ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 5581–5583

www.rsc.org/chemcomm

COMMUNICATION

Generation of cyclopenta[*c*]chromenes *via* a palladium-catalyzed reaction of 2-alkynylphenol with 2-alkynylvinyl bromide†

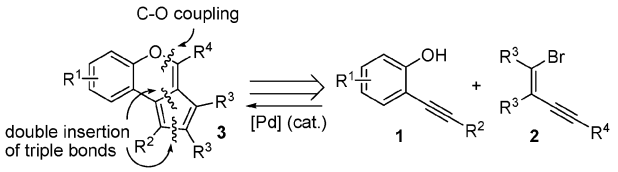
Huanhuan Wang,[a] Yong Luo,[a] Biao Zhu*[b] and Jie Wu*[ac]

Received 22nd March 2012, Accepted 12th April 2012
DOI: 10.1039/c2cc32077k

A palladium-catalyzed tandem reaction of 2-alkynylphenol with 2-alkynylvinyl bromide gives rise to cyclopenta[*c*]chromenes in good yields. Three bonds are formed during the process and a double insertion of triple bonds is believed to be the key step.

It is well known that heterocyclic compounds hold a special and essential place among pharmaceutically important natural products.[1] Currently, heterocyclic compounds with a core of natural products are in great demand in the field of chemical genetics.[2] So far, diversity-oriented synthesis has been utilized successfully for the preparation of such molecules. The cyclopenta[*c*]chromene system is the subunit of natural products (iridoids).[3] Compounds with the core of cyclopenta[*c*]chromene have attracted considerable attention due to their important biological activities.[3,4] For instance, they were found to exhibit a potent cytotoxicity *in vitro* against HTC hepatoma cells and anti-tumor activity *in vivo* against KREBS II ascitic tumor.[4] However, researchers seldom manage to find efficient ways to the cyclopenta[*c*]chromene structural skeletons.[5] For example, Hong and co-workers reported a hetero [6 + 3] cycloaddition of 6-dimethylaminofulvene to benzoquinone leading to cyclopenta[*c*]-chromene derivatives.[5a,b] The existing methods usually suffer from scope limitation. Thus, it is highly desirable to develop an efficient and novel pathway for rapid access to cyclopenta[*c*]chromenes, especially in a combinatorial format.

In conjunction with our continuing efforts for accessing natural product-like compounds,[6] we are interested in cyclopenta[*c*]chromene derivatives. Retrosynthetically, we hypothesized that the scaffold of compound **3** could be generated *via* a tandem process[7] from the reaction of 2-alkynylphenol **1** with 2-alkynylvinyl bromide **2** (Scheme 1). 2-Alkynylphenol **1** has been demonstrated as a versatile building block in organic synthesis.[8] 2-Alkynylvinyl bromide **2** is a useful synthon as well



Scheme 1 A proposed palladium-catalyzed tandem reaction for the generation of cyclopenta[*c*]chromenes.

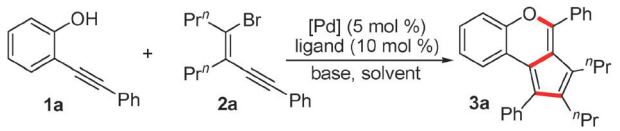
and it is easily available.[9] We envisioned that the reaction of 2-alkynylphenol **1** with 2-alkynylvinyl bromide **2** might proceed through a double insertion of triple bonds and C–O coupling in the presence of a palladium catalyst. We anticipated that the three bonds would be formed in a tandem one-pot procedure. Recently, the use of the strategy of intramolecular or intermolecular double insertion of triple bonds for the formation of heterocyclic or carbocyclic compounds has been demonstrated.[10,11] For example, Lu *et al.* described the synthesis of 8*H*-acenaphtho-[1,2-*c*]pyrroles *via* a palladium-catalyzed bicyclization of 1,8-diarenynyl naphthalenes and primary amines using the intramolecular double insertion of triple bonds as the key step.[10b] Prompted by these results, we conceived that the hypothesis presented in Scheme 1 seemed feasible although there are several possible competitive pathways (such as direct C–O coupling[12] and benzofuran formation[8]) existing theoretically during the transformation.

At the outset, we studied the model reaction of 2-alkynyl-phenol **1a** with 2-alkynylvinyl bromide **2a** in the presence of a palladium catalyst (5 mol%) (Table 1). Initially, the reaction was catalyzed by $Pd(OAc)_2$ (5 mol%) and PCy_3 (10 mol%) in the presence of K_2CO_3 (2.0 equiv.) in 1,4-dioxane at 90 °C (Table 1, entry 1). Gratifyingly, the expected cyclopenta-[*c*]chromene **3a** was obtained and isolated in 54% yield. This product could not be formed in a control experiment without the addition of a phosphine ligand (data not shown in Table 1). In light of this result, we further screened different bases (Table 1, entries 2–6). When NaOMe was employed in the reaction, the reaction afforded the corresponding product **3a** in 85% yield. The yield increased to 92% when the reaction occurred at 95 °C (Table 1, entry 8). The result could not be improved when the temperature was lower or higher (Table 1, entries 7 and 9). No better yields were obtained by evaluation of phosphine ligands (Table 1, entries 10–14). The efficiency was retarded when the amount of palladium catalyst was reduced to

[a] *Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China. E-mail: jie_wu@fudan.edu.cn; Fax: +86 21 6564 1740; Tel: +86 21 6510 2412*
[b] *The Affiliated Zhongshan Hospital of Fudan University, 180 Fenglin Road, Shanghai 200032, China*
[c] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*

† Electronic supplementary information (ESI) available: Experimental procedure, characterization data, ^1H and ^{13}C NMR spectra of compounds **3**. CCDC 872666. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc32077k

Table 1 Initial studies of the palladium-catalyzed reaction of 2-alkynylphenol **1a** with 2-alkynylvinyl bromide **2a**[a]



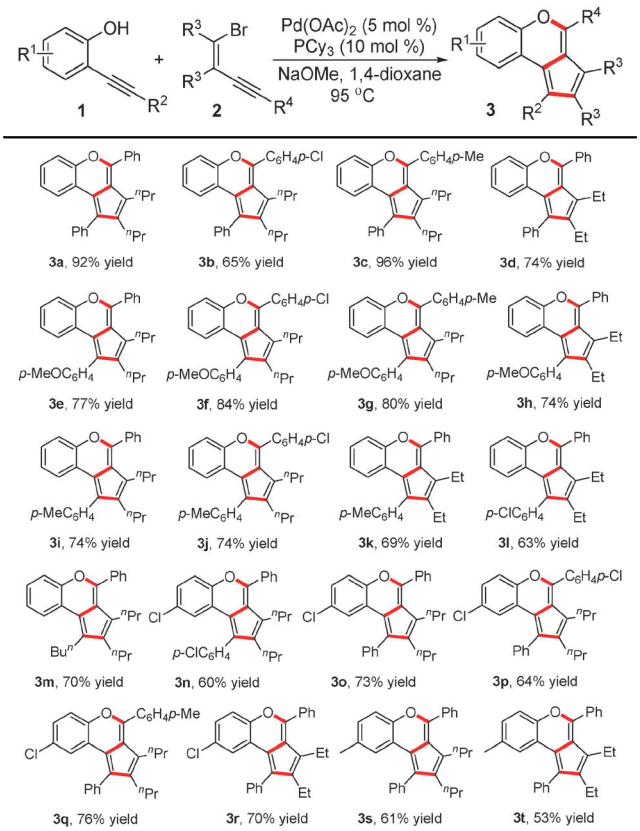
Entry	[Pd]	Ligand	Base	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	PCy_3	K_2CO_3	1,4-Dioxane	54
2	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	1,4-Dioxane	40
3	$Pd(OAc)_2$	PCy_3	*t*-BuOK	1,4-Dioxane	23
4	$Pd(OAc)_2$	PCy_3	K_3PO_4	1,4-Dioxane	51
5	$Pd(OAc)_2$	PCy_3	KOH	1,4-Dioxane	45
6	$Pd(OAc)_2$	PCy_3	NaOMe	1,4-Dioxane	85
7[c]	$Pd(OAc)_2$	PCy_3	NaOMe	1,4-Dioxane	70
8[d]	$Pd(OAc)_2$	PCy_3	NaOMe	1,4-Dioxane	92
9[e]	$Pd(OAc)_2$	PCy_3	NaOMe	1,4-Dioxane	77
10[d]	$Pd(OAc)_2$	Xantphos	NaOMe	1,4-Dioxane	Trace
11[d]	$Pd(OAc)_2$	X-phos	NaOMe	1,4-Dioxane	78
12[d]	$Pd(OAc)_2$	PPh_3	NaOMe	1,4-Dioxane	81
13[d]	$Pd(OAc)_2$	DPPF	NaOMe	1,4-Dioxane	84
14[d]	$Pd(OAc)_2$	DPPP	NaOMe	1,4-Dioxane	80
15[d]	$PdCl_2$	PCy_3	NaOMe	1,4-Dioxane	43
16[d]	$Pd_2(dba)_3$	PCy_3	NaOMe	1,4-Dioxane	85
17[d]	$PdCl_2(PPh_3)_2$	PCy_3	NaOMe	1,4-Dioxane	81
18[d]	$Pd(OAc)_2$	PCy_3	NaOMe	Toluene	Trace
19[d]	$Pd(OAc)_2$	PCy_3	NaOMe	DMF	67

[a] Reaction conditions: 2-alkynylphenol **1a** (1.0 equiv.), 2-alkynylvinyl bromide **2a** (1.2 equiv.), palladium catalyst (5 mol%), ligand (10 mol%), base (2.0 equiv.), 90 °C. [b] Isolated yield based on 2-alkynylphenol **1a**. [c] The reaction was performed at 70 °C. [d] The reaction occurred at 95 °C. [e] The reaction was performed at 105 °C.

2 mol% (data not shown in Table 1). Changing the palladium sources or solvents did not result in further improvement (Table 1, entries 15–19).

The generality of this palladium-catalyzed tandem reaction of 2-alkynylphenols **1** with 2-alkynylvinyl bromides **2** was then explored under the optimized conditions (5 mol% of $Pd(OAc)_2$, 10 mol% of PCy_3, 2.0 equiv. of NaOMe, 1,4-dioxane, 95 °C). The results are exemplified in Table 2. A range of cyclopenta[*c*]-chromenes **3** were obtained in good to excellent yields. Various 2-alkynylphenols **1** were demonstrated to be tolerated in the transformation. The nature of the substituents on the aromatic ring of 2-alkynylphenols **1** could not affect the conversion. Reactions employing 2-alkynylphenols **1** with aryl or alkyl groups attached on the triple bond all worked well to afford the desired products **3**. During the reaction process, only a trace amount of benzofuran was detected under the standard conditions, which indicated the high selectivity of this transformation. Additionally, the substituents in 2-alkynylvinyl bromides **2** did not affect the final outcomes. Interestingly, the chloro group in both substrates was retained during the conversion, which indicated that the oxidative addition of aryl chloride did not take place under the optimized conditions. The structure of cyclopenta[*c*]chromene **3n** was unambiguously illustrated by X-ray diffraction analysis (Fig. 1) (see the ESI†). For the possible mechanism (Scheme 2), we envisioned that an oxidative addition of Pd(0) to vinyl bromide **2** would occur first, which then coordinated with the triple bond of 2-alkynylphenols **1**. After insertion, a vinyl Pd(II) **B** was generated, which subsequently underwent an intramolecular insertion of another triple bond. Further C–O coupling afforded the desired cyclopenta[*c*]chromene **3**.

Table 2 Synthesis of cyclopenta[*c*]chromenes **3** *via* a palladium-catalyzed reaction of 2-alkynylphenol **1** with 2-alkynylvinyl bromide **2**[a]



[a] Isolated yield based on 2-alkynylphenol **1**.

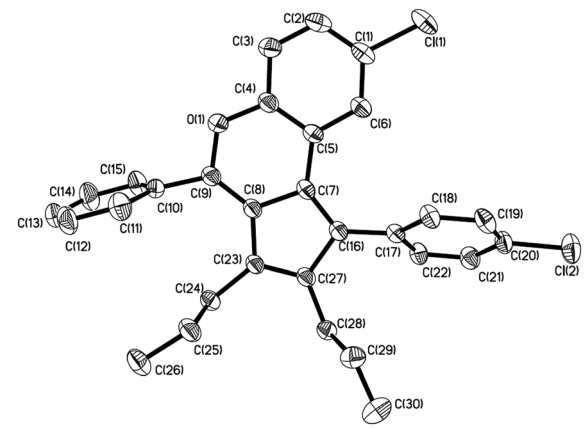
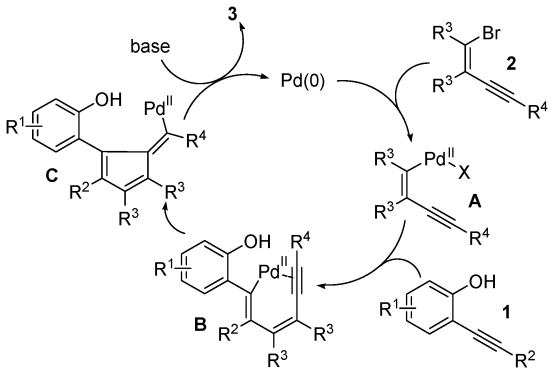


Fig. 1 X-ray ORTEP illustration of cyclopenta[*c*]chromene **3n** (30% probability ellipsoids).

In conclusion, we have described a novel and efficient route for the preparation of cyclopenta[*c*]chromenes *via* a palladium-catalyzed tandem reaction of 2-alkynylphenol with 2-alkynylvinyl bromide. Three bonds are formed in a tandem one-pot procedure. During the reaction process, the transformation proceeds through a double insertion of triple bonds and C–O coupling in the presence of a palladium catalyst. Currently, the use of the strategy of intramolecular or intermolecular double insertion of triple bonds for the formation of other heterocyclic compounds is ongoing in our laboratory.



Scheme 2 A proposed mechanism for the generation of cyclopenta[*c*]chromenes.

Financial support from the National Natural Science Foundation of China (Nos 21032007 and 21172038) is gratefully acknowledged.

Notes and references

1 Recent reviews for the synthesis of heterocycles: (*a*) A. Armstrong and J. C. Collins, *Angew. Chem., Int. Ed.*, 2010, **49**, 2282; (*b*) A. R. Katritzky and S. Rachwal, *Chem. Rev.*, 2010, **110**, 1564; (*c*) M. A. P. Martins, C. P. Frizzo, D. N. Moreira, L. Buriol and P. Machado, *Chem. Rev.*, 2009, **109**, 4140; (*d*) M. Alvarez-Corral, M. Munoz-Dorado and I. Rodrıguez-Garcıa, *Chem. Rev.*, 2008, **108**, 3174; (*e*) A. Minatti and K. Muniz, *Chem. Soc. Rev.*, 2007, **36**, 1142; (*f*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2006, **106**, 4644.

2 (*a*) D. P. Walsh and Y.-T. Chang, *Chem. Rev.*, 2006, **106**, 2476; (*b*) P. Arya, D. T. H. Chou and M.-G. Baek, *Angew. Chem., Int. Ed.*, 2001, **40**, 339; (*c*) S. L. Schreiber, *Science*, 2000, **287**, 1964.

3 (*a*) A. Nangia, G. Prasuna and P. B. Rao, *Tetrahedron*, 1997, **53**, 14507; (*b*) M. Tintas, E. Bogdan and I. Grosu, *J. Heterocycl. Chem.*, 2011, **48**, 747.

4 S. Isoe, *Stud. Nat. Prod. Chem.*, 1995, **16**, 289.

5 (*a*) B.-C. Hong, H.-I. Sun and Z.-Y. Chen, *Chem. Commun.*, 1999, 2125; (*b*) B.-C. Hong, Z.-Y. Chen and W.-H. Chen, *Org. Lett.*, 2000, **2**, 2647; (*c*) M. Chakraborty, D. B. McConville, T. Saito, H. Meng, P. L. Rinaldi, C. A. Tessier and W. J. Youngs, *Tetrahedron Lett.*, 1998, **39**, 8237.

6 For recent selected examples, see: (*a*) S. Li and J. Wu, *Org. Lett.*, 2011, **13**, 712; (*b*) Z. Chen, D. Zheng and J. Wu, *Org. Lett.*, 2011, **13**, 848; (*c*) H. Ren, Y. Luo, S. Ye and J. Wu, *Org. Lett.*, 2011, **13**, 2552; (*d*) G. Qiu, G. Liu, S. Pu and J. Wu, *Chem. Commun.*, 2012, **48**, 2903; (*e*) S. Ye, G. Liu, S. Pu and J. Wu, *Org. Lett.*, 2012, **14**, 70; (*f*) G. Qiu, Y. He and J. Wu, *Chem. Commun.*, 2012, **48**, 3836; (*g*) Z. Chen, L. Gao, S. Ye, Q. Ding and J. Wu, *Chem. Commun.*, 2012, **48**, 3975.

7 For reviews, see: (*a*) J. Montgomery, *Angew. Chem., Int. Ed.*, 2004, **43**, 3890; (*b*) E. Negishi, C. Coperet, S. Ma, S. Y. Liou and F. Liu, *Chem. Rev.*, 1996, **96**, 365; (*c*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*d*) R. Grigg and V. Sridharan, *J. Organomet. Chem.*, 1999, **576**, 65; (*e*) T. Miura and M. Murakami, *Chem. Commun.*, 2007, 217; (*f*) M. Malacria, *Chem. Rev.*, 1996, **96**, 289; (*g*) K. C. Nicolaou, T. Montagnon and S. A. Snyder, *Chem. Commun.*, 2003, 551; (*h*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134; (*i*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*j*) L. F. Tietze, G. Brasche and K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, Germany, 2006; (*k*) L. F. Tietze, M. A. Düfert, T. Hungerland, K. Oum and T. Lenzer, *Chem.–Eur. J.*, 2011, **17**, 8452.

8 For selected examples, see: (*a*) A. Arcadi, S. Cacchi, G. Fabrizi and L. Moro, *Eur. J. Org. Chem.*, 1999, 1137; (*b*) Y. Hu, Y. Zhang, Z. Yang and R. Fathi, *J. Org. Chem.*, 2002, **67**, 2365; (*c*) Y. Hu, K. J. Nawoschik, Y. Liao, J. Ma, R. Fathi and Z. Yang, *J. Org. Chem.*, 2004, **69**, 2235; (*d*) Y. Nan, H. Miao and Z. Yang, *Org. Lett.*, 2000, **2**, 297; (*e*) H.-A. Du, X.-G. Zhang, R.-Y. Tang and J.-H. Li, *J. Org. Chem.*, 2009, **74**, 7844; (*f*) Y. Liao, J. Smith, R. Fathi and Z. Yang, *Org. Lett.*, 2005, **7**, 2707; (*g*) Y. Liang, S. Tang, X.-D. Zhang, L.-Q. Mao, Y.-X. Xie and J.-H. Li, *Org. Lett.*, 2006, **8**, 3017; (*h*) C. Martínez, R. Álvarez and J. M. Aurrecoechea, *Org. Lett.*, 2009, **11**, 1083; (*i*) M. Nakamura, L. Ilies and S. Otsubo, *Angew. Chem., Int. Ed.*, 2006, **45**, 944.

9 Y. Li, X. Liu, H. Jiang and Z. Feng, *Angew. Chem., Int. Ed.*, 2010, **49**, 3338, and references cited therein.

10 (*a*) X. Chen, P. Lu and Y. Wang, *Chem.–Eur. J.*, 2011, **17**, 8105; (*b*) X. Chen, J. Jin, Y. Wang and P. Lu, *Chem.–Eur. J.*, 2011, **17**, 9920.

11 (*a*) Y. Luo, X. Pan and J. Wu, *Org. Lett.*, 2011, **13**, 1150; (*b*) Y. Luo, L. Hong and J. Wu, *Chem. Commun.*, 2011, **47**, 5298; (*c*) X. Pan, Y. Luo and J. Wu, *Chem. Commun.*, 2011, **47**, 8967; (*d*) Y. Luo and J. Wu, *Chem. Commun.*, 2011, **47**, 11137; (*e*) X. Pan, Y. Luo, G. Liu, S. Pu and J. Wu, *Adv. Synth. Catal.*, 2012, **354**, 171; (*f*) X. Pan, Y. Luo and J. Wu, *Org. Biomol. Chem.*, 2012, **10**, 1969; (*g*) Y. Luo and J. Wu, *Org. Lett.*, 2012, **14**, 1592.

12 Selected examples for Pd-catalyzed intermolecular C–O bond formation: (*a*) A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 4369; (*b*) Q. Shelby, N. Kataoka, G. Mann and J. Hartwig, *J. Am. Chem. Soc.*, 2000, **122**, 10718; (*c*) S. Harkal, K. Kumar, D. Michalik, A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monseesb and M. Beller, *Tetrahedron Lett.*, 2005, **46**, 3237.