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Cyclization–oxidation of 1,6-enyne derivatived from Baylis–Hillman adducts via Pd(II)/Pd(IV)-catalyzed reactions: stereoselective synthesis of multi-substituted bicyclo[3.1.0] hexanes and insight into reaction pathways

Hui Liu, Jianjun Yu, Limin Wang, Xiaofeng Tong *

Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, People's Republic of China

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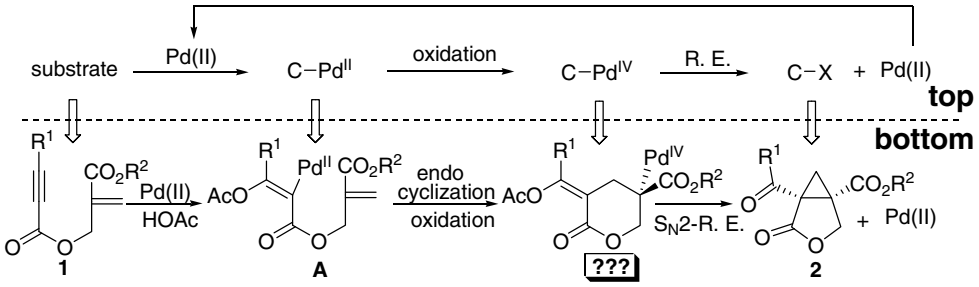
ABSTRACT

Cyclization–oxidation of Baylis–Hillman adducts provides a convenient method to stereoselectively synthesize variety of multi-substituted bicyclo[3.1.0] ring systems via Pd(II)/Pd(IV)-catalyzed reactions. We also disclose that C–Pd(IV) intermediate can undergo reductive elimination through S_N2-type attack by the latent nucleophile of vinyl acetate to afford C_{sp^3}–C_{sp^3} bond formation with inversion of configuration at the Pd(IV)-bounded carbon.

Pd(IV)-complexes as key intermediate have recently been proposed in a number of Pd(II)-catalyzed reactions. Among these reaction manifolds, the crucial step is the formation of a C–Pd(IV) species from the C–Pd(II) intermediate in the presence of a strong oxidant such as $PhI(OAc)_2$, PhIO, Oxone, and $PhICl_2$. Then the C–Pd(IV) intermediate undergoes reductive elimination to form C–X bond (X = O, N, halogen) and release the Pd(II)-complex.[1] Thus, this process is a complete catalytic cycle if one reaction is triggered by Pd(II)-catalyst (Scheme 1, **top**). These oxidative transformations provide complementary routes to traditional Pd(0)-catalyzed reactions that go through Pd(0)/Pd(II) mechanism.[2] Exploration of Pd(II)/Pd(IV) catalysis on 1,6-enyne substrate has led to some interesting results.[3] 1,6-Enynes readily undergo cascade reaction catalyzed by transition-metal catalysts partially because alkyne and alkene are in suitable positions to be incorporated into one molecule.[4] Herein, we report $Pd(OAc)_2$-catalyzed cyclization–oxidation of a novel type of 1,6-enyne, which derives from Baylis–Hillman adduct, in the presence of $PhI(OAc)_2$ to afford bicyclo[3.1.0] compound **2** (Scheme 1, **bottom**). Importantly, several control experiments elucidated the mechanistic details involving an



Scheme 1.

* Corresponding author. Fax: +86 21 6425 3881.
E-mail address: tongxf@ecust.edu.cn (X. Tong).

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endo-mode cyclization and S_N2-type C_{sp^3}–C_{sp^3} bond formation, which are believed to be principles for further development of Pd(II)/Pd(IV)-catalyzed reactions.

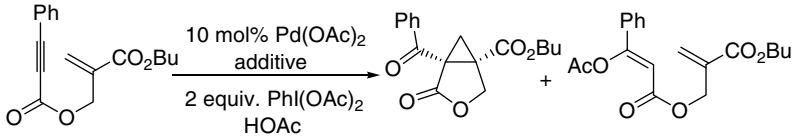
The Baylis–Hillman adducts have been increasingly attractive to synthetic organic chemists, as they are versatile molecules with a minimum of three functional groups (i.e., hydroxyl, olefin, and ester).[5] We are interested in exploiting transition-metal-catalyzed reaction of 1,6-enyne to develop new methods for the synthesis of various carbon- and hetero-cycles.[6] Obviously, condensation of a Baylis–Hillman adduct and propiolic acid provides a convenient way to 1,6-enyne substrate **1**. To the best of our knowledge, the chemistry of this type of enynes has rarely been studied.[7] Our initial studies focused on the behavior of substrate **1a** under similar conditions as in our previous report.[3a] It was discovered that **1a** was completely consumed to give product **2a** in 20% yield (Table 1, entry 1). NaOAc (2 equiv) did not influence the reaction very much, although this additive was proposed to increase the concentration of AcO^- to facilitate trans-acetoxypalladation of alkyne (Table 1, entry 2). To our delight, the yield was significantly increased to 72% with longer reaction time when 1,2-bipyridine (bipy) was added as a ligand (Table 1, entry 3), although byproduct **3a,** which apparently derived from protonolysis of intermediate **A**[8] (Scheme 1), was also isolated in 11% yield. Attempt to reduce the amount of **3a** by the means of increasing $PhI(OAc)_2$ even to 4 equiv was not successful (Table 1, entry 6). Lower catalyst loading or lower reaction temperature with much longer reaction time gave similar selectivity of the reaction (Table 1, entries 4–5). It is worth noting that in the absence of oxidant $PhI(OAc)_2$, **2a** was not detected at all, meanwhile transesterification product **4a** was isolated in 56% yield (entry 7). This indicated that the role of $PhI(OAc)_2$ was not a mere re-oxidant of palladium, but could be involved during the course of this reaction. Hence, a process only based on Pd(0)/Pd(II) catalysis appeared to be less likely.[9]

This reaction shows good generality for the synthesis of multi-substituted bicyclo[3.1.0] hexane derivatives under optimized conditions (Table 1, entry 3). As summarized in Table 2, a variety of bicyclo[3.1.0] ring systems containing lactone (Table 2, entries 1–3), tetrahydrofuran (Table 2, entries 6–7), and pyrrolidine (Table 2, entry 8) were prepared using this cascade reaction. For substrates with electron-deficient triple bond (**1a–c**), protonolysis side products (**3a–c**) were isolated in around 10% yield (Table 2, entries 1–3). In contrast, this kind of side product was not detected for substrates **1f–h** with electron-rich triple bond (Table 2, entries 6–8). Enyne **1e** with an electron-rich alkene was completely transformed to cyclic product **2e** (Table 2, entry 5). Enyne **1d** with α,β-unsaturated ketone gave only trace amount of cyclic product **2d** with 43% of protonolysis product **3e** (Table 2, entry 4). It occurs to us that not only the electronic property of alkyne moiety but also that of alkene moiety affects the selectivity of products.[10]

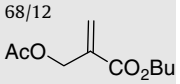
In order to have a better insight of the mechanism, the γ-substituted enyne **1i** was subjected to the reaction conditions (Scheme 2, eq 2). Surprisingly, only the *trans*-isomer **2i**[11] and the protonolysis product **3i** were observed in the reaction mixture. Based on these results (Table 2 and eq 2), we proposed the following mechanism (Scheme 3), which should be consistent with the observed stereochemistry (eq 2). In the first step, anti-acetoxypalladation of the Pd(II)-coordinated alkyne may occur to afford a vinyl-Pd(II) intermediate **A**.[12] Protonolysis of intermediate **A** should give the side product **3i**. Alternatively, insertion of the double bond to vinyl-Pd(II) bond in **A** could pass through competitive pathways. As shown in Scheme 3, different insertion modes resulted in opposite stereochemistry for substrate **1i**. In the *exo*-insertion mode, vinyl-Pd(II) bond of intermediate **A** could approach the *re*-face of olefin due to the bulkiness of phenyl group (Scheme 4). Then the intermediate **B2** could be formed via transition state **TS-b** (Scheme 4) and *cis*-stereochemistry of CO_2Me in C_β position and phenyl in C_γ position would be constructed. Importantly, the stereochemistry of C_β would be defined for further transformation via intermediate **B2**, which could lead to the product in disagreement with the stereochemistry found in compound **2i**. Hence, the *exo*-insertion mode was firstly excluded in proposed mechanism. Contrarily, C_β of intermediate **B1**, which could be obtained via transition state **TS-a** in endo-insertion mode (Scheme 4), should be involved in further transformations, with groups CO_2Me and Ph of **B1** in cis-form. After the formation of C–Pd(IV) intermediate **C1** through the oxidation of **B1** with $PhI(OAc)_2$, the key cyclopropane-forming step could proceed via an S_N2-type attack by the electron-rich tethered olefin on C_β of **C1** to afford intermediate **D1**. Hence, an inversion of configuration at C_β should occur while one C_{sp^3}–C_{sp^3} bond would be formed to give final product. This experimental result is consistent with mechanism proposed by Sanford's group.[3b]

As shown in Table 2 and Scheme 3, the insertion step for intermediate **A**, which stereoselectively controlled the formation of product, seemed strongly depending on the electronic property

Table 1
Optimization of cyclization-oxidation of **1a**[a]

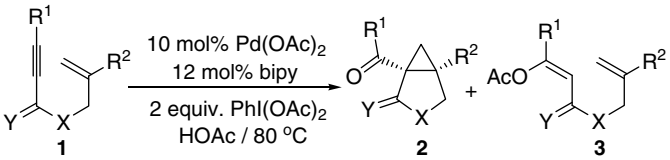


1a **2a** **3a**

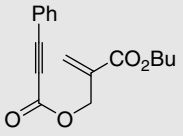
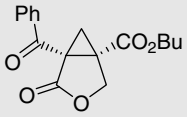
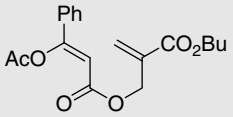
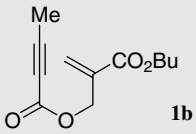
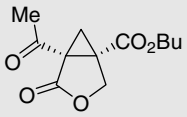
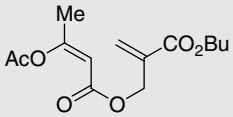
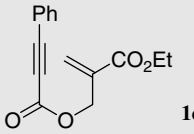
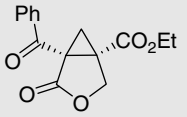
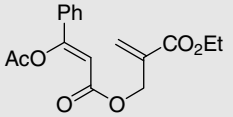
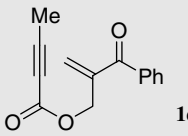
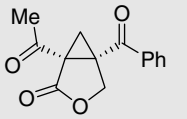
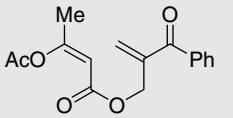
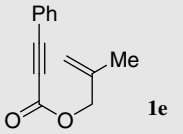
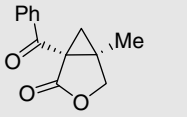
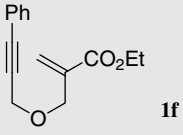
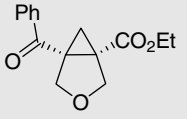
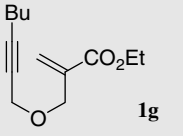
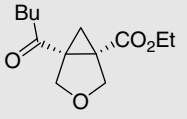
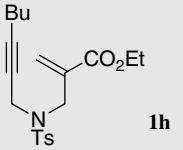
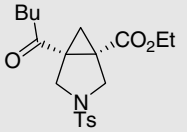
Entry	Additive	Temp. (°C)	Time (h)	Yield[b] (%) **2a/3a**
1	—	80	2	20/ND
2	2 equiv NaOAc	80	2	21/ND
3	**12 mol % bipy**	**80**	**6**	**72/11**
4	12 mol % bipy	50	30	63/7
5	6 mol % bipy	80	30	60/10
6[c]	12 mol % bipy	80	6	68/12
7[d]	—	80	3	 **4a** 56%

[a] Reaction conditions: **1a** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), $PhI(OAc)_2$ (0.6 mmol), and HOAc (3 mL).
[b] Isolated yield; ND = not detected.
[c] 4 equiv $PhI(OAc)_2$ was used.
[d] Without $PhI(OAc)_2$.

Table 2
Cyclization–oxidation of **1**[a]

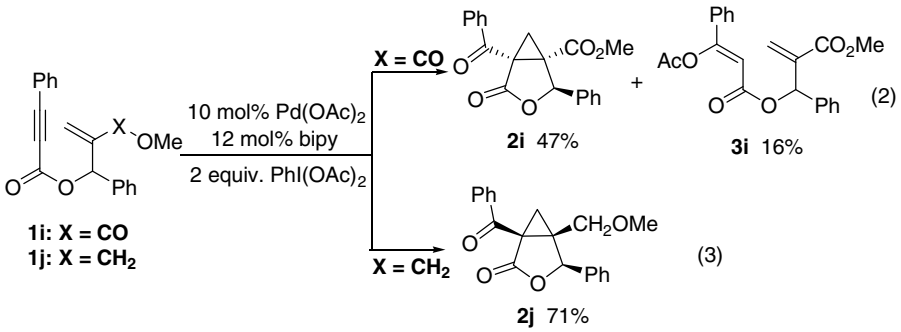


1 **2** **3**

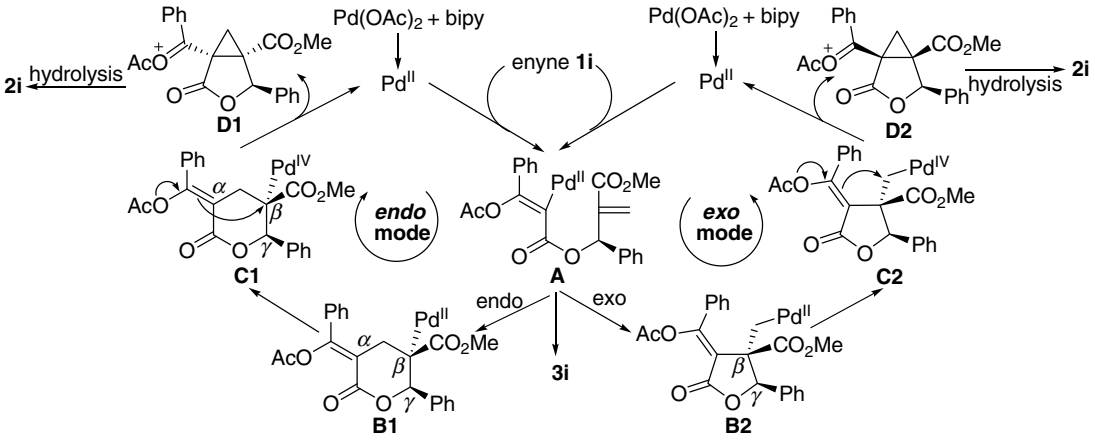
Entry	Substrate **1**	Product **2** (Yield %)[b]	Product **3** (Yield %)[b]
1	 **1a**	 **2a** (72)	 **3a** (11)
2	 **1b**	 **2b** (59)	 **3b** (10)
3	 **1c**	 **2c** (60)	 **3c** (6)
4	 **1d**	 **2d** (<5)[c]	 **3e** (43)[c]
5	 **1e**	 **2e** (70)	ND[d]
6	 **1f**	 **2f** (63)	ND
7	 **1g**	 **2g** (68)	ND
8	 **1h**	 **2h** (78)	ND

[a] Reaction conditions: **1** (0.3 mmol), $Pd(OAc)_2$ (0.03 mmol), $PhI(OAc)_2$ (0.6 mmol), and HOAc (3 mL), within 7 h. For details please see supporting information.
[b] Isolated yield.
[c] Recovered 27% starting material.
[d] ND = not detected.

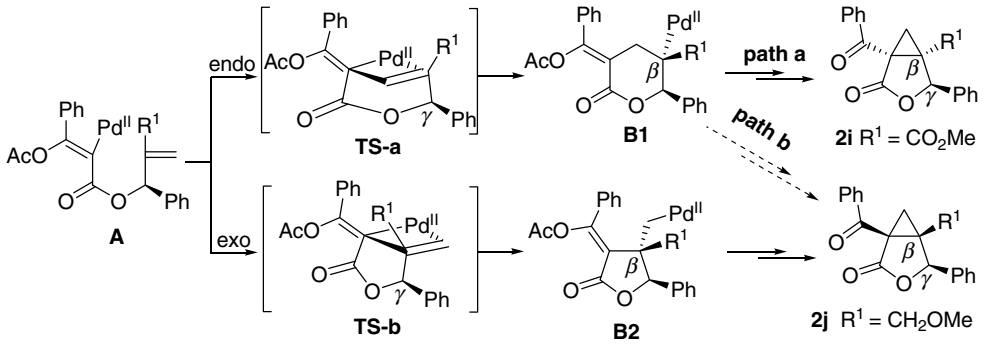
of the double bond. To further elucidate this crucial step, enyne **1j** with electron-rich alkene was synthesized and subjected to the same conditions (Scheme 2, eq 3). Unexpectedly, only *cis*-isomer **2j** was detected and isolated in 71% yield.[11] This stereochemistry was obviously consistent with that of intermediate **B2** obtained via *exo*-insertion mode (Scheme 4). In this case, protonolysis product was also not observed. These results again confirmed that (1) the destination of intermediate **A** was subtly determined by the



Scheme 2.



Scheme 3.



Scheme 4.

electronic property of the alkyne and, especially, the alkene moiety; (2) the *exo*-insertion seemed to be more facile than the *endo*-insertion.

In summary, we realized cyclization-oxidation of Baylis–Hillman adducts via Pd(II)/Pd(IV)-catalyzed reactions. This transformation provides a convenient method to stereoselectively synthesize variety of multi-substituted bicyclo[3.1.0] ring systems. Some mechanistic details disclosed from the control experiments show that the cyclization type (*endo* and/or *exo*) is controlled by electronic property of the alkene in the enyne substrate. More importantly, this transformation also discloses that C-Pd(IV) intermediate can undergo reductive elimination through S_N2-type attack by the latent nucleophile of vinyl acetate to form C_{sp^3}–C_{sp^3} bond with inversion of configuration at the Pd(IV)-bounded carbon. We believe that these discoveries would be useful for further development of Pd(II)/Pd(IV)-catalyzed reactions. Further studies on the potential applications and reaction mechanism are ongoing in our laboratories, and will be reported in due course.

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