Asymmetric Induction by (*S*)-4-Isopropyl-1-phenylimidazolidin-2-thione in Titanium-Mediated Aldol Reactions and Its Application in Enantioselective Synthesis of (*R*)-Baclofen

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Abstract: The usefulness of (*S*)-4-isopropyl-1-phenylimidazolidin-2-thione as a chiral auxiliary in stereoselective propionate and acetate aldol reactions is discussed. Further, the enantioselective synthesis of (*R*)-baclofen by acetate aldol reaction using the chiral auxiliary was demonstrated.

Key words: titanium, aldol reaction, asymmetric synthesis, chiral auxiliaries, stereoselectivity

The stereoselectivity in kinetically controlled aldol reaction is defined by enolate geometry where new stereocenters are created. For sterically demanding *Z*- and *E*-lithium enolates a high level of diasteroselection have been reported, forming the *erythro* and *threo* aldol adducts, respectively.[1] The reactions are assumed to proceed through pericyclic transition states and greater stereochemical control has been achieved by increasing the pseudo 1,3-diaxial interaction between the aldehyde substituent and the metal ligands. Using boron enolates, it was demonstrated that minimizing the metal–oxygen and metal–ligand bond lengths and maximizing the bulk of the ligand results in a high degree of diastereoselection.[2]

Masamune had successfully employed the strategy of chiral boron enolates to obtain enantiopure aldol adducts for the synthesis of the biosynthetic precursor 6-deoxyerythronolide,[3a] while Evans and co-workers demonstrated the usefulness of oxazolidinone and (1*S*,2*R*)-norephidrine as chiral auxiliaries in *erythro* selective aldol condensations.[3b] Unfortunately the high level of asymmetric induction observed with *N*-propionyloxazolidinone was not reflected in the case of *N*-acetyloxazolidinone. Titanium enolates are also known to afford stereoselectivity comparable to that of the boron enolates.[4] It has been exemplified that the stereoselectivity in titanium-mediated aldol reactions is dependent on the amine base. The titanium-mediated aldol reaction remains appealing to the synthetic chemists on account of the advantages like low cost, low toxicity, and ease of handling.[5] Heathcock had examined the scope of Evans asymmetric aldol reaction for *anti*- and non-Evans *syn*-aldols in Lewis acid mediated reactions of boron enolates, providing access to either of the desired product diastereoselectively.[6] Open transition states were hypothesized for the reactions where the bulk of the Lewis acid was thought to have a significant bearing on the outcome. Fujita and Nagao had successfully employed 4-alkylthiazolidinethione as a chiral auxiliary in aldol type reactions of α,β-unsaturated aldehydes, using tin(II) triflate as the Lewis acid.[7a] A chiral synthesis of (+)-Prelog–Djerassi lactonic acid methyl ester had been illustrated by chiral induction using thiazolidinethione.[7b] Lithium and titanium(IV) enolates of conformationally rigid camphor-derived *N*-propionyloxazolidinones exhibited *syn*-selective aldol condensation.[8] The diastereofacial selectivity is attributed to intramolecular chelation between the oxazolidinone carbonyl oxygen and the metal in the transition state, which induces π-facial differentiation of the enolate. Significant improvement in aldol reaction to obtain either Evans or non-Evans *syn*-aldol in high diasteromeric purity was illustrated by changing the stoichiometry of the Lewis acid and the nature of the amine base in the reactions of titanium enolates of *N*-acyloxazolidinethiones and thiazolidinethiones.[9,10a,b] It has been proposed that the reactions proceed through a highly ordered and rigid transition state due to the higher affinity of titanium for sulfur. Though expensive, the use of (–)-sparteine with $TiCl_4$ afforded higher selectivities, while the mechanistic details are unclear.[10] The (thio)oxazolidinethione auxiliaries are easily cleavable, facilitating the transformation of the aldol adducts to various functional groups.[10d]

The aldol reactions of boron enolates of *N*-propionyl-2-imidazolidinones, synthesized from L-valinol and L-phenylalaninol, with aldehydes afforded high diastereoselectivity.[11] The utility of these auxiliaries were also explored for stereoselective alkylation reactions, and Diels–Alder reactions.[12] The acetate aldol reaction of valine-derived oxazolidinethione auxiliary is known to occur in high diastereoselectivity with aliphatic aldehydes. Titanium(IV) chloride, along with (–)-sparteine and *N*-methylpyrrolidinone, was used for enolization.[13] A highly diastereoselective acetate aldol reaction that employed a *tert*-leucine-derived thiazolidinethione auxiliary and dichlorophenylborane has also been reported.[14] *N*-Acetylthiazolidinethione undergoes highly diastereoselective aldol reactions upon enolization with dichlorophenylborane and (–)-sparteine and subsequent treatment with a variety of aldehydes.[15] Acetate aldol additions using chlorotitanium enolates of mesityl-substituted *N*-acetyloxazolidinethione

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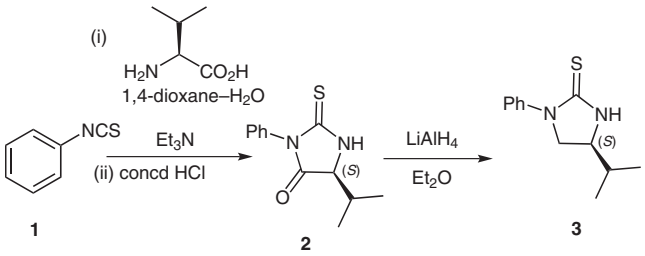
and *N*-acetylthiazolidin-2-thione auxiliaries also proceed in high yields and diastereoselectivities for aliphatic, aromatic, and α,β-unsaturated aldehydes.[16] A highly diastereoselective *anti*-aldol reaction with chiral acyloxazolidinone promoted by catalytic amount of $MgCl_2$ in the presence of triethylamine and chlorotrimethylsilane was reported.[17] Computational investigations on the aldol reactions of the chiral titanium enolates derived from Evans propionyloxazolidinone and its variants, oxazolidinethione and thiazolidinethione led to the identification of a nonchelated transition state pathway for the Evans *syn*-aldol and a chelated transition state pathway for the non-Evans *syn*-aldol.[18] With the support of the exhaustive literature available on aldol reactions,[19] it was intriguing to explore the stereoselectivity in aldol reactions attainable with the *N*-propionyl- and *N*-acetylimidiazolidine-2-thiones, which remains uninvestigated. These systems would have the advantages of the previously discussed auxiliaries incorporated into one template. A UV absorbance (λ_{max}) of 310 nm will facilitate chromatographic monitoring of the reaction. Also a highly organized and chelated transition state can be expected due to the presence of the thione group, providing diastereofacial selectivity in favor of the *syn*-aldol products. The imidazolidin-2-thione may tolerate wider experimental conditions/reagents allowing the release of the aldol adducts from the auxiliary, with the desired functional group transformations.

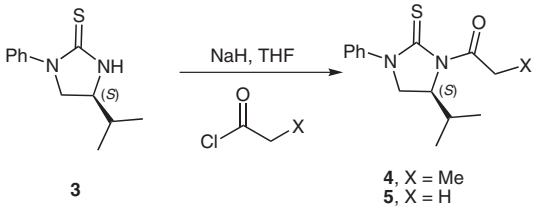
Our current research pursuits on reactions of heterocyclic substrates,[20] prompted us to investigate the aldol reactions of imidazolidin-2-thione nucleus. These substrates could be prepared by a simple and straight forward synthetic strategy from less expensive starting materials. The synthesis as outlined in Scheme 1 involves the addition of phenyl isothiocyanate (**1**) to a solution of L-valine in 1,4-dioxane–water mixture (1:1) at 0 °C in the presence of triethylamine to yield (*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-4-one (**2**).[21] Reduction of **2** with lithium aluminum hydride in anhydrous diethyl ether afforded (*S*)-4-isopropyl-1-phenylimidazolidin-2-thione (**3**) in 60% yield with 97% ee. Recrystallization in methanol afforded the desired product with 99% ee, as determined by chiral HPLC.

To investigate the aldol reactions, N-propionylated **4** and N-acetylated **5** derivatives of (*S*)-4-isopropyl-1-phenylimidazolidin-2-thione (**3**) were prepared (Scheme 2). The acidic thioureido proton was removed by treating a solution of the imidazolidin-2-thione (**3**) in anhydrous THF at 0 °C and under N_2 atmosphere with sodium hydride. The



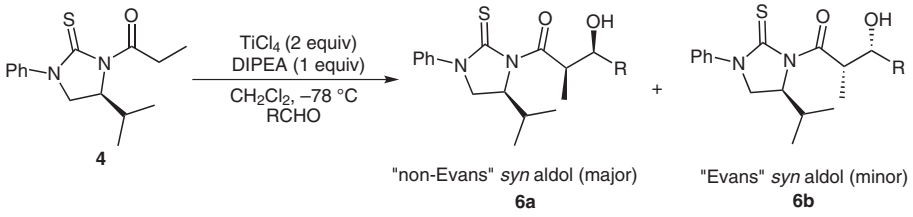
Scheme 1 Synthesis of (*S*)-4-isopropyl-1-phenylimidazolidin-2-thione

reaction mixture was subsequently reacted with the corresponding acid chlorides. After completion of the reaction and workup, the N-acylated products were obtained in reasonable yields.

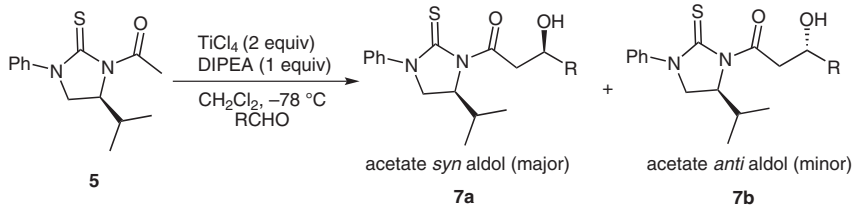


Scheme 2 *N*-acylation of (*S*)-4-isopropyl-1-phenylimidazolidin-2-thione

N-Propionylimidazolidin-2-thione (**4**) was reacted with 2 equivalents of titanium(IV) chloride and 1 equivalent of DIPEA in freshly distilled dichloromethane and under N_2 atmosphere in the presence of benzaldehyde. Chromatographic separation of the crude product afforded two diastereomers of the *syn*-aldol in the ratio 99:01. A vicinal coupling constant[22] of $J_{2',3'} = 4.0$ Hz observed in the NMR spectral data of the major isomer indicated it to be the non-Evans *syn*-aldol, while the other diastereomer turned out to be the Evans *syn*-aldol (Scheme 3). The absolute stereochemistry of the major isomer was further confirmed by hydrolysis of **6a(i)** to furnish the (2*R*,3*R*)-3-hydroxy-2-methyl-3-phenylpropanoic acid [**8a(i)**] (Scheme 6) and measurement of its specific rotation.[23] The high diastereoselectivity observed for non-Evans *syn*-aldol with benzaldehyde was faithfully reproduced in the reactions of aryl aldehydes bearing both electron-withdrawing and electron-donating groups (Table 1). Employing one equivalent of $TiCl_4$ with DIPEA gave inconsistent results. Aliphatic aldehydes like propionaldehyde and isobutyraldehyde gave good diastereoselectivity. The reaction with α,β-unsaturated compound, *trans*-cinnamaldehyde also afforded a high diastereoselectivity.

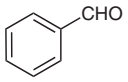
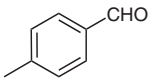
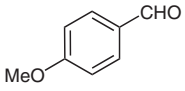
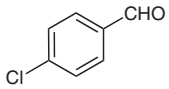
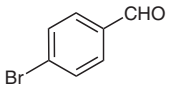
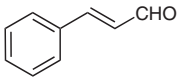


Scheme 3 Aldol reactions of *N*-propionylimidazoldin-2-thione



Scheme 4 Aldol reactions of *N*-acetylimidazoldin-2-thione

Table 1 Reactions of Aldehydes with Titanium Enolate of *N*-Propionylimidazoldin-2-thione

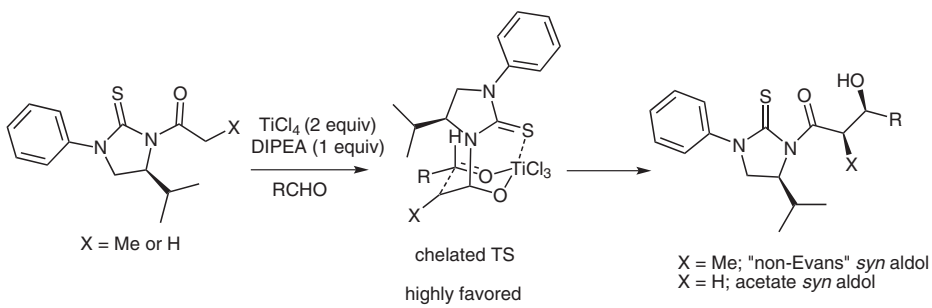
Entry	Aldehyde	Product	Yield (%)[a]	dr (**6a/6b**)[b]
1		**6a(i):6b(i)**	65	99:1
2		**6a(ii):6b(ii)**	63	98:2
3		**6a(iii):6b(iii)**	70	99:1
4		**6a(iv):6b(iv)**	68	99:1
5		**6a(v):6b(v)**	67	99:1
6		**6a(vi):6b(vi)**	61	93:7
7		**6a(vii):6b(vii)**	72	93:7
8		**6a(viii):6b(viii)**	69	90:10

[a] Total yield of the isomers after chromatographic purification.
[b] The diastereomeric ratio was determined from ^{1}H NMR spectra and HPLC of the crude product.

Our efforts were further directed to examine the diastereoselectivity in acetate aldol reactions. *N*-Acetylimidazolidin-2-thione (**5**) was subjected to aldol reactions with aldehydes using 2 equivalents of $TiCl_4$ and 1 equivalent of DIPEA (Scheme 4). As expected, the reactions favored the *syn*-aldol products. ^{1}H NMR spectrum of the aldol product obtained from the typical reaction of the titanium enolate with benzaldehyde indicated the characteristic chemical shifts for the α-protons at 3.81 ppm (dd, J = 17.2, 9.4 Hz) and 4.05 ppm (dd, J = 17.2, 3.0 Hz). The minor less polar *anti*-product showed the corresponding chemical shift values at 3.72 ppm (dd, J = 16.5, 3.0 Hz) and 4.17 ppm (dd, J = 16.5, 9.6 Hz), respectively.[10b] The absolute stereochemistry of the product was further confirmed by hydrolysis of the compound **7a(i)** to afford (*R*)-3-hydroxy-3-phenylpropanoic acid [**9a(i)**] (Scheme 6) and measurement of its specific rotation.[24] Very high diastereoselectivity for the *syn*-isomer was observed in the cases of aryl aldehydes (Table 2). A similar pattern was witnessed with pivaldehyde and α,β-unsaturated aldehydes, while the selectivity with propionaldehyde and isobutyraldehyde were only moderate.

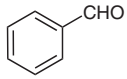
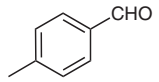
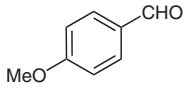
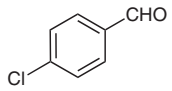
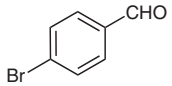
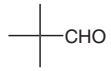
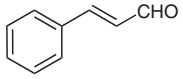
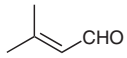
Concordant with the well validated theories we propose a chelated transition state for the observed selectivity (Scheme 5). The thiophilic nature of the titanium leading to chelation is contemplated in this model, affording the acetate *syn*-aldol with *N*-acetylimidazolidin-2-thione and the non-Evans *syn*-aldol with *N*-propionylimidazolidin-2-thione. The steric factors appear to play a prominent role in the diastereoselectivity. Overall, very high selectivities were observed with aryl aldehydes when compared to aliphatic aldehydes. Various other parameters like solvent effect, chelation, dipole moment etc. could also contribute to the stereoselectivity in aldol reactions.[3b,6,25]

The aldol adducts were successfully cleaved from the chiral acetate and propionate templates under various reaction conditions to afford different chiral intermediates



Scheme 5 Proposed transition state models for the formation of aldol diastereomers

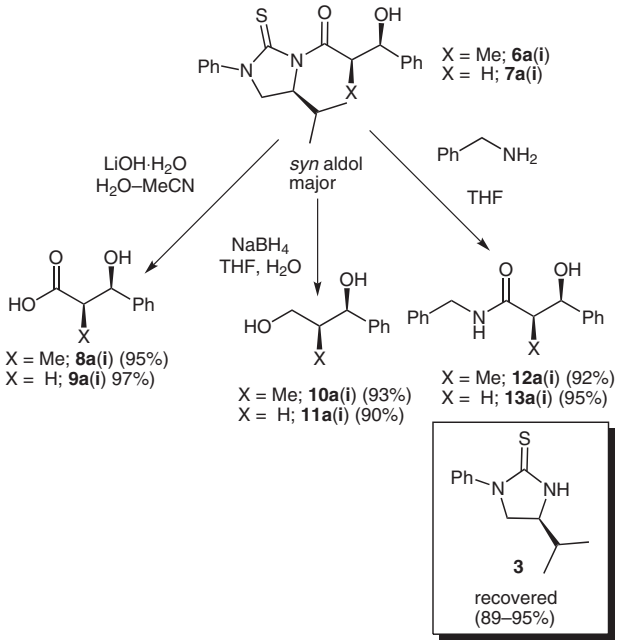
Table 2 Reactions of Aldehydes with Titanium Enolate of *N*-Acetylimidazoldin-2-thione

Entry	Aldehyde	Product	Yield (%)[a]	dr (**7a/7b**)[b]
1		**7a(i)**:**7b(i)**	77	90:10
2		**7a(ii)**:**7b(ii)**	68	97:3
3		**7a(iii)**:**7b(iii)**	65	99:1
4		**7a(iv)**:**7b(iv)**	69	98:2
5		**7a(v)**:**7b(v)**	72	92:8
6		**7a(vi)**:**7b(vi)**	73	98:2
7		**7a(vii)**:**7b(vii)**	75	99:1
8		**7a(viii)**:**7b(viii)**	60	98:2

[a] Total yield of the isomers after chromatographic purification.
[b] The diastereomeric ratio was determined from ^{1}H NMR and HPLC of the crude product.

demonstrating the usefulness of the auxiliary. Reaction with LiOH in acetonitrile–water medium afforded β-hydroxy carboxylic acids **8**, **9**. Reduction with $NaBH_4$ yielded the corresponding alcohols **10**, **11** and reactions with amines gave the respective amides **12**, **13** (Scheme 6). The chiral auxiliary was quantitatively recovered in all the cases and successfully reused. Subsequently the usefulness of this auxiliary was explored in the enantioselective synthesis of (*R*)-baclofen, a drug molecule. Baclofen, an antispasmodic drug and a lipophilic analogue of the neurotransmitter GABA (γ-aminobutyric acid), is administered as racemic mixture, but the biological activity mainly resides with the *R*-enantiomer.[26a]

A few reports are available on the stereoselective synthesis of (*R*)-baclofen through resolution,[26] chemoenzymatic,[27] or by asymmetric synthesis/organocatalysis.[28] Synthesis of (*R*)-baclofen using Evans auxiliary involved a lengthy procedure.[29,30] The high stereoselectivity observed in acetate aldol reactions of aryl aldehydes using the auxiliary prompted us to explore its efficiency in the stereospecific synthesis of (*R*)-baclofen. Thus, an acetate type aldol approach attempted with *N*-acetylimidazolidin-2-thione and 4-chlorobenzaldehyde afforded the *syn*- and *anti*-aldol adducts in a ratio of 98:02 (Scheme 7). The desired *syn* aldol product was purified and cleaved with K_2CO_3 in ethanol medium to obtain ethyl (*R*)-3-hydroxy-

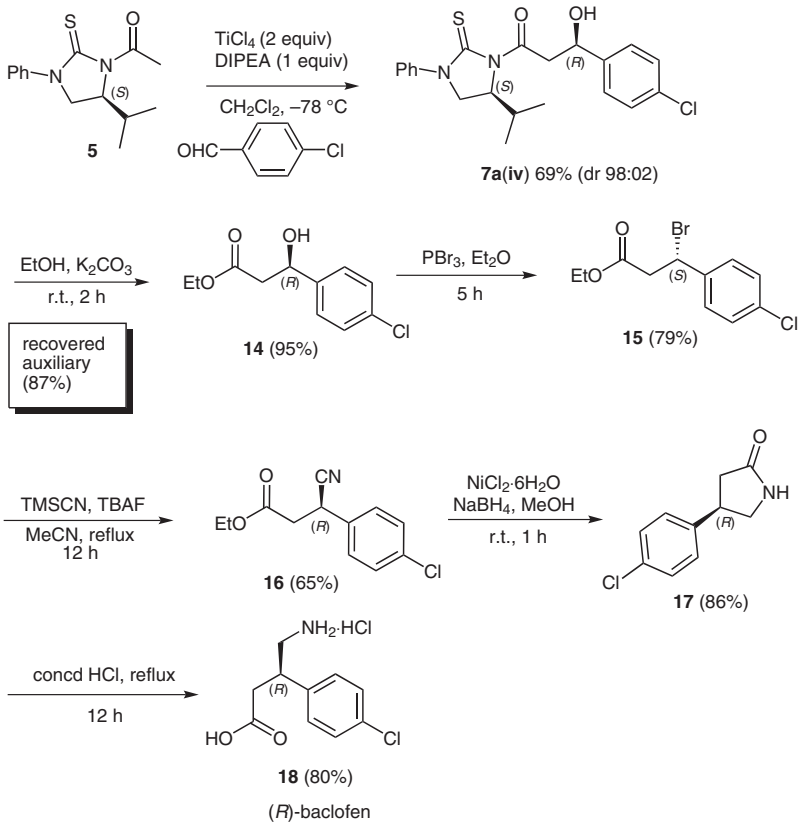


Scheme 6 Cleavage of the aldol products **6a(i)** and **7a(i)**

3-(4-chlorophenyl)propanoate (**14**). It was subsequently converted into ethyl (*S*)-3-bromo-3-(4-chlorophenyl)propanoate (**15**) with PBr_3, and then to ethyl (*R*)-3-cyano-3-(4-chlorophenyl)propanoate (**16**) with TMSCN/TBAF[31] under reflux conditions. Reduction using $NiCl_2/NaBH_4$ gave (*R*)-4-(4-chlorophenyl)pyrrolidin-2-one (**17**), and hydrolysis by concentrated HCl under reflux afforded the (*R*)-baclofen hydrochloride salt **18** in good yields and high enantiopurity.

To conclude, the efficiency of (*S*)-4-isopropyl-1-phenylimidazolidin-2-thione as a chiral auxiliary in stereoselective propionate and acetate aldol reactions were examined. The reactions are expected to proceed through a highly organized chelated transition state. Further, the utility of the auxiliary in the enantioselective synthesis of (*R*)-baclofen was demonstrated. A detailed investigation of this auxiliary in metal-mediated reactions is currently underway.

The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on Bruker Avance DPX 400 spectrometers in $CDCl_3$ using TMS as the internal standard. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvent. Coupling constants are given in Hz. Standard abbreviations are used to indicate the multiplicity. Specific rotations were taken on Rudolph Autopol IV instrument and HRMS spectra were recorded on Bruker Maxis TOF. The reactions were monitored by TLC (Merck). Evaporation of solvents was performed under reduced pressure using a rotary evaporator. Melting points are uncorrected. Commercial grade reagents and solvents were used without further purification: diisopropylamine (DIPEA), Et_3N, $CSCl_2$, 1,4-dioxane, benzaldehyde, *trans*-cinnamaldehyde, 4-bromobenzaldehyde, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, propionaldehyde, isobutyraldehyde, 4-methylbenzaldehyde, trimethylsilyl cyanide (TMSCN), PBr_3, LiOH, CH_2Cl_2, THF (Spectrochem), $TiCl_4$, 3-methylbut-2-enal, trimethylacetaldehyde, $NiCl_2$, Bu_4NF (TBAF)



Scheme 7 Stereospecific synthesis of (*R*)-baclofen

(Aldrich), and NH_4Cl, $NaHCO_3$, and $NaBH_4$ (CDH). THF was dried by distillation over sodium metal and benzophenone. CH_2Cl_2 was dried by distillation over CaH_2.

(*S*)-5-Isopropyl-3-phenyl-2-thioxoimidazolidin-4-one (2)

L-Valine (5.0 g, 42.7 mmol, 1.0 equiv) was added to a solution of phenyl isothiocyanate (5.8 mL, 42.7 mmol, 1.0 equiv) in 1,4-dioxane–H_2O (100 mL; 1:1, v/v) and cooled to 0 °C. Et_3N (11.9 mL, 85.4 mmol, 2.0 equiv) was added slowly to it and the solution was stirred for 1 h, followed by the addition of concd HCl (13.0 mL, 128.1 mmol, 3.0 equiv) at 0 °C until the pH became ~2. The reaction mixture was stirred for another 12 h at r.t., and the precipitate formed was filtered and dried to yield the desired compound **2** (9.5 g, 95%); white solid; mp 148–151 °C; $[\alpha]_D^{20}$ –54.4 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.8 Hz, 3 H), 1.15 (d, *J* = 6.8 Hz, 3 H), 2.38–2.40 (m, 1 H), 4.18–4.20 (m, 1 H), 7.19–7.34 (m, 2 H), 7.39–7.60 (m, 3 H), 8.04 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.21, 18.80, 31.18, 64.99, 128.26, 129.21, 129.32, 132.61, 172.97, 184.29.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{14}N_2OS$ ([M + Na]$^+$): 257.0725; found: 257.0722.

(*S*)-4-Isopropyl-1-phenylimidazolidin-2-thione (3)

To a stirred solution of **2** (5.0 g, 21.4 mmol, 1.0 equiv) in anhyd Et_2O (100 mL) under N_2 atmosphere was added $LiAlH_4$ (8.2 g, 214.0 mmol, 10.0 equiv) portionwise at 0 °C. The reaction mixture was stirred at reflux for 12 h, cooled, and slowly quenched with aq NaOH (1 M, 30 mL) to form a slurry, which was filtered through a Celite bed. The filtrate was taken in EtOAc (100 mL), washed with brine (50 mL), dried (Na_2SO_4), and evaporated under vacuum to give a crude solid. The crude product was purified by column chromatography on silica gel (60–120 mesh) by eluting with a mixture of EtOAc–hexane (20:80) to give the title compound **3** (2.8 g, 60%); white solid; mp 63–65 °C; $[\alpha]_D^{20}$ –35.4 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.8 Hz, 3 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.81–1.86 (m, 1 H), 3.72–3.76 (m, 1 H), 3.82–3.86 (m, 1 H), 4.17–4.20 (m, 1 H), 6.62 (br s, 1 H), 7.22–7.24 (m, 1 H), 7.37–7.42 (m, 2 H), 7.55–7.58 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.94, 18.10, 32.76, 55.65, 59.55, 124.40, 126.35, 128.78, 139.92, 181.95.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{16}N_2S$ ([M + Na]$^+$): 243.0932; found: 243.0938.

(*S*)-*N*-Propionyl-4-isopropyl-1-phenylimidazolidin-2-thione (4) and (*S*)-*N*-Acetyl-4-isopropyl-1-phenylimidazolidin-2-thione (5)

To a stirred solution of **3** (1.0 g, 4.5 mmol, 1.0 equiv) in anhyd THF (20 mL) under N_2 atmosphere was added NaH (0.2 g, 4.9 mmol, 1.1 equiv) portionwise at 0 °C. After 1 h, propionyl or acetyl chloride (1.1 equiv) was added dropwise and the mixture was stirred for 1 h. The reaction mixture was washed with aq $NaHCO_3$ (20 mL), dried (Na_2SO_4), evaporated under vacuum to give a gum, which solidified in *n*-hexane on refrigeration for 2 days.

4

Yield: 1.2 g (97%); white solid; mp 64–67 °C; $[\alpha]_D^{20}$ +98.2 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 1.20 (t, *J* = 7.3 Hz, 3 H), 2.36–2.49 (m, 1 H), 3.33 (dq, *J* = 17.8, 7.2 Hz, 1 H), 3.51 (dq, *J* = 17.8, 7.4 Hz, 1 H), 3.64 (dd, *J* = 10.7, 2.4 Hz, 1 H), 4.06 (dd, *J* = 10.8, 9.3 Hz, 1 H), 4.73 (ddd, *J* = 9.3, 3.6, 2.4 Hz, 1 H), 7.32–7.40 (m, 3 H), 7.42–7.50 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.05, 15.00, 18.19, 29.51, 31.86, 50.27, 60.32, 126.14, 127.91, 129.36, 139.92, 175.80, 179.15.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{15}H_{20}N_2OS$ ([M + H]$^+$): 277.1375; found: 277.1378.

5

Yield: 1.15 g (98%); white solid; mp 62–65 °C; $[\alpha]_D^{20}$ +125.2 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 2.44 (m, *J* = 6.9, 3.7 Hz, 1 H), 2.89 (s, 3 H), 3.65 (dd, *J* = 10.7, 2.4 Hz, 1 H), 4.06 (dd, *J* = 10.7, 9.2 Hz, 1 H), 4.73 (ddd, *J* = 9.2, 3.6, 2.3 Hz, 1 H), 7.33–7.41 (m, 3 H), 7.43–7.50 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.97, 18.20, 27.11, 29.41, 50.24, 60.19, 126.09, 128.00, 129.41, 139.84, 172.01, 179.45.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{14}H_{18}N_2OS$ ([M + H]$^+$): 263.1218; found: 263.1222.

Aldol Reaction of 4 with Aldehydes; (2*R*,3*R*)-3-Hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-2-methyl-3-phenylpropan-1-one [6a(i)]; Typical Procedure

To a stirred solution of **4** (0.2 g, 0.72 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at –78 °C and under N_2 atmosphere was added $TiCl_4$ (1.44 mL, 1.44 mmol, 2.0 equiv, 1.0 M in CH_2Cl_2), followed by DIPEA (0.12 mL, 0.72 mmol, 1.0 equiv) after 10 min. Stirring was continued for 1 h and then benzaldehyde (0.08 mL, 0.72 mmol, 1.0 equiv) was introduced into the reaction. The reaction mixture was quenched after 30 min with sat. aq NH_4Cl (5 mL). The CH_2Cl_2 layer was washed with brine (10 mL), dried (Na_2SO_4), and concentrated under vacuum to obtain a crude mixture. Separation of the mixture by column chromatography using a combination of EtOAc–hexane (25:75) as the eluent on silica gel (230–400 mesh) afforded the diastereomers of the aldol adduct; yield: 0.18 g (65%); gum; $[\alpha]_D^{20}$ +153.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H), 1.13 (d, *J* = 6.8 Hz, 3 H), 2.22–2.29 (m, 1 H), 3.60 (dd, *J* = 10.8, 2.3 Hz, 1 H), 4.00 (dd, *J* = 10.8, 9.3 Hz, 1 H), 4.72–4.74 (m, 1 H), 5.26 (d, *J* = 4.0 Hz, 1 H), 5.60 (dd, *J* = 6.8, 4.0 Hz, 1 H), 7.19–7.28 (m, 1 H), 7.28–7.37 (m, 4 H), 7.39–7.51 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.34, 14.83, 18.20, 29.50, 43.97, 49.97, 60.34, 74.03, 126.47, 127.27, 128.17, 128.42, 129.45, 129.50, 139.66, 141.62, 178.47, 178.64.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{22}H_{26}N_2O_2S$ ([M + Na]$^+$): 405.1613; found: 405.1620.

(2*R*,3*R*)-3-Hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-2-methyl-3-*p*-tolylpropan-1-one [6a(ii)]

Gum; $[\alpha]_D^{20}$ +110.4 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 3.5 Hz, 3 H), 1.12 (d, *J* = 8.3 Hz, 3 H), 2.16–2.31 (m, 1 H), 2.40 (s, 3 H), 3.60 (dd, *J* = 10.7, 3.2 Hz, 1 H), 3.99 (dd, *J* = 10.7, 9.2 Hz, 1 H), 4.71–4.75 (m, 1 H), 5.21 (d, *J* = 4.1 Hz, 1 H), 5.59 (dd, 6.8, 4.1 Hz, 1 H), 7.12 (d, *J* = 7.9 Hz, 2 H), 7.32–7.37 (m, 5 H), 7.34–7.37 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.37, 14.79, 18.20, 21.14, 29.50, 44.02, 49.96, 60.30, 74.01, 126.38, 128.14, 128.79, 129.17, 129.44, 130.18, 138.63, 139.71, 178.50, 178.67.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{28}N_2O_2S$ ([M + Na]$^+$): 419.1769; found: 419.1776.

(2*R*,3*R*)-3-Hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-3-(4-methoxyphenyl)-2-methylpropan-1-one [6a(iii)]

Gum; $[\alpha]_D^{20}$ +21.8 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.66–0.95 (m, 6 H), 1.15 (d, *J* = 6.7 Hz, 3 H), 2.21–2.24 (m, 1 H), 3.61 (dd, *J* = 10.8, 4.3 Hz, 1 H), 3.78 (s, 3 H), 4.01 (dd, *J* = 10.8, 9.1 Hz, 1 H), 4.72–4.74 (m, 1 H), 5.19 (d, *J* = 4.0 Hz, 1 H), 5.57 (dd, *J* = 6.7, 4.0 Hz, 1 H), 6.85–6.93 (m, 2 H), 7.34–7.45 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.60, 14.86, 18.31, 29.59, 44.09, 50.00, 55.36, 60.37, 73.59, 113.55, 126.29, 127.74, 128.30, 129.58, 133.84, 139.72, 158.88, 178.47, 178.73.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{28}N_2O_3S$ ([M + Na]$^+$): 435.1718; found: 435.1719.

(2*R*,3*R*)-3-(4-Chlorophenyl)-3-hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-2-methylpropan-1-one [6a(iv)]

Gum; $[\alpha]_D^{20}$ +63.2 (*c* 0.25, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92–0.95 (m, 6 H), 1.09 (d, *J* = 6.0 Hz, 3 H), 2.13–2.22 (m, 1 H), 3.64 (dd, *J* = 10.5, 3.8 Hz, 1 H), 4.05 (dd, *J* = 10.5, 9.1 Hz, 1 H), 4.73–4.75 (m, 1 H), 5.24 (d, *J* = 3.9 Hz, 1 H), 5.58 (dd, *J* = 6.5, 3.9 Hz, 1 H), 7.29–7.31 (m, 2 H), 7.33–7.38 (m, 3 H), 7.42 (d, *J* = 7.7 Hz, 2 H), 7.47 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.17, 14.91, 18.30, 29.66, 43.72, 50.12, 60.58, 73.40, 126.15, 126.24, 127.92, 128.31, 128.39, 129.61, 139.54, 140.84, 178.40, 178.70.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{22}H_{25}ClN_2O_2S$ ([M + Na]$^+$): 439.1223; found: 439.1226.

(2*R*,3*R*)-3-(4-Bromophenyl)-3-hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-2-methylpropan-1-one [6a(v)]

Gum; $[\alpha]_D^{20}$ +148.4 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 3.5 Hz, 3 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 2.27–2.29 (m, 1 H), 3.60–3.63 (m, 1 H), 4.02–4.05 (m, 1 H), 4.71–4.74 (m, 1 H), 5.21 (d, *J* = 3.8 Hz, 1 H), 5.58 (dd, *J* = 6.7, 3.8 Hz, 1 H), 7.32–7.39 (m, 5 H), 7.42–7.49 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.87, 14.95, 18.19, 29.66, 42.48, 50.19, 60.57, 73.82, 126.61, 128.24, 128.49, 128.95, 129.49, 131.27, 136.93, 139.66, 177.62, 178.91.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{22}H_{25}BrN_2O_2S$ ([M + Na]$^+$): 483.0718; found: 483.0723.

(2*R*,3*S*)-3-Hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-2-methylpentan-1-one [6a(vi)]

Gum; $[\alpha]_D^{20}$ +257.4 (*c* 0.25, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82–1.01 (m, 9 H), 1.16 (d, *J* = 6.6 Hz, 3 H), 1.51–1.62 (m, 2 H), 2.39–2.43 (m, 1 H), 3.65 (dd, *J* = 10.7, 2.4 Hz, 1 H), 3.95–3.99 (m, 1 H), 4.04 (dd, *J* = 10.7, 9.2 Hz, 1 H), 4.76 (ddd, *J* = 9.1, 3.7, 2.4 Hz, 1 H), 5.26 (dq, *J* = 6.9, 4.0 Hz, 1 H), 7.34–7.38 (m, 2 H), 7.45–7.49 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.51, 10.54, 15.00, 18.21, 26.50, 29.63, 41.33, 50.11, 60.47, 73.67, 126.18, 128.17, 129.46, 139.67, 178.86, 179.22.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{18}H_{26}N_2O_2S$ ([M + H]$^+$): 335.1793; found: 335.1797.

(2*R*,3*S*)-3-Hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-2,4-dimethylpentan-1-one [6a(vii)]

Gum; $[\alpha]_D^{20}$ +105.4 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93–0.98 (m, 9 H), 1.06 (d, *J* = 6.5 Hz, 3 H), 1.18 (d, *J* = 6.5 Hz, 3 H), 1.70–1.78 (m, 1 H), 2.37–2.44 (m, 1 H), 3.63–3.65 (m, 2 H), 4.06 (dd, *J* = 10.9, 9.2 Hz, 1 H), 4.75 (ddd, *J* = 9.2, 3.7, 2.4 Hz, 1 H), 5.42 (dq, *J* = 6.9, 3.8 Hz, 1 H), 7.32–7.37 (m, 3 H), 7.34–7.37 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.33, 14.95, 18.24, 18.94, 19.53, 29.57, 30.98, 39.53, 50.02, 60.40, 76.98, 126.17, 128.12, 129.43, 139.69, 178.71, 180.13.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{28}N_2O_2S$ ([M + H]$^+$): 349.1950; found: 349.1954.

(2*R*,3*S*,*E*)-3-Hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-2-methyl-5-phenylpent-4-en-1-one [6a(viii)]
Gum; $[\alpha]_D^{20}$ +40.6 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94–0.98 (m, 6 H), 1.26 (d, *J* = 6.9 Hz, 3 H), 2.40–2.42 (m, 1 H), 3.64 (dd, *J* = 10.8, 2.4 Hz, 1 H), 4.05 (dd, *J* = 10.8, 9.2 Hz, 1 H), 4.78–4.82 (m, 2 H), 5.48–5.50 (m, 1 H), 6.32 (dd, *J* = 6.0, 15.8 Hz, 1 H), 6.70 (d, *J* = 15.8 Hz, 1 H), 7.21–7.25 (m, 1 H), 7.30–7.33 (m, 2 H), 7.37–7.39 (m, 5 H), 7.39–7.43 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.87, 14.95, 18.19, 29.66, 42.48, 50.19, 60.57, 73.82, 126.21, 126.61, 127.50, 128.24, 128.49, 128.95, 129.49, 131.27, 136.93, 139.66, 177.62, 178.91.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{24}H_{28}N_2O_2S$ ([M + Na]$^+$): 431.1769; found: 431.1779.

(*R*)-3-Hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-3-phenylpropan-1-one [7a(i)]
Gum; $[\alpha]_D^{20}$ +152.9 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (dd, *J* = 6.8 Hz, 3 H), 0.97 (dd, *J* = 6.8 Hz, 3 H), 2.42–2.44 (m, 1 H), 3.63 (dd, *J* = 10.8, 2.3 Hz, 1 H), 3.81 (dd, *J* = 17.2, 9.4 Hz, 1 H), 3.95–4.00 (m, 1 H), 4.05 (dd, *J* = 17.2, 3.0 Hz, 1 H), 4.72 (ddd, *J* = 9.1, 3.7, 2.3 Hz, 1 H), 5.25–5.31 (m, 1 H), 7.24–7.30 (m, 1 H), 7.31–7.38 (m, 5 H), 7.41–7.48 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.08, 18.18, 29.66, 46.45, 50.45, 60.47, 70.55, 125.92, 126.07, 127.51, 128.13, 128.43, 129.43, 139.58, 142.83, 173.84, 178.82.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{24}N_2O_2S$ ([M + Na]$^+$): 391.1456; found: 391.1462.

(*R*)-3-Hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-3-*p*-tolylpropan-1-one [7a(ii)]
Gum; $[\alpha]_D^{20}$ +146.7 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.7 Hz, 3 H), 0.86 (d, *J* = 6.7 Hz, 3 H), 2.42–2.45 (m, 1 H), 3.65 (dd, *J* = 10.8, 2.3 Hz, 1 H), 3.78 (s, 3 H), 3.84 (dd, *J* = 17.0, 9.0 Hz, 1 H), 3.97–4.07 (m, 2 H), 4.74 (ddd, *J* = 9.0, 3.8, 2.3 Hz, 1 H), 5.26 (dd, *J* = 9.3, 2.8 Hz, 1 H), 6.86–6.93 (m, 2 H), 7.34–7.40 (m, 5 H), 7.42–7.50 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.07, 18.20, 29.64, 46.55, 50.41, 55.29, 60.45, 70.16, 113.80, 126.05, 127.22, 128.13, 129.44, 135.07, 139.59, 158.97, 173.84, 178.80.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{26}N_2O_2S$ ([M + Na]$^+$): 405.1613; found: 405.1790.

(*R*)-3-Hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-3-(4-methoxyphenyl)propan-1-one [7a(iii)]
Gum; $[\alpha]_D^{20}$ +78.6 (*c* 0.50, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89–0.91 (m, 6 H), 2.28–2.42 (m, 1 H), 3.58 (dd, *J* = 10.5, 2.3 Hz, 1 H), 3.72 (s, 3 H), 3.78 (dd, *J* = 17.1, 9.0 Hz, 1 H), 3.89 (dd, *J* = 10.5, 9.1 Hz, 1 H), 4.00 (dd, *J* = 17.1, 3.7 Hz, 1 H), 4.67 (ddd, *J* = 9.0, 3.7, 2.3 Hz, 1 H), 5.11–5.27 (m, 1 H), 6.81 (d, *J* = 7.3 Hz, 2 H), 7.21–7.34 (m, 5 H), 7.34–7.43 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.14, 18.19, 29.61, 46.61, 50.48, 55.38, 60.53, 70.24, 113.87, 126.18, 127.29, 128.27, 129.56, 135.03, 139.63, 159.06, 174.00, 178.69.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{22}H_{26}N_2O_3S$ ([M + Na]$^+$): 421.1562; found: 421.1554.

(*R*)-3-(4-Chlorophenyl)-3-hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]propan-1-one [7a(iv)]
Gum; $[\alpha]_D^{20}$ +90.4 (*c* 0.50, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84–0.88 (m, 6 H), 2.35 (m, 1 H), 3.56 (dd, *J* = 10.0, 2.5 Hz, 1 H), 3.65 (dd, *J* = 16.5, 9.2 Hz, 1 H), 3.92 (dd, *J* = 10.0, 9.2 Hz, 1 H), 4.00 (dd, *J* = 16.5, 2.5 Hz, 1 H), 4.54–4.78 (m, 1 H), 5.18 (m, 1 H), 7.05–7.31 (m, 7 H), 7.37 (d, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.13, 18.29, 29.71, 46.50, 50.50, 60.55, 69.95, 126.15, 127.44, 128.54, 128.66, 129.59, 133.21, 139.54, 141.40, 173.70, 178.79.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{23}ClN_2O_2S$ ([M + Na]$^+$): 425.1066; found: 425.1069.

(*R*)-3-(4-Bromophenyl)-3-hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]propan-1-one [7a(v)]
Gum; $[\alpha]_D^{20}$ +124.9 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95–0.98 (m, 6 H), 2.37–2.48 (m, 1 H), 3.65 (dd, *J* = 11.0, 2.3 Hz, 1 H), 3.72 (dd, *J* = 17.2, 9.2 Hz, 1 H), 4.01 (dd, *J* = 11.0, 9.0 Hz, 1 H), 4.05 (dd, *J* = 17.2, 2.5 Hz, 1 H), 4.72 (ddd, *J* = 9.1, 3.6, 2.4 Hz, 1 H), 5.24 (dd, *J* = 9.3, 2.8 Hz, 1 H), 7.29–7.39 (m, 5 H), 7.42–7.50 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.06, 18.18, 29.63, 46.30, 50.44, 60.47, 69.92, 121.30, 126.04, 127.68, 128.22, 129.48, 131.50, 139.47, 141.87, 173.58, 178.73.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{21}H_{23}BrN_2O_2S$ ([M + Na]$^+$): 469.0561; found: 469.0562.

(*R*)-3-Hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-4,4-dimethylpentan-1-one [7a(vi)]
Gum; $[\alpha]_D^{20}$ +169.2 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93–1.00 (m, 15 H), 2.41–2.43 (m, 1 H), 3.44 (dd, *J* = 17.1, 10.8 Hz, 1 H), 3.65 (dd, *J* = 10.8, 2.3 Hz, 1 H), 3.79 (dd, *J* = 16.9, 1.9 Hz, 1 H), 3.84 (dd, *J* = 10.8, 1.8 Hz, 1 H), 4.05 (dd, *J* = 10.8, 9.3 Hz, 1 H), 4.75 (ddd, *J* = 9.2, 3.6, 2.3 Hz, 1 H), 7.33–7.38 (m, 3 H), 7.41–7.49 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.09, 18.18, 25.88, 29.67, 34.63, 40.47, 50.43, 60.44, 75.78, 126.14, 128.08, 129.41, 139.67, 175.24, 179.11.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{19}H_{28}N_2O_2S$ ([M + Na]$^+$): 371.1769; found: 371.1777.

(*R*,*E*)-3-Hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-5-phenylpent-4-en-1-one [7a(vii)]
Gum; $[\alpha]_D^{20}$ +99.1 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94–1.02 (m, 6 H), 2.41–2.52 (m, 1 H), 3.62–3.73 (m, 2 H), 3.99 (dd, *J* = 17.2, 3.1 Hz, 1 H), 4.02–4.10 (m, 1 H), 4.77 (ddd, *J* = 9.1, 3.6, 2.4 Hz, 1 H), 4.85–4.94 (m, 1 H), 6.35 (dd, *J* = 15.9, 6.0 Hz, 1 H), 6.73 (d, *J* = 15.9 Hz, 1 H), 7.20–7.28 (m, 1 H), 7.32–7.41 (m, 4 H), 7.42–7.52 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.06, 18.21, 29.62, 44.91, 50.40, 60.43, 69.12, 126.09, 126.58, 127.62, 128.19, 128.56, 129.48, 130.22, 130.46, 136.73, 139.55, 173.66, 178.83.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{26}N_2O_2S$ ([M + Na]$^+$): 417.1613; found: 417.1620.

(*R*)-3-Hydroxy-1-[(*S*)-5-isopropyl-3-phenyl-2-thioxoimidazolidin-1-yl]-5-methylhex-4-en-1-one [7a(viii)]

Gum; $[\alpha]_D^{20}$ +82.1 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95–1.00 (m, 6 H), 1.69–1.76 (m, 6 H), 2.44 (m, 1 H), 3.49 (dd, *J* = 17.4, 8.9 Hz, 1 H), 3.66 (dd, *J* = 10.8, 2.3 Hz, 1 H), 3.77 (dd, *J* = 17.3, 3.0 Hz, 1 H), 4.06 (dd, *J* = 10.8, 9.3 Hz, 1 H), 4.75 (ddd, *J* = 9.2, 3.6, 2.3 Hz, 1 H), 4.83–5.00 (m, 1 H), 5.30 (dd, *J* = 8.7, 1.4 Hz, 1 H), 7.30–7.43 (m, 3 H), 7.43–7.51 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.06, 18.20, 18.37, 25.82, 29.64, 45.29, 50.40, 60.41, 65.41, 125.83, 126.11, 128.14, 129.46, 135.62, 139.61, 174.05, 178.86.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{23}H_{26}N_2O_2S$ ([M + Na]$^+$): 369.1613; found: 369.1617.

Hydroxyphenylpropanoic Acids; (2*R*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid [8a(i)]; Typical Procedure

To a solution of **6a(i)** (0.2 g, 0.52 mmol, 1.0 equiv) in MeCN–H_2O mixture (10 mL, 1:1, v/v) was added LiOH·H_2O (0.1 g, 2.6 mmol, 5.0 equiv) and the mixture was stirred for 2 h. The mixture was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layers were dried (Na_2SO_4), and concentrated under vacuum to recover the chiral auxiliary **3** (0.1 g, 89%). The aqueous layer was acidified, extracted with EtOAc (2 × 10 mL), the combined organic layers were dried (Na_2SO_4), and concentrated to afford the corresponding hydroxy acid **8a(i)** (0.09 g, 95%); mp 90–95 °C; $[\alpha]_D^{20}$ +28.0 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.18 (m, 3 H), 2.80–2.86 (m, 1 H), 5.17–5.18 (d, *J* = 3.9 Hz, 1 H), 7.26–7.32 (m, 1 H), 7.34–7.37 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.26, 46.23, 73.48, 125.97, 127.64, 128.60, 141.07, 180.68.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{10}H_{12}O_3$ ([M + Na]$^+$): 203.0684; found: 203.0681.

(*R*)-3-Hydroxy-3-phenylpropanoic Acid [9a(i)]

Mp 116–118 °C; $[\alpha]_D^{20}$ +54.8 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$); δ = 2.71–2.86 (m, 2 H), 5.15 (dd, *J* = 9.3, 3.8 Hz, 1 H), 7.31 (dd, *J* = 5.5, 3.0 Hz, 1 H), 7.33–7.40 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.04, 70.24, 125.69, 128.00, 128.66, 142.18, 176.55.

HRMS (ESI-TOF): *m*/*z* calcd for $C_9H_{10}O_3$ ([M + Na]$^+$): 189.0528; found: 189.0526.

1,3-Diols; (1*R*,2*S*)-2-Methyl-1-phenylpropane-1,3-diol [10a(i)]; Typical Procedure

To a solution of **6a(i)** (0.2 g, 0.52 mmol, 1.0 equiv) in THF–H_2O mixture (10 mL, 1:1, v/v) was added $NaBH_4$ (0.1 g, 2.6 mmol, 5 equiv), and the mixture was stirred for 1 h at r.t. The reaction mixture was extracted with EtOAc (2 × 10 mL), the combined organic phases were dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography using EtOAc–hexane (1:1) as the eluent to afford the chiral auxiliary (0.1 g, 89%) and the corresponding 1,3-diol **10a(i)** (0.08 g, 93%); mp 73–76 °C; $[\alpha]_D^{20}$ +41.15 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.75–0.77 (d, *J* = 7.0 Hz, 3 H), 1.98–2.06 (m, 1 H), 3.59–3.63 (m, 2 H), 4.07 (br s, 2 H), 4.89–4.90 (d, *J* = 3.4 Hz, 1 H), 6.97–7.04 (m, 1 H), 7.15–7.46 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.62, 41.38, 65.97, 75.95, 126.14, 127.09, 128.08, 142.72.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{10}H_{14}O_2$ ([M + Na]$^+$): 189.0891; found: 189.1387.

(*R*)-1-Phenylpropane-1,3-diol [11a(i)]

Mp 60–64 °C; $[\alpha]_D^{20}$ +50.7 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83–1.93 (m, 2 H), 3.65–3.88 (m, 2 H), 4.92 (dd, *J* = 8.8, 3.8 Hz, 1 H), 5.32 (br s, 2 H), 7.19–7.24 (m, 1 H) 7.29–7.39 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.35, 61.01, 73.79, 125.67, 127.49, 128.46, 144.23.

HRMS (ESI-TOF): *m*/*z* calcd for $C_9H_{12}O_3$ ([M + Na]$^+$): 175.0735; found: 175.0733.

Hydroxy Amides; (2*R*,3*R*)-*N*-Benzyl-3-hydroxy-2-methyl-3-phenylpropanamide [12a(i)]; Typical Procedure

To a solution of **6a(i)** (0.2 g, 0.52 mmol, 1.0 equiv) in THF (10 mL) was added benzylamine (0.06 mL, 0.52 mmol, 1.0 equiv), and the mixture was stirred for 5 h at r.t. The mixture was extracted with EtOAc (2 × 10 mL), the combined organic layers were dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography on silica gel (eluent: EtOAc–hexane, 1:1) to afford the chiral auxiliary (0.11 g, 95%) and the corresponding hydroxy amide **12a(i)** (0.13 g, 92%); $[\alpha]_D^{20}$ +60.0 (*c* 0.25, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 7.1 Hz, 3 H), 2.51–2.56 (m, 2 H), 4.25–4.36 (m, 2 H), 4.95–4.96 (d, *J* = 4.0 Hz, 1 H), 6.61 (br s, 1 H), 7.05–7.06 (m, 2 H), 7.13–7.26 (m, 5 H), 7.27–7.32 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.60, 43.23, 47.27, 74.04, 126.10, 127.37, 127.57, 128.21, 128.39, 128.65, 138.01, 141.80, 175.98.

MS (APCI): *m*/*z* = 269.97 (M + 1)$^+$.

(*R*)-*N*-Benzyl-3-hydroxy-3-phenylpropanamide [13a(i)]

Mp 102–106 °C; $[\alpha]_D^{20}$ +40.6 (*c* 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.58–2.63 (m, 2 H), 4.13 (br s, 1 H), 4.38–4.49 (m, 2 H), 5.13 (dd, *J* = 8.0, 4.3 Hz, 1 H), 6.23 (br s, 1 H), 7.19–7.24 (m, 2 H), 7.26–7.33 (m, 4 H), 7.34–7.38 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.48, 44.68, 70.91, 125.60, 127.57, 127.71, 127.85, 128.55, 128.73, 137.81, 142.97, 171.62.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{16}H_{17}NO_2$ ([M + Na]$^+$): 278.1157; found: 278.1154.

Ethyl (3*R*)-3-Hydroxy-3-(4-chlorophenyl)propanoate (14)

To a solution of **7a(iv)** (0.9 g, 2.2 mmol) in EtOH (20 mL) was added K_2CO_3 (1.5 g, 11.0 mmol) and the mixture was stirred at r.t. for 2 h. After completion of the reaction, the solvent was evaporated, washed with H_2O (10 mL), and the reaction mixture was extracted into EtOAc (2 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under vacuum to afford the crude product. Column chromatography on silica gel (60–120 mesh) using EtOAc–hexane (10:90) as the eluent afforded the pure product; yield: 0.48 g (95%); oil; $[\alpha]_D^{20}$ +44.1 (*c* 1.5, $CHCl_3$) {Lit.[29e] $[\alpha]_D^{25}$ +38.7 (*c* 1.5, $CHCl_3$)}, and the chiral auxiliary.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 2.65–2.75 (m, 2 H), 3.38 (br s, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 5.07–5.10 (m, 1 H), 7.27–7.32 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.13, 43.16, 61.00, 69.63, 127.07, 128.68, 133.48, 140.97, 172.26.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{11}H_{13}ClO_3$ ([M + Na]$^+$): 251.0451; found: 251.0451.

Ethyl (3*S*)-3-Bromo-3-(4-chlorophenyl)propanoate (15)

To the solution of **14** (0.4 g, 1.75 mmol) in Et_2O (50 mL) cooled to –20 °C was added pyridine (0.17 mL, 2.1 mmol) followed by PBr_3 (0.2 mL, 2.1 mmol) dropwise and the mixture was stirred for 2 h. The mixture was then slowly brought to r.t. and stirred for 12 h. It was washed with H_2O (20 mL), dried (Na_2SO_4), and concentrated to afford the desired compound **15**; yield: 0.41 g (79%); oil; $[\alpha]_D^{20}$ +101.3 (*c* 2.00, $CHCl_3$) {Lit.[29e] $[\alpha]_D^{25}$ +96.3 (*c* 2.00, $CHCl_3$)}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.0 Hz, 3 H), 3.16–3.34 (m, 2 H), 4.16 (q, *J* = 7.0 Hz, 2 H), 5.36 (dd, *J* = 6.6, 8.6 Hz, 1 H), 7.31–7.39 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.10, 44.79, 46.70, 61.16, 128.59, 129.16, 134.50, 139.34, 169.38.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{11}H_{12}BrClO_2$ ([M + Na]$^+$): 312.9607; found: 312.9598.

Ethyl (3*R*)-3-Cyano-3-(4-chlorophenyl)propanoate (16)

To the solution of **15** (0.4 g, 1.37 mmol) in MeCN (15 mL) were added TMSCN (1.2 mL, 10.2 mmol) and TBAF (2.9 mL, 10.2 mmol), and the mixture was stirred at reflux for 24 h. The solvent was evaporated and the crude mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to afford the desired compound **16**; yield: 0.21 g (65%); yellow solid; mp 64–66 °C; $[\alpha]_D^{20}$ +14.8 (*c* 1.5, $CHCl_3$) {Lit.[29e] $[\alpha]_D^{25}$ +12.9 (*c* 1.5, $CHCl_3$)}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.0 Hz, 3 H), 2.78 (dd, *J* = 8.0, 16.0 Hz, 1 H), 2.97 (dd, *J* = 8.0, 16.0 Hz, 1 H), 4.01–4.30 (m, 3 H), 7.30–7.46 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.66, 32.57, 39.80, 61.58, 119.54, 128.79, 129.46, 132.94, 134.64, 168.90.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{12}H_{12}ClNO_2$ ([M + Na]$^+$): 260.0454; found: 260.0446.

(*R*)-4-(4-Chlorophenyl)pyrrolidin-2-one (17)

$NiCl_2{\cdot}6H_2O$ (0.29 g, 1.26 mmol) followed by $NaBH_4$ (0.11 g, 3.15 mmol) were added to a solution of **16** (0.15 g, 0.63 mmol) in MeOH (20 mL). During addition, evolution of H_2 was observed and the reaction mixture turned black. The mixture was stirred at r.t. for 1 h, filtered through a Celite bed, concentrated, and extracted with EtOAc (2 × 20 mL). The solvent was evaporated to afford the desired compound **17**; yield: 0.11 g (86%); mp 114–116 °C; white solid; $[\alpha]_D^{20}$ –45.7 (*c* 1.0, EtOH) {Lit.[30] [α] –39.0 (*c* 1.0, EtOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (dd, *J* = 8.4, 16.7 Hz, 1 H), 2.77 (dd, *J* = 8.4, 16.7 Hz, 1 H), 3.34–3.45 (m, 1 H), 3.61–3.85 (m, 2 H), 7.20–7.33 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.43, 40.12, 51.21, 128.09, 129.33, 133.14, 140.44, 177.56.

MS (Maldi-TOF/TOF): *m*/*z* = 194.03 (M – 1)$^+$.

(*R*)-Baclofen Hydrochloride (18)

A solution of compound **17** (0.1 g, 0.51 mmol) in concd HCl (5.0 mL, 10 N) was heated at 100 °C for 12 h. The reaction mixture was concentrated under reduced pressure to afford the desired compound **18**; yield: 0.1 g (80%); white solid; $[\alpha]_D^{20}$ –2.2 (*c* 0.2, H_2O) {Lit.[29a] $[\alpha]_D^{20}$ –2.0 (*c* 0.2, H_2O); Lit.[30] $[\alpha]_D^{20}$ –1.7 (*c* 0.2, H_2O)}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.55–2.60 (m, 1 H), 2.82–2.89 (m, 1 H), 2.98–3.19 (m, 3 H), 7.34–7.53 (m, 4 H), 8.06 (br s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 38.34, 39.31, 43.75, 127.66, 128.29, 129.13, 140.78, 172.89.

MS (Maldi-TOF/TOF): *m*/*z* = 214.06 (M + 1)$^+$.

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