Applications of and alternatives to π-electron-deficient azine organometallics in metal catalyzed cross-coupling reactions

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While the use of π-deficient azine halides in palladium catalyzed cross-coupling reactions is common, the use of π-electron deficient azine organometallics has been less intensively examined. In recent years, important advances have been made that are beginning to address this deficiency and need. The purpose of this *tutorial review* is to highlight and discuss the innovations that facilitate the synthesis of azine-containing biaryls with a focus on the pyridine structural motif. Given the number of important compounds which exhibit azine-heterobiaryls and the wide use of cross-coupling methods in their synthesis, this review should be of interest among synthetic organic chemists and organometallic chemists alike.

Introduction

Pyridines are among the most prevalent heterocycles in bioactive compounds and have been claimed to be the most prevalent heterocycle in pharmaceutically active compounds (Scheme 1).[1] The biaryl core is another privileged motif that occurs in nearly one in every twenty medicinal compounds on the market.[2] Heterobiaryls, a sub-class of biaryls, have one or both of the aryl units replaced by heteroaromatic rings. Examples include micrococcin P1,[3] Streptonigrin[4] and Nemerelline.[5] Etoricoxib,[6] Rosuvastatin[7] and Glivec[8] are three examples of commercialized drugs bearing an arylpyridine motif. This motif is also found in seretonin receptor agonists[9] and MAP kinase inhibitors.[10] Many P,N ligands are based on arylazine frameworks such as QUINAP.[11]

When considering the synthesis of one of these compounds, the development of palladium catalyzed cross-coupling methods has had the greatest impact. The Suzuki, Stille, Kumada–Corriu, Negishi and Hiyama couplings are among the most powerful and versatile tools in biaryl synthesis, exhibiting high functional group compatibility and broad reaction scope.[12]

Although reaction conditions and the nature of the organometallic component vary from one type of cross-coupling reaction to another, all of these reactions are mechanistically related (Scheme 2). The first step of the catalytic cycle involves the oxidative addition of a Pd^0 catalyst into a carbon–halide bond (or equivalent) to generate an electrophlic aryl-palladium(II) intermediate. Reaction of this species with the nucleophilic organometallic component *via* transmetallation provides a diaryl-palladium(II) species which undergoes reductive elimination to form the biaryl carbon–carbon bond and regenerate the Pd^0 catalyst.

Important progress has been made over the last decade in catalyst development leading to mild, high yielding processes that can be performed with low catalyst loadings.[12] The majority of catalyst development efforts have been directed at

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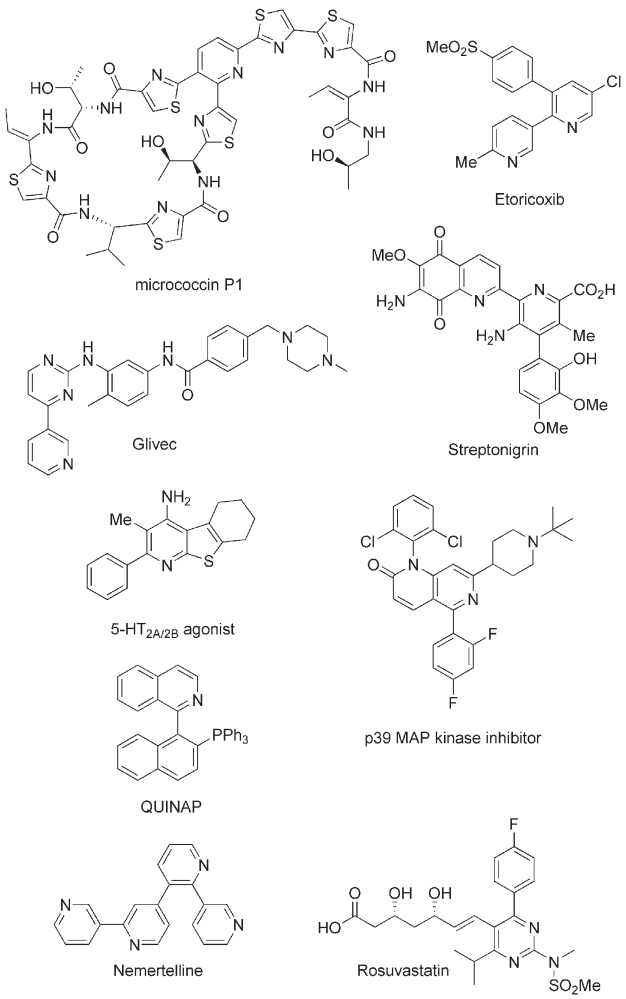
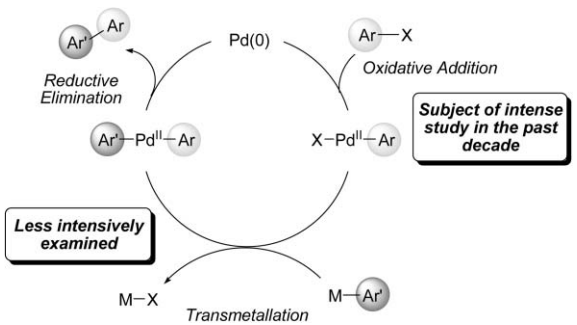
Keith Fagnou was born in Saskatoon, Saskatchewan Canada in 1971. He received a Bachelor of Education (BEd) degree with distinction from the University of Saskatchewan in 1995 and, after teaching at the high school level for a short period, continued his studies in chemistry at the University of Toronto. In 2000 he received a MSc degree and in 2002 completed a PhD under the supervision of Mark Lautens. After this he joined the faculty at the University of Ottawa and has initiated research programs focusing on the development of new catalytic reactions for use in organic synthesis.



Scheme 1 Important arylazines.

the first step of the catalytic cycle, oxidative addition, which in most cases is the rate determining step of the catalytic cycle. Notably, this work has enabled extension of these reactions to include very challenging aryl halides including deactivated aryl chlorides[13] and very sterically hindered bis *ortho*-substituted aryl halides.[14]

In contrast, the transmetallation step has been less extensively studied and optimized. Since transmetallation is typically not rate-determining or problematic, this reduced attention compared to oxidative insertion is reasonable.



Scheme 2 Catalytic cycle of palladium catalyzed cross-coupling reactions.

Regardless, there are important organometallic classes that tend to be less frequently employed due to sluggish or poor reactivity. Examples of a challenging organometallic class are the π-electron deficient azine organometallics including the metallapyridines which, in addition to exhibiting diminished stability, are less nucleophilic and undergo transmetallation more slowly.[14] In some cases, transmetallation can even be the rate determining step of the catalytic cycle.[15] Nonetheless, important advances have recently been made with these challenging substrates.

This review will address the use of azine organometallics in palladium catalyzed cross-coupling reactions, with a focus on pyridyl organometallics. Emphasis has been placed on the most recent examples and on emerging alternatives to traditional cross-couplings. The review is divided into two sections. The first section describes cross-coupling reactions of 3- and 4-pyridyl organometallics. The second deals with the use of 2-metallapyridines, which are typically more challenging to use. Each of these sections is further subdivided into methods that are more commonly employed and have the strongest literature precedent, methods that have been less intensively investigated, and alternative processes to the traditional cross-coupling processes.

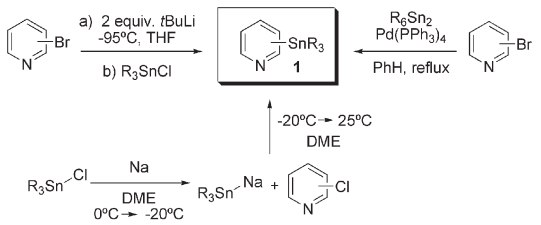
Discussion

3- and 4-azine organometallics

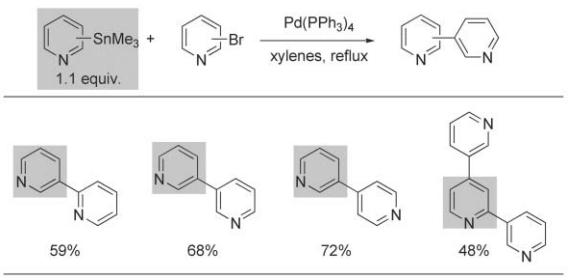
Use of 3- and 4-pyridyl organometallics in cross-coupling reactions is more challenging than with simple arene organometallics. As mentioned, they are less nucleophilic and transmetallate the arylPdX complex at slower rates.[14] They are also more prone to dimerization[16] and protodeboronation.[17] In spite of these hurdles, reliable methods exist for the use of these compounds in cross-coupling methodology. For example, the robustness and reliability of the Stille reaction make it a good tool for the coupling of 3- and 4-stannylpyridines with aryl and heteroaryl bromides and iodides. Recent advances in the synthesis (commercial availability) and use of pyridyl boronic acids and esters have also made Suzuki couplings a very attractive choice. While Negishi, Kumada and Hiyama couplings are less prevalent, good precendent exists for their use. Alternatively, interesting reactions of pyridine *N*-oxides and benzyne can be used to access 3-arylpyridines.

Common methods

Stille coupling. Pyridyl stannanes (**1**) were among the first azine organometallics to be used successfully in palladium catalyzed cross-couplings and are still commonly employed in spite of the toxicity associated with the use of stoichiometric tin reagents. This trend is likely attributable to the fact that, for aryl iodides and some aryl bromides, no special reaction conditions need to be developed for the use of heteroarenes as substrates,[18] and is further related to the relatively good stability of the pyridyl stannanes compared to other pyridyl organometallics. In most cases, isolation and characterization of the pyridyl stannane is possible, which is usually prepared *via* one of three methods (Scheme 3).[19] The coupling of a pyridyl anion with a tin halide species is often used but is



Scheme 3 Preperation of stannylpyridines.

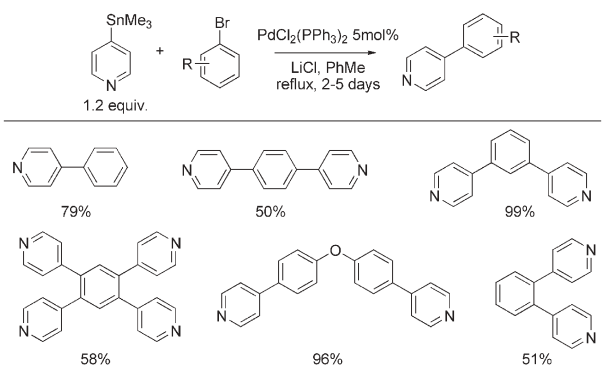


Scheme 4 $Pd(PPh_3)_4$ Catalyzed Stille cross-coupling of stannylpyridines with bromopyridines.

limited to substrates that are insensitive to strongly basic conditions and are compatible with the use of alkyl lithium reagents.[19] Nucleophilic aromatic substitution with triorganostannyl anions and pyridyl halides has also been reported.[20] The mildest method for the synthesis of pyridyl stannanes is palladium cross-coupling of halogenated heterocycles with hexamethylditin.[21]

In 1986, Yamamoto and co-workers reported one of the first uses of trimethylstannyl pyridines and quinolines in various palladium catalyzed Stille reactions.[22] All three isomers of stannyl pyridine were reported to undergo palladium-catalyzed Stille coupling with various bromopyridines to afford bis pyridine derivatives in modest to good yield. A slight excess of stannane is typically used with 1.5 to 5 mol% $Pd(PPh_3)_4$ in refluxing xylenes. Selected examples are shown in Scheme 4.

In 1995, Ogura and co-workers reported the use of $PdCl_2(PPh_3)_2$/LiCl in the Stille coupling of 4-trimethylstannylpyridine with aryl bromides (Scheme 5).[23] The two other isomers of trimethylstannylpyridine may also be coupled using standard reaction conditions without any addition of LiCl.

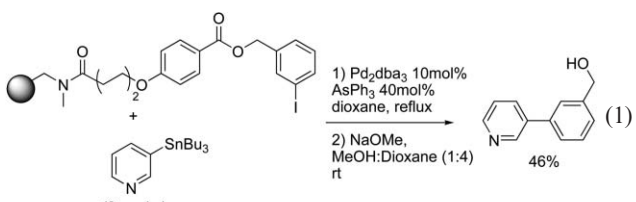


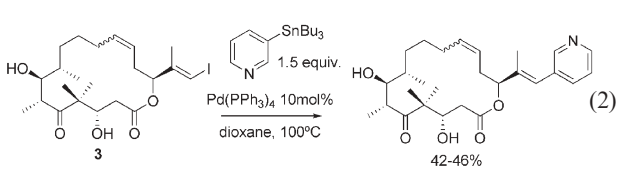
Scheme 5 LiCl promoted Stille cross-coupling of 4-trimethylstannylpyridine.

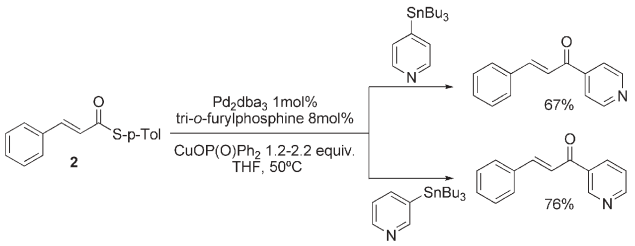
The authors propose that nucleophilic attack of the chloride anion on the organostannane may produce a hypervalent anionic tin species which is more nucleophilic and promotes the transmetallation step of the catalytic cycle.

In 2003, Liebeskind and co-workers reported the use of thiol esters in Stille cross-couplings.[24] Under optimized reaction conditions, they reported two examples of cross-coupling with 3- and 4-tri-*n*-butylstannylpyridine and (*E*)-β-styryl-thiol ester (**2**) in 76% and 67% yields respectively (Scheme 6). They also reported that these reaction conditions were amenable to the use of 2-pyridyl and 2-pyrazyl stannanes. The use of tri-*o*-furylphosphine (TFP) instead of triphenylphosphine led to higher yields, which has previously been observed in Stille cross-coupling reactions. It is believed that the highly dissociative nature of the TFP ligand facilitates the formation of the pre-requisite π-complex between palladium and the organotin species enabling transmetallation to occur.[25] The use of 1.2 to 2.2 equiv. of the copper additive is also essential to achieve synthetically useful yields. The authors propose that the copper interacts with the acylpalladium(II) species and facilitates Pd–Sn transmetallation. Given that CuCl also promotes the reaction, albeit in lower yield, it is unclear whether the phosphonate counterion also activates the organostannane for transmetallation. It was also noted that the use of a copper phosphonate salt facilitates separation of the copper and tin by-product during purification.

The robustness and reproducibility of cross-coupling reactions with stannylpyridines is also demonstrated by their use in solid-supported synthesis and in the total synthesis of complex molecules. In 1998, De Mesmaeker and co-workers reported a study of various cross-coupling methods on solid support,[26] including an example where 3-tri-*n*-butylstannylpyridine could be cross-coupled onto a solid-supported aryl iodide using 3 equiv. of the 3-pyridylstannane and 10 mol% $Pd(PPh_3)_4$ (eqn (1)). When undertaking the synthesis of analogues of Epothilone E, Nicolaou and co-workers used Stille couplings to append various heterocycles to the Epothilone framework.[27] 3-Trimethylstannylpyridine was coupled to a large macrocyclic vinyl iodide (**3**) using 10 mol% $Ph(PPh_3)_4$ in 42–46% yield depending on the isomer of the macrocyclic olefin used (eqn (2)). The reaction conditions are mild enough to be carried out in the presence of unprotected alcohols with no epimerization of any chiral centers.



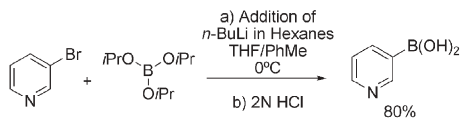




Scheme 6 Stille coupling of stannylpyridines with thiol esters.

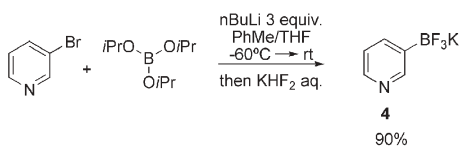
Suzuki coupling. Although Stille reactions of stannylpyridines tend to be robust, the high toxicity of tin has prompted chemists to investigate the use of other coupling partners. In recent years, attention has been directed at the development of Suzuki couplings which use more environmentally benign boronic acids and esters as the organometallic coupling partner. Whereas haloazines have often been employed in Suzuki reactions, there are far fewer methodological studies of Suzuki cross-couplings with azine boronic acids.[28]

In 2002, three research groups reported advances in the synthesis of pyridyl boronic acids. The groups of Rault[29] and Bryce[30] both described the synthesis of 6-halopyridyl-3-boronic acids, and researchers at Merck reported a high yielding process for the synthesis of 3- and 4-pyridylboronic acids as well as 3-quinolylboronic acid and 5-pyrimidylboronic acid.[31] The order of addition was found to be extremely important to obtain reproducibly high yields. While addition of 3-bromopyridine to a solution of *n*-butyllithium followed by triisopropyl borate can lead to high yields, the reaction must be cooled to −78 °C, which can make it inconvenient for large scale preparation. As an alternative, they found that addition of *n*-butyllithium to a solution of 3-bromopyridine and triisopropyl borate at −40 °C followed by an acid quench provides 90–95% isolated yields. The reaction was also carried out at 0 °C giving 80% yield (eqn (3)).



(3)

Pyridyltrifluoroborates (**4**) have also been employed as coupling partners and can offer some advantages over boronic acids and esters. They can frequently be more easily isolated than boronic acids since they often precipitate out of solution upon addition of aqueous KHF_2 (eqn (4)).[32]



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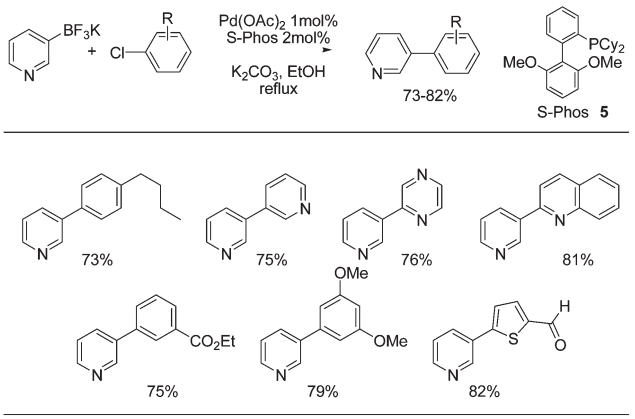
In methodological studies aimed at evaluating the use of aryltrifluoroborate salts in cross-coupling reactions Batey[33] and Molander[34] each reported single examples of 3-pyridyltrifluoroborate in the cross-coupling of an aryl bromide in 69% and 64% yield. In a subsequent report, focusing more intensively on heterocyclic compounds, Buchwald reported the use of potassium 3-pyridyltrifluoroborate in Suzuki coupling reactions with a variety of aryl and heteroaryl chlorides using

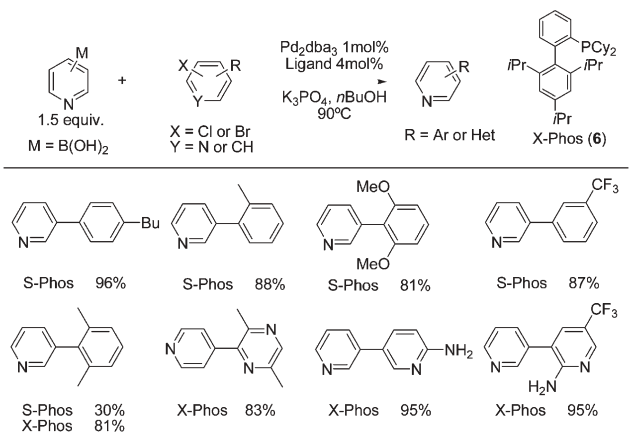


Scheme 7 $Pd(OAc)_2$/S-Phos catalyzed Suzuki coupling of potassium 3-pyridyltrifluoroborates.

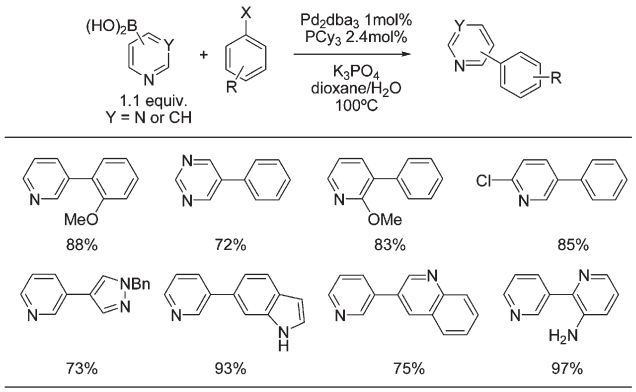
their newly developed S-Phos ligand (**5**) (Scheme 7).[35] These reaction conditions exhibit broad scope, but were not compatible with sterically encumbered aryl chlorides.

In 2005, Buchwald and co-workers extended the scope of Suzuki coupling to also include 3-pyridylboronic acid with hindered aryl chlorides and bromides.[14] They found Pd_2dba_3/S-Phos to be an excellent catalyst for this transformation. Using 2 mol% Pd, they were even able to couple bis-*ortho*-substituted aryl halides. Following this report, Buchwald disclosed the use of another biaryl phosphine ligand, the very sterically encumbered X-Phos ligand (**6**).[36] The use of **6** leads to a very active catalyst, enabling even sterically encumbered aryl chlorides to be cross-coupled in high yield as illustrated by a reaction with 2-chloro-*m*-xylene resulting in 81% yield (compared to only 30% yield with S-Phos) (Scheme 8). The authors propose that the increased activity is due to a larger amount of monophosphine *vs* bisphosphine arylpalladium(II) complexes.[14] Since transmetallation should be sensitive to steric effects, it may be anticipated to be faster on the monophophine complex than the bisphosphine one.

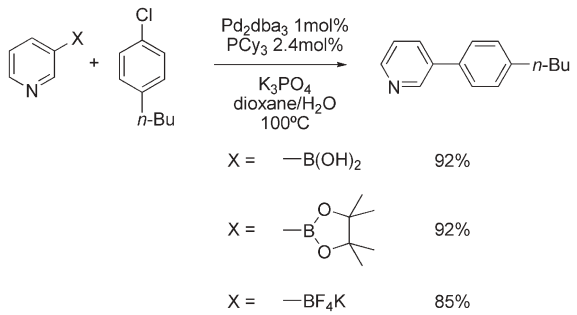
Fu and co-workers have also recently reported reaction conditions for the Suzuki coupling of azine boronic acids as well as other nitrogen containing heterocycles.[37] Their catalyst



Scheme 8 Suzuki coupling of 3- and 4-pyridylboronic acid catalyzed by biarylphosphine catalysts.



Scheme 9 Pd/PCy_3 catalyzed Suzuki coupling of azine boronic acids.

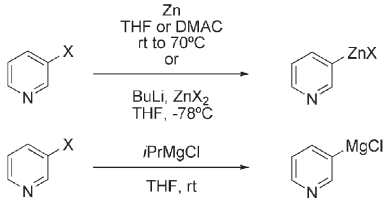


Scheme 10 Effects of boron substitution on Suzuki coupling of pyridyl boronic acids.

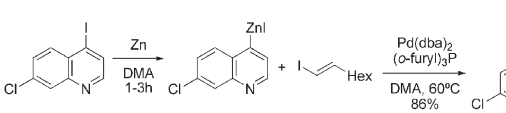
system is based on earlier observations from their group that Pd/PCy_3 in the presence of KF could be an effective catalyst of Suzuki coupling reactions with simple aryl boronic acids.[38] While this system was not effective with 3-pyridylboronic acid, an optimization of reaction conditions led to the finding that K_3PO_4 in conjunction with a dioxane–H_2O co-solvent mixture provided high yields of the corresponding heterobiaryls.[37] Under optimized conditions, consisting of 1% Pd_2dba_3, 2.4% PCy_3, 1.7 equiv. K_3PO_4 in dioxane–H_2O and heating to 100 °C, they were able to achieve the Suzuki coupling of a variety of 3- and 4-pyridylboronic acids as well as 5-pyrimidylboronic acid in high yields (Scheme 9). The reaction conditions were also compatible with boronate esters and trifluoroboroate salts (Scheme 10).

Less common methods

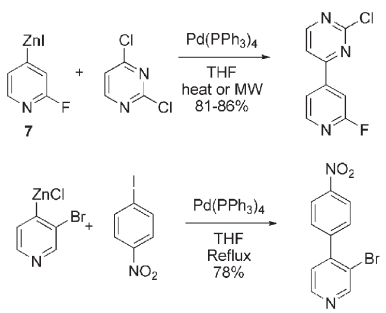
Negishi and Kumada couplings. Given the availability of haloazines, it is not surprising that there are a number of reports dealing with their application in Negishi and Kumada cross-couplings. The organozinc and Grignard reagents needed for these coupling reactions can usually be prepared *in situ* from the halopyridine and used in the cross-coupling reaction without the need for purification. Organozinc reagents can be synthesized by oxidative addition of zinc to a heteroaryl halide or *via* transmetallation of an organolithium species to a zinc salt (eqn (5)).[39] Pyridyl Grignards are easily prepared *via* transmetallation of isopropylmagnesium chloride with a heteroarylhalide (eqn (6)).[40] Although less frequently used than Stille or Suzuki coupling reactions, the convenience of the one-pot procedure, as well as the ready availability of the starting materials, make this a good strategy in the synthesis of heterobiaryls using π-electron deficient azines.



In a study on the preparation and reaction of nitrogen-containing organozinc heterocycles, Knochel and co-workers reported a few examples of Negishi couplings using azine organometallics including the use of 4-quinolyl zinc iodide derivatives (eqn (7)) and 4-quinolyl and 2-pyridyl compounds.[39] Tri-*o*-furylphosphine[25] in conjunction with $Pd(dba)_2$ can be employed with vinyl and aryl iodides and an organozinc reagent generated with zinc dust and the corresponding 4-iodoquinoline derivative in *N,N*-dimethylacetamide.



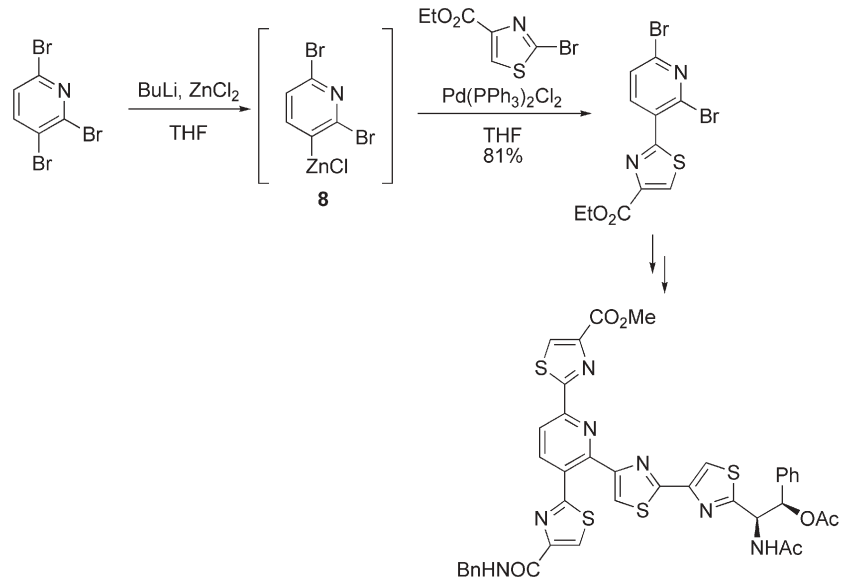
More recently, Stanetty and co-workers studied the Negishi cross-coupling of 4-(2-fluoropyridyl) zinc iodide (**7**) with 2,4-dichloropyrimidine using $Pd(PPh_3)_4$ as the catalyst (eqn (8)).[41] Gallagher and co-workers also used $Pd(PPh_3)_4$ for the Negishi coupling of a variety metallated bromopyridines (eqn (9)).[42]



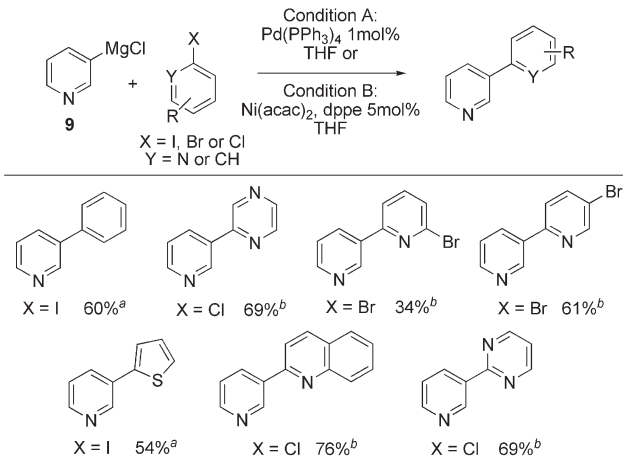
In a recent paper by Bach and Heckmann,[70] selective cross-coupling of a 3-pyridylzinc chloride (**8**) and a 2-bromothiazole was used in the synthesis of a thiazolyl peptide fragment (Scheme 11).

The Kumada coupling of π-deficient heteroaromatic Grignard reagents, on the other hand, has received less attention. Following an early report by Kumada,[43] Mongin, and Knochel described the use of 3-pyridylmagnesium chloride (**9**) in palladium catalyzed Kumada couplings of aryl iodides.[1b] With aryl bromides, on the other hand, use of a $Ni(acac)_2$/dppe catalyst was found to be optimal (Scheme 12). Only heterocyclic aryl bromides and chlorides are reported with yields ranging from 34 to 76% yield.

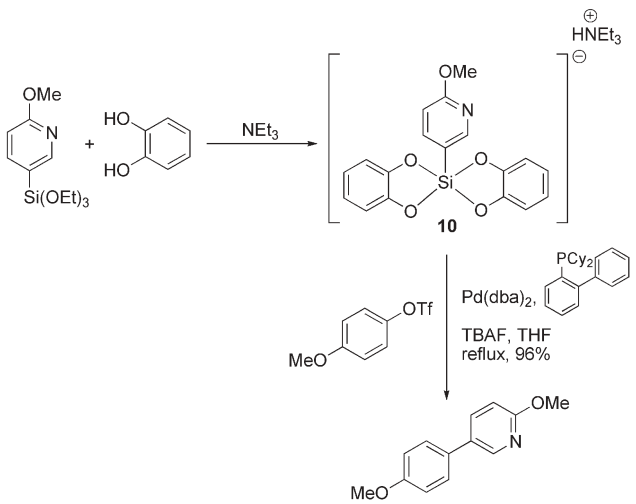
Fürstner and co-workers have described an iron catalyzed Kumada coupling of 3-pyridyl Grignard reagents with heterocyclic aryl chlorides (eqn (10)).[44] This provides an interesting alternative to the use of the more expensive



Scheme 11 Negishi cross-coupling in the synthesis of a GE2270A fragment.

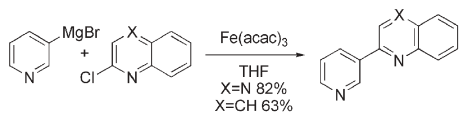


Scheme 12 Kumada coupling of 3-pyridylmagnesium chloride. [a]Conditions: $Pd(PPh_3)_4$ 1 mol%. [b]Conditions: $Ni(acac)_2$ dppe 5 mol%.



Scheme 13 Hiyama coupling of 3-(6-methoxypyridyl) triethylammonium bis (catecol) silicate.

palladium or toxic nickel based systems. Notable are the short reaction and the fact that the reactions can be carried out at low temperatures.

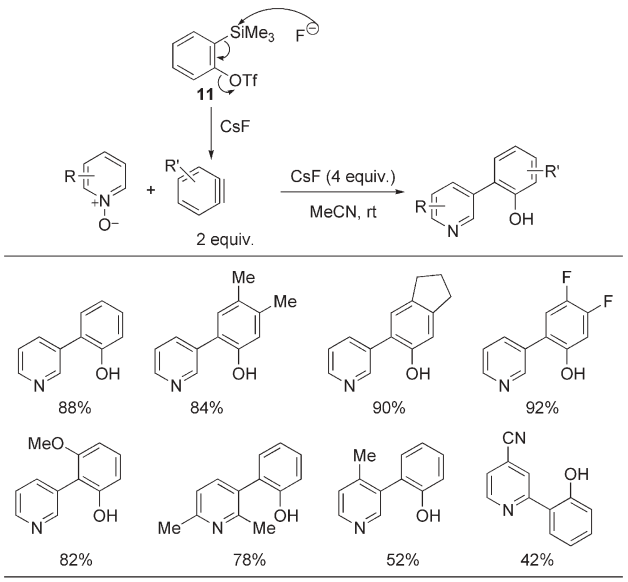


(10)

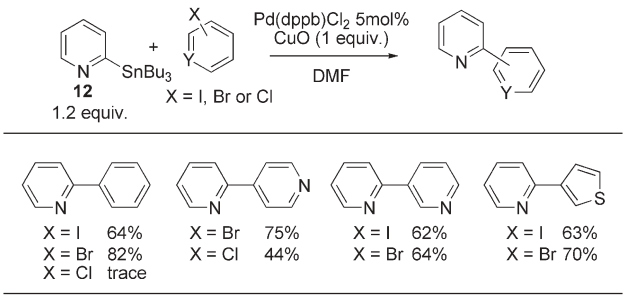
Hiyama coupling. The use of 3- or 4-silyl pyridines in Hiyama cross-couplings is scarce. A rare example, using 3-(6-methoxypyridyl) triethylammonium bis (catechol) silicate (**10**), was recently reported by Seganish and DeShong.[45] The silicate is prepared from the corresponding pyridyl siloxane by treatment with catechol and triethylamine. While the cross-coupling of aryl bromides and chlorides was low yielding, good yields were obtained for the coupling of aryl iodides and triflates using $Pd(dba)_2$ and dicyclohexylphosphinobiphenyl as the ancillary ligand. The use of TBAF as an additive is also necessary for high yields to be obtained (Scheme 13).

Alternative methods

An alternative method for the synthesis of 3-(2-hydroxyaryl) pyridines was recently described by Larock and co-workers.[46] Based on earlier work by Abramovitch,[47] they were able to achieve selective arylation of pyridine *N*-oxides at the 3-position by reaction with an aryne that is generated *in situ* from 2-trimethylsilylphenyltriflate (**11**). The mechanism was studied by Abramovitch and co-workers and involves an initial [3 + 2] cycloaddition followed by rearrangement to give the product.[47] In the process, the *N*-oxide oxygen atom is transferred to the arene at the 2′-position. Selected examples are presented in Scheme 14. While high yields are obtained in most cases, the selectivity observed is modest in the case where regioisomeric phenols can be generated (Scheme 15).



Scheme 14 Synthesis of 3-(2-hydroxyaryl)pyridines *via* aryne and pyridine *N*-oxide.



Scheme 16 CuO mediated palladium catalyzed Stille coupling of 2-pyridyltributylstannane.

2-Azine organometallics

2-Azine organometallics are less commonly employed in cross-couplings which is likely due to their greater instability. In particular, the instability of 2-matallapyridines makes the organometallic preparation and cross-coupling reactions very problematic except in special cases. Nevertheless, chemists have been developing methods to circumvent these limitations by either carefully choosing coupling partners or by developing novel methods. Although there are fewer examples of these species used in cross-coupling, the following section represents a collection of successful applications with emphasis on methodological studies whenever possible. The dominance of the Stille coupling reactions should be noted as it is likely the most reliable use of 2-metallapyridines in cross-couplings. Recent advances in the synthesis of stabilized boron species have allowed for the use of these in Suzuki couplings, albeit in limited scope. Alternatively, new direct arylation methods have begun to appear as alternatives to problematic cross-coupling processes.

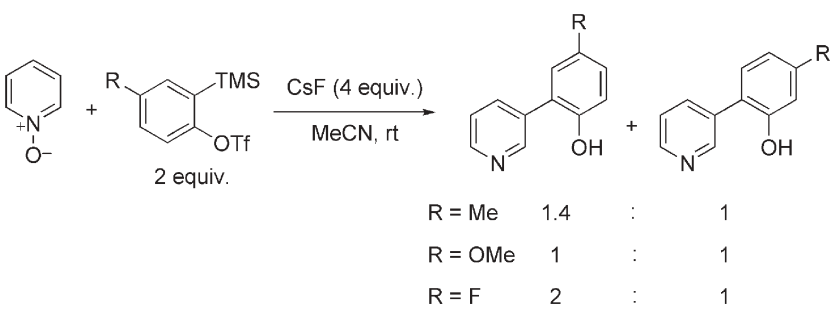
Common methods

Stille coupling. As with the other regioisomers, the prevalence of Stille cross-couplings with 2-stannylpyridines is likely attributable to the relatively high stability of the stannane. Generally, it can be anticipated that reactions of 2-pyridylstannanes with aryl iodides and some aryl bromides will occur in synthetically useful yields.

In 1993, Gronowitz and co-workers reported that addition of cupric oxide to Stille reactions using 2-tributylstannylpyridine led to much faster reaction times and higher yields.[48] The beneficial effect of copper additives in Stille reactions has been studied extensively and can operate *via* various mechanisms. It could accelerate reactions by binding free phosphine which would otherwise bind palladium and increase steric congestion around the metal center therefore slowing transmetallation.[49] Alternatively, copper additives have also been proposed to transmetallate the organostannane generating organocuprates *in-situ* which are more nucleophilic than the corresponding stannanes.[50] Using 5 mol% $Pd(dppb)Cl_2$ and 1 equiv. of CuO in DMF, 2-pyridyltributylstannane (**12**) can be coupled with aryl and heteroaryl iodides and bromides in good yield (Scheme 16). In contrast, they were unable to achieve reactions with aryl chlorides and the more activated 4-chloropyridine was coupled in a modest 44% yield. 2-Stannylpyridines have also been extensively used in the synthesis of functionalized bis- and tris-pyridyl ligands.[51]

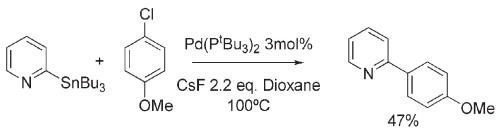
It is also possible to synthesize and use certain 2-stannyl diazines in Stille couplings.[52] Yields for the synthesis of the organometallic vary from 9% to 98% and the Stille coupling using heteroaromatic aryl halides and iodobenzene is achieved using $Pd(PPh_3)_4$ in refluxing toluene over 2 days with yield ranging from 21% to 82% depending on the substrates.

A rare example of a cross-coupling with an aryl chloride and 2-tributylstannylpyridine was reported by Littke, Schwarz and Fu.[53] Their highly active catalyst, based on $Pd(P^tBu_3)_2$



Scheme 15 Regioselectivity of unsymmetrical arynes in 3+2 cycloaddition.

and CsF, promotes the Stille coupling of aryl chlorides and bromides at room temperature. In this report they describe a single example employing 2-stannylpyridine and 4-chloroanisole in refluxing dioxane, resulting in a 47% yield (eqn (11)).

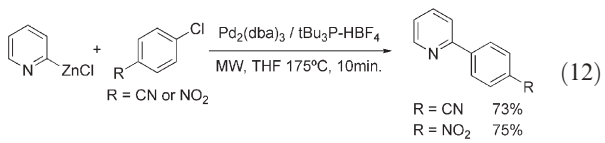


(11)

Negishi coupling. The use of 2-pyridylzinc reagents in Negishi couplings can also be a reliable method. The increased stability and *in situ* formation of these species facilitates their application in cross-coupling reactions.[54] An added advantage is the establishment of well developed techniques for the generation of organozinc reagents.[55] The 2-pyridylzinc halides are usually synthesized either by transmetallation of 2-lithiopyridines or by direct insertion of 2-halopyridines with Rieke zinc.[39] In general reaction conditions used for Negishi couplings with regular aryl zinc halides can be used without modification, and the efficiency of the reaction relies predominantly on the nature of the coupling partners.

In 2003, Fang and Hanan demonstrated that 2-pyridylzinc bromide (**13**) could be efficiently coupled with various 2-bromo and 2-chloroazines to give functionalized bipyridines.[56] A slight excess (1.5 equiv.) of the organozinc reagent is used in conjunction with $Pd(PPh_3)_4$ in THF. Reactions with bromides can be performed at room temperature, whereas the reactions of chlorides necessitate heating to 60 °C (Scheme 17).

Kappe and Walla reported two examples of microwave accelerated Negishi cross-coupling with activated aryl chlorides and 2-pyridylzinc chloride using $Pd_2(dba)_3$ in conjunction with tri-*tert*-butylphosphine as the supporting ligand (eqn (12)).[57]



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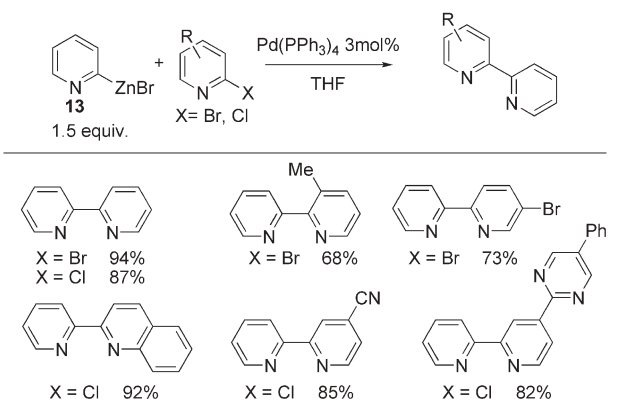


Scheme 17 Bipyridine synthesis *via* Negishi coupling of 2-pyridylzinc bromide.

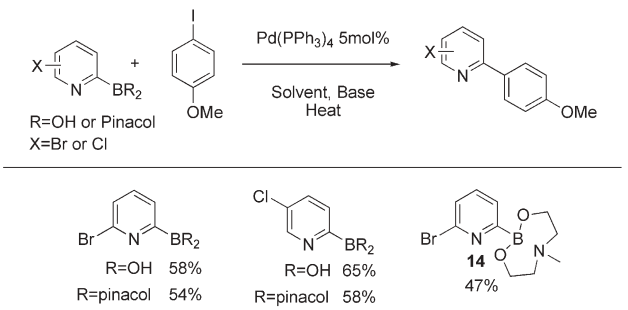
Less common methods

Suzuki coupling. Progress in the use of 2-pyridylboron species in Suzuki cross-coupling has been slower to appear. This can be attributed to the instability of the boron functionality at the 2-position of the pyridine ring,[58] making their use in coupling reactions challenging.

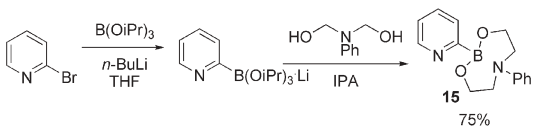
In 2003, Rault and co-workers reported that 5- and 6-halopyridin-2-ylboronic acids and esters could be synthesized and isolated in modest yields.[59] In a series of four papers dealing with the synthesis of halogenated pyridyl boron reagents, they report that the halogenated species are more stable than their non-halogenated counterparts.[29,59] Eleven halo-2-pyridyl boron compounds were synthesized, and five were shown to be suitable cross-coupling partners in the Suzuki reaction. The choice of solvent and base for the cross-coupling depends on the nature of the boron reagent used. If a boronic acid is employed, dimethoxyethane and Na_2CO_3 are optimal, whereas if a boronic ester is used, dimethylformamide and K_3PO_4 is best. A single example with the dioxazaborocane **14** was conducted using a toluene–ethanol mixture and Na_2CO_3 (Scheme 18). Although no explanation is given regarding the increased stability of these halogenated pyridylboron species compared to the non-halogenated compounds, it is plausible that attenuated nitrogen basicity, as a result of the electronegative halide atoms, will diminish protodeboronation.

In the following year, Hodgson and Salingue reported the use of 2-pyridyl dioxazaborocanes (**15**) based on *N*-phenyldiethanolamine in Sukuzki cross-coupling reactions.[60] The one-pot synthesis provides the boronic ester in 75% yield (Scheme 19).

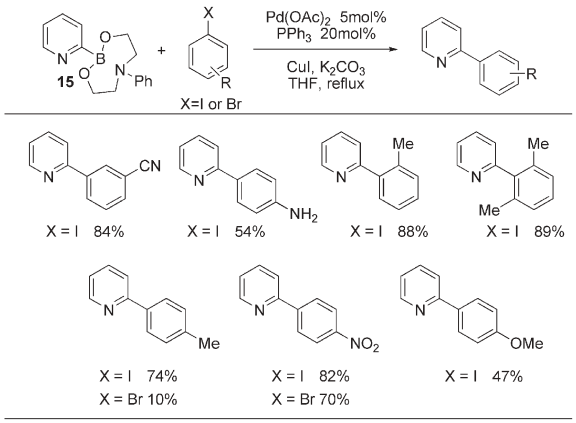
Scope of reaction conditions revealed that **15** is suitable for cross-coupling with activated aryl bromides and iodides as well as non-activated aryl iodides.[60] In contrast, deactivated aryl iodides and non-activated aryl bromides are poor substrates for this reaction. The added stability of **15** likely results from a



Scheme 18 Suzuki coupling of halogenated 2-pyridylboron species.



Scheme 19 Synthesis of dioxazaborocane.

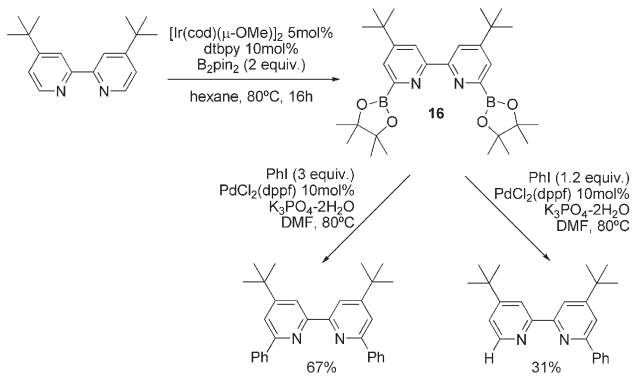


Scheme 20 Suzuki cross-coupling using dioxazaborocane **15**.

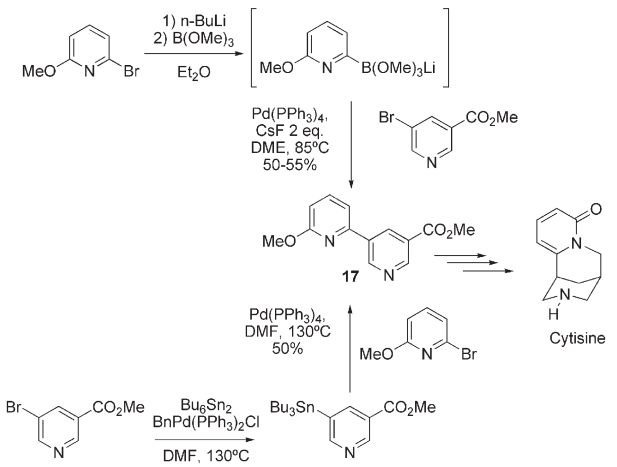
donation of the nitrogen lone pair onto the boron atom resulting in diminished Lewis acidity (Scheme 20).

Marder and co-workers recently reported that it is possible to achieve the direct borylation of pyridines *via* iridium-catalysis.[61] To succeed, the pyridine must bear a substituent at the 2-position to inhibit unproductive binding of the pyridine to the iridium catalyst *via* the nitrogen atom. In one example, 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy), was reacted with the catalyst to provide the bis 2-pyridylboronate pinacol ester **16**, which was then reacted without purification with 3 equiv. of iodobenzene and a palladium catalyst to provide the bis-arylated product in 67% yield. If only 1.2 equiv. of iodobenzene is used, monoarylation is obtained along with protodeboronation of the second boronate ester (Scheme 21).

An *in situ* generation of the organoboron species has also been applied in the total synthesis of Cytisine.[62] O'Neill and co-workers explored the possibility of using a Suzuki coupling to provide **17**. Unfortunately, isolation of the requisite 2-pyridyl boron compound was problematic, leading to low yields (20–30%). To circumvent this limitation they opted for the use of an *in situ* protocol by generating lithium 2-pyridyltrimethoxyborate and subjecting it to the Suzuki cross-coupling conditions without isolation. Using this approach they were able to obtain the cross-coupled compound **17** in 50–55% yield. An alternative synthetic route employing 3-pyridyltributyltin gave similar results.



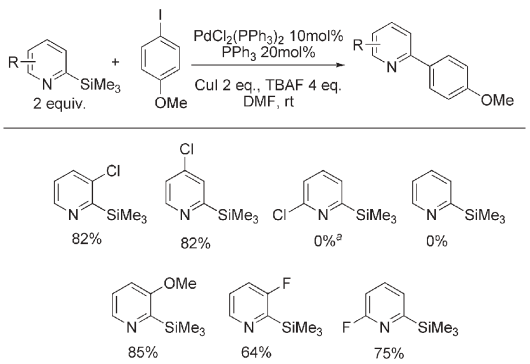
Scheme 21 Iridium-catalyzed borylation of 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy).



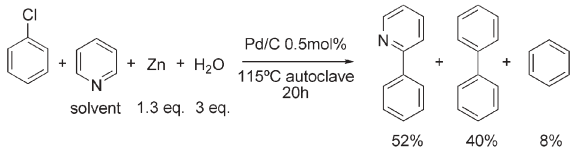
Scheme 22 Total synthesis of Cytisine.

Hiyama and Kumada coupling. In 2005 Gros and co-workers reported that chloropyridyltrimethylsilanes are stable enough to be isolated and used in Hiyama cross-couplings. For example, 3- and 4-chloro-2-pyridylsilanes can be reacted with aryl iodides and heteroarylbromides in good yields using 10 mol% $PdCl_2(PPh_3)_2$ in the presence of 20 mol% PPh_3, 2 equiv. CuI and 4 equiv. TBAF (Scheme 23).[63] 3-Methoxy-2-pyridylsilane, as well as 3- and 6-fluoro-2-pyridylsilanes, can also be cross-coupled in useful yields. The authors propose that the heteroatom on the pyridyl ring plays a dual role. First, these substituents may increase the polarization of the carbon–silicon bond, which can assist the formation of silicate species by reaction with a fluoride anion and facilitate transmetallation. Second, they can attenuate the basicity of the pyridyl nitrogen atom, which could reduce its propensity to bind the palladium catalyst in unproductive modes. This type of substitution appears to be necessary for cross-coupling to occur as illustrated by the fact that reaction with 2-trimethylsilylpyridine does not occur.

There are very few examples of Kumada coupling reactions using 2-pyridyl Grignard reagents largely due to their inherent instability.[43] These, along with 2-pyridyl organolithiums, are usually handled at very low temperature and under very anhydrous conditions to avoid protodemetallation and/or decomposition.



Scheme 23 Hiyama cross-coupling with 2-pyridylsilanes.



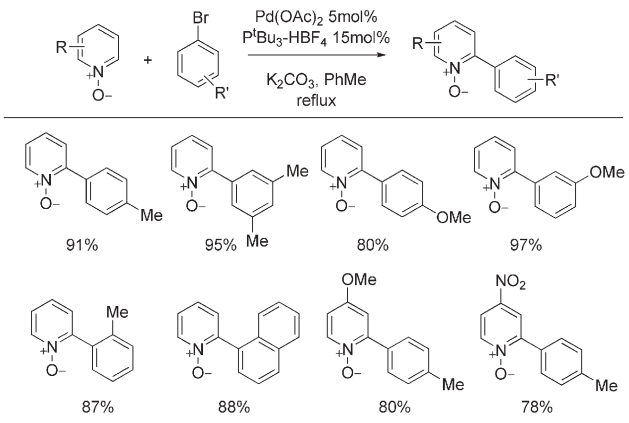
Scheme 24 Direct arylation of pyridine with chlorobenzene.

Alternative methods

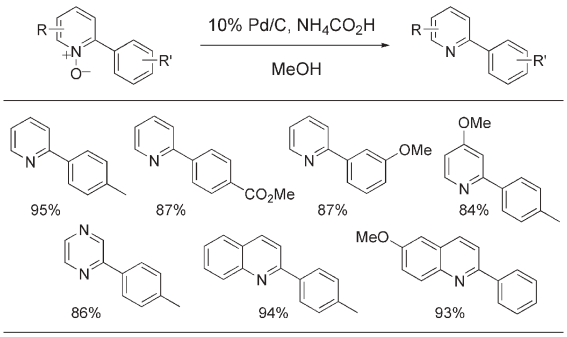
Direct arylation. In light of the greater challenge associated with the use of 2-metalla-azines in cross-coupling reactions, new methods for their preparation and use are warranted. Alternatively, new strategies are also being developed to circumvent the use of organometallics altogether. One such strategy is direct arylation[64] where the unstable organometallic component is replaced with a cheap and bench stable alternative.

In 2000, Sasson and co-workers reported that it was possible to prepare 2-phenylpyridine by using a Pd/C, zinc, water catalyst system in conjunction with chlorobenzene and pyridine (Scheme 24).[65] Addition of 5% 2,6-di-*tert*-butyl-4-methylphenol (BHT) to the reaction leads to a reduction of the reaction rate by two orders of magnitude. The authors suggest the participation of free radicals in the rate-determining step, although the observation that no chlorobiphenyls are detected suggests that these radicals would only exist in close proximity to the catalyst surface. The use of the zinc–water–palladium system was demonstrated to produce hydrogen *in situ* which is critical for catalytic turnover.[66]

In 2005, Fagnou, Campeau and Rousseaux reported that bench-stable pyridine *N*-oxides are useful substitutes for 2-metallapyridines in palladium catalyzed cross-coupling reactions.[67] Direct arylation of pyridine *N*-oxide occurs in good to excellent yields with complete selectivity for the 2-position (Scheme 25). Reactions are typically performed with 5 mol% $Pd(OAc)_2$, 5 to 15 mol% of a trialkylphosphine ligand (added as the air-stable hydrogen tertafluoroborate salt), and K_2CO_3 as the base in refluxing toluene or dioxane. Using similar reaction conditions it is possible to obtain successful cross-coupling with quinolines, isoquinolines, pyrazines, pyridazines and their derivatives.[68]



Scheme 25 Direct arylation of pyridine *N*-oxide.



Scheme 26 Reduction of *N*-oxide function with palladium and ammonium formate.

More than 70 examples have been demonstrated with yields ranging from 40–99% using various aryl chlorides, bromides and iodides. The 2-arylpyridine *N*-oxide product can then be readily removed under mild conditions[69] to afford the 2-aryl azine products (Scheme 26).

Conclusion

The importance of azine-containing biaryls in pharmaceutical and materials chemistry has prompted many methods for their synthesis. The cross-coupling protocols developed over the past few years for the use of azine organometallics will undoubtedly find significant use by synthetic chemists. While Stille reactions remain the most reliable method for the use of azine organometallics in cross-coupling, recent advances in Suzkui coupling of borylated azines are enabling their use in a growing number of circumstances. Alternative methods such as direct arylation have also allowed for the synthesis of a variety of 2-arylazines in high yield from cheap and readily available starting materials and will undoubtedly grow in scope and application in the coming years. Given the need for efficient methods for the incorporation of heterocyclic moieties in pharmaceutical compounds, it can be anticipated that continued growth and exciting new advances will continue in this important subdomain of metal catalyzed cross-coupling research.

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