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Palladium-Catalyzed Intermolecular Aerobic Annulation of *o*-Alkenylanilines and Alkynes for Quinoline Synthesis

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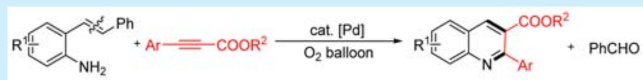
Supporting Information

ABSTRACT: A new approach to construct 2,3-disubstituted quinolines is described via Pd-catalyzed oxidative cyclization of *o*-vinylanilines and alkynes with molecular oxygen. This transformation is supposed to undergo intermolecular amination of alkyne, insertion of the olefin, and oxidative cleavage of C−C bond sequence.



Quinolines represent an interesting class of *N*-containing heterocycles that frequently occur in natural products[1] and are key structures of several pharmaceutical compounds[2] (Figure 1). These moieties have been reported to possess a

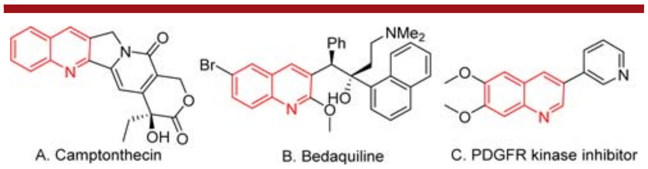
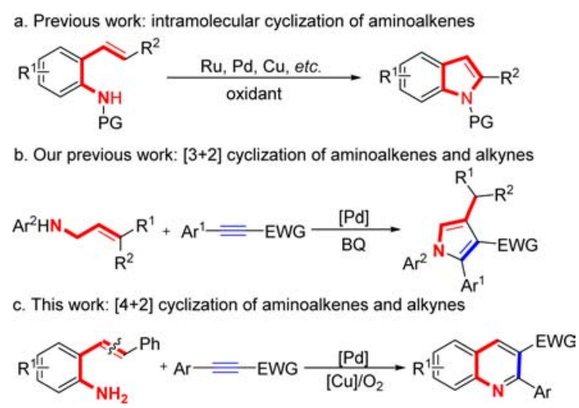


Figure 1. Selected Bioactive Molecules Containing the Quinoline Moiety.

diverse range of biological properties that are anticancer,[3] antimicrobial,[4] anti-inflammatory,[2b] and antipsychotics.[5] In view of the tremendous biological importance of quinolines, numerous synthetic protocols to elaborate this molecular scaffold have been developed over the years.[6−10] Among them, *o*-substituted anilines, a type of useful building blocks, have proven potential in the synthesis of quinolines.[8−10] For example, Korivi's group demonstrated a Ni-catalyzed cyclization of 2-iodoanilines with aroylalkynes to produce 2,4-disubstituted quinolines.[8] 2-Carbonyl and ethynyl-anilines have also been employed to construct polysubstituted quinoline derivatives which were catalyzed by Au, Pd, Cu, etc.[9,10] However, the development of efficient protocols for the assembly of this molecular scaffold still remains a demanding goal due to their significance.

Alternately, transition metal-catalyzed amination of C−C multiple bonds has emerged as a powerful tool for versatile synthesis of *N*-containing molecules.[11] Generally, fast intramolecular aminometalation occurs to achieve annulations, which affords the corresponding heterocyclic compounds (e.g., indoles, Scheme 1, a).[12] By contrast, achieving intermolecular cyclizations of amino-alkenes/alkynes is challenging and relatively rare.[13,14] Typically, two strategies are employed. The first is choosing a more favored process of nucleometalation to activate the C−C multiple bonds, such as

Scheme 1. Transformations of Aminoalkenes



halopalladation.[13] In the second scenario, there are two key features: (a) removing the *N*-substituents to increase the nucleophilic ability, which leads to coordination instead of aminometalation; (b) employing another substrate with enough activity, such as CO, isonitrile.[14] In our previous report about Pd-catalyzed [3 + 2] oxidative cyclization of allylamines and alkynes, the active alkynes with electron-withdrawing group are required for the insertion of the N−Pd bond (Scheme 1,b).[15] On the basis of the strategy above, a Pd-catalyzed aerobic [4 + 2] annulation of *o*-vinylanilines and alkynes with the aid of Cu salt and O_2 is developed (Scheme 1, c). This protocol enables rapid assembly of quinolines via C−N, C−C bond formations and aerobic C−C bond cleavage.

After our initial investigation, we found that palladium catalyst, ligand, and O_2 are all crucial features and no reaction occurred without any of them (see the Supporting Information for details). Thus, we chose $PdCl_2$, PPh_3, and O_2 for further optimization. Employing 20 mol % of $Cu(OAc)_2$ could increase the yield from 5% to 25% (Table 1, entries 1 and 2). A certain

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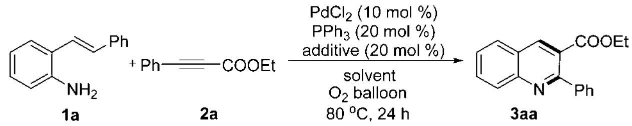
Table 1. Optimization of Reaction Conditions[a]



entry	additive	solvent	yield (%)[b]
1		MeCN	5
2	$Cu(OAc)_2$	MeCN	25
3	$Cu(OAc)_2$	DMSO	trace
4	$Cu(OAc)_2$	MeCN/DMSO = 5/1	44
5	$Cu(OAc)_2$	MeCN/DMSO = 10/1	53
6	$Cu(OAc)_2$	MeCN/DMSO = 20/1	59
7	$Cu(OAc)_2$	MeCN/EtOH = 20/1	53
8	$Cu(OAc)_2$	MeCN/MeOH = 20/1	50
9[c]	$Cu(OAc)_2$	MeCN/DMSO = 20/1	n.r.
10	$Cu(OTf)_2$	MeCN/DMSO = 20/1	16
11	$Cu(TFA)_2{\cdot}xH_2O$	MeCN/DMSO = 20/1	65
12	CuCl	MeCN/DMSO = 20/1	26
13[d]	$Cu(TFA)_2{\cdot}xH_2O$	MeCN/DMSO = 20/1	57
14[e]	$Cu(TFA)_2\ xH_2O$	MeCN/DMSO = 20/1	n.r.
15[f]	$Cu(TFA)_2{\cdot}xH_2O$	MeCN/DMSO = 20/1	86 (82)[g]
16[h]	$Cu(TFA)_2{\cdot}xH_2O$	MeCN/DMSO = 20/1	n.r.

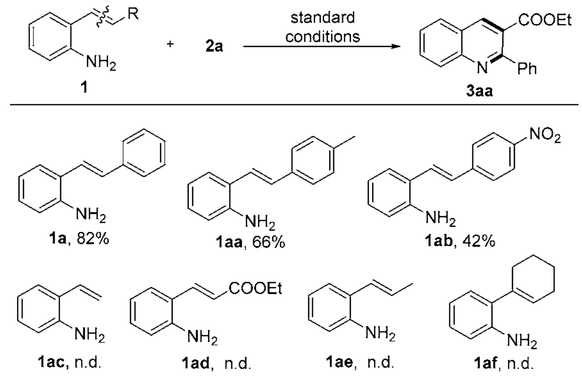
[a]Reaction conditions: All reactions were performed with **1a** (0.2 mmol), **2a** (0.2 mmol), $PdCl_2$ (10 mol %), PPh_3 (20 mol %), additive (20 mol %) and solvent (1.0 mL) with an O_2 balloon at 80 °C for 24 h. [b]Determined by GC analysis using dodecane as an internal standard, n.r. = no reaction. [c]Under N_2. [d]Addition of Et_3N (0.1 mmol). [e]Addition of K_2CO_3 (0.1 mmol). [f]Addition of PivOH (0.1 mmol). [g]Isolated yield. [h]Reaction temperature was 60 °C.

amount of DMSO could promote this reaction efficiently while increasing the amount leads to gradual inhibition (Table 1, entries 3–6). Other reductive solvents, including EtOH and MeOH, promoted this process as well (Table 1, entries 7–8). However, no reaction occurred under N_2 atmosphere (Table 1, entry 9). The screening of different additives revealed that $Cu(TFA)_2{\cdot}xH_2O$ is better than others (Table 1, entries 10–12). The addition of Et_3N provided a slightly lower yield while K_2CO_3 led to no reaction (Table 1, entries 13–14). Gratifyingly, the yield of **3aa** increased to 86% when 1 equiv of PivOH was employed (Table 1, entry 15). Further investigation indicated lower temperature was negative to this reaction (Table 1, entry 16). Therefore, the optimal reaction condition was obtained: $PdCl_2$ (10 mol %), PPh_3 (20 mol %), $Cu(TFA)_2{\cdot}xH_2O$ (20 mol %), PivOH (1 equiv) in MeCN/DMSO (20/1) with an O_2 balloon at 80 °C.

As the optimized conditions were established, we next turned to examine the scope of 2-alkenylanilines under the optimized reaction conditions, and the results are summarized in Scheme 2. This transformation proceeds smoothly when R is phenyl, though phenyl-substituents such as Me and NO_2 have negative effects on this transformation (**1aa**, **1ab**), with the corresponding aldehydes obtained. No desired product was detected when terminal and alkyl-substituted alkenes were used (**1ac**–**1af**).

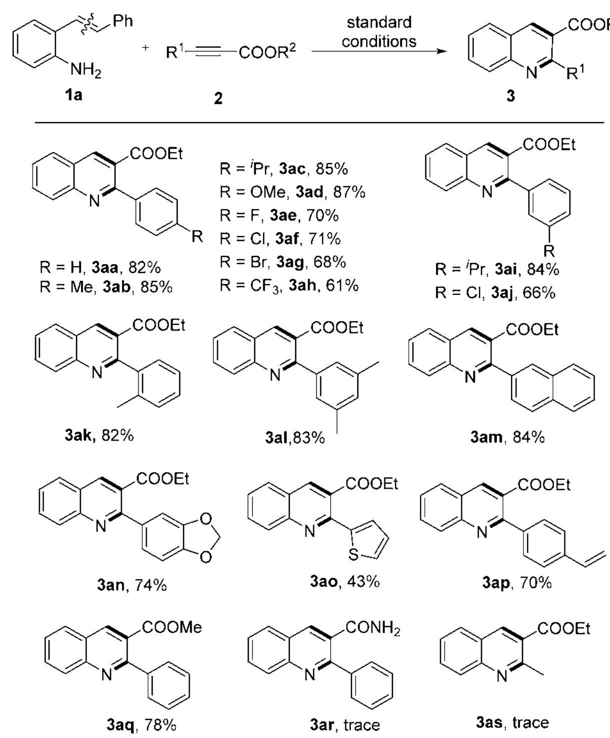
Subsequently, the scope of alkynes was investigated under the optimal conditions (Scheme 3). Alkynyl esters bearing 4-substitued electron-donating groups, such as alkyl and alkoxy groups, gave the desired quinolines in excellent yields (**3ab**–**3ad**). Substrates with electron-withdrawing groups (halogen and trifluoromethyl) were relatively sluggish and afforded moderate yields (**3ae**–**3ah**). Similarly, *ortho*-, *meta*- and disubstitued alkynyl esters underwent the annulation success-

Scheme 2. Screening for the Alkenes[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), $PdCl_2$ (10 mol %), PPh_3 (20 mol %), $Cu(TFA)_2{\cdot}xH_2O$ (20 mol %) and PivOH (1 equiv) in 2 mL of MeCN/DMSO (20/1), with an O_2 balloon, 80 °C for 24 h.

Scheme 3. Substrate Scope for Alkynyl Esters[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), $PdCl_2$ (10 mol %), PPh_3 (20 mol %), $Cu(TFA)_2{\cdot}xH_2O$ (20 mol %) and PivOH (1 equiv) in 2 mL of MeCN/DMSO (20/1), with an O_2 balloon, 80 °C for 24 h.

fully to afford the corresponding products in considerable yields (**3ai**–**3al**). Naphthyl substrate participated efficiently as well to give the corresponding product **3am** in 84% yield. In addition, the alkynyl ester bearing benzo[*d*][1,3]dioxole moiety reacted smoothly to deliver **3an** in 74% yield. Gratifyingly, thiophene-containing substrate was tolerated, though the expected product **3ao** was provided in relatively lower yield. Notably, the alkenyl group was fully compatible as well (**3ap**). Switching ethyl phenylpropiolate to methyl phenylpropiolate showed no obvious influence to the yield (**3aq**). Unfortunately, 3-phenylpropiolamide and ethyl but-2-ynoate failed to afford the desired products **3ar** and **3as**.

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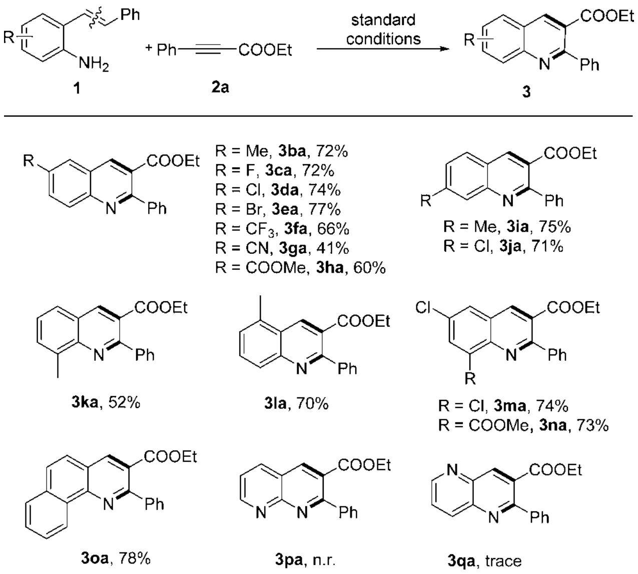
Then our attention was turned to explore the effect of substituents on the anilines (Scheme 4). As shown in Scheme 4, functional groups such as methyl, halogen (F, Cl, Br), trifluoromethyl, cyano, and ester groups all exhibited good compatibility in this reaction. *para*-Substituted anilines with both electron-donating group and electron-withdrawing group proceeded smoothly to afford corresponding products **3ba**–**3ha** in moderate to good yields. Similarly, 5-Me- and 5-Cl-substituted substrates gave **3ia** and **3ja** in 75% and 71% yields, respectively. 4-Methyl-quinoline (**3la**) was obtained in 70% yield, while only 52% yield of 8-methyl-quinoline (**3ka**) was provided. To our delight, disubstituted compounds also worked well to offer 6,8-dichloro-quinoline (**3ma**) and 6-chloro-8-ester-quinoline (**3na**) in good yields. As expected, this protocol is also applicable to naphthylamine, which transferred to benzo[*h*]quinoline **3oa** in 78% yield. However, pyridine was not tolerant in this transformation (**3pa**, **3qa**).

Scheme 4. Substrate Scope for *o*-Alkenyl Anilines[a]

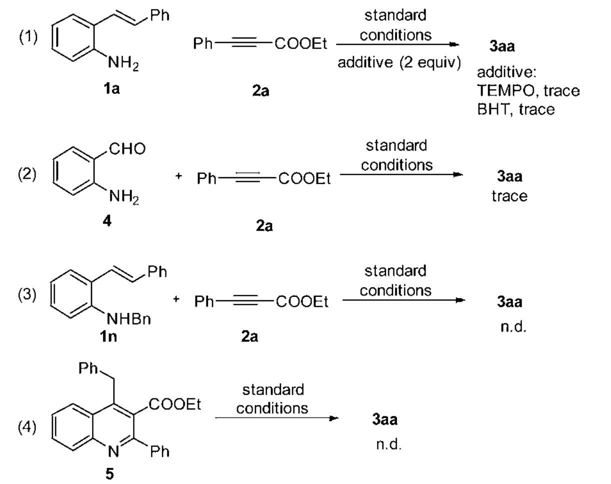


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), $PdCl_2$ (10 mol %), PPh_3 (20 mol %), $Cu(TFA)_2{\cdot}xH_2O$ (20 mol %) and PivOH (1 equiv) in 2 mL of MeCN/DMSO (20/1), with an O_2 balloon, 80 °C for 24 h.

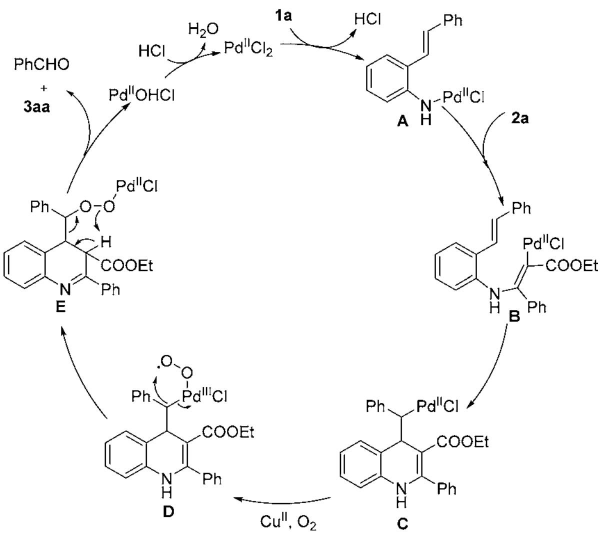
To better understand this transformation, some control experiments were conducted (Scheme 5). Only a trace amount of desired product was detected when 2 equiv of TEMPO or BHT was employed (Scheme 5, eq 1), which indicates that this transformation might undergo a radical process. When *o*-aminobenzaldehyde **4** was employed instead of **1a**, only a trace amount of **3aa** was observed. Thus, this reaction is supposed not to undergo an oxidative cleavage of alkene first to give aldehyde as the intermediate (Scheme 5, eq 2). *N*-Benzyl-protecting aniline **1n** decomposed under the standard conditions, which afforded no corresponding product (Scheme 5, eq 3). In this transformation, no *β*-H elimination product **5** was observed. We also synthesized **5** and found it could not convert into **3aa** under the standard conditions (Scheme 5, eq 4). Thus, this reaction did not undergo the oxidative cleavage of *β*-H elimination product.

On the basis of the above results and literature precedents, a plausible mechanism is proposed in Scheme 6. The reaction is initiated by interaction of Pd^{II} and **1a** to form the intermediate

Scheme 5. Control Experiments



Scheme 6. Possible Mechanism



A,[14,15] followed by the intermolecular *cis*-insertion of **2a**. Alkyl-Pd species **C** is obtained via the intramolecular migratory insertion of alkene. In path A, with the aid of Cu^{II}, a subsequent reaction between **C** and O_2 affords peroxopalladuim(III) **D**, which would be converted to intermediate **E** by rearrangement.[16] Then, product **3aa** and aldehyde are obtained by the elimination of Pd^{II}–OH and cleavage of C–C bonds in intermediate **E**. Finally, the active Pd^{II} species would be regenerated by the reaction between Pd(OH)Cl with HCl.

In summary, a Pd-catalyzed intermolecular oxidative annulation of *o*-alkenylanilines and alkynes has been developed. Assisted by Cu and O_2, this transformation undergoes a sequential intermolecular alkyne amination, alkenyl migration insertion, and aerobic C–C bond cleavage. Molecular oxygen is used as the terminal oxidant which is also the key feature to the cleavage of the C–C bond. This protocol provides an efficient route to access polysubstituted quinolines, which shows good functional group compatibility and high regioselectivity.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01008.

Typical experimental procedure and characterization for all products (DOC)

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Notes

The authors declare no competing financial interest.

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