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Scope and Mechanism of Palladium-Catalyzed Amination of Five-Membered Heterocyclic Halides

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Received October 30, 2002

Detailed studies have been conducted to determine the activity of palladium catalysts for the amination of five-membered heterocyclic halides and to determine the factors that control the scope of this reaction. Palladium-catalyzed aminations of the electron-rich furanyl, thiophenyl, and indolyl halides and of the related 2-halogenated thiazoles, benzimidazole, and benzoxazole have been shown to occur with a subset of amines. Various combinations of palladium precursors and P^tBu_3 were tested as catalysts for reaction of 3-bromothiophene with *N*-methylaniline, and the fastest reactions occurred with the Pd(I) dimer, $[PdBr(P^tBu_3)]_2$. The fastest aminations of thiazoles, benzimidazoles, and benzoxazoles occurred with the combination of palladium trifluoroacetate and P^tBu_3 as catalyst.

Introduction

The palladium-catalyzed amination of aryl halides with a large range of aryl halides and amines has been extensively investigated in recent years.[1−5] Third-generation ligands such as P^tBu_3,[6−8] biphenylP^tBu_2,[9] and heterocyclic carbenes[10,11] create catalysts with increased activity and allow milder conditions to be used. For example, reactions can be run at room temperature, with low catalyst loading, and with previously inactive substrates, such as aryl chlorides.[6−10,12] In contrast, the application of this methodology to heteroaromatic substrates such as halofurans, -thiophenes, -pyrroles, -indoles, -thiazoles, and -imidazoles has been limited.

Five-membered heteroaryl groups are common in natural products and pharmaceutical targets.[13−16] These groups often act as surrogates for a phenyl group and tune the properties of the molecule.[17] Heteroaromatic amines also show novel intrinsic electronic properties.[18−20] Many of the classical routes to heteroarylamines are limited in scope or occur at high temperatures. Although uncatalyzed amination of pyridyl and related six-membered heterocyclic halides can occur at high temperatures or pressures,[21] direct amination of five-membered heteroaryl halides containing a single heteroatom is restricted to systems containing strongly electron-withdrawing substituents, such as nitro or acyl groups.[22] Various systems have been developed for the arylation of amines with stoichiometric amounts of copper and heteroaryl boronic acids or tin reagents instead of heteroaryl halides.[23,24] However, the substrate tolerance is limited, and aryltin reagents are highly toxic. Some electrophilic aminations of heteroaromatic carbanions have also been performed.[25,26] This reaction requires more complex amine reagents and strongly basic conditions for formation of the carbanions. Finally, some multistep, indirect syntheses of heteroaromatic amines have been reported.[27,28]

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10.1021/jo0266339 CCC: $25.00
Published on Web 03/13/2003

Watanabe reported that unfunctionalized bromothiophenes react with diarylamines in the presence of catalysts bearing P^tBu_3 as ligand, but yields were moderate, and no reactions of furanyl or indolyl halides were reported.[29] Luker[30] demonstrated that conjugated, electron-deficient bromothiophenes react with a range of amines in the presence of palladium and BINAP as catalyst and Cs_2CO_3 as base but did not report reactions of electron-neutral bromothiophenes. Rasmussen[31] has shown that palladium and P^tBu_3 is a superior catalyst for the amination of 3-bromothiophene, but did not report reactions of other isomers or other five-membered heterocycles.

The amination of heteroaromatic halides containing two oxygen, nitrogen, or sulfur atoms, such as halothiazoles or -imidazoles, has been equally limited,[32−34] despite the importance of 2-amino-thiazoles and -imidazoles in pharmaceutical applications.[15,35] Most reported aminations of these heterocyclic halides have been conducted with BINAP as ligand; only one published[33] and one patented[36] example conducted with palladium catalysts bearing sterically hindered monodentate ligands have been reported, and no studies that evaluate the scope of these aminations with these recently developed catalysts have been conducted. It is unclear if catalysts containing these ligands would show high activity for reactions of heteroaryl halides. They could display high activity for the same reasons they are highly active for reactions of deactivated aryl halides, or they could display low activity if the hindered ligand is displaced by the heterocyclic substrate.

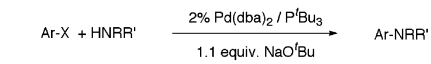
This paper delineates in a more comprehensive manner the scope of the formation of heteroarylamines from halofurans, -thiophenes, -pyrroles, -indoles, -thiazoles, and -imidazoles. In addition, we conducted both qualitative and quantitative kinetic studies on the reactions catalyzed by various combinations of palladium precursors and P^tBu_3. These studies revealed the classes of amines and five-membered heteroaryl halides that undergo the amination and ruled out several likely palladium complexes as active species in these reactions.

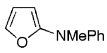
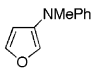
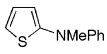
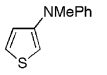
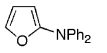
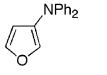
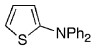
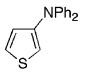
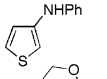
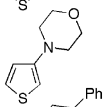
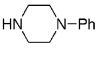
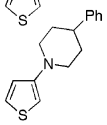
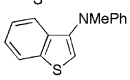
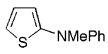
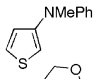
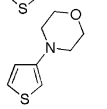
Results

Evaluation of Reaction Scope. 1. Reactions of Halofurans, -thiophenes, and -indoles. Aminations of simple, unactivated bromofurans and bromothiophenes in the presence of catalytic amounts of $Pd(dba)_2$ and P^tBu_3 in a 1:1 ratio are summarized in Table 1. Reactions of bromofurans and -thiophenes with *N*-methylaniline occurred at room temperature (Table 1, entries 1−4). Reactions of chlorothiophenes with this amine required 120 °C to ensure complete conversion (entries 13 and 14). Reactions of bromofurans and -thiophenes with diarylamines occurred at 100 °C. Isolated yields of 2-aminofurans (entries 1 and 5) were somewhat lower than the isolated yields of aminothiophenes because of the difficulty in isolating these acid and slightly air-sensitive amines. In general, 3-bromothiophene reacted in higher yields (entries 4 and 8) and broader scope than other five-membered heteroaryl halides. Most striking, 3-bromothiophene reacted with aniline (entries 9), but no reaction was observed between 2-bromothiophene, 2-bromofuran, or 3-bromofuran and aniline, even at 100 °C over several days.

Reactions of bromofurans and thiophenes with primary or secondary alkylamines in the presence of P^tBu_3 and $Pd(dba)_2$ as catalyst were also evaluated. Little or no

TABLE 1. Amination of Heteroaryl Halides with $Pd(dba)_2/P^tBu_3$



Entry	Aryl Halide	Amine	Product	Cond.	Yield [a]
1		HNMePh		rt 16 h	56% (80%)
2		HNMePh		rt 16 h	85%
3		HNMePh		rt 16 h	82%
4		HNMePh		rt 16 h	93%
5		$HNPh_2$		100 °C 16 h	51% (85%)
6		$HNPh_2$		100 °C 16 h	55% (94%)
7		$HNPh_2$		100 °C 16 h	63% (78%)
8		$HNPh_2$		100 °C 16 h	97% (99%)
9		H_2NPh		100 °C 16 h	88%
10				120 °C 24 h	77% [c]
11 [b]				120 °C 24 h	40% [c]
12 [b]		HNMePh		rt 20 h	84% [c]
13 [b]		HNMePh		120 °C 24 h	49% [c]
14 [b]		HNMePh		120 °C 24 h	50% [c]
15 [b]				120 °C 30 h	41% [c]

[a] Isolated yields (GC yields). [b] 5 mol % of catalyst. [c] Average of 2 runs.

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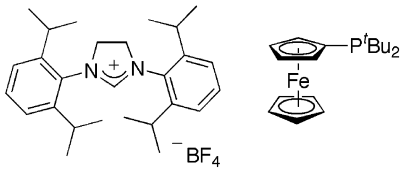


FIGURE 1. Two ligands tested in the amination of heteroaryl halides.

arylamine was observed from reaction of hexylamine, dibutylamine, piperidine, or morpholine with most of the heteroaryl halides. However, 3-halothiophenes did react with cyclic secondary amines such as morpholine and 4-phenylpiperazine (entries 10, 11, and 15). Dibutylamine and hexylamine also reacted with 3-bromothiophene, but the yields (ca. 20−30%) were lower than those from reactions of cyclic secondary amines.

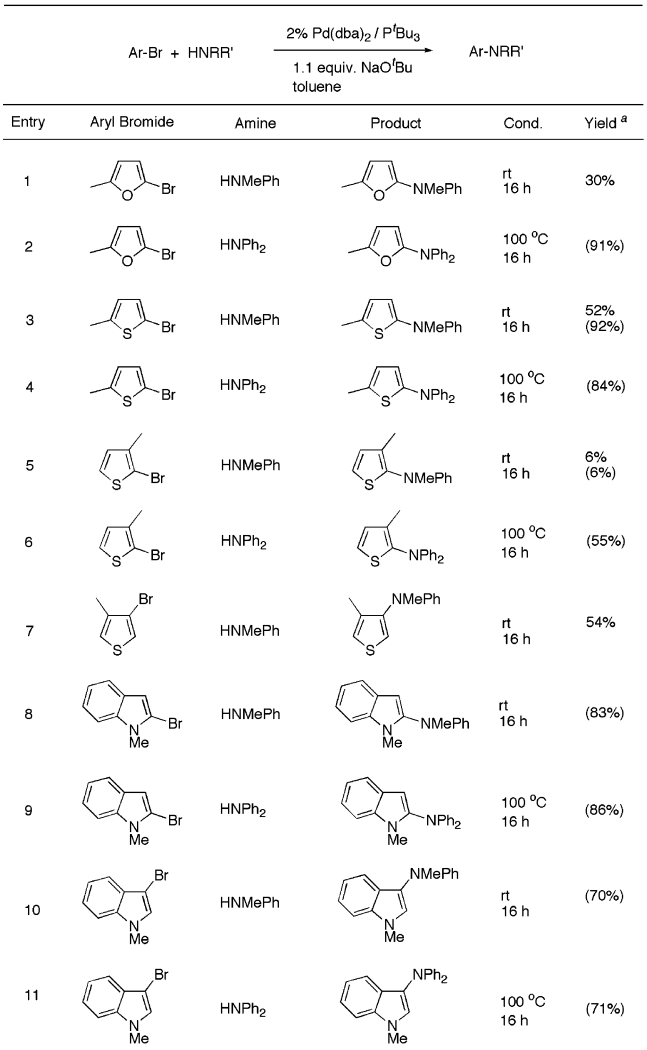
Various alternative catalysts were tested for the amination of bromofurans and thiophenes. Complexes generated from P^{t}Bu$_3$, and Pd(OAc)$_2$ or Pd(dba)$_2$ were tested as catalysts for the reaction of 3-bromothiophene with *N*-methylaniline. Similar yields of 3-(*N*-methyl-*N*-phenylamino)thiophene were observed in both cases, but significantly slower rates were observed for reactions catalyzed by the combination of P^{t}Bu$_3$ and Pd(OAc)$_2$. Reactions of bromothiophenes and bromofurans with *N*-methylaniline in the presence of catalysts comprised of Pd(dba)$_2$ and the carbene or ferrocenyldi-*tert*-butylphosphine ligands in Figure 1 occurred in lower yields than reactions of these heteroaryl bromides with *N*-methylaniline in the presence of P^{t}Bu$_3$ and Pd(dba)$_2$. We also evaluated reactions of *N*-methylaniline catalyzed by the combination of DPPF or BINAP and Pd(dba)$_2$ or Pd(OAc)$_2$. Low to moderate yields and slow rates were observed. Reactions attempted in the presence of triethylamine, cesium carbonate, and sodium phenoxide as base all failed to form any coupled product between this amine and bromofurans or bromothiophenes.

Table 2 summarizes our results on the amination of some methyl-substituted bromofurans, methyl-substituted bromothiophenes, and *N*-methyl bromoindoles. This simple substitution on the heterocycle led to differences in rates and yields that were large in some cases and that depended on the position of the methyl group. Again, reactions of these heteroaromatic halides with *N*-methylaniline proceeded to completion at room temperature, whereas reactions of these substrates with diarylamines required heating at 100 °C.

5-Methyl-2-bromofuran displayed similar reactivity to the unsubstituted 2-bromofuran (Table 2, entries 1 and 2), and 5-methyl-2-bromothiophene displayed similar reactivity to the parent 2-bromothiophene (Table 2, entries 3 and 4). Isolated yields of the 5-methyl-2-aminofurans were lower than the isolated yields of the parent 2-aminofurans and 2-aminothiophenes simply because the methyl-substituted products were more prone to decomposition.

In contrast, a large difference was observed between the reactivity of 3-methyl-2-bromothiophene (Table 2, entry 7) and the reactivity of the unsubstituted parent 2-bromothiophene (Table 1, entry 3) toward *N*-methylaniline. A low yield (6%) of coupled product was obtained from the reaction of 2-bromo-3-methylthiophene and

TABLE 2. Amination of Heteroaryl Bromides with Pd(dba)$_2$/P^{t}Bu$_3$



Entry	Aryl Bromide	Amine	Product	Cond.	Yield [a]
1		HNMePh		rt 16 h	30%
2		$HNPh_2$		100 °C 16 h	(91%)
3		HNMePh		rt 16 h	52% (92%)
4		$HNPh_2$		100 °C 16 h	(84%)
5		HNMePh		rt 16 h	6% (6%)
6		$HNPh_2$		100 °C 16 h	(55%)
7		HNMePh		rt 16 h	54%
8		HNMePh		rt 16 h	(83%)
9		$HNPh_2$		100 °C 16 h	(86%)
10		HNMePh		rt 16 h	(70%)
11		$HNPh_2$		100 °C 16 h	(71%)

[a] Isolated yields (GC yields).

N-methylaniline. The major product was the amidine PhN=C(H)NMePh formed from the known[37] metal-mediated disproportionation of the unstable imine CH$_2$=N(H)Ph, which would result from β-hydride elimination of the palladium *N*-methylanilide intermediate. This result is in contrast with the reactions of *N*-methylaniline with *o*-tolyl bromides and phenyl bromide[6−8] that both occur in high yield; a single ortho-substituent often leads to faster reductive elimination[38] and higher yields in the amination chemistry.[8,9,39] In contrast to the reaction of 2-bromo-3-methylthiophene with *N*-methylaniline, the reaction of 3-bromo-4-methylthiophene with *N*-methylaniline provided a substantial 54% yield of the coupled product. Thus, the position of the pseudo-ortho methyl group has a larger affect on the yield of aminothiophenes than does the position of the halide.

Reactivities of 2- and 3-bromo-*N*-methylindoles were similar to those of 2- and 3-bromofurans and thiophenes

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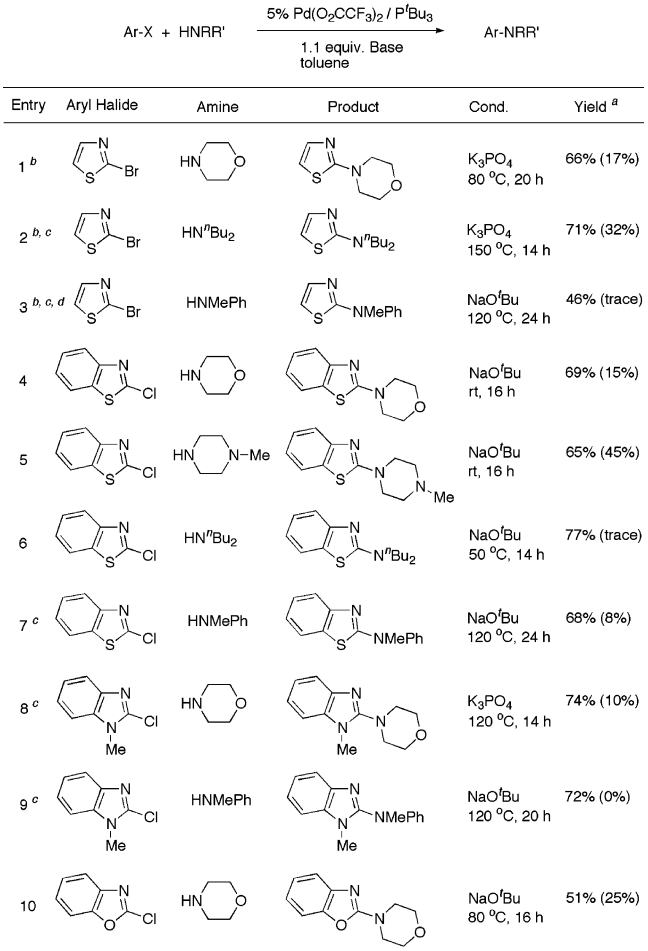
in amination reactions catalyzed by P^tBu_3 and $Pd(dba)_2$. *N*-Methylindoles were used instead of the parent indoles to prevent competition between the reacting amine and an indole N−H. Reactions of the free bromoindole with amines did not produce any product from coupling with the amine. Reactions of 2- and 3-bromo-*N*-methylindoles with *N*-methylaniline occurred at room temperature, whereas reactions of 2- and 3-bromo-*N*-methylindoles with diphenylamine occurred at 100 °C. Little or no reaction of these bromoindoles was observed with primary or secondary alkylamines or with primary arylamines. The reaction of 2-bromo-*N*-methylindole with *N*-methylaniline or diphenylamine produced slightly higher yields of coupled product than did the reaction of 3-bromo-*N*-methylindole with these amines (Table 2, entries 8−11). Studies on the reactions of 2- and 3-bromopyrrole were not conducted because of the instability of these substrates.

2. Amination of Thiazoles, Benzimidazoles, and Oxazoles. Substrates containing two heteroatoms in a five-membered ring are less electron-rich than furans, thiophenes, and indoles. Thus, we compared the palladium-catalyzed aminations of halothiazoles and -imidazoles to those of halofurans and -thiophenes and to those of uncatalyzed reactions (Table 3). Reaction conditions that were different from those for the amination of halothiophenes, furans, and indoles were required because 2-bromothiazole decomposed in the presence of the strong base NaO^tBu. The yield of coupled product in the presence of NaO^tBu and the combination of $Pd(dba)_2$ and P^tBu_3 as catalyst was less than 20%. After testing various bases and palladium precursors, we obtained 70% yield of coupled product from the reaction of 2-bromothiazole with dibutylamine in the presence of K_3PO_4 and catalytic amounts of $Pd(O_2CCF_3)_2$ and P^tBu_3 (Table 3, entry 2). This palladium precursor has rarely been used in coupling chemistry, but did provide yields for these amination processes that were superior to those obtained with $Pd(OAc)_2$ (57%) or $Pd(dba)_2$ (35%). The combination of $Pd(O_2CCF_3)_2$ and P^tBu_3 was also effective for the reaction of morpholine with 2-bromothiazole (Table 3, entry 1). In contrast to reactions of furans, thiophenes, and indoles, which occurred in higher yield with *N*-methyl aniline than with dialkylamines, reactions of bromothiazole with *N*-methyl aniline occurred in lower yield than reactions with dialkylamines. Reactions of *N*-methylaniline were most favorable with NaO^tBu as base, $Pd(OAc)_2$ as precursor, and ferrocenyl-di-*tert*-butylphosphine as ligand. Under these conditions, 46% yield of the coupled product was isolated. Reactions of thiazoles and imidazoles with primary alkyl- and arylamines in the presence of catalysts containing $Pd(dba)_2$, $Pd(OAc)_2$, or $Pd(O_2CCF_3)$ and either P^tBu_3, ferrocenyl di-*tert*-butylphosphine, pentaphenylferrocenyl di-*tert*-butylphosphine, biphenylP^tBu_2, BINAP, or DPPF occurred in low yields.

Reactions of related benzo-fused 2-haloheteroaryl compounds with secondary amines were also evaluated (Table 3, entries 4−10). 2-Chlorobenzothiazole and 2-chloro-*N*-methylbenzimidazole both reacted with the cyclic secondary amine morpholine and the *N*-alkylarylamine *N*-methyl aniline in good yield. 2-Chlorobenzothiazole also reacted with dibutylamine. Reactions of the benzothiazole were best conducted with NaO^tBu as base,

TABLE 3. Amination of Heteroaryl Halides with $Pd(O_2CCF_3)_2/P^tBu_3$



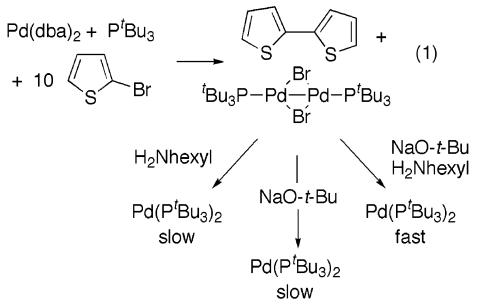
Entry	Aryl Halide	Amine	Product	Cond.	Yield [a]
1 [b]				K_3PO_4 80 °C, 20 h	66% (17%)
2 [b, c]		HN^nBu_2		K_3PO_4 150 °C, 14 h	71% (32%)
3 [b, c, d]		HNMePh		NaO^tBu 120 °C, 24 h	46% (trace)
4				NaO^tBu rt, 16 h	69% (15%)
5				NaO^tBu rt, 16 h	65% (45%)
6		HN^nBu_2		NaO^tBu 50 °C, 14 h	77% (trace)
7 [c]		HNMePh		NaO^tBu 120 °C, 24 h	68% (8%)
8 [c]				K_3PO_4 120 °C, 14 h	74% (10%)
9 [c]		HNMePh		NaO^tBu 120 °C, 20 h	72% (0%)
10				NaO^tBu 80 °C, 16 h	51% (25%)

[a] Isolated yields which are an average of 2 runs (yields without catalyst). [b] 4 equiv of amine was used. [c] Xylene was used as solvent. [d] $Pd(OAc)_2$ and ferrocenyl di-*tert*-butylphosphine ligand were used.

while the reaction of the benzimidazole with morpholine (entry 8) was best conducted with K_3PO_4. In addition, the reaction of 2-chlorobenzoxazole with morpholine gave the coupled product in substantial yield (Table 3, entry 10). Reactions of other five-membered heterocyclic halides were limited. Reactions of dibutylamine with 2-chloroimidazole and reactions of dibutylamine or *N*-methylaniline with 2-chlorooxazole gave the heteroarylamine in less than 30% yield. Moreover, reactions of amines with 4-bromo- or 5-bromoimidazoles and 3-choloro-isobenzothiazole did not occur in the presence of palladium and P^tBu_3.

Many of the reactions of thiazoles and imidazoles with amines proceeded to partial conversions without catalyst, but the palladium-catalyzed reactions occurred under milder conditions or in improved yields or both. In some cases (Table 3, entries 3, 6, and 9), catalytic conditions were required to generate any amination product. In no case did reaction of the electron-rich halofurans or thiophenes occur without catalyst, and the thermal sensitivity limits direct aminations of 2- or 3-bromoindoles.

SCHEME 1



Mechanistic Studies. Catalytic reactions were monitored in situ by ^{1}H and ^{31}P NMR spectroscopy to determine how the catalyst resting state and the fate of the catalyst and substrates varied between reactions that formed coupled product and reactions that did not form coupled product. In addition, the dependence of reaction rate on the concentration of base and amine was evaluated.

Generation of the Catalyst from Pd(dba)$_2$ and P^{t}Bu$_3$ and Reactions with Bromothiophene. A 1:1 ratio of Pd(dba)$_2$ and P^{t}Bu$_3$ forms Pd(P^{t}Bu$_3$)$_2$ and leaves half of the Pd(dba)$_2$ unreacted.[40,41] This equilibrium required only 5 min to be established in tetrahydrofuran-d_8, but required about 1 h to be established in benzene-d_6 or toluene, most likely because of the lower solubility of Pd(dba)$_2$ in aromatic solvents. Reaction of the equilibrated mixture of Pd(P^{t}Bu$_3$)$_2$ and Pd(dba)$_2$ with 2-bromothiophene formed a green solution containing [PdBr(P^{t}Bu$_3$)]$_2$ (eq 1).[42−44] This material was isolated in 83% yield as dark green crystals. 2,2′-Bithiophene was identified as a byproduct by ^{1}H NMR spectroscopy. This reaction provides a practical synthesis of the Pd(I) dimer from commercially available materials. A similar reaction was observed when aryl bromides were allowed to react with a combination of Pd(dba)$_2$ and P^{t}Bu$_3$.[44,45] However, this reaction required an excess of aryl bromide and heating to ensure complete conversion to [PdBr(P^{t}Bu$_3$)]$_2$. The Pd(I) dimer is only moderately air-sensitive as a solid. Standing in air for 72 h resulted in only about 25% decomposition.

Reactions of 2-bromothiophene or phenyl bromide with Pd(dba)$_2$ and P^{t}Bu$_3$ in the presence of *N*-methylaniline, aniline, or hexylamine formed only small amounts of the palladium(I) dimer [PdBr(P^{t}Bu$_3$)]$_2$. The same reactions in the presence of NaO^{t}Bu instead of amine formed Pd(P^{t}Bu$_3$)$_2$ and no Pd(I) dimer. No reaction occurred between the isolated Pd(I) dimer and the heteroaryl halides. Reaction of the dimer with hexylamine or NaO^{t}Bu occurred slowly and with low conversion to Pd(P^{t}Bu$_3$)$_2$ (Scheme 1). In contrast, reaction of the dimer with hexylamine and NaO^{t}Bu together formed Pd(P^{t}Bu$_3$)$_2$ at room temperature. We did not determine the identity of the remaining palladium in these transformations.

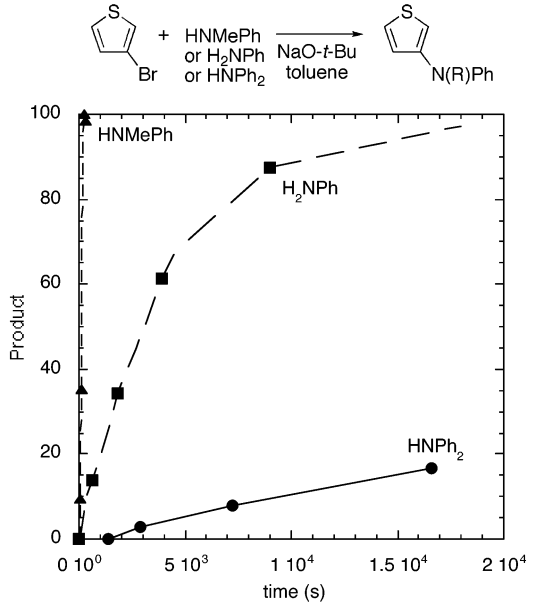


FIGURE 2. Comparison of rates for reaction of arylamines with 3-bromothiophene catalyzed by a combination of Pd(dba)$_2$ and P^{t}Bu$_3$.

Monitoring by NMR Spectroscopy of Amination Reactions Catalyzed by Pd(dba)$_2$ and P^{t}Bu$_3$. Aminations of the heteroaryl halides were monitored by ^{1}H and ^{31}P NMR spectroscopy with P(mesityl)$_3$ as an internal reference in benzene-d_6 solvent. Prior to addition of the reagents, the combination of Pd(dba)$_2$ and P^{t}Bu$_3$ was allowed to stir for 1 h. In all reactions, the major phosphine-ligated palladium complex in solution was Pd(P^{t}Bu$_3$)$_2$. This species accounted for greater than 90% of the phosphorus signals. Approximately 5% of the signal was due to free P^{t}Bu$_3$. Integration of these signals vs that of the internal standard showed that 75% or more of the P^{t}Bu$_3$ that was added to the system was present as Pd(P^{t}Bu$_3$)$_2$.

1. Influence of the Heteroaryl Halide. Both the reactions that gave coupled product, such as the reaction of 2-bromofuran with *N*-methylaniline, and the reactions that gave little or no coupled product, such as the reaction of 2-bromofuran with H$_2$NPh, contained Pd(P^{t}Bu$_3$)$_2$ as the major phosphine-ligated complex in solution. The reaction of 2-bromofuran with *N*-methylaniline, which generated 80% yield of *N*-methyl *N*-phenyl-2-aminofuran, and the reaction of 2-bromofuran with H$_2$NPh, which gave no *N*-phenyl-2-aminofuran, catalyzed by Pd(dba)$_2$ and P^{t}Bu$_3$ at room temperature were monitored in detail by ^{1}H NMR spectroscopy and by GC. The reaction of *N*-methylaniline with 2-bromofuran was complete within 30 min, while the reaction of aniline with 2-bromofuran consumed less than 10% of the heteroaryl bromide after 24 h at 100 °C. A similar difference in rate was observed between reactions of 3-bromothiophene with *N*-methylaniline and reactions of 3-bromothiophene with either aniline or diphenylamine (Figure 2). These reactions all produced coupled product, but the half-life for the reactions catalyzed by a 1:1 combination of Pd(dba)$_2$ and P^{t}Bu$_3$ differed by a factor of approximately 300 between

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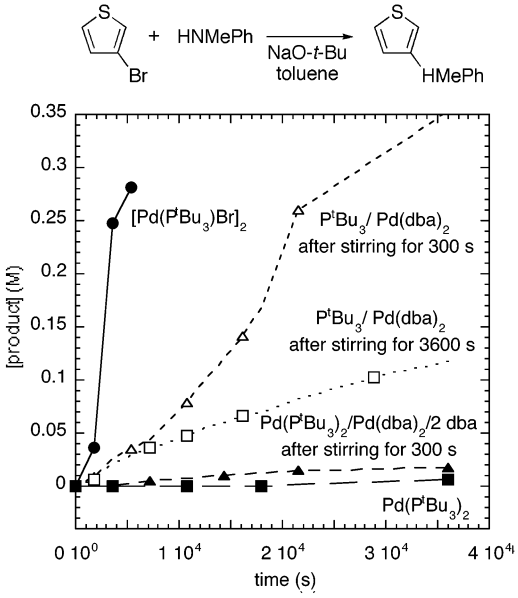

FIGURE 3. Reaction of 3-bromothiophene with *N*-methylaniline in the presence of five different catalyst precursors containing palladium and P^{t}Bu$_3$.

the reaction of *N*-methylaniline, which was the fastest, and the reaction of diphenylamine, which was the slowest.

A dramatic difference in rate was also detected for reactions of isomeric halofurans and thiophenes. For example, the palladium-catalyzed reaction of diphenylamine with 2-bromofuran was faster than the reaction of diphenylamine with 3-bromofuran. In contrast, the palladium-catalyzed reactions of 3-bromothiophene with diphenylamine or *N*-methylaniline were faster than the reactions of 2-bromothiophene with these amines. These differences in rates parallel the differences in yields for catalytic reactions of the isomeric thiophenes in Table 1 and parallel the rates and yields for stoichiometric reductive elimination from heteroarylpalladium amides reported separately.[46]

2. Influence of Catalyst Precursor. To begin to understand the relationship between the catalyst precursor and the composition of the active catalyst, we monitored the reaction of *N*-methylaniline with 3-bromothiophene in benzene-d_6 in the presence of five different combinations of P^{t}Bu$_3$ and palladium. These data are presented in Figure 3. Reactions catalyzed by the palladium(I) dimer [PdBr(P^{t}Bu$_3$)]$_2$[42,44] were the fastest. Reactions catalyzed by a 1:1 ratio of Pd(dba)$_2$ and P^{t}Bu$_3$ were slower but occurred to completion. With this combination of precursors, the reaction rate depended on the time that the catalyst and ligand were mixed prior to addition of the reagents. As noted above, complete conversion of Pd(dba)$_2$ or Pd$_2$(dba)$_3$ and P^{t}Bu$_3$ to Pd[P(^{t}Bu)]$_3$ in toluene solvent required about 1 h because the palladium precursor is only modestly soluble in toluene. Catalytic reactions conducted after allowing Pd(dba)$_2$ and P^{t}Bu$_3$ to mix for 5 min proceeded about three times faster than reactions conducted after allowing Pd(dba)$_2$ and P^{t}Bu$_3$ to mix for 1 h. Reactions conducted in the presence of pure Pd(P^{t}Bu$_3$)$_2$ were considerably slower. Reactions conducted in the presence of a combination of Pd(P^{t}Bu$_3$)$_2$ and Pd(dba)$_2$ were faster than those catalyzed by Pd(P^{t}Bu$_3$)$_2$ alone, but they were slower than those catalyzed by the Pd(I) species or mixtures of Pd(dba)$_2$ and P^{t}Bu$_3$. Pd(dba)$_2$, Pd(OAc)$_2$, or Pd(trifluoroacetate)$_2$ without added ligand did not catalyze the reaction between any heteroaryl bromide and *N*-methylaniline. Although large differences in rate were observed for reactions containing these different catalyst compositions, the fastest catalysts did not broaden the scope of the reaction.

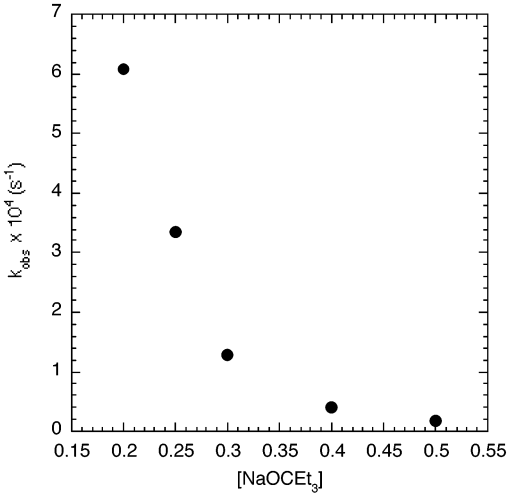

FIGURE 4. k_{obs} vs [NaOCEt$_3$] for the reaction of *N*-methylaniline (0.025 M) with 2-bromothiophene (0.8 M) catalyzed by 10% of Pd(P^{t}Bu$_3$)$_2$ at 75 °C.

Monitoring of Reactions under Pseudo-First-Order Conditions by ^{1}H NMR Spectroscopy. To correlate aminations of the heteroaryl halides with aminations of aryl halides, we measured the reaction orders in amine and base. We have recently reported kinetic studies on the reactions of *N*-methylbenzylamine with phenyl chloride catalyzed by Pd(P^{t}Bu$_3$)$_2$ and by a 1:1 ratio of Pd(dba)$_2$ and P^{t}Bu$_3$.[47] These studies revealed a zero-order dependence of the rate on the concentration of amine and a combination of first- and zero-order dependence on the concentration of base. Rates for reaction of 2-bromothiophene with *N*-methylaniline were measured at 75 °C in benzene-d_6 solvent in the presence of NaOCEt$_3$ as a soluble base and Pd(P^{t}Bu$_3$)$_2$ as catalyst. Final concentrations of the reaction components were 2.50 mM Pd(P^{t}Bu$_3$)$_2$, 0.20−0.50 M NaOCEt$_3$, 0.80 M 2-bromothiophene, and 0.025 M *N*-methylaniline. Both decay of amine and appearance of product were monitored.

Linear plots of the concentration of *N*-methylaniline vs time were obtained for all reactions in the presence of NaOCEt$_3$ as base. These data are consistent with a reaction that is zero order in amine. Figure 4 shows the dependence of k_{obs} on the concentration of NaOCEt$_3$ for the reaction of 2-bromothiophene with *N*-methylaniline under the above conditions. The observed rate constant was clearly smaller for reactions with higher concentrations of base. Although evaluated in less detail, the dependence of k_{obs} on the concentration of NaO^{t}Bu for

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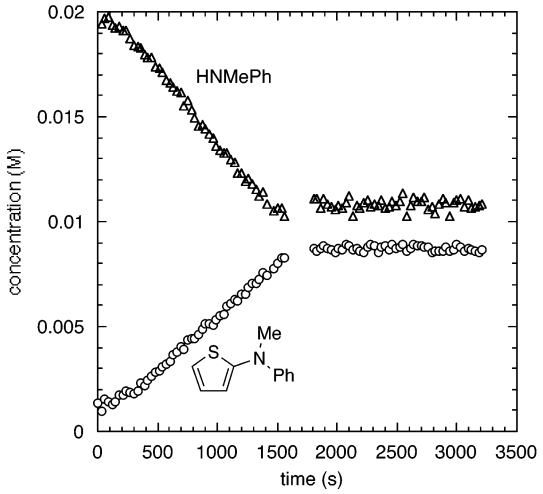

FIGURE 5. Reaction of *N*-methylaniline (0.025 M) with 2-bromothiophene (0.8 M) in the presence of $NaOCEt_3$ (0.3 M) catalyzed by 10% of $Pd(P^tBu_3)_2$ at 75 °C. $H_2NHexyl$ (0.025 M) was added at $t = 1600$ s.

the same reaction was similar. Again, the observed rate constant *decreased* with increasing concentrations of base.

Reactions of 2-bromothiophene with *N*-methylaniline were also monitored before and after adding hexylamine, aniline, or piperidine (0.025 M). These amines were added when approximately 50% of the heteroaryl bromide had been consumed by reaction with *N*-methylaniline. The reaction in which hexylamine was added at $t = 1600$ s is shown in Figure 5. The reaction immediately stopped upon addition of the unreactive amine. The same result was observed when adding aniline and piperidine. Thus, the amines that do not undergo coupling poison the catalyst that is active for the coupling of heteroaryl halides. An analogous experiment involving the addition of hexylamine to the reaction of *N*-methylaniline with bromobenzene did *not* show the same poisoning by the primary alkylamine.

Discussion

Connection between the Identity of the Heteroaryl Halide and the Yields of Coupled Product. The yields for catalytic amination of thiophenyl and furyl halides can be correlated with the yields obtained from reductive eliminations of amine from DPPF-ligated aryl- and heteroarylpalladium amides.[46] Carbon−nitrogen bond-forming reductive elimination is faster from complexes with more electron-donating amido groups and less electron-donating aryl groups.[48] Because a furyl group is less electron-rich at the 2-position and a thiophenyl group is less electron-rich at the 3-position, aminations of 2-bromothiophene and 3-bromofuran should occur in higher yields than aminations of the isomeric heteroaryl halides. Moreover, oxidative addition to palladium(0) occurs faster with electron-poor aryl bromides.[49,50] If oxidative addition is the turnover limiting step in the catalytic process, then the reactions of 2-bromofuran should be faster than those of 3-bromofuran, and reactions of 3-bromothiophene should be faster than those of 2-bromothiophene. This predicted reactivity was observed experimentally. Finally, arylpalladium complexes with two ortho substituents undergo reductive elimination slower than those with one substituent, most likely because the two ortho substituents inhibit binding of the metal to the π-system at either C(ipso)−C(ortho) bond. This effect was revealed by previous work on reductive eliminations from heteroarylpalladium amides[46] and on reductive elimination from arylpalladium thiolates.[38] An analogous substituent effect with the heteroaromatic substrates accounts for the larger difference in yield between aminations of 3-methyl-2-bromothiophene and 2-bromothiophene with *N*-methylaniline than between aminations of 4-methyl-3-bromothiophene and 3-bromothiophene with *N*-methylaniline.

The origin of the effect of amine on reaction rate is less straightforward. Reductive elimination of amine is unlikely to be the turnover-limiting step of the catalytic process because it is generally faster than oxidative addition of electron-rich aryl or heteroaryl halides and because Pd(0) complexes were observed as the major species in solution. Thus, the rate of oxidative addition and reductive elimination with the active catalyst does not account for the differences in reactivity of amines with the heteroaryl bromides. The reactions of some amines consumed neither the heteroaryl halide nor the amine. In these cases, the catalyst seemed to be poisoned, as demonstrated by the interruption of an ongoing catalytic reaction by addition of hexylamine. We cannot explain the reversal of the relative reactivity of aryl- and alkylamines toward the five-membered heteroaryl systems containing two heteroatoms, such as thiazoles, benzimidazoles, and benzoxazoles, relative to the reactivity of these amines toward furans and thiophenes. These substrates were more reactive toward alkylamines than toward *N*-methylaniline, while the furans and thiophenes were more reactive toward *N*-methylaniline and diphenylamine than toward dialkylamines.

Several reactions were uncovered that accounted for side products formed from reactions of *N*-methylaniline that did consume the aryl bromide. Amidine and 2-methylthiophene most likely form by β-hydrogen elimination of the heteroarylpalladium amido intermediate and reductive elimination of 2-methylthiophene. We previously showed that β-hydrogen elimination of an *N*-methylanilide complex formed this amidine by formal disproportionation of the resulting unstable imine $PhN{=}CH_2$.[37] *N*-Methylaniline apparently forms by addition of a proton from a source we did not identify. Bithiophene was formed as an additional side product, and homocoupling of both aryl[51−53] and heteroaryl[54,55] groups has been observed previously. This homocoupling has been rationalized by disproportionation of arylpalladium halide

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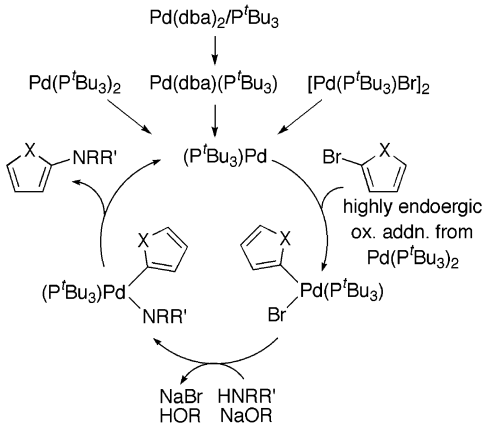
complexes to form dihalo- and diarylpalladium complexes,[56] the latter of which forms biaryl by reductive elimination.[55]

Identifying the Resting State and Active Catalyst. Identification of the true catalyst for the amination of these five-membered, heteroaryl halides was difficult. Monitoring by NMR of reactions that formed coupled product showed that $Pd(P^tBu_3)_2$ was the major phosphorus-containing species. Yet $Pd(P^tBu_3)_2$ was also the major phosphorus-containing species in reactions that did not consume the heteroaryl halide or amine. Consistent with this observation, $Pd(P^tBu_3)_2$ was present in similar concentrations before and after poisoning of the reactions of *N*-methylaniline by addition of hexylamine. Thus, the lack of reactivity of some amines toward the heteroaryl bromides cannot be explained by precipitation of palladium or conversion of $Pd(P^tBu_3)_2$ to a species that is silent by ^{31}P NMR spectroscopy. These results show that $Pd(P^tBu_3)_2$ is unlikely to lie directly on the catalytic cycle or even to exist in dynamic equilibrium with the Pd(0) species that does lie on the catalytic cycle. However, several lines of evidence indicate that the reaction is catalyzed by phosphine-ligated palladium: the product distributions were affected by the identity of the ligand, and systems with palladium but without added ligand did not generate any coupled product.

Previous results suggest that the palladium(0) complex $Pd(P^tBu_3)_2$ adds aryl halides fast enough and with favorable enough thermodynamics to initiate aryl halide amination.[47,57,58] Yet, the oxidative addition of aryl halides to $Pd(P^tBu_3)_2$ is thermodynamically unfavorable in some cases[59] and forms unusual three-coordinate monophosphine complexes.[58] The thermodynamics for addition of the electron-rich heteroaryl halides may be even more unfavorable. Thus, the unfavorable thermodynamics for reaction of heteroaryl halides with $Pd(P^tBu_3)_2$ to form a monophosphine heteroarylpalladium complex may make the addition too slow or the population of arylpalladium halide complex too small to allow subsequent formation of an arylpalladium amide complex and reductive elimination to form amine.

Thus, we suggest that the efficiency at which the monoligated Pd(0) fragment $Pd(P^tBu_3)$ is formed from the combination of palladium catalyst precursor and P^tBu_3 controls the rates of the amination of five-membered heteroaryl halides. Generation of this fragment from $Pd(dba)_2$ and P^tBu_3 or from the Pd(I) dimer most likely creates higher concentrations of this intermediate than does ligand dissociation from $Pd(P^tBu_3)_2$. The slow generation of $Pd(P^tBu_3)_2$ from $Pd(dba)_2$ and P^tBu_3 in toluene solvent may allow for continuous generation of $Pd(dba)(P^tBu_3)$, which could add heteroaryl halide faster than it undergoes disproportionation to $Pd(P^tBu_3)_2$ and $Pd(dba)_2$. The Pd(I) dimer should generate the catalyst efficiently because it contains the same 1:1 ratio of ligand to palladium that is present in the complex that is proposed to add the heteroaryl halide. The mechanism for generation of the $Pd(P^tBu_3)$ from the Pd(I) dimer is unclear, however.

SCHEME 2



The amount of the active catalyst also appears to be influenced by the identity of the amine. The large variation in rate for reactions of different amines with the same heteroaryl halide indicates that the amine is involved directly in the turnover-limiting step or that the identity of the amine affects the concentration of the palladium complex that lies on the catalytic cycle. We suggest that the identity of the amine influences the amount of active catalyst and that the amine does not participate in the rate-determining step. Monitoring under pseudo-first-order conditions the reactions that occurred in good yield suggested that the reaction was zero-order in amine. Moreover, reactions of an amine that formed coupled product in good yield were poisoned by addition of an amine that formed coupled product in low yield.

The amount of active catalyst also appears to be influenced by the concentration of base. The apparent negative order of reaction in the presence of base implies that high concentrations of base lead to low concentrations of the active catalyst. Conversion of the active catalyst to the inactive catalyst could not be observed upon addition of the alkylamines or the base because the active species is present in low concentration. However, the presence of alkoxide base did accelerate the conversion of P^tBu_3 and several catalyst precursors to $Pd(P^tBu_3)_2$, which does not catalyze amination of these heteroaryl halides at these reaction temperatures. Reaction of the heteroaryl halide with the combination of $Pd(dba)_2$ and P^tBu_3 in the presence of NaO^tBu rapidly generated $Pd(P^tBu_3)_2$. Reaction of the Pd(I) dimer with NaO^tBu formed $Pd(P^tBu_3)_2$, and reaction of the Pd(I) dimer with the combination of NaO^tBu and amine formed $Pd(P^tBu_3)_2$ even faster.

Our conclusions on the reaction mechanism are summarized in Scheme 2. This mechanism parallels one of the two mechanisms for coupling of aryl chlorides with amines catalyzed by palladium complexes of P^tBu_3.[47] However, the studies reported here suggest that efficient generation of the $Pd(P^tBu_3)$ intermediate is crucial to observing amination with less reactive substrates, such as bromothiophenes and bromofurans. It is clear that $Pd(P^tBu_3)_2$ cannot initiate most of the couplings of the heteroaryl bromides, and we suggest that unfavorable

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thermodynamics for ligand dissociation and oxidative addition to $Pd(P^tBu_3)_2$ makes the addition unfavorable enough to prevent formation of the amido complex. Instead, mixing of $Pd(dba)_2$ and P^tBu_3 may feed the system higher concentrations of $Pd(P^tBu_3)(dba)$ and $Pd(P^tBu_3)$ than would be generated from full equilibration of $Pd(dba)_2$ and $Pd(P^tBu_3)_2$ or from dissociation of ligand from $Pd(P^tBu_3)_2$. Consistent with the assertion that a 1:1 stoichiometry of ligand and metal is present in the active catalyst, the palladium(I) dimer $[Pd(Br)(P^tBu_3)]_2$ serves as one of the most active precatalysts.

Conclusion

Palladium-catalyzed amination has been shown to proceed with a range of electron-rich heteroaromatic bromides and chlorides with certain classes of amines. The reactivity of heteroaryl bromides in palladium-catalyzed amination appears to be controlled by several factors. First, the concentration of catalyst that can add the electron-rich, five-membered heteroaryl halides appears to be lower than the concentration of catalyst that can add aryl halides. The concentration of this complex that adds heteroaryl halides is apparently depleted in the presence of alkylamines, aniline, or excess base. Second, the scope of the catalytic reactions is controlled not only by the concentration of the active catalyst, but by the ability of the intermediate heteroarylpalladium amides to undergo reductive elimination. The yields of heteroarylamine formed during a study of reductive elimination from DPPF-ligated complexes[46] paralleled closely the yields of heteroarylamine formed from reactions catalyzed by complexes of palladium and P^tBu_3.

Experimental Section

General Methods. Unless otherwise noted, all reactions and manipulations were performed in an inert atmosphere glovebox. All $^{31}P\{^1H\}$ NMR chemical shifts are reported in parts per million relative to an 85% H_3PO_4 external standard. Shifts downfield of the standard are reported as positive. Benzene, toluene, and pentane solvents were distilled from sodium/benzophenone prior to use. 3-Bromofuran was distilled prior to use. 2-Bromofuran,[60] 2-bromo-5-methylfuran,[60] 2-bromo-5-methylthiophene,[60] 2-bromo-*N*-methylindole[61] 3-bromo-*N*-methylindole,[62] 2-chloro-*N*-methylbenzimidazole,[63] and ferrocenyldi-*tert*-butylphosphine[64] were all prepared according to literature procedures. All other chemicals were used as received from commercial suppliers.

General Procedure for Catalytic Amination of Heteroaromatic Halides. Method A: In a drybox, aryl bromide (0.5−2.5 mmol), amine (0.5−2.5 mmol), and NaO^tBu (0.55−2.75 mmol) were weighed directly into a screw capped vial. A stir bar and 0.5−2.5 mL of toluene were added. $Pd(dba)_2$ (2 mol %, 0.01−0.05 mmol) and P^tBu_3 (2 mol %, 0.01−0.05 mmol) were weighed directly into a small vial and suspended in 0.5−2.5 mL of toluene. The catalyst suspension was then added to the reactants to give a purple mixture. The mixture was allowed to stir for 16 h at room temperature in the drybox or at 100 °C for 16 h outside the drybox. After this time, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and purified by flash chromatography. Naphthalene or trimethoxybenzene were used as internal standards when obtaining yields by GC.

Method B: In a drybox, aryl halide (1.0 mmol), NaO^tBu or K_3PO_4 (1.10 mmol), and amine (1.0−4.0 mmol) were added to a suspension of $Pd(dba)_2$ (0.02−0.05 mmol) or $Pd(O_2CCF_3)_2$ and P^tBu_3 (0.02−0.05 mmol) in 1.0−2.0 mL of toluene in a screw capped vial. A small stirbar was added, and the vial was sealed with a cap containing a PTFE septum. The mixture was allowed to stir at room temperature in the drybox or at elevated temperature outside of the drybox. After the reaction, the mixture was adsorbed onto neutral alumina and purified by flash chromatography. Dodecane was used as internal standard when yields were determined by GC.

2-(*N*-Methyl-*N*-phenylamino)furan (Table 1, entry 1). Method A of the above general procedure was followed with 2-bromofuran (368 mg, 221 μL, 2.5 mmol), 1.0 equiv of *N*-methylaniline (268 mg, 2.5 mmol), 1.1 equiv of NaO^tBu (265 mg, 2.8 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 5 mL of toluene. After 16 h at room temperature, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 242 mg (56%) of 2-(*N*-methyl-*N*-phenylamino)furan as a colorless oil: ^1H NMR (500 MHz, C_6D_6) δ 7.23 (dd, J = 7.3, 8.6 Hz, 2H), 7.00 (m, 1H), 6.94 (m, 3H), 6.21 (m, 1H), 5.74 (m, 1H), 2.99 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, C_6D_6) δ 155.62, 148.38, 137.68, 129.60, 120.73, 116.58, 111.54, 97.67, 38.92; MS (EI) 173 (M^+), 144, 130, 104, 77, 51. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.30; H, 6.36; N, 8.09. Found: C, 76.17; H, 6.35; N, 8.18.

3-(*N*-Methyl-*N*-phenylamino)furan (Table 1, entry 2). Method A of the above general procedure was followed with 3-bromofuran (368 mg, 225 μL, 2.5 mmol), 1.0 equiv of *N*-methylaniline (268 mg, 2.5 mmol), 1.1 equiv of NaO^tBu (265 mg, 2.8 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 5 mL of toluene. After 16 h at room temperature, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 367 mg (85%) of 3-(*N*-methyl-*N*-phenylamino)furan as a colorless oil: ^1H NMR (500 MHz, C_6D_6) δ 7.25 (dd, J = 7.3, 8.7 Hz, 2H), 7.14 (m, 1H), 7.08 (m, 1H), 7.04 (m, 1H), 7.03 (m, 1H), 6.93 (m, 1H), 6.20 (m, 1H), 2.89 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ 149.67, 143.05, 137.00, 132.76, 129.67, 120.70, 118.15, 108.00, 40.87; MS (EI) 173 (M^+), 144, 130, 77, 51. Anal. Calcd for $C_{11}H_{11}NO$: C, 76.30; H, 6.36; N, 8.09. Found: C, 76.07; H, 6.60; N, 8.18.

2-(*N*-Methyl-*N*-phenylamino)thiophene (Table 1, entry 3). Method A of the above general procedure was followed with 2-bromothiophene (408 mg, 244 μL, 2.5 mmol), 1.0 equiv of *N*-methylaniline (268 mg, 2.5 mmol), 1.1 equiv of NaO^tBu (265 mg, 2.8 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 5 mL of toluene. After 16 h at room temperature, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 387 mg (82%) of 2-(*N*-methyl-*N*-phenylamino)thiophene as a colorless oil: ^1H NMR (500 MHz, C_6D_6) δ 7.22 (dd, J = 7.4, 8.7 Hz, 2H), 6.99 (m, 2H), 6.92 (m, 1H), 6.73 (m, 1H), 6.70 (m, 1H), 6.57 (m, 1H), 3.02 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ 154.52, 150.13, 129.61, 127.24, 126.30, 120.69, 119.45, 117.12, 42.18; MS (EI) 189 (M^+), 173, 147, 130, 77, 51. Anal. Calcd for $C_{11}H_{11}NS$: C, 69.84; H, 5.82; N, 7.41; S, 16.93. Found: C, 70.08; H, 5.84; N, 7.66; S, 16.98.

3-(*N*-Methyl-N-phenylamino)thiophene (Table 1, entry 4). Method A of the above general procedure was followed with 3-bromothiophene (408 mg, 234 μL, 2.5 mmol), 1.0 equiv of *N*-methylaniline (268 mg, 2.5 mmol), 1.1 equiv of NaO^tBu (265

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mg, 2.8 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 5 mL of toluene. After 16 h at room temperature, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 439 mg (93%) of 3-(*N*-methyl-*N*-phenylamino)thiophene as a colorless oil: ^{1}H NMR (500 MHz, C_6D_6) δ 7.12 (m, 2H), 6.92 (m, 2H), 6.84 (t, J = 8.4 Hz, 1H), 6.79 (dd, J = 3.2 Hz, 5.2 Hz, 1H), 6.70 (dd, J = 1.5, 5.2 Hz, 1H), 6.24 (dd, J = 1.5, 3.1 Hz, 1H), 2.87 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, CD_2Cl_2) δ 150.15, 149.14, 129.69, 125.39, 123.85, 121.46, 119.69, 108.35, 41.13; MS (EI): 189 (M^+), 173, 156, 144, 130, 77, 51. Anal. Calcd for $C_{11}H_{11}NS$: C, 69.84; H, 5.82; N, 7.41; S, 16.93. Found: C, 70.10; H, 5.89; N, 7.58; S, 16.90.

2-(Diphenylamino)furan (Table 1, entry 5). Method A of the above general procedure was followed with 2-bromofuran (368 mg, 221 μL, 2.5 mmol), 1.0 equiv of diphenylamine (423 mg, 2.5 mmol), 1.1 equiv of NaO^{t}Bu (265 mg, 2.8 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 5 mL of toluene. After 16 h at 100 °C, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 300 mg (51%) of 2-(diphenylamino)furan as a white solid: ^{1}H NMR (400 MHz, C_6D_6) δ 709−7.01 (m, 8H), 6.86 (m, 1H), 6.84 (m, 1H), 6.81 (m, 1H), 6.05 (dd, J = 3.3, 2.1 Hz, 1H), 5.76 (dd, J = 3.2, 1.0 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 153.76, 146.99, 138.70, 129.88, 123.61, 122.66, 111.82, 101.48; MS (EI) 235 (M^+), 206, 77, 51. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.70; H, 5.53; N, 5.96. Found: C, 81.44; H, 5.53; N, 5.88.

3-(Diphenylamino)furan (Table 1, entry 6). Method A of the above general procedure was followed with 3-bromofuran (368 mg, 225 μL, 2.5 mmol), 1.0 equiv of diphenylamine (432 mg, 2.5 mmol), 1.1 equiv of NaO^{t}Bu (265 mg, 2.8 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 5 mL of toluene. After 16 h at 100 °C, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 324 mg (55%) of 3-(diphenylamino)furan as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, J = 1.7 Hz, 1H), 7.19−7.15 (m, 5H), 7.04 (m, 4H), 6.92 (t, J = 7.3 Hz, 2H), 6.25 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, C_6D_6) δ 148.41, 143.24, 136.12, 135.51, 129.86, 123.26, 123.12, 109.49; MS (EI) 235 (M^+), 206, 128, 77, 51. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.70; H, 5.53; N, 5.96. Found: C, 81.48; H, 5.68; N, 5.85.

2-(Diphenylamino)thiophene (Table 1, entry 7). Method A of the above general procedure was followed with 2-bromothiophene (408 mg, 244 μL, 2.5 mmol), 1.0 equiv of diphenylamine (432 mg, 2.5 mmol), 1.1 equiv of NaO^{t}Bu (265 mg, 2.8 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 5 mL of toluene. After 16 h at 100 °C, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 370 mg (63%) of 2-(diphenylamino)thiophene as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 5.6 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 7.7 Hz, 4H), 6.94 (m, 3H), 6.81 (dd, J = 3.7, 5.6 Hz, 1H), 6.65 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.85, 148.40, 129.50, 126.26, 123.15, 122.71, 121.92, 121.21; MS (EI) 251 (M^+), 173, 147, 115, 77, 51. Anal. Calcd for $C_{16}H_{13}NS$: C, 76.49; H, 5.18; N, 5.58; S, 12.75. Found: C, 76.58; H, 5.38; N, 5.58; S, 12.77.

3-(Diphenylamino)thiophene (Table 1, entry 8). Method A of the above general procedure was followed with 3-bromothiophene (408 mg, 234 μL, 2.5 mmol), 1.0 equiv of diphenylamine (432 mg, 2.5 mmol), 1.1 equiv of NaO^{t}Bu (265 mg, 2.8 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 5 mL of toluene. After 16 h at 100 °C, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 601 mg (97%) of 3-(diphenylamino)thiophene as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19−7.15 (m, 5H), 7.03 (d, J = 8.6 Hz, 4H), 6.93 (t, J = 7.3 Hz, 2H), 6.81 (dd, J = 1.4, 5.2 Hz, 1H), 6.59 (dd, J = 3.7, 5.6 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 148.24, 146.96, 129.54, 125.54, 125.28, 123.50, 123.02, 113.26; MS (EI) 251 (M^+), 217, 174, 77, 51. Anal. Calcd for $C_{16}H_{13}NS$: C, 76.49; H, 5.18; N, 5.58; S, 12.75. Found: C, 76.59; H, 5.09; N, 5.59; S, 12.75.

3-(*N*-Phenylamino)thiophene (Table 1, entry 9). Method A of the above general procedure was followed with 3-bromothiophene (408 mg, 234 μL, 2.5 mmol), 1.0 equiv of aniline (233 mg, 2.5 mmol), 1.1 equiv of NaO^{t}Bu (265 mg, 2.8 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 5 mL of toluene. After 16 h at 100 °C, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 386 mg (88%) of 3-(*N*-phenylamino)thiophene as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6) δ 7.12 (m, 2H), 6.80 (m, 2H), 6.75 (m, 1H), 6.74 (m, 1H), 6.54 (dd, J = 1.5, 5.1 Hz, 1H), 6.34 (dd, J = 1.5, 4.3 Hz, 1H), 4.92 (br s, 1H); ^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 145.42, 142.20, 129.92, 125.41, 123.44, 120.41, 116.27, 106.88; MS (EI) 175 (M^+), 130, 77, 51. Anal. Calcd for $C_{10}H_9NS$: C, 68.55; H, 5.18; N, 8.00. Found: C, 68.99; H, 5.40; N, 7.72.

3-(Morpholino)thiophene[65] (Table 1, entry 10). Method B of the above general procedure was followed with 3-bromothiophene (162 mg, 1.0 mmol), 1.0 equiv of morpholine (87.2 μL, 1.0 mmol), 1.1 equiv of NaO^{t}Bu (106 mg, 1.1 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 1 mL of xylene. After 24 h at 120 °C, the mixture was adsorbed onto neutral alumina and eluted with 10% ethyl acetate in hexanes to give 134 mg (80%) of 3-(morpholino)thiophene as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 5.4, 3.1 Hz, 1H), 6.85 (dd, J = 5.2, 1.3 Hz, 1H), 6.19 (dd, J = 3.0, 1.6 Hz, 1H), 3.84 (t, J = 4.8 Hz, 4H), 3.08 (t, J = 4.8 Hz, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.4, 125.5, 119.6, 100.4, 66.6, 50.7.

3-(4-Phenylpiperazino)thiophene (Table 1, entry 11). Method B of the above general procedure was followed with 3-bromothiophene (163 mg, 1.0 mmol), 1.0 equiv of *N*-phenylpiperazine (153 μL, 1.0 mmol), 1.1 equiv of NaO^{t}Bu (106 mg, 1.1 mmol), 5 mol % of $Pd(dba)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of xylene. After 24 h at 120 °C, the mixture was adsorbed onto neutral alumina and eluted with 10% ethyl acetate in hexanes to give 103 mg (42%) of 3-(4-phenylpiperazino)thiophene as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.9 (m, 3H), 6.99 (dd, J = 7.8, 0.9 Hz, 2H), 6.90 (m, 2H), 6.26 (dd, J = 3.1, 1.7 Hz, 1H), 3.33 (m, 4H), 3.25 (m, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.2, 151.2, 129.2, 125.5, 120.1, 116.4, 100.9, 90.7, 50.6, 49.2. Anal. Calcd for $C_{14}H_{16}N_2S$: C, 68.81; H, 6.60; N, 11.46. Found: C, 68.63; H, 6.56; N, 11.19.

3-(*N*-Methyl-*N*-phenylamino)thionaphthene[66] (Table 1, entry 12). Method B of the above general procedure was followed with 3-bromothionaphthene (213 mg, 1.0 mmol), 1.0 equiv of *N*-methylaniline (108 μL, 1.0 mmol), 1.1 equiv of NaO^{t}Bu (106 mg, 1.1 mmol), 5 mol % of $Pd(dba)_2$, and 5 mol % of tri-*tert*-butylphosphine in 2 mL of toluene. After 20 h at room temperature in a drybox, the mixture was adsorbed onto neutral alumina and eluted with 2% ethyl acetate in hexanes to give 206 mg (86%) of 3-(*N*-methyl-*N*-phenylamino)thionaphthene as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.32 (dt, J = 7.6, 1.5 Hz, 1H), 7.20 (m, 3H), 7.11 (s, 1H), 6.81 (t, J = 7.3 Hz, 1H), 6.76 (dd, J = 8.5, 1.0 Hz, 2H), 3.38 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.1, 141.9, 139.0, 135.2, 128.9, 124.6, 123.9, 123.2, 122.4, 118.8, 117.7, 115.5, 40.7.

2-(*N*-Methyl-*N*-phenylamino)thiophene (Table 1, entry 13). Method B of the above general procedure was followed

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with 2-chlorothiophene (118 mg, 1.0 mmol), 1.0 equiv of *N*-methylaniline (108 μL, 1.0 mmol), 1.1 equiv of NaO*t*Bu (106 mg, 1.1 mmol), 5 mol % of $Pd(dba)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of xylene. After 24 h at 120 °C, the mixture was adsorbed onto neutral alumina and eluted with 2% ethyl acetate in hexanes to give 97.8 mg (52%) of 2-(*N*-methyl-*N*-phenylamino)thiophene as an oil.

3-(*N*-Methyl-*N*-phenylamino)thiophene (Table 1, entry 14). Method B of the above general procedure was followed with 3-chlorothiophene (118 mg, 1.0 mmol), 1.0 equiv of *N*-methylaniline (108 μL, 1.0 mmol), 1.1 equiv of NaO*t*Bu (106 mg, 1.1 mmol), 5 mol % of $Pd(dba)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of xylene. After 24 h at 120 °C, the mixture was adsorbed onto neutral alumina and eluted with 2% ethyl acetate in hexanes to give 90.5 mg (48%) of 3-(*N*-methyl-*N*-phenylamino)thiophene as an oil.

3-(Morpholino)thiophene[65] (Table 1, entry 15). Method B of the above general procedure was followed with 3-chlorothiophene (119 mg, 1.0 mmol), morpholine (87.2 μL, 1.0 mmol), 1.1 equiv of NaO*t*Bu (106 mg, 1.1 mmol), 5 mol % of $Pd(dba)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of xylene. After 30 h at 120 °C, the mixture was adsorbed onto neutral alumina and eluted with 20% ethyl acetate in hexanes to give 72.4 mg (43%) of 3-(morpholino)thiophene as a solid.

2-(*N*-Methyl-*N*-phenylamino)-5-methylfuran (Table 2, entry 1). Method A of the above general procedure was followed with 2-bromo-5-methylfuran (161 mg, 101 μL, 1.0 mmol), 1.0 equiv of *N*-methylaniline (107 mg, 1.0 mmol), 1.1 equiv of NaO*t*Bu (106 mg, 1.1 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 2 mL of toluene. After 16 h at room temperature, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 56 mg (30%) of 2-(*N*-methyl-*N*-phenylamino)-5-methylfuran as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6) δ 7.15 (m, 2H), 6.76 (m, 3H), 5.87 (m, 1H), 5.70 (d, J = 3.0 Hz, 1H), 3.17 (s, 3H), 2.18 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.92, 148.34, 147.64, 129.31, 119.69, 115.13, 106.71, 100.13, 39.45, 14.17; MS (EI) 187 (M^+), 172, 144, 77, 51. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.96; H, 7.00; N, 7.48. Found: C, 76.73; H, 6.88; N, 7.72.

2-(Diphenylamino)-5-methylfuran (Table 2, entry 2). Method A of the above general procedure was followed with 5-methyl-2-bromofuran (81 mg, 51 μL, 0.5 mmol), 1.0 equiv of diphenylamine (85 mg, 0.5 mmol), 1.1 equiv of NaO*t*Bu (53 mg, 0.6 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 1 mL of toluene. After 16 h at 100 °C, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 102 mg (82%) of 2-(diphenylamino)-5-methylfuran as a white solid: ^{1}H NMR (400 MHz, C_6D_6) δ 7.15 (m, 4H), 7.05 (m, 4H), 6.83 (t, J = 7.3 Hz, 2H), 5.79 (d, J = 3.1 Hz, 1H), 5.75 (m, 1H), 1.91 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, C_6D_6) δ 151.74, 148.70, 147.30, 129.86, 123.37, 122.41, 107.56, 103.51, 13.99; MS (EI) 249 (M^+), 206, 172, 103, 77, 51. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.76; H, 6.21; N, 5.54.

2-(*N*-Methyl-*N*-phenylamino)-5-methylthiophene (Table 2, entry 3). Method A of the above general procedure was followed with 2-bromo-5-methylthiophene (177 mg, 111 μL, 1.0 mmol), 1.0 equiv of *N*-methylaniline (107 mg, 1.0 mmol), 1.1 equiv of NaO*t*Bu (106 mg, 1.1 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 2 mL of toluene. After 16 h at room temperature, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 106 mg (52%) of 2-(*N*-methyl-*N*-phenylamino)-5-methylthiophene as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, J = 7.3, 8.8 Hz, 2H), 6.81 (m, 2H), 6.76 (t, J = 7.3 Hz, 1H), 6.47 (m, 1H), 6.43 (d, J = 3.6 Hz, 1H), 3.21 (s, 3H), 2.36 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.90, 149.82, 135.55, 129.25, 123.55, 121.13, 119.47, 115.48, 42.19, 16.34; MS (EI) 203 (M^+), 188, 173, 155, 77, 51. Anal. Calcd for $C_{12}H_{13}NS$: C, 70.90; H, 6.45; N, 6.89; S, 15.58. Found: C, 71.14; H, 6.57; N, 6.90; S, 15.58.

2-(Diphenylamino)-5-methylthiophene (Table 2, entry 4). Method A of the above general procedure was followed with 5-methyl-2-bromothiophene (89 mg, 55 μL, 0.5 mmol), 1.0 equiv of diphenylamine (85 mg, 0.5 mmol), 1.1 equiv of NaO*t*Bu (53 mg, 0.6 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 1 mL of toluene. After 16 h at 100 °C, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 101 mg (76%) of 2-(diphenylamino)-5-methylthiophene as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (m, 4H), 7.04 (m, 4H), 6.92 (t, J = 8.1 Hz, 2H), 6.47 (m, 2H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 148.69, 148.34, 136.36, 129.44, 123.88, 123.00, 122.83, 122.31, 16.37; MS (EI) 265 (M^+), 97, 77, 51. Anal. Calcd for $C_{17}H_{15}NS$: C, 76.94; H, 5.70; N, 5.28. Found: C, 76.93; H, 5.51; N, 5.21.

2-(*N*-Methyl-*N*-phenylamino)-3-methylthiophene (Table 2, entry 5). Method A of the above general procedure was followed with 2-bromo-3-methylthiophene (177 mg, 108 μL, 1.0 mmol), 1.0 equiv of *N*-methylaniline (107 mg, 1.0 mmol), 1.1 equiv of NaOtBu (106 mg, 1.1 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 2 mL of toluene. After 16 h at room temperature, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 12 mg (6%) of 2-(*N*-methyl-*N*-phenylamino)-3-methylthiophene as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 7.3 Hz, 8.8 Hz, 2H), 7.09 (d, J = 5.7 Hz, 1H), 6.84 (d, J = 5.7 Hz, 1H), 6.81 (t, J = 7.3 Hz, 1H), 6.71 (m, 2H), 3.29 (s, 3H), 2.04 (s, 3H); ^{13}C-{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 147.93, 127.90, 127.36, 126.85, 124.79, 120.48, 116.94, 112.26, 39.36, 11.85; MS (EI) 203 (M^+), 188, 173, 154, 77, 51. The low yield of this reaction prevented our obtaining samples that were analytically pure.

2-(Diphenylamino)-3-methylthiophene (Table 2, entry 6). Method A of the above general procedure was followed with 3-methyl-2-bromothiophene (89 mg, 54 μL, 0.5 mmol), 1.0 equiv of diphenylamine (85 mg, 0.5 mmol), 1.1 equiv of NaO*t*Bu (53 mg, 0.6 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 1 mL of toluene. After 16 h at 100 °C, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 66 mg (50%) of 2-(diphenylamino)-3-methylthiophene as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (m, 4H), 6.98 (m, 5H), 6.90 (t, J = 7.3 Hz, 2H), 6.42 (d, J = 5.6 Hz, 1H), 1.88 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 147.54, 144.03, 133.07, 129.42, 129.12, 122.49, 122.18, 121.63, 13.51; MS (EI) 265 (M^+), 186, 173, 77, 51. Anal. Calcd for $C_{17}H_{15}NS$: C, 76.94; H, 5.70; N, 5.28. Found: C, 76.66; H, 5.74; N, 4.99.

3-(*N*-Methyl-*N*-phenylamino)-4-methylthiophene (Table 2, entry 7). Method A of the above general procedure was followed with 3-bromo-4-methylthiophene (177 mg, 112 μL, 1.0 mmol), 1.0 equiv of *N*-methylaniline (107 mg, 1.0 mmol), 1.1 equiv of NaO*t*Bu (106 mg, 1.1 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 2 mL of toluene. After 16 h at room temperature, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 112 mg (55%) of 3-(*N*-methyl-*N*-phenylamino)-4-methylthiophene as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (m, 2H), 6.99 (m, 2H), 6.71 (m, 1H), 6.66 (m, 1H), 6.64 (m, 1H), 3.26 (s, 3H'), 1.96 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.73, 147.32, 136.16, 129.34, 121.63, 118.50, 118.13, 114.34, 40.49, 14.17; MS (EI) 203 (M^+), 203, 188, 170, 77, 51.

2-(*N*′-Methyl-*N*′-phenylamino)-*N*-methylindole (Table 2, entry 8). Method A of the above general procedure was

followed with 2-bromo-*N*-methylindole (210 mg, 1.0 mmol), 1.0 equiv of *N*-methylaniline (107 mg, 1.0 mmol), 1.1 equiv of NaO^{t}Bu (106 mg, 1.1 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 2 mL of toluene. After 16 h at room temperature, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 185 mg (78%) of 2-(*N*-methyl-*N*-phenylamino)-*N*-methylindole as a white solid: ^{1}H NMR (400 MHz, C_6D_6) δ 7.51 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 8.1 Hz, 1H), 7.14 (m, 3H), 7.05 (m, 1H), 6.76 (m, 1H), 6.62 (d, J = 8.8 Hz, 2H), 6.20 (s, 1H), 3.38 (s, 3H), 3.30 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.15, 144.04, 134.97, 129.35, 127.39, 121.42, 120.52, 119.88, 119.24, 114.73, 109.45, 94.69, 40.78, 29.11; MS (EI) 236 (M^+), 221, 118, 77, 51. Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.31; H, 6.85; N, 11.69.

2-(*N*′,*N*′-Diphenylamino)-*N*-methylindole (Table 2, entry 9). Method A of the above general procedure was followed with 2-bromo-*N*-methylindole (105 mg, 0.5 mmol), 1.0 equiv of diphenylamine (85 mg, 0.5 mmol), 1.1 equiv of NaO^{t}Bu (53 mg, 0.6 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 1 mL of toluene. After 16 h at 100 °C, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 121 mg (81%) of 2-(*N*′,*N*′-diphenylamino)-*N*-methylindole as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.8 Hz, 1H), 7.21−7.13 (m, 5H), 7.03 (t, J = 8.0 Hz, 2H), 6.97 (d, J = 7.7 Hz, 4H), 6.92 (t, J = 7.3 Hz, 2H), 6.16 (s, 1H), 3.37 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 147.17, 142.46, 135.22, 129.56, 127.85, 122.95, 121.96, 121.61, 120.69, 120.13, 109.58, 97.35, 29.61; MS (EI) 298 (M^+), 282, 221, 206, 131, 91, 77, 51. Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.36; H, 6.08; N, 9.33.

3-(*N*′-Methyl-*N*′-phenylamino)-*N*-methylindole (Table 2, entry 10). Method A of the above general procedure was followed with 3-bromo-*N*-methylindole (105 mg, 0.5 mmol), 1.0 equiv of *N*-methylaniline (54 mg, 0.5 mmol), 1.1 equiv of NaO^{t}Bu (53 mg, 0.6 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 1 mL of toluene. After 16 h at room temperature, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 97 mg (82%) of 3-(*N*-methyl-*N*-phenylamino)-*N*-methylindole as a white solid: ^{1}H NMR (400 MHz, C_6D_6) δ 7.26 (m, 2H), 7.16 (m, 1H), 7.08 (t, J = 8.4 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H), 6.91 (s, 1H), 6.69 (d, J = 8.1 Hz, 2H), 6.63 (t, J = 7.2 Hz, 1H), 3.71 (s, 3H), 3.28 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.52, 136.28, 129.16, 125.01, 124.96, 124.82, 122.34, 119.60, 119.41, 117.30, 113.80, 109.78, 41.36, 33.17; MS (EI) 236 (M^+), 221, 206, 118, 91, 77, 51. Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.06; H, 6.71; N, 11.63.

3-(*N*′,*N*′-Diphenylamino)-*N*-methylindole (Table 2, entry 11). Method A of the above general procedure was followed with 3-bromo-*N*-methylindole (105 mg, 0.5 mmol), 1.0 equiv of diphenylamine (85 mg, 0.5 mmol), 1.1 equiv of NaO^{t}Bu (53 mg, 0.6 mmol), 2 mol % of $Pd(dba)_2$, and 2 mol % of tri-*tert*-butylphosphine in 1 mL of toluene. After 16 h at 100 °C, the mixture was poured into pentane (15 mL), filtered, and concentrated in vacuo. The crude product was adsorbed onto neutral alumina and eluted with 5% diethyl ether in hexanes to give 97 mg (65%) of 3-(*N*′,*N*′-diphenylamino)-*N*-methylindole as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.1 Hz, 1H), 7.25−7.18 (m, 6H), 7.12 (d, J = 6.9 Hz, 4H), 7.01 (t, J = 5.6 Hz, 1H), 6.98 (s, 1H), 6.92 (t, J = 5.8 Hz, 2H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 148.63, 136.37, 129.28, 125.97, 125.07, 123.31, 122.39, 121.70, 121.61, 119.82, 119.62, 109.76, 33.26; MS (EI) 298 (M^+), 283, 221, 180, 152, 77, 51. Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.28; H, 6.20; N, 9.15.

2-(Morpholino)thiazole[67] **(Table 3, entry 1).** Method B of the above general procedure was followed with 2-bromothiazole (166 mg, 1.0 mmol), 4.0 equiv of morpholine (349 μL, 4.0 mmol), 1.1 equiv of K_3PO_4 (234 mg, 1.1 mmol), 5 mol % of $Pd(O_2CCF_3)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of toluene. After 20 h at 80 °C, the mixture was adsorbed onto neutral alumina and eluted with 20% ethyl acetate in hexanes to give 117 mg (68%) of 2-(morpholino)thiazole as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 3.4 Hz, 1H), 6.60 (d, J = 3.8 Hz, 1H), 3.81 (dt, J = 4.8, 1.2 Hz, 4H), 3.46 (dt, J = 4.9, 1.1 Hz, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.4, 139.6, 107.7, 66.2, 48.7.

2-(Dibutylamino)thiazole (Table 3, entry 2). Method B of the above general procedure was followed with 2-bromothiazole (164.9 mg, 1.01 mmol), 4.0 equiv of dibuthylamine (674.1 μL, 4.00 mmol), 1.1 equiv of K_3PO_4 (234 mg, 1.1 mmol), 5 mol % of $Pd(O_2CCF_3)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of xylene. After 16 h at 150 °C, the mixture was adsorbed onto neutral alumina and eluted with 5% ethyl acetate in hexanes to give 149 mg (70%) of 2-(dibutylamino)thiazole as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 3.5 Hz, 1H), 6.42 (d, J = 3.9 Hz, 1H), 3.41 (t, J = 7.6 Hz, 4H), 1.63 (quintet, J = 7.7 Hz, 4H), 1.36 (sextet, J = 7.5 Hz, 4H), 0.95 (t, J = 7.4 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 139.5, 105.1, 51.4, 29.4, 20.2, 13.9. Anal. Calcd for $C_{11}H_{20}N_2S$: C, 62.22; H, 9.49; N, 13.19. Found: C, 62.17; H, 9.43; N, 13.20.

2-(*N*-Methyl-*N*-phenylamino)thiazole[68] **(Table 3, entry 3).** Method B of the above general procedure was followed with 2-bromothiazole (164 mg, 1.0 mmol), 3.0 equiv of *N*-methylaniline (325 μL, 3.00 mmol), 1.1 equiv of NaO^{t}Bu (106 mg, 1.1 mmol), 5 mol % of $Pd(OAc)_2$, and 5 mol % ferrocenyldi-*tert*-butylphosphine (17.4 mg, 0.05 mmol) in 1 mL of xylene. After 24 h at 120 °C, the mixture was adsorbed onto neutral alumina and eluted with 5% ethyl acetate in hexanes to give 91.8 mg (48%) of 2-(*N*-methyl-*N*-phenylamino)thiazole as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 4H), 7.24 (m, 2H), 6.47 (d, J = 3.8 Hz, 1H), 3.53 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.6, 146.4, 139.3, 129.6, 126.2, 124.8, 107.4, 40.3.

2-(Morpholino)benzothiazole[69] **(Table 3, entry 4).** Method B of the above general procedure was followed with 2-chlorobenzothiazole (171 mg, 1.0 mmol), 1.0 equiv of morpholine (87.2 μL, 1.0 mmol), 1.1 equiv of NaO^{t}Bu (106 mg, 1.1 mmol), 5 mol % of $Pd(O_2CCF_3)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of toluene. After 16 h at room temperature, the mixture was adsorbed onto neutral alumina and eluted with 20% ethyl acetate in hexanes to give 155 mg (70%) of 2-(morpholino)benzothiazole as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.30 (dt, J = 7.7, 1.1 Hz, 1H), 7.09 (dt, J = 7.6, 0.9 Hz, 1H), 3.81 (t, J = 4.9 Hz, 4H), 3.60 (t, J = 4.9 Hz, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.9, 152.4, 130.5, 126.0, 121.6, 120.7, 119.2, 66.1, 48.4.

2-(4-Methylpiperazino)benzothiazole (Table 3, entry 5). Method B of the above general procedure was followed with 2-chlorobenzothiazole (173 mg, 1.0 mmol), 1.0 equiv of 4-methylpiperazine (116 μL, 1.0 mmol), 1.1 equiv of NaO^{t}Bu (106 mg, 1.1 mmol), 5 mol % of $Pd(O_2CCF_3)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of toluene. After 16 h at room temperature, the mixture was adsorbed onto neutral alumina and eluted with 80% ethyl acetate in hexanes to give 162 mg (68%) of 2-(4-methylpiperazino)benzothiazole as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.29 (dt, J = 7.7, 1.3 Hz, 1H), 7.07 (dt, J = 7.6, 1.0 Hz, 1H), 3.65 (t, J = 5.3 Hz, 4H), 2.53 (t, J = 5.3 Hz, 4H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.8, 152.7, 130.8, 126.0, 121.4, 120.7, 119.1, 54.3, 48.3, 46.2. Anal. Calcd

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for $C_{12}H_{15}N_3S$: C, 61.77; H, 6.48; N, 18.01. Found: C, 61.55; H, 6.43; N, 17.84.

2-(Dibutylamino)benzothiazole[70] **(Table 3, entry 6).** Method B of the above general procedure was followed with 2-chlorobenzothiazole (169 mg, 1.0 mmol), 1.0 equiv of dibutylamine (169 μL, 1.0 mmol), 1.1 equiv of NaO^{t}Bu (106 mg, 1.1 mmol), 5 mol % of $Pd(O_2CCF_3)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of toluene. After 16 h at 50 °C, the mixture was adsorbed onto neutral alumina and eluted with 2% ethyl acetate in hexanes to give 203 mg (78%) of 2-(dibutylamino)benzothiazole as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.3 Hz, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.26 (dt, J = 7.7, 1.2 Hz, 1H), 7.01 (dt, J = 7.6, 1.1 Hz, 1H), 3.49 (t, J = 7.6 Hz, 4H), 1.68 (quintet, J = 7.6 Hz, 4H), 1.40 (sextet, J = 7.6 Hz, 4H), 0.97 (t, J = 7.5 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.8, 153.2, 130.6, 125.6, 120.5, 120.3, 118.4, 50.9, 29.5, 20.0, 13.8.

2-(*N*-Methyl-*N*-phenylamino)benzothiazole[69] **(Table 3, entry 7).** Method B of the above general procedure was followed with 2-chlorobenzothiazole (172 mg, 1.0 mmol), 1.0 equiv of *N*-methylaniline (108 μL, 1.0 mmol), 1.1 equiv of NaO^{t}Bu (106 mg, 1.1 mmol), 5 mol % of $Pd(O_2CCF_3)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of xylene. After 24 h at 120 °C, the mixture was adsorbed onto neutral alumina and eluted with 20% ethyl acetate in hexanes to give 163 mg (67%) of 2-(*N*-methyl-*N*-phenylamino)benzothiazole as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.2 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.39 (m, 4H), 7.28 (m, 2H), 7.03 (t, J = 8.2 Hz, 1H), 3.59 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.1, 152.6, 145.7, 131.1, 129.9, 127.3, 125.9, 125.8, 121.7, 120.4, 119.1, 40.4.

2-(Morpholino)-*N*-methylbenzimidazole[71] **(Table 3, entry 8).** Method B of the above general procedure was followed with 2-chloro-*N*-methylbenzimidazole (166 mg, 1.0 mmol), 1.0 equiv of morpholine (87.2 μL, 1.0 mmol), 1.1 equiv of K_3PO_4 (234 mg, 1.1 mmol), 5 mol % of $Pd(O_2CCF_3)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of xylene. After 14 h at 120 °C, the mixture was adsorbed onto neutral alumina and eluted with 50% ethyl acetate in hexanes to give 168 mg (77%) of 2-(morpholino)-*N*-methylbenzimidazole as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (m, 1H), 7.21 (m, 3H), 3.90 (t, J = 4.6 Hz, 4H), 3.63 (s, 3H), 3.34 (t, J = 4.6 Hz, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.3, 140.7, 135.4, 121.9, 121.5, 118.0, 108.4, 66.5, 50.5, 30.5.

2-(*N*′-Methyl-*N*′-phenylamino)-*N*-methylbenzimidazole[72]**(Table 3, entry 9).** Method B of the above general procedure was followed with 2-chloro-*N*-methylbenzimidazole (166 mg, 1.0 mmol), 1.0 equiv of *N*-methylaniline (108 μL, 1.0 mmol), 1.1 equiv of NaO^{t}Bu (106 mg, 1.1 mmol), 5 mol % of $Pd(O_2CCF_3)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of xylene. After 16 h at 120 °C, the mixture was adsorbed onto neutral alumina and eluted with 20% ethyl acetate in hexanes to give 176 mg (75%) of 2-(*N*′-methyl-*N*′-phenylamino)-*N*-methylbenzimidazole as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 6.5, 1.8 Hz, 1H), 7.30 (t, J = 8.0 Hz, 2H), 7.20 (m, 3H), 7.05 (t, J = 7.4 Hz, 1H), 6.94 (d, J = 8.1 Hz, 2H), 3.56 (s, 3H), 3.23 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.7, 147.5, 141.4, 135.2, 129.5, 123.2, 121.7, 121.3, 120.7, 118.0, 108.4, 41.5, 30.5.

2-(Morpholino)benzoxazole (Table 3, entry 10). Method B of the above general procedure was followed with 2-chlorobenzoxazole (153 mg, 1.0 mmol), 1.0 equiv of morpholine (87.2 μL, 1.0 mmol), 1.1 equiv of NaO^{t}Bu (106 mg, 1.1 mmol), 5 mol % of $Pd(O_2CCF_3)_2$, and 5 mol % of tri-*tert*-butylphosphine in 1 mL of toluene. After 16 h at 80 °C, the mixture was adsorbed onto neutral alumina and eluted with 20% ethyl acetate in hexanes to give 106 mg (52%) of 2-(morpholino)-benzoxazole as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 7.9, 0.9 Hz, 1H), 7.26 (dd, J = 8.0, 0.5 Hz, 1H), 7.17 (dt, J = 7.6, 1.1 Hz, 1H), 7.03 (dt, J = 7.7, 1.2 Hz, 1H), 3.81 (t, J = 4.9 Hz, 4H), 3.68 (t, J = 4.9 Hz, 4H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.1, 148.8, 142.9, 124.1, 120.9, 116.5, 108.8, 66.2, 45.7. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.52; H, 5.90; N, 13.51.

Preparation of $[Pd_2(\mu\text{-Br})_2(P^tBu_3)_2]$.[43,44] In a drybox, $Pd(dba)_2$ (140 mg, 0.243 mmol) and P^{t}Bu$_3$ (50 mg, 0.247 mmol) were weighed directly into a screw capped vial. A stir bar was added followed by 5 mL of toluene. 2-Bromothiophene (242 μL, 2.5 mmol) was added and the mixture was stirred for 30 min. The reaction was monitored by removing an aliquot and obtaining a ^{31}P NMR spectrum. Upon completion of the reaction, the mixture was concentrated in vacuo to approximately 2 mL, layered with 10 mL of ether, and placed at −40 °C for 24 h. The supernatant was removed, and the resulting green crystals were washed with 2 × 3 mL of pentane and dried in vacuo to give 78 mg (83%) of $[Pd_2(\mu\text{-Br})_2(P^tBu_3)_2]$ as dark green crystals: ^{1}H NMR (C_6D_6, 400 MHz) δ 1.31 (pseudo-triplet, J_{HP} = 5.96 Hz, 54H). ^{31}P{^{1}H} NMR (162 MHz, C_6D_6) δ 86.8 (s).

Amination Reactions Catalyzed by the Combination of $Pd(dba)_2$ and P^{t}Bu$_3$ Monitored by NMR Spectroscopy. In a drybox, heteroaryl bromide (0.25 mmol), NaO^{t}Bu (26 mg, 0.275 mmol), and amine (0.25 mmol) were weighed directly into a small vial. Benzene-d_6 (0.25 mL) was added and the resulting suspension was transferred to a screw cap NMR tube. $Pd(dba)_2$ (7 mg, 0.0125 mmol, 5 mol %), P^{t}Bu$_3$ (2.5 mg, 0.0125 mmol, 5 mol %), and P(mesityl)$_3$ (3 mg) were weighed into a small vial. Benzene-d_6 (0.25 mL) was added. After 60 min the catalyst suspension was added to the NMR tube. The reactions were monitored by obtaining ^{1}H and ^{31}P NMR spectra.

Amination Reactions Monitored by GC. In a drybox, heteroaryl bromide (0.25 mmol), NaO^{t}Bu (26 mg, 0.275 mmol), and amine (0.25 mmol) were weighed directly into a screw-capped vial with a Teflon septa. Toluene (0.25 mL) was added followed by 50 μL of a 0.5 M solution of naphthalene in toluene. $Pd(dba)_2$ (7 mg, 0.0125 mmol, 5 mol %) and P^{t}Bu$_3$ (2.5 mg, 0.0125 mmol, 5 mol %) were weighed into a small vial. Benzene-d_6 (0.2 mL) was added. After 5 min the catalyst suspension was added to the reaction mixture (t = 0). Aliquots of approximately 10 μL were removed from the reaction mixture at defined times and immediately diluted with ether (1 mL). The resulting solutions were analyzed by GC with comparison to isolated compounds. Reactions with other catalysts were performed in a similar procedure. Timing was always started upon addition of the catalyst to the reaction mixture.

Kinetic Experiments Measured by ^{1}H NMR Spectroscopy. Stock solutions of each reagent in benzene-d_6 were made up and stored at −35 °C: HNMePh (0.65 M, 70 μL in 1 mL of benzene-d_6), $NaOCEt_3$ (1.67 M, 315 mg in 1.5 mL), 2-bromothiophene (2.66 M, 387 μL in 1.5 mL of benzene-d_6), $Pd(P^tBu_3)_2$ (0.0126 M, 6.4 mg in 1 mL of benzene-d_6) and 1,3,5-trimethoxybenzene (0.06 M, 10 mg in 1 mL of benzene-d_6). A typical reaction mixture was prepared in a screw-capped NMR tube by mixing C_6D_6 stock solutions of HNMePh (20 μL), $NaOCEt_3$ (90 μL), 2-bromothiophene (150 μL), $Pd(P^tBu_3)_2$ (100 μL), and 1,3,5-trimethoxybenzene (50 μL) with enough C_6D_6 to make a total volume of 0.5 mL. The amine was added immediately prior to initiation of the data acquisition program. Zero-order rate constants were obtained by fitting a plot of the amine versus time to the expression $y = mx + b$, where m is the zero-order rate constant k_{obs}. NaO^{t}Bu was added as a solid in place of $NaOCEt_3$ when necessary.

Acknowledgment. We thank the NIH (GM-55382) for support of this work and Johnson-Matthey for a gift of palladium. M.U. was supported by Mitsubishi Chemical Corporation.

JO0266339

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