DOI: 10.1002/adsc.201000376

Enantioselective Organocatalytic Rearrangement of α-Acyloxy-β-keto Sulfides to α-Acyloxy Thioesters

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Received: May 14, 2010; Revised: September 15, 2010; Published online: November 17, 2010

Dedicated to Professor Saverio Florio on the occasion of his 70th birthday.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000376.

Abstract: The first highly enantioselective organocatalytic rearrangement of α-acyloxy-β-keto sulfides to α-acyloxy thioesters has been developed which provides a number of important synthetic building blocks in high yield and with excellent enantioselectivities (*ee*: up to 92%).

Keywords: *Cinchona* alkaloids; domino reaction; enantioselectivity; organocatalysis; protonation; Pummerer reaction

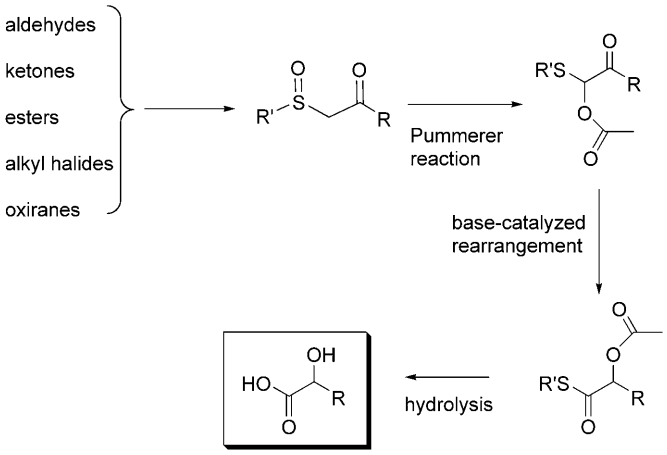
Asymmetric organocatalysis has emerged as a very powerful methodological approach for the enantioselective preparation of chiral compounds, and currently it constitutes a very interesting alternative to the standard metal-catalysed reactions.[1] Anyhow, despite the important advances in asymmetric organocatalysis, several issues still remain unsolved. In particular, the application of organocatalytic reactions to carry out key transformations in the context of the synthesis of complex molecules or natural products still remains rather unexplored.

For this reason, we consider that the development of organocatalytic synthetic procedures for the preparation of basic organic skeletons in a simple and modular way is an area of particular interest which would also contribute to the progress in the field.

Within this context, the Pummerer reaction of β-keto sulfoxides, followed by acyl migration, is a well-documented strategy[2] for a simple route to α-acyloxy thioesters, which can be easily transformed into sulfur-free products such as α-hydroxy acids, amides, esters and ketones without racemisation.

β-Keto sulfoxides can be prepared by several methods like: (i) oxidation of β-hydroxy sulfoxides which are obtained by reaction of α-sulfinylcarbanions with aldehydes;[3] (ii) reaction of methylsulfinylcarbanion with esters;[3a] (iii) reaction of phenylsulfinylacetone dianion with alkyl halides, aldehydes, ketones, α,β-unsaturated esters, or oxiranes.[4] This method provides therefore a direct and efficient route for the synthesis of versatile building blocks from easily available materials (Scheme 1).

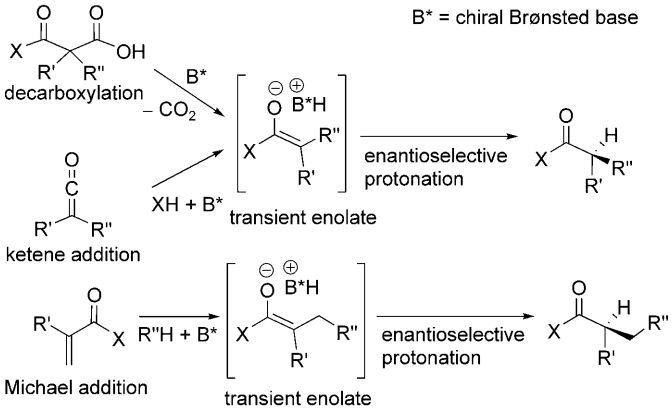
Although this pathway is frequently used for the synthesis of relevant molecules,[2d,e] no catalytic asymmetric version has been reported to date. Realising the potential of such reaction products for the synthesis of α-hydroxy acids and their derivatives,[5] it would be interesting to develop an organocatalysed asymmetric variant of this important reaction.



Scheme 1. Pummerer reaction of β-keto sulfoxides, followed by acyl migration.

Herein we report the first highly enantioselective organocatalytic rearrangement of an α-acyloxy-β-keto sulfide to an α-acyloxy thioester which involves the generation of a transient enolate through a proton abstraction from terminal carbon by a chiral base (*Cinchona* alkaloids), followed by an *in situ* enantioselective protonation.

Recent research witnesses an increasing application of organocatalysis in enantioselective protonation reactions.[6] These methods are based on the use of an enol or enolate prepared *in situ* from a suitable precursor in the absence of metal components (Scheme 2).[7]



Scheme 2. Organocatalysed enantioselective protonation of transient enolates, formed *in situ* from enolate precursors.

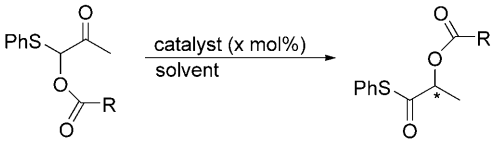
In this connection, *Cinchona* alkaloids have emerged as a class of powerful and versatile asymmetric catalysts[8] that may act as an acid-base bifunctional catalyst by first deprotonating the substrate to generate the enolate and then, as an acid (chiral proton source), by reprotonating the carbanion.

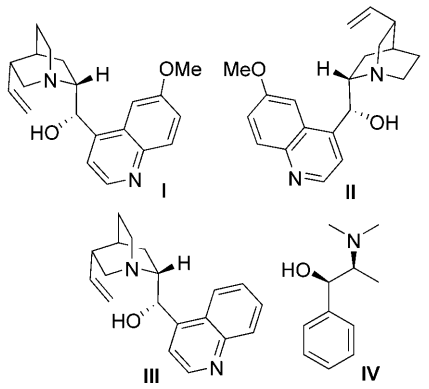
Inspired by the proven ability of *Cinchona* alkaloids to behave as effective bifunctional organic catalysts, we began our investigation by examining the ability of quinidine **I** (20 mol%) to promote the organocatalytic asymmetric rearrangement of the α-acyloxy β-keto sulfide **1a** to the α-acyloxy thioester **2a**. To our delight, by performing the reaction in CH_2Cl_2 we were able to isolate the desired adduct **2a** in 92% yield and 73% *ee* (Table 1, entry 1). At lower temperature (entry 2), the reaction rate is considerably reduced, but a slightly improved enantioselectivity was observed (75% *ee*). In order to improve the enantioselectivity, we screened different solvents and also the catalysts **II–IV** (the results are summarised in Table 1).

For what concerns the reaction medium it appeared that the polarity of the solvent had a pronounced effect on the yield and/or enantioselectivity. More polar solvents such as DMF and DMSO proved to be less effective for the selectivity but gave excellent chemical yields (Table 1, entries 3 and 4). Changing the solvent to *n*-hexane led to decreases in both enantioselectivity and yield of the product (Table 1, entry 5), while a considerable improvement of the enantioselectivity with values of 84% *ee* was obtained in toluene (Table 1, entry 6).

Next we examined the catalyst loading. It should be noted that the catalyst loading could be reduced to 10 and 5 mol% without any detrimental effect on the selectivity (*ee* values ranging from 84 to 88%), although with concomitant decreasing chemical yield (Table 1, entries 7 and 8).

Table 1. Initial screening studies: catalyst, solvent and reaction temperatures.[a]





Entry	Catalyst [x mol%]	Solvent	*T* [°C]	Yield[b] [%]	*ee*[c] [%]
1	**I** [20]	CH_2Cl_2	r.t.	92	73
2	**I** [20]	CH_2Cl_2	0	33	75
3	**I** [20]	DMF	r.t.	98	14
4	**I** [20]	DMSO	r.t.	96	rac
5	**I** [20]	*n*-hexane	r.t.	54	38
6	**I** [20]	toluene	r.t.	96	84
7	**I** [10]	toluene	r.t.	80	88
8	**I** [5]	toluene	r.t.	50	84
9	**II** [20]	toluene	r.t.	90	−80
10	**III** [20]	toluene	r.t.	34	80
11	**IV** [20]	toluene	r.t.	36	−54
12[d]	**I** [20]	toluene	r.t.	50	56

[a] *Reaction conditions*: **1a** (0.135 mmol), catalyst (x mol%) in solvent (0.5 mL), 24 h.
[b] Isolated yield after chromatography.
[c] Determined by HPLC analysis using a chiral stationary column.
[d] The reaction of **1b** in the presence of **I** was examined.

Access to *ent*-**2a** could be achieved by changing the catalyst employed. Indeed, the opposite configuration of **2a** (90% yield and −80% *ee*) was obtained using quinine **II** (*pseudo*-enantiomer of **I**) as catalyst (Table 1, entry 9). On the other hand cinchonine **III** (Table 1, entry 10) gave a satisfying *ee* (80%) albeit with moderate conversion (34% yield), whereas (−)-*N*-methylephedrine **IV** (Table 1, entry 11) displayed poor reactivity (36% yield) and enantioselectivity (−54% *ee*) giving, as expected, the desired product with the opposite configuration.[9]

Only moderate *ee* (56%) was achieved with the less reactive *O*-benzoyl substituted substrate **1b** (Table 1, entry 12). As the best results were obtained using quinidine **I** in toluene, we decided to pursue this study using these reaction conditions for examining the substrate scope and the results are reported in Table 2.

Linear and branched 3-alkyl-substituted α-acyloxy β-keto sulfides **1c–e** were both effective in the reaction (Table 2, entries 2–4), leading to increased *ee* values (88 to 92%) in comparison with the results obtained with **1a**, **b**. On the other hand the more sterically congested *tert*-butyl derivative **1f** (entry 5) did not react at room temperature, but after 65 h at 70 °C the adduct was obtained in good yield (60%) and good enantioselectivity (70% *ee*).

When an aromatic α-acyloxy β-keto sulfide (R″ = C_6H_5, entries 6 and 7, Table 2), was subjected to the same reaction conditions, the rearrangement proceeded with almost no selectivity even at 0 °C (0% *ee* and 16% *ee*, respectively). In this case, the stereocenter formed in the reaction should be prone to be racemised due to the phenyl group attached to it (here deprotonation at the α-carbon is facilitated by the enhanced acidity provided by phenyl substitution). However, as shown in Table 2, introduction of a methoxy group in the *para* position of the aromatic ring gave significant improvement of the *ee* (entry 8, 40% *ee* at 0 °C) although the reaction rate was considerably reduced.

The use of different substituents in the phenylthio group does not affect the outcome of the reaction. Indeed, the presence of an electron-withdrawing group such as bromine in **1i** (Table 2, entry 9) or of a methyl electron-donating group in **1k** (Table 2, entry 10) does not have any influence on the enantioselectivity of the reaction. When R′ was an aliphatic group, a relatively slow reaction was observed in the case of **1l**, bearing an ethyl substituent on sulfur (R′ = Et), that gave **2l** in 62% yield with 62% *ee* (Table 2, entry 11). Replacing the ethyl with a benzyl group, as in α-acyloxy β-keto sulfide **1m**, the reaction failed to afford the desired product **2m** (Table 2, entry 12).[10]

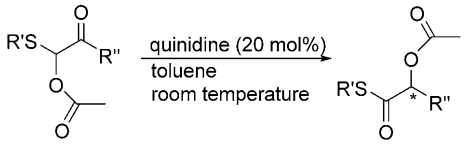
The mechanism of this stereoselective rearrangement still remains to be determined. We currently speculate that the quinidine deprotonates the more acidic methine position of **1** furnishing the enolate species **A** (Scheme 3).

An acyl migration may reasonably be expected to furnish a transient enolate **B** followed by an *in situ* enantioselective protonation. Proton transfer from the protonated quinidine catalyst to species **B** provides the product and releases the catalyst back into the cycle. The protonation can occur within the catalyst-enolate ion pair.

The absolute stereochemistries of compounds **2a–l** were assigned by analogy with that assigned to **2d** after its conversion (*via* an established and racemisation-free hydrolysis) to the (−)-2-hydroxy-4-phenylbutanoic acid **3** that is an important building block for the production of a large variety of angiotensin converting enzyme (ACE) inhibitors. Previously published characterisation of α-hydroxy acid **3**[11] indicates that the absolute stereochemistry at the 2 position is *R*, with $[\alpha]_D^{20}$: −8.5 (*c* 1.0, EtOH), matching our experimental data for intermediate **3** prepared *via* Scheme 4.

Using the method described in Scheme 4, we were able also to prepare 4-[(*R*)-2-hydroxypropionyl]morpholine **4**. The intermediate **4** can be easily modified

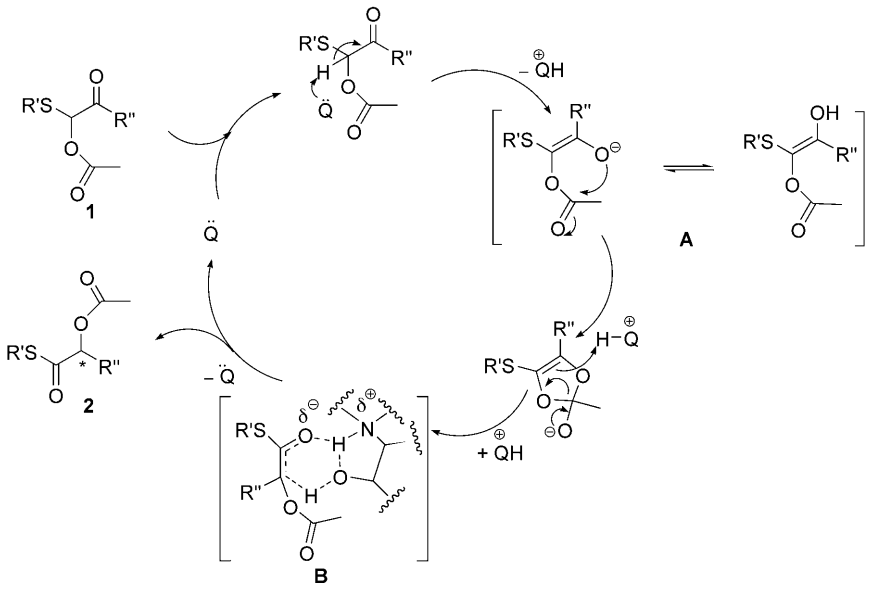
Table 2. Preliminary scope of the organocatalytic asymmetric rearrangement of α-acyloxy β-keto sulfides **1** to α-acyloxy thioesters **2**.[a]



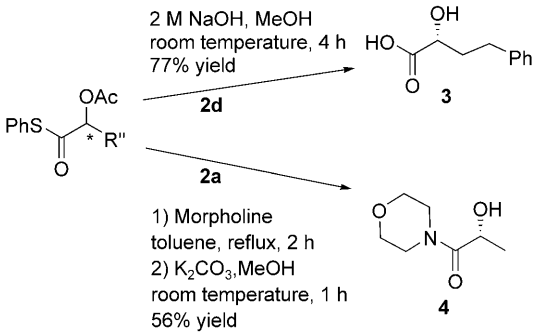
1a – m **2a – l**

Entry	R′	R″	Product	Yield [%][b]	*ee*[c] [%]
1	Ph	Me	**2a**	96	84
2	Ph	Et	**2c**	85	90
3	Ph	CH_2CH_2Ph	**2d**	98	88
4	Ph	*i*-Pr	**2e**	93	92
5[d]	Ph	*t*-Bu	**2f**	60	70
6	Ph	Ph	**2g**	96	rac
7[e]	Ph	Ph	**2g**	90	16
8[e]	Ph	*p*-$MeOC_6H_4$	**2h**	70	40
9	*p*-BrC_6H_4	Me	**2i**	95	84
10	*p*-MeC_6H_4	*i*-Pr	**2k**	90	90
11[f]	Et	CH_2CH_2Ph	**2l**	62	62
12	Bn	Me	**2m**	0	–

[a] *Reaction conditions*: **1** (0.135 mmol), quinidine (20 mol%) in toluene (0.5 mL) at room temperature, 30 h.
[b] Isolated yield after chromatography.
[c] Determined by HPLC analysis using a chiral stationary column.
[d] At 70 °C, 65 h.
[e] At 0 °C, 96 h.
[f] At room temperature, 48 h.



Scheme 3. Proposed catalytic cycle.



Scheme 4. Synthesis of the α-hydroxy acid **3** and morpholino amide **4**.

to prepare optically active antifungal azoles[12] and tricyclic NMDA-glycine antagonists indole-2-carboxylic acids.[13] Moreover, this formal synthesis allowed us to confirm the absolute stereochemistry of our α-acyloxy thioester.

In summary, the methodology reported in this study adds to the repertoires of organocatalysed enantioselective protonation of transient enolates, formed *in situ* from enolate precursors and catalysed by *Cinchona* alkaloid derivatives. To the best of our knowledge this is the first example of an enantioselective protonation-terminated base-catalysed intramolecular oxidation-reduction, with concomitant acetyl transfer, tandem reaction.

Applying this newly developed organocatalytic reaction we prepared important synthetic building blocks in high yield and with excellent enantioselectivities (*ee*: up to 92%).

Further extension of this method toward the preparation of chiral α-amino acids, a detailed mechanism and expanded substrate scope, are under investigation in our laboratory.

Experimental Section

General Procedure for the Synthesis of Optically Active α-Acyloxy Thioesters

To a solution of **1a–m** (0.135 mmol) in toluene (0.5 mL) was added quinidine (8.5 mg, 0.027 mmol), and the mixture was stirred for 30–48 h at room temperature. The crude reaction mixture was directly loaded on silica gel column without aqueous work-up and pure products were obtained by flash column chromatography (silica gel, mixture of hexane/ether).

1-[(Phenylthio)carbonyl]ethyl acetate (2a): Colourless oil; yield: 96%. IR (neat): $\nu = 1753$, 1710 cm^{-1}; $[\alpha]_D^{22}$: +60 (*c* 2.88, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.53$ (d, 3H, $J = 6.9$ Hz), 2.2 (s, 3H), 5.3 (q, 1H, $J = 6.9$), 7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.7$, 20.7, 74.8, 126.2, 129.2, 129.5, 134.7, 169.8, 197.6; MS: $m/z = 137$ ($M^+ - 87$, 3%), 115 (100%), 87 (65%), 65 (17%), 51 (4%). The *ee* was determined to be 84% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): t_R(major) = 21.27 min, t_R(minor) = 17.27 min; anal. calcd. for $C_{11}H_{12}O_3S$: C 58.91, H 5.39, S 14.30; found: C 58.97, H 5.43, S14.25.

1-[(Phenylthio)carbonyl]ethyl benzoate (2b): Colourless oil; yield: 50%. IR (neat): $\nu = 1729$ cm^{-1}; $[\alpha]_D^{22}$: −14 (*c* 1.13, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.64$ (d, 3H, $J =$ 6.9 Hz), 6.56 (q, 1H, $J = 6.9$ Hz), 7.39–7.6 (m, 8H), 8.13–8.17 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.9$, 75.2, 126.1, 128.4, 129.1, 129.4, 129.8, 133.4, 134.6, 165.1, 197.7; MS: $m/z = 177$ ($M^+ - 109$, 30%), 105 (100%), 77 (28%), 51 (7%). The *ee* was determined to be 56% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): t_R(major) = 22.83 min, t_R(minor) = 19.11 min;

anal. calcd. for $C_{16}H_{14}O_3S$: C 67.11, H 4.93, S 11.20; found: C 67.06, H 4.85, S 11.09.

1-[(Phenylthio)carbonyl]propyl acetate (2c): Colourless oil; yield: 85%. IR (neat): ν = 1756, 1708 cm^{-1}; $[\alpha]_D^{19}$: +87.5 (*c* 2.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.99 (t, 3H), 1.88–1.95 (m, 2H), 2.19 (s, 3H), 5.23–5.27 (m, 1H), 7.35–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.3, 20.6, 25.3, 79.1, 126.2, 129.1, 129.4, 134.6, 169.9, 197.0; MS: *m*/*z* = 129 (M^+−109, 93%), 110 (100%), 101 (93%), 65 (22%). The *ee* was determined to be 90% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R(major) = 26.05 min, t_R(minor) = 21.76 min; anal. calcd. for $C_{12}H_{14}O_3S$: C 60.48, H 5.92, S 13.46; found: C 60.57, H 5.83, S 13.51.

1-[(Phenylthio)carbonyl]-3-phenylpropyl acetate (2d): Colourless oil; yield: 98%. IR (neat): ν = 1750, 1708 cm^{-1}; $[\alpha]_D^{19}$: +63 (*c* 2.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.20–2.28 (m, 2H), 2.22 (s, 3H), 2.74–2.80 (m, 2H), 5.33–5.37 (m, 1H), 7.18–7.47 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 31.1, 33.5, 77.7, 126.1, 126.2, 128.3, 128.5, 129.2, 129.6, 134.7, 140.2, 169.9, 197.0; MS: *m*/*z* = 205 (M^+−109, 37%), 163 (22%), 117 (100%), 91 (24%), 77 (6%). The *ee* was determined to be 88% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R(major) = 36.20 min, t_R(minor) = 29.02 min; anal. calcd. for $C_{18}H_{18}O_3S$: C 68.76, H 5.77, S 10.20; found: C 68.69, H 5.81, S 10.13.

1-[(Phenylthio)carbonyl]-2-methylpropyl acetate (2e): Colourless oil; yield: 93%. IR (neat): ν = 1756, 1704 cm^{-1}; $[\alpha]_D^{30}$: +119 (*c* 1.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, 3H, *J* = 1.5 Hz), 1.03 (d, 3H, *J* = 1.5 Hz), 2.23 (s, 3H), 2.27–2.36 (m, 1H), 5.21 (d, 1H, *J* = 4.5 Hz), 7.34–7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.7, 18.7, 20.7, 31.0, 82.2, 126.5, 129.2, 129.5, 134.7, 170.2, 197.0; MS: *m*/*z* = 143 (M^+−109, 77%), 115 (100%), 110 (95%), 65 (15%). The *ee* was determined to be 92% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R(major) = 29.95 min, t_R(minor) = 42.35 min; anal. calcd. for $C_{13}H_{16}O_3S$: C 61.88, H 6.39, S 12.71; found: C 61.76, H 6.43, S 12.80.

1-[(Phenylthio)carbonyl]-2,2-dimethylpropyl acetate (2f): Reaction performed over 65 h at 70 °C; colourless oil; yield: 60%. IR (neat): ν = 1756, 1707 cm^{-1}. $[\alpha]_D^{22}$: +81.3 (*c* 2.09, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.04 (s, 9H), 2.22 (s, 3H), 5.02 (s, 1H), 7.34–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 26.0, 34.5, 84.4, 126.8, 129.0, 129.3, 134.6, 170.0, 196.4; MS: *m*/*z* = 157 (M^+−109, 55%), 129 (63%), 110 (96%), 87 (100%). The *ee* was determined to be 70% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R(major) = 11.28 min, t_R(minor) = 13.86 min; anal. calcd. for $C_{14}H_{18}O_3S$: C 63.13, H 6.81, S 12.04; found: C 63.05, H 6.70, S 11.92.

[(Phenylthio)carbonyl](phenyl)methyl acetate (2g): Reaction performed over 96 h at 0 °C; colourless oil; yield: 90%. IR (neat): ν = 1753, 1710 cm^{-1}; $[\alpha]_D^{24}$: +1.4 (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.23 (s, 3H), 6.24 (s,1H), 7.32–7.51 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 79.9, 126.2, 127.7, 128.8, 129.2, 129.3, 129.6, 133.8, 134.7, 169.6, 195.0; MS: *m*/*z* = 199 (M^+−87, 4%), 177 (39%), 149 (66%), 107 (100%), 77 (21%), 65 (11%). The *ee* was determined to be 16% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R(major) = 46.07 min, t_R(minor) = 32.63 min; anal. calcd. for $C_{16}H_{14}O_3S$: C 67.11, H 4.93, S 11.20; found: C 67.20, H 4.98, S 11.31.

[(Phenylthio)carbonyl](4-methoxyphenyl)methyl acetate (2h): Reaction performed over 96 h at 0 °C; colourless oil; yield: 70%. IR (neat): ν = 1750, 1707 cm^{-1}. $[\alpha]_D^{19}$: −25 (*c* 0.71, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 3H), 3.81 (s, 3H), 6.19 (s, 1H), 6.92 (d, 2H), 7.36–7.42 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 55.3, 79.6, 114.3, 125.8, 129.1, 129.2, 129.3, 129.5, 134.7, 160.4, 169.7, 195.1; MS: *m*/*z* = 229 (M^+−87, 3%), 179 (31%), 137 (100%), 109 (14%), 77 (7%). The *ee* was determined to be 40% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 70:30, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R(major) = 56.59 min, t_R(minor) = 47.95 min; anal. calcd. for $C_{17}H_{16}O_4S$: C 64.54, H 5.10, S 10.14; found: C 64.61, H 4.99, S 9.97.

1-[(4-Bromophenylthio)carbonyl]ethyl acetate (2i): Colourless oil; yield: 95%. IR (neat): ν = 1753, 1711 cm^{-1}; $[\alpha]_D^{22}$: +67 (*c* 1.57, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.49 (d, 3H, *J* = 6.9 Hz), 2.17 (s, 3H), 5.35 (q, 1H, *J* = 6.9 Hz), 7.22 (d, 2H, *J* = 6.9 Hz), 7.51 (d, 2H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 20.6, 74.6, 124.2, 125.2, 132.3, 136.0, 169.6, 196.9; MS: *m*/*z* = 188 (M^+−116, 25%), 115 (100%), 87 (97%), 69 (10%). The *ee* was determined to be 84% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R(major) = 14.32 min, t_R(minor) = 12.89 min; anal. calcd. for $C_{11}H_{11}BrO_3S$: C 43.58, H 3.66, S 10.58; found: C 43.47, H 3.58, S 10.49.

1-[(*p*-Tolylthio)carbonyl]-2-methylpropyl acetate (2k): Colourless oil; yield: 90%. IR (neat): ν = 1756, 1704 cm^{-1}; $[\alpha]_D^{19}$: +106.8 (*c* 1.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, 3H, *J* = 1.5 Hz), 1.02 (d, 3H, *J* = 1.5 Hz), 2.22 (s, 3H), 2.36 (s, 3H), 5.20 (d, 1H, *J* = 4.5 Hz), 7.19–7.27 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.7, 18.7, 20.7, 21.3, 30.9, 82.2, 122.9, 130.0, 134.6, 139.8, 170.1, 197.4; MS: *m*/*z* = 143 (M^+−123, 61%), 124 (100%), 91 (25%), 77 (10%). The *ee* was determined to be 90% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R(major) = 17.37 min, t_R(minor) = 15.00 min; anal. calcd. for $C_{14}H_{18}O_3S$: C 63.13, H 6.81, S 12.04; found: C 63.20, H 6.90, S 12.13.

1-[(Ethylthio)carbonyl]-3-phenylpropyl acetate (2l): Colourless oil; yield: 62%. IR (neat): ν = 1753, 1689 cm^{-1}; $[\alpha]_D^{20}$: +33.6 (*c* 1.19, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, 3H), 2.11–2.22 (m, 2H), 2.17 (s, 3H), 2.68–2.74 (m, 2H), 2.85–2.92 (m, 2H), 5.20–5.24 (m, 1H), 7.16–7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 20.7, 22.7, 31.1, 33.6, 77.7, 126.1, 128.3, 128.4, 140.3, 170.0, 198.9; MS: *m*/*z* = 206 (M^+−60, 51%), 145 (20%), 117 (100%), 91 (53%), 77 (8%). The *ee* was determined to be 62% *ee* by HPLC (Chiralcel OJ column, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R(major) = 9.62 min, t_R(minor) = 13.07 min; anal. calcd. for $C_{14}H_{18}O_3S$: C 63.13, H 6.81, S 12.04; found: C 63.05, H 6.73, S 11.97.

Acknowledgements

Financial support from the MIUR, Rome, and by the University of Cagliari (National Project "Stereoselezione in Sintesi

Organica Metodologie ed applicazioni") and from CINMPIS is gratefully acknowledged.

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[9] It is noteworthy that both quinine **II** and (−)-*N*-methylephedrine **IV** have the same configuration (1*R*,2*S*) of the amino alcohol moiety.

[10] There seem to be two different factors that could be held responsible for these two results: either the steric effects, due to 1,3-torsional strain induced between the substituents R′ and R″ in the enolate specie **A** (higher for the derivative **2m** than for the **2l**), and the non-existence of a resonance stabilised transient enolic form **B** (see Scheme 3), as the driving force of these reactions may be considered to be the stabilisation energy resulting in the products, having the carbonyl conjugated with the phenylthio group (see ref.[2c]).

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