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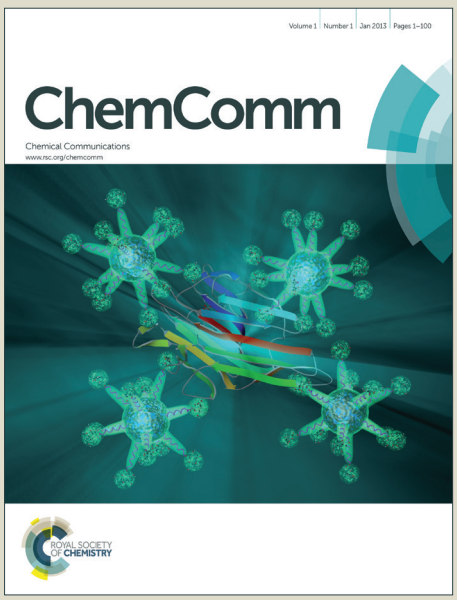

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ARTICLE TYPE

Palladium-Catalyzed Synthesis of Polysubstituted Quinolines from 2-Amino Aromatic Ketones and Alkynes

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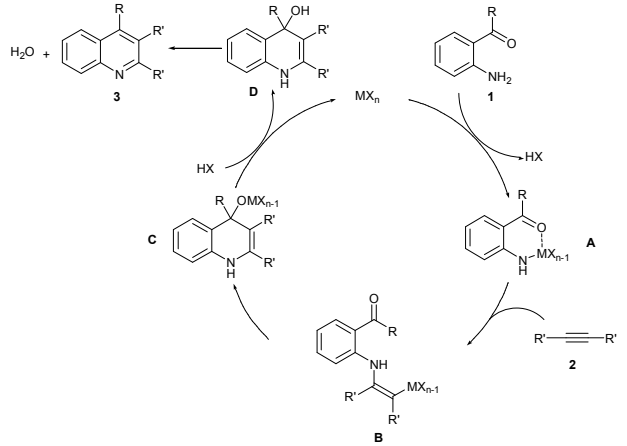
A palladium-catalyzed one-pot method for the synthesis of quinolines from commercial or readily available 2-amino aromatic ketones and alkynes is reported for the first time. This transformation offers an alternative method for the synthesis of polysubstituted quinoline.

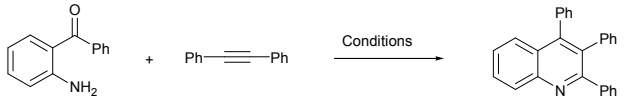
Quinolines are ubiquitous motifs in the frameworks of natural products[1] and bioactive compounds.[2] Also, they are valuable synthons for the preparation of materials with uniquely electronic and optical properties.[3] Therefor, a variety of methods have been developed to assemble this kind of skeletons.[4] Previously, we reported an intramolecular direct amination of sp^2 C–H bonds, finding that *ortho* carbonyl group could facilitate the metalation of amino N-H bond.[5] Based on this result and our recent study on hydroarylation of alkyne,[6] a new strategy for the synthesis of quinoline was envisioned, which involves five transformations, namely, (i) carbonyl group directed metalation of N-H bond to form intramolecular insertion into carbonyl group to form intermediate **C**, (iv) protolysis of the resulting metal alkoxide to liberate alcohol **D** and regenerate catalyst, (v) dehydration-aromatization of compound **D** delivering the desired quinoline (Scheme 1).



Scheme 1 An envisioned strategy for the synthesis of quinoline

To test our hypothesis, $Pd(CH_3CN)_2Cl_2$ was initially chosen as catalyst for the intermolecular reaction of 2-aminobenzophenone **1a** and diphenyl acetylene **2a**. Gratifyingly, in the presence of acetic acid, 2,3,4-triphenyl quinoline **3aa** was obtained in 48% yield (Table 1, entry 1), but, in the absence of acid or palladium, almost no product was observed (Table 1, entry 2 and 3). Further

Table 1 Optimization of reaction conditions[a]



1a **2a** **3aa**

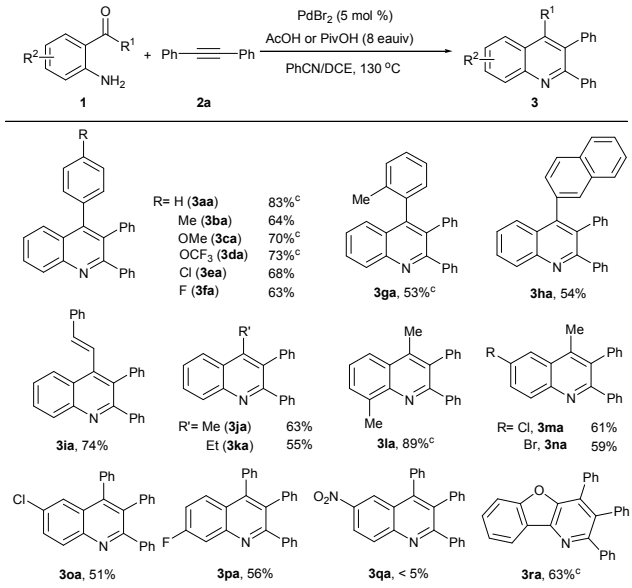
entry	catalyst (5 mol %)	additive (8 equiv)	solvent	yield (%)[b]
1	$Pd(CH_3CN)_2Cl_2$	AcOH	DCE	48
2	$Pd(CH_3CN)_2Cl_2$	----	DCE	trace
3	----	AcOH	DCE	0
4	$Pd(CH_3CN)_2Cl_2$	AcOH	1,4-Dioxane	39
5	$Pd(CH_3CN)_2Cl_2$	AcOH	DCM	42
6	$Pd(CH_3CN)_2Cl_2$	AcOH	Toluene	44
7	$Pd(CH_3CN)_2Cl_2$	AcOH	DMF	trace
8	$Pd(CH_3CN)_2Cl_2$	AcOH	THF	11
9	$Pd(CH_3CN)_2Cl_2$	AcOH	DMSO	0
10	$PdCl_2$	AcOH	DCE	31
11	$PdBr_2$	AcOH	DCE	59
12	$Pd(COD)Cl_2$	AcOH	DCE	34
13	$Pd(acac)_2$	AcOH	DCE	20
14	$Pd(CF_3COO)_2$	AcOH	DCE	13
15	$Pd(OH)_2$	AcOH	DCE	8
16	$Pd(PPh_3)_2Cl_2$	AcOH	DCE	17
17	$Pd(OAc)_2$	AcOH	DCE	31
18	CuI	AcOH	DCE	10
19	$CuBr_2$	AcOH	DCE	trace
20	$[Rh(\eta^5\text{-}C_5Me_5)Cl_2]_2$	AcOH	DCE	0
21	$PdBr_2$	PivOH	DCE	63
22	$PdBr_2$	TFA	DCE	63
23[c]	$PdBr_2$	PivOH	DCE	54
24[d]	$PdBr_2$	PivOH	DCE	60
25[e]	$PdBr_2$	PivOH	DCE	38
26	$PdBr_2$	PivOH	DCE/Acetonitrile (1:1)	74
27	**$PdBr_2$**	**PivOH**	**DCE/Benzonitrile (1:1)**	**83**
28	$PdBr_2$	AcOH	DCE/Benzonitrile (1:1)	74

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst, additive (1.6 mmol) and solvent (1.6 mL) at 130 °C in seal tube for 18 h. [b] Isolated yield. [c] Additive (1.2 mmol). [d] 150 °C. [e] 100 °C.

investigation showed that DCE and $PdBr_2$ were the best choices as solvent and catalyst, respectively (Table 1, entries 4-20). It is worth noting that copper could not catalyze the reaction efficiently (Table 1, entries 18 and 19). Moreover, compared to the noticeable effect of temperature, the kind of acid affected the yield slightly (Table 1, entries 21-25). Finally, carrying out the reaction in a mixed solvent resulted in an acceptable yield of the desired product (Table 1, entry 27).

Subsequently, substrate scope was explored under the optimized conditions. The reaction of various 2-amino aromatic ketone **1** with diphenylacetylene **2a** is summarized in Table 2. First of all, a variety of 2-aminobenzophenones, which could be readily available *via* one-step synthesis from 2-cyano aniline and aromatic boronic acid,[7] with functional groups, such as methyl, methoxy, trifluoromethoxy, chloro and fluoro, were tolerated, giving the corresponding products in moderate to good yields (**3aa-3ga**). It is worth mentioning that, in many cases, N-pivalation product of **1** was detected when PivOH was used, which could not be isolated from the desired quinoline and lead to the product as a mixture. Using AcOH instead of PivOH could solve this problem easily. This reaction proceeded successfully and afforded products with naphthalenyl and styryl substituent (**3ha** and **3ia**). On the other hand, this approach could be also used for the assembling of 4-alkyl substituted quinolines effectively (**3ja** and **3ka**). The structure of product **3ka** was further identified by the single-crystal study (see ESI for details). Secondly, substrates with functional groups, such as methyl, or halo substituents, such as bromo, chloro and fluoro, on amino substituted aromatic ring could be readily transformed to the desired products **3la-3pa**, but quinoline with nitro group (**3qa**) was only obtained in trace of yield. Moreover, this method furnished polycyclic product **3ra** in 63% yield.

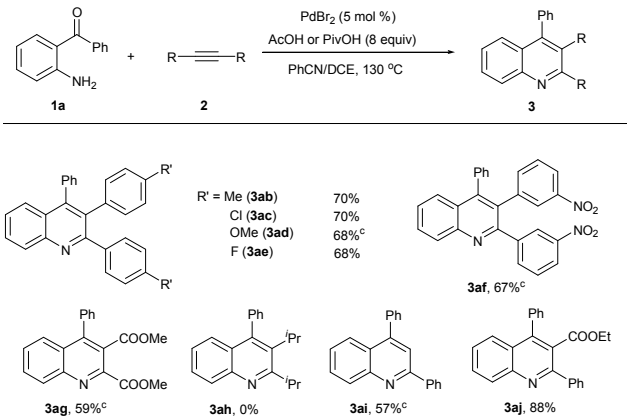
Table 2 The reaction of diphenylacetylene (**2a**) with various 2-acyl anilines (**1**) [a,b]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $PdBr_2$ (5.0 mol %), AcOH (1.6 mmol) at 130 °C for 18 h. [b] Isolated yield. [c] PivOH was used instead of AcOH.

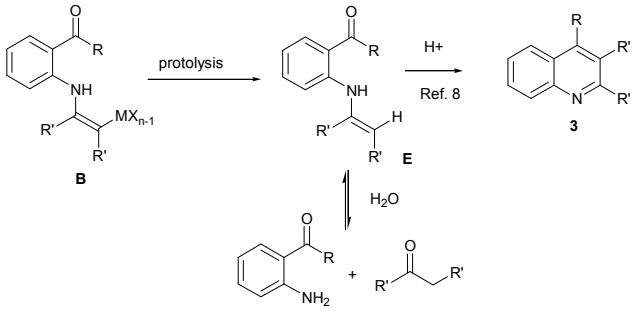
Encouraged by the preliminary scope of the reaction, we began to explore the scope of acetylenes **(**Table 3). Diphenyl acetylenes with substituents, such as methyl, methoxy, chloro, fuloro, nitro could be smoothly converted into the desired products in moderate yields (**3ab-3af**). 2,3-Dimethoxycarbonyl quinoline **3ag** could be obtained from the corrosponding methyl acetylenedicarboxylate. Moreover, single isomer (**3ai and 3aj**) was detected when phenylacetylene and ethyl 3-phenylpropiolate were employed.[8] Unfortunately, dialkyl acetylene could not be the reaction partner in this transformation (**3ah**).

Table 3 The reaction of various acetylenes (**2**) with 2-aminobenzo phenone (**1a**) [a,b]

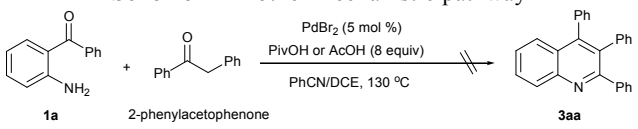


[a] Reaction conditions: substrate: **1a** (0.2 mmol), **2** (0.4 mmol), $PdBr_2$ (5.0 mol %), AcOH (1.6 mmol) at 130 °C for 18 h. [b] Isolated yield. [c] PivOH was used in stead of AcOH.

In addition to the mechanism that metal-vinyl intermediate **B** inserts into carbonyl group, there is an other possible pathway that intermediate **B** undergos protolysis to form enamine **E**, which lead to the formation of quinoline by intermolecular annulation process (Scheme 2).[9] If the formtion of an enamine **E** occured, we should observe the existence of the corresponding enamine or its hydrolysis-product 2-phenylacetophenone when 2-aminobenzophenone **1a** and diphenyl acetylene **2a** were employed. However, we did not detect the existence of them.



Scheme 2 An other mechanistic pathway



Scheme 3

Moreover, 2-aminobenzophenone **1a** could not be converted into quinoline **3aa** in the presence of 2-phenylacetophenone

(Scheme 3). These results indicated that protolysis of intermediate **B** is less likely.

In conclusion, we demonstrate for the first time a palladium-catalyzed one-pot method for the synthesis of quinolines from 2-amino aromatic ketones and alkynes. This transformation offers an alternative method for the synthesis of polysubstituted quinoline.

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