Tetrahedron Letters 51 (2010) 317–320

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-catalyzed cyclization of 1,6-enyne with 2-bromoarylaldehyde: domino sequence to [5-7-6] tricyclic ring systems

Xianjie Fang, Xiaofeng Tong *

Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Shanghai 200237, China

A R T I C L E   I N F O

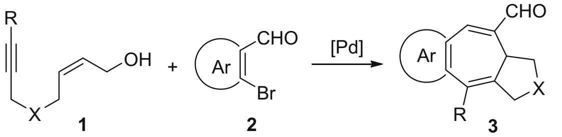
Article history:
Received 5 September 2009
Revised 2 November 2009
Accepted 3 November 2009
Available online 10 November 2009

Keywords:
Palladium catalyst
Domino sequence
1,6-Enyne
[5-7-6] Tricyclic ring
Intramolecular Aldol-condensation

A B S T R A C T

A domino sequence of cyclization of 1,6-enyne with 2-bromoarylaldehyde followed by the intramolecular Aldol-condensation has been realized in the presence of 5 mol % of palladium catalyst. This sequence provides a convenient protocol to access polycyclic ring systems with readily available starting materials under simple Pd(0)-catalyzed conditions. The intramolecular Aldol-condensation has been proposed as the key step for the catalytic cycle.

The [5-7-6] tricyclic ring systems are important structural components and widely occur in a range of polycyclic natural products, such as Dilatriol,[1] Rameswaralide,[2] Grayanotoxin,[3] Guanacastepene A,[4] etc. Inspired by their interesting structure and diverse biological activities, a variety of synthetic approaches toward [5-7-6] tricyclic ring systems has been developed.[5] Although the current methods can efficiently construct the [5-7-6] tricyclic ring systems, they always require multi-steps synthetic route and some complex substrates**,** which are not so easy to obtain. Thus, other versatile and flexible methodologies to construct [5-7-6] tricyclic ring systems using readily accessible building blocks are still needed. Herein, we report an one-pot synthesis of [5-7-6] tricyclic ring compound **3** from the commercially available 1,6-enyne **1** and 2-bromoarylaldehyde **2** under simple palladium-catalyzed conditions Eq. 1:



(1)

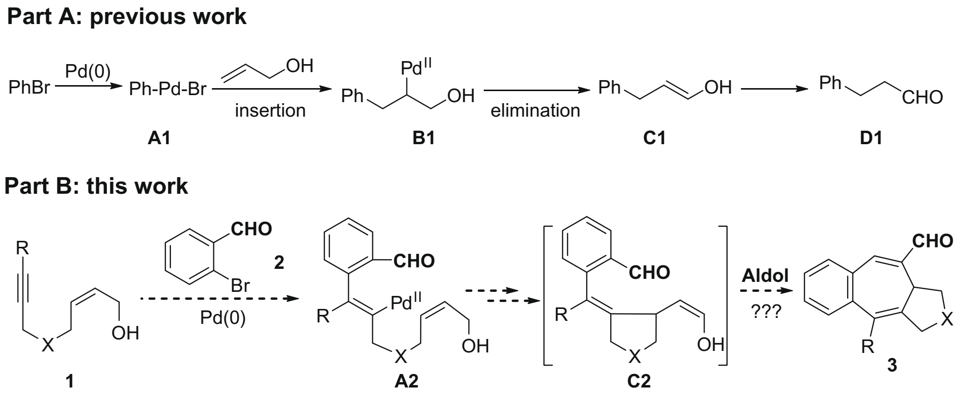
The so-called tandem Heck-isomerization process between the aryl halides (ArX) and allylic or homoallylic alcohols has been widely utilized to synthesize various aldehydes and ketones as illustrated by the reaction of bromobenzene with propenol in Part A, Scheme 1.[6] In general, these reactions are triggered by the oxidative addition of Pd(0) to ArX, which leads to the formation of Ar-Pd(II) intermediate **A1**. Then sequential insertion of double bond to Ar-Pd(II) and selective β-H elimination will afford the enolate species **C1**. Finally, the isomerization of **C1** gives the carbonyl product.[7] As part of our program to design new sequence of cyclization of 1,6-enyne, we are particularly interested in the transition-metal-catalyzed one-pot processes for both the synthesis of structurally complex molecules and the entry into synthetic building blocks.[8] Intrigued by the mechanism of the above-mentioned Heck-isomerization process, we envisioned that the corresponding vinyl-Pd(II) species **A2** also would be presumably formed when 1,6-enyne **1** and 2-bromoarylaldehyde **2** were encountered with the presence of catalytic amount of Pd(0)-species (Part B, Scheme 1). At this stage, we anticipated that the newly formed enolate intermediate **C2** would be trapped by the intramolecular aldehyde group of the substrate **2** to deliver the [5-7-6] tricyclic ring product **3**.

To test our strategy, we start our investigation from the reaction of 1,6-enyne **1a** and 2-bromophenylaldehyde **2a**. The treatment of the substrates by using the combination of $Pd(OAc)_2$ catalyst (5 mol %), Bu_4NBr (2.0 equiv), and NaOAc (2.5 equiv) furnishes the desired product **3a** in 39% yield (Table 1, entry 1). Interestingly, PPh_3 (15 mol %), normally working as the ligand to palladium, almost has no effect to the yield (entry 2). However, the additive LiCl takes a positive effect on the yield and the best results is consequently obtained when 1 equiv LiCl is used (entry 3). The nature of the base also seems to impose an important impact on the reaction results. Other bases, such as $NaHCO_3$, Na_2CO_3, K_2CO_3, NaOMe,

---

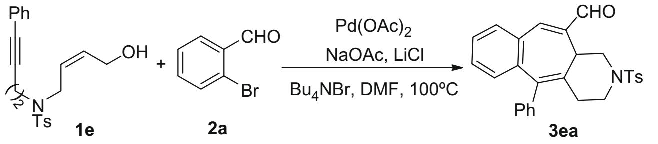
* Corresponding author. Tel.: +86 21 64253881.
E-mail address: tongxf@ecust.edu.cn (X. Tong).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.11.006

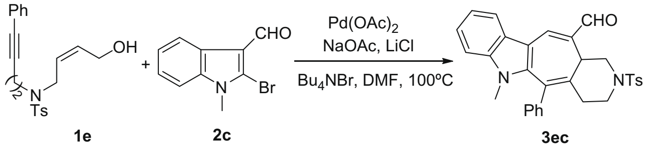


Scheme 1. New strategy for the tandem Heck-isomerization process.

and Et_3N, were much less efficient than NaOAc (entries 7–12). Bu_4NBr exhibits better effect to the yield than Bu_4NCl (entry 6). The yield will dramatically drop without Bu_4NBr (entry 5).[9]



(2)



(3)

With the optimized conditions in hand, we next examined the generality of this catalytic method for the synthesis of [5-7-6] tricyclic ring using a variety of enynes **1** and 2-bromoarylaldehyde **2** (Table 2). Primary alkyl groups and phenyl group can be used as substituents on the alkyne. The 1,6-enyne **1c** with terminal alkyne group gives the best results probably due to the smallest stereo bulk (entry 3). Notably, nitrogen linked 1,6-enynes exhibit similar reactivity under the reaction conditions (entry 4). With regard to 2-bromoarylaldehyde, both **2b** and **2c** also are good choices for the construction of poly-cyclic systems. It is worth noting that the novel domino sequence can be performed with 1,7-enynes (Eqs. 2 and 3). Hence, other two different poly-cyclic systems[10], **3ea** and **3ec**, are obtained in 38% and 37% yields, respectively. These reactions provide valuable products in only one step from readily available compounds.

Our mechanistic proposal for the reaction is as follows (Scheme 2). The interaction of 2-bromoarylaldehyde **2** with Pd(0)-species leads to the formation of the aryl-Pd(II) intermediate. Insertion of alkyne of 1,6-enyne substrate to aryl-Pd(II) bond produces the vinylpalladium intermediate **A2**, which undergoes intramolecular insertion of olefins to give **B2**. Then H_a-elimination selectively occurs to release palladium catalyst and yields enolate intermediate **C2**. In the end, the newly formed enolate is expected to be trapped through the intramolecular Aldol-condensation to give the desired product **3**.[11]

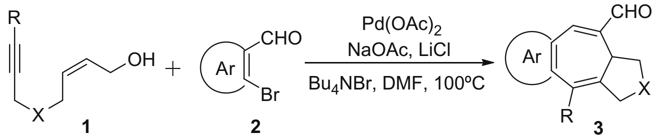
In summary, our effort to investigate the sequence of cyclization of 1,6-enyne has led us to the rational design of a new reaction to produce [5-7-6] tricyclic ring systems. The feature of this protocol is to employ 1,6-enyne **1** and bromoarylaldehyde **2** as starting materials which are readily available. With regard to the mecha-

Table 1
Optimizations for Pd(OAc)$_2$-Catalyzd reaction of **1a** with **2a**[a]

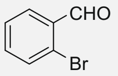
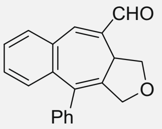
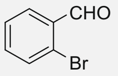
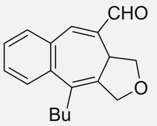
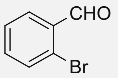
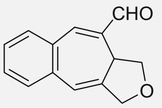
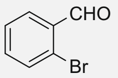
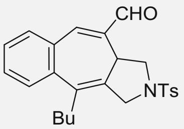
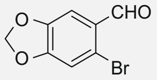
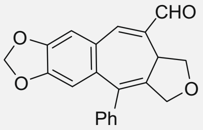
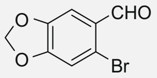
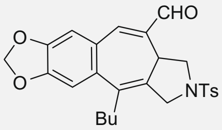
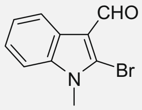
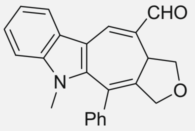
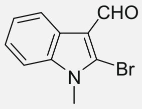
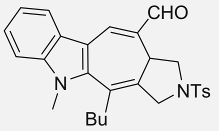
Entry	Bu_4NBr (equiv)	Base (equiv)	Additive (equiv)	Yield[b] (%)
1	2.0	NaOAc (2.5)	/	39
2	2.0	NaOAc (2.5)	PPh_3 (0.15)	35
3	**2.0**	**NaOAc (2.5)**	**LiCl (1.0)**	**61**
4	2.0	NaOAc (2.5)	LiCl (3.0)	45
5	/	NaOAc (2.5)	LiCl (1.0)	19
6[c]	2.0	NaOAc (2.5)	LiCl (1.0)	27
7	2.0	$NaHCO_3$ (2.5)	LiCl (1.0)	17
8	2.0	Na_2CO_3 (2.5)	LiCl (1.0)	15
9	2.0	K_2CO_3 (2.5)	LiCl (1.0)	<5
10	2.0	NaOMe (2.5)	LiCl (1.0)	18
11	2.0	NEt_3 (2.5)	LiCl (1.0)	17
12	2.0	NEt_3 (8.0)	LiCl (1.0)	19

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), and Pd(OAc)$_2$ (0.015 mmol) in DMF (3 mL) at 100 °C for 24 h.
[b] Isolated yield.
[c] Bu_4NCl was used.

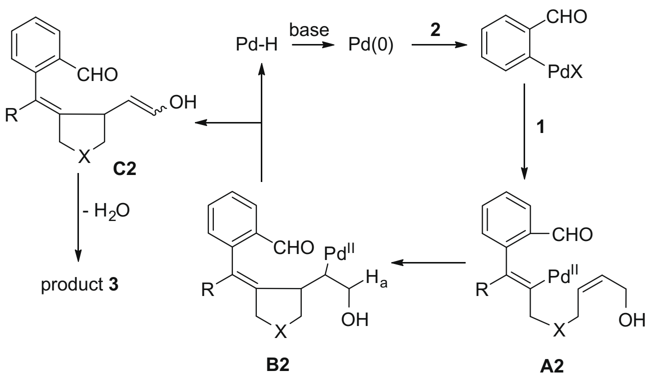
Table 2
Synthesis of [5-7-6] tricyclic ring compound **3** from **1** and **2**[a]



[a]

Entry	1	2	3	Yield[b] (%)
1	**1a** R = Ph X = O	 **2a**		**3aa** 61
2	**1b** R = Bu, X = O	 **2a**		**3ba** 53
3	**1c** R = H, X = O	 **2a**		**3ca** 77
4	**1d** R = Bu, X = NTs	 **2a**		**3da** 55
5	**1a** R = Ph, X = O	 **2b**		**3ab** 31
6	**1d** R = Bu, X = NTs	 **2b**		**3db** 48
7	**1a** R = Ph, X = O	 **2c**		**3ac** 30
8	**1d** R = Bu, X = NTs	 **2c**		**3dc** 45

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), Pd(OAc)$_2$ (0.015 mmol), NaOAc (0.75 mmol), Bu$_4$NBr (0.6 mmol), and LiCl (0.3 mmol) in DMF (3 mL) at 100 °C for 24 h.
[b] Isolated yield.



Scheme 2. Proposed mechanism for the formation of **3**.

nism, we believe that the intramolecular Aldol-condensation is a key step to fulfill the whole of design plan. Further studies on the application of products are ongoing in our laboratories and will be reported in due course.

Acknowledgment

Financial support from Shanghai Municipal Committee of Science and Technology is greatly appreciated (09ZR1408500).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.006.

References and notes

1. Pettit, G. R.; Ode, R. H.; Herald, C. L.; Von Dreele, R. B.; Michel, C. *J. Am. Chem. Soc.* **1976**, *98*, 4677–4678.
2. Ramesh, P.; Reddy, N. S.; Venkateswarlu, Y.; Reddy, M. V. R.; Faulkner, D. J. *Tetrahedron Lett.* **1998**, *39*, 8217–8220.
3. Kan, T.; Hosokawa, S.; Nara, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532–5534.
4. (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, J. *J. Am. Chem. Soc.* **2000**, *122*, 2116–2217; (b) Brady, S. F.; Bondi, S. M.; Clardy, J. *J. Am. Chem. Soc.* **2001**, *123*, 9900–9901.
5. (a) Trost, B. M.; Shen, H. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2313–2315; (b) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2185–2188; (c) Shi, B.; Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2003**, *68*, 1030–1042; (d) Mehta, G.; Umarye, J. D.; Srinivas, K. *Tetrahedron Lett.* **2003**, *44*, 4233–4237; (e) Du, X.; Chu, H. V.; Kwon, O. *Org. Lett.* **2003**, *5*, 1923–1926; (f) Brummond, K. M.; Gao, D. *Org. Lett.* **2003**, *5*, 3491–3494; (g) Srikrishna, A.; Dethe, D. H. *Org. Lett.* **2004**, *6*, 165–168; (h) Mandal, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2004**, *45*, 3831–3833; (i) Chiu, P.; Li, S. *Org. Lett.* **2004**, *6*, 613–616; (j) Boyer, F. D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817–1820; (k) Li, C. C.; Liang, S.; Zhang, X. H.; Xie, Z. X.; Chen, J. H.; Wu, Y. D.; Yang, Z. *Org. Lett.* **2005**, *7*, 3709–3712; (m) Yao, L.; Shi, M. *Eur. J. Org. Chem.* **2009**, 4036–4040.
6. For selected reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066; (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2964; (c) Muzart, J. *Tetrahedron* **2005**, *61*, 4179–4212.
7. (a) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265–272; (b) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 273–278; (c) Tietze, L. F.; Kahle, K.; Raschke, T. *Chem. Eur. J.* **2002**, *8*, 401–407; (d) Berthiol, F.; Doucet, H.; Santelli, M. *Tetrahedron* **2006**, *62*, 4372–4383; (e) Crawley, M. L.; Phipps, K. M.; Goljer, I.; Mehlmann, J. F.; Lundquist, J. T.; Ullrich, J. W.; Yang, C. J.; Mahaney, P. E. *Org. Lett.* **2009**, *11*, 1183–1185.
8. (a) Liu, H.; Yu, J.; Wang, L.; Tong, X. *Tetrahedron Lett.* **2008**, *49*, 6924–6928; (b) Fang, X.; Li, C.; Tong, X. *Chem. Commun.* **2009**, 5311–5313; (c) Tong, X.; Beller, M.; Tse, M. *J. Am. Chem. Soc.* **2007**, *129*, 4906–4907; (d) Tong, X.; Li, D.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 7601–7607.
9. (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287–1289; (b) Larock, R. C.; Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629–6632; (c) Taylor, E. C.; Gillepsie, P.; Patel, M. *J. Org. Chem.* **1992**, *57*, 3218–3225; (d) Larock, R. C.; Yum, E. K.; Yang, H. *Tetrahedron* **1994**, *50*, 305–321; (e) Basavaiah, D.; Muthukumaran, K. *Tetrahedron* **1998**, *54*, 4943–4948.
10. (a) Majetich, G.; Grove, J. L. *Org. Lett.* **2009**, *11*, 2904–2907; (b) Majetich, G.; Zou, G. *Org. Lett.* **2008**, *10*, 81–84; (c) Majetich, G.; Zou, G.; Grove, J. *Org. Lett.* **2008**, *10*, 85–87.
11. (a) Dyker, G.; Thöne, A. *J. Prakt. Chem.* **1993**, *341*, 138–141; (b) Dyker, G.; Grundt, P. *Tetrahedron Lett.* **1996**, *37*, 619–622.