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SHORT COMMUNICATION

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Simple Azo Dyes Provide Access to Versatile Chiroptical Switches

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Azo dyes have played an important role in the development of the chemical industry for 150 years. The azo-core of these dyes can undergo *trans* to *cis* photoisomerization, which allows azobenzene derivatives to act as light triggered molecular switches. Here, we showed that simple derivatization of Sudan I provides access to chiroptical molecular switches, and that the properties of these switches can be readily tuned by modification of the molecular structure. The synthesis, characterization, photoisomerization, thermal stability, chiral HPLC resolution, determination of absolute configuration and chiroptical properties of chiroptical switches based on Sudan I are reported. *ortho*-difluorinated Sudan I derivatives have improved thermal stabilities and switching properties compared to switches based on Sudan I itself. Transfer of stereochemical information from a non-racemic chiral unit to the π-conjugated system of the dye and exciton-coupled circular dichroism are both observed. The chiral unit influences the geometry and hence the spectra of *cis* and *trans*-isomers differently, which is the mechanistic basis of chiroptical switching.

Humans appear to have been purposefully coloring textiles for at least 30,000 years,[1] and Perkin's discovery of mauveine, the first synthetic dye, may have been the spark that ignited the modern chemical industry.[2] Azobenzene was first described in 1834[3] and synthesized by Noble in 1856.[4] An azobenzene unit is the core structural feature of azo dyes which have tremendous contemporary and historical importance to chemistry.[5]

In 1937, Hartley characterized the *cis* isomer of azobenzene;[6] and observation that azobenzenes undergo *trans* to *cis* photoisomerization allowed the design of useful molecular switches.[7,8] Besides in the dye industry,[5] aryl-substituted azo-compounds have found applications as diverse as pH indicators[9] and in optical data storage,[10] and are widely used across materials and biological science.[11,12] Because of their extensive applications and relative ease of synthesis, there are many commercially available azo dyes[5a] and these molecules represent a valuable bank of easily accessible and modifiable molecules for the development of new applications.

Light-triggered chiroptical molecular switches based on overcrowded alkenes,[13] diarylethenes[14] fulgides[15] azobenzenes[16] and ensembles of molecules (gels, liquid crystals, etc.) have been extensively studied[17] with the aim of developing materials capable of non-destructive readout between switchable optical states. Here, we demonstrate that simply adding a chiral auxiliary to a commercially available azo dye produces a light-triggered chiroptical switch where differences in optical rotation and circular dichroism (CD) spectra between the *cis* and *trans* isomers are observed (Figure 1, b). These switches are easy to prepare and we use simple synthetic modifications to tune the thermal stability and circular dichroism spectra of the dyes. Switches containing fluoro-substituents have improved thermal stability and exhibit dramatic differences in optical rotation (inversion of sign) and CD spectra (in the 250 to 500 nm range) between the *trans* and *cis* isomers.

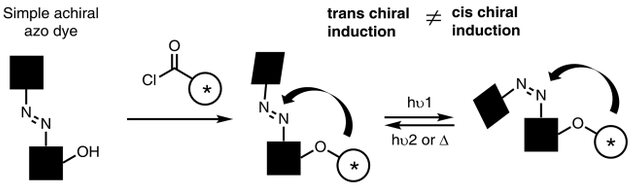

Figure 1. Concept of converting an industrial dye to a light-triggered chiroptical switch.

The sheer number of commercially available or known azo dyes with different spectral characteristic, solubilities, structural features and preexisting functional groups for derivatization suggests that this approach could be used to access a vast number of inexpensive tailor-made chiroptical switches with highly tunable properties.

Esterification of Sudan I with (*S*)-Naproxen chloride gave the racemic ester *trans*-**1a** in 65% yield (Scheme 1, a) due to the formation of an achiral ketene intermediate during the reaction.[18] Isomerization of **1a** using a light-emitting diode (LED) with λ_{max} = 570 nm gave a 1:1 mixture of *trans*-**1a** and *cis*-**1b** (Scheme 1, b). The *cis* and *trans* isomers can be separated by flash column chromatography and the

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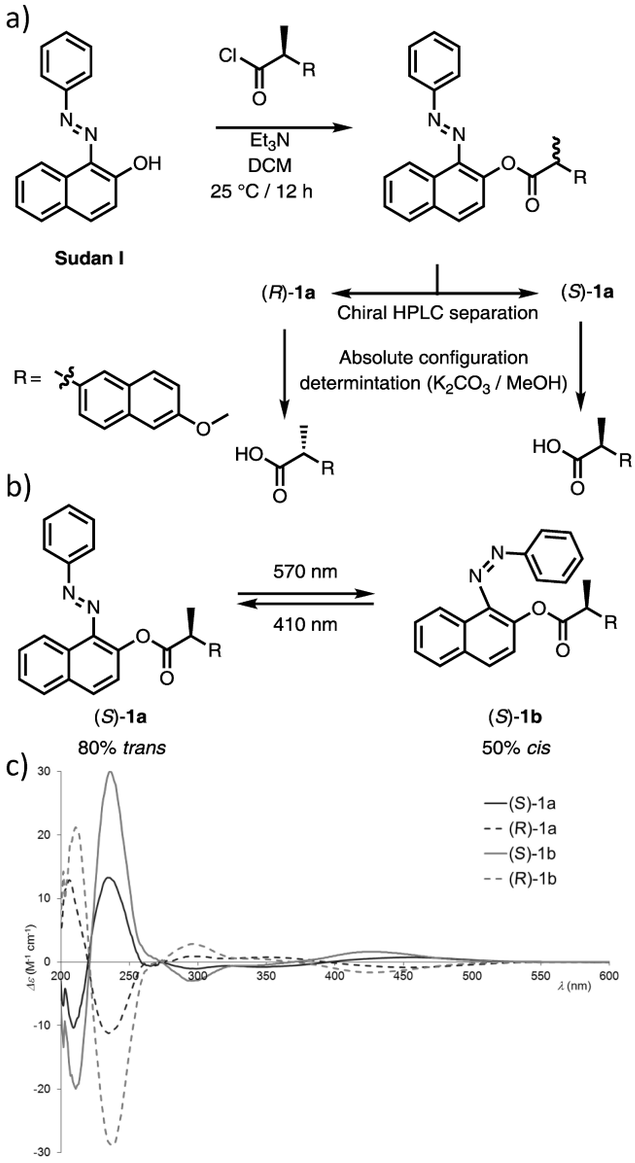
NMR spectra (see Supporting Information) of *cis*-**1b** indicates restricted rotation about the azo group. Compound **1b** has a half-life of 3 d at 25 °C in $CDCl_3$.



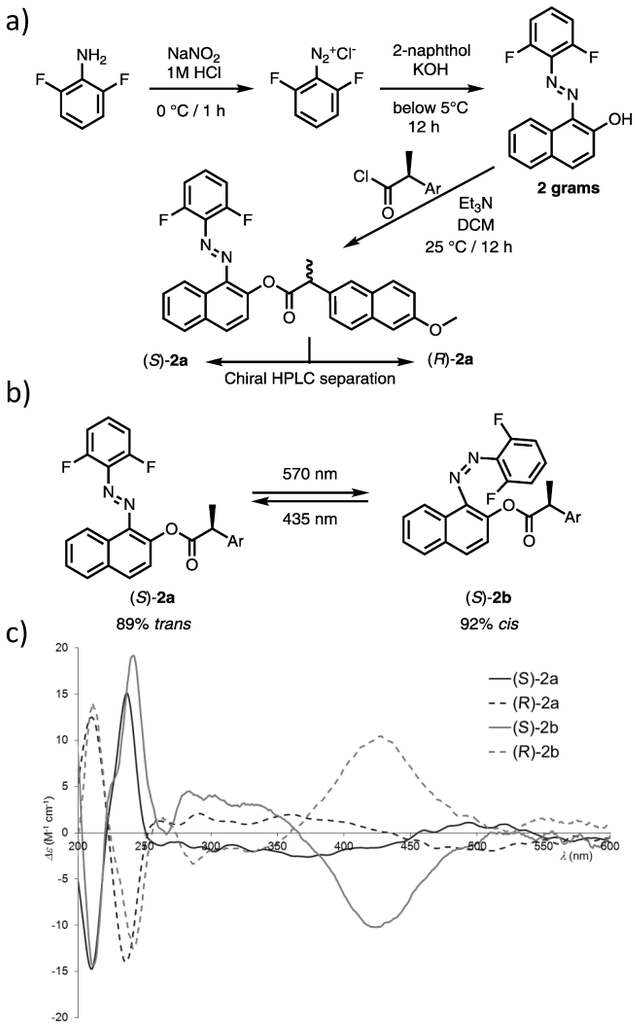
Scheme 1. a) Synthesis, resolution and determination of absolute configuration of **1a**; b) photoisomerization of (*S*)-**1a** to (*S*)-**1b**; c) CD spectra of (S)- and (*R*)-**1a**–**b** in solution in acetonitrile ($c = 6 \times 10^{-6}$ M).

HPLC on a chiral non-racemic stationary phase was used to separate the enantiomers of *trans*-**1a** (see Supporting Information). Using repeated 100 µL [10 mg/mL in a solvent mixture of hexane/chloroform (8:2)] injections and a Chiralpak® IC analytical column with an eluent mixture of hexane/chloroform/2-propanol (79:20:1) and collecting enantiomerically pure material with an automated semi-preparative fraction collector allowed about 30 mg of enantiopure (*R*) and (*S*)-**1a** to be separated using less than a liter of solvent within a working day. The absolute configuration of the enantiomers was determined by hydrolysis of the ester group of (+)-**1a** and (–)-**1a** and comparing the optical rotation of the resulting acids to previously reported specific rotations.[19]

Chiroptical properties of enantiopure (*R*) and (*S*)-**1** were studied using pure *cis*-**1b** and *trans*-**1a** isomers. The asymmetry in molecules **1** is derived from (*S*)-Naproxen chloride and we empirically observe that the switches have higher specific rotations [*trans*-(*S*)-**1a** = +100; *cis*-(*S*)-**1b** = +280] than the starting acid chloride. ECD spectra of (*S*)-Naproxen chloride in acetonitrile display two active CD bands at 260 nm ($\Delta\varepsilon$ = +4 $M^{-1}cm^{-1}$) and 230 nm ($\Delta\varepsilon$ = –6 $M^{-1}cm^{-1}$). Compound *trans*-(*S*)-**1a** displays four active CD bands between 200 and 550 nm (see Scheme 1, c). The two first ECD bands at 205 nm ($\Delta\varepsilon$ = –12.1 $M^{-1}cm^{-1}$) and 235 nm ($\Delta\varepsilon$ = +11.1 $M^{-1}cm^{-1}$) correspond to a positive exciton-coupled circular dichroism (ECCD) phenomenon[20] between the naphthyl and azo dye moieties of (*S*)-**1a**. The two active weak broad bands in the near UV/Vis region at 300 nm ($\Delta\varepsilon$ = –0.9 $M^{-1}cm^{-1}$) and 460 nm ($\Delta\varepsilon$ = 0.8 $M^{-1}cm^{-1}$) are attributed to induction of chirality from the stereogenic center to the extended π-conjugated system of Sudan I. Compound *cis*-(*S*)-**1b** displays four ECD active bands between 200 and 500 nm. Two first narrow bands, a negative band at 210 nm ($\Delta\varepsilon$ = –19.9 $M^{-1}cm^{-1}$) and a positive band at 235 nm ($\Delta\varepsilon$ = +29.9 $M^{-1}cm^{-1}$), are stronger than the corresponding bands found in *trans*-(*S*)-**1a** indicating that the ECCD phenomenon is more prominent in the *cis*-isomer. The last two bands, a negative broad band between 250 and 320 nm ($\Delta\varepsilon$ = –2.9 $M^{-1}cm^{-1}$) and a positive band at 430 nm ($\Delta\varepsilon$ = +1.6 $M^{-1}cm^{-1}$), corresponding to the chiral induction, are slightly stronger than those found in the ECD spectrum of (*S*)-**1a** (see Scheme 1, c).

Fluorination of symmetrical *ortho*-azobenzenes has been reported to modify the relative energies of the n-π* absorption in azo-isomers, this causes band separation between *cis*- and *trans*-isomers so that they can be selectively interconverted using different wavelengths of light, additionally these *cis*-isomers of *ortho*-tetrafluoroazobenzene also display longer thermal isomerization half-lives, which was attributed to the negative inductive effect of the fluorines that decreases the repulsive interaction of the nitrogen lone pairs.[21]

In an attempt to improve the *trans* to *cis* isomerization behavior of our switch described above, we prepared gram quantities of *ortho*-difluorinated Sudan I by allowing the diazonium salt of the 2,6-difluoroaniline and 2-naphthol to react in presence of KOH below 5 °C. Esterification then gave *trans*-compounds **2a** (70% yield) (Scheme 2, a). Compounds *cis*-**2b** were obtained by irradiating **2a** at the tail of the n–π* absorption band (see Supporting Information for UV/Vis spectra) using a LED (λ_{max} = 570 nm). After 30 min of irradiation the photo-stationary state (PSS) was reached giving a mixture of isomers, of which 92% were *cis*-isomers **2b**. *cis*-**2b** was purified using flash column chromatography over silica gel. ^1H and ^{13}C NMR spectra of **2b** show some broad signals, suggesting that free rotation of the azo-moiety is restricted. Compound **2b** has a thermal half-life of about 15 d in solution at room temperature.



Scheme 2. a) Synthesis and resolution of **2a**; b) photoisomerization of (*S*)-**2a** to (*S*)-**2b**; c) CD spectra of (*S*)- and (*R*)-**2a**–**b** in solution in acetonitrile ($c = 8.5 \times 10^{-6}$ M).

Selective *cis* to *trans* isomerization was achieved by irradiation with a 435 nm LED, giving a photostationary state of 89:11 for *trans*-**2a**/*cis*-**2b** (Scheme 2, b). Thermal conversion of *cis*-**2b** to *trans*-**2a** can also be accomplished by heating at 80 °C for 1 h in acetonitrile. These light-triggered chiroptical switches are robust as determined by ^{1}H NMR spectroscopy, no detectable degradation was observed after ten *trans*/*cis* and *cis*/*trans* isomerization cycles.

HPLC with a chiral non-racemic stationary phase using an analytical column was used to separate the enantiomers of **2** in a manner similar to that used above to obtain **1** (see Supporting Information for HPLC traces and detailed conditions). The absolute configurations were determined by ester hydrolysis of (+)-**2a** and (–)-**2a** and comparing the optical rotation of the resulting acid products with known values.[22]

The chiroptical properties of (*R*)- and (*S*)-**2** were studied using chemically and enantiomerically pure *trans* (**2a**) and *cis* (**2b**) isomers (Scheme 2, c). The specific rotation of *trans*-(*S*)-**2a** is more than six times higher than the specific rotation of Naproxen chloride (Table 1). Interestingly, the specific rotation of *cis*-(*S*)-**2b** is almost the same magnitude, *but opposite in sign*, of the specific rotation of *trans*-(*S*)-**2a**. *trans*-(*S*)-**2a** displays four active CD bands between 200 and 550 nm (see Scheme 2, c). The ECD bands at 210 nm ($\Delta\varepsilon$ = –14.2 $M^{-1}cm^{-1}$) and 235 nm ($\Delta\varepsilon$ = +14.5 $M^{-1}cm^{-1}$) are due to ECCD phenomenon between the two naphthyl moieties. The two broad bands in the near UV/Vis region between 250 and 450 nm ($\Delta\varepsilon$ = –2.5 $M^{-1}cm^{-1}$) and at 490 nm ($\Delta\varepsilon$ = +1.5 $M^{-1}cm^{-1}$) are attributed to the stereogenic center influencing the geometry of the extended π-conjugated system of *ortho*-difluoro-Sudan I unit. Compound *cis*-(*S*)-**2b** displays four ECD active bands between 200 and 500 nm. The first two narrow bands, a negative band at 215 nm ($\Delta\varepsilon$ = –14.2 $M^{-1}cm^{-1}$) and a positive band at 240 nm ($\Delta\varepsilon$ = +19.2 $M^{-1}cm^{-1}$), remain almost unchanged from those found in *trans*-(*S*)-**2a**, however the last two bands, a positive broad band between 250 and 320 nm ($\Delta\varepsilon$ = +4.3 $M^{-1}cm^{-1}$) and a negative band at 430 nm ($\Delta\varepsilon$ = –10.4 $M^{-1}cm^{-1}$), corresponding to asymmetry about the *cis*-azo unit, are completely inverted and stronger in intensity than those found in the ECD spectrum of *trans*-(*S*)-**2a** (see Scheme 2, c).

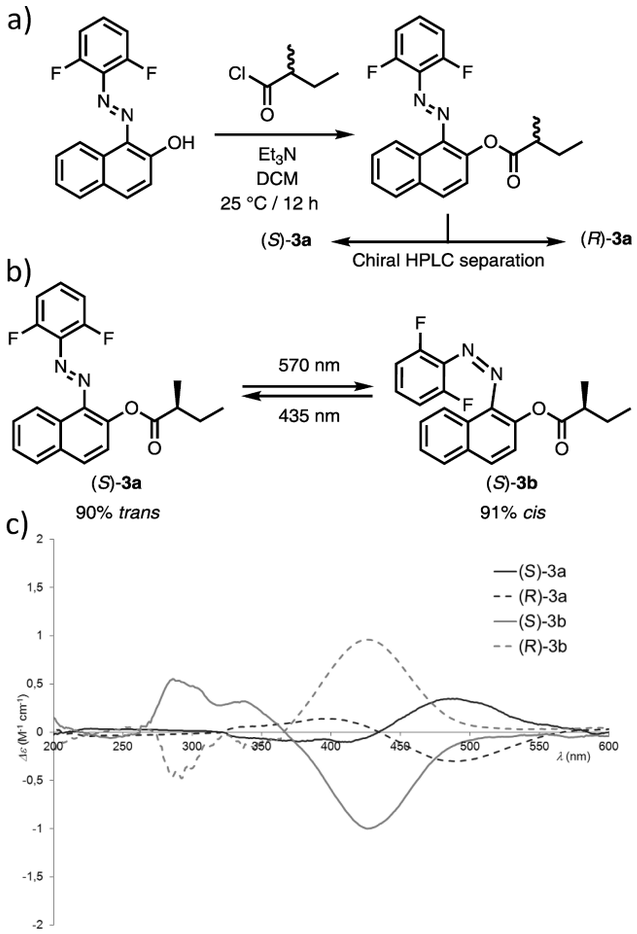
Table 1. Specific rotation of *trans* (**a**) and *cis* (**b**) isomers of compounds (*S*)-**1**–**3**.

OA (°·mL·g^{-1}·dm^{-1}) Starting acyl chloride	(*S*)-**1** +66[a]	(*S*)-**2** +66[a]	(*S*)-**3** +19[a]
a (*trans*)	+100[b]	+420[b]	+180[b]
b (*cis*)	+280[b]	–380[b]	–175[b]

[a] From literature in dichloromethane. [b] Measured in dichloromethane at 25 °C with the D line (c = 0.1).

To study the origins of the observed chiroptical properties, the CD active Naproxen-based chiral auxiliary in **1** and **2** was replaced by a saturated chiral auxiliary to eliminate exciton-coupling. Esterification of difluoro-Sudan I with (*S*)-2-methylbutyryl chloride gave racemic **3a** in 65% yield (Scheme 3, a). Compound **3b** was obtained by irradiating **3a** in the tail of the n–π* absorption band using a LED (λ_{max} = 570 nm). After 30 min of irradiation the photo-stationary state was reached (10:90, *trans*/*cis*) (Scheme 3, b), and **3b** has a thermal half-life of 16 d at room temperature. After separating the enantiomers of **3** by HPLC the absolute configurations were determined by base mediated cleavage of the esters in (+)-**3a** and (–)-**3a** and examining the optical rotations of recovered 2-methylbutyric acid.[23] The specific rotation of *trans*-(*S*)-**3a** is more than nine times higher than the specific rotation of (*S*)-2-methylbutyryl chloride. As observed with **2**, the specific rotation of *cis*-(*S*)-**3b** is almost the opposite of *trans*-(*S*)-**3a**. *trans*-(*S*)-**3a** displays only two weak and broad active CD bands from 320–550 nm. The first is between 320 and 420 nm ($\Delta\varepsilon$ = –0.1 $M^{-1}cm^{-1}$) and the other is centered at 490 nm ($\Delta\varepsilon$ = +0.3 $M^{-1}cm^{-1}$) (Scheme 3, c). *cis*-(*S*)-**3b** displays two active bands, a first positive broad active band between 260 and 320 nm ($\Delta\varepsilon$ = +0.5 $M^{-1}cm^{-1}$) and a second negative active band at 430 nm ($\Delta\varepsilon$ = –1.0 $M^{-1}cm^{-1}$). As observed in (*S*)-**2** ECD study, the CD-active bands of the *cis*-(*S*)-**3b** are

stronger in intensity and with the opposite sign of those in *trans*-(*S*)-**3a**.



Scheme 3. a) Synthesis and resolution of **3a**; b) photoisomerization of (*S*)-**3a** to (*S*)-**3b**; c) CD spectra of (*S*)- and (*R*)-*trans*-**3a** and (*S*)- and (*R*)-*cis*-**3b** in acetonitrile ($c = 6 \times 10^{-5}$ M).

Since the chiral auxiliary in **3** is CD silent, we conclude that the CD spectra of these compounds **3** are caused by chiral induction and that the CD-active bands between 200 and 250 nm in compounds **1** and **2** can only be attributed to an ECCD phenomenon between the naphthalene units. Specific rotation values and ECD spectroscopy studies demonstrate that the chiroptical properties of dyes **1**–**3** are strongly dependent on (i) the *trans* or *cis* configuration of the dye, (ii) substitution (i.e. H vs. F atoms) of the π-conjugated system, (iii) the grafted stereogenic center.

Single crystals of *rac*-**2b** and (*R*)-**3b** (Figure 2) were obtained by slow crystallization (diffusing pentane vapor over dichloromethane solutions) and X-ray crystallographic studies of *rac*-**2b** ($P2_1/n$ group) and (*R*)-**3b** ($P2_1$ group) clearly show the difluorinated-phenyl ring occupying a side of the central naphthyl moiety where it points away from the ester group.

In summary, simply adding a chiral auxiliary to a common industrially used azo dye gives robust and tunable chiroptical switches. Esterification of Sudan I and *ortho*-difluoro-Sudan I with Naproxen chloride gave switches with

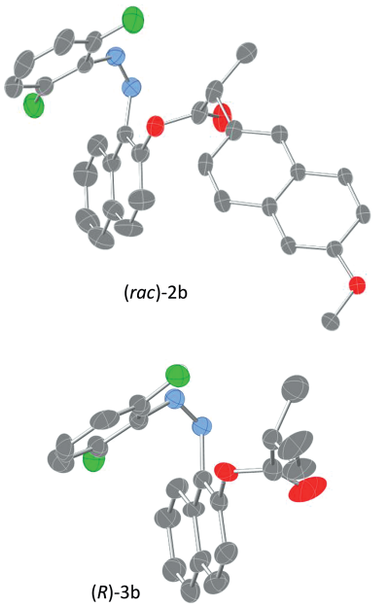


Figure 2. X-ray crystallographic structures of *cis*-*rac*-**2b** (top) and *cis*-(*R*)-**3b** (bottom). Hydrogen atoms have been omitted for clarity.

significantly different optical rotations and CD spectra of the *cis*- and *trans*-isomers The transfer of stereochemical information from the chiral ester to the π-conjugated dye system and exciton coupling significantly differ in photoswitchable isomers which can be read out without disturbing the isomeric ratio. Difluoro-substitution, as in **2** and **3**, gave improved control over *cis*-*trans* isomerization, more dramatic changes in chiroptical properties, and improved thermal stability of the *cis*-isomers. Study of *ortho*-difluorinated Sudan I bearing a saturated chiral ester shows that CD bands in 270–550 nm range is due to through space transmission of chiral information from the stereogenic center to the azo dye unit.

Acknowledgments

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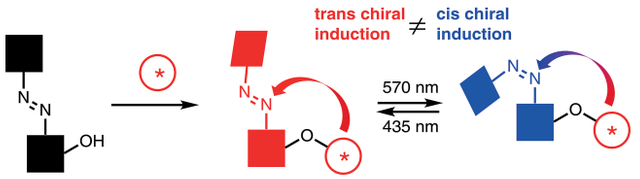

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Chiral Industrial Azo Dye

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