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L-Proline amides catalyze direct asymmetric aldol reactions of aldehydes with methylthioacetone and fluoroacetone

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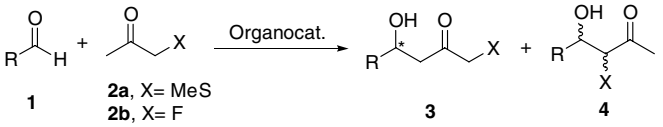
Abstract—Direct aldol reactions of aldehydes with methylthio- and fluoroacetone catalyzed by proline amides have been investigated. L-Prolinamide **5e** was found to be the best catalyst. Under the optimized reaction conditions, a series of aromatic and aliphatic aldehydes reacted smoothly with methylthioacetone, to generate 1-methylthio-4-hydroxyketones **3** in good yields and with high regio- and enantioselectivities. Excellent enantioselectivities of up to 98% ee were observed for aromatic aldehydes and even higher enantioselectivities of >99% ee were observed for aliphatic aldehydes. Asymmetric direct aldol reactions of fluoroacetone with aldehydes in the presence of 20 mol % of **5e** preferentially occurred at the fluoromethyl group, yielding products with high enantioselectivities (up to 98% ee).

1. Introduction

Direct asymmetric aldol reactions provide an atom-economic approach to β-hydroxyl carbonyls, which make up a large family of chiral intermediates for the synthesis of biologically active substances and natural products.[1,2] Recently, important advances have been made with regards to direct asymmetric aldol reactions catalyzed either by biocatalysts,[3] transition metal complexes,[4–6] or organocatalysts.[7–13] However, simple ketones are usually examined as aldol donors in most cases. The reactions of α-heteroatom substituted ketones have received less attention with the exception of those of α-hydroxyketones. In the direct aldol reactions between α-hydroxyketones and aldehydes, both 1,2- and 1,4-diols with high enantioselectivities have been accessible.[11] Asymmetric direct aldol reactions between aldehydes and chloroacetone catalyzed by proline amides was also performed with high enantioselectivities.[14] Although a direct asymmetric aldol reaction of fluoroacetone with aldehydes was investigated by using prolinol as a catalyst, *anti*-α-fluoro-β-hydroxylacetones were produced with moderate enantioselectivities (up to 87% ee).[15] In addition, there has been no report on an organocatalytic direct aldol reaction of aldehydes with methylthioacetone, except using antibodies as catalysts.[16] Thus, the discovery of organocatalytic asymmetric direct aldol reactions of methylthio- and fluoroacetones is still desirable. Herein, we report highly enantioselective direct aldol reactions of methylthio- and fluoroacetones with aldehydes mediated by L-proline amides (Eq. 1).



(1)

2. Results and discussion

α-Sulfenylated carbonyl compounds are very useful in organic synthesis, particularly in the synthesis of cyclopropane derivatives.[17] Accordingly, asymmetric sulfenylations of enolates in the presence of chiral transition metal complexes[18] and asymmetric organocatalytic α-sulfenylations of unmodified ketones and aldehydes were

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disclosed.[19] The direct aldol reaction of aldehydes with methylthioacetone provides an alternative method for the preparation of α-sulfenylated carbonyl compounds. Encouraged by our recent advances on L-proline amide-catalyzed direct aldol reactions,[10,11,14] we were interested in extending the application of these organocatalysts (Fig. 1) to the direct aldol reactions of methylthio- and fluoroacetones with aldehydes.

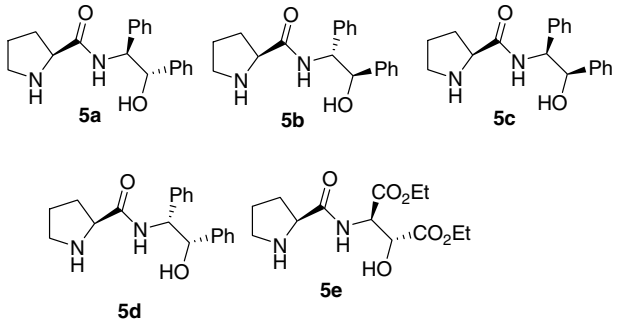


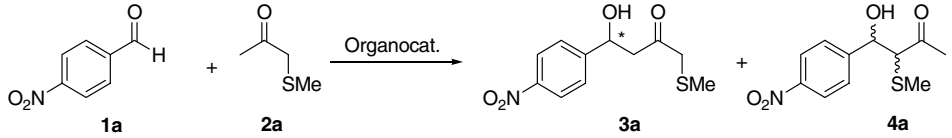
Figure 1. L-Proline amides evaluated in this study.

Initially the direct aldol reaction of 4-nitrobenzaldehyde with methylthioacetone in the presence of 20 mol % of **5a** was carried out at room temperature in $CHCl_3$ (Table 1). The reaction took place preferentially at the methyl group of methylthioacetone to give 1-methylthio-4-hydroxy-4-(4′-nitrophenyl)-butan-2-one **3a** as the major product with 59% ee. On the contrary, direct aldol reactions of hydroxyacetone and chloroacetone, catalyzed either by proline or proline derivatives, preferentially occurred at the hydroxy- and chloromethyl groups in organic solvents[7i,j,14] with the exception of cases performed in aqueous media.[11] The use of proline amides **5b–d** as catalysts favourably afforded **3a** in modest yields and enantioselectivities, accompanied by a small amount of **4a**. Compared with hydoxyl-[7i,j,11] and fluoroacetones,[15] methylthioacetone is less reactive and thus leads to lower yields. In terms of the stereochemical outcome, proline amide **5a** is the catalyst of choice, which afforded 59% ee (entry 1). In contrast, proline exhibited very little catalytic activity (entry 5). The yield and enantioselectivity were improved to 53% and 71% ee, respectively, by performing the reaction in CH_2Cl_2 (entry 6). Lowering the reaction temperature and using an excess amount of methylthioacetone led to a further improvement in the yield and enantioselectivity (entry 7). Interestingly, the enantioselectivity seemingly benefited from a decrease in catalyst loading (entries 7–9). The ee value increased to 91% using 5 mol % of **5a** (entry 9) while the highest ee (95%ee) was given by using **5e** to replace **5a** (entry 10).

The optimized protocol was then extended to direct aldol reactions of methylthioacetone with various aromatic and aliphatic aldehydes. As shown in Table 2, organocatalyst **5e** generally exhibited high enantioselectivities ranging from 91% to >99% ee for all the substrates. Benzaldehydes with *para*-electron-withdrawing substituents underwent aldol reactions to generate aldol adducts **3a–d** in fairly good yields and with excellent enantioselectivities (entries 1–4). The direct aldol reactions of mono-halogen-substituted benzaldehydes afforded high enatioselectivities ranging from 92% to 94% ee, albeit with moderate yields (entries 5–7). Benzaldehydes bearing two electron-withdrawing substituents also gave good yields and high enantioselctivties (entries 8–10). In particular, a very high enantioselectivity of 98% ee was observed for **3i** (entry 9). In contrast, benzaldehyde is much less reactive and offers a low yield of **3k** albeit with 92% ee (entry 11). Notably, α-branched aliphatic aldehydes reacted smoothly with methylthioacetone in moderate yields and with high enantioselectivities (entries 12–14). Extremely high enantioselectivties of up to >99% ee were observed for *iso*-butylaldehyde and cyclohexylformaldehyde (entries 13–14).

Fluorinated organic compounds play an important role in the preparation of pharmaceuticals.[20] A great number of studies have indicated that α-fluoro carbonyl compounds

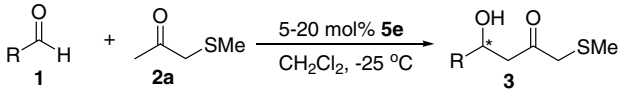
Table 1. Catalyst screening and the optimization of reaction conditions[a]



Entry	Cat. (mol %)	Solvent	Yield of **3a**[b] (%)	ee[c] (%)	Yield of **4a**[b] (%)
1	**5a** (20)	$CHCl_3$	37	59	—
2	**5b** (20)	$CHCl_3$	35	32	—
3	**5c** (20)	$CHCl_3$	21	42	—
4	**5d** (20)	$CHCl_3$	45	42	—
5	Proline (20)	$CHCl_3$	10	—	—
6	**5a** (20)	CH_2Cl_2	53	71	—
7	**5a** (20)[d]	CH_2Cl_2	74	86	6
8	**5a** (10)[d]	CH_2Cl_2	52	89	4
9	**5a** (5)[d]	CH_2Cl_2	43	91	3
10	**5e** (5)[d]	CH_2Cl_2	72	95	5

[a] Unless otherwise indicated, the reaction of aldehyde (0.3 mmol) with methylthioacetone (150 μL) and a solvent (1.0 mL).
[b] The yield of **3a** or **4a** is calculated on the basis of the isolated yields of **3a** and **4a**.
[c] Determined by HPLC.
[d] The reaction of methylthioacetone (600 μL) was performed at −25 °C.

Table 2. Study on the scope and limitation of aldehydes[a]



Entry	Product	R	Yield[b] (%)	ee[c] (%)
1	**3a**	4-$NO_2C_6H_4$	72	95[d]
2	**3b**	4-CNC_6H_4	60	93[d]
3	**3c**	4-$CF_3C_6H_4$	72	95
4	**3d**	4-$MeO_2CC_6H_4$	81	93[e]
5	**3e**	4-ClC_6H_4	44	94
6	**3f**	2-FC_6H_4	58	92
7	**3g**	2-ClC_6H_4	52	92
8	**3h**	3,5-$Br_2C_6H_3$	76	96[d]
9	**3i**	3,5-$(CF_3)_2C_6H_3$	77	98[d]
10	**3j**	2,6-$Cl_2C_6H_3$	73	94
11	**3k**	Ph	24	92[e]
12	**3l**	*t*-Bu	63	95[e]
13	**3m**	*i*-Pr	48	>99[e]
14	**3n**	*c*-C_6H_{11}	59	>99[e]

[a] Unless otherwise indicated, the reaction of the aldehyde (0.3 mmol) is carried out with methylthioacetone (150 μL) and a solvent (1.0 mL).
[b] The yield of **3a** or **4a** is calculated on the basis of the isolated yields of **3a** and **4a**.
[c] Determined by HPLC.
[d] The reaction of methylthioacetone (600 μL) was performed at −25 °C.
[e] In the presence of 20 mol% **5e**.

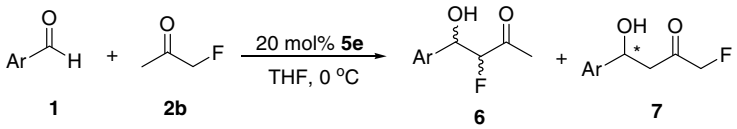
are particularly useful in glycobiology research.[21] Direct asymmetric aldol reactions between aldehydes and fluoroacetone conveniently access the optically active α-fluoro carbonyl compounds, but it is challenging to control the reaction to selectively generate a single isomer because a mixture of at least six isomers is produced. Even though a direct aldol reaction of fluoroacetone with aldehydes was performed using prolinol as a catalyst, the *anti*-α-fluoro-β-hydroxy ketones were obtained in modest yield and moderate enantioselectivities.[15]

In the presence of 20 mol % of organocatalyst **5e**,[11b] the direct aldol reaction of aldehydes with fluoroacetone was attempted (Table 3). To our delight, the reaction predominantly afforded **6** with regiomeric ratios of 6/7 ranging from 83/17 to 98/2 and excellent enantioselectivities ranging from 94% to 98% ee.

3. Conclusion

In conclusion, we have described direct aldol reactions of aldehydes with methylthio- and fluoroacetone catalyzed by proline amides. L-Prolinamide **5e** was found to be the best catalyst. Under the optimal reaction conditions, a series of aromatic and aliphatic aldehydes reacted smoothly with methylthioacetone, generating 1-methylthio-4-hydroxyketones **3** in good yields and with high regio- and enantioselectivities. Excellent enantioselectivities of up to 98% ee were observed for aromatic aldehydes and even higher enantioselectivities of >99% ee were observed for aliphatic aldehydes. Direct asymmetric aldol reactions of fluoroacetone with aldehydes mediated by 20 mol % of **5e** preferentially occurred at the fluoromethyl group, yielding products with high enantioselectivities (up to 98% ee). Although a large number of organocatalytic direct aldol

Table 3. Direct aldol reaction of fluoroacetone with aldehydes[a]



Entry	Ar	Time (days)	**6/7**[b]	dr of **6**[c] (*anti*/*syn*)	Yield[d] (%)	ee[e] (%)
1	4-$NO_2C_6H_4$	1	98/2	2/1	96	95[f]
2	3,5-$F_2C_6H_3$	1.5	90/10	4/1	95	94
3	3,5-$Br_2C_6H_3$	5	83/17	4/1	89	98

[a] Unless otherwise specified, the concentration of aldehyde is 0.25 M.
[b] Determined by ^{1}H NMR.
[c] The ratio was determined by ^{1}H NMR analysis of the crude product.
[d] Overall isolated yield of **5** and **6**.
[e] Determined by HPLC.
[f] The result was reported in Ref. 11b.

reactions exist, this work adds new knowledge to the field because methylthioacetone had never been used as an aldol donor in organocatalytic direct aldol reactions.

4. Experimental

4.1. General data

Chemicals were purchased from Acros and Lancaster. Organic solvents were distilled before use. NMR spectra were recorded on a Bruker-300 MHz spectrometer. High-resolution mass spectra were recorded on a Bruker BIO TOF Q mass spectrometer. Infrared spectra were recorded on a Nicolet MX-1E FT-IR spectrometer. HPLC analysis was performed on Waters-Breeze (2487 Dual λ Absorbance Detector and 1525 Binary HPLC Pump). Chiralpak AS, AD and OD columns were purchased from Daicel Chemical Industries, LTD.

4.2. General procedure for direct aldol reactions of methylthioacetone with aldehydes

To a solution of an aldehyde (0.3 mmol) and methylthioacetone (600 μL) in anhydrous CH_2Cl_2 (1.0 mL) was added L-prolinamide **5e**. After being stirred at –25 °C for 124 h, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (3×10 mL) and dried over anhydrous $MgSO_4$. After removal of solvent under reduced pressure, the residue was purified through a flash column chromatography on silica gel to give desired aldol products **3**.

4.3. 1-Methylthio-4-hydroxy-4-(4′-nitrophenyl)-butan-2-one 3a

Yield: 72%, $[\alpha]_D^{20} = +39.4$ (*c* 0.5, DCM), mp = 63–65 °C (DCE); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.03 (s, 3H), 3.04 (d, $J = 6.1$, 2H), 3.19 (s, 2H), 3.58 (s, 1H), 5.27 (t, $J = 6.2$, 1H), 7.53–7.57 (m, 2H), 8.16–8.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.6, 43.4, 48.1, 69.3, 123.7, 126.4, 147.3, 150.0, 204.6; IR (neat): γ 3492, 2916, 1688, 1599, 1520, 1342, 1194, 1067, 858, 747, 697, 520 cm^{-1}; enantiomeric excess: 95%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane = 30/70), UV 254 nm, flow rate 1.0 mL/min, $t_R = 18.539$ min (minor); $t_R = 12.022$ min (major); HRMS (ESI) for $C_{11}H_{13}NSO_4$-Na: calcd: 291.0662; found: 291.065.

4.4. 1-Methylthio-4-hydroxy-4-(4′-cyanophenyl)-butan-2-one 3b

Yield: 60%, $[\alpha]_D^{20} = 43.2$ (*c* 0.22, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.04 (s, 3H), 3.03 (d, $J = 6.0$ Hz, 2H), 3.19 (s, 1H), 3.45 (d, $J = 3.5$ Hz, 1H), 5.20–5.26 (m, 1H), 7.51 (d, $J = 8.3$ Hz, 2H), 7.65 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.5, 43.4, 48.0, 69.4, 111.3, 118.6, 126.3, 132.3, 148.0, 204.6; IR (neat): γ 3477, 2919, 2228, 1703, 1608, 1407, 1061, 842, 566 cm^{-1}; enantiomeric excess: 93%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane = 30/70), UV 254 nm, flow rate 1.0 mL/min, $t_R = 26.641$ min (minor); $t_R = 11.531$min (major); HRMS (ESI) for $C_{12}H_{13}N_1SO_2Na$: calcd: 258.0559; found: 258.0558.

4.5. 1-Methylthio-4-hydroxy-4-(4′-trifluoromethyl-phenyl)-butan-2-one 3c

Yield: 72%, $[\alpha]_D^{20} = +40.0$ (*c* 0.5, DCM); mp = 54–56 °C (DCE); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.04 (s, 3H), 3.03–3.06 (m, 2H), 3.19 (s, 2H), 3.40 (br s, 1H), 5.22–5.25 (m, 1H), 7.50 (d, $J = 8.2$ Hz, 2H), 7.61 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.5, 43.4, 48.0, 69.6, 124.0 (q, $J = 270.2$ Hz), 125.4 (q, $J = 3.4$ Hz), 125.9, 129.8 (q, $J = 32.3$ Hz), 146.6, 204.9; IR (neat): 3437, 2922, 1705, 1620, 1414, 1325, 1122, 1067, 844, 604, 530 cm^{-1}; enantiomeric excess: 95%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane = 15/85), UV 254 nm, flow rate 1.0 mL/min, $t_R = 18.588$ min (minor); $t_R = 16.306$ min (major); HRMS (ESI) for $C_{12}H_{13}SO_2F_3Na$: calcd: 301.0481; found: 301.0484.

4.6. 4-(4-Methylthio-1-hydroxy-3-oxo-butyl)-benzoic acid methyl ester 3d

Yield: 81%, $[\alpha]_D^{20} = +39.2$ (*c* 0.5, DCM); mp = 62–64 °C (DCE); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.04 (s, 3H), 3.04–3.07 (m, 2H), 3.19 (s, 2H), 3.32 (d, $J = 3.3$ Hz, 1H), 3.92 (s, 3H), 5.23–5.25 (m, 1H), 7.46 (d, $J = 8.2$ Hz, 2H), 8.01–8.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.5, 43.5, 48.2, 69.8, 125.5, 128.8, 147.8, 166.8, 204.8; IR (neat): 3488, 2951, 2920, 1721, 1611, 1435, 1280, 1112, 1017, 965, 859, 768, 706, 541 cm^{-1}; enantiomeric excess: 93%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane = 5/95), UV 254 nm, flow rate 1.0 mL/min, $t_R = 11.645$ min (minor); $t_R = 9.714$ (major); HRMS (ESI) for $C_{13}H_{16}SO_4Na$: calcd: 291.0662; found: 291.0650.

4.7. 1-Methylthio-4-hydroxy-4-(4′-chlorophenyl)-butan-2-one 3e

Yield: 44%, $[\alpha]_D^{20} = +39.8$ (*c* 0.6, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.04 (s, 3H), 3.00–3.03 (m, 2H), 3.18 (s, 2H), 3.25 (d, $J = 3.4$ Hz, 1H), 5.14–5.17 (m, 1H), 7.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.6, 43.5, 48.4, 69.6, 127.1, 128.7, 133.4, 141.2, 205.0; IR (neat): 3475, 2920, 1707, 1492, 1407, 1090, 1012, 832, 538 cm^{-1}; enantiomeric excess: 94%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane = 15/85), UV 254 nm, flow rate 1.0 mL/min, $t_R = 9.488$ min (minor); $t_R = 10.332$ min (major); HRMS (ESI) for $C_{11}H_{13}ClO_2$-SNa: calcd: 267.0217; found: 267.0216.

4.8. 1-Methylthio-4-hydroxy-4-(2′-fluorophenyl)-butan-2-one 3f

Yield: 58%, $[\alpha]_D^{20} = +42.5$ (*c* 0.44, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.02 (s, 3H), 3.05 (d, $J = 6.1$Hz, 2H), 3.18 (s, 2H), 3.46 (br s, 1H), 5.42–5.46 (m, 1H), 6.97–7.55 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.5, 43.4, 47.0, 64.5, 115.2 (d, $J = 21.3$ Hz), 124.3 (d, $J = 2.9$ Hz), 127.2 (d, $J = 4.0$ Hz), 129.0 (d, $J = 8.2$ Hz), 129.6 (d, $J = 13.0$ Hz), 159.3 (d, $J = 244$ Hz),

205.3; IR (neat): 3452, 2920, 1707, 1586, 1487, 1223, 1061, 760, 487 cm^{-1}; enantiomeric excess: 92%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane = 5/95), UV 254 nm, flow rate 1.0 mL/min, $t_R = 18.004$ min (minor); $t_R = 19.566$ min (major); HRMS (ESI) for $C_{11}H_{13}SO_2FNa$: calcd: 251.0512; found: 251.0508.

4.9. 1-Methylthio-4-hydroxy-4-(2′-chlorophenyl)-butan-2-one 3g

Yield: 52%, $[\alpha]_D^{20} = +69.5$ (*c* 0.44, DCM); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.06 (s, 3H), 2.86–3.18 (m, 2H), 3.21 (s, 2H), 3.49 (br s, 1H), 5.50–5.55 (m, 1H), 7.17–7.34 (m, 3H), 7.61–7.64 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.6, 43.4, 46.6, 66.9, 127.0, 127.2, 128.6, 129.3, 131.2, 140.1, 205.5; IR (neat): 3450, 2918, 1703, 1437, 1048, 757, 704, 462 cm^{-1}; enantiomeric excess: 92%, determined by HPLC (Daicel Chiralpak AS, *i*-PrOH/hexane = 10/90), UV 254 nm, flow rate 1.0 mL/min, $t_R = 9.947$ min (minor); $t_R = 11.983$ min (major); HRMS (ESI) for $C_{11}H_{13}SO_2ClNa$: calcd: 267.0217; found: 267.0223.

4.10. 1-Methylthio-4-hydroxy-4-(3′,5′-dibromophenyl)-butan-2-one 3h

Yield: 76%, $[\alpha]_D^{20} = +32.0$ (*c* 0.5, DCM); mp = 55–57 °C (DCE); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.04 (s, 3H), 3.00 (t, $J = 4.5$ Hz, 2H), 3.17 (s, 2H), 3.44 (br s, 1H), 5.08–5.10 (m, 1H), 7.46 (m, 2H), 7.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.6, 43.4, 48.0, 68.9, 123.0, 127.6, 133.2, 146.6, 204.6; IR (neat): 3485, 2918, 1702, 1586, 1557, 1422, 1193, 1061, 857, 741, 684, 486 cm^{-1}; enantiomeric excess: 96%, determined by HPLC (Daicel Chiralpak OD, *i*-PrOH/hexane = 5/95), UV 254 nm, flow rate 1.0 mL/min, $t_R = 14.175$ min (minor); $t_R = 17.240$ (major); HRMS (ESI) for $C_{11}H_{12}Br_2SO_2Na$: calcd: 388.8817; found: 388.8832.

4.11. 1-Methylthio-4-hydroxy-4-(3′,5′-bis-trifluoromethyl-phenyl)-butan-2-one 3i

Yield: 77%, $[\alpha]_D^{20} = +29.0$ (*c* 0.5, DCM); mp = 67–69 °C (DCE); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.04 (s, 3H), 3.04–3.09 (m, 2H), 3.20 (s, 2H), 3.59 (d, $J = 3.6$ Hz, 1H), 5.28–5.33 (m, 1H), 7.8 0 (s, 1H), 7.87 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.6, 43.3, 48.0, 69.1, 121.6, 123.2 (q, $J = 271.1$ Hz), 126.0, 131.8 (q, $J = 33.1$ Hz), 145.3, 204.5; IR (neat): 3391, 2928, 1701, 1623, 1381, 1283, 1185, 1122, 1070, 899, 705, 682 cm^{-1}; enantiomeric excess: 98%, determined by HPLC (Daicel Chiralpak OD, *i*-PrOH/hexane = 5/95), UV 254 nm, flow rate 1.0 mL/min, $t_R = 8.758$ min (minor); $t_R = 10.534$ min (major); HRMS (ESI) for $C_{13}H_{12}SO_2F_6Na$: calcd: 369.0354; found: 369.0358.

4.12. 1-Methylthio-4-hydroxy-4-(2′,6′-dichlorophenyl)-butan-2-one 3j

Yield: 73%, mp = 40.0–42.0 °C; $[\alpha]_D^{20} = -23.9$ (*c* 0.64, DCM); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.07 (s, 3H), 2.91–2.98 (m, 1H), 3.25 (s, 2H), 3.24 (d, $J = 6.8$ Hz, 1H), 3.61–3.70 (m, 1H), 5.96–6.03 (m, 1H), 7.12–7.27 (m, 1H), 7.26–7.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.5, 43.4, 44.3, 67.6, 129.2, 129.4, 134.4, 136.1, 203.3; IR (neat): 3485, 2919, 1703, 1561, 1436, 1185, 1084, 768, 729, 551 cm^{-1}; enantiomeric excess: 93%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane = 15/85), UV 254 nm, flow rate 1.0 mL/min, $t_R = 11.645$ min (minor); $t_R = 9.714$ min (major); HRMS (ESI) for $C_{11}H_{12}Cl_2SO_2Na$: calcd: 300.9827; found: 300.9813.

4.13. 1-Methylthio-4-hydroxy-4-phenyl-butan-2-one 3k

Yield: 24%, $[\alpha]_D^{20} = +15.2$ (*c* 0.5, DCM); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.04 (s, 3H), 2.98–3.14 (m, 2H), 3.19 (s, 2H), 5.16–5.21 (m, 1H), 7.28–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.6, 43.6, 48.5, 70.3, 125.6, 127.8, 128.6, 142.7, 205.3; IR (neat): 3416, 2921, 2869, 1760, 1704, 1604, 1435, 1027, 760, 699 cm^{-1}; enantiomeric excess: >92%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane = 10/90), UV 254 nm, flow rate 1.0 mL/min, $t_R = 13.211$ min (minor); $t_R = 12.088$ min (major); HRMS (ESI) for $C_{11}H_{14}SO_2Na$: calcd: 233.0607; found: 233.0606.

4.14. 1-Methylthio-4-hydroxy-5,5-dimethyl-hexan-2-one 3l

Yield: 63%, $[\alpha]_D^{20} = +59.0$ (*c* 0.71, DCM); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.92 (s, 9H), 2.04 (s, 3H), 2.58–2.82 (m, 3H), 3.20 (s, 2H), 3.71 (d, $J = 10.2$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.5, 25.5, 34.3, 41.8, 43.7, 75.3, 206.7; IR (neat): 3471, 2923, 1702, 1466, 1385, 1041, 1005, 887 cm^{-1}; enantiomeric excess 95%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane = 5/95), UV 254 nm, flow rate 1.0 mL/min, $t_R = 11.656$ min (minor); $t_R = 9.242$ min (major); HRMS (ESI) for $C_9H_{18}SO_2Na$: calcd: 213.0920; found: 213.0921.

4.15. 1-Methylthio-4-hydroxy-5-methyl-hexan-2-one 3m

Yield: 48%, $[\alpha]_D^{20} = +48.9$ (*c* 0.8, DCM); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.91–0.95 (m, 6H), 1.64–1.75 (m, 1H), 2.07 (s, 3H), 2.42 (br s, 1H), 2.65–2.83 (m, 2H), 3.20 (s, 2H), 3.80–3.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.5, 17.6, 18.3, 33.2, 43.6, 43.7, 72.6, 206.5; IR (neat): 3483, 2956, 1701, 1364, 1087, 1011, 801 cm^{-1}; enantiomeric excess: >99%, determined by HPLC (Daicel Chiralpak AD, *i*-PrOH/hexane = 5/95), UV 254 nm, flow rate 1.0 mL/min, $t_R = 13.717$ min (minor); $t_R = 12.304$ min (major); HRMS (ESI) for $C_8H_{16}SO_2Na$: calcd: 199.0763; found: 199.0765.

4.16. 1-Methylthio-4-(cyclohexyl)-4-hydroxy-2-butanone 3n

Yield: 59%, $[\alpha]_D^{20} = +42.8$ (*c* 0.5, DCM); mp = 48–50 °C (DCE); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.02–1.79 (m, 11H), 2.07 (s, 3H), 2.72–2.80 (m, 3H), 3.20 (s, 2H), 3.81–3.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 15.6, 26.0, 26.1, 26.4, 28.2, 28.8, 43.1, 43.7, 43.9, 72.1, 206.7; IR (neat): γ 3395, 2921, 2851, 1703, 1446, 1270, 1082, 892, 555 cm^{-1}; enantiomeric excess: >99%, determined by HPLC (Daicel Chiralpak AD,

i-PrOH/hexane = 5/95), UV 254 nm, flow rate 1.0 mL/min, $t_R = 16.945$ min (minor); $t_R = 14.108$ min (major); HRMS (ESI) for $C_{11}H_{20}SO_2Na$: calcd: 239.1076; found: 239.1075.

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