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Pd(0)-Catalyzed [1,5]-Sigmatropic Hydrogen Shift of Propargylic Esters toward Substituent Naphthylamines

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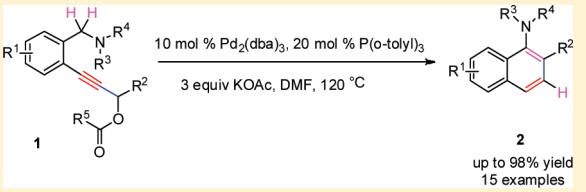
Supporting Information

ABSTRACT: A novel and convenient carboannulation method for the synthesis of highly substituted naphthylamine derivatives has been developed though a Pd(0)-catalyzed [1,5]-sigmatropic hydrogen shift and cyclization reaction of propargyl esters.



The development of catalytic reactions which involve the cleavage of C−H bonds is one of the most challenging projects in organic synthesis.[1] Despite significant progress in this area, catalytic transformations of sp^3 C−H bonds to C−C bonds still remain rare.[2] Among powerful methods for this purpose, the tandem [1,5]-hydride transfer/cyclization reaction is an attractive strategy. The most typical examples of this internal redox process involve the coupling of sp^3 C−H bonds with double bonds (Scheme 1a).[3] In this process, activation of an electron-deficient alkene by a Lewis acid triggers a 1,5-hydride transfer and the formation of carbocation, which induces the cyclization of the C−C bond. More recently, the strategy has been extended to the coupling of sp^3 C−H with triple bonds (Scheme 1b,c).[4] However, except for limited examples when a terminal alkyne group was used to form a metal allene intermediate to induce a 1,5-hydride transfer (Scheme 1c),[4d−4f] a strong electron-withdrawing group on the terminal position of the double or triple bond was needed in almost all cases. This strongly restricts its application, although the process has been applied in some cases, such as the synthesis of (−)-PNU-286607.[5]

Very recently, we have extended the cascade [1,5]-hydride transfer/cyclization reaction to propargylic ester via platinum catalysis.[6] The key steps involve a [1,5]-hydride transfer to allene intermediate, which is formed by platinum-catalyzed 1,3-OAc migration of the propargylic ester (Scheme 2a). However, the reaction is limited in naphthalenyl acetate synthesis. Previously introduced heteroatom groups are lost in most cases. On the basis of our works on palladium-catalyzed transformation of propargylic ester,[7] we envisioned that the allene palladium intermediate might also induce the [1,5]-hydride transfer in suitable systems (Scheme 2b). Furthermore, because of the high tendency for the C−Pd bond to participate in insertion and β-elimination processes,[8] the reaction might afford products different from that obtained by using a platinum catalyst. Herein, we reported our new results in the study of the cascade [1,5]-hydride transfer/cyclization reaction involving the propargylic ester group via palladium catalysis.

Initial studies showed that substrates with the benzyl position substituted by a nitrogen atom worked in palladium catalysis. When we treated propargylic ester **1a** (0.1 mmol), K_2CO_3 (0.2 mmol), $Pd_2(dba)_3$ (10 mmol %), and PPh_3 (20 mmol %) in DMF (1 mL) under argon atmosphere at 100 °C, naphthylamine product **2a**[9] was isolated in 30% yield after 4 h (Table 1, entry 1). Further investigation revealed that the reaction will benefit from the addition of a weakly inorganic base such as KOAc, the increase of base loading, and the higher reaction temperature (Table 1, entries 2−9). Except for DMF, neither polar nor nonpolar solvents gave acceptable results (Table 1, entries 10−13). The effect of ligand should be noted. When monodentate phosphine ligands such as P(*o*-tolyl)$_3$ or P(2-furyl)$_3$ were used, an almost quantitative yield of desired product was obtained, whereas bidentate phosphine ligands, like dppe and dppp, failed to improve the yield of product **2a** (Table 1, entries 14, 15 vs 16, 17). Compared with $Pd_2(dba)_3$, other precatalysts were less effective (Table 1, entries 18−20). Thus, the use of 10 mol % of $Pd_2(dba)_3$, 20 mol % of P(*o*-tolyl)$_3$, and 3 equiv of KOAc in DMF at 120 °C were found to be the most efficient and were used as the standard.

Under the optimized reaction conditions, the scope of this reaction was then examined. The results are summarized in Table 2. Apart from the phenyl group, various aryl substituents were tolerated at the propargylic position (Table 2, entries 1−8). Propargylic esters with electron-rich aryl groups always gave better yields than the ones with electron-withdrawing substituents. The electron effect also appeared in methyl-substituted substrates **1e** (para position) and **1f** (ortho position), which afforded the desired products in 71% and 59% yields, respectively (Table 2, entries 5 vs 6). When alkyl substituents were investigated, we failed to obtain any desired product (Table 2, entry 9). Interestingly, when a methyl group was introduced to the benzene ring, an excellent yield of naphthylamine **2j** was

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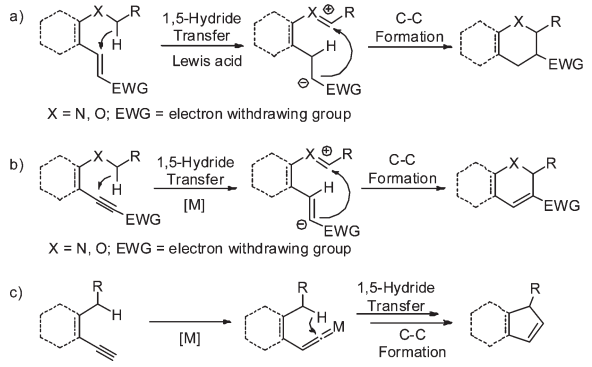
obtained, whereas chloro-substituted substrate only gave 21% yield of product **2k** (Table 2, entries 10 and 11).

Furthermore, to expand the scope of this reaction, we also investigated a range of propargylic esters **1*l*−p** with different R^3 and R^4 groups. It was found that under the optimized conditions, the substrates **1*l*−n** with an electron-withdrawing acyl substituent were transferred into naphthylamines **2*l*−n** in moderate to good yields, as depicted in Table 3. However, the substrate like **1o** with two methyl groups cannot afford the corresponding product, demonstrating the fact that the acyl substituent is required to activate the α C(sp^3)−H bond adjacent to the nitrogen in the [1,5]-hydride transfer/cyclization reaction. When the nitrogen atom was protected by one acyl substituent, like substrate **1p**, the corresponding naphthylamine **2p** was obtained in only 30% yield, compared with 70% yield of **2*l*** synthesized from methyl-substituted amide **1*l***. This might be due to that the amide with low electron density in nitrogen will benefit the 1,5-hydride transfer as shown in Scheme 3.

Additionally, we also investigated a range of propargylic carbonates **1q−t**, as depicted in Table 4. It was found that

Scheme 1. General Groups Used for Tandem [1,5]-Hydride Transfer/Cyclization Reactions



Scheme 2. Propargylic Ester Applied for Tandem [1,5]-Hydride Transfer/Cyclization Reactions

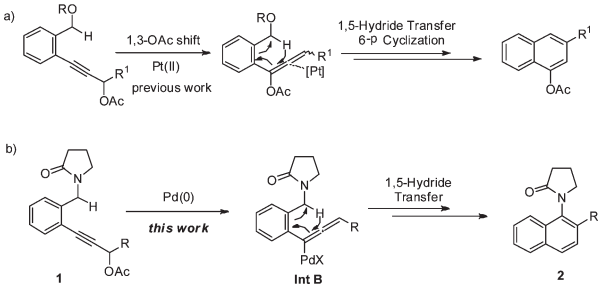
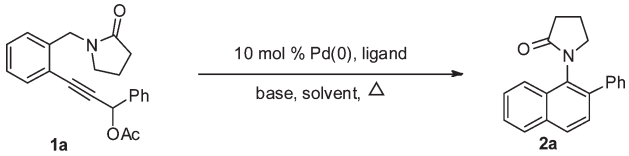


Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	base (equiv)	ligand (mol %)	solvent	T (°C)	yield (%)[b]
1	$Pd_2(dba)_3$	K_2CO_3 (2)	PPh_3 (20)	DMF	100	30
2	$Pd_2(dba)_3$	Cs_2CO_3 (2)	PPh_3 (20)	DMF	100	15
3	$Pd_2(dba)_3$	KOt-Bu (2)	PPh_3 (20)	DMF	100	D[c]
4	$Pd_2(dba)_3$	NaOAc (2)	PPh_3 (20)	DMF	100	26
5	$Pd_2(dba)_3$	Et_3N (2)	PPh_3 (20)	DMF	100	NR[d]
6	$Pd_2(dba)_3$	DMAP (2)	PPh_3 (20)	DMF	100	30.8
7	$Pd_2(dba)_3$	KOAc (2)	PPh_3 (20)	DMF	100	49
8	$Pd_2(dba)_3$	KOAc (3)	PPh_3 (20)	DMF	100	67
9	$Pd_2(dba)_3$	KOAc (3)	PPh_3 (20)	DMF	120	75
10	$Pd_2(dba)_3$	KOAc (3)	PPh_3 (20)	toluene	100	NR[d]
11	$Pd_2(dba)_3$	KOAc (3)	PPh_3 (20)	THF	100	NR[d]
12	$Pd_2(dba)_3$	KOAc (3)	PPh_3 (20)	NMP	100	20
13	$Pd_2(dba)_3$	KOAc (3)	PPh_3 (20)	DMSO	100	40
14	$Pd_2(dba)_3$	KOAc (3)	P(2-furyl)$_3$ (20)	DMF	120	95
15	$Pd_2(dba)_3$	KOAc (3)	P(*o*-tolyl)$_3$(20)	DMF	120	98
16	$Pd_2(dba)_3$	KOAc (3)	dppe (10)	DMF	120	23
17	$Pd_2(dba)_3$	KOAc (3)	dppp (10)	DMF	120	49
18	$Pd(PPh_3)_4$	KOAc (3)	−	DMF	100	20
19	$Pd_2(dba)_3.CH_3Cl$	KOAc (3)	PPh_3 (20)	DMF	100	32
20	$Pd(OAc)_2$	KOAc (3)	PPh_3 (30)	DMF	100	18

[a] Unless otherwise specified, the reaction was carried out by using **1a** (0.20 mmol), Pd catalysts (10 mol %), and bases in solvent (2 mL) under Ar atmosphere for 2 h . [b] Isolated yield. [c] Decomposed. [d] No reaction.

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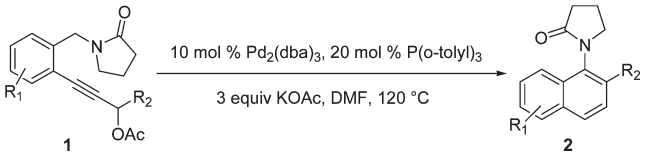
Table 2. Scope Studies of Pd-Catalyzed Synthesis of Naphthylamine 2[a]



entry	substrate,	R^2	yield(%)[b]
1		Ph (**1a**)	**2a** (98%)
2		4-ClC_6H_4 (**1b**)	**2b** (45%)
3		2-ClC_6H_4 (**1c**)	**2c** (42%)
4		3-ClC_6H_4 (**1d**)	**2d** (40%)
5		4-MeC_6H_4 (**1e**)	**2e** (71%)
6		3-MeC_6H_4 (**1f**)	**2f** (59%)
7		3,4-Methylenedioxyphenyl (**1g**)	**2g** (62%)
8		2-OMe (**1h**)	**2h** (27%)
9		n-propyl (**1i**)	NR[c]
10		R^1 = 2-Me (**1j**)	**2j** (90%)
11		R^1 = 5-Cl (**1k**)	**2k** (21%)

[a] Unless otherwise specified, the reaction was carried out by using **1** (0.2 mmol), $Pd_2(dba)_3$ (10 mol %), P(*o*-tolyl)$_3$ (20 mol %), and KOAc (3 equiv) in DMF (2 mL), at 120 °C under argon atmosphere. [b] Isolated yield. [c] No reaction.

under the optimized conditions, only substrate **1q** afforded the naphthylamine **2a** in moderate yield (entry 1). Other propargylic carbonates **1r**−**t** gave only modest results (entries 2−4).

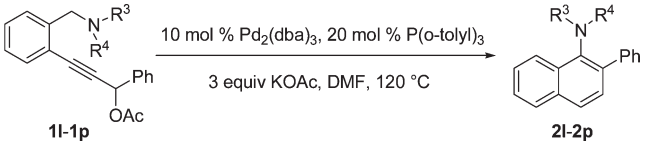
The deuterium-labeling experiments (Scheme 3) showed that the deuterium on the benzyl position transferred into the C5 position of the ester after reaction. This observation is consistent with our proposed mechanism, as depicted in Scheme 3. This plausible mechanism involves the following key steps: (a) Pd(0)-catalyzed transformation of the propargylic compound **D-1u** generates allenylpalladium intermediate **B**. (b) Then the 1,5-D transfer process, which might be promoted by the nitrogen atom, affords the intermediate **C**.[3−6] (c) Finally the direct 6π cyclization of compound **C** leads to the intermediate **E**, which undergoes a 1,3-H shift[10] and a hydrogen elimination affording the final product **D-2u** (path I). Alternatively, the intermediate **G** may also be formed after a 1,3-palladium shift of the intermediate **C**.[11] The insertion of the C−Pd bond, following hydrogen elimination, affords the product **D-2u** (path II).

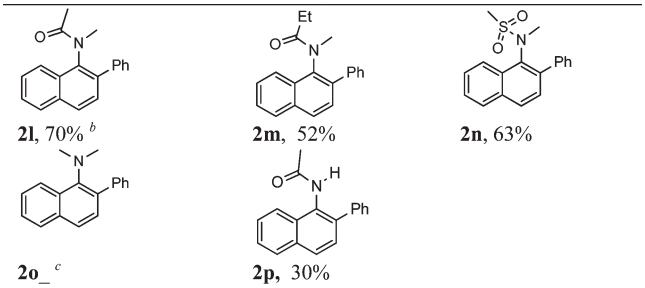
In conclusion, we have developed a novel and convenient carboannulation method for the synthesis of highly substituted naphthylamine derivatives through Pd(0)-catalyzed [1,5]-sigmatropic hydrogen shift of propargyl esters. The study of details of the reaction mechanism is in progress.

EXPERIMENTAL SECTION

General Procedure for the Palladium-Catalyzed 1,5-Hydride Shift and Cyclization Reaction of Propargylic Ester 1a. A mixture of 3-(2-((2-oxopyrrolidin-1-yl)methyl)phenyl)-1-phenylprop-2-ynyl acetate **1a** (69.5 mg, 0.2 mmol), $Pd_2(dba)_3$ (18.3 mg, 10% mmol), KOAc (58.8 mg, 0.6 mmol), P(*o*-tolyl)$_3$ (12.2 mg, 20% mmol), and DMF(2 mL) was placed in a 20 mL tube under argon atmosphere. The resulting mixture was then heated at 120 °C. When the reaction was considered complete as determined by thin-layer chromatography, the reaction mixture was allowed to cool to room temperature and quenched by a saturated aqueous solution of ammonium chloride. After being extracted with ethyl acetate, the combined organic extracts were washed with water and saturated brine and dried over Na_2SO_4. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel, using hexane−ethyl acetate (4:1), to afford **2a** (54.3 mg, 98%) as a solid. Mp 169−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.89 (m, 2 H), 7.78−7.76 (d, J = 8.0 Hz, 1 H), 7.59−7.39 (m, 8 H), 3.52−3.46 (m, 1 H), 3.12−3.05 (m, 1 H), 2.70−2.61 (m, 1 H), 2.50−2.41 (m, 1 H), 2.19−2.04 (m, 1 H), 1.89−1.79 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 139.4, 138.2, 133.9, 132.0, 130.1, 128.7, 128.6, 128.5, 128.4, 128.0, 127.7, 127.4, 126.4, 122.8, 49.9, 31.1, 19.4; IR (neat, cm^{-1}) 3359, 3054, 2923, 2889, 1681, 1410; (ESI)HRMS found m/z 288.1378, calcd for $C_{20}H_{17}NO$ (M + H)$^+$ 288.1383.

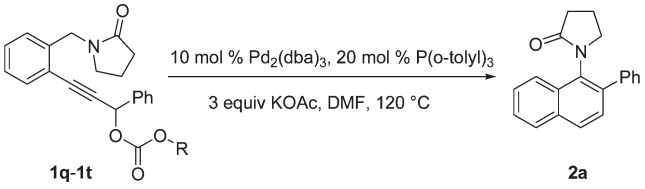
Table 3. Scope Studies of Pd-Catalyzed Synthesis of Naphthylamine 2[a]





[a] Unless otherwise specified, the reaction was carried out by using **1** (0.2 mmol), $Pd_2(dba)_3$ (10 mol %), P(*o*-tolyl)$_3$ (20 mol %), and KOAc (3 equiv) in DMF (2 mL), at 120 °C under argon atmosphere. [b] Isolated yield. [c] Decompose.

Table 4. Study the Scope of Propargylic Carbonate 1q−t[a]



Entry	Substrate,	R	yield(%)[b]
1		R = ^{t}Bu (**1q**)	71
2		R = Me (**1r**)	41
3		R = Et (**1s**)	21
4		R = Bn (**1t**)	19

[a] Unless otherwise specified, the reaction was carried out by using **1** (0.2 mmol), $Pd_2(dba)_3$ (10 mol %), P(*o*-tolyl)$_3$ (20 mol %), and KOAc (**3** equiv) in DMF (2 mL), at 120 °C under argon atmosphere. [b] Isolated yield.

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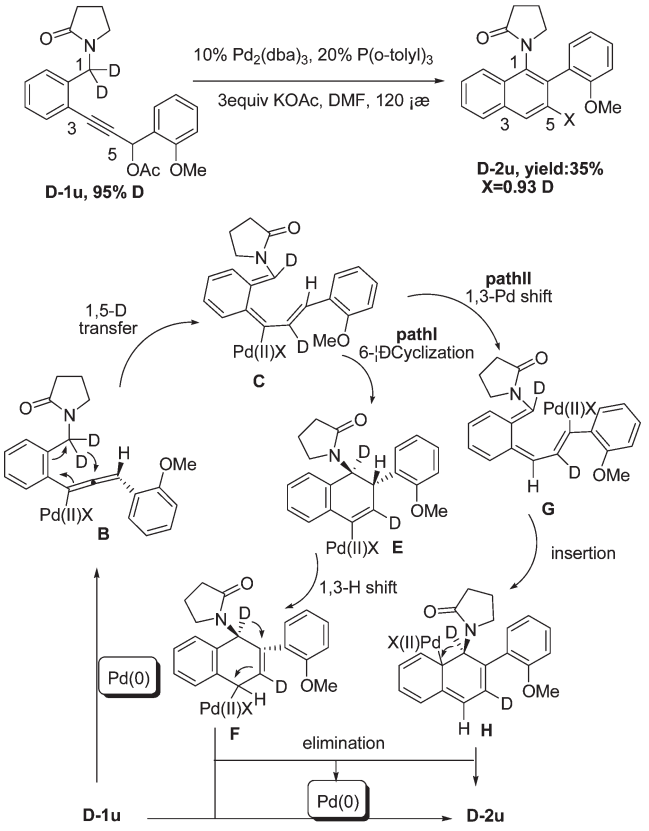
Scheme 3. Deuterium-Labeling Experiments and Proposed Mechanism



■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedure and copies of ^{1}H NMR and ^{13}C NMR spectra of all compounds and X-ray data of **2a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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