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Air-Stable Pd(R-allyl)LCl (L= Q-Phos, P(*t*-Bu)$_3$, etc.) Systems for C−C/N Couplings: Insight into the Structure−Activity Relationship and Catalyst Activation Pathway

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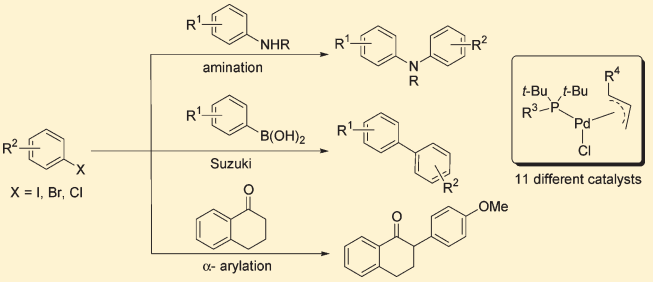
Supporting Information

ABSTRACT: A series of Pd(R-allyl)LCl complexes [R = H, 1-Me, 1-Ph, 1-*gem*-Me$_2$, 2-Me; L = Q-Phos, P(*t*-Bu)$_3$, P(*t*-Bu)$_2$-(*p*-NMe$_2$C$_6$H$_4$), P(*t*-Bu)$_2$Np] have been synthesized and evaluated in the Buchwald−Hartwig aminations in detail, in addition to the preliminary studies on Suzuki coupling and α-arylation reactions. Pd(crotyl)Q-PhosCl (**9**) was found to be a superior catalyst to the other Q-Phos-based catalysts, and the reported in situ systems, in model coupling reactions involving 4-bromoanisole substrate with either *N*-methylaniline or 4-*tert*-butylbenzeneboronic acid. Precatalyst **9** also performed better than the catalysts bearing P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$) ligand; however, it is comparable to the new crotyl catalysts bearing P(*t*-Bu)$_3$ or P(*t*-Bu)$_2$Np ligands. In α-arylation of a biologically important model substrate, 1-tetralone, Pd(allyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl (**15**) was found to be the best catalyst. The reason for the relatively higher activity of the crotyl complexes in comparison to the allyl derivatives in C−N bond formation reactions was investigated using X-ray crystallography in conjunction with NMR spectroscopic studies.



INTRODUCTION

The use of palladium-based cross-coupling catalysis for the production of pharmaceutical, agro- and fine chemicals, liquid crystals, and OLED materials has been well established over the past two decades and has been recently recognized by the award of the 2010 Nobel Prize in Chemistry.[1] There is a plethora of ligand structures available for palladium-mediated carbon−carbon and carbon−heteroatom bond formations, most of them falling into one of two main categories: tertiary phosphines (mono- or bidentate)[2] or N-heterocyclic carbenes.[3] There are also examples of bidentate P,N and P,C (palladacycle) ligands.[4] The quest for lowering the catalyst loading and reducing the reaction time and temperature while maintaining high yields of the many challenging cross-coupling processes has led to the development of a number of trialkylphosphine and aryldialkylphosphines.[5] In many protocols, the active catalyst is formed in situ by the addition of a palladium precursor, such as Pd(OAc)$_2$ or Pd(dba)$_x$ (x = 1.5 or 2) to the ligand of choice. In these processes, typically an excess amount of ligand is required, which could be a disadvantage if the ligand is expensive, in addition to the storage and handling difficulties when the ligands are air sensitive or pyrophoric. As a solution to these problems, a few research groups, including us, have reported the synthesis and applications of preformed air-stable palladium complexes of highly air-sensitive phosphine ligands. One of the most prominent advantages of using preformed palladium complexes as catalysts is the well-defined Pd to ligand ratio. In many cases these complexes perform better than the corresponding in situ systems. This has been demonstrated by several groups, such as those of Buchwald, Bedford, and Hartwig.[6]

Some of the most striking efforts in the area of preformed catalysts are depicted in Scheme 1. Nolan has shown that palladium cinnamyl complexes of NHCs **1** can mediate C−N bond-forming reactions and Suzuki couplings very efficiently.[7] Organ et al. have also developed an NHC-based palladium precatalyst **2** that has been demonstrated to be highly active, especially in the Kumada couplings of hindered substrates.[8] Buchwald and co-workers recently reported palladacycles **3a** and **3b** as precatalysts, bearing dialkylaryl phosphine ligands, and their effectiveness in amination reactions.[9] The advantages of using the P(*t*-Bu)$_3$-based preformed catalysts Pd[P(*t*-Bu)$_3$]$_2$ (**4**) and {Pd(μ-Br)$_2$-[P(*t*-Bu)$_3$]}$_2$ (**5**) in coupling reactions have been well demonstrated by many groups including Fu[10] and Hartwig.[11] Work from our lab also established the beneficial effect of preformed catalysts in Suzuki couplings[12] and α-arylation reactions of ketones,[13] where the air-stable preformed D*t*-BPF (1,1′-di-*tert*-butylphosphinoferrocene) complex PdCl$_2$D*t*-BPF (**6**) showed remarkably high activity in the coupling of aryl bromides and chlorides. In a recent study, our group in collaboration with

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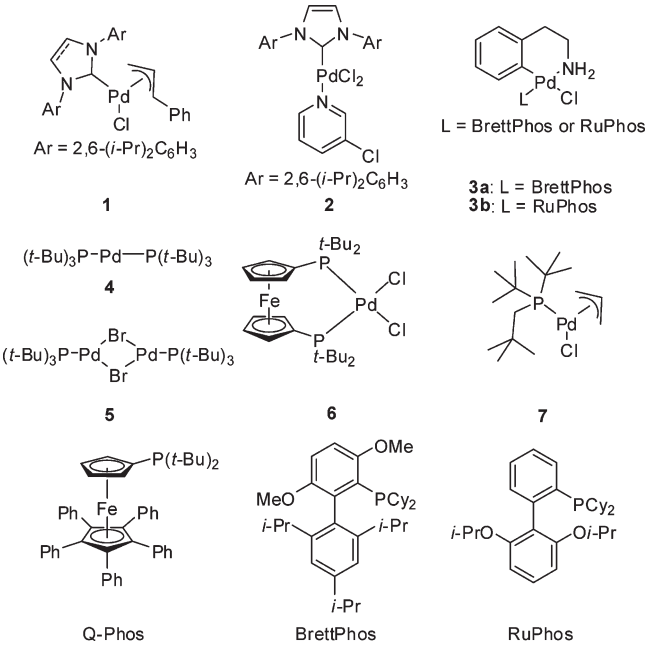
Scheme 1. Examples of Preformed Palladium Catalysts (1−7) and Monophosphine Ligands



Shaughnessy et al. reported the use of Pd(allyl)P(*t*-Bu)$_2$NpCl (Np = neopentyl) (**7**) in amination at mild temperatures, in addition to their uses in the α-arylation reactions of ketones.[14]

Ferrocenyl ligands have been thoroughly studied by a number of research groups.[15] A few years ago Hartwig and co-workers reported the synthesis and catalytic activity of a bulky electron rich monodentate ferrocenyl phosphine ligand, Q-Phos (Scheme 1),[16] as a highly active commercially available ligand for a number of coupling processes, such as amination, Suzuki, etherification, and α-arylation of esters, amides, and aldehydes.[17]

We were initially interested in exploring the possible benefits of using preformed palladium catalysts bearing the highly active Q-Phos ligand, compared to in situ catalysis. In this regard, we have recently reported the novel synthesis of Pd(Q-Phos)$_2$,[18] whose application in a new C−C bond-forming reaction, namely, carbohalogenation reactions, was demonstrated by Lautens.[19] In addition, recently we, in collaboration with the Shaughnessy group, disclosed the synthesis and applications of Pd(allyl)P(*t*-Bu)$_2$NpCl precatalyst.[14] In the current study, we decided to carry out a more detailed catalytic investigation on the role of the various π-allyl moieties as well as the role of monophosphine ligands, with a view to gain more insight into the structure−activity relationships of palladium(π-allyl) phosphine-based halide complexes.

Five new complexes of Q-Phos were prepared during this study: Pd(allyl)Q-PhosCl, Pd(crotyl)Q-PhosCl, Pd(prenyl)-Q-PhosCl, Pd(cinnamyl)Q-PhosCl, and Pd(2-methylallyl)-Q-PhosCl. For comparison purposes, Pd(allyl)(P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl and the already known Pd(allyl)P(*t*-Bu)$_3$Cl[20] were also synthesized. In addition, new Pd(crotyl)P(*t*-Bu)$_2$NpCl and Pd(crotyl)P(*t*-Bu)$_3$Cl were prepared for the structure − activity and mechanistic studies.

RESULTS AND DISCUSSION

Catalyst Syntheses. As outlined in the introduction, a number of palladium π-allyl complexes bearing the sterically demanding electron-rich Q-Phos ligand were prepared in yields ranging from 85 to 98% by reacting the [Pd(R-allyl)Cl]$_2$ dimers with the ligand (Scheme 2) as in the case of the known Pd(allyl)P(*t*-Bu)$_2$NpCl[14] complex. All palladium dimer complexes were prepared using the literature procedures,[7,21] except [Pd(allyl)Cl]$_2$ which was obtained from our plant. The corresponding new crotyl complex containing P(*t*-Bu$_3$), as well as Pd(crotyl)P(*t*-Bu)$_2$-NpCl, was also synthesized in this study to compare the mechanism of the mode of activation of the precatalysts and the identification of the major intermediates in the C−N bond formation reactions. In addition, we also synthesized the allyl and crotyl complexes of P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$) to compare their activities with the known, preformed catalyst PdCl$_2$[P(*t*-Bu)$_2$(*p*-NMe$_2$-C$_6$H$_4$)]$_2$ (**Pd-132**), which has been previously used in cross-coupling reactions with impressive results.[22]

All the complexes were air stable, except Pd(allyl)P(*t*-Bu)$_3$Cl (**13**), which underwent decomposition relatively rapidly, when stored outside of the glovebox. The complex, which we reported earlier in collaboration with Shaughnessy, Pd(allyl)P(*t*-Bu)$_2$NpCl (**7**)[14] is somewhat temperature sensitive, while the crotyl complexes of both P(*t*-Bu)$_3$ and P(*t*-Bu)$_2$Np are stable to air even at room temperature.

Amination of Aryl Halides. To get an idea of the relative activities of catalysts **7**−**17**, a model C−N coupling reaction of 4-bromoanisole with *N*-methylaniline at room temperature (Table 1) was carried out. At 1 mol % palladium loading, the Q-Phos-based catalysts **8**, **9**, and **11** all provided the product with nearly quantitative conversions (entries 1, 2, and 6), within 3 h of reaction time for **9** vs 6 h for **8** and **11**. The Pd(crotyl)Q-PhosCl complex (**9**) gave the desired product in higher conversion even at 0.1 mol % palladium loading (entry 4), while compound **11** gave high activity at 0.5 mol % (entry 7), although the reaction time was much longer. Pd(cinnamyl)Q-PhosCl **10** (entry 5) and Pd(2-methylallyl)Q-PhosCl **12** (entry 8) gave yields of 81% and 62%, respectively. The P(*t*-Bu)$_3$-based precatalyst **13** provided the product in a lower conversion (entry 9) in comparison to its Q-Phos analogue **8** (entry 1); however, the crotyl complex of P(*t*-Bu)$_3$ (**14**) was as effective as **9** (entry 2) in the model reaction, showing full conversion to product within 3 h (entry 10). Pd(allyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl (**15**) also gave lower activity at room temperature (entry 11), in contrast to its crotyl analogue (**16**) that resulted in 95% conversion to the product within 22 h (entry 12), while the Pd complexes of P(*t*-Bu)$_2$Np ligand showed a trend similar to that of their Q-Phos analogues (entries 13 and 14).

Subsequent optimization of the reaction conditions of the C−N bond formation showed a significant concentration effect (Table 2). The catalyst Pd(allyl)Q-PhosCl (**8**) at a 0.5 mol % loading and at 0.4 M substrate concentration gave 54% conversion within 23 h vs 93% conversion within 7 h at 0.8 M substrate concentration (Table 2, entries 1 and 2). At a higher catalyst loading of 1.0 mol %, but under more dilute conditions, the yield was increased to 97% at 6 h of reaction time (Table 1, entry 1). Interestingly, catalyst **9** gave 100% conversion to the product in shorter reaction time under similar conditions even at lower Pd loading, demonstrating its superiority as a catalyst (Table 1, entry 2; Table 2, entries 3 and 4) in comparison to **8**.

Subsequently, the performance of catalyst **9** was compared to the performance of in situ-formed Q-Phos-based palladium catalysts, as well as the preformed L$_2$Pd(0) catalyst Pd(Q-Phos)$_2$, for the same coupling partners (coupling of 4-bromoanisole with

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Scheme 2. π-Allyl Catalysts Investigated in This Study

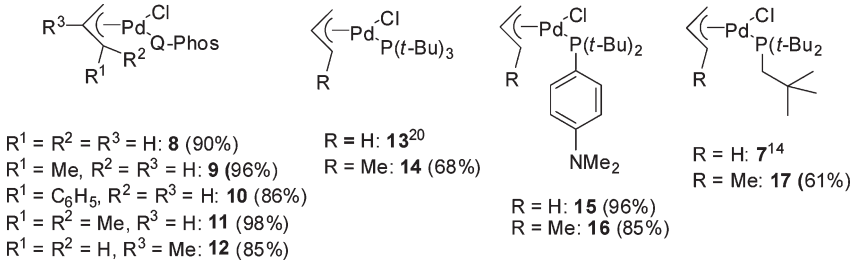
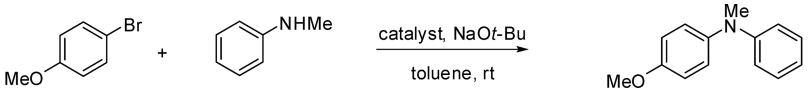


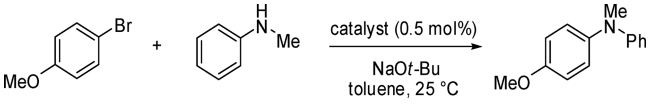
Table 1. Evaluation of Pd(R-allyl)PR_3Cl Complexes in a Model Aryl Bromide Amination Study[a]



entry	catalyst (mol %)	time (h)	conv[b] (%)	entry	catalyst (mol %)	time (h)	conv[b] (%)
1	**8** (1.0)	6	97	8	**12** (1.0)	18	62
2	**9** (1.0)	3	100	9	**13** (1.0)	6	80
3	**9** (0.5)	18	99	10	**14** (1.0)	3	100
4	**9** (0.1)	18	95	11	**15** (1.0)	22	18
5	**10** (1.0)	22	81	12	**16** (1.0)	22	95
6	**11** (1.0)	6	100	13	**7** (1.0)	6	99
7	**11** (0.5)	22	100	14	**17** (1.0)	3	100

[a] 4-Bromoanisole (200 μL, 1.6 mmol), *N*-methylaniline (217 μL, 2.0 mmol), NaO*t*-Bu (230 mg, 2.4 mmol), toluene (4.0 mL). [b] GC conversion.

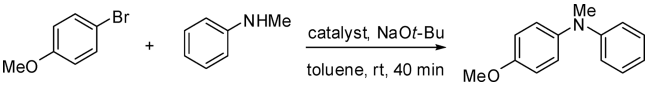
Table 2. Concentration Effect[a]



entry	catalyst	toluene (mL)	time (h)	conv[b] (%)
1	**8**	4.0	23	54
2	**8**	2.0	7	93
3	**9**	4.0	5	100
4	**9**	2.0	0.67	100

[a] 4-Bromoanisole (1.6 mmol), *N*-methylaniline (2.0 mmol), NaO*t*-Bu (2.4 mmol). [b] GC conversion.

Table 3. Activity Comparison of Preformed Catalysts 9 (entry 4, Table 2) and Pd(Q-Phos)$_2$ versus in Situ[a]



entry	catalyst	conv[b] (%)
1	0.25 mol % $Pd_2(dba)_3$/0.5mol % Q-Phos	35
2	0.5 mol % $Pd(dba)_2$/0.5 mol % Q-Phos	80
3	0.5 mol % Pd(Q-Phos)$_2$	9

[a] 4-Bromoanisole (1.6 mmol), *N*-methylaniline (2.0 mmol), NaO*t*-Bu (2.4 mmol), toluene (2.0 mL). [b] GC conversion, average of at least two runs.

N-methylaniline). As shown in Table 2 (entry 4) and Table 3, the use of the preformed Pd(crotyl)Q-PhosCl (**9**) catalyst allowed a reaction time significantly shorter than that of the other Q-Phos-based catalyst systems. Under the reaction conditions employed in the study, we believe that complex **9** is a practical catalyst, in comparison to the previously reported in situ $Pd(OAc)_2$/Q-Phos catalyst system for the same set of reagents.[23] Under those reported conditions, the reaction was carried out at 100 °C for 25 h to give 93% yield of the product, when the Pd to ligand ratio was 1:2. In our case, 80% conversion was achieved within 40 min using $Pd(dba)_2$/Q-Phos in a 1:1 ratio at room temperature (entry 2), demonstrating the importance of the coordinatively unsaturated, 12 electron Pd(0) catalytic species in amination. However, we observed reproducibility inconsistencies in the in situ system, especially during scale up (in one case the yield was as low as 5%). On the other hand, using **9** we could reproduce the results with 100% conversion to product several times within 40 min of reaction

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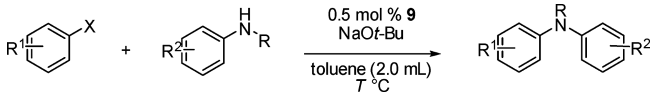
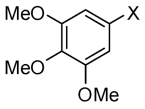
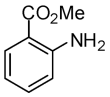
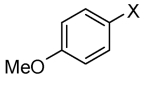
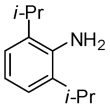
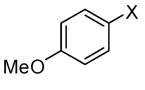
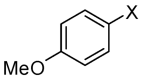
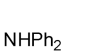
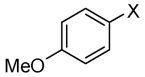
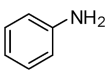
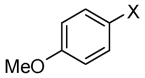
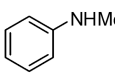
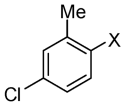
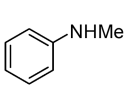
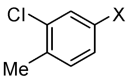
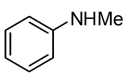
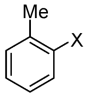
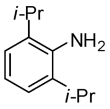
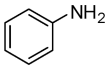
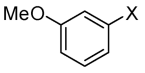
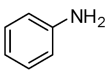
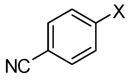
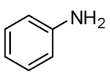
Table 4. Amination of Aryl Bromides and Chlorides Using Pd(crotyl)Q-PhosCl (9)[a]



Ar-X	amine	X	T °C	time (h)	product	yield (%)
		Br	110	20	**18a**	65[b]
		Br Cl	25 100	1.5 0.5	**18b**	96[c] 95
		Br Cl	50 100	16 2.5	**18c**	98 96
		Br Cl	25 100	3 3	**18d**	84[d] 68[d]
		Br	50	2	**18e**	91
		Br Cl I	25 100 25	1 1 2	**18f**	93 98 95
		Br	50	3	**18g**	88
		Br	25	1	**18h**	97
		Br Cl	50 100	2.5 21	**18i**	96 87[e]
		Br Cl	50 100	22 2.5	**18j**	91 83
		Cl	80	3	**18k**	91[c]
		Br	80	4	**18l**	93[c]

[a] Aryl halide (1.6 mmol), amine (2.0 mmol), NaO*t*-Bu (2.4 mmol), toluene (2.0 mL). [b] Using 2 mol % Pd(crotyl)Q-PhosCl. [c] Using 1 mol % Pd(crotyl)Q-PhosCl. [d] NMR yield based on isolated mixture of excess diphenylamine and desired product. [e] GC conversion.

time (Table 2, entry 4), demonstrating the superiority of the new catalyst system in terms of its robustness.

Pd(crotyl)Q-PhosCl (**9**) was subsequently evaluated for several other substrates in the amination using a range of aryl bromides and chlorides with both secondary and primary aryl amines (Table 4). With less nucleophilic aniline, or sterically hindered aryl bromides, the temperature had to be increased to 50 °C to get satisfactory yields, although in many cases the coupling could be achieved at ambient temperature. Aryl chlorides required a temperature of ca. 100 °C for completion of the reaction, although the reaction times remained relatively short. We also successfully demonstrated a few examples of chemoselective amination of an aryl bromide in the presence of the chloride functionality (**18g** and **18h**) where the oxidative

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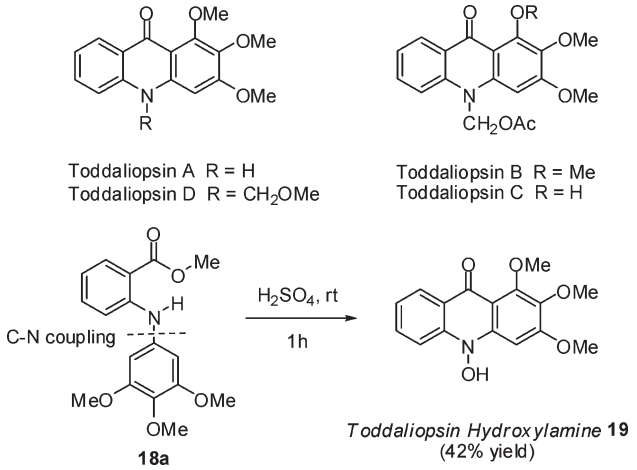
addition of the aryl chloride presumably occurs much less readily than that of the aryl bromide. In addition, complex **9** showed a great potential (see formation of **18f**) in the amination of aryl iodides, which have been problematic coupling partners in the Pd-catalyzed C−N bond formation processes.[24]

Interestingly, the order of reactivity in amination mediated by **9** was opposite to that of conventional Pd-mediated coupling reactions. Here, electron-rich aryl halides were coupled in higher yields at shorter reaction times than that of the electron-deficient electrophiles (cf. **18e** vs **18l**). Noteworthy is the unprecedented amination of a very electron-rich tris-methoxybromobenzene in 65% isolated yield. Product **18a**, resulting from this coupling reaction, underwent an intramolecular Friedel−Crafts acylation reaction when treated with H_2SO_4 to form the framework for the toddaliopsin family, in 42% unoptimized yield (Scheme 3). Toddaliopsin A, B, C, and D have recently been isolated from the leaves of *Toddaliopsis bremekampii*, and the members of the family possess various degrees of antiinflammatory activity.[25]

Scheme 3. Intramolecular Friedel−Crafts Reaction To Form Toddaliopsin Hydroxylamine 19



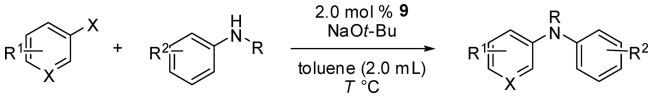
Heterocyclic halides were also successfully coupled, although a slightly higher loading of **9** was necessary to achieve good conversions (Table 5). Pyridine-, pyrimidine-, and thiophene halides gave C−N coupled products in good yields at 100 °C. The reaction using 3-bromothiophene was demonstrated at room temperature, albeit with a slightly lower yield of the product (**18p**).

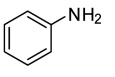
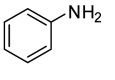
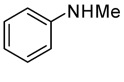
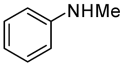
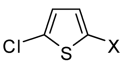
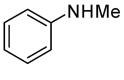
We also evaluated arylation of amines at lower catalyst loadings (Table 6) in selected cases. Reactions carried out with 0.05 or 0.1 mol % loading underwent completion at 100 °C. Noteworthy is the coupling between the sterically hindered 2, 6-diisopropylaniline and 2-chlorotoluene (**18i**), which previously gave only 87% GC conversion at 0.5 mol % catalyst loading, with the aryl halide concentration of 0.8 M (Table 4). In this case, a significant concentration effect was observed, where increasing the molarity of the reaction mixture to 3.2 M at reduced catalyst loading (0.1 mol %) gave the desired product in 95% isolated yield (Table 6, **18i**). This concentration effect, however, was not observed for all other substrate combinations.

Catalyst Evaluation in Suzuki Couplings. The activities of palladium π-allyl complexes **7**−**17** were also investigated in a model Suzuki reaction between 4-bromoanisole and 4-*tert*-butylbenzeneboronic acid. Preliminary studies using Pd(crotyl)Q-PhosCl (**9**) showed that a catalyst loading as low as 0.05 mol % could be used to achieve full conversion to the product at room temperature (Table 7, entry 2). Subsequently, the remaining catalysts were investigated in the same coupling reaction, and the conversion after 45 min reaction time for each complex was measured by GC.

As was the case of the amine arylation studies, Pd(crotyl)-Q-PhosCl (**9**) was notably the most active catalyst among the

Table 5. Amination of Heterocyclic Aryl Bromides and Chlorides Using Pd(crotyl)Q-PhosCl (9)[a]

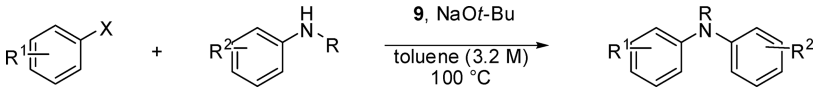


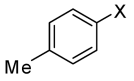
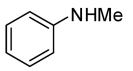
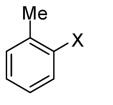
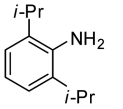
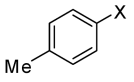
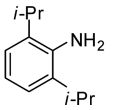
Ar-X	amine	X	T °C	time (h)	product	yield (%)
		Br Cl	100 100	3.5 3.5	**18m**	94 86
		Br Cl	100 100	2 2.5	**18n**	79 88
		Br	50	3	**18o**	83
		Br Br Cl	100 25 100	3 18 3	**18p**	90 76[b] 57
		Br	25	20	**18q**	44

[a] Aryl halide (1.6 mmol), amine (2.0 mmol), NaO*t*-Bu (2.4 mmol), toluene (2.0 mL). [b] Isolated yield using 1 mol % Pd(crotyl)Q-PhosCl. Unreacted aryl bromide could be detected by TLC before purification, indicating an incomplete reaction.

dx.doi.org/10.1021/jo2013324 |*J. Org. Chem.* 2011, 76, 7918–7932

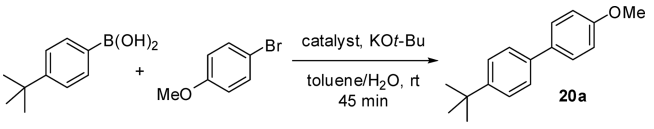
Table 6. Amination at Low Catalyst Loading[a]



Ar-X	amine	X	loading (mol %)	time (h)	product	yield (%)
		Br Cl	0.05 0.10	1 1	**18r**	83 92
		Cl	0.05 0.10	16 2	**18i**	90[b] 95
		Br	0.05	2	**18s**	91

[a] Aryl halide (1.6 mmol), amine (2.0 mmol), NaO*t*-Bu (2.4 mmol), toluene (0.5 mL). [b] GC conversion.

Table 7. Suzuki Coupling at Room Temperature[a]



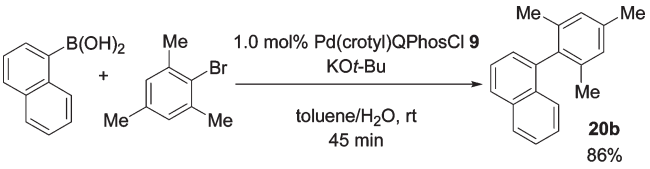
entry	catalyst (0.05 mol %)	conv (%)[b]
1	Pd(allyl)Q-PhosCl (**8**)	2
2	Pd(crotyl)Q-PhosCl (**9**)	100[c]
3	Pd(cinnamyl)Q-PhosCl (**10**)	19
4	Pd(prenyl)Q-PhosCl (**11**)	81
5	Pd(2-Methylallyl)Q-PhosCl (**12**)	11
6	Pd(allyl)P(*t*-Bu)$_3$Cl (**13**)	94
7	Pd(crotyl)P(*t*-Bu)$_3$Cl (**14**)	100
8	Pd(allyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl (**15**)	3
9	Pd(crotyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl (**16**)	7
10	Pd(allyl)P(*t*-Bu)$_2$NpCl (**7**)	13
11	Pd(crotyl)P(*t*-Bu)$_2$NpCl (**17**)	99

[a] 4-Bromoanisole (1.6 mmol), 4-*tert*-butylbenzeneboronic acid (1.76 mmol), KO*t*-Bu (1.92 mmol), toluene (1.8 mL), water (0.2 mL). [b] GC conversion, average of at least two runs. [c] 85% isolated yield.

Q-Phos-based catalysts (entry 2 vs 1, 3−5) in Suzuki coupling. Interestingly, P(*t*-Bu)$_3$-based catalysts **13** and **14** also displayed higher activity (entries 6 and 7), along with Pd(crotyl)-P(*t*-Bu)$_2$NpCl (**17**) (entry 11). The use of its allyl analogue **7**, however, only gave product in 13% conversion (entry 10) under identical conditions. P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$) catalysts **15** and **16** were inefficient under these reaction conditions, providing the product in 3% and 7% conversion, respectively (entries 8 and 9).

The high activity of Pd(crotyl)Q-PhosCl (**9**) was subsequently demonstrated in a sterically challenging Suzuki reaction

Scheme 4. Sterically Challenging Suzuki Coupling

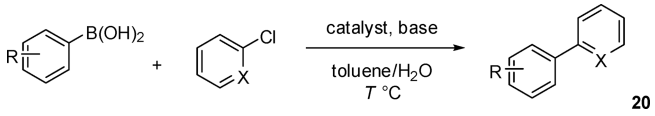


of bromomesitylene and 1-naphthaleneboronic acid (Scheme 4). This coupling could be carried out at ambient temperature with 100% GC conversion and 86% isolated yield within 45 min of reaction time.

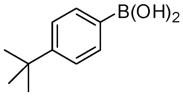
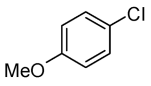
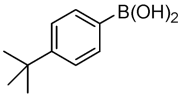
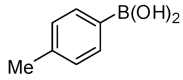
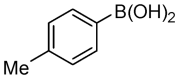
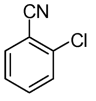
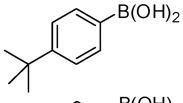
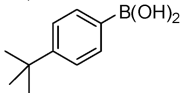
In an extension of the scope of the substrates to aryl chlorides, 4-chloroanisole coupled with 4-*tert*-butylbenzeneboronic acid gave the product in 90% conversion (Table 8, entry 1) using the same reaction conditions as those employed for the aryl bromides, but at 80 °C. Inspired by Guram's report on the use of PdCl$_2$[P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)]$_2$ (Pd-132) in the Suzuki coupling of heterocyclic aryl chlorides,[22] we decided to investigate the base effect in the coupling of heterocyclic chlorides employing our π-allyl catalysts. Substituting K_2CO_3 for KO*t*-Bu in the case of 4-chloroanisole provided the coupling product in very low conversions using both Pd(crotyl)Q-PhosCl (**9**) and Pd(allyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl (**15**) (entries 2 and 3). However, employing 2-chlorothiophene in the Suzuki reaction, we found that the yield of the product was comparable to that achieved under the Guram conditions for PdCl$_2$(P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$))$_2$ and the new Pd(allyl)P(*t*-Bu)$_2$-(*p*-NMe$_2$C$_6$H$_4$)Cl (**15**) (entries 4−5, 6−7, 8−9), demonstrating that a Pd:L ratio of 1:1 was sufficient for an efficient reaction. Using the reaction conditions developed for the aryl bromides, we coupled 2-chlorothiophene with 4-*tert*-butylbenzeneboronic acid to obtain product in 52% yield, with Pd(crotyl)Q-PhosCl (**9**) as catalyst (entry 10). The same reaction gave a lower yield (33%) under the Guram conditions (entry 11). A similar low yield (29%) was also obtained for Pd(crotyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl (**16**) catalyst when used in place of **9** (entry

dx.doi.org/10.1021/jo2013324 |J. Org. Chem. 2011, 76, 7918–7932

Table 8. Aryl Chlorides in Suzuki Coupling[a]

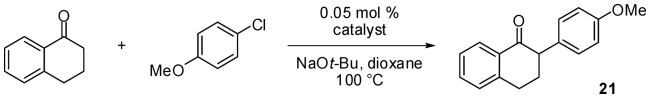


20

entry	catalyst	conditions	$RB(OH)_2$	Ar-Cl		yield (%)[a]
1	1 mol % **9**	A			**20a**	90[b]
2	1 mol % **9**	B				38[b]
3	1 mol % **15**	B				29[b]
4	1 mol % **15**	B			**20c**	64
5[c]	1 mol % **Pd-132**					68
6	1 mol % **15**	B			**20d**	70
7[c]	1 mol % **Pd-132**					84
8[d]	0.01 mol % **15**	B			**20e**	85
9[c,d]	0.01 mol % **Pd-132**					79
10	1 mol % **9**	A			**20c**	52
11	1 mol % **9**	B				33
12	1 mol % **16**	B				29
13	1 mol % **15**	B			**20f**	73

[a] Conditions A: aryl chloride (1.6 mmol), boronic acid (1.76 mmol), KO*t*-Bu (1.92 mmol), toluene (1.8 mL), water (0.2 mL), 80 °C. Conditions B: aryl chloride (1.0 mmol), boronic acid (1.2 mmol), K_2CO_3 (2.0 mmol), toluene (5.0 mL), water (0.5 mL), 100 °C. Isolated yield. [b] GC conversion. [c] Pd-132, $PdCl_2[P(t\text{-}Bu)_2(p\text{-}NMe_2C_6H_4)]_2$. [d] Using K_3PO_4 as base.

Table 9. α-Arylation of 1-Tetralone Using 0.05 mol % Pd Loading[a]



21

entry	catalyst	time (h)	conv[b] (%)
1	Pd(allyl)Q-PhosCl (**8**)	3	80
2	Pd(allyl)$P(t\text{-}Bu)_2(p\text{-}NMe_2C_6H_4)$Cl (**15**)	3	96
3	Pd(allyl)$P(t\text{-}Bu)_2(p\text{-}NMe_2C_6H_4)$Cl (**15**)	22	100(91)
4	Pd(crotyl)Q-PhosCl (**9**)	3	23
5	Pd(crotyl)$P(t\text{-}Bu)_2(p\text{-}NMe_2C_6H_4)$Cl (**16**)	3	7

[a] 4-Chloroanisole (2.0 mmol), 1-tetralone (2.0 mmol), NaO*t*-Bu (3.8 mmol), dioxane (2.0 mL). [b] GC conversion. Average of two runs. Isolated yield in parentheses.

12). For the relatively easier chloropyridine substrate, **15** gave 73% yield (entry 13).

The described investigation of aryl chlorides in Suzuki coupling illustrates the importance of a careful choice of catalyst and reaction conditions to get optimized yields. However, additional work is needed to fully optimize the Suzuki reactions of aryl chlorides.

Notably, in the Suzuki reactions of 2-chlorothiophene, Pd(allyl)$P(t\text{-}Bu)_2(p\text{-}NMe_2C_6H_4)$Cl (**15**) was found to be superior to its crotyl counterpart under equivalent conditions (Table 8, entry 4 vs entry 12).

Preliminary Investigations of α-Arylation Reactions. Subsequently, the activities of the π-allyl catalysts bearing the Q-Phos and $P(t\text{-}Bu)_2(p\text{-}NMe_2C_6H_4)$ ligands were evaluated in the α-arylation of cyclic ketone 1-tetralone. Pd(allyl)Q-PhosCl (**8**) provided the product in 80% conversion after 3 h reaction time, whereas Pd(allyl)$P(t\text{-}Bu)_2(p\text{-}NMe_2C_6H_4)$Cl (**15**) gave 96% conversion within the same time (Table 9, entries 1 and 2), demonstrating the importance of ligands in specific chemistries. The product was isolated in 91% yield after an overnight reaction using catalyst loading as low as 0.05 mol % of Pd(allyl)$P(t\text{-}Bu)_2(p\text{-}NMe_2C_6H_4)$Cl (**15**) (entry 3). This is a notable improvement to previously reported results, when the use of 2 mol % $PdCl_2$(D*t*-BPF) in an identical coupling reaction gave 75% conversion.[13a]

To our surprise, the activity trend of the catalysts that was observed in the amine arylation and Suzuki reactions using aryl bromides was reversed in the α-arylation of 1-tetralone. In this model reaction, Pd(crotyl)Q-PhosCl (**9**) and Pd(crotyl)$P(t\text{-}Bu)_2(p\text{-}NMe_2C_6H_4)$Cl (**16**) only provided the product in 23% and 7% conversion, respectively (entries 4 and 5). At the moment, we do not understand this trend; however, the reaction pathway may be different from the conventional mechanism.

For the use of aryl chlorides in Suzuki and α-arylation reactions, the allyl-based catalysts seem to perform superior to

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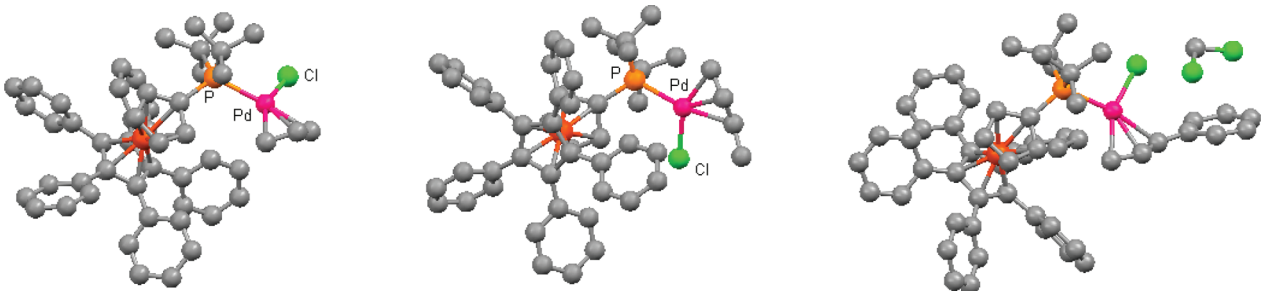
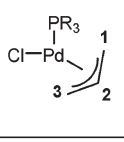
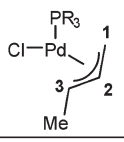
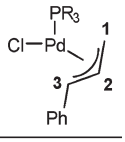
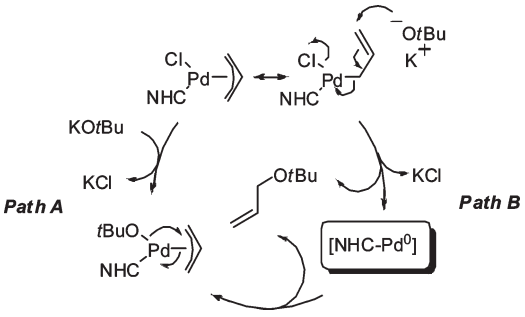


Figure 1. Crystal structures of Pd(allyl)Q-PhosCl (**8**), Pd(crotyl)Q-PhosCl (**9**), and Pd(cinnamyl)Q-PhosCl (**10**).

Table 10. Selected Bond Lengths in 8−10

bond distance (Å)			
Pd-C(1)	2.130(10)	2.127(7)	2.123
Pd-C(2)	2.145(10)	2.152(7)	2.139
Pd-C(3)	2.169(10)	2.251(6)	2.324

Scheme 5. Nolan's Proposed Activation Pathway of (π-Allyl)Pd(L)Cl Catalysts



the crotyl complexes. The reason for this observation is not clear at this stage and warrants further investigations.

Mechanistic Investigations: Activation of the Precatalyst. With the aim of rationalizing the difference in reactivity between the various Q-Phos-based π-allyl complexes, the X-ray crystal structures of Pd(allyl)Q-PhosCl (**8**), Pd(crotyl)Q-PhosCl (**9**), and Pd(cinnamyl)Q-PhosCl (**10**) were determined (Figure 1). As observed by Nolan,[7] an increase in dissymmetry of the π-allyl moiety of the catalysts was observed in the order Pd(allyl)-Q-PhosCl < Pd(crotyl)Q-PhosCl < Pd(cinnamyl)Q-PhosCl (Table 10) . The proposed activation pathway involves either the σ-bond metathesis with the chloride (path A) or nucleophilic attack by the *tert*-butoxide anion onto the π-allyl moiety (path B) as depicted in Scheme 5. On the basis of Nolan's observation, this dissymmetry in theory could affect the rate of the activation step and hence the rate of the coupling reaction. Despite the fact that Pd(cinnamyl)Q-PhosCl (**10**) showed the highest degree of dissymmetry, it led to lower yields of C−N and C−C coupled products (Tables 1 and 7).

The major observation from the crystal structures was that the orientation of chloride with respect to the allyl substituents vs the R groups on the phosphine moiety was in the opposite direction for **9**, in comparison to that in **8** and **10**. Therefore, the allyl and the cinnamyl moieties are less available for nucleophilic attack by the *tert*-butoxide anion due to the steric hindrance exerted by the large pentaphenyl ferrocenyl moiety. The crotyl-based complex **9** on the other hand does not experience such a steric hindrance and is easily activated. On the basis of this observation, we believe that this series of precatalysts are activated by nucleophilic attack onto the π-allyl moieties (path B) rather than by a chloride/alkoxide σ-bond metathesis followed by reductive elimination (Scheme 5). This may explain the room temperature high activity of **9** vs **8** and **10** (see Table 1).

Considering that this is the solid-state structure of the catalyst, the steric barrier may be less important when the reaction temperature is increased in the solution phase. The activities of **8** and **9** were subsequently compared in the coupling of 2-bromotoluene and 2,6-diisopropylaniline, which required a temperature of 50 °C for a good conversion (Table 11). In this case, the crotyl-based catalyst **9** was still superior to the allyl complex **8**, providing the product in 100% conversion within 2 h. However, when the coupling of 4-chloroanisole and 2,6-diisopropylaniline was carried out at 100 °C, catalysts **8** and **9** performed at a similar rate, giving 99% conversion within 40 min of the reaction period. Therefore, at higher temperatures, the rate of activation of catalysts **8** and **9** to Q-PhosPd(0) could be comparable due to the Pd−P bond rotation and hence coupling occurs at comparable rates for both catalysts.

The fate of the Pd(allyl)P(*t*-Bu)$_2$NpCl in the C−N bond-forming reaction has recently been briefly studied by Shaughnessy's group in collaboration with our group.[14] From the NMR studies of the reaction mixture, it was proposed that after activation of the precatalyst with *tert*-butoxide, there was the formation of an equilibrium mixture of three species; Pd(0)P(*t*-Bu)$_2$Np, Pd(0)[P(*t*-Bu)$_2$Np]$_2$, and Pd$_2$(I)(μ-Cl)(μ-C$_3$H$_5$)[P(*t*-Bu)$_2$Np]$_2$ dimer, prior to the oxidative addition of the aryl halide onto the Pd(0)L species. We believe that all the allyl-based catalysts proceed via this pathway, because the treatment of each of the catalysts: Pd(allyl)Q-Phos, Pd(allyl)P*t*-Bu$_3$Cl, and Pd-(allyl)P(*t*-Bu)$_2$NpCl with NaO*t*-Bu in C$_6$D$_6$ produced new peaks in the ^{1}H NMR spectrum in the same regions (~1.7 and 2.5 ppm). This can be correlated to the NMR chemicals shifts of the isolated dimer, Pd$_2$(I)(μ-Cl)(μ-C$_3$H$_5$)[P(*t*-Bu)$_2$Np]$_2$, reported recently.[14] The respective ^{31}P NMR resonances of the Pd(I) dimers are tentatively assigned in Table 12 in analogy with the reported neopentyl system.

Attempts to isolate and identify the products obtained by the treatment of Pd(crotyl)LCl complexes with NaO*t*-Bu were not successful; however, new peaks appeared in the ^{1}H NMR spectra

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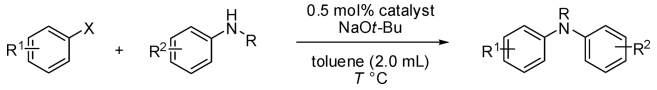
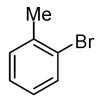
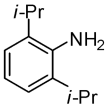
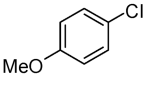
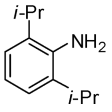
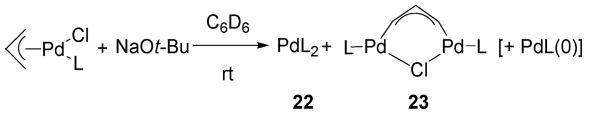
Table 11. Comparison of the Relative Activities of 8 and 9[a]



Ar-X	amine	T (°C)	catalyst	time (h)	conv[b] (%)
		50	**8**	6.5	97
		50	**9**	2	100
		100	**8**	0.6	99
		100	**9**	0.6	99

[a] Aryl halide (1.6 mmol), amine (2.0 mmol), NaO*t*-Bu (2.4 mmol), toluene (2.0 mL). [b] GC conversion.

Table 12. Treatment of Pd(allyl)LCl with NaO*t*-Bu



22 **23**

L	^{31}P NMR (δ, ppm) **23**
Q-Phos	60.4[a]
P(*t*-Bu)$_2$Np	49.8
P(*t*-Bu)$_3$	86.0[a]

[a] Tentatively assigned to the dimer products because the ^{1}H NMR spectrum show peaks in the same region as that for the fully characterized Pd$_2$(I)(μ-Cl)(μ-C$_3$H$_5$)[P(*t*-Bu)$_2$Np]$_2$, and only one new peak appeared in the ^{31}P spectra.

in the same region in the cases of Pd(crotyl)Q-Phos, Pd(crotyl)P(*t*-Bu)$_3$Cl and Pd(crotyl)P(*t*-Bu)$_2$Np (~2.8, 3.2, 5.1, 5.2, and 6.4 ppm). This indicates that they all presumably proceed via an identical activation pathway.

It should be noted that in these investigations we employed the conditions for the C–N bond formation reactions, where NaO*t*-Bu was used as the base. In the Suzuki coupling reactions, we were the first ones to demonstrate that K_2CO_3 can be used as the base in conjunction with π-allyl precatalysts, in which case the activation of the precatalysts via nucleophilic attack may be less likely. We are currently studying the Suzuki reactions in detail.

Mechanistic Investigations: Oxidative Addition Products. It should be noted that the subsequent mechanistic studies were all carried out at room temperature. Once the precatalyst is activated presumably to a "Pd(0)L" species, the oxidative addition product and the subsequent intermediates should give identical intermediates in the reactions catalyzed by Pd(allyl)LCl or Pd(crotyl)LCl, assuming that the conventional pathway is followed, consisting of oxidative addition to Pd(0)L, followed by transmetalation and reductive elimination (Scheme 6).

Scheme 6. Conventional Catalytic Cycle for Cross-Coupling Reactions

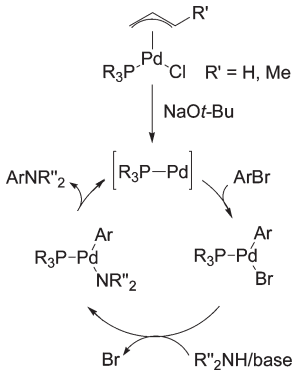
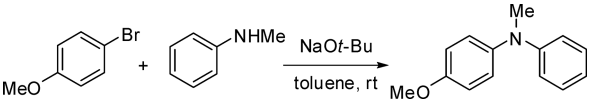


Table 13. Major ^{31}P NMR Peaks in C–N Bond Formation Reactions



L	Pd(allyl)LCl	Pd(crotyl)LCl
Q-Phos	64.8	67.1
P*t*-Bu$_3$	89.3	85.1
P(*t*-Bu)$_2$Np	53.0	63.0, 51.8

[a] Aliquots removed from the reaction mixture after 10 min and diluted with C$_6$D$_6$.

However, the ^{31}P NMR monitoring of the C–N bond formation reactions of 4-bromoanisole and *N*-methylaniline catalyzed by Pd(allyl)P(*t*-Bu)$_2$NpCl and Pd(crotyl)P(*t*-Bu)$_2$NpCl produced noticeably different spectra. Alongside several minor resonances, the major peak observed in the Pd(allyl)P(*t*-Bu)$_2$NpCl reaction was at 53.0 ppm, whereas for the Pd(crotyl)P(*t*-Bu)$_2$NpCl-catalyzed reaction, two major peaks (~63.0 and

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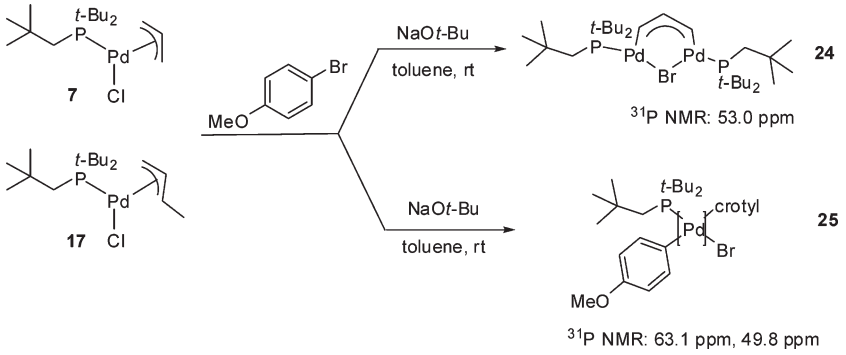
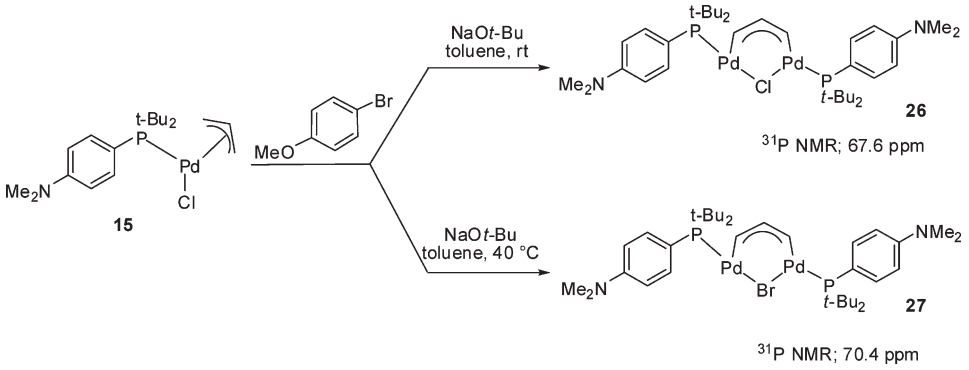
Scheme 7. Reactivity Difference of 7 and 17 with Base and Aryl Bromide



Scheme 8. Reactivity of Pd(allyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl 15 with Base and Aryl Bromide



51.8 ppm) were observed. The same difference was seen for the reaction catalyzed by Pd(allyl)Q-PhosCl vs Pd(crotyl)Q-PhosCl and Pd(allyl)P(*t*-Bu)$_3$Cl vs Pd(crotyl)P(*t*-Bu)$_3$Cl (Table 13).

This indicates that different reaction pathways or different intermediates are operating for the allyl-based and the crotyl-based precatalysts. In addition, the mechanism involving the precatalysts containing various ligands in the crotyl series may differ, because two major peaks were observed in the P(*t*-Bu$_2$)Np case, compared to a single one in the other systems (Table 13).

To gain an insight into the nature of these different intermediates, Pd(allyl)P(*t*-Bu)$_2$NpCl was reacted with a stoichiometric amount of 4-bromoanisole in the presence of a small excess of NaO*t*-Bu in toluene. The yellow solid obtained (^{31}P NMR; 53.0 ppm) was confirmed by crystal structure determination to be a Pd(I) dimer, however bridged by a Br rather than a Cl (Scheme 7, **24**). This species was shown to be the main component of the coupling reaction of 4-bromoanisole and *N*-methylaniline, catalyzed by Pd(allyl)P(*t*-Bu)$_2$NpCl, when monitored by ^{31}P NMR, and was previously left unidentified.[14]

Carrying out similar experiments but with Pd(crotyl)-P(*t*-Bu)$_2$NpCl provided a yellow solid containing a mixture of two P species (^{31}P NMR; 63.1 ppm, 49.8 ppm, **25**). The ^{1}H NMR of this mixture showed the presence of aryl groups and a methoxy group, alongside alkene peaks, suggesting the presence of the crotyl moiety (Scheme 7, **25**). Resonances in the same regions were observed as the major peaks when monitoring the coupling reaction of 4-bromoanisole and *N*-methylaniline. Despite several attempts, it was not possible to obtain a crystal structure of the components of this reaction, because the two compounds could not be separated. It was hypothesized that the intermediates of this reaction exist in equilibrium with one another and are too unstable in solution for crystal growth to occur.

To conclude, we believe that the allyl-based catalysts differ from the crotyl-based catalysts on two points: (i) the spatial arrangement of the ligands around the Pd, and (ii) the mechanism of the subsequent coupling reaction after precatalyst activation.

Mechanistic Investigations: The Low Activity of Pd(allyl)P-(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl in Room Temperature Reactions. Finally, the low activity of Pd(allyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl in the coupling of 4-bromoanisole and *N*-methylaniline is somewhat understood by monitoring the reaction of catalyst **15** with NaO*t*-Bu and 4-bromoanisole at room temperature. After 1 h reaction period, a mixture of peaks was observed in the ^{31}P NMR spectrum but eventually changed into a single peak at 67.6 ppm. This compound was isolated and characterized as the Pd(I) chloride dimer complex (Scheme 8, **26**). The oxidative addition had not occurred to a significant extent, which is in stark contrast to the P(*t*-Bu)$_3$, P(*t*-Bu)$_2$Np, and Q-Phos-based catalysts.

Carrying out the same reaction, but increasing the temperature to 40 °C, provided a dimer different from **26**. X-ray crystal structure determination confirmed dimer **27** to be the bridged bromide species, proving that the oxidative addition had occurred (Scheme 8). Indeed, employing Pd(allyl)P(*t*-Bu)$_2$-(*p*-NMe$_2$C$_6$H$_4$)Cl **15** in the coupling of 4-bromoanisole with

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N-methylaniline at 40 °C provided the desired coupling product in 100% conversion after 18 h reaction time compared to 18% conversion after the same time at ambient temperature (Table 1, entry 11).

CONCLUSION

In summary, we have synthesized a series of Pd(R-allyl)LCl complexes [R = H, 1-Me, Ph, 1-*gem*-Me_2, 2-Me; L = Q-Phos, P(*t*-Bu)$_3$, P(*t*-Bu)$_2$Ph, P(*t*-Bu)$_2$(*p*-$NMe_2C_6H_4$), Q-Phos, P(*t*-Bu)$_2$-Np] and demonstrated that Pd(allyl)Q-PhosCl **8** and Pd-(crotyl)Q-PhosCl **9** are highly active precatalysts for C−N bond formation using aryl bromides and chlorides and for Suzuki couplings of aryl bromides. Pd(allyl)P(*t*-Bu)$_2$(*p*-$NMe_2C_6H_4$)Cl **15** has showed promising potential in the Suzuki and α-arylation reactions for aryl chlorides. The difference in reactivity between the allyl and the crotyl series of catalysts was attributed to the formation of different reaction intermediates. The allyl-based catalysts proceed via the Pd(I) bromide dimer species, Pd_2-(μ-Br)(μ-C_3H_5)L_2, whereas the crotyl-based catalysts believed to proceed via a proposed oxidative addition intermediate still bearing the crotyl ligand. Furthermore, a comparison of the X-ray crystal structures of **8**, **9**, and **10** revealed increasing dissymmetry of the π-allyl moiety in this catalyst series, alongside different spatial arrangements of **9** compared to **8** and **10**.

Although this study was able to provide more insight into the possible activation pathways and the subsequent catalysis, the mechanism of cross-coupling is not as simple as we expected or depicted in the text. Several factors can affect the catalysis such as the role of the precatalysts, ligands, base, temperature, and the substrate. More detailed studies might be needed to understand fully the mechanism involving each of these catalysts. However, this study hopefully might probe others, especially those from academia, to do more mechanistic investigations in detail.

Despite the fact that the mechanism is not clearly understood, we believe that for arylation of amines, monocoordinated Pd−phosphine complexes are superior catalysts to dicoordinated complexes.

EXPERIMENTAL SECTION

General Considerations. All solvents and reagents were purchased from commercial sources and used as received. All catalysts, ligands, or precious metal precursors are available from Johnson Matthey Catalysis & Chiral Technologies or Alfa Aesar. The [Pd(R-allyl)Cl]$_2$ precursors were synthesized using modified literature procedures,[7,26] except [Pd(allyl)Cl]$_2$ which was obtained from Johnson Matthey Catalysis & Chiral Technologies. ^{1}H and ^{13}C NMR spectra were referenced to the NMR solvent peaks or internal TMS. ^{31}P{^{1}H} NMR spectra were externally referenced to 85% H_3PO_4. Single crystals of Pd(allyl)QPhosCl **8** were obtained by slow diffusion of diethyl ether into a CH_2Cl_2 solution, while those of Pd(crotyl)QPhosCl **9** and Pd(cinnamyl)QPhosCl **10** were obtained by slow diffusion of 40−60 petroleum ether into an EtOAc solution at −18 °C. The X-ray crystal structures were deposited at the CCDC (Cambridge Crystallographic Data Centre; **8**: CCDC 686842; **9**: CCDC 753265, **10**: CCDC 753264). All reactions were carried out in individual Schlenk tubes under a nitrogen atmosphere. The identity of known isolated products was confirmed by comparison with literature spectroscopic data. The purity of the isolated products was >95% as determined by ^{1}H NMR, GC/MS, or elemental analysis.

Synthesis of π-Allyl Pd Catalysts. Catalyst **7** was obtained from JM plants. Complexes **8**−**17** are also available through JM CCT and were synthesized using modified literature procedures.[14]

Pd(allyl)(Q-Phos)Cl (8). [Pd(allyl)Cl]$_2$ (2.0 mmol); Q-Phos (4.4 mmol); THF (45 mL); 18 h. The product was obtained as a pink solid (3.2 g, 90%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17−7.12 (m, 15H), 7.08−6.98 (m, 10H), 5.41 (m, 1H), 5.33 (s, 1H), 5.08 (s, 1H), 4.83 (t, *J* 6.4, 1H), 4.55 (d, *J* 8.4, 2H), 4.04 (d, *J* 4.8, 1H), 3.87 (dd, *J* 13.6, 8.8, 1H), 2.78 (d, *J* 12.0, 1H), 1.17 (d, *J* 14.0, 18H); ^{13}C ($CDCl_3$, 100 MHz): δ 135.2, 132.7, 127.3, 126.5, 114.3, 87.7, 67.1, 57.6, 37.6, 30.5; ^{31}P NMR ($CDCl_3$, 162 MHz): δ 61.7. Anal. Calcd for $C_{51}H_{52}$-ClFePPd: C, 68.54; H, 5.87; P, 3.47; Pd 11.91. Found: C, 68.47; H, 5.91; P, 3.31; Pd, 11.50.

Pd(crotyl)(Q-Phos)Cl (9). [Pd(crotyl)Cl]$_2$ (200 mg, 0.51 mmol); Q-Phos (798 mg, 1.12 mmol); THF (10 mL); 18 h. The complex was obtained as a pink solid (891 mg, 96%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15−7.03 (m, 25H), 5.34 (br s, 1H), 5.09−5.00 (m, 2H), 4.54−4.53 (m, 2H), 4.49−4.39 (m, 1H), 3.77 (d, *J* 6.4, 1H), 2.54 (d, *J* 11.6, 1H), 1.74 (dd, *J* 8.4, 6.8, 3H), 1.17 (t, *J* 13.2, 18H); ^{13}C ($CDCl_3$, 100 MHz): δ 135.2, 132.6, 127.3, 126.5, 113.2, 103.0, 102.7, 87.7, 80.8, 80.1, 52.2, 37.8, 30.6; ^{31}P NMR ($CDCl_3$, 162 MHz): δ 65.0. Anal. Calcd for $C_{52}H_{54}$ClFePPd: C, 68.81; H, 6.00; Cl, 3.91; P, 3.41. Found: C, 68.90; H, 6.16; Cl, 3.77; P, 3.40.

Pd(cinnamyl)(Q-Phos)Cl (10). [Pd(cinnamyl)Cl]$_2$ (74 mg, 0.14 mmol); Q-Phos (223 mg, 0.31 mmol); THF (2.8 mL); 18 h. Product obtained as a pink solid (233 mg, 86%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48−7.46 (m, 2H), 7.37−7.35 (m, 3H), 7.14−7.03 (m, 25H), 5.68−5.60 (m, 1H), 5.20 (dd, *J* 13.2, 9.6, 1H), 5.08 (br s, 1H), 4.84−4.81 (m, 1H), 4.53 (app s, 2H), 4.02 (br s, 1H), 2.79 (br s, 1H), 1.27−1.07 (m, 18H); ^{13}C ($CDCl_3$, 100 MHz): δ 136.4, 135.1, 132.6, 128.6, 128.3, 127.4, 126.5, 107.3, 87.7, 68.0, 53.9, 30.7; ^{31}P NMR ($CDCl_3$, 162 MHz): δ 67.4. Anal. Calcd for $C_{57}H_{56}$ClFePPd: C, 70.60; H, 5.82; Cl, 3.66; P, 3.19. Found: C, 70.39; H, 5.93; Cl, 3.52; P, 3.18.

Pd(prenyl)(Q-Phos)Cl (11). [Pd(prenyl)Cl]$_2$ (200 mg, 0.48 mmol); Q-Phos (751 mg, 1.06 mmol); THF (10 mL); 18 h. Product obtained as a pink solid (867 mg, 98%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19−7.04 (m, 25H), 5.44 (br s, 1H), 4.94−4.81 (m, 2H), 4.51 (s, 2H), 3.52 (d, *J* 6.8, 1H), 2.71 (d, *J* 12.0), 1.80 (d, *J* 8.4, 3H), 1.62 (t, *J* 7.2, 3H), 1.24 (d, *J* 14.4, 9H), 1.15 (d, *J* 14.4, 9H); ^{13}C ($CDCl_3$, 100 MHz): δ 135.2, 132.6, 127.3, 126.5, 121.2, 106.8, 87.7, 80.3, 47.4, 37.8, 30.9, 30.6; ^{31}P NMR ($CDCl_3$, 162 MHz): δ 68.3. Anal. Calcd for $C_{53}H_{56}$ClFePPd: C, 69.06; H, 6.12; Cl, 3.85; P, 3.36. Found: C, 68.81; H, 6.44; Cl, 4.57; P, 3.25.

Pd(2-methylallyl)(Q-Phos)Cl (12). [Pd(2-crotyl)Cl]$_2$ (200 mg, 0.51 mmol); Q-Phos (798 mg, 1.12 mmol); THF (5 mL); 18 h. The complex was obtained as a pink solid (788 mg, 85%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.19−6.98 (m, 25H), 5.27 (br s, 1H), 4.93 (br s, 1H), 4.65 (dd, *J* 6.4, 2.8, 1H), 4.55 (br s, 2H), 3.84 (d, *J* 2.8, 1H), 3.77 (d, *J* 8.4, 1H), 2.68 (s, 1H), 1.94 (s, 3H), 1.18 (d, *J* 14.0, 9H), 1.13 (d, *J* 14.0, 9H); ^{13}C ($CDCl_3$, 100 MHz): δ 134.5, 131.9, 128.6, 126.7, 126.6, 125.9, 87.1, 79.4, 57.2, 30.0, 29.9, 29.6, 29.5, 21.8; ^{31}P NMR ($CDCl_3$, 162 MHz): δ 62.0. Anal. Calcd for $C_{52}H_{54}$ClFePPd: C, 68.81; H, 6.00; Cl, 3.91; P, 3.41. Found: C, 69.59; H, 6.23; Cl, 3.41; P, 3.42.

Pd(allyl)(P*t*-Bu$_3$)Cl (13):[20] [Pd(allyl)Cl]$_2$ (397 mg, 1.08 mmol); P*t*-Bu_3 (0.45 g, 2.22 mmol); THF (2.2 mL); 20 min. After the reported procedure, the crude product was recrystallized from CH_2Cl_2/hexane to give a yellow precipitate and a yellow filtrate. The precipitate was removed by filtration, and the filtrate was concentrated and dried in vacuo to give the product as a yellow crystalline solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.47−5.37 (m, 1H), 4.73 (t, *J* 8.0), 4.12 (app s, 1H), 3.83 (dd, *J* 12.0, 8.0, 1H), 2.81 (d, *J* 8.0, 1H), 1.53 (d, *J* 12.0, 28H); ^{13}C ($CDCl_3$, 100 MHz): δ 113.7, 83.6, 83.4, 56.9, 39.4, 32.7; ^{31}P NMR ($CDCl_3$, 162 MHz): δ 86.0. Anal. Calcd for $C_{15}H_{32}$ClPPd: C, 46.76; H, 8.37; Cl, 9.20; P, 8.04. Found: C, 46.80; H, 8.28; Cl, 8.64; P, 8.14.

Pd(crotyl)(P*t*-Bu$_3$)Cl (14). [Pd(crotyl)Cl]$_2$ (276 mg, 0.71 mmol); P*t*-Bu$_3$ (0.29 g, 1.46 mmol); THF (2.8 mL); 30 min. Product obtained as a yellow solid (384 mg, 68%); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.12−5.04 (m, 1H), 4.45−4.38 (m, 1H), 3.85 (d, *J* 5.2, 1H), 2.56 (d, *J* 11.2, 1H), 1.68−1.66 (m, 3H), 1.53 (d, *J* 12.0, 27H); ^{13}C (CDCl$_3$, 100 MHz): δ 112.7, 103.6, 103.4, 50.9, 39.4, 32.8, 29.1, 17.9; ^{31}P NMR (CDCl$_3$, 162 MHz): δ 89.7. Anal. Calcd for C$_{16}$H$_{34}$ClPPd: C, 48.13; H, 8.58; P, 7.76. Found: C, 48.32; H, 8.62; P, 7.84.

Pd(allyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl (15). [Pd(allyl)Cl]$_2$ (311 mg, 0.85 mmol); P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$) (496 mg, 1.87 mmol); THF (17 mL); 18 h. Product obtained as a yellow solid (727 mg, 96%); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.50 (app t, *J* 8.8, 2H), 6.65 (d, *J* 8.0, 2H), 5.50 (heptet, *J* 7.2, 1H), 4.63 (dt, *J* 6.8, 2.0, 1H), 3.69 (dd, *J* 13.2, 9.2, 1H), 3.39 (d, *J* 6.0, 1H), 3.01 (s, 6H), 2.68 (d, *J* 12.0, 1H), 1.47 (d, *J* 14.0, 9H), 1.39 (d, *J* 14.0, 9H); ^{13}C (CDCl$_3$, 100 MHz): δ 150.9, 136.7, 136.6, 116.9, 116.6, 115.2, 110.4, 110.3, 80.7, 80.4, 58.8, 39.9, 36.0, 30.6, 29.9; ^{31}P NMR (CDCl$_3$, 162 MHz): δ 61.9. Anal. Calcd for C$_{19}$H$_{33}$ClNPPd: C, 50.90; H, 7.42; Cl, 7.91; P, 6.91. Found: C, 51.44; H, 7.51; Cl, 7.54; P, 6.94.

Pd(crotyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl (16). [Pd(crotyl)Cl]$_2$ (132 mg, 0.34 mmol); P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$) (180 mg, 0.68 mmol); THF (3.7 mL); 90 min. Product obtained as a yellow solid (263 mg, 85%); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.52 (t, *J* 8.8, 2H), 6.65 (d, *J* 8.0, 2H), 5.25−5.17 (m, 1H), 4.40−4.29 (m, 1H), 3.21−3.19 (m, 1H), 3.00 (s, 3H), 2.47 (d, *J* 11.6, 1H), 1.77 (dd, *J* 8.4, 6.4, 3H), 1.44 (d, *J* 13.6, 9H), 1.38 (d, *J* 13.6, 9H); ^{13}C (CDCl$_3$, 100 MHz): δ 150.9, 149.6, 136.9, 136.7, 117.1, 116.8, 114.1, 110.3, 99.8, 99.6, 53.5, 40.0, 35.8, 30.6, 29.9, 17.4; ^{31}P NMR (CDCl$_3$, 162 MHz): δ 65.5. Anal. Calcd for C$_{20}$H$_{35}$ClNPPd: C, 51.96; H, 7.63; N, 3.03; P, 6.70. Found: C, 51.93; H, 7.54; N, 2.84; P, 6.58.

Pd(crotyl)(P(*t*-Bu$_2$)Np)Cl (17). [Pd(crotyl)Cl]$_2$ (451 mg, 1.14 mmol); P(*t*-Bu$_2$)Np (10 wt % in hexane, used as solvent) (5.0 g, 2.31 mmol); 60 min. Product obtained as a yellow solid (577 mg, 61%); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.14−5.06 (m, 1H), 4.40−4.33 (m, 1H), 3.66 (d, *J* 5.6, 1H), 2.53 (d, *J* 11.6, 1H), 2.18−2.02 (m, 2H), 1.72 (dd, *J* 8.0, 6.4, 3H), 1.38 (dd, *J* 17.6, 13.6, 18H), 1.22 (s, 9H); ^{13}C (CDCl$_3$, 100 MHz): δ 113.0, 101.2, 101.0, 49.6, 35.5, 35.2, 33.0, 31.1, 30.6, 17.7; ^{31}P NMR (CDCl$_3$, 162 MHz): δ 59.8. Anal. Calcd for C$_{17}$H$_{36}$ClPPd: C, 49.40; H, 8.78; P, 7.49. Found: C, 49.40; H, 8.70; P, 7.43.

General Procedure for the Buchwald−Hartwig Coupling Reaction. A Schlenk flask was charged with the catalyst, NaO*t*-Bu, and aryl halide, if solid, and the flask was evacuated and backfilled with nitrogen three times. Subsequently, a solution of the aryl halide, if liquid, and the amine in toluene was added. The resulting reaction mixture was stirred under nitrogen at the indicated temperature and time (see Table 4). The crude reaction mixture was absorbed onto silica gel and purified by flash column chromatography (MTBE/40−60 petroleum ether eluent).

2-CO$_2$Me-3′,4′,5′-trimethoxy-diphenylamine (18a). Methyl anthranilate (390 μL, 3.0 mmol); 5-bromo-1,2,3-trimethoxybenzene (594 mg, 2.3 mmol); NaO*t*-Bu (345 mg, 3.6 mmol); Pd(crotyl)-Q-PhosCl (43.5 mg, 0.06 mmol, 2.0 mol %); toluene (5.0 mL). The general procedure afforded the title compound as an off-white solid (462 mg, 65%); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 9.39 (br s, 1H), 7.96 (dd, *J* 4.4, 1.6, 1H), 7.33 (dd, *J* 6.8, 1.6, 1H), 7.21 (d, *J* 8.4, 1H), 6.73 (dd, *J* 8.0, 0.8, 1H), 6.49 (s, 2H), 3.91 (s, 3H), 3.85 (s, 3H), 3.83 (s, 6H); ^{13}C (CDCl$_3$, 100 MHz): δ 169.0, 153.8, 148.4, 136.6, 134.6, 134.2, 131.6, 116.9, 114.1, 111.6, 100.7, 61.0, 56.1, 51.8. Anal. Calcd for C$_{17}$H$_{19}$NO$_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.30; H, 6.06; N, 4.41.

***N*-(2,6-Diisopropylphenyl)-N-(*p*-methoxy)amine (18b).** 4-bromoanisole (200 μL, 1.6 mmol) or 4-chloroanisole (196 μL, 1.6 mmol); 2,6-diisopropylaniline (377 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (X = Br; 14.4 mg, 0.016 mmol, 1.0 mol %) or Pd(crotyl)Q-PhosCl (X = Cl; 7.2 mg, 0.008 mmol, 0.5 mol %) toluene (2.0 mL). The general procedure afforded the title compound in 96% yield (434 mg; X = Br) and 95% yield (429 mg; X = Cl); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.29−7.19 (m, 3H), 6.73 (d, *J* 6.8, 2H), 6.44 (d, *J* 6.8, 2H), 4.95 (br s, 1H), 3.73 (s, 3H), 3.19 (heptet, *J* 6.8, 2H), 1.14 (d, *J* 7.2, 12H); ^{13}C (CDCl$_3$, 100 MHz): δ 152.2, 147.1, 142.2, 136.0, 126.7, 123.8, 115.0, 114.2, 55.7, 28.0, 23.8. Anal. Calcd for C$_{19}$H$_{25}$NO: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.95; H, 9.05; N, 5.03.

***N*-(4-Methoxyphenyl)morpholine (18c):**[27] 4-Bromoanisole (200 μL, 1.6 mmol) or 4-chloroanisole (196 μL, 1.6 mmol); morpholine (175 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (7.2 mg, 0.008 mmol, 0.5 mol %); toluene (2.0 mL). The general procedure afforded the title compound in 98% yield (302 mg; X = Br) and 96% yield (297 mg; X = Cl); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 6.91−6.84 (m, 4H), 3.86 (t, *J* 4.4, 4H), 3.77 (s, 3H), 3.05 (t, *J* 4.8, 4H).

***N*-(4-Methoxyphenyl)diphenylamine (18d):**[28,29] 4-Bromoanisole (200 μL, 1.6 mmol) or 4-chloroanisole (196 μL, 1.6 mmol); diphenylaniline (338 mg, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (7.2 mg, 0.008 mmol, 0.5 mol %); toluene (2.0 mL). The general procedure afforded the title compound in 84% yield (370 mg; X = Br) and 68% yield (298 mg; X = Cl); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.22−7.18 (m, 4H), 7.08−7.02 (m, 6H), 6.95−6.92 (m, 2H), 6.85−6.81 (m, 2H), 3.80 (s, 3H).

4-Methoxydiphenylamine (18e):[30] 4-Bromoanisole (200 μL, 1.6 mmol); aniline (182 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (7.2 mg, 0.008 mmol, 0.5 mol %); toluene (2.0 mL). The general procedure afforded the title compound in 91% yield (288 mg); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.24−7.19 (m, 2H), 7.08−7.06 (m, 2H), 6.91−6.81 (m, 5H), 5.48 (s, 1H), 3.79 (s, 3H).

***N*-(4-Methoxyphenyl)-*N*-methylaniline (18f):**[28] 4-Bromoanisole (200 μL, 1.6 mmol), 4-chloroanisole (196 μL, 1.6 mmol), or 4-iodoanisole (374 mg, 1.6 mmol); *N*-methylaniline (217 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (7.2 mg, 0.008 mmol, 0.5 mol %); toluene (2.0 mL). The general procedure afforded the title compound in 93% yield (315 mg; X = Br), 98% yield (335 mg; X = Cl) and 95% yield (325 mg; X = I); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.17 (dd, *J* 8.4, 2H), 7.09−7.05 (m, 2H), 6.88−6.84 (m, 2H), 6.78−6.74 (m, 3H), 3.77 (s, 3H), 3.22 (s, 3H).

4-Chloro-2-methyldiphenyl-methylamine (18g). 2-Bromo-5-chlorotoluene (213 μL, 1.6 mmol); *N*-methylaniline (217 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (7.2 mg, 0.008 mmol, 0.5 mol %); toluene (2.0 mL). The general procedure afforded the title compound in 88% yield (324 mg); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.27 (d, *J* 2.0, 1H), 7.21−7.16 (m, 3H), 7.07 (d, *J* 8.4, 1H), 6.73 (t, *J* 7.2, 1H), 6.53 (d, *J* 8.0, 2H), 3.19 (s, 3H), 2.11 (s, 3H); ^{13}C (CDCl$_3$, 100 MHz) δ 146.5, 143.1, 136.4, 129.1, 128.9, 127.2, 126.7, 125.3, 114.9, 110.7, 36.8, 15.5. Anal. Calcd for C$_{14}$H$_{14}$ClN: C, 72.57; H, 6.09; N, 6.04. Found: C, 72.31; H, 6.13; N, 6.05.

3-Chloro-4-methyldiphenyl-methylamine (18h). 4-Bromo-2-chlorotoluene (217 μL, 1.6 mmol); *N*-methylaniline (217 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (7.2 mg, 0.008 mmol, 0.5 mol %); toluene (2.0 mL). The general procedure afforded the title compound in 97% yield (358 mg); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.30−7.26 (m, 2H), 7.08 (d, *J* 8.4, 1H), 7.02−6.96 (m, 4H), 6.79 (dd, *J* 8.4, 2.4, 1H), 3.27 (s, 3H), 2.30 (s, 3H); ^{13}C (CDCl$_3$, 100 MHz): δ 148.7, 148.1, 134.7, 131.2, 129.4, 128.2, 121.9, 121.0, 120.3, 118.5, 40.4, 19.2. Anal. Calcd for C$_{14}$H$_{14}$ClN: C, 72.57; H, 6.09; N, 6.04. Found: C, 72.01; H, 6.04; N, 5.98.

***N*-(2,6-Diisopropylphenyl)-*N*-(*o*-tolyl)amine (18i):**[31] 2-Bromotoluene (274 mg, 1.6 mmol) or 2-chlorotoluene (168 μL, 1.6 mmol); 2,6-diisopropylaniline (377 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (7.2 mg, 0.008 mmol, 0.5 mol %); toluene (2.0 mL). The general procedure afforded the title compound in 96% yield (410 mg; X = Br) and 87% conversion (X = Cl); ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.31−7.21 (m, 3H), 7.12 (d, *J* 7.2, 1H), 6.94 (t, *J* 7.6, 1H),

6.66 (td, *J* 7.2, 0.8, 1H), 6.11 (d, *J* 7.6, 1H), 4.89 (s, 1H), 3.11 (heptet, *J* 6.8, 2H), 2.34 (s, 3H), 1.17 (d, *J* 6.8, 6H), 1.11 (d, *J* 6.8, 6H).

2-Methyldiphenylamine (18j):[30] 2-Bromotoluene (274 mg, 1.6 mmol) or 2-chlorotoluene (168 μL, 1.6 mmol); aniline (182 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (7.2 mg, 0.008 mmol, 0.5 mol %); toluene (2.0 mL). The general procedure afforded the title compound in 91% yield (267 mg; X = Br) and 83% yield (242 mg; X = Cl); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26−7.18 (m, 4H), 7.13 (t, *J* 8.0, 1H), 6.96−6.87 (m, 4H), 5.36 (s, 1H), 2.25 (s, 3H).

3-Methoxydiphenylamine (18k):[32] 3-Chloroanisole (196 μL, 1.6 mmol); aniline (182 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotylQ-PhosCl (14.4 mg, 0.016 mmol, 1.0 mol %); toluene (2.0 mL). The general procedure afforded the title compound as a white solid in 91% yield (290 mg); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27−7.23 (m, 2H), 7.17−7.13 (m, 1H), 7.10−7.06 (m, 2H), 6.93 (t, *J* 7.2, 1H), 6.65−6.62 (m, 2H), 6.48−6.45 (m, 1H), 5.69 (s, 1H), 3.75 (s, 3H).

4-Cyanodiphenylamine (18l):[23] 4-Bromobenzonitrile (292 mg, 1.6 mmol); aniline (182 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (14.4 mg, 0.016 mmol, 1.0 mol %); toluene (2.0 mL). The general procedure afforded the title compound as an off-white solid (288 mg, 93%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50−7.46 (m, 2H), 7.38−7.34 (m, 2H), 7.17 (d, *J* 7.6, 2H), 7.12 (t, *J* 7.6, 1H), 6.99−6.96 (m, 2H), 6.09 (s, 1H).

2-Aniline-pyridine (18m). 2-Bromopyridine (153 μL, 1.6 mmol) or 2-chloropyridine (151 μL, 1.6 mmol); aniline (182 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (28.8 mg, 0.032 mmol, 2.0 mol %); toluene (2.0 mL). The general procedure afforded the title compound in 94% yield (257 mg; X = Br) and 86% yield (235 mg; X = Cl); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, *J* 4.0, 1H), 7.50−7.46 (m, 1H), 7.33 (d, *J* 4.0, 4H), 7.08−7.02 (m, 2H), 6.89 (d, *J* 8.4, 1H), 6.74−6.71 (m, 1H); ^{13}C ($CDCl_3$, 100 MHz): δ 156.1, 148.4, 140.6, 137.7, 132.5, 129.3, 122.8, 120.7, 120.4, 115.0, 108.2. Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.11; H, 5.99; N, 16.20.

3-Aniline-pyridine (18n). 3-Bromopyridine (154 μL, 1.6 mmol) or 3-chloropyridine (152 μL, 1.6 mmol); aniline (182 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (28.8 mg, 0.032 mmol, 2.0 mol %); toluene (2.0 mL). The general procedure afforded the title compound in 79% yield (215 mg; X = Br) and 88% yield (239 mg; X = Cl): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (d, *J* 2.0, 1H), 8.15 (d, *J* 4.0, 1H), 7.42 (d, *J* 7.2, 1H), 7.30 (t, *J* 7.6, 2H), 7.16 (dd, *J* 8.0, 4.4, 1H), 7.08 (d, *J* 8.0, 2H), 6.99 (t, *J* 7.2, 1H), 6.01 (br s, 1H); ^{13}C ($CDCl_3$, 100 MHz): δ 142.0, 141.8, 140.1, 139.9, 129.6, 123.8, 123.4, 122.0, 118.3. Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.19; H, 6.02; N, 15.96.

2-*N*-Methylaniline-pyrimidine (18o):[33] 2-Bromopyrimidine (127 mg, 0.8 mmol); *N*-methylaniline (109 μL, 1.0 mmol); NaO*t*-Bu (115 mg, 1.2 mmol); Pd(crotyl)Q-PhosCl (14.4 mg, 0.016 mmol, 2.0 mol %); toluene (1.0 mL). The general procedure afforded the title compound in 83% yield (123 mg): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.34 (d, *J* 4.4, 2H), 7.42 (t, *J* 8.0, 2H), 7.32 (d, *J* 7.6, 2H), 7.24−7.22 (m, 1H), 6.57 (t, *J* 4.8, 1H), 3.53 (s, 3H); ^{13}C ($CDCl_3$, 100 MHz): δ 162.0, 157.7, 145.5, 129.2, 126.6, 125.9, 110.8, 38.7. Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.33; H, 6.08; N, 22.51.

2-(*N*-Methyl-*N*-phenylamino)thiophene (18p):[34] 3-Bromothiophene (150 μL, 1.6 mmol) or 3-chlorothiophene (149 μL, 1.6 mmol); *N*-methylaniline (217 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (28.8 mg, 0.032 mmol, 2.0 mol %); toluene (2.0 mL). The general procedure afforded the title compound in 90% yield (272 mg; X = Br) and 57% yield (172 mg; X = Cl): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27−7.20 (m, 3H); 7.01 (d, *J* 7.6, 2H), 6.91 (t, *J* 7.6, 1H), 6.87 (dd, *J* 5.2, 1.6, 1H), 6.57 (dd, *J* 3.2, 1.2, 1H), 3.29 (s, 3H); ^{13}C ($CDCl_3$, 100 MHz): δ 149.3, 148.4, 129.1, 124.9, 123.3, 120.7, 118.8, 107.8, 41.0. Anal. Calcd for $C_{11}H_{11}NS$: C, 69.80; H, 5.86; N, 7.40. Found: C, 70.13; H, 5.84; N, 7.32.

2-Chloro-5-*N*-methylaniline-thiophene (18q). 2-Bromo-5-chlorothiophene (175 μL, 1.6 mmol); *N*-methylaniline (217 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (28.8 mg, 0.032 mmol, 2.0 mol %); toluene (2.0 mL); 25 °C; 20 h. The general procedure afforded the title compound as an off-white oil in 44% yield (155 mg): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26−7.23 (m, 2H), 6.94−6.88 (m, 3H), 6.70 (d, *J* 4.0, 1H), 6.44 (d, *J* 4.0, 1H), 3.28 (s, 3H); ^{13}C ($CDCl_3$, 100 MHz): δ 151.3, 148.8, 129.1, 124.6, 123.3, 120.3, 119.1, 116.1, 41.8. Anal. Calcd for $C_{11}H_{10}ClNS$: C, 59.05; H, 4.51; N, 6.26. Found: C, 59.28; H, 4.54; N, 6.29.

4-Methyldiphenyl-methylamine (18r). 4-Bromotoluene (274 mg, 1.6 mmol); *N*-methylaniline (217 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (0.7 mg, 0.0008, 0.05 mol %); toluene (0.5 mL). The general procedure afforded the title compound in 83% yield (261 mg): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24−7.20 (m, 2H), 7.11 (d, *J* 8.4, 2H), 7.01−6.97 (m, 2H), 6.91 (app d, *J* 7.6, 2H), 6.86 (app t, *J* 7.6, 1H), 3.28 (s, 3H), 2.31 (s, 3H); ^{13}C ($CDCl_3$, 100 MHz): δ 149.4, 146.6, 132.1, 130.0, 129.1, 122.6, 119.8, 118.2, 40.4, 20.8. Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.25; H, 7.75; N, 7.29.

***N*-4-Toluene-2,6-diisopropylaniline (18s).** 4-Bromotoluene (274 mg, 1.6 mmol); 2,6-diisopropylaniline (377 μL, 2.0 mmol); NaO*t*-Bu (230 mg, 2.4 mmol); Pd(crotyl)Q-PhosCl (0.7 mg, 0.0008, 0.05 mol %); toluene (0.5 mL). The general procedure afforded the title compound in 91% yield (387 mg): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30−7.25 (m, 1H), 7.22−7.19 (m, 2H), 6.94 (d, *J* 8.0, 2H), 6.39 (d, *J* 8.4, 2H), 5.02 (br s, 1H), 3.19 (heptet, *J* 6.8, 2H), 2.23 (s, 3H), 1.13 (d, *J* 6.8, 12H); ^{13}C ($CDCl_3$, 100 MHz): δ 147.4, 145.9, 135.6, 129.8, 127.0, 126.9, 123.9, 113.1, 28.2, 23.9, 20.5. Anal. Calcd for $C_{19}H_{25}N$: C, 85.34; H, 9.42; N, 5.24. Found: C, 85.22; H, 9.45; N, 5.29.

Toddaliopsin Hydroxylamine (19). A solution of **18a** (50 mg, 0.16 mmol) was stirred in concd H_2SO_4 (1.0 mL) at room temperature for 2 h. The reaction mixture was then poured into ice−water and carefully neutralized with solid NaOH. The product was extracted with EtOAc (3 × 25 mL), and the organic fractions were combined, dried over Na_2SO_4, and filtered. The filtrate was concentrated and the resulting residue purified by flash column chromatography (1:1 petroleum ether 40−60:EtOAc) to give the title compound as an orange solid (19 mg, 42%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (dd, *J* 8.0, 1.2, 1H), 7.53 (td, *J* 7.6, 1.2, 1H), 7.25−7.21 (m, 1H), 6.75−6.73 (m, 1H), 6.49 (d, *J* 2.0, 1H), 5.81 (d, *J* 2.4, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.60 (s, 3H); ^{13}C ($CDCl_3$, 100 MHz): δ 176.6, 166.3, 156.6, 155.3, 154.7, 151.3, 132.9, 131.2, 124.4, 120.5, 111.4, 99.0, 56.2, 56.0, 52.2; HRMS (ESI) *m*/*z* calcd. $C_{16}H_{15}NO_5$ ($M+1^+$) 302.1028, found 302.1032. Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.70; H, 5.13; N, 4.54.

General Procedure for Suzuki Coupling A. A Schlenk flask was charged with Pd(crotyl)Q-PhosCl (0.72 mg, 0.0008 mmol), *tert*-butylbenzeneboronic acid (313 mg, 1.76 mmol), and KO*t*-Bu (216 mg, 1.9 mmol). The flask was evacuated and backfilled with nitrogen three times, and then 4-bromoanisole (200 μL, 1.6 mmol), toluene (1.8 mL), and water (0.2 mL) were added. The reaction mixture was stirred at room temperature for 40 min, and then an aliquot was removed for analysis by GC/MS. When isolated yield is reported, the same workup as in general procedure B was applied.

General Procedure for Suzuki Coupling B. A Schlenk flask was charged with Pd(allyl)P(*t*-Bu_2)(*p*-$NMe_2C_6H_4$)Cl (4.4 mg, 0.01 mmol), boronic acid (1.2 mmol), and K_2CO_3 (276 mg, 2.0 mmol). The flask was evacuated and backfilled with nitrogen three times, and then aryl chloride (1.0 mmol), toluene (5.0 mL), and water (0.5 mL) were added. The reaction mixture was stirred at room temperature (no external heat source was applied, however, an exothermal reaction was noted in some cases) for 16 h, diluted with MTBE, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated on rotary evaporator. The crude product was purified by flash column chromatography (petroleum ether 40−60:MTBE).

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4-Methoxy-4′-*tert*-butylbiphenyl (20a):[35] Using General Procedure A: The reaction mixture was stirred at room temperature for 1 h, diluted with MTBE, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated on rotary evaporator. The crude product was purified by flash column chromatography (petroleum ether 40−60:MTBE) to give the title compound as a white solid (326 mg, 85% yield): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54−7.48 (m, 4H), 7.45−7.42 (m, 2H), 6.99−6.94 (m, 2H), 3.84 (s, 3H), 1.36 (s, 9H).

1-(2′,4′,6′-Trimethylphenyl)naphthalene (20b):[36] Bromomesitylene (200 μL, 1.3 mmol); 1-naphthaleneboronic acid (303 mg, 1.4 mmol); KO*t*-Bu (216 mg, 1.9 mmol); Pd(crotyl)Q-PhosCl (14.4 mg, 0.013 mmol); toluene (1.8 mL); H_2O (0.2 mL). Using General Procedure A: The reaction mixture was stirred at room temperature for 1 h, diluted with MTBE, and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated on rotary evaporator. The crude product was purified by flash column chromatography (petroleum ether 40−60:MTBE) to give the title compound as a white solid in 86% yield (278 mg): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (d, *J* 8.4, 1H), 7.85 (d, *J* 8.0, 1H), 7.53 (dd, *J* 8.4, 7.2, 1H), 7.46 (td, *J* 5.6, 2.4, 1H), 7.35−7.31 (m, 2H), 7.26 (dd, *J* 6.8, 1.2, 1H), 7.00 (s, 2H), 2.39 (s, 3H), 1.87 (s, 6H).

2-(*p*-*tert*-Butylbenzene)thiophene (20c). 2-Chlorothiophene (92 μL, 1.0 mmol); *tert*-butylbenzeneboronic acid (214 mg, 1.2 mmol); K_2CO_3 (276 mg, 2.0 mmol); Pd(allyl)P(*t*-Bu_2)(*p*-$NMe_2C_6H_4$)Cl (4.4 mg, 0.01 mmol); toluene (5.0 mL); H_2O (0.5 mL). The general procedure B afforded the title compound in 64% yield (139 mg): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56−7.54 (m, 2H), 7.41−7.39 (m, 2H), 7.27 (dd, *J* 3.6, 1.2, 1H), 7.24 (dd, *J* 5.2, 1.2), 1.34 (s, 9H); ^{13}C ($CDCl_3$, 100 MHz): δ 148.3, 142.2, 129.4, 125.7, 123.6, 123.5, 123.4, 122.1, 120.4, 32.3, 29.1. Anal. Calcd for $C_{14}H_{16}S$: C, 77.72; H, 7.45. Found: C, 78.30; H, 7.64.

2-(*p*-Toluene)thiophene (20d):[22] 2-Chlorothiophene (92 μL, 1.0 mmol); *p*-tolueneboronic acid (163 mg, 1.2 mmol); K_2CO_3 (276 mg, 2.0 mmol); Pd(allyl)P(*t*-Bu_2)(*p*-$NMe_2C_6H_4$)Cl (4.4 mg, 0.01 mmol); toluene (5.0 mL); H_2O (0.5 mL). The general procedure B afforded the title compound in 70% yield (122 mg): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52−7.49 (m, 2H), 7.27 (dd, *J* 3.6, 0.8, 1H), 7.24 (dd, *J* 5.2, 1.2, 1H), 7.19−7.17 (m, 2H), 7.06 (dd, *J* 5.2, 3.6, 1H), 2.37 (s, 3H).

2-(*p*-Toluene)benzonitrile (20e):[22] 2-Chlorobenzonitrile (137 mg, 1.0 mmol); *p*-tolueneboronic acid (163 mg, 1.2 mmol); K_3PO_4 (425 mg, 2.0 mmol); Pd(allyl)P(*t*-Bu_2)(*p*-$NMe_2C_6H_4$)Cl (0.044 mg, 0.0001 mmol); toluene (5.0 mL); H_2O (0.5 mL). The general procedure B afforded the title compound in 85% yield (165 mg): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76−7.74 (m, 1H), 7.63 (td, *J* 8.0, 1.2, 1H), 7.51−7.49 (m, 1H), 7.46 (d, *J* 8.0, 2H), 7.42 (td, *J* 7.6, 0.8, 1H), 7.30 (d, *J* 8.0, 2H), 2.42 (s, 3H).

3-(*p*-*tert*-Butylbenzene)pyridine (20f):[37] 3-Chloropyridine (94 μL, 1.0 mmol); *tert*-butylbenzeneboronic acid (214 mg, 1.2 mmol); K_2CO_3 (276 mg, 2.0 mmol); Pd(allyl)P(*t*-Bu_2)(*p*-$NMe_2C_6H_4$)Cl (4.4 mg, 0.01 mmol); toluene (5.0 mL); H_2O (0.5 mL). The general procedure B afforded the title compound in 73% yield (154 mg): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.85 (d, *J* 2.4, 1H), 8.57 (dd, *J* 4.8, 1.6, 1H), 7.87 (dt, *J* 8.0, 1.6, 1H), 7.55−7.50 (m, 4H), 7.35 (dd, *J* 7.6, 4.8, 1H), 1.37 (s, 9H).

Representative Procedure for α-Arylation. A Schlenk flask was charged with Pd(X)LCl (0.05 mol %, 0.001 mmol) and NaO*t*-Bu (365 mg, 3.8 mmol). The flask was evacuated and backfilled with nitrogen three times, and then dioxane (2.0 mL), 4-chloroanisole (245 μL, 2.0 mmol), and α-tetralone (266 μL, 2.0 mmol) were added. The reaction mixture was stirred for 16 h, and then an aliquot was removed for analysis by GC/MS.

2-(4′-Methoxyphenyl)tetralone (21):[38] Pd(allyl)P(*t*-Bu_2)(*p*-$NMe_2C_6H_4$)Cl (0.44 mg). Following the general procedure for α-arylation, the reaction mixture was filtered through a plug of silica gel and washed with MTBE. The filtrate was concentrated to give the title compound without further purification necessary (558 mg, 91%): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (dd, *J* 8.0, 1.2, 1H), 7.50 (td, *J* 7.2, 1.2, 1H), 7.36−7.27 (m, 2H), 7.13−7.10 (m, 2H), 6.91−6.88 (m, 2H), 3.80 (s, 3H), 3.75 (t, *J* 8.0, 1H), 3.16−3.01 (m, 2H), 2.46−2.38 (m, 2H).

Mechanistic Investigations. *General Procedure for the Preparation of Reaction Intermediates* ***24***−***27***. To a Schlenk flask containing Pd(R-allyl)LCl (0.5 mmol) and NaO*t*-Bu (0.6 mmol) were added under N_2 4-bromoanisole (0.5 mmol) and toluene (4.0 mL). The reaction mixture was stirred for 16 h at room temperature, the reaction mixture was filtered on Celite, and the Celite was washed with toluene. The toluene filtrate was concentrated using rotary evaporator, and the resulting solid was triturated with large amounts of hexane. The final product was analyzed by ^{31}P NMR and X-ray crystal structure determination.

*Pd(μ-Br)(μ-C_3H_5)P(t-Bu)$_2$Np (**24**).* Crystals were grown from slow evaporation of a concentrated hexane solution (CCDC 809993). ^{31}P NMR (C_6D_6, 162 MHz): δ 53.1.

*Pd(μ-Cl)(μ-C_3H_5)Amphos (**26**).* Crystals were grown from slow diffusion of hexane into a CH_2Cl_2 solution (CCDC 809991). ^{31}P NMR (C_6D_6, 162 MHz): δ 67.6.

*Pd(μ-Br)(μ-C_3H_5)Amphos (**27**).* Crystals were grown from slow diffusion of hexane into a CH_2Cl_2 solution (CCDC 809992). ^{31}P NMR (C_6D_6, 162 MHz): δ 70.4.

NMR Studies of Amination Reactions. See Supporting Information for NMR spectra.

Reaction 1: Catalyst + NaOt-Bu. The catalyst (0.015 mmol) and NaO*t*-Bu (0.022 mmol) were weighed outside the glovebox and put in a scintillation vial. The vial was then transferred into the glovebox, and C_6D_6 (0.6 mL) was added to the catalyst and the NaO*t*-Bu. The resulting mixture was transferred to a screw-cap NMR tube, which was further sealed with PTFE tape. The NMR tube was removed from the glovebox and analyzed by ^{1}H and ^{31}P NMR after 20 min.

Reaction 2: Catalyst + NaOt-Bu + 4-Bromoanisole. The catalyst (0.015 mmol) and NaO*t*-Bu (0.022 mmol) were weighed outside the glovebox and put in a scintillation vial. 4-Bromoanisole (0.020 mmol) was measured by microsyringe into a second vial. Both vials were transferred into the glovebox, where the 4-bromoanisole was dissolved in C_6D_6 (0.6 mL) and added to the vial containing the catalyst and NaO*t*-Bu. The resulting reaction mixture was transferred into a screw-cap NMR tube which was further sealed with PTFE tape, removed from the glovebox, and analyzed by ^{1}H and ^{31}P NMR after 30 min.

Reaction 3: Catalyst + NaOt-Bu + 4-Bromoanisole + N-Methylaniline. The catalyst (0.06 mmol) and NaO*t*-Bu (1.0 mmol) were weighed outside the glovebox and put in a scintillation vial. 4-Bromoanisole (0.80 mmol) and *N*-methylaniline (1.02 mmol) were measured into a second vial, and both vials were subsequently transferred into the glovebox. 4-Bromoanisole and *N*-methylaniline were dissolved in degassed toluene (1.0 mL), and the solution was transferred to the vial containing the catalyst and NaO*t*-Bu. The reaction mixture was left for 10 min, and then a 0.3 mL aliquot was transferred to a screw-cap NMR tube and diluted with 0.4 mL of C_6D_6. The NMR tube was sealed with PTFE tape, removed from the glovebox, and analyzed by ^{31}P NMR.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra for compounds **8**−**21** and **24**−**27**, X-ray crystal data for **8**, **9**, **10**, **24**, **26**, and **27** (.cif). ^{1}H and ^{31}P NMR spectra from mechanistic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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