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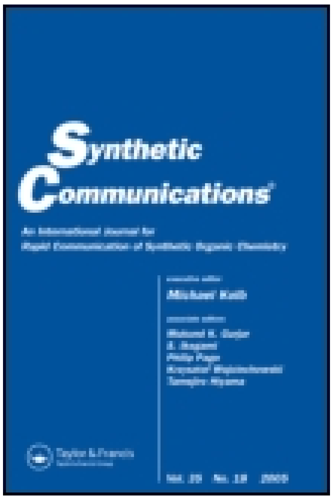

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A FACILE REGIO- AND STEREOCONTROLLED SYNTHESIS OF (Z)-1,3-ENYLNYLSELENIDES VIA CROSS COUPLING OF (E)-α-IODOVINYLSELENIDES WITH TERMINAL ALKYNES

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Published online: 21 Aug 2006.

To cite this article: Ping Zhong & Nanping Huang (2002) A FACILE REGIO- AND STEREOCONTROLLED SYNTHESIS OF (Z)-1,3-ENYLNYLSELENIDES VIA CROSS COUPLING OF (E)-α-IODOVINYLSELENIDES WITH TERMINAL ALKYNES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:1, 139-145, DOI: 10.1081/SCC-120001521

To link to this article: http://dx.doi.org/10.1081/SCC-120001521

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SYNTHETIC COMMUNICATIONS, 32(1), 139–145 (2002)

A FACILE REGIO- AND STEREOCONTROLLED SYNTHESIS OF (*Z*)-1,3-ENYLNYLSELENIDES VIA CROSS COUPLING OF (*E*)-α-IODOVINYLSELENIDES WITH TERMINAL ALKYNES

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ABSTRACT

(*Z*)-1,3-Enylnylselenides were conveniently obtained under mild condition via the cross coupling of the corresponding (*E*)-α-iodovinylselenides with terminal alkynes in the presence of $Pd(PPh_3)_4$ and CuBr.

The conjugated enynes are of great in organic synthesis,[1,2] because they are incorporated in a number of natural products and can be readily converted in a stereospecific manner into the corresponding diene system.[3,4] A number of methods for the preparation of conjugated enynes have been previously reported. The synthesis of enynes has been performed using coupling of halloalkynes with vinyl metals like as vinylboron,[5] vinylcopper,[6] vinylzinc,[7] vinylaluminum,[8] vinylaluminum reagents[9] or vinylzirconium.[10]

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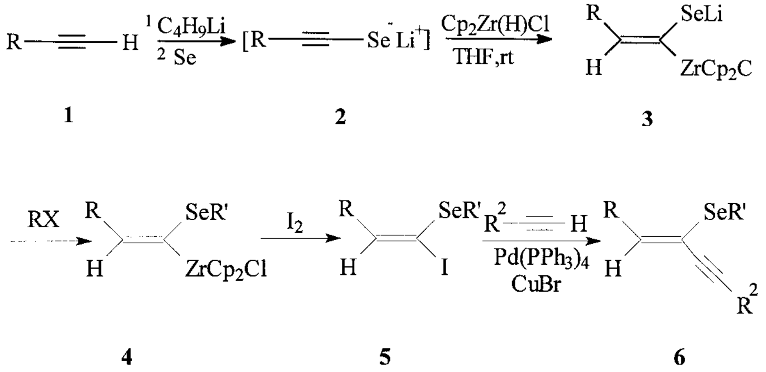
The synthesis of enynes has also been performed using coupling of vinylic iodides with terminal alkynes.[11]

Recently, it has become popular that *syn*-addition of Schwarte's reagent onto a alkyne followed by treatment with electrophiles provides a functionalized alkene with a high level of stereochemical purity.[12] We had tried to synthesize (*Z*)-1,3-enylnylselenides *via* coupling of (*E*)-selanylvinylzirconium with alkynyl halides like phenylethynyl iodide, but failed to do it. It was reported that the cross-couple of (*E*)-α-selanylvinylzirconium with alkynyliodonium tosylates afforded (*Z*)-1,3-enylnylselenides,[13] but the alkynyliodonium tosylates were not easily available. Herein we report the stereoselective formation of selanyl-substituted 1,3-enynes *via* a new carbon–carbon bond-forming reaction, involving the coupling of (*E*)-α-iodovinylselenides with terminal alkynes in the presence of $Pd(PPh_3)_4$ and CuBr.

Treatment of terminal alkynes **1** with butyllithium in THF at 0°C gave lithium alkynylselenolate anions **2**. Treatment of **2** with $Cp_2Zr(H)Cl$[14] in THF at room temperature afforded the α-zirconated vinylselenolate intermediates **3**,[15] which by treatment with an alkyl halide afforded the α-zirconated vinyl alkylselenide intermediates **4**, **4** reacted with iodine at room temperature to afford (*E*)-α-iodovinylselenides **5**. In one pot reaction, the crude iodides **5** were treated directly with terminal alkynes under Pd–Cu catalysis to accomplish coupling reactions, work up and chromatography of the concentrated reaction mixtures on silica gel afforded the pure (*Z*)-1,3-enynylselenides **6** in good overall yields (see Table and Scheme **1**).



R = Ph, n-C_4H_9, CH_2OCH_3; $R^1X = CH_3I$, C_2H_5Br, n-C_4H_9Br; R^3= Ph, n- C_4H_9, CH_2OCH_3

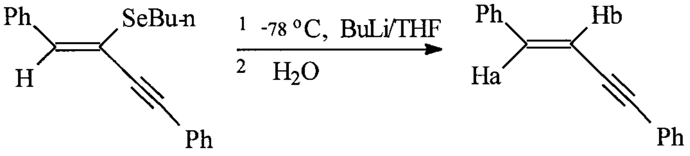
Scheme 1.

Table 1. Synthesis of (*Z*)-1,3-Enylylselenides **6a–i**[a]

Product	R	R^1	R^2	Yield (%)[b]
6a	Ph	n-C_4H_9	Ph	54
6b	Ph	Me	CH_3OCH_2	50
6c	Ph	Et	CH_3OCH_2	45
6d	Ph	n-C_4H_9	n-C_4H_9	48
6e	CH_3OCH_2	n-C_4H_9	Ph	45
6f	CH_3OCH_2	Et	Ph	46
6g	n-C_4H_9	Et	Ph	51

[a] The products were identified by MS, ^{1}H NMR and IR spectroscopy.
[b] Isolated yield.

All the compounds **6a**, **6b**,[13] **6c**,[13] **6d**, **6e**, **6f**[13] and **6g**[13] were fully characterized by NMR spectroscopy. The configuration of selenoenyne **6a** could be confirmed from compound **7** which was obtained by treatment of **6a** with *n*-butyllithium in THF followed by hydrolysis; the reaction occurs stereoselectively (Scheme **2**).[16,17] Particularly diagnostic for the stereochemistry of **6** was the coupling constant between the vicinal protons H_a and H_b which show a typical value of J_{HH} of 16 Hz which is consistent with an *E* configuration. Therefore, we could confirm that the 1,3-enynylselenides **6** have *Z* configuration.

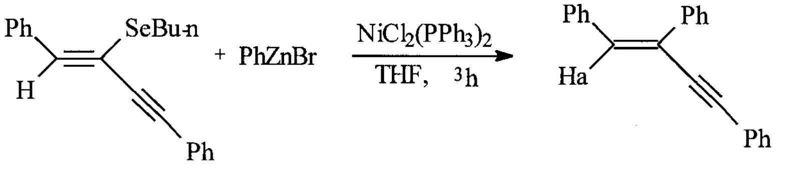


6a **7**

Scheme 2.

(*Z*)-1,3-enynylselenides **6** are important useful synthetic intermediates and are effective precursors for preparation of conjugated enynes. For example, the coupling of (*Z*)-1,3-enynylselenide **6a** with PhZrBr at room temperature in the presence of $NiCl_2(PPh_3)_2$ for 3 h to give 1,3-enyne **8** in 61% yield (Scheme **3**).

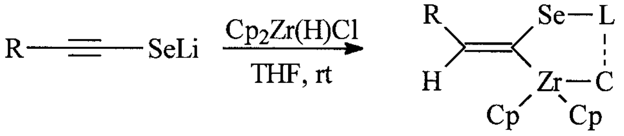
It was reported[16] that hydrozirconation of 1-(butylseleno)-2-alkynes resulted in a mixture of the α-zirconated vinyl selenide and β-zirconated



6a **8**

Scheme 3.

vinyl selenide. Hydrozirconation of Lithium alkynylselenolate anions, however, resulted in the α-zirconated vinylselenolate intermediates **3**. In this way a plausible mechanism to explain the exclusive formation of the α-zircozirconated vinylselenolate intermediates **3**, and the necessity of only 1.0 equiv. of Schwartz's reagent, is based on the postulated formation of a cyclic five-membered intermediate **9** (Scheme **4**).



2 **9**

Scheme 4.

In conclusion, the hydrozirconation/coupling strategy provides a direct route to (Z)-1,3-enynylselenides from terminal alkynes. The method has some attractive advantages such as readily available starting materials, mild reaction conditions, simple procedure (one pot reaction), lower reaction time and high regio- and stereoselectivity.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer with TMS as internal standard. Mass spectra were obtained on a Finnigan 4021 mass spectrometer. IR spectra were taken on a Shimadzu IR400 spectra meter. All reactions were carried out in pre-dried glassware (140°C, 4h) and cooled under a stream of dry nitrogen. All solvents were dried, deoxygenated and redistilled before use.

General Procedure for the Synthesis of 6a–g

To a solution of the terminal alkyne **1** (2.0 mmol) in THF (8 ml) under a nitrogen atmosphere was added butyllithium (2.0 mmol, 2 ml, 1.0 M in hexane) at 0°C, and the solution was stirred for 15 min. The mixture was allowed to reach room temperature, and elemental selenium (0.158 g, 2.0 mmol) was added. After total disappearance of selenium, the solid $Cp_2Zr(H)Cl$ (2 mmol) was added rapidly. The resulting mixture was stirred for 30 min. The alkyl halide (2.0 mmol) was added, and the reaction mixture was stirred at room temperature for an additional 1 h. The resulting solution was cooled to 0°C and I_2 (2 mmol) was added, than the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. To a mixture of this crude material in pyrrolidine (5 ml) were added successively $Pd(PPh_3)_4$ (0.1 mmol), 1-alkyne (4 mmol) and CuBr (0.2 mmol). The reaction was stirred at room temperature and monitored by TLC analysis until complete consumption of the unsaturated vinyl iodide **5** before to be treated with a saturated aqueous solution of ammonium chloride and extracted with Et_2O. The organic extract was dried over $MgSO_4$ and the solvent was removed in *vacuum*. The residue was purified by preparative TLC on silica gel and eluted with light petroleum.

(*Z*)-1,4-diphenyl-2-(butylselanyl)but-1-en-3-yne 6a, a pale yellow oil. (Found: C, 70.52; H, 5.90. Calc. for $C_{20}H_{20}Se$: C, 70.79; H, 5.94); ν_{max} (film)/cm^{-1}: 3080, 2200, 1610, 1480, 1015, 750; δ_H (300 MHz; $CDCl_3$): 7.42–7.02 (m, 11H, Ph, *HC*=), 1.50–0.65 (m, 9H, Bu); *m*/*z* 340 (M^+).

(*Z*)-5-methoxy-1-phenyl-2-(methylselanyl)pent-1-en-3-yen 6b, a pale yellow oil. (Found: C, 58.68; H, 5.39. Calc. for $C_{13}H_{14}OSe$: C, 58.87; H, 5.32.); ν_{max} (film)/cm^{-1}: 3085, 2205, 1590, 1482, 1020, 810; δ_H (300 MHz; $CDCl_3$): 7.50–7.10 (m, 6H, Ph, *HC*=), 4.10 (s, 2H, C*H₂*O), 3.28 (s, 3H, OC*H₃*), 2.15 (s, 3H, C*H₃*); *m*/*z* 266 (M^+).

(*Z*)-5-methoxy-1-phenyl-2-(ethylselanyl)pent-1-en-3-yne 6c, a pale yellow oil (Found: C, 60.43; H, 5.71. Calc. for $C_{14}H_{16}OSe$: C, 60.22; H, 5.78); ν_{max} (film)/cm^{-1}: 3080, 3020, 2340, 1490, 1440, 1075; δ_H (300 MHz; $CDCl_3$): 7.45–7.00 (m, 6H, Ph, *HC*=), 4.10 (s, 2H, C*H₂*O), 3.25 (s, 3H, OC*H₃*), 2.65 (q. 2H, SeC*H₂*), 1.50 (t, 3H, C*H₃*); *m*/*z* 280 (M^+).

(*Z*)-1-phenyl-2-(butylselanyl)oct-1-en-3-yne 6d, a pale yellow oil (Found: C, 67.52; H, 7.52. Calc. for $C_{18}H_{24}Se$: C, 67.70; H, 7.57); ν_{max} (film)/cm^{-1}: 3080, 3010, 2360, 1590, 1490, 1140, 1075, 1030; δ_H (300 MHz; $CDCl_3$): 7.50–7.05 (m, 6H, Ph, *HC*=), 2.20–0.70 (m, 18H, C_4H_9); *m*/*z* 320 (M^+).

(*Z*)-5-methoxy-1-phenyl-3-(butylselanyl)-pent-3-en-1-yne 6e, a pale yellow oil. (Found: C, 62.68; H, 6.50. Calc. for $C_{16}H_{20}OSe$: C, 62.54; H, 6.56); ν_{max} (film)/cm^{-1}: 3085, 2210, 1610, 1580, 1015, 810; δ_H (300 MHz; $CDCl_3$): 7.45–7.25 (m, 5H, Ph), 5.95 (t, $J = 6$ Hz, 1H, *HC*=), 3.85

(d, $J = 6.5$ Hz, 2H, OCH_2), 3.26 (s, 3H, CH_3O), 2.55 (q. 2H, SeCH_2), 1.55 (t, 3H, CH_3); m/z 308 (M^+).

(*Z*)-5-methoxy-1-phenyl-3-(ethylselanyl)-pent-3-en-1-yne 6f, a pale yellow oil. (Found: C, 60.48; H, 5.74. Calc. for $C_{14}H_{16}OSn$: C, 60.22; H, 5.78); ν_{max} (film)/cm^{-1}: 3085, 2210, 1610, 1580, 1015, 810; δ_H (300 MHz; $CDCl_3$): 7.45–7.25 (m, 5H, Ph), 6.10 (t, $J = 6.5$ Hz, 1H, HC=), 3.85 (d, $J = 6.5$ Hz, 2H, OCH_2), 3.26 (s, 3H, CH_3O), 2.55 (q. 2H, SeCH_2), 1.55 (t, 3H, CH_3); m/z 280 (M^+).

(*Z*)-1-phenyl-3-(ethylselanyl)oct-3-en-1-yne 6g, a pale yellow oil. (Found: C, 65.62; H, 6.98. Calc. for $C_{16}H_{20}Se$: C, 65.97; H, 6.92); ν_{max} (film)/cm^{-1}: 3080, 3010, 2360, 1590, 1490, 1440, 1075, 1030; δ_H (300 MHz; $CDCl_3$): 7.65–7.15 (m, 5H, Ph), 6.10 (t, $J = 6.5$ Hz, 1H, HC=), 2.52 (q, 2H, SeCH_2), 1.98–2.25 (m, 2H), 1.48 (t, 3H, CH_3), 1.15–1.50 (m, 4H), 0.80 (t, 3H, CH_3); m/z 292 (M^+).

The Synthesis of (*E*)-1,4-Diphenylbut-1-en-3-yne 7

1 ml BuLi (1.1 M hexane solution) was added to a THF (5.0 ml) solution of **6a** (1.0 mmol) at $-78°$C. After stirring for 30 min, the mixture was hydrolyzed with saturated aq. NH_4Cl and extracted with CH_2Cl_2 (2×10 ml). The organic extract was dried with $MgSO_4$, filtered and concentrated in *vacuum*. The residue was purified by column chromatography over silica gel, eluting with petroleum to give (*E*)-enyne **7**. (yield: 86%) as a pale yellow oil;[18] ν_{max} (film)/cm^{-1}: 3010, 2190, 1590, 1480, 1240, 950, 800; δ_H (300 MHz; $CDCl_3$) 7.50–7.00 (m, 11H, Ph, HC=), 6.43 (d, 1H, $J = 16$, =CH).

The Synthesis of (*E*)-1,2,4-Triphenylbut-1-en-3-yen 8

(*Z*)-1,3-enynylselenide **6a** (0.5 mmol) and PhZnBr (0.5 mmol) were dissolved in THF (5 ml) under nitrogen at room temperature. $NiCl_2(PPh_3)_2$ (0.05 mol) (0.4 mmol) was then added. The mixture was stirred at room temperature and monitored by TLC for the disappearance of **6a**. The reaction mixture was diluted with CH_2Cl_2 (15 ml) and washed with saturated aq. NH_4Cl. The product was extracted with hexane and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel, eluting with light petroleum to give enyne **8** (yield: 61%) as a solid, mp 49–50°C (lit.[19] 49–50°C); ν_{max} (film)/cm^{-1}: 3090, 2210, 1590, 1460, 740; δ_H (300 MHz; $CDCl_3$): 7.75–7.05 (m, 15H, Ph), 6.95 (s, 1H, HC=).

ACKNOWLEDGMENT

This work was supported by The National Nature Science Foundation of Zhejiang Province.

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