ORGANIC
LETTERS

2005
Vol. 7, No. 14
3085−3088

Enynylation of 2-Iodo-4-(phenylchalcogenyl)-1-butenes via Intramolecular Chelation: Approach to the Synthesis of Conjugated Dienynes or Trienynes

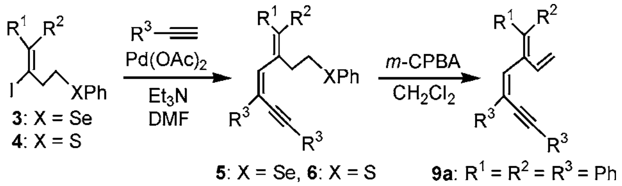
Min Shi,*,[†] Le-Ping Liu,[‡] and Jie Tang[‡]

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China, and Department of Chemistry, East China Normal University, 3663 Zhongshanbei Lu, Shanghai 200062, China

mshi@pub.sioc.ac.cn

Received May 12, 2005

ABSTRACT



2-Iodo-4-(phenylchalcogenyl)-1-butenes 3 and 4, which are derived from methylenecyclopropanes 1, can be enynylated with alkynes catalyzed by Pd(OAc)$_2$ to give conjugated dienynes 5 and 6 in the absence of any phosphine ligand and copper salt, and trienyne 9a can be obtained by oxidation of compound 5a. A plausible reaction mechanism has been proposed.

Methylenecyclopropanes (MCPs) **1** are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[1,2] Recently, we have been investigating the dihalogenation of MCPs **1** and the coupling reactions of the resulting products 2,4-diiodo-1-butenes **2** under mild conditions.[3,4] To explore the further transformation of **1**, we investigated the reactions of **1** with a variety of reactants having selenium or sulfur heteroatoms,[5] because selenium- or sulfur-containing organic molecules are extremely useful compounds in synthetic organic chemistry[6] and selenium or sulfur-ligated Pd(II) complexes are active catalysts for some coupling reactions.[7] Herein, we wish to report the synthesis of 2-iodo-4-(phenylchalcogenyl)-1-

---

[†] Chinese Academy of Sciences.

[‡] East China Normal University.

(1) For synthesis of MCPs: Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589.

(2) For recent reviews, see: (a) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (c) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867. See also: (d) Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298. (e) Oh, B. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6203. (f) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 270. (g) Yamago, S.; Nakamura, E. *J. Org. Chem.* **1990**, *55*, 5553. (h) Yamago, S.; Yanagawa, M.; Nakamura, E. *Chem. Lett.* **1999**, 879. (i) Lautens, M.; Han, W.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 4028. (j) Shi, M.; Chen, Y.; Xu, B. *Org. Lett.* **2003**, *5*, 1225. (k) Shi, M.; Xu, B. *Tetrahedron Lett.* **2003**, *44*, 3839. (l) Chen, Y.; Shi, M. *J. Org. Chem.* **2004**, *69*, 426.

(3) Shi, M.; Shao, L.-X. *Synlett* **2004**, 807.

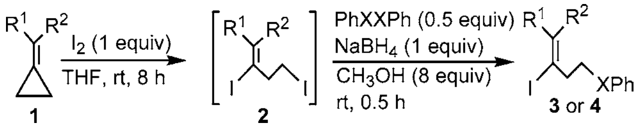
(4) Zhou, H.-W.; Huang, X.; Chen, W.-L. *Synlett* **2003**, 2080.

(5) (a) Liu, L.-P.; Shi, M. *J. Org. Chem.* **2004**, *69*, 2805. (b) Liu, L.-P.; Shi, M. *Chem. Commun.* **2004**, 2878. (c) Shi, M.; Wang, B.-Y.; Li, J. *Eur. J. Org. Chem.* **2005**, 759−765.

(6) For reviews on organoselenium and organosulfur compounds: (a) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986. (b) *Organoselenium Chemistry*; Back, T. G., Ed.; Oxford: New York, 1999. (c) *Organoselenium Chemistry*; Wirth, T., Ed.; Springer: Berlin, 2000. (d) Oae, S. *Organic Chemistry of Sulfur*; Plenum Press: New York, 1977; p 232. (e) *Top. Curr. Chem.* **1999**, *204*, 205 (Vol. Ed. Page, P. C. B.). (f) *Top. Curr. Chem.* **2003**, *230*, 231 (Vol. Ed. Steudel, R.).

10.1021/ol051101a CCC: $30.25

Table 1. Synthesis of 2-Iodo-4-(phenylchalcogenyl)-1-butenes **3** and **4** from MCPs **1** in a One-Pot Manner



entry	R^1, R^2	X	yield[a] of **3** or **4** (%)
1	C_6H_5, C_6H_5 (**1a**)	Se	**3a**, 88
2	*p*-MeC_6H_4, *p*-MeC_6H_4 (**1b**)	Se	**3b**, 88
3	*p*-$MeOC_6H_4$, *p*-$MeOC_6H_4$ (**1c**)	Se	**3c**, 92
4	*p*-ClC_6H_4, *p*-ClC_6H_4 (**1d**)	Se	**3d**, 78
5	*p*-FC_6H_4, *p*-FC_6H_4 (**1e**)	Se	**3e**, 86
6	*p*-$MeOC_6H_4$, H (**1f**)	Se	**3f**, 89
7	*o,p*-$(MeO)_2C_6H_3$, H (**1g**)	Se	**3g**, 79
8	*m,m,p*-$(MeO)_3C_6H_2$, H (**1h**)	Se	**3h**, 73
9	*p*-ClC_6H_4, H (**1i**)	Se	**3i**, 62
10	*p*-$MeOC_6H_4$, C_6H_5 (**1j**)	Se	**3j**, 83[b]
11	*o*-ClC_6H_4, C_6H_5 (**1k**)	Se	**3k**, 55[b]
12	C_6H_5, C_6H_5 (**1a**)	S	**4a**, 87
13	*p*-$MeOC_6H_4$, *p*-$MeOC_6H_4$ (**1c**)	S	**4c**, 90
14	*p*-ClC_6H_4, *p*-ClC_6H_4 (**1d**)	S	**4d**, 82

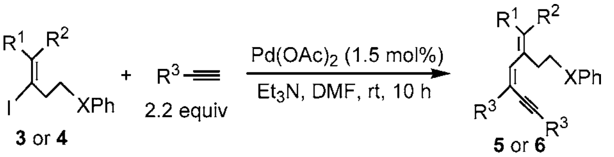
[a] Isolated yields. [b] Mixtures of *Z* and *E* isomers in a 1:1 ratio, determined by ^1H NMR spectroscopic data.

butenes **3** and **4** from MCPs **1** and subsequent enynylation with alkynes under mild conditions. In this coupling reaction, neither a phosphine ligand nor a copper salt was used, and the reaction proceeded smoothly at room temperature (20 °C) in most cases. A plausible reaction mechanism has been proposed on the basis of a ^{77}Se NMR spectroscopic investigation.

Compounds **3** and **4**, which have a vinylic iodine atom and a phenylchalcogenyl group, were synthesized from MCPs **1a**−**k** in a one-pot manner in THF at room temperature (Table 1). After the starting materials **1** were consumed, the in situ formed products **2** were sequentially treated with diphenyl diselenide or diphenyl disulfide, sodium borohydride, and methanol to give the compounds **3** and **4** in good to high yields (for experimental details, see the Supporting Information). The results are summarized in Table 1 (entries 1−14). For the unsymmetrical MCPs **1j**,**k**, the corresponding products **3j**,**k** were obtained as mixtures of *Z* and *E* isomers in a 1:1 ratio (Table 1, entries 10 and 11). For the unsymmetrical MCPs **1f**−**i**, the corresponding products **3f**−**i** were obtained as a single *Z* isomer (Table 1, entries 6−9). Their configurations were determined by NOESY spectroscopic data (see the Supporting Information).

Next we carried out the Sonogashira-type coupling reaction of compounds **3** and **4** with arylacetylenes or other alkynes catalyzed by $Pd(OAc)_2$ in DMF without any phosphine ligand, copper salt, or other additives. We found that the corresponding conjugated dienynes **5** and **6**,[8] derived from the enynylation of **3** and **4**, respectively, were obtained in moderate to good yields under mild conditions rather than the normal Sonogashira-type coupling reaction product (Table 2).[9,10]

Table 2. Enynylation of the Compounds **3** or **4** (1.0 Equiv)



entry	R^1, R^2	X	R^3	yield[a] of **5** or **6** (%)
1	C_6H_5, C_6H_5 (**3a**)	Se	C_6H_5	**5a**, 82
2	*p*-MeC_6H_4, *p*-MeC_6H_4 (**3b**)	Se	C_6H_5	**5b**, 72
3	*p*-$MeOC_6H_4$, *p*-$MeOC_6H_4$ (**3c**)	Se	C_6H_5	**5c**, 78
4	*p*-ClC_6H_4, *p*-ClC_6H_4 (**3d**)	Se	C_6H_5	**5d**, 77
5	*p*-FC_6H_4, *p*-FC_6H_4 (**3e**)	Se	C_6H_5	**5e**, 74
6	*p*-$MeOC_6H_4$, H (**3f**)	Se	C_6H_5	**5f**, 58
7	*o,p*-$(MeO)_2C_6H_3$, H (**3g**)	Se	C_6H_5	**5g**, 55
8	*m,m,p*-$(MeO)_3C_6H_2$, H (**3h**)	Se	C_6H_5	**5h**, 60
9	*p*-ClC_6H_4, H (**3i**)	Se	C_6H_5	**5i**, 64
10	*p*-$MeOC_6H_4$, C_6H_5 (**3j**)[b]	Se	C_6H_5	**5j**, 69[b]
11	*o*-ClC_6H_4, C6H5 (**3k**)[b]	Se	C_6H_5	**5k**, 73[b]
12	C_6H_5, C_6H_5 (**3a**)	Se	*n*-C_4H_9	**5l**, 42[c]
13	C_6H_5, C_6H_5 (**3a**)	Se	CH_2OH	**5m**, 38[c]
14	C_6H_5, C_6H_5 (**3a**)	Se	*p*-$CH_3C_6H_4$	**5n**, 78
15	C_6H_5, C_6H_5 (**3a**)	Se	*p*-$CH_3OC_6H_4$	**5o**, 86
16	C_6H_5, C_6H_5 (**3a**)	Se	*p*-ClC_6H_4	**5p**, 84
17	C_6H_5, C_6H_5 (**3a**)	Se	*p*-BrC_6H_4	**5q**, 85
18	C_6H_5, C_6H_5 (**3a**)	Se	*o*-$CF_3C_6H_4$	**5r**, 78
19	C_6H_5, C_6H_5 (**4a**)	S	C_6H_5	**6a**, 78
20	*p*-$MeOC_6H_4$, *p*-$MeOC_6H_4$ (**4c**)	S	C_6H_5	**6c**, 74
21	*p*-ClC_6H_4, *p*-ClC_6H_4 (**4d**)	S	C_6H_5	**6d**, 72

[a] Isolated yields. [b] Mixtures of *Z* and *E* isomers in a 1:1 ratio, determined by ^1H NMR spectroscopic data. [c] Conducted at 80 °C.

Their structures were determined by ^1H and ^{13}C NMR spectroscopic data, HRMS, and microanalysis. The X-ray crystal structure of **5d** is provided in the Supporting Information.[11]

Using phenylacetylene and other arylacetylenes as coupling reagents, the reactions were conducted at room temperature and the corresponding dienynes were obtained

---

(7) For examples: (a) Yao, Q.-W.; Kinney, E. P.; Zheng, C. *Org. Lett.* **2004**, *6*, 2997. (b) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287. (c) Zim, D.; Gruber, A. S.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *2*, 2881. (d) Zim, D.; Monteiro, A. L.; Dupont, J. *Tetrahedron Lett.* **2000**, *41*, 8199. (e) Silveira, P. B.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Tetrahedron Lett.* **2002**, *43*, 2327. (f) Dupont, J.; Gruber, A. S.; Fonseca, G. S.; Monteiro, A. L.; Ebeling, G.; Burrow, R. A. *Organometallics* **2001**, *20*, 171.

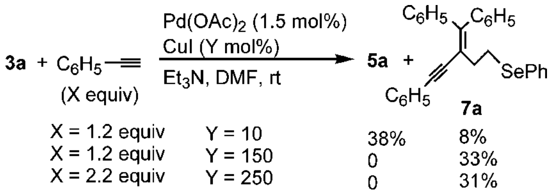
(8) Conjugated dienynes are found to be integral parts in some medicinal molecules: (a) Olivo, H. F.; Velazquez, F.; Trevisam, H. C. *Org. Lett.* **2000**, *2*, 4055. (b) Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555. (c) Fiandanese, V.; Babudvi, F.; Marchese, G.; Punzi, A. *Tetrahedron* **2002**, *58*, 9547.

(9) There are very few examples of enynylation with alkynes; see: (a) Pal, M.; Parasuraman, K.; Subramanian, V.; Dakarapu, R.; Yeleswarapu, K. R. *Tetrahedron Lett.* **2004**, *45*, 2305. (b) Pottier, L. R.; Peyrat, J. F.; Alami, M.; Brion, J. D. *Synlett* **2004**, 1503.

(10) This reaction also can be performed in toluene, tetrahydrofuran (THF), dichloromethane, acetonitrile, and dimethylacetamide as well, but **5a** was obtained in lower yields or a prolonged reaction time was required. Other bases such as sodium hydrogen carbonate, potassium carbonate, and cesium carbonate were not as effective as Et_3N (see the Supporting Information).

(11) The crystal data of **5d** have been deposited in the CCDC with the file number 246799: empirical formula, $C_{38}H_{28}Cl_2Se$; formula weight, 634.46; crystal color, habit, yellow, prismatic; crystal dimensions, 0.505 × 0.278 × 0.093 mm; crystal system, monoclinic; lattice type, primitive; lattice parameters, $a = 9.322(3)$ Å, $b = 28.033(10)$ Å, $c = 25.438(9)$ Å, $\alpha = 90°$, $\beta = 92.491(8)°$, $\gamma = 90°$, $V = 6642(4)$ Å^3; space group, $P2_1/c$; $Z = 8$; $D_{\text{calcd}} = 1.269$ g/cm^3; $F_{000} = 2592$; diffractometer, Rigaku AFC7R; residuals, $R = 0.0850$, $R_w = 0.2072$.

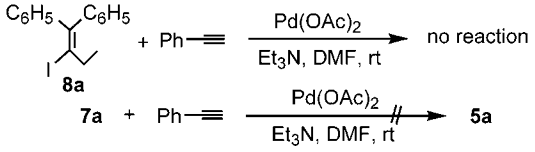
Scheme 1. Effect of Copper(I) Iodide in the Reaction



in moderate to good yields (Table 2, entries 1−11 and 14−21). The substituents on the benzene rings of compounds **3**, **4**, and arylacetylenes did not significantly affect the yields of **5** and **6** (Table 2, entries 1−11 and 14−21). Using other alkynes such as *n*-hexyne and propynol as coupling reagents, the reactions were conducted at 80 °C and the products were obtained in moderate yields (Table 2, entries 12 and 13). The normal Sonogashira-type coupling reaction[12] product **7a** can be obtained in low yield along with the formation of dienyne **5a** in the presence of copper(I) iodide (10 mol %) in the reaction of compound **3a** with phenylacetylene. When the employed amount of copper(I) iodide was increased to 150 or 250 mol %, compound **7a** was formed as a single product in moderate yields without the formation of dienyne **5a** (Scheme 1).

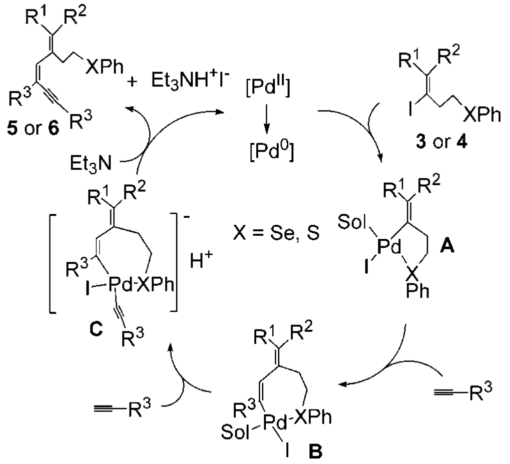
The control experiment showed that the selenium or sulfur atom in **3** or **4** is crucial for this coupling reaction because no reaction occurred using compound **8a**, 1,1-diphenyl-2-iodo-1-butene, as a starting material under identical conditions (Scheme 2). Compound **7a** cannot be transformed into compound **5a** with phenylacetylene under the same conditions (Scheme 2).

Scheme 2. Control Experiments in This Reaction



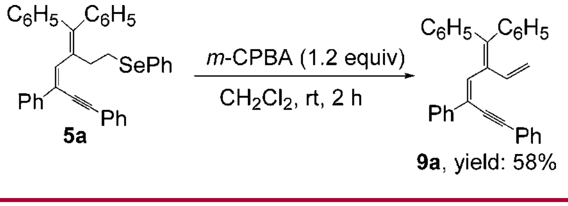
The mechanism for this unusual enynylation of 2-iodo-4-(phenylchalcogenyl)-1-butenes **3** and **4** with alkynes is described in Scheme 3 on the basis of the above results. The in situ formed Pd(0) catalyst inserts into compounds **3** and **4** via an oxidative addition to afford the Pd intermediate **A**, which was chelated by the intramolecular phenylchalcogenyl group.[13,14] The evidence for this intramolecular chelation was confirmed on the basis of a ^{77}Se NMR spectroscopic investigation (see the Supporting Information). The Pd intermediate **A** inserts into an alkyne molecule to produce the intermediate **B** regioselectively. Intermediate **B** adds into another alkyne molecule to afford intermediate **C**, which produces the dienynes **5** and **6** via a reductive elimination in the presence of base and regenerates the Pd(0) catalyst. These coordinating groups might retard the direct transmetalation of intermediate **A** with an alkyne (Scheme 3), and carbopalladation across an alkyne would be operative to give the intermediate **B**, in which a rather labile seven-membered chelate would enable its transmetalation with another alkyne, giving an alkenyl(alkynyl)palladium(II) species (intermediate **C**), a product-forming intermediate. Addition of CuI would facilitate the direct transmetalation of intermediate **A** with an alkyne, resulting in the normal Sonogashira product.

Scheme 3. Plausible Reaction Mechanism



Furthermore, oxidation of the dienyne **5a** with *m*-CPBA furnishes the corresponding trienyne **9a** by a selenoxide elimination[15] in 58% yield under mild conditions (Scheme 4).

Scheme 4. Transformation of Dienyne **5a** to Trienyne **9a**



In conclusion, we have found a one-pot method for the synthesis of 2-iodo-4-(phenylchalcogenyl)-1-butenes **3** and **4** from MCPs **1** and a synthetic approach to the formation

---

[12] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. See also: (b) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 5. (c) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer-Verlag: Berlin, 1998; Chapter 10. (d) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* **1995**, *27*, 127. (e) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M. Ed.; Pergamon: New York, 1991; Vol. 3, Chapter 2.4. There have been a few Sonogashira-type coupling reactions performed without copper salts; see: (f) Liang, B.; Dai, M.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391 and references therein.

[13] (a) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917. (b) Bedford, R. B. *Chem. Commun.* **2003**, 1787. (c) Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 9058.

[14] There is a significant chemical shift change of the ^{77}Se NMR spectrum between compound **3a** and the mixture of compounds **3a** and $Pd(OAc)_2$ (see the Supporting Information).

of dienynes **5** and **6** and trienyne **9a** by the subsequent Pd-catalyzed enynylation of the products with alkynes under mild conditions. To the best of our knowledge, this is a good example of intramolecular phenylchalcogenyl group chelation promoted enynylation of vinylic iodides with alkynes.

Acknowledgment. We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), the Shanghai Municipal Committee of Science and Technology, the Chinese Academy of Sciences (No. KGCX2-210-01), and the National Natural Science Foundation of China for financial support (Nos. 20025206, 203900502, and 20272069).

Supporting Information Available: Spectroscopic data (^{1}H, ^{13}C, ^{77}Se and NOESY NMR spectroscopic data), HRMS, analytical data, and X-ray crystal structures of the compounds shown in Tables 1 and 2 and Schemes 1, 2, and 4 and a detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051101A

---

(15) For recent reviews, see: (a) Reich, H. J.; Wollowitz, S. *Org. React.* **1993**, *44*, 1−296. (b) Back, T. G. In *Organoselenium Chemistry*, Back, T. G., Ed.; Oxford University Press: Oxford, U.K., 1999; pp 7−33. (c) Nishibayashi, Y.; Uemura, S. *Top. Curr. Chem.* **2000**, *208*, 201−235 (Vol. Ed. Wirth, T.).