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Direct Lewis Acid-Catalyzed Conversion of Enantioenriched *N*-Acyl Oxazolidinones to Chiral Esters, Amides, and Acids

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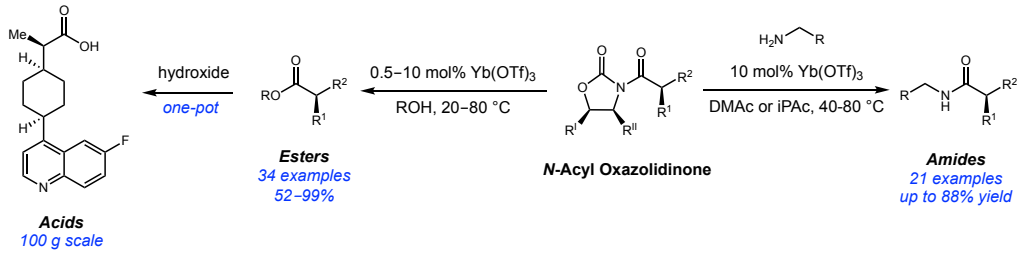
Supporting Information Placeholder



ABSTRACT: The identification of $Yb(OTf)_3$ through a multivariable high-throughput experimentation strategy has enabled a unified protocol for the direct conversion of enantioenriched *N*-acyl oxazolidinones to the corresponding chiral esters, amides and carboxylic acids. This straightforward and catalytic method has shown remarkable chemoselectivity for substitution at the acyclic *N*-acyl carbonyl for a diverse array of *N*-acyl oxazolidinone substrates. The ionic radius of the Lewis acid catalyst was demonstrated as a key driver of catalyst performance that lead to the identification of a robust and scalable esterification of a pharmaceutical intermediate using catalytic $Y(OTf)_3$.

■ INTRODUCTION

N-Acyl oxazolidinones are mainstays of modern organic synthesis as substrates for diastereoselective alkylation[1] and aldol[2] reactions as well as for enantioselective catalytic transformations.[3] Reactions of *N*-acyl oxazolidinones for the synthesis of chiral natural products[4] and pharmaceutical intermediates[5] have enjoyed enduring popularity due to overall reaction efficiency, reliable predictive models for stereoinduction, and excellent observed stereoselectivity. Despite the privileged status of *N*-acyl oxazolidinones as latent chiral scaffolds, the identification and development of direct and general methods to access their respective chiral esters and chiral amides has lingered as an unsolved problem for over three decades. Presently, the most common transformations of *N*-acyl oxazolidinones are $LiBH_4$-mediated reduction to the corresponding alcohol and hydrolysis to the carboxylic acid using $LiOH/H_2O_2$ (Figure **1**).[6–8] Direct access to the corresponding chiral esters and amides would be advantageous and desirable as the oxidation state of the starting material would be retained, thereby rendering redox manipulations and additional synthetic steps unnecessary. Herein we report a general method to access esters and amides bearing α-stereocenters with high levels of selectivity from functionalized *N*-acyl oxazolidinone intermediates in a single step; moreover, a one-pot variation of the esterification protocol enables access to chiral acids as an alternative to *in situ* generated LiOOH.

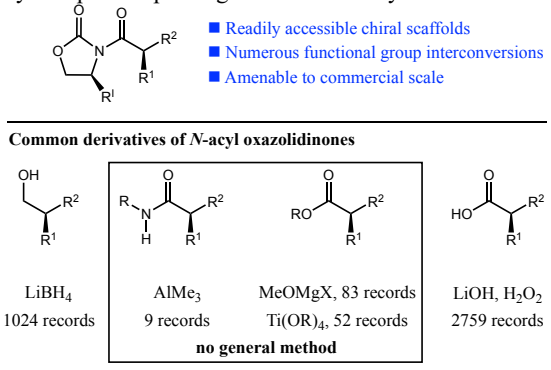


Figure 1. Common derivatization of *N*-acyl oxazolidinones based on literature search

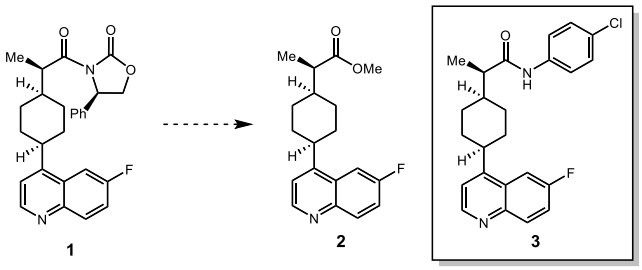
Since the seminal report of utilizing oxazolidinones as chiral auxiliaries by Evans in 1981, only a sparse number of methods have been developed to convert *N*-acyl oxazolidinone reaction products to esters, amides or carboxylic acids.[7–11] The most frequently utilized method to access esters relies on the *in situ* generation of stoichiometric $Ti(OBn)_4$ for generation of the corresponding benzyl esters.[8] A recent report demonstrated access to ester products *via* catalytic $Ni(cod)_2$/2,2`-bpy although glovebox conditions were required to generate the active catalyst.[9] The direct access of amides most frequently employs the stoichiometric $AlMe_3$[7c] procedure developed by Evans although many reports access the amides indirectly through the carboxylic acid prepared using the $LiOH/H_2O_2$

protocol. Since the *N*-acyloxazolidinone motif is utilized so frequently – the hydrolytic conditions alone appearing in the literature nearly 2,000 times – and on significant scale (e.g. > 100 kg),[5e] a general and operationally simple unified strategy to access each chiral esters, amides, and acids from *N*-acyloxazolidinones would be highly desirable. We would like to mention, however, that during the course of our work a report from the Evano group appeared for the direct synthesis of esters, amides and acids from *N*-acyloxazolidinones using similar conditions to those reported here.[10]

■ RESULTS AND DISCUSSION

Development of a broadly applicable and general method for preparation of high value chiral esters. The pressing need for innovation toward the direct transesterification of *N*-acyl oxazolidinones was starkly revealed during the progression of **3** through the clinic as a potential inhibitor of indoleamine 2,3-deoxygenase (IDO)[12] (Table **1**). During synthetic route innovation it became critical to access ester **2** from *N*-acyl oxazolidinone **1**. The most expedient method to access the desired ester appeared to be through a transesterification reaction utilizing conditions originally reported by Evans.[8] It was therefore disappointing to find that initial attempts using these conditions were not promising. A literature search revealed several additional methods for Lewis acid mediated generation of esters from *N*-acyl oxazolidinones had appeared since Evans MgX_2 and $Ti(OBn)_4$ mediated protocols[11] as well as methods for the general transesterification of amides.[13] However, upon a detailed inspection of these methods it was found that their limitations were exceptional. In particular, the existing methods had focused mainly on substrates that were of low synthetic complexity, whose achiral ester products could have either been purchased from commercial suppliers or prepared from the commercially available acid or acid chloride. When these methods were analyzed for complex substrates that produced chiral esters, it was found that the only viable conditions were using 30 mol% $Sm(OTf)_3$[11f] (3 chiral examples) or 100 mol% LaI_3.[11c] Furthermore, only in the latter case was tolerance outside of methanol reported and ee values of the

Table 1. Initial Investigation of Known Esterification Protocols to a Pharmaceutical Intermediate[a]

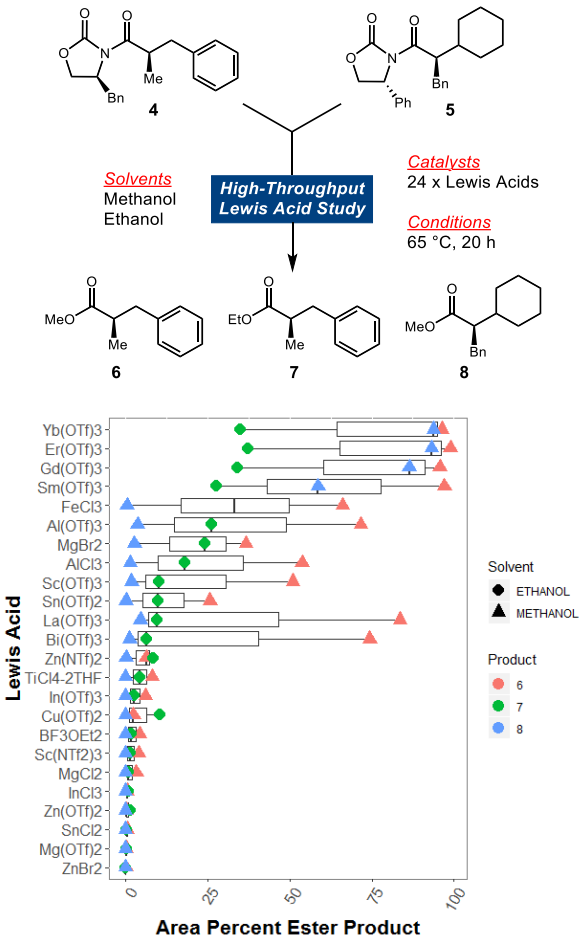


Entry	*Catalyst*	*Solvent*	*In Process Yield*	*Selectivity*
1	MeOMgCl	MeOH	< 1%	< 0.05
2	$Mg(OMe)_2$	THF/MeOH (1:1)	1.5%	< 0.05
3	$Mg(O\textit{t}\text{-}Bu)_2$	EtOH/THF (1:1)	0%	< 0.05
4	$MgCl_2$	EtOH	< 1%	< 0.05
5	$MgBr_2$	EtOH	< 1%	< 0.05
6	$Ti(OEt)_4$	EtOH	5.3%	0.21

[a]Acyl oxazolidinone (1.0 equiv), 150 mol% catalyst at 60 °C. Selectivity refers to the ratio of the desired ester to the undesired oxazolidinone ring-opened hydroxyamide.

product esters provided. The difficulty associated with direct Lewis acid catalyzed esterification of complex enantioenriched *N*-acyl oxazolidinones substrates was exemplified yet again by the Evano report where Evans' alkylation and aldol products were found not to be viable substrates as the hydroxyamides were afforded as the predominant products.[10] A similar survey of the literature found that the direct amidation protocols were even more limited and that access to acids relies on the use of super stoichiometric peroxide. Therefore, it was pertinent for the progression of a clinical asset that this longstanding problem of *N*-acyl oxazolidinone diversification be addressed sufficiently.

Table 2. High-Throughput Lewis Acid Screen[a,b,c]



[a]All reactions were screened at 50 mol% catalyst loading except for lanthanides that were screened at 10 mol% catalyst loading. [b]The reaction performance was determined by UHPLCMS area percent at a single 20 h time point, [c]Substrate **5** was only surveyed in MeOH as the solvent.

The criteria for a successful method would include the use of bench stable reaction components, wide substrate scope, high chemoselectivity for substitution at the acyclic *N*-acyl carbonyl[7b] and minimal risk of epimerization. Therefore, the identification of a broadly applicable Lewis acid catalyst for the direct synthesis of esters from *N*-acyl oxazolidinones was initiated through the use of high-throughput experimentation (HTE). It was envisioned that a successful catalytic esterification method would be readily translated to the analogous transamidation and that a single flask protocol to access the carboxylic acids could be achieved via hydrolysis.

A multivariable approach was undertaken that examined each of the critical factors previously outlined for a successful method to accelerate the identification of globally optimized reaction conditions using HTE.[14] A panel of 24 Lewis acid catalysts were examined against two substrates featuring different chiral auxiliaries and acyl components in both methanol and ethanol solvents (Table **2**).

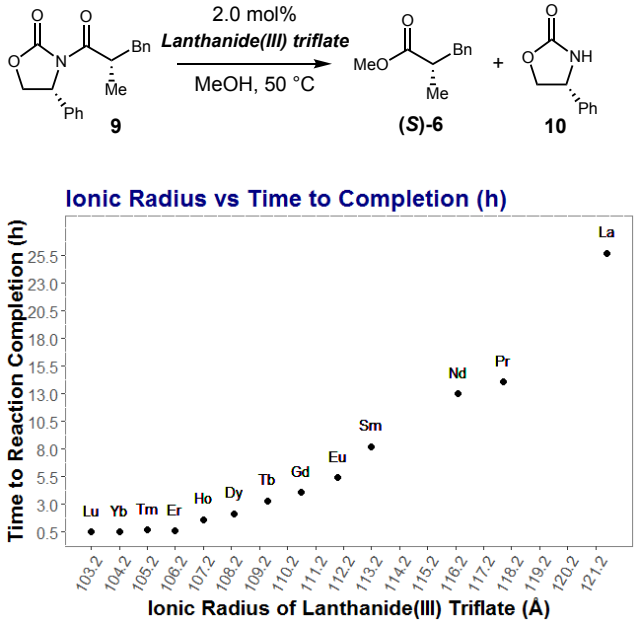
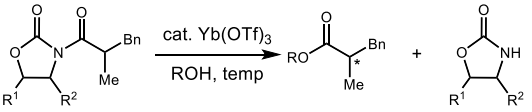


Figure 2. Examination of the effect of lanthanide ionic radius on time to reaction completion.

Many common Lewis acids such as $Al(OTf)_3$, $AlCl_3$, $Bi(OTf)_3$, $FeCl_3$, and $MgBr_2$ provided a significant amount of the desired methyl ester product **6** from oxazolidinone **4**, but were ineffective for the generation of the corresponding ethyl ester product **7**. These catalysts were similarly ineffective for generating the methyl ester **8** from the more sterically demanding substrate **5**. In these instances the reactions formed significant quantities of hydroxyamide side product resulting from solvent attack at the oxazolidinone carbonyl.[7b,15–16] Several lanthanide catalysts, $Gd(OTf)_3$, $Er(OTf)_3$, and $Yb(OTf)_3$, afforded high levels of methyl esters **6** and **8** from *N*-acyl oxazolidinones **4** and **5**, respectively, while ethyl ester product **7** was delivered in up to 37 area percent by UHPLCMS analysis. Although the conversion to the ethyl ester was low, the results were encouraging as these catalysts afforded the highest mean results across the HTE array. Additionally, these catalysts did not produce any significant side products such as the hydroxyamide that were observed with other Lewis acids. The utilization of a multivariable HTE strategy provided clear differentiation of catalyst performance and engendered high confidence for the identification a broadly applicable catalytic system moving forward.

The data from the Lewis acid HTE demonstrated a trend of increasing reactivity across the row of lanthanides ($La(OTf)_3$ < $Sm(OTf)_3$ < $Gd(OTf)_3$ = $Er(OTf)_3$ = $Yb(OTf)_3$). To gain additional insight into this trend the methanolysis of **9** was examined against the complete set of lanthanide(III) triflates. Kinetic data were collected for each catalyst at 2 mol% catalyst loading over the course of 24 h and a regression model was constructed to determine the time of reaction completion. When the kinetic data were analyzed against literature data for lanthanide ionic radii[17] it was observed that the catalysts with smallest ionic radii $Er(OTf)_3$ (106.2 Å), $Tm(OTf)_3$ (105.2 Å), $Yb(OTf)_3$ (104.2 Å), and $Lu(OTf)_3$ (103.2 Å) reached completion in 0.60 h, 0.66 h, 0.50 h, & 0.50 h, respectively. In contrast, the catalyst with the largest ionic radius, $La(OTf)_3$ (121.6 Å) required a reaction time of 25.70 h (Figure **2**). Of the four lanthanide catalysts that afforded the shortest reaction times, $Yb(OTf)_3$ was of particular interest for further optimization due its broad utility as a Lewis acid catalyst[18] and its known propensity for catalyzing reactions involving amines as the corresponding transamidation would be subsequently investigated. It is noteworthy that $Yb(OTf)_3$ has been identified as an effective catalyst for other transformations using oxazolidinones.[19]

Table 3. Auxiliary and Alcohol Scope[a]



9: R^1/R^2 = *H/R-Ph*
4: R^1/R^2 = *H/S-Bn*
12: R^1/R^2 = *H/R-i-Pr*
13: R^1/R^2 = *R-Ph/S-Me*

6: *R* = *Me*
7: *R* = *Et*
14: *R* = *Allyl*
15: *R* = *n-Bu*

10: R^1/R^2 = *H/R-Ph*
16: R^1/R^2 = *H/S-Bn*
17: R^1/R^2 = *H/R-i-Pr*
18: R^1/R^2 = *R-Ph/S-Me*

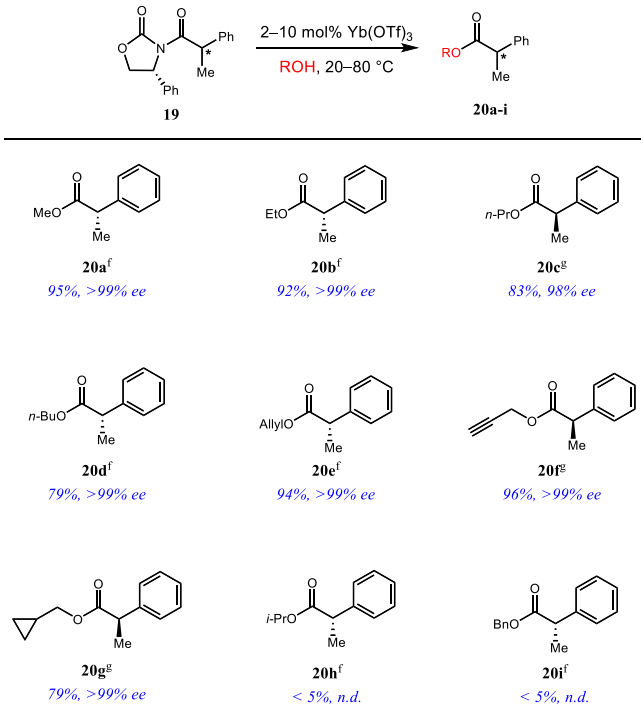
Entry	Starting Material	R	$Yb(OTf)_3$ (mol%)	Temp. (°C)	Product	Yield % (ee)
1	**9**	Me	2	20	***S*-6**	97% (>99%)
2	**9**	Me	2	60	***S*-6**	99% (>99%)
3	**9**	Et	10	75	***S*-7**	88% (>99%)
4	**9**	Allyl	10	80	***S*-14**	99% (>99%)
5	**9**	*n*-Bu	10	80	***S*-15**	94% (>99%)
6	**4**	Me	2	20	***R*-6**	97% (>99%)
7	**4**	Me	2	60	***R*-6**	87% (>99%)
8	**4**	Et	10	75	***R*-7**	85% (>99%)
9	**4**	Allyl	10	80	***R*-14**	96% (>99%)
10	**4**	*n*-Bu	10	80	***R*-15**	94% (>99%)
11[b]	**12**	Me	2	60	***S*-6**	87% (93%)
12[b]	**12**	Et	10	75	***S*-7**	86% (93%)
13[b]	**12**	Allyl	10	80	***S*-14**	93% (93%)
14[b]	**12**	*n*-Bu	10	80	***S*-15**	79% (92%)
15[c]	**13**	Me	2	60	***R*-6**	99% (98%)
16[c]	**13**	Et	10	75	***R*-7**	89% (98%)
17[c]	**13**	Allyl	10	80	***R*-14**	92% (98%)
18[c]	**13**	*n*-Bu	10	80	***R*-15**	82% (98%)
19[d]	**4**	Me	0	60	***R*-6**	0% (n.d.)
20	**4**	Me	0	60	***R*-6**	0% (n.d.)

[a]Acyl oxazolidinone (1.0 equiv), ROH (30 mL/g), 2–10% $Yb(OTf)_3$, 20–80 °C; isolated yields of chromatographically pure products are displayed, unless otherwise noted. [b]The de of the input material was 93%. [c] The de of the input material was 98%. [d]Reaction was performed with 5 mol% TfOH and analyzed at 24 h by UHPLCMS.

The general utility of the $Yb(OTf)_3$ catalytic protocol was gauged through a systematic study of the solvolysis of four chiral *N*-acyl oxazolidinones, featuring four common chiral auxiliaries, with four alcohols (Table **3**). It was observed that the methanolysis of all four auxiliaries occurred readily at 60 °C with 2 mol% $Yb(OTf)_3$ (87–99%, Entries 2, 7, 11, 15) and even milder conditions at 20 °C (97%, Entries 1, 6). Moving to longer chain alcohols, it was found that ethanolysis required 10 mol% catalyst and 75 °C to achieve full conversion (85–88%, Entries 3, 8, 12, 16). Similarly, solvolysis with allyl alcohol (92–99%, Entries 4, 9, 13, 17) and *n*-butanol (79–99%, Entries 5, 10, 14, 18) could be achieved with 10 mol% catalyst at 80 °C. In all cases, (Entries 1–18) no erosion of stereochemistry was observed. Control experiments that were performed using 5 mol% TfOH in the absence of $Yb(OTf)_3$ (Entry 19) as well as in absence of both the acid and the Lewis acid (Entry 20) did not show any detectable ester product.

To further examine the scope of this method both the alcohol component and impact of the oxazolidinone stereochemistry were

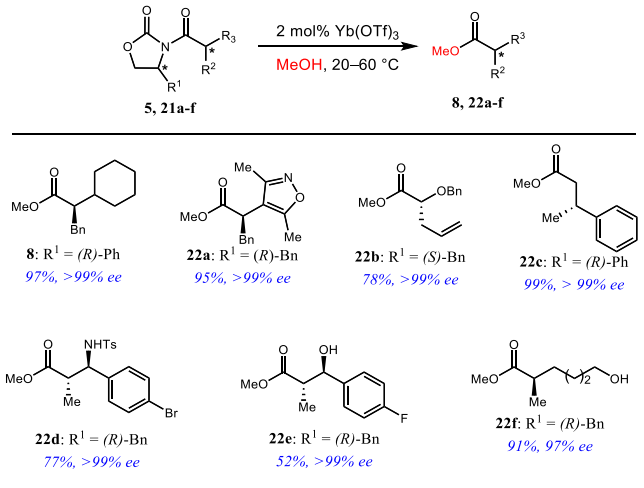
Table 4. Alcohol Scope[a]



[a]Acyl oxazolidinone (1.0 equiv), ROH (30 mL/g), isolated yields of chromatographically pure products are displayed, unless otherwise noted. [b]2 mol% $Yb(OTf)_3$ at 20 °C. [c]2 mol% $Yb(OTf)_3$ at 60 °C; [d]10 mol% $Yb(OTf)_3$ at 75 °C. [e]10 mol% $Yb(OTf)_3$ at 80 °C. [f]Utilized (*R,S*)-**19**. [g]Utilized (*R,R*)-**19**.

explored in greater detail (Table **4**). A series of enantioenriched phenylacetic esters were prepared from a selection of alcohols to give the methyl (**20a**, 95%), ethyl (**20b**, 92%), *n*-propyl (**20c**, 83%), *n*-butyl (**20d**, 79%), allyl (**20e**, 94%), propargyl (**20f**, 96%), and cyclopropylmethyl (**20g**, 79%) ester products in high yield with no detectable stereoerosion. Additionally, the products from this series (**20a–g**) were prepared from both diastereomers of the *N*-acyl oxazolidinone, indicating there was no detectable matched/mismatched phenomenon. Further exploration of the alcohol component revealed isopropanol, and benzyl alcohol failed to deliver appreciable amounts of the ester products **20h**, and **20i**, respectively, giving the undesired hydroxyamide side product.

Table 5. Scope of the Acyl Component[a]



[a]Acyl oxazolidinone (1.0 equiv), ROH (30 mL/g), isolated yields of chromatographically pure products are displayed, unless otherwise noted. [b]Reaction was performed at 20 °C. [c]Reaction was performed at 60 °C.

Assessment of the substrate scope with respect to the acyl component was conducted using a diverse set of enantioenriched substrates (Table **5**). The method was amenable to sterically demanding substrates such as **5** to produce methyl ester **8**, which was noteworthy as many of the surveyed Lewis acids were ineffective for this substrate (Table **2**). Heteroaryl substrates were tolerated as shown by the isolation of isoxazole ester **22a.** Glycoloxy ethers, a common *N*-acyl oxazolidinone modality accessible through glycolate alkylation,[1b] were readily translated to the corresponding ester, such as glycoloxy ester **22b**.The preparation of methyl ester **22c** bearing a β-stereocenter was also observed to be highly efficient. Both β-amino and β-hydroxy substrates were able to deliver methyl esters **22d** and **22e**, respectively. These two results also demonstrate the tolerance of aryl bromides and fluorides to the reaction as reflected by the yields for these methyl esters. Methyl ester **22f** was obtained from the corresponding *N*-acyl oxazolidinone protected as the primary TBS ether, demonstrating that acid labile functional groups may be impacted.

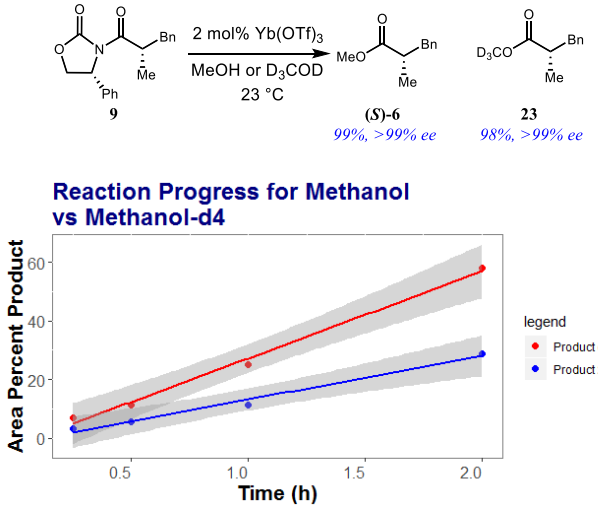


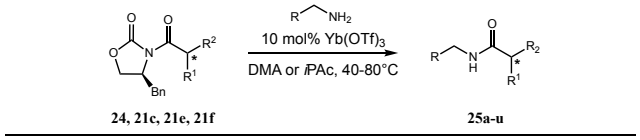
Figure 3. Examination of kinetic isotope effect

The nature of the catalytic species was examined spectroscopically to gain insight into the mechanism of *N*-acyl oxazolidinone solvolysis. From these experiments it was observed that triflic acid (1178 cm^{-1} by IR and -78 ppm by ^{19}F NMR) was generated instantaneously upon exposure of $Yb(OTf)_3$ to methanol. These results were consistent with previous studies suggesting that lanthanide alkoxides were the true catalytic species in lanthanide triflate mediated alcoholyses.[20] However, as was previously demonstrated, triflic acid itself did not appear to be catalytically active (Table **3**, Entry 19). Additionally, experiments measuring the rates of conversion of *N*-acyl oxazolidinone **9** to the methyl and d^3-methyl esters **6** and **23** with methanol and d^4-methanol, respectively, showed a kinetic isotope effect of 2.1, suggesting proton transfer in the rate determining step (Figure **3**).[21] Although kinetically slower, the d^4-methanol reacted efficiently to give d^3-methylester **23** in 98% yield on 2 mmol scale.

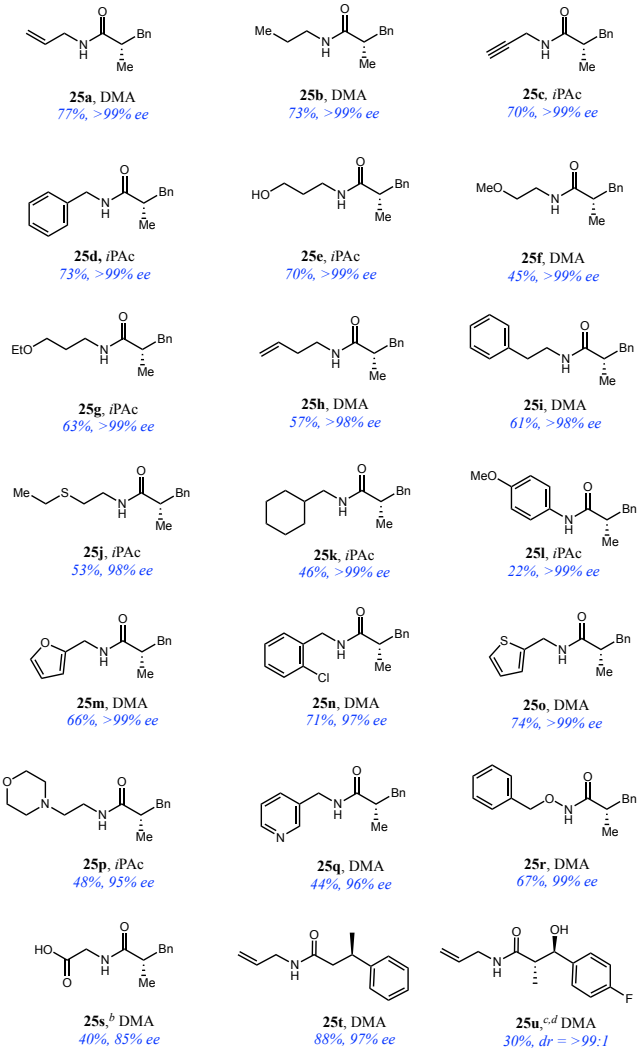
The initial HTE effort lead to the identification of $Yb(OTf)_3$ as a suitable catalyst for the esterification of a broad spectrum of complex chiral *N*-acyl oxazolidinone substrates. The combined knowledge from the lanthanide ionic radius study and the investigation into the catalytic species and mechanism illustrated that the unique characteristics of $Yb(OTf)_3$ provided that it was an optimal catalyst for these challenging substrates. With the goal of delivering a unified strategy for the synthesis of each chiral esters, amides, and acids, the synthesis of chiral amides with this system was initiated.

Development of a protocol for the synthesis of chiral amides. The aminolysis of chiral *N*-acyloxazolidinones to access enantioenriched chiral amides represents one of the most direct synthetic approaches to these valuable building blocks.[22] Given the success with alcohols under Yb-catalysis, it was envisioned that a complementary method using amines might be plausible. From the onset, however, it was recognized that the higher Lewis basicity of amines might negatively attenuate the catalytic activity of the Yb-catalyst.

Table 6. Scope of the Amine Component[a]



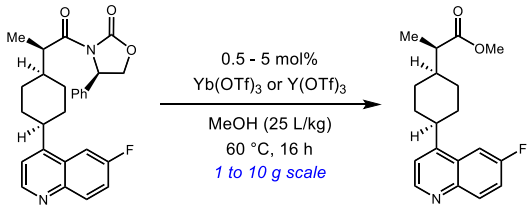
24, 21c, 21e, 21f — 25a-u



[a]Isolate yields reported. [b]Product was isolated as the methyl ester after treatment of the crude reaction mixture (TMSCl/MeOH). [c](*R*)-enantiomer of the Evans' chiral auxillary was used in this case. [d]Isolated as the TBDMS-protected alcohol.

Furthermore, the large excess of the amine nucleophile that could potentially promote racemization of the amide product was a point of concern. Nonetheless, it was envisioned that the increased nucleophilicity of amines compared to alcohols would counterbalance these concerns. With this in mind, initial efforts focused on the identification of compatible solvents that would assist in minimizing the equivalents of amine necessary for high conversion while minimizing the potential for racemization. It was found that both *N,N*-dimethylacetamide (DMA) and isopropyl acetate (*i*PAc) were suitable solvents for the aminolysis reaction allowing for the use of three equivalents of amine and 10 mol % of $Yb(OTf)_3$ to obtain the enantioenriched amides in high yields under relatively mild reaction conditions (Table **6**). A broad range of primary amines has been successfully employed with excellent functional group tolerability, chemoselectivity (e.g., **25e**) and stereoretention. Even anilines proved successful under these conditions (**25l**), albeit

Table 7. Application of the Esterification Protocol to a Pharmaceutical Intermediate[a]



1 — 2

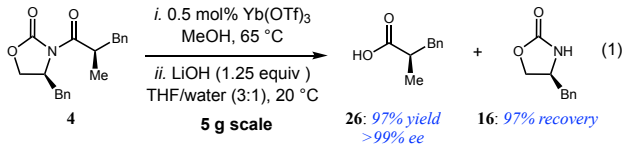
Entry	*Catalyst*	*Co-Catalyst*	*mol% Cat./Co-Cat.*	*Solvent*	*Yield*[a]	*Selectivity*[b]
1[c]	$Yb(OTf)_3$	None	2.0/n.a.	MeOH	60%	1.8:1
2[d]	$Yb(OTf)_3$	None	2.0/n.a.	MeOH	93%	12.9:1
3[c]	$Yb(OTf)_3$	TfOH	2.0/4.0	MeOH/TMOF (3:1)	92%	11.7:1
4[c]	$Y(OTf)_3$	TfOH	2.0/4.0	MeOH/TMOF (3:1)	94%	15.1:1
5[c]	None	None	n.a./n.a.	MeOH/TMOF (3:1)	< 1%	n.a.
6[c]	None	TfOH	n.a./4.0	MeOH/TMOF (3:1)	< 1%	n.a.
7[e]	**$Y(OTf)_3$**	**TfOH**	**0.5/1.0**	**MeOH/TMOF (3:1)**	**93%**	**14.1:1**
8[f]	**$Y(OTf)_3$**	**TfOH**	**2.0/4.0**	**MeOH/TMOF (3:1)**	**95%**	**16.7:1**

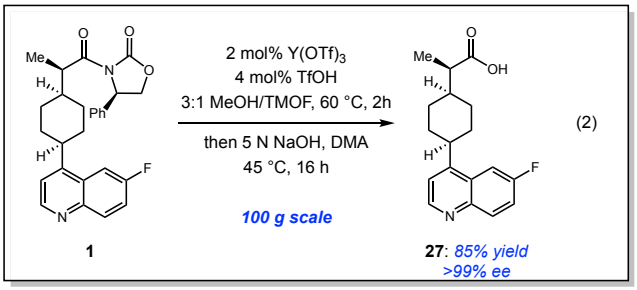
[a] Solution yields as determined by HPLC method calibrated against a reference standard of the product **2** unless otherwise specified. [b]The selectivity refers to the ratio of product **2** to the oxazolidinone ring opened products. [c]The starting material was the mono-hydrate (1.5 wt% water), 1 g scale. [d]The starting material was the anhydrous form, 1 g scale. [e]Reaction was run on 10 g scale with **1**-monohydrate. [f]Isolated yield on 10 g scale from **1**-monohydrate.

in lower yields that can be attributed to the decreased nucleophilicity of these substrates. Additional examples worth highlighting include the success with glycine as the nucleophile (**25s**) with potential implications towards peptide synthesis and the extension to *O*-alkyl hydroxylamines as in **25r** that have served as synthetic precursors towards vasopeptidase inhibitors as well as reverse hydroxamate inhibitors of Bone Morphogentic Protein 1 (BMP1).[23] In contrast to the mild catalytic reaction conditions used here for hydroxylamines, previous methods have relied on the use of pyrophoric $AlMe_3$ to effect the same transformation.

During the course of the study with amine nucleophiles, several limitations were discovered that were worth discussion. First, primary amines with α-substitution (e.g., α-methylbenzylamine, and cyclohexylamine) failed to provide any of the corresponding chiral amide. Likewise, secondary amines such as diethylamine also proved ineffective in the aminolysis reaction even at elevated reaction temperatures (80 °C). These failures were attributed to the increased steric bulk around these nucleophiles in combination with the intrinsic steric bulk of the starting chiral *N*-acyloxazolidinones that impeded product formation. However, it is worth emphasizing that more forcing conditions with these nucleophiles may promote product formation but the central focus was to demonstrate general substrate scope under practical, scalable reaction parameters.

Development of an optimized system for the multi-gram scale synthesis of a pharmaceutical intermediate. The protocol for the transesterification of *N*-acyl oxazolidinones had shown a broad tolerance for variation in the structure of the alcohol component and substitution on the *N*-acyl oxazolidinone substrate. Additionally, the experimental evidence that ionic radius was a reliable predictor of reaction performance enabled a strong position to develop a highly efficient catalytic system for the preparation of **2**. It was envisioned that the knowledge at hand could be exploited to identify a catalytic system that combined lower cost and process mass intensity (PMI)[24] while maintaining reaction performance and





Scheme 1. One-Pot Synthesis of Carboxylic Acids

robustness. An extensive literature search of Lewis acid catalysts and cost information from several commercial vendors revealed that $Y(OTf)_3$ (ionic radius = 102 Å)[25] would be of interest due to lower cost/kg catalyst ($1,252 vs $1,359)[26] and lower MW (536.11 vs 620.25) compared to $Yb(OTf)_3$, respectively. To test the hypothesis the $Y(OTf)_3$ system was compared to $Yb(OTf)_3$ (Table **7**). Surprisingly, it was found that the initial attempt gave only 60% yield and only 1.8:1 selectivity for the desired methyl ester versus the undesired hydroxyamide side product (Table **7**, Entry 1). After careful consideration it was hypothesized that the key difference could be the water content of the reaction mixture even though anhydrous methanol was utilized. In fact, the material for the initial verification was discovered to be the monohydrate form (1.5 wt% water). To verify the hypothesis a sample of the monohydrate was dried to the anhydrous form and the reaction was conducted in a glovebox. Under these strictly anhydrous conditions it was found that the expected reactivity had been restored (93% yield, 12.9:1 selectivity). The unexpected sensitivity to water presented a significant challenge for process development as the need to utilize anhydrous methanol would drive up processing costs immensely on a commercial scale. A cost-effective and readily implementable solution was thus required.

The water sensitivity issue could potentially be addressed through the addition of a dessicant to remove moisture *in situ* during the reaction (Table **7**). This hypothesis was tested by drying the monohydrate of **1** in plant grade methanol by adding 20 vol% trimethylorthoformate (TMOF) and catalytic triflic acid to sequester the water through the generation of methyl formate and methanol. Under these conditions it was found that the initial reaction stream containing **1**, methanol, and TMOF afforded a Karl Fischer (KF) titration of 0.32 weight% water that was reduced to a measured KF of 39 ppm water after the addition of the catalytic triflic acid. Under these conditions the reaction proceeded as expected (92% yield, 11.7:1 selectivity). With a reliable and robust method to achieve the desired reactivity the reaction was explored using the more cost effective $Y(OTf)_3$ catalyst. Gratifyingly, it was observed that the $Y(OTf)_3$ catalyst system was highly effective, delivering the product in 94% in process yield with slightly improved selectivity over the $Yb(OTf)_3$ system. It was then verified that no background reaction was occurring and the optimal results were demonstrated on 10 g scale to deliver **2** in 93% in process yield using only 0.5 mol% catalyst and in 95% isolated yield utilizing 2 mol% catalyst. The foundational work exploring the critical attributes for catalyst performance yielded a cheaper, greener, and more robust catalytic system.[27]

Development of a protocol for the synthesis of carboxylic acids. A primary objective for pursuing this work was to identify an operationally simple protocol for the preparation of acids from the chiral esters using mild and safe reaction conditions. This transformation was of particular interest as derivatization to chiral carboxylic acids was found to be the most common transformation of enantioenriched oxazolidinones (Figure **1**). Toward that end, a one-pot esterification/hydrolysis protocol was demonstrated on 5 g scale (15.4 mmol) as *N*-acyl oxazolidinone **4** was converted in a single flask to the corresponding carboxylic acid **26** (97% yield, > 99% ee) with 97% recovery of the chiral auxiliary **16** with 0.5 mol% $Yb(OTf)_3$ (Scheme 1, eq 1). The only additional operation needed to accomplish this transformation was a solvent exchange from methanol to THF followed by the addition of aqueous lithium hydroxide. Furthermore, it was shown that a one pot protocol could be employed to effect the net hydrolysis of **1** on 100 g scale to afford carboxylic acid **27** (Scheme 1, eq 2). Many catalytic processes have derived their value from the use of safe and mild reaction conditions in place of highly reactive ones. The present case was no exception, providing for the use of 2 mol% Lewis acid catalyst and stoichiometric hydroxide as an alternative to highly energetic peroxide based system.[28]

■ CONCLUSION

In summary, a Lewis acid-catalyzed protocol has been developed for the direct conversion of enantioenriched *N*-acyl oxazolidinones to their corresponding esters and amides using $Yb(OTf)_3$ while preserving the integrity of the adjacent stereocenters. A multivariable approach to HTE was utilized to rapidly identify a globally optimized catalyst system. The resulting chemistry addressed a longstanding problem for the diversification of the products of reliable and widespread auxiliary based synthetic methods to an array of complex enantioenriched esters, amides, and carboxylic acids. The method was applied to the one-pot synthesis of a complex pharmaceutical intermediate on 100 g scale using equally efficient $Y(OTf)_3$. Future work will be aimed at additional mechanistic understanding and optimizing the catalyst framework to increase efficiency and reaction scope.

■ EXPERIMENTAL SECTION

General Information. Standard benchtop techniques were employed for handling air-sensitive reagents. NMR spectra were recorded on a 400 or 500 MHz spectrometer. The chemical shifts (δ) and coupling constants (*J*) are reported in ppm and Hz, respectively. Analytical thin-layer chromatography (TLC) was performed on TLC silica gel plates (0.25 mm) pre-coated with a fluorescent indicator. Visualization of the TLC plates was effected with ultraviolet light and ceric ammonium molybdate (CAM) stain with heat. Chiral HPLC analysis was carried out on an HPLC with a multiple wavelength detector by commercial chiral columns. HRMS samples were run on the Thermo LTQ-Orbitrap with Acquity Classic inlet.

General Procedure for Coupling Carboxylic Acids with Oxazolidinones. To a nitrogen flushed round bottomed flask, with active nitrogen flow, was added oxazolidinone (1.0 equiv) and DMAP (0.05 equiv) followed by anhydrous dichloromethane (10 mL/g). The reaction mixture was cooled with a room temperature water bath followed by the addition of the carboxylic acid (1.3 equiv) and the drop-wise addition of *N*,*N*'-diisopropylcarbodiimide (1.15 equiv) at a rate sufficient to maintain the internal temperature below 30 °C. The reaction mixture was then stirred overnight at room temperature. Solids were removed via filtration then the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography.

General Procedure for Alkylation of *N*-Acyl Oxazolidinones. To a nitrogen flushed 3-neck round bottomed flask with active nitrogen flow was added oxazolidinone (1.0 equiv) followed by anhydrous THF (10.0 mL/g). The solution was cooled to -78 °C then treated with NaHMDS 40 wt% solution in THF (1.22 equiv) at a rate sufficient to keep the internal temperature below -70 °C. The reaction mixture was aged for 15 minutes. then treated with alkyl halide (1.20 equiv) at a rate sufficient to keep the internal temperature below -70 °C. The reaction was aged 1 h at -78 °C, warmed to -40 °C and aged for 1 h, then warmed to 0 °C and quenched by the addition of 23 wt% ammonium chloride in water (10 mL/g) and diluted with 2-methyltetrahydrofuran (20 mL/g). The aqueous layer was removed and the organic layer was washed 2 x aqueous 0.25 M KOH solution (10 mL/g), 1 x 23 wt% ammonium chloride in water (10 mL/g), then 1 x saturated aqueous sodium bicarbonate solution (10 mL/g). The isolated organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography unless otherwise specified.

Experimental Procedure for Esterification HTE. In a glovebox, solid Lewis acids (16.1 μmol; 3.21 μmol for Lanthanides) were transferred to 1.0 mL vials in a deep well plate. Substrate **5** (20 mg, 32.1 μmol) was transferred to the appropriate vials followed by a solution of biphenyl in MeOH (600 μL of a 5.35 μM solution). A stock solution of substrate **4** and biphenyl (53.5 μM **4**, 5.35 μM biphenyl) in both MeOH (600 μL) and EtOH (600 μL) were transferred to their respective vials. The liquid Lewis acid (16.1 μmol) was transferred to the appropriate vials. The plate was sealed, heated to 65 °C, and aged for 20 h. The plate was cooled and the reactions were sampled for UPLCMS analysis.

Experimental Procedure for Lanthanide Kinetic Study. Procedure: In a glovebox, solid Lewis acids (9.7 μmol) were transferred to 8.0 mL vials. Substrate **9** (150 mg, 485 μmol) and biphenyl (7.5 mg, 48.5 μmol) were transferred to the appropriate vials as a stock solution in MeOH (4500 μL). The reactions were set into a pre-heated 50 °C deep-well stirring block and sampled at 0.5, 1, 2.5, 4, 6, 9, and 24.5 h into 4:1 acetonitrile/water diluent. Reaction progress was determined by UHPLCMS analysis using a Supelco Ascentis Express C18 2.7 μm 2.1 x 50 mm column at 40 C (Solvent A/B = 0.05% TFA in acetonitrile/water (5:95)/0.05% TFA in acetonitrile/water (95:5) at 0.8 mL/min; %B = 0 min 0%, 2.5 min 100%, stop time = 3.0 min).

General Procedure for Alcoholysis of *N*-Acyl Oxazolidinones. On the benchtop, 0.5–10 mol% $Yb(OTf)_3$ was added to a 40 mL vial followed by anhydrous methanol (30 mL/g). The vial was sealed with a pressure relief cap and warmed to the desired temperature for 30 min (room temperature or 60 °C). The catalyst solution was removed from the heat for 10 min then treated with the desired substrate in one portion and warmed to the desired temperature (23 – 60 °C). If the substrate is an oil, a solution can be prepared in anhydrous methanol (15 mL/g) and added to the catalyst solution (15 mL/g). When the reaction was deemed complete by HPLC (or UHPLCMS) analysis, the solvent was carefully removed under reduced pressure and the crude mixture was purified by silica gel chromatography (10–80% CH_2Cl_2/hexanes unless otherwise specified).

Parallel Kinetic Isotope Experiment

$Yb(OTf)_3$ (25 mg, 0.040 mmol) was dissolved in CD_3OD (18.0 mL, 100 mass%) and methanol (18.0 mL, 99.5 mass%) in separate vials then warmed to 60 °C for 30 min. The catalyst solution was then allowed to cool to room temperature followed by the addition of **9** (0.62 g, 2.0 mmol) all at once to each catalyst solution. Each reaction mixture was sampled at 0.25, 0.5, 1, 2, 6, and 8 h and analyzed by HPLC.

General Procedures for the Aminolysis of *N*-Acyl Oxazolidinones. Procedure A: On the benchtop, 10 mol% $Yb(OTf)_3$ was added to a 5 mL vial with a stir bar, sealed with a pressure relief cap and purged with N_2 for 5 min followed by the addition of corresponding amine (3.0 equiv) and anhydrous DMAc or *i*PAc (5M). The solution was left stirring for 30 minutes at the desired temperature (40 or 80 °C). The solution was removed from the heat then treated with the desired substrate (1.0 equiv) in one portion and warmed back to the desired temperature (40 or 80°C). When the reaction was deemed complete by HPLC analysis, the crude mixture with solvent was purified by silica gel chromatography (10–80% CH_2Cl_2/hexanes or EtOAc/hexanes).

Procedure B: On the benchtop, 10 mol% $Yb(OTf)_3$ was added to a 5 mL vial with a stir bar, sealed with a pressure relief cap and purged with N_2 for 5 min followed by the addition of corresponding amine hydrochloride (3.0 equiv), DBU (3.5 equiv), and anhydrous DMAc or *i*PAc (5M). The solution was left stirring for 30 min at desired temperature (40 or 80 °C). The solution was removed from the heat then treated with the desired substrate (1.0 equiv) in one portion and warmed back to the desired temperature (40 or 80°C). When the reaction was deemed complete by HPLC analysis, the crude mixture with solvent was purified by silica gel chromatography (10–80% CH_2Cl_2/hexane or EtOAc/hexanes).

Experimental Data of Substrates.

*(S)-4-benzyl-3-((R)-2-methyl-3-phenylpropanoyl)oxazolidin-2-one, **4***. Prepared according to the general alkylation procedure with purification by silica gel chromatography (0–30 % ethyl acetate/hexanes gradient) to afford **4** in 56% yield (15.5 g, 48.0 mmol) from *(4S)*-4-benzyl-3-propanoyl-oxazolidin-2-one (20.0 g, 85.7 mmol). Spectral data matches that of previously reported.[38] ^{1}H NMR (400 MHz, chloroform-d) δ 7.35–7.18 (m, 8H), 7.11–7.04 (m, 2H), 4.68 (ddt, *J* = 9.2, 7.9, 3.2 Hz, 1H), 4.23–4.08 (m, 3H), 3.21–3.04 (m, 2H), 2.69 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.57 (dd, *J* = 13.4, 9.3 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 3H).

*(R)-3-((R)-2-cyclohexyl-3-phenylpropanoyl)-4-phenyloxazolidin-2-one, (**5**)*. Prepared according to the general acid coupling procedure with purification by silica gel chromatography(5 – 50% ethylacetate/hexanes) to afford (*4R*)-3-(2-cyclohexylacetyl)-4-phenyl-oxazolidin-2-one in in 92% yield (22.6 g, 78.5 mmol) as a white solid starting from (*4R*)-4-phenyloxazolidin-2-one (13.60 g, 83.35 mmol). ^{1}H NMR (400 MHz, chloroform-d) δ 7.42–7.27 (m, 5H), 5.44 (dd, *J* = 8.8, 3.8 Hz, 1H), 4.69 (t, *J* = 8.8 Hz, 1H), 4.27 (dd, *J* = 9.0, 3.7 Hz, 1H), 2.88 (dd, *J* = 16.0, 6.2 Hz, 1H), 2.76 (dd, *J* = 16.0, 7.5 Hz, 1H), 1.87–1.72 (m, 1H), 1.70–1.57 (m, 5H), 1.29–1.06 (m, 3H), 1.06–0.88 (m, 2H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 172.1, 153.7, 139.2, 129.1, 128.7, 125.9, 69.8, 57.6, 42.7, 34.2, 33.0, 32.9, 26.1, 26.1, 26.0. (*R*)-3-((R)-2-cyclohexyl-3-phenylpropanoyl)-4-phenyloxazolidin-2-one, (**5**) was prepared according to the general alkylation procedure starting from (4*R*)-3-(2-cyclohexylacetyl)-4-phenyloxazolidin-2-one (7.0 g, 24.35 mmol). The isolated crude product was dissolved in EtOAc (65 mL) at 60 °C and treated dropwise with heptane (50 mL) over 20 min at 60 °C. The stirring was halted and the solution was allowed to cool to 23 °C over 2 h and held for 3 days at 23 °C to give white crystals. The solids were isolated by filtration to afford **5** (6.9 g, 17.78 mmol) in 73% yield. ^{1}H NMR (400 MHz, chloroform-d) δ 7.31–7.08 (m, 6H), 7.08–6.99 (m, 2H), 6.78–6.71 (m, 2H), 5.38 (dd, *J* = 8.6, 3.8 Hz, 1H), 4.58 (t, *J* = 8.7 Hz, 1H), 4.36 (ddd, *J* = 11.2, 7.0, 4.3 Hz, 1H), 4.07 (dd, *J* = 8.8, 3.8 Hz, 1H), 2.95 (dd, *J* = 13.4, 4.0 Hz, 1H), 2.81 (dd, *J* = 13.4, 11.4 Hz, 1H), 1.96 (br d, *J* = 12.1 Hz, 1H), 1.86–1.64 (m, 5H), 1.35–1.09 (m, 5H); ^{13}C{H} NMR (100 MHz, chloroform-d) δ 175.2, 153.3, 139.3, 138.7, 129.0, 128.9, 128.3, 127.9, 125.9, 125.2, 69.4, 57.6, 49.4, 41.2, 35.4, 30.8, 29.9, 26.3; IR (film) ν_{max} 3034, 2928, 2848, 1698, 1493, 1454, 1380, 1302, 1240, 1203, 1188 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{28}NO_3$ 378.2064; found 378.2067; $[\alpha]^D_{20}$ -81.5 (c 0.850, $CHCl_3$); mp: 152.6 °C (DSC).

*(R)-3-((S)-2-methyl-3-phenylpropanoyl)-4-phenyloxazolidin-2-one, (**9**)*. Prepared according to the general alkylation procedure with purification by silica gel chromatography (0–30 % ethyl acetate/hexanes gradient) to afford **9** in 50% yield (7.06 g, 22.8 mmol) as a white solid starting from (*R*)-4-phenyl-3-propionyloxazolidin-2-one (10 g, 45.61 mmol). Recrystallized after column chromatography from 100 mL 1:1 PhMe:heptane at 60 °C then cooled to room temperature. Isolated via filtration. ^{1}H NMR (400 MHz, chloroform-d) δ 7.36–7.29 (m, 3H), 7.25–7.18 (m, 3H), 7.16–7.08 (m, 4H), 5.44 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.68 (t, *J* = 8.8 Hz, 1H), 4.32–4.12 (m, 2H), 3.06 (dd, *J* = 13.4, 7.1 Hz, 1H), 2.52 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.14 (d, *J* = 6.6 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 176.0, 153.4, 138.9, 138.8, 129.2, 129.1, 128.4, 128.3, 126.2, 125.7, 69.7, 57.7, 39.7, 39.5, 16.3; IR (film) ν_{max} 3061, 3031, 2972, 2922, 2878, 1760, 1703, 1450, 1389, 1180 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{20}NO_3$ 310.1438; found 310.1451; $[\alpha]^D_{20}$ -15.5 (c 0.787, $CHCl_3$); mp: 121.5 °C (DSC).

*(R)-4-isopropyl-3-((S)-2-methyl-3-phenylpropanoyl)oxazolidin-2-one, (**12**)*. Prepared according to the general alkylation procedure with purification by silica gel chromatography (0 – 30% ethylacetate/hexanes) to afford **12** in 60% yield (8.92 g, 32.41 mmol, 93% de) as a white solid starting from (*R*)-4-isopropyl-3-propionyloxazolidin-2-one (10.0 g, 54.02 mmol). Spectral data matches that of previously reported.[39] ^{1}H NMR (400 MHz, chloroform-d) δ 7.27–6.81 (m, 5H) 4.27 (dt, *J* = 8.3, 3.4 Hz, 1H), 4.11–3.93 (m, 3H), 2.97 (dd, *J* = 13.1, 7.3 Hz, 1H), 2.47 (dd, *J* = 13.1, 7.6 Hz, 1H), 2.00 (dtd, *J* = 14.0, 7.0, 3.8 Hz, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.67 (d, *J* = 7.1 Hz, 3H), 0.44 (d, *J* = 6.8 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 176.5, 153.7, 139.2, 129.2, 128.3, 126.3, 63.0, 58.4, 40.2, 39.4, 28.3, 17.9, 16.5, 14.3.

*(4S,5R)-4-methyl-3-((R)-2-methyl-3-phenylpropanoyl)-5-phenyloxazolidin-2-one, (**13**)*. Prepared according to the general alkylation procedure with purification by silica gel chromatography (0–30 % ethyl acetate/hexanes gradient) to afford **13** in 64% yield (9.57 g, 29.6 mmol) as a colorless gum starting from (*4S,5R*)-4-methyl-5-phenyl-3-propionyloxazolidin-2-one (10.79 g, 46.25 mmol). Purified using semi-preparative supercritical fluid chromatography (column: Chiral Technologies OJ-H, 5 µm, 21 mm x 250 mm; mobile phase A: carbon dioxide; mobile phase B: methanol; injections: stacked isocratic at 10 %B; flow: 70 mL/min; backpressure regulation: 100 bar; column temperature: 40 °C; detection: UV at 220 nm). Spectral data matches that of previously reported.[40] ^{1}H NMR (400 MHz, chloroform-d) δ 7.43–7.17 (m, 10H), 5.64 (d, *J* = 7.6 Hz, 1H), 4.83–4.72 (m, 1H), 4.16 (dt, *J* = 8.1, 6.8 Hz, 1H), 3.13 (dd, *J* = 13.4, 6.8 Hz, 1H), 2.66 (dd, *J* = 13.3, 8.0 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 176.4, 152.6, 139.0, 133.3, 129.2, 128.7, 128.6, 128.2, 126.3, 125.6, 78.7, 54.7, 39.8, 39.3, 16.5, 14.4.

*(R)-4-phenyl-3-((S)-2-phenylpropanoyl)oxazolidin-2-one, (**19**)*. Prepared according to the general alkylation procedure with purification by silica gel chromatography (0 – 50% ethyl acetate/hexanes) to afford **19** in 80% combined yield (7.23 g, 24.48 mmol) of diastereomers as white solids starting from (*4R*)-4-phenyloxazolidin-2-one (5.00 g, 30.6 mmol). Spectral data matches that of previously reported.[40] *(R)-4-phenyl-3-((S)-2-phenylpropanoyl)oxazolidin-2-one:* ^{1}H NMR (400 MHz, chloroform-d) δ 7.38–7.19 (m, 6H), 7.19–7.09 (m, 2H), 6.97 (br d, *J* = 7.8 Hz, 2H), 5.49 (br dd, *J* = 9.1, 5.3 Hz, 1H), 5.14 (q, *J* = 6.8 Hz, 1H), 4.68 (br t, *J* = 9.0 Hz, 1H), 4.13 (dd, *J* = 9.0, 5.2 Hz, 1H), 1.44 (d, *J* = 7.1 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 173.7, 153.1, 139.8, 138.2, 128.8, 128.6, 128.4, 128.2, 127.1, 125.8, 69.5, 57.8, 43.8, 18.6. *(R)-4-phenyl-3-((R)-2-phenylpropanoyl)oxazolidin-2-one*: ^{1}H NMR (400 MHz, chloroform-d) δ 7.47–7.24 (m, 10H), 5.35 (dd, *J* = 8.6, 3.3 Hz, 1H), 5.14 (q, *J* = 6.9 Hz, 1H), 4.57 (t, *J* = 8.6 Hz, 1H), 4.23 (dd, *J* = 8.8, 3.3 Hz, 1H), 1.43 (d, *J* = 7.1 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 174.0, 153.2, 140.1, 139.3, 129.2, 128.7, 128.6, 128.2, 127.2, 125.8, 69.7, 58.0, 43.1, 19.4.

*(R)-4-benzyl-3-((R)-2-(3,5-dimethylisoxazol-4-yl)-3-phenylpropanoyl)oxazolidin-2-one, (**21a**)*. Prepared according to the general acid coupling procedure with purification by silica gel chromatography (25–100% ethyl acetate/hexanes) to afford (*R*)-4-benzyl-3-(2-(3,5-dimethylisoxazol-4-yl)acetyl)oxazolidin-2-one in 40% yield (2.97 g, 9.46 mmol) as a white solid starting from (4*R*)-4-benzyloxazolidin-2-one (4.19 g, 23.65 mmol). ^{1}H NMR (400 MHz, chloroform-d) δ 7.42–7.24 (m, 3H), 7.24–7.16 (m, 2H), 4.78–4.65 (m, 1H), 4.38–4.16 (m, 2H), 4.09–4.00 (m, 1H), 4.00–3.92 (m, 1H), 3.29 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.82 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.41–2.34 (m, 3H), 2.23 (s, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 169.4, 166.7, 160.0, 153.5, 134.8, 129.3, 129.0, 127.5, 106.6, 66.5, 55.3, 37.8, 29.4, 11.2, 10.4; IR (film) ν_{max} 3061, 3030, 2998, 2974, 2920, 1769, 1713, 1396, 1384, 1287, 1169 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{19}N_2O_4$ 315.1339; found 315.1345; $[\alpha]^D_{20}$ -70.6 (c 1.12, $CHCl_3$); mp: 131.1 °C (DSC). Prepared according to general alkylation procedure with purification by silica gel chromatography (0–30 % ethyl acetate/hexanes gradient) to afford **21a** in 41% yield (1.32 g, 3.26 mmol) as a white solid starting from (*R*)-4-benzyl-3-(2-(3,5-dimethylisoxazol-4-yl)acetyl)oxazolidin-2-one (2.50 g, 7.95 mmol). ^{1}H NMR (400 MHz, chloroform-d) δ 6.63–6.35 (m, 10H), 4.38–4.28 (m, 1H), 4.02–3.84 (m, 1H), 3.38 (d, *J* = 4.8 Hz, 2H), 2.65 (br dd, *J* = 13.4, 7.1 Hz, 1H), 2.44 (dd, *J* = 13.4, 3.0 Hz, 1H), 2.20 (br dd, *J* = 13.4, 8.6 Hz, 1H), 1.97 (dd, *J* = 13.4, 9.3 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 171.8, 171.2, 167.3,

159.7, 152.7, 138.1, 134.9, 129.4, 129.3, 129.0, 128.5, 127.4, 126.8, 110.0, 65.9, 60.4, 55.6, 41.0, 37.7, 37.6, 21.1, 14.2, 11.3, 10.6; IR (film) ν_{max} 3086, 3061, 3029, 2979, 2920, 2858, 1772, 1694, 1396, 1228 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{25}N_2O_4$ 405.1819; found 405.1812; $[\alpha]^{D}_{20}$ -159.8 (c 0.525, $CHCl_3$); mp: 111.6 °C (DSC).

*(S)-4-benzyl-3-((R)-2-(benzyloxy)pent-4-enoyl)oxazolidin-2-one, (**21b**)*. Prepared according to general alkylation procedure in with purification by silica gel chromatography (10–100% ethyl acetate/hexanes) to afford **21b** in 50% yield (1.29 g, 3.54 mmol) as a colorless gum from ((4*S*)-4-benzyl-3-(2-benzyloxyacetyl)oxazolidin-2-one (2.30 g, 7.07 mmol). Spectral data matches that of previously reported.[43] ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42–7.20 (m, 10H), 5.84 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.23–5.00 (m, 3H), 4.81–4.65 (m, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.46–4.33 (m, 1H), 4.25 (dd, *J* = 8.8, 3.3 Hz, 1H), 4.10 (q, *J* = 5.1 Hz, 1H), 3.02 (br dd, *J* = 13.4, 3.3 Hz, 1H), 2.92 (br dd, *J* = 13.5, 8.0 Hz, 1H), 2.48–2.34 (m, 2H); ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 171.5, 153.2, 138.1, 135.6, 133.8, 129.5, 128.5, 128.2, 127.6, 127.5, 127.0, 117.6, 76.3, 71.0, 66.9, 54.3, 36.8, 36.6.

*(R)-4-phenyl-3-((R)-3-phenylbutanoyl)oxazolidin-2-one, (**21c**)*. Prepared according to the general acid coupling procedure with purification by silica gel chromatography (80–100 % dichloromethane/hexanes gradient)to afford **21c** in 96% yield (1.82 g, 5.88 mmol) as a white solid from (4*R*)-4-phenyloxazolidin-2-one (1.00 g, 6.13 mmol). Spectral data matches that of previously reported.[41] ^{1}H NMR (400 MHz, chloroform-d) δ 7.41–7.16 (m, 10H), 5.31 (dd, *J* = 8.6, 3.5 Hz, 1H), 4.55 (t, *J* = 8.7 Hz, 1H), 4.22 (dd, *J* = 8.8, 3.3 Hz, 1H), 3.48–3.25 (m, 2H), 3.14 (dd, *J* = 15.9, 5.8 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 171.3, 153.7, 145.6, 139.0, 129.1, 128.6, 128.4, 127.0, 126.3, 125.9, 69.9, 57.5, 43.2, 35.9, 22.2.

*N-((1R,2S)-1-(4-bromophenyl)-2-methyl-3-oxo-3-((R)-2-oxo-4-phenyloxazolidin-3-yl)propyl)-4-methylbenzenesulfonamide, (**21d**)*. Sodium bis(trimethylsilyl)amide (2.6 mL, 5.2 mmol, 2.0 M) was added drop-wise to a solution of (*4R*)-4-benzyl-3-propanoyl-oxazolidin-2-one (1.00 g, 4.29 mmol) in THF (15 mL) at -78 °C under nitrogen then stirred for 30 min. *N*-[(4-bromophenyl)methylene]-4-methyl-benzenesulfonamide (1.59 g, 4.70 mmol) in THF (35 mL) was added drop-wise over 10 min, stirred for 2.5 h at -78 °C, then quenched with saturated NH_4Cl (20 mL), extracted with EtOAc (2 x 50 mL), washed with brine (50 mL) then concentrated in vacuo. Purified by semi-preparative supercritical fluid chromatography (column: Chiral Technologies OD-H, 5 µm, 30 mm x 250 mm; mobile phase A: carbon dioxide; mobile phase B: acetonitrile; injections: stacked isocratic at 35 %B; flow: 100 mL/min; backpressure regulation: 100 bar; column temperature: 40 °C; detection: UV at 220 nm) affording the first peak **21d** in 40% yield (987.5 mg, 1.73 mmol) as a colorless gum. ^{1}H NMR (400 MHz, chloroform-d) δ 7.49–7.42 (m, 2H), 7.35–7.21 (m, 5H), 7.13–7.02 (m, 4H), 7.01–6.94 (m, 2H), 6.21–6.06 (m, 1H), 4.72–4.58 (m, 1H), 4.58–4.48 (m, 1H), 4.37–4.23 (m, 1H), 4.23–4.12 (m, 2H), 3.25–3.11 (m, 1H), 2.64–2.51 (m, 1H), 2.39–2.28 (m, 3H), 1.18–1.06 (m, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 174.8, 153.9, 143.2, 137.9, 137.7, 135.1, 131.5, 129.4, 129.2, 128.9, 128.6, 127.3, 126.9, 126.8, 121.6, 66.2, 61.0, 55.7, 42.6, 37.3, 21.3, 15.5, 15.4; IR (film) ν_{max} 3540 (br), 3282 (br), 3062, 3028, 2979, 2922, 1776, 1701, 1489, 1455, 1387, 1340, 1212, 1161 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{27}H_{28}BrN_2O_5S$ 573.0880; found 573.0867; $[\alpha]^{20}_{D}$ -20.4 (c 0.515, $CHCl_3$).

*(R)-4-benzyl-3-((2S,3R)-3-(4-fluorophenyl)-3-hydroxy-2-methylpropanoyl)oxazolidin-2-one, (**21e**)*. To (4*R*)-4-benzyl-3-propanoyl-oxazolidin-2-one (5.10 g, 21.9 mmol), 4-fluorobenzaldehyde (2.5 mL, 23.0 mmol) and $MgCl_2$ (0.21 g, 2.2 mmol) in EtOAc (40.0 mL) at room temperature was added trimethylamine (6.4 mL, 46 mmol) and TMSCl (4.3 mL, 34 mmol). The reaction mixture was then stirred overnight and monitored for completion by TLC and UHPLC-MS. Filtered through a pad of silica gel and rinsed with EtOAc. The filtrate was concentrated in vacuo followed by the addition of MeOH (40 mL). TFA (3.0 mL) was added to the suspension at room temperature and stirred for 1 h. Concentrated in vacuo, triturated with MeOH, washed with MeOH then heptane, and dried in a vacuum oven at 50 °C with a N_2 sweep affording **21e** in 81% yield (6.30 g, 17.62 mmol) as a white solid. ^{1}H NMR (400 MHz, chloroform-d) δ 7.46–7.38 (m, 2H), 7.38–7.26 (m, 3H), 7.22–7.16 (m, 2H), 7.13–7.04 (m, 2H), 4.83 (d, *J* = 8.1 Hz, 1H), 4.76–4.68 (m, 1H), 4.36–4.27 (m, 1H), 4.26–4.15 (m, 2H), 3.22 (dd, *J* = 13.6, 3.3 Hz, 1H), 3.20 (br s, 1H), 2.71 (dd, *J* = 13.4, 9.3 Hz, 1H), 1.11 (d, *J* = 6.8 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 176.4, 162.4 (d, *J* = 246.6 Hz, 1C), 153.5, 137.8 (d, *J* = 2.9 Hz, 1C), 135.1, 129.4, 128.9, 128.3 (d, *J* = 8.1 Hz, 1C), 127.3, 115.4 (d, *J* = 22.0 Hz, 1C), 76.7, 66.0, 55.4, 44.4, 37.6, 14.8; ^{19}F NMR (376 MHz, chloroform-d) δ -114.07 – -114.47 (m, 1F); IR (film) ν_{max} 3487 (br), 3079, 2970, 2940, 2889, 1782, 1682, 1384, 1212 cm^{-1}; HRMS (DCI-CH_4) *m/z*: $[M+H-H_2O]^+$ $C_{20}H_{19}FNO_3$ 340.1349; found 340.1359; $[\alpha]^{20}_{D}$ 10.42 (c 0.787, $CHCl_3$).

*(R)-4-benzyl-3-((R)-6-((tert-butyldimethylsilyl)oxy)-2-methylhexanoyl)oxazolidin-2-one, (**21f**)*. A 500-mL 3-neck round bottom flask was charged with tetrahydrofuran (342 mL) and LiHMDS 1.0 M in THF (107.9 mL, 107.9 mmol, 1.25 equiv) and cooled to -5 °C. To the mixture was added a (*R*)-4-benzyl-3-(6-((tert-butyldimethylsilyl)oxy)hexanoyl)oxazolidin-2-one (34.7 g, 85.7 mmol) dissolved in tetrahydrofuran (100 mL) over 1 h. The reaction mixture aged at -5 °C for 20 min and was then treated with iodomethane (16.0 mL, 257 mmol, 3.0 equiv) dissolved in tetrahydrofuran (30 mL) dropwise over 45 min at -5 °C. The reaction mixture aged for 45 min at -5 °C and was determined to be complete by HPLC analysis. A 0.5 M aqueous ammonium chloride solution (171 mL; 682 mmol) was added to the reaction mixture and the heterogeneous mixture was warmed to 23 °C. To the mixture was added water (30 mL) and ethyl acetate (100 mL). The layers were separated and the isolated aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to orange oil. ^{1}H NMR of the crude oil indicated a 9.1:1 diastereomeric mixture. Purification by silica gel chromatography (5–10% ethyl acetate/hexanes gradient) afforded **21f** (31.7 g, 75.54 mmol) in 70% yield as a single diastereomer. Spectral data matches that of previously reported.[42] ^{1}H NMR (400 MHz, chloroform-d) δ 7.37–7.19 (m, 5H), 4.68 (ddt, *J*=9.8, 6.7, 3.2 Hz, 1H), 4.25–4.13 (m, 2H), 3.79–3.66 (m, 1H), 3.60 (td, *J*=6.4, 1.0 Hz, 2H), 3.27 (dd, *J*=13.4, 3.3 Hz, 1H), 2.78 (dd, *J*=13.1, 9.6 Hz, 1H), 1.83–1.66 (m, 1H), 1.56–1.32 (m, 5H), 1.28–1.22 (m, 3H), 0.94–0.86 (m, 9H), 0.00–0.06 (m, 6H) ; ^{13}C{H} NMR (101 MHz, chloroform-d) δ 177.2, 153.0, 135.3, 129.4, 128.9, 127.3, 66.0, 62.9, 55.3, 37.9, 37.6, 33.2, 32.8, 25.9, 25.6, 23.5, 18.3, 17.3, -5.3.

*(S)-4-benzyl-3-((S)-2-methyl-3-phenylpropanoyl)oxazolidin-2-one, (**24**)*. Prepared according to the general alkylation procedure with purification by silica gel chromatography (0-30% ethyl acetate/hexanes gradient) to afford **24** in 57% yield (6.30 g, 19 mmol) from (*S*)-4-benzyl-3-(3-phenylpropanoyl)oxazolidin-2-one (10.6 g, 34 mmol). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.31 (m, 2H), 7.28 – 7.16 (m, 7H), 4.55 – 4.50 (m, 1H), 4.17 – 4.06 (m, 2H), 3.96 (t, *J* = 8.4 Hz, 1H), 3.24 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.02 (dd, *J* = 13.3, 7.8 Hz, 1H), 2.79 – 2.67 (m, 2H), 1.25 (d, J = 6.8 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-d) δ 176.4, 152.9, 139.1,

135.2, 129.3, 129.1, 128.8, 128.2, 127.2, 126.3, 65.9, 55.3, 39.8, 39.3, 37.8, 16.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{22}NO_3$ 324.1594; found 324.1603.

Experimental Procedures for the Preparation of the Ester Products.

*Methyl 2-methyl-3-phenylpropanoate, (**6**).*[29] *Table 1 Entry 1:* Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 20 °C (8 h) to give **(*S*)-6** (346 mg) as colorless oil in 97% yield and >99% ee from **9**. *Table 1 Entry 2*: Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 60 °C (1 h) to give **(*S*)-6** (353 mg) as colorless oil in 99% yield and >99% ee from **9**. *Table 1 Entry 6*: Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 20 °C (12 h) to give **(*R*)-6** (346 mg) as colorless oil in 97% yield and >99% ee from **4**. *Table 1 Entry 7*: Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 60 °C (1 h) to give **(*R*)-6** (310 mg) as colorless oil in 87% yield and >99% ee from **4**. *Table 1 Entry 11*: Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 60 °C (1 h) to give **(*S*)-6** (310 mg) as colorless oil in 87% yield and 93% ee from **12**. Diastereomeric excess of **12** is 93%. *Table 1 Entry 15*: Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 60 °C (2 h) to give **(*R*)-6** (356 mg) as colorless oil in 99% yield and 98% ee from **8**. Diastereomeric excess of **13** is 98%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.35–7.15 (m, 5H), 3.66 (s, 3H), 3.05 (dd, *J* = 13.1, 6.6 Hz, 1H), 2.81–2.66 (m, 2H), 1.18 (d, *J* = 6.8 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 176.6, 139.4, 129.0, 128.4, 126.3, 51.6, 41.4, 39.7, 16.8. Enantioselectivity was determined by HPLC analysis using a Phenomenex Lux Cellulose-1 column at 20 °C (Solvent A/B = Heptane/iPrOH at 1.0 mL/min; %B = 0 min 3%, 2 min 3%, 3 min 60%, 9 min 60%, stop time = 9 min), giving retention times of 3.63 min (*R* enantiomer) and 4.10 min (*S* enantiomer). The absolute stereochemistry was assumed by analogy.

Ethyl 2-methyl-3-phenylpropanoate (7).[29] *Table 1 Entry 3*: Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 75 °C (16 h) to give **(*S*)-7** (338 mg) as colorless oil in 88% yield and >99% ee from **9**. *Table 1 Entry 8*: Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 75 °C (24 h) to give **(*R*)-7** (327 mg) as colorless oil in 85% yield and >99% ee from **4**. *Table 1 Entry 12*: Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 75 °C (20 h) to give **(*S*)-7** (331 mg) as colorless oil in 86% yield and 93% ee from **12**. Diastereomeric excess of **12** is 93%. *Table 1 Entry 16*: Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 75 °C (27 h) to give **(*R*)-7** (342 mg) as colorless oil in 89% yield and 98% ee from **13**. Diastereomeric excess of **13** is 98%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.41–7.17 (m, 5H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.09–3.01 (m, 1H), 2.86–2.66 (m, 2H), 1.26–1.15 (m, 6H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 176.1, 139.4, 129.0, 128.3, 126.2, 60.2, 41.5, 39.7, 16.8, 14.1. Enantioselectivity was determined by HPLC analysis using a Chiralpak OB-H 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B = Heptane/iPrOH at 0.7 mL/min; 2% B isocratic, stop time = 10 min), giving retention times of 4.28 min (*R* enantiomer) and 4.68 min (*S* enantiomer). The absolute stereochemistry was assumed by analogy.

*Allyl 2-methyl-3-phenylpropanoate (**14**). Table 1 Entry 4*: Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 80 °C (20 h) to give **(*S*)-14** (404 mg) as colorless oil in 99% yield and >99% ee from **9**. *Table 1 Entry 9*: Prepared according to general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 80 °C (48 h) to give **(*R*)-14** (392 mg) as colorless oil in 96% yield and >99% ee from **4**. *Table 1 Entry 13*: Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 80 °C (96 h) to give **(*S*)-14** (380 mg) as colorless oil in 93% yield and 93% ee from **12**. Diastereomeric excess of **12** is 93%. *Table 1 Entry 17*: Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 80 °C (30 h) to give **(*R*)-14** (376 mg) as colorless oil in 92% yield and 98% ee from **13**. Diastereomeric excess of **12** is 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32–7.16 (m, 5H), 5.83 (ddt, *J* = 17.2, 10.6, 5.4 Hz, 1H), 5.27–5.11 (m, 2H), 4.50 (dt, *J* = 5.3, 1.4 Hz, 2H), 2.96–2.85 (m, 1H), 2.83–2.56 (m, 2H), 1.08 (d, *J* = 6.8 Hz, 3H); ^{13}C{H} NMR (101 MHz, DMSO-d_6) δ 174.8, 139.1, 132.6, 128.9, 128.2, 126.2, 117.6, 64.2, 40.6, 38.9, 16.7; IR (film) ν_{max} 3086, 3028, 2975, 2937, 2878, 1735, 1496, 1454, 1380, 1165 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{17}O_2$ 205.1223; found 205.1223; $[\alpha]^D_{20}$ -25.73 (c 0.715, DMSO). Enantioselectivity was determined by HPLC analysis using a Chiralpak ID-3 3 μm 4.6 x 150 mm column at 30 °C (Solvent A/B = 0.05% TFA in MeOH/Water (1:4)/0.05% TFA in MeOH/acetonitrile (1:4) at 1.2 mL/min; %B = 0 min 0%, 2 min 0%, 20 min 100%, 24 min 100%, stop time = 24 min), giving retention times of 13.35 min (*R* enantiomer) and 13.59 min (*S* enantiomer). The absolute stereochemistry was assumed by analogy.

*n-Butyl 2-methyl-3-phenylpropanoate (**15**).*[27] *Table 1 Entry 5*: Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 80 °C (96 h) to give **(*S*)-15** (436 mg) as colorless oil in 94% yield and >99% ee from **9**. *Table 1 Entry 10*: Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 80 °C (60 h) to give **(*R*)-15** (414 mg) as colorless oil in 94% yield and >99% ee from **4**. *Table 1 Entry 14*: Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 80 °C (120 h) to give **(*S*)-15** (383 mg) as colorless oil in 87% yield and 92% ee from **12**. Diastereomeric excess of **12** is 93%. *Table 1 Entry 18*: Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 80 °C (72 h) to give **(*R*)-15** (361 mg) as colorless oil in 82% yield and 98% ee from **13**. Diastereomeric excess of **13** is 98%. ^{1}H NMR (400 MHz, chloroform-d) δ 7.32–7.25 (m, 2H), 7.24–7.12 (m, 3H), 4.04 (t, *J* = 6.6 Hz, 2H), 3.03 (dd, *J* = 13.0, 6.4 Hz, 1H), 2.79–2.64 (m, 2H), 1.62–1.50 (m, 2H), 1.31 (dq, *J* = 15.0, 7.5 Hz, 2H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 176.2, 139.4, 128.9, 128.3, 126.2, 64.2, 41.5, 39.8, 30.6, 19.0, 16.8, 13.7. Enantioselectivity was determined by HPLC analysis using a Phenomenex Lux Cellulose-3 3 μm 4.6 x 150 mm column at 25 °C (Solvent A/B = 0.05% TFA in MeOH/Water (1:4)/0.05% TFA in MeOH/acetonitrile (1:4) at 1.2 mL/min; %B = 0 min 0%, 2 min 0%, 20 min 100%, 24 min 100%, stop time = 24 min), giving retention times of 15.10 min (*S* enantiomer) and 15.55 min (*R* enantiomer). The absolute stereochemistry was assumed by analogy.

*Methyl (R)-2-phenylpropanoate (**20a**).*[31] Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 60 °C (1 h) to give **20a** (312 mg) as colorless oil in 95% yield and >99% ee from **19**. ^{1}H NMR (400 MHz, chloroform-d) δ 7.48–7.22 (m, 5H), 3.76 (q, *J* = 7.1 Hz, 1H), 3.69 (s, 3H), 1.54 (d, *J* = 7.1 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 175.0, 140.6, 128.7, 127.5, 127.2, 52.0, 45.4, 18.6. Enantioselectivity was determined by HPLC analysis using a Chiralpak ID-3 3 μm 4.6 x 150 mm column at 30 °C (Solvent A/B = 0.05% TFA in MeOH/Water (1:4)/0.05% TFA in MeOH/acetonitrile (1:4) at 1.2 mL/min; %B = 0 min 30%, 2 min 30%, 7 min 37%, 9 min 100%, 12 min 100%, stop time = 12 min), giving retention times of 4.87 min (major *R* enantiomer) and 5.49 min (minor *S* enantiomer). The absolute stereochemistry was assumed by analogy.

*Ethyl (S)-2-phenylpropanoate, (**20b**)*.[31] Prepared according t the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 75 °C (12 h) to give **20b** (328 mg) as colorless oil in 92% yield and >99% ee from **19**. ^{1}H NMR (400 MHz, chloroform-d) δ 7.43–7.32 (m, 4H), 7.32–7.24 (m, 1H), 4.28–4.02 (m, 2H), 3.74 (q, *J* = 7.2 Hz, 1H), 1.53 (d, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 174.6, 140.7, 128.6, 127.5, 127.1, 60.7, 45.6, 18.6, 14.1. Enantioselectivity was determined by HPLC analysis using a Chiralpak IG 5 µm 4.6 x 150 mm column at 30 °C (Solvent A/B = 0.05% TFA in acetonitrile/water (5:95)/0.05% TFA in acetonitrile/water (95:5) at 1.2 mL/min; %B = 0 min 30%, 2 min 30%, 12 min 45%, 15 min 100%, 18 min 100%, stop time = 18 min), giving retention times of 11.69 min (major *S* enantiomer) and 12.39 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*n-Propyl (R)-2-phenylpropanoate (**20c**)*.[32] Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ 80 °C (20 h) to give **20c** (319 mg) as colorless oil in 83% yield and 98% ee from **19**. ^{1}H NMR (400 MHz, chloroform-d) δ 7.35–7.18 (m, 5H), 3.99 (t, *J* = 6.7 Hz, 2H), 3.68 (q, *J* = 7.1 Hz, 1H), 1.60–1.45 (m, 5H), 0.82 (t, *J* = 7.5Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 174.6, 140.7, 128.5, 127.5, 127.0, 66.3, 45.6, 21.9, 18.5, 10.2. Enantioselectivity was determined by HPLC analysis using a Regis (R,R) Whelk-O1 3 µm 4.6 x 150 mm column at 25 °C (Solvent A/B = Heptane/iPrOH at 1.0 mL/min; %B = 4% isocratic, stop time = 10 min), giving retention times of 4.17 min (minor *S* enantiomer) and 4.56 min (major *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*n-Butyl (S)-2-phenylpropanoate (**20d**)*.[32] Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 80 °C (24 h) to give **20d** (326 mg) as colorless oil in 79% yield and >99% ee from **19**. ^{1}H NMR (400 MHz, chloroform-d) δ 7.35–7.19 (m, 5H), 4.09–3.98 (m, 2H), 3.68 (q, *J* = 7.1 Hz, 1H), 1.56–1.44 (m, 5H), 1.32–1.20 (m, 2H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 174.6, 140.7, 128.5, 127.4, 127.0, 64.6, 45.6, 30.5, 19.0, 18.5, 13.6. Enantioselectivity was determined by HPLC analysis using a Regis (R,R) Whelk-O1 3 µm 4.6 x 150 mm column at 25 °C (Solvent A/B = Heptane/iPrOH at 1.0 mL/min; %B = 4% isocratic, stop time = 10 min), giving retention times of 3.96 min (major *S* enantiomer) and 4.38 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*Allyl (S)-2-phenylpropanoate (**20e**)*.[33] Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 80 °C (22 h) to give **20e** (358 mg) as colorless oil in 94% yield and >99% ee from **19**. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.35–7.24 (m, 5H), 5.85 (ddt, *J* = 17.2, 10.6, 5.3 Hz, 1H), 5.18–5.11 (m, 2H), 4.54 (dt, *J* = 5.2, 1.5 Hz, 2H), 3.83 (q, *J* = 7.1 Hz, 1H), 1.40 (d, *J* = 7.2 Hz, 3H); ^{13}C{H} NMR (126 MHz, DMSO-d_6) δ 173.4, 140.5, 132.5, 128.5, 127.3, 127.0, 117.4, 64.5, 44.4, 18.4. Enantioselectivity was determined by HPLC analysis using a Regis (R,R) Whelk-O1 3 µm 4.6 x 150 mm column at 25 °C (Solvent A/B = Heptane/iPrOH at 1.0 mL/min; %B = 4% isocratic, stop time = 10 min), giving retention times of 4.15 min (major *S* enantiomer) and 4.51 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*Propargyl (R)-2-phenylpropanoate (**20f**)*. Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 80 °C (22 h) to give **20f** (361 mg) as colorless oil in 96% yield and >99% ee from **19**. The product has a strong acrylic odor. ^{1}H NMR (400 MHz, chloroform-d) δ 7.34–7.19 (m, 5H), 4.67 (dd, *J* = 15.7, 2.5 Hz, 1H), 4.56 (dd, *J* = 15.7, 2.5 Hz, 1H), 3.73 (q, *J* = 7.2 Hz, 1H), 2.39 (t, *J* = 2.5 Hz, 1H), 1.48 (d, *J* = 7.3 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 173.7, 139.9, 128.6, 127.5, 127.2, 77.5, 74.8, 52.2, 45.2, 18.5; IR (film) ν_{max} 3291, 3064, 3030, 2981, 2938, 2877, 2129, 1736, 1496, 1453, 1377, 1326, 1199, 1154 cm^{-1}; HRMS (DCI-CH_4) *m/z*: $[M]^+$ calcd for $C_{12}H_{12}O_2$ 188.0837; found 188.0835; $[\alpha]^D_{20}$ -52.5 (c 1.12, $CHCl_3$). Enantioselectivity was determined by HPLC analysis using a Chiralpak OB-H 5 µm 4.6 x 150 mm column at 30 °C (Solvent A/B = 0.05% TFA in MeOH/Water (1:4)/0.05% TFA in MeOH/acetonitrile (1:4) at 1.2 mL/min; %B = 0 min 25%, 27 min 25%, 31 min 100%, 35 min 100%, stop time = 35 min), giving retention times of 19.23 min (minor *S* enantiomer) and 21.37 min (major *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*Cyclopropylmethyl (R)-2-phenylpropanoate (**20g**)*. Prepared according to the general procedure on 2 mmol scale with 10 mol% $Yb(OTf)_3$ at 80 °C (22 h) to give **20g** (323 mg) as colorless oil in 79% yield and >99% ee from **19**. ^{1}H NMR (400 MHz, chloroform-d) δ 7.35–7.17 (m, 5H), 3.96–3.77 (m, 2H), 3.70 (q, *J* = 7.3 Hz, 1H), 1.46 (d, *J* = 7.1 Hz, 3H), 1.22–0.98 (m, 1H), 0.56–0.38 (m, 2H), 0.24–0.14 (m, 2H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 174.7, 140.7, 128.5, 127.5, 127.0, 69.3, 45.5, 18.6, 9.7, 3.1 (2); IR (film) ν_{max} 3085, 3029, 2979, 2939, 2877, 1735, 1496, 1453, 1204, 1165 cm^{-1} HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{17}O_2$ 205.1223; found 205.1230; $[\alpha]^D_{20}$ -37.5 (c 0.850, $CHCl_3$). Enantioselectivity was determined by HPLC analysis using a Regis (R,R) Whelk-O1 3 µm 4.6 x 150 mm column at 25 °C (Solvent A/B = Heptane/iPrOH at 1.0 mL/min; %B = 4% isocratic, stop time = 10 min), giving retention times of 4.38 min (minor *S* enantiomer) and 4.92 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

Methyl (R)-2-cyclohexyl-3-phenylpropanoate (**8**). Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 60 °C (20 h) to give **8** (478 mg) as colorless oil in 97% yield and >99% ee from **5**. ^{1}H NMR (400 MHz, chloroform-d) δ 7.34–7.25 (m, 2H), 7.25–7.13 (m, 3H), 3.54 (s, 3H), 3.01–2.79 (m, 2H), 2.53 (ddd, *J* = 10.3, 7.3, 5.2 Hz, 1H), 1.91 (br d, *J* = 12.4 Hz, 1H), 1.85–1.74 (m, 2H), 1.74–1.57 (m, 3H), 1.39–1.03 (m, 5H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 175.4, 140.0, 128.8, 128.3, 126.1, 54.3, 51.1, 40.4, 35.7, 30.9, 30.8, 26.4, 26.3, 26.3; IR (film) ν_{max} 3086, 3064, 3030, 2919, 2853, 2670, 1739, 1733, 1604, 1495, 1456, 1360, 1160 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{23}O_2$ 247.1693; found 247.1693; $[\alpha]^D_{20}$ 33.19 (c 1.12, CHCl3). Enantioselectivity was determined by HPLC analysis using a Phenomenex Lux Amylose 3 µm 4.6 x 150 mm column at 30 °C (Solvent A/B = 0.05% TFA in acetonitrile/water (5:95)/0.05% TFA in acetonitrile/water (95:5) at 1.2 mL/min; %B = 0 min 40%, 2 min 40%, 16 min 100%, 20 min 100%, stop time = 20 min), giving retention times of 9.65 min (major *R* enantiomer) and 10.26 min (minor *S* enantiomer). The absolute stereochemistry was assumed by analogy.

*Methyl (R)-2-(3,5-dimethylisoxazol-4-yl)-3-phenylpropanoate, (**22a**)*. Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 60 °C (20 h) to give **22a** (493 mg) as colorless oil after silica gel purification (0-40% ethyl acetate/hexanes) in 95% yield and >99%ee from **21a**. ^{1}H NMR (400 MHz, chloroform-d) δ 7.28–7.19 (m, 3H), 7.08–7.01 (m, 2H), 3.71 (s, 3H), 3.63 (dd, *J*= 9 .1, 6.3 Hz, 1H), 3.42 (br d, *J* = 13.6 Hz, 1H), 2.92 (dd, *J* = 13.6, 9.4 Hz, 1H), 2.14 (s, 3H), 2.13 (s, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 172.6, 166.4, 159.1, 138.3, 128.9, 128.5, 126.7, 110.8, 52.2, 42.4, 37.2, 11.1, 10.5; IR (film) ν_{max} 3087, 3030, 3003, 2849, 1729, 1634, 1496 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{18}NO_3$ 260.1281; found 260.1284; $[\alpha]^D_{20}$ -98.5 (c 0.585, $CHCl_3$). Enantioselectivity was determined by HPLC analysis using a Phenomenex Lux Cellulose-1 3 µm 4.6 x 150 mm column at 30 °C (Solvent A/B = 0.05% TFA

in acetonitrile/water (5:95)/0.05% TFA in acetonitrile/water (95:5) at 1.2 mL/min; %B = 0 min 40%, 2 min 40%, 16 min 100%, 20 min = 100%, stop time = 20 min), giving retention times of 7.21 min (minor *S* enantiomer) and 7.69 min (major *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*Methyl (R)-2-(benzyloxy)pent-4-enoate (**22b**)*. Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 60 °C (30 h) to give **22b** (344 mg) as colorless oil after purification by silica gel chromatography in 78% yield and >99% ee from **21b**. ^{1}H NMR (400 MHz, methanol-d_4) d 7.42–7.26 (m, 5H), 5.82 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.17–5.03 (m, 2H), 4.65 (d, *J* = 11.6 Hz, 1H),4.44 (d, *J* = 11.4 Hz, 1H), 4.06 (dd, *J* = 6.9, 5.4 Hz, 1H), 3.72 (s, 3H), 2.58-2.43 (m, 2H); ^{13}C{H} NMR (101 MHz, methanol-d_4) δ 174.3, 139.1, 134.6, 129.5, 129.3, 129.0, 118.4, 79.2, 73.5, 52.4, 38.5; IR (film) ν_{max} 3480 (br), 3066, 3032, 2953, 2873, 1748, 1643, 1455, 1435, 1275, 1203, 1112 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{17}O_3$ 221.1172; found 221.1167; $[\alpha]^{20}_D$ 45.8 (c 1.005, CH_3CN). Enantioselectivity was determined by HPLC analysis using a Chiralpak IG 5 µm 4..6 x 150 mm column at 30 °C (Solvent A/B = 0.05% NH_4OAc in acetonitrile/water (5:95)/0.05% NH_4OAc in acetonitrile/water (95:5) at 1.2 mL/min; %B = 0 min 35%, 2 min 35%, 10 min 50%, 15 min 100%, stop time = 19 min), giving retention times of 9.2 min (minor *S* enantiomer) and 10.2 min (major *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*Methyl (R)-3-phenylbutanoate, (**22c**)*.[34] Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 60 °C (1 h) to give **22c** (353 mg) as colorless oil in 99% yield and >99% ee from **21c**. ^{1}H NMR (400 MHz, chloroform-d) δ 7.42–7.22 (m, 5H), 3.66 (s, 3H), 3.48–3.27 (m, 1H), 2.75–2.56 (m, 2H), 1.34 (d, *J* = 7.1 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 172.8, 145.7, 128.5, 126.7, 126.4, 51.5, 42.7, 36.4, 21.7.

*Methyl (2S,3R)-3-(4-bromophenyl)-2-methyl-3-((4-methylphenyl)sulfonamido)propanoate (**22d**)*. Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 60 °C (8 h) to give **22d** (657 mg) as colorless oil in 77% yield and >99% ee from **21d**. ^{1}H NMR (400 MHz, chloroform-d) δ 7.47 (br d, *J* = 8.1 Hz, 2H), 7.26–7.18 (m, 2H), 7.07 (br d, *J* = 8.3 Hz, 2H), 6.89 (br d, *J* = 8.3 Hz, 2H), 6.23 (br d, *J* = 9.1 Hz, 1H), 4.47 (br dd, *J* = 9.1, 6.8 Hz, 1H), 3.59 (s, 3H), 2.90–2.75 (m, 1H), 2.35 (s, 3H), 1.12 (d, *J* = 7.1 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 174.7, 143.1, 137.7, 137.5, 131.3, 129.2, 128.4, 126.9, 121.4, 59.7, 52.0, 45.7, 21.4, 15.2; IR (film) ν_{max} 3270, 3067, 3047, 2947, 2920, 1737, 1705, 1491, 1448, 1335, 1265, 1106 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{21}BrNO_4S$ 428.0350; found 428.0363; $[\alpha]^{20}_D$ +61.6 (c 0.525, $CHCl_3$); mp: 119.3 °C (DSC). Enantioselectivity was determined by HPLC analysis using a Phenomenex Lux Cellulose-3 3 µm 4.6 x 150 mm column at 30 °C (Solvent A/B = 0.05% TFA in MeOH/Water (1:4)/0.05% TFA in MeOH/acetonitrile (1:4) at 1.2 mL/min; %B = 0 min 30%, 2 min 30%, 11 min 51%, 14 min 100%, 18 min = 100% stop time = 18 min), giving retention times of 9.88 min (major 2*S*/3*R* diastereomer) and 10.55 min (minor 2*R*/3*R* diastereomer). The absolute stereochemistry was assumed by analogy.

*Methyl (2S,3R)-3-(4-fluorophenyl)-3-hydroxy-2-methylpropanoate, (**22e**)*.[36] Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ 20 °C (24 h) to give **22e** (221 mg) as white solids in 52% yield and >99% ee from **21e**. ^{1}H NMR (400 MHz, chloroform-d) δ 7.38–7.25 (m, 2H), 7.10–7.01 (m, 2H), 4.75 (dd, *J* = 8.3, 4.3 Hz, 1H), 3.74 (s, 3H), 3.06 (br s, 1H), 2.84–2.72 (m, 1H), 1.01 (d, *J* = 7.1 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 176.1, 163.7, 161.2, 137.3, 137.3, 128.3, 128.2, 115.5, 115.3, 75.7, 52.0, 47.1, 14.4; ^{19}F NMR (376 MHz, chloroform-d) δ -114.14 – -114.27 (m, 1F). Enantioselectivity was determined by HPLC analysis using a Chiralpak IG 5 µm 4.6 x 150 mm column at 30 °C (Solvent A/B = 0.05% TFA in acetonitrile/water (5:95)/0.05% TFA in acetonitrile/water (95:5) at 1.2 mL/min; %B = 0 min 20%, 2 min 20%, 10 min 40%, 13 min 100%, 16 min = 100%, stop time = 16 min), giving retention times of 10.31 min (minor 2*S*/3*R* enantiomer) and 11.35 min (minor 2*R*/3*R* enantiomer). The absolute stereochemistry was assumed by analogy.

*Methyl (R)-6-hydroxy-2-methylhexanoate (**22f**)*.[35] Prepared according to the general procedure on 0.67 mmol scale (1.5 mol% $Yb(OTf)_3$) at 20 °C (16 h) to give **22f** (98 mg) as colorless oil in 91% yield and 97% ee from **21f**. Diastereomeric excess of **21f** is 97%. Spectral data matches that of previously reported.[1] ^{1}H NMR (400 MHz, chloroform-d) δ 3.71–3.58 (m, 5H), 2.45 (dq, *J* =13.8, 7.0 Hz, 1H), 1.93 (s, 1H), 1.75–1.63 (m, 1H), 1.61–1.51 (m, 2H), 1.49–1.29 (m, 3H), 1.21–1.13 (d, *J* =4.0 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 177.3, 62.6, 51.5, 39.4, 33.4, 32.5, 23.4, 17.0 Enantioselectivity was determined by GC analysis using a Restek RT-βDEXsm column 30 m x 0.25 mm x 0.25 µm (80 °C at 0 min with increase of 2 °C/min to 230 °C; Inj 200 °C, Det 250 °C; He 1.9 mL/min 30:1), giving retention times of 25.48 min (major *R* enantiomer) and 25.71 min (minor *S* enantiomer). The absolute stereochemistry was assumed by analogy.

*Methyl-d^3 (S)-2-methyl-3-phenylpropanoate (**23**)*. Prepared according to the general procedure on 2 mmol scale with 2 mol% $Yb(OTf)_3$ at 20 °C (10 h) to give **23** (355 mg) as colorless oil in 98% yield and >99% ee from **9**. ^{1}H NMR (400 MHz, chloroform-d) δ 7.34–7.13 (m, 5H), 3.02 (dd, *J* = 13.0, 6.4 Hz, 1H), 2.80–2.62 (m, 2H), 1.14 (d, *J* = 6.8 Hz, 3H); ^{13}C{H} NMR (101 MHz, chloroform-d) δ 176.6, 139.3, 128.9, 128.3, 126.3, 77.0, 41.4, 39.7, 16.7; IR (film) ν_{max} 3449, 3029, 2976, 2936, 2879, 1732, 1496, 1455, 1366, 1291, 1219, 1188, 1088 cm^{-1}; HRMS (DCI-CH_4) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{12}D_3O_2$ 181.1182; found 181.1185; $[\alpha]^{20}_D$ +25.9 (c 1.415, $CHCl_3$). Enantioselectivity was determined by HPLC analysis using a Phenomenex Lux Cellulose-1 column at 25 °C (Solvent A/B = Heptane/iPrOH at 0.7 mL/min; %B = 0 min 3%, 2 min 3%, 3 min 60%, 9 min 60%, stop time = 9 min), giving retention times of 4.86 min (minor *R* enantiomer) and 4.10 min (*S* enantiomer). The absolute stereochemistry was assumed by analogy.

*(S)-N-allyl-2-methyl-3-phenylpropanamide (**25a**)*. Prepared according to procedure A on 0.62 mmol scale at 40 °C (4 h) to give **(*S*)-25a** (97 mg) as a white solid in 77% yield and >99 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.26 (m, 2H), 7.21 – 7.16 (m, 3H), 5.68 (ddt, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.23 (s, 1H), 5.03 (dq, *J* = 10.3, 1.4 Hz, 1H), 4.99 (dq, *J* = 17.1, 1.6 Hz, 1H), 3.84 – 3.73 (m, 2H), 2.97 (dd, *J* = 13.4, 8.4 Hz, 1H), 2.68 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.47 - 2.40 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.4, 140.0, 134.3, 129.1, 128.5, 126.4, 116.3, 44.2, 41.8, 40.7, 17.9. Spectral data matches that of previously reported.[22c] HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{18}NO$ 204.1383; found 204.1386. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 µm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:1.2) stop time = 20 min), giving retention of 12.18 min (major *S* enantiomer) and 13.21 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*(S)-2-methyl-3-phenyl-N-propylpropanamide (**25b**)*. Prepared according to procedure A on 0.62 mmol scale at 40 °C (4 h) to give **(*S*)-25** (92 mg) as a white solid in 73% yield and >99 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28 – 7.25 (m, 2H), 7.21 –

7.16 (m, 3H), 5.14 (s, 1H), 3.18 – 3.02 (m, 2H), 2.95 (dd, *J* = 13.4, 8.5 Hz, 1H), 2.68 (dd, *J* = 13.5, 6.4 Hz, 1H), 2.44 - 2.34 (m, 1H), 1.39 – 1.31 (m, 2H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.78 (t, *J* = 7.4 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.8, 140.4, 129.4, 128.8, 126.6, 44.5, 41.4, 41.0, 23.1, 18.2, 11.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{20}NO$ 206.1539; found 206.1542. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:1.9) stop time = 10 min), giving retention of 5.36 min (major *S* enantiomer) and 5.94 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

(S)-2-methyl-3-phenyl-N-(prop-2-yn-1-yl)propenamide ***(25c)***. Prepared according to procedure A on 0.53 mmol scale at 40 °C (4 h) to give **(*S*)-25c** (74 mg) as a white solid in 70% yield and >99 ee% from **24**.^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.25 (m, 3H), 7.22 – 7.15 (m, 2H), 5.35 (s, 1H), 4.06 – 3.89 (m, 2H), 2.98 (dd, *J* = 13.5, 8.1 Hz, 1H), 2.68 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.47 – 2.40 (m, 1H), 2.18 (t, *J* = 2.6 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.3, 139.8, 129.1, 128.6, 126.5, 79.6, 71.7, 43.8, 40.5, 29.2, 17.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{16}NO$ 202.1226; found 202.1231. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:4) stop time = 10 min), giving retention of 3.20 min (major *S* enantiomer) and 3.51 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

(S)-N-benzyl-2-methyl-3-phenylpropanamide ***(25d)***. Prepared according to procedure A on 0.62 mmol scale at 80 °C (12 h) to give **(*S*)-25d** (114 mg) as a white solid in 73% yield and >99 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28 – 7.16 (m, 8H), 7.05 – 7.00 (m, 2H), 5.44 (s, 1H), 4.40 (dd, *J* = 14.7, 6.0 Hz, 1H), 4.29 (dd, *J* = 14.7, 5.3 Hz, 1H), 2.99 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.72 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.50 – 2.42 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.4, 140.0, 138.3, 129.1, 128.7, 128.6, 127.8, 127.5, 126.4, 44.3, 43.5, 40.7, 18.0. Spectral data matches that of previously reported.[22a] HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{20}NO$ 254.1539; found 254.1542. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:4) stop time = 10 min), giving retention of 5.98 min (major *S* enantiomer) and 7.43 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

(S)-N-(3-hydroxypropyl)-2-methyl-3-phenylpropanamide ***(25e)***. Prepared according to procedure A on 0.62 mmol scale at 40 °C (4 h) to give **(*S*)-25e** (97 mg) as a white solid in 70% yield and >99 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28-7.20 (m, 3H), 7.19 – 7.14 (m, 2H), 5.56 (s, 1H), 3.46 – 3.33 (m, 2H), 3.28 – 3.22 (m, 2H), 2.97 – 2.90 (m, 2H), 2.71 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.49 – 2.42 (m, 1H), 1.56 – 1.47 (m, 2H), 1.22 (d, *J* = 6.8 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 177.2, 140.2, 129.4, 128.8, 126.7, 59.5, 44.5, 40.9, 36.4, 32.6, 18.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{20}NO_2$ 222.1489; found 222.1492. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:1) stop time = 10 min), giving retention of 5.42 min (major *S* enantiomer) and 5.99 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

(S)-N-(2-methoxyethyl)-2-methyl-3-phenylpropanamide ***(25f)***. Prepared according to procedure A on 0.62 mmol scale at 40 °C (12 h) to give **(*S*)-25f** (61 mg) as a colorless oil in 45% yield and >99 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28 – 7.23 (m, 2H), 7.20 – 7.13 (m, 3H), 5.60 (s, 1H), 3.38 – 3.26 (m, 3H), 3.24 (s, 3H), 3.22 – 3.20 (m, 1H), 2.94 (dd, *J* = 13.5, 8.3 Hz, 1H), 2.66 (dd, *J* = 13.5, 6.6 Hz, 1H), 2.47 – 2.39 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.7, 140.0, 129.1, 128.5, 126.4, 71.3, 58.8, 44.0, 40.6, 39.0, 17.8. Spectral data matches that of previously reported.[22b] HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{20}NO_2$ 222.1489; found 222.1491. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:1.9) stop time = 10 min), giving retention of 4.06 min (major *S* enantiomer) and 4.55 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

(S)-N-(3-ethoxypropyl)-2-methyl-3-phenylpropanamide ***(25g)***. Prepared according to procedure A on 0.62 mmol scale at 40 °C (12 h) to give **(*S*)-25g** (98 mg) as a white solid in 63% yield and >99 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28 – 7.24 (m, 2H), 7.20 – 7.13 (m, 3H), 5.92 (s, 1H), 3.43 – 3.30 (m, 4H), 3.30 – 3.26 (m, 2H), 2.97 (dd, *J* = 13.4, 8.0 Hz, 1 H), 2.66 (dd, *J* = 13.4, 6.8 Hz, 1H), 2.42 – 2.35 (m, 1H), 1.70 – 1.57 (m, 2H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.15 (t, *J* = 3.6 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.5, 140.1, 129.1, 128.5, 126.3, 69.9, 66.5, 44.1, 40.7, 38.4, 29.0, 17.6, 15.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{24}NO_2$ 250.1802; found 250.1805. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:1.9) stop time = 10 min), giving retention of 5.09 min (major *S* enantiomer) and 5.77 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

(S)-N-(but-3-en-1-yl)-2-methyl-3-phenylpropanamide ***(25h)***. Prepared according to procedure B on 0.53 mmol scale at 40 °C (12 h) to give **(*S*)-25h** (66 mg) as a white solid in 57% yield and 98 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.26 (m, 2H), 7.21 – 7.15 (m, 3H), 5.61 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.19 (s, 1H), 5.00 (dq, *J* = 10.2, 2.2, 1.2 Hz, 1H), 4.96 (dq, *J* = 17.1, 1.6 Hz, 1H), 3.30 – 3.15 (m, 2H), 2.95 (dd, *J* = 13.4, 8.5 Hz, 1H), 2.66 (dd, *J* = 13.4, 6.4 Hz, 1H), 2.42 - 2.35 (m, 1H), 2.17 – 2.02 (m, 2H), 1.17 (d, *J* = 6.9 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.5, 140.1, 135.4, 129.1, 128.5, 126.4, 117.2, 44.2, 40.7, 38.2, 33.8, 17.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{20}NO$ 218.1539; found 218.1542. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:1.9) stop time = 10 min), giving retention of 6.84 min (major *S* enantiomer) and 7.55 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

(S)-2-methyl-N-phenethyl-3-phenylpropanamide ***(25i)***. Prepared according to procedure B on 0.62 mmol scale at 40 °C (12 h) to give **(*S*)-25i** (101 mg) as a white solid in 61% yield and 98 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.21 (m, 4H), 7.21 – 7.15 (m, 4H), 7.01 (d, 2H), 5.17 (s, 1H), 3.52 – 3.45 (m, 1H), 3.37 – 3.31 (m, 1H), 2.95 (dd, *J* = 13.4, 8.5 Hz, 1H), 2.73 - 2.63 (m, 2H), 2.61 - 2.55 (m, 1H), 2.37 – 2.30 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H). ^{13}C{H}C NMR (126 MHz, Chloroform-*d*) δ 175.8, 140.4, 139.3, 129.4, 129.1, 129.0, 128.8, 126.8, 126.7, 44.5, 40.9, 40.8, 36.1, 18.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{22}NO$ 268.1696; found 268.1701. Enantioselectivity was determined by HPLC analysis using Chiral Pak AY-H 5 μm 4.6 x 250 mm column at 30 °C (Solvent A/B= hexanes/*i*PrOH (3:1) stop time = 11 min), giving retention of 9.78 min (major *S* enantiomer) and 9.36 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

(S)-N-(2-(ethylthio)ethyl)-2-methyl-3-phenylpropanamide ***(25j)***. Prepared according to procedure B on 0.62 mmol scale at 40 °C (12

h) to give **(*S*)-25j** (82 mg) as a white solid in 53% yield and 98 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.27 – 7.24 (m, 2H), 7.20 – 7.15 (m, 3H), 5.73 (s, 1H), 3.38 – 3.24 (m, 2H), 2.94 (dd, *J* = 13.4, 8.5 Hz, 1H), 2.67 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.57 – 2.52 (m, 1H), 2.47 – 2.38 (m, 4H), 1.21 (t, *J* = 7.4 Hz, 3 H), 1.18 (d, *J* = 6.8 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.6, 139.9, 129.0, 128.5, 126.4, 43.9, 40.6, 38.1, 31.3, 25.4, 17.7, 14.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{22}NOS$ 252.1417; found 252.1426. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:4) stop time = 12 min), giving retention of 3.81 min (major *S* enantiomer) and 4.59 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*(S)-N-(cyclohexylmethyl)-2-methyl-3-phenylpropanamide (**25k**).* Prepared according to procedure A on 0.62 mmol scale at 40 °C (12 h) to give **(*S*)-25k** (119 mg) as a colorless oil in 46% yield and >99 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.28 – 7.25 (m, 2H), 7.20 – 7.16 (m, 3H), 5.18 (s, 1H), 3.07 - 3.02 (m, 1H), 2.96 – 2.87 (m, 2H), 2.68 (dd, *J* = 13.5, 6.1 Hz, 1H), 2.44 – 2.37 (m, 1H), 1.67 – 1.59 (m, 3H), 1.52 – 1.41 (m, 2H), 1.31 – 1.22 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.15 – 1.05 (m, 3H), 0.80 – 0.72 (m, 2H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.2, 139.9, 128.8, 128.3, 126.1, 45.4, 44.1, 40.5, 37.7, 30.6, 30.5, 26.2, 25.7, 25.7, 17.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{26}NO$ 260.2009; found 260.2014. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:4) stop time = 12 min), giving retention of 3.73 min (major *S* enantiomer) and 4.85 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*(S)-N-(4-methoxyphenyl)-2-methyl-3-phenylpropanamide (**25l**).* Prepared according to procedure A on 0.62 mmol scale at 80 °C (24 h) to give **(*S*)-25l** (36 mg) as a white solid in 22% yield and >99 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 – 7.24 (m, 3H), 7.24 – 7.20 (m, 4H), 6.81 (d, 2H), 3.77 (s, 3H), 3.03 (dd, *J* = 13.5, 8.6 Hz, 1H), 2.76 (dd, *J* = 13.5, 6.2 Hz, 1H), 2.59 – 2.52 (m, 1H), 1.27 (d, *J* = 6.8 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 173.8, 156.5, 139.9, 130.8, 129.1, 128.7, 126.6, 122.1, 114.2, 55.6, 44.9, 40.8, 17.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{20}NO_2$ 270.1489; found 270.1494. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:4) stop time = 12 min), giving retention of 7.49 min (major *S* enantiomer) and 8.14 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*(S)-N-(furan-2-ylmethyl)-2-methyl-3-phenylpropanamide (**25m**).* Prepared according to procedure A on 0.62 mmol scale at 40 °C (12 h) to give **(*S*)-25m** (100 mg) as a white solid in 66% yield and >99 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 - 7.12 (m, 6H), 6.28 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.08 (dd, *J* = 3.2, 0.8 Hz, 1H), 5.48 (s, 1H), 4.36 (d, *J* = 5.5 Hz, 2H), 2.97 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.69 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.47 – 2.40 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.4, 151.4, 142.2, 139.9, 129.1, 128.6, 126.4, 110.5, 107.4, 43.9, 40.6, 36.5, 17.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{18}NO_2$ 244.1332; found 244.1337. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:4) stop time = 10 min), giving retention of 4.02 min (major *S* enantiomer) and 5.13 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*(S)-N-(2-chlorobenzyl)-2-methyl-3-phenylpropanamide (**25n**).* Prepared according to procedure A on 0.62 mmol scale at 80 °C (12 h) to give **(*S*)-25n** (126 mg) as a white solid in 71% yield and 97 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 – 7.24 (m, 2H), 7.21 – 7.07 (m, 7H), 5.61 (s, 1H), 4.51 – 4.34 (m, 2H), 2.95 (dd, *J* = 13.5, 8.7 Hz, 1H), 2.70 (dd, *J* = 13.5, 6.1 Hz, 1H), 2.53 - 2.42 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.8, 140.1, 136.0, 133.9, 130.4, 129.8, 129.3, 129.1, 128.8, 127.4, 126.7, 44.4, 41.6, 40.9, 18.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{19}ClNO$ 288.1150; found 288.1155. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:4) stop time = 10 min), giving retention of 6.34 min (major *S* enantiomer) and 7.16 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*(S)-2-methyl-3-phenyl-N-(thiophen-2-ylmethyl)propenamide (**25o**).* Prepared according to procedure A on 0.62 mmol scale at 80 °C (12 h) to give **(*S*)-25o** (119 mg) as a white solid in 74% yield and >99 ee% from **24**. ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.46 (s, 1H), 7.27 – 7.14 (m, 6H), 6.89 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.84 (dq, *J* = 3.4, 1.0 Hz, 1H), 4.50 (dd, *J* = 5.9, 1.0 Hz, 2H), 3.03 – 2.96 (m, 1H), 2.66 – 2.57 (m, 2H), 1.09 (d, *J* = 6.6 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.0, 140.7, 139.6, 128.8, 128.3, 126.7, 126.2, 125.8, 125.0, 43.7, 43.6, 40.3, 38.0, 17.5. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{18}NOS$ 260.1104; found 260.1111. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:4) stop time = 12 min), giving retention of 6.02 min (major *S* enantiomer) and 7.97 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*(S)-2-methyl-N-(2-morpholinoethyl)-3-phenylpropanamide (**25p**).* Prepared according to procedure A on 0.62 mmol scale at 40 °C (12 h) to give **(*S*)-25p** (82.3 mg) as a white solid in 48% yield and 95% ee from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.27 – 7.24 (m, 3H), 7.19 – 7.16 (m, 2H), 5.70 (s, 1H), 3.64 – 3.56 (m, 4H), 3.23 – 3.18 (m, 2H), 2.92 (dd, *J* = 13.4, 8.9 Hz, 1H), 2.70 (dd, *J* = 13.4, 6.1 Hz, 1H), 2.48 – 2.41 (m, 1H), 2.38 – 2.31 (m, 3H), 2.27 – 2.21 (m, 3H), 1.19 (d, *J* = 6.8 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.3, 139.9, 128.8, 128.2, 126.0, 66.8, 56.5, 52.9, 43.8, 40.6, 35.1, 17.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{25}N_2O_2$ 277.1911; found 277.1921. Enantioselectivity was determined by HPLC analysis using Chiralpak IG-3 3 μm 4.6 x 150 mm column at 30 °C (Solvent A = 0.1% H_4NOAc in acetonitrile/water (1:20), Solvent B = 0.1% H_4NOAc in acetonitrile/water (20:1) at 1.2 mL/min; %B = 0 min 20%, 2 min 20%, 8 min 30%, 10 min 100%, stop time = 13 min), giving retention of 5.66 min (major *S* enantiomer) and 5.24 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy

*(S)-2-methyl-3-phenyl-N-(pyridin-3-ylmethyl)propenamide (**25q**).* Prepared according to procedure A on 0.62 mmol scale at 80 °C (12 h) to give **(*S*)-25q** (70 mg) as a white solid in 43% yield (corrected for 3 wt% EtOAc) and 96 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.34 (d, *J* = 69.9 Hz, 2H), 7.31 – 7.11 (m, 7H), 5.56 (s, 1H), 4.44 (dd, *J* = 15.1, 6.4 Hz, 1H), 4.23 (dd, *J* = 15.1, 5.5 Hz, 1H), 2.95 (dd, *J* = 13.4, 9.1 Hz, 1H), 2.73 (dd, *J* = 13.4, 6.0 Hz, 1H), 2.51 – 2.44 (m, 1H), 1.24 (d, *J* = 6.8 Hz, 3H). ^{13}C{H} NMR (126 MHz, Chloroform-*d*) δ 175.4, 148.8, 148.6, 139.6, 135.4, 133.8, 128.8, 128.4, 126.3, 123.4, 44.0, 40.7, 40.5, 17.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{19}N2O$ 255.1492; found 255.1497. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column

at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:1.9) stop time = 10 min), giving retention of 3.19 min (major *S* enantiomer) and 3.62 min (minor *R* enantiomer). The absolute stereochemistry was assumed by analogy.

*(S)-N-(benzyloxy)-2-methyl-3-phenylpropanamide (**25r**).* Prepared according to procedure A on 0.62 mmol scale at 40 °C (12 h) to give **(*S*)-25r** (112 mg) as a white solid in 67% yield and 99 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.61 (s, 1H), 7.33 – 7.24 (m, 5H), 7.22 – 7.16 (m, 5H), 4.83 (d, *J* = 11.5 Hz, 1H), 4.66 (d, *J* = 11.4 Hz, 1H), 2.97 (dd, *J* = 13.5, 9.2 Hz, 1H), 2.67 (dd, *J* = 13.5, 5.8 Hz, 1H), 2.24 (s, 1H), 1.19 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 129.7, 129.4, 129.1, 128.9, 126.9, 78.6, 41.3, 40.5, 18.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{17}H_{20}NO_2$ 270.1489; found 270.1493. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:1) stop time = 30 min), giving retention of 25.93 min (major *S* enantiomer) and 28.01 min (minor *R* enantiomer).). The absolute stereochemistry was assumed by analogy.

*methyl (S)-(2-methyl-3-phenylpropanoyl)glycinate (**25s**).* Prepared according to procedure B on 0.62 mmol scale at 80 °C (12 h) to give **(*S*)-25s** (59 mg) as a white solid in 40% yield and 85 ee% from **24**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 - 7.24 (m, 2 H), 7.21 – 7.14 (m, 3H), 5.77 (s, 1H), 4.04 (dd, *J* = 18.4, 5.4 Hz, 1H), 3.91 (dd, *J* = 18.5, 4.8 Hz, 1H), 3.73 (s, 2H), 3.00 (dd, *J* = 13.5, 7.7 Hz, 1H), 2.68 (dd, *J* = 13.5, 7.1 Hz, 1H), 2.53 (h, *J* = 7.1 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.1, 170.8, 140.0, 129.3, 128.8, 126.7, 52.7, 43.8, 41.5, 40.6, 17.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{18}NO_3$ 236.1281; found 236.1282. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (4:1) stop time = 10 min), giving retention of 2.86 min (major *S* enantiomer) and 3.16 min (minor *R* enantiomer).). The absolute stereochemistry was assumed by analogy.

*(R)-N-allyl-3-phenylbutanamide (**25t**).* Prepared according to procedure A on 0.62 mmol scale at 40 °C (12 h) to give **(*S*)-25t** (111 mg) as a white solid in 88% yield and 98 ee% from **21c**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.32 – 7.29 (m, 2H), 7.26 – 7.18 (m, 3H), 5.68 (m, 1H), 5.24 (s, 1H), 5.04 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.98 (dd, *J* = 17.2, 1.6 Hz, 1H), 3.83 – 3.75 (m, 2H), 3.32 (h, *J* = 7.2 Hz, 1H), 2.48 - 2.40 (m, 2H), 1.32 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.5, 146.0, 134.3, 128.8, 126.9, 126.6, 116.3, 46.1, 41.9, 37.2, 21.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{18}NO$ 204.1383; found 204.1383. Enantioselectivity was determined by HPLC analysis using Chiral Cel OJ-RH 5 μm 4.6 x 150 mm column at 30 °C (Solvent A/B= 0.1% formic acid in H_2O/MeOH (1:1.9) stop time = 10 min), giving retention of 7.73 min (major *R* enantiomer) and 6.24 min (minor *S* enantiomer).). The absolute stereochemistry was assumed by analogy.

*(2S,3R)-N-allyl-3-((tert-butyldimethylsilyl)oxy)-3-(4-fluorophenyl)-2-methylpropanamide (**25u**).* Prepared according to procedure A on 0.618 mmol scale at 40 °C (12 h) to give **(*S,R*)-25u** (65 mg) as a white solid in 30% yield and >99:1 d.r from **21e**. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.26 – 7.21 (m, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 5.92 – 5.80 (m, 2H), 5.19 (dq, *J* = 17.3, 1.6 Hz, 1H), 5.14 (dq, *J* = 10.1, 1.3 Hz, 1H) 4.70 (d, *J* = 7.8 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.82 – 3.75 (m, 1H), 2.40 (p, *J* = 7.2 Hz, 1H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.83 (s, 9H), 0.0 (s, 3H), -0.24 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 174.3, 138.7, 134.4, 128.4, 128.4, 117.0, 115.3, 115.1, 51.0, 42.2, 26.0, 18.2, 15.1, -4.6, -5.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{31}FNO_2Si$ 352.2103; found 352.2103.

*(2R)-2-methyl-3-phenyl-propanoic acid (**26**).*[37] Prepared according to the general esterification procedure on 15.5 mmol scale with 0.5 mol% $Yb(OTf)_3$ at 60 °C (3 h). The solvent was then removed by evaporation and diluted with a tetrahydrofuran/water mixture (3:1 vol/vol, 110 mL) and treated with lithium hydroxide (0.56 g, 23.3 mmol) and stirred at 23 °C for 2 h. The reaction mixture was treated with conc. HCl to bring the pH to 4.0 and the mixture was diluted with saturated aqueous ammonium chloride (100 mL) and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride (100 mL), dried over magnesium sulfate, filtered, and concentrated to crude oil. The oil was purified by silica gel chromatography (10–100% ethyl acetate/hexanes) to give **26** (2.46 g, 15.0 mmol) as colorless oil in 97% yield and >99% ee and **16** (2.65 g, 14.94 mmol) as white solids from **4**. Spectral data matches that as previously reported. ^{1}H NMR (400 MHz, chloroform-d) δ 7.40 - 7.20 (m, 5H), 3.13 (dd, *J* = 13.4, 6.3 Hz, 1H), 2.89 - 2.76 (m, 1H), 2.76 - 2.68 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 3H); Enantioselectivity was determined by HPLC analysis using a Chiralcel OJ-3 3 μm 4.6 x 150 mm column at 30 °C (Solvent A/B = Heptane/iPrOH at 1.0 mL/min; %B = 1% isocratic, stop time = 37 min), giving retention times of 15.3 min (major *R* enantiomer) and 18.3 min (minor *S* enantiomer). The absolute stereochemistry was assumed by analogy.

*(R)-2-((1S,4S)-4-(6-fluoroquinolin-4-yl)cyclohexyl)propanoic acid (**27**)* To an inert 5 L reaction vessel was added **1** (100 g, 224 mmol) followed by a prepared solution of 3:1 methanol/trimethylorthoformate (2.9 L, 0.32 wt% water by Karl Fischer titration). The reaction mixture was heated to 45 °C then treated trifluoromethanesulfonic acid (0.8 mL, 9 mmol) and aged for 45 min. The reaction mixture was then heated to 60 °C internal temperature and treated with a prepared solution of yttrium trifluoromethanesulfonate (2.43 g, 448 mmol) in 3:1 methanol/trimethylorthoformate solution (100 mL) and aged for 2 h. The reaction was cooled to 40 °C and the solvent was removed *in vacuo*. The concentrated reaction mass was treated with dimethylacetamide (500 mL) and warmed to 45 °C. The reaction mixture was treated with 5N NaOH (135 mL, 680 mmol) over 10 min, aged for 16 h, then quenched by the addition of 50 wt% citric acid aqueous solution (250 mL). The temperature was raised to 70 °C, treated with water (250 mL) over 40 min, then cooled to 20 °C over 6 h and held at 20 °C for an additional 12 h. The product was isolated by filtration and the wet cake was washed with 1:1 DMAc/water (500 mL) followed by 1:3 acetonitrile/water (600 mL) and dried in a 50 °C vacuum oven for 18 h to afford **27** (57.3 g, 190 mmol) as a light tan solid in 85% yield. ^{1}H NMR (600 MHz, DMSO-d6) δ 12.09 (s, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.06 (dd, *J* = 9.2, 5.8 Hz, 1H), 7.91 (dd, *J* = 10.9, 2.8 Hz, 1H), 7.61 (ddd, *J* = 9.1, 8.2, 2.8 Hz, 1H), 7.45 (d, *J* = 4.5 Hz, 1H), 3.41-3.27 (m, 1H), 2.72 - 2.63 (m, 1H), 1.86 - 1.61 (m, 9H), 1.08 (d, *J* = 6.8 Hz, 3H); ^{13}C{H} NMR (101 MHz, DMSO-d6) δ 177.7, 159.9 (d, *J* = 245.4 Hz, 1C), 152.2, 149.8, 145.1, 132.6 (d, *J* = 10.1 Hz, 1C), 127.2 (d, *J* = 10.1 Hz, 1C), 118.9 (d, *J* = 26.3 Hz, 1C), 118.7, 107.1 (d, *J* = 22.2 Hz, 1C), 37.2, 35.7, 28.7, 27.8, 27.2, 26.2, 15.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{22}FNO_2$ 302.1551, found 302.1563. Stereochemical purity was determined by HPLC analysis using Chiral Cel OJ-3 .0 mm 4.6 x 150 mm column at 25 °C (Solvent A = heptane, Solvent B = MeOH/EtOH (1:1) at 1.0 mL/min; %B = 0 min 5%, 25 min 15%, 30 min 15% stop time = 30 min), giving retention of 10.10 min (major *R* diastereomer) and 13.20 min (minor *S* diastereomer). The absolute stereochemistry was confirmed through comparison to an authentic sample.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: ( )

High-throughput data, regression Model R-Code, parallel kinetic isotope experiment, spectral and HPLC data for all compounds (PDF)

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Notes

The authors declare no competing interest

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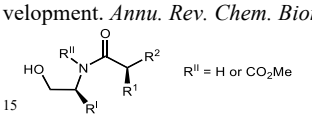

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