Cross-Coupling

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Selective Monoarylation of Primary Amines Using the Pd-PEPPSI-IPent^{Cl} Precatalyst**

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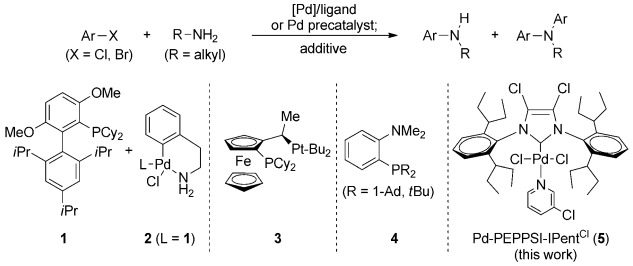
Abstract: *A single set of reaction conditions for the palladium-catalyzed amination of a wide variety of (hetero)aryl halides using primary alkyl amines has been developed. By combining the exceptionally high reactivity of the Pd-PEPPSI-IPent^{Cl} catalyst (PEPPSI = pyridine enhanced precatalyst preparation, stabilization, and initiation) with the soluble and non-aggressive sodium salt of BHT (BHT = 2,6-di-tert-butyl-hydroxytoluene), both six- and five-membered (hetero)aryl halides undergo efficient and selective amination.*

Secondary amines are not only important synthetic intermediates, but are also valuable commodities for investigation in the fields of medicine, materials science, and drug discovery.[1] Of the various routes available for preparing secondary aromatic amines, the palladium-catalyzed amination of aryl-(pseudo)halides[2,3] is one of the most robust methods available and serves as a valuable complement to reductive amination and substitution reactions.[4] Whereas the use of secondary amines as nucleophiles in this transformation is straightforward and leads to tertiary aniline products, the use of primary amines can produce either secondary or tertiary anilines resulting from mono- and diarylation, respectively, of the amine.[5] In practice, such mixtures of mono- and diarylated amines are often observed, and these mixtures can be difficult to separate and also have the disadvantage of lowering the reaction's efficiency for preparing the desired secondary aniline. Fundamentally, the ratio of secondary to tertiary aniline products observed for any particular amination is a consequence of the catalyst's ability to discriminate between the starting primary amine and the secondary aniline, which is the product of the initial catalytic cycle.

To address this selectivity problem, the steric and electronic properties of ancillary ligands have been varied in an effort to enhance catalyst binding with the primary amine over that of the secondary aniline product. This effort has led to some notable successes, such as the BrettPhos ligand **1** in conjunction with the BrettPhos precatalyst **2**,[6] the Josiphos ligand **3**,[7,5a] the DalPhos family (**4**),[8] as well as limited examples utilizing NHC (N-heterocyclic carbene) ligands (Scheme 1).[9] Despite these efforts, no single universal catalyst, which is capable of promoting the amination of aryl and five- and six-membered heteroaryl halides using either simple or functionalized primary amines, has been developed. We have previously reported that the Pd-PEPPSI-IPent family[10] of palladium precatalysts has shown extremely high reactivity for the coupling of secondary alkyl amines[11] and primary and secondary anilines[12] with six-membered aryl and heteroaryl chlorides and bromides. Herein, we demonstrate the application of these catalysts in the selective amination of six- and five-membered (hetero)aryl chlorides and bromides using simple or functionalized primary aliphatic amines governed under one general protocol.



Scheme 1. Previously reported systems (**1**–**4**) for selective amination of primary amines. The palladium precatalyst **5** is the focus of this study. PEPPSI = pyridine enhanced precatalyst preparation, stabilization, and initiation.

In an initial experiment, we probed the reactivity of Pd-PEPPSI-Pent^{Cl} (**5**)[13] in the amination of 4-chloroanisole (**6**) by using octyl amine (**7**) and cesium carbonate according to the conditions we previously outlined for the analogous amination of aryl chlorides by electron-deficient anilines (Table 1, entry 1).[12a] While complete conversion of the halide was observed at 80 °C, the reaction proceeded with low selectivity for the desired monocoupled product **8**. The use of other inorganic bases (e.g., entry 3) did not improve selectivity. However, in a reaction utilizing sodium *tert*-butoxide, which has been employed extensively by others,[14] the product **8** was formed with moderate selectivity (entry 4). We could improve the selective formation of **8** by lowering the catalyst loading and decreasing the reaction concentration such that **8** could be isolated in 90 % yield with high selectivity (65.6:1 **8**/**9**) after 90 min at 80 °C, and using just 0.5 mol % of

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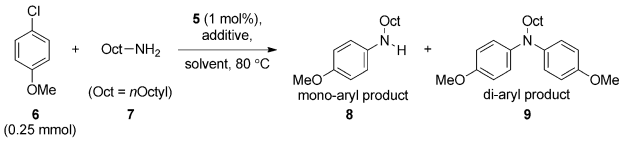
Table 1: Influence of basic additives on the selectivity and conversion of 4-chloroanisole **6** and octylamine (**7**) into **8** in the presence of **5**.[a]

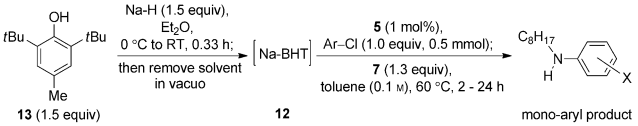


	Base (equiv)	Solvent (conc.)[b]	**8**/**9**[c]	ArCl Conv. [%]	**8** Conv. [%]
1[d]	Cs_2CO_3 (3.0)	DME (1.0)	3.3:1	100	71
2[d]	Cs_2CO_3 (3.0)	DME (0.25)	5.3:1	100	77
3[d]	$K_3PO_4 \cdot H_2O$ (3.0)	DME (0.25)	3.0:1	89	34
4[d]	NaO*t*Bu (1.3)	toluene (0.4)	4.9:1	86	58
5[e]	NaO*t*Bu (1.1)	toluene (0.1)	65.6:1	100	90[g]
6[g]	K-Chromanoxide (**10**; 1.3)	toluene (0.1)	1.7:1	100	32
7[g]	K-BHT (**11**; 1.3)	toluene (0.1)	7.4:1	100	63
8[h]	Na-BHT (**12**; 1.3)	toluene (0.1)	28.6:1	100	81
9[g]	Na-BHT (**12**; 1.3)	toluene (0.1)	25:1	100	95[e]

[a] Unless otherwise noted, the conversion of **6** and conversion into **8** were determined using ^{1}H NMR spectral analysis of the crude reaction mixture containing 1,4-$(CCl_3)_2$-C_6H_4 as internal standard. [b] Concentration with respect to **6** given in [mol L^{-1}]. [c] The ratio of **8**/**9** represents the ratio of desired monoarylation to the undesired diarylation. [d] Using 3 mol% of **5** and 1.3 equiv **7**. [e] Using 0.5 mol% of **5**, 1.1 mmol **7**, and 1.0 mmol of **6**. [f] Yield of **8** isolated after column chromatography. [g] Using isolated phenolate salt stored and weighed in glove box. [h] Using phenolate salt prepared in situ. DME = dimethyl ether.

catalyst (entry 5). Unfortunately, the use of sodium *tert*-butoxide and other alkali alkoxides is often problematic when functionalized aryl halides or amines are present.[15] To address this deficiency, we next examined the ability of phenolate derivatives to promote the selective formation of **8**. The use of potassium chromanoxide (**10**), previously reported by us to affect the arylation of highly functionalized starting materials with the Pd-PEPPSI-IPent catalyst,[15a] resulted in complete conversion of **6** but with no selectivity for **8** (entry 6). However, the use of the isolated potassium salt of BHT [2,6-di-*tert*-butyl hydroxytoluene (**11**)] did show enhanced selectivity (7.4:1 **8**/**9**) with full conversion of the electrophile. Unfortunately, there was only 63% conversion into **8** (entry 7). In an analogous reaction conducted with the isolated sodium BHT salt **12**, both the conversion into **8** increased as well as the selectivity (entry 8). In the course of these experiments, a significant increase in conversion into **8** was observed when **12** was prepared in situ rather than isolated and stored in a glove box. Therefore, we designed a simple procedure in which **12** is first prepared prior to adding the other reagents and the reaction solvent. By using this protocol, **8** was isolated in 95% yield and high selectivity (25:1 **8**/**9** in crude reaction mixture; entry 9) after purification of the crude reaction mixture using silica gel column chromatography. Although phenoxide derivatives have been employed in carbonylation[16] and closely related etherification reactions,[17] we did not observe the etherification product of **12** with **6**. Phenoxides such as **12** possess similar pK_b values as the inorganic carbonate and phosphate bases,

Table 2: Selective amination of aryl chlorides by **7** to give secondary aniline products.[a]



X = 4-OMe (**14**)	90% (22:1)	X = 4-CF_3 (**18**)	85%
X = 4-C(O)Me (**15**)	84% (32:1)	X = 2,6-Me_2 (**19**)	90%
X = 4-CN (**16**)	92% (12:1)	X = 4-NO_2 (**20**)	57%
X = 4-CO_2Me (**17**)	92%	X = 3-(CF_3) (**21**)	80%

[a] Yield of monoaryl product after purification of crude reaction mixture by column chromatography using silica gel. Unless otherwise noted, only the monocoupled product was observed in the ^{1}H NMR spectrum of the crude reaction mixture. See the Supporting Information for experimental setup.

but importantly they are much more soluble in organic solvents. Despite these merits, there appear to be only a limited number of examples where they are used as basic additives in palladium-catalyzed amination reactions.[15a,18]

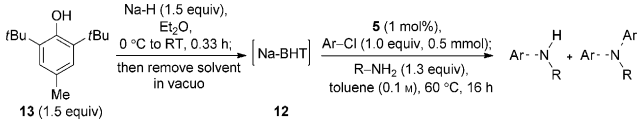
Using the productive results with Na-BHT, we were able to develop a robust method for the amination of (hetero)aryl halides with primary aliphatic amines catalyzed by Pd-PEPPSI-IPent^{Cl} complex **5**. The final conditions are shown at the top of Table 2. We found that a variety of interesting aryl chloride electrophiles with functionality including methoxy (**14**), keto (**15**), cyano (**16**), carbomethoxy (**17**), 4-trifluoromethyl (**18**), *o*-methyl disubstituted (**19**), and 4-nitro (**20**) groups could all be coupled in very high yield for the mono-aryl product, thus illustrating that the procedure is highly monoselective and broadly functional-group tolerant. In all instances where trace products were formed from over-arylation, the desired mono-aryl product was readily isolated in pure form after column chromatography on silica gel.

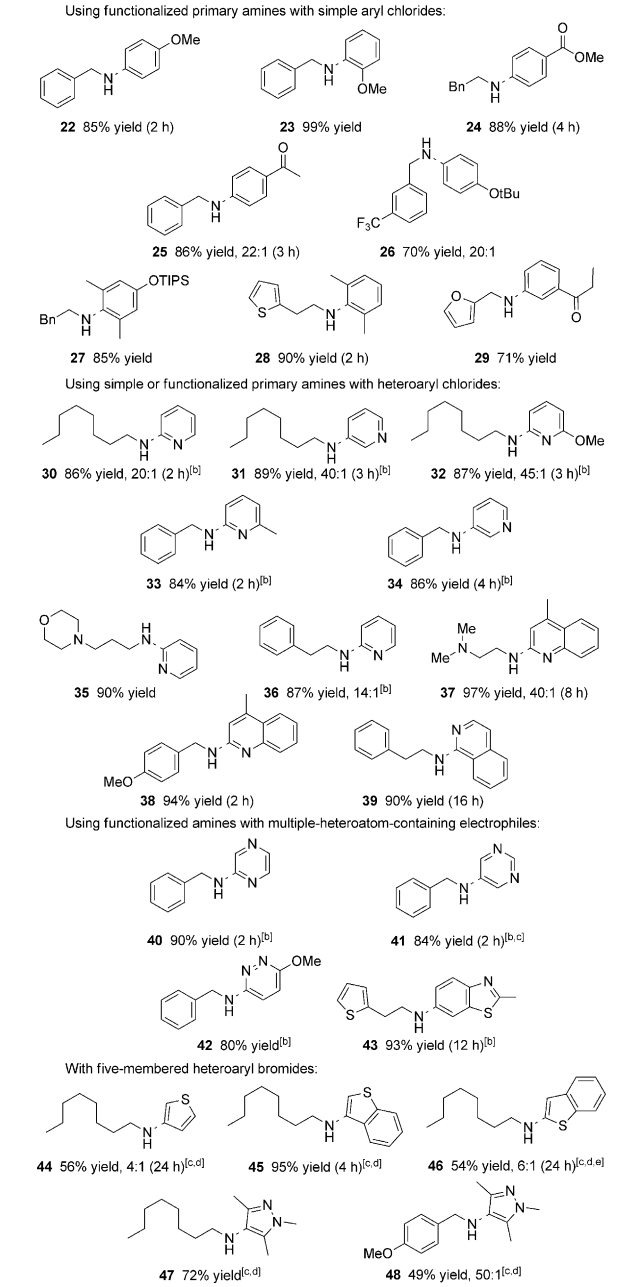
Having established that the reaction conditions outlined above were effective in promoting the amination of simple aryl chlorides using octyl amine, we next examined whether more elaborate amines could be coupled as effectively. Under the standard reaction conditions, benzylic, phenethyl, 2-furylmethyl, and 2-thiophenethyl derivatives were all competent nucleophiles in combination with activated and deactivated *ortho*-, *meta*-, and *para*-substituted electrophiles (**22**–**29**, Table 3).

These standard reaction conditions also facilitated the effective amination of six-membered heterocyclic chlorides and bromides, including 2- and 3-chloropyridines (**30**–**36**, Table 3), 2-chloro-4-methylquinoline (**37** and **38**), and 1-chloroisoquinoline (**39**) with simple or functionalized primary amines. Compounds possessing tertiary alkyl amine functionality (**35** and **37**) could be isolated in high purity using a simple extractive workup. Additionally, this single set of reaction conditions utilizing **5** could also promote the amination of electrophiles bearing multiple heteroatoms, such as 2-chloropyrazine (**40**), 5-bromopyrimidine (**41**), as well as pyridazine (**42**) and benzothiazole (**43**) derivatives.

The amination of five-membered heteroaryl halides is much more challenging than their six-membered heteroaryl halide counterparts.[19] However, we found that simply

Table 3: Scope of amination of (hetero)aryl halides using primary amines.[a]

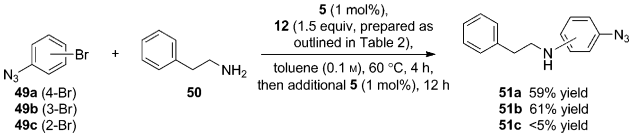




[a] Unless otherwise indicated, only the monoaryl product was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Yields are those of the products isolated after purification by column chromatography on silica gel. [b] 50 °C. [c] Using Ar–Br. [d] 80 °C. [e] Using 3 mol % of **5**.

elevating the temperature to 80 °C, and in some cases increasing the catalyst loading to 3 mol %, led to excellent results without otherwise altering the standard conditions (Table 3). Thus, the electrophiles 3-bromothiophene (**44**), 3-bromobenzothiophene (**45**), 2-bromobenzothiophene (**46**), and 4-bromo-1,3,5-trimethyl-1*H*-pyrazole (**47** and **48**) were coupled nicely to primary alkyl amines with excellent mono-selectivity.

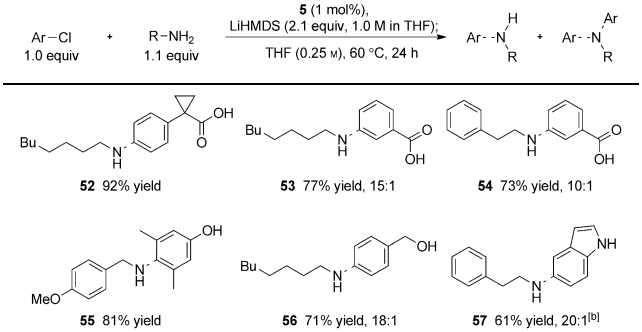
The mild reaction conditions described above result from the combination of the highly active and selective palladium catalyst **5** with the soluble and nonaggressive basic additive **12**, thus prompting us to investigate the possibility of halo-(azido)benzene electrophiles participating in the amination reaction. To the best of our knowledge, such electrophiles have not been explored in any palladium- or nickel-catalyzed aminations using primary aliphatic amines.[20] By using the reaction conditions outlined in Scheme 2, the amine **50** reacted with both *para*- (**49a**) and *meta*-azidobromobenzene (**49b**) participated to provide the products **51a** and **51b**, respectively. The *ortho* derivative **49c** generated only 5 % yield of the aminated product. In these cases, none of the diarylation product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.



Scheme 2. Selective monoarylation of primary amines with azide-containing oxidative addition partners.

To extend the scope of the amination employing **5**, electrophiles bearing acidic functional groups were next examined (Table 4). Possibly as a result of the complete insolubility of the starting materials in this case, we found that the amination worked best with LiHMDS as the base.[21,22] The amination of benzoic acid and cyclopropanecarboxylic acid derivatives (**52**–**54**) with a variety of primary amines occurred smoothly in the presence of 1 mol % of **5** and an

Table 4: Representative amination of electrophiles bearing carboxylic acid, alcohol, or 1*H*-indole functionality using **5** (1 mol %) in conjunction with LiHMDS.[a]



[a] Yield of product isolated after column chromatography using 0.5 mmol of (hetero)aryl halide. Unless otherwise indicated, only the mono-aryl product was observed by analysis of the crude reaction mixture using ^{1}H NMR spectroscopy. See the Supporting Information for experimental setup. [b] Using Ar-Br. HMDS = hexamethyldisilazide, THF = tetrahydrofuran.

extra equivalent of LiHMDS.[6a,7c,22] Through the same approach, phenol (**55**) and even benzylic-alcohol-containing electrophiles (**56**) were readily aminated. Finally, the amination of a free, unprotected indole (**57**) was also feasible through this approach.

In conclusion, we have demonstrated that Pd-PEPPSI-IPent^{Cl}[23] (**5**) is a highly effective catalyst for the amination of both six- and five-membered (hetero)aryl halides in combination with the mild and soluble sodium salt of butylated hydroxytoluene (Na-BHT; **12**). By simply preparing **12**, and then adding the other components to the reaction flask, a wide variety of functionalized aryl halides and amines smoothly undergo coupling to selectively give secondary anilines and heteroaromatic amines.

Keywords: amination · cross-coupling · palladium · PEPPSI · selectivity

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[21] It is also possible that protic functional groups participate in a rapid and reversible equilibrium with solvated LiHMDS aggregates. See: B. L. Lucht, D. B. Collum, *Acc. Chem. Res.* **1999**, *32*, 1035–1042.

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[23] Pd-PEPPSI-IPent^{Cl} precatalyst is available through Total Synthesis Ltd (http://www.totalsynthesis.ca).

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