Tetrahedron 70 (2014) 5834–5842

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Enantioselective conjugate addition of aliphatic thiols to divergently activated electron poor alkenes and dienes

Rafał Kowalczyk [a,*], Aleksandra J. Wierzba [a], Przemysław J. Boratyński [a], Julia Bąkowicz [b]

[a] Department of Organic Chemistry, Wrocław University of Technology, Wyspiańskiego 27, Wrocław, Poland
[b] Institute of Physical and Theoretical Chemistry, Wrocław University of Technology, Wyspiańskiego 27, Wrocław, Poland

ARTICLE INFO

Article history:
Received 31 March 2014
Received in revised form 28 May 2014
Accepted 10 June 2014
Available online 14 June 2014

Keywords:
Asymmetric catalysis
Thia-Michael addition
Regioselectivity
Alkaloids

ABSTRACT

Divergently activated double bonds in electron poor 4-oxo-butenoates and (2*E*,4*E*)-6-oxo-2,4-dienoates underwent stereoselective and regioselective addition of mercaptans catalyzed by simple *Cinchona* alkaloids. Application of quinine and quinidine afforded both enantiomers of the 1,4-adducts with respect to the ketone carbonyl group in ees of up to 80%. Single recrystallization of some adducts resulted in further enrichment of up to 99%ee.

1. Introduction

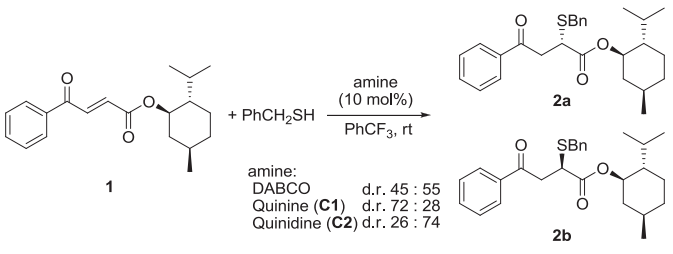
Direct addition of sulfur-centered nucleophiles to Michael acceptors offers an access to products with new C–S bonds.[1] Generally, thiols are recognized as good partners in additions to Michael acceptors. However, in the case of α,β-unsaturated carboxylic acid esters the activation of the double bond is often insufficient.[2] This lack of reactivity can be overcome in substrates where an extra electron withdrawing group is introduced. When such a group is at the opposite end of the π-system it competes with the ester functionality altering regioslectivity,[3] and as a result the addition of thiol may occur at the α-carbon to the ester group. This formally inverted reactivity pattern[4] as compared to simple acrylates gives access to products that are otherwise difficult to obtain. Consequently, addition of various nucleophiles to modified acrylates leads to multifunctional molecules, which are valuable synthetic intermediates and are relevant to medicinal chemistry.[5]

Another challenge is associated with providing stereoselectivity for the addition of thiols to such a system. Although 4-oxo-buteonoates received significant attention as electrophiles in metal- and organocatalytic variants of asymmetric Michael addition and Friedel–Crafts reactions,[6] no enantioselective addition of thiols was reported.[7]

Here we present the direct and enantioselective addition of mercaptans to 4-oxo-butenoates and (2*E*,4*E*)-6-oxo-2,4-dienoates catalyzed by quinine and quinidine.

2. Results and discussion

Previous attempts to perform the addition of thiols to 4-oxo-butenoates applying triethylamine revealed that the reaction occurs regioselectively at the β-position relative to the ketone group.[8] With no precedent of a stereoselective variant of such addition, search for the direct stereoselective thia-Michael addition to 4-oxo-buteonates began with the application of chiral Michael acceptor **1**. In the reaction with benzyl mercaptan and DABCO the respective adducts **2a**,**b** were formed with only 55:45 dr (Scheme 1). Therefore, the effect of the chiral auxiliary attached directly to the Michael acceptor is rather limited.



Scheme 1.

* Corresponding author. Tel.: +48 713203302; fax: +48 713202727; e-mail address: rafal.kowalczyk@pwr.edu.pl (R. Kowalczyk).
URL: http://org.wch.pwr.edu.pl

http://dx.doi.org/10.1016/j.tet.2014.06.035
0040-4020/

However, an application of a chiral base (quinidine) led to diastereomerically enriched product and 74:26 dr was achieved. With quinine catalyst a different isomer of the adduct was obtained in 72:28 dr. The formation of antipodes of the product with the use of catalysts of different configuration demonstrates that the chiral catalyst, rather than the auxiliary, was able to control the stereoselectivity. The action of both these modalities is independent as evidenced by the difference in diastereoselectivity for the pseudoenantiomeric catalysts being in qualitative agreement with the value obtained in the reaction with achiral catalyst. Consequently, simple *Cinchona* alkaloids were found to perform the addition of benzyl thiol to acceptor **3** in an enantioselective manner (catalysts **C1**–**C5**, Fig. 1). In each case the configuration at the 8-position in the alkaloid determines the stereochemical result of the addition. Hence, application of quinine (**C1**), cinchonidine (**C3**), as well as *epi*-quinine (**C5**, all 8*S*) gave product of opposite configuration to the one obtained when quinidine (**C2**) and cinchonine (**C4**) were applied. Modifications at the 9-position in parent alkaloid (**C6**–**7**)[9] did not provide higher level of stereoselectivity. Application of 9-*O*-benzoyl quinine (**C9**) and $(DHQ)_2AQN$ (**C10**) gave products in 37 and 50%ee, respectively.

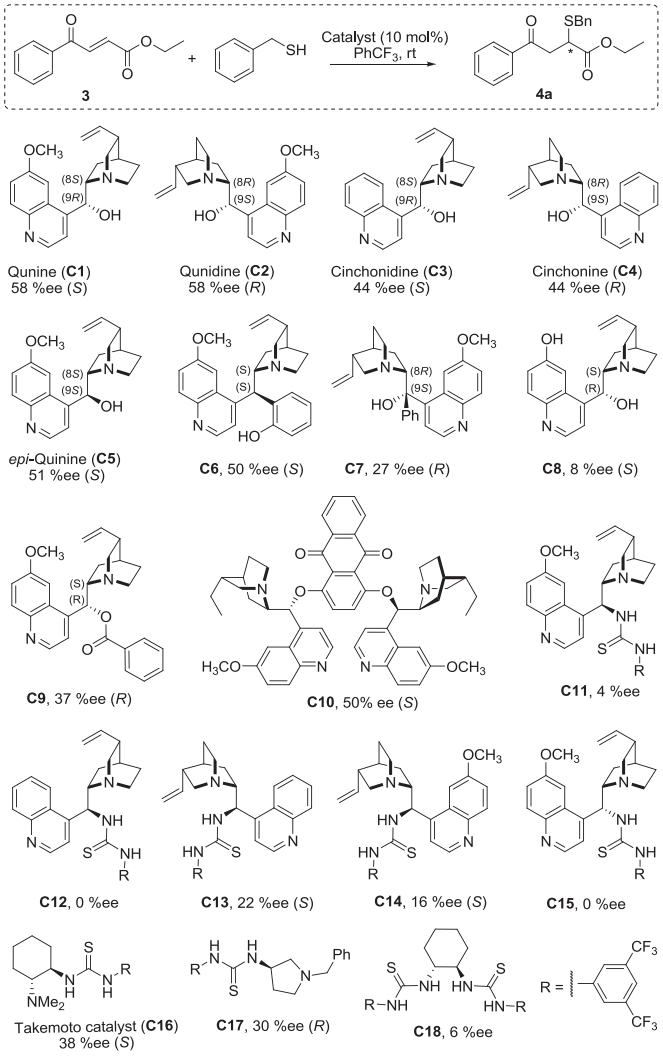
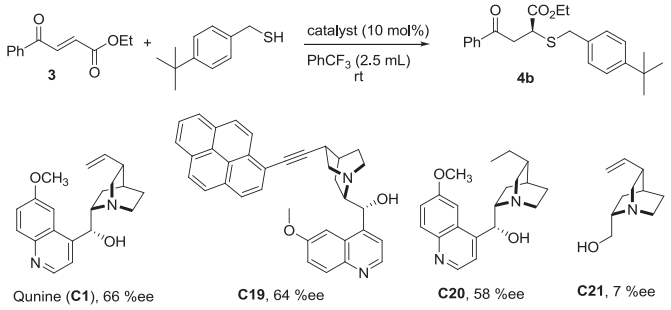


Fig. 1. Catalyst screening for asymmetric conjugate addition.

Based on the assumption that an increase in the subtle interactions in hydrogen-bond donors leads to better control of stereoselectivity in catalytic asymmetric reactions,[10] bifunctional thiourea catalysts[11] were applied (Fig. 1, **C11**–**18**). To our surprise, all of the tested catalysts were inferior to simple alkaloids, while thiourea **C17**[12] and Takemoto catalyst (**C16**)[13] provided less than 40%ee. Introduction of additional interacting sites in the catalyst, as in cupreine (**C8**), also resulted in poor selectivity. Furthermore, an approach involving stronger interactions with the catalyst, by the expected[14] formation of an iminium salt was tested. Although 9-aminoalkaloids work perfectly in the thia-Michael reaction of alkyl thiols and enones,[15] application of *epi*-9-amino-deoxyquinine and 2-fluorobenzoic acid mixture led to nearly racemic products. It must be emphasized that such a strategy in the case of ethyl (*E*)-4-oxo-2-pentenoate was effective when a nitrogen-centered nucleophile was applied.[16] Moreover, only racemic products were observed when thiophenol was applied. Thus, the aromatic nature of the nucleophile is detrimental to the stereoselectivity in the tested reaction.

In order to further investigate the impact of the structural elements in the most efficient catalyst on the chirality transfer, several analogues of quinine were tested. These aminoalcohols were then assayed in the reaction of bulky 4-*tert*-butylbenzylmercaptan with acceptor **3** (Scheme 2). Modification of the vinyl group of quinine as in **C19** and dihydroquinine (**C20**) had a limited impact on the stereoselectivity. However, the presence of a complete alkaloid framework proved to be crucial, while application of aminoalcohol **C21** led to product with low ee.

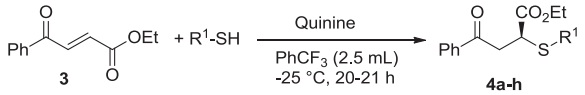


Scheme 2.

Therefore quinine (**C1**), a simple and readily available catalyst[17] was chosen for further studies. This alkaloid is believed to act as a bifunctional catalyst offering both a basic site to activate nucleophile and a hydroxyl group to form hydrogen bond with reactants.[18] The efficiency of such a system often relies on careful solvent selection. The enantioselectivities increased gradually from 33 to 59%ee, as the solvent was changed from DME, xylenes, toluene, DCM, chlorobenzene to $PhCF_3$. Even though in the last solvent the reaction mixture remained inhomogeneous, lowering the temperature to −25 °C resulted in formation of the product with 69%ee. At this temperature, the reaction without the catalyst proceeds very slowly, and conversion was estimated at less than 0.1% per hour. Homogenous reaction mixtures obtained with DCM as a solvent, provided up to 62%ee at −30 °C.

Having in hand the efficient catalytic system, we investigated the scope of the reaction. Thus, different thiols (Table 1) and acceptors (Tables 2 and 3) were examined in reactions catalyzed by quinine. The catalytic system was efficient in all the tested concentrations of quinine, which did not affect enantioselectivity giving products **4** in ee ranging from 67 to 71%, allowing catalyst loading to be reduced to 0.5 mol %. Further decrease in the catalyst loading to 0.2% resulted in only moderate deterioration of enantioselectivity (Table 1). Nevertheless, such low catalyst loadings are exceptional in organocatalysis. The reduction in catalyst amount without compromising the reaction outcome could be performed for other mercaptans with the exception of 4-*tert*-butylbenzyl thiol,

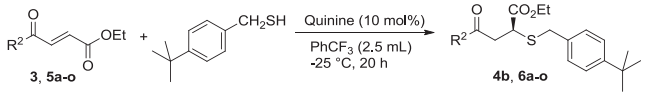
Table 1
Reaction of various thiols with (*E*)-4-oxo-4-phenylbut-2-enoate[a]



Entry	R^1	Quinine, mol %	Product	Yield,[b] %	ee,[c] %
1	Bn	20	**4a**	65	67
2	Bn	10	**4a**	62	69
3	Bn	1	**4a**	79	68
4	Bn	0.5	**4a**	78	71
5	Bn	0.2	**4a**	74	52
6[d]	Bn	10	**4a**	92	69
7	4-*t*-Bu$C_6H_4CH_2$	10	**4b**	78	80
8	$PhCH_2CH_2$	1	**4c**	69	66
9	4-$ClC_6H_4CH_2$	10	**4d**	82	55
10	4-$MeOC_6H_4CH_2$	10	**4e**	74	69
11	Cyclohexyl	1	**4f**	73	65
12	*n*-$C_{12}H_{25}$	1	**4g**	63	59

[a] Reactions were performed on a 0.5-mmol scale of **3** and 1.5 equiv of thiol.
[b] Isolated yield.
[c] Determined using chiral HPLC.
[d] Reaction performed in 7.5 mL of solvent.

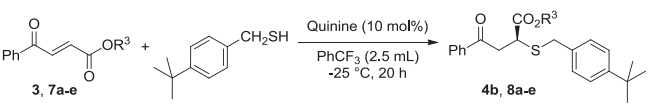
Table 2
Reaction of various ethyl (*E*)-4-oxo-but-2-enoates with 4-*tert*-butylbenzyl thiol (1.5 equiv)[a]



Entry	R^2	Alkene	Product	Yield,[b] %	ee,[c] %
1	Ph	**3**	**4b**	78 (73)[d]	80 (−76)[d]
2	4-*t*-BuC_6H_4	**5a**	**6a**	90	75
3	4-*i*-PrC_6H_4	**5b**	**6b**	95	76
4	2,4,6-$(CH_3)_3C_6H_2$	**5c**	**6c**	94	50
5	2-Naphthyl	**5d**	**6d**	97 (91)[d]	79 (−74)[d]
6	4-$AcNHC_6H_4$	**5e**	**6e**	91	70
7	4-$OMeC_6H_4$	**5f**	**6f**	91	73
8	4-BrC_6H_4	**5g**	**6g**	84	75
9	4-ClC_6H_4	**5h**	**6h**	99 (99)[d]	79 (−71)[d]
10[e]	4-FC_6H_4	**5i**	**6i**	96 (92)[d]	80 (−74)[d]
11	4-$NO_2C_6H_4$	**5j**	**6j**	99	62
12	*t*-Bu	**5k**	**6k**	90	50
13	(*Z*)-*t*-Bu	**5l**	**6k**	92	3
14	*i*-Pr	**5m**	**6m**	88	72
15	Me	**5n**	**6n**	94	77
16[f]	EtO_2C	**5o**	**6o**	25	0

[a] Unless indicated otherwise, reactions were performed on a 0.5-mmol scale and 1.5 equiv of thiol.
[b] Isolated yield.
[c] Determined using chiral HPLC.
[d] In parentheses, reaction catalyzed by 10 mol % of quinidine.
[e] Performed on a 2 mmol scale.
[f] Performed at rt.

Table 3
The effect of ester group in 4-oxo-4-phenylbut-2-enoates on reaction with 4-*tert*-butylbenzyl thiol[a]



Entry	R^3	Alkene	Product	Yield,[b] %	ee,[c] %
1	Et	**3**	**4b**	78	80
2	*n*-C_6H_{13}	**7a**	**8a**	83	79
3	*n*-$C_{10}H_{21}$	**7b**	**8b**	88	80
4	*i*-Pr	**7c**	**8c**	94	75
5	*i*-Bu	**7d**	**8d**	91	77
6	4-$NO_2C_6H_4CH_2$	**7e**	**8e**	84	60

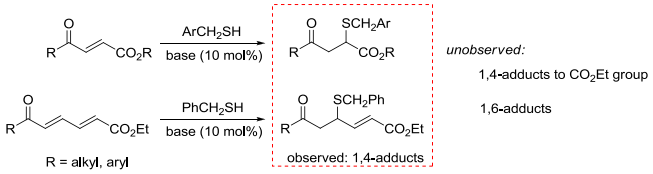
[a] Reactions were performed on a 0.5-mmol scale and 1.5 equiv of thiol.
[b] Isolated yield.
[c] Determined using chiral HPLC.

which gave slightly better outcome with 10 mol % **C1**. The selectivity in this reaction was unchanged in an upscale procedure (1.5 g of **3**). The 4-*tert*-butylbenzyl thiol was chosen to study the effect of Michael acceptor structure on enantioselectivity (Table 2).

Reactions of various 4-aryl-4-oxo-butenoates **3**, **5a**–**o** afforded thia-Michael adducts with good to excellent yields and ees ranging from 50% for bulky mesityl substituent (Table 2, entry 4) up to 80% for other butenoates. The influence of steric factor was also noted for 4-alkyl-4-oxo-butenenoates. There, a gradual increase of stereoselection was noted along with lowering of the steric demand of the alkyl substituent. However, the configuration of the unsaturated bond of the Michael acceptor turned out to be crucial for enantioselection. Alkene of *Z* configuration **5l** reacted with 4-*tert*-butylbenzylmercaptan giving nearly racemic product, while the application of *E*-isomer **5k** led to a corresponding adduct with 50% ee. Also a complete lack of stereoselection was noted when a α-ketoester moiety was incorporated to the substrate instead of simple ketone (Table 2, entry 16). On the other hand, replacing the alkyl in the ester group had little impact on stereoselection (Table 3), although decreased stereoselectivity was noted for the benzyl ester. Like in the initial screening, application of quinidine (Table 2, entries 1, 5, 9, and 10) instead of quinine led to adducts with similar ees and of opposite absolute configuration.

Several products obtained in the addition are crystalline and their enantiomeric composition can be further enriched. Single recrystallization of adducts **6d** and **6i** from ethanol resulted in ees of 98 (**6d**) and 99% (**6i**). No measurable *Self-Disproportionation of Enantiomers* (SDE)[19] at the chromatographic separation stage influenced the observed ees.

A more profound derivation in the structure of the Michael acceptor was made by extending the π-system (Scheme 3). In comparison to 4-oxo-butenoates, (2*E*,4*E*)-6-oxo-2,4-dienoates **9a**–**c**[20] exhibited lower reactivity. Competitive experiments in which equimolar amounts of ethyl 4-oxo-phenyl butenoate (**3**) and related diene **9a** were reacted with inexcess of benzyl thiol at 20 °C revealed that **3** was totally consumed within the first minutes of reaction leaving **9a** unreacted. Composition of the reaction mixture was unchanged after 24 h, suggesting that the formed adduct was stable under the tested conditions. Several dienes with flanking ketone and ester functionalities were reacted with benzyl mercaptan to give regioselectively only one product (Scheme 3).

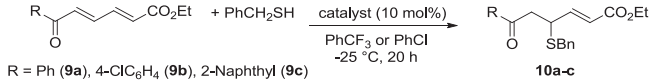


Scheme 3.

Application of the conditions previously developed for 4-oxo-butenoates resulted in heterogeneous mixtures due to limited solubility of **9a** in $PhCF_3$. Therefore, various solvents were tested and chlorobenzene turned out to be superior to both chloroalkanes and comparable to $PhCF_3$. As a result, the adduct was obtained with moderate ee. Slightly better stereoselection was achieved when $(DHQ)_2AQN$ was applied (Table 4, entry 4).

A reaction performed on a 2-mmol scale gave a crystalline product with nearly the same enantioselectivity (45%ee). Surprisingly, a single recrystallization led to a solid product with only 35% ee, whilst the filtrate turned out to be enantiomerically enriched giving a waxy solid with 72%ee. Application of quinidine afforded a different enantiomer with comparable ee and excellent yield. Also, the outcome of the reaction was similar for other dienes, such as naphthyl and chlorophenyl (Table 4).

Table 4
Reaction of dienes and benzyl thiol catalyzed by **C1**, **C2**, and **C10**[a]



R = Ph (**9a**), 4-ClC_6H_4 (**9b**), 2-Naphthyl (**9c**) **10a-c**

Entry	R	Catalyst, solvent	Product	Yield,[b] %	ee,[c] %
1	Ph	**C1**, $PhCF_3$	**10a**	75	47
2[d]	Ph	**C1**, PhCl	**10a**	82	45 (72)[e]
3	Ph	**C2**, PhCl	*ent*-**10a**	95	54
4	Ph	**C10**, PhCl	**10a**	82	56
5	4-ClC_6H_4	**C1**, $PhCF_3$	**10b**	87	51
6	4-ClC_6H_4	**C10**, PhCl	**10b**	82	57
7	2-Naphthyl	**C1**, $PhCF_3$	**10c**	69	44

[a] Unless indicated otherwise, reactions were performed on a 0.3-mmol scale of **9** and 1.5 equiv of benzyl mercaptan.
[b] Isolated yield.
[c] Determined using chiral HPLC.
[d] Reaction performed on a 2-mmol scale.
[e] Supernatant after single crystallization from EtOH.

In contrast to 4-oxo-butenoates having virtually two reactive sites, dienes **9** offer multiple possible routes of addition[21] (Scheme 3). However, in all the examined reactions the only products formed resulted from β-addition with respect to ketone group.

The structures of the products were unambiguously proved using ^1H,^{13}C HSQC and HMBC NMR experiments. Though, in case of adducts of 4-oxo-butenoates such experiments turned out to bring no clear answer. Therefore, adduct **4b** was transformed to a cyclic derivative. The ketone was first reduced by $NaBH_4$ and spontaneous intramolecular transesterification gave nearly equimolar ratio of diastereomeric lactones **11** and **12**. For the rigid compound **12**, the connectivity was unambiguously assigned using NOESY and HMBC experiments. Thus, it was proven that 1,4-addition of the sulfur nucleophile with respect to carbonyl group must have occurred (Fig. 2).

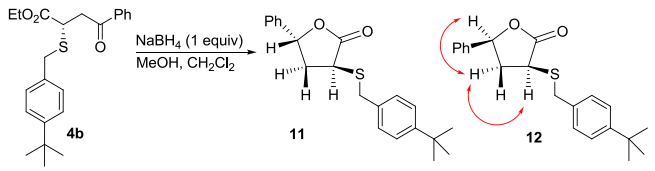


Fig. 2. Synthesis of lactones and crucial NOESY interactions.

Finally both the regiochemistry and absolute configuration of the adducts of *tert*-butylbenzyl thiol to 4-oxo-butenoates was assigned by X-ray crystallography (Fig. 3) with appropriate value of Flack parameter (−0.06). Thus, for the quinine-catalyzed reaction *S* configuration of the formed adducts was established. Tentatively the same stereochemical course of the reaction may be expected in the addition to extended π-systems.

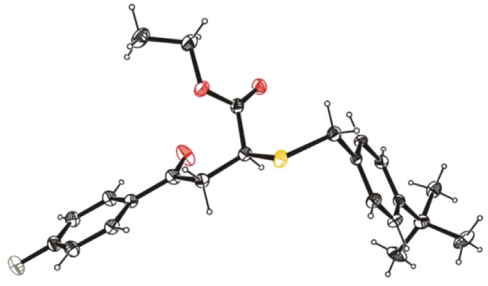


Fig. 3. ORTEP plot of (*S*)-**6i**, obtained in the quinine-catalyzed reaction. For clarity disorder is not shown, and displacement ellipsoids are drawn at the 10% probability level.[22]

The regiochemical outcome was unaltered under different activating conditions. Bifunctional quinine catalyst can form hydrogen bond from its hydroxyl to the ketone group of the substrate, which may lower the LUMO energy.[18] In addition, basic quinuclidine nitrogen can activate a thiol group. This activation mode is the only accessible for DABCO. When a system composed of a primary amine and an acid is used, it may activate 4-oxo-butenoates via formation of an iminium salt, thereby increasing the reactivity of the resulting α,β-unsaturated system and directing the nucleophile to the β-position.[15] Nevertheless, each approach afforded the same 1,4-adducts indicating that all activation modes converge to the same end product. Considering the factors, which might be responsible for the regioselectivity in the studied additions, it may be assumed that increased electron density arising after nucleophilic addition is better stabilized by the ketone group in comparison to the ester moiety. Calculations at the DFT level of theory for simplified anion structures indicate marked energy differences in favor of additions directed by the ketone moiety (Section S2, Supplementary data).

However, for the extended π-systems of the dienes the observed 1,4-addition relative to the ketone group is better explained considering the electronic character of the double bonds. There, electrostatic parameters, such as ChelpG charges indicate the most electron-poor site (Fig. 4). Even though such approach relies only on the acceptor structure giving no insight into the possible reaction mechanism, the carbon of the most positive ChelpG charge corresponds to the observed addition site.

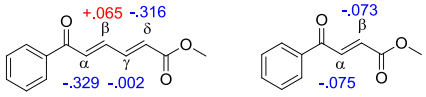


Fig. 4. Calculated electrostatic charges (ChelpG, DFT/B3LYP/CC-pVDZ) for Michael acceptors.

3. Conclusions

The unprecedented addition of mercaptans to 4-oxo-butenoates and (2*E*,4*E*)-6-oxo-2,4-dienoates occurs with complete regioselection in a 1,4-manner with respect to the ketone group. DFT calculations of the Michael acceptors may indicate the reactive sites in such divergently activated electron poor double bonds. Regioselection in the tested reaction was controlled by the electronic structure of the Michael acceptor and remained unchanged regardless of the method of activation.

Stereoselectivity was secured by the catalyst. Among the tested chiral bifunctional catalysts, easily available quinine afforded Michael adducts with good to excellent yields and ees of up to 80%. Further recrystallization of some enantiomerically enriched products led to ees reaching 99%. The use of quinidine led to another enantiomer, and thus presented protocol offers the access to both antipodes of sulfides. The reaction is easily scalable and can be performed with exceptionally low catalyst loading (0.2 mol %) without incurring substantial loss of enantioselectivity.

4. Experimental section

4.1. General

Catalytic reactions were performed in reaction tubes with the gas inlet. Tubes were heated to 550 °C for 3–5 min under high vacuum, cooled down, and then flushed with argon.

^1H and ^{13}C NMR (300, 600 MHz and 75.5, 151 MHz, respectively) spectra were recorded in $CDCl_3$ on Bruker Avance DRX 300 and NMR Bruker Avance II 600 MHz. ^1H NMR chemical shifts are

reported in parts per million (δ) relative to tetramethylsilane (TMS) and $CDCl_3$ (δ 7.26 ppm). ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) and $CDCl_3$ (δ 77.16 ppm). IR spectra were recorded on System 2000 FT-IR Perkin–Elmer spectrometer. ESI HRMS spectra were recorded on Waters LCT Premier XE apparatus. HPLC analysis was performed on Thermo Scientific System using Chiralpak AD-H, Chiralcel OD-H columns (4.6 mm×25 cm) without guard columns. Each HPLC analysis has been controlled by comparison with the pure sample and the racemate. Optical rotations were measured on anautomatic polarimeter at λ=589 nm (*c* g/100 mL).

Flash chromatography was performed using silica gel 35–70 μm.

Commercially available starting materials were used without further purification. Chlorobenzene, xylenes, and α,α,α-triflurotoluene were used as received. 1,2-Dichloroethane was distilled over P_2O_5 under argon. Dichloromethane and dimethoxyethane were distilled with CaH_2 under argon and further stored over 3 Å molecular sieves. Toluene was dried over sodium wire.

4.2. General procedure for reactions of 4-oxo-phenyl-butenoate with thiols (GP1, Fig. 1)

Chiral base (10 mol %, 0.05 mmol) was added to a solution of benzyl mercaptan (93 mg, 0.75 mmol, 1.5 equiv) in $PhCF_3$ (2 mL) at 20 °C and the resulted mixture was stirred for 15 min. Then 4-oxo-phenyl-butenoate (**3**) (102 mg, 0.5 mmol, 1.0 equiv) in $PhCF_3$ (0.5 mL) was added dropwise with a syringe. After 20 h at 20 °C reaction was quenched by AcOEt or chloroform/AcOEt mixture (1:1, v/v) until become homogenous and filtered through a plug of silica gel (5–10 g). Elution with a total volume of 100–150 mL of AcOEt or chloroform/AcOEt mixture (1:1, v/v) afforded crude product, which was further purified using column chromatography (silicagel, hexanes/AcOEt, 10:1, v/v). Enantiomeric excess was determined using HPLC on chiral stationary phases (OD-H, AD-H).

4.3. General procedure for reactions of 4-oxo-phenyl-butenoate with thiols catalyzed by thioureas C11–C18 (GP2, Fig. 1)

Chiral thiourea catalyst (10 mol %, 0.05 mmol) and 4-oxo-phenyl-butenoate (102 mg, 0.5 mmol, 1.0 equiv) were treated with $PhCF_3$ (2.0 mL) and resulted mixture was stirred at 20 °C for 20 min. Then, a solution of thiol (0.75 mmol, 1.5 equiv) in $PhCF_3$ (0.5 mL) was added dropwise. Reaction was performed at 20 °C for 20 h and then filtered through a plug of silica, as described above in **GP1**.

4.4. General procedure for reactions of 4-oxo-butenoates and (2*E*,4*E*)-6-oxo-2,4-dienoates with thiols at lower temperatures (GP 3, Tables 1–4)

Quinine, quinidine or $(DHQ)_2AQN$ (10 mol %) was treated with a solution of thiol (1.5 equiv) in $PhCF_3$ (1.5 mL/0.5 mmol of acceptor) and the resulted mixture was stirred at 20 °C for 15–20 min, then cooled to −25 °C, and stirred for next 10 min. Then, a solution of Michael acceptor (1.0 equiv) in $PhCF_3$ (1.0 mL/0.5 mmol of acceptor) was added slowly (0.75–1 h) via a syringe under positive argon pressure. When addition was finished, reaction tube was flushed with argon, sealed, and stirred for additional 20–21 h at −25 °C. Cold reaction mixtures were directly loaded on a plug of silica gel analogously to procedure **GP1**. In cases when other solvent than $PhCF_3$ was used, this procedure was applied without further modifications.

*4.4.1. Ethyl (S)-2-(benzylsulfanyl)-4-oxo-4-phenylbutanoate (**4a**).* Colorless oil; $[\alpha]_D^{20}$ −117 (*c* 0.73, $CHCl_3$), 71%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.86–7.91 (m, 2H), 7.52–7.59 (m, 1H), 7.22–7.47 (m, 7H), 4.18–4.28 (m, 2H), 3.98 (d, *J*=13.4 Hz, 1H), 3.89 (d, *J*=13.4 Hz, 1H), 3.80 (dd, *J*=10.7, 3.7 Hz, 1H), 3.67 (dd, *J*=17.5, 10.7 Hz, 1H), 3.16 (dd, *J*=17.5, 3.7 Hz, 1H), 1.31 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 196.9, 172.1, 137.6, 136.2, 133.5, 129.2, 128.72, 128.70, 128.1, 127.4, 61.4, 40.9, 40.7, 36.3, 14.3. IR (neat): ν=3062, 3029, 2981, 1731, 1686, 1450, 1213, 1158, 758, 703, 690 cm^{-1}. HPLC (Chiralcel OD-H, hexane/*i*-PrOH=97:3, flow rate: 1.0 mL/min, λ=220 nm): t_R=18.80 (major), 21.03 (minor). HRMS (ESI): $[C_{19}H_{20}O_3S+H]^+$ requires: 329.1206; found: 329.1201.

*4.4.2. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-oxo-4-phenylbutanoate (**4b**).* Colorless oil; $[\alpha]_D^{20}$ −111 (*c* 1.1, $CHCl_3$), 80% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.88 (dd, *J*=7.8, 1.4 Hz, 2H), 7.56 (tt, *J*=7.2, 1.4 Hz, 1H), 7.43 (dd, *J*=7.8, 7.2 Hz, 2H), 7.35 (d, *J*=8.6 Hz, 2H), 7.31 (d, *J*=8.6 Hz, 2H), 4.22 (q, *J*=7.2 Hz, 2H), 3.95 (d, *J*=13.4 Hz, 1H), 3.86 (d, *J*=13.4 Hz, 1H), 3.81 (dd, *J*=10.8, 3.6 Hz, 1H), 3.67 (dd, *J*=17.6, 10.8 Hz, 1H), 3.15 (dd, *J*=17.6, 3.6 Hz, 1H), 1.31 (t, *J*=7.2 Hz, 3H), 1.31 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.9, 172.1, 150.3, 136.1, 134.6, 133.5, 128.8, 128.7, 128.1, 125.6, 61.4, 41.0, 40.7, 35.8, 34.6, 31.4, 14.3. IR (neat): ν=3059, 3027, 2963, 1732, 1687, 1449, 1364, 1328, 1261, 1213, 1158, 757, 690 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=97:3, flow rate: 0.7 mL/min, λ=220 nm): t_R=18.57 (major), 21.85 (minor). HRMS (ESI): $[C_{23}H_{28}O_3S+H]^+$ requires: 385.1832; found: 385.1839. For reaction catalyzed by quinidine (*R*)-isomer was obtained, $[\alpha]_D^{20}$ +103 (*c* 1.3, $CHCl_3$), 76%ee.

*4.4.3. Ethyl (S)-4-oxo-2-(phenethylsulfanyl)-4-phenylbutanoate (**4c**).* Colorless oil; $[\alpha]_D^{20}$ −55 (*c* 0.5, $CHCl_3$), 66%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.96 (dd, *J*=7.8, 1.7 Hz, 2H), 7.58 (tt, *J*=7.4, 1.7 Hz, 1H), 7.47 (dd, *J*=7.8, 7.4 Hz, 2H), 7.28–7.34 (m, 2H), 7.19–7.26 (m, 3H), 4.24 (q, *J*=7.1 Hz, 2H), 3.90 (dd, *J*=10.5, 4.1 Hz, 1H), 3.71 (dd, *J*=17.8, 10.5 Hz, 1H), 3.28 (dd, *J*=17.8, 4.1 Hz, 1H), 2.86–3.09 (m, 4H), 1.30 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 197.0, 172.2, 140.2, 136.2, 133.6, 128.8, 128.7, 128.6, 128.2, 126.6, 61.5, 41.11, 41.10, 36.0, 33.3, 14.3. IR (neat): ν=3063, 3028, 2981, 2933, 1731, 1686, 1449, 1328, 1213, 1157, 757, 690 cm^{-1}. HPLC (Chiralcel OD-H, hexane/*i*-PrOH=99:1, flow rate: 1.0 mL/min, λ=220 nm): t_R=26.99 (major), 32.82 (minor). HRMS (ESI): $[C_{20}H_{22}O_3S+Na]^+$ requires: 365.1182; found: 365.1192.

*4.4.4. Ethyl (S)-2-(4-chlorobenzylsulfanyl)-4-oxo-4-phenylbutanoate (**4d**).* Colorless oil; $[\alpha]_D^{20}$ −78 (*c* 0.5, $CHCl_3$), 55%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.88 (dd, *J*=8.4, 1.5 Hz, 2H), 7.56 (tt, *J*=7.4, 1.5 Hz, 1H), 7.44 (dd, *J*=8.4, 7.4 Hz, 2H), 7.32 (d, *J*=8.8 Hz, 2H), 7.28 (d, *J*=8.8 Hz, 2H), 4.22 (q, *J*=7.1 Hz, 2H), 3.94 (d, *J*=13.5 Hz, 1H), 3.83 (d, *J*=13.5 Hz, 1H), 3.75 (dd, *J*=10.6, 3.6 Hz, 1H), 3.65 (dd, *J*=17.3, 10.6 Hz, 1H), 3.16 (dd, *J*=17.3, 3.6 Hz, 1H), 1.30 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.7, 171.9, 136.1, 136.0, 133.6, 133.2, 130.5, 128.8, 128.7, 128.1, 61.5, 40.7, 40.5, 35.5, 14.3. IR (neat): ν=3063, 2981, 1731, 1686, 1491, 1449, 1329, 1262, 1214, 1158, 1093, 1016, 757, 690 cm^{-1}. HPLC (Chiralcel OD-H, hexane/*i*-PrOH=97:3, flow rate: 0.7 mL/min, λ=220 nm): t_R=18.12 (major), 20.67 (minor). HRMS (ESI): $[C_{19}H_{19}Cl^{35}O_3S+Na]^+$ requires: 385.0636; found: 385.0637.

*4.4.5. Ethyl (S)-2-(4-methoxybenzylsulfanyl)-4-oxo-4-phenylbutanoate (**4e**).* Colorless oil; $[\alpha]_D^{20}$ −92 (*c* 0.5, $CHCl_3$), 69% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.88 (d, *J*=7.7 Hz, 2H), 7.54 (t, *J*=7.2 Hz, 1H), 7.42 (dd, *J*=7.7, 7.2 Hz, 2H), 7.30 (d, *J*=8.7 Hz, 2H), 6.84 (d, *J*=8.7 Hz, 2H), 4.17–4.29 (m, 2H), 3.93 (d, *J*=13.3 Hz, 1H), 3.84 (d, *J*=13.3 Hz, 1H), 3.77 (dd, *J*=10.7, 3.6 Hz, 1H), 3.77 (s, 3H), 3.66 (dd, *J*=17.3, 10.7 Hz, 1H), 3.15 (dd, *J*=17.3, 3.6 Hz, 1H), 1.31 (t, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.8, 172.0, 158.9, 136.0, 133.4, 130.2, 129.3, 128.6, 128.0, 114.0, 61.3, 55.2, 40.8, 40.5, 35.6, 14.2. IR (neat): ν=3062, 3032, 2980, 1730, 1686, 1610, 1512, 1249, 1213, 1175,

1033, 758, 690 cm^{-1}. HPLC (Chiralcel OD-H, hexane/*i*-PrOH=9:1, flow rate: 1.0 mL/min, λ=220 nm): t_R=12.33 (major), 17.63 (minor). HRMS (ESI): $[C_{20}H_{22}O_4S+H]^+$ requires: 359.1312; found: 359.1309.

*4.4.6. Ethyl (S)-2-(cyclohexylsulfanyl)-4-oxo-4-phenylbutanoate (**4f**).* Colorless oil; $[\alpha]_D^{20}$ −64 (*c* 0.7, $CHCl_3$), 65%ee; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.93–7.97 (m, 2H), 7.57 (tt, *J*=7.4, 1.7 Hz, 1H), 7.42–7.48 (m, 2H), 4.12–4.29 (m, 2H), 3.93 (dd, *J*=10.4, 4.4 Hz, 1H), 3.70 (dd, *J*=17.9, 10.4 Hz, 1H), 3.27 (dd, *J*=17.9, 4.4 Hz, 1H), 2.91–3.01 (m, 1H), 2.07–2.16 (m, 1H), 1.90–2.01 (m, 1H), 1.70–1.81 (m, 2H), 1.56–1.65 (m, 1H), 1.24–1.42 (m, 5H), 1.28 (t, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 197.2, 172.8, 136.3, 133.6, 128.8, 128.2, 61.3, 44.5, 41.6, 39.9, 33.8, 33.6, 26.2, 26.0, 25.8, 14.2. IR (neat): ν=3062, 2931, 2853, 1733, 1686, 1449, 1328, 1259, 1214, 1158, 1029, 1001, 989, 757, 690 cm^{-1}. HPLC (Chiralcel OD-H, hexane/*i*-PrOH=98:2, flow rate: 1.0 mL/min, λ=220 nm): t_R=8.78 (major), 9.94 (minor). HRMS (ESI): $[C_{18}H_{24}O_3S+Na]^+$ requires: 343.1338; found: 343.1347.

*4.4.7. Ethyl (S)-2-(dodecylsulfanyl)-4-oxo-4-phenylbutanoate (**4g**).* Colorless oil; $[\alpha]_D^{20}$ −39 (*c* 0.5, $CHCl_3$), 59%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.94–7.98 (m, 2H), 7.58 (tt, *J*=7.5, 1.5 Hz, 1H), 7.43–7.50 (m, 2H), 4.17–4.27 (m, 2H), 3.85 (dd, *J*=10.4, 3.9 Hz, 1H), 3.72 (dd, *J*=17.6, 10.4 Hz, 1H), 3.29 (dd, *J*=17.6, 3.9 Hz, 1H), 2.63–2.81 (m, 2H), 1.54–1.71 (m, 2H), 1.22–1.42 (m, 18H), 1.29 (t, *J*=7.1 Hz, 3H), 0.88 (t, *J*=6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 197.2, 172.4, 136.3, 133.6, 128.8, 128.3, 61.4, 41.25, 41.17, 32.1, 32.0, 29.79, 29.76, 29.73, 29.65, 29.5, 29.4, 29.3, 29.0, 22.8, 14.3, 14.3. IR (neat): ν=3063, 2926, 2854, 1733, 1688, 1449, 1212, 1157, 756, 690 cm^{-1}. HPLC (Chiralcel OD-H, hexane/*i*-PrOH=99:1, flow rate: 1.0 mL/min, λ=220 nm): t_R=9.11 (major), 10.21 (minor). HRMS (ESI): $[C_{24}H_{38}O_3S+H]^+$ requires: 407.2614; found: 407.2619.

*4.4.8. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-(4-tert-butylphenyl)-4-oxobutanoate (**6a**).* Colorless oil; $[\alpha]_D^{20}$ −56 (*c* 3.2, $CHCl_3$), 75%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.84 (d, *J*=8.7 Hz, 2H), 7.46 (d, *J*=8.7 Hz, 2H), 7.36 (d, *J*=8.6 Hz, 2H), 7.33 (d, *J*=8.6 Hz, 2H), 4.23 (q, *J*=7.1 Hz, 2H), 3.97 (d, *J*=13.4 Hz, 1H), 3.88 (d, *J*=13.4 Hz, 1H), 3.83 (dd, *J*=10.9, 3.9 Hz, 1H), 3.66 (dd, *J*=17.7, 10.9 Hz, 1H), 3.15 (dd, *J*=17.7, 3.9 Hz, 1H), 1.34 (s, 9H), 1.32 (s, 9H), 1.31 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.5, 172.1, 157.2, 150.2, 134.6, 133.6, 128.8, 128.1, 125.60, 125.58, 61.3, 40.9, 35.9, 35.2, 34.6, 31.4, 31.1 (2C overlapped), 14.3. IR (neat): ν=2964, 1732, 1683, 1607, 1406, 1365, 1268, 1217, 1157, 1108, 1025, 991, 830 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=97:3, flow rate: 1.0 mL/min, λ=220 nm): t_R=17.94 (major), 24.41 (minor). HRMS (ESI): $[C_{27}H_{36}O_3S+H]^+$ requires: 441.2458; found: 441.2451.

*4.4.9. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-(4-isopropylphenyl)-4-oxobutanoate (**6b**).* Colorless oil; $[\alpha]_D^{20}$ −84 (*c* 1.7, $CHCl_3$), 76%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.83 (d, *J*=8.3 Hz, 2H), 7.37 (d, *J*=8.7 Hz, 2H), 7.33 (d, *J*=8.7 Hz, 2H), 7.29 (d, *J*=8.3 Hz, 2H), 4.23 (q, *J*=7.1 Hz, 2H), 3.97 (d, *J*=13.5 Hz, 1H), 3.88 (d, *J*=13.5 Hz, 1H), 3.83 (dd, *J*=10.9, 3.8 Hz, 1H), 3.67 (dd, *J*=17.7, 10.9 Hz, 1H), 3.15 (dd, *J*=17.7, 3.8 Hz, 1H), 2.96 (sept, *J*=6.9 Hz, 1H), 1.33 (s, 9H), 1.32 (t, *J*=7.1 Hz, 3H), 1.27 (d, *J*=6.9 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.5, 172.1, 155.0, 150.2, 134.6, 134.0, 128.8, 128.4, 126.7, 125.6, 61.3, 40.8 (2C overlapped), 35.8, 34.6, 34.3, 31.4, 23.7 (2C overlapped), 14.3. IR (neat): 2963, 1732, 1684, 1607, 1216, 828 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=97:3, flow rate: 1.0 mL/min, λ=220 nm): t_R=13.83 (major), 18.78 (minor). HRMS (ESI): $[C_{26}H_{34}O_3S+H]^+$ requires: 427.2301; found: 427.2298.

*4.4.10. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-mesityl-4-oxobutanoate (**6c**).* Colorless oil; $[\alpha]_D^{20}$ −33 (*c* 0.5, $CHCl_3$), 50%ee. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.35 (d, *J*=8.2 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 6.82 (s, 2H), 4.22–4.29 (m, 2H), 3.93 (d, *J*=13.2 Hz, 1H), 3.86 (d, *J*=13.2 Hz, 1H), 3.76 (dd, *J*=10.7, 3.8 Hz, 1H), 3.41 (dd, *J*=19.0, 10.7 Hz, 1H), 2.92 (dd, *J*=19.0, 3.8 Hz, 1H), 2.27 (s, 3H), 2.16 (s, 6H), 1.34 (t, *J*=7.2 Hz, 3H), 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 207.1, 172.0, 150.3, 138.7, 138.2, 134.2, 132.9, 128.8, 128.5, 125.6, 61.5, 46.9, 40.2, 36.0, 34.6, 31.4, 21.1, 19.0, 14.3. IR (neat): ν=2963, 1732, 1701, 1153, 851 cm^{-1}; HPLC (Chiralpak AD-H, hexane/*i*-PrOH=97:3, flow rate: 1.0 mL/min, λ=220 nm): t_R=7.32 (major), 8.70 (minor). HRMS (ESI): $[C_{26}H_{34}O_3S+H]^+$ requires: 427.2301; found: 427.2322.

*4.4.11. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-(naphtalen-2-yl)-4-oxobutanoate (**6d**).* Amorphous solid; 79%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.40 (s, 1H), 7.90–7.97 (m, 2H), 7.82–7.87 (m, 2H), 7.50–7.61 (m, 2H), 7.35–7.41 (m, 4H), 4.27 (q, *J*=7.1 Hz, 2H), 4.03 (d, *J*=13.3 Hz, 1H), 3.93 (d, *J*=13.3 Hz, 1H), 3.78–3.93 (m, 2H), 3.24–3.38 (m, 1H), 1.34 (t, *J*=7.1 Hz, 3H), 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.7, 172.1, 150.2, 135.7, 134.5, 133.4, 132.4, 129.9, 129.6, 128.8, 128.6, 128.5, 127.8, 126.8, 125.6, 123.6, 61.4, 40.9, 40.8, 35.8, 34.5, 31.4, 14.3. IR (neat): 2959, 1728, 1677, 1175, 827 cm^{-1}. After recrystallization from ethanol (96%) of 211 mg of solid, sample (61 mg) of colorless crystals was obtained, mp=81.6–82.4 °C; $[\alpha]_D^{20}$ −97 (*c* 0.5, $CHCl_3$), 98%ee. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=95:5, flow rate: 1.0 mL/min, λ=220 nm): t_R=18.32 (major), 21.13 (minor). HRMS (ESI): $[C_{27}H_{30}O_3S+Na]^+$ requires: 457.1808; found: 457.1809. In a reaction catalyzed by quinidine, (*R*)-isomer was obtained $[\alpha]_D^{20}$ +73 (*c* 0.6, $CHCl_3$), 74%ee.

*4.4.12. Ethyl (S)-4-(4-acetamidophenyl)-2-(4-tert-butylbenzylsulfanyl)-4-oxobutanoate (**6e**).* Colorless foam; $[\alpha]_D^{20}$ −68 (*c* 0.5, $CHCl_3$), 70%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.1 (br, 1H), 7.78 (d, *J*=8.8 Hz, 2H), 7.56 (d, *J*=8.8 Hz, 2H), 7.34 (d, *J*=8.6 Hz, 2H), 7.29 (d, *J*=8.6 Hz, 2H), 4.16–4.26 (m, 2H), 3.94 (d, *J*=13.5 Hz, 1H), 3.85 (d, *J*=13.5 Hz, 1H), 3.78 (dd, *J*=10.9, 3.8 Hz, 1H), 3.59 (dd, *J*=17.8, 10.9 Hz, 1H), 3.12 (dd, *J*=17.8, 3.8 Hz, 1H), 2.16 (s, 3H), 1.30 (s, 9H), 1.30 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 195.7, 172.6, 169.0, 150.4, 143.0, 134.4, 131.5, 129.5, 128.8, 125.6, 118.9, 61.5, 40.8, 40.7, 35.9, 34.6, 31.4, 24.8, 14.3. IR (neat): ν=3347, 2963, 1730, 1705, 1678, 1595, 1528, 1409, 1369, 1322, 1262, 1217, 1176, 1023, 991, 835 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=90:10, flow rate: 1.0 mL/min, λ=220 nm): t_R=22.16 (major), 26.69 (minor). HRMS (ESI): $[C_{25}H_{31}NO_4S+Na]^+$ requires: 464.1866; found: 464.1866.

*4.4.13. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-(4-methoxyphenyl)-4-oxobutanoate (**6f**).* Colorless oil; $[\alpha]_D^{20}$ −52 (*c* 0.7, $CHCl_3$), 73%ee. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.86 (d, *J*=8.8 Hz, 2H), 7.35 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 6.90 (d, *J*=8.8 Hz, 2H), 4.18–4.26 (m, 2H), 3.94 (d, *J*=13.4 Hz, 1H), 3.86 (d, *J*=13.4 Hz, 1H), 3.84 (s, 3H), 3.80 (dd, *J*=10.9, 4.0 Hz, 1H), 3.62 (dd, *J*=17.7, 10.9 Hz, 1H), 3.12 (dd, *J*=17.7, 4.0 Hz, 1H), 1.31 (s, 9H), 1.30 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 195.4, 172.2, 163.8, 150.3, 134.6, 130.4, 129.3, 128.8, 125.6, 113.8, 61.3, 55.5, 40.9, 40.6, 35.8, 34.6, 31.4, 14.3. IR (neat): ν=3056, 2954, 2908, 2870, 1732, 1679, 1600, 1576, 1512, 1464, 1420, 1357, 1261, 1216, 1166, 1031, 989, 911, 832, 733, 559 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=95:5, flow rate: 1.0 mL/min, λ=220 nm): t_R=23.11 (major), 29.03 (minor). HRMS (ESI): $[C_{24}H_{30}O_4S+Na]^+$ requires: 437.1757; found: 437.1765.

*4.4.14. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-(4-bromophenyl)-4-oxobutanoate (**6g**).* Waxy yellowish solid; $[\alpha]_D^{20}$ −75 (*c* 0.5, $CHCl_3$), 75%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.73 (d, *J*=8.8 Hz, 2H), 7.56 (d, *J*=8.8 Hz, 2H), 7.35 (d, *J*=8.6 Hz, 2H), 7.31 (d, *J*=8.6 Hz, 2H), 4.18–4.26 (m, 2H), 3.95 (d, *J*=13.5 Hz, 1H), 3.86 (d, *J*=13.5 Hz, 1H), 3.80 (dd, *J*=10.7, 3.8 Hz, 1H), 3.62 (dd, *J*=17.7, 10.7 Hz, 1H), 3.10 (dd, *J*=17.7, 3.8 Hz, 1H), 1.31 (s, 9H), 1.31 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 195.9, 172.0, 150.3, 134.8, 134.5, 132.0, 129.6, 128.8, 128.7, 125.6, 61.5, 40.9, 40.6, 35.9, 34.6, 31.4, 14.3. IR (neat): ν=3057,

2964, 2907, 1732, 1681, 1585, 1398, 1357, 1260, 1211, 1165, 1070, 1010, 987, 818, 555 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=95:5, flow rate: 1.0 mL/min, λ=220 nm): t_R=14.47 (major), 19.13 (minor). HRMS (ESI): $[C_{23}H_{27}Br^{79}O_3S+Na]^+$ requires: 485.0756; found: 485.0790; $[C_{23}H_{27}Br^{81}O_3S+Na]^+$ requires: 487.0736; found: 485.0747.

*4.4.15. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-(4-chlorophenyl)-4-oxobutanoate (**6h**).* Waxy solid; $[\alpha]_D^{20}$ −92 (*c* 0.5, $CHCl_3$), 79%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.81 (d, *J*=8.7 Hz, 2H), 7.39 (d, *J*=8.7 Hz, 2H), 7.36 (d, *J*=8.7 Hz, 2H), 7.32 (d, *J*=8.7 Hz, 2H), 4.18–4.28 (m, 2H), 3.96 (d, *J*=13.5 Hz, 1H), 3.87 (d, *J*=13.5 Hz, 1H), 3.81 (dd, *J*=10.8, 3.8 Hz, 1H), 3.64 (dd, *J*=17.7, 10.8 Hz, 1H), 3.11 (dd, *J*=17.7, 3.8 Hz, 1H), 1.32 (s, 9H), 1.31 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ: 195.8, 172.0, 150.4, 140.0, 134.49, 134.47, 129.5, 129.0, 128.8, 125.6, 61.5, 40.9, 40.6, 35.9, 34.6, 31.4, 14.3. IR (neat): ν=2963, 1731, 1688, 1590, 1401, 1261, 1212, 1167, 1092, 989, 822 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=97:3, flow rate: 1.0 mL/min, λ=220 nm): t_R=22.55 (major), 28.59 (minor). HRMS (ESI): $[C_{23}H_{27}Cl^{35}O_3S+H]^+$ requires: 419.1442; found: 419.1457; $[C_{23}H_{27}Cl^{37}O_3S+H]^+$ requires: 421.1413; found: 421.1400. In a reaction catalyzed by quinidine (*R*)-isomer was obtained, $[\alpha]_D^{20}$ +87 (*c* 0.5, $CHCl_3$), 71%ee.

*4.4.16. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-(4-fluorophenyl)-4-oxobutanoate (**6i**).* Reaction was performed in a 2 mmol scale; colorless crystals, $[\alpha]_D^{20}$ −106 (*c* 0.5, $CHCl_3$), 80%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.90 (dd, *J*=8.8, 5.4 Hz, 2H), 7.35 (d, *J*=8.7 Hz, 2H), 7.32 (d, *J*=8.7 Hz, 2H), 7.10 (t, *J*=8.6 Hz, 2H), 4.19–4.27 (m, 2H), 3.95 (d, *J*=13.4 Hz, 1H), 3.87 (d, *J*=13.4 Hz, 1H), 3.80 (dd, *J*=10.9, 3.8 Hz, 1H), 3.64 (dd, *J*=17.7, 10.9 Hz, 1H), 3.11 (dd, *J*=17.7, 3.8 Hz, 1H), 1.32 (s, 9H), 1.32 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 195.3, 172.0, 165.9 (d, J_{CF}=255 Hz), 150.3, 134.5, 132.6, 130.8 (d, J_{CF}=9.5 Hz), 128.8, 125.6, 115.8 (d, J_{CF}=22 Hz), 61.4, 40.9, 40.7, 35.8, 34.6, 31.4, 14.3. IR (KBr): ν=3057, 2964, 2909, 1731, 1683, 1598, 1508, 1411, 1359, 1299, 1158, 1099, 1023, 992, 911, 836, 734, 557 cm^{-1}. After recrystallization from ethanol (96%) of 502 mg of solid, 208 mg of colorless crystals was obtained: mp=61–62 °C; $[\alpha]_D^{20}$ −136 (*c* 0.5, $CHCl_3$), 99%ee, HPLC (Chiralpak AD-H, hexane/*i*-PrOH=95:5, flow rate: 1.0 mL/min, λ=254 nm): t_R=12.35 (major), 14.19 (minor). HRMS (ESI): $[C_{23}H_{27}FO_3S+Na]^+$ requires: 425.1557; found: 425.1555. In a reaction catalyzed by quinidine, (*R*)-isomer was obtained, $[\alpha]_D^{20}$ +102 (*c* 0.6, $CHCl_3$), 74%ee.

*4.4.17. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-(4-nitrophenyl)-4-oxobutanoate (**6j**).* Waxy yellow solid; $[\alpha]_D^{20}$ −63 (*c* 3.5, $CHCl_3$), 62%ee. ^1H NMR ($CDCl_3$, 600 MHz): δ 8.28 (d, *J*=9.0 Hz, 2H), 8.02 (d, *J*=9.0 Hz, 2H), 7.35 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 4.19–4.26 (m, 2H), 3.95 (d, *J*=13.5 Hz, 1H), 3.87 (d, *J*=13.5 Hz, 1H), 3.81 (dd, *J*=10.6, 3.9 Hz, 1H), 3.68 (dd, *J*=18.0, 10.6 Hz, 1H), 3.16 (dd, *J*=18.0, 3.9 Hz, 1H), 1.32 (t, *J*=7.1 Hz, 3H), 1.30 (s, 9H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 195.6, 171.9, 150.6, 150.5, 140.5, 134.4, 129.2, 128.9, 125.7, 124.0, 61.7, 41.5, 40.5, 36.0, 34.6, 31.4, 14.3. IR (neat): ν=2964, 1728, 1695, 1603, 1526, 1345, 1211, 1172, 995, 852, 749 cm^{-1}. HPLC (Chiralcel OD-H, hexane/*i*-PrOH=95:5, flow rate: 1.0 mL/min, λ=220 nm): t_R=31.00 (minor), 42.42 (major). HRMS (ESI): $[C_{23}H_{27}NO_5S+Na]^+$ requires: 452.1502; found: 452.1491.

*4.4.18. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-5,5-dimethyl-4-oxohexanoate (**6k**).* Colorless oil; $[\alpha]_D^{20}$ −70 (*c* 0.8, $CHCl_3$), 50%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34 (d, *J*=8.5 Hz, 2H), 7.28 (d, *J*=8.5 Hz, 2H), 4.12–4.23 (m, 2H), 3.89 (d, *J*=13.5 Hz, 1H), 3.80 (d, *J*=13.5 Hz, 1H), 3.62 (dd, *J*=10.9, 4.0 Hz, 1H), 3.18 (dd, *J*=18.1, 10.9 Hz, 1H), 2.63 (dd, *J*=18.1, 4.0 Hz, 1H), 1.30 (s, 9H), 1.29 (t, *J*=7.1 Hz, 3H), 1.09 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 212.9, 172.0, 150.2, 134.6, 128.8, 125.6, 61.2, 43.8, 40.7, 39.3, 35.9, 34.6, 31.4, 26.4, 14.2. IR (neat): ν=2965, 1733, 1707 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=99:1, flow rate: 1.0 mL/min, λ=254 nm): t_R=7.48 (major), 11.98 (minor). HRMS (ESI): $[C_{21}H_{32}O_3S+H]^+$ requires: 365.2145; found: 365.2146.

*4.4.19. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-5-methyl-4-oxohexanoate (**6m**).* Colorless oil; $[\alpha]_D^{20}$ −121 (*c* 0.5, $CHCl_3$), 72%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34 (d, *J*=8.5 Hz, 2H), 7.27 (d, *J*=8.5 Hz, 2H), 4.12–4.23 (m, 2H), 3.89 (d, *J*=13.4 Hz, 1H), 3.81 (d, *J*=13.4 Hz, 1H), 3.63 (dd, *J*=10.7, 4.4 Hz, 1H), 3.13 (dd, *J*=18.0, 10.7 Hz, 1H), 2.63 (dd, *J*=18.0, 4.4 Hz, 1H), 2.53 (sept, *J*=6.9 Hz, 1H), 1.31 (s, 9H), 1.29 (t, *J*=7.1 Hz, 3H), 1.07 (d, *J*=6.9 Hz, 3H), 1.06 (d, *J*=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ: 211.4, 172.1, 150.3, 134.4, 128.8, 125.6, 61.3, 42.1, 40.7, 40.4, 35.9, 34.6, 31.4, 18.15, 18.06, 14.2. IR (neat): ν=2967, 1732, 1715, 1466, 1367, 1268, 1227, 1157, 758 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=97:3, flow rate: 0.7 mL/min, λ=220 nm): t_R=9.90 (major), 12.18 (minor). HRMS (ESI): $[C_{20}H_{30}O_3S+H]^+$ requires: 351.1988; found: 351.2000.

*4.4.20. Ethyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-oxopentanoate (**6n**).* Colorless oil; $[\alpha]_D^{20}$ −163 (*c* 2.1, $CHCl_3$), 77%ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34 (d, *J*=8.3 Hz, 2H), 7.27 (d, *J*=8.3 Hz, 2H), 4.18 (q, *J*=7.1 Hz, 2H), 3.89 (d, *J*=13.3 Hz, 1H), 3.80 (d, *J*=13.3 Hz, 1H), 3.60 (dd, *J*=10.5, 4.4 Hz, 1H), 3.11 (dd, *J*=17.9, 10.5 Hz, 1H), 2.64 (dd, *J*=17.9, 4.5 Hz, 1H), 2.10 (s, 3H), 1.32 (s, 9H), 1.30 (t, *J*=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 205.2, 172.0, 150.2, 134.2, 128.8, 125.5, 61.3, 45.1, 40.1, 35.7, 34.5, 31.4, 29.7, 14.2. IR (neat): 3055, 2963, 2908, 1725, 1515, 1400, 1364, 1321, 1264, 1232, 1161, 1042, 1021, 837, 560 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=97:3, flow rate: 0.7 mL/min, λ=220 nm): t_R=11.30 (major), 12.44 (minor). HRMS (ESI): $[C_{18}H_{26}O_3S+H]^+$ requires: 323.1675; found: 323.1696.

*4.4.21. Diethyl rac-2-(4-tert-butylbenzylsulfanyl)-4-oxopentadienoate (**6o**).* Colorless oil; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34 (d, *J*=8.5 Hz, 2H), 7.27 (d, *J*=8.5 Hz, 2H), 4.30 (q, *J*=7.2 Hz, 2H), 4.13–4.23 (m, 2H), 3.91 (d, *J*=13.2 Hz, 1H), 3.82 (d, *J*=13.2 Hz, 1H), 3.63 (dd, *J*=10.3, 4.2 Hz, 1H), 3.52 (dd, *J*=18.6, 10.3 Hz, 1H), 3.10 (dd, *J*=18.6, 4.2 Hz, 1H), 1.35 (t, *J*=7.2 Hz, 3H), 1.31 (s, 9H), 1.30 (t, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 191.2, 171.5, 160.1, 150.5, 133.9, 128.9, 125.7, 62.9, 61.7, 41.4, 39.9, 35.8, 34.6, 31.4, 14.3, 14.1. IR (neat): ν=2964, 1732, 1366, 1268, 1155, 1109 cm^{-1}. HPLC (Chiralcel OD-H, hexane/*i*-PrOH=97:3, flow rate: 0.7 mL/min, λ=220 nm): t_R=14.68, 18.33, racemate. HRMS (ESI): $[C_{20}H_{28}O_5S+H]^+$ requires: 381.1730; found: 381.1748.

*4.4.22. Hexyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-oxo-4-phenylbutanoate (**8a**).* Colorless oil; $[\alpha]_D^{20}$ −92 (*c* 1.5, $CHCl_3$), 79% ee. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.88 (d, *J*=8.0 Hz, 2H), 7.55 (t, *J*=7.3 Hz, 1H), 7.43 (t, *J*=7.8 Hz, 2H), 7.36 (d, *J*=8.3 Hz, 2H), 7.33 (d, *J*=8.3 Hz, 2H), 4.13–4.22 (m, 2H), 3.96 (d, *J*=13.5 Hz, 1H), 3.88 (d, *J*=13.5 Hz, 1H), 3.83 (dd, *J*=10.9, 3.8 Hz, 1H), 3.68 (dd, *J*=17.9, 10.9 Hz, 1H), 3.15 (dd, *J*=17.9, 3.8 Hz, 1H), 1.65–1.72 (m, 2H), 1.35–1.42 (m, 2H), 1.32 (s, 9H), 1.28–1.34 (m, 4H), 0.89 (t, *J*=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.9, 172.2, 150.3, 136.2, 134.6, 133.5, 128.9, 128.7, 128.1, 125.6, 65.6, 41.0, 40.8, 35.9, 34.6, 31.5, 31.4, 28.7, 25.7, 22.6, 14.1. IR (neat): ν=3059, 3028, 2959, 2932, 2870, 1732, 1688, 1450, 1362, 1329, 1268, 1214, 1160, 757, 690, 558 cm^{-1}; HPLC (Chiralpak AD-H, hexane/*i*-PrOH=97:3, flow rate: 1.0 mL/min, λ=220 nm): t_R=9.27 (major), 11.06 (minor). HRMS (ESI): $[C_{27}H_{36}O_3S+Na]^+$ requires: 463.2277; found: 463.2301.

*4.4.23. Decyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-oxo-4-phenylbutanoate (**8b**).* Colorless oil; $[\alpha]_D^{20}$ −91 (*c* 1.6, $CHCl_3$), 80% ee. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.87–7.91 (m, 2H), 7.52–7.58 (m, 1H), 7.41–7.46 (m, 2H), 7.37 (d, *J*=8.7 Hz, 2H), 7.33 (d, *J*=8.7 Hz, 2H), 4.12–4.25 (m, 2H), 3.98 (d, *J*=13.4 Hz, 1H), 3.88 (d, *J*=13.4 Hz, 1H),

3.84 (dd, J=11.0, 3.8 Hz, 1H), 3.69 (dd, J=17.8, 11.0 Hz, 1H), 3.15 (dd, J=17.8, 3.8 Hz, 1H), 1.64–1.75 (m, 2H), 1.25–1.44 (m, 14H), 1.33 (s, 9H), 0.90 (t, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.8, 172.1, 150.2, 136.1, 134.5, 133.4, 128.8, 128.7, 128.1, 125.6, 65.5, 40.9, 40.8, 35.8, 34.6, 32.0, 31.4, 29.6 (2C overlapped), 29.4, 29.3, 28.7, 26.0, 22.8, 14.2. IR (neat): ν=3060, 2958, 2926, 2856, 1732, 1689, 1470, 1362, 1329, 1267, 1213, 1159, 991, 757, 690 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=99:1, flow rate: 1.0 mL/min, λ=220 nm): t_R=18.51 (major), 30.28 (minor). HRMS (ESI): $[C_{31}H_{44}O_3S+H]^+$ requires: 497.3084; found: 497.3091.

*4.4.24. Isopropyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-oxo-4-phenylbutanoate (**8c**).* Colorless oil; $[\alpha]_D^{20}$ −104 (*c* 0.4, $CHCl_3$), 75% ee. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.86–7.90 (m, 2H), 7.52–7.58 (m, 1H), 7.39–7.46 (m, 2H), 7.37 (d, J=8.9 Hz, 2H), 7.33 (d, J=8.9 Hz, 2H), 5.11 (sept, J=6.3 Hz, 1H), 3.98 (d, J=13.3 Hz, 1H), 3.88 (d, J=13.3 Hz, 1H), 3.79 (dd, J=10.8, 3.4 Hz, 1H), 3.69 (dd, J=17.5, 10.8 Hz, 1H), 3.14 (dd, J=17.5, 3.4 Hz, 1H), 1.34 (d, J=6.3 Hz, 3H), 1.33 (s, 9H), 1.30 (d, J=6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.9, 171.5, 150.2, 136.2, 134.6, 133.4, 128.8, 128.6, 128.1, 125.6, 68.8, 40.9, 40.8, 35.7, 34.6, 31.4, 21.82, 21.79. IR (neat): ν=3060, 3028, 2964, 2871, 1732, 1683, 1598, 1516, 1464, 1449, 1396, 1365, 1323, 1267, 1214, 1165, 1108, 991, 932, 920, 827, 759, 690, 558 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=95:5, flow rate: 1.0 mL/min, λ=220 nm): t_R=8.72 (major), 11.09 (minor). HRMS (ESI): $[C_{24}H_{30}O_3S+H]^+$ requires: 399.1988; found: 399.1990.

*4.4.25. Isobutyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-oxo-4-phenylbutanoate (**8d**).* Colorless oil; $[\alpha]_D^{20}$ −89 (*c* 0.4, $CHCl_3$), 77% ee. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.89 (d, J=7.9 Hz, 2H), 7.55 (t, J=7.4 Hz, 1H), 7.43 (t, J=7.7 Hz, 2H), 7.36 (d, J=8.1 Hz, 2H), 7.33 (d, J=8.1 Hz, 2H), 3.94–3.99 (m, 3H), 3.89 (d, J=13.4 Hz, 1H), 3.85 (dd, J=10.8, 3.8 Hz, 1H), 3.69 (dd, J=17.7, 10.8 Hz, 1H), 3.17 (dd, J=17.7, 3.8 Hz, 1H), 2.00 (nonet, J=6.7 Hz, 1H), 1.32 (s, 9H), 0.98 (d, J=6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.9, 172.1, 150.3, 136.2, 134.5, 133.5, 128.8, 128.7, 128.1, 125.6, 71.4, 41.0, 40.8, 35.9, 34.6, 31.4, 27.9, 19.23, 19.20. IR (neat): ν=3059, 2963, 2909, 2874, 1732, 1449, 1361, 1328, 1268, 1214, 1157, 1001, 757, 690 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=97:3, flow rate: 1.0 mL/min, λ=220 nm): t_R=10.72 (major), 12.69 (minor). HRMS (ESI): $[C_{25}H_{32}O_3S+H]^+$ requires: 413.2145; found: 413.2164.

*4.4.26. 4-Nitrobenzyl (S)-2-(4-tert-butylbenzylsulfanyl)-4-oxo-4-phenylbutanoate (**8e**).* White solid, mp=128–132 °C; $[\alpha]_D^{20}$ −75 (*c* 0.5, $CHCl_3$), 60%ee. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.21 (d, J=8.8 Hz, 2H), 7.87 (d, J=8.0 Hz, 2H), 7.57 (t, J=7.5 Hz, 1H), 7.55 (d, J=8.8 Hz, 2H), 7.44 (t, J=7.8 Hz, 2H), 7.34 (d, J=8.3 Hz, 2H), 7.26 (d, J=8.3 Hz, 2H), 5.29 (d, J=13.6 Hz, 1H), 5.27 (d, J=13.6 Hz, 1H), 3.89 (d, J=13.4 Hz, 1H), 3.89 (dd, J=11.3, 3.8 Hz 1H), 3.85 (d, J=13.4 Hz, 1H), 3.70 (dd, J=18.0, 11.3 Hz, 1H), 3.22 (dd, J=18.0, 3.8 Hz, 1H), 1.31 (s, 9H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 196.9, 171.6, 150.5, 147.7, 143.3, 135.9, 134.2, 133.7, 128.80, 128.78, 128.3, 128.1, 125.7, 123.8, 65.4, 41.1, 40.8, 35.8, 34.6, 31.4. IR (neat): ν=3115, 3086, 1723, 1676, 1521, 1349, 1331, 1208, 1143, 754, 685 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=9:1, flow rate: 0.75 mL/min, λ=220 nm): t_R=44.25 (minor), 48.83 (major). HRMS (ESI): $[C_{28}H_{29}O_5NS+H]^+$ requires: 492.1839; found: 492.1845.

*4.4.27. Ethyl (S)-(E)-4-(benzylsulfanyl)-6-oxo-6-phenylhex-2-enoate (**10a**).* After chromatography, obtained product was recrystallized from EtOH (96%) giving 230 mg of amorphous solid, 43%ee and further 162 mg of waxy solid that was obtained from supernatant, $[\alpha]_D^{20}$ −86.1 (*c* 0.9, $CHCl_3$), 72%ee. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84–7.88 (m, 2H), 7.53–7.59 (m, 1H), 7.41–7.47 (m, 2H), 7.29–7.32 (m, 4H), 7.20–7.27 (m, 1H), 6.80 (dd, J=15.5, 9.1 Hz, 1H), 5.84 (d, J=15.5 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 3.94 (dt, J=9.1, 6.9 Hz, 1H), 3.74 (d, J=13.5 Hz, 1H), 3.66 (d, J=13.5 Hz, 1H), 3.27 (d, J=6.9 Hz, 2H), 1.30 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 196.0, 166.2, 146.5, 137.5, 136.4, 133.5, 129.1, 128.8, 128.7, 128.1, 127.3, 121.9, 60.6, 42.4, 40.9, 35.6, 14.3. IR (neat): ν=3063, 3031, 2986, 1705, 1677, 1645, 1447, 1370, 1264, 1250, 1234, 1167, 759, 713, 689 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=97:3, flow rate: 0.7 mL/min, λ=220 nm): t_R=39.11 (major), 40.75 (minor). HRMS (ESI): $[C_{21}H_{22}O_3S+Na]^+$ requires: 377.1182; found: 377.1181. Reaction catalyzed by quinidine afforded opposite enantiomer: $[\alpha]_D^{20}$ +84 (*c* 0.9, $CHCl_3$), 54%ee.

*4.4.28. Ethyl (S)-(E)-4-(benzylsulfanyl)-6-oxo-6-(4-chlorophenyl) hex-2-enoate (**10b**).* Light yellow oil; $[\alpha]_D^{20}$ −66.8 (*c* 1.6, $CHCl_3$), 57% ee. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.79 (d, J=8.7 Hz, 2H), 7.40 (d, J=8.7 Hz, 2H), 7.20–7.31 (m, 5H), 6.78 (dd, J=15.5, 9.2 Hz, 1H), 5.84 (d, J=15.5 Hz, 1H), 4.20 (q, J=7.1 Hz, 2H), 3.90 (ddd, J=9.2, 7.5, 6.3 Hz, 1H), 3.74 (d, J=13.6 Hz, 1H), 3.65 (d, J=13.6 Hz, 1H), 3.22 (d, J=6.3 Hz, 1H), 3.22 (d, J=7.5 Hz, 1H), 1.29 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 194.8, 166.2, 146.3, 140.0, 137.5, 134.8, 129.5, 129.12, 129.05, 128.7, 127.4, 122.0, 60.7, 42.5, 40.9, 35.6, 14.3. IR (neat): ν=3062, 3030, 2982, 1716, 1689, 1590, 1271, 1218, 1157, 1093, 979, 820, 705 cm^{-1}. HPLC (Chiralpak AD-H, hexane/*i*-PrOH=9:1, flow rate: 1.0 mL/min, λ=220 nm): t_R=21.04 (major), 25.07 (minor). HRMS (ESI): $[C_{21}H_{21}ClO_3S+H]^+$ requires: 389.0973; found: 389.0984.

*4.4.29. Ethyl (S)-(E)-4-(benzylsulfanyl)-6-oxo-6-(naphtalene-2-yl) hex-2-enoate (**10c**).* Light yellow oil; $[\alpha]_D^{20}$ −51.3 (*c* 1.0, $CHCl_3$), 44% ee. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.34 (s, 1H), 7.89–7.96 (m, 2H), 7.85 (d, J=8.5 Hz, 2H), 7.51–7.62 (m, 2H), 7.19–7.35 (m, 5H), 6.88 (dd, J=15.5, 9.1 Hz, 1H), 5.90 (d, J=15.5 Hz, 1H), 4.21 (q, J=7.1 Hz, 2H), 4.01 (dt, J=9.1, 6.9 Hz, 1H), 3.77 (d, J=13.5 Hz, 1H), 3.69 (d, J=13.5 Hz, 1H), 3.39 (d, J=6.9 Hz, 2H), 1.30 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 195.8, 166.2, 146.5, 137.5, 135.7, 133.7, 132.4, 129.9, 129.6, 129.0, 128.70, 128.65, 128.58, 127.8, 127.3, 126.9, 123.6, 121.8, 60.5, 42.4, 41.0, 35.6, 14.3. IR (neat): ν=3062, 2978, 1710, 1673, 1643, 1369, 1264, 1228, 1166, 1034, 862, 822, 714, 698 cm^{-1}. HPLC (Chiralcel OD-H, hexane/*i*-PrOH=9:1, flow rate: 1.0 mL/min, λ=220 nm): t_R=29.1 (minor), 37.34 (major). HRMS (ESI): $[C_{25}H_{24}O_3S+H]^+$ requires: 405.1519; found: 405.1507.

Acknowledgements

The authors are grateful to National Science Centre, Poland for funding (Grant No. 03/D/ST5/05766).

Supplementary data

Supplementary data contains additional experimental and computational details, copies of NMR spectra and HPLC chromatograms. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.06.035.

References and notes

1. (a) Koval', I. V. *Russ. J. Org. Chem.* **2007**, *43*, 319–346; (b) Enders, D.; Luttgen, K.; Narine, A. A. *Synthesis* **2007**, 959–980; (c) Liu, W.; Zhao, X. *Synthesis* **2013**, *45*, 2051–2069.
2. (a) Kobayashi, Y.; Taniguchi, Y.; Hayama, N.; Inokuma, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 11114–11118; (b) Fang, X.; Li, J.; Wang, C.-J. *Org. Lett.* **2013**, *15*, 3448–3451; (c) Dong, X.-Q.; Fang, X.; Tao, H.-Y.; Zhou, X.; Wang, C.-J. *Adv. Synth. Catal.* **2012**, *354*, 1141–1147.
3. (a) Kamimura, A.; Murakami, N.; Kawahara, F.; Yokota, K.; Omata, Y.; Matsuura, K.; Oishi, Y.; Morita, R.; Mitsudera, H.; Suzukawa, H.; Kakehi, A.; Shirai, M.; Okamoto, H. *Tetrahedron* **2003**, *59*, 9537–9546; (b) Kamimura, A.; Kawahara, F.; Omata, Y.; Murakami, N.; Morita, R.; Otake, H.; Mitsudera, H.; Shirai, M.; Kakehi, A. *Tetrahedron Lett.* **2001**, *42*, 8497–8500; (c) Zaderenko, P.; López, M. C.; Ballesteros, P. *J. Org. Chem.* **1996**, *61*, 6825–6828; (d) Gawroński, J.; Gawrońska, K.; Kolbon, H.; Wynberg, H. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 479–483.

4. (a) Zhao, F.; Zhang, W.; Yang, Y.; Pan, Y.; Chen, W.; Liu, H.; Yan, L.; Tan, C.-H.; Jiang, Z. *Adv. Synth. Catal.* **2011**, *353*, 2624–2630; (b) Lewandowska, E. *Tetrahedron* **2007**, *63*, 2107–2122; (c) Lewandowska, E.; Chatfield, D. C. *Eur. J. Org. Chem.* **2005**, 3297–3303; (d) Chatfield, D. C.; Augsten, A.; D'Cunha, C.; Lewandowska, E.; Wnuk, S. F. *Eur. J. Org. Chem.* **2004**, 313–322 for the influence of other non-electron withdrawing substituents on the reactivity of Michael-acceptor, see; (e) Mulliner, D.; Wondrousch, D.; Schüürmann, G. *Org. Biomol. Chem.* **2011**, *9*, 8400–8412; (f) Krenske, E. H.; Petter, R. C.; Zhu, Z.; Houk, K. N. *J. Org. Chem.* **2011**, *76*, 5074–5081; (g) Paasche, A.; Schiller, M.; Schirmeister, T.; Engels, B. *ChemMedChem* **2010**, *5*, 869–880.
5. (a) Yamada, M.; Nagashima, N.; Hasegawa, J.; Takahashi, S. *Tetrahedron Lett.* **1998**, *49*, 9019–9022; (b) Kameo, K.; Ogawa, K.; Takeshita, K.; Nakaike, S.; Tomisawa, K.; Sota, K. *Chem. Pharm. Bull.* **1988**, *36*, 2050–2060; (c) Tomisawa, K.; Kameo, K.; Matsunaga, T.; Saito, S.; Hosoda, K.; Asami, Y.; Sota, K. *Chem. Pharm. Bull.* **1985**, *33*, 2386–2394.
6. For selected examples, see: (a) Žari, S.; Kudrjashova, M.; Pehk, T.; Lopp, M.; Kanger, T. *Org. Lett.* **2014**, *16*, 1740–1743; (b) Zhao, S.; Lin, J.-B.; Zhao, Y.-Y.; Liang, Y.-M.; Xu, P.-F. *Org. Lett.* **2014**, *16*, 1802–1805; (c) Jing, C.; Xing, D.; Qian, Y.; Shi, T.; Zhao, Y.; Hu, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 9289–9292; (d) Das, U.; Chen, Y.-R.; Tsai, Y.-L.; Lin, W. *Chem.—Eur. J.* **2013**, *19*, 7713–7717; (e) Bai, S.; Liu, X.; Wang, Z.; Cao, W.; Lin, L.; Feng, X. *Adv. Synth. Catal.* **2012**, *354*, 2096–2100; (f) Wang, Z.; Chen, D.; Yang, Z.; Bai, S.; Liu, X.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2010**, *16*, 10130–10136; (g) Lv, J.; Li, X.; Zhong, L.; Luo, S.; Cheng, J.-P. *Org. Lett.* **2010**, *12*, 1096–1099; (h) Lu, H.-H.; Wang, X.-F.; Yao, C.-J.; Zhang, J.-M.; Wu, H.; Xiao, W.-J. *Chem. Commun.* **2009**, 4251–4253; (i) Blay, G.; Fernandez, I.; Monleon, A.; Munoz, M. C.; Pedro, J. R.; Vila, C. *Adv. Synth. Catal.* **2009**, *351*, 2433–2440.
7. For a precedent addition of thiophenol to symmetrical maleates catalyzed by quinine see: Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 363–366; for addition of dodecyl mercaptan to dimethyl maleate and dimethyl fumarate applying chiral polymeric catalyst, see: Inoue, S.; Ohashi, S.; Unno, Y. *Polym. J.* **1972**, *3*, 611–616.
8. Liu, H.; Lv, X.; Zhou, L.; Yin, R.; Wang, X. *J. Serb. Chem. Soc.* **2012**, *77*, 581–588.
9. (a) Boratyński, P. J.; Turowska-Tyrk, I.; Skarżewski, J. *Tetrahedron: Asymmetry* **2012**, *23*, 876–883; (b) Boratyński, P. J.; Skarżewski, J. *Synthesis* **2009**, 3113–3119.
10. Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678–20685.
11. For reviews, see: (a) Wende, R. C.; Schreiner, P. R. *Green Chem.* **2012**, *14*, 1821–1849; (b) Siau, W.-Y.; Wang, J. *Catal. Sci. Technol.* **2011**, *1*, 1298–1310 for squaramides as bifunctional catalysts, see; (c) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem.—Eur. J.* **2011**, *17*, 6890–6899 for *Cinchona* alkaloid based urea and thiourea catalysts, see; (d) Connon, S. J. *Chem. Commun.* **2008**, 2499–2510.
12. (a) Kowalczyk, R.; Nowak, A. E.; Skarżewski, J. *Tetrahedron: Asymmetry* **2013**, *24*, 505–514.
13. Takemoto, Y. *Chem. Pharm. Bull.* **2010**, *58*, 593–601.
14. Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748–9770.
15. (a) Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 17934–17941; (b) Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal.* **2008**, *350*, 49–53.
16. Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8703–8706.
17. Simple *Cinchona* alkaloids are still attractive catalysts, for some recent examples, see: (a) Bootwicha, T.; Liu, X.; Pluta, R.; Atodiresei, I.; Rueping, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12856–12859; (b) Wang, X.; Yang, T.; Cheng, X.; Shen, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 12860–12864; (c) Baś, S.; Woźniak, Ł.; Cygan, J.; Młynarski, J. *Eur. J. Org. Chem.* **2013**, 6917–6923.
18. Cucinotta, C. S.; Kosa, M.; Melchiorre, P.; Cavalli, A.; Gervasio, F. L. *Chem.—Eur. J.* **2009**, *15*, 7913–7921; for different type of catalysis used in conjugate additions, see: Nair, D. P.; Podgórski, M.; Chatani, S.; Gong, T.; Xi, W.; Fenoli, C. R.; Bowman, C. N. *Chem. Mater.* **2014**, *26*, 724–744.
19. Soloshonok, V. A.; Roussel, C.; Kitagawa, O.; Sorochinsky, A. E. *Chem. Soc. Rev.* **2012**, *41*, 4180–4188.
20. For application of (2*E*,4*E*)-6-oxo-2,4-dienoates, see: (a) Ma, J.; Xie, P.; Hu, C.; Huang, Y.; Chen, R. *Chem.—Eur. J.* **2011**, *17*, 7418–7422; (b) Schuler, M.; Duvvuru, D.; Retailleau, P.; Betzer, J.-F.; Marinetti, A. *Org. Lett.* **2009**, *11*, 4406–4409.
21. For recent reviews on addition to the extended Michael acceptors, see: (a) Silva, E. M. P.; Silva, A. M. S. *Synthesis* **2012**, *44*, 3109–3128; (b) Csákÿ, A. G.; Herrán, G.; Murcia, M. C. *Chem. Soc. Rev.* **2010**, *39*, 4080–4102; for remote 1,6-stereocontrol in conjugate addition, see: Lear, M. J.; Hayashi, Y. *ChemCatChem* **2013**, *5*, 3499–3501.
22. CDC-984180 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.