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Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands

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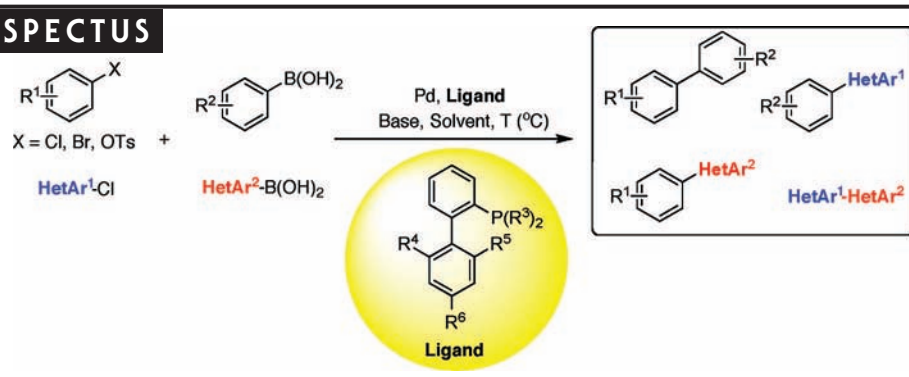

The cores of many types of polymers, ligands, natural products, and pharmaceuticals contain biaryl or substituted aromatic structures, and efficient methods of synthesizing these structures are crucial to the work of a broad spectrum of organic chemists. Recently, Pd-catalyzed carbon–carbon bond-forming processes, particularly the Suzuki–Miyaura cross-coupling reaction (SMC), have risen in popularity for this purpose. The SMC has many advantages over other methods for constructing these moieties, including mild conditions, high tolerance toward functional groups, the commercial availability and stability of its reagents, and the ease of handling and separating byproducts from its reaction mixtures.

Until 1998, most catalysts for the SMC employed triarylphosphine ligands. More recently, new bulky and electron-rich phosphine ligands, which can dramatically improve the efficiency and selectivity of such cross-coupling reactions, have been introduced. In the course of our studies on carbon–nitrogen bond-forming reactions, we found that the use of electron-rich and bulky phosphines enhanced the rate of both the oxidative addition and reductive elimination processes; this was the beginning of our development of a new family of ligands, the dialkylbiarylphosphines **L1**–**L12**. These ligands can be used for a wide variety of palladium-catalyzed carbon–carbon, carbon–nitrogen, and carbon–oxygen bond-forming processes as well as serving as supporting ligands for a number of other reactions.

The enhanced reactivity of these catalysts has expanded the scope of cross-coupling partners that can be employed in the SMC. With use of such dialkylbiarylphosphine ligands, the coupling of unactivated aryl chlorides, aryl tosylates, heteroaryl systems, and very hindered substrate combinations have become routine. The utility of these ligands has been successfully demonstrated in a wide number of synthetic applications, including industrially relevant processes.

In this Account, we provide an overview of the use and impact of dialkylbiarylphosphine ligands in the SMC. We discuss our studies on the mechanistic framework of the reaction, which have allowed us to rationally modify the ligand structures in order to tune their properties. We also describe selected applications in the synthesis of natural products and new materials to illustrate the utility of these dialkylbiarylphosphine ligands in various "real-world" synthetic applications.

Introduction

The impact of the Suzuki–Miyaura reaction (SMC) on academic and industrial research, as well as on production, has been immense.[1] Over the past two decades, it has become arguably one of the most efficient methods for the construction of biaryl or substituted aromatic moieties; com-

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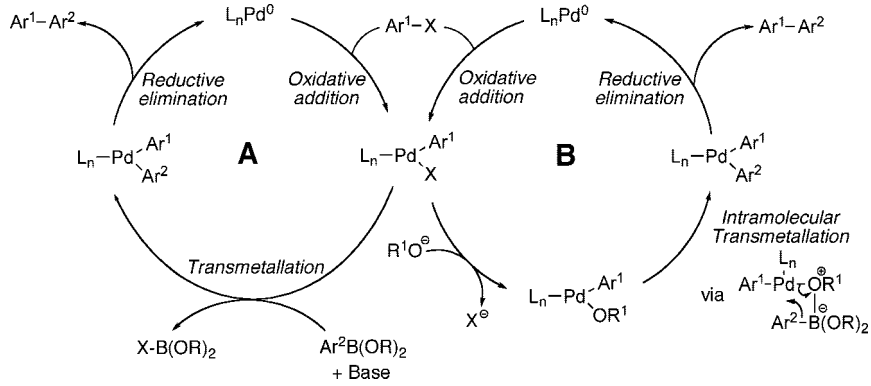


FIGURE 1. General catalytic cycle for Suzuki–Miyaura couplings.

pounds that contain these substructures constitute important building blocks of polymers,[2] ligands,[3] a wide range of natural products such as alkaloids, and numerous biologically active pharmaceuticals.[4] The key advantages of the SMC are the mild conditions under which it is conducted, the high tolerance toward functional groups that is observed, the commercial availability and stability of boronic acids to heat, oxygen, and water, and the ease of handling and separation of boron-containing byproducts from the reaction mixtures.[5] These desirable features make the SMC an important tool in medicinal chemistry as well as in the large-scale synthesis of pharmaceuticals and fine chemicals.[6] In addition to aryl and heteroaryl boronic acids and esters, vinyl and alkyl derivatives are also commonly used in the SMC. In order to simplify the text of this Account, we will focus most of the discussion on the use of the aryl and heteroaryl species.

As in other cross-coupling reactions, the catalytic cycle of the palladium-catalyzed SMC is thought to follow a sequence involving the oxidative addition of an aryl halide to a Pd(0) complex to form an arylpalladium(II) halide intermediate. Transmetalation with a boronic acid and reductive elimination from the resulting diarylpalladium complex affords the corresponding biaryl and regenerates the Pd(0) complex (Figure 1).[7] The bases we have most commonly employed for these processes are K_3PO_4 and K_2CO_3. Others including KOH or KF have also been used. At present, however, the choice of base is still empirical, and no general rule for their selection has been established. The role of the base in these reactions is to facilitate the otherwise slow transmetalation of the boronic acid by forming a more reactive boronate species that can interact with the Pd center and transmetalate in an intramolecular fashion (path A).[8] Alternatively, it has also been proposed that the base replaces the halide in the coordination sphere of the palladium complex and facilitates an intramolecular transmetalation (path B).[9] While in most cases the exact nature of the actual catalyst remains ambiguous, recent reports with bulky ligands have provided circumstantial evidence of a mechanism involving highly reactive monoligated L_1Pd species, where the L/Pd ratio can play a large role in the catalytic performance.[10]

Most early work in the SMC was conducted using triarylphosphines as supporting ligands. During the last ten years, the application of new ligands has dramatically improved the efficiency and selectivity attainable in such cross-coupling reactions. In the ever-growing catalogue of available ligands for cross-coupling reactions, bulky dialkylbiaryl-[11] and trialkylphosphines[12] remain the most widely used, followed by *N*-heterocyclic carbenes (NHCs).[13]

The purpose of this Account is to provide an overview of the use and impact of dialkylbiarylphosphine ligands in SMC. Selected applications in the synthesis of natural products and new materials that illustrate the utility of these ligands will also be discussed.

Background: Dialkylbiarylphosphines

Since their introduction in 1998, monodentate, bulky, and electron-rich dialkylbiarylphosphines (Figure 2) have seen wide use as supporting ligands in a variety of transformations, especially in Pd-catalyzed carbon–carbon,[14] carbon–nitrogen,[15] and carbon–oxygen bond-forming processes.[16]

These ligands can be prepared in a direct one-pot protocol by addition of an aryl Grignard or an aryllithium reagent to an in situ generated benzyne intermediate, followed by trapping the intermediate with an appropriate chlorophosphine (Scheme 1).[3] These compounds have been prepared on a >10 kg scale, and efforts to increase the scale of their production are underway. The ready availability of Grignard and organolithium reagents makes the route highly modular, thereby allowing the preparation of a variety of new and structurally diverse ligands.

In addition to the high reactivity of catalytic systems based upon biarylphosphines, these ligands possess a number of

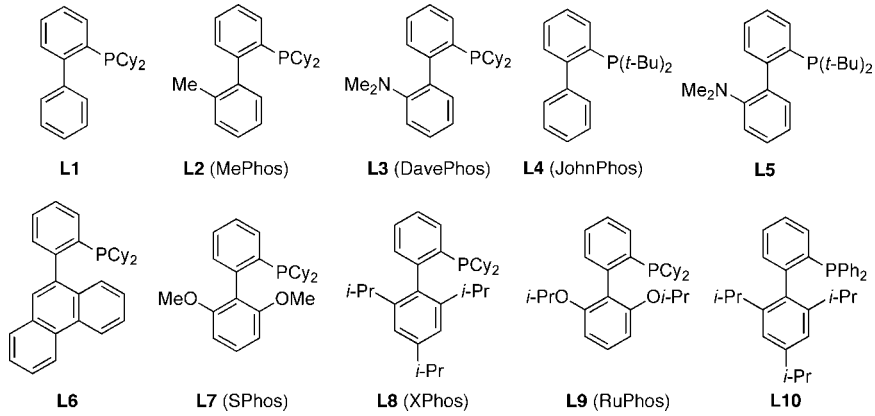
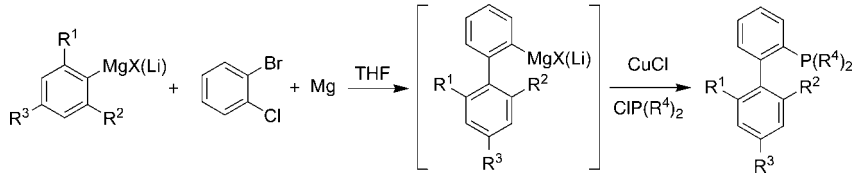


FIGURE 2

SCHEME 1



attributes that make them particularly attractive for organic synthesis: (a) they are crystalline materials, (b) they are air stable, even in solution,[17] (c) they possess a high degree of thermal stability, (d) many of these ligands are commercially available from either Strem or Aldrich, and (e) the processes that employ these ligands are operationally simple, not requiring the use of a glovebox.

In Figure 3, we show the different structural features of the biarylphosphine ligands and how each of these contributes to the efficiency of the catalysts that are derived from them. The studies that we have carried out provide us with a mechanistic framework with which to rationally modify the ligand structures in order to tune their properties. This and the fact that their synthesis is short and modular provide us with a mechanistically guided process for the evolution of ligands that confer enhanced properties on the catalysts derived from them.

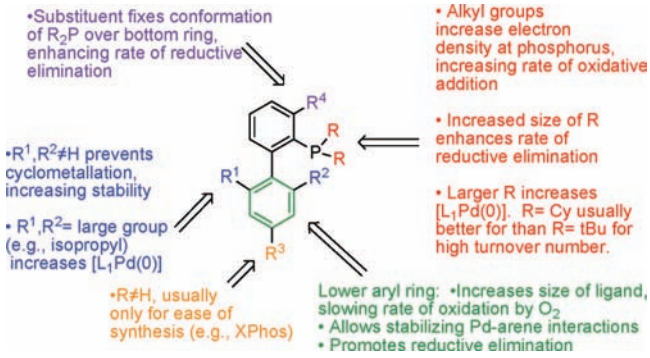


FIGURE 3. Structural features of the dialkylbiarylphosphines and their impact on the efficacy of catalysts using these ligands.

As indicated, the outstanding activity of the catalysts derived from the biarylphosphine ligands has been attributed to a combination of electronic and steric properties that enhances the rates of oxidative addition, transmetalation, and reductive elimination steps in the catalytic cycle. This can be rationalized as follows: (a) The bulky and electron-donating character of these ligands is important for stabilizing the monoligated L_1Pd intermediates, which are believed to be key species in the catalytic cycle (Figure 1).[10] (b) With both these and related ligands it has been shown that oxidative addition of aryl halides is much faster with $L_1Pd(0)$ species than with more highly coordinated complexes.[18] This is simply due to the smaller size of a $L_1Pd(0)$ complex compared with a $L_2Pd(0)$ one, allowing the substrate to approach the latter more closely and, hence, react at a faster rate. We presume that transmetalation to a $L_1Pd(Ar)X$ intermediate is faster, in general, than to a $L_2Pd(Ar)X$ complex for related reasons. (c) It is well-documented that the rate of reductive elimination from LPd(Ar)R (R = aryl, NR_2, OR) is faster than that for the same process for an analogous $L_2Pd(Ar)R$ complex.[19] (d) Finally, studies in our laboratories have demonstrated that the addition of *ortho* substituents on the bottom ring of the biarylphosphine (eg., SPhos (**L7**) and XPhos (**L8**)) lead to a significant increase in activity and stability by preventing palladacycle formation.[20] Additionally, this *ortho*, *ortho'* substitution increases the size of the ligand relative to those with no *ortho* substituents (thus increasing the concentration of L_1Pd species).

TABLE 1

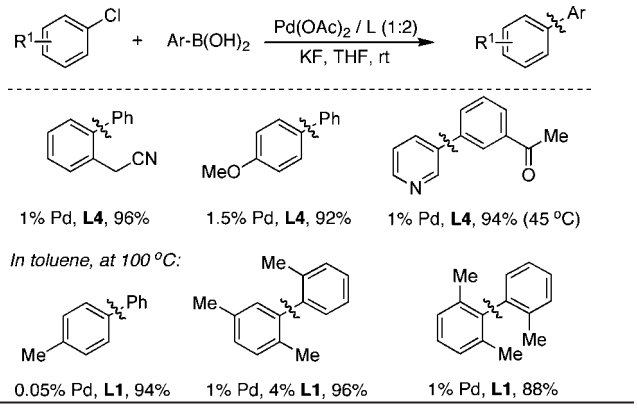
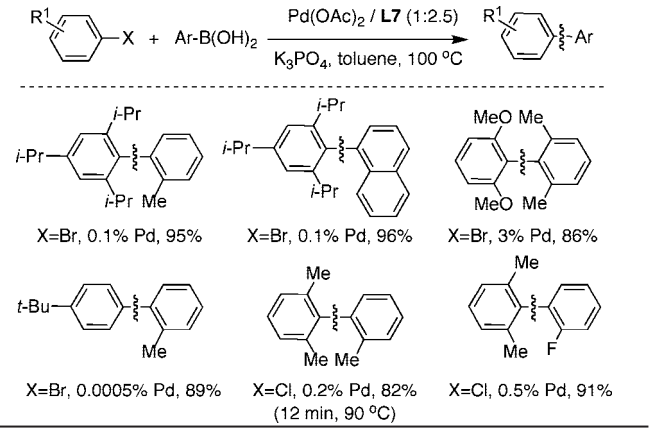


TABLE 2



Development of General Catalysts for Suzuki–Miyaura Reactions

There has been an impetus to develop catalysts for the SMC that can efficiently couple hindered substrate combinations, utilize unactivated aryl chlorides[21] and heteroaryl substrates, and operate at low catalyst loadings or at room temperature or both.

While evaluating the efficacy of dialkylbiaryl phosphine ligands in carbon–nitrogen bond-forming reactions, we found that the use of DavePhos (**L3**) provided a particularly active catalyst for SMC as well.[22] We note that, at the same time, our colleagues in the Fu group developed their important chemistry for SMC using P^tBu_3 as a supporting ligand.[23] Further studies revealed that catalysts supported by JohnPhos (**L4**) were substantially more reactive than those with DavePhos (**L3**) in SMC at room temperature (Table 1).[24] These results indicated that the dimethylamino group in DavePhos (**L3**) was not necessary for effective catalysis. While JohnPhos (**L4**) provided the best results for room-temperature reactions, the use of the dicyclohexyl analogue (**L1**), provided a more active system when low catalyst loadings were used or with more hindered substrate combinations.[25] That JohnPhos (**L4**) gives a more active system at room temperature than ligands with a dicyclohexyl phosphino group is almost certainly due to the greater concentration of $L_1Pd(0)$ and $L_1Pd(Ar)Cl$ intermediates (instead of the corresponding L_2Pd complexes) with JohnPhos (**L4**) than with the latter class of ligands.

Reactions involving the cross-coupling of two hindered arenes where each reactant possessed two *ortho* substituents remained difficult. At the time of this work, the only example reported in the literature for the synthesis of unsymmetrical tetra-*ortho*-substituted biaryls had been accomplished using a Negishi cross-coupling reaction.[26] Our initial efforts utilized phenanthrene derivative **L6**, which proved to be an excellent ligand for the construction of tetra-*ortho*-substituted biaryls via SMC.[27]

We later found that SPhos (**L7**), which can be prepared in an experimentally convenient one-pot protocol from 1,3-dimethoxybenzene, was an outstanding ligand for this and other purposes. The reactions with catalysts based upon SPhos (**L7**) exhibited unprecedented scope, reaction rate, and stability.[28] The new catalytic system was also found to be remarkably efficient for the cross-coupling of unactivated aryl chlorides and bromides at catalyst loadings as low as 5×10^{-4} mol % Pd (Table 2).

We attribute the longevity of catalysts based on SPhos (**L7**) to two main factors. First is the stabilization of Pd(0) intermediates by favorable interactions of the aromatic π system with the Pd center as supported by X-ray crystallography of the **L7**/Pd^0(dba) complex. As shown in Figure 4, this complex possesses a Pd(0) η^1-arene interaction with the *ipso* carbon.[29] We also believe that the high activity of catalysts based on SPhos (**L7**) is due to the ability of this ligand to stabilize and maximize the concentration of the L_1Pd intermediates with a relatively small ligand (e.g., compared with XPhos (**L8**)). These intermediates would be expected to be particularly reactive in oxidative addition and transmetalation processes for the reasons previously discussed.

In order to probe the reasons for the high stability and activity of SPhos (**L7**) as a supporting ligand in SMC, we conducted ground-state energy optimizations on the corresponding oxidative addition complex (**L7**–Pd(Ph)Cl) by DFT computational studies, and four minima were found (Figure 5).[30]

The most favored structures possess either a Pd–arene interaction with the *ipso* carbon (**II**) or a Pd–O interaction with an oxygen atom of the methoxy group of the bottom ring of

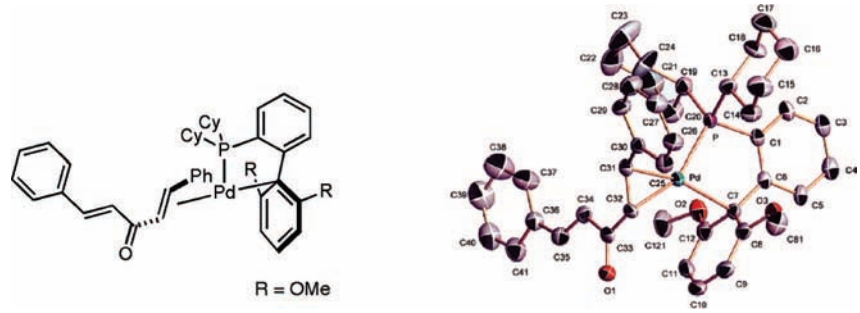


FIGURE 4. Reproduced with permission from ref 28b. Copyright 2005 American Chemical Society.

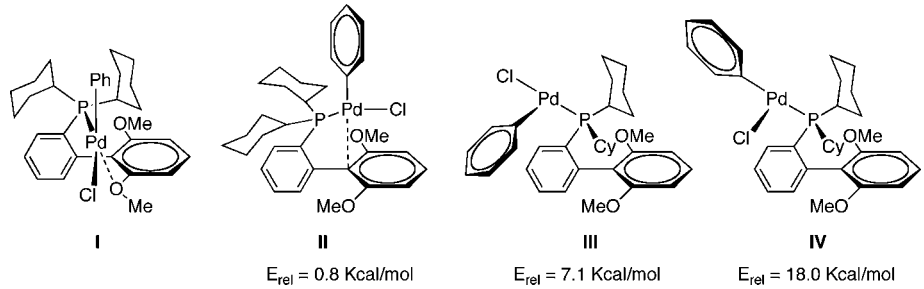


FIGURE 5. Ground-state energy optimizations of L7–Pd(Ph)Cl.

the ligand (**I**). We believe that both the Pd–arene and Pd–O interactions contribute to the stability and hence to the efficiency of catalysts based on SPhos (**L7**). In particular, the existence of this extra Pd–O interaction relative to other dialkylbiarylphosphines likely further stabilizes the oxidative addition intermediate before the transmetalation step. Because this is believed to be the rate-limiting step in SMC,[31] this complex should be present in a relatively high concentration, and hence its stabilization is of great importance. Supporting evidence consistent with these theoretical findings was found experimentally by NMR spectroscopy of the isolated oxidative addition product **L7**–Pd(Ph)Cl.[30] While at 25 °C the ^{31}P NMR spectra showed two main peaks with a relative ratio of 72:28, the two peaks rapidly and reversibly coalesce at about 45 °C (Figure 6). This experimental data is consistent with two rotameric species of **L7**–Pd(Ph)Cl, for example, **I** and **II**, which were the two lowest energy conformers found by DFT calculations (Figure 5).

Overall, these results shed light on the specific nature of the interactions accessible to Pd complexes based upon SPhos (**L7**) and are consistent with the notion that they stabilize the intermediate complexes and contribute to the long-lived nature of these catalysts.

The green character of water has prompted many groups to investigate the use of this reaction medium for cross-coupling reactions.[32] We found that SPhos (**L7**) could be sulfonated on the bottom ring in quantitative yield by simple treatment with H_2SO_4.[33] This water-soluble version of SPhos (**L11**) allowed SMC to proceed in excellent yields with a wide

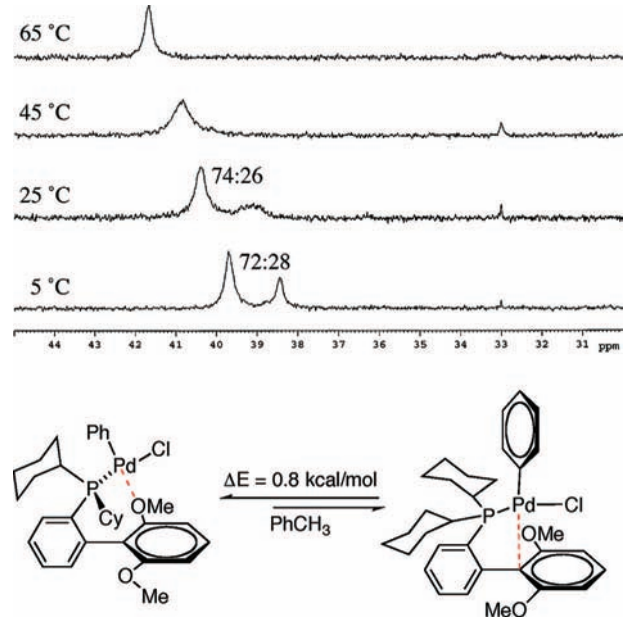


FIGURE 6. Reproduced with permission from ref 30. Copyright 2007 American Chemical Society.

variety of substrates, including highly functionalized aryl chlorides or heteroaryl halides with either aryl or alkyl boronic acids in aqueous media (Table 3).

Nitrogen heterocycles are structural constituents of a wide variety of biologically active natural products, medicinally important compounds, and organic materials. Their construction and derivatization by cross-coupling processes is widespread.[34] In general, however, cross-coupling reactions with heteroaryl substrates have proven significantly more challenging than those with all-carbon substrates.[35] Consequently, the

TABLE 3

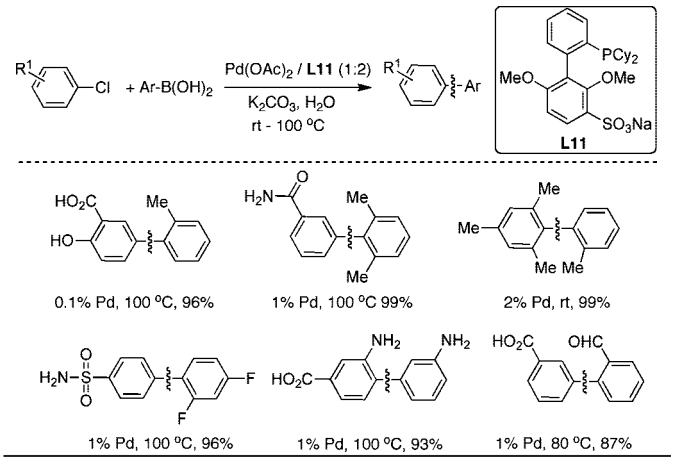
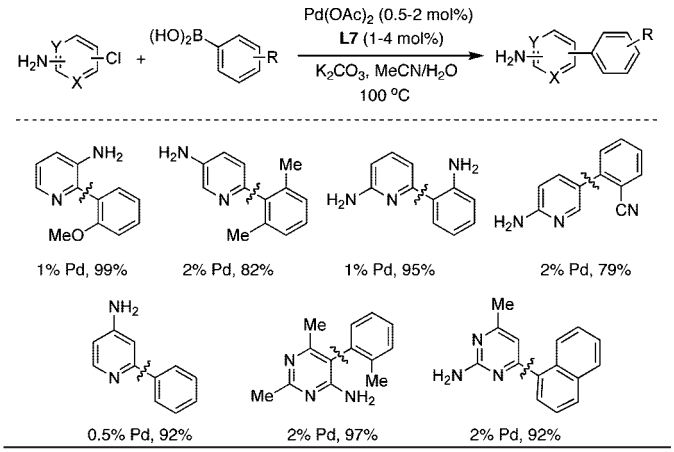
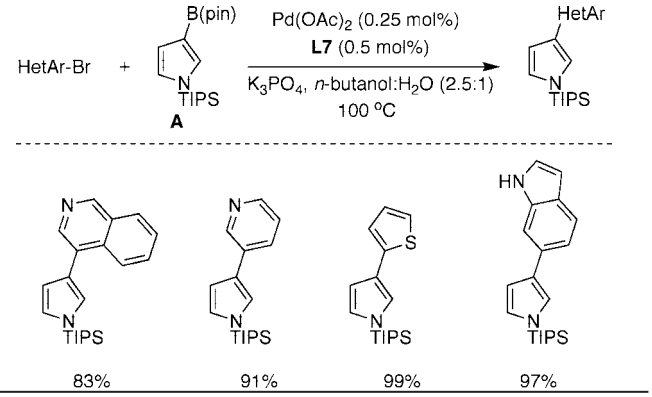


TABLE 4



problems associated with these coupling processes have, to some extent, limited their application in drug development. As one example, chloroaminopyridines and chloroaminopyrimidines are quite difficult substrates to employ in cross-coupling processes. In some instances, chemists have resorted to protecting the free amino group in order to use these substrates.[36] It has also been suggested that it is requisite to employ bidentate ligands in order to prevent binding of the substrate or product to Pd(II) intermediates, which would result in catalyst deactivation.[37] Given these reports, we decided to examine the SMC of heteroaryl compounds using SPhos (**L7**) and XPhos (**L8**) as the supporting ligands. We found, in contrast to what had been suggested for the earliest versions of dialkylbiarylphosphines,[37] that catalysts based on SPhos (**L7**) were not inhibited by the presence of aminopyridines or aminopyrimidines (Table 4).[38] In addition, electron-rich, electron-deficient, and sterically hindered boronic acids reacted smoothly, producing the desired biaryls in high yields. An interesting example was the coupling of phenylboronic acid

TABLE 5



with 4-amino-2-chloropyridine, the most basic among the substrates used to provide the products shown in Table 4. While this coupling has been reported to proceed in low yields, even with bidentate ligands,[37] with SPhos (**L7**) the product was efficiently formed.

As part of our study of the SMC of heterocycles, we examined in detail the use of pyrrole-derived boronic acids and esters. A key to achieving success in this venture was when we studied the solvent dependence of the reaction of *N*-TIPS-3-pinacolboronatepyrrole (**A**) with heteroaryl bromides.[39] The key to these coupling reactions was the use of alcoholic solvents, with *n*-butanol being the most efficient. The effect of alcohol solvents can be rationalized by Miyaura's results.[9] We also discovered that the presence of water was critical to the success of the reactions, presumably due to the need for partial or complete hydrolysis of the boronate ester. In addition, its presence led to higher yields of product and less reduction of the aryl halide. A study was conducted in which it was determined that the optimum ratio of *n*-butanol/water was 2.5:1 with respect to the rate and efficiency of the reaction of **A** and 2-bromothiophene (Table 5).

Similarly, *n*-butanol proved to be the ideal solvent for the SMC of *N*-Boc-pyrrole-2-boronic acid (**B**) with aryl and heteroaryl bromides possessing a variety of functional groups (Table 6);[39] in this case, however, the addition of water resulted in poor yields due to an increased production of reduced aryl halide. In constrast to prior reports,[40] significant homocoupling or protodeboronation of **B** was not detected using a catalyst system based upon SPhos (**L7**).

The use of XPhos (**L8**) as supporting ligand allowed an expansion of the scope of the SMC for the combination of thiophene and pyridylboronic acids with a wide range of activated and unactivated heteroaryl chlorides, even highly basic aminopyridines, with high efficiency and relatively low catalyst loadings (Table 7).[39] These results are of particular signif-

TABLE 6

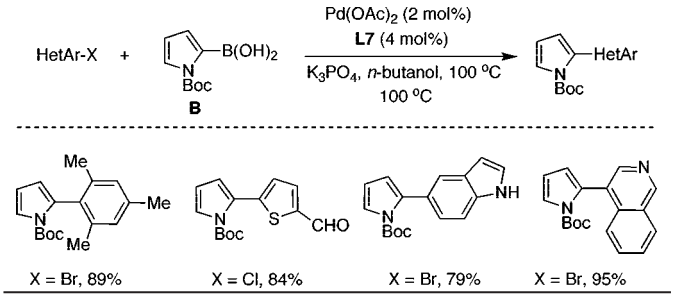
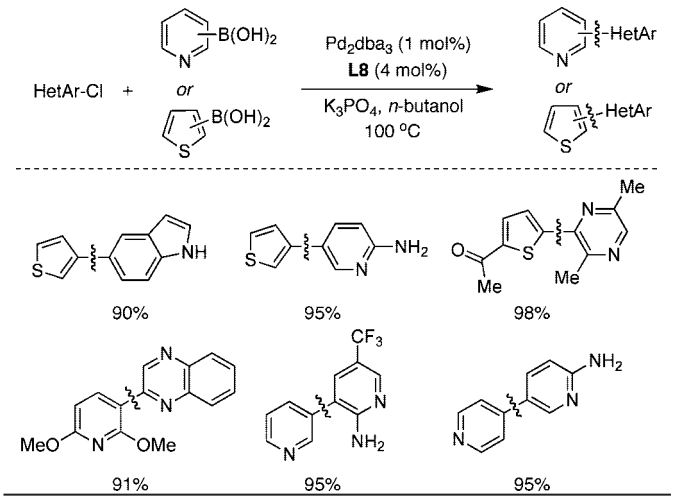


TABLE 7



icance due to the slow rate of transmetalation and the tendency of these coupling counterparts to undergo protodeboronation in polar solvents.

In recent years Pd-catalyzed methods have emerged for the preparation of aryl boronate esters from unactivated aryl chlorides.[41] Unfortunately, they typically require high catalyst loadings and long reaction times and manifest a limited ability to utilize functionalized substrates or sterically encumbered substrates. We have recently demonstrated that SPhos (**L7**) or XPhos (**L8**) provide highly active catalysts for the borylation of aryl chlorides under mild reaction conditions (Table 8).[42]

A catalyst system based on SPhos (**L7**) could be employed for the direct, one-pot synthesis of unsymmetrical biaryls from different aryl or heteroaryl chlorides. In this process, the substrates were subjected to the standard Pd-catalyzed borylation conditions with subsequent addition of the second aryl chloride and aqueous K_3PO_4, resulting in the clean formation of the desired biaryls (Table 9).[42]

Selected Synthetic Applications

Once it became clear that catalysts derived from biarylphosphine ligands possessed a higher level of activity than previous systems, their application in target-oriented and other

TABLE 8

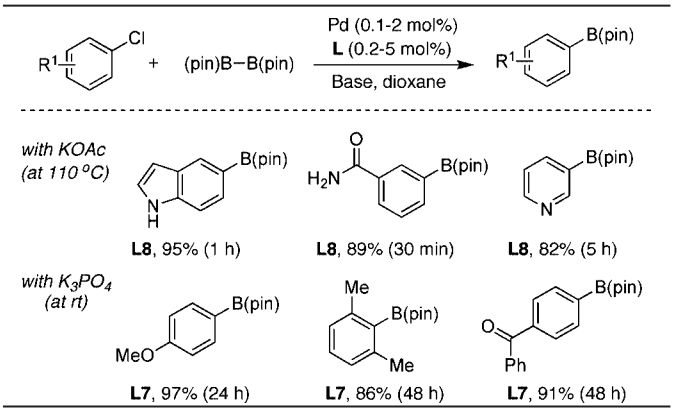
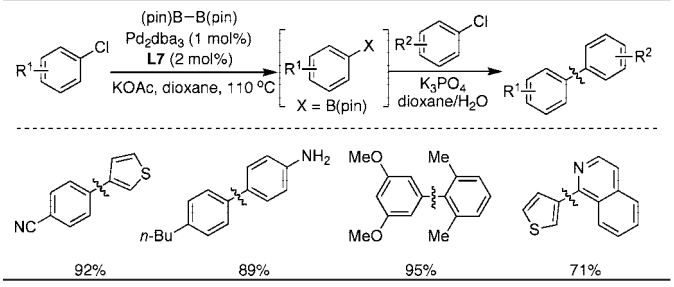


TABLE 9



areas of organic synthesis began to appear rapidly. The examples discussed are illustrative of the utility of these catalysts in a variety of venues.

In early 2004, Jacobsen reported the first catalytic asymmetric synthesis of quinine and quinidine.[43] Along the way, he needed to conduct the cross-coupling of an advanced boronate ester intermediate with the bromoquinoline compound. Attempts under standard SMC conditions proved unsuccessful. However, the use of SPhos (**L7**) at room temperature afforded the desired *trans* olefin in a selective fashion (Figure 7).

In 2005, the group of Hall and our research group reported the total syntheses of several members of the family of the eupomatilones.[44] Both approaches relied upon a highly efficient SMC of different highly oxygenated aryl halides using SPhos (**L7**) as the ligand (Figure 8). In the MIT approach,[44a] a very low catalyst loading (0.005 mol % palladium) could be achieved for this transformation, in part because of the presence of an *ortho* carbomethoxy group. Hall's route had the advantage of being more convergent but required a very challenging SMC.[44b] In his publication, he stated, "All other attempted conditions and catalysts failed in this notoriously difficult substitution pattern for a Suzuki–Miyaura biaryl cross-coupling."

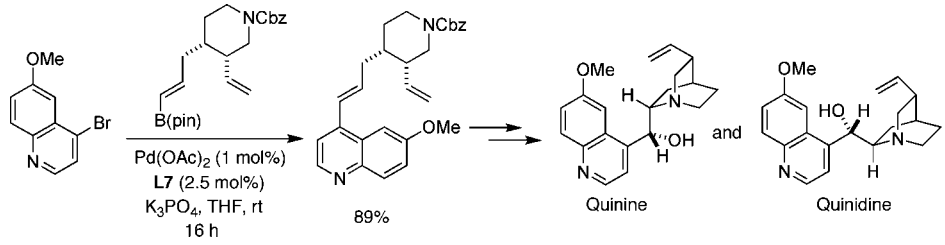


FIGURE 7

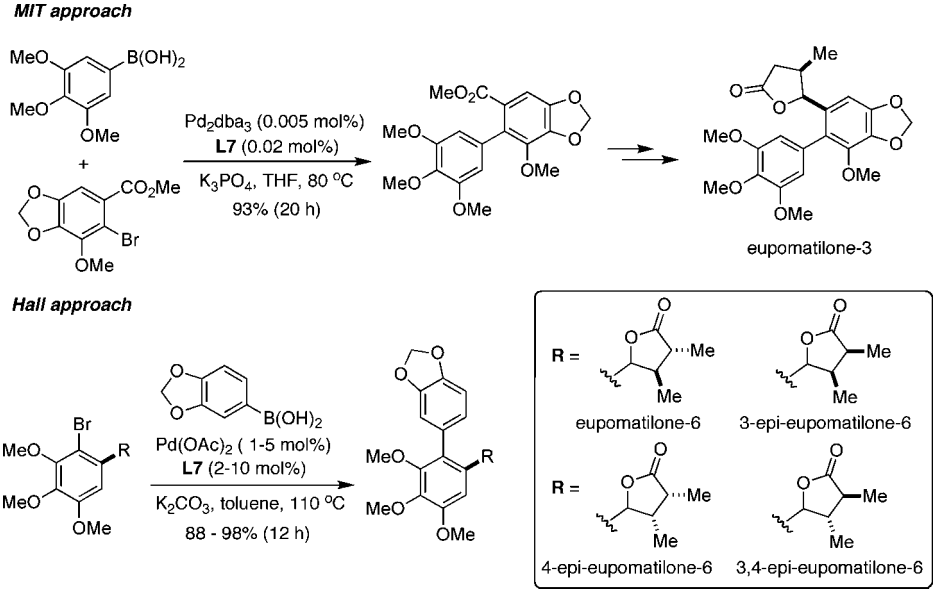


FIGURE 8

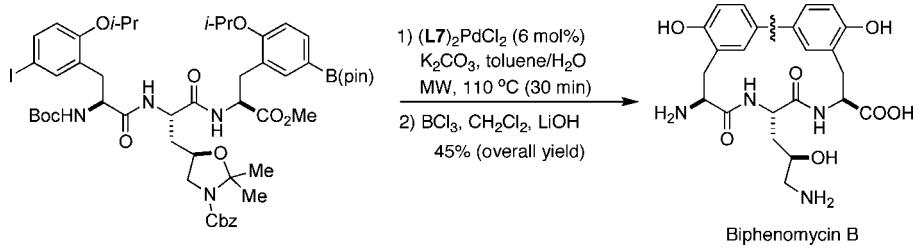


FIGURE 9

Biphenomycin B, a compound structurally related to the vancomycin glycopeptide antibiotics, displays potent activity against β-lactam-resistant bacteria. Recently, Zhu has disclosed a concise total synthesis of this important alkaloid by way of an intramolecular SMC (Figure 9).[45] The synthetic challenges posed by the seemingly simple biaryl fragment should not be underestimated. A detailed survey of reaction conditions led to a process that demonstrated the superior activity of SPhos (**L7**), affording an intermediate containing the desired biaryl backbone. Global deprotection provided biphenomycin B in high overall yield.

In 2006, Podlech reported the total synthesis of altenuene, a compound with activity toward HeLa cells.[46] In his approach, two highly functionalized precursors were combined to give the intermediate shown below by means of SMC using SPhos (**L7**) as the ligand (Figure 10). In this work, the formation of the carbon–carbon bond precedes creation of the lactone unit, which forms with liberation of the phenolic hydroxyl group previously protected as an acetal. Subsequent deprotection of the diol moiety in acidic media afforded altenuene in good overall yield.

The molecular complexity of natural products such as vindoline, a biosynthetic precursor of the potent antitumor agent vinblastine, constitutes another example to test the use of the dialkylbiaryl phosphine ligands. As shown below, Rawal used the SMC of alkenyl boronic acids with C15-bromovindoline, a heavily functionalized coupling counterpart that proceeded in good yield using XPhos (**L8**) as a supporting ligand (Figure

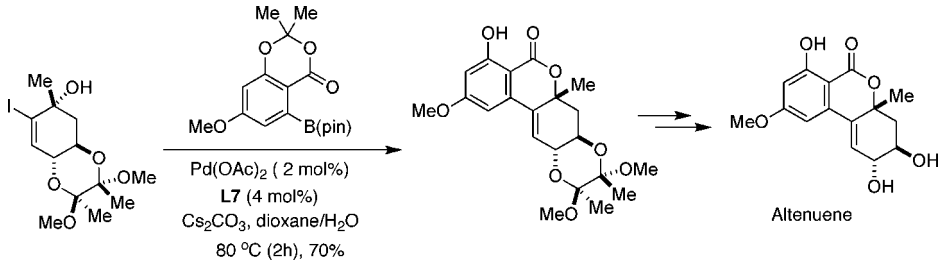


FIGURE 10

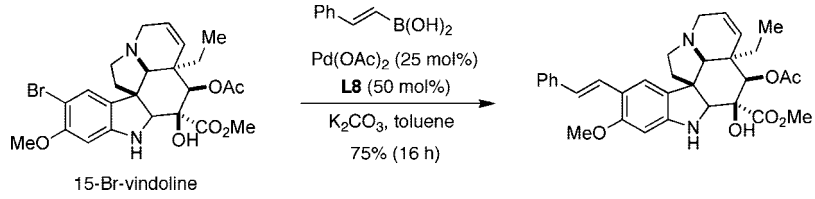


FIGURE 11

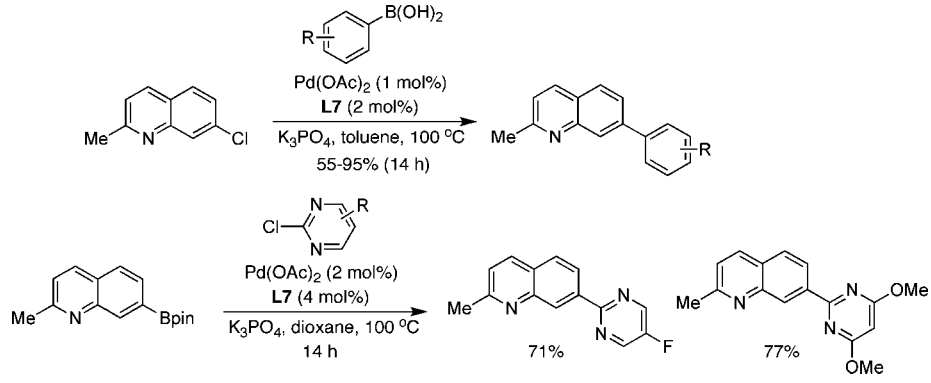


FIGURE 12

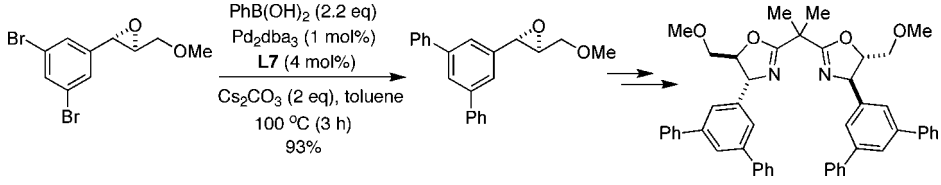


FIGURE 13

11).[47] It is worth mentioning that only XPhos allowed for an efficient coupling process with alkenyl boronic acids; other ligands tested by the authors gave the desired product in low yield. Despite the high catalyst loading required, this example illustrates the applicability of the method to the derivatization of highly functionalized molecules.

Studies of metabotropic glutamate receptors have shown that they are involved in maladies such as anxiety, depression, mental retardation, and pain. Recently, Newman has designed a series of heterobicyclic templates with essential features of the pharmacophores of mGluR5 antagonists.[48] His approach relied on the SMC of heteroaryl halides and heteroarylboronic acids or esters. SPhos (**L7**) turned out to be the most efficient ligand, giving rise to the desired heterobicyclic cores in good yields (Figure 12).

Although the tolerance of activated epoxides in transition-metal catalyzed cross-coupling reactions has little precedent,[49] Pericàs showed that SPhos (**L7**) was the optimal supporting ligand in the SMC of enantiomerically pure epoxides in high yield.[50] The straightforward synthesis of these compounds allowed rapid access to chiral C_2 symmetrical bis(oxazolines), potentially useful ligands for asymmetric catalysis (Figure 13).

Another application of SPhos (**L7**) is the preparation of 2,6-di(quinolin-8-yl)-pyridine compounds, which have been reported to be excellent bistridentate ligands for Ru(II) complexes, providing complexes with microsecond luminescent lifetimes. Johansson demonstrated that these compounds can be efficiently prepared by the double SMC of an heteroarylboronic acid and halopyridine derivatives (Figure 14).[51]

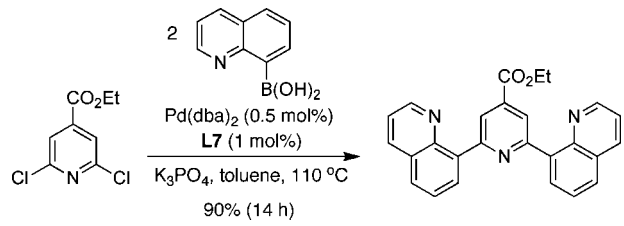


FIGURE 14

Deprés recently described the first total synthesis of naturally occurring geigerin, a member of the guaiane class of sesquiterpenes.[52] This approach was accomplished in only 8 steps from the tropylium cation without the need for protecting groups. The installation of the C4 methyl group was achieved by SMC of an advanced synthetic intermediate using SPhos (**L7**) as the supporting ligand (Figure 15). This is one of the few examples of a SMC with alkylboronic acids that has been described in the total synthesis of a natural product.[53]

Cacchi has recently described the synthesis of derivatives of the catechins, biologically active compounds that have exhibited anticarcinogenic properties and the inhibition of platelet aggregation. In his report, a small library of 8-arylated analogues of the relatively hindered and highly electron-rich catechin core was prepared using the SMC (Figure 16).[54] While most of the commonly employed catalyst systems gave unsatisfactory results, the use of SPhos (**L7**) afforded the desired compounds in excellent yield.

The unusual structural features of allocolchicine and steganacin have spurred a number of studies on their synthesis. Baudoin described the asymmetric synthesis of biaryl hybrids of these important molecules that featured an atropodiastereoselective biaryl SMC in which a benzylic hydroxyl stereocenter was able to confer diastereoselectivity in the constitution of the biaryl axis (Figure 17).[55] As shown in the figure, the use of DavePhos (**L3**) as the ligand in the optimized reaction conditions afforded the best compromise of yield and diastereoselectivity.

Ratanhine is a complex neolignan. Its total synthesis by Burke reflects the effect of the availability of general SMC methods in retrosynthetic planning (Figure 18).[56] This route involves the clever assembly of coupling partners that contains both an aryl bromide and a protected (in an inactive form) boronic acid. It is worth mentioning that all of the carbon–carbon bond-forming reactions in the iterative route shown in the figure are Pd-catalyzed SMCs. In this particular case, the use of **L1** proved to be optimal when using highly stable *N*-methyliminodiacetic acid protected organoboranes.

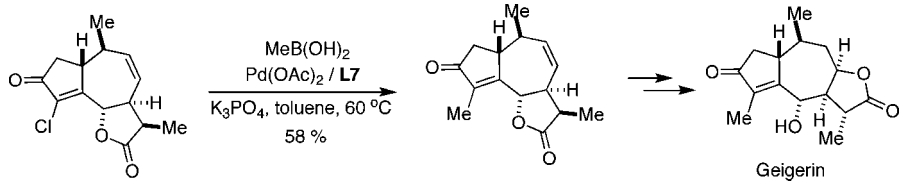


FIGURE 15

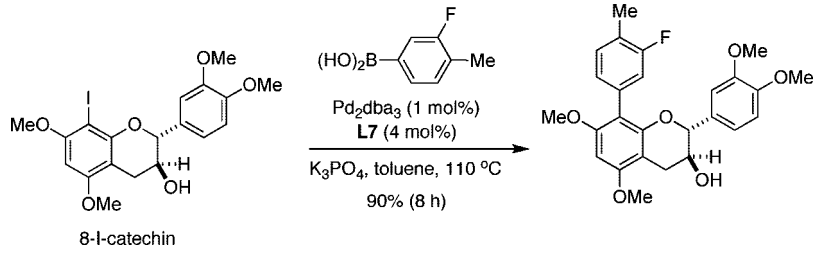


FIGURE 16

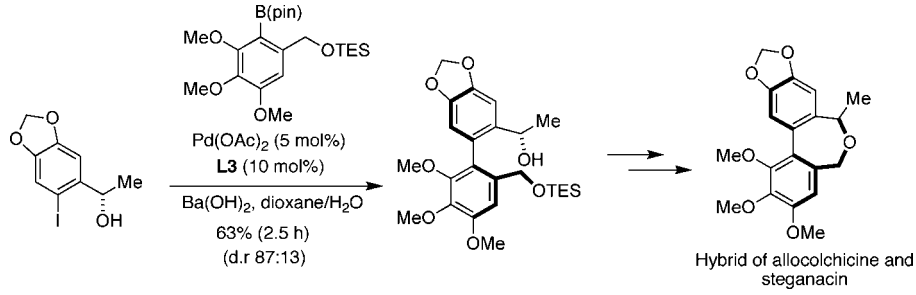


FIGURE 17

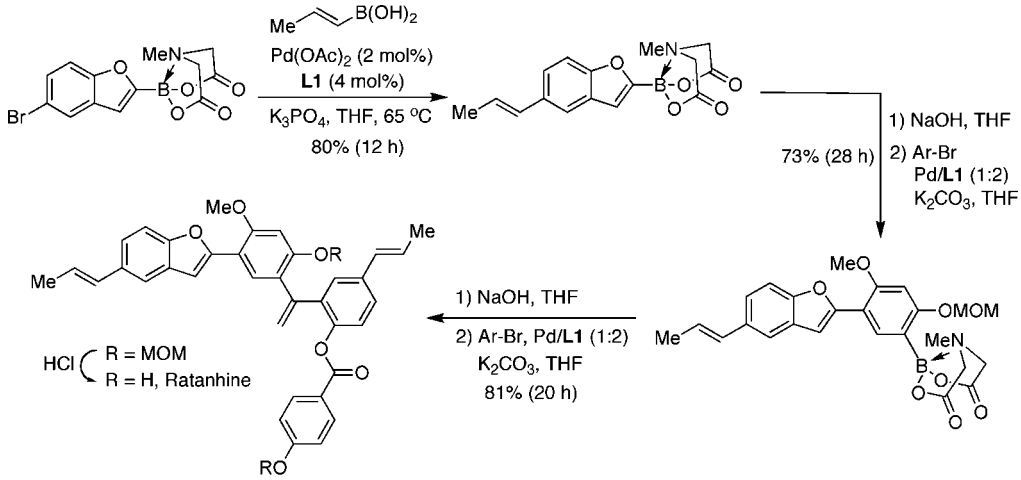


FIGURE 18

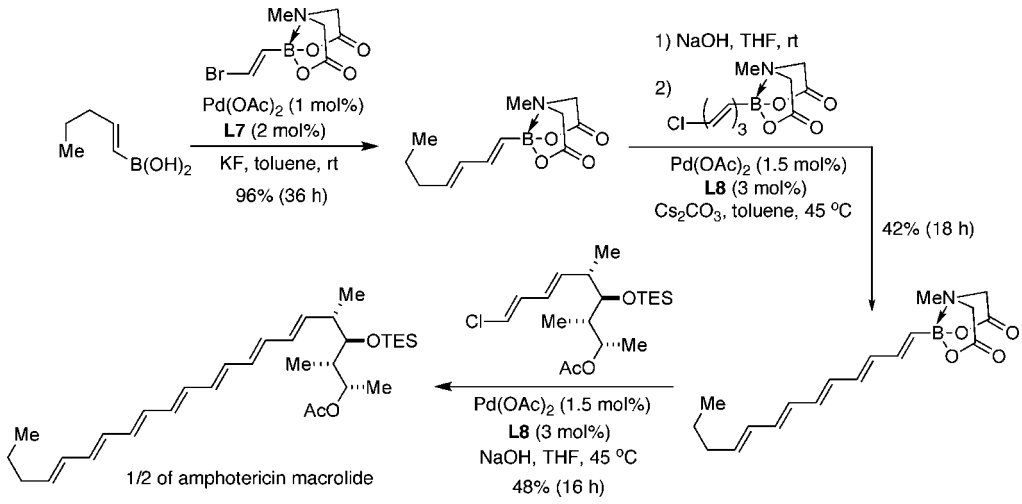


FIGURE 19

The same concept was used by Burke as an impressive illustration of the power of the iterative Suzuki–Miyaura approach in the synthesis of the amphotericin B skeleton.[57] In this particular case, SPhos (**L7**) and XPhos **(L8)** proved to be necessary supporting ligands for the key SMC (Figure 19). In view of its high efficiency, the route depicted in this figure holds promise for the application of B-protected haloalkenylboronic acids to the synthesis of a variety of complex polyene-containing natural products.

Organic semiconductors and materials are important components of many optoelectronic and photonic applications, such as light-emitting diodes, photovoltaics, lasers, or sensors. Most of these systems include a π-conjugated backbone, such as oligothiophene or indolo[3,2-*b*]carbazole skeletons. Yamaguchi[58] and Leclerc[59] have described highly modular routes to these interesting compounds with formation of several carbon–carbon bonds by SMC using SPhos (**L7**) as the ligand (Figure 20).

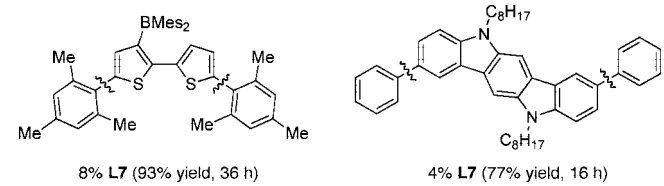


FIGURE 20

The examples shown herein illustrate the broad applicability of the SMC supported by dialkylbiarylphosphine ligands. Given that SPhos (**L7**), perhaps the most versatile ligand for these reactions, was only reported in 2004, we are confident that a great number of important applications will be reported in the future.

Summary

Dialkylbiarylphosphine ligands have been demonstrated to be applicable to a wide variety of Pd-catalyzed cross-coupling reactions.

The range of substrates for SMC based on these ligands include aryl bromides, aryl triflates, unactivated aryl chlorides, aryl tosylates, a variety of heteroaryl systems, and very hindered substrate combinations. Such processes are highlighted by their broad scope and often can be carried out at room temperature or with low catalyst loadings or both. The properties of these ligands can be varied with respect to the steric and electronic effects associated with the substituents in the biaryl backbone due to the modular nature of their synthesis.

Upon the basis of the use of these ligands in Pd-catalyzed C–C bond-forming processes in target-oriented synthesis to date, we strongly believe that the performance and the synthetic applicability of dialkylbiarylphosphine ligands in metal-catalyzed cross-coupling reactions will be utilized even further in future endeavors.

We sincerely thank all co-workers from the Buchwald laboratory and in particular those involved in the studies referred to in this Account for their invaluable intellectual and experimental contributions. This research has been supported by the National Institutes of Health (Grant GM-46059). Merck, Amgen, BASF (gifts of Pd compounds), Nippon Chemical, and Boehringer Ingelheim are gratefully acknowledged for additional support.

BIOGRAPHICAL INFORMATION

Ruben Martin received his Ph.D. in 2003 at the University of Barcelona with Prof. Antoni Riera. In 2004, he moved to the Max-Planck-Institut für Kohlenforschung as a Humboldt postdoctoral fellow with Prof. Alois Fürstner, where he worked in the application of Fe-catalysts for cross-coupling and Alder-ene type reactions. He then undertook further postdoctoral studies at MIT with Prof. Stephen L. Buchwald where he is currently working on new synthetic strategies for metal-catalyzed C–C and C–N bond-forming reactions.

Stephen L. Buchwald is currently the Camille Dreyfus Professor of Chemistry at the Massachusetts Institute of Technology (MIT). He has been a member of the MIT faculty since 1984. He has received numerous awards including the American Chemical Society award in Organometallic Chemistry (2000) and for Creative Work in Synthetic Organic Chemistry (2006), the Bristol-Myers Squibb Award for Distinguished Achievement in Organic Synthesis (2005), and the Siegfried medal (2006). He has also been elected as a fellow of the American Academy of Arts and Sciences (2000) and as a member of the National Academy of Science (2008).

FOOTNOTES

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