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One-Pot Synthesis of Highly Substituted Aromatic Amine Derivatives via Pd-Catalyzed Aminobenzannulation Reaction

Fa-Rong Gou,[†] Peng-Fei Huo,[†] Hai-Peng Bi,[†] Zheng-Hui Guan,[†] and Yong-Min Liang*[,†,‡]

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China, and State Key Laboratory of Solid Lubrication, Lanzhou Institute of Chemical Physics, Chinese Academy of Science, Lanzhou 730000, People's Republic of China

liangym@lzu.edu.cn

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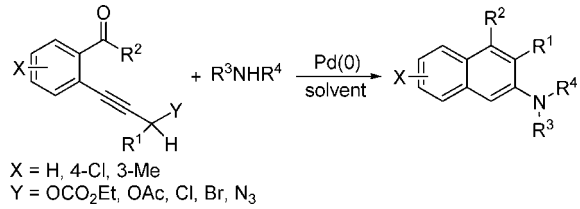
ABSTRACT



A novel and convenient Pd(0)-catalyzed carboannulation with propargylic compounds for the synthesis of highly substituted aromatic amine derivatives in a one-pot operation was developed. In this process, a significant breakthrough in aminobenzannulation is observed. Moreover, the reaction appears to be very general and suitable for a variety of amines.

Transition metal-catalyzed annulation reactions represent an effective and straightforward methodology for the synthesis of cyclic and polycyclic structures, which has attracted much attention during the past years.[1] However, a drawback of this methodology is that it is difficult to control the regio- and chemoselectivity. Thus, the regio- and chemoselective construction of cyclic compounds remains a challenging problem in synthetic organic chemistry.

The synthetic potential of *o*-alkynyl(oxo)benzenes has attracted great attention of organic chemists.[2] Recently, Tsukamoto and co-workers reported a series of Pd-catalyzed annulations of alkynes with unsaturated carbon−heteroatom bonds.[3] Herndon et al. reported a palladium-catalyzed synthetic route to aminonaphthalenes using the coupling of *o*-bromoacetophenone with monoalkyl acetylenes.[4] The excellent reactivity of *o*-alkynyl(oxo)benzenes led us to focus on the development of a new type of cyclization. As a continuation of our research on the carboannulation reaction with propargylic compounds,[5] we envisioned that the sub-

[†] Lanzhou University.
[‡] Chinese Academy of Science.

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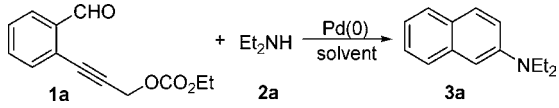
strate ethyl 3-(2-formylphenyl)prop-2-ynyl carbonate **1a** might act similarly to these *o*-alkynyl(oxo)benzenes to afford indene or naphthalene derivatives.[3b,4,6−8]

Our preliminary study of the cyclization of **1a** at 60 °C in MeOH in the presence of a catalytic amount of $Pd(PPh_3)_4$ was unsuccessful. Further attempts, including increasing temperature and using other solvents, exhibit no effect. We then turned our attention to the introduction of amine functionality. Instead of affording the preconceived products under the above-mentioned condition in the presence of Et_2NH, an unexpected and interesting product β-naphthylamine **3a** was formed in 52% isolated yield (Table 1, entry 1). The reaction should not proceed through iminium formation but through high regio- and chemoselective intramolecular nucleophilic attack, since formation of neither indenamine or α-naphthylamine was observed.[3b,4,7,8]

Table 1. Optimization of the Pd-Catalyzed Cyclization of 1.0 equiv of Propargylic Carbonate **1a** with 1.5 equiv of Amine **2a**[a]

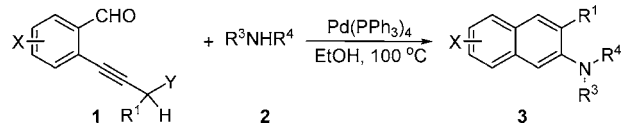


entry	catalyst	solvent	temp (°C)	time (h)	yield (%)[b]
1	$Pd(PPh_3)_4$	MeOH	60	2	52
2	$Pd(PPh_3)_4$	MeCN	60	2	45
3	$Pd(PPh_3)_4$	EtOH	60	2	61
4	$Pd(PPh_3)_4$	THF	60	2	n.r.[c]
5	$Pd(PPh_3)_4$	DMF	60	2	22
6	$Pd_2(dba)_3$	EtOH	60	6	trace
7	$Pd_2(dba)_3$/dppf	EtOH	60	4	18
8	$Pd(OAc)_2/PPh_3$	EtOH	60	2	55
9	$Pd(OAc)_2$/dppe	EtOH	60	4	32
10	$Pd(PPh_3)_4$	EtOH	40	5	47
11	$Pd(PPh_3)_4$	EtOH	80	1	68
12	$Pd(PPh_3)_4$	EtOH	100	0.5	73

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of solvent under argon with 1.0 equiv of **1a**, 1.5 equiv of **2a**, and 0.05 equiv of [Pd]. [b] Isolated yields. [c] n.r. = no reaction.

To the best of our knowledge, few reports are known concerning the direct formation of highly substituted naphthylamine derivatives via a net Pd-catalyzed aminobenzannulation. This result encouraged us to extend our protocol to investigate this novel cyclization. Consequently, we investigated this reaction under various conditions. When $Pd(PPh_3)_4$ was used as the catalyst, the reaction proceeded smoothly in MeCN and EtOH (Table 1, entries 2 and 3). Compared with other solvents such as THF and DMF, EtOH gave the best yield (entries 4 and 5). During a survey of the effect of different catalysts, it was determined that $Pd(PPh_3)_4$ was a superior catalyst than others (entries 6−9). And significant improvement was achieved by conducting the reaction at 100 °C. This means a higher temperature was beneficial for both the rate and the yield of the reaction

Table 2. Pd-Catalyzed Cyclization of 1.0 Equiv of Propargylic Compounds **1** with 1.5 Equiv of Amines **2**[a]



entry	1	2	time (h)	3	yield (%)[b]
1	R^1 = H, Y = OCO_2Et (**1a**)	**2a** (Et_2NH)	0.5	**3a**	73
2	R^1 = H, Y = OAc (**1b**)	**2a**	1	**3a**	65
3	R^1 = H, Y = Cl (**1c**)	**2a**	1	**3a**	66
4	R^1 = H, Y = Br (**1d**)	**2a**	0.5	**3a**	70
5	R^1 = H, Y = N_3 (**1e**)	**2a**	0.5	**3a**	62
6	R^1 = Me, Y = OCO_2Et (**1f**)	**2a**	1	**3b**	44
7	R^1 = Ph, Y = OCO_2Et (**1g**)	**2a**	1	**3c**	58
8	R^1 = 1-naphthyl, Y = OCO_2Et (**1h**)	**2a**	2	**3d**	55
9	R^1 = 2,4-diClC_6H_3, Y = OCO_2Et (**1i**)	**2a**	2	**3e**	64
10	R^1 = 3,4,5-tri$MeOC_6H_2$, Y = OCO_2Et (**1j**)	**2a**	2	-	-[c]
11	X = 4-Cl, R^1 = H, Y = OCO_2Et (**1k**)	**2a**	1	**3f**	68
12	X = 3-Me, R^1 = H, Y = OCO_2Et (**1l**)	**2a**	1	**3g**	63
13	**1a**	**2b** (pyrrolidine)	1	**3h**	50
14	**1a**	**2c** ()	1	**3i**	36
15	**1a**	**2d** (i-Pr_2NH)	6	-	n.r.[d]
16	**1a**	**2e** (PhNHMe)	6	-	n.r.[d]

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of solvent at 100 °C under argon with 1.0 equiv of **1**, 1.5 equiv of **2**, and 0.05 equiv of [Pd]. [b] Isolated yields. [c] Decomposed. [d] n.r. = no reaction.

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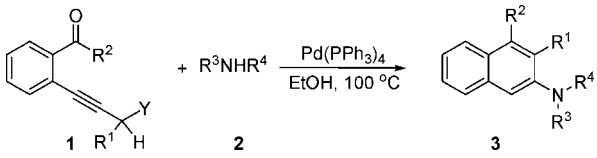
Table 3. Pd-Catalyzed Cyclization of 1.0 equiv of Propargylic Compounds **1** with 1.5 equiv of Amines **2**[a]



entry	1	2	time (h)	3	yield (%)[b]
1	R^1 = H, R^2 = Me, Y = OCO_2Et (**1m**)	**2a**	1	**3j**	82
2	R^1 = H, R^2 = Me, Y = OAc (**1n**)	**2a**	2	**3j**	70
3	R^1 = H, R^2 = *n*-Pr, Y = OCO_2Et (**1o**)	**2a**	2	**3k**	75
4	R^1 = H, R^2 = *n*-Pent, Y = OCO_2Et (**1p**)	**2a**	2	**3l**	65
5	R^1 = H, R^2 = Ph, Y = OCO_2Et (**1q**)	**2a**	2	**3m**	60
6	R^1 = H, R^2 =  , Y = OCO_2Et (**1r**)	**2a**	2	**3n**	57
7	R^1 = Ph, R^2 = Me, Y = OCO_2Et (**1s**)	**2a**	2	**3o**	68
8	**1m**	**2b**	1	**3p**	75
9	**1m**	**2f** (piperidine)	2	**3q**	63
10	**1m**	**2g** (morpholine)	2	**3r**	77
11	**1m**	**2h** ()	3	**3s**	45
12	**1m**	**2i** (*n*-Pr_2NH)	2	**3t**	76
13	**1m**	**2j** (*n*-Bu_2NH)	3	**3u**	68
14	**1m**	**2k** (*i*-Bu_2NH)	3	**3v**	52
15	**1m**	**2l** (dioctylamine)	3	**3w**	71
16	**1m**	**2m** (Me_2NH, 33% aq)	1	**3x**	48
17	**1m**	**2n** (Me_2NH·HCl)	6	**3x**	35
18	**1m**	**2o** (BnNHMe)	3	**3y**	59

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of solvent at 100 °C under argon with 1.0 equiv of **1**, 1.5 equiv of **2**, and 0.05 equiv of [Pd]. [b] Isolated yields.

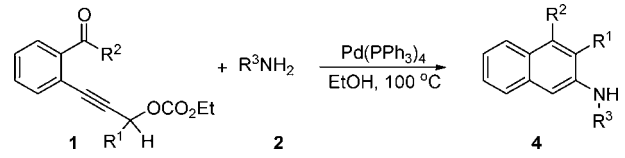
(entries 10−12). Herein, the optimum reaction conditions thus far developed employ 1.0 equiv of **1a**, 1.5 equiv of amine, and 5 mol % of $Pd(PPh_3)_4$ in EtOH at 100 °C under argon.

Next, the substrate scope of propargylic compound **1** was surveyed under the optimized reaction conditions. Generally, the reaction of primary propargylic compounds proceeded smoothly and led to the desired product **3a** in moderate to good yields (Table 2, entries 2−5). Various substituents at the propargylic position, such as methyl, phenyl, naphthyl, and electron-withdrawing aromatic, were well tolerated (entries 6−9). However, aryl-substituted electron-rich substrate decomposed quickly (entry 10). Furthermore, substituents on the benzene ring did not affect the reaction, and good results were always obtained (entries 11 and 12). And we tested the reactions with various amines. Among these, cyclic secondary aliphatic amines **2b** and **2c** both led to comparable yields of the products (entries 13 and 14). No reaction was observed when the reaction was carried out by using amines **2d** and **2e**. This might due to the nature of their poor nucleophilicity (entries 15 and 16).

This methodology is also applicable to phenylketones. The reaction of propargylic carbonate **1m** with Et_2NH afforded naphthylamine **3j** in 82% yield (Table 3, entry 1). In the case of propargyl acetate **1n**, the product **3j** was also obtained (entry 2). Various substituents of ketone carbonyl, such as an alkyl or aryl group, were well tolerated (entries 3−6). Secondary carbonates possessing phenyl substituted at the propargylic position also worked well, affording the corresponding product in moderate yield (entry 7). And the reactivities of secondary amines were investigated. Both cyclic and acyclic secondary aliphatic amines, even dimethylamine in aqueous solution **2m** or dimethylamine hydrochloride **2n**, are also applicable in this process and provided naphthylamines **3p**−**x** in moderate yields (entries 8−17). With the purpose of getting an asymmetric tertiary amine, amine **2o** was tested. Rewardingly, the reaction furnished the desired product **3y** in 59% yield (entry 18). It is worth noting that tertiary amine **3y** might be engaged in post-transformation for constructing secondary amine by the removal of the benzyl group.

We were very pleased to find that primary amine **2p** could efficiently react with propargylic carbonate **1m** and furnish secondary naphthylamine **4a** in 77% yield exclusively (Table 4, entry 1). This was somewhat of a surprise, because the

Table 4. Pd-Catalyzed Cyclization of 1.0 equiv of Propargylic Compounds **1** with 1.5 equiv of Amines **2**[a]



entry	1	2	time (h)	4	yield (%)[b]
1	**1m**	**2p** (*t*-$BuNH_2$)	2	**4a**	77
2	**1m**	**2q** (*s*-$BuNH_2$)	2	**4b**	68
3	**1m**	**2r** (cyclohexanamine)	2	**4c**	72
4	**1m**	**2s** (1-phenylethanamine)	3	**4d**	56
5	R^1 = H, R^2 = Et (**1t**)	**2p**	2	**4e**	75
6	R^1 = H, R^2 = *n*-Pr (**1o**)	**2p**	2	**4f**	71
7	R^1 = H, R^2 = *n*-Bu (**1u**)	**2p**	2	**4g**	66
8	R^1 = H, R^2 = *n*-Pent (**1p**)	**2p**	3	**4h**	60

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of solvent at 100 °C under argon with 1.0 equiv of **1**, 1.5 equiv of **2**, and 0.05 equiv of [Pd]. [b] Isolated yields.

reaction of propargylic carbonate **1a** with various primary amines did not provide any cyclized product. Next, a series

of primary amines were investigated, the most active amines being shown in Table 4. Likewise, all of them resulted in good yields of desired products (entries 2−4). The cyclization reaction was sightly affected by the tether length of the substituent of ketone carbonyl, and always led to moderate yields of the desired products (entries 5−8).

Although the NMR spectroscopic data support the formation of naphthylamines **3**, the structure was unambiguously confirmed through an X-ray crystal structure analysis of compound **3n** (Figure 1).[9]

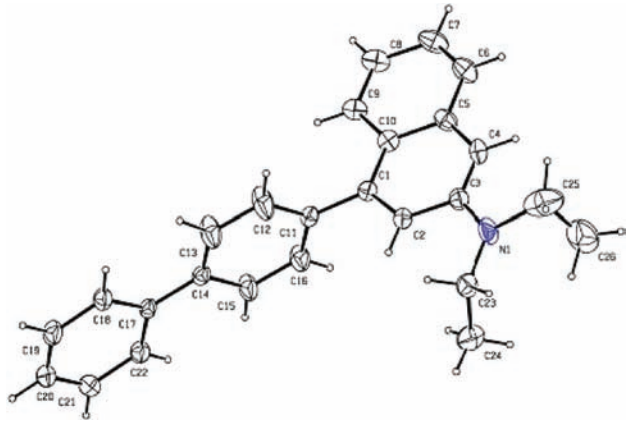
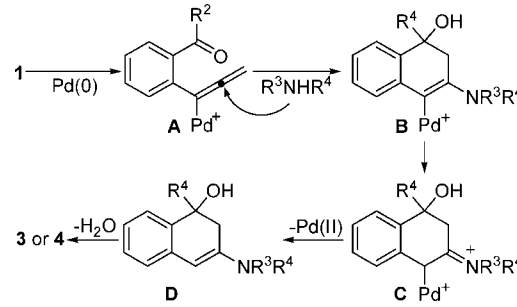


Figure 1. Structure of **3n**.

On the basis of our knowledge and combined with the above observations,[10−14] a plausible mechanism is proposed in Scheme 1. It involves the following key steps: (a) transformation of propargylic compound **1** by Pd(0) catalyst

Scheme 1



generates allenylpalladium intermediate **A**; (b) nucleophile attacks the center sp-carbon of **A** followed by 6-endo cyclization, using the carbonyl group, to form alkenylpalladium(II) intermediate **B**; (c) intramolecular delivery and the iminium formation affords intermediate **C**; and (d) elimination of palladium(II) gives the desired products **3** or **4** after dehydration of **D**.

In conclusion, we have developed a novel and convenient Pd(0)-catalyzed aminobenzannulation with propargylic compounds for the synthesis of highly substituted aromatic amine derivatives. A variety of primary, secondary, and tertiary amines are applicable in this process, affording various products in moderate to good yields. In particular, a carbon−nitrogen and a carbon−carbon bond are sequentially formed in a single operative step. Moreover, the high regio- and chemoselectivity makes this unprecedented transformation attractive in organic synthesis. The study of details of the reaction mechanism is in progress.

Acknowledgment. We thank the NSF (NSF-20621091, NSF-20672049) for financial support.

Supporting Information Available: Typical experimental procedure, characterization data for all products, and X-ray data for **3n**, in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Crystal data for **3n** are listed in the Supporting Information.

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