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Development of Novel Diastereoselective Alkenylation of Enolates Using Alkenylselenonium Salts

Shin-ichi Watanabe, Takahiro Ikeda, Tadashi Kataoka,* Genzoh Tanabe, and Osamu Muraoka

Gifu Pharmaceutical University, 6-1 Mitahora-higashi 5-chome, Gifu 502-8585, Japan

kataoka@gifu-pu.ac.jp

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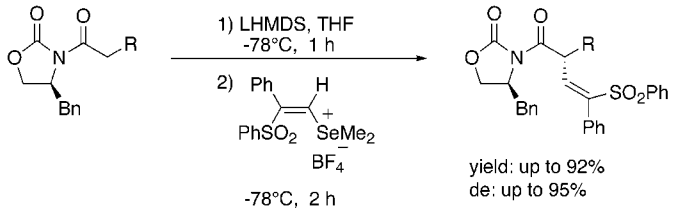
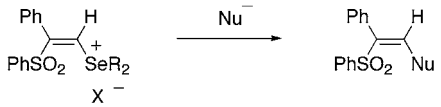
ABSTRACT



A novel alkenylation of enolates using alkenylselenonium salts is described. A reaction of lithium enolates, which were prepared in situ by the reaction of LiHMDS and carbonyl compounds, with alkenylselenonium salts gave the ethenylation products of carbonyl compounds in high yield. Diastereoselective alkenylation was also accomplished by the reaction of the enolates derived from *N*-acyl-1,3-oxazolidin-2-ones with the alkenylselenonium salt to afford good results (up to 92% yield and up to 95% de).

The alkylation reaction of enolates is generally regarded as one of the main avenues for regio- and stereoselective carbon−carbon bond formation reactions, and the thorough investigation of these reactions has contributed to the development of organic synthesis.[1] However, there are not many reports on the effective alkenylation of enolates, which are the coupling reactions of a transition metal complex of enolate with alkenyl halide [2] and the addition−elimination reaction of highly electron-deficient alkenyl halide with enolate.[3] In addition, the diastereoselective alkenylation of enolates bearing a chiral auxiliary, which is a very interesting field, has not been reported. Although the research on alkenylselenonium salts has hardly been studied until now,[4] we found that the selenonium salts acted as the synthetic equivalent of alkenyl cation (Scheme 1).[5] Therefore, the alkenylation of enolates with selenonium salts bearing the β-sulfonylalkenyl group was investigated.

Scheme 1. Reactivity of Alkenylselenonium Salts **1**



1a: R=Ph, X=TfO
1b: R=Me, X=BF_4

We first examined the alkenylation reaction of enolate, which was formed by the deprotonation of propiophenone with a 1.1 equiv of LHMDS (lithium hexamethyldisilazide) at room temperature for 30 min, with β-phenylsulfonyldiphenylalkenylselenonium salt **1a**[5a] at −78 °C for 2 h (Table

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(2) (a) Caine, D. In *Carbon−Carbon Bond Formation*; Augustine, R. L., Eds.; Dekker: New York, 1979; Vol. 1, p 152. (b) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831. (c) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242. (d) Hashimoto, S.; Miyazaki, Y.; Shinoda, T.; Ikegami, S. *Tetrahedron Lett.* **1989**, *30*, 7195. (e) Moloney, M. G.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2847.

(3) (a) Jończyk, A.; Gierczak, A. H. *Tetrahedron* **2000**, *56*, 6083. (b) Padwa, A.; Muller, C. L.; Rodriguez, A.; Watterson, S. H. *Tetrahedron* **1998**, *54*, 9651. (c) Padwa, A.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1990**, *55*, 4241. (d) Smith, A. B., III; Kilenyi, S. N. *Tetrahedron Lett.* **1985**, *26*, 4419. (e) Hartke, K.; Richter, W. F.; Kämpchen, T. *Chem. Ber.* **1989**, *122*, 669.

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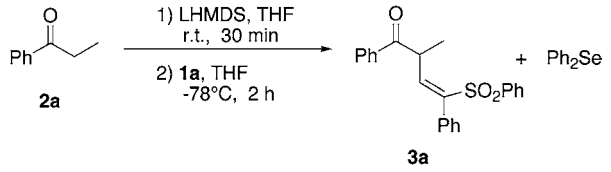
Table 1. Alkenylation Reaction of Enolate with Alkenylselenonium Salt **1a**



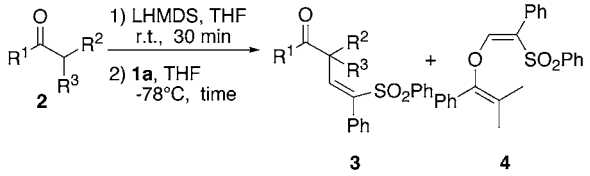
	molar ratio			products[a]	
entry	ketone	LHMDS	**1a**	**3a**	Ph_2Se
1	1.5 equiv	1.7 equiv	1.0 equiv	91%	97%
2	1.2 equiv	1.35 equiv	1.0 equiv	85%	91%
3	1.0 equiv	1.1 equiv	1.0 equiv	65%	95%
4	1.0 equiv	1.1 equiv	1.5 equiv	80%	91%

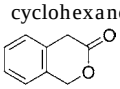
[a] Isolated yield after preparative TLC.

1). The use of a small excess of the ketone gave good results, and the desired alkenylation product **3a** was obtained with over 85% yield as a single geometric isomer under the conditions in entries 1 and 2. The yield of a β,γ-unsaturated ketone, however, decreased when employing the same equivalent of ketone and selenonium salt (entry 3) or an excess amount of selenonium salt (entry 4).

Second, to broaden the scope, we demonstrated this alkenylation reaction using a variety of carbonyl compounds (Table 2).[6] To avoid waste of the starting materials, the

Table 2. Alkenylation Reaction of Various Enolates with Alkenylselenonium Salt **1a**



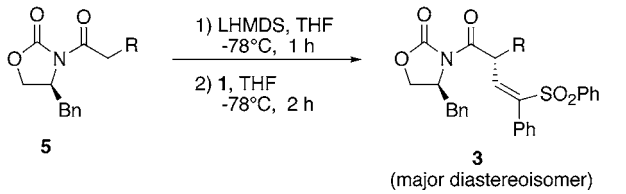
entry	carbonyl compound	time	products (% yield)[a]
1	**2b**: R^1 = Ph, R^2 = Bn, R^3 = H	2 h	**3b** (91)
2	**2c**: R^1 = Ph, R^2 = ^{n}Pr, R^3 = H	2 h	**3c** (86)
3	**2d**: cyclohexanone	1 h	**3d** (43)
4	**2e**: 	2 h	**3e** (66)
5	**2f**: R^1 = Ph, R^2 = R^3 = Me	2 h	**3f** (8), **4** (41)

[a] Isolated yield after preparative TLC.

conditions of entry 2 in Table 1, which gave relatively good yield of the desired product, were selected for the alkenylation reaction. The enolate derived from 1,3-diphenyl-1-propanone reacted with alkenylselenonium salt to afford the alkenylation product **3b** in a 91% yield, and also a high yield of the desired compound was obtained from the reaction with valerophenone (entry 2). On the other hand, the reaction with cyclic ketone and ester gave the β,γ-unsaturated ketone and ester in a lower yield (entries 3 and 4). In particular, the O-alkenylation compound was obtained as the main product from the reaction of isobutyrophenone and the corresponding C-alkenylation compound **3f** was formed only in an 8% yield because of the steric hindrance of the ketone bearing a tertiary carbon at the α position of the carbonyl group (entry 5). In all cases, diphenyl selenide was formed in over 84% yield (data not shown). Compounds **3** were isolated as single geometric isomers from these reactions. The stereochemistry of compound **3e** was determined to be (*Z*) by the NOE enhancement between the vinyl proton and the *ortho*-protons of the (*Z*)-phenyl group (17%).

To develop the diastereoselective alkenylation of enolates, we investigated the reaction of enolate bearing (4*S*)-benzyl oxazolidinone chiral auxiliary with alkenylselenonium salts (Table 3). In these reactions, 1.2 equiv of alkenyl selenonium

Table 3. Diastereoselective Alkenylation Reaction of Oxazolidinone Derivatives with Alkenylselenonium Salts **1**



entry	5	selenonium salt	product (%yield)[a]	de[b] (%)
1	**5a**: R = Me	**1b**	**3g** (68)	47
2	**5b**: R = Et	**1b**	**3h** (78)	83
3	**5c**: R = *i*-Pr	**1a**	**3i** (63)	79
4	**5c**	**1b**	**3i** (64)	95
5	**5d**: R=Bn	**1b**	**3j** (92)	87

[a] Isolated yield of a mixture of diastereomers after preparative TLC. [b] Diastereoselectivities were determined by ^{1}H NMR measurement.

salts was employed against chiral oxazolidinone derivatives to economize chiral compounds.[7] Dimethylalkenylselenonium salt **1b** [5a] was used to investigate diastereoselective reactions because the diastereoselectivity of diphenylalkenylselenonium salt **1a** was lower than that of **1b** (entries 3 and 4). The reactions gave the desired alkenylation products in high yields, which were in a range between 63 and 92%.

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(5) (a) Watanabe, S.; Yamamoto, K.; Itagaki, Y.; Iwamura, T.; Iwama, T.; Kataoka, T.; Tanabe, G.; Muraoka, O. *J. Chem. Soc., Perkin Trans. 1* **2001**, 239. (b) Watanabe, S.; Mori, E.; Nagai, H.; Iwamura, T.; Iwama, T.; Kataoka, T. *J. Org. Chem.* **2000**, *65*, 8893. (c) Watanabe, S.; Mori, E.; Nagai, H.; Kataoka, T. *Synlett* **2000**, 49. (d) Watanabe, S.; Yamamoto, K.; Itagaki, Y.; Kataoka, T, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2053.

(6) Typical procedure: A mixture of carbonyl compound (0.24 mmol) and LHMDS (1 M in THF, 0.27 mmol) in THF (2 mL) was stirred at room temperature for 30 min, and the reaction mixture was cooled to −78 °C followed by the addition of a THF solution (2 mL) of alkenylselenonium salt **1a** (0.20 mmol). The mixture was stirred at the same temperature for 1 or 2 h. The typical workup with water, extraction with ethyl acetate, and preparative TLC purification afforded **3** and **4**.

The diastereoselectivity of the reaction with oxazolidinone derivative **5a** (R = Me) was not good, i.e., 47% de. Higher diastereoselectivities were observed in the case of an oxazolidinone derivative with a bulkier side chain for the formation of **3**, and 95% de was obtained when **5c** was employed. A (*Z*)-isomer was only isolated in all cases in the formation of **3**.

(4*S*,2′*R*)-**3** was observed in the main product. The absolute configuration of the major diastereomer **3i** was established by X-ray analysis (Figure 1). Thus, the absolute stereochemistry of C2′ was determined to be (*R*). The (*Z*)-configuration of the olefin part was also indicated.[8] A plausible mechanism for the reaction of enolates with alkenylselenonium salts contains the processes of addition of the carbanion to α-carbon of alkenylselenonium salt and the elimination of a selenide or ligand coupling of selenurane, which is formed by the attack of the carbanion to a selenonio group.[5a] The predominant formation of (4*S*,2′*R*)-**3** is caused by an attack of the carbanion on the alkenylselenonium salt from the oppsite side of the benzyl group in the (*Z*)-enolate.

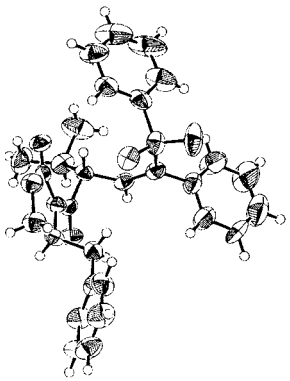

Figure 1. Perspective View of Compound **3i**.

In summary, we have developed the novel alkenylation reaction of various enolates using alkenylselenonium salts. This method produced (*Z*)-*β*,*γ*-unsaturated carbonyl compounds in good yields. The application to the diastereoselective alkenylation of enolate was also successful for giving a high diastereoselectivity (up to 95% de). We demonstrated the utilization of alkenylselenonium salts in organic synthesis. Further applications of this strategy are currently underway in our laboratory.

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Supporting Information Available: Complete analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Typical procedure: A mixture of oxazolidinone derivative (0.20 mmol) and LHMDS (1 M in THF, 0.23 mmol) in THF (1.6 mL) was stirred at −78 °C for 1 h, and this mixture was added to a THF solution (2.4 mL) of alkenylselenonium salt **1** (0.24 mmol). The mixture was stirred at the same temperature for 2 h. The typical workup with water, extraction with ethyl acetate, and preparative TLC purification afforded **3**.

(8) Stereochemistries of **3g**,**h**,**j** were similarly determined.