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Unusual Diastereofacial Selectivity in the Michael Addition Reactions of Lithiated 2-Aminoacetates and -acetamides to α,β-Unsaturated Carbonyl Compounds

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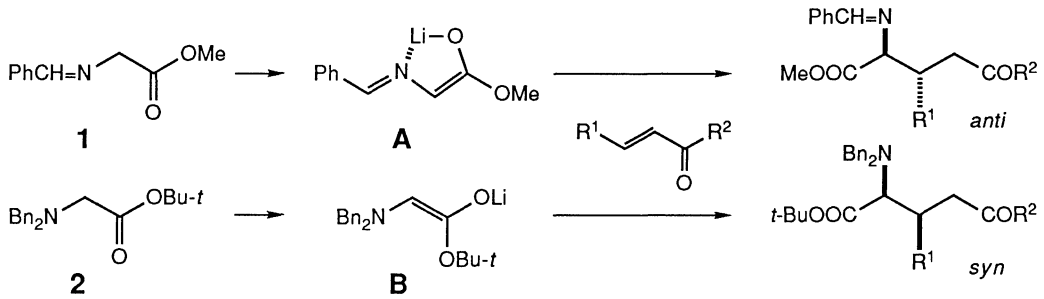
Unusual diastereofacial selectivities are observed in the Michael addition reactions of lithiated aminoacetates and -acetamides to α,β-unsaturated carbonyl acceptors. Lithiated (methylamino)acetates and -acetamides show opposite *anti*- and *syn*-selectivities, respectively, while lithiated (dialkylamino)acetates and -acetamides are both highly *syn*-selective.

Although Michael addition is one of the most valuable carbon-carbon bond forming processes, systematic study has only recently started on the diastereofacial selectivity between the prostereogenic reaction centers. The mechanistic aspect still remains ambiguous.[1,2] Michael addition of metalated aminoacetates to α,β-unsaturated esters, leading to glutamate derivatives, is important in the field of α-amino acid chemistry. We have reported the exclusively *anti*-selective Michael additions of lithiated (alkylideneamino)acetates **1** to α,β-unsaturated carbonyl compounds. Frontier orbital- and chelation-controlled rigid transition state of *Z*-enolates **A** was proposed to be responsible for high *anti*-selectivities.[3] The lithium *E*-enolates **B** derived from α-dibenzylamino esters **2**[4] undergo exclusively *syn*-selective Michael addition, making a striking contrast to our results.[5]

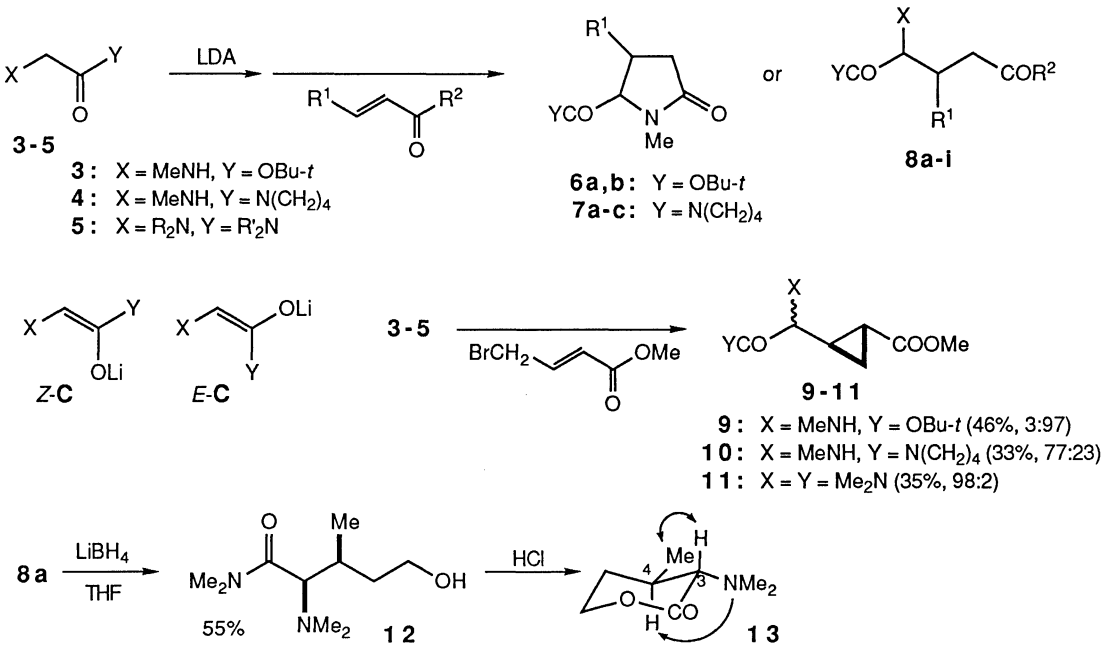


Lithiated alkoxyacetates have shown rather poor selectivities in the Michael additions to α,β-unsaturated carbonyl acceptors, while reactions of lithiated alkoxyacetamides are highly *syn*-selective.[6] We were interested in such dependence of selectivity on the nature of enolate-stabilizing and α-hetero substituents, and continued a study of Michael additions of lithiated α-hetero acetates and acetamides.[7]

In this communication, we describe the unusual diastereofacial selectivities observed in the study of Michael additions of lithiated aminoacetates and -acetamides. Lithiated (methylamino)acetates and -acetamides

show high selectivities, but with opposite combinations of unlike and like faces (or with *anti*- and *syn*-selectivities), respectively. On the other hand, reactions of lithiated (dialkylamino)acetates and -acetamides are both *syn*-selective, with excellent selectivities in the latter cases.

t-Butyl (methylamino)acetate (**3**) and *N*-[(methylamino)acetyl]pyrrolidine (**4**) were lithiated with LDA in THF at –78 °C and allowed to react with α,β-unsaturated esters. Although structures of the enolates generated could not be directly assigned, selective formation of *Z*-enolates *Z*-**C** is more likely by analogy to the previous cases of *Z*-enolate generation from α-alkoxyacetates and -acetamides.[8] The products were diastereomers of 5-oxopyrrolidines **6a,b** and **7a-c** which were formed through cyclization of the initial Michael adducts (Scheme 1 and Table 1, Entries 1-5). The pyrrolidinones **6a,b** derived from aminoacetate **3** were almost pure 2,3-*trans*-isomers,[9] indicating the far predominant formation of *anti*-Michael adducts as unisolable products. On the other hand, pyrrolidinones **7a-c** derived from aminoacetamide **4** were composed of more *cis*-isomers. The selectivity was satisfactorily high when the β-substituent of acceptor molecules was bulky (Entry 5).[10] No satisfactory explanation is available so far for the reversal of stereoselectivity.



Scheme 1.

Lithiation of α-dialkylamino esters **2** is known to generate *E*-enolates **B**,[4,11] while the exclusive formation of *Z*-enolates *Z*-**C** is expected from α-dialkylamino amides **5** on the ground of steric repulsion between two bulky amino moieties.[1a,12] Michael additions of the lithium enolates of amides **5** to a variety of α,β-unsaturated carbonyl compounds were highly diastereoselective (Entries 6-14). The major isomers of **8a-i** were assigned to be *syn*-Michael adducts by a conversion of adduct **8a** (*syn:anti* = 96:4). Thus, the $LiBH_4$ reduction of **8a** gave amide alcohol **12** (55%) which was then cyclized to lactone **13** as a single isomer. Its stereochemistry was based on NOE spectrum (Scheme 1). Such high *syn*-selectivities from *Z*-enolates are also unusual from the standpoint of Heathcock's transition model.[1a,b]

Several Michael additions of **5** are thermodynamically controlled. For example, reactions of **5a,c** with methyl cinnamate showed much lower selectivities at –78 °C (*syn:anti* = 60:40 and 71:29) than those at 0 °C or

room temperature (*syn:anti* = 91:9 and 81:19, respectively). These results contrast with the virtually unchanged selectivities of the reactions with methyl crotonate (Entries 6, 11, and 12). When a thermodynamically more stable acceptor like the cinnamate is incorporated in Michael adduct, the retro process becomes relatively more favored under severe conditions.[13] Michael reactions of enones such as (*E*)-1-phenyl-2-buten-1-one and (*E*)-2,2-dimethyl-4-hexen-3-one would be also thermodynamically controlled at 0 °C or higher.

Table 1. Michael Addition of Lithiated α-Amino Acetate **3** and Amides **4**, **5** to α,β-Unsaturated Carbonyl Compounds[a]

Entry		X	Y	R^1	R^2	Temp/°C	Time/h	Product	Yield/%[b]	*syn:anti*[c]
1	**3**	MeNH	OBu-*t*	Me	OMe	–78/–50	3/2	**6a**	39	4:96
2	**3**	MeNH	OBu-*t*	Ph	OMe	–78/–50	4/12	**6b**	27	2:98
3	**4**	MeNH	$N(CH_2)_4$	Me	OMe	–78/–50	3/22	**7a**	67	68:32
4	**4**	MeNH	$N(CH_2)_4$	Ph	OMe	–78/–50	3/21	**7b**	75	75:25
5	**4**	MeNH	$N(CH_2)_4$	*i*-Pr	OMe	–78/–50	3/12	**7c**	60	>99:1
6	**5a**	Me_2N	NMe_2	Me	OMe	0	5	**8a**	71	97:3[d]
7	**5a**	Me_2N	NMe_2	Ph	OMe	0	7	**8b**	64	91:9[d]
8	**5a**	Me_2N	NMe_2	*i*-Pr	OMe	0	8	**8c**	42	75:25[d]
9	**5a**	Me_2N	NMe_2	Me	Ph	0	7	**8d**	87	88:12[d]
10	**5a**	Me_2N	NMe_2	Me	*t*-Bu	0	9	**8e**	85	77:23
11	**5b**	Me_2N	$N(CH_2)_4$	Me	OMe	0	6	**8f**	73	92:8[d]
12	**5c**	$N(CH_2)_4$	$N(CH_2)_4$	Me	OMe	0	7	**8g**	65	98:2[d]
13	**5c**	$N(CH_2)_4$	$N(CH_2)_4$	Ph	OMe	rt	8	**8h**	58	81:19[d]
14	**5c**	$N(CH_2)_4$	$N(CH_2)_4$	Ph	$N(CH_2)_4$	0	7	**8i**	70	91:9[d]

a) Lithiation was performed with LDA in THF. b) Isolated yield. c) Determined by ^1H NMR and/or HPLC. d) Selectivities observed in the reactions at –78 °C are as follows: Entries 6 (99:1); 7 (60:40); 8 (78:22); 9 (84:16); 11 (94:6); 12 (99:1); 13 (71:29); 14 (85:15).

As mentioned above, reactions of lithium enolates of **3-5** with 3-alkylacrylates were kinetically controlled. Constantly high selectivities were observed regardless of the reaction temperatures (between –78 °C and 0 °C). In addition, reactions of the lithium enolates of **3-5** with methyl (*E*)-4-bromo-3-butenoate at –78 °C produced methyl *trans*-cyclopropanecarboxylates **9-11** through intramolecular cyclization of the Michael adduct enolates. The observed selectivities are shown in Scheme 1 for *syn:anti* ratios which are almost comparable to the kinetic selectivities observed in the reactions of enolates of **3-5** with methyl crotonate.[14]

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8) Structural assignment of the resulting lithium enolates by *O*-silylation or *O*-acetylation was unsuccessful because of the formation of labile trihetero-substituted ethenes. See Ref. 6 for the structural determination of lithiated methoxyacetates and -acetamides.

9) The far major isomer of **6a** was assigned to be 2,3-*trans*-isomer on the basis of $J_{2\text{-}3}$ = 4.0 Hz and NOE between H-2/3-Me.

10) The both isomers of **7b** were assigned as follows on the basis of the spectral data shown in parenthesis. the major isomer: 2,3-*cis* ($J_{2\text{-}3}$ = 8.4 Hz and NOE between H-2/H-3); the minor isomer: 2,3-*trans* ($J_{2\text{-}3}$ = 4.4 Hz).

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14) Stereochemistries of **9-11** were tentatively assigned on the basis of those observed in the Michael reaction with methyl crotonate.

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