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Crystal structures of (2-substituted-5-*N*-tosyl)bicyclo[3.3.0]-5-azacyclooct-2-enone: a pseudo achiral crystal from enantiopure compound and a counter-example of Wallach's rule

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ABSTRACT

An unusual crystallization affording an apparently pseudoachiral crystal from single enantiomers **1a** and **1b** was observed. In cases of enantiopure molecules such as **1a** and **1b** with structural flexibility, the tendency toward a centrosymmetric arrangement was so overwhelming that apparently achiral crystals were formed even by homochiral compounds via the formation of a pseudo-centrosymmetric asymmetric unit accompanying structural adjustment. In addition, these crystals of **1a** constitute as a counter-example of Wallach's rule.

1. Introduction

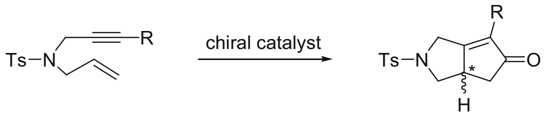
Molecular shape is a primary factor in determining the crystal packing patterns, when there are no strong intermolecular forces, such as ionic interactions and hydrogen bonds.[1,2] In addition, chirality is another important factor determining the final crystal structure during the crystallization of chiral molecules. Crystallization of chiral molecules can be classified according to the outcome of crystal chirality and the input of chirality of the molecules subjected to crystallization. Of the four possible manners of crystallization, all but one have been observed experimentally. Achiral crystals from racemic mixtures and chiral crystals from enantiopure compounds are conceived as natural.[3] In addition, as observed by Pasteur, spontaneous resolutions of racemic mixtures providing two kinds of crystals with opposite handedness were also reported, although the cases of this are still rare.[4] However, a well-defined achiral crystal from enantiopure molecules is not allowed by an intrinsic symmetry requirement. Herein, we report interesting examples of isomorphic crystals from homochiral molecules with those from racemic mixtures. These belong to the less explored class of crystallization of chiral molecules: the formation of apparently achiral crystals from single enantiomers.

Normally, organic materials provide thermodynamically stable crystals by taking on centrosymmetric arrangements.[2] This tendency is one of the fundamental working principles in crystallization as manifested by the estimated centro-/non-centrosymmetric arrangement ratio of 4:1 found in all crystal structures.[3] This tendency toward centrosymmetric arrangements is intensified particularly in the case of chiral molecules.[3b,c] In fact, most crystals formed from racemic mixtures (>90% of reported examples) are found to have asymmetric units that adopt centrosymmetric arrangements via enantiomeric pairing. On the other hand, homochiral molecules usually afford crystals belonging to chiral space groups and, since their symmetry requirement in crystallization is different from that of racemic mixtures, the crystallization of homochiral molecules is best understood case by case.[5]

During our study on crystallization and self-assembly, we observed that crystals of compounds **1** constituted as distinctive examples of pseudo achiral crystals from homochiral molecules. This seemed to be motivated by a tendency to mimic a characteristic feature of most racemates, a centrosymmetric arrangement,[6] even with a substantial structural change.

2. Results and discussion

Compounds **1** were obtained either as an enantiomerically pure form or as a racemic mixture by a Pauson–Khand reaction we have developed (Scheme 1).[7]



2a. R = Ph
2b. R = H

1a. R = Ph
1b. R = H

Scheme 1. Synthesis of **1a** and **1b** by an asymmetric Pauson–Khand reaction.

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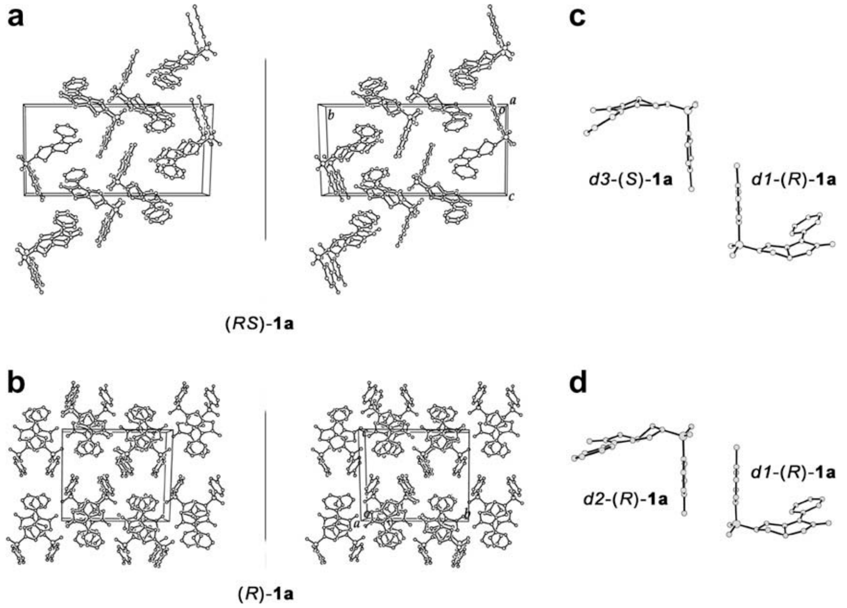


Figure 1. Crystal structures of crystal (*RS*)-**1a** and crystal (*R*)-**1a**. The unit cell origin has been moved to (0.25, −0.25, −0.25) in (b) for easy comparison with (a).

The respective crystals of **1a**, (*R*)-**1a** and (*RS*)-**1a**, were obtained from single enantiomers and a racemic mixture in ethyl acetate with a diffusion of *n*-hexane. Their crystal structures were determined by a single-crystal X-ray diffraction study and their crystal data are summarized in Table 1 and their structures are shown in Figure 1.

The crystal structure for (*R*)-**1a** indicates an interesting feature that the asymmetric unit contains two independent molecules. Two conformers of a single enantiomer were used to achieve the pseudo-centrosymmetric arrangement. Thus, in order to understand the situation more clearly, it is worthwhile looking at all the possible stereoisomers of **1** and their structural relationship.

For a detailed description, it is necessary to define the notations. In a strict sense, compound **1a** has four possible stereoisomers because there exist two stereogenic centers at C* and N (Fig. 2). However, since the configuration at the N stereogenic center is invertible at ambient temperature, the two diastereomers bearing the same configuration at C* are often indistinguishable, especially in solution. Thus we use notations of (*R*)-**1a** and (*S*)-**1a** to highlight the invariable absolute configuration at C* in compound **1a**. Compound (*R*)-**1a** intrinsically denotes a pair of diastereomers, [(*R*(C*),*R*(N))]-**1a** (assigned as *d1*-(*R*)-**1a**) and [*R*(C*),*S*(N)]-**1a** (*d2*-(*R*)-**1a**). Likewise, (*S*)-**1a** indicates a pair of diastereomers, [(*S*(C*),*S*(N)]-**1a** (*d3*-(*S*)-**1a**) and [*S*(C*),*R*(N)]-**1a** (*d4*-(*S*)-**1a**). Thus, *d1*-(*R*)-**1a** and *d3*-(*S*)-**1a**, and *d2*-(*R*)-**1a** and *d4*-(*S*)-**1a** are enantiomeric pairs, respectively. Meanwhile, (*RS*)-**1a** is used to indicate a mixture of (*R*)-**1a** and (*S*)-**1a**, that is, all four stereoisomers. In a solution, since there is no significant barrier between two diastereomers having an identical configuration around C*, only one of them is expected to be present predominantly in solution, if there is a significant energy difference between two diastereomers.[8]

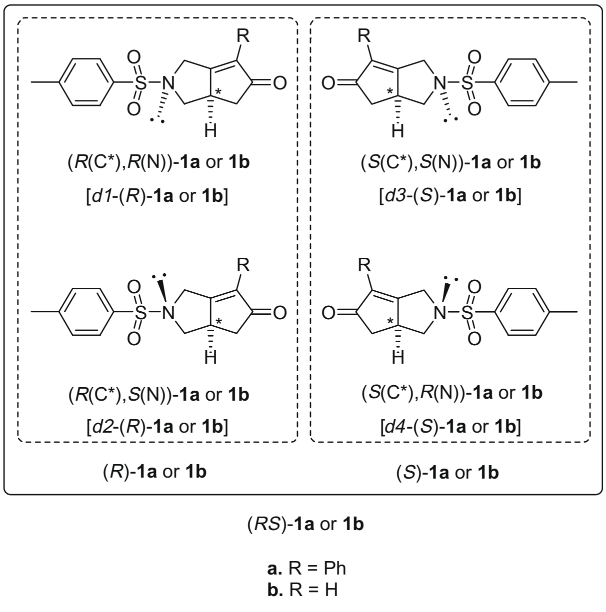


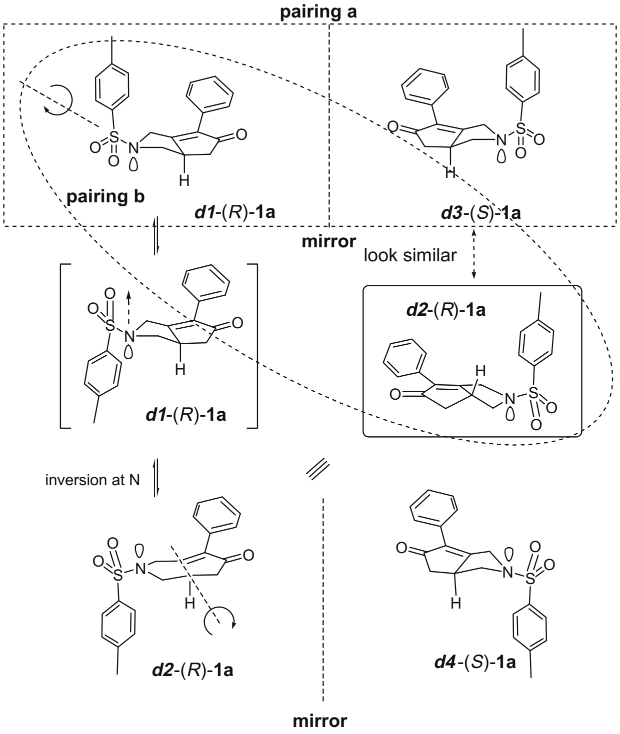
Figure 2. All possible stereoisomers of **1a** and **1b**.

The crystal (*RS*)-**1a** when formed from a racemic mixture belongs to an achiral space group $P2_1/n$ (Table 1), where two enantiomers, *d1*-(*R*)-**1a** and *d3*-(*S*)-**1a**, are paired to form a centrosymmetric asymmetric unit (**pairing a** in Scheme 2).

On the other hand, crystal (*R*)-**1a**, whose component has an enantiomeric purity of greater than 99% ee, belongs to a non-centrosymmetric space group $P2_1$ (Table 1). Interestingly, two enantiomer-like diastereomers, *d1*-(*R*)-**1a** and *d2*-(*R*)-**1a** (Fig. 3b), which are in rapid equilibrium at ambient temperature, are paired to form a pseudo-centrosymmetric asymmetric unit for the imitation of a centrosymmetric asymmetric unit in crystal (*RS*)-**1a** (Fig. 3a). As a result, crystal (*R*)-**1a** looked like an achiral crystal, rather than a chiral crystal of a pure enantiomer.

This unusual pairing of *d1*-(*R*)-**1a** and *d2*-(*R*)-**1a** (**pairing b** in Scheme 2) might occur because the shape of *d2*-(*R*)-**1a** was very similar to that of *d3*-(*S*)-**1a**. The overlay of *d2*-(*R*)-**1a** taken from crystal (*R*)-**1a** on *d3*-(*S*)-**1a** obtained either directly from crystal (*RS*)-**1a** (Fig. 3a and c) or by inverting *d1*-(*R*)-**1a** found in crystal (*R*)-**1a** (Fig. 3b and d) shows their near perfect superimposition. The only difference between *d2*-(*R*)-**1a** and *d3*-(*S*)-**1a** is the thickness in the middle section of the relatively flat bicyclic skeleton and the direction of the phenyl ring.

Thus, under given circumstances, *d2*-(*R*)-**1a** disguises itself as *d3*-(*S*)-**1a** so that it can be paired with *d1*-(*R*)-**1a** to form a pseudo-centrosymmetric asymmetric unit resulting in an apparently



Scheme 2. A schematic representation of the structural relationship between the diastereomers of **1a** in solution.

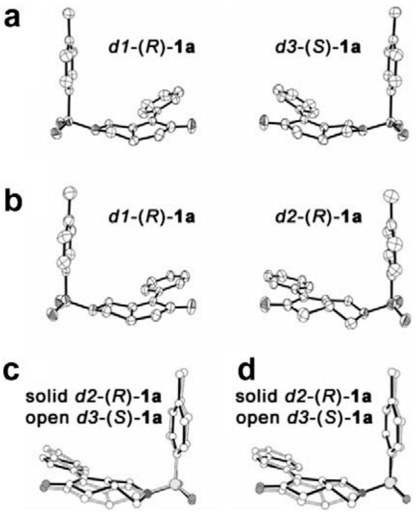


Figure 3. ORTEP drawings of molecular structures with 30% thermal ellipsoids depicted for *d1*-(*R*)-**1a** and *d3*-(*S*)-**1a** in crystal (*RS*)-**1a** (a) and for *d1*-(*R*)-**1a** and *d2*-(*R*)-**1a** in crystal (*R*)-**1a** (b). (c) Superposition of *d2*-(*R*)-**1a** (solid line) in crystal (*R*)-**1a** onto *d3*-(*S*)-**1a** (open line) in crystal (*RS*)-**1a**. (d) Superposition of *d2*-(*R*)-**1a** (solid line) in crystal (*R*)-**1a** onto *d3*-(*S*)-**1a** (open line) which was obtained by inverting *d1*-(*R*)-**1a** in crystal (*R*)-**1a**.

achiral crystal from enantiopure (*R*)-**1a**. Consequently, the overall crystal structures of (*R*)-**1a** and (*RS*)-**1a** look very much alike. This pseudo achiral crystal mimicking a racemic compound constitutes as an interesting example of the aforementioned case; achiral crystal formation by single enantiomers.[9]

The thermodynamic stability and hence the packing efficiency of crystal (*RS*)-**1a** and crystal (*R*)-**1a** were determined by DSC. Crystal (*RS*)-**1a** exhibits a substantially higher melting point and enthalpy of fusion than crystal (*R*)-**1a**: crystal (*RS*)-**1a**, 167.8 °C and 36.1 kJ/mol; crystal (*R*)-**1a**, 125.3 °C and 25.9 kJ/mol. Therefore, the racemate is significantly more stable than the pseudo achiral crystal. However, it is worth pointing out that the density of crystal (*R*)-**1a** (1.359 g/cm^3) is noticeably higher than that of crystal (*RS*)-**1a** (1.340 g/cm^3) (Table 1). Despite their close resemblance in an asymmetric unit, a pair of molecules in crystal (*R*)-**1a** packs differently from that in crystal (*RS*)-**1a,** which results in crystal (*R*)-**1a** being denser than crystal (*RS*)-**1a.**

This is contradictory to the expectation from Wallach's rule, which was documented as racemic crystals tended to be denser than their chiral counterparts.[10] Thus, our observation demonstrated again that density was no longer a good measure of thermodynamic stability (the close packing principle),[11a,b] and reinforced Yu's suggestion to use other means, such as eutectic-melting and/or solubility data, for a fair comparison of the relative stability of crystals.[11c]

Next, the crystallization of **1b**, a congener of **1a**, in which the phenyl ring at the 2-position of bicyclic octenone of **1a** is replaced by a hydrogen atom, was attempted. Although the results are not much different from those of crystals of **1a** (Table 1), a couple of points are worth mentioning.

Firstly, crystal (*RS*)-**1b** consists of only enantiomeric stereoisomers, *d2*-(*R*)-**1b** and *d4*-(*S*)-**1b**, which are alternately arranged in the crystal with a centrosymmetric arrangement. Conversely to crystal (*RS*)-**1a**, crystal (*RS*)-**1b** contains *d2*-(*R*)-**1b** and *d4*-(*S*)-**1b** instead of *d1* and *d3*, respectively (Fig. 4a). Secondly, crystal (*R*)-**1b** comprises two diastereomers of (*R*)-**1b**, *d1*-(*R*)-**1b** and *d2*-(*R*)-**1b** (Fig. 4b) as expected by an analogy with **1a**. However, the ratio of diastereomers *d1* to *d2* in crystal (*R*)-**1b** is 38:62 instead of the expected number of 50:50 (Fig. 4c).

It appears that contrary to **1a**, there is no distinct difference between *d1*-(*R*)-**1b** and *d2*-(*R*)-**1b** in shape and, furthermore, all four stereoisomers of **1b** are not structurally very different from each other (Scheme 3).

Thus, any combination of pairing does not exhibit a noticeable difference in stability. As a result, the pairing of *d1*-(*R*)-**1b** and *d2*-(*R*)-**1b** (**pairing b** in Scheme 3) could not be easily distinguished from the self-pairing of two *d2*-(*R*)-**1b** molecules during crystallization of (*R*)-**1b**.

Thus, although there is still a strong tendency to adopt a pseudo-centrosymmetric arrangement by the matched pairing of the two different diastereomers [*d1*-(*R*)-**1b** and *d2*-(*R*)-**1b**] (**pairing a** in Scheme 3), a significant proportion of the mismatched pair by two identical diastereomers *d2*-(*R*)-**1b** is found in the crystal. The inclusion of the mismatched pair in the crystal is unlikely to make a significant difference in the overall crystal stability of (*R*)-**1b**. In

Table 1
Summary of crystal data and refinement results

Crystal	Formula	Space group	*a* (Å)	*b* (Å)	*c* (Å)	α (deg)	β (deg)	γ (deg)	Z	D_{cacld}	R_1	wR_2	GOF
(*RS*)-**1a**	$C_{20}H_{19}NO_3S$	$P2_1/n$	7.277 (1)	22.243 (1)	11.286 (1)	90	106.42 (1)	90	4	**1.340**	0.0431	0.1264	1.078
(*R*)-**1a**	$C_{20}H_{19}NO_3S$	$P2_1$	9.272 (1)	14.863 (1)	13.181 (1)	90	108.01 (1)	90	4	**1.359**	0.0450	0.1042	0.853
(*RS*)-**1b**	$C_{14}H_{15}NO_3S$	$P2_1/n$	6.017 (1)	10.775 (1)	20.613 (1)	90	90.96 (1)	90	4	1.379	0.0498	0.1382	1.054
(*R*)-**1b**	$C_{14}H_{15}NO_3S$	$P2_1$	6.066 (1)	10.767 (1)	20.659 (1)	90	91.53 (1)	90	4	1.366	0.0486	0.0856	0.825

The bold is used to highlight the violation of Wallach's Rule.

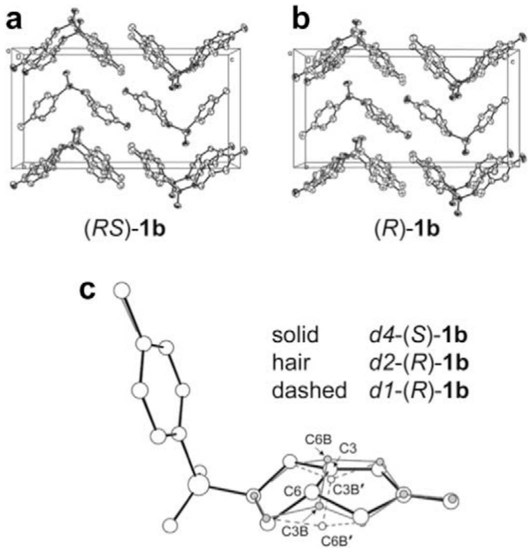
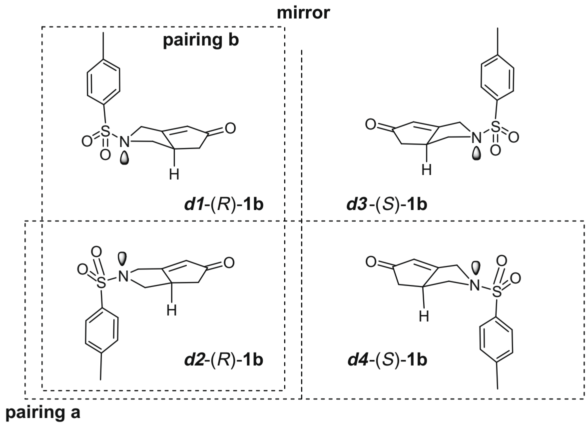


Figure 4. ORTEP drawings of crystal and molecular structures of **1b**. The unit cell packing diagrams of crystal (*RS*)-**1b** (a) and crystal (*R*)-**1b** (b) are drawn along the a-axis. In crystal (*R*)-**1b**, there are two molecules in the asymmetric unit, which contains a pair of diastereomers, viz. either *d1*-(*R*)-**1b**/*d2*-(*R*)-**1b** (76%) or *d2*-(*R*)-**1b**/*d2*-(*R*)-**1b** (24%), resulting in an overall *d1*/*d2* ratio of 38:62. One of the two occupied sites in the asymmetric unit is disordered due to the overlay of the two different diastereomers, *d1*-(*R*)-**1b** and *d2*-(*R*)-**1b**, at the same site as shown in (c): *d4*-(*S*)-**1b** (solid line) in crystal (*RS*)-**1b** has been super-positioned onto *d2*-(*R*)-**1b** (hair line) and *d1*-(*R*)-**1b** (dashed line) occupying 24% and 76% of the disordered sites in crystal (*R*)-**1b**, respectively. Notice the mirror symmetry relation between *d4*-(*S*)-**1b** and *d2*-(*R*)-**1b**.



Scheme 3. A schematic representation of the structural relationship between the diastereomers of **1b** in solution.

this case, the ratio of diastereomers in the crystal presumably reflects that in solution at the crystallization temperature.

The DSC study shows that crystal (*RS*)-**1b** exhibits a higher melting point and enthalpy of fusion than crystal (*R*)-**1b**: crystal (*RS*)-**1b**, 154.0 °C and 32.9 kJ/mol; crystal (*R*)-**1b**, 139.8 °C and 24.5 kJ/mol. This indicates that the racemate is still more stable than the pseudo achiral crystal. However, the stability difference between the racemic compound and the pseudo achiral crystal of **1b** is substantially smaller than that of **1a**. This specific example satisfied Wallach's rule (Table 1).

Attempts to determine the rationale behind these phenomena and formulate a method to predict the crystal structure from the constituting chiral molecules are very tempting.[12] However, this will need more relevant data, and thus, the efforts will be put off until the accumulation of data reaches a certain level.

3. Conclusion

Herein, we have reported examples of apparently achiral crystal formation by single enantiomers. From the X-ray crystallographic studies of compound **1a**, we noticed that the heterochiral molecules strongly favored the formation of a racemic compound, and even the homochiral molecules provided *a pseudo achiral crystal* of a pure enantiomer through the adoption of a pseudo-centrosymmetric arrangement accompanying a structural adjustment. This observation could be explained by the strong propensity of any molecule to take on centrosymmetric and pseudo-centrosymmetric arrangements in crystals, if possible. In addition, we found that, especially for **1a**, densities of crystals do not necessarily reflect the thermodynamic stabilities, thus the century-old Wallach's rule has to be re-stated.

4. Experimental

4.1. Preparation of racemic-1a, (*RS*)-1a[7a]

A mixture of $Co_2(CO)_8$ (252 mg, 0.737 mmol) and the enyne **2a** (200 mg, 0.615 mmol) in CH_2Cl_2 (6 mL) was stirred at room temperature for 1 h. After confirming the formation of the enyne-dicobalt hexacarbonyl complex by TLC analysis, a solution of trimethylamine *N*-oxide dihydrate (342 mg, 3.08 mmol) in CH_2Cl_2 (4 mL) was added. After stirring at room temperature for 1 h, the reaction mixture was passed through a small pad of silica gel 60 (230−400 mesh, Merck, Darmstadt) with 1:2 EtOAc/*n*-hexane eluent to remove the purple precipitates. The filtrate was concentrated in vacuo and then purified by flash column chromatography (EtOAc/*n*-hexane = 1:5) on silica gel 60 to afford (*RS*)-**1a** (180 mg, 0.510 mmol, 83%) as a white solid.

4.2. Preparation of (*R*)-1a in 65% ee[7b–d]

A mixture of (*R*)-(+)-BINAP (34.4 mg, 0.055 mmol, 9 mol %) and $[Rh(CO)_2Cl]_2$ (7.2 mg, 0.018 mmol, 3 mol %) in THF (5 mL) was stirred at room temperature for 10 min under an argon atmosphere. To the mixture was then added a solution of AgOTf (18.9 mg, 0.074 mmol, 12 mol %) in THF (5 mL). The formation of white precipitates of silver chloride was observed. To the resulting mixture was added a solution of enyne **2a** (200 mg, 0.615 mmol) in THF (5 mL), and then the argon atmosphere was replaced by a CO balloon. After refluxing at 80 °C for 4 h, the reaction mixture was cooled to room temperature and the carbon monoxide was released into the hood. The resulting mixture was passed through a small pad of silica gel with 1:3 EtOAc/*n*-hexane eluent and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc/*n*-hexane = 1:5) on silica gel to afford (*R*)-**1a** (158 mg, 72%, 65% ee). The ee was determined by HPLC analysis on a chiral column (Chiralpak AD-H, 0.46 × 25 cm, Daicel) under isocratic conditions (2-propanol/*n*-hexane = 1:3, 1.2 mL/min flow rate, 254 nm). Retention time: (*R*)-**1a**, τ_R = 11.16 min; (*S*)-**1a**, τ_R = 13.01 min.

4.3. Preparation of (R)-1a in >91% ee[7f]

A mixture of (*R*)-tol-BINAP (312 mg, 0.46 mmol, 30 mol %) and $[Ir(COD)Cl]_2$ (113 mg, 0.23 mmol, 15 mol %) in toluene (10 mL) was stirred at 40 °C for 30 min under an atmospheric pressure of CO. To the resulting yellow mixture was then added a solution of enyne **2a** (500 mg, 1.54 mmol) in toluene (10 mL). After refluxing at 130 °C for 24 h, the reaction mixture was cooled to room temperature and the carbon monoxide was released into the hood. The resulting mixture was passed through a small pad of silica gel with 1:3 EtOAc/*n*-hexane eluent and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc/*n*-hexane = 1:5) on silica gel to afford (*R*)-**1a** (420 mg, 78%, >91% ee).

4.4. Preparation of racemic-1b, (*RS*)-1b[7a]

The title compound (*RS*)-**1b** (440 mg, 1.59 mmol, 78%) was obtained from enyne **2b** (500 mg, 2.01 mmol) according to the procedure used for the preparation of (*RS*)-**1a** from **2a**.

4.5. Preparation of (*R*)-1b in 85% ee[7g]

A mixture of (*R*)-(+)-BINAP (250 mg, 0.40 mmol, 20 mol %) and $Co_2(CO)_8$ (138 mg, 0.40 mmol, 20 mol %) in toluene (10 mL) was stirred at 40 °C for 2 h under an atmospheric pressure of CO. To the mixture was then added a solution of enyne **2b** (500 mg, 2.01 mmol) in toluene (5 mL). After heating at 80 °C with stirring for 16 h, the reaction mixture was cooled to room temperature and the carbon monoxide was released into the hood. The resulting mixture was passed through a small pad of silica gel with 1:3 EtOAc/*n*-hexane eluent and the filtrate was concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc/*n*-hexane = 1:5) on silica gel to afford (*R*)-**1b** (200 mg, 36%, 85% ee). The ee was determined by HPLC analysis on a chiral column (Chiralpak AS, 0.46 × 25 cm, Daicel) under isocratic conditions (2-propanol/*n*-hexane = 1:2, 2.0 mL/min flow rate, 254 nm). Retention time: (*R*)-**1b**, τ_R = 21.05 min; (*S*)-**1b**, τ_R = 30.82 min.

4.6. Crystal (*RS*)-1a and crystal (*RS*)-1b

A vial containing (*RS*)-**1a** (15 mg, 0.042 mmol) in EtOAc (1 mL) or (*RS*)-**1b** (50 mg, 0.18 mmol) in acetone (1 mL) was placed in a bottle charged with *n*-hexane (7 mL). Slow diffusion of *n*-hexane into a solution of (*RS*)-**1a** in EtOAc or (*RS*)-**1b** in acetone provided a single crystal suitable for the single-crystal X-ray diffraction experiment. Elemental analysis (wt %): crystal (*RS*)-**1a**. Calcd for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96; S, 9.07. Found: C, 67.59; H, 5.32; N, 3.93; S, 9.17. Crystal (*RS*)-**1b**. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05; S, 11.56. Found: C, 60.30; H, 5.43; N, 4.96; S, 11.60.

4.7. Crystal (*R*)-1a and crystal (*R*)-1b

Since none of the synthetic methods allowed the preparation of (*R*)-**1a** or (*R*)-**1b** in greater than 99% ee, it was necessary to perfect their enantiomeric purity prior to their crystallization. A vial containing (*R*)-**1a** (20 mg, 91% ee) in EtOAc (1 mL) was placed in a bottle charged with *n*-hexane (10 mL). As the first drops of crystals were formed, the supernatant was taken and its ee was measured. When the ee of the supernatant exceeded 99%, the crystals were filtered off and the filtrate was concentrated in vacuo. The white precipitate thus obtained was then recrystallized by the diffusion of *n*-hexane (5 mL) into its solution in EtOAc (1 mL) to give a single crystal of (*R*)-**1a** suitable for the single-crystal X-ray diffraction experiment. Crystal (*R*)-**1b** was obtained according to the procedure used for that of (*R*)-**1a**. Elemental analysis (wt %): crystal (*R*)-**1a**. Calcd for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96; S, 9.07. Found: C, 68.25; H, 5.53; N, 4.30; S, 8.74. Crystal (*R*)-**1b**. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05; S, 11.56. Found: C, 61.06; H, 5.69; N, 4.99; S, 11.96.

4.8. Crystallographic data of crystal (*RS*)-1a

Colorless block crystal, 0.30 × 0.22 × 0.20 mm^3, $C_{20}H_{19}NO_3S$, M = 353.42, monoclinic, space group $P2_1/n$ (No. 14), T = 296(2) K, a = 7.277(1) Å, b = 22.243(1) Å, c = 11.286(1) Å, β = 106.42(1)°, V = 1752.3(1) Å^3, Z = 4, d_{calc} = 1.340 g/cm^3, μ(Mo Kα) = 0.203 mm^{-1}. A total of 17,866 reflections were collected in the range $1.83° \leqslant \theta \leqslant 28.36°$ of which 4379 were independent and 3196 were observed ($I > 2\sigma(I)$). CCDC reference number 711,864.

4.9. Crystallographic data of crystal (*R*)-1a

Colorless block crystal, 0.34 × 0.25 × 0.16 mm^3, C_{20} $H_{19}NO_3S$, M = 353.42, monoclinic, space group $P2_1$ (No. 4), T = 296(2) K, a = 9.272(1) Å, b = 14.863(1) Å, c = 13.181(1) Å, β = 108.01(1)°, V = 1727.5(1) Å^3, Z = 4, d_{calc} = 1.359 g/cm^3, μ(Mo Kα) = 0.206 mm^{-1}. A total of 32,882 reflections were collected in the range $1.62° \leqslant \theta \leqslant 28.28°$ of which 8452 were independent and 3659 were observed ($I > 2\sigma(I)$). CCDC reference number 711,863.

4.10. Crystallographic data of crystal (*RS*)-1b

Colorless block crystal, 0.34 × 0.28 × 0.18 mm^3, $C_{14}H_{15}NO_3S$, M = 277.33, monoclinic, space group $P2_1/n$ (No. 14), T = 296(2) K, a = 6.017(1) Å, b = 10.775(1) Å, c = 20.613(1) Å, β = 90.96(1)°, V = 1336.3(1) Å^3, Z = 4, d_{calc} = 1.379 g/cm^3, μ(Mo Kα) = 0.245 mm^{-1}. A total of 11,401 reflections were collected in the range $2.13° \leqslant \theta \leqslant 28.30°$ of which 3280 were independent and 2171 were observed ($I > 2\sigma(I)$). CCDC reference number 711,866.

4.11. Crystallographic data for crystal (*R*)-1b

Colorless rectangular crystal, 0.28 × 0.20 × 0.16 mm^3, $C_{14}H_{15}NO_3S$, M = 277.33, monoclinic, space group $P2_1$ (No. 4), T = 296(2) K, a = 6.066(1) Å, b = 10.767(1) Å, c = 20.659(1) Å, β = 91.53(1)°, V = 1348.8(1) Å^3, Z = 4, d_{calc} = 1.366 g/cm^3, μ(Mo Kα) = 0.243 mm^{-1}. A total of 12,777 reflections were collected in the range $1.97° \leqslant \theta \leqslant 28.32°$ of which 5590 were independent and 1989 were observed ($I > 2\sigma(I)$). CCDC reference number 711,865.

All the intensity data were collected on a Bruker SMART CCD diffractometer with a normal focus and graphite monochromated Mo-target X-ray tube (λ = 0.71,073 Å), and integrated with the SAINT+ software package[13] with a narrow frame algorithm. Absorption corrections were applied using SADABS.[14] All the structures were solved by direct methods and subsequent difference Fourier syntheses and refined with the SHELXTL software package.[15] All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were generated with the ideal geometry.

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8. For example, (*R*(C*),*R*(N))-**1a** is calculated to be more stable than (*R*(C*),*S*(N))-**1a**. However, the NMR spectra and HPLC analysis of (*R*)-**1a** with a chiral column showed peaks corresponding to only one compound. Therefore, (*R*)-**1a** can be considered as a single chiral molecule as well as a pair of diastereomers. By analogy, (*RS*)-**1a** can be considered as a pair of enantiomers or a racemate of two chiral molecules as well as all of the four stereoisomers. We also use the additional notation *d*#-(*R* or *S*)-**1a** for each of the four stereoisomers as shown in the bracket, where *d*# means a specific diastereomer, and (*R* or *S*) indicates the configuration around C*. Note that *d1*-(*R*)-**1a** and *d2*-(*R*)-**1a** are the mirror images of *d3*-(*S*)-**1a** and *d4*-(*S*)-**1a**, respectively. Similar notations can be applied for compound **1b**.
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12. Since there is probably a group of these types of compounds in the CSD, we have tried to search similar examples that could be classified as such. More than a thousand crystal structures with $Z = 4$ and $P2_1$ (a minimum condition for possible pseudo achiral crystals for the monoclinic crystal system) were identified from CSD data since 1989. Since scrutinizing all the results would have been too time-consuming, the search results were further narrowed down with the constraint that the target molecule contained only C, H, N, O, and S atoms. The search provided 173 hits. If two molecules in an asymmetric unit were related to each other via pseudo-inversion or pseudo-mirror planes, they would have the possibility of forming a pseudo achiral crystal. However, we were not able to identify many compounds in this class so far. Although we have some candidates for further elucidation, either the coordinates of the crystal structures or the data required for the comparison, such as the crystal structures of the racemic compounds, are lacking. Nevertheless, more cases would be expected to be found when previous and prospective crystal structures are scrutinized based on our suggestion. (a) Valente, E. J.; Trager, W. F.; Lingafelter, E. C. *Acta Crystallogr., Sect. B* **1976**, *32*, 277–279; (b) Baert, F.; Fouret, R.; Oonk, H. A. J.; Kroon, J. *Acta Crystallogr., Sect. B* **1978**, *34*, 222–226; (c) Kroon, J.; van Gurp, P. R. E.; Oonk, H. A. J.; Baert, F.; Fouret, R. *Acta Crystallogr., Sect. B* **1976**, *32*, 2561–2564; (d) Oonk, H. A. J.; Kroon, J. *Acta Crystallogr., Sect. B* **1976**, *32*, 500–504.
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