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Dynamic Control over Supramolecular Handedness by Selecting Chiral Induction Pathways at the Solution-Solid Interface

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Abstract:

A dominant theme within the research on two-dimensional (2D) chirality is the sergeant-soldiers principle, where a small fraction of chiral molecules is used to skew the handedness of achiral molecules to generate a homochiral surface. Here we present an eloquent combination of sergeant-soldiers principle and temperature-dependent molecular self-assembly to unravel a unique chiral amplification mechanism at the solution-solid interface. We demonstrate that, depending on the concentration of a sergeant-soldiers solution, the majority handedness of the system can be amplified or entirely reversed after an annealing step furnishing a homochiral surface. Two discrete pathways that affect different stages of 2D crystal growth are invoked for rationalizing this phenomenon. We present a unique set of experiments where the access to each pathway can be precisely controlled. Our results demonstrate that a detailed understanding of subtle intermolecular and interfacial interactions can be used to induce drastic changes in the handedness of a supramolecular network.

Homochirality, a hallmark of the (bio)chemistry that supports life on planet earth, is believed to have evolved in three discrete steps namely, mirror-symmetry breaking, chiral amplification and chiral transmission.¹ The study of these aspects in noncovalent systems has been a subject of immense interest for more than a decade.² The fact that only small amount of chiral molecules (the sergeants) are necessary to bias the handedness of the supramolecular structure of achiral building blocks (the soldiers) was established through the pioneering studies of Green et al. on macromolecular assemblies in solution and has since become popular as the 'sergeant and soldiers' principle.³

One of the simpler ways to understand chiral induction phenomena is via the study of self-assembly of organic building blocks on solid surfaces.⁴⁻⁶ The non-centrosymmetric nature of an interface ensures that chirality is easily achieved in two dimensions. Enantiomers often undergo spontaneous resolution into a conglomerate of mirror image domains. Even prochiral molecules form chiral domains however, the surface remains globally achiral due to formation of equal areas of opposite handed domains.⁶ Mirror symmetry breaking in such globally achiral surfaces can be achieved by forcing the achiral molecules to assemble in only one particular handedness to produce homochiral networks. Analogous to supramolecular systems in solution, chiral induction principles have been successfully used to fabricate homochiral surfaces.⁷⁻¹⁴

The general principles of supramolecular chemistry have come in handy for understanding different aspects of chiral induction phenomena. Conversely, handedness of a supramolecular aggregate can also be used as a probe to comprehend fundamentals of molecular self-assembly.¹⁵⁻¹⁷ An elegant example of such synergistic approach is a report by Meijer and coworkers¹⁸ who used the helicity of a chiral supramolecular polymer as an indicator to provide quantitative insight into competing pathways accessible to the self-assembling system in solution. With the mechanistic information obtained from temperature and concentration dependent experiments, they could change the thermodynamic preference of the assembly process to promote exclusive formation of metastable assemblies.¹⁸

In the recent past we have employed the sergeant-soldiers principle to fabricate low-density homochiral networks at the solution-solid interface using alkoxy dehydrobenzo[12]annulene derivatives (DBAs, Fig. 1a) as the model system.¹⁹ The design of chiral DBAs (cDBAs), provided precise control over the subtle intermolecular interactions between cDBA and achiral DBA molecules in a sergeant-soldiers experiment, where the chirality of the sergeant cDBA defined the handedness of the supramolecular network.²⁰ The resulting periodic lattice of shallow nanowells with well-defined handedness can serve as a unique platform for segregation of enantiomers based on enantioselective host-guest adsorption. We recently validated this concept where cDBAs were found to exhibit enantioselective adsorption in chiral nanowells.²¹

Using scanning tunneling microscopy (STM) as an experimental tool and combining concentration control with temperature variation in classic sergeant-soldiers experiments, here we unveil competitive chiral amplification pathways transpiring at the solution-solid interface. Employing the handedness of the network as a marker to identify two discrete pathways operative during different stages of 2D crystal growth, we report a unique chiral amplification pathway based on enantioselective guest adsorption. Notably, the competing amplification pathways lead to monolayers of opposite handedness. We show that it is possible to ‘select’ between the two pathways not only based on solute concentration and annealing protocol, but also on the type of the sergeant and the solvent. Finally, the annealing experiments described here furnish homochiral surfaces composed of only achiral molecules, a feat that has been rarely^{11, 12} achieved (Fig. 2). These results demonstrate that the chiral composition of the self-assembling system critically depends on the sample history.

Results and discussion

Induction and reversal of the initial majority handedness. Alkoxy substituted DBAs are arguably one of the most intensively studied building blocks at the solution-solid interface.¹⁶ DBA derivatives form porous supramolecular networks via interdigitation of peripheral alkoxy chains.

Fig. 1b shows “clockwise” (CW) and “counterclockwise” (CCW) nanowells. The labels CW and CCW refer to the sense of rotation of the six alkoxy chains making up the rim of the nanowell. The chirality of the nanowells is domain specific.^{19, 20}

The design principle underlying the formation of porous homochiral networks using cDBA-OC12(S) and cDBA-OC12(R) (Fig. 1a) has been described in detail elsewhere.^{20, 21} The S- and the R- enantiomers exclusively form CW and CCW nanowells, respectively. These cDBAs can also act as chiral seeds in a sergeant-soldiers experiment and induce their own handedness in monolayers of achiral DBA-OC12 (Supplementary Fig. S2). While such design principles provide an eloquent tool to control the handedness of supramolecular networks, recent wisdom indicates that self-assembling systems often follow competing pathways and the access to each can be tuned by choice of experimental parameters such as temperature,^{22, 23} solvents,^{24, 25} light^{26, 27} and growth history.²⁸ It is well-known that annealing of samples leads to an increase in size of molecular domains. This coarsening is reminiscent of Ostwald ripening observed during bulk crystallization of materials. The results described below originate from such temperature-assisted ripening experiments, which were employed to improve the efficiency of homochiral induction in sergeant-soldiers experiments involving cDBA-OC12(S).²⁰

Deposition of a 1-phenyloctane solution of DBA-OC12 containing 10 mol% cDBA-OC12(S) ($C = 5.0 \times 10^{-7}$ M) on HOPG yields a surface with 91% CW nanowells at room temperature (RT, Fig. 3a). Annealing this sample slowly (2 °C/min) to 80 °C resulted in coarsening of domains which reach sizes of more than 300×300 nm². The increase in domain size was also accompanied by improvement in the chiral composition of the system with the surface exclusively covered with CW nanowells at 80 °C (Fig. 3d). This result is in line with the expectation that ripening will promote the growth of CW domains thus consuming the underrepresented CCW molecular domains. Annealing of the samples thus improved the efficiency of chiral induction. The characteristic STM contrast of cDBAs (Fig. 3b) makes it relatively straightforward to identify them from DBA-OC12 molecules in the monolayer. A careful inspection of the samples after cooling

down to RT revealed a homochiral surface entirely composed of achiral DBA molecules. This observation implies desorption of cDBA-OC12(S) during the annealing step due to its lower adsorption energy relative to DBA-OC12 (Supplementary Fig. S3).²⁰

Annealing experiment carried out with cDBA-OC12(S)/DBA-OC12 system at higher concentration ($C = 2.5 \times 10^{-6}$ M) however, furnished a rather puzzling result. Starting with 81% surface coverage of CW nanowells at RT (Fig. 3e), the system evolved into a homochiral network of CCW nanowells upon annealing at 80 °C (Supplementary Fig. S4). This reversal of the majority handedness upon annealing is unprecedented and thus the mechanism behind such chiral reversal process merits special scrutiny. It must be noted that at RT, the preferred (majority) handedness of the network is CW and it is induced by incorporation of cDBA-OC12(S) sergeants in the monolayer formed by DBA-OC12. Thus, the initial mirror symmetry breaking in the system occurs via the sergeant-soldiers pathway which has been well-documented.²⁰ The reversal was observed only after the annealing step, which indicates that there emerges a second induction pathway during annealing that primarily affects the ripening stage of the 2D crystal growth. Furthermore, the homochiral CCW phase obtained after the annealing step did not appear as a new phase but instead grew from the existing surface composition at the expense of CW domains during ripening. This fact was corroborated by starting with a homochiral CW surface at RT, which led to no reversal of the majority handedness upon annealing (Supplementary Table S2). At intermediate concentrations, the system showed varying degree of chiral induction after annealing (Fig. 3e), which is in line with the presence of two competing concentration regimes.

In the experiments described above, the handedness of the network obtained after annealing did not change upon returning to RT over an observation window of 24 hours. This indicates that the homochiral surface obtained at higher temperatures is stable at RT. Perturbation of such homochiral surface using voltage pulses applied to the STM tip however, results in the local generation of opposite handed domains (Supplementary Fig. S5).

The monolayer obtained from a mixture of cDBA-OC12(*R*)/DBA-OC12 gave rise to CW homochiral surface (majority handedness at RT is CCW) after annealing, further confirming the reversal of the majority handedness under similar experimental conditions. Last but not the least, annealing of achiral DBA-OC12 monolayers did not furnish a homochiral surface and the system always remained globally racemic similar to that observed at RT (Supplementary Fig. S6).

Mechanism behind the chiral reversal process. The contrasting results obtained in the two concentration regimes should be interpreted in the context of the different stages involved in 2D crystal growth. Similar to bulk crystallization of materials, self-assembly of molecules at the solution-solid interface also proceeds in three distinct stages namely, nucleation, free growth and ripening.²⁹ Nucleation involves adsorption of molecules from the solution onto the surface followed by their 2D diffusion to form small clusters. This highly dynamic process involves constant formation and dissolution of molecular clusters till they reach a certain critical size. Nucleation is followed by free growth of the domains, where molecules are added to growing crystallites. Growth is terminated when the domains touch each other producing grain boundaries that limit further growth. Once the entire surface is covered with molecules, ripening starts between neighboring domains via a net flux of molecules from one domain to the other. This process is typically believed to occur via gradual shift of the interdomain border such that it leads: (1) to growth of the most stable phase and/or (2) to the reduction of domain boundaries to produce larger domains.³⁰

Analysis of the STM images obtained in the two concentration regimes revealed that the relative sizes of the CW and CCW domains are comparable (Supplementary Table S1). The CW and CCW domains represent enantiomorphous structures formed at the interface of an achiral solid (HOPG) and an achiral solvent (1-phenyloctane). Incorporation of cDBA-OC12(*S*) changes the chiral composition of the system via the sergeant-soldiers mechanism where CW supramolecular handedness defined by the chirality of cDBA-OC12(*S*) is amplified (Fig. 3b,c).²⁰ The cDBA-OC12(*S*) molecules also occupy CCW nanowells (preferentially) as guests (Fig. 4).²¹ The cDBA-

OC12(*S*) molecules respond differently to the increase in the concentration and temperature in these two different roles.

By design, cDBA-OC12(*S*) sergeants can only be incorporated in CW domains of achiral DBA-OC12. Although enthalpically disfavored due to lower adsorption energy of cDBA-OC12(*S*), this incorporation is an entropically favored process yielding 4-6% sergeants in the CW domains at RT for a wide range of concentrations. At higher temperatures, cDBA-OC12(*S*) sergeants are desorbed from the surface (Supplementary Table S1). The cDBA-OC12(*S*) guests which preferentially adsorb in the CCW nanowells²¹ (Table 1) however, form stable host-guest complexes which could be observed even at elevated temperatures (Supplementary Fig. S7). The most stable host-guest configuration consists of a tightly bound complex between a CCW nanowell and a single cDBA-OC12(*S*) molecule that adopts a windmill-like conformation in the nanowell (Fig. 4c). A major energy difference between the adsorption in CCW over CW nanowells comes from fewer van der Waals contacts between the methylene units when the chirality of the nanowell does not match the direction of the windmill-like conformation of the guest. The guest conformation is defined by the absolute configuration of the stereogenic methyl groups of the cDBA molecule. Such enantioselective guest inclusion increases the relative stability of the CCW domains (Supplementary Fig. S8).

Sergeant-soldiers experiments carried out at RT clearly reveal that the host-guest pathway is not dominant during nucleation and growth stages since the handedness at RT is always determined by chirality of the sergeant. Molecular modeling revealed that the stabilization offered by an adsorbed cDBA molecule to a growing nucleus is higher when it integrates into the network as a ‘sergeant’ than when it adsorbs as a ‘guest’ into a nanowell (Supplementary Fig. S9). This analysis paints the hierarchical picture of the self-assembly process. Once the surface is entirely covered by the DBA monolayer (with a small percentage of cDBA sergeants), additional inclusion of cDBA sergeants in the network is not favored since it can only occur via replacement of achiral DBA-OC12 molecules that have higher adsorption energy. Additional stabilization of the monolayer then

occurs via host-guest complexation. The percentage of these cDBA-OC12(*S*) guests depends on the total solution concentration and determines whether or not the CCW nanowells are amplified upon annealing. It must be noted however that the relative stabilization of the nanowells is not sufficient to explain the reversal of the handedness as experiments carried out by varying the thermal history of the sample (*vide infra*) indicate that the system is not at equilibrium and strong kinetic effects are also at play.

The results obtained at intermediate concentrations where the system does not evolve into a homochiral surface can be understood as follows. The rate of ripening depends on the total length of domain borders. As ripening progresses, the rate of ripening decreases, since the length of domain borders decreases with increasing domain size. At a certain point, the energetic gain from reducing the domain borders becomes smaller than thermal energy and then ripening is said to have reached equilibrium. Experimental data suggests that under such circumstances, large domains cannot consume the neighboring large domains but the system simply oscillates on either side of the domain border (Supplementary Fig. S10). The understanding of aforementioned dichotomy in the chiral induction/reversal pathways allows manipulation of the assembly process in a predictable manner. Beginning with the premise that the sergeant-soldiers pathway prevails mostly during the nucleation and free growth stages and the host-guest based chiral reversal is pronounced during the temperature-assisted ripening, we show below multiple ways to influence the outcome of the chiral assembly process.

Table 1 Percent occupation of cDBA guest molecules in nanowells at room temperature.

System	Solvent	Concentration	% of occupied nanowells	
			CCW	CW
9:1 DBA-OC12:cDBA-OC12(<i>S</i>)	1-phenyloctane	5.0×10^{-7} M	4.5±1	1.4±1
	1-phenyloctane	2.5×10^{-6} M	33±1	1±1
	1,2,4-trichlorobenzene	1.0×10^{-3} M	1.8±0.5	1.6±0.5
94:6 DBA-OC12:cDBA-OC12(<i>S</i>)-OC13(<i>R</i>)	1-phenyloctane	2.5×10^{-6} M	0.5±0.3	0.6±0.3
1:1 DBA-OC10:cDBA-OC12(<i>S</i>)	1-phenyloctane	5.0×10^{-6} M	17.7±6.1	3.3±0.5

Control over the induction/reversal processes: Thermal history. The induction of chirality through sergeant-soldiers mechanism occurs at the nucleation step when the sergeants contribute to the formation of the nuclei equal to or larger than the critical size. The sergeants are chiral and can incorporate only into one of the two enantiomeric assemblies thus changing the chiral balance of the system. The probability of such incorporation is higher for larger critical nuclei, and hence the induction efficiency will be higher for larger critical nuclei. Classical nucleation theory articulates that an increase in temperature leads to the formation of larger critical nuclei.^{28, 31} We explored this hypothesis by performing a chiral induction experiment, where a hot solution ($C = 2.5 \times 10^{-6}$ M, DBA-OC12:cDBA-OC12(*S*) = 9:1, ~80 °C) was deposited on HOPG held at 80 °C. In line with expectation, the handedness of the network remained 100% CW (Supplementary Fig. S11) despite the fact that the same composition furnished reversal of the majority handedness (100% CCW) when RT deposition was followed by gradual annealing (Fig. 3e and Supplementary Fig. S4). Working along the same train of arguments, decreasing of the deposition temperature should lead to lower induction efficiency. Deposition of a cold solution ($C = 5.0 \times 10^{-7}$ M) on a precooled HOPG substrate (~8 °C) resulted in the formation of monolayers with significantly lower CW induction (75%), [which did not change upon annealing](#) (76% CW nanowells, Supplementary Table S1).

Control over the induction/reversal processes: Solvents. Another way to influence the outcome of the chiral assembly process is via the choice of solvents. The enantioselective host-guest interactions responsible for the reversal process were found to be solvent dependent. For example, the tendency of cDBA-OC12(*S*) molecules to occupy the CCW nanowells is significantly lower when 1,2,4-trichlorobenzene (TCB) is used as the solvent instead of 1-phenyloctane (Table 1). Temperature dependent sergeant-soldiers experiments performed in TCB yielded no reversal of chirality even at the highest possible concentration ($C = 1.0 \times 10^{-3}$ M). This result can be readily explained by the excellent solvating ability of TCB,^{19,30} which reduces stable host-guest interactions

and allows the evolution of the system only through the sergeant-soldiers pathway (Supplementary Fig. S12).

Control over the induction/reversal processes: Molecular design. Whether the system evolves through the sergeant-soldiers or the host-guest pathway is also determined by molecular design of DBAs involved (Fig. 5). When cDBA-OC12(*S*)-OC13(*R*) (Fig. 1) was used as the sergeant, the system did not show reversal of chirality upon annealing and the final handedness of the network (CW) indicated the exclusive evolution through the sergeant-soldiers pathway. This is because cDBA-OC12(*S*)-OC13(*R*) does not show any noticeable enantioselective guest adsorption (Table 1 and Supplementary Figs. S8 and S13). It must be noted that this cDBA is a better sergeant and induces single handedness in DBA-OC12 networks with much lower mole ratio in solution compared to DBA-OC12-(*S*).²⁰ The higher thermodynamic stability of cDBA-OC12(*S*)-OC13(*R*)/DBA-OC12 co-assemblies is also illustrated by the increased surface coverage of cDBA-OC12(*S*)-OC13(*R*) after annealing (Fig. 5b, Table S2 and Supplementary Fig. S14).

On the contrary, one can also design a system that only evolves through the host-guest pathway. This can be achieved by employing a combination of cDBA-OC12(*S*) and DBA-OC10. In this case, cDBA-OC12(*S*) cannot act as a sergeant due to its longer alkoxy chains and thus can only serve as a guest in the DBA-OC10 nanowells. Sequential deposition of DBA-OC10 followed by that of cDBA-OC12(*S*) furnished equal surface coverage of the opposite handed domains of DBA-OC10 without any cDBA-OC12(*S*) sergeants indicating lack of any sergeant-soldiers effect. In agreement with previous results, cDBA-OC12(*S*) molecules adsorbed as guests preferentially in CCW nanowells (Fig. 5a, Supplementary Fig. S15). Annealing this system led to a CCW homochiral surface of DBA-OC10 (Fig. 5b, Supplementary Table S2). The validation of the host-guest based chiral induction pathway thus reaffirms the high fidelity of the proposed mechanism.

Conclusions

Using the tenets and tools of supramolecular chemistry and surface science, we have unearthed a unique chiral self-assembly phenomenon where the initial majority handedness of the network could be amplified or reversed to produce a homochiral surface. A rather prosaic implication of the sergeant-soldiers experiments reported here is that annealing improves the chiral composition of system. The major finding however, is a novel enantioselective host-guest interaction based amplification pathway, which drives the system to opposite handedness if the concentration of the building blocks is high enough. An intriguing practical implication of our findings is that one can fabricate a homochiral surface of either handedness using a single type of chiral modifier. Identification of such novel chiral induction pathways represents a significant advance in the control and manipulation of homochiral supramolecular interfaces.

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Methods

Details of STM experiments

All STM-images were acquired using an Agilent PicoLE system operating in constant current mode with the tip immersed in the supernatant liquid. STM tips were prepared by mechanical cutting of Pt/Ir wire (80/20, diameter 0.25 mm). Several samples were investigated, and for each sample, several locations were probed. The imaging parameters I_{set} (tunneling current) and V_{bias} (substrate bias) are described in the figure captions. The substrate bias was always kept negative, indicating a tunneling current from the substrate to the STM-tip. All the DBA-derivatives used in the manuscript were synthesized using previously published synthesis protocols.^{20, 21, 32} The solvents, 1-phenyloctane (Sigma, 98%) and 1,2,4-trichlorobenzene (TCB, Sigma-Aldrich, 99%)

were used without further purification. Concentrated (1×10^{-3} M) stock solutions of the achiral and chiral DBA-derivatives were prepared by weighing appropriate amount of solid powders. The solutions for sergeant-soldiers experiments were prepared by mixing the stock solutions at a certain molar ratio and these were further diluted. The mol% of cDBA in the sergeant-soldiers experiment was always 10% unless mentioned otherwise.

Immediately prior to use, the HOPG substrate (grade ZYB, Advanced Ceramics Inc., Cleveland, USA) was freshly cleaved using an adhesive tape. The substrate was then placed onto an in-situ temperature control stage, which consisted of a copper base plate with an inbuilt resistive heating element and a thermocouple. The temperature of the heating stage was controlled via a feedback loop using a Lakeshore model 331 temperature controller. This arrangement gave an accessible temperature range from room temperature up to ~ 80 °C (353 K). At temperatures greater than this, the thermal instability of the system and the rate of solvent evaporation became too large to obtain good quality STM images. An open liquid cell (inner diameter = 3.1 mm) constructed of polytetrafluoroethylene (PTFE) was used to hold ~ 40 μ L of the desired solution on the HOPG substrate (Fig. S1). For sequential heating experiments, all solutions were deposited at RT (19 °C-24 °C, humidity 27%-44%). The temperature was increased slowly at the rate of 2 °C/min to 80 °C. At elevated temperatures, the samples were imaged for a maximum of 1 hour. The loss of solvent and thus the changes in the concentration upon annealing were not significant as the sample showed only a weight loss of 9% upon annealing at 80 °C for 2 hours.

The percentage distribution of the CW and CCW honeycomb nanowells on the surface was determined as an average based on more than three experimental sessions. Each value of surface coverage was determined by using more than 10 large-area images (70×70 nm²) per session. This procedure was satisfactory for confirming the equal probability of the CW and CCW honeycomb structures formed by achiral DBA-OC12. Experimental errors (standard deviations) of the network coverage of each structure were also defined by averaging the values obtained in more than three sessions.

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Author contributions

Y.F., E.G., O.I., H.C. and A.N. acquired the STM data. O.I. performed MM simulations. Y.F., E.G., O.I. and H.C. analyzed the STM data. K.T. and Y.T. contributed to the synthesis of the DBA derivatives. O.I., K.M., K.T., Y.T and S.D.F. conceived and designed the concepts. O.I., K.M., K.T., Y.T. and S.D.F. co-wrote the paper. Y.F. and E.G. contributed equally. All authors contributed to the conception of experiments and discussion of the results, and commented on the manuscript.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at <http://www.nature.com/reprints>. Correspondence and requests for materials should be addressed to O.I., K.M., K.T., Y.T. and S.D.F.

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Figures

Figure 1: Molecular structures and models for the DBA self-assembly. **a**, Molecular structures of the chiral and achiral DBAs. **b**, Molecular models depicting the clockwise (CW) and counterclockwise (CCW) nanowells.

Figure 2: Summary of the major chiral induction experiments carried out in this study. The CW and CCW domains on the surface are represented in blue and orange, respectively and are separated by domain borders (white dashed lines). This simple schematic shows that depending on the total concentration of the solution, the outcome of a sergeant-soldiers experiment involving DBA derivatives is drastically different if the samples are annealed at elevated temperature. At lower overall concentration, amplification of the initial majority handedness is observed whereas higher concentrations lead to reversal of the majority handedness. In both cases the end result is a homochiral surface that does not contain any adsorbed chiral molecules.

Figure 3: Amplification/reversal of the initial majority (CW) handedness upon annealing as a function of total concentration. (a),(d), Representative STM images of the DBA monolayer formed at the 1-phenyloctane/HOPG interface before (a) and after (d) annealing at 80 °C ($C = 5.0 \times 10^{-7}$ M containing 10 mol% of cDBA-OC12(S) and 90 mol% of DBA-OC12). b, High-resolution STM image (12×12 nm²) showing characteristic 'black contour' cDBA sergeants co-adsorbed in the DBA-OC12 monolayer. c, Molecular model corresponding to the STM image provided in panel (b). C, H, O atoms are cyan, white and red, respectively; stereogenic centers together with the surrounding methylene groups are marked in black, thus showing correspondence with black contours in the STM image. Imaging conditions: $I_{\text{set}} = 200$ pA and $V_{\text{bias}} = -200$ mV. e, Histograms of composition-dependent chiral induction at RT and its change upon annealing to 80 °C. The bars show the percentage population of CW and CCW nanowells at each temperature.

Figure 4. Enantioselective adsorption of cDBA-OC12(S). **a**, Representative STM image highlighting the enantioselective adsorption of cDBA-OC12(S) guests in CCW domains of the DBA-OC12 monolayer. In the top of the image, the black rings mark the cDBA-OC12(S) sergeants whereas the yellow and the green circles mark the cDBA-OC12(S) guests in CW and CCW nanowells, respectively. **b**, High-resolution STM image ($12 \times 12 \text{ nm}^2$) showing cDBA-OC12(S) molecules incorporated as guests in the CCW nanowells. **c**, Molecular model corresponding to the STM image presented in panel **b**. C, H, O atoms are cyan, white and red, respectively; cDBA guests are shown in green color. Imaging conditions: $I_{\text{set}} = 200 \text{ pA}$ and $V_{\text{bias}} = -200 \text{ mV}$. For detailed experimental conditions see Supplementary Fig. S17.

Figure 5: Control over the sergent-soldiers and host-guest pathways by molecular design. **a**, Representative STM image of the DBA-OC12/cDBA-OC12(S)-OC13(R) system ($94:6$, $C = 2.5 \times 10^{-6}$ M) at the 1-phenyloctane/HOPG interface obtained at RT. White dashed lines indicate domain borders. Black rings mark the cDBA sergeants whereas the yellow and green circles highlight the guests in CW and CCW nanowells, respectively. **b**, CW homochiral surface obtained after annealing the system to $80\text{ }^{\circ}\text{C}$. The domain size as well as the number of sergeants increases significantly after annealing. **c**, Representative STM image of a monolayer obtained after addition of cDBA-OC12(S) ($20\text{ }\mu\text{L}$, 3.0×10^{-5} M, 1-phenyloctane) onto a preformed monolayer of DBA-OC10 ($20\text{ }\mu\text{L}$, 1.0×10^{-6} M, 1-phenyloctane). Preferential guest adsorption in the CCW nanowells is evident. **d**, CCW homochiral surface after annealing the cDBA-OC12(S)/ DBA-OC10 system to $80\text{ }^{\circ}\text{C}$. The presence of cDBA-OC12(S) guests at $80\text{ }^{\circ}\text{C}$ underscores the strength of the host-guest interactions. Imaging conditions: $I_{\text{set}} = 200\text{ pA}$ and $V_{\text{bias}} = -200\text{ mV}$. Corresponding images without colored markers can be found in the supplementary information Fig. S19.