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Enantioselective organocatalytic α-sulfenylation of substituted diketopiperazines

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ABSTRACT

The asymmetric organocatalytic α-sulfenylation of substituted piperazine-2,5-diones is reported, with cinchona alkaloids as chiral Lewis bases and electrophilic sulfur transfer reagents. Catalyst loadings, the type of sulfur transfer reagent, temperature and solvent were investigated in order to optimize the reaction conditions. The effects of ring substitution and the type of catalyst on the yield and enantioselectivity of the reaction are reported.

1. Introduction

The organocatalytic asymmetric α-heterofunctionalization of carbonyl compounds has recently emerged as a powerful synthetic methodology due to its efficiency, simplicity and low catalyst costs.[1–5] As a result, numerous examples of α-hydroxylation, α-amination,[6–8] α-halogenation,[9–17] α-selenenylation,[9,18,19] and their applications in the synthesis of complex natural products have been reported. Whereas synthetic methods for the α-sulfenylation of aldehydes,[20] ketones,[21] lactones and β-dicarbonyl compounds,[22] both via organocatalysis as well as by alternative multistep procedures[23–30] have been developed, direct organocatalytic methods for the asymmetric α-sulfenylation of less reactive β-amido esters and substituted piperazine-2,5-diones have not been explored.

The direct enantioselective α-sulfenylation of substituted β-amido esters and piperazine-2,5-diones could facilitate the synthesis of epidithiodioxopiperazines (ETPs), a class of biologically active secondary metabolites produced by the filamentous fungi *Chaetomium* and *Pithomyces* sp. These natural products contain one or two ETP rings (Fig. 1) and display a broad spectrum of biological activity.[31–35] Under physiological conditions, the bridging disulfides can exist either in disulfide or dithiol forms and are thought to be essential for the biological activity of this class of natural products.[36] While many ETPs are toxic to mammalian cells, recent reports have shown that several members of this diverse family may have anticancer activity. Among these, chetomin **1** is the most extensively studied natural product (Fig. 1).[31,37–39] Recently, chetomin has been shown to disrupt the interaction of hypoxia-inducible factor 1α (HIF-1α) with its cognate transcriptional coactivator, p300/CBP.[40,41] In cells and tissues, the interaction of these two proteins leads to the overexpression of vascular endothelial growth factor (*VEGF*), which is essential for the induction of new blood vessels that facilitate growth and metastatic spread of solid tumors.[42] Chetomin, through its ability to disrupt the hypoxia-inducible transcription of VEGF and its receptors, has potential for therapeutic use.[40]

Due to the lack of reliable methods for the stereoselective placement of the disulfide bridges and the difficulties arising from the instability of the bridging disulfides toward bases and reducing agents only a few syntheses of ETPs have been reported to date. Notably, hyalodendrin,[43–45] sporidesmins A[46] and B **2**–**3**,[47] have been prepared as racemic mixtures. While gliotoxin **4**,[45] and (+)-11,11′-dideoxyverticillin A **5** have been obtained in enantiopure form, the route to (+)-**4** involved the separation of the enantiomers which included a low-yielding chiral auxiliary step, while synthesis of (+)-**5** relied on conformational rigidity of its scaffold to perform the late-step tetrathiolation reactions. The two ETP rings of chetomin with distinctly different substitution and quaternary stereocenters, and C3–N1′ heterodimeric indoline linkage, the south fragment with its cyclotryptophan motif make stereoselective construction of its ring system even more challenging. In order to better understand the biological activity of chetomin and other ETP metabolites, the development of a general synthetic methodology for the enantioselective construction of the ETP core is needed.

In this context, organocatalytic α-sulfenylation of the piperazine-2,5-dione ring system[48] is an important transformation whose utility could be significantly expanded upon if it were rendered stereoselective. Herein we describe development of the first organocatalytic asymmetric α-sulfenylation of the substituted piperazine-2,5-dione ring system.

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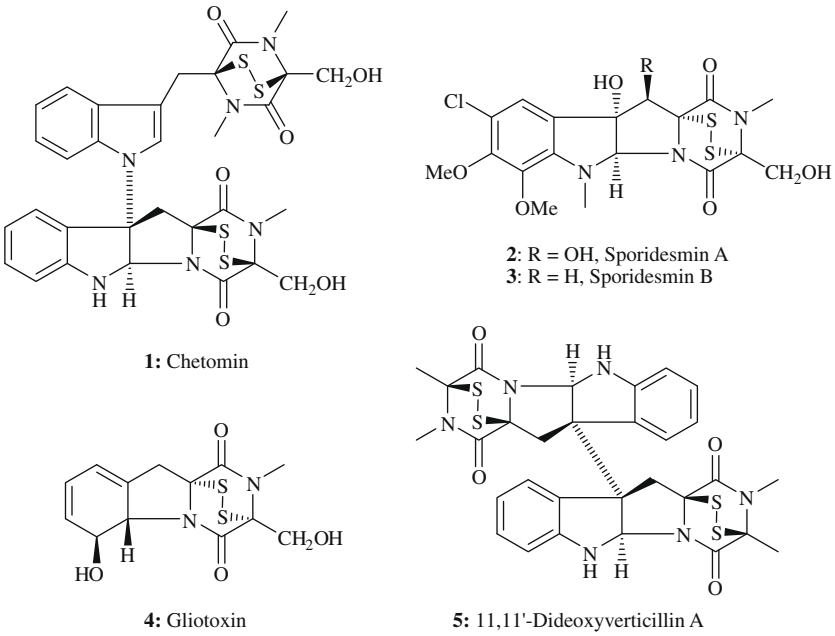
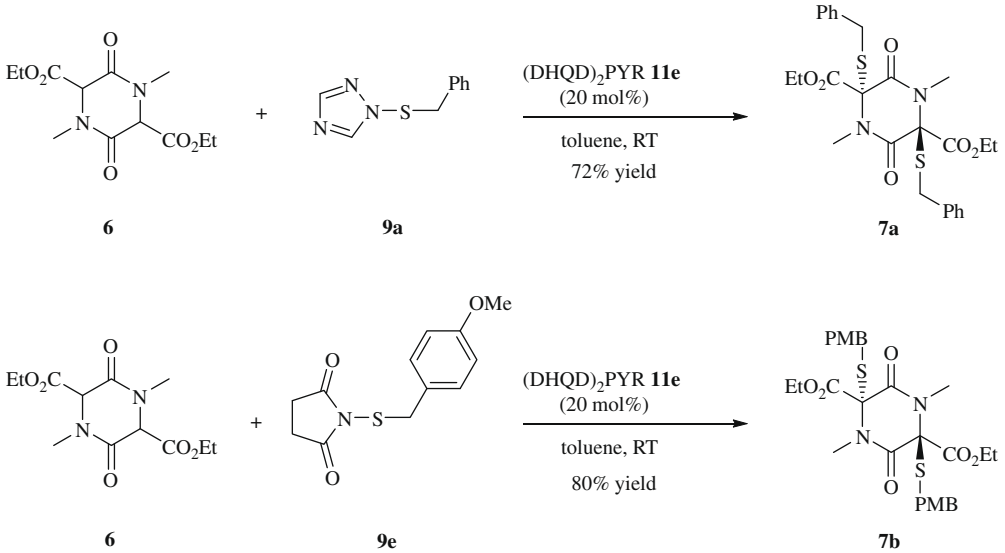


Figure 1. Epidithiodioxopiperazine fungal metabolites.

2. Results and discussion

Our initial goal was to investigate the reactivity of disubstituted piperazine-2,5-diones in an effort to introduce both sulfur-containing groups in a single step. Hence, piperazine-2,5-dione **6** was subjected to conditions of α-sulfenylation with the recently introduced electrophilic sulfur reagents 1-benzylsulfanyl-[1,2,4]-triazole,[6,8] and 1-(*p*-methoxybenzyl)sulfanyl succinimide and cinchona alkaloids as catalysts (Scheme 1).[21] Our choice of the benzyl and *p*-methoxybenzyl group in an electrophilic sulfenylation reagent was primarily because of the relative ease of their deprotection, which may facilitate subsequent synthetic transformations. Both reactions proceeded in good yields. However, the X-ray crystal structure of **7b** clearly showed that the sulfenylation proceeded in an *anti*-fashion, leading to an achiral product.[49] Since it was unclear whether the cinchona alkaloid had any effect on directing the stereochemistry of the sulfenylation, an approach involving sulfenylation of mono-substituted β-amido esters was next explored.

To test the reactivity of monosubstituted diketopiperazines toward sulfur electrophiles under conditions of organocatalysis with chiral Lewis bases, a series of derivatives of 1,4-dimethyl-2,5-piperazinedione were synthesized and examined (Scheme 2). Whereas β-amido esters **8c–8e** have shown promise, the results with β-amido ketones **8a** and **8b** were disappointing, showing only the formation of racemic products in low yields. Within the ester series, a positive correlation between the steric bulk of the ester and the enantioselectivity was observed: that is, an increase of the steric bulk of substrate **8** resulted in the increase in the enantioselectivity of the reaction. Unfortunately, an increase of the ee of the product was accompanied by a decrease in the product yields, necessitating further optimization of the reaction conditions.



Scheme 1. Organocatalytic sulfenylation of disubstituted piperazinedione **6**. PMB = *p*-methoxybenzyl.

Similar to organocatalytic α-halogenation reactions,[3,4] sulfenylations are inherently more difficult to perform with high enantioselectivity than addition reactions because of the more dynamic, less well-defined nature of the transition state. Hence, the choice of the electrophilic sulfur transfer reagent with a suitable leaving group is critical. This led us to further explore the reactivity of the β-amido esters by varying the nature of the electrophilic sulfenylating reagent (Fig. 2). The previously reported 1-benzylsulfanylsuccinimide **9d** and 1-benzylsulfanylphthalimide[22] **9f** showed no reactivity toward β-amido esters, while 1-(*p*-methoxybenzyl)-sulfanylsuccinimide[50] **9e** did react slowly with selected β-amido esters, low yields and poor enantioselectivity made its application impractical. The 1-(*p*-methoxybenzyl)-sulfenyl-[1,2,4]-triazole **9b** and 1-(*p*-nitrobenzyl)-sulfenyl-[1,2,4]-triazole **9c** were also considered, but were found to be too unstable for practical application. These results have prompted us to continue experimentation with 1-benzylsulfanyl-[1,2,4]-triazole[20,22] **9a** and 1-phenylsulfanyl-[1,2,4]-triazole **9g**[48] as these electrophilic sulfur transfer reagents had superior reactivity and higher stability when compared to the other reagents.

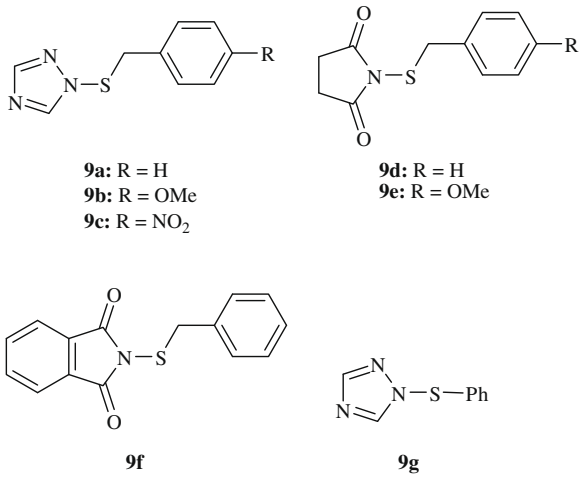
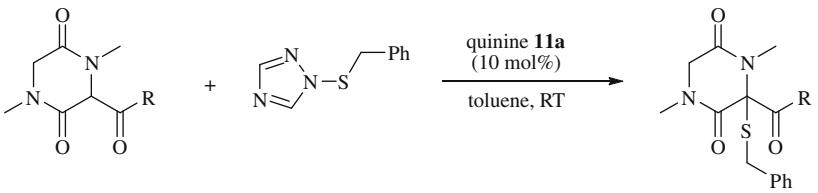


Figure 2. Scope of electrophilic sulfenylating reagents.

The accurate measurement of the enantioselectivity of the sulfenylation process was the main issue encountered in this phase of the study. The use of HPLC with a chiral stationary phase was attempted but no separation of the two enantiomers could be achieved. However, the use of chiral lanthanide shift reagents in NMR spectroscopy was successful and resulted in a quick method of measuring the enantioselectivity of the sulfur addition. 1-Benzylsulfanyl[1,2,4]triazole **9a**,[22] and 1-phenylsulfanyl[1,2,4]triazole **9g**,[48] an electrophilic sulfur transfer reagent that has been reported to sulfenylate substituted piperazines-2,5-diones in high yields, was examined for enantioselectivity under conditions of asymmetric sulfenylation. We first tested the reactivity of the bulky piperazine-2,5-dione **8e** toward the reagents **9a** and **9g** under typical sulfenylation conditions in different solvents (Table 1). The results clearly indicated that the sulfur transfer reagent **9a** gave better enantioselectivity while the use of **9g** resulted in higher yields. In keeping with the goal of achieving higher enantioselectivity, the main focus was placed on reactions with sulfur electrophile **9a**; further optimizations of the conditions were carried out with this reagent. An initial screening of a variety of solvents in the reaction revealed that they play a key role in the enantioselectivity of the reaction and product yield. Benzene was found to give superior results at room temperature, although it was noted that toluene also gave acceptable yields. As expected, a decrease in the reaction temperature increased the enantioselectivity and product ees (Table 1, entries 7–10); however the relatively high melting point of benzene made its application impractical at this temperature. Lowering the temperature from −20 °C to −78 °C resulted in the precipitation of the reactants even when dilute conditions were employed (data not shown). However, when a 3:1 mixture of benzene and toluene was used, the temperature of −10 °C could be reached without precipitating the reactants out of the solution (Table 1, entries 11–14). This two-component solvent mixture gave superior enantioselectivity as compared to toluene (entry 4). The slight decrease in yields that resulted from lowering the reaction temperature could be compensated for by adding a larger amount of sulfenylating reagent **9a**. The enantioselectivity of the reaction was not affected even after using a 10-fold excess of sulfenylating reagent **9a** (Table 1, entry 14).

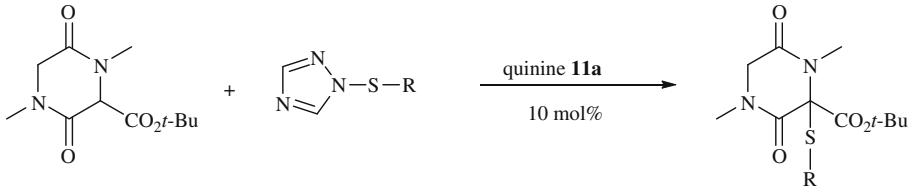
In order to determine the best catalyst for the process, six cinchona alkaloids were tested (Fig. 3). We found that the activities of each catalyst differed significantly. Under similar reaction conditions, quinine **11a** and dihydroquinine **11b** were found to be superior to phenanthryl ether **11c**, thiourea **11d**, and the more bulky catalysts $(DHQD)_2PYR$ **11e** and $(DHQD)_2PHAL$ **11f** (Table 2). This is somewhat surprising, given previous reports indicating that dimeric cinchona alkaloid derivatives **11e** and **11f** yielded better results in electrophilic α-heterofunctionalization reactions.[22] This suggests that the presence of a free hydroxyl group on the cinchona alkaloid could play a critical role in increasing both the yield and enantioselectivity of the reaction. A detailed investigation of the role of the catalyst is the subject of ongoing mechanistic studies.

Having established optimal reaction conditions, we probed the generality of this process. To further explore the reactivity of the 3-substituted piperazine-2,5-dione system, the substituents were varied as shown in Table 3. Interestingly, we found that the yield and ee of the reaction depends largely on the substituents at the *N*-4 position. With only hydrogen as the *N*-4 substituent, the sulfenylation reactions proceeded quickly with excellent yields, although with low levels of stereochemical control, resulting in the product ees ranging from 10% to 12% (Table 3, entries 1–2).



Scheme 2. Survey of enantioselective organocatalytic α-sulfenylation reactions.

Table 1
Screening of solvents, temperatures, and stoichiometry of sulfenylating reagents for the organocatalytic enantioselective α-sulfenylation of **8e**[a]



8e

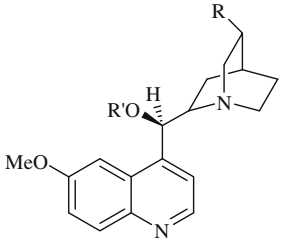
9a: R = Bn
9g: R = Ph

10e (R = Bn)
16e (R = Ph)

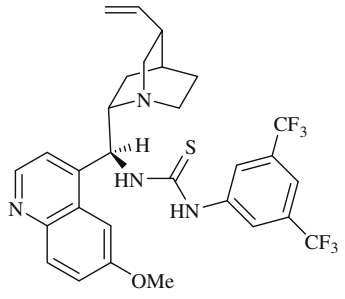
Entry	Sulfur transfer reagent	Solvent	Time (h)	Temp (°C)	Equiv of **9**	Yield[b] (%)	ee[c] (%)
1	**9a**	MeCN	24	rt	2.6	15	28
2	**9a**	CH_2Cl_2	24	rt	2.6	20	45
3	**9g**	CH_2Cl_2	24	rt	2.0	79	30
4	**9g**	Toluene	36	rt	2.0	91	30
5	**9g**	PhH/PhMe (3:1)	48	−10	3.0	96	35
6	**9g**	Toluene	48	0	3.0	97	30
7	**9a**	Toluene	24	rt	2.6	25	58
8	**9a**	Toluene	72	−20	2.6	14	66
9	**9a**	Benzene	24	rt	2.6	47	60
10	**9a**	Benzene	72	4	2.6	27	70
11	**9a**	PhH/PhMe (3:1)	120	−10	2.6	22	75
12	**9a**	PhH/PhMe (3:1)	120	−10	1.3	15	73
13	**9a**	PhH/PhMe (3:1)	120	−10	5.0	35	72
14	**9a**	PhH/PhMe (3:1)	120	−10	10	68	75

[a] Reaction conditions: a mixture of **8e** (0.5 mmol) and **11a** (0.05 mmol) was dissolved in the specified solvent (2.5 mL) under an N_2 atmosphere. After the mixture was brought to the specified temperature, **9a** or **9g** was added and the reaction stirred for the specified time.
[b] Yield of purified product.
[c] ee was measured by ^1H NMR using $Eu(hfc)_3$.

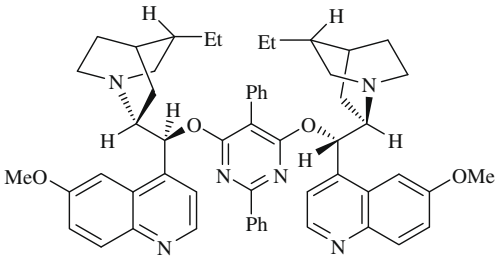
A similar result was observed for the formation of **18** from the methyl lactim ether **17** (Scheme 3), where excellent yield but low enantioselectivity was observed. An increase of the steric bulk of the *N*-4 substitution to methyl resulted in good yields and moderate to good enantioselectivities (Table 3, entries 3–6) even due to the typical difficulties of achieving enantioselective sulfur addition under typical conditions of organocatalysis.[22] A further increase of the steric bulk of the *N*-4 substituents with an ethyl group or a benzyl group resulted in no reaction with the sulfur electrophile **9a** (Table 3, entries 7–8). However, while employing a less bulky sulf-



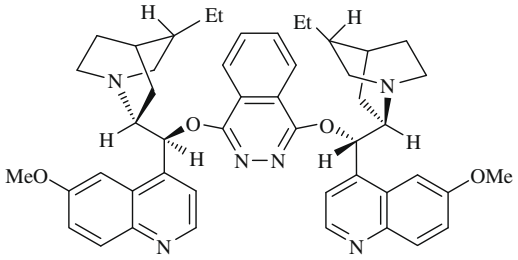
11a: R = CH_2=CH, R' = H, Quinine
11b: R = Ett, R' = H, dihydroquinine
11c: R = Et, R' = 9-phenenthryl



11d



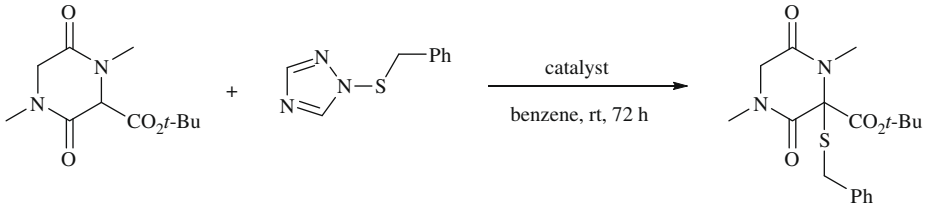
11e: $(DHQD)_2PYR$



11f: $(DHQ)_2PHAL$

Figure 3. Cinchona alkaloids screened as organocatalysts.

Table 2
Screening of cinchona alkaloid catalysts and catalyst loading for the organocatalytic enantioselective α-sulfenylation of **8e**[a]



8e **9a** **10e**

Entry	Catalyst	Catalyst loading (mol %)	Yield[b] (%)	ee[c] (%)
1	**11a**	10	47	60
2	**11a**	5	23	60
3	**11a**	40	42	62
4	**11b**	10	50	58
5	**11c**	10	36	36
6	**11d**	10	—	—
7	**11e**	10	32	30
8	**11f**	10	34	32

[a] Reaction conditions: a mixture of **8e** (0.5 mmol) and catalyst (0.05 mmol) was dissolved in benzene (2.5 mL) under an N_2 atmosphere. then **9a** (1.3 mmol) was added and the reaction was stirred for 72 h.
[b] Yield of purified product.
[c] ee was measured by ^{1}H NMR using Eu(hfc)$_3$.

enylating reagent **9g**, good yields of the products were obtained, albeit with low ees (Table 3, entries 9–11). Finally, even the most bulky substrate **8i** was successfully sulfenylated with this reagent (Table 3, entry 12).

3. Conclusion

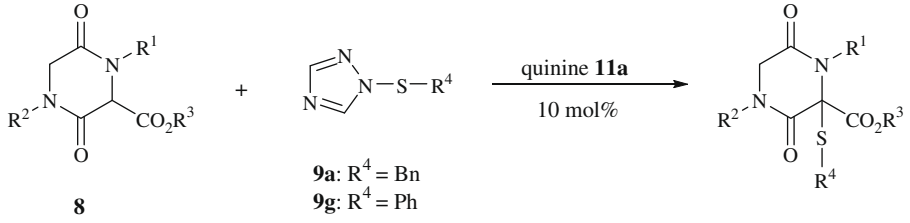
In conclusion, a novel methodology for the enantioselective organocatalytic α-heterofunctionalization of substituted piperazine-2,5-diones has been developed. The reactions proceed in moderate to good yields and up to 75% ees using commercially available cinchona alkaloids and their derivatives as organocatalysts under optimized conditions. Systematic variation of the steric bulk of the substrate, screening of the solvents and temperatures and a search for suitable catalysts and sulfur electrophiles resulted in conditions suitable for efficient α-sulfenylation of several classes of substituted piperazine-2,5-diones. Current efforts are focused on the expansion of the scope of this methodology to new substrates and the development of enantioselective α-selenenylation. Further synthetic transformation of the α-sulfenylated products and utilization of this methodology in the construction of the epidithiodioxopiperazine ring system is currently under investigation.

4. Experimental section

4.1. General

All reagents and solvents were obtained from commercial sources and used as received unless otherwise stated. All reactions

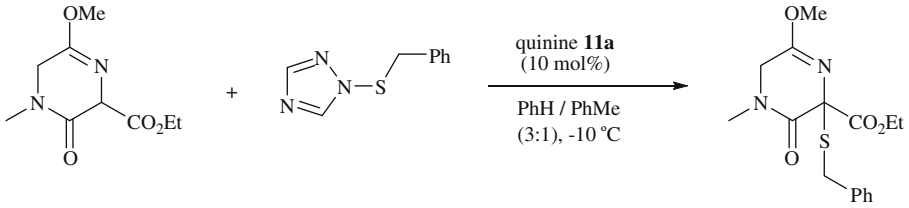
Table 3
Organocatalytic enantioselective α-sulfenylation of substituted piperazine-2,5-diones **8c–8i** with sulfenylating reagents **9a** and **9g** catalyzed by quinine **11a** (10 mol %)



8 **9a**: R^4 = Bn **9g**: R^4 = Ph

Entry	Substrate	Sulfur transfer reagent	R^1	R^2	R^3	Solvent	Temp (°C)	Equiv **9a**	Time (h)	Product	Yield[a] (%)	ee[b] (%)
1	**8h**	**9a**	H	Me	|Et	Toluene	rt	2.0	24	**10h**	95	10
2	**8h**	**9a**	H	Me	Et	Toluene	−10	1.5	24	**10h**	90	12
3	**8e**	**9a**	Me	Me	*t*-Bu	Benzene	4	2.6	72	**10e**	27	70
4	**8c**	**9a**	Me	Me	Me	Toluene	rt	2.6	24	**10c**	67	40
5	**8d**	**9a**	Me	Me	Et	PhH/PhMe (3:1)	−10	5.0	120	**10d**	70	62
6	**8e**	**9a**	Me	Me	*t*-Bu	PhH/PhMe (3:1)	−10	10	120	**10e**	68	75
7	**8f**	**9a**	Et	Et	Et	Benzene	rt	2.6	72	**10f**	NR	—
8	**8g**	**9a**	Bn	Bn	Et	Benzene	rt	2.6	72	**10g**	NR	—
9	**8e**	**9g**	Me	Me	*t*-Bu	PhH/PhMe (3:1	−10	3.0	48	**16e**	96	35
10	**8f**	**9g**	Et	Et	Et	Toluene	rt	3.0	60	**16f**	77	15
11	**8g**	**9g**	Bn	Bn	Et	Toluene	rt	3.0	60	**16g**	75	20
12	**8i**	**9g**	Bn	Bn	*t*-Bu	Toluene	rt	10	72	**16i**	52	42

[a] Yield of purified product.
[b] ee was measured by ^{1}H NMR using Eu(hfc)$_3$.



17 **9a** **18**: 95% yield, 5% *ee*

Scheme 3. Organocatalytic α-sulfenylation of lactim ether **17**.

involving moisture-sensitive reagents were conducted under a dry N_2 atmosphere with anhydrous solvent and flame dried glassware. Hygroscopic liquids were transferred via a syringe and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated using a rotary evaporator at 30–150 mm Hg. Gravity chromatography was performed on silica gel (230–400 mesh) using reagent grade solvents. Analytical thin-layer chromatography was performed on glass-backed, pre-coated plates (0.25 ram, Silica Gel 60, F-254, EM Science). Nuclear Magnetic Resonance (NMR) spectra were collected on Varian Unity 300 MHz, or Bruker 250 MHz, 500 MHz or 600 MHz instruments in the indicated solvents.

The peak positions are reported with chemical shifts (δ) in ppm referenced to tetramethylsilane (0 ppm), or the signals resulting from the incomplete deuteration of the solvent: $CDCl_3$ (7.26 ppm), or the center line of the multiplet of CD_3OD (3.31 ppm). ^{13}C NMR spectra were referenced to signals of $CDCl_3$ (77.0 ppm) or CD_3OD (49.2 ppm). The coupling constants (J) are reported in hertz (Hz). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), broad (br), multiplet (m). Mass spectra were obtained from the Mass Spectrometry Laboratory in the Department of Chemistry at the University of Arizona. Infrared spectra (IR) were collected on polyethylene spotted with the compound in the indicated solvent and recorded in cm^{-1}. Melting points were measured on Mel-Temp capillary melting point apparatus and all were uncorrected. Optical rotations were determined using a JASCO P-1020 polarimeter. 1,4-Dimethyl-3,6-diethoxycarbonyl-3,6-di-*S*-(4-methoxy-benzyl)-piperazine-2,5-dione **7b**,[49] 3-(methoxycarbonyl)-1,4-dimethyl-piperazine-2,5-dione **8c**[51] and ethyl-2-(dibenzylamino)-3-[(2-benzyloxycarbonyl)methylamino]-3-oxopropanoate **13**[48] were synthesized as previously described.

4.2. Synthesis of substituted piperazine-2,5-diones

4.2.1. 1,4-Dimethyl-3,6-diethoxycarbonyl-3,6-di-*S*-benzylpiperazine-2,5-dione 7a

1,4-Dimethyl-3,6-diethoxycarbonyl-2,5-piperazinedione (72 mg, 0.25 mmol) and $(DHQD)_2PYR$ (44 mg, 0.050 mmol) was combined in a dry flask. The compounds were dried under vacuum for 15 min. Then, 1-benzylsulfanyl-[1,2,4] triazole (115 mg, 0.60 mmol) and CH_2Cl_2 were added under an N_2 atmosphere. The reaction mixture was stirred 48 h. After quenching with 1 M $KHSO_4$, the mixture was extracted three times with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure to yield a white solid. The product was purified by column chromatography (silica-gel, hexane/EtOAc (3:1)) using a dry load to yield **7a** (96 mg, 72% yield). ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 1.24$ (t, $J = 14$ Hz, 6H), 3.13 (s, 6H), 3.71 (d, $J = 23$ Hz, 2H), 3.99 (d, $J = 23$ Hz, 2H) 4.26–4.35 (m, 4H), 7.26–7.30 (m, 10H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): $\delta = 13.91$, 32.13, 34.29, 64.28, 78.14, 127.6, 128.7, 129.3, 134.8, 161.8, 164.6. HRMS-ESI: m/z $[M+H]^+$ calcd for $C_{26}H_{31}N_2O_6S_2$: 531.1624; found: 531.1629.

4.2.2. General procedure for the preparation of compounds 8a, 8b and 8d

A suspension of the specified amount of sarcosine anhydride (see below) in dry THF under a N_2 atmosphere was cooled to −78 °C. To this solution, an appropriate amount of KO*t*-Bu (1.0 M solution in THF) was added dropwise with stirring. Once the addition was complete, the mixture was allowed to stir for 5 min. Then, methyl benzoate, methyl isovalerate or diethyl carbonate (vide infra) were added dropwise. The temperature was maintained for 15 min, and then the reaction was warmed to room temperature and stirred for an additional 3 h. A saturated NH_4Cl solution (8 mL) was added and stirring continued for 10 min. Most of the THF was removed under reduced pressure, and the remaining residue was extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by column chromatography (silica-gel, CH_2Cl_2/acetone (4:1)) to afford the product.

4.2.2.1. 3-Benzoyl-1,4-dimethylpiperazine-2,5-dione 8a. Reactants: sarcosine anhydride (250 mg, 1.76 mmol), methyl benzoate (719 mg, 0.60 mL, 5.28 mmol). Base: 1.0 M solution of KO*t*-Bu in THF (4.6 mL, 4.6 mmol). Yield of **8a** 305 mg, 70%. White solid. Mp 119–122 °C. IR (CH_2Cl_2) ν_{max} (cm^{-1}) 3050, 1678, 1602, 1405, 1330, 1237, 1031, 961, 688, 623. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.05–8.04$ (2H, m), 7.58–7.56 (1H, m), 7.49–7.47 (2H, m), 5.97 (1H, s), 4.89 (1H, d, $J = 14$ Hz), 4.59 (1H, d, $J = 14$ Hz), 3.87 (3H, s), 3.83 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.7, 166.1, 160.4, 134.8, 133.9, 130.1, 128.9, 68.59, 52.16, 33.98, 33.11. HRMS-EI: m/z $M^{\cdot+}$ calcd for $C_{13}H_{14}N_2O_3$: 246.1004; found: 246.1010.

4.2.2.2. 3-(Isobutylcarbonyl)-1,4-dimethylpiperazine-2,5-dione 8b. Reactants: sarcosine anhydride (250 mg, 1.76 mmol), methyl isovalerate (613 mg, 0.696 mL, 5.28 mmol). Base: 1.0 M solution of KO*t*-Bu in THF (4.4 mL, 4.4 mmol). Yield of **8b** 304 mg, 75%. White solid. Mp 81–83 °C. IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1723, 1673, 1405, 1327, 1256, 1017. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.63$ (1H, s), 3.93 (1H, d, $J = 18$ Hz), 3.70 (1H, d, $J = 18$ Hz), 2.85 (3H, s), 2.75 (3H, s), 2.61 (1H, dd, $J = 17$ Hz and $J = 8$ Hz), 2.46 (1H, dd, $J = 17$ Hz and J = 7 Hz), 2.08 (1H, septet, $J = 7$ Hz), 0.87 (3H, d, $J = 7$ Hz), 0.78 (3H, d, $J = 7$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 201.6$, 164.7, 159.9, 72.68, 51.50, 48.90, 33.59, 32.74, 24.23, 22.36, 21.79. HRMS-FAB: m/z $[M+H]^+$ calcd for $C_{11}H_{19}N_2O_3$: 227.1396; found: 227.1390.

4.2.2.3. 3-(Ethoxycarbonyl)-1,4-dimethylpiperazine-2,5-dione 8d. Reactants: sarcosine anhydride (2.00 g, 14.1 mmol), diethyl carbonate (5.00 g, 5.13 mL, 42.3 mmol). Base: 1.0 M solution of KO*t*-Bu in THF (35.2 mL, 35.2 mmol). Yield of **8d** 2.33 g, 77%. White solid. Mp 69–71 °C. IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1738, 1665, 1410, 1264, 1032. ^1H NMR (500 MHz, $CDCl_3$) δ 4.55 (1H, s), 4.33–4.25 (2H, m), 4.18 (1H, d, $J = 17$ Hz), 3.85 (1H, d, $J = 17$ Hz), 2.99 (3H, s), 2.96 (3H, s), 1.33 (3H, dt, $J = 6$ Hz and $J = 2$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 164.5, 160.2, 66.13, 63.08, 51.78,

33.90, 32.91, 14.11.HRMS-EI: *m/z* $M^{\cdot+}$ calcd for $C_9H_{14}N_2O_4$: 214.0954; found: 214.0959.

4.2.3. 1,4-Diethylpiperazine-2,5-dione 12

A suspension of 2,5-piperazinedione (2.50 g, 21.9 mmol) in dry DMF (50 mL) under an N_2 atmosphere was cooled to 0 °C in an ice bath. Then NaH (60% in mineral oil) (2.63 g, 65.8 mmol) was added in portions over the course of 5 min, and the mixture was allowed to stir for 15 min. Then, iodoethane (7.23 g, 3.71 mL, 46.0 mmol) was added dropwise with stirring. The reaction was warmed to room temperature and stirred overnight. Then MeOH (25 mL) was added, and the solvent was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated. The crude solid was purified by column chromatography (silica-gel, CH_2Cl_2/acetone (7:3)) to afford **12** (2.49 g, 67% yield) as a white solid. Mp 125–127 °C. IR (acetone) ν_{max} (cm^{-1}) 1723, 1673, 1405, 1327, 1256, 1017. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.89 (4H, s), 3.39 (4H, q, J = 7 Hz), 1.10 (6H, t, J = 7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8, 49.16, 40.58, 11.65. HRMS-EI: *m/z* $M^{\cdot+}$ calcd for $C_8H_{14}N_2O_2$: 170.1055; found: 170.1060.

4.2.4. General procedure for the preparation of compounds 8e–8g

A suspension of sarcosine anhydride, 1,4-diethylpiperazine-2,5dione **12** or 1,4-dibenzylpiperazine-2,5-dione (vide infra) in dry THF (40 mL) under a N_2 atmosphere was cooled to −78 °C. Then LHMDS (1.0 M solution in THF) was added dropwise with stirring. Once the addition was complete, the mixture was allowed to stir for 5 min. Then, Boc_2O or diethyl carbonate in dry THF (10 mL) was added dropwise. The temperature was maintained for 15 min, and then the reaction was warmed to room temperature and stirred for an additional 3 h. A saturated NH_4Cl solution (40 mL) was added and stirring was continued for 10 min. Most of the THF was removed under reduced pressure, and the remaining residue was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by column chromatography (silica-gel, CH_2Cl_2/acetone (85:15)) to afford the product.

4.2.4.1. 3-(*tert*-Butoxycarbonyl)-1,4-dimethylpiperazine-2,5-dione 8e. Reactants: sarcosine anhydride (2.00 g, 14.1 mmol), Boc_2O (9.23 g, 42.3 mmol). Base: 1.0 M solution of LHMDS in THF (35.2 mL, 35.2 mmol). Yield of **8e** 2.03 g, 60%. White solid. Mp 71–73 °C. IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1737, 1678, 1156, 1030. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.39 (1H, s), 4.13 (1H, d, J = 17 Hz), 3.80 (1H, d, J = 17 Hz), 2.95 (3H, s), 2.91 (3H, s), 1.46 (9H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.4, 164.5, 160.6, 84.35, 66.86, 51.71, 33.68, 32.66, 27.78. HRMS-FAB: *m/z* $[M+H]^+$ calcd for $C_{11}H_{18}N_2O_4$: 243.1346; found: 243.1353.

4.2.4.2. 3-(Ethoxycarbonyl)-1,4-diethylpiperazine-2,5-dione 8f. Reactants: 1,4-diethyl-2,5-piperazinedione (500 mg, 2.94 mmol), diethyl carbonate (1.04 g, 1.10 mL, 8.82 mmol). Base: 1.0 M solution of LHMDS in THF (7.35 mL, 7.35 mmol). Yield of **8f** 624 mg, 88%. Colorless oil. IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1742, 1677, 1350, 1302, 1263, 1202, 1052, 1020. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.52 (1H, s), 4.26–4.16 (2H, m), 4.14 (1H, d, J = 17 Hz), 3.75 (1H, d, J = 17 Hz), 3.61 (1H, sextet, J = 7 Hz), 3.50 (1H, sextet, J = 7 Hz), 3.29 (1H, sextet, J = 7 Hz), 3.20 (1H, sextet, J = 7 Hz), 1.24 (3H, t, J = 7 Hz), 1.13–1.07 (6H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.0, 164.4, 160.1, 64.06, 62.79, 49.45, 41.26, 40.74, 13.93, 12.17, 11.67.

HRMS-EI: *m/z* $M^{\cdot+}$ calcd for $C_{11}H_{18}N_2O_4$: 242.1267; found: 242.1256.

4.2.4.3. 3-(Ethoxycarbonyl)-1,4-dibenzylpiperazine-2,5-dione 8g. Reactants: 1,4-dibenzyl-2,5-piperazinedione (750 mg, 2.54 mmol), diethyl carbonate (900 mg, 0.923 mL, 7.26 mmol). Base: 1.0 M solution of LHMDS in THF (6.36 mL, 6.36 mmol). Yield of **8g** 725 mg, 78%. White solid. Mp 136–137 °C. IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1728, 1672, 1380, 1082. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.20 (10H, m), 4.90 (1H, d, J = 15 Hz), 4.78 (1H, d, J = 15 Hz), 4.58 (1H, s), 4.39 (1H, d, J = 15 Hz), 4.31 (1H, d, J = 15 Hz), 4.12–4.07 (3H, m), 3.83 (1H, d, J = 17 Hz), 1.18 (3H, t, J = 7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 164.8, 160.6, 134.7, 134.4, 128.9, 128.8, 128.3, 128.2, 128.1, 63.46, 62.88, 49.77, 49.57, 48.84. 13.95. HRMS-FAB: *m/z* $[M+H]^+$ calcd for $C_{21}H_{22}N_2O_4$: 367.1658; found: 367.1658.

4.2.5. 3-(Ethoxycarbonyl)-1-methylpiperazine-2,5-dione 8h

To a solution of **13** (12.0 g, 24.6 mmol) in 60 mL of ethanol was added 10% palladium on carbon (2.5 g). The walls of the flask were washed with an additional 10 mL of ethanol and the reaction mixture was stirred under a hydrogen atmosphere at room temperature for 72 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (silica-gel, CH_2Cl_2/acetone (1:1)) to yield **8h** (3.84 g, 78% yield) as a white solid. Mp 93–95 °C. IR (acetone) ν_{max} (cm^{-1}) 1741, 1677, 1259, 1199, 1025. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.49 (1H, s), 4.68 (1H, d, J = 2 Hz), 4.30–4.17 (2H, m), 4.19 (1H, d, J = 17 Hz), 3.84 (1H, d, J = 17 Hz), 3.00 (3H, s), 1.32 (3H, dt, J = 7 Hz and J = 1 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.3, 166.8, 160.4, 62.98, 59.23, 51.57, 34.20, 13.95. HRMS-FAB: *m/z* $[M+H]^+$ calcd for $C_8H_{13}N_2O_4$: 201.0876; found: 201.0883.

4.2.6. 5-Methoxy-1-methyl-3,6-dihydropyrazin-2-one 14

To a solution of 1-methyl-2,5-piperazinedione (1.00 g, 7.87 mmol) in dry CH_2Cl_2 (30 mL) was added methyltriflate (1.94 g, 11.8 mmol) dropwise at room temperature. The mixture was stirred overnight. Then, the reaction was quenched by the addition of a saturated solution of K_2CO_3 (30 mL) and was extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by column chromatography (silica-gel, CH_2Cl_2/acetone (7:3)) to afford **14** (726 mg, 65% yield) as a colorless oil. IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1702, 1641, 1510, 1378, 1330, 1021. ^1H NMR (600 MHz, $CDCl_3$): δ = 4.13 (2H, t, J = 3 Hz), 3.92 (2H, t, J = 3 Hz), 3.70 (3H, s), 2.96 (3H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 166.5, 157.3, 52.89, 50.10, 48.23, 33.28. HRMS-EI: *m/z* $M^{\cdot+}$ calcd for $C_6H_{10}N_2O_2$: 144.0742; found: 144.0748.

4.2.7. 3-(Ethoxycarbonyl)-5-methoxy-1-methyl-6-hydropyrazin-2-one 17

A solution of 5-methoxy-1-methyl-3,6-dihydropyrazin-2-one **14** (250 mg, 1.77 mmol) and Et_2CO_3 (634 mg, 5.32 mmol) in dry THF (6 mL) under an N_2 atmosphere was cooled to −78 °C. The LHMDS (1.0 M solution in THF) (4.43 mL, 4.43 mmol) was added dropwise with stirring. Once the addition was complete, the mixture was allowed to stir for 15 min, and then the reaction was warmed to room temperature and stirred for an additional 3 h. A saturated NH_4Cl solution (10 mL) was added and stirring was continued for 10 min. Most of the THF was removed under reduced pressure, and the remaining residue was extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated. The crude oil was purified by column chromatography (silica-gel, CH_2Cl_2/acetone (85:15)) to afford **17** (265 mg, 70% yield) as a colorless oil. IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1736, 1658, 1374, 1191, 1038. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.87 (1H, s), 4.22–4.17 (2H, m), 4.15 (1H, dd, J = 17 Hz and

J = 2 Hz), 3.83 (1H, dd, J = 17 Hz and J = 2 Hz), 3.73 (3H, s), 2.96 (3H, s), 1.28 (3H, dt, J = 6 Hz and J = 1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 163.1, 160.6, 64.01, 62.06, 53.51, 48.54, 33.65, 13.97.

HRMS-EI: m/z $M^{\cdot+}$ calcd for $C_9H_{14}N_2O_4$: 214.0954; found: 214.0955.

4.3. General procedure for asymmetric α-sulfenylation

To a flame dried flask purged with N_2 and equipped with a stir bar was added the β-amido ester, catalyst, and solvent. This solution was brought to the desired temperature, followed by addition of the sulfenylating reagent. The mixture was stirred for the appropriate period of time. Then, the reaction was quenched with a saturated solution of NH_4Cl (same volume as solvent) and extracted three times with CH_2Cl_2. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated. The crude oils were purified by column chromatography (silica-gel). Enantiomeric excess (ee) was determined by ^{1}H NMR spectroscopy using $Eu(hfc)_3$.

4.3.1. 3-Benzylsulfanyl-3-(methoxycarbonyl)-1,4-dimethylpiperazine-2,5-dione 10c

$[\alpha]_D$ = +15.4 (c 0.01, CH_2Cl_2, 40% ee). IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1751, 1671, 1461, 1396, 1248, 1045. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.26 (5H, m), 3.91–3.76 (4H, m), 3.88 (3H, s), 2.99 (3H, s), 2.76 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.63, 163.1, 160.6, 135.5, 128.6, 128.5, 127.5, 54.22, 50.88, 34.63, 33.83, 30.58. HRMS-FAB: m/z $[M+H]^+$ calcd for $C_{15}H_{18}N_2O_4S$: 323.1066; found: 323.1062.

4.3.2. 3-Benzylsulfanyl-3-(ethoxycarbonyl)-1,4-dimethylpiperazine-2,5-dione 10d

$[\alpha]_D$ = +22.1 (c 0.01, CH_2Cl_2, 62% ee). IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1745, 1668, 1460, 1390, 1263, 1048. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.26 (5H, m), 4.40–4.30 (2H, m), 3.91–3.77 (4H, m), 3.00 (3H, s), 2.76 (3H, s), 1.34 (3H, t, J = 7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.0, 163.2, 160.7, 135.6, 128.6, 128.5, 127.5, 76.79, 63.75, 50.89, 34.61, 33.79, 30.51, 13.93. HRMS-FAB: m/z $[M+H]^+$ calcd for $C_{16}H_{20}N_2O_4S$: 337.1222; found: 337.1236.

4.3.3. 3-Benzylsulfanyl-3-(*tert*-butoxycarbonyl)-1,4-dimethylpiperazine-2,5-dione 10e

$[\alpha]_D$ = +33.0 (c 0.01, CH_2Cl_2 75% ee).

IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1740, 1665, 1464, 1390, 1261, 1062.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.25 (5H, m), 3.88 (1H, d, J = 17 Hz), 3.79 (2H, s), 3.77 (1H, d, J = 17 Hz), 3.01 (3H, s), 2.74 (3H, s), 1.53 (9H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.7, 163.1, 161.0, 135.6, 128.4, 127.3, 85.15, 77.33, 50.81, 34.43, 33.65, 30.25, 27.54.

HRMS-FAB: m/z $[M+H]^+$ calcd for $C_{18}H_{24}N_2O_4S$: 365.1536; found: 365.1552.

4.3.4. 3-Benzylsulfanyl-3-(ethoxycarbonyl)-1-methylpiperazine-2,5-dione 10h

$[\alpha]_D$ = 3.1 (c = 0.01, CH_2Cl_2 7% ee).

IR (acetone) ν_{max} (cm^{-1}) 3219, 3107, 1746, 1680, 1403, 1239, 1039.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.96 (1H, s), 7.33 (5H, m), 4.30–3.96 (4H, m), 4.95 (1H, d, J = 18 Hz), 3.87 (1H, d, J = 18 Hz), 2.82 (3H, s), 1.31 (3H, t, J = 7 Hz).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.9, 165.6, 160.3, 135.6, 128.9, 128.4, 127.3, 68.54, 63.61, 51.53, 35.26, 34.24, 13.70.

HRMS-FAB: m/z $[M+H]^+$ calcd for $C_{15}H_{19}N_2O_4S$: 323.1066; found: 323.1078.

4.3.5. 3-Phenylsulfanyl-3-(*tert*-butoxycarbonyl)-1,4-dimethyl-2,5-piperazinedione 16e

$[\alpha]_D$ = 27.1350 (c = 30 mg mL^{-1}, CH_2Cl_2, 35% ee).

IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1744, 1677, 1463, 1387, 1336, 1258, 1157, 1045.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.36 (5H, m), 3.41 (1H, d, J = 18 Hz), 3.14 (3H, s), 2.75 (3H, s), 2.04 (1H, d, 18 Hz), 1.57 (9H, s).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.49, 163.10, 161.03, 138.02, 130.92, 129.03, 128.75, 85.58, 81.74, 50.07, 33.47, 30.00, 27.70.

HRMS (EI) calcd for $C_{17}H_{22}N_2O_4SNa^+$: 373.1192, found: 373.1189.

4.3.6. 3-Phenylsulfanyl-3-(ethoxycarbonyl)-1,4-diethyl-2,5-piperazinedione 16f

$[\alpha]_D$ = −4.760 (c = 10 mg mL^{-1}, CH_2Cl_2, 10% ee).

IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1748, 1673, 1460, 1414, 1357, 1294, 1248, 1165, 1069, 1019.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.33 (5H, m), 4.44–4.31 (2H, m), 3.93–3.88 (1H, m), 3.44 (1H, d, J = 18 Hz), 3.33–3.22 (3H, m), 2.20 (1H, d, J = 18 Hz), 1.36 (3H, t, J = 7 Hz), 1.28 (3H, t, J = 7 Hz), 1.0 (3H, t, J = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.25, 163.44, 160.67, 138.22, 130.88, 129.15, 128.11, 81.30, 63.75, 47.72, 41.56, 41.34, 13.86, 12.72, 11.41.

HRMS (EI) calcd for $C_{17}H_{22}N_2O_4SNa^+$: 373.1192, found: 373.1204.

4.3.7. 3-Phenylsulfanyl-3-(ethoxycarbonyl)-1,4-dibenzyl-2,5-piperazinedione 16g

$[\alpha]_D$ = −1.134 (c = 10 mg mL^{-1}, CH_2Cl_2, 5% ee).

IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1749, 1675, 1465, 1245, 1172, 1025.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.09 (15H, m), 5.46 (1H, d, J = 16 Hz), 4.58 (1H, d, J = 15 Hz), 4.46 (1H, d, J = 16 Hz), 4.13 (1H, d, J = 15 Hz), 3.93–3.89 (1H, m), 3.52 (1H, d, J = 18 Hz), 3.17–3.13 (1H, m), 2.19 (1H, d, J = 18 Hz), 0.86 (3H, t, J = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.56, 164.11, 161.41, 138.02, 135.79, 134.22, 130.85, 129.09, 129.01, 128.82, 128.63, 128.31, 128.17, 127.71, 127.56, 81.13, 63.18, 50.12, 47.69, 47.07, 13.20.

HRMS (EI) calcd for $C_{27}H_{26}N_2O_4SNa^+$: 497.1505, found: 497.1501.

4.3.8. 3-Phenylsulfanyl-3-(*tert*-butoxycarbonyl)-1,4-dibenzyl-2,5-piperazinedione 16i

$[\alpha]_D$ = 30.1857 (c = 30 mg mL^{-1}, CH_2Cl_2, 42% ee).

IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1746, 1680, 1462, 1402, 1238, 1038.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.18 (15H, m), 5.3 (1H, d, J = 16 Hz), 4.86 (1H, d, J = 14 Hz), 4.63 (1H, d, J = 16 Hz), 3.94 (J = 14 Hz), 3.56 (1H, d, J = 18 Hz), 2.17 (1H, d, J = 18 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 164.26, 163.38, 161.77, 138.06, 135.38, 134.38, 130.79, 129.03, 128.77, 128.63, 128.20, 128.17, 128.01, 127.64, 127.21, 85.55, 82.49, 49.70, 47.96, 47.52, 26.99.

HRMS (EI) calcd for $C_{29}H_{31}N_2O_4S$ $[M+H]^+$: 503.1999, found: 503.2.

4.3.9. 3-Benzylsulfanyl-3-(ethoxycarbonyl)-5-methoxy-1-methyl-3,6-dihydro-1*H*-pyrazin-2-one 18

$[\alpha]_D$ = 1.1 (c = 0.01, CH_2Cl_2 5% ee).

IR (CH_2Cl_2) ν_{max} (cm^{-1}) 1744, 1672, 1385, 1252, 1031.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.21 (5H, m), 4.28–4.24 (2H, m), 4.06 (1H, d, J = 13 Hz), 3.98 (1H, d, J = 13 Hz), 3.90 (2H, s), 3.76 (3H, s), 2.88 (3H, s), 1.30 (3H, t, J = 7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7, 163.5, 160.9, 137.0, 129.0, 128.3, 127.0, 62.76, 53.97, 48.55, 35.17, 33.82, 13.94.

HRMS-FAB: m/z $[M+H]^+$ calcd for $C_{16}H_{20}N_2O_4S$: 337.1222; found: 337.1236.

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