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Michael Additions of the Lithium Enolates of α-Heterosubstituted Esters and Amides to a Chiral α,β-Unsaturated Carbonyl Acceptor, Ethyl (*E*)-3-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]propenoate. High Stereoselection and Chiral Induction

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Abstract: α-Heterosubstituted esters and amides, after lithiation with LDA in THF at –78 °C, undergo highly syn- or anti-selective Michael additions to ethyl (E)-3-[(S)-2,2-dimethyl-1,3-dioxolan-4-yl]-propenoate, while similar reactions of acetamide and propanamide are poor in selectivity.

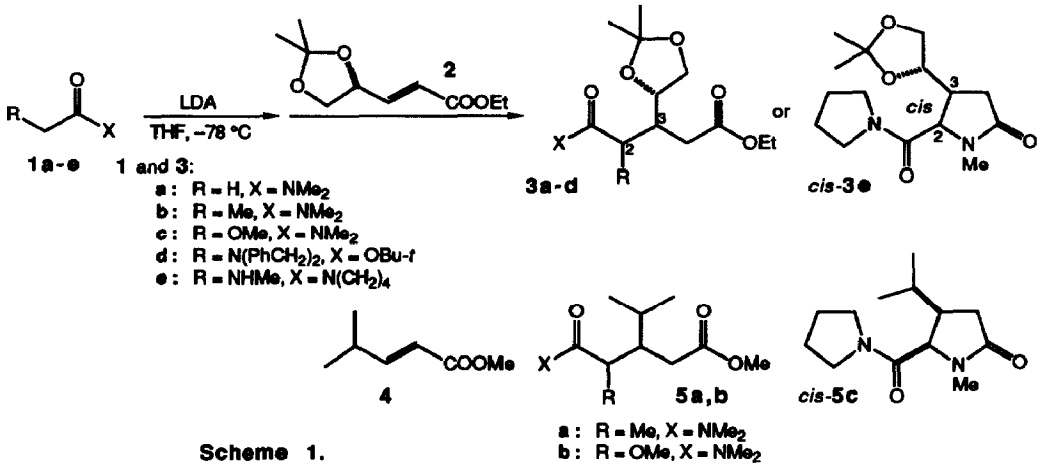
We have recently reported that the lithium enolates of α-heterosubstituted esters and amides show high levels of unusual *syn*-selectivity in Michael additions to α,β-unsaturated carbonyl acceptors.[1] Extension of these stereoselective reactions to asymmetric versions would be of great use as stereoselective carbon-carbon bond formation. However, limited examples are only known for the asymmetric Michael additions using achiral metal enolates and related nucleophiles with prostereogenic chiral acceptors.[2]

(*E*)-3-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]propenoates, which belong to the α,β-unsaturated esters bearing a chiral center at γ-position, have found wide synthetic applications in asymmetric reactions. Examples include the cyclizations with cyclic 1,3-dien-2-olates,[3] the conjugate additions by nucleophiles such as cuprates,[4] phosphorus ylides,[5] alkoxides,[6] and amines.[7] The lithium *Z*-enolates of *N*-alkylideneglycinates undergo *lk*-inductive Michael additions to these acceptors,[8] and the double chiral induction in the Michael reaction between ethyl *N*-[(1*R*,4*R*)-bornylidene]glycinate and ethyl (*E*)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propenoate is absolutely *ul,lk*-selective.[9] Even in the mismatching combination in the latter case, configuration of the product exclusively depends upon the chirality of the acceptor molecule.

Combination of such reliable 1,2-chiral induction by the aid of dioxolanyl auxiliary with the excellent stereoselectivity of Michael additions of the lithium enolates of α-heterosubstituted donor molecules would provide a useful entry to a straightforward construction of three contiguous chiral centers. In the present work we aimed at extending these unusual Michael additions to asymmetric versions and also at confirming the transition structure.

N,N-Dimethylacetamide (**1a**) and *N,N*-dimethylpropanamide (**1b**), after lithiation with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at –78 °C, were reacted with ethyl (*E*)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propenoate (**2**) to give Michael adducts **3a,b**, respectively, as mixtures of diastereomers (Scheme 1 and Table 1, entries 1, 2). Although lithium *Z*-enolates are selectively generated by lithiation of propanamides, their Michael additions are much less stereoselective.[10] In order to assign the stereoselectivity observed in the reaction of **1b** with **2**, we replaced **2** with methyl (*E*)-4-methylpropenoate (**4**) as an achiral acceptor bearing a secondary β-substituent to obtain a 66:34 mixture (*anti:syn*) of diastereomers of **5a** (entry 3) whose stereochemitries were detrmined on the basis of the difference of ^{13}C chemical shifts for 2-Me (*anti*-**5a**: 15.35; *syn*-**5a**: 12.88, Scheme 2). Thus, the first major product of **3b** can be assigned to be an *anti*-isomer by analogy of stereoselectivity, but other two remained unidentified.

Lithium *Z*-enolates stabilized by intramolecular coordination are formed by the lithiation of *N,N*-dimethylmethoxyacetamide (**1c**) and (methylamino)acetylpyrrolidine (**1e**), and their Michael additions to α,β-unsaturated carbonyl acceptors proceed in a highly *syn*-selective manner.[1] So, the exclusively high *syn*-selectivities observed in their reactions with **4** are not surprising (entries 5, 8). Although similar reactions with the dioxolanylacrylate **2** were both highly *syn*-selective as anticipated, the level of chiral induction was totally different: Almost perfect chiral induction was observed for **1c** (entry 4), but the reaction of **1e** gave a 54:46 mixture of *syn*-**3e** as cyclized product (entry 7).



Scheme 1.

Table 1. Michael Reactions of 1a-e with 2 or 4 Leading to 3a-e or 5a-c

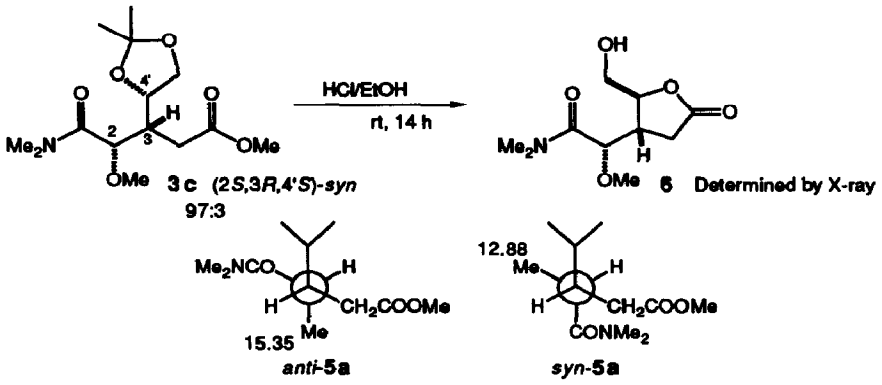
Entry	Donor	R	X	Acceptor	Temp/°C	Time/h	Adduct	Yield/%[a]	Isomer ratio[b]
1	**1a**	H	NMe_2	**2**	–78	3	**3a**	57	80:20 (-)[c]
2	**1b**	Me	NMe_2	**2**	–78	1.5	**3b**	63	69:18:13 (-)[c]
3	**1b**	Me	NMe_2	**4**	–78	1.5	**5a**	52	66:34 (*anti*-**5a**:*syn*-**5a**)
4	**1c**	MeO	NMe_2	**2**	–78	2.5	**3c**	64	97:3 (*syn*-**3c**:*anti*-**3c**)
5	**1c**	MeO	NMe_2	**4**	–78	2	**5b**	78	>99:1 (*syn*-**5b**:*anti*-**5b**)
6	**1d**	Bn_2N	OBu-*t*	**2**	–78	2	**3d**	65	93:7 (both *syn*-**3d**)
7	**1e**	MeNH	$N(CH_2)_4$	**2**	–78/–50	9/14	**3e**	36	54:46 (both *syn*-**3e**)
8	**1e**	MeNH	$N(CH_2)_4$	**4**	–78/–40	9/15	**5c**	60	>99:1 (*syn*-**5c**:*anti*-**5c**)

[a]Combined yield. [b]Determined by ^{13}C NMR spectrum of the crude mixture. [c]Not assigned.

The major diastereomer of **3c** was determined to be *syn*-**3c**[11] with a 2*S*,3*R*,4'*S* absolute stereochemistry on the basis of an X-ray crystallography[12] of its derivative **6**, which was produced by the acid-catalyzed hydrolysis of **3c** followed by lactonization (Scheme 2). The minor isomer was determined to be *anti*-**3c**[11] by comparison of the ^{13}C chemical shifts for C-2 and C-4 with those of *syn*-**3c**. On the other hand, the two diastereomers of lactam **3e** are both *syn*-isomers since (1) their $J_{2\text{-}3}$ couplings (7.7 Hz) are the same which are consistent with the *cis* stereochemistry, (2) the notable NOE was recorded between H-2 and H-3 of **5c** ($J_{2\text{-}3}$ = 7.3 Hz), and (3) their ^{13}C chemical shifts are similar except for that of C-3 (δ = 33.35 and 31.83).

It is known that the ester **1d** bearing a bulky dibenzylamino group at α-position is lithiated to form a lithium *E*-enolate whose Michael additions to α,β-unsaturated ester acceptors are highly *syn*-selective.[13] Reaction of this enolate with the dioxolanylacrylate **2** was also highly *syn*-selective to give **3d** in a 93:7

diastereoselectivity (entry 6). Their structural assignment was based on the analysis of ^1H NMR spectrum[14] and comparison of their ^{13}C chemical shifts.



Scheme 2.

In the previous communications,[1] we did not refer to the transition structure which explains the unusual *syn*-selectivity observed in the Michael additions of α-heterosubstituted esters and amides. Along with the present results, it is likely that, when the intramolecularly coordinated lithium *Z*-enolate approaches to **2** by the aid of chelation, the orbital interaction working between the highest occupied molecular orbital (HOMO) of the reacting enolate and the lowest unoccupied molecular orbital (LUMO) of the reacting acceptor **2** stabilizes the transition state as shown with **TS-A** (Figure 1). Similar stabilization by orbital interaction has been discussed in the Michael additions of the lithium *Z*-enolates of *N*-alkylideneglycinates.[2d,e,g,15] Chirality control by the dioxolanyl auxiliary is based on an extension of the Felkin-Ahn model, and a mechanism for the chiral induction by such five-membered heterocyclic auxiliaries has been reviewed.[9]

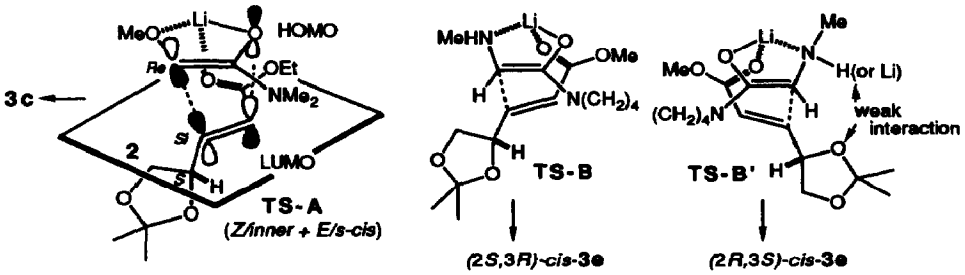


Figure 1. Transition states proposed for the *syn*-selective Michael additions of the lithium *Z*-enolates of α-heterosubstituted amides to the chiral α,β-unsaturated ester 2.

The contrastive outcomes of chiral induction between **1c** and **1e** are surprising since it is known that they both generate the intermolecularly coordinated lithium *Z*-enolates which then undergo highly *syn*-selective reactions through the transition states like **TS-A**. Although we are not confident so far whether the lithium enolate of **1e** is of the monoanion or dianion type, some weak interaction should exist between the oxygen atom adjacent to the chiral center of **2** and the NH (or NLi) moiety of the enolate so that the reaction via **TS-B'** becomes competitive to that via **TS-B**. This is we believe the case observed (entry 7).

In conclusion, the highly stereoselective and chirality-inductive Michael additions of the lithium enolates of α-heterosubstituted esters and amides to ethyl (*E*)-3-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propenoate provide a convenient synthetic entry to compounds with three contiguous chiral centers.

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11. New compounds described in this communication were characterized by spectral data and elemental analysis. *syn*-**3c**: Colorless liquid; IR (neat) 2950, 2910, 2800, 1720, 1640, 1450, 1390, 1360, 1250, 1210, 1150, 1100, 1050, 1030, 960, 910, 850, and 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.26 (3H, t, J = 7.1 Hz, Me of COOEt), 1.30, 1.37 (each 3H, s, 2'-Me), 2.42 - 2.72 (3H, m, H-2 and H-3), 2.94, 3.17 (each 3H, s, NMe_2), 3.32 (3H, s, 4-OMe), 3.54 (1H, dd, J_{gem} = 8.8 and $J_{5'-4'}$ = 7.0 Hz, one of H-5'), and 4.05 - 4.30 (5H, m, H-4, H-4', the other of H-5, and CH_2 of COOEt). ^{13}C NMR ($CDCl_3$) δ = 14.23 (Me of COOEt), 25.18, 26.39 (each 2'-Me), 32.04 (C-2), 36.20, 36.51 (each NMe), 41.17 (C-3), 57.80 (4-OMe), 60.46 (CH_2 of COOEt), 68.85 (C-5'), 74.94 (C-4'), 81.49 (C-4), 108.09 (C-2'), 170.12 (C-5), and 173.08 (C-1); MS (rel intensity, %) 318 (M^+, 5), 302 (27), 245 (25), 214 (27), 155 (29), 117 (37), 101 (base peak), 72 (42), and 43 (32). Found: C, 56.83; H, 8.56; N, 4.35%. Calcd for $C_{15}H_{27}NO_6$: 56.77; H, 8.57; N, 4.41%. ^{13}C NMR (partial, $CDCl_3$) of *anti*-**3c**: δ = 14.10 (Me of COOEt), 33.40 (C-2), 58.23 (4-OMe), 60.59 (CH_2 of COOEt), 65.94 (C-5'), 74.38 (C-4'), 78.38 (C-4), 107.56 (C-2'), and 173.43 (C-1).
12. The authors deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.
13. Yamaguchi, M.; Torisu, K.; Minami, T. *Chem. Lett.* **1990**, 377-380.
14. The major isomer of **3d** [δ = 2.01 (1H, dd, J_{gem} = 17.6 and J_{4-3} = 4.2 Hz, one of H-4), 2.46 (1H, dd, J_{gem} = 17.6 and J_{4-3} = 5.1 Hz, the other of H-4), and 3.35 (1H, d, J_{2-3} = 11.0 Hz, H-2)] was assigned to be *syn* because H-2 and H-3 occupy antiperiplanar to each other (J_{2-3} = 11.0 Hz) and the difference of magnetic shielding for two H-4s (δ = 2.01 and 2.46) are only moderate. *Anti*-isomer in general shows much larger difference due to a strong anisotropy from the nitrogen atom attached at the 2-position.
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