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Asymmetric organocatalytic synthesis of tertiary azomethyl alcohols: key intermediates towards azoxy compounds and α-hydroxy-β-amino esters

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A series of peracylated glycosamine-derived thioureas has been synthesized and its behavior as bifunctional organocatalysts has been tested in the enantioselective nucleophilic addition of formaldehyde *tert*-butyl hydrazone to aliphatic α-keto esters for the synthesis of tertiary azomethyl alcohols. Using the 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy-β-D-glucosamine derived 3,5-bis-(trifluoromethyl)phenyl thiourea the reaction could be accomplished with high yields (75-98%) and moderate enantioselectivities (50-64% ee). Subsequent high-yielding and razemization-free tranformations of both aromatic- and aliphatic-substituted diazene products in *one pot* fashion provides a direct entry to valuable azoxy compounds and α-hydroxy-β-amino esters.

Introduction

Chiral non-racemic tertiary alcohols and derivatives bearing aryl or alkyl substituents at the stereogenic center are recurrent scaffolds in many bioactive molecules. The selected examples shown in Figure 1 include lactones Campothecin[1] and Tripranavir,[2] β-amino alcohol derivative SSR-241586,[3] Voriconazole,[4] and 2-substituted α-hydroxy-β-amino acids (isoserines) which are present in several taxoid-based anticancer agents.[5] The increasing interest in known or predicted biological properties exerted by 2-alkyl or 2-aryl substituted isoserine fragments, for example in conformationally restricted peptidomimetics,[6] contrast, however, with the narrow palette of available methodologies for the asymmetric synthesis of suitable precursors for such molecules.[7] Therefore, there is a strong interest in the introduction of molecular diversity based on functionalized tertiary alcohols. One straightforward approach relies on the asymmetric nucleophilic addition to ketones and derivatives.[8] During years, we have extensively investigated the nucleophilic reactivity of formaldehyde *N*,*N*-dialkyl hydrazones for the stereoselective introduction of single-carbon functional groups into several electrophilic substrates.[9]

More recently, we have also exploited the superior

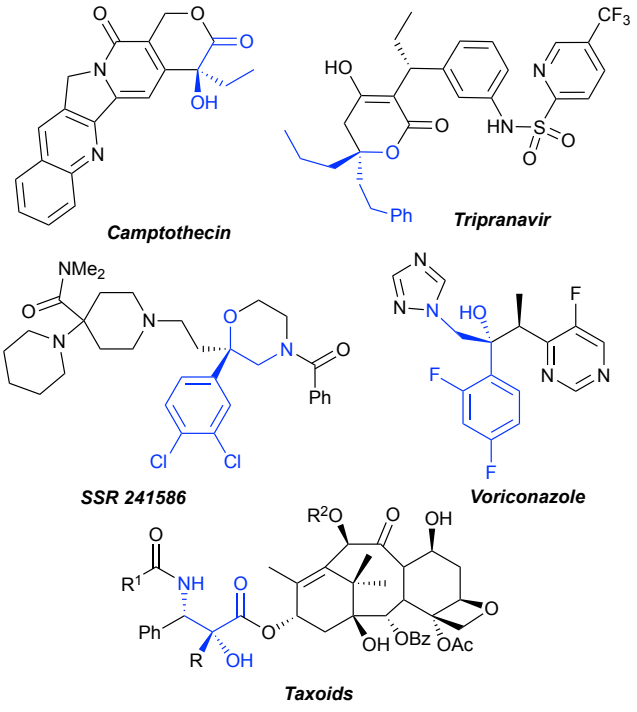

Figure 1. Bioactive tertiary alcohols and derivatives.

performance of formaldehyde *tert*-butyl hydrazone (**1**)[10] in combination with organocalytic activations.[11] The asymmetric nucleophilic addition of **1** to aryl-substituted di-carbonyl compounds such as α-keto esters **2** (Scheme 1, A)[10a] isatins,[10c] and related bidentate electrophiles such as α-keto phosphonates[10d] using BINAM-*bis*-urea as the organocatalyst provides densely functionalized azomethyl carbinols (formally hetero-carbonyl-ene products), which could be further

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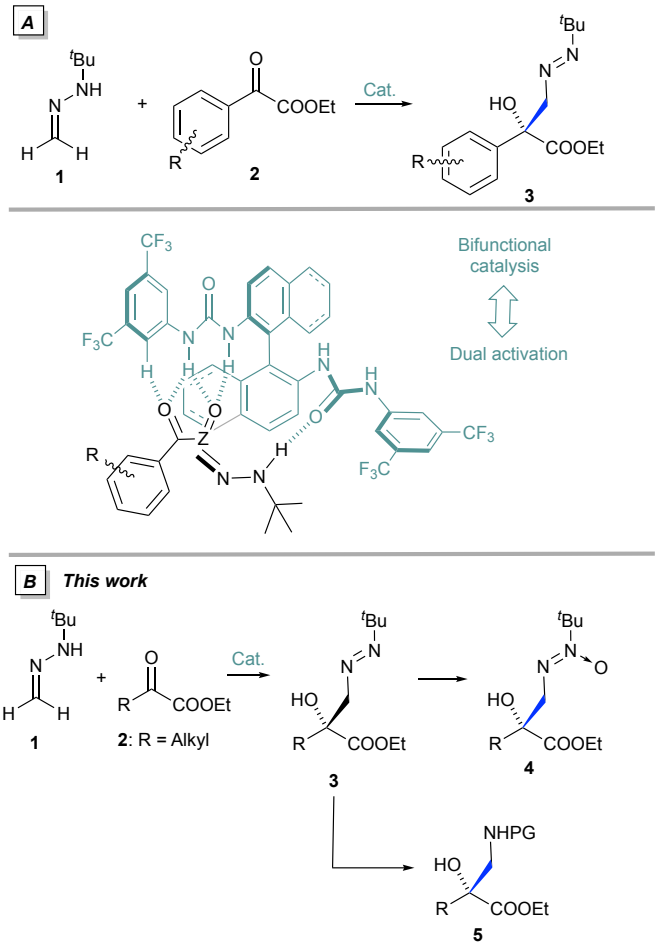


Scheme 1. Synthesis of aryl- and alkyl-substituted azomethyl tertiary alcohols **3**: a route to biologically relevant azoxy compounds **4** and α-hydroxy-β-amino esters **5**.

transformed into enantioenriched tertiary α-aryl α-hydroxy aldehydes and derivatives thereof. In the originally proposed working model, a bifunctional behaviour by the organocatalyst results in the activation of both the hydrazone (*via* N**H**–O=Chydrogen bonds) and the di-oxygenated electrophile (using a second urea unit as multiple H-bond donor), while the stereochemical outcome is explained by the relative bulkiness of the aromatic group, oriented away from the more crowded inner region of this ternary complex. In spite of the experimental support collected for this model when ethyl phenyl glyoxylate was used as the substrate,[10a] preliminary experiments performed with aliphatic derivatives revealed a poorer enantioselectivity, suggesting a priori that any kind of π–π interactions might contribute to the stabilization of the transition state.

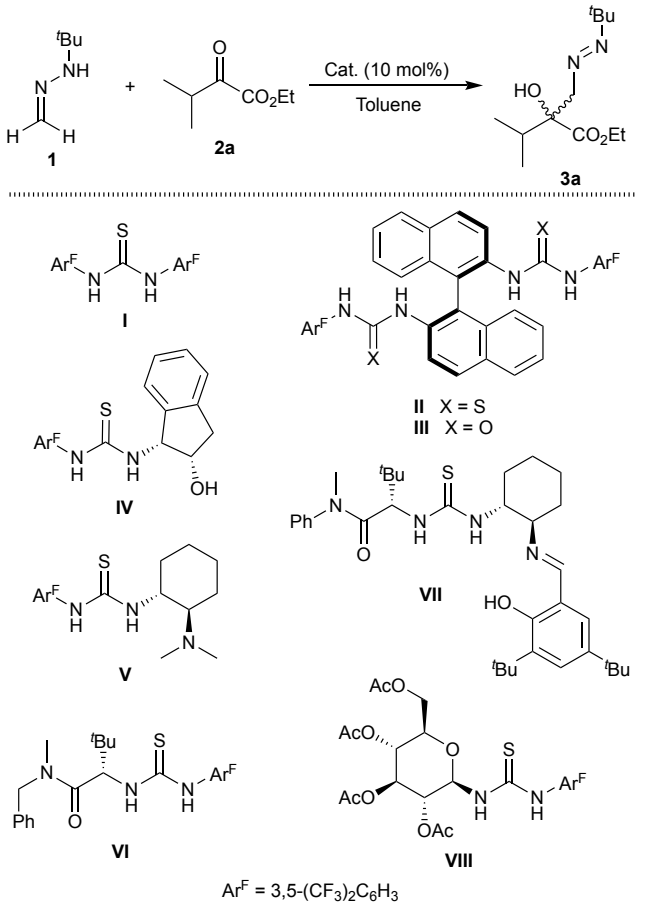
Aiming to expand the scope and applicability of azomethyl tertiary alcohols 3, we report herein on the use of novel saccharide-based organocatalysts for accessing enantiomerically enriched alkyl-substituted products and their subsequent one pot transformations into azoxymethyl alcohols 4 and α-hydroxy-β-amino esters 5 (Scheme 1, B).

Results and discussion

Synthesis of alkyl-substituted azomethyl alcohols 3

Preliminary experiments towards alkyl-substituted adducts **3** were performed with commercially available ethyl 3-methyl-2-oxobutanoate (**2a**) as model substrate (Table 1). At room temperature, the reaction of **1** with **2a** afforded the azomethyl alcohol **3a** at a reasonable rate (85% conversion after 2 h in toluene (entry 1). Cooling to –15 °C strongly decelerated the uncatalyzed reaction (entry 2), while a significant acceleration by the Schreiner`s thiourea **I** (10 mol%) was observed at this

Table 1. Screening of organocatalysts in the model reaction.[a]



Entry	Cat.	T (°C)	t (h)	Conv. (%)[b]	ee (%)[c,d]
1	none	rt	2	85	-
2	none	–15	48	30	-
3	**I**	–15	48	>95	-
4	**II**	–15	48	66	40 (S)
5	**III**	–15	48	>95	72 (R)
6	**IV**	–15	48	>95	10 (R)
7	**V**	–15	48	85	14 (R)
8	**VI**	–15	48	87	16 (S)
9	**VII**	–15	67	41	60 (R)
10	**VIII**	–15	43	>95	22 (S)

[a]Reactions performed employing **2a** (0.3 mmol), **1** (0.6 mmol) in toluene [1M]. [b]Determined by ^{1}H-NMR. [c]Determined by chiral GC. [d]In parentheses, absolute configuration of the major enantiomer.

temperature (>95% conversion, 48 h, entry 3). Therefore, we explored the behavior of diverse bifunctional H-bonding organocatalysts under these reaction conditions (entries 4-10).∫ As observed for aryl-substituted α-keto esters, (*R*)-BINAM-derived *bis*-urea **III** proved to be a superior catalyst than its *bis*-thiourea analogue **II** (entry 5 *vs* 4), affording (*R*)-**3a** in full conversion and 72% ee. The divergent stereochemical outcome observed for these two catalysts is in agreement with different activation modes operating in each case and the major (*R*) absolute configuration provided by bis-urea **III** is consistent with the dual activation mode proposed for the aromatic substrates (see model in Scheme 1). Bifunctional 3,5-bis(trifluoromethyl)phenyl-substituted thioureas bearing *cis*-1-amino-2-indanol (**IV**), *trans*-1,2-diaminocyclohexane (**V**) and *tert*-leucine (**VI**) chiral fragments afforded acceptable activation levels, albeit with low enantioselections (entries 6-8). The Jacobsen-type catalyst **VII** showed a higher selectivity (60% ee) but lower activity (41% conversion, 67 h, entry 9), probably due to its reduced acidity associated with the lack of electron-poor aryl groups.[12] Finally, multifunctional D-glucose-derived thiourea **VIII** was tested and the results revealed a slightly superior catalytic activity, reaching full conversion in a cleaner reaction, albeit in a low enantioselectivity (entry 10). The performance exhibited by catalyst **VIII** suggests that the carbohydrate unit might serve as a bulky-electron-withdrawing group,[13] increasing the acidity of thiourea and affording additional interactions with mono-alkyl hydrazone **1** *via* N**H**–O=C bonding (similar to that proposed in the BINAM-*bis*-urea) to the ester carbonyl groups. Considering this hypothesis, and the enormous modulation possibilities of carbohydrates as chiral scaffolds[14] we decided to synthesize and evaluate a small library of per-acylated hexosamine-derived organocatalysts placing a (thio)urea group at the C2 position (Figure 2). To the best of our knowledge, (thio)ureas with this alternative design have not been evaluated in asymmetric

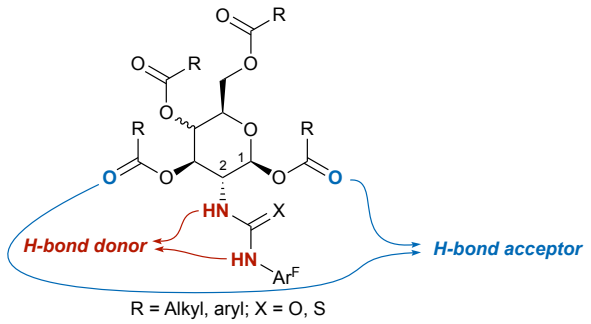
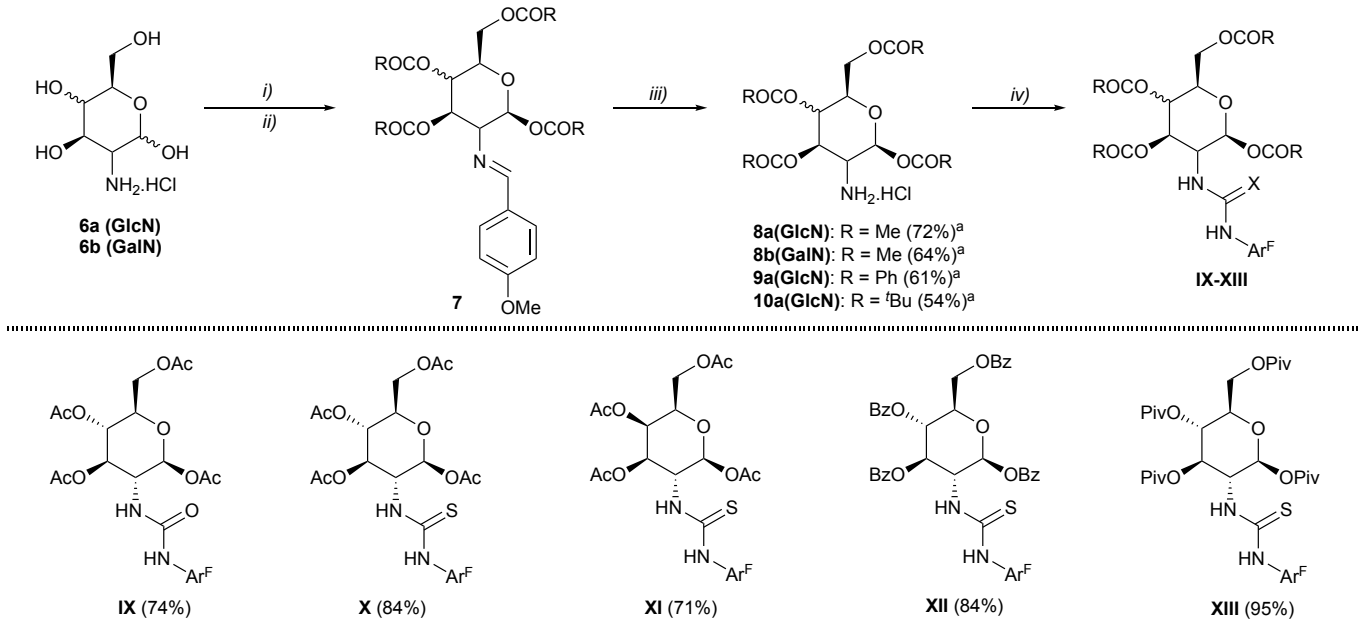


Figure 2. Hexosamine-derived (thio)ureas design.

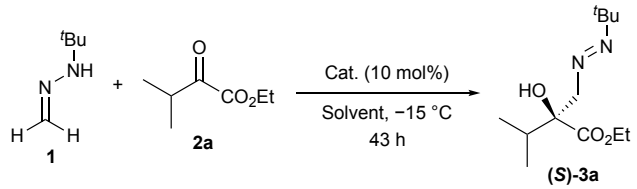
organocatalysis.[15] These compounds were synthesized in good overall yields according to the general strategy depicted in Scheme 2. First, commercially available hexosamine hydrochlorides [D-glucosamine (**6a**) and D-galactosamine (**6b**)] were efficiently converted into 1,3,4,6-tetra-*O*-acyl-β-D-glycosamine hydrochlorides **8-10** following a three step procedure: a) amine protection employing *p*-anisaldehyde; b) standard esterifications; and c) removal of *p*-methoxybenzylidene group with HCl in acetone. Subsequently, the *in situ* generated free glycosamines were reacted with 3,5-bis-(trifluoromethyl)phenyl isocyanate or thiocyanate, to afford the corresponding urea **IX** and thioureas **X-XIII** in good overall yields (71-95%).

Next, the new set of saccharide-based organocatalysts were tested in the model reaction (Table 2). To our delight, D-per-acetylated glucosamine-derived organocatalysts **IX** and **X** were more selective than **VIII** (entries 1-3), being thiourea **X** more active than urea **IX**, and affording (*S*)-**3a** in full conversion and a higher enantioselectivity (58% ee, entry 3). It is convenient to remark that, in contrast with catalysts **II/III**, good H-bond acceptor functionalities (the carbonyl groups) are available in both cases, so that the better performance of **X** can be



Scheme 2. Synthesis of hexosamine-based (thio)ureas. *a*) *p*-anisaldehyde, aq. NaOH; *b*) *O*-Acylations; *c*) aq. HCl, acetone. *3-step (**6**→**8**) yields. *d*) Ar^FNCX, Et_3N, CH_2Cl_2.

Table 2. Screening of saccharide-based organocatalysts.[a]

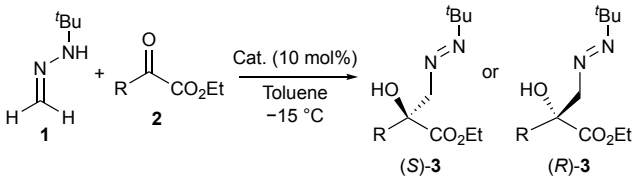


Entry	Cat.	Solvent	Conv. (%)[b]	ee (%)[c]
1	**VIII**	Toluene	>95	22
2	**IX**	Toluene	65	42
3	**X**	Toluene	>95	58
4	**XI**	Toluene	>95	8
5	**XII**	Toluene	85	24
6	**XIII**	Toluene	78	*rac*
7	**X**	Trifluorotoluene	86	58
8	**X**	TBME	30	34
9	**X**	*n*-Hexane	70	48
10	**X**	CH_2Cl_2	60	54

[a]Reactions performed employing **2a** (0.3 mmol) and **1** (0.6 mmol). [b]Determined by ^{1}H-NMR. [c]Determined by chiral GC.

explained by the higher acidity of the thiourea moiety. Notably, D-galactosamine derivative **XI** induced the lower selectivity within the series (entry 4). The stereoelectronic influence by different acyl groups was analyzed employing catalyst **XII** (per-benzoylated) and **XIII** (per-pivaloylated). Acceptable levels of activation, albeit low enantioselectivies, were observed in both cases (entries 5 and 6). Finally, poorer conversions and/or enantioselectivities were observed in solvents such as trifluorotoluene (entry 8), *tert*-butyl methyl ether (TBME, entry 8), *n*-hexane (entry 9) or CH_2Cl_2 (entry 10). Thus, the model reaction revealed BINAM *bis*-urea **III** and D-glucosamine derivative **X** as the most selective and active organocatalysts, respectively. Consequently, the scope of the reaction with a range of alkyl-substituted α-keto esters was then explored employing both organocatalysts. The collected data (Table 3) indicates that the expected products (*R*)-**3** were obtained with acceptable yields (60-88%) when catalyst **III** was used, although the enantioselectivities were highly dependent on the alkyl substituents (entries 1, 3, 5, 7, 9 and 11), dropping for those α-keto esters bearing linear alkyl chains [**3a**, R = ^{i}Pr (72% ee); **3b**, R = Me (49% ee); **3c**, R = ^{n}Pr (16% ee); **3d**, R = ^{n}Hex (16% ee); **3e**,R = Bn (50% ee); **3f**, R = CH_2CH_2Ph (14% ee)].¶ On the other hand, faster and cleaner reactions catalyzed by **X** afforded products (*S*)-**3** in good to excellent yields (75-98%) and moderate enantioselectivities (50-64% ee), without significant variations depending on the alkyl chain structures (entries 2, 4, 6, 8, 10 and 12). Substrate **2e** carrying a benzyl substituent reacted much faster, reaching completion in shorter times (24 h), even at –45 °C. In this case, both organocatalysts provided similar ee's (above 50% ee, entries 9 and 10). As limitation, a poorer reactivity was observed for *t*Bu-substituted α-keto ester **2g** (entries 13 and 14). Even at 0 °C for prolonged reaction times, (*S*)-**3g** was obtained with 20% yield and 64% ee in presence of catalyst **X**.

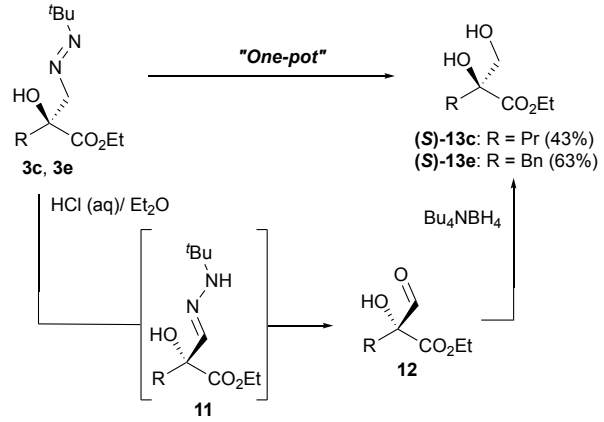
Table 3. Organocatalytic additions of **1** to alkyl-substituted α-keto esters **2**.[a]



Entry	**2**	R	Cat.	**3**	Yield (%)[b]	ee (%)
1	**2a**	^{i}Pr	**III**	(*R*)-**3a**	74	[c] 72
2	**2a**	^{i}Pr	**X**	(*S*)-**3a**	98	58[c]
3	**2b**	Me	**III**	(*R*)-**3b**	75	49[c]
4	**2b**	Me	**X**	(*S*)-**3b**	85	62[c]
5	**2c**	*n*-Pr	**III**	(*R*)-**3c**	62	16[d]
6	**2c**	*n*-Pr	**X**	(*S*)-**3c**	85	45[d]
7	**2d**	*n*-C_6H_{13}	**III**	(*R*)-**3d**	60	16[e]
8	**2d**	*n*-C_6H_{13}	**X**	(*S*)-**3d**	90	63[e]
9[f]	**2e**	Bn	**III**	(*R*)-**3e**	80	50[d]
10[f]	**2e**	Bn	**X**	(*S*)-**3e**	88	56[d]
11	**2f**	$Ph(CH_2)_2$	**III**	(*R*)-**3f**	88	14[e]
12	**2f**	$Ph(CH_2)_2$	**X**	(*S*)-**3f**	86	64[e]
13[g]	**2g**	^{t}Bu	**III**	(*R*)-**3g**	14	42[e]
14[g]	**2g**	^{t}Bu	**X**	(*S*)-**3g**	20	64[e]

[a]Reactions performed employing **2** (0.6 mmol), **1** (1.2 mmol) for 48 h (**III**) or 43 h (**X**). [b]Isolated yield. [c]Determined by chiral GC. [d]Determined by chiral HPLC. [e]Determined by chiral HPLC of its corresponding azoxymethyl alcohol **4**. [f]Reaction performed at –45 °C for 24 h. [g]Reaction performed at 0 °C for 72 h.

The versatility of the *N*-tert-butyldiazenylmethylene group is in good part attributed to its equivalence with the formyl group. Thus, representative azomethyl alcohols **3c,e** were transformed into aldehydes **12c,e** via a tautomerization–hydrolysis sequence accomplished by simple treatment with HCl in a biphasic H_2O/Et_2O medium (Scheme 3). Crude aldehydes **12** did not resist chromatographic purifications but were isolated with a high degree of purity (>90%, estimated by 1H-NMR). These intermediates were treated with Bu_4NBH_4 to yield diols **13c,e** in satisfactory overall yields. The absolute (*S*) configuration of adducts **3c,e** (stereochemistry induced by **X**) was determined by chemical correlation of diols **13c,e**.[16] The absolute configuration of other adducts **3** and derivatives thereof was assigned by analogy assuming a uniform reaction pathway [(*S*) induced by **X** and (*R*) induced by **III**].



Scheme 3. Synthesis of optically active diols (*S*)-13.

Synthesis of azoxymethyl alcohols 4

The azoxy-containing natural products[17] constitute a small but growing family of compounds with varied biological activities, the common structural feature of which is the presence of an azoxy group (N=N→O). Compounds in this family include the antitumour agent valanimycin, the carcinogen elaiomycin, the antifungal agents maniwamycin A and azoxybacilin, and the nematocidal compounds jietacins A and B, among others (Figure 3). The increasing interest in this class of bioactive compounds, however, contrasts with the lack of available reactions for the direct introduction of azoxy groups. In this context, oxidation of diazenes is a reasonably straightforward methodology, although the control of regioselectivity usually appears as an issue to overcome.[18] Previous studies performed in our laboratories,[10c,d] however, revealed that the N-oxidationtakes place selectively at the most hindered *tert*-butyl substituted nitrogen atom in similar derivatives. Therefore, we decided to explore the use of different oxidizing reagents for the regioselective *N*-oxidation of compounds **3** leading to azoxy compunds **4** (Table 4). Azomethyl alcohol **3a** toluene/CH_2Cl_2 mixture (full conversion in 4 hours) or magnesium monoperoxyphthalate (MMPP) in a toluene/MeOH mixture (full conversion in 1 hour). It was found out that elimination of toluene after the addition step facilitates the isolation of product **4a** in excellent yield (98%

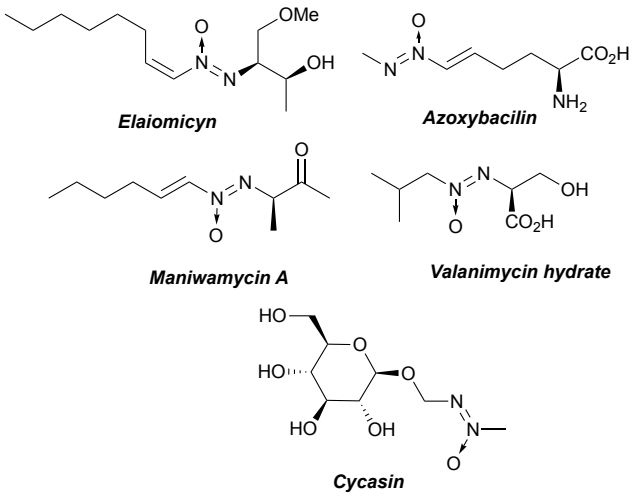
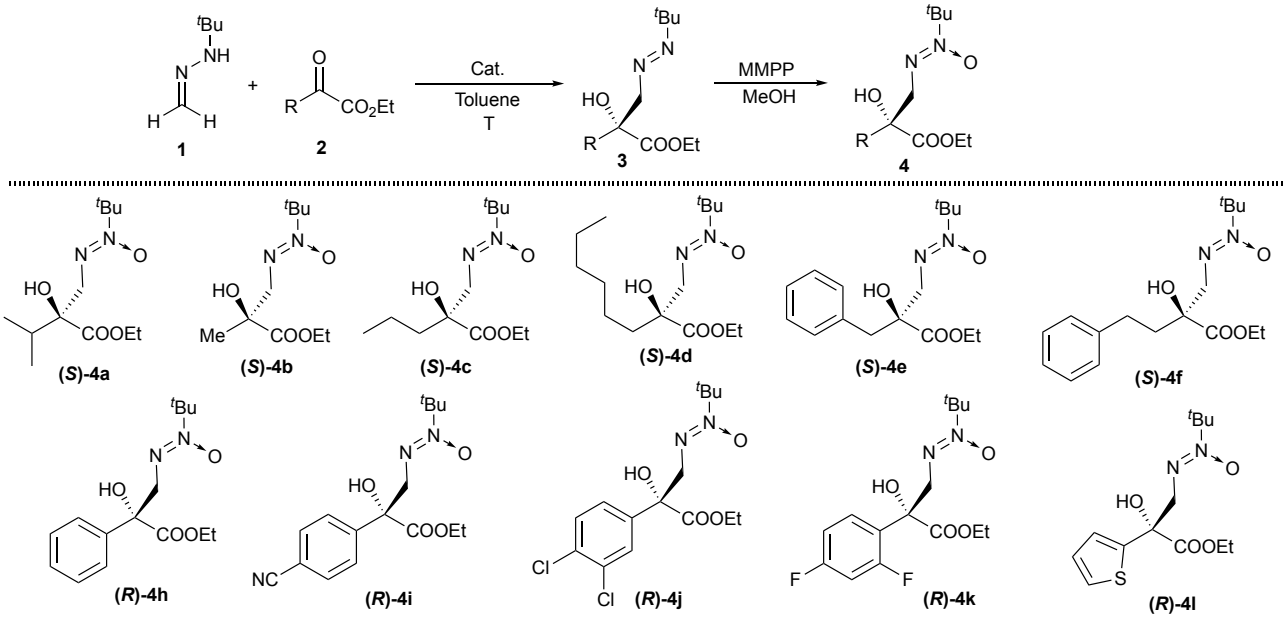


Figure 3. Bioactive molecules containing an azoxy moiety.

Table 4. One-pot synthesis of azoxymethyl alcohols **4**.[a]



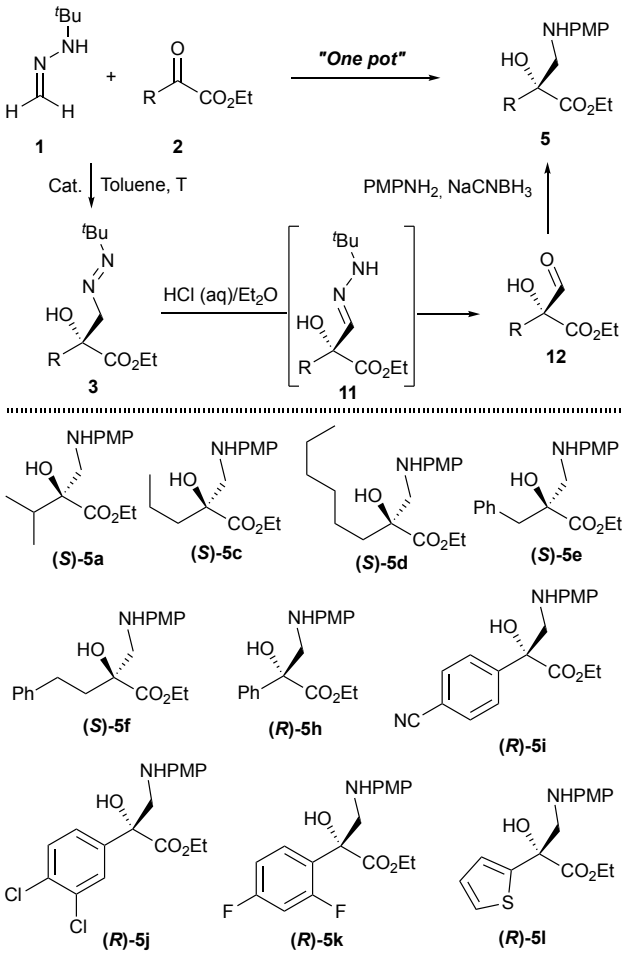
Entry	2	Cat.	T (°C)	t (h)[b]	4	Yield (%)[c]	ee (%)[d]
1	**2a**	**X**	−15	43	(*S*)-**4a**	98	57
2	**2b**	**X**	−15	43	(*S*)-**4b**	77	61
3	**2c**	**X**	−15	43	(*S*)-**4c**	78	49
4	**2d**	**X**	−15	43	(*S*)-**4d**	84	63
5	**2e**	**X**	−45	24	(*S*)-**4e**	88	58
6	**2f**	**X**	−15	43	(*S*)-**4f**	77	64
7[e]	**2g**	**III**	−30	48	(*R*)-**4h**	80	89
8[f]	**2h**	**III**	−45	7	(*R*)-**4i**	90	88
9	**2i**	**III**	−45	9	(*R*)-**4j**	83	86
10	**2j**	**III**	−45	6	(*R*)-**4k**	82	90
11	**2k**	**III**	−30	72	(*R*)-**4l**	79	85

[a]Reactions performed employing **2** (0.6 mmol), **1** (1.2 mmol) and **Cat.** (10 mol%) at the temperature and for the time indicated. [b]Reaction time of the first step. [c]Isolated yield. [d]Determined by chiral HPLC.

overall, 2-steps), with total regioselectivity and without racemization. Performing the addition with catalyst **X** in toluene at –15/–45 °C, followed by the optimized oxidation protocol, alkyl-substituted azoxymethyl alcohols (*S*)-**4a**-**f** were synthesized in good overall yields (77-98% over 2-steps) and moderate enantioselectivities (50-64% ee), consistent with those measured in their parent azomethyl alcohols **3** (entries 1-6). In the aromatic series, (*R*)-BINAM *bis*-urea **III** was used at lower temperatures (–30/–45 °C) for the first step to yield aryl-/heteroaryl-substituted azoxymethyl alcohols (*R*)-**4g**-**k** with several substitution patterns (entries 7-11) in high yields (79-90%) and enantioselectivities (85-90% ee).

Synthesis of α-hydroxy-β-amino esters 5

Azomethyl alcohols **3** proved to be also suitable precursors for quaternary α-hydroxy-β-amino acids (isoserines). The required transformation of the *N*-tert-butyldiazenylmethylene group of **3** into the aminomethyl group in **5** was accomplished via a one-pot tautomerization/hydrolysis/reductive amination sequence, as depicted in Scheme 4. Treatment of enantiomerically enriched diazene (*S*)-**3a**, with HCl in a biphasic H_2O/Et_2O medium, followed by simple L–L extractions afforded crude α-hydroxy aldehyde (*S*)-**12a** with a high degree of purity. Subsequent reductive amination using *p*-anisidine ($PMPNH_2$) and sodium cyanoborohydride ($NaCNBH_3$) in



Scheme 4. Synthesis of α-hydroxy-β-amino esters **5.**

Table 5. Synthesis of α-hydroxy-β-amino esters 5.[a]

Entry	2	Cat.	T (°C)	t (h)[b]	5	Yield (%)[c]	ee (%)[d]
1	**2a**	**X**	−15	43	(*S*)-**5a**	49	61
2	**2c**	**X**	−15	43	(*S*)-**5c**	40	55
3	**2d**	**X**	−15	43	(*S*)-**5d**	50	61
4	**2e**	**X**	−45	24	(*S*)-**5e**	45	51
5	**2f**	**X**	−15	43	(*S*)-**5f**	41	62
6	**2h**	**III**	−30	48	(*R*)-**5h**	51	90
7	**2i**	**III**	−45	7	(*R*)-**5i**	46	90
8	**2j**	**III**	−45	9	(*R*)-**5j**	46	84
9	**2k**	**III**	−45	6	(*R*)-**5k**	44	93
10	**2l**	**III**	−30	72	(*R*)-**5l**	41	84

[a]Reactions performed employing **2** (0.6 mmol), **1** (1.2 mmol) and **Cat**. (10 mol%) at the temperature and for the time indicated. [b]Reaction time of the first step. [c]Isolated yield. [d]Determined by chiral HPLC.

CH_2Cl_2,[‡] afforded (*S*)-**5a** in a satisfactory overall yield (49%, 4 steps) and enantioselectivity consistent with the azomethyl alcohol precursor (*S*)-**3a** (entry 1, Table 5).

Employing organocatalysts **X** or **III** for the asymmetric functionalization of alkyl- or aryl-substituted α-keto esters followed by the above discussed protocol in a *pseudo one pot* fashion, gave the targeted α-hydroxy-β-amino esters **5** in satisfactory overall yields (41-51%) and moderate to good enantiomeric excesses (Table 5).

Conclusions

In summary, readily available per-acetylated β-D-glucosamine thiourea **X** appears as a competent organocatalyst for the asymmetric nucleophilic addition of formaldehyde *tert*-butyl hydrazone **1** to α-keto esters **2**. Compared to previously established BINAM *bis*-urea **III** catalysts, these new family of bifunctional thioureas shows a fair catalytic activity and a complementary scope, enabling the obtention of aliphatic tertiary azomethyl alcohols **3** with high yields and moderate enantioselectivities. Both aromatic- and aliphatic-substituted products **3** have been employed as key precursors for the synthesis of biologically relevant azoxy compounds **4** and α-hydroxy-β-amino esters **5**.

Experimental

Spectra were recorded at [^{1}H NMR (300, 400 or 500 MHz); ^{13}C NMR (75, 100 or 125 MHz); ^{19}F NMR (470.6 MHz)] with the solvent peak used as the internal reference (7.26 and 77.0 ppm for ^{1}H and ^{13}C respectively). Column chromatography was performed on silica gel (Merck Kieselgel 60). Analytical TLC was performed on aluminium backed plates (1.5 × 5 cm) pre-coated (0.25 mm) with silica gel (Merck, Silica Gel 60 F254). Compounds were visualized by exposure to UV light or by dipping the plates in solutions of $KMnO_4$, vainilline or phosphomolibdic acid stains followed by heating. Melting points were recorded in a metal block and are uncorrected. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. Formaldehyde *tert*-butyl hydrazone **1**,[20] organocatalysts **II**-**IV**[21] and

not commercially available α-keto esters **2**[22] were synthesized according to literature procedures.

Synthesis of saccharide-based organocatalysts

VIII: 3,5-Bis(trifluoromethyl)phenyl isothiocyanate (151 µL, 0.8 mmol) was added to a solution of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamine[23] (256 mg, 0.7 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 20 h at rt and the solvent was removed *in vacuo*. Flash chromatography (Et_2O/*n*-hexane/CH_2Cl_2 5:1:1) afforded **VIII** (243 mg, 56%) as a white solid. M.P. = 68-70 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.94 (s, 2H), 7.61 (s, 1H), 7.03 (d, *J* = 10.0 Hz, 1H), 5.73 (t, *J* = 5.0 Hz, 1H), 5.38 (t, *J* = 10.0 Hz, 1H), 5.21 (t, *J* = 10.0 Hz, 1H), 5.09 (t, *J* = 10.0 Hz, 1H), 4.71 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.99 (d, *J* = 10.0 Hz, 1H), 3.93-3.89 (m, 1H), 2.09 (s, 3H), 2.06 (s, 6H), 2.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4, 172.3, 171.1, 170.2, 169.5, 139.1, 131.6 (q, *J* = 34.0 Hz), 124.3 (q, *J* = 262.0 Hz), 124.2, 119.0 (t, *J* = 2.5 Hz), 82.8, 75.5, 73.7, 70.9, 68.7, 62.5, 21.1, 20.7, 20.6, 20.5. HRMS: *m/z* calculated for $[C_{23}H_{24}F_6N_2O_9SNa]^+$: 641.0999; found: 641.1002. $[\alpha]_D^{20}$ = +22.6 (*c* 1.0, $CHCl_3$).

General procedure for the synthesis of hexosamine-derived amine hydrochlorides 8-10

p-Anisaldehyde (2.8 mL, 36.6 mmol) was added to a solution of D-hexosamine hydrochloride **6a,b** (5 g, 23.2 mmol) in NaOH aq. (1M, 25 mL) at 0 °C. The mixture was stirred for ~3 h until a crystalline solid was formed, which was then filtered and washed with cold H_2O (2x50 mL), EtOH (50 mL) and Et_2O (50 mL). The crude imine intermediates were directly subjected to *O*-acylation reactions to afford per-*O*-acylated imines **7**. ***O*-acetylation:** Acetic anhydride (16.8 mL, 118 mmol) was added to a solution of the crude imine (5.9 g, 19.8 mmol) in pyridine (17.6 mL, 218 mmol) at 0 °C. The reaction mixture was allowed to reach rt and stirred for ~24 h. An ice-H_2O (50 mL) mixture was added and the resulting solid was filtered, washed with cold H_2O (2 × 30 mL) and recrystallized from EtOH. ***O*-benzoylation:** Et_3N (30.4 mL, 217.8 mmol) and benzoyl chloride (20.7 mL, 178.2 mmol) were added to a solution of the crude imine (5.9 g, 19.8 mmol) in CH_2Cl_2 (150 mL) at 0 °C. The reaction mixture was allowed to warm to rt, stirred for ~24 h, washed with $NaHCO_3$ (4 × 30 mL) and concentrated to dryness. ***O*-pivaloylation:** Et_3N (30.4 mL, 217.8 mmol) and pivaloyl chloride (26.8 mL, 218 mmol) were added to a solution of the crude imine (5.9 g, 19.8 mmol) in CH_2Cl_2 (150 mL) at 60 °C. The reaction mixture was stirred for ~24 h, washed with $NaHCO_3$ (4 × 30 mL) and concentrated to dryness.

Imine hydrolysis: HCl (5M, 5 mL) was added to a solution of per-acylated imine **7** (17.8 mmol) in acetone (40 mL) at 0 °C. The reaction was stirred for 2 h, concentrated to dryness and the resulting residue was washed with cold Et_2O (2x50 mL) to afford *O*-acyl amine hydrochlorides **8**-**10**.

8a: White solid (6.4 g, 72%). Characterization data is in agreement with a literature report.[24]

8b: White solid (5.7 g, 64%). Characterization data is in agreement with a literature report.[25]

9a: White solid (8.9 g, 61%), M.P. = 202-204 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 8.18 (dd, *J* = 8.1, 1.0 Hz, 2H), 7.98 (td, *J* = 8.3, 1.4 Hz, 4H), 7.85 (dd, *J* = 7.9, 1.0 Hz, 2H), 7.71 (t, *J* = 10.0 Hz, 1H), 7.60-7.52 (m, 6H), 7.42 (td, *J* = 8.0, 2.1 Hz, 4H), 7.36 (t, *J* = 8.2 Hz, 2H), 6.38 (d, *J* = 10.0 Hz, 1H), 5.93 (t, *J* = 10.0 Hz, 1H), 5.80 (t, *J* = 10.0 Hz, 1H), 4.65-4.64 (m, 1H), 4.49-4.40 (m, 2H), 4.17 (dd, *J* = 10.2, 8.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 167.4, 166.7, 165.7, 135.5, 135.0, 134.9, 134.5, 131.4, 131.0, 130.7, 129.9, 129.6, 129.6, 129.5, 92.8, 74.2, 73.2, 70.4, 63.6, 54.8. HRMS: *m/z* calculated for $[C_{34}H_{30}NO_9Cl]^+$: 596.6100; found: 596.6110.

10a: White solid (6.9 g, 54%), M.P. = 205-207 °C. ^{1}H NMR (500 MHz, CD_3OD) δ 5.93 (d, *J* = 10.0 Hz, 1H), 5.45 (t, *J* = 10.0 Hz, 1H), 5.18 (t, *J* = 10.0 Hz, 1H), 4.14 (d, *J* = 5.0 Hz, 2H), 4.08-4.04 (m, 1H), 3.69 (t, *J* = 5.0 Hz, 1H), 1.27 (s, 9H), 1.22 (s, 9H), 1.19 (s, 9H), 1.18 (s, 9H). ^{13}C NMR (125 MHz, CD_3OD) δ 179.3, 178.8, 177.9, 177.4, 92.0, 74.0, 72.7, 69.3, 62.5, 54.4, 40.1, 40.0, 39.9, 39.8, 27.5, 27.4, 27.2. HRMS: *m/z* calculated for $[C_{26}H_{46}NO_9Cl]^+$: 516.6525; found: 516.6529.

General procedure for the synthesis of hexosamine-derived (thio)ureas IX-XIII

Et_3N (0.7 mL, 5.3 mmol) and 3,5-bis(trifluoromethyl)phenyl isocyanate or isothiocyanate (2.4 mmol) were sequentially added to a solution of amine hydrochloride **8-10** (2.2 mmol) in CH_2Cl_2 (10 mL) at room temperature. Reaction mixture was stirred for 24 h. Solvent was removed *in vacuo* and the obtained solid was purified by flash chromatography (Et_2O/*n*-hexane/CH_2Cl_2 5:1:1) to afford the desired (thio)urea.

IX: White solid (981 mg, 74%), M.P. = 194-196 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 2H), 7.50 (s, 2H), 5.87 (d, *J* = 8.6 Hz, 1H), 5.42 (d, *J* = 8.6 Hz, 1H), 5.31 (t, *J* = 9.8 Hz, 1H), 5.16 (t, *J* = 9.8 Hz, 1H), 4.30 (dd, *J* = 12.5, 4.0 Hz, 1H), 4.19-4.15 (m, 2H), 3.97-3.93 (m, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 170.8, 169.8, 169.4, 153.9, 140.1, 132.2 (q, *J* = 33.1 Hz), 120.9 (q, *J* = 271.2 Hz), 118.6, 116.3, 92.8, 72.7, 72.6, 68.0, 61.7, 54.2, 20.9, 20.7, 20.6, 20.5. HRMS: *m/z* calculated for $[C_{23}H_{24}F_6N_2O_{10}Na]^+$: 625.4310; found: 625.4320. $[\alpha]_D^{20}$ = +9.2 (*c* 1.0, $CHCl_3$).

X: White solid (1.1 g, 84%), M.P. = 64-66 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.91 (s, 2H), 7.69 (s, 1H), 6.32 (br s, 1H), 5.81 (d, *J* = 8.5 Hz, 1H), 5.26-5.22 (m, 2H), 5.12 (br s, 1H), 4.28 (dd, *J* = 12.5, 4.5 Hz, 1H), 4.16 (dd, *J* = 12.5, 2.5 Hz, 1H), 3.89-3.86 (m, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.1, 171.8, 170.8, 169.7, 169.4, 139.2, 132.5 (q, *J* = 33.3 Hz), 124.1 (q, *J* = 271.3 Hz), 122.9, 119.4, 92.9, 72.9, 72.8, 67.8, 61.7, 57.7, 20.9, 20.7, 20.7, 20.5. HRMS: *m/z* calculated for $[C_{23}H_{24}F_6N_2O_9SNa]^+$: 641.1004; found: 641.1015. $[\alpha]_D^{20}$ = −1.6 (*c* 1.0, $CHCl_3$).

XI: White solid (966 mg, 71%), M.P. = 68-70 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.91 (s, 2H), 7.68 (s, 1H), 6.52 (br s, 1H), 5.83 (d, *J* = 8.1 Hz, 1H), 5.42 (s, 1H), 5.22 (d, *J* = 9.0 Hz, 1H), 5.08 (br s, 1H), 4.20-4.15 (m, 3H), 2.21 (s, 3H), 2.16 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.5, 171.4, 170.9, 170.6, 169.9, 139.2, 132.7 (q, *J* = 34.0 Hz), 124.1 (q, *J* = 244.0 Hz), 123.9, 119.5,

93.5, 72.2, 71.0, 66.6, 61.6, 55.0, 21.1, 20.9, 20.8, 20.8. HRMS: *m/z* calculated for $[C_{23}H_{24}F_6N_2O_9SNa]^+$: 641.0999; found: 641.0989. $[\alpha]_D^{20}$ = +19.8 (*c* 1.0, $CHCl_3$).

XII: White solid (1.6 g, 84%), M.P. = 75-77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.0 Hz, 2H), 8.09 (br s, 1H), 8.01 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.58-7.50 (m, 6H), 7.43-7.32 (m, 8H), 7.22-7.10 (m, 1H), 6.89 (d, *J* = 7.1 Hz, 1H), 6.35 (d, *J* = 8.0 Hz, 1H), 5.87-5.78 (m, 2H), 5.67 (br s, 1H), 4.71 (d, *J* = 8.0 Hz, 1H), 4.60-4.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.3, 167.9, 166.4, 165.6, 165.5, 139.2, 134.3, 133.8, 133.4, 132.3 (q, *J* = 26.7 Hz), 130.7, 130.2, 130.0, 129.8, 129.6, 128.8, 128.8, 128.6, 128.6, 128.3, 124.7, 123.0 (q, *J* = 272.1 Hz), 119.2, 93.9, 73.8, 73.3, 69.7, 63.1, 58.1. HRMS: *m/z* calculated for $[C_{43}H_{32}F_6N_2O_9SNa]^+$: 889.1625; found: 889.1611. $[\alpha]_D^{20}$ = –28.5 (*c* 0.5, $CHCl_3$).

XIII: White solid (1.6 g, 95%), M.P. = 80-82 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (br s, 1H), 7.79 (s, 2H), 7.72 (s, 1H), 6.4 (br s, 1H), 5.73 (d, *J* = 8.4 Hz, 1H), 5.27 (d, *J* = 9.1 Hz, 2H), 4.17 (d, *J* = 3.0 Hz, 2H), 3.89-3.86 (m, 1H), 2.04 (s, 1H), 1.22 (s, 9H), 1.22 (s, 9H), 1.17 (s, 9H), 1.15 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.1, 180.1, 178.3, 176.5, 139.1, 133.3 (q, *J* = 33.0 Hz), 124.9, 122.8 (q, *J* = 271.0 Hz), 120.0, 93.2, 73.5, 72.7, 67.4, 61.8, 57.3, 39.3, 39.1, 39.1, 39.0, 27.3, 27.2, 27.2, 27.0. HRMS: *m/z* calculated for $[C_{35}H_{48}F_6N_2O_9SNa]^+$: 809.2877; found: 809.2866. $[\alpha]_D^{20}$ = +13.6 (*c* 1.0, $CHCl_3$).

General procedure for the catalytic enantioselective reactions of tert-butyl hydrazone 1 with α-keto esters 2.

Formaldehyde *tert*-butyl hydrazone **1** (134 µL, 1.2 mmol) was added to a solution of α-keto ester **2** (0.6 mmol) and catalyst **X** or **III** (0.06 mmol) in toluene (0.6 mL) at the specified temperature (Tables 3-5). The mixture was stirred for the time specified (TLC monitoring). Solvent was removed *in vacuo*. Flash chromatography (Toluene/EtOAc) afforded the corresponding azomethyl alcohols **3**.

Ethyl (*S*,*E*)-2-[(*tert*-butyldiazenyl)methyl]-2-hydroxy-3-methyl butanoate [(*S*)-**3a**]: Yelow oil (144 mg, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, *J* = 6.8 Hz, 2H), 4.11 (d, *J* = 12.8 Hz, 1H), 3.85 (d, *J* = 12.8 Hz, 1H), 3.29 (s, 1H), 2.18-2.11 (m, 1H), 1.28 (t, *J* = 6.8 Hz, 3H), 1.15 (s, 9 H), 1.02 (d, *J* = 6.8 Hz, 3H,), 0.91 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 78.8, 73.7, 67.7, 61.7, 34.0, 26.6, 17.0, 16.1, 14.1. HRMS: *m/z* calculated for $[C_{12}H_{24}N_2O_3]^+$: 244.3314; found: 244.3318. The enantiomeric excess was determined by GC [Chrompack CP7500, cyclodextrin-β, 225 m x 0.25 mm x 0.25 µm, He as mobile phase, τ_{major} = 14.3 min, τ_{minor} = 13.8 min, (58% ee)]; $[\alpha]_D^{20}$ = +17.8 (*c* 0.8, CH_2Cl_2).

Ethyl (*R*,*E*)-2-[(*tert*-butyldiazenyl)methyl]-2-hydroxy-3-methyl butanoate [(*R*)-**3a**]**:** Yelow oil (109 mg, 74%). $[\alpha]_D^{20}$ = +21.1 (*c* 1.0, CH_2Cl_2, 72% ee).

Ethyl (*S*,*E*)-3-(*tert*-butyldiazenyl)-2-hydroxy-2-methylpropanoate [(*S*)-**3b**]: Yelow oil (110 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25-4.19 (m, 2H), 4.17 (d, *J* = 13.2 Hz, 1H), 3.83 (d, *J* = 13.2 Hz, 1H), 3.46 (s, 1H), 1.52 (s, 3 H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.17 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 77.1, 75.2, 73.8, 61.7, 26.6, 23.9, 14.1. HRMS: *m/z* calculated for $[C_{10}H_{20}N_2O_3]^+$: 216.1474; found: 216.1468. The enantiomeric excess was determined by GC [Chrompack CP7500, cyclodextrin-β, 225 m x 0.25 mm x 0.25 µm, He as mobile phase, τ_{major} = 17.3 min, τ_{minor} = 17.1 min, (62% ee)]; $[\alpha]_D^{20}$ = –5.8 (*c* 1.0, CH_2Cl_2).

Ethyl (*S*,*E*)-2-[(*tert*-butyldiazenyl)methyl]-2-hydroxypentanoate [(*S*)-**3c**]: Yelow oil (124 mg, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25-4.15 (m, 2H), 4.10 (d, *J* = 13.0 Hz, 1H), 3.78 (d, *J* = 13.0 Hz, 1H), 3.39 (s, 1H), 1.84-1.46 (m, 4H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.13 (s, 9H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 76.6, 75.0, 67.7, 61.6, 39.4, 26.7, 16.4, 14.2, 14.1. HRMS: *m/z* calculated for $[C_{12}H_{25}N_2O_3]^+$: 245.1860; found: 245.1862. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/*i*-PrOH (98:2)]; flow rate 1 mL/min; τ_{major} = 6.7 min, τ_{minor} = 5.6 min (45% ee); $[\alpha]_D^{20}$ = +23.0 (*c* 0.6, $CHCl_3$).

Ethyl (*S*,*E*)-2-[(*tert*-butyldiazenyl)methyl]-2-hydroxyoctanoate [(*S*)-**3d**]: Yelow oil (155 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, *J* = 7.2 Hz, 2H), 4.13 (d, *J* = 13.2 Hz, 1H), 3.80 (d, *J* = 13.2 Hz, 1H), 3.39 (s, 1H), 1.86-1.71 (m, 2H), 1.56-1.49 (m, 2H), 1.30-1.26 (m, 6H), 1.28 (t, *J* = 6.8 Hz, 3H), 1.16 (s, 9H), 0.87 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 77.4, 75.3, 68.0, 61.9, 37.4, 31.8, 29.5, 26.9, 23.1, 22.7, 14.4, 14.2. HRMS: *m/z* calculated for $[C_{15}H_{30}N_2O_3Na]^+$: 309.2149; found: 309.2142. The enantiomeric excess was determined by HPLC of its corresponding azoxymethyl alcohol (*S*)-**4d**; $[\alpha]_D^{20}$ = +5.9 (*c* 1.0, $CHCl_3$, 63% ee).

Ethyl (*S*,*E*)-2-benzyl-3-(*tert*-butyldiazenyl)-2-hydroxypropanoate [(*S*)-**3e**]: Yellow oil (154 mg, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.13 (m, 5H), 4.21 (d, *J* = 13.2 Hz, 1H), 4.10 (qd, *J* = 7.1, 2.9 Hz, 2H), 3.77 (d, *J* = 13.2 Hz, 1H), 3.09 (d, *J* = 13.5 Hz, 1H), 3.01 (d, *J* = 13.5 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 135.2, 130.4, 128.1, 127.0, 77.1, 74.6, 68.0, 61.9, 43.4, 26.8, 14.2. HRMS: *m/z* calculated for $[C_{16}H_{25}O_3N_2]^+$: 293.1860; found: 293.1851. The enantiomeric excess was determined by HPLC using a Chiralpak OJ-H column [hexane:^{i}PrOH (98:2)]; flow rate 1 mL/min; 30 °C, τ_{major} = 6.5 min, τ_{minor} = 7.2 min (56% ee); $[\alpha]_D^{27}$ = −4.83 (*c* 0.4, $CHCl_3$).

Ethyl (*S*,*E*)-2-[(tert-butyldiazenyl)methyl]-2-hydroxy-4-phenyl butanoate [(*S*)-**3f**]: Yelow oil (158 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 3H), 7.19 (d, *J* = 7.2 Hz, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 4.17 (d, *J* = 13.2 Hz, 1H), 4.01 (br s, 1H), 3.80 (d, *J* = 13.2 Hz, 1H), 2.94-2.85 (m, 1H), 2.62-2.51 (m, 1H), 2.22-2.08 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.17 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 141.4, 128.6, 128.4, 76.4, 75.1, 68.0, 61.9, 39.0, 29.5, 26.8, 14.3. HRMS: *m/z* calculated for $[C_{17}H_{26}N_2O_3Na]^+$: 329.1836; found: 329.1829. The enantiomeric excess was determined by HPLC of its corresponding azoxymethyl alcohol (*S*)-**4f**; $[\alpha]_D^{20}$ = +4.7 (*c* 1.0, $CHCl_3$, 64% ee).

Ethyl (*S*,*E*)-2-[(*tert*-butyldiazenyl)methyl]-2-hydroxy-3,3-dimethyl butanoate [(*S*)-**3g**]: Yelow oil (31 mg, 20%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (d, *J* = 13.2 Hz, 1H), 4.31-4.22 (m, 2H), 3.77 (d, *J* = 13.1 Hz, 1H), 3.46 (s, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.14 (s, 9H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 81.0, 70.9, 67.8, 61.7, 37.2, 26.8, 25.7, 14.3. HRMS: *m/z* calculated for $[C_{13}H_{27}N_2O_3]^+$: 259.2016; found: 259.2010. The enantiomeric excess was determined by HPLC of its corresponding azoxymethyl alcohol (*S*)-**4g** using a Chiralpak AD-H column [hexane/*i*-PrOH (80:20)]; flow rate 1 mL/min; τ_{major} = 4.5 min, τ_{minor} = 4.1 min (64% ee); $[\alpha]_D^{20}$ = +2.9 (*c* 0.7, $CHCl_3$).

General procedure for the synthesis of azoxymethyl alcohols 4.

Following the general procedure for the catalytic enantioselective reactions of hydrazone **1** (1.2 mmol) with α-keto esters **2** (0.6 mmol). After consumption of starting material, the solvent was removed *in vacuo* and the residue was dissolved in MeOH (2 mL), cooled to 0 °C, and MMPP (1.48 g, 5 equiv.) was added. The reaction mixture was stirred until consumption of the azomethyl alcohol **3** (tlc monitoring, 2-3 h.), diluted with H_2O (5 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (Toluene/EtOAc) to afford azoxymethyl alcohol **4**.

[(*S*)-**4a**]: Yellow oil (154 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22-4.20 (m, 2H), 3.63 (d, *J* = 17.0 Hz, 1H), 3.59 (d, *J* = 17.0 Hz, 1H), 3.36 (s, 1H), 2.10-2.07 (m, 1H), 1.49 (s, 9H), 1.24 (t, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 78.6, 76.6, 61.7, 58.8, 33.8, 28.2, 17.2, 16.1, 14.3. HRMS: *m/z* calculated for $[C_{12}H_{24}N_2O_4Na]^+$: 283.1628; found: 283.1623. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/*i*-PrOH (98:2)]; flow rate 1 mL/min; τ_{major} = 10.4 min, τ_{minor} = 9.9 min (57% ee); $[\alpha]_D^{20}$ = +7.5 (*c* 1.0, $CHCl_3$).

[(*S*)-**4b**]: White solid (108 mg, 77%), M.P.: 97-99 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24-4.13 (m, 2H), 3.64 (d, *J* = 15.0 Hz, 1H,), 3.49 (d, *J* = 15.0 Hz, 1H), 3.44 (s, 1H), 1.48 (s, 9H), 1.46 (s, 3H), 1.22 (t, *J* = 5.0 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 76.6, 73.3, 61.7, 60.5, 28.1, 23.7, 14.1. HRMS: *m/z* calculated for $[C_{10}H_{21}N_2O_4Na]^+$: 255.1315; found: 255.1311. The enantiomeric excess was determined by HPLC using a Chiralpak OJ column [hexane/*i*-PrOH (98:2)]; flow rate 1 mL/min; τ_{major} = 11.5 min, τ_{minor} = 13.5 min (61% ee); $[\alpha]_D^{20}$ = –3.5 (*c* 0.5, $CHCl_3$).

[(*S*)-**4c**]: Yellow oil (122 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27-4.15 (m, 2H), 3.72 (d, *J* = 17.0 Hz, 1H), 3.61 (d, *J* = 17.0 Hz, 1H), 3.43 (s, 1H), 1.79-1.72 (m, 2H), 1.60-1.53 (m, 2H), 1.50 (s, 9H), 1.25 (t, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 76.3, 61.7, 60.1, 39.1, 28.2, 16.6, 14.3, 14.1. HRMS: *m/z* calculated for $[C_{12}H_{24}N_2O_4Na]$: 283.1628; found: 283.1622. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/*i*-PrOH (98:2)]; flow rate 1 mL/min; τ_{major} = 15.1 min, τ_{minor} = 12.0 min (49% ee); $[\alpha]_D^{20}$ = +15.5 (*c* 0.5, $CHCl_3$).

[(*S*)-**4d**]: Yellow oil (152 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23-4.12 (m, 2H), 3.60 (d, *J* = 18.0 Hz, 1H), 3.49 (d, *J* = 18.0 Hz, 1H), 3.41 (s, 1H), 1.73-1.69 (m, 2H), 1.56-1.49 (m, 2H), 1.47 (s, 9H), 1.27-1.19 (m, 9H), 0.83 (t, *J* = 5.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 76.6, 76.3, 61.7, 60.1, 36.9, 31.6, 29.3, 28.1, 23.1, 22.5, 13.9, 14.3. HRMS: *m/z* calculated for $[C_{15}H_{30}N_2O_4Na]^+$: 325.2098; found: 325.2091. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/*i*-PrOH (80:20)]; flow rate 1 mL/min; τ_{major} = 5.0 min, τ_{minor} = 4.3 min (63% ee); $[\alpha]_D^{20}$ = +6.2 (*c* 1.0, $CHCl_3$).

[(*S*)-**4e**]: Yellowish oil (163 mg, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), 4.33-4.07 (m, 2H), 3.80 (d, *J* = 18.0 Hz, 1H), 3.63 (d, *J* = 18.0 Hz, 1H), 3.14 (d, *J* = 17.3 Hz, 1H), 3.10 (d, *J* = 17.3 Hz, 1H), 1.53 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 135.2, 130.3, 128.2, 127.0, 76.8, 61.8, 59.7, 43.1, 28.2, 14.2. HRMS: *m/z* calculated for $[C_{16}H_{24}O_4N_2Na]^+$: 331.1628; found: 331.1621. The enantiomeric excess was determined by HPLC using a Chiralpak OJ-H column [hexane:^{i}PrOH (98:2)]; flow rate 1 mL/min; 30 °C, τ_{major} = 13.6 min, τ_{minor} = 15.0 min (58% ee); $[\alpha]_D^{27}$ = +1.52 (*c* 0.6, $CHCl_3$).

[(*S*)-**4f**]: Yellow oil (150 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.21 (m, 3H), 7.15 (d, *J* = 6.8 Hz, 2H,), 4.14 (m, 2H), 3.65 (d, *J* = 18.0 Hz, 1H), 3.56 (d, *J* = 18.0 Hz, 1H), 3.54 (s, 1H), 2.84-2.80 (m, 1H), 2.54-2.45 (m, 1H), 2.11-2.03 (m, 2H), 1.48 (s, 9H), 1.22 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 141.4, 128.4, 126.0, 76.8, 76.0, 61.9, 60.1, 38.6, 29.6, 28.2, 14.3. HRMS: *m/z* calculated for $[C_{17}H_{26}N_2O_4Na]^+$: 345.1785; found: 345.1780. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/*i*-PrOH (80:20)]; flow rate 1 mL/min; τ_{major} = 6.1 min, τ_{minor} = 5.6 min (64% ee); $[\alpha]_D^{20}$ = +21.9 (*c* 1.0, $CHCl_3$).

[(*R*)-**4h**]: White solid (141 mg, 80%); M.P.: 100-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.2 Hz, 2H), 7.44-7.26 (m, 3H), 4.31-4.17 (m, 2H), 4.16 (d, *J* = 17.6 Hz, 1H), 3.98 (s, 1H), 3.81 (d, *J* = 17.6 Hz, 1H), 1.53 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 139.4, 128.3, 128.2, 125.7, 77.2, 76.8, 62.4, 60.6, 28.2, 14.2. HRMS: *m/z* calculated for $[C_{15}H_{22}N_2O_4Na]^+$: 317.1472; found: 317.1468. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/*i*-PrOH (80:20)]; flow rate 1 mL/min; τ_{major} = 6.6 min, τ_{minor} = 7.6 min (89% ee); $[\alpha]_D^{20}$ = +8.3 (*c* 1.0, $CHCl_3$).

[(*R*)-**4i**]: Yellow oil (174 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 4.29-4.16 (m, 2H), 4.12 (s, 1H), 4.08 (d, *J* = 18.0 Hz, 1H), 3.75 (d, *J* = 18.0 Hz, 1H), 1.49 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 144.6, 132.1, 126.8, 118.5, 112.2, 77.1, 76.8, 63.0, 60.5, 28.2, 14.2. HRMS: *m/z* calculated for $[C_{16}H_{21}N_3O_4Na]^+$: 342.1424; found: 342.1419. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/*i*-PrOH (80:20)]; flow rate 1 mL/min; τ_{major} = 10.6 min, τ_{minor} = 11.6 min (88% ee); $[\alpha]_D^{20}$ = +13.6 (*c* 1.3, $CHCl_3$).

[(*R*)-**4j**]: White solid (181 mg, 83%); M.P.: 102-104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 4.39-4.16 (m, 2H), 4.09 (s, 1H), 4.09 (d, *J* = 17.9 Hz, 1H), 3.77 (d, *J* = 17.9 Hz, 1H), 1.54 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 139.6, 132.6, 132.5, 130.3, 128.2, 125.4, 76.8, 76.5, 62.9, 60.5, 28.2, 14.2. HRMS: *m/z* calculated for $[C_{15}H_{20}Cl_2N_2O_4Na]^+$: 385.0692; found: 385.0689. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/*i*-PrOH (80:20)]; flow rate 1 mL/min; τ_{major} = 5.6 min, τ_{minor} = 6.3 min (86% ee); $[\alpha]_D^{20}$ = +12.3 (*c* 1.0, $CHCl_3$).

[(*R*)-**4k**]**:** Yellowish oil (162 mg, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (td, *J* = 8.7, 6.3 Hz, 1H), 688-6.78 (m, 1H), 6.74 (ddd, *J* = 11.3, 8.7, 2.6 Hz, 1H), 4.25-4.08 (m, 2H), 4.11 (s, 1H), 4.09 (d, *J* = 17.8 Hz, 1H), 3.96 (d, *J* = 17.8 Hz, 1H), 1.45 (s, 9H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 162.9 (dd, *J* = 250.2, 12.3 Hz), 160.4 (dd, *J* = 252.0, 11.9 Hz), 129.1 (dd, *J* = 9.8, 5.3 Hz), 123.4 (dd, *J* = 12.6, 3.9 Hz), 111.1 (dd, *J* = 21.0, 3.5 Hz), 104.6 (dd, *J* = 26.6, 25.6 Hz), 77.2, 74.9 (d, *J* = 2.0 Hz), 62.5, 58.3 (d, *J* = 3.6 Hz), 28.1, 14.0. ^{19}F NMR (283 MHz, $CDCl_3$) δ −107.49 (d, *J* = 8.7 Hz), −109.87 (d, *J* = 8.7 Hz). HRMS: *m/z* calculated for $[C_{15}H_{20}O_4N_2F_2Na]^+$: 353.1283; found: 353.1276. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane:^{i}PrOH (80:20)]; flow rate 1 mL/min;

30 °C, τ_{major} = 5.7 min, τ_{minor} = 6.7 min (90 % ee); $[\alpha]_D^{27}$ = +2.5 (*c* 0.7, $CHCl_3$).

[(*R*)-**4l**]: Yellowish oil (142 mg, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.09 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.92 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.30-4.09 (m, 2H), 4.18 (s, 1H), 4.02 (d, *J* = 18.0 Hz, 1H), 3.79 (d, *J* = 18.0 Hz, 1H), 1.46 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 143.9, 127.1, 125.5, 124.7, 76.9, 76.1, 62.7, 61.4, 28.2, 14.2. HRMS: *m/z* calculated for $[C_{13}H_{20}O_4N_2NaS]^+$: 293.1860; found: 293.1851. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane:^{i}PrOH (80:20)]; flow rate 1 mL/min; 30 °C, τ_{major} = 6.4 min, τ_{minor} = 7.7 min (85% ee); $[\alpha]_D^{27}$ = +3.8 (*c* 0.4, $CHCl_3$).

General procedure for the synthesis of α-hydroxy-β-amino esters 5

Following the general procedure for the catalytic enantioselective reactions of hydrazone **1** (1.2 mmol) with α-keto esters **2** (0.6 mmol). After consumption of starting material, the solvent was removed *in vacuo* and the residue was dissolved in Et_2O (5.5 mL), cooled to 0 °C, and HCl (6 M, 2.5 mL) was added. The reaction mixture was allowed to warm to rt, stirred for 2 h, and extracted with Et_2O (2 × 5 mL) and CH_2Cl_2 (2 × 5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford α-hydroxy aldehyde **12**. *p*-Anisidine (121 mg, 0.9 mmol) and $NaCNBH_3$ (88 mg, 1.4 mmol) were added to a solution of crude aldehyde in CH_2Cl_2 (3 mL) at room temperature. The reaction mixture was stirred for 2-3 h, H_2O was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (hexane/EtOAc) afforded the corresponding β-amino-α-hydroxyester **5**.

Ethyl (*S*)-2-hydroxy-2-{[(4-methoxyphenyl)amino]methyl}-3-methylbutanoate [(*S*)-**5a**]: Yellowish oil (83 mg, 49%):^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73-6.63 (m, 2H), 6.60-6.48 (m, 2H), 4.22-3.98 (m, 2H), 3.66 (s, 3H), 3.44 (br s, 1H), 3.40 (d, *J* = 12.0 Hz, 1H), 3.18 (d, *J* = 12.0 Hz, 1H), 1.99 (hept, *J* = 6.8 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 152.5, 142.5, 115.2, 114.7, 80.1, 62.1, 55.8, 50.7, 33.9, 17.3, 16.4, 14.6. HRMS: *m/z* calculated for $[C_{15}H_{24}NO_4]^+$: 282.1700; found: 282.1693. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane:^{i}PrOH (80:20)]; flow rate 1 mL/min; 30 °C, τ_{major} = 7.7 min, τ_{minor} = 9.9 min (61% ee); $[\alpha]_D^{23}$ = +4.5 (*c* 0.9, $CHCl_3$).

Ethyl (*S*)-2-hydroxy-2-{[(4-methoxyphenyl)amino]methyl} pentanoate [(*S*)-**5c**]: Yellow oil (67 mg, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, *J* = 9.0 Hz, 2H), 6.61 (d, *J* = 9.0 Hz, 2H), 4.26-4.08 (m, 2H), 3.74 (s, 3H), 3.57 (br s, 1H), 3.49 (d, *J* = 12.3 Hz, 2H), 3.15 (d, *J* = 12.3 Hz, 2H), 1.76-1.65 (m, 2H), 1.57-1.41 (m, 1H), 1.24 (t, *J* = 14.3 Hz, 3H), 1.20-1.07 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 152.6, 142.1, 115.3, 114.8, 77.6, 62.1, 55.8, 52.7, 39.1, 16.6, 14.2, 14.1. HRMS: *m/z* calculated for $[C_{15}H_{23}NO_4]^+$: 282.1635; found: 282.1630. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/*i*-PrOH (80:20)]; flow rate 1 mL/min; τ_{major} = 8.8 min, τ_{minor} = 11.5 min (55% ee); $[\alpha]_D^{20}$ = –4.9 (*c* 0.5, $CHCl_3$).

Ethyl (*S*)-2-hydroxy-2-{[(4-methoxyphenyl)amino]methyl} octanoate [(*S*)-**5d**]: Yellowish oil (97 mg, 50%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73-6.64 (m, 2H), 6.61-6.54 (m, 2H), 4.20-3.99 (m, 2H), 3.67 (s, 3H), 3.43 (d, *J* = 12.3 Hz, 1H), 3.10 (d, *J* = 12.3 Hz, 1H), 1.74-1.55 (m, 2H), 1.49-1.33 (m, 1H), 1.27-1.13 (m, 9H), 1.12-0.94 (m, 1H) 0.80 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 152.8, 141.8, 115.5, 114.7, 77.6, 62.2, 55.8, 52.9, 37.0, 31.6, 29.3, 23.1, 22.5, 14.2, 14.0. HRMS: *m/z* calculated for $[C_{18}H_{30}NO_4]^+$: 324.2095; found: 324.2063. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane:^{i}PrOH (80:20)]; flow rate 0.7 mL/min; 30 °C, τ_{major} = 10.9 min, τ_{minor} = 12.1 min (61% ee); $[\alpha]_D^{27}$ = +7.4 (*c* 1.6, $CHCl_3$).

Ethyl (*S*)-2-benzyl-2-hydroxy-3-[(4-methoxyphenyl)amino] propanoate [(*S*)-**5e**]: Yellowish oil (89 mg, 45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.22 (m, 5H), 6.84-6.77 (m, 2H), 6.70-6.64 (m, 2H), 4.20-4.09 (m, 2H), 3.78 (s, 3H), 3.67 (d, *J* = 12.2 Hz, 1H), 3.48 (br s, 1H), 3.30 (d, *J* = 12.2 Hz, 1H), 3.13 (d, *J* = 13.6 Hz, 1H), 3.06 (d, *J* = 13.6 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 152.6, 142.2, 135.2, 130.1, 128.2, 127.1, 115.2, 114.8, 78.2, 62.2, 55.8, 52.5, 43.1, 14.1. HRMS: *m/z* calculated for $[C_{19}H_{24}O_4N]^+$: 330.1700; found: 330.1691. The enantiomeric excess was determined by HPLC using a Chiralpak OJ-H column [hexane:^{i}PrOH (90:10)]; flow rate 1 mL/min; 30 °C, τ_{major} = 27.7 min, τ_{minor} = 29.9 min (51% ee); $[\alpha]_D^{27}$ = +10.7 (*c* 1.5, $CHCl_3$).

Ethyl (*S*)-2-hydroxy-2-{[(4-methoxyphenyl)amino]methyl}-4-phenylbutanoate [(*S*)-**5f**]: Yellowish oil (84 mg, 41%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 2H), 7.27-7.16 (m, 3H), 6.86-6.73 (m, 2H), 6.68-6.59 (m, 2H), 4.16 (qq, *J* = 10.7, 7.1 Hz, 2H), 3.77 (s, 3H), 3.71 (br s, 1H), 3.55 (d, *J* = 12.4 Hz, 1H), 3.24 (d, *J* = 12.3 Hz, 1H), 2.86 (ddd, *J* = 13.6, 10.9, 5.6 Hz, 1H), 2.50 (ddd, *J* = 13.6, 11.2, 5.8 Hz, 1H), 2.18-2.03 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 152.6, 142.2, 141.3, 128.5, 128.4, 126.1, 115.2, 114.8, 77.4, 62.4, 55.8, 52.8, 38.6, 29.7, 14.2. HRMS: *m/z* calculated for $[C_{20}H_{25}NO_4]^+$: 343.1856; found: 343.1847. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane:^{i}PrOH (80:20)]; flow rate 1 mL/min; 30 °C, τ_{major} = 9.8 min, τ_{minor} = 12.4 min (62% ee); $[\alpha]_D^{23}$ = −6.3 (*c* 1.0, $CHCl_3$).

Ethyl (*R*)-2-hydroxy-3-[(4-methoxyphenyl)amino]-2-phenyl propanoate [(*R*)-**5h**]: Yellowish oil (101 mg, 51%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.6 Hz, 2H), 7.45-7.32 (m, 3H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.19 (br s, 1H)4.01 (d, *J* = 12.4 Hz, 1H), 3.75 (s, 3H), 3.39 (d, *J* = 12.4 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 152.7, 142.2, 139.7, 128.5, 128.2, 125.5, 115.5, 114.8, 78.7, 62.8, 55.8, 53.4, 14.0. HRMS: *m/z* calculated for $[C_{18}H_{23}NO_4]^+$: 316.1543; found: 316.1540. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane:^{i}PrOH (80:20)]; flow rate 1 mL/min; 30 °C, τ_{major} = 16.2 min, τ_{minor} = 12.6 min (90% ee); $[\alpha]_D^{20}$ = +11.7 (*c* 1.01, $CHCl_3$).

Ethyl (*R*)-2-(4-cyanophenyl)-2-hydroxy-3-[(4-methoxyphenyl) amino]propanoate [(*R*)-**5i**]: Yellowish oil (94 mg, 46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 6.72-6.66 (m, 2H), 6.64-6.55 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.87 (d, *J* = 12.6 Hz, 1H), 3.66 (s, 3H), 3.28 (d, *J* = 12.6 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 151.9, 143.7, 140.6, 131.2,

125.5, 117.5, 114.6, 113.8, 111.2, 77.5, 62.3, 54.7, 52.6, 13.0. HRMS: *m/z* calculated for $[C_{19}H_{22}N_2O_4]^+$: 341.1496; found: 341.1496. The enantiomeric excess was determined by HPLC using a Chiralpak IB column [hexane:^{i}PrOH (90:10)]; flow rate 1 mL/min; 30 °C, τ_{major} = 15.9 min, τ_{minor} = 14.2 min (90% ee); $[\alpha]_D^{23}$ = +11.3 (*c* 1.2, $CHCl_3$).

Ethyl (*R*)-2-(3,4-dichlorophenyl)-2-hydroxy-3-[(4-methoxyphenyl) amino]propanoate [(*R*)-**5j**]: Yellow oil (106 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 2.1 Hz, 1H), 7.54 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 6.83-6.77 (m, 2H), 6.73-6.66 (m, 2H), 4.27-4.24 (m, 2H), 3.94 (d, *J* = 12.5 Hz, 1H), 3.77 (s, 3H), 3.36 (d, *J* = 12.5 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 152.9, 141.7, 139.8, 132.7, 132.5, 130.4, 127.9, 125.1, 115.6, 114.8, 78.0, 63.3, 55.8, 53.6, 14.0. HRMS: *m/z* calculated for $[C_{18}H_{20}NO_4Cl_2]^+$: 384.0764; found: 384.0757. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane/*i*-PrOH (80:20)]; flow rate 1 mL/min; τ_{major} = 11.6 min, τ_{minor} = 10.3 min (84% ee); $[\alpha]_D^{20}$ = +10.4 (*c* 0.5, $CHCl_3$).

Ethyl (*R*)-2-(2,4-difluorophenyl)-2-hydroxy-3-[(4-methoxyphenyl) amino]propanoate [(*R*)-**5k**]: Yellowish oil (93 mg, 44%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 1H), 6.87-6.79 (m, 1H), 6.79-6.73 (m, 1H), 6.73-6.67 (m, 2H), 6.65-6.58 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.97 (d, *J* = 12.5 Hz, 1H), 3.47 (d, *J* = 12.5 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 162.9 (dd, *J* = 250.2, 12.2 Hz), 160.4 (dd, *J* = 250.9, 11.8 Hz), 153.0, 141.7, 128.9 (dd, *J* = 9.7, 5.5 Hz), 123.4 (dd, *J* = 12.7, 3.9 Hz), 115.6, 114.8, 111.3 (dd, *J* = 21.0, 3.5 Hz), 104.6 (dd, *J* = 26.6, 25.6 Hz), 75.8 (d, *J* = 2.5 Hz), 62.8, 55.8, 51.4 (d, *J* = 4.0 Hz), 13.9. ^{19}F NMR (283 MHz, $CDCl_3$) δ −108.39 (d, *J* = 8.5 Hz), −109.89 (d, *J* = 8.5 Hz). HRMS: *m/z* calculated for $[C_{18}H_{21}F_2NO_4]^+$: 352.1355; found: 352.1350. The enantiomeric excess was determined by HPLC using a Chiralpak IA column [hexane:^{i}PrOH (80:20)]; flow rate 1 mL/min; 30 °C, τ_{major} =9.6 min, τ_{minor} = 12.6 min (93% ee); $[\alpha]_D^{23}$ = +8.0 (*c* 1.0, $CHCl_3$).

Ethyl (*R*)-2-hydroxy-3-[(4-methoxyphenyl)amino]-2-(thiophen-2-yl) propanoate [(*R*)-**5l**]: Yellowish oil (79 mg, 41%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.10 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.70 (d, *J* = 8.3 Hz, 2H), 6.59 (d, *J* = 8.3 Hz, 2H), 4.19-4.10 (m, 2H), 4.07 (d, *J* = 6.5 Hz, 1H), 3.66 (s, 3H), 3.38 (d, *J* = 6.5 Hz, 1H), 1.18 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 152.8, 144.1, 141.8, 127.2, 125.4, 124.4, 115.5, 114.6, 77.7, 63.1, 55.8, 54.5, 14.0. HRMS: *m/z* calculated for $[C_{16}H_{21}NO_4S]^+$: 322.1108; found: 322.1103. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane:^{i}PrOH (80:20)]; flow rate 1 mL/min; 30 °C, τ_{major} = 19.2 min, τ_{minor} = 15.3 min (84% ee); $[\alpha]_D^{23}$ = +11.8 (*c* 0.9, $CHCl_3$).

General procedure for the synthesis of diols 13

Following the general procedure for the catalytic enantioselective reactions of hydrazone **1** (1.2 mmol) with α-keto esters **2** (0.6 mmol). After consumption of starting material, solvent was removed *in vacuo* and the residue was dissolved in Et_2O (5.5 mL), cooled to 0 ˚C, and HCl (6 M, 2.5 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h., then extracted with Et_2O (2 x 5 mL) and CH_2Cl_2 (2 x 5 mL). Organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to afford α-hydroxy aldehyde **12**. Bu_4NBH_4 (112 mg, 0.4 mmol) was added to a solution of crude aldehyde in CH_2Cl_2 (3 mL) at room temperature. The reaction mixture was stirred for 2-3 h. Flash chromatography (CH_2Cl_2/MeOH 97:3) afforded the pure diols **13**.

Ethyl (*S*)-2-hydroxy-2-(hydroxymethyl)pentanoate [(*S*)-**13c**]: yellow oil (45 mg, 43%). $[\alpha]_D^{25}$ = −5.6 (*c* 1.7, $CHCl_3$, 50% ee). Lit. $[\alpha]_D^{25}$ = 11.1 [*c* 4.0, $CHCl_3$, 44% ee, (*R*)].[16a]

Ethyl (*S*)-2-benzyl-2,3-dihydroxypropanoate [(*S*)-**13e**]: yellow oil (85 mg, 63%). $[\alpha]_D^{25}$ = +9.8 (*c* 0.8, $CHCl_3$, 60% ee). Lit. $[\alpha]_D^{25}$ = +10.4 (*c* 0.9, $CHCl_3$, 76% ee).[16b]

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Notes and references

∫ Reactions performed at lower temperatures resulted in longer reaction times without improvement of the enantioselectivities. Additionally, 1 M concentration of **2** was selected as the best option: the enantioselectivities slightly dropped at higher concentrations (2 M) while reactions performed at *c* = 0.5 M required longer times without improvement of the enantioselectivities.

¶ These results apparently indicates that the working model depicted in Scheme 1 apply also to aliphatic derivatives, but a smaller methylene group in primary alkyl chains may accommodate better in the inner region of the catalyst resulting in lower enantioselectivities.

‡ Alternative reductive amination conditions ($BnNH_2$ instead of $PMPNH_2$ or $NaBH_4$ in MeOH/TFE medium) gave lower yields (5-30%).

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