1
Cross-Coupling Arylations: Precedents and Rapid Historical Review of the Field

If a man will begin with certainty, he will end in doubts; but if he will be content to begin with doubts, he will end in certainties.

(Francis Bacon)

1.1
Metal-Catalyzed Cross-Couplings: From Its Origins to the Nobel Prize and Beyond

Organic synthesis is a highly useful and creative endeavor. Since its humble origins only about 200 years ago, with the simple synthesis of urea from ammonium cyanate by Wöhler (1828), it has become a very systematic, cornerstone field of science that touches many other scientific areas, such as medicine, agriculture, food science, materials science, and so on. For the first part of the last century, many important synthetic achievements were made, which included: hemin (Fischer, 1929, Nobel prize 1930), tropinone (Robinson, 1917 – Nobel prize 1947), pyridoxine hydrochloride (Folkers, 1939), and equilenin (Bachmann, 1939) [1]. However, this period was followed by a "golden period," which lasted from about the 1950s to the mid-1990s, and where important benchmarks for this field were set, these benchmark syntheses were highlighted by the brilliant synthetic achievements, some of which include: strychnine (Woodward, 1954, Nobel Prize 1965), vitamin B_{12} (Woodward/Eschemmoser), progesterone (Johnson, 1971), prostaglandin A_2 (Stork, 1976), ginkgolide (Corey, 1988, Nobel prize 1990), indolizomycin (Danishefsky, 1990), rapamycin (Nicolaou, 1993), and taxol (Nicolaou and Holton (independent of each other), 1994) [1].

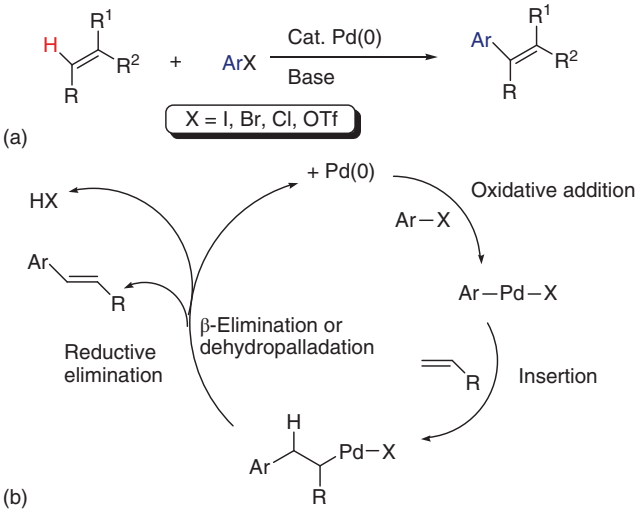
In most of these elegant syntheses, the creation of key carbon–carbon bonds was a fundamental step, and novel methods – generally employing metals, whether at a stoichiometric or catalytic level – were developed. But in fact, these developments have had a significant effect on a lot of organic and analytical chemistry, promoting the development of new analytical techniques, such as NMR, mass spectrometry, liquid chromatography, which have facilitated a better understanding of the three-dimensional molecular structures of these compounds and of the mechanisms underpinning the reactions involved. During this time, all these endeavors had certainly improved the lives of countless individuals. However, during the flurry of activity on the synthesis of these remarkable molecules, one important issue was frequently ignored – that of reaction efficiency and sustainability. In some key syntheses during this period, these aspects were considered, for example, in the synthesis of (*rac*)-FR-900482 by Danishefsky's group [2] (see below) – where an intramolecular version of the Mizoroki–Heck was successfully demonstrated. It was not until 1998 that these issues had been "officialized" with the announcement of Anastas's and Warner's [3] 10 rules of green chemistry.

It should also be noted that even before this "golden period" got started and in many cases coinciding with the important milestones of this period, a number of key unforgettable developments had occurred in the field of organometallic chemistry – undoubtedly spurred on by industrial needs – which have had an enormous impact on the current state of this field. For example, the

Catalytic Arylation Methods: From the Academic Lab to Industrial Processes, First Edition.
Anthony J. Burke and Carolina Silva Marques.

hydroformylation of alkenes with carbon monoxide and hydrogen using cobalt catalysts to give aldehydes developed by Otto Roelen in the 1930s – known as the *oxo process* [4], which currently is part of the BASF process for the synthesis of methyl methacrylate – produced in a very elegant sequential manner via aldol condensation/dehydration/oxidation/esterification of the intermediate aldehyde product [4, 5]. Speaking of aldehydes and acetaldehyde in particular, in 1894, a method was developed for the transformation of ethene to acetaldehyde using $PdCl_2$, but it was not until 1960 that it became industrially useful, and it became known as the *Wacker oxidation reaction* [5]. The Monsanto process is a little more recent (late 1970s) and concerns the Rh(I)-catalyzed carbonylation of methanol to afford acetic acid [5]. The Cu(I)-catalyzed cyclopropanation of Salomon and Kochi [6] in the early 1970s and the asymmetric version which had already been developed using a chiral Cu(II) catalyst by Nozaki's group [7] in 1966 were clear demonstrations of the utility of metallocarbenes for the creation of C–C bonds. In the context of metallocarbenes, the seminal work of Yves Chauvin in the early 1970s – working on industrial polymerizations – cannot be ignored, as it led to the creation of new C–C bonds by way of a process termed the *ring-closing metathesis* [8], and was the subject of the Nobel prize in Chemistry in 2005 [9]. All of this background knowledge appeared to serve as an important stimulation for the next big step in organic synthesis, the creation of C–C and C–X bonds (and of course includes arylation processes) that started in the early 1970s.

Throughout this flurry of activity in the field of organometallic catalysis, in the mid-1970s, the field of organic synthesis underwent another revolution with the discovery of a very efficient, mild, catalytic method using palladium for the construction of carbon–carbon bonds, but particularly for those that contain at least one aromatic carbon atom – or in other words, for arylation reactions (the importance of this process is discussed below). After the pioneering work of Mizoroki and coworkers in 1971 on the palladium-catalyzed arylation of olefinic compounds with aryl iodides in MeOH at high temperature [10], Heck and Nolley [11] developed a milder version which has now become known as the *Mizoroki–Heck reaction* – to this date, it has received an impressive 15 796 hits[1)] on ISI web of science. It should be noted that Heck had previously worked with stoichiometric quantities of palladium and organomercury compounds, but the toxic nature of mercury prevented further advances with this method. The accepted catalytic cycle for the Mizoroki–Heck reaction is shown in Scheme 1.1. In terms of reactivity, aryl iodides and aryl bromides are usually



Scheme 1.1 (a) Mizoroki–Heck reaction conditions and (b) accepted mechanism for the Mizoroki–Heck reaction [12e, f].

1) Using the search term *Heck Reaction* in February 2014.

the best [12d], but the reaction is not restricted to activated substrates, but can be simple olefins, or olefins substituted with ester, ether, carboxyl, phenolic, or cyano groups [12c]. Generally, the reaction is performed using palladium acetate (needing to be reduced to Pd(0) with PPh_3), or a Pd(0) source such as $Pd_2(dba)_3$ (dba = *trans*, *trans*-dibenzylideneacetone), $Pd(Ph_3P)_4$, or even Pd on carbon, and a base such as triethylamine, or potassium acetate, heterocyclic halides, and alkenes, can be coupled using this reaction [12d]. The reaction is stereospecific, yielding products that are arrived at via *syn* addition followed by *syn* elinination [12d, e]. The Heck–Mizoroki reaction cannot be regarded as a traditional cross-coupling reaction as there is no transmetallation step.

In Figure 1.1, we present a time line for the most important developments in cross-coupling reactions as taken from Ref. [14].

The asymmetric Heck–Mizoroki reaction (Scheme 1.2) was first reported by Hayashi's group in 1991 [12d, e, 13, 15]. The prototype benchmark reaction involves the reaction of phenyl triflate with 2,3-dihydrofuran using 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) as the ligand and it can afford the 2-phenyl-2,3-dihydrofuran product with an enantioselectivity of 96% ee. This was a remarkable development, as it afforded a very powerful tool for accessing many natural products or reported biologically active compounds [16], one such example was the elegant synthesis of physostigmine by Overman's group in 1993 (Scheme 1.3) [17].

Despite the obvious qualities of the Mizoroki–Heck reaction, some of the disadvantages of this procedure are that the active palladium catalysts used require stabilization with phosphanes, which are generally sensitive to oxidation, thus necessitating the use of inert atmospheric conditions, and high temperatures are normally required, leading to side reactions and catalyst deactivation.

The use of arenediazonium salts as arylating reagents of olefins was first reported by Matsuda in 1977 [18, 19]. This reaction has been appropriately coined the Heck–Matsuda reaction (Scheme 1.4a).

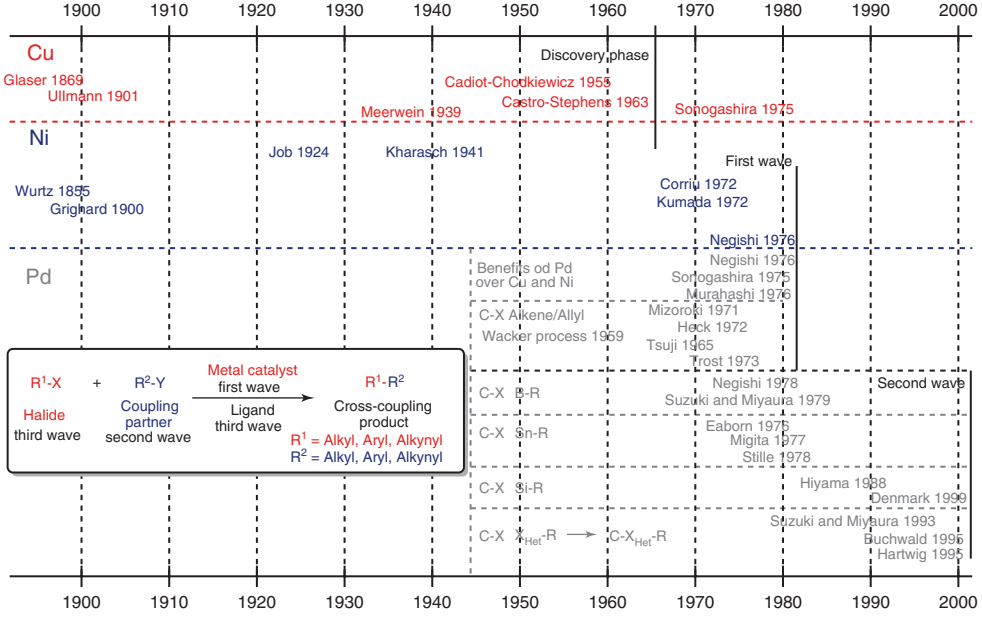
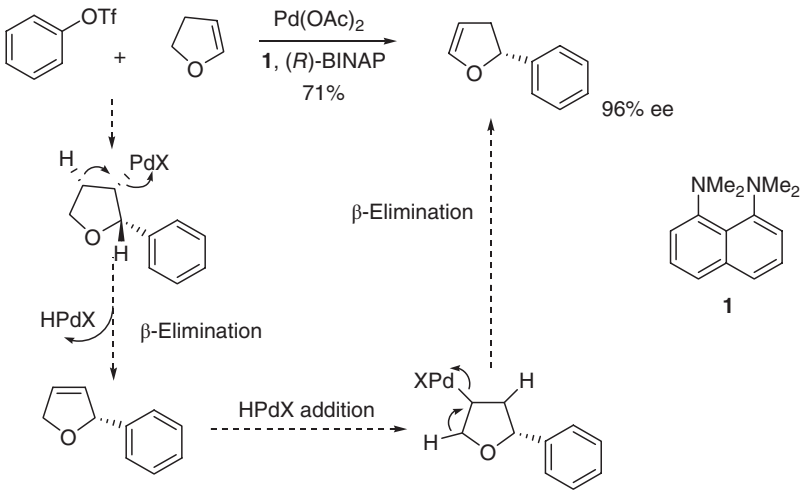
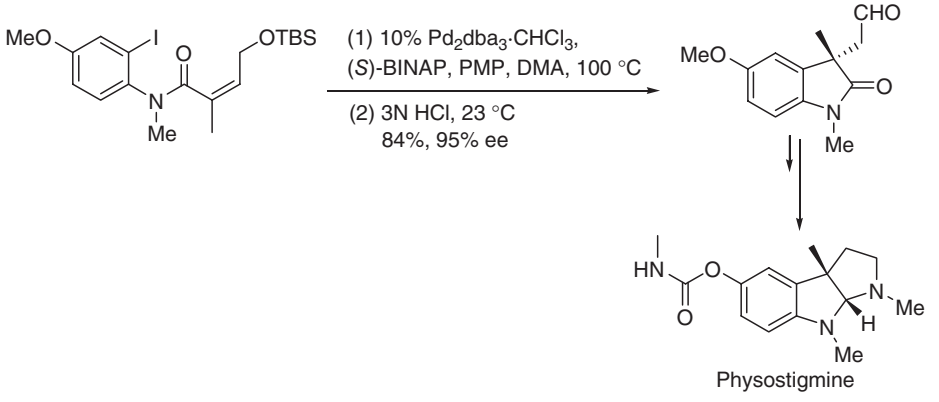


Figure 1.1 A History of the discovery and development of metal-catalyzed cross-coupling reactions [14]. (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)



Scheme 1.2 The prototype asymmetric Heck–Mizoroki reaction and its proposed mechanism [12e, f, 13].

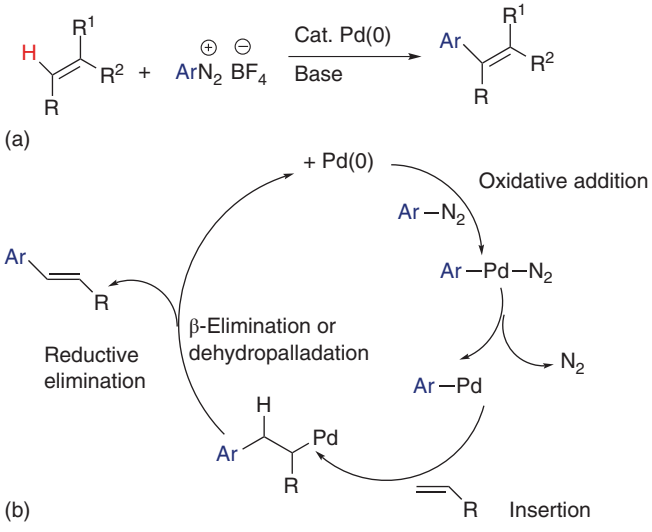


Scheme 1.3 Application of the asymmetric Heck reaction as a pivotal step in the synthesis of physostigmine by Overman [17].

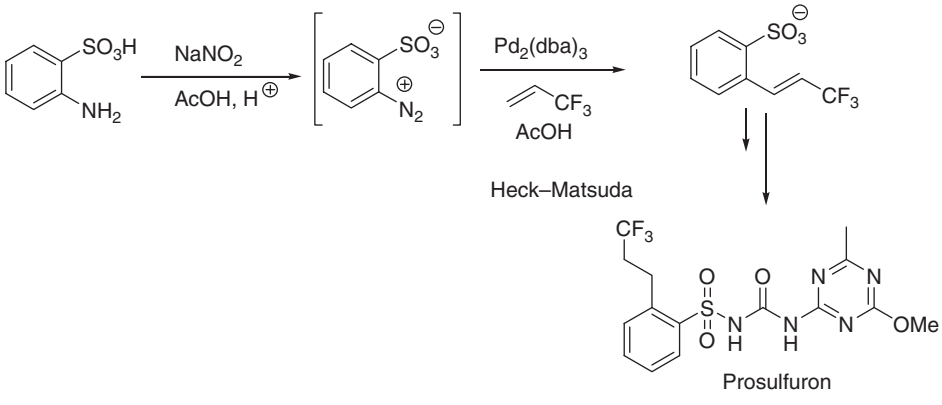
This reaction involves the arylation of olefins with arenediazonium salts using $Pd(OAc)_2$ or $Pd_2(dba)_3$ as the source of Pd(0). The counter-ion is generally BF_4. This reaction is carried out in a variety of common solvents, including ionic liquids (ILs) and mixed organic/aqueous solvent systems. Sodium acetate is the best base for this reaction [19]. One of the disadvantages of this reaction is that it can be difficult to control the reactivity of the arenediazonium salts [19]. The catalytic cycle is shown in Scheme 1.4b.

This reaction was very elegantly applied by Ciba Geigy AG in 1997 for the industrial synthesis of the herbicide prosulfuron, the key steps are shown in Scheme 1.5 [20].

In 1984, the late John Stille and his team developed a variant of the Mizoroki–Heck reaction [21] applying it in the synthesis of pleraplysillin. This method proved to be a very general and applicable reaction, which involved a transmetallation step involving an alkyl or aryl stannane. The catalytic cycle is shown in Scheme 1.6. Even though the organotin reagents are easy to prepare, they are rather



Scheme 1.4 (a) The Heck–Matsuda reaction conditions and (b) accepted mechanism for the Heck–Matsuda reaction [19].

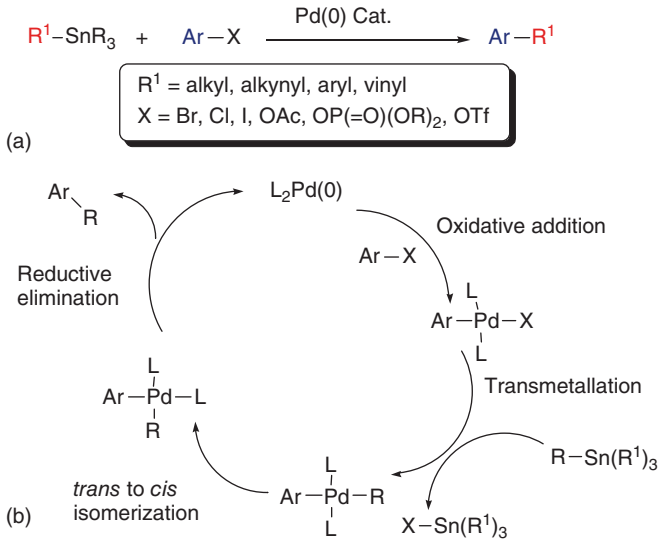


Scheme 1.5 The synthesis of Prosulfuron by Ciba Geigy AG employing a Heck–Matsuda reaction as a pivotal step [20].

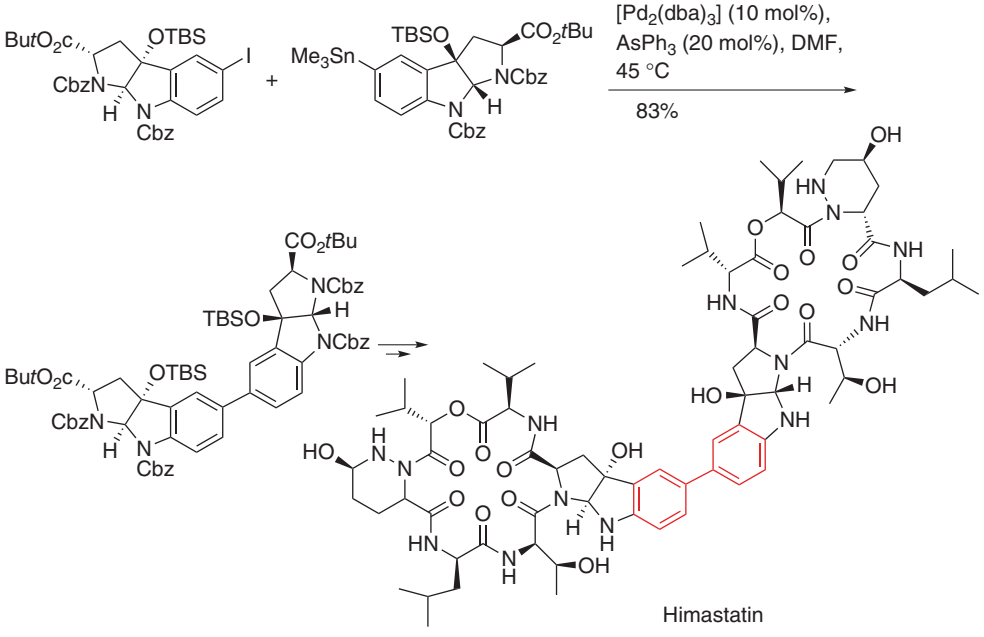
unwelcome because of their toxicity, and thus in recent years, this reaction has become overshadowed by the other cross-coupling reactions. Even so, it was used for the synthesis of a variety of important targets, such as rapamycin, by Nicolaou [1]. Vinyl or aryl triflates have been successfully used as substrates. Triphenylphosphane (TPP) is a good ligand for this process, although Ph_3As is a good ligand for the coupling of triflates [12e]. Tin compounds of heterocycles can be readily coupled with aryl halides [12e].

One good example of the application of an arylating cross-coupling method was for the synthesis of himastatin by Danishefsky and Kamenecka [22] reported in 1998 (Scheme 1.7).

In 1975, Sonogashira and coworkers [23] reported a novel Pd(0) cross-coupling (more appropriately known as the *Sonogashira–Hagihara reaction*) reaction of terminal alkynes with vinyl and aryl

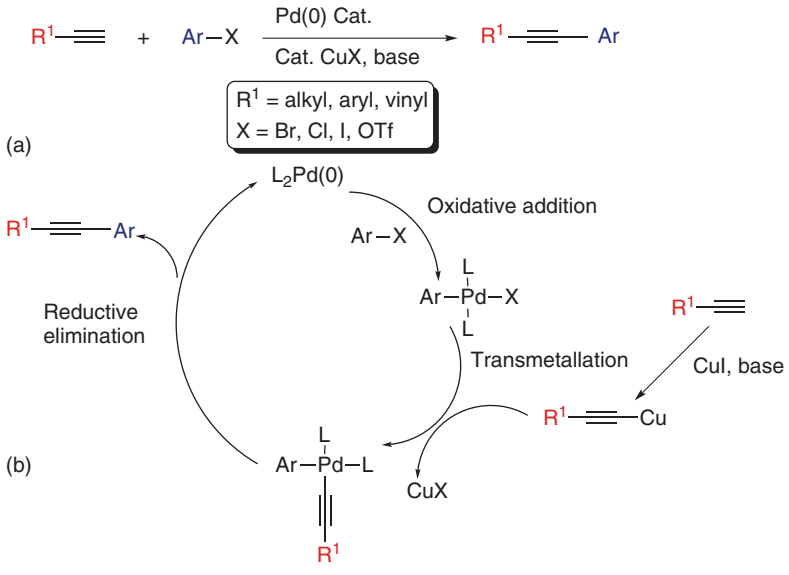


Scheme 1.6 (a) General conditions for the Stille cross-coupling reaction. (b) The proposed mechanism for the Stille cross-coupling arylation procedure [12a].



Scheme 1.7 The synthesis of Himastatin by Danishefsky and Kamenecka reported in 1998 [22].

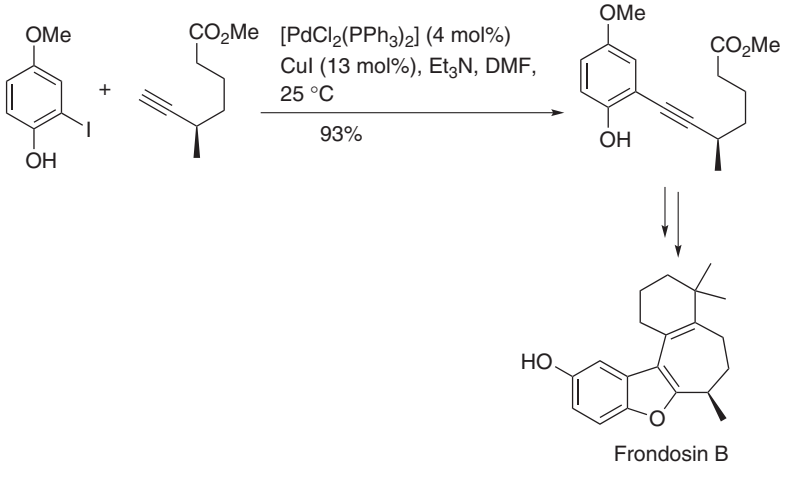
halides; this was actually based on the Castro–Stevens reaction [12a, 23], but is run under milder conditions (Scheme 1.8a). The reaction mechanism is akin to that of the Stille coupling reaction, and involves a transmetallation step from a copper acetylide intermediate (Scheme 1.8b).



Scheme 1.8 (a) General conditions for the Songashira–Hagihara cross-coupling reaction. (b) The proposed mechanism for the Sonogashira–Hagihara cross-coupling arylation procedure [12, 24].

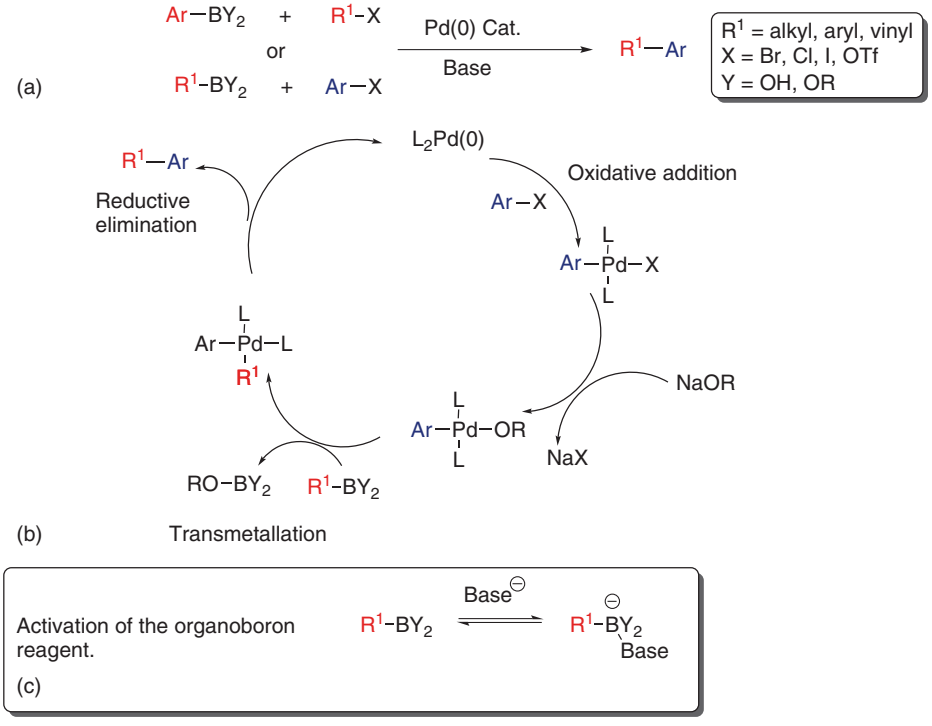
In the Sonogashira reaction, CuI is a cocatalyst used to form the copper acetylide reagent, which takes part in the transmetallation step. For the formation of the copper acetylide species, bases such as Et_3N, Pr_2NH, Et_2NH, or morpholine are used [12].

Many good applications of this reaction have been shown during the years, a very good example was the synthesis of frondosin B, an interleukin-8 receptor antagonist, reported by Danishefsky's group [25] in 2001 (Scheme 1.9).



Scheme 1.9 The synthesis of Frondosin B by Danishefsky and coworkers [25] employing a Sonogashira reaction as the key step.

The most widely used cross-coupling arylation reaction is the Suzuki–Miyaura reaction (Scheme 1.10), which was first reported in 1979 [12, 26, 27]. The reaction involves transmetallation with an organoboron reagent that is usually a boronic acid or ester. No transmetallation occurs under neutral conditions only in the presence of a base, which is usually an alkaline earth metal alkoxide, although weak bases such as K_2CO_3 can be used [12] (Scheme 1.10b). $Pd(OAc)_2$ or $Pd_2(dba)_3$ are the common sources of Pd(0). In some circumstances, arenediazonium tetrafluoroborates have been used [12e]. Nickel complexes can be used under some circumstance instead of Pd.



Scheme 1.10 (a) General conditions for the Suzuki–Miyaura cross-coupling reaction. (b) The proposed mechanism for the Suzuki–Miyaura cross-coupling arylation procedure. (c) Activation of the organoboron reagent (note the base used was an alkoxide or hydroxide), [12, 26, 27].

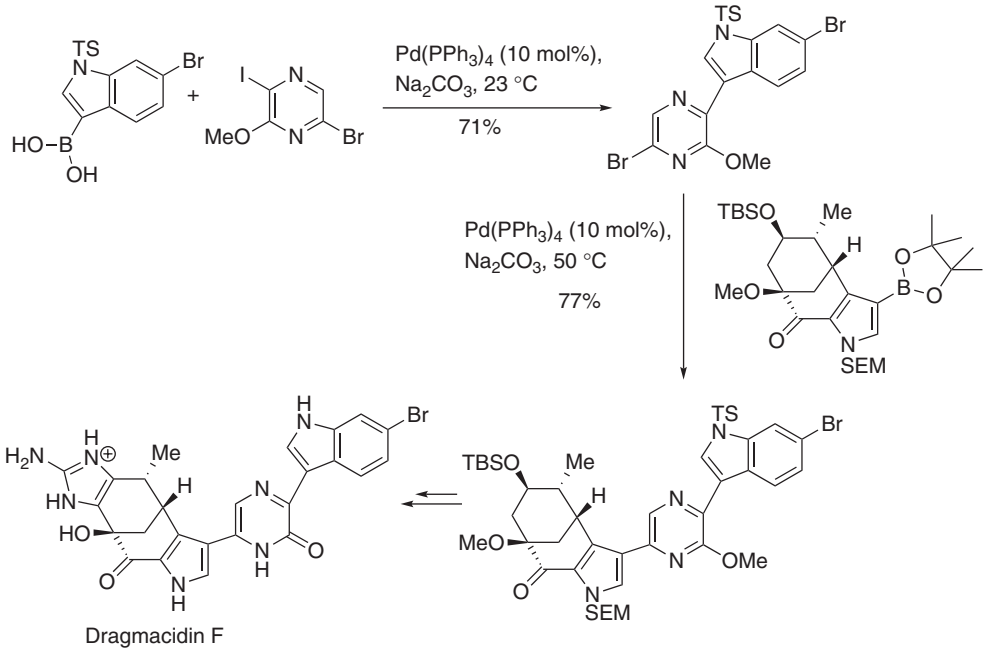
The number of important biologically active targets accessed with this method is quite astounding, some of these examples include indole [1], vancomycin aglycon (Boger, Nicolaou) [12h], michellamine B (Dawson) [12h], korupensamine A (Uemura) [12h], and diazonamide A (Nicolaou) [12h]. We would like to highlight Stoltz's [28] elegant synthesis of dragmacidin F, which involved a sequence of reactions that included two Suzuki–Miyaura coupling events and one intramoleular Heck-Mizoroki arylation event (Scheme 1.11).

The Suzuki–Miyaura reaction is also amenable to large-scale production [27d].

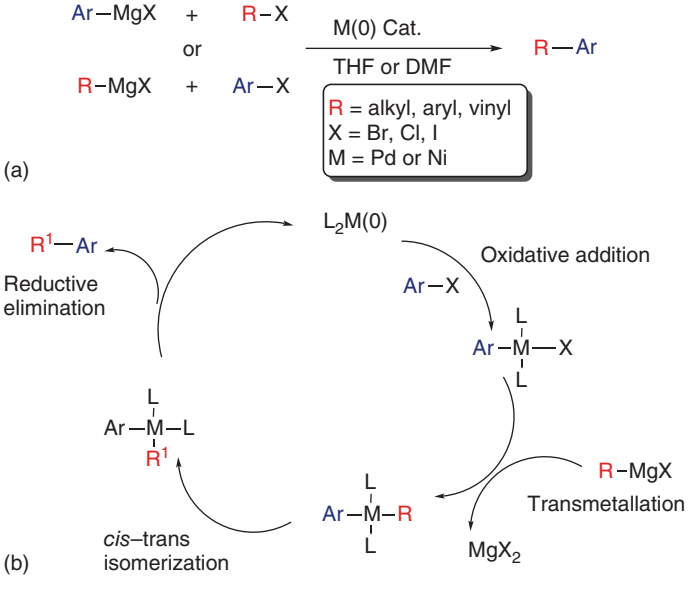
As shown in scheme (Scheme 1.10c), it should be noted that the function of the base is in fact to activate the boronic acid or boronate ester, converting it to a borate complex, which can easily participate in the transmetallation event [27].

For further references, readers are encouraged to see Ref. [27].

A cross-coupling arylation procedure was developed independently in 1972 by Tamao and Kumada in Japan and Corriu in France and is known as the *Tamao–Kumada–Corriu cross-coupling reaction*



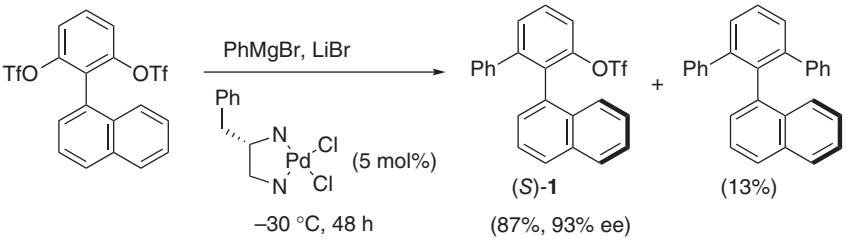
Scheme 1.11 The synthesis of dragmacidin F by Stotlz's group employing two Suzuki–Miyaura cross-coupling arylation reactions as key steps [28].



Scheme 1.12 (a) General conditions for the Tamao–Kumada–Corriu cross-coupling reaction. (b) The proposed mechanism for the Tamao–Kumada–Corriu cross-coupling arylation procedure (note the base used is an alkoxide or hydroxide) [12a].

(Scheme 1.12a) [29]. In this reaction, aryl or alkeneyl halides are reacted with Grignard reagents [12]. It is conducted with either Ni or Pd catalysts, but the Ni catalyst is used more frequently as it is more active for chlorides. The catalytic cycle is shown in Scheme 1.12b. The reaction is limited by the presence of any functional group that will normally react with a Grignard reagent [12e].

In 1995, Hayashi *et al.* [30] reported an enantioselective aryl–aryl coupling procedure based on this method using di-tosylated biaryl substrates and a chiral Pd catalyst (Scheme 1.13).

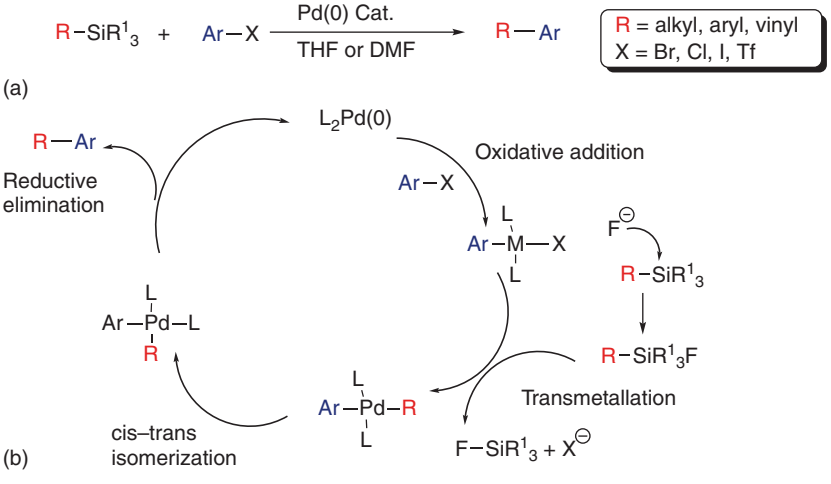


Scheme 1.13 The enantioselective catalytic variant of the Tamao–Kumada–Corriu cross-coupling reaction as developed by Hayashi *et al.* [30].

The monoalkylated biaryl compound (*S*)-**1** formed in this coupling reaction can be used as a useful chiral building block, as the triflate group can be readily substituted with carboxylic acid functions or diphenylphosphane groups.

More on this particular topic is given below.

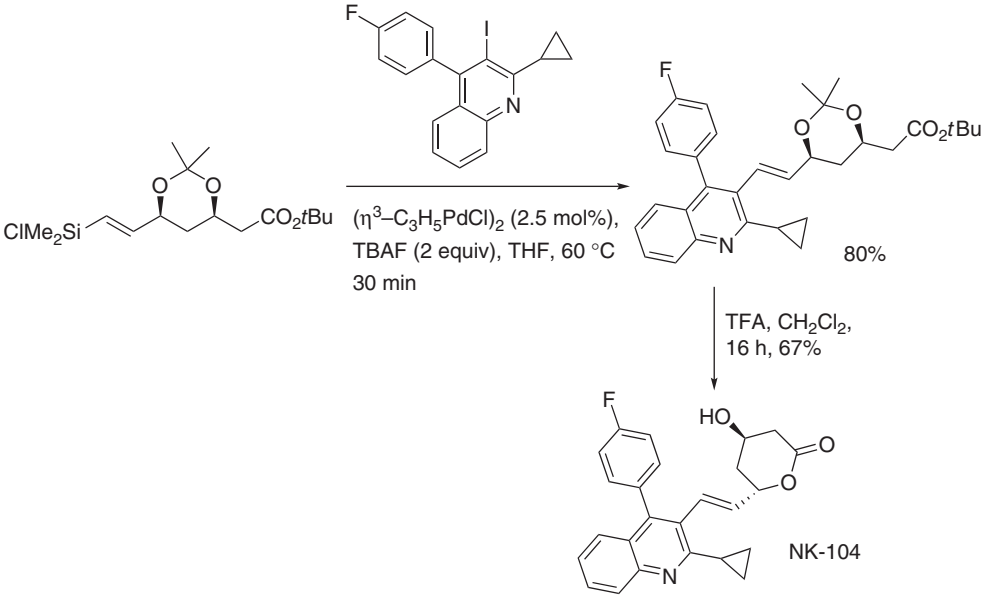
The Hiyama–Hatanaka cross-coupling reaction is a more recent arylation coupling reaction that was reported by these workers in 1988 [12e, 31]. These workers demonstrated that trimethylsilylethylene reacts with aryl halides in the presence of a Pd(0) catalyst, a base, and a source of fluoride ion to give styrene derivatives [12e]. The source of Pd can be $(\pi\text{-}C_3H_5PdCl)_2$, $Pd(Ph_3P)_4$, or even $Pd_2(dba)_3$; the base could be a hydroxide, an acetate, a phosphane, or a phosphite; and the source of the fluoride ion could be tris(diethylamino)sulfonium difluoro(trimethyl)silicate (TASF), tetrabutylammonium fluoride (TBAF) or even KF (See Scheme 1.14a). The role of this reagent is shown in the catalytic cycle



Scheme 1.14 (a) General conditions for the Hiyama–Hatanaka cross-coupling reaction. (b) The proposed mechanism for the Hiyama–Hatanaka cross-coupling arylation procedure [31].

(Scheme 1.14b, a much more detailed mechanistic treatment is given in Ref. [31a]), but it is thought to form five-coordinate silicate compounds. The presence of a Si group in the substrate is thought to enhance the rate of transmetallation. The reaction proceeds under mild conditions and shows good functional group tolerance. One interesting application was the arylation of a ketene silyl acetal with an aryl triflate by Carfagna *et al.* [32] in 1991, using 1,1′-bis(diphenylphosphino)ferreocene (dppf) to give an α-arylcarboxylate. Yields of up to 70% were achieved using aryl bromides and triflates.

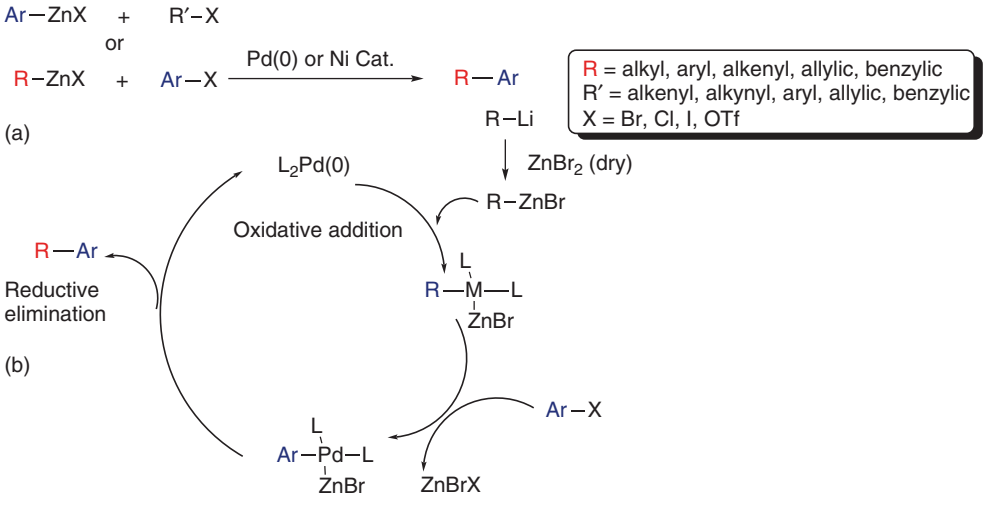
A successful application is the synthesis of the artificial HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitor, NK-104, which was reported by Hiyama's group (Scheme 1.15) [33].



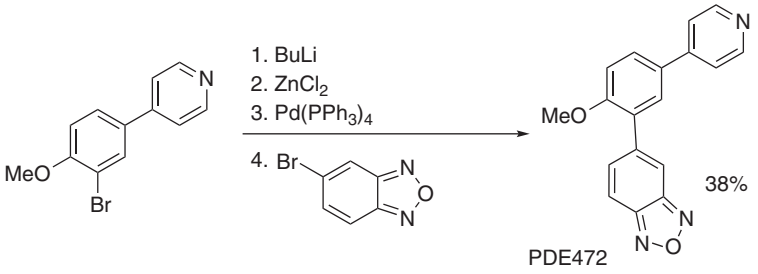
Scheme 1.15 Synthesis of the HMG-CoA reductase inhibitor, NK-104, by Hiyama and coworkers [34].

The Negishi–Baba reaction is another Pd-catalyzed reaction of outstanding importance [12]. It was first reported by Baba and Negishi in 1976 [35] – after initial explorative studies with organozirconium and organoaluminum compounds as coupling partners – and used for the coupling of aryl halides with alkenyl substrates. It involves organozinc reagents that are prepared *in situ* from organolithium, magnesium, or aluminum compounds and $ZnCl_2$, but use of Zn–Cu couple with reactive halides is another approach [12e, 36]. The main impulse for the development of this reaction was that the cross-coupling reactions with Grignard or organolithium reagents do not tolerate certain functional groups and show low chemoselectivity [12j]. The advantage of this method is that the organozinc reagents are inert to a variety of functional groups including ketones, esters, amino, and cyano groups. This reaction has wide synthetic application in the field of arylation. The general conditions and the catalytic cycle are shown in Scheme 1.16 [12a]. It should be noted that, in 1977, both Fauvarque and Jutand reported that Reformatzky reagents couple with aryl halides in the presence of Pd(0) to give C–C bonds. Recently, Knochel's group has expanded the synthetic utility of this reaction (see Section 1.3.8).

This coupling arylation method was applied very nicely in the large-scale synthesis of the phosphodiesterase-type 4D inhibitor PDE472, by a group at Novartis (Scheme 1.17) [37], and for the synthesis of pumiliotoxin A [12j].



Scheme 1.16 (a) General conditions for the Negishi–Baba cross-coupling reaction. (b) The proposed mechanism for the Negishi–Baba cross-coupling arylation procedure [12a].



Scheme 1.17 Synthesis of the phosphodiesterase type 4D inhibitor PDE472 by a group at Novartis [37].

Other methods exist with other metals, such as aluminum, zirconium, and even chromium, but we will not go into this here. The reader is urged to consult Tsuji's book [12e] for some details and references on these methods.

The Ullmann-type coupling reaction using copper is a classic in cross-coupling chemistry; it is in fact the oldest method that involves biaryl synthesis (about 1901) – the Glaser coupling reaction, which involves homocoupling of metallic (Cu or Ag) acetylides is even older (about 1869) [12a]. In 1905, Ullmann and Sponagel showed that catalytic quantities of Cu promote the C–O coupling reaction of phenols with aryl halides [38]. The necessity to use high temperatures, high polar solvents, and often large amounts of copper reagents has prevented these reactions from reaching their full potential.

This reaction or the part that concerns C–N bond formation is discussed in Section 2.3.1.1.

1.2
Arylation: What Is So Special?

So what is all the fuss about arylation methods? What is so special about this group? The answer is very simple and obvious. Many important compounds require the presence of at least one aromatic

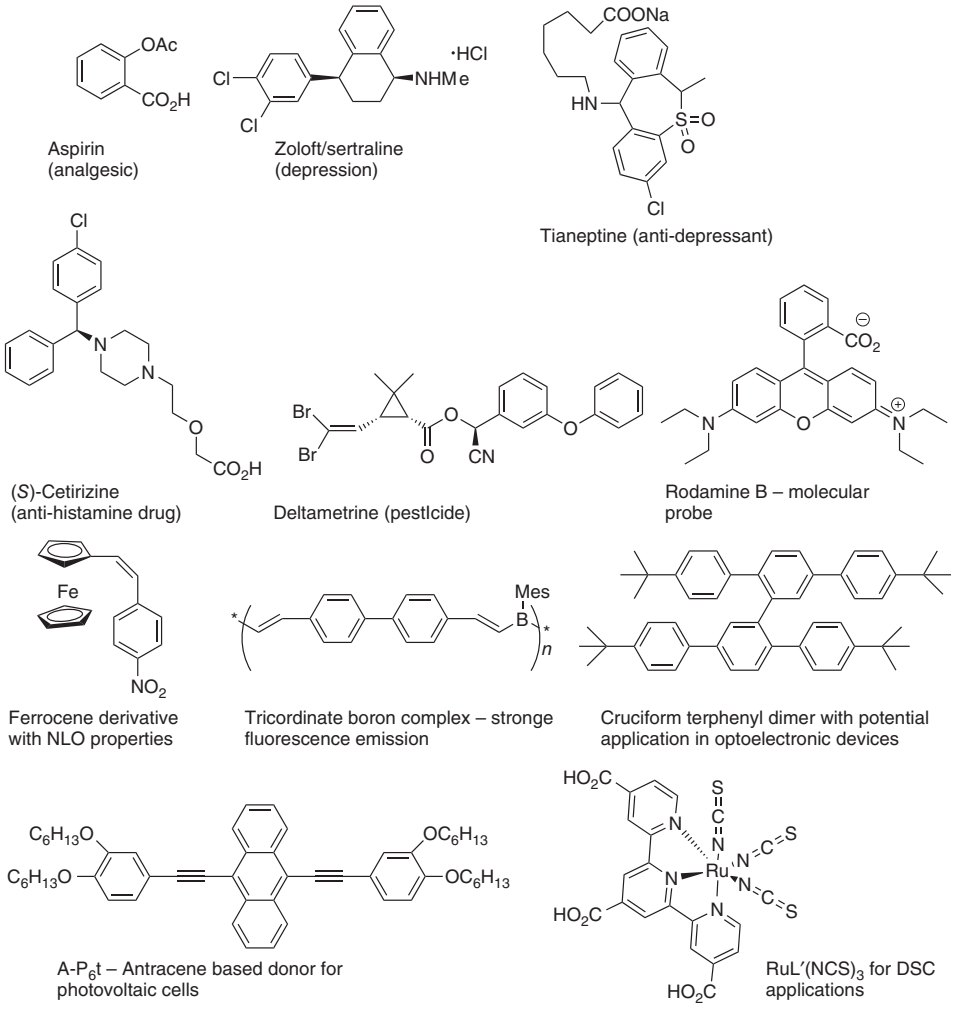


Figure 1.2 Important chemical substances and materials containing aryl units.

ring in order to carry out their functions, whether it be an active catalyst performing its function in a reaction process (particularly important for asymmetric catalysis), a drug interacting and inhibiting a biological target (for instance, the active site of an enzyme), an agrochemical (for example, a pesticide or growth hormone interacting on a plant cell), an electronic material responsible for electrical conduction or with special optoelectric properties, for crystal engineering applications, and so on. Therefore, the introduction of these units into these compounds or materials is very important. In the context of medicinal chemistry, it seems that a prerequisite for any *pharmacophore*[2] is the presence of at least one aromatic system, in other words a cyclic conjugated π-system (the reasons for this are given below). In Figure 1.2, a number of interesting chemical structures are shown, all containing at least one aromatic ring, which is vital for its activity.

2) The benzene ring appears to be the most abundant structural unit in a whole data set studied in the following report: Ref. [39].

In many of these cases they manifest weak interactions involving the aromatic rings, like π–π [40] (including edge-to-face [40b,c] or CH/π interactions [40d]) which are of pivotal importance in many areas of chemistry and biology. These attractions control such diverse phenomena as the interaction of drugs with DNA and other biomolecules, the tertiary structures of proteins, packing of aromatic molecules in crystals, and the functioning of host–guest systems.

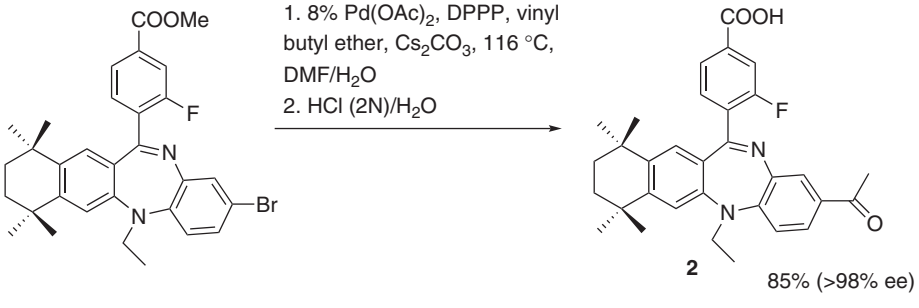
The field of organic electronics has grown exponentially from the seminal work of Heeger, MacDiarmid, and Shirakama in the 1970s [41]. The special case of the application of this methodology for the efficient, green/sustainable synthesis of π-conjugated small molecules, and macromolecules for organic electronic materials recently evaluated by Seth Marder's group cannot be overlooked [41]. This approach has been used to synthetize organic field-effect transistors (OFETs), organic photovoltaic (OPV) devices, and organic light-emitting diodes (OLEDs). In their 2013 review, Marder's group [41] clearly identified the most common metal-catalyzed coupling reactions for crucial C^{Ar}–C^{Ar} and C^{Ar}–C^{Vinyl} bond formation (including Ullmann reactions, Suzuki–Miyaura, Migita–Kosugi–Stille, Negishi–Baba, Mizoroki–Heck, and Kumada–Tamao–Corriu coupling) and for polythiophene synthesis. Direct arylation (see Chapter 4) was highlighted as one of the more efficacious methods.

1.3 Recent New Developments

Considering the enormous amount of literature [12] that exists on these classical cross-coupling reactions, particularly in the context of arylation, we will confine our discussion only to very recent important applications (over the last 8–10 years) of these reactions, particularly from the industrial point of view [42].

1.3.1 Arylations with the Heck–Mizoroki Reaction

The reader's attention is drawn to the following recent key references, including a textbook [42a] on the topic of the Heck–Mizoroki and the other sister coupling reactions. Of the applications that caught our attention the following are representative. Jiang *et al.* [43] reported the application of a Heck–Mizoroki reaction in the multi-kilogram industrial synthesis of the diazepinylbenzoic acid (**2**) (Scheme 1.18), a promising drug candidate, which is a retinoid × receptor antagonist (**2**) and used to treat diabetes and other metabolic diseases. The key reaction involved a one-pot Heck–Mizoroki between the arylbromide substrate and vinyl butyl ether, vinyl ether hydrolysis, and ester hydrolysis. The optimized conditions are shown in Scheme 1.18 and afforded the target molecule with a yield of 85% (two steps) and an enantioselectivity of >98% ee.



Scheme 1.18 Synthesis of the retinoid × receptor antagonist 2 by a group at Novartis [43].

Fu's group has made significant advances over the last number of years in making the Heck–Mizoroki and other coupling procedures more amenable for milder reaction conditions. This has been achieved notably via the use of $P(t\text{Bu})_3$ and PCy_3 ligands [44]. By 1999, many groups had shown the amenability of aryl chlorides for this reaction, but there were still significant hurdles to overcome, such as the choice of substrate (no reactions on highly hindered or electron-rich chlorides, including styrene and acrylic acid derivatives, gave more than 50% yields, and temperatures of ≥120 °C were required). Because aryl chlorides are more economical and more readily available, more attention has been given to the development of useful catalysts for the Heck–Mizoroki reaction of aryl chlorides. Fu's group showed that by using $Pd/P(t\text{Bu})_3$ with Cs_2CO_3 as the stoichiometric base it was possible to expand the range of aryl chloride substrates [44]. It was also discovered that Cy_2NMe could successfully substitute Cs_2CO_3 in these reactions, making the reactions occur under even milder conditions [44]. A number of examples are shown in Figure 1.3, including the general conditions that were used.

These reactions have been exploited in a range of contexts, including bioorganic chemistry and materials science [44].

Continuing on the topic of aryl chloride substrates, in 2011, Xu *et al.* [45] reported the use of mild reaction conditions using tetrabutylammounium acetate (TBAA) as base, a range of olefin products could be obtained in very high yields. The conditions are shown in Figure 1.4, along with some prominent examples. Dave-Phos was used as the ligand.

In the realm of biological chemistry, in 2008, Lagisetty *et al.* [46] reported for the first time a simple method for the arylation at C-8 of adenine nucleosides. The motivation for this investigation was the observation that substitution at the C-8 position can influence the *syn–anti* conformational equilibrium around the glycosidic bond or produce structural factors that can influence enzymatic recognition. Purine derivatives are also of great importance in medicinal chemistry as they display a broad spectrum of antiviral and antimycobacterial activity. In this account iodo-, bromo-, and even chloro-aromatics were coupled with vinyl nucleosides. The reaction was catalyzed by the simple combination of $Pd(OAc)_2$, $(o\text{-tol})_3P$, and Et_3N. The best conditions and some of the best representative results are shown in Figure 1.5.

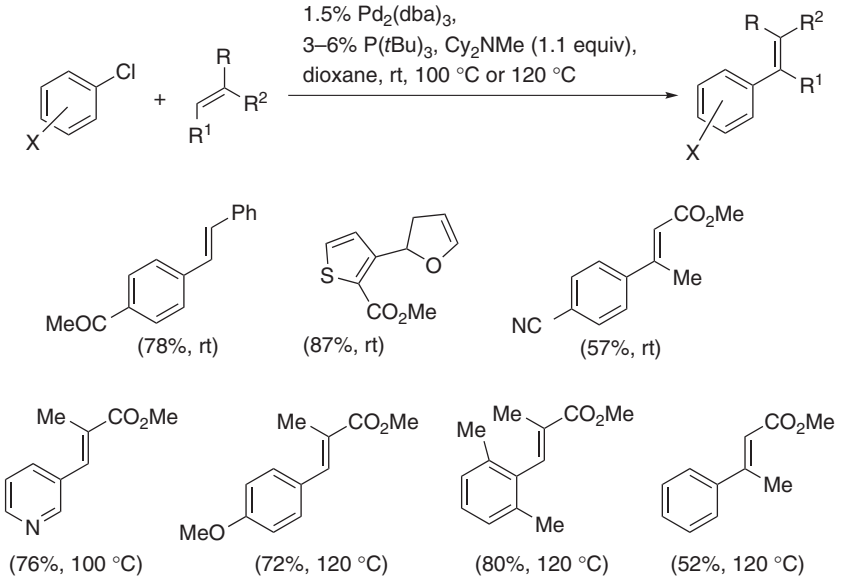


Figure 1.3 Heck–Mizoroki reactions of aryl chlorides catalyzed by $Pd/P(t\text{Bu})_3$ [44].

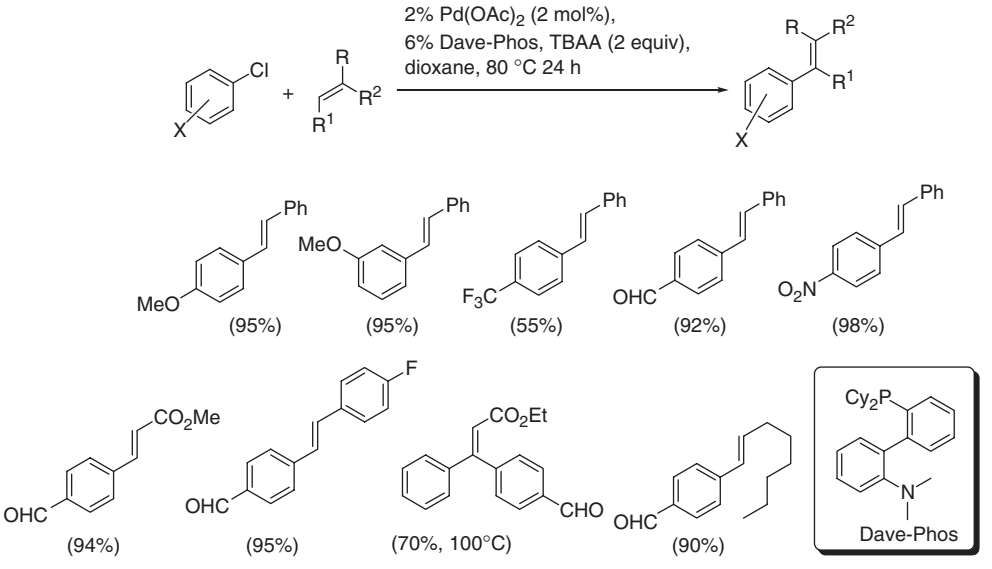


Figure 1.4 Heck–Mizoroki reactions of aryl chlorides using TBAA and Dave-Phos [45].

A similar approach was used by Guo *et al.* for the palladium-catalyzed diarylation of 9-allyl-9*H*-purines [47]. However, in their case, they relied on a chelation-assisted Pd-catalyzed highly regioselective diarylation reaction of olefins via a possible Pd(II)/Pd(IV) catalyst cycle (Table 1.1).

In 2009, Li and Ye [48] reported the arylation of pyranoid glycals using aryl iodides and $Pd(OAc)_2$ catalyst, with Ag_2CO_3 and $Cu(OAc)_2$ as additives, to efficiently afford aryl 2-deoxy-*C*-glycopyranosides under mild and simple conditions (Figure 1.6). Aryl-*C*-glycosides are present in a number of important biologically active compounds, such as the pluramycins, angucyclines, and benzoisochromanequinones, and in fact, are stable analogs of *O*- and *N*-glycosides that are resistant to enzymatic cleavage [48]. It should be noted that the reaction only underwent a Heck *syn*-β-hydride elimination. The reaction could be performed in the open air, so no phosphane ligands were used. In all cases, only a single anomer was obtained. The authors proposed that the configuration of the newly introduced group is opposite to the C-3–*O*-substituent of the starting glycan, resulting from the *syn*-addition to the opposite face because of steric hindrance.

The ligand is perhaps one of the key elements making up the conditions of this reaction or any other coupling reaction for that matter. Until 1990, triphenylphosphane was used as the ligand of choice; however, a number of other contenders have appeared in the literature, the most notable being the *N*-heterocyclic carbenes (NHCs), but besides these well-studied ligands, others such as imines, ureas, thioureas, and selenides have been used [49]. Returning to the topic of NHC ligands, these have the advantage of being better σ-donors than tertiary phosphanes, making the oxidative addition of the aryl halide or triflate to the Pd metal more facile, and the availability of bulky NHCs facilitates elimination of the product [50]. The strong interaction between the metal and the carbenic carbon inhibits the dissociation thus reducing the requirement for excess ligand [50]. The group of Herrmann [51, 52] was the first to use NHCs in the Heck–Mizoroki reaction. They were prepared *in situ* (Scheme 1.19) and they were found to exist as palladacycles. Nolan later went on to investigate the Hiyama–Hatanaka reaction with these ligands [53] (see below) and since then other groups have exploited these catalytic systems in other palladium-catalyzed cross-coupling reactions [54]. Recently, de Vries and Minnaard [55] have used some NHC-based palladacycles for useful Heck–Mizoroki reactions

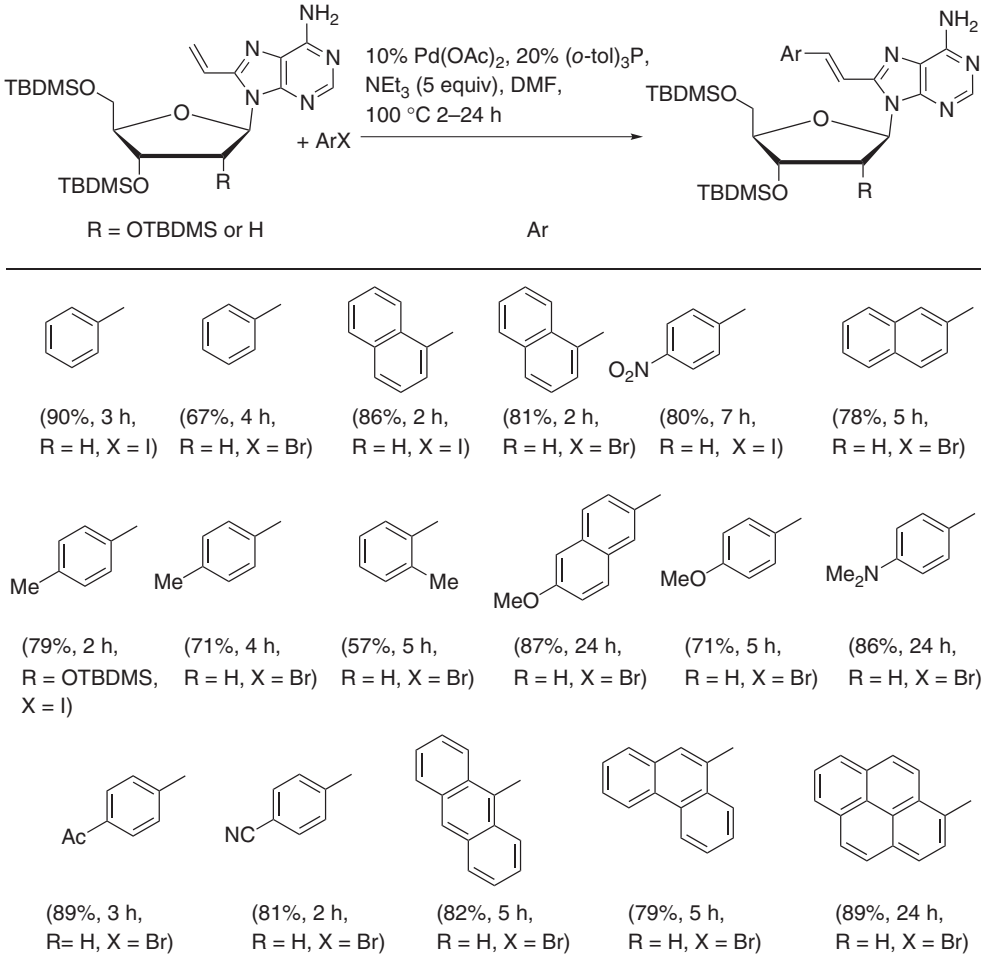
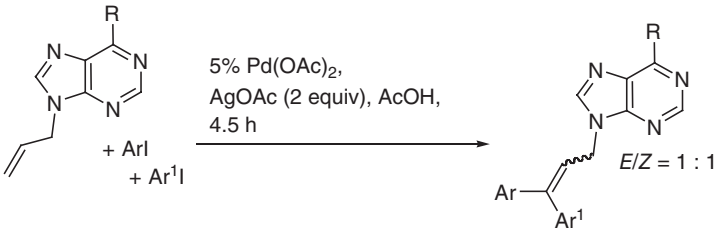


Figure 1.5 Heck–Mizoroki reactions at C-8 of adenine nucleosides [46].

(Scheme 1.20). By changing the base to tributylamine, the competing conjugate addition process was favored. The reason for this, as proposed by the authors, was that, in the presence of this base, the alkyl palladium species remains coordinatively saturated, thus avoiding β-hydride elimination from the substrate but promoting β-hydride elimination from the NBu_3. The reaction failed to work with either aryl chlorides or bromides. To promote the Heck–Mizoroki reaction, bases such as cesium pivalate (CsOPiv) – incapable of reducing Pd through hydride donation – were used.

Closely related to these studies were some recent studies using imidazolium ILs. ILs are nonconventional solvents that have enjoyed an immense spectrum of application in catalysis over the last 15 years or so. When decorated with suitable metal binding groups they become useful ligands for catalytic purposes. The group of Liu [56] has been quite successful with this strategy and besides the previously reported diol containing ILs, such as 1-(2,3-dihydroxypropyl)-3-methylimidazolium hexafluorophosphate **3** and 2,2-bis(1-methyl-methylimidazolium)propane-1,3-diol hexafluorophosphate **4** (Figure 1.7), which showed high efficiency and reusability for the Heck–Mizoroki reaction, along with two other derivatives **5** and **6**. The presence of the diol units in **3** and **4** was important

Table 1.1 Chelation-assisted Pd-catalyzed Heck–Mizoroki diarylation of terminal olefins [47].



Entry	R	Ar-I	Ar^1-I	Product yield (%)
1	MeO	Ph	Ph	93
2	MeO	Ph	*p*-MeC_6H_4	89
3	MeO	Ph	*p*-$MeOC_6H_4$	66
4	MeO	*p*-MeC_6H_4	*p*-MeC_6H_4	98
5	Me	Ph	Ph	91
6	MeO	Ph	*p*-$EtO_2CC_6H_4$	22
7	MeO	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	87
8	MeO	*p*-$EtO_2CC_6H_4$	*p*-$EtO_2CC_6H_4$	93
9	MeO	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	68
10	MeO	3,5-Bis(Me)C_6H_4	3,5-Bis(Me)C_6H_4	96
11	Me	*p*-MeC_6H_4	*p*-MeC_6H_4	86

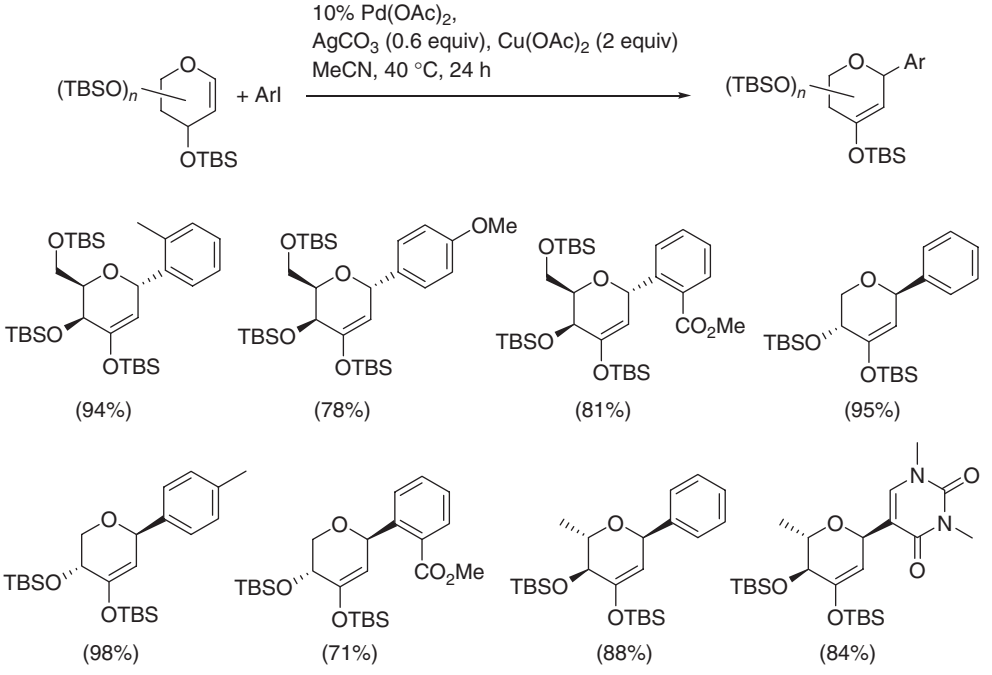
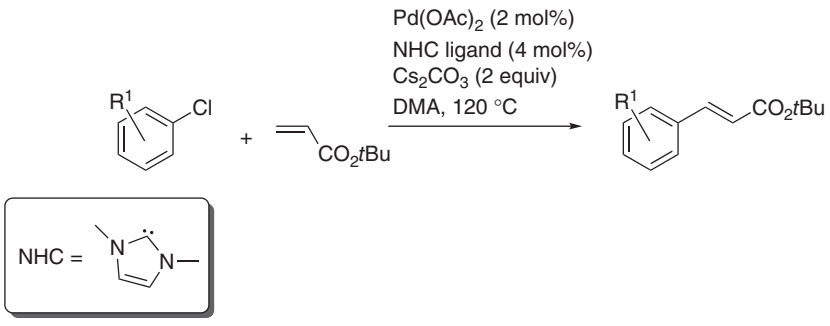
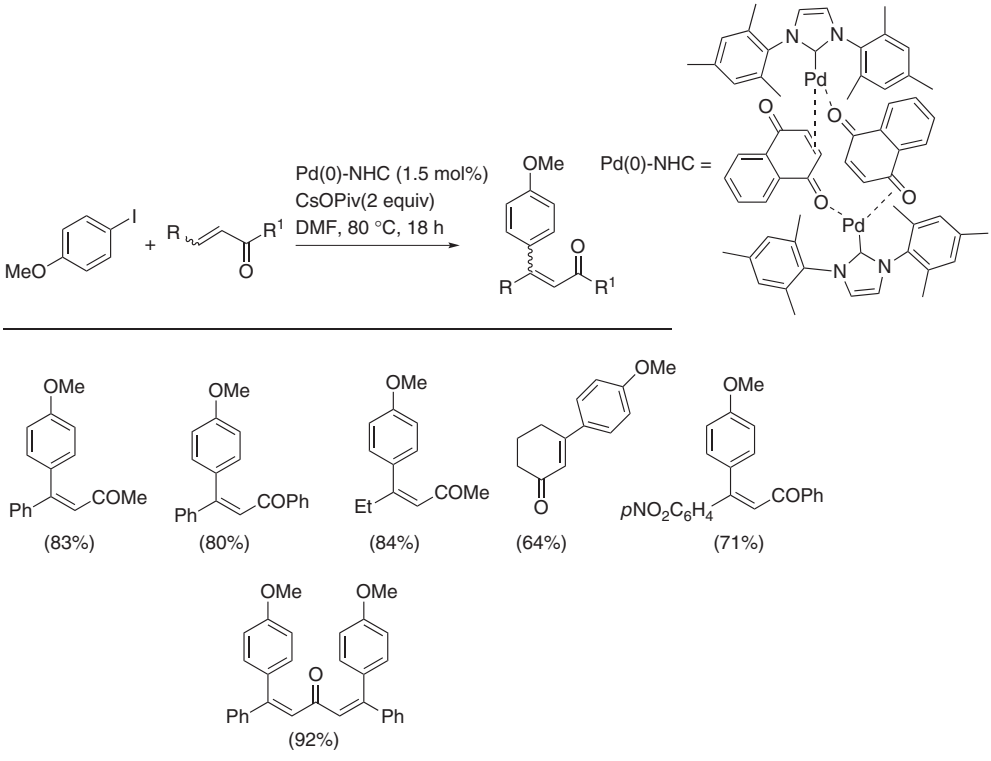


Figure 1.6 Arylation of pyranoid glycals using aryl iodides and $Pd(OAc)_2$ catalyst [48].



Scheme 1.19 The first NHC-catalyzed Heck–Mizoroki reaction reported by Herrmann's group [51].



Scheme 1.20 The NHC-catalyzed Heck–Mizoroki reaction reported by Vries and Minnaard [55].

for giving rise to multiple binding sites, and the reactions could be performed under aerobic conditions.

Other types of ligands have been used. Of note are the benzotriazole ligands developed by Verma *et al.* [49]. These ligands have been applied in a variety of cross-coupling reactions, including the Heck–Mizoroki reaction (Figure 1.8).

The benzotriazole ligand could be synthesized on a multi-gram scale and it was air stable and thermally stable up to 274.7 °C.

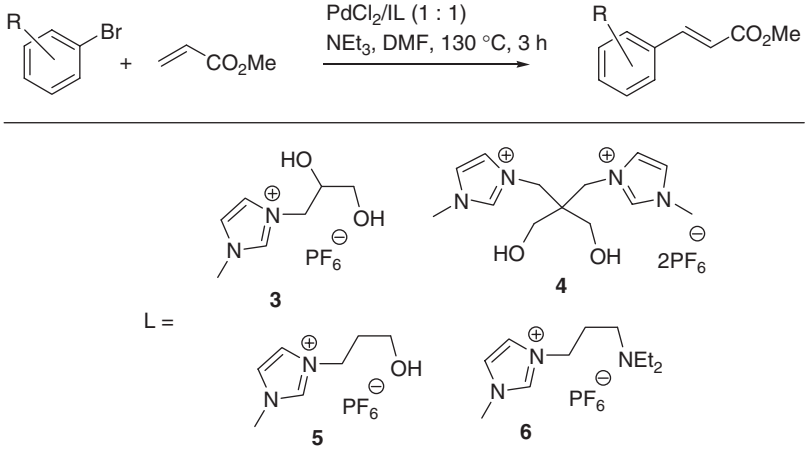


Figure 1.7 Heck–Mizoroki reactions using suitably functionalized ILs as reported by Cai and Liu [56].

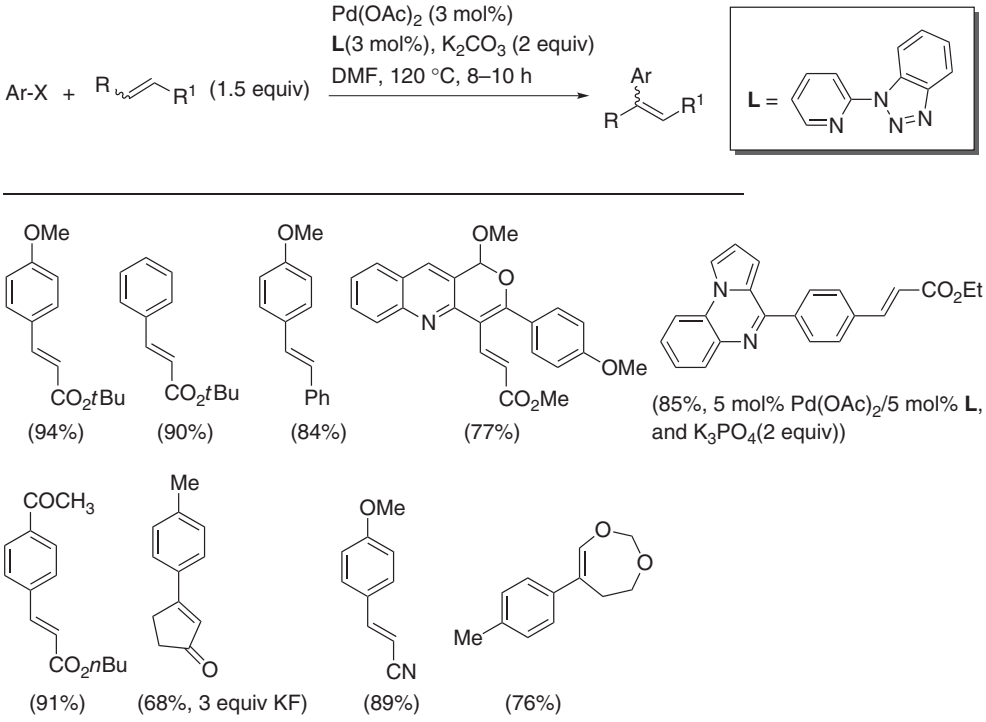
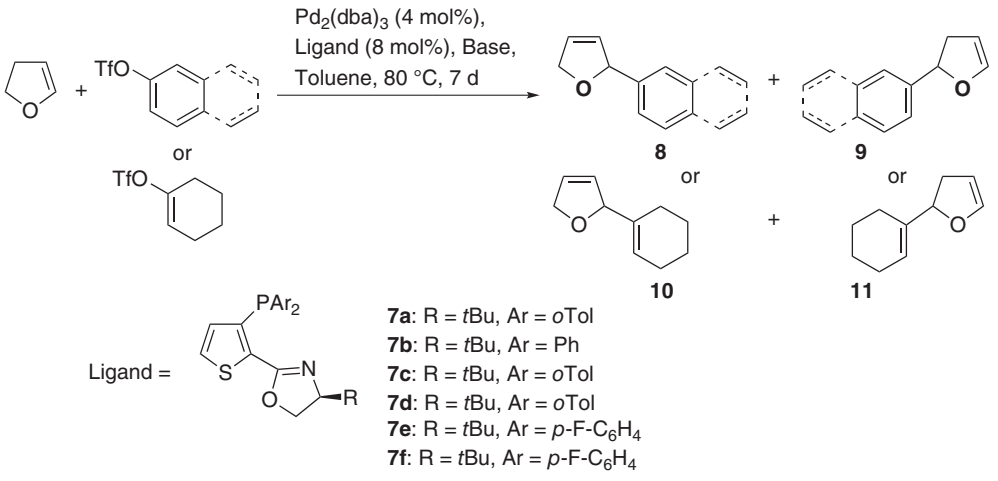


Figure 1.8 Heck–Mizoroki reactions using the benzotriazole ligand of Verma *et al.* [49].

As already mentioned above, the intermolecular asymmetric catalytic Heck–Mizoroki reaction was first reported by Hayashi [12d,e, 13, 15] and since then various groups have made contributions in this area. Of note was the report in 2009 by Guiry's group [57] who achieved enantioselectivities of up to 96% ee, using novel HetPHOX ligands **7a–f** for the benchmark reaction with cyclohexenyl, phenyl, and 2-naphthyl triflate with 2,3-dihydrofuran (Scheme 1.21). The problem with this reaction is the extensive reaction time (7 days) at the elevated temperature of 80 °C. The kinetic product **8** (or



Scheme 1.21 Asymmetric Heck–Mizoroki reactions using HetPHOX ligands as reported by Fitzpartick *et al.* [57].

10) was, in all cases, the major regioisomer. Ligand **7a** was the most successful ligand used and, in all cases, the *R*-enantiomer of the kinetic product (**8** or **10**) was preferred.

One recent development in this area was the report by Xiao's group in 2012 of the Heck–Mizoroki reaction of electron-rich allylamines with aryl bromides under ligand-free conditions. $Pd(OAc)_2$ was the catalyst used in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or hydroquinone (HQ) as the additive, leading exclusively to γ-arylated (*E*)-allylamines in good to excellent yields [58] (Figure 1.9). The reactions were very short (<2 h) and the regioselectivity in favor of the terminal olefin was excellent (>99 : 1). The reaction could tolerate electronically different substituents on the aromatic ring, but there was a slight preference for electron-deficient aryl bromides.

When the reaction was carried out with other allylamine derivatives, the yields were low. However, on substituting the TEMPO with HQ, the yields improved dramatically, as can be seen from Figure 1.10.

The Heck–Mizoroki reaction has also been heavily applied in one-pot sequential reaction sequences. The topic of sequential, domino, consecutive, or tandem catalytic reactions is a very timely subject, as at its core is efficiency, economy, and waste minimization in organic synthesis.[3] In 2010 [59], one of us published a review of this topic which explains the current state of play and includes relevant references on the subject. However, the topic is still rather murky in terms of definitions, and this is something that we feel needs urgent attention. The Heck–Mizoroki is a very suitable transformation for inclusion in a sequential catalytic process, given that it leads to the formation of C=C units, a common functionality for further catalytic transformation.

In 2008, Fields *et al.* [60] reported a one-pot tandem decarboxylative[4] allylation–Heck cyclization of allyl diphenylglycinate imines, leading to 1-aminoindanes. These reactions involve a $\eta^3-\pi$-allyl palladium intermediate. After initial preliminary investigative studies to determine the reaction conditions, a series of reactions using the *o*-halobenzaldimine **12** were conducted using $Pd(PPh_3)_4$, with Ag_2SO_4 as a double-bond migration inhibitor under microwave conditions. The results are shown in Figure 1.11.

Electro-deficient substrates afforded superior yields and rates as opposed to their electron-rich counterparts. In order to expand the diversity of allyl–imine substrates for this reaction, the olefin

3) We actually believe that more should be done to encourage this particular reaction strategy.
4) The subject of decarboxylative couplings is discussed in Chapter 3.

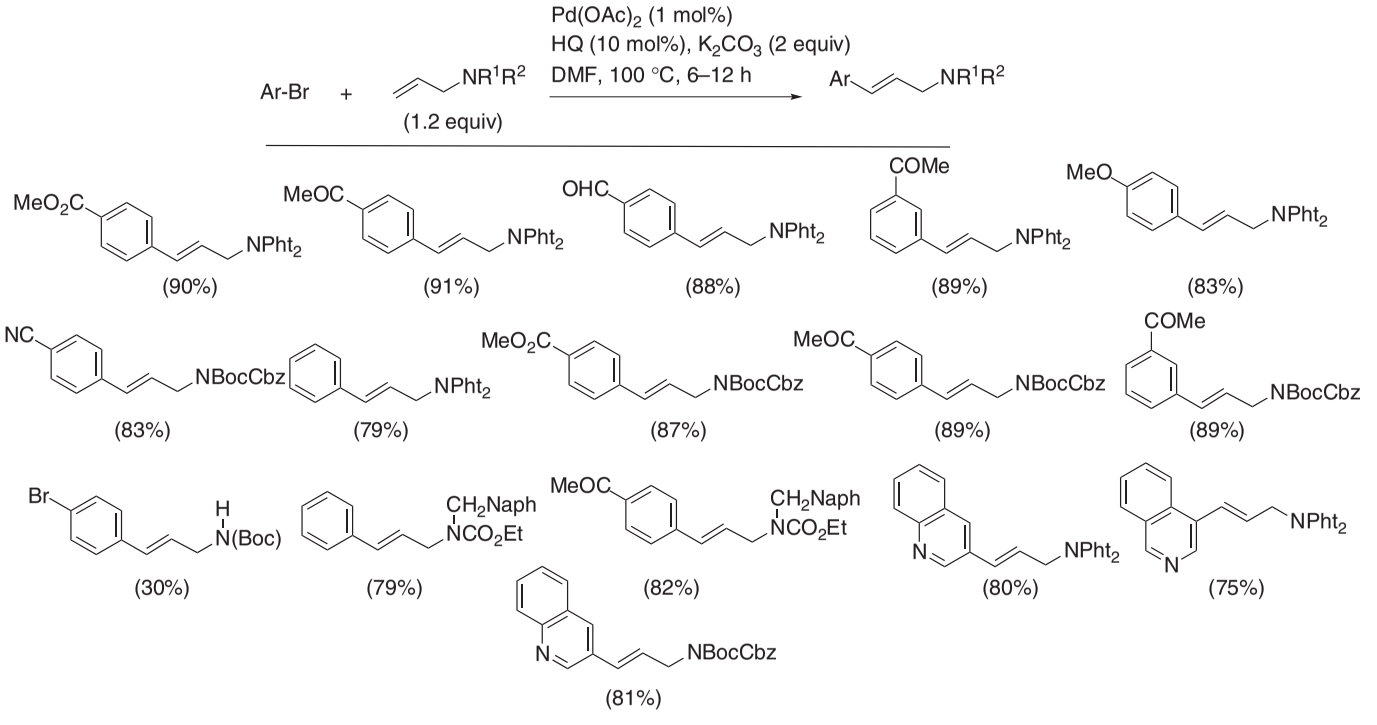


Figure 1.9 Heck–Mizoroki reactions on other *N*-protected allylamines with aryl bromides by Xiao and coworkers [58].

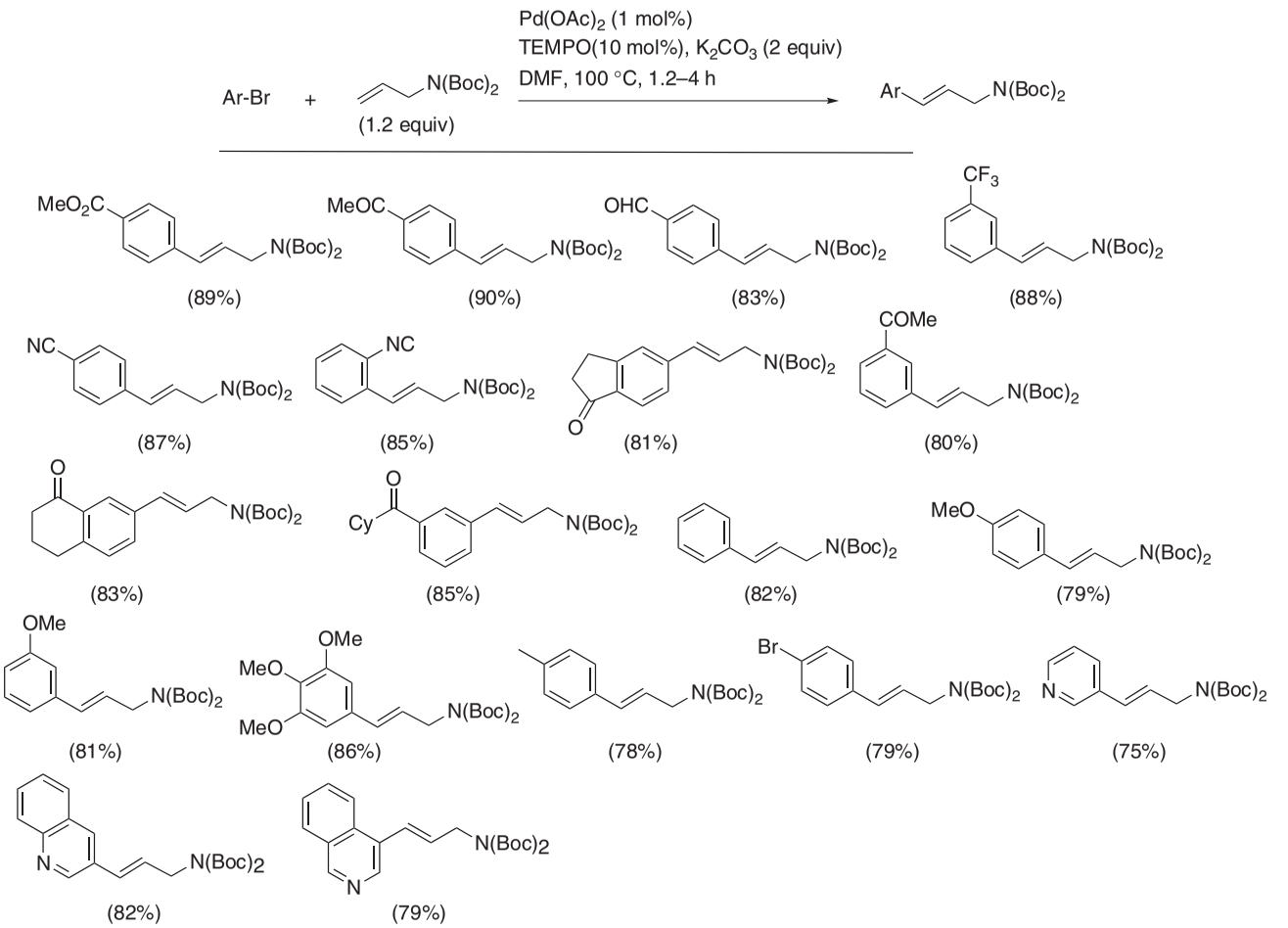


Figure 1.10 Heck–Mizoroki reactions on *N*-Boc protected allylamines with aryl bromides by Xiao and coworkers [58].

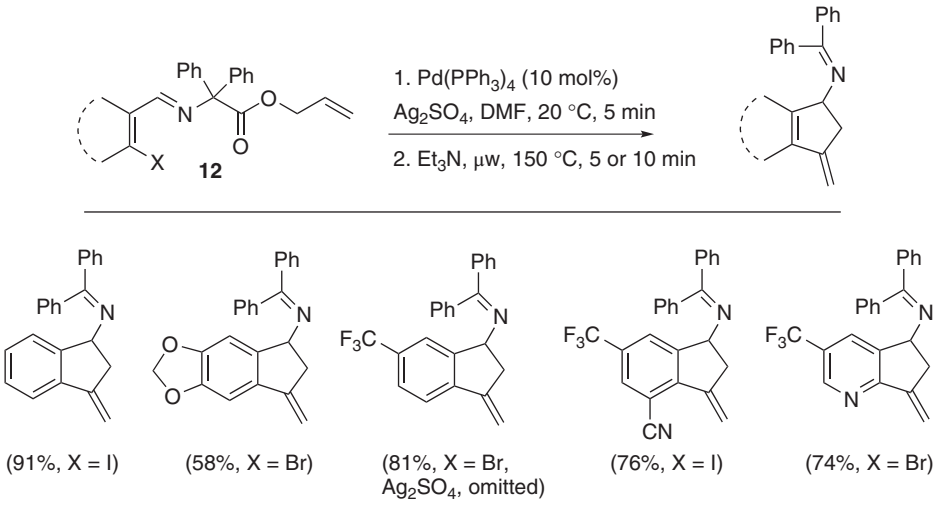


Figure 1.11 One-pot tandem decarboxylative allylation–Heck cyclization of allyl diphenylglycinate imines leading to 1-aminoindanes [60].

cross-metathesis reaction was employed using Grubbs' second-generation catalyst. The results with the allyl-substituted substrates were less promising as mixtures of double-bond regioisomers were obtained (Figure 1.12). Of note was that extensive NOSEY (nuclear overhauser effect spectroscopy) experiments indicated the preference for *E*-alkene products, this of course implied that a formal *anti*-β-hydride elimination of the Pd(II) intermediate in the Heck–Mizoroki cyclization (Figure 1.12).

Sinha's group has reported a Heck–Decarboxylation–Heck (HDH) strategy of 4-halophenols with acrylic acid, leading to hydroxylated stilbenoid compounds with CO_2 as the only by-product [61]. The reaction conditions and scope of this procedure are given in Figure 1.13.

These authors envisioned a mechanism that involved the Heck–Mizoroki coupling of acrylic acid with the 4-halophenol to form 4-hydroxycinnamic acid, which undergoes decarboxylation according to the quinomethide mechanism to form 4-hydroxystyrene *in situ.* This is followed by the second Heck–Mizoroki coupling to give the stilbene product.

These workers took this strategy one step forward with the synthesis of unsymmetrical hydroxylated stilbenoids, which are biologically important (see Figure 1.14).

A very interesting development was reported by Guo *et al.* [62] in 2011 when they reported a Heck–Aldol–Heck reaction by a combination of transition-metal and amino catalysis. The reaction allows for the occurrence of three C–C bond forming reactions in a sequential process. Various aryl iodides could perform the cascade reaction with propenol and formaldehyde to afford novel (*E*)-trisubstituted alkenes in 66–81% yields. The reaction conditions and some of the best results that were obtained are shown in Figure 1.15. A variety of organocatalysts were used, but it was pyrrolidine **18** that gave the best results. The reaction could also be extended to unsymmetric products using two different aryl iodide reagents. The plausible mechanism that was proposed included the insertion of the C=C bond of the allylic alcohol in the organopalladium species, leading to a β-arylated intermediate instead of an α-arylated intermediate due to steric hindrance; this then is followed by β-elimination of HPdI to give the aldehyde precursor for the aldol reaction (catalyzed by an amine organocatalyst), giving an α,β-unsaturated aldehyde which in turn undergoes the second Heck–Mizoroki coupling to give the final product. This sequence is summarized in Scheme 1.22.

One other innovation in this area that we would like to mention is the carbonylative Heck–Mizoroki reaction that was reported by Skrydstrup's group [63] in 2011. It must be mentioned that this methodology was first described by Beller's [64] group in 2010. The beauty of

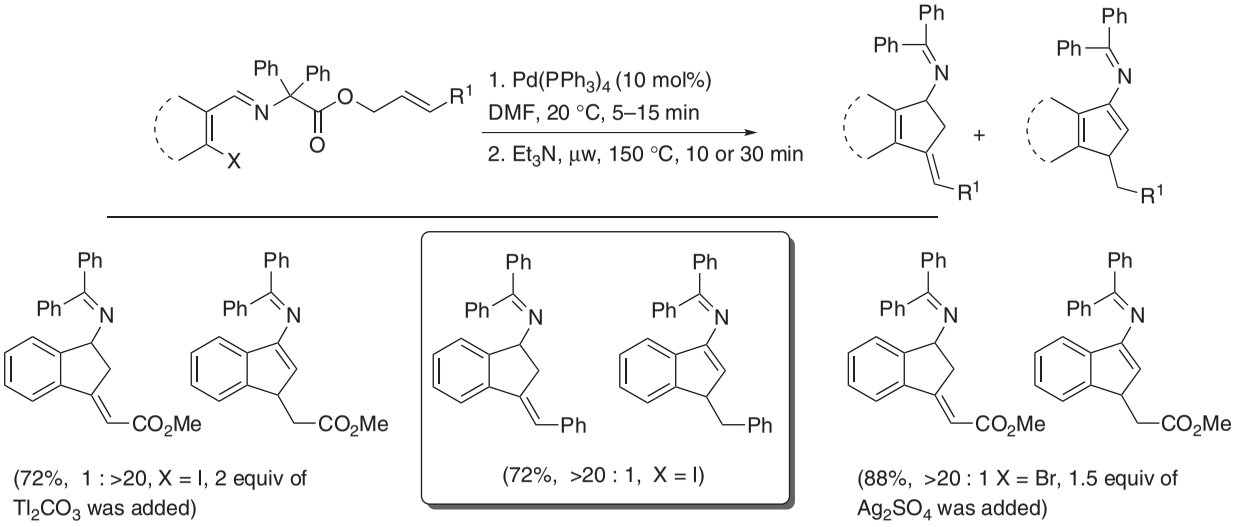


Figure 1.12 One-pot tandem decarboxylative allylation–Heck cyclization of allyl-substituted diphenylglycinate imines [60].

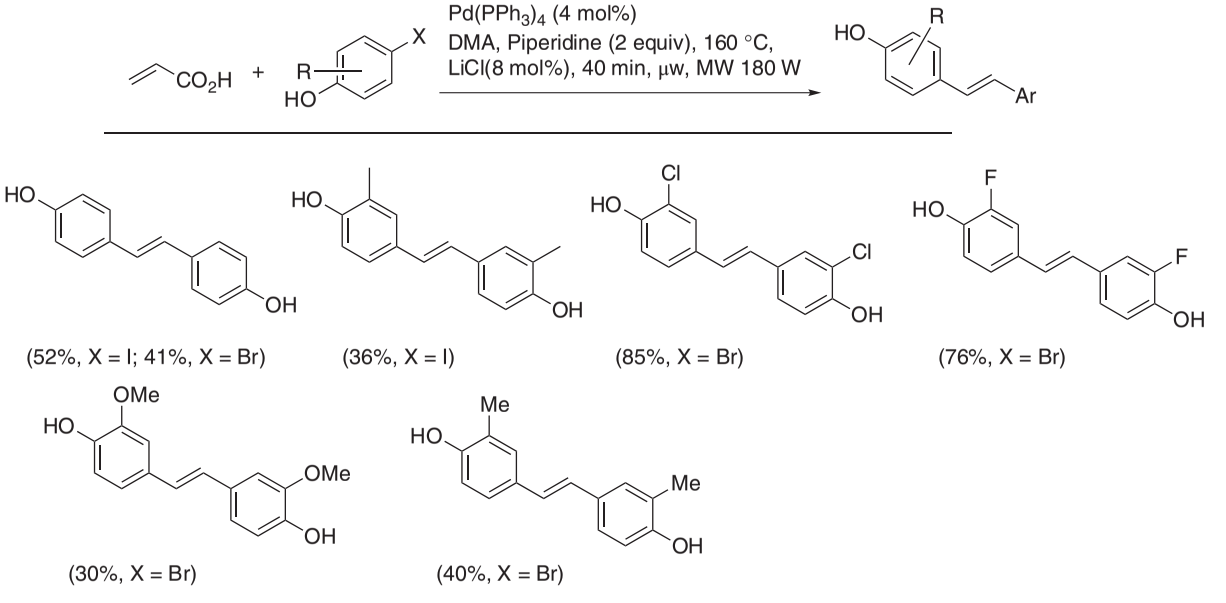


Figure 1.13 The Heck–Decarboxylation–Heck (HDH) strategy leading to symmetric hydroxylated stilbenoids [61].

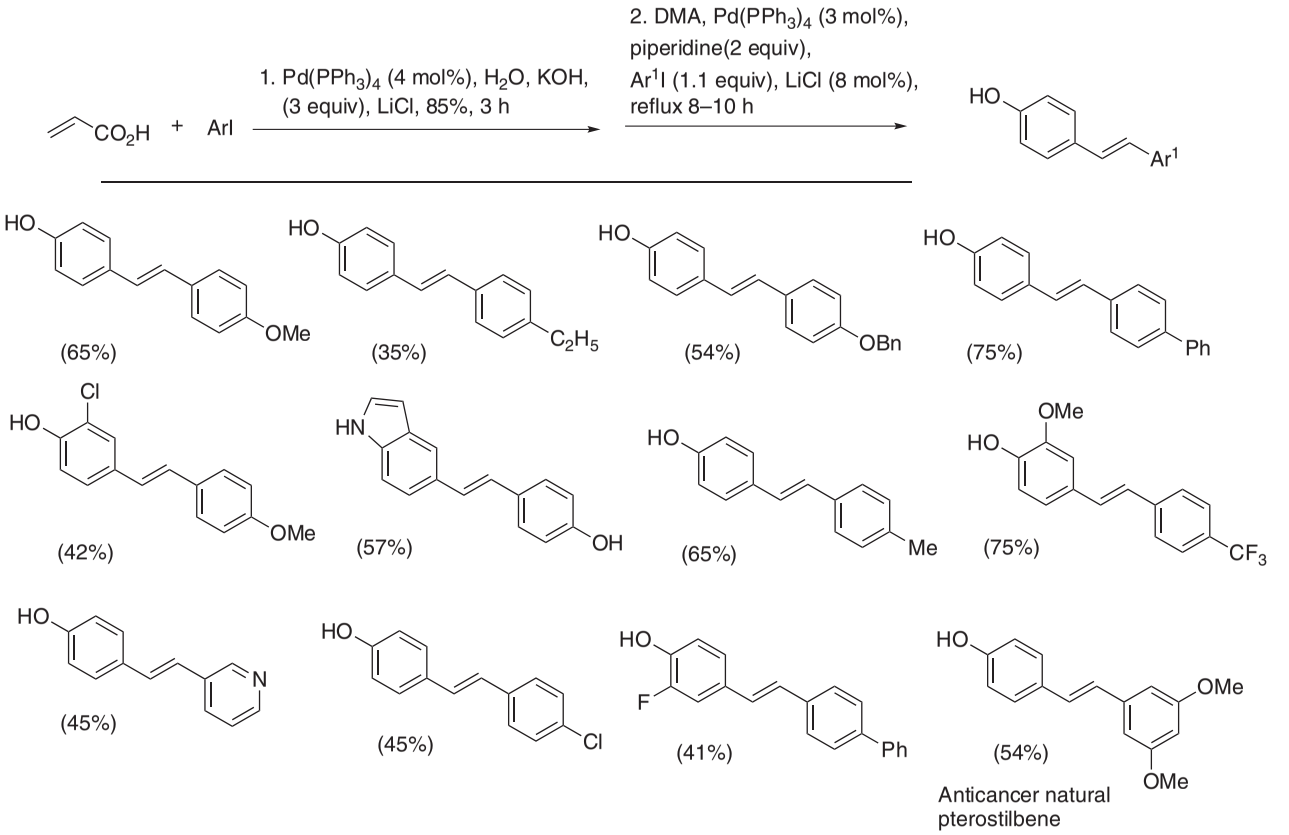


Figure 1.14 The Heck–Decarboxylation–Heck (HDH) strategy leading to unsymmetrical hydroxylated stilbenoids [61].

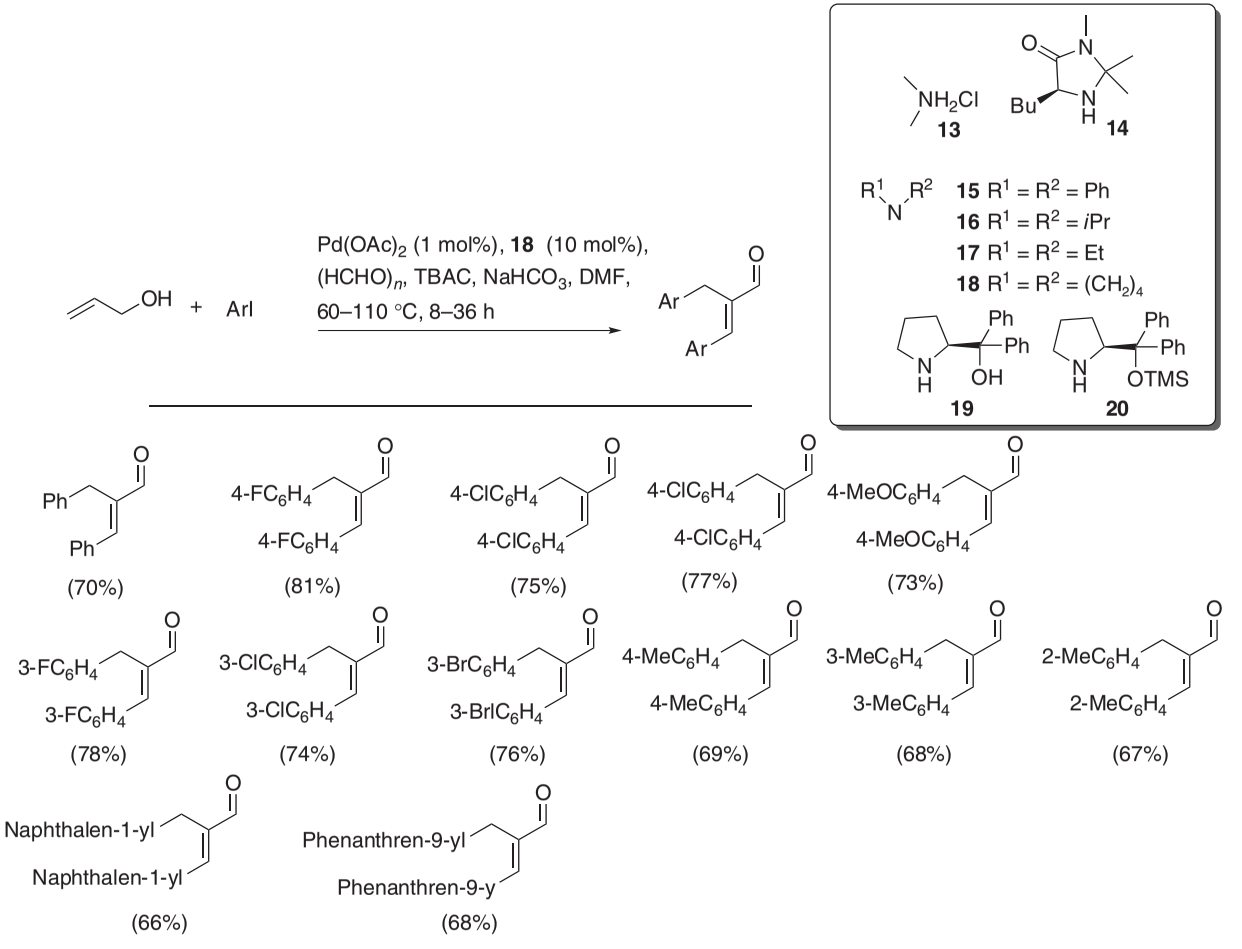
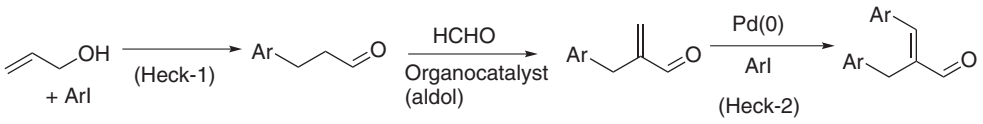


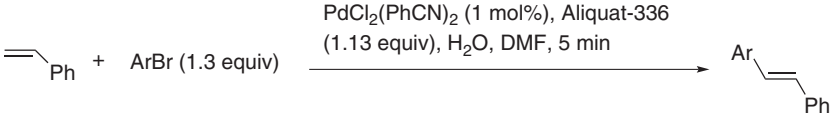
Figure 1.15 The Heck–Aldol–Heck reaction strategy of Guo *et al.* [62].



Scheme 1.22 Outline of the Heck–Aldol–Heck catalytic sequence as reported by Guo *et al.* [62].

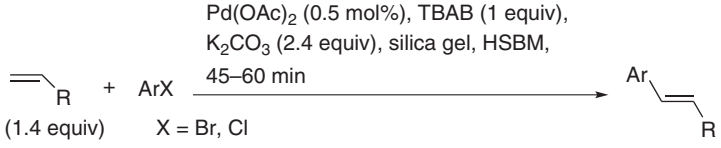
this approach was that the carbon monoxide was generated *in situ,* using a two-chamber system in which, from chamber A, which contained 9-methyl-fluorene-9-carbonyl chloride (CO supplier), in the presence of a Pd(II) catalyst, a phosphane, and a tertiary amine, the CO was produced and passed to chamber B, in which the carbonylative Heck–Mizoroki reaction proceeded with an aryl iodide and a styrene with $[(\text{cinnamyl})\text{PdCl}]_2$, cataCXium® A (Di(1-adamantyl)-*n*-butylphosphane) as ligand, and *N,N*-dicyclohexylmethylamine (Cy_2NMe), giving a plethora of chalcone products. The best reaction setup is shown in Figure 1.16. This procedure was also demonstrated to be a valuable ^{13}C isotope labeling technique.

(*E*)-Stilbene derivatives have a wide range of biological activities, including reputed potential as nutraceuticals, as well as applications in molecular photonics and optoelectronics. Of note is DMU-212, which has anticancer properties [65], and trimethylated resveratrol, which is a potent and selective human cytochrome P_{450} 1B1 inhibitor [66]. The group of Ben Salem [67] in 2011 reported a very interesting Heck–Mizoroki reaction using the quaternary ammonium phase-transfer reagent, Aliquat-336, with ultrasonic irradiation. Using aryl bromides and either styrene or acrylates, good to excellent yields of the products, including (*E*)-stilbenes, could be obtained and the reaction scope was demonstrated. Ultrasound is known to accelerate diverse types of organic reaction by increasing the reaction rate. The Aliquat-336's central function is to convert the Pd(II) precursor to the Pd(0) active catalyst, and to stabilize and solubilize this catalyst. It was thought that hydrogen bonding between the hydridopalladium halide and Aliquat-336 promotes the regeneration of the Pd(0) catalyst. Typical conditions for the arylation of styrene are shown in Scheme 1.23.



Scheme 1.23 The Heck–Mizoroki reaction using Aliquat-336 with ultrasonic irradiation as reported by Ben Salem [67].

In 2012, the group of Su reported the application of the Heck–Mizoroki reaction for the synthesis of (*E*)-stilbene using the technique of high-speed ball milling (HSBM) [68]. HSBM is an attractive mechanically activated method that has gained attention, but this was the first report on the application of this method in the Heck–Mizoroki reaction. These reactions were performed using $Pd(OAc)_2$, tetra-*n*-butylammonium bromide (TBAB) as additive, K_2CO_3, and silica gel (Scheme 1.24). The ball mill was run at a rotational speed of 1290 rpm for 15 min, followed by a 5-min pause. The silica gel served as the grinding auxiliary, and it proved to be the best choice. Both aryl bromides and chlorides



Scheme 1.24 The Heck–Mizoroki reaction using the high-speed ball milling (HSBM) technique as described by Su's group [68].

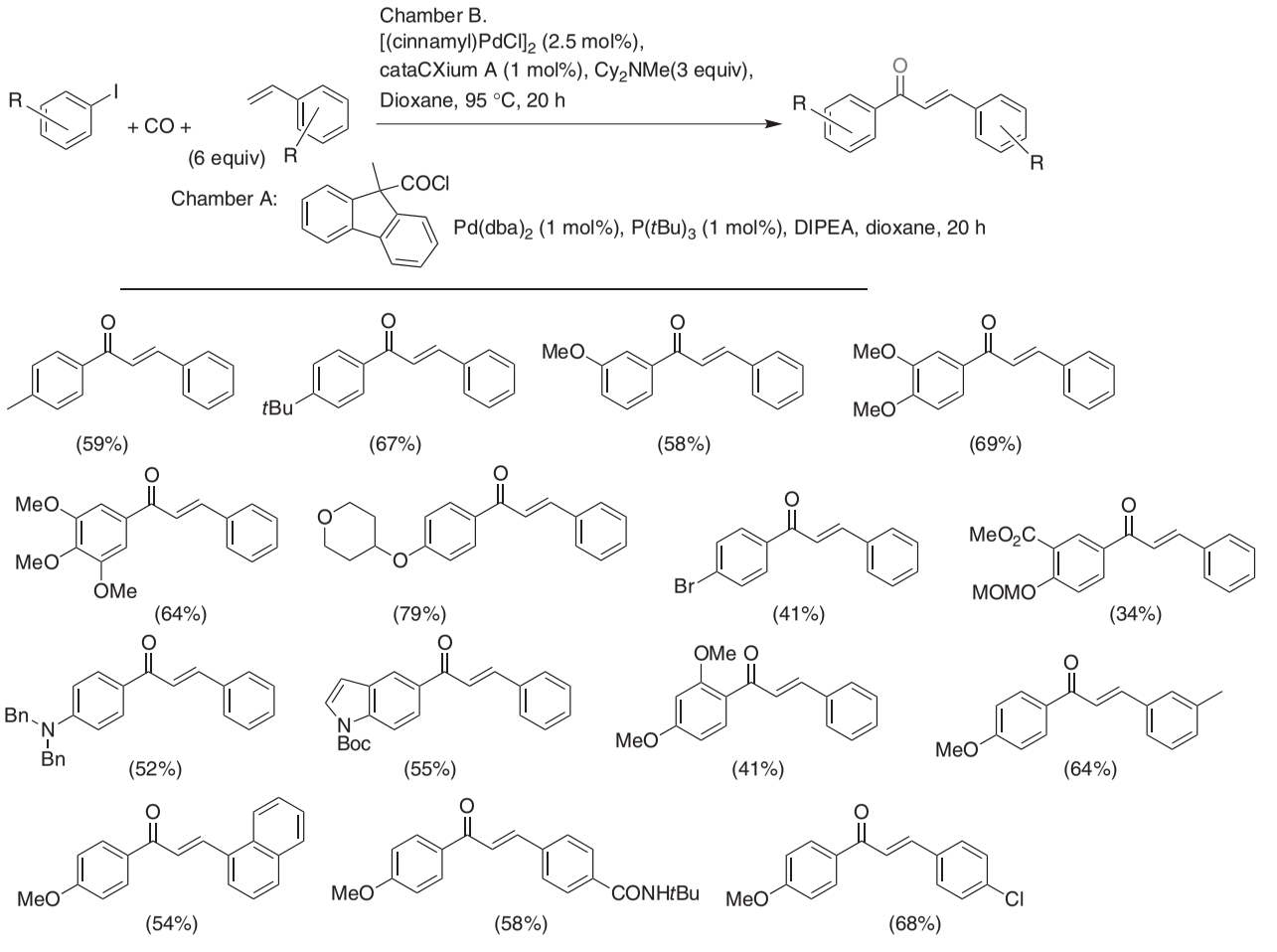
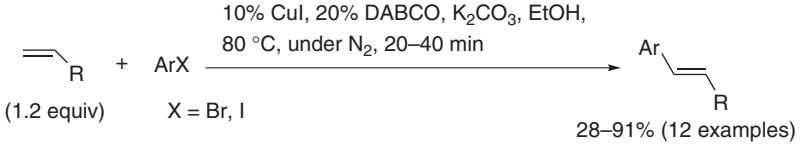


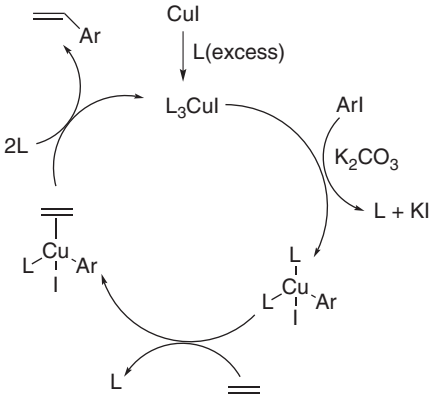
Figure 1.16 The carbonylative Heck–Mizoroki reaction reported by Skrydstrup's group [63].

could be used. There was no requirement for ligands or an inert atmosphere. Yields between 67% and 92% could be achieved.

Given the expensive nature of Pd, other metals have been used as a replacement for this metal. In 2005, Li *et al.* [69] showed that copper(I) could be used as the catalyst for the Heck–Mizoroki reaction. They used 10 mol% CuI and 20 mol% 1,4-diazabicyclo[2.2.2]octane (DABCO) for the coupling of a number of aryl iodides and an aryl bromide giving the corresponding internal olefins in moderate to good yields. The reaction conditions are shown in Scheme 1.25. The reaction mechanism that was proposed by these authors involved a four-centered transition state that was originally proposed by Castro and Stephens in 1963 (Scheme 1.26) [23].



Scheme 1.25 The Heck–Mizoroki reaction using Cu(I) as described by Li *et al.* [69].



Scheme 1.26 The proposed mechanism for the Cu(I)- catalyzed Heck–Mizoroki by Li *et al.* [69] (L = DABCO).

In 2010, Chatani and coworkers reported a new variant of the Heck–Mizoroki reaction, in which an aryl-metal species is generated from aryl cyanides using a rhodium (I) catalyst [70]. The reaction conditions and reaction results are shown in Figure 1.17.

As a further application of this method, it was used along with a bromination/Suzuki–Miyaura sequence to give asymmetric oligo(phenylenevinylene)s.

The mechanism proposed for this novel transformation is shown in Scheme 1.27.

These authors also proposed an alternative mechanism for the active catalyst regeneration, and this involved a hydrorhodation of the triethylvinylsilane to give $RhCH_2CH_2SiEt_3$, which undergoes a β-silyl elimination to form another active catalytic species $Rh\text{-}SiEt_3$.

The limitation of this method is that it is confined to the synthesis of alkenylsilanes at the current time.

In Chapter 6 , we discuss the arylation of activated imines, which is a useful novel way of approaching aromatic amine products, particularly optically pure products using chiral catalysts; this is also a research topic at the heart of our research group. Therefore, in this context, the report in 2000 by Hartwig's group on Rh(I)-catalyzed coupling of aryl halides with *N*-pyrazyl aldmines, which was considered a Heck-type reaction on C=N groups (Scheme 1.28) [71, 72] is particularly relevant. The

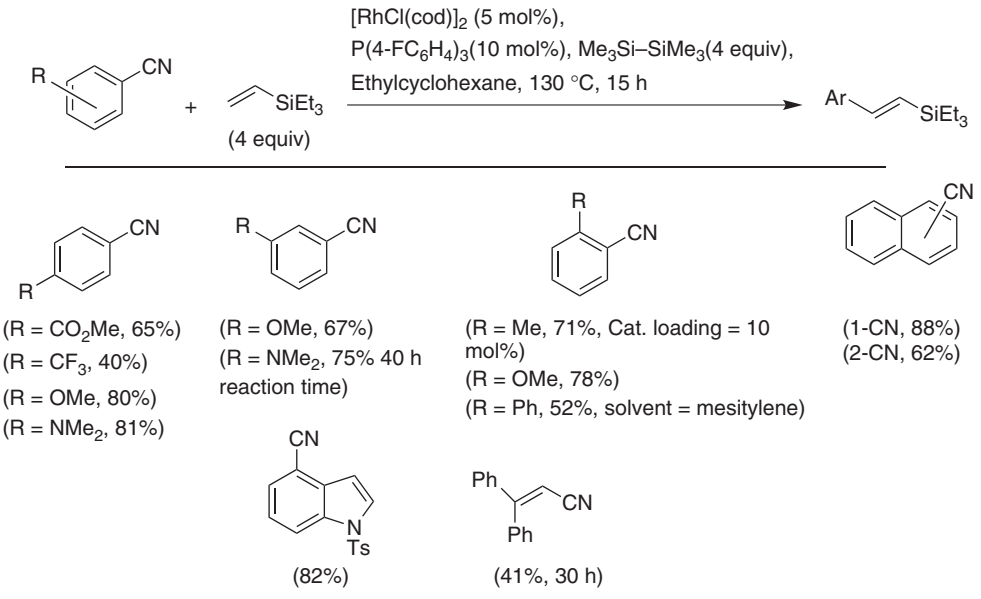
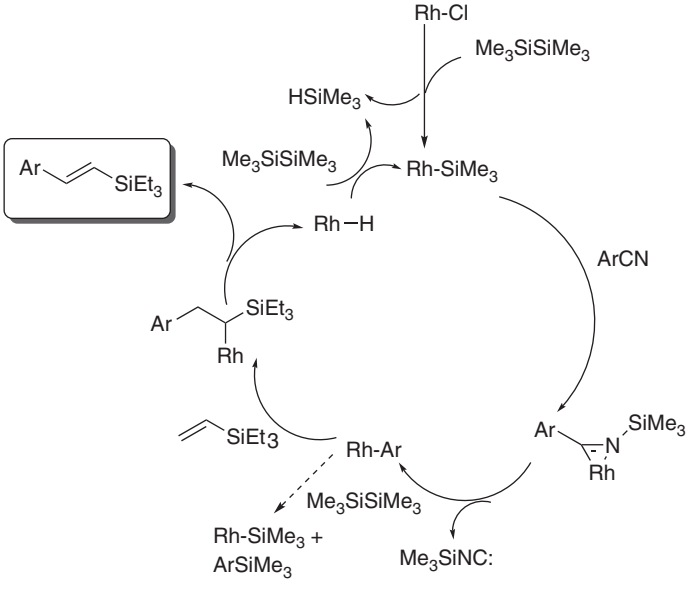
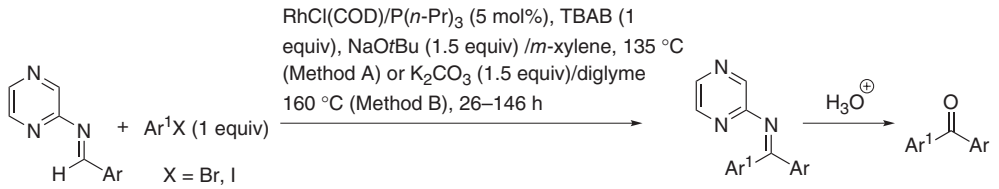


Figure 1.17 The Rh(I)-catalyzed reaction as reported by Chatani and coworkers [70].



Scheme 1.27 The proposed mechanism for the Rh(I)-catalyzed Heck–Mizoroki by Chatani and coworkers [70].

pyrazyl unit was chosen as it contained an ancillary donor nitrogen to coordinate to the Rh, and the second nitrogen in the fourth position provides an electronic effect. The reaction could be performed under two types of conditions, one using NaO*t*Bu in *m*-xylene at 135 °C (Method A) and the other K_2CO_3 in diglyme at 160 °C. For convenient analysis, the ketimine intermediate was converted via acid hydrolysis to the ketone product. The reaction went very smoothly with aryl iodides, but with



Scheme 1.28 The Heck–Mizoroki-type reaction on *N*-pyrazyl imines using Rh(I) as described by Ishiyama and Hartwig [71].

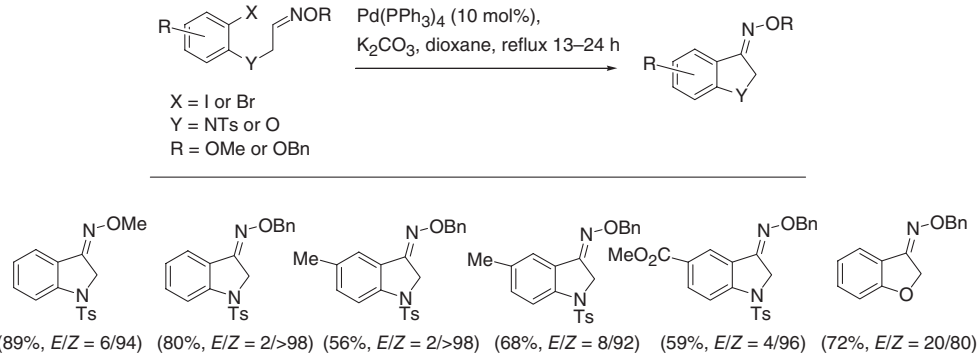


Figure 1.18 Heck–Mizoroki-type cyclization of oxime ethers as reported by Ohno *et al*. [73].

the corresponding bromides, the reactions were much slower, and with aryl chlorides, there was no reaction at all. The yields ranged from 19% to 83% with Method A and 47% to 95% with Method B. Taking a lead from this work, in 2007, Ohno *et al.* [73] reported a very important breakthrough in the Heck–Mizoroki coupling of aryl halides with oxime ethers (Figure 1.18). A variety of *O*-iodo and bromo-*N*-tosylamine-protected oxime ethers, including an *o*-bromophenol-derived benzyl oxime ether, were treated with $Pd(PPh_3)_4$ and K_2CO_3 in dioxane at reflux, giving a range of indolin-3-one *O*-methyloximes, including the benzofuran-3-one *O*-benzyl oxime in moderate to good yields. The Z-selectivity was excellent (up to >98 : 2). This was followed by a report by Cheng's group in 2008 on annulations between aromatic aldoxime ethers and aryl iodides through Pd-catalyzed C–H activation and subsequent intramolecular oxidative Heck cyclizations (see below) followed by hydrolysis to give 9-fluorenone derivatives (Figure 1.19) [74]. The yields were very good and a large substrate scope was demonstrated. An anionic palladacycle intermediate was proposed to be involved.

Considering the expensive nature of the Pd catalyst for the Heck–Mizoroki reaction, over the last 10 years some great strides have been made at immobilizing the catalyst. For example, in 2010, Patel *et al.* [75] reported the synthesis and application of a series of polymer anchored Schiff bases for coordination to $PdCl_2$ and use in the Heck–Mizoroki reaction of aryl bromides and iodides. The main objective was to enhance the lifetime of the resulting catalyst by immobilization on a polymer matrix. Four immobilized catalysts were prepared by loading $PdCl_2$ in ethanol at room temperature to four types of styrene–divinylbenzene copolymer beads with either different linker groups or degree of cross-linking (Figure 1.20). However, it was immobilized catalyst **14** that gave the best results because of its cross-linking and catalyst loading. The reactions were performed in water with a small quantity of cetyltrimethylammonium bromide (CTAB) as promoter. The results were very good, giving generally very good yields and turnover numbers (TONs) (Figure 1.20), and what was remarkable about this method was the very low catalyst loadings. Mostly the *trans*-isomer was obtained. The catalysts could be recycled up to three times without any significant loss in the conversion; however,

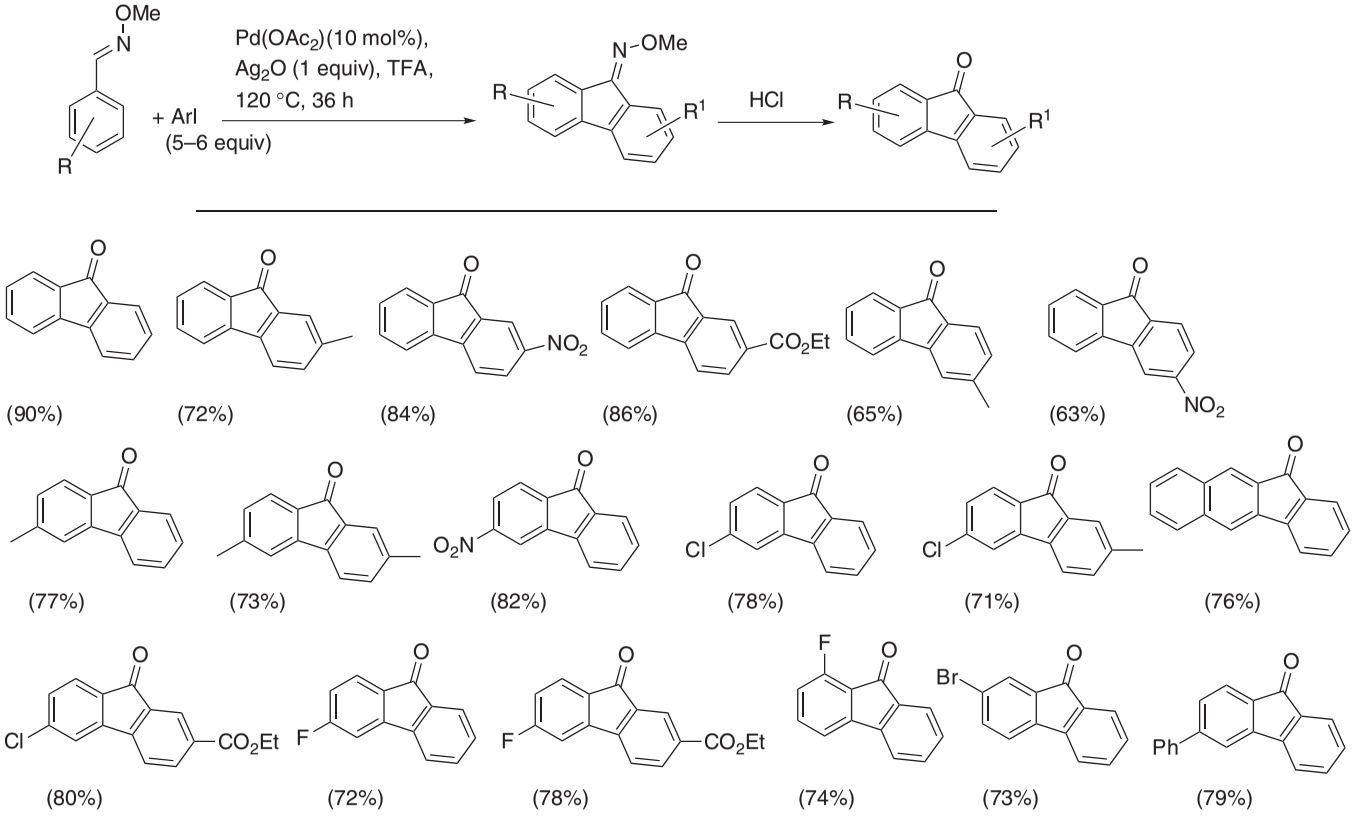


Figure 1.19 Synthesis of fluorenones from oxime ethers and aryl iodides by palladium-catalyzed dual C–H activation and Heck cyclization reported by Cheng [74].

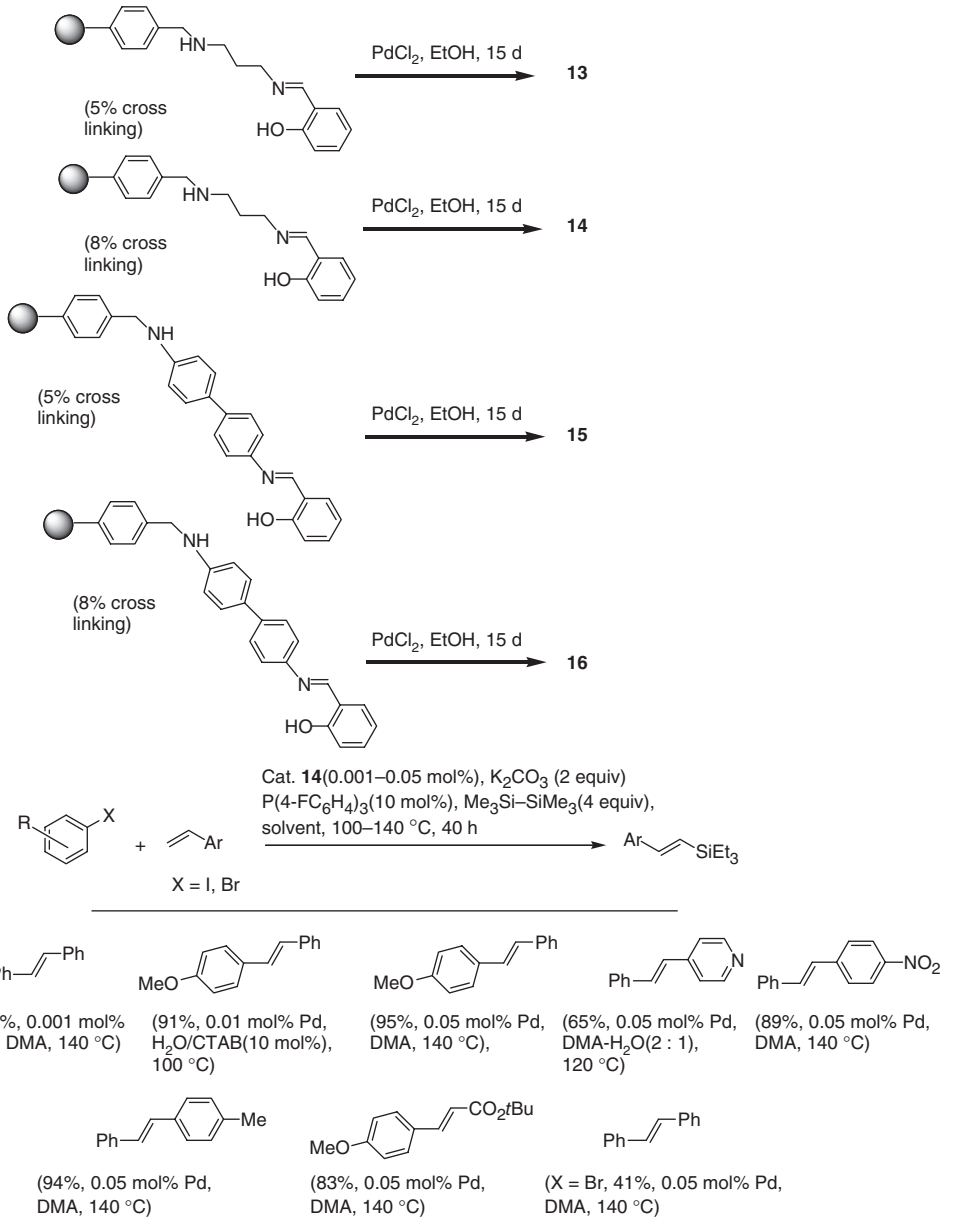


Figure 1.20 Use of a polymer supported Pd catalyst for the Heck–Mizoroki reaction reported by Patel *et al*. [75].

after the fourth cycle, there was a noticeable drop in the conversion, which was most likely due to styrene polymerization, as a white material was observed as a coating on the beads.

In 2008, Portnoy's group [76] reported the use of bidentate phosphine ligands immobilized to Wang polystyrene beads with polyether dendron spacers, which formed active catalysts for the Heck–Mizoroki reaction when treated with $Pd(dba)_2$ (Figure 1.21). Two series of immobilized palladium catalysts were investigated, one series termed **Gn-I** was prepared by incubating the

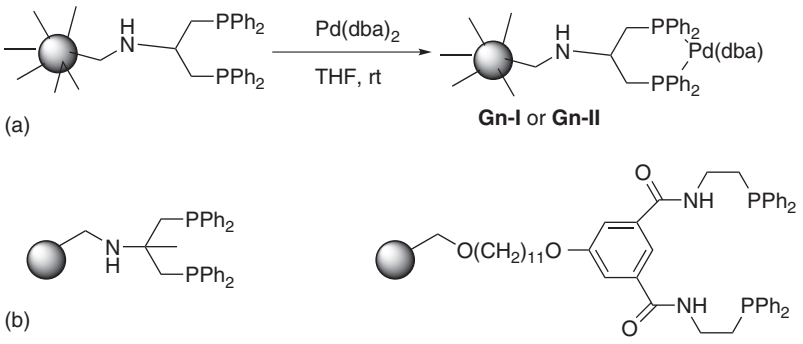


Figure 1.21 (a) Dendron supported diphosphane ligands/catalysts and (b) nondendritic diphosphane ligands reported by Mansour *et al*. [76].

diphosphane and the precatalyst in a 1 : 1 ratio. The second series **Gn-II** was prepared by using a 2 : 1 ratio, thus leaving only half of the ligating sites being occupied by Pd. This series, including their nondendronized (**G0-II**), their first- (**G1-II**), second- (**G2-II**), and third- (**G3-II**) generation dendrons, was screened in the Heck–Mizoroki reaction using bromobenzene and methylacrylate and 3.75 mol% catalyst at 110 °C in *N*-methylpyrrolidinone (NMP) for 14 h. There was a notable drop in the yield on going from (**G0-II**) to (**G3-II**), and this was accounted for by the increase in dendron generation – negative dendritic effect. The yield of the *trans*-methylcinnamate product plummeted from 68% to 12% on going from **G0-II** to **G3-II.** This was attributed to reduced pore volume and diminished swelling, leading to restricted access of the reagents to the pores.

For comparison, some other nondendritic immobilized (on Wang resin) diphosphane ligands were also investigated in the same reaction (Figure 1.21b), giving better yields than their dendronized counterparts.

The use of palladium nanoparticles as catalysts in C–C bond forming reactions is an area of great interest because the possibility of fine-tuning the shape and size of the colloidal system that controls the catalytic efficacy [77]. Colloidal palladium systems have some inherent problems such as thermodynamic instability, leading to aggregations, especially at high temperatures [77]. These aggregations can result in the loss of active surface area for satisfactory catalysis, complicating their potential recycling [77]. In 2011, Raston's group [77] reported the application of palladium nanoparticles assembled in a polymeric nanosphere for the Heck–Mizoroki reaction. They used spinning disc processing together with hydrogen gas as the reducing agent as the method of choice for the scalable size controlled synthesis of heterogeneous catalysts. The nanospheres were held together by a poly(vinylpyrrolidone) scaffold. The nanoparticles were shown to be of 160 nm in diameter. They were screened in the Heck–Mizoroki reaction with *n*-butyl acrylate and a variety of aryl bromides and iodides (see Figure 1.22), giving excellent results for the aryl iodides under considerably mild conditions, but mixed results for the aryl bromides.

The use of magnetic nanoparticles (MNPs) for immobilizing catalysts has emerged as a very useful technology over the last 10 years [78]. Laska *et al.* [79] have developed three novel easy-separable MNP-supported Pd catalysts for use in simple Heck coupling reactions. The MNPs were easily prepared using a known procedure. The Pd catalysts were then immobilized using two different methods according to Scheme 1.29. In the case of the first procedure (a) (Scheme 1.29) Scheme 1.29a, commercially available palladium(II) acetate or bis(triphenylphosphine)palladium(II) diacetate were used, in the case of the other method (b) (Scheme 1.29), Pd(0) was immobilized via a reductive immobilization procedure with H_2PdCl_4 and $NaBH_4$. The size of the synthesized nanoparticles ranged from 7 to 17 nm.

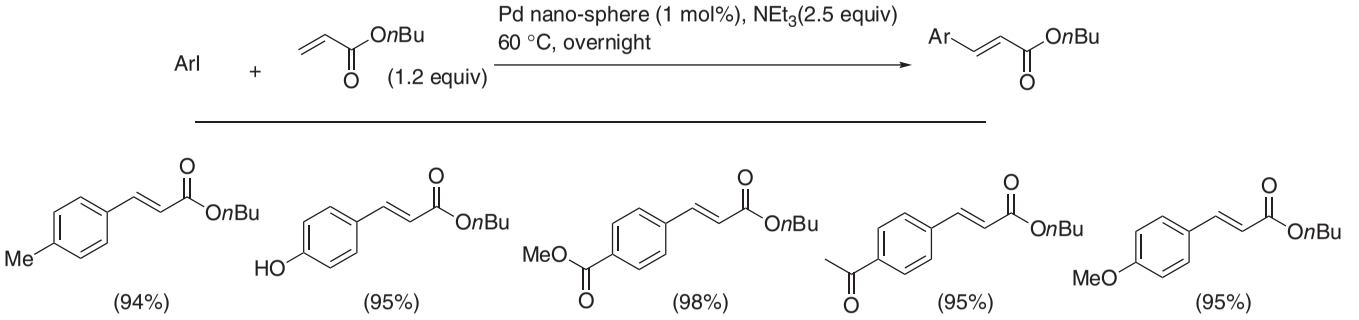
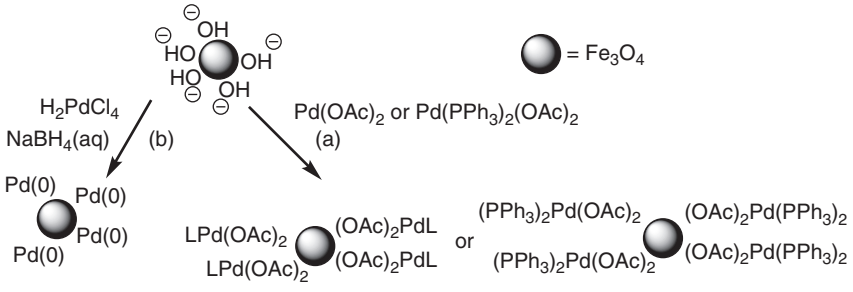


Figure 1.22 Results for the Heck–Mizoroki reaction with palladium nanoparticles in a poly(vinylpyrrolidone) scaffold as reported by Raston's group [77].

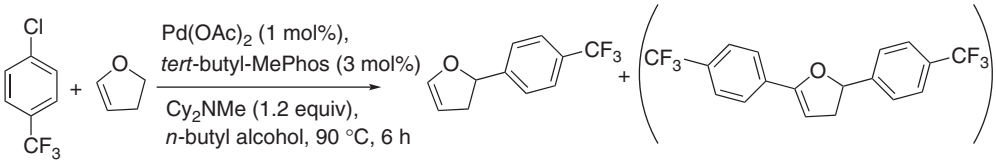


Scheme 1.29 The Heck–Mizoroki-type reaction using Pd immobilized MNPS as described by Laska *et al.* [79].

Investigation of these supported Pd catalysts revealed quantitative conversions (as determined by gas chromatography (GC)) for the Heck–Mizoroki reaction between styrene and *p*-bromonitrobenzene at a loading of 5 mol% Pd catalyst using KOAc as base and NMP as the solvent at 130 °C. It was shown that the bare MNP failed to catalyze the reaction. Naturally, recycling studies were also performed and it was observed that MNP-$[Pd(OAc)_2]$ could be recycled up to three times without any loss in conversion. MNP-Pd(0) showed the same behavior but it was only recycled twice. MNP-$[Pd(TPP)_2(OAc)_2]$ (Triphenylphosphane) showed substantial reductions in the conversions for the second (91%) and third (12%) cycles, this was accounted for on the basis of MNP-$[Pd(TPP)_2(OAc)_2]$ agglomeration during the reaction leading to lower availability of catalytic sites.

The development of Heck–Mizoroki reactions in flow (continuous flow) has been undertaken over the last few years; this has arisen because of the need for improving and optimizing the reaction conditions [80]. This technology has emerged as a new tool for both synthetic and process chemists. These reactors provide several advantages compared to batch reactors, like: enhanced heat- and mass-transfer characteristics; safety when using highly exothermic, explosive, or toxic reagents; precise control over residence time; isolation of sensitive reaction intermediates/products from air and moisture; high surface to volume ratio; the ease of automation; or the possibility of scale-up or using several devices in parallel and over all with a significant time-gain compared to traditional batch processes [81].

Buchwald and Jensen's groups [82] in 2010 reported the synthesis of 5-(*p*-trifluoromethylphenyl)-2,3-dihydrofuran using a continuous flow technique (Scheme 1.30).



Scheme 1.30 The Heck–Mizoroki-type reaction explored by McMullen *et al.* [82] under continuous flow conditions.

The reaction components were divided into three lots and loaded into three syringes (see Experimental section for full details) (Figure 1.23). Syringe **A** contained the aryl chloride, the amine base, and the palladium catalyst, syringe **B** contained the dihydrofuran, and syringe **C,** *n*-butyl alcohol. The three solutions were combined and mixed in an interdigital micromixer and then heated to 90 °C in a 140 µl silicon microreactor. The outlet of the reactor was connected to a high performance liquid

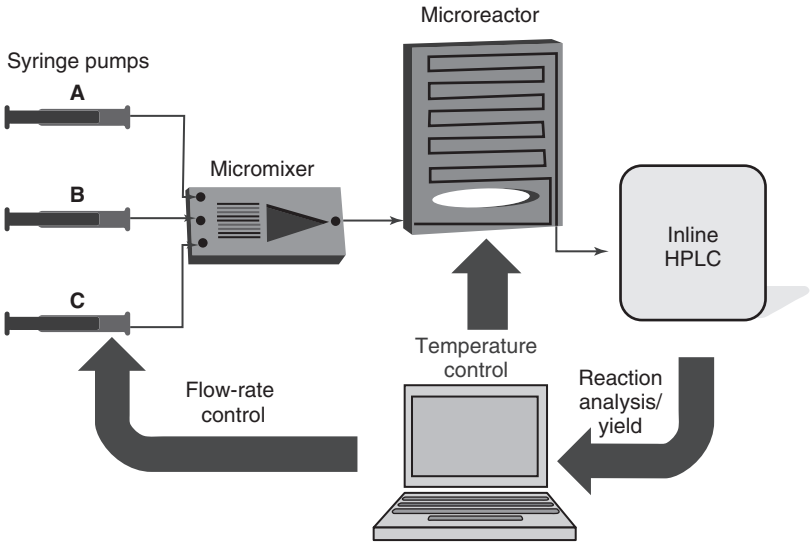
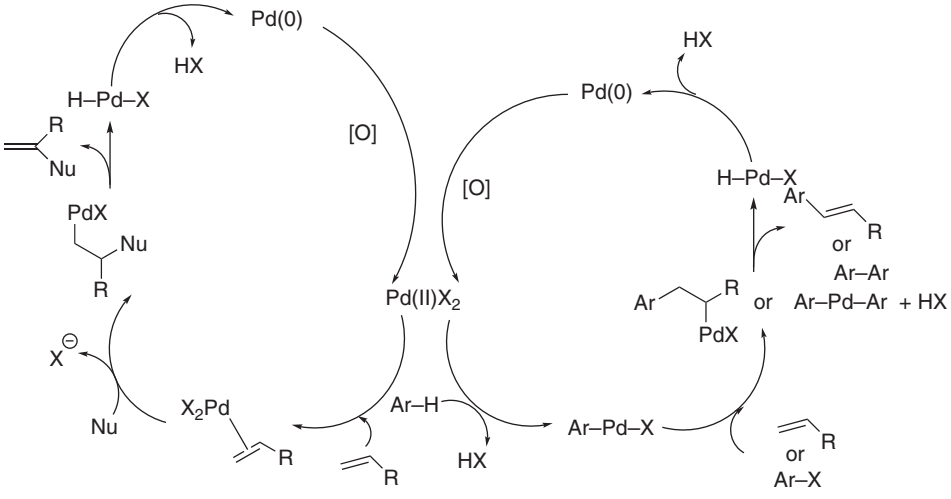


Figure 1.23 The continuous flow-system employed by McMullen *et al*. [82]. Syringe **A** contained the aryl chloride, the amine base, and the palladium catalyst, syringe **B** contained the dihydrofuran, and syringe **C**, *n*-butyl alcohol. (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

chromatography (HPLC). The optimization process was carried out using the Nelder–Mead Simplex Method. This was optimized by varying just two variables: residence time and the equivalents of the dihydrofuran. It was shown that 4.5–5.5 equiv gave an optimum yield. After this, these workers investigated the scale-up of this reaction to obtain preparative quantities of the product. For this purpose, a 7-ml Corning Advanced-Flow Glass Reactor Module was used. In this setup designed to achieve a 50-fold increase in scale (mesoscale system), a dual piston pump system was used. Nine different reaction conditions were investigated, and it was found that the best yields were obtained using a residence time of 5.5–6.5 min and 5 equiv of the olefin. The monoarylated product (Scheme 1.30) was isolated by distillation and chromatography providing 26.9 g of the product with a yield of 80%. This corresponds to an annual production rate of 114 kg year^{-1}. Of note is the fact that the integration of automation into the continuous flow system presents an efficient new approach to reaction development.

Further interesting examples can be found in Noël and Buchwald's review, including the adaptation of this method to RTILs by Ryu and coworkers [83]. In this reaction, iodobenzene was reacted with butyl acrylate with a palladium–NHC catalyst (1 mol%) system in [BMim]NTf_2 (1-Butyl-3-methylimidazolium). The system was run for 11.5 h giving 115.3 g of *trans*-butylcinnamate product. The catalyst could be recycled up to five times.

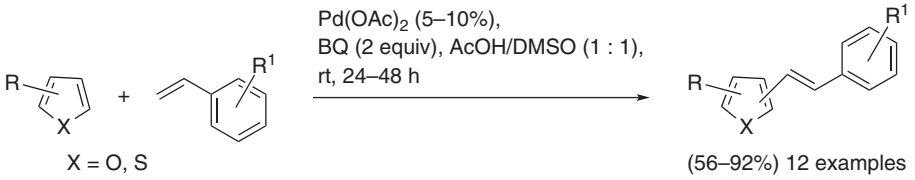
The oxidative-Heck reaction is a variant of the Heck–Mizoroki reaction, which has captured quite a lot of interest owing to the fact that Pd(II) is used as catalyst. It is regenerated by oxidation in order to sustain the catalytic cycle, and nonfunctionalized substrates can be used (Scheme 1.31) [84, 85]. The mechanism proposed for alkene substrates is designated (a), while that for aromatic substrates is designated (b). The mechanism shown in Scheme 1.31 is self-explanatory; however, the following points need to be clarified: reactions involving conjugated dienes generally lead to double functionalizations [84b]. Examples of oxidants for this process include Ag(I), Cu(II), TBHP (tert-Butyl hydroperoxide), $PhCO_3Bu$, benzoquinone and oxygen. When the latter is used as the oxidant, insertion of O_2 into the Pd(II) hydride is possible [84b].



Scheme 1.31 The accepted catalytic cycle for the oxidative-Heck reaction [84].

In 2006, Enquist *et al.* [86] reported a new variation of the oxidative-Heck reaction that employed arylboronic acids as the arylating species which was carried out at room temperature in the open air (in the context of Heck–Mizoroki couplings, this is a rare event!). A range of different ligands were screened, but it was inexpensive 2,9-dimethyl-1,10-phenanthroline (dmphen) that gave the best results. The results – including the conditions for the oxidative arylation of *n*-butyl acrylate with a range of arylboronic acids – are shown in Figure 1.24. The reaction worked best with electron-rich arylboronic acids, and *p*-acetylphenylboronic acid underwent this type of reaction for the first time. This reaction could be smoothly scaled up from 1 to 50 mmol.

In 2011, Jean Le Bras's team [87] reported a very mild Pd-catalyzed dehydrogenative Heck–Mizoroki reaction of furans and thiophenes with styrenes at room temperature (Scheme 1.32)! $Pd(OAc)_2$ was used as the catalyst with benzoquinone (BQ) as the oxidizing agent.



Scheme 1.32 The room temperature oxidative Heck–Mizoroki reaction developed by Le Bras's group [87].

It was believed that the dimethyl sulfoxide (DMSO) can coordinate to the Pd intermediate, giving a more electron poor species that is more susceptible to attack by electron-rich styrenes.

The oxidative Heck–Mizoroki reaction has also been adapted to flow-chemistry systems. Lahred and coworkers have used this procedure to couple *n*-butyl acrylate and *n*-butyl vinyl ether with arylboronic acids using $Pd(OAc)_2$ with *p*-benzoquinone as the oxidant [88]. The yields were generally good (56–85%).

Organ and coworkers developed a microwave-assisted flow system, which was used successfully for the synthesis of a key intermediate of the ICMT (isoprenylcysteine carboxylmethyltransferase) inhibitor aplysamine 6 (Scheme 1.33) [89].

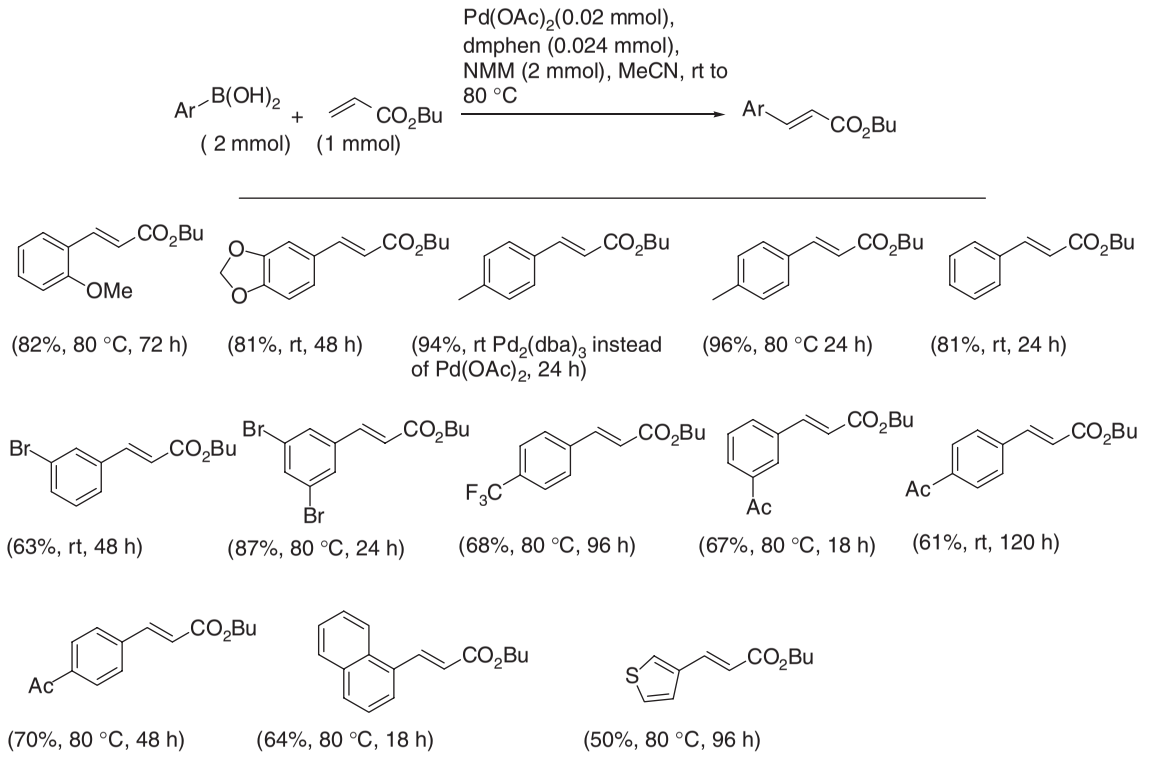
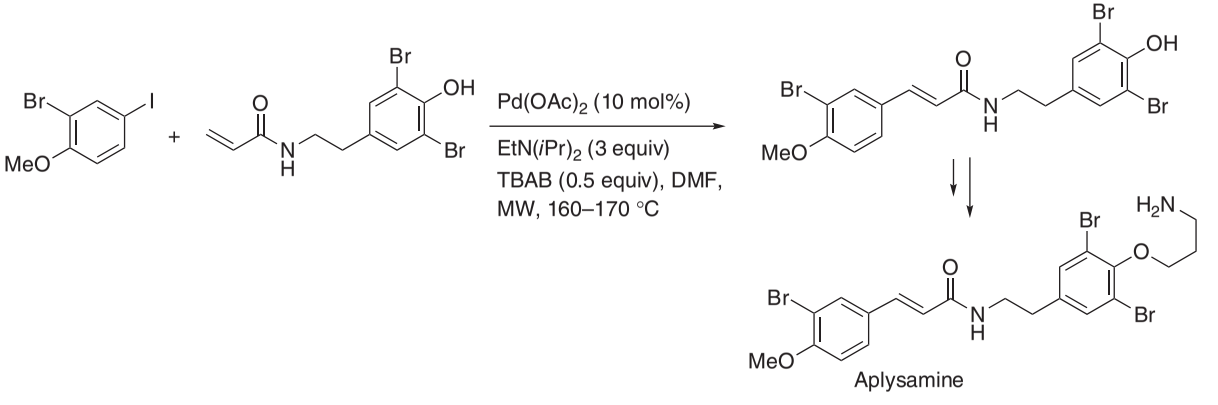


Figure 1.24 A cross-section of results obtained for the oxidative-Heck reaction with arylboronic acids as described by Enquist *et al.* [86].



Scheme 1.33 The microwave-assisted flow chemistry procedure to a key aplysamine intermediate developed by Organ's group [89].

1.3.2
Arylations with the Heck–Matsuda Reaction – Recent Developments

This reaction has come much to the fore over the last few years. A number of prominent reviews have been published on the topic [19]. Given the limitations of the Heck–Mizoroki reaction (some of which are mentioned above), which are principally (i) the use of an inert atmosphere, (ii) the use of one reagent in excess, and (iii) the use of high temperatures which are accompanied by issues of side-product formation and catalyst deactivation [84a], it was inevitable that the Heck–Matsuda reaction conditions would be devised by these workers in 1977 [18]. In this reaction, arenediazonium (with generally BF_4 or acetate as the counter-anion) salts are used with olefins (Scheme 1.4). The reaction doesn't work well with electron-poor arenediazonium salts nor with severely sterically hindered arenediazonium salts [19a]. This reaction has been used successfully to access a number of important target compounds such as (−)-isoaltholactone (Figure 1.25) [90], an FTY720 derivative – FTY720 is a potent immunosuppressive agent used to treat autoimmune diseases such as multiple sclerosis (Figure 1.25) [91], an aza-derivative of goniothalesdiol – (+)-Goniothalesdiol, isolated from the bark of the Malaysian tree *Gonystylus borneensis*, a tetrahydrofuran (THF) based compound known to have significant cytotoxic effects against P388 murine leukemia cells including pesticidal activities [92] (*R*)-tolterodine, which is an antimuscarinic drug that is used for symptomatic treatment of urinary incontinence (Figure 1.25) [93], and the sphingosine 1-phosphate receptor-subtype 1 (SIP1) agonist VPC01091 [94].

Alternative solvents have been developed for the Heck–Matsuda reaction. This reaction has recently been performed in neat water by Nájera's group [95]. The reaction was carried out using an oxime-derived palladacycle catalyst and palladium acetate using a variety of different diazonium tetrafluoroborates giving styrenes, stilbenes, arylideneketones, and cinnamate esters (Figure 1.26). The reactions could be performed at room temperature and very good yields could be obtained. It was observed that $Pd(OAc)_2$ was more adaptable to the water conditions (Figure 1.26).

A chiral version of this reaction was developed by Correia's group [96] using chiral RTILs. This approach was used to access enantiomerically enriched paroxetine, which is an antidepressant drug (Figure 1.27). The chiral RTILs were used in solvent quantities. Although some good yields could be obtained, despite the best efforts of these workers, no asymmetric induction was observed.

In 2012, Gholinejad reported the Heck–Matsuda reaction (as well as the Suzuki–Miyaura reaction) using palladium nanoparticles [97]. The nanoparticles were supported on agarose beads, and at a loading of 2.6 μmol a variety of aryl diazonium tetrafluoroborate salts could be coupled with

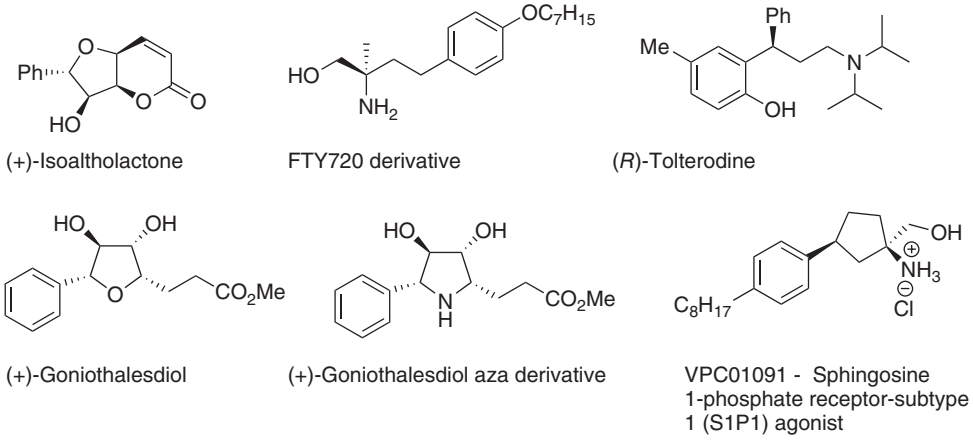


Figure 1.25 A cross-section of key synthetic targets accessed by the Heck–Matsuda reaction in recent years.

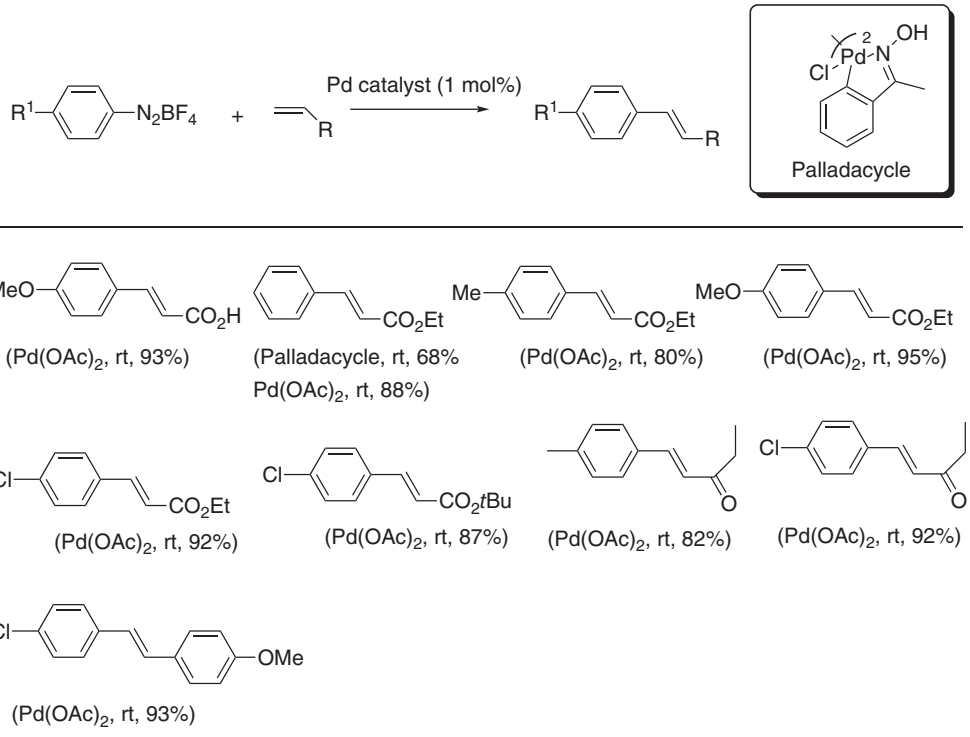


Figure 1.26 A cross-section of products successfully prepared by the Heck–Matsuda reaction in neat water [95].

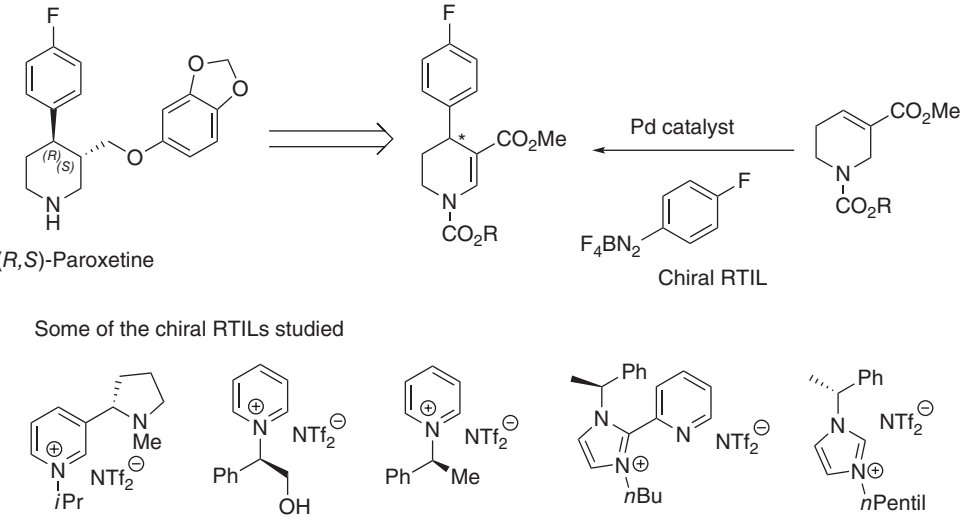


Figure 1.27 Attempts by Correia's group [96] at developing an asymmetric Heck–Matsuda reaction in chiral RTILs leading to (*R,S*)-paroxetine.

a variety of alkenes at 40 °C. Water was shown to be the best solvent and yields of over 80% were achieved. The catalyst could be recycled for up to three consecutive runs without any appreciable drop in the isolated reaction yield. Scanning electron microscopy (SEM) analysis showed no observable agglomeration of the nanoparticles.

In 2012, Burkhard König's group [98] reported a very interesting development in this area when they reported a photoredox application of this reaction using arenediazonium tetrafluoroborate salts with activated olefins and $[Rh(bpy)_3]^{2+}$ (bpy = 2,2′-bypyridine). In fact, this reaction is a derivative of the Meerwein reaction, which involves copper-catalyzed coupling of aryl daiazonium salts to unsaturated compounds. The reaction involves a radical mechanism. The problems with this reaction are the low yields and high catalyst loadings. In the knowledge that $[Rh(bpy)_3]^{2+}$ is known to undergo one-electron transfer reactions and that visible-light photocatalysis has been successfully used for initiating radical based coupling reactions, König's group applied this catalyst with blue light ($\lambda = 452$ nm or even with sunlight!) for the coupling of aryl diazonium tetrafluoroborate salts with activated olefins. A variety of stilbene products were obtained in highly satisfactory yields (66–94%) at 20 °C. The reaction supports a plethora of functional groups, including aryl halides. However, the reaction was not stereospecific and it gave mixtures of *cis* and *trans* isomers. This was obviously a consequence of the radical mechanism at play (a detailed mechanistic proposal was presented in this paper).

Given the paucity of Cu-catalyzed Heck-type reactions available in the chemical literature, in 2012, Gaunt's group[5] [99] reported an operationally simple Cu-catalyzed coupling reaction between a diaryliodonium salt and various arenes (Figure 1.28). The first test reaction performed by this group involved the reaction of 1-decene with diphenyliodonium triflate, 2,6-di-*tert*-butylpyridine (DTBP) as the base, 10 mol% $Cu(OTf)_2$ (trifluoromethylsulfonate) in dichloroethane (DCE) at 70 °C, and it gave a mixture of two regioisomers in good yield, with (surprisingly, and different from the Heck–Mizoroki procedure!) the nonconjugated product being the major product (the best result is shown in Scheme 1.34). After much optimization, the scope of the reaction was demonstrated (Figure 1.28).

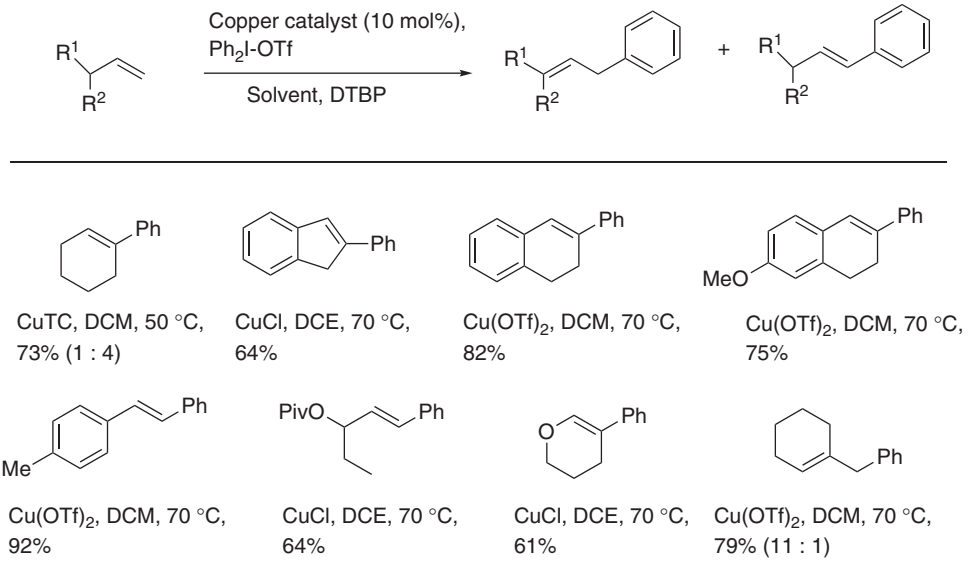
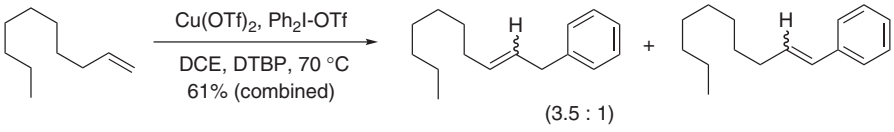


Figure 1.28 A cross-section of products successfully prepared by the Cu-catalyzed alkene arylation by Gaunt's laboratory [99].

5) More work from this group with copper catalysts is discussed in Chapter 4.

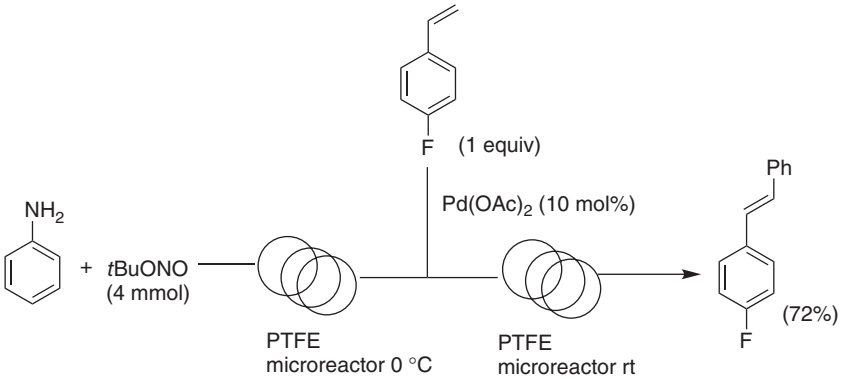


Scheme 1.34 The copper-catalyzed alkene arylation procedure developed by Gaunt's group [99].

Both Cu(I) and Cu(II) catalyze the reaction, and it was reported to proceed without Cu only at 110 °C. It is thought that the mechanism involves a carbocation-type intermediate.

In addition to these studies, this group has also investigated carbonyl-directed alkene arylation, including the arylation of complex molecular scaffolds [99].

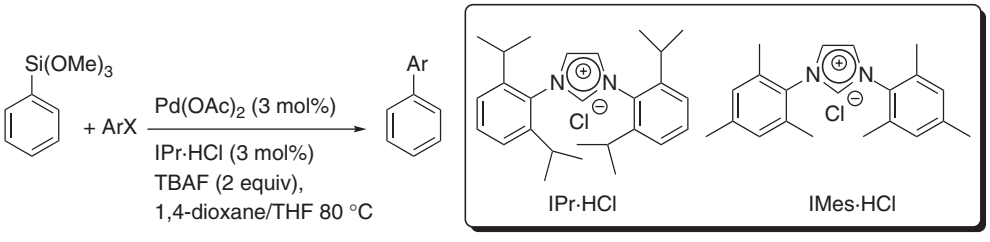
The Heck–Matsuda reaction has also been subjected to continuous flow chemistry conditions, as reported by Wirth *et al.* [100]. The reaction that was studied involved the reaction between an *in situ* generated diazonium ion and *p*-fluorostyrene to give (*E*)-*p*-fluorostilbene (Scheme 1.35) and the device used by this group relied on a segmented flow (liquid–liquid slug flow) to increase reaction rates in microfluidic flow. They used perfluorodecalin as an inert and immiscible liquid spacer.



Scheme 1.35 The segmented flow process for the Heck-Matsuda reaction developed by Wirth's group [100].

1.3.3
Hiyama–Hatanaka Cross-Coupling Reaction

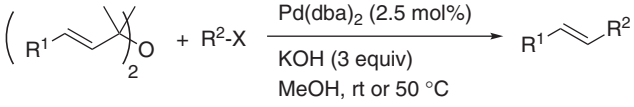
In 2000, Nolan and Lee reported the successful application of NHC ligands in this particular arylation reaction [101]. By combining palladium acetate and the imidazolium salt IPr·HCl (IPr = 1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene), it was possible to react phenyltrimethoxysilane (as well as vinyltrimethoxysilane) with a variety of aryl bromides and aryl chlorides, including 2-bromopyridine giving the arylated product in high yields (Scheme 1.36) (see Experimental Procedure below).



Scheme 1.36 Application of a palladium/imidazolium chloride system for the Hiyama–Hatanaka cross–coupling reaction [101].

In 2012, Yanase *et al.* [102] reported a ligand-free Hiyama–Hatanaka reaction using Pd/C only. Phenyltriethoxysilane was reacted with *p*-nitrobromobenzene using Pd/C (5 mol%) with TBAF as the fluoride source in toluene at reflux temperature, giving the coupled product in a yield of 65% (see Experimental procedure below). It was found that the solvent greatly influenced the reaction progress. The scope of the reaction was established on showing that it worked for both aryl chloride and aryl bromide substrates and a variety of aryltriethoxysilanes containing both electron-withdrawing and electron-donating substituents. Industrial application of this method is expected.

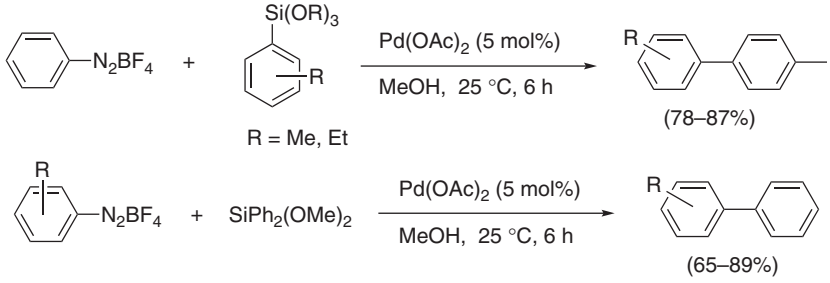
A significant recent development with this reaction was reported in 2009 by Spring's group [103], who showed that vinyldisiloxanes – which equilibrate with the corresponding silanolates under basic conditions and subsequently undergo palladium-catalyzed cross coupling with aryl iodides or aryl bromides. The substituted vinyldisiloxanes act as masked silanolate precursors. The advantage of this method is that fluoride activation is not required. The reaction conditions are shown in Scheme 1.37. The study unfortunately was limited in scope to the formation of stilbene derivatives.



Scheme 1.37 The novel fluoride-free cross-coupling procedure using vinyldisiloxanes developed by Spring's laboratory in 2009 [102].

In 2013, Yus and coworkers [104] also developed a fluorine-free Hiyama–Hatanaka reaction that used a Pd/NHC system, and was used to access a variety of biphenyl groups in good yields, using bromoarenes and chloroarenes and phenyltrimethoxysilane under microwave irradiation conditions and a temperature of 120 °C. By using a 3^2 factorial design, it was possible to predict that both the Pd/NHC ratio and the amount of Pd were important for obtaining good yields. The best catalyst loading was found to be 0.1 mol% with a ratio of 1 : 5 Pd/NHC, and the best NHC was that derived from 1-benzyl-3-(2-hydroxy-2-phenylethyl)-1*H*-imidazolium chloride.

In 2011, Cheng *et al.* [33] demonstrated that was possible to carry out the Hiyama–Hatanaka reaction with arenediazonium salts (Scheme 1.38). The reaction accommodates a plethora of functional groups, including both electron-withdrawing and electron-donating groups, can be conducted with monosilanes and dimethoxydiphenylsilane, and is run under room temperature conditions.



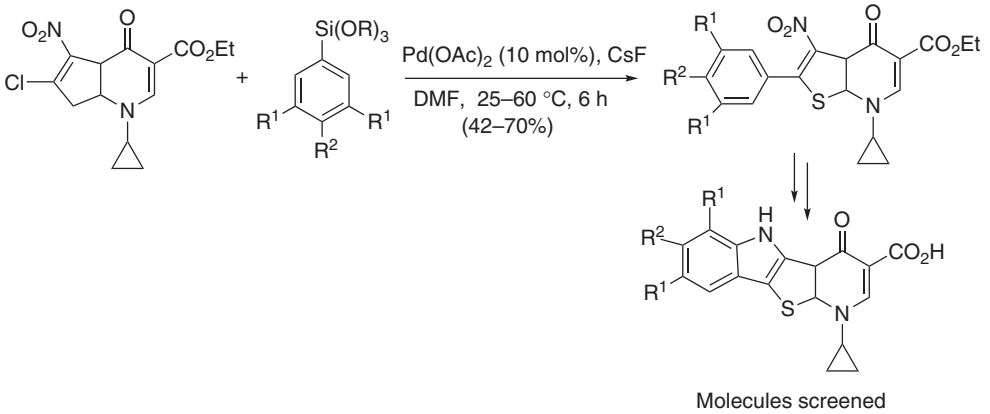
Scheme 1.38 The Hiyama–Hatanaka reaction with arenediazonium salts [33].

In 2013, Diebold *et al.* [105] reported a heterogenous catalytic Hiyama–Hatanaka reaction, which employed a reusable polystyrene-supported palladium catalyst. A variety of aryl iodides and aryltrialoxysilanes were coupled using a diphenylphosphinomethylpolystyrene-supported palladium catalyst at a loading of only 0.1 mol% of Pd. The reactions were carried out in toluene at 100 °C for 20 h and the yields were generally very high. The catalyst could be recycled up to four times with minimal leaching (~1%).

1.3.4
Arylations with the Stille Reaction

As far as we are aware, generally speaking, over the last number of years there have been very few innovations reported for the Stille reaction, this is probably because of the toxic nature of the reagents and the availability of many other less toxic and competing coupling procedures in the literature. Some of the methods that caught our attention are as follows:

- Work by Al-Trawneh *et al.* [106a] in 2011 who reported the application of a Stille coupling reaction as the key step to access a library of tetracyclic thienopyridones as antibacterial and antitumor agents (Scheme 1.39).
- A report in 2005 by Black and Arndtsen [106a] who reported a copper-catalyzed multicomponent method that leads to α-substituted amides using acid chlorides with organostannanes (Figure 1.29). The reaction showed reasonable scope.



Scheme 1.39 The Stille reaction in the synthesis of tetracyclic thienopyridones [106a].

1.3.5
Arylations with the Sonogashira–Hagihara Reaction

For a very recent 2011 review on this subject, the reader is encouraged to consult the review of Chinchilla and Nájera [107a].

Traditionally, Pd or Pd/Cu salts have been used but over the years, this reaction can be "stretched" to include other metals such as iron, ruthenium, cobalt, nickel, silver indium, and gold [107b]. In the case of gold, there was some controversy, and in certain quarters, there was talk of contamination of the gold catalyst with palladium (see below).

The copper-free Sonogashira–Hagihara reaction has been of great interest during recent years. In 2010, Shirbin *et al.* [108] used a variety of aryl imidazylates with phenylacetylene and employed them in a copper-free reaction with $Pd(OAc)_2$ as the catalyst (Figure 1.30). After some initial optimization studies it was found that the best results were obtained using 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos), as it is known to promote the formation of highly reactive 12-electron monovalent Pd(0) complexes.

In 2006, Dupont's group also reported a simple and efficient copper-free catalytic system based on some palladacycle catalysts (Figure 1.31) [109]. The coupling of iodoarenes and activated bromoarenes could be conducted with terminal alkynes at room temperature. The yields were generally good and TONs of up to 100 000 could be obtained with iodoarene substrates (Figure 1.31).

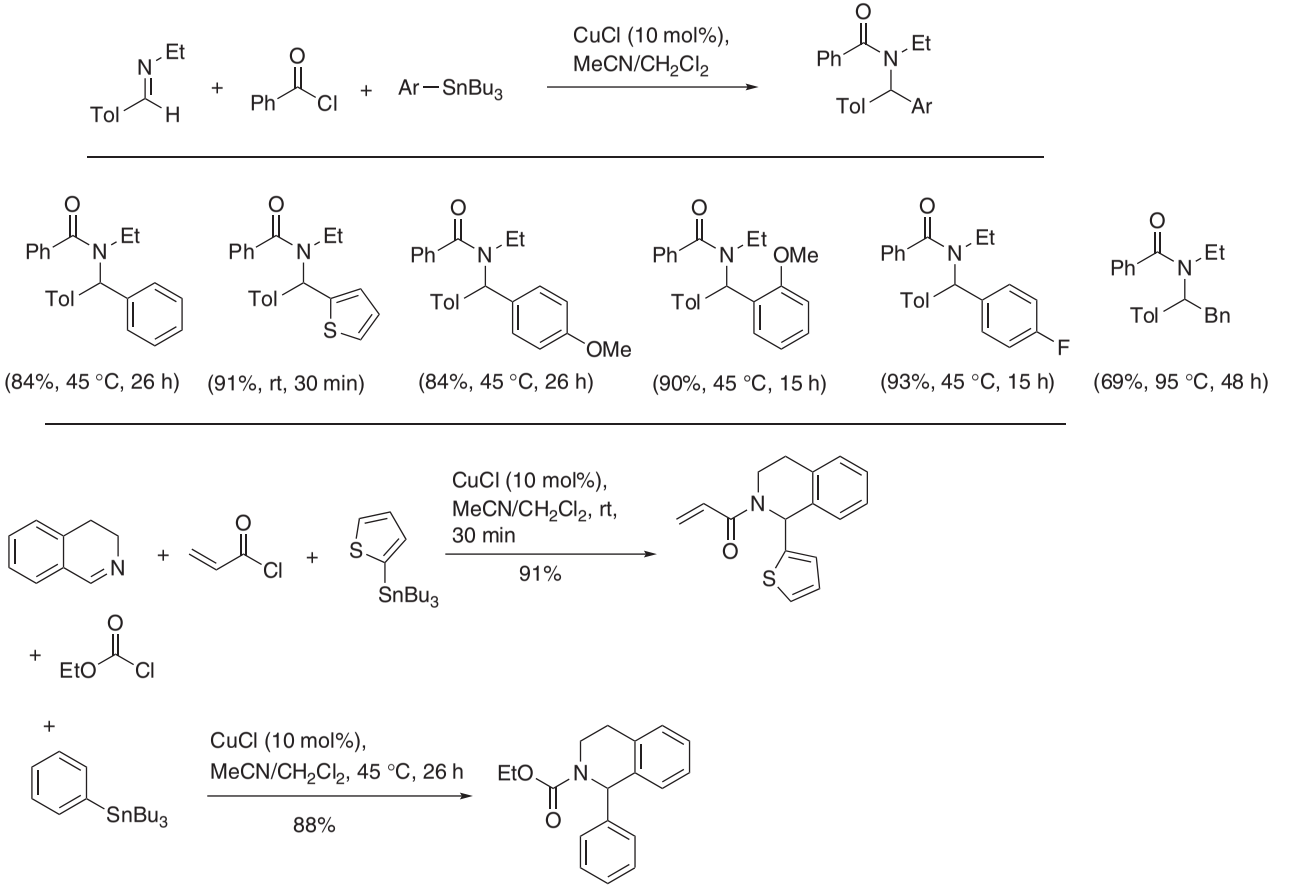


Figure 1.29 Some of the results reported by Black and Arndtsen [106b] for the copper-catalyzed multicomponent method to α-substituted amides.

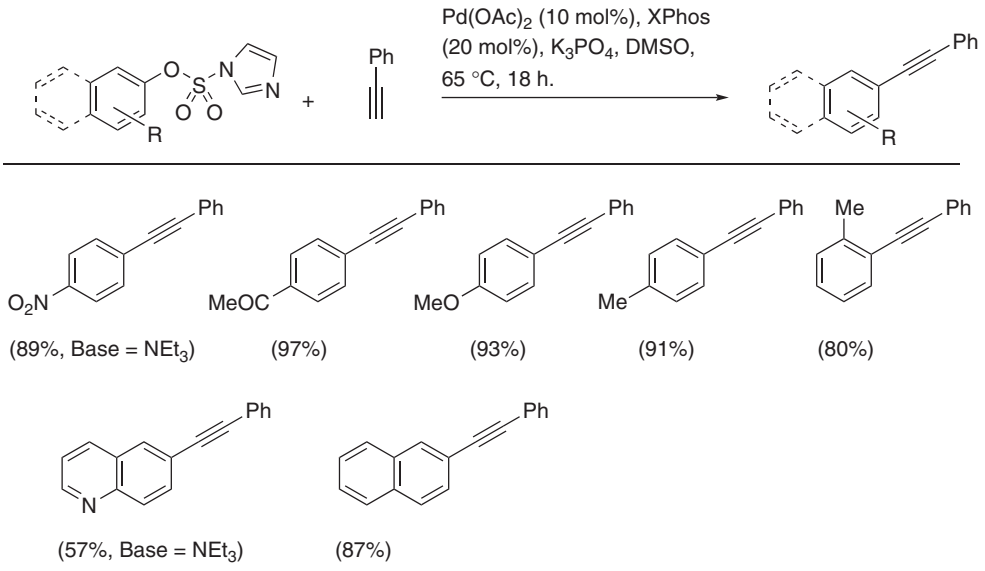


Figure 1.30 A cross-section of products successfully prepared by the Pd-catalyzed alkyne arylation by William's laboratory [108].

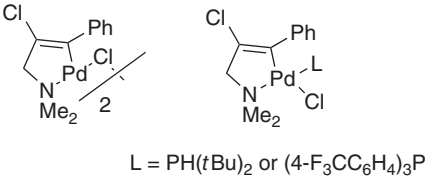


Figure 1.31 The palladacycle catalysts used by Dupont's group [109] for copper-free Sonogashira–Hagihara reaction arylations.

The Sonogashira–Hagihara reaction is very useful for accessing molecular wires and molecular scale electronic devices. In 2005, Li *et al.* [110] reported this reaction for the synthesis of oligo(1,4-phenylenethynylene)s (Figure 1.32). The strategy that was employed involved a novel *in situ* deprotection/coupling and iterative divergent/convergent strategy.

From the industrial world, a team at Evonik Degussa GMBH published a patent on the application of new phosphane compounds for various cross-coupling reactions, including the Sonogashira reaction [111]. Some of the ligands used and the results obtained for the coupling reaction with 4-bromotoluene with phenylacetylene using Na_2PdCl_4/phosphane/CuI (4 : 8 : 3) and dry diisopropylamine as base, at 50 °C for 24 h, are shown in Table 1.2.

In 2007, Corma's group [112a] reported the use of Au supported on CeO_2 nanoparticles for the Sonogashira coupling of terminal alkynes with aryl iodides. Owing to the lack of reactivity of the Au nanoparticles on their own, the activity was ascribed to the formation of Au(I) species on the CeO_2 nanoparticles. Au(I) complexes were prepared and they showed activity. However, in 2010 the groups of Espinet and Echavarren [112b] published a paper that cast doubt on the possibility that Au(I) catalyzes the Sonogashira reaction. Their rational was based on the premise (that in fact has been validated) that high-purity gold contains traces of palladium. In their communication, they carried out experiments using AuI and added small incremental

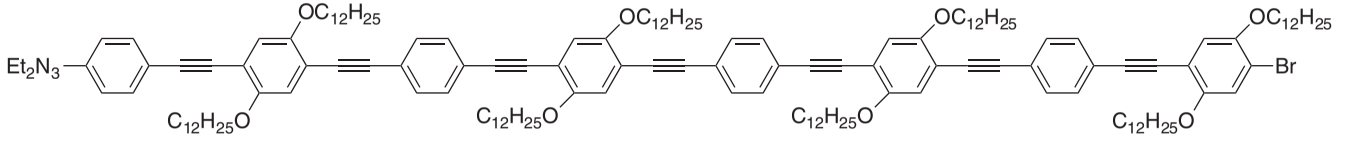
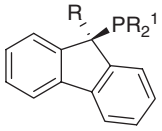


Figure 1.32 An oligo(1,4-phenyleneethynylene) obtained from a normal Sonogashira–Hagihara reaction by Li *et al.* [110].

Table 1.2 The ligands and the TON values reported and obtained in the Sonogashira–Hagihara reaction reported by Evonik Degussa [111].

Ligand = 

Ligand	TON[a) b)]
$R = C_{18}H_{37}$; $R^1 = Cy$	5900
$R = Et$; $R^1 = Cy$	5600
$R = Me$; $R^1 = Cy$	5600
$R = C_{18}H_{37}$; $R^1 = i$Pr	5500
$R = C_{18}H_{37}$; $R^1 = Cy$	3600
$R = Me$; $R^1 = i$Pr	3500
$R = Et$; $R^1 = i$Pr	3200
$R = i$Pr; $R^1 = Cy$	906
$R = i$Pr; $R^1 = i$Pr	500
$R = H$; $R^1 = t$Bu	330
$R = Ph$; $R^1 = i$Pr	250

a) Average of two runs. Determined by the mass of the isolated ammonium salt.
b) CataCXium® A was used as a reference and this had a TON of 3600.

amounts of Pd(0) (source = $Pd_2(dba)_3.CHCl_3$), and they showed that the reaction between *p*-methylphenylacetylene and methyl *p*-iodobenzoate occurred to give *p*-tolyl-*p*-acetylethyne. At a loading of 0.012 mol%, there was a significant amount of alkyne product formed (24% yield). Corma's team then reassessed their work [112c], and these experiments showed that an induction period is required before the Au complexes – which are now considered to be Au nanoparticles – become active. The rate was in fact enhanced by the Pd-free Au nanoparticle already had a significant activity. This view has been supported by density functional theory (DFT) calculations by Lambert's group, that showed the cooperation of adjacent metal sites in the C–I cleavage step [112d]. The assessment of this situation has been supported by Robert Crabtree in a recent review [112d].

In 2010, Fabrizi *et al.* [113] reported the use of arenediazonium salts in the Sonogashira–Hagihara reaction. By using phenylacetylene and 4-methoxybenezendiazonium tetrafluoroborate with $[PdCl_2(PPh_3)_2]$ (2 mol%), CuI (4 mol%), nBu$_4$NI (2 equiv), diisopropylamine base (10 equiv) at room temperature for 1 h (only!) they obtained the *p*-methoxyphenylphenyethylene product in a yield of 79%. This was a remarkable development for the Sonogashira–Hagihara reaction. The scope of this reaction was also demonstrated (Figure 1.33). They also developed a one-pot cross-coupling of anilines with phenylacetylene, by forming the diazonium ion *in situ.* The scope of this process was also demonstrated.

In 2011, Park *et al.* [114] reported a Pd-catalyzed decarboxylative coupling (see Chapter 3 for further details on decarboxylative coupling reactions) of propiolic acids, which involves a Sonogashira–Hagihara homocoupling sequence. Their reaction represents a new approach to the synthesis of 1,3-diynes, besides the classical approaches, which include Glaser coupling, Chodkiewicz–Cadiot coupling, Rossi's protocol, and Lei's protocol. The scope of this reaction was comprehensively demonstrated, using a plethora of iodoarenes and propiolic acid (Figure 1.34). The reaction commences with the Sonogashira–Hagihara coupling and then is followed by a Pd-catalyzed decarboxylative homocoupling. Both Pd(0) and Ag_2CO_3 are required for this coupling.

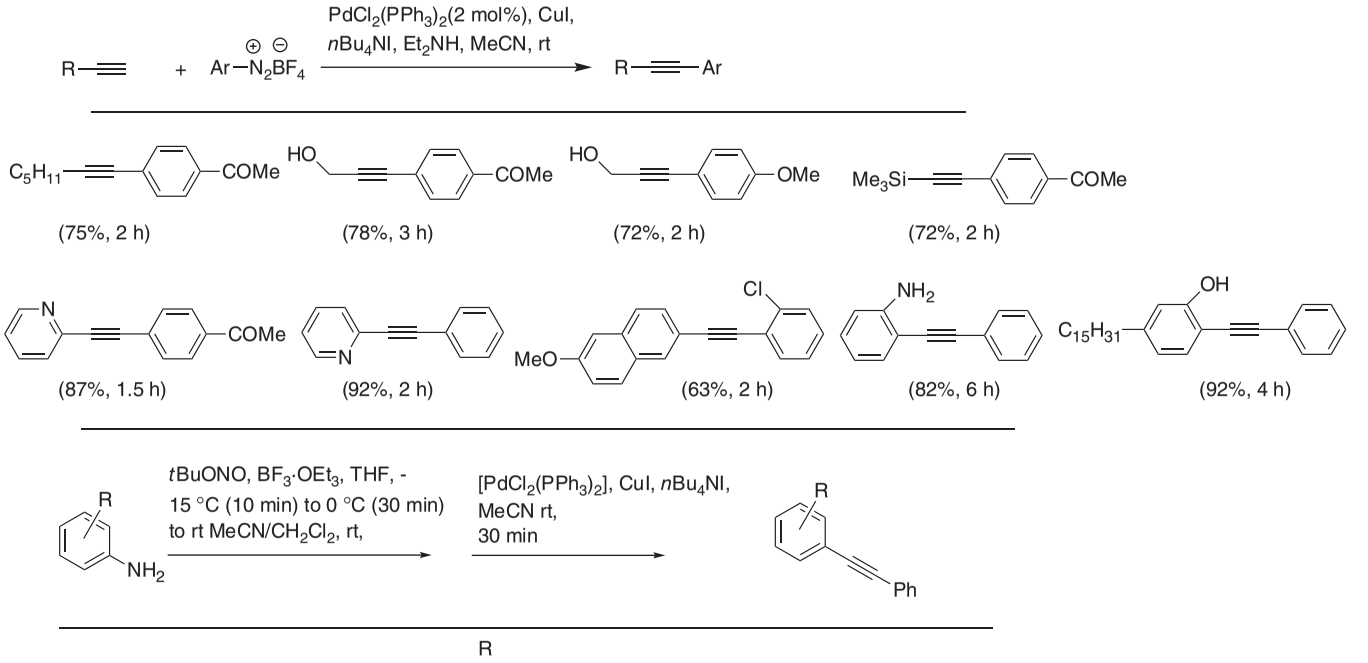


Figure 1.33 The Sonogashira–Hagihara reaction variant of Fabrizi *et al.* [113] with arenediazonium salts.

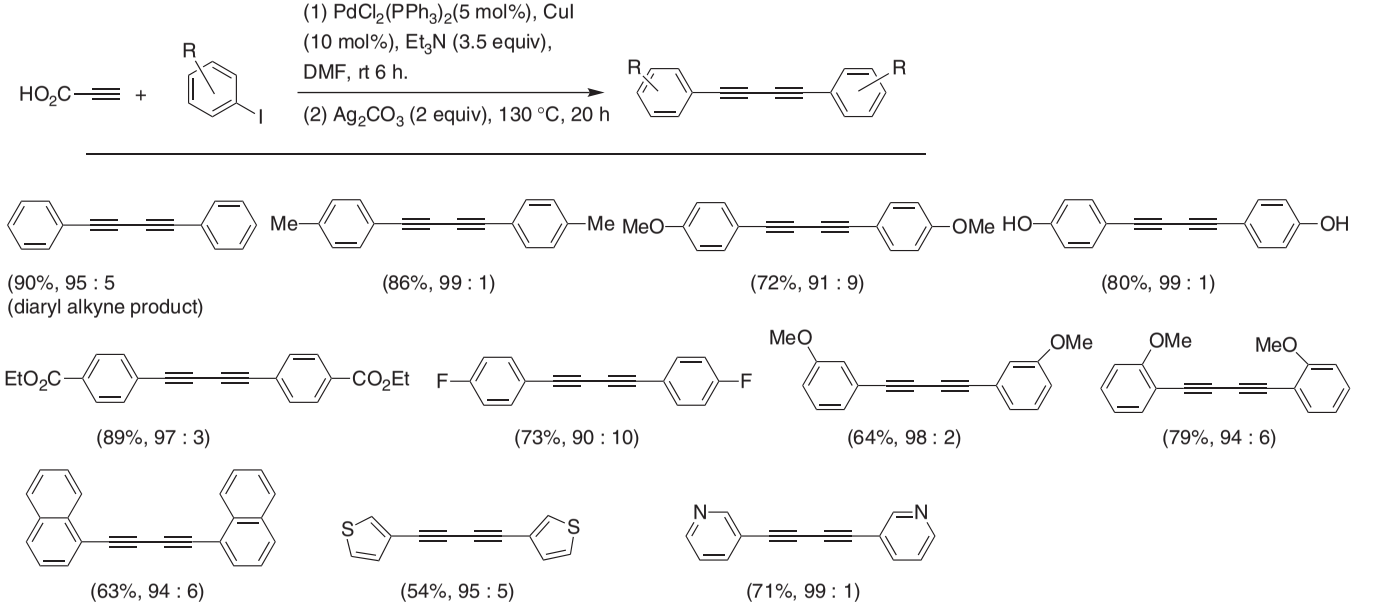
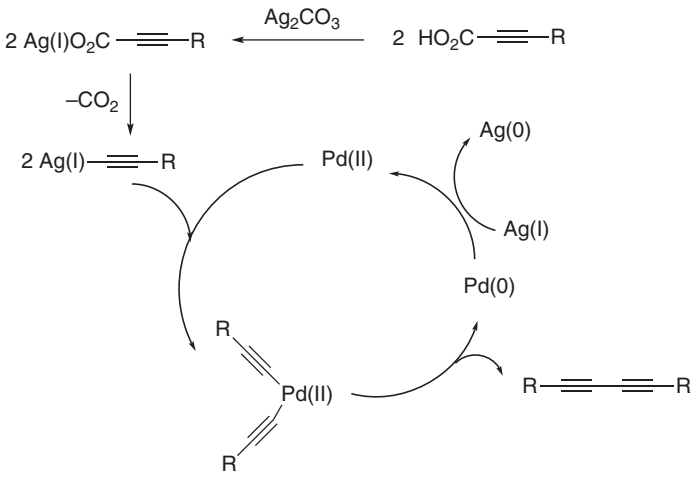


Figure 1.34 The Pd-catalyzed decarboxylative coupling as described by Park *et al.* [114].



Scheme 1.40 Proposed catalytic cycle for the Pd-catalyzed decarboxylative coupling reaction of Park *et al.* [114].

A small amount of the diaryl alkyne product was obtained. The proposed catalytic cycle is shown in Scheme 1.40. It is believed that the silver carbonate is responsible for oxidizing the Pd(0) to Pd(II) in order to conclude the catalytic cycle. The Pd(0) species is presumed to be obtained via reductive elimination of the dialkynylpalladium(II) intermediate.

In 2011, Lipshutz's team reported the successful application of the amphiphile TPGS-750-M for the realization of Sonogashira–Hagihara coupling reactions (as well as Heck–Mizoroki, Suzuki–Miyaura, Buchwald–Hartwig, Negishi–like couplings, C–H activation reactions, and so on [115]). This amphiphile was designed to self-aggregate spontaneously in water, and provide a micellar environment within which organic substrates and catalysts may readily react. The amphiphile consists of α-tocopherol as its main lipophilic component, and a PEG-750-M (monomethylated poly(ethylene glycol) = MPEG) linked by succinic acid. Only two reactions were studied, one with *p*-bromoanisole and 6-chloro-1-hexyne giving the coupled product in a yield of 66% (which was higher than that achieved using the first generation amphiphile polyoxyethanyl α-tocopheryl sebacate (PTS) which was 55%). The reaction was carried out at room temperature for 25 h, using $Pd(P(tBu)_3)_2$ (2 mol%) as the catalyst and NEt_3 (3 equiv) with 5% TPGS-750-M in water. The second reaction involved 2-bromonaphthalene with 1-ethynylcyclohex-1-ene for 21 h under the same conditions, and gave the product in 99% yield (84% was the best yield obtained with PTS.)

1.3.6
Arylations with the Suzuki–Miyaura Reaction

The Suzuki–Miyaura reaction is one of the most prominent and useful coupling reactions; over the last few years, its usefulness has been reported in several papers and patents, and in this section, a cross-section of these reports is given.

Monoligated Pd-NHCs have been very useful over the last 10 years for this catalytic transformation. In 2009, Organ's group reported the use of a Pd-PEPPSI-IPent ([1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride) catalyst for the synthesis of tetra-*ortho*-substituted biaryls (Figure 1.35) [54, 116a]; it should be noted that the formation of tetra-*ortho*-substituted biaryl under mild conditions is a challenge. Previously, this group has used other less hindered Pd-PEPPSI catalysts, such as Pd-PEPPSI-IMes (1,3-bis(2,4,6-trimethylphenyl)-imidazolium) and Pd-PEPPSI-IPr, and it was observed that better yields were

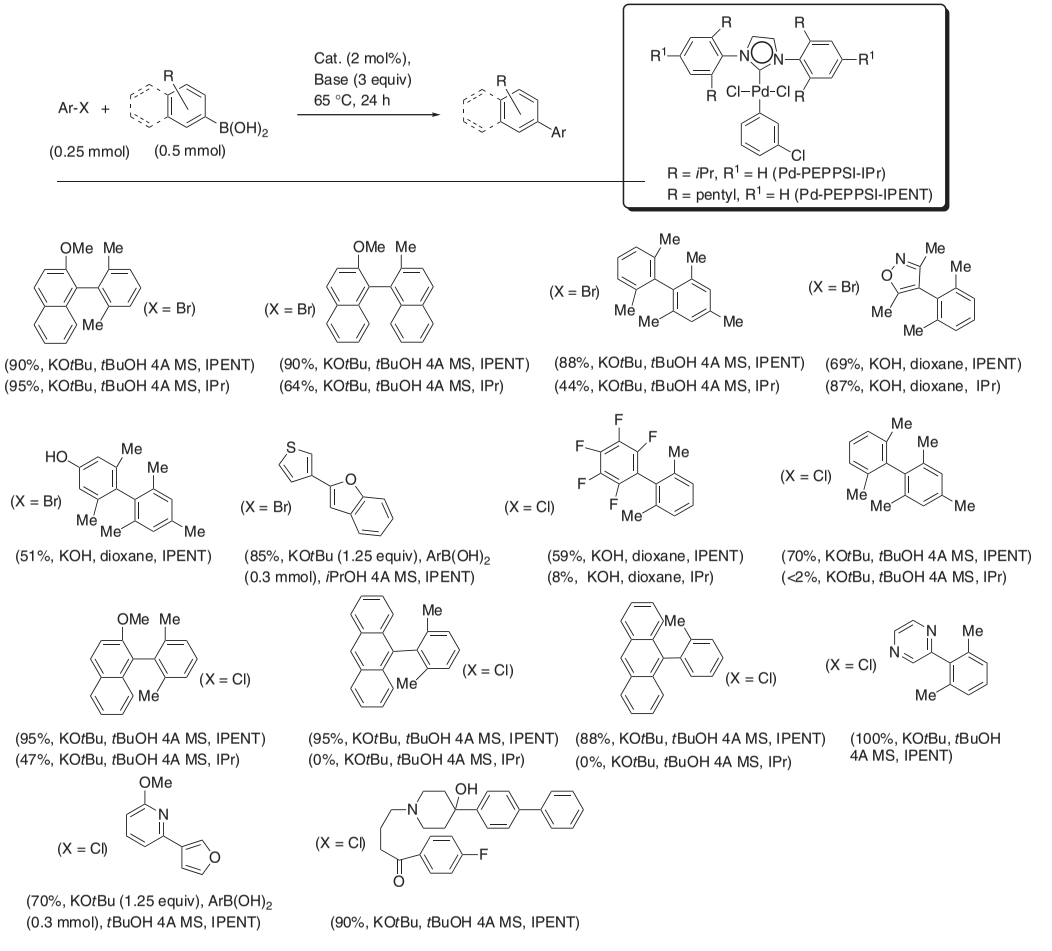


Figure 1.35 The application of Pd-PEPPSI catalysts developed by Organ *et al.* [54, 116].

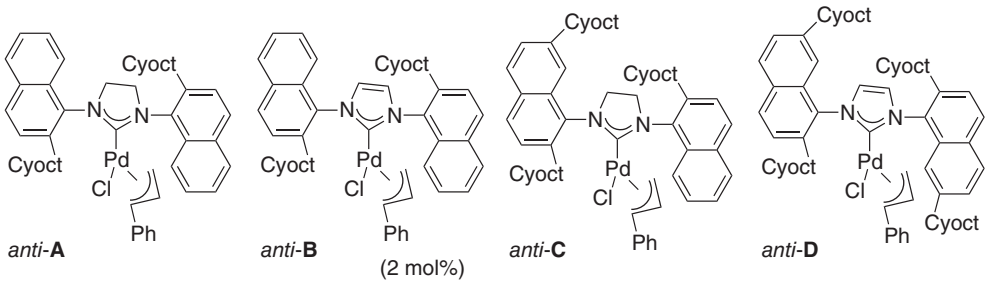


Figure 1.36 The Pd-NHC(allyl) catalysts developed by Dorta and coworkers [118].

obtained with the latter, more hindered catalyst, and for this reason, they decided to investigate the more bulky Pd-PEPPSI-IPent catalyst [54, 116a]. Using calculations, these workers have shown that by increasing the steric bulk, it appears that although the oxidative addition is not altered, the metal–metal exchange and the reductive elimination are affected [54, 116a].

They also coined the phrase "flexible steric bulk" used to refer to the fact that, for effective cross-coupling reactions, a sterically demanding yet conformationally flexible environment seems to be required [54, 116a]. The reaction showed very good scope with the Pd-PEPPSI-IPENT catalyst that incidentally was compared with the Pd-PEPPSI-IPr catalyst (Figure 1.35). Some very good yields were obtained, and generally, the Pd-PEPPSI-IPENT catalyst was better than the Pd-PEPPSI-IPr catalyst. The beauty of this methodology was that it gave tetra-*ortho*-substituted products in good yield.

Given the enormous industrial potential of this procedure, this group has patented the technology [117].

Dorta's group [118] in 2011 reported a similar methodology, in their case, they used a series of proprietary-saturated NHC ligands bearing naphthyl-derived side chains, and formed the catalysts by coordinating them with Pd and an allyl group (Figure 1.36). Four anticonfigured single isomers were prepared and screened in the Suzuki–Miyaura reaction with bromoarenes and chloroarenes. This protocol allowed for the synthesis of tetra-*ortho*-substituted biaryls in very good yields. The conditions were somewhat analogous to those of Organ's group, and very good yields could be achieved.

A team at BASF also developed a series of NHC-metal catalysts that have also been used in this reaction [119]. The catalysts that are included here are Au(I)-NHC and Pd(II)-NHC complexes, containing isonitrile ligands (Figure 1.37). Although some results for the performance of the latter ligands were included in the patent (generally good under very mild conditions – room temperature and at a loading of only 0.1 mol%!!!), the results for the former catalysts were not.

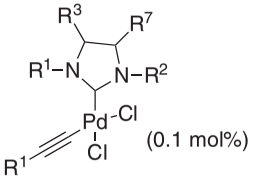
Another interesting catalytic system that has recently been introduced by Trzeciak and Albrecht is the PEPSI-type palladium complex containing basic 1,2,3-triazolylidene units [120] (Scheme 1.41). The actual synthesis of this family of catalysts was very interesting, involving click chemistry. Unfortunately, only three reactions were performed with one of them (R = Et, R^1 = Ph, Scheme 1.41) at a loading of 1 mol% and the best yield was 80%, and thus the reaction scope with these catalysts was not demonstrated.

The use of these types of ligands was reviewed very recently by Albrecht [121].

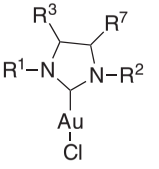
In 2012, Huang *et al.* reported the preparation and evaluation of another set of PEPPSI-type-triazol-5-ylidene Pd complexes that were successfully evaluated in the Suzuki–Miyaura reaction (Figure 1.38) [122]. The reactions – which were generally of a very short duration, 2–3 h – were carried out on chloroarene substrates, using 0.5 mol% of catalyst at room temperature and the yields ranged from 72% to 99%. The scope of these catalysts was clearly demonstrated.

In 2013, Azua *et al.* reported an interesting ultrasound-promoted Suzuki–Miyaura reaction using PEPPSI-type catalysts (Figure 1.38) [124]. These authors' credo, which is mentioned right at the start

Bromobenzene with 2,5-dimethylphenylboronic acid
with KO*t*Bu (base) at rt for 12 h



Au(I)-NHC



Specific examples of prepared complexes

R^1 = 2,6-$Me_2C_6H_3$, R^2 = *i*Pr, R^3 = R^7 = H (77%)
R^1 = 2,6-$Me_2C_6H_3$, R^2 = Cy, R^3 = R^7 = H (84%)
R^1 = 2,4,6-$Me_3C_6H_2$, R^2 = Cy, R^3 = R^7 = H (80%)
R^1 = 2,6-*i*$Pr_2C_6H_3$, R^2 = *i*Pr, R^3 = R^7 = H (79%)
R^1 = 2,6-*i*$Pr_2C_6H_3$, R^2 = Cy, R^3 = R^7 = H (81%)
R^1 = 2,6-*i*$Pr_2C_6H_3$, R^2 = Cy, R^3 = Ph, R^7 = H (83%)

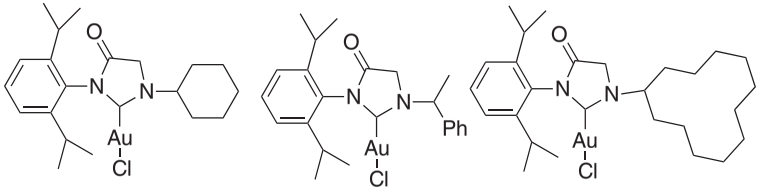
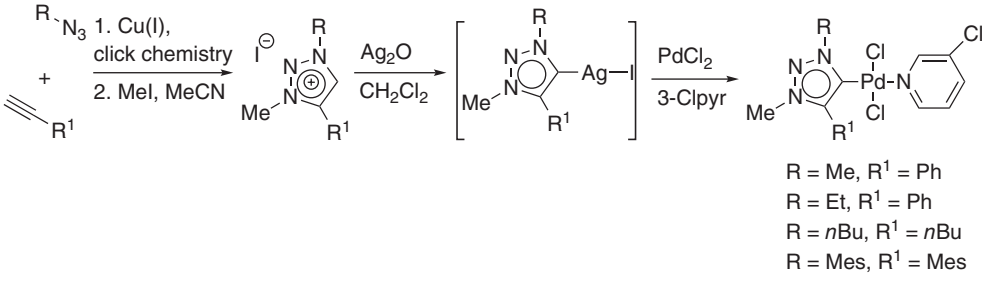


Figure 1.37 The Pd(II)- and Au(I)-NHCs reported by Hashmi and Lothschütz for the Suzuki–Miyaura reaction [119].



Scheme 1.41 The PEPPSI-type Pd complexes developed and used for the Suzuki–Miyaura reaction by Canseco-Gonzalez *et al.* [119].

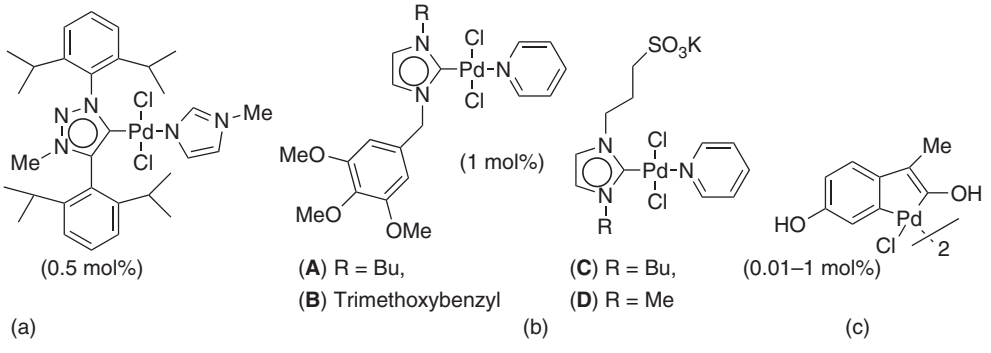


Figure 1.38 (a) The PEPPSI-type-triazol-5-ylidene Pd catalyst reported by Huang *et al.* [121], (b) by Azua *et al.* under ultrasound conditions in glycerol [122], and (c) the 4-hydroxyacetophenone oxime-derived palladacycle reported by Alacid and Nájera [123].

of the paper, is "benign by design," and for this reason, they have used glycerol, a renewable resource, as their reaction medium. However, the main motivation for this paper has come from two seminal papers by Wolfson [124]. The reaction afforded a number of interesting products with good to high yields under relatively mild conditions (40 °C) and a catalyst loading of 1 mol%. An example of this reaction is included in the experimental section below. Pulsed ultrasound is a promising activation technique for developing new catalytic processes in glycerol. Out of interest, it was shown that this microwave technique afforded superior yields to those obtained with normal oil baths.

In 2008, Alacid and Nájera reported the use of an oxime-derived palladacycle in the Suzuki–Miyaura reaction (Figure 1.38) [123]. The reaction was carried with both aryl and heteroaryl chlorides with potassium aryltrifluoroborates using K_2CO_3 as base and TBAB as additive in refluxing water under conventional and microwave heating. It should be noted that this group was the first to report the Suzuki–Miyaura reaction of aryl chlorides with arylboronic acids in water with the same catalyst. Water was used as the solvent as it was envisaged that it would facilitate hydrolysis of the potassium aryltrifluoroborates to aryl boronic acids, and thus increase the reactivity. The yields were generally good, and nitrogenated heterocyclic chlorides, for example, 3-chloropyridine, 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone, and 2,4,6-trichloropyrimidine, were transformed to their mono-, di-, and tri-phenylated products.

Phosphane ligands have traditionally been the ligand of choice in the Suzuki–Miyaura reaction [27] before NHC ligands started an intense rivalry with them. Over the last number of years, the phosphanes developed by Buchwald's group [125] were shown to be very useful. They used two biphenyl-*o*-phosphanes (Figure 1.39a) that were used with $Pd(OAc)_2$ for the arylation of aryl chlorides and

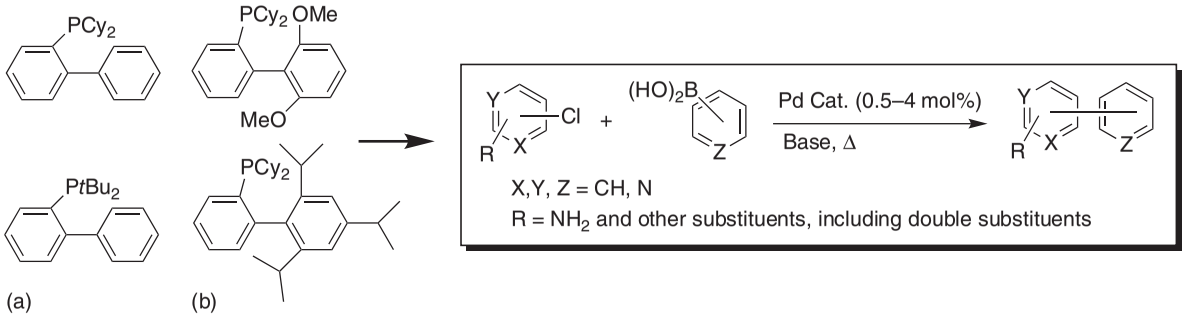


Figure 1.39 (a) The-first generation hindered phosphanes developed by Buchwald's group [126] and (b) the second generation phosphanes developed by Buchwald's group for coupling with heteroaryl compounds [126].

bromides under room-temperature conditions. In the case of the cyclohexyl-substituted phosphane loadings of only 0.000001–0.02 mol% of catalyst could be used, whereas with the *tert*-butyl derivative, the loading was between 0.5 and 1 mol%. The yields of products were very good, and the process tolerates a broad range of functional groups and substrate combinations including the use of sterically hindered substrates.

This group more recently developed other hindered phosphanes (Figure 1.39b) that were used in the Suzuki–Miyaura coupling reaction of heteroaryl compounds [126]. Heterocyclic compounds, but notably, nitrogen-containing heterocycles, are pervasive in medicinal chemistry. Both substituted pyridyl chlorides, pyrazine chlorides, benzopyrazine chlorides and substituted 2-chlorothiophenes and 2-bromothiophenes were used as substrates, and arylboronic acids, including pyridyl, pyrrole, and indole boronic acids and pinocol esters (in the case of the pyrrole organoboron reagents), were investigated. The yields were excellent, the only downside was the high temperatures that were needed (100 or 120 °C).

Interestingly, in 2006, Fu and coworkers [127] reported a similar Suzuki–Miyaura reaction of heterocyclic boronic acids with chloroarenes, bromoarenes, and iodoarenes. This group used the simple, low-cost phosphane, PCy_3, in their reactions, and they achieved spectacular results, for example, they could react 3-pyridineboronic acid with 4-butylchlorobenzene with $Pd_2(dba)_3$ (1 mol%)/PCy_3(4.2 mol%)/K_3PO_4/dioxane/water at 100 °C to give the 3-(4-butylphenyl)pyridine in a yield of 92%. An array of nitrogen heterocycles was studied.

In 2001, Fu's group [128] reported the application of Pd-triarylphosphane-ferrocene catalysts for the Suzuki–Miyaura reaction on aryl chloride substrates (Figure 1.40a). Activated aryl chlorides could be coupled at room temperature, while unactivated aryl chlorides, including sterically hindered and electron-rich substrates, at 70 °C. The triarylphosphane – which is air stable – was mixed with either $Pd_2(dba)_3$ or $Pd(OAc)_2$ with $K_3PO_4 \cdot H_2O$ as base in toluene at room temperature, and very good yields were obtained.

After a preliminary report [129], in 2006, Adjabeng *et al.* [130] reported the synthesis and application of novel phospa-adamantane ligands for the Pd-catalyzed Suzuki–Miyaura reaction. These compounds were originally reported by Epstein and Buckler in 1961 [132]. In this procedure, the phenyl derivative – 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane (Figure 1.40b) – was used in the arylation of aryl iodides, bromides, and activated chlorides with a variety of boronic acids at room temperature in a few hours with high yields. The ligand is comparable to P(*t*Bu)$_3$ [126] with

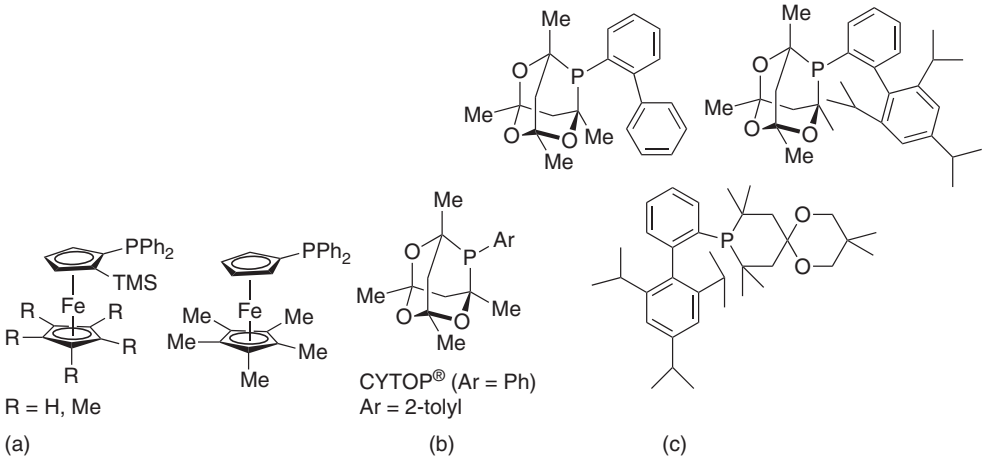


Figure 1.40 (a) The ferrocene-based ligands of Fu and coworkers [127, 128]. (b) The phospha-adamantane ligands of Adjaberg *et al.* [129, 130]. (c) The phosphacycle ligands used for Pd-catalyzed Suzuki–Miyaura reactions by Shashank *et al.* [131].

regard to reaction yield and conditions and could be recovered by chromatography on silica gel. It should also be noted that these ligands are effective for both the Sonogashira (see above) and the α-arylation of ketones (see Chapter 8).

In 2012, a group at Abbott laboratories submitted a patent application on the synthesis and application of a very similar family of phosphacycle ligands (Figure 1.40c) [132]. These ligands reputedly form Pd catalysts that catalyze the Suzuki–Miyaura reaction. A number of phosphacycle ligand examples were given, but only one example of a Suzuki–Miyaura reaction was given, in which, 1,2-dibromo-4,5-dimethoxybenzene was reacted with 2,4,6-triisopropylphenylboronic acid using Pd_2dba_3 (2 mol%) with the phosphatricyclo[3.3.1.1]decane, CYTOP® (4.8 mol%) and also previously reported to be used in the Pd-catalyzed Sonogashira reactions with aryl iodides and bromides [132], K_3PO_4 in THF/H_2O at 80 °C for 21 h, giving the product 2-bromo-2′,4′,6′-triisopropyl-4,5-dimethoxybiphenyl with a yield of 32% only! Some of the other ligands mentioned in the experimental part are shown in Figure 1.40c.

Configurationally stable chiral biaryls need at least three ortho substituents [133] and this leads to the question of the asymmetric Suzuki–Miyaura reaction. Yin and Buchwald [133], in 2000, used a number of binaphthyl-based phosphane ligands (traditionally phosphane ligands have been the most frequently used and we will see a lot of applications in the examples that follow). These workers managed to successfully obtain an enantioselective version (Figure 1.41), and enantioselectivities of up to 92% ee could be achieved, using the chiral electron-rich amino phosphane indicated in Figure 1.41. The catalyst loading ranged from 0.2 to 10 mol%. A cross-section of results is shown in Figure 1.41.

At the same time as Yin and Buchwald, Cammidge and Crépy [134] also reported on the asymmetric Suzuki–Miyaura reaction; they used a variety of chiral ligands, including (*R*)-(+)-BINAP, (*R*)-(+)-BINAM (2,2′-Bis(diphenylphosphinoamino)-1,1′-binaphthyl), monophosphane-ferrocene derivatives, and oxazoline binaphthalene ligands (Figure 1.42a). $PdCl_2$ was used as the precatalyst and a highest enantioselectivity of 85% ee was obtained with the ligand (*S*)-(*R*)-PFNMe.

In 2010, Zhang *et al.* [135] reported on the asymmetric Pd-catalyzed Suzuki–Miyaura coupling reaction. These workers, in an unprecedented report, used a family of chiral dienes (Figure 1.42b) to form the active catalyst with $PdCl_2(PhCN)_2$, the isolated catalyst was then used in the reaction with various bromoarenes and areneboronic acids with Cs_2CO_3 (2.5 equiv) as the base, to give axially chiral biaryls at room temperature in toluene with good to very good enantioselectivities (the highest enantioselectivity achieved was 90% ee with catalyst **D**, Figure 1.42b). It was necessary to include the preformed catalyst (at 5 mol% loading) and the chiral diene ligand (at a loading of 15 mol%).

One other ligand that should be mentioned is ClickPhos (Figure 1.42c), which was developed by Zhang's group [136]. It was used effectively at an optimal loading of 0.2 mol% with $Pd(dba)_2$ (0.1 mol%) using K_3PO_4 as the base and toluene as the solvent at 100 °C, yields as high as 99% were obtained, and the scope was good.

These ligands were also used for aryl chloride aminations (see Chapter 2).

Some key developments in the methodology or conditions of the Suzuki–Miyaura reaction have been reported in recent years. In 2006, Liu *et al.* [137] reported a ligand-free Suzuki–Miyaura reaction. What was remarkable about this reaction was that without added ligand, the reaction could be carried out with 0.5 mol% $Pd(OAc)_2$ and sodium carbonate as the base, at 35 °C in air, with water as cosolvent over 0.5–1 h, and give a plethora of compounds all in excellent yields. This methodology was also applied in consecutive multicoupling reactions to afford di- and tri-haloaromatics.

Another ligand-free Suzuki–Miyaura reaction methodology was reported by Tiffin and coworkers [138a] in 2001 and employs palladium(0) on carbon as the active catalyst with sodium carbonate as the base; it was used to arylate 4-bromomandelic acid, for which the corresponding biaryl derivatives were obtained in very good yields with enantioselectivities of >99% ee. Since this time, other groups have applied this methodology [138b]. It has also been applied in the process synthesis of a lead candidate (see below).

Traditionally, arylboronic acids have been used in the Suzuki–Miyaura reaction, but considering the fact that arylboronic acids do not participate in the transmetallation process, different types of borate complexes have been devised. In 2006, Cammidge's group [139a] reported the application

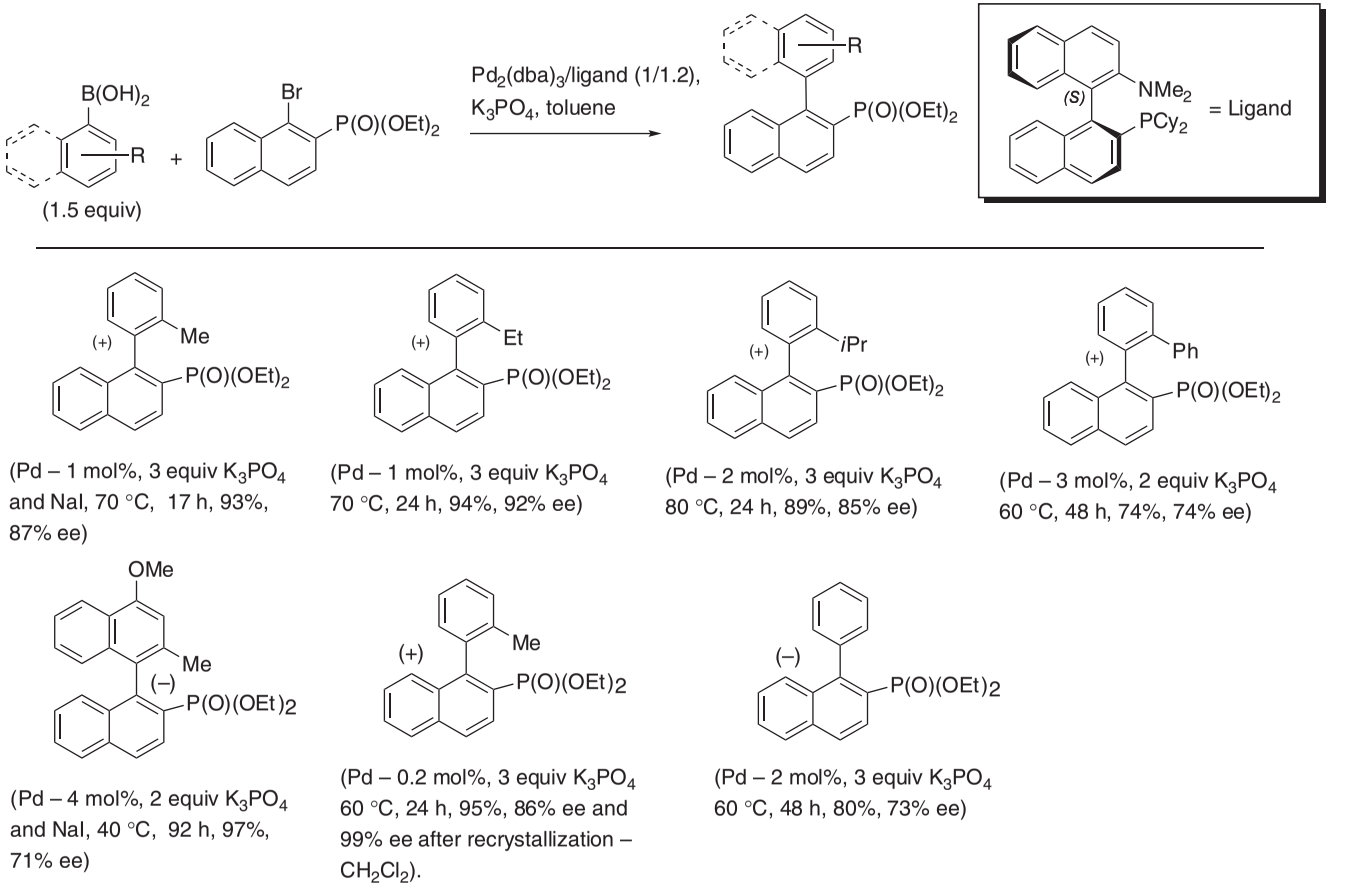


Figure 1.41 The asymmetric Pd-catalyzed Suzuki–Miyaura reaction reported by Yin and Buchwald [133].

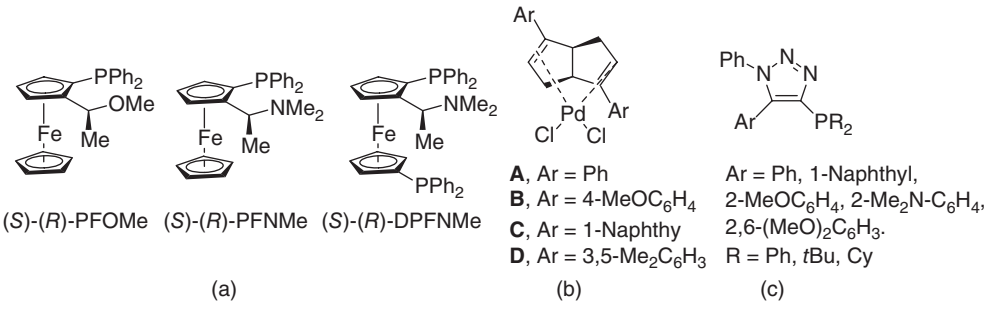


Figure 1.42 The ligands used by (a) Cammidge and Crépy [134], (b) Zhang *et al.* [135], and (c) Zhang's group [136] – ClickPhos.

of aryltrihydroxyborates in this reaction. The aryltrihydroxyborates were prepared by treating the corresponding boronic acid with NaOH in THF, the pure borate salt is isolated as a free flowing salt on filtering and drying under vacuum. The borate salts were successfully used in the Suzuki–Miyaura reaction, giving very good yields of product. The Pd catalyst used was $PdCl_2$(dppf) in toluene at reflux temperature. A cross-section of the isolated borate salts is shown in Figure 1.43a.

Molander and Shin [139b], in 2011, reported the synthesis and application of air-stable potassium Boc-protected aminomethyltrifluoroborate – a primary aminomethyl equivalent – which was then arylated via Suzuki–Miyaura coupling with a plethora of aryl halides (including aryl chlorides; Figure 1.43b) giving the arylated products in very good yields.

Please note that there have been a number of reports in the literature on the direct Suzuki–Miyaura reaction [140]; as this is basically a C–H activation process, we have decided to include this in Chapter 4, which deals with C–H activation facilitated arylations.

To conclude this part of this section, we include an interesting study that was reported in 2012 by Ikawa *et al.* [141], in which phenols treated with nonafluorobutenesulfonyl fluoride (where Nf = $SO_2(CF_2)_3CF_3$) underwent the Suzuki–Miyaura reaction in moderate yields under palladium catalysis ($Pd(OAc)_2$ or $Pd_2(dba)_3$), using SPhos as the ligand and a weak base. The reaction proceeds through nonaflation of the phenols, that is, via an activated nonafluorobutanesulfonyl intermediate.

Let us now consider some key synthetic applications of the Suzuki–Miyaura reaction in recent years. In the case of the synthesis of pharmaceuticals, this reaction has played a very prominent role. The excellent review by Magano and Dunetz [12k] describes many interesting examples of the application of this reaction in this industry. In our case, the following examples are particularly interesting and relevant.

In 2009, a group at Amgen reported the multi-kilogram-synthesis of a phthalazine derivative, which is a p38 MAP kinase inhibitor for the treatment of rheumatoid arthritis, Crohn's disease, and psoriasis (Scheme 1.42) [142]. The Suzuki–Miyaura reaction was the key reaction in this synthesis, $Pd_2(dba)_3$/SPhos was used as the catalyst system, and sodium carbonate in aqueous ethanol as the solvent system at 80 °C for 17 h. The coupled product (about 5 kg) was obtained with a yield of 90% and an enantiopurity of 99.8% ee. The beauty of this protocol was that the final product could be crystallized from the reaction mixture by adding water; this purged the *p*-toluic acid product and the Pd, as well as upgrading the optical purity of the drug intermediate. During the optimization studies, other bases were used, for example, dicyclohexylamine, but the reaction workup and product isolation were hampered.

A team at Merck, in 2005, used the Suzuki–Miyaura reaction as a key step in the synthesis of an orally active α2/3-selective GABAA (Gamma-aminobutyric acid receptor) agonist candidate for the treatment of central nervous system conditions (Scheme 1.43) [143]. The biaryl product was crystallized from water/*i*-PrOH in 85% and it had a purity of 96.3% (HPLC).

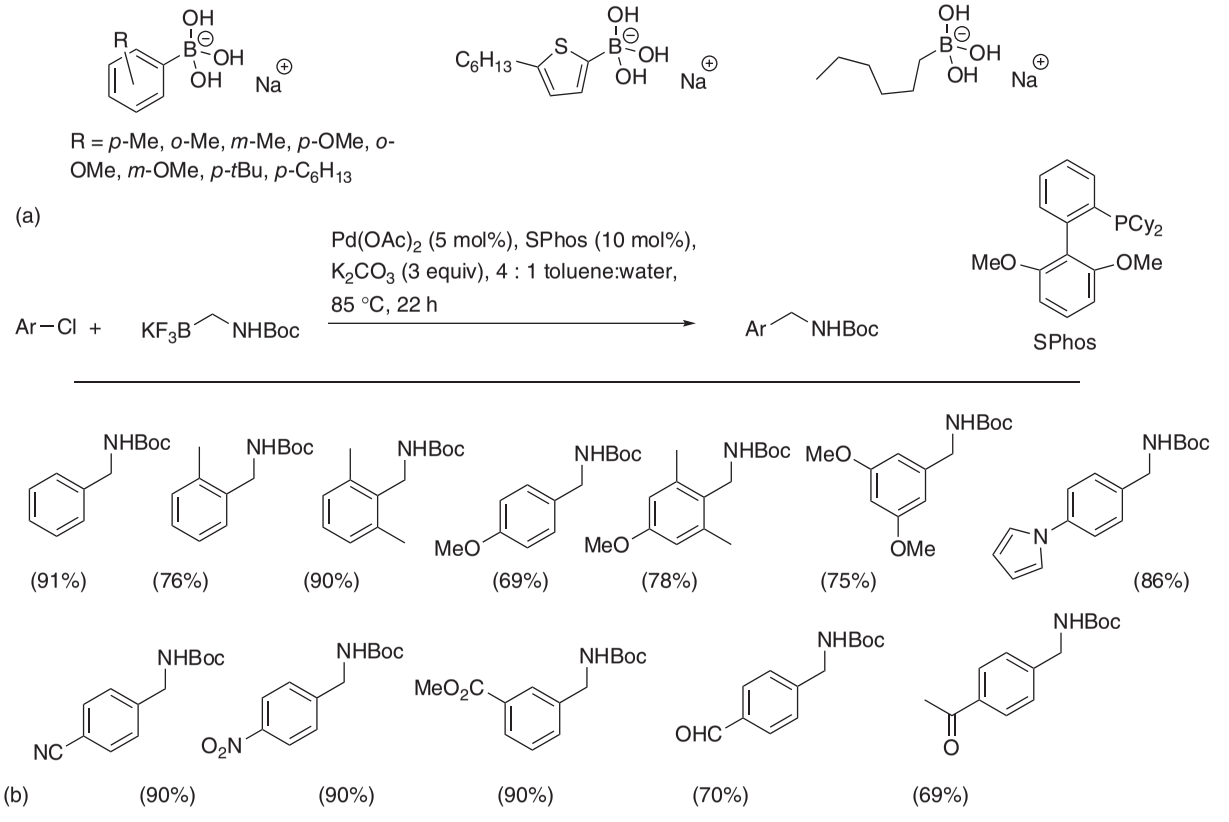
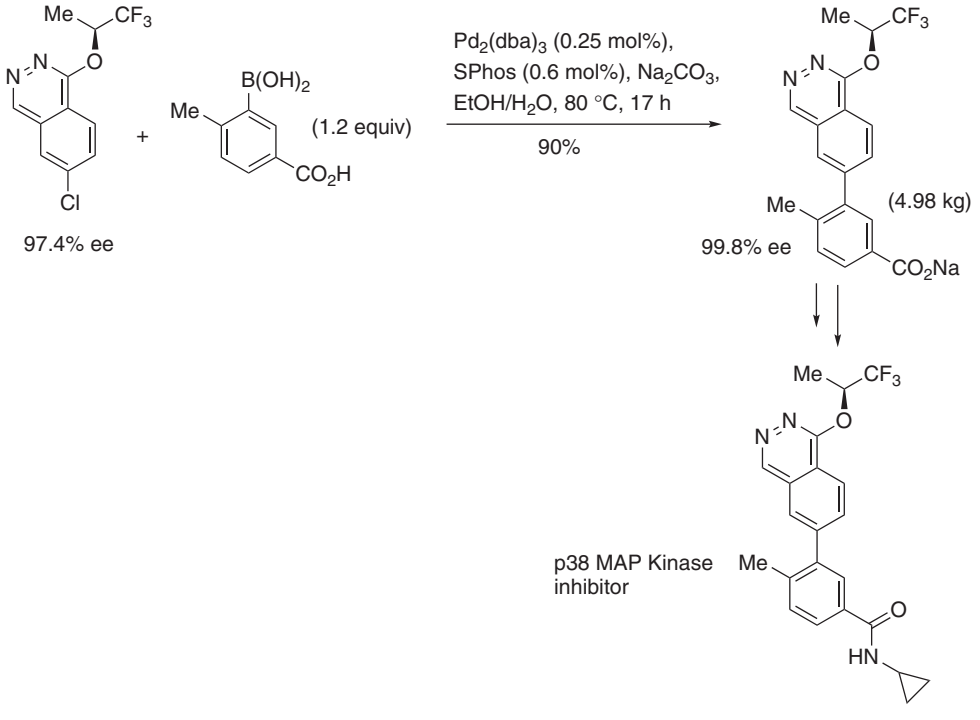
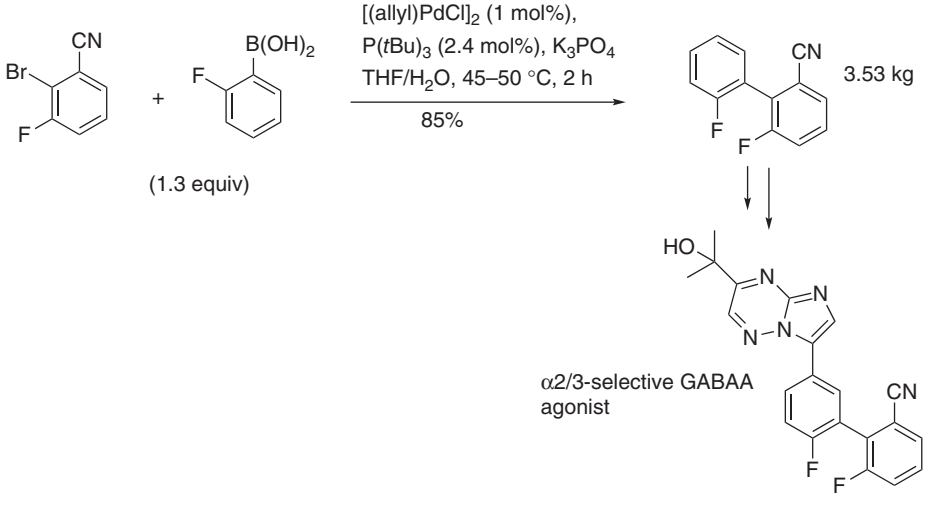


Figure 1.43 (a) The aryltrihydroxyborates and alkyltrihydroxyborates synthesized by Cammidge and coworkers [139a] and (b) Suzuki–Miyaura reaction with Boc-protected aminomethyltrifluoroborate reported by Molander and Shin [139b].

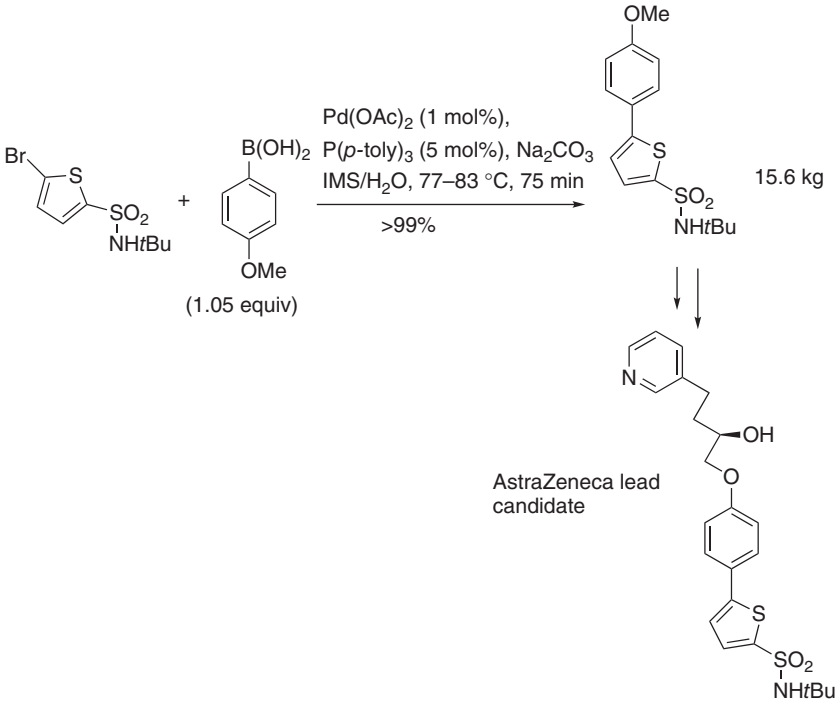


Scheme 1.42 Amgen's multi-kilogram synthesis of the MAP kinase inhibitor p38 [142].



Scheme 1.43 Merck's multi-kilogram synthesis of an α2/3-selective GABAA agonist candidate p38 [143].

A team at AstraZeneca, in 2009, used this reaction to access ~16 kg of a key biaryl intermediate that led to a candidate for the treatment of inflammatory and allergic conditions such as asthma and rhinitis (Scheme 1.44) [144].

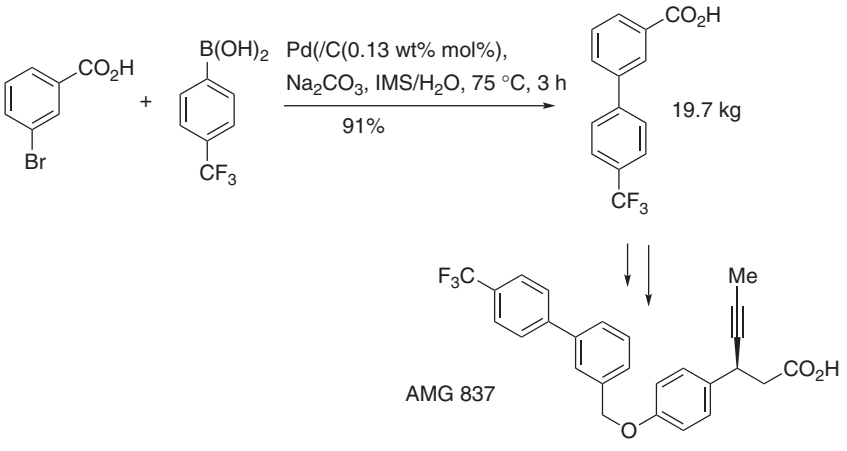


Scheme 1.44 AstraZeneca's multi-kilogram synthesis of a key lead candidate for asthma and rhinitis [144].

The best catalyst combination was $Pd(OAc)_2/P(p\text{-tolyl})_3$ (1/5 mol%). The product was precipitated by the addition of water at the end, which was then isolated by filtration. The level of homocoupling product was kept below 1% on the laboratory scale and even lower on pilot-plant scale. The Pd residue was between 2000 and 3000 ppm, but was lowered to acceptable levels downstream.

In 2011, Faul and her team [145] at Amgen reported a scalable synthesis of the G-protein-coupled receptor GPR40 agonist AMG 837 (this protein amplifies glucose-stimulated insulin secretion and lowers plasma glucose concentrations in multiple animal models) which is a potentially new therapeutic agent for type-2 diabetes treatment, and where a Suzuki–Miyaura reaction was used as the key step. The Suzuki–Miyaura reaction was accomplished at large scale using *m*-bromobenzoic acid and *p*-(trifluoromethyl)phenylboronic acid (Scheme 1.45) using palladium on carbon – the method introduced by Tiffin and coworkers and others [138a] and sodium carbonate in IPA/water (isopropylalcohol) at 75 °C for 3 h. Using this process, an ~20 kg batch of Suzuki–Miyaura product was obtained, with a purity of >99%, including a bulk density of 0.2 g ml^{-1}.

Palladium removal is a perennial problem when the Pd-catalyzed Suzuki–Miyaura reaction is used in the chemical industry. A group at GlaxoSmithKline have tried to address this issue [146]. In their drug discovery program leading to the key synthetic intermediate, ethyl 3-[4-(1,1-dimethylethyl)phenyl]-1*H*-indole-2-carboxylate, which involved the synthesis of a biaryl compound



Scheme 1.45 The key Suzuki–Miyaura reaction in Amgen's multi-kilogram synthesis of a GPR40 receptor agonist [145].

on a 20-l scale, they discovered that by using $NaHSO_3$ at elevated temperatures they could lower the Pd content from about 8000 to <100 ppm.

The Suzuki–Miyaura reaction has been used with significant effect in the field of chemical biology. In 2013, Cahová and Jäschke [147] reported the remarkable synthesis and application of nucleoside-based diarylethene photoswitches.[6] As the conditions of Omumi *et al.* did not work, conditions for the derivatization of sensitive nucleoside triphosphates with the arylboronic acid, 3,3′,3″-phosphanetriyltris(benzenesulfonic acid) trisodium salt (sodium triphenylphosphane trisulfonate) (TPPTS) as the ligand, $CsCO_3$, water/acetonitrile, and the reaction worked, affording a variety of different modified oligionucleotides (15- and 19-mers) bearing one or two photoswitchable groups (see Table 1.3 for a cross-section of results). The yields were only moderate, and this was on account of (i) steric hindrance – the coupling at terminal positions was more efficient than coupling at internal positions and (ii) dehalogenation side reactions taking place.

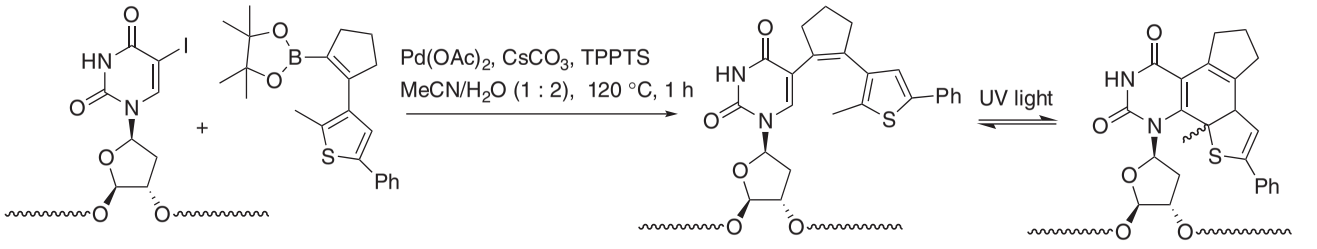
Other workers in the field have used the Suzuki–Miyaura reaction for making fluorescent analogs of nucleotides; in the case of Fairlamb and coworkers, they have prepared novel rigid 8-biaryl-2′-deoxyadenosines with tunable fluorescent properties [149].

In 2013, Davies and Schofield [150] took this a step further, and actually carried out this reaction under biologically benign conditions (37 °C, pH 8.5) with oligiodeoxynucleotides and boronic acids, $Pd(OAc)_2$ and 2-aminopyrimidine-4,6-diol or its *N,N*-dimethylated analog as the ligands. An 80% yield of coupled product could be obtained with a Pd loading of 5 mol%. They were able to generate DNA-bearing multiple modification types, including sensitive reporter modifications (for example, photocross-linkers) combined with sensitive natural modifications (for example, 5-hydroxymethylcytosine) as probes for DNA-protein interactions.

In 2008, Barluenga's group [151] reported the arylation of phenylalanine and tyrosine units of unprotected peptides using the Suzuki–Miyaura reaction. The reactions were performed on a series of six different iodinated peptides using two types of potassium aryltrifluoroborate reagents (see Table 1.4). The robustness and applicability of this methodology was further demonstrated by this group, when they successfully conducted a one-pot sequential iodination (with bis(pyridine)iodonium tetrafluoroborate-IPy_2BF_4) of a tyrosine unit in a variety of small peptides. This was applied to the synthesis of Leu-enkephalin.

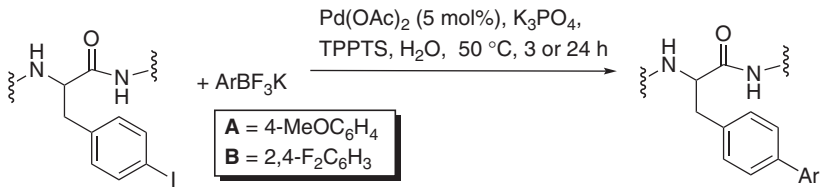
6) At the time of submission of this manuscript there had only been one other report on the Suzuki–Miyaura reaction of oligionucleotides and that was of Omumi *et al.* [148].

Table 1.3 The sequences of oligonucleotide substrates for the Suzuki–Miyaura reactions [147].



Oligo	Substrate	Yield (%)
15mer-dU^{PS}1	5′-AGCAACA**IU**CGATCGG-3′	25
15mer-dU^{PS}2	5′-**IU**GCAACATCGATCGG-3′	26
15mer-dU^{PS}3	5′-AGCAACA**T**CGATCG**IU**-3′	25
19mer-dU^{PS}1	5′-TCTAATACGACTCAC**IU**ATA-3′	20
19mer-dU^{PS}2	5′-TCTAATACGACTCACTA**IU**A-3′	19
19mer-dU^{PS}3	5′-TCTAATACGACTCAC**IU**A**IU**A-3′	16

Table 1.4 Pd-catalyzed Suzuki–Miyaura reactions on iodonated peptides in water [151].



Peptide	$ArBF_3K$	Conversion (time)
H–Tyr–Gly–Gly–4-I–Phe–Leu–OH	**A**	26% (24 h)
H–Tyr–Gly–Gly–4-I–Phe–Leu–OH	**B**	98% (24 h)
H–Gly–Gly–4-I–Phe–Leu–OH	**A**	92% (3 h)
H–Gly–Gly–4-I–Phe–Leu–OH	**B**	84% (3 h)
H–For–Met–Leu–4-I–Phe–OH	**A**	100% (3 h)
H–For–Met–Leu–4-I–Phe–OH	**B**	100% (3 h)
H–Tyr–Gly–Gly–4-I–Phe–Met–OH	**A**	52% (24 h)
H–Tyr–Gly–Gly–4-I–Phe–Met–OH	**B**	90% (3 h)
H–Tyr–D-Ala–4-I–Phe–Gly–Tyr–Pro–Ser–NH_2	**A**	82% (24 h)
H–Tyr–D-Ala–4-I–Phe–Gly–Tyr–Pro–Ser–NH_2	**B**	76% (3 h)
H–Met–Glu–Gly–His–4-I–Arg–Trp–Gly–OH	**A**	15% (24 h)
H–Met–Glu–Gly–His–4-I–Arg–Trp–Gly–OH	**B**	24% (24 h)

Queiroz and coworkers [152] have used this reaction for the efficient synthesis of 6-(hetero)arylthieno[3,2-*b*]pyridines (Figure 1.44) which have shown application in the growth inhibition of human tumor cell lines. The organoboron reagent varied between the pinacol boronic ester and potassium aryltrifluoroboronate salts, the yields were generally very good.

In 2010, Lipshutz's group [153] reported the synthesis of (+)-korupensamine via an atropselective intermolecular Suzuki–Miyaura coupling reaction, the study was very interesting as the stereocontrol (atropdiastereoselectivity – ratio of M to P axial isomers [154]) in the reaction was proposed to be controlled by π-stacking[7] [155]. These workers managed to achieve a highest selectivity of 11 : 1 (M:P) using the conditions shown in Scheme 1.46. This adduct was then converted to the target compound.

In the realm of electronic materials, the Suzuki–Miyaura reaction has been very useful. In 2005, Nehls *et al.* [156] reported the preparation using microwave irradiation of a cruciform-type π-system for opto-electronic applications, using the Suzuki–Miyaura reaction as the key step (Scheme 1.47).

One-pot reaction sequences comprising the Suzuki–Miyaura reaction as a key step are also common, basically, as they represent sustainable processes. Some useful recent examples include the work of Wang *et al.* [157], which involved a one-pot borylation/Suzuki–Miyaura reaction. Various biaryl compounds (up to 37) were obtained in good to excellent yields. Both bromoarenes and chloroarenes were used, including heteroaryl halides. The catalyst involved was a cyclopalladated ferrocenylimine and bis(pinacolato)diboron, the boron transfer agent. The reactions were performed at 100 °C.

Chai and Lautens [158] reported in 2009 an elegant tandem Pd-catalyzed Suzuki–Miyaura/direct arylation reaction (Scheme 1.48). A wide range of aryl, alkenyl, and alkyl boronic acids were screened. The reactions were performed using *gem*-dibromovinyl substrates, which were catalyzed by SPhos, and gave *N*-fused heterocycles. Water was found to accelerate the reaction. The mechanism is quite involved, and we will not go into it here, but first indications are that the Suzuki–Miyaura reaction occurring before the direct arylation.

7) Some years ago, one of us suggested the relevance of π–π effects in the diastereoselectivity of an aldol reaction; Ref. [155].

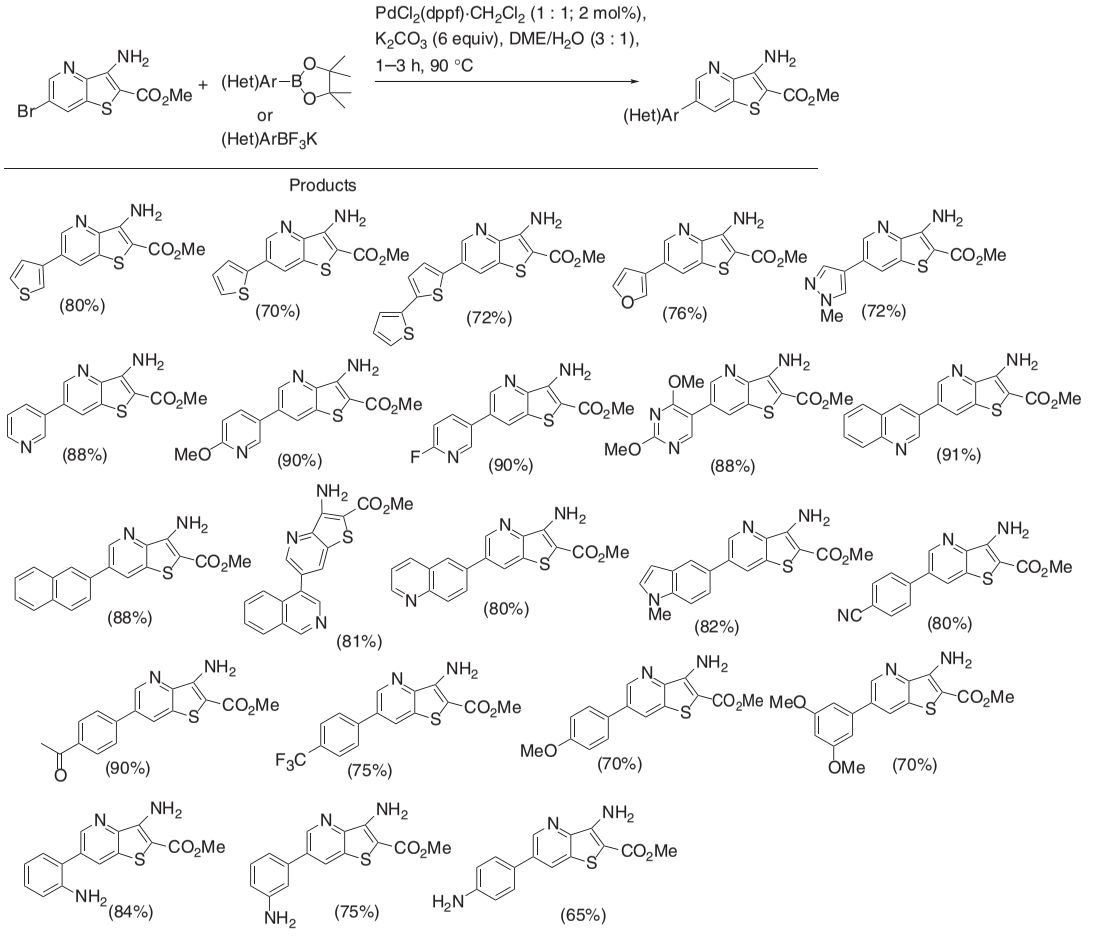
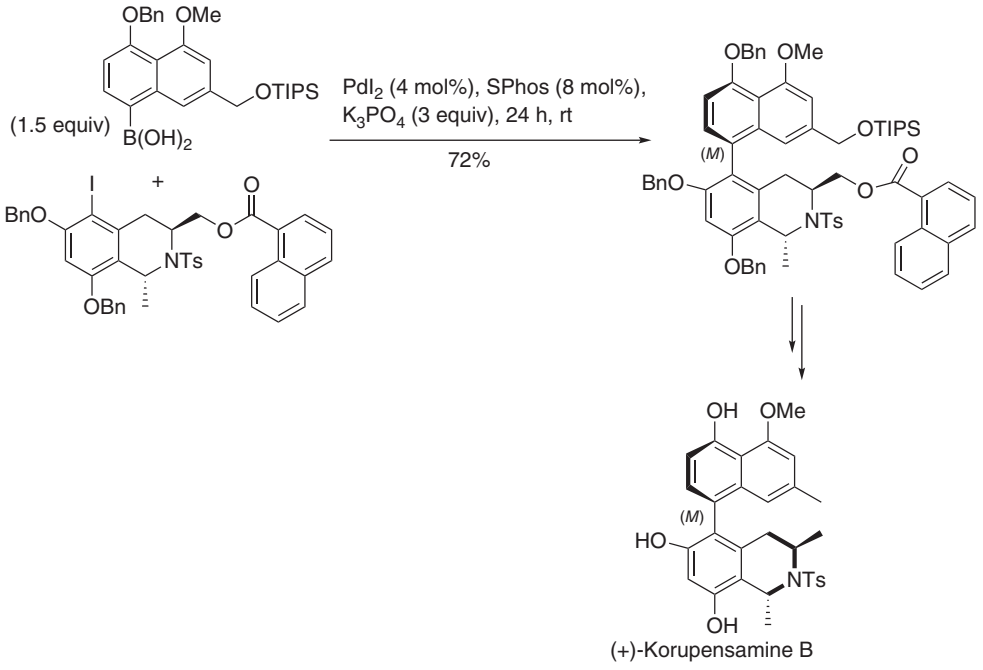


Figure 1.44 The library of 6-(hetero)arylthieno[3,2-*b*]pyridines synthesized by Queiroz and coworkers [152].

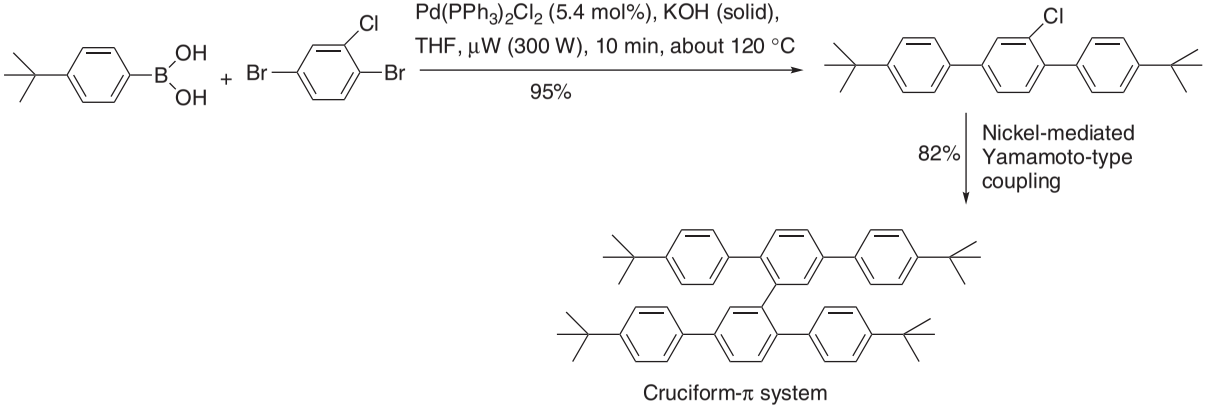


Scheme 1.46 The synthesis of (+)-korupensamine via an atropselective intermolecular Suzuki–Miyaura coupling reaction by Lipshutz's group [153].

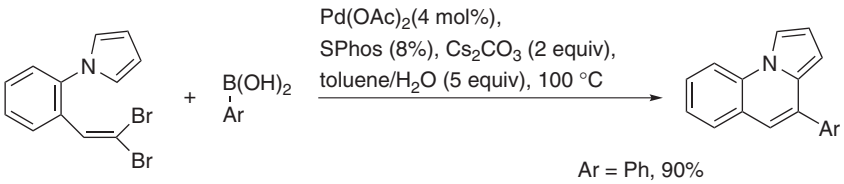
The issue of metal contamination is a big concern for the pharmaceutical industry, and thus is critical for the Suzuki–Miyaura reaction that is heavily used. A team at Johnson Matthey Catalysis has developed tunable palladium-FibreCats for the aryl chloride Suzuki–Miyaura reaction [159]. A variety of tunable polypropylene-supported Pd complexes were prepared using Q-Phos, $t\text{Bu}_3\text{P}$, $(\text{Me}_2\text{NC}_6\text{H}_4)\text{P}(t\text{Bu})_2$, and IPr-carbene, including some bidentate ligands such as BINAP, dppf, and dippf with a loading of 4–8% Pd. Both aryl chlorides and bromides were used and the conversions were quantitative in most cases. The TOFs were also good, with a highest of 200 h^{-1} being achieved with FC-1029, using *p*-bromoanisole with PhB(OH)_2. A lot of the catalysts were recycled a few times and no Pd leaching was detected. It should be noted that several big pharmaceutical companies, such as Abbott and Novartis, have also used such immobilized catalyst systems for their work with the Suzuki–Miyaura reaction [160].

We ourselves have an active program looking at the development of efficient sequential or dual catalytic processes leading to the construction of molecules containing the biaryl motif using the Suzuki–Miyaura reaction.[8] We have looked at a sequential one-pot imine arylation/Suzuki–Miyaura reaction to afford interesting biarylarylmethylamines, which are a key component of many interesting bioactive compounds such as Valsartan [8] (Diovan®) – an important angiotensin receptor blocker indicated for the treatment of high blood pressure, congestive heart failure, or post-myocardial infarction; the well-known glycopeptide antibiotic, Vancomycin, used for prophylaxis and treatment of infections caused by Gram-positive bacteria; telmisartan, which is an angiotensin II receptor antagonist that is highly selective for type-1 angiotensin II receptors and used to treat hypertension; and lotarsan used for the same reason (Figure 1.45). Then there is arylomycin-A2, an antibacterial compound originally isolated from *Streptomyces* strain TU6075. These units – particularly chiral

8) Marques, C.M., Locati, S., Ramalho, P.J., and Burke A.J. (2004), RSC Adv.



Scheme 1.47 The preparation of a cruciform-type π-system, using a Suzuki–Miyaura reaction by Nehls *et al.* [156].



Ar = Ph, 90%
Ar = 4-$MeOC_6H_4$, 76%
Ar = 2-$MeOC_6H_4$, 75%
Ar = 3,4-$(MeO)_2C_6H_3$, 71%
Ar = 4-ClC_6H_4, 62%
Ar = 4-$CF_3C_6H_4$, 62%
Ar = 2-FC_6H_4, 46%
Ar = 4-FC_6H_4, 86%
Ar = 3-Thiopheno, 67%
Ar = 1-Napthyl, 64%
Ar = 3-$TMSC_6H_4$, 74%
Ar = 2-MeC_6H_4, 87%
Ar = 2-PhC_6H_4, 45%
Ar = 4-$NHBocC_6H_4$, 74%
Ar = 2-MeO-4-FC_6H_4, 56%

Scheme 1.48 The tandem Pd-Catalyzed Suzuki–Miyaura/direct arylation reaction reported by Chai and Lautens [158].

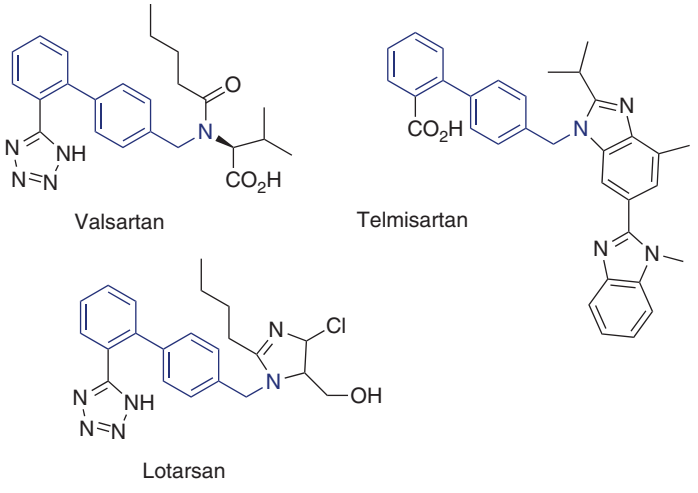
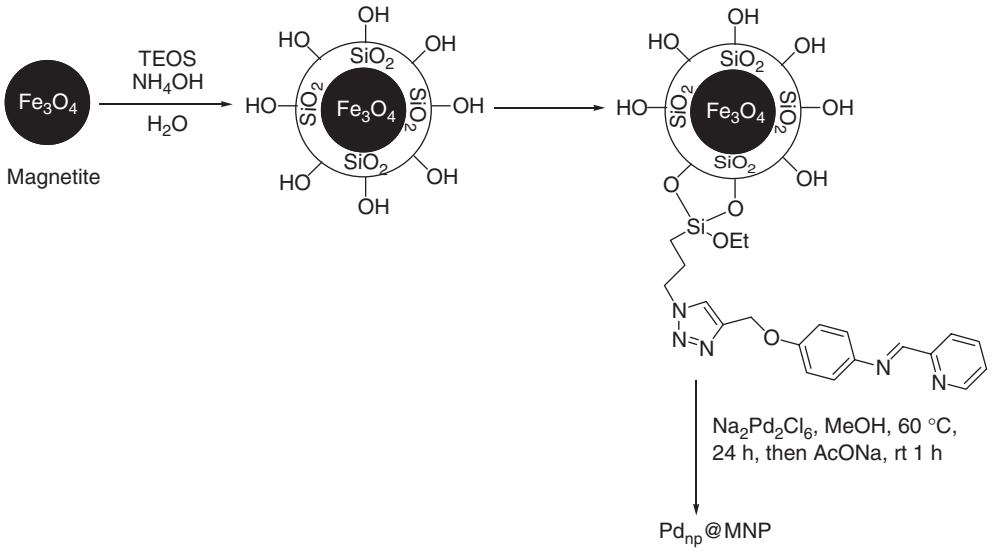


Figure 1.45 Some interesting molecules containing the biarylarylmethylamine unit.

ones – also are of interest for the construction of certain electronic materials, such as liquid crystals [134].

In 2013, Zhang *et al.* [160] reported the use of a MNP-supported palladium catalyst for the Suzuki–Miyaura reaction (Scheme 1.49). It was used at a loading of 0.2 mol% for the arylation of aryl bromides with arylboronic acids under phosphane-free conditions. Some very good yields could be obtained.



Scheme 1.49 The synthesis of the magnetic nanoparticle-supported nano-palladium catalyst Pd_{np}@MNP by Zhang *et al.* [160].

To finalize this section, we mention a report by Christakakou *et al.* [162] in 2013 on the application of a simple Suzuki–Miyaura coupling reaction under continuous flow conditions with $Pd(PPh_3)_4$ as the catalyst. Note the reactor was of a simple, homemade construction, and the designs are given in the supporting information section of their paper.

1.3.7
Tamao–Kumada–Corriu Cross Coupling

This reaction has recently been reviewed by Knappke and von Wangelin [36] and Heravi and Hajiabbasi [163]. As mentioned above, the reaction was originally catalyzed by nickel catalysts, using aryl or alkyl halides (Kumada, Tamao, Corriu, and Massa), but then later, a palladium-catalyzed variant was developed by Murahashi's group [164]. In 2011, Liu and Wang [165] reported the use of amido pincer nickel complexes, the reactions proceeded at room temperature and could be used with a wide range of aryl chlorides. Heterochloro compounds could also be used very successfully (Figure 1.46).

Similar work was reported by Liang *et al.* [166] in 2012 by using an amido phosphane chelate with a pendant amine arm as a ligand to form a nickel complex. A variety of alkyl and arylmagnesium chlorides were coupled with iodoarenes, bromoarenes, and chloroarenes using these nickel complexes under mild conditions.

Ackermann's group [167] has also been active in this field and has conducted Tamao–Kumada–Corriu cross-couplings with 2-pyridyl Grignard reagents contrary to Liu and Wang [165] who used aryl Grignards. In this reaction, the catalyst was obtained by complexing $Ad_2P(O)H$ with a palladium source such as $[Pd_2(dba)_3]$ to form the active catalyst *in situ.* The 2-arylated pyridyl compounds were obtained in very good yields generally. To get insight into the structure of the active catalyst, palladium acetate was complexed with $Ad_2P(O)H$ to give a catalyst containing a self-assembled bidentate ligand according to Scheme 1.50. In fact, this bi-dentate-ligand-coordinated Pd catalyst itself showed remarkable catalytic activity in the cross-coupling of 2-pyridyl Grignard reagents. The loading was lower in this case (1 mol% as opposed to 4 mol% in the *in situ* case).

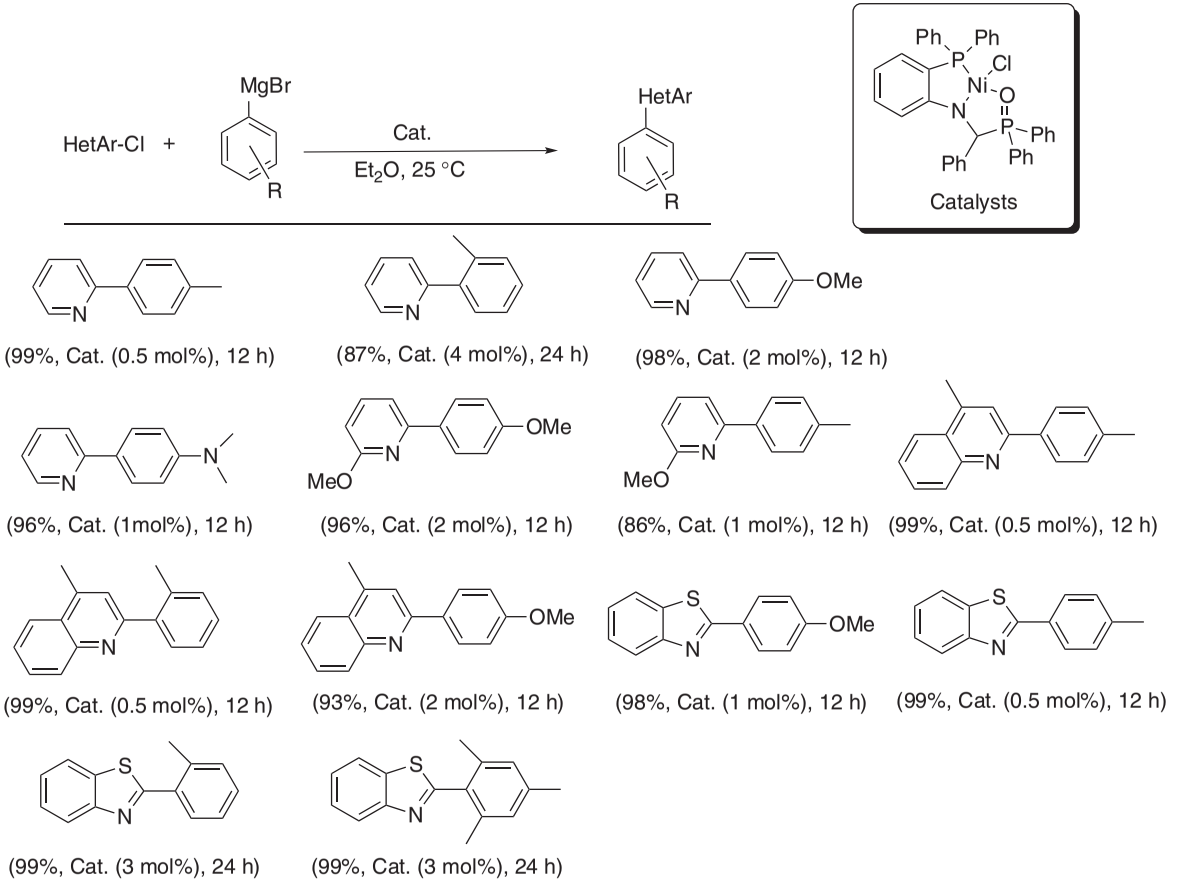
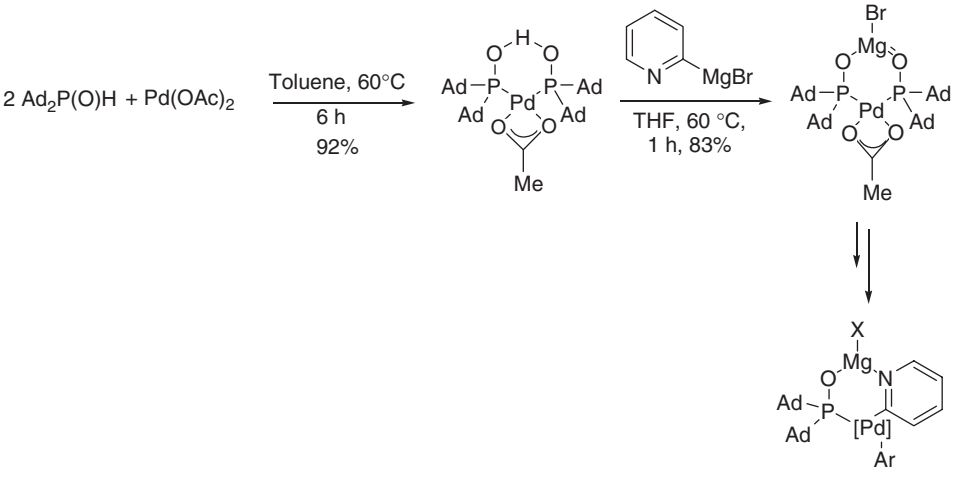


Figure 1.46 The Tamao–Kumada–Corriu cross-coupling of heteroaryl chlorides reported by Liu and Wang [165].



Scheme 1.50 Synthesis of a self-assembled palladium complex for the Tamao–Kumada–Corriu cross-coupling of pyridyl Grignard reagents reported by Ackermann and coworkers [167].

It should also be noted that these workers transformed the initial bridged palladium complex to a heterobimetallic complex with 2-pyridylmagnesium bromide, which is expected to form the diadamantylated pyridine complex (Scheme 1.50).

In 2013, Przyojski *et al.* [168] reported the application of Cobalt(II) NHC complexes. Overall, the conversions were rather moderate, but two examples of >98% were reported. The precatalyst that was investigated [$CoCl_2(IMes)_2$] (Figure 1.47) was prepared by reacting $CoCl_2$ with 2 equiv of IMes NHC ligand for 16 h at room temperature. The complex existed as a blue solid and was obtained in a yield of 83%.

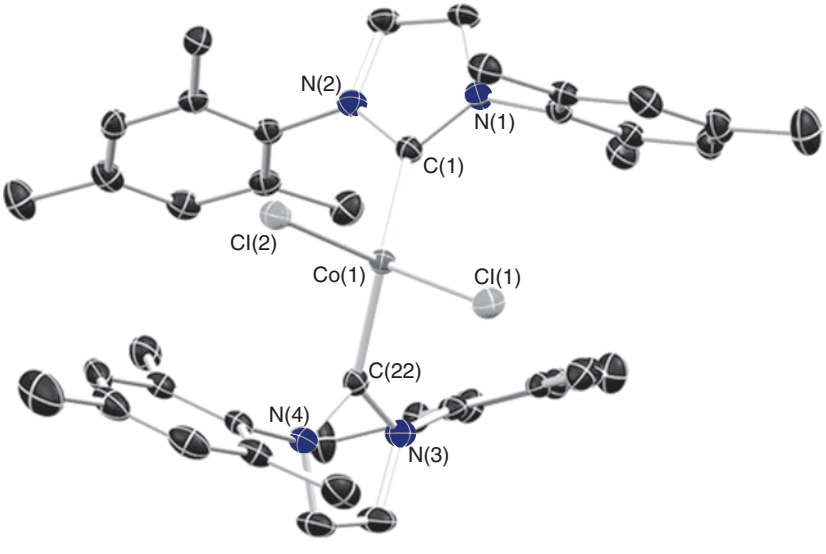


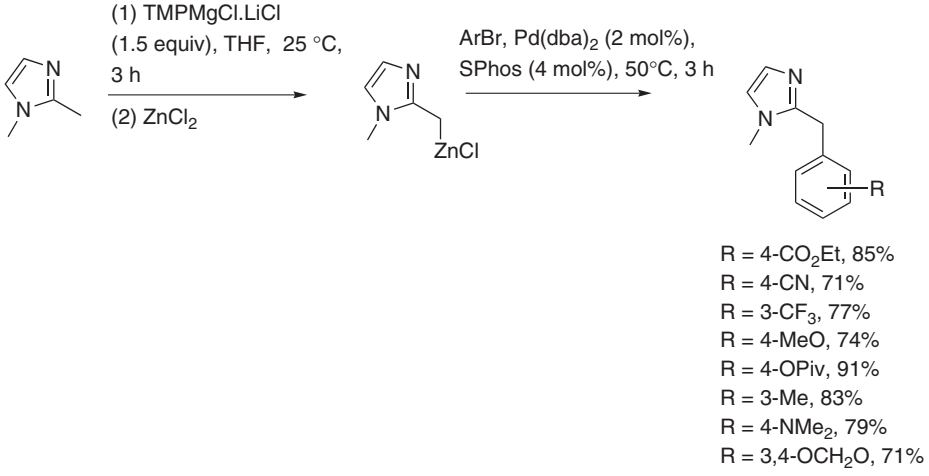
Figure 1.47 The X-ray structure of [$CoCl_2(IMes)_2$] as reported by Przyojski *et al.* [168]. (Reprinted with permission from the American Chemical Society, Copyright 2013, American Chemical Society.)

The Tamao–Kumada–Corriu reaction has also been carried out with supported catalytic systems. One interesting recent example has been the use of a multichannel microreactor to perform this reaction [169]. The glass microreactor was designed so as to increase the catalytic surface area and ensure a uniform distribution of the velocity/temperature field. The sol–gel procedure was used to immobilize the nickel catalyst to the channel walls. The Tamao–Kumada–Corriu reaction was conducted using bromobenzene and phenylmagnesium bromide, and was also carried out in the batch configuration for comparison, and it was observed that the reaction in-flow was four orders of magnitude more rapid than that performed under batch conditions and there was a threefold increase in the yield of the biaryl compound.

1.3.8
Negishi-Baba Cross-Coupling

This is another very useful cross-coupling reaction that relies on organozinc reagents with Pd catalysts. Some key highlights during recent years are discussed in the following paragraphs.

Knochel's group has been active in this field [170]. In 2012, the group published a report on the arylation of 2-methyl-5-membered heterocycles with 2,2,6,6-tetramethylpiperidyl (TMP) bases [170]. This had been, until then, an unsolved problem. In this report, 1,2-dimethylimidazole was converted to its zincated product and this was coupled with a variety of aryl bromides using $Pd(dba)_2$ and SPhos (Scheme 1.51).

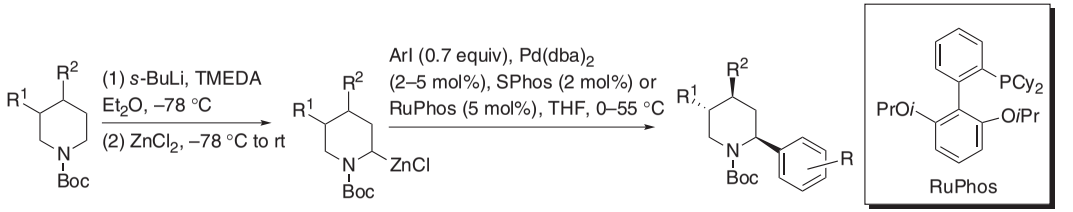


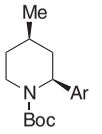
Scheme 1.51 Pd-catalyzed benzylic Negishi–Baba coupling arylation of 1,2-dimethylimidazole by Knochel and coworkers [170].

They also successfully conducted benzylic Negishi–Baba coupling on 2-methylbenzo[*b*]thiophen, 2-methylbenzofuran, indole, and benzo[*d*]imidazole.

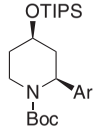
Staying with Knochel's [171a] work, in 2011, the group reported remarkable diastereoselective arylations of substituted piperidines (Scheme 1.52 – only for substituted piperidin-2-ylzinc reagents). Both substituted piperidin-2-ylzinc and 4-ylzinc reagents (not shown in Scheme 1.52, but the conditions are otherwise identical) were formed. These authors also reported a 1,2-migration of Pd in the diastereoselective cross-coupling of *N*-Boc-6-methylpiperidin-2-ylzinc chloride.

Similar work was reported by Coldham and Leonori, who applied this methodology to the synthesis of the alkaloid anabasine [171b]. These workers used $t\text{Bu}_3\text{P-HBF}_4$ as the ligand.

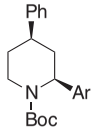




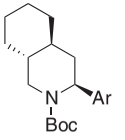
R = 4-MeO, 78%, >99 : 1 (2% Cat., SPhos, 55 °C, 12 h)
R = 4-CF_3, 81%, 95 : 5 (2% Cat., SPhos, 55 °C, 12 h)
R = 3-Cl, 76%, 96 : 4 (2% Cat., SPhos, 55 °C, 12 h)
R = 3-CN, 64%, 97 : 3 (2% Cat., SPhos, 55 °C, 12 h)
R = 4-EtO_2C, 67%, 98 : 2 (2% Cat., SPhos, 55 °C, 12 h)
R = 4-Pyridinyl, 73%, 95 : 5 (2% Cat., SPhos, 55 °C, 12 h)



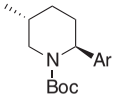
R = 4-EtO_2C, 84%, 97 : 3 (5% Cat., RuPhos, 55 °C, 60 h)
R = 4-F, 83%, 95 : 5 (5% Cat., RuPhos, 55 °C, 60 h)
R = 4-F_3C, 81%, 95 : 5 (5% Cat., RuPhos, 55 °C, 60 h)
R = 4-CN, 81%, 97 : 3 (5% Cat., RuPhos, 55 °C, 60 h)



R = 4-CF_3, 64%, 97 : 3 (5% Cat., RuPhos, 55 °C, 12 h)
R = 4-CN, 79%, >99 : 1 (5% Cat., RuPhos, 55 °C, 12 h)
R = 4-MeO_2C, 67%, 99 : 1 (5% Cat., RuPhos, 55 °C, 12 h)



R = 4-CF_3, 69%, >99 : 1 (5% Cat., RuPhos, 55 °C, 12 h)
R = 4-CN 54%, >99 : 1 (5% Cat., RuPhos, 55 °C, 12 h)
R = 4-MeO, 60%, 97 : 3 (5% Cat., RuPhos, 55 °C, 12 h)

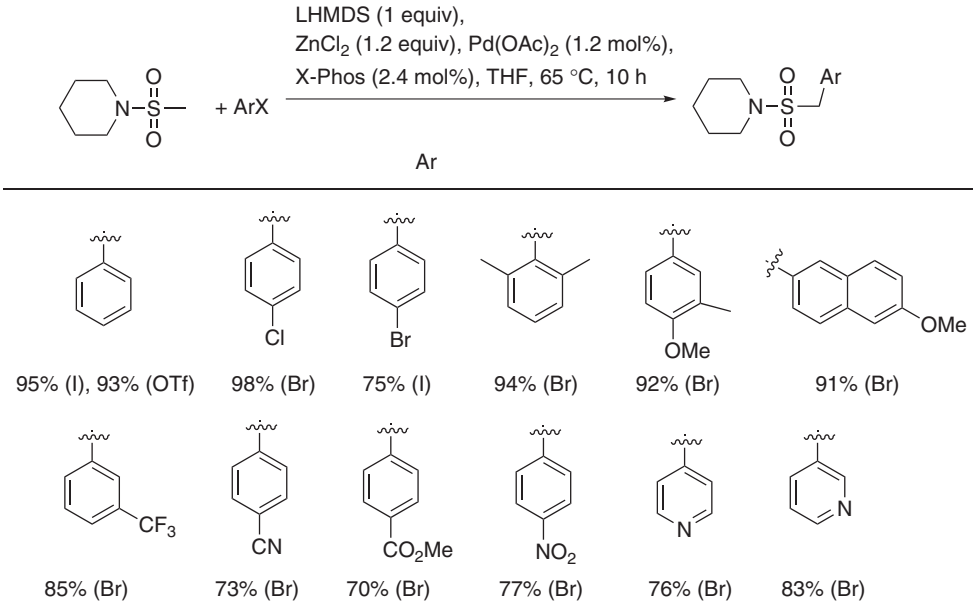


R = 4-CN 62%, 96 : 4 (5% Cat., RuPhos, 0 °C, 6 h, then rt,12 h, then 40 °C 12 h)
R = 4-EtO_2C, 59%, 95 : 5 (5% Cat., RuPhos, 0 °C, 6 h, then rt,12 h, then 40 °C 12 h)

Scheme 1.52 Highly diastereoselective Negishi–Baba coupling arylation of substituted piperidines by Knochel and coworkers [116].

NHC catalysts have enjoyed much application in this reaction. In 2012, Organ's group published a review on the development of bulky palladium complexes for challenging cross-coupling reactions [172]. These Pd catalysts have been very useful for the formation of tetra-*ortho*-substituted (hetero)biaryl compounds under mild conditions. Most of this work has been reported in their review on this topic and thus we will not go over this again here, except that we have highlighted the work of Organ's group in an experimental example below.

In the context of useful Pd-catalyzed Negishi coupling, the approach of Zhou *et al.* [173] using benzylic sulfonamide derivatives is interesting. The driving force behind this study is the knowledge that the sulfonamide functional group is widely found in both natural products and medicines such as Axert and Zonisamide for treatment of seizures. In this reaction, first the sulfonamide substrate was zincated using lithium hexamethyldisilizane (LHMDS) and $ZnCl_2$ and this was followed by the palladium-coupling step using $Pd(OAc)_2$ and XPhos (Scheme 1.53), which worked very efficiently.

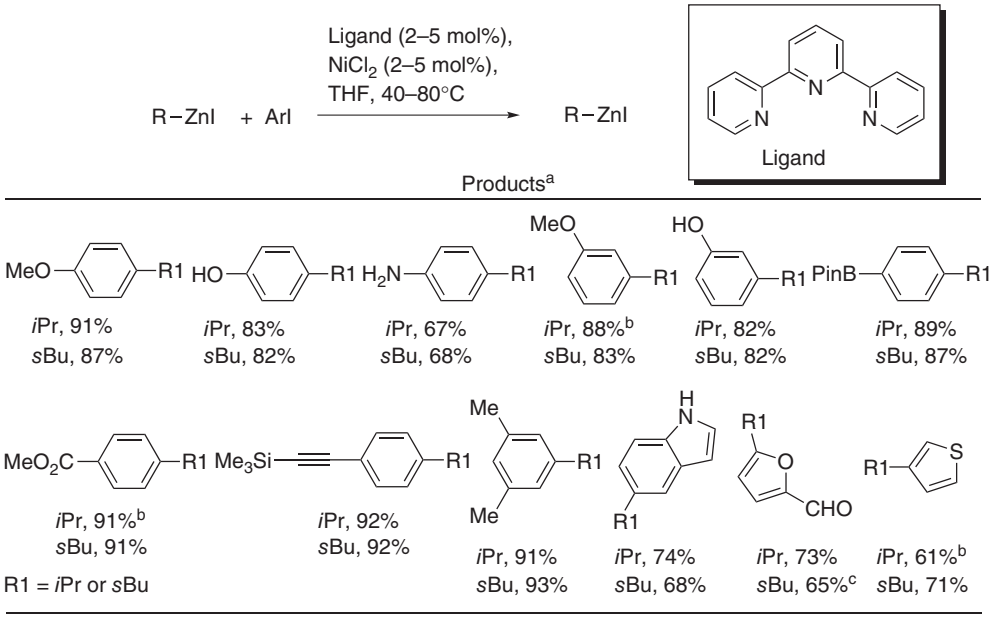


Scheme 1.53 Highly efficient Negishi–Baba coupling arylation of sulfonamides by Zhou *et al.* [173].

In 2010, Andreas Leitner and coworkers [174] at BASF reported the preparation of a very stable 2-pyridylzinc bromide (an sp^2 organometallic nucleophile) on a multi-kilogram scale using Rieke technology and its application in the Negishi–Baba cross-coupling reaction.

It has to be noted that some stereochemical issues have plagued the Negishi–Baba reaction for some time. In a very insightful 2011 communication by Krasovsky and Lipshutz [175], it was pointed out that the coupling reaction of Z-olefins gives a mixture of Z and E isomeric products, the ratio of which was influenced by the catalyst. This remarkable detailed study showed that the outcome of the coupling reaction with *Z*-olefins is determined by the ligand(s) on the Pd catalyst. It should also be noted that from a practical standpoint the best results were achieved with Zn dust rather than Zn powder.

In 2011, Joshi-Pangu *et al.* [176] reported a very successful nickel-catalyzed Negishi–Baba coupling of secondary alkylzinc halides and aryl iodides (Scheme 1.54). This group has presented the first process that overcomes the isomerization and β-hydride elimination problems that are associated with the use of secondary nucleophiles, and that have limited the equivalent Pd-catalyzed reactions.

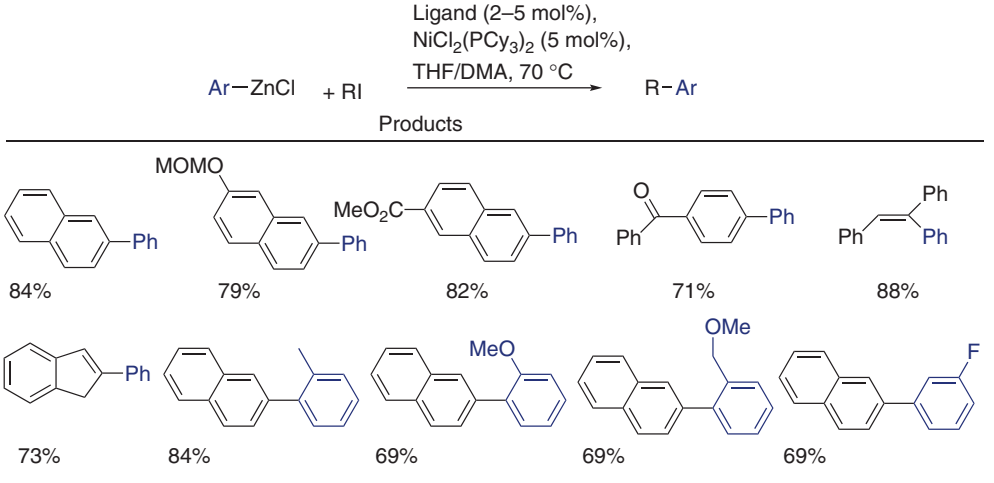


a: RZnI (1.5 – 2.5 mmol). b: with the addititive $LiBF_4$ (1 equiv). c: 70 : 1 *s*–Bu to *n*–Bu.

Scheme 1.54 Nickel-catalyzed Negishi–Baba cross-coupling arylation of secondary alkylzinc halides by Joshi-Pangu *et al.* [176]

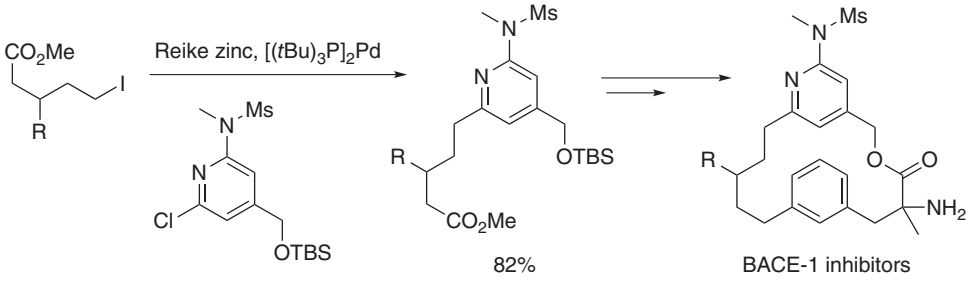
Sticking with the nickel-catalyzed Negishi–Baba reaction, aryl ether electrophiles have been used [177]. For example, various naphthyl and activated phenyl pivalates underwent this reaction cleanly giving the corresponding products in very good yields (Scheme 1.55).

It was also reported in 2011 that diaryl tellurides could be coupled with organozincs using palladium and copper catalysts [178]. The products were obtained in moderate yields.



Scheme 1.55 Nickel-catalyzed Negishi–Baba cross-coupling arylation of aryl/alkenyl pivalates [177].

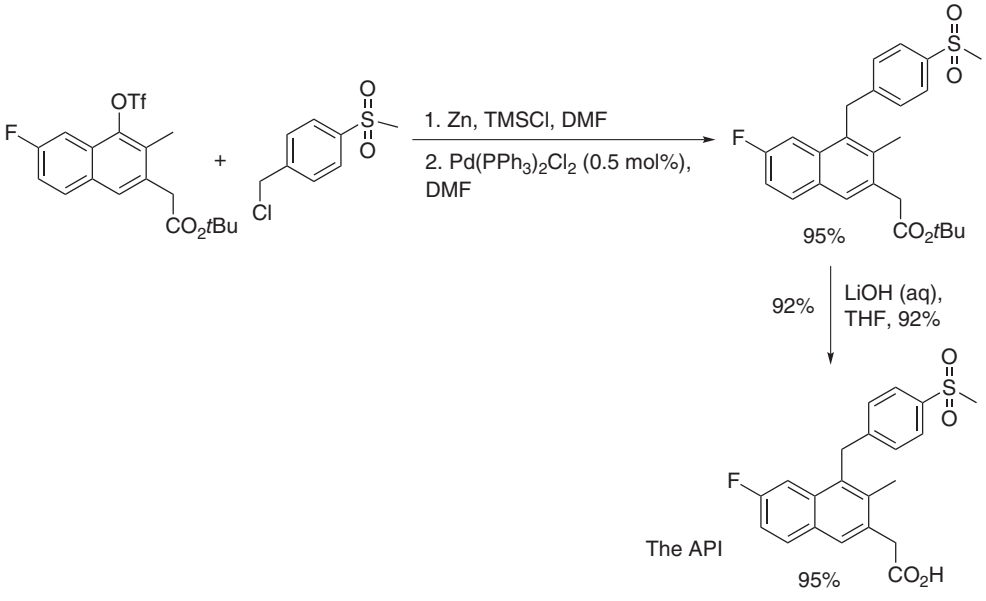
Industrially, this reaction is very useful, and, in 2007, Merck research labs reported the synthesis of macrocyclic tertiary carbinamine BACE-1 inhibitors – BACE-1 inhibition is widely regarded to be one of the promising therapeutic approaches for the treatment of Alzheimer's disease – where the Negishi reaction was used as a key step (Scheme 1.56) [179].



Scheme 1.56 Nickel-catalyzed Negishi–Baba cross-coupling arylation step for the synthesis of macrocyclic tertiary carbinamine BACE-1 inhibitors by Merck research labs [179].

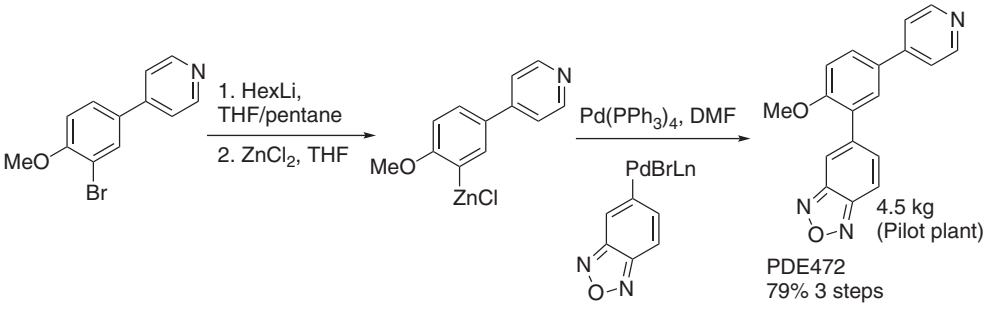
A team at Hoffmann-La Roche, in 2013, reported the application of this reaction as a key step in an efficient large-scale synthesis (about 3 kg) of a naphthylacetic acid CRTH2 receptor (involved in inflammation events, and thus important therapeutically for the treatment of asthma, allergic inflammation, COPD (chronic obstructive pulmonary disease), allergic rhinitis, and atopic dermatitis) antagonist, which is a naphthylacetic acid (Scheme 1.57) [180]. This whole process was scaled up to produce over 2 kg of the active pharmaceutical ingredient (API).

In 2003, a group at Novartis Pharma AG developed a process for the phosphodiesterase type 4D inhibitor compound, PDE472, in which a large-scale Negishi–Baba coupling was applied



Scheme 1.57 Negishi–Baba cross-coupling arylation step in the large-scale synthesis of a naphthylacetic acid CRTH2 receptor antagonist by Hoffmann-La Roche [180].

(Scheme 1.58) [37]. The Negishi–Baba reaction was optimized by preforming the arylpalladium complex, which was then added to the arylzinc intermediate to give 4.5 kg of the API in a pilot plant. For safety reasons, hexyllithium was used instead of BuLi. Unfortunately, there Pd contamination issues at the unacceptable levels of 300–800 ppm (it should be below 2 ppm), which were due to the fact that the last step in the process involved a Pd catalyst and the API was a good ligand for Pd. Various methods were studied, including the use of trimercaptotriazine, but the one that worked was that which involved formation of the hemi-maleate salt, and conversion of the salt back to the free base with aqueous sodium carbonate, followed by treatment with active charcoal and recrystallization from acetone.



Scheme 1.58 Large-scale Negishi–Baba coupling in the synthesis of PDE472 by Novartis Pharma AG [37].

When this reaction was carried out in a hastelloy-steel reactor, the Ni content rose to 23 ppm (from <2 ppm) and metal complexation was again an issue.

The Negishi reaction has also been performed using immobilized systems. For example, in 2013, Wu *et al.* [181] reported on the Negishi coupling of aryl bromides or acyl chlorides with organozinc chlorides catalyzed by a palladium bipyridyl complex anchored on nanosized mobile crystalline material 41 (MCM-41). The reactions proceeded smoothly with a very low catalyst loading in THF at 70 °C for electron-deficient aryl bromides, which gave moderate to high yields of the Negishi coupling products. However, reactions in toluene at 110 °C were required if electron-rich aryl bromides were employed. For acyl chlorides, the reactions could be performed in THF at 50 °C and the corresponding ketones and ynones were obtained in high yields. It was possible to easily recover the supported catalyst from the reaction mixture, and this could be reused several times without any retreatment or regeneration with only a slight decrease in activity.

1.3.9
Beyond the Ullmann and Suzuki–Miyaura Reactions, Other Newer Approaches to Functional Biaryl Synthesis: Pd, Fe, Co, and Other Metals

To wrap up this chapter, we will rapidly consider some significant miscellaneous reactions for forming biaryl units.[9)]

1.3.9.1 With Palladium

In 2013, Feringa's group [182] reported the application of hindered aryllithium reagents as substrates (or intermediates) in palladium-catalyzed cross-coupling, this in fact allowed access to tri- and tetra-*ortho*-substituted products. This group used the Pd-PEPPSI-IPent catalyst for this transformation,

9) We have gone over the limit of number of pages for this chapter, so to avoid the wrath of our editor we will start coming to a halt, and gentle tug the reins. We have decided to include few schemes here.

which showed broad scope and very good yields (Figure 1.48). From an industrial point of view, the disadvantage of this method is the use of aryllithium substrates.

1.3.9.2 With Iron

In 2011, Chandrasekharam *et al.* [183] reported the Fe-catalyzed regioselective direct oxidative aryl–aryl cross-coupling (via cross-dehydrogenative coupling (CDC)) using *N,N*-dimethylanilines with 2-naphthol/1-naphthol and TBHP as the oxidant at 0 °C. $FeCl_3$ (20 mol%) was used. The reaction was regioselective for the *ortho*-coupled products (2,2′-birayls), and good functional group scope in the aniline reagent was demonstrated. The yields were generally good.

1.3.9.3 With Nickel

In 2013, Sengmany *et al.* [184] reported the Ni-catalyzed synthesis of 3-amino-6-aryl- and 3-amino-6-heteroarylpyridazines – compounds that exhibit diverse biological activities – using an electrochemical method. A large functional group diversity was shown on both the 3-amino-6-chloropyridazine and the aryl or heteroaryl halide reagent. The yields were satisfactory.

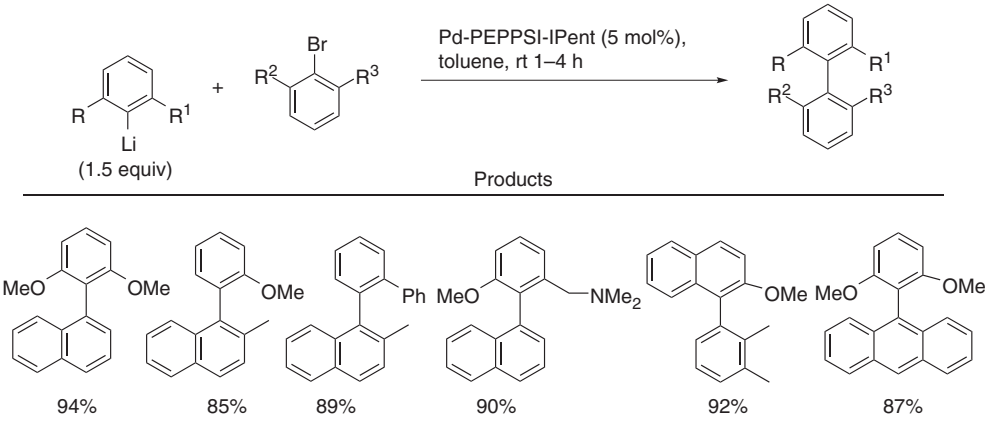


Figure 1.48 A cross-section of results for the Pd-catalyzed synthesis of hindered biaryls using aryllithium reagents as reported by Feringa and coworkers [182].

1.3.9.4 With Cobalt

In 2009, von Wangelin's group [185] demonstrated an operationally simple biaryl coupling reaction with $CoCl_2$ to form functionalized biaryl compounds. In fact, the process involved *in situ* aryl Grignard formation from aryl bromides and subsequent homocoupling with the Co catalyst (5 mol%) with 1 atm of bottled air at 0 °C.

1.3.10 Conclusions

As a final comment, although restricted in its essence to palladium chemistry – but which is nonetheless at the heart of modern cross-coupling arylation reactions – we quote from Astruc [12i], "in conclusion, the field of palladium-catalyzed cross-coupling reactions for their work in which Heck, Negishi, and Suzuki were awarded the 2010 Nobel Prize in chemistry is extremely rich and productive and will continue to grow with major synthetic applications and 'green' implications in the future."

1.4
Selected Experiments from the Literature

1.4.1
The Heck–Mizoroki Reaction

1.4.1.1 Heterogeneous Catalytic Synthesis of (*E*)-Butyl Cinnamate Using a Palladium Nanosphere Catalyst

Catalyst Preparation A solution of H_2PdCl_4 (50 ml, 0.6 mmol l^{-1}) is mixed with PVP40 (Polyvinylpyrrolidone) (34 mg, molecular weight is 40 000) (molar ratio of PVP monomer to palladium should be 10 : 1) and then fed into a jet feed at a flow rate of 0.7 ml s^{-1} onto a spinning disc for which the speed should be set at 1500 rpm, with hydrogen gas fed into another jet feed, affording a colloidal suspension of composite nanomaterials (see *http://www.rsc.org/suppdata/nj/c0/c0nj00898b/c0nj00898b.pdf* for a schematic of this equipment). Products can be collected from beneath the disc through an exit port. The palladium composite nanospheres are washed using MilliQ water (>18 MO) (Molecular orbital) three times and then freeze-dried. The nanoparticles are highly stable for several months and can be used directly [76].

Catalyst Performance (a) Iodobenzene (0.2 g, 0.98 mmol, 1 equiv), butyl acrylate (0.151 g, 1.18 mmol, 1.2 equiv), Et_3N (0.248 g, 2.45 mmol, 2.5 equiv) in *N*,*N*-dimethylformamide (DMF) (2 ml) are treated in one portion with the palladium nanosphere catalyst (1 mol%). The reaction mixture is degassed (freeze–pump–thaw method) before heating to 60 °C and left overnight. The ensuing reaction mixture is centrifuged and the palladium nanosphere catalyst is washed three times with DMF (3 × 5 ml). The combined DMF is washed with HCl (0.1 M) and ethyl acetate (V/V = 1 : 4) once and water and ethyl acetate (V : V = 1 : 4) twice. The ethyl acetate layers are collected and concentrated under reduced pressure and the resulting mixture subjected to column chromatography (2% ethyl acetate in hexane) to give the *title compound* (0.192 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): $\delta = 0.97$ (t, $J = 7.6$ Hz, 3H), 1.44 (sex, $J = 7.4$ Hz, 2H), 1.69 (quint, $J = 7.2$ Hz, 2H), 4.21 (t, $J = 6.6$ Hz, 2H), 6.44 (d, $J = 16.0$ Hz, 1H), 7.39 to 7.37 (m, 3H), 7.54 to 7.52 (m, 2H), 7.68 (d, $J = 16.0$ Hz, 1H); gas chromatography–molecular sieves (GC-MS) *m*/*z* (relative intensity): 204 (M^+, 18), 148 (74), 131 (100), 103 (57), 77 (38).

For recycling studies, the palladium nanosphere catalyst is separated by centrifugation, washed by DMF three times, and stored in DMF under argon before the next catalytic run.

1.4.1.2 The Preparative Catalytic Synthesis of 5-(*p*-Trifluoromethylphenyl)-2,3-dihydrofuran in Continuous Flow

A Corning Advanced-Flow Reactor is used in this experiment. Dimensions of the reaction channels correspond to 0.7 mm in depth and 4 mm in width, and has an internal volume of 7 ml (Figure 1.49) [82]. A circulating temperature bath pumped water at 15 l min^{-1} through the integrated heat exchanger to maintain a reactor temperature of 90 °C. A 1000 psi back pressure regulator (Idex) is added to the outlet of each dual piston pump (LabAlliance, 1500 series) to provide stable flow rates. Flow rates are controlled remotely through the central computer control and analog output device (National Instruments). A solution of 4-chlorobenzotrifluoride (2.0 M), *N*,*N*-dicyclohexylmethylamine (2.4 M), palladium(II) acetate (0.02 M), and 2-di-*tert*-butylphosphino-2′-methylbiphenyl (0.06 M) in *n*-butyl alcohol with a small amount of dioxane as a cosolvent is loaded into reservoir 1. A solution of 2,3-dihydrofuran in *n*-butyl alcohol is loaded into reservoir 2. To ensure a high degree of mixing, a commercial static packed bed mixer (HPLC gradient mixer, Waters) containing stainless steel ball bearings can be added immediately upstream of the reactor. On exiting the reactor, the concentration of the solution is diluted to one-seventh. Inline analysis of the reaction can be carried out by HPLC.

1.4.2
The Heck–Matsuda Reaction

1.4.2.1 Catalytic Synthesis of (*E*)-3-(4-Methoxyphenyl)acrylic acid Using Palladium Acetate in Water

4-Methoxyphenyldiazonium tetrafluoroborate (0.054 g, 0.5 mmol) is placed in a flask with $Pd(OAc)_2$ (1.1 mg, 5 µmol, 1 mol%) and water (5 ml) [95]. Acrylic acid (0.054 g, 0.75 mmol) is added and the mixture stirred at room

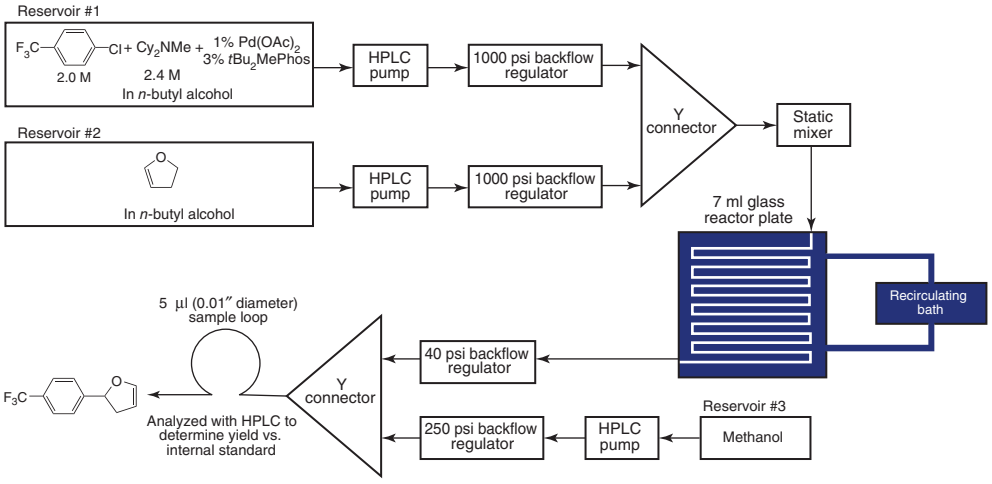


Figure 1.49 The continuous flow system employed by McMullen *et al.* [82]. (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

temperature for 16 h. The reaction mixture is extracted with CH_2Cl_2 (10 ml) and the organic layer is filtered through a celite pad, and then dried with anhydrous $NaSO_4$. The solvent is removed *in vacuo* and the crude product purified by silica gel 60 flash chromatography (230–400 mesh ASTM) to give the *title compound* (0.083 g, 93%). ^{1}H NMR (360 MHz, $CDCl_3$, ppm) δ_H 7.75 (1H, d, $J = 15.8$ Hz), 7.51 (2H, d, $J = 8.3$ Hz, 6.92 (2H, d, $J = 8.3$ Hz, 6.32 (1H, d, $J = 15.8$ Hz), 3.85 (3H, s).

1.4.2.2 Catalytic Synthesis of 2-Phenyl-1*H*-Indene Using Copper Chloride

Indene (41 mg, 0.50 mmol), CuCl (5 mg, 10 mol%), Ph_2IOTf (430 mg, 1.00 mmol), and DTBP (224 µl, 1.00 mmol) are dissolved in CH_2Cl_2 (5 ml) [99]. The reaction mixture is heated for 20 h at 70 °C. The reaction is quenched with a 3N HCl solution and the aqueous phase extracted with CH_2Cl_2. The combined organic phases are dried ($MgSO_4$) and the solvent stripped. The product is purified by flash column chromatography to afford the desired *title compound* as a white solid (0.32 mmol, 64%). Mp: 148 °C ^{1}H NMR (400 MHz, $CDCl_3$, ppm): $\delta = 3.84$ (s, 2H); 7.25 (dt, $J = 7.4$, 1.1 Hz, 1H), 7.28 (s, 1H), 7.30–7.36 (m, 2H), 7.42–7.48 (m, 3H), 7.69 (d, $J = 8.1$ Hz, 2H), 7.53 (d, $J = 7.3$ Hz, 1H), 7.42–7.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): $\delta = 146.4$, 145.3, 143.1, 135.9, 128.6, 127.4, 126.6, 126.5, 125.6, 124.7, 123.6, 120.9, 38.9; IR (thin film): $\nu_{max} = 1491$, 1459, 1446, 1387, 1245, 1204, 1075, 1028, 906, 754, 730 cm^{-1}.

1.4.2.3 Catalytic Synthesis of (*E*)-Ethyl 3-(4-methoxyphenyl)acrylate Using Palladium Nanoparticles Supported on Agarose Hydrogel

The supported palladium nanoparticle catalyst is prepared by adding $Pd(OAc)_2$ (0.022 g, 1 mmol) to a solution of agarose (1 g) in water (100 ml) and then adding this solution to a aqueous acid solution (100 ml, with the pH fixed to 4 by adding HCl) and stirring at 80 °C [97]. An aqueous solution of citric acid (4 mmol in 20 ml H_2O) is added dropwise. The mixture is then refluxed for 1 h and cooled to room temperature giving a gray–brown hydrogel. On drying the resulting hydrogel under a flow of air overnight, and then under vacuum for 24 h, the agarose-supported palladium nanoparticles of 20–30 nm size are obtained. 4-Methoxyphenyl diazonium tetrafluoroborate (0.107 g, 1 mmol) and ethyl acrylate (0.15 g, 1.5 mmol) are added to a flask containing the immobilized Pd catalyst (2.6 µmol%) and water (3 ml) at 40 °C. The reaction mixture is stirred in air for 5 h. The reaction mixture is then cooled to room temperature and washed with diethyl ether (3 × 5 ml).[10] The crude product is purified by silica gel column chromatography using *n*-hexane/ethyl acetate as the eluent, to give the *title compound* as a yellowish white solid (0.175 g, 85%); mp 48.5–50.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): $\delta = 1.35$ ppm (t, $J = 7.2$, 3H), 3.85 (s, 3H), 4.30

10) The resulting gelatinous mass can be reused for further cycles under identical conditions.

to 4.25(m, 2H), 6.33 (d, $J = 16$, 1H), 6.92 (d, $J = 8.8$, 2H), 7.50 (d, $J = 8.4$, 2H), 7.67 (d, $J = 16$, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): $\delta = 14.39$ ppm, 55.39, 60.36, 114.31, 115.74, 127.19, 129.71, 144.27, 161.33, 167.38.

1.4.3 The Heck–Hiyama Reaction

1.4.3.1 Catalytic Synthesis of *p*-Nitrobiphenyl: Ligand-Free Coupling Using Pd/C

A mixture of 4-bromonitrobenzene (0.101 g, 500 µmol), phenyltriethoxysilane (182 µl, 750 µmol, 1.5 equiv), Pd/C (5.00 mol%), TBAF (0.316 g, 1.00 mmol), toluene (1 ml), and acetic acid (1.5 equiv) is stirred under an inert atmosphere at 120 °C for 24 h and then passed through a celite pad (3.0 cm) to remove the catalyst [102]. To the filtrate is added EtOAc (50 ml) and H_2O (50 ml), and the layers are separated. The aqueous layer is extracted with EtOAc (10 ml) and the combined organic layers are dried over $MgSO_4$, filtered, and concentrated *in vacuo* and the crude product purified by silica gel column chromatography (hexane/EtOAc, 50 : 1) to give the *title compound* (0.081 g, 81%). ^1H NMR (400 MHz, $CDCl_3$, ppm): $\delta = 8.25$ (d, $J = 8.9$ Hz, 2H), 7.69 (d, $J = 8.9$ Hz, 2H), 7.60 (d, $J = 7.4$ Hz, 2H), 7.49 to 7.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): $\delta = 147.4$, 146.9, 138.6, 129.0, 128.8, 127.6, 127.2, 123.9.

1.4.4 The Stille Reaction

1.4.4.1 The Cu Catalyzed Stille Reaction – Synthesis of *N*-Ethyl-*N*-(phenyl-*p*-tolylmethyl)benzamide

N-Ethyl *o*-tolylimine (0.071 g, 0.48 mmol) and benzoyl chloride (0.087 g, 0.62 mmol) are dissolved in acetonitrile (3 ml) [106b]. This solution is then added to a solution of CuCl (4.2 mg, 0.048 mmol) in dry acetonitrile (1 ml). The reaction mixture is transferred to a 25 ml reaction bomb. Bu_3SnPh (0.176 g, 0.48 mmol) in CH_2Cl_2 (3 ml) is added and the reaction mixture heated to 45 °C for 26 h. The reaction mixture is then stripped of solvents and redissolved in ethyl acetate (50 ml). A saturated KF solution (15 ml) is added and this mixture is stirred for 2 h. The white solid that is formed is then filtered off through Celite, and the organic layer is separated, and washed with distilled H_2O (2×50 ml). The KF solution is extracted with ethyl acetate (2×50 ml), and the organic layers are combined and dried over anhydrous $MgSO_4$, then filtered and the solvents stripped, the residual crude product is purified by column chromatography using ethyl acetate/hexane as eluent to afford the *title compound* (0.118 g, 84%). ^1H NMR (270 MHz, 80 °C, DMSO-d_6, ppm): $\delta = 0.63$ (t, $J = 7.2$ Hz, 3H), 2.31(s, 3H), 3.38 (q, $J = 6.7$ Hz, 2H), 6.34 (s, 1H), 7.49 to 7.04 (m, 14H); ^{13}C NMR (68.0 MHz, 80 °C, DMSO-d_6): $\delta = 170.5$, 140.1, 14.1, 40.2, 64.3, 126.2, 127.5, 128.5, 128.6, 129.1, 129.2, 136.9, 137.9. IR (neat): $\nu_{max} = 1628\ cm^{-1}$ (C=O).

1.4.5 The Sonogashira-Hagihara Reaction

1.4.5.1 The Copper-Free Catalytic Synthesis of Diphenylethyne

A resealable Schlenk flask (10 ml) is evacuated and back-filled with argon and charged with tetrabutylammonium acetate (0.224 g, 0.7 mmol), *N,N*-dimethylacetamide (3 ml), iodobenzene (0.102 g, 0.5 mmol), phenylacetylene (0.061 g, 0.6 mmol), and methyl benzoate as internal standard (35 mg) [108]. After the addition of $\{Pd[k^2\text{-}C,N\text{–}C{=}(Ph)C(Cl)CH_2NMe_2](\mu\text{-}Cl)\}_2$ (the palladacycle) in *N,N*-dimethylacetamide (1.6 mg, 5×10^{-3} mmol), the reaction mixture is stirred at 30 °C for 4 h. GC analysis indicates a 98% yield of the diphenylacetylene product and 2% of the homocoupling acetylene product. The solution is added to a 10-wt% HCl (20 ml) and the product extracted with hexane (2×10 ml). The organic phase is dried over $MgSO_4$ and the solvent stripped to give the *title compound* (84 mg, 95%). ^1H NMR ($CDCl_3$, ppm): $\delta = 7.23$ (m, 10H).

1.4.5.2 Sonogashira-Hagihara Cross-Coupling with Arenediazonium Salts – Synthesis of 1-(4-Methoxyphenyl)-2-phenylacetylene

An oven-dried Schlenk tube is charged under argon with 4-methoxybenzenediazonium tetrafluoroborate (0.111 g, 0.5 mmol), *n*-Bu_4NI (0.369, 1.0 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), CuI (3.8 mg, 0.02 mmol), diethylamine

(0.366 g, 5.0 mmol), phenylacetylene (0.102 g, 1.0 mmol), and anhydrous MeCN (3 ml) [113]. The tube is sealed and stirred at room temperature for 1 h. Then the reaction mixture is diluted with Et_2O and washed twice with HCl (1 N) and with brine. The organic phase is separated, dried over Na_2SO_4, filtered, and the solvents stripped. The residue is purified by chromatography on silica gel, eluted with *n*-hexane/AcOEt, giving the *title compound* as a pale orange solid (0.081 g, 78%), ^{1}H NMR (400 MHz, $CDCl_3$, ppm): $\delta = 3.85$ (s, 3H), 6.92 (d, $J = 8.7$ Hz, 2H), 7.41–7.34 (m, 3H), 7.59–7.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.3, 88.2, 89.5, 114.1, 115.5, 123.7, 128.0, 128.4, 131.6, 133.2, 159.7$.

1.4.6 The Suzuki–Miyaura Reaction

1.4.6.1 Synthesis of 4-(2,6-Dimethylphenyl)-3,5-dimethylisoxazole Using Pd-PEPPSI-IPENT

A flask is equipped with a stir-bar and charged with the Pd-PEPPSI-IPENT catalyst (4 mg, 2 mol%), 2,6-dimethylboronic acid (0.5 mmol), potassium hydroxide (42 mg, 0.75 mmol), and the 4-bromo-3,5-dimethylisooxazoline (0.25 mmol) [54, 117]. The flask is sealed and purged with argon (three times). Dioxane (1.0 ml) is then added via syringe and the reaction is stirred at 65 °C for 24 h. Then the reaction mixture is diluted with diethyl ether (2 ml) and filtered through a plug of celite. The reaction flask and the celite pad are rinsed with additional diethyl ether (10 ml) and the organic layers combined. The solvent is stripped and the residue purified by flash chromatography (EtOAc/hexane, 5 : 95, rf = 0.32) to afford the *title compound* as a yellow solid (0.035 g, 69%). Mp: 110–112 °C.[11)]

1.4.6.2 Synthesis *p*-Phenylanisole via the Suzuki–Miyaura Reaction with a FibreCat-1034 Catalyst

The synthesis of FibreCat-1034 is given in the publication [159].

A flask is loaded with the FibreCat catalyst (1 mol%), *p*-bromoanisole solution (100 mg, 0.53 mmol, in 1 ml of solvent), phenylboronic acid solution (1.05 mol of $PhB(OH)_2$/mol substrate in 1 ml of solvent), KF (3 mol equiv in 1 ml of nanopure water), and an additional 2 ml of solvent (EtOH). The reaction flask is then degassed five times and kept under a nitrogen blanket. The carousel is heated to 80 °C for a 4-h period with vigorous stirring using magnetic stir bars. When the reaction is over, the reaction mixture is cooled to room temperature. The crude reaction mixture is stirred with CH_2Cl_2 (20 ml) and water (10 ml) for 5 min. The organic layer is then separated via gravity and dried with anhydrous sodium sulfate for 30 min to remove any remaining water. The mixtures are then filtered to remove any catalyst and sodium sulfate. The volatiles are removed by evaporation *in vacuo.* The solid is redissolved in a minimum amount of ethanol, followed by slow addition of water to obtain a white precipitate. The solid is filtered and dried at 45 °C in a vacuum oven to obtain analytically pure material. The *title compound* is further recrystallized with ethanol–water (0.087 g, 89% yield). ^{1}H NMR (CD_2Cl_2, ppm): $\delta = 7.56$ (m, 4 H), 7.43 (m, 2 H), 7.31 (m, 1H), 7.01 (m, 2H), 3.85 (s, 3H).

1.4.7 Tamao–Kumada–Corriu Cross-Coupling Reaction

1.4.7.1 Synthesis of 2-(4-Methoxyphenyl)pyridine

A suspension of $[Pd_2dba_3]$ (18 mg, 0.02 mmol, 2.0 mol%) and 1-$Ad_2P(O)H$ (25 mg, 0.08 mmol, 8.0 mol%) in THF (1.0 ml) was stirred for 10 min at room temperature [167]. *p*-Bromoanisole (187 mg, 1.00 mmol) was added and the suspension was stirred for a further 5 min. 2-Pyridylmagnesium bromide (5.0 ml, 1.50 mmol, 0.3 M in THF) was added dropwise over 3 min and the resulting suspension was stirred for 20 h at 60 °C. EtOAc (50 ml) and H_2O (50 ml) were added to the cold reaction mixture. The separated aqueous phase was extracted with EtOAc (2 × 50 ml). The combined organic layers were washed with H_2O (50 ml) and brine (50 ml), dried over Na_2SO_4, and concentrated *in vacuo.* The remaining residue was purified by silica gel column chromatography (*n*-hexane/EtOAc 10/1) to yield the *title compound* as a colorless solid (124 mg, 67%). (M.p 53–55 °C) ^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta = 8.63$ (ddd, $J = 4.9, 1.7, 1.1$ Hz, 1H), 7.93 (d, $J = 8.5$ Hz, 2H), 7.73–7.61 (m, 2H), 7.14 (m, 1H), 6.98 (d, $J = 8.5$ Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): $\delta = 160.6$ (Cq), 157.3 (Cq), 149.7 (CH), 136.8 (CH), 132.2 (Cq), 128.3 (CH), 121.5 (CH), 119.9 (CH), 114.3 (CH), 55.5 (CH3). IR (KBr): $\nu_{max} = 2839, 1610, 1589, 1516, 1467, 1249, 1040, 841, 783, 746\ cm^{-1}$.

11) For the ^{1}H NMR spectrum, see the Supporting Information to Refs [54, 116].

1.4.8

Negishi-Baba Cross-Coupling

1.4.8.1 Synthesis of 1-Mesitylnaphthalene

A vial is charged with PEPPSI-IPr (3.4 mg, 1 mol%) in air and then under an inert atmosphere, $ZnCl_2$ (0.8 mmol) and a stirrer bar are added. The vial is then sealed with a septum and purged with argon [172]. THF/NMP is then added followed by 1-chloromesitylene (0.8 ml, 1.0 m in THF, 0.8 mmol) and stirring is continued for a further 15 min, at which time a white precipitate forms. NMP is then added followed by the 1-bromonapthalene (0.5 mmol). The septum is replaced with a TeflonR-lined screw cap under an inert atmosphere and the reaction stirred for 2 h. After this time, the reaction mixture is diluted with diethyl ether (15 ml) and washed successively with Na_3 EDTA (ethylenediaminetetraacetic acid) solution (1 m; prepared from EDTA and 3 equiv of NaOH), water, and brine. After drying (anhydrous $MgSO_4$) the solution is filtered, the solvent removed *in vacuo,* and the residue purified by flash chromatography ($R_f = 0.65$, pentane) to give the *title compound* as a colorless, viscous oil (118 mg, 96% yield). ^{1}H NMR (200 MHz, $CDCl_3$, ppm): $\delta = 7.99-7.90$ (m, 2H), 7.64–7.32 (m, 5H), 7.09 (s, 2H), 2.47 (s, 3H), 1.97 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 138.9$, 2×136.9, 133.8, 132.0, 129.1, 128.3, 2×128.1, 127.2, 127.0, 126.8, 126.1, 2×125.8, 125.6, 21.2, 2×20.4.

1.4.9

Biaryl Synthesis with the Hindered Aryllithium Reagent, 2,6-Dimethoxyphenyllithium: Catalytic Synthesis of 1,3-Dimethoxy-2-(1-naphthyl)benzene[12)]

In a dry Schlenk flask, 1,3-dimethoxybenzene (0.249 g, 1.8 mmol) is dissolved in dry THF (0.9 ml) and the solution is cooled down to −10 °C [182]. *n*-BuLi (1.13 ml, 1.6 M in hexane, 1 equiv) is added slowly and the solution is stirred for 30 min. Then the solution is allowed to reach room temperature and stirred for 1 h at this temperature. The resulting solution of the lithium reagent is diluted with toluene (1 ml). In a dry Schlenk flask, PEPPSI-IPent (11.9 mg, 5 mol%, 0.015 mmol) and 1-bromonapthalene (62 mg, 0.3 mmol) are dissolved in dry toluene (2 ml) and the mixture is stirred at room temperature. The corresponding lithium reagent (1.5 equiv) is slowly added over 1 h by syringe pump. When the addition is complete, the reaction is stopped and a saturated aqueous solution of NH_4Cl is added, and the mixture is extracted with ether (3×5 ml). The organic phases are combined and evaporation of the solvent under reduced pressure affords the crude product that is then purified by column chromatography (SiO_2, *n*-pentane/EtOAc 200 : 1), to give the pure *title compound* as a white solid (0.075 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): $\delta = 7.91$ (t, $J = 8.4$ Hz, 2H), 7.59 (t, $J = 8.1$ Hz, 1H), 7.56 −7.37 (m, 5H), 6.76 (d, $J = 8.4$ Hz, 2H), 3.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.5$, 133.6, 132.7, 132.6, 129.1, 128.2, 128.1, 127.5, 126.0, 125.51, 125.46, 125.39, 117.6, 104.2, 56.0.

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