4
The Contemporary Suzuki–Miyaura Reaction

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4.1
Introduction

4.1.1
Preamble and Outlook

The "tried, tested, and true" transformations that are relied upon most heavily by synthetic chemists all have one underlying commonality – they are general. It is no wonder, then, that much effort is continuously dedicated to realizing new thresholds for reactions that aim to further improve their general application. This quest is largely fueled by an ever-evolving understanding of reaction mechanisms in parallel with the discovery of novel chemicals and methodologies. Since its discovery, Pd-mediated (and to a lesser extent Ni-mediated) cross-coupling has evolved into one of the most reliable means to construct C−C and C−N bonds; indeed, many synthetic routes contain at least one step that relies on this methodology [1–3]. Sifting out all the nuances that distinguish one cross-coupling from another makes it clear that the reaction conditions that are the most general unsurprisingly constitute the most widely utilized cross-coupling, namely, the Suzuki–Miyaura reaction [2–10].

Over the past decade, the Suzuki–Miyaura reaction has been pushed to new limits by way of the rational design of highly active and efficient catalysts [11–13]. These endeavors have paid off handsomely and have garnered enhanced scope and generality for this reaction. This chapter will serve to ledger these recent achievements, placing focus on (i) new ligands that yield highly active catalysts capable of coupling (ii) aryl chlorides and (iii) sterically hindered substrates and (iv) unactivated alkyl electrophiles, with advances in the last two areas making possible (v) the asymmetric Suzuki–Miyaura reaction. The chapter will close with a synopsis of (vi) iterative and orthogonal Suzuki–Miyaura cross-couplings. Although the focus of this chapter is on boronic acids, a variety of organoboron derivatives will be discussed for the sake of completeness.

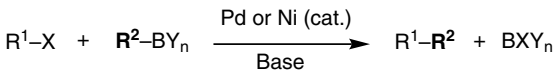
Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials, Second Edition.
Edited by Dennis G. Hall.

4.1.2
A Brief History

In 1978, Negishi and coworkers discovered that 2-iodotoluene could be coupled with lithium 1-heptynyltributylborate, establishing for the first time that organoboranes were effective transmetalating agents in Pd-mediated cross-couplings [14, 15]. Neutral alkenylboranes were next applied by Suzuki and Miyaura, where they found that the addition of an exogenous base was necessary to effect the cross-coupling of these organometallic species [16, 17]. The Suzuki–Miyaura reaction has since evolved into the most commonly applied cross-coupling reaction in both academia and industry alike [5–7]. This stems primarily from the many attractive attributes of boronic acids and their derivatives, including trifluoroborates (discussed in detail in Chapter 14), such as their air and moisture insensitivity, thermal stability, functional group tolerance, and negligible toxicity, with myriad boronic acids being commercially available [18–20].

4.1.3
Mechanistic Aspects

The general scheme for the Suzuki–Miyaura reaction is presented in Scheme 4.1. The catalytic cycle begins and ends as it does for most other cross-couplings, with oxidative addition and reductive elimination, respectively (Figure 4.1). The Suzuki–Miyaura reaction is unique in that it is the only cross-coupling that requires the addition of a stoichiometric excess of base. Base has been found to drastically accelerate the transmetalation step of the catalytic cycle [1]. Two proposed pathways for metal–metal exchange have been put forward to rationalize the observed enhancement in rate (Path A and B) [21]. In Path A, the boronic acid and base react to form a borate that is sufficiently electron-rich to transmetalate with the Pd(II) oxidative addition adduct. The rate of transmetalation also depends on the cation of the base in addition to the halide (X) of the electrophile, that is, the rate decreases in the order X = Cl > Br > I, suggesting that transmetalation is more facile with more electrophilic Pd species. In Path B, a transient (oxo)palladium(II) intermediate is formed prior to transmetalation with a neutral organoborane. Path B is consistent with experimental results showing that preformed (oxo)palladium(II) intermediates undergo transmetalation with neutral organoboranes in the absence of added base. In most



R^1, $\mathbf{R^2}$ = Aryl, Alkenyl, Benzyl, Allyl, Alkyl
X = I, Br, Cl, OTf, OTs, OPiv
BY_n = $B(OH)_2$, $B(OC(Me_2)C(Me_2)O)$, 9-BBN, BF_3^-
Base = ^-OH, CO_3^{2-}, PO_4^{3-}, F^-

Scheme 4.1 The general reaction scheme for the Suzuki–Miyayra reaction. BBN = borabicyclo [3.3.1]nonane; Piv = pivalate; Tf = trifluoromethanesulfonate; Ts = 4-toluenesulfonate.

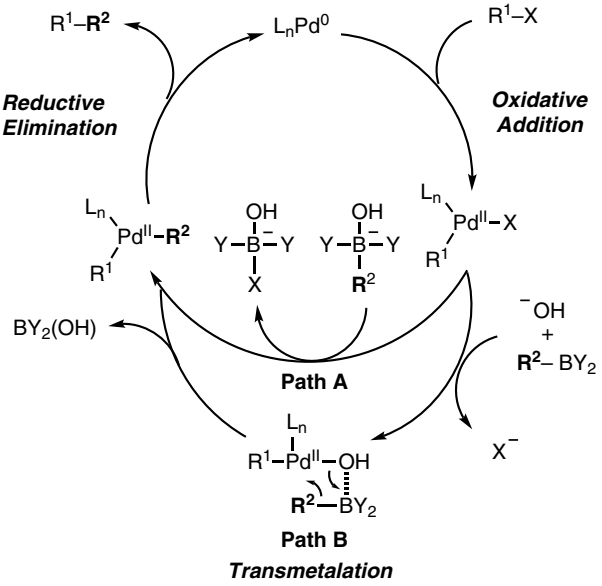


Figure 4.1 The general catalytic cycle of the Suzuki–Miyaura reaction. Refer to Scheme 4.1 for the definition of R^1, R^2, Y, and X, and the text for elaboration.

Suzuki–Miyaura cross-couplings, both Path A and B are believed to be operational concurrently, and it is not immediately obvious as to why one pathway predominates under a particular set of reaction conditions.

The choice of base and solvent in the Suzuki–Miyaura reaction is still largely empirical; however, ethereal and aromatic hydrocarbon solvents tend to be optimal as are carbonate, phosphate, hydroxide, and fluoride bases. Water can have a beneficial effect on the reaction, and much work has gone into translating the Suzuki–Miyaura reaction to a green platform [22, 23]. The Suzuki–Miyaura reaction is most commonly associated with the formation of a $C_{sp2}-C_{sp2}$ bond between an aryl or alkenyl iodide or bromide and an aryl or alkenylboronic acid and many reviews dealing with this subject matter have been written, and the reader is directed to these materials for further information [2–10].

4.2
Developments Made in the Coupling of Nontrivial Substrates

4.2.1
Rational Design of Ligands for Use in the Suzuki–Miyaura Reaction

In being able to fully understand what has led to effectively a "second wind" for not only the Suzuki–Miyaura reaction but also cross-coupling reactions in general, it is important to first describe the basis upon which such advancements have been made. The barriers that once excluded sterically and electronically demanding

substrates [24–30] from undergoing cross-coupling have been resolved primarily through advanced ligand design; this has been aided by greater mechanistic insight into the catalytic cycle, leading to more finely tuned catalysts [11–13, 31, 32]. The most effective ligands utilized in cross-couplings can be grouped into two main categories, namely, organophosphines possessing at least two alkyl fragments (Figure 4.2) [32–34] and N-heterocyclic carbenes (NHCs) [35–41], specifically

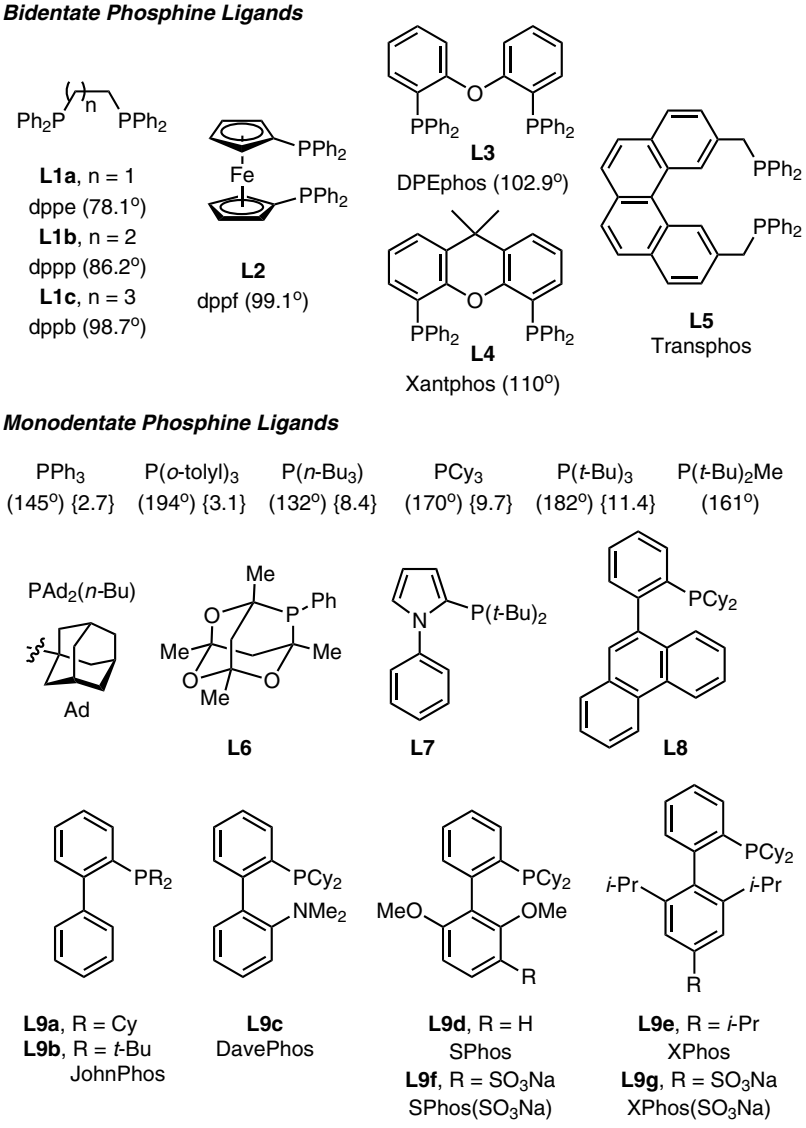


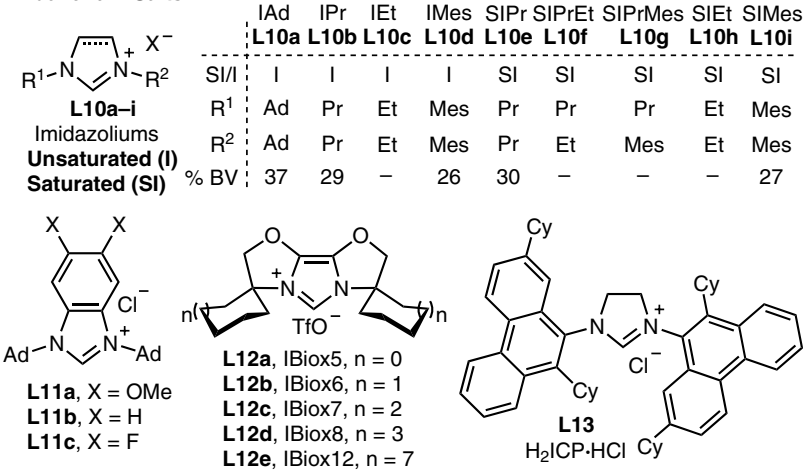
Figure 4.2 A selection of organophosphines used as ligands in the Suzuki–Miyaura reaction. Selected cone and bite angles are given in parentheses for bi- and monodentate ligands, respectively. Selected pK_a's of the conjugate acids are given in braces [44, 45]. Ad = adamantyl; Cy = cyclohexyl.

N, *N*′-disubstituted imidazolylidines (Figure 4.3). A select number of amine-based ligands have also proven very useful, especially in Ni-catalyzed couplings of secondary alkyl halides (see below) [26, 27]. Both main classes of ligands are excellent σ-donors that increase the electron density on Pd, which benefits the oxidative addition step, while possessing suitable steric bulk that enhances reductive elimination. There is a fine balance between ligand structure and the optimal steric topography around the metal center. For example, the use of two bulky monodentate ligands is only capable of complexing Pd *trans* so as to minimize ligand–ligand steric repulsion, the consequence being that reductive elimination is arrested. By optimizing the ligand sterics, monoligated Pd-adducts become favorable and reductive elimination can proceed [31, 42, 43]. Second, the increased steric topography around the monoligated metal center (i.e., [(L)R^1PdR^2]) forces the coupling fragments R^1 and R^2*cis*, which is a prerequisite for reductive elimination, and provides an added "push" to expel the cross-coupled product and relieve the steric congestion.

4.2.1.1 **Organophosphine Ligands and Properties**

Organophosphines are the most routinely employed ligands in cross-coupling reactions. Diphosphines of the type **L1**–**L4** (Figure 4.2) form a variety of bisligated Pd and Ni species, coordinating *cis* positions on the transition metal. This ensures that R^1 and R^2 in the $R^1R^2Pd\swarrow L$ intermediate are also oriented *cis*. Varying the bite angle (see Figure 4.2 for selected bite angles) of these bis(diphenylphosphino) ligands has a substantial effect on the rate of reductive elimination [46–48]; dppf (**L2**), dppp (**L1b**), dppb (**L1c**), and DPEphos (**L3**) have been shown to be superior to dppe (**L1a**) and Xantphos (**L4**) in a variety of examples [1, 46, 47, 49, 50]. For example, the rate of reductive elimination from $Me_2Ni\swarrow L$ complexes has been shown to be 46 times faster when L = dppp (**L1b**, bite angle 86.2°) compared to when L = dppe (**L1a**, bite angle 78.1°) [51]. This trend occurs until a maximum bite angle is reached, above which the geometric constraints become counterproductive for the catalytic cycle [1, 46–54]. For example, Transphos (**L5**) prevents reductive elimination from occurring, as the two coupling fragments cannot adopt a *cis* orientation on Pd [53]. Ligand electronic properties also have been found to significantly influence the rate of reductive elimination [55, 56]. More recently, organophosphines harnessing sterically laden, electron-donating secondary and tertiary *alkyl* groups as "activating" ligands in Pd-catalyzed cross-couplings have been demonstrated to be greatly superior to triarylphosphines and less bulky trialkylphosphines [32–34, 57]. These benefits source from optimal cone angles and better overall σ-donation to Pd via inductive effects from the secondary and tertiary alkyl groups of these ligands [57, 58]. In particular, dialkylbiaryl phosphines **L7**–**L9** [32] and trialkylphosphines PCy_3 and $P(t\text{-}Bu)_3$ [33] have emerged as optimal ligands, providing highly active catalysts that have expanded considerably the scope of the Suzuki–Miyaura reaction. Buchwald and Fu have largely led this charge, and each have recently published accounts of their endeavors from the past decade [32, 33]. In terms of ease of use, trialkylphosphines tend to be pyrophoric, and some organophoshines can be oxidized to their corresponding phosphine oxide upon prolonged exposure to air. To circumvent this impediment,

Imidazolium Salts



NHC–Pd Complexes

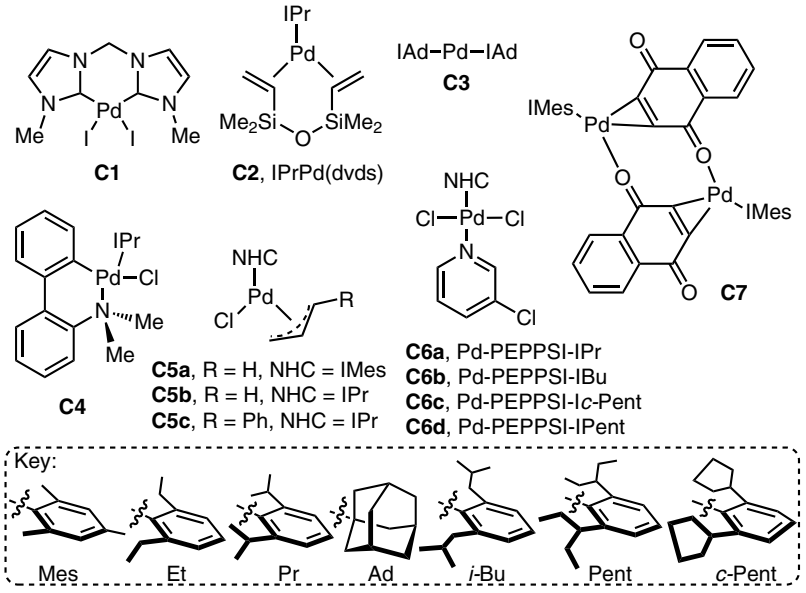


Figure 4.3 A selection of imidazolium salts and NHC–Pd complexes used in the Suzuki–Miyaura reaction. Selected % buried volumes (%BV) are given for imidazolium salts **L10a–i**. Biox = bioxazoline; Cy = cyclohexyl; dvds = 1,1,3,3-tetramethyl-1,3-divinyldisiloxane; H_2ICP = *N*,*N*-bis-(2,9-dicyclohexyl-10-phenanthryl)-4,5-dihydroimidazolium; PEPPSI = pyridine enhanced precatalyst preparation, stabilization, and initiation.

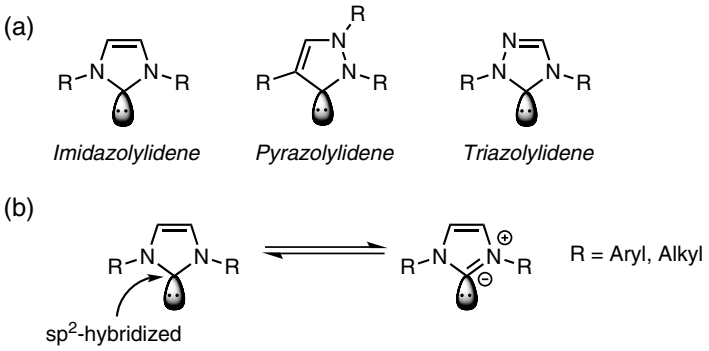


Figure 4.4 (a) Selected structures of N-heterocyclic carbenes and (b) the stabilization of the carbene carbon by neighboring nitrogen atoms.

air-stable trialkyl phosphonium salts have been employed that are converted into their neutral organophosphine counterpart *in situ* under the basic reaction conditions [59].

4.2.1.2 *N*-Heterocyclic Carbene Ligands and their Properties

Nitrogen-stabilized singlet carbenes (Figure 4.4a) were first described in the early 1960s [60] and by the end of that decade Wanzlick [61] and Öfele [62] had independently prepared transition metal complexes of these carbenes. The sp^2-hybridized singlet carbene is stabilized by the σ-electron-withdrawing neighboring nitrogen atom(s) whose electron lone pairs interact with the vacant p-orbital of the carbene. As a result, these carbenes are electron-rich, nucleophilic entities (Figure 4.4b) [63, 64]. Not until 1991 when Arduengo isolated and characterized for the first time the free and crystalline IAd carbene [65] were NHCs more seriously considered for transition metal-catalyzed reactions [35, 41, 66–70], among other applications [71, 72]. Overall, NHCs are better σ-donors than the most basic trialkylphosphines and relief of electron density on Pd via backbonding is not as prominent as it is on Pd-organophosphine adducts [41, 73–79]. Moreover, NHCs do not dissociate readily from their ligated transition metal. These attributes combined, the metal center is more electron-rich in NHC complexes than it is in organophosphine complexes. NHCs are also unique in that alterations made to substituents on the imidazolium ring do not appreciably alter the level of σ-donation of the carbene [13, 80, 81]. This facet renders the electronic component independent of the steric component of NHCs, thereby permitting the fine-tuning of the steric topography around its ligated metal center without deleterious effects to the electronic properties of the metal. Experimentally, it has been shown that sterically similar/electronically dissimilar benzimidazolium ligands **L11a–c** (Figure 4.3) are comparable in their ability to "activate" Pd toward the Suzuki–Miyaura reaction involving aryl chlorides [13, 82]. As such, the carbene carbon is sufficiently electron-rich to overshadow substituent alterations made to the backbone of the NHC.

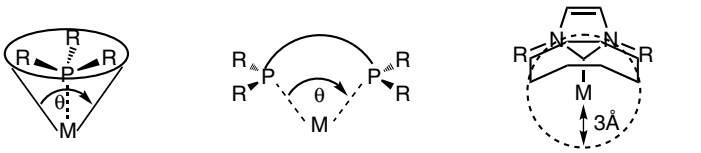


Figure 4.5 Steric descriptors for organophosphine and NHC ligands.

The steric topography around the metal center imposed by NHCs is very different from that of organophosphines (Figure 4.5). In the case of NHCs, the substituents on the imidazolium ring are directed toward the metal center; for organophosphines, the substituents point away. As such, the steric contribution of an NHC to a metal center cannot be measured by Tolman's cone angle descriptor [83–85]. Instead, the buried volume of the ligand is calculated as the percentage of occupied space by the NHC that lies within a sphere of a 3 Å radius centered at the metal [75, 79, 81, 86]. A selection of these values is included in Figure 4.3. As is in the case for organophosphines, the rate of reductive elimination is affected by alterations made to the structure of the NHC [36, 82, 86]. For example, the effect of variably substituted NHC ligands on the room temperature alkyl–alkyl Negishi reaction has been related indirectly to the reductive elimination step, where azolium salt/$Pd_2(dba)_3$ catalyst systems perform in the order of decreasing sterics, where IPr (**L10b**) ≈ SIPr (**L10e**) > SIPr-Et (**L10f**) > SIPr-Mes (**L10g**) > IEt (**L10c**) ≈ SIEt (**L10h**) > IMes (**L10d**) ≈ SIMes (**L10i**) [13].

The use of bulky, electron-rich organophosphines and NHCs as ligands in the Pd-catalyzed Suzuki–Miyaura reaction is reviewed in the following sections. Given intense interest in this field, only pertinent examples that have most significantly contributed to the advancement of the field will be reviewed, and these examples best portray the present state of the art.

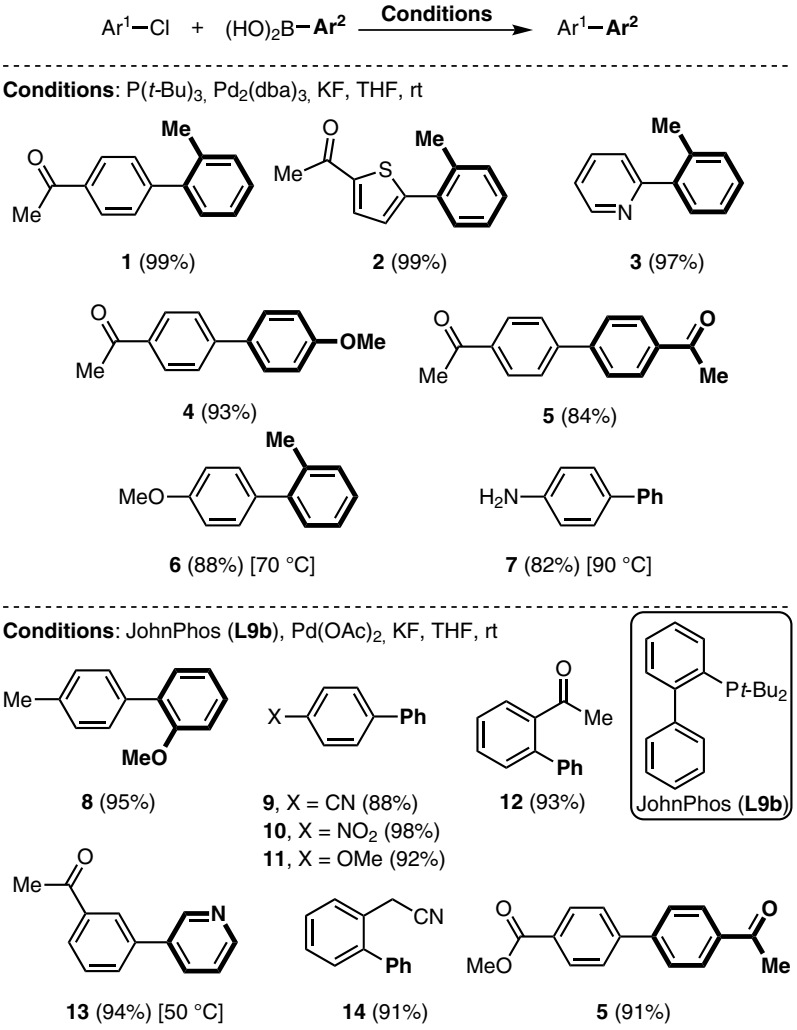
4.2.2
The Suzuki–Miyaura Cross-Coupling of Challenging Aryl Halides

4.2.2.1 Overview of Challenges

Aryl bromides and iodides are the electrophiles used most routinely in the Suzuki–Miyaura reaction, despite the fact that aryl chlorides are considerably more commercially abundant and economical. In part, this constraint is the direct consequence of bond dissociation energies, such that C−Br and C−I bonds are reduced more readily relative to that of a C−Cl bond during oxidative addition to Pd(0) [24, 25, 30]. Di-, tri-, and tetra-*ortho*-substituted biaryls have also been elusive products as sterically hindered aryl halide and arylboronic acid precursors are prone to protodehalogenation and protodeborylation, respectively. Functionalized heterocycles can be challenging substrates in cross-couplings given they are prone to protodeborylation and can serve as catalyst poisons [87, 88]. With the above challenges in mind, most new catalyst systems are designed for and evaluated in the cross-coupling of one or more of these difficult substrate classes.

4.2.2.2 Organophosphine-Derived Catalysts

4.2.2.2.1 **Coupling of Carbocyclic Substrates** Seminal work by the groups of Fu [89] and Buchwald [90] revealed that P(*t*-Bu)$_3$ and DavePhos (**L9c**, Figure 4.2) were effective ligands for coupling aryl chlorides with arylboronic acids. With preliminary results from these experiments in hand, both groups refined the reaction conditions to be milder, hence more general to permit a broader range of functionalized substrates (Scheme 4.2). For example, a variety of "activated" (electron-deficient) aryl chlorides were coupled with arylboronic acids to provide functionalized products

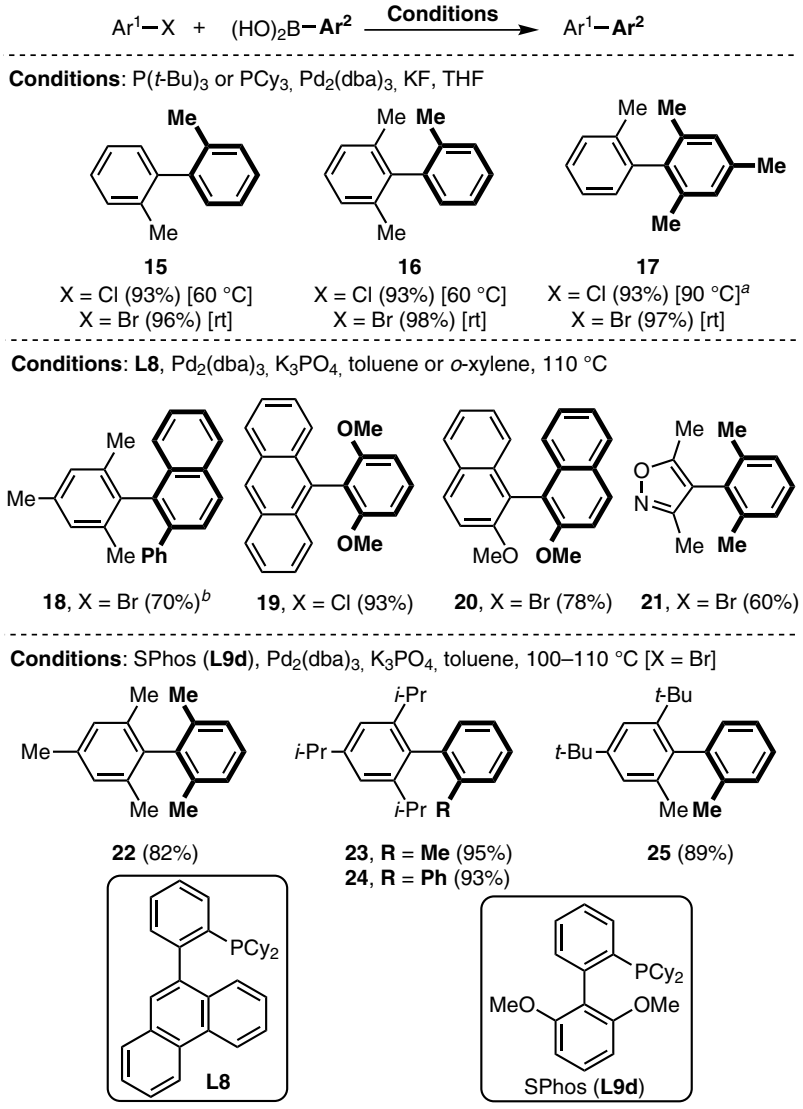


Scheme 4.2 The Suzuki–Miyaura cross-coupling of aryl chlorides with arylboronic acids in the presence of bulky, electron-rich organophosphines.

(**1–5**) using the P(*t*-Bu)$_3$/Pd$_2$(dba)$_3$ catalyst system at room temperature [91]. Electron-rich aryl chlorides were also coupled effectively (leading to **6** and **7**) by heating the reaction at or above 70 °C. Similarly, the JohnPhos (**L9b**)/Pd(OAc)$_2$ catalyst system was demonstrated to be general in substrate scope [42, 92], and a range of functionalized biaryls (**5** and **8–14**) were prepared in excellent yield from both electron-deficient and electron-rich aryl chlorides alike. Aryl bromides and iodides were also found to be suitable electrophiles under these very mild reaction conditions.

Subsequently, bulky trialkylphosphine and dialkylbiaryl phosphine ligands were evaluated in the Suzuki–Miyaura coupling of sterically hindered aryl substrates (Scheme 4.3). Using either P(*t*-Bu)$_3$ or PCy$_3$ in the presence of Pd$_2$(dba)$_3$, di- and tri-*ortho*-methylbiphenyls (**15–17**) were provided at *room temperature* from their corresponding *ortho*-substituted aryl bromides and arylboronic acids [91]; substituting aryl bromides with aryl chlorides required elevated temperatures to achieve comparable product yields. Tetra-*ortho*-substituted biaryls were not obtained under the specified reaction conditions. However, in the presence of **L8**/Pd$_2$(dba)$_3$, di-*ortho*-substituted aryl bromides and chlorides were effectively coupled with di-*ortho*-substituted arylboronic acids to give the corresponding tetra-*ortho*-substituted biaryl products (**18–21**) in impressive yields at 110 °C [93]. Stepwise optimization of the pendant groups on the dialkylbiphenyl phosphine ligand backbone eventually resulted in SPhos (**L9d**, Figure 4.2), which has since emerged as a fairly general ligand both for Pd-catalyzed Suzuki–Miyaura reactions [12, 32, 94] and for aryl aminations [34]. The application of SPhos in the Pd-catalyzed coupling of di-*ortho*-substituted aryl bromides, where the *ortho* substituents are methyl or *i*-propyl or a *t*-butyl/methyl combination, provided excellent yields of the corresponding tri- and tetra-*ortho*-substituted biaryls **22–25**. One *ortho*-*t*-butyl group is tolerated, while the presence of two *ortho*-*t*-butyl groups is not. Specifically, oxidative addition of 2,4,6-tri-*t*-butylbromobenzene to Pd(0) was found to proceed smoothly; however, the substantial sterics imparted by the two *ortho*-*t*-butyl groups discourages subsequent transmetalation with phenylboronic acid (Scheme 4.4) [94]. Instead, an alternative pathway takes over wherein the oxidative addition adduct undergoes cyclometalation to provide the corresponding palladacycle. Subsequent protonation of the palladacycle provides an alkyl palladium halide that is incapable of undergoing β-hydride elimination, and is sufficiently stable to transmetalate with arylboronic acids. This alternate catalytic cycle directs the formation of a new $C_{alkyl}-C_{aryl}$ bond upon reductive elimination to give cross-coupled products **26–28**. These examples are among the reported few alkyl–aryl Suzuki–Miyaura cross-couplings utilizing dialkylbiaryl phosphine ligands – a handful of examples of aryl halides being coupled with alkyl-9-BBN or methylboronic acid reagents have been reported [12].

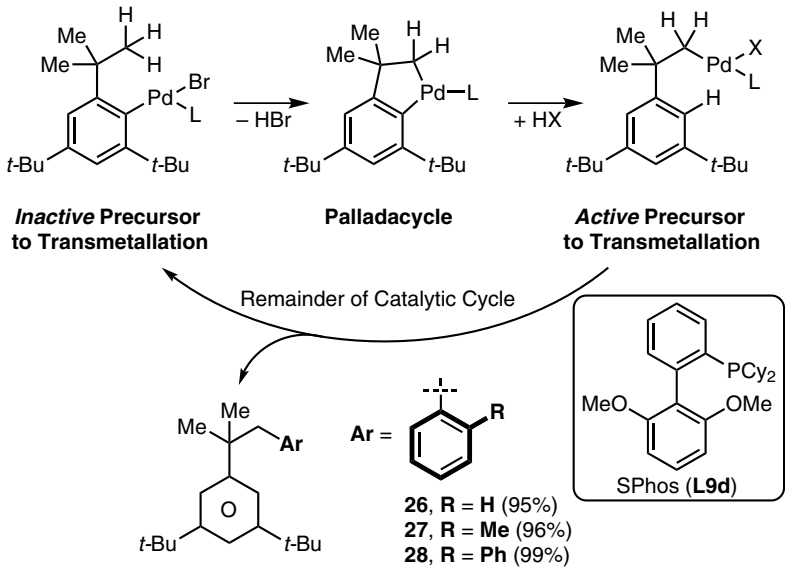
4.2.2.2.2 **Coupling of Heterocyclic Substrates** The cross-couplings discussed in the previous section primarily involved carbocycles. However, cross-couplings involving functionalized heterocycles are paramount given their ubiquitous presence in natural products, pharmaceuticals, and agrochemicals [95]. Overcoming the aforementioned difficulties in coupling such substrates, the application of the PCy$_3$/Pd$_2$(dba)$_3$ catalyst system to the coupling of a variety of nitrogen-containing hetero-



Scheme 4.3 The Suzuki–Miyaura cross-coupling of sterically hindered aryl chlorides and bromides with arylboronic acids in the presence of bulky, electron-rich organophosphines.

[a]Reaction was completed using K_3PO_4 and toluene in place of KF and THF, respectively.
[b]Reaction was conducted in *o*-xylene at 120 °C in place of toluene at 110 °C.

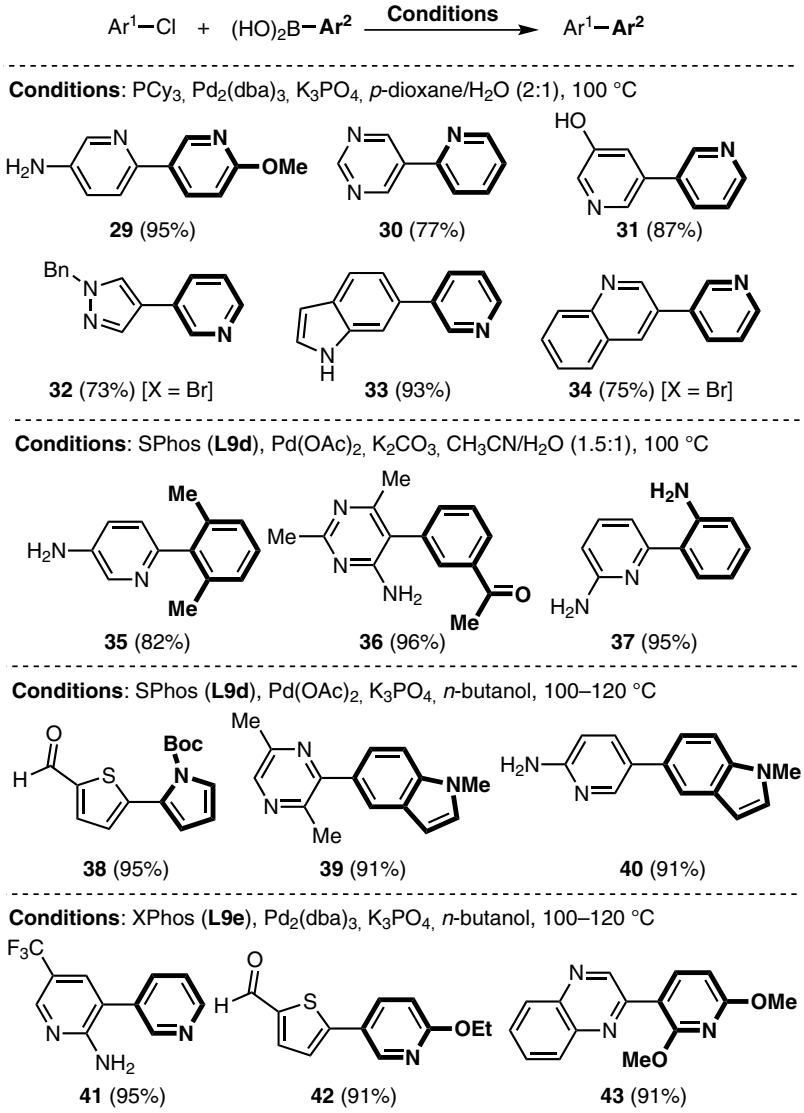
cyclic chlorides and bromides with pyridine-based boronic acids, which tend to have a slow rate of transmetalation [96], provided excellent yields of the corresponding products (Scheme 4.5) [97]. Notably, unprotected aryl alcohols and amines (leading to **29** and **31**) were compatible substrates under these reaction conditions. The application of dialkylbiaryl phosphine ligands has provided a more general route



Scheme 4.4 This alternate catalytic cycle is proposed to account for the formation of **26**–**28** when coupling aryl halides that possess *t*-butyl substituents at both *ortho* positions.

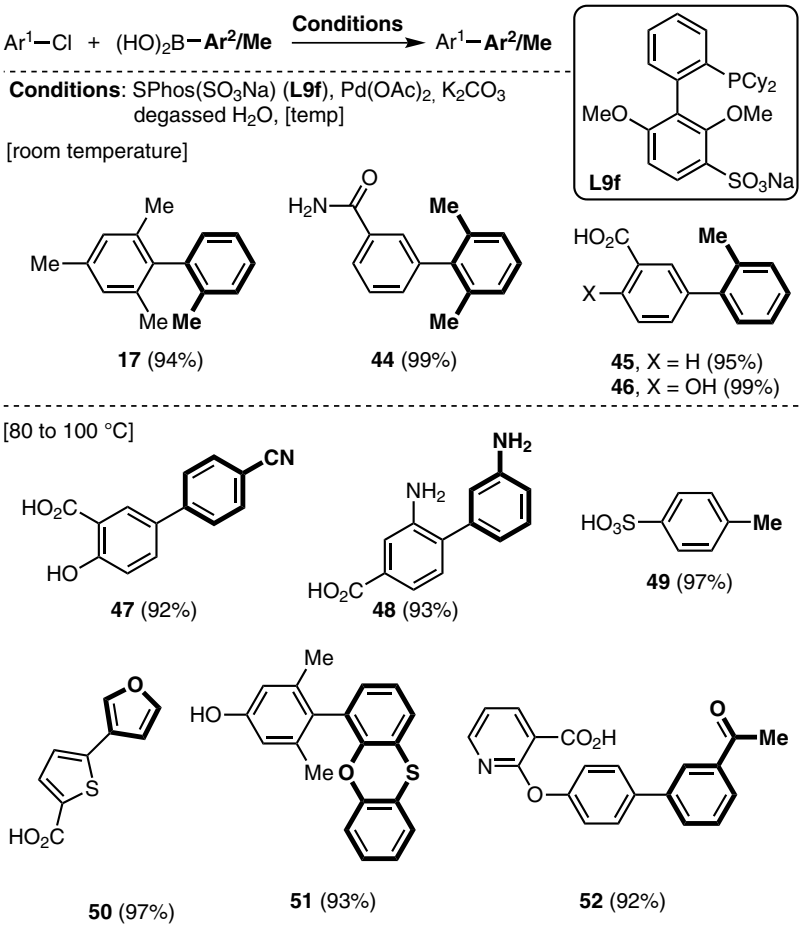
to the preparation of heterobiaryls, as illustrated by the variety of functionalized products in Scheme 4.5 [96]. SPhos (**L9d**, Figure 4.2) was found to be an effective ligand for coupling unprotected chloroaminopyridines and -pyrimidines with arylboronic acids (leading to **35**–**37**) [98]. Pyrrole and indole boronic acids are scarcely reported in the Suzuki–Miyaura reaction for a variety of reasons [96]; however, SPhos (**L9d**)/$Pd(OAc)_2$ was found to be a fairly general catalyst system for the coupling of these transmetalating species with heterocyclic chlorides providing access to functionalized heterocycles **38**–**40**. The coupling of deactivated aryl and heteroaryl chlorides were sluggish when using SPhos as the ancillary ligand, whereas the sterically more hindered XPhos (**L9e**, Figure 4.2) ligand enabled the coupling of such electrophiles (leading to **41**–**43**) [96]. The authors attribute the pronounced catalyst activity to the increased sterics of XPhos (**L9e**), which raises the relative concentration of the monoligated oxidative addition intermediate (e.g., [(XPhos)Pd(Ar)Cl]).

4.2.2.2.3 **Suzuki–Miyaura Reactions in Water** Replacing organic solvent for water has clear implications in the presence of mounting environmental concerns. Treatment of SPhos (**L9d**) or XPhos (**L9e**) with H_2SO_4 in CH_2Cl_2 provided their monosulfonated sodium salt derivatives (**L9f** and **L9g**, respectively, Figure 4.2) [99] that are as active as the parent ligands. A collection of hydrophilic functionalized heterocycles (**44**–**52**) were prepared from their heteroaryl chloride and boronic acid precursors using SPhos(SO_3Na) (**L9f**) as the spectator ligand in water (Scheme 4.6).



Scheme 4.5 The Suzuki–Miyaura cross-coupling of functionalized heterocyclic aryl chlorides and bromides and aryl- and heteroarylboronic acids in the presence of bulky, electron-rich organophosphines.

There is a clear advantage over similar couplings carried out in anhydrous organic solvents where solubility is a concern. Selected couplings were achievable at room temperature, but for the most part these cross-couplings were carried out at 100 °C. Heating to 150 °C in a microwave reactor accelerated the reaction to provide the cross-coupled products in 10 min.

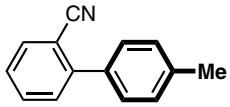
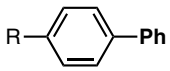
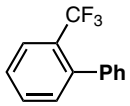
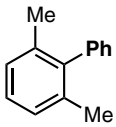
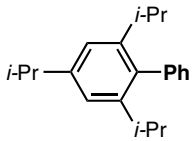
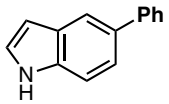
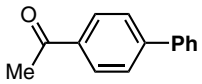


Scheme 4.6 The Suzuki–Miyaura cross-coupling in water of functionalized heterocyclic aryl chlorides and arylboronic in the presence of **L9f** (Figure 4.2), a water-soluble monosulfonated derivative of SPhos (**L9d**).

4.2.2.2.4 **Low Catalyst Loadings** The majority of Suzuki–Miyaura cross-couplings require catalyst loadings in the range of 0.5–5 mol% Pd. However, there are examples with catalyst loadings at or below 0.05 mol% (Table 4.1). Low catalyst loadings have obvious implications when considering large-scale transformations. The catalyst turnover number (TON) is a quantitative measure for evaluating a catalyst's activity. Using bulky trialkylphosphines, in particular P(*t*-Bu)$_3$, as the supporting ligand, catalyst TONs on the order of approximately 10 000 have been achieved for electron-deficient aryl chlorides (entry 1); catalyst TONs for electron-neutral aryl chlorides fall on average an order of magnitude below that (entry 2) [91]. Relatively low catalyst loadings were also possible when using the *N*-aryl-2-(dialkylphosphino)pyrrole **L7** (Figure 4.2) [100] in the coupling of a variety of aryl chlorides with phenylboronic acid (entries 3–5 and 7). In particular, catalyst TONs approached 10 000 with **L7** for the

Table 4.1 The Suzuki–Miyaura cross-coupling at low loadings of Pd in the presence of bulky, electron-rich organophosphines.

$Ar^1–X + (HO)_2B–Ar^2 \xrightarrow[\text{Base}]{\text{Conditions}} Ar^1–Ar^2$

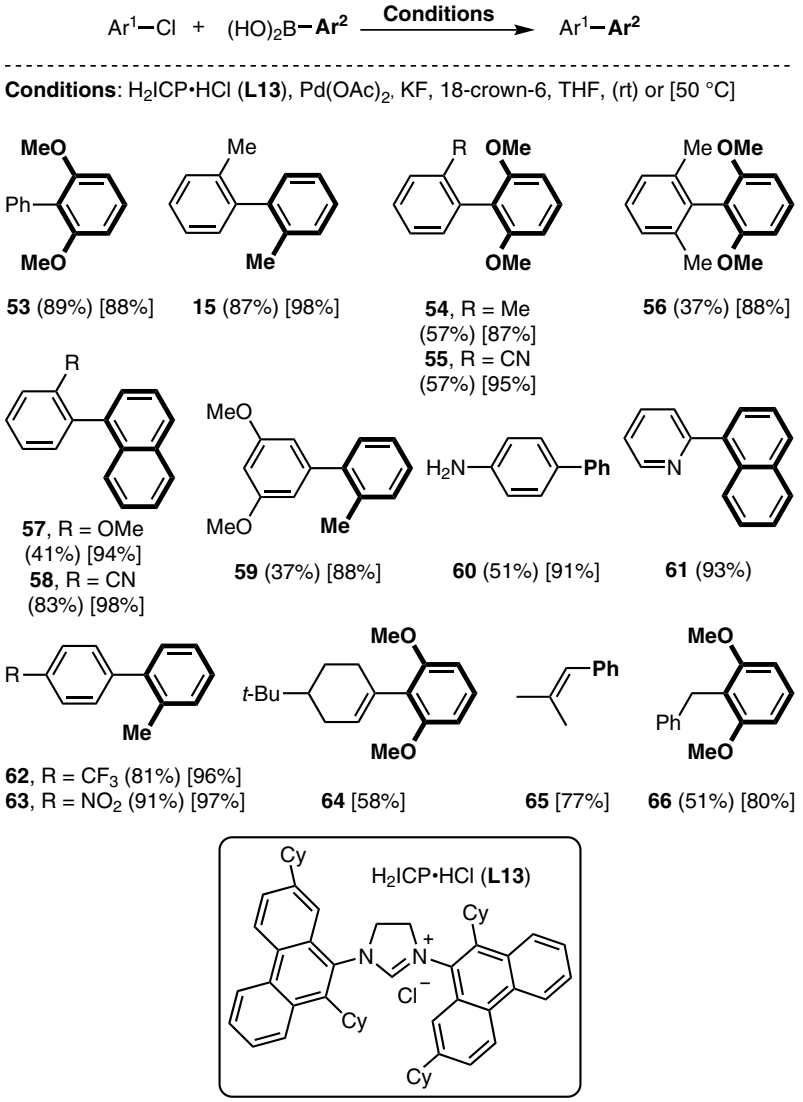
Entry	Product	X	Pd (mol %)	Ligand	Temp. (°C) (Time, h)	Yield (%)	TON
1		Cl	0.01	P(*t*-Bu)$_3$	90 (25)	97	9700
2		Cl	0.1	P(*t*-Bu)$_3$	100 (43)	92	920
3		R Me Cl	0.01	**L7**	60 (24)	>99	9900
		Me Cl	0.005	**L7**	100 (24)	98	19 600
		Me Cl	0.05	JohnPhos	100 (25)	93	1860
		n-Bu Cl	0.003	SPhos	100 (24)	93	31 000
4		Cl	0.05	**L7**	60 (24)	90	1800
		Cl	0.01	**L7**	60 (24)	91	9100
5		Cl	0.005	**L7**	60 (24)	16	320
6		Br	0.01	SPhos	100 (16)	97	9700
7		Cl	0.05	**L7**	100 (24)	97	1940
8		Br	0.000001	DavePhos	100 (24)	91	91×10^6
		Br	0.001	—	100 (19)	>99	99 000
		Cl	0.02	DavePhos	100 (23)	92	4600

coupling of 4-chlorotoluene at 60 °C; increasing the temperature to 100 °C allowed for lower catalyst loadings (TON ~20 000, entry 3). While JohnPhos (**L9b**) was less effective for the same coupling [42, 92], SPhos (**L9d**) yielded catalyst TONs above 30 000 (entry 3) [12, 94]. In the case of **L7**, the presence of *ortho* substituents on the electrophile lowered catalyst activity (entry 3 versus 5). Although the same is true for SPhos (**L9d**), relatively high TONs are still achieved for the very sterically hindered 2,4,6-tri-*i*-propylbromobenzene (entry 6). Catalyst TONs are comparatively low in the coupling of heterocyclic aryl chlorides (entry 7). The use of DavePhos (**L9c**) as the supporting ligand for the coupling of 4-acetylbromobenzene improved the catalyst TON by three orders of magnitude compared to that where no ligand is present (entry 8) – as this was an "activated" aryl bromide, both catalysts were able to achieve quantitative conversions. As expected, the derivative 4-acetylchlorobenzene was more sluggish, leading to catalyst TONs approximately four orders of magnitude lower than the coupling of the corresponding aryl bromide in the presence of DavePhos (**L9c**). Aside from the ligand/Pd combinations in Table 4.1, the use of $PAd_2(n\text{-Bu})/Pd(OAc)_2$ at 100 °C has also proven effective for the coupling of a variety of aryl chlorides with arylboronic acids at 0.001–0.005 mol% Pd loading, achieving catalyst TONs ranging from 11 600 to 69 000 [101].

4.2.2.3 NHC-Derived Catalysts

4.2.2.3.1 ***In-Situ*-Generated Catalysts from Imidazolium Salt Precursors** Imidazolium salts are shelf-stable, free-flowing crystalline materials that can be prepared on a large-scale, stored for long periods of time, and conveniently weighed out in air as needed. Their conversion to the free carbene is mediated by deprotonation of the imidazolium salt. This process typically occurs under the basic conditions of the Suzuki–Miyaura reaction, where capture by Pd generates the active catalyst *in situ*. Alternatively, the free carbene may be generated as a solution that is then added to a Pd source to generate the catalytically active NHC(Pd) species. An early report by Nolan and coworkers demonstrated the use of IMes•HCl (**L10d**, Figure 4.3) in the presence of $Pd_2(dba)_3$ and Cs_2CO_3 to generate *in situ* the (IMes)Pd catalyst that was able to couple relatively simple electron-rich aryl chlorides with arylboronic acids in *p*-dioxane at 80 °C in near quantitative yields [102]. A follow-up study showed that the success of the cross-coupling highly depended on the sterics of the NHC used; among a variety of *unsaturated* NHC ligands evaluated, IMes (**L10d**) and IPr (**L10b**) were found to be optimal and were equally effective [103].

Various *saturated* imidazolium salts have also been evaluated as ligands in the coupling of both electron-rich and electron-deficient aryl chlorides and arylboronic acids at room temperature [104]. Under the conditions specified in Scheme 4.7, H_2ICP•HCl (**L13**, Figure 4.3) was superior to both SIMes•HCl (**L10i**) and SIPr•HCl (**L10e**) in the preparation of biaryls **15** and **53–66**. Removal of two or all of the pendant cyclohexyl groups from H_2ICP•HCl (**L13**) significantly attenuated the activity of the *in situ* generated (NHC)Pd complex, again demonstrating the strict dependence of cross-couplings on the precise sterics of the ancillary ligand. Di-*ortho*-substituted



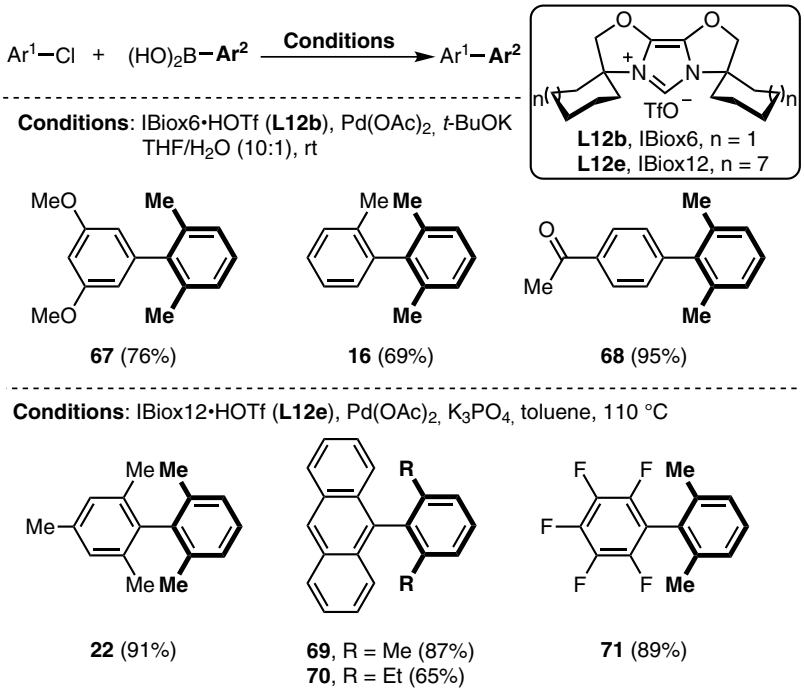
Scheme 4.7 The Suzuki–Miyaura cross-coupling of aryl and alkenyl chlorides with arylboronic acids using the NHC precursor $H_2ICP•HCl$ (**L13**, Figure 4.3).

products (**15**, **53**, **57**, and **58**) were obtained in mostly excellent yields at room temperature. Tri- and tetra-*ortho*-substituted products (**54**–**56**) were also coupled in moderate yields; however, warming the reaction to 50 °C improved the yields in shorter reaction times. Aryl chlorides functionalized with trifluoromethyl, nitro, and nitrile groups as well as primary amines were well tolerated, as was 2-chloropyridine (leading to **60**–**63**). Alkenyl and benzylic chlorides (leading to **64**–**66**) were also suitable substrates. In addition, boronic acid derivatives phenyl pinacolatoborane and

trimethylboroxine were evaluated and found to be suitable transmetalating agents [104].

NHCs possessing "flexible" steric bulk give rise to highly active catalysts that are able to adapt their conformation to best suit various stages of the catalytic cycle [86]. Ir-complexes of bioxazoline (IBiox) (**L12**, Figure 4.3) and cyclic (alkyl)(amino) carbenes (CAAC) [105] are more electron-rich than their IPr and IMes derivatives making these NHCs among the best-known σ-donor ligands for transition metals. This enhanced σ-donor ability of these ligands is an artifact of the alkylated quaternary carbons neighboring the carbene carbon.

The IBiox6 (**L12b**, Figure 4.3)/$Pd(OAc)_2$ catalyst system is effective for coupling aryl chlorides at room temperature (Scheme 4.8) [31]. Sterically hindered arylboronic acids leading to di- and tri-*ortho*-substituted biphenyls (**16**, **67**, and **68**) were coupled with aryl chlorides in good yield. Following these initial results, a series of IBiox•HOTf imidazolium salts were prepared with five (**L12a**), seven (**L12c**), eight (**L12d**), and twelve-membered (**L12e**) aliphatic rings branching off from the quaternary carbon. They were each evaluated along with IBiox6 (**L12b**) in the cross-coupling of 1-chloro-2,6-dimethylbenzene with mesitylboronic acid to give tetra-*ortho*-substituted biphenyl **22** [106]. IBiox7 (**L12c**), IBiox8 (**L12d**), and IBiox12 (**L12e**) ligands outperformed IBiox5 (**L12a**) and IBiox6 (**L12b**), with IBiox12 (**L12e**) being optimal. For comparison, the use of either IMes (**L10d**) or IAd (**L10a**) as spectator ligands



Scheme 4.8 The Suzuki–Miyaura cross-coupling of sterically hindered aryl chlorides with arylboronic acids using NHC ligands possessing "flexible" steric bulk.

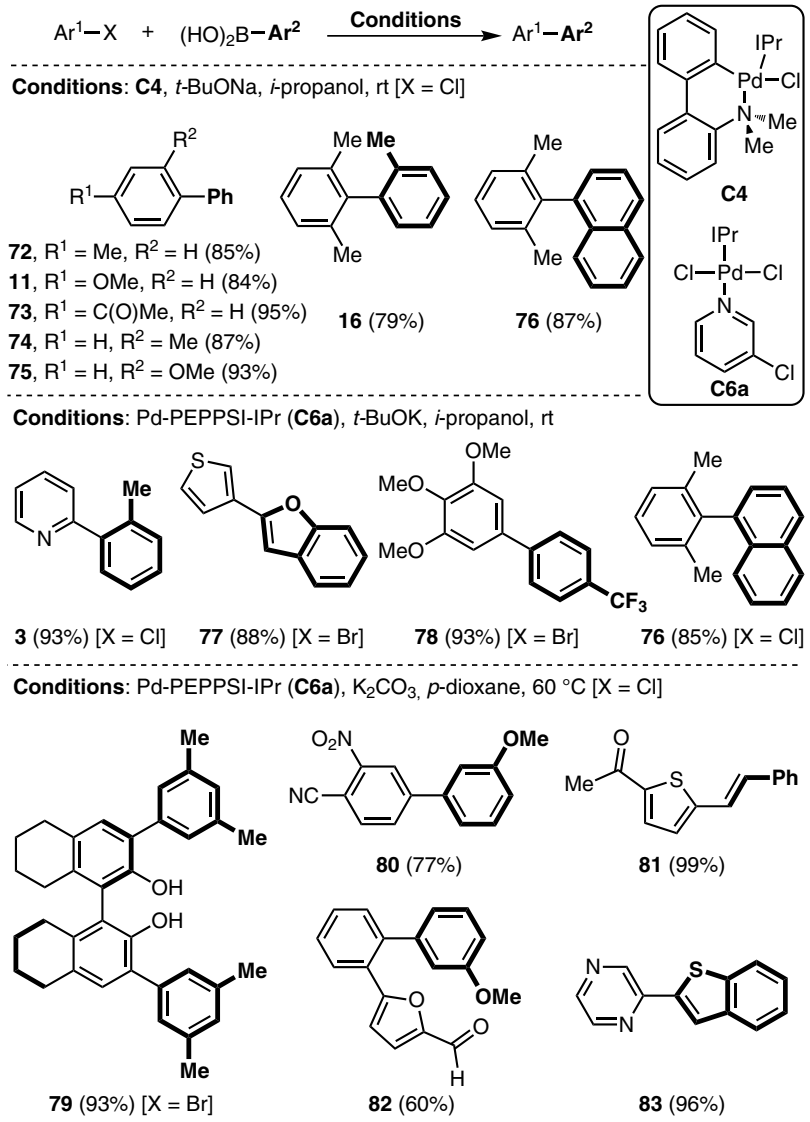
provided none of the desired products. The IBiox12 (**L12e**) ligand was found to be effective for a variety of challenging cross-couplings of sterically hindered substrates leading to tetra-*ortho*-substituted biaryls **22** and **69–71** (Scheme 4.8).

4.2.2.3.2 **Preformed NHC–Pd Complexes** The *in situ* generation of free carbenes from their imidazolium salt precursors is highly sensitive to moisture, reaction conditions, and the technical skill of the practitioner. These inherent factors lead to poor reproducibility from one experiment to the next when using *in-situ*-derived carbene-based catalysts. Although the active catalytic species is believed to be monoligated (NHC)Pd, twofold excess to Pd of the NHC or imidazolium salt is often employed in order to attain optimal results. It has been demonstrated that only a fraction of the active (NHC)Pd(0) catalyst is actually formed *in situ* from a 2:1 mixture of IPr•HCl (**L10b**) and a Pd(0) source [107]. Thus, there exists an uncertainty surrounding the stoichiometry and composition of the active catalytic species for *in situ* prepared NHC catalysts [108]. To bypass these drawbacks and concerns, discrete (NHC)Pd(0) and (NHC)Pd(II) complexes (Figure 4.3, **C1–C7**) have been prepared [109]. (NHC)Pd complexes are typically stabilized with noncarbene-based coligands; however, examples of stable $(NHC)_2Pd$ complexes are known [108, 110].

Bischelated (NHC)Pd(II) complex **C1** was first reported for use in the Heck and Suzuki–Miyaura reactions [43]. For the latter, aryl bromides and a single aryl chloride were coupled with phenylboronic acid at 120 °C. $(IAd)_2Pd(0)$ (**C3**) has also been prepared and was found to be effective for the coupling of aryl chlorides with phenyl and *p*-anisylboronic acids at room temperature [110]. In this system, one IAd ligand is shed *in situ* to generate the catalytically active monoligated species.

A variety of (NHC)Pd complexes that utilize noncarbene-based coligands have been prepared and evaluated. The (IMes)Pd(dvds) complex (**C2**, Figure 4.3) was found to be capable in the coupling of simple aryl chlorides with phenylboronic acid in moderate-to-good yields; however, heating to 100 °C was required [111]. The diminished catalytic activity stems from the strong binding of the olefins in dvds to Pd, effectively poisoning the catalyst [112]. Naphthoquinone (NQ) coordinates Pd via both the carbonyl oxygens and the α,β-unsaturated ketone olefins to give the bridged $[(IMes)Pd(NQ)]_2$ dimer (**C7**). This catalyst was evaluated in the coupling of aryldiazonium salts with arylboronic acids in MeOH at 50 °C with good results [113].

The most successful and generally applicable NHC-based Pd catalysts that have been developed are IPr-palladacycle **C4** [114], (IPr)Pd(allyl)Cl (**C5b**) [115], and Pd-PEPPSI-IPr (**C6a**, structures in Figure 4.3) [38]. All these (NHC)Pd(II) precatalysts are reduced *in situ* to presumably generate the same catalytically active species, namely, (IPr)Pd(0). However, IPr–palladacycle **C4** was found to be superior to (IPr)Pd(allyl)Cl (**C5b**) in room-temperature Suzuki–Miyaura cross-couplings [116], indicating that either (1) there are substantial differences in the rate of *in situ* reduction of these two precatalysts or (2) there is a coligand "memory effect," which includes the possibility of catalyst poisoning by the coligand under the reaction conditions. Both **C4** and Pd-PEPPSI-IPr (**C6a**) were comparably effective precatalysts for the room temperature Suzuki–Miyaura reaction in technical grade *i*-propanol (Scheme 4.9), providing access to biaryls **3**, **11**, **16**, and **72–78** [107, 114]. Sterically hindered aryl

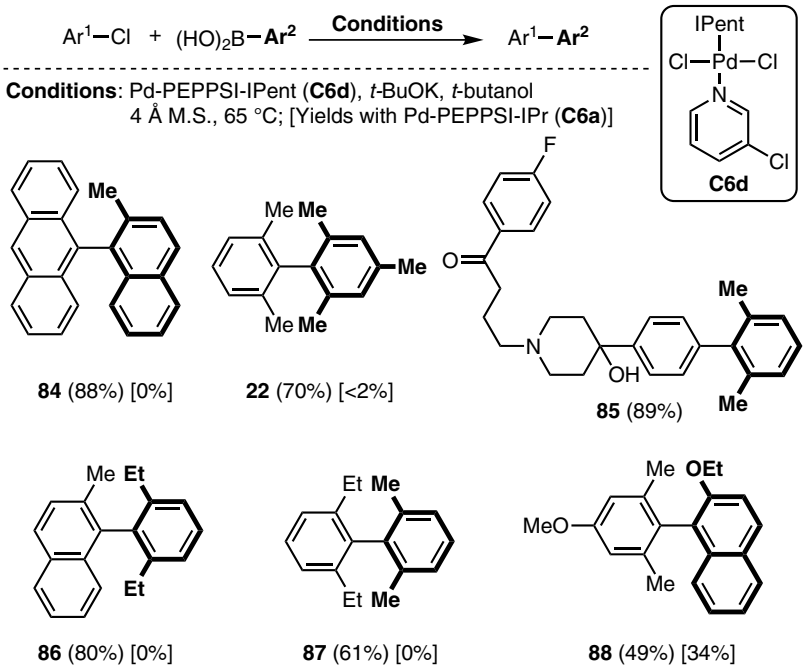


Scheme 4.9 The Suzuki–Miyaura cross-coupling of aryl halides and arylboronic acids using NHC–Pd precatalysts at room temperature. Functionalized and heteroaryl substrates were coupled in the presence of a less nucleophilic base at 60 °C.

chlorides leading to **16** and **76** were well tolerated. Select-few heteroaryl substrates (leading to **3** and **77**) were shown to be compatible using the precatalyst Pd-PEPPSI-IPr (**C6a**) under these reaction conditions. For the most part, *t*-BuO^- is too harsh of a base rendering it only moderately functional group tolerant. As such, milder reaction conditions consisting of K_2CO_3 base in *p*-dioxane were developed that permitted the cross-coupling of a variety of functionalized and heterocyclic substrates (leading to

79–83) with Pd-PEPPSI-IPr (**C6a**), albeit at a slightly elevated temperature. Nitrile, nitro, and unprotected hydroxyl, ketone, and aldehyde functionality on heteroaryl frameworks was well tolerated. Notably, each of the functionalized and heteroaryl precursors leading to these products were not tolerated under the *i*-propanol/*t*-BuO$^-$ conditions and led to decomposition products.

Generally speaking, IPr-based catalysts are considerably more active than their IMes counterparts. This "trend" prompted the question as to whether further increasing the sterics of the substituents on the *N*-aryl moiety of the NHC would prove beneficial. As such, IBu, I*c*-Pent, and IPent-based Pd-PEPPSI complexes (**C6b, 6c**, and **6d**, respectively, Figure 4.3) were prepared and evaluated by Organ and coworkers [117]. While IBu and I*c*-Pent were ineffective ancillary ligands for cross-couplings leading to tetra-*ortho*-substituted biaryls, IPent proved to be very effective (Scheme 4.10). A variety of tetra-*ortho*-substituted biaryls (**22**, **84**, and **86–88**) were produced under one of the lowest reaction temperatures reported to date for this transformation. In addition to aryl chlorides, aryl bromides were equally effective electrophiles. Functional group tolerance of this catalyst is demonstrated through cross-coupling leading to **85**. In all cases, Pd-PEPPSI-IPent (**C6d**) greatly outperformed Pd-PEPPSI-IPr (**C6a**). The major side reaction when using Pd-PEPPSI-IPr (**C6a**) is hydroxydeborylation, which was found to consume the balance of the boronic acid and thus stall the cross-coupling reaction. The increased sterics around the metal



Scheme 4.10 The Suzuki–Miyaura cross-coupling of sterically hindered aryl chlorides and arylboronic acids using Pd-PEPPSI-IPent (**C6d**, Figure 4.3). Yields in square brackets are for cross-couplings carried out using Pd-PEPPSI-IPr (**C6a**) in place of Pd-PEPPSI-IPent (**C6d**).

center is thought to have little effect on the rate of oxidative addition but instead significantly influences transmetalation and reductive elimination.

A variety of (NHC)Pd catalysts have been developed that are effective at low-catalyst loadings. In general, (NHC)Pd complexes are not effective on their own, and an auxiliary ligand is usually required, presumably to prolong active catalyst lifetime. Most commonly, organophosphines are added for this purpose [118–120]. Among the most active and general catalysts is (IPr)Pd(cinnamyl)Cl (**C5c**), which is effective at Pd loadings in the range of 50 ppm [121, 122].

All told, NHC-based catalysts provide conversions on par with electron-rich organophosphine ligated species. NHCs have an advantage over organophosphines in that they form air- and moisture-stable Pd adducts, and so are more attractive from a user standpoint in terms of ease of use, safety, and practicality. Furthermore, the large number of (NHC)Pd precatylst complexes that are commercially available make for their convenient use.

4.2.3
The Suzuki–Miyaura Reaction Involving Unactivated Alkyl Halides

4.2.3.1 Associated Difficulties

The use of unactivated alkyl halides (i.e., nonbenzylic, allylic, or α-carbonyl halides) as the electrophilic cross-coupling partner has only recently been realized [26, 28, 123]. For the most part, these substrates are poor candidates for Pd and Ni-catalyzed cross-couplings due to the comparatively low propensity of the unactivated C_{sp3}–X bond to undergo oxidative addition and the tendency for the resulting adduct to encounter *intra*molecular β-hydride elimination or hydrodehalogenation side reactions in preference to *inter*molecular transmetalation (Figure 4.6) [26, 28]. These obstacles have been significantly marginalized through the use of bulky, electron-rich ligands

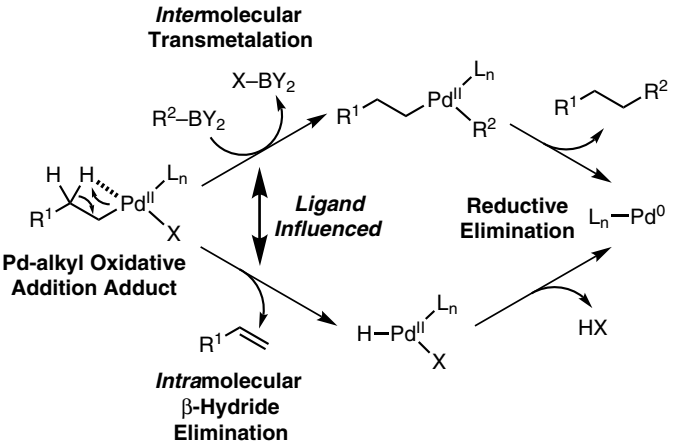
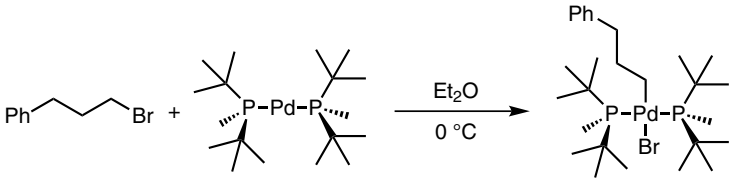


Figure 4.6 β-Hydride elimination is a facile intramolecular process in cross-couplings. Rational ligand design has provided ligands that disfavor β-hydride elimination so that intermolecular transmetalation can proceed.

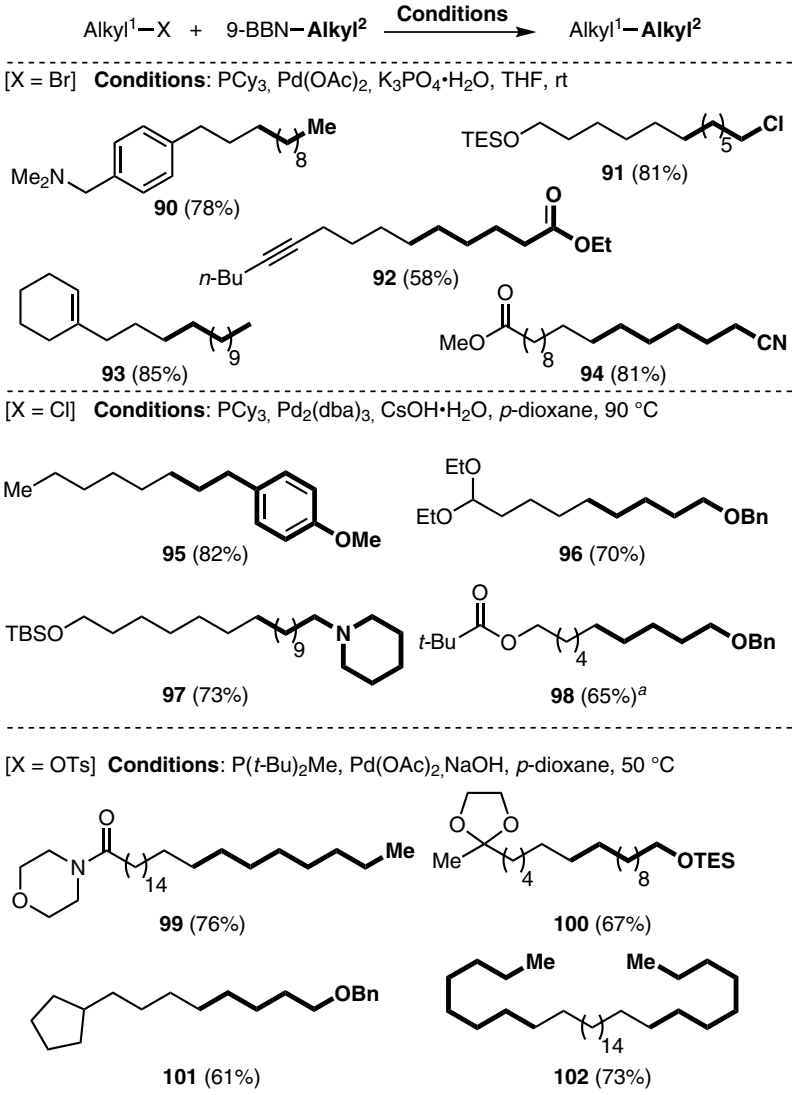


Scheme 4.11 Fu and coworkers characterized using X-ray crystallography the alkyl–Pd complex [89•C8] that possesses β-hydrogens and that is stabilized by bulky, electron-rich phosphine ligands.

that prevent Pd-alkyl species from reaching geometries required for β-hydride elimination. In addition, the imparted electron density on the metal center renders it more nucleophilic and thus the energetic barrier to oxidative addition is attenuated. This increased electron density on the metal, in conjunction with the imposed steric topography from the ligand, lessens the agostic and anagostic [124] interactions of the metals d-orbitals with β-hydrogen(s) in the alkyl moiety. The ligand's sterics also favor reductive elimination of these less bulky alkyl fragments (relative to aryl groups), thereby shortening the lifetime of the transient $R^1R^2PdL_n$ species (refer to Figure 4.1) that provides less opportunity for deleterious side reactions to occur. The enhanced reactivity of Pd(0) using bulky, electron-rich ligands and the stability of the alkyl-Pd intermediates is evident in the elegant near-quantitative isolation of the oxidative addition adduct [89•C8] that was sufficiently stable to characterize by X-ray crystallography (Scheme 4.11) [125].

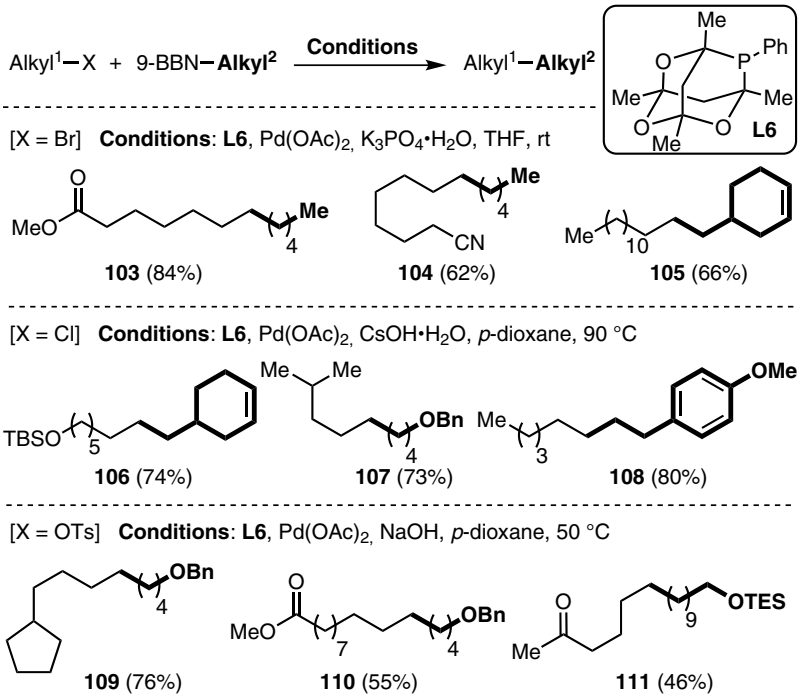
4.2.3.2 **Cross-Couplings Promoted by Phosphines and Amine-Based Ligands**

4.2.3.2.1 **Cross-Couplings of Primary Alkyl Halides** The early part of 2000 witnessed the first reports of the C_{sp3}–C_{sp3} Suzuki–Miyaura cross-coupling of unactivated primary alkyl bromides [126], chlorides [127], and tosylates [128] with alkyl-9-BBN reagents (Scheme 4.12). The sterically demanding organophosphine PCy_3 was optimal for the coupling of primary alkyl bromides (leading to **90–94** at room temperature) and chlorides (leading to **95–98** at 90 °C) in the presence of $Pd(OAc)_2$ or $Pd_2(dba)_3$, respectively. While organophosphines P(*t*-Bu)$_2$Et and P(*t*-Bu)$_2$*i*-Pr provided only a trace amount of product, P(*t*-Bu)$_2$Me was optimal for coupling primary alkyl tosylates (leading to **99–102**). This result suggests that there exists a strict dependence on the precise sterics of the ligand for this cross-coupling. It is not immediately obvious what stage(s) of the catalytic cycle is(are) so highly dependent on such subtle changes to ligand structure or more specifically how the halide/pseudohalide influences this fine balance. Computational analysis has indicated that the transmetalation step is greatly affected by ligand sterics in the alkyl–alkyl Negishi cross-coupling [38]. Of course, the electronic contribution from the organophosphine cannot be ruled out as minor structural changes do attenuate their basicity. Regardless of the mechanistic underpinnings, a variety of functionalized products were prepared, with tertiary amines (**90** and **97**), esters (**92**, **94**, and **98**), nitriles (**94**), silyl



Scheme 4.12 The Suzuki–Miyaura cross-coupling of unactivated primary alkyl chlorides, bromides, and tosylates with alkyl-9-BBN reagents carried out in the presence of PCy_3 and $P(t\text{-Bu})_2Me$. [a]KOH was used in place of $CsOH{\bullet}H_2O$. Bn = benzyl; TBS = *t*-butyldimethylsilyl; TES = triethylsilyl.

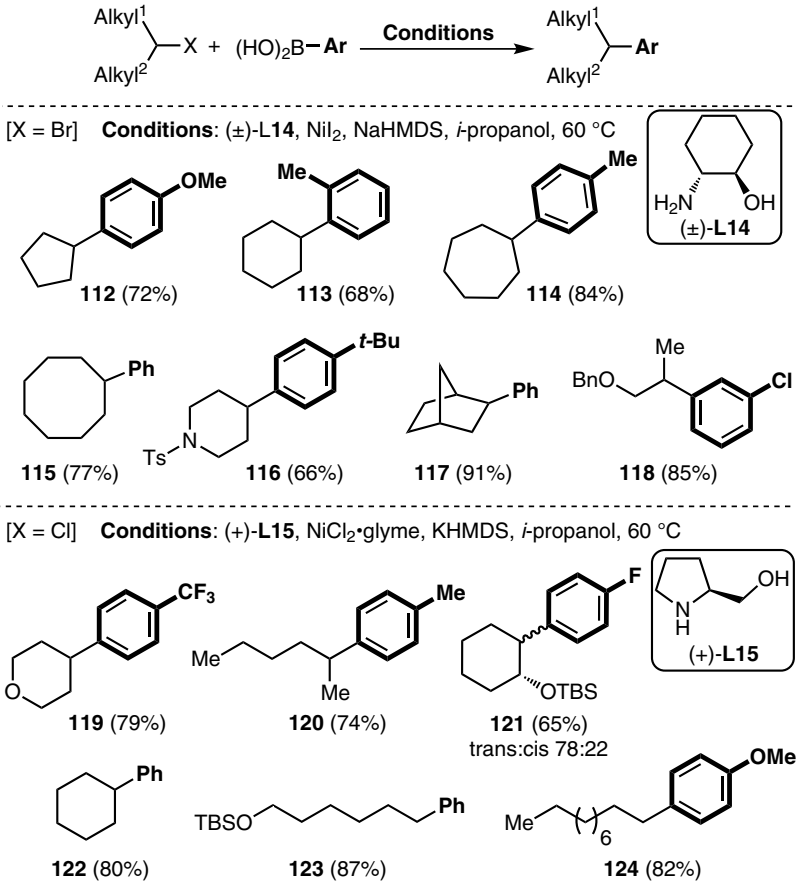
ethers (**91**, **97**, and **100**), and amides (**99**) being compatible with the reaction conditions. Ketones and aldehydes may not be tolerated, as inferred from the use of acetal (**96**) and ketal (**100**) masking groups. In addition, alkyl bromides are selectively coupled in the presence of alkyl chlorides, as seen in the coupling leading to **91**, and monosubstituted alkenes can be selectively hydroborated in the presence of disubstituted alkenes, providing access to **93**.



Scheme 4.13 The Suzuki–Miyaura cross-coupling of unactivated primary alkyl chlorides, bromides, and tosylates with alkyl-9-BBN reagents carried out in the presence of phosphaadamantane-derived ligand **L6** (Figure 4.2).

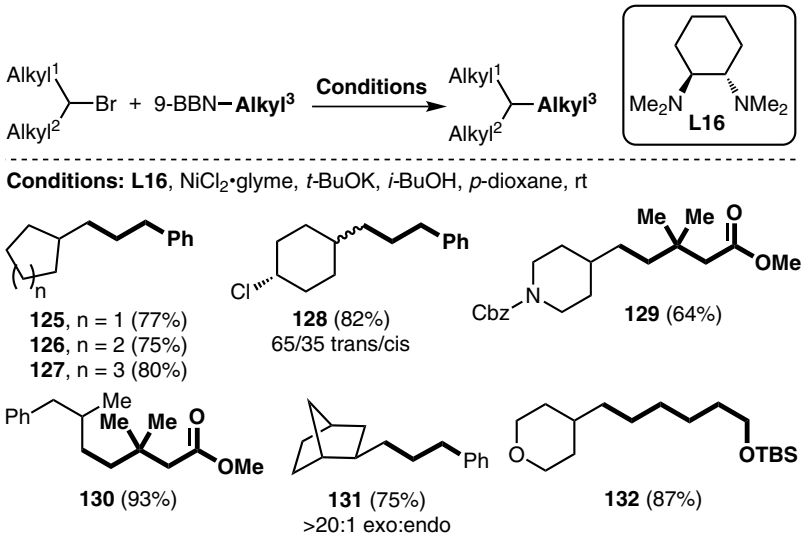
Under the reaction conditions that were optimal for coupling using PCy_3 and $P(t\text{-Bu})_2Me$ (Scheme 4.12), phosphaadamantane **L6 (**Figure 4.2) has been shown to be a general ligand for the coupling of unactivated primary alkyl bromides, chlorides, and tosylates providing a means to access aliphatic products **103–111** (Scheme 4.13) [129]. Functional group compatibility is on par with couplings carried out in the presence of PCy_3 and $P(t\text{-Bu})_2Me$. That a single organophosphine ligand can couple each of these three electrophiles is an advantage of this system. Phosphaadamantane **L6** (Figure 4.2) was also effective at coupling unactivated primary alkyl bromides and chlorides with arylboronic acids [130]. As such, this ligand is as effective as trialkylphosphines for a variety of cross-couplings; however, it has received less attention presumably as a consequence of it being synthetically more laborious to prepare, limited studies on its use in C_{sp2}–C_{sp2} cross-couplings, and being commercially unavailable at the time this chapter was composed.

4.2.3.2.2 **Coupling of Secondary Alkyl Halides** Unactivated secondary alkyl halides are more challenging electrophiles than primary ones due to the more electron-rich C−X bond and increased sterics surrounding the reactive site, as well as the presence of additional β-hydrogens that can interact with the metals d-orbitals. The employment of more reactive Ni-based catalysts has bypassed some of these barriers, as Ni(0)



Scheme 4.14 The Suzuki–Miyaura cross-coupling of unactivated secondary alkyl bromides and chlorides with arylboronic acids carried out in the presence of amino alcohol-based ligands **L14** and **L15**.

has a lower oxidation potential than does Pd(0) and proceeds via a radical mechanism (see below). Suzuki–Miyaura cross-couplings of secondary alkyl bromides and iodides with arylboronic acids were first demonstrated using $Ni(cod)_2$ (cod = cyclooctadiene) and bathophenanthroline as the spectator ligand in the presence of *t*-BuOK and *s*-butanol at 60 °C [131]. Yields of cross-coupled products ranged from 44 to 90%; however, as acknowledged by the authors the substrate scope is limited. This prompted a follow-up study that elucidated highly active Ni/amino alcohol-based catalyst systems (ligands **L14** and **L15**, Scheme 4.14) [132]. A variety of unactivated secondary bromides (leading to **112–118**) and chlorides (leading to **119–124**) were coupled with arylboronic acids in high yields. The use of heteroaryl-, alkenyl-, and alkylboronic acids were less effective substrates than arylboronic acids, often resulting in <30% yields. Electron-rich arylboronic acids were required in excess due to protodeborylation, which may stem from the use of *i*-propanol as solvent that



Scheme 4.15 The Suzuki–Miyaura cross-coupling of unactivated secondary alkyl bromides with primary alkyl-9-BBN reagents in the presence of the diamino ligand **L16**.

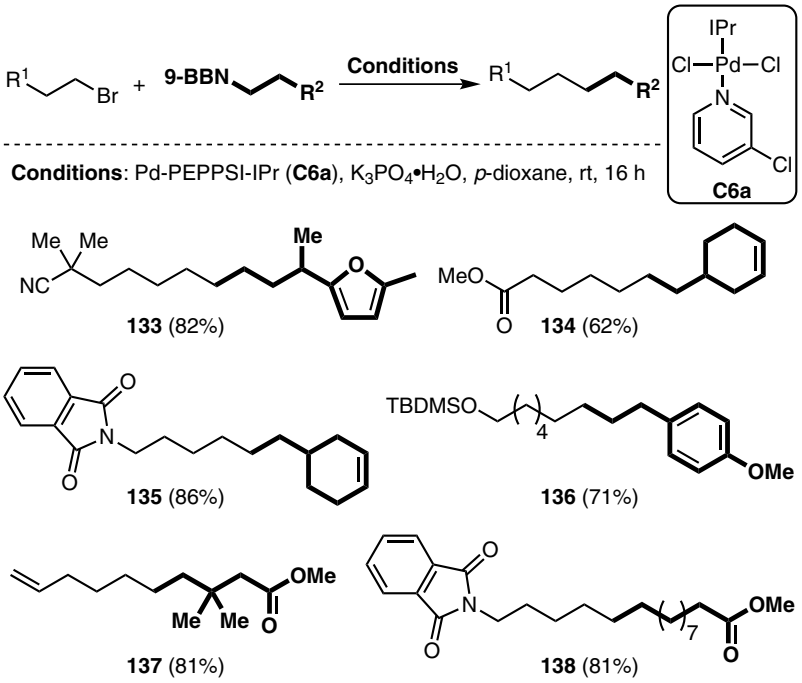
undergoes β-hydride elimination to give acetone and the corresponding Pd(II) hydride species [114, 133]. As well, *ortho*-substituted arylboronic acids were poor substrates in the coupling of secondary alkyl chlorides. Notwithstanding these shortcomings, in terms of cross-coupling protocols this method is relatively general, and a variety of secondary alkyl benzene derivatives were prepared that otherwise would be difficult to prepare in a single synthetic transformation. The authors did not comment on whether the use of (*S*)-(+)-proline (**L15**) provides asymmetric induction in the coupling of racemic secondary alkyl chlorides.

The cross-coupling of secondary alkyl bromides with *alkyl*-9-BBN reagents has also been achieved (Scheme 4.15) [134]. The optimal Ni-based catalyst systems utilizing amino alcohol-based ligands **L14** or **L15** that were viable for coupling secondary alkyl halides with arylboronic acids provided only trace (<5%) amounts of product in the coupling of bromocyclohexane with 9-(3-phenylpropyl)-9-BBN. Instead *trans-N,N′*-dimethyl-1,2-cyclohexanediamine (**L16**) was found to be an effective ligand for this Ni-catalyzed transformation. A range of unactivated secondary alkyl bromides were coupled with various primary alkyl-9-BBN reagents (leading to **125–132**) in good-to-excellent yields at *room temperature*! Protic solvent was necessary for effective coupling of these secondary electrophiles. Unactivated primary and secondary alkyl iodides and primary alkyl bromides were also suitable substrates under these reaction conditions. Interestingly, secondary alkyl bromides were coupled selectively in the presence of primary alkyl bromides in a competition experiment, and both greatly outperformed tertiary alkyl bromides. The two-electron oxidative addition commonly associated with aryl halides and Pd-mediated cross-couplings gives way to a radical mechanism for the coupling of secondary alkyl halides with low-valent Ni catalysts [132, 135, 136]. Ligand-dependant one-electron oxidation of Ni by the

secondary alkyl bromide provides an sp^2-hybridized alkyl radical alongside the formation of X^- [137]. The alkyl radical is in the vicinity of the metal and undergoes oxidative radical addition to Ni so long as radical dimerization and other side processes are slower kinetically. This perhaps accounts for the observed preference of secondary alkyl bromides over primary alkyl bromides as their radicals are more stable. It is likely that the sterics of tertiary alkyl electrophiles impede one or more steps of this revised catalytic cycle.

4.2.3.3 Cross-Couplings Promoted by NHC Ligands

N-Heterocyclic carbenes have also proven effective as ligands in the Suzuki–Miyaura C_{sp3}–C_{sp3} reactions; however, their range of use is less advanced relative to organophosphine and amine-based ligands. An *in-situ*-prepared catalyst from the imidazolium salt IPr•HCl and $Pd_2(dba)_3$ generated yields of cross-coupled aliphatic products ranging in 28–56% yields from primary alkyl bromides and alkyl-9-BBN reagents at 40 °C [138]. The preformed complex Pd-PEPPSI-IPr (**C6a**, Figure 4.3) was used in similar couplings and was found to be superior to the *in-situ*-generated (NHC) Pd catalyst [139]. At room temperature, a range of primary C_{sp3}–C_{sp3} cross-couplings were carried out to provide the corresponding products (**133–138**) in good-to-excellent yields (Scheme 4.16). Functional group compatibility was quite good under the mild reaction conditions. The alkylation of aryl bromides and chlorides was



Scheme 4.16 The Suzuki–Miyaura cross-coupling of unactivated primary alkyl bromides with primary alkyl-9-BBN reagents in the presence of Pd-PEPPSI-IPr (**C6a**, Figure 4.3).

also reported using the same reaction conditions, with free aniline and phenol derivatives being compatible substrates, thus removing the need to implement protecting group chemistry [139].

4.3
Asymmetric Suzuki–Miyaura Cross-Couplings

Recently developing apace is the asymmetric Suzuki–Miyaura reaction wherein asymmetric induction by way of chrial ligands and/or substrates results in the stereoselective formation of a new C−C bond [140, 141]. Advanced ligand design to facilitate more effective cross-coupling has aided in overcoming the steric and electronic barriers that once marginalized the use of challenging *ortho*-substituted haloarenes or secondary aliphatic halides, species capable of achieving *axial* and *point* chirality in the coupling step, respectively. The vast majority of research in this realm has been focused on preparing biaryl compounds that possess hindered rotation about the newly formed aryl–aryl (axial) bond such that if the magnitude of the barrier to rotation is large enough [141], two isomers, more specifically atropisomers, are possible. Approaches to achieve atroposelective Suzuki–Miyaura cross-couplings rely on asymmetric induction via (1) chiral phosphine and nitrogen-based ligands for the metal catalyst (Section 4.3.1.1), (2) coordination of the metal catalyst by a stereogenic *ortho*-substituent on the electrophilic coupling partner (Section 4.3.1.2), and (3) (arene)chromium complexes that possess an axis of planar chirality (Section 4.3.1.3) [140, 141]. All methods provide a chiral environment for the metal center, with the first of these techniques being the most general and thus most exploited approach. Cross-couplings where point chirality is introduced into the product are much less developed due to the inherent difficulty in effectively coupling secondary alkyl halides via transition metal-mediated catalysis. However, some success has been made and approaches include the use of chiral catalyst systems or "advanced" substrates in which the point chirality is preestablished in the reactive C−X or C−B bonds that is transferred to the forming C−C bond (i.e., stereoretention). Each of these approaches will be discussed in the following sections.

4.3.1
Achieving Axial Chirality in the Suzuki–Miyaura Reaction

4.3.1.1 Axial Chirality Induced by Chiral Ligands/Catalysts

The use of chiral ligands to prepare atropisomers is desirable as it is potentially quite general and avoids the need to employ advanced enantiopure precursors with functionality that must later be removed. Progress has been slow and largely unfruitful in this area; however, a handful of recent investigations have achieved excellent atroposelectivities for this transformation (i.e., >85% *ee*). The atroposelective formation of the $C_{aryl}-C_{aryl}$ bond in 1-phenylnaphthalene and 1,1′-binaphthalene derivatives has become the benchmark for the evaluation of chiral ligands (i.e.,

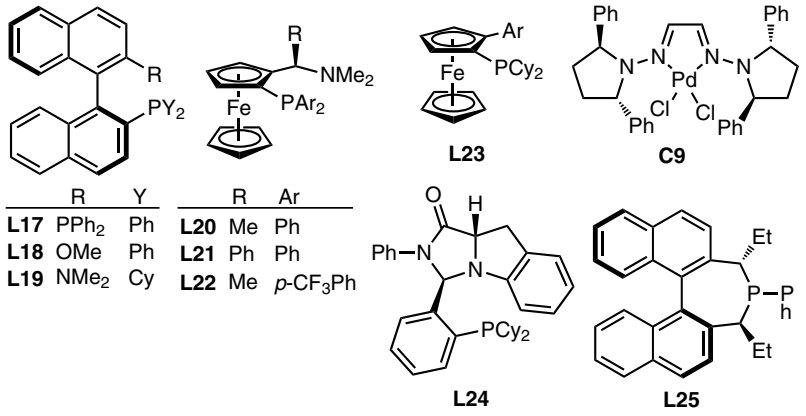
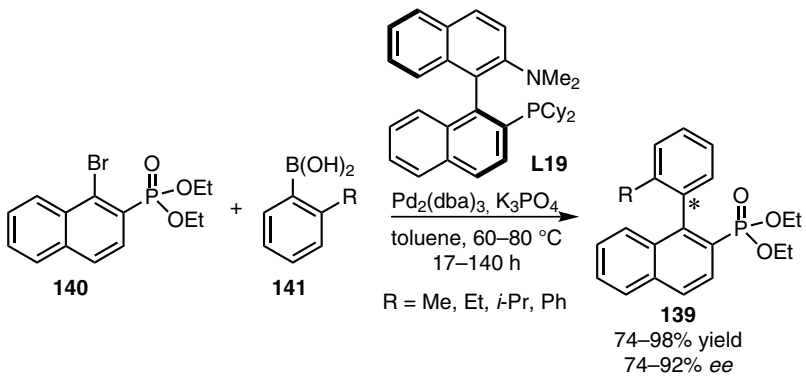


Figure 4.7 Chiral ligands used in the asymmetric Suzuki–Miyaura reaction.

L17–L25 and **C9**, Figure 4.7) developed for use in the asymmetric Suzuki–Miyaura reaction [140, 141]. Most couplings leading to these products are plagued by low *ee*'s and/or low yields that stems in part from protodeborylation due to increased sterics in the boronic acid substrate [142–150].

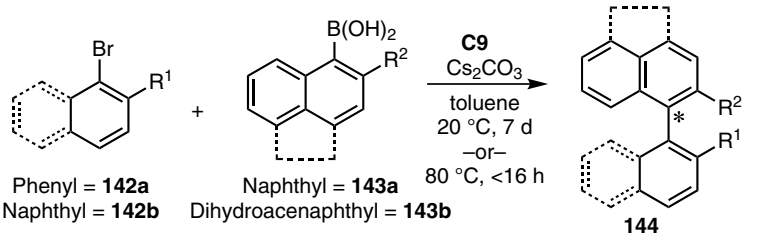
The use of chiral binaphthyl ligand **L19** in combination with $Pd_2(dba)_3$ under the conditions outlined in Scheme 4.17 was one of the earliest developed conditions to achieve consistently high atroposelectivities [151]. Long reaction times were typically required; however, excellent ee's and yields were obtained for a variety of 1-aryl-2-naphthylphosphonates (**139**) produced from their precursor 1-bromo-2-naphthyl-phosphonates (**140**) and *ortho*-substituted phenylboronic acids (**141**).

More recently, some of the highest ee's achieved to date were reported using the C_2-symmetric bis-hydrazone–$PdCl_2$ complex **C9** (Table 4.2) [152]. Coupling of substituted 1-bromobenzene or 1-bromonaphthalenes (**142**) with 1-naphthyl- or 1-dihydroacenaphthylboronic acid (**143**) derivatives possessing *ortho* substituents provided their corresponding chiral biaryl products (**144**) in excellent ee's and yields (entries

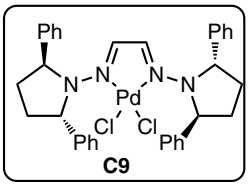


Scheme 4.17 Atroposelective Suzuki–Miyaura cross-couplings using chiral ligand **L19**.

Table 4.2 The Suzuki–Miyaura cross-coupling employing chiral catalyst **C9** for the preparation of biaryl atropisomers.



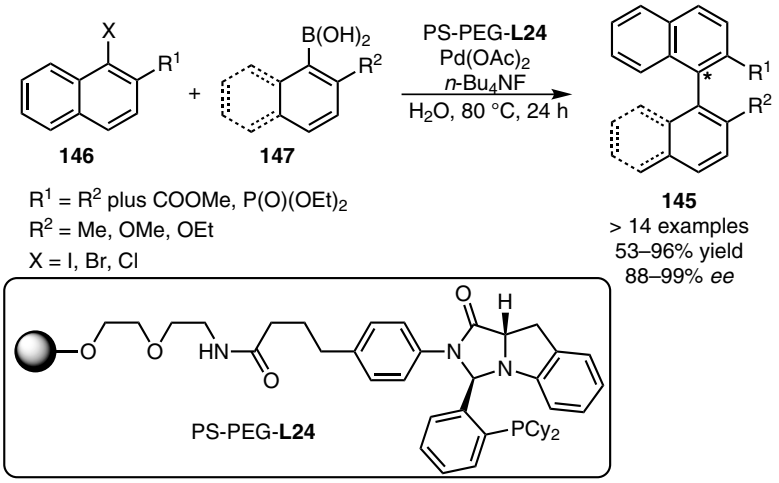
Entry	Ar–R^1	Ar–R^2	20 °C yield% (*ee*)	80 °C yield% (*ee*)	Config.
1	**142b**–OMe	**143a**–H	97 (86)	99 (75)	*S*
2	**142b**–Me	**143a**–H	80 (95)	98 (90)	*R*
3	**142b**–H	**143a**–Me	71 (98)	99 (86)	*R*
4	**142b**–Me	**143b**–H	40 (>98)	98 (70)	*R*
5	**142a**–Ph	**143a**–Me	97 (84)	—	*S*



1–5). Although no tetra-*ortho*-substituted biaryls could be formed, tri-*ortho*-substituted biaryls were easily accessible. The reaction can be accelerated from 7 days to less than 16 h by heating to 80 °C. Yields are generally improved; however, there is a concomitant erosion in *ee*.

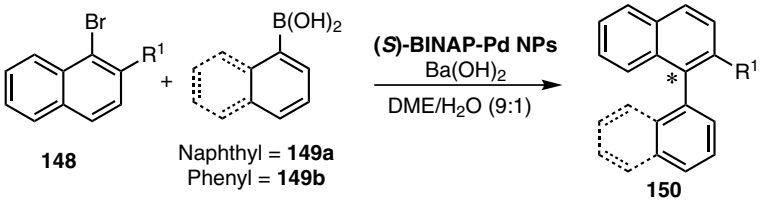
Remarkable reactivity and atroposelectivity come by way of ligand **L24** and $Pd(OAc)_2$ in toluene at 100 °C using K_3PO_4 base [153]. 1-Iodo-2-methylnaphthalene and 2-methyl-1-naphthylboronic acid were coupled to give the corresponding tetra-*ortho*-substituted binaphthyl derivative in 98% yield and 92% *ee* in just 5 h! The halide derivative 1-chloro-2-methylnaphthalene was also coupled in excellent *ee* (88%) and moderate yield (57%), making this protocol unprecedented in terms of its reactivity and atroposelectivity. Chiral ligand **L24** was subsequently attached to a polystyrene-poly(ethyleneglycol) copolymer (PS-PEG) resin (Scheme 4.18). In the presence of $Pd(OAc)_2$ and TBAF in H_2O at 80 °C, a wide variety of chiral biaryls (**145**, from the cross-coupling of **146** and **147**) were prepared in excellent *ee* and yield. The obvious environmental benefits from using solid-supported reagents and H_2O as solvent greatly add to the attractiveness of this approach. The PS-PEG-**L24** resin was reused up to four times without loss in *ee* and only marginal erosion in yield. At the time of writing, this study stands as the "state of the art" in the asymmetric Suzuki–Miyaura reaction for the atroposelective preparation of biaryls.

Palladium nanoparticles (1.2–1.7 nm) stabilized by (*S*)-BINAP (**L17**) have also been utilized in the asymmetric Suzuki–Miyaura reaction (Table 4.3) [154], establishing a new approach for the design and development of catalyst systems for use in this reaction. Cross-couplings of substituted 1-bromonaphthylenes (**148**) with naphthyl-



Scheme 4.18 Atroposelective Suzuki–Miyaura cross-couplings using a solid-supported chiral ligand **PS-PEG-L24**.

Table 4.3 The Suzuki–Miyaura cross-coupling employing chiral Pd nanoparticles for the preparation of biaryl atropisomers.

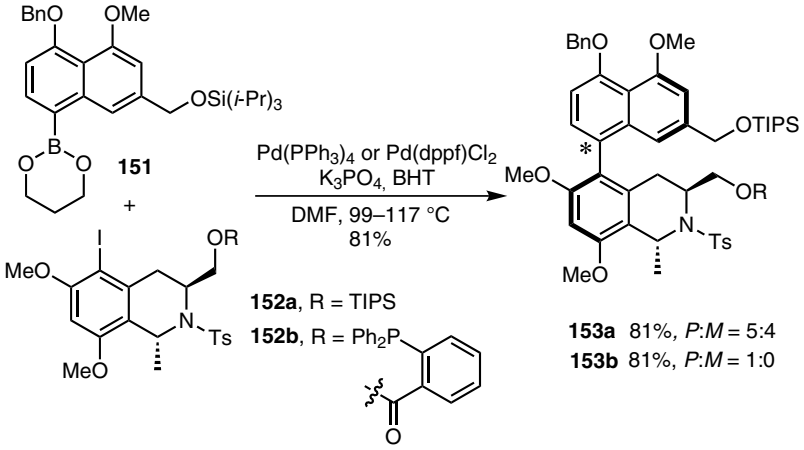


Entry	Ar–R^1	Ar–$B(OH)_2$	Temp. (°C)	Time (h)	Yield, % (*ee*, %)
1	**148**–OMe	**149a**	25	3	96 (69)
2	**148**–OMe	**149a**	−7	72	42 (74)
3	**148**–OEt	**149a**	25	3	90 (70)
4	**148**–OMe	**149b**	25	24	89 (55)

(**149a**) and phenylboronic acids (**149b**) leading to substituted 1-arylnaphthalenes (**150**) were achieved in excellent yields and moderate atroposelectivities (entries 1, 3, and 4). Impressively, all couplings were carried out at room temperature; cooling to −7 °C cut the yield roughly by half while improving the *ee* only slightly (entry 2).

4.3.1.2 Axial Chirality Induced by Point Chirality

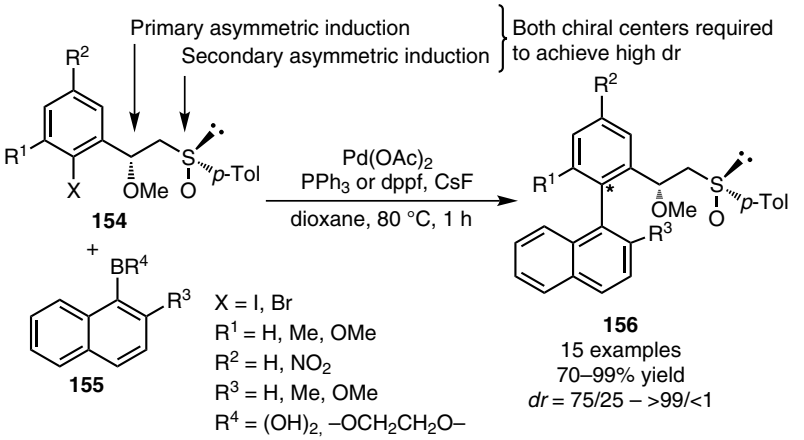
Installing metal chelating functionality that is stereogenic *ortho* to the oxidative addition site on the electrophile induces a transient asymmetric topography around the metal center that can bias the atropstereoselectivity of the forming $C_{aryl}–C_{aryl}$



Scheme 4.19 Atroposelective Suzuki–Miyaura cross-couplings using Pd-chelating substituents that possess point chirality on one of the coupling partners. TIPS = tri-*i*-propylsilyl; BHT = 3,5-di-*t*-butyl-4-methylphenol.

bond. In essence, the electrophile becomes an asymmetric ligand for the metal. This approach was utilized in the coupling of the boronic ester **151** with derivatives of **152** (Scheme 4.19) [155]. The silyl derivative (**152a**, weak Pd ligation) provides poor atropdiastereoselectivity, whereas the phosphine derivative (**152b**, good Pd ligation) provides a single atropdiastereomer of **153**, a precursor to *korupensamine A*, which is a component of the naturally occurring Michellamine alkaloids.

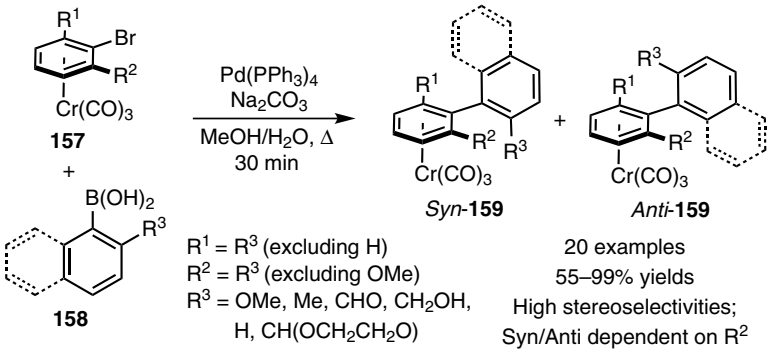
Another example involves the coupling of a single diastereomer of the sulfinyl derivative **154** with naphthylboronic acids and esters of the type **155** (Scheme 4.20) [156, 157]. Again, the induced chiral environment around Pd provides sulfinyl-containing biaryls **156** in good-to-excellent atropdiastereoselectivities.



Scheme 4.20 Suzuki–Miyaura cross-couplings using point chirality in *ortho* substituents of aryl bromides and iodides to achieve atroposelectivity.

4.3.1.3 Axial Chirality Induced by Planar Chirality

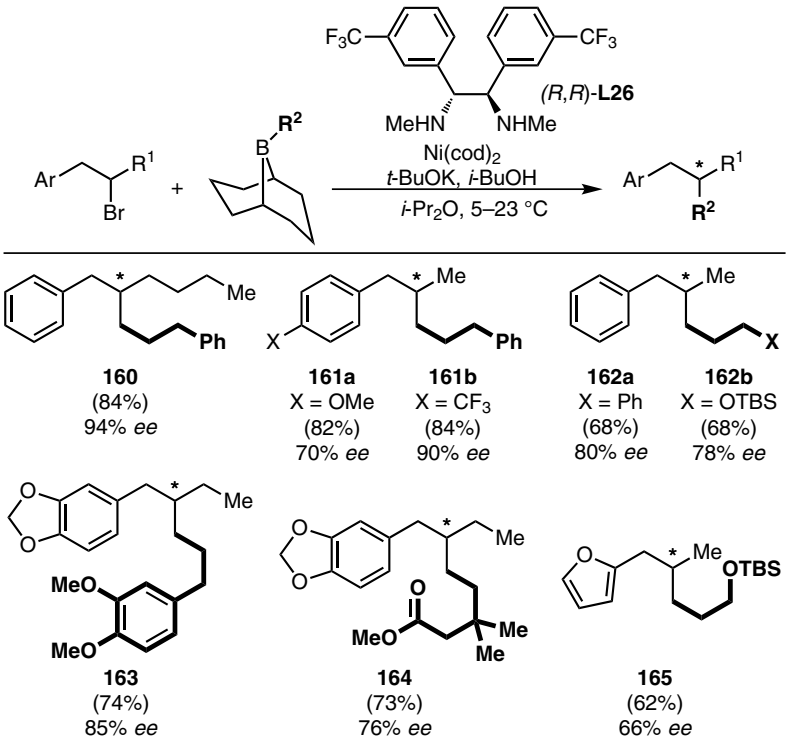
Axially chiral *ortho*-substituted biphenyls and phenylnaphthalenes have been prepared from arylboronic acids and (haloarene)chromium complexes (**157**) that possess a plane of chirality (Scheme 4.21) [158–163]. The atroposelectivity is highly dependent on the *ortho* substituent on the boronic acid (**158**). *Syn*-**159** atropisomers are formed exclusively in these couplings; however, the product can isomerize to the thermodynamically more stable isomer *anti*-**159** if the energetic barrier to axial rotation is sufficiently low. For the reverse reaction, (arylboronic acid)chromium complexes were found to be ineffective coupling partners with aryl halides forming only trace quantities of cross-coupled product. This approach has limited applications due to the use of a stoichiometric amount of toxic chromium and the difficulty associated with isolating single enantiomers of the chiral(arene)tricarbonylchromium complexes, which is typically accomplished by chromatography or fractional crystallization of their diastereoisomeric salts [164–167].



Scheme 4.21 Suzuki–Miyaura cross-couplings using planar chirality in the substrate to achieve atroposelectivity.

4.3.2
Achieving Point Chirality in the Suzuki–Miyaura Reaction

Unactivated secondary alkyl halides have been elusive substrates in transition metal-mediated couplings as a result of both the increased sterics and unfavorable electronics of these electrophiles. Only recently have examples emerged in which Ni-based catalysts, among others, have shown appreciable reactivity (Section 4.2.3.2.2) [136, 168]. Impressively, an asymmetric variant of this challenging reaction using the chiral diamine (*R,R*)-**L26** in the presence of $Ni(cod)_2$ provided access to products possessing a new stereogenic tertiary carbon (**160–165**) in good yields and enantioselectivities at or below room temperature (Scheme 4.22) [169]. There is a strict homobenzylic structural requirement for the alkyl halides as extending the chain length between the "bulky" aryl moiety and the C_{sp3}—Br bond leads to drastically reduced enantioselectivities. The observed stereoconvergence can be accounted for by the radical mechanism for oxidative addition (described in

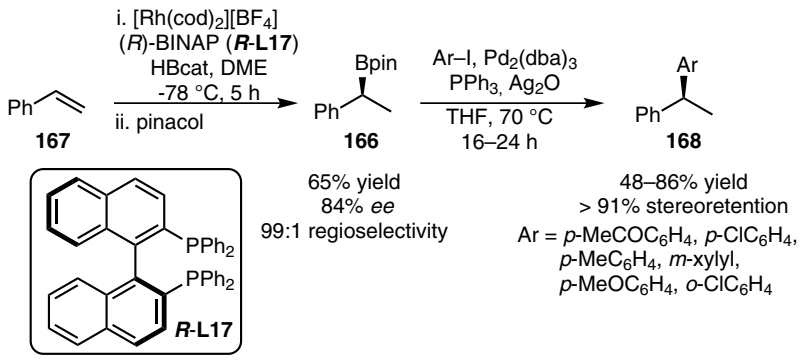


Scheme 4.22 The asymmetric Suzuki–Miyaura cross-coupling of unactivated racemic secondary alkyl bromides with primary alkyl-9-BBN reagents in the presence of the diamino ligand (*R*,*R*)-**L26**.

Section 4.2.3.2.2) for Ni-catalyzed couplings of secondary alkyl bromides; the planar sp^2-hybridized alkyl radical is under the influence of the asymmetric environment imposed by the chiral ligand and induces enantioselective oxidative radical addition to Ni [137].

A different approach to the asymmetric Suzuki–Miyaura coupling has been reported that uses chiral organoboranes (**166**, Scheme 4.23). These are prepared in high levels of regio- and enantioselectivties by the Rh-catalyzed asymmetric hydroboration of styrene (**167**) and its analogues. These chiral secondary benzylic pinacol boranes are then coupled with aryl iodides in the presence of $Pd_2(dba)_3$, PPh_3, and AgO to yield the corresponding α-substituted phenylethanes (**168**) in good yields with excellent stereoretention of the stereogenic center [170]. Interestingly, achiral primary alkylboranes are not reactive under these reaction conditions.

To date, the above examples are the only known asymmetric Suzuki–Miyaura reactions of alkyl halides and alkylboranes. Although both couplings require stringent placement of aromatic motifs in one of the reacting substrates to achieve high levels of enantioselectivity, they nonetheless succeed in the long-sought goal of bringing the most widely used cross-coupling reaction into the realm of asymmetric catalysis.



Scheme 4.23 The Suzuki–Miyaura cross-coupling of chiral organoboranes (**166**) to provide the stereoconserved chiral products (**168**). Yields of cross-coupled product based on ^{1}H NMR spectroscopy versus an internal standard. HBcat = catecholborane.

4.4
Iterative Suzuki–Miyaura Cross-Couplings

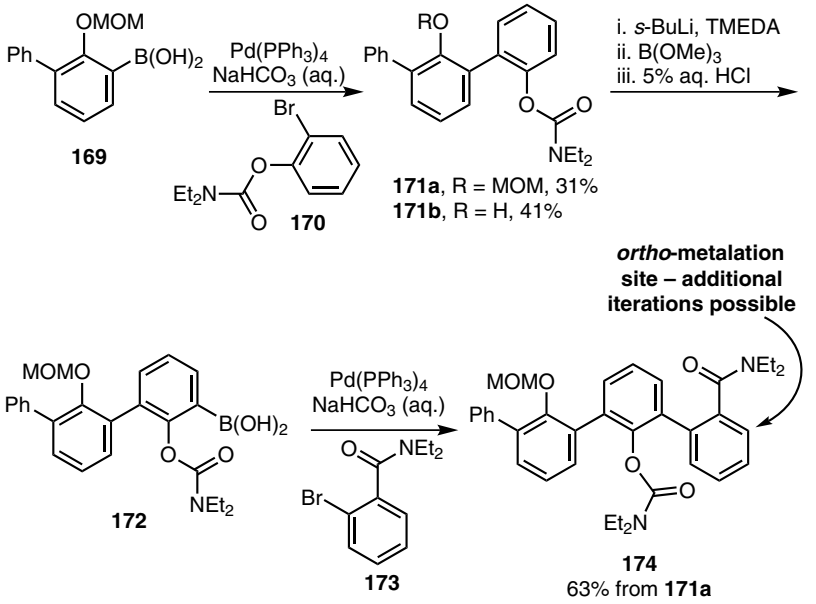
Robust methods for the facile preparation of oligoarenes are of interest as these are key structural components both for molecules of biological relevance, including enzyme mimics, and for use in molecular electronics and self-assembly [171, 172]. The Suzuki–Miyaura reaction has been applied to the preparation of such materials [173].

4.4.1
ortho Metalation–Cross-coupling Iterations

ortho Metalation is a powerful method for selectively functionalizing arenes that possess a directed metalation group. Such methodology has been applied to the preparation of tetraphenylenes as a means of realizing the iterative Suzuki–Miyaura reaction (Scheme 4.24) [174]. Biphenylboronic acid derivative **169** was cross-coupled with *o*-bromophenyl diethylcarbamate **170** to provide **171a** along with its unmasked derivative **171b**. Subsequent *ortho* metalation of **171a** and quenching the intermediate phenylide with trimethylborate provided boronic acid **172** after acid hydrolysis. Iteration of the cross-coupling step provided tetraphenyl **174** in good overall yield. Successive iterations of (i) *ortho* metalation and (ii) cross-coupling should be possible given the presence of a directed metalation group in **174**.

4.4.2
Triflating–Cross-Coupling Iterations

Another strategy involves the iteration of (i) the cross-coupling of aryl triflates functionalized with either a free or a methyl-protected hydroxyl group and (ii) triflation of the unmasked hydroxyl group in the product [171, 172, 175]. This



Scheme 4.24 Iterative functionalization by *ortho*-lithiation and Suzuki–Miyaura cross-couplings. MOM = methoxymethyl; TMEDA = *N*,*N*,*N*′,*N*′-tetraethylenediamine.

approach (Figure 4.8a) was used to prepare the functionalized oligoarene **175** (Figure 4.8b) in excellent yields for each iteration [171, 172].

4.4.3 Iterative Cross-Couplings via Orthogonal Reactivity

4.4.3.1 Bifunctional Electrophiles

4.4.3.1.1 **Organohalides** Other iteration strategies exploit chemo- and regioselectivity in coupling bromoiodoarenes or dibromoarenes followed by conversion of the remaining bromide functionality to a boronic acid [176–180]. An example is presented in Scheme 4.25. The boronic acid **176** was coupled to bromoiodobiphenyl **177** chemoselectively to give the corresponding bromotetraarene **178a**. Conversion of the TMS group to iodide provided **178b** that was then selectively coupled to a second equivalent of **176** to give **179a**. Lithium–bromide exchange followed by quenching with a source of iodine provided **179b** that was then converted to pinacol boronate **180**. Dimerization of **180** provided macrocyclic oligophenylene **181** [177]. A similar strategy was applied for the preparation of a cyclotetraicosaphenylene, a macrocycle possessing 24 phenylene units [176].

4.4.3.1.2 **Alternate Electrophiles** The scope of tolerated electrophiles in the Suzuki–Miyaura reaction has recently been expanded to include ArOR derivatives, including aryl methyl ethers [181], allylic ethers [182], carboxylates [183, 184],

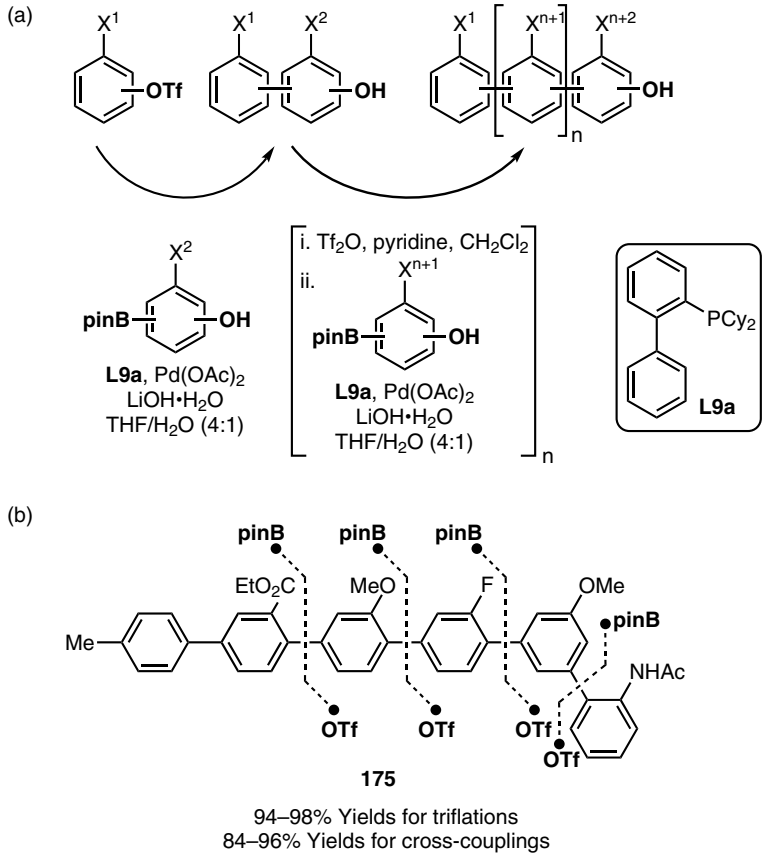
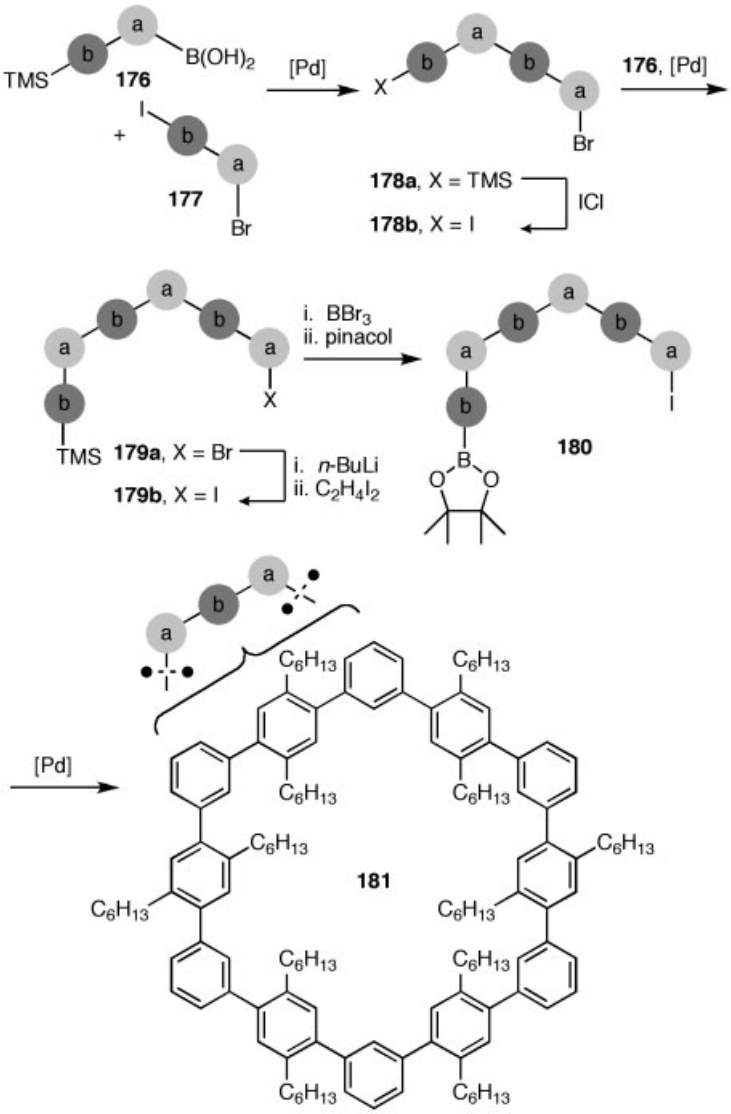


Figure 4.8 (a) An iterative Suzuki–Miyaura cross-coupling and triflation strategy that (b) has been applied to the synthesis of polyarene **175**.

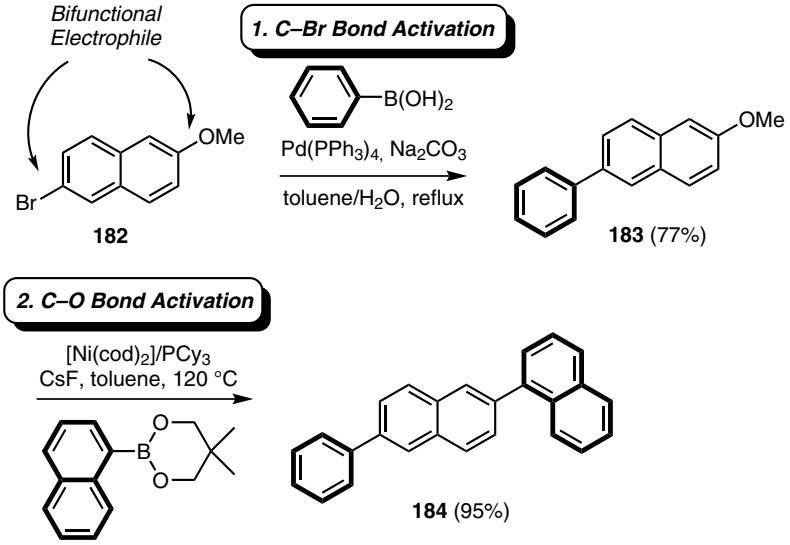
carbamates, carbonates, and sulfamates [185]. This allows one to use the relatively dormant C_{aryl}–O bond, and in doing so allows for the development of new sequential strategies that play off of the cross-coupling step. While the C_{aryl}–halide bond is susceptible to oxidative addition by both Pd and Ni catalysts, the C_{aryl}–O bond is, for the main part, inert toward Pd. This has also opened the door for iterative processes. For example, 2-bromo-6-methoxynaphthalene (**182**) has been shown to undergo a double cross-coupling sequence that begins with a Pd-catalyzed cross-coupling of the C_{aryl}–Br (providing **183**) that is followed up with a Ni-catalyzed cross-coupling of the C_{aryl}–OMe bond to provide the polyaryl scaffold present in **184** (Scheme 4.26) [181].

In addition to aryl methyl ethers, the more reactive aryl carbonates [186] have also been used as electrophiles successfully in the Suzuki–Miyaura reaction. The inert behavior of boronic acids toward carbonyl groups renders these functionalized electrophiles well matched to the Suzuki–Miyaura reaction, with the C_{aryl}–O bond undergoing chemoselective oxidative addition in the presence of the relatively weaker



Scheme 4.25 Iteration of Suzuki–Miyaura cross-couplings to provide macrocyclic oligophenylenes by means of orthogonal reactivity of aryl—I and aryl—Br bonds.

C_{acyl}—O bond (~106 and 80 kcal/mol, respectively). Aryl pivalates are the carbonate of choice, as they undergo relatively slow hydrolytic cleavage, and their application to iterative cross-coupling strategies was demonstrated in two seminal reports [183, 184]. One of these approaches (Scheme 4.27a) makes use of 4-acetylphenyl pivalate (**185**), wherein the C_{aryl}—OPiv bond is cross-coupled in the presence of commercially available $NiCl_2(PCy_3)_2$, followed by transformation of the remaining acetyl group in



Scheme 4.26 Iterative cross-couplings/orthogonal reactivity of aryl methyl ethers, and aryl bromides.

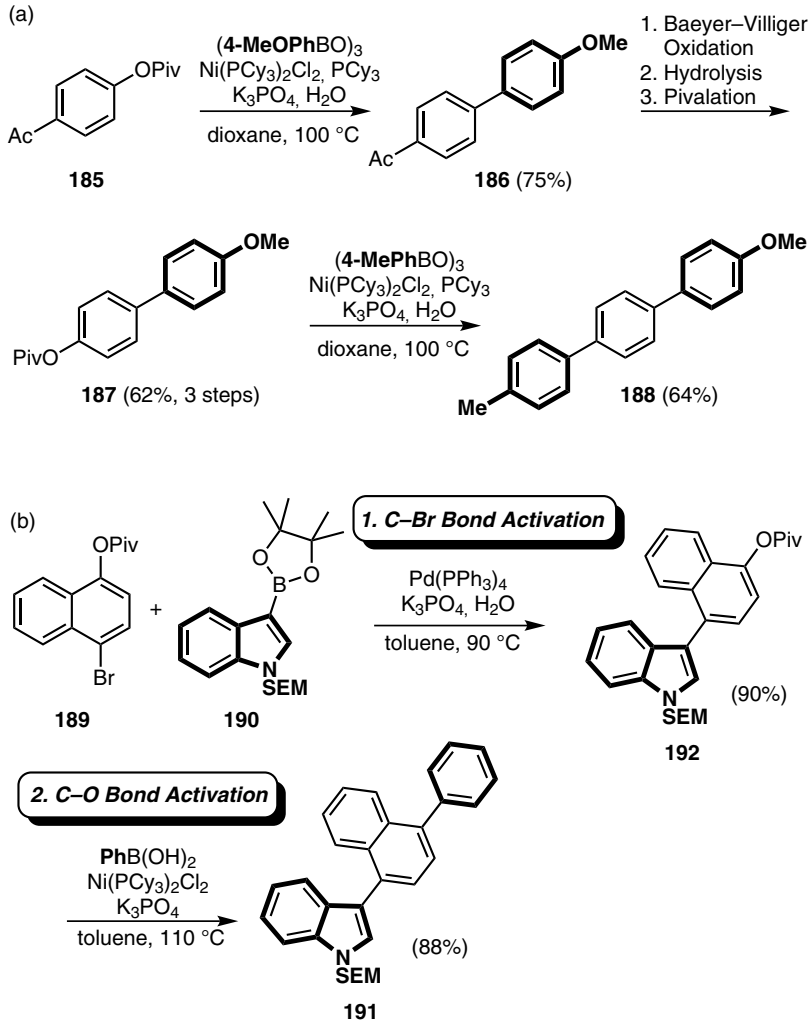
186 into a second pivalate group via a three-step process (to provide **187**) that is rounded off with a second cross-coupling to provide the triphenylene **188**. A second approach (Scheme 4.27b) begins with the bifunctional bromonaphthyl pivalate **189** that undergoes successive cross-couplings of the C_{aryl}—Br with **190** followed by C_{aryl}—OPiv with phenylboronic acid using Pd and Ni catalysts, respectively, to provide **191** via intermediate **192**.

Perhaps the most useful strategy lies in the directing functionalization potential of aryl carbamates and sulfamates [185]. These readily available substrates can be *ortho*- and *para*-functionalized by *ortho* lithiation/quenching strategies [187, 188] and/or electrophilic aromatic substitution chemistry (Scheme 4.28). Hence, densely functionalized aromatic lynchpins with unique substitution patterns are readily available for subsequent derivatization via, among other processes, cross-couplings.

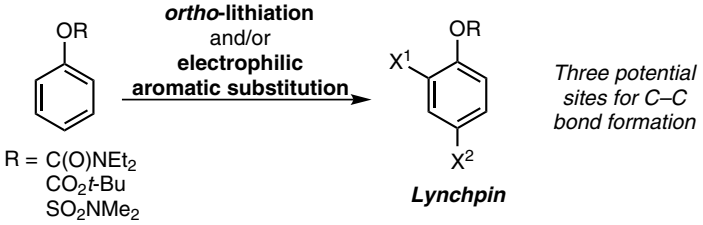
4.4.3.2 Bifunctional Organoboranes

Molander and Sandrock have demonstrated the orthogonal cross-coupling reactivity in 9-BBN/BF_3K substrates (Scheme 4.29) [189]. These diboryl substrates are prepared by the hydroboration of alkenyl-containing BF_3K salts with 9-BBN and are used directly in a one-pot sequential cross-coupling strategy with high efficiencies.

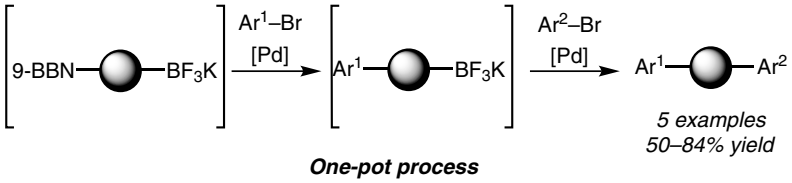
Boron-masking groups such as 1,8-diaminonaphthalene (dan) [190–193] and *N*-methyliminodiacetic acid (MIDA) [194–198] have been exploited as a means to "deactivate" the C—B bond. This has made possible the sequential coupling of *lynchpins* via orthogonal reactivity that contain both an "active" electrophilic site and an "inactive" nucleophilic site that can subsequently be "activated" through acid- or base-catalyzed hydrolysis [199]. Both dan and MIDA function to deactivate the



Scheme 4.27 Iterative cross-coupling/orthogonal reactivity strategies involving aryl pivalates as an alternative electrophile.

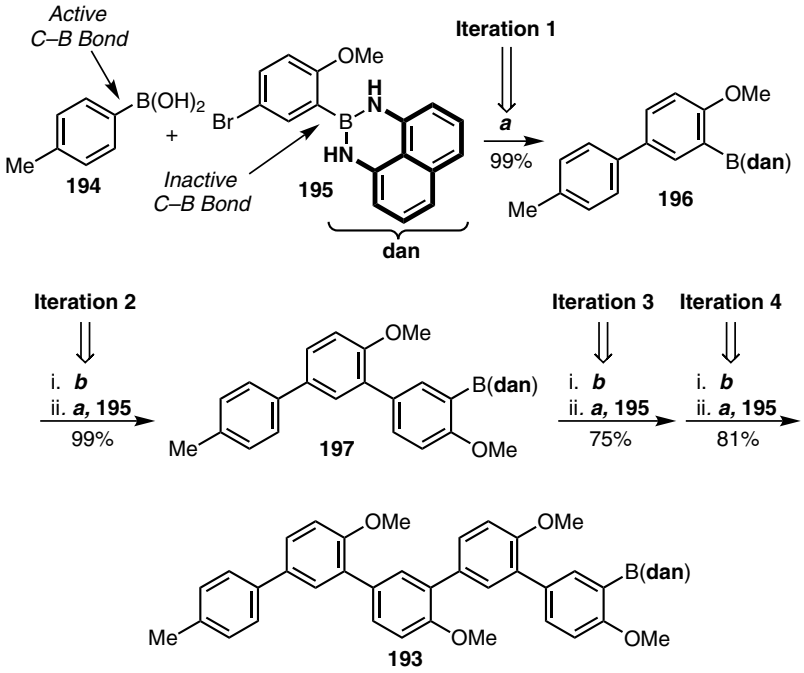


Scheme 4.28 Aryl sulfamates and carbamates are valuable synthons in cross-couplings as they can be *ortho*- and/or *para*-functionalized, lending these species to synthetic strategies unavailable to aryl halides.



Scheme 4.29 Differentially activated diboron reagents as substrates capable of orthogonal reactivity and iterative cross-couplings.

organoboronic ester by reducing the Lewis acidity of boron via stabilization of the vacant p-orbital on boron with that of the neighboring nitrogen lone pairs. This renders the organoborane inert toward transmetalation by effectively masking the C−B bond. The synthesis of oligophenylene **193** (Scheme 4.30) by Suginome and coworkers demonstrates how this principle can be applied to the iterative Suzuki–Miyaura reaction [192]. *p*-Tolylboronic acid (**194**) was coupled with haloboronamide **195** to provide the substituted biphenyl intermediate **196**. Acid-catalyzed hydrolysis of the boronamide provides the boronic acid derivative that can then participate in the



(*a*) Cross-coupling conditions: Pd[P(*t*-Bu)$_3$]$_2$, CsF, THF, 60 °C
(*b*) Hydrolysis conditions: H_2SO_4 aq. or HCl aq., THF, rt

Scheme 4.30 Iterative Suzuki–Miyaura reactions (step ***a***) that utilize masked bifunctional substrates (**195**) containing a "deactivated" boronamide that can be "activated" by acid-catalyzed hydrolysis (step ***b***).

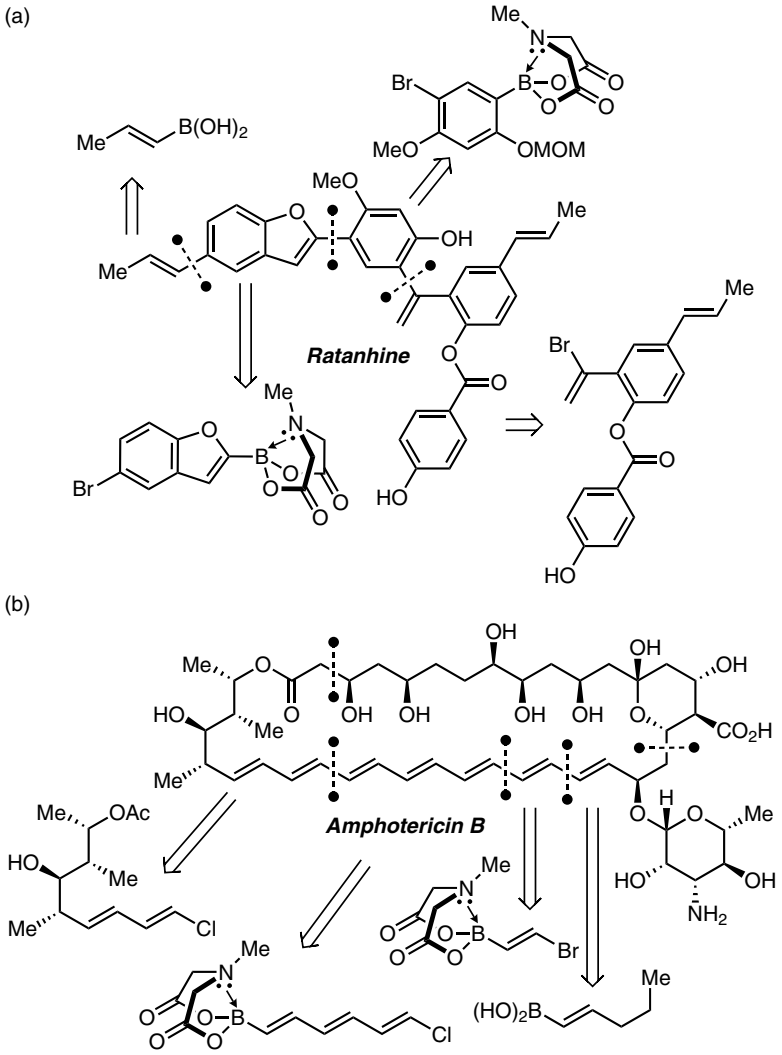
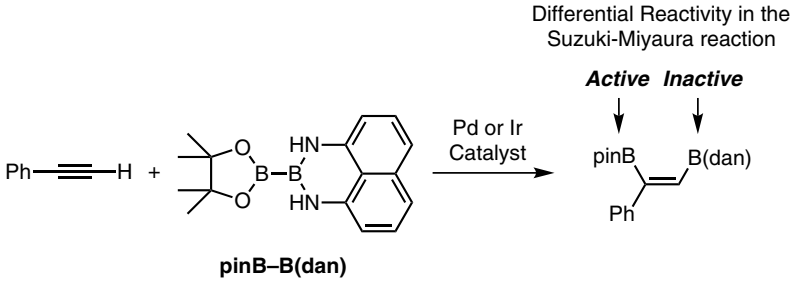


Figure 4.9 Retrosynthetic breakdown to functionalized precursors for the total and partial synthesis of (a) *ratanhine* and (b) *amphotericin B*, respectively.

subsequent cross-coupling reaction with **195** to provide triarylboronamide **197**. Iteration of this sequence extends the phenylene chain to provide **193**.

Iterative Suzuki–Miyaura reactions have also been applied for the total synthesis of *ratanhine* [194] and a partial synthesis of *amphotericin B* (Figure 4.9) [196]. This work by Burke and coworkers was accomplished through the use of MIDA as the boronic acid-masking group. Notably, while polyenylboronic acids are unstable entities, haloalkenyl and polyenyl MIDA boronate esters are shelf stable. Conversion of the MIDA group back to the boronic acid was achieved under mild basic conditions (1M aq. NaOH/THF, 10 min; $NaHCO_3$/MeOH, 6 h) at room temperature.



Scheme 4.31 The reagent (pin)B–B(dan) can regioselectively diborylate teminal alkynes in the presence of a Pd or Ir catalyst. The 1-alkene-1,2-diboronic acid derivative contains both an active and an inactive C—B bond that can be selectively manipulated.

A variety of MIDA boronates are now commercially available. They are both air and chromatographically stable and are easily handled as free-flowing powders, as are the dan-protected derivatives. Although the latter arylboronamides can be prepared readily via condensation of 1,8-diaminonaphthalene with the desired boronic acid, a few recent studies illustrate their preparation via the stereoselective iridium-catalyzed (i) hydroboration of terminal alkynes [191], (ii) C–H borylation of functionalized arenes with (dan)BH [190], and (iii) diboration of alkynes with (pin)B–B(dan) to provide differentially protected 1,2-diboron alkenes (Scheme 4.31) [200]. Recent reports demonstrate that MIDA organoboronate derivatives are stable to a variety of chemical reactions that allows for their elaboration and functionalization. MIDA-protected haloalkenylboronic acids are easily derivatized via the Suzuki–Miyaura, Negishi, Heck–Mizoroki, and Sonogashira cross-couplings. In addition, MIDA boronates tolerate a wide variety of reactions including, for example, Swern–Moffat and Jones oxidations, Horner–Wadsworth–Emmons, Takai, Evans aldol, cyclopropanation, epoxidation, olefin metathesis reactions, silylation, and HF•Py-mediated desilylations, acid-catalyzed *p*-methoxybenzylation and subsequent unmasking with DDQ, and reductive amination [195]. As such, the preparation of advanced, functionalized MIDA boronate synthons is possible, making these masked boronic acid derivatives well suited for application in complex synthesis.

4.5 Conclusions and Future Outlook

The design, synthesis, and application of bulky, electron-rich ligands has made possible the facile coupling of nontrivial substrates, including a myriad of aryl chlorides, unactivated alkyl halides, and both sterically hindered aryl halides and arylboronic acids. It now remains to the rest of the synthetic community to leave behind "traditional" cross-coupling protocols and more widely embrace these "contemporary" methods by applying them to challenging cross-couplings in synthesis.

The community has cracked the surface in terms of asymmetric Suzuki–Miyaura couplings, iterative processes, and alternate electrophiles, and further development of these areas will occupy the next decade of research in this field. The results from this future research will be of paramount importance as the application of these transformations in industry and academia seems limitless.

Still, despite the great advances that have been made over the past decade, the predictability of success in a given cross-coupling is not yet a certainty. With a virtually unlimited set of cross-coupling conditions now available to the synthetic chemist, it has become rather difficult to assign a particular set of reaction conditions *a priori*. Ensuing optimization of the Pd-catalyzed cross-coupling for a particular substrate pairing is to a large extent a long and tedious process as variables include the Pd source, ligand, organometallic reagent, solvent, additive(s), and temperature. The goal of developing a truly universal catalyst and global set of reaction conditions for this coupling may likely never be reached. Time and again, it has been observed that a strict balance between ligand and substrate structure is at play, notwithstanding the high dependence of the reaction on solvent polarity and additives. Thus, further elucidation of the intricacies of the cross-coupling mechanism and its reliance on substrate electronics and structure is requisite for the further rational development of this field. Once better understood, it will become more likely to be able to rationally choose a catalyst and conditions for any given Suzuki–Miyaura cross-coupling.

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