ORGANIC LETTERS

2007
Vol. 9, No. 26
5425−5428

Synthesis of Fused Polycycles from Propargylic Compounds with Terminal Alkynes via a Palladium-Catalyzed Tandem C–H Activation/Biscyclization Process

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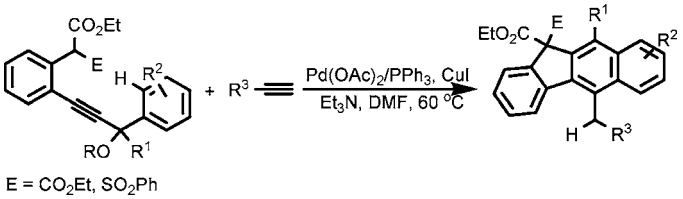
Received September 24, 2007

ABSTRACT



Various benzo[*b*]fluorene and fluorene derivatives have been prepared from propargylic compounds with terminal alkynes through a novel palladium-catalyzed tandem biscyclization reaction. This reaction involved a sequence of carboannulation, coupling, C–H activation and C–C bond formation process. A plausible mechanism has been proposed that was consistent with the deuterium-labeling experiment.

Palladium-catalyzed C−C bond formation via C−H bond activation is a highly attractive method in organic synthesis since it can give the products directly from readily available and unreactive starting materials without forming copious amounts of byproducts.[1] Recently, palladium-catalyzed tandem cyclization involving C−H bond functionalization has received considerable attention.[2] However, most of those transformations were initiated with aryl halides. To the best of our knowledge, there has been no report on the tandem biscyclization reaction involving C−H bond activation initiated by propargylic compounds with terminal alkynes.[3] Herein, we wish to report a novel palladium-catalyzed tandem reaction involving a sequence of carboannulation,

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(1) For recent reviews on C−H activation, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (d) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (e) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (f) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

(2) For some recent tandem processes involving C−H funtionalization, see: (a) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (b) Cuny, G.; Bois-Choussy, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4774. (c) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. (d) Huang, Q.; Campo, M. A.; Yao, T.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 8251. (e) Cuny, G.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2004**, *126*, 14475. (f) Bour, C.; Suffert, J. *Org. Lett.* **2005**, *7*, 653. (g) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 701. (h) Ohno, H.; Miyamura, K.; Mizutani, T.; Kadoh, Y.; Takeoka, Y.; Hamaguchi, H.; Tanaka, T. *Chem. Eur. J.* **2005**, *11*, 3728 and references therein. (i) Ohno, H.; Yamamoto, M.; Iuchi, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5103 and references therein. (j) Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927 and references therein. (k) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627. (l) Pinto, A.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291. (m) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288.

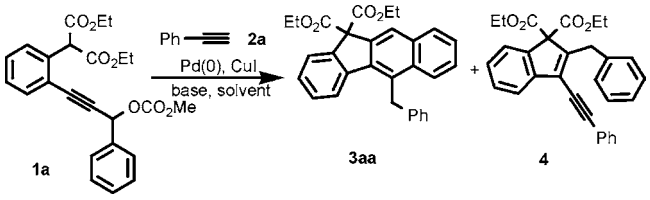
(3) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed.* **1995**, *34*, 2589.

10.1021/ol702311z CCC: $37.00
Published on Web 11/22/2007

C−H activation, coupling, and carbopalladium cyclization. In this process, more than one carbon−carbon bond can be formed, and polycyclic aromatic rings can also be constructed in a one−pot manner.

We initially focused on palladium-catalyzed cyclization/coupling reaction of propargylic carbonate **1a** and phenylacetylene (**2a**) to synthesize the highly substituted indene **4** (Scheme 1).[4,5] Surprisingly, when compound **1a** was treated

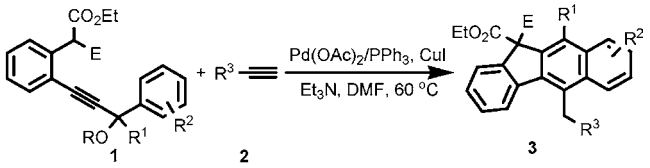
Scheme 1



with **2a** at 60 °C in DMF in the presence of $Pd(PPh_3)_4$ (5 mol %) and CuI (10 mol %), using Et_3N as a base, the 2,3-disubstituted indene **4** was isolated in only 6% yield, and an unexpected diethyl 5-benzyl 11*H*-benzo[*b*]fluorene-11,11-dicarboxylate (**3aa**) was obtained as a major product. The formation of polycyclic compound **3aa** shows that this tandem reaction involved a novel C−H activation process in which three carbon−carbon bonds and two carbocycles were constructed. This result encouraged us to extend our protocol to investigate this novel C−H activation reaction. Consequently, we investigated the tandem cyclization reaction of **1a** and **2a** under various conditions.[6] $Pd(PPh_3)_4$/CuI and $Pd(OAc)_2/PPh_3$/CuI proved to be the best catalysts. $Pd_2(dba)_3$•$CHCl_3$/CuI were less effective. DMF turned out to be a better solvent than THF and dioxane. As a base, Et_3N gave the best result. It is noteworthy that the reaction in the absence of CuI resulted in a dramatic decrease in the yield of **3aa**.

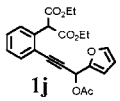
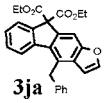
To evaluate the scope of this C−H activation process, a number of different substrates were examined (Table 1). The reaction of **1a** with various substituted terminal alkynes often led to good yields of the polycyclic carbocycles (entries 1−5). The use of tetrahydropyranyl propargyl ether (**2f**) gave the desired product in 67% yield (entry 6). Secondary carbonates **1b**−**e** possessing various substituents at the propargylic position also worked well to give the desired products in good to excellent yields (entries 7−10). Propargylic carbonate **1f** with different electron-withdrawing groups also afforded the desired product **3fa** in 30% yield (entry 11). Propargylic acetate **1g** has also proven successful

Table 1. Tandem C−H Activation/Biscyclization Reaction of Propargylic Compounds with Terminal Alkynes[a]



R = CO_2Me, E = CO_2Et; **1a-1e**
R = CO_2Me, E = SO_2Ph; **1f**
R = Ac, E = CO_2Et; **1g-1j**

E = CO_2Et; **3aa-3ea** and **3ha-3ia**
E = SO_2Ph; **3fa**

Entry	R^1, R^2	**1**	R^3	**2**	t (h)	**3**	Yield[b] (%)
1	H, H	**1a**	Ph	**2a**	2	**3aa**	85
2	H, H	**1a**	4-$MeOC_6H_4$	**2b**	2	**3ab**	75
3	H, H	**1a**	4-ClC_6H_4	**2c**	2	**3ac**	88
4	H, H	**1a**	4-BrC_6H_4	**2d**	2	**3ad**	65
5	H, H	**1a**	*n*-pentyl	**2e**	2	**3ae**	56
6	H, H	**1a**	CH_2OTHP	**2f**	2	**3af**	67
7	H, 4-Me	**1b**	Ph	**2a**	2	**3ba**	78
8	H, 4-Cl	**1c**	Ph	**2a**	2	**3ca**	72
9	H, 2-Cl	**1d**	Ph	**2a**	2	**3da**	91
10	H, 2,4-dichloro	**1e**	Ph	**2a**	2	**3ea**	93
11	H, H	**1f**	Ph	**2a**	6	**3fa**	30
12	H, H	**1g**	Ph	**2a**	2	**3aa**	83
13	Me, Ph	**1h**	Ph	**2a**	6	**3ha**	77
14	Ph, Ph	**1i**	Ph	**2a**	12	**3ia**	56
			Ph	**2a**	2		
15		**1j**				 **3ja**	81

[a] Reaction conditions: **1** (1.0 equiv), **2** (2.0 equiv), Et_3N (5.0 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and CuI (10 mol %), in DMF, at 60 °C. [b] Isolated yield.

and gave a similar yield to **1a** (entry 12). To our delight, propargylic tertiary acetates **1h** and **1i** also afforded the products **3ha** and **3ia** in moderate yields after longer reaction times, perhaps due to steric hindrance (entries 13 and 14).[7] In addition, a secondary propargyl acetate bearing a heteroaromatic substituent such as a furyl group also proceeded well in this tandem reaction (entry 15).

Although the NMR spectroscopic data support the formation of polycyclic compounds **3**, the structure was unambiguously confirmed through an X-ray crystal structure analysis of compound **3ca** (Figure 1).[8]

(4) (a) Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 5777. (b) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 1538.

(5) For the coupling reaction of propargylic compounds and terminal alkynes, see: (a) Mandai, T.; Nakata, T.; Murayama, H.; Yamaoki, H.; Ogawa, M.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1990**, *31*, 7179. (b) Mandai, T.; Murayama, H.; Nakata, T.; Yamaoki, H.; Ogawa, M.; Kawada, M.; Tsuji, J. *J. Organomet. Chem.* **1991**, *417*, 305. (c) Hayashi, M.; Saigo, K. *Tetrahedron Lett.* **1997**, *38*, 6241. (d) Yoshida, M.; Hayashi, M.; Shishido, K. *Org. Lett.* **2007**, *9*, 1643.

(6) Detailed results are listed in the Supporting Information.

(7) For propargylic tertiary carbonate, the nucleophile is inhibited from attacking the 3-position of the indene; see ref 4a.

(8) Crystal data for **3ca** have been deposited in CCDC as deposition number 658187: $C_{30}H_{25}ClO_4$, MW = 484.14, T = 294(2) K, λ = 0.71073 Å, triclinic space group, $P1$, a = 11.9038(10) Å, b = 14.2082(12) Å, c = 16.4475(13) Å, α = 73.5420(10)°, β = 80.3940(10)°, γ = 87.3350(10)°, V = 2630.4(4) Å^3, Z = 2, D_c = 1.279 mg/m^3, μ = 0.182 mm^{-1}, $F(000)$ = 1062, crystal size 0.26 × 0.24 × 0.22 mm, independent reflections 9585 [R(int) = 0.0274], reflections collected 13757, refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 1.555, final R indices [$I > 2\sigma(I)$] R_1 = 0.1194, wR_2 = 0.0927, R indices (all date) R_1 = 0.0651, wR_2 = 0.0833, extinction coefficient 0.0043(2), largest diff peak and hole 0.641 and −0.548 e Å^{-3}.

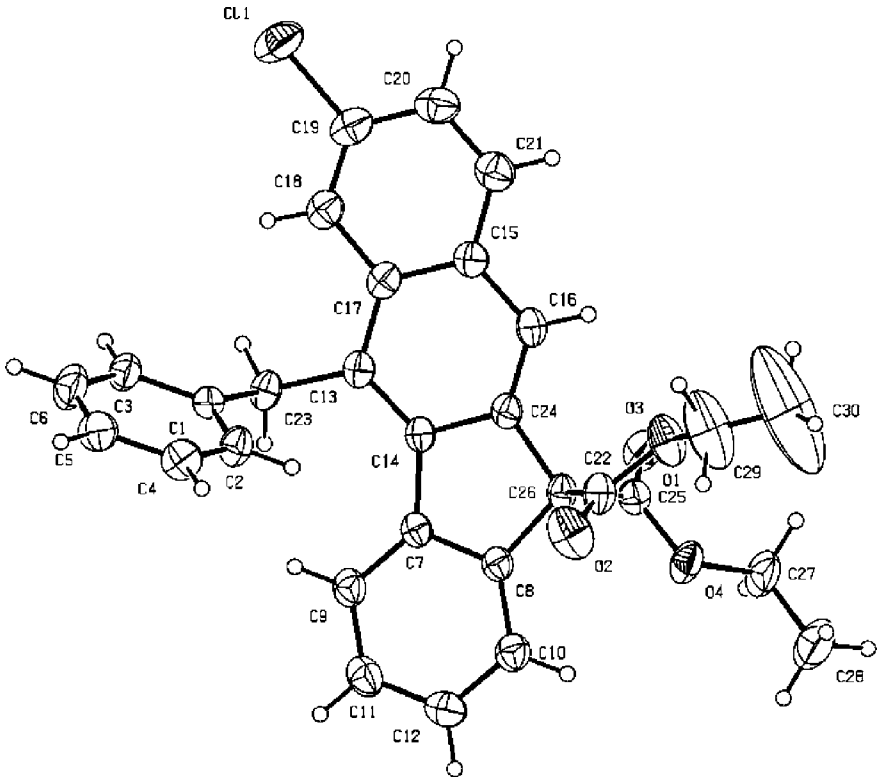
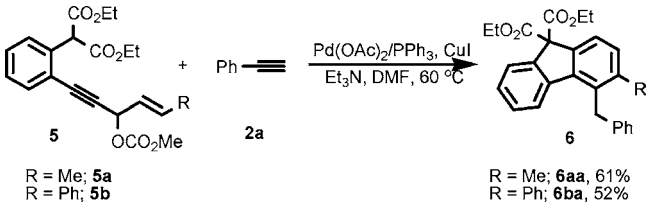


Figure 1. Structure of **3ca**.

Furthermore, secondary carbonates having a vinyl or a styryl group such as **5a** and **5b** were also employed in this reaction (Scheme 2). Satisfactorily, the hydrogen on the simple double bond can also be activated under the above-

Scheme 2

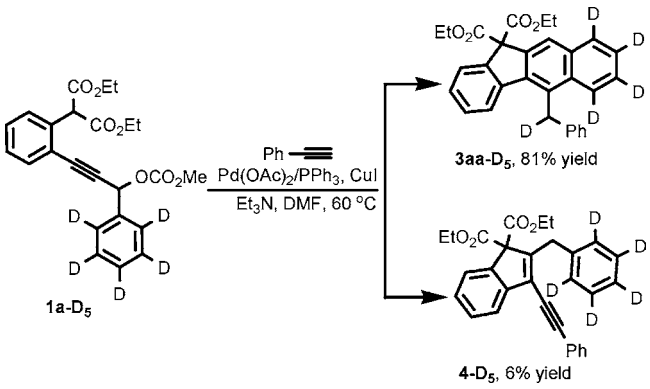


optimized conditions. The reaction proceeded smoothly to give the 9*H*-fluorene derivatives **6aa** and **6ba** in 61% and 52% yields, respectively.

To study the mechanism of this C−H activation process, labeled **1a-D$_5$** was used as a modified substrate (Scheme 3). When compound **1a-D$_5$** was treated with **2a** under the conditions used above, **3aa-D$_5$** was isolated in 81% yield. In the ^{1}H NMR spectra of **3aa-D$_5$**, it was obvious that one of the deuteriums in the ortho position of benzene-d_5 has been transferred to the benzyl position of the product. The result indicated that there is an intramolecular proton transfer in this C−H activation process.

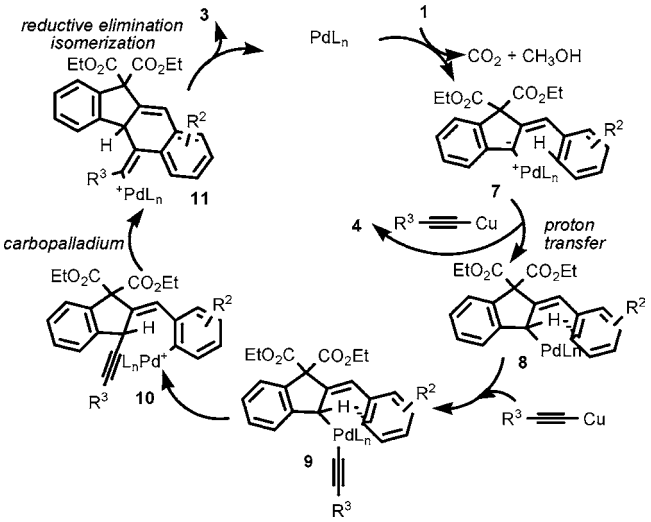
A plausible mechanism for this new C−H activation process is outlined in Scheme 4. It may be rationalized in terms of the following steps: (a) cyclization of propargylic carbonate under palladium catalysis to give the palladium

Scheme 3



complex **7**,[3,4] (b) intramolecular proton transfer of the palladium complex **7** to form the palladacycle intermediate **8**,[2f] (c) reaction of **8** with the copper acetylide to give intermediate **9**,[2f] (d) intramolecular coupling to generate intermediate **10**, and (e) intramolecular carbopalladium cyclization of **10** to produce intermediate **11**, followed by reductive elimination and isomerization to furnish the desired product and regenerate the Pd(0) catalyst. When the palladium complex **7** picks up an active hydrogen from the nucleophilic moiety or the reaction system, and then couples

Scheme 4



with the copper acetylide directly, side product **4** can be formed.

In conclusion, we have developed a novel tandem biscyclization reaction of propargylic compounds with terminal alkynes, which afforded a simple and efficient route to polycyclic aromatic compounds. This study has demonstrated for the first time that propargylic compounds can initiate a tandem biscyclization process involving a C−H functionalization of benzene, heteroaromatic rings, or simple C−C double bonds in the presence of a palladium catalyst. Further investigation on the scope and the mechanism of the reaction is process.

Acknowledgment. We thank the NSF (NSF-20621091, NSF-20672049) and the "Hundred Scientist Program" from the Chinese Academy of Sciences for financial support.

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

OL702311Z