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Zinc Hydroxide-Catalyzed Asymmetric Allylation of Acetophenones with Amido-Functionalized Allylboronate in Water

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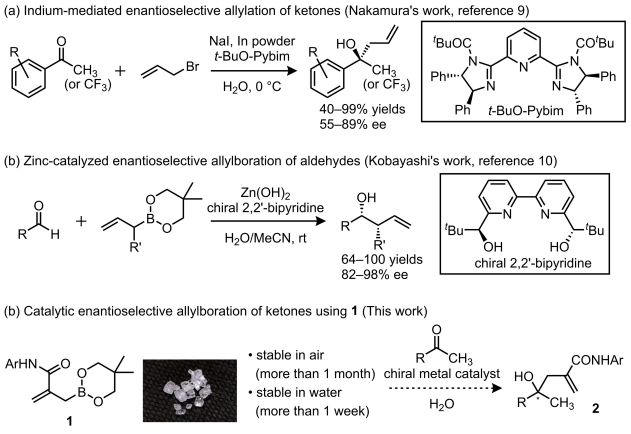
Abstract: Enantioselective allylation of aldehydes and ketones is a widely used approach for preparing chiral homoallylic alcohols, however, most of the reactions are still mainly performed in organic solvents. Considering their environmental impact, expansion of synthetic technology in water has the highest priority in the organic chemistry field. Here, we report enantioselective reaction of water-stable amido-functionalized allylboronates with acetophenone derivatives in water. The reaction was catalyzed with zinc hydroxide and a didecylamino-functionalized chiral aminophenol reagent, affording a variety of homoallylic alcohols in up to 99% yield. There is a definite proportional correlation between the enantioselectivity and the size of an *ortho*-substituent on the substrate, and the enantiomeric excess of the product reached up to 98%.

Keywords: Allylation; Amides; Amino alcohols; Boron; Zinc

Introduction

Enantioselective allylation of aldehydes and ketones is an extensively studied and widely used carbon-carbon bond forming reaction. This type of reaction enables not only to construct a chiral alcohol unit but also to install a carbon-carbon double bond which can be readily transformed into other functional groups. Therefore, the products serve as chiral building blocks for the syntheses of bioactive molecules including natural products. Great efforts have been devoted toward the development of enantioselective allylation in past decades, and homoallylic alcohols as well as homoallylic amines are nowadays accessible with high levels of stereocontrol through various catalytic systems.[1–5] Thus, allylation chemistry in organic solvents is well-developed and is continuously investigated.

Considering environmental impact of organic solvents, expansion of synthetic technology of organic compounds in water has the highest priority and becomes a major issue in the current synthetic chemistry field. Biomimetic reactions represented by aldol reaction have become controllable to some extent in water.[6] However, many catalytic enantioselective carbon-carbon bond forming reactions are still mainly performed in organic solvents because reagents and in situ generated reactive species are incompatible with water. Development of asymmetric allylation in aqueous media has been one of the major challenges in these decades and reactions using allylindium species have attracted attention because of its water stability.[7] Loh and Zhou reported the first example of enantioselective allylation of aldehydes using indium species in aqueous media, in which (*S*,*S*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)pyridine was used as a chiral source.[8] More recently, the Nakamura's research group reported enantioselective allylation of ketones using allylindium reagent prepared from allyl bromide and indium metal (Scheme 1a).[9] Their reaction system, to the best of our knowledge, provided the most successful result on the reaction with ketones in pure water, giving the adduct with up to 89% ee. However, despite of the high ees, major drawback is the stoichiometric use of relatively expensive indium metal. Besides indium species, allylboronates can be used for catalytic



Scheme 1. Enantioselective allylation in aqueous media.

enantioselective allylation in aqueous media. Kobayashi and his co-workers realized the relevant reaction of aldehydes by employing chiral zinc catalysis in water-acetonitrile solution (Scheme 1b).[10,11] They also succeeded the development of an analogous reaction using imino substrates, where chiral allylglycine derivatives were provided with up to 88% ee.[12] These results show the potential utility of allylboronates in asymmetric allylation in water.

In addition to the reaction using nonsubstituted allylmetal reagents, allylation with functionalized ones is of great importance due to the broad utility in complex molecule synthesis.[13–19] In this context, we demonstrated the utility of allylboronate (**1**) bearing amide functionality at the β position for the construction of spiroheterocycles and have succeeded the syntheses of four types of bisheterocyclic spiro compounds.[17,20,21] Moreover, we recently discovered the remarkable air- and water-stability of **1**, which remained intact even after exposure to air and water for more than one week.[17] These synthetic utility and chemical stability of **1** motivated us to explore a new catalytic enantioselective amido-functionalized allylation in water (Scheme 1c). In this paper, we report our work towards the development of highly enantioselective addition of **1** to acetophenone derivatives utilizing water as the reaction solvent. The reaction was accomplished by using practically water-insoluble Zn $(OH)_2$ and a newly prepared chiral aminophenol derivative.

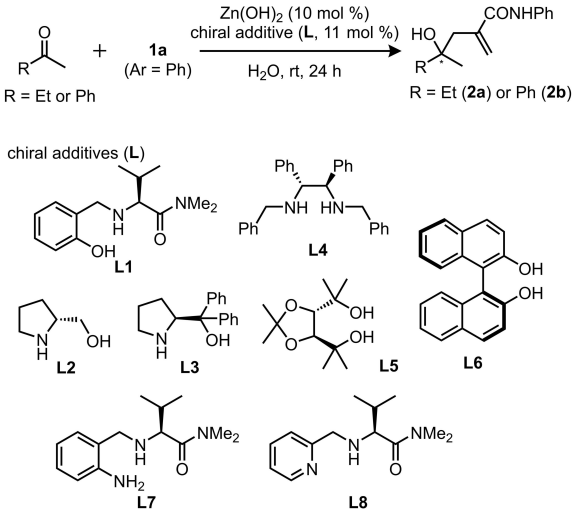
Results and Discussion

In the preliminary stage of this research, we evaluated the reactivity of amido-functionalized allylboronate in water in the absence/presence of additives. We chose 2-butanone as a substrate because of its water-soluble property. Similar to the results obtained in the previous experiment performed in toluene,[20] **1a** did not show sufficient reactivity without additives (Entry 1 in the Table S1 in the Supporting Information). Variety of alkali or alkaline-earth metal salts were first examined as a water-soluble additive, but no or only a trace amount of the desired product was observed (Entries 2–5). Then, we employed commercially available zinc, copper, and indium salts with the expectation of activation of the allylboronate (Entries 6–12).[22–26] Use of $ZnBr_2$, $Zn(OTf)_2$, CuI, or $CuBr_2$ resulted in almost no reaction. On the other hand, $Zn(OMe)_2$ and Zn $(OH)_2$ successfully mediated the desired nucleophilic addition to provide **2a** in 28% and 26% yields, respectively, even though the reactions were carried out in a suspension (Entries 8 and 9).

Next, we explored a promising chiral source for asymmetric induction (Table 1). For this purpose, Zn $(OH)_2$ was chosen as a metal additive due to its easy availability and high cost efficiency. Initially, the reaction was performed by employing a catalytic amount of L-valine derived aminophenol **L1**, which has an efficient chiral motif for zinc-mediated asymmetric allylboration[27–29] and has been recently applied to amido-functionalized allylboration of isatins by our group in organic solvents,[21] to provide low but significant enantiomeric enrichment of the product (Entry 1, 56% yield, 13% ee). On the other hand, chiral reagents bearing 1,2-aminoalcohol, diamine, or diol structure (**L2**–**6**) showed almost no or poor effects on both yields and enantioselectivities (Entries 2–6). Promising potential of the chiral aminophenol reagent was further affirmed through the experiments using acetophenone (Entries 7–12), in which **2b** was given in 76% with 53% ee in the presence of $Zn(OH)_2$ and **L1** under highly diluted conditions (0.04 M for acetophenone). Moreover, the phenol moiety of **L1** was found to be important for asymmetric induction by comparing the results obtained with analogous aniline (**L7**) or pyridine (**L8**) derivative (Entries 13 and 14).[30]

With the acceptable results obtained in zinc-aminophenol catalysis, we turned our attention to structural optimization of the aminophenol additive. Moderate yields in the reactions using *N*,*N*-dimethylamide derivative **L1** would be attributed to the fact that **L1** is a solid and hardly water-soluble material and gives a heterogeneous solid-solution system during the course of the reaction (Figure 1a). Therefore, our initial interest on structure modification was to introduce aliphatic residues on the amide moiety in order to obtain chiral aminophenols as oily materials. Thus, installation of dialkylamino (didecyl- and didodecylamino) or monoalkylamino (benzyl-, pentyl-, decyl-, and *tert*-butylamino) groups gave several kinds of chiral aminophenols **L9**–**14** as an oil, respectively (Figure 1b). As we expected, **L9**–**14** were well-dispersed in water by vigorous stirring, and the reaction efficiency was increased with comparable levels of stereocontrol (79–90% yields, 55–65% ee).

Table 1. Screening of chiral additives for $Zn(OH)_2$-catalyzed allylation in water.[a]



Entry	ketone (R)	L	Yield [%]	Ee [% ee][b]
1	Et	**L1**	56	13
2	Et	**L2**	27	8
3	Et	**L3**	20	6
4	Et	**L4**	11	1
5	Et	**L5**	26	1
6	Et	**L6**	24	3
7	Ph	**L1**	76	53
8	Ph	**L2**	78	12
9	Ph	**L3**	62	0
10	Ph	**L4**	15	22
11	Ph	**L5**	92	0
12	Ph	**L6**	58	1
13	Ph	**L7**	74	45
14	Ph	**L8**	52	14

[a] Reactions were carried out with ketone (0.200 mmol), **1a** (0.300 mmol), $Zn(OH)_2$ (10 mol%), and **L** (11 mol%) in water (1.0 mL for 2-butanone or 5.0 mL for acetophenone) for 24 h.

[b] The ee values were determined by chiral HPLC analysis using Daicel Chiralpak IF (for **2a**) or IC (for **2b**).

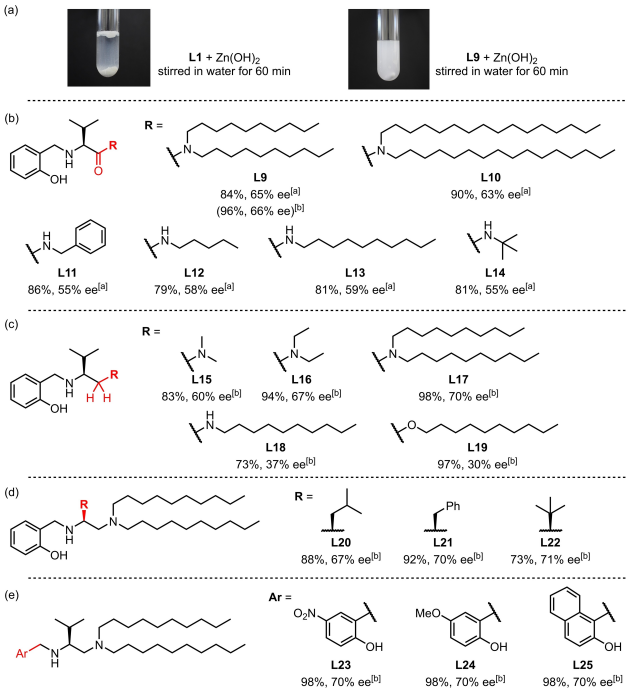
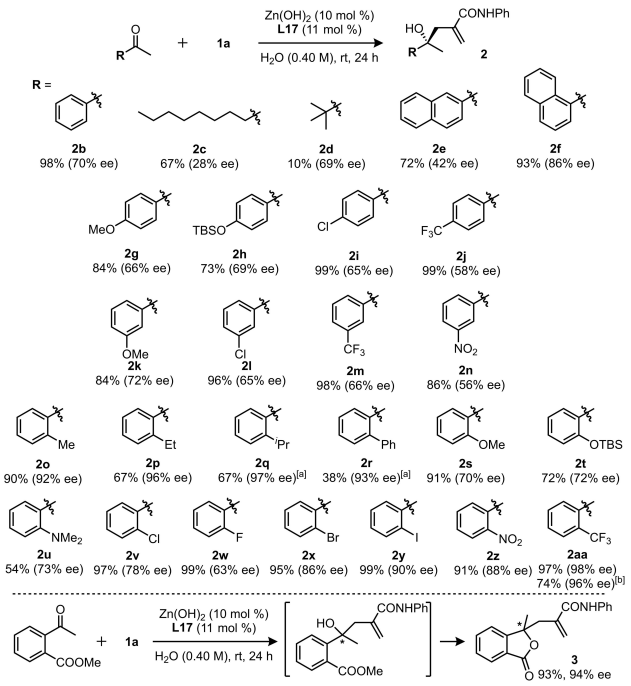


Figure 1. Screening of chiral aminophenols for $Zn(OH)_2$-catalyzed allylation of acetophenone in water. Reactions were carried out with acetophenone (0.200 mmol), **1a** (0.300 mmol), $Zn(OH)_2$ (10 mol%), and **L** (11 mol%) in water ([a] 0.04 M or [b] 0.4 M for acetophenone, respectively) for 24 h.

Additionally, this reagent property fortunately allowed to increase the substrate concentration to 0.4 M without any loss of enantioselectivity (**L9**, 96% yield, 66% ee). Subsequently, we further modified the amide moiety to the corresponding amine by reduction with $LiAlH_4$ in order to evaluate the effect of the carbonyl group (Figure 1c). Tertiary amine derivatives **L15–17** showed improved activity and stereoselectivity compared with the amide derivatives **L1** and **L9**, providing **2b** in up to 98% yield and 70% ee (**L17**). Meanwhile, *mono*-decylamine **L18** and its analogous ether **L19** led to significant decrease of enantioselectivity, indicating that the dialkylamino moiety plays a critical role in enantiodifferentiation of a prochiral ketone. Then, we attempted to control the steric environment around the amine moiety of **L17** by preparing chiral amionophenol derivatives from L-leucine, L-phenylalanine, and 3-methyl-L-valine, respectively (Figure 1d). Contrary to our expectation, reactions using **L20–22** indicated the almost same levels of enantioselectivities (67–71% ee), demonstrating that the steric factor of the alkyl side chain does not influence the stereochemical outcome. Finally, we carried out reactions using **L23–25** for evaluating the effect of electron density on phenol moiety (Figure 1e). As a result, installation of electron-withdrawing or electron-donating group to the aromatic ring brings no effect on the reaction efficiency to give **1a** in the identical yield and stereoselectivity. Thus, we found that the reagent combination of $Zn(OH)_2$ and **L17** exhibited the best performance in terms of reaction efficiency and asymmetric induction.

Having optimized both the metal salt and the chiral aminophenol reagent, we surveyed asymmetric allylation of a variety of methyl ketones with **1a** in water (Scheme 2).[31] 2-Decanone gave the corresponding product in 67% yield, albeit with low asymmetric induction (**2c**: 28% ee). Substrate reactivity is strongly dependent on the steric bulkiness around the keto group, whereby reaction of *tert*-butyl methyl ketone resulted in only 10% yield of **2d** (69% ee). Meanwhile, allylation of methyl 1-naphthyl ketone with a moderate

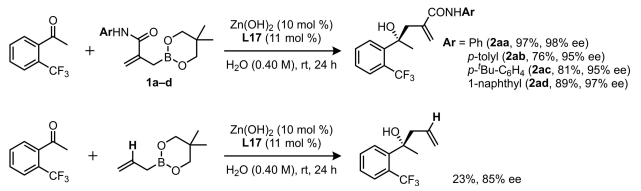


Scheme 2. Reactions of ketones with **1a** in water. The ee values were determined by HPLC analysis on a chiral stationary phase. The absolute configurations of acetophenone derivatives were tentatively assigned to be *S* by analogy (see Scheme S1). [a] Reactions were carried out for 72 h. [b] The reaction was carried out with 2 mol% of $Zn(OH)_2$ and **L17**.

steric environment proceeded with high facial selectivity rather than the case with 2-naphthyl methyl ketone (**2e**: 72%, 42% ee), affording the desired adduct **2f** in 93% yield with 86% ee. As for functional groups, this protocol can tolerate not only electron-donating but also electron-withdrawing functionalities at *para*- and *meta*-positions of acetophenone derivatives, providing **2g**–**2n** in excellent yields with comparable enantioselectivities. The substrate bearing a relatively small *ortho*-methyl group gave **2o** with 92% ee, meanwhile *ortho*-ethyl and *ortho*-isopropyl derivatives provided the corresponding adducts with remarkably high enantioselectivities, respectively (**2p**: 96% ee, **2q**: 97% ee). A similar trend in enantioselectivity was observed in the case of *ortho*-halophenyl derivatives, where the values of product ees are approximately proportional to the sizes of halogens (**2w** (F): 63% ee, **2v** (Cl): 78% ee, **2x** (Br): 86% ee, **2y** (I): 90% ee). Among a series of acetophenones bearing an *ortho*-substituent, 2'-(trifluoromethyl)acetophenone gave the corresponding product **2aa** with the highest enantioselectivity (98% ee). From these results, it is apparent that the enantioselectivity is not influenced by the electronic effect of substrates but is heavily influenced by the appropriate size of *ortho*-substituents. The highest performance for **2aa** was almost maintained even when the reaction was carried out with only 2 mol% of $Zn(OH)_2$ and **L17** (96% ee). On the basis of these reaction profiles, we estimated that our reaction system should be advantageous for the preparation of highly enantioenriched 3,3-disubstituted phthalides[32] possessing a synthetically useful carbonyl functionality on its side chain. Thus, use of methyl 2-acetylbenzoate as a substrate was found to give **3** in one pot via spontaneous cyclization of the resulting adduct (93% yield, 94% ee).

Furthermore, we evaluated the effect of amide functionality on the allylboronate (Scheme 3). When the reaction was carried out with *para*-substituted phenyl derivatives **1b**, **c**, the corresponding adducts **2ab** and **2ac** were given in good yields with consistently excellent enantioselectivities (95% ee). Our reaction system was also applicable to relatively sterically hindered *N*-1-naphthyl allylboronate **1d**, providing **2ad** in excellent yield and enantioselectivity (89%, 97% ee).[33] On the other hand, the reaction using commercially available 2-allyl-5,5-dimethyl-1,3,2-dioxaborinane gave the corresponding product in only 23% yield with 85% ee along with the recovery of a substantial amount of the ketone. These results highlight the utility of the amido-functionalized allylboronates for organic synthesis in water.

We subsequently focused on the confirmation of the absolute configuration of the newly formed stereocenter (Scheme S1 in the Supporting Information). Fortunately, compound **2y** could be further purified by recrystallization from ethyl acetate/hexane (99% ee) to afford X-ray quality crystals. The single-crystal X-ray diffraction analysis showed that the molecules adopt the monoclinic space group $P2_1$ with the Flack parameter of −0.035(9), clearly demonstrating that the absolute configuration of the newly formed stereocenter is *S*.[34,35] The iodine atom of ***S*-2y** was then removed by hydrogenation with Pd/C to form **2a** in 30% yield with no erosion of stereointegrity (99% ee). By comparison of the HPLC profiles, the major enantiomer obtained in Table 1 was found to be identical to ***S*-2a**. Furthermore, we attempted to determine the stereochemistry of **2f** and **2aa** through the single-crystal X-ray diffraction analysis using the anomalous dispersion method.[35] Initially, **2f** and **2aa** were recrystallized from ethyl acetate/hexane to provide the highly optically pure materials (99% ee). γ-Hydroxylactam moiety of these compounds was



Scheme 3. Effect of amide functionality on **1**.

successfully cyclized in the presence of *p*-toluenesulfonic acid in dichloromethane to give the corresponding lactams, which were in turn subjected to 1,4-addition of *p*-chlorothiophenol in the presence of trimethylamine. The resulting diastereomeric mixture (39:61) of both products **4a**, **b** were separated by silica gel column chromatography, and subsequent oxidization of the more polar diastereomers (major diastereomers) with *m*-chloroperbenzoic acid generated the corresponding sulfones **5a** and **5b** in 81 and 74% yield, respectively (99% ee). These products afforded X-ray quality crystals from EtOAc-hexane and the single-crystal X-ray diffraction analyses gave small Flack parameters of 0.00(5) and 0.00(2), respectively, allowing the unambiguous assignment of the absolute configurations of both compounds as *S*.[36,37] These results suggest that amido-functionalized allylation of acetophenone derivatives would proceed in the same manner to give the *S* adducts as a major enantiomer.

As mentioned in the screening of chiral aminophenols, **L9**–**25** dispersed in water by stirring, but $Zn(OH)_2$ still remained insoluble (solubility 1.0×10^{-5} mol/L–H_2O)[38] under all the reaction conditions discussed above. However, there is no doubt that the presence of water-insoluble $Zn(OH)_2$ was indeed essential to achieve excellent reaction efficiency as well as asymmetric induction. We speculated that dispersion of $Zn(OH)_2$, even though the amount is quite small, into water should be critical to induce the reaction, and probably a chiral aminophenol would support dispersion of $Zn(OH)_2$ by complexation. To verify this hypothesis, we next made analysis of the reaction time-product yield profiles with/without the chiral aminophenol reagent (Figure S1 in the Supporting Information). The yield of **2b** reached a maximum of 98% in the presence of **L17** within 5 hours, whereas only 38% yield of the product was obtained in the absence of the chiral reagent even after 9 hour reaction time. On the other hand, the enantiomeric excess of **2b** was constant at 70% ee at any time point during the course of the reaction. We also conducted a systematic evaluation of the effect of catalyst loading (Scheme S2 in the Supporting Information), in which the product enantioselectivity was 70% ee, irrespective of the amount of $Zn(OH)_2$ (5–100 mol%). These results suggest that the rate of background reaction without involvement of aminophenols **L** is likely to be negligible in our reaction system and the desired allylation reaction would be successfully accelerated by a chiral complex composed of aminophenol reagent and $Zn(OH)_2$.

As for the effect of water in our reaction system, the enantiomeric excess of the product was found to be independent of the amount of water added since **2aa** was constantly given with 98% ee in all reactions carried out in various aqueous THF media (Figure S2 in the Supporting Information). Meanwhile, reaction efficiency depended to a large extent on the THF-water ratio, and the reaction performed in pure water provided **2aa** in the highest yield (97%) with excellent enantioselectivity (98% ee). In addition, reactions carried out with **L1** in organic solvents resulted in almost no product formation (Table S3 in the Supporting Information). On the basis of these observations, we inferred that water would support the degradation of the product-catalyst complex to release $Zn(OH)_2$-aminophenol catalyst. Furthermore, ^{1}H NMR spectra of a suspension of **1a** and $Zn(OH)_2$ (1:1 mixture) in D_2O shows that the allylboronate was partly transformed into 2-(hydroxymethyl)-*N*-phenylacrylamide and a new structurally unidentified species which was not identical to *N*-phenylmethacrylamide (Figure S3 in the Supporting Information). Notably, **1a** was almost completely converted to 2-(hydroxymethyl)-*N*-phenylacrylamide within 10 minutes in the case of 1:1:1 mixture of **1a**, $Zn(OH)_2$ and **L17**, clearly indicating that the chiral aminophenol accelerated the relevant transformation.[39] Considering these outcomes, we estimated that allylboronate would be in situ transformed into an allylzinc species by $Zn(OH)_2$-aminophenol complex and then undergo enantioselective addition to the ketone as opposed to the Hoveyda's allylboration[40] in an organic solvent where zinc reagent works as a Lewis acid. Furthermore, the resultant homoallylic alkoxyzinc species should be hydrolyzed in water to recover $Zn(OH)_2$-aminophenol complex.

Facial selectivity is briefly discussed with reaction modes **A**–**C**, in which cyclic structure consisting of a substrate and an allylic species would be formed (Figure 2).[40] The interaction between the catalyst's didecylamino moiety and the amide hydrogen of **1** may be responsible for the high reaction efficiency and enantiocontrol because of the fact that the amide hydrogen atom on **1** was essential to the success of the

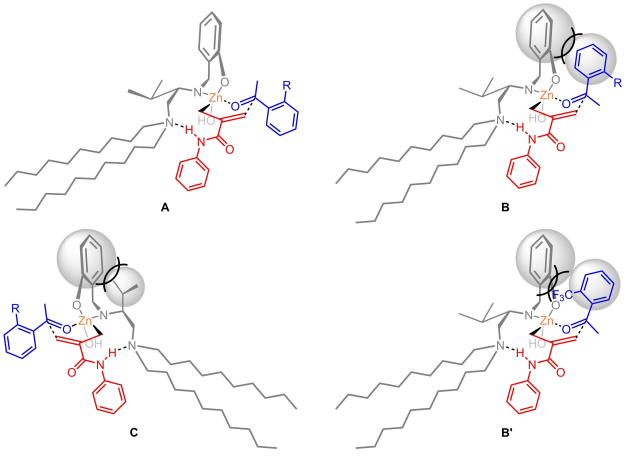


Figure 2. Plausible transition states for enantioselective amido-functionalized allylation in water.

reaction.[33,11] Modes **B** and **C** would be destabilized due to the steric repulsion between the catalyst's aryl group and the substrate phenyl group (mode **B**) or the catalyst's side chain (mode **C**). The high enantiomeric excess of **2 aa** can be explained with mode **A** (R=CF_3) in consideration of the increased steric repulsion observed on **B′** in which the ortho substituent is oriented toward the aryl group to minimize nonbonded interaction with the methyl group.

Finally, we attempted to render our protocol more environmentally friendly by testing reusability and reducibility of the chiral catalyst. The chiral aminophenol **L17** could be separated from the reaction mixture of **2 aa** by silica gel column chromatography (hexane/EtOAc = 7/1 as an eluent) and was obtained with sufficiently high purity (recovery yields on three cycles: 40–60%). Recovered **L17** was used for the next cycles to afford **2 aa** in comparable yields and enantioselectivities (the second cycle: 93% yield, 94% ee; the third cycle: 97% yield, 95% ee). As for the effect of catalyst amounts, **2 aa** was given in 79% yield with 96% ee, even when the reaction was performed in the presence of 2.5 mol% of $Zn(OH)_2$ and **L17** (Figure S4 in the Supporting Information). In addition to these investigations, we tried to simplify the work-up procedure by skipping the extraction step. The reaction mixture including **2 aa** obtained under the optimum reaction conditions was concentrated under the reduced pressure, and the resultant was transferred directly to the silica gel column. As a result, the desired product was successfully isolated in 91% yield with 95% ee. Thus, from the viewpoint of reuse and reduction, we could provide more environmentally benign protocol for amido-functionalized allylation with this chiral reagent.

Conclusion

In conclusion, we have succeeded in the development of a catalytic enantioselective allylation of acetophenones in water. Our reaction system consists of water-stable allylboronate bearing an amide functionality and $Zn(OH)_2$-chiral aminophenol catalyst and gave the corresponding allyl adducts with up to 98% ee. There is a definite proportional correlation between the reaction enantioselectivity and the size of an *ortho*-substituent on a substrate. Water would work as not only the reaction solvent but also a reagent for the degradation of the Zn–O bond in the product-catalyst complex. The present work providing chiral homoallylic alcohols bearing an amide unit under organic solvent-free reaction conditions will be valuable for future pharmaceutical development and can open new perspectives in stereoselective organic synthesis in water.

Experimental Section

General methods

All solvents and reagents were of reagent grade quality and used without further purification unless otherwise stated. Chloroform, acetonitrile, toluene and dichloromethane were dried over MS 4 Å or MS 3 Å prior to use, respectively. Tetrahydrofuran was dried over Na wire under a nitrogen atmosphere. The ^1H and $^{13}C\{^1H\}$ nuclear magnetic resonance (NMR) spectra operating at the frequencies of 300 and 75 MHz, respectively, on a JEOL JNM-AL300 spectrometer were recorded in chloroform-*d* ($CDCl_3$) unless otherwise noted. Chemical shifts are reported in parts per million (ppm) relative to TMS and the solvent used as internal standards, and the coupling constants are reported in hertz (Hz). Thin layer chromatography (TLC) was performed using Merck TLC silica gel $60F_{254}$, visualized by irradiation with UV light and/or by treatment with phosphomolybdic acid or *p*-anisaldehyde stain followed by heating. Column chromatography was performed using silica gel 60 N (spherical neutral) from Kanto Chemical Co. and eluting with the indicated solvent system. Fourier transform infrared (FTIR) spectra were recorded on a JASCO FT/IR-550 spectrometer. Optical rotations were measured in 1 dm path length cell of 2 mL capacity using a JASCO Model DIP-1000 and P-2200 polarimeter at a wavelength of 589 nm. Elemental analyses were performed by JSL Model JM 10 instruments. Allylboronates **1** were prepared according to the literature procedure.[17] Aminophenols (**L11**, **L12**, and **L14**) were prepared according to the literature procedure.[21,41] Synthetic schemes are summarized in the Supporting Information (Schemes S3–S7).

Synthesis and characterization of (*S*)-2-((2-aminobenzyl)amino)-*N*,*N*,3-trimethylbutanamide (L7)

To a solution of *N*-Boc-L-valine (928 mg, 4.27 mmol) in anhydrous dichloromethane (17 mL), dimethylamine (*ca.* 50% in water, 1.1 mL, 11 mmol, 2.5 equiv.), 1-(2-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 901 mg, 4.70 mmol, 1.1 equiv.) and 1-hydroxybenzotriazole (HOBt, 635 mg, 4.70 mmol, 1.1 equiv.) were added at room temperature. After stirring the mixture at the same temperature for 16 hours, the reaction was quenched by addition of saturated aqueous citric acid (20 mL). The resulting solution was filtered through a pad of celite and the filtrate was extracted with dichloromethane (20 mL). The organic extract was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material (1.04 g), which was used without further purification: R_f = 0.43 (silica gel, hexane/EtOAc = 1/1).

To a solution of the crude material (1.04 g) in 1,4-dioxane (8.5 mL), *conc.* hydrochloric acid (2.6 mL, 25 mmol, 6.0 equiv.) was added at 0 °C. The solution was warmed to room temperature and stirred for 4 hours. The reaction mixture was concentrated in vacuo and the resulting material was dissolved in anhydrous dichloromethane (14 mL). Triethylamine (1.8 mL, 13 mmol, 3.0 equiv.), 2-(Boc-amino)benzaldehyde (924 mg, 4.18 mmol, 1.0 equiv.) and magnesium sulfate (1.54 g, 12.8 mmol, 3.0 equiv.) were added to the solution at room temperature. After stirring the mixture at the same temperature

for 12 hours, the resulting mixture was concentrated in vacuo. The resulting material was roughly purified by column chromatography (silica gel, hexane/EtOAc = 1/1) to give a crude material (1.71 g), which was used without further purification: R_f = 0.23 (silica gel, hexane/EtOAc = 2/1).

To a solution of the crude material (1.71 g) in methanol (11 mL), sodium borohydride (646 mg, 17.0 mmol, 4.0 equiv.) and *conc.* hydrochloric acid (1 drop) were added at 0 °C. The solution was warmed to room temperature and stirred for 2 hours. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (5.0 mL), and the resulting mixture was extracted with dichloromethane (20 mL × 2). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material (1.20 g), which was used without further purification: R_f = 0.31 (silica gel, hexane/EtOAc = 2/1).

To a solution of the crude material (1.20 g) in 1,4-dioxane (12 mL), *conc.* hydrochloric acid (2.0 mL, 21 mmol, 6.0 equiv.) was added at 0 °C. The solution was warmed to room temperature and stirred for 2 hours. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (30 mL), and the resulting mixture was extracted with EtOAc (30 mL). The organic extract was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1 to 2/1) to give **L7** (439 mg, 41% in 5 steps) as a white solid: *Rf* = 0.60 (silica gel, hexane/EtOAc = 1/2); $[\alpha]_D^{22}$ −58.1 (1.01 in $CHCl_3$); IR (NaCl) 3386 (N–H), 3304 (N–H), 1631 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (dt, *J* = 7.5, 1.5 Hz, 1H), 6.93 (d, *J* = 7.8, 1.2 Hz, 1H), 6.66–6.61 (m, 2H), 4.79 (brs, 1H), 3.83 (d, *J* = 12.6 Hz, 1H), 3.43 (d, *J* = 12.6 Hz, 1H), 3.20 (d, *J* = 6.3 Hz, 1H), 3.03 (s, 3H), 2.91 (s, 3H), 1.77 (m, 1H), 0.91 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 147.0, 130.0, 128.2, 123.4, 117.4, 115.5, 61.3, 51.1, 36.8, 35.5, 31.3, 19.9, 18.1. Anal. Calcd for $C_{14}H_{23}N_3O$: C, 67.43; H, 9.30; N, 16.85. Found: C, 67.35; H, 9.45; N, 16.79.

Synthesis and characterization of (*S*)-*N*,*N*,3-trimethyl-2-((pyridin-2-ylmethyl)amino)butanamide (L8)

To a solution of *N*-Boc-L-valine (741 mg, 3.41 mmol) in anhydrous dichloromethane (14 mL), dimethylamine (*ca.* 50% in water, 1.0 mL, 8.5 mmol, 2.5 equiv.), 1-(2-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 719 mg, 3.75 mmol, 1.1 equiv.) and 1-hydroxybenzotriazole (HOBt, 507 mg, 3.75 mmol, 1.1 equiv.) were added at room temperature. After stirring the mixture at the same temperature for 24 hours, the reaction was quenched by addition of saturated aqueous citric acid (20 mL). The resulting solution was filtered through a pad of celite and the filtrate was extracted with dichloromethane (20 mL). The organic extract was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material (932 mg), which was used without further purification: R_f = 0.33 (silica gel, hexane/EtOAc = 1/1).

To a solution of the crude material (932 mg) in anhydrous dichloromethane (6.8 mL), trifluoroacetic acid (2.1 mL, 21 mmol, 6.0 equiv.) was added at 0 °C. The solution was warmed to room temperature and stirred for 4 hours. The reaction mixture was concentrated in vacuo and the resulting material was dissolved in anhydrous dichloromethane (11 mL). Triethylamine (1.4 mL, 10 mmol, 3.0 equiv.), picolinaldehyde (440 mg, 4.11 mmol, 1.2 equiv.) and magnesium sulfate (1.23 g, 10.2 mmol, 3.0 equiv.) were added to the solution at room temperature. After stirring the solution at the same temperature for 18 hours, the reaction mixture was concentrated in vacuo. The resulting material was roughly purified by column chromatography (silica gel, hexane/EtOAc = 1/3) to give a crude material (451 mg), which was used without further purification: R_f = 0.15 (silica gel, hexane/EtOAc = 1/3).

To a solution of the crude material (451 mg) in methanol (11 mL), sodium borohydride (516 mg, 13.6 mmol, 4.0 equiv.) and *conc.* hydrochloric acid (1 drop) were added at 0 °C. The solution was warmed to room temperature and stirred for 1 hour. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (10 mL), and the resulting mixture was extracted with dichloromethane (20 mL × 2). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 1/2 to 1/3) to give **L8** (34.9 mg, 4.3% in 4 steps) as a pale yellow oil: *Rf* = 0.33 (silica gel, hexane/EtOAc = 1/3); $[\alpha]_D^{23}$ −30.7 (*c* 0.48 in $CHCl_3$); IR (NaCl) 3433 (N–H), 1632 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, *J* = 5.7 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.94 (t, *J* = 7.8 Hz, 1H), 7.32 (m, 1H), 4.22 (d, *J* = 18.3 Hz, 1H), 3.99 (d, *J* = 18.3 Hz, 1H), 3.28 (d, *J* = 6.0 Hz, 1H), 3.03 (s, 3H), 3.02 (s, 3H), 2.31 (brs, 1H), 1.88 (sextet, *J* = 6.3 Hz, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 160.4, 148.7, 136.4, 122.2, 121.7, 62.4, 54.0, 37.0, 35.6, 31.5, 19.7, 18.3. Anal. Calcd for $C_{13}H_{21}N_3O$: C, 66.35; H, 8.99; N, 17.86. Found: C, 66.00; H, 8.66; N, 17.48.

Characterization of (*S*)-*N*,*N*-didecyl-2-((2-hydroxybenzyl)amino)-3-methylbutanamide (L9)

According the synthetic procedure of **L8**, **L9** (900 mg, 52% in 4 steps) was obtained from *N*-Boc-L-valine (1.08 g, 4.98 mmol), didecylamine (1.76 g, 5.91 mmol, 1.2 equiv.) and salicylaldehyde (608 mg, 4.98 mmol, 1.0 equiv.) as a colorless oil after chromatographic purification (silica gel, hexane/EtOAc = 15/1 to 8/1): *Rf* = 0.16 (silica gel, hexane/EtOAc = 10/1); $[\alpha]_D^{23}$ −7.0 (*c* 1.07 in $CHCl_3$); IR (NaCl) 3287 (O–H), 1634 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (dt, *J* = 7.8, 1.2 Hz, 1H), 6.91 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.84 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.74 (dt, *J* = 7.8 Hz, 0.9 Hz, 1H), 4.05 (d, *J* = 14.0 Hz, 1H), 3.73–3.64 (m, 1H), 3.54 (d, *J* = 14.0 Hz, 1H), 3.28–3.17 (m, 2H), 3.11–2.93 (m, 2H), 1.84 (sext, *J* = 5.1 Hz, 1H), 1.57–1.21 (m, 32H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 158.1, 128.7, 128.5, 122.3, 118.9, 116.3, 61.6, 51.2, 47.2, 45.9, 31.81, 31.79, 31.4, 29.53, 29.45, 29.4, 29.3, 29.22, 29.17, 29.1, 27.6, 27.0, 26.7, 22.6, 20.4, 17.2, 14.0. Anal. Calcd for $C_{32}H_{58}N_2O_2$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.27; H, 11.28; N, 5.68.

Characterization of (*S*)-*N*,*N*-dihexadecyl-2-((2-hydroxybenzyl)amino)-3-methylbutanamide (L10)

According the synthetic procedure of **L8**, **L10** (1.35 g, 47% in 4 steps) was obtained from *N*-Boc-L-valine (928 mg, 4.27 mmol), dipalmitoylamine (3.69 g, 7.92 mmol, 1.9 equiv.) and salicylaldehyde (521 mg, 4.27 mmol, 1.0 equiv.) as a colorless oil after chromatographic purification (silica gel, hexane/EtOAc = 10/1): *Rf* = 0.50 (silica gel, hexane/EtOAc = 5/1); $[\alpha]_D^{23}$ −5.4 (*c* 1.00 in $CHCl_3$); IR (NaCl) 3280 (O–H), 1636 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.91 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 4.05 (d, *J* = 13.8 Hz, 1H), 3.70 (quintet, *J* = 7.5 Hz, 1H), 3.54 (d, *J* = 13.8 Hz, 1H), 3.28–3.17 (m, 2H), 3.11–2.93 (m, 2H), 1.84 (sext, *J* = 6.6 Hz 1H), 1.57–1.26 (s, 56H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 158.1, 128.8, 128.6, 122.4, 119.0, 116.3, 61.6, 51.2, 47.3, 46.0, 31.9, 31.4, 29.7, 29.63, 29.59, 29.52, 29.46, 29.3, 29.1, 27.7, 27.0, 26.8, 22.7, 20.4, 17.3, 14.1. Anal. Calcd for $C_{44}H_{82}N_2O_2$: C, 78.74; H, 12.32; N, 4.17. Found: C, 78.37; H, 12.06; N, 4.11.

Characterization of (*S*)-*N*-decyl-2-((2-hydroxybenzyl)amino)-3-methylbutanamide (L13)

According the synthetic procedure of **L8**, **L13** (881 mg, 94% in 4 steps) was obtained from *N*-Boc-L-valine (563 mg, 2.59 mmol), decylamine (1.02 g, 6.48 mmol, 2.5 equiv.) and salicylaldehyde (316 mg, 2.59 mmol, 1.0 equiv.) as a colorless oil after chromatographic purification (silica gel, hexane/EtOAc = 3/1): *Rf* = 0.60 (silica gel, hexane/EtOAc = 1/1); $[\alpha]_D^{24}$ −26.3 (*c* 1.12 in $CHCl_3$); IR (NaCl) 3311 (O–H), 1648 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (m, 1H), 6.94 (m, 1H), 6.85 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.77 (dt, *J* = 7.2, 0.9 Hz, 1H), 5.52 (d, *J* = 5.7 Hz, 1H), 4.10 (d, *J* = 13.8 Hz, 1H), 3.64 (s, *J* = 13.8 Hz, 1H), 3.33 (q, *J* = 6.0 Hz, 2H), 2.66 (d, *J* = 7.2 Hz, 1H), 1.89 (q, *J* = 3.6 Hz, 1H), 1.52 (q, *J* = 6.9 Hz, 2H), 1.36–1.23 (m, 14H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 157.6, 128.8, 128.6, 122.4, 119.1, 116.0, 67.2, 50.7, 39.4, 31.8, 31.4, 29.6, 29.49, 29.46, 29.22, 29.19, 26.9, 22.6, 19.6, 18.8, 14.0. Anal. Calcd for $C_{22}H_{38}N_2O_2$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.66; H, 10.95; N, 7.45.

Characterization of (*S*)-*N*,*N*-diethyl-2-((2-hydroxybenzyl)amino)-3-methylbutanamide (pre-L16)

According the synthetic procedure of **L8**, **pre-L16** (2.03 g 71% in 4 steps) was obtained from *N*-Boc-L-valine (2.22 g, 10.2 mmol), dimethylamine (1.87 g, 25.5 mmol, 2.5 equiv.) and salicylaldehyde (1.25 g, 10.2 mmol, 1.0 equiv.) as a colorless oil after chromatographic purification (silica gel, hexane/EtOAc = 4/1): *Rf* = 0.27 (silica gel, hexane/EtOAc = 2/1); $[\alpha]_D^{22}$ −3.3 (*c* 0.78 in $CHCl_3$); IR (NaCl) 3446 (O–H), 3294 (N–H), 1633 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (dt, *J* = 8.1, 1.5 Hz, 1H), 6.92 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.85 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.75 (dt, *J* = 8.1, 0.9 Hz, 1H), 4.05 (d, *J* = 14.0 Hz, 1H), 3.69 (m, 1H), 3.55 (d, *J* = 14.0 Hz, 1H), 3.40–3.06 (m, 4H), 1.85 (m, 1H), 1.17 (t, *J* = 6.9 Hz, 3H), 1.12 (t, *J* = 6.9 Hz, 3H), 1.00–0.97 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 158.2, 128.9, 128.5, 122.4, 119.1, 116.3, 61.6, 51.2, 41.4, 40.3, 31.6, 20.2, 17.7, 14.6, 13.0. Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.78; H, 9.09; N, 9.93.

Characterization of (*S*)-*N*,*N*-didecyl-2-((2-hydroxybenzyl)amino)-4-methylpentanamide (pre-L20)

According the synthetic procedure of **L8**, **pre-L20** (318 mg, 38% in 4 steps) was obtained from *N*-Boc-L-leucine (391 mg, 1.69 mmol), didecylamine (855 mg, 2.87 mmol, 1.7 equiv.) and salicylaldehyde (206 mg, 1.69 mmol, 1.0 equiv.) as a colorless oil after chromatographic purification (silica gel, hexane/EtOAc = 30/1 to 20/1 to 15/1): *Rf* = 0.43 (silica gel, hexane/EtOAc = 10/1); $[\alpha]_D^{23}$ −26.7 (*c* 0.99 in $CHCl_3$); IR (NaCl) 3286 (O–H), 1729 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.75 (dt, *J* = 7.5, 1.2 Hz, 1H), 4.07 (d, *J* = 13.8 Hz, 1H), 3.61–3.44 (m, 3H), 3.14 (m, 2H), 2.97 (m, 1H), 1.94 (m, 1H), 1.56–1.19 (m, 32H), 0.94–0.85 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 158.3, 128.8, 128.6, 122.4, 119.0, 116.3, 54.6, 51.0, 47.2, 46.3, 42.9, 31.9, 29.6, 29.4, 29.3, 29.3, 29.2, 29.1, 27.7, 27.0, 26.8, 24.6, 23.8, 22.6, 21.0, 14.1. Anal. Calcd for $C_{33}H_{60}N_2O_2$: C, 76.69; H, 11.70; N, 5.42. Found: C, 76.32; H, 11.34; N, 5.48.

Characterization of (*S*)-*N*,*N*-didecyl-2-((2-hydroxybenzyl)amino)-3-phenylpropanamide (pre-L21)

According the synthetic procedure of **L8**, **pre-L21** (193 mg, 22% in 4 steps) was obtained from *N*-Boc-L-phenylalanine (424 mg, 1.60 mmol), didecylamine (809 mg, 2.72 mmol, 1.7 equiv.) and salicylaldehyde (195 mg, 1.60 mmol, 1.0 equiv.) as a colorless oil after chromatographic purification (silica gel, hexane/EtOAc = 30/1 to 20/1 to 15/1): *Rf* = 0.17 (silica gel, hexane/EtOAc = 10/1); $[\alpha]_D^{24}$ −3.2 (*c* 1.10 in $CHCl_3$); *Rf* = 0.33 (silica gel, hexane/EtOAc = 15/1); IR (NaCl) 3289 (O–H), 1637 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 1H), 7.25–7.21 (m, 2H), 7.17–7.12 (m, 3H), 6.89 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.80 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.73 (dt, *J* = 7.5, 1.2 Hz, 1H), 4.02 (d, *J* = 14.1 Hz, 1H), 3.66 (t, *J* = 1.2 Hz, 1H), 3.60 (d, *J* = 14.1 Hz, 1H), 3.49 (m, 1H), 3.09 (m, 1H), 2.95–2.78 (m, 3H), 2.62 (m, 1H), 1.57–1.28 (m, 32H), 0.91–0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 158.1, 136.8, 129.3, 128.8, 128.6, 128.5, 126.9, 121.9, 119.0, 116.5, 57.7, 50.6, 47.0, 46.6, 40.4, 31.9, 29.6, 29.53, 29.46, 29.37, 29.28, 29.22, 29.1, 29.0, 27.6, 27.1, 26.7, 22.6, 14.1. Anal. Calcd for $C_{36}H_{58}N_2O_2$: C,78.49; H, 10.61; N, 5.09. Found: C, 78.47; H, 10.24; N, 5.37.

Characterization of (*S*)-*N*,*N*-didecyl-2-((2-hydroxybenzyl)amino)-3,3-dimethylbutanamide (pre-L22)

According the synthetic procedure of **L8**, **pre-L22** (677 mg, 63% in 4 steps) was obtained from *N*-Boc-L-tert-leucine (500 mg, 2.16 mmol), didecylamine (770 mg, 2.59 mmol,

1.2 equiv.) and salicylaldehyde (227 mg, 1.86 mmol, 0.9 equiv.) as a pale yellow oil after chromatographic purification (silica gel, hexane/EtOAc = 15/1 to 8/1 to 5/1): $[\alpha]_D^{22}$ + 16.0 (*c* 0.97 in $CHCl_3$); IR (NaCl) 3293 (O–H), 1634 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.74 (dt, *J* = 7.5, 1.5 Hz, 1H), 3.94 (d, *J* = 13.5 Hz, 1H), 3.74 (m, 1H), 3.57 (d, *J* = 13.5 Hz, 1H), 3.43 (m, 1H), 3.32 (s, 1H), 3.09–2.94 (m, 2H), 1.60–1.25 (m, 32H), 1.02 (s, 9H), 0.88 (t, *J* = 6.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 158.1, 128.8, 128.5, 122.4, 118.9, 116.3, 63.7, 51.4, 48.2, 46.2, 34.8, 31.8, 29.6, 29.5, 29.3, 29.24, 29.20, 29.17, 27.7, 27.2, 27.1, 26.9, 22.6, 14.1. Anal. Calcd for $C_{33}H_{60}N_2O_2$: C, 76.69; H, 11.70; N, 5.42. Found: C, 76.60; H, 12.06; N, 5.44.

Synthesis and characterization of (*S*)-2-(((1-(dimethylamino)-3-methylbutan-2-yl)amino)methyl)phenol (L15)

To a solution of **pre-L15**[2] (201 mg) in tetrahydrofuran (THF, 2.7 mL), $LiAlH_4$ (76.2 mg, 2.01 mmol, 2.5 equiv.) was added at 0 °C. The solution was then stirred at reflux for 19 hours. The reaction was quenched by addition of water (0.08 mL and 0.24 mL) and aqueous NaOH (*ca.* 10% in water, 0.08 mL). The resulting solution was filtered through a pad of celite and dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 2/1 to 1/1) to give **L15** (139 mg, 73%) as a white solid: *Rf* = 0.17 (silica gel, hexane/EtOAc = 2/1); $[\alpha]_D^{19}$ + 108.4 (*c* 0.80 in $CHCl_3$); IR (NaCl) 3231 (O–H), 1599 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.76 (dt, *J* = 7.5, 1.2 Hz, 1H), 4.01 (d, *J* = 13.4 Hz, 1H), 3.83 (d, *J* = 13.4 Hz, 1H) 2.54 (m, 1H), 2.35 (t, *J* = 12.0 Hz, 1H), 2.23 (s, 6H), 2.16 (dd, *J* = 12.0 Hz, 3.9 Hz, 1H), 2.04–1.91 (m, 1H), 0.97 (d, *J* = 5.1 Hz, 3H), 0.94 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 128.6, 128.2, 124.1, 118.8, 116.5, 60.3, 59.8, 50.9, 45.7, 28.9, 19.0, 17.7. Anal. Calcd for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.24; N, 11.85. Found: C, 71.23; H, 9.84; N, 11.57.

Characterization of (*S*)-2-(((1-(diethylamino)-3-methylbutan-2-yl)amino)methyl)phenol (L16)

According the synthetic procedure of **L15**, **L16** (1.19 g, 62% yield) was obtained from **pre-L16** (2.03 g, 7.29 mmol) as a yellow oil after chromatographic purification (silica gel, hexane/EtOAc = 2/1 to 1/3): *Rf* = 0.17 (silica gel, hexane/EtOAc = 2/1); $[\alpha]_D^{21}$ + 116.5 (*c* 1.09 in $CHCl_3$); IR (NaCl) 3250 (O–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.76 (m, 1H), 4.01 (d, *J* = 13.5 Hz, 1H), 3.80 (d, *J* = 13.5 Hz, 1H), 2.65–2.29 (m, 6H), 1.98 (m, 1H), 0.99 (d, *J* = 7.2 Hz, 6H), 0.95 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 128.4, 127.9, 123.9, 118.6, 116.3, 60.5, 53.0, 51.2, 47.1, 28.6, 18.9, 17.4, 11.7. Anal. Calcd for $C_{16}H_{28}N_2O$: C, 72.68; H, 10.67; N, 10.59. Found: C, 72.36; H, 10.50; N, 10.53.

Characterization of (*S*)-2-(((1-(didecylamino)-3-methylbutan-2-yl)amino)methyl)phenol (L17)

According the synthetic procedure of **L15**, **L17** (582 mg, 71% yield) was obtained from **L9** (849 mg, 1.73 mmol) as a colorless oil after chromatographic purification (silica gel, hexane/EtOAc = 80/1 to 30/1 to 20/1): *Rf* = 0.20 (silica gel, hexane/EtOAc = 20/1); $[\alpha]_D^{24}$ + 82.4 (*c* 1.10 in $CHCl_3$); IR (NaCl) 3249 (O–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (dt, *J* = 8.1, 1.5 Hz, 1H), 6.98 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.83 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.75 (dt, *J* = 7.2, 0.9 Hz, 1H), 4.02 (d, *J* = 13.5 Hz, 1H), 3.78 (d, *J* = 13.5 Hz, 1H), 2.52–2.39 (m, 3H), 2.35–2.26 (m, 4H), 2.05–1.93 (m, 1H), 1.40–1.24 (m, 32H), 0.97–0.94 (m, 6H), 0.88 (t, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 128.4, 127.9, 123.9, 118.7, 116.4, 60.9, 54.5, 54.4, 51.5, 31.9, 29.7, 29.62, 29.59, 29.3, 28.5, 27.6, 27.0, 22.7, 19.0, 17.4, 14.1. Anal. Calcd for $C_{32}H_{60}N_2O$: C, 78.62; H, 12.37; N, 5.73. Found: C, 79.01; H, 12.64; N, 5.74.

Characterization of (*S*)-2-(((1-(decylamino)-3-methylbutan-2-yl)amino)methyl)phenol (L18)

According the synthetic procedure of **L15**, **L18** (28.1 mg, 13% yield) was obtained from **L13** (217 mg, 0.600 mmol) as a colorless oil after chromatographic purification (silica gel, hexane/EtOAc = 3/1 to 1/3): *Rf* = 0.17 (silica gel, hexane/EtOAc = 1/1); $[\alpha]_D^{22}$ + 24.6 (*c* 0.66 in $CHCl_3$); IR (NaCl) 3266 (O–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 1H), 7.00 (dd, *J* = 7.2, 1.8 Hz, 1H), 6.84 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.77 (dt, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.88 (d, *J* = 13.5 Hz, 1H), 2.76 (d, *J* = 12.0, 3.8 Hz, 1H), 2.65–2.51 (m, 3H), 2.45 (m, 1H), 1.93 (m, 1H), 1.48–1.26 (m, 16H), 0.97 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 128.6, 128.2, 123.8, 118.8, 116.5, 62.6, 50.9, 50.1, 49.1, 31.9, 29.9, 29.59, 29.56, 29.51, 29.3, 28.9, 27.3, 22.7, 19.1, 18.1, 14.1. Anal. Calcd for $C_{22}H_{40}N_2O$: C, 75.81; H, 11.57; N, 8.04. Found: C, 75.90; H, 11.21; N, 7.85.

Characterization of (*S*)-2-(((1-(didecylamino)-4-methylpentan-2-yl)amino)methyl)phenol (L20)

According the synthetic procedure of **L15**, **L20** (126 mg, 59% yield) was obtained from **pre-L20** (221 mg, 0.428 mmol) as a colorless oil after chromatographic purification (silica gel, hexane/EtOAc = 30/1 20/1 10/1): *Rf* = 0.17 (silica gel, hexane/EtOAc = 10/1); $[\alpha]_D^{24}$ + 83.3 (*c* 1.04 in $CHCl_3$); IR (NaCl) 3257 (O–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (m, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.76 (m, 1H), 4.00 (d, *J* = 13.7 Hz, 1H), 3.83 (d, *J* = 13.7 Hz, 1H), 2.67 (sep, *J* = 4.8 Hz, 1H), 2.49–2.27 (m, 6H), 1.71 (sep, *J* = 6.5 Hz, 1H), 1.23 (s, 34H), 0.93–0.87 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 128.4, 127.8, 123.8, 118.6, 116.4, 58.8, 54.5, 53.7, 50.1, 42.0, 31.9, 29.7, 29.6, 29.3, 27.5, 27.0, 25.0, 23.3, 22.7, 22.6, 14.1. Anal. Calcd for $C_{33}H_{62}N_2O$: C, 78.82; H, 12.43; N, 5.57. Found: C, 78.82; H, 12.52; N, 5.60.

Characterization of (*S*)-2-(((1-(didecylamino)-3-phenylpropan-2-yl)amino)methyl)phenol (L21)

According the synthetic procedure of **L15**, **L21** (87.0 mg, 34% yield) was obtained from **pre-L21** (264 mg, 0.479 mmol) as a colorless oil after chromatographic purification (silica gel, hexane/EtOAc = 30/1 to 20/1 to 10/1): *Rf* = 0.17 (silica gel, hexane/EtOAc = 10/1); $[\alpha]_D^{24}$ + 53.6 (*c* 0.97 in $CHCl_3$); IR (NaCl) 3249 (O–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.26 (m, 2H), 7.22–7.11 (m, 4H), 6.95 (d, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.74 (dt, *J* = 7.4 Hz, *J* = 1.2 Hz, 1H), 3.97 (d, *J* = 13.7 Hz, 1H), 3.86 (d, *J* = 13.7 Hz, 1H), 2.95–2.84 (m, 2H), 2.65 (sext, *J* = 6.4 Hz, 1H), 2.42–2.23 (m, 6H), 1.23 (s, 32H), 0.88 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 138.7, 129.1, 128.5, 127.8, 126.3, 123.7, 118.8, 116.5, 58.2, 57.8, 54.4, 51.0, 39.4, 31.9, 31.5, 29.7, 29.6, 29.3, 27.5, 27.0, 22.7, 14.1. Anal. Calcd for $C_{36}H_{60}N_2O$: C, 80.54; H, 11.26; N, 5.22. Found: C, 80.33; H, 10.91; N, 5.27.

Characterization of (*S*)-2-(((1-(didecylamino)-3,3-dimethylbutan-2-yl)amino)methyl)phenol (L22)

According the synthetic procedure of **L15**, **L22** (121 mg, 38% yield) was obtained from **pre-L22** (677 mg, 1.35 mmol) as a yellow oily material after chromatographic purification (silica gel, hexane/EtOAc = 15/1 to 8/1): *Rf* = 0.43 (silica gel, hexane/EtOAc = 8/1); $[\alpha]_D^{23}$ + 77.4 (*c* 1.08 in $CHCl_3$); IR (NaCl) 3188 (O–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.70 (t, *J* = 7.5 Hz, 1H), 4.06 (d, *J* = 13.2 Hz, 1H), 3.92 (d, *J* = 13.2 Hz, 1H), 2.56–2.42 (m, 3H), 2.34–2.23 (m, 4H), 1.45–1.14 (m, 33H), 0.99 (s, 9H), 0.88 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 128.4, 127.9, 124.1, 118.7, 116.4, 64.7, 55.6, 55.1, 54.2, 34.5, 31.9, 29.7, 29.6, 29.3, 27.6, 27.3, 26.8, 22.7, 14.1. Anal. Calcd for $C_{33}H_{62}N_2O$: C, 78.82; H, 12.43; N, 5.57. Found: C, 78.69; H, 12.07; N, 5.81.

Synthesis and characterization of (*S*)-2-(((1-(decyloxy)-3-methylbutan-2-yl)amino)methyl)phenol (L19)

To a solution of L-valinol (330 mg, 3.19 mmol) in THF (5.8 mL), sodium hydride (136 mg, 3.40 mmol, 1.2 equiv.) was added at 0 °C. After stirring the mixture at the same temperature for 30 min, 1-bromodecane (0.6 mL, 2.9 mmol, 0.9 equiv.) was added. The resulting solution was stirred at reflux for 7 hours. The reaction was quenched by addition of water (0.2 mL), and the resulting mixture was filtered through a pad of celite (washed with EtOAc). The organic solution was dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material (872 mg), which was used without further purification: R_f = 0.26 (silica gel, hexane/EtOAc = 3/1).

To a solution of the crude material (872 mg) in ethanol (5.8 mL), salicylaldehyde (346 mg, 2.83 mmol, 1.0 equiv.) was added at room temperature. After stirring the mixture at reflux for 3 hours, the resulting mixture was concentrated in vacuo to give a crude material (1.48 g), which was used without further purification: R_f = 0.30 (silica gel, hexane/EtOAc = 3/1).

To a solution of the crude material (1.48 g) in ethanol (5.8 mL), sodium borohydride (439 mg, 11.6 mmol, 4.0 equiv.) and *conc.* hydrochloric acid (1 drop) were added at 0 °C. The solution was warmed to room temperature and stirred for 2 hours. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (5.0 mL), and the resulting mixture was extracted with dichloromethane (20 mL × 2). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material (834 mg). The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 20/1 to 15/1) to give **L19** (474 mg, 47% in 3 steps) as a colorless oil: *Rf* = 0.33 (silica gel, hexane/EtOAc = 10/1); $[\alpha]_D^{23}$ + 11.7 (*c* 1.13 in $CHCl_3$); IR (NaCl) 3303 (O–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, *J* = 6.6 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 1H), 6.76 (t, *J* = 7.2 Hz, 1H), 4.01 (d, *J* = 13.7 Hz, 1H), 3.94 (d, *J* = 13.7 Hz, 1H), 3.56 (dd, *J* = 9.0 Hz, *J* = 3.0 Hz, 1H), 3.44–3.36 (m, 3H), 2.56 (q, *J* = 5.1 Hz, 1H), 1.93 (sextet, *J* = 6.9 Hz, 1H), 1.55 (s, 2H), 1.27 (s, 16H), 1.01–0.84 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 128.5, 128.0, 123.2, 118.7, 116.2, 71.4, 69.2, 62.2, 50.8, 31.8, 31.5, 29.53, 29.50, 29.46, 29.3, 29.2, 29.1, 26.1, 22.6, 19.1, 18.7, 14.0. Anal. Calcd for $C_{22}H_{39}NO_2$: C, 75.59; H, 11.25; N, 4.01. Found: C, 75.19; H, 10.94; N, 4.12.

Synthesis and characterization of (*S*)-2-(((1-(didecylamino)-3-methylbutan-2-yl)amino)methyl)-4-nitrophenol (L23)

According the synthetic procedure of **L8**, a crude material including **A** was obtained from *N*-Boc-L-valine (350 mg, 1.61 mmol) and didecylamine (0.4 mL, 4.0 mmol, 2.5 equiv.). The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 10/1 to 4/1 to 0/1) to give **A** (542 mg, 82% in 2 steps) as a yellow oil: *Rf* = 0.40 (silica gel, hexane/EtOAc = 6/1); $[\alpha]_D^{23}$ + 18.0 (*c* 0.91 in $CHCl_3$); IR (NaCl) 3384 (N–H), 1641 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.18 (brs, 1H), 4.16 (d, *J* = 4.2 Hz, 1H), 3.66 (m, 1H), 3.28 (m, 1H), 3.11 (m, 1H), 2.97 (m, 1H), 2.16 (m, 1H), 1.57–1.26 (m, 32H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 55.6, 46.7, 45.2, 31.6, 31.1, 28.8, 28.7, 28.6, 28.5, 26.9, 26.2, 26.0, 21.8, 19.2, 16.2, 13.2; Anal. Calcd for $C_{25}H_{52}N_2O$: C, 75.69; H, 13.21; N, 7.06. Found: C, 75.42; H, 12.82; N, 6.86.

To a solution of **A** (542 mg) in THF (4.6 mL), $LiAlH_4$ (140 mg, 3.43 mmol, 2.5 equiv.) was added at 0 °C. The solution was warmed to room temperature and stirred for 2 hours. The reaction was quenched by addition of water (0.14 mL and 0.42 mL) and aqueous NaOH (*ca.* 10% in water, 4.6 mL). The resulting solution was filtered through a pad of celite and dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 5/1 to 2/1 to 0/1) to give **B** (440 mg, 84%) as a yellow oil: *Rf* = 0.27 (silica gel, hexane/EtOAc = 0/1); $[\alpha]_D^{23}$ + 47.9 (*c* 0.44 in $CHCl_3$); IR (NaCl) 3388 (N–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.58 (m, 1H), 2.50–2.12 (m, 6H), 1.51 (m, 1H), 1.42–1.26 (m, 32H), 0.93–0.86 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 59.5, 54.7, 54.2, 32.1, 31.9, 31.6, 29.7, 29.6, 29.3, 27.5, 27.3, 22.7, 19.4, 18.4,

14.1; Anal. Calcd for $C_{25}H_{54}N_3$: C, 78.46; H, 14.22; N, 7.31. Found: C, 78.06; H, 13.92; N, 7.13.

To a solution of **B** (440 mg) in dichloromethane (3.8 mL), 2-hydroxy-5-nitrobenzaldehyde (231 mg, 1.38 mmol, 1.2 equiv.) was added at room temperature. After stirring the mixture for 12 hours, the resulting mixture was concentrated in vacuo to give a crude material (726 mg), which was used without further purification: R_f = 0.60 (silica gel, hexane/EtOAc = 3/1).

To a solution of the crude material (726 mg) in ethanol (5.8 mL), sodium borohydride (348 mg, 9.21 mmol, 4.0 equiv.) and *conc.* hydrochloric acid (1 drop) were added at 0 °C. The solution was warmed to room temperature and stirred for 4 hours. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (20 mL), and the resulting mixture was extracted with dichloromethane (20 mL × 2). The combined extracts were dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material (683 mg). The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 10/1 to 5/1) to give **L23** (483 mg, 57% in 5 steps) as a yellow oil: *Rf* = 0.43 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ + 65.0 (*c* 1.08 in $CHCl_3$); IR (NaCl) 3224 (O–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.93 (d, *J* = 2.7 Hz, 1H), 7.64 (brs, 1H), 6.80 (d, *J* = 9.0 Hz, 1H), 4.03 (d, *J* = 13.8 Hz, 1H), 3.87 (d, *J* = 13.8 Hz, 1H), 2.58–2.33 (m, 7H), 1.96 (m, 1H), 1.50–1.20 (s, 33H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 139.0, 125.3, 124.3, 123.8, 116.8, 60.5, 54.3, 54.1, 54.0, 50.1, 31.8, 29.6, 29.5, 29.41, 29.36, 29.3, 28.6, 27.5, 26.6, 22.6, 19.1, 17.4, 14.0. Anal. Calcd for $C_{32}H_{59}N_3O_3$: C, 72.00; H, 11.14; N, 7.87. Found: C, 72.09; H, 11.06; N, 7.88.

Characterization of (*S*)-2-(((1-(didecylamino)-3-methylbutan-2-yl)amino)methyl)-4-methoxyphenol (L24)

According the synthetic procedure of **L23**, **L24** (98.7 mg, 45% in 5 steps) was obtained from *N*-Boc-L-valine (91.3 mg, 0.420 mmol) as a colorless oil after chromatographic purification (silica gel, hexane/EtOAc = 15/1 to 8/1): *Rf* = 0.40 (silica gel, hexane/EtOAc = 8/1); $[\alpha]_D^{23}$ + 69.0 (*c* 1.15 in $CHCl_3$); IR (NaCl) 3399 (O–H), 3255 (N–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76–6.69 (m, 2H), 6.57 (d, *J* = 2.7 Hz, 1H), 3.98 (d, *J* = 13.5 Hz, 1H), 3.76–3.72 (m, 4H), 2.51–2.40 (m, 3H), 2.34–2.26 (m, 4H), 1.98 (m, 1H), 1.43–1.25 (s, 32H), 0.96–0.93 (m, 6H), 0.89 (t, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 152.0, 124.6, 116.6, 113.9, 113.2, 60.9, 55.7, 54.5, 54.4, 51.7, 31.9, 29.7, 29.6, 29.3, 28.5, 27.6, 27.0, 22.7, 19.0, 17.3, 14.0. Anal. Calcd for $C_{33}H_{62}N_2O_2$: C, 76.39; H, 12.04; N, 5.40. Found: C, 76.01; H, 11.67; N, 5.36.

Characterization of (*S*)-1-(((1-(didecylamino)-3-methylbutan-2-yl)amino)methyl)naphthalen-2-ol (L25)

According the synthetic procedure of **L23**, **L25** (98.2 mg, 5.5% in 5 steps) was obtained from *N*-Boc-L-valine (516 mg, 2.38 mmol) as a pale yellow oil after chromatographic purification (silica gel, hexane/EtOAc = 18/1 to 15/1 to 10/1): *Rf* = 0.30 (silica gel, hexane/EtOAc = 5/1); $[\alpha]_D^{23}$ + 49.7 (*c* 0.40 in $CHCl_3$); IR (NaCl) 3245 (O–H), 3058 (N–H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (t, *J* = 9.0 Hz, 2H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.41 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.26 (m, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 4.53 (d, *J* = 14.2 Hz, 1H), 4.22 (d, *J* = 14.2 Hz, 1H), 2.61–2.28 (m, 8H), 2.06 (m, 1H), 1.21 (s, 31H), 1.01–0.99 (m, 6H), 0.87 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 132.2, 128.81, 128.76, 128.3, 126.1, 122.2, 121.0, 119.7, 113.2, 61.4, 54.6, 46.7, 31.9, 29.64, 29.62, 29.6, 29.3, 28.8, 27.6, 27.1, 22.7, 19.2, 17.4, 14.1. Anal. Calcd for $C_{36}H_{62}N_2O_2$: C, 80.24; H, 11.60; N, 5.20. Found: C, 80.05; H, 11.48; N, 4.86.

General procedure for amido-functionalized allylation of ketones

To a suspension of zinc hydroxide (2.0 mg, 0.020 mmol, 0.10 equiv.) and **L17** (10.9 mg, 0.0220 mmol, 0.11 equiv.) in water (0.50 mL). After stirring the mixture at the same temperature for 1 hour, **1a** (0.300 mmol, 1.5 equiv.) and ketone (0.200 mmol) were added at room temperature. After stirring the mixture at the same temperature for 24 hours, the reaction was quenched by addition of saturated aqueous sodium periodate (3.0 mL). The resulting mixture was extracted with dichloromethane (8.0 mL × 2). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material. This material was purified by column chromatography to give **2**.

Synthesis and characterization of (−)-4-hydroxy-4-methyl-2-methylene-*N*-phenylhexanamide (2a)

According to the general procedure, the reaction of 2-butanone (23.5 mg, 0.326 mmol) with **1a** (134 mg, 0.489 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 4/1) to give **2a** (42.3 mg, 56%, 13% ee) as a colorless oil: *Rf* = 0.37 (silica gel, hexane/EtOAc = 1/1); $[\alpha]_D^{22}$ −0.83 (*c* 0.64 in $CHCl_3$); m.p. 83–85 °C; IR (NaCl) 3214 (O–H), 3120 (N–H), 1647 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.19 (brs, 1H), 7.55 (d, *J* = 6.9 Hz, 2H), 7.30 (t, *J* = 6.9 Hz, 2H), 7.09 (t, *J* = 6.9 Hz, 1H), 6.11 (s, 1H), 5.41 (s, 1H), 3.46 (s, 4H), 2.62 (d, *J* = 14.3 Hz, 1H), 2.46 (d, *J* = 14.3 Hz, 1H), 1.58 (q, *J* = 7.5 Hz, 2H), 1.20 (s, 3H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 141.9, 138.1, 128.9, 124.7, 124.2, 120.2, 72.8, 44.0, 35.3, 26.1, 8.4. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.40; H, 8.04; N, 6.00. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IF column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 30.0 min, t_R (minor) = 32.8 min.

Synthesis and characterization of (*S*)-4-hydroxy-2-methylene-N,4-diphenylpentanamide (2b)

According to the general procedure, the reaction of acetophenone (24.0 mg, 0.200 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 7/1 to 4/1) to give **2b** (547 mg, 98%, 70% ee) as a white solid: *Rf* = 0.30

(silica gel, hexane/EtOAc = 2/1); $[\alpha]_D^{18}$ −32.6 (*c* 1.00 in $CHCl_3$); m.p. 114–116 °C; IR (KBr) 3271 (O–H), 3158 (N–H), 3134 (N–H), 1650 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.53 (brs, 1H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.31 (m, 1H), 7.21 (t, *J* = 7.2 Hz 1H), 7.11 (t, *J* = 7.2 Hz 1H), 5.79 (s, 1H), 5.10 (s, 1H), 4.73 (brs, 1H), 2.81 (s, 2H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 147.3, 141.2, 137.7, 128.9, 128.0, 126.6, 125.0, 124.5, 120.2, 74.4, 47.5, 29.7. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.55; H, 6.43; N, 4.88. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 16.3 min, t_R (minor) = 14.9 min.

Synthesis and characterization of (−)-4-hydroxy-4-methyl-2-methylene-*N*-phenyldodecanamide (2 c)

According to the general procedure, the reaction of 2-decanone (31.3 mg, 0.200 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, toluene/EtOAc = 20/1 to 10/1) to give **2 c** (42.8 mg, 67%, 28% ee) as a colorless solid: *Rf* = 0.21 (silica gel, toluene/EtOAc = 10/1); $[\alpha]_D^{20}$ −0.72 (*c* 0.77 in $CHCl_3$); IR (NaCl) 3297 (O–H), 3137 (N–H), 1661 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.19 (brs, 1H), 7.57–7.53 (m, 2H), 7.33–7.27 (m, 2H), 7.09 (tt, *J* = 7.4, 1.2 Hz, 1H), 6.10 (s, 1H), 5.40 (s, 1H), 3.43 (brs, 1H), 2.62 (d, *J* = 14.1 Hz, 1H), 2.46 (d, *J* = 14.1 Hz, 1H), 1.56–1.50 (m, 2H), 1.28 (s, 12H), 1.21 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8, 141.8, 138.2, 128.8, 124.9, 124.2, 120.1, 72.6, 44.4, 42.9, 31.8, 30.1, 29.6, 29.2, 26.6, 24.0, 22.6, 14.0. Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67, H, 9.84; N, 4.41. Found: C, 75.49; H, 9.59; N, 4.54. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IG column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 23.0 min, t_R (minor) = 27.1 min.

Synthesis and characterization of (+)-4-hydroxy-4,5,5-trimethyl-2-methylene-*N*-phenylhexanamide (2 d)

According to the general procedure, the reaction of 3,3-dimethyl-2-butanone (19.8 mg, 0.198 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, toluene/EtOAc = 20/1 to 10/1) to give **2 d** (5.2 mg, 10%, 69% ee) as a colorless oil: *Rf* = 0.21 (silica gel, toluene/EtOAc = 10/1); $[\alpha]_D^{21}$ +6.1 (*c* 0.75 in $CHCl_3$); IR (NaCl) 3299 (O–H), 3136 (N–H), 1661 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.93 (brs, 1H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.15 (s, 1H), 5.43 (s, 1H), 2.80 (d, *J* = 13.8 Hz, 1H), 2.78 (brs, 1H), 2.41 (d, *J* = 13.8 Hz, 1H), 1.17 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 142.5, 138.2, 128.9, 124.8, 124.2, 120.0, 39.1, 38.4, 25.2, 21.2, 14.1. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.85; H, 8.91; N, 5.32. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IF column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 22.9 min, t_R (minor) = 26.4 min.

Synthesis and characterization of (*S*)-4-hydroxy-2-methylene-4-(naphthalen-2-yl)-*N*-phenylpentanamide (2 e)

According to the general procedure, the reaction of 2'-acetonaphthone (34.2 mg, 0.201 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 5/1 to 4/1) to give **2 e** (42.8 mg, 72%, 42% ee) as a white solid: *Rf* = 0.23 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ −62.8 (*c* 1.00 in $CHCl_3$); m.p. 174–176 °C; IR (KBr) 3195 (O–H), 3135 (N–H), 1649 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (brs, 1H), 7.97 (s, 1H), 7.83–7.78 (m, 3H), 7.54–7.43 (m, 5H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.11 (t, *J* = 7.2 Hz, 1H), 5.71 (s, 1H), 5.10 (s, 1H), 4.84 (s, 1H), 2.93 (s, 2H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 144.7, 141.5, 137.5, 133.1, 132.2, 129.0, 128.2, 127.7, 127.4, 126.0, 125.7, 124.6, 123.8, 123.7, 123.6, 120.2, 74.5, 47.3, 30.1. Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.84; H, 6.66; N, 4.30. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 36.4 min, t_R (minor) = 32.9 min.

Synthesis and characterization of (*S*)-4-hydroxy-2-methylene-4-(naphthalen-1-yl)-*N*-phenylpentanamide (2 f)

According to the general procedure, the reaction of 1'-acetonaphthone (34.1 mg, 0.201 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 5/1 to 4/1) to give **2 f** (61.8 mg, 93%, 86% ee) as a white solid: *Rf* = 0.21 (silica gel, hexane/EtOAc = 4/1); $[\alpha]_D^{17}$ −126.3 (*c* 1.00 in $CHCl_3$); m.p. 123–125 °C; IR (KBr) 3285 (O–H), 3191 (N–H), 3139 (N–H), 1650 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.4 Hz, 1H), 8.18 (brs, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.77 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.75 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.53–7.29 (m, 7H), 7.12 (t, *J* = 7.5 Hz, 1H), 5.69 (s, 1H), 5.12 (s, 1H), 4.82 (s, 1H), 3.45 (d, *J* = 14.7 Hz, 1H), 3.08 (d, *J* = 14.7 Hz, 1H), 1.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 142.5, 141.8, 137.5, 134.7, 130.3, 129.4, 128.9, 128.5, 126.1, 125.4, 125.0, 124.9, 124.6, 124.0, 123.7, 120.3, 75.4, 45.7, 29.7. Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.54; H, 6.22; N, 4.18. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IG column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 19.4 min, t_R (minor) = 14.0 min.

Synthesis and characterization of (*S*)-4-hydroxy-4-(4-methoxyphenyl)-2-methylene-*N*-phenylpentanamide (2 g)

According to the general procedure, the reaction of 4'-methoxyacetophenone (29.8 mg, 0.198 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 7/1 to 5/1) to give **2 g** (51.9 mg, 84%, 66% ee) as a white solid: *Rf* = 0.13 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{18}$

−76.9 (*c* 1.00 in $CHCl_3$); m.p. 120–122 °C; IR (KBr) 3286 (O–H), 3192 (N–H), 3136 (N–H), 1650 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.81 (brs, 1H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.37–7.25 (m, 4H), 7.09 (tt, *J* = 7.5, 1.2 Hz, 1H), 6.82 (tt, *J* = 8.7, 2.7 Hz, 1H), 5.80 (s, 1H), 5.07 (s, 1H), 4.81 (brs, 1H), 3.75 (s, 3H), 2.75 (s, 2H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 158.2, 141.7, 139.5, 137.7, 129.0, 126.2, 124.5, 123.9, 120.1, 113.3, 74.2, 55.2, 47.6, 30.0. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.89; H, 6.66; N, 4.74. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 22.8 min, t_R (minor) = 20.8 min.

Synthesis and characterization of (*S*)-4-(4-((tert-butyldimethylsilyl)oxy)phenyl)-4-hydroxy-2-methylene-*N*-phenylpentanamide (2 h)

According to the general procedure, the reaction of 4'-*tert*-butyldimethylsiloxyacetophenone (50.1 mg, 0.200 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 8/1 to 5/1) to give **2 h** (60.2 mg, 73%, 69% ee) as a white solid: *Rf* = 0.28 (silica gel, hexane/EtOAc = 5/1); $[\alpha]_D^{18}$ −60.0 (*c* 1.00 in $CHCl_3$); m.p. 139–141 °C; IR (KBr) 3196 (O–H), 3134 (N–H), 1650 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (brs, 1H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.33–7.26 (m, 4H), 7.11 (tt, *J* = 7.2, 1.2 Hz, 1H), 6.78 (tt, *J* = 8.4, 2.4 Hz, 1H), 5.80 (s, 1H), 5.06 (s, 1H), 4.51 (brs, 1H), 2.80 (d, *J* = 14.3 Hz, 1H), 2.74 (d, *J* = 14.3 Hz, 1H), 1.61 (s, 3H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 154.3, 141.5, 140.0, 137.8, 128.9, 126.2, 124.5, 124.2, 120.1, 119.5, 74.3, 47.6, 29.8, 25.7, 18.2, −4.4. Anal. Calcd for $C_{24}H_{33}NO_3Si$: C, 70.03; H, 8.08; N, 3.40. Found: C, 70.41; H, 7.73; N, 3.59. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 97/3), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 29.8 min, t_R (minor) = 27.6 min.

Synthesis and characterization of (*S*)-4-(4-chlorophenyl)-4-hydroxy-2-methylene-*N*-phenylpentanamide (2 i)

According to the general procedure, the reaction of 4'-chloroacetophenone (156 mg, 1.00 mmol) with **1 a** (410 mg, 1.50 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1 to 4/1) to give **2 i** (312 mg, 99%, 65% ee) as a white solid: *Rf* = 0.35 (silica gel, hexane/EtOAc = 2/1); $[\alpha]_D^{18}$ −88.6 (*c* 1.00 in $CHCl_3$); m.p. 118–120 °C; IR (KBr) 3280 (O–H), 3171 (N–H), 3140 (N–H), 1649 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (brs, 1H), 7.48 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.39–7.24 (m, 6H), 7.12 (tt, *J* = 7.3, 1.5 Hz, 1H), 5.75 (s, 1H), 5.29 (s, 1H), 5.07 (s, 1H), 2.80 (d, *J* = 14.1 Hz, 1H), 2.72 (d, *J* = 14.1 Hz, 1H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 145.9, 141.1, 137.4, 132.3, 129.0, 128.0, 126.7, 124.8, 124.0, 120.3, 73.9, 47.5, 29.9. Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.75; N, 4.44. Found: C, 68.44; H, 5.80; N, 4.50. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 97/3), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 39.7 min, t_R (minor) = 36.3 min.

Synthesis and characterization of (*S*)-4-hydroxy-2-methylene-*N*-phenyl-4-(4-(trifluoromethyl)phenyl)pentanamide (2 j)

According to the general procedure, the reaction of 4'-(trifluoromethyl)acetophenone (37.4 mg, 0.199 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1 to 4/1) to give **2 j** (66.1 mg, 99%, 58% ee) as a white solid: *Rf* = 0.28 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{19}$ −62.5 (*c* 1.00 in $CHCl_3$); m.p. 93–95 °C; IR (KBr) 3276 (O–H), 3187 (N–H), 3140 (N–H), 1649 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (brs, 1H), 7.55 (s, 4H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 5.74 (s, 1H), 5.69 (brs, 1H), 5.07 (s, 1H), 2.81 (d, *J* = 14.0 Hz, 1H), 2.75 (d, *J* = 14.0 Hz, 1H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 151.5, 140.9, 137.3, 129.0, 128.7 (q, *J* = 32.0 Hz), 125.6, 124.9, 124.207 (q, *J* = 270.1 Hz), 124.205, 120.5, 74.0, 47.4, 29.8. Anal. Calcd for $C_{19}H_{18}F_3NO_2$: C, 65.32; H, 5.19; N, 4.01. Found: C, 65.16; H, 5.48; N, 4.06. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 97/3), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 29.2 min, t_R (minor) = 25.5 min.

Synthesis and characterization of (*S*)-4-hydroxy-4-(3-methoxyphenyl)-2-methylene-*N*-phenylpentanamide (2 k)

According to the general procedure, the reaction of 3'-methoxyacetophenone (31.3 mg, 0.208 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 7/1 to 4/1) to give **2 k** (54.7 mg, 84%, 69% ee) as a white solid: *Rf* = 0.20 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −74.7 (*c* 1.06 in $CHCl_3$); m.p. 114–116 °C; IR (KBr) 3273 (N–H), 3197 (O–H), 3135 (N–H), 1650 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (brs, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.31–7.20 (m, 3H), 7.12–6.98 (m, 3H), 6.74 (dd, *J* = 8.1, 2.6 Hz, 1H), 5.80 (s, 1H), 5.12 (s, 1H), 4.94 (s, 1H), 3.76 (s, 3H), 2.78 (s, 2H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 159.4, 149.2, 141.2, 137.7, 129.0, 128.9, 124.5, 124.3, 120.2, 117.5, 111.6, 111.2, 74.3, 55.1, 47.3, 29.8. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.03; H, 6.77; N, 4.57. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 97/3), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 88.4 min, t_R (minor) = 83.5 min.

Synthesis and characterization of (*S*)-4-(3-chlorophenyl)-4-hydroxy-2-methylene-*N*-phenylpentanamide (2 l)

According to the general procedure, the reaction of 3'-chloroacetophenone (31.2 mg, 0.202 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/

EtOAc = 7/1 to 4/1) to give **2l** (61.1 mg, 96%, 65% ee) as a white solid: *Rf* = 0.23 (silica gel, $CHCl_3$/EtOAc = 15/1); $[\alpha]_D^{21}$ −71.0 (*c* 0.72 in $CHCl_3$); m.p. 107–109 °C; IR (KBr) 3274 (O–H), 3184 (N–H), 3136 (N–H), 1645 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (brs, 1H), 7.51–7.46 (m, 3H), 7.33–7.18 (m, 5H), 7.12 (tt, *J* = 7.5, 1.2 Hz, 1H), 5.77 (s, 1H), 5.38 (brs, 1H), 5.11 (s, 1H), 2.80 (d, *J* = 14.1 Hz, 1H), 2.73 (d, *J* = 14.1 Hz, 1H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 149.7, 141.0, 137.4, 134.0, 129.3, 129.0, 126.7, 125.5, 124.8, 124.1, 123.4, 120.4, 73.9, 47.4, 29.7. Anal. Calcd for $C_{19}H_{18}F_3NO_2$: C, 68.46; H, 5.75; N, 4.44. Found: C, 68.26; H, 5.62; N, 4.48. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 25.1 min, t_R (minor) = 22.7 min.

Synthesis and characterization of (*S*)-4-hydroxy-2-methylene-*N*-phenyl-4-(3-(trifluoromethyl) phenyl)pentanamide (2 m)

According to the general procedure, the reaction of 3'-(trifluoromethyl)acetophenone (37.6 mg, 0.200 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 8/1 to 4/1) to give **2m** (68.6 mg, 98%, 66% ee) as a white solid: *Rf* = 0.30 (silica gel, hexane/EtOAc = 2/1); $[\alpha]_D^{19}$ −70.0 (*c* 1.00 in $CHCl_3$); m.p. 77–79 °C; IR (KBr) 3281 (O–H), 3140 (N–H), 1660 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (brs, 1H), 7.73 (s, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.50–7.39 (m, 4H), 7.33–7.28 (m, 2H), 7.13 (tt, *J* = 7.2, 1.2 Hz, 1H), 5.74 (s, 1H), 5.56 (brs, 1H), 5.09 (s, 1H), 2.83 (d, *J* = 14.1 Hz, 1H), 2.76 (d, *J* = 14.1 Hz, 1H), 1.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 148.6, 141.0, 137.3, 130.2 (q, *J* = 31.6 Hz), 129.0, 128.7, 128.5, 124.9, 124.3 (q, *J* = 270.2 Hz), 124.0, 123.4, 122.0, 120.4, 73.9, 47.5, 29.8. Anal. Calcd for $C_{19}H_{18}F_3NO_2$: C, 65.32, H, 5.19; N, 4.01. Found: C, 65.06; H, 5.44; N, 4.08. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 17.2 min, t_R (minor) = 15.5 min.

Synthesis and characterization of (*S*)-4-hydroxy-2-methylene-4-(3-nitrophenyl)-*N*-phenylpentanamide (2 n)

According to the general procedure, the reaction of 3'-nitroacetophenone (32.9 mg, 0.199 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1 to 3/1) to give **2n** (56.0 mg, 86%, 56% ee) as a white solid: *Rf* = 0.24 (silica gel, hexane/EtOAc = 2/1); $[\alpha]_D^{19}$ −78.6 (*c* 1.00 in $CHCl_3$); m.p. 109–111 °C; IR (KBr) 3283 (O–H), 3192 (N–H), 3138 (N–H), 1649 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.33 (brs, 1H), 8.06 (tt, *J* = 8.1, 1.2 Hz, 2H), 7.85 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.49 (t, *J* = 8.1 Hz, 3H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.15 (m, 1H), 5.85 (s, 1H), 5.74 (s, 1H), 5.15 (s, 1H), 2.89 (d, *J* = 14.1 Hz, 1H), 2.80 (d, *J* = 14.1 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 150.0, 148.0, 140.9, 137.1, 131.6, 129.0, 125.0, 123.9, 121.6, 120.4, 120.4, 73.7, 47.5, 29.9. Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.63; H, 5.61; N, 8.36. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IF column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 29.0 min, t_R (minor) = 43.2 min.

Synthesis and characterization of (*S*)-4-hydroxy-2-methylene-*N*-phenyl-4-(*o*-tolyl)pentanamide (2 o)

According to the general procedure, the reaction of 2'-methylacetophenone (26.8 mg, 0.200 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1 to 4/1) to give **2o** (53.5 mg, 90%, 92% ee) as a white solid: *Rf* = 0.39 (silica gel, hexane/EtOAc = 2/1); $[\alpha]_D^{18}$ −102.1 (*c* 1.00 in $CHCl_3$); m.p. 88–90 °C; IR (KBr) 3276 (O–H), 3199 (N–H), 3136 (N–H), 1648 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (brs, 1H), 7.54–7.47 (m, 3H), 7.32–7.26 (m, 2H), 7.15–7.07 (m, 4H), 5.86 (s, 1H), 5.23 (s, 1H), 4.49 (brs, 1H), 3.05 (d, *J* = 14.7 Hz, 1H), 2.78 (d, *J* = 14.7 Hz, 1H), 2.55 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 144.7, 142.0, 137.7, 134.8, 132.6, 128.9, 127.1, 126.1, 125.8, 124.5, 123.8, 120.2, 75.4, 45.0, 28.9, 22.6. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.09; H, 7.52; N, 4.76. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 31.7 min, t_R (minor) = 25.1 min.

Synthesis and characterization of (*S*)-4-(2-ethylphenyl)-4-hydroxy-2-methylene-*N*-phenylpentanamide (2 p)

According to the general procedure, the reaction of 2'-ethylacetophenone (29.4 mg, 0.198 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 h. The crude material was purified by column chromatography (silica gel, chloroform/EtOAc = 40/1 to 10/1) to give **2p** (40.9 mg, 67%, 96% ee) as a white solid: *Rf* = 0.25 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{19}$ −91.0 (*c* 1.00 in $CHCl_3$); m.p. 117–119 °C; IR (KBr) 3267 (O–H), 3134 (N–H), 1662 (C=O), 1637 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.67 (brs, 1H), 7.50 (d, *J* = 7.8 Hz, 3H), 7.30 (t, *J* = 8.0 Hz, 2H), 7.23–7.08 (m, 4H), 5.89 (s, 1H), 5.25 (s, 1H), 4.38 (brs, 1H), 3.09–2.79 (m, 4H), 1.69 (s, 3H), 1.27 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 144.1, 142.0, 141.6, 137.8, 131.0, 129.0, 127.2, 126.0, 125.5, 124.5, 123.9, 120.1, 75.4, 45.9, 29.6, 27.2, 16.9. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.79; H, 7.10; N, 4.45. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 24.4 min, t_R (minor) = 21.0 min.

Synthesis and characterization of (*S*)-4-hydroxy-4-(2-isopropylphenyl)-2-methylene-*N*-phenylpentanamide (2 q)

According to the general procedure, the reaction of 2'-isopropylacetophenone (32.4 mg, 0.200 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 h. The crude

material was purified by column chromatography (silica gel, chloroform/EtOAc = 40/1 to 20/1) to give **2q** (43.3 mg, 67%, 97% ee) as a white solid: *Rf* = 0.20 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{18}$ −89.5 (*c* 1.00 in $CHCl_3$); m.p. 151–153 °C; IR (KBr) 3238 (O–H), 3135 (N–H), 1663 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.64 (brs, 1H), 7.56–7.51 (m, 3H), 7.38–7.22 (m, 4H), 7.15–7.09 (m, 2H), 5.95 (s, 1H), 5.29 (s, 1H), 4.11 (s, 1H), 3.69 (sept, *J* = 6.9 Hz, 1H), 3.08 (d, *J* = 14.4 Hz, 1H), 2.87 (d, *J* = 14.4 Hz, 1H), 1.70 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 3H), 1.26 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 146.7, 143.4, 141.9, 137.8, 128.9, 127.5, 125.6, 125.4, 124.5, 124.3, 120.1, 75.1, 45.7, 29.6, 29.5, 24.9, 24.6. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.58; H, 7.76; N, 4.62. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 12.6 min, t_R (minor) = 11.6 min.

Synthesis and characterization of (*S*)-4-([1,1′-biphenyl]-2-yl)-4-hydroxy-2-methylene-*N*-phenylpentanamide (2r)

According to the general procedure, the reaction of 2'-phenylacetophenone (39.3 mg, 0.200 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 72 h. The crude material was purified by column chromatography (silica gel, chloroform/EtOAc = 40/1 to 20/1) to give **2r** (27.5 mg, 38%, 93% ee) as a white solid: *Rf* = 0.20 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{17}$ −97.4 (*c* 1.00 in $CHCl_3$); m.p. 156–158 °C; IR (KBr) 3276 (O–H), 3199 (N–H), 3136 (N–H), 1649 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.68 (brs, 1H), 7.69 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.43–7.22 (m, 11H), 7.12–7.07 (m, 2H), 5.96 (s, 1H), 5.09 (s, 1H), 3.41 (brs, 1H), 2.89 (d, *J* = 14.4 Hz, 1H), 2.78 (d, *J* = 14.4 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 144.3, 143.7, 141.4, 139.8, 138.0, 132.2, 129.8, 128.8, 127.8, 127.4, 127.1, 126.7, 126.3, 125.1, 124.2, 120.0, 76.3, 46.7, 30.6. Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.25; H, 6.84; N, 3.85. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 27.3 min, t_R (minor) = 25.7 min.

Synthesis and characterization of (*S*)-4-hydroxy-4-(2-methoxyphenyl)-2-methylene-*N*-phenylpentanamide (2s)

According to the general procedure, the reaction of 2'-methoxyacetophenone (29.9 mg, 0.199 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 7/1 to 4/1) to give **2s** (56.4 mg, 91%, 70% ee) as a white solid: *Rf* = 0.17 (silica gel, hexane/EtOAc = 4/1); $[\alpha]_D^{18}$ −42.8 (*c* 1.00 in $CHCl_3$); m.p. 109–111 °C; IR (KBr) 3299 (O–H), 3138 (N–H), 1658 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.53 (brs, 1H), 7.52–7.47 (m, 3H), 7.33–7.27 (m, 2H), 7.23 (m, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.95 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 5.83 (s, 1H), 5.21 (s, 1H), 5.02 (s, 1H), 3.89 (s, 3H), 3.20 (d, *J* = 13.8 Hz, 1H), 2.91 (d, *J* = 13.8 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 156.1, 142.2, 138.0, 134.2, 128.8, 128.4, 126.7, 124.2, 123.7, 120.9, 120.0, 111.1, 74.8, 55.2, 44.3, 27.8. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.06; H, 6.44; N, 4.48. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 24.2 min, t_R (minor) = 16.8 min.

Synthesis and characterization of (*S*)-4-(2-((*tert*-butyldimethylsilyl)oxy)phenyl)-4-hydroxy-2-methylene-*N*-phenylpentanamide (2t)

According to the general procedure, the reaction of 2'-*tert*-butyldimethylsiloxyacetophenone (50.3 mg, 0.201 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, chloroform/EtOAc = 40/1) to give **2t** (60.0 mg, 72%, 72% ee) as a white solid: *Rf* = 0.33 (silica gel, hexane/EtOAc = 5/1); $[\alpha]_D^{21}$ −21.5 (*c* 0.59 in $CHCl_3$); m.p. 124–126 °C; IR (KBr) 3283 (O–H), 3198 (N–H), 3138 (N–H), 1650 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.81 (brs, 1H), 7.53–7.45 (m, 3H), 7.34–7.28 (m, 2H), 7.16–7.07 (m, 2H), 6.94 (dt, *J* = 7.5, 1.2 Hz, 1H), 6.84 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.89 (s, 1H), 5.41 (s, 1H), 5.24 (s, 1H), 3.20 (d, *J* = 13.8 Hz, 1H), 2.92 (d, *J* = 13.8 Hz, 1H), 1.67 (s, 3H), 1.04 (s, 9H), 0.37 (s, 3H), 0.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 152.4, 142.1, 138.1, 135.5, 128.9, 128.1, 127.4, 124.2, 121.2, 120.0, 118.4, 75.2, 44.2, 28.2, 26.1, 18.5, −3.6, −3.8. Anal. Calcd for $C_{24}H_{33}NO_3Si$: C, 70.03; H, 8.08; N, 3.40. Found: C, 70.41; H, 7.80; N, 3.37. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 13.1 min, t_R (minor) = 10.9 min.

Synthesis and characterization of (*S*)-4-(2-(dimethylamino)phenyl)-4-hydroxy-2-methylene-*N*-phenylpentanamide (2u)

According to the general procedure, the reaction of 2'-(dimethylamino)acetophenone (32.6 mg, 0.200 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 3/1 to 1/1) to give **2u** (35.1 mg, 54%, 73% ee) as a colorless oil: *Rf* = 0.10 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −103.5 (*c* 0.41 in $CHCl_3$); IR (KBr) 3272 (O–H), 3128 (N–H), 1675 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.52 (brs, 1H), 11.10 (brs, 1H), 7.66 (d, *J* = 7.5 Hz, 2H), 7.36–7.25 (m, 6H), 7.08 (m, 1H), 6.12 (d, *J* = 1.8 Hz, 1H), 4.93 (d, *J* = 1.8 Hz, 1H), 2.94 (s, 2H), 2.70 (s, 3H), 2.59 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 150.9, 141.4, 139.3, 139.1, 128.8, 128.2, 127.9, 126.9, 126.6, 123.5, 123.4, 119.5, 78.9, 48.3, 46.3, 32.6. Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.05; H, 7.46; N, 8.63. Found: C, 74.20; H, 7.34; N, 8.73. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 25.2 min, t_R (minor) = 29.4 min.

Synthesis and characterization of (*S*)-4-(2-chlorophenyl)-4-hydroxy-2-methylene-*N*-phenylpentanamide (2 v)

According to the general procedure, the reaction of 2'-chloroacetophenone (31.3 mg, 0.202 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, chloroform/EtOAc = 30/1) to give **2 v** (62.0 mg, 97%, 78% ee) as a white solid: *Rf* = 0.21 (silica gel, hexane/EtOAc = 4/1); $[\alpha]_D^{22}$ −123.1 (*c* 1.27 in $CHCl_3$); IR (KBr) 3288 (O–H), 3162 (N–H), 1649 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (brs, 1H), 7.66 (d, *J* = 8.7, 1.1 Hz, 2H), 7.39–7.24 (m, 6H), 7.12 (tt, *J* = 7.4, 1.2 Hz, 1H), 5.75 (s, 1H), 5.29 (s, 1H), 5.07 (s, 1H), 2.80 (d, *J* = 14.1 Hz, 1H), 2.72 (d, *J* = 14.1 Hz, 1H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 143.9, 141.9, 137.2, 131.0, 130.5, 129.0, 128.7, 128.2, 127.0, 124.9, 123.0, 120.4, 74.7, 43.3, 27.8. Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.75; N, 4.44. Found: C, 68.74; H, 5.96; N, 4.58. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 15.3 min, t_R (minor) = 11.7 min.

Synthesis and characterization of (*S*)-4-(2-fluorophenyl)-4-hydroxy-2-methylene-*N*-phenylpentanamide (2 w)

According to the general procedure, the reaction of 2'-fluoroacetophenone (27.7 mg, 0.201 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, chloroform/EtOAc = 1/0 to 30/1 to 10/1) to give **2 w** (59.6 mg, 99%, 63% ee) as a white solid: *Rf* = 0.30 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ −74.8 (*c* 0.97 in $CHCl_3$); IR (KBr) 3238 (O–H), 1649 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (brs, 1H), 7.67 (dt, *J* = 8.1, 1.8 Hz, 1H), 7.49–7.46 (m, 2H), 7.34–7.29 (m, 2H), 7.24–7.07 (m, 3H), 6.99 (ddd, *J* = 12.0, 8.1, 1.2 Hz, 1H), 5.68 (s, 1H), 5.65 (s, 1H), 5.27 (s, 1H), 3.08 (d, *J* = 14.1 Hz, 1H), 2.92 (d, *J* = 14.1 Hz, 1H), 1.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 159.0 (d, *J* = 242.3 Hz), 141.8, 137.3, 133.8 (d, *J* = 12.9 Hz), 129.0, 128.6 (d, *J* = 8.6 Hz), 128.0 (d, *J* = 4.3 Hz), 124.9, 124.1 (d, *J* = 3.2 Hz), 123.1, 120.4, 115.4 (d, *J* = 24.1 Hz) 73.4, 45.1, 29.1. Anal. Calcd for $C_{18}H_{18}FNO_2$: C, 72.22, H, 6.06; N, 4.68. Found: C, 72.41; H, 6.22; N, 4.94. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 26.6 min, t_R (minor) = 20.0 min.

Synthesis and characterization of (*S*)-4-(2-bromophenyl)-4-hydroxy-2-methylene-*N*-phenylpentanamide (2 x)

According to the general procedure, the reaction of 2'-bromoacetophenone (39.6 mg, 0.199 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, chloroform/EtOAc = 40/1 to 10/1) to give **2 x** (68.1 mg, 95%, 86% ee) as a white solid: *Rf* = 0.31 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{18}$ −144.4 (*c* 1.00 in $CHCl_3$); IR (KBr) 3262 (O–H), 3137 (N–H), 1649 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (brs, 1H), 7.90 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.55 (d, *J* = 7.8, 1.2 Hz, 1H), 7.49–7.46 (m, 2H), 7.34–7.23 (m, 3H), 7.12 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.06 (m, 1H), 5.79 (s, 1H), 5.69 (s, 1H), 5.39 (s, 1H), 3.41 (d, *J* = 14.4 Hz, 1H), 2.95 (d, *J* = 14.4 Hz, 1H), 1.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 145.4, 141.8, 137.2, 134.7, 129.0, 128.9, 128.5, 127.5, 124.9, 123.2, 120.4, 120.1, 75.1, 42.9, 27.7. Anal. Calcd for $C_{18}H_{18}BrNO_2$: C, 60.01; H, 5.04; N, 3.89. Found: C, 59.94; H, 5.24; N, 3.86. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 16.9 min, t_R (minor) = 12.7 min.

Synthesis and characterization of (*S*)-4-hydroxy-4-(2-iodophenyl)-2-methylene-*N*-phenylpentanamide (2 y)

According to the general procedure, the reaction of 2'-iodoacetophenone (49.2 mg, 0.201 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, chloroform/EtOAc = 40/1 to 10/1) to give **2 y** (81.0 mg, 99%, 90% ee) as a white solid: *Rf* = 0.27 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −124.7 (*c* 0.47 in $CHCl_3$); IR (KBr) 3254 (O–H), 3232 (N–H), 3136 (N–H), 1659 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (brs, 1H), 7.95 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.90 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.51–7.47 (m, 2H), 7.36–7.28 (m, 3H), 7.13 (tt, *J* = 7.4, 1.2 Hz, 1H), 6.86 (dt, *J* = 7.5, 1.8 Hz, 1H), 5.75 (s, 1H), 5.47 (brs, 1H), 5.45 (s, 1H), 3.57 (d, *J* = 14.4 Hz, 1H), 2.93 (d, *J* = 14.4 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 148.2, 142.4, 141.7, 137.3, 129.0, 128.5, 128.3, 128.2, 124.8, 123.6, 120.3, 93.9, 75.1, 42.6, 27.7. Anal. Calcd for $C_{18}H_{18}INO_2$: C, 53.09; H, 4.46; N, 3.44. Found: C, 52.97; H, 4.45; N, 3.40. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 17.4 min, t_R (minor) = 13.4 min.

Synthesis and characterization of (*S*)-4-hydroxy-2-methylene-4-(2-nitrophenyl)-*N*-phenylpentanamide (2 z)

According to the general procedure, the reaction of 2'-nitroacetophenone (33.5 mg, 0.203 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 5/1 to 3/1) to give **2 z** (60.3 mg, 91%, 88% ee) as a white solid: *Rf* = 0.14 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{18}$ −65.1 (*c* 1.00 in $CHCl_3$); IR (KBr) 3303 (O–H), 3137 (N–H), 3088 (N–H), 1655 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (brs, 1H), 7.60 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.53–7.43 (m, 3H), 7.38–7.28 (m, 4H), 7.13 (tt, *J* = 7.5, 1.3 Hz, 1H), 5.89 (s, 1H), 5.40 (s, 1H), 5.13 (brs, 1H), 3.22 (d, *J* = 14.1 Hz, 1H), 2.88 (d, *J* = 14.1 Hz, 1H), 1.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 149.7, 140.8, 139.5, 137.4, 130.7, 128.9, 128.4, 127.9, 124.7, 124.6, 123.6, 120.3, 74.4, 46.1, 28.7. Anal. Calcd for $C_{18}H_{18}INO_2$: C, 66.25; H, 5.56; N, 8.56. Found: C, 66.02; H, 5.83; N, 8.42. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 90/

10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 27.4 min, t_R (minor) = 22.5 min.

Synthesis and characterization of (*S*)-4-hydroxy-2-methylene-*N*-phenyl-4-(2-(trifluoromethyl) phenyl)pentanamide (2 aa)

According to the general procedure, the reaction of 2'-(trifluoromethyl)acetophenone (37.2 mg, 0.198 mmol) with **1 a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 7/1 to 4/1) to give **2 aa** (64.6 mg, 97%, 98% ee) as a white solid: *Rf* = 0.30 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{17}$ −76.1 (*c* 1.00 in $CHCl_3$); m.p. 125–127 °C; IR (KBr) 3274 (O–H), 3139 (N–H), 1656 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.39 (brs, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.56–7.49 (m, 3H), 7.37–7.30 (m, 3H), 7.13 (t, *J* = 7.5 Hz, 1H), 5.97 (s, 1H), 5.34 (s, 1H), 4.50 (s, 1H), 3.10 (d, *J* = 14.3 Hz, 1H), 2.84 (d, *J* = 14.3 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 146.9, 141.0, 137.8, 131.5, 128.9, 127.9, 127.05 (q, *J* = 30.5 Hz), 127.02, 125.3, 125.2, 124.5, 123.0, 120.1, 75.3, 46.5, 29.7. Anal. Calcd for $C_{19}H_{18}F_3NO_2$: C, 65.32, H, 5.19; N, 4.01. Found: C, 65.27; H, 5.13; N, 3.97. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 19.8 min, t_R (minor) = 17.7 min.

Synthesis and characterization of (*S*)-4-hydroxy-2-methylene-*N*-(*p*-tolyl)-4-(2-(trifluoromethyl) phenyl)pentanamide (2 ab)

According to the general procedure, the reaction of 2'-(trifluoromethyl)acetophenone (36.8 mg, 0.196 mmol) with **1 b** (86.2 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give **2 ab** (53.6 mg, 76%, 95% ee) as a white solid: *Rf* = 0.23 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −76.8 (*c* 1.02 in $CHCl_3$); m.p. 134–136 °C; IR (KBr) 3344 (O–H), 3125 (N–H), 1651 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (brs, 1H), 7.73 (dd, *J* = 14.7, 7.8 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.12 (t, *J* = 8.4 Hz, 2H), 5.92 (s, 1H), 5.30 (s, 1H), 4.80 (s, 1H), 3.07 (d, *J* = 14.4 Hz, 1H), 2.81 (d, *J* = 14.4 Hz, 1H), 2.32 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 146.9, 141.2, 135.1, 134.2, 131.5, 129.4, 128.8, 127.8 (q, *J* = 7.2 Hz), 127.1 (q, *J* = 30.8 Hz), 127.0, 124.6, 123.0, 120.2, 75.2, 46.6, 29.8, 20.8. Anal. Calcd for $C_{20}H_{20}F_3NO_2$: C, 66.11, H, 5.55; N, 3.85. Found: C, 66.04; H, 5.88; N, 4.03. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 22.2 min, t_R (minor) = 20.4 min.

Synthesis and characterization of (*S*)-*N*-(4-(*tert*-butyl)phenyl)-4-hydroxy-2-methylene-4-(2-(trifluoromethyl)phenyl)pentanamide (2 ac)

According to the general procedure, the reaction of 2'-(trifluoromethyl)acetophenone (40.3 mg, 0.214 mmol) with **1 c** (98.8 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give **2 ac** (63.8 mg, 74%, 95% ee) as a white solid: *Rf* = 0.33 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −76.5 (*c* 1.03 in $CHCl_3$); m.p. 174–176 °C; IR (KBr) 3304 (O–H), 3159 (N–H), 1651 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (brs, 1H), 7.75 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.52–7.43 (m, 3H), 7.36–7.31 (m, 3H), 5.92 (s, 1H), 5.30 (s, 1H), 4.77 (brs, 1H), 3.07 (d, *J* = 14.3 Hz, 1H), 2.82 (d, *J* = 14.3 Hz, 1H), 1.73 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 147.7, 146.9, 141.4, 135.0, 131.5, 128.9, 127.9 (q, *J* = 7.2 Hz), 127.1 (q, *J* = 30.8 Hz), 127.0, 125.8, 124.3, 120.0, 75.2, 46.6, 34.4, 31.3, 29.9. Anal. Calcd for $C_{23}H_{26}F_3NO_2$: C, 68.13, H, 6.46; N, 3.45. Found: C, 67.84; H, 6.32; N, 3.63. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 16.7 min, t_R (minor) = 14.6 min.

Synthesis and characterization of (*S*)-4-hydroxy-2-methylene-*N*-(naphthalen-1-yl)-4-(2-(trifluoromethyl)phenyl)pentanamide (2 ad)

According to the general procedure, the reaction of 2'-(trifluoromethyl)acetophenone (37.2 mg, 0.198 mmol) with **1 d** (97.0 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1 to 4/1) to give **2 ad** (70.3 mg, 89%, 97% ee) as a white solid: *Rf* = 0.22 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −59.2 (*c* 1.03 in $CHCl_3$); m.p. 130–132 °C; IR (KBr) 3297 (O–H), 3057 (N–H), 1661 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.71 (brs, 1H), 7.86–7.83 (m, 3H), 7.76–7.68 (m, 3H), 7.50–7.40 (m, 4H), 7.33 (t, *J* = 7.7 Hz, 1H), 6.01 (s, 1H), 5.31 (s, 1H), 4.82 (s, 1H), 3.10 (d, *J* = 14.4 Hz, 1H), 2.88 (d, *J* = 14.4 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 146.8, 141.2, 134.0, 132.2, 131.5, 128.9, 128.6, 127.8 (q, *J* = 7.0 Hz), 127.4, 127.1 (q, *J* = 30.2 Hz), 127.0, 126.3, 126.1, 126.0, 125.6, 124.7, 123.0, 121.2, 121.0, 75.4, 46.6, 30.1. Anal. Calcd for $C_{23}H_{20}F_3NO_2$: C, 69.16, H, 5.05; N, 3.51. Found: C, 68.84; H, 4.94; N, 3.68. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 23.0 min, t_R (minor) = 17.6 min.

Synthesis and characterization of (*S*)-2-(2-(trifluoromethyl)phenyl)pent-4-en-2-ol[42]

According to the general procedure, the reaction of 2'-(trifluoromethyl)acetophenone (37.3 mg, 0.198 mmol) with 2-allyl-5,5-dimethyl-1,3,2-dioxaborinane (43.2 mg, 0.280 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 15/1 to 10/1) to give (*S*)-2-(2-(trifluoromethyl)phenyl)pent-4-en-2-ol (10.3 mg, 23%, 85% ee) as a colorless oil: $[\alpha]_D^{22}$ −75.4 (*c* 0.0082 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.52–7.47 (m, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 5.65 (m, 1H), 5.20–5.14 (m, 2H), 2.92 (dd, *J* = 14.1, 6.3 Hz, 1H), 2.54 (dd, *J* = 14.1, 8.3 Hz, 1H), 2.38 (s, 1H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 133.2, 131.4 (q, *J* = 1.2 Hz), 128.5, 128.0 (q, *J* = 7.3 Hz), 127.3 (q, *J* =

30.8 Hz), 126.8, 124.8 (q, J = 271 Hz), 120.1, 74.6, 48.3 (q, J = 1.9 Hz), 30.6 (q, J = 1.8 Hz). The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IG column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 8.1 min, t_R (minor) = 9.8 min.

Synthesis and characterization of (+)-2-((1-methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)methyl)-*N*-phenylacrylamide (3)

According to the general procedure, the reaction of methyl 2-acetylbenzoate (35.6 mg, 0.200 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 3/1 to 1/1) to give **3** (57.3 mg, 93%, 94% ee) as a white solid: Rf = 0.38 (silica gel, hexane/EtOAc = 3/2); $[\alpha]_D^{22}$ + 16.4 (c 0.77 in $CHCl_3$); m.p. 139–141 °C; IR (KBr) 3352 (N–H), 1753 (C=O), 1672 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 7.5 Hz, 1H), 7.55–7.36 (m, 3H), 7.31–7.23 (m, 4H), 7.07 (m, 1H), 5.70 (s, 1H), 5.49 (s, 1H), 3.29 (d, J = 14.1 Hz, 1H), 3.05 (d, J = 14.1 Hz, 1H), 1.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 166.7, 151.8, 139.9, 137.5, 134.1, 129.2, 128.7, 126.2, 125.1, 124.3, 123.1, 122.4, 120.1, 86.6, 41.2, 25.9. Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25, H, 5.58; N, 4.56. Found: C, 74.41; H, 5.79; N, 4.83. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IE column (hexane/EtOH = 85/15), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 30.8 min, t_R (minor) = 28.5 min.

Synthesis and characterization of (+)-4-hydroxy-4-(4-methoxyphenyl)-2-methylene-*N*,4-diphenylbutanamide (I)

According to the general procedure, the reaction of 4-methoxybenzophenone (42.4 mg, 0.200 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 7/1 to 4/1) to give **I** (13.4 mg, 18%, 9% ee) as a white solid: Rf = 0.20 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{24}$ + 57.2 (c 0.011 in $CHCl_3$); m.p. 56–58 °C; IR (KBr) 3261 (O–H), 1654 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (brs, 1H), 7.48–7.27 (m, 10H), 7.23–7.09 (m, 2H), 6.83 (m, 2H), 5.62 (s, 1H), 4.94 (s, 1H), 4.59 (s, 1H), 3.76 (s, 3H), 3.41 (d, J = 13.8 Hz, 1H), 3.35 (d, J = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 158.3, 146.7, 141.6, 138.7, 137.6, 129.0, 127.9, 127.6, 126.8, 126.3, 124.7, 123.0, 120.2, 113.3, 77.7, 55.2, 45.0. Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19, H, 6.21; N, 3.75. Found: C, 77.51; H, 5.81; N, 3.80. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 17.1 min, t_R (minor) = 14.6 min.

Synthesis and characterization of (+)-4-hydroxy-2-methylene-4-(4-nitrophenyl)-*N*,4-diphenylbutanamide (II)

According to the general procedure, the reaction of 4-nitrobenzophenone (45.4 mg, 0.200 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, $CHCl_3$/EtOAc = 40/1) to give **II** (44.9 mg, 58%, 13% ee) as a white solid: Rf = 0.20 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{23}$ + 8.0 (c 0.41 in $CHCl_3$); m.p. 165–167 °C; IR (KBr) 3285 (O–H), 1648 (C=O), 1617 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (dt, J = 9.3, 2.1 Hz, 2H), 7.67 (dt, J = 9.3, 2.1 Hz, 2H), 7.59 (brs, 1H), 7.50–7.46 (m, 4H), 7.38–7.14 (m, 6H), 5.95 (s, 1H), 5.61 (s, 1H), 4.96 (s, 1H), 3.46 (d, J = 13.8 Hz, 1H), 3.37 (d, J = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 154.2, 146.6, 145.6, 140.7, 136.9, 129.1, 128.3, 127.5, 127.4, 126.23, 126.17, 125.2, 123.2, 120.4, 77.3, 44.8. Anal. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12, H, 5.19; N, 7.21. Found: C, 70.72; H, 5.35; N, 6.87. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (hexane/EtOH = 70/30), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 17.6 min, t_R (minor) = 22.7 min.

Synthesis and characterization of (*S*)-2-((3-hydroxy-1-methyl-2-oxoindolin-3-yl)methyl)-*N*-phenylacrylamide (III)[21]

According to the general procedure, the reaction of *N*-methylisatin (31.9 mg, 0.198 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 3/2 to $CHCl_3$/MeOH = 20/1) to give **III** (23.0 mg, 36%, 38% ee) as a white solid: Rf = 0.23 (silica gel, hexane/EtOAc = 2/3); ^1H NMR (300 MHz, DMSO-d_6) δ 9.52 (s, 1H), 7.47 (d, J = 8.7 Hz, 2H), 7.30–7.18 (m, 4H), 7.02 (m, 1H), 6.93–6.87 (m, 2H), 6.19 (s, 1H), 5.72 (s, 1H), 5.27 (s, 1H), 3.10–3.06 (m, 4H), 2.73 (d, J = 12.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.8, 166.5, 143.1, 139.3, 138.9, 130.0, 129.0, 128.3, 124.4, 123.3, 122.6, 121.8, 120.3, 108.3, 75.4, 25.8. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 70/30), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 20.2 min, t_R (minor) = 17.0 min.

Synthesis and characterization of (−)-methyl 2-hydroxy-2-phenyl-4-(phenylcarbamoyl)pent-4-enoate (IV)[19]

According to the general procedure, the reaction of methyl benzoylformate (32.8 mg, 0.200 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 7/1 to 4/1) to give **IV** (38.1 mg, 59%, 79% ee) as a white solid: Rf = 0.47 (silica gel, hexane/EtOAc = 2/1); $[\alpha]_D^{18}$ −13.5 (c 0.60 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.66–7.53 (m, 4H), 7.40–7.26 (m, 5H), 7.11 (t, J = 7.5 Hz, 1H), 5.96 (s, 1H), 5.38 (s, 1H), 5.15 (s, 1H), 3.77 (s, 3H), 3.38 (d, J = 14.1 Hz, 1H), 3.08 (d, J = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 167.5, 140.7, 140.2, 137.8, 128.9, 128.3, 128.1, 125.5, 125.1, 124.4, 120.0, 79.1, 53.3, 42.4. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IA column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 46.2 min, t_R (minor) = 41.5 min.

Synthesis and characterization of (−)-4-cyclopentyl-4-hydroxy-2-methylene-*N*-phenylpentanamide (V)

According to the general procedure, the reaction of cyclopentyl methyl ketone (22.4 mg, 0.200 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 7/1 to 4/1) to give **V** (30.5 mg, 56%, 54% ee) as a colorless oil: *Rf* = 0.23 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −45.5 (*c* 0.020 in $CHCl_3$); IR (NaCl) 3295 (O–H), 1658 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.29 (brs, 1H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.32–7.27 (m, 2H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.13 (s, 1H), 5.40 (s, 1H), 3.23 (brs, 1H), 2.70 (d, *J* = 14.1 Hz, 1H), 2.39 (d, *J* = 14.1 Hz, 1H), 2.08–1.97 (m, 1H), 1.84—1.22 (m, 8H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 141.9, 138.5, 128.8, 125.0, 124.1, 120.0, 74.3, 50.7, 43.6, 27.5, 26.8, 25.9, 25.9, 24.2. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69, H, 8.48; N, 5.12. Found: C, 74.95; H, 8.58; N, 5.22. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 98/2), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 40.4 min, t_R (minor) = 47.4 min.

Synthesis and characterization of (+)-4-ethyl-4-hydroxy-2-methylene-N-phenyldodecanamide (VI)

According to the general procedure, the reaction of 3-undecanone (34.1 mg, 0.200 mmol) with **1a** (81.9 mg, 0.300 mmol) was performed for 24 hours. The crude material was purified by column chromatography (silica gel, $CHCl_3$/EtOAc = 20/1 to 15/1) to give **VI** (16.7 mg, 49%, 4% ee) as a colorless oil: *Rf* = 0.30 (silica gel, $CHCl_3$/EtOAc = 10/1); $[\alpha]_D^{23}$ +14.7 (*c* 0.0098 in $CHCl_3$); IR (NaCl) 3282 (O–H), 1658 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.07 (brs, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.33–7.26 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.13 (s, 1H), 5.42 (s, 1H), 3.04 (brs, 1H), 2.56 (s, 2H), 1.59–1.47 (m, 4H), 1.28 (s, 12H), 0.94–0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 141.9, 138.1, 128.9, 124.7, 124.2, 120.0, 74.7, 42.1, 38.5, 31.8, 31.5, 30.1, 29.6, 29.3, 23.6, 22.6, 14.1, 8.1. Anal. Calcd for $C_{21}H_{33}NO_2$: C, 76.09, H, 10.03; N, 4.23. Found: C, 76.37; H, 9.63; N, 4.11. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IG column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 27.3 min, t_R (minor) = 31.2 min.

Synthesis and characterization of *N*-(2-((5,5-dimethyl-1,3,2-dioxaborinan-2-yl)methyl)acryloyl)-*N*-phenylbenzamide (Bz-1a)

To a solutin of **1a** (507 mg, 1.86 mmol) in anhydrous dichloromethane (3.7 mL) were added triethylamine (563 mg, 5.57 mmol, 3.0 equiv.) and benzoyl chloride (523 mg, 3.72 mmol, 2.0 equiv.) at 0 °C. The solution was warmed to room temperature and stirred for 3 hours, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (15 mL). The resulting mixture was extracted with dichloromethane (20 mL). The organic extract was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 8/1) and recrystallization (EtOAc–hexane) to give **Bz-1a** (448 mg, 64%) as a white solid: *Rf* = 0.27 (silica gel, hexane/EtOAc = 2/1); m.p. 123–125 °C; IR (KBr) 1700 (C=O), 1662 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.3 Hz, 2H), 7.48–7.27 (m, 6H), 7.18 (d, *J* = 7.7 Hz, 2H), 5.71 (s, 1H), 5.46 (s, 1H), 3.58 (s, 4H), 1.74 (s, 2H), 0.93 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 173.4, 143.7, 140.1, 135.4, 132.0, 129.3, 129.1, 128.4, 127.5, 127.4, 122.8, 72.1, 31.6, 21.8. Anal. Calcd for $C_{22}H_{24}BNO_4$: C, 70.04; H, 6.41; N, 3.71. Found: C, 69.93; H, 6.77; N, 3.76.

Synthesis and characterization of (5*S*)-3-(((4-chlorophenyl)thio)methyl)-5-methyl-5-(naphthalen-1-yl)dihydrofuran-2(3H)-one (4a)

To a solution of **2f** (107 mg, 0.323 mmol) in anhydrous dichloromethane (5.4 mL) was added *p*-toluenesulfonic acid (67.6 mg, 0.355 mmol, 1.1 equiv.) at room temperature. After stirring the mixture at the same temperature for 14 hours, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (15 mL). The resulting mixture was extracted with dichloromethane (25 mL). The organic extract was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material. The resulting material was roughly purified by column chromatography (silica gel, hexane/EtOAc = 8/1) to give a crude material (76.5 mg), which was used without further purification: R_f = 0.40 (silica gel, hexane/EtOAc = 3/1).

To a solution of the crude material (76.5 mg) in anhydrous chloroform (0.88 mL), *p*-chlorothiophenol (49.8 mg, 0.345 mmol, 1.3 equiv.) and triethylamine (16 mg, 0.159 mmol, 0.2 equiv.) were added at room temperature. After stirring the mixture at the same temperature for 20 hours, the reaction mixture was diluted with water (10 mL). The resulting mixture was extracted with dichloromethane (20 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 20/1 to 7/1) to give **4a** (109 mg, 88% in 2 steps, diastereomer ratio 39:61) as a colorless oil: *Rf* = 0.38, 0.33 (silica gel, hexane/EtOAc = 5/1); IR (NaCl) 1769 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.2 Hz, 1H, major), 8.04–8.01 (m, 1H, minor), 7.89–7.86 (m, 1H), 7.81–7.78 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 6.9 Hz, 1H, major), 7.60 (d, *J* = 7.2 Hz, 1H, minor), 7.57–7.40 (m, 3H), 7.21–7.14 (m, 4H), 3.48 (dd, *J* = 13.5, 3.6 Hz, 1H major), 3.46–3.41 (m, 1H, minor), 3.29 (dd, *J* = 12.6, 8.7 Hz, 1H, minor), 3.18–3.02 (m, 2H, minor), 2.76 (dd, *J* = 13.5, 9.6 Hz, 1H, major), 2.70–2.64 (m, 1H, minor), 2.57 (dd, *J* = 12.3, 9.3 Hz, 1H, major), 2.40 (t, *J* = 12.0 Hz, 1H, minor), 2.03 (s, 3H, minor), 1.89 (s, 3H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 175.5, 140.0, 138.2, 134.7, 134.5, 133.4, 133.1, 132.8, 132.6, 131.2, 131.0, 129.6, 129.4, 129.2, 129.14, 129.11, 129.0, 128.82, 128.77, 126.0, 125.9, 125.44, 125.41, 125.0, 124.8, 124.5, 122.2, 122.1, 86.1, 85.9, 41.3, 41.1, 40.5, 40.3, 35.2, 34.6, 29.8, 28.7. Anal. Calcd for $C_{22}H_{19}ClO_2S$: C, 69.01, H, 5.00; N, 0.00. Found: C, 69.28; H, 5.26; N, 0.00. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 95/5), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 32.9 min, t_R (minor) = 27.3 min.

Major diastereomer of **4a** was isolated by further purification by column chromatography (silica gel, hexane/EtOAc = 12/1): *Rf* = 0.33 (silica gel, hexane/EtOAc = 5/1); $[\alpha]_D^{23}$ + 21.5 (*c* 1.12 in $CHCl_3$); IR (NaCl) 1769 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.2 Hz, 1H), 7.90 (m, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 7.3 Hz, 1H), 7.56–7.41 (m, 3H), 7.22–7.18 (s, 4H), 3.50 (dd, *J* = 13.5, 3.6 Hz, 1H), 3.22–3.05 (m, 2H), 2.76 (dd, *J* = 13.5, 9.6 Hz, 1H), 2.59 (dd, *J* = 12.3, 9.6 Hz, 1H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 140.0, 134.6, 133.1, 132.9, 131.3, 129.5, 129.2, 129.1, 128.9, 126.1, 125.5, 125.1, 124.8, 122.2, 86.2, 41.4, 40.4, 35.3, 28.8. Anal. Calcd for $C_{22}H_{19}ClO_2S$: C, 69.01, H, 5.00; N, 0.00. Found: C, 68.74; H, 5.31; N, 0.00.

Synthesis and characterization of (5*S*)-3-(((4-chlorophenyl)thio)methyl)-5-methyl-5-(2-(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one (4b)

To a solution of **2aa** (314 mg, 0.899 mmol) in anhydrous dichloromethane (15 mL) was added *p*-toluenesulfonic acid (188 mg, 0.989 mmol, 1.1 equiv.) at room temperature. After stirring the mixture at the same temperature for 14 hours, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (15 mL). The resulting mixture was extracted with dichloromethane (25 mL). The organic extract was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material. The resulting material was roughly purified by column chromatography (silica gel, hexane/EtOAc = 8/1) to give a crude material (227 mg), which was used without further purification: R_f = 0.50 (silica gel, hexane/EtOAc = 3/1).

To a solution of the crude material (227 mg) in anhydrous chloroform (2.6 mL), *p*-chlorothiophenol (149 mg, 1.03 mmol, 1.3 equiv.) and triethylamine (16 mg, 0.159 mmol, 0.2 equiv.) were added at room temperature. After stirring the mixture at the same temperature for 20 hours, the reaction mixture was diluted with water (10 mL). The resulting mixture was extracted with dichloromethane (20 mL). The organic extract was dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 20/1 to 7/1) to give **4b** (317 mg, 88% in 2 steps, diastereomer ratio 39:61) as a colorless oil: *Rf* = 0.39, 0.37 (silica gel, hexane/EtOAc = 5/1); IR (NaCl) 1773 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (t, *J* = 8.3 Hz, 2H, major), 7.74–7.67 (m, 2H, minor), 7.57 (t, *J* = 7.5 Hz, 1H, major), 7.57–7.52 (m, 1H, minor), 7.44 (t, *J* = 7.5 Hz, 1H, major), 7.30–7.22 (m, 4H), 3.51 (dd, *J* = 13.2, 3.6 Hz, 1H, major), 3.49–3.44 (m, 1H, minor), 3.16–2.82 (m, 3H), 2.67 (m, 1H, minor), 2.37–2.28 (m, 1H, minor), 2.35 (t, *J* = 12.0 Hz, 1H, major), 1.85 (s, 3H, minor), 1.74 (s, 3H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 175.0, 142.7, 141.5, 133.18, 133.15, 132.8, 132.1, 131.29, 131.26, 129.2, 129.1, 128.5 (q, *J* = 6.5 Hz), 128.2, 128.0, 127.9 (q, *J* = 6.5 Hz), 127.1, 126.7, 126.3 (q, *J* = 30.8 Hz), 125.8 (q, *J* = 31.0 Hz), 124.2 (q, *J* = 271.3 Hz), 124.1 (q, *J* = 271.9 Hz), 85.6, 85.4, 41.8, 40.9, 40.2, 40.1, 34.8, 34.7, 30.2, 28.6. Anal. Calcd for $C_{19}H_{16}ClF_3O_2S$: C, 56.93, H, 4.02; N, 0.00. Found: C, 57.25; H, 3.88; N, 0.00. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IG column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 23.3 min, t_R (minor) = 18.0 min.

Major diastereomer of **4b** was isolated by further purification by column chromatography (silica gel, hexane/EtOAc = 12/1): *Rf* = 0.37 (silica gel, hexane/EtOAc = 5/1); $[\alpha]_D^{21}$ + 62.6 (*c* 0.56 in $CHCl_3$); IR (NaCl) 1773 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (t, *J* = 8.3 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.30–7.24 (m, 4H), 3.51 (dd, *J* = 13.2, 3.6 Hz, 1H), 3.16–3.05 (m, 1H), 2.99–2.81 (m, 2H), 2.35 (t, *J* = 12.0 Hz, 1H), 1.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 142.7, 133.1, 133.0, 132.2, 131.4, 129.3, 128.0, 127.9 (q, *J* = 6.8 Hz), 127.1, 125.8 (q, *J* = 31.0 Hz), 124.1 (q, *J* = 271.5 Hz), 85.5, 40.9, 40.2, 34.9, 28.7. Anal. Calcd for $C_{19}H_{16}ClF_3O_2S$: C, 56.93, H, 4.02; N, 0.00. Found: C, 56.96; H, 4.12; N, 0.00.

Synthesis and characterization of (3*S*,5*S*)-3-(((4-chlorophenyl)sulfonyl)methyl)-5-methyl-5-(naphthalen-1-yl)dihydrofuran-2(3H)-one (5a)

To a solution of the major diastereomer of **4a** (52.3 mg, 0.137 mmol) in anhydrous dichloromethane (2.3 mL), *m*-chloroperbenzoic acid (35% water suspension, 109 mg, 0.411 mmol, 3.0 equiv.) was added at 0 °C. The solution was warmed to room temperature and stirred for 15 hours. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (15 mL), and the resulting mixture was extracted with dichloromethane (30 mL). The organic extract was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude material. The crude material was purified by recrystallization (EtOAc-hexane) to give **5a** (45.8 mg, 81%, 99% ee) as a white solid: *Rf* = 0.30 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −81.6 (*c* 1.27 in $CHCl_3$); m.p. 164–166 °C; IR (KBr) 1766 (C=O), 1310 (S=O), 1151 (S=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.91–7.81 (m, 4H), 7.66 (dd, *J* = 7.2, 0.9 Hz, 1H), 7.58–7.41 (m, 5H), 3.73 (dd, *J* = 13.8, 2.1 Hz, 1H), 3.58 (m, 1H), 3.43 (dd, *J* = 12.9, 9.0 Hz, 1H), 3.00 (dd, *J* = 13.8, 11.1 Hz, 1H), 2.63 (dd, *J* = 12.8, 11.1 Hz, 1H), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 141.1, 139.5, 137.3, 134.6, 129.9, 129.44, 129.36, 129.3, 128.9, 126.4, 125.6, 125.0, 124.9, 122.2, 87.3, 57.1, 42.1, 35.1, 28.2. Anal. Calcd for $C_{22}H_{19}ClO_4S$: C, 63.69; H, 4.62; N, 0.00. Found: C, 63.79; H, 4.64; N, 0.00. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 60/40), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 22.4 min, t_R (minor) = 25.6 min.

Synthesis and characterization of (3*S*,5*S*)-3-(((4-chlorophenyl)sulfonyl)methyl)-5-methyl-5-(2-(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one (5b)

To a solution of the major diastereomer of **4b** (87.2 mg, 0.218 mmol) in anhydrous dichloromethane (3.6 mL), *m*-chloroperbenzoic acid (35% water suspension, 174 mg, 0.654 mmol, 3.0 equiv.) was added at 0 °C. The solution was warmed to room temperature and stirred for 15 hours. The reaction was quenched by addition of saturated aqueous $Na_2S_2O_3$ (15 mL), and the resulting mixture was extracted with dichloromethane (30 mL). The organic extract was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give a

crude material. The crude material was purified by recrystallization (EtOAc-hexane) to give **5b** (69.5 mg, 74%, 99% ee) as a white solid: *Rf* = 0.32 (silica gel, hexane/EtOAc = 3/1); $[\alpha]_D^{22}$ −27.4 (*c* 1.06 in $CHCl_3$); m.p. 123–125 °C; IR (KBr) 1774 (C=O), 1309 (S=O), 1119 (S=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.77–7.69 (m, 2H), 7.60–7.55 (m, 3H), 7.45 (t, *J* = 7.5 Hz, 1H), 3.76 (dd, *J* = 14.1, 2.1 Hz, 1H), 3.53–3.41 (m, 1H), 3.18 (m, 1H), 3.07 (m, 1H), 2.40 (t, *J* = 12.3 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 142.2, 141.1, 137.3, 132.2, 129.9, 129.4, 128.2, 128.0 (q, *J* = 6.8 Hz), 127.1, 126.0 (q, *J* = 31.0 Hz), 122.2, 86.1, 57.0, 41.8, 35.1, 28.4. Anal. Calcd for $C_{19}H_{16}ClF_3O_4S$: C, 52.72; H, 3.73; N, 0.00. Found: C, 52.42; H, 4.02; N, 0.00. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 60/40), flow rate 0.5 mL/min, UV detection 254 nm, t_R (major) = 18.0 min, t_R (minor) = 21.1 min.

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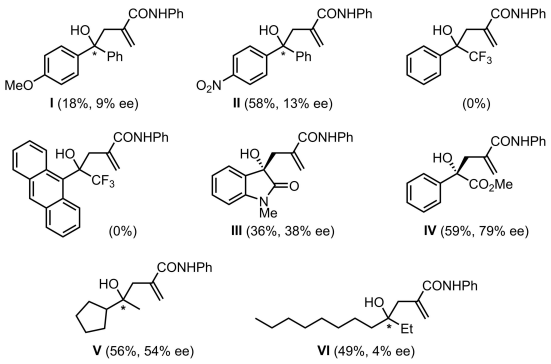
[30] At this stage, we reinvestigated the effect of other metal salts on this reaction prior to further optimization of chiral additives. However, it was demonstrated that Zn $(OH)_2$ still gave the best results both in terms of reactivity and enantioselectivity (Table S2 in the Supporting Information).
[31] Besides methylketones listed in Scheme 2, various types of ketones were screened. The results are summarized below. The absolute configurations of compounds **III** and **IV** were determined by comparison with the reported data.[16,19]



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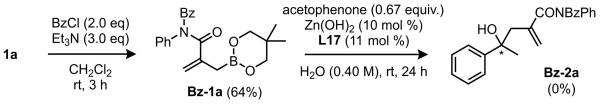
[33] In contrast, *N*-benzoyl derivative of **1a** (**Bz-1a**) showed no reactivity and was recovered even after 24 hour reaction. We also examined a reaction using an ester-functionalized allylboronate, resulting in decomposition of the reagent.



[34] Crystal data for **2y**: monoclinic, space group $P2_1$, $a=6.9701(5)$ Å, $b=7.9988(5)$ Å, $c=15.6423(16)$ Å, $V=855.02(12)$ Å^3, $Z=2$, $\rho=1.582$ Mgm^{-3}, μ(MoKα)$=1.880$ mm^{-1}, $T=173$ K; in the final least-squares refinement cycles on F^2, the model converged at $R_1=0.0496$ ($I>2\rho(I)$), $wR_2=0.1578$, Flack parameter $=-0.035(9)$, and GOF $=1.12$ for 3887 reflections and 208 parameters (CCDC deposition number 1968880).

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[36] Crystal data for **5a**: tetragonal, space group $P4_3$, $a=b=10.0081(2)$ Å, $c=20.3967(9)$ Å, $V=2042.98(11)$ Å^3, $Z=4$, $\rho=1.349$ Mgm^{-3}, μ(MoKα)$=0.314$ mm^{-1}, $T=173$ K; in the final least-squares refinement cycles on F^2, the model converged at $R_1=0.0464$ ($I>2\rho(I)$), $wR_2=0.1298$, Flack parameter $=0.00(5)$, and GOF $=1.01$ for 4519 reflections and 254 parameters (CCDC deposition number 1968882).

[37] Crystal data for **5b**: monoclinic, space group $P2_1$, $a=5.4285(5)$ Å, $b=12.5034(12)$ Å, $c=13.7618(11)$ Å, $V=927.39(14)$ Å^3, $Z=2$, $\rho=1.550$ Mgm^{-3}, μ(MoKα)$=0.371$ mm^{-1}, $T=173$ K; in the final least-squares refinement cycles on F^2, the model converged at $R_1=0.0327$ ($I>2\rho(I)$), $wR_2=0.0894$, Flack parameter $=0.00(2)$, and GOF $=1.02$ for 4218 reflections and 254 parameters (CCDC deposition number 1968883).

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[39] During the course of the reaction for **2aa** in Scheme 2, 12% of **1a** was transformed into 2-(hydroxymethyl)-*N*-phenylacrylamide. Meanwhile, in the absence of **L17**, the yield of this transformation was significantly increased to 40%. In this case, the ketone substrate was partially consumed after 76 h. The chiral aminophenol is undoubtedly involved in both steps, formation of an allylzinc species and subsequent addition to the ketone, to accelerate the reaction.

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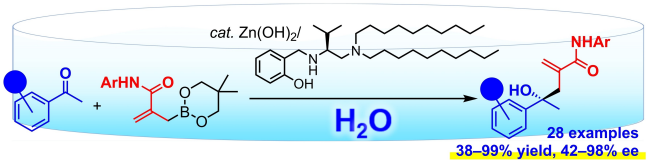
FULL PAPER

Zinc Hydroxide-Catalyzed Asymmetric Allylation of Acetophenones with Amido-Functionalized Allylboronate in Water



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T. Sengoku, R. Maegawa, H. Imamura, M. Wada, H. Yoda*