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Asymmetric Synthesis of Succinic Semialdehyde Derivatives

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The nucleophilic Michael addition of 2-(diphenylmethoxymethyl)-1-methyleneamino pyrrolidine **1D** to prochiral aliphatic and aromatic alkylidene malonates **2** takes place in the presence of MgI_2 to afford the corresponding Michael adducts **3** in excellent yields and good selectivities. In the aromatic series, optically pure (de > 98%) major diastereomers (*S*,*S*)-**3** were isolated in good yields (77−93%) after chromatographic separation. Direct, racemization-free $BF_3{\cdot}OEt_2$-catalyzed thiolysis of compounds **3** afforded dithioacetals **7**. These compounds were transformed into malonates **8** and succinic semialdehyde derivatives **9** by Raney Nickel mediated desulfuration or decarboxylation, respectively.

Introduction

The asymmetric Michael addition of nucleophiles to conjugated carbonyl compounds is one of the most powerful methods for carbon−carbon bond formation.[1] Thus, a wide range of compounds can be synthesized by using this tool, depending on the variability of nucleophiles and types of acceptor used. Among the latter, alkylidene malonates appear as a suitable class of substrates presenting interesting characteristics: (1) they are easily available through Knoevenagel condensation of malonates and different carbonyl compounds; (2) for the most common type of malonates, the presence of two identical carboxyl groups at the same olephinic carbon eliminates the *Z*/*E* isomerism, which constitutes a problem in other classes of substrates; (3) the enhanced electrophilic reactivity provided by the geminal carboxylate functions allows addition reactions to be carried out with poorer nucleophiles and/or under milder conditions with respect to other Michael acceptors; and (4) the presence of two geminal carbonyl groups provides chelating ability to these substrates, which is an essential tool for the control of the stereochemistry for metal-promoted or catalyzed additions.

These properties have been exploited for the synthesis of a variety of compounds. In particular, many examples of the asymmetric Michael addition to prochiral alkylidene malonates have been reported. The asymmetric addition of simple aliphatic or aromatic rests has been accomplished by using dialkylzinc and trialkylaluminum reagents in the presence of $Cu(OTf)_2$ and chiral phosphorus ligands.[2] The addition of optically enriched allenyltitanium reagents allows the introduction of a versatile silylacetylene moiety.[3] The addition of lithiated benzylic and allylic amine derivatives in the presence of (−)-sparteine has been successfully used for the synthesis of nitrogenated adducts.[4] Other bifunctional compounds also have been synthesized with use of this strategy. Thus, Box-type ligands were used in the Cu(II)-catalyzed asymmetric aza-Michael addition of hydroxylamine to several alkylidene malonates,[5] while the phospha-Michael addition of TADDOL-derived phosphites to these compounds affords phosphonomalonates with high diastereoselectivities.[6]

The asymmetric synthesis of several 1,5-dicarbonyl compounds also has been accomplished from alkylidene malonates as the Michael acceptors with use of several enolates[7] and enolate equivalents as silylketene acetals,[8] enamines,[9] lithioenamines,[10] and aza-enolates from hydrazones,[11] while the direct addition of ketones also has been developed by using proline as the catalyst.[12] In a

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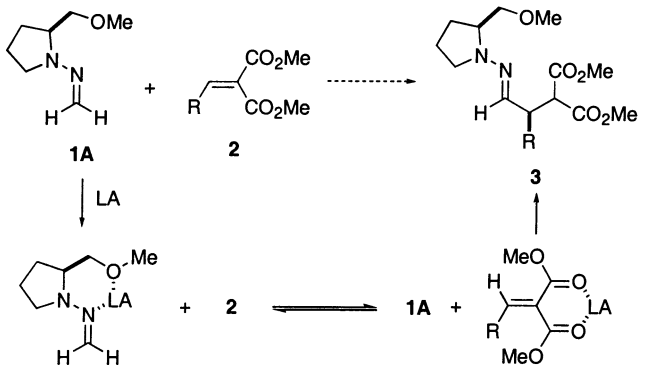
similar way, the asymmetric addition of acyl (formyl) anion equivalents would open access to less accessible 1,4-dicarbonyl compounds. A few reports have been described for such a reaction in racemic fashion,[13] but to the best of our knowledge, the *asymmetric* acylation of alkylidene malonates has not been reported so far.[14] On the other hand, SAMP-derived formaldehyde hydrazone **1A** had been successfully used as a neutral formyl anion equivalent[15] for the asymmetric formylation of enones[16] and α,β-unsaturated lactones,[17] but the extension of this methodology to acyclic α,β-unsaturated esters was unsuccessfully investigated. The precedent of the addition of **1A** to nitroalkenes,[18] which exhibit similar levels of reactivity to that of alkylidene malonates,[19] suggested that the addition of formaldehyde *N*,*N*-dialkylhydrazones to the latter should also be possible under non-catalyzed conditions, or, at least, under mild conditions compatible with the hydrazone moiety. Results collected on the basis of this hypothesis are given herein.[20]

Results and Discussion

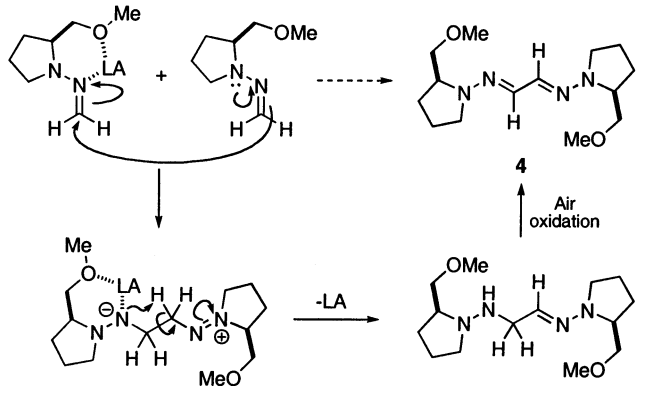
The initial experiments were carried out with formaldehyde SAMP-hydrazone **1A** and several easily available, prochiral dimethyl alkylidene malonates **2**.[21] To our surprise, no reaction was observed under a variety of uncatalized conditions. Therefore, we decided to activate the substrates **2** by means of a Lewis acid as the catalyst or promoter. Taking into account the chelating ability of **1A**, the reaction was expected to proceed after establishment of an equilibrium between metal−hydrazone and metal−malonate complexes (Scheme 1).

The selection of a suitable catalyst, however, presented some difficulties. For instance, it was found that common Lewis acids, such as $ZnCl_2$, $AlCl_3$, $Ti(O^iPr)_4$, or trialkylsilyl triflates, either in catalytic or stoichiometric amounts, afforded the expected hydrazono dicarboxylates **3** in low

SCHEME 1



SCHEME 2



yields, due to the formation of variable amounts of glyoxal bis-hydrazone **4** as an undesired byproduct (Scheme 2).

The formation of this product is consistent with an activation of the reagent **1A** by the Lewis acid, followed by nucleophilic attack of a second molecule of free reagent to the electrophilic complex formed. Air oxidation of the resulting α-hydrazinohydrazone finally affords the undesired product **4**.[22] In the case of the aromatic substrate **2e** (R = Ph), benzaldehyde SAMP-hydrazone **5** was also isolated as a byproduct, even in dry media. Its formation can be explained by a [2+2] cycloaddition[23] of the hydrazone to the activated alkylidene malonate followed by a retrocycloaddition to the observed highly conjugated byproduct **5** (Scheme 3), along with dimethyl methylidene malonate, unstable against polymerization.

Finally, it was found that use of catalytic amounts of MgI_2 or $MgBr_2$ in methylene chloride as the solvent minimized the side reactions mentioned above and led to the almost exclusive formation of compounds **3**, presumably due to the establishment of the equilibrium shown in Scheme 1. Use of other solvents including THF, Et_2O, MeOH, or toluene resulted in lower yields of the desired adducts. These conditions allowed the isolation of adducts **3** in good yields, but unfortunately, the observed diastereoselectivities were disappointing in all cases. In the light of these results, formaldehyde hydrazones **1B**−**H** were synthesized[24] and used in a second screening performed to analyze the effect of the modified

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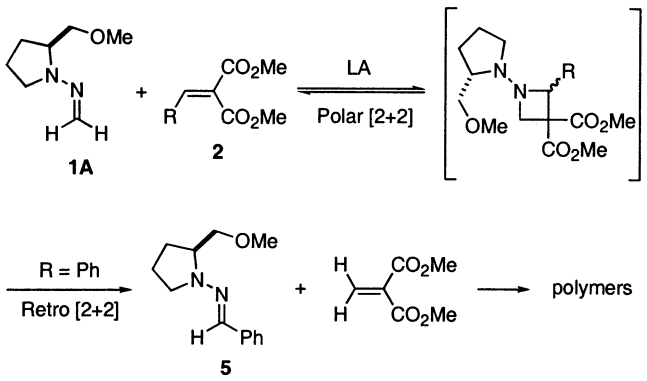
SCHEME 3



SCHEME 4

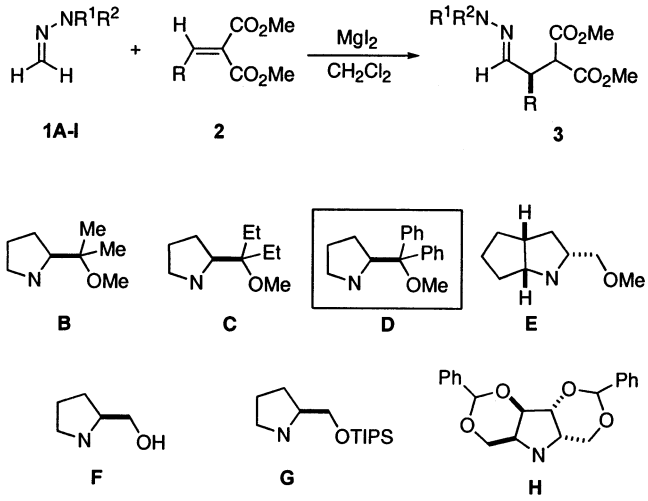


TABLE 1. Addition to Hydrazones 1A−H to 2b[a]

reagent	1A	1B	1C	1D	1E	1F	1G	1H
de[b]	30	28	—[c]	52	43	—[c]	45	—[c]

[a] In CH_2Cl_2 at −78 °C in the presence of 10% MgI_2. [b] Determined by ^1H NMR analysis of the crude reaction mixtures. [c] No reaction.

auxiliaries in the stereochemical outcome of the conjugate addition (Scheme 4).

To keep the reactivity of the reagent as high as possible, the pyrrolidine ring was maintained as a common characteristic in these reagents, as we had previously noticed that this structural motif confers a high nucleophilicity to the aza-enamine system.[25] The results of the reactions of **1A**−**H** with ethylidene derivative **2b** as a model substrate are collected in Table 1.

From this study, 1-methyleneamino-2-(1-methoxydiphenylmethyl)pyrrolidine **1D** emerged as the most convenient reagent, affording the corresponding adduct **3b** in 78% yield as a 76:24 mixture of diastereomers. Further improvement of this result was observed by using a stoichiometric amount of MgI_2, which promoted formation of **3b** in 95% yield as a 84:16 mixture of diastereomers. The optimized conditions and auxiliary were then extended to the addition of reagent **1D** to alkylidene malonates **2a**−**i** with the results collected in Table 2.

As deduced from these results, a high reactivity was found for both aliphatic and aromatic substrates, though the optimized experimental conditions were different for the two groups of substrates. In the case of aliphatic substrates, higher yields and cleaner reaction mixtures were observed for reactions performed by adding the hydrazone reagent to the MgI_2-precomplexed malonates (see the Experimental Section). Surprisingly, when these conditions were applied to aromatic compounds **2e**−**i** clean but incomplete reactions were observed. In these cases, better results (higher conversions) were achieved by addition of MgI_2 to a solution containing the alkylidene malonate and the hydrazone **1D**. Additionally, optimal reaction temperatures of −78 and 0 °C were applied to the addition to aliphatic and aromatic substrates, respectively. In the former case, high yields and moderate stereoselectivities [de 68−78%, major (*S*,*R*)-isomer] were observed with the only exception of the more hindered substrate **2c** (R = isopropyl): at −78 °C, this compound afforded adduct **3c** in 94% yield, but with a very low (de 10%) and reversed [major (*S*,*S*)-isomer] selectivity, while the reaction carried out at 0 °C gave (*R*,*S*)-**3c** as the major isomer (de 16%). Better inductions (de 78−90%) were observed in the aromatic series, even at the higher reaction temperature (0 °C) applied to maintain high yields of adducts. At this point it is important to stress that the resolving properties of the selected diphenylmethoxymethyl pyrrolidine as the auxiliary allowed an easy chromatographic separation for many of the diasteromeric mixtures obtained,[26] and that this behavior proved to be uniform for the aromatic adducts investigated. In this way, good yields (77−93%) of optically pure (de > 98%) adducts **3e**−**i** were obtained in a single reaction step.

Regeneration of the formyl group to obtain aldehydes **6** was accomplished by ozonolytic cleavage of the hydrazone C=N double bond in moderate yields (55−74%) (Scheme 5). Unfortunately, condensation of aldehyde **6e** [obtained from optically pure hydrazone (*S*,*S*)-**3e**] with (*S*)-1-amino-2-(diphenylmethoxymethyl)pyrrolidine, conducted for the determination of its enantiomeric excess, afforded **3e** as a near 50:50 mixture of (*S*,*S*)-**3e** and (*S*,*R*)-**3e**. As the mild conditions used for the ozonolytic cleavage of hydrazones usually keep the stereogenic centers untouched, this result suggests that extensive racemization of this sensitive aldehyde **6e** takes place during the chromatographic purification. A much higher stability was expected for the aliphatic series, but starting from **3a** or **3c**, a 5−20% of racemization was also observed after chromatography of the resulting aldehydes. Even though the crude products were obtained with a reasonable purity and could be eventually used without purification at this step, alternative removals of the auxiliary were also investigated. Fortunately, it was found that the

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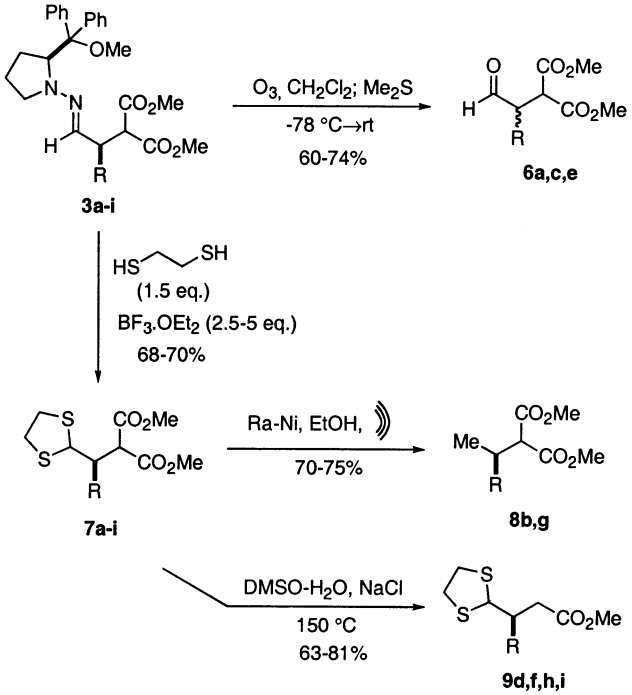
TABLE 2. Addition of 1D to Aliphatic and Aromatic Alkylidene Malonates 2a−i

educt **2**	R	T (°C)	time (h)	product **3**	yield[a] (%)	dr[b]	conf. of major isomer	yld. of major isomer (%)	de (%)[c]
2a	Me	-78	24	**3a**	91[d]	89:11[e]	(*S*,*R*)	-	78
2b	Et	-78	24	**3b**	95[d]	84:16[e]	(*S*,*R*)	-	70
2c	^{i}Pr	-78	24	**3c**	94[d]	45:55	(*S*,*S*)	50	>98
2c	^{i}Pr	0	7	**3c**	98[d]	58:42	(*S*,*R*)	57	>98
2d	CH_2CH_2Ph	-78	48	**3d**	70[d]	85:15[e]	(*S*,*R*)	-	70
2e	Ph	0	7	**3e**	88[f]	88:12	(*S*,*S*)	77	>98
2f	*p*-$NO_2C_6H_4$	0	3	**3f**	98[f]	90:10	(*S*,*S*)	88	>98
2g	2-naphthyl	0	6	**3g**	98[f]	95:5	(*S*,*S*)	93	>98
2h	biphenyl	0	6	**3h**	98[f]	93:7	(*S*,*S*)	91	>98
2i		0	6	**3i**	77[f,g]	89:11	(*S*,*S*)	77[g]	>98

[a] Isolated yield. If applicable, given as a sum of individual yields of diastereomers. [b] Determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] Determined by ^{1}H NMR of the purified major isomer. [d] Addition of **1D** to precomplexed **2**. [e] Inseparable mixture of diastereoisomers. [f] Addition of MgI_2 to a solution containing **2** and **1D**. [g] The minor (*S*,*R*) isomer decomposed upon chromatographic purification.

SCHEME 5. Synthesis of Compounds 6, 7, 8, and 9



direct dithioketalation of the hydrazone moiety[27] was a suitable reaction to this aim. Thus, treatment of adducts **3a**−**i** with ethanedithiol in the presence of an excess of $BF_3{\cdot}OEt_2$ (2.5−5 equiv) as the promoter afforded the desired dithioketals **7a**−**i** (Scheme 5, Table 3).

The enantiomeric purity of compounds **7** was independently measured by HPLC or ^{1}H NMR LIS experiments, using $Eu(hfc)_3$ as the shift reagent (see the Experimental Section). These data demonstrated that the dithioketalation proceeds without racemization, even for the more sensitive aromatic derivatives. Compounds **7a**−**i** are versatile intermediates, which can also be transformed into other useful derivatives by making use of the chemistry of the dithioketal moiety. As an illustrative example, ultrasound-assisted Ra−Ni mediated desulfuration of **7b** and **7g** was effected to afford known malonates **8b**[28] (75%) and **8g**[29] (71%), respectively. As the overall result, reagent **1D** has been used as a chiral reagent for the asymmetric nucleophilic methylation of alkylidene malonates, being the racemization-free direct dithioketalation the key step in this process. Other useful compounds can also be obtained upon typical transformation of the malonate terminus. For instance, optically pure adducts **7d**,**f**,**h**,**i** readily undergo decarboxylation under Krapcho conditions[30] (NaCl, wet DMSO, 150 °C) to afford succinic semialdehyde derivatives **9d**,**f**,**h**,**i** in moderate-to-good yields (63−81%) as an interesting class of differentiated 1,4-dicarbonyl compounds.

The absolute configuration of malonate **8g** was determined by comparison of its optical rotation with literature data: **8g** had $[\alpha]^{21}_D$ +44.3 (*c* 0.7, MeOH) [lit.[29] $[\alpha]^{24}_D$ +45.0 (*c* 1, MeOH)]. As the transformations **3** → **7** and **7** → **8** are assumed to proceed with retention of configuration in neighbor stereogenic centers, the (3*S*) configurations of **3g** and **7g** were deduced thereof. The absolute configurations of **3a**,**b**,**d**−**f**,**h**,**i** and **7a**,**b**,**d**−**f**,**h**,**i** were assigned by analogy. In the case of adduct **3c**, however, the abnormal low selectivity observed does not allow assigning the absolute configuration in this way. Fortu-

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(28) Mori, K.; Kamada, A.; Kido, M. *Liebigs Ann. Chem.* **1991**, 775.

(29) Legros, J.-Y.; Toffano, M.; Fiaud, J.-C. *Tetrahedron* **1995**, *51*, 3235.

(30) Krapcho, A. P. *Synthesis* **1982**, 805.

TABLE 3. Synthesis of Dithioketals 7

R	product	time (h)	yield[a] (%)	ee	Conf.	$[\alpha]_D$ (c, CH_2Cl_2)
Me	**7a**	96	87	78[b]	(*R*)	+5.1 (1.1)
Et	**7b**	48	70	68[c]	(*R*)	+11.8 (0.9)
^{i}Pr	**7c**[d]	96	85	>98[c]	(*R*)	+25.5 (1.0)
CH_2-CH_2-Ph	**7d**	96	60	70[b]	(*R*)	+0.8 (1.0)
Ph	**7e**	48	61	>98[c]	(*S*)	+6.6 (1.1)
p-$O_2NC_6H_4$	**7f**	24	65	>98[b]	(*S*)	-2.1 (1.0)
2-naphthyl	**7g**	48	63	>98[b]	(*S*)	+10.2 (1.2)
3-biphenyl	**7h**	48	75	>98[c]	(*S*)	-5.8 (1.0)
	**7i**	16	70	>98[b]	(*S*)	+28.1 (1.3)

[a] Isolated yield. [b] Determined by HPLC, using a chiral stationary phase column (Daicel Chiralpak AD). [c] Determined by ^{1}H NMR shift experiments, using Eu(hfc)$_3$. [d] From (*S*,*R*)-**3c**.

nately, the (*S*,*R*)-**3c** isomer could be crystallized and its absolute configuration was established by X-ray diffraction analysis.

Conclusions

In summary, the conjugate addition of chiral formaldehyde hydrazone **1D**, acting as a neutral d^1 reagent, to alkylidene malonates **2** appears as a new entry to 1,4-dicarbonyl derivatives as are compounds **3**, **7**, and **9**. Though good inductions were observed in general, the method is particularly useful in the aromatic (**e**−**i**) series, where the resolving properties of the chosen auxiliary led to good yields of optically pure adducts in a single step. Extension of this methodology to related substrates bearing two different electron-withdrawing groups on the same carbon of olefinic substrates is a current object of study in our laboratories.

Experimental Section

Melting points were determined by using a metal block and are uncorrected. Optical rotations were measured at room temperature. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ with either TMS (0.00 ppm ^{1}H, 0.00 ppm ^{13}C) or $CDCl_3$ (7.26 ppm ^{1}H, 77.00 ppm ^{13}C) as an internal reference or C_6D_6 with either TMS (0.00 ppm ^{1}H, 0.00 ppm ^{13}C) or C_6D_6 (7.15 ppm ^{1}H, 128.0 ppm ^{13}C) as an internal reference. FT-IR spectra were recorded for KBr pellets or films. EI-mass spectra were recorded at 70 eV, using an ionizing current of 100 μA, an accelerating voltage of 4 kV, and a resolution of 1000 or 10000 (10% valley definition). The reactions were monitored by TLC. Purification of the products was carried out by chromatography (silica gel). The light petroleum ether used had a boiling range 40−65 °C. Enantiomeric mixtures of compounds **7** were used as references for the ee determination of the purified compounds by HPLC or ^{1}H NMR.

Synthesis of Adducts 3. General Procedure: Method A. To a stirred, cooled solution of **2a**−**d** (1 mmol) (−78 °C for **2a**,**b**,**d**; 0 °C for **2c**) and MgI_2 (1 mmol) in dry CH_2Cl_2 (1 mL) was added a solution of hydrazone **1D** (1.5 mmol) in CH_2Cl_2 (1 mL) under an argon atmosphere. The mixture was stirred until completion of the reaction (TLC), washed with H_2O, dried ($MgSO_4$), and purified by flash chromatography. **Method B.** To a stirred, cooled (0 °C) solution of **2e**−**i** (1 mmol) and hydrazone **1D** (2 mmol) in dry CH_2Cl_2 (1 mL) was added MgI_2 (1 mmol) under an argon atmosphere. The mixture was then treated as described above. Representative spectral and analytical data for compounds **3a** and **3e** are as follows:

3a. Flash chromatography (Et_2O−PE 1:6, 1% Et_3N) gave 412 mg (91%) of **3a** as a 89:11 mixture of diastereoisomers. (*S*,*R*)-**3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11−0.22 (m, 1H), 1.05 (d, 3H, J = 6.95 Hz), 1.37−1.40 (m, 1H), 1.79−2.03 (m, 2H), 2.52−2.58 (m, 1H), 2.79−2.85 (m, 1H), 3.03 (s, 3H), 3.04−3.14 (m, 1H), 3.50 (d, 1H, J = 9.4 Hz), 3.74 (s, 3H), 3.75 (s, 3H), 4.68 (dd, 1H, J = 8.9 Hz, J = 2.0 Hz), 6.38 (d, 1H, J = 4.4 Hz), 7.22−7.43 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 22.0, 25.8, 36.6, 50.2, 51.2, 52.0, 52.2, 56.1, 67.2, 85.6, 126.7, 126.8, 127.0, 129.4, 130.1, 133.5, 140.8, 141.7, 168.9, 169.2. (*S*,*S*)-**3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.11−0.22 (m, 1H), 1.10 (d, 3H, J = 6.95 Hz, CH_3), 1.37−1.40 (m, 1H), 1.79−2.03 (m, 2H), 2.52−2.58 (m, 1H), 2.79−2.85 (m, 1H), 3.02 (s, 3H), 3.04−3.14 (m, 1H), 3.56 (d, 1H, J = 8.3 Hz), 3.69 (s, 3H), 3.75-(s, 3H), 4.71 (dd, 1H, J = 7.9 Hz, J = 2.1 Hz), 6.44 (d, 1H, J = 4.5 Hz), 7.22−7.43 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 21.9, 26.0, 36.3, 50.2, 51.1, 52.0, 52.2, 55.7, 66.8, 85.6, 126.7, 126.8, 127.0, 129.4, 130.0, 130.1, 133.6, 141.0, 141.8, 168.9, 169.2. IR (film, cm^{-1}) 2949, 1736, 1597. MS (CI) m/z 453 (11, M^+ + 1), 421 (28), 188 (100). Anal. Calcd for $C_{26}H_{32}O_5N_2$: C, 69.00; H, 7.13; N, 6.19. Found: C, 68.53; H, 7.31; N, 6.16.

3e. Flash chromatography (Et_2O−PE 1:7, 1% Et_3N) gave 398 mg (77%) of (*S*,*S*)-**3e** and 54 mg (11%) of (*S*,*R*)-**3e** as oils. (*S*,*S*)-**3e**: $[\alpha]^{25}_D$ +16.9 (c 0.9, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6) δ 0.10−0.24 (m, 1H), 0.90−1.17 (m, 1H), 1.65−1.79 (m, 1H), 1.96−2.03 (m, 1H), 2.29−2.38 (m, 1H), 2.60−2.66 (m, 1H), 3.09 (s, 3H), 3.11 (s, 3H), 3.51 (s, 3H), 4.55 (d, 1H, J = 11.6 Hz), 4.64 (dd, 1H, J = 11.6 Hz, J = 3.6), 4.90 (dd, 1H, J = 9.4 Hz, J = 1.5 Hz), 6.44 (d, 1H, J = 3.6 Hz), 7.04−7.86 (m, 15H); ^{13}C NMR (75 MHz, C_6D_6) δ 22.4, 25.9, 48.7, 50.2, 51.6, 51.7, 51.9, 56.5, 68.8, 86.2, 127.1, 127.3, 127.4, 127.4, 128.7, 129.4, 130.0, 131.3, 132.3, 139.8, 140.7, 141.6, 168.7, 168.8. IR (film, cm^{-1}) 3059, 2949, 1757, 1600. EM (CI) m/z 515 (39, M^+ + 1), 483 (100). Anal. Calcd for $C_{31}H_{34}O_5N_2$: C, 72.35; H, 6.66; N, 5.44. Found: C, 72.33; H, 6.93; N, 5.42. (*S*,*R*)-**3e**: $[\alpha]^{23}_D$ −65.6 (c 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6) δ 0.25−0.36 (m, 1H), 0.95−1.08 (m, 1H), 1.67−1.86 (m, 2H), 2.27−2.36 (m, 1H), 2.61−2.67 (m, 1H), 3.13 (s, 6H), 3.43 (s, 3H), 4.57 (d, 1H, J = 11.3 Hz), 4.68 (dd, 1H, J = 11.3 Hz, J = 4.4 Hz), 4.79 (dd, 1H, J = 9.4 Hz, J = 2.3 Hz), 6.66 (d, 1H, J = 4.6 Hz), 7.05−7.80 (m, 15H). ^{13}C NMR (75 MHz, C_6D_6) δ 22.0, 26.5, 48.1, 50.2, 51.1, 51.6, 52.0, 56.2, 66.5, 86.1, 127.3, 127.3, 127.5, 128.6, 129.3, 130.1, 130.4, 133.1, 140.1, 141.9, 142.9, 168.6, 168.9.

MS (CI) *m*/*z* 515 (16, $M^+ + 1$), 483 (100, $M^+ - OCH_3$). HRMS *m*/*z* calcd for $C_{31}H_{35}N_2O_5$ 515.2546, found 515. 2547.

Synthesis of Dithioketals 7a−i. General Procedure. To a cooled (0 °C) solution of **3** (1 mmol) in dry CH_2Cl_2 (5 mL) was added 1,2-ethanedithiol (126 μL, 1.5 mmol) and then $BF_3 \cdot Et_2O$ (2.5 mmol for **3a**,**b**,**e**,**f** and 5 mmol for **3c**,**d**,**g**−**i**) under an argon atmosphere. The mixture was allowed to warm to room temperature and stirred until TLC indicated consumption of the starting material. The mixture was then washed with saturated $NaHCO_3$ solution (2 × 10 mL), dried ($MgSO_4$), concentrated, and the resulting residue was purified by column chromatography. Representative spectral and analytical data for compounds **7a** and **7e** are as follows:

7a. Flash chromatography (AcOEt−PE 1:10) gave 230 mg (87%) of **7a** as an oil: 78% ee by HPLC (Chiralpak AD, 2-propanol−hexane 5:95, 0.5 mL/min, 25 °C), *R* isomer 6.3 min, *S* isomer 6.9 min. $[\alpha]^{25}_D$ +5.1 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, 3H, J = 6.8 Hz), 2.52 (m, 1H), 3.16−3.18 (m, 4H), 3.69 (d, 1H, J = 6.6 Hz), 3.72 (s, 3H), 3.73 (s, 3H), 4.62 (d, 1H, J = 6.9 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 14.9, 38.5, 38.7, 41.5, 51.7, 51.9, 55.9, 57.8, 168.4, 168.9. IR (film, cm^{-1}) 3053, 2847, 1732. MS (CI) *m*/*z* 265 (6, $M^+ + 1$), 233 (100). HRMS *m*/*z* calcd for $C_{10}H_{17}O_4S_2$ 265.0568, found 265.0544.

7e. Flash chromatography (Et_2O−PE 1:6) gave 199 mg (61%) of **7e** as an oil: >98% ee by ^{1}H NMR [25% Eu(hfc)$_3$]. $[\alpha]^{20}_D$ +8.6 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53−2.63 (m, 1H), 2.79−2.89 (m, 1H), 2.97−3.05 (m, 2H), 3.44 (s, 3H), 3.78 (dd, 1H), 3.77 (s, 3H), 4.07 (d, 1H, J = 9.7 Hz), 4.99 (d, 1H, J = 6.5 Hz), 7.25−7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.7, 38.7, 51.9, 52.3, 52.7, 56.0, 56.4, 127.5, 127.7, 129.6, 137.2, 167.6, 168.5. IR (film, cm^{-1}) 2845, 1736. MS (CI) *m*/*z* 327 (33, $M^+ + 1$), 295 (77), 105 (100). HRMS *m*/*z* calcd for $C_{15}H_{19}O_4S_2$ 327.0725, found 327.0716.

Synthesis of Aldehydes 6. General Procedure. Ozone was bubbled through a solution of **3** (1 mmol) in dry CH_2Cl_2 (6 mL) at −78 °C until the appearance of a permanent blue color (5−10 min). Me_2S (5 mmol) was added. The mixture was allowed to warm to room temperature and concentrated, and the resulting residue was purified by column chromatography. Representative spectral and analytical data for compound **6a** are as follows:

6a. Flash chromatography (AcOEt-PE 1:10) gave 117 mg (62%) of **6a** as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, 3H, J = 7.5 Hz, CH_3), 3.12−3.22 (m, 1H), 3.73 (d, 1H, J = 7.1 Hz, H-1), 3.74 (s, 3H), 3.75 (s, 3H), 9.71 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 45.2, 52.1, 52.4, 53.8, 168.2, 168.2, 200.7. IR (film, cm^{-1}) 2959, 2851, 1738, 1397, 1092. MS (CI): *m*/*z* 189 (35%, $M^+ + 1$), 157 (100, $M^+ - OCH_3$), 143 (17), 128 (19). HRMS *m*/*z* calcd for $C_8H_{12}O_5$ 189.0763, found 189.0763.

Synthesis of Carboxylates 9. General Procedure. To a solution of dithioketals **7** (1 mmol) in DMSO (20 mL) was added H_2O (1 mmol, 18 μL) and NaCl (1.2 mmol, 70 mg). The mixture was heated at 150 °C until total consumption of starting material (tlc control, 2−3 h). The mixture of the reaction was washed with water (2 × 200 mL), and the water layer was extracted with ether (4 × 100 mL). The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by column chromatography (Et_2O−PE 1:4). Representative spectral and analytical data for compound **9d** are as follows:

9d: 240 mg (81%, oil). $[\alpha]^{26}_D$ +2.7 (*c* 1.1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.79−1.86 (m, 2H), 2.33−2.35 (m, 1H), 2.47 (dd, 1H, J = 15.7 Hz, J = 7.2 Hz), 2.67 (t, 2H, J = 8.2 Hz), 2.73 (dd, 1H, J = 15.7 Hz, J = 5.3 Hz), 3.17−3.23 (m, 4H), 3.68 (s, 3H), 4.80 (d, 1H, J = 5.3 Hz), 7.18−7.30 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.1, 35.3, 36.2, 38.6, 38.8, 41.1, 51.6, 57.5, 125.9, 128.3, 128.4, 141.6, 173.3. IR (film, cm^{-1}) 2924, 2855, 1736, 1435, 1092. MS (FAB) *m*/*z* 319 (15%, $M^+ + 23$), 295 (40, $M^+ - 1$), 265 (100). Anal. Calcd for $C_{15}H_{20}O_2S_2$: C, 60.77; H, 6.80. Found: C, 60.96; H, 6.86.

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Supporting Information Available: Characterization data for compounds **3b**−**d**,**f**−**i**, **6c**,**e**, **7b**−**d**,**f**−**i**, and **9f**,**h**,**i**, ^{13}C NMR spectra for compounds (*S*,*R*)-**3e**, (*S*,*R*)-**3f**, (*S*,*S*)-**3g**, (*S*,*R*)-**3g**, (*S*,*R*)-**3h**, (*S*,*R*)-**3e**, (*S*,*S*)-**3i**, **6a**,**c**,**e**, **7a**,**c**,**e**, and **9f**, and ORTEP drawing and X-ray data for compound (*S*,*R*)-**3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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