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A Mild, One-Pot Synthesis of 4-Quinolones via Sequential Pd-Catalyzed Amidation and Base-Promoted Cyclization†

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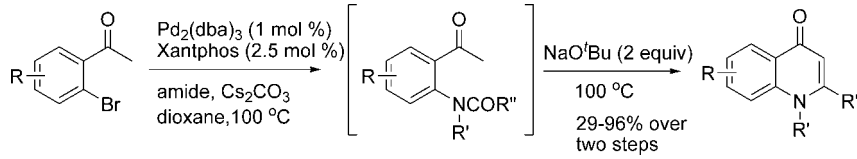
ABSTRACT



A mild, one-pot synthesis of 4-quinolones is described. Under the optimal conditions, a variety of 2-substituted 4-quinolones were synthesized via sequential palladium-catalyzed amidation of 2′-bromoacetophenones followed by base-promoted intramolecular cyclization.

Quinoline derivatives represent a major class of nitrogen-containing heterocycles frequently found in naturally occurring alkaloids and synthetic biologically active molecules.[1] Compounds containing 4-substituted quinoline scaffolds are of particular pharmaceutical value. For example, the historically well-known quinine, isolated from the bark of Cinchona trees, is an active ingredient for the treatment of malaria.[2] Chimanine alkaloids are responsible for the treatment of leishmaniasis, a tropical disease in South America.[3] Chloroquine, a synthetic quinoline, has been used for a long time to treat and prevent malaria attacks.[4] 4-Quinolones[5] are also versatile synthetic intermediates due to their facile derivatization of the 4-hydroxyl group.[6] Many synthetic methods for 4-quinolone have been documented.[7] One classical and commonly used approach is the condensation of an aniline with Meldrum's acid (or its derivatives) and trimethyl orthoformate to afford the corresponding enamine. The enamine intermediate is then cyclized in high-boiling solvents, such as diphenyl ether, at high temperature (250 °C)[8] or under microwave (300 °C) conditions.[9] This method suffers not only from the harsh reaction conditions but also the limitation of substrate scope. Alternatively, the mild, base-promoted cyclization of *N*-(*o*-ketoaryl)

† Dedicated with great admiration to Professor E. J. Corey, Nobel Laureate, on the occasion of his 80th birthday.

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(5) There is considerable interest in quinolones as antibacterial agents: (a) Andriole, V. T. *The Quinolones*; Academic Press: London, 1988.

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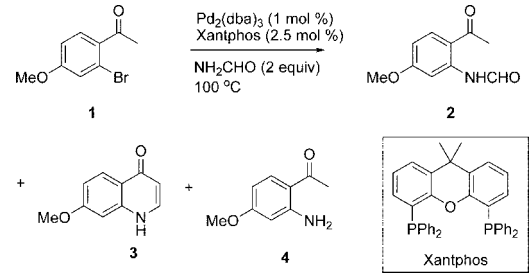
amides, known as the Camps cyclization,[10] is more attractive and has been widely employed to synthesize a variety of quinolones. However, the synthetic utility of the Camps cyclization is restricted by the limited access to *N*-(*o*-ketoaryl)amides. Although the scope of copper-[11] and palladium-catalyzed[12] amidation of aryl halides is broad in general, aryl halides bearing a ketone functional group have been reported to be incompatible due to the competitive arylation of the ketone enolate.[13] In this paper, we report our preliminary results on the efficient synthesis *N*-(*o*-ketoaryl)amides via a Pd-catalyzed amidation of 2-acetylbromoarenes and the subsequent base-promoted cyclization to form a wide range of 4-quinolones in one pot.[14]

We envisioned that the side reaction of ketone arylation might be suppressed by appropriate choice of a mild base, the ligand, and the solvent. Furthermore, it is desirable that the subsequent cyclization can be facilitated by addition of a stronger base without isolation of the resultant amide intermediate. To test our hypothesis, we selected (2-bromo-4-methoxy)acetophenone (**1**) as the model substrate for reaction condition screening. Our earlier examination of Pd-catalyzed amination of **1** employing either lithium[15] or zinc[16] trimethylsilylamide was unsuccessful, presumably due to the complications associated with steric hindrance and/or the strong basicity of the metal amide reagents. We then carried out screening of a variety of bases and solvents using the $Pd_2(dba)_3$/Xantphos catalyst system.[12,13,17] When Cs_2CO_3 was used as the base with polar solvents such as DMF and NMP, the reaction formed a complicated mixture with three major products identified (Table 1, entries 1 and 2): the desired amide **2**, the cyclized quinolone **3**, and the hydrolysis product aniline **4**. Reaction in toluene was sluggish due to the poor solubility of formamide in toluene (Table 1, entry 3).[18] To our surprise, the reaction in dioxane showed the highest combined yield of the desired amide **2** and quinolone **3** (90%, Table 1, entry 4). The undesired products related to the potential arylation of the ketone were not detected. However, a longer reaction time at 100 °C in dioxane yielded more cyclized product as well as the undesired aniline **4** resulting from the amide hydrolysis. To avoid the hydrolysis of the amide before cyclization, we found that addition of a stronger base, either NaOH or NaO^{t}Bu, led to full conversion of the amide to 7-methoxyquinolone **2** in 4 h (Table 1, entries 8 and 9). Other bases examined were either less effective (K_3PO_4, K_2CO_3, Na_2CO_3, and KOAc, Table 1, entries 5, 6, 7, and 10) or led to formation of complicated mixtures (NaOH and NaO^{t}Bu, Table 1, entries 11 and 12).

Table 1. Evaluation of Reaction Conditions[a,b]



1 2 3 4

entry	solvent	base	time (h)	**2** (%)	**3** (%)	**4** (%)
1	DMF	Cs_2CO_3	24	22	48	6
2	NMP	Cs_2CO_3	24	22	41	6
3	toluene	Cs_2CO_3	24	7	47	0
4	dioxane	Cs_2CO_3	24	29	61	0
5	dioxane	K_3PO_4	24	40	22	4
6	dioxane	K_2CO_3	24	0	47	0
7	dioxane	Na_2CO_3	24	0	17	0
8[c]	dioxane	Cs_2CO_3/NaOH	24/4	29/85	61/2	0/0
9[c]	dioxane	Cs_2CO_3/NaO^{t}Bu	24/4	29/89	61/0	0/0
10	dioxane	KOAc	24	0	4	0
11	dioxane	NaOH	24	3	0	0
12	dioxane	NaO^{t}Bu	24	12	22	0

[a] HPLC assay yield. [b] Reaction conditions: A mixture of $Pd_2(dba)_3$ (1 mol %) and Xantphos (2.5 mol %) in dioxane (5 mL) was stirred at room temperature for 5−10 min followed by addition of **1**, formamide (2 equiv), and the base (3 equiv). The resultant mixture was heated to 100 °C for 24 h and analyzed by HPLC. [c] The second base was added to the reaction mixture, which was then heated to 100 °C for another 4 h.

With the optimal conditions in hand, we examined the couplings of a variety of 2-bromoacetophenones with different amides (Table 2). The scope of the one-pot synthesis of 4-quinolones was demonstrated to be quite general for both coupling partners. The reaction proceeded smoothly with alkyl, aryl, and heterocyclic amides. More specifically, alkylamides with one or no α-proton are suitable substrates providing high yields of quinolones

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(13) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043.
(14) During the process of this study, Buchwald et al. reported a mild, two-step synthesis of 4-quinolone via Cu-catalyzed amidation followed by the base-promoted cyclization. The substrate scope was limited to the preparation of 2-aryl-4-quinolones: (a) Jones, A. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968.
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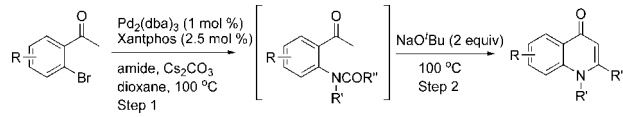
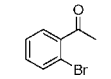
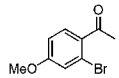
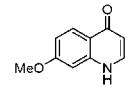
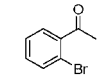
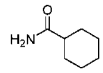
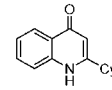
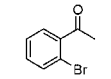
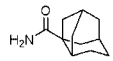
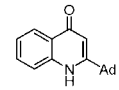
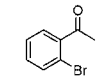
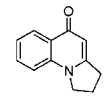
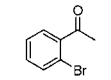
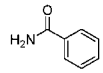
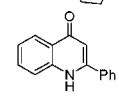
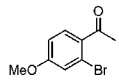
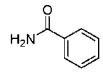
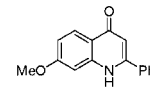
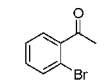
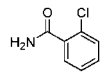
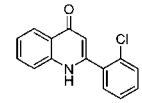
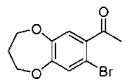
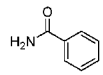
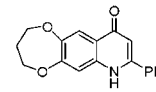
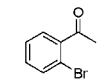
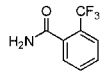
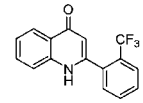
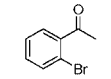
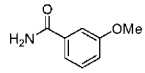
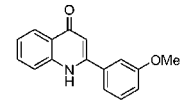
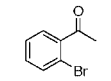
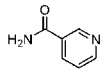
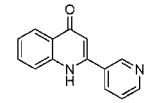
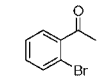
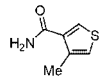
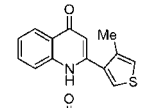
(18) Addition of formamide to the reaction mixture in toluene led to formation of a gel which resulted in difficult stirring.

Table 2. Substrate Scope



entry	bromoketone	amide	time (h, Step 1)	time (h, Step 2)	product	yield[a,b] (%)
1			24	4		52
2			24	4		77
3			4	18		82
4			4	18		91
5			24	18		85
6			2	2		92
7			2	2		96
8			4	18		87
9			48	24		29
10			4	18		83
11			4	18		90
12			18	18		91
13			18	18		91
14			2	18		94

[a] Isolated yield. [b] See the Supporting Information for detailed experimental procedures.

(Table 2, entries 1−4).[19] Interestingly, the five-membered lactam couples with high efficiency (Table 2, entry 5), while acyclic secondary amides have not been successful thus far. Arylamides were found to be excellent coupling partners. The resultant amides were cyclized effectively thereafter. The reaction of benzamide with different 2-bromoacetophenones was effective (Table 2, entries 6

(19) However, the use of acetamide which has more than one α-protons led to lower yield of 4-quinolone due to formation of 2-quinolone. Also see ref 10.

and 7), although a substrate with two electron-donating groups led to significantly lower yield (Table 2, entry 9). The reaction appears robust to the electronic and steric properties of the arylamides as 2-chloro-, 2-trifluoromethyl-, and 3-methoxybenzoamide all gave excellent yields of the desired quinolones (Table 2, entries 8, 10, and 11). The reaction with heterocyclic amides performed smoothly under similar conditions (Table 2, entries 12−14).

In conclusion, we have developed a mild, one-pot synthesis of 4-quinolones. The current method has been demonstrated to be general for the synthesis of a wide range of 2-substitued 4-quinolones. The easily accessible starting materials, mild reaction conditions, and simple manipulation render this an attractive methodology. Further scope investigation is ongoing and will be reported in due course.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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