The effects of the nature of catalyst and of the solvent on the stereoselectivity in amine-catalyzed asymmetric synthesis of substituted cyclohexa-1,3-dienes from prenal and monoesters of ylidenemalonic acids

E. P. Serebryakov, A. G. Nigmatov, M. A. Shcherbakov, and M. I. Struchkova*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: +7 (095) 135 5328

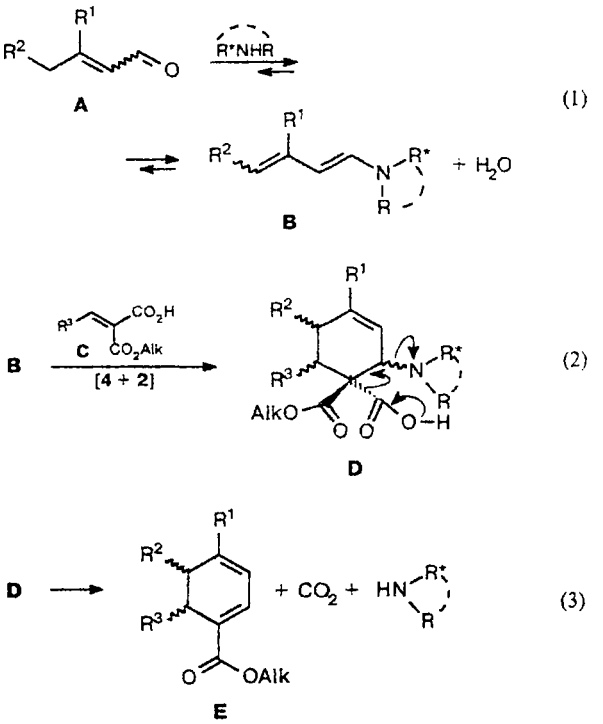
In the amine-catalyzed reactions of prenal with (*Z*)-5-methyl-2-(methoxycarbonyl)hexa-2,4-dienoic or (*Z*)-3-phenyl-2-(ethoxycarbonyl)prop-2-enoic acid chiral β-amino alcohols provide for higher enantiomeric purity of the resulting alkyl 4-methyl-6-(2-methylprop-1-enyl)- and 4-methyl-6-phenylcyclohexa-1,3-dienoates than that provided by related chiral amines without hydroxy group. The values of *ee* attained in nonpolar solvents are higher than those observed in the polar ones. Substituting stoichiometric amounts of a chiral 1-amino-3-methylbuta-1,3-diene for a combination of prenal with 0.1 equiv. of the corresponding chiral amine results in the products of much lower enantiomeric purity.

Key words: 3-methylbut-2-enal; chiral secondary amines and hydroxy amines; chiral dienamines; monoalkyl ylidenemalonates; net enantioselectivity.

Employing homochiral 2-amino-1,3-dienes in asymmetric Diels—Alder cycloaddition reactions[1,2] involves preparing them preliminarily. On the other hand, chiral six-membered carbocycles can be obtained following the same pattern, but in a single step, by generating a chiral 1-amino-1,3-diene from a branched α,β-enal **A** and a chiral secondary amine in the presence of an alkyl hydrogen ylidenemalonate as the dienopile.[3] Then the nascent dieneamine **B** cycloadds to the dienophile **C** to give unstable β-amino acids **D** which readily release CO_2 (this makes the whole process irreversible) and leave a chiral cyclohexadiene **E** and the starting chiral amine which re-enters the catalytic cycle (Scheme 1).

Here we report on the effects of the structure and absolute configuration of chiral amines on the net enantioselectivity (NES) and its trend in the amine-catalyzed asymmetric synthesis of methyl 4-methyl-6-(2-methylprop-1-enyl)cyclohexa-1,3-dienecarboxylate (**1**) or ethyl 4-methyl-6-phenylcyclohexa-1,3-dienecarboxylate (**2**) from prenal (**3**) and 5-methyl-2-(methoxycarbonyl)hexa-2,4-dienoic (**4**) or 5-methyl-2-(ethoxycarbonyl)prop-2-enoic acid (**5**), respectively.* All experiments were carried out using crystalline monoesters **4** and **5** consisting entirely of the *Z* isomers (according to ^1H NMR data, *cf.* Ref. 4), which makes it possible to interpret the stereochemical outcome of the whole process with somewhat greater certainty.

Scheme 1



Catalysts studied in this work were (*S*)-prolinol (**6**), already used to produce optically active cyclohexadienes

* In fact, the formation of compounds **1** and **2** involves two *diastereoselective* steps, that is, the formation and fragmentation of the corresponding cycloadducts of the type **D**. Hence, as a matter of convenience, the stereochemical outcome of the whole process should be termed *net enantioselectivity*.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 84—92, January, 1998.

1066-5285/98/4701-0082$20.00 ©1998 Plenum Publishing Corporation

Table 1. Effectiveness and enantioselectivity of formation of cyclic dienes **1** and **2** in the presence of chiral β-amino alcohols (molecular ratio prenal : dienophile : amine = 1.0 : 1.0 : 0.1, in benzene)

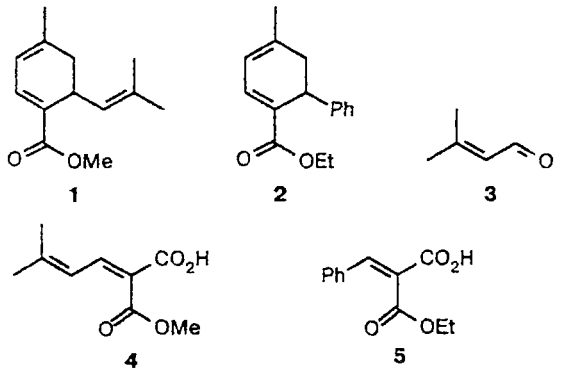
Entry	Amino alcohol	*T*/°C	Reaction duration/h	Reaction product[a]	Yield (%)	$[\alpha]_D$ (*c* 1.0, PhH)	*ee* (%)
1	**6**	20	168	(*S*)-**1**	52	+81	27.4
2	**6**	4	72		34	+184	62.1[b]
3	**6**	4	336		48	+104	35.2
4	*ent*-**6**	20	168	(*R*)-**1**	54	−70	23.7
5	*ent*-**6**	4	96		10	−183	61.8
6	*ent*-**6**	4	336		45	−145	49.0
7	*ent*-**6**	7	120		30.5	−149	51.5[c]
8	**7**	50	120	(*S*)-**1**	23	+256	86.7
9	**7**	20	168		40	+296	100.0[d]
10	**12**	20	168	(*S*)-**1**	41	+129	43.7
11	**12**	4	168		20	+173	58.4[e]
12	**12**	−10[f]	480		11	+185	62.5[g]
13	**6**	20	360	(*R*)-**2**	16	−14.05	7.8[h]
14	*ent*-**6**	20	360	(*S*)-**1**	19	+16.0	8.6[h]

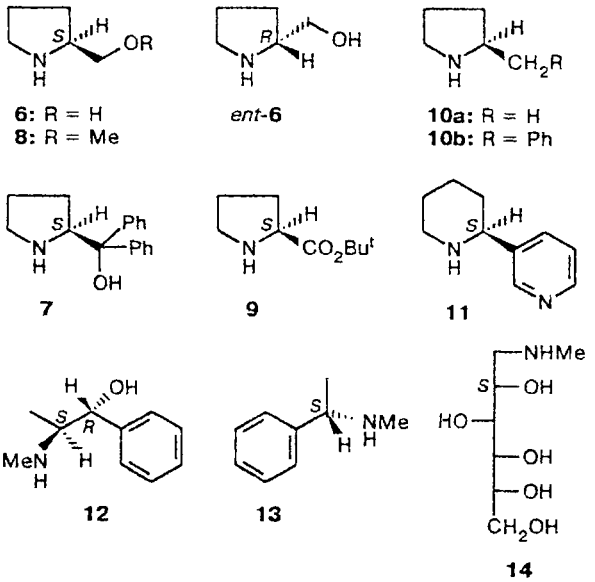
[a] Configurations were assigned using ^{1}H NMR spectroscopy in combination with chiral solvating agents, (*R*)- or (*S*)-1,1′-bi(2-naphthol) (Ref. 5). [b] Assignment according to Ref. 5 gives 68% *ee*. [c] Assignment according to Ref. 5 gives 34.3% *ee*. [d] Assignment according to Ref. 5 gives ~100% *ee*: consequently, for the specimens of (*S*)-**1** or (*R*)-**1** with $|[\alpha]_D|$ = 296° the value of *ee* should be assessed at *ca.* 100%. [e] Assignment according to Ref. 5 gives 67% *ee*. [f] In toluene. [g] Assignment according to Ref. 5 gives 72% *ee*. [h] By extrapolation of the value of *ee*, determined earlier according to Ref. 5 for a specimen of (*R*)-**2** with $[\alpha]_D$ −52° (28%), the value of $[\alpha]_D$ corresponding to enantiomerically pure specimens of (*R*)-**2** or (*S*)-**2** was assessed at $|[\alpha]_D|$ = 186°.

and hexahydronaphthalenes (Refs. 3, 5), (*R*)-prolinol (*ent*-**6**), (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (**7**), (*S*)-2-(methoxymethyl)-pyrrolidine (**8**), (*S*)-proline *tert*-butyl ester (**9**), (*R*)-2-methylpyrrolidine (**10a**), (*S*)-2-benzylpyrrolidine (**10b**), (*S*)-anabasine (**11**), (1*R*,2*S*)-ephedrine (**12**), (*S*)-*N*-methyl-1-phenylethylamine (**13**), and *N*-methyl-D-glucamine (**14**).

The reaction of enal **3** with dienophiles **4** and **5** in the presence of these amines was carried out under conditions analogous to those described earlier,[5] except when the reaction **3** + **4** → **1** was catalyzed by amino polyol **14**. In that case the reaction was performed in methanol (20 °C, 96 h); the yield of cyclohexadiene **1** was only 6.4%, and its optical purity was quite insignificant ($[\alpha]_D^{20}$ +1.0° in benzene, ~0.3% *ee*). The results of all other experiments, summarized in Scheme 2, are presented in Tables 1 and 2.

The analysis of these data provides some clues for understanding the effects of certain reaction parameters





on the effectiveness and NES of the formation of chiral cyclohexadienes **1** and **2**.

Stereoselectivity factors and their effects

The structure of the catalyst markedly affects the stereoselectivity of the process and enantiomeric purity of its product. As can be anticipated, the use of amines with opposite absolute configuration, such as **6** and *ent*-**6**, gives specimens of cyclic dienes **1** or **2** of opposite absolute configuration, but with nearly the same values

Scheme 2

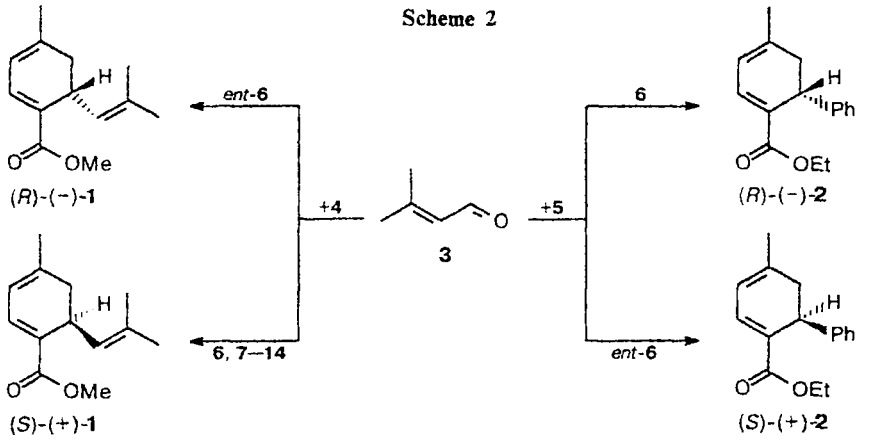


Table 2. Effectiveness and enantoselectivity of formation of cyclohexadiene (*S*)-**1** in the presence of non-hydroxylic amines as catalysts[a]

Entry	Amine	*T* /°C	Reaction duration/h	Yield (%)	$[\alpha]_D$ (*c* 1.0, PhH)	*ee* (%)
1	**8**	7	144	37	+46	15.6[b]
2	**9**	20	144	23	+2.8	0.9
3	**9**	10	144	20	+3.9	1.3
4	**10a**	20	96	62	+22	7.4
5	**10a**	4	168	3	+77	26.0
6	**10b**[c]	20	72	64	+44.5	15.0[c]
7	**10b**[c]	10	144	47	+98	33.1[c]
8	**11**[d]	4	288	16	+57	19.3[d]
9	**13**	20	96	25	+32	10.8
10	**13**	4	168	21	+61	20.6

[a] The conditions of the experiments and concentration ratios of the reactants and catalysts are the same as given in Table 1. [b] Assignment according to the procedure of Ref. 5 gave 14.0% *ee*. [c] According to the value of $[\alpha]_D$ −28.8° (MeOH), the specimen of the (*S*)-2-benzylpyrrolidine used had 85.7% *ee*. [d] According to the value of $[\alpha]_D$ −41.6° (neat liquid), the starting (*S*)-anabasine had *ca.* 50% *ee*.

of *ee* (*cf.* Table 1, entries *1—3* and *4—6* for compound **1**, as well as entries *13*, *14* for compound **2**). Such a relationship allows one to transform achiral reactants (*e.g.*, **3** and **4**, **5**) into chiral cyclohexadienes, such as **1** or **2**, with an "ordered" absolute configuration at the asymmetric carbon atom by employing only catalytic amount of a homochiral secondary amine of a known absolute configuration.

Comparing the data of Tables 1 and 2 obtained under similar conditions, one observes that the reaction **3** + **4** → **1**, when catalyzed by β-hydroxy-substituted amines (**6**, *ent*-**6**, **7**, and **12**), affords a product of markedly higher enantiomeric purity than in the case of amines containing no free hydroxy group (**8—11** and **13**). The highest NES was attained using sterically demanding amino alcohol **7** as the catalyst (see Table 1, entries *8* and *9*): not only at 20 °C, but even at 50 °C, were the values of *ee* of the resulting specimens of (*S*)-**1** higher than those obtained with other hydroxyamine catalysts at +4 to −10 °C. Relatively high *ee* values of compounds (*S*)-**1** or (*R*)-**1** were obtained when the reaction was catalyzed by amines **6** and *ent*-**6**, or by the acyclic amino alcohol **12**. Among the amines bearing no HO group (see Table 2), it is (*S*)-anabasine that appears to be the best catalyst: in spite of its only 50% enantiomeric purity, it afforded a specimen of (*S*)-**1** with a 19% *ee* (*ca.* 38% *ee*, if enantiopure specimen of **12** were used). Other amines in Table 1 (**8—10** and **13**) do not provide even for such a modest enantioselectivity.

Solvent polarity exerts a negative effect upon the NES of the process. The relationship between the dielectric constant (ε) of a solvent and enantiomeric purity of cyclohexadiene (*S*)-**1** was studied using the most effective catalyst, amino alcohol **7** (Table 3). Under given conditions, four solvents among the eight tried (benzene, dioxane, THF, and MeCN) can be considered as inert media. The rest could, in principle, react with the catalyst (AcOEt, Me_2CO), aldehyde **3** (MeOH), or dienophile **4** (pyridine, MeOH). However, the yields of (*S*)-**1**, attained in a fixed time span, were fairly similar. Hence, the interaction of solvent molecules with any of the three components of the reaction system can be assumed negligible.*

The products formed in solvents of low polarity (ε < 10) invariably induce high enantiomeric purity (88—*ca.* 100% *ee*), whereas in polar media the resulting specimens of (*S*)-**1** have significantly lower values of *ee*. Both the lowering of *ee* of compound (*S*)-**1** upon transition from non-polar solvents to polar ones (see Table 3) and the above-mentioned positive effect of the OH group in the molecule of amine catalyst upon *ee* suggest the importance of a hydrogen bond in the mechanism of asymmetric induction.

Reaction temperature and duration. As was already shown,[5] the lower reaction rate and lower yield of compound (*S*)-**1**, due to the lowering of the reaction

* With the exception of pyridine, where the formation of a pyridinium salt of monoester **4** (a weaker dienophile) cannot be excluded.

Table 3. The effect of solvent polarity on the yield and enantiomeric purity of cyclic diene (*S*)-**1**

Solvent	ε	Yield of **1** (%)	$[\alpha]_D^{20}$ (*c* 1.0, PhH)	*ee* (%)
1,4-Dioxane	2.21	20	+261	88
Benzene	2.28	40	+296	100
Ethyl acetate	6.02	28	+290	98
Tetrahydrofuran	7.32	26	+296	100
Pyridine	12.3	11	+162	54
Acetone	20.7	26	+32	10.8
Methanol	32.6	20	+138	46.6
Acetonitrile	36.2	20	+181	61.1

Note. The reactions of equimolecuar amounts of enal **3** and monoester **4** in the presence of amine **7** (0.1 equiv.) were performed at 20 °C for 168 h in benzene (see Table 1) or for 120 h in all other solvents.

temperature from 20 °C to +4 or −10 °C, are compensated for by a strong increase of *ee* in the product (*cf.* entries *1—2*, *4—5*, and *10—12* in Table 1 as well as entries *4—5*, *6—7*, and *9—10* in Table 2). In the case of sterically demanding amine **7** the same trend is observed when the reaction temperature is lowered from 50 to 20 °C (*cf.* entries *8* and *9* in Table 1). It is not unlikely that the lower enantioselectivity observed at elevated reaction temperatures could be due to the breaking of a weak hydrogen bond between the hydroxy group and the π-system of the transient chiral dienamine and/or to the accelerated internal rotation of counterions in a salt-like associate of dienophile **4** (or **5**) with a chiral amine catalyst. In either case, the steric non-equivalence of the opposite faces of either of the diastereodiscriminating planes* (accommodating either of the reacting species) diminishes as the temperature increases.

At any fixed temperature, the yields increase upon prolonging the reaction periods, but at the expense of enantioselectivity (*cf.* entries *2* and *3* or *5* and *6* in Table 1). Apparently, in the course of long exposure the product is gradually enriched with that of the two enantiomers which is formed *via* a less favorable transition state corresponding to one of the possible diastereomeric cycloadducts of the type **D** (see Scheme 1).

An argument in favor of this assumption may be seen in the opposite signs of optical rotation of the two specimens of cyclohexadiene **1** obtained from a single experiment upon fractionating the crude product of the reaction **3** + **4** → **1** catalyzed by amine **10b** (0.1 equiv). After the isolation of the main product, dextrorotatory compound (*S*)-**1**, from the hexane-soluble fraction, the insoluble tar-like fraction was heated (80 °C, 30 min) to give an additional amount of cyclic diene **1** (14% yield). The latter differed from the first crop only in the sign and magnitude of specific optical rotation ($[\alpha]_D$ −38.4° in PhH, which corresponds to *ca.* 13% *ee*). Evidently, the more polar tar-like fraction (TLC data) contained predominantly the more stable diastereomer of the originally formed cycloadduct (as a betain and/or ammonium salt of the corresponding amino acid **D**) in amounts roughly equivalent to that of the catalyst (thence, not exceeding 0.1 equiv. of each of the achiral reactants, **3** and **4**). The lowering of *ee* of the main product (*S*)-**1** is hardly due to the amine-induced racemization, as it was shown earlier[5] that this process practically did not occur under the given conditions.

* The diastereodiscriminating plane is defined as a molecular plane accommodating both the sp^2-prochiral centers and one asymmetric center (see Ref. 6).

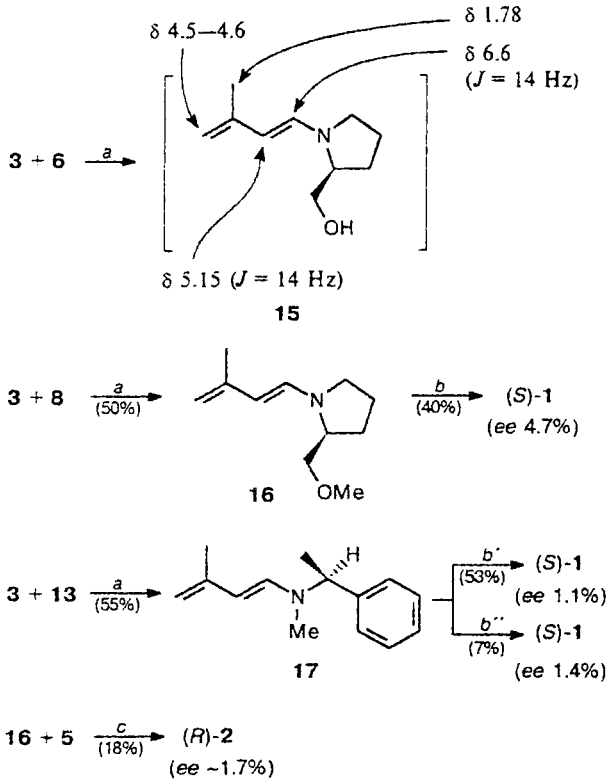
Comparing variants of the cyclohexadiene synthesis: catalytic *vs.* stoichiometric

The formation of dienamines from prenal and achiral amines R_2NH in the presence of dienophiles was proven earlier.[7,8] Therefore, the formation of chiral cyclohexadienes **E** (Scheme 1) was assumed to follow the same pattern, *i.e.*, to begin with *in situ* generation of a chiral dienamine[3,5] which subsequently cycloadds by its sterically less hindered face to a dienophile either in the *endo* or *exo* mode. With a view to comparing the effectiveness and enantioselectivity of the catalytic synthesis of compounds **1**, **2** (embracing all steps of Scheme 1) with those of the direct interaction of equimolecular amounts of chiral 1-amino-3-methylbuta-1,3-dienes with dienophiles **4**, **5** we prepared dienamines **15—17** from enal **3** and amines **6**, **8**, and **13**, correspondingly. The unstable dienamine **15** could not be isolated in the pure state, so it was characterized only by the diagnostic signals present in the ^1H NMR spectrum of the crude reaction mixture. The more volatile dieneamines **16** and **17** were isolated as pure liquids in 50—55% yields upon distillation *in vacuo*, and characterized by ^1H NMR spectra (Scheme 3).

The reaction of dienophile **4** with equimolecular amounts of dienamine **16** or **17** proceeded readily to give compound (*S*)-**1** in somewhat higher yield, but with substantially lower values of *ee* than the reaction **3** + **4** → **1** in the presence of 0.1 equiv. of the corresponding amines **8** and **13**. Thus, when the reaction **3** + **4** → **1** was catalyzed by acyclic amine **13** at 20 °C (exposure 96 h), the isolated specimen of (*S*)-**1** had 10.8% *ee*; at 4 °C (exposure 168 h) the resulting cyclic diene (*S*)-**1** had 20.6% *ee* (see Table 2, entries *9* and *10*). On the other hand, direct [4+2] cycloaddition of the corresponding dienamine **17** to ylidenemalonate **4** at 20 °C (exposure 15 h) afforded a specimen of (*S*)-**1** with only *ca.* 1.1% *ee*; at 6 °C (exposure 2.5 h) the resulting (*S*)-**1** had *ca.* 1.4% *ee*. In both cases the transition from catalytic mode to the stoichiometric one was accompanied by an about 10-fold decrease of *ee* in compound (*S*)-**1**.

The reaction of acidic benzylidenemalonate **5** with dieneamine **16** (20 °C, 96 h) gave a specimen of cyclohexadiene (*R*)-**2** with $[\alpha]_D^{16}$ −3.2° (in PhH) in 18% yield. By extrapolating the polarimetric data (see footnote *h* to Table 1), the value of its *ee* was assessed at ~1.7%. When the reaction **3** + **5** → **2** was performed at

Scheme 3



Reagents and conditions: *a*. K_2CO_3(sol.)/PhH, 20 °C, 24 h; *b*. **4**/PhH, 20 °C, 0.5 h; *b'*. **4**/PhH, 20 °C, 15 h; *b''*. **4**/PhH, 6 °C, 2.5 h; *c*. **5**/PhH, 20 °C, 96 h.

the same temperature using either (*S*)- or (*R*)-prolinol as the catalyst, the *ee* values of the resulting specimens of (*R*)-**2** or (*S*)-**2** were about 2.5-fold higher (see entries *13* and *14* in Table 1).

It should be noted that the transition from the catalytic synthesis of cyclic dienes **1** and **2** to the "stoichiometric" variant is not accompanied by a steep increase of their yields. This may be due to the acceleration of side reactions with increasing concentration of secondary amines in the reaction medium (*cf.* Refs. 4 and 5).*

* Although at the moment of mixing together the reactants **16** + **4**, **17** + **4**, or **16** + **5** the reaction medium contains no free secondary amine (**8** or **13**), the high velocity of the process (stages (2) and (3) in Scheme 1) brings about the appearance of substantial quantities of these amines. The latter can compete with dienamines **16** or **17** by adding to dienophiles **4**, **5** as Michael-type nucleophiles and inducing their fragmentation. Moreover, free amines can form chiral ammonium salts with monoesters **4**, **5**; in this case not only the reactivity of the latter as dienophiles would be lowered, but the stereoselectivity of the cycloaddition could be reversed; as a result, the NES of the whole process would be affected. We intend to return to these aspects in subsequent communications.

Conformatonal effects and net enantioselectivity

The plane accommodating the five backbone atoms of the delocalized π system of a dienamine like **15**—**17** has sterically non-equivalent faces. As the dienamine approaches the plane formed by the Δ^2 bond of monoesters **4**, **5**, its molecule assumes that of the planar reactive *s-cis* conformations ($\mathbf{B'}_1$ or $\mathbf{B'}_2$) which provides for the closest suprafacial interaction of the two reacting π systems. Here, four favorable orientational complexes can be visualized, two of them corresponding to the "*endo*" mode of approach, and two others — to the "*exo*" mode (Scheme 4). The rotamers $\mathbf{B'}_1$ and $\mathbf{B'}_2$ entering these orientational complexes are almost isoenergetic.*

Both the *endo* and *exo* approach of dienamine to the "upper" side of the dienophile (2*re*, 3*si*, see Scheme 4, *A*) lead to the *S*-configured products *via* epimeric cycloadducts **I** and **II**, respectively. In exactly the same manner, both the *endo* and *exo* approach of the dienamine to the "lower" side of the dienophile (2*si*, 3*re*, see Scheme 4, *B*) would result in *R*-configured cyclohexadienes, arising from intermediates *ent*-**I** and *ent*-**II**.

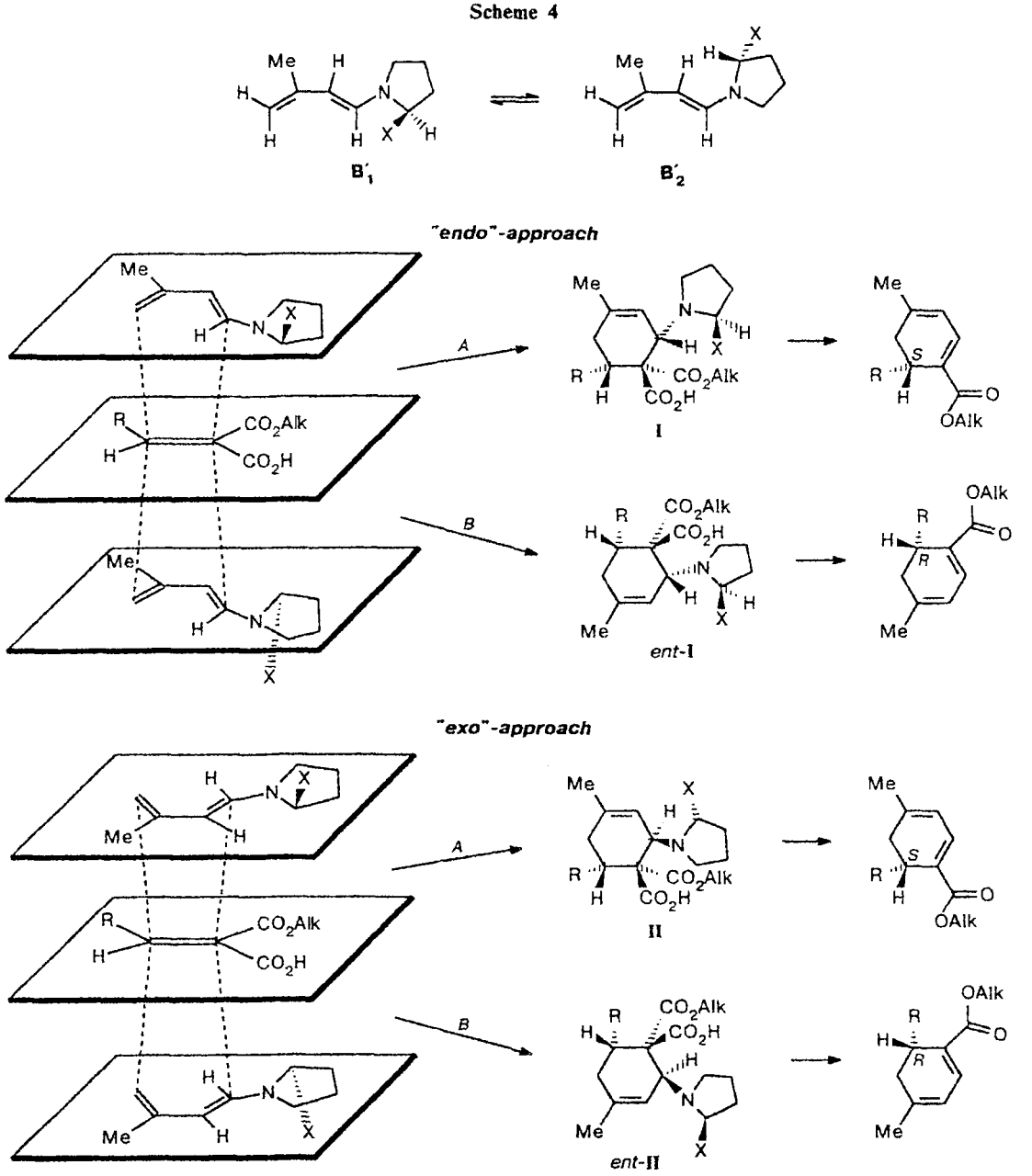
A point of special interest is the formation of cyclohexadienes of opposite absolute configuration when prenal reacts with dienophiles **4** and **5** in the presence of identical amine catalysts, *e.g.*, (*S*)-prolinol (see Table 1, as well as earlier data[5]).

The reversal of cycloaddition enantioselectivity upon the transition from the peripherically hydroxylated 1,3-dienes to their nearest non-hydroxylated analogues was already recorded for a few reactions involving some traditional dienophiles; this discrepancy was convincingly explained by the formation of diene—dienophile complexes stabilized, in the former case, by an intermolecular hydrogen bond.[9,10] But the opposite enantioselectivity in reactions **3** + **4** → **1** and **3** + **5** → **2** cannot be explained similarly. As can be seen from Tables 1 and 2, the presence or absence of a hydroxy group in the amines with identical stereochemistry at the asymmetric carbon atom does not affect the reaction qualitatively (that is, the sense of enantioselectivity), but only quantitatively (that is, the value of *ee* in the product).

On the other hand, the increase of enantioselectivity of formation of cyclic diene (*S*)-(+)-**1** (that is, of *ee* in this product), occurring upon the transition from the non-hydroxylic catalysts (**8**—**11** and **13**) to β-hydroxy-substituted amines **6**, **7**, and **12**, could be explained by the weak *intramolecular* hydrogen bond between the OH group and the five delocalized p-orbitals of the C=C—C=C—N system in the intermediate dienamines. Due to this bond, the planar *s-cis* conformation of the dienamine becomes more fixed. In non-polar solvents such a fixation enhances the steric non-equivalence of the opposite faces of the diastereodiscriminating plane corresponding to this

* MM2 calculations show that at 25 °C the total energy-minimized conformations $\mathbf{B'}_1$ and $\mathbf{B'}_2$ differ only by 0.08 kcal mol^{-1}.

Scheme 4



R = Me_2C=CH, Ph; X = CH_2OH, Ph_2COH, Me, CH_2Ph, CO_2Bu^t

planar conformation of the dienamine; as a consequence, the specimens of (*S*)-**1** obtained by using β-amino alcohols display higher values of *ee* than those attained upon catalyzing the reaction by non-hydroxylic amines **8**—**11** and **13**.

The opposite enantioselectivity of transformations **3** + **4** → **1** and **3** + **5** → **2**, each catalyzed by the same catalyst, can hardly be explained by the formation of a salt (or salt-like associate) from the starting chiral amine and acidic dienophile, a process competing with the dienamine-generating step, under the conditions of catalytic synthesis of cyclic dienes **1** and **2**. Be that as it may, adding a chiral secondary amine to an equimolecular mixture of the corresponding dienamine and acidic dienophile would most likely increase the *ee* in the resulting product, if the sense of enantioselectivity is the same for the catalytic and "stoichiometric" synthesis. In fact, when a small amount (*ca.* 2.5 mol.%) of the most effective catalyst **7** was added to an equimolecular mixture of (*S*)-dienamine **17** with monoester **4**, both the rate of formation and enantiomeric purity of cyclohexadiene (*S*)-**1** were somewhat lowered; under identi-

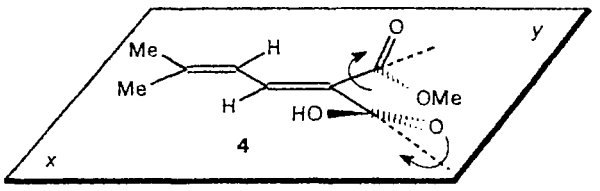
cal conditions (20 °C, 15 h) the yields and the values of $[\alpha]_D$ (in PhH) of specimens obtained from **17** and **4** in the presence and in the absence of catalyst **7** were 48% and +2.2° against 53% and +3.2°, respectively.

However, the opposite stereoselectivity observed for the reactions of dienophiles **4** and **5** with chiral dienamines generated from enal **3** can be explained by two interrelated assumptions. (1) The fully planar conformation of the cross-conjugated dienophiles **4** and **5** is sterically congested and hence less favored than a conformation in which the oxygen atoms of the COOH and/or COOAlk grouping are projected from the σ-plane of the C=C bond. (2) The dienamine approaches this thermodynamically favored conformation of **4** or **5** mainly from that side of the plane formed by the sp^2-hybridized C atoms, where the acidic OH group is located. In the limit, such an approach leads to an unstable dienammonium salt (which involves rehibridization of the N atom),[11] but [4+2] cycloaddition successfully competes with this process.

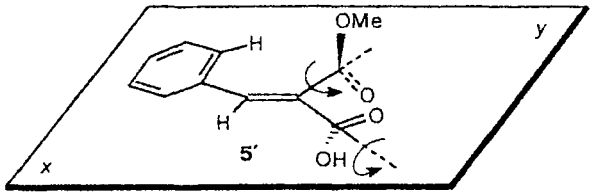
Indeed, the calculations, employing a PC MODEL program that takes into account p,π-conjugation of sp^2-hybridized atoms, showed that in the most stable conformation of monoester **4** all oxygen ligands in the COOH and COOMe groups are projected from the *xy* plane accommodating the carbon atoms of the cross-conjugated $C{=}C(C{=}O)_2$ moiety. In this conformation (**F**) the dihedral angles formed by the oxygen atoms of the OH and OMe groups with the *xy* plane amount to 17.8° and −160.2°, respectively; and the dihedral angles between the carbonyl O atoms in the COOH and COOMe groups and the *xy* plane are −163.4° and 19.3°, respectively. This arrangement favors the approach of the dienamine to monoester **4** from the "upper" (2*re*,3*si*) side of the latter, which results in the *S*-configured products.

Analogous calculations for a more sterically conjested model compound **5′** (where in the fully planar conformation the distance between an H atom in the *ortho*-position of the benzene ring and any of the oxygen atoms in the COOMe group is less than the sum of the respective van der Waals radii) show that in the most favored conformation of **5′** (**G**) the oxygen atoms of the COOH and COOMe groupings are oriented differently with respect to the plane *xy*. The dihedral angles between the latter and the oxygen atoms in the OH and OMe groups amount to −145.6° and 94°, respectively, while the dihedral angles formed by the sp^2-hybridized oxygen atoms of the COOH and COOMe groupings with this plane are 34.5° and −86°, respectively.

In this case the approach of the dienamine to the "lower" (2*si*,3*re*) face of the *xy* plane becomes more favored, which accounts for the preponderance of the *R* enantiomer in the resulting product **2**. In comparison with the transformation **3** + **4** → **1**, the formation of cyclohexadiene **2** from enal **3** and monoester **5** proceeds inefficiently, which might be attributed to the almost complete deconjugation of the ester group and the C=C bond in the dienophile **5**.



F



G

Experimental

The course of the reactions and the purity of the isolated products were controlled by TLC using standard Silufol sheets. Column chromatography was performed on Poroquartz silica gel (50—150 mm, Russia). ^1H NMR spectra were recorded at 20 °C using a Bruker WM-250 (for routine overview spectra) and a Bruker AM-300 instrument (for determining the enantiomeric purity of compounds **1** and **2** by a previously described procedure[5]). The values of *ee* were assessed employing standard ultraprecision NMR sample tubes for solutions containing a specimen of **1** or **2** and (*S*)- or (*R*)-BINOL as the chiral shift agent in benzene at concentrations 0.1 and 0.3 mol L^{-1}, respectively. The values of $[\alpha]_D$ were determined using a JASCO-DIP 360 polarimeter for solutions of **1** and **2** in benzene at 16—25 °C.

Aldehyde **3** was prepared from the isomeric 2-methylbut-3-yn-2-ol by the previously described rearrangement.[12] The pure *Z* isomer of monoester **5** was obtained as prism-like crystals with m.p. 95.0—95.5 °C and R_f 0.4 (AcOEt—heptane, 1 : 1, v/v) by repeated recrystallization from benzene—hexane of the fraction with m.p. 88—93 °C isolated after extraction of the acidified reaction mixture with Et_2O (*cf.* Ref. 4). (*S*)-Prolinol (**6**) and (*S*)-2-(methoxymethyl)pyrrolidine (**8**) were synthesized from (*S*)-proline (Reanal, Hungary) according to a known procedure,[13] and their constants coincided with those given there. (*R*)-2-Methylpyrrolidine (**10a**) with $[\alpha]_D^{20}$ −29.6° (*c* 1.0, hexane) was prepared according to an earlier procedure[14] and had *ca.* 95% *ee*. Ref. 14: $[\alpha]_D^{20}$ −31.2° (*c* 1.0, hexane). (*S*)-2-Benzylpyrrolidine (**10b**), obtained by a known procedure,[15] had $[\alpha]_D^{20}$ −28.8° (*c* 1.07, MeOH) and *ca.* 86% *ee*; Ref. 15: $[\alpha]_D^{20}$ −33.6° (*c* 1.07, MeOH). (*R*)-Prolinol (*ent*-**6**), (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (**7**), and *N*-methyl-D-glucamine (**14**) were purchased from Fluka AG, Switzerland. (*S*)-Proline *tert*-butyl ester (**9**) and (1*R*,2*S*)-ephedrine (**12**) were obtained by treating with alkali aqueous solutions of their commercially available hydrochlorides (from Reanal (Hungary), and Reakhim (USSR), respectively) and extracting the free amines with Et_2O. A specimen of (*S*)-anabasine with $[\alpha]_D^{20}$ −43.9° (neat), obtained from technical grade anabasine sulfate, had ~53% *ee*. Ref. 16: $[\alpha]_D^{20}$ −82.2° (neat). Enantiomerically pure specimens of (*S*)-(−)-BINOL and (*R*)-(+)-BINOL were prepared by a known procedure.[17]

5-Methyl-2-(methoxycarbonyl)hexa-2(*Z*),4-dienoic acid (4). To a solution of dimethyl prenylidenemalonate (5.2 g, 26.3 mmol, obtained according to Ref. 4) in 15 mL of THF a solution of KOH (1.62 g, 28.8 mmol) in 35 mL of water was added, and the reaction mixture was stirred at 20 °C for 3 h. The solution was concentrated *in vacuo* to one half of its volume, and extracted with Et_2O (3×15 mL).The aqueous layer was acidified to pH 3.0, and the extract was washed with water (2×5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The remainder was column chromatographed on SiO_2 (90 g) using a hexane—AcOEt gradient system as the eluent to afford 2.73 g (56%) of a pure solid (TLC) which was recrystallized from benzene—hexane. The yield of pure *Z*-monoester **4** was 1.45 g (30%). ^{1}H NMR ($CDCl_3$), δ: 2.06 (d, 6 H, J = 2 Hz); 3.95 (s, 3 H); 6.88 (d, 1 H, J = 12.5 Hz); 8.43 (d, 1 H, J = 12.5 Hz); 10.3 (br.s, 1 H). Signals attributed previously to the *E* isomer of monoester **4** in a specimen with m.p. 65—68 °C (where the content of the latter was 80%, see Ref. 4) were not visible in this spectrum.

(*S*)-*N*-Methyl-1-phenylethylamine (13). To a stirred solution of (*S*)-1-phenylethylamine (Fluka AG; 6.04 g, 49.8 mmol) and triethylamine (8.3 mL, 60 mmol) in 20 mL of dry THF freshly distilled ethyl chloroformate (5.2 mL, 55.8 mmol) was added at 15—20 °C. The reaction was continued for 1 h, and the precipitated solid was removed by filtration and washed with dry THF (20 mL). The combined filtrates were concentrated in a rotary evaporator, the residue was treated with hexane (30 mL), and the organic liquid phase was sucsessively washed with 15% HCl and water. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was distilled at b.p. 87—88 °C (0.3 Torr) to give crystalline ethyl *N*-(1-phenylethyl)carbamate, m.p. 32—34 °C, $[\alpha]_D^{20}$ −89.0° (*c* 1.0, MeOH). Yield 4.3 g (45%). ^{1}H NMR (acetone-d_6), δ: 1.17 (t, 3 H, J = 7 Hz); 4.03 (q, 2 H, J = 7 Hz); 5.84 (m, 1 H, $J \cong 7$ Hz); 6.53 (br.s, 1 H); 7.15—7.50 (m, 5 H). A two-neck flask, equiped wuth a reflux condenser and a dropping funnel, was loaded (under argon) with $LiAlH_4$ (110 mg, 2.8 mmol) in absolute Et_2O (10 mL), to which a solution of the above carbamate (540 mg, 2.8 mmol) in 5 mL of the same solvent was then added dropwise. The mixture was refluxed for 1 h, cooled to 0—5 °C, and quenched with 10% HCl (to pH 1—2). The organic layer was separated and concentrated, and the residue was extracted with CH_2Cl_2 (2×15 mL) in order to recover the unreacted carbamate. The acidic aqueous layer was made alkaline to pH 14 and filtered from inorganic contaminants, the filtrate was extracted with CH_2Cl_2 (3×5 mL), and the precipitate was washed with CH_2Cl_2 (2×5 mL). The combined organic liquid phase was concentrated in a rotary evaporator, and the residue was distilled *in vacuo* to afford pure amine **13** as a colorless oil with b.p. 82—84 °C (15 Torr) and $[\alpha]_D^{20}$ −73.4° (*c* 2.0, $CHCl_3$). Yield 203 mg (61%, *i.e.*, 27.5% over two stages of the synthesis). ^{1}H NMR (acetone-d_6), δ: 1.28 (d, 3 H, J = 7 Hz); 2.24 (s, 3 H); 3.62 (q, 1 H, J = 7 Hz); 7.17 (m, 5 H).

Methyl 4-methyl-6-(2-methylprop-1-enyl)cyclohexa-1,3-dienecarboxylate [(*S*)-(+)-1 or (*R*)-(−)-1] (typical procedure). To a mixture of monoester **4** (73 mg, 0.4 mmol) with an amine catalyst (**6—13** or *ent*-**6**, 0.04 mmol) in 2 mL of dry benzene,* thermostatted to one of the temperatures indicated in Tables 1 and 2, enal **3** (38 mL, 0.4 mmol) was added in one portion. The reaction mass was left to stand for the period indicated in Tables 1 and 2 either at 18—20 °C, or at 4—7 °C or else at −10 °C (on a lower shelf or in the freezer section of the refrigerator). After the disappearance of starting reactants (TLC), the reaction mixture was concentrated *in vacuo* to half of its volume and applied to a column filled with SiO_2 (5 g). Compound **1**, whose purity was monitored by TLC (R_f 0.55 on Silufol, development with hexane—AcOEt, 6 : 1), was eluted with dry benzene as an optically active, transparent yellowish oil free of detectable admixtures (TLC and ^{1}H NMR data). The yields and assigned absolute configurations of specimens of **1** thus obtained are given in Tables 1 and 2. ^{1}H NMR (C_6D_6), δ: 1.64 (s, 3 H); 1.73 (s, 3 H); 1.96 (A-part of ABM system, J_{AB} = 18, J_{AM} = 1.8 Hz); 2.52 (B-part of ABM system, 1 H, J_{AB} = 18, J_{BM} = 9 Hz); 3.52 (M-part of ABM, J_{AM} = 1.8, J_{BM} = 9, J_{vic} = 10 Hz); 3.72 (s, 3 H); 5.15 (m, 1 H); 5.79 (m, 1 H, $J_{H(2),H(3)}$ = 6, $J_{allylic}$ =1.5 Hz); 6.93 (B-part of AB system, 1 H, $J_{H(2),H(3)}$ = 6 Hz). The use of all amines except *ent*-**6** led to dextrorotatory specimens of **1**.

Ethyl 4-methyl-6-phenylcyclohexa-1,3-dienecarboxylate [(*R*)-(−)-2 or (*S*)-(+)-2]. Experiments corresponding to entries *13* and *14* in Table 1 were carried out by analogy with those described above for the transformations **3** + **4** → **1**, *i.e.*, by taking 0.05 mmol of amine **6** or *ent*-**6** per 0.5 mmol of enal **3** and 0.5 mmol of monoester **5** in 2 mL of benzene as the solvent. Specimens of enantiomers (*R*)-**2** and (*S*)-**2** displayed practically identical ^{1}H NMR spectra which coincided with that of a previously obtained specimen of (*R*)-**2** (*cf.* Ref. 5).

Isolation of both enantiomers of cyclic diene 1 from a single experiment with a single catalyst. To a solution of monoester **4** (90 mg, 0.48 mmol) in dry benzene (2 mL) a solution of (*S*)-2-benzylpyrrolidine **10b** (8 mg, *ca.* 0.05 mmol) and enal **3** (47 mL, 0.48 mmol) was added, and the reaction vessel was filled with argon and left at 20 °C for 72 h. The reaction mixture was concentrated in a rotary evaporator to 1 mL and diluted with 5 mL of hexane. The precipitated brown gum was washed with hexane (2×5 mL), and the transparent hexane supernatant was evaporated to leave a residue which was column chromatographed on SiO_2 (15 g). Eluting with benzene afforded a specimen of (*S*)-**1** with $[\alpha]_D^{20}$ +44.5° (*c* 1.0, PhH) which was practically identical with the specimens of (*S*)-**1** by its ^{1}H NMR spectrum and the value of R_f on Silufol. The pecipitated gum was dissolved in 4 mL of benzene, and the solution was refluxed for 30 min. Then it was concentrated to 1 mL and diluted with hexane (5 mL) to precipitate another portion of brownish gum which was washed with hexane (2×5 mL). The combined hexane extracts were evaporated, and the residue was chromatographed on SiO_2 (see above) to give a second batch of the cyclic diene [(*R*)-**1**] indistinguishable from (*S*)-**1** by its R_f and ^{1}H NMR spectrum, but displaying $[\alpha]_D^{25}$ −38.4° (*c* 1.0, PhH). Yield 14.2 mg (14%).

(*S*)-1-(3-Methylbuta-1,3-dienyl)-2-(methoxymethyl)pyrrolidine (16) was prepared by analogy with an earlier procedure[19] by reacting amine **8** (603 mg, 5.2 mmol) with gradually added enal **3** (530 mg, 6.3 mmol) and anhydrous K_2CO_3 (1 g) in dry benzene (10 mL) under argon. The reaction mass was stirred for an additional 24 h, the supernatant was decanted, the cake of K_2CO_3 was washed with benzene (2×3 mL), and the combined organic solution was filtered from traces of K_2CO_3 and concentrated *in vacuo*. The residue was distilled *in vacuo* to afford pure dienamine **16** with b.p. 100—101 °C (1 Torr) and n_D^{20} 1.5208. Yield 470 mg (50%). ^{1}H NMR (acetone-d_6), δ: 1.78 (s, 3 H); 1.8—2.04 (m, 4 H); 2.95—3.10 (m, 2 H); 3.34 (s, 3 H); 3.47—3.60 (m, 2 H); 4.35 (δ, 1 H, J_{gem} = 2.5 Hz); 4.51 (d, 1 H, J_{gem} = 2.5 Hz); 5.06 (A-part of AM system, 1 H, J_{AM} = 14 Hz); 6.63 (M-part of AM system, 1 H, J_{AM} = 14 Hz).

(*S*)-*N*-Methyl-*N*-(3-methylbuta-1,3-dienyl)-1-phenylethylamine (17) was prepared in the same way as dienamine **16**, *i.e.*, by reacting amine **13** (216 mg, 1.6 mmol), enal **3**

* Or toluene (at −10 °C).

(0.16 mL, 1.62 mmol), and K_2CO_3 (2 g) in 5 mL of benzene for 24 h at 20 °C. Yield 172 mg (55%). Colorless oil, m.p. 70—71 °C (0.5 Torr). ^{1}H NMR (acetone-d_6), δ: 1.51 (d, 3 H, J = 7 Hz); 1.80 (s, 3 H); 2.50 (s, 3 H); 2.62 (m, 2 H); 4.40 (d, 1 H, J_{gem} = 3.5 Hz); 4.55 (d, 1 H, J_{gem} = 3.5 Hz); 5.15 (A-part of AM system, 1 H, J_{AM} = 13 Hz); 6.53 (M-part of AM-system, 1 H, J_{AM} = 13 Hz); 7.15—7.40 (m, 5 H).

(*S*)-2-Hydroxymethyl-1-(3-methylbuta-1,3-dienyl)pyrrolidine (15), formed upon condensing amine **6** with enal **3** by analogy with the two earlier procedures, rapidly darkened and polymerized in the course of an attempt to purify it by vacuum distillation at 100—120 °C (bath temperature) (0.5 Torr). In order to characterize its structure, the reaction mass was filtered from K_2CO_3, the filtrate was concentrated in a rotary evaporator (40 °C, 5 Torr), and the residual crude product was analyzed spectroscopically. ^{1}H NMR (acetone-d_6), δ: 1.78 (s, 3 H); 3.70—3.80 (m, ~2 H); 4.52 (br.s, ~1 H); 4.60 (br.s, 1 H); 5.15 (d, 1 H, J = 14 Hz); 6.60 (d, 1 H, J = 14 Hz). The integral intensities of these signals relate to the intensities of the latter two, which are not overlaped by the others (see Scheme 3); in the area of δ < 3.5 the indicated signals were overlapped by those of other components of the reaction mass which accounted for *ca.* 75—80% of the total integral intensity of the spectrum.

Preparation of cyclohexadienes (*S*)-1 and (*R*)-1 from dienamines 16 and 17 ("stoichiometric" variant). ***A.*** A solution of dienophile **4** (50 mg, 0.27 mmol) in 2 mL of dry benzene was added at 20 °C to a solution of dienamine **16** (50 mg, 0.27 mmol); the reaction mass was left for 30 min and then worked up in the same manner as described above for the catalytic protocol of obtaining compound (*S*)-**1**. Column chromatography afforded a specimen identical with other specimens of (*S*)-**1** by its R_f and ^{1}H NMR, but its $[\alpha]_D^{20}$ was only +14.0°, which corresponded to 4.7% *ee*. Yield 23.1 mg (40%).

B. To a solution of dienamine **17** (21 mg, 0.1 mmol) in dry benzene (1 ml) a solution of monoester **4** (20 mg, 0.1 mmol) in 1 mL of the same solvent was added at 20 °C, and the mixture was left for 15 h and then worked up as above. The isolated specimen of cyclohexadiene (*S*)-**1** (TLC, ^{1}H NMR) had $[\alpha]_D^{20}$ +3.2° (*c* 1.0, PhH), which corresponded to 1.1% *ee*. Yield 11 mg (53%).

Another analogous experiment (6 °C, 2.5 h) and subsequent standard work-up afforded a specimen of (*S*)-**1** with $[\alpha]_D^{20}$ +4.0° (*c* 1.0, PhH), whose yield and *ee* were 7 and *ca.* 1.4%, respectively.

C. To a solution of dienamine **16** (224 mg, 1.23 mmol) in dry benzene (1 mL) a solution of monoester **5** (263 mg, 1.23 mmol) in 1 mL of the same solvent was added at 20 °C (under argon). The gradually darkening reaction mass was left at 20 °C for 96 h, and then worked up as disclosed above for the catalytic protocol of preparing compound (*R*)-**2**. Column chromatography (SiO_2) of the dark-red gum afforded a specimen of compound (*R*)-**2** (TLC, ^{1}H NMR) as a yellowish oil with $[\alpha]_D^{16}$ −3.2° (*c* 1.0, PhH), wich corresponds to *ca.* 1.7% *ee*. Yield 52.6 mg (18%).

The effect of solvents on the net enantioselectivity of formation of cyclic diene (*S*)-1 was studied at 20 °C and concentration ratio [**3**] : [**4**] : [**7**] = 0.1 : 0.1 : 0.01 (mol·L^{-1}) in solvents purified according to recommended procedures.[20] After 120 h of exposure (168 h for benzene) the solvents were stripped off at 40—50 °C (5 Torr), and the residues were column chromatographed (SiO_2) using benzene as the eluent. The values of *ee* for the specimens of (*S*)-**1** thus obtained were deduced from their $[\alpha]_D$ values in benzene.

This work was supported by the Russian Foundation for Basic Research (Grant No. 96-03-33396) and the National Program for Supporting Leading Scientific Schools (Grant No. 96-15-97461).

References

1. D. Enders, O. Meyer, and G. Raabe, *Synthesis*, 1992, 1242; D. Enders, O. Meyer, G. Raabe, and J. Runsink, *Synthesis*, 1994, 66.
2. J. Barluenga, F. Aznar, C. Valdés, and J. A. Martin, *Anal. de Quim.*, 1993, **89**, 115; J. Barluenga, F. Aznar, C. Valdés, J. A. Martin, S. Garcia-Grandez, and E. Martin, *J. Am. Chem. Soc.*, 1993, **115**, 4403.
3. A. G. Nigmatov and E. P. Serebryakov, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 233 [*Russ. Chem. Bull.*, 1993, **42**, 213 (Engl. Transl.)].
4. A. G. Nigmatov, I. N. Kornilova, and E. P. Serebryakov, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 154 [*Russ. Chem. Bull.*, 1996, **45**, 144 (Engl. Transl.)].
5. A. G. Nigmatov and E. P. Serebryakov, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 663 [*Russ. Chem. Bull.*, 1996, **45**, 623 (Engl. Transl.)].
6. Y. Izumi and A. Tai, *Stereo-diferentiating Reactions*, Kodansha, Tokyo, 1977, Ch. 3.
7. E. P. Serebryakov and A. G. Nigmatov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 605 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 527 (Engl. Transl.)].
8. A. G. Nigmatov and E. P. Serebryakov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 1079 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 961 (Engl. Transl.)].
9. R. Tripathy, P. J. Carroll, and E. R. Thornton, *J. Am. Chem. Soc.*, 1991, **113**, 7630.
10. B. M. Trost and D. C. Lee, *J Org. Chem.*, 1989, **54**, 2271; J. C. Lopez and G. Lukas, *Cycloaddition Reactions in Carbohydrate Chemistry. ACS Symp. Ser.*, 1992, Issue 494, 33.
11. G. Opitz and W. Merz, *Liebigs Ann. Chem.*, 1962, **652**, 139; 158.
12. M. B. Erman, I. S. Aulchenko, L. A. Kheifits, V. G. Dulova, and M. E. Vol'pin, *Tetrahedron Lett.*, 1976, **34**, 2981.
13. D. Enders, P. Fey, and H. Kipphardt, *Org. Prepn. Proc. Int.*, 1985, **17**, 1.
14. R. G. Kostyanovsky, I. M. Gella, V. I. Markov, and Z. E. Samoilova, *Tetrahedron*, 1974, **30**, 39.
15. G. F. Cooper, K. E. McCarthy, and M. G. Martin, *Tetrahedron Lett.*, 1992, **33**, 5895.
16. A. Orechoff and G. Menschikoff, *Ber.*, 1931, **64**, 266.
17. F. Toda, K. Tanaka, L. Nassimbeni, and M. Niven, *Chem. Lett.*, 1988, 1371.
18. *Fluka Chemika-Biochemika-Analytika*, Fluka Chemie AG, CH-9471 Buchs (Switzerland), 1995/1996, 1022, Cat. No. 68622.
19. S. Hünig and H. Kahanek, *Chem. Ber.*, 1957, **90**, 238.
20. J. A. Riddick and W. B. Bunger, *Techniques of Chemistry*, **2**, *Organic Solvents*, Wiley, New York, 1971.

Received August 28, 1997