Palladium-Catalyzed N-Monoarylation of Amidines and a One-Pot Synthesis of Quinazoline Derivatives
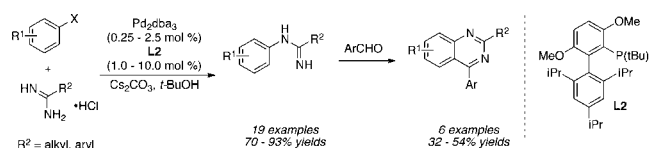
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ABSTRACT

A method for the Pd-catalyzed N-arylation of both aryl and alkyl amidines with a wide range of aryl bromides, chlorides, and triflates is described. The reactions proceed in short reaction times and with excellent selectivity for monoarylation. A one-pot synthesis of quinazoline derivatives, via addition of an aldehyde to the crude reaction mixture following Pd-catalyzed N-arylation, is also demonstrated.

Amidines are important functional groups in modern drug synthesis, due in part to their ability to form water-soluble salts[1] and their structural similarity to the biologically ubiquitous guanidines. In fact, many of the top-selling pharmaceuticals of the past few years feature an amidine as a key structural component.[2]

Recently, compounds containing *N*-arylamidines have shown promise as treatments for inflammation[1] and pain.[3]

N-Arylamidines can also serve as precursors for the synthesis of other biologically important heterocycles such as imidazoles,[4] benzimidazoles,[5] quinazolinones,[6] and quinazolines.[7] Traditionally, *N*-arylamidines have been prepared via addition of aniline into an activated nitrile or amide (variation of the Pinner reaction), or via addition into the corresponding thioimidic ester.[8] Recently, trihaloethyl imidates have also been identified as excellent reagents for the synthesis of substituted amidines.[9] Nonetheless, these methods all require the use of either strongly acidic or basic conditions, and/or the preparation of activated intermediates. The direct N-monoarylation of free amidines, many of which are commercially available as their corresponding HCl salts, represents an attractive alternative for rapid and efficient access to a wide range of such compounds.

Despite significant advances in the field of transition-metal catalyzed C−N cross-coupling, the application of this technology for substrates such as amidines that can bind strongly to the reactive metal center remain challenging. Even so, there have been several recent reports of

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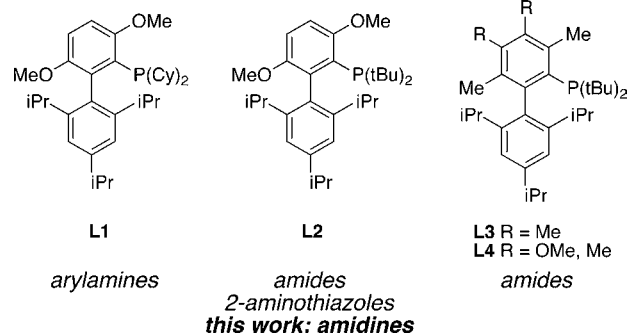
(8) For a review of amidine synthesis, see: Dunn, P. J. Amidines and *N*-Aryl Amidines. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, I., Taylor, R., Eds.; Elsevier: Oxford, U.K., 2005; Vol. 5, pp 655−699.

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successful amidine N-arylation, particularly in the area of copper catalysis.[10] While most of these require *ortho*-directing groups[11] or 1,2-dihaloarene electrophiles[12] to provide fused heterocycles directly, there has been a single report of the copper-catalyzed mono-N-arylation of benzamidine and acetamidine derivatives by Antilla.[13] Interestingly, the addition of ligands to the copper-based salt precursor had no effect on reaction rate, likely due to chelation of the amidine substrate.[14] While Antilla was able to obtain a variety of phenyl amidine-derived *N*-monoarylamidines, the use of other amidine nucleophiles was less successful. Further, neither aryl sulfonates nor aryl chlorides or bromides were viable substrates. Thus, there remains a need for a more general coupling method.

Over the past several years, our group has demonstrated the effectiveness of biarylphosphine ligands for the palladium-catalyzed monoarylation of amine nucleophiles, which previously were shown to poison active catalytic Pd-based species via competitive chelation to the metal center. Using such catalytic systems we were able to achieve efficient C−N cross-coupling of a variety of arylamines containing embedded amidine structures (using **L1** and **L2**)[15] and amides (using **L2** and **L3**).[16] We thus postulated that a similar system might be effective for the N-monoarylation of amidines. To our knowledge, there have been no previous reports of palladium-catalyzed amidine arylation, though there is a single report of the N-arylation of *O*-methylamidoximes using a Pd-Xantphos system.[17] Herein, we report the development of a palladium-catalyzed N-monoarylation of a wide range of amidine nucleophiles with aryl electrophiles.

We began our investigation by examining the coupling of benzamidine with aryl bromides and quickly discovered that, analogously to the coupling of primary amides and 2-aminothiazoles, tBuBrettPhos (**L2**) was the optimal ligand, and *t*-BuOH, the optimal solvent. In line with many of the copper-catalyzed methods for amidine coupling, we also found Cs₂CO₃ to be uniquely effective as the

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(13) Cortes-Salva, M.; Garvin, C.; Antilla, J. C. *J. Org. Chem.* **2011**, *76*, 1456. A mono-N-arylation of guanidine (not isolated) has also recently been described: Xing, H.; Zhang, Y.; Lai, Y.; Jiang, Y.; Ma, D. *J. Org. Chem.* **2012**, *77*, 5449.

(14) For a review on the coordination chemistry of amidine ligands, see: Barker, J.; Kilner, M. *Coord. Chem. Rev.* **1994**, *133*, 219.
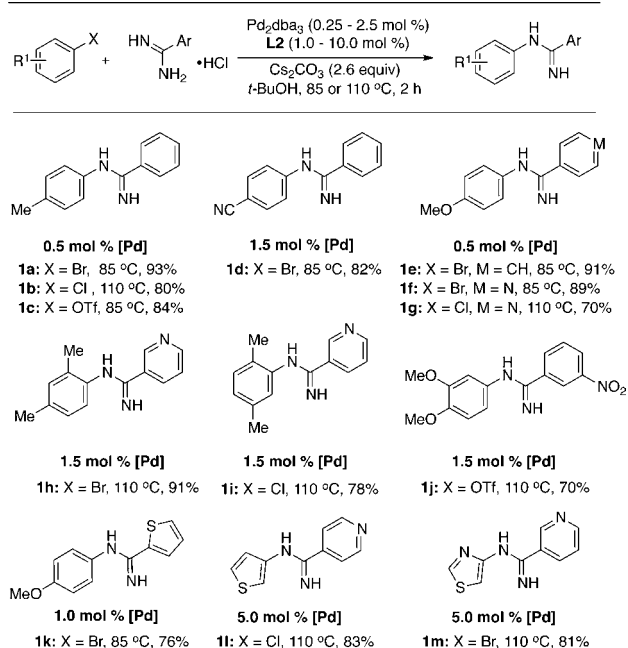
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(18) See Supporting Information, Table S1 for further optimization details.

Figure 1. Biaryl phosphine ligands utilized in the catalytic Pd-based C−N cross-coupling reactions with N-containing and potentially chelating substrates.

base component.[18] Significantly, we found the particle size of Cs₂CO₃ to be crucial; no reaction or very low conversion resulted when the base was used directly from the commercial source. However, when the base was ground thoroughly with a mortar and pestle prior to use,[19] the reaction consistently proceeded to full conversion and with yields ranging from 70 to 93%.[20] We also found that, in order for the transformation to be effective and reproducible for a wide range of electrophiles and nucleophiles, a preactivation method was required to obtain the active catalyst.[21,22]

Under these optimized reaction conditions, a variety of aryl amidines could be coupled with a wide range of aryl bromides, chlorides, and triflates in short reaction times (2 h)[23] and with relatively low catalyst loadings (Scheme 1). In particular, electron-rich bromides and triflates were excellent substrates, undergoing the N-monarylation with just 0.5 mol % of Pd at 85 °C (**1a−b, 1e−f**). Electron-poor electrophiles (**1d**), as well as a nitro-substituted aryl amidine nucleophile (**1j**), required slightly higher catalyst loadings (1.5 mol % of Pd). Moderately sterically hindered electrophiles (**1 h−i**), as well as electron-rich aryl chlorides (**1c, 1g**), also required elevated reaction temperatures (110 °C) to achieve full conversion. Significantly, we found that both heterocyclic amidines and aryl halides coupled to form the corresponding *N*-arylamidines in high yields (**1f−g, 1h−i, 1k**), though five-membered heterocyclic aryl halides required a higher catalyst loading (5 mol % of Pd) to achieve high yields of coupled products (**1l−m**).

(19) See Supporting Information for full experimental details.

(20) In most cases complete conversion of the electrophile was observed. Yields of less than 90% can be explained by the presence of small amounts of the *N*,*N*′-bisarylamidine products along with, in some cases, loss of product in isolation due to the extremely polar nature of the compounds.

(21) Ueda, S.; Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8944.

(22) Consistently higher yields were observed when the amidine hydrochloride salt was prestirred and heated with Cs₂CO₃ in *t*-BuOH prior to introduction of the preactivated catalyst solution.

(23) In general, no further conversion was observed after 2 h; reactions that were not complete in that amount of time were instead rerun with higher catalyst loadings.

Scheme 1. N-Monoarylation of Aryl Amidines[a]

0.5 mol % [Pd]
1a: X = Br, 85 °C, 93%
1b: X = Cl, 110 °C, 80%
1c: X = OTf, 85 °C, 84%

1.5 mol % [Pd]
1d: X = Br, 85 °C, 82%

0.5 mol % [Pd]
1e: X = Br, M = CH, 85 °C, 91%
1f: X = Br, M = N, 85 °C, 89%
1g: X = Cl, M = N, 110 °C, 70%

1.5 mol % [Pd]
1h: X = Br, 110 °C, 91%

1.5 mol % [Pd]
1i: X = Cl, 110 °C, 78%

1.5 mol % [Pd]
1j: X = OTf, 110 °C, 70%

1.0 mol % [Pd]
1k: X = Br, 85 °C, 76%

5.0 mol % [Pd]
1l: X = Cl, 110 °C, 83%
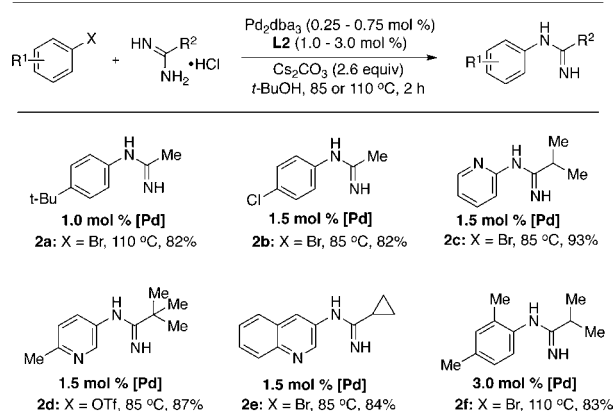
5.0 mol % [Pd]
1m: X = Br, 110 °C, 81%

[a] Reaction conditions: ArX (1.0 mmol), amidine hydrochloride (1.1 mmol), Pd$_2$dba$_3$ (n mol %), L2 (2n mol %), Cs$_2$CO$_3$ (2.6 mmol), t-BuOH (4 mL/mmol of ArX), 85 or 110 °C, 2 h; isolated yields, average of two runs.

Scheme 2. N-Monoarylation of Alkyl Amidines[a]

1.0 mol % [Pd]
2a: X = Br, 110 °C, 82%

1.5 mol % [Pd]
2b: X = Br, 85 °C, 82%

1.5 mol % [Pd]
2c: X = Br, 85 °C, 93%

1.5 mol % [Pd]
2d: X = OTf, 85 °C, 87%

1.5 mol % [Pd]
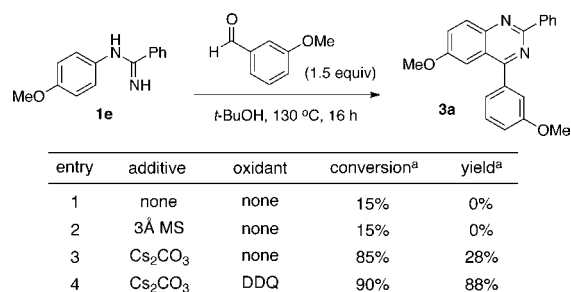2e: X = Br, 85 °C, 84%

3.0 mol % [Pd]
2f: X = Br, 110 °C, 83%

[a] Reaction conditions: ArX (1.0 mmol), amidine hydrochloride (1.1 mmol), Pd$_2$dba$_3$ (n mol %), L2 (2n mol %), Cs$_2$CO$_3$ (2.6 mmol), t-BuOH (4 mL/mmol), 85 or 110 °C, 2 h; isolated yields, average of two runs.

We next evaluated alkyl amidines as coupling partners and found that a range of alkyl amidines could be arylated under the same reaction conditions (Scheme 2). Significantly, acetamidine was a competent nucleophile, and while more electron-rich electrophiles required slightly elevated temperatures and catalyst loadings (**2a**), more activated electrophiles such as 4-chlorobromobenzene reacted under the same conditions as required for the N-arylation of aryl amidines (**2b**). Notably, the coupling of 4-chlorobromobenzene also proceeded with excellent selectivity for bromide coupling. Both branched (**2c**, **2d**) and cyclopropenyl (**2e**) amidines also coupled readily, and with a range of heteroaryl halides. In the case of a more hindered electrophile such as 2,4-dimethylbromobenzene, however, the coupling was significantly more difficult with an alkyl amidine than with an aryl amidine, and a catalyst loading of 3 mol % was required in order to achieve full conversion (**2f**).

Having realized a general and efficient method for the N-monoarylation of amidines, we next sought to extend this method to a one-pot synthesis of quinazoline derivatives. The conversion of N-monoarylamidines to quinazolines, via condensation of the unsubstituted nitrogen onto an aldehyde and subsequent electrocyclization and oxidation, is known. However, only substrates derived from benzamidine were reported.[24] We sought to develop a method that could be implemented into a sequential,

one-pot procedure via simply introducing the aldehyde to the crude reaction mixture following arylation of the amidine.

The feasibility of the proposed transformation was evaluated by examining the reaction of purified N-arylamidine **1e** with m-anisaldehyde in t-BuOH (Scheme 3). We found that simply mixing the two and heating to 130 °C for 16 h resulted in very low conversion of the amidine and none of the desired product was obtained (entry 1). The inclusion of molecular sieves, to potentially aid in imine formation, offered no improvement (entry 2). However, the addition of Cs$_2$CO$_3$ (conveniently the same base used for the amidine coupling, *vide supra*) was successful in promoting the desired reaction, and the quinazoline product was obtained in 28% yield (entry 3). Interestingly, we noticed that in this case the N-arylamidine was almost entirely consumed, and analysis of ^{1}H NMR and LCMS data suggested the presence of a large amount of the cyclized but unoxidized dihydroquinazoline adduct. Indeed, the addition of DDQ as a final step for this transformation dramatically increased the yield of quinazoline product significantly to 88% (entry 4).

Scheme 3. Optimization of Quinazoline Formation[a]

entry	additive	oxidant	conversion[a]	yield[a]
1	none	none	15%	0%
2	3Å MS	none	15%	0%
3	Cs$_2$CO$_3$	none	85%	28%
4	Cs$_2$CO$_3$	DDQ	90%	88%

[a] Conversion and yield were calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

(24) (a) Kumar, V.; Sharma, A. K.; Mahajan, M. P. *Synth. Commun.* **2004**, *34*, 49. (b) Kumar, V.; Mohan, C.; Gupta, M.; Mahajan, M. P. *Tetrahedron* **2005**, *61*, 3533.

We next applied these conditions to the one-pot synthesis of quinazolines and were pleased to discover that **3a** could be obtained in 51% isolated yield from 4-bromoanisole (Scheme 4). For the one-pot procedure, we found that employing the aryl halide and amidine in a 1:1 ratio, as opposed to the 1:1.1 ratio which is optimal in obtaining N-monoarylated products, resulted in slightly higher yields and a cleaner overall reaction. We also found that the extra equivalent of Cs_2CO_3 required for the quinazoline formation could be included from the beginning, simplifying the reaction setup routine.
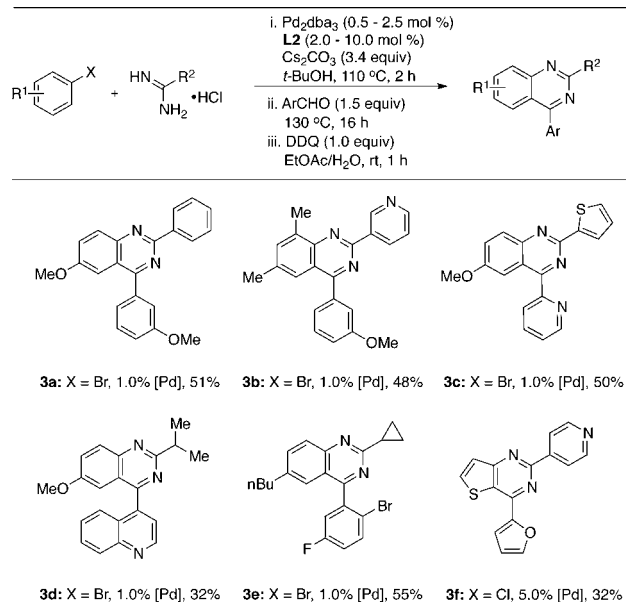
An evaluation of the scope of this reaction revealed that heterocyclic amidines (**3b−c**, **3f**) and aldehydes (**3c−d**, **3f**) worked well as substrates under the optimal conditions, as did *ortho*-substituted aryl bromides (**3b**). While the quinazoline derived from isobutanamidine was obtained in more modest yield (**3d**), cyclopropaneamidine was a good substrate and provided quinazoline **3e**, which is derived from a polyhalogenated aldehyde capable of further transformation, in 55% yield. We could also obtain a polyheterocyclic thienopyrimidine product (**3f**) under these same reaction conditions in 32% yield.

While this one-pot procedure was effective for the rapid generation of many interesting substituted quinazolines, it should be noted that the substrate scope has some limitations. For a successful transformation, only relatively electron-rich aryl halides were effective; the use of electron-poor aryl halides resulted in little or no desired product. The same is true, to an extent, for the amidine component. With respect to the aldehyde component, only aryl aldehydes have been successful to date at producing synthetically useful amounts of products.[25]

In conclusion, we have developed a palladium-catalyzed N-monoarylation of amidines that proceeds in short reaction times and with excellent selectivity for monoarylation. Further, we combined this transformation with a base-promoted imine formation/electrocyclization/oxidation sequence to synthesize substituted quinazolines via a facile, one-pot procedure. Given the importance of amidines and quinazolines in the field of medicinal chemistry, we expect these methods to find use as practical and convenient alternatives to the existing approaches in their synthesis.

(25) See Supporting Information, Table S2 for specific examples of quinazoline syntheses which proceeded in lower yields or failed to produce appreciable amounts of product.

Scheme 4. One-Pot Synthesis of Quinazoline Derivatives[a]

3a: X = Br, 1.0% [Pd], 51% **3b:** X = Br, 1.0% [Pd], 48% **3c:** X = Br, 1.0% [Pd], 50%

3d: X = Br, 1.0% [Pd], 32% **3e:** X = Br, 1.0% [Pd], 55% **3f:** X = Cl, 5.0% [Pd], 32%

[a] Reaction conditions: (i) ArX (1.0 mmol), amidine hydrochloride (1.0 mmol), Pd_2dba_3 (*n* mol %), **L2** (2*n* mol %), Cs_2CO_3 (3.4 mmol), *t*-BuOH (4 mL/mmol of ArX), 110 °C, 2 h; (ii) aldehyde (1.5 mmol), 130 °C, 16 h; (iii) DDQ (1 mmol), EtOAc/H_2O, rt, 1 h; isolated yields, average of two runs.

Supporting Information Available. Experimental procedures along with experimental and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.