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Palladium-Catalyzed Tandem Amination Reaction for the Synthesis of 4-Quinolones

Tiankun Zhao and Bin Xu*

Department of Chemistry, Shanghai University, Shanghai 200444, China

xubin@shu.edu.cn

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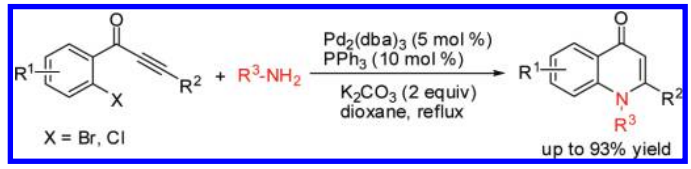
ABSTRACT



An efficient palladium-catalyzed tandem amination approach was developed in one step to afford functionalized 4-quinolones in good to excellent yields from easily accessible *o*-haloaryl acetylenic ketones and primary amines.

Quinolone derivatives represent a major class of nitrogen-containing heterocycles,[1] which play an increasingly important role in drug discovery. These compounds are structural units found in a vast array of natural products,[2] synthetic materials,[3] and bioactive molecules as antimitotic,[4] antiviral,[5] and anticancer agents[6] and HIV-1 integrase inhibitors[7] and serve as a crucial category of antibacterial agents as exemplified by marketing drugs such as Avelox, Ciprodex, Levaquin, and Vigamox. Such characteristics have made the molecules significant synthetic targets and, therefore, have resulted in sustained interest in developing new methods for the preparation of this valuable structural unit.[1c,3a,8] Among these methods, the Camps-type cyclization[9] has been widely used. Other improved synthetic methods include the reaction of isatoic anhydrides with ketone-derived enolates,[10] triph-

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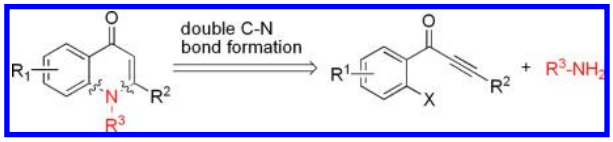
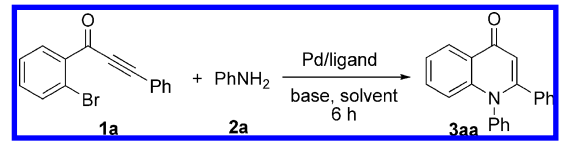
enylphosphonium salts,[11] or alkynes,[12] cyclization reaction of N-substituted phenacyl or acetonyl anthranilates in polyphosphoric acid,[13] base, or copper-promoted intermolecular cyclization of 1-(2-halo-phenyl)-2-en-3-amin-1-ones,[14] cycloacylation of aniline derivatives in the presence of Eaton's reagent,[15] and palladium-catalyzed carbonylative Sonogashira coupling of 2-iodo-5-methoxyaniline with thiazolyl-acetylene.[3d] Recently, Huang has reported a one-pot synthesis of 4-quinolones using sequential palladium-catalyzed amidation of 2′-bromoacetophenones followed by base-promoted intramolecular cyclization.[16] Although these methods are effective, the reactions are incompatible with sensitive functionalities[10a] or need harsh reaction conditions,[9b,15] and some starting materials are not readily available.[11b] To continue our program aiming at efficient construction of nitrogen-containing heterocycles,[17] we herein report a palladium-catalyzed tandem reaction consisting of a sequential double C−N bond formation to give 4-quinolones from readily available *o*-haloaryl acetylenic ketones and primary amines (Scheme 1).[18]

Scheme 1. Tandem Amination Strategy to 4-Quinolones from Alkynones and Amines



To determine the feasibility of this double C−N bond formation process, we initially examined the reaction by exploring **1a**[19] with aniline in the presence of $Pd(PPh_3)_4$ (5 mol %) in dioxane using K_2CO_3 as a base. The reaction gave 4-quinolone **3aa** in 71% yield (Table 1, entry 1). A similar result was obtained using the Pd−DPPF complex as a catalyst (entry 2). When $Pd_2(dba)_3$−$CHCl_3$ was used as catalyst and combined with Xantphos or DPPP, the yields were improved slightly (entries 3 and 4). The use of PPh_3 turned out to be the best ligand choice and resulted in 84% yield (entry 5, Condition A). In comparison with K_2CO_3, other bases such as Cs_2CO_3 or K_3PO_4 resulted in diminished yields (entries 6 and 7) or were less effective with NaOH, *t*-BuOK, or Et_3N as base (entries 8−10). When the solvent was switched to DMF, toluene, or CH_3CN, the yield of **3aa** decreased (entries 11−13). Lower reaction temperature failed to give a good result (entry 14), and little product was detected in the absence of catalyst and ligand (entries 15 and 16).

Table 1. Condition Optimizations for 4-Quinolones[a]



entry	Pd	ligand	solvent	base	temp (°C)	yield[b] (%)
1	$Pd(PPh_3)_4$	/	dioxane	K_2CO_3	reflux	71
2	Pd-DPPF	/	dioxane	K_2CO_3	reflux	71
3	$Pd_2(dba)_3$	Xantphos	dioxane	K_2CO_3	reflux	72
4	$Pd_2(dba)_3$	DPPP	dioxane	K_2CO_3	reflux	75
5	**$Pd_2(dba)_3$**	**PPh_3**	**dioxane**	**K_2CO_3**	**reflux**	**84**
6	$Pd_2(dba)_3$	PPh_3	dioxane	Cs_2CO_3	reflux	63
7	$Pd_2(dba)_3$	PPh_3	dioxane	K_3PO_4	reflux	77
8	$Pd_2(dba)_3$	PPh_3	dioxane	NaOH	reflux	17
9	$Pd_2(dba)_3$	PPh_3	dioxane	*t*-BuOK	reflux	<5
10	$Pd_2(dba)_3$	PPh_3	dioxane	Et_3N	reflux	<5
11	$Pd_2(dba)_3$	PPh_3	DMF	K_2CO_3	120	59
12	$Pd_2(dba)_3$	PPh_3	toluene	K_2CO_3	reflux	72
13	$Pd_2(dba)_3$	PPh_3	CH_3CN	K_2CO_3	reflux	35
14	$Pd_2(dba)_3$	PPh_3	dioxane	K_2CO_3	60	<5
15[c]	$Pd_2(dba)_3$	/	dioxane	K_2CO_3	reflux	10
16	/	/	dioxane	K_2CO_3	reflux	<5

[a] Reaction conditions: **1a** (0.21 mmol), aniline **2a** (0.25 mmol), $Pd_2(dba)_3$−$CHCl_3$ (5 mol %), ligand (10 mol %), base (0.42 mmol), and solvent (1.5 mL), under nitrogen. DPPP = 1,3-bis(diphenylphosphino)-propane, Pd-DPPF = (1,1′-bis(diphenylphosphino)ferrocene)dichloro-palladium(II)-CH_2Cl_2, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. [b] Isolated yield. [c] **1a** was recovered in 63%.

With the optimized reaction conditions in hand, we then extended the reaction with a range of commercially available aryl amines. As illustrated in Table 2, **1a** was readily reacted with functionalized aryl amines bearing *ortho*, *meta*, and *para* substitutions on the aryl ring to give the corresponding products **3ab**−**3am** in moderate to good yields (entries 2−13). The reactions performed smoothly with aryl amines containing electron-donating (entries 2−5 and entries 11−13)

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(18) During the preparation of this manuscript, a single example to prepare 4-quinolone was reported by copper-catalyzed sequential two-step process from α,β-ynone and aniline without isolation of the intermediate. See ref 14c.

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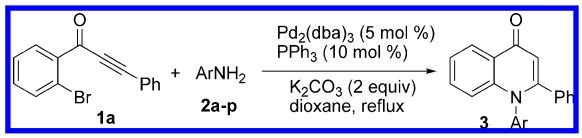
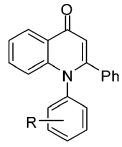
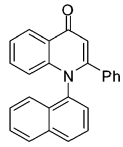
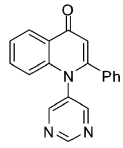
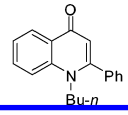
Table 2. Reaction of **1a** with Primary Amines[a]



entry	amine	R	product		time (h)	yield (%)[b]
1		H		**3aa**	7	84
2		*p*-Me		**3ab**	6	86
3		*p*-OMe		**3ac**	3	75
4		*p*-NH_2		**3ad**	4.5	88
5		*p*-OH		**3ae**	3	74
6		*p*-Cl		**3af**	5	86
7		*p*-Br		**3ag**	5	61
8		*p*-NO_2		**3ah**	5.5	93
9	**2a-m**	*p*-COOEt		**3ai**	9	64
10		*p*-Ac		**3aj**	4.5	82
11		*m*-Me		**3ak**	6	81
12		*o*-Me		**3al**	6	76
13		*o*-OMe		**3am**	4.5	84
14	 **2n**			**3an**	19	74
15	 **2o**			**3ao**	23	81
16	*n*-$BuNH_2$ **2p**			**3ap**	6	42

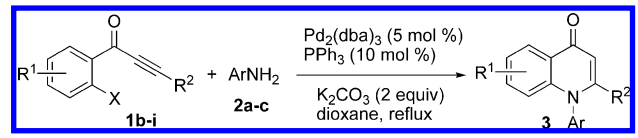
[a] All reactions were performed under N_2 on a 0.5 mmol scale, using aryl amines (1.2 equiv), $Pd_2(dba)_3$-$CHCl_3$ (5 mol %), PPh_3 (10 mol %), and K_2CO_3 (2.0 equiv) in dioxane (3 mL) under reflux. [b] Isolated yield.

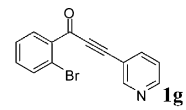
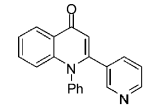
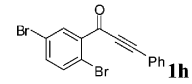
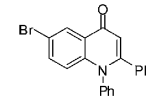
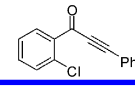
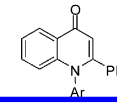
and electron-withdrawing groups (entries 6−9). Substrates with active amino and hydroxy groups remained intact under the reaction conditions (entries 4 and 5). This reaction was not limited to simple aromatic amines, and the naphthalene- and pyrimidine-containing substrates **2n** and **2o** also afforded **3an** and **3ao**[20] in good yields, respectively (entries 14 and 15). It should also be noted that aliphatic amines such as *n*-butylamine gave product **3ap** successfully in moderate yield (entry 16).

To further explore the generality and scope of this practical approach, a variety of ynones **1b**−**1i**[19] were investigated, and the results are summarized in Table 3. This method was compatible with different types of ynones substituted with aryl and pyridinyl groups (entries 1−6). Substrates containing electron-donating groups afforded products in good yields

(20) Crystal data for **3ao**: $C_{19}H_{13}N_3O$, MW = 299.32, Orthorhombic, Pbca, final *R* indices [$I > 2\sigma(I)$], $R1$ = 0.0420, w$R2$ = 0.0925, a = 7.0652(11) Å, b = 20.188(3) Å, c = 21.214(3) Å, $\alpha = 90°$, $\beta = 90.921(2)°$, $\gamma = 90°$, V = 3025.8(8) Å^3, Crystal size: 0.30 × 0.25 × 0.20 mm, T = 296(2) K, Z = 8, reflections collected/unique: 14 591/2679 (Rint = 0.0413), Data: 2679, restraints: 0, parameters: 209.

Table 3. Reaction of Alkynones with Aryl Amines[a]



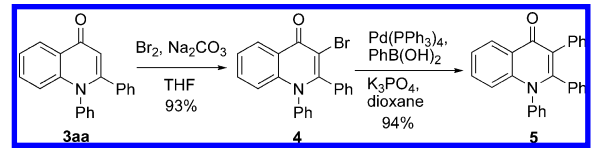
entry	reactant	R	product		time (h)	yield (%)[b]
1		*p*-Et-C_6H_4		**3ba**	6	81
2		*p*-$OMeC_6H_4$		**3ca**	6	77
3		*p*-PhCl		**3da**	7	63
4		*p*-PhF		**3ea**	11	73
5	**1b-f**	*m*-PhCl		**3fa**	8	60
6	 **1g**			**3ga**	9	63
7	 **1h**			**3ha**	18	79
8	 **1i**			**3ab**	30	52[c]
9				**3ac**	36	45[d]

[a] All reactions were performed under N_2 on a 0.5 mmol scale, using aryl amines (1.2 equiv), $Pd_2(dba)_3$-$CHCl_3$ (5 mol %), PPh_3 (10 mol %), and K_2CO_3 (2.0 equiv) in dioxane (3 mL) under reflux. [b] Isolated yield. [c] Toluidine was used at 140 °C. [d] 4-Methoxyaniline was used at 140 °C.

(entries 1 and 2). For those substrates consisting of fluoro and chloro groups, the yields turned out to be slightly lower (entries 3−5). Pyridine-containing substrate **1g** also showed good reactivity and gave **3ga** in moderate yield (entry 6). It is interesting to note that the dibromo-substituted ynone **1h** afforded the corresponding quinolone **3ha** in good yield without the competitive reaction on the other bromine (entry 7). Furthermore, the less reactive chloro-substituted substrates also gave products **3ab** and **3ac** in moderate yields upon raised temperature (entries 8 and 9).

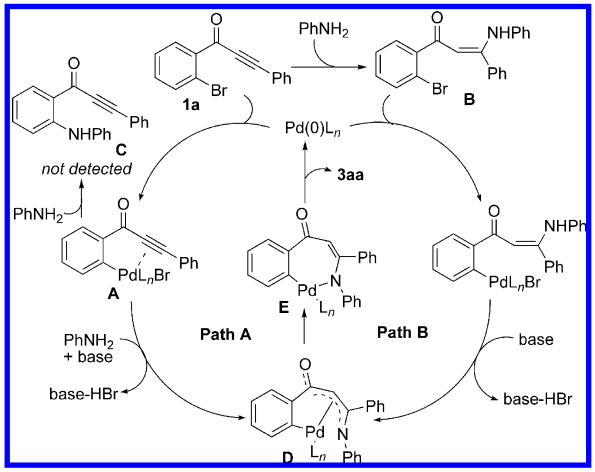
The product derivatived 3-halogenated quinolones are versatile synthetic intermediates[21] and could be further elaborated. For example, 3-bromo-substituted **4** was easily prepared from **3aa**, which gave rise to the corresponding 3-phenyl derivatived quinolone **5** in 94% yield via Suzuki reaction (Scheme 2). Thus, the multisubstituted 4-quinolones could be generated smoothly.

Scheme 2. Formation of 3-Phenyl-Substituted Quinolone



Two pathways are proposed as a possible mechanism for this reaction (Scheme 3), which may involve either oxidative

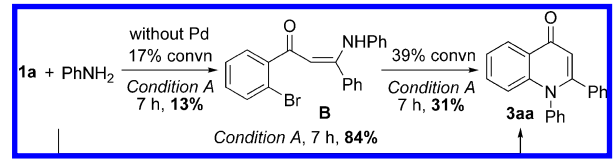
Scheme 3. Plausible Mechanism for Synthesis of **3aa** from **1a**



addition of Pd(0) to the C−Br bond in **1a** (intermediate **A** in Path A) or conjugate addition of aniline to **1a**[14] (intermediate **B** in Path B) in the first step. The formed intermediate **A** presumably leads to **C** through Buchwald−Hartwig amination,[22] or the C≡C bond in **A** could be actived through coordination to the palladium and attacked by aniline to form intermediate **D**.[14c,23] Both pathways will go through intermediates **D** and **E**,[14c,24] followed by reductive elimination of Pd(0) to give product **3aa**.

To define the mechanism, several experiments were explored, including: (i) under Condition A (Table 1, entry 5), intermediate **B** was isolated in 13% yield in the absence of palladium after reaction for 7 h,[25] and **3aa** was produced in 31% yield from synthesized **B** with 39% conversion (Scheme 4). The total yield for the two steps is far less than

Scheme 4. Formation of **B** and **3aa** under Condition A



84%. (ii) No **3aa** and intermediate **C** were detected from the chloro-substituted substrates **1i** under Condition A after reaction for 24 h, and only a trace amount of conjugate addition product was observed, which may be due to the low oxidative addition reactivity of the C−Cl bond. (iii) When the reaction was conducted under Condition A, at 80 °C or under reflux, no intermediate **C** was detected by LC-MS. Furthermore, no product **3aa** could be found from synthesized intermediate **C**[26] under Condition A. On the basis of these results, we envisioned that the Path A in Scheme 3 could be the major pathway to afford the target quinolone **3aa**.

In summary, we have developed an efficient palladium-catalyzed tandem amination protocol for the straightforward synthesis of 4-quinolones. This approach provides one of the easiest pathways for accessing this class of valuable compounds from easily available starting materials, and a wide range of multisubstituted 4-quinolones could be generated accordingly for chemical library construction. The scope of this reaction and its applications for bioactive compounds are currently under investigation in our laboratory.

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Supporting Information Available: Characterization data and copies of the ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra for all compounds, X-ray structure of **3ao**, and representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) For the timescale needed for addition of aniline to substrate **1a** in the absence of palladium, see Supporting Information.

(26) For preparation of intermediate **C**, see Supporting Information.