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Direct Organocatalytic Asymmetric α-Sulfenylation of Activated C–H Bonds in Lactones, Lactams, and β-Dicarbonyl Compounds

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Abstract: The application of cinchona alkaloid derivatives as catalysts for enantioselective α-sulfenylation of activated C–H bonds in lactones, lactams, and β-dicarbonyl compounds by different electrophilic sulfur reagents is presented. Optically active products are obtained in good to excellent yields and up to 91 % *ee*. Furthermore, the diastereoselective reduction of α-sulfenylated β-keto esters to give optically active α-sulfenylated β-hydroxy esters has been studied. A model for the intermediate is presented, in which the protonated cinchona alkaloid interacts with the substrate leading to face-shielding in accordance with the enantioselective α-sulfenylation step.

Keywords: asymmetric organocatalysis · cinchona alkaloids · electrophilic sulfur reagents · lactams · lactones · sulfenylation

Introduction

The application of optically active α-heterosubstituted carbonyl compounds in chemistry, pharmacology, and biology has led to an increased focus on simple and efficient procedures for the formation of enantiomerically enriched α-heteroatom-substituted carbonyl compounds. The presence of enolizable carbon–hydrogen bonds in aldehydes, ketones, and α-acidic hydrogen(s) in β-keto esters allows the possibility for reactions with different classes of electrophiles leading to the formation of carbon–heteroatom bonds. Therefore, the enantioselective conversion of carbon–hydrogen bonds to carbon–heteroatom bonds for these classes of compounds is a simple method for the synthesis of optically active compounds having these functionalities and, consequently, is attractive to chemists.[1] In recent years, a great deal of attention have been paid to the enantioselective α-functionalization of carbonyl compounds using chiral organic compounds rather than chiral metal complexes as catalysts.[2] Along this line, several examples of organocatalytic α-functionalization of carbonyl compounds such as α-amination, α-hydroxylation, and α-halogenation have been presented.[3–5] For example, enantioselective α-amination of aldehydes, ketones, and β-keto esters can be achieved with azodicarboxylates by chiral organocatalysts.[3] α-Oxidation of aldehydes and ketones have been reported by using mainly L-proline as the catalyst and nitrosobenzene or singlet oxygen as the oxidant.[4] Cinchona alkaloid derivatives can act as catalysts for the α-hydroxylation of β-keto esters using organic peroxide as the oxidant.[4d] Chiral amines have been used for the enantioselective chlorination and fluorination of aldehydes,[5a–f] and the chlorination of ketones in the presence of different chlorinating agents.[5g]

In spite of the usefulness of optically active α-sulfenylated carbonyl compounds as versatile synthetic intermediates, the procedures for their preparation are rare.[6] To the best of our knowledge, there are no reports on the direct enantioselective α-sulfenylation of activated C–H bonds in lactones, lactams, and β-dicarbonyl compounds. Recently, we introduced 1-benzylsulfanyl[1,2,4]triazole as an electrophilic sulfur source for the catalytic enantioselective α-sulfenylation of aldehydes.[7] We envisioned that this kind of electrophilic sulfur reagent could be applied for the enantioselective synthesis of optically active α-sulfenylated lactones, lactams, and β-dicarbonyl compounds by the reaction of the activated C–H bonds in these compounds catalyzed by cinchona alkaloid derivatives [Eq. (1)].

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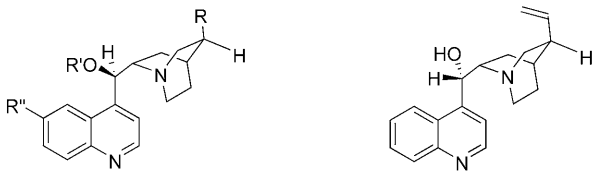
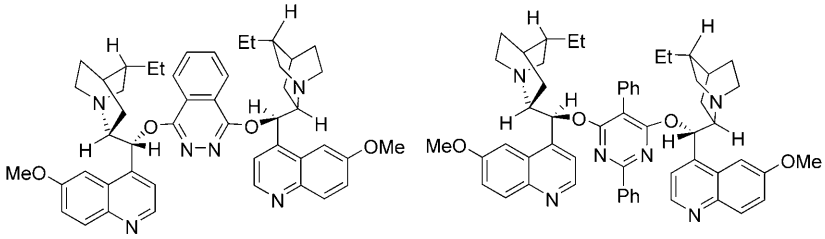


4a: R = CH_2=CH, R' = H, R'' = OMe (quinine)
4b: R = Et, R' = H, R'' = OMe (dihydroquinine)
4c: R = Et, R' = H, R'' = OH
4d: R = Et, R' = 9-phenantryl, R'' = OMe
4e: R = Et, R' = 4-Me-2-quinolyl, R'' = OMe
4f: R = CH_2=CH, R' = $Ph_2P(O)$-, R'' = OMe

4g: cinchonine



4h: $(DHQ)_2PHAL$ **4i**: $(DHQD)_2PYR$

Results and Discussion

First, we examined the feasibility of the reaction between ethyl 2-oxocyclopentanecarboxylate (**1a**) and the sulfur electrophile reagent 1-benzylsulfanyl[1,2,4]triazole (**2a**), applying catalytic amounts of quinine (**4a**) as a starting point for further optimization [Eq. (2)]. The results are summarized in Table 1.

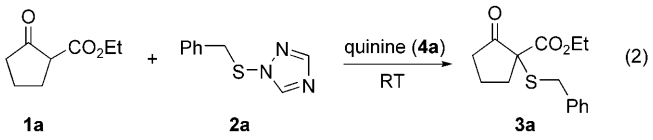


Table 1. Screening of solvents and catalyst loading (**4a**) for the direct enantioselective α-sulfenylation of ethyl 2-oxocyclopentanecarboxylate (**1a**) [Eq. (2)].[a]

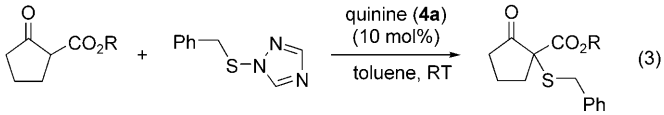
Entry	Solvent	Quinine [mol%]	Time [h]	Yield[b] [%]	*ee*[c] [%]
1	CH_2Cl_2	10	1	98	36
2	CH_2Br_2	10	1	93	32
3	hexane	10	1	65	8
4	toluene	10	0.5	85	44
5	toluene	40	4	82	43
6	toluene	2.5	4	77	33

[a] Reaction conditions: 0.1 mmol of **2a** was added to a mixture of **1a** (0.1 mmol) and **4a** in the solvent (1 mL) at room temperature. [b] Yield of isolated product. [c] *ee* was measured by HPLC (see Experimental Section for details).

Several solvents were investigated and toluene was found to be the best as shown in Table 1, entries 1–4. It appears also from entries 4–6 that the reaction rate and enantioselectivities were influenced by the amount of the quinine (**4a**).

To study if the size of the ester group can influence the enantioselectivity, the organocatalytic α-sulfenylation of the β-keto esters **1a–c** catalyzed by quinine (**4a**) (10 mol%) was investigated [Eq. (3)].

The results of this study revealed a strong effect of the size of the ester group in the β-keto esters on the enantioselectivity of the product. Whereas the reaction of the *tert*-butyl ester (**1c**) with the sulfenylation reagent (**2a**) produced the desired product **3c** with 70% *ee*, the α-sulfenylation reactions of



the corresponding ethyl (**1a**) and isopropyl esters (**1b**), respectively, under the same reaction conditions were faster, however, the products **3a** and **3b** were formed with 44 and 45% *ee*, respectively.

The key step in the optimization of the conditions of the α-sulfenylation was to evaluate the catalytic properties of different cinchona alkaloid derivatives. Based on the screening results presented above, we chose the *tert*-butyl ester (**1c**) and the sulfenylating reagent (**2a**) as the standard system for the catalyst screening using different cinchona alkaloid derivatives **4a–i** (Table 2).

Among the cinchona alkaloid derivatives tested, **4d**, $(DHQ)_2PHAL$ (**4h**), and $(DHQD)_2PYR$ (**4i**) turned out to be the most effective organocatalysts leading to **3c** in up to 73% yield and 77% *ee* at room temperature (Table 2, entries 4, 9, 11). It was found that the enantioselectivity was dependent on the reaction temperature. Performing the reaction at, for example, −30°C gave **3c** in good yields and with 89%, 81% and 89% *ee* using **4d**, **4h**, or **4i** as catalysts, respectively (Table 2, entries 5, 10, 13). A further reduction of the temperature to −40°C lowered the yield of **3a** to

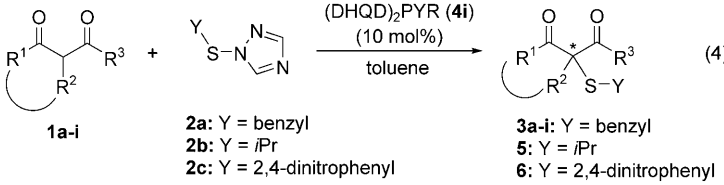
Table 2. α-Sulfenylation of *tert*-butyl 2-oxocyclopentanecarboxylate (**1c**) with 1-benzylsulfanyl[1,2,4]triazole (**2a**) catalyzed by different cinchona alkaloid derivatives (10 mol%) (**4a–i**).[a]

Entry	Catalyst	Reaction temp [°C]	Time	Yield[b] [%]	*ee*[c] [%]
1	**4a**	RT	1 day	70	70
2	**4b**	RT	2 h	73	60
3	**4c**	RT	3 days	52	27
4	**4d**	RT	3 h	73	72
5	**4d**	−30	3 days	76	89
6	**4e**	RT	2 h	63	43
7	**4f**	RT	5 days	10	33
8	**4g**	RT	2 h	80	48
9	**4h**	RT	5 h	70	70
10	**4h**	−30	3 days	78	81
11	**4i**	RT	5 h	73	77
12	**4i**	−24	3 days	54	87
13	**4i**	−30	1 day	55	89
14	**4i**	−40	3 days	23	91

[a]Reaction conditions: 0.1 mmol of **2a** was added to a mixture of **1c** (0.1 mmol) and **4** (10 mol%) in toluene (1 mL). [b] Yield of isolated product. [c] *ee* was measured by HPLC.

only 23%, however, the enantioselectivity was improved to 91% *ee* (Table 2, entry 14).

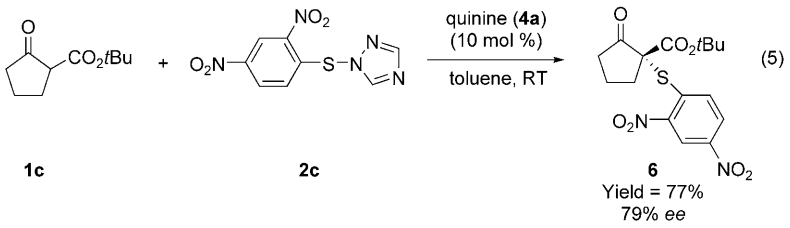
With the optimized reaction conditions in hand, we decided to investigate the organocatalytic enantioselective α-sulfenylation of a series of lactones, lactams, and a β-dicarbonyl compound, all having an activated C–H bond, with different electrophilic sulfur reagents (**2a–c**) using $(DHQD)_2PYR$ (**4i**) as the catalyst [Eq. (4)]. The results of these studies are presented in Table 3.



(4)

The catalytic enantioselective α-sulfenylation of the standard substrate **1c** proceeds well with the different sulfenylating reagents. 1-Benzylsulfanyl[1,2,4]triazole (**2a**), 1-isobutylsulfanyl[1,2,4]triazole (**2b**), and 1-(2,4-dinitrophenylsulfanyl)[1,2,4]triazole (**2c**) reacted with **1c** to produce the corresponding optically active α-sulfenylated β-keto esters with enantioselectivities in the range of 83–89% *ee* (Table 3, entries 3–5). These results demonstrate that both the yield and enantioselectivity of the optically active α-sulfenylated products are relatively independent of the sulfur-protecting group in the sulfenylating reagents **2a–c**. Methyl 5-chloro-1-oxo-2-indan carboxylate (**1d**), benzyl-1-oxo-2-indan carboxylate (**1e**), and methyl 2-oxo-1-indane carboxylate (**1f**) also undergo the enantioselective α-sulfenylation reaction with **2a** to give the corresponding α-sulfenyl-β-keto esters **3d–f** in 84–95% yields and with moderate asymmetric induction (Table 3, entries 6–8). The α-sulfenylation reaction of *N*-tosyl-2-pyrolidone-3-carboxylate esters using ethyl (**1g**) and *tert*-butyl (**1h**) esters with **2a** gave the products **3g** and **3h** with 59 and 85% *ee*, respectively (Table 3, entries 9 and 10). Furthermore, it should be noted that the sulfenylation reaction of the β-diketone **1i** with **2a** catalyzed by $(DHQD)_2PYR$ (**4h**) occurred at room temperature with 70% *ee* (Table 3, entry 11). We have also reacted acyclic β-keto esters with the sulfenylating reagents **2a–c** under various reaction conditions with different cinchona alkaloid catalysts, however, the results were not as positive as those presented above.

The absolute configuration of the stereogenic carbon center in the α-sulfenylated product **6** was determined to be (*R*) by X-ray crystal-structure analysis of the optically active product **6** obtained in Equation (5).[8]



(5)

This absolute configuration is in agreement with the *Re*-face attack of the sulfur-centered electrophile on the intermediate which is formed by deprotonation of **1c** with **4a**. A proposal for the intermediate is outlined in Figure 1. The protonated catalyst interacts with the two oxygen atoms of the β-keto ester (the keto-form exists probably as the enolate). The *Si*-face is shielded as outlined in Figure 1 leaving the *Re*-face available for attack by the sulfur electrophile.

To show the synthetic versatility of optically active α-sulfenylated β-keto esters in the preparation of chiral sulfur

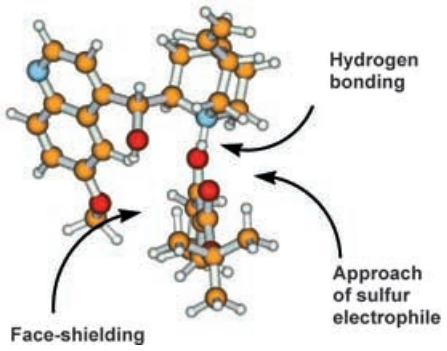
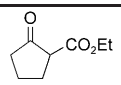
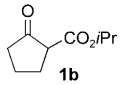
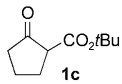
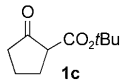
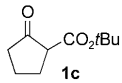
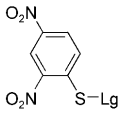
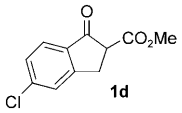
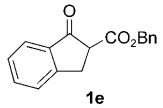
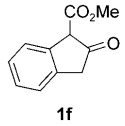
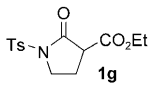
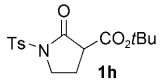
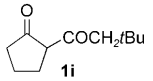


Figure 1. Postulated intermediate which is formed by deprotonation of **1c** with **4a** *Re*-face attack of the sulfur electrophile.

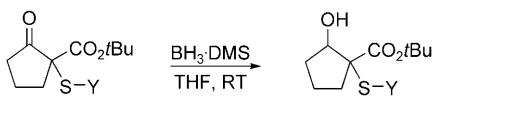
Table 3. Enantioselective α-sulfenylation of cyclic β-keto esters and lactams **1a–h** and β-diketone **1i** with the electrophilic sulfur reagents **2a–c** (Lg = traizole) catalyzed by $(DHQD)_2PYR$ (**4i**) (10 mol%) in toluene.

Entry	Substrate	Sulfur reagent	Reaction temp. [°C]	Time [days]	Product	Yield[a] [%]	*ee*[b] [%]
1	 **1a**	 **2a**	−30	4	**3a**	91	63
2	 **1b**	 **2a**	−30	5	**3b**	78	71
3	 **1c**	 **2a**	−30	5	**3c**	88	89
4	 **1c**	 **2b**	RT	2	**5a**	80	79
5	 **1c**	 **2c**	RT	2	**6a**	83	83
6	 **1d**	 **2a**	−30	3	**3d**	95	51
7	 **1e**	 **2a**	−40	3	**3e**	84	60
8	 **1f**	 **2a**	−30	3	**3f**	94	53
9	 **1g**	 **2a**	−30	1	**3g**	89	59
10	 **1h**	 **2a**	−40	1	**3h**	87	85
11	 **1i**	 **2a**	RT	1	**3I**	66	70

[a] Yield of isolated product. [b] *ee* was measured by HPLC.

compounds, reduction of the β-keto functionality in **3c**, **5** and **6** was investigated (Scheme 1).

In the presence of BH_3·DMS, reduction of the β-keto group in **3c** and **5** proceeded in a highly diastereoselective manner to give the α-sulfenylated β-hydroxy esters **7** and **8** with d.r. values of 95:5 and 98:2, respectively. A lower diastereoselectivity in the reduction of **6** with the same reducing agent was observed (d.r. = 70:30).



3c: Y = benzyl
5: Y = *i*Pr
6: Y = 2,4-dinitrophenyl

7: yield = 42%, d.r. = 95:5
8: yield = 76%, d.r. = 98:2
9: yield = 36%, d.r. = 70:30

Scheme 1. Reduction of α-sulfenylated β-keto esters.

In conclusion, we have introduced the first enantioselective catalytic asymmetric α-sulfenylation of lactones, lactams, and a β-dicarbonyl compound, all having an activated C–H bond, which afford optically active α-sulfenylated functionalized compounds. The reactions proceed in moderate to high yields (up to 95%) and enantioselectivities (up to 91% *ee*) using 1-benzylsulfanyl[1,2,4]triazole as the electrophilic sulfur reagent and commercially available cinchona alkaloid derivatives as organocatalysts. We have extended the application of 1-benzylsulfanyl[1,2,4]triazole as the electrophilic sulfur reagent for the preparation of optically active α-sulfenylated products and have also shown that 1-(2,4-dinitrophenylsulfanyl)-[1,2,4]triazole and isopropylsulfanyl[1,2,4]triazole are efficient electrophilic sulfur reagents for this reaction. Furthermore, the diastereoselective reduction of the α-sulfenylated β-keto esters gives optically active α-sulfenylated β-hydroxy esters.

Experimental Section

General methods: The ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm downfield to $CDCl_3$ ($\delta = 7.26$ ppm) for ^1H NMR spectra and relative to the central $CDCl_3$ resonance ($\delta = 77$ ppm) for ^{13}C NMR spectra. Coupling constants in ^1H NMR measurements are in Hz. The enantiomeric excess (*ee*) of the products was determined by HPLC using Chiralpack AD or AS or Chiralcel OD with *i*PrOH/hexane as eluent.

Materials: β-Keto esters **1a, 1f**, β-dicarbonyl compound **1i**, and cinchona alkaloids **4a–i** were purchased from Aldrich and used as received. β-Keto esters **1b–e** and sulfur reagents **2a–c** were prepared according to references [7,9]. Compounds **1g** and **1h** were prepared according to the standard literature procedures (deprotonation of corresponding *N*-Ts and reaction with ethyl chloroformate or $(Boc)_2O$, respectively, in THF).

General procedure for the organocatalytic α-sulfenylation of β-keto esters: The catalyst (0.05 mmol) was dried in a Schlenk tube by evacuating for 15 min. Toluene (5 mL) was added under an N_2 atmosphere. Then the β-keto ester (0.5 mmol) was added to the solution at appropriate temperature (Table 3), followed by the addition of the electrophilic sulfur reagent (0.6 mmol). The reaction mixture was stirred for the appropriate time (Table 3) and then quenched with 1 M aqueous $KHSO_4$ (3 mL). After standard aqueous workup, the product was purified by flash chromatography.

Ethyl 1-benzylsulfanyl-2-oxocyclopentanecarboxylate (3a): The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AD column (hexane/*i*PrOH) (90:10); flow rate 1.0 mL min^{-1}; $\tau_{major}=6.0$; $\tau_{minor}=6.5$; ^{1}H NMR: $\delta=1.22$ (t, $J=6.8$ Hz, 3H; CH_2CH_3), 1.88–2.12 (m, 3H; CH_2), 2.27–2.39 (m, 1H; CH_2), 2.48–2.61 (m, 2H; CH_2), 3.70 (d, $J=12$ Hz, 1H; $CH_2C_6H_5$), 4.00 (d, $J=12$ Hz, 1H; $CH_2C_6H_5$), 4.14 (q, $J=6.8$ Hz, 2H; CH_2CH_3), 7.15–7.23 ppm (m, 5H; Ar*H*); ^{13}C NMR: $\delta=14.5$, 19.6, 35.2, 35.7, 36.7, 62.5, 69.3, 127.6, 129.1, 129.7, 131.7, 169.7, 206.8 ppm; HRMS: *m/z* calcd for $C_{15}H_{18}O_3S$: 301.0874; found: 301.0862 $[M+Na]^+$; $[\alpha]_D=-76.9$ ($c=10$ mg mL^{-1}, 63% *ee*).

Isopropyl 1-benzylsulfanyl-2-oxocyclopentanecarboxylate (3b): The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AD column (hexane/*i*PrOH) (98:2); flow rate 1.0 mL min^{-1}; $\tau_{major}=7.3$; $\tau_{minor}=8.3$; ^{1}H NMR: $\delta=1.28$ (d, $J=5.6$ Hz, 6H; CH_3), 1.93–2.17 (m, 3H; CH_2), 2.32–2.43 (m, 1H; CH_2), 2.53–2.67 (m, 2H; CH_2), 3.79 (d, $J=11.6$ Hz, 1H; $CH_2C_6H_5$), 4.07 (d, $J=11.6$ Hz, 1H; $CH_2C_6H_5$), 5.08 (hep, $J=6.4$ Hz, 1H; $CHCH_3$), 7.19–7.33 ppm (m, 5H; Ar*H*); ^{13}C NMR: $\delta=$ 19.7, 22.1, 35.2, 35.4, 36.8, 60.9, 70.4, 127.7, 129.0, 129.8, 136.9, 169.4, 207.0 ppm; HRMS: *m/z* calcd for $C_{16}H_{20}O_3S$: 315.1031; found: 315.1024 $[M+Na]^+$; $[\alpha]_D=-102.9$ ($c=10$ mg mL^{-1}, 71% *ee*).

***tert*-Butyl 1-benzylsulfanyl-2-oxocyclopentanecarboxylate (3c)**: The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AD column (hexane/*i*PrOH) (98:2); flow rate 1.0 mL min^{-1}; $\tau_{major}=6.3$; $\tau_{minor}=7.5$; ^{1}H NMR: $\delta=1.42$ (s, 9H; C_4H_9), 1.84–2.07 (m, 3H; CH_2), 2.13–2.34 (m, 1H; CH_2), 2.43–2.57 (m, 2H; CH_2), 3.73 (d, $J=11.6$ Hz, 1H; $CH_2C_6H_5$), 4.00 (d, $J=11.6$ Hz, 1H; $CH_2C_6H_5$), 7.13–7.28 ppm (m, 5H; Ar*H*); ^{13}C NMR: $\delta=19.7$, 28.3, 35.2, 35.9, 36.9, 61.4, 83.3, 127.7, 129.8, 129.8, 136.9, 168.8, 207.4 ppm; HRMS: *m/z* calcd for $C_{17}H_{22}O_3S$: 329.1187; found: 329.1179 $[M+Na]^+$; $[\alpha]_D=-106.0$ ($c=10$ mg mL^{-1}, 89% *ee*).

***tert*-Butyl 1-isopropylsulfanyl-2-oxocyclopentanecarboxylate (5)**: The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AD column (hexane/*i*PrOH) (98:2); flow rate 1.0 mL min^{-1}; $\tau_{major}=4.3$; $\tau_{minor}=4.7$; ^{1}H NMR: $\delta=1.12$ (d, $J=6.4$ Hz, 3H; CH_3), 1.25 (d, $J=6.4$ Hz, 3H; CH_3), 1.40 (s, 9H; C_4H_9), 1.83–1.96 (m, 2H; CH_2), 1.99–2.11 (m, 1H; CH_2), 2.20–2.29 (m, 1H; CH_2), 2.39–2.52 (m, 2H; CH_2), 3.15 ppm (hep, $J=6.8$ Hz, 1H; $CHCH_3$); ^{13}C NMR: $\delta=19.3$, 25.1, 28.2, 35.5, 36.3, 36.9, 60.9, 82.8, 169.5, 207.7 ppm; HRMS: *m/z* calcd for $C_{13}H_{22}O_3S$: 281.1187; found: 281.1194 $[M+Na]^+$; $[\alpha]_D=-83.2$ ($c=$ 10 mg mL^{-1}, 79% *ee*).

***tert*-Butyl 1-(2,4-dinitrophenylsulfanyl)-2-oxocyclopentanecarboxylate (6)**: The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AD column (hexane/*i*PrOH) (90:10); flow rate 1.0 mL min^{-1}; $\tau_{major}=10.0$; $\tau_{minor}=12.8$; ^{1}H NMR: $\delta=1.36$ (s, 9H; C_4H_9), 2.04–2.12 (m, 2H; CH_2), 2.28–2.35 (m, 1H; CH_2), 2,41–2,50 (m, 1H; CH_2), 2.51–2.67 (m, 2H; CH_2), 8.05 (d, $J=9.2$ Hz, 1H; Ar*H*), 8.24 (d, $J=9.2$ Hz, 1H; Ar*H*), 8.90 ppm (s, 1H; Ar*H*); ^{13}C NMR: $\delta=19.9$, 28.2, 37.6, 37.7, 64.4, 85.1, 121.5, 126.8, 131.9, 142.8, 145.5, 167.8, 208.0 ppm; HRMS: *m/z* calcd for $C_{16}H_{18}N_2O_7S$: 405.0732 found: 405.0740 $[M+Na]^+$; $[\alpha]_D=+363$ ($c=$ 5 mg mL^{-1}, 83% *ee*).

Methyl 2-benzylsulfanyl-5-chloro-1-oxoindan-2-carboxylate (3d): The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AD column (hexane/*i*PrOH) (90:10); flow rate 1.0 mL min^{-1}; $\tau_{major}=11.4$; $\tau_{minor}=12.2$; ^{1}H NMR: $\delta=2.99$ (d, $J=18$ Hz, 1H; CH_2), 3.63 (s, 3H; CH_3), 3.74 (d, $J=18$ Hz, 1H; CH_2), 3.95 (d, $J=12$ Hz, 1H; $CH_2C_6H_5$), 4.09 (d, $J=12$ Hz, 1H; $CH_2C_6H_5$), 7.11–7.23 (m, 6H; Ar*H*), 7.29 (d, $J=$ 7.6 Hz, 1H; Ar*H*), 7.66 ppm (d, $J=8.8$ Hz, 1H; Ar*H*); ^{13}C NMR: $\delta=$ 35.3, 39.9, 53.8, 59.3, 126.5–129.7, 136.5, 142.4, 152.2, 169.7, 195.4 ppm; HRMS: *m/z* calcd for $C_{18}H_{15}ClO_3S$: 369.0328; found: 369.0318 $[M+Na]^+$; $[\alpha]_D=+33.8$ ($c=10$ mg mL^{-1}, 51% *ee*).

Benzyl 2-benzylsulfanyl-1-oxoindan-2-carboxylate (3e): The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AD column (hexane/*i*PrOH) (90:10); flow rate 1.0 mL min^{-1}; $\tau_{major}=14.9$; $\tau_{minor}=16.1$; ^{1}H NMR: $\delta=3.02$ (d, $J=18$ Hz, 1H; CH_2), 3.78 (d, $J=18$ Hz, 1H; CH_2), 3.98 (d, $J=12$ Hz, 1H; $CH_2C_6H_5$), 4.07 (d, $J=12$ Hz, 1H; $CH_2C_6H_5$), 5,10 (d, $J=12.4$ Hz, 1H; $CH_2C_6H_5$), 5.16 (d, $J=12.4$ Hz, 1H; $CH_2C_6H_5$), 7.08–7.40 (m, 12H; Ar*H*), 7.50–7.54 (m, 1H; Ar*H*), 7.77 ppm (d, $J=7.6$ Hz, 1H; Ar*H*); ^{13}C NMR: $\delta=35.3$, 40.2, 59.3, 68.3, 126.0, 126.6, 127.7–129.9, 135.9, 150.7, 169.6, 196.8 ppm; HRMS: *m/z* calcd for $C_{24}H_{20}O_3S$: 411.1031; found: 411.1096 $[M+Na]^+$; $[\alpha]_D=+15.2$ ($c=10$ mg mL^{-1}, 60% *ee*).

Methyl 1-benzylsulfanyl-2-oxoindan-1-carboxylate (3f): The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AS column (hexane/*i*PrOH) (99:1); flow rate 1.0 mL min^{-1}; $\tau_{major}=14.7$; $\tau_{minor}=11.3$; ^{1}H NMR: $\delta=3.68$ (s, 3H; CH_3), 3.71 (d, $J=8.8$ Hz, 2H; CH_2), 3.89 (d, $J=12$ Hz, 1H; $CH_2C_6H_5$), 3.99 (d, $J=12$ Hz, 1H; $CH_2C_6H_5$), 7.20–7.38 (m, 8H; Ar*H*), 7.44–7.46 ppm (m, 1H; Ar*H*); ^{13}C NMR: $\delta=35.9$, 42.0, 53.8, 64.6, 125.6, 127.6–130.0, 136.4, 138.2, 168.3, 205.7 ppm; HRMS: *m/z* calcd for $C_{18}H_{16}O_3S$: 335.0718; found: 335.0709 $[M+Na]^+$; $[\alpha]_D=+18.7$ ($c=10$ mg mL^{-1}, 53% *ee*).

Ethyl 3-benzylsulfanyl-2-oxo-1-(toluene-4-sulfonyl)pyrolidine-3-carboxylate (3g): The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AS column (hexane/*i*PrOH) (95:5); flow rate 1.0 mL min^{-1}; $\tau_{major}=33.8$; $\tau_{minor}=30.1$; ^{1}H NMR: $\delta=1.15$ (t, $J=7.2$ Hz, 3H; CH_2CH_3),1.89–1.95 (m, 1H; CH_2), 2.38 (s, 3H; CH_3), 2.62–2.70 (m, 1H; CH_2), 3.38 (d, $J=11.2$ Hz, 1H; $CH_2C_6H_5$), 3.71–3.77 (m, 1H; CH_2), 3.86 (d, $J=11.2$ Hz, 1H; $CH_2C_6H_5$), 3.90–3.92 (m, 1H; CH_2), 4.10 (q, $J=$ 7.2 Hz, 2H; CH_2CH_3) 6.91–6.93 (m, 2H; Ar*H*), 7.13–7.18 (m, 3H; Ar*H*), 7.29 (d, $J=8.4$ Hz, 2H; Ar*H*), 7.88 ppm (d, $J=8.4$ Hz, 2H; Ar*H*); ^{13}C NMR: $\delta=14.4$, 22.1, 30.5, 35.3, 44.6, 57.6, 63.2, 127.8, 129.0, 129.6, 130.1, 134.3, 135.7, 146.0, 166.9, 167.8 ppm; HRMS: *m/z* calcd for $C_{21}H_{23}NO_5S_2$: 456.0915; found: 456.0920 $[M+Na]^+$; $[\alpha]_D=-14.4$ ($c=$ 10 mg mL^{-1}, 59% *ee*).

***tert*-Butyl 3-benzylsulanyl-2-oxo-1-(toluene-4-sulfonyl)pyrolidine-3-carboxylate (3h)**: The enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD column (hexane/*i*PrOH) (98:2); flow rate 1.0 mL min^{-1}; $\tau_{major}=22.5$; $\tau_{minor}=20.3$; ^{1}H NMR: $\delta=1.37$ (s, 9H; C_4H_9), 1.85–1.91 (m, 1H; CH_2), 2.38 (s, 3H; CH_3), 2.60–2.68 (m, 1H; CH_2), 3.37 (d, $J=11.2$ Hz, 1H; $CH_2C_6H_5$), 3.69–3.75 (m, 1H; CH_2), 3.87 (d, $J=$ 12 Hz, 1H; $CH_2C_6H_5$), 3.91–3.94 (m, 1H; CH_2), 6.90–6.95 (m, 2H; Ar*H*), 7.10–7.28 (m, 5H; Ar*H*), 7.87–7.89 ppm (m, 2H; Ar*H*); ^{13}C NMR: $\delta=$ 22.1, 28.2, 30.6, 35.3, 44.7, 58.5, 84.4, 127.8, 128.8, 130.0, 134.5, 135.9, 145.9, 166.6, 167.2 ppm; HRMS: *m/z* calcd for $C_{21}H_{23}NO_5S_2$: 484.1228; found: 484.1294 $[M+Na]^+$; $[\alpha]_D=-42.8$ ($c=5$ mg mL^{-1}, 85% *ee*).

2-Benzylsulfanyl-2-(3,3-dimethyl-butyryl)cyclopentanone (3i): The enantiomeric excess was determined by HPLC using a Daicel Chiralpack AD column (hexane/*i*PrOH) (90:10); flow rate 1.0 mL min^{-1}; $\tau_{major}=4.8$; $\tau_{minor}=5.4$; ^{1}H NMR: $\delta=0.92$ (s, 9H; C_4H_9), 1.76–2.04 (m, 3H; CH_2), 2.22–2.34 (m, 2H; CH_2), 2.40–2.56 (m, 3H; CH_2), 3.59 (d, $J=12$ Hz, 1H; $CH_2C_6H_5$), 3.66 (d, $J=12$, 1H; $CH_2C_6H_5$), 7.14–7.25 ppm (m, 5H; Ar*H*); ^{13}C NMR: $\delta=19.4$, 29.8, 30.3, 34.0, 38.1, 50.1, 67.5, 127.7, 128.9, 129.5, 136.6, 198.7, 209.4 ppm; HRMS: *m/z* calcd for $C_{18}H_{24}O_2S$: 327.1395; found: 327.1393 $[M+Na]^+$; $[\alpha]_D=-33.7$ ($c=10$ mg mL^{-1}, 70% *ee*).

General procedure for the diastereoselective reduction of optically active α-sulfanyl β-keto esters: To a solution of α-sulfanyl β-keto ester (0.5 mmol) in THF (5 mL) was added one equivalent of BH_3·DMS. After the reaction mixture had been stirred at room temperature for 1–2 days, the reaction was quenched with H_2O (5 mL) and the mixture was extracted with Et_2O (3×5 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered, and evaporated. The crude reaction mixture was purified by flash chromatography to give the optically active α-sulfanyl β-hydroxy esters.

***tert*-Butyl 1-benzylsulfanyl-2-hydroxycyclopentanecarboxylate (7)**: ^{1}H NMR: $\delta=1.45$ (s, 9H; C_4H_9), 1.50–1.55 (m, 1H; CH_2), 1.70–1.84 (m, 4H; CH_2), 2.15–2.22 (m, 1H; CH_2), 3.70 (d, $J=12.4$ Hz, 1H; $CH_2C_6H_5$), 3.79 (d, $J=12.4$ Hz, 1H; $CH_2C_6H_5$), 4.25 (t, $J=4$ Hz, 1H; CH), 7.16–

7.26 ppm (m, 5H; Ar*H*); ^{13}C NMR: δ = 20.3, 28.4, 31.0, 32.6, 35.1, 64.8, 75.0, 82.3, 127.8, 129.2, 129.4, 138.0, 172.0 ppm; HRMS: *m/z* calcd for $C_{17}H_{24}O_3S$: 331.1344; found: 331.1315 $[M+Na]^+$.

***tert*-Butyl 2-hydroxy-1-isopropylsulfanylcyclopentanecarboxylate (8)**: ^{1}H NMR: δ = 1.25 (d, J = 6.8 Hz, 3H; CH_3), 1.34 (d, J = 6.8 Hz, 3H; CH_3), 1.48 (s, 9H; C_4H_9), 1.57–1.63 (m, 1H; CH_2), 1.73–1.93 (m, 4H; CH_2), 2.24–2.29 (m, 1H; CH_2), 3.06 (hep, J = 6.8 Hz, 1H; CH), 4.33–4.35 ppm (m, 1H); ^{13}C NMR: δ = 20.4, 24.9, 26.0, 28.4, 31.2, 33.3, 35.4, 65.0, 74.8, 82.2, 172.3 ppm; HRMS: *m/z* calcd for $C_{13}H_{24}O_3S$: 283.1314; found: 283.13552 $[M+Na]^+$.

***tert*-Butyl 1-(2,4-dnitrophenylsulfanyl)-2-hydroxycyclopentanecarboxylate (9)**: ^{1}H NMR: δ = 1.51 (s, 9H; C_4H_9), 1.89–2.07 (m, 2H; CH_2), 2.16–2.34 (m, 2H; CH_2), 2.57–2.67 (m, 2H; CH_2), 4.80–4.83 (m, 1H; CH), 7.92 (d, J = 8.8 Hz, 1H; Ar*H*), 8.34 (d, J = 6.4 Hz, 1H; Ar*H*), 9.03 ppm (s, 1H; Ar*H*); ^{13}C NMR: δ = 28.2, 33.1, 33.6, 35.6, 37.7, 66.9, 80.0, 83.9, 121.7, 126.9, 130.3, 131.3, 144.4, 172.0 ppm; HRMS: *m/z* calcd for $C_{16}H_{20}N_2O_7S$: 407.0889; found: 407.0896 $[M+Na]^+$.

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