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Highly Regioselective Synthesis of Benz[*a*]anthracene Derivatives via a Pd-Catalyzed Tandem C−H Activation/Biscyclization Reaction

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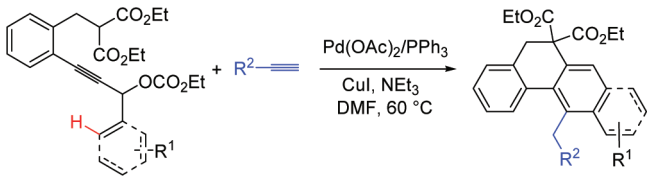
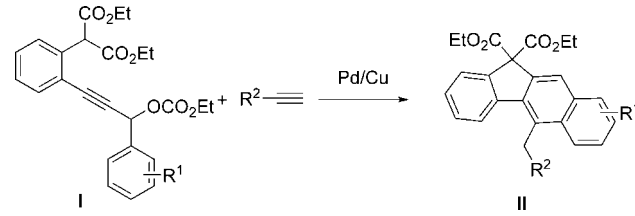


A palladium-catalyzed tandem C−H activation/biscyclization reaction of propargylic carbonates with terminal alkynes was determined, which allowed the tetracyclic benz[*a*]anthracene framework to be constructed with high regioselectivity. A possible mechanism for this tandem C−H activation/biscyclization process was discussed.

Transition metal-catalyzed C−C bond formation via C−H bond activation has been intensively investigated.[1,2] Recently, the palladium-catalyzed tandem cyclization involving C−H bond functionalization has also received considerable attention because of the possibilities to construct complex structural motifs from relatively simple starting materials.[3] However, highly selective intermolecular tandem reactions for the preparation of polycyclic aromatic compounds via C−H bond activation remain challenging.[4−6]

SCHEME 1



The activation of propargylic compounds with palladium catalysts is well established for the construction of carbon−carbon and carbon−heteroatom bonds.[7] Recently, we have reported an efficient tandem cyclization reaction for the synthesis of highly substituted indenes[8] and spirocyclic compounds[9] from propargylic compounds. Furthermore, when the cyclization was performed in the presence of alkynes, the reaction underwent a tandem C−H activation/biscyclization process affording fluorene derivatives (Scheme 1).[10] Very recently, Gevorgyan reported a Pd-catalyzed hydroarylation of *o*-alkynyl biaryls proceeding via direct aromatic C−H activation pathways.[11] Thus we envisioned that the analogues of compound **1**, which differ from our previous substrates **I** by one carbon elongation, may be used to construct the tetracyclic skeleton of benz[*a*]anthracene via a tandem C−H activation/biscyclization reaction.

However, the execution of the sequential steps in this biscyclization reaction represents a formidable challenge for the following two reasons: (1) formation of allenyl indene derivatives from intramolecular carboannulation reaction is faster than intermolecular coupling (Scheme 2)[8b−d,9] and (2) subsequent biscyclization products could not be obtained if the following C−H activation process is not sufficiently fast. In this paper, we present a palladium-catalyzed tandem C−H activation/biscyclization reaction of propargylic carbonates with terminal alkynes to offer an efficient and direct route to the tetracyclic benz[*a*]anthracene framework. The mechanistic studies indicated that this tandem C−H activation/biscyclization reaction proceeds from a different pathway than reported in our previous paper.[10]

We first investigated the reaction of propargylic carbonate **1a** with phenylacetylene **2a**. To our delight, the desired tetracyclic product **3aa** was isolated in 78% yield when $Pd(OAc)_2/PPh_3$ and CuI were used as the catalysts (Table 1, entry 1). The structure of this product was unambiguously

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SCHEME 2

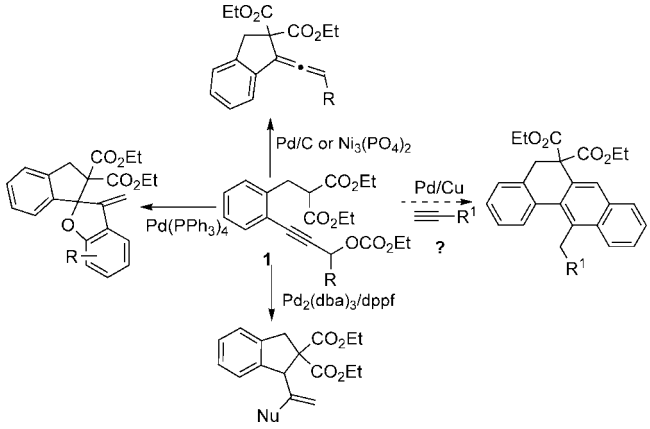
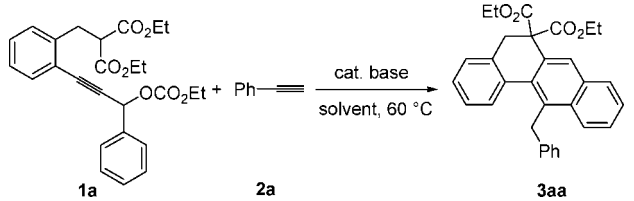


TABLE 1. Optimization of the C−H Activation/Biscyclization Reaction[a]



entry	catalyst	base	solvent	yield (%)
1	$Pd(OAc)_2/PPh_3$, CuI	Et_3N	THF	78
2	$Pd(OAc)_2/PPh_3$, CuI	Et_3N	DMF	86
3	$Pd(OAc)_2/PPh_3$, CuI	Et_3N	CH_3CN	51
4	$Pd(OAc)_2/PPh_3$, CuI	Et_3N	toluene	62
5	$Pd(OAc)_2/PPh_3$, CuI	K_2CO_3	DMF	58 (54)[b]
6	$Pd(OAc)_2/PPh_3$, CuI	Cs_2CO_3	DMF	43 (40)[b]
7	$Pd(PPh_3)_4$, CuI	Et_3N	DMF	81
8	$Pd_2(dba)_3$, CuI	Et_3N	DMF	5
9	$Pd(OAc)_2/PPh_3$	Et_3N	DMF	10
10	CuI	Et_3N	DMF	nr[c]

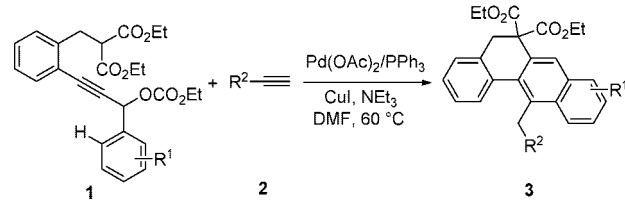
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2.0 equiv), base (5.0 equiv), Pd (5 mol %), PPh_3 (10 mol %), and CuI (10 mol %), in solvent (2 mL), at 60 °C for 2 h. [b] 2.0 equiv of base was used. [c] No reaction.

established as the tetracyclic product **3aa** by X-ray diffraction analysis.[12] Screening of reaction conditions showed that DMF was better than THF for this reaction (entry 2). Other solvents, such as CH_3CN and toluene, gave relatively lower yields (entries 3 and 4). Changing the base from Et_3N to K_2CO_3 or Cs_2CO_3 did not improve the yield of **3aa** (entries 5 and 6). The $Pd(PPh_3)_4$/CuI catalytic system was also effective for this reaction (entry 7), but lower conversion was observed when $Pd_2(dba)_3$/CuI was employed (entry 8). In the absence of CuI, the reaction resulted in a dramatic decrease in the yield of **3aa** (enty 9). And no reaction occurred without the palladium catalyst (entry 10). These results indicated that both Pd and CuI played a crucial role in this transformation.

Having gained an understanding of the factors that influence the biscyclization process, we have explored the scope of this reaction. The results are summarized in Table 2. The reaction

(12) Crystal data for **3aa**: $C_{31}H_{28}O_4$, MW = 464.53, T = 296(2) K, λ = 0.71073 Å, triclinic space group, $P1$, a = 10.160(6) Å, b = 23.332(14) Å, c = 10.763(6) Å, α = 90.00°, β = 110.534(9)°, γ = 90.00 °, V = 2390(2) Å^3, Z = 4, D_c = 1.291 mg/m^3, μ = 0.084 mm^{-1}, $F(000)$ = 984, crystal size 0.24 × 0.23 × 0.20 mm^3, independent reflections 5483 [R(int) = 0.0298], reflections collected 13981; refinement method full-matrix least-squares on $F2$, goodness-of-fit on $F2$ 1.020, final R indices [$I > 2\sigma(I)$] R_1 = 0.0475, wR_2 = 0.1392, R indices (all date) R_1 = 0.0704, wR_2 = 0.1582, largest difference peak and hole 0.243 and −0.225 e Å^{-3}.

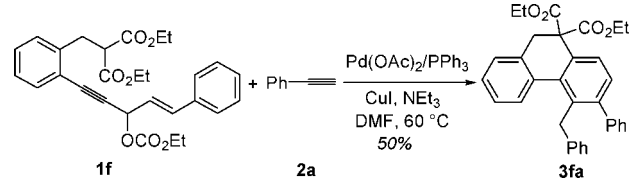
TABLE 2. Palladium-Catalyzed Tandem C−H Activation/ Biscyclization of Propargylic Carbonates with Terminal Alkynes[a]



entry	**1** (R^1)	**2** (R^2)	**3**	yield (%)
1	**1a** (H)	**2a** (C_6H_5)	**3aa**	86
2	**1a** (H)	**2b** (p-ClC_6H_4)	**3ab**	87
3	**1a** (H)	**2c** (p-BrC_6H_4)	**3ac**	83
4	**1a** (H)	**2d** (p-$MeOC_6H_4$)	**3ad**	77
5	**1a** (H)	**2e** (n-propyl)	**3ae**	43
6	**1a** (H)	**2f** (n-pentyl)	**3af**	52
7	**1a** (H)	**2g** ($THPOCH_2$)	**3ag**	53
8	**1a** (H)	**2h** ($PhCH_2OCH_2$)	**3ah**	40
9	**1b** (p-CH_3)	**2a** (C_6H_5)	**3ba**	86
10	**1c** (p-Cl)	**2a** (C_6H_5)	**3ca**	80
11	**1d** (p-Br)	**2a** (C_6H_5)	**3da**	72
12	**1e** (o-Cl)	**2a** (C_6H_5)	**3ea**	69

[a] Reaction conditions: **1** (0.2 mmol), **2** (2.0 equiv), Et_3N (5.0 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and CuI (10 mol %), in DMF (2 mL), at 60 °C for 2 h.

SCHEME 3



of **1a** with various aryl alkynes often led to excellent yields of the desired products (entries 1−4). In this transformation, electron-deficient aryl alkynes showed more reactivity and gave slightly higher yields than electron-rich aryl alkynes (entries 2−4). Aliphatic alkynes can also be used successfully in this tandem C−H activation/biscyclization process, even with lower yields (entries 5 and 6). Additionally, propargyl ethers were tolerated in this reaction and **3ag**−**ah** were given in moderate yields (entries 7and 8). Secondary carbonates **1b**−**e** possessing various substituents at the propargylic position also worked well, and gave good to excellent yields of the desired products, respectively. In the reaction, secondary carbonates with electron-rich arene substituents gave better results than those bearing electron-deficient substrates (entries 9−12). Notably, the Cl and Br groups on the aromatic substituents were tolerated in these transformations and no cross-coupling side products were observed (entries 10−12).[13] In this manner, the resulting halide-substituted products could be further expanded to a wider variety of functionalized tetracyclic benz[a]anthracene derivatives by undergoing cross-coupling reactions.

Furthermore, secondary carbonate **1f** possessing a styryl group was also investigated (Scheme 3). The tandem reaction proceeded well to give the desired product **3fa** in 50% yield. However, the reactions of secondary carbonates, having a propenyl group or an alkyl group such as ethyl and propyl, resulted in a complex mixture.[14]

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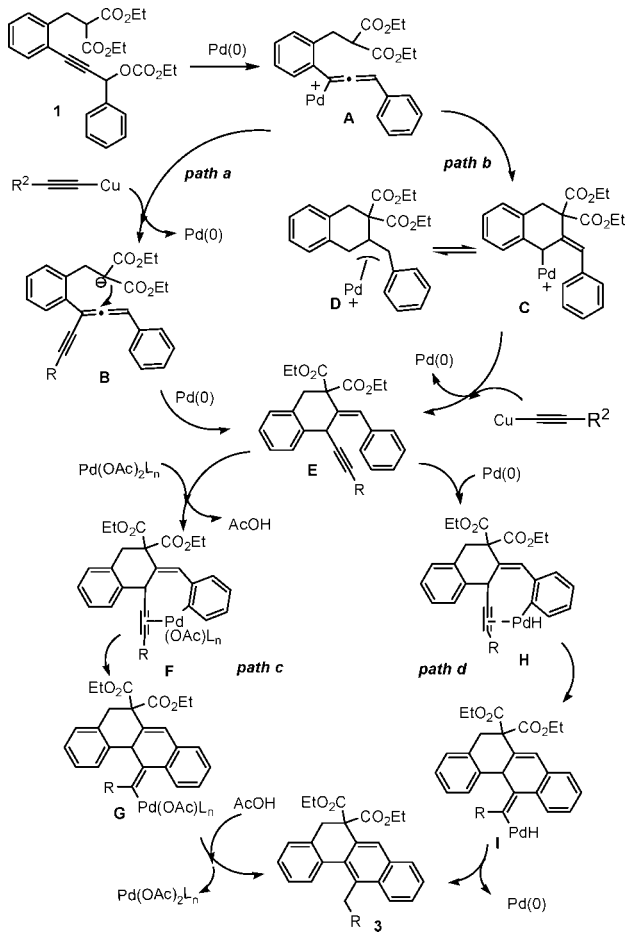
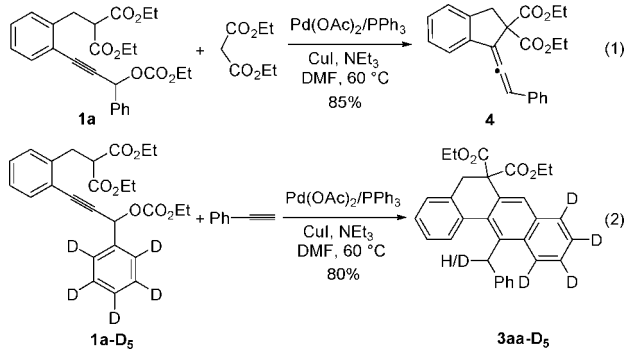
(14) The reasons for this difference in reactivity are unclear at this time and are currently under investigation.

SCHEME 4



SCHEME 5



The plausible mechanism for this tandem biscyclization is summarized in Scheme 4. The key intermediate **E** can be formed by two different ways. Path a involves coupling of **A** with copper(I) acetylide followed by carboannulation of **B**, while path b involves carboannulation of **A** followed by coupling of **C** with copper(I) acetylide.[7−10,15] Following the intermediate **E**, the desired product **3** could be formed via a C−H activation step by path c or d (occurring either at Pd(0) or at Pd(II)).[3,11]

To gain insight into the mechanism, several experiments were carried out. As depicted in Scheme 5 (eq 1), when diethyl malonate was used as the nucleophile, the allene product **4** was obtained exclusively in 85% yield. The regioselective formation of five-membered indene derivative was in agreement with our previous results.[8b−d,9] The result indicated that path b was less likely to be the operating mechanism. Next, deuterium labeled **1a-D$_5$** was used as a modified substrate to distinguish between paths c and d (Scheme 5, eq 2). When the reaction proceeded though path d, one of the deuterium atoms in the ortho position of benzene-d_5 should be transferred completely to the benzyl position of the product. However, product loss of deuterium was observed in the biscyclization.[16] Additionally, the Friedel−Crafts-type electrophilic cyclization of intermediate **E** was considered to be less likely based on the higher propensity of the electron-deficient alkynes toward this cyclization reaction. So we proposed that path c may be the most likely route to the product.

In conclusion, we have developed an efficient palladium-catalyzed tandem C−H activation/biscyclization reaction of propargylic carbonates with terminal alkynes. In this process, three carbon−carbon bonds were formed, and high regioselectivity was achieved. The reaction provided an efficient route for construction of the complex tetracyclic benz[*a*]anthracene derivatives. The possible mechanism was discussed in detail in this paper.

Experimental Section

Typical Procedure for the Synthesis of Propargylic Carbonates 1. Ethyl chloroformate (0.87 g, 8.0 mmol) was added to a solution of propargylic alcohol (2.0 mmol), pyridine (0.63 g, 8.0 mmol), and DMAP (44.8 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction was quenched with H_2O (30 mL) after being stirred for 2 h at room temperature. Then, the solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 solution was washed with a saturated aqueous copper sulfate solution followed by concentration. The residue was purified by column chromatography on silica gel to afford the corresponding propargylic carbonates **1**.

Typical Procedure for the Synthesis of Benz[*a*]anthracene Derivatives 3. $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol %), PPh_3 (5.2 mg, 0.02 mmol, 10 mol %), and CuI (3.8 mg, 0.02 mmol, 10 mol %) were added to a solution of propargylic carbonates **1** (0.20 mmol), terminal alkynes **2** (0.40 mmol), and Et_3N (101.0 mg, 1.0 mmol) in DMF (2.0 mL) under an argon atmosphere. Then, the reaction mixture was stirred at 60 °C for 2 h. When the reaction was completed, the reaction was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layer was dried over Na_2SO_4 followed by concentration. The residue was purified by chromatography on silica gel to afford the corresponding product **3**.

Spectroscopic data for product 3aa: 80 mg, 0.17 mmol, 86%; mp 132−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81−7.79 (d, J = 8.4 Hz, 2H), 7.68 (s, 1H), 7.42−7.40 (m, 2H), 7.36−7.28 (m, 4H), 7.22−7.16 (m, 4H), 7.09−7.05 (m, 1H), 4.73 (s, 2H), 4.18 (s, 4H), 3.50 (s, 2H), 1.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 141.6, 134.9, 134.5, 134.2, 133.3, 133.1, 132.6, 131.6, 128.7, 128.5, 128.4, 128.3, 127.6, 126.8, 126.5, 125.9, 125.8, 125.7, 124.7, 61.7, 61.5, 37.7, 37.1, 13.9; HRMS (ESI) calcd for $C_{31}H_{28}O_4$ (M + Na) 487.1880, found (M + Na) 487.1894.

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Supporting Information Available: Typical experimental procedures and characterization for all products and X-ray data of **3aa** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Biscyclization of **1a-D$_5$** produced **3aa-D$_5$** in 80% yield with 34% deuterium incorporated at the benzyl position (see the Supporting Information for details).