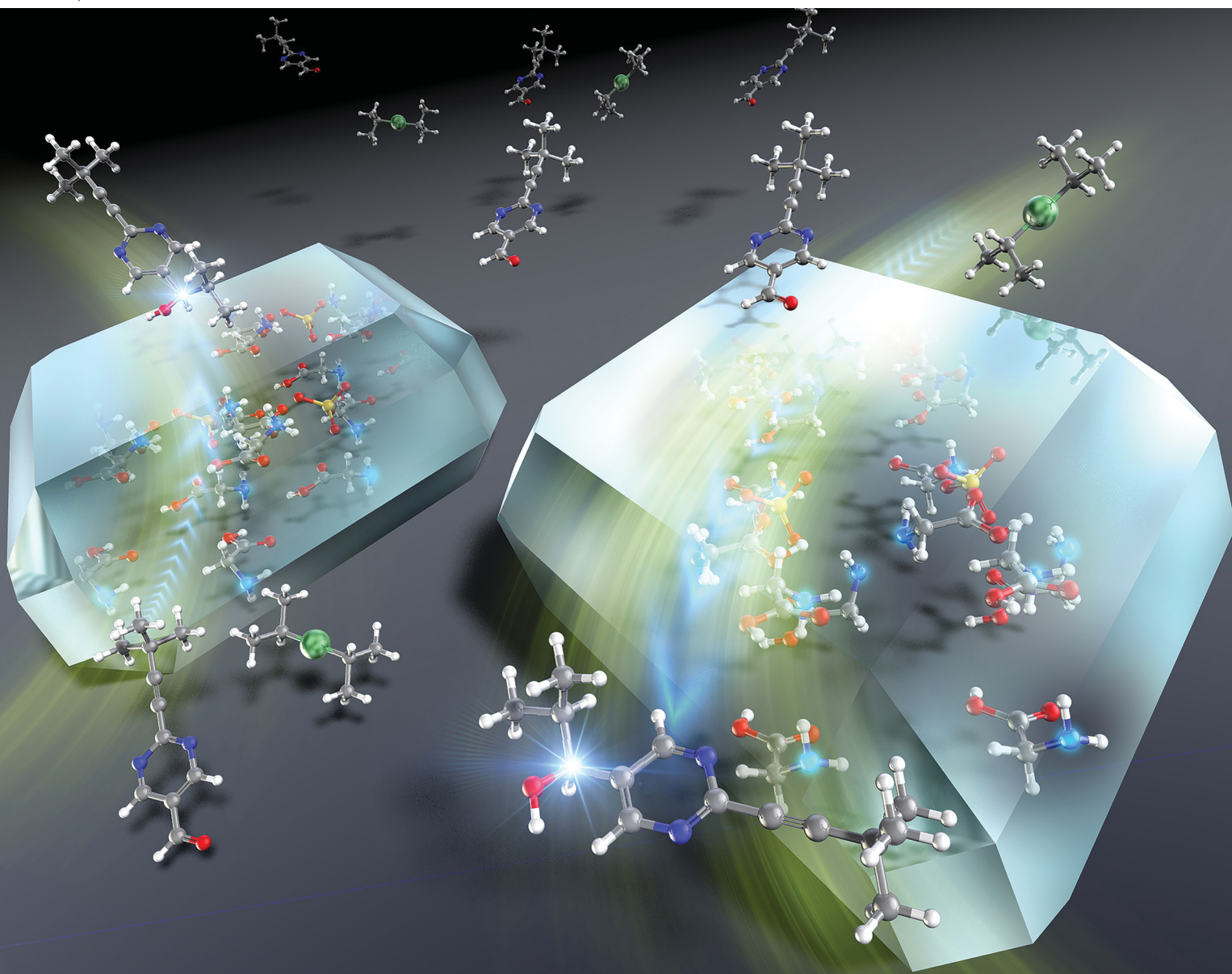


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# Asymmetric autocatalysis triggered by triglycine sulfate with switchable chirality by altering the direction of the applied electric field†

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**Triglycine sulfate (TGS) acts as a chiral trigger for asymmetric autocatalysis with amplification of enantiomeric excess, i.e., the Soai reaction. Therefore, molecular chirality of highly enantioenriched organic compounds is controlled by a ferroelectric crystal TGS, whose polarization is altered by an electric field.**

Control of molecular chirality by the application of physical force is one of the most challenging topics in science,<sup>1–3</sup> and this approach can provide a new methodology for enantioselective synthesis.<sup>4–7</sup> The induction of chirality by physical force<sup>8</sup> is an important topic to consider with respect to the origin of biological homochirality,<sup>9</sup> which continues to attract tremendous attention from scientists in many fields of research.<sup>10–12</sup> An electromagnetic force is often considered a possible inducer of molecular chirality because electromagnetic waves can directly interact with organic molecules. Actually, chiral electromagnetic force, circularly polarized light (CPL), can induce enantioselective decomposition<sup>13</sup> and reactions<sup>14</sup> of organic compounds, and asymmetric amplification during the crystallization<sup>15</sup> or asymmetric autocatalysis<sup>16,17</sup> can provide chiral organic products with a high enantiomeric excess (ee) initiated by CPL irradiation. Furthermore, recent observations have experimentally demonstrated that the combination of path direction of linearly polarized light and magnetic field can provide chiral effects leading to the formation of enantioenriched compounds.<sup>3,18</sup> To our knowledge, there has

been no apparent example of the control of molecular chirality in enantioselective reaction by a ferroelectric crystal, whose chirality is induced by the application of a static electric field, an achiral physical force.

Here, we describe the asymmetric autocatalysis of 5-pyrimidyl alkanol (the Soai reaction)<sup>12,16,19–24</sup> initiated with ferroelectric triglycine sulfate (TGS: (NH<sub>2</sub>CH<sub>2</sub>COOH)<sub>3</sub>·H<sub>2</sub>SO<sub>4</sub>) crystal, whose handedness is controlled by the application of a static electric field (Fig. 1).

We first reported asymmetric autocatalysis with amplification of ee as a real chemical reaction.<sup>16</sup> When diisopropylzinc (*i*-Pr<sub>2</sub>Zn) addition to pyrimidine-5-carbaldehyde **1** was performed in the presence of a catalytic amount of pyrimidyl alkanol **2** with a very low ee (*ca.* 0.00005% ee), asymmetric autocatalysis could enhance the ee significantly to produce a final product with very high ee (>99.5% ee).<sup>25</sup> Asymmetric autocatalysis, named as the Soai reaction,<sup>19,20</sup> has enormous power to recognize and amplify small chiral imbalances such as carbon isotope chirality<sup>7</sup> and crystal chirality;<sup>26,27</sup> therefore, asymmetric autocatalysis can connect the proposed origins of chirality with enantiomerically enriched organic compounds.<sup>12</sup> To induce molecular chirality using the controlled chirality of TGS, asymmetric autocatalysis of 5-pyrimidyl alkanol **2** (its isopropylzinc alkoxide **2'**) in the addition reaction of *i*-Pr<sub>2</sub>Zn to pyrimidine-5-carbaldehyde **1** was performed with TGS operating as a chiral trigger (Fig. 1b). We assumed that this reaction would allow the crystal chirality of TGS to be discriminated and afford highly enantioenriched product with the handedness corresponding to TGS.

TGS (Fig. 2a) is a well-known ferroelectric crystal.<sup>28</sup> Crystals of this compound exhibit spontaneous electric polarization and polarities, which can be controlled by the application of an external static electric field. Moreover, crystals of TGS have chirality even though the components including glycine and sulfate ions are achiral. However, chiral crystals of TGS have rarely been used as a chiral source for enantioselective reactions despite their wide application as a ferroelectric material.

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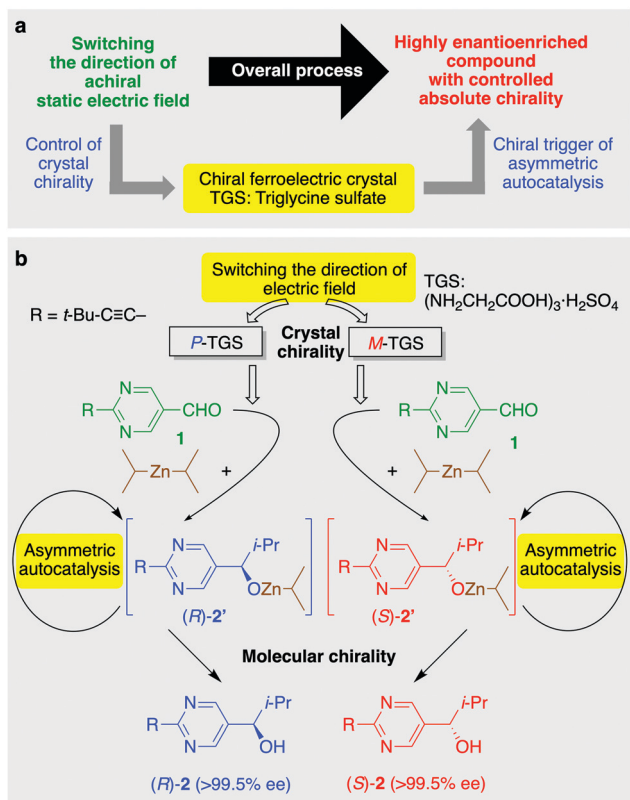
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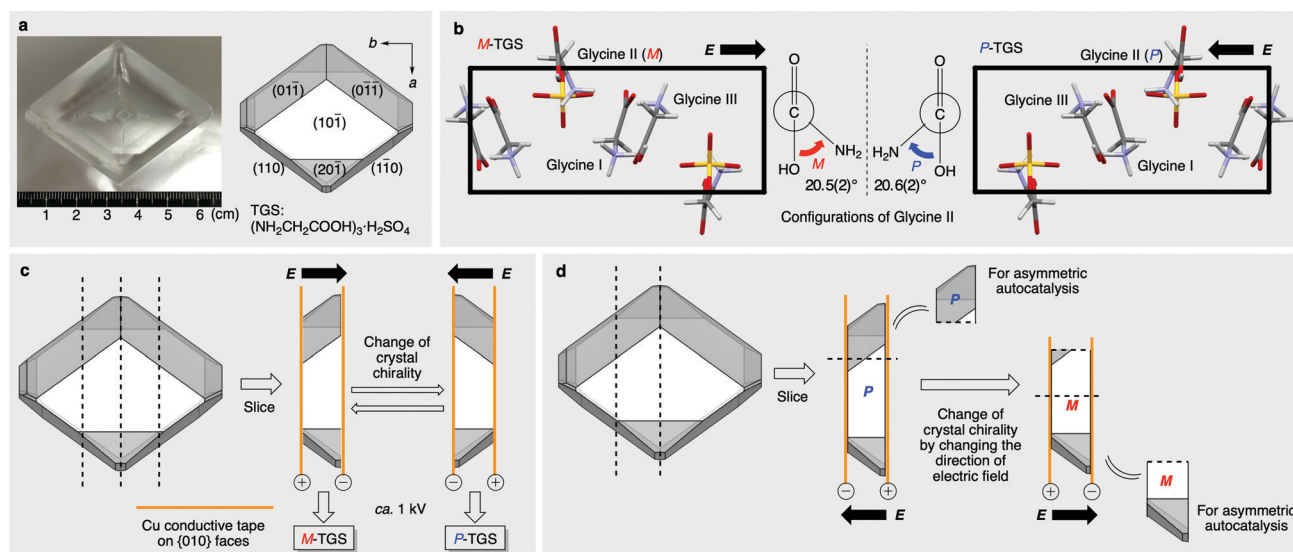




**Fig. 1** Concept and scheme of the present work: (a) control of the absolute molecular chirality by selecting the direction of the static electric field applied to triglycine sulfate (TGS) and asymmetric autocatalysis with amplification of ee. (b) Asymmetric autocatalysis of 5-pyrimidyl alkanol **2** induced by *P*- and *M*-TGS as a heterogeneous chiral trigger, leading to highly enantioenriched (*R*)- and (*S*)-alkanol **2**, respectively.

TGS crystal belongs to the monoclinic  $P2_1$  space group ( $a = 9.44 \text{ \AA}$ ,  $b = 12.6 \text{ \AA}$ ,  $c = 5.74 \text{ \AA}$ ,  $\beta = 110^\circ$ ),<sup>29</sup> which does not have inversion or mirror symmetry (Fig. 2b and Fig. S1, S2, ESI†). There are three symmetrically independent glycine molecules in a unit cell. One glycine molecule (glycine II) exists in the zwitterion form and has a large torsion angle of *ca.*  $+21^\circ$  (*P*-conformation) or  $-21^\circ$  (*M*-conformation) for the N-C-C-O bond, whereas the other two glycine molecules (glycines I and III) exist as almost planar structures in the protonated form. The twisted glycine II induces crystal polarity because no symmetry operator can invert or rotate the *b*-axis direction in the  $P2_1$  space group. Typically, TGS crystals that are grown from an aqueous solution are twinned crystals of both domains, in which spontaneous polarizations align parallelly or anti-parallelly to the *b*-axis. The ferroelectricity is induced by expanding and shrinking these twin domain areas in the crystal in an electric field. The important point is that the symmetrical relationship between these two domains is not a  $180^\circ$  rotation but a reflection.<sup>30</sup> This means that the electric field application also inverts the crystal chirality in addition to the polarity under an electric field.

To examine the control of chirality of TGS, we prepared single crystals of TGS and undertook an absolute structure determination by single-crystal X-ray diffraction analysis after the application of an electric field. The naturally grown TGS obtained from the slow evaporation of an aqueous solution of sulfuric acid and glycine was elongated in the  $[010]$  direction and had well-developed  $\{10\bar{1}\}$  faces with characteristic  $\{0\bar{1}\}$ ,  $\{110\}$  and  $\{20\bar{1}\}$  faces (Fig. 2a). When the crystal is placed with the  $(01\bar{1})$  and  $(0\bar{1}1)$  faces up and triangle  $(20\bar{1})$  face down against the large front  $(10\bar{1})$  surface, the polar *b*-axis was directed and left in this axis setting. The crystal was sliced



**Fig. 2** The chirality of TGS and its control by application of a static electric field. (a) Morphology of a single crystal of TGS [(NH<sub>2</sub>CH<sub>2</sub>COOH)<sub>3</sub>·H<sub>2</sub>SO<sub>4</sub>]. (b) Comparison of the enantiomorphs of TGS at the molecular level and the twisted chiral structure of one glycine (glycine II) among three glycines in the crystal lattice. (c) The absolute correlation between the direction of the applied electric field and the crystal chirality of the resulting TGS. (d) The control of the chirality of TGS by switching the direction of the applied static electric field to one specific piece of TGS.





perpendicular to the *b*-axis to give {010} surfaces (Fig. 2c). And a static electric field was applied to this by attaching conductive Cu tape on the {010} faces for poling the crystal. The chirality of the resulting crystal was confirmed by anomalous dispersion measurements in single-crystal X-ray diffraction analysis for several points of the crystal, which revealed that the absolute crystal chirality of TGS was well-controlled by this method even in the bulk size slice of the crystal (*ca.* 4 cm long and 5–7 mm thick). When the electric field was applied antiparallel to the *b*-axis, the handedness of the resulting crystal was the *M*-conformation, and generation of the opposite *P*-conformation was observed when the electric field was applied parallel to the *b*-axis. The Flack parameter with inversion twin refinement is typically estimated to be around 0.1–0.2 with the standard uncertainty around 0.1. The results mean that the glycine molecules predominantly twist in one direction and have controlled chirality by the electric field (*ca.* 60–80% crystal ee).

A mixture of pyrimidine-5-carbaldehyde **1**<sup>31,32</sup> and TGS was ground into a powder using a pestle and mortar, and then *i*-Pr<sub>2</sub>Zn was added dropwise. Furthermore, asymmetric autocatalysis by subsequent addition of aldehyde **1** and *i*-Pr<sub>2</sub>Zn to the mixture gave highly enantioenriched 5-pyrimidyl alkanol **2** by the amplification of ee (Fig. 1b). When the reaction was performed in the presence of *M*-TGS, obtained from the application of an electric field parallel to the *b*-axis, (*S*)-pyrimidyl alkanol **2** was obtained with 65% ee (Table 1, series A, run 1). In contrast, *P*-TGS was produced as a result of the application of a static electric field from the direction antiparallel to the *b*-axis, giving oppositely configured (*R*)-alkanol **2** with 68% ee after the amplification of the ee by asymmetric autocatalysis (run 2). These results demonstrate that the direction of the static electric field can be used to control the molecular chirality of organic compounds through chiral ferroelectric TGS and asymmetric autocatalysis. It should be noted that *P*- and *M*-TGS used in the experiments detailed in runs 1 and 2 were generated from the one specific mother single crystal (crystal #1) by the application of oppositely directed static electric fields. The sense of enantioselectivity between TGS and alkanol **2** was reproducible, as shown in runs 3–6. Moreover, the ee of product **2** could be enhanced to near enantiopure levels (>99.5% ee) by conducting additional rounds of asymmetric autocatalysis, as shown in runs 7 and 8.

It was also found that the chirality of the same piece of TGS crystal is controlled repeatedly by applying the parallel and anti-parallel electric field successively (Fig. 2d and Table 1, series B). Thus, to confirm the stereochemical relationship between the direction of the electric field and the molecular handedness of the product of the asymmetric autocatalysis, switching experiments with chiral TGS and its use as a chiral trigger for asymmetric autocatalysis were conducted (Table 1, runs 9–12). After the application of an electric field parallel to the *b*-axis, half of the resulting *P*-crystal piece was used for the asymmetric autocatalysis affording (*R*)-product **2** with 92% ee (series B, run 9). The other piece was exposed to the electric field directed in the opposite direction, leading to its

**Table 1** Asymmetric autocatalysis initiated with a TGS crystal after application of an electric field. Series A: *M*- and *P*-TGS submitted to the asymmetric autocatalysis were prepared by applying parallel and anti-parallel electric fields to the sliced two pieces of TGS originating from one specific single crystal, respectively (see also Fig. 2c). Series B: *P*- and *M*-TGS submitted to the asymmetric autocatalysis were prepared by applying parallel and anti-parallel electric fields successively to one specific sliced piece of TGS (see also Fig. 2d)

TGS			Pyrimidyl alkanol 2			
Run	Single-crystal batch	Direction of <i>E</i>	Chirality	Yield (%)	ee (%)	Config.
Series A						
1	#1	→	<i>M</i>	73	65	<i>S</i>
2	#1	←	<i>P</i>	62	68	<i>R</i>
3	#2	→	<i>M</i>	41	43	<i>S</i>
4	#2	←	<i>P</i>	50	40	<i>R</i>
5	#3	→	<i>M</i>	69	76	<i>S</i>
6	#3	←	<i>P</i>	74	39	<i>R</i>
7	#4	→	<i>M</i>	67 (87) <sup>a</sup>	44	<i>S</i>
8	#4	←	<i>P</i>	80 (95) <sup>a</sup>	54	<i>R</i>
( > 99.5 ) <sup>a</sup>						
( > 99.5 ) <sup>a</sup>						
Series B						
9	#5	←	<i>P</i>	91	92	<i>R</i>
10 <sup>b</sup>	#5	← then →	<i>M</i>	91	91	<i>S</i>
11	#6	←	<i>P</i>	85	88	<i>R</i>
12 <sup>c</sup>	#6	← then →	<i>M</i>	89	93	<i>S</i>

<sup>a</sup> Additional rounds of asymmetric autocatalyses were performed to amplify the ee value significantly. <sup>b</sup> TGS crystal #5 was first applied with the static electric field parallel to the *b*-axis of TGS. The resulting *P*-TGS was used in run 9. The chirality of the same *P*-TGS crystal in run 9 was switched to *M* by applying the static electric field of the opposite direction of anti-parallel to the *b*-axis of TGS. <sup>c</sup> TGS crystal #6 was treated in the same manner with the footnote b.

reconstruction as the opposite *M*-enantiomorph, which was also used as a chiral trigger for asymmetric autocatalysis. As a result, the enantioselectivity of the reaction was reversed to form the opposite (*S*)-alkanol **2** with a high 91% ee after significant amplification of the ee by asymmetric autocatalysis (run 10). The results were reproducible, as shown in runs 11 and 12. Therefore, the switch of the direction of the electric field is responsible for the change in the absolute configuration of the resulting product of asymmetric autocatalysis *via* ferroelectric TGS.

In summary, we have demonstrated that ferroelectric TGS, whose chirality is switchable by changing the direction of the applied static electric field, can induce a highly enantioselective synthesis through the significant amplification of ee by asymmetric autocatalysis of 5-pyrimidyl alkanol. The direction of an achiral static electric field and highly enantioenriched organic products were successfully linked with each other *via* the ferroelectric crystal of TGS; therefore, the present results provide new insight into the origin and amplification of biological homochirality.

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## Conflicts of interest

There are no conflicts to declare.

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