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Synthesis of amine functionalized oxazolines with applications in asymmetric catalysis

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ABSTRACT

This paper describes the synthesis of three classes of amine functionalized oxazolines that have been successfully used in asymmetric catalysis in our laboratory. Failed synthetic routes and significantly improved procedures are discussed including the synthesis of ligands for Nozaki–Hiyama–Kishi (NHK) carbonyl allylation reactions that do not require chromatography for purification.

1. Introduction

As the field of asymmetric catalysis has grown in the past few decades, the need for novel chiral catalysts, which can facilitate new and exciting asymmetric reactions has become vital. Oxazoline based chiral motifs are one class of ligands that have been extensively used in asymmetric methodologies and the oxazoline moiety can be considered a privileged ligand structure.[1] This is primarily due to a number of attractive qualities of the oxazoline framework including rigidity, modularity, and the ability to bind metals through the nitrogen lone pair.[2,3] As oxazoline based ligands have grown in popularity, the need for short and concise syntheses of new derivatives is desirable. In considering oxazoline synthesis, numerous methods have been reported. [2–7] However, seldom described are the subtleties that one encounters during synthesis of the desired oxazoline. This report is focused on the pitfalls and successes our laboratory encountered in the synthesis of our oxazoline based catalysts.

2. Results and discussion

A key element of our catalyst design is the ability to expand the diversity of accessible structures while incorporating recognized metal binding motifs used in reported asymmetric catalysts. Additionally, the catalyst must be easily synthesized from readily available chiral building blocks in order to make systematic changes more facile. Based on these criteria, we have focused on the amine functionalized oxazoline core structure depicted in Figure 1.[8,9] This oxazoline template contains three noteworthy features: (1) multiple chiral centers can be introduced bearing various substituents, (2) the building blocks are commercially available amino acids and alcohols or can be easily synthesized, and (3) the pendant amine can be systematically elaborated. These characteristics led our laboratory to pursue the use of this scaffold in two distinct reaction types: (1) an asymmetric hydrogen bond catalyzed hetero-Diels–Alder reaction,[10,11] and (2) a chromium catalyzed addition of allyl fragments to carbonyls (Fig. 2).[12–14]

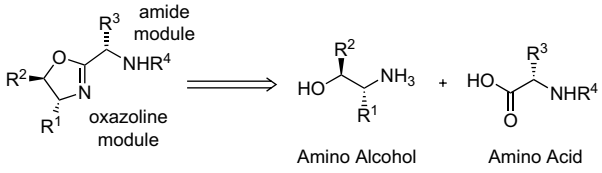

Figure 1. Modular oxazoline scaffold.

2.1. One-pot oxazoline synthesis

Many methods for the synthesis of oxazolines rely on a two-step procedure of β-hydroxyamide formation followed by cyclic dehydration to form the oxazoline.[15] The peptide coupling can be accomplished with various standard methods (vida infra) but the key step in accessing the amino-oxazoline is the cyclization of the peptide. To access our desired amino-oxazoline template, the approach would require the coupling of a suitably *N*-protected α-amino acid and an amino alcohol, followed by deprotection to furnish the free amine (Scheme 1).

Early efforts in our lab to perform this reaction using standard oxazoline forming reactions (conversion of the alcohol to a good leaving group) lead to poor yields of the desired template. This brought us to investigate a more synthetically concise approach by

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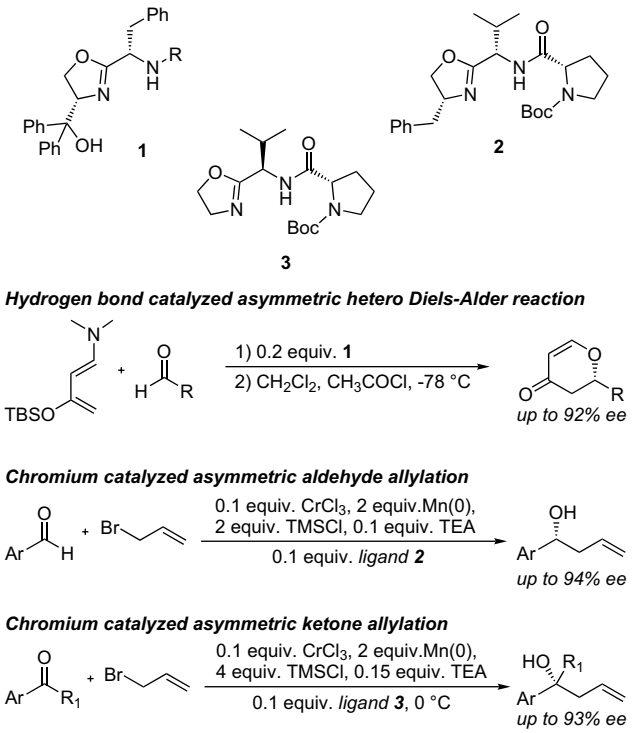
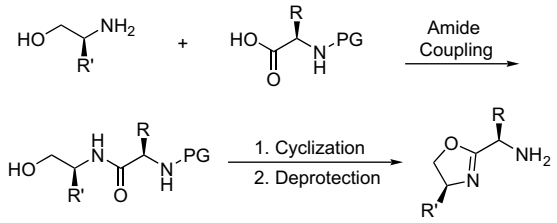
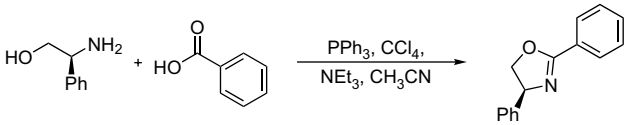


Figure 2. Implementation of our oxazoline framework in asymmetric catalysis.



Scheme 1. Multistep route to desired oxazoline amine scaffold.

combining the amide bond formation and the cyclic dehydration in a single reaction pot. This is especially attractive in the rapid preparation of analogues. We have found this is indeed possible by modifying the conditions originally developed by Vorbrüggen and Krolikiewicz for oxazoline synthesis (Scheme 2).[8,16,17]



Scheme 2. Vorbrüggen and Krolikiewicz oxazoline cyclization.

To successfully utilize this one-pot approach, identification of a protecting group on the amino acid coupling partner was required especially considering the basic reaction conditions initially reported by Vorbrüggen and Krolikiewicz. One goal of this study was to identify a robust protecting group, which is easily removed to allow for the rapid synthesis of analogues. Initial studies indicated that the trifluoroacetamide group was both tolerated and readily removed from an oxazoline by treatment with K_2CO_3 in methanol (Fig. 3). Unfortunately, the chiral center of the amino substituent was epimerized during oxazoline formation (**4**).[18] The synthesis of oxazoline **5** proceeded smoothly although reductive

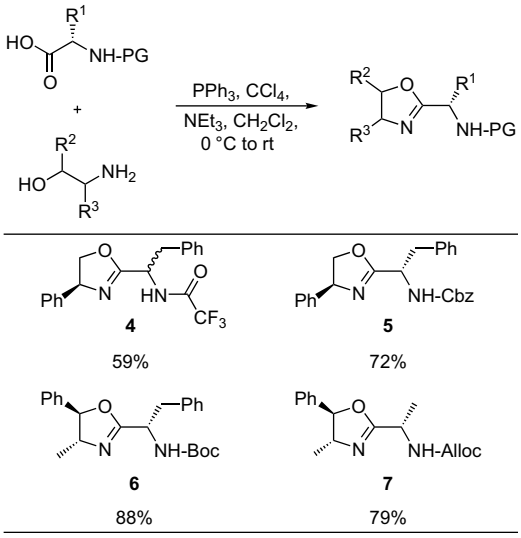


Figure 3. Screening of protecting groups.

removal of the benzyl carbamate (Cbz) protecting group in the presence of a phenyl substituent on the oxazoline ring led to decomposition.[19] It should be noted though, this group is easily removed in the absence of a phenyl substituted oxazoline (vida infra). Attention was then focused on the *tert*-butyl carbamate (Boc) and allyl carbamate (alloc) protecting groups. While the oxazolines were formed in high yields in both cases (**6** and **7**) deprotection once again proved to be ineffective. The acidic conditions required for the removal of the Boc group lead to the concomitant hydrolysis of the oxazoline and Pd-catalyzed removal of the alloc group proved to be futile, possibly due to ligating ability of the starting material.

The 9-flourenylmethyl protecting group (Fmoc) was then investigated. The Vorbrüggen protocol, like most of the commonly used methods for oxazoline synthesis, uses basic reaction conditions. Typically, this would be incompatible with the use of an Fmoc protecting group. A compromise was achieved by careful choice of reaction conditions. Replacing triethylamine with the bulkier Hünig's base and changing the solvent from CH_3CN to CH_2Cl_2 served to enhance the stability of the Fmoc-group. It was found that slow addition of the CCl_4 (dropwise over 3 h) increased the yield of the reaction. In addition, when the reaction was performed under dilute conditions (0.05 M) the transformation proceeded with less observable byproducts. Gratifyingly, when amino alcohol **8** was treated with Fmoc–phenylalanine **9** with these modifications, the protected oxazoline **10** was isolated in 92% yield after chromatography (Fig. 4). With this success, attention was turned to the deprotection of the Fmoc-protected oxazoline. Using the standard protocol of piperidine/MeOH, the deprotection of Fmoc-protected oxazolines proceeded smoothly; although the resulting free

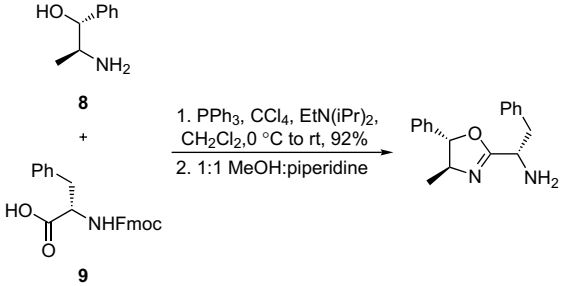
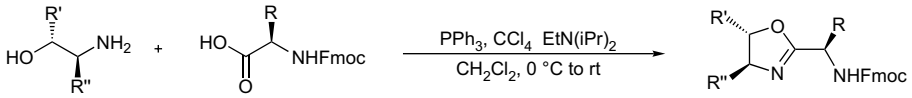
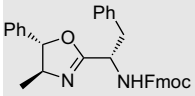
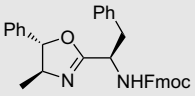
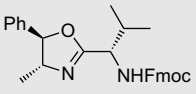
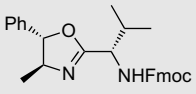
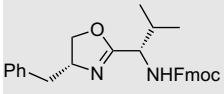
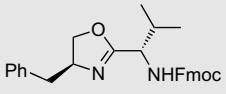
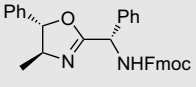
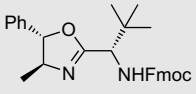
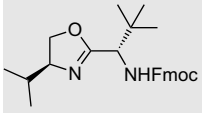
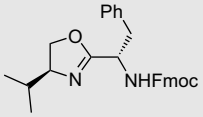
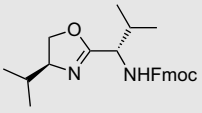
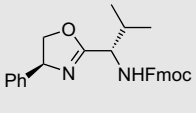
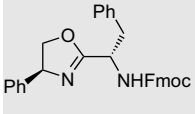
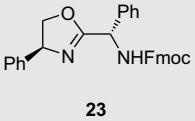
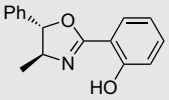
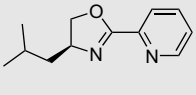


Figure 4. Synthesis of oxazoline amines.

Table 1
Synthesis of functionalized oxazoline amines



Oxazoline	% Yield	Oxazoline	% Yield	Oxazoline	% Yield	Oxazoline	% Yield
 **10**	92	 **11**	89	 **12**	87	 **13**	88
 **14**	65	 **15**	70	 **16**	90	 **17**	78
 **18**	57	 **19**	73	 **20**	75	 **21**	58
 **22**	78	 **23**	78	 **24**	68	 **25**	68

oxazoline amine is moderately unstable and best used promptly after preparation.

The scope of the reaction was evaluated with different Fmoc-protected amino acids and amino alcohols (Table 1). Relative stereochemistry between the reaction partners was seen to be inconsequential as diastereomers could be accessed easily (**10**–**15**), which has proven essential in the optimization of these ligands for asymmetric catalysis. Primary and secondary alcohols were tolerated well, with the secondary alcohols undergoing clean cyclization to yield the diastereomerically pure *trans*-oxazolines (**10**–**13**, **16**, **17**). Steric bulk on the amino acid is well tolerated as shown by the formation of *tert*-leucine derived oxazolines in good yields (**17** and **18**). Other potentially useful ligands like the salicyloxazoline and pyridyl oxazoline were also synthesized using this procedure (**24** and **25**). The phenolic hydroxyl in salicylic acid did not require protection.[20]

As had been discovered with the trifluoracetamide protecting group, an important concern is the racemization of the α-chiral center to the protected amine. This would lead to the formation of epimeric products. In order to test this, Fmoc–phenylglycine, which is susceptible to epimerization at the benzylic position, was used as the amino acid module (Table 1, **16** and **23**).[21] Analysis of the product oxazolines by ^{1}H NMR indicated minimal (<10%) epimerization had occurred.

This protocol proved to be general for the synthesis of a myriad of Fmoc-protected oxazolines and was utilized in analogue synthesis for catalyst optimization in several projects. However, as described below, this method has two main limitations: (1) purification, especially on larger scale, of the Fmoc derived oxazolines has proven difficult due to decomposition during column chromatography and (2) this approach does not necessarily allow us access to all of the oxazoline frameworks desired during our studies of asymmetric catalysis.

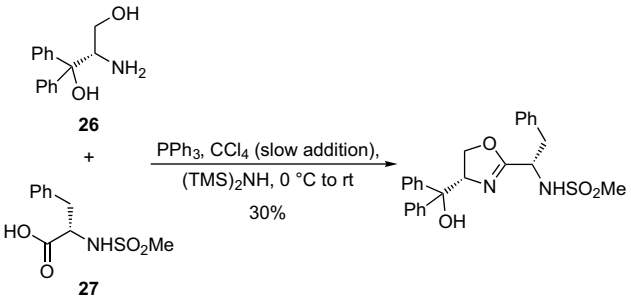
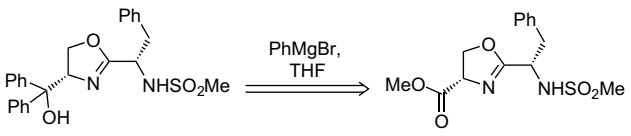


Figure 5. Inadequate synthesis of desired hydrogen bond catalyst.

2.2. Synthetic routes to hydrogen bond catalysts

A hydrogen bond catalyst, bearing two independently tunable sites for hydrogen bonding, has been identified to catalyze the enantioselective hetero-Diels–Alder reaction and has been used to investigate the impact of catalyst acidity on enantioselectivity in this reaction (Fig. 2, **1**).[10,11] Initially, it was thought that this structure would be easily accessed using the modified Vorbrüggen protocol. After considerable optimization, the best result was obtained using the amino alcohol **26** and protected amino acid **27** to yield the desired catalyst in only 30% yield (Fig. 5). Considering this result, alternative routes were pursued.



Scheme 3. Grignard addition to introduce tertiary alcohol.

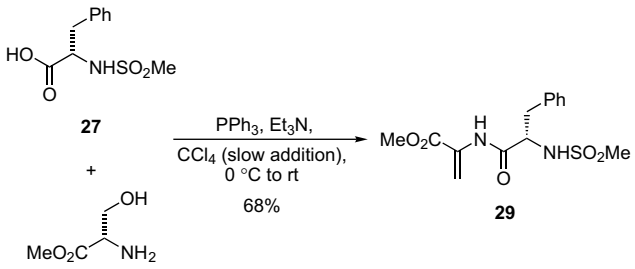


Figure 6. Attempted formation of oxazoline methyl ester.

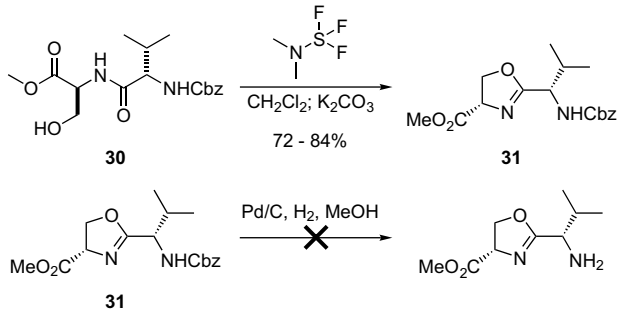


Figure 7. Unsuccessful deprotection of Cbz-protected oxazoline.

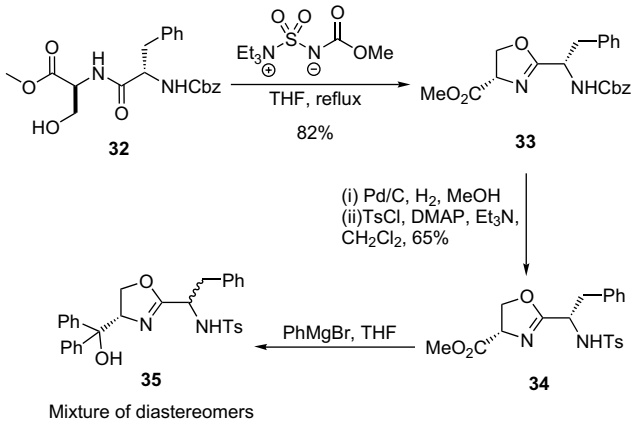


Figure 8. Cyclization of protected peptide with Burgess reagent.

One possible route was considered in which the tertiary alcohol could be introduced in the last step by the addition of a Grignard reagent to an oxazoline ester, as depicted in Scheme 3. The one-pot procedure was performed with phenylalanine derivative **27** and (*S*)-serine methyl ester. Contrary to our expectation, the elimination product **29** was isolated in 68% yield instead of the oxazoline (Fig. 6).

To circumvent this issue, other methods of oxazoline ring closure for this particular scaffold were explored. Of interest was the report by Wipf and co-workers of DAST promoted cyclization of β-hydroxyamides derived from serine esters to the corresponding oxazolines.[22,23] This method was successfully utilized in the cyclization of **30** to oxazoline **31**. Disappointingly, deprotection of the Cbz-protecting group was irreproducible (Fig. 7). This was postulated to be due to the presence of a sulfur containing impurity that is carried over from the cyclization reaction. Extensive purification failed to resolve this issue.

The Burgess reagent was then successfully used in the synthesis of oxazoline **33** in 82% yield (Fig. 8).[24] Deprotection proceeded to completion reproducibly and the free amine was immediately converted to the sulfonamide **34**. However, addition of the Grignard reagent to the oxazoline sulfonamide led to epimerization of the chiral center of the amino acid module of **35**. Attempted addition of alkyl lanthanum or alkyl cerium compounds failed to yield useful amounts of the expected oxazoline.

In view of the problems faced with the addition of Grignard reagents, we decided to revisit oxazoline synthesis from the aminodiol **26**. Upon coupling with Cbz-(*S*)-phenylalanine (**36**) using Anderson's conditions (isobutyl chloroformate (IBCF)/NMM), the amide **37** was obtained in 88% yield (Fig. 9).[25,26] Treatment of amide **37** with *p*-toluenesulfonyl chloride and triethylamine in DCE at room temperature led to the selective formation of the primary tosylate, which can be isolated. Heating to reflux provided the oxazoline in 64% yield over two steps (Fig. 9).[27] It should be noted, if the tosylate formation and thermal induced cyclization is carried out in one pot without isolation of tosylate **38**, an increased yield of 72% over the two steps was observed. Facile deprotection of the benzyl carbamate was achieved by Pd-catalyzed hydrogenolysis.[28] The reaction mixture was filtered through Celite and taken forward without further purification, due to the inherent instability of the free amine functionalized oxazoline. Treatment of the crude product with sulfonyl chloride derivatives at room temperature led to the selective formation of the desired sulfonamide (Table 2).

This sequence proved to be of general applicability in the synthesis of analogues of **1** (Fig. 2). Diastereomers are synthesized with similar yields and variations in the amino acid module are tolerated. Conversion of the Cbz-protected oxazoline to sulfonamides has been accomplished with a wide variety of sulfonyl chlorides (Table 2).

The yields for this reaction were optimized only for the camphorsulfonamides (**43**–**45**). Using these improved and optimized conditions leads to the development of the preferred hydrogen bond catalyst **44**.[10]

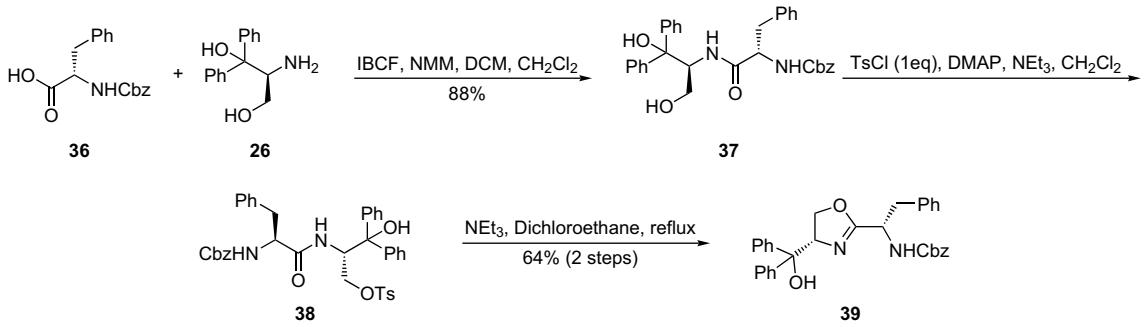
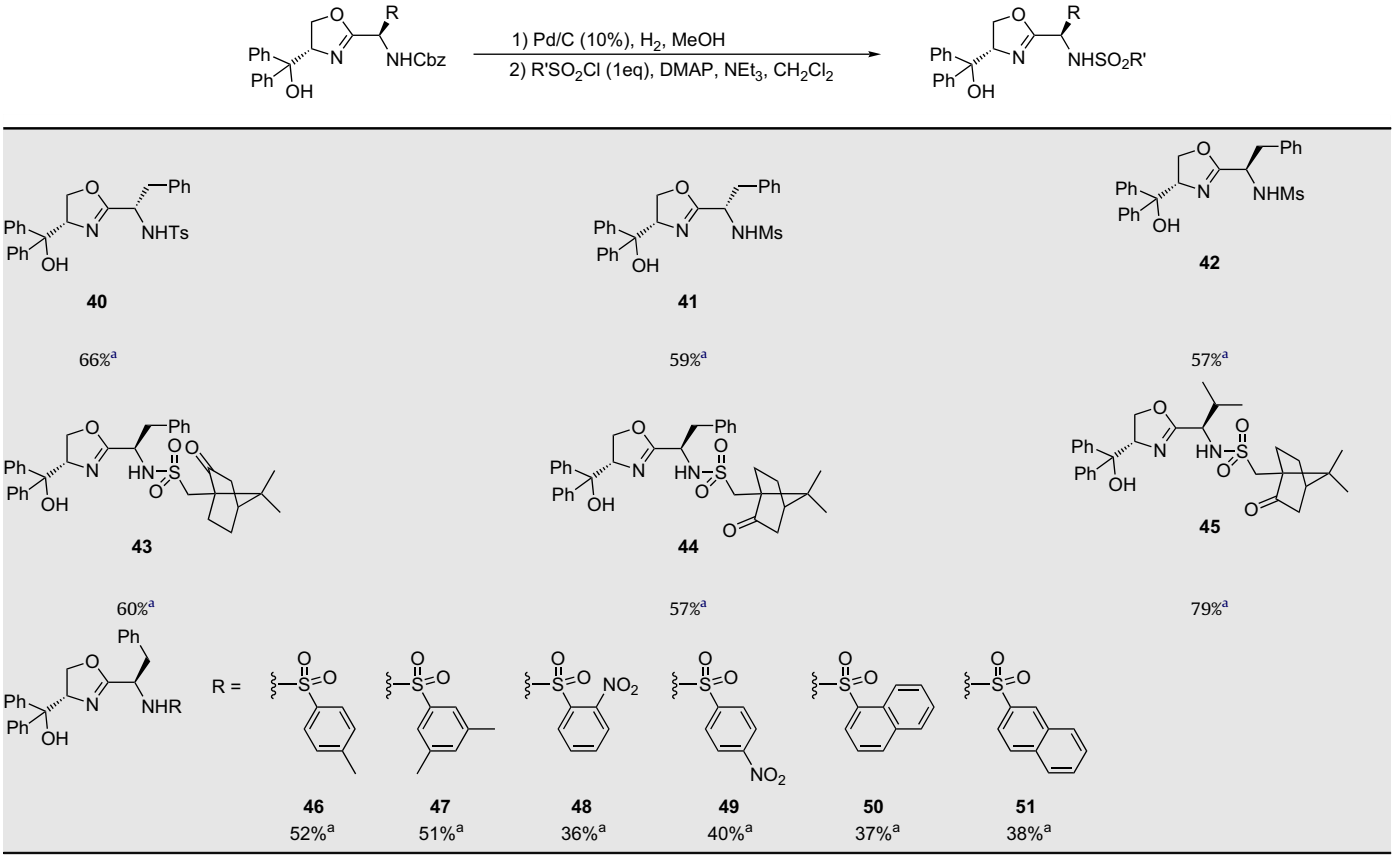


Figure 9. Successful synthesis of desired Cbz-protected oxazoline.

Table 2
Synthesis of a myriad of oxazoline amine catalysts



[a] Yield of sulfonamides from the corresponding Cbz-protecting oxazolines.

2.3. Synthetic routes to oxazoline ligand for implementation in NHK allylation of aldehydes

In our efforts to develop a general catalyst for the asymmetric allylation of aldehydes, oxazoline ligand **2** (Fig. 2) was identified as a highly effective ligand in the chromium catalyzed addition of allyl halides to aryl aldehydes.[12] The initial synthesis of **2** utilized the Vorbrüggen method discussed above where Fmoc-protected valine was coupled and cyclized with phenylalaninol in a one-pot fashion (Fig. 10). Unfortunately, this synthetic route was not applicable to scale up, as the resulting Fmoc-protected oxazoline was difficult to crystallize and decomposed rapidly during column chromatography. With this knowledge other avenues of synthesis were explored, which would alleviate the scale up issues. Initially, (*R*)-phenylalaninol and Cbz-protected valine were coupled using Anderson's conditions, a parallel scheme to the synthesis of hydrogen bond catalyst **44**.[10] It was found that deprotection of the oxazoline **52** after cyclization with TsCl was sluggish and would not progress to full conversion. It was clear from these results that this synthetic path would not yield material in an efficient manner.

In a linear approach, it was thought that the Boc protected proline module of **2** could be installed first by coupling with (*S*)-valine methyl ester using Anderson's conditions to furnish **53** (Fig. 11). Purification of **53** could be effectively performed by recrystallization.

In order to further functionalize **53** to the oxazoline precursor **54**, an acyl transfer procedure developed by Dodd and co-workers was explored.[29] After initial modest success, two important modifications were made to this procedure to improve the yield: (1) use of butyllithium in place of sodium hydride to deprotonate the amino alcohol, and (2) addition of THF as a cosolvent to solubilize the reactants. Execution of this proved fruitful, furnishing the coupled product **54** in good yield (74%) on >10 g scale of **53**. Additionally, this synthetic intermediate is crystalline, which aided in purification and scale up.

With the oxazoline precursor **54** in hand we turned our attention toward methods for oxazoline formation. DAST was initially evaluated to successfully yield the desired oxazoline, but purification required multiple recrystallizations to remove sulfur containing impurities. However, when **54** was submitted to Mitsunobu reaction conditions (PPh_3/DIAD) the reaction progressed cleanly to the cyclized oxazoline **2**.[24] On large scale (>5 g), *the oxazoline **2** is purified by recrystallization making the entire route chromatography*

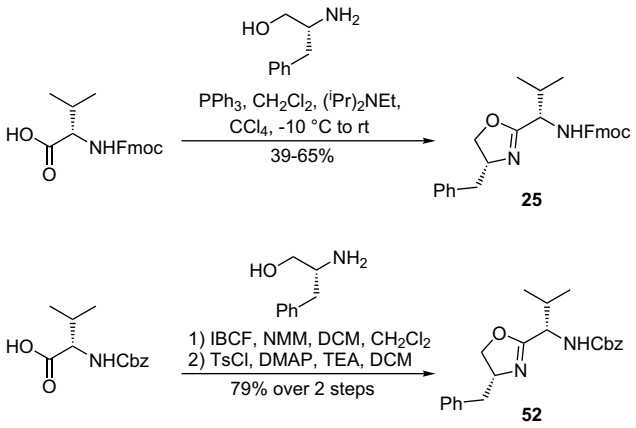


Figure 10. Oxazoline formation methods for oxazoline based ligand.

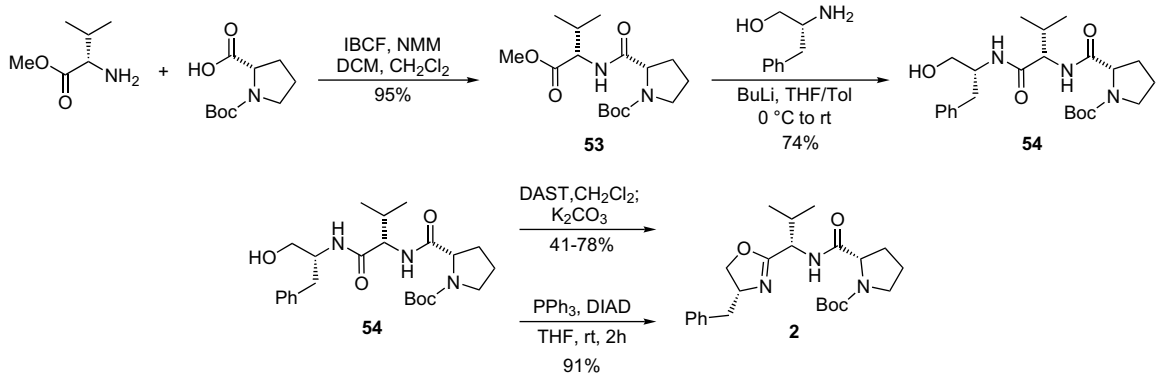


Figure 11. Synthesis of oxazoline ligand **2**.

free. Smaller scale reactions require a small plug of silica to remove highly polar byproducts. Employing this efficient route to ligand **2**, each step in the sequence has been performed on >10 g scale. An additional attractive feature of this synthetic pathway was the ability to now easily derivatize the oxazoline module of the ligand from a common precursor **53**. This both added a degree of convergence to the synthesis and allowed for the access of oxazoline substituents that were not tolerated under other conditions. Oxazoline ligand **3** is one such ligand that matured from this pathway.

2.4. Synthetic routes to a truncated oxazoline ligand for the use in ketone allylation

With the success of oxazoline **2** as an efficient ligand for the NHK allylation of aldehydes, we hypothesized that this same ligand scaffold could be applied to other carbonyl allylation reactions. Through directed screening, ligand **3** was found to be a good ligand for the catalytic asymmetric allylation of ketones.[13] Ligand **3** resembled **2** and it was thought that the synthesis of this ligand motif could parallel that of **2** (Fig. 11). The first step in the synthetic path was the coupling of Boc protected proline with valine methyl ester, using Anderson's conditions, to deliver the diastereomer of **53**, where recrystallization is again used for purification.[25]

The modified Dodd conditions were then used to couple *epi*-**53** with glycinol. However, insolubility of deprotonated glycinol proved to be a significant problem, furnishing the product in only modest yield. With failure to cleanly convert the methyl ester to the desired β-hydroxyamide through an anionic method, a thermally induced amide bond forming reaction was performed. When *epi*-**53** was treated with glycinol (5 equiv) in a toluene/THF mixture at reflux, clean conversion to the oxazoline precursor **55** was observed. This reaction proved to also be applicable to scale up, furnishing multigram quantities of the desired synthetic intermediate. It should be noted that multiple equivalents of glycinol were required in order to carry out the reaction in a timely manner (<3 days). The excess glycinol was efficiently removed through a mild acidic workup to furnish analytically pure **55**. Amide bond formation in this manner was found to be ineffective when substituted amino alcohols such as phenylalaninol (Fig. 12).

Cyclization of **55** to the desired oxazoline ligand **3** proved to be challenging. It was found that when **55** was submitted to TsCl/TEA/DMAP conditions, the reaction would not progress to completion even after prolonged reaction times (>36 h) at reflux in DCE. Interestingly, when the reaction was allowed to progress at ambient temperature in DCM the product could be isolated in an acceptable yield of 75%. Prior experimentation revealed that PPh_3 and DIAD served as an excellent method for the cyclization of our optimal aldehyde allylation ligand **2**. When applying this method to the cyclization of **55**, the desired oxazoline **3** could be obtained in an excellent yield of 93%. This reaction was again applicable to scale up and was conducted on multi-gram scale (10 g) with no reduction in overall yield. Also, this synthetic scheme is chromatography free.

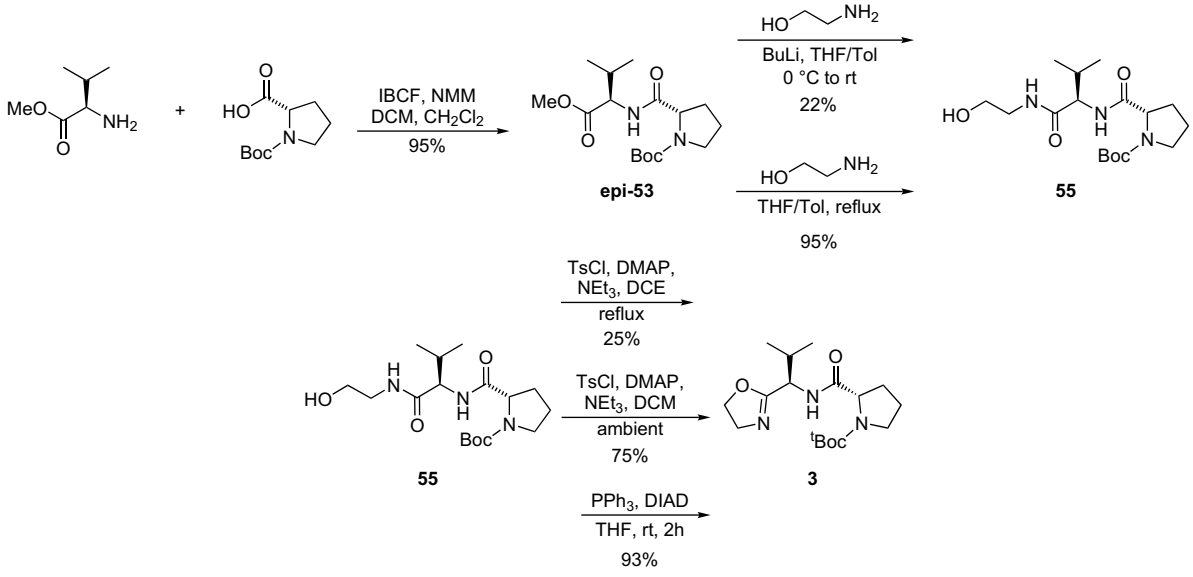


Figure 12. Synthesis of oxazoline ligand **3**.

The use of PPh_3 and DIAD as the optimal regents for oxazoline ring closure has rendered a large majority of our ligand synthesis chromatography free. This is extremely appealing when undertaking the synthesis of new oxazoline ligands for further methodology studies.

3. Conclusions

In conclusion, we have described the synthesis of three ligand classes based on amine functionalized oxazolines. While use of a one-pot method to access the oxazoline amine core is exceptionally useful for analog synthesis, the method is limited especially in terms of scale up. Therefore, alternative methods have been developed, particularly for ligands **2** and **3**, which are used in NHK allylations of carbonyl compounds. These new routes provide the desired ligands in high yields from commercially available chiral building blocks and do not require the use of chromatography for purification. Future work will be focused on extending our use of amine functionalized oxazoline based ligands and utilizing the important synthetic information from this study to access new catalysts.

4. Experimental section

4.1. General

Unless otherwise noted all reactions were performed under an argon or nitrogen atmosphere with stirring. Dichloromethane and dichloroethane were freshly distilled from CaH_2. Tetrahydrofuran was distilled from benzophenone and sodium ketyl prior to use. Toluene was purified by passing through a packed column of activated alumina. DIPEA (Lancaster) was distilled from CaH_2 and stored under nitrogen in the dark. Methanol was distilled from magnesium methoxide.[30] Triethylamine was distilled from CaH_2 prior to use. *N*-Methyl morpholine and isobutyl chloroformate were purchased from Acros and used without further purification. Fmoc amino acids were obtained from Advanced Chemtech and rigorously dried by azeotroping with dry toluene before use. Amino alcohols were purchased or prepared by methods reported in the literature.[31] Cbz amino acids were obtained from Advanced Chemtech and used without further purification. PPh_3 was purified by recrystallization from hexane after a hot filtration. The crystals were washed with hexane and repeatedly azeotroped with dry toluene followed by drying under high vacuum. CCl_4 was purified by stirring overnight with one-fifth its volume of satd KOH. After washing with water, nitrogen was bubbled through for 2 h. It was then percolated through a 2,4-dinitrophenylhydrazine column, distilled from CaH_2, and stored under N_2. *p*-Toluenesulfonyl chloride was purified by dissolving approximately 10 g in 25 mL of $CHCl_3$. To the resulting solution, 125 mL of pentane was added. After standing for 20 min, the precipitated sulfonic acid was removed by filtration. The filtrate was concentrated to about 10 mL and on standing overnight, crystals were obtained. The crystals were filtered, washed with pentane, and dried overnight under high vacuum. Methanesulfonyl chloride was purchased from Acros and used without purification. All the other sulfonyl chlorides were obtained from Aldrich. DMAP was recrystallized from toluene. Thin-layer chromatography was performed with EMD silica gel 60 F_{254} plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained with potassium permanganate or either an ethanolic solution of *p*-anisaldehyde, phosphomolybdic acid, or ninhydrin. Flash column chromatography was performed with EcoChrom MP Silitech 32-63D 60 Å silica gel, slurry packed with solvents indicated in glass columns. All melting points are uncorrected and were recorded on a Electrothermal Melting Point apparatus or a Thomas Hoover Unimelt capillary melting point apparatus. Optical rotations were recorded on a Perkin Elmer Model 343 Polarimeter. IR spectra were recorded using a Mattson Satellite FTIR instrument. NMR spectra were recorded using one of the following: (i) Varian Unity-300 Spectrometer, (ii) Varian XL-300 Spectrometer, (iii) Varian VXR-500 Spectrometer. HRMS were recorded using a Finnigan MAT 95 spectrometer. The following compounds were previously synthesized as well as characterized: (**10**, **11**, **12**, **13**, **16**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, **24**);[8] (**14**, **15**);[12] (**25**);[32] (**26**)[10] (**30**, **31**) ;[33] (**32**, **33**);[28] (**37**, **39**, *epi*-**39**, **40**, **41**, **42**, **43**, **44**, **45**, **46**, **47**);[10] (**3**, **52**, **53**, *epi*-**53**, **55**).[14]

4.2. 2,2,2-Trifluoro-*N*-((*R*)-2-phenyl-1-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)ethyl)acetamide (4)

To a flame-dried 10 mL Schlenk tube, 35 mg of (*S*)-phenylglycinol, (0.25 mmol, measured specific rotation=23.5, lit.=26.5°) 65 mg of (*S*)-trifluoroacteamido phenylalanine (0.25 mmol, measured specific rotation=19.2, lit.=17.2) and 196 mg of PPh_3 (0.75 mmol) were added. The tube was flushed with argon and 2.0 mL of CH_2Cl_2 was added followed by 105 μL of Et_3N (0.75 mmol). The tube was cooled to 0 °C with an ice bath. Using a syringe pump, 97 μL of CCl_4 (1 mmol) was added over 3 h, during which time the tube is allowed to warm up to ambient temperature. The reaction mixture was stirred for 24 h. The contents were directly loaded onto a column and chromatographed with 15% EtOAc in hexanes. The spot with R_f=0.48 (35% EtOAc in hexanes) is the major diastereomer and is isolated in 30% yield as a yellow solid. The minor diastereomer (R_f=0.40, 35% EtOAc in hexanes) is collected along with major diastereomer as the impurity. The combined overall yield was 59%. Mp: 125–128 °C (dec); major diastereomer: $[\alpha]_D^{20}$ −54.8 (*c* 0.14, $CHCl_3$); IR (KBr) 3030, 1710, 1658, 1559, 1551, 1209, 1193 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.22 (dd, *J*=14.0, 4.9 Hz, 1H), 3.41 (dd, *J*=14.0, 5.1 Hz, 1H), 4.14 (dd, *J*=8.9, 8.7 Hz, 1H), 4.79 (dd, *J*=10.2, 8.6 Hz, 1H), 4.79 (dd, *J*=10.2, 8.6 Hz, 1H), 5.03 (dd, *J*=10.1, 4.8 Hz, 1H), 5.17 (dd, *J*=10.5, 10.2 Hz, 1H), 6.85 (m, 2H), 7.14–7.18 (m, 2H), 7.28–7.35 (m, 7H); ^{13}C NMR {^1H} (75 MHz, $CDCl_3$) δ 37.0, 49.6, 69.3, 76.5, 115.8, 126.8, 127.7, 128.1, 128.9, 129.0, 130.1, 135.1, 141.0, 156.7, 165.8; HRMS (CI, isobutane) *m*/*z* $(M+H)^+$ calcd 363.1320, obsd 363.1328.

4.3. Benzyl (*S*)-2-phenyl-1-((*S*)-4-phenyl-4,5-dihydrooxazol-2-yl)ethylcarbamate (5)

This compound was synthesized using similar methods shown above for the synthesis of **4** The reaction was performed with 1 mmol of amino alcohol, 1 mmol of protected amino acid, 3 mmol of PPh_3, 3 mmol of Et_3N, and 5.1 mmol of CCl_4 in 4 mL of CH_2Cl_2. Yield: 72%; yellow oil; $[\alpha]_D^{20}$ −4.5 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$, salt plate), 3028, 3018, 1719, 1667, 1508, 1454, 1217 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.16 (dd, *J*=13.8, 5.9 Hz, 1H), 3.23 (dd, *J*=13.6, 6.0 Hz, 1H), 4.15 (dd, *J*=8.6, 8.2 Hz, 1H), 4.67 (dd, *J*=9.5, 8.9 Hz, 1H), 4.89 (dd, *J*=13.7, 6.3 Hz, 1H), 5.09–5.16 (m, 3H), 5.49 (d, *J*=3.6 Hz, 1H), 7.11–7.38 (m, 15H); ^{13}C NMR {^1H} (125 MHz, $CDCl_3$) δ 38.9, 50.6, 67.1, 69.5, 75.7, 126.8, 127.2, 128.2, 128.3, 128.7. 128.9, 129.0, 129.7, 136.2, 136.6, 141.8, 155.8, 167.2; LRMS (CI, isobutane) *m*/*z* $(M+H)^+$ calcd 401.1, obsd 401.1.

4.4. *tert*-Butyl (*S*)-1-((4*R*,5*R*)-4-methyl-5-phenyl-4,5-dihydrooxazol-2-yl)-2-phenylethylcarbamate (6)

This compound was synthesized using similar methods shown above for the synthesis of **4**. The reaction was performed with 1 mmol of amino alcohol, 1 mmol of protected amino acid, 3 mmol of PPh_3, 3 mmol of Et_3N, and 5.1 mmol of CCl_4 in 4 mL of CH_2Cl_2l. Yield: 88%; colorless oil; $[\alpha]_D^{20}$ 17 (*c* 0.36, $CHCl_3$); IR ($CHCl_3$, salt plate) 3019, 2980, 1709, 1671, 1499, 1216, 1169 cm^{-1}; ^1H NMR

(500 MHz, $CDCl_3$) δ 1.24 (d, J=3.3 Hz, 3H), 1.44 (s, 9H), 3.13 (dd, J=13.7, 5.3 Hz, 1H), 3.24 (dd, J=13.7, 5.4 Hz, 1H), 3.98 (m, 1H), 4.79 (dd, J=11.8, 5.6 Hz, 1H), 4.95(d, J=4.0 Hz, 1H), 5.28 (d, J=3.5 Hz, 1H), 7.19–7.39 (m, 10H); ^{13}C NMR {^{1}H} (125 MHz, $CDCl_3$) δ 21.4, 28.6, 38.8, 49.8, 70.3, 79.9, 89.3, 125.9, 127.1, 128.5, 128.7, 129.1, 130.0, 136.4, 140.0; 155.1; 165.4; LRMS (CI, isobutane) m/z $(M+H)^+$ calcd 381.1, obsd 381.1.

4.5. Allyl (*S*)-1-((4*R*,5*R*)-4-methyl-5-phenyl-4,5-dihydrooxazol-2-yl)ethylcarbamate (7)

This compound was synthesized using similar methods shown above for the synthesis of **4**. The reaction was performed with 0.76 mmol of amino alcohol, 0.75 mmol of protected amino acid, 2.25 mmol of PPh_3, 2.25 mmol of Et_3N, and 3.1 mmol of CCl_4 in 4 mL of CH_2Cl_2. Yield: 79%; colorless oil; $[\alpha]_D^{20}$ 7.8 (c 0.14, $CHCl_3$); IR ($CHCl_3$, salt plate) 3436, 3019, 1719, 1671, 1509, 1215, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (d, J=3.3 Hz, 3H), 1.50 (d, J=3.5 Hz, 3H), 4.04 (dq, J=6.7, 6.7 Hz, 1H), 4.59 (m, 3H), 4.97 (d, J=3.9 Hz, 1H), 5.21 (d, J=5.3 Hz, 1H), 5.32 (d, J=8.6 Hz, 1H), 5.50 (d, J=2.6 Hz, 1H), 5.93 (ddt, J=16.8, 11.0, 5.6 Hz, 1H), 7.27–7.40 (m. 5H); ^{13}C NMR {^{1}H} (125 MHz, $CDCl_3$) δ 19.9, 21.5. 45.5, 65.9, 70.4, 89.3, 117.9, 125.8, 128.7, 129.1, 133.0, 140.1, 155.6, 167.0; LRMS (CI, isobutane) m/z $(M+H)^+$ calcd 289.1, obsd 289.1.

4.6. (*S*)-Methyl 2-(2-(methylsulfonamido)-3-phenylpropanamido)acrylate (29)

This compound was synthesized using similar methods shown above for the synthesis of **4**. The reaction was performed with 1 mmol of amino alcohol, 1 mmol of protected amino acid, 3 mmol of PPh_3, 4 mmol of Et_3N, and 5.2 mmol of CCl_4 in 4 mL of CH_2Cl_2. Approximately 60 mL of SiO_2 was packed into a column with 30% EtOAc and hexanes as the solvent. The reaction mixture is loaded directly onto the column. After an initial elution of nine fractions (16×125 test tubes) with 30% EtOAc and hexanes as the solvent, the eluting solvent was switched to a 40% EtOAc and hexanes as the solvent. Fractions 12–18 were concentrated to yield 222.2 mg of **29** as a white solid (% yield: 68). Mp: 103–105 °C (dec); $[\alpha]_D^{20}$ 60.3 (c 0.14, $CHCl_3$); IR (KBr) 3254, 3217, 1720, 1696, 1684, 1516, 1442, 1329, 1313, 1156, 1143 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (s, 3H), 3.02 (dd, J=14.2, 9.0 Hz, 1H), 3.31 (dd, J=14.2, 5.2 Hz, 1H), 3.82 (s, 3H), 4.22 (ddd, J=8.8, 5.1, 5.1 Hz, 1H), 5.27 (d, J=4.0 Hz, 1H), 5.94 (d, J=0.6 Hz, 1H), 6.62 (s, 1H), 7.26–7.3 (m, 3H), 7.33–7.36 (m, 2H), 8.52 (s, 1H); ^{13}C NMR {^{1}H} (125 MHz, $CDCl_3$) δ 39.0, 40.8, 53.3, 59.8, 110.0, 127.8, 129.3, 129.8, 130.8, 136.2, 164.3, 169.5; LRMS (ESI) m/z $(M+Na)^+$ calcd 349.1, obsd 349.1.

4.7. (*S*)-Methyl 2-((*S*)-1-(4-methylphenylsulfonamido)-2-phenylethyl)-4,5-dihydrooxazole-4-carboxylate (34)

A Schlenk tube was charged with 54 mg of 10% Pd/C and the tube was flushed with argon. In a 25 mL flask, 448 mg of oxazoline **33** (1.17 mmol) was dissolved in 8 mL of dry MeOH and cannulated into the Schlenk tube. A further 4 mL was used for rinsing. The tube was then evacuated under aspirator pressure and filled with H_2 from a balloon. The cycle was repeated thrice more and the tube was left under an H_2 balloon. On completion of reaction (3.5–4 h, by disappearance of oxazoline **33** on TLC; R_f for oxazoline **33**=0.57, 2:1, EtOAc/hexane), the reaction mixture is filtered through a pad of Celite. The filtrate is concentrated and rotavaped with benzene (2×30 mL). The residue is dried for 2 h. under high vacuum and used without further purification. The residue from deprotection was dissolved in 7 mL of dry CH_2Cl_2 under argon along with 29 mg of DMAP (0.23 mmol, 20 mol %). To this solution, 330 μL of freshly distilled triethylamine was added. In a separate flask, 320 mg of p-toluenesulfonyl chloride (1.67 mmol) was dissolved in 4 mL CH_2Cl_2 and cannulated into the flask containing the amine. A further 1 mL of CH_2Cl_2 was used for rinsing. On completion (by TLC: R_f for deprotected oxazoline=0.5 in 10% MeOH in CH_2Cl_2), the reaction mixture is diluted with 20 mL of CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (2×20 mL). The organic layer is dried over Na_2SO_4 and concentrated. After purification by column chromatography, 283 mg of **34** is obtained a yellowish white solid (60% yield). Mp: 130–133 °C (dec); $[\alpha]_D^{20}$ 29.1 (c 0.11, $CHCl_3$); IR (KBr) 3294, 1727, 1670, 1449, 1334, 1176, 1163 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.06 (d, J=3.0 Hz, 2H), 3.73 (s, 3H), 4.19 (dd, J=10.2, 8.2 Hz, 1H), 4.28–4.44 (m, 3H), 7.07–7.10 (m, 2H), 7.22–7.25 (m, 5H), 7.66 (d, J=4.3 Hz, 2H); ^{13}C NMR {^{1}H} (125 MHz, $CDCl_3$) δ 21.8, 40.2, 52.3, 52.9, 67.7, 70.2, 127.3, 127.6, 128.6, 129.7, 129.9, 135.0, 137.0, 143.7, 168.3, 170.6; LRMS (ESI) m/z $(M+H)^+$ calcd 403.1, obsd 403.1.

4.8. (*S*)-2-((*S*)-2-(Benzyloxycarbonylamino)-3-phenylpropanamido)-3-hydroxy-3,3-diphenylpropyl 4-methylbenzenesulfonate (38)

A 25 mL flask was charged with 200 mg of **37** (0.38 mmol) and 4.6 mg of DMAP (0.038 mmol). The flask was flushed with argon and 2 mL of CH_2Cl_2 was added followed by 117.5 μL of NEt_3 (0.84 mmol). In a separate flask, 67.3 mg of TsCl was dissolved in 1 mL of CH_2Cl_2, and cannulated into the flask containing **37**. The contents were stirred until completion of reaction by TLC (R_f for **37**: 0.23 in 50% EtOAc in hexanes; R_f for **38**: 0.53 in 50% EtOAc in hexanes). Approximately 40 mL of SiO_2 was packed into a column with 35% EtOAc in hexanes as solvent. The reaction mixture was loaded as such onto the column and eluted with 30% EtOAc in hexanes as solvent. Concentration of product containing fractions yields 214 mg of **38** as a white solid (%yield: 83). $[\alpha]_D^{20}$ −52.8 (c 0.13, $CHCl_3$); IR (KBr) 3342, 1696, 1664, 1533, 1508, 1367, 1175 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.78 (br s, 2H), 3.75 (br s, 1H), 4.06 (dd, J=11.0, 2.9 Hz, 1H), 4.14–4.18 (m, 1H), 4.25 (dd, J=14.6, 7.1 Hz, 1H), 5.01–5.09 (m, 3H), 5.23 (br s, 1H), 6.49 (br s, 1H), 6.88–6.90 (m, 2H), 7.16–7.41 (m, 20H), 7.61 (d, J=4.0 Hz, 1H); ^{13}C NMR {^{1}H} (125 MHz, $CDCl_3$) δ 21.8, 38.2, 55.4, 56.2, 67.3, 69.4, 79.8, 125.2, 125.5, 125.6, 127.1, 127.6, 127.7, 128.1, 128.2, 128.4, 128.5, 128.7, 128.8, 128.9, 129.3, 129.4, 130.1, 132.5, 136.3, 136.6, 143.7, 144.4, 145.2, 156.0, 171.8; HRMS (CI, isobutane) m/z $(M-OH)^+$ calcd 661.2372, obsd 661.2375.

4.9. *N*-((*S*)-1-((*S*)-4-(Hydroxydiphenylmethyl)-4,5-dihydrooxazol-2-yl)-2-phenylethyl)-2-nitrobenzenesulfonamide (48)

A Schlenk tube was charged with 54 mg of 10% Pd/C and the tube was flushed with argon. In a 25 mL flask, 448 mg of oxazoline *epi*-**39** (1.17 mmol) was dissolved in 8 mL of dry MeOH and cannulated into the Schlenk tube. A further 4 mL was used for rinsing. The tube was then evacuated under aspirator pressure and filled with H_2 from a balloon. The cycle was repeated thrice more and the tube was left under an H_2 balloon. The reaction was monitored by TLC, monitoring the disappearance of the protected oxazoline. Upon completion, the reaction mixture is filtered through a pad of Celite, eluting with MeOH. The filtrate was concentrated and rotavaped with benzene (2×30 mL). The residue is dried for 2 h under high vacuum and used without further purification. The residue from deprotection was dissolved in 5 mL of dry CH_2Cl_2 under argon along with 8 mg of DMAP (0.7 mmol, 20 mol %). To this solution, 398 μL of freshly distilled triethylamine was added. In a separate flask, 133 mg of o-nitrosulfonyl chloride was dissolved in 3 mL CH_2Cl_2 and cannulated into the flask containing the amine. A further 1 mL of CH_2Cl_2 was used for rinsing. The reaction was then monitored by TLC observing the disappearance of the free amine. Upon completion, the reaction mixture was diluted with 20 mL of CH_2Cl_2 and extracted with saturated aqueous $NaHCO_3$ (2×20 mL).

The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification was accomplished by flash chromatography on a 4.5×12 cm column, eluting initially with 100 mL of 50% ether/hexanes followed by 66% ether/hexanes. The product containing fractions were combined and concentrated under reduced pressure. Yield: 36%; yellow solid. Mp: 63–65 °C (dec); $[\alpha]_D^{20}$ 16.8 (*c* 0.11, $CHCl_3$); IR (KBr) 3504, 3366, 1664, 1541, 1448, 1354, 1171 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.10 (dd, *J*=13.9, 6.8 Hz, 1H), 3.16 (dd, *J*=13.8, 5.9 Hz, 1H), 3.92 (dd, *J*=9.4, 9.2 Hz, 1H), 4.03 (dd, *J*=8.6, 8.4 Hz, 1H), 4.58 (dd, *J*=14.6, 6.6 Hz, 1H), 4.95 (dd, *J*=9.4, 9.3 Hz, 1H), 6.21 (d, *J*=4.0 Hz, 1H), 7.15–7.32 (m, 16H), 7.48–7.51 (m, 1H), 7.60–7.64 (m, 1H), 8.00 (dd, *J*=8.2, 1.3 Hz, 1H); ^{13}C NMR {^1H} (125 MHz, $CDCl_3$) major diastereomer δ 39.9, 53.8, 70.4, 72.4, 77.8; 125.7, 125.9, 127.2, 127.3, 127.5, 128.3, 128.5, 128.9, 129.8, 130.3, 132.7, 133.5, 134.4, 135.2, 143.8, 145.2, 147.5, 168; LRMS (CI, isobutane) *m*/*z* $(M+H)^+$ calcd 558.2, obsd 558.3.

4.10. *N*-((*S*)-1-((*S*)-4-(Hydroxydiphenylmethyl)-4,5-dihydrooxazol-2-yl)-2-phenylethyl)-4-nitrobenzenesulfonamide (49)

This compound was synthesized using similar methods shown above for the synthesis of **48** The reaction was performed with 0.7 mmol of amine, 0.7 mmol of sulfonyl chloride, 0.07 mmol of DMAP, and 2.86 mmol of NEt_3 in 5 mL of CH_2Cl_2 and 1 mL of DCE. Yield: 40%; yellow solid. Mp: 85 °C (glassy mass); $[\alpha]_D^{20}$ 27.8 (*c* 0.12, $CHCl_3$); IR (KBr) 3490, 1664, 1606, 1530, 1495, 1448, 1349, 1312, 1165, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.05 (s, 1H), 2.94 (dd, *J*=13.9, 7.6 Hz, 1H), 3.01 (dd, *J*=13.9, 5.1 Hz, 1H), 4.01 (dd, *J*=9.5, 9.4 Hz, 1H), 4.16–4.24 (m, 2H), 5.12 (dd, *J*=9.8, 7.8 Hz, 1H), 5.36 (d, *J*=5.0 Hz, 1H), 7.06–7.08 (m, 2H), 7.17–7.34 (m, 11H), 7.42 (d, *J*=3.7 Hz, 2H), 7.73 (d, *J*=4.5 Hz, 2H), 8.00 (d, *J*=4.5 Hz, 2H); ^{13}C NMR {^1H} (125 MHz, $CDCl_3$) δ 39.6, 53.1, 70.9, 72.6, 78.5, 124.2, 125.8, 126.7, 127.3, 127.5, 127.6, 128.50, 128.58, 128.64, 128.9, 129.7, 135. 3, 143.7, 145.2, 145.5, 130.1, 168.6; LRMS (ESI) *m*/*z* $(M+Na)^+$ calcd 580.2, obsd 580.1.

4.11. *N*-((*S*)-1-((*S*)-4-(Hydroxydiphenylmethyl)-4,5-dihydrooxazol-2-yl)-2-phenylethyl)naphthalene-1-sulfonamide (50)

This compound was synthesized using similar methods shown above for the synthesis of **48** The reaction was performed with 0.7 mmol of amine, 0.7 mmol of sulfonyl chloride, 0.07 mmol of DMAP, and 2.86 mmol of NEt_3 in 5 mL of CH_2Cl_2. Yield: 37%; white solid. Mp: 150–151 °C (dec); $[\alpha]_D^{20}$ 70.0 (*c* 0.07, $CHCl_3$); IR (KBr) 3447, 1664, 1339, 1161, 1075 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.84 (s, 1H), 1.92 (dd, *J*=13.7, 6.6 Hz, 1H), 3.01 (dd, *J*=13.7, 6.1 Hz, 1H), 3.75 (dd, *J*=10.0, 9.3 Hz, 1H), 3.96 (dd, *J*=8.5, 8.3 Hz, 1H), 4.06–4.10 (m, 1H), 4.81 (dd, *J*=9.9, 8.2 Hz, 1H), 5.53 (d, *J*=4.3 Hz, 1H), 6.98–7.00 (m, 2H), 7.08–7.10 (m, 3H), 7.14–7.18 (m, 2H), 7.21–7.35 (m, 9H), 7.45 (ddd, *J*=8.1, 6.8, 1.0 Hz, 1H), 7.50 (t, *J*=7.8 Hz, 1H), 7.89 (d, *J*=4.2 Hz, 1H), 8.06 (d, *J*=4.0 Hz, 1H), 8.23 (dd, *J*=7.3, 1.3 Hz, 1H), 8.34 (d, *J*=4.3 Hz, 1H); ^{13}C NMR {^1H} (125 MHz, $CDCl_3$) δ 39.5, 52.8, 70.5, 72.4, 78.1, 124.3, 124.6, 125.8, 126.9, 127.10, 127.14, 127.2, 127.3, 128.1, 128.3, 128.44, 128.46, 128.51, 129.0, 129.6, 130.6, 133.6, 134.3, 134.8, 135.3, 144.1, 145.6; LRMS (ESI) *m*/*z* $(M+H)^+$ calcd 585.1, obsd 585.2.

4.12. *N*-((*S*)-1-((*S*)-4-(Hydroxydiphenylmethyl)-4,5-dihydrooxazol-2-yl)-2-phenylethyl)naphthalene-2-sulfonamide (51)

This compound was synthesized using similar methods shown above for the synthesis of **48** The reaction was performed with 0.7 mmol of amine, 0.7 mmol of sulfonyl chloride, 0.07 mmol of DMAP, and 2.86 mmol of NEt_3 in 5 mL of CH_2Cl_2. Yield: 38%; white solid. Mp: 89 °C (glassy mass); $[\alpha]_D^{20}$ 34.8 (*c* 0.11, $CHCl_3$); IR (KBr) 3484, 3290, 1665, 1449, 1338, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.97 (s, 1H), 3.00 (dd, *J*=13.7, 6.7 Hz, 1H), 3.03 (dd, *J*=13.7, 6.1 Hz, 1H), 3.83 (dd, *J*=9.3, 9.3 Hz, 1H), 4.00 (dd, *J*=8.3, 8.1 Hz, 1H), 4.25–4.30 (m, 1H), 4.74 (dd, *J*=9.5, 8.5 Hz, 1H), 5.29 (br s, 1H), 7.05–7.07 (m, 2H), 7.13–7.29 (m, 14H), 7.54 (dd, *J*=8.5, 2.0 Hz, 1H), 7.62–7.70 (m, 3H), 7.89 (dd, *J*=7.6, 7.3 Hz, 2H), 8.33 (d, *J*=0.9 Hz, 1H); ^{13}C NMR {^1H} (125 MHz, $CDCl_3$) δ 39.7, 52.8, 70.3, 72.7, 78.1, 122.7, 125.7, 126.6, 127.1, 127.3, 127.4, 127.8, 128.1, 128.4, 128.5, 128.7, 129.2, 129.3, 129.4, 129.6, 129.7, 132.1, 135.0, 135.4, 136.0, 144.0, 145.6, 168.0; LRMS (ESI) *m*/*z* $(M+Na)^+$ calcd 563.1. obsd 563.1.

4.13. (*S*)-*tert*-Butyl 2-((*S*)-1-((*R*)-1-hydroxy-3-phenylpropan-2-ylamino)-3-methyl-1-oxobutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (54)

To a stirring solution of (*R*)-phenylalaninol (5.2 g, 34.4 mmol, 1.1 equiv) in toluene (72 mL) and THF (48 mL), which was cooled to 0 °C, was added *n*-butyllithium (34.4 mL, 1 M in hexanes, 1.1 equiv) dropwise. The mixture was allowed to stir for 15 min at which time **53** (10.3 g, 31.4 mmol, 1.0 equiv) was added in five equal portions. The reaction mixture was allowed to warm to room temperature and monitored by TLC. Upon complete consumption of **53** based on TLC, the reaction mixture was cooled to 0 °C and H_2O (85 mL) was added dropwise to the stirring solution. The organic solvent was then removed under reduced pressure and the contents of the flask was placed in a separatory funnel and extracted with CH_2Cl_2 (3×50 mL). The combined organics were dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. Purification was accomplished by mixed solvent recrystallization (1:1, CH_2Cl_2/hexanes) to give **54**. Yield: 74%; white powder. Mp: 183–185 °C; $[\alpha]_D^{23}$ −57.9 (*c* 0.53, $CHCl_3$); IR (thin film) 3494, 2964, 2931, 2873, 1685, 1644, 1538, 1414, 1392, 1162 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) at 50 °C δ 7.33–7.13 (m, 5H), 6.95–6.33 (br m, 2H), 4.31–4.06 (br m, 3H), 3.70–3.61 (br m, 1H), 3.58–3.35 (br m, 3H), 3.10–2.78 (br m, 3H), 2.36–2.02 (br m, 3H), 1.95–1.80 (br m, 2H), 1.48 (br s, 9H), 0.89–0.72 (br m, 6H); ^{13}C NMR {^1H} (125 MHz, $CDCl_3$) at 50 °C δ 129.3, 128.5, 126.5, 64.1, 60.9, 59.0, 53.4, 47.4, 37.0, 29.2, 28.4, 24.5, 19.4, 17.3; LRMS (ESI) *m*/*z* $(M+Na)^+$ calcd 470.2. obsd 470.2.

4.14. (*S*)-*tert*-Butyl 2-((*S*)-1-((*R*)-4-benzyl-4,5-dihydrooxazol-2-yl)-2-methylpropylcarbamoyl)pyrrolidine-1-carboxylate (2)

To a stirring solution of **54** (10.10 g, 22.56 mmol, 1 equiv) and tetrahydrofuran (150 mL) was added triphenylphosphine (7.10 g, 27.07 mmol, 1.2 equiv) in one portion. This was followed by dropwise addition of diisopropyl azodicarboxylate (5.36 mL, 27.07 mmol, 1.2 equiv) via syringe, to the reaction mixture. The reaction mixture was allowed to clear between drops. The progress of the reaction was monitored by TLC analysis. After 2 h of stirring, the mixture was concentrated under reduced pressure. The residue was taken up in EtOAc (50 mL) and hexanes (50 mL) was added to the mixture. The contents of the flask were allowed to set for 20 min while white precipitate (triphenylphosphene oxide) formed. The precipitate was removed via filtration. The filtrate was concentrated under reduced pressure and the process was repeated twice. The solid was dissolved in ca. 50 mL of 1:1 Et_2O/Hexanes and Et_2O was removed in vacuo until solid began to precipitate. Et_2O was then added dropwise to redissolve the solid. The flask was then placed in a ca. 10 °C refrigerator to recrystallize the product. The mother liquor was removed by filtration and the crystals were washed with 15 mL of cold hexanes and dried in vacuo to yield **2**. Yield: 91%; white powder. Mp: 83.3–85.8 °C; $[\alpha]_D^{20}$ −70 (*c* 0.25, MeOH); IR (KBr) 3273.8, 3061.6, 2962.4, 2872.6, 1702.3, 1661.0, 1550.0, 1453.4, 1398.5, 1226.6, 1162.5, 982.8, 700.7 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) at 70 °C δ 7.31–6.97 (m, 5H), 4.58 (dd, *J*=8.30, 5.37 Hz, 1H), 4.42–4.27 (m, 2H), 4.22 (t, *J*=8.79 Hz, 1H), 3.96 (t, *J*=7.81 Hz, 1H), 3.49–3.42 (m, 2H), 3.09 (dd,

J=14.16, 5.37, 1H), 2.65 (dd, J=13.67, 8.30 Hz, 1H), 2.36–2.21 (m, 2H), 2.12 (sext, J=13.62, 6.92, 1H), 2.04–1.82 (m, 2H), 1.47 (s, 9H), 0.92 (dd, J=6.84, 1.47 Hz, 6H); ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) at 70 °C δ 171.8, 166.4, 155.1, 138.0, 129.3, 128.5, 126.5, 80.3, 72.2, 67.2, 60.6, 52.5, 47.0, 41.8, 31.8, 28.4, 24.2, 24.0, 18.8, 17.7; HRMS (EI) m/z $(M)^+$ calcd 429.2628, obsd 429.2611.

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