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# *p*-Nitrophenyl Ethylthioester in Enantioselective Organocatalytic Michael Additions: Different Behaviour of β-Aryl and β-Alkyl Enals

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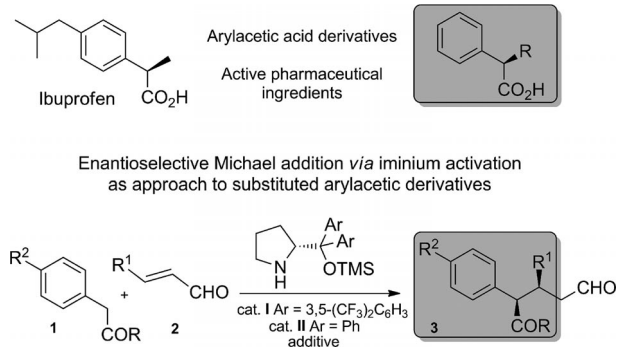
*Dedicated to the memory of Christian Claessens*

**Keywords:** Asymmetric catalysis / Organocatalysis / Michael addition

Although several nucleophiles derived from arylacetic acids have been described in catalysis via iminium activation, none have presented good enantioselectivity and reactivity with both β-alkyl and β-aryl enals. This study on the Michael addition of *p*-nitrophenylacetic thioesters suggests that this behavior is due to the different reactivity and distinct tendency to reversibility exhibited by these types of enal. Independent optimization of the conditions for β-alkyl and β-aryl enals provide good yields and enantioselectivities with both substrates, affording Michael adducts that are versatile building blocks for the preparation of an interesting variety of arylacetic acid derivatives.

## Introduction

Substituted 2-phenylacetic acids and their derivatives are important synthetic building blocks for agrochemicals and active pharmaceutical ingredients[1] such as nonsteroidal anti-inflammatory drugs. Because enantioselective organocatalysis involving iminium activation[2] provides an excellent procedure for the incorporation of nucleophiles to the β-position of α,β-unsaturated aldehydes,[3] the use of synthetic equivalents of 2-phenylacetic acids as nucleophiles in these processes is very promising for the preparation of highly functionalized 2-phenylacetic acids (Scheme 1).




Scheme 1. Approach to enantiomerically pure substituted arylacetic acid.

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Because the simple arylacetic ester is not able to participate in this process due to the low acidity of the methylenic protons,[4] this approach has mainly been applied starting from two types of precursors, trifluoroethyl thioesters[4] and *p*-nitrophenyl derivatives[5–7] (Figure 1), with higher acidities than the corresponding benzyl ester.

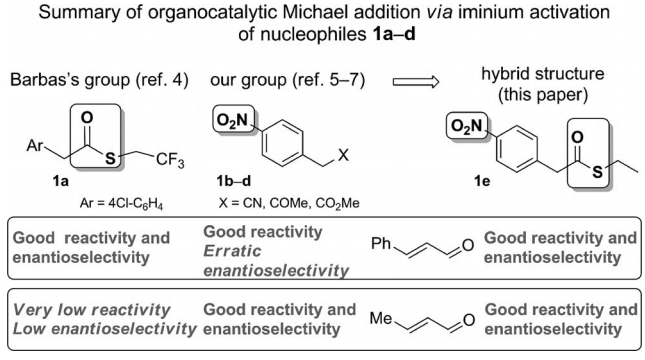



Figure 1. Design of a hybrid nucleophile based on the structure of other nucleophiles.

A detailed analysis of the results provided in these papers seems to indicate that the behavior of β-alkyl and β-aryl enals under the optimized conditions for each precursor is different. β-Alkyl enals exhibit low or moderate reactivity and enantioselectivity with trifluoroethyl thioester **1a**[4] but provide very good yields and *ee* values with nitrile **1b**,[5] ketone **1c**,[6] and ester **1d**,[7] whereas β-aryl enals give good yields and *ee* values with **1a** but erratic and lower enantioselectivity with **1b–d** (Figure 1).

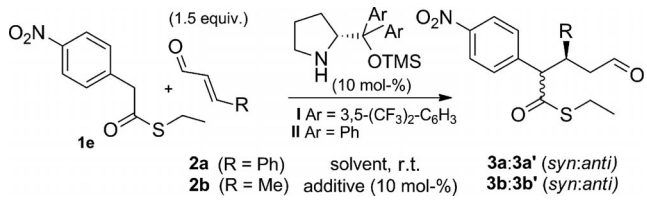
Optimization studies for nucleophile **1a** were performed on the *trans*-cynamic aldehyde, whereas *trans*-crotonalde-

hyde was used with **1b–d**. Because the optimal conditions established in each case are different, we hypothesized that this indiscriminate optimization could be a possible cause of the failures of yield and enantioselectivity for nucleophiles **1** with either aromatic or aliphatic enals.[8] The results reported for the ester **1d** under different conditions with different enals corroborate our hypothesis.[7,9] Those reported by Duce et al.[7] were appropriate for obtaining good results with β-alkyl enals but erratic *ee* values were obtained with the β-aryl enals, whereas conditions reported by Seo and Kim[9] were suitable for the latter enals but not for β-alkyl enals. This suggests that an independent optimization of both types of electrophiles could improve the results for every nucleophile.

To confirm this interesting practical question, we investigated the reactions of ethyl thioester **1e**, derived from *p*-nitrophenyl acetic acid (Figure 1). The selection of this new pronucleophile, with structural features of **1a** and **1d**, was based on the synthetic usefulness of the nitro group for introducing different functions to the aromatic ring, and also on the chemical versatility of the thioester group. The latter characteristic allows this moiety to be used as mild acyl transfer reagent[10] in the preparation of a variety of carboxylic acid derivatives and has been used in medicinal chemistry[11] and as key intermediates in various biological processes.[12] We present herein the results obtained in the organocatalytic Michael addition of thioester **1e** to enals; by changing the reaction conditions this approach is satisfactory for both β-aryl and β-alkyl derivatives. Moreover, some synthetic transformations illustrating the chemical versatility of the resulting compounds are also presented.

Table 1. Optimization of the reactions of **1e** with **2a** and **2b**.[a]




| Entry | R | Catalyst | Solvent | Additive | *t* [h] | Conv. [%][b] | *ee* (**4**) [%][c] |
|---|---|---|---|---|---|---|---|
| 1 | Ph | **I** | $CH_2Cl_2$ | – | 6 | 5 | – |
| 2 | Ph | **II** | $CH_2Cl_2$ | – | 6 | 90 | 10 |
| 3 | Ph | **I** | EtOH | – | 0.25 | 50 | 87 |
| 4 | Ph | **II** | EtOH | – | 0.25 | 91 | 60 |
| 5 | Ph | **I** | EtOH | – | 3.5 | 95 | 87 |
| 6 | Ph | **II** | EtOH | – | 3.5 | 95 | <5 |
| 7 | Ph | **I** | EtOH | TBAB[d] | 3.5 | >95 | 74 |
| 8 | Ph | **I** | EtOH | LiOAc | 3.5 | >95 | 86 |
| 9 | Ph | **I** | EtOH | $PhCO_2H$ | 3.5 | 95 | 90 |
| **10**[e] | **Ph** | **I** | **EtOH** | **$PhCO_2H$** | **36** | **95** | **94** |
| 11 | Me | **I** | $CH_2Cl_2$ | – | 6 | <5 | – |
| 12 | Me | **II** | $CH_2Cl_2$ | – | 6 | 70 | – |
| 13 | Me | **I** | EtOH | – | 6 | 36 | 75 |
| 14 | Me | **II** | EtOH | – | 6 | 61 | 75 |
| 15 | Me | **II** | EtOH | – | 48 | 85 | 75 |
| **16** | **Me** | **II** | **EtOH** | **TBAB**[d] | **3** | **>95** | **80** |
| 17 | Me | **II** | EtOH | LiOAc | 6 | 95 | 68 |
| 18 | Me | **II** | EtOH | $PhCO_2H$ | 6 | 35 | 74 |

[a] Reactions were carried out at room temp. on a 0.2 mmol scale with **2** (1.5 equiv.) and [**1e**] = 0.5 M. [b] Determined by $^1H$ NMR analysis of the crude material from the Michael addition. [c] Determined by chiral-phase HPLC analysis of alcohol **4** resulting in the reduction of the major *syn*-**3** diastereoisomer. [d] 1 equiv. was used. [e] Reaction performed at –20 °C.

## Results and Discussion

Independent optimization of reactions of **1e** with cinnamaldehyde (**2a**) and crotonaldehyde (**2b**) are depicted in Table 1. The role of the catalyst (**I** and **II**), solvent ($CH_2Cl_2$ and EtOH), and additive ($PhCO_2$ H, TBAB, and LiOAc) on the reactivity and stereoselectivity was studied.

In all the cases, Michael reactions afforded mixtures of two diastereomers (**3** and **3′**, epimers at C-2), with *dr* values ranging between 1:1 and 2.3:1.[13] Concerning the reactions with cinnamaldehyde (**2a**), it is clear that EtOH is more efficient as solvent than $CH_2Cl_2$, and that catalyst **II** leads to faster reaction than catalyst **I** (compare Table 1, entries 1 and 2 with 3 and 4). However, the influence of the catalyst on the enantioselectivity is remarkable. In the case of catalyst **I**, the enantioselectivity is higher and remains almost constant with longer reaction times (compare entries 3 and 5), whereas the *ee* is lower with catalyst **II** and significantly decreases with time (compare entries 4 and 6). This behavior suggests that the decrease of the *ee* could be due to the reversibility of the process in reactions catalyzed by **II**. Therefore, catalyst **I**, although it is less effective in terms of reactivity, should be chosen for these reactions because it is less prone to reversibility. Finally, we studied the effect of additives in these reactions, with $PhCO_2H$ providing better *ee* than TBAB and LiOAc (compare entries 7, 8 and 9). This analysis suggests that the best conditions for reacting **1e** with β-aryl enals are those involving the use of catalyst **I** in the presence of $PhCO_2H$ as additive. Finally, an improvement in the *ee* value was achieved by decreasing the temperature (entry 10).

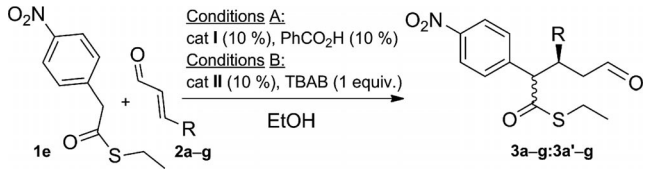
Reactions carried out with crotonaldehyde **2b** (entries 11–18) were slower than those with cinnamaldehyde (**2a**) under similar conditions. The influence of the catalyst and the solvent on the reaction rate was less significant in the case of **2b**, although reactions catalyzed by **II** were still slightly faster (entries 11–14).

Nevertheless, the main difference regarding aromatic enals is that the reaction time had no influence on the *ee* values with catalyst **II** (Table 1, entries 14 and 15), which suggests that reactions with **2b** are less prone to reversibility than those with **2a**. As a consequence, catalyst **II** was selected to continue the optimization process. To compare the influence of additives on the reaction with the aromatic enals (entries 7–10), the reactions were performed in EtOH.[14] It was observed that reaction times decreased with the addition of TBAB and LiOAc (entries 16 and 17) and increased with the inclusion of $PhCO_2H$ (entry 18). The best reactivity/enantioselectivity balance for aliphatic enals was achieved by using catalyst **II** in the presence of TBAB (entry 16).

As a result of the optimization studies, two sets of conditions, Conditions A (Table 1, entry 10; catalyst **I** and $PhCO_2H$ as additive) and Conditions B (Table 1, entry 16; catalyst **II** and TBAB as additive), were established as optimal for β-aryl and β-alkyl enals, respectively. The scope of the reactions of **1e** with conjugated aldehydes **2c**–**g** was then investigated; the results are collected in Table 2.

Table 2. Scope of the Michael addition.[a]




| Entry | Enal 2 | R | Cond | 3 | *T* [°C] | *t* [h] | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|---|
| 1 | **2a** | Ph | **A** | **3a** | –20 | 36 | 93 | 94 |
| 2 | **2d** | *p*MeO-$C_6H_4$ | **A** | **3d** | –20 | 60 | 70 | 87 |
| 3 | **2e** | *o*MeO-$C_6H_4$ | **A** | **3e** | 15 | 36 | 90 | 88 |
| 4 | **2f** | *p*$O_2$N-$C_6H_4$ | **A** | **3f** | 15 | 84 | 75 | 86 |
| 5 | **2g** | 2-furyl | **A** | **3g** | r.t. | 48 | 60 | 70 |
| 6 | **2b** | Me | **B** | **3b** | r.t. | 6 | 85 | 80 |
| 7 | **2c** | *i*Pr | **B** | **3c** | r.t. | 48 | 80 | 80 |
| 8 | **2a** | Ph | **B** | **3a** | r.t. | 15 min | 50 | 44 |
| 9 | **2a** | Ph | **B** | **3a** | r.t. | 3 | 85 | <5 |
| 10 | **2b** | Me | **A** | **3b** | r.t. | 96 | 80 | 83 |
| 11 | **2c** | *i*Pr | **A** | **3c** | r.t. | 48 | 50 | 92 |

[a] Reactions were carried out on 0.3 mmol scale with 3 equiv. of the corresponding aldehyde and [**1e**] = 0.5 M. [b] Isolated yield of **3**. [c] Determined by chiral-phase HPLC analysis of the corresponding alcohol **4** resulting in the reduction of the major *syn*-**3** diastereoisomer.

Aryl derivative **2a** and aryl-substituted enals **2d**–**f**, react with similar *ee* values (>86%) under Conditions A, regardless of the electron character of the substituents on the aryl ring. Even the heteroaryl-substituted enal **2g** reacted in a similar way, albeit with a slightly lower stereoselectivity (Table 2, entry 5). Concerning β-alkyl enals, an increase in the size of the substituent did not significant influence the stereoselectivity but clearly decreased the reactivity (compare entries 5 and 6).

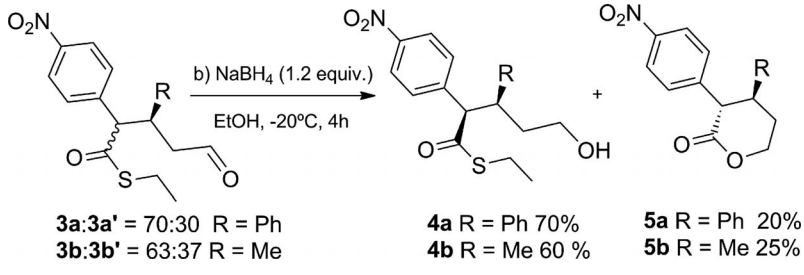
To confirm the importance of selecting appropriate reaction conditions depending on the nature of the enal, we employed the optimized conditions for aromatic enals with the aliphatic enals and vice versa. The results (Table 2, entries 8–11) clearly show this detrimental effect. When catalyst **II** was used with TBAB as additive (Conditions B, optimized for aliphatic enals) in the reaction with cinnamaldehyde, a fast reaction took place but very low *ee* was observed (entry 8), evolving to the racemic compound after 3 h reaction (entry 9). When Conditions A (optimized for aromatic enals) were employed with the aliphatic enals and **1e**, the corresponding adducts were obtained with good enantioselectivity but required remarkably longer reaction times than when TBAB was used (compare entries 6 with 10 and 7 with 11).

We suspect that this behavior was not limited to nucleophile **1e**, because it was even more acute with the less reactive ester **1d**,[7–9] which did not afford the desired products when catalyst **I** was used with aliphatic enals.

The reduction of the Michael adducts with $NaBH_4$ was optimized in the case of compounds **3a** and **3b**,[15] with the use of low temperatures being necessary to avoid thioester reduction. Reductions of the mixture of the two diastereomers (epimers at C-2) provided a new mixture composed of alcohol **4a** or **4b** and lactones **5** (Scheme 2). Alcohols **4** resulted from the reduction of the major aldehydes **3**, whereas lactones **5**[16] were obtained by spontaneous cyclization of the alcohols[17] obtained from the minor diastereomers **3′**.[18] This reaction was general for the rest of the aldehydes studied (Table 2), and the separation of the corresponding alcohols **4a**–**g** by chromatography allowed the enantiomeric excesses to be determined (Table 1 and Table 2).

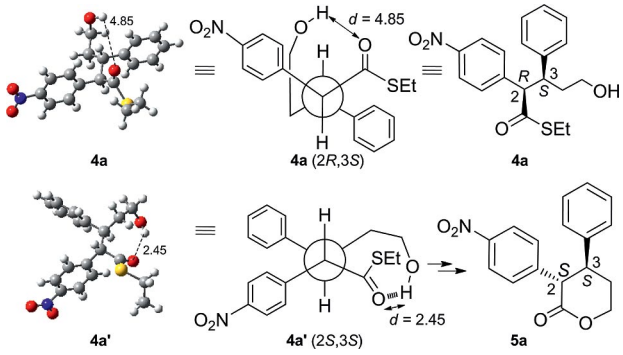
The relative configuration of alcohols **4a** and **4a′**[19] was determined by comparison of the chemical shifts in their respective $^1$H NMR spectra with those generated by theoretical calculations at the DFT (B3LYP)[20] level by using Gaussian 09.[21] Molecular structures of the most stable conformer of each diastereomer are shown in Scheme 3.[13] Interestingly, a hydrogen bond between the hydroxyl group and the thioester group is only observed in the minor diastereoisomer **4a′**, which could explain the easy formation of lactone **5a**, preventing the isolation of **4a′** (Scheme 3).

To illustrate the versatility of the thioester group, several transformations were carried out. Formation of lactones **5** and the decarboxylation reaction had been previously optimized in the adducts obtained from aldehydes with aliphatic substituents and the nitrile and ester nucleophiles **1b**[5] and **1d**,[7] respectively. Because these nucleophiles did not afford high enantioselectivities with aromatic enals, we optimized the reactions of lactonization and decarboxylation from alcohol **4a**, featuring the thioester moiety, to ob-




Scheme 2. Reduction of adducts **3**.

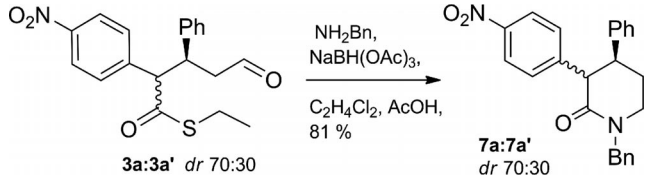



Scheme 3. Molecular structures of alcohols **4a** and **4a′**. Representative distances [Å] H–O are indicated.

tain these compounds in high enantioselectivities. Thus, these transformations allowed the absolute configuration of adducts **3** to be unequivocally determined by chemical correlation of lactone **5b**.[22]

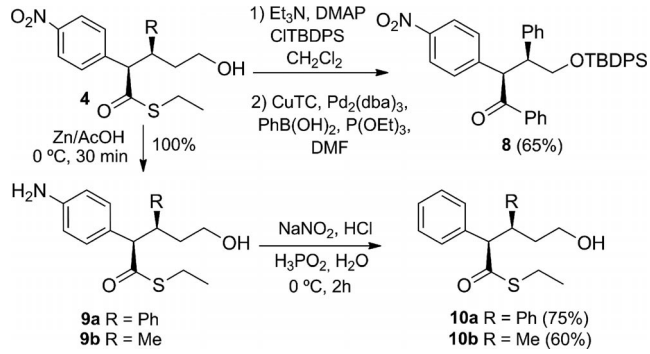
Diastereomerically pure lactones were formed by treatment of the corresponding alcohols **4a** and **4b** with NaH, indicating that reactions take place with complete inversion of configuration at C-2 (Scheme 4). Decarboxylation of alcohol **4a** to give compound **6** converts pronucleophile **1e** into a masked reagent for the enantioselective β-benzylation of enals, which is significant because the introduction of functionalized benzylic substituents is not evident, even in a racemic version.[23] Compound **6** was prepared by hydrolysis of the thioester group to the acid under basic conditions followed by decarboxylation (Scheme 4).

The reductive amination of aldehyde **3a/3a′** and its subsequent cyclization[24] led to the formation of lactams **7a/7a′** as a 67:33 diastereomeric mixture in 81% yield. Interestingly, whereas lactone **5a** was obtained in diastereomerically pure form (Scheme 4), the afforded lactam **7** retained the diastereoisomeric ratio of the starting material (70:30; Scheme 5).




Scheme 5. Reductive amination of **3a** to prepare lactam **7**.

We also performed a cross-coupling reaction[25] of the protected alcohol with phenyl boronic acid, yielding ketone **8** in 65% yield (Scheme 6). The synthesis of compound **8** shows that it is possible to prepare enantio and diastereomerically pure α-aryl ketones. The alternative method of α-arylation of ketones is not an evident transformation.[26] The reduction of the nitro group to the corresponding amine also offers a plethora of possible transformations through diazonium salt reactions, such as substitution by a hydrogen atom[27] to afford **10**.



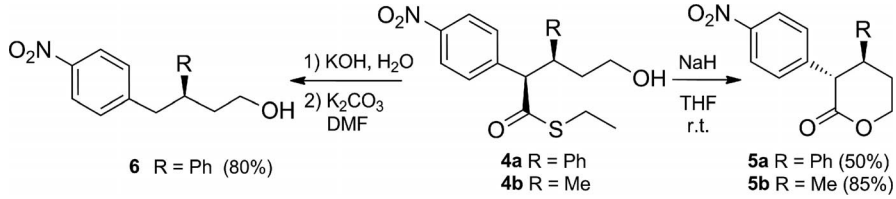

Scheme 6. Transformation of thioester and nitro groups of **4**.

## Conclusions

Thioester **1e** can be used to efficiently transfer the arylacetic residue in a highly stereoselective way to both β-alkyl and β-aryl-substituted enals through iminium activation. The corresponding adducts have proven to be very versatile substrates. Interestingly, the independent optimization of aromatic and aliphatic enals has highlighted very different behavior of these types of enals with pronucleophile **1e**. The lower reactivity of aliphatic enals seems to be palliated with the use of catalyst **II** and TBAB as additive; nevertheless, these conditions were shown to be detrimental for aromatic enals, which present problems of reversibility. This tendency seems to decrease with the use of catalyst **I** and an acidic additive. These findings can have important consequences in the optimization of this kind of reaction; the causes and generality of this behavior is being investigated in further detail in our laboratory.

## Experimental Section

**General Methods and Materials:** NMR spectra were acquired using $CDCl_3$ or $C_6D_6$ as solvents, recording at 300 and 75 MHz for $^1H$ and $^{13}C$, respectively. Chemical shifts ($\delta$) are reported in ppm relative to residual solvent signals ($CHCl_3$: $\delta$ = 7.26 ppm for $^1H$; $CDCl_3$: $\delta$ = 77.0 ppm for $^{13}C$; $C_6H_6$: $\delta$ = 7.16 ppm for $^1H$; $C_6D_6$: $\delta$




Scheme 4. Decarboxylation and lactonization reactions.

= 128.0 ppm for $^{13}C$). For thin layer chromatography (TLC), silica gel plates were used, and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (12 g), in EtOH (250 mL) followed by heating or treatment with a solution of $KMnO_4$ (1.5 g), $K_2CO_3$ (10 g), and 10% NaOH (1.25 mL) in $H_2O$ (200 mL). Mass spectra were recorder in positive electrospray ionisation (ESI+) or electron impact ionisation (EI). Obtained data are expressed in mass/charge (*m*/*z*) units. Values between parentheses indicate relative intensities with regard to the base peak. Commercial grade reagents and solvents were used without further purification.

**Synthesis of Thioester 1e:** Synthesized following a typical procedure reported for thioester formation from the corresponding ester.[28] A solution of trimethylaluminum (2 M in hexane, 10.0 mL, 20.0 mmol) was diluted with anhydrous $CH_2Cl_2$ (50 mL) followed by ethane thiol (4.5 mL, 60 mmol) at –78 °C. Methane evolution occurred and the solution was warmed to ambient temperature to give a solution of $Me_2AlSEt$. *p*-Nitrophenyl ethyl acetate (2.1 g, 10 mmol) was dissolved in $CH_2Cl_2$ (20 mL), cooled to –78 °C, and treated with the aluminum thiolate. The reaction was warmed to 0 °C and stirring was continued for 6 h. The reaction was recooled and quenched with saturated aqueous sodium potassium tartrate (30 mL) and stirred vigorously for 1 h. The resulting solution was transferred to a separatory funnel and the aqueous fraction was extracted with $CH_2Cl_2$ (3× 30 mL). The combined organics were dried with anhydrous $MgSO_4$, filtered, concentrated, and purified by flash chromatography (*n*-hexane/EtOAc, 20:1) to give the title compound (1.5 g, 75%) as a yellow oil. $^1H$ NMR (300 MHz): $\delta$ = 8.20 (d, $J$ = 10.1 Hz, 2 H), 7.47 (d, $J$ = 10.1 Hz, 2 H), 3.92 (s, 2 H), 2.92 (q, $J$ = 6.9 Hz, 2 H), 1.25 (t, $J$ = 6.9 Hz, 3 H) ppm. $^{13}C$ NMR (75 MHz): $\delta$ = 196.0 (CO), 147.4 (C), 141.3 (C), 130.6 (2CH), 124.0 (2CH), 50.1 ($CH_2$), 24.0 ($CH_2$), 14.6 ($CH_3$) ppm. MS (FAB): *m*/*z* (%) = 226 (100) [M + 1$^+$]. HRMS (ESI): Calcd. for $C_{10}H_{12}NO_3S$ [M + 1] 226.0538; found 226.0535.

**General Procedure for the Catalytic Michael Addition of 1e to α,β-Unsaturated Aldehydes 2a–g:** To a solution of (*R*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether (**I**; 0.1 equiv., 0.03 mmol) in EtOH (0.5 M) were sequentially added the corresponding α,β-unsaturated aldehyde **2a**–**g** (3 equiv., 0.9 mmol) and benzoic acid (0.1 equiv., 0.03 mmol). The resulting mixture was stirred at room temperature for 10 min, then thioester **1e** (67 mg, 0.3 mmol) was added. The reactions were followed by TLC until disappearance of the starting thioester **1e** was observed. The resulting Michael adducts were purified by flash column chromatography (*n*-hexane/EtOAc, 10:1 for aliphatic aldehydes and 8:1 for aromatic aldehydes) to afford the corresponding aldehydes **3a**–**g** in the yields indicated in Table 2.

**General Procedure for the Reduction of Aldehydes 3a–g:** To a cooled solution (–20 °C) of the corresponding aldehyde **3a**–**g** (0.3 mmol) in EtOH (0.05 M), $NaBH_4$ (1.2 equiv.) was added. The reaction mixture was stirred at –20 °C for 4 h and quenched at the reaction temperature with water (10 mL). The aqueous layer was extracted with EtOAc (3× 15 mL) and the combined organic layers were washed with brine and dried with $MgSO_4$. The solvent was finally evaporated and the crude product was purified by flash column chromatography using the eluent indicated in each case. The enantiomeric excesses of the Michael addition were determined for the major diastereomer of alcohols **4a**–**g** by chiral HPLC analysis.

***S*-Ethyl (2*R*,3*S*)- and (2*S*,3*S*)-2-(4-Nitrophenyl)-5-oxo-3-phenylpentanethioate (3a/3a′):** The title compound was obtained as a 70:30 mixture of diastereomers according to the general procedure (Michael addition, 93% yield); m.p. 121–123 °C. Data obtained from the major diastereomer. $^1H$ NMR (300 MHz): $\delta$ = 9.41 (s, 1 H), 8.23 (d, $J$ = 8.8 Hz, 2 H), 7.63 (d, $J$ = 8.8 Hz, 2 H), 7.38–7.20 (m, 5 H), 4.20 (d, $J$ = 11.1 Hz, 1 H), 4.07 (td, $J_t$ = 11.1, $J_d$ = 4.0 Hz, 1 H), 2.75–2.48 (m, 3 H), 2.41 (dd, $J$ = 17.1, 4.1 Hz, 1 H), 0.94 (t, $J$ = 6.8 Hz, 3 H) ppm. $^{13}C$ NMR (75 MHz): $\delta$ = 199.6 (CHO), 197.5 (C), 147.8 (C), 143.4 (C), 139.7 (C), 129.6 (2CH), 128.8 (2CH), 128.3 (2CH), 127.6 (CH), 124.2 (2CH), 65.5 (CH), 47.1 ($CH_2$), 43.6 (CH), 23.81 ($CH_2$), 14.3 ($CH_3$) ppm. MS (ESI): *m*/*z* (%) = 358 (4) [M + 1$^+$], 279 (95), 149 (56). HRMS (ESI): Calcd. for $C_{19}H_{20}NO_4S$ [M + 1] 358.1107; found 358.1101. The *ee* was determined for the corresponding alcohol, obtained after reduction with $NaBH_4$ in EtOH at –20 °C. The crude compound was purified by flash chromatography (*n*-hexane/EtOAc, 4:1).

***S*-Ethyl (2*S*,3*R*)-5-Hydroxy-2-(4-nitrophenyl)-3-phenylpentanethioate (4a):** M.p. 134–135 °C. $^1H$ NMR (300 MHz): $\delta$ = 8.21 (d, $J$ = 8.7 Hz, 2 H), 7.63 (d, $J$ = 8.7 Hz, 2 H), 7.35–7.18 (m, 5 H), 4.09 (d, $J$ = 11.4 Hz, 1 H), 3.61 (td, $J_t$ = 11.4, $J_d$ = 3.0 Hz, 1 H), 3.43–3.31 (m, 1 H), 3.30–3.18 (m, 1 H), 2.71–2.42 (m, 2 H), 1.73–1.54 (m, 2 H), 0.88 (t, $J$ = 7.6 Hz, 3 H) ppm. $^{13}C$ NMR (75 MHz): $\delta$ = 197.8 (C), 147.5 (C), 144.3 (C), 140.4 (C), 129.6 (2CH), 128.6 (2CH), 128.4 (2CH), 127.2 (CH), 124.0 (2CH), 66.5 ($CH_2$), 60.2 (CH), 46.0 ($CH_2$), 35.8 (CH), 23.7 ($CH_2$), 14.2 ($CH_3$) ppm. MS (FAB): *m*/*z* (%) = 361 (5) [M + 1$^+$], 360 (28), 298 (100). HRMS (ESI): Calcd. for $C_{19}H_{22}NO_4S$ [M + 1] 360.1264; found 360.1277. The enantiomeric excess was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH, 90:10]; flow rate 1.0 mL/min; $t_R$ = 19.1 (major), 15.4 (minor) min (94%*ee*). $[\alpha]_D^{20}$ = + 10.6 (*c* = 0.5, $CHCl_3$) [this compound was obtained using catalyst (*S*)-**I** instead of (*R*)-**I**].

***S*-Ethyl (2*R*,3*S*)- and (2*S*,3*S*)-3-Methyl-2-(4-nitrophenyl)-5-oxopentanethioate (3b/3b′):** The title compound was obtained as a 62:38 mixture of diastereomers according to the general procedure (72% yield). Data obtained from the mixture of diastereomers. $^1H$ NMR: $\delta$ = 9.75 (s, 1 H, minor), 9.57 (s, 1 H, major), 8.19 (d, $J$ = 8.8 Hz, 2 H, minor), 8.17 (d, $J$ = 8.7 Hz, 2 H, major), 7.51 [d, $J$ = 8.8 Hz, 2 H (major), 2 H (minor)], 3.78 (d, $J$ = 10.5 Hz, 1 H, major), 3.74 (d, $J$ = 10.2 Hz, 1 H, minor), 3.00–2.73 [m, 3 H (major), 3 H (minor)], 2.58 (dd, $J_d$ = 17.3, 3.6 Hz, 1 H, minor), 2.35 (ddd, $J$ = 16.6, 8.6, 2.2 Hz, 1 H, minor), 2.18 (dd, $J$ = 17.3, 3.6 Hz, 1 H, major), 2.05 (ddd, $J$ = 17.4, 8.6, 2.2 Hz, 1 H, minor), 1.14 (t, $J$ = 7.5 Hz, 3 H, major), 1.13 (t, $J$ = 7.4 Hz, 3 H, minor), 1.07 (d, $J$ = 6.6 Hz, 3 H, major), 0.73 (d, $J$ = 6.6 Hz, 3 H, minor) ppm. $^{13}C$ NMR (75 MHz): $\delta$ = 200.5 (CHO), 200.4 (CHO), 198.7 (C), 198.5 (C), 147.6 (C), 147.5 (C), 144.2 (2CH), 129.5 (2CH), 124.0 (2CH), 124.0 (2CH), 65.4 (CH), 65.3 (CH), 48.4 (CH), 47.7 (CH), 32.4 ($CH_2$), 31.9 ($CH_2$), 18.5 ($CH_3$), 17.9.3 ($CH_3$), 14.4 ($CH_3$), 14.3 ($CH_3$) ppm. MS (IE): *m*/*z* (%) = 295 (1) [M$^+$], 206 (100), 160 (5), 142 (40), 118 (25), 115 (40), 89 (28). HRMS (IE): Calcd. for $C_{14}H_{17}NO_4S$ [M$^+$] 295.0878; found 295.0891. The *ee* was determined for the corresponding alcohol, obtained after reduction with $NaBH_4$ in EtOH at –20 °C. The crude compound was purified by flash chromatography (*n*-hexane/EtOAc, 4:1).

***S*-Ethyl (2*R*,3*S*)-5-Hydroxy-3-methyl-2-(4-nitrophenyl)pentanethioate (4b):** $^1H$ NMR (300 MHz): $\delta$ = 8.17 (d, $J$ = 8.4 Hz, 2 H), 7.51 (d, $J$ = 8.4 Hz, 2 H), 3.62 (d, $J$ = 9.1 Hz, 1 H), 3.67–3.49 (m, 2 H), 2.94–2.74 (m, 2 H), 2.56–2.44 (m, 2 H), 1.63–1.45 (m, 1 H), 1.42–1.29 (m, 1 H), 1.19 (t, $J$ = 7.6 Hz, 3 H), 1.07 (d, $J$ = 6.5 Hz, 3 H) ppm. $^{13}C$ NMR (75 MHz): $\delta$ = 198.9 (CO), 147.3 (C), 144.8 (C), 129.6 (2CH), 124.0 (2CH), 66.9 ($CH_2$), 60.0 (CH), 36.4 (CH), 34.0 ($CH_2$), 23.8 ($CH_2$), 17.4 ($CH_3$), 14.5 ($CH_3$) ppm. MS (ESI): *m*/*z* (%) = 326 (12) [M + 1$^+$], 236 (100), 79 (47). HRMS (ESI): Calcd. for $C_{14}H_{20}NO_4S$ [M + 1] 298.1107; found 298.1035. The

enantiomeric excess was determined by HPLC using a Chiralcel IA column [hexane/*i*PrOH, 90:10]; flow rate 1.0 mL/min; $t_R$ = 16.7 (major), 14.1 (minor) min (83%*ee*). $[\alpha]_D^{20}$ = –66.9 (*c* = 2.0, $CHCl_3$).

***S*-Ethyl (2*R*,3*S*)- and (2*S*,3*S*)-2-(4-Nitrophenyl)-5-oxo-3-isopropylpentanethioate (3c/3c′):** The title compound was obtained as a 68:32 mixture of diastereomers according to the general procedure (50% yield). Data obtained from the mixture of diastereomers. $^1$H NMR (300 MHz): $\delta$ = 9.63 (s, 1 H, minor), 9.24 (s, 1 H, major), 8.13 (d, *J* = 8.8 Hz, 2 H, minor), 8.09 (d, *J* = 8.8 Hz, 2 H, major), 7.47 [d, *J* = 8.8 Hz, 2 H (major), 2 H (minor)], 3.83 (d, *J* = 11.1 Hz, 1 H, major), 3.80 (d, *J* = 10.7 Hz, 1 H, minor), 3.04–2.96 (m, 1 H, major), 2.88–2.68 (m, 5 H), 2.47–2.3958 (m, 1 H, minor), 2.32–2.18 (m, 2 H), 1.97–1.87 (m, 2 H), 1.37 (dsept, $J_d$ = 3.2, $J_{sept}$ = 6.8 Hz, 1 H, major), 0.87 (t, *J* = 5.8 Hz, 6 H), 0.78 (d, *J* = 6.8 Hz, 3 H, major), 0.65 (d, *J* = 6.8 Hz, 3 H, minor) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 200. 9 (CHO), 199.9 (CHO), 198.8 (C), 198.6 (C), 147.6 (2 C), 144.4 (C), 144.0 (CH), 129.8 (2CH), 129.4 (2CH), 124.1 (2CH), 124.0 (2CH), 63.5 (CH), 63.1 (CH), 42.1 (CH), 41.8 (CH), 41.6 (CH), 41.4 (CH), 29.1 ($CH_2$), 27.8 ($CH_2$), 24.1 ($CH_2$), 23.9 ($CH_2$), 21.6 ($CH_3$), 21.2 ($CH_3$), 16.6 ($CH_3$), 15.8 ($CH_3$), 14.3 ($CH_3$), 14.2 ($CH_3$) ppm. MS (ESI): *m*/*z* (%) = 324 (20) [M + 1$^+$], 262 (24), 216 (20), 79 (3). HRMS (ESI): Calcd. for $C_{16}H_{22}NO_4S$ [M + 1$^+$] 324.1264; found 324.1273. The *ee* was determined in the corresponding alcohol, obtained after reduction with $NaBH_4$ in EtOH at –20 °C. The crude compound was purified by flash chromatography (*n*-hexane/EtOAc, 4:1).

***S*-Ethyl (2*R*,3*R*)-5-Hydroxy-3-isopropyl-2-(4-nitrophenyl)pentanethioate (4c):** M.p. 86–87 °C. $^1$H NMR (300 MHz): $\delta$ = 8.17 (d, *J* = 8.5 Hz, 2 H), 8.18 (d, *J* = 8.5 Hz, 2 H), 3.82 (d, *J* = 11.3 Hz, 1 H), 3.24–3.12 (m, 1 H), 3.11–2.98 (m, 1 H), 2.96–2.72 (m, 2 H), 2.41–2.24 (m, 1 H), 1.94 (dsept, $J_{sept}$ = 7.1, $J_d$ = 2.8 Hz, 1 H), 1.67–1.42 (m, 2 H), 1.18 (t, *J* = 7.4 Hz, 3 H), 0.98 (d, *J* = 6.7 Hz, 3 H), 0.95 (d, *J* = 6.7 Hz, 3 H) ppm. $^{13}$C NRM (75 MHz): $\delta$ = 199.3 (CO), 147.7 (C), 144.9 (C), 130.4 (2CH), 123.7 (2CH), 64.2 ($CH_2$), 62.2 (CH), 43.7 (CH), 30.6 ($CH_2$), 29.6 (CH), 23.9 ($CH_2$), 21.2 ($CH_3$), 16.8 ($CH_3$), 14.2 ($CH_3$) ppm. MS (ESI): *m*/*z* (%) = 326 (25) [M + 1$^+$], 264 (100). HRMS (ESI): Calcd. for $C_{16}H_{24}NO_4S$ [M + 1] 326.1420; found 326.1418. The enantiomeric excess was determined by HPLC using a Chiralcel AD column [hexane/*i*PrOH, 80:20]; flow rate 1.0 mL/min; $t_R$ = 8.8 (major), 5.8 (minor) min (92%*ee*). $[\alpha]_D^{20}$ = –20.0 (*c* = 1.0, $CHCl_3$).

***S*-Ethyl (2*R*,3*S*)- and (2*S*,3*S*)-3-(4-Methoxyphenyl)-2-(4-nitrophenyl)-5-oxopentanethioate (3d/3d′):** The title compound was obtained as a 64:36 mixture of diastereomers according to the general procedure (Michael addition, 70% yield). Data obtained from the mixture of diastereomers. $^1$H NMR (300 MHz): $\delta$ = 9.55 (s, 1 H), 9.40 (s, 1 H), 8.22 (d, *J* = 8.6 Hz, 2 H), 8.00 (d, *J* = 8.8 Hz, 2 H), 7.61 (d, *J* = 8.8 Hz, 2 H), 7.29 (d, *J* = 8.6 Hz, 2 H), 7.19 (d, *J* = 8.7 Hz, 2 H), 6.89 (d, *J* = 8.9 Hz, 2 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 6.64 (d, *J* = 8.9 Hz, 2 H), 4.14 (d, *J* = 11.1 Hz, 1 H), 4.08 (d, *J* = 11.4 Hz, 1 H), 4.00 (m, 2 H), 3.78 (s, 3 H), 3.68 (s, 3 H), 2.94–2.84 (m, 3 H), 2.74–2.53 (m, 4 H), 2.37 (dd, *J* = 17.1, 4.1 Hz, 1 H), 1.22 (t, *J* = 7.5 Hz, 3 H), 0.96 (t, *J* = 7.4 Hz, 3 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 199.9 (CHO), 199.8 (CHO), 198.4 (C), 197.6 (C), 158.9 (C), 158.5 (C), 147.8 (C), 147.2 (C), 143.7 (C), 143.5 (C), 131.6 (C), 131.1 (C), 129.6 (2CH), 129.4 (2CH), 129.3 (2CH), 128.9 (2CH), 124.2 (2CH), 123.5 (2CH), 114.2 (2CH), 114.1 (2CH), 65.7 (CH), 65.6 (CH), 55.2 ($CH_3$), 55.1 ($CH_3$), 48.0 ($CH_2$), 47.2 ($CH_2$), 43.1 (CH), 42.9 (CH), 24.1 ($CH_2$), 23.8 ($CH_2$), 14.4 ($CH_3$), 14.2 ($CH_3$) ppm. MS (ESI): *m*/*z* (%) = 388 (4) [M + 1$^+$], 149 (56). HRMS (ESI): Calcd. for $C_{20}H_{22}NO_5S$ [M + 1$^+$] 388.1213; found 388.1216. The *ee* was determined for the corresponding alcohol, obtained after reduction with $NaBH_4$ in EtOH at –20 °C. The crude compound was purified by flash chromatography (*n*-hexane/EtOAc, 6:1).

***S*-Ethyl (2*R*,3*S*)-5-Hydroxy-3-(4-methoxyphenyl)-2-(4-nitrophenyl)-pentanethioate (4d):** M.p. 115–116 °C. $^1$H NMR (300 MHz): $\delta$ = 8.22 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.4 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 4.06 (d, *J* = 11.2 Hz, 1 H), 3.81 (s, 3 H), 3.58 (td, $J_t$ = 11.2, $J_d$ = 3.6 Hz, 1 H), 3.44–3.33 (m, 1 H), 3.32–3.21 (m, 1 H), 2.72–2.47 (m, 2 H), 1.69–1.50 (m, 2 H), 0.93 (t, *J* = 7.6 Hz, 3 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 198.0 (CO), 158.7 (C), 147.7 (C), 144.5 (C), 132.2 (C), 129.6 (2CH), 129.3 (2CH), 124.0 (2CH), 114.1 (2CH), 66.9 (CH), 60.2 ($CH_2$), 55.3 ($CH_3$), 45.2 ($CH_2$), 35.9 (CH), 23.7 ($CH_2$), 14.4 ($CH_3$) ppm. MS (ESI): *m*/*z* (%) = 390 (32) [M + 1$^+$], 328 (100), 135 (45). HRMS (ESI): Calcd. for $C_{20}H_{24}NO_5S$ [M + 1] 390.1369; found 390.1373. The enantiomeric excess was determined by HPLC using a Chiralcel IA column [hexane/*i*PrOH, 90:10]; flow rate 1.0 mL/min; $t_R$ = 23.5 (major), 18.7 (minor) min (87%*ee*). $[\alpha]_D^{20}$ = –1.97 (*c* = 1.0, $CHCl_3$).

***S*-Ethyl (2*S*,3*S*)- and (2*R*,3*S*)-3-(2-Methoxyphenyl)-2-(4-nitrophenyl)-5-oxopentanethioate (3e/3e′):** The title compound was obtained as a 64:36 mixture of diastereomers according to the general procedure (Michael addition, 90% yield). Data obtained from the mixture of diastereomers. $^1$H NMR (300 MHz): $\delta$ = 9.54 (s, 1 H), 9.38 (s, 1 H), 8.20 (d, *J* = 8.7 Hz, 2 H), 7.95 (d, *J* = 8.7 Hz, 2 H), 7.62 (d, *J* = 8.7 Hz, 2 H), 7.32 (d, *J* = 8.7 Hz, 2 H), 7.19 (m, 2 H), 7.03 (m, 1 H), 6.95–6.85 (m, 3 H), 6.72–6.64 (m, 2 H), 4.57 (d, *J* = 11.4 Hz, 1 H), 4.44 (d, *J* = 11.2 Hz, 1 H), 4.35 (td, $J_t$ = 9.7, $J_d$ = 4.2 Hz, 1 H), 4.22 (td, $J_t$ = 10.3, $J_d$ = 4.2 Hz, 1 H), 3.92 (s, 3 H), 3.77 (s, 3 H), 3.04–3.74 (m, 5 H), 2.72–2.47 (m, 2 H), 2.35 (ddd, *J* = 17.1, 4.4, 1.5 Hz, 1 H), 1.21 (t, *J* = 7.6 Hz, 3 H), 0.90 (t, *J* = 7.4 Hz, 3 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 200.6 (CHO), 200.5 (CHO), 198.7 (C), 197.8 (C), 157.4 (C), 156.8 (C), 147.7 (C), 147.1 (C), 144.1 (C), 143.8 (C), 130.7 (CH), 129.9 (CH), 129.8 (2CH), 129.2 (2CH), 128.8 (CH), 128.6 (CH), 127.1 (C), 126.9 (C), 123.9 (2CH), 123.2 (2CH), 120.8 (CH), 120.7 (CH), 111.1 (CH), 110.8 (CH), 63.3 (CH), 62.3 (CH), 55.4 ($CH_3$), 55.2 ($CH_3$), 46.6 ($CH_2$), 45.3 ($CH_2$), 40.8 (CH), 39.4 (CH), 24.0 ($CH_2$), 23.5 ($CH_2$), 14.3 ($CH_3$), 14.2 ($CH_3$) ppm. MS (ESI): *m*/*z* (%) = 388 (4) [M + 1$^+$], 326 (8), 163 (6). HRMS (ESI): Calcd. for $C_{20}H_{22}NO_5S$ [M + 1$^+$] 388.1213; found 388.1232. The *ee* was determined for the corresponding alcohol, obtained after reduction with $NaBH_4$ in EtOH at –20 °C. The crude compound was purified by flash chromatography (*n*-hexane/EtOAc, 6:1).

***S*-Ethyl (2*R*,3*S*)-5-Hydroxy-3-(2-methoxyphenyl)-2-(4-nitrophenyl)-pentanethioate (4e):** $^1$H NMR (500 MHz, $C_2D_2Cl_4$): $\delta$ = 8.13 (d, *J* = 8.7 Hz, 2 H), 7.58 (d, *J* = 8.7 Hz, 2 H), 7.17 (td, $J_t$ = 8.2, $J_d$ = 1.7 Hz, 1 H), 7.11 (dd, *J* = 7.6, 1.7 Hz, 1 H), 6.86 (m, 2 H), 4.42 (d, *J* = 10.6 Hz, 1 H), 3.32–3.27 (m, 1 H), 3.23–3.19 (m, 1 H), 2.65–2.58 (m, 1 H), 2.54–2.46 (m, 1 H), 1.78–1.71 (m 1 H), 1.54–1.48 (m 1 H), 0.80 (t, *J* = 7.4 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz): $\delta$ = 198.0 (C), 158.1 (C), 148.0 (C), 144.9 (C), 129.9 (2CH), 128.6 (C), 128.3 (CH), 123.8 (2CH), 121.1 (CH), 111.9 (CH), 64.2 (CH), 60.6 ($CH_2$), 55.9 ($CH_3$), 34.9 ($CH_2$), 29.6 (CH), 23.6 ($CH_2$), 14.2 ($CH_3$) ppm. MS (ESI): *m*/*z* (%) = 390 (14) [M + 1$^+$], 328 (100), 149 (49), 135 (54), 64 (56). HRMS (ESI): Calcd. for $C_{20}H_{24}NO_5S$ [M + 1] 390.1369; found 390.1371. The enantiomeric excess was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH, 90:10]; flow rate 1.0 mL/min; $t_R$ = 13.8 (major), 18.9 (minor) min (88%*ee*). $[\alpha]_D^{20}$ = –12.4 (*c* = 1.0, $CHCl_3$).

***S*-Ethyl (2*S*,3*S*)- and (2*R*,3*S*)-2,3-bis(4-nitrophenyl)-5-oxopentanethioate (3f/3f′):** The title compound was obtained as a 70:30 mix-

ture of diastereomers according to the general procedure (Michael addition, 75% yield). Data obtained from the major diastereomer. $^1$H NMR (300 MHz): $\delta$ = 9.41 (s, 1 H), 8.23 (d, $J$ = 8.8 Hz, 2 H), 8.17 (d, $J$ = 8.6 Hz, 2 H), 7.60 (d, $J$ = 8.6 Hz, 2 H), 8.50 (d, $J$ = 8.8 Hz, 2 H), 4.21 (m, 2 H), 2.71 (m, 1 H), 2.61 (m, 2 H), 2.53 (m, 1 H), 0.93 (t, $J$ = 7.3 Hz, 3 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 198.2 (CHO), 197.0 (C), 148.0 (C), 147.8 (C), 147.2 (C), 142.6 (CH), 129.5 (2CH), 129.4 (2CH), 124.3 (2CH), 123.8 (2CH), 64.5 (CH), 47.0 ($CH_2$), 42.9 (CH), 23.9 ($CH_2$), 14.5 ($CH_3$) ppm. MS (ESI): $m/z$ (%) = 403 (5) [M + 1$^+$], 341 (50), 149 (100). HRMS (ESI): Calcd. for $C_{19}H_{19}N_2O_6S$ [M + 1] 402.0886; found 402,0896. The *ee* was determined for the corresponding alcohol, obtained after reduction with $NaBH_4$ in EtOH at –20 °C. The crude compound was purified by flash chromatography (*n*-hexane/EtOAc, 6:1).

***S*-Ethyl (2*R*,3*S*)-5-Hydroxy-2,3-bis(4-nitrophenyl)pentanethioate (4f):** M.p. 157–158 °C. $^1$H NMR (300 MHz): $\delta$ = 8.23 (d, $J$ = 8.8 Hz, 2 H), 8.19 (d, $J$ = 8.7 Hz, 2 H), 7.64 (d, $J$ = 8.2 Hz, 2 H), 7.48 (d, $J$ = 8.19 Hz, 2 H), 4.12 (d, $J$ = 9.8 Hz, 1 H), 3.82 (td, $J_t$ = 9.8, $J_d$ = 5.1 Hz, 1 H), 3.44–3.33 (m, 1 H), 3.24–3.12 (m, 1 H), 2.69–2.47 (m, 2 H), 1.71–1.54 (m, 2 H), 0.90 (t, $J$ = 7.1 Hz, 3 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 197.4 (CO), 148.5 (C), 147.8 (C), 147.1 (C), 143.5 (C), 129.6 (2CH), 129.5 (2CH), 124.2 (2CH), 123.8 (2CH), 65.6 ($CH_2$), 59.4 (CH), 45.5 ($CH_2$), 35.6 (CH), 23.8 ($CH_2$), 14.2 ($CH_3$) ppm. MS (ESI): $m/z$ (%) = 405 (13) [M + 1$^+$], 343 (88), 282 (100), 225 (44), 149 (90), 79 (42), 64 (77). HRMS (ESI): Calcd. for $C_{19}H_{21}NO_6S$ [M + 1] 405.1138; found 405.1114. The enantiomeric excess was determined by HPLC using a Chiralcel IC column [hexane/*i*PrOH, 90:10]; flow rate 1.0 mL/min; $t_R$ = 56.9 (major), 43.6 (minor) min (86%*ee*). $[\alpha]_D^{20}$ = –14.5 ($c$ = 0.7, $CHCl_3$).

***S*-Ethyl (2*S*,3*S*)- and (2*R*,3*S*)-3-(Furan-2-yl)-2-(4-nitrophenyl)-5-oxopentanethioate (3g/3g′):** The title compound was obtained as a 70:30 mixture of diastereomers according to the general procedure (Michael addition, 60% yield). Data obtained from the mixture of diastereomers. $^1$H NMR (300 MHz): $\delta$ = 9.60 (s, 1 H), 9.50 (s, 1 H), 8.20 (d, $J$ = 8.8 Hz, 2 H), 8.05 (d, $J$ = 8.8 Hz, 2 H), 7.53 (d, $J$ = 8.8 Hz, 4 H), 7.37–7.32 (m, 2 H), 6.28 (dd, $J$ = 3.3, 1.9 Hz, 1 H), 6.14 (d, $J$ = 3.3 Hz, 1 H), 6.05 (dd, $J$ = 3.3, 1.9 Hz, 1 H), 5.49 (d, $J$ = 3.3 Hz, 1 H), 4.29 (d, $J$ = 10.3 Hz, 1 H), 4.25–4.08 (m, 2 H), 4.23 (d, $J$ = 10.8 Hz, 1 H), 2.99–2.60 (m, 7 H), 2.41 (dd, $J$ = 17.4, 3.9 Hz, 1 H), 1.22 (t, $J$ = 7.5 Hz, 3 H), 1.09 (t, $J$ = 7.4 Hz, 3 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 199.2 (C), 199.1 (CHO), 197.6 (C), 192.9 (CHO), 152.4 (2C), 145.9 (2C), 142.8 (C × 2), 142.0 (CH), 141.9 (CH), 129.6 (2CH), 129.2 (2CH), 124.1 (2CH), 123.6 (2CH), 110.4 (CH), 110.2 (CH), 108.3 (CH), 108.1 (CH), 63.0 (CH), 62.7 (CH), 45.4 ($CH_2$), 44.4 ($CH_2$), 37.3 (CH), 36.7 (CH), 24.1 ($CH_2$), 23.8 ($CH_2$), 14.3 ($CH_3$), 14.2 ($CH_3$) ppm. MS (ESI): $m/z$ (%) = 370 (4) [M + Na$^+$], 360 (12), 149 (4). HRMS (ESI): Calcd. for $C_{17}H_{17}NO_5SNa$ [M + Na$^+$] 370.0719; found 370.0724. The *ee* was determined for the corresponding alcohol, obtained after reduction with $NaBH_4$ in EtOH at –20 °C. The crude compound was purified by flash chromatography (*n*-hexane/EtOAc, 4:1).

***S*-Ethyl (2*S*,3*S*)- and (2*R*,3*S*)-3-(Furan-2-yl)-5-hydroxy-2-(4-nitrophenyl)pentanethioate (4g):** $^1$H NMR (300 MHz): $\delta$ = 8.20 (d, $J$ = 8.5 Hz, 2 H), 7.58 (d, $J$ = 8.5 Hz, 2 H), 7.24 (dd, $J$ = 0.61, 1.71 Hz, 1 H), 6.29 (dd, $J$ = 1.71, 3.20 Hz, 1 H), 6.17 (dd, $J$ = 0.61, 3.20 Hz, 1 H), 4.21 (d, $J$ = 10.7 Hz, 1 H), 3.79 (td, $J_t$ = 10.7, $J_d$ = 4.1 Hz, 1 H), 3.50–3.27 (m, 2 H), 2.81–2.58 (m, 2 H), 1.77–1.66 (m 1 H), 1.54–1.42 (m 1 H), 1.05 (t, $J$ = 6.7 Hz, 3 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 198.0 (CO), 153.3 (C), 147.5 (C), 143.7 (C), 142.0 (CH), 129.7 (2CH), 124.0 (2CH), 110.2 (CH), 108.1 (CH), 64.1 (CH), 60.2 ($CH_2$), 39.3 ($CH_2$), 34.0 ($CH_2$), 23.7 (CH), 14.2 ($CH_3$) ppm. MS (FAB): $m/z$ (%) = 350 (22) [M + 1], 327 (67), 283 (100). HRMS (FAB): Calcd. for $C_{17}H_{20}NO_5$ [M + 1] 350.1062; found 350.1058. The enantiomeric excess was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH, 90:10]; flow rate 1.0 mL/min; $t_R$ = 13.8 (major), 18.9 (minor) min (70%*ee*). $[\alpha]_D^{20}$ = –10.8 ($c$ = 2.0, $CHCl_3$).

**(3*S*,4*S*)-3-(4-Nitrophenyl)-4-phenyltetrahydro-2*H*-pyran-2-one (5a):** To a solution of alcohol **4a** (0.2 mmol) in anhydrous THF (0.03 M), NaH (1.1 equiv.) was added. After stirring the resulting mixture at room temperature for 1 h, the reaction was quenched by addition of a saturated solution of $NH_4Cl$ (10 mL) and extracted with EtOAc (2 × 15 mL). The organic extracts were washed with brine and dried with anhydrous $MgSO_4$. The solvent was evaporated and the crude product was purified by flash chromatography (*n*-hexane/EtOAc, 4:1) to afford the desired product (50% yield). $^1$H NMR (300 MHz): $\delta$ = 8.11 (d, $J$ = 9 Hz, 2 H), 7.30 (d, $J$ = 8.2 Hz, 2 H), 7.19 (m, 3 H), 7.04 (d, $J$ = 7.8 Hz, 2 H), 4.71 (m, 2 H), 4.02 (d, $J$ = 11.8 Hz, 1 H), 3.32 (m, 1 H), 2.39 (m, 2 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 169.6 (CO), 141.2 (C), 133.4 (C), 133.3 (C), 128.8 (2CH), 128.6 (2CH), 127.5 (2CH), 127.2 (2CH), 126.0 (CH), 68.8 (CH), 46.1 (CH), 45.3 (CH), 35.5 ($CH_2$) ppm. MS (FAB): $m/z$ (%) = 298 (100) [M + 1], 154 (27), 136 (30), 55 (100). HRMS (FAB): Calcd. for $C_{17}H_{16}NO_4$ [M + 1] 298.1079; found 298.1072.

**(3*S*,4*S*)-4-Methyl-3-(4-nitrophenyl)-tetrahydropyran-2-one (5b):** Following the same procedure described for **4a** but starting from alcohol **4b**, lactone **5b** was obtained as a single diastereomer (85% yield). $^1$H NMR (300 MHz): $\delta$ = 8.23 (d, $J$ = 8.8 Hz, 2 H), 7.38 (d, $J$ = 8.8 Hz, 2 H), 4.58–4.42 (m, 2 H), 3.38 (d, $J$ = 11 Hz, 1 H), 2.33–2.22 (m, 1 H), 2.20–2.07 (m, 1 H), 1.74–0.98 (m, 1 H), 0.95 (d, $J$ = 6.0 Hz, 3 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 171.0 (CO), 147.3 (C), 145.2 (C), 130.0 (2CH), 123.9 (2CH), 68.2 ($CH_2$), 55.6 (CH), 34.3 (CH), 30.9 ($CH_2$), 20.3 ($CH_3$) ppm. MS (FAB): $m/z$ (%) = 236 (100) [M + 1], 219 (13), 107 (35), 71 (44), 57 (58), 55 (85). HRMS (FAB): Calcd. for $C_{12}H_{13}NO_4$ [M + 1] 236.0917; found 236.0923. The enantiomeric excess was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH, 90:10]; flow rate 1.0 mL/min; $t_R$ = 30.3 (major), 26.4 (minor) min (83%*ee*). $[\alpha]_D^{20}$ = +20 ($c$ = 1.0, $CHCl_3$) {ref.[5] $[\alpha]_D^{20}$ = +25 ($c$ = 1.0, $CHCl_3$, 96%*ee*)]. IR (film): $\tilde{\nu}$ = 2964, 1723, 1526, 1347 cm$^{-1}$.

**(*R*)-4-(4-Nitrophenyl)-3-phenylbutan-1-ol (6):** To a solution of alcohol **4a** (36 mg, 0.1 mmol) in MeOH (0.5 mL) were added KOH (1.2 equiv.) and water (2 mL). The reaction was stirred for 2 h until the starting material was consumed. After this time, the solvent was evaporated and $K_2CO_3$ (2.0 equiv.) and DMF (5 mL) were added. The reaction was performed in an ultrasonic bath for 6 h at room temperature, then water was added to the reaction mixture and the aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine and dried with anhydrous $MgSO_4$. The solvent was finally evaporated and the crude compound was purified by flash chromatography (*n*-hexane/EtOAc, 4:1) to give **6** (80% yield). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.00 (d, $J$ = 8.7 Hz, 2 H), 7.21 (m, 3 H), 7.08 (m, 4 H), 3.56 (m, 1 H), 3.44 (m, 1 H), 3.03 (m, 3 H), 1.95 (m, 2 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 148.2 (C), 146.4 (C), 142.9 (C), 129.9 (2 CH), 128.6 (2 CH), 127.7 (2 CH), 126.8 (CH), 123.3 (2 CH), 60.7 ($CH_2$), 44.2 (CH), 43.5 ($CH_2$), 38.5 ($CH_2$) ppm. MS (ESI): $m/z$ (%) = 272 [M + 1], 149 (21), 79 (100), 64 (22). HRMS (ESI): Calcd. $C_{16}H_{18}NO_3$ [M + 1] 272.1281; found 272.1290. The enantiomeric excess was determined by HPLC using a Chiralpak OD column [hexane/*i*-PrOH, 95:5]; flow rate 1.0 mL/min; $t_R$ = 20.1 (major), 17.9 (minor) min (90%*ee*).

**(3*S*,4*S*)- and (3*R*,4*S*)-1-Benzyl-3-(4-nitrophenyl)-4-phenylpiperidin-2-one (7a/7a′):** To a solution of **3a/3a′** (72 mg, 0.2 mmol) in 1,2-dichloroethane (166 mL) at 0 °C, benzylamine (3 equiv., 0.6 mmol), acetic acid (12 μL, 0.2 mmol) and sodium triacetoxyborohydride (5 equiv.) were added. The resulting mixture was stirred at room temp. for 24 h. After this time, the reaction was quenched by the addition of aqueous $NaHCO_3$ (10 mL) and the product was extracted with $CH_2Cl_2$ (3× 20 mL). The combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give the crude product, which was purified by flash chromatography (*n*-hexane/EtOAc, 4:1) to afford the lactam as a mixture of diastereomers (81% yield). $^1$H NMR (300 MHz): $\delta$ = 8.05 (d, $J$ = 8.7 Hz, 2H, major), 7.90 (d, $J$ = 8.5 Hz, 2 H, minor), 7.45–7.31 [m, 6 H (major), 5 H (minor)], 7.22–7.15 [m, 2 H (major), 3 H (minor)], 7.12 (d, $J$ = 9.0 Hz, 2 H, major), 6.98–6.93 (m, 2 H, major), 6.81 (d, $J$ = 8.7 Hz, 2 H, minor), 6.77–6.73 (m, 2 H, minor), 5.03 (d, $J$ = 14.3 Hz, 1 H, minor), 4.75 (d, $J$ = 14.1 Hz, 1 H, major), 4.56 (d, $J$ = 14.5 Hz, 1 H, major), 4.52 (d, $J$ = 13.1 Hz, 1 H, minor), 4.21 (d, $J$ = 5.7 Hz, 1 H, minor), 3.93 (d, $J$ = 11.3 Hz, 1 H, major), 3.49–3.64 (m, 2 H, major), 3.48–3.38 (m, 3 H, minor), 3.15 (td, $J_t$ = 11.4, $J_d$ = 4.1 Hz, 1 H, major), 2.37–2.08 [m, 2 H (major), 2 H (minor)] ppm. $^{13}$C NMR (75 MHz): $\delta$ = 169.3 (CO), 169.1 (CO), 147.9 (C), 147.2 (C), 146.7 (C), 145.0 (C), 141.6 (C), 139.7 (C), 137.0 (C), 136.9 (C), 130.7 (2CH), 129.9 (2CH), 128.9 (2CH), 128.8 (2CH), 128.7 (2CH), 128.5 (2CH), 128.4 (2CH), 127.9 (2CH), 127.8 (2CH), 127.4 (2CH), 127.2 (2CH), 126.9 (2CH), 123.4 (2CH), 122.6 (2CH), 56.4 ($CH_2$), 54.5 (CH), 50.9 ($CH_2$), 50.7 (CH), 47.8 ($CH_2$), 46.7 ($CH_2$), 46.5 (CH), 43.2 (CH), 29.6 ($CH_2$), 22.3 ($CH_2$) ppm. MS (EI): *m*/*z* (%) = 386 (46) [M$^+$], 91 (100). HRMS (EI): Calcd. for $C_{24}H_{22}NO_3$ [M$^+$] 386.1630; found 386.1647.

**(2*R*,3*S*)-4-(*tert*-Butyldiphenylsilyloxy)-2-(4-nitrophenyl)-1,3-diphenylbutan-1-one (8):** A solution of alcohol **4a** (36 mg, 0.10 mmol), *tert*-butyl(choro)diphenylsilane (1.2 equiv., 0.12 mmol), triethylamine (2.0 equiv., 0.20 mmol) and DMAP (6 mg, 0.05 mmol) in dichloromethane (2 mL) was stirred overnight at room temperature. The resulting mixture was filtered through a short pad of silica gel using $CH_2Cl_2$ as eluent to obtain the protected alcohol as a single diastereomer in quantitative yield. The protected alcohol (63 mg, 0.10 mmol), copper(I) thiophene-2-carboxylate (32 mg, 0.17 mmol), phenylboronic acid (13 mg, 0.11 mmol), tris(dibenzylideneacetone)dipalladium(0) (2.2 mg, 0.025 mmol), and triethylphosphite (3.3 mg, 0.2 mmol) were placed in a sealed tube previously flushed with argon. DMF (300 μL) was added and the mixture was stirred for 3 d at 100 °C. $Et_2O$ (10 mL) was added and the suspension was washed with water (3× 15 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered, and the solvents evaporated. The resulting solid was purified by column chromatography (*n*-hexane/EtOAc, 12:1) to afford **8** (65% yield) as a single diastereomer. $^1$H NMR (300 MHz): $\delta$ = 8.20 (d, $J$ = 8.7 Hz, 2 H), 7.60 (dd, $J$ = 8.6, 6.5 Hz, 3 H), 7.44 (t, $J$ = 7.05 Hz, 6 H), 4.05 (d, $J$ = 11.9 Hz, 1 H), 3.80–3.68 (m, 1 H), 3.40–3.20 (m, 2 H), 2.68–2.41 (m, 2 H), 0.99 (s, 9 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 211.9 (CO), 152.4 (C), 151.9 (C), 147.2 (C), 145.3 (CH), 141.6 (CH), 137.0 (CH), 133.6 (C), 133.2 (2CH), 129.9 (2CH), 129.6 (2CH), 129.5 (2CH), 128.5 (2CH), 128.4 (2CH), 128.3 (2CH), 128.1 (2CH), 127.5 (2CH), 127.4 (2CH), 124.1 (2CH), 60.9 (CH), 59.5 (CH), 45.4 ($CH_2$), 36.1 (CH), 26.7 ($3CH_3$) ppm. MS (ESI): *m*/*z* (%) = 614 [M + 1], 242 (100), 149 (72). HRMS (ESI): Calcd. $C_{39}H_{40}NO_4Si$ [M + 1] 614.2721; found 614.26.

***S*-Ethyl (2*R*,3*S*)-5-Hydroxy-2,3-diphenylpentanethioate (9a):** To a solution of **4a** (0.30 mmol, 110 mg) in $CH_2Cl_2$ (4 mL) was added sequentially Zn dust (14 equiv., 270 mg) and AcOH (28 equiv., 490 μL) at 0 °C. After stirring at room temperature for 30 min, the reaction mixture was filtered through Celite and the filtrate was neutralized with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with dichloromethane (3× 15 mL) and the combined organic layers were washed with brine and dried with $MgSO_4$. The solvent was evaporated to give pure amine **8a** in quantitative yield. The crude material was treated with aqueous 50% $H_3PO_2$ (2.5 mL), and $NaNO_2$ (2.6 equiv., 54 mg) was added at 0 °C. After 2 h, $K_2CO_3$ was added to the reaction mixture and the aqueous layer was extracted with $Et_2O$ (3× 15 mL). The combined organic layer was dried with $MgSO_4$, filtered, and the solvents evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate, 6:1) to afford **9a** (75% yield). $^1$H NMR (300 MHz): $\delta$ = 7.46–7.27 (m, 10 H), 3.98 (d, $J$ = 11.3 Hz, 1 H), 3.58 (dt, $J_d$ = 11.3, $J_t$ = 7.7 Hz, 1 H), 3.40–3.22 (m, 2 H), 2.69–2.44 (m, 2 H), 1.67–1.60 (m, 2 H), 0.88 (t, $J$ = 7.6 Hz, 3 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 198.9 (C), 141.4 (C), 137.1 (C), 128.8 (2CH), 128.6 (2CH), 128.5 (2CH), 128.4 (2CH), 127.8 (CH), 126.9 (CH), 66.9 (CH), 60.7 ($CH_2$), 45.8 (CH), 36.2 ($CH_2$), 23.4 ($CH_2$), 14.3 ($CH_3$) ppm. MS (ESI): *m*/*z* (%) = 315 (19) [M + 1$^+$], 297 (45), 253 (100). HRMS (ESI): Calcd. for $C_{19}H_{23}O_2S$ [M + 1] 314.1346; found 314.1356.

***S*-Ethyl (2*R*,3*S*)-5-Hydroxy-3-methyl-2-phenylpentanethioate (9b):** Following the same procedure described above for **9a**, **9b** was obtained in 60% yield from **4b**. $^1$H NMR (300 MHz): $\delta$ = 7.34–7.29 (m, 5 H), 3.65–3.48 (m, 2 H), 3.48 (d, $J$ = 10.6 Hz, 1 H), 2.93–2.73 (m, 2 H), 2.56–2.42 (m, 1 H), 1.50–1.39 (m, 2 H), 1.19 (t, $J$ = 7.4 Hz, 3 H), 1.07 (d, $J$ = 6.6 Hz, 1 H) ppm. $^{13}$C NMR (75 MHz): $\delta$ = 200.2 (C), 137.5 (C), 128.7 (2CH), 128.6 (2CH), 127.5 (CH), 67.4 (CH), 60.6 ($CH_2$), 36.8 ($CH_2$), 33.5 (CH), 23.6 ($CH_2$), 18.0 ($CH_3$), 14.5 ($CH_3$) ppm. MS (ESI): *m*/*z* (%) = 253 (22) [M + 1$^+$], 235 (43), 191 (100). HRMS (ESI): Calcd. for $C_{14}H_{21}O_2S$ [M + 1] 253.1256; found 253.1266.

**Supporting Information** (see footnote on the first page of this article): Experimental data, computational details of the configurational assignment of **4a** and **4a′**, $^1$H NMR and $^{13}$C NMR spectra; chiral HPLC conditions; and computational details.

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[8] Reaction conditions used for each nucleophile: **1a**: catalyst **I**, $PhCO_2H$ (ref.[4]); **1b**: catalyst **I**, LiOAc (ref.[5]); **1c**: catalyst **I**, LiOAc (ref.[6]); **1d**: catalyst **II**, TBAB (ref.[7]). It is important to note that in the reactions of **1d** with aromatic enals using TBAB as additive only good enantioselectivities were obtained with cat **I** controlling the reaction times (see also the ESI of ref.[7]).

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[13] For more details see the Supporting Information.

[14] No improvement in the reactivity was achieved by using $CH_2Cl_2$ with other additives.

[15] The reduction of Michael adducts **3** to the corresponding alcohols **4** was necessary to determine the enantioselectivity of the addition because aldehydes **3** decompose in the HPLC columns.

[16] Lactones **5a** and **5b** had been previously prepared by us in ref.[5]

[17] Traces of these alcohols were detected when the reactions were performed on a large scale.

[18] We have confirmed that diastereomerically pure aldehyde **3a** afforded **4a** quantitatively under the reduction conditions with no epimerization.

[19] The same configuration was assigned to the rest of the alcohols. The absolute configuration has been determined by chemical correlation (see the Supporting Information and ref.[22]).

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[22] Comparison of its spectroscopic parameters, sign of the specific rotation, and chiral HPLC chromatogram with those obtained for **5b** in ref.[5] (the absolute configuration of which had been unequivocally determined by X-ray diffraction analysis) allowed the absolute configuration of adducts **3** to be assigned. The absolute configurations of the other products were assigned by analogy.

[23] See, for example: a) A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, *10*, 1107–1110; b) A. Metzger, M. A. Schade, G. Manolikakes, P. Knochel, *Chem. Asian J.* **2008**, *3*, 1678–1691 and references cited therein.

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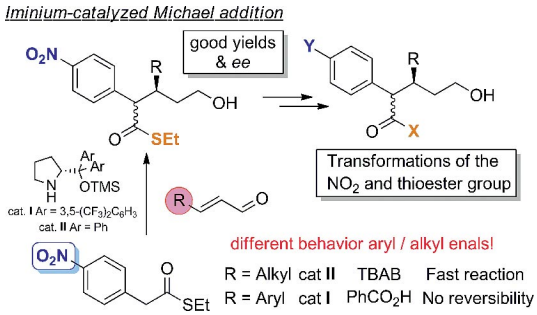
**Organocatalysis**




*S*-Ethyl 4-nitrophenylthioacetate presents excellent reactivity and enantioselectivity in organocatalytic asymmetric Michael reactions with both aromatic and aliphatic enals under different conditions. The corresponding adducts have proven to be versatile intermediates.



**Keywords:** Asymmetric catalysis / Organocatalysis / Michael addition