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*Published in:*  
Angewandte Chemie - International Edition

*DOI:*  
[10.1002/anie.202102559](https://doi.org/10.1002/anie.202102559)

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*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2021

[Link to publication in University of Groningen/UMCG research database](#)

### *Citation for published version (APA):*

Dubey, R., Yan, K. K., Kikuchi, T., Sairenji, S., Rossen, A., Goh, S. S., Feringa, B. L., & Fujita, M. (2021). Absolute Configuration Determination from Low ee Compounds by the Crystalline Sponge Method. Unusual Conglomerate Formation in a Pre-Determined Crystalline Lattice. *Angewandte Chemie - International Edition*, 60(21), 11809-11813. <https://doi.org/10.1002/anie.202102559>

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## Chirality

How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 11809–11813

International Edition: doi.org/10.1002/anie.202102559

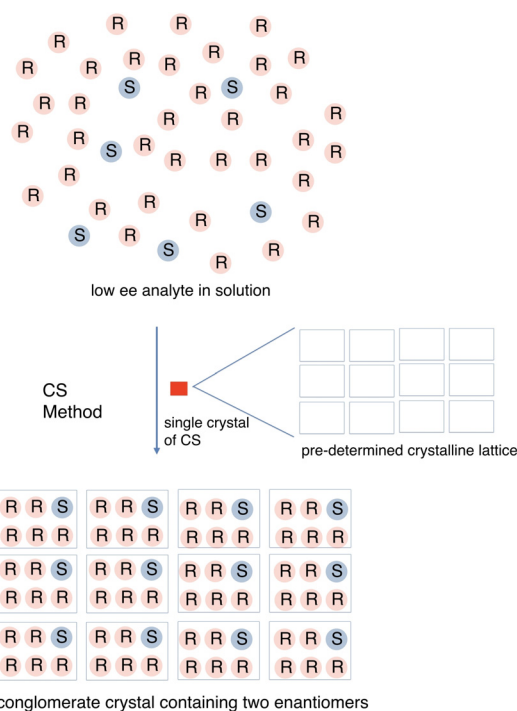
German Edition: doi.org/10.1002/ange.202102559

# Absolute Configuration Determination from Low *ee* Compounds by the Crystalline Sponge Method. Unusual Conglomerate Formation in a Pre-Determined Crystalline Lattice

Ritesh Dubey<sup>+</sup>, KaKing Yan<sup>+</sup>, Takashi Kikuchi, Shiho Sairenji, Anouk Rossen, Shermin S. Goh, Ben L. Feringa, and Makoto Fujita\*

**Abstract:** When chiral compounds with low enantiomeric excess (*ee*,  $R:S=m:n$ ) were absorbed into the void of the crystalline sponge (CS), enantiomerically pure  $[(R)_m(S)_n]$  chiral composites were formed, changing the centrosymmetric space group into non-centrosymmetric one. The absolute configuration of the analyte compounds was elucidated with a reasonable Flack (Parsons) parameter value. This phenomenon is characteristic to the “post-crystallization” in the pre-determined CS crystalline lattice, seldom found in common crystallization where the crystalline lattice is defined by an analyte itself. The results highlight the potential of the CS method for absolute configuration determination of low *ee* samples, an often encountered situation in asymmetric synthesis studies.

When a low enantiomeric excess (*ee*) compound is crystallized from its solution, there are in principle three ways in their crystallization manner: (i) conglomerate crystal formation, in which each crystal consists of only one enantiomer; (ii) racemic compound crystal formation, in which a racemic pair forms an elementary unit; (iii) solid-solution crystal formation, in which the two enantiomers are not discriminated and randomly blended.<sup>[1–4]</sup> In practice, the combination of these three cases often resulted in the common crystallization of low *ee* compounds.<sup>[5–7]</sup> Reported herein is our observation that is categorized as none of the cases (i) to (iii), but rather as a new category (Figure 1), in which a low *ee* compound is crystallized within a *predetermined* crystalline lattice to give the unusual conglomerate of a chiral composites consisting of both enantiomers in an unequal ratio.



**Figure 1.** Post-crystallization within a pre-determined crystalline lattice of CS. Conglomerate crystal of a  $[(R)_m(S)_n]$  asymmetric composite containing both enantiomers in an unequal ratio is formed. The  $m$ ,  $n$  values in  $(R)_m(S)_n$  account for the number of symmetry-independent binding sites. Taking guest occupancies and disordered solvents into account, the  $m:n$  ratio does not reflect the true  $R/S$  population in the pores.

We experienced this phenomenon in the structure analysis of chiral molecules by the crystalline sponge (CS) method.<sup>[8–17]</sup> In the CS method, analyte molecules are absorbed and ordered in the crystalline lattice of the CS crystals,  $[(ZnI_2)_3\text{-}(tpt)_2 \cdot x(\text{solvent})]$  (**1**,  $tpt = 2,4,6\text{-tris}(4\text{-pyridyl})\text{-}1,3,5\text{-triazine}$ ).<sup>[18–20]</sup> Chemically, the *ee* of the analyte is not enriched during the analyte absorption into the CS and the crystal still contains a low *ee* analyte. Crystallographically, however, the asymmetric unit of the crystal structure contains enantiomerically pure  $[(R)_m(S)_n]$  composite (Figure 1). Diffraction patterns do not show any sign of racemic twin or solid-solution formation. As a result, the Flack (Parsons) parameter value goes down to zero,<sup>[21–23]</sup> validating the absolute configuration determination of the analyte without any experimental processes to enrich the *ee* of the analyte.<sup>[24]</sup> The CS method thus offers a great help for synthetic chemistry where

\*] Dr. R. Dubey,<sup>[†]</sup> Dr. K. Yan,<sup>[†]</sup> Dr. S. Sairenji, A. Rossen, Prof. Dr. M. Fujita  
Department of Applied Chemistry, School of Engineering,  
The University of Tokyo  
7-3-1 Hongo, Bunkyo-Ku, Tokyo 113-8656 (Japan)  
E-mail: mfujita@appchem.t.u-tokyo.ac.jp

Dr. T. Kikuchi  
Rigaku Corporation  
3-9-12 Matsubara-cho, Akishima-shi, Tokyo 196-8628 (Japan)

Dr. S. S. Goh, Prof. Dr. B. L. Feringa  
Stratingh Institute for Chemistry, University of Groningen  
Nijenborgh 4, 9747 AG Groningen (The Netherlands)

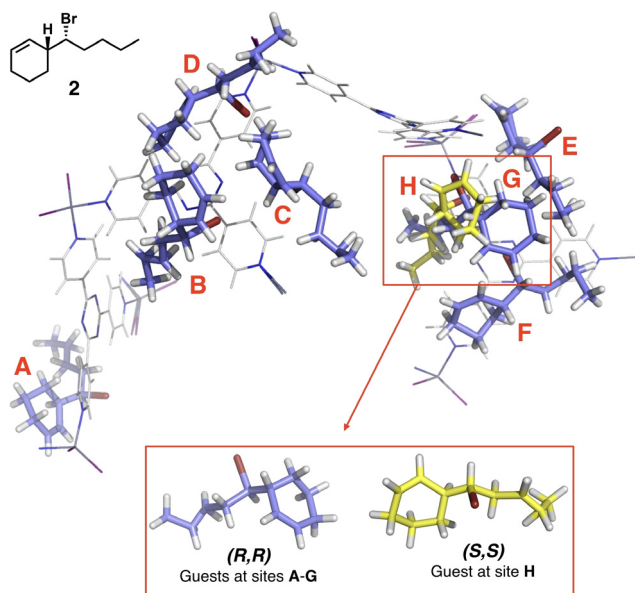
[†] These authors contributed equally to this work.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:  
https://doi.org/10.1002/anie.202102559.

researchers often have to deal with low *ee* compounds, particularly in asymmetric synthesis studies.

The CS method was applied to chiral homoallylic bromide **2**, which was synthesized in 88% *ee* in the asymmetric synthesis study by the Feringa group.<sup>[25]</sup> After guest-soaking experiment, the space group (*C2/c*) turned into non-centrosymmetric *C2* and the crystal structure of guest-absorbed **1-2** was solved in this space group. In the large asymmetric unit of the **1-2** structure, eight independent guest molecules were observed at sites **A** to **H** (Figure 2).<sup>[25]</sup> Seven of them at sites **A** to **G** showed *R,R* configuration. Interestingly, *S,S* configuration was observed for the guest trapped at the site **H**. All the guests show normal pyramidalization angles at the  $sp^3$  stereogenic centers, indicating that the disorder of *S,S* and *R,R* enantiomers at every site is negligible. The two guests at sites **G** and **H** are overlapped, but reasonably solved with 41% and 59% populations, respectively. The guest molecules thus form an enantiomerically pure [(*RR*)<sub>7</sub>(*SS*)<sub>1</sub>] composite in the asymmetric unit. Based on Flack (Parsons) parameter value of 0.031(17), configuration of major enantiomer was determined as *RR*. The site-occupancies of these guests range from 41% to 100%. From this population, the *ee* of the absorbed guest was estimated to be 87%, almost the same to the *ee* of the sample employed. Thus, the *ee* of the guest was chemically not enriched, but the 88% *ee* guest formed  $\approx 100\%$  *ee* [(*RR*)<sub>7</sub>(*SS*)<sub>1</sub>] composite through guest absorption into the CS **1**.

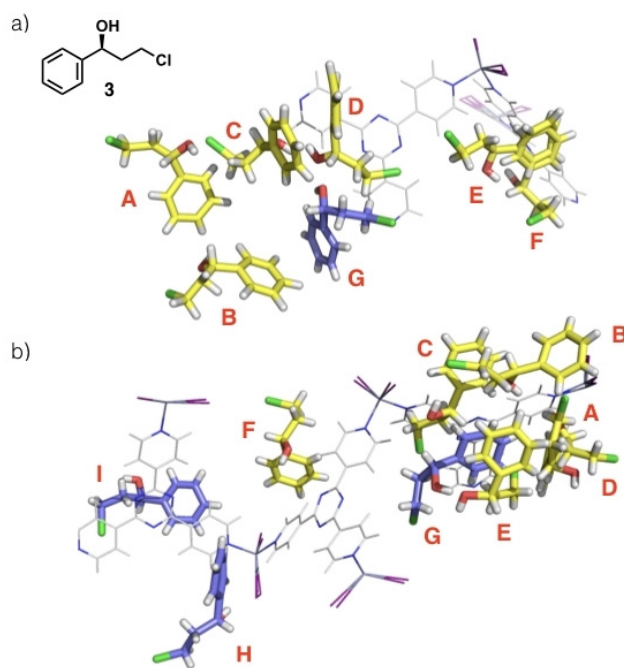
To confirm the generality of this uncommon phenomenon, the CS method was applied to another chiral compound with low *ee* values. When guest **3** in 82% *ee* (*R:S*  $\approx 1:9$ ) was examined, crystallographic analysis of **1-3** inclusion crystal



**Figure 2.** An asymmetric unit of **1-2** inclusion crystal. Guest molecules at sites **A** to **H** are shown in stick models, where guests at sites **A** to **F** exhibit *R,R* configuration. Sites **G** and **H** demonstrate an overlapping of a (*R,R*)-**2** and a (*S,S*)-**2** guests, respectively. Here, both enantiomers are color coded; *R,R* (blue) and *S,S* (yellow). Solvent molecules are omitted for clarity. In  $R_mS_n$  description, *m* and *n* values simply count the binding sites and do not reflect the true *R/S* population.

revealed seven independent guest molecules at sites ranging from **A** to **G** (Figure 3a and Figure S1). Six independent guest molecules with *S* configuration were observed at sites **A** to **F**; while one *R* enantiomer was observed at the site **G** in the crystal structure. The asymmetric unit of **1-3** inclusion complex contains an enantiomerically pure [(*S*)<sub>6</sub>(*R*)<sub>1</sub>] composite; its enantiomeric [(*S*)<sub>1</sub>(*R*)<sub>6</sub>] composite can hardly occur because of the low population of *R* enantiomer. From the [(*S*)<sub>6</sub>(*R*)<sub>1</sub>] composite, the chirality is perfectly transferred to the host framework giving a diffraction pattern of enantiomerically pure crystal with a reasonable Flack (Parsons) parameter of 0.030(3); thus the *S* configuration of the major enantiomer of **3** (82% *ee*) was crystallographically confirmed.

With the same guest **3** in 59% *ee* (*R:S* = 2:8), we observed nine independent guests at sites **A** to **I** in the asymmetric unit of the **1-3**<sub>59%*ee*</sub> structure (Figure 3b and Figure S2). Guest molecules at sites **A** to **F** showed *S* configuration; while guest molecules found at **G** to **I** showed *R* configuration. In this instance, the *R:S* ratio based on the overall site-occupancies of the absorbed guest was estimated to be 3:7. Although slightly excess *R* guests were estimated in the crystal structure, compound **3** re-extracted from **1-3**<sub>59%*ee*</sub> inclusion complex was analyzed by HPLC and found to be 59% *ee*, indicating that the minor *R* enantiomer was not enriched during guest-soaking (Figure S11). The slight overpopulation of *R* enantiomer is presumably because a part of *S* enantiomers is smeared in the crystalline lattice below the X-ray resolution limit. This [(*R*)<sub>3</sub>(*S*)<sub>6</sub>] composite can still be regarded as



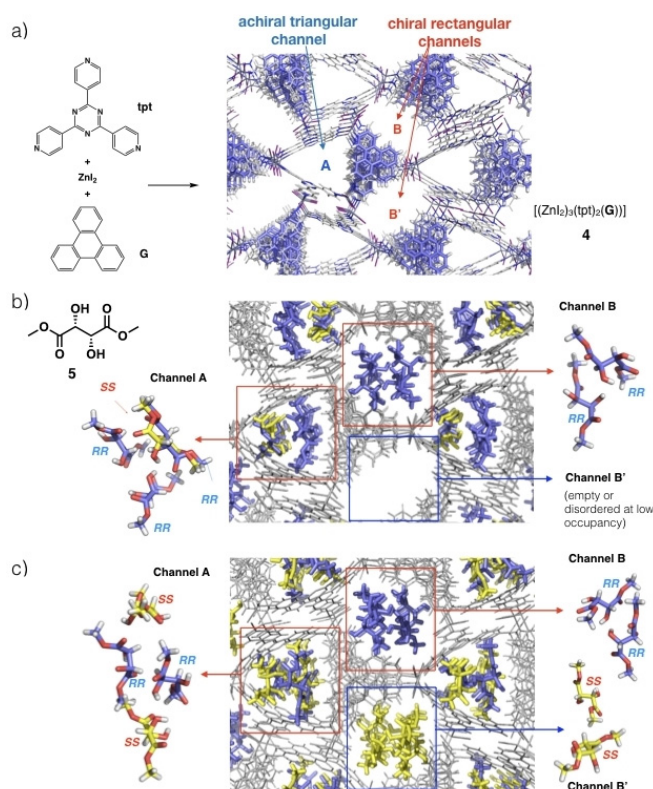
**Figure 3.** An asymmetric unit of **1-3** inclusion crystals. a) *S* enriched sample of **3** (82% *ee*). Guest molecules at sites **A** to **G** are shown in stick model. Guest molecules at sites **A** to **F** exhibit *S* configuration (yellow); while the guest at site **G** shows *R* configuration (blue). b) *S* enriched sample of **3** (59% *ee*). Here, guest molecules at sites **A** to **F** exhibit *S* configuration (yellow); while the guest at site **G** to **I** shows *R* configuration (blue).



enantiomerically pure as its enantiomeric  $[(R)_6(S)_3]$  composite can hardly occur. Accordingly, the Flack (Parsons) parameter of 0.091(4) validates the absolute configuration analysis with major *S* enantiomer.

With guest **3** in 31% *ee* (*R*:*S* = 3:7), however, we obtained a high Flack (Parsons) parameter of 0.252(6) for the **1**·**3**<sub>31%*ee*</sub> inclusion complex, which does not validate the absolute structure analysis. Presumably, the host lattice shows the nature of solid-solution crystal due to incomplete chirality transfer from the guest to the host that changes the host framework from centrosymmetric to non-centrosymmetric. Thus, the lower limit of the method for compound **3** is shown to be at around 60% *ee*.

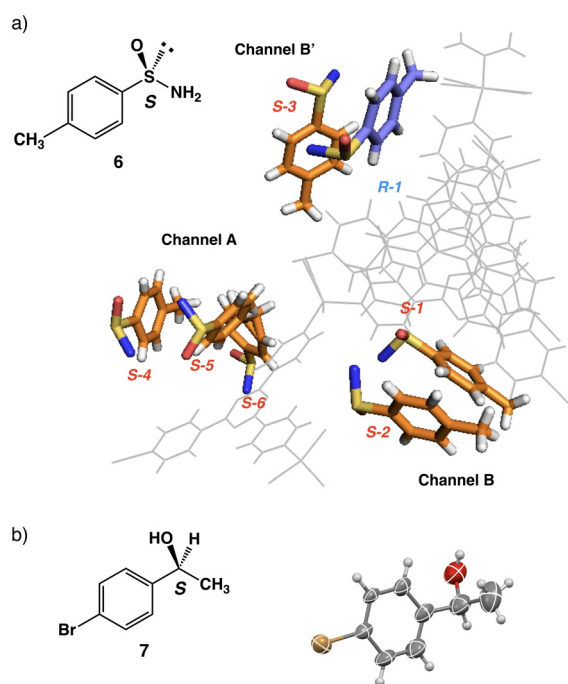
When another CS,  $[(ZnI_2)_3(tpt)_2(G) \cdot x(\text{solvent})]$  (**4**, **G** = triphenylene),<sup>[26]</sup> was used for analyzing low *ee* compounds, we observed more distinct results: even with 17–52% *ee* samples, we were able to determine the absolute configurations of chiral guests. The CS **4** is characterized by triphenylene cartridge (**G**), which is pre-installed in the host network as a platform for the functionalization of the CS pores.<sup>[27]</sup> Unlike **1**, the CS **4** contains three types of one-dimensional channels for the guest absorption: a triangular-shaped achiral channel (**A**) with an inversion centre and two rectangular-shaped chiral channels (**B** and **B'**) that are enantiomeric to each other (Figure 4 a and Figure S3). Inclusion experiment of dimethyl tartrate (**5**) with CS **4** was performed by using a low *ee* sample (52% *ee*) of (*R,R*)-**5**. The structure was solved in the noncentrosymmetric space group  $P2_12_12_1$ . In the achiral channel **A**, three molecules of (*R,R*)-**5** and one molecule of (*S,S*)-**5** were observed (Figure 4b and Figure S3). On the other hand, the guest absorption by the enantiomeric channels **B** and **B'** occurred in favor of (*R,R*)-**5**. Only two molecules of (*R,R*)-**5** (Occ. 100%, 100%) were observed in the pore **B**, whereas we could not see any guests within its enantiomeric pore **B'**. We thus conclude that 52% *ee* sample formed, overall, enantiomerically pure  $\{[(RR)_3(SS)_1] \cdot (RR)_2\}$  composite in the asymmetric unit of CS **4**. The Flack (Parsons) parameter value was  $-0.004(1)$ , which validated to assign the configuration of the major enantiomer to be *R,R*. Surprisingly, even with a 17% *ee* sample of (*S,S*)-**5**, we observed effective anomalous scattering with the Flack (Parsons) parameter value of 0.068(2). In this case, the achiral channel **A** absorbed two racemic pairs of (*S,S*)- and (*R,R*)-**5**, and the two chiral channels **B** and **B'** absorbed two molecules of their preferred enantiomers, (*S,S*)- and (*R,R*)-**5**, respectively (Figure 4c and Figure S4). The guest composite is thus formulated as  $\{[(RR)_2(SS)_2] \cdot (RR)_2(SS)_2\}$ , which favors neither *RR* nor *SS* enantiomers. In this case, however, the guest occupancies are unequal and much in favor of (*S,S*)-**5**. Channel **A** includes two (*S,S*)-**5** guests in 71% and 53% occupancy, and concomitantly two (*R,R*)-**5** guests in 44% and 40% occupancy. Similarly, channel **B** includes two (*R,R*)-**5** guests in 74% and 72% occupancies, whereas channel **B'** contains two (*S,S*)-**5** guests in 96% and 93% occupancies. Most probably, the noncentrosymmetric space group  $P2_12_12_1$  stemmed from the difference in the occupancies of the two enantiomers, which are in favor of (*S,S*)-**5** enantiomers. Accordingly, the crystallographic observation confirms the configuration of the major enantiomer of **5** to be *SS*.



**Figure 4.** a) X-ray crystal structure of **4** that possesses a triangular-shaped achiral channel (**A**) and two rectangular-shaped chiral channels (**B** and **B'**, enantiomeric). b, c) Crystal structure of **4**·**5** inclusion complex. “*R*” (blue) and “*S*” (red) in the drawings represent *RR* and *SS* enantiomers, respectively. b) *RR* enriched sample of **5** (52% *ee*). c) *SS* enriched sample of **5** (17% *ee*). Top views of **4**·**5** complex are shown along with the side views of the accommodated guests. *RR* and *SS* enantiomers are shown in blue and yellow, respectively. Solvent molecules are omitted for clarity.

It is noteworthy that the noncentrosymmetric space group arises from only the unequal occupancies of the two enantiomers included in the centrosymmetric host lattice. To confirm the validity for the absolute structure assignment, we also examined the 20% *ee* sample of (*R,R*)-**5**. In the crystal structure, once again guest occupancies are in favor of (*R,R*)-**5**, being almost a mirror image to that of 17% *ee* (*S,S*)-**5** (Figure S5).

The distinct discrimination of absolute structure with CS **4** was further demonstrated for some other low *ee* chiral compounds. The inclusion of *p*-toluenesulfonamide (**6**), a sulfur-chirogenic auxiliary that finds important application in chiral amine synthesis, was examined with CS **4**. A sample with 66% *ee* of (*S*)-**6** was subjected to guest inclusion with CS **4** at 50 °C for 1 d. Crystallographic analysis of the inclusion crystal **4**·**6** demonstrated the distinct recognition features of channels **A**, **B** and **B'** (Figure 5a and Figure S6). Three (*S*)-**6** guest molecules (Occ. 48%, 46%, 45%) are found in channel **A**. Channel **B** shows the occurrence of two (*S*)-**6** (Occ. 92% and 91%), whereas **B'** is filled with one (*S*)-**6** and one (*R*)-**6** (Occ. 51% and 65%, respectively). The ratio of the total occupancies of (*S*)-**6** to (*R*)-**6** is roughly estimated to be 5:1, comparable to the enantiomeric ratio of the analyte exam-



**Figure 5.** a) An asymmetric unit of 4-6 crystal structure obtained from 66% *ee* (*S*) sample of 6. b) Molecular structure of (*S*)-7 observed in the 4-7 crystal structure. Thermal ellipsoids (50% probability level) of (*S*)-7 with the highest occupancy are shown.

ined. This ratio was also experimentally confirmed by chiral HPLC analysis after extracting the absorbed guest from the CS 4 (67% *ee* *S*, Figure S18). In this *S*-enriched crystal, Flack (Parsons) parameter of 0.041(2) suggests the effective chirality transfer to the host framework. Likewise, we performed guest absorption with 55% *ee* sample of (*R*)-6. Guest occupancies are now in favor of (*R*)-6 and we observed an enantiomerically pure composite with a Flack (Parsons) parameter of essentially zero (0.000(2)) (Figure S7).

For another example, 4-bromo- $\alpha$ -methylbenzylalcohol (7) with 47% *ee* gave inclusion crystal 4-7 for X-ray diffraction analysis (Figure 5 b and Figures S8 and S9). The structure was solved in a non-centrosymmetric  $P2_12_12_1$  space group. Notably, ten independent guests are observed in favor of the *S* enantiomer (Figure S9): one molecules of (*S*)-7 and two molecules of (*R*)-7 in channel A, while five molecules of (*S*)-7 and two molecules of (*R*)-7 in the channels B and B', respectively. Flack (Parsons) value of 0.012(1) confirmed *S* absolute configuration assignment for the major enantiomer.<sup>[28]</sup>

In summary, we have discovered a new crystallization phenomenon on non-enantiopure chiral compounds, namely, conglomerate crystal formation of both enantiomers with unequal proportion within a CS lattice. This phenomenon is characteristic to "post-crystallization" that is a guest ordering process in the predetermined CS lattice, and is conceptually different from what was observed in common batch crystallization. In a practical standpoint, we provide here a new method to determine the absolute configurations of low *ee* samples using the CS method. This is particularly important in

the analysis of non-enantiopure compounds at situations frequently encountered in asymmetric synthesis studies.

## Experimental Section

**Guest inclusion using CS 1.** A solution of compound 3 (500  $\mu\text{g}$ ) in hexane (50  $\mu\text{L}$ ) was added to a microvial including a crystal of crystalline sponge 1 in hexane (5  $\mu\text{L}$ ). A screw cap of the microvial was pierced with a syringe needle and the solvent was slowly evaporated over 1 d at 50  $^\circ\text{C}$ . The resulting crystal was subjected to single crystal X-ray analysis.

**Guest inclusion using CS 4.** A crystal of 4 was soaked in a solution of hexane (45  $\mu\text{L}$ )/dichloromethane (5  $\mu\text{L}$ ) of compound 5 (27  $\mu\text{g}$ ) in a microvial. A screw cap of the microvial was pierced with a syringe needle and the solvent was slowly evaporated over 1 d at 50  $^\circ\text{C}$ . The resulting crystal was subjected to single crystal X-ray analysis.

**HPLC analysis of inclusion crystal extract.** The inclusion crystals (3–5 crystals) were picked out from the vial with analyte samples and placed in a new vial. The sponge crystals were subsequently washed with hexane/dichloromethane (9:1 ratio, 500  $\mu\text{L} \times 3$ ) to remove physisorbed analyte on the crystal surface. THF (500  $\mu\text{L}$ ) was next added to the vial and it was incubated at rt. After 12 h, the crystals were digested and the solvent was removed under reduced pressure. The residual was extracted with DCM (400  $\mu\text{L}$ ) and the extract was subjected to HPLC analysis.

**X-ray structures.** CCDC numbers for 1-3 (82% *ee*), 1-3 (59% *ee*), 4-5 (52% *ee* *R,R*), 4-5 (17% *ee* *S,S*), 4-5 (20% *ee* *R,R*), 4-6 (66% *ee* *S*), 4-6 (55% *ee* *R*), 4-7 (65% *ee* *S*) are 1810852, 1810853, 1810854, 1810855, 1810856, 1810857, 1810858, 1810859, respectively. These supplementary crystallographic data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service [www.ccdc.cam.ac.uk/structures](http://www.ccdc.cam.ac.uk/structures).

## Acknowledgements

This research was supported by Grants-in-Aid for Specially Promoted Research (24000009 and 19H05461), JST-ACCEL (Grant No. JPMJAC1304) and AMED (Grant No. 18ak0101101).

## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** absolute configuration determination · crystalline sponge method · host-guest systems · X-ray crystallography

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- [28] Inclusion crystals using 5–10% *ee* sample of **7** were prepared with CS **4** and analyzed by SCD, and Parson's Flack values close to 0.5 were obtained. It suggested that **4** cannot sense and differentiate such small differences of enantiomeric excess. However, Flack value close to zero was obtained for sample with *ee* close to 50%.

Manuscript received: February 19, 2021

Accepted manuscript online: March 21, 2021

Version of record online: April 15, 2021