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Efficient approach to allylated quinolines via palladium-catalyzed cyclization–allylation of 1-azido-2-(2-propynyl) benzenes with allyl methyl carbonate

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ABSTRACT

The palladium-catalyzed cyclization–allylation reaction of *ortho*-azido propynylbenzenes **1** and allyl methyl carbonate **2d** gives the corresponding allylated quinolines in moderate to good yields. The reaction of 1-azido-2-(2-propynyl)benzene **1a** proceeds smoothly with 10 mol % $Pd(PPh_3)_4$ and 5 equiv K_3PO_4 or NaOAc in DMF at 100 °C to afford 3,4-diallylquinoline **3a** in 69% yield in the case of $R^2 = H$ and 3-allylquinoline **4** in 67% yield in the case of $R^2 \neq H$.

Introduction

Quinoline skeletons are a major class of compounds which occur in many natural products and pharmaceuticals. Substituted quinolines are often used for structural frameworks of many synthetic compounds with bioactive properties such as antimalarial, antibacterial, antihypertensive, antiasthmatic, and anti-inflammatory agents.[1–3] Furthermore, substituted quinolines can be used as organocatalysts and as meaningful tools for the syntheses of chiral molecules with high enantioselectivity.[4] In particular, allyl-substituted quinolines are of special interest because the allyl group sometimes plays an important role in the compound's bioactivity.[5] Besides that, the presence of the allyl group makes further cyclization feasible.[6]

Due to their importance, much attention has been paid to the preparation and functionalization of allyl-substituted quinolines. A number of regioselective synthetic methods for allyl-substituted quinolines have been reported, like 2-allylquinolines,[7] and 3-allylquinolines.[8] A frequently used method for the synthesis of allyl-substituted quinolines is the metal-catalyzed coupling between halogen-containing quinolines and allylic substrates.[7,8] However, the use of complex catalysts, prolonged reaction times, and/or use of strong acids and bases are needed in the coupling procedure. Therefore, the development of an efficient and environmentally benign protocol for the synthesis of allyl-substituted quinolines is still desirable. Previously, we reported metal-catalyzed or non-metal-catalyzed synthesis of substituted dihydroisoquinolines, and iodine-mediated or gold-catalyzed synthesis of substituted isoquinolines.[9] Also we reported the synthesis of substituted quinolines via electrophilic cyclization of 1-azido-2-(2-propynyl) benzenes in the presence of electrophilic reagents or electrophilic catalysts.[10] It occurred to us that the transition-metal catalyzed-reaction of 1-azido-2-(2-propynyl) benzenes and allyl compounds might produce allyl-substituted quinolines.

Herein, we report a novel method for the one-step synthesis of allylated products selectively via palladium-catalyzed cyclization–allylation reaction of 1-azido-2-(2-propynyl) benzenes **1** with allyl methyl carbonate **2d**. The reaction proceeded smoothly to afford 3,4-diallylquinolines 3 in the case of $R^2 = H$ and 3-allylquinolines **4** in the case of $R^2 \neq H$ in moderate to good yields with no by-products (Scheme 1). To the best of our knowledge, it is the first time for the synthesis of 3,4-diallylquinolines and 3-allylquinolines to date. Furthermore, this palladium-catalyzed reaction is mechanistically interesting, compared to the Au^+-catalyzed and I^+-mediated reactions, as mentioned later.

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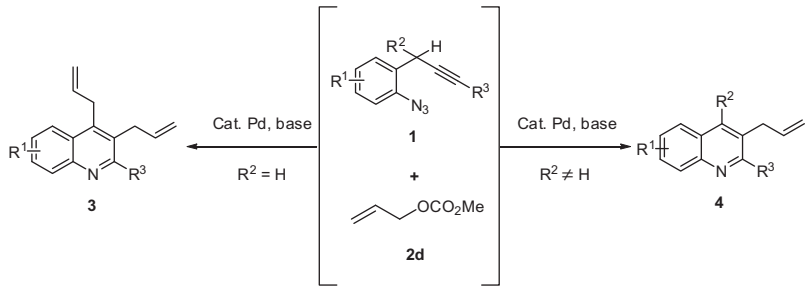


Scheme 1. Pd-catalyzed synthesis of 3,4-diallylquinolines and 3-allylquinolines.

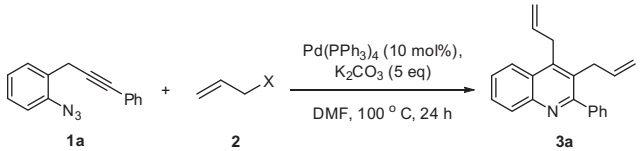
Results and discussion

Initially, we selected 1-azido-2-(3-phenylprop-2-ynyl) benzene **1a** as a model substrate. The results are summarized in Table 1. When allyl acetate **2a** was used, the reaction proceeded smoothly and gave the desired 3,4-diallylquinoline **3a** in 39% isolated yield (entry 1). Allyl chloride **2b** produced the desired product **3a** in low yield (entry 2). No desired product was obtained with allyl tributyltin **2c** (entry 3). The best result was obtained with allyl methyl carbonate **2d**, giving the product **3a** in 47% isolated yield together with unidentified products (entry 4). Also, the use of **2a** together with **2d** produced **3a** in lower yield (entry 5). Thus, allyl methyl carbonate was utilized as an allyl source for further optimization of reaction conditions.

Our research was focused on the optimization of palladium catalysts, solvents, bases, and temperatures, and the results are summarized in Table 2. No desired product **3a** was obtained in the absence of palladium catalyst (entry 1). A low yield (26%) was obtained when the reaction was carried out in the presence of $Pd(PPh_3)_4$ but in the absence of base (entry 5), indicating the importance of the combined use of both palladium catalyst and base. Next we tested two palladium catalysts, $Pd_2(dba)_3{\cdot}CHCl_3$ and $Pd(PPh_3)_4$ (entries 2–4 and 6), the latter gave much better result. The use of ligands, XantPhos, and S-Phos, gave 8% and 35% yields in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$, respectively (entries 3 and 4). Among the various bases we investigated (entries 6–13), the use of K_3PO_4 and NaOAc afforded **3a** in high yields (entries 10 and 11). The screening of various solvents, such as 1,4-dioxane, AcOEt, benzene, CH_3CN, $CH_3CN + H_2O$, THF, DMF, revealed that the choice of solvents played an important role for the formation of **3a** (entries 11, 14–19). DMF was found to be the most suitable solvent, and the product **3a** was obtained in 69% isolated yield (entry 11). The decrease in reaction temperature to 80 °C gave the product **3a** in 60% isolated yield (entry 20). Decreasing the amounts of base and catalyst resulted in lower yields (entries 21 and 22).

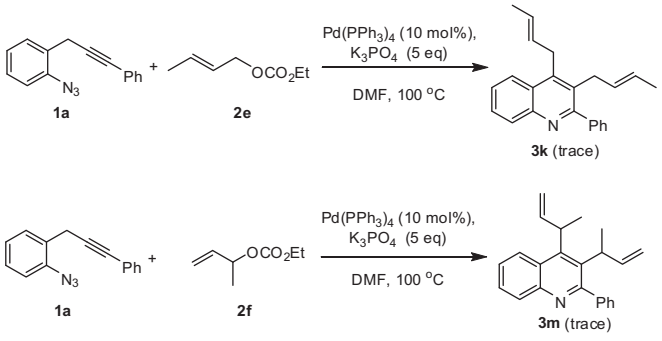
With optimized conditions in hand, we carried out the reactions between various 1-azido-2-(2-propynyl) benzenes **1** and allyl methyl carbonate **2d**, and the results are summarized in Table 3. The substrate **1b**, having a methyl at the *para*-position of the aromatic ring, afforded the corresponding cyclized product **3b** in 66% isolate yield through method A (entry 1). The substrate **1c**, bearing fluorine atoms at 3,5-positions on the aromatic ring, afforded the desired product **3c** in 55% yield (entry 2). Furthermore, the substrates **1d**, having a cyclohexyl group at the alkyne terminus, gave the expected products **3d** in moderate yields via the methods A and B (entries 3 and 4, respectively); here, a mixture of unidentified by-products was formed, but they were easily separated from the desired quinoline by column chromatography. It is noteworthy that the method B gave a little higher yield than the method A, although it took a longer reaction time. The substrates **1e** and **1f**, having a methyl at the *meta*-position and a chloro group at *para*-position of the aromatic ring, afforded products **3e** and **3f** in 60% and 64% isolate yield through method A (entries 5 and 6). The substrates **1g**, **1h** and **1i**, in which the aromatic ring was substituted with bromo and chloro groups, afforded the corresponding products **3g**, **3h** and **3i** in moderate yields, respectively (entries 7–9, 10). The substrate **1j** afforded the desired product **3j** in 45% yield with method A and 58% yield with method B (entries 11 and 12). Other substituted allyl carbonates such as crotyl ethyl carbonate **2e** and ethyl 2-methylallyl carbonate **2f**, instead of allyl methyl carbonate **2d**, were also investigated and gave only trace amounts of the products, 2-phenylquinoline as main product[10] was formed (yield 60% for **2e**, 67% for **2f**).

Table 1
Optimization of the allyl sources[a]



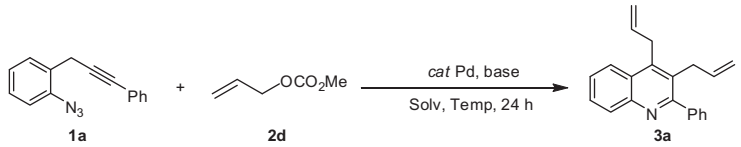
Entry	Allyl sources	**3a**, Yield[b] (%)
1	OAc	44 (39)[c]
2	Cl	23
3	$SnBu_3$	0
4	OCO_2Me	52 (47)[c]
5	**2a** + **2d**	21[d]

[a] All the reactions were carried out using 0.05 mmol of **1a** and 5 equiv of **2** in the presence of $Pd(PPh_3)_4$ (10 mol %), and K_2CO_3 (5 equiv), in 1 mL DMF at 100 °C for 24 h.
[b] ^1H NMR yield was determined by using *p*-xylene as an internal standard.
[c] Isolated yield is shown in parentheses.
[d] 2.5 equiv **2a** and 2.5 equiv **2d** were used respectively.



It is noteworthy that the reaction of **1n**, having the OAc group at R^2 (at the benzylic position), proceeded smoothly and gave the 3-allylquinoline **4** in 67% isolated yield (Scheme 2). On the basis of the results above, it is clearly indicated that R^2 group plays a key role in the selective synthesis of allylated quinolines.

Table 2
Optimization of the reaction conditions[a]

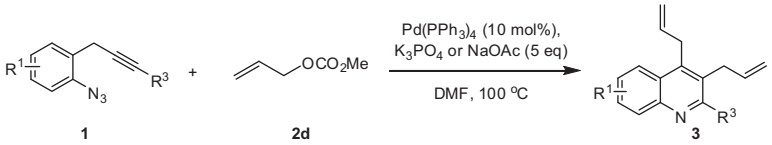


1a **2d** **3a**

Entry	*cat* Pd	Bases	Solvent	Yield[b] (%)	SM recov.[b] (%)
1	—	K_3CO_3	DMF	0	0
2	$Pd_2(dba)_3{\cdot}CHCl_3$[c]	K_3CO_3	DMF	4	0
3	$Pd_2(dba)_3{\cdot}CHCl_3$[c,d]	K_3CO_3	DMF	8	0
4	$Pd_2(dba)_3{\cdot}CHCl_3$[c,e]	K_3CO_3	DMF	35	0
5	$Pd(PPh_3)_4$	—	DMF	26	0
6	$Pd(PPh_3)_4$	K_2CO_3	DMF	(47)[f]	0
7	$Pd(PPh_3)_4$	Na_2CO_3	DMF	42	0
8	$Pd(PPh_3)_4$	$NaHCO_3$	DMF	46	0
9	$Pd(PPh_3)_4$	NaOH	DMF	56	0
10	$Pd(PPh_3)_4$	NaOAc	DMF	66	0
11	$Pd(PPh_3)_4$	K_3PO_4	DMF	75 (69)[f]	0
12	$Pd(PPh_3)_4$	KH_2PO_4	DMF	37	0
13	$Pd(PPh_3)_4$	Et_3N	DMF	48	0
14	$Pd(PPh_3)_4$	K_3PO_4	1,4-Dioxane	27	5
15	$Pd(PPh_3)_4$	K_3PO_4	AcOEt	29	8
16	$Pd(PPh_3)_4$	K_3PO_4	Benzene	26	11
17	$Pd(PPh_3)_4$	K_3PO_4	CH_3CN	66	0
18	$Pd(PPh_3)_4$	K_3PO_4	CH_3CN+H_2O	15	0
19	$Pd(PPh_3)_4$	K_3PO_4	THF	30	8
20	$Pd(PPh_3)_4$[g]	K_3PO_4	DMF	69 (60)[f]	0
21	$Pd(PPh_3)_4$[h]	K_3PO_4	DMF	63	0
22	$Pd(PPh_3)_4$[i]	K_3PO_4	DMF	65 (59)[f]	0

[a] The reactions were performed with **1a** (0.05 mmol) and **2d** (5 equiv) in the presence of Pd catalyst (10 mol %) and base (5 equiv) in 1 mL DMF at 100 °C for 24 h under a argon atmosphere.
[b] ^1H NMR yield was determined by using *p*-xylene as an internal standard.
[c] 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ was used.
[d] 5 mol % XantPhos was used.
[e] 10 mol % S-Phos was used.
[f] Isolated yield is shown in parentheses.
[g] The reaction temperature was 80 °C.
[h] 5 mol % $Pd(PPh_3)_4$ was used.
[i] 3 equiv K_3PO_4 was used.

Table 3
Sythesis of 3,4-diallylquinolines with various substrates[a]



1 **2d** **3**

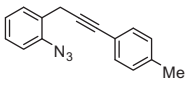
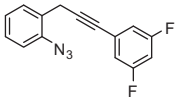
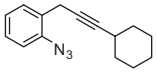
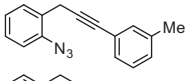
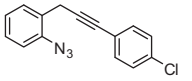
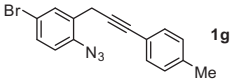
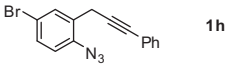
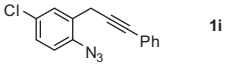
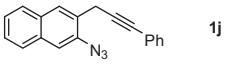
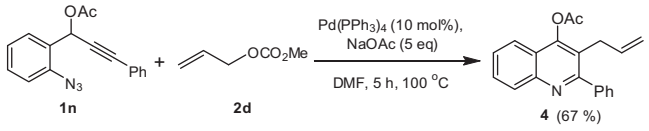
Entry	Substrate (**1**)	Method	Time (h)	Product (**3**)	Yield[b] (%)
1	 **1b**	A	4	**3b**	66
2	 **1c**	A	3	**3c**	55
3	 **1d**	A	5	**3d**	26
4		B	24		38
5	 **1e**	A	5	**3e**	60
6	 **1f**	A	5	**3f**	64

Table 3 (*continued*)

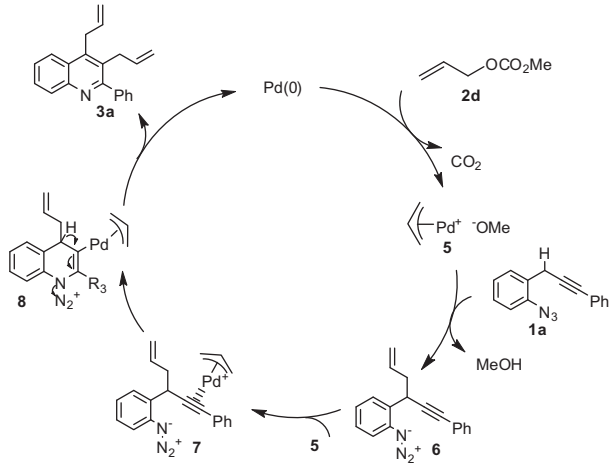
Entry	Substrate (**1**)	Method	Time (h)	Product (**3**)	Yield[b] (%)
7	 **1g**	A	5	**3g**	42
8	 **1h**	A	1	**3h**	36
9		B	2		45
10	 **1i**	A	5	**3i**	33
11	 **1j**	A	3	**3j**	45
12		B	5		58

[a] All the reactions were carried out using 0.05 mmol of **1** and 5 equiv of **2** in the presence of $Pd(PPh_3)_4$ (10 mol %) under argon atmosphere in 1 mL DMF at 100 °C; method A, K_3PO_4 (5 equiv); method B, NaOAc (5 equiv).
[b] Isolated yield.

A proposed mechanism for the formation of 3,4-diallylquinoline **3a** via palladium-catalyzed cyclization–allylation of 1-azido-2-(2-propynyl) benzene with allyl methyl carbonate is illustrated in Scheme 3. Initially, Pd(0) reacts with allyl methyl carbonate **2d** to form the π-allyl palladium species **5**[11,12] with concomitant evolution of CO_2. Deprotonation of propargylic proton of **1a** takes place with methoxide formed. Then nucleophilic attack of propargylic anion to allylpalladium cation results in propargylic allylation **6** and regeneration of Pd(0). Next, oxidative addition of allyl carbonate **2d** occurs again to form **5**, the intermediate **6** reacts with **5** again to generate intermediate **7** and subsequent nucleophilic attack of a nitrogen atom to the electron-deficient alkyne forms an intermediate **8**. Finally, elimination of N_2 and H^+, together with elimination of Pd(0), produces 3,4-diallylquinoline **3a**. It is noteworthy that, for the azide–alkyne cyclization, Pd(II) acts similarly as I^+ reagent, Bronsted acid and Au catalyst. Perhaps, the most important point of the present Pd methodology, compared to the previous Au^+ and I^+ methods,[13] is that the Pd-catalyzed azide–alkyne cyclization is able to incorporate another organic ligand of Pd (see **6**), which is allyl in present, into quinoline framework.



Scheme 2. Sythesis of 3-allylquinolines.



Scheme 3. A proposed mechanism for the formation of **3a**.

Conclusions

In conclusion, we have developed an effective strategy for the regioselective synthesis of allylated quinolines via the palladium-catalyzed cyclization–allylation reaction of 1-azido-2-(2-propynyl) benzene and allyl methyl carbonate. R^2 group (at the propargylic position) plays a key role for the transformation. This reaction provides a useful method for the synthesis of allylated quinolines with a wide variety of substrates. Further works to expand the scope and synthetic utility of this methodology to the synthesis of biologically important natural and unnatural compounds are in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.068.

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