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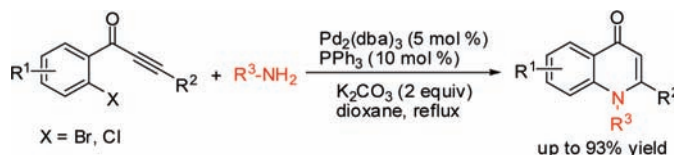
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ABSTRACT

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 poly-phosphoric acid,[13] base, or copper-promoted intermolecular cyclization of 1-(2-halo-phenyl)-2-en-3-amin-1-ones,[14] cy-cloacylation 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-quino-lones using sequential palladium-catalyzed amidation of 2′-bromoacetophenones followed by base-promoted intramolecular cyclization.[16] Although these methods are effective, the reac-tions 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 acety-lenic ketones and primary amines (Scheme 1).[18]

Scheme 1. Tandem Amination Strategy to 4-Quinolones from Alkynones and Amines
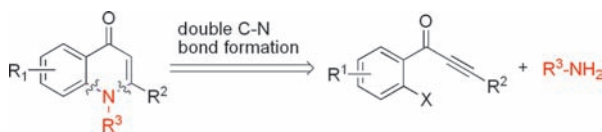
To determine the feasibility of this double C−N bond formation process, we initially examined the reaction by

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exploring **1a**[19] with aniline in the presence of Pd(PPh₃)₄ (5 mol %) in dioxane using K₂CO₃ as a base. The reaction gave 4-quinolone **3aa** in 71% yield (Table 1, entry 1). A similar

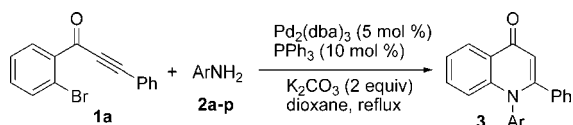**Table 1.** Condition Optimizations for 4-Quinolones[a]

entry	Pd	ligand	solvent	base	temp (°C)	yield[b] (%)
1	Pd(PPh₃)₄	/	dioxane	K₂CO₃	reflux	71
2	Pd-DPPF	/	dioxane	K₂CO₃	reflux	71
3	Pd₂(dba)₃	Xantphos	dioxane	K₂CO₃	reflux	72
4	Pd₂(dba)₃	DPPP	dioxane	K₂CO₃	reflux	75
5	**Pd₂(dba)₃**	**PPh₃**	**dioxane**	**K₂CO₃**	**reflux**	**84**
6	Pd₂(dba)₃	PPh₃	dioxane	Cs₂CO₃	reflux	63
7	Pd₂(dba)₃	PPh₃	dioxane	K₃PO₄	reflux	77
8	Pd₂(dba)₃	PPh₃	dioxane	NaOH	reflux	17
9	Pd₂(dba)₃	PPh₃	dioxane	t-BuOK	reflux	<5
10	Pd₂(dba)₃	PPh₃	dioxane	Et₃N	reflux	<5
11	Pd₂(dba)₃	PPh₃	DMF	K₂CO₃	120	59
12	Pd₂(dba)₃	PPh₃	toluene	K₂CO₃	reflux	72
13	Pd₂(dba)₃	PPh₃	CH₃CN	K₂CO₃	reflux	35
14	Pd₂(dba)₃	PPh₃	dioxane	K₂CO₃	60	<5
15[c]	Pd₂(dba)₃	/	dioxane	K₂CO₃	reflux	10
16	/	/	dioxane	K₂CO₃	reflux	<5

[a] Reaction conditions: **1a** (0.21 mmol), aniline **2a** (0.25 mmol), Pd₂(dba)₃−CHCl₃ (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-pal-ladium(II)-CH₂Cl₂, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxan-thene. [b] Isolated yield. [c] **1a** was recovered in 63%.

result was obtained using the Pd−DPPF complex as a catalyst (entry 2). When Pd₂(dba)₃−CHCl₃ was used as catalyst and combined with Xantphos or DPPP, the yields were improved slightly (entries 3 and 4). The use of PPh₃ turned out to be the best ligand choice and resulted in 84% yield (entry 5, Condition A). In comparison with K₂CO₃, other bases such as Cs₂CO₃ or K₃PO₄ resulted in diminished yields (entries 6 and 7) or were less effective with NaOH, t-BuOK, or Et₃N as base (entries 8−10). When the solvent was switched to DMF, toluene, or CH₃CN, 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).

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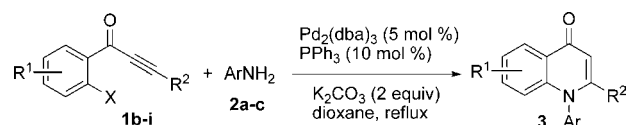
Table 2. Reaction of **1a** with Primary Amines[a]

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-NH2	3ad	4.5	88
5	2a-m	p-OH	3ae	3	74
6		p-Cl	3af	5	86
7		p-Br	3ag	5	61
8		p-NO2	3ah	5.5	93
9		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-BuNH2 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.

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

entry	reactant	R	product	time (h)	yield (%)[b]
1		p-Et-C6H4		3ba	6	81
2	1b-f	p-OMeC6H4		3ca	6	77
3		p-PhCl		3da	7	63
4		p-PhF		3ea	11	73
5		m-PhCl		3fa	8	60
6	1g			3ga	9	63
7	1h			3ha	18	79
8				3ab	30	52[c]
9	1i			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.

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

(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 derivative quinolone **5** in 94% yield via Suzuki reaction (Scheme 2). Thus, the multisubstituted 4-quinolones could be generated smoothly.

(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, wR2 = 0.0925, a = 7.0652(11) Å, b = 20.188(3) Å, c = 21.214(3) Å, α = 90°, β = 90.921(2)°, γ = 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.
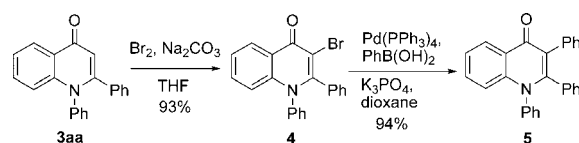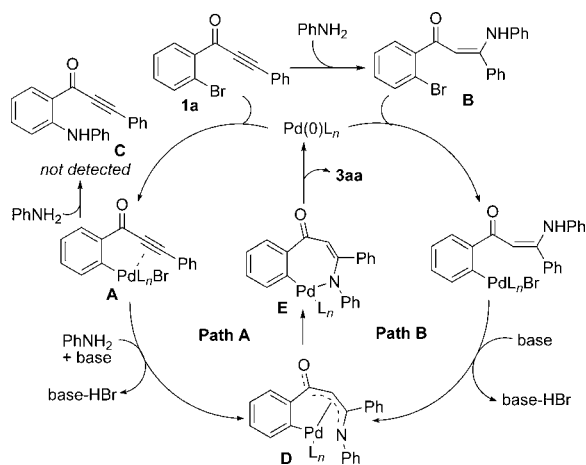
Scheme 2. Formation of 3-Phenyl-Substituted Quinolone

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

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 activated 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

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.

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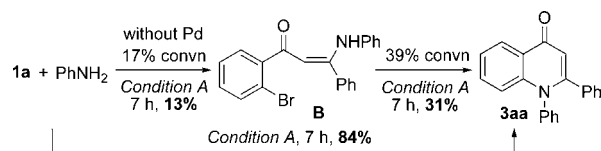
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(25) For the timescale needed for addition of aniline to substrate **1a** in the absence of palladium, see Supporting Information.

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