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Absolutely Diastereoselective Asymmetric Michael Addition of the Camphor Imine of t-Butyl Aminoacetate with 2-Alkylidenemalonates

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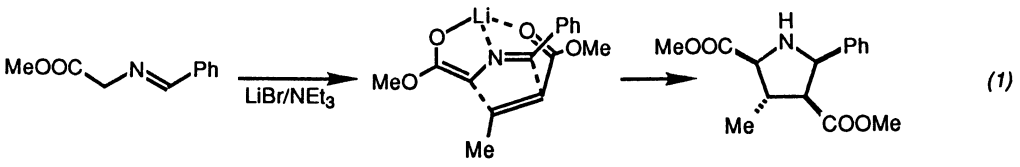
The lithium enolate generated from t-butyl (bornylideneamino)-acetate and butyllithium in the presence of t-butyl alcohol undergoes highly diastereoselective asymmetric Michael addition with a variety of α,β-unsaturated esters to afford the anti derivatives of 3-substituted glutamates with 2R-configuration as major products. Use of 2-alkylidenemalonates as Michael acceptors leads to 100% diastereoselective Michael additions.

It has been recently found[1] that action of lithium bromide/triethylamine (or 1,8-diazabicyclo[5.4.0]undec-7-ene, DBU) on methyl (benzylideneamino)acetate in tetrahydrofuran (THF) generates N-lithiated azomethine ylide, which can be stereoselectively trapped with α,β-unsaturated carbonyl compounds to produce pyrrolidine-2-carboxylates. Equation 1 shows the reaction with methyl crotonate as a typical example. A tight chelation of the lithium atom with the imine nitrogen and the carbonyl oxygen atoms is presumably responsible for this high stereoselectivity. Since it has been later found that these cycloadditions proceed stepwise via the corresponding Michael adduct intermediates,[2] it is expected that a new entry to highly stereoselective Michael additions would be open by utilization of this reaction sequence. The path leading to Michael addition would predominate over the path leading to cycloaddition if the starting imines are derived from a sterically bulky carbonyl compound.[3]



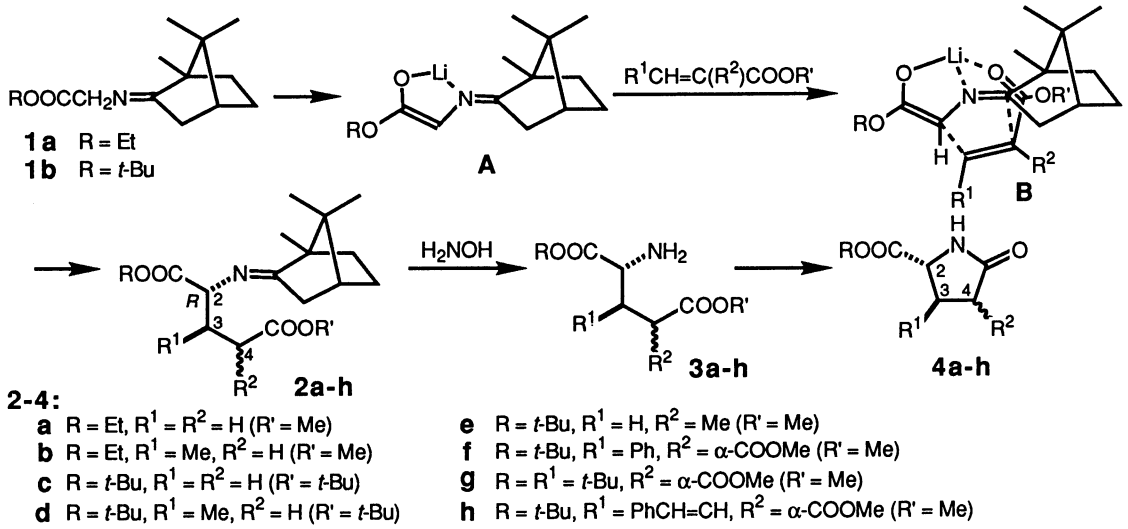
(1)

Although a number of nucleophilic reagents as chiral glycine derivatives have been developed for amino acid synthesis,[4] examples of Michael additions utilizing these reagents are quite limited.[5] In the reported examples of Michael additions, a satisfactory level of diastereofacial selectivity has been established, but the

stereoselectivity between both ends of the newly formed bond remains unimproved.

This communication describes highly diastereoselective asymmetric Michael additions of the lithium enolate (or N-lithiated azomethine ylide) of t-butyl (bornylideneamino)acetate with a variety of α,β-unsaturated esters. Selection of the re-face of the enolate intermediate leads to 3-substituted anti derivatives of unnatural glutamates.

Ethyl (bornylideneamino)acetate (1a) could be deprotonated with lithium bromide/DBU in THF at room temperature to generate chiral lithium enolate A (R = Et), which was trapped with methyl acrylate or crotonate to give the corresponding Michael adduct 2a (diastereomer ratio: 77:23) or 2b (76:24) (Scheme 1 and Table 1). Thus, the diastereoselectivity between both ends of the newly formed bond (C_2-C_3) was exclusively high, while the diastereofacial selectivity was rather unsatisfactory. Although a lower reaction temperature was desired to achieve higher diastereoselectivity, the lithium bromide/DBU-induced generation of enolate A was awfully sluggish at 0 °C.



Scheme 1.

Action of t-butyl (bornylideneamino)acetate (1b) with butyllithium in THF smoothly generated enolate A (R = t-Bu) at -78 °C, which underwent the Michael addition with t-butyl acrylate[6] in the presence of t-butyl alcohol[7] to furnish 2c in 89% yield as a far major isomer (diastereomer ratio: 95:5). With t-butyl crotonate, 2d was obtained as a 95:5 mixture of two diastereomers, again indicating the exclusive selectivity between both ends of the newly formed bond.

On treatment of 2d with hydroxylamine in ethanol, a single stereoisomeric pyrrolidine 4d was obtained independently of the diastereomer ratios of the used adduct 2d. The stereostructure of 4d was confirmed as t-butyl 2,3-trans-3-methyl-5-oxo-2-pyrrolidinecarboxylate on the basis of a notable NOE observed between 2-H and 3-Me,[8] indicating the exclusive anti-selectivity of the Michael addition,

which was anticipated from the transition state shown in Equation 1.

Absolute configuration at the 2-position of 2 was determined as follows: The camphor moiety was removed from adduct 2c (diastereomer ratio: 95:5) by heating it with hydroxylamine under reflux in ethanol to give di(t-butyl) glutamate (3c) in 68% yield, the major isomer of which was assigned as 2R-configuration by comparison of its optical rotation with that of the authentic sample synthesized from natural (2S)-glutamic acid. The re-face selective Michael addition with respect to the intermediate enolate A may be extended to acceptors other than acrylate; the chelation-controlled approach B is the most likely transition state by which all the observed stereochemical outcomes can be explained.

Table 1. Reaction of Camphor Imines **1a,b** with α,β-Unsaturated Esters

Imine	Base[a]	Acceptor[b]	Conditions	Product	Yield/%[c]	Isomer ratio[d]
1a	A	CH_2=CHCOOMe	rt, 30 min	**2a**	73[e]	77:23
1a	A	MeCH=CHCOOMe (*E*)	rt, 2 day	**2b**	35[e]	76:24
1b	B	CH_2=CHCOOBu-*t*	-78 °C, 17 h	**2c**[f]	89	95:5
1b	B	MeCH=CHCOOBu-*t* (*E*)	-78 °C, 17 h	**2d**[g]	88	95:5
1b	B	CH_2=C(Me)COOMe	-78 °C, 15 h	**2e**[h]	90	single (60:40)[i]
1b	B	PhCH=C(COOMe)$_2$	-78 °C, 5 h	**2f**[j]	94	single
1b	B	*t*-BuCH=C(COOMe)$_2$	-78 °C, 12 h	**2g**	86	single
1b	B	PhCH=CHCH=C(COOMe)$_2$	-78 °C, 6 h	**2h**[k]	68	single

a) A: LiBr (1.5 equiv.)/DBU (1.2 equiv.) in THF; B: *n*-BuLi (1.1 equiv.) and *t*-BuOH (1-1.2 equiv.) in THF at -78 °C. b) One and half equivalent of an acceptor was used. c) Yield of isolated products. d) The ratio of two diastereomers between C-2 and the chiral source (determined by ^{1}H NMR). e) Accompanied by the unreacted starting imine **1a**. f-h,j,k) The camphor moiety was removed by heating **2** with NH_2OH (2 equiv.) in ethanol for 2 h [f) **3c** (68%). g) **4d** (72%, single). h) **4e** (88%, 60:40). j) **4f** (64%, single). k) **4h** (75%, single)]. i) Isomer ratio of two 4-epimers.

Reaction of 1b with methyl methacrylate, under similar reaction conditions, gave a 60:40 mixture of two diastereomers of 2e. Since the stereochemistry at the 4-position was constructed presumably at random upon quenching the reaction mixture with water, the 2-position of 2e must be absolutely pure in a stereochemical sence. This was confirmed by transforming 2e into 4e through a hydrolysis and cyclization sequence in 88% yield, which also consisted of two diastereomers in a 60:40 ratio. Accordingly, the α-substituent in α,β-unsaturated esters would play an important role in the determination of diastereofacial selectivity in these Michael addition reactions.

This was the case actually observed. Reactions of 1b with 2-alkylidenemalonates such as 2-benzylidene-, 2-(2,2-dimethylpropylidene)-, and (E)-2-(3-phenyl-2-propenylidene)malonates produced only one diastereomers of the corresponding Michael adducts 2f-h in satisfactory yields (Scheme 1 and Table 1). Hydrolytic removal of the camphor moiety and subsequent cyclization gave 5-oxopyrrolidine-2,4-dicarboxylates 4f-h all as single diastereomers. Stereochemistry at the 4-position is not very important because this position is substituted by two electron-with-

drawing substituents so as to undergo ready epimerization into a thermodynamically more stabilized configuration. Accordingly, the stereostructures of 4f-h were determined to be 2,3-trans:3,4-trans-5-oxopyrrolidine-2,4-dicarboxylates with 2R-configuration.

Thus, lithiated intermediates generated from the camphor imines of α-amino esters undergo absolutely diastereoselective Michael additions with 2-alkylidenemalonates. Decarboalkylation of one of the geminal ester moieties,[9] which are involved in the Michael adducts of 2-alkylidenemalonates, should lead to an easy synthesis of optically pure anti derivatives of 3-substituted unnatural glutamates. Wide synthetic applications are possible by use of other Michael acceptors;[10] chiral carbonyl auxiliaries other than camphor would be employed as well. A study along these lines is now in progress.

References

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