Asymmetric Conjugate Addition of Organometallic Reagents in the Presence of Tertiary Amines to Chiral α,β-Unsaturated Amido Carboxylic Acids. Addition Order of Reagents as an Unprecedented Factor in the Determination of the Sense of Asymmetric Induction

Kenso Soai * and Atsuhiro Ookawa
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo, 162 Japan

Optically active 3-substituted carboxylic acids have been obtained in moderate enantiomeric excesses (e.e.) by asymmetric conjugate addition of alkyl-lithium, in the presence of tertiary amines, to chiral α,β-unsaturated amido carboxylic acids derived from (*S*)-proline. The presence of tertiary amine is effective in increasing both the synthetic yields and the e.e.'s. A change in the addition order of tertiary amine and alkyl-lithium to the amido-carboxylic acid changes the sense of asymmetric induction.

Asymmetric synthesis has been the subject of increasing interest in recent years.[1] One of the considerations in variable asymmetric synthesis is whether both enantiomers of a compound can be synthesized separately and the following methods have been used to achieve this. (i) Use of a chiral auxiliary of appropriate configuration.[2] This method, however, can be applied only if both enantiomers of the chiral auxiliary are available; unfortunately this is not usually the case.[3] (ii) Use of reagents with opposite stereoselectivity.[4] (iii) Use of different combinations of substrates and reagents.[2c,5] The number of examples of (ii) and (iii) are limited.

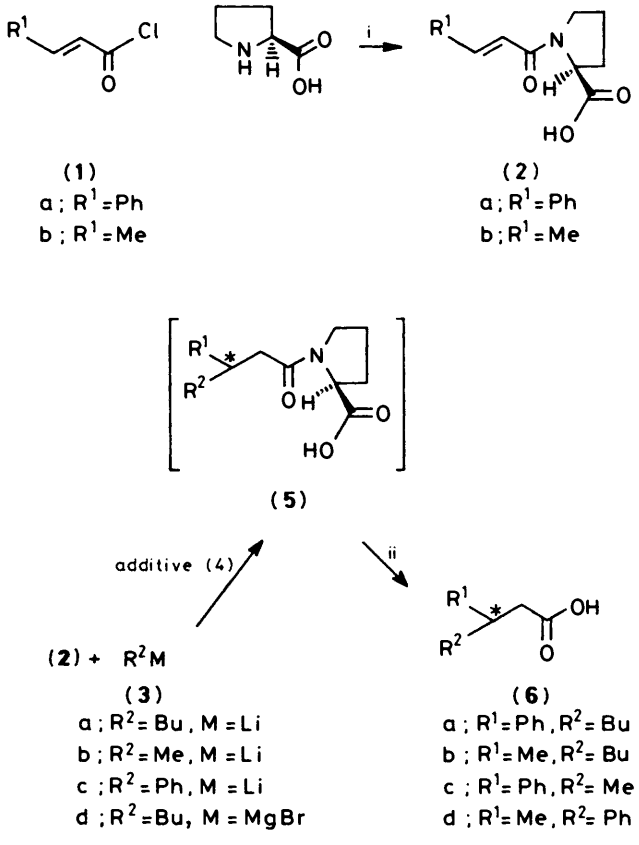
Asymmetric reactions are known to be greatly affected by reaction conditions,[6-9] to the extent that the sense of asymmetric induction may change according to the conditions. For example, in asymmetric hydrogenation of Schiff bases, the predominant configuration of the amine product varies with temperature[6b] and polarity of the solvent.[7a] Control of the stereochemical course of a reaction by varying the conditions is both theoretically and synthetically interesting, since it means that both enantiomers can be obtained from one enantiomer of the chiral auxiliary merely by changing the reaction conditions.

Various methods have been published describing the synthesis of optically active 3-substituted carboxylic acids (or their equivalents) by the asymmetric conjugate addition of organometallic reagents to chiral α,β-unsaturated carbonyl compounds (or their equivalents) such as unsaturated amides, esters, aldimines, acetals, and oxazepines.[2c,5b,c,10] Although amido alcohols have been utilised as chiral auxiliaries,[5c,10b] chiral amido carboxylic acids have not hitherto been utilised in asymmetric conjugate addition.[11] We recently reported the use of an amido carboxylic acid, *N,N'*-dibenzoylcystine, in the enantioselective reduction of ketones with lithium borohydride.[2a,12]

Here we describe an asymmetric conjugate addition of organometallic reagents to α,β-unsaturated (*S*)-proline derivatives in the presence of a tertiary amine, where either enantiomer of the 3-substituted carboxylic acid can be synthesized using only one enantiomer of (*S*)-proline, simply by changing the addition order of the reagents.

Results and Discussion

The chiral α,β-unsaturated amido carboxylic acids (**2**) were synthesized from (*S*)-proline and the corresponding acyl chlorides (**1**) in aqueous sodium hydroxide (Scheme 1). The organometallic reagent (**3**) was allowed to react with (**2**) both in the presence and absence of an additive (**4**), such as a tertiary amine. Subsequent acidic hydrolysis (6M, H_2SO_4–AcOH) of the 1,4-adduct (**5**) afforded the optically active 3-substituted carboxylic acid (**6**). The results are summarised in Table 1.



Scheme 1. *Reagents*: i, aq. NaOH; ii, 6M-H_2SO_4, AcOH

Our first attempt at asymmetric conjugate addition without the use of a tertiary amine gave a disappointing result; *i.e.* reaction of butyl-lithium (**3a**) with (**2a**) in tetrahydrofuran (THF), followed by acidic hydrolysis, gave (*S*)-(+)-3-phenylheptanoic acid (**6a**) in low enantiomeric excess (21% e.e.) (entry 1).

It was found, however, that the presence of *N,N,N',N'*-tetramethylethylenediamine (**4a**, TMEDA) in the reaction mixture was effective in increasing both the synthetic yield[13] and the e.e.

Table 1. Effect of additives (**4**) on diastereoselective conjugate addition of butyl-lithium (**3a**) to (**2a**)[a]

Entry	Additive (**4**)	(**6a**) Yield (%)[b]	$[\alpha]_{577}$ (*c*, C_6H_6)	E.e. (%)[c]	Config'n
1	None	24	+7.30° (8.63)	21	*S*
2	Hexamethylenetetramine (**c**)	30	−1.00° (7.98)	3	*R*
3	Me_3N (**d**)	48	−16.4° (8.03)	48	*R*
4	Et_3N (**e**)	36	−17.0° (8.47)	49	*R*
5	TMEDA (**a**)[d]	29	−17.7° (9.05)	51	*R*
6	DBU (**b**)[d]	48	−18.9° (7.93)	55	*R*
7	(−)-Sparteine (**f**)	41	−19.8° (7.69)	57	*R*
8	*N*,*N*-Dimethylaniline (**g**)	24	+8.24° (8.07)	24	*S*
9	Proton sponge (**h**)[d]	40	−8.42° (7.60)	24	*R*
10	Bu^{t}OK (**i**)	35	+2.21° (6.80)	6	*S*
11	12-Crown-4 (**j**)[e]	44	+2.64° (7.95)	8	*S*

[a] Addition order = (**2a**), (**4**), (**3a**). Molar ratio (**2a**):(**3a**):(**4**) = 1:3:4.5. [b] Isolated overall yield from (**2**). ^{1}H N.m.r., i.r., and g.l.c. analyses showed that (**6**) was pure. Yields of (**5**) to (**6**) were over 95%. However, yields of (**2**) to (**5**) were moderate because of a side reaction (probably 1, 2-addition). ^{1}H N.m.r. and h.p.l.c. analyses of (**5**) failed to reveal the diastereoisomeric ratios. [c] Enantiomeric excess, based on the reported value of the specific rotation for (*R*)-(−)-(**6a**), $[\alpha]_{577}$ −34.4 (*c* 8, benzene). See ref. 16. [d] For names, see the text. [e] 1,4,7,10-Tetraoxacyclododecane.

Table 2. Effect of molar ratio of DBU (**4b**)[a] to (**2a**) on diastereoselective conjugate addition of BuLi (**3a**)

Entry	Molar ratio[b] (**2**):(**3a**):(**4b**)	(**6a**) Yield (%)[c]	$[\alpha]_{577}$ (*c*, C_6H_6)	E.e. (%)[d]	Config'n
1	1 3 0	24	+7.30° (8.63)	21	*S*
2	1 3 0.5	43	−12.8° (7.88)	37	*R*
3	1 3 1	55	−20.5° (7.67)	60	*R*
4	1 3 4.5	48	−18.9° (7.73)	55	*R*
5	1 3 9.0	51	−17.3° (8.40)	50	*R*
6[e]	1 3 1	34	+10.1° (5.42)	29	*S*
7[f]	1 3 1	35	−19.7° (8.17)	57	*R*

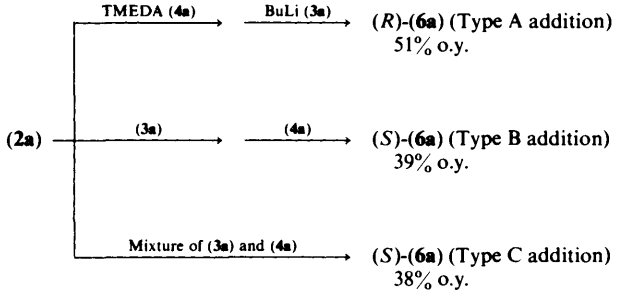
[a] For name, see the text. [b] Addition order = (**2**), (**4b**), (**3a**). [c] See footnote *b* of Table 1. [d] See footnote *c* of Table 1. [e] Addition order = (**2**), (**3b**), (**4a**). [f] Addition order = (**2**) then a mixture of (**3a**) and (**4b**).

of (**6a**). When BuLi (**3a**) was added to the mixture of (**2a**) and (**4a**), the e.e. of (**6a**) increased to 51%, its configuration was found to be (*R*) (entry 5; this reversal of the sense of asymmetric induction will be discussed below).

We next examined the effect of other additives (**4**) on the e.e.'s of (**6a**). Aliphatic tertiary amines such as trimethyl-and triethylamine (**4d**,**e**) afforded 48 and 49% e.e.'s of (*R*)-(−)-(**6a**), respectively (entries 3 and 4). Cyclic amines such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, **4b**) and (−)-sparteine (**4f**) were found to be more effective, the e.e.'s of (*R*)-(−)-(**6a**) being 55% and 57%, respectively. On the other hand, the aromatic tertiary amine *N*,*N*,*N*′,*N*′-tetramethyl-1,8-diaminonaphthalene (proton sponge, **4h**) caused low asymmetric induction (entry 9) in spite of its strong basicity. In the case of the weak aromatic amine *N*,*N*-dimethylaniline (**4g**), (*S*)-(+)-(**6a**) (24% e.e.) was obtained (entry 8). This degree and sense of asymmetric induction were almost the same as that without any additive (entry 1). The reaction of *N*,*N*-dimethylaniline with (**2a**) seemed to be slow. A THF suspension of (**2a**) and the amine remained unchanged until BuLi was added, while in the case of other amines of strong basicity, the suspension becomes a solution when the amine is allowed to react with (**2a**). When potassium t-butoxide (**4i**) or 12-crown-4 (**4j**) were used as additives, yields of (*S*)-(**6a**) of low e.e.'s were obtained (entries 10 and 11).

We investigated the effect of the molar ratio of DBU to (**2a**) on the e.e. of (**6a**). The results are summarised in Table 2. The presence of DBU reversed the sense of asymmetric induction. Equimolar amounts of DBU and (**2a**) were found to be sufficient for good asymmetric induction (entry 3, 60% e.e.). Even when the molar ratio of DBU to (**2a**) was 0.5, some compound (**6a**) of (*R*) configuration was obtained (entry 2). A molar excess of DBU slightly decreased the e.e.'s of (**6a**) (entries 4 and 5, 55 and 50% e.e., respectively).

Surprisingly, a change in the order of addition of the reagents caused a reverse of the configuration of the predominant isomer of (**6a**). When BuLi (**3a**) was added to a mixture of (**2a**) and TMEDA (**4a**) (Type A addition), (*R*)-(−)-(**6a**) was obtained in 29% yield and in 51% e.e. (entry 1). In contrast, when (**4a**) was added to the mixture of (**2a**) and (**3a**) (Type B addition), (*S*)-(+)-(**6a**) was obtained in 43% yield and in 39% e.e. (entry 2) (Scheme 2).



Scheme 2.

As shown in Table 3, the observed reverse in the configuration of (**6**) brought about by a change in the addition order of the reagents also applied to other tertiary amines such as DBU (entries 6—13) and (−)-sparteine (entries 4 and 5), other amido carboxylic acids (**2b**) (entries 8, 9, 12, and 13), and

Table 3. Effect of the adding order of alkyl-lithium (3) and tertiary amine (4) to amido carboxylic acids (2) on the sense of asymmetric induction.

Entry	(2)	(3)	(4)[a]	Molar ratio (2):(3):(4)	Addition order[b]	(6)	Config'n	$[\alpha]_{577}$ (c, C_6H_6)	Yield (%)[c]	E.e. (%)[d]
1	a	a	a	1 3 4.5	A	a	*R*	−17.7° (9.05)	29	51
2	a	a	a	1 3 4.5	B	a	*S*	+13.5° (13.2)	43	39
3	a	a	a	1 3 4.5	C	a	*S*	+13.2° (8.42)	25	38
4	a	a	f	1 3 4.5	A	a	*R*	−19.8° (7.69)	41	57
5	a	a	f	1 3 4.5	B	a	*S*	−5.42° (4.98)	26	16
6	a	a	b	1 3 1	A	a	*R*	−20.5° (7.67)	55	60
7	a	a	b	1 3 1	B	a	*S*	+10.1° (5.42)	34	29
8	b	a	b	1 3 1	A	b	*R*	+1.55° (neat)	60	37
9	b	a	b	1 3 1	B	b	*S*	−0.42° (neat)	47	10
10	a	b	b	1 3 1	A	c	*S*	+6.34° (4.10)	36	11
11	a	b	b	1 3 1	B	c	*R*	−7.79° (2.05)	10	14
12	b	c	b	1 3 1	A	d	*S*	+7.99° (6.63)	29	14
13	b	c	b	1 3 1	B	d	*R*	−4.38° (7.08)	33	8

[a] For names, see Table 1. [b] A = (2), (4), (3); B = (2), (3), (4); C = (2) then a mixture of (3) and (4). [c] See footnote *b* of Table 1. [d] See footnote *c* of Table 1.

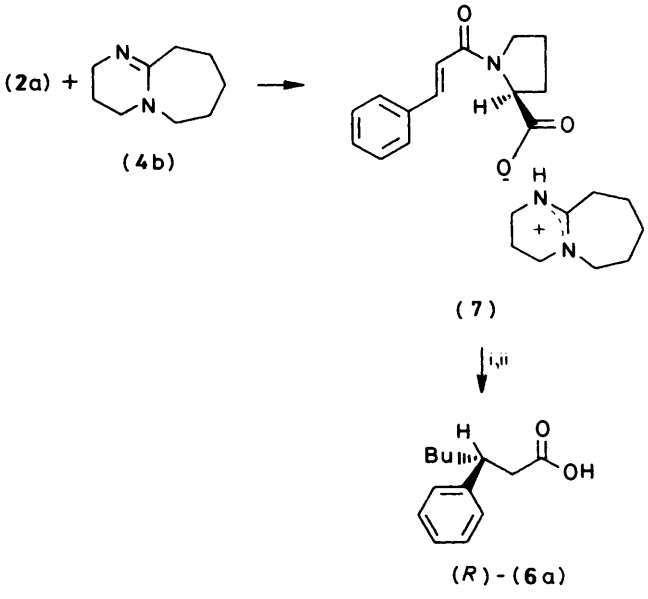
other alkyl-lithium reagents such as methyl-lithium and phenyl-lithium (entries 10—13). A moderate e.e. (60%) of (*R*)-(−)-(**6a**) was attained when BuLi was added to a mixture of (**2a**) and DBU (entry 6) (Type A addition). Type A addition afforded higher e.e.'s of (**6**) than did type B addition. It should be noted, however, that even type B addition afforded both higher synthetic yields and e.e.'s of (**6**) than did the reaction in the absence of tertiary amine (Table 1, entry 1). To the best of our knowledge, this is the first example of an asymmetric induction in which the addition order of reagents determines the absolute configuration of the product.

In order to investigate this further, a mixture of TMEDA and BuLi was added to a THF solution of (**2a**) (Type C addition) (Scheme 2). After hydrolysis, (*S*)-(**6a**) was obtained in 38% e.e. (Table 3, entry 3). This e.e. is almost the same as that obtained with type B addition (entry 2). Because (**2**) contains carboxylic acid, it is considered to form either lithium carboxylate or ammonium carboxylate during the reaction. In type B addition, lithium carboxylate is considered to form at the first stage. The fact that type C and type B additions gave similar results suggests the formation of lithium carboxylate at the first stage, in spite of the simultaneous addition of BuLi and TMEDA. This is probably because BuLi is a stronger base than TMEDA. On the other hand, in type A addition, ammonium carboxylate is considered to form at the first stage.

In order to test this theory, the DBU salt (**7**) of (**2a**) was isolated (Scheme 3). When BuLi was added to the isolated DBU salt (**7**) of (**2a**), (*R*)-(**6a**) was obtained in 57% e.e. (entry 7). This e.e. of (*R*)-(**6a**) is the same as that obtained from type A addition (entry 6), within experimental error.

The mechanism of this reverse in the sense of asymmetric induction by a change in the addition order of the tertiary amine and BuLi may be attributed to differences in the structure of the diastereoisomeric transition state. In fact, the colours of the reaction mixtures were different in the two types of addition. In type A addition (Table 3, entry 6), the colour of the reaction mixture was dark red; in type B addition (Table 3, entry 7), it was orange.

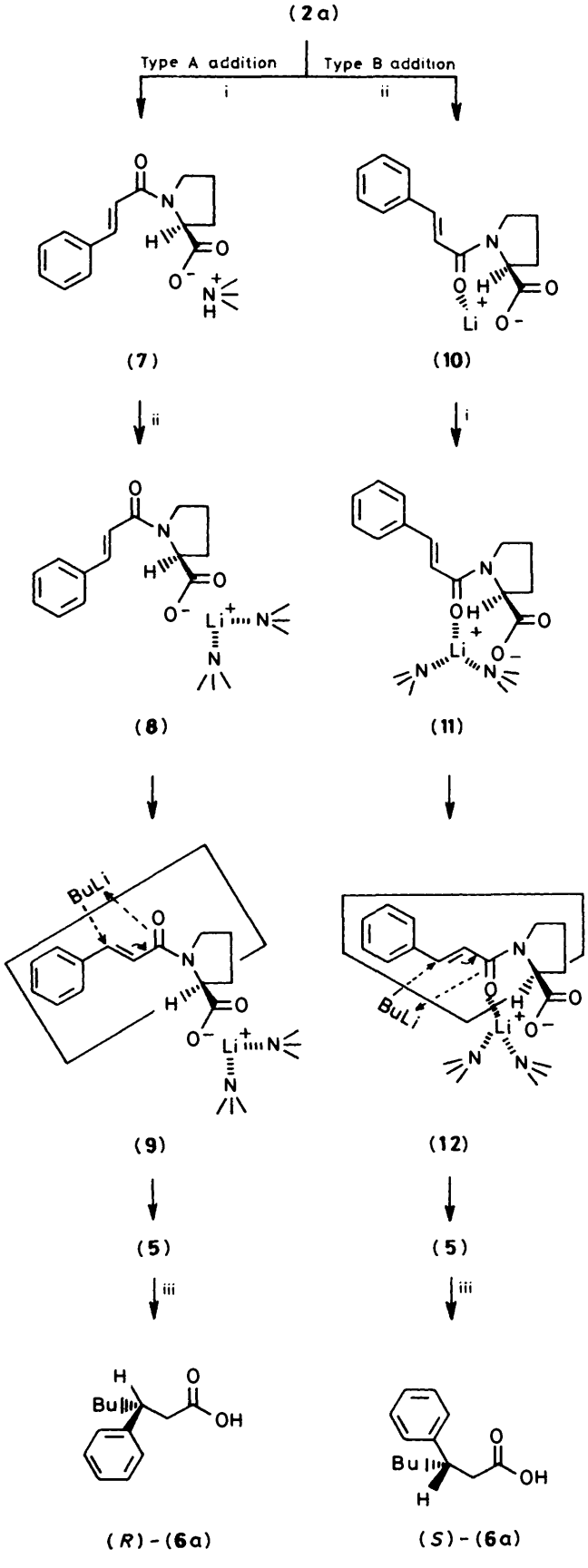
Although further study is necessary to disclose the mechanism completely, our working hypothesis is as follows: the difference between types A and B addition may be ascribed in part differences in the chelation of the lithium cation of the carboxylate to the oxygen atom of the amido carbonyl group (Scheme 4). In type A addition, as described above, it is likely that ammonium carboxylate (**7**) forms in the first stage and



Scheme 3. *Reagents*: i, BuLi (**3a**); ii, 6M H_2SO_4, AcOH

upon addition of BuLi loses a proton to given lithium carboxylate, co-ordinated with the tertiary amine (**8**). Because tertiary amine already exists in the reaction mixture, immediate co-ordination between lithium cation and tertiary amine may occur, there being no co-ordination with the oxygen atom of amide. Conjugate addition of BuLi may occur *via* s-*cis* geometry.* BuLi may approach from the side opposite the bulky lithium carboxylate group co-ordinated with the tertiary amine (**8**). Thus (*R*)-(**6a**) forms predominantly from type A addition. On the other hand, in type B addition, the lithium cation of the initially formed carboxylate may chelate the oxygen atom of the amido-carbonyl (**10**). Subsequently added tertiary amine may co-ordinate with the lithium cation. However, the amine may not destroy kinetically the chelation between Li^+ and the amide oxygen (**11**). Conjugate addition

* s-*cis* Geometry is also postulated in other asymmetric conjugate additions. See refs. 5*c* and 10*c*.



Scheme 4. *Reagents*: i, tertiary amine (**4**); ii, BuLi (**3a**); iii, 6M-H_2SO_4–AcOH

may occur, as in type A addition, *via* s-*cis* geometry (**12**). BuLi approaches from the less hindered side, and the subsequent hydrolysis affords (*S*)-(**6a**).*†

The effect of the organometallic reagent (**3**) is shown in Table 4. In the presence of DBU, BuLi was more effective than butylmagnesium bromide (BuMgBr), which gave a disappointing result compared with that of BuLi (entries 1 and 2). Interestingly, however, the synthetic yield increased to 65% and the e.e. improved (50% e.e.) when BuMgBr (2 equiv.) was added after the addition of BuLi (1 equiv.) (entry 3). This result shows that the cation of the carboxylate derived from (**2a**) largely effects the degree of asymmetric induction. Formation of lithium carboxylate from (**2a**) is essential for high diastereoselectivity. Potassium carboxylate was less effective for asymmetric induction than lithium carboxylate co-ordinated by tertiary amine (Table 1, entry 10; Table 4, entry 1).

The effect of the solvent is shown in Table 5. Toluene and THF–hexane (1:1, v/v) were found to be effective, as was THF (entries 1, 3, and 4). On the other hand, conjugate addition hardly proceeded in ether and hexane (entries 2 and 5).

Experimental

M.p.s were measured with a Yamato MP-21 melting point apparatus and are uncorrected. I.r. spectra, high resolution mass spectra, and optical rotations were recorded with a Hitachi 260-10 spectrophotometer, a Hitachi M-80 mass spectrometer, and a JASCO DIP-181 polarimeter, respectively. ^{1}H N.m.r. spectra (60 MHz) were recorded using either a Varian EM-360A or a JEOL JNM-PMX-60 n.m.r. spectrometer.

Materials.—Tetrahydrofuran (THF), diethyl ether, hexane, and toluene were distilled from lithium aluminium hydride prior to use. Tertiary amines were stored over 3A molecular sieves. Trimethylamine was generated from trimethylamine hydrochloride and sodium hydroxide and dried over soda lime.[14]

Butyl-lithium(BuLi) in hexane and phenyl-lithium in cyclohexane–ether (7:3 v/v) were purchased from the Aldrich Chemical Co., and methyl-lithium in Et_2O was purchased from Merck.

The concentrations of organolithium and Grignard reagents were determined by the method of Watson and Eastham[15] prior to use. Most of the organic compounds utilised in this study were commercial products and, purified by distillation when necessary.

All reactions were carried out under argon except the syntheses of (*S*)-*N*-*trans*-cinnamoyl- and crotonoyl-proline (**2a**,**b**).

(S)-N-trans-*Cinnamoylproline* (**2a**).—*trans*-Cinnamoyl chloride (4.76 g, 28.6 mmol) in ether (15 ml) was added to an

* This explanation is, of course, merely one of many other possible mechanisms. Although the above mechanism may explain the phenomenon, the relation between the addition types (A and B) and the resulting configuration of (**6**) is complicated. The above mechanism can not be consistently applied when the reagents are not BuLi and (**2a**). Reversal of the sense of asymmetric induction caused by a change of alkyl-lithium reagent is known in the enantioselective alkylation of aldehydes. (T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, and K. Suzuki, *J. Am. Chem. Soc.*, 1979, **101**, 1455).

† The effect of tertiary amines on the aggregation states of lithio species may also be an important factor of the mechanism. BuLi, which exists as a hexamer, becomes monomeric in the presence of tertiary amines (C. G. Screttas and J. F. Eastham, *J. Am. Chem. Soc.*, 1965, **87**, 3276; A. W. Langer Jr., *Trans. N. Y. Acad. Sci.*, 1965, **27**, 741). These monomeric species show different reactivity from that of polymeric species (E. J. Corey and D. Seebach, *J. Org. Chem.*, 1966, **31**, 4097; S. Akiyama and J. Hooz, *Tetrahedron Lett.*, 1973, 4115).

Table 4. Effect of organometallic reagents (3) on conjugate addition to α,β-unsaturated amido carboxylic acid (**2a**) in the presence of DBU (**4b**)[a]

		(6a)			
Entry	(3)	Yield (%)	$[\alpha]_{577}$ (*c*, C_6H_6)	E.e. (%)[b]	Config'n
1	BuLi (**3a**)	48	−18.9° (7.73)	55	*R*
2	BuMgBr (**3d**)	21	−0.81° (8.63)	2	*R*
3	(**3a**) (1 equiv.) then (**3d**) (2 equiv.)	65	−17.3° (7.93)	50	*R*

[a] Type A addition, see footnote *b* of Table 3. Molar ratio (**2a**):(**3**):(**4b**) = 1:3:4.5. [b] See footnote *c* of Table 1.

Table 5. Effect of solvent on diastereoselective conjugate addition of butyl-lithium (**3a**) to (**2a**) in the presence of DBU (**4b**)[a]

		(6a)			
Entry	Solvent	Yield (%)	$[\alpha]_{577}$ (*c*, C_6H_6)	E.e. (%)[b]	Config'n
1	THF	48	−18.9° (7.93)	55	*R*
2	Et_2O	2			
3	THF–hexane (1:1)	55	−20.8° (8.48)	60	*R*
4	Toluene	49	−18.3° (8.01)	53	*R*
5	Hexane				

[a] Type A addition, see footnote *b* of Table 3. Molar ratio (**2a**):(**3a**):(**4b**) = 1:3:4.5. [b] See footnote *c* of Table 1.

ice-cooled solution of (*S*)-proline (3.84 g, 33.3 mmol) in NaOH (1M; 73 ml, 73 mmol) and the mixture was stirred for 1.5 h. After additional stirring for 3 h at room temperature, the mixture was washed with Et_2O (20 ml) and the aqueous layer acidified to pH 1 with 6M-HCl. The resulting precipitate was collected by suction and dissolved in chloroform. The filtrate was extracted with $CHCl_3$ and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. Two crops of reprecipitation from $CHCl_3$–hexane gave (*S*)-(**2a**) (6.03 g, 86%), m.p. 178.5—180.0 °C, $[\alpha]_D^{22}$ −244.1° (*c* 1.95, $CHCl_3$); $\nu_{max.}$ 1 735, 1 650, 1 575, 1 450, 1 195, and 775 cm^{-1}; δ[$CDCl_3$–$(CD_3)_2SO$] 1.73—2.50 (m, 4 H), 3.5—4.0 (m, 2 H), 3.4—4.75 (m, 1 H), and 6.5—7.9 (m, 7 H) [Found: C, 68.5; H, 6.25; N, 5.75%; M^+ (e.i.), 245.1060. $C_{14}H_{15}NO_3$ requires C, 68.55; H, 6.16; N, 5.71%; *M*, 245.1053.].

(S)-N-trans-*Crotonoylproline* (**2b**).—A mixture containing (*S*)-proline (7.68 g, 66.7 mmol) in aqueous NaOH (1M; 130 ml) and crotonoyl chloride (6.1 g, 60 mmol) in Et_2O (20 ml) was vigorously stirred for 1 h at 0 °C and then for a further 1 h at room temperature. After the separation of that organic layer, the aqueous layer was washed with $CHCl_3$ (20 ml), acidified to pH 1 with 6M-HCl, and extracted with $CHCl_3$ and ethyl acetate. The extracts were dried (Na_2SO_4) and concentrated on a rotary evaporator and the residue reprecipitated twice from $CHCl_3$—hexane to give (*S*)-(**2b**) (8.96 g, 83%), m.p. 160.5—161.0 °C, $[\alpha]_D^{22}$ −295.2° (*c* 1.01, $CHCl_3$); $\nu_{max.}$ 2 960, 1 722, 1 670, 1 590, 1 460, and 1 240 cm^{-1}; δ[$CDCl_3$–$(CD_3)_2SO$] 1.75—2.40 (m, 7 H), 3.4—3.85 (m, 2 H), 4.4—4.7 (m, 1 H), 5.8—6.4 (m, 1 H), 6.65—7.35 (m, 1 H), and 10.1 (s, 1 H). [Found: M^+ (e.i.), 183.0889. $C_9H_{13}O_3N$ requires *M*, 183.0896].

(R)-3-*Phenylheptanoic Acid* (**6a**) (*Type A Addition*) (*Table* 1, *Entry* 6).—DBU (**4b**) (2.0 ml, 13.5 mmol) was added to a suspension of (**2a**) (0.736 g, 3.0 mmol) in THF (9 ml) and the mixture was stirred for 30 min at room temperature. The resulting clear solution was cooled to −40 °C and BuLi (**3a**) in hexane (5.56 ml, 9.0 mmol) was added over 30 min. The reaction mixture was kept at −40 °C for 8 h and then quenched with saturated aqueous ammonium chloride and acidified to pH 1 with 3M-HCl. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ and ethyl acetate. The organic layer was combined with these extracts, and then dried (Na_2SO_4) and evaporated under reduced pressure. The resulting oily material was hydrolysed in 6M-H_2SO_4 (15 ml) and acetic acid (7.5 ml) at reflux temperature for 4 h. The mixture was extracted with $CHCl_3$ and the extract dried (Na_2SO_4) and evaporated. The residue was distilled under reduced pressure by the bulb-to-bulb method (180—220 °C/2 mmHg) and the resulting oil purified by preparative t.l.c. [chloroform–methanol–acetic acid (30:1:trace) as developing solvent] to give (*R*)-(**6a**) (0.297 g, 48%). G.l.c. of (**6a**) showed only one peak. SE-30, 25 m capillary column, column temp. 150 °C, flame ionisation detector; R_t 11.3 min, b.p. 200 °C/2 mmHg (bath temp.) [lit.,[5b] 180—190 °C/1.5 mmHg (bath temp.)]; 55% e.e. $[\alpha]_{577}^{21}$ −18.9° (*c* 7.73, benzene) (lit.,[16] $[\alpha]_{577}$ −34.4° (*c* 8, benzene)]; $\nu_{max.}$ 2 940, 1 715, 770, and 710 cm^{-1}; δ ($CDCl_3$) 0.55—1.9 (m, 9 H), 2.4—2.7 (d, 2 H), 2.7—3.3 (m, 1 H), 7.15 (s, 5 H), and 11.5 (s, 1 H).

In another run of the same conjugate addition, pure (**5a**) (59%) was isolated by t.l.c.; $\nu_{max.}$ 2 950, 1 835, 1 600, 1 460, and 1 205 cm^{-1}; δ ($CDCl_3$) 0.6—1.0 (t, 3 H), 1.0—1.45 (br, 4 H), 1.45—2.3 (m, 6 H), 2.3—2.9 (d, 6 H), 2.9—3.7 (m, 3 H), 4.2—4.65 (m, 1 H), 7.25 (s, 1 H), and 10.2 (br, 1 H); [Found: M^+ (e.i.) 303.1841. $C_{18}H_{25}O_3N$ requires *M*, 303.1836].

The same acidic hydrolysis of (**5a**) afforded (**6a**) in 95% [overall 56% from (**2a**)] yield; $[\alpha]_{577}^{27}$ −20.1° (*c* 8.09, benzene), 58% e.e.[16]

(S)-3-*Phenylheptanoic Acid* (**6a**) (*Type B Addition*) (*Table* 3, *Entry* 7).—BuLi in hexane (5.1 ml, 8.76 mmol) was added dropwise over 30 min to a suspension of (**2a**) (0.716 g, 2.92 mmol) in THF (9 ml) at −40 °C and then DBU (**4b**) (0.44 ml, 2.92 mmol) was added. After 8 h, the temperature was gradually raised to room temperature from −40 °C. Saturated aqueous NH_4Cl was added to quench the reaction. The same work-up as in the preceding paragraph gave (*S*)-(**6a**) (0.207 g, 34%), 29% e.e. $[\alpha]_{577}^{22}$ +10.1° (*c* 5.42, benzene).

(*S*)-3-*Phenylheptanoic Acid* (**6a**) (*Type C Addition*) (*Table* 3. *Entry* 3.—A mixture of hexane solution of BuLi (5.56 ml, 3.0 mmol) and TMEDA (**4a**) (1.57 g, 4.5 mmol) was added, at room temperature, to a THF suspension of (**2a**) (0.736 g, 3.0 mmol) at −40 °C. After being stirred for 8 h at −40 °C, the reaction

mixture was quenched with saturated aqueous NH_4Cl. The same work-up procedure as described above gave (*S*)-(**6a**) (0.155 g, 25%), 38% e.e., $[\alpha]_{577}^{20}$ +13.2° (*c* 8.48, benzene).

DBU Salt of (*S*)-trans-N-*Cinnamoylproline* (*Table* 2, *Entry* 7).—DBU (**4b**) (0.805 g, 5.28 mmol) in THF (15 ml) was added to a suspension of (**2a**) (1.294 g, 5.28 mmol) in THF (15 ml). Removal of solvent gave the title salt in quantitative yield; $[\alpha]_D^{23}$ −81.2° (*c* 0.82, $CHCl_3$); $\nu_{max.}$ 3 240, 2 940, 1 650, 1 590, 1 430, and 1 200 cm^{-1}; δ ($CDCl_3$) 1.3—2.5 (m, 14 H; 1 H disappeared on the addition of D_2O), 2.5—3.0 (br, 2 H), 3.0—4.1 (m, 8 H), 4.2—4.7 (m, 1 H), and 6.6—7.85 (m, 7 H) [Found: M^+ (e.i.) 398. $C_{23}H_{31}N_3O_3$ requires *M*, 398].

The salt obtained above (1.288 g, 3.24 mmol) was dissolved in THF (10 ml) and the solution cooled to −40 °C. BuLi in hexane (6.66 ml, 9.72 mmol) was added to the mixture over 30 min after which it was set aside for 8 h at −40 °C. Work-up gave (*R*)-(**6a**) (0.235 g, 35%), 57% e.e., $[\alpha]_{577}^{27}$ −19.7° (*c* 8.17, benzene).

(R)-3-*Phenylheptanoic Acid* (**6a**) (*Table* 4, *Entry* 3).—BuLi in hexane (2.34 ml, 3.06 mmol) was added to suspension of (**2a**) (0.750 g, 3.06 mmol) in THF (9 ml) over 10 min; BuMgBr in THF (6.4 ml, 6.12 mmol) was then added over 20 min. After being stirred for 8 h at −40 °C, the reaction mixture was gradually warmed to room temperature. Work-up gave (*R*)-(**6a**) {0.413 g, 65%, 50% e.e., $[\alpha]_{577}^{21}$ −17.3° (*c* 7.93, benzene)}.

(R)-3-*Phenylheptanoic Acid* (**6a**) (*Table* 5, *Entry* 8).—DBU (**4b**) (2.02 ml, 13.5 mmol) was added to a suspension of (**2a**) (0.736 g, 3.0 mmol) in THF (9 ml). The solution was then cooled to −40 °C, when hexane (10 ml), followed by BuLi in hexane (5.23 ml, 9.0 mmol), was added. After being stirred for 6 h at −40 °C the mixture was warmed to room temperature and worked up to give (*R*)-(**6a**) {0.340 g, 55%, 60% e.e., $[\alpha]_{577}^{27}$ −20.8° (*c* 8.48, benzene)}.

(R)-3-*Methylheptanoic Acid* (**6b**) (Table 3, entry 8).—DBU(**4b**) (0.45 ml, 2.99 mmol) was added to a suspension of (**2b**) (0.548 g, 2.99 mmol) in THF (9 ml). After being stirred for 30 min, the clear solution was cooled to −40 °C and BuLi in hexane (6.15 ml, 8.98 mmol) was added. The reaction mixture was set aside for 8 h at −40 °C and then gradually warmed to room temperature. Work-up gave (*R*)-(**6b**) (0.258 g, 60%)., b.p. 150—170 °C/18 mmHg (bath temp.) (lit.,[17] 98 °C/4 mmHg); 37% e.e. $[\alpha]_D^{27}$ +1.55° (neat) {lit.,[18] $[\alpha]_D^{27}$ −4.21° (neat)}; $\nu_{max.}$ 2 940, 1 710, 1 465, 1 415, and 1 300 cm^{-1}; δ ($CDCl_3$) 0.6—1.6 (m, 12 H), 1.6—2.45 (m, 3 H), and 11.0 (s, 1 H).

(S)-3-*Phenylbutanoic Acid* (**6d**) (*Table* 3, *Entry* 12).—DBU (0.45 ml, 2.98 mmol) was added to a suspension of (**2b**) (0.546 g, 2.98 mmol) in THF (9 ml), and the mixture was stirred for 30 min before being cooled to −40 °C. PhLi cyclohexane—Et_2O (7:3 v/v, 4.16 ml, 8.94 mmol) was added to the mixture over 30 min, after which the mixture was stirred for 8 h at −40 °C, and then gradually warmed to room temperature. Work-up gave (*S*)-(**6d**) (0.143 g, 29%, 14% e.e.), b.p. 160—180 °C/3 mmHg (bath temp.), (lit.,[19] 127 °C/1 mmHg); $[\alpha]_D^{16}$ +7.99° (*c* 6.63, benzene) {lit.,[20] $[\alpha]_D$ +57.23° (*c* 9, benzene)}; $\nu_{max.}$ 2 960, 1 705, 1 450, 1 410, 1 290, and 700 cm^{-1}; δ ($CDCl_3$) 1.25 (d, 3 H), 2.45—2.70 (m, 2 H), 3.0—3.5 (s, 1 H), 7.15 (s, 5 H), and 11.4 (s, 1 H).

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