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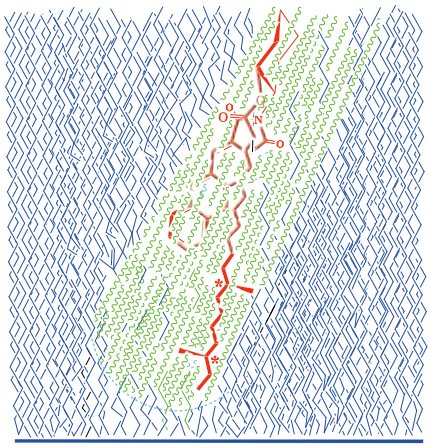

Induced Chiral Fields

CONTENTS

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Contribution

Development of Highly Potent Chiral Discrimination Methods that Solve the Problems of Diastereomer Method

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The development of highly potent chiral discrimination methods that solve the problems of the diastereomer method is described. Explaining the significant results of separations of diastereomers having chiral centers separated by 13 – 27 bonds with reversed-phase HPLC was hitherto impossible. To attract more scientific interest toward the mechanism of the separation, the author proposes a hypothesis, Induced Chiral Fields, that the achiral reversed phases can provide chiral fields depending on the structures of the substrates.

1 Introduction

Since the discovery of enantiomerism by Pasteur in 1848,[1] discrimination of optical isomers has always been one of the major subjects in the fields of chemistry and biology because optical purities of substrates with asymmetries are critical for the evaluation of their biological activities.

In the existing methods for chiral discrimination, it has been recognized that the most reliable one is the diastereomer method. Until recently, however, the most widely used diastereomer method has a fatal problem in that it is impossible to discriminate the diastereomers having chiral centers separated by more than 4 bonds. The problem has been assumed to be intrinsic to the diastereomer method and has been very difficult to solve.

The following hypothesis has been proposed by the author as a solution to the problem: if diastereomers were provided with a helically chiral conformation by the chirality of the chiral labeling reagent, the other chiral center in the diastereomers would be involved in the helically chiral molecule (no longer the chiral center remote from the other chiral center) and, therefore, would be discriminated by some means (Fig. 1).[2-4]

A study to examine the validity of this hypothesis has been pursued. On the basis of the results obtained, a new hypothesis, "Induced Chiral Fields namely that the achiral reversed phase can provide chiral fields depending on the the structure of substrates," is proposed to explain the significant results of separation of the diastereomers derived from new chiral labeling reagents and optical isomers by reversed-phase HPLC, which was hitherto impossible.

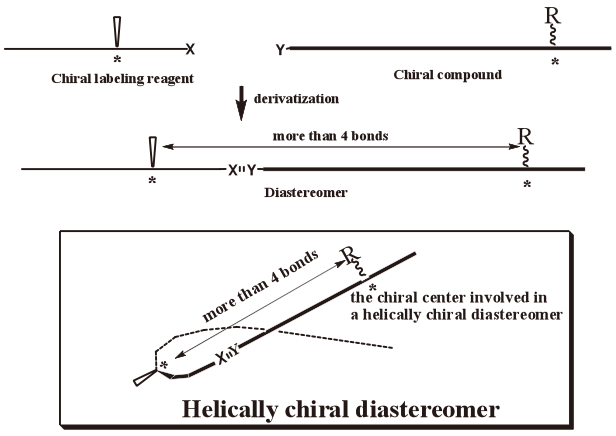


Fig 1. A solution of the problem of the diastereomer method by providing the diastereomer with a helically chiral conformation by the chirality of the labeling reagent.

2 Design of Fluorescent and Chiral Labeling Reagents That Provide Diastereomers with a Helically Chiral Conformation by the *Gauche* Effect and the Ability of such Reagents

2-(Anthracene-2,3-dicarboximido)propanol (**1**) and 1-(anthracene-2,3-dicarboximido)-2-propanol (**2**) and their *O*-triflates (**3**,**4**) were designed as fluorescent and chiral labeling reagents for chiral carboxylic acids (Fig. 2);[3,4] it was expected that the preferred conformation of their esters would be the helically chiral *gauche-trans* (*gt*) as the result of the *gauche* effect[5] between the oxygen atom of ester and the nitrogen atom of imido group and that the *gt* conformation could be further stabilized by CH-π interaction (Fig. 3).[6] The anthracenedicarboximido group is useful for both highly sensitive fluorometry and anisotropy for ^{1}H-NMR study (Fig. 2).

Chiral carboxylic acids can be labeled with reagent **1** - **4** to give diastereomers, for example **5** in Fig. 3. The preferred conformation of **5** will be *gt* among the three possible conformations due to the *gauche* effect between the ester oxygen atom and the imido nitrogen atom. The *gt* conformer is a helically chiral molecule. Thus, the diastereomer could be provided with a helical chiral conformation by the chirality of the labeling reagent, and the other chiral center in the diastereomer originated from the chiral carboxylic acid is the one involved in the helically chiral molecule (no longer the chirality remote from the other chiral center irrespective of the distance between the two chiral centers) and therefore could be discriminated by some means (Figs. 1 and 3).

The enantiomers of anteiso fatty acids (C5 - C14) were separated by means of reversed-phase HPLC and were detected at the femto (10^{-15}) mole level by fluorometry. There is a rule in the elution order between (*R*)- and (*S*)-configuration of the branched methyl groups, namely, that the diastereomers of (*S*)-reagents with (*S*)-fatty acids having a chiral center at an even number carbon will elute faster than the diastereomers of (*S*)-reagents with (*R*)-fatty acids and that the elution order will change with those at an odd number carbon.[3,4]

However, the enantiomers of C15 anteiso fatty acid (12-methyltetradecanoic acid) could not be separated as the diastereomers of these reagents by HPLC. Therefore, the HPLC discrimination of higher anteiso fatty acids was not studied.

The chirality of hydroxyl carboxylic acids could also be discriminated by labeling with these reagents and using normal-phase HPLC. The labeling reaction of hydroxyl carboxylic acids with *O*-triflate reagents (**3**, **4**) can be performed in an SN2 manner using tetraethyl ammonium carbonate (TEAC) as the base in CH_3CN or DMF at room temperature without the formation of either intra- or intermolecular esters of substrates. It should be noted that the labeling with **4** proceeds with complete inversion of the stereochemistry of **4** (Fig. 3).

Esters and lactones are labeled with **3** or **4** in one pot, first by treatment of them with TEAC in MeOH and then by evaporation of MeOH followed by treatment with **3** or **4** in CH_3CN (or DMF). The diastereomers are next separated by means of normal-phase HPLC. For example, all four stereoisomers of beraprost sodium[7] and 3-hydroxy-4-methyloctanoic acid (Fig.4)[8] were separated by labeling with **4**.

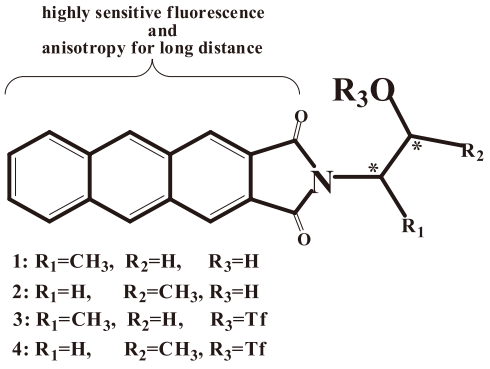


Fig 2. Fluorescent and chiral labeling reagents that are expected to provide a helically chiral diastereomer by the chirality of labeling reagents and *gauche* effect between the oxygen atom and the nitrogen atom.

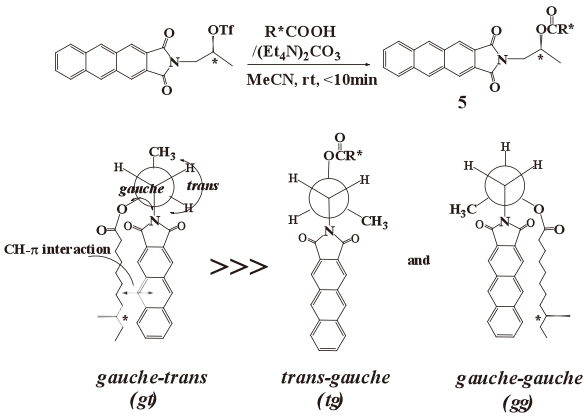


Fig 3. Expected preferred *gauche-trans* conformation of the esters of the fluorescent and chiral labeling reagents, **1** - **4**.

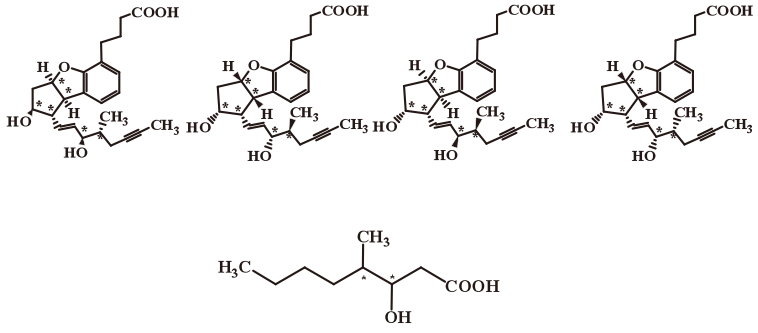


Fig 4. Structures of the four stereoisomers of beraprost and 3-hydroxy-4-methyloctanoic acid.

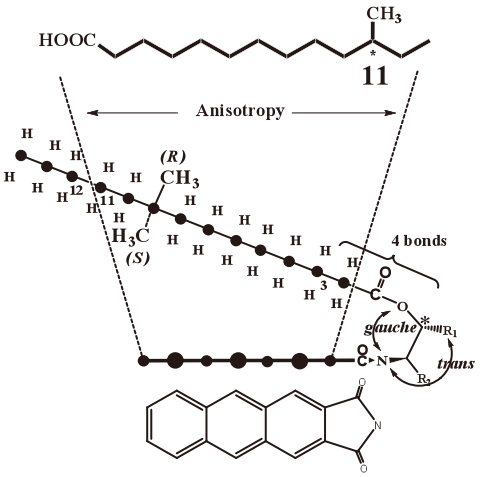


Fig 5. Side view of the *gauche-trans* conformer of the ester of a methyl branched long chain carboxylic acid derived with the fluorescent and chiral labeling reagents, **1 - 4**.

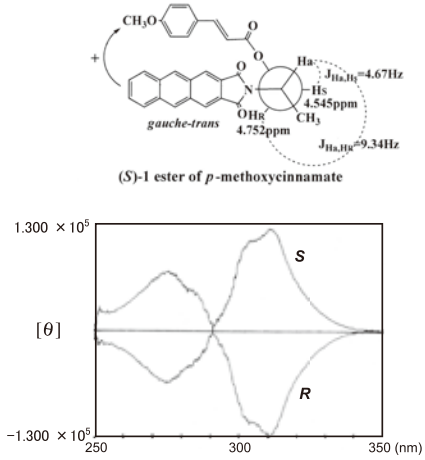
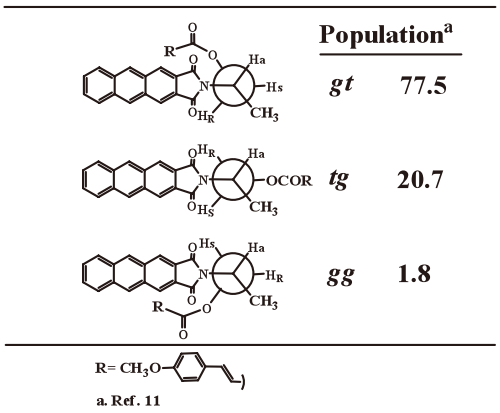


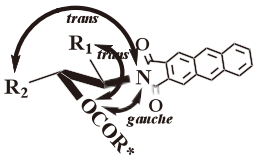
Fig 6. CD spectrum of (*S*)-2-(2,3-anthracenedicarboximido)propyl-*p*-methoxycinnamate and the vicinal coupling constants of protons of the aminoethanol moiety of the reagent.

On the other hand, by means of ^{1}H-NMR, the (*R*)- and (*S*)-stereochemistries of the branched methyl groups of methyl-branched carboxylic acids can be discriminated up to C11-methyl branching, which indicates that the anisotropy of the anthracene ring of these reagents can reach up to the C11-methyl group (Fig. 5).[3,4]

The conformational analysis of *p*-methoxycinnamate of **1** by both exciton CD and ^{1}H-NMR studies showed that the proportion of *gauche-trans:trans-gauche: gauche-gauche* conformations was *ca.* 77 : 21 : 2 (Fig. 6 and Table 1).[8-11] The results suggested that the chiral labeling reagent that provides the helically chiral *gauche* conformer in 100% will give better chiral discrimination.

Table 1. Population of *gt*, *tg*, and *gg* of *p*-methoxycynnamate of **1.**





The preferred *gauche-trans* conformation of the esters with reagents 1-4.

6 7

Fig 7. The structures of cyclohexane reagents, **6** and **7** that have a fixed chiral *gauche* conformation.

3 Design of the Fluorescent and Chiral Labeling Reagents That Provide Diastereomers with a Single Helically Chiral *Gauche* Conformer and the Ability of such Reagents

The *gt* conformation of the diastereomers derived from reagents **1 - 4** by the *gauche* effect could be fixed by forming a ring as shown in Fig. 7. In this way, the fluorescent and chiral labeling reagents **6** for chiral carboxylic acid and **7** for chiral alcohol were prepared.[12,13] It should be noted that the *gauche* effect is not necessary for either **6** or **7** to provide helically chiral *gauche* diastereomers.

3-1 Reversed-phase HPLC discrimination of diastereomers derived from 6 and 7

Enantiomers of anteiso fatty acids (C7 - C29) were separated by C30 reversed-phase HPLC as the diastereomers labeled with **6**.[12,13] There is a rule regarding the elution order, namely, that the elution order of the fatty acids having a methyl group at C4 - C11 is the same as that of diastereomers with the reagents **1 - 4**, but the elution order will change at the fatty acid having a methyl group at C12.[13] A similar turning point in the elution order was observed at C10 with the diastereomers derived from

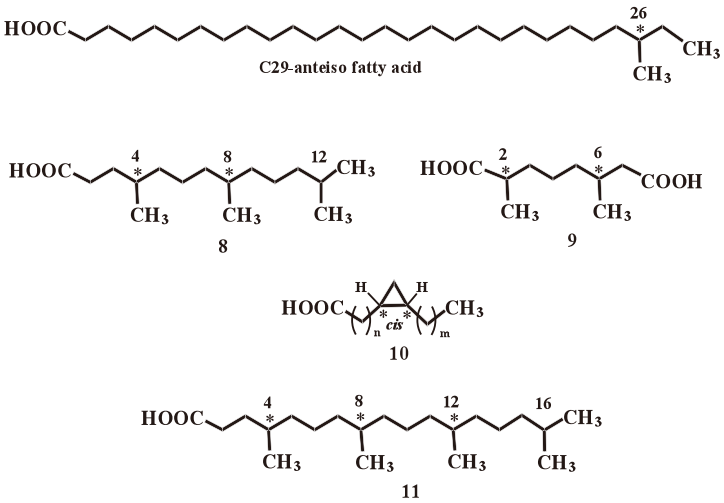


Fig 8. Structures of chiral carboxylic acids. All the stereoisomers of them except **11** can be separated by the present method.

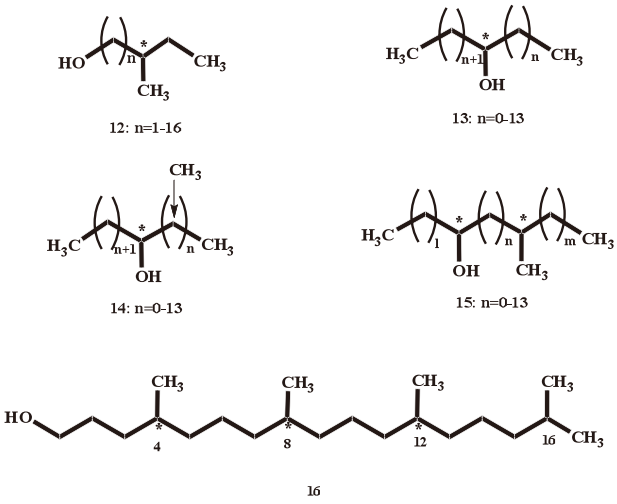


Fig 9. Structures of chiral alcohols. All the stereoisomers of them except **16** can be separated by the present method.

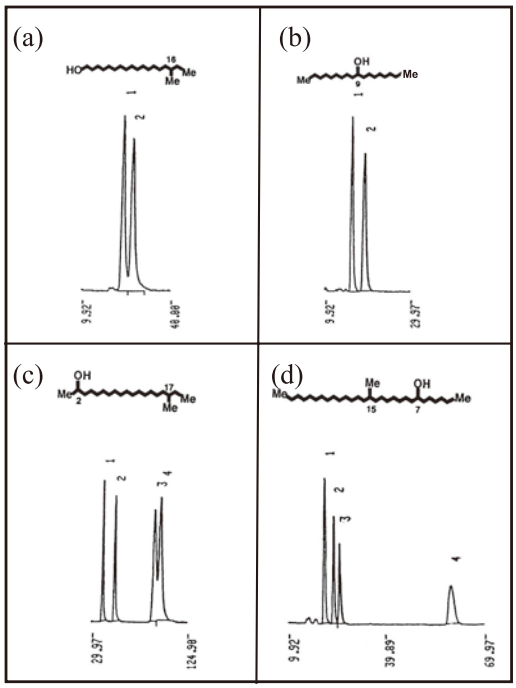


Fig 10. Representative HPLC chromatograms of (1*R*,2*R*)-2-(anthracene-2,3-dicarboximido)cyclohexane carboxylic acid derivatives of chiral alcohols.

(1*R*,2*R*)-naphtharene-2',3'-dicarboximidocyclohexanol, which is one benzene ring smaller than **6**, and methyl branched fatty acids.[14]

The change of the elution order indicated that the chiral discrimination mechanism will be different for the diastereomers having the branched methyl group over the anthracene ring and those having the branched methyl group beyond the anthracene ring.

It should be noted that ODS (C18) can separate the enantiomers up to C21 anteiso fatty acid (18-methylicosanoic acid) but not the enantiomers of higher anteiso fatty acids.[13] These results suggested that the chain length of the reversed phase played an important role in the discrimination. They also suggest that the methylene chains of the diastereomers and those of the reversed-phases did not bend and did fully interact with each other.

Reagent **6** can discriminate the four stereoisomers of 4,8,12-trimethyltridecanoic acid (**8**),[4] 2,6-dimethyloctane-1,8-dioic acid (**9**),[16] and cyclopropanecarboxylic acid (**10**).[16] However, **6** can not completely discriminate all eight stereoisomers of 4,8,12,16-tetramethylheptadecanoic acid (**11**).[4] In this case as well, up to the C11-branched methyl group of fatty acid can be discriminated by means of ^{1}H-NMR as the diastereomers derived from **6**. The structures of C29-anteiso fatty acid and **8 - 11** are shown in Fig. 8.

Enantiomers of anteiso fatty alcohols (C5 - C19) (**12**) were separated by C30-reversed-phase HPLC as the diastereomers derived from **7**.[12-14] The enantiomers of chiral secondary alcohols up to C30 with methylene chains that are different by only one carbon at the asymmetric carbon (**13**),[17] secondary

alcohols with a branched methyl group on any carbon of the shorter methylene chain of **13** (**14**),[17] and all four stereoisomers of secondary alcohols with a branched methyl group (**15**)[18] could be discriminated by labeling with **7** and reversed-phase HPLC. However, **7** cannot completely discriminate all eight stereoisomers of 4,8,12,16-tetramethylheptadecanol (**16**). The structures of **12** - **16**, and their representative HPLC chromatograms are shown in Figs. 9 and 10.

3-2 ^{1}H-NMR chiral discrimination of secondary alcohols by 7

Mosher's methods[19] and Kusumi's new Mosher's method[20] are useful means for the determination of absolute configurations of chiral secondary alcohols.

The preferred conformations of the ester of **7** and secondary alcohol are the 1,3-*syn* relationship between the the oxygen atom of the carbonyl group and the α-hydrogen atom of the alcohol and the *s-trans* relationship between the oxygen atom of the carbonyl group and the α-hydrogen on the cyclohexane ring. Since one substituent of the secondary alcohol stays over the anthracene ring, as can be seen in Fig. 14, reagent **7** could act as a modified Mosher's reagent for ^{1}H-NMR study and could also be used for a longer distance than the preceding Mosher's reagents.

The ^{1}H-NMR spectra of the **7**-tridecanol ester of (1*R*, 2*R*)-**7** is shown in Fig.11. The signals of the terminal methyl groups appeared at different positions that were more shielded than those of 7-tridecanol. The results indicated that both methyl groups have a chance to come over the anthraceneimido group by rotation, however, N.O.E. was observed only between the more shielded methyl group and the protons of the anthracene ring.[17] Judging from the preferred conformation, one can assign the more shielded methyl signal to that of the pro-*S* methylene chain.

The ^{1}H-NMR spectra of the (*S*)-5-undecanol ester of (1*R*, 2*R*)-**7** (**17**) are shown in Fig. 12. The terminal methyl groups have different chemical shifts that are more shielded than those of (*S*)-5-undecanol.[17] Judging from the preferred conformation of **17**, one can assign the more shielded methyl signal to that of the C5-terminal. The assignment was confirmed by the study of the HOHAHA spectrum of **17** conducted by Bax and Davis.[21] Thus, the methyl signal at 0.52 ppm, which appeared faster than the other one by irradiation of the signal of alcohol methine proton at 4.75 ppm, was assigned to the methyl group of the shorter methylene chain.

The ^{1}H-NMR spectra of the (1*R*,2*R*)-**7** amide of (*R*)- and (*S*)-2-heptylamine (**18*R*** and **18*S***) are shown in Fig. 13. In this case as well, the spectra showed that the preferred conformations of **18** are the 1,3-*syn* relation between the carbonyl oxygen and the methine hydrogen of the amine and the *s-trans* relation between the carbonyl oxygen and the α-hydrogen on the cyclohexane ring, which are similar to those of the **7**-esters of secondary alcohols. Thus, the absolute configuration of chiral amines can be determined by the ^{1}H-NMR of their **7**-amides.[21] Thus, **7** is a very useful reagent for chiral discrimination by ^{1}H-NMR.

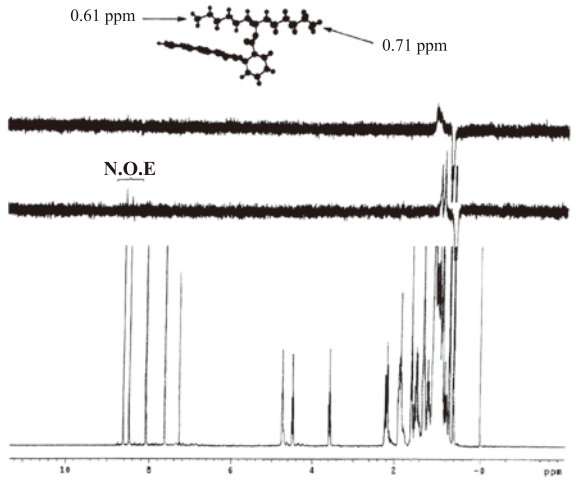


Fig 11. ^{1}H-NMR spectra of (*R*)-7-tridecanoyl (1*R*,2*R*)-2-(anthracene-2,3-dicarboximido)cyclohexane carboxylate and N.O.E between the protons of the terminal methyl group and those of anthracene ring.

3-3 Application of 7 to X-ray crystallography

One of the characteristics of the anthracenedicarboximino reagents is that they give crystalline derivatives that are suitable for X-ray studies. The X-ray structures of the (1*R*,2*R*)-**7** ester of (*S*)-11-docosanol (**19**)[17] and (1*R*,2*R*)-**7** amide of (*S*)-2-heptamine (**18*S***)[21] are shown in Figs. 14 and 15, respectively. In Fig. 14, the shorter methylene chain of **19** is laid over the anthracenedicarboximido group to show that the preferred conformation (the 1,3-*syn* relationship between the carbonyl

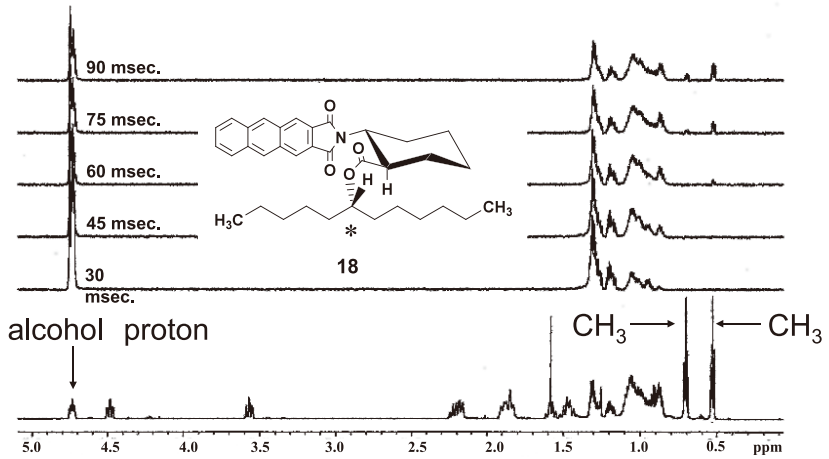


Fig 12. HOHAHA spectrum of (*S*)-6-dodecanoyl (1*R*,2*R*)-2-(anthracene-2,3-dicarboximido)-cyclohexane carboxylate by irradiation of the alcohol proton.

oxygen and the α-hydrogen of the secondary alcohol and the *s-trans* relationship between the carbonyl oxygen and the α-hydrogen on the cyclohexane ring) continues to have a crystalline structure. On the other hand, in Fig. 15, the pentyl group of **18*S*** is laid over the anthracenecarboximido group to show that the 1,3-*syn* conformation between the carbonyl oxygen and the α-hydrogen of amino group of **18*S***, which is preferred in solution, continues to have a crystalline structure but the *s-trans* conformation between the carbonyl oxygen and the α-hydrogen on the cyclohexane ring was changed to *s-cis* in the crystalline structure due to the intra- and intermolecular CH-τ interactions between the pentyl methylene groups and the anthracenedicarboximido group that are necessary for crystallization. Thus, **7** is a useful reagent for determination of the absolute configuration of alcohols and amines by X-ray crystallography.

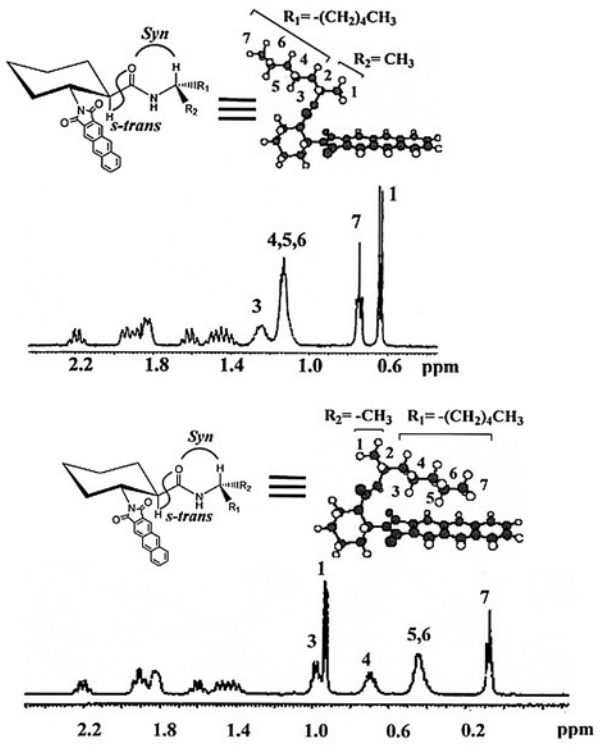


Fig 13. ^{1}H-NMR spectra of (*S*)-heptyl (1*R*,2*R*)-2-(anthracene-2,3-dicarboximido)cyclohexane carboxamide (**18*S***) and its (*R*)-isomer (**18*R***).

4 Design of Sugar Labeling Reagents

It is known that 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-gluopyranose (**20**) gives β-glycoside selectively by Lewis-acid catalyzed glycosidation of alcohols.[23]

In order to examine the effect of the polarity of the labeling reagents on the reversed-phase HPLC separation, we prepared 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(anthracene-2,3-dicarboximido)-β-D-glucopyranose (**21**), its *O*-benzoyl (**22**), and the *O*-methyl analog (**23**) as fluorescent and chiral labeling reagents (Fig. 16).[23]

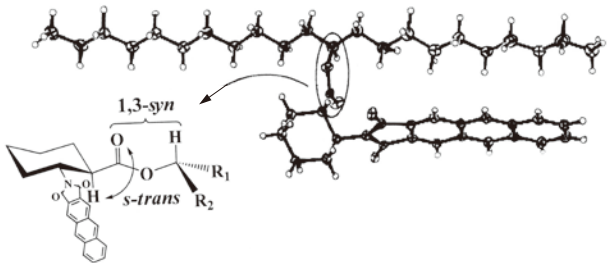


Fig 14. X-ray structure of (*R*)-11-docosanoyl (1*S*,2*S*)-2-(anthracene-2,3-dicarboximido)cyclohexane carboxylate (**18*R***).

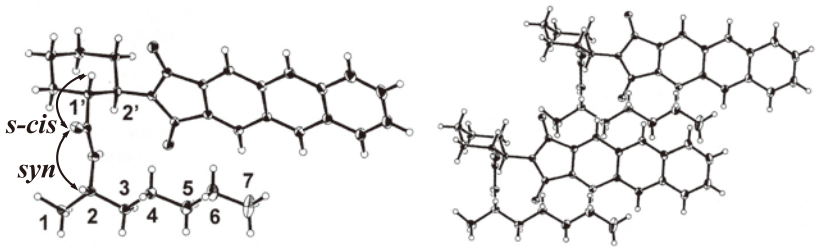


Fig 15. X-ray structure of (*S*)-heptyl (1*R*,2*R*)-2-anthracene-2,3-dicarboximido)cyclohexane carboxamide (**18*S***).

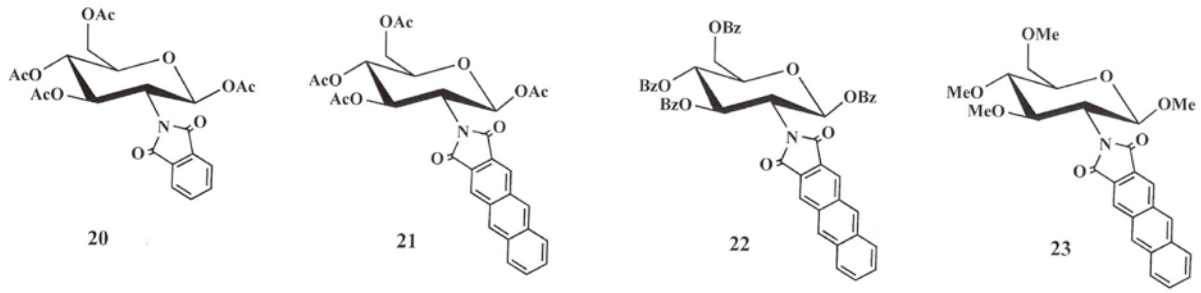


Fig 16. Structures of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (**20**) and sugar reagents, **21**,**22**, and **23**.

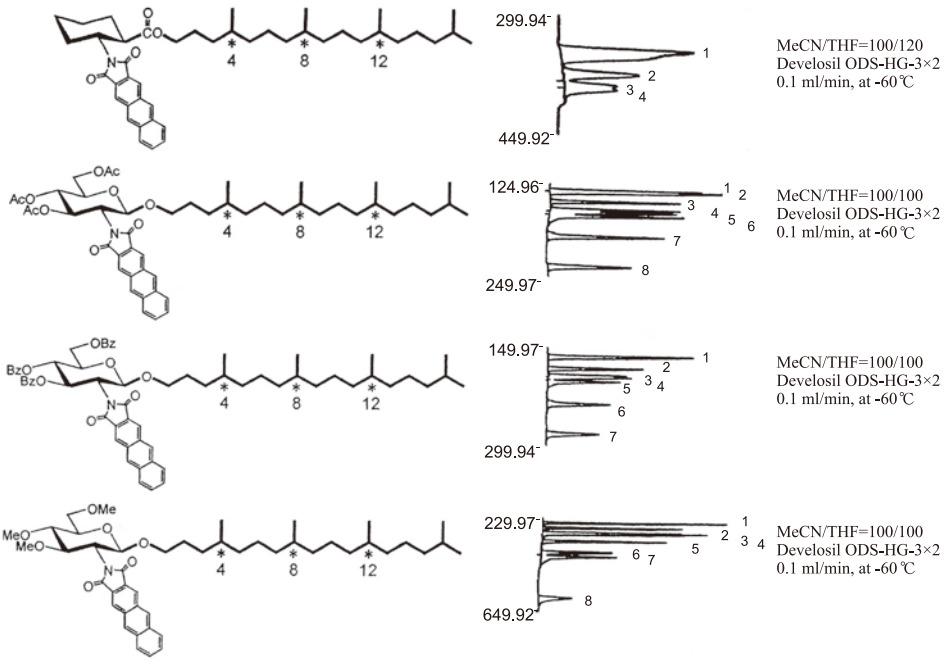


Fig 17. HPLC chromatograms of the diastereomers of 4,8,12,16-tetramethyl heptadecanol labeled with the cyclohexane reagent and sugar reagents.

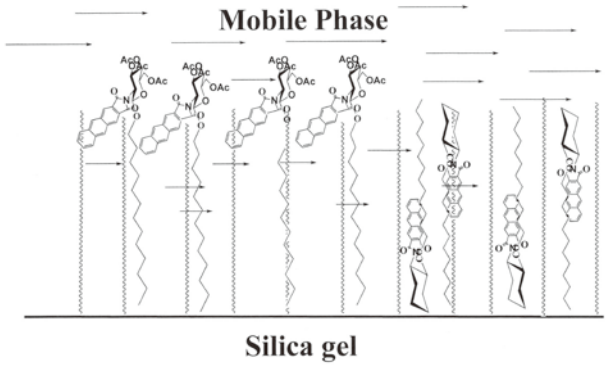


Fig 18. Difference of the mode of interaction with the reversed phase between the derivatives labeled with the nonpolar cyclohexane reagent and those labeled with polar sugar reagents.

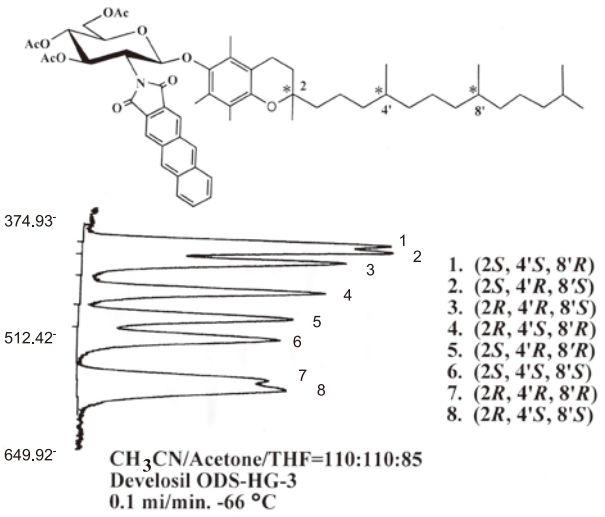


Fig 19. HPLC chromatogram of stereoisomers of α-tocopherol labeled with 1,3,4,6-tetra-*O*-acetyl-2-anthracene-2',3'-dicarboximido-2-deoxy-β-D-glucopyranose.

The HPLC chromatograms of the 4,8,12,16-tetrametyl-heptadecanoyl glycosides of **21**, **22**, and **23**, together with that of the **16** ester of **7**, are shown in Fig. 17. The sugar regents **21** and **23** can discriminate all eight stereoisomers of **16**, but **7** cannot.

The most remarkable difference between **7** and the sugar reagents is their polarity. Thus, the difference in their ability for HPLC separation could be explained as follows.The non-polar diastereomers derived from **7** and **16** will interact with the methylene chains of the reversed phase in two ways, as shown in Fig. 18; one interaction is cyclohexane part of the molecule directed to the mobile phase, and the other interaction is the cyclohexane part directed to silica gel (upside down). The mechanism of chiral discrimination between the two ways will be different. Therefore, good separation of diastereomers cannot be attained. On the other hand, the polar diastereomers derived from sugar reagents and **16** will interact with the reversed phase mostly in a way in which the polar sugar part is directed to the mobile phase. Thus, the more orderly interaction of the polar diastereomer with the reversed phase will result in the separation of all eight diastereomers.

In addition, it should be noted that **21** can separate all eight stereoisomers of α-tocopherol (Fig. 19).[24] These results indicate that the reversed-phase column is a kind of chiral column.

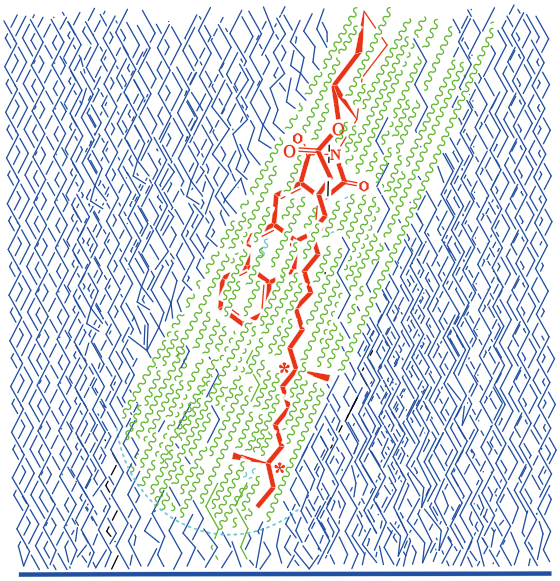


Fig 20. Induced Chiral Fields.

5 Proposal of Induced Chiral Fields

The separation of the diastereomers by reversed-phase HPLC can usually be explained by the differences of the three-dimensional shapes among diastereomers.

The separation of diastereomers up to C11 methyl branched anteiso-carboxylic acids could be understood to be in this category.

However, it is very difficult to identify the differences between the shapes of the diastereomers derived from **7** and those of the enantiomers of C29-anteiso fatty acid well enough to achieve separation by reversed-phase HPLC. Furthermore, the results described above suggest that the methylene chains of the diastereomer and those of the reversed-phase fully interact with each other. Taking these results into account and in order to attract the scientific interest toward the mechanism of the separation, I would like to propose here a hypothesis, "Induced Chiral Fields," to explain the results of separation of diastereomers by reversed-phase HPLC.

The hypothesis of Induced Chiral Fields proposes that the interaction of large helically chiral molecules having a long methylene chain, such as the diastereomer derived from **7** and C29-anteiso fatty acids, and an anthracenecarboximido group with the methylene chains of reversed-phase chirally bends or twists the methylene chains of the reversed-phase to create the appearance of new chiral fields. (Fig.20) The rate at which the diastereomers move from the chiral fields to the achiral methylene chains of the reversed-phase to create new Induced Chiral Fields is different in the (*R*)- and (*S*)-stereochemistry of the branched methyl groups in the diastereomers. Thus, the diastereomers are separated by reversed-phase HPLC.

Thus, the Induced Chiral Fields hypothesis proposes that the achiral reversed phase could be the chiral phase depending on the structure of the substrate.

6 Conclusion

Highly potent chiral discrimination methods for both ^{1}H-NMR and HPLC that have solved the problems assumed to be intrinsic to the diastereomer method were developed, and a hypothesis to explain the significant separation of diastereomers by reversed phase was proposed. I hope that the study presented in this paper is a contribution to the advance of chiral discrimination.

7 Acknowledgement

The work described in this paper was achieved through the remarkable effort of many researchers, whose names are listed in the references below.

8 References

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Introduction of the author :

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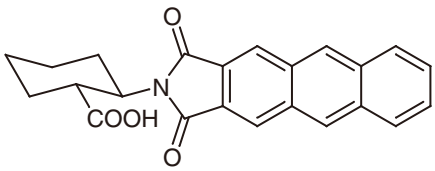
Hiroshi Ohrui received his B.S. (1965) and Ph.D. degrees (1971) from The University of Tokyo. He worked for Ube Industries, Ltd. (1966). He joined the Laboratory of Dr. Umetaro Suzuki at the Institute for Physical and Chemical Research (RIKEN) in 1967. He worked at the Dr. J. J. Fox at Sloan-Kettering Institute for Cancer Research as a research associate (1972-1973), at the Dr. J. G. Moffatt at Syntex Research as a postdoctoral fellow (1973-1974). He was promoted to an associate professor at the Department of Food Chemistry, Faculty of Agriculture, Tohoku University in 1981, a visiting professor at the Technische Universität Darmstadt in 1991, a professor at the Graduate School of Life Sciences, Tohoku University in 1997. He has been a professor at the Yokohama College of Pharmacy since 2006. His awards include The Agricaltual Chemical Society of Japan Award for Young Scientists in 1974, Inoue Prize for Science in 2001, Japan Prize of Agricultural Science in 2004, and The Japan Society for Analytical Chemistry Award in 2004.
[Specialties] Bioorganic, analytical chemistry.

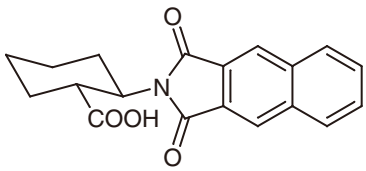
TCI Related Compounds

Highly Potent Chiral Derivatizing Reagents

see. Fig.7 cyclohexane reagents **6**, **7**



(1*R*,2*R*)- : A1657
(1*S*,2*S*)- : A1658

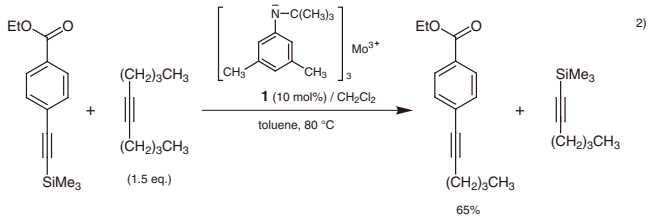


(1*R*,2*R*)- : N0713
(1*S*,2*S*)- : N0714

A1657	(1R,2R)-2-(Anthracene-2,3-dicarboximido)cyclohexanecarboxylic Acid	100mg
A1658	(1S,2S)-2-(Anthracene-2,3-dicarboximido)cyclohexanecarboxylic Acid	100mg
N0713	(1R,2R)-2-(Naphthalene-2,3-dicarboximido)cyclohexanecarboxylic Acid	100mg
N0714	(1S,2S)-2-(Naphthalene-2,3-dicarboximido)cyclohexanecarboxylic Acid	100mg

Alkyne Cross Metathesis Reaction

T2358 Tris(*N-tert*-butyl-3,5-dimethylanilino)molybdenum(III) (1) 100 mg



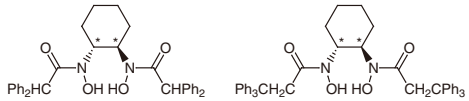
Tris(*N-tert*-butyl-3,5-dimethylanilino)molybdenum(III) (**1**) is a three-coordinate molybdenum(III) complex developed by Cummins *et al*. The said compound **1**, reacts with dinitrogen to give the corresponding nitridomolybdenum complex. Fürstner *et al.* have reported alkyne metathesis reactions using **1** as a catalyst. Since these reactions proceed under mild conditions and the protocol permits the use of various functionalized alkynes, **1** has attracted much attention.

References

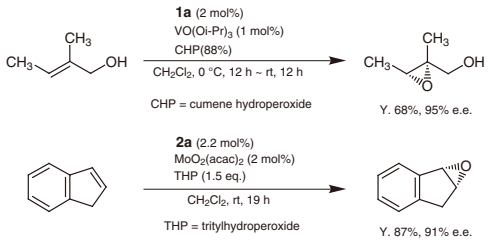
1) Three-coordinate molybdenum(III) complex
C. C. Cummins, *Chem. Commun.* **1998**, 1777.
2) Alkyne cross metathesis reactions
A. Fürstner, C. Mathes, *Org. Lett.* **2001**, *3*, 221.

Useful Ligands for Asymmetric Oxidation

D3715 (1*R*,2*R*)-*N*,*N*′-Dihydroxy-*N*,*N*′-bis(diphenylacetyl)cyclohexane-1,2-diamine (1a) 100mg
D3716 (1*S*,2*S*)-*N*,*N*′-Dihydroxy-*N*,*N*′-bis(diphenylacetyl)cyclohexane-1,2-diamine (1b) 100mg
D3719 (1*R*,2*R*)-*N*,*N*′-Dihydroxy-*N*,*N*′-bis(3,3,3-triphenylpropionyl)cyclohexane-1,2-diamine (2a) 100mg
D3720 (1*S*,2*S*)-*N*,*N*′-Dihydroxy-*N*,*N*′-bis(3,3,3-triphenylpropionyl)cyclohexane-1,2-diamine (2b) 100mg



1a **2a**



Chiral bishydroxamic acids (CBHA) **1** and **2** are ligands used for asymmetric oxidation developed by Yamamoto and his group. For example, a complex with vanadium is used to catalyze the asymmetric epoxidation of allylic alcohols and homoallylic alcohols,[1a-c] while a complex with molybdenum is used to catalyze the asymmetric epoxidation of olefins[1d] and asymmetric oxidation of sulfides.[1e] Asymmetric oxidation reactions using ligands **1** and **2** proceed with high stereoselectivity and can be applied to a wide range of substrates. Application to an industrial-scale synthesis would be expected because the reaction has the following benefits: (1) no dehydration agents are required; (2) the work-up procedure is simple; (3) and the reaction proceeds at 0 °C to room temperature.

References

1) Versatile bis-hydroxamic acids for catalytic asymmetric oxidation
a) A. U. Barlan, W. Zhang, H. Yamamoto, *Tetrahedron* **2007**, *63*, 6075. b) W. Zhang, A. Basak, Y. Kosugi, Y. Hoshino, H. Yamamoto, *Angew. Chem. Int. Ed.* **2005**, *44*, 4389. c) W. Zhang, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 286. d) A. U. Barlan, A. Basak, H. Yamamoto, *Angew. Chem. Int. Ed.* **2006**, *45*, 5849. e) A. Basak, A. U. Barlan, H. Yamamoto, *Tetrahedron: Asymmetry* **2006**, *17*, 508.

Highly Efficient Alkylating Agent

E0778 Ethylmagnesium Chloride

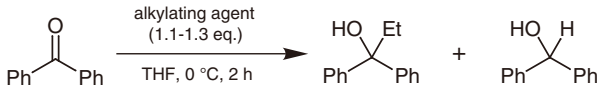
(*ca.* 0.8 mol/L in Tetrahydrofuran) activated with Zinc Chloride (*ca.* 10 mol%) (**1**)

250g

Tertiary alcohols are synthesized industrially on large scale by addition of alkylating agents to ketones, and are mainly used as starting materials in the preparation of pharmaceuticals and agricultural chemicals. Although Grignard reagents are frequently used as alkylating agents in these reactions, an excess amount of Grignard reagents is required. Furthermore, aldol adducts, reduction products, and pinacol derivatives are generated as by-products and adequate control of reaction is difficult even at low temperatures. Taken together, these problems render the synthesis of the desired tertiary alcohols selectively and in high yields, difficult.

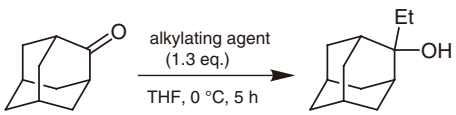
Previously, Ishihara *et al.* have found that the desired tertiary alcohols may be obtained in high yields by using magnesium-ate complexes $RR'_2MgLi{\cdot}LiCl$ prepared from Grignard reagents (1 eq.) and organolithium reagents (2 eq.). The corresponding reactions proceed smoothly and without the generation of by-products which normally accompany the corresponding reactions utilizing the Grignard reagent alone. It is considered that this is because the ate complexes concerned are more nucleophilic and less basic than the parent Grignard reagents. However, this method still requires the use of 2 molar equivalents of expensive organolithium reagents although a stoichiometric amount of the Grignard reagents can be used. Clearly, the development of more efficient alkylating agent is desirable.

More recently, Ishihara *et al.* re-examined this reaction using various metal-ate complexes. As a result, they discovered that tertiary alcohols may be synthesized in high yields with minimum side reactions by the addition of a substoichiometric amount of zinc chloride to the Grignard reagents. They rationalized this observation by invoking the formation of highly active zinc-ate complexes $R_3ZnMgCl$ *in situ* in an efficient catalytic cycle. They have applied this method the alkylation of various ketones.



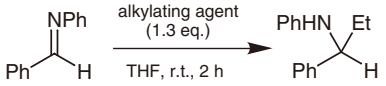
alkylating agent	tertiary alcohol [Y.(%)]	reductant [Y.(%)]
EtMgCl	25	71
EtMgCl + $ZnCl_2$ (10 mol%) (**1**)	84	15

In the alkylation of 2-adamantanone, which is typically considered to be difficult since reduction occurs in preference to the desired alkylation when only Grignard reagents are used, the yield of desired product was improved greatly by using this protocol. Furthermore, addition of lithium chloride increased the yields up to 81%. 2-Alkyl-2-adamantanol is a useful photoresist material, so it is anticipated that this method will be of great utility in various fields.



alkylating agent	Y.(%)
EtMgCl	29
EtMgCl + $ZnCl_2$ (10 mol%)	58
EtMgCl + $ZnCl_2$ (10 mol%) + LiCl	81

Furthermore, it was also reported that this reaction is applicable to the related, but much less reactive aldimines and that the addition reaction proceeds efficiently.



alkylating agent	Y.(%)
EtMgCl	41
EtMgCl + $ZnCl_2$ (10 mol%)	81

In this way, the reactions mentioned above constitute simple and practical methods for the generation of tertiary alcohols, which can be performed under mild conditions, and which are also useful industrially. The original paper by Ishihara *et al.* qualified as the 1st “Most-Accessed Articles” in the category of communications for the *Journal of the American Chemical Society* (Web Edition) from July to September, 2006.

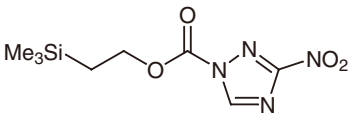
TCI is happy to make available the following zinc chloride-activated Grignard reagent which is convenient to use for the above alkylation.

References

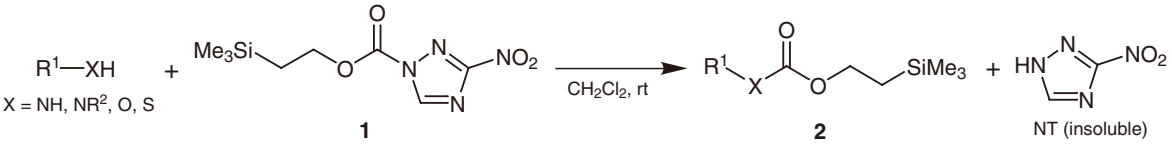
1) Highly efficient alkylation to ketones and aldimines with Grignard reagents catalyzed by zinc(II) chloride
M. Hatano, S. Suzuki, K. Ishihara, *J. Am. Chem. Soc.* **2006**, *128*, 9998.
M. Hatano, S. Suzuki, K. Ishihara, *Kagaku* **2007**, *62* (3), 16.

A Useful Protecting Reagent

T2544 2-(Trimethylsilyl)ethyl 3-Nitro-1*H*-1,2,4-triazole-1-carboxylate (Teoc-NT) (**1**) 1g

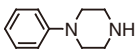
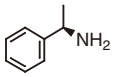
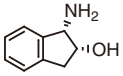
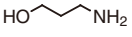
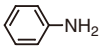
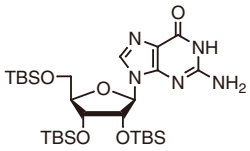
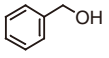


Teoc-NT (**1**)



Carbamates, carbonates, and thiocarbonates have been known for some time as versatile protecting groups for amines, alcohols, and thiols. Although alkyl chloroformates are the most frequently used reagents for the preparation of these protecting groups, they are hazardous liquids and are susceptible to thermolysis and hydrolysis, requiring careful handling and storage. Furthermore, the protection procedure normally requires the addition of base and long reaction times for complete coverage. Thus development of more practical and convenient protecting reagents is desirable.

Recently, Sodeoka and Shimizu have developed a useful reagent for the transformation, Teoc-NT (**1**) which is stable and easy to handle. They reported that **1** reacts rapidly with various amines, alcohols, and thiols at room temperature to give the corresponding protected compounds in high yields, respectively.

Entry	R^1-XH	**1** (eq.)	additive	time	Y. (%)
1		1	—	5 min	quant.
2		1	—	5 min	95 [a]
3		1	—	5 min	96 [b]
4		1	—	30 min	quant.[b]
5		2	Et_3N (5 eq.)	60 min	94
6		4	Et_3N (10 eq.)	4 h	80
7		1	Et_3N (2 eq.)	5 min	92 [c]

[a] In CH_2Cl_2 / 5% $NaHCO_3$ (1:1). The biphasic system was also effective, and the reaction was completed within 5 min. Simple phase separation and evaporation afforded highly pure (>99%) carbamates. [b] Selective amino group protection. [c] Yield after washing with 5% $NaHCO_3$.

For example, **1** reacts rapidly with a stoichiometric amount of amines in methylene chloride at room temperature to give corresponding protected compounds almost quantitatively. The by-product nitrotriazole (NT) has low solubility in the reaction solvent and precipitates out as a crystalline solid. As a result, NT can be removed by simple filtration and highly pure products can be obtained easily in many cases. Removal of trace amounts of NT in the reaction mixture can be readily effected by washing with 5% $NaHCO_3$ obviating the need for column chromatographic purification. In Entries 2-3, the reaction proceeded rapidly to completion using a biphasic system (CH_2Cl_2 / 5%$NaHCO_3$ (1:1)). Subsequent separation of the phases and removal of solvents *in vacuo* afforded highly pure products. In the case of primary amino alcohols, although longer reaction times were required, selective protection of the amino group was observed without formation of the carbonate or the cyclic carbamate (Entry 4). In the case of aromatic amines, which are less reactive than the associated aliphatic amines, addition of triethylamine as a base was required for the preparation of the desired protected compounds in high yields (Entry 5).

Introduction of the Teoc group at 2-NH_2 of guanosine derivatives, a reaction hitherto undocumented, also proceeded rapidly with the addition of triethylamine to give corresponding protected compounds in high yields (Entry 6). The Teoc group can be removed easily by the action of fluoride ions in neutral condition, rendering **1** applicable to the synthesis of various base-sensitive oligonucleotide derivatives.

Furthermore, the reaction of **1** with alcohols and thiols also proceeds rapidly in the presence of triethylamine to give corresponding *O*-Teoc compounds in high yields (Entry 7).

Thus, **1** is a useful protecting reagent which reacts rapidly with amines, alcohols, and thiols to give the respective carbamates, carbonates, and thiocarbonates with a simple and convenient procedure under mild conditions.

References

Convenient method for the preparation of carbamates, carbonates, and thiocarbonates
M. Shimizu, M. Sodeoka, *Org. Lett.* **2007**, *9*, 5231.

This product received license of invention of RIKEN (Jpn Patent Appl. 2007-260255).

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