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Catalyst-Directed Chemoselective Double Amination of Bromo-chloro(hetero)arenes: A Synthetic Route toward Advanced Amino-aniline Intermediates

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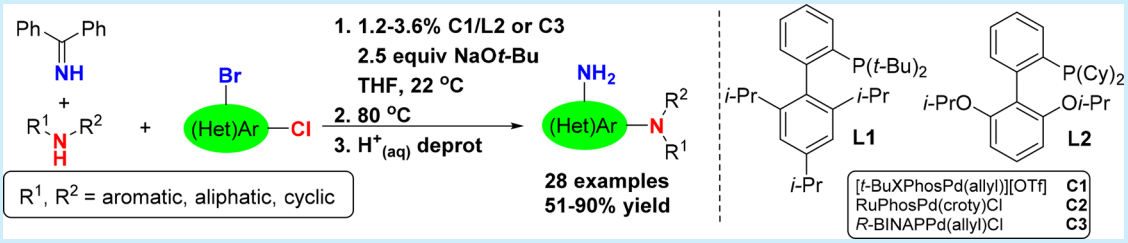
Supporting Information



ABSTRACT: A chemoselective sequential one-pot coupling protocol was developed for preparing several amino-anilines in high yield as building blocks for active pharmaceutical ingredients (APIs). Site (Cl vs Br on electrophile) and nucleophile (amine vs imine) selectivity is dictated by the catalyst employed. A Pd-crotyl(*t*-BuXPhos) precatalyst selectively coupled the Ar−Br of the polyhaloarene with benzophenone imine, even in the presence of a secondary amine, while Pd-based RuPhos or (BINAP)Pd(allyl)Cl coupled the Ar−Cl site with secondary amines.

Combining a multistep synthesis into a one-pot protocol dramatically increases the process efficiency, safety, and economics, in addition to making the synthesis environmentally friendly by limiting the isolation, purification, and exposure of the intermediates.[1] Despite obvious advantages, the practicality of multicomponent reactions is limited due to challenges associated with the selectivity, which can lead to byproduct formation. In theory, orthogonal reactivity provided by the different catalytic systems can be effectively utilized for selective one-pot transformations with higher control over the selectivity.[2] The use of catalytic sequential multicomponent reactions was earlier demonstrated for the selective coupling of various nucleophiles with polyhaloarenes. Initial reports from the Heck group highlighted the sequential alkenylation of di-iodo- and bromo-iodo-benzene.[3] However, the selectivity and overall yield of the reactions were poor. The scope of selective sequential coupling reactions was subsequently extended to borylation−Suzuki,[4] Suzuki−Suzuki,[5] Heck−Suzuki,[6] Heck−Sonogashira,[7] and Heck−Heck[7,8] coupling reactions. Aromatic and heteroaromatic amines have also been accessed by exploiting sequential amination−Sonogashira[9] and amination−Suzuki−Stille reactions.[10] Intra- and intermolecular double-*N*-arylation[11] were also employed for the synthesis of carbazole[12] and triaryl amines,[13] respectively. Both selectivity and efficiency of the processes were enhanced for those reactions that utilized well-defined catalytic systems containing specialty ligands.[4b,c]

The amino-aniline linkage that encompasses both NH_2 and secondary amine functionalities on a single terminal aryl or heteroaryl ring is an important pharmaceutical core that is encountered in new drugs and drug candidates with various therapeutic applications.[14] Notable examples include new oncology drugs such as anaplastic lymphoma kinase (ALK) tyrosine kinase receptor inhibitor *Brigatinib*[14c] and drug candidates such as ATP-competitive cyclin-dependent kinase (CDK) *Milciclib*[14a] and selective FAK inhibitor PND-1186[14b] (Figure 1A).

The most common strategy to prepare amino-anilines involves a two-step synthesis: amination of a nitro-haloarene via noncatalytic nucleophilic aromatic substitution, followed by Pd/C-catalyzed reduction of nitro groups (Figure 1B, top).[15] The utility is restricted due to limited substrate scope, poor functional group tolerance of the nucleophilic aromatic substitution, limited substrate availability, and cost.[16] The free amino-anilines are known to undergo oxidative degradation during workup, isolation, and storage. These advanced intermediates are often used toward the end of the synthesis of complex drug molecules. Therefore, the impurity profile may impose complications during the purification process, thereby incurring lower overall efficiency and process economics. In order to address these limitations, we were interested in preparing protected amino-anilines via a sequential catalytic double amination of dihaloarenes (Figure 1B, bottom) with secondary amines and an ammonia generating imine. This synthetic strategy would also provide access to a library of intermediates for quick availability at the drug discovery stage.[17]

The Pd-catalyzed coupling of secondary amines is well established in the literature.[18] The direct synthesis of primary aryl amines using ammonia with an aryl halide has not become a practical method due to low functional group tolerance of the substrates

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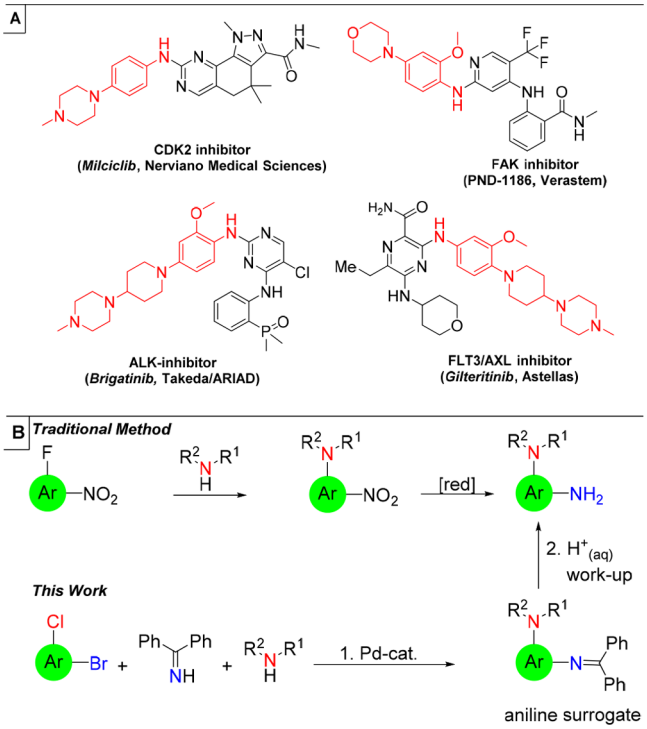
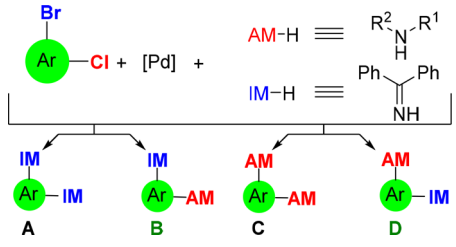


Figure 1. (A) Examples of relevant pharmaceutical targets. (B) Synthetic routes for the preparation of amino-anilines.

and potential overamination.[19] More reliable ammonia surrogates such as benzophenone imine or carbamates are more desirable,[18a,20] as the deprotection process is high yielding and scalable under mild conditions.[21]

A four-vector catalytic reaction involving oxidative addition, transmetalation, and reductive elimination steps, in the presence of a nonselective catalyst, assuming full conversion, can statistically generate a complex mixture of products (Scheme 1).

Scheme 1. Possible Product Distribution Arising from 4-Vector Coupling Reaction



The reactivity has commonly been proclaimed to depend on C−X bond dissociation energy, although the nature of the catalyst, solvent, and other reaction parameters are also known to be important.[22,23] The selectivity of the subsequent transmetalation and reductive elimination steps will primarily depend on the propensity of the catalytically active species to interact with one nucleophile over the other (e.g., amine vs imine) to generate up to four possible products (Scheme 1). We have undertaken this investigation with an objective of finding catalytic systems that will be highly selective for directed, streamlined oxidative addition and transmetalation steps toward the formation of the desired product (Scheme 1, **B** and/or **D**).

Initial selectivity tests were performed using *t*-BuXPhos (**L1**)- and RuPhos (**L2**)-based catalysts, which were previously reported to be effective for imination and secondary amination, respectively by Buchwald and others.[18a,21a,24] The selectivity of the precatalysts was first examined in a model three-component, 4-vector reaction mixture, containing 1-bromo-3-chlorobenzene, piperidine, and benzophenone imine (Table 1).

At room temperature, **C1** showed exceptional selectivity toward the formation of product **2**, while **C2** was practically inactive at room temperature (Table 1, entries 1 and 2). The predominant formation of product **2** was also observed when both precatalysts were present in the reaction mixture, indicating that **C2** does not interfere with the performance of **C1** (entry 3). The reaction involving **C1** at 22 °C for 90 min, followed by heating at 80 °C, gave the desired product **6** in poor yield (entry 4). This result shows that **C1** efficiently and selectively catalyzes the coupling of the benzophenone imine in the presence of piperidine, but it is a poor catalyst for the amination with piperidine (secondary amine) even at elevated temperatures. When the reaction was performed in the presence of imine and piperidine at 80 °C, precatalyst **C2** showed no conversion to the desired product **6** (entry 5). Surprisingly, when the reaction was repeated with no imine, aminated product **3** was isolated quantitatively, indicating that the imine is deterring the efficiency of **C2** (entry 6). The reaction, where both precatalysts were present, gave **6** in good yield (entry 7), with major byproducts **4** and **5**. These originated from undesired amination during the first coupling step. To determine whether the use of preisolated **C2** can be eliminated, RuPhos (**L2**) was added, instead of **C2**. Product **6** was obtained in 83% yield, indicating that ligand exchange is taking place at elevated temperature to provide the required metal ligand combination for the second coupling to occur (entry 8 vs 7).[25] It should be noted that the reaction conditions could be further fine-tuned for individual substrates to gain optimal selectivity toward the desired product.

The conditions for the one-pot sequential coupling (entry 8) were successfully applied to various bromo-chloro(hetero)arene electrophiles. The isolated yields of the amino-anilines after imine cleavage are reported, with the conversions of the corresponding imine protected anilines in parentheses (Scheme 2). The amination of unsubstituted *meta*- and *para*- bromo-chlorobenzene resulted in selective formation of **7** and **8** in good yields, while the *ortho*-substituted substrate gave no appreciable amount of **9**. The sequential coupling of methoxy- (**10**−**12**), fluoro- (**13** and **14**), and methyl- (**15**−**17**) substituted bromo-chloro-arenes gave the desired products in good to excellent yields, with exceptional selectivity. However, higher catalyst loadings were required to achieve full conversions for **11**, **12**, **14**, **16**, and **17**.

The product arising from this *ortho* isomer (**9**) is a chelating ligand, capable of replacing a phosphine ligand from the Pd-coordination sphere. The resulting catalyst poisoning may be responsible for the poor reactivity observed for this electrophile, compared to *para*- and *meta*-isomers.

Finally, coupling of pyridine-based substrates was attempted using a **C1**/**L2** mixture as a catalytic system, which gave chloroiminopyridines (monocoupled) as the major product, regardless of the amount of substrate, catalyst loading, temperature, and reaction time. Similarly, poor reactivities have been reported for substrates containing pyridine rings, where the catalyst is deactivated via Pd-pyridine coordination.The catalysts containing chelating ligands, on the other hand, exhibited an increased stability toward coordinating substrates and showed superior activity.[26] To test this concept, a precatalyst, containing a chelating ligand ((*R*-BINAP)Pd(allyl)Cl), was used in place of **L1** to obtain the desired coupling products (**18**−**20**) in excellent yields.

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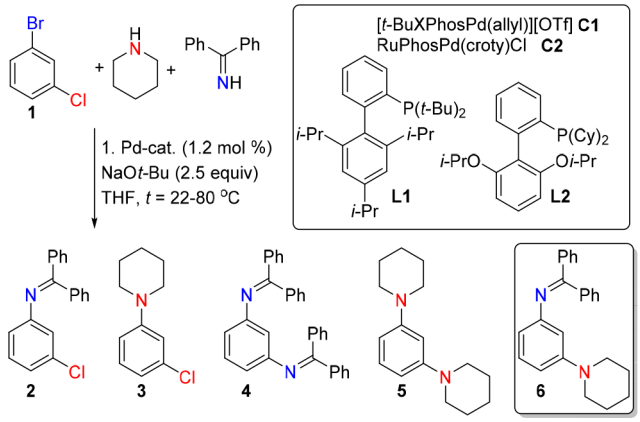
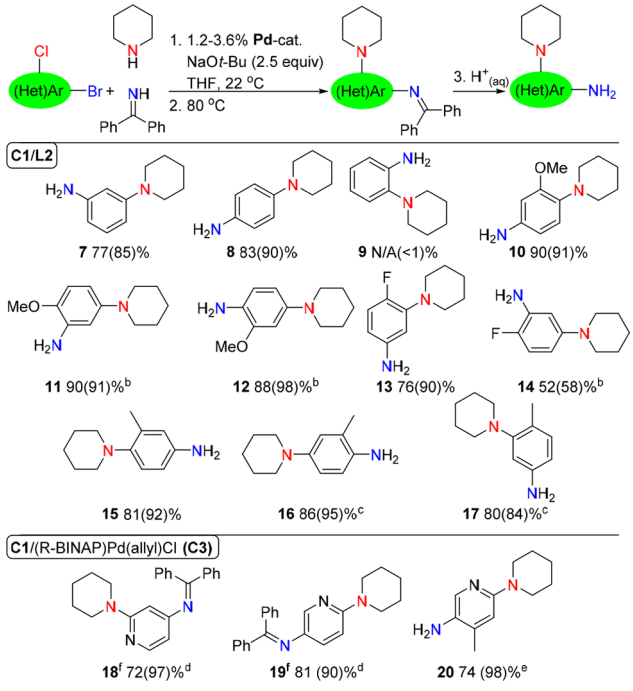
Table 1. Selectivity and Activity of Palladium Precatalysts toward Sequential Double Amination of 1-Bromo-3-chlorobenzene (1)[a]



entry	cat.	*t* (°C)	**1** (%)[c]	**2** (%)[c]	**3** (%)[c]	**4** (%)[c]	**5** (%)[c]	**6** (%)[c]
1	**C1**	22	1	89	10	0	0	**0**
2	**C2**	22	92	4	4	0	0	**0**
3	**C1/C2**[b]	22	0	88	12	0	0	**0**
4	**C1**	22−80[d]	0	68	9	10	0	**13**
5	**C2**	22−80[d]	87	9	4	0	0	**0**
6	**C2**	80[e]	0	0	87	0	13	**0**
7	**C1/C2**[b]	22−80[d]	0	0	0	14	10	**76**
8	**C1/L2**[f]	22−80[d]	0	0	0	9	8	**83**

[a]Conditions: 2.5 mmol of NaO*t*-Bu, 1.0 mmol of **1**, 1.1 mmol of benzophenone imine, 1.1 mmol of piperidine, 1.2 mol % of catalyst, 4 mL of THF, with reaction time of 1.5 h. [b]1.2 mol % of C1 and 1.2 mol % of C2. [c]Determined as relative integrations of GC peaks. [d]Reacted for 1.5 h at 22 °C followed by 2 h at 80 °C. [e]Imine was not added to the reaction mixture. [f]1.2 mol % of **C1** and 1.2 mol % of **L2**.

Scheme 2. Substrate Scope of Double Amination of (Hetero)aryl-dihalides[a]



[a]Conditions: 2.5 mmol of NaO*t*-Bu, 1.0 mmol of aryl-dihalide, 1.1 mmol of benzophenone imine, 1.1 mmol of amine, 1.2 mol % of **C1** and 1.2 mol % of **L2**, 4 mL of THF, 1.5 h at 22 °C followed by 12 h at 80 °C. Yields reported: isolated; in parentheses GC-yield of the imine product. [b]3.6 mol % of **C1** and 3.6 mol % of **L2**. [c]2.4 mol % of **C1** and 2.4 mol % of **L2**. [d]1.0 mol % of **C1** and 2.0 mol % of **C3**. [e]2.0 mol % of **C1** and 4.0 mol % of **C3**. [f]The product was isolated as imine protected aniline, due to poor stability of the corresponding amino-anilline.

Addition of *R*-BINAP as a ligand instead of **C3** gave inferior results, unlike in the earlier cases.

Unfortunately, only activated 2-chloro-substituted pyridines yielded the desired products, indicating the importance of the activated carbon−chloride vector for a successful reaction. We are currently exploring other catalysts to resolve this limitation. It should be noted that the products **18** and **19** are isolated as protected anilines, because their corresponding free amines are unstable. Particularly, decomposition was more pronounced with the aniline derived from **19**. This observation illustrates an additional advantage of this method, compared to the conventional preparation routes.

Unsubstituted *para*- and *meta*-1-bromo-chlorobenzene were chosen to explore the reactivity of different secondary amines in the sequential amination (Scheme 3). The coupling of important (hetero)cyclic amines, such as *N*-methyl piperazine and morpholine, gave **21**, **28** and **22**, **29** in good yields, respectively. The reaction of acyclic aliphatic and aromatic secondary amines successfully gave the desired products in good yields (**23**−**25** and **30**−**32**). Slightly lower yields were observed with bicyclic amines featuring an adjacent benzene ring, when approximately 20% formation of the diamine byproduct was observed (**26**, **27**, **33**, and **34**).

Considering the complexity of the multicomponent or catalyst-controlled one-pot reactions, the results of this study are quite impressive from an academic point of view. On the other hand, higher efficiency of the process is usually preferred for industrial applications. To maximize the potential of these findings, experiments were conducted, where the secondary amine was added after the completion of the first coupling step. The yields of the final products were increased by 5−25% (**21**, **22**, **32**−**34**), while still enjoying the benefits of the one-pot reaction.

The practical utility of the one-pot protocol was further demonstrated by synthesizing a precursor used for the preparation of

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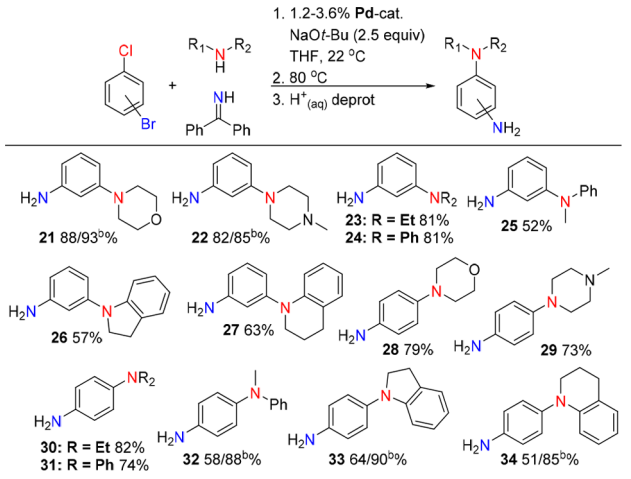
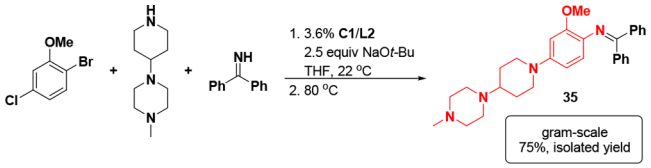
Scheme 3. Reactivity of Various Amines in the Sequence[a]



[a]Conditions: 2.5 mmol of NaO*t*-Bu, 1.0 mmol of aryl-dihalide, 1.1 mmol of benzophenone imine, 1.1 mmol of amine, 1.2 mol % of **C1** and 1.2 mol % of **L2**, 0.25 M THF, 1.5 h at 22 °C followed by 12 h at 80 °C. Yields reported: isolated. [b]The amine was added after 2 h at 22 °C.

Brigatinib, a novel commercial oncology drug with ALK and EGFR inhibitory functions (Scheme 4). The imine-protected product was isolated by simple extraction and recrystallization from methanol as a stable solid in good yield (75%) on 1 g scale. However, further process optimization could be possible.

Scheme 4. Synthesis of *Brigatinib* Precursor



In summary, we have developed an efficient and versatile protocol for the one-pot sequential multicomponent preparation of a class of amino-anilines and their derivatives. Many (hetero)aryl substrates were successfully aminated with a range of biologically active secondary amines using the recently discovered Pd-allyl complexes[27] as air- and moisture-stable precatalysts. Practical utility of the process was demonstrated on a gram-scale synthesis of a major building block for *Brigatinib*.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00646.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare the following competing financial interest(s): Catalysts and organic intermediates will be made commercial.

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