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Synthesis of 3-Aryl-2-Aminoquinolines: Palladium-Catalyzed Cascade Reactions of *Gem*-dibromovinylanilines with *tert*-Butyl Isocyanide and Arylboronic Acids

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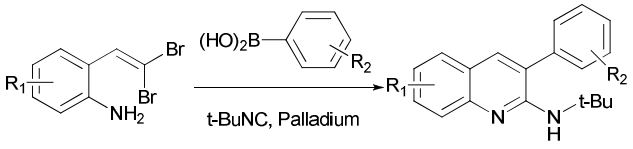
A three-component cascade reaction involving *gem*-dibromovinylanilines, *tert*-butyl isocyanide and arylboronic acids for the efficient synthesis of 3-aryl-2-aminoquinolines has been developed. The reaction proceeds through palladium-catalyzed isocyanide insertion, intramolecular cyclization of *gem*-dibromovinylanilines followed by Suzuki coupling with arylboronic acids, and the corresponding products were obtained in good to excellent isolated yields.

The quinoline nucleus is a privileged scaffold that exists in a large number of natural products and synthetic drugs with varied bioactivities.[1] In particular, the 2-aminoquinoline derivatives have been frequently studied during the past decades because of their pharmacological potential covering a range of possible applications, including anti-Alzheimer's,[2] anti-hypertensive[3] and anti-cancer[4] activities. While a great number of synthetic methods have been developed for quinolines synthesis,[5] only few examples have been reported for the synthesis of 2-aminoqunolines, including (a) Buchward-Hartwig aminations of 2-halo-quinolines,[6a] (b) palladium-catalyzed oxidation cyclizations of 2-ethynylanilines with isocyanides,[6b] (c) thermal rearrangement reactions of aldehydes, secondary amines and aryl azides,[6c] and (d) direct amination of quinoline N-Oxides.[6d,6e] The major drawbacks of the existing methods are their complicated multistep procedures, limited availability of substrates or high reaction temperatures, which usually hinder them from constructing a large number of structural derivatives of 2-aminoquinolines. Therefore, development of general and efficient strategies for the preparation of 2-aminoquinolines, especially via multi-component cascade reactions starting from readily available sources, is still highly desirable.

Gem-dibromovinylanilines are valuable synthetic intermediates in organic synthesis because they are highly reactive and can be easily obtained from inexpensive aldehydes.[7] In recent years, Lautens and other groups have reported a number of elegant strategies for the synthesis of various indole derivatives from *gem*-dibromovinylanilines via Palladium and/or Copper-catalyzed cascade cross-coupling reactions, such as C-N/C-N,[8] C-N/C-C,[9] C-N/C-H,[10] C-N/C-P,[9f] C-N/ carbonylation,[11a] and C-N/carbonylation/C-C reactions.[11b] However, to the best of our knowledge, the construction of 2-aminoquinoline scaffolds from *gem*-dibromovinylanilines remains scarce.

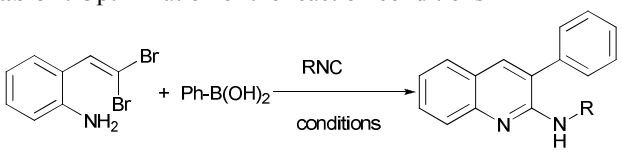
Compared to the traditional stepwise synthesis, the cascade (tandem) reaction is the most facile and economic synthetic approach. It enhances the reaction efficiency and avoids the tedious step-by-step separations and purifications of intermediates.[12] In our continuous studies of 1,1-dibromoolefins[13] and our interests in looking for 2-aminoquinoline anti-cancer agents, we disclose herein an efficient synthesis of 3-aryl-2-aminoquinoline derivatives via cascade palladium-catalyzed isocyanide insertion, intramolecular cyclization and Suzuki coupling of *gem*-dibromovinylanilines (Scheme 1). The reaction involves *gem*-dibromovinylanilines, arylboronic acids, and *tert*-butyl isocyanide.

Our study commenced with the treatment of *gem*-dibromovinylaniline (**1a**), phenylboronic acid (**2a**), and *t*-butyl isocyanide in the presence of $Pd(dppf)Cl_2$ and K_2CO_3 in toluene for 6h at 100°C. Gratifyingly, the expected quinoline product **3a** was obtained in 47% yield (Table 1, entry 1). To improve the yield, screening of the reaction conditions was then carried out. Firstly, by using $Pd(dppf)Cl_2$ as catalyst, the effect of different solvents including toluene, CH_3CN, DMF, THF and 1,4-dioxane was studied (Table 1, entries 1-5). Among them, 1,4-dioxane gave **3a** in the highest yield (Table 1, entry 5). After screening on a series of palladium catalysts including $Pd(dppf)Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(acac)_2$, $PdCl_2$, $Pd(OAc)_2$ and $Pd(TFA)_2$ (Table 1, entries 5-10), $Pd(dppf)Cl_2$ turned out to be the best choice (Table 1, entry 5). Among the tested bases, Cs_2CO_3 gave **3a** the highest yield (Table1, entries 11-14). In addition, elevating or lowering reaction temperature resulted in decreased yields (Table 1, entries 15-16).



Scheme 1. Strategic approach to the synthesis of 3-aryl-2-aminoquinolines

Table 1. Optimization of the reaction conditions[a]



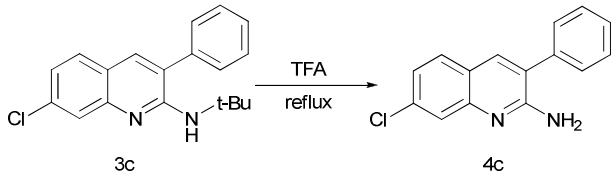
1a 2a 3

Entry	Catalyst	Solvent	Base	Yield[b] (%)
1	$Pd(dppf)Cl_2$	Toluene	K_2CO_3	47
2	$Pd(dppf)Cl_2$	CH_3CN	K_2CO_3	21
3	$Pd(dppf)Cl_2$	DMF	K_2CO_3	40
4	$Pd(dppf)Cl_2$	THF	K_2CO_3	58
5	$Pd(dppf)Cl_2$	Dioxane	K_2CO_3	70
6	$Pd(PPh_3)_2Cl_2$	Dioxane	K_2CO_3	46
7	$Pd(acac)_2$	Dioxane	K_2CO_3	35
8	$PdCl_2$	Dioxane	K_2CO_3	14
9	$Pd(OAc)_2$	Dioxane	K_2CO_3	31
10	$Pd(TFA)_2$	Dioxane	K_2CO_3	35
11	$Pd(dppf)Cl_2$	Dioxane	K_3PO_4	63
12	$Pd(dppf)Cl_2$	Dioxane	Na_2CO_3	61
13	$Pd(dppf)Cl_2$	Dioxane	NaOH	46
14	$Pd(dppf)Cl_2$	Dioxane	Cs_2CO_3	78
15	$Pd(dppf)Cl_2$	Dioxane	Cs_2CO_3	57[d]
16	$Pd(dppf)Cl_2$	Dioxane	Cs_2CO_3	66[e]

[a)] Reaction conditions: **1a** (0.2 mmol), *t*-BuNC (0.22 mmol), **2a** (0.22 mmol), base (0.44 mmol), catalyst (0.01 mmol), sealed tube, 100°C, 8h. [b)] Isolated yields. [c)] *t*-BuNC (0.6 mmol). [d)]120°C. [e)] 80°C.

With the optimized reaction condition in hand (Table 1, entry 14), the scope of the reaction for different *gem*-dibromovinylanilines was investigated firstly, and the results are summarized in Table 2. Overall, we were pleased with the generality of our protocol. As showed in Table 2, the expected products **3** were obtained in good isolated yields (**3b-l**). Several functional groups were well tolerated including chloro (**3b**, **3c**), fluro (**3d**, **3e**). It is obvious that the electronic effects of the substituted groups on the *gem*-dibromovinylanilines did not affect the efficacy of the cascade reaction (**3f-l**).

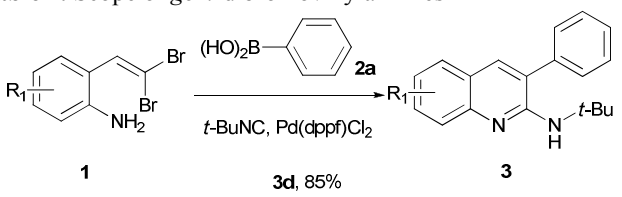
The influence of the substituents in the arylboronic acids was also evaluated and the results are presented in Table 3. In all cases, the desired products were obtained in good to excellent isolated yields. Halogen substitutes, including chloro and fluro, on the aromatic ring of boronic acid were tolerated (**3m**, **3n**). Electron-donating substrates (**3o-r**) afforded the quinoline products **3** in better yields compared with the electron-withdrawing ones (**3s-v**). Other heteroaryl boronic acid like 3-thienylboronic acid proved to be an efficient partner of the cascade reaction providing the desired product **3w** in good yield. Isocyanides other than *tert*-butyl isocyanide were also applied in this process, however limited success was achieved (**3x**, **3y**).



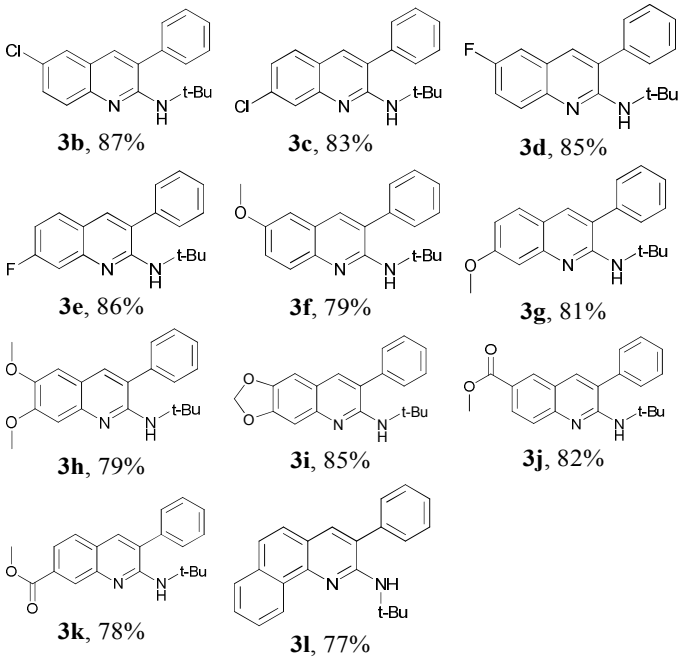
3c 4c

Scheme 2. Transformation of *N*-*t*-butyl amines into simple amines

Table 2. Scope of *gem*-dibromovinylanilines **1**[a]



1 **3d**, 85% **3**



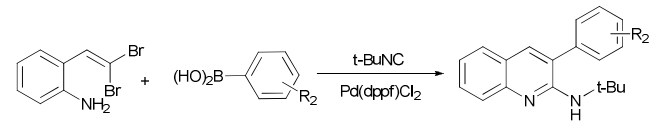
[a)] Reaction conditions: **1** (0.2 mmol), RNC (0.22 mmol), **2a** (0.22 mmol), Cs_2CO_3 (0.44 mmol), $Pd(dppf)Cl_2$ (0.01 mmol), 1,4-dioxane (2.0 mL), sealed tube, 100°C, 8h.

The synthesized 3-aryl-2-aminoquinolines are very useful intermediates as the *t*-butyl group can be easily removed according to a method reported in the literature,[14] releasing a free amine group which may then be subject to various futher transformations.[15] For example, when **3c** was heated to reflux in trifluroacetic acid, the desired 2-aminoquinoline **4c** was obtained in 83% isolated yield (Scheme 2).

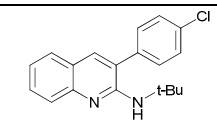
To gain some insights into the mechanism of the reaction, several control experiments were conducted as shown in Scheme 3. When **1a** and *t*-BuNC (1.1 equiv.) were treated under the optimized reaction conditions, 86% of the 3-bromo quinoline **5** was obtained 3h later. After **1a** was consumed monitored by TLC, phenylboronic acid (1.1 equiv.) was added directly to the cooled reaction mixture and heated to 100°C for 6h, 82% of the desired product **3a** was obtained. When the three components were carried out under the optimized conditions for 0.5h, 81% of the newly formed products was 3-bromo quinoline **5** (determined by LC-MS). These experimental results revealed that this reaction proceeded through the migratory insertion of isocyanide, and then the Suzuki reaction.

Based on literature reports[16] and our experimental observations, a plausible mechanism was proposed (Scheme 4). The isocyanide-complexed Pd species **A** was firstly formed. Then, oxidative addition of cis-bromovinyl of **1a** to the Pd species **A** formed the vinylpalladium complex **B** via ortho-aniline assistance. Subsequent migratory insertion of *t*-BuNC

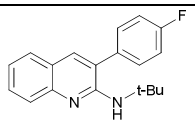
Table 3. Scope of arylboronic acids **2**[a]



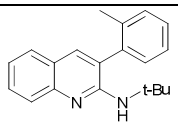
1a 2 3



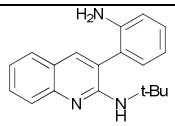
3m, 83%



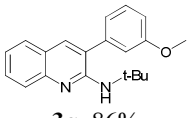
3n, 92%



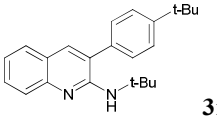
3o, 87%



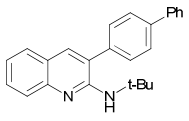
3p, 83%



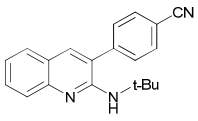
3q, 86%



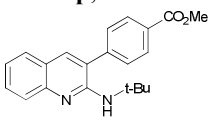
3r, 79%



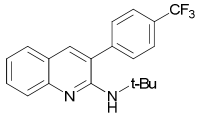
3s, 70%



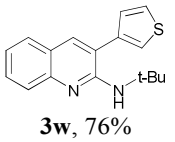
3t, 71%



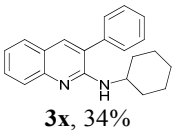
3u, 76%



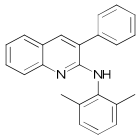
3v, 72%



3w, 76%

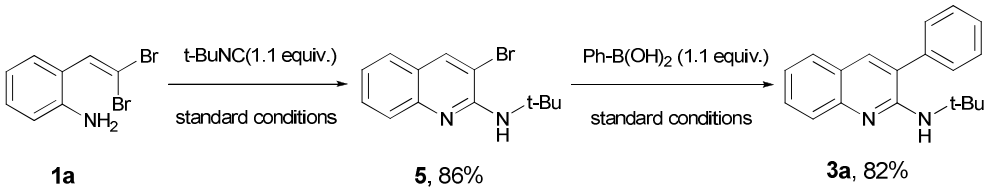


3x, 34%



3y, <5%

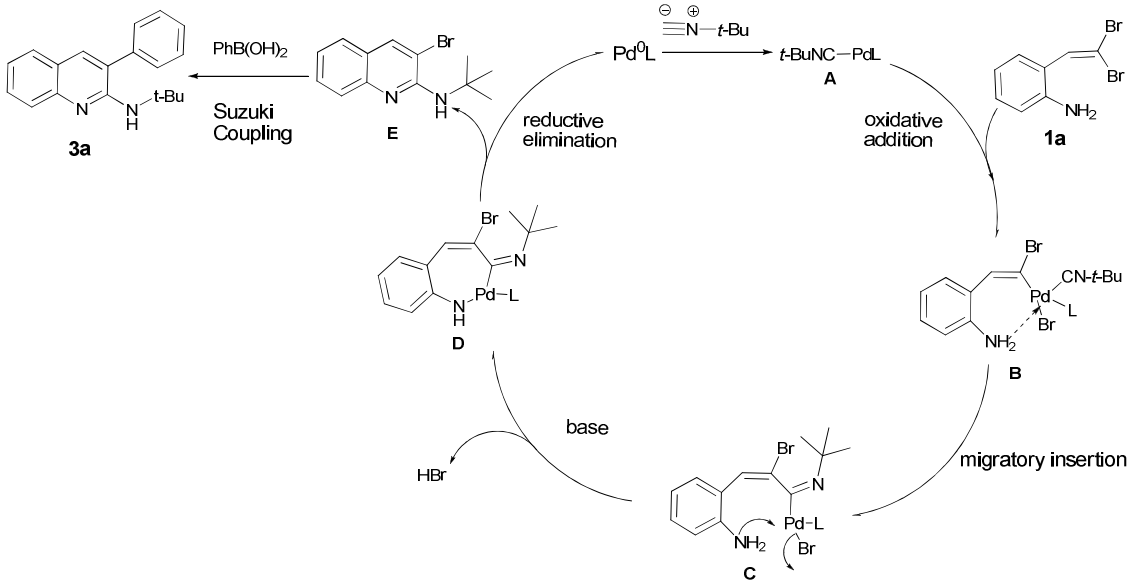
[a] Reaction conditions: **1a** (0.2 mmol), *t*-BuNC (0.22 mmol), **2** (0.22 mmol), Cs_2CO_3 (0.44 mmol), $Pd(dppf)Cl_2$ (0.01 mmol), 1,4-dioxane (2.0 mL), sealed tube, 100°C, 8h.



1a **5**, 86% **3a**, 82%

Scheme 3. Investigation of the reaction mechanism.

assistance. Subsequent migratory insertion of *t*-butyl isocyanide to **B** gave intermediate **C**, followed by intramolecular nucleophilic attack of the aniline to provide intermediate **D** and hydrogen bromide. Reductive elimination of **D** afforded intermediate **E**, generating the Pd(0) catalyst. **E** was then subjected to Suzuki coupling reaction with phenylboronic acid giving the final product **3a**.



Scheme 4. Proposed mechanism.

Conclusions

In conclusion, we have developed a novel and efficient procedure for the synthesis of 3-aryl-2-aminoquinolines via a palladium-catalyzed three-component cascade reaction of *gem*-dibromo-vinylanilines, tert-butyl isocyanide and arylboronic acids. The reaction proceeds through palladium-catalyzed isocyanide insertion, intramolecular cyclization of *gem*-dibromovinylanilines followed by Suzuki coupling with arylboronic acids, and the corresponding products were obtained in good to excellent isolated yields. Furthermore, the *tert*-butyl group of the synthesized 3-aryl-2-aminoquinolines can be easily removed, releasing a free amine group which could easily bring structural diversity at the C2 position of the quinoline core. Further studies on the detailed mechanism and synthetic applications are ongoing in our laboratory and will be reported in due course.

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Notes and references

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