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Stereoselective Michael–Aldol Tandem Reaction of Phenylselenomagnesium Bromide with Acetylenic Sulfones and Aldehydes. An Efficient Synthesis of Polyfunctionalized Allylic Alcohols

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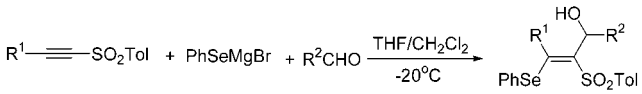
ABSTRACT



A mixture of phenylselenomagnesium bromide, an acetylenic sulfone, and an aldehyde in THF/CH_2Cl_2 afforded Michael–aldol tandem adduct, i.e., (*Z*)-*β*-phenylseleno-α-(*p*-tolylsulfonyl)allylic alcohol, in good yield with high stereoselectivity. The stereoselectivity greatly depended on solvent.

The tandem reaction has recently been of interest for organic synthesis because it offers a convenient and economical method to prepare desired organic molecules.[1] The Michael addition and the aldol reaction are acknowledged as useful tools for constructing complex organic molecules, and combining the two reactions in one pot has attracted much attention in organic synthesis.[2]

The stereoselective synthesis of multifunctional alkenes is an important goal in organic chemistry and is still being actively explored because of the fact that many biologically active compounds have the structure of substituted alkenes.[3] Difunctional group reagents, which have two different functional groups linked to the olefinic carbon atoms (such as Sn−Si, Sn−Mg, Sn−Zr, Sn−Se, Se−Zr, Se−Al, and Se−Cu), are useful intermediates in developing convenient methods for the synthesis of various alkenes.[4] Organomagnesium reagents[5] and vinyl selenides[6] have been widely used as building blocks in organic chemistry. However, to the best of our knowledge, there are no reports on the synthesis of functionalized alkenes from Se−Mg difunctional reagent. Acetylenic sulfones are known as electrophiles,[7] whereas

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(1) For review of tandem reaction, see: (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (c) Bunce, R. A. *Tetrahedron* **1995**, *48*, 13103. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

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(5) (a) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333. (b) Thibonnet, J.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 3319.

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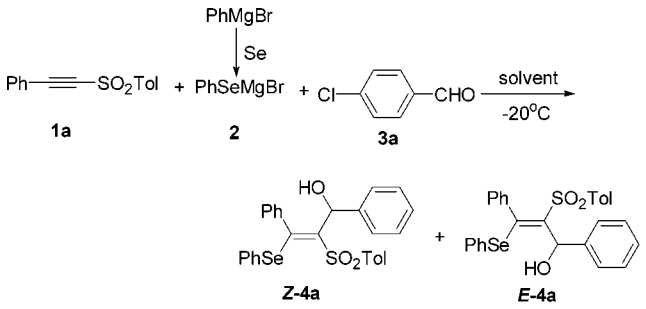
selenolate and its analogues are good nucleophiles[8] for Michael addition. Therefore we studied the Michael addition of magnesium selenolate with acetylenic sulfone to obtain the Se−Mg difunctional reagent, which was captured with aldehyde. Herein, we wish to report our preliminary results of the Michael−aldol tandem reactions and provide a simple and efficient one-pot protocol for the synthesis of functionalized tetrasubstituted alkenes, (*Z*)-*β*-phenylseleno-α-(*p*-tolylsulfonyl)allylic alcohols.

1-Phenyl-2-(*p*-tolylsulfonyl)ethyne (**1a**), phenylselenomagnesium bromide (**2**), and *p*-chlorobenzaldehyde (**3a**) were chosen to optimize the tandem reaction conditions. The results are summarized in Table 1. At −20 °C, **1a** was added to the solution of magnesium selenolate **2** in THF/acetonitrile (1/4 v/v), which was prepared in situ from phenylmagnesium bromide and powder selenium. When the Michael addition was complete (monitored by TLC), **3a** was added to the reaction mixture. The reaction mixture was maintained at −20 °C for 90 min (method A). The desired Michael−aldol adduct *Z*-**4a** and *E*-**4a** were obtained in 30% yield with the ratio of *Z*/*E* = 62:38 (ratio of *Z*/*E* determined by 400 MHz ^{1}H NMR spectrum based on the methyne proton of **4a**) (entry 1, Table 1). When acetonitrile was replaced by toluene, similar yield and higher stereoselectivity were obtained (entry 2, Table 1). However, the yield was dramatically improved with good stereoselectivity when the reaction was carried out in THF or THF/CH_2Cl_2 (1/4 v/v) (entries 3 and 4, Table 1). So THF or THF/CH_2Cl_2 is the optimal solvent for the tandem reaction.

Table 1. Reaction of 1-Phenyl-2-(*p*-tolylsulfonyl)ethyne, Phenylselenomagnesium Bromide, and *p*-Chlorobenzaldehyde



entry	solvent	method[a]	time (min)	yield (%)[b]	ratio of *Z*/*E*[c]
1	THF/CH_3CN	A	90	30	62/38
2	THF/Toluene	A	90	29	85/15
3	THF	A	70	70	70/30
4	THF/CH_2Cl_2	A	80	75	73/27
5	THF	B	60	81	88/12
6	THF/CH_2Cl_2	B	60	87	>96/4

[a] The reaction was carried out at −20 °C using **1a** (0.5 mmol), **2** (0.6 mmol), and **3a** (0.5 mmol). Method A: **4a** was added after the Michael addition of **2** with **1a** was complete. Method B: **1a**, **2**, and **3a** were added simultaneously in solvent. [b] Determined by ^{1}H NMR based on **1a** using CH_2Br_2 as an internal standard. [c] Determined by 400 MHz ^{1}H NMR analysis based on the methyne proton of **4a**.

We further investigated the reaction of magnesium selenolate **2** with *p*-chlorobenzaldehyde **3a**. By adding **3a** directly to the solution of **2** in THF/CH_2Cl_2 at −20 °C and stirring for 3h, no adduct was formed because there are no proton signals of methyne and hydroxy in the ^{1}H NMR spectrum of the crude reaction mixture. This result suggests that phenylselenomagnesium bromide **2** can react with **1a** selectively when **1a**, **2**, and **3a** were added in one pot. So it is possible for **3a** to capture alkenylmagnesium intermediate immediately when the intermediate formed by adding **1a**, **2**, and **3a** simultaneously in solvent (method B). Fortunately, both the yield and the *Z*/*E* selectivity were greatly improved by this method (entries 5 and 6, Table 1).

The present reaction conditions were compatible with the reaction of phenyl or aliphatic acetylenic sulfones with other aromatic, aliphatic aldehydes or α,*β*-unsaturated aldehydes, giving *Z*-type tandem adducts in good yields. The results are summarized in Table 2.

The configuration of the product **4b** was determined as *Z*-type by single-crystal X-ray diffraction analysis [9] (Figure 1). The NOESY spectrum of **4k** also shows that CH(OH)-C_6H_4-Cl-*p* group is in a *cis* orientation with *n*-C_5H_{11}. The fact that all of the products shared almost the same NMR patterns suggests the stereochemistry of these compounds to be identical. Therefore, the double bond in compounds **4** is in Z-configuration.

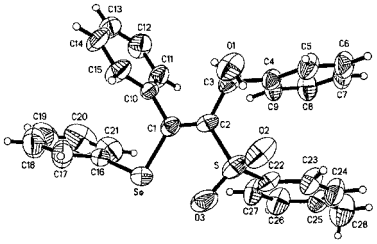


Figure 1. The crystal structure of **4b**.

Vinyl selenides[6] and unsaturated sulfones[10] have numerous uses in organic synthesis. Certain *β*-selenovinyl sulfones are known to undergo substitution reactions of the selenium moiety with organocuprates and other nucleophiles, as well as *syn*-elimination reactions of their corresponding selenox-

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(8) (a) Kamimura, A.; Mitsudera, H.; Asano, S.; Kidera, S.; Kakehi, A. *J. Org. Chem.* **1999**, *64*, 6353 and references therein. (b) Mitsudera, H.; Kakehi, A.; Kamimura, A. *Tetrahedron Lett.* **1999**, *40*, 7389.

(9) **Crystal data for 4b:** $C_{28}H_{24}O_3SSe$, MW = 519.49, monoclinic, space group $P2_1/n$, a = 7.0710(4), b = 14.6604(9), c = 24.3432(5) Å; α = 90°, β = 94.7550(10)°, γ = 90°. V = 2514.8(3) Å^3, T = 293 K, Z = 4, D_c = 1.372 g cm^{-1}, μ = 1.603 mm^{-1}, λ = 0.71073 Å; F(000) 1064, 4688 independent reflections (R_{int} = 0.0754), 13113 reflections collected; refinement method, full-matrix least-squares on F^2; goodness-of-fit on F^2 = 0.657; final R indices [$I > 2\sigma(I)$] R_1 = 0.0371, wR_2 = 0.0499.

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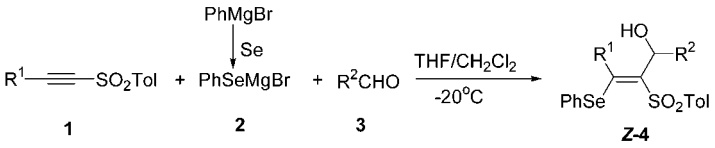
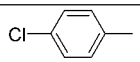
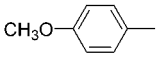
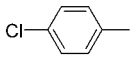
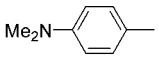
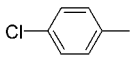
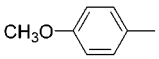
Table 2. Reaction of Acetylenic Sulfones with Phenylselenomagnesium Bromide and Aldehydes[a]



1 2 3 Z-4

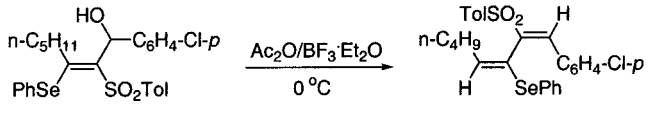
entry	R^1	R^2	time (min)	yield of Z-**4**(%)(Z/E) [b]
1	Ph		50	82 (**4a**, >96/4)
2	Ph		50	76 (**4b**, >98/2)
3	Ph		55	84 (**4c**, >98/2)
4	Ph		80	89 (**4d**, >97/3)
5	Ph	n-C_4H_9	75	85 (**4e**, >97/3)
6	n-C_4H_9		70	82 (**4f**, >99/1)
7	n-C_4H_9		60	82 (**4g**, >98/2)
8	n-C_4H_9		50	76 (**4h**, >99/1)
9	n-C_4H_9		80	85 (**4i**, >99/1)
10	n-C_4H_9		90	74 (**4j**, >97/3)
11	n-C_5H_{11}		60	83 (**4k**, >98/2)
12	n-C_5H_{11}		60	88 (**4l**, >98/2)
13	n-C_5H_{11}		70	73 (**4m**, >99/1)
14	n-C_5H_{11}		80	89 (**4n**, >96/4)
15	n-C_5H_{11}		90	88 (**4o**, >96/4)
16	n-C_5H_{11}	n-C_4H_9	70	76 (**4p**, >97/3)

[a] The reaction was carried out at −20 °C by adding **1** (0.5 mmol), **2** (0.6 mmol), and **3** (0.5 mmol) simultaneously in THF/CH_2Cl_2 (1/4 v/v). [b] Isolated yield of purified *Z*-**4** based on **1**. The ratio of *Z*/*E* was determined by 400 MHz ^{1}H NMR spectra of the unpurified reaction mixture.

ides.[11] Therefore, it is predictable that the tandem adducts **4** can be useful building blocks in organic synthesis. We also found an efficient method for the synthesis of heteroatom-substituted 1,3-dienes from **4**. Heteroatom-substituted 1,3-dienes are useful precursors to construct highly functionalized ring systems in Diels−Alder reactions.[12] Our experimental results show that the treatment of **4k** with $Ac_2O/BF_3{\cdot}Et_2O$ can give 2-(*p*-tolylsulfonyl)-3-phenylselenoocta-1,3-diene **5** in high yield (96%) with high stereoselectivity (isomer purity >95%, determined by ^{1}H NMR) (Scheme 1). The configuration of **5** was verified by the ^{1}H−^{1}H 2D NOESY spectrum. The strong NOE correlation between H4 and 3-phenylseleno protons and the NOE correlation between H1 and *p*-tolylsulfonyl protons were observed, indicating the stereochemistry of **5** is 1*E*,3*E*.

In summary, we have developed a one-pot method for the synthesis of *β*-phenylseleno-α-(*p*-tolylsulfonyl)allylic alcohols **4** efficiently and stereoselectively. The method is convenient, starting from easily available materials. Tandem adducts **4** obtained from aliphatic acetylenic sulfones can be readily converted to heteroatom substituted 1,3-dienes in

Scheme 1



Z-4k 5

(11) Back, T. G.; Bethell, R. J.; Parvez, M.; Wehrli, D. *J. Org. Chem.* **1998**, *63*, 7908 and references therein.

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high yield and high stereoselectivity. Further application of the β-seleno alkenylmagnesium intermediate formed in Michael addition and the tandem adducts **4** in organic synthesis are now in progress in our laboratory.

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Supporting Information Available: Experimental procedures and spectral data for compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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