A New Methodology for Stereocontrolled Carbon-Carbon Bond Formation. Frontier Orbital- and Chelation-Controlled Diastereoselective Michael Additions of α-Amino Esters Leading to Unnatural Amino Acid Derivatives

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A New Methodology for Stereocontrolled Carbon-Carbon Bond Formation. Frontier Orbital- and Chelation-Controlled Diastereoselective Michael Additions of α-Amino Esters Leading to Unnatural Amino Acid Derivatives

Shuji KANEMASA

The rigid transition state, proposed previously for the stereoselective cycloadditions of *N*-metalated azomethine ylides, has been successfully applied to establish highly stereoselective Michael additions of methyl (2,2-dimethylpropylideneamino) acetate with α, β-unsaturated carbonyl compounds. Use of camphor imines of glycinates offers an efficient method for diastereoselective Michael additions to produce the optically active α-amino ester derivatives of unnatural types.

Introduction

In 1987, we have reported for the fist time the generation of *N*-metalated azomethine ylides of cyano-stabilized types, as a new 1,3-dipole, by treating imines of α-amino nitriles with lithium diisopropylamide (LDA) or Grignard reagents.[1] Next year, this concept has been extended to the reversible generation of *N*-lithiated azomethine ylides of ester-stabilized types.[2,3] Thus, treatment of imines of α-amino esters with a weak base in tetrahydrofuran (THF), such as lithium bromide and triethylamine (or lithium bromide and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU)), generates *N*-lithiated azomethine ylides.

It should be emphasized that these *N*-metalated ylides undergo exclusively high regio- and stereoselective cycloadditions with α, β-unsaturated carbonyl compounds to produce pyrrolidine-2-carboxylates as single stereoisomers. Chelation-stablized rigid transition state is the most likely mechanism involved in the reaction, and this is certainly responsible for the observed high selectivity.[2]

Metals such as lithium, sodium, magnesium, zinc, aluminum, and titanium can be successfully incorporated in *N*-metalated azomethine ylides of ester-stabilized types. Their reactivity, regioselectivity, and stereoselectivity in cycloadditions with α, β-unsaturated carbonyl compounds are found to change depending upon the properties of metals.[4-6] Especially influential are the ability of chelate formation and the size of metal ligands.

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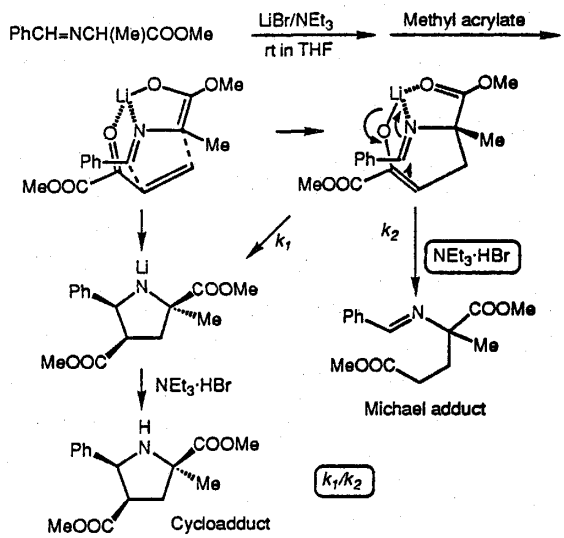
During our investigation on these unusual and reactive intermediates, we have found that the reaction of methyl 2-(benzylideneamino) propanoate with methyl acrylate, as a dipolarophile, in the presence of lithium bromide/triethylamine leads to the formation of a single stereoisomer of pyrrolidine-2,4-dicarboxylate cycloadduct (79%) together with the corresponding Michael adduct (16%) as a minor product (SCHEME I).[4] Our intensive screening study of the reaction conditions, aiming at the development of a procedure to suppress the formation of undesired Michael adducts, has unveiled that 1) this reaction takes place through a rigid chelation-stabilized transition state, 2) a new carbon-carbon bond is formed between the α-carbon of ylide and the β-carbon of acrylate to give a Michael adduct enolate intermediate, 3) the intramolecular cyclization of this intermediate leads to the cycloadduct, and 4) the quenching of the intermediate with triethylammonium chloride produces the Michael adduct.



SCHEME I

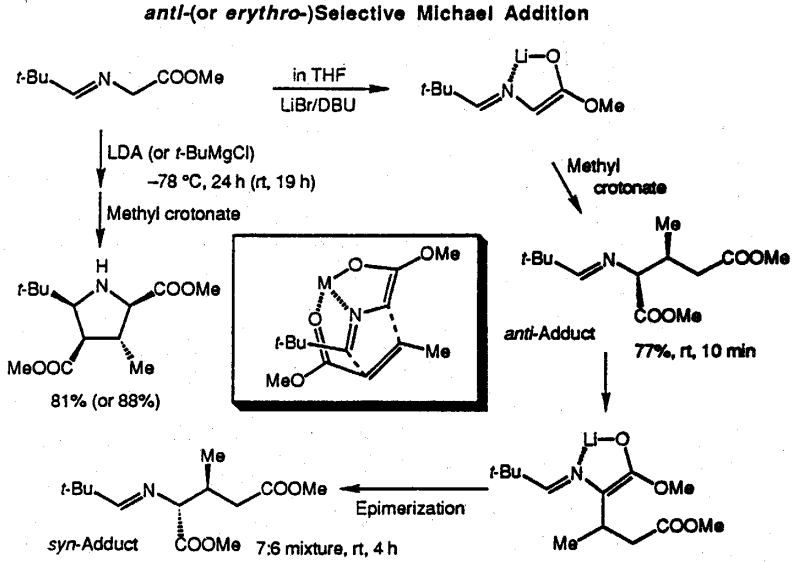
Based on our conclusion that cycloaddition and Michael addition compete each other by starting from the Michael adduct enolate as common intermediate, the successful control of relative rate k_1/k_2 would make this competitive reaction system useful as a stereoselective route leading to both pyrrolidine-2,4-dicarboxylates and *N*-alkylideneglutamates. A little later, we have found that the Michael addition pathway can be sufficiently suppressed by performing the reaction in a diluted solution.[4] This is quite reasonable because the rate of intramolecular cyclization must be relatively independent of the concentration of reactants.

If the intramolecular cyclization by the second carbon-carbon bond formation can be effectively inhibited, the formation of Michael adduct would become a major pathway. Since these Michael reactions proceed through a rigid chelation-stabilized transition state, exclusively high stereoselectivity is expected, presumably *anti*- or *erythro*-selective Michael addition on the basis of the stereoselectivity

observed previously in cycloadditions. Our plan was to utilize the imines of α-amino esters which consist of a bulky carbonyl compound such as 2,2-dimethylpropanal (pivalaldehyde).

Stereoselective Michael Additions

The *N*-lithio- or *N*-magnesioazomethine ylide, when generated from methyl (2,2-dimethylpropylideneamino) acetate (hereafter referred to as the glycinate imine) by treatment with lithium diisopropylamide (LDA) or *t*-butylmagnesium chloride in THF, unexpectedly undergoes a stereoselective cycloaddition with methyl crotonate to give the pyrrolidine-2,4-dicarboxylate as a single stereoisomer, indicating that the irreversible ylide generation method is not suitable for Michael addition (SCHEME II).[7]



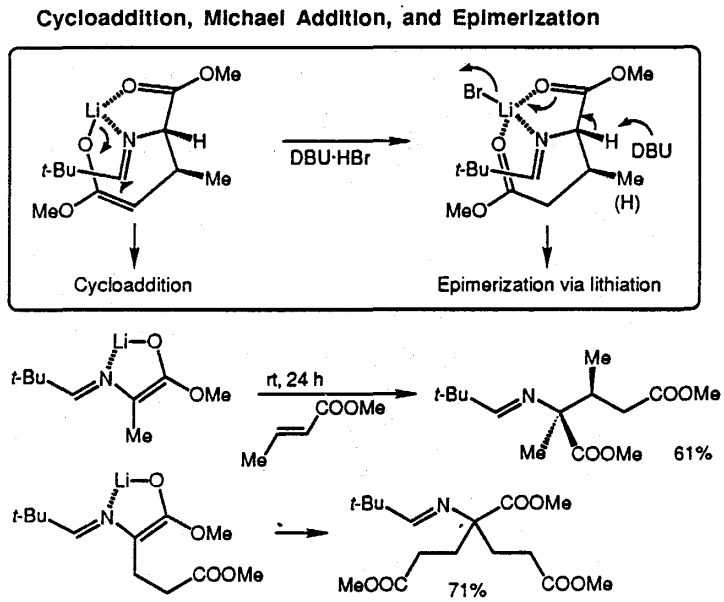
SCHEME II

In contrast with this result, the same *N*-lithiated ylide, when generated by treatment with lithium bromide/DBU in THF, is found to react with methyl crotonate to give *anti*-Michael adduct as a single stereoisomer. This *anti*-selectivity is the one expected from the chelation-stabilized transition state which was previously proposed for stereoselective cycloadditions.[2]

Treatment of this imine with lithium bromide/triethylamine in THF at room temprature fails to generate the *N*-lithiated ylide, indicating that the lack of ylide stabilization in the present case, compared with the ready ylide generation from methyl (benzylideneamino)acetate, is only overwhelmed by use of a combination of stronger base.[2]

The *anti*-Michael adduct gradually isomerizes into the *syn*-Michael adduct under the conditions of Michael addition, a 7:6 equiliberating mixture of these isomers having resulted after 4 h at room temperature. Accordingly, the optimization of reaction conditions is strongly required.

The above results are summarized as follows:[7] The *N*-lithiated azomethine ylides derived from the glycinate imine reacts with methyl crotonate to form the stereoselective Michael adduct enolate. When the ylide has been generated irreversibly, no quenching reagent exists in the reaction system, allowing the adduct enolate intermediate to survive. The only pathway allowed to this intermediate is cyclization leading to the stereoselective cycloadduct (SCHEME III). On the other hand, when the ylide has been generated reversibly, the Michael adduct enolate is quenched with triethylammonium bromide to give the *anti*-Michael adduct. However, the resulting stereoselective Michael adduct, which corresponds to an α-alkylated derivative of the starting imine, can be again lithiated by the action with lithium bromide/DBU. This is the route for epimerization.

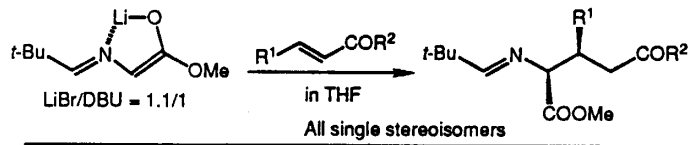


SCHEME III

No optimization of reaction temperature and time is needed when the α-carbon of imines is already substituted since there is no possibility for subsequent epimerization. Thus, the Michael addition of methyl 2-(2,2-dimethylpropylideneamino)propanoate (hereafter referred to as the alanate imine) with methyl crotonate is exclusively stereoselective, no trace of epimerization being observed after the lapse of prolonged reaction time.

It is quite difficult to control the reaction at the step of 1:1 adduct formation between the glycinate imine and methyl acrylate. As described above, the 1:1 Michael adduct suffers from α-lithiation under the reaction conditions. The second lithiation in this case is extremely easy, compared with the case of 1:1 adduct derived from methyl crotonate, since the α-carbon of 1:1 Michael adduct is only substituted by a sterically less hindered primary alkyl substituent.

Reactions with Enones



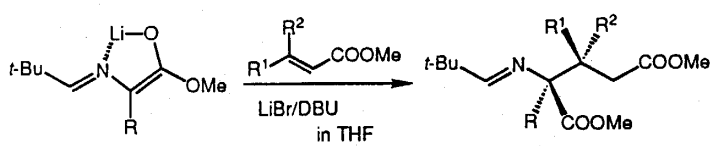
All single stereoisomers

Reaction conditions	Substituent	Yield/%
–5 °C, 15 min	$R^1 = R^2 = Me$	80
–5 °C, 15 min	$R^1 = Ph$, $R^2 = Me$	97
–5 °C, 1 h	$R^1 = t$-Bu, $R^2 = Me$	44
–5 °C, 15 min	$R^1 = Me$, $R^2 = Ph$	93
–5 °C, 30 min	$R^1 = PhCH{=}CH(E)$, $R^2 = Ph$	93

SCHEME IV

Under carefully controlled reaction conditions, reactions of the glycinate imine with a variety of enones in the presence of lithium bromide/DBU (1.1/1) in THF produce satisfactory yields of *anti*-Michael adducts as single diastereomers in all cases, where the contamination by undesired epimerization products has beenabsolutely suppressed (SCHEME IV).[7]

Reactions with Dimethyl Fumarate and Maleate



With Dimethyl fumarate (R^1 = COOMe, R^2 = H)

R = Me	1.1/1	rt, 17 h	88%	6:1
	1.1/1	–10 °C, 10 min	52%	32:1
R = H	1.1/1	–15 °C, 15 min	97%	6.7:1
	0.1/0.1	–15 °C, 80 min	quant	single
	0.1/0.1	rt, 15 h	94%	single

With Dimethyl maleate (R^2 = COOMe, R^1 = H)

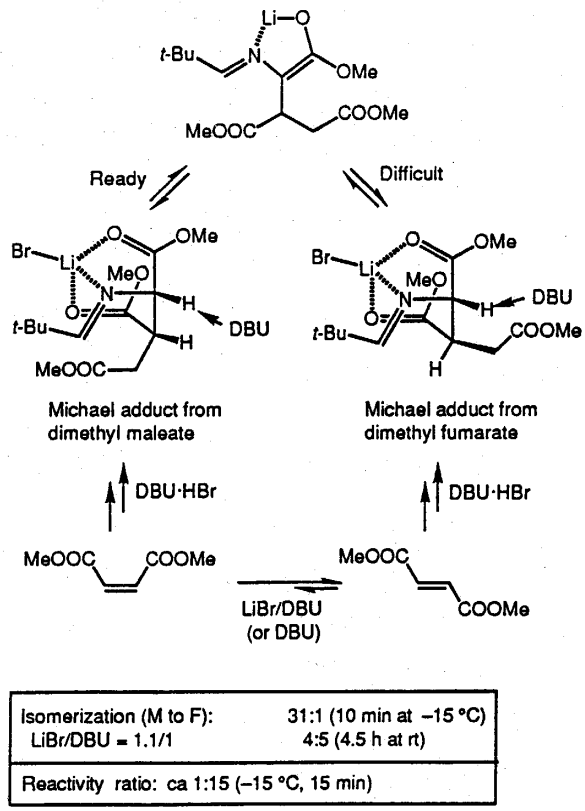
R = Me	1.1/1	rt, 5 h	85%	4:1
	0.1/0.1	rt, 20 h	64%	12:1
R = H	1.1/1	–15 °C, 5 min	91%	2.5:1
	0.1/0.1	–15 °C, 90 min	quant	single

SCHEME V

Dimethyl fumarate and maleate stereospecifically produce *anti*- and *syn*-Michael adducts, respectively, in Michael reactions with *N*-lithiated azomethine ylides. Although no epimerization is possible, the diastereoselectivities observed in reactions of the alanate imine at room temperature are

rather low (SCHEME V). It is not very surprising that a better selectivity (32:1) has been obtained at a lower temperature, but it is noteworthy that employment of a catalytic amount of lithium bromide/DBU has increased selectivity (12:1).

High diastereoselectivity is observed again when a catalytic amount of lithium bromide/DBU is employed in Michael additions of the *N*-lithiated azomethine ylide derived from the glycinate imine with dimethyl fumarate and maleate.

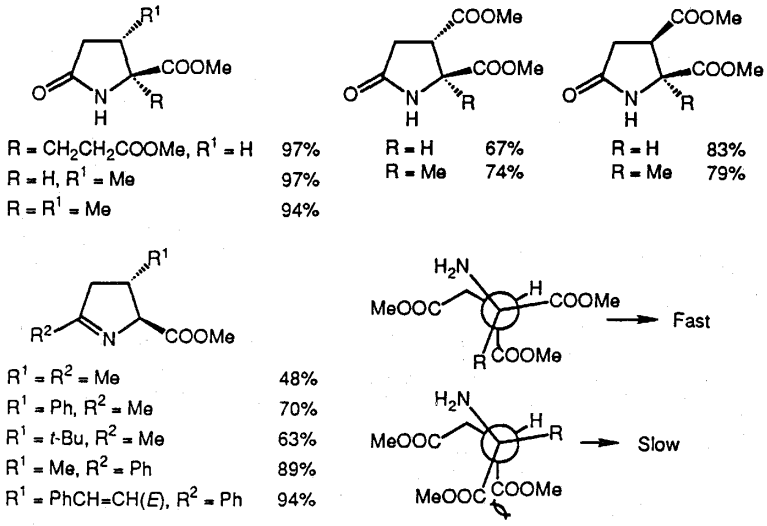


SCHEME VI

Michael additions of dimethyl fumarate, both with *N*-lithiated azomethine ylides derived from the glycinate imine and the alanate imines, are more diastereoselective than those of dimethyl maleate. In addition, the Michael adduct formed from dimethyl maleate undergoes epimerization more rapidly than the adduct formed from dimethyl fumarate. More rapid epimerization of the maleate adduct is explained by the less steric congestion around the α-hydrogen which is to be abstracted (SCHEME VI). Although dimethyl maleate is found to isomerize into dimethyl fumarate under the conditions of Michael addition, the rate of isomerization is too slow compared with that of Michael addition: Dimethyl maleate changes into a 31:1 mixture with dimethyl fumarate when treated with lithium bromide/DBU at −15°C for 10min, and a 4:5 mixture at room temperature for 4.5 h. Even if the faster reaction rate in the Michael addition with dimethyl fumarate (15:1 at −15°C) is taken into

account, the difference of diastereoselectivity can not be fully interpreted.

Hydrolytic Cyclization of Michael Adducts



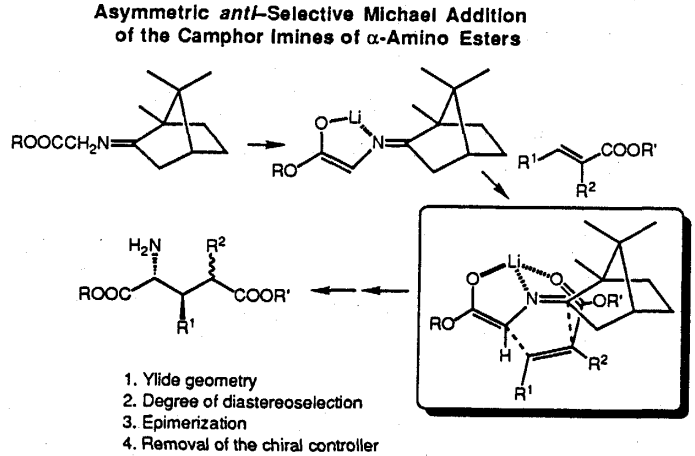
SCHEME VII

Stereoselective Michael adducts thus formed undergo readily and quantitative hydrolytic cleavage of the imine bond when treated with aqueous acetic acid (SCHEME VII). The Michael adducts formed from α, β-unsaturated esters and α, β-ketones are stereospecifically converted into 5-oxopyrrolidine-2-carboxylates and 1-pyrroline-5-carboxylates, respectively.

Asymmetric and Diastereoselective Michael Additions

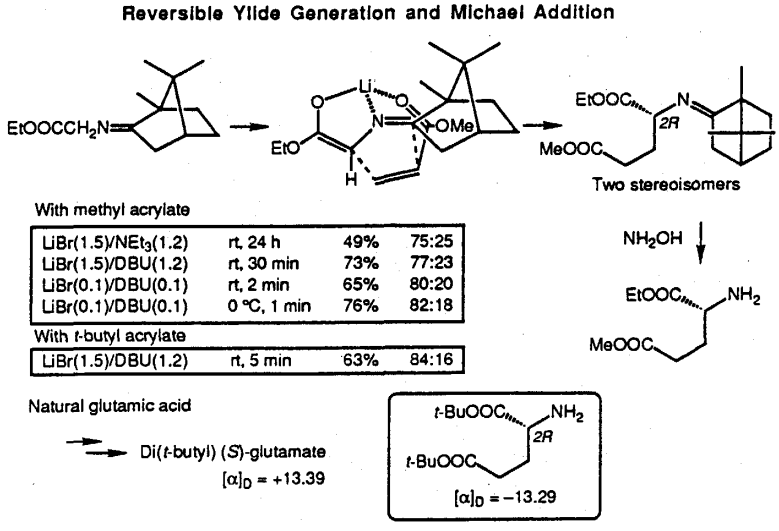
The stereoselective Michael addition mentioned above is now found to offer a powerful and versatile strategy for the stereoselective synthesis of α-substituted α-amino acids. To increase their synthetic versatility, we have next challenged to open asymmetric versions of these stereoselective Michael additions. There are some strategic approaches possible to attain this purpose, containing the use of chiral imine esters derived from optically active alcohols or carbonyl compounds and the use of chiral dipolarophiles.[8]

The camphor imines of glycinates are the chiral imines of our choice.[9] Since *(R)*-camphor is inexpensive ketone available in an optically pure form, which would be sterically bulky enough to inhibit the cycloaddition pathway (See SCHEME I), they are expected to work well as chiral auxiliary in these reactions. Some points to be solved are: [1] the stereoselective generation of *N*-lithiated azomethine ylides, or lithium enolates, [2] the achievement of an excellent diastereofacial selectivity, [3] the effective inhibition of α-epimerization, and [4] the removal of camphor auxiliary without epimerization (SCHEME VIII).



SCHEME VIII

Ethyl (bornylideneamino)acetate (camphor imine of ethyl glycinate) is readily accessible by condensation of *(R)*-camphor with ethyl aminoacetate.[10] Although the camphor imine of ethyl glycinate can be lithiated with lithium bromide/triethylamine or lithium bromide/DBU, a higher temperature than 0°C is needed (SCHEME IX). The *N*-lithiated ylide thus generated undergoes a smooth Michael addition with methyl acrylate to provide a mixture of two diastereomeric Michael adducts. When the reaction is carried out with a catalytic amount of lithium bromide/DBU at 0°C, the maximum selectivity achieved is 82:18. Use of *t*-butyl acrylate instead of methyl ester increases the selectivity, but a little bit (84:16). This will be discussed below.

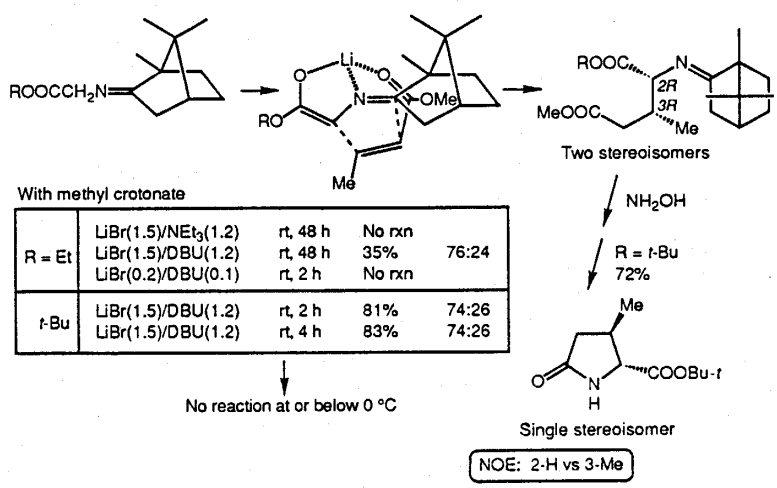


SCHEME IX

Under the conditions of Michael addition, no epimerization at the α-position of Michael adducts takes place. The steric inhibition of epimerization is so effective that no 2:1 Michael adducts with acrylates are formed. This result makes a striking contrast with the ready 2:1 adduct formation in the Michael reaction of methyl (2,2-dimethylpropylideneamino)acetate with methyl acrylate (See SCHEME III).

The camphor auxiliary can be readily removed by treating Michael adducts with hydroxylamine. Thus, the Michael adduct, obtained from *t*-butyl (bornylideneamino)acetate (camphor imine of *t*-butyl glycinate) and *t*-butyl acrylate, is treated with hydroxylamine under reflux in ethanol to give di(*t*-butyl) glutamate. By comparison of the sign of its optical rotation with that of the di(*t*-butyl) glutamate derived from natural glutamic acid, Micahel additions of camphor imines are found to occur at the *re*-face of the ylide (or enolate) plane. The α-substituted α-amino esters formed in these Michael additions are therefore unnatural types.

Reactions of the camphor imines with crotonates at room temperature are too sluggish when lithium bromide/triethylamine or a catalytic amount of lithium bromide/DBU is used. Use of more than one equivalent amount of lithium bromide/DBU is needed to generate *N*-lithiated ylides, which undergo exclusively *anti*-selective Michael additions with crotonates (SCHEME X). Thus, only two diastereomeric adducts are produced among four possible diastereomers, which are further transformed into single stereoisomers of *trans*-3-methyl-5-oxopyrrolidine-2-carboxylates by removal of the camphor auxiliary.



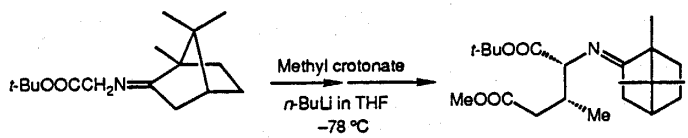
SCHEME X

As descrived above (SCHEME II),[4] *N*-metalated azomethine ylides undergo cycloadditions with α, β-unsaturated esters rather than Michael additions when the irreversible ylide generation employing LDA or *t*-butylmagnesium chloride is applied. In the cases of camphor imines, however, irreversible ylide generation can be employed as well for Michael reactions, indicating the effective inhibition of

cyclization due to a high steric congestion around the imine carbon.

Irreversible ylide generation can be performed at −78°C by treating LDA with the camphor imine of methyl glycinate, or by using butyllithium to the camphor imine of *t*-butyl glycinate (SCHEME XI). Although ylide generation using only LDA results in a poor diastereoselectivity or a poor yield of Michael adduct, the addition of a basic or acidic additive such as triethylamine, water, or boron trifluoride is found to improve both of them. In the end, a sequence of ylide generation with butyllithium at −78°C in THF, pretreatment of the resulting ylide with *t*-butyl alcohol, and Michael addition is found as an effective procedure to attain a satisfactory result.

Irreversible Ylide Generation and Michael Addition

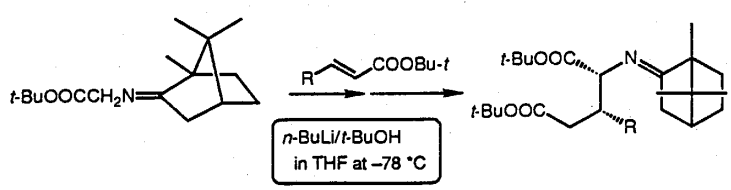


n-BuLi	Additive (equiv)	Yield/%	Isomer ratio
1.1	DIA (1.1)	88	60:40
0.5	DIA (1.1)	14	87:13
1.1	DIA (0.5) + NEt_3 (0.6)	67	78:22
1.1	DIA (1.1) + H_2O (1)	88	80:20
1.1	DIA (1.1) + BF_3•Et_2O (1)	95	84:16
1.1	DIA (1.1) + *t*-BuOH (1)	100	85:15
1.1	*t*-BuOH (1)	98	86:14

Maximum ratio: 86:14

SCHEME XI

Use of *t*-Butyl Acrylate and Crotonate



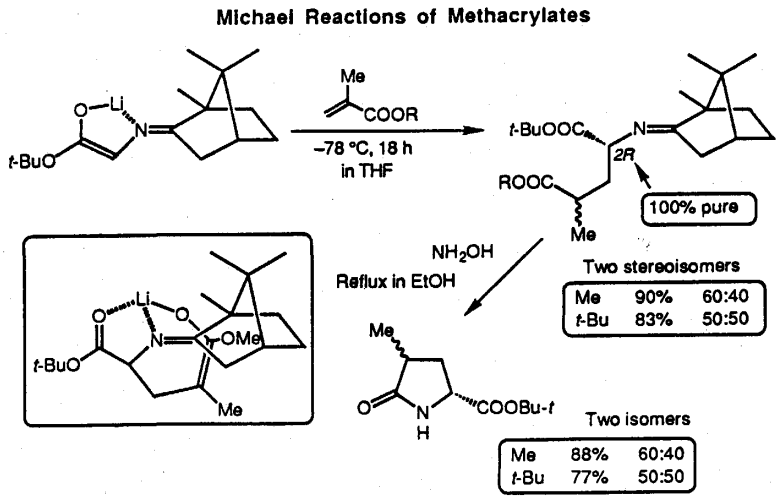
	t-BuOH	Yield/%	Isomer ratio
R = H	1	89	95:5
Me	0.5	69	94:6
	1	88	95:5
	2	78	93:7
	3	80	92:8

Maximum ratio: 95:5

SCHEME XII

As described above (See SCHEME IX), *t*-butyl esters of acrylic and crotonic acids show higher diastereoselectivity than the corresponding methyl esters in Michael additions using the camphor imines. Combination of the irreversible ylide generation, by using butyllithium and *t*-butyl alcohol in THF at −78°C, and t-butyl esters of olefinic dipolarophiles leads to a diastereomer ratio as high as 95:5 at best (SCHEME XII). Three equivalent amounts of *t*-butyl alcohol can be employed without trouble.

It is quite interesting that the Michael reaction using a methacrylate, under similar reaction conditions, gives a mixture of only two diastereomeric adducts, albeit in a very poor diastereomer ratio (60:40 to 50:50), after hydrolytic quenching (SCHEME XIII). Since the hydrolytic quenching of Michael adduct anions must be nonstereoselective, the diastereofacial selectivity with respect to the ylide face is concluded to be 100% selective. Actually, removal of the camphor auxiliary provides a comparable mixture of two stereoisomers of 5-oxopyrrolidine-2-carboxylate.



SCHEME XIII

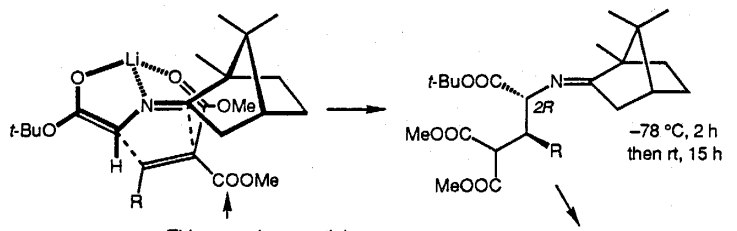
The absolute diastereofacial selectivity observed in the reactions with methacrylates indicates that [1] the camphor imines generate the *Z,E*-isomers of *N*-lithiated ylides in an absolutely stereoselective manner and [2] the resulting ylides undergo perfectly diastereoselective Michael additions with the α, β-unsaturated carbonyl compounds bearing an α-substituent.

Alkylidenemalonates would work as excellent Michael acceptors in which a conjugated *gem*-diester structure exists.[11] Since one of these ester moieties functions as an α-substituent to the other ester moiety, this group is expected to work to achieve the 100% diastereofacial selectivity in Michael additions with the camphor imines. Unlike methacrylate acceptors, use of alkylidenemalonates has another synthetic advantage that hydrolytic quenching of the Michael adduct anions adds no chiral center.[11]

As expected, Michael additions of the camphor imines with a variety of alkylidenemalonates are

found to take place in exclusively diastereoselective manners. Single diastereomers are produced in all cases, except for the reaction of dimethyl ethylidenemalonate, in which the anti adduct is accompanied by a small amount of syn adduct (SCHEME XIV). Contamination by the syn adduct in the case of ethylidenemalonate would be due to the relatively small steric size of the methyl substituent.

Absolutely Diastereoselective Michael Additions of Alkylidenemalonates



R	Yield	Ratio	Yield*
Me	67%	86:16	93%
Et	92%	single	84%
t-Bu	86%	single	64%
Ph	94%	single	64%
MeCH=CH (*E*)	96%	single	90%
PhCH=CH (*E*)	68%	single	75%
MeOCH=CH (*E*)	60%	single	77%

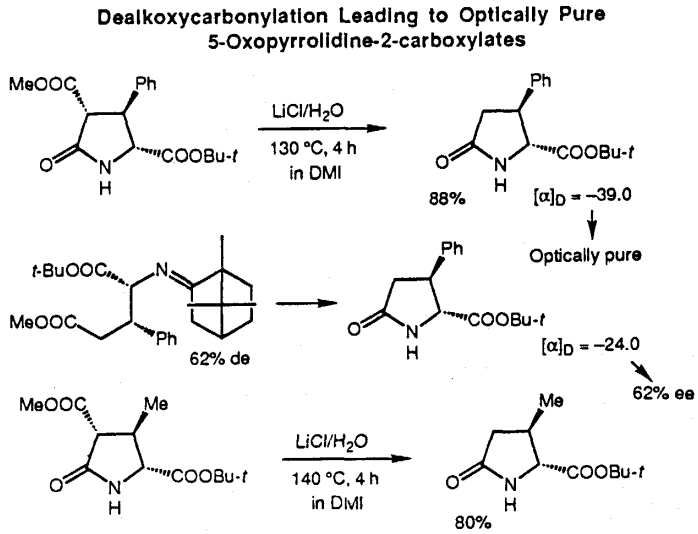
*Yield of 5-oxopyrrolidine-2,5-dicarboxylates

SCHEME XIV

Removal of the camphor auxiliary leads to *2R,4S*-enantiomers of 2,3-*trans*-3,4-*trans*-5-oxopyrrolidine-2,4-dicarboxylates. Stereoselective formation of the *4S*-configuration (4-COOMe) is not important since this position is readily enolizable so as to be settled to the thermodynamically most stable configuration.

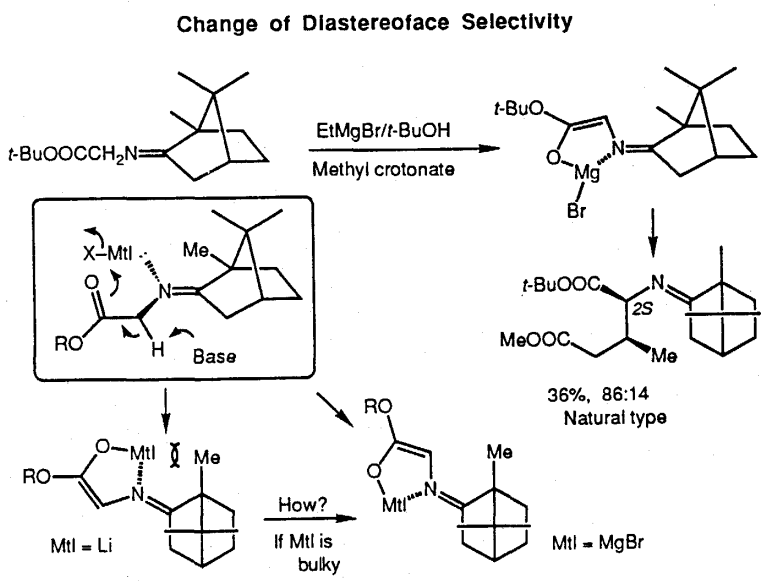
The methoxycarbonyl moiety at the 4-position of optically pure 5-oxopyrrolidine-2,4-dicarboxylates can be directly removed through a dealkoxycarbonylation process where 1,3-dimethyl-imidazolidin-2-one (DMI) can be used as an excellent polar solvent (SCHEME XV). The demethoxycarbonylation products thus obtained correspond to optically pure enantiomers of the compounds which are derived from a sequence of Michael additions of the camphor imines with α , β -unsaturated esters, removal of the camphor chiral auxiliary, and subsequent cyclization. Thus, the Michael additions using alkylidenemalonates presents an alternative synthetic route to 3-substituted 2,3-*trans*-5-oxopyrrolidine-2-carboxylates in optically pure forms.

When *t*-butyl (bornylideneamino) acetate is treated with a Grignard reagent such as ethylmagnesium bromide in THF, the corresponding *N*-magnesioazomethine ylide is generated. This ylide, after pretreated with *t*-butyl alcohol, undergoes Michael addition with methyl crotonate to produce an 86:14 diastereomeric mixture of *anti*-Michael adduct. To our surprise, the major isomer has a *2S*-configuration, natural type stereochemistry (SCHEME XVI). A likely explanation is the predominant generation of *Z,Z*-ylide in this case. The steric size of magnesium itself or that of metal group



SCHEME XV

including the bromine ligand is much larger than lithium. Steric repulsion of the metal part to the 1-methyl substituent of camphor would be one reason for the reverse of selectivity. However, details for the inversion mechanism of the imine nitrogen are not clear.



SCHEME XVI

This result indicates a possibility that the diastereofacial selectivity may be reversed only by changing the metal of ylides. Intensive research along this line is now in progress.

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