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Palladium-Catalyzed Tandem *N*-Vinylation and Cyclization of Anilines and Haloenynes: An Efficient Approach to Substituted Quinolines

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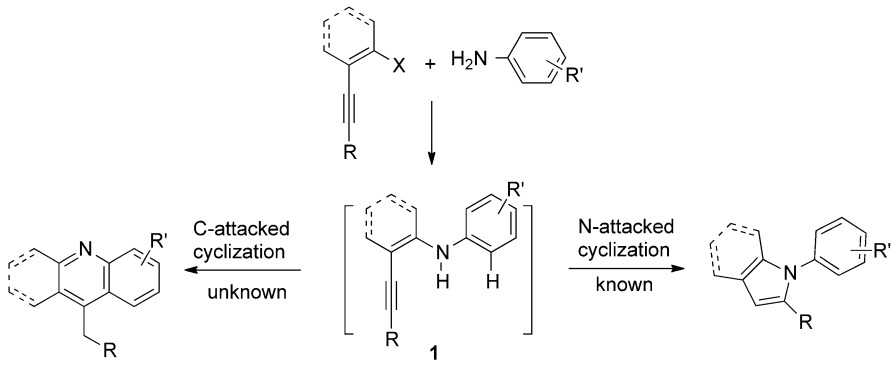
Abstract: The palladium-catalyzed tandem amination of haloenynes and intramolecular cyclization has been developed. The reaction provides a novel route for the synthesis of quinoline derivatives with high yields.

Keywords: coupling reactions; cyclization; haloenynes; palladium; quinolines

Transition metal-catalyzed tandem reactions have emerged as a useful tool for the synthesis of N-heterocyclic compounds, since they can directly lead to complicated molecules from readily accessible starting materials under mild conditions with high efficiency.[1,2] Among the reactions developed, Pd- or Cu-catalyzed transformations of *o*-haloalkynylarenes or haloenynes *via* amination to form *o*-alkynylanilines or alkynylenamines **1** followed by intramolecular hydroamination of alkynes have been studied, which represent a fruitful strategy to access indoles[3,4] or pyrroles and pyrazoles[5] (Scheme 1, *right*). Based on an analysis of the possible routes to the key intermediate **1**, we wondered whether it would be possible to effect a transformation by intramolecular hydroarylation of alkynes,[6] to gain access to other important nitrogen heterocycles, such as quinolines (Scheme 1, *left*).

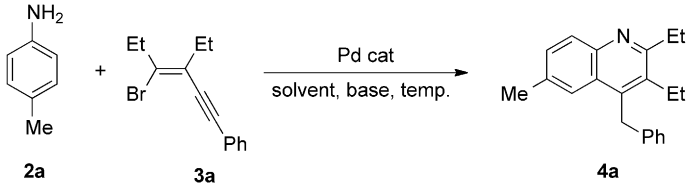
Quinoline skeletons play important roles as components of bioactive compounds.[7] Many methods have been developed for the construction of quinolines.[8,9] Among the various synthetic routines, transition metal-catalyzed processes are highly attractive.[9] Despite this progress, the development of novel approaches to quinoline derivatives from common building blocks is still desired. Herein we report an efficient approach to substituted quinolines by palladium-catalyzed tandem *N*-vinylation and cyclization of anilines and haloenynes.

To identify the optimal reaction conditions for the reaction, a number of palladium catalysts, including $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2$, $Pd(CH_3CN)_2Cl_2$, and



Scheme 1. Design of the synthesis of N-heterocyclic molecules by a tandem reaction.

Table 1. Optimization of the reaction conditions.[a]



2a **3a** **4a**

Entry	Pd cat. (mol %)	Base	Solvent	Temp. [°C]	Time [h]	Yield of **4a** [%][b]
1	$Pd(PPh_3)_2Cl_2$ (5)	*t*-BuONa	NMP	90	24	N.R.
2	$Pd(PPh_3)_2Cl_2$ (5)	*t*-BuONa	toluene	90	24	80
3	$Pd(PPh_3)_2Cl_2$ (5)	*t*-BuONa	DMF	90	24	5
4	$Pd(PPh_3)_2Cl_2$ (5)	*t*-BuONa	DMSO	90	24	5
5	$Pd(PPh_3)_2Cl_2$ (5)	*t*-BuONa	toluene	90	40	95
6	$Pd(PPh_3)_2Cl_2$ (5)	NaOH	toluene	90	40	15
7	$Pd(PPh_3)_2Cl_2$ (5)	Cs_2CO_3	toluene	90	40	N.R.
8	$Pd(PPh_3)_2Cl_2$ (5)	K_3PO_4	toluene	90	40	N.R.
9	$Pd(PPh_3)_2Cl_2$ (2.5)	*t*-BuONa	toluene	90	40	37
10	$Pd(OAc)_2$ (5)	*t*-BuONa	toluene	90	40	N.R.
11	$Pd(CH_3CN)_2Cl_2$ (5)	*t*-BuONa	toluene	90	40	N.R.
12	$Pd(PPh_3)_4$ (5)	*t*-BuONa	toluene	90	40	65
13	$Pd(CH_3CN)_2Cl_2$ (5) + PPh_3(10)	*t*-BuONa	toluene	90	40	41
14	$Pd(OAc)_2$ (2) + XPhos (5)	*t*-BuONa	toluene	90	40	61
15	$Pd(OAc)_2$ (2) + *t*-Bu-XPhos (5)	*t*-BuONa	toluene	90	40	75
16	$Pd(OAc)_2$ (2) + $P(C_6H_5)_3$ (5)	*t*-BuONa	toluene	90	40	N.R.
17	$Pd(OAc)_2$ (2) + PCy_3 (5)	*t*-BuONa	toluene	90	40	24
18	$Pd(PPh_3)_2Cl_2$ (5)	*t*-BuONa	toluene	110	40	75
19	$Pd(PPh_3)_2Cl_2$ (5)	*t*-BuONa	toluene	130	40	42

[a] All the reactions were performed with **2a** (1.1 mmol) and **3a** (1.0 mmol) under a nitrogen atmosphere.
[b] Determined by ^{1}H NMR. NMP = *N*-methyl-2-pyrrolidone; DMF = *N*,*N*-dimethylformamide; DMSO = dimethyl sulfoxide.

$Pd(PPh_3)_4$, and several different organic solvents and bases were examined in a model reaction of *para*-toluidine (**2a**) with (*Z*)-4-bromo-3-ethyl-1-phenylhex-3-en-1-yne (**3a**). Interesting observations emerged from the data in Table 1. We first tried the reaction of **2a** (1.1 mmol) with bromoenyne **3a** (1.0 mmol), which was readily prepared by the direct bromoalkynylation of 3-hexyne,[10] 5 mol% of $Pd(PPh_3)_2Cl_2$, and 2.0 equivalents of *t*-BuONa in 2.0 mL of NMP at 90 °C for 24 h. The desired product **4a** was not observed (entry 1). The screening of various solvents revealed that the solvent played an important role in this reaction (entries 1–4). Toluene was found to be quite successful for the transformation, and compound **4a** was obtained in 80% yield (entry 2). When DMF or DMSO was used as a solvent, the reactions were messy with less than 5% of the desired product (entries 3 and 4). On prolonging the reaction time to 40 h, the expected product **4a** was formed in 95% yield (entry 5). The structure of product **4a** was confirmed by ^{1}H NMR, ^{13}C NMR, COSY, HMQC, and HMBC.[11] It is noteworthy that no 2-benzyl-3,4-diethyl-6-methylquinoline produced by initial intermolecular hydroamidation of the alkyne portion and subsequent intramolecular *ortho*-vinylation was obtained during the reaction. Different bases were also tested in this reaction system (entries 5–8), *t*-BuONa proved to be the most effective (entry 5).

On decreasing the catalyst loading from 5 to 2.5 mol%, the product **4a** was obtained in only 37% yield (entry 9). We next tested the reaction in the presence of different catalysts. $Pd(PPh_3)_2Cl_2$, was superior to any other palladium catalysts so far tested (entries 5, 10–17). Notably, the reaction was not effective when only $Pd(OAc)_2$ or $Pd(CH_3CN)_2Cl_2$ was employed (entries 10 and 11). It is noteworthy that increasing the reaction temperature resulted in decreased yield of the product (entries 18 and 19).

On the basis of these results, the optimal conditions included the following parameters: $Pd(PPh_3)_2Cl_2$ as a catalyst, *t*-BuONa as a base, and toluene as a solvent with a reaction temperature at 90 °C. Under these optimized conditions, a study on the substrate scope was carried out, and the results are summarized in Table 2. First, various aromatic amine derivatives **2** were used for the reaction with (*Z*)-4-bromo-3-ethyl-1-phenylhex-3-en-1-yne **3a** under the optimized conditions. The reaction was applicable to various aromatic amines. For example, reaction of **3a** with *para*-methoxyaniline **2b** gave **4b** in 87% yield (entry 2). When 1-naphthylamine **2d** was used as a substrate, the desired product **4d** was also formed in high yield after 60 h (entry 4). Furthermore, the reaction of **3a** with *para*-fluoroaniline **2e** and *para*-chloroaniline **2f** gave the desired product **4e** and **4f** in 97% and 83% yields, respectively (entries 5 and 6). Notably, much longer

Table 2. Tandem synthesis of diversely substituted quinolines catalyzed by palladium.[a]

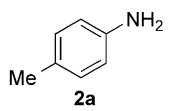
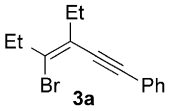
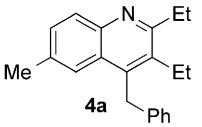
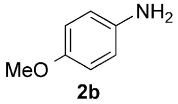
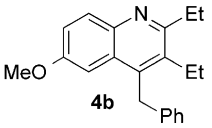
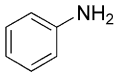
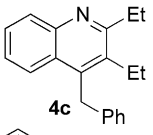
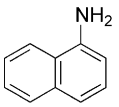
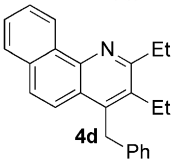
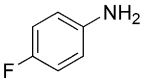
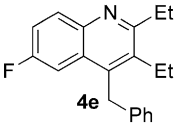
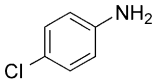
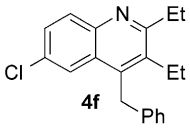
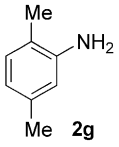
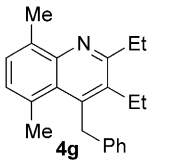
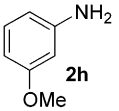
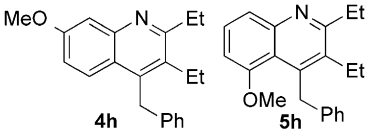
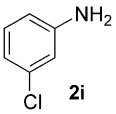
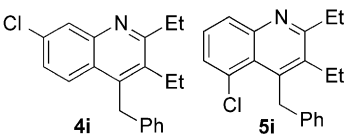
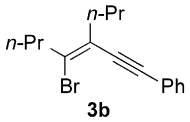
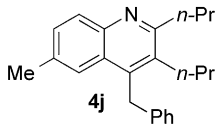
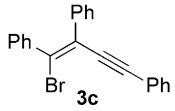
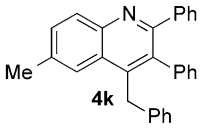
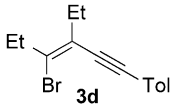
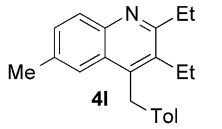
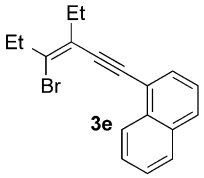
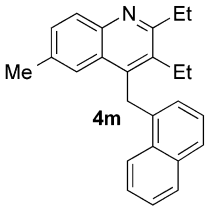
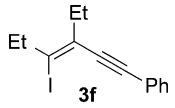
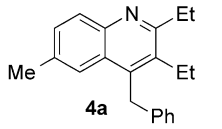
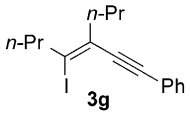
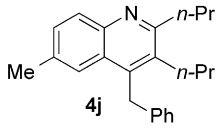
Entry	Aniline	Haloenyne	Time [h]	Product	Yield [%][b]
1	 **2a**	 **3a**	40	 **4a**	95 (90)
2	 **2b**	**3a**	32	 **4b**	87 (73)
3	 **2c**	**3a**	40	 **4c**	93 (82)
4	 **2d**	**3a**	60	 **4d**	88 (81)
5	 **2e**	**3a**	72	 **4e**	97 (90)
6	 **2f**	**3a**	60	 **4f**	83 (72)
7	 **2g**	**3a**	72	 **4g**	43 (30)[c]
8	 **2h**	**3a**	40	 **4h** **5h**	**4h**: 18 (10) **5h**: 73 (70)
9	 **2i**	**3a**	60	 **4i** **5i**	**4i**: 30 (15) **5i**: 27 (13)

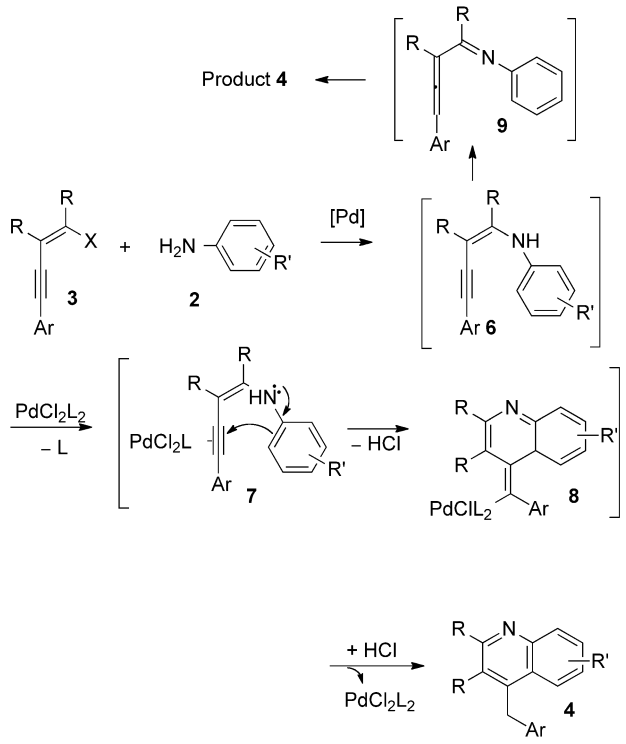
Table 2. (Continued)

Entry	Aniline	Haloenyne	Time [h]	Product	Yield [%][b]
10	**2a**	 **3b**	48	 **4j**	93 (90)
11	**2a**	 **3c**	48	 **4k**	83 (80)
12	**2a**	 **3d**	40	 **4l**	97 (91)
13	**2a**	 **3e**	40	 **4m**	95 (87)
14	**2a**	 **3f**	40	 **4a**	47 (22)
15	**2a**	 **3g**	40	 **4j**	43 (20)

[a] All the reaction were carried out using 1.1 mmol of aniline **2** and 1.0 mmol of haloenyne **3** in the presence of $Pd(PPh_3)_2Cl_2$ (5.0 mol%), and *t*-BuONa (2.0 mmol), in 3 mL toluene at 90 °C.
[b] Determined by ^1H NMR, isolated yield in parenthese.
[c] 1-(2,5-Dimethylphenyl)-2,3-diethyl-5-phenyl-1*H*-pyrrole was isolated in 40% yield as by-product.

reaction times were needed for the *para*-halogen substituted anilines. It is noteworthy that the aniline with a strong electron-withdrawing group, such as CO_2Et and CN group, on the *para*-position of he ring failed to generate any product and starting materials remained. When 2,5-dimethylaniline **2g**, which has one methyl group at the *ortho*-position, was used as a substrate, the desired product **4g** was formed in 43% yield after 72 h (entry 7), along with 40% of 1-(2,5-dimethylphenyl)-2,3-diethyl-5-phenyl-1*H*-pyrrole as a by-product. This may be attributed to the steric hindrance of the *ortho*-methyl group. The regioselectivity of the reaction has also been investigated. *meta*-Methoxyaniline derivative **2h** afforded the *para*-cyclization regioisomer **4h** and *ortho*-cyclization isomer **5h** in 18% and 73% yields, respectively (entry 8). *meta*-Chloroaniline **2i** afforded the *para*-cyclization regioisomer **4i** and *ortho*-cyclization isomer **5i** in 30% and 27% yields (entry 9).

On the other hand, different combinations of substituents on the alkyne and alkene of bromoenynes can be used to allow the synthesis of alkyl- and aryl-substituted quinolines (entries 10–13). When alkyl substituents were on the end of alkyne, the desired product could not be observed. When a bromoenyne with one substituent on the alkene, such as (*Z*)-4-bromo-4-phenyl-1-phenylbut-3-en-1-yne or (*Z*)-4-bromo-4-butyl-1-phenylbut-3-en-1-yne was used, the desired product could not be observed. It is noteworthy that reaction of iodoenynes with aniline afforded the desired products in moderate yields (entries 14 and 15) along with some uncharacterized by-products. The reaction of 1-bromo-2-(phenylethynyl)benzene with anilines was evaluated under the optimized con-



Scheme 2. Proposed reaction mechanism.

ditions. In this case, no products were observed, and starting materials remained.

Based on above study, the mechanism of this reaction was proposed as shown in Scheme 2. First, haloenyne **3** reacts with anilines **2** *via* Pd-catalyzed C–N coupling to afford alkynyl enamine **6**.[12,13] The triple bond of intermediate **6** could be activated by complexation with Pd(II) species[14] to promote an intramolecular nucleophilic attack by the N-substituted phenyl ring to afford intermediate **8**.[6] Finally, quinoline derivative **4** is formed after protonation and isomerization. Alternatively, base-mediated isomerization to imino-allene **9** and electrocyclic ring-closure/tautomerization to product **4** cannot be ruled out.[6a,c]

In summary, we have reported a novel palladium-catalyzed tandem synthesis of quinolines that consists of an *N*-vinylation and a cyclization of anilines with haloenynes. Studies are ongoing to apply this C–N/C–C bond formation cascade to the synthesis of other heterocycles.

Experimental Section

General Procedure

$Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), arylamine (1.1 mmol) and *t*-BuONa (192 mg, 2.0 mmol) were added to a pre-dried screw-capped test tube with a Teflon-lined septum. The tube was then evacuated and backfilled with N_2 and this procedure was repeated three times. Haloenyne (1 mmol) and toluene (2 mL) were added by syringe at room temperature. The tube was then sealed with a Teflon valve and the reaction mixture was stirred at 90 °C for the indicated time. Then the mixture was cooled to room temperature. Water (5 mL) and ethyl acetate (5 mL) were added and stirred for 30 min. The aqueous layer was washed with ethyl acetate (5 mL) for three times. The organic phase was combined and the solvent was removed under vacuum and the crude product was purified by column chromatography on neutral alumina to get the corresponding quinoline products.

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