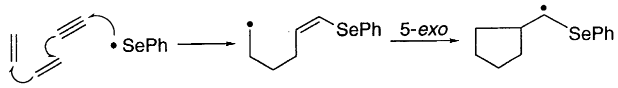
Domino Radical Reactions

Highly Selective Sequential Addition and Cyclization Reactions Involving Diphenyl Diselenide, an Alkyne, and Alkenes under Visible-Light Irradiation[**]

*Kaname Tsuchii, Mikio Doi, Toshikazu Hirao, and Akiya Ogawa**

Dedicated to Professor Noboru Sonoda
on the occasion of his 70th birthday

The development of highly selective carbon–carbon bond-forming reactions with the simultaneous introduction of heteroatom functional groups is of great importance in organic synthesis. A variety of compounds with carbon–carbon unsaturation can be utilized for this purpose.[1] However, the use of several such unsaturated compounds together in a radical reaction usually results in their polymerization. In contrast, we have discovered that the addition of diphenyl diselenide, which has an appropriate carbon-radical-capturing ability,[2] depresses the undesired polymerization and makes it possible to carry out a highly selective sequential addition of $(PhSe)_2$ to unsaturated compounds.[3] Herein, we report a novel four-component coupling of an alkyne, two olefin molecules, and diphenyl diselenide, which proceeds through selective bond formation to connect these four molecules, and a subsequent 5-*exo* cyclization, as depicted in Scheme 1.



Scheme 1. Sequential addition and cyclization strategy.

We started our study of this type of reaction by examining the combination of alkynes that bear an electron-withdrawing group with alkenes that bear an electron-donating group.[4] When a mixture of ethyl propiolate (**1**), *n*-butyl vinyl ether

---

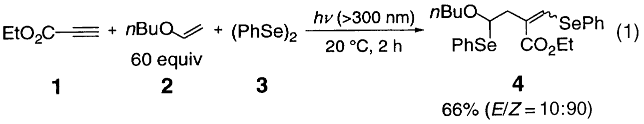
[*] Prof. A. Ogawa, K. Tsuchii
Department of Chemistry, Faculty of Science
Nara Women's University
Kitauoyanishi-machi, Nara 630–8506 (Japan)
Fax: (+81) 742-20-3979
E-mail: a.ogawa@cc.nara-wu.ac.jp
M. Doi, Prof. T. Hirao
Department of Applied Chemistry, Faculty of Engineering
Osaka University

[**] This research was supported by a Grant-in-Aid for Scientific Research on Priority Areas (A) (No. 14044063) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

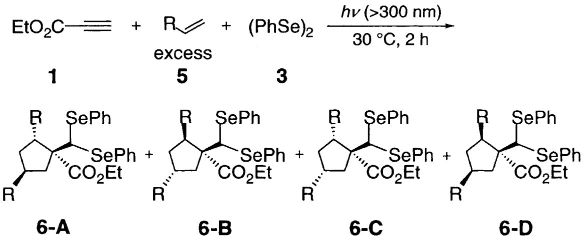
Supporting information for this article, including full procedures and characterization data, is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/ange.200250790

(**2**), and diphenyl diselenide (**3**) was irradiated through pyrex with a tungsten lamp ($h\nu > 300$ nm) in the absence of solvent, none of the desired sequential addition and cyclization product was formed, and instead the corresponding three-component coupling product **4** was formed selectively, as shown in Equation (1).[3]



Surprisingly, however, when an electron-deficient alkene was employed for this reaction instead of *n*-butyl vinyl ether, the desired sequential addition and 5-*exo* radical cyclization took place selectively. For example, the reaction of *tert*-butyl acrylate (**5a**) under the same conditions provided **6a** in 61 % yield (Scheme 2 and Table 1, entry 1),[5] along with small amounts of by-products, such as the corresponding acyclic three-component coupling product and the adduct of $(PhSe)_2$ with **1**. The use of $(PhS)_2$ in place of $(PhSe)_2$ under similar reaction conditions led to the polymerization of the olefins and did not provide the desired sequential addition and cyclization product, which is probably a result of the poor carbon-radical-capturing ability of $(PhS)_2$. On the other hand, when $(PhTe)_2$ was used, most of the starting ethyl propiolate (**1**) was recovered, which is probably a result of the lower reactivity of the phenyltelluro radical (PhTe·) toward unsaturated bonds. When a similar reaction was conducted in the presence of nBu$_3$SnH as a mediator, most of the starting ethyl propiolate (**1**) was also recovered.[6] Thus, the appropriate carbon-radical-trapping ability of $(PhSe)_2$ facilitates its selective sequential addition and cyclization with an alkyne and two olefin molecules.[7]



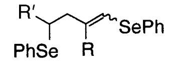
Scheme 2. Synthesis of substituted cyclopentanes from ethyl propiolate, an alkene, and $(PhSe)_2$ through sequential radical addition and cyclization.

Table 1: Sequential addition and cyclization reactions of ethyl propiolate, alkenes, and $(PhSe)_2$.[a]

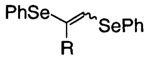
Entry	**6**	R	Yield [%][b]	**A/B/C/D**
1	**a**	tBuO$_2$C	61	72:11:11:6
2	**b**	MeO$_2$C	49	79:21:0:0
3	**c**	NC	41	18:14:60:8
4	**d**	Me(O)C	58	71:16:7:6

[a] Reaction conditions: ethyl propiolate (0.20 mmol), $(PhSe)_2$ (1 equiv), alkene (40–60 equiv), 30 °C, $h\nu$: tungsten lamp (500 W, pyrex). [b] Yield of isolated products.

Methyl acrylate, acrylonitrile, and methyl vinyl ketone can be employed for this sequential addition and cyclization reaction (Table 1). However, when alkynes without an electron-withdrawing group were used in place of ethyl propiolate, the desired product was obtained in very poor yield. For example, the main products isolated from the reactions of phenylacetylene and 1-octyne were the corresponding three-component coupling products (**7a** and **7b**, respectively) and bisselenation products (**8a** and **8b**, respectively).

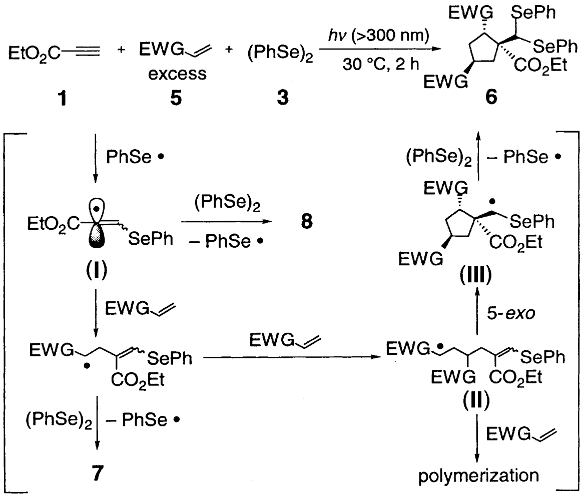


7a (R = Ph, R' = tBuO$_2$C)
7b (R = n-C$_6$H$_{13}$, R' = tBuO$_2$C)



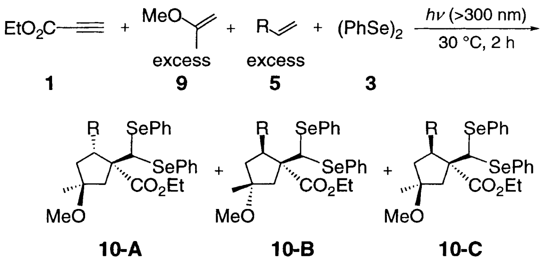
8a (R = Ph)
8b (R = n-C$_6$H$_{13}$)

A possible mechanistic pathway is shown in Scheme 3: 1) Upon irradiation with light of wavelength over 300 nm, diphenyl diselenide (**3**; $\lambda_{max} = 330$ nm) undergoes homolytic dissociation to generate PhSe·,[8] which adds to ethyl propiolate (**1**) selectively to form the β-phenylseleno-substituted vinylic radical **I**;[9,10] 2) the vinylic radical **I** reacts with two olefin molecules to produce the secondary alkyl radical **II**; 3) the radical intermediate **II** cyclizes in a 5-*exo* manner to give the α-seleno radical **III**, which in turn undergoes an S$_H$2 reaction with $(PhSe)_2$ to provide **6**.



Scheme 3. Proposed mechanism for the formation of cyclopentanes **6** (and by-products) through sequential radical addition and cyclization; EWG = electron-withdrawing group.

We next examined the four-component coupling reaction in the presence of two types of olefin: an olefin with an electron-withdrawing group and an olefin with an electron-donating group. When the reaction of diphenyl diselenide (**3**) with ethyl propiolate (**1**) and a large excess of both *tert*-butyl acrylate (**5a**) and 2-methoxypropene (**9**) was performed in the absence of solvent, sequential addition of the diselenide to the alkyne, of the resulting intermediate to the electron-rich olefin **9**, and of the next intermediate to the electron-poor olefin (**5a**), followed by a 5-*exo* radical cyclization, took place to provide the corresponding cyclic four-component coupling product **10a** in good yield (Scheme 4 and Table 2, entry 1).[11] Small amounts of by-products, such as the corresponding acyclic three-component coupling product and the adduct of $(PhSe)_2$ with the alkyne, were also formed. Similar conditions can be employed with methyl acrylate, acrylonitrile, and methyl vinyl ketone as the electron-deficient alkenes, and the corresponding cyclic four-component coupling products are obtained selectively in good yields (Table 2, entries 2–4). In the case of acrylonitrile, the desired four-component coupling reaction proceeds successfully to give the corresponding five-membered-ring product in 76% yield (Table 2, entry 3).



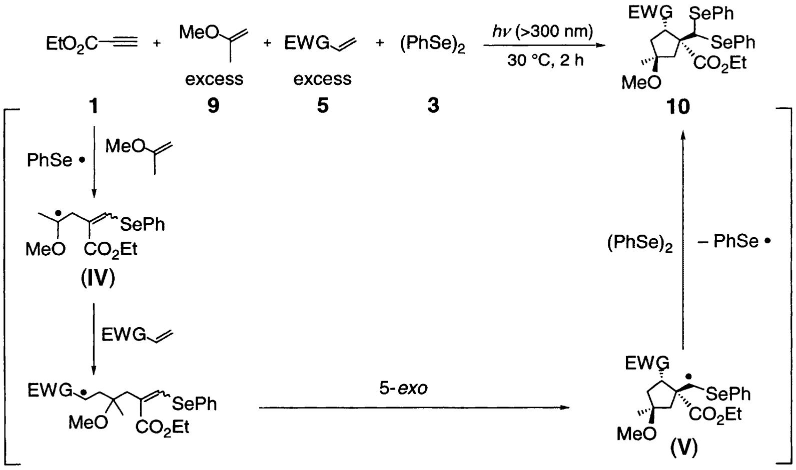
Scheme 4. Four-component coupling of ethyl propiolate, 2-methoxypropene, a second alkene, and $(PhSe)_2$.

Table 2: Four-component coupling of ethyl propiolate, 2-methoxypropene, a second alkene, and $(PhSe)_2$.[a]

Entry	**10**	R	Yield [%][b]	**A/B/C**
1	**a**	tBuO$_2$C	47	81:19:0
2	**b**	MeO$_2$C	47	43:37:20
3	**c**	NC	76	60:14:26
4	**d**	Me(O)C	41	72:24:4

[a] Reaction conditions: ethyl propiolate (0.20 mmol), $(PhSe)_2$ (1 equiv), 2-methoxypropene (10–30 equiv), $RCH{=}CH_2$ (10–30 equiv), *hν*: tungsten lamp (500 W, pyrex). [b] Yield of isolated products.

The formation of **10** may be explained by the following proposed mechanism (see Scheme 5): 1) PhSe·, generated from $(PhSe)_2$ by irradiation with light of wavelength over 300 nm, adds to ethyl propiolate (**1**) selectively to form the β-phenylseleno-substituted vinylic radical **I**; 2) the vinylic radical **I** reacts with an electron-rich olefin preferentially to produce the α-methoxyl radical **IV**; 3) the radical intermediate **IV** reacts with an electron-poor olefin and then cyclizes to provide the α-seleno radical **V**, which is trapped with $(PhSe)_2$ to yield the cyclic four-component coupling product **10**, with regeneration of PhSe·.



Scheme 5. Proposed mechanism for the formation of cyclopentanes **10** through sequential radical addition and cyclization.

In summary, diphenyl diselenide has proved to be an excellent mediator for highly selective sequential bond formation between unsaturated compounds. The rate of carbon-radical-capturing by $(PhSe)_2$, appropriate for these transformations, combined with the efficiency of the 5-*exo* radical cyclization, prevent the undesired potential polymerization and make it possible to carry out four-component coupling reactions of unsaturated compounds and $(PhSe)_2$.

Experimental Section

Representative procedure: Ethyl propiolate (19.6 mg, 0.20 mmol), 2-methoxypropene (389 mg, 5.4 mmol), and acrylonitrile (106 mg, 2.0 mmol) were placed in a pyrex glass tube (10 mm × 75 mm) under a N_2 atmosphere. The mixture was irradiated with a tungsten lamp (500 W) at 30 °C for 2 h, and diphenyl diselenide (62.4 mg, 0.20 mmol in total) was added in eight portions during the irradiation.[12] When the reaction was complete, the purification of the products was performed on a recycling preparative HPLC instrument (Japan Analytical Industry Co. Ltd., Model LC-908) equipped with JAIGEL-1H and -2H columns, with $CHCl_3$ as the eluent, to yield **10c** (76%) as a stereoisomeric mixture (60:26:14). The stereochemistry of the diastereoisomers of **10c** was determined by NOE experiments.

10c: Pale yellow oil; ^{1}H NMR (major isomer; 300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.29$ (s, 3H; CH_3), 1.34 (t, $^3J(H,H) = 7.2$ Hz, 3H; $CH_3CH_2O_2C$), 1.95 (dd, $^3J(H,H) = 12.6$ Hz, $^2J(H,H) = 13.2$ Hz, 1H; CCH_2CH), 2.30 (ddd, $^4J(H,H) = 2.1$ Hz, $^3J(H,H) = 6.3$ Hz, $^2J(H,H) = 13.2$ Hz, 1H; CCH_2CH), 2.32 (dd, $^4J(H,H) = 2.1$ Hz, $^2J(H, H) = 14.7$ Hz, 1H; CCH_2C), 2.42 (d, $^2J(H,H) = 14.7$ Hz, 1H; CCH_2C), 2.90 (s, 3H; CH_3O), 3.50 (dd, $^3J(H,H) = 6.3$, 12.6 Hz, 1H; NCCH), 4.16–4.34 (m, 2H; $CH_3CH_2O_2C$), 4.58 (s, 1H; $(PhSe)_2CH$), 7.15–7.31 (m, 6H; Ph), 7.43–7.46 ppm (m, 4H; Ph); ^{13}C NMR (major isomer; 75 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 13.9$, 21.0, 38.6, 42.4, 45.6, 49.1, 54.7, 62.5, 64.6, 82.3, 119.6, 128.2, 128.3, 129.3, 134.2, 134.8, 172.2 ppm; IR (NaCl): $\tilde{\nu} = 2977$, 2245 (C≡N), 1718 (C=O), 1578, 1478, 1439, 1369, 860, 746, 690 cm^{-1}; HRMS (*m/z*): calcd for $C_{24}H_{27}NO_3Se_2$: 537.0322; found: 537.0311; elemental analysis: calcd for $C_{24}H_{27}NO_3Se_2$: C 53.84, H 5.08, N 2.62; found: C 53.50, H 5.00, N 2.85.

Received: December 17, 2002
Revised: April 11, 2003 [Z50790]

Keywords: alkenes · alkynes · cyclizations · domino reactions · radicals

---

[1] *Radicals in Organic Synthesis, Vol. 1* and *2*, (Eds.: P. Renaud, M. P. Sibi), VCH, Weinheim, **2001**.

[2] The rate constant for the S_H2 reaction of the 5-hexenyl radical with $(PhSe)_2$ is $1.2\times10^7\,\text{M}^{-1}\,\text{s}^{-1}$: a) G. A. Russell, H. Tashtoush, *J. Am. Chem. Soc.* **1983**, *105,* 1398–1399; b) M. J. Perkins, E. S. Turner, *J. Chem. Soc. Chem. Commun.* **1981**, 139–140.

[3] a) A. Ogawa, M. Doi, K. Tsuchii, T. Hirao, *Tetrahedron Lett.* **2001**, *42*, 2317–2319; b) A. Ogawa, I. Ogawa, N. Sonoda, *J. Org. Chem.* **2000**, *65*, 7682–7685; c) A. Ogawa, M. Doi, I. Ogawa, T. Hirao, *Angew. Chem.* **1999**, *111*, 2066–2069; *Angew. Chem. Int. Ed.* **1999**, *38*, 2027–2029.

[4] B. Giese, *Angew. Chem.* **1983**, *95*, 771–782; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753–764.

[5] The stereochemistry of the sequential addition and cyclization products was determined by NOE experiments (see Supporting Information).

[6] E. Lee, C. U. Hur, Y. H. Rhee, Y. C. Park, S. Y. Kim, *J. Chem. Soc. Chem. Commun.* **1993**, 1466–1468.

[7] The use of $(p\text{-CF}_3\text{-C}_6\text{H}_4\text{Se})_2$ and $(MeSe)_2$ in place of $(PhSe)_2$ led to the successful formation of the corresponding four-component coupling products. However, when $(PhCH_2Se)_2$ was used none of the desired four-component coupling products were obtained, probably because of C–Se bond cleavage in $(PhCH_2Se)_2$.

[8] U. Schmidt, A. Müller, K. Markau, *Chem. Ber.* **1964**, *97*, 405–414.

[9] For the radical addition of $(PhSe)_2$ to alkynes, see: a) T. G. Back, M. V. Krishna, *J. Org. Chem.* **1988**, *53*, 2533–2536; b) A. Ogawa, H. Yokoyama, K. Yokoyama, T. Masawaki, N. Kambe, N. Sonoda, *J. Org. Chem.* **1991**, *56,* 5721–5723; c) A. Ogawa, N. Takami, M. Sekiguchi, H. Yokoyama, H. Kuniyasu, I. Ryu, N. Sonoda, *Chem. Lett.* **1991**, 2241–2242.

[10] In general, vinyl radicals are believed to be a stereoisomeric mixture of σ radicals that are in rapid equilibrium: a) R. W. Fessenden, R. H. Schuler, *J. Chem. Phys.* **1963**, *39*, 2147–2195. In contrast, α-aryl-substituted vinylic radicals are thought to be π radicals: b) L. A. Singer, J. Chen, *Tetrahedron Lett.* **1969**, *10*, 4849–4854. The corresponding radical species derived from ethyl propiolate is thought to be a vinylic π radical: c) C. Galli, A. Guarnieri, H. Koch, P. Mencarelli, Z. Rappoport, *J. Org. Chem.* **1997**, *62*, 4072–4077; d) H. Rubin, H. Fischer, *Helv. Chim. Acta* **1996**, *79*, 1670–1682; e) J. O. Metzger, M. Blumenstein, *Chem. Ber.* **1993**, *126*, 2493–2499.

[11] The stereochemistry of the four-component coupling products was determined by NOE experiments (see Supporting Information).

[12] The four-component coupling of ethyl propiolate (**1**) with olefins **5** and **9** and $(PhSe)_2$ described requires the use of excess amounts of the olefins. When the molar ratio of **5** to **1** or **9** to **1** was decreased, the yield of the four-component coupling product also decreased, and the adduct of $(PhSe)_2$ with **1** was formed as a by-product.