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Highly Stereoselective Intramolecular Michael Addition Using α-Sulfinyl Vinyllithium as an Unprecedented Michael Donor

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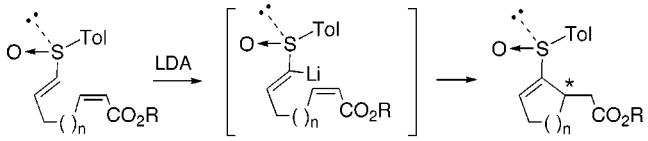
ABSTRACT



The first example of an asymmetric intramolecular Michael addition reaction using α-lithiated vinylic sulfoxide as a Michael donor is reported. Michael addition of the α-lithiated vinylic sulfoxide to (*Z*)-enoates proceeds with high diastereoselectivity to give the adducts having a stereogenic center with (*R*)-configuration at the *β*-position of the ester in the cyclopentene ring formation. The selectivity was reversed in the six-membered ring formation. On the other hand, the corresponding (*E*)-enoates provided Michael adducts with poor diastereoselectivity.

Vinylic sulfoxides are well-known chiral Michael acceptors, and the efficacy of the sulfoxide to differentiate the diastereotopic face of double bonds has made this reaction an attractive subject for study.[1,2] In contrast, the use of vinylic sulfoxide as a "Michael donor" has remained unexplored. Recently, we have reported a novel intramolecular alkylation of a vinylic lithium species generated by α-deprotonation of vinylic sulfoxides with LDA.[3] Next, we turned our attention to Michael addition reactions of the α-lithiated vinylic sulfoxides to enoates, since the addition of the chiral carbanions to the prochiral Michael acceptor should proceed diastereoselectively, thereby creating a stereogenic center at the *β*-position of the ester. Although asymmetric reaction by means of the chiral α-sulfinyl vinylic carbanions has been extensively examined on the intermolecular nucleophilic addition to aldehydes[4] or ketones,[5] this type of reaction generally proceeds with moderate to poor diastereoselectivity, except for one example.[6] Furthermore, to the best of our knowledge, there is no report regarding the order of acidity between the α-proton of the vinylic sulfoxide and the α,*β*- or *γ*-protons of the enoate, which can be abstracted by a strong base such as LDA.[7] In addition, this reaction provides a convenient access to functionalized cyclohexene and cyclopentene derivatives, which would be functionalized diastereoselectively.[1,2] In this paper, we report a highly diastereoselective intramolecular Michael addition reaction of the vinylic sulfoxides with (*Z*)-enoates.

The required four geometric isomers of methyl 7-sulfinyl-

(1) For a review, see: Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760.
(2) Priego, J.; Carretero, J. C. *Synlett* **1999**, 1603−1605.
(3) (a) Maezaki, N.; Izumi, M.; Yuyama, S.; Sawamoto, H.; Iwata, C.; Tanaka, T *Tetrahedron* **2000**, *56*, 7927−7945. (b) Maezaki, N.; Izumi, M.; Yuyama, S.; Iwata, C.; Tanaka, T. *Chem. Commun.* **1999**, 1825−1826.
(4) Fawcett, J.; House, S.; Jenkins, P. R.; Lawrence, N. J.; Russell, D. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 67−73 and references therein.
(5) Haynes, R. K.; Katsifis, A. G. *Aust. J. Chem.* **1989**, *42*, 1473−1483. Haynes, R. K.; Katsifis, A. G. *J. Chem. Soc., Chem. Commun.* **1987**, 340−342.
(6) Solladié, G.; Moine, G. *J. Am. Chem. Soc.* **1984**, *106*, 6097−6098.
(7) Selected references, see: Jeyaraj, D. A.; Kapoor, K. K.; Yadav, V. K.; Gauniyal, H. M.; Parvez, M. *J. Org. Chem.* **1998**, *63*, 287−294. Ihara, M.; Suzuki, S.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2251−2258. Feit, B. A.; Melamed, U.; Schmidt, R. R.; Speer, H. *J. Chem Soc., Perkin Trans. 1* **1981**, 1329−1338.

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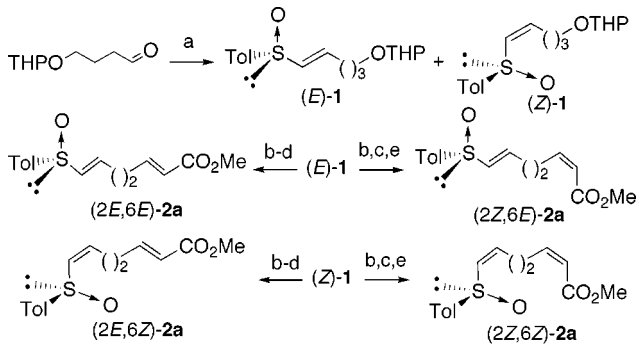
1,6-heptadienoates (**2a**) were prepared from the known 4-(tetrahydro-2*H*-pyran-2-yloxy)butanal[8] as shown in Scheme 1.

Scheme 1

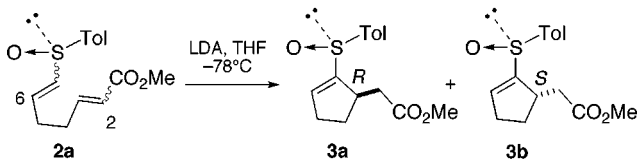


[a] Reagents and conditions: (a) $(MeO)_2P(O)CH_2S(O)Tol$, *n*-BuLi, THF, rt [(*E*)-**1**, 33%; (*Z*)-**1**, 45%]; (b) *p*-TsOH·H_2O, THF, rt; (c) Dess−Martin periodinane, CH_2Cl_2, rt; (d) $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, −20 °C [(2*E*,6*E*)-**2a**; 62% in three steps, (2*E*,6*Z*)-**2a**; 48% in three steps]; (e) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF, −20 °C [(2*Z*,6*E*)-**2a**; 64% in three steps, (2*Z*,6*Z*)-**2a**: 45% in three steps].

Upon treatment with (*R*)-dimethylphosphorylmethyl *p*-tolyl sulfoxide,[9] the aldehyde afforded (*E*)- and (*Z*)-isomers of α,β-unsaturated sulfoxides **1** in 33% and 45% yields, respectively.[10] Then, both isomers were converted into the (*E*)- and (*Z*)-enoates **2a** by sequential reactions: (1) hydrolysis of the THP ether with *p*-TsOH in MeOH; (2) oxidation of the resulting alcohol with Dess−Martin periodinane; (3) Horner−Wadsworth−Emmons reaction[11] or Still and Gennari's method.[12] Thus, the four geometric isomers of **2a** were obtained in satisfactory yields (45−64% in three steps).

With all the geometric isomers in hand, we examined the intramolecular Michael addition reaction (Scheme 2, Table 1).

Scheme 2



Diastereoselectivity of the Michael addition reactions was remarkably affected by the geometry of the "enoate" but not that of the "vinylic sulfoxide", whose geometry is labile under the reaction conditions and rapidly isomerizes to the thermodynamically stable (*E*)-vinylic sulfoxide.[3,13] Upon treatment of the (*E*)-enoate (2*E*,6*E*)-**2a** with 1.5 equiv of LDA in THF at −78 °C, intramolecular Michael addition reaction proceeded promptly to give the cyclic sulfoxides **3a** and **3b** in good yield, but without selectivity (entry 1). In contrast, cyclization of the corresponding (*Z*)-enoate exclusively afforded **3a** having a stereogenic center with the (*R*)-configuration at the β-position of the ester (entry 2). (*Z*)-Vinylic sulfoxides (2*E*,6*Z*)- and (2*Z*,6*Z*)-**2a** also afforded cyclized products via base-promoted isomerization of the vinylic sulfoxide moiety. Although the predominant formation of the (*R*)-diastereomeric isomer in (*Z*)-enoate (2*Z*,6*Z*)-**2a** was the same as that of (2*Z*,6*E*)-**2a**, the yields were lowered, presumably as a result of the low reactivity of the (*Z*)-vinylic sulfoxide, which has to be isomerized prior to cyclization (entries 3 and 4). It should be noted that products arising from deprotonation at the α,β- or γ-positions of the enoates were not detected at all. Moreover, treatment of the cyclized products **3a** and **3b**, respectively, with 1.5 equiv of LDA at −78 °C for 30 min followed by reprotonation resulted in complete recovery of the starting materials, wherein neither the retro-Michael product **2a** nor a mixture of **3a** and **3b** formed by recyclization was produced. Consequently, this cyclization is apparently irreversible. When the reaction of (2*Z*,6*E*)-**2a** was carried out in the presence of an additive, such as TMEDA and HMPA, both the yield and the diastereoselectivity were lowered depending on the amount of addition (Table 2).

Table 1. Intramolecular Michael Addition of Vinylic Sulfoxides **2a**[a]

				yield (%)[b]		
entry	substrate	enoate	vinylic sulfoxide	**3a**	**3b**	de (%)
1	(2*E*,6*E*)-**2a**	E	E	44	40	5
2	(2*Z*,6*E*)-**2a**	Z	E	71	0	100
3	(2*E*,6*Z*)-**2a**	E	Z	12	10	9
4	(2*Z*,6*Z*)-**2a**	Z	Z	19	0	100

[a] All reactions were carried out using LDA (1.5 equiv) in THF at −78 °C. [b] Isolated yield.

Table 2. Effects of Additives on Intramolecular Michael Addition[a]

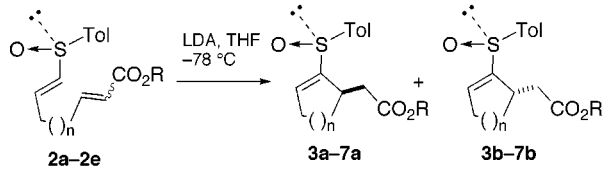
		yield (%)[b]		
entry	additive (equiv)	**3a**	**3b**	de (%)
1		71	0	100
2	HMPA (0.2)	52	8	73
3	HMPA (1)	33	7	65
4	HMPA (5)	21	11	31
5	TMEDA (1)	51	7	76

[a] All reactions were carried out using LDA (1.5 equiv) in THF at −78 °C. [b] Isolated yield.

(8) Amanda, J.; Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1989**, *45*, 7835−7858.

(9) Mikolajczyk, M.; Midura, W.; Grzejszczak, S.; Zatorski, A.; Chefczynska, A. *J. Org. Chem.* **1978**, *43*, 473−478. Mikolajczyk, M.; Grzejszczak, S.; Zatorski, A. *J. Org. Chem.* **1975**, *40*, 1979−1984.

Scheme 3



The size of the ester moiety in the (*Z*)-enoates **2b**−**d**[14] showed significant effects on the yield of intramolecular Michael addition reactions (Scheme 3, Table 3, entries 1−4).

Table 3. Intramolecular Michael Addition of Vinylic Sulfoxides **2a**−**e**[a]

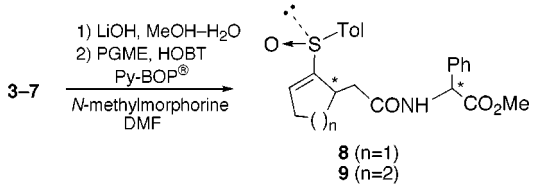
						yield (%)[c]	
entry	substrate[b]	enoate	R	*n*	product	**a**	**b**
1	(2*Z*,6*E*)-**2a**	Z	Me	1	**3**	71	0
2	(2*Z*,6*E*)-**2b**	Z	Et	1	**4**[d]	54	tr
3	(2*Z*,6*E*)-**2c**	Z	*i*-Pr	1	**5**[d]	45	tr
4	(2*Z*,6*E*)-**2d**	Z	*t*-Bu	1	**6**	0	0
5	(2*E*,7*E*)-**2e**	E	Me	2	**7**	38	40
6	(2*Z*,7*E*)-**2e**	Z	Me	2	**7**	tr	60

[a] All reactions were carried out using LDA (1.5 equiv) in THF at −78 °C. [b] The substrates **2b**−**e** were prepared in a similar manner for (2*Z*,6*E*)-**2a**. [c] Isolated yield. [d] The absolute configuration of **4a** and **5a** was determined by comparing the ^{1}H NMR spectral data of the PGME amides from **4a** and **5a** with that from **3a**.

Replacement of the methyl ester in (2*Z*,6*E*)-**2a** with other esters (Et, *i*-Pr, and *t*-Bu) caused decrease of the yield in the order Me > Et > *i*-Pr ≫ *t*-Bu. and the selectivities are also slightly reduced. Cyclohexene ring formations using (2*E*,7*E*)- and (2*Z*,7*E*)-**2e**[15] also proceeded in a fashion similar to the cyclopentene ring formation. The diastereoselectivity of the Michael addition to the (*Z*)-enoate is higher than that of the corresponding (*E*)-enoate. Interestingly, the selectivity was reversed completely (entries 5 and 6).

To determine the optical purity and absolute configuration, the products **3**−**7** were converted into the amides **8** and **9** with optically pure phenylglycine methyl ester (PGME) via hydrolysis of esters (LiOH in aqueous MeOH) followed by condensation with (*R*)- or (*S*)-PGME (PyBOP, HOBT, and *N*-methylmorphorine) as shown in Scheme 4. ^{1}H NMR

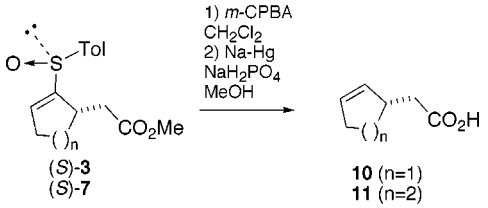
Scheme 4



spectroscopic data of **8** and **9** revealed that all amides were optically pure and no loss of optical purity resulted from cyclization. The absolute configurations of the *β*,*β*-disubstituted propionates were established by the PGME method recently developed by Yabuuchi and Kusumi.[16]

This assignment of the absolute configuration was consistent with that determined by transformation of **3b** and **7b** into known compounds **10** and **11**, respectively, via oxidation of the sulfoxide to the sulfone (*m*-CPBA, CH_2Cl_2) followed by desulfurization (Na−Hg, NaH_2PO_4, MeOH) as shown in Scheme 5.[17,18]

Scheme 5



In conclusion, we have developed a novel route for the synthesis of fuctionalized five- and six-membered ring cycloalkenyl sulfoxides via unprecedented asymmetric intramolecular Michael addition reaction of the α-sulfinyl carbanion with the enoate. Deprotonation with LDA underwent at the α-sulfinyl position rather than at the enoate part to give 2-[2-(*p*-tolylsulfinyl)-2-cycloalkenyl]acetate. Stereoselectivity of the intramolecular Michael addition was dependent on the geometry of the enoate, and very high diastereoselectivity was observed when the (*Z*)-enoate was used as a Michael acceptor. Further work is in progress to explore the full scope of this methodology.

Supporting Information Available: Experimental procedure for intramolecular Michael addition and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Selective synthesis of (*E*)- and (*Z*)-**1** is also possible; see: ref 3a and Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. *J. Org. Chem.* **1987**, *52*, 1078−1082.

(11) Horner, L.; Hoffmann, H.; Klink, W.; Ertel, H.; Toscano, V. G. *Chem. Ber.* **1962**, *95*, 581−601. Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733−1738.

(12) Still, W. C.; Gennari, C. *Tetrahedon Lett.* **1983**, *24*, 4405−4408.

(13) (a) Posner, G. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2A, pp 225−241. (b) Schmidt, R. R.; Speer, H.; Schmid, B. *Tetrahedron Lett.* **1979**, 4277−7280. (c) Posner, G. H.; Tang, P.-W.; Mallamo, J. P. *Tetrahedron Lett.* **1978**, *42*, 3995−3998. (d) Okamura, H.; Mitsuhira, Y.; Miura, M.; Takei, H. *Chem. Lett.* **1978**, 517−520.

(14) The esters (2*Z*,6*E*)-**2b**−**d** were selectively synthesized from (*E*)-**1** by a procedure similar to that for **2a** except that Ando's protocol (Ando, K. *J. Org. Chem.* **1999**, *64*, 8406−8408) was used for construction of the (*Z*)-enoate moiety.

(15) The substrates (2*E*,7*E*)- and (2*Z*,7*E*)-**2e** were synthesized by a procedure similar to that for **2a** using 5-(tetrahydro-2*H*-pyran-2-yloxy)-pentanal as a starting material.

(16) Yabuuchi, T.; Kusumi, T. *J. Org. Chem.* **2000**, *65*, 397−404.

(17) Takano, S.; Yamada, O.; Iida, H.; Ogasawara, K. *Synthesis* **1994**, 592−596. In the case of compound **10**, considerable loss of optical purity during derivatization was observed presumably as a result of strong alkaline conditions in the desulfurization reaction [**10**: $[\alpha]^{26}_D$ +78.0 (lit. $[\alpha]^{30}_D$ +107.4), **11**: $[\alpha]^{26}_D$ +81.9 (lit. $[\alpha]^{30}_D$ +84.4)].

(18) The compound **10** was used as a starting material of (+)-hirsutic acid (Nishida, M.; Iseki, K.; Shibasaki, M.; Ikegami, S. *Chem. Pharm. Bull.* **1991**, *38*, 3230−3237) and chaulmoogric acid (Mislow, K.; Steinberg, I. V. *J. Am. Chem. Soc.* **1955**, *77*, 3807−3810).