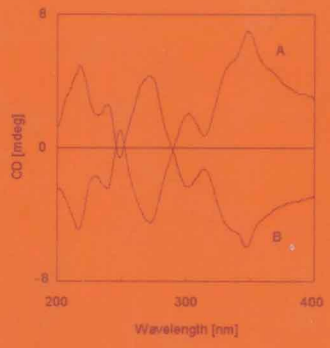
Enantiomer Separation

Fundamentals and Practical Methods

Edited by
Fumio Toda



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Edited by

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PREFACE

In spite of important advances in asymmetric synthesis, chiral compounds cannot all be obtained in a pure state by asymmetric synthesis. As a result, enantiomer separation remains an important technique for obtaining optically active materials. Although asymmetric synthesis is a once-only procedure, an enantiomer separation process can be repeated until the optically pure sample is obtained.

This book discusses several new enantiomer separation methods using modern techniques developed by experts in the field. These methods consist mainly of the following three types:

1) Enantiomer separation by inclusion complexation with a chiral host compound

2) Enantiomer separation using biological methods

3) Enantiomer separation by HPLC chromatography using a column containing a chiral stationary phase.

Separation of a racemic compound has been called "optical resolution" or simply "resolution". Nowadays, the descriptions "enantiomer resolution" or "enantiomer separation" are also commonly used. Accordingly, "Enantiomer Separation" is used in the title of this book. The editor and all chapter contributors hope that this book is helpful for scientists and engineers working in this field.

Fumio Toda
Okayama, March 2004

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OPTICAL RESOLUTIONS BY INCLUSION COMPLEXATION WITH A CHIRAL HOST COMPOUND

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1. Introduction

When a chiral host compound includes one enantiomer of racemic guest compound selectively, optical resolution of the guest can be accomplished. In this chapter, efficient resolutions of racemic compounds by the complexation with various artificial chiral hosts are described. All the data described in this chapter are those obtained in the author's research group.

In most cases, chiral alcohol and phenol derivatives are used as host compounds for the resolution. In these cases, guest molecules are accommodated in the complex by formation of hydrogen bond with the hydroxyl group of the host. Since the hydrogen bond is not very strong, the included guest compound can be recovered easily from the inclusion complex by distillation, recrystallization, chromatography or some other simple procedures.

This chapter consists mainly of two sections, 1) preparation of artificial chiral host compounds and 2) optical resolution of various racemic guest compounds by inclusion complexation with these hosts.

Some other resolutions by inclusion complexation with achiral host and by distillation technique are also described. In the last section, progress of the resolution of binaphthol, biphenols and related compounds is described.

Although mechanism of the precise chiral recognition between host and guest molecules in their inclusion crystal has been studied in detail by X-ray structural analysis, these X-ray structures are not shown in this chapter, since this chapter deals with practical procedures of optical resolutions.

2. Preparation of Artificial Chiral Host Compounds

In 1986, we have found that 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol (**1**) includes various guest molecules in a stoichiometrical ratio and forms crystalline inclusion complexes.[1] X-ray analysis of a 1:2 inclusion complex of **1** and acetone showed that the guest molecules are accommodated in inclusion crystalline cavity by the formation of hydrogen bond with the hydroxyl groups of **1**.[2] It was also found that inclusion complexation with **1** occurs selectively, and a mixture of isomers can be separated by the selective inclusion process.[3] This suggests that racemic guest compound can be separated into enantiomers by inclusion

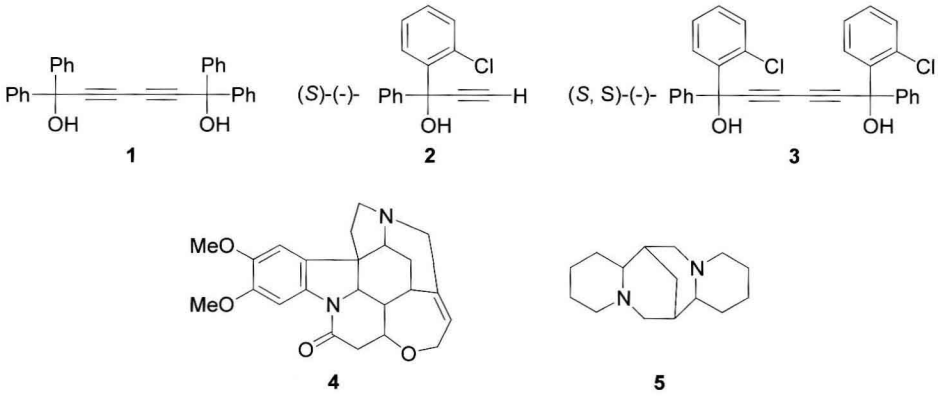
F. Toda (ed.), Enantiomer Separation, 1-47.

complexation with a chiral derivative of **1**. According to this idea, (*S,S*)-(-)-1,6-di(*o*-chlorophenyl)-1,6-diphenyl- hexa-2,4-diyne-1,6-diol (**3**) was prepared.[4] Since the optically active host **3** was found to be effective for optical resolution of various guest compounds,[4] some other chiral alcohol and phenol host compounds were also prepared. Some chiral amide hosts were also designed for optical resolution of phenol derivatives. In the section 4, miscellaneous resolutions by using some other interesting chiral host compounds are also described.

All yields of the chiral hosts obtained by the resolution are calculated based on the amount of enantiomers containing in the racemic host compounds used for the resolution.

2-1 Acetylenic Alcohols

Firstly, we found that *rac*-1-(*o*-chlorophenyl)-1-phenylprop-2-yn-1-ol (**2**) can easily be resolved by formation of a 1:1 inclusion complex with brucine (**4**)[5] or sparteine (**5**).[5,6] For example, when a solution of *rac*-**2** (16.0 g, 66 mmol) and **5** (15.4 g, 66 mmol) in acetone (50 ml) was kept at room temperature for 12 h, a 1:1 complex of (*S*)-(-)-**2** and **5** was formed (16.0 g). Pure complex obtained after two recrystallizations of the crude complex from acetone was decomposed by dil HCl to give (*S*)-(-)-**2** of 100% ee (4.2 g, 52%).[6] Inclusion complexation of *rac*-**2** with **4** also gave optically pure (*S*)-(-)-**2** in good yield. Mechanism of the precise chiral recognition of **2** with **4** in their inclusion complexes has been clarified by X-ray structural study. In both cases, the inclusion complexes are constructed by formation of hydrogen bond between the hydroxyl group of **2** and the amine nitrogen atom of the alkaloid.[5,6] Partially resolved optically impure **2** can easily be purified to pure enantiomers by complexation with achiral amine such as DABCO, *N,N'*-dialkylpiperazine, *N,N,N',N'*-tetramethyl- ethylenediamine and pyrazine.[6c,6d] Oxidative coupling reaction of (*S*)-(-)-**2** gave (*S,S*)-(-)-**3**.[4] Since **2** itself is also useful as a host compound for optical resolution of guests, its chiral derivatives were also prepared by the enantioselective complexation procedure with **4** or **5**. Mutual resolution between **2** and alkaloid can also be accomplished. For example, complexation of racemic sparteine (**5**) with (*S*)-(-)-**2** gave (-)-**5** of 100% ee in 38% yield.[6]

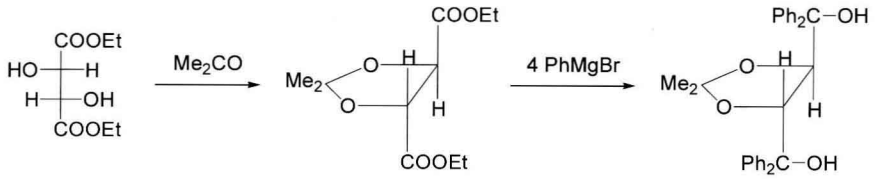


2-2. Tartaric Acid Derivatives

By using cheap chiral source, tartaric acid, some useful chiral hosts were designed.

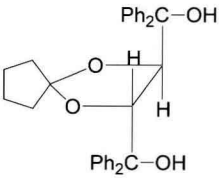
(*R,R*)-(+)-*trans*-4,5-bis(hydroxydiphenylmethyl)-2,3-dimethyl-1,3-dioxacyclopentane (**8a**) was prepared by the reaction with PhMgBr of the acetal (**7**) derived from diethyl tartarate (**6**) and acetone.[7] By the same method, **9** and **10** were also prepared.[8]

Some amide derivatives have been reported to form inclusion complex with a wide variety of organic compounds.[9] Optically active amide derivatives are expected to include one enantiomer of a racemic guest selectively. According to this idea, some amide derivatives of tartaric acid (**11-13**) were designed as chiral hosts.[10] As will be described in the following section, these amide hosts were found to be useful for resolution of binaphthol (BNO) (**14**) and related compounds (**15, 16**).



6 **7** **8**

a: *rac*-form
b: (*R*, *R*)-(-)-form
c: (*S*, *S*)-(+)-form



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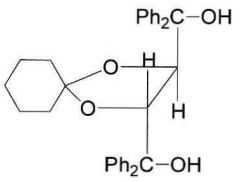

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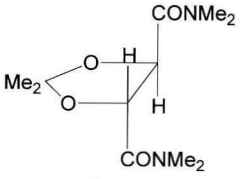

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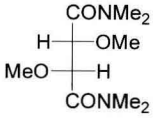

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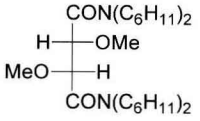
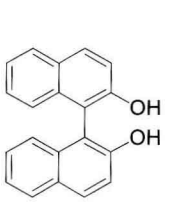


13

a: (*R*, *R*)-(-)-form
b: (*S*, *S*)-(+)-form

2-3. Binaphthols and Related Compounds

It has been known that phenol derivatives work as a good host compound for various organic guest molecules, since the acidic hydroxyl groups of phenols form a relatively strong hydrogen bond with various organic functional groups.[10] These data strongly suggest that chiral phenol derivatives such as 2,2'-dihydroxy-1,1'-binaphthyl (**14**) (binaphthol, BNO) and its derivatives (**15, 16**) work as a good host for optical resolution.



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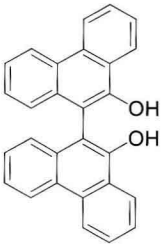

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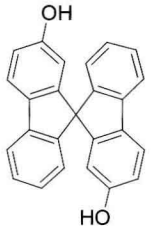


16

a: *rac*-form
b: (*R*)-(+)-form
c: (*S*)-(-)-form

Firstly, **14a** was resolved by inclusion complexation with **12a**. For example, when a solution of **12a** (4.06 g, 17.5 mmol) and **14a** (5.0 g, 17.5 mmol) in benzene (5 ml)-hexane (5 ml) was kept at room temperature for 12 h, a 1:1 complex of **12a** and **14b** was formed, which upon recrystallization from benzene gave a pure complex as colorless prisms of mp 149-150 °C (3.70 g, 82%). Column chromatography of the complex on silica gel (benzene) gave **14b** of 100% ee (1.8 g, 72%). From the filtrate left after separation of the 1:1 complex of **12a** and **14b**, **14 c** of 100% ee (1.48 g, 59%) was isolated by inclusion complexation with **12b**.[10]

By similar complexation process of **15a** with **11a** and **11b**, **15c** of 100% ee (74%) and **15b** of 100% ee (80%) were obtained in the yields indicated. Similar treatment of **16a** with **13a** gave **16b** of 100% ee in 90% yield.[10]

Some other optical resolution procedures of *rac*-BNO (**14a)** by complexation with various chiral ammonium salts are summarized in the section 6 of this chapter as an example of the progress on novel enantiomer separation technique.

3. Optical Resolutions

3-1. General Procedures

A solution of chiral host and racemic guest compounds in an appropriate solvent is kept at room temperature until inclusion complex crystallizes out. In the complexation, it is necessary to use a solvent which does not form inclusion complex with the host compound. The inclusion complex formed is filtered and purified by recrystallization from solvent, if necessary. Host:guest molar ratio is

usually a 1:1 or 1:2. The ratio was determined by elemental analysis, NMR spectrum or TG measurement. The purified inclusion complex can be dissociated into the components by an appropriate procedure such as distillation, recrystallization, chromatography, and extraction with base or acid. In case of the inclusion complex of phenol derivative with ammonium salt, it is easily dissociated into the components by dissolving in a mixture of organic solvent and water. The phenol derivative and ammonium salt dissolve in organic solvent and water, respectively. Optical purity of the enantiomer obtained was determined by HPLC on a chiral stationary phase, ^{1}H NMR method using a chiral shift reagent or by comparison of the $[\alpha]_D$ value with that of an authentic sample. All optical purities are shown by the enantiomeric excess (ee) value. All yields of the enantiomers obtained by the resolution are calculated based on the amount of enantiomers containing in the racemic compounds used for the resolution.

Reason for the effective optical resolution by the inclusion complexation with a chiral host has been clarified by X-ray analysis of the complex formed. By the X-ray structural study of the host-guest complex, absolute configuration of the chiral guest resolved has also been elucidated easily, since absolute configuration of the chiral host is known. These X-ray data have been reported in the literature cited together with the detailed experimental procedure of the resolution.

In the case of volatile racemic guest, optical resolution can be carried out by using distillation technique in the presence of a non-volatile chiral host compound. The resolution by distillation is summarized in the section of 5. In the section 5, optical resolution by inclusion crystallization in a suspension medium in hexane or water is also described.

3-2. Hydrocarbons and Halogeno Compounds

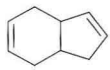
Optical resolution of some hydrocarbonds and halogeno compounds by inclusion complexation with the chiral host (**9a**) has been accomplished.[11,12] Preparation of optically active hydrocarbons is not easy and only a few example of the preparation of optically active hydrocarbons have been reported. For example, optically active 3-phenylcyclohexene has been derived from tartaric acid through eight synthetic steps.[11] Although one-step synthesis of optically active 3-methylcyclohexene from 2-cyclo- hexanol by the Grignard reaction using chiral nickel complex as a catalyst has been reported, the enantiomeric purity of the product is low, 15.9%.[11] In this section, much more fruitful results by our inclusion method are shown.

When a solution of *rac*-3-methylcyclohexene (**17a**) (0.58 g, 6.1 mmol) and **9a** (3 g, 6.1 mmol) in ether (15 ml) was kept at room temperature for 12 h, a 2:1 inclusion complex of **9a** and (-)-**17a** (2.5 g, 75%) was obtained as colorless prisms. The crystals were purified by recrystallization from ether to give the inclusion complex (2.4 g, 71%), which upon heating *in vacuo* afforded (-)-**17a** of 75% ee by distillation (0.19 g, 66%). Inclusion complexation with (-)-**17a,** OH absoptions of **9a** (3590 and 3400 cm^{-1}) were shifted to lower frequencies (3400 and 3230 cm^{-1}). Since cyclohexane does not form an inclusion complex with **9a**, hydrogen bonding between π-orbital of **17a** and the OH group of **9a** would be important for the

inclusion complex formation. Dissociation energies of the 2:1 complex of **9a** and **17a** were determined to be 45 kJ mol^{-1}. This data show that the stabilization energy of the complex is quite high.

17

a: R = 3-Me
b: R = 4-Me
c: R = 4-CH=CH_2



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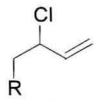
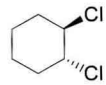


19

a: R = H
b: R = Cl



20

By the same inclusion complexation followed by two recrystallizations of the complex formed, 4-methyl- (**17b**) (33% ee, 55%), 4-vinylcyclohexene (**17c**) (28% ee, 73%), bicyclo[4.3]nonane-2,5-diene (**18**) (ee value was not determined, 90%), and 3-chloro- (**19a**, 56% ee, 48%) and 3,4-dichloro-1-butene (**19b**) (ee value was not determined, 42%) were also resolved in the ee values and yields indicated.[11]

Optical resolution of *trans*-1,2-Dichlorocyclohexane (**20**) was also accomplished by complexation with **9a**. When a solution of **9a** (50 g, 0.1 mol) in *rac*-**20** (50 g, 0.33 mol) was kept at room temperature for 12 h, a 2:1 inclusion complex of **9a** and (-)-**20** was obtained as colorless prisms (45.8 g, 80% based on **9a**, mp 108-109 °C). Heating of the complex at 200 C/20 mmHg gave (-)-**20** of 43% ee by distillation (6 g, 77% based on **9a**). The same treatment of the (-)-**20** of 43% ee (6 g) with **9a** (5 g) followed by distillation gave (-)-**20** of 72% ee (0.7 g, 90% based on **9a**). When the (-)-**20** of 72% ee (0.6 g) was treated again with **9a** (0.7 g) as described above, (-)-**20** of 90% ee was obtained as colorless oil (0.06 g, 55%).[12] X-ray analysis of the complex of **9a** with (-)-**20** of 90% ee showed that (-)-**20** molecules exist as diequatorial form in the complex. The absolute configuration of the (-)-**20** was also found to be (*R,R*) by the X-ray study.[12]

3-3. Amines, Amine *N*-Oxides, Oximes, and Amino Acid Esters

Nitrogen atoms of organic compounds form relatively strong hydrogen bond with OH group of a host compound and amines, amine *N*-oxides, oximes, and esters of amino acids can be resolved efficiently by complexation with a chiral host. Optical resolutions of these compounds are described.

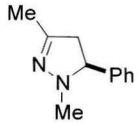
When a solution of **2** (243 g, 1 mol) and *rac*-2-methylpiperazine (**21a**, 100g, 1 mol) in BuOH (50 ml) was kept at room temperature for 12 h, a 2:1 inclusion complex of **2** and (*S*)-(+)-2-methylpiperazine (**21c**) was obtained as colorless prisms, which upon three recrystallizations from BuOH gave pure complex crystals (60 g, 20%). Heating of the crystals *in vacuo* gave **21c** of 100% ee by distillation (9.5 g, 19%).[13] Optical resolution of **21a** can also be accomplished by complexation with the host **3**.

When a solution **3** (242 g, 0.5 mol) and **21a** (100 g ,1 mmol) in MeOH (500 ml) was kept at room temperature for 12 h, a 1:1 complex of **3** and (*R*)-(-)-2-methylpiperazine (**21b**) was obtained as colorless prisms, which upon three

recrystallizations from MeOH gave pure crystals (75 g, 26%, mp 86-88 °C). Heating of the crystals *in vacuo* gave **21b** of 100% ee by distillation (12.5 g, 25%). The host compounds left after the distillation can be used again for resolution. Treatments of the filtrate left after the former and the latter resolution experiments with **3** and **2**, respectively, gave optically pure **21b** and **21c**, respectively in the yield around 20%.[13]

21

a: *rac*-form
b: (*R*)-(-)-form
c: (*S*)-(+)-form



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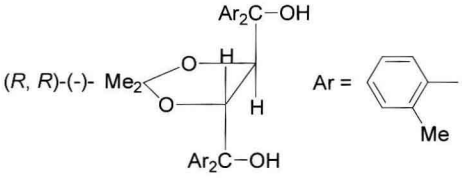
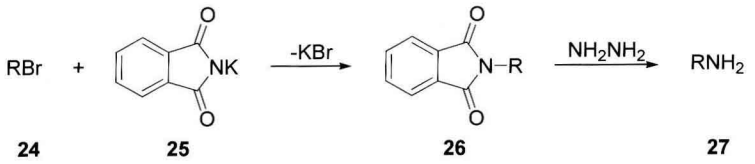


23

X-ray analysis of the 2:1 complex of **2** and **21c** showed that the two **2** molecules are binding to one **21c** molecule by the formation of two OH---N hydrogen bonds. The data also showed that the combination of **2** of the (*S*)-configuration and **21c** of the (*S*)-configuration is important. This agrees with the fact that **2** does not form complex with **21b** of the (*R*)-configuration.[13]

For an optical resolution of 1,3-dimethyl-5-phenyl-∇^2-pyrazoline (**22**), tetra-(*o*-tolyl) derivative of **8a**, (*R,R*)-(-)-*trans*-4,4-bis[hydroxydi(*o*-tolyl)methyl]-2,2-dimethyl-1,3-dioxacyclopentane (**23**) was prepared.[7] When a solution of **23** (1.5 g, 2.87 mmol) and *rac*-**22** (1.0 g, 5.75 mmol) in toluene-hexane (1:4, 25 ml) was kept at room temperature for 12 h, a 1:1 inclusion complex of **23** and (*S*)-(-)-**22** was obtained as colorless prisms (0.90 g, mp 128-130 °C), which upon heating *in vacuo* (200 °C/2 mmHg) gave (*S*)-(-)- **22** of 96% ee (0.21 g, 42%).[14] X-ray crystal structure of the complex has also been reported.[14]

The Gabriel synthesis is a classical but useful preparative method for primary amines. Reaction of an alkyl bromide (**24**) with potassium phthalimide (**25**) gives the corresponding *N*-alkylphthalimide (**26**), which upon treatment with hydrazine followed by KOH affords the primary amine (**27**). When a chiral alkyl halide is used in the Gabriel synthesis, a chiral primary amine is obtained. However, preparation of optically active alkyl halides is not easy. If optical resolution of **26** which has a chiral alkyl group can be done, a new preparative method for optically active amines can be established by a combination of the resolution with the Gabriel synthetic method. Some examples of the combination method are described.

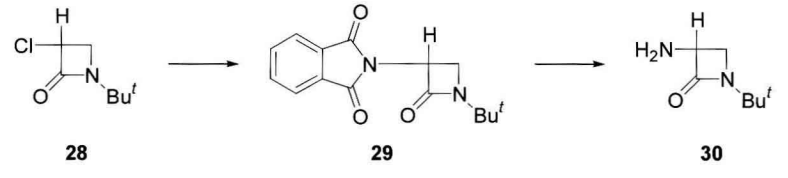


24 **25** **26** **27**

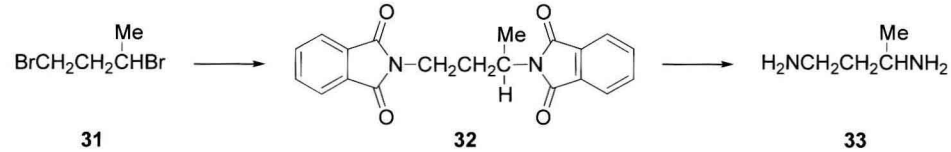
a: R = PhMeCH-
b: R = Me_2CHCH_2MeCH-
c: R = EtMeCH-
d: R = $EtMeCHCH_2$-

When a solution of **3** and two molar equivalents of *rac*-**26a** in ether-light petroleum was kept at room temperature for 12 h, a crystalline 1:1 inclusion complex of **3** and (+)-**26a** was obtained. Two recrystallizations of the crude crystals from ether-light petroleum gave pure crystals which upon distillation *in vacuo* gave (+)-**26a** of 55% ee. Decomposition of (+)-**26a** with hydrazine gave (+)-**27a** of 55% ee in 40% yield. By the same procedure, (-)-**27b** of 30% ee, (+)-**27c** of 30% ee, and (-)-**27d** (ee was not determined) were obtained.[15]

Reaction of *rac*-1-*tert*-butyl-3-chloroazetidin-2-one (**28**) with **25** gave the *rac*-phthalimide derivative (**29**). Optical resolution of *rac*-**29** was accomplished efficiently by complexation with **15**. When a solution of **15b** and two molar equivalents of *rac*-**29** in benzene-hexane (1:1) was kept at room temperature for 12 h, a crystalline 1:1 inclusion complex of **15b** and (-)-**29** was obtained. After one recrystallization from benzene-hexane, the crystals were chromatographed on silica gel to give pure complex consisting of (-)-**29** of 100% ee in 63% yield. Decomposition of the complex with hydrazine gave optically pure (-)-3-amino-1-*tert*-butylazetidin-2-one (**30**) in 44% yield.[15] Mechanism of the precise chiral recognition between **15b** and (-)-**29** in their 1:1 complex was clarified by X-ray crystal structural analysis.[15]



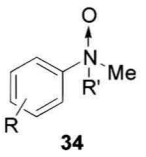
28 **29** **30**



31 **32** **33**

This method can be applied for preparation of an optically active diamine. For example, reaction of *rac*-1,3-dibromobutane (**31**) with **25** gave the *rac*-diphthalimide (**32**). Optical resolution of *rac*-**32** was accomplished efficiently by complexation with **3** to give optically pure **32**. Decomposition of the optically pure **32** gave optically pure (-)-butane-1,3-diamine (**33**) in 50% yield.[15]

Amine *N*-oxides (**34a-e**) were resolved very efficiently by complexation with **14b**. In this case, both enantiomers of **34** were obtained in an optically pure form.[16] For example, when a solution of **14b** (1.0 g, 3.6 mmol) and *rac*-**34b** (1.2 g, 7.2 mmol) in THF (20 ml)-hexane (10 ml) was kept at room temperature for 5 h, a 1:1 complex of **14b** and (+)-**34b** was obtained as colorless prisms. The crystals were recrystallized from THF-hexane to give pure crystals (0.85 g, 53%, mp 167-169 °C). The complex was separated to its components by column chromatography on silica gel. Firstly, **14a** (0.5 g) was recovered from a fraction eluted by ethyl acetate-benzene (1:4). Secondly, (+)-**34b** of 100% ee (0.29 g, 48%) was obtained from a fraction eluted by MeOH. Evaporation of the filtrate left after separation of the complex between **14b** and (+)-**34b**, gave crude (-)-**34b**. Treatment of the crude **(-)-34b** with **14c** by a similar manner to that described above, followed by column chromatography, yielded finally (-)-**34b** of 100% ee in 40% yield.[16] Compounds **34a** and **34c-e** were also resolved effectively by complexation with **14b**, and the corresponding (+)-enantiomers were obtained in the optical and chemical yields indicated, (+)-**34a** (100% ee, 21%), (+)-**34c** (73% ee, 39%), (+)-**34d** (100% ee, 30%), and (+)-**34e** (100% ee, 68%).[16]

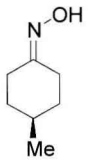


34

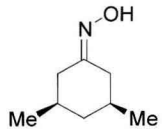
a: R = H; R' = Et
b: R = *m*-Me; R' = Et
c: R = *m*-Me; R' = ^{i}Pr
d: R = *p*-Me; R' = Et
e: R = *p*-Me; R' = ^{i}Pr

By X-ray structural study of the complexes of **14b** with (-)-**34b** and of **14c** with (+)-**34b**, mechanism of the chiral recognition has been clarified.[16] Optical purities of all enantiomers obtained by the resolution were determined by ^{1}H NMR measurements in the presence of the new chiral shift reagent **3**.[17]

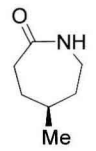
Optical resolution of two oximes of cyclohexanone derivatives, 4-methyl-1-(hydroxyimino)cyclohexane (**35**) and *cis*-3,5-dimethyl-1-(hydroxyimino)cyclohex- ane (**36**) has been accomplished by an enantioselective complexation with **3**.[18] For example, when a solution of *rac*-**35** and **3** in ether-petroleum ether was kept at room temperature, a 1:1 complex of **3** and (+)-**35** was obtained as colorless needles. Treatment of the complex with alkylamine gave an alkylamine complex of **3** and (+)-**35**. Since the optical purity of the (+)-**35** was not determined directly, its O-benzoyl derivative was prepared and its optical purity was determined to be 79% ee by HPLC method. Therefore, the optical purity of the (+)-**35** obtained by the resolution can be estimated to be higher than 79% ee.[18] By the same treatment of *rac*-**36** with **3**, (+)-**36** of approximately 59% ee was obtained.[18] In order to determined the optical purity of (+)-**35** in its complex with **3** more precisely, Beckmann rearrangement of the oxime in the inclusion compound was carried out. Heating of the inclusion complex of (+)-**35** and **3** with conc H_2SO_4 gave (-)-5-methylcaprolactam of 89% ee (**37**). Therefore, it is certain that the optical purity of the (+)-**35** enantioselectively included in the complex with **3** is higher than 89% ee.[18]



35



36



37

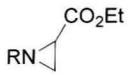
Amino acids, especially artificial ones, are interesting targets for optical resolution. Since amino acids themselves are difficultly included with host compounds due to their ionic character, their ester derivatives were resolved.

For example, when a solution of **10a** (2.5 g, 4.9 mmol) and *rac-N*-ethyl-ethoxycarbonylaziridine (**38a**) (1.4 g, 9.8 mmol) in benzene (20 ml)-hexane (20 ml) was kept at room temperature for 5 h, a 1:1 inclusion compound of **10a** and (-)-**38a** was formed as colorless needles (1.9 g, 59%, mp 127-131 °C), which upon distillation in *vacuo* gave (-)-**38a** of 100% ee (0.24 g, 34%).[19] By the same method, **38b-i** were also resolved efficiently (Table 1). Of these, **38b, 38d** and **38i** were resolved more efficiently with the host **9a**. Although the optical purities of the resolved **38c, 38g, 38h**, and **38i** were not determined, these were assumed to be optically pure because theit $[\alpha]_D$ values did not change by repeating the complexation with **10a**. The (+)-**38b** of 64% ee which had been obtained by one complexation gave the optically pure enantiomer by repeating the complexation with **10a**.[19]

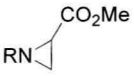
Table 1. Optically active **38** obtained by one complex with **9a** or **10a**.

38	Host	Yield (%)	% ee
a	**10a**	34	100
b	**10a**	32	---[a]
c	**9a**	43	64
d	**9a**	44	100
e	**10a**	28	100
f	**10a**	33	100
g	**10a**	42	---[a]
h	**10a**	74	---[a]
i	**9a**	30	---[a]

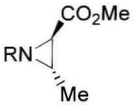
[a] Purity was not determined.



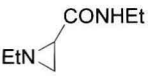
38a: R = Et
38b: R = ^{n}Pr



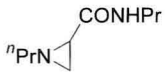
38c: R = Et
38d: R = ^{n}Pr



38e: R = ^{n}Pr
38f: R = ^{i}Pr



38g



38h

38i

Some real amino acid esters and related compounds were resolved by complexation with **9a** or **10a**. When a solution of **10a** (10.87 g, 21.5 mmol) and *rac*-methyl 2-aminopropanoate (**39**) (4.43 g, 43.0 mmol) in benzene (9 ml)-light petroleum (9 ml) was kept at room temperature for 4 h, a 2:1 complex of **10a** and (+)-**39** was obtained, after three recrystallizations (1.51 g, 13%, mp 195-197 °C). Heating the complex *in vacuo* gave (+)-**39** of 100% ee by distillation (0.12 g, 12%).[20] Although *rac*-methyl 2-aminophenylpropanoate (**40**) was also resolved efficiently by complex- ation with **9a** to give **(+)-40** of 100% ee in 40% yield, optical resolution of *rac*-ethyl 2-amino-2-phenylethanoate (**41**) gave very poor result (Table 2). Similar resolutions of hydroxycarboxylic acid esters such as methyl 3-hydroxybutanoate (**42**) and its derivatives (**43-45**) were successful (Table 2).[20] In order to know the reason for the efficient chiral recognition ability between the host and guest molecules, X-ray crystal structure of the inclusion complex of **9a** and (+)-**42** was studied.[20]

Table 2. Optical resolution by complexation with **9a** or **10a**.

		Enantiomers obtained		
Guest	Host		Yield (%)	Optical purity (% ee)
39	**10a**	(+)-**39**	12	100
40	**9a**	(+)-**40**	40	100
41	**10a**	(-)-**41**	65	6
42	**9a**	(+)-**42**	44	100
43	**9a**	(+)-**43**	28	100
44	**9a**	(+)-**44**	15	64
45	**10a**	(+)-**45**	45	40

Resolutions of diethyl 2-imidazol-1-ylsuccinates (**46a-e**) by complexation with **8-10** were also successful.[21]