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Chiral Vanadyl(V) Complexes Enable Efficient Asymmetric Reduction of β-Ketoamides: Application towards (*S*)-Duloxetine

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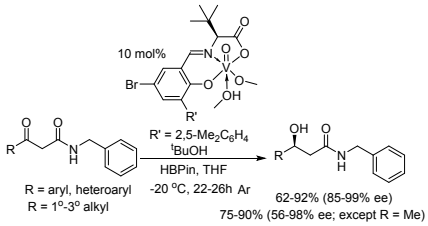
KEYWORDS. Oxidovanadium, pinacolborane, β-hydroxyamides, antidepressant.



ABSTRACT: High valent chiral oxidovanadium(V) complexes derived from 3,5-substituted-*N*-salicylidene-L-*tert*-leucine were used as catalysts in asymmetric reduction of *N*-benzyl-β-keto-amides. Among 6 different solvents, 3 different alcohol additives and 2 different boranes examined, the use of pinacolborane in THF with *t*-BuOH additive led to the best results at -20 °C. The corresponding β-hydroxy-amides can be furnished with yields up to 92% and ee up to 99%. We have successfully extended this catalytic protocol for the synthesis of (*S*)-duloxetine precursor.

1. INTRODUCTION

Enantiomerically pure alcohols and amides are profoundly used in the pharmaceuticals, flavours, fragrances and fine chemicals industries.[1] Enantiopure β-oxo-amides/nitriles and gamma amino alcohols are important building blocks for the synthesis of natural products and pharmaceutically active compounds. Such as Fluoxetine, Duloxetine and Nisoxetine which serve as serotonin specific reuptake inhibition whereas Ritonavir and Lopinavir serve as anti HIV(Figure 1).[2] For the synthesis of the optically active alcohols, various ruthenium(II) catalysts bearing chiral amine and/or phosphine ligands that were first developed by Noyori are available.[3] These catalysts efficiently hydrogenate ketones by using hydrogen to produce the corresponding alcohols with enantiopurity of ≥95% in many cases.[4] Excellent TON (Turnover Number) and enantiomeric excess (ee) for asymmetric hydrogenation of β-keto esters can be realized.[5]

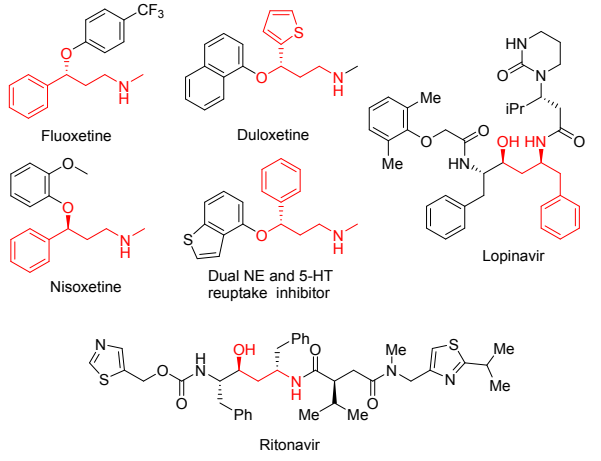
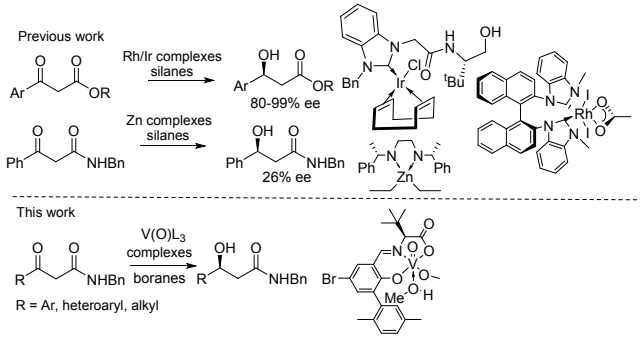


Figure 1. The chiral anti-depressant drugs derived from the enantioselective synthesis of β-hydroxy-amides

Wills and co-worker carried out asymmetric transfer hydrogenation of acetyl ketones and diketones with Ru(II)/TsDPEN-derived catalyst with excellent yields and ees in most cases.[6] Zhang et al. designed a series of chiral diphosphine ligands with ruthenium(II) for the asymmetric hydrogenation of β-keto esters which had given alcohols with ees up to 99%.[7] By using ruthenium complexes equipped with chiral 2,2'-binap ligands, Lin and co-workers achieved chiral β-hydroxy-esters with ees up to 99.8% for the asymmetric hydrogenation of β-aryl-β–keto esters.[8] Zhou and co-workers developed chiral iridium(I) complexes of SpiroPAP ligand which had led to excellent enantioselectivities (up to 99.9% ee) and extremely high TON (1,230,000) for the asymmetric hydrogenation of β-keto esters.[9] Touati and co-workers successfully demonstrated that chiral SYNPHOS and DIFLUORPHOS ligands with ruthenium(II) can be efficiently used in the asymmetric reduction of β-keto-amides with good to excellent enantioselectivities (up to 99%).[10]



Scheme 1. Asymmetric reduction of β-keto eaters and amides.

Alternatively, asymmetric reductions of β-keto-esters by bio-enzymatic means in aqueous[11] or organic phase were also workable.[12] Gotor and co-workers successfully carried out the bio-catalyzed asymmetric reductions of β-keto-amides with good to excellent yields and ees (up to 99%).[13] Gandolfi and co-workers further extended their uses for the synthesis of Duloxetine precursor.[14] The biocatalytic reduction of β-keto-nitriles led to Duloxetine (*S*)-precursor with good to excellent enantioselectivities (up to 99%). Toste and co-workers carried out asymmetric hydrosilylation of aldehydes/ketones[15-18] and imines[19] with good yields and enantioselectivities. Enantioselective hydrosilylation of β-keto-esters was also a promising protocol for the synthesis of enantioenriched β-hydroxy esters by chiral Rh(I)-NHC complexes (Scheme 1).[20]

Asymmetric hydroboration of ketones constitutes a beneficial strategy for the synthesis of enantio-enriched alcohols in view of the weaker O-B bond relative to the O-Si bond in the hydrosilylation. Since the seminal works by Itsuno[21] and Corey[22] on the asymmetric reduction of ketones with chiral amino alcohol-based borane reagents, enormous progress has been made in that aspect. Hydroboration reagents like catecholborane (HBCat), pinacolborane (HBPin) and etc. are easily available reagents which tolerate a variety of diverse functional groups.[23] Ghorai and co-workers utilized cinchona-derived thioureas or squaramides for intramolecular oxa-Michael to enones by incipient borates from reduction of an aldehyde by HBPin.[24] Du and coworkers explored H_3N-BH_3-mediated asymmetric reduction of imines in 84-95% ees by using $HB(C_6F_5)_2$/chiral *tert*-butylsulfinamide adduct as catalyst.[25]

While there are considerable examples of asymmetric reductions of β-keto esters but there are very few reports on the asymmetric reduction of the β-keto amides by 3d-high valent, oxometallic complexes with boranes. In view of economic and environmental viewpoints, they are much more attractive than the rare earth families. Carpentier had carried out asymmetric hydrosilylation of β-keto amides with chiral Zinc(II)-diamine complexes with only 28% ee (Scheme 1).[26]

As part of our continuing interests in asymmetric aerobic oxidation/coupling events by chiral vanadyl(V) catalysts that are stable to moisture and air, we began to evaluate their catalytic reduction profiles. Herein, we have disclosed, for the first time, oxidovanadium(V) complexes derived from *N*-salicyliden-L-*tert*-leucine towards practical asymmetric reduction of β-keto amides by HBPin to afford nearly enantiopure β-hydroxy amides (Scheme 1).

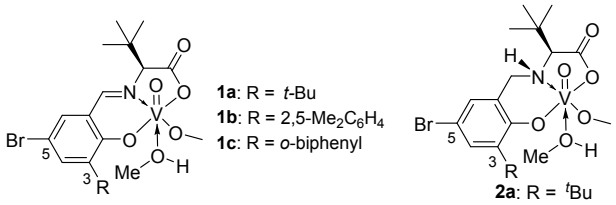
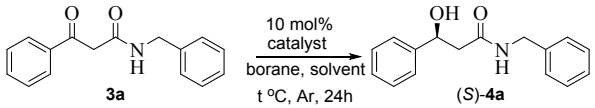


Figure 2. Vanadyl(V) complexes as catalysts

2. RESULTS AND DISCUSSION

Both HBCat and HBPin were selected as reducing agents (3 equiv) and the reactions were catalyzed by various vanadyl complexes (Figure 2). When catalyst **1a** was first tested with *N*-benzyl-benzoylacetamide (**3a**) in THF at -20 °C for 24h (Table 1), it was found that HBCat (45%, 6% ee) was much inferior to HBPin (70%, 53% ee) both in terms of yields and ees for product-(*S*)-**4a** (entries 1 and 2) presumably due to its background reaction. The imine-reduced catalyst 2a from 1a led to comparable or better yields (75 and 81%) and ees (55 and 75%) in CH_2Cl_2 and THF (entries 3 and 5), respectively. The reduction in strong coordination solvents like CH_3CN led to reduced yields by 20-26% and lower ee (55%, entry 4). On the other hand, the reduction in nonpolar toluene led to the β-hydroxy-amide but with very poor ee of 6% in 87% yield (entry 6) due to poor substrate solubility. The use of a mixed toluene/THF solvent (1/1) could maintain a similar yield (84%) but with diminished ee to 60% (entry 7). Notably, the ee of the product was further improved to 80% when the reduction was performed at -40 °C albeit with 14% drop in yield (entry 8). When the reduction was done at ambient temperature, the product yield reached 92% but with a dramatic drop in product ee to 24% (entry 9).

Table 1. Effects of catalysts and solvents on the asymmetric reduction of *N*-benzyl-benzoylacetamide[a]



entry	cat.	borane	solvent	t, °C	yield, %[b]	ee, %[c]
1	**1a**	HB(cat)	THF	-20	45	6
2	**1a**	HB(pin)	THF	-20	70	53
3	**2a**	HB(pin)	THF	-20	81	75
4	**2a**	HB(pin)	CH_3CN	-20	55	51
5	**2a**	HB(pin)	CH_2Cl_2	-20	75	55
6	**2a**	HB(Pin)	toluene	-20	87	6
7	**2a**	HB(pin)	THF/toluene (1:1)	-20	84	60
8	**2a**	HB(pin)	THF	-40	70	80
9	**2a**	HB(pin)	THF	26	92	24

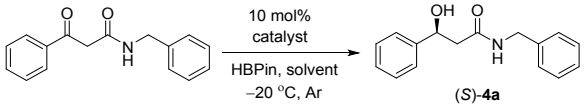
[a]Reaction conditions: catalyst (10 mol%), solvent (1 mL), substrate (0.1 mmol), HBCat/HBPin (3 equiv.). [b]Isolated yield.

[c]Enantiomeric excess (ee) determined by HPLC analysis on a Daicel CHIRALPAK® AD-H column.

To facilitate the O-B bond cleavage of original reduction product, we further tested the effect of alcohol additives (Table 2). The color of catalyst solution changed from dark brown to burgundy red upon addition of an alcohol. The product ees dropped significantly with decreasing steric of the additive presumably due to competing coordination with the substrate-3a to the vanadyl(V) center. Among the three alcohols (MeOH, *i*-PrOH, and *t*-BuOH) examined, *t*-butanol gave the best result (82% yield and 85% ee, entry 3). On the other hand, MeOH and *i*-PrOH furnished the product, (*S*)-**4a** with similar yields but with ees of 35% and 65%, respectively (entries 1-2). To prove the role of alcohol additive as a proton donor for O-B to O-H exchange, CD_3OD was used to replace MeOH. Deuterium incorporation both to the alcohol and one of the C2 proton was observed (see ESI). The D-migration indicated that there was a substantial keto-enol tautomerization of the β-keto amide reactant during the reaction.

With the optimized reaction conditions in hand, further catalyst variation was carried out. Out of the four catalysts examined, catalyst-**1b** bearing 2,5-dimethylphenyl group at C3 of the salicylidene template led to the best result (86% yield, 97% ee, entry 4). Conversely, catalyst 1a gave the worst result (70%, 53% ee in entry 2, Table 1). Increasing the steric bulk at C3 (i.e., o-biphenyl) as in catalyst-1c led to a decrease in yield (by 19%) and ee (by 13%), entry 5. The result indicated that π–π interaction between the benzoyl group in 3a with the C3 aryl group in catalysts 1b and 1c may play an important role. Furthermore, the o-biphenyl unit in **1c** that can provide an extra shielding underneath the salicylidene unit did not help in improving the enantiofacial control.

Table 2. Effects of catalysts, solvents, and alcohol additives on the asymmetric reduction of *N*-benzyl-benzoylacetamide[a]



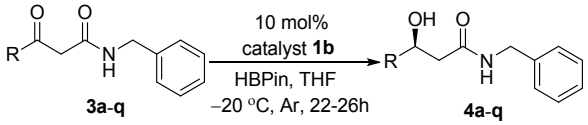
entry	Cat.	solvent	additive	yield, %[b]	ee, %[c]
1	**2a**	THF	MeOH	85	35
2	**2a**	THF	*i*-PrOH	80	65
3	**2a**	THF	*t*BuOH	82	85
4	**1b**	THF	*t*-BuOH	86(74[#])	97(94[#])
5	**1c**	THF	*t*-BuOH	67	84
6	**1b**	TBME	*t*-BuOH	75	90
7	**1b**	DME	*t*-BuOH	77	89
8	**1b**	acetone	*t*-BuOH	64	91
9	**1b**	CH_3CN	*t*-BuOH	20	80
10	**1b**	CH_2Cl_2	*t*-BuOH	58	83
11	**---**	THF	*t*-BuOH	~0	-
12	**1b**	THF[d]	*t*-BuOH	81	96

[a]Catalyst (10 mol%), #catalyst (5 mol%); solvent (1 mL), substrate (20 mg, 0.08 mmol), additive (1.0 equiv.), HBPin (3 equiv.). [b]Isolated yield. [c]Enantiomeric excess (ee) was determined *via* HPLC using Daicel CHIRALPAK AD-H column. [d]Yield was determined via ^{1}H NMR of the reaction mass at -40 °C.

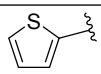
To gain further insight into the effect of other ether type solvents, TBME (*tert*-butylmethyl ether, entry 6) and DME (1,2-dimethoxyethane, entry 7) were examined. Poorer chemical yields and ees were observed (75- 77%, 89-90% ee). Since the coordination ability of THF sits right between TBME and DME, it seems there exists a delicate balance for the solvent to help breaking the dimeric form of HBPin but not to interfere with the substrate coordination to the vanadyl(V) center. Acetone, both a more polar solvent and a competitive ketone, led to (*S*)-**4a** with a similar ee of 91% but with reduced yield to 64% (entry 8). The reduction in CH_3CN led to further reduced yield to 20% and lower ee (80%, entry 9). Similar solvent effect was also found in β-borylation of α,β-enaldimines by Pujol.[27] The use of nonpolar CH_2Cl_2 led to moderate yield of 58% and reduced ee to 83% (entry 10). Lowering catalyst loading from 10% to 5% in THF resulted in lowering of both the yield and the ee to 74% and 94%, respectively (# in entry 4). Notably, no reaction took place in absence of any catalyst (entry 11), indicating a negligible background reduction. Further lowering of the reaction temperature to -40 °C in THF did not help in improving both yield and ee of the product (96% ee, entry 12).

This optimal protocol with catalyst **1b** was extended to β-keto amides bearing various 3-aryl, -alkynyl, and -alkyl groups. Highly enantio-enriched (*S*)-β-hydroxy amides **4a-q** were furnished except the 3-methyl case (R = Me) due to size and priority change based on CIP (Cahn-Ingold-Prelog) rule (Table 3). For substituted phenyl family, substrates bearing electron donating *p*-methyl- and *p*-methoxy-phenyl groups (entries 2 - 3) reacted slightly slower than those with electron-withdrawing *p*-chloro- and *p*-bromo-phenyl ones (entries 4-5). With a fixed reaction time of 24 h, the former two cases led to the corresponding products in 82-85% yields with 98-99% ees as compared to those of the latter two cases with 89-92% yields with 96-99% ees. For electron withdrawing groups but with coordinating ability like NO_2, both the reduction yield (79%) and ee (79%) dropped significantly (entry 6). The substantial amount of enol form (38% at rt) in **3f** may be responsible for the reduced yield and ee (see ESI†).[28]

Table 3. Substrate scope for asymmetric reduction of β-keto amides by catalyst **1b**[a]



entry	R	yield,[c] %	ee,[d] %
1	C_6H_5	86 (**4a**)	97
2	*p*-MeC_6H_4	85 (**4b**)	98
3	*p*-$MeOC_6H_4$	82 (**4c**)	99
4	*p*-ClC_6H_4	92/88[e] (**4d**)	96/98 [e]
5	*p*-BrC_6H_4	89 (**4e**)	99
6	*p*-$NO_2C_6H_4$	79 (**4f**)	79
7	*m*-$MeOC_6H_4$	43 (**4g**)	88
8	2-Np	90 (**4h**)	98

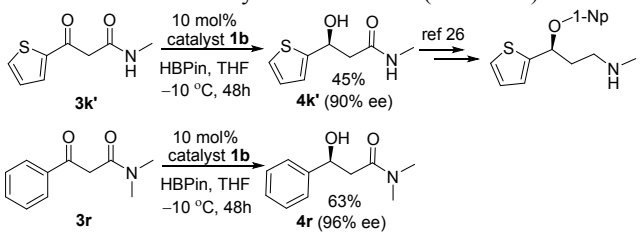
9[b]	1-Np	65/83[f] (**4i**)	85/90[f]
10		60 (**4j**)	90
11		65/71 (**4k**)	95/93
12	*o*-$MeOC_6H_4$	18 (**4l**)	88
13	PhC≡C	56 (**4m**)	11
14	CH_3	75 (**4n**)	14
15	$PhCH_2CH_2$	90 (**4o**)	98
16	*i*-Pr	84 (**4p**)	56
17	*t*-Bu	82 (**4q**)	80

[a]Substrate (0.08 mmol), dry THF (1.0 mL), *t*-BuOH (1.0 equiv), catalyst (10 mol%), HBPin (3.0 equiv). [c]Isolated yield. [b]2.5 equiv of *t*-BuOH was used. [d]Enantiomeric excess (ee) was determined by HPLC on Diacel CHIRALPAK AD-H or AS-H column. Configurations were found to be *S* or determined by analogy.[12] [e]2.00 mmol scale reaction. [f]The second data corresponds to reaction at -5 to 0 °C for 48h.

For aryl substrates bearing *m*- or *o*-methoxy-phenyl groups, the reduction yields dropped to 43 and 18%, respectively, presumably due to increasing steric interactions with the 2,5-dimethylphenyl unit in catalyst **1b**. Nevertheless, the asymmetric inductions were maintained at 88% ee in both cases (entries 7 and 12). For naphthyl and heteroaryl series (entries 8-11), the 1-naphthyl case showed much poorer yield (23%) and ee (85%) than those (90% and 98% ee) in the 2-naphthyl system presumably due to increasing steric effects during the coordination to the vanadyl center in the former case. An additional 24 h of the reaction time at 0 °C led to an improved yield to 83% with further increased ee to 90%. Evidently, a facile stereo-electronic between the substrate and the catalyst was paramount for its bidentate coordination to the vanadyl center for smooth and secured enantiofacial preference in reduction. The reduction proceeded slower in the heteroaryl systems (entries 10-11) than the aromatic substrate (entry 1). By increasing reaction temperature to −10 °C, the product yield in **4k** was 65% and the ee can be maintained at 95%. (entry 11). Further bringing the reaction to −5 °C, the optimal reduction yield and ee of the product (*S*)-**4k** were 71% and 93% ee. The analogous furan case (entry 10) can be performed at −20 °C in 24h, leading to (*S*)-**4j** in 60% and 90% ee.

The propargyl derivative (entry 13) gave very poor results (56% and ee ~11%) due to negligible steric interaction between the catalyst-**1b** and the substrate-**3m**. The cylindrical π-cloud in the C≡C bond may interfere with ketone coordination to the vanadyl center, thus hampering the reduction. For 3-alkyl family, the asymmetric inductions were much inferior but can be improved with increasing steric from methyl (14% ee), *i*-propyl (56% ee) to *t*-butyl (80% ee). The chemical yields fell in the range of 75-84%. Nevertheless, high chemical yield (90%) and ee (98%) can be secured in the 2-phenethyl case (entry 15). This result indicated that the zig-zag motion of the ethylene linker may still orient the phenyl ring to interact with the 2,5-dimethylphenyl unit.

We have successfully extended this protocol for the synthesis of Duloxetine precursor. The requisite starting material **3k'** could be readily synthesized from the corresponding methyl ester. Asymmetric reduction of **3k'** under optimal reaction conditions led to (*S*)-*N*-methyl-3-hydroxy-3-(thiophin-2-yl)propanamide[29] **4k'** in moderate, 45% yield and slightly diminish enantioselectivity, 90% ee due to smaller *N*-methyl as compared to *N*-benzyl (Scheme 2).[31] Its structure was confirmed by X-ray crystallographic analysis after recrystallization (Figure S2). It depicts that the single stereocenter has *S*-conformation and through retrosynthetic strategy that enantiopure (*S*)-**4k'** proved to be an excellent building block for the synthesis of (*S*)-Duloxetine. Only the (*S*)-enantiomer of Duloxetine is pharmaceutically active for the treatment of anxiety, diabetes related pain, chronic musculoskeletal etc.[30] Since it has been proposed that *N*,*N*-disubstitution can be used to modify amide-*O*-metal coordination,[31a] *N*,*N*-dimethyl-3-oxo-3-phenylpropanamide (**3r**) was prepared and tested for a similar asymmetric reduction, the corresponding β-hydroxyamide (*S*)-**4r** was isolated in 63% yield and 96% ee (Scheme 2).



Scheme 2. Representative *N*-methyl and *N*,*N*-dimethyl analogs

3. Proposed Origin of Enantiofacial Control

Nonlinear effect study was performed with 25%, 50% and 75% ee of the catalyst-**1b**. The results show a linear correlation (Table S1). Therefore, the catalytic reduction system works in a monomeric species. Notably, the mixing of either V(O)(*i*-$OPr)_3$ (δ -626 ppm) or catalyst **1b** (δ -559.4 ppm) with 3 equiv of HBPin only led to broadening of their signals with slight upfield shifts by 2 ppm in their ^{51}V NMR spectra. To explain the origin of enantiocontrol in the asymmetric reduction, we proposed two favourable reductant-directed, coordination modes (Figure 3) based on our X-ray crystal structure of a vanadyl(V) complex/*N*-benzyl-mandelamide adduct.[31b] The amide carbonyl group was coordinated anti to the V=O unit in such a way that N-benzyl moiety was positioned underneath the salicylidene template as in catalyst-**1b** (Figure 3a). As a result, the β-keto unit would rotate clockwise and away from the 2,5-dimethylphenyl group at C3 and the vanadyl-bound methoxide in **1b**. The bulky HBPin would deliver the hydride from *Re*-face of the ketone moiety to give the resulting alcohol in *S*-configuration (mode-I).

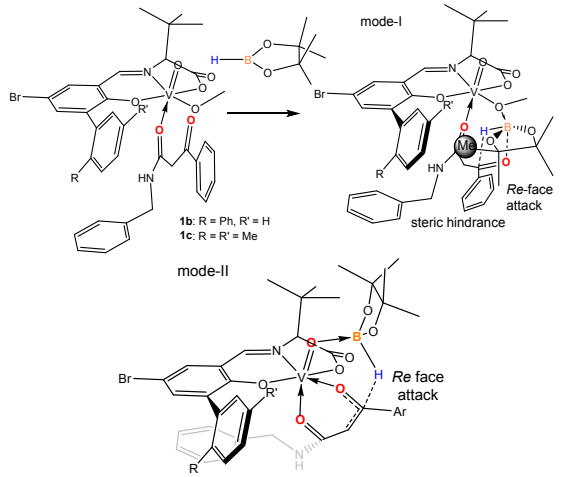


Figure 3. Chem 3D presentations for the proposed origins of enantiofacial controls in the asymmetric reduction catalyzed by **1b**: (a) mode-I; (b) mode-II

Alternatively, the HBPin may first interact with the vanadyl methoxide **1b** to form pinacol-bound, vanadyl-activated hydride, in which would bring the bidendate, β-keto unit in the substrate in close proximity. Under such circumstance, there may exist a sandwich type, π–π interaction among the salicylidene template in **1b** and *N*-benzylunit in the substrate. The vanadyl-activated hydride would attack to the *Re* face of the benzoyl moiety thru a 6-membered ring, cyclic transition state assembly (mode-II, Figure 3b).

4. Conclusion

We have developed an efficient method for enantioselective reduction of *N*-benzyl-β-ketoamides catalyzed by air stable chiral oxidovanadium(V) complexes in THF at -20 °C. With a judicious choice of HBPin as a reductant and *t*-BuOH as a turn-over additive. The resultant reduced products were furnished in good to excellent yields and with enantioselectivities of 85-99% ee except in β-*p*-nitrophenyl, -propargyl, and -alkyl ketoamides. Nevertheless, the 2-phenethyl and *t*-butyl cases could make up to a satisfactory level of asymmetric inductions in 98% and 80% ee. To best of our knowledge, this new protocol was the best non-rare earth, high oxidation state, metal complex catalyzed asymmetric reduction of β-keto amides. The optimal catalytic protocol was successfully applied to Duloxetine precursor synthesis in 90% ee. Two preferential modes of BPin-directed substrate coordination were proposed to explain the origin of high level enantiocontrols. Further studies on the applications of this catalyst class for asymmetric reductions of different functional substrate family are currently underway and will be reported in due course.

Experimental Section

1. Materials and Methods:

^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz ^{1}H (100 MHz ^{13}C) spectrometers in deutero chloroform with chloroform or deutero methanol with methanol as an internal reference unless otherwise stated. Chemical shifts are reported in ppm (δ). Coupling constants, *J*, are reported in Hz. The abbreviations s, d, t, pent, quint, sext, dd, ddd, dt, and m stand for the resonance multiplicities singlet, doublet, triplet, pentet, quintet, sextet, doublet of doublets, doublet of doublet of doublets, doublet of triplets, and multiplet, respectively. Infrared spectra were recorded on a FTIR spectrometer. Peaks are reported in units of cm^{-1} with the following relative intensities: br (broad), s (strong 67–100%), m (medium 33–67 %), or w (weak 0 – 33%). Mass spectra were recorded with an ionization voltage of 70 or 20 eV unless otherwise stated. Elemental analyses were obtained by the Department of Chemistry, National Tsing Hua University, Taiwan or Department of Photonics, National Chiao Tung University, Taiwan. Fast atom bombardment (FAB) and electrospray ionization (ESI) mass spectra were recorded with data reported in the form m/e (intensity relative to base peak). Analytical TLC was performed on silica gel plates. Visualization was accomplished with UV light (254 nm) or with KMnO4 staining agents. Column (flash) chromatography was performed using 32–63 μm silica gel. Analytical high pressure liquid chromatography (HPLC) was performed with a built-in photometric detector (λ = 220 nm or 254 nm) using a Chiralpak AS-H, AD-H (0.46 cm × 25cm). Solvents for HPLC analyses were of spectroscopic grade and filtered before use. All enantiomeric excess determinations for optically enriched products were correlated with the corresponding racemic samples by HPLC analyses on chiral columns. Solvents for extraction and chromatography were reagent grade. Optical rotations are reported as follows: $[\alpha]_D^T$ (c = g/100mL, solvent). Toluene, Tetrahydrofuran (THF) and 1,2 Dimethoxyethane (DME) were dried over sodium benzophenone-ketyl intermediate under N_2 atmosphere and distilled before use. Dichloromethane (DCM) were dried over CaH_2 and distilled before use. *i*-Pr_2NH was distilled from calcium hydride prior to use. Chlorobenzene was distilled from anhydrous K_2CO_3 prior to use. *tert*-Butanol (*t*-BuOH) was dried over flame dried molecular sieves and distilled before use. Acetone was dried over dry $CaSO_4$ and distilled before use. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (Pinacolborane), Catecholborane and *N*-benzyl-3-oxobutanamide (**3n**) were brought from Acros Organics and are used as such without any further purification. All reaction products were isolated as chromatographically pure materials. All the chemicals were brought from Sigma Aldrich or Acros Organics and are used as such without any purification. Racemic β-hydroxy amide were synthesized by reduction of the corresponding β-keto amides using half equivalent sodium borohydride ($NaBH_4$) at 0 °C. Subsequently, the product was purified over silica gel chromatography using hexane-ethyl acetate as eluents to get the racemic β-hydroxy amide. Catalysts were synthesized according to our previously reported procedure.[31,32]

2. General synthetic procedures for the preparation of substrates:

2.1 Method-a: Substrates were synthesized by modifying previously reported synthetic procedure.[33,34] To a flame dried two-necked round bottom flask was charged with NaH (28 mmol) under argon. The sodium hydride (60% in mineral oil) was washed with dry toluene (2 × 20 mL). Again the flask was charged with toluene (70 mL) and dimethyl carbonate (20 mmol) and the solution was heated to reflux. The appropriate ketone (10 mmol) dissolved in dry toluene (10 mL) was added dropwise to the reaction mixture (caution: hydrogen gas evolution was vigorous). The reaction was allowed to stir for

additional four hours after the evolution of hydrogen gas ceased. The reaction was cooled to room temperature; water (20 mL) and glacial acetic acid (3 mL) were added successively. Ice cold water was added until the solid was dissolved completely. The toluene layer was separated, and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed successively with water (2 × 50 mL) and brine (3 × 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc in hexane) or crystallization or directly used in the next step.

To a solution of β-keto ester (8.6 mmol) in degassed ethanol (30 mL) was rapidly added solid DMAP (317 mg, 2.6 mmol) and the solution was heated to refluxed under argon atmosphere for 1 h. Distilled benzyl amine (1.1 gm, 10.3 mmol) dissolved in ethanol (5 mL) was injected drop wise *via* syringe. The reaction mixture was refluxed for 24 h and the solvent was removed under reduced pressure. The solid residue was washed with water (3 × 50 mL) and brine (3 × 30 mL) successively. Finally, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (eluent: ethyl acetate in hexane) to afford the β-keto amide in 70–92% yield.

2.2 Method-b: Substrates were synthesized by modifying the synthetic procedure reported previously.[35] To a flame dried two-necked round bottom flask was charged with NaH (28 mmol, 60% dispersion in mineral oil) under argon. The NaH was washed with dry DME (2 × 20 mL). Again the flask was charged with DME (70 mL) and methyl acetate (20 mmol) (caution: hydrogen gas evolution was vigorous). The mixture was heated to reflux. The appropriate methyl ester (10 mmol) dissolved in dry DME (10 mL) was added drop wise to the reaction mixture. The reaction was allowed to stir additional four hours after the evolution of hydrogen gas ceased. When the reaction was cooled to room temperature, water (20 mL) and glacial acetic acid (3 mL) were added successively. Ice cold water was added until the solid was dissolved completely. The DME layer was separated, and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic layer was washed successively with water (2 × 50 mL) and brine (3 × 50 mL), then dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified on silica gel column chromatography (eluent: ethyl acetate in hexane) to afford the β-keto ester with 80–90% yield.

To a solution of β-keto ester (8.6 mmol) in degassed ethanol (30 mL) was rapidly added solid DMAP (317 mg, 2.6 mmol) and the solution was heated to refluxed under argon atmosphere for 1 h. Freshly distilled Benzyl amine (1.1 gm, 10.3 mmol) dissolved in ethanol (5 mL) was injected drop wise inside the flask via syringe. The reaction mixture was refluxed for 24 h and the solvent was removed under reduced pressure. The solid residue was extracted in ethyl acetate (50 mL) and the organic layer was washed with water (3 × 50 mL) and brine (3 × 30 mL) successively and then dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified on silica gel column chromatography (eluent: ethyl acetate in hexane) to afford the β-keto amide with 70–92% yield.

2.3 Method-c: Propargyl derivative was synthesized via the modified procedure reported previously.[36] In a flame dried two necked round flask was charged with dry THF (80 mL) and dry *i*-Pr_2NH (diisoproylamine, 1.7 g, 17.02 mmol) under argon atmosphere. Temperature of the solution was lowered to –20 °C and *n*-BuLi (10.64 mL of 1.6 M solution in hexane, 17.02 mmol) was injected via syringe slowly. After stirring for 10 min, *N*-benzylacetamide dissolved in THF (10 mL) was added dropwise via syringe. The reaction temperature was slowly raised to room temperature and was allowed to stirred for 30 min at ambient temperature. The mixture was cooled to –78 °C and ethyl phenylpropiolate (1.3 gm, 7.4 mmol) in THF (5 mL) was added dropwise. The resulting solution was slowly raised to 0 °C and the solution was stirred for 2 h at this temperature, then quenched with cooled saturated NH_4Cl (30 mL) solution. Organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layer was washed successively with 1 N HCl (40 mL), water (2 × 30 mL), brine (2 × 30 mL), then dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc = 75/25) to afford 0.4 g (20%) of the desire β-keto amide. (Precaution: *N*-benzyl-3-hydroxy-5-phenylpent-4-ynamide is thermally highly unstable and is needed to be stored in refrigerator).

2.4 Synthesis of *N*-methyl-3-oxo-3-(thiophen-2-yl)propanamide: In a flame dried two necked round flask, dry *i*-Pr_2NH (0.9 gm, 8.8 mmol) was dissolved into dry THF (30 mL) under argon atmosphere. Temperature of the solution was lowered to –20 °C and *n*-Butyllithium (5.5 mL of 1.6 M solution in hexane, 8.8 mmol) was injected into the flask via syringe slowly. After stirring for 10 min at this temperature, *N*-methylacetamide[37] (0.3 gm, 4.2 mmol) dissolved in THF (5 mL) was added dropwise into the reaction mixture *via* syringe. The reaction temperature was slowly raised to room temperature and was allowed to stir for 30 min at ambient temperature. The mixture was cooled to –78 °C and methyl thiophene-2-carboxylate (0.5 gm, 3.5 mmol) in THF (5 mL) was added dropwise. The resulting solution was slowly raised to room temperature and was stirred for 3 h at room temperature, then it was quenched with cold saturated NH_4Cl (20 mL) solution. Organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed successively with 1 N HCl (10 mL), water (2 × 50 mL), brine (2 × 50 mL), then dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc = 10/90) to afford 0.3 g (46%) of the title product as white solid.

2.5 Synthesis of *N*-benzyl-3-oxo-5-phenylpentanamide: **Step I**:[38] In a flame dried two necked round bottom flask (250 mL), dry *i*-Pr_2NH (10.9 g, 0.1 mol) was taken with dry THF (50 mL) under argon atmosphere at –20 °C and n-BuLi (63 mL of 1.6 M solution in hexane, 0.1 mol) was added slowly to the reaction mixture at –20 °C. Methyl acetoacetate (4.6 g, 40 mmol) was added into the reaction mixture slowly at this temperature. Temperature of the reaction mixture was slowly raised to 0 °C and it was stirred for additional 1 h at this temperature. Temperature of the reaction mixture was again lowered to -78 °C and the benzyl bromide (7.5 g, 44 mmol) was added to the

reaction mass slowly. Subsequently the reaction mixture was brought to room temperature and was stirred for 14 h at room temperature. After that the reaction was quenched by saturated NH_4Cl solution (20 mL) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 50 mL) and the combined organic layers were washed with brine (2 × 50 mL) and finally dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1) to afford 6.7 g (82%) of methyl 3-oxo-5-phenylpentanoate as light yellow oil.

Step II:[39] A flame dried two necked round bottom flask (50 mL) was charged with dry chlorobenzene (50 mL) along with methyl 3-oxo-5-phenylpentanoate (2 g, 9.7 mmol). Catalytic amount of $Ti(O\textit{i}\text{-}Pr)_4$ (0.3 g, 0.97 mmol) was added to the reaction mixture and was stirred for 30 min. Benzyl amine (1.1 g, 10.7 mmol) was added to the reaction mixture slowly. The reaction mixture was refluxed at 130 °C for 24 h. After that solvent was evaporated and the solid residue was extracted with ethyl acetate (50 mL). Organic layer was washed successively with water (2 × 50 mL) and brine (2 × 50 mL) and finally dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the residue was purified by silica gel chromatography (hexane/ethyl acetate = 2/3) as eluents to afford 0.9 g (33%) of *N*-benzyl-3-oxo-5-phenylpentanamide as white solid.

3. General reaction procedure for the asymmetric reduction of β-keto amides: In an oven dried Schlenk tube, the β-keto amide (0.08 mmol) was taken along with catalyst (0.008 mmol) under argon atmosphere. The respective dry solvent (1 mL) was injected into the Schlenk tube via syringe. After stirring the reaction mixture for 15 minutes at ambient temperature, the schlenk tube was put into the cooling bath. The reducing agent (0.24 mmol) diluted by the dry reaction solvent was added to the reaction mixture via flame dried syringe slowly over 1 h (caution: HB(pin) and HB(cat) are highly moisture sensitive). After the reaction was over (checked by TLC), double distilled water was injected into the Schlenk tube via syringe to quench the reducing agent. The reaction mixture was stirred for 30 min under room temperature followed by removable of the organic solvent under reduced pressure. The residue was extracted with ethyl acetate (2 mL) and the organic layer was washed with water and drying over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and then the product β-hydroxy amide was isolated by silica gel column chromatography (eluent: ethyl acetate in hexane).

4. Reaction procedure for the synthesis of the (*S*)-duloxetine precursor: **(*S*)-3-hydroxy-*N*-methyl-3-(thiophen-2-yl)propanamide:** In an oven dried Schlenk tube, *N*-methyl-3-oxo-3-(thiophen-2-yl)propanamide (0.4 mmol) was taken along with catalyst (0.04 mmol) under argon atmosphere. Dry THF (4 mL) was injected into the Schlenk tube via syringe. After stirring the reaction mixture for 15 minutes at ambient temperature, the schlenk tube was put into the cooling bath. The reducing agent (1.2 mmol) diluted by the dry reaction solvent (400 μL) was added to the reaction mixture via flame dried syringe slowly over 1 h. After 72 h, double distilled water (100 μL) was injected into the Schlenk tube via syringe to quench the reducing agent. The reaction mixture was stirred for 30 min under room temperature followed by removable of the organic solvent under reduced pressure. The residue was extracted with ethyl acetate (10 mL) and the organic layer was washed with water and drying over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and then the product (*S*)-3-hydroxy-*N*-methyl-3-(thiophen-2-yl)propanamide was isolated by silica gel column chromatography (eluent: 80% ethyl acetate in hexane).

5. General procedure for deuterium exchange reaction: In an oven dried Schlenk tube, *N*-benzyl-3-oxo-3-phenyl propanamide (20 mg, 0.08 mmol) was taken along with the catalyst **1b** (4 mg, 0.008 mmol) under argon atmosphere. Dry THF (1 mL) and CD_3OD (3 equiv.) were injected into the tube *via* syringe and the reaction mass was stirred for 10 minutes at room temperature before cooling the Schlenk tube at −10 °C. H-B(pin) (3 equiv., in 200 μL dry THF) was injected slowly into the reaction tube via syringe. The reaction mixture was allowed to come room temperature and was stirred for additional 14 hours at ambient temperature. After that the reaction solvent was evaporated under reduced pressure and the *N*-benzyl-3-hydroxy-3-phenyl propanamide was isolated from the residue by flash chromatography with silica gel column chromatography (hexane/ethyl acetate = 2/3) to afford 18 mg (91%) of the desire deuterated β-hydroxy amide as white solid.

6. Synthesis of the catalysts: Catalyst were synthesized according to the procedure previously reported.[31,32]

Data for catalyst 1a: ^{1}H NMR (CD_3OD, 400 MHz) δ 8.53 (bs, 1H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.62 (d, *J* = 2.4 Hz, 1H), 4.14 (s, 1H), 3.34 (s, OCH_3), 1.44 (s, 9H), 1.19 (s, 9H); ^{51}V NMR (CD_3OD, 105 MHz) δ −567.7; ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 167.7, 142.3, 137.0, 136.3, 135.1, 134.7, 123.8, 111.9, 84.7, 49.8, 38.3, 37.2, 36.3, 29.9, 28.1, 27.4; IR (KBr) 2965 (s), 2913 (m), 2869 (m), 1663 (s), 1615 (s, C=N), 1578 (m), 1548 (m, COO), 1480 (w), 1429 (m), 1368 (m), 1320 (m), 1297 (s), 1181 (m), 1055 (w), 1031 (w), 993 (m, V=O); $[\alpha]_D^{34}$+306.53 (*c* 0.1, CH_3OH); TLC R_f 0.20 (CH_3OH/CH_2Cl_2, 1/9); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{26}BrNO_5V$ 466.0436; Found 466.0434.

Data for catalyst 2a: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.39 (d, *J* = 2.0 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 3.93 (d, *J* = 11.6 Hz, 1H), 3.73 (d, *J* = 11.2 Hz, 1H), 1.47 (s, 9H), 1.20 (s, 9H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 164.8, 140.4, 130.9, 130.5, 129.1, 128.4, 113.3, 76.0, 53.6, 37.2, 36.2, 30.6, 30.2, 27.2; ^{51}V NMR (CD_3OD, 105 MHz) δ −514.7, −528.3; IR (KBr) 3449 (br, w, NH), 2958 (m), 2872 (m), 1654 (s), 1463 (m), 1434 (s), 1409 (m), 1340 (m), 1267 (s), 1247 (s), 1053 (s), 970 (m, V=O); $[\alpha]_D^{34}$+562.00 (*c* 0.1, CH_3OH); TLC R_f 0.10 (^{i}PrOH/Hexanes, 1/10); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{28}BrNO_5V$ 468.0592; Found 468.0589.

Data for catalyst 1b: ^{1}H NMR (CD_3OD, 400 MHz) δ 8.61 (s, 1H), 7.80 (s, 1H), 7.52 (s, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 4.17 (s, 1H), 3.34 (s, OCH_3), 2.31 (s, 3H), 2.22 (s, 3H), 1.20 (s, 9H); ^{51}V NMR (CD_3OD, 105 MHz) δ −559.4; ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 167.4, 140.5, 137.6, 136.2, 136.0, 135.0, 131.8, 130.7, 129.7, 123.4, 111.5, 84.7, 38.3, 28.1, 21.0, 19.8; IR (KBr) 3446 (br, w, NH), 2961 (m), 1687 (m), 1616 (s), 1553 (s), 1432 (s), 1314 (s), 1002 (m, V=O); $[\alpha]_D^{25}$+236.43 (*c* 0.1, CH_3OH); TLC R_f 0.28

(*i*PrOH/Hexanes, 1/5); HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{22}H_{26}BrNO_5V$ 514.0429; Found 514.0434.

Data for catalyst 1c: ^{1}H NMR (CD_3OD, 400 MHz) δ 8.48 (s, 1H), 7.64 (d, *J* = 2.8 Hz, 1H), 7.45–7.40 (m, 4H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.22–7.20 (m, 2H), 7.17–7.13 (m, 3H), 4.11 (s, 1H), 3.34 (s, OCH_3), 1.14 (s, 9H); ^{51}V NMR (CD_3OD, 105 MHz) δ −557.9; ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 179.3, 167.1, 160.7, 143.1, 142.5, 141.3, 136.3, 135.9, 134.1, 132.1, 130.9, 130.4, 130.2, 129.2, 128.8, 127.9, 127.6, 123.4, 111.1, 84.6, 38.2, 28.0; IR (KBr) 3424 (br, w, NH), 2962 (m), 1700 (s), 1687 (s), 1616 (s), 1555 (s), 1428 (s), 1411 (s), 1311 (m), 1267 (s), 1215 (s), 1141 (s), 1002 (m, V=O); $[\alpha]_D^{25}$+381.02 (*c* 0.1, CH_3OH); TLC R_f 0.28 (*i*PrOH/Hexanes, 1/5); HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{26}H_{26}BrNO_5V$ 562.0429; Found 562.0438.

7. Characterization data of the catalyst precursors[31,32]

5-Bromo-3-(*tert*-butyl)-2-hydroxybenzaldehyde: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.72 (s, 1H), 9.81 (s, 1H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 195.9, 160.1, 141.0, 136.9, 133.5, 121.5, 111.0, 35.0, 28.9; TLC R_f 0.50 (EtOAc/Hexanes, 1/10); HRMS (ESI) m/z: [M]$^+$ Calcd for $C_{11}H_{13}BrO_2$ 256.0099; Found 256.0101.

(*S*)-2-((5-Bromo-3-(*tert*-butyl)-2-hydroxybenzyl)-amino)-3,3-dimethylbutanoic acid: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.24 (d, *J* = 2.0 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 4.07 (d, *J* = 13.6 Hz, 1H), 3.65 (d, *J* = 13.6 Hz, 1H), 2.90 (s, 1H), 1.36 (s, 9H), 1.00 (s, 9H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 176.6, 157.0, 140.6, 130.9, 130.1, 126.2, 111.9, 71.7, 51.6, 35.7, 34.0, 29.8, 27.6; $[\alpha]_D^{28}$−31.33 (*c* 0.1, CH_2Cl_2); TLC R_f 0.30 (CH_3OH/CH_2Cl_2, 1/10); HRMS (ESI) m/z: [M]$^+$ Calcd for $C_{17}H_{26}BrNO_3$ 371.1096; Found 371.1097.

2-Hydroxy-2',5'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde:[31,32] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.31 (s, 1H), 9.97 (s, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 2.36 (s, 3H), 2.16 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 196.7, 158.8, 138.2, 136.0, 135.1, 133.6, 133.0, 131.1, 130.5, 129.8, 128.8, 120.5, 119.6, 20.9, 19.4; TLC R_f 0.33 (Ether/Hexanes, 1/15); HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{15}H_{15}O_2$ 227.1072; Found 227.1067.

5-Bromo-2-hydroxy-2',5'-dimethyl-[1,1'-biphenyl]-3-carbaldehyde:[31,32] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.2 (s, 1H), 9.90 (s, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 6.99 (s, 1H), 2.35 (s, 3H), 2.15 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 195.6, 157.9, 140.5, 135.3, 134.8, 134.6, 133.7, 130.3, 129.9, 129.2, 121.5, 111.1, 20.9, 19.3; TLC R_f 0.40 (Ether/Hexanes, 1/15); HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{15}H_{14}BrO_2$ 305.0177; Found 305.0172.

2-Hydroxy-[1,1':2',1''-terphenyl]-3-carbaldehyde:[31,32] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.16 (s, 1H), 9.86 (s, 1H), 7.48–7.45 (m, 3H), 7.44–7.43 (m, 2H), 7.24 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.18–7.15 (m, 5H), 6.88 (t, *J* = 7.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 196.6, 158.9, 141.7, 141.3, 139.1, 134.7, 132.9, 130.9, 130.6, 130.2, 129.2, 128.1, 127.7, 127.0, 126.5, 120.4,119.2; TLC R_f 0.10 (CH_2Cl_2/Hexanes, 1/5); HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{19}H_{15}O_2$ 275.1072; Found 275.1067.

5-Bromo-2-hydroxy-[1,1':2',1''-terphenyl]-3-carbaldehyde:[31,32] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.01 (s, 1H), 9.78 (s, 1H), 7.56 (d, *J* = 2.8 Hz, 1H), 7.47–7.40 (m, 5H), 7.22–7.19 (m, 3H), 7.17–7.14 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 195.3, 157.8, 141.7, 141.1, 140.9, 134.6, 133.4, 133.1, 130.6, 130.1, 129.0, 128.5, 127.8, 127.1, 126.7, 121.3, 110.7; TLC R_f 0.20 (CH_2Cl_2/Hexanes, 1/5); HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{19}H_{14}BrO_2$ 353.017; Found 353.0172.

8. Characterization data of the substrates and products:

***N*-Benzyl-3-oxo-3-phenylpropanamide (3a)**:[40] The product **3a** was obtained as white solid with 90% yield (1.96 g, 7.74 mmol) ^{1}H NMR ($CDCl_3$, 400 MHz) δ keto form (major) 8.00 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.35–7.27 (m, 5H), 4.51 (d, *J* = 6.0 Hz, 2H), 4.01 (s, 2H); enol form (minor) 5.50 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ keto form (major) 195.9, 165.7, 137.8, 136.0, 134.0, 128.8, 128.6, 128.5, 127.6, 127.4, 45.2, 43.5; enol form (minor) 128.3, 125.6; TLC R_f 0.21 (EtOAc/Hexanes, 1/2); HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{16}H_{15}NO_2Na$ 276.1000; Found 276.0999.

(*S*)-*N*-Benzyl-3-hydroxy-3-phenylpropanamide (4a):[41a] The product **4a** was obtained as white solid with 86% yield (17 mg, 0.0688 mmol).^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.27 (m, 8H), 7.21–7.19 (m, 2H), 6.14 (bs, 1H, NH), 5.14–5.13 (m, 1H), 4.43 (dd, *J* = 3.2, 5.6 Hz, 2H), 4.08 (s, 1H), 2.60 (m, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 173.2, 145.2, 139.7, 129.4, 128.5, 128.4, 128.0, 127.0, 72.1, 46.7, 43.9; $[\alpha]_D^{25}$–49.5 (*c* 0.43, $CHCl_3$); TLC R_f 0.20 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{16}H_{18}NO_2$ 256.1338; Found 256.1342. HPLC analysis: t_R 12.07 min (*S*-isomer), 14.99 min (*R*-isomer) (Chiralpak AD-H, hexanes/*i*PrOH, 90/10, 1.0 mL/min, λ = 254 nm) for 97% ee.

***N*-Benzyl-3-oxo-3-(*p*-tolyl)propanamide (3b)**:[40] The product **3b** was obtained as white solid with 81% yield (1.86 g, 6.97 mmol).^{1}H NMR ($CDCl_3$, 400 MHz) δ keto form (major) 7.89 (d, *J* = 8.4 Hz, 2H), 7.52 (bs, 1H, NH), 7.34–7.26 (m, 7H), 4.50 (d, *J* = 5.6 Hz, 2H), 3.97 (s, 2H), 2.42 (s, 3H); enol form (minor) 5.47 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 195.6, 165.8, 145.1, 137.9, 133.7, 129.5, 128.6, 127.6, 127.4, 45.0, 43.6, 21.7; TLC R_f 0.21 (EtOAc/Hexanes, 1/2); HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{17}H_{17}NO_2Na$ 290.1157; Found 290.1152.

(*S*)-*N*-benzyl-3-hydroxy-3-(*p*-tolyl)propanamide (4b): The product **4b** was obtained as white solid with 85% yield (18 mg, 0.068 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.25–7.17 (m, 5H), 7.13–7.09 (m, 4H), 5.04 (dd, *J* = 8.4, 5.8 Hz, 1H), 4.31 (dd, *J* = 48.8, 15.2 Hz, 2H), 2.62 (ddd, *J* = 22.0, 14.0, 8.0 Hz, 2H), 2.31 (s, 3H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 173.3, 142.1, 139.7, 138.3, 130.0, 129.3, 128.4, 127.0, 128.0, 72.0, 46.6, 43.9, 21.1; $[\alpha]_D^{26}$–42.0 (*c* 0.05, $CHCl_3$); TLC R_f 0.21 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{17}H_{20}NO_2$ 270.1494; Found 270.1492. HPLC analysis: t_R 12.00 min (*S*-isomer), 14.40 min (*R*-isomer) (Chiralpak AD-H, hexanes/*i*PrOH, 90/10, 1.0 mL/min, λ = 254 nm) for 98% *ee*.

***N*-Benzyl-3-(4-methoxyphenyl)-3-oxopropanamide (3c)**: The product **3c** was obtained as crystalline white solid with 73% yield (1.78 g, 6.28 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ keto form (major) 7.97 (d, *J* = 8.8 Hz, 2H), 7.55 (s, 1H, NH), 7.34–7.26 (m, 5H), 6.95 (d, *J* = 9.2 Hz, 2H), 4.49 (d, *J* = 6.0 Hz, 2H), 3.94 (s, 2H), 3.88 (s, 1H); enol form (minor) 5.43 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 194.3, 165.9, 164.3, 137.9,

131.0, 129.1, 128.6, 127.6, 114.0, 55.5, 44.9, 43.5; TLC R_f 0.21 (EtOAc/Hexanes, 1/2); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{17}NO_3Na$ 306.1106; Found 306.1102.

(*S*)-*N*-Benzyl-3-hydroxy-3-(4-methoxyphenyl)propanamide (4c):[41a] The product **4c** was obtained as white solid with 82% yield (18 mg, 0.065 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31–7.24 (m, 5H), 7.23 (d, J = 2.0 Hz, 2H), 7.17–7.15 (m, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.48 (bs, 1H, NH), 5.00 (dd, J = 8.8, 3.2 Hz, 1H), 4.36 (d, J = 5.6 Hz, 2H), 4.17 (bs, 1H, OH), 3.77 (s, 3H), 2.59–2.50 (m, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 173.2, 160.6, 139.6, 137.0, 129.3, 128.3, 128.0, 114.7, 71.8, 55.6, 46.6, 43.8; $[\alpha]_D^{25}$ −31.5 (*c* 0.7, $CHCl_3$); TLC R_f 0.20 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{20}NO_3$ 286.1443; Found 286.1445. HPLC analysis: t_R 16.88 min (*S*-isomer), 19.90 min (*R*-isomer) (Chiralpak AD-H, hexanes/^{i}PrOH, 90/10, 1.0 mL/min, λ = 254 nm) for 99% ee.

***N*-Benzyl-3-(4-chlorophenyl)-3-oxopropanamide (3d)**:[40] The product **3d** was obtained as white solid with 92% yield (2.27 g, 7.91 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ keto form (major) 7.91 (t, J = 2.4 Hz, 1H), 7.88 (t, J = 2.0 Hz, 1H), 7.44 (t, J = 2.4 Hz, 1H), 7.42 (t, J = 2.0 Hz, 1H), 7.32–7.29 (m, 3H), 7.26 (m, 1H), 7.25–7.24 (m, 1H), 4.45 (d, J = 5.6 Hz, 2H), 3.90 (s, 2H); enol form (minor) 5.51 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ keto form (major) 194.6, 165.2, 140.7, 137.7, 134.4, 130.0, 129.2, 128.7, 127.6, 127.5, 45.5, 43.7; enol form (minor) 127.0; TLC R_f 0.21 (EtOAc/Hexanes, 1/2); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{14}ClNO_2Na$ 310.0611; Found 310.0604.

(*S*)-*N*-Benzyl-3-(4-chlorophenyl)-3-hydroxypropanamide (4d):[40,41a] The product **4d** was obtained as crystalline white solid with 92% yield (21 mg, 0.07 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.35–7.19 (m, 7H), 7.09 (dd, J = 8.0, 1.6 Hz, 2H), 5.07 (dd, J = 13.6, 7.6 Hz, 1H), 4.30 (dd, J = 14.8, 54.8 Hz, 2H), 2.61 (ddd, J = 21.6, 13.6, 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 172.9, 144.0, 139.6, 134.1, 129.4, 129.4, 128.7, 128.4, 128.0, 71.4, 46.6, 43.9; $[\alpha]_D^{25}$ −54.5 (*c* 0.4, $CHCl_3$); TLC R_f 0.21 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{17}ClNO_2$ 290.0948; Found 290.0951. HPLC conditions: t_R 11.70 min (*S*-isomer), 17.26 min (*R*-isomer) (Chiralpak AD-H, hexanes/^{i}PrOH, 90/10, 1.0 mL/min, λ = 254 nm) for 96% ee.

***N*-Benzyl-3-(4-bromophenyl)3-oxopropanamide (3e)**:[40] The product **3e** was obtained as crystalline white solid with 84% yield (2.39 g, 7.22 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ keto form (major) 7.86 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.33–7.28 (m, 5H), 4.49 (d, J = 5.6 Hz, 2H), 3.95 (s, 2H); enol form (minor) 5.48 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ keto form (major) 194.7, 165.2, 137.7, 134.8, 132.1, 131.6, 130.0, 128.6, 127.6, 127.5, 45.5, 43.6; enol form (minor) 129.4, 127.2; TLC R_f 0.13 (EtOAc/Hexanes, 1/2); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{14}BrNO_2Na$ 354.0106; Found 354.0105.

(*S*)-*N*-Benzyl-3-(4-bromophenyl)-3-hydroxypropanamide (4e):[40] The product **4e** was obtained as white solid with 89% yield (23 mg, 0.071 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.45 (d, J = 8.4 Hz, 2H), 7.29–7.17 (m, 5H), 7.08 (dd, J = 7.6, 0.8 Hz, 2H), 5.05 (t, J = 7.2 Hz, 1H), 4.30 (dd, J = 57.6, 15.2 Hz, 2H), 2.61 (ddd, J = 21.6, 13.6, 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 172.8, 144.5, 139.6, 132.4, 129.4, 129.0, 128.4, 128.0, 122.1, 71.5, 46.5, 43.9; $[\alpha]_D^{25}$ −37.3 (*c* 0.5, $CHCl_3$); TLC R_f 0.21 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{17}BrNO_2$ 334.0443; Found 334.0443. HPLC analysis: t_R 12.23 min (*S*-isomer), 18.18 min (*R*-isomer) (Chiralpak AD-H, hexanes/^{i}PrOH, 90/10, 1.0 mL/min, λ = 254 nm) for 99% ee.

***N*-Benzyl-3-(4-nitrophenyl)-3-oxopropanamide (3f)**: The product **3f** was obtained as crystalline white solid with 80% yield (2.05 g, 6.88 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ keto form (major) 8.33 (d, J = 8.8 Hz, 1H), 8.25 (d, J = 8.8 Hz, 1H), 8.17 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.38–7.27 (m,5H), 4.56 (d, J = 6.0 Hz, 1H), 4.49 (d, J = 6.0 Hz, 1H), 4.02 (s, 1H); enol form (minor) 5.60 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ keto form (major) 193.9, 164.9, 150.6, 148.8, 137.5, 129.6, 126.5, 123.9, 123.6, 91.3, 43.7, 43.2; enol form (minor) 171.1, 166.6, 140.3, 140.2, 137.4, 128.7, 128.7, 127.7, 127.6, 46.3; $[\alpha]_D^{25}$ −38.3 (*c* 0.4, $CHCl_3$); TLC R_f 0.20 (EtOAc/Hexanes, 1/2); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}N_2O_4$ 299.1032; Found 299.1025.

(*S*)-*N*-Benzyl-3-hydroxy-3-(4-nitrophenyl)propan-amide (4f): The product **4f** was obtained as white solid with 79% yield (19 mg, 0.063 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.14 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.25–7.12 (m, 5H), 5.21–5.17 (m, 1H), 4.30 (dd, J = 46.8, 14.8 Hz, 2H), 2.64 (ddd, J = 22.0, 14.0, 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 172.5, 153.0, 148.6, 139.7, 129.4, 128.5, 128.1, 128.0, 124.4, 71.2, 46.5, 43.9; TLC R_f 0.20 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{16}N_2O_4Na$ 323.1008; Found 323.0997. HPLC analysis: t_R 10.47 min (*S*-isomer), 18.55 min (*R*-isomer) (Chiralpak AD-H, hexanes/^{i}PrOH, 85/15, 1.0 mL/min, λ = 254 nm) for 79% ee.

***N*-Benzyl-3-(3-methoxyphenyl)-3-oxopropanamide (3g)**: The product **3g** was obtained as white solid with 82% yield (1.99 g, 7.05 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ keto form (major) 7.57 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 2.0 Hz, 1H), 7.45 (s, 1H, NH), 7.39 (t, J = 8.0 Hz, 1H), 7.34–7.26 (m, 5H), 7.15 (ddd, J = 8.2, 2.8, 0.8 Hz, 1H), 4.50 (d, J = 5.6 Hz, 2H), 3.98 (s, 2H), 3.85 (s, 1H); enol form (minor) 5.50 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ keto form (major) 195.7, 165.6, 159.8, 137.8, 137.4, 129.8, 128.6, 127.6, 127.4, 121.2, 120.6, 112.4, 55.4, 45.3, 43.5; enol form (minor) 129.3, 118.0 116.5, 110.8; TLC R_f 0.22 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{17}NO_3Na$ 306.1106; Found 306.1102.

(*S*)-*N*-Benzyl-3-hydroxy-3-(3-methoxyphenyl)propanamide (4g): The product **4g** was obtained as white solid with 43% yield (10 mg, 0.034 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.62–7.19 (m, 5H), 7.13–7.11 (m, 1H), 6.95–6.93 (m, 2H), 6.81 (ddd, J = 3.2, 2.4, 0.8 Hz, 1H), 5.06 (dd, J = 8.0, 6.0 Hz, 1H), 4.32 (dd, J = 44.4, 14.8 Hz, 2H), 3.76 (s, 3H), 2.62 (ddd, J = 21.6, 13.6, 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 173.2, 161.2, 146.8, 139.6, 130.4, 129.4, 128.3, 128.0, 119.2, 114.0, 112.5, 72.1, 55.5, 46.7, 43.9; $[\alpha]_D^{26}$ −51.2 (*c* 0.1, $CHCl_3$); TLC R_f 0.20 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{19}NO_3Na$ 308.1263; Found 308.1259. HPLC analysis: t_R 18.32 min (*S*-isomer), 21.53 min (*R*-isomer) (Chiralpak AD-H, hexanes/^{i}PrOH, 90/10, 1.0 mL/min, λ = 254 nm) for 88% ee.

***N*-Benzyl-3-(naphthalen-2-yl)-3-oxopropanamide (3h)**: The product **3h** was obtained as white solid with 85% yield (2.21 g,

7.31 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ keto form (major) 8.55 (s, 1H), 8.03–7.97 (m, 2H), 7.92–7.87 (m, 2H), 7.66–7.62 (m, 1H), 7.60–7.56 (m, 1H), 7.53–7.50 (m, 1H), 7.34–7.27 (m, 1H), 4.52 (d, J = 5.6 Hz, 2H), 4.13 (s, 2H); enol form (minor) 5.65 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 195.8, 165.7, 137.8, 135.9, 133.4, 132.3, 130.9, 129.8, 128.7, 128.6, 127.7, 127.6, 127.4, 127.0, 123.5, 45.4, 43.6; TLC R_f 0.20 (EtOAc/Hexanes, 1/3); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{17}NO_2Na$ 326.1157; Found 326.1153.

(*S*)-*N*-Benzyl-3-hydroxy-3-(naphthalen-2-yl)propan-amide (**4h**): The product **4h** was obtained as white solid with 90% yield (21 mg, 0.072 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.82–7.79 (m, 4H), 7.53 (dd, J = 8.8, 1.6 Hz, 1H), 7.48–7.44 (m, 2H), 7.10–7.06 (m, 1H), 7.04–7.00 (m, 2H), 6.94 (d, J = 7.2 Hz, 2H), 5.26 (dd, J = 7.6, 6.4 Hz, 1H), 4.28 (dd, J = 70.4, 15.2 Hz, 2H), 2.75 (ddd, J = 21.6, 14.0, 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 173.1, 142.4, 139.5, 134.7, 134.5, 129.2, 129.2, 129.0, 128.6, 128.1, 127.9, 127.1, 126.8, 125.9, 125.2, 72.4, 46.6, 43.8; $[\alpha]_D^{25}$–40.3 (*c* 0.6, $CHCl_3$); TLC R_f 0.20 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{20}NO_2$ 306.1494, Found 306.1492. HPLC analysis: t_R 19.56 min (*S*-isomer), 28.20 min (*R*-isomer) (Chiralpak AD-H, hexanes/^{i}PrOH, 90/10, 1.0 mL/min, λ = 254 nm) for 98% ee.

***N*-Benzyl-3-(naphthalen-1-yl)-3-oxopropanamide** (**3i**): The product **3i** was obtained as white solid with 70% yield (1.82 g, 6.02 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ keto form (major) 8.65 (d, J = 8.8 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.91–7.89 (m, 1H), 7.62–7.60 (m, 1H), 7.56–7.51 (m, 2H), 7.36–7.28 (m, 5H), 4.53 (d, J = 5.6 Hz, 2H), 4.09 (s, 2H); enol form (minor) 5.31 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ keto form (major) 199.2, 165.6, 137.8, 134.4, 134.0, 130.3, 130.1, 129.4, 128.7, 128.6, 128.4, 127.6, 127.4, 126.7, 125.5, 124.4, 49.0, 43.7; enol form (minor) 133.9, 127.8; TLC R_f 0.20 (EtOAc/Hexanes, 1/3); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{17}NO_2Na$ 326.1157; Found 326.1155.

(*S*)-*N*-Benzyl-3-hydroxy-3-(naphthalene-1-yl)propan-amide (**4i**): The product **4i** was obtained as white solid with 83% yield (20 mg, 0.066 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 8.22 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.52–7.42 (m, 3H), 7.26–7.16 (m, 5H), 5.93 (dd, J = 8.4, 4.8 Hz, 1H), 4.35 (d, J = 3.2 Hz, 2H), 2.80–2.70 (m, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 173.5, 141.0, 139.7, 135.3, 131.5, 129.8, 129.4, 128.9, 128.4, 128.0, 127.0, 126.5, 126.4, 124.2, 124.1, 68.7, 46.1, 44.0; $[\alpha]_D^{25}$ –61.7 (*c* 0.4, $CHCl_3$); TLC R_f 0.20 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{19}NO_2Na$ 328.1313; Found 328.1311. HPLC analysis: t_R 9.00 min (*S*-isomer), 12.60 min (*R*-isomer) (Chiralpak AD-H, hexanes/^{i}PrOH, 85/15, 1.0 mL/min, λ = 254 nm) for 90% ee.

***N*-Benzyl-3-(furan-2-yl)-3-oxopropanamide** (**3j**): The product **3j** was obtained as colourless viscous liquid with 82% yield (1.71 g, 7.05 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ keto form (major) 7.62 (m, 1H), 7.48 (bs, 1H, NH), 7.31–7.26 (m, 5H), 6.55 (dd, J = 3.6, 1.6 Hz, 1H), 4.45 (d, J = 6.0 Hz, 2H); enol form (minor) 5.53 (s, H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 183.6, 165.3, 151.6, 147.5, 137.7, 128.4, 127.4, 127.2, 119.4, 112.6, 44.9, 43.4; TLC R_f 0.25 (EtOAc/Hexanes, 1/2); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{13}NO_3Na$ 266.0793; Found 266.0787.

(*S*)-*N*-Benzyl-3-(furan-2-yl)-3-hydroxypropanamide (**4j**): The product **4j** was obtained as white solid with 60% yield (11 mg, 0.048 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.42 (dd, J = 1.6, 0.8 Hz, 1H), 7.29–7.20 (m, 5H), 6.34 (dd, J = 3.2, 1.6 Hz, 1H), 6.28 (d, J = 3.2 Hz, 1H), 5.10 (t, J = 6.8 Hz, 1H), 4.35 (d, J = 10.4 Hz, 2H), 2.75–2.73 (m, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 172.7, 157.2, 143.2, 139.6, 129.4, 128.4, 128.0, 111.1, 107.1, 65.4, 43.9, 43.1; $[\alpha]_D^{26}$–11.0 (*c* 0.2, $CHCl_3$); TLC R_f 0.20 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{15}NO_3Na$ 268.0950; Found 268.0951. HPLC analysis: t_R 22.18 min (*S*-isomer), 32.91 min (*R*-isomer) (Chiralpak AS-H, hexanes/^{i}PrOH, 80/20, 1.0 mL/min, λ = 220 nm) for 90% ee.

***N*-Benzyl-3-oxo-3-(thiophen-2-yl)propanamide** (**3k**): The product **3k** was obtained as light brown solid with 77% yield (1.71 g, 6.62 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (dd, J = 3.6, 0.8 Hz, 1H), 7.74 (dd, J = 4.8, 0.8 Hz, 1H), 7.50 (bs, 1H, NH), 7.35–7.25 (m, 5H), 7.17 (d, J = 4.8, 4.0 Hz, 1H), 4.49 (d, J = 5.6 Hz, 2H), 3.94 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 188.4, 165.1, 143.2, 137.8, 135.6, 133.8, 128.6, 128.6, 127.6, 127.4, 45.7, 43.6; TLC R_f 0.25 (EtOAc/Hexanes, 1/2); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{13}NO_2SNa$ 282.0565; Found 282.0557.

(*S*)-*N*-Benzyl-3-hydroxy-3-(thiophen-2-yl)propan-amide (**4k**): The product **4k** was obtained as white solid with 71% yield (15 mg, 0.057 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.30 (dd, J = 5.2, 1.2 Hz, 1H), 7.28–7.24 (m, 2H), 7.22–7.16 (m, 3H), 6.97 (dt, J = 3.6, 0.8 Hz, 1H), 6.93 (dd, J = 4.8, 3.6 Hz, 1H), 5.35 (dd, J = 8.0, 6.0 Hz, 1H), 4.34 (dd, J = 32.8, 15.2 Hz, 2H), 2.73 (ddd, J = 22.0, 14.0, 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 172.7, 149.2, 139.7, 129.4, 128.4, 128.0, 127.5, 125.4, 124.7, 68.0, 46.8, 43.9; $[\alpha]_D^{25}$–50.3 (*c* 0.05, $CHCl_3$); TLC R_f 0.20 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_2S$ 262.0902; Found 262.0901. HPLC analysis: t_R 14.05 min (*S*-isomer), 22.97 min (*R*-isomer) (Chiralpak AS-H, hexanes/^{i}PrOH, 70/30, 1.0 mL/min, λ = 254 nm) for 95% ee at -20°C and 93% ee at -5 to 0°C.

***N*-Benzyl-3-(2-methoxyphenyl)-3-oxopropanamide** (**3l**): The product **3l** was obtained as white solid with 74% yield (1.80 g, 0.64 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (dd, J = 7.6, 1.6 Hz, 1H), 7.50 (t, J = 6.8 Hz, 1H), 7.44 (bs, 1H, NH), 7.34–7.27 (m, 5H), 7.01 (t, J = 7.6 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.50 (d, J = 6.0 Hz, 1H), 4.03 (s, 2H), 3.88 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 179.7, 166.4, 158.7, 138.1, 134.4, 130.4, 128.4, 127.5, 127.1, 120.6, 115.1, 55.3, 49.8, 43.3; TLC R_f 0.25 (EtOAc/Hexanes, 2/3); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{17}NO_3Na$ 306.1106; Found 306.1101.

(*S*)-*N*-Benzyl-3-hydroxy-3-(2-methoxyphenyl)propanamide (**4l**): The product **4l** was obtained as white solid with 18% yield (4 mg, 0.014 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.44–7.42 (m, 1H), 7.29–7.19 (m, 6H), 6.94–6.91 (m, 2H), 5.42 (dd, J = 8.8, 4.0 Hz, 1H), 4.36 (s, 2H), 3.81 (s, 3H), 2.61 (ddd, J = 18.4, 14.4, 4.0 Hz, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 173.8, 157.4, 139.8, 133.1, 129.4, 128.4, 128.0, 127.3, 121.5, 111.4, 66.7, 55.7, 44.7, 43.9; $[\alpha]_D^{26}$–33.0 (*c* 0.03, $CHCl_3$); TLC R_f 0.20 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{19}NO_3Na$ 308.1263; Found 308.1257. HPLC analysis: t_R

19.28 min (*S*-isomer), 22.46 min (*R*-isomer) (Chiralpak AD-H, hexanes/^{i}PrOH, 90/10, 1.0 mL/min, λ = 254 nm) for 88% *ee*.

***N*-Benzyl-3-oxo-5-phenylpent-4-ynamide** (**3m**): The product **3m** was obtained as light yellow viscous liquid with 20% yield (0.4 g, 1.4 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ keto form (major) 7.56–7.54 (m, 1H), 7.50–7.46 (m, 1H), 7.40–7.36 (m, 2H), 7.32–7.27 (m, 6H), 4.47 (d, *J* = 5.2 Hz, 2H), 3.69 (s, 2H); enol form (minor) 5.39 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ keto form (major) 181.7, 164.6, 137.6, 133.1, 128.5, 128.2, 127.3, 119.0, 98.5, 93.7, 51.3, 43.4, 42.8; enol form (minor) 170.8, 153.3, 153.2, 137.7, 137.7, 137.1, 132.3, 131.9, 131.1, 129.9, 129.4, 128.5, 128.3, 127.7, 127.5, 127.3, 120.9, 119.9, 91.6, 87.5, 85.0, 83.9, 82.7, 43.7, 30.7; TLC R_f 0.30 (EtOAc/Hexanes, 1/2); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{15}NO_2Na$ 300.1000; Found 300.0995.

(*S*)-Benzyl-3-hydroxy-5-phenylpent-4-ynamide (**4m**): The product **4m** was obtained as white solid with 56% yield (12 mg, 0.0448 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.36–7.34 (m, 2H), 7.32–7.27 (m, 5H), 7.21–7.15 (m, 3H), 4.97 (t, *J* = 7.2 Hz, 1H), 4.39 (dd, *J* = 53.2, 14.8 Hz, 2H), 2.75–2.65 (m, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 172.1, 139.7, 132.6, 129.5, 129.4, 129.4, 128.4, 128.0, 132.9, 90.4, 85.4, 60.4, 45.5, 44.0; $[\alpha]_D^{25}$ −1.5 (*c* 0.03, $CHCl_3$); TLC R_f 0.22 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{17}NO_2Na$ 302.1157; Found: 302.1153. HPLC analysis: t_R 14.46 min (*S*-isomer), 21.85 min (*R*-isomer) (Chiralpak AS-H, hexanes/^{i}PrOH, 75/25, 1.0 mL/min, λ = 254 nm) for 11% ee.

(*R*)-*N*-Benzyl-3-hydroxybutanamide (**4n**):[42] The product **4n** was obtained as white solid with 75% yield (12 mg, 0.06 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.31–7.26 (m, 4H), 7.24–7.19 (m, 1H), 4.36 (s, 2H), 4.20–4.12 (m, 1H), 2.41–2.29 (m, 2H), 1.19 (d, *J* = 6.4 Hz, 3H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 173.8, 139.8, 129.4, 128.5, 128.1, 65.9, 46.2, 44.0, 23.3; $[\alpha]_D^{25}$ −5.2 (*c* 0.08, $CHCl_3$); TLC R_f 0.24 (Acetone/Hexanes, 1/4); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{15}NO_2Na$ 216.1000; Found 216.0992. HPLC analysis: t_R 18.69 min (*R*-isomer), 21.14 min (*S*-isomer) (Chiralpak AD-H, hexanes/^{i}PrOH, 95/5, 0.7 mL/min, λ = 254 nm) for 14% ee.

***N*-Benzyl-3-oxo-5-phenylpentanamide** (**3o**): The product **3o** was obtained as white solid with 33% yield (0.9 g, 3.20 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ keto form (major) 7.35–7.29 (m, 3H), 7.28–7.26 (m, 4H), 7.21–7.15 (m, 3H), 4.44 (d, *J* = 5.6 Hz, 2H), 3.41 (s, 2H), 2.89 (m, 4H); enol form (minor) 5.31 (s, 1H); enol form (minor) 5.46 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 205.5, 165.3, 140.1, 137.7, 128.5, 128.4, 128.1, 127.5, 127.3, 126.1, 49.0, 44.9, 43.4, 29.1; TLC R_f 0.30 (EtOAc/Hexanes, 1/3); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{19}NO_2Na$ 304.1313; Found 304.1314.

(*R*)-*N*-Benzyl-3-hydroxy-5-phenylpentanamide (**4o**):[43] The product **4o** was obtained as white solid with 90% yield (20 mg, 0.072 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.29–7.28 (m, 4H), 7.25–7.21 (m, 3H), 7.17–7.13 (m, 3H), 4.36 (d, *J* = 2.0 Hz, 2H), 4.03–3.97 (m, 1H), 2.80–2.59 (m, 2H), 2.39 (d, *J* = 6.4 Hz, 2H), 1.78–1.72 (m, 2H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 173.8, 143.3, 139.9, 129.5, 129.4, 129.3, 128.5, 128.1, 126.7, 69.2, 44.8, 44.0, 40.1, 32.8; $[\alpha]_D^{25}$ −9.5 (*c* 0.4, $CHCl_3$); TLC R_f 0.22 (EtOAc/Hexanes, 3/7 HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{21}NO_2Na$ 306.1470; Found 306.1469. HPLC analysis: t_R 34.41 min (*R*-isomer), 39.13 min (*S*-isomer) (Chiralpak AS-H, hexanes/^{i}PrOH, 90/10, 1.0 mL/min, λ = 220 nm) for 98% ee.

***N*-Benzyl-4-methyl-3-oxopentanamide** (**3p**):[44] The product **3p** was obtained as white solid with 76% yield (1.43 g, 6.53 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (bs, 1H, NH), 7.35–7.26 (m, 5H), 4.46 (d, *J* = 5.6 Hz, 2H), 3.49 (s, 2H), 2.69 (hep, *J* = 7.2 Hz, 1H), 1.12 (d, *J* = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 210.7, 165.5, 137.9, 128.6, 127.6, 127.4, 46.5, 43.5, 42.0, 17.7; TLC R_f 0.25 (Acetone/Hexanes, 1/2); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{17}NO_2Na$ 242.1157; Found: 242.1156.

(*S*)-*N*-Benzyl-3-hydroxy-4-methylpentanamide (**4p**):[41b] The product **4p** was obtained as white solid with 84% Yield (15 mg, 0.0672 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.29–7.28 (m, 4H), 7.25–7.19 (m, 1H), 4.37 (d, *J* = 2.4 Hz, 2H), 3.80–3.76 (m, 1H), 2.41–2.26 (m, 2H), 1.69–1.61 (m, 1H), 0.92 (dd, *J* = 6.8, 2.4 Hz, 6H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 174.6, 139.9, 129.4, 128.5, 128.1, 74.5, 44.0, 41.6, 34.9, 19.0, 17.8; $[\alpha]_D^{25}$ −18.4 (*c* 0.1, $CHCl_3$); TLC R_f 0.23 (Acetone/Hexanes, 1/4); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{19}NO_2Na$ 244.1313; Found 244.1308. HPLC analysis: t_R 12.50 min (*S*-isomer), 14.82 min (*R*-isomer) (Chiralpak AD-H, hexanes/^{i}PrOH, 95/5, 1.0 mL/min, λ = 254 nm) for 56% ee.

***N*-Benzyl-4,4-dimethyl-3-oxopentanamide** (**3q**): The product **3q** was obtained as white solid with 83% yield (1.66 g, 7.13 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (bs, 1H, NH), 7.33–7.29 (m, 2H), 7.27–7.25 (m, 3H), 4.45 (d, *J* = 6.0 Hz, 2H), 3.52 (s, 2H), 1.15 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 212.1, 165.8, 137.9, 128.5, 127.5, 127.3, 45.0, 43.4, 43.2, 27.4, 25.7; TLC R_f 0.25 (Acetone/Hexanes, 1/2); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}NO_2$ 234.1494; Found 234.1489.

(*S*)-*N*-Benzyl-3-hydroxy-4,4-dimethylpentanamide (**4q**):[41a,44] The product **4q** was obtained as white solid with 82% yield (15 mg, 0.0656 mmol). ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.29 (d, *J* = 4.4 Hz, 4H), 7.24–7.19 (m, 1H), 4.38 (dd, *J* = 38.8, 24.0 Hz, 2H), 3.69 (dd, *J* = 10.4, 2.4 Hz, 1H), 2.44–2.21 (m, 2H), 0.90 (s, 9H); ^{13}C{^{1}H} NMR (CD_3OD, 100 MHz) δ 175.2, 139.9, 129.4, 128.5, 128.1, 77.3, 44.1, 39.5, 35.7, 26.1; $[\alpha]_D^{25}$ −25.3 (*c* 0.6, $CHCl_3$); TLC R_f 0.23 (Acetone/Hexanes, 1/4); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{22}NO_2$ 236.1651; Found 236.1645. HPLC analysis: t_R 20.54 min (*S*-isomer), 20.53 min (*R*-isomer) (Chiralpak AS-H, hexanes/^{i}PrOH, 90/10, 0.9 mL/min, λ = 254 nm) for 80% ee.

***N*,*N*-dimethyl-3-oxo-3-phenylpropanamide (3r):[46]** The product **3r** was obtained as white solid with 76% yield (1.3 g, 6.70 mmol). **^{1}H NMR** (MeOD, 400 MHz) δ keto form (major) 8.00 (d, *J* = 8.0 Hz, 2H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 4.22 (d, *J* = 8.4 Hz, 1H), 3.05 (s, 3H), 2.98 (s, 3H); enol form (minor) 7.82(d, *J* = 6.4 Hz, 2 H), 7.43(m, 3H), 6.00(s, 1H), 3.13 (s, 1H), 3.01 (s, 1H); **^{13}C{^{1}H} NMR** (MeOD, 100 MHz) δ keto form (major) 195.9, 170.2, 137.5, 134.8, 129.8, 129.5, 126.9,46.1 38.3, 35.7; enol form (minor) 173.5, 171.5, 135.9, 131.7, 85.9, 45.8, 37.4, 35.2; **TLC** R_f 0.35 (EtOAc/Hexanes, 1/1); HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{13}NO_2$: 192.1025, found: 192.1027.

(*S*)-3-hydroxy-*N*,*N*-dimethyl-3-phenylpropanamide-4r:[47] The product **4r** was obtained as slight yellow oil with 63% yield (24.3 mg, 12.57 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.41-

7.34(m, 4H), 7.29(d, J = 7.2 Hz, 1H), 5.15(d, J = 8.8 Hz, 1H), 3.84(s, 1H), 2.98(s, 6H), 2.74-261(m, 2H); **$^{13}C\{^1H\}$ NMR** ($CDCl_3$, 100 MHz) δ 172.2, 143.1, 128.4, 127.5, 125.7, 70.4, 41.9, 37.1, 35.0; $[\alpha]_D^{25}$ −96.5 (*c* 0.60, $CHCl_3$); **TLC** R_f 0.25 (EtOAc/Hexanes, 1/1); **HRMS** (ESI) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{15}NO_2$: 216.1001, found: 216.1002. **HPLC** conditions: t_R 12.44 min (*S*-isomer, Major), 14.41 min (*R*-isomer, Minor) (Chiralcel OD-H, hexanes/^{i}PrOH, 90/10, 1.0 mL/min, λ = 254 nm) for 96% *ee*.

***N*-Methyl-3-oxo-3-(thiophen-2-yl)propanamide (3k')**:[45] The product **3k'** was obtained as white solid with 46% yield (0.3 g, 1.6 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 4.0, 1.2 Hz, 1 H), 7.72–7.70 (m, 1 H), 7.14 (dd, *J* = 4.0, 4.8 Hz, 1 H), 3.87 (s, 2 H), 2.82 (d, 4.8 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 188.2, 165.9, 143.2, 135.4, 133.8, 128.4, 45.8, 26.2. TLC R*f* = 0.3 (EtOAc/Hexane = 4/1.5); HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_8H_9NO_2SNa$ 206.0252; Found 206.0248.

(*S*)-3-Hydroxy-*N*-methyl-3-(thiophen-2-yl)propan-amide (4k'):[45] The product **4k'** was obtained as crystalline white solid with 45% yield (33 mg, 0.18 mmol). ^1H NMR (400 MHz, CD_3OD) δ: 7.29 (dd, *J* = 4.8, 1.2 Hz, 1 H), 6.97 (dt, *J* = 3.2, 1.2 Hz, 1 H), 6.93 (dd, *J* = 4.8, 3.6 Hz, 1 H), 5.33 – 5.29 (m, 1 H), 2.71 – 2.58 (m, 5 H). $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ: 173.5, 149.3, 127.5, 125.4, 124.5, 67.9, 46.8, 26.3. TLC R*f* = 0.25 (EtOAc/Hexane = 4/1.5); $[\alpha]_D^{25}$−20.2 (1.3, CHCl3) for 90% ee; HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_8H_{11}NO_2SNa$: 208.0408; Found 208.0407; HPLC analysis: t_R 17.3 major (*S*-isomer), 22.3 minor (*R*-isomer) (Chiralpak AS-H, hexanes/^{i}PrOH, 85/15, 1.0 mL/min, λ = 254 nm), ee 90% for (*S*)-isomer.

Procedure for 2 mmol Scale preparation of (*S*)-*N*-Benzyl-3-(4-chlorophenyl)-3-hydroxypropanamide (4d):

In an oven dried 50 mL Schlenk tube, 3d (0.575.4 g, 2 mmol) was taken along with 1b catalyst (109.3 mg, 0.2 mmol) under argon atmosphere. Dry THF (16 mL) was injected into the Schlenk tube via syringe. After stirring the reaction mixture for 15 minutes at ambient temperature, the schlenk tube was put into the cooling bath. The reducing agent (870μL, 6 mmol) diluted by dry THF (4mL) was added to the reaction mixture via flame dried syringe slowly over 1 h. After the reaction was over (checked by TLC), distilled water (5mL) was injected into the Schlenk tube via syringe to quench the reducing agent. The reaction mixture was stirred for 30 min under room temperature followed by extraction with ethyl acetate (20mL × 3). Collected organic solvent was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (Hexanes/EA = 2:1) to afford the product 4d as white solid (472 mg, 88% yield, 98% ee).

ASSOCIATED CONTENT

Supporting Information

NMR spectra, HPLC Chromatographs, crystal structure preparation, and Crystal data for compound **4k'** (PDF).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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REFERENCES

1. (a) Lin, G. Q.; You; Q. D. and Cheng, J. F. Chiral Drugs: Chemistry and Biological Action. John Wiley & Sons, **2011**; (b) Zuo, W. W.; Morris, R. H. Synthesis and use of an asymmetric transfer hydrogenation catalyst based on iron(II) for the synthesis of enantioenriched alcohols and amines. *Nat. Protoc.* **2015,** *10*, 241-257 (c) Gao, T. T.; Zhang, W. W.; Sun, X.; Lu, H. X. and Li, B. J. Stereodivergent Synthesis through Catalytic Asymmetric Reversed Hydroboration. *J. Am. Chem. Soc.*, **2019**, *141*, 4670-4677. (d) Štefane, B. and Požgan, F. Metal-Catalysed Transfer Hydrogenation of Ketones. *Top. Curr. Chem.*, **2016**, *374*.

2. (a) Chen, J.; Zhang, T.; Liu, X.; and Shen, L. Enantioselective Synthesis of (*S*)-γ-Amino Alcohols by Ru/Rh/Ir Catalyzed Asymmetric Transfer Hydrogenation (ATH) with Tunable Chiral Tetraaza Ligands in Water. *Catal. Lett.* **2019**, *149*, 601-609. (b) Kong, D.; Li, M.; Wang, R.; Zi, G. and Hou, G. Asymmetric Hydrogenation of β-Aryloxy/Alkoxy Cinnamic Nitriles and Esters. *Org. Lett.*, **2016**, *18*, 4916-4919. (c) Verkade, J. M. M.; Quaedflieg, P. J. L. M.; Verzijl, G. K. M.; Lefort, L.; van Delft, F. L.; de Vries, J. G.; Rutjes, F. P. J. T. Enantio- and Diastereoselective Synthesis of γ-Amino Alcohols. *Chem. Commun.* **2015**, *51*, 14462–14464.

3. (a) Ohkuma, T.; Ishii, D.; Takeno, H. and Noyori, R. Asymmetric Hydrogenation of Amino Ketones Using Chiral $RuCl_2$(diphophine)(1,2-diamine) Complexes. *J. Am. Chem. Soc.*, **2000**, *122*, 6510-6511; (b) Noyori, R. Asymmetric Catalysis: Science and Opportunities (Nobel Lecture 2001). *Adv. Synth. Catal.*, **2003**, *345*, 15-32; (c) Noyori, R. and Ohkuma, T. Asymmetric Catalysis by Architectural and Functional Molecular Engineering: Practical Chemo- and Stereoselective Hydrogenation of Ketones. *Angew. Chem. Int. Ed.*, **2001**, *40*, 40-73.

4. (a) Seo, C. S. G. and Morris, R. H. Catalytic Homogeneous Asymmetric Hydrogenation: Successes and Opportunities. *Organometallics*, **2019**, *38*, 47-65. (b) Rodríguez, S.; Qu, B.; Fandrick, K. R.; Buono, F.; Haddad, N.; Xu, Y.; Herbage, M. A.; Zeng, X.; Ma, S.; Grinberg, N.; Lee, H.; Han, Z. S.; Yee, N. K. and Senanayake, C. H. Amine-Tunable Ruthenium Catalysts for Asymmetric Reduction of Ketones. *Adv. Synth. Catal.*, **2014**, *356*, 301-307

5. (a) Bao, D.-H.; Wu, H.-L.; Liu, C. -L.; Xie, J. -H. and Zhou, Q. -L. Development of Chiral Spiro P-N-S Ligands for Iridium-Catalyzed Asymmetric Hydrogenation of β-Alkyl-β-Ketoesters. *Angew. Chem.*, **2015**, *127*, 8915-8918. (b) Kesselgruber, M.; Lotz, M.; Martin, P.; Melone, G.; Müller, M.; Pugin, B.; Naud, F.; Spindler, F.; Thommen, M.; Zbinden, P. and Blaser, H. -U. Solphos: A New Family of Efficient Biaryl Diphosphine Ligands. *Chem. Asian. J.*, **2008**, *3*, 1384-1389.

6. Nedden, H. G.; Zanotti-Gerosa, A. and Wills, M. The Development of Phosphine-Free "Tethered" Ruthenium(II) Catalysts for the Asymmetric Reduction of Ketones and Imines. *Chem. Rec.*, **2016**, *16*, 2623-2643.

7. (a) Sun, X.; Li, W.; Hou, G.; Zhou, L. and Zhang, X. Axial Chirality Control by 2,4-Pentanediol for the Alternative Synthesis of C3*-TunePhos Chiral Diphosphine Ligands and Their Applications in Highly Enantioselective Ruthenium-Catalyzed Hydrogenation of β-Keto Esters. *Adv. Synth. Catal.*, **2009**, *351*, 2553-2557. (b) Tan, X.; Gao, S.; Zeng, W.; Xin, S.; Yin, Q. and Zhang, X. Asymmetric Synthesis of Chiral Primary Amines by Ruthenium-Catalyzed Direct

Reductive Amination of Alkyl Aryl Ketones with Ammonium Salts and Molecular H_2. *J. Am. Chem. Soc.*, **2018**, *140*, 2024 -2027.
8. Hu, A.; Ngo, H. L. and Lin, W. Remarkable 4,4′-Substituent Effects on Binap: Highly Enantioselective Ru Catalysts for Asymmetric Hydrogenation of β-Aryl Ketoesters and Their Immobilization in Room-Temperature Ionic Liquids. *Angew. Chem. Int. Ed.*, **2004**, *43*, 2501-2504.
9. Xie, J. -H.; Liu, X. -Y.; Yang, X.-H.; Xie, J.-B.; Wang, L. -X. and Zhou, Q.-L. Chiral Iridium Catalysts Bearing Spiro Pyridine-Aminophosphine Ligands Enable Highly Efficient Asymmetric Hydrogenation of β-Aryl β-Ketoesters. *Angew. Chem. Int. Ed.*, **2012**, *51*, 201-203.
10. Touati, R.; Gmiza, T.; Jeulin, S.; Deport, C.; Vidal, V. R.; Hassine, B. B.; Genet, J.-P. Ru-SYNPHOS® and Ru-DIFLUORPHOS®: Highly Efficient Catalysts for Practical Preparation of β-Hydroxy Amides. *Synlett*, **2005**, *16*, 2478-2482.
11. Servi, S. Baker's Yeast as a Reagent in Organic Synthesis. *Synthesis*, **1990**, *1*, 1-25.
12. Rotthaus, O.; Krüger, D.; Demuth, M. and Schaffner, K. Reductions of keto esters with baker's yeast in organic solvents - a comparison with the results in water. *Tetrahedron*, **1997**, *53*, 935-938.
13. Quirós, M.; Rebolledo, F.; Liz, R. and Gotor, V. Enantioselective reduction of β-keto amides by the fungus Mortierella isabellina. *Tetrahedron: Asymmetry*, **1997**, *8*, 3035-3038.
14. Rimoldi, I.; Facchetti, G.; Nava, D.; Contente, M. L. and Gandolfi, R. Efficient methodology to produce a duloxetine precursor using whole cells of *Rhodotorula rubra*. *Tetrahedron: Asymmetry*, **2016**, *27*, 389-396.
15. Kennedy-Smith, J. J.; Nolin, K. A.; Gunterman, H. P. and Toste, F. D. Reversing the Role of the Metal−Oxygen π-Bond. Chemoselective Catalytic Reductions with a Rhenium(V)-Dioxo Complex. *J. Am. Chem. Soc.*, **2003**, *125*, 4056-4057.
16. For Fe(II)/BOXMI with $(EtO)_2MeSiH$, see: Bleith, T.; Wadepohl, H.; Gade, L. H. Iron Achieves Noble Metal Reactivity and Selectivity: Highly Reactive and Enantioselective Iron Complexes as Catalysts in the Hydrosilylation of Ketones. *J. Am. Chem. Soc.* **2015**, *137*, 2456−2459.
17. For Mn(II)(CH_2SiMe_3)/BOXMI complex with HBPin and HBCat, see: Vasilenko, V.; Blasius, C. K.; Wadepohl, H.; Gade, L. H. Mechanism-Based Enantiodivergence in Manganese Reduction Catalysis: A Chiral Pincer Complex for the Highly Enantioselective Hydroboration of Ketones *Angew. Chem. Int. Ed.*, 2017, **56**, 8393–8397.
18. For achiral La$(NTMS_2)_3$-catalyst with HBPin, see: Weidner, V. L.; Barger, C. J.; Delferro, M.; Lohr, T. L.; Marks, T. J. Rapid, Mild, and Selective Ketone and Aldehyde Hydroboration/Reduction Mediated by a Simple Lanthanide Catalyst *ACS Catal.* **2017**, *7*, 1244-1247.
19. Nolin, K. A.; Ahn, R. W. and Toste, F. D. Enantioselective Reduction of Imines Catalyzed by a Rhenium(V)−Oxo Complex. *J. Am. Chem. Soc.*, **2005**, *127*, 12462-12463.
20. (a) Xu, Q.; Gu, X.; Liu, S.; Dou, Q. and Shi, M. The Use of Chiral BINAM NHC-Rh(III) Complexes in Enantioselective Hydrosilylation of 3-Oxo-3-arylpropionic Acid Methyl or Ethyl Esters. *J. Org. Chem.*, **2007**, *72*, 2240-2242. (b) Shinohara, K.; Kawabata, S.; Nakamura, H.; Manabe, Y. and Sakaguchi, S. Enantioselective Hydrosilylation of Ketones Catalyzed by a Readily Accessible *N*-Heterocyclic Carbene–Ir Complex at Room Temperature. *Eur. J. Org. Chem.*, **2014**, 5532.
21. Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A. and Nakahama, S. Asymmetric synthesis using chirally modified borohydrides. Part 3. Enantioselective reduction of ketones and oxime ethers with reagents prepared from borane and chiral amino alcohols. *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2039-2044.
22. Corey, E. J.; Azimioara, M. and Sarshar, S. X-Ray crystal structure of a chiral oxazaborolidine catalyst for enantioselective carbonyl reduction. *Tetrahedron Lett.*, **1992**, *33*, 3429-3430.
23. Hartwig, J. F. Borylation and Silylation of C–H Bonds: A Platform for Diverse C–H Bond Functionalizations. *Acc. Chem. Res.*, **2012**, *45*, 864-873.
24. Ravindra, B.; Das, B. G. and Ghorai, P. Organocatalytic, Enantioselective, Intramolecular Oxa-Michael Reaction of Alkoxyboronate: A New Strategy for Enantioenriched 1-Substituted 1,3-Dihydroisobenzofurans. *Org. Lett.*, **2014**, *16*, 5580- 5583.
25. Li, S.; Li, G.; Meng, W. and Du, H. A. Frustrated Lewis Pair Catalyzed Asymmetric Transfer Hydrogenation of Imines Using Ammonia Borane. *J. Am. Chem. Soc.*, **2016**, *138*, 12956-12962.
26. Bette, V.; Mortreux, A.; Savoia, D. and Carpentier, J. F. [Zinc-Diamine]-Catalyzed Hydrosilylation of Ketones in Methanol. New Developments and Mechanistic Insights. *Adv. Synth. Catal.*, **2005**, *347*, 289-302.
27. Pujol, A.; Calow, A. D. J.; Batsanov, A. S. and Whiting, A. One-pot catalytic asymmetric borylation of unsaturated aldehyde-derived imines; functionalisation to homoallylic boronate carboxylate ester derivatives. *Org. Biomol. Chem.*, **2015**, *13*, 5122- 5130.
28. Neo., A. G.; Delgado, J.; Polo, C.; Marcaccini, S. and Marcos, C. F. A new synthesis of β-keto amides by reduction of Passerini adducts. *Tetrahedron Lett.*, **2005**, *46*, 23-26.
29. (a) Takehara, J.; Qu, J.; Kanno, K.; Kawabata, H.; Dekishima, Y.; Ueda, M.; Endo, K.; Murakami, T.; Sasaki, T.; Uehara, H.; Matsumoto, Y.; Suzuki, S. 3-Hydroxy-3-(2-thienyl)propanamides and production method thereof, and production method of 3-amino-1-(2-thienyl)1-propanols using the same, Mitsubishi Chemical Co., Tokyo, U.S. Patent 2005/0107621 A1. May 19, **2005**; (b) Tang, C. G.; Lin, H.; Zhang, C.; Liu, Z. Q.; Yang, T. and Wu, Z. L. Highly enantioselective bioreduction of N-methyl-3-oxo-3-(thiophen-2-yl) propanamide for the production of (*S*)-duloxetine. *Biotechnol. Lett.*, **2011**, *33*, 1435-1440.
30. Ren, Z. Q.; Liu, Y.; Pei, X. Q.; Wang, H. B. and Wu, Z. L. Bioreductive production of enantiopure (*S*)-duloxetine intermediates catalyzed with ketoreductase C*h*KRED15. *J. Mol. Catal. B-Enzym.*, **2015**, *113*, 76-81.
31. (a) Weng, S. -S.; M. -W. Shen; J. -Q, Kao; Munot, Y. S.; Chen, C. -T. Chiral *N*-salicylidene vanadyl carboxylate-catalyzed enantioselective aerobic oxidation of α-hydroxy esters and amides. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 3522-3527. (b) For *N*,*N*-substitution effect metal coordination, see: Shi, S.; Nolan, S. P.; and Szostak, M. Well-Defined Palladium(II)−NHC Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective N−C/O−C Cleavage. *Acc. Chem. Res.* **2018**, *51*, 2589−2599.
32. Chen, C. T.; Kao, J. Q.; Salunke, S. B. and Lin, Y. H. Enantioselective Aerobic Oxidation of α-Hydroxy-Ketones Catalyzed by Oxidovanadium(V) Methoxides Bearing Chiral, *N*-Salicylidene-tert-butylglycinates. *Org. Lett.*, **2011**, *13*, 26-29.

33. Jiang, Y.; Chen, X.; Zheng, Y.; Xue, Z.; Shu, C.; Yuan, W. and Zhang, X. Highly Diastereoselective and Enantioselective Synthesis of α-Hydroxy β-Amino Acid Derivatives: Lewis Base Catalyzed Hydrosilylation of α-Acetoxy β-Enamino Esters. *Angew. Chem. Int. Ed.*, **2011**, *50*, 7304-7307.

34. Russo, A.; Galdi, G.; Croce, G.; Lattanzi, A. Highly Enantioselective Epoxidation Catalyzed by Cinchona Thioureas: Synthesis of Functionalized Terminal Epoxides Bearing a Quaternary Stereogenic Center. *Chem. Eur. J.* **2012**, *18*, 6152–6157.

35. Rostovskii, N. V.; Novikov, M. S.; Khlebnikov, A. F.; Khlebnikov, V. A. and Korneev, S. M. Rh(II)-carbenoid mediated 2H-azirine ring-expansion as a convenient route to non-fused photo- and thermochromic 2H-1,4-oxazines. *Tetrahedron*, **2013**, *69*, 4292-4301.

36. Kern, N.; Hoffmann, M.; Blanc, A.; Weibel, J. M. and Pale, P. Gold(I)-Catalyzed Rearrangement of N-Aryl 2-Alkynylazetidines to Pyrrolo[1,2-a]indoles. *Org. Lett.*, **2013**, *15*, 836-839.

37. Grandi, M. J. D.; Bennett, C.; Cagino, K.; Muccini, A.; Suraci, C. and Saba, S. Direct Preparation of Amides from Amine Hydrochloride Salts and Orthoesters: A Synthetic and Mechanistic Perspective. *Synth. Commun.*, **2015**, *45*, 2601-2607.

38. Lin, Z.; Li, J.; Huang, Q.; Huang, Q.; Wang, Q.; Tang, L.; Gong, D.; Yang, J.; Zhu, J.; Deng, J.; Chiral Surfactant-Type Catalyst: Enantioselective Reduction of Long-Chain Aliphatic Ketoesters in Water. *J. Org. Chem*., **2015**, *80*, 4419-4429.

39. Catalytic amidation reaction of ester and amine using alkoxide catalyst., J.P. patent 2013163657, 2013.

40. Neo, A. G.; Delgado, J.; Polo, C.; Marcaccini, S. and Marcos, C. F. A new synthesis of β-keto amides by reduction of Passerini adducts. *Tetrahedron Lett*., **2005**, *46*, 23-26.

41. (a) Shimada, N.; Hirata, M.; Koshizuka, M.; Ohse, N.; Kaito, R.; Makino, K. Diboronic Acid Anhydrides as Effective Catalysts for the Hydroxy-Directed Dehydrative Amidation of Carboxylic Acids. *Org. Lett.* **2019**, *21*, 4303-4308. (b) Wang, Y.-C.; Yan, T.-H. Al–Hg promoted chemoselective dehalogenation of halohydrin aldol adducts. *Chem. Commun.* **2000**, *7*, 545-546.

42. Mendez-Sanchez, D.; Mourelle-Insua, A.; Gotor-Fernandez, V.; Lavandera, I. Synthesis of α-Alkyl-β-Hydroxy Amides through Biocatalytic Dynamic Kinetic Resolution Employing Alcohol Dehydrogenases. *Adv. Synth. & Catal.* **2019**, *361*, 2706-2712.

43. (a) Kakei, H.; Nemoto, T.; T, Ohshima.; and Shibasaki, M. Efficient Synthesis of Chiral α- and β-Hydroxy Amides: Application to the Synthesis of (*R*)-Fluoxetine. *Angew. Chem. Int. Ed*., **2004**, *43*, 317-320. (b) Tsuji, H.; Yamamoto, H. Hydroxy-Directed Amidation of Carboxylic Acid Esters Using a Tantalum Alkoxide Catalyst. *J. Am. Chem. Soc.* **2016**, *138*, 14218-14221.

44. Tsuji, H.; Yamamoto, H. Hydroxy-Directed Amidation of Carboxylic Acid Esters Using a Tantalum Alkoxide Catalyst. *J. Am. Chem. Soc.* **2016**, *138*, 14218-14221.

45. Tang, C.-G.; Lin, H.; Zhang, C.; Liu, Z.-Q.; Yang, T. and Wu, Z.-L. Highly enantioselective bioreduction of N-methyl-3-oxo-3-(thiophen-2-yl) propanamide for the production of (*S*)-duloxetine. *Biotechnol. Lett*., **2011**, *33*, 1435-1440.

46. Goldys, A. M.; Núñez, M. G.; Dixon, D. J. Creation through Immobilization: A New Family of High Performance Heterogeneous Bifunctional Iminophosphorane (BIMP) Superbase Organocatalysts. *Org. Lett.* **2014**, *16* , 6294–6297.

47. Kobayashi, S.; Xu, P.; Endo, T.; Ueno, M.; Kitanosono, T. Chiral Copper(II)-Catalyzed Enantioselective Boron Conjugate Additions to α,β-Unsaturated Carbonyl Compounds in Water. *Angew. Chemie Int. Ed.* **2012**, *51* , 12763–12766.