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Novel Approach to 3,4-Dihydro-2(1H)-quinolinone Derivatives via Cyclopropane Ring Expansion

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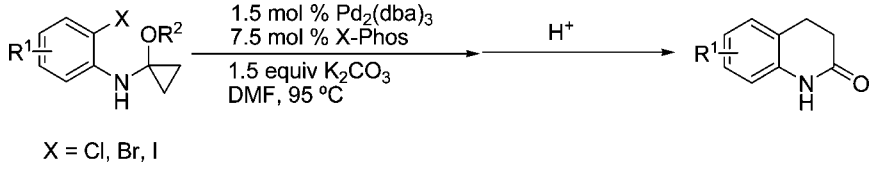
ABSTRACT



***N*-(1′-Alkoxy)cyclopropyl-2-haloanilines are transformed to 3,4-dihydro-2(1H)-quinolinones via palladium-catalyzed cyclopropane ring expansion. The reaction tolerates a variety of functional groups such as ester, nitrile, ether, and ketone groups.**

The benzo-fused lactam skeleton is an important element in a number of pharmacologically and biologically active compounds. The 3,4-dihydro-2(1H)-quinolinone scaffold is one important member of this class, and its derivatives are found in many natural products and drug candidates.[1] 3,4-Dihydro-2(1H)-quinolinones are classically synthesized via electrophilic aromatic substitution reactions, such as the Friedel−Crafts reaction,[2a] Beckmann rearrangement of indanone oxime,[2b] and cyclization of nitrenium ion;[2c,d] however, these methods require a stoichiometric amount of metal salt. Moreover, the reactions with electron deficient substrates in general give unsatisfactory results. Recently, various reports of efficient catalytic systems for the preparation of 3,4-dihydro-2(1H)-quinolinones have been published.[3]

During the course of our study we found that 2-methoxy-3,4-dihydroquinoline (**2a**) was formed as a byproduct when *N*-(1′-methoxy)cyclopropyl-2-iodoaniline (**1a**) was subjected to Larock indole synthesis conditions (Scheme 1).[4,5] This result prompted us to examine this palladium-catalyzed cyclopropane ring expansion reaction. The 3,4-dihydroquino-

Scheme 1. Larock Indole Synthesis against *N*-(1′-Methoxy)cyclopropyl-2-iodoaniline

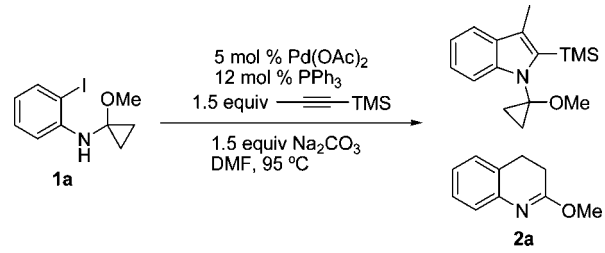


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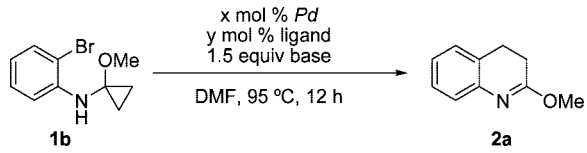
Table 1. Optimization of the Pd(0)-Catalyzed Cyclopropane Ring-Expansion Reaction of **1b**[a]



1b **2a**

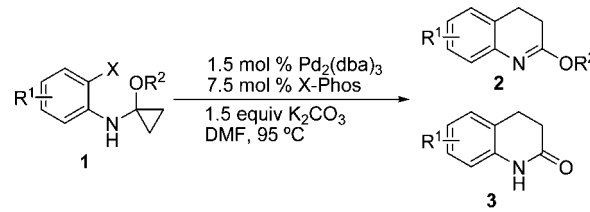
entry	Pd (x)	ligand (y)	base	yield [%][b]
1	$Pd(OAc)_2$ (5)	PPh_3 (12)	Na_2CO_3	14
2	$Pd_2(dba)_3$ (1.5)	PPh_3 (7.5)	Na_2CO_3	11
3	Pd(OAc)-P(biphenyl)(t-Bu)$_2$ (3.0)		Na_2CO_3	39
4	$Pd_2(dba)_3$ (1.5)	X-Phos (7.5)	Na_2CO_3	82
5	$Pd_2(dba)_3$ (1.5)	BIPHEP (3.8)	Na_2CO_3	22
6	$Pd_2(dba)_3$ (1.5)	X-Phos (7.5)	K_2CO_3	93
7	$Pd_2(dba)_3$ (1.5)	X-Phos (7.5)	t-BuOK	0
8[c]	$Pd_2(dba)_3$ (1.5)	X-Phos (7.5)	K_2CO_3	42
9[d]	$Pd_2(dba)_3$ (1.5)	X-Phos (7.5)	K_2CO_3	7

[a] Reaction was conducted under nitrogen atmosphere on 1.0 mmol scale. [b] Yield was determined by HPLC. [c] Reaction was conducted at 60 °C. [d] Reaction was conducted at 40 °C.

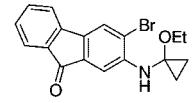
line **2a** was thought to be obtained through an intramolecular reaction of **1a**, and hence when the reaction was conducted in the absence of the alkyne, 2-methoxy-3,4-dihydroquinoline (**2a**) was obtained in a better yield. Herein we report a novel synthesis of 3,4-dihydro-2(^{1}H)-quinolinones from *N*-(1′-alkoxy)cyclopropyl-2-haloanilines. *N*-(1′-Alkoxy)cyclopropyl-2-haloanilines were readily synthesized from the corresponding 2-haloanilines with (1-ethoxycyclopropoxy)-trimethylsilane according to Yoshida's procedure.[6]

When we applied this protocol to the corresponding bromo derivative **1b** instead of iodide **1a**, the desired compound **2a** was obtained in only 14% yield (Table 1, entry 1). To improve the yield, the reaction conditions were extensively examined. The results are summarized in Table 1. It was found that the choice of palladium ligand was quite important. The use of the electron-rich biphenyl-based phosphine ligands[7] delivered the desired compound **2a** in good yield (Table 1, entries 3 and 4). Especially, when the more sterically demanding ligand, X-Phos, was employed, a significant improvement was achieved.[8] The use of K_2CO_3 as base led to the best result (Table 1, entry 4 vs 6) while *t*-BuOK gave no desired compound (Table 1, entry 7). A lower reaction temperature resulted in a lower yield (Table 1, entries 8 and 9). When the reaction was performed in toluene or dioxane as a solvent instead of DMF under the optimized conditions, the conversion became lower (10% conversion in toluene and 35% conversion in dioxane).

Table 2. Synthesis of Substituted 3,4-Dihydro-2(^{1}H)-quinolinones[a]



1 **2** **3**

entry	substrate X	substrate R^1	substrate R^2		time [h]	product[b] (yield [%])
1	I	H	Me	**1a**	6	**2a** (88)
2	Br	H	Me	**1b**	6	**2a** (90)
3				**1b**	6	**3a** (77)[c]
4	Cl	H	Me	**1c**	12	**2a** (70)
5	I	4-CO_2Me	Me	**1d**	12	**2b** (73) **3b** (12)[d]
6				**1d**	12	**3b** (83)[c]
7	I	4-CO_2Me	Et	**1e**	12	**2c** (90)
8	I	4-CO_2Me	*i*-Pr	**1f**	12	**2d** (73)
9	Br	4-F	Me	**1g**	12	**3c** (87)[c]
10	Br	4-CN	Et	**1h**	12	**3d** (58)[c,d]
11	Br	5-CF_3	Et	**1i**	12	**3e** (88)[c]
12	Br	5-MeO	Et	**1j**	6	**3f** (82)[c]
13	Cl	5-MeO	Me	**1k**	20	**3f** (41)[c]
14	Br	4-F, 6-F	Et	**1l**	6	**3g** (70)[c]
15	Br	4-Me	Et	**1m**	6	**3h** (66)[c,d]
16	Cl	6-Me	Et	**1n**	20	**3i** (64)[c]
17	Br	4-NO_2	Et	**1o**	12	-
18				**1p**	6	**3j** (71)[c]

[a] Reaction was conducted under a nitrogen atmosphere on 1.0 mmol scale. [b] Yield of the isolated product. [c] Reaction was quenched with 1N HCl instead of H_2O. [d] Average yield for 2 experiments.

With optimized reaction conditions in hand, we next examined the scope and limitations of this reaction. The results are summarized in Table 2. Chloroaniline derivatives also furnished the desired cyclized products in moderate yield although the corresponding bromo- and iodoaniline derivatives gave better yields with a shorter reaction period (Table 2, entries 4, 13, and 16). In some cases, the 2-alkoxy-3,4-dihydroquinoline **2** was partially hydrolyzed during aqueous workup operations, and 3,4-dihydro-2(^{1}H)-quinolinone **3** was obtained as byproduct (Table 2, entry 5). Though this hydrolysis was suppressed when the substrate bearing the more sterically demanding group, such as isopropyl, was employed, the conversion was lower (Table 2, compare entries 5, 7, and 8).[9] Therefore, we decided to conduct the hydrolysis of the 2-alkoxy-3,4-dihydroquinolines before the extraction. The reaction tolerated a variety of functional groups, such as ester (Table 2, entries 5−8), nitrile (Table 2, entry 10), ether (Table 2, entries 12 and 13), and ketone (Table 2, entry 18) groups. The substrate bearing a NO_2

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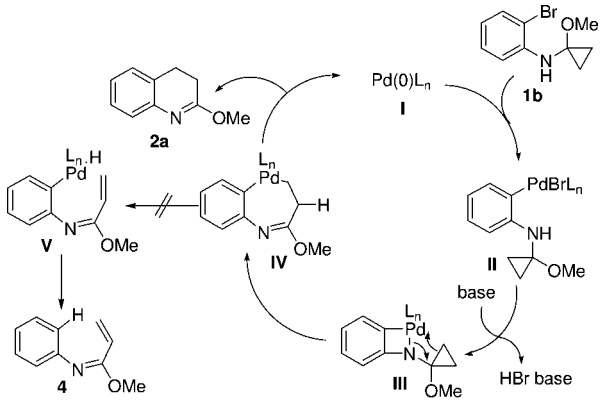
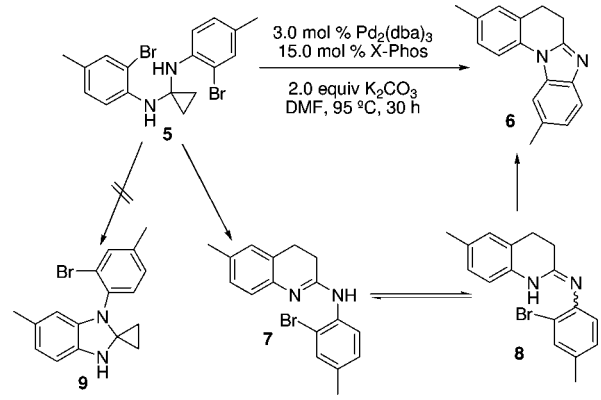
(8) We also examined other biphenyl-based phosphine ligands, such as S-Phos, Ru-Phos, and Dm-Phos with the reaction of **1k**; however, better results were not obtained (Table 2, entry 13).

(9) About 10% of 3,4-dihydro-2(^{1}H)-quinolinone was generated when the reaction of **1j** or **1p** was quenched with water.

Scheme 2. Plausible Reaction Mechanism



Scheme 3. Reaction with Diaminoacetal **5**



substituent gave no desired compound while the substrate was consumed completely (Table 2, entry 17).

A plausible reaction mechanism is shown in Scheme 2. The oxidative addition of aryl halide **1b** to palladium(0) **I** followed by intramolecular ligand exchange would give the four-membered azapalladacycle **III**.[10] Then, palladium rearrangement accompanied with cyclopropane ring opening furnishes the energetically favorable seven-membered azapalladacycle **IV**.[11] Finally, reductive elimination produces 2-methoxy-3,4-dihydroquinoline (**2a**), and the regeneration of the reactive palladium(0) species **I**. The formation of *N*-aryl-α,*β*-unsaturated imidate **4**, which would be generated by *β*-hydride elimination from the palladacycle **IV**, was not observed.

Interestingly, when 1,1-dianilinocyclopropane **5** was employed instead of *N*-(1′-alkoxy)cyclopropyl-2-haloanilines **1**, 5,6-dihydrobenzimidazo[1,2-a]quinoline **6** was obtained in 37% yield along with **7** and **8** in 28% yield (Scheme 3). This transformation can be explained by the cyclopropane ring expansion of **5** followed by palladium-catalyzed intramolecular *N*-arylation.[12] The formation of *N*-aryl-2,3-dihydro-[1]H-benzoimidazole **9**, which would be generated by palladium-catalyzed intramolecular *N*-arylation of 1,1-dianilinocyclopropane **5**, was not observed.

In conclusion, we have developed a novel synthetic method for the construction of 3,4-dihydro-2([1]H)-quinolinones via cyclopropane ring expansion. This method is also applicable to synthesize 5,6-dihydrobenzimidazo[1,2-a]quinoline. Further studies to expand this chemistry and provide deeper insight into the mechanism are currently under investigation in our laboratory.

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Supporting Information Available: Detailed experimental procedures and characterization data of each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A similar type of this palladium-catalyzed intramolecular *N*-arylation was reported by Junjappa: Venkatesh, C.; Sundaram, G. S. M.; Ha, H.; Junjappa, H. *J. Org. Chem.* **2006**, *71*, 1280.