ligand.^[120] The structure of the catalytically active species was later shown by Herrmann and Beller to be a palladacycle formed upon heating $\text{Pd}(\text{OAc})_2$ and $\text{P}(o\text{-tol})_3$ in a suitable solvent.^[121] In the same year as the Kumada publication on alternative ligands, Osborn reported the use of PCy_3 as a ligand in carbonylation reactions, and noted that “*significant catalytic activity is found only with phosphines which are both strongly basic ($pK_a > 6.5$) and with well-defined steric volume, that is, the cone angle must exceed 160°*”^[122] clearly informing chemists that the *electronic properties* of the phosphine were often also crucial for the catalytic activity. During the same period, Milstein employed the electron-rich bidentate ligand, 1,3-bis(diisopropylphosphino)propane (dipp) for the reductive carbonylation of chlorobenzene.^[123] These considerations started new waves in the cross-coupling chemistry field, stimulating the preparation of more reactive catalyst complexes. Thus, coupling partners that had not previously been suitable for cross-coupling reactions, owing to either their lack of reactivity or their propensity to undergo unwanted side reactions, could now be included in the substrate scope. Even before Osborn’s observations, Nicholas demonstrated the use of the pyrophoric PtBu_3 in palladium-catalyzed carbonylative amidation of vinyl chlorides.^[124] Fu and Koie subsequently and independently expanded the scope of Pd/PtBu_3 -based catalysts in coupling reactions involving unactivated substrates, such as, aryl chlorides.^[125] Fu’s original publications in 1998 rekindled the interest^[125a] of both academic and industrial scientists to seriously revisit the area and hence played an important role in the rapid growth of ligand variation studies in the last decade. In 2000, Fu and co-workers reported the use of pyrophoric, bulky electron-rich PtBu_3 and the relatively less air-sensitive PCy_3 in Suzuki–Miyaura couplings, for coupling of aryl boronic acids with $\text{C}(\text{sp}^2)\text{-halides}$ and $\text{C}(\text{sp}^2)\text{-triflates}$, respectively.^[126] This work dramatically illustrated that impressive chemoselectivities are attained through appropriate ligand selection as a reversal in the reactivity order of $\text{Ar}-\text{OTf}$ and $\text{Ar}-\text{Cl}$ observed between the two ligand sets. DFT calculations by Schoenebeck and Houk provided an explanation for the origins of the chemoselectivity.^[127] These studies indicated that a monocoordinate $\text{Pd}(\text{PtBu}_3)$ species was responsible for the $\text{C}-\text{Cl}$ insertion, whereas a bicoordinate $\text{Pd}(\text{PCy}_3)_2$ species favored $\text{C}-\text{OTf}$ insertion. However, Schoenebeck has shown subsequently, by theoretical and experimental studies, that even PtBu_3 can have a reversal of selectivity for $\text{C}-\text{Cl}$ and $\text{C}-\text{OTf}$ in polar solvents in the presence of coordinating coupling partners or additives as a result of the formation of anionic Pd species.^[128]

A year after his seminal publication, Fu showed the advantage of using the less-bulky PCy_3 ligand in the coupling of alkyl halides with alkyl or vinyl organoboron reagents.^[129] Although B-alkyl-9-BBN systems had been successfully employed in coupling with aryl iodides by Suzuki as early as 1986,^[130] by inclusion of alkyl halide coupling partners, Fu took a giant step forward in expanding the substrate scope. In spite of this work, the analogous transformation utilizing boronic acids continued to represent a challenging goal because of competitive β -hydrogen elimination from the alkyl palladium intermediate in the catalytic cycle. This challenge

was partially solved in 2002, when Fu disclosed room temperature conditions utilizing another ligand, PtBu_2Me (sterically and electronically in-between PCy_3 and PtBu_3), which was capable of achieving this transformation.^[131] These results represent, as reflected in the last 10 years, the crest of a sizable wave in the development of new ligands.^[114a, 132, 133] Note-worthy examples are the diadamantyl ligands by Beller (CatacXium),^[134] the dialkylbiaryl phosphines introduced by Buchwald,^[135] and the highly active dialkylferrocene phosphine based ligand, Q-Phos, synthesized by Hartwig (Scheme 24).^[136] Also noteworthy is the recently evolving work of Nolan on nucleophilic carbenes for Pd-catalyzed cross-couplings.^[137]

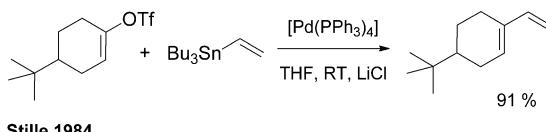


Scheme 24. Highly active tertiary phosphine ligands.^[124, 125, 134–136]

3.2. Pseudohalides as Cross-Coupling Partners

As seen above, the early work of the pioneering cross-couplers had focused, “in the second wave”, on expanding the scope of the organometallic component. In this context, the organohalides remained the same, varying between the aryl iodide, bromide, and on occasion, activated aryl chloride. In later years, the promise of expanding the scope of this component to include other leaving groups, now referred to as *pseudohalides*, that is, any functional group which can undergo reaction in the same fashion as an aryl iodide or bromide in cross-coupling reactions, tempted chemists to explore other functional groups for cross-coupling. Hence, the possibility of achieving oxidative addition of palladium(0) to a C–O bond was demonstrated in the early 1980s when Negishi and Semmelhack independently reported palladium-catalyzed coupling reactions of allylic sulfonates with a number of different nucleophiles.^[138] This work was further extended in 1984 by Stille with the demonstration of the first coupling of vinyl triflates with organotin reagents (Scheme 25).^[139]

As may have been predicted from the ready accessibility of vinyl triflates, this finding greatly enhanced the substrate scope for cross-coupling reactions. The lengthy list of pseudohalides that participate in palladium-catalyzed cross-coupling reactions now includes sulfonates, such as OMs^[140] and OTs,^[141, 142] diazonium salts,^[143] and hypervalent iodine



Scheme 25. The first cross-coupling reaction of vinyl triflates.^[139]

reagents,^[144] among others. Not all pseudohalides are appropriate for palladium-catalyzed coupling reactions because of problems in oxidative-addition reactivity; in such cases, nickel-catalysts appear to complement the palladium systems, allowing a wider range of successful transformations.^[145]

3.3. The Introduction of Large Scale Cross-Coupling: Use of Preformed Catalysts

In 1969, Woodward provided a view of the different aspects and driving forces behind research carried out in academia versus industry.^[146] Typical of his many quotable statements, he suggested that, in academia, intuition is a dominant skill, whereas in industry logic and proof were significant (Table 2)—views that are still valid today although

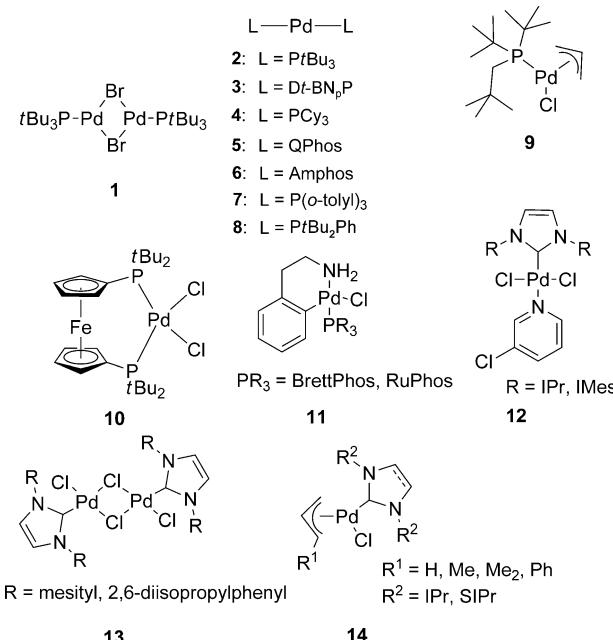
Table 2: Excerpt from a R. B. Woodward lecture on academic versus industrial research.^[146]

Discovery	Understanding
Right brain—intuition (art and craft)	Left brain—logic and proof
Academia	Industry
Education—mentoring—instruction	Efficiency—practicality—profit

with a great degree of fuzziness. Although industrial and academic chemists may differ in terms of the main objectives, they still share a common driving force—scientific curiosity leading to innovation! The significant progress made within academic research groups to expand the scope and to develop ever milder cross-coupling reaction conditions may be juxtaposed with different issues that are experienced by process chemists in the scaling-up of these processes in the fine-chemical and pharmaceutical industry.

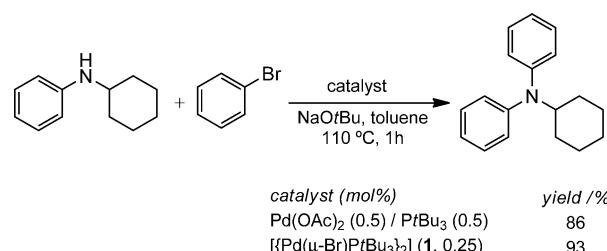
The cost of the process (today called process economics) is the major factor considered by the chemical industry in developing routes to pharmaceuticals, agrochemicals, and fine chemicals. For a given catalytic reaction, the holy grail of cost minimization is to employ an inexpensive, extremely active catalyst that can be used at low loadings whilst providing the product in high yield. In the context of the cross-coupling technology, an account of the cost of the coupling partners needs attention, for example, the general trend is that organic chlorides are less expensive than organic bromides. Finally, *practicality* is the key influence on the cost of a process—perhaps stated oversimplified—a fast reaction at room temperature is considerably less expensive than an overnight reaction at higher temperature. With reference to Woodward’s notion regarding curiosity-driven academic work, there is a common ground with research by industrial

chemists who search for more effective, practical catalysts to lower metal loading, increase selectivity and thereby minimize waste. These are important factors from reagent economy and sustainability point of views. A significant point to mention is that although academic discoveries on the role of bulky electron-rich trialkylphosphines as highly effective ligands for coupling reactions, many of these ligands are highly *pyrophoric* liquids or solids. This was a considerable drawback for their use in scale-up of reactions in the chemical industry. For example, Fu demonstrated the superior properties of the sterically demanding trialkylphosphine, PtBu_3 , ligand for a wide range of coupling reactions. However, the pyrophoric property of this ligand detracted from its practical use in many, inadequately equipped, industries. In addition, typically these ligands are used in excess. A solution to its pyrophoric nature proved to be the use of preformed palladium complexes incorporating the PtBu_3 ligand. Two front-line solid crystalline precatalysts, $[\{\text{Pd}(\mu\text{-Br})\text{P}(\text{tBu}_3)\}_2]$ (**1**) and $[\text{Pd}(\text{PtBu}_3)_2]$ (**2**; Scheme 26) evolved, both of which were shown to be only slightly air-sensitive (comparable to $[\text{Pd}(\text{PPh}_3)_4]$), and thus attractive for use on large scale synthesis. Hartwig, among others, demonstrated the efficacy of the Pd^{I} dimer **1** in Suzuki–Miyaura couplings and Buchwald–Hartwig aminations.^[147] Furthermore, the Pd^{0} catalyst **2** has been used, for example, in many reactions including Heck, Suzuki, and Negishi reactions, displaying excellent reactivity even at low palladium loadings.^[148] These observations triggered the development and commercial availability of a large range of preformed $[\text{L}_2\text{Pd}^{\text{0}}]$ catalysts, bearing various tertiary phosphine ligands (**2–8**) for use in small and large-scale synthesis.^[149] All of these new Pd^{0} catalysts turned out to be unique for certain chemistries, an example being a new C–C bond forming carbohalogenation reaction using $[\text{Pd}(\text{Q-Phos})_2]$.^[150]



Scheme 26. Selected preformed palladium catalysts for various cross-coupling reactions.^[147–150, 153–159] Amphos = $\text{PtBu}_2\text{C}_6\text{H}_4\text{NMe}_2$; Dt-BNpP = di(*tert*-butyl)neopentylphosphine.

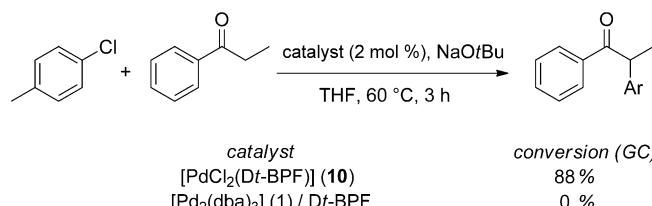
The use of preformed palladium complexes as catalysts leads, unavoidably, to a second point for consideration: the often observed, more efficient reaction using a preformed complex as opposed to one formed *in situ*. Prashad and co-workers showed that the use of precatalyst **1** results in higher yields of isolated tertiary amine in Buchwald–Hartwig aminations than those obtained using a $\text{Pd}(\text{OAc})_2/\text{PtBu}_3$ catalyst system (Scheme 27).^[151] As further recent examples, catalyst **2** was found to give 98% conversion into product



Scheme 27. Preformed catalysts in Prashad's Buchwald–Hartwig aminations.^[151]

compared to 69% yield obtained by an *in situ* $[\text{Pd}(\text{dba})_2]/2\text{PtBu}_3$ system for a one-pot conversion of isoindolines to 1-arylisooindoles,^[152] and Shaughnessy and Colacot reported that, in amination reactions, the preformed π -allyl catalyst **9** is not only air-stable but shows a performance superior to that of the *in situ* $[\text{Pd}_2(\text{dba})_3]/\text{Dt-BNpP}$ catalyst system when excess ligand is used.^[153] A number of highly active preformed Pd π -allyl and crotyl catalysts containing dialkylaryl phosphine ligands, have recently been reported by Colacot and co-workers.^[154]

Similarly, the preformed air-stable palladium(II) catalyst bearing the 1,1'-bis(di-*tert*-butylphosphino)ferrocene (DtBPF) **10** shows definite superior activity in both Suzuki–Miyaura and α -arylation reactions, compared to the catalyst generated *in situ* from $[\text{Pd}_2(\text{dba})_3]$ and DtBPF (Scheme 28).^[155]



Scheme 28. Advantage of preformed catalysts.^[155] Ar = *p*-tolyl.

In recent years, a number of research groups have introduced other preformed Pd complexes as highly effective catalysts for cross-coupling reactions. Among these, Buchwald's palladacycles **11**,^[156] the PEPPSI catalyst **12**,^[157] and Nolan's^[137] carbene-containing complexes **13**^[158] and **14**,^[159] are noteworthy.

In addition to the practicality and efficiency aspects, the third point that is of higher significance in industry compared

to academic research is the amount of remaining palladium contamination in the isolated organic product.^[160] Typically, approximately 5 ppm is the allowable limit. This can critically influence the route selection by which a pharmaceutical material is synthesized. Apart from the evident solution of choosing a highly active catalytic system which can be operated at a lower loading, this issue has been addressed by the development of several solid-supported preformed palladium complexes which have been launched onto the catalyst market.^[161] Often, as noted previously, the additional beneficial effects, such as air-stability (for pyrophoric phosphine ligands) and higher activity, are observed using these polymer supported catalysts. An example of this technology is the development of air-stable tunable Pd-FibreCat series, which contains air-sensitive or pyrophoric mono- and bidentate ligands, such as *t*Bu₃P and 1,1'-bis(diisopropylphosphino)ferrocene (dippf).^[162]

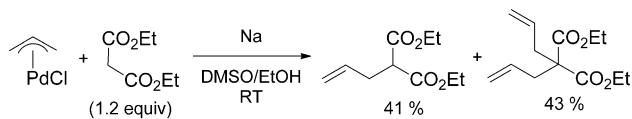
4. Cross-Coupling Reactions Involving Alternative Coupling Partners: History Repeats Itself

As is evident from the above discussion, a common trend is apparent in the historical development of cross-coupling processes involving organohalides and organometallic components: a coupling reaction is studied using stoichiometric amount of transition metal, usually copper or nickel and optimization of the procedure leads to conditions of catalytic loadings. Often these observations prompt further research into these processes, ultimately yielding catalytic palladium-mediated variants of these transformations. As this story unfolded in the 20th century, punctuated by the discovery of the named reaction processes, other types of new coupling procedures emerged with this recurring theme and with rarely a divergence from this chronology.

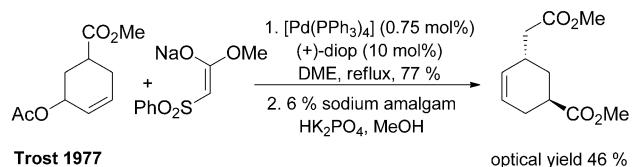
The cross-coupling reactions discussed so far are mechanistically rationalized to follow the general catalytic cycle depicted in Scheme 1, with the common features of an organohalide (or pseudohalide) and an organometallic reagent (or a nucleophilic heteroatom) as coupling partners. A number of other cross-coupling reactions in which one (or both) of the coupling partners is replaced by a reagent not exhibiting these general features have been developed. Although not the focus of this Review, these methods are highlighted briefly below.

4.1. Allylic Alkylation

The Tsuji–Trost allylation,^[163,164] is conceptually also a palladium(0)-mediated coupling reaction but is mechanistically different from the conventional cross-coupling processes and achieves an allylic substitution via an intermediate π -allylpalladium complex. This type of reactivity was first described in 1965 by Tsuji, who observed the reaction of diethyl malonate with the stoichiometric preformed palladium allyl complex (Scheme 29).^[50] Following initial results in 1973,^[164] Trost reported the first asymmetric transformation in 1977 which marked his defining contributions to the field.^[165]



Tsuji 1965



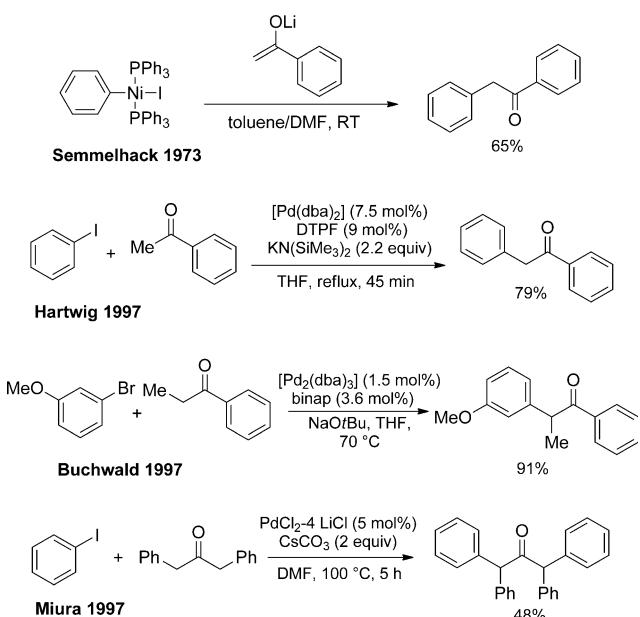
Trost 1977

Scheme 29. The Tsuji–Trost allylation reaction.^[163] Optical yield is the ratio of optial purity of product to that of the catalyst.

Before this seminal work, Pd was not known to participate in chiral induction reactions because of the β -hydride elimination complications.

4.2. α -Arylation of Carbonyl Compounds^[166]

In the α -arylation process, an enolate coupling partner, generated in situ from a carbonyl compound and a base, is treated with an aryl halide or pseudohalide in the presence of a nickel(0) or palladium(0) catalyst to achieve a formal C(sp³)–H–C(sp²) coupling result. This reaction also follows the historical sequence noted above, namely the movement from stoichiometric to catalytic conditions. Discovered by Semmelhack in 1973 with a stoichiometric organonickel species (Scheme 30), the α -arylation process was applied also in stoichiometric fashion in the total synthesis of Cephalotaxus alkaloids.^[167] Almost 20 years later, simultaneous reports from Hartwig,^[168] Buchwald,^[169] and Miura^[170] set the stage for the development of the Pd-based α -arylation

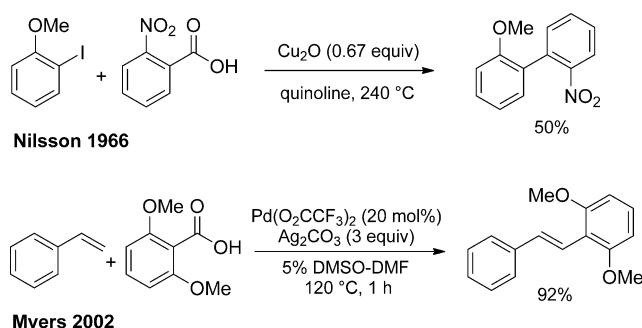


Scheme 30. History of the α -arylation reaction.^[167–170] DTPF = 1,1'-bis(di-*o*-tolylphosphino)ferrocene.

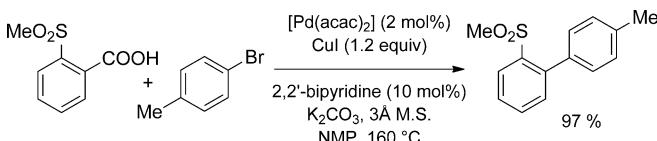
which, today, is a highly promising C–C bond forming reaction with application in industry.^[166]

4.3. Decarboxylative Coupling Reactions

The original decarboxylative cross-coupling reaction was reported by Nilsson in 1966 employing nearly stoichiometric quantities of copper under harsh conditions (Scheme 31).^[171] Almost 40 years later, Myers disclosed a catalytic process employing palladium(II) salts,^[172] and, in further variants, other researchers showed that the organometallic component may be generated *in situ* from a carboxylic acid by, for example, the action of an additional metal (Scheme 32)^[173] or an additive, such as $n\text{Bu}_4\text{NCl}$.^[174]



Scheme 31. The first examples of the decarboxylative cross-coupling reaction.^[171, 172]



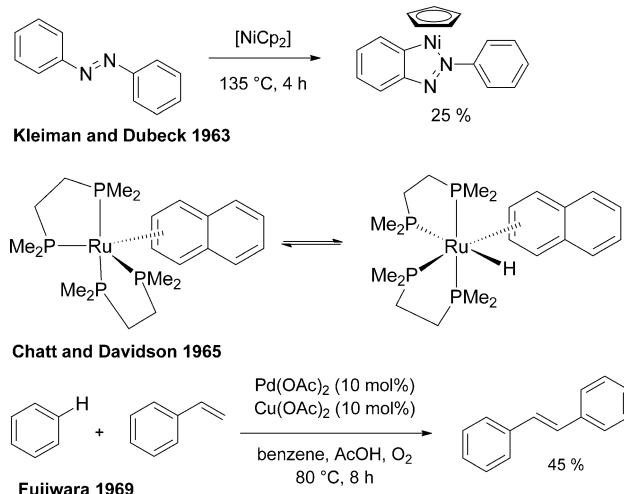
Scheme 32. The Pd–Cu catalyzed decarboxylative cross-coupling reaction.^[173]

Compared to the complementary C–H activation methodology discussed below, the decarboxylative coupling does not suffer from regioselectivity issues since the site for coupling is predefined. The elevated temperatures for the reaction, availability of benzoic acid derivatives, and functional-group tolerance need to be addressed for further evolution of the decarboxylative coupling as a competing coupling methodology. The interested reader is referred to the Review by Goossen^[173b] for a detailed account of this topic.

4.4. C–H Activation Reactions

A dream of organic chemists has been the discovery of coupling reactions with no prefunctionalization of the coupling partners. In other words, imagine a route which avoids the use of aryl halides or pseudohalides and organometallic

reagents, the only by-product is H_2 , and the term high atom-economy may be used without embarrassment. This dream is rapidly and undeniably becoming reality, as numerous research groups are recognizing the opportunities to develop new synthetic methods by processes given the umbrella title of C–H activation. The first hint in the literature concerning successful C–H activation reactions *predate* the palladium-mediated cross-couplings. Thus, in 1963 Kleiman and Dubeck reported the isolation of a nickel Cp complex ($\text{Cp} = \text{C}_5\text{H}_5$) resulting from *ortho* C–H activation of azobenzene formed by the action of stoichiometric quantities of nickel (Scheme 33).^[175] Shortly after, Chatt and Davidson noted



Scheme 33. Early C–H activation processes.^[175–177]

the equilibrium of a ruthenium naphthalene species between the π -complex and the C–H insertion complex.^[176] In fact, C–H activation had successfully moved into the catalytic realm even *before the discovery of catalytic palladium-mediated cross-coupling*. This is evidenced by the work of Fujiwara who, in 1969, reported on the oxidative Heck reaction^[177] two years before the initial disclosures of Heck and Mizoroki.

Following these early results, C–H activation has witnessed a surge of activity in the last 20 years, pioneered by the contributions of Murai and his school, using ruthenium catalysis.^[178] Bergman and Graham initiated the quest for the “holy grail” of cross-coupling, investigating alternative metals for these transformations.^[179] Today, the direct C–H activation wave employing palladium catalysis stimulated by results from the laboratories of Du Bois, Fagnou,^[180] Gaunt, Hartwig, Miura, Sanford, Yu, among others, are pushing the boundaries of the probable and possible.^[181] We will leave this topic here at the origins and developments, and refer the reader to Reviews in the rapidly evolving C–H activation area.^[182, 183]

5. Industrial Applications

In organic synthesis methodology, the ultimate testimony of value is utility. The Nobel Prize winning Heck, Suzuki, and

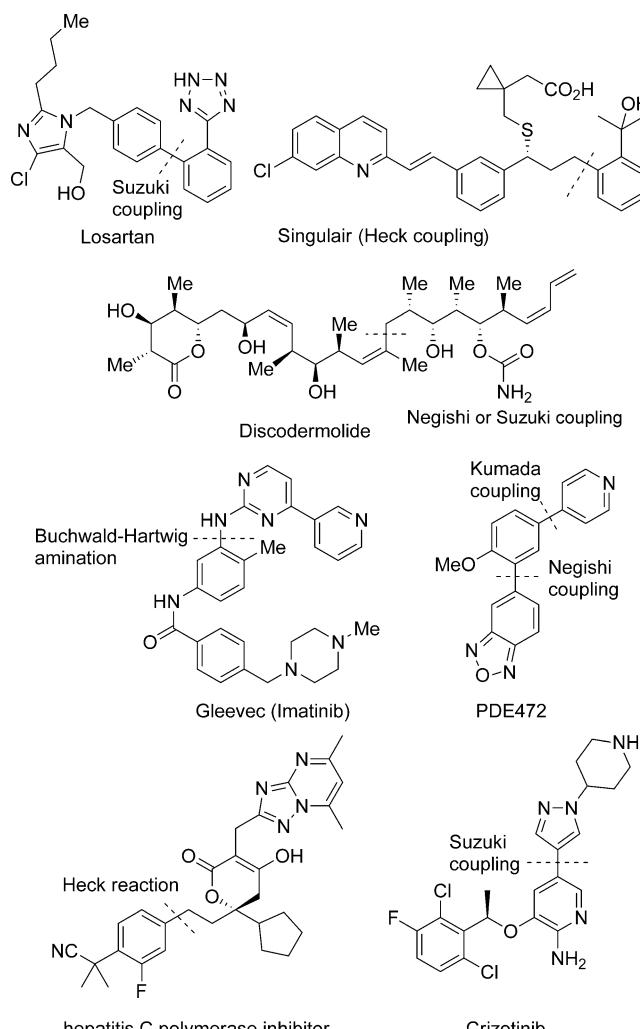
Negishi coupling chemistries, alongside the other discoveries and technologies outlined above, amply substantiate this maxim. Thus, syntheses of natural products and drug molecules abound where the key step(s) consists of metal-catalyzed cross-coupling reactions as selectively exemplified by the well-established BMS (originally Dupont–Merck) synthesis of Losartan,^[184] the Merck Singulair process (a Heck coupling involving isomerization of an allylic alcohol),^[185] and the total synthesis of discodermolide by Smith (Negishi coupling) and later Novartis (Suzuki coupling; Scheme 34).^[186] Examples are continuously appearing, such as the Novartis route to Gleevec (Imatinib) which employs a Buchwald–Hartwig amination as the key step.^[187] Manley and co-workers have demonstrated large-scale Corriu–Kumada and Negishi couplings in the synthesis of PDE472, a potential drug for the treatment of asthma.^[189] Pfizer’s process for the production of a hepatitis C polymerase inhibitor incorporates a Heck reaction carried out on 40 kg scale.^[188] In a very recent report, Koning and co-workers provide an example of a Suzuki–Miyaura coupling on a 50 kg scale in the synthesis of Crizotinib, a potent anti-cancer agent.^[190] A large number of Reviews published on the

application of cross-coupling methodologies in total synthesis^[191] reflect the fertile evolution of the subject and the obvious revolution that these methodologies have brought about for natural-product and drug-molecule synthesis for which the 2010 Nobel Prize has been fittingly awarded.

6. Coupling Reactions: Unsolved Problems, Challenges, and Outlook

Despite the many significant discoveries and developments since the first reports of transition-metal-catalyzed organic transformations, there remain, as expected in the incremental waves of scientific progress, numerous unsolved problems. Thus, only partial success in $C(sp^3)$ – $C(sp^3)$ and $C(sp^2)$ – $C(sp^3)$ cross-coupling reactions involving alkyl halides has been achieved. Further, achievement of selective mono α -arylation requires effort in cases where the product of the reaction can partake in secondary coupling (e.g., α -arylation of CH_3COR and arylation of primary amines). In the area of asymmetric catalysis, although simple methods using chiral ligands to form enantioenriched products have been developed, fundamental studies are essential to achieve practical and hence widely applied methodology. Finally, determination of the mechanism is essential for successful use in synthesis. Thus, although the steric and electronic effects of the ligands involved in the various steps of the catalytic cycle are now reasonably well rationalized, there remains, in many cases, a lack of understanding of the mechanism of formation of the active Pd^0 catalytic species from preformed Pd^{II} complexes. The newest wave of C–H activation reactions will increasingly find advantages by the use of alternative metals, such as ruthenium, iridium, and—the oldest catalytic metal—copper. To predict whether or not palladium will always be the metal of choice is, as always in science prognosis, a treacherous undertaking. For now, the future of palladium is bright since, in a vast array of conditions for a multitude of disconnections, the unique qualities of palladium are demonstrable, serving only to reinforce its power especially in C–C bond construction.

To conclude, gigantic progress has been achieved in the last 40 years within the palladium-catalyzed cross-coupling field using functionalized leaving group and metal coupling partners. Assessed by recent developments, the increasing focus on the development of direct C–H activation processes will become the next prevailing wave of reactions for synthesis. This reaction also awaits the development of more practical and economical conditions and procedures for application in large-scale syntheses whilst finding robust solutions to the selectivity issues encountered for less-straightforward coupling partners. The sometime expressed notion that the market is becoming saturated with catalysts and methods for coupling reactions can easily be dismissed by another observation by Woodward who, in 1969, noted that comments such as "... well, now you have shown that anything can be synthesized, so the field has had it..." were common place.^[146] Three Nobel Prizes in Chemistry for homogeneous catalysis during the last decade,^[192] culminating with the 2010 Nobel prize for palladium-catalyzed cross-



Scheme 34. Cross-coupling reactions in total synthesis.^{[184]–[190]}

coupling,^[193] sharply contrast with such notions and continue to ascertain the significance of fundamental research in discovery and practical application for the benefit of society.^[194]

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