Suzuki−Miyaura Cross-Coupling Reactions Mediated by Palladium/Imidazolium Salt Systems

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Nucleophilic *N*-heterocyclic carbenes (NHC) have been used as ancillary ligands in palladium-mediated Suzuki−Miyaura cross-coupling reactions involving aryl chlorides or aryl triflates with arylboronic acids. The scope of the coupling process using Pd(0) or Pd(II) sources and an imidazolium salt in the presence of a base, Cs_2CO_3, was tested using various substrates. The $Pd(OAc)_2$ or $Pd_2(dba)_3$/IMes·HCl (**2**, IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazol-2-ylidene) system presents very high activity with respect to electron-neutral and electron-rich aryl chlorides. The ligand IPr·HCl (**3**, IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene) is also effective for the Suzuki−Miyaura cross-coupling involving a wide spectrum of aryl chlorides and aryl triflates. The general protocol developed has been applied successfully to the synthesis of an antiinflammatory drug (Fenbufen) and to a key intermediate in the synthesis of sartans. Mechanistically, palladium-to-ligand ratio studies support an active palladium species bearing one nucleophilic carbene ligand.

Introduction

Cross-coupling reactions represent an extremely versatile tool in organic synthesis.[1] This methodology has permitted the synthesis of a wide variety of organic compounds ranging from polymers, materials, and liquid crystals[2] to pharmaceuticals and natural products.[3] The Suzuki−Miyaura reaction,[4] where organoboron reagents are employed as coupling partner with aryl halides (or pseudo halides) to form C−C bonds, is one of the most successful strategies for C−C bond formation. This reaction belongs to a broader family of coupling processes where a variety of transmetallating agents such as organomagnesium,[5] organotin,[6] organosilicon,[7] and organozinc[8] reagents can be used. Organoboron compounds possess many attractive features.[3c,d,9]

They are widely commercially available and are air- and moisture-stable reagents. Monodentate tertiary phosphines are usually employed as ancillary ligands in such systems.[1a,10] Important examples of the use of tertiary phosphines as ancillary ligands in the Suzuki−Miyaura reaction are found in the recent work of Fu and Buchwald,[11] who have used sterically demanding, electron-rich tertiary phosphines as catalyst modifiers. The ligand properties in these examples make possible the activation of inexpensive aryl chlorides as coupling partners in the Suzuki−Miyaura reaction. This transformation has been reported using electron-rich ligands at room temperature.[12] Despite their effectiveness in controlling reactivity and selectivity in organometallic chemistry and homogeneous catalysis,[10] tertiary phosphines require air-free handling to prevent their oxidation and, more significantly, are subject to P−C bond degradation at elevated temperatures.[1b] To circumvent

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Scheme 1
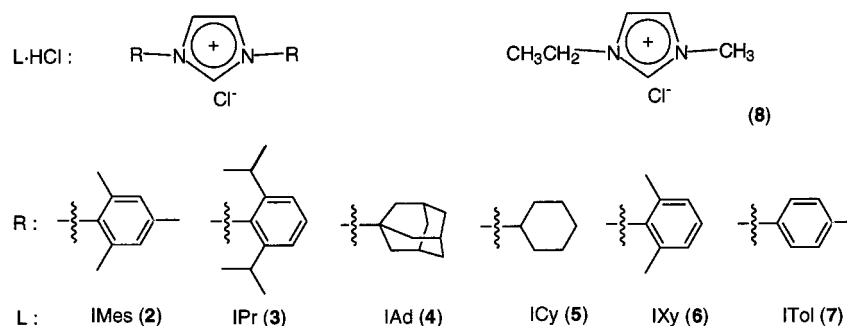
these problems, the use of higher phosphine concentration in such catalytic processes is often practiced.[1b]

N-Heterocyclic carbenes (NHC)[13] represent a versatile class of ligands due to their tunable steric and electronic properties. Following a fundamental thermochemical study allowing a better understanding of the electronic properties of this ligand family,[14] early reports from the Fu and Buchwald groups (see above) suggested to us that these compounds could possibly act as supporting ligands in the Suzuki−Miyaura reaction. The primary advantage of these ligands appears to be that they do not easily dissociate from the metal center; as a result, an excess of the ligand is not required in order to prevent aggregation of the catalyst to yield bulk metal.[15] The recent popularity of the NHC has resulted in their use in hydrosilylation,[16] Ru-catalyzed furan synthesis,[17] and olefin metathesis.[18] In addition, successful use of NHC as supporting ligands in various cross-coupling reactions has been reported involving aryl halides with amines,[19] organomagnesium,[20] organosilicon,[21] and organotin[22] reagents. A number of groups have recently reported the use of NHC in metal-mediated cross-coupling involving organoboron.[23] A preliminary report from our group has appeared on the Suzuki−Miyaura cross-coupling reaction of aryl chlorides and arylboronic acids employing $Pd_2(dba)_3$ and an imidazolium salt as catalytic system.[23a] We now wish to present a broader

study into the use of NHC as ancillary ligands in the Suzuki−Miyaura reaction.

Results and Discussion

Solution calorimetry experiments of transition metal-centered ligand substitution reactions involving NHC have shown that this class of ligand exhibits a considerable stabilizing effect in organometallic systems.[24] On the basis of tertiary phosphine stereoelectronic factors required in the reports of Fu and Littke[25] and results from thermochemical studies which more clearly define the electron-donating ability (better donating than PCy_3) and steric demand (larger than PCy_3) of NHC ligands, 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (**1**, IMes)[14,18b] was examined as a potential ancillary ligand in Suzuki−Miyaura cross-coupling reactions of aryl chlorides with arylboronic acids.
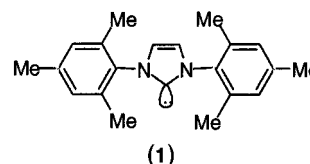
In our initial experiments,[23a] we observed that the coupling of 4-chlorotoluene and phenylboronic acid (1.5 equiv) in the presence of 1.5 mol % of $Pd_2(dba)_3$, 3.0 mol % of the carbene **1**,[24] and Cs_2CO_3 in dioxane at 80 °C proceeded to give 4-methylbiphenyl in 59% isolated yield. The reaction proceeded rapidly with complete consumption of the aryl chloride as observed by TLC within 1.5 h.

Since imidazol-2-ylidene carbenes are considerably less stable to air and moisture than their corresponding imidazolium salts and to circumvent the preparation and isolation of the carbenes, we developed a protocol in which the NHC ligand could be generated in situ from the imidazolium salt. A list of imidazolium salts used in this study is presented in Scheme 1.

Effect of the Base on Suzuki−Miyaura Cross-Coupling of 4-Chlorotoluene with Phenylboronic Acid. An investigation of the effects of various bases on the in situ generation of the carbene ligand **1** from the salt **2** and subsequent catalysis revealed that Cs_2-

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**Table 1. Effect of the Base on the Rate of
Pd$_2$(dba)$_3$/IMes·HCl (2) Catalyzed Suzuki−Miyaura
Cross-Coupling Reactions of 4-Chlorotoluene with
Phenylboronic Acid^a**
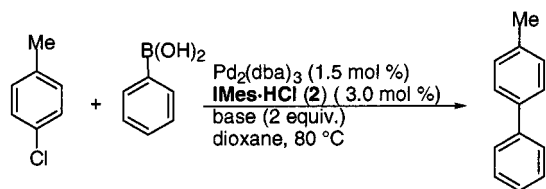
entry	base	time (h)	yield (%)^{b,c}
1	Et$_3$N	24	<5^d
2	Na$_2$CO$_3$	43	6^d
3	KOAc	43	42^d
4	K$_2$CO$_3$	24	53
5	Cs$_2$CO$_3$	1.5	96
6	KF	48	70^{d,e}
7	CsF	2	65^d
8	Ba(OH)$_2$	24	35^{d,f}
9	Ba(OH)$_2$	5	82^{d,f,g}

^{a} Reaction conditions: 1.0 mmol of 4-chlorotoluene, 1.5 mmol of phenylboronic acid, 2 mmol of base, 1.5 mol % Pd$_2$(dba)$_3$ 3.0% IMes·HCl (2), 3 mL of dioxane, 80 °C. ^{b} Isolated yields. ^{c} All reactions were monitored by TLC. ^{d} 4-Chlorotoluene was not completely consumed within the indicated reaction time (TLC). ^{e} 2.5 mol % Pd(OAc)$_2$ was used. ^{f} 250 μL of H$_2$O was added. ^{g} 2 mol % IPr·HCl (3).

CO$_3$ was the reagent of choice (Table 1). Other inorganic bases such as Na$_2$CO$_3$, KOAc, and CsF required longer reaction times for complete consumption of the aryl chloride and afforded moderate to low yields of coupling products.

One of the most notable entries is KF, a very effective base for Pd$_2$(dba)$_3$/phosphine Suzuki−Miyaura catalyzed reactions,[11] which afforded the coupling product in 70% yield only when Pd(OAc)$_2$ was used as the palladium source. A generally effective base employed in this cross-coupling, K$_2$CO$_3$,[26] proved to be less effective in the present case (Table 1, entry 4). Another common base for the Suzuki−Miyaura reaction,[27] Ba(OH)$_2$·xH$_2$O, resulted in low yield (Table 1, entry 8). Employing the more sterically demanding IPr·HCl (3) with this inorganic base afforded the product in 80% yield (Table 1, entry 9).[28] When an organic base such as triethylamine was employed, the reaction ceased within minutes and precipitation of palladium black was observed. The use of the bulky base Cy$_2$NMe, employed by Fu[29] to perform Heck reactions with P^{t}Bu$_3$ at room temperature, did not prove efficient in the present system.

Effect of the Imidazolium Salt and Palladium Source on Suzuki−Miyaura Cross-Coupling of 4-Chlorotoluene with Phenylboronic Acid. Since the coupling of 4-chlorotoluene with phenylboronic acid using the Pd$_2$(dba)$_3$/IMes·HCl (2) system in the presence of Cs$_2$CO$_3$ as a base proved optimum, we sought the use of a combination of the air-stable Pd(OAc)$_2$ and the imidazolium chloride as catalytic system. Such a system would make use of two salts. Our initial catalytic

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(28) The coupling reaction of 4-bromotoluene using Ba(OH)$_2$·H$_2$O/ IPr·HCl (3) has proven to be slower than the similar reaction of 4-chlorotoluene.
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**Table 2. Effect of Imidazolium Salts on Pd(OAc)$_2$
or Pd$_2$(dba)$_3$/L·HCl Catalyzed Suzuki−Miyaura
Cross-Coupling Reactions^a**
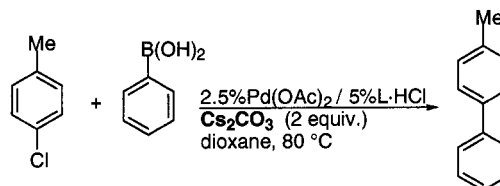
entry	L	time (h)	yield (%)^{b,e}
1	none	24	NR
2	IMes (2)	2	99
3	IPr (3)	2	53
4	IAd (4)	2	44
5	ICy (5)	2	14
6	IXy (6)	2	51
7	ITol (7)	2	5
8	IEtMe (8)	2	16
9	IEtMe (8)	39	75
10	IMes (2)	1.5	90^c
11	IPr (3)	1.5	95^d
12	IXy (6)	1.5	90^d

^{a} Reaction conditions: 1.0 mmol of 4-chlorotoluene, 1.5 mmol of phenylboronic acid, 2 mmol of Cs$_2$CO$_3$, 2.5 mol % Pd(OAc)$_2$, 5.0% L·HCl 2L/Pd), 3 mL of dioxane, 80 °C. ^{b} Isolated yields. ^{c} 1.5% Pd$_2$(dba)$_3$ was used. ^{d} 1% Pd$_2$(dba)$_3$ was used. ^{e} All reactions were monitored by TLC.

experiments focused on using the protocol established for the palladium(0) system. The imidazolium salt IMes· HCl (2) was the salt selected for initial studies. Loading all components at once in the reaction vessel under argon flush and heating the reaction mixture for 2 h led to low yield of the desired coupled products. It was then determined that the Pd(II) salt might require some time to react with the base and the IMes·HCl (2) in order to generate the NHC ligand 1 and an active Pd(0) species. The apparent low catalyst activation was circumvented by allowing Pd(OAc)$_2$, the imidazolium salt (2), and the base (Cs$_2$CO$_3$) to react in dioxane for 30 min at 80 °C. This catalyst formation procedure was followed by cooling the reaction mixture to room temperature. The substrates were then added, and the mixture was heated at 80° C for 2 h. When the coupling reaction of 4-chlorotoluene with phenylboronic acid was performed with 2 using the described protocol, the product 4-methylbiphenyl was isolated in 99% yield (Table 2, entry 2).
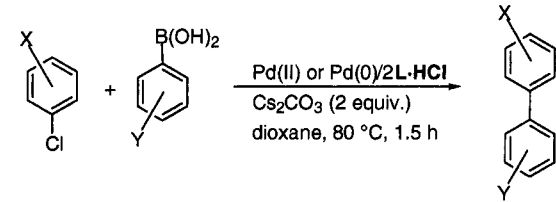
An investigation of the activity of the catalytic system as a function of the imidazolium salt revealed that IMes· HCl (2) displayed the best catalytic behavior (Table 2). All other imidazolium salts (3−8) that were investigated required longer reaction times to achieve complete consumption of the aryl chloride and afforded moderate to low yields. The commercially available 1-ethyl-3-methylimidazolium hydrochloride (8), which affords a very modest 16% isolated yield using reaction conditions described above (after 2 h), can lead to reasonable yields (75% isolated) if the reaction is allowed to proceed for 39 h. This example is significant since a number of structurally related imidazolium salts have been used as ionic liquid solvents, some as coupling chemistry medium.[30] This specific example again shows that ionic liquid solvents can act as noninnocent reagents. Recent reports have proposed the formation of and even identified nucleophilic carbene species in the Heck reaction

Table 3. Functional Group Tolerance of Pd₂(dba)₃/IPr·HCl and Pd(OAc)₂/IMes·HCl Catalyzed Suzuki−Miyaura Cross-Coupling Reactions of Aryl Chlorides with Phenylboronic Acid Derivatives[a]

entry	aryl halide	boronic acid	product	yield(%)[b, g] IPr·HCl [c]	IMes·HCl [d]
1				95	99
2				99	80
3				97	50
4				95	93
5				99	85
6				95	94
7				79[e]	98
8				98	99
9				99[f]	95
10				100[f]	98

[a] Reaction conditions: 1.0 mmol of aryl chloride, 1.5 mmol of arylboronic acid, 2.0 mmol of Cs₂CO₃, 2L/Pd, 80 °C. [b] Isolated yields. [c] 1 mol % Pd(dba)₂ was used. [d] 1 mol % Pd(OAc)₂ was used; reaction time was 2.5 h. [e] Reaction time was 16 h. [f] Reaction time was 3 h. [g] All reactions were monitored by TLC.

performed in ionic liquids.[31] Steric factors appear to dictate catalytic activity; the low activity of **8** is a case in point. Another example, ICy, an electronically superior donor to IMes and IPr[24b] but less bulky, leads to a low yield (Table 2, entry 5). Investigation of Pd₂(dba)₃/IPr·HCl (**3**) and of Pd₂(dba)₃/IXy·HCl (**6**) resulted in very good yields, 95% (Table 2, entry 11) and 90% (Table 2, entry 12), respectively, which further confirms the importance of specific steric and electronic ligand properties.

Functional Group Tolerance/Substitution Patterns on Aryl Chlorides and Arylboronic Acids. As illustrated in Table 3, the Pd(0)/IPr·HCl (**3**)-catalyzed Suzuki−Miyaura reactions were exceptionally tolerant of a variety of functional groups on the aryl chlorides and arylboronic acids. Electron-donating and electron-

withdrawing substituents, as well as sterically hindered substrates (Table 3, entry 6), were well tolerated by the catalytic systems and provided the corresponding coupling products in excellent yields.

Furthermore, this functional group tolerance/activity is also observed when the Pd(II)/imidazolium salt system is used. In fact, the Pd(OAc)₂/IMes·HCl (**2**) system was found to be equally effective as Pd₂(dba)₃ under reaction conditions described above (Table 3). The catalytic system based on Pd(OAc)₂/IMes·HCl (**2**) represents a very simple Suzuki−Miyaura coupling procedure since catalytic components can be loaded in air, the reactor can then be purged and substrates added under inert atmosphere.
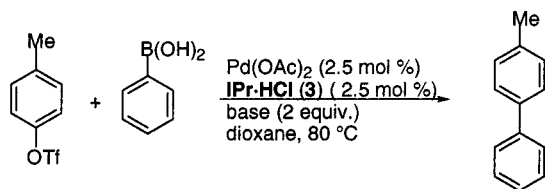
Suzuki−Miyaura Cross-Coupling with Aryl Triflates. It is well known that aryl triflates (trifluoromethanesulfonates) represent a valuable partner for various cross-coupling reactions involving organostannanes,[32] organozinc,[33] and organoboron[4a] reagents due

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Table 4. Effect of the Base on the Rate of Pd(OAc)₂/IPr·HCl (3) Catalyzed Suzuki−Miyaura Cross-Coupling Reactions of 4-Methylphenyl Trifluoromethanesulfonate with Phenylboronic Acid[a]

Me—C₆H₄—OTf + PhB(OH)₂ → Pd(OAc)₂ (2.5 mol %), IPr·HCl (3) (2.5 mol %), base (2 equiv.), dioxane, 80 °C → 4-methylbiphenyl

entry	base	time (h)	yield (%)[b,c]
1	K₂CO₃	16	90
2	Cs₂CO₃	5	94
3	KF	16	28
4	K₃PO₄	16	94

[a] Reaction conditions: 1.0 mmol of 4-methylphenyl trifluoromethanesulfonate, 1.5 mmol of phenylboronic acid, 2 mmol of base, 2.5 mol % Pd(OAc)₂, 2.5 mol % IPr·HCl (3) (L/Pd), 3 mL of dioxane, 80 °C. [b] Isolated yields. [c] All reactions were monitored by TLC.

to their easy synthesis from readily available phenols.[34] In an effort to extend the scope of the palladium/imidazolium salt-catalyzed Suzuki−Miyaura reaction, we investigated the cross-coupling reaction of aryl triflates with arylboronic acids. We found that our initial conditions can be successfully applied to aryl triflates (Table 4, entry 2). Similar to aryl chlorides, KF proved to be ineffective for the palladium/imidazolium salt catalytic system. Other inorganic bases, K₂CO₃ and K₃PO₄, lead to higher yields of the coupled product (Table 4, entries 1 and 4).[35]

Investigation of the effect of substrate on the Suzuki−Miyaura cross-coupling reaction of aryl triflates with various *para*-substituted arylboronic acids showed a high tolerance with regard to electronic modulation (Table 5).

Effect of the Palladium(0)/Imidazolium Salt Ratio on Suzuki Cross-Coupling Reactions. During our optimization efforts and in order to better understand the reaction mechanism, the influence of the palladium-to-ligand ratio was investigated. We observed that a 1:1 palladium−ligand ratio afforded optimum reaction rates for both IMes·HCl (2) and IPr·HCl (3) reactions (Table 6). This ratio has also been observed as optimum in a number of cross-coupling protocols.[19−25]

A general catalytic cycle[4a] for the cross-coupling reaction of organoboron reagents with aryl halides involves an oxidative-addition of the arylhalide, transmetalation, and reductive-elimination steps, as outlined in Figure 1. The electron-rich carbene ligands, usually better donors than tertiary phosphines,[24,36,37] favor the oxidative-addition step.[38] Theoretical studies[39] have suggested that a Pd/L ratio of 1:2 (mutually *cis* ligands)
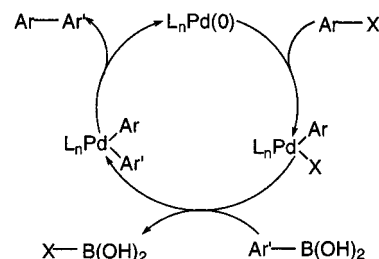

Figure 1. General cycle for the palladium-catalyzed Suzuki−Miyaura cross-coupling reaction.

favors the oxidative-addition step,[40] and, as a consequence, the reductive-elimination step is thermodynamically disfavored. This is in agreement with the slower reaction rate given by a palladium/imidazolium salt ratio of 1:2 observed for IMes·HCl (2) and IPr·HCl (3). In addition, we now have evidence that two of these bulky ligands can indeed bind a square planar metal center occupying mutually *cis* positions. This increase in coordination number at higher ligand loadings would inevitably retard catalysis.[41] Three major factors seem to influence the activity of palladium/imidazolium salt systems: electronic properties of the carbene ligands affect the oxidative-addition ability of palladium, while their bulk and the number of ligands around palladium accelerate/slow the reductive-elimination.[34,42] On the basis of these observations, an intermediate can be envisioned as a reactive three-coordinate or most likely a solvent-stabilized or halide-bridging four-coordinate species. The formation of similar reactive intermediates has been proposed by Buchwald in the Suzuki−Miyaura reaction with phosphine ligands.[40b]

Since the palladium/imidazolium salt systems display high reactivity with aryl chlorides in the Suzuki−Miyaura cross-coupling reaction, we tested their use in the synthesis of two pharmaceutical targets. Fenbufen[43] (γ-oxo-{1,1′-biphenyl}-4-butanoic acid) belongs to a class of nonsteroidal antiinflammatory drugs having analgesic properties and displays activity due to inhibition of prostaglandin synthesis. Cross-coupling of two commercially available compounds, 3-(4-chlorobenzoil)propionic acid and phenylboronic acid (Scheme 2), afforded Fenbufen in high isolated yields (Table 7). The presence of an acidic group in the aryl chloride starting material, which was initially thought to be problematic, since catalytic conditions are alkaline, proved to be of significant advantage. Aqueous extraction of the crude reaction mixture, followed by acidification of the extract, afforded the desired product in high purity. *This was achieved without the use of any chromatography!* The acid functionality is restored upon workup (see Experimental Section).

The use of air-stable Pd(OAc)₂ and either IMes·HCl (2) or IPr·HCl (3) as catalyst system afforded high isolated yields (Table 7).

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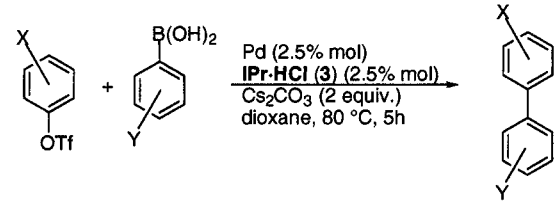
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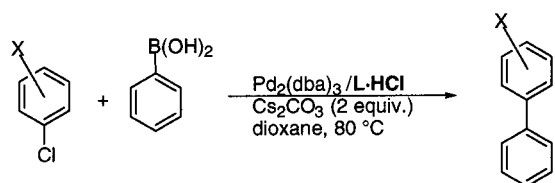
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Table 5. Functional Group Tolerance of Pd(OAc)₂(Pd(dba)₂)/IPr·HCl (3) Catalyzed Suzuki−Miyaura Cross-Coupling Reactions of Aryl Triflates with Phenylboronic Acid Derivatives[a]

Scheme (reaction conditions): aryl triflate (X...OTf) + boronic acid (B(OH)₂, Y) → biphenyl product, with Pd (2.5% mol), IPr·HCl (3) (2.5% mol), Cs₂CO₃ (2 equiv.), dioxane, 80 °C, 5h.

entry	aryl triflate	boronic acid	product	yield(%) [b, e]
1	MeO-C₆H₄-OTf	C₆H₅-B(OH)₂	MeO-biphenyl	86[c]
2		MeO-C₆H₄-B(OH)₂	MeO-biphenyl-OMe	81[c]
3	C₆H₅-OTf	MeO-C₆H₄-B(OH)₂	MeO-biphenyl	85[c]
4		Me-C₆H₄-B(OH)₂	Me-biphenyl	99[d]
5	MeO-C₆H₄-OTf	C₆H₅-B(OH)₂	MeO-biphenyl	97[d]
6		Me-C₆H₄-B(OH)₂	MeO-biphenyl-Me	98[d]
7	Me(O)C-C₆H₄-OTf	C₆H₅-B(OH)₂	Me(O)C-biphenyl	76[c]
8		MeO-C₆H₄-B(OH)₂	Me(O)C-biphenyl-OMe	77[c]
9		Me-C₆H₄-B(OH)₂	Me(O)C-biphenyl-Me	97[d]

[a] Reaction conditions: 1.0 mmol of aryl triflate, 1.5 mmol of arylboronic acid, 2.0 mmol of Cs₂CO₃, 2.5 mol% Pd(OAc)₂ or 2.5 mol% Pd(dba)₂, 2.5 mol% 1Pr·HCl (**3**) (1L/Pd), 80 °C. [b] Isolated yields. [c] 2.5 mol % Pd(OAc)₂ was used. [d] 2.5 mol % Pd(dba)₂ was used. [e] All reactions were monitored by TLC.

Table 6. Influence of Palladium(0)/Imidazolium Salt Ratio on Suzuki−Miyaura Cross-Coupling Reactions

Scheme: aryl halide (X...Cl) + phenylboronic acid (B(OH)₂) → biphenyl product, with Pd₂(dba)₃/L·HCl, Cs₂CO₃ (2 equiv.), dioxane, 80 °C.

entry	L·HCl	Pd(0):L	X	Pd₂(dba)₃ (mol %)	time (h)	yield (%)[a]
1	none		4-Me	1	24	NR
2	IMes·HCl	1:2	4-Me	1.5	1.5	90
3		1:1	4-Me	1	1.5	96
4	IMes·HCl	1:2	4-OMe	1.5	1.5	93
5		1:1	4-OMe	1	1.5	97
6	IMes·HCl	1:2	4-CO₂Me	1.5	1.5	99
7		1:1	4-CO₂M	1	0.5	99
8	IPr·HCl	1:2	4-Me	1	1.5	95
9		1:1	4-Me	1	1	98
10	IPr·HCl	1:2	4-OMe	1	1.5	99
11		1:1	4-OMe	1	1	99
12	IPr·HCl	1:2	4-CO₂Me	1	1.5	98
13		1:1	4-CO₂Me	1	0.5	98

[a] Isolated yields.

Losartan[44] (**10**) is a nopeptide angiotensin II receptor antagonist playing a critical role in blood pressure regulation.[45] One of the important features of the AII

Table 7. Pd/L·HCl Catalyzed Suzuki−Miyaura Reaction in the Synthesis of Fenbufen

entry	L	Pd source	yield[a]
1	IPr	2% Pd(dba)₂	94
2	IPr	2.5% Pd(OAc)₂	97
3	IMes	3% Pd(dba)₂	86
4	IMes	2.5% Pd(OAc)₂	99

[a] Isolated yields.

antagonists is a biphenyl moiety (Scheme 3); therefore, a potential key step in the synthesis of Losartan (or any sartan family member) is the aryl−aryl coupling. The synthesis of the strategic intermediate to the sartans, 2-cyano-4′-methylbiphenyl (**9**), was achieved in high yields (Scheme 3).[46]

Conclusion

In summary, palladium/imidazolium salt systems were found to be efficient in mediating the Suzuki−Miyaura cross-coupling of aryl chlorides and aryl tri-

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(46) Fu has also recently reported the synthesis of this strategic intermediate with a phosphine-modified palladium system; see ref 11a.

Scheme 2

Scheme 3

94-97% isolated yields
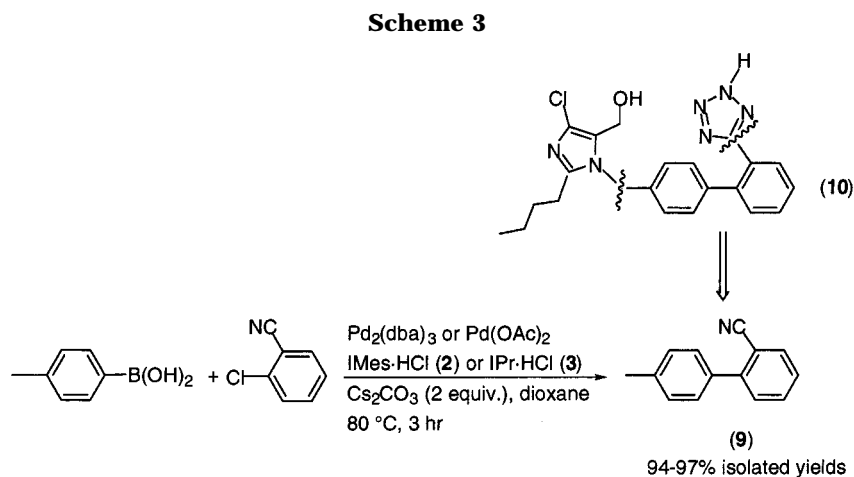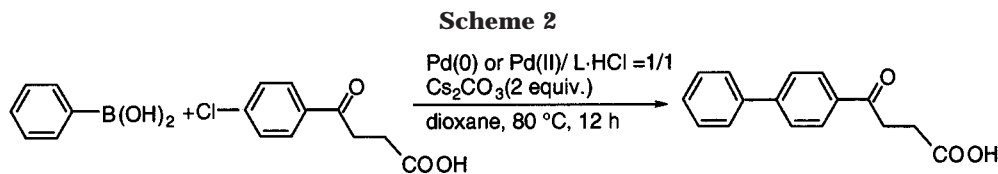
flates with various arylboronic acids. Electron-rich and electron-poor aryl chlorides, as well as sterically hindered substrates, lead to high conversions under general conditions using Pd(0)/IPr·HCl (**3**) or Pd(II)/IMes·HCl (**2**). Moreover, the air stability of Pd(OAc)₂/IMes·HCl (**2**) or IPr·HCl (**3**) systems simplifies the handling and execution of the process. We support at this stage that the strong donating ability of carbene ligands facilitates the oxidative-addition step, while the bulkiness of the ligands provides the necessary steric hindrance/repulsion to assist the reductive-elimination step. The methodology has been successfully applied to the synthesis of two pharmaceutically relevant compounds with excellent yields. Workup procedures by chromatography or extraction have led to product isolation depleted of ligand or ligand fragmentation. This is an important issue in palladium-phosphine-mediated cross-coupling, as phosphines and phosphine oxides can prove difficult to remove from organic products. To further exploit the advantageous properties displayed by the palladium/ NHC systems, catalytic investigations focusing on a number of cross-coupling reactions are ongoing.

Experimental Section

General Considerations. All aryl halides (Aldrich), aryl triflates, and arylboronic acids were simply degassed prior to use. 1,4-Dioxane (anhydrous, Aldrich) was distilled under argon from sodium benzophenone ketyl prior to use. Cesium carbonate, sodium carbonate, potassium phosphate, cesium fluoride, potassium carbonate, and barium hydroxide (Aldrich) were stored under argon in a MBraun glovebox or in desiccators over anhydrous calcium carbonate. Triethylamine (J. T. Baker) and dicyclohexylmethylamine (Aldrich) were degassed before use. Tris(dibenzylideneacetone)dipalladium(0), bis-(dibenzylideneacetone)palladium(0), and palladium acetate were purchased from Strem Chemical Company. Flash chromatography was performed on silica gel 60 (230−400 mesh) (Natland International corporation) using hexanes or hexanes/ ethyl acetate, 15:1. The NHC and imidazolium salts 1,3-bis-(2,4,6-trimethylphenyl)imidazole-2-ylidene (**1**), IMes·HCl (**2**, 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride), IPr·HCl

(**3**, 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride, IAd·HCl (**4**, 1,3-bis(adamantanyl)imidazolium chloride, ICy·HCl (**5**, 1,3-bis(cyclohexyl)imidazolium chloride, IXy·HCl (**6**, 1,3-bis-(2,6-dimethylphenyl)imidazolium, and ITol·HCl (**7**, 1,3-bis-(tolyl)imidazolium chloride) were prepared according to reported procedures;[47] 1-ethyl-3-methylimidazolium chloride **8** was purchased from Aldrich. It should be mentioned that both IMes·HCl and IPr·HCl are now commercially available from Strem Chemicals Inc. and Aldrich Chemical Co. ¹H and ¹³C nuclear magnetic resonance spectra were recorded on a Varian-300 or Varian-400 MHz spectrometer at ambient temperature in CDCl₃ (Cambridge Isotope Laboratories, Inc.). All reactions were carried out under an atmosphere of argon in oven-dried glassware or in screw cap vials with magnetic stirring, unless otherwise indicated. All reported yields are isolated yields, unless otherwise stated, and are the average of two runs.

General Protocol Used for Suzuki−Miyaura Reaction with Pd(0). Under an atmosphere of argon, 1,4-dioxane (3 mL), 4-chlorotoluene (120 μL, 1 mmol), and phenylboronic acid (183 mg, 1.5 mmol) were added in turn to a Schlenk tube charged with Pd₂(dba)₃ (10 mg, 0.01 mmol), IPr·HCl(**3**) (17 mg, 0.04 mmol), base (2 mmol), and a magnetic stirring bar. The Schlenk tube was placed in a 80 °C oil bath and stirred for 1.5−2.0 h. The mixture was then allowed to cool to room temperature. The mixture was purified either directly by flash chromatography or by filtering through a pad of Celite, concentrated, and then purified by flash chromatography.

General Protocol Used for Suzuki−Miyaura Reaction with Pd(II). Under an atmosphere of argon, a Schlenk tube was charged with 1,4-dioxane (3 mL), 2.5 mol % Pd(OAc)₂, 5 mol % IMes·HCl (**2**), and Cs₂CO₃ (2 mmol). After 30 min at 80 °C, the reaction mixture was cooled to room temperature and the aryl halide (1 mmol) and arylboronic acid (1.5 mmol) were added in turn. The Schlenk tube was placed in an 80 °C oil bath and stirred for 2 h. The mixture was then allowed to cool to room temperature. The mixture was purified either directly by flash chromatography or by filtering through a pad of Celite, concentrated, and then purified by flash chromatography.

Procedure for Pd/L·HCl-Catalyzed Synthesis of Fenbufen. Under an atmosphere of argon, 1,4-dioxane (3 mL),

(47) (a) Arduengo, A. J., III. US patent 5,077,414, 1991. (b) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530−5534.

3-(4-chlorobenzoyl)propionic acid (1.0 mmol), and phenyl-boronic acid (1.5 mmol) were added in turn to a Schlenk tube charged with either 2 mol % Pd(dba)$_2$ or 2.5 mol % Pd(OAc)$_2$, IPr·HCl (**3**) (L/Pd), Cs$_2$CO$_3$ (2.0 mmol), and a magnetic stirring bar. The Schlenk tube was placed in a 80 °C oil bath and stirred for 12 h. The mixture was then filtered through a pad of Celite packed with H$_2$O at 60 °C. The filtrate was acidified with concentrated HCl to pH 2. The resulting white precipitate was stirred at room temperature for 15 min, collected by filtration, and washed with cold H$_2$O. The precipitate was dried in vacuo to give Fenbufen as a white solid.

Supporting Information Available: Experimental procedures and references to known compounds are provided. This material is free of charge via the Internet at http://pubs.acs.org.

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