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Stereoselective Reactions. I. A highly Efficient Asymmetric Synthesis of β-Substituted Aldehydes *via* 1,4-Addition of Grignard Reagents to optically Active α,β-Unsaturated Aldimines[1]

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The 1,4-addition of Grignard reagents to the chiral α,β-unsaturated aldimines (**3d, e**), prepared from α,β-unsaturated aldehydes (**1**) and optically active *tert*-leucine *tert*-butyl ester (**2d**), afforded, after hydrolysis, optically active β-substituted aldehydes (**4**) in 91—98% enantiomeric excess. The present method has advantages in giving aldehydes (**4**) in high enantiomeric purities, allowing easy preparation of the aldimines as well as easy recovery of optically active *tert*-leucine *tert*-butyl ester (**2d**) without any racemization for reuse, and exhibiting general utility. The possible mechanism of the reaction, by which the absolute configuration of the aldehydes (**4**) is unequivocally predictable, is proposed.

Keywords——asymmetric synthesis; chiral Schiff base; α,β-unsaturated aldimine; *tert*-leucine; *s-cis*-conformation; chelation; optically active compounds; 1,4-addition; reaction mechanism; organometallic reagents

The problem of devising efficient methods for asymmetric syntheses still remains as a major challenge, despite a large number of approaches in this field.[3] Considering that carbon-carbon bond forming reactions play a central role in synthetic organic chemistry,[4] it is extremely desirable to effect these reactions highly asymmetrically.

We wish to describe in this and the following papers highly efficient asymmetric carbon-carbon bond forming reactions, providing optically active α- and β-substituted carbonyl compounds, promising synthons for the syntheses of a variety of optically active natural products, pharmaceuticals, *etc.*, in quite high enantiomeric purities.

It has been previously found that an asymmetric hydrocyanation of optically active aldimines prepared from benzaldehyde and (*S*)-α-amino acid *tert*-butyl esters proceeds highly efficiently to give (*R*)-(−)-phenylglycine.[5] In particular, when *tert*-leucine *tert*-butyl ester was used as a chiral reagent, the optical purity of the product approached to as high as 97%. Detailed studies have revealed that the rigid cyclic intermediate formed by intramolecular hydrogen bonding is responsible for the high degree of asymmetric induction as shown in Chart 1.

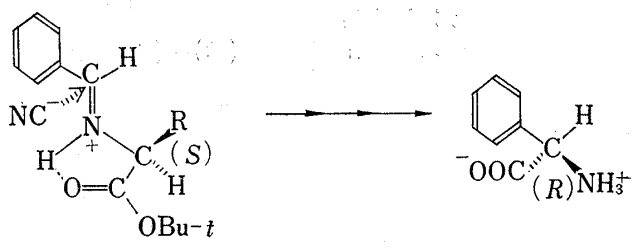


Chart 1

Our strategy in the present investigation involves the similar principle of fixing the conformation of the chiral moiety as A in Chart 2 by chelation of metals with the unshared electron pairs on the imine nitrogen and the ester oxygen suitably situated in place of the

1) Preliminary communication: S. Hashimoto, S. Yamada, and K. Koga, *J. Am. Chem. Soc.*, **98**, 7450 (1976).
2) Location: *7-3-1, Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
3) *a*) J.D. Morrison and H.S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N.J., 1971; *b*) J.W. Scott and D. Valentine, Jr., *Science*, **184**, 943 (1974); *c*) D. Valentine, Jr. and J.W. Scott, *Synthesis*, **1978**, 329.
4) H.O. House, "Modern Synthetic Reactions," W.A. Benjamin, Inc., Menlo Park, California, 1972.
5) S. Yamada and S. Hashimoto, *Chem. Lett.*, **1976**, 921.

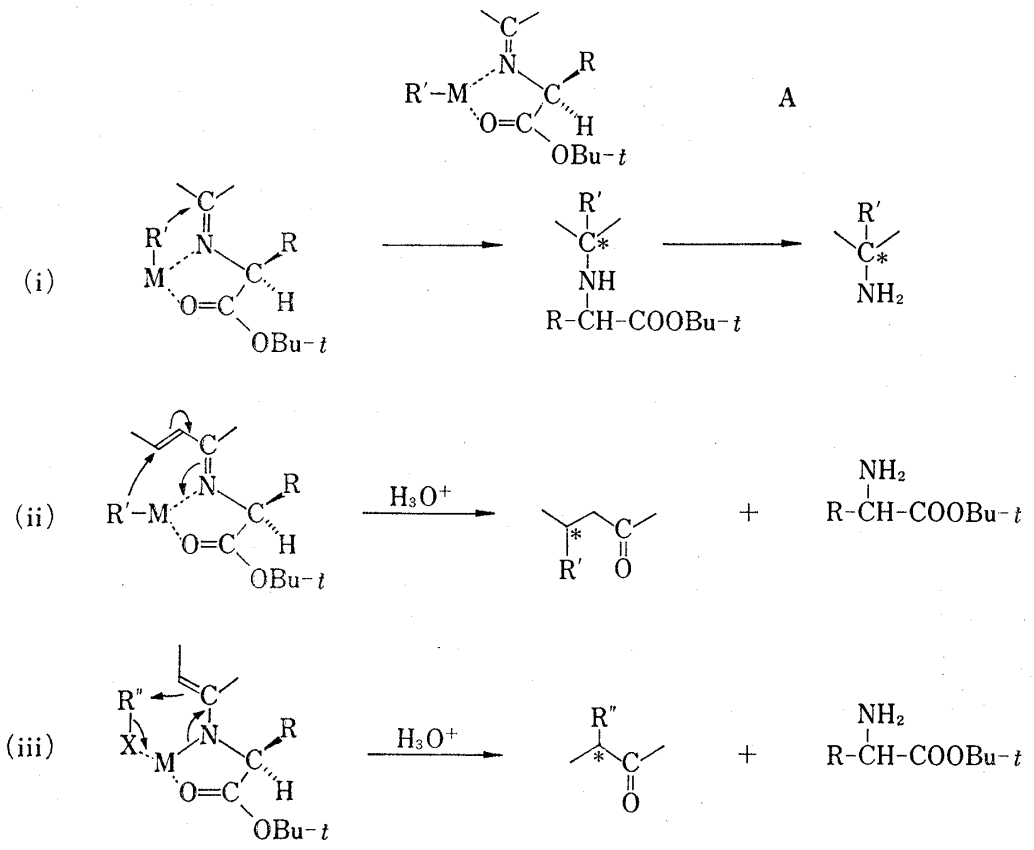


Chart 2

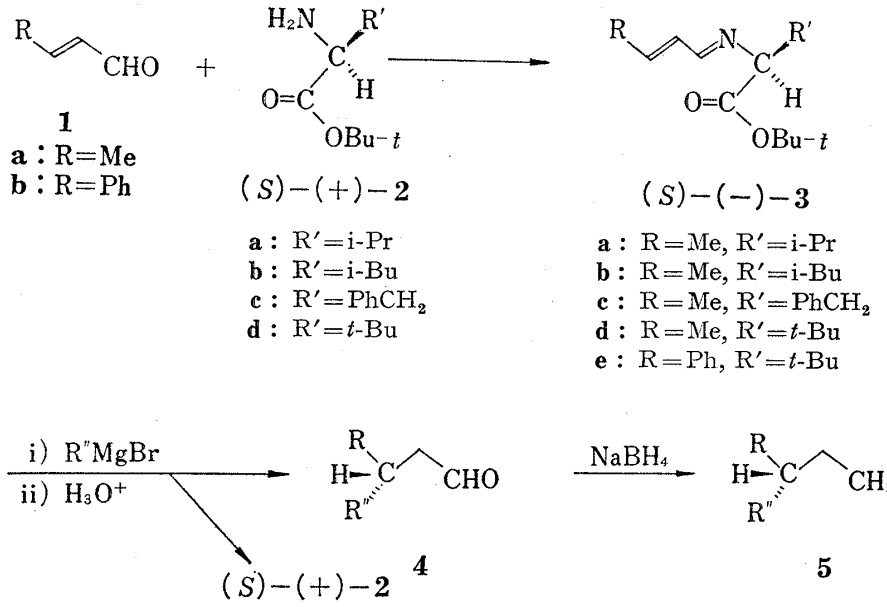


Chart 3

intramolecular hydrogen bonding. This strategy allowed us to design the following three types of asymmetric carbon-carbon bond forming reactions.

(i) The 1,2-addition of organometallic reagents (R′–M) to the chiral imines would afford, after hydrolysis and subsequent oxidative decarboxylation,[5,6] optically active amines with destruction of the chiral reagent.

(ii) The 1,4-addition of R′–M to the chiral α,β-unsaturated imines would produce, after hydrolysis, optically active β-substituted carbonyl compounds, allowing the recovery of the chiral reagent for reuse.

(iii) The abstraction of a proton from the carbon atom adjacent to the imines by R′–M as a base would lead to metalloenamines, which would react with alkyl halides, to give, after hydrolysis, optically active α-substituted carbonyl compounds, allowing the recovery of the chiral reagent for reuse.

The transition state of the first approach is quite similar to that of the asymmetric hydrocyanation described above, and the high optical yields are expected. However, in the latter two approaches wherein the reaction centers are β and α to the imines, the products would be obtained in high enantiomeric excess, provided that the reactions proceed through cyclic transition states as described in Chart 2.

This paper deals with an asymmetric 1,4-addition of Grignard reagents to the chiral α,β-unsaturated aldimines (**3**) prepared from α,β-unsaturated aldehydes (**1**) and optically active α-amino acid *tert*-butyl esters (**2**), giving, after hydrolysis, optically active β-substituted aldehydes (**4**) as shown in Chart 3.

As for this type of asymmetric carbon-carbon bond forming reactions, the 1,4-addition of Grignard reagents to the α,β-unsaturated esters of optically active alcohols was reported[7] before we undertook this work, and the highly effective methods have only recently been reported using chiral oxazoline[8] and oxazepine derivatives.[9] However, these attempts are intrinsically restricted to β-substituted alkanoic acids.

The present method has advantages in giving β-substituted aldehydes (**4**) of predictable configuration in a high level of optical purity, allowing easy preparation of aldimines (**3**) as well as easy recovery of the chiral reagent (**2d**) without any racemization for reuse, and exhibiting general utility.

Results and Discussion

A. Chiral Reagents (2) and α,β-Unsaturated Aldimines (3)

In order to fix the chiral moiety by virtue of chelation, the chiral reagents should be bidentate amines. We therefore selected optically active amino acid *tert*-butyl esters (**2**), which were prepared in one step from the corresponding, easily accessible, optically active amino acids according to Roeske's method.[10a] DL-*tert*-Leucine was prepared in quantities by the modified Knoop method,[11] and was resolved into optical antipodes with brucine, according to the reported method.[12] (*R*)-(+)-*tert*-Leucine, obtained after repeated resolution, showed $[\alpha]_D^{25}$ +9.44° (c=4.94, H_2O), and was transformed to the corresponding *tert*-butyl

6) S. Yamada and S. Hashimoto, *Tetrahedron Lett.*, **1976**, 997.
7) *a*) Y. Inoue and H.M. Walborsky, *J. Org. Chem.*, **27**, 2706 (1962); *b*) M. Kawana and S. Emoto, *Bull. Chem. Soc. Jpn.*, **39**, 910 (1966).
8) *a*) A.I. Meyers and C.E. Whitten, *J. Am. Chem. Soc.*, **97**, 6266 (1975); *b*) *Idem, Tetrahedron Lett.*, **1976**, 1947; *c*) *Idem, Heterocycles*, **4**, 1687 (1976).
9) T. Mukaiyama, T. Takeda, and M. Osaki, *Chem. Lett.*, **1977**, 1165.
10) *a*) R.W. Roeske, *Chem. Ind.* (London), **1959**, 1121; *b*) G.W. Anderson and F.M. Callahan, *J. Am. Chem. Soc.*, **82**, 3359 (1960).
11) *a*) F. Knoop and G. Laudmann, *Z. Physiol. Chem.*, **89**, 157 (1914); *b*) N. Komeshima, S. Hashimoto, and K. Koga, Unpublished results.
12) E. Abderhalden, W. Faust, and E. Haase, *Z. Physiol. Chem.*, **228**, 187 (1934).

ester ((*R*)-(−)-**2d**), α_D^{20} −1.68° (*l*=0.03, neat). Since optically pure *tert*-leucine is reported to have $[\alpha]_D^{20}$ 10.15° (*c*=4.63, H_2O) as the highest value,[12,13] the determination of the optical purity was attempted by analyzing NMR spectra of (*R*)-(−)-**2d** obtained above and several enantiomeric compositions of **2d** in the presence of tris(3-trifluoroacetyl-*d*-camphorato)-europium(III) (Eu-Optishift I). This NMR analysis has disclosed that the present values of $[\alpha]_D^{25}$ +9.44° (H_2O) and α_D^{20} −1.68° (*l*=0.03, neat) are reliable for optically pure (*R*)-*tert*-leucine and its *tert*-butyl ester (**2d**), respectively.

Chiral α,β-unsaturated aldimines (**3**) were readily prepared by mixing **1** and **2** in the presence of molecular sieves 4A.

B. Reaction of optically Active α,β-Unsaturated Aldimines with Organometallic Reagents

Since only few published papers[14] concerned the reaction of α,β-unsaturated imines with nucleophiles despite a number of reports with electrophiles,[15] we first examined the reaction of the chiral α,β-unsaturated aldimines ((*S*)-(−)-**3a—d**) readily prepared from crotonaldehyde (**1a**) and a variety of optically active amino acid *tert*-butyl esters ((*S*)-(+)-**2a—d**) with several kinds of Grignard reagents.

Theoretically, besides 1,4-addition, several competitive reactions seem to be possible as shown in Chart 4, *i.e.*, abstraction of a proton from the asymmetric carbon atom and from the carbon atom adjacent to the olefinic double bond by the Grignard reagent as a base, as well as addition to the ester carbonyl and 1,2-addition by the same reagent as a nucleophile.

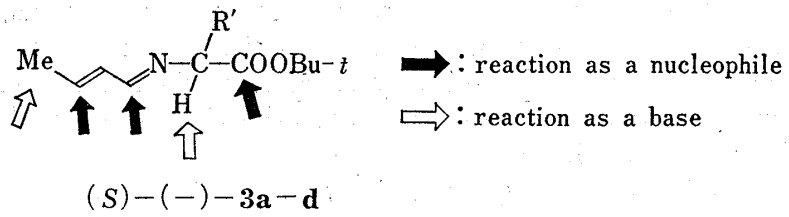


Chart 4

By exhaustive examinations, these competitive reactions were found to be highly dependent on the properties of the Grignard reagents as well as the bulkiness of R′ group attached to the asymmetric carbon atom. Thus, the reactions of (*S*)-(−)-**3b** or (*S*)-(−)-**3c** with Grignard reagents afforded complex mixtures and no 1,4-adducts (**4**) were obtained. On the other hand, 1,4-adducts (**4**) were obtained in the reactions of (*S*)-(−)-**3a** with aryl and hindered alkyl Grignard reagents. Fortunately, in cases where (*S*)-(−)-**3d** with the bulkiest R′ group, *tert*-butyl, was used, 1,4-adducts (**4**) were obtained as the only isolable compounds regardless of the properties of the Grignard reagents used. These successful data are summarized in Table II (see Section C).

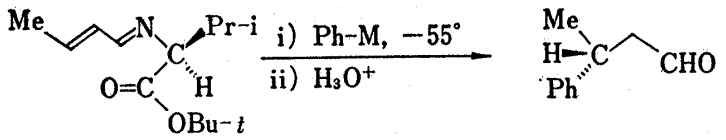
We next examined the reaction of (*S*)-(−)-**3a** with other organometallics, *i.e.*, diorganomagnesium and catalytic organocopper reagents. The results are summarized in Table I, where the results with phenylmagnesium bromide are included for comparison. As shown in Table I, higher synthetic yields were obtained in tetrahydrofuran (THF), while higher

13) For the specific rotations of optically pure **2d** other than in ref. 12, see; *a*) N. Izumiya, S.-C. J. Fu, S.M. Birnbaum, and J.P. Greenstein, *J. Biol. Chem.*, **205**, 221 (1953), $[\alpha]_D^{25}$ 9.7° (H_2O); *b*) H. Pracejus and S. Winter, *Chem. Ber.*, **97**, 3173 (1964), $[\alpha]_D^{21}$ 9.4° (H_2O).

14) *a*) N. Singh, J.S. Sandhu, and S. Mohan, *Chem. Ind.* (London), **1969**, 585; *b*) N. Singh and J.S. Sandhu, *J. Indian Chem. Soc.*, **46**, 9 (1969); *c*) H. Gilman and J. Morton, *J. Am. Chem. Soc.*, **70**, 2514 (1948).

15) *a*) G. Stork and J. Benaim, *J. Am. Chem. Soc.*, **93**, 5938 (1971); *b*) K. Takabe, H. Fujiwara, T. Katagiri, and J. Tanaka, *Tetrahedron Lett.*, **1975**, 1237, 4375; *c*) W. Oppolzer and W. Fröstel, *Helv. Chim. Acta.*, **58**, 578 (1975); *d*) G.R. Kieczykowski, R.H. Schlessinger, and R.B. Sulsky, *Tetrahedron Lett.*, **1976**, 597.

TABLE I. Reaction of (*S*)-(−)-**3a** with Phenylmetallic Reagents



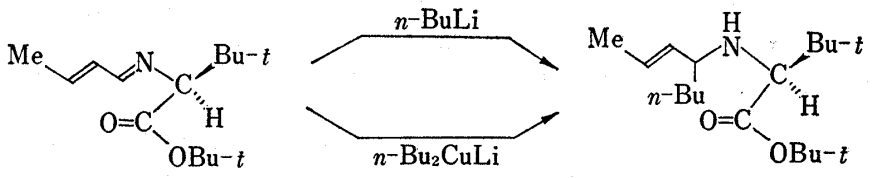
(*S*)−(−)−**3a** (*R*)−(−)−**4a**

Run	Ph-M (eq. mol)	Solvent	Isolated yield (%)	$[\alpha]_D^{20}$ (*c*, EtOH)	Optical yield (%)[b]
1	PhMgBr (2.0)	Ether	11	−26.5° (2.35)	67
2		THF	55	−21.0° (2.94)	53
3		THF–ether (5: 1)	53	−22.6° (2.58)	57
4		Ether–THF (5: 1)	49	−25.7° (2.96)	65
5		Toluene–THF (6: 1)	36	−19.4° (2.61)	49
6		Hexane–THF (3: 1)	38	−17.0° (2.74)	44
7	Ph_2Mg (2.0)	Ether	31	−26.3° (2.42)	67
8		THF	64	−20.7° (2.02)	52
9	PhMgBr (2.0)	Ether	12	−25.5° (2.33)	65
10	–CuI[a]	THF	61	−20.5° (2.21)	52

a) 20 mol % of CuI with respect to phenylmagnesium bromide was used.
b) Calculated from the specific rotation of optically pure (*R*)-(−)-**4a** of $[\alpha]_D^{20}$ −39.5° (EtOH), obtained by correlation with (*R*)-(−)-**5a**.

optical yields were achieved in ether. Since little differences in the products were recognized among the organometallic reagents used, solvent systems to satisfy both synthetic and optical yields were sought with the readily accessible phenylmagnesium bromide. As a result, ether–THF (5: 1) was found to be suitable for this purpose among several kinds of solvent systems, and these conditions were applied to the asymmetric synthesis described in Section C.

On the other hand, the reactions of *n*-butyl lithium and lithium di-*n*-butylcuprate to (*S*)-(−)-**3d** were found to proceed preferentially *via* 1,2-mode to give optically active amine ((−)-**6**), $[\alpha]_D^{20}$ −42.6° (EtOH) and $[\alpha]_D^{20}$ −42.5° (EtOH), in 68% and 72% yields, respectively.



(*S*)−(−)−**3d** **6**

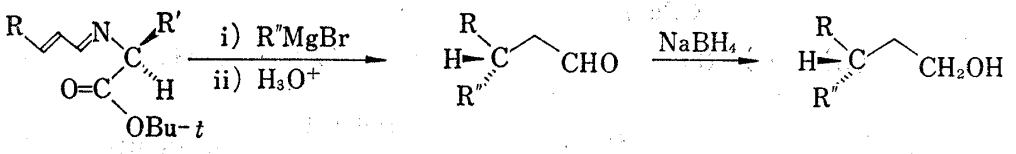
Chart 5

C. Asymmetric 1,4-Addition of Grignard Reagents to optically Active α,β-Unsaturated Aldimines ((*S*)-(−)-**3a, d, e, and** (*R*)-(+)-**3d**)

Due to the reasons described in Section B, asymmetric synthesis of β-substituted aldehydes (**4**) was carried out primarily with **3d** containing optically active *tert*-leucine *tert*-butyl ester (**2d**) as a chiral reagent. The 1,4-addition reactions were performed with 2.0 equivalents of several kinds of Grignard reagents in ether–THF (5: 1) at −55° under nitrogen atmosphere. Since the absolute configuration and specific rotations of aldehydes (**4**) are not described previously, and in addition aldehydes (**4**) were relatively unstable, the crude aldehydes (**4**) obtained after acidic hydrolysis were reduced with sodium borohydride to the corresponding alcohols (**5**). The usual work-up recovered optically active amino acid esters (**2a** and **2d**) utilized as a chiral reagent from the acidic aqueous phase in good yield. (*S*)-(+)-Valine *tert*-butyl ester (**2a**) recovered was accompanied with 8% racemization, while (*R*)-(−)-

and (*S*)-(+)-*tert*-leucine *tert*-butyl ester (**2d**) were recovered without any racemization for reuse. The results obtained with a variety of Grignard reagents are summarized in Table II.

Table II. Asymmetric 1,4-Addition of Grignard Reagents to α,β-Unsaturated Aldimines



(*S*)-(−)-**3** **4** **5**

Run	R	R′	R″	5 Isolated yield (%)	5 Optical rotation[d] Obsd. (Calcd.)[e]	5 Lit.	5 Optical yield (%)[i] (Confign.)
1	Me	i-Pr[a]	Ph	42	α_D^{25} −25.4°	−39.0°[f]	65(*R*)
2	Me	i-Pr[a]	c-C_6H_{11}	6	$[\alpha]_D^{20}$ +8.65°	+12.1°[g]	71(*R*)
3	Me	*t*-Bu[b]	Ph	52	α_D^{25} −32.8°(−35.5°)	−39.0°[f]	91(*R*)
4	Me	*t*-Bu[b]	c-C_6H_{11}	53	$[\alpha]_D^{20}$ +10.7°(+11.6°)	+12.1°[g]	96(*R*)
5	Me	*t*-Bu[b]	*n*-Bu	40	$[\alpha]_D^{25}$ −2.76°(−2.99°)	−3.07°[h]	98(*S*)
6	Me	*t*-Bu[c]	$(CH_3)_2C{=}CHCH_2CH_2$	48	$[\alpha]_D^{25}$ +5.22°(+5.58°)	+5.68°[g]	98(*R*)
7	Ph	*t*-Bu[b]	Et	56	$[\alpha]_D^{25}$ +14.2°(+15.4°)	+16.3°[g]	95(*S*)

a) Optically pure (*S*)-(+)-**2a** was used.
b) (*S*)-(+)-**2d** of 92.3% optical purity was used.
c) (*R*)-(−)-**2d** of 93.5% optical purity was used.
d) Optical rotations were taken neat, and specific rotations were calculated using the reported densities (see ref. 16).
e) Values in parentheses were obtained after correction for the optical purity of **2d** used.
f) See ref. 17.
g) This value was obtained by correlation described in Section D.
h) See P.A. Levene and A. Rothen, *J. Org. Chem.*, **1**, 76 (1936).
i) Corrected for the optical purity of **2d** used.

The optical yields obtained by the present method were remarkably high in all instances, and *tert*-leucine *tert*-butyl ester (**2d**) induced a higher percent asymmetric synthesis than valine *tert*-butyl ester (**2a**) (runs 1, 2, 3, and 4). (*R*)-(+)-Citronellol ((*R*)-(+)-**5d**) and (*S*)-(−)-3-phenyl-1-pentanol ((*S*)-(−)-**5e**) obtained in this manner possessed greater specific rotations, after correction for the optical purity of **2d** used (runs 6 and 7), than those previously reported, and there was some doubt as to the reliability of the reported values. In fact, the chemical correlation described in Section D disclosed that reported values should be corrected somewhat.

The absolute configuration of the alcohols (**5**) obtained using (*S*)-amino ester ((*S*)-(+)-**2a** or (*S*)-(+)-**2d**)) as a chiral reagent was as shown in Table II, while that of the alcohols was reversed by using (*R*)-amino ester ((*R*)-(−)-**2d**) as exemplified by the synthesis of (*R*)-(+)-**5d** (run 6). It is now possible to prepare, in a predictable manner, either R or S aldehyde (**4**) by choosing either enantiomer of the amino ester (**2d**). Furthermore, the results from runs 2 and 6 show that either enantiomer of the aldehydes (**4**) can also be prepared by simply exchanging the R group in α,β-unsaturated aldimine (**3d**) for R″ group in Grignard reagent using a common chiral reagent.

16) For the density of the compound, see; *a*) (*R*)-(+)-**5b**: P.A. Levene and R.E. Marker, *J. Biol. Chem.*, **97**, 563 (1932); *b*) (*S*)-(−)-**5c**: *Idem*, *ibid.*, **91**, 77 (1931); *c*) (*R*)-(+)-**5d**: R. Lukes, A. Zabacova, and J. Plesek, *Chem. Abstr.*, **53**, 17898 (1959); *d*) (*S*)-(+)-**5e**: P.A. Levene and R.E. Marker, *J. Biol. Chem.*, **93**, 749 (1931); *e*) (*R*)-(+)-**8**: G.W. O'Donnell and M.D. Sutherland, *Aust. J. Chem.*, **19**, 525 (1966); *f*) (*S*)-(+)-**9**: P.A. Levene and R.E. Marker, *J. Biol. Chem.*, **100**, 685 (1933).
17) D.J. Cram, *J. Am. Chem. Soc.*, **74**, 2137 (1952).

D. Determination of the Specific Rotation for optically Pure (*R*)-(+)-5b, (*R*)-(+)-5d and (*S*)-(+)-5e

Since there was some doubt about the specific rotations reported for optically pure (*R*)-(+)-**5b**,[16a,f] (*R*)-(+)-**5d**,[18] and (*S*)-(+)-**5e**,[19] the correlation of these alcohols with compounds of known optical purity was carried out as shown in Chart 6.

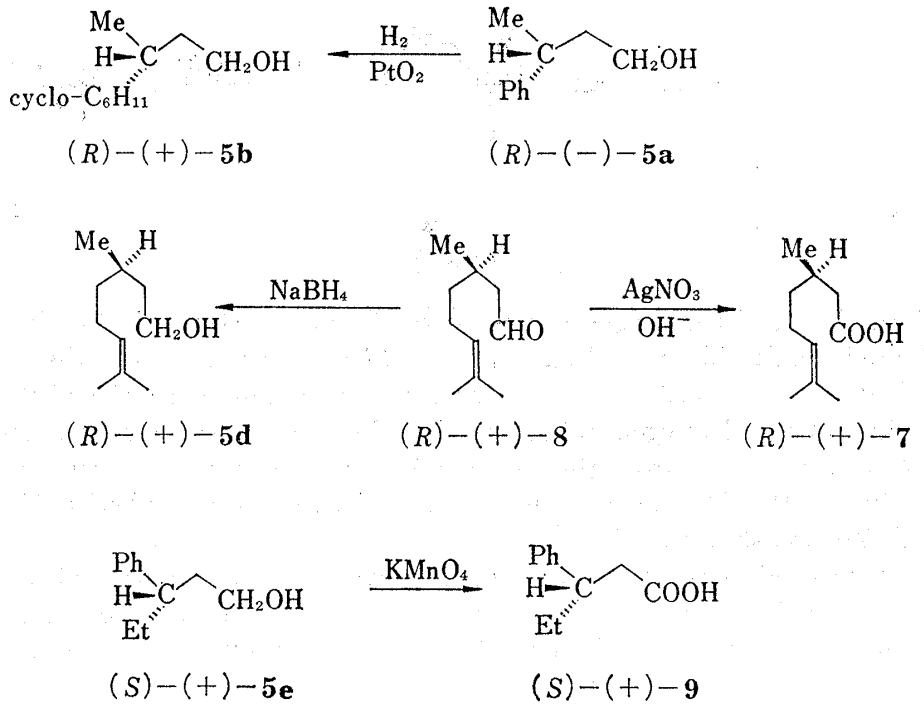


Chart 6

(*R*)-(+)-3-Cyclohexyl-1-butanol ((*R*)-(+)-5b)——Two values, $[\alpha]_D^{22}$ +11.7° (neat) and $[\alpha]_D^{25}$ +16.2° (neat) were reported for optically pure (*R*)-(+)-**5b**.[16a,f] We reexamined the correlation of (*R*)-(+)-**5b** with (*R*)-(−)-3-phenyl-1-butanol ((*R*-(−)-**5a**) according to the reported method.[16a] Catalytic reduction of (*R*)-(−)-**5a** (α_D^{25} −20.6° (*l*=1, neat), 52.8% optically pure[17]) with platinum catalyst afforded (*R*)-(+)-**5b**, $[\alpha]_D^{20}$ +6.40° (neat), in 73% yield. Therefore, optically pure (*R*)-(+)-**5b** was estimated to be $[\alpha]_D^{20}$ +12.1° (neat).

(*R*)-(+)-Citronellol ((*R*)-(+)-5d)——Optically pure (*R*)-(+)-**5d** is reported to have $[\alpha]_D^{25}$ +5.51° (neat),[18] but Valentine *et al.*[20] have recently thrown doubt on this value. Therefore, (*R*)-(+)-**5d** was correlated with (*R*)-(+)-citronellic acid ((*R*)-(+)-**7**), whose absolute specific rotation was determined to be $[\alpha]_D^{25}$ +10.5° (chloroform) with NMR and HPLC methods by them.[20] (*R*)-(+)-citronellal ((*R*)-(+)-**8**), $[\alpha]_D^{25}$ +12.8° (neat) was reduced with sodium borohydride to (*R*)-(+)-**5d**, $[\alpha]_D^{25}$ +4.34° (neat), in 88% yield, while oxidation of (*R*)-(+)-**8** of the same optical purity with silver oxide afforded (*R*)-(+)-**7**, $[\alpha]_D^{25}$ +8.02° (chloroform), in 72% yield. The above correlation clearly established that optically pure (*R*)-(+)-**5d** should have $[\alpha]_D^{25}$ +5.68° (neat). In addition, the specific rotation of optically pure (*R*)-(+)-**8** was determined to be $[\alpha]_D^{25}$ +16.8° (neat).

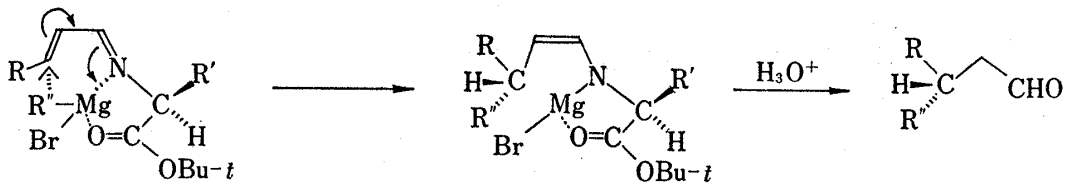
(*S*)-(+)-3-Phenyl-1-pentanol ((*S*)-(+)-5e)[19]——Permanganate oxidation of (*S*)-(+)-**5e**, $[\alpha]_D^{25}$ +14.2° (neat) obtained by the present asymmetric synthesis in aqueous alkali afforded (*S*)-(+)-3-phenylpentanoic acid ((*S*)-(+)-**9**), $[\alpha]_D^{25}$ +41.3° (neat), in 66% yield. Since optically

18) C.G. Oberberger and H. Kaye, *J. Am. Chem. Soc.*, **89**, 5640 (1967).
19) Optically pure (*R*)-(−)-**5e** was reported to have $[\alpha]_D^{25}$ −15.1° (neat) (see ref. 16*f*).
20) D. Valentine, Jr., K.K. Chan, C.G. Scott, K.K. Johnson, K. Toth, and G. Saucy, *J. Org. Chem.*, **41**, 62 (1976).

pure (*S*)-(+)-**9** was reported to have $[\alpha]_D^{25}$ −47.3° (neat),[16f] it was determined that optically pure (*S*)-(+)-**5e** should have $[\alpha]_D^{25}$ +16.3° (neat).

E. Mechanism of Asymmetric 1,4-Addition

Since all the experimental results have suggested that the asymmetric reaction should proceed *via* a common steric course, the mechanism shown in Chart 7 may be set forth.



10 **11** **4**

Chart 7

The initial attack of the Grignard reagent to the α,β-unsaturated aldimine ((*S*)-(−)-**3a**, **d**, or **e**) prepared from **1** and (*S*)-(+)-**2a** or (*S*)-(+)-**2d** is expected to form the cyclic complex ((*S*)-**10**) by virtue of the chelation of the Grignard magnesium with the unshared electron pairs on the nitrogen and oxygen atoms suitably disposed. Subsequent attack of the R″ group to the β-carbon atom from the less hindered side of s-*cis* conformer would lead to magnesioenamines (**11**), which provide, upon acidic cleavage, the β-substituted aldehydes (**4**) with the configuration shown in Chart 7.

This six-membered cyclic mechanism which appears consistent with all the facts relies on the work of Munch-Petersen *et al.*, who reported that the addition of Grignard reagents to α,β- and $\alpha,\beta,\gamma,\delta$-unsaturated esters may proceed preferentially *via* 1,4-mode through cyclic intermediates.[21]

It is of particular significance that the alkylation of magnesioenamines (**11**)[22] should be capable of producing optically active α,β-disubstituted aldehydes, key precursors for a variety of natural products. We are currently investigating the exploitation of the asymmetric 1,4-addition developed here to cyclic enones as well as the creation of a second chiral center by alkylation of **11**.

Experimental[23]

Preparation of optically Active Amino Acid *tert*-Butyl Esters (2)——These esters were prepared from their corresponding amino acids according to Roeske's method.[10a]

(*S*)-(+)-Valine *tert*-Butyl Ester ((*S*)-(+)-**2a**): bp 78° (15 mmHg), $[\alpha]_D^{25}$ +25.8° (neat) (lit.[10b] bp 63° (1.25 mmHg), $[\alpha]_D^{25}$ +25.5° (neat)).

(*S*)-(+)-Leucine *tert*-Butyl Ester ((*S*)-(+)-**2b**): bp 85° (14 mmHg), $[\alpha]_D^{25}$ +21.9° (c=2.70, EtOH) (lit.[10b] bp 45° (0.15 mmHg), $[\alpha]_D^{25}$ +21.6° (c=2.5, EtOH)).

(*S*)-(+)-Phenylalanine *tert*-Butyl Ester ((*S*)-(+)-**2c**): bp 140° (3 mmHg), $[\alpha]_D^{25}$ +24.5° (neat) (lit.[10b] bp 115° (0.75 mmHg), $[\alpha]_D^{25}$ +24.5° (neat)).

21) *a*) J. Munch-Petersen, C. Bretting, P.M. Jørgensen, S. Refn, and V.K. Andersen, *Acta. Chem. Scand.*, **15**, 277 (1961); *b*) S. Jacobsen A. Jart, T. Kindt-Larsen, I.G.K. Andersen, and J. Munch-Petersen, *ibid.*, **17**, 2423 (1963); *c*) J. Munch-Petersen, *Bull. Soc. Chim. Fr.*, **1966**, 471.

22) G. Stork and S.R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).

23) All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded with a JASCO DS-402G or a JASCO IRA-1 Grating Infrared Spectrometer. Nuclear magnetic resonance (NMR) spectra were measured with a JNM PS-100 (100 MHz) or a Hitachi R-24 (60 MHz) Spectrometer. Tetramethylsilane was used as an internal standard. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; d of t, doublet of triplet; br, broad. Optical rotations were recorded with a YANACO OR-50 Automatic Polarimeter. Mass spectra (MS) were recorded with a JOEL JMS-01 SG-2 Mass Spectrometer. Vapor phase chromatographic (VPC) analyses were carried out using a Hitachi 023 Gas Chromatograph. The organic solutions were dried over magnesium sulfate before vacuum evaporation.

(*R*)-(−)- and (*S*)-(+)-*tert*-Leucine *tert*-Butyl Ester ((*R*)-(−)- and (*S*)-(+)-**2d**): DL-*tert*-Leucine synthesized in 37% overall yield from pinacolone by the modified Knoop procedure[11] was resolved into (*R*)-(+)-*tert*-leucine, $[\alpha]_D^{25}$ +8.84° (*c*=5.01, H_2O), and (*S*)-(−)-*tert*-leucine, $[\alpha]_D^{25}$ −8.73° (*c*=4.98, H_2O), with brucine according to the reported method.[12] They were transformed by the above procedure to their corresponding *tert*-butyl esters ((*R*)-(−)- and (*S*)-(+)-**2d**) in 62% and 64% yields, respectively, wherein the starting (*R*)-(+)- and (*S*)-(−)*tert*-leucine were recovered in 14 and 12% yields, respectively. These esters showed the following physical data.

(*R*)-(−)-**2d**: α_D^{20} −1.57° (*l*=0.03, neat) (corresponding to be 93.5% optically pure), bp 90—91° (21 mmHg). IR ν_{max}^{film} cm^{-1}: 3400 (NH_2), 1735 ($COOC(CH_3)_3$). NMR ($CDCl_3$) δ: 0.99 (9H, s, $C(CH_3)_3$), 1.40 (2H, s, exchangeable with D_2O, NH_2), 1.47 (9H, s, $COOC(CH_3)_3$), 3.01 (1H, s, $CHCOOC(CH_3)_3$). MS *m/e*: 188 [$(M+1)^+$], 86 [$M^+-COOC(CH_3)_3$]. This sample was confirmed as its acid oxalate, colorless needles from EtOH, mp 157.5—158.5° (dec.). *Anal.* Calcd. for $C_{12}H_{23}NO_6$: C, 51.97; H, 8.36; N, 5.05. Found: C, 52.10; H, 8.54; N, 5.19.

(*S*)-(+)-**2d**: α_D^{20} +1.55° (*l*=0.03, neat) (corresponding to be 92.3% optically pure), bp 87—89° (18 mmHg). This sample showed identical IR and NMR spectra with those of (*R*)-(−)-**2d**.

Optically pure (*R*)-(−)-**2d**, α_D^{20} −1.68° (*l*=0.03, neat) was prepared from optically pure (*R*)-(+)-*tert*-leucine, $[\alpha]_D^{25}$ +9.44° (*c*=4.94, H_2O), which was obtained by repeating the above resolution procedure. The reliability for the optical purity of this sample was confirmed NMR spectroscopically using the chiral shift reagent Eu-Optishift I. For example, NMR (DL-**2d** and Eu-Optishift I (42 mol %) in CCl_4) δ: 0.92, 1.00 (9H, two s (1:1)), 1.18, 1.33 (9H, two s, (1:1)). ((*R*)-(−)-**2d** of α_D^{20} −1.68° (*l*=0.03, neat) and Eu-Optishift I (42 mol %) in CCl_4) δ: 1.00 (9H, s), 1.18 (9H, s).

Preparation of α,β-Unsaturated Aldimines (3)——(*S*)-(−)-**3a**: A solution of crotonaldehyde (**1a**) (1.40 g, 20 mmol) in hexane (15 ml) was added to an ice-cooled solution of (*S*)-(+)-**2a** (2.60 g, 15 mmol) in hexane (30 ml) under nitrogen atmosphere. Molecular sieves 4A (*ca.* 2.5 g) was added to the resulting cloudy mixture, and the whole was allowed to warm to room temperature, then left overnight. Filtration and evaporation *in vacuo* afforded (*S*)-(−)-**3a** (3.31 g, 98%) as a pale brown oil, $[\alpha]_D^{20}$ −194.5° (*c*=4.80, benzene). IR ν_{max}^{film} cm^{-1}: 1738, 1727 ($COOC(CH_3)_3$), 1658, 1622 (C=C–C=N), 975 (trans-disubstituted olefin). NMR (CCl_4) δ: 0.83 and 0.89 (6H, two *d*, *J*=6 Hz, $(CH_3)_2CH$), 1.45 (9H, s, $COOC(CH_3)_3$), 1.91 (3H, d, *J*=5.5 Hz, CH_3CH=), 1.95—2.34 (1H, m, $(CH_3)_2CH$), 3.16 (1H, d, *J*=7 Hz, $CHCOOC(CH_3)_3$), 5.87—6.38 (2H, m, CH=CH), 7.61 (1H, d, *J*=7.5 Hz, CH=N). MS *m/e*: 226 [$(M+1)^+$], 225 (M^+), 124 [$M^+-COOC(CH_3)_3$]. This oil was immediately used for the next step.

The same treatment of **1a** with (*S*)-(+)-**2b**, (*S*)-(+)-**2c**, (*S*)-(+)-**2d** (92.3% optically pure), and (*R*)-(−)-**2d** (93.5% optically pure) as that described above gave the corresponding aldimines ((*S*)-(−)-**3b**, (*S*)-(−)-**3c**, (*S*)-(−)-**3d**, and (*R*)-(+)-**3d**) as a pale brown oil in quantitative yields. Spectral properties of them are shown below.

(*S*)-(−)-**3b**: $[\alpha]_D^{20}$ −107.7° (*c*=3.96, benzene). IR ν_{max}^{film} cm^{-1}: 1735 ($COOC(CH_3)_3$), 1655, 1620 (C=C–C=N), 965 (*trans*-disubstituted olefin). NMR (CCl_4) δ: 0.80—1.03 (6H, m, $(CH_3)_2CH$), 1.43 (9H, s, $COOC(CH_3)_3$), 1.50—1.72 (3H, m, $(CH_3)_2CH-CH_2$), 1.91 (3H, d, *J*=5.5 Hz, CH_3CH=), 3.60 (1H, t, *J*=7 Hz, $CHCOOC(CH_3)_3$), 5.92—6.36 (2H, m, CH=CH), 7.68 (1H, d, *J*=7.5 Hz, CH=N). MS *m/e*: 240 [$(M+1)^+$], 239 (M^+), 138 [$M^+-COOC(CH_3)_3$].

(*S*)-(−)-**3c**: $[\alpha]_D^{20}$ −139.1° (*c*=2.76, benzene). IR ν_{max}^{film} cm^{-1}: 1730 ($COOC(CH_3)_3$), 1656, 1620 (C=C–C=N), 970 (*trans*-disubstituted olefin). NMR (CCl_4) δ: 1.38 (9H, s, $COOC(CH_3)_3$), 1.84 (3H, d, *J*=5.5 Hz, CH_3CH=), 2.64—3.25 (2H, m, $PhCH_2$), 3.73 (1H, d of d, *J*=6 and 7 Hz, $CH-COOC(CH_3)_3$), 5.76—6.32 (2H, m, CH=CH), 7.06 (5H, s, C_6H_5), 7.38 (1H, d, *J*=7.5 Hz, CH=N). MS *m/e*: 273 (M^+), 172 [$M^+-COOC(CH_3)_3$].

(*S*)-(−)-**3d**: $[\alpha]_D^{20}$ −129.1° (*c*=3.47, benzene). IR ν_{max}^{film} cm^{-1}: 1739, 1724 ($COOC(CH_3)_3$), 1655, 1620 (C=C–C=N), 970 (*trans*-disubstituted olefin). NMR (CCl_4) δ: 0.96 (9H, s, $(CH_3)_3C$), 1.45 (9H, s, $COOC(CH_3)_3$), 1.91 (3H, d, *J*=5.5 Hz, CH_3CH=), 3.23 (1H, s, $CHCOOC(CH_3)_3$), 5.90—6.43 (2H, m, CH=CH), 7.65 (1H, d, *J*=7.5 Hz, CH=N). MS *m/e*: 240 [$(M+1)^+$], 239 (M^+), 138 [$M^+-COOC(CH_3)_3$].

(*R*)-(+)-**3d**: $[\alpha]_D^{20}$ +130.6° (*c*=3.17, benzene). IR and NMR spectra of this oil were completely identical with those of (*S*)-(−)-**3d**.

(*S*)-(−)-**3e**: Treatment of a solution of cinnamaldehyde (**1b**) (1.98 g, 15 mmol) and (*S*)-(+)-**2d** (92.3% optically pure) (2.81 g, 15 mmol) in benzene (50 ml) in a manner similar to the case for (*S*)-(−)-**3a** gave (*S*)-(−)-**3e** (4.44 g, 98%) as a pale yellow solid, mp 64.5—66°, $[\alpha]_D^{20}$ −79.5° (*c*=2.40, benzene). IR ν_{max}^{KBr} cm^{-1}: 1730 ($COOC(CH_3)_3$), 1635, 1612 (C=C–C=N), 975 (*trans*-disubstituted olefin). NMR (CCl_4) δ: 0.99 (9H, s, $(CH_3)_3C$), 1.46 (9H, s, $COOC(CH_3)_3$), 3.34 (1H, s, $CHCOOC(CH_3)_3$), 6.76—6.88 (2H, m, CH=CH), 7.12—7.42 (5H, m, C_6H_5), 7.77 and 7.82 (1H, two d, *J*=each 5 Hz, CH=N). MS *m/e*: 302 [$(M+1)^+$], 301 (M^+), 200 [$M^+-COOC(CH_3)_3$]. This solid was used immediately for the next step. Two recrystallization of a part of this solid from hexane at −50° gave a pure sample as colorless prisms, mp 66.5—67.5°, $[\alpha]_D^{20}$ −86.1° (*c*=1.05, benzene). *Anal.* Calcd. for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.44; H, 9.05; N, 4.70.

Reaction of (*S*)-(−)-3a with Phenylmetallic Reagents——a) Table I, Run 2: A solution of (*S*)-(−)-**3a** (676 mg, 3.0 mmol) and dibenzyl (VPC internal standard) (73.4 mg) in THF (10 ml) was added dropwise to a stirred solution of phenylmagnesium bromide (1.34 M in THF) (4.48 ml, 6.0 mmol) in THF (7 ml) at −55°

under nitrogen atmosphere, giving a tan mixture immediately. After 30 min, VPC analysis (5% OV-7, 1 m, 110° 1 kg/cm²) of an aliquot hydrolyzed with 2 N HCl showed **4a** (retention time, 2.8 min) to be present in 65% yield, while the VPC analysis of an aliquot quenched with satd. aq. NH_4Cl indicated 7% of (*S*)-(−)-**3a** (retention time, 5.6 min) to remain. After stirring for an additional 1.0 hr, the reaction mixture was poured into vigorously stirred, ice-cold 2 N HCl (17 ml). After 25 min with ice-cooling, the whole mixture was extracted with ether (30 ml×2). The ethereal extracts were washed with satd. aq. NaCl, dried, and evaporated *in vacuo* leaving reddish brown oil (492 mg). This oily residue was purified by column chromatography on silica gel with ether–hexane (1: 9) to give (*R*)-(−)-**4a** (245 mg, 55%) as a slightly yellow oil, $[\alpha]_D^{20}$ −21.0° (*c*=2.94, EtOH). IR ν_{max}^{film} cm^{-1}: 2820, 2720, 1725 (CHO). NMR (CCl_4) δ: 1.23 (3H, d, *J*=7 Hz, $C\underline{H}_3$), 2.45—2.74 (2H, m, $CHC\underline{H}_2CHO$), 3.07—3.58 (1H, m, $C\underline{H}CH_2CHO$), 7.12 (5H, s, $C_6\underline{H}_5$), 9.54 (1H, t, *J*=2 Hz, C<u>H</u>O). MS *m/e*: 148 (M^+). These spectra were completely identical with those of DL-**4a** prepared by the reported method.[24]

b) Table I, Run 8: The same treatment of (*S*)-(−)-**3a** (1.01 g, 4.5 mmol) with diphenylmagnesium (0.73 M in THF) (12.3 ml, 9 mmol) as that described above, afforded (*R*)-(−)-**4a** (425 mg, 64%) as a pale yellow oil, $[\alpha]_D^{20}$ −20.7° (*c*=2.02, EtOH). Spectral (IR and NMR) and chromatographic (TLC) behavior of this sample was identical with that of the sample prepared in a).

c) Table I, Run 10: Cuprous iodide (343 mg, 1.8 mmol) was gradually added to a stirred solution of phenylmagnesium bromide (1.24 M in THF) (7.26 ml, 9 mmol) in THF (15 ml) at −23° under nitrogen atmosphere. After the resulting mixture was cooled to −55°, a solution of (*S*)-(−)-**3a** (1.01 g, 4.5 mmol) in THF (10 ml) was added dropwise. After 1.5 hr, the reaction mixture was poured into rapidly stirred, ice-cold 2 N HCl (25 ml). The same work-up and purification as those described in a) gave (*R*)-(−)-**4a** (407 mg, 61%) as a pale yellow oil, $[\alpha]_D^{20}$ −20.5° (*c*=2.21, EtOH). Spectral (IR and NMR) and chromatographic (TLC) properties of this sample were identical with those of the sample prepared in a).

Reaction of (*S*)-(−)-3d with *n*-Butyl Lithium——A solutoin of (*S*)-(−)-**3d** ($[\alpha]_D^{20}$ −129.1° (*c*=3.47, benzene)) (599 mg, 2.5 mmol) in THF (8 ml) was added dropwise to a stirred solution of *n*-butyl lithium (1.46 M in hexane) (1.78 ml, 2.6 mmol) in THF (5 ml) at −55° under nitrogen atmosphere. After 1.0 hr at the same temperature, the pale yellow mixture was poured into rapidly stirred, ice-cold satd. aq. NH_4Cl (20 ml). The whole mixture was extracted with ether (35 ml×2), and the ethereal extracts were washed with satd. aq. NaCl and dried. Filtration and evaporation *in vacuo* afforded an orange oil (710 mg), which was chromatographed on silica gel with ether–hexane (1: 12) to give (−)-**6** (506 mg, 68%) as a slightly yellow oil, $[\alpha]_D^{20}$ −42.6° (*c*=2.23, EtOH). IR ν_{max}^{film} cm^{-1}: 3430, 3340 (NH), 1728 ($COOC(CH_3)_3$), 966 (*trans*-disubstituted olefin). NMR ($CDCl_3$) δ: 0.86—1.00 (3H, m, $CH(CH_2)_3C\underline{H}_3$), 0.94 (9H, s, $(C\underline{H}_3)_3C$), 1.06—1.40 (6H, m, $CH(C\underline{H}_2)_3CH_3$), 1.45 (9H, s, $COOC(C\underline{H}_3)_3$), 1.65 (1H, s, exchangeable with D_2O, N<u>H</u>), 1.70 (3H, d, *J*=6 Hz, $C\underline{H}_3CH$=), 2.58—2.78 (1H, m, $C\underline{H}(CH_2)_3CH_3$), 2.81 (1H, s, $C\underline{H}COOC(CH_3)_3$), 4.92—5.60 (2H, m, C<u>H</u>=C<u>H</u>). MS *m/e*: 298 [$(M+1)^+$], 297 (M^+), 196 [$M^+-COOC(CH_3)_3$]. This sample gave acid oxalate as colorless needles (recrystallized from AcOEt) of mp 100—101°. *Anal.* Calcd. for $C_{20}H_{37}NO_6\cdot H_2O$: C, 59.23; H, 9.69; N, 3.45. Found: C, 59.09; H, 9.43; N, 3.27.

Reaction of (*S*)-(−)-3d with Lithium Di-*n*-butylcuprate——*n*-Butyl lithium (1.46 M in hexane) (2.19 ml, 3.2 mmol) was gradually added to a stirred slurry of cuprous iodide (305 mg, 1.6 mmol) in THF (4 ml) at −55° under nitrogen atmosphere. The resulting black solution of lithium di-*n*-butylcuprate was stirred at the same temperature for 15 min, and then a solution of (*S*)-(−)-**3d** (360 mg, 1.5 mmol) in THF (4 ml) was added dropwise. After 1.0 hr, the reaction mixture was poured into vigorously stirred, ice-cold satd. aq. NH_4Cl (25 ml), and the insoluble materials were filtered off. The same work-up and purification as those described above, gave (−)-**6** (319 mg, 72%) as a slightly yellow oil, $[\alpha]_D^{20}$ −42.5° (*c*=2.14, EtOH). Spectral (IR and NMR) and chromatographic (TLC) behavior of this sample were identical with that of (−)-**6** prepared above.

Asymmetric 1,4-Addition of Grignard Reagents to α,β-Unsaturated Aldimines ((*S*)-(−)-3a, (*S*)-(−)- and (*R*)-(+)-3d)——Reaction procedure for the asymmetric synthesis of (*R*)-(−)-**5a** from (*S*)-(−)-**3d** (run 3 in Table II) is described as a typical example.

A solution of (*S*)-(−)-**3d** ($[\alpha]_D^{20}$ −129.1° (*c*=3.47, benzene), 92.3% optically pure based on the optical purtiy of (*S*)-(+)-**2d** of α_D^{20} +1.55° (*l*=0.03, neat)) (2.64 g, 11 mmol) in ether–THF (5: 1) (18 ml) was added dropwise to a stirred solution of phenylmagnesium bromide (1.24 M in ether–THF (5: 1)) (17.7 ml, 22 mmol) in ether-THF (5: 1) (25 ml) at −55° under nitrogen atmosphere. After 1.5 hr of stirring at the same temperature, the resulting tan solution was poured into vigorously stirred, ice-cold 2 N HCl (60 ml). After 25 min of stirring in an ice-water bath, the whole mixture was extracted with ether (100 ml×2), and the ethereal extracts were washed with satd. aq. NaCl and dried. Filtration and evaporation *in vacuo* afforded a reddish brown oil (1.68 g), which was submitted to column chromatography on silica gel with ether–hexane (1: 10) to give (*R*)-(−)-**4a** (950 mg, 58%) as a pale yellow oil, $[\alpha]_D^{20}$ −33.2° (*c*=2.52, EtOH). Spectral (IR and NMR) and chromatographic (TLC) properties of this sample were identical with those of the sample prepared in run 2 in Table I. A solution of (*R*)-(−)-**4a** (815 mg, 5.5 mmol) obtained here in EtOH (5 ml) was added to a

24) R. Adams and J.D. Garber, *J. Am. Chem. Soc.*, 71, 22 (1949).

stirred suspension of sodium borohydride (114 mg, 3 mmol) in EtOH (4 ml) under ice-cooling. After stirring for 30 min, water (25 ml) was added to the reaction mixture. The whole was extracted with ether (60 ml×2), and then the ethereal extracts were washed with 5% HCl, satd. aq. NaCl, and dried. Filtration and evaporation *in vacuo* gave a pale yellow oil (812 mg), which was chromatographed on silica gel with ether-hexane (2: 3) to give (*R*)-(−)-3-phenyl-1-butanol ((*R*)-(−)-**5a**) (743 mg, 90%, 52% overall from (*S*)-(−)-**3d**) as a slightly yellow oil. Vacuum distillation afforded completely pure (*R*)-(−)-**5a** as a colorless oil (651 mg, 79%, 46% overall from (*S*)-(−)-**3d**), bp 85° (4 mmHg) (lit.[16d] bp 117° (8 mmHg)), α_D^{25} −1.64° (*l*=0.05, neat) (corresponding to be α_D^{25} −32.8° (*l*=1, neat)). IR ν_{max}^{film} cm^{-1}: 3330, 1043 (OH). NMR (CCl_4) δ: 1.20 (3H, d, *J*=7 Hz, $C\underline{H}_3CH$), 1.73 (2H, d of t, *J*=each 7 Hz, $CHC\underline{H}_2C\underline{H}_2OH$), 2.56—2.97 (1H, m, $C\underline{H}(CH_2)_2OH$), 3.32 (2H, t, *J*=7 Hz, $C\underline{H}_2OH$), 4.18 (1H, br s, $CH_2O\underline{H}$), 7.06 (5H, s, $C_6\underline{H}_5$). MS *m/e*: 150 (M^+). *Anal.* Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.29; H, 9.48. This sample should show α_D^{25} −35.5° (*l*=1, neat) after correction for 92.3% optical purity of (*S*)-(+)-**2d** used, and thus the optical purity was calculated to be 91%, based on α_D^{25} −39.0° (*l*=1 neat),[17] the highest rotation for (*R*)-(−)-**5a** available in literature. Furthermore, the above correlation clearly established that optically pure (*R*)-(−)-**4a** should have $[\alpha]_D^{20}$ −39.5° (EtOH).

The original 2 N aq. HCl phase was poured into ice-cold 20% NaOH (50 ml). After saturated with NaCl, the whole alkaline mixture was extracted with ether (120 ml×2), and the ethereal extracts were washed with satd. aq. NaCl, dried, and evaporated *in vacuo*, leaving a brown oil (1.75 g). Purification by column chromatography on silica gel with ether–hexane (1: 1) gave (*S*)-(+)-**2d** (1.30 g, 63%) as a pale yellow oil, α_D^{20} +1.55° (*l*=0.03, neat), which was comfirmed by spectral (IR and NMR) and chromatographic (TLC) comparisons with those of the starting sample.

Other asymmetric 1,4-additions were carried out in a manner similar to that described above, except for the purification at aldehyde stages. Physical properties of (*R*)-(+)-**5b**, (*S*)-(−)-**5c**, (*R*)-(+)-**5d**, and (*S*)-(+)-**5e**, other than those shown in Table II, are listed below.

(*R*)-(+)-3-Cyclohexyl-1-butanol ((*R*)-(+)-**5b**): bp 98° (5 mmHg) (lit.[16a] bp 128° (15 mmHg)). IR ν_{max}^{film} cm^{-1}: 3315, 1053 (OH). NMR (CCl_4) δ: 0.83 (3H, d, *J*=6 Hz, $C\underline{H}_3CH$), 0.90—1.95 (14H, m, $C_6\underline{H}_{11}$ and $C\underline{H}C\underline{H}_2C\underline{H}_2OH$), 3.22—3.67 (2H, m, $C\underline{H}_2OH$), 4.45 (1H, br s, $CH_2O\underline{H}$). MS *m/e*: 156 (M^+). *Anal.* Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.57; H, 13.03.

(*S*)-(−)-3-Methyl-1-heptanol ((*S*)-(−)-**5c**): bp 102° (38 mmHg) (lit.[16b] bp 99° (25 mmHg)). IR ν_{max}^{film} cm^{-1}: 3325, 1054 (OH). NMR (CCl_4) δ: 0.78—1.04 (3H, m, $C\underline{H}_3(CH_2)_3$), 0.87 (3H, d, *J*=6 Hz, $C\underline{H}_3CH$), 1.04—1.73 (9H, m, $CH_3(C\underline{H}_2)_3C\underline{H}C\underline{H}_2C\underline{H}_2OH$), 3.52 (2H, t, *J*=7 Hz, $C\underline{H}_2OH$), 4.52 (1H, br s, $CH_2O\underline{H}$). MS *m/e*: 130 (M^+).

(*R*)-(+)-Citronellol ((*R*)-(+)-**5d**): bp 93° (8 mmHg) (lit.[16c] bp 110° (10 mmHg)). IR ν_{max}^{film} cm^{-1}: 3315, 1056 (OH). NMR (CCl_4) δ: 0.86 (3H, d, *J*=6 Hz, $C\underline{H}_3CH$), 1.01—1.53 (5H, m, $C\underline{H}_2C\underline{H}C\underline{H}_2C\underline{H}_2OH$), 1.55, 1.65 (6H, two s, $(C\underline{H}_3)_2C$=), 1.94 (2H, d of t, *J*=each 6.5 Hz, $(CH_3)_2$=$CHC\underline{H}_2$), 3.52 (2H, t, *J*=6 Hz, $C\underline{H}_2OH$), 3.79 (1H, br s, $CH_2O\underline{H}$), 5.02 (1H, t, *J*=6.5 Hz, $(CH_3)_2C$=$C\underline{H}$). MS *m/e*: 156 (M^+).

(*S*)-(+)-3-phenyl-1-pentanol ((*S*)-(+)-**5e**): bp 98° (2 mmHg) (lit.[16d] bp 108° (1 mmHg)). IR ν_{max}^{film} cm^{-1}: 3315, 1048 (OH). NMR (CCl_4) δ: 0.74 (3H, t, *J*=7 Hz, $C\underline{H}_3CH_2$), 1.37—1.92 (4H, m, $CH_3C\underline{H}_2CHC\underline{H}_2$-$CH_2OH$), 2.35—2.66 (1H, m, $C\underline{H}(CH_2)_2OH$), 3.29 (2H, t, *J*=7 Hz, $C\underline{H}_2OH$), 3.48 (1H, br s, $CH_2O\underline{H}$), 7.05 (5H, s, $C_6\underline{H}_5$). MS *m/e*: 164 (M^+). *Anal.* Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.74; H, 9.98.

Determination of the Specific Rotation for Optically Pure (*R*)-(+)-5b, (*R*)-(+)-5d, and (*S*)-(+)-5e——(*R*)-(+)-**5b**: A solution of (*R*)-(−)-**5a** (α_D^{25} −1.03° (*l*=0.05, neat). 52.8% optically pure[17]) in AcOH was catalytically reduced with platinum according to the reported method.[16a] (*R*)-(+)-**5b** thus obtained showed α_D^{20} +0.294° (*l*=0.05, neat) (corresponding to be $[\alpha]_D^{20}$ +6.40° (neat))[16a] and was identified with the sample prepared in the above asymmetric 1,4-addition by comparison of their spectral (IR and NMR) and chromatographic (TLC) properties.

(*R*)-(+)-**5d**: (*R*)-(+)-Citronellal ((*R*)-(+)-**8**) (from Takasago Perfumery Co., Ltd.) was purified by silica gel column chromatography with ether–hexane (1: 20) and subsequent vacuum distillation (bp 84° (10 mmHg)) (lit.[16e] bp 83.5° (10 mmHg)) to a colorless liquid of α_D^{25} +1.08° (*l*=0.1, neat) (corresponding to be $[\alpha]_D^{25}$ +12.8° (neat)).[16e]

Treatment of this (*R*)-(+)-**8** (1.54 g, 10 mmol) with $NaBH_4$ (190 mg, 5 mmol) as previously described afforded (*R*)-(+)-**5d** (1.37 g, 88%) as a colorless oil of bp 94° (6 mmHg), α_D^{25} +0.371° (*l*=0.1, neat) (corresponding to be $[\alpha]_D^{25}$ +4.34° (neat)).[16c] Spectral (IR and NMR) and chromatographic (TLC) behavior of this sample was identical with that of the sample prepared in the above asymmetric 1,4-addition.

(*R*)-(+)-**7**: Fresh Ag_2O was prepared by adding a solution of $AgNO_3$ (5.10 g, 30 mmol) in H_2O (30 ml) to a stirred solution of NaOH (2.40 g, 60 mmol) in H_2O (40 ml) under ice-cooling. To the resulting brown semisolid mixture, (*R*)-(+)-**8** of α_D^{20} +1.08° (*l*=0.1, neat) (2.01 g, 13 mmol) was added, and then the whole was allowed to warm to room temperature. After 1.0 hr, the black Ag suspension was filtered, and washed with hot water (15 ml×2). After the combined filtrate and washings were extracted with ether (50 ml×2), the pH of the alkaline aq. phase was adjusted to 1 with 20% HCl, then the resulting aq. solution was extracted with ether (100 ml×2). The ethereal extracts were washed with satd. aq. NaCl, dried, and evaporated *in vacuo* to give a colorless oil (1.75 g). Vacuum distillation afforded (*R*)-(+)-citronellic acid ((*R*)-(+)-**7**) (1.59 g, 72%) as a colorless oil, bp 84—85° (0.6 mmHg) (lit.[18] bp 82—82.5° (0.1 mmHg)), $[\alpha]_D^{25}$ +8.02° (*c*=5.04,

$CHCl_3$). MS *m/e*: 170 (M^+). This sample showed identical IR and NMR spectra with those previously reported.[18]

(*S*)-(+)-**9**: $KMnO_4$ (1.56 g, 10 mmol) was added to a solution of (*S*)-(+)-**5e** (α_D^{25} +0.687° (*l*=0.05, neat) (corresponding to be $[\alpha]_D^{25}$ +14.2° (neat))[16d] (821 mg, 5 mmol) in 1 N aq. NaOH (10 ml) under ice-cooling. The mixture was stirred at room temperature overnight, then MeOH (0.5 ml) was added to the reaction mixture. After filtration and extraction with ether (20 ml×2), the pH of the alkaline aq. phase was adjusted to 1 with 20% HCl, then the acidic aq. solution was extracted with ether (40 ml×2). The ethereal extracts were washed with satd. aq. NaCl, dried, and evaporated *in vacuo* to afford a colorless oil (814 mg), which was purified by vacuum distillation (bp 130° (0.8 mmHg) (lit.[16f] bp 135° (1 mmHg)) and with silica gel preparative TLC using ether–hexane (2: 1) to give (*S*)-(+)-3-phenylpentanoic acid ((*S*)-(+)-**9**) (589 mg, 66%) as a colorless oil, α_D^{25} +1.70° (*l*=0.04, neat) (corresponding to be $[\alpha]_D^{25}$ +41.3° (neat)).[16f] IR ν_{max}^{film} cm^{-1}: 1710 (COOH). NMR (CCl_4) δ: 0.76 (3H, t, *J*=7 Hz, $C\underline{H}_3CH_2$), 1.27—1.94 (2H m, $CH_3C\underline{H}_2$), 2.52 (2H, d, *J*=7 Hz, $C\underline{H}_2COOH$), 2.71—3.09 (1H, m, $C\underline{H}CH_2COOH$), 7.09 (5H, s, $C_6\underline{H}_5$), 11.43 (1H, s, $COO\underline{H}$). MS *m/e*: 178 (M^+).

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