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Solid State Organic Chemistry: Efficient Reactions, Remarkable Yields, and Stereoselectivity

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Received November 9, 1994

1. Introduction

Most organic reactions have been studied in solution. One reason for this might be Aristotle's famous philosophy, "No Coopora nisi Fluida", which means, "No reaction occurs in the absence of solvent." This philosophy had a big influence on the evolution of the modern sciences in Europe. In the ancient period of Aristotle, it was not realized that many reactions occur in the absence of solvent. For example, many biological reactions, such as digestion of food in the stomach and bowels, the reaction between cells such as ovum and spermatid, and the multiplication of the cell, are more solid state than solution reactions. Nevertheless, it is very curious that almost all reactions are still carried out in solution, even when a special reason for the use of solvent cannot be found. We have found that quite a few reactions proceed well in the solid state. In some cases, the solid state organic reaction occurs more efficiently and more selectively than does the solution reaction, since molecules in a crystal are arranged tightly and regularly. When more selective reaction in the solid state is required, the host–guest chemistry technique, for example, is applicable. Reaction of the guest compound as its inclusion complex crystal with a chiral host compound in the solid state gives an optically active reaction product. Various host compounds were designed by our simple principle. Although both thermal and photochemical reactions can be carried out selectively in inclusion crystals, the selectivity of the latter reaction is usually higher than that of the former.

The occurrence of efficient solid state reactions shows that molecules of reactant and reagent can move in the solid state. In fact, host–guest inclusion complexation occurs by mixing both crystals in the solid state. Surprisingly, solid state complexation even occurs selectively. For example, mixing of racemic guest and optically active host in the solid state gives an inclusion complex of one enantiomer of the guest with the host, from which optically active guest is obtained. Such efficient chiral recognition was observed in many inclusion crystals, and efficient optical resolution was achieved by using this phenomenon. The most interesting application of chiral recognition in the solid state is resolution of racemic guest by fractional distillation in the presence of optically active host. When racemic guest and chiral host are mixed in the solid state, one enantiomer of the guest is included by the host, and when the mixture is heated, the other uncomplexed guest distills at relatively low temperature. Thereafter the complexed enantiomer distills at relatively high temperature.

In an inclusion crystal of prochiral guest and chiral host, molecules of the former are arranged in a chiral form and the chirality is fixed by the solid state reaction. This is the principle of enantioselective reactions in inclusion crystals using chiral hosts. The inclusion crystal is usually prepared by recrystallization of both components. Surprisingly, however, it was discovered that movement and chiral arrangement of achiral molecules occur by mixing host and guest crystals in the solid state. In other words, an optically active product results from mixing achiral guest with chiral host and irradiation.

2. Solid State Reactions

Organic reactions were found to occur efficiently in the solid state. Organic solid state reactions are usually carried out by keeping a mixture of finely powdered reactant and reagent at room temperature. In some cases, solid state reactions are accelerated by heating, shaking, irradiation with ultrasound, or grinding of the reaction mixture using a mortar and pestle. Generation of local heat by grinding of crystals of substrate and reagent by mortar and pestle is also helpful. In special cases, a mixture of reactant and reagent turns to a glassy material. This seems not to be a real solid state reaction, but it is understandable that organic reactions occur in the absence of solvent.

The relationship between reaction rate and particle size of powdered reactant and reagent was investigated. These data showed that the smaller the particle size, the faster the reaction rate. For example, Baeyer–Villiger oxidation of benzophenone derivatives with *m*-chloroperbenzoic acid in the solid state proceeded 10 times faster when the particle diameter of both components was 50 μm compared to 100 μm. However, in some cases, the size of the particle is not related to reaction rate and reaction is accomplished smoothly by simple mixing of crystals of reactant and reagent without grinding.

Since the chemistry of solid state organic reactions has only a very short history, it is not easy to interpret

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Table 1. Yields of Baeyer–Villiger Oxidation Products

ketone	reactn time	product	yield(%) solid state	yield(%) $CHCl_3$[a]
p-BrC_6H_4COMe	30 min	*p*-BrC_6H_4OCOMe	64	30
$PhCOCH_2Ph$	5 days	$PhOCOCH_2Ph$	97	46
PhCOPh	24 h	PhCOOPh	85	13
p-MeC_6H_4COPh	24 h	*p*-MeC_6H_4OCOPh	50	12

[a] The reaction was carried out at a concentration used for a normal Baeyer–Villiger reaction.

such reactions uniformly. Theoretical treatments of solid state reactions have many problems, because theory which has been developed to describe solution reactions is not simply applicable to solid state reactions.

In this Account, a survey of new organic solid state reactions which have been developed in the author's laboratory is introduced. Since we are studying mechanisms of these solid state reactions through collaborative work with experts in modern instrumentation such as AFM, HAUP, and high-speed X-ray analysis, more information on these reactions should become available in the future.

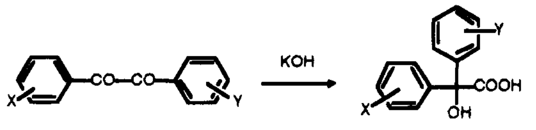
2.1. Baeyer–Villiger Oxidation and Benzilic Acid Rearrangement. Some Baeyer–Villiger oxidations of ketones with *m*-chloroperbenzoic acid proceed much faster in the solid state than in solution. When a mixture of powdered ketone and 2 equiv of *m*-chloroperbenzoic acid was kept at room temperature, the oxidation product was obtained in the yield shown in Table 1.[1] Each yield is much higher than that obtained by the reaction in $CHCl_3$ (Table 1).

It was also found that the benzilic acid rearrangement proceeds faster in the solid state than in solution. For example, a mixture of finely powdered benzil (**1a**) and two molar equiv of KOH was heated at 80 °C for 12 min, and the mixture was washed with dilute HCl to give benzilic acid (**2a**) in 90% yield.[2] Similar treatment of benzil derivatives **1b–g** in the solid state gave the corresponding benzilic acids **2b–g** in the yields shown in Table 2.[2]

The effect of different alkali metal hydroxides on the rate of the benzilic acid rearrangement in the solid state was different from that in solution. The effect on the rearrangement of **1a** in the solid state increased in the order KOH > $Ba(OH)_2$ > RbOH > NaOH > CsOH. On the other hand, the rate of rearrangement of **1a** in boiling 50% aqueous EtOH increased in the order KOH > NaOH > $Sr(OH)_2$ > LiOH > $Ba(OH)_2$ > $Rb(OH)_2$ > CsOH.

However, the reaction mechanisms in the solid state and in solution are the same. The benzilic acid rearrangement in solution has been proven to proceed via a radical intermediate by ESR.[3] For the rearrangement of **1a** in the solid state, a radical intermediate was also detected.[2]

Table 2. Yield of Benzilic Acid 2 Produced by Treatment of Benzil 1 with KOH at 80 °C in the Solid State



1 **2**

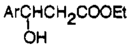
1	X	Y	reactn time (h)	yield of **2** (%)
a	H	H	0.2	90
b	H	*p*-Cl	0.5	92
c	*p*-Cl	*p*-Cl	6	68
d	H	*p*-NO_2	0.1[a]	93
e	*m*-NO_2	*m*-NO_2	0.1[a]	72
f	H	*m*-MeO	6	91
g	*p*-MeO	*p*-MeO	6	32

[a] Reaction was carried out at room temperature.

2.2. Grignard, Reformatsky, and Luche Reactions. Grignard reactions also proceed in the solid state, although the reactions give more reduction product than the normal carbonyl addition product.[4] In contrast, Reformatsky and Luche reactions occurred more efficiently in the absence of solvent. Treatment of the aromatic aldehydes **3a–e** with ethyl bromoacetate (**4**) and Zn–NH_4Cl at room temperature for 2–3 h gave the corresponding Reformatsky reaction products **5a** (91%), **5b** (94%), **5c** (94%), **5d** (83%), and **5e** (80%).[5] Luche reaction can also be carried out efficiently in the solid state.[5] Treatment of **3a** and **3e** with 3-bromopropene (**6**) and Zn–NH_4Cl in the absence of solvent gave the corresponding Luche reaction products **7a** (99%) and **7e** (87%).[6]

$ArCHO$ **3**

$BrCH_2COOEt$ **4**



$$Ar\underset{OH}{CH}CH_2COOEt$$

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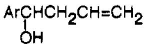
$BrCH_2CH{=}CH_2$ **6**



$$Ar\underset{OH}{CH}CH_2CH{=}CH_2$$

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a Ar=Ph; b Ar=*p*-BrC_6H_4; c Ar=3,4-methylenedioxyphenyl;
d Ar=*p*-PhC_6H_4; e Ar=2-naphthyl

2.3. Coupling Reactions of Acetylene and Phenol Derivatives. The Glaser coupling reaction of acetylenic compounds, which is usually carried out in water,[6] can be accomplished more efficiently in the solid state. For example, when a mixture of powdered cuprous phenylacetylide and $CuCl{\cdot}H_2O$ was kept at room temperature for 3 h, the coupling product diphenyldiacetylene was obtained in 60% yield.[7] The Eglinton coupling reaction,[8] which is carried out in pyridine, can also be accomplished in the solid state. When a mixture of powdered propargyl alcohols and $CuCl_2{\cdot}2Py$ or $Cu(OAc)_2{\cdot}Py$ complex was allowed to react, the coupling products were obtained in 60–92% yields.[7]

The most useful solid state coupling reaction is that of phenol derivatives. For example, when a mixture of powdered 2-hydroxynaphthalene (**8**) and $FeCl_3{\cdot}6H_2O$ was kept at 50 °C for 2 h and the reaction mixture was washed with dilute HCl, 2,2′-dihydroxy-1,1′-binaphthyl (**9**) was obtained in 95% yield.[9] Coupling of 9-hydroxyphenanthrene also occurs in the solid state efficiently, and 10,10′-dihydroxy-9,9′-biphenanthryl was obtained in 68% yield.[9]

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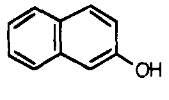

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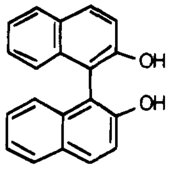

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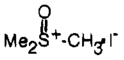
2.4. Ylide Reactions. Methylene transfer reactions from ylides to electrophilic unsaturated linkages, C=C, C=O, and C=N, are useful for the synthesis of cyclopropanes, oxiranes, and aziridines, respectively.[10] Dimethyloxosulfonium methylide (**11**), which is generated from trimethyloxosulfonium iodide (**10**) by treatment with base in solution, has been reported as a source of active methylene.[10] However, the experimental procedure for ylide generation in solution is complicated.[10] Recently, an improved procedure of the methylene transfer reaction carried out in dry CH_2Cl_2 has been reported.[11] Nevertheless, solid state methylene transfer is much simpler and has many advantages.



$\mathrm{Me_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{S}}}{}^{+}\text{-}\mathrm{CH_3}\,\mathrm{I}^{-}$

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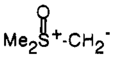

$\mathrm{Me_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{S}}}{}^{+}\text{-}\mathrm{CH_2}^{-}$

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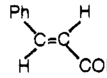

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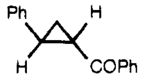

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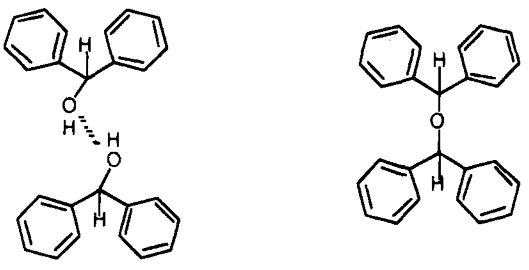
A mixture of powdered chalcone (**12**) (0.5 g), **10** (1.1 g), and KOH (1.5 g) was kept at room temperature for 3 h, and then the reaction mixture was washed with water and the remaining residue was taken up in ether. From the ether solution was obtained *rac-trans*-1-benzoyl-2-phenylcyclopropane (**13**) in 79% yield.[12] Similar methylene transfer reactions to ketones and imines also proceed efficiently in the solid state.[12]

Scheme 1



14 **15**

2.5. Etherification and Some Other Reactions. When a mixtrure of powdered benzhydrol (**14**) and an equimolar amount of *p*-TsOH was kept at room temperature for 10 min, bis(diphenylmethyl) ether (**15**) was obtained in 95% yield.[13,14] When the reaction is carried out in benzene or MeOH, the yield of **15** is relatively low, 45% or 34%, respectively.[13] In order to know why the etherification proceeds more efficiently in the solid state, the X-ray crystal structure of **14** was analyzed.[15] The data showed that two molecules of **14** make a pair through hydrogen bonding as shown in Scheme 1. The paired structure shows that two **14** molecules, reactant and reagent, are located in close proximity, and the etherification reaction occurs readily by treatment with *p*-TsOH in the solid state.

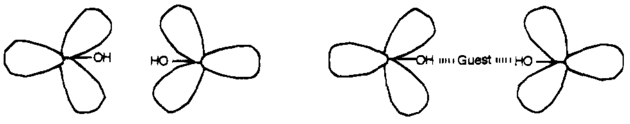


Figure 1. Alcohol host substituted with bulky groups.

Many other organic reactions, such as pinacol rearrangement,[16] $NaBH_4$ reduction of ketones,[17] Wittig reaction,[18] dehydration and chlorination reactions of alcohols,[13] aldol condensation reactions,[19] and Michael addition reactions,[20] have been carried out efficiently in the solid state. These solid state reactions can be accomplished selectively by carrying out the reaction in host–guest inclusion crystals.

3. Solid State Reactions in Host–Guest Inclusion Crystals

3.1. Design of Host Compounds. Host compounds for solid state reactions should be simple, stable, easily obtainable compounds. In 1968, we found that 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol (**16**) includes a large variety of guest compounds in stoichiometric ratios and forms stable inclusion crystals.[21] Spectral and X-ray structure analytical data showed that the guest molecules are included by forming hydrogen bonds with the hydroxyl group of the host.[22,23] The acetylenic linkage is not essential, because 1,1,2,2-tetraphenylethane-1,2-diol also shows similar inclusion ability.[24] The rigid structure of **16** is important, since 1,1,6,6-tetraphenylhexane-1,6-diol shows very poor inclusion ability. The sterically crowded structure around the hydroxyl group of the host is also important. Due to this steric restriction, host molecules cannot associate intermolecularly through the formation of hydrogen bonds and so a guest molecule is accommodated as depicted schematically in Figure 1, forming the hydrogen bond network host–OH---guest---HO–host. Alcohols which have rigid structures and sterically bulky substituents should therefore be good hosts.[25] One of the most interesting hosts which contains the 3-hydroxy-3,3-diphenyl-1-propynyl moiety is hexakis(3-hydroxy-3,3-diphenyl-1-propynyl)benzene (**17**).[26] The sexipedal host **17** includes several guest molecules in 1:6 ratio. Of the chiral hosts, (*S*,*S*)-(−)-1,6-bis(*o*-chlorophenyl)-

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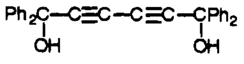
1,6-diphenylhexa-2,4-diyne-1,6-diol (**18a**)[27] and its derivatives (**18b**,[28] **18c**[29]) and (*R,R*)-(−)-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane (**19a**)[30] and its derivatives (**19b**, **19c**)[19,30] were found to be especially useful.



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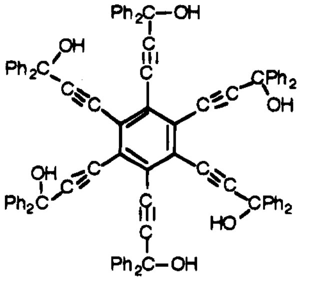

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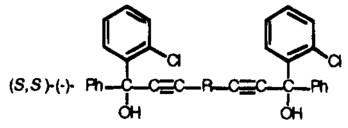

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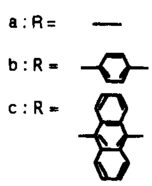

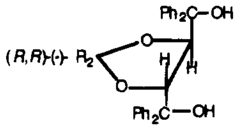

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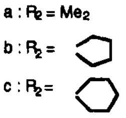


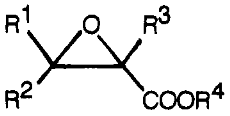
3.2. Molecular Recognition in Inclusion Crystals. Host−guest inclusion crystals are usually prepared by recrystallization of the components in a stoichiometric ratio from a solvent. Any solvent which shows a lower affinity toward the host compound relative to that of the guest molecule is useful. In some cases, inclusion crystals are prepared by recrystallization of crystalline host from liquid guest. Recrystallization of a host−guest crystal from another liquid guest gives a new host−guest inclusion crystal by replacement of the first guest. By this method, inclusion complexes can be decomposed to their components. Guest compounds can also be separated from inclusion crystals by column chromatography or by heating the inclusion crystals in vacuo, which gives the volatile guest by distillation.

The most interesting inclusion complexation was observed in the solid state. In some cases, inclusion complexation occurred simply by mixing powdered host and guest compounds.[31]

Inclusion crystals can be purified by recrystallization and, when pure, show sharp melting points.

3.3. Application of Molecular Recognition: Separation of Isomers and Enantiomers. Host and guest molecules recognize each other in the inclusion crystal. Inclusion crystallization of host with a mixture of guest compounds therefore occurs selectively, and one guest compound is included selectively. Application of selective inclusion to separation of isomers is well established.[25] Separation of enantiomers by this method is more important, and optically active hosts (**18**, **19**) are useful for the efficient optical resolution of various racemic compounds.[25]

Table 3. Optical Resolution of Ethylene Oxides (20) by Inclusion Complexation with 19



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	guest (20)					resolution product		
host		R^1	R^2	R^3	R^4	enantiomer	opt. purity (% ee)	yield (%)
19b	**a**	Me	Me	H	Me	(+)-**20a**	93	32
19c	**b**	Me	Me	H	Et	(+)-**20b**	96	32
19b	**c**	Et	Et	H	Et	(+)-**20c**	100	51
19c	**c**	Et	Et	H	Et	(+)-**20c**	96	86
19b	**d**	Me	H	Me	Me	(+)-**20d**	93	42
19b	**e**	H	H	Me	Me	(−)-**20e**	77	34

For example, when a solution of **19b** and an equimolar amount of *rac*-1-carbomethoxy-2,2-dimethylethylene oxide (**20a**) in ether was kept at room temperature for 3 h, a 2:1 inclusion crystal of **19b** and (−)-**20a** was obtained.[32] After purification by recrystallization from ether, the complex was heated in vacuo to give (−)-**20a** of 93% ee in 32% yield. By the same procedure, ethylene oxides (**20b**−**e**) were also resolved efficiently (Table 3).[32] It is very difficult to prepare a trisubstituted ethylene oxide of high optical purity by asymmetric epoxidation of olefins. Therefore, this simple optical resolution method is especially valuable.

In some cases, solvent molecules are included together with the guest molecule and necessarily occupy vacant space and stabilize the host−guest inclusion crystalline lattice. In special cases, the solvent molecule which is included along with the guest molecule plays an important and interesting role in molecular recognition. For example, recrystallization of **18b** and *rac*-4-hydroxy-2-cyclopentenone (**21**) from toluene and MeOH gave a 1:2 inclusion crystal of **18b** and (+)-**21** and a 1:1:1 inclusion crystal of **18b**, (−)-**21**, and MeOH, respectively.[29] Similarly, recrystallization of **18c** and *rac*-2-methylpiperidine (**22**) from toluene and MeOH gave a 1:1 inclusion crystal of **18c** and (−)-**22** and a 1:1:1 inclusion crystal of **18c**, (+)-**22**, and MeOH, respectively.[29] In the absence and presence of MeOH, the chiral hosts **18b** and **18c** recognize the different enantiomers of **21** and **22**, respectively.

3.4. Enantioselective Molecular Movement in the Solid State and Optical Resolution by Fractional Distillation. As indicated earlier, host−guest inclusion complexation can be achieved by simply mixing powdered host and guest compounds.[31] For example, when a mixture of powdered **16** and chalcone (**12**) was kept at room temperature for 6 h, a 1:2 inclusion complex of **16** and **12** was formed. The complexation can be followed by measurement of the UV spectrum in the solid state. As the complexation proceeded, molecules of **12** having a coplanar structure increased, accompanied by an increase in absorption. It is to be noted that the coplanar structure of **12** in

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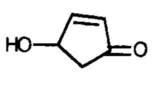
the inclusion crystal had already been established from earlier X-ray analytical work.[33]

It was also discovered that solid state inclusion complexation occurs enantioselectively. For example, a mixture of finely powdered **19c** and *rac*-β-ionone oxide (**23**) was kept at room temperature for 1 day and then washed with hexane to give an inclusion complex of **19c** and (+)-**23** and a hexane solution. From the complex, (+)-**23** of 88% ee was obtained in 24% yield by distillation in vacuo. From the hexane solution, (−)-**23** of 36% ee was obtained in 60% yield.[34] A much more efficient enantioselective inclusion in the solid state was observed for oxime **24**. A mixture of **18a** and *rac*-**24** was irradiated with ultrasound (28 kHz) for 8 h, and the reaction mixture was washed with light petroleum to leave an insoluble 1:1 complex of **18a** and (+)-**24** in 95% yield. Upon treatment with H_2SO_4 in the solid state according to the reported method,[18] this gave the Beckmann rearranged product (+)-**25** of 79% ee in 68% yield. Therefore, the optical purity of the (+)-**24** in the complex with **18a** must be higher than 79% ee.[34] These data show that molecules of one enantiomer move from crystalline *rac* compound to optically active host compound in the solid state. This enantioselective molecular movement in the solid state is an exciting finding.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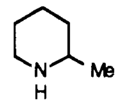
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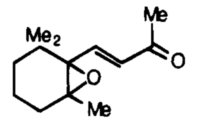
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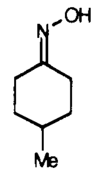
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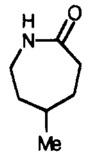
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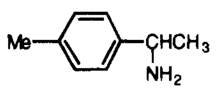
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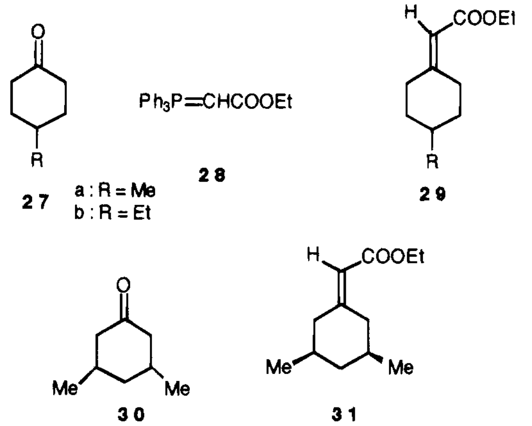
When the enantioselective molecular movement in the solid state is combined with distillation, both enantiomers can be separated easily by fractional distillation.[35] For example, heating a mixture of **19c** (1.41 g, 2.79 mmol) and *rac*-1-(*p*-tolyl)ethylamine (**26**) (0.75 g, 5.58 mmol) at 70 °C/2 mmHg gave (+)-**26** of 98% ee in 100% yield, and further heating of the residue at 150 °C/2 mmHg gave (−)-**26** of 100% ee in 98% yield. A certain economy about the latter procedure was that the recovered **19c** could be used again. The resolution method by distillation is applicable to various kinds of compounds, namely, epoxides, epoxy ketones, alcohols, alkyl hydroxy carboxylates, amino alcohols, and amines.[35] Of course, this method of separating enantiomers by distillation can be applied to the separation of isomers which have the same or very similar boiling points.

Table 4. Enantioselective Wittig–Horner Reactions of 27 and 30 in Their 1:1 Inclusion Crystals with 19[a]



host	ketone	reactn temp (°C)	product		
				Yield (%)	Opt. purity (% ee)
19a	**27a**	70	(−)-**28a**	51	43
19b	**27a**	70	(−)-**28a**	73	42
19c	**27a**	80	(−)-**28a**	48	39
19b	**27b**	70	(−)-**28b**	73	45
19c	**30**	80	(−)-**31**	58	57

[a] Reactions were carried out for 4 h.

4. Enantioselective Solid–Solid Reactions

When solid–solid reactions are carried out in an inclusion crystal with a chiral host, the reactions can be controlled to proceed enantioselectively.

4.1. Wittig Reaction. Only three enantioselective Wittig reactions using optically active reagents have been reported.[36] The solid state Wittig–Horner reaction was found to be efficient and enantioselective. Treatment of a 1:1 inclusion crystal of 4-methylcyclohexanone (**27a**) and **19a** with (carbethoxymethyl)triphenylphosphorane (**28**) at 70 °C for 4 h gave the optically active Wittig–Horner reaction product (−)-**29a** of 43% ee in 51% yield.[18] By a similar method, (−)-**29b** and (−)-**31** were obtained from **27b** and **30**, respectively, in the optical and chemical yields shown in Table 4. In this reaction, all the optically active hosts **19a–c** work quite well.

4.2. Reduction of Ketones with $NaBH_4$. $NaBH_4$ reduction of ketones to alcohols in the solid state has also been reported.[17] In order to carry out the reaction enantioselectively, the inclusion crystal of ketone **32** and **18a** was reacted with borane–ethylenediamine complex, $2BH_2{\cdot}NH_2CH_2CH_2NH_2$, in the solid state, and the optically active alcohols **33** were obtained (Table 5).[17]

$NaBH_4$ reduction of **32** included in β-cyclodextrin also proceeded quite easily in the solid state. However, the product alcohol **33** in all cases gave only a modest level of optical purity.[37]

4.3. Michael Addition Reaction. The Michael addition of thiol derivatives (**34**) to 2-cyclohexenone (**35**) included in **19c** in the solid state proceeded enantioselectively.[20] For example, when a mixture of powdered 1:1 inclusion crystals of **35** and **19c**, 2-mercaptopyridine (**34a**), and a catalytic amount of ben-

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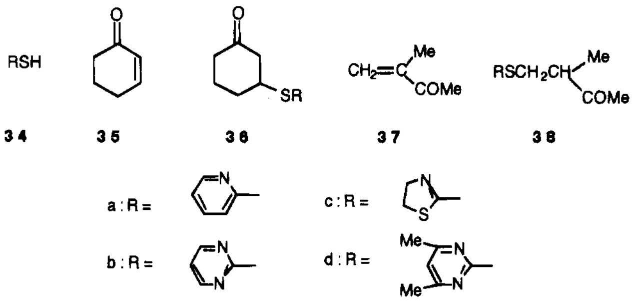
Table 5. Yield, Optical Purity, and Absolute Configuration of the Alcohol 33 Obtained by Solid–Solid Reaction of a 1:1 Inclusion Crystal of 32 and 18a with $2BH_3\cdot NH_2CH_2CH_2NH_2$

ArCOR **32** ArCH(OH)R **33**

a: Ar=Ph; R=Me
b: Ar=o-MeC_6H_4; R=Me
c: Ar=1-naphthyl; R=Me
d: Ar=Ph; R=Et
e: Ar=o-MeC_6H_4; R=Et

ketone	alcohol	yield (%)	opt. purity (% ee)
32a	(*R*)-(+)-)33a	96	44
32b	(*R*)-(+)-**33b**	57	59
32c	(*R*)-(+)-**33c**	20	22
32d	(*R*)-(+)-**33d**	55	42
32e	(*R*)-(+)-**33e**	64	42

zyltrimethylammonium hydroxide, $PhCH_2N^+Me_3OH^-$, was irradiated with ultrasound (28 kHz) for 1 h at room temperature, (+)-**36a** of 80% ee was obtained in 51% yield.[17] Similar treatments of the inclusion crystal of **35** and **19c** with **34b**, **34c**, and **34d** gave **36b** of 78% ee (58%), **36c** (58%, optical purity was not determined), and **36d** of 74% ee (77%), respectively, in the yields indicated. The Michael addition of **34a** and **34c** to 2-methyl-1-buten-2-one (**37**) included in **19c** gave (+)-**38a** of 49% ee and (+)-**38c** of 53% ee in 76% and 78% yields, respectively.[20]



5. Photochemical Reactions in Inclusion Crystals

5.1. Regio- and Stereoselective Photoreactions. The photodimerization of chalcone (**12**) is not easy either in solution or in the solid state. For example, irradiation of **12** in solution gives a mixture of **12** and its cis isomer[38] or a polymer.[39] Irradiation of **12** in the solid state results in a complex mixture of all possible stereoisomeric photodimers in low yield.[20] X-ray crystal structure studies of two dimorphs of **12** show that the distances between the double-bond centers are 5.2 Å in one dimorph and >4.8 Å in another, although the molecules are packed in a parallel manner in both cases.[40] Those distances are longer than the limit of an intermolecular reaction (4.2 Å),[41] and therefore the two dimorphs are photoinactive.

In contrast, irradiation for 6 h in the solid state of a 1:2 inclusion complex (**39**) of **16** and **12** gave the syn head-to-tail dimer **40** selectively in 90% yield.[42] X-ray structure analysis of the 1:2 inclusion crystal **39** showed that two molecules of **12** are packed in a very close position between the two host molecules through hydrogen bond formation, as depicted schematically in Figure 2.[33] In the inclusion crystal, the double bonds of **12** are parallel and the distance between them is short enough (3.682 Å) for easy reaction. This arrangement enables the photodimerization to give the syn head-to-tail product **40**, but not other isomers.[33]

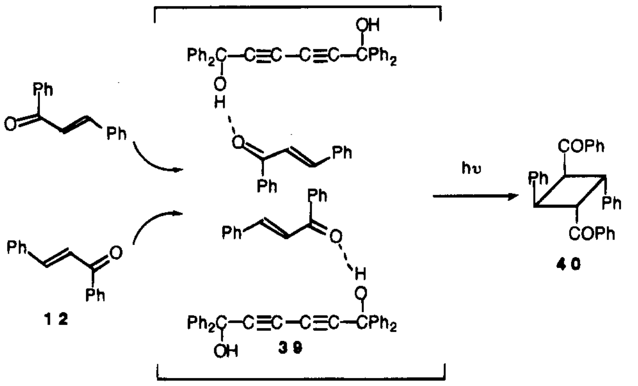


Figure 2. Catalytic photodimerization of **12** in the inclusion crystal (**39**) with the host **16**.

By a similar method, regio- and stereoselective photodimerization of 9-formyl- and 9-acetylnaphthalenes,[43,44] 2-pyridones,[43,44] 2-cyclohexenone (**35**),[28] and coumarin[45] has been accomplished.

When the photodimerization of **12** in **39** is combined with inclusion complex formation by solid–solid reaction,[31] stereoselective photoreaction of **12** can be carried out continuously. By irradiation of 1:1 and 1:2 mixtures of **16** and **12** in the solid state (with occasional mixing with an agate mortar and pestle) for 10 and 40 h, respectively, **40** was obtained selectively in 80 and 82% yields, respectively.[31] These results suggest the formation of **39** previous to the photodimerization reaction, since plain **12** does not give **40** by irradiation in the solid state.[39,40] Furthermore, irradiation of a 1:4 mixture of **16** and **12** under the same conditions as above for 72 h gave **40** in 87% yield. This result shows that the host compound **16** was used almost twice as a catalyst. This is illustrated in Figure 2. By mixing of **17** and **12**, **39** is formed, and the irradiation of **39** gives **16** and **40**. Further mixing of the recovered **16** and excess **12** forms a new complex **39** which upon irradiation gives **40** again.

5.2. Formation of Inclusion Crystals in Which Achiral Guest Molecules Are Arranged in a Chiral Form by Mixing Chiral Host and Achiral Guest, and Freezing of the Chirality by Photoreaction. Room temperature irradiation for 10 h of powdered 2:1 inclusion crystals of **19b** with *N*-allyl-*N*-benzyl-3-oxo-2-cyclohexenecarboxamide (**41**) (prepared by recrystallization of both from ether), in a water suspension containing sodium alkylsulfate as a surfactant, gave (−)-**42** of 100% ee in 90% yield. Similar irradiation of a 2:1 inclusion crystal of **19c**

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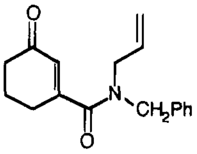
with **41** prepared by recrystallization from benzene gave (−)-**42** of 100% ee in 87% yield.[46]



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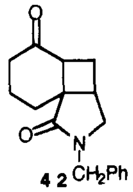

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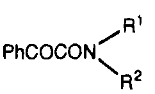
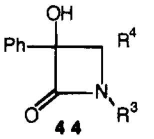


43

a: $R^1 = R^2 = Me$
b: $R^1 = Me$; $R^2 = iPr$
c: $R^1 = nPr$; $R^2 = iPr$



44

a: $R^3 = Me$; $R^4 = H$
b: $R^3 = iPr$; $R^4 = H$
c: $R^3 = nPr$; $R^4 = Me$

On the other hand, irradiation for 10 h of a water suspension of inclusion crystals which had been prepared by mixing for 1 h powdered **19b** and oily **41**gave (−)-**42** of 99% ee in 48% yield. Similar mixing of **19c** and **41** for 1 h followed by irradiation for 10 h gave (−)-**42** of 87% ee in 40% yield.[46] These data clearly show that inclusion crystals of **19** and **41** in which molecules of achiral **41** are arranged in a chiral form are formed just by mixing both components.

Table 6. Enantioselective Photocyclization of 43 to 44 by Inclusion Complexation with 19 in the Solid State and by Irradiation

		product		
43	19		yield (%)	opt. purity (% ee)
a	b	(−)-**44a**	54	78
b	b	(−)-**44b**	45	87
c	c	(−)-**44c**	39	93

Such molecular movement in the solid state and arrangement into a chiral form are not special for **41** but are rather common. For example, *N*,*N*-dialkylphenylglyoxylamides **43** also form inclusion crystals with **19** in which the achiral molecules of **43** are arranged in a chiral form. Mixing of **19b** with **43a** for 1 h followed by irradiation for 10 h gave (−)-**44a** of 78% ee in 54% yield. Similarly, **43b** and **43c** gave optically active photocyclization products (Table 6).[46]

The efficient enantioselective photocyclization of achiral molecules in an inclusion crystal with a chiral host has also been accomplished for various compounds such as tropolone alkyl ethers,[47],[48] *N*-methylpyridones,[49,50] nitrones,[51] acryalanilides,[52] *N*-(acylmethyl)-δ-valerolactams,[53] 2-[*N*-(2-propenyl)amino]cyclohex-2-enones,[54] *N*-benzyl-3-oxo-2-cyclohexenecarboxamide,[54] and 4-carbomethoxy-4-(3-butenyl)cyclohexa-2,5-dien-1-one.[54] In all cases, inclusion crystals can be prepared by recrystallization from solvent and just by mixing.

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