Achieving Chiral Crystallization through Tailored Silyl-Substituted Dipolar Molecular Designs

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ABSTRACT

Herein, we present a molecular design based on trimethylsilyl (TMS)-and triisopropylsilyl (TIPS)-substituted dipolar units, which enable the formation of chiral crystals ($P2_12_12_1$ space group) from achiral molecules. Single-crystal X-ray diffraction analysis revealed that the smaller steric effects introduced by the TMS led to the formation of crossed chiral dimers, while the bulky TIPS groups acted as shielding sites, allowing the chiral dimers to stack one-dimensionally into polar chains via dipole-dipole interactions of 2,3-difluorobenzene units with 2_1 helical symmetries.

Comparative analyses of related derivatives indicated that a delicate balance is required in the molecular design to achieve such chiral assemblies. This study highlights the importance of introducing appropriate bulky shielding sites and interactive sites to achieve chiral crystallization and provides valuable guidance for designing chiral assemblies from achiral dipolar molecules.

■ Introduction

Chiral crystallization of achiral molecule is an uncommon phenomenon in organic chemistry.[1–3] Some achiral molecules, such as benzophenone, phenol, phenanthrene, and 4-aminopyridine, are known to form chiral crystals from their solutions despite the absence of an asymmetric center in the molecule.[1] In these crystals, C=O···HC(ph) interaction,[1,4] hydrogen bonding,[1,5] and CH–π interactions[1,6,7] serve as the main intra- and intermolecular interactions (Table S1). It has also been reported that achiral molecules such as diaryl ethers,[8] diaryl ketones,[1] indolyl sulfonamides,[9] and nitroanilines[10] tend to form chiral crystals. This mainly occurs through mirror symmetry breaking in the formation of the crystalline nuclei, followed by the growth of crystalline lattice, which is important for understanding the origin of homochirality in biological systems. Achiral molecules that form chiral crystals are often discovered by chance, and among them, chiral crystals exhibiting $P2_12_12_1$ space group are relatively common.[2,3] However, prediction of the crystal structure of an organic molecule based on its chemical structure is challenging, and rational design of achiral molecules that can form homochiral crystals is still difficult.[11–13] Development of novel achiral molecular design principles for constructing a chiral crystal structure and detailed investigation of the intermolecular interactions can provide crucial insight into the design of chiral crystallization.[1,8–10,13–29] In addition, chiral crystals have also found applications in chiroptical

materials and absolute asymmetric synthesis.[1,2] Therefore, the molecular design for chiral crystallization is also an important research topic in the material applications of molecular crystals.

In a previous study, we discovered achiral molecules in which a halogen (Br or I) atom and bulky triisopropylsilyl (TIPS) groups were introduced at the *para*-position of polar 2,3-difluorobenzene to form chiral crystals ($P6_1$ and $P6_5$ space groups) (Figure 1a and Table 1).[30] These molecules form chiral trimers through attractive and directional halogen–halogen interactions among the three Br or I substituents. The TIPS group functions as a bulky shielding site around the polar units, allowing the chiral trimers to stack into polar chains via dipole-dipole interactions of the 2,3-difluorobenzene units, leading to the formation of chiral crystals. The corresponding molecules without halogen atoms form achiral crystals.[30] This study suggests that molecular design that introduces an attractive interaction site to form chiral molecular assemblies and employs a bulky shielding site around the polar units to separate stacked polar chains is important for chiral crystallization. Therefore, this study will provide valuable guidance for the design of chiral crystals.

Inspired by these results, we conducted several screenings to discover other examples and generalize the chiral crystallization of achiral molecules using similar molecular design. As a result, we discovered achiral molecule **1** forming a chiral crystal ($P2_12_12_1$ space group) (Figure 1b and Table 1). Single-crystal X-ray diffraction (XRD) analysis revealed that **1** formed a crossed chiral dimer as a result of the weak steric hindrance between the TMS and the phenyl group, which were closely stacked through CH-π interactions. The TIPS group functions as a bulky shielding site around the dipole units, allowing the chiral dimers to arrange one-dimensionally into polar chains via dipole-dipole interactions among the polar 2,3-difluorobenzene units with 2_1 helical symmetries. We further found that this molecular design relies on a delicate balance of intermolecular interactions, so that either the reversal of the positions of the interaction site (TMS)

and the shielding site (TIPS) or the change of TIPS to *tert*-butyldimethylsilyl (TBS) results in a packing with a symmetry center, leading to the formation of achiral crystals.

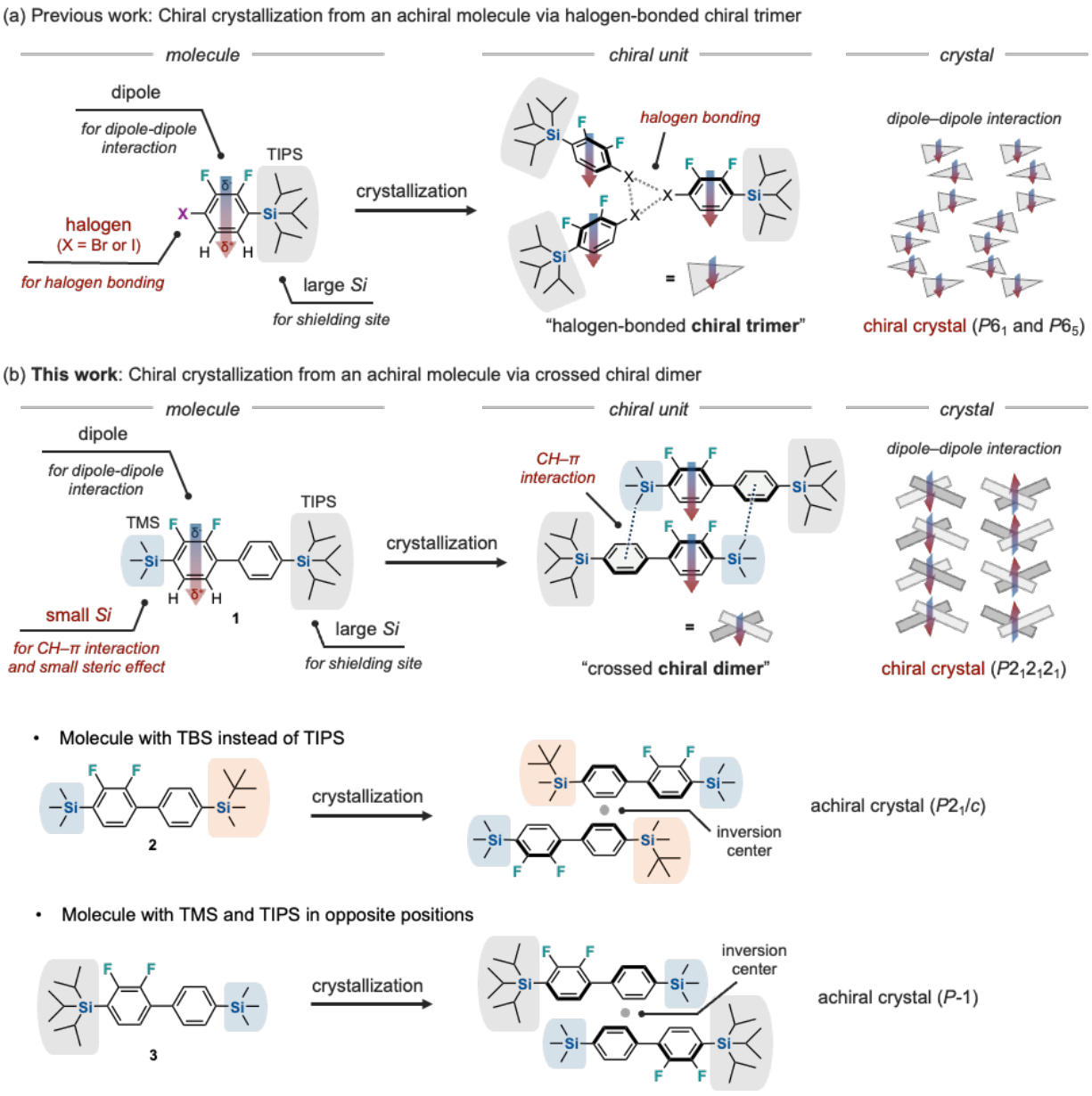
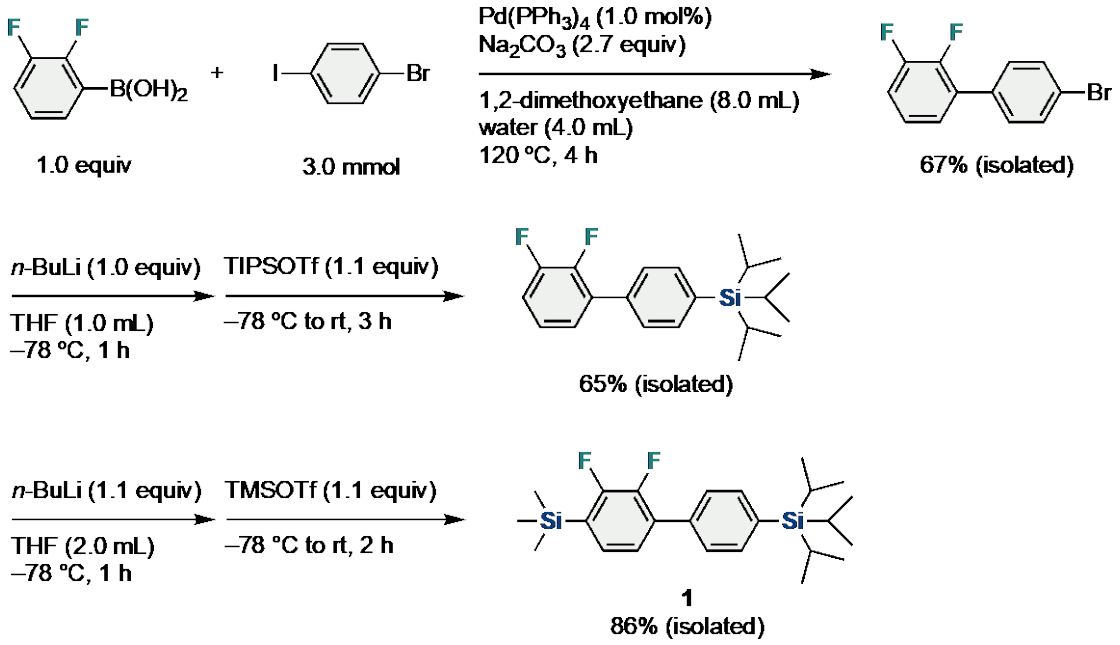


Figure 1. (a) Previous work; chiral crystallization from an achiral molecule via halogen-bonded chiral trimer. (b) This work; chiral crystallization from an achiral molecule via crossed chiral dimer.

■ Results and Discussion

Synthesis and preparation

Dipolar compound **1** was synthesized in three steps (Scheme 1). Palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of (2,3-difluorophenyl)boronic acid and 1-bromo-4-iodobenzene afforded 4'-bromo-2,3-difluoro-biphenyl in 67% yield.[31] The TIPS group was first introduced to the phenyl moiety in good yield with triisopropylsilyl trifluoromethane sulfonates (TIPSOTf) after the lithiation of the C–Br bond by *n*-BuLi.[30] The TMS group was then introduced by C–H lithiation at the 4-position of the 2,3-difluorophenyl group with *n*-BuLi and subsequent addition of trimethylsilyl trifluoromethane sulfonates (TMSOTf) in good yield. The crystals of **1** were obtained by slow evaporation of a hexane solution of **1** at room temperature in air.



Scheme 1. Synthesis of dipolar compound **1** with TMS and TIPS.

Crystal structure analysis of 1

To investigate the crystal structure of **1**, the crystals prepared using the above method were analyzed by single-crystal XRD. Molecule **1** crystallized in the $P2_12_12_1$ space group (Figure 2 and Table 1). Interestingly, **1** formed a crossed dimer in the crystal and these two molecules were oriented head-to-head (Figure 2a). In the dimer, one of the hydrogen atoms of the TMS group is located on top of the neighboring phenyl group at the distances of 2.671 or 2.806 Å, indicating the formation of CH–π interactions (Figure 2b). The steric hindrance between the TMS and phenyl groups causes a distorted antiparallel orientation of the two molecules, resulting in the formation of a crossed dimer. The steric effect involving the TMS moiety and the phenyl group also resulted in the crossed π–π interaction of the dipolar 2,3-difluorophenyl groups with 3.627 Å in the crystal. The crossed dimers were arranged into one-dimensional polar chains through dipole-dipole interactions among the 2,3-difluorophenyl groups, with intermolecular fluorine-hydrogen atom

distances ranging from 2.614 to 2.646 Å (Figure 2c). The bulky TIPS groups of the dimer act as shielding sites for the polar units, packing adjacent to the less sterically crowded biaryl moieties (Figure 2d). The distances between the hydrogen atoms of the TIPS groups and π units of the phenyl group and 2,3-difluorophenyl group are 2.868–3.145 Å, suggesting the formation of CH–π interactions. These intermolecular CH–π interactions, along with the steric repulsion caused by the bulky TIPS, led to a zigzag arrangement of the dimer in the crystal (Figure 2d).

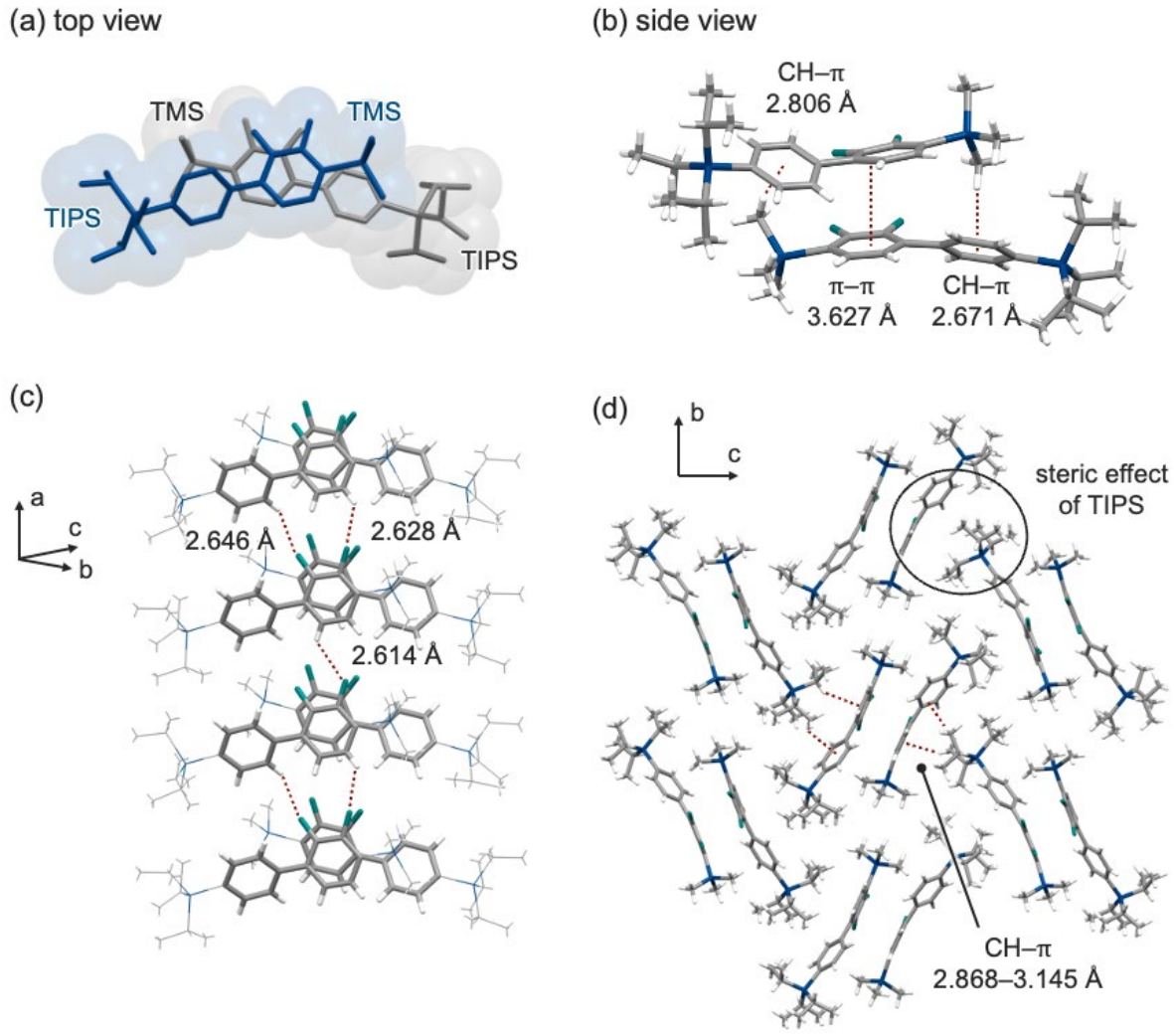


Figure 2. Crystal structure of **1**. (a) Top view of the dimer. Hydrogen atoms are omitted for clarity. (b) Side view of the dimer. CH–π distances and a π–π distance in the dimer are shown. (c) One-dimensional grown polar chain of the dimers. Intermolecular F–H distances are shown. (d) Packing structure of the dimer in the *bc* plane. CH–π distances between the hydrogen atoms of the TIPS groups and π units of the phenyl group and 2,3-difluorophenyl group are shown.

We investigated the chirality of the crystal structure of **1**. In the crystal structure of **1**, the asymmetric unit is the chiral dimer of **1** (Figure 2a and b). Identical enantiomeric dimer structures were observed in the crystal. The second structural feature of chirality is the molecular packing. The $P2_12_12_1$ space group exhibits 2_1 helical symmetries along all axes.[32] In the crystal of **1**, 2_1 helical symmetries were observed for all axes, as shown in Figure 3. The crossed dimers elongated the linear polar chains, resulting in the formation of 2_1 helical symmetries along the *a*-axis (Figure 3, left). For the *b* and *c* axes, the dimers were packed in zigzag 2_1 helical structures, while avoiding the steric hindrance of the TIPS groups between adjacent molecules (Figure 3, center and right).

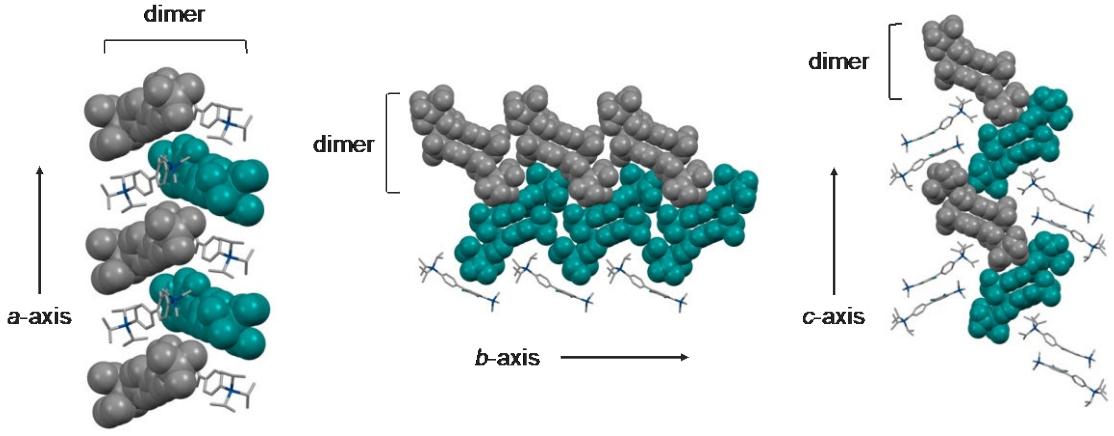


Figure 3. 2_1 Helical symmetries for all axes. Hydrogen atoms are omitted for clarity.

Molecule 2 with TBS instead of TIPS

To investigate the effects of the TIPS group as a shielding site in the crystal structure of **1**, we synthesized compound **2** with a TBS group that differs in size and shape from the TIPS group. **2** was synthesized by a synthetic procedure similar to that of **1** using TBSOTf instead of TIPSOTf (Supporting Information). Single crystals of **2** were obtained by the slow addition of EtOH to a diethyl ether solution of **2**. Single-crystal XRD analysis revealed that **2** crystallized in the achiral $P2_1/c$ space group (Figure 4 and Table 1). In the crystal structure of **2**, hydrogen bonding between a fluorine atom on the 2,3-difluorophenyl group and a hydrogen atom of the TMS moiety was observed at a distance of 2.557 Å, which was not observed in the crystal of **1** (Figure 4a). Additionally, the distance between the phenyl group and the nearest hydrogen atoms of methyl group on the TBS is 2.882 Å, indicating the presence of intermolecular CH–π interaction (Figure 4a). The molecular packing of **2** shows a symmetric center, resulting in the formation of achiral crystal (Figure 4a and b). One possible reason for the symmetric packing is that the shape of the TBS, particularly its two small methyl groups, was not an ideal shielding site, and instead leads to its participation in the CH–π interactions with the phenyl group. These results suggest that the asymmetric crystal structure of **1** relies on a delicate balance of intermolecular interactions and that TIPS is an appropriately shaped and sized shielding site for **1** to form a crossed chiral dimer and 2_1 helical structures in the crystal.

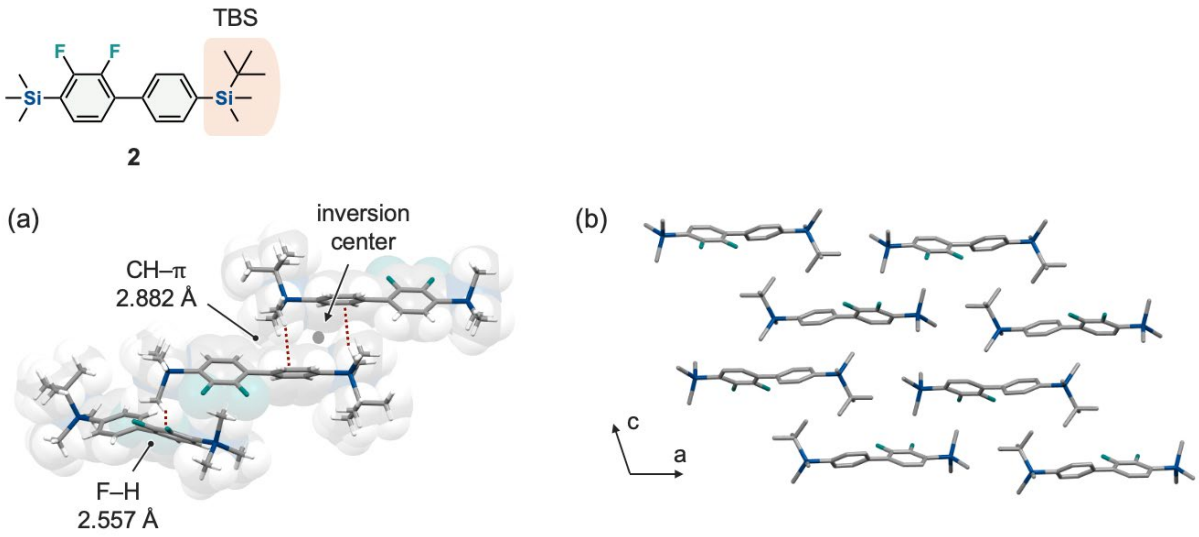


Figure 4. Crystal structure of **2**. (a) Intermolecular interactions in the crystal. CH–π distances and F–H distances are shown. (b) Packing structure. Hydrogen atoms are omitted for clarity.

Molecule 3 with TMS and TIPS in opposite positions

Next, we synthesized compound **3** to study the effect of the positions of the two silyl groups (for the synthesis, see Supporting Information). In **3**, a TMS group was introduced at the 4-position of the phenyl group, and a TIPS group was introduced at the 4-position of the 2,3-difluorobenzene group, so that the two silyl groups are introduced at the opposite sites in comparison to **1**. The crystals of **3** were obtained by slowly cooling the heated methanol solution of **3** to room temperature. Interestingly, single-crystal XRD analysis revealed that **3** crystallized in the achiral *P*-1 space group, even though its molecular components were the same as those of **1** (Figure 5 and Table 1). In the crystal of **3**, a dimer structure via CH–π interactions and a π–π interaction was observed, similar to crystal **1** (Figure 5a). However, molecule **3** formed a nonpolar dimer in the crystal with an inversion center, as shown in Figure 5a. These results show that the positions of the interactive sites (TMS and Ph) and the bulky shielding group (TIPS) around the polar moiety

are crucial for enabling **1** to form a chiral dimer unit and chiral molecular arrangement in the crystal. Although the achiral dimer was formed, the bulky TIPS groups also acted as shielding sites in the crystal of **3**, separating the diagonally stacked structures where the dimers elongated the polar chains through dipole-dipole interactions (Figure 5b). These results also suggest that the chiral crystal structure of **1** relies on a delicate balance of intermolecular interactions of the TIPS, TMS, phenyl, and 2,3-difluorobenzene groups.

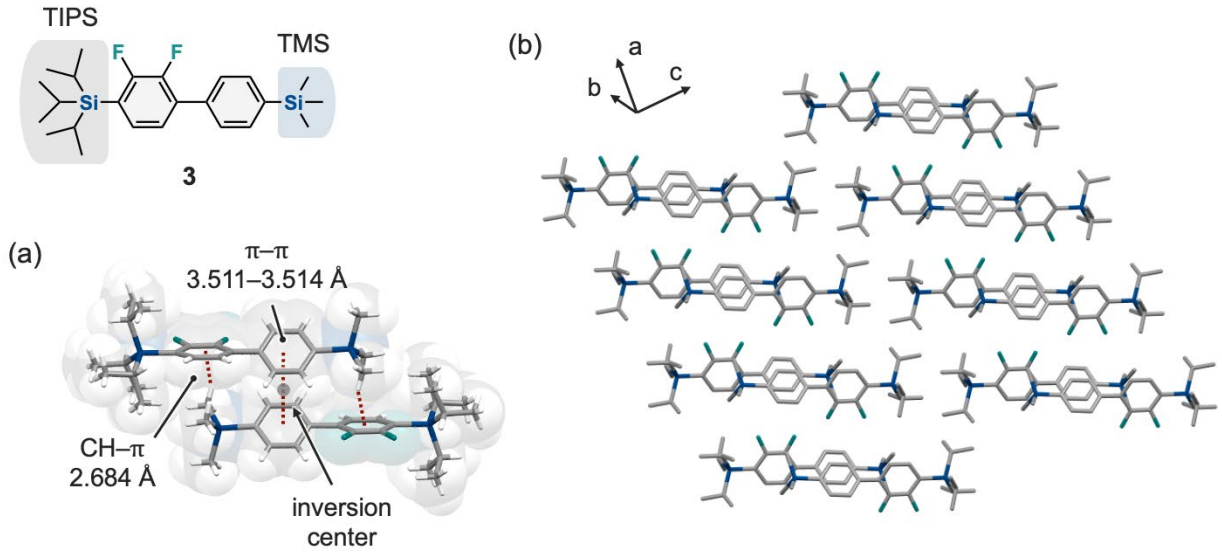


Figure 5. Crystal structure of **3**. (a) Dimer structure of **3** and their intermolecular interactions. CH–π distances and a π–π distance are shown. (b) Packing structure. Hydrogen atoms are omitted for clarity.

Table 1. Summary of X-ray crystallographic data of the crystal **1**–**3** and two previously reported chiral crystals.

Compound	**1**	**2**	**3**	**ref 30-Br**[d]	**ref 30-I**[d]
CCDC Number	2422351	2422352	2422353	2244412	2244414
Empirical Formula	$C_{24}H_{36}F_2Si_2$	$C_{21}H_{30}F_2Si_2$	$C_{24}H_{36}F_2Si_2$	$C_{15}H_{23}BrF_2Si$	$C_{15}H_{23}IF_2Si$
Formula Weight	418.71	376.63	418.71	349.33	396.32

Crystal System	orthorhombic	monoclinic	triclinic	hexagonal	hexagonal
Crystal Size / mm	0.1× 0.1 × 0.1	0.1× 0.1 × 0.1	0.1× 0.1 × 0.1	0.1 × 0.1 × 0.05	0.1 × 0.02 × 0.02
a / Å	13.75950(10)	15.8492(2)	7.7895(2)	14.94670(10)	15.27480(10)
b / Å	14.59960(10)	7.16140(10)	8.8353(2)	14.94670(10)	15.27480(10)
c / Å	24.3505(2)	20.4904(2)	19.2669(3)	39.0988(2)	38.7387(4)
α / °	90	90	78.2210(10)	90	90
β / °	90	105.6720(10)	78.464(2)	90	90
γ / °	90	90	70.915(2)	120	120
V / Å^3	4891.61(6)	2239.25(5)	1213.94(5)	7564.57(11)	7827.56(13)
Space Group	$P2_12_12_1$	$P2_1$/c	P-1	$P6_1$	$P6_1$
Z value	8	4	2	18	18
D_{calc} / g cm^{-3}	1.137	1.117	1.145	1.380	1.513
Temperature / K	153	153	153	153	153
$2\theta_{max}$ / °	153.49	152.706	152.724	150.386	153.26
μ (Cu Kα) / mm^{-1}	1.491	1.580	1.502	4.076	15.184
No. of Reflections	Total: 47100 Unique: 9966 R_{int} = 0.0338	Total: 16119 Unique: 4532 R_{int} = 0.0315	Total: 44561 Unique: 4883 R_{int} = 0.0758	Total: 58358 Unique: 10186 R_{int} = 0.0409	Total: 69644 Unique: 10668 R_{int} = 0.0493
R_1[a]	0.0299	0.0371	0.0607	0.0365	0.0359
wR_2[b]	0.0840	0.1034	0.1906	0.0972	0.0866
GOF[c]	1.054	1.065	1.088	1.030	1.032
Max./Mini. peak I/ Å^3	0.20 e$^-$/−0.24 e$^-$	0.28 e$^-$/−0.41 e$^-$	0.77 e$^-$/−0.63 e$^-$	0.59 e$^-$/−0.55 e$^-$	0.96 e$^-$/−0.76 e$^-$
Flack parameter	–0.007(7)			0.007(12)	0.002(3)
Main interaction	Small steric effect (Ph and TMS) Dipole-dipole interaction Bulky shielding site	CH–π interaction	CH–π and π–π interaction Bulky shielding site	Halogen bonding Dipole-dipole interaction Bulky shielding site	Halogen bonding Dipole-dipole interaction Bulky shielding site

[a]: $I > 2.00\sigma(I)$. [b]: All reflections. [c]: Goodness of Fit Indicator. [d] For these molecules, crystals of $P6_5$ space group were also obtained.[30]

Potential symmetry breaking in a crystallization vessel

During the measurement of multiple chiral crystals of **1**, we discovered an intriguing symmetry breaking phenomenon. We performed single-crystal XRD analysis on 10 different single crystals of **1** in the vial in which crystallization was performed. Interestingly, the results showed that all 10 crystals were the same enantiomers. In another vial, where crystallization was performed under the same conditions, only the opposite enantiomers were present. These results suggest that the initial nucleation step in the crystallization of **1** is slow. Once the chiral crystal nucleus is formed, its rapid dispersion into the second nucleus and subsequent crystal growth result in the formation of a single-enantiomer crystal.[33,34] We note that only one enantiomer of crystalline sample was observed in each vial.

Conclusion

We constructed a chiral crystal from an achiral molecule using a crossed chiral dimer based on a silyl-substituted dipolar molecule. Single-crystal XRD analysis of **1** revealed that the TMS and the phenyl group were closely stacked through CH–π interactions, and their small steric effects led to the formation of head-to-head crossed dimers. The TIPS groups acted as bulky shielding sites around the polar units, enabling the chiral dimers to stack one-dimensionally into polar chains through the dipole-dipole interactions of the polar 2,3-difluorobenzene units with 2_1 helical symmetries. This result demonstrates the importance of introducing appropriate bulky shielding sites and interactive sites to form chiral dimer units for achieving chiral crystallization. Comparative analyses of the crystal structures of **1**, **2** and **3** revealed that the chiral crystal structure of **1** relies on a delicate balance of intermolecular interactions. This study provides valuable

insights into the design of chiral crystals from achiral molecules based on the combination of silyl substitution and dipolar moieties.

ASSOCIATED CONTENT

Supporting Information.

X-ray crystallography, NMR profiles, and other additional information. These materials are available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written with contributions from all authors. All the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Manuscript title: Achieving Chiral Crystallization through Tailored Silyl-Substituted Dipolar Molecular Designs

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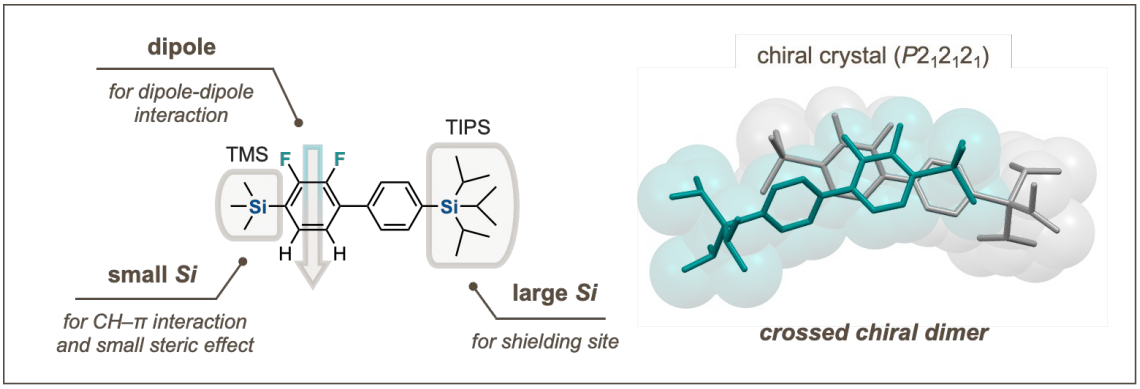
TOC graphic:



Synopsis:

A novel molecular design based on trimethylsilyl (TMS)-and triisopropylsilyl (TIPS)-substituted dipolar units is reported, which enable the formation of chiral crystals ($P2_12_12_1$ space group) from achiral molecules.