Supramolecular Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713649759

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To cite this Article Toda, Fumio(1995) 'Chiral lock and chiral key in inclusion crystals', Supramolecular Chemistry, 6: 1, 159 — 163
To link to this Article: DOI: 10.1080/10610279508032531
URL: http://dx.doi.org/10.1080/10610279508032531

SUPRAMOLECULAR CHEMISTRY, Vol. 6, pp. 159–163
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Chiral lock and chiral key in inclusion crystals

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(Received August 5, 1994)

By combining the enantioselective molecular movement from a *rac*-guest to an optically active host in the solid state with a distillation procedure, enantiomers of the *rac*-guest were separated by fractional distillation. When the enantioselective molecular movement in the solid state was applied to an optically active host and an achiral guest, the inclusion complex of the host and the achiral guest in which the latter molecules are arranged in a chiral form is obtained. Photoirradiation of the inclusion crystal in the solid state gave optically active photocyclization product.

We found that molecular movement from guest crystal to host crystal occurs quite easily in the solid state. For example, when a mixture of finely powdered 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol (**1**) and two molar amounts of chalcone (**2**) was kept at room temperature for 6 h, a 1:2 inclusion complex of 1 and 2 was obtained in quantitative yield.[1] It was further found that the molecular movement occurs enantioselectively. For example, a mixture of powdered chiral host compound *(R,R)*-(-)-trans-2,3-bis-(hydroxydiphenylmethyl)-1,4-dioxaspiro[5.4]decane (**3c**)[2] and two molar amounts of *rac*-β-ionone epoxide (**4**) was kept at room temperature for one day and the mixture was washed with hexane in order to remove uncomplexed (-)-enantiomer to leave a complex of **3** and (+)-**4**, from which (+)-**4** of 88% ee was obtained.[3] The result clearly shows that enantioselective molecular transfer occurs very efficiently in the solid state. The enantioselective inclusion complexation can be well exemplified by an adaptation between chiral lock (host) and chiral key (guest).

Optical resolution by enantioselective inclusion crystallization usually are carried out by recrystallization of a chiral host and *rac*-guest from a solvent.[4] For example, recrystallization of the chiral *(R,R)*-(-)-trans-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane (**3b**)[2] and an equimolar amount of *rac*-2-methylpiperidine (**5**) from benzene gave a 2:1 inclusion crystal of **3b**

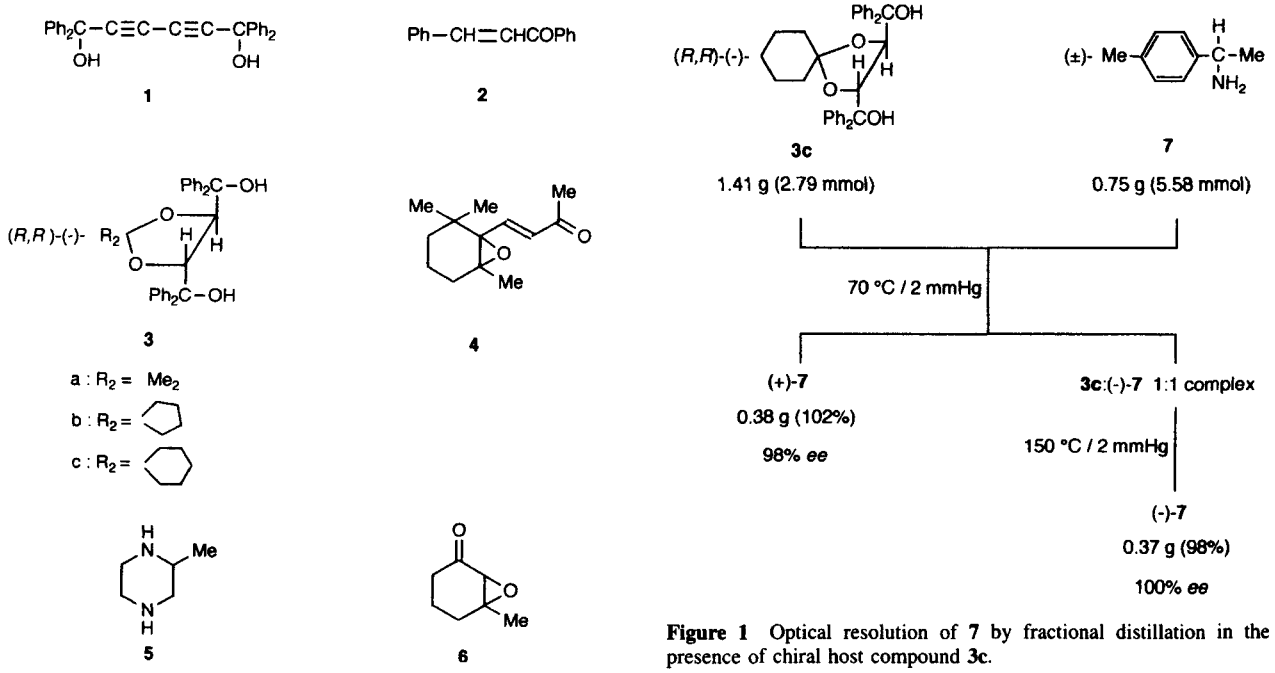


Figure 1 Optical resolution of **7** by fractional distillation in the presence of chiral host compound **3c**.

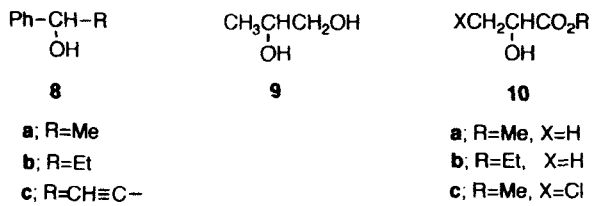


Table 1 Optical resolution of alcohols by fractional distillation[a]

Dist. times	*Host*	*Guest*	*Yield (%)*	*Optical purity (% e.e.)*
2	**1a**	**8a**	46	96[b]
2	**1a**	**8b**	57	92[c]
3	**1a**	**8c**	17	96[b]
2	**2**	**9**	49	90[d]
3	**1c**	**10a**	42	94[d]
3	**1c**	**10b**	51	92[d]
3	**1c**	**10c**	44	0[d]

[a]Only the enantiomer which forms an inclusion complex with the host used and then distils at a relatively high temperature is indicated.
[b]Optical purity was determined by HPLC on Chiralpak AS.
[c]Optical purity was determined by HPLC on Chiralcel OJ.
[d]Optical purity was determined by comparision of the $[\alpha]_D$ value with that reported.

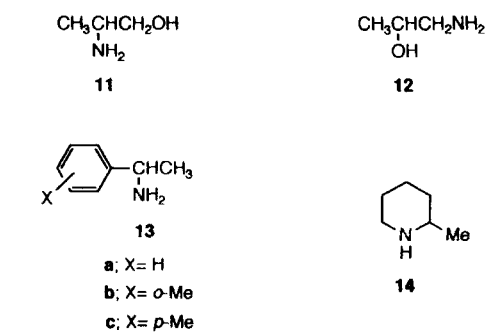


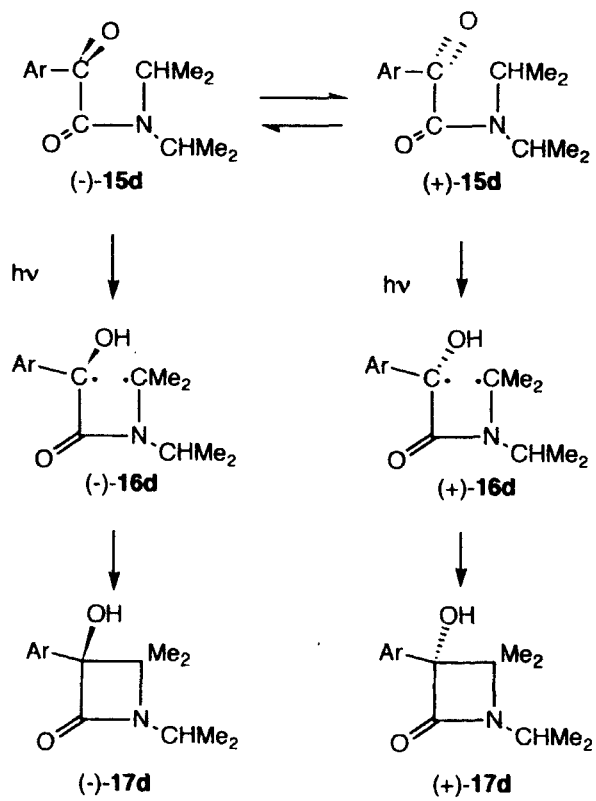
Table 2 Optical resolution of amines by fractional distillation[a]

Dist. times	*Host*	*Guest*	*Yield (%)*	*Optical purity (% e.e.)*
2	**1c**	**11**	33	100[b]
2	**1d**	**11**	37	100[b]
1	**1b**	**12**	95	25[b]
1	**1a**	**13a**	3	62[c]
3	**1d**	**13b**	26	95[b]
1	**1d**	**13c**	98	100[b]
1	**1a**	**14**	98	42[b]

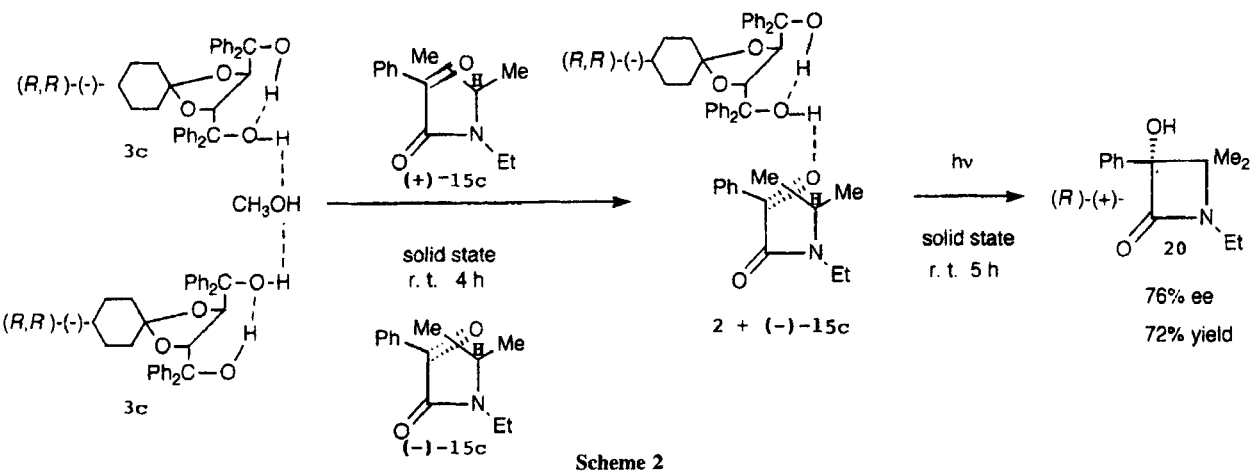
[a]Only the enantiomer which forms an inclusion complex with the host used and then distils at a relatively hight temperature is indicated.
[b]Optical purity was determined by measurement of ^{1}H NMR spectrum in the presence of chiral shift reagent.
[c]Optical purity was determined by comparision of $[\alpha]_D$ value to that reported.

and (+)-**5**, from which (+)-**5** of 100% ee was isolated in52% yield.[5] However, a new optical resolution method by distillation was established by combination of the enantioselective molecular movement in the solid state and distillation procedure.[6] For example, when a mixture of **3c** (1.03 g, 2.03 mmol) and *rac*-epoxyketone **6** (0.512 g, 4.06 mmol) was heated at 70°C/3 mmHg, (+)-**6** of 90% ee (0.231 g, 89% yield) was obtained by distillation. Further heating of the residue at 150°C/3 mmHg gave (-)-**6** of 78% ee (0.232 g, 90% yield). Much more efficient resolution by the distillation was achieved for 1-(*p*-tolyl)ethyl alcohol (**7**). As shown in Fig. 1, almost perfect resolution of **7** by distillation was achieved in the presence of the host **3c**. By mixing **3c** and *rac*-**7**, (-)-**7** is included with **3c**, and uncomplexed (+)-**7** distils at a relatively low temperature but the complexed (-)-**7** distils at a relatively high temperature.

The resolution method by distillation can be applied to various kinds of compounds. Secondary alcohols (**8a–c**), 1,3-butanediol (**9**), and α-hydroxycarboxylic acid esters (**10a-b**) were resolved efficiently (Table 1), although methyl 3-chloro-2-hydroxypropionate (**10c**) was not resolved. When the efficiency of the resolution by distillation is not perfect, optically pure enantiomers can be obtained by repeating the distillation in the presence of optically active host. 2-Aminopropanol (**11**), 2-hydroxypropylamine (**12**), phenethylamines (**13a-c**), and 2-methylpiperidine (**14**) were also resolved by this method, although efficiency of the resolution of **12, 13a** and **14** was not very high (Table 2). In Tables 1 and 2, only the enantiomer which forms an inclusion complex with the host and then distils at a relatively high tempera-



Scheme 1



Scheme 2

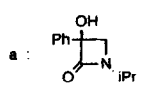
ture is summarized. The enantiomer which does not form an inclusion complex with the host and then distils at a relatively low temperature can also be purified by repeating the distillation.

Previously we have reported that oxoamide **15** forms chiral crystal which upon photoirradiation in the solid state gives optically active β-lactam **17** of 93–95% ee in quantitative yield.[7,8] X-ray structure analysis of the chiral crystal of **15** showed that oxoamide molecules are arranged in a chiral form as shown in Scheme 1.[9] This is a typical example of generation of chirality in the solid state, and is valuable as an absolute asymmetric synthesis. Of the oxoamides **15a-h**, only the **15c** and **15d** formed chiral crystals and **15f-h** formed achiral crystals. **15a-b** and **15e** are oily materials. Of the oxoamides **18a-k**, **18a-e** formed chiral crystals and **18f-k** formed achiral crystals, and photoirradiation of the former and latter in the solid state gave optically active and *rac*-β-lactams, respectively.[8] Both **19a** and **19b** formed achiral crystal and their photoirradiation in the solid state gave the corresponding *rac*-β-lactam.[8]

Recently, we found very interesting inclusion complexation of **3** with *rac*-**15** in the solid state accompanied with enantiomerization of the latter. For example, when a mixture of finely powdered 1:2 methanol complex of **3c** and *rac*-**15c** was kept at room temperature for 4 h, a 1:1 inclusion complex of **3c** with (-)-**15c** was formed. Photoirradiation of the complex in the solid state for 5 h gave *(R)*-(-)-**20** of 76% ee in 72% yield. The same result was obtained by using (+)-**15c** or (-)-**15c** crystal instead of the *rac*-**15c** crystal (Scheme 2). These data show that **15c** molecules enantiomerize during the complexation with **3c** in the solid state. This suggests that an interconversion between (+)-**15c** and (-)-**15c** occurs easily in the solid state. When *(S,S)*-(+)-host is used instead of the

Table 3 Photoreaction of oxoamides in inclusion complex

	α-oxoamide		*host*	*product 17 optical purity (% ee)*	
	15		*3*	*(l)*	*(-)*
b	R = Me	oil	(+)-**2a**	64[a]	
			(-)-**2a**		94[a]
			(+)-**2b**		59
			(-)-**2b**	61	
c	R =Et	mp 61–63 °C	(+)-**2b**		100
			(-)-**2b**	76	
e	R = nPr	oil	(+)-**2b**		56
			(-)-**2b**	80	



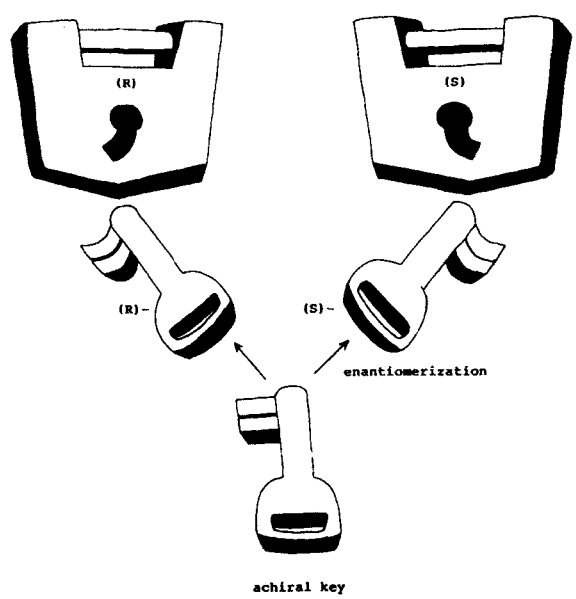


Figure 2 "lock and key" illustration of enantio-selective inclusion complexation of a chiral host with an achiral guest accompanied by enantiomerization of the latter in the solid state.

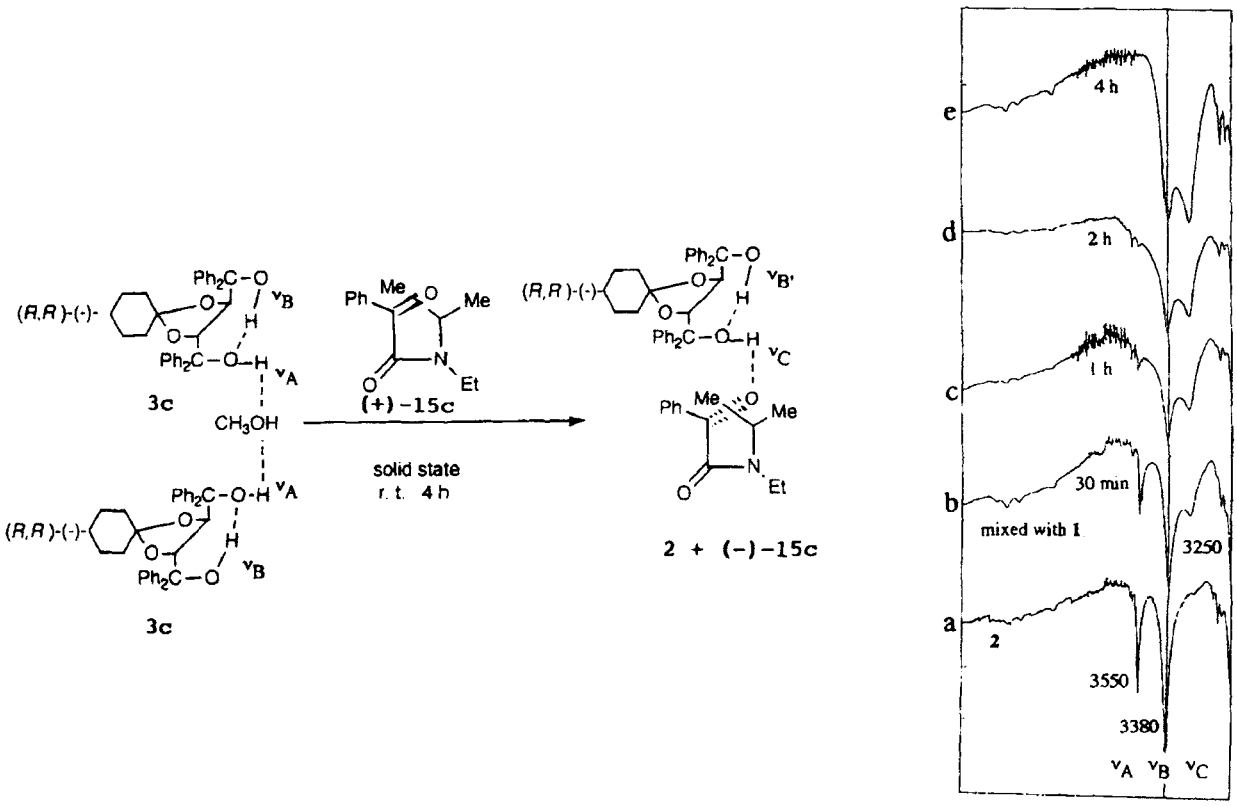
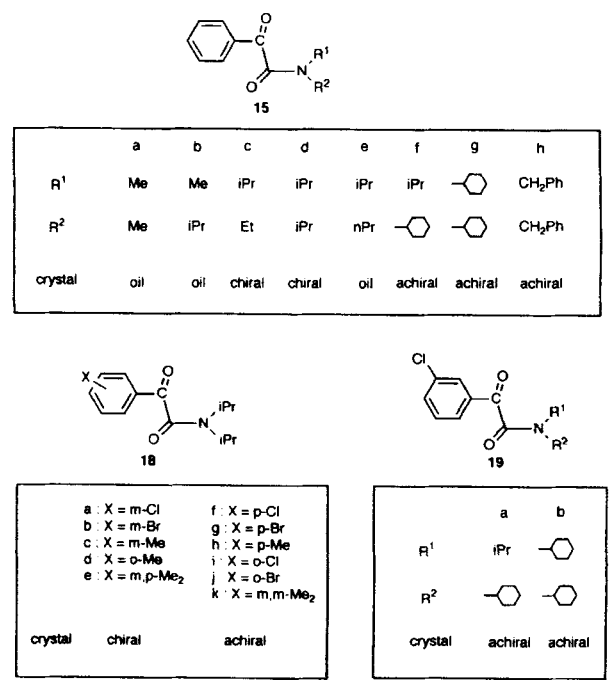


Figure 3 Measurements of inclusion complexation by IR spectra in the solid state (Nujol mull): 3c + (+)-15c.

(R,R)-(-)-host **3c** in the complexation with **15c**, a 1:1 inclusion complex of the host with (+)-**15c** was formed and its photoreaction gave *(S)*-(-)-**20**. Inclusion complexation of oily oxoamides such as **15b** and **15e** with **3c** are also accompanied by enantiomerization in the solid state. For example, complexation of *rac*-**15e** with **3c** and its *(S,S)*-(+)-enantiomer gave 1:1 complexes of (+)-**15e** with **3c** and of (-)-**15e** with *(S,S)*-(+)-host, respectively, and their photoreaction gave (+)- and (-)-β-lactams, respectively (Table 3). These interesting solid state inclusion complexation which are accompanied by enantiomerization are well exemplified by the chiral lock and chiral key shown in Fig. 2.

Complexation of **3c** with crystalline **15** in the solid state proceeds very slowly, for example, complexation of **3c** with **15c** at room temperature takes 20 h. However, the complexation is complete within 4 h, when the MeOH complex of **3c** is used. Complexation of **3c** with oily **15**, however, proceeds much more easily.

Complexation of **3c** with **15c** in the solid state was followed by measurement of IR spectra. As shown in Fig. 3, the 2:1 complex of **3c** with MeOH shows two OH absorptions, ν_A at 3550 cm^{-1} which is attributed to intermolecularly hydrogen bonded OH of **3c** to MeOH and ν_B at 3380 cm^{-1} which is attributed to intramolecularly hydrogen bonded OH of **3c**. By mixing the MeOH complex of **3c** with (+)-**15c**, the ν_A decreases and a new OH absorption ν_C at 3250 cm^{-1} which is attributed to intermolecularly hydrogen bonded OH of **3c** to (-)-**15c** appears, and ν_A finally disappeared after 4 h.



ACKNOWLEDGMENTS

This work is financially supported by Grant-in-Aid for Scientific Research on Priority Areas, No. 06242105.

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