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Diastereoselective Copper-Mediated Conjugate Addition of Functionalized Magnesiates for the Preparation of Bisaryl Nrf2 Activators

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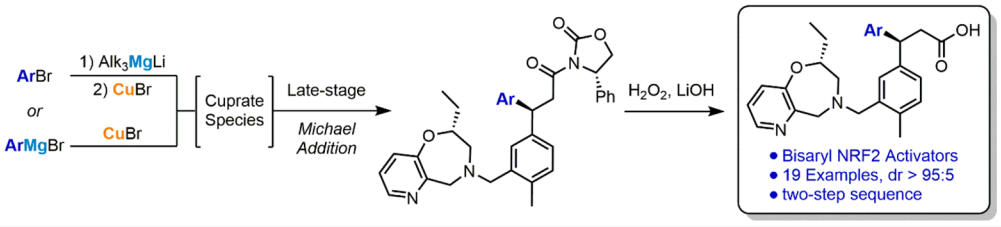

ABSTRACT: A two-step metal−halogen exchange and diastereoselective copper-mediated Michael addition onto a complex α,β-unsaturated system has been developed and applied toward the synthesis of bisaryl Nrf2 activators. Optimization of metal−halogen exchange using $(n\text{-Bu})_3\text{MgLi}$ allowed for the preparation of custom aryl-functionalized magnesiate reagents at noncryogenic temperatures. Following transmetalation, these reagents were used in highly diastereoselective Michael addition reactions.

INTRODUCTION

Michael additions to α,β-unsaturated systems allow for facile synthesis of complex chiral molecules and remain as some of the most well-studied and robust C−C and C−heteroatom bond-forming reactions.[1] Since the simultaneous discovery of copper-mediated conjugate additions (CA) by Näf and Corey in 1972, development of various other metal catalysts and ligands as well as chiral auxiliaries led to ease of control of the regio- and stereochemical outcome of these reactions.[2−12] To date, Michael addition reactions have seen extensive utilization for the synthesis of complex natural products as well as pharmaceuticals (Figure 1).[13−18]

In particular, multiple routes for the synthesis of the 3,3-bisarylpropionic acid series of noncovalent Nrf2 activators developed via a collaboration of GlaxoSmithKline and Astex Pharmaceuticals featured a key step of racemic rhodium-catalyzed conjugate addition.[19,20] Originally synthesized utilizing these methods, GSK '419 (**419**) and relative compounds were identified as leads of interest possessing favorable physicochemical property profiles.[21,22] In an effort to expand the structure−activity relationship (SAR) in this series, a study of the steric and electronic contributions of the aryl group exemplified by the benzotriazole moiety was undertaken. However, the legacy synthetic routes were not amenable to such rapid SAR exploration; in all cases, the point of diversity would be introduced early on in the sequence and the shortest route required six steps, including a chiral HPLC separation to isolate the desired enantiomer (Scheme 1; top).

In this paper, we present a shortened synthesis of **419**, as well as other analogues in the bisaryl series, requiring only two synthetic steps from an aryl bromide and a common late-stage intermediate (Scheme 1; bottom). In this sequence, the bisaryl chiral center is forged via copper-mediated conjugate addition of an arylmagnesium species. While a chiral variant of Rh-catalyzed conjugate addition would be an attractive approach for synthesis, such conditions typically require optimization of catalyst and ligand for each substrate in order to obtain excellent selectivity. Therefore, we sought to develop a method of high selectivity for a broad array of analogues. The complexity of the Nrf2 bisaryl system necessitated the development of a robust procedure for the generation of an organometallic species which could not be achieved via traditional Grignard reagent formation using magnesium metal or metal−halogen exchange with organolithium reagents. For this reason, herein we describe results of optimization of metal−halogen exchange with various magnesium complexes and the associated substrate scope to generate species for late-stage Michael addition with >95:5 diastereomeric ratio.

RESULTS AND DISCUSSION

Examples of 1,4-additions affording chiral centers with excellent diastereoselectivity and high yields have been

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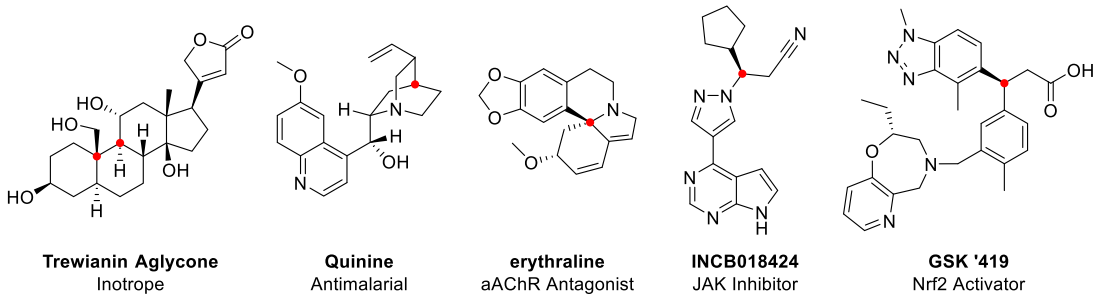
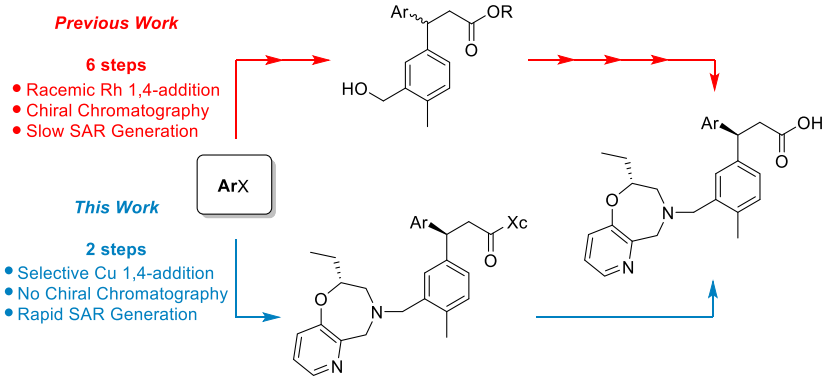
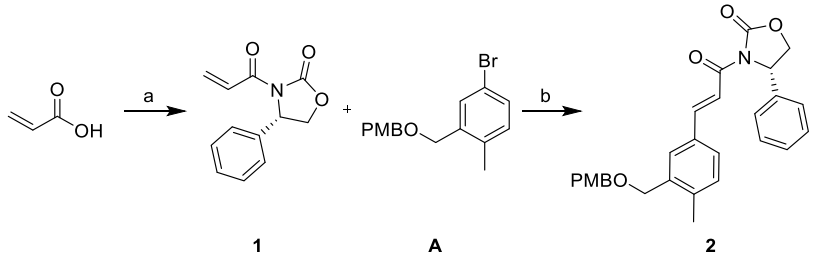


Figure 1. Examples of compounds of pharmaceutical interest where marked centers (red dot) were established via Michael addition reactions.

Scheme 1. Synthesis of Bisaryl Propionic Acid Nrf2 Activators



Scheme 2. Synthesis of Chiral *N*-Enoyloxazolidin-2-one 2

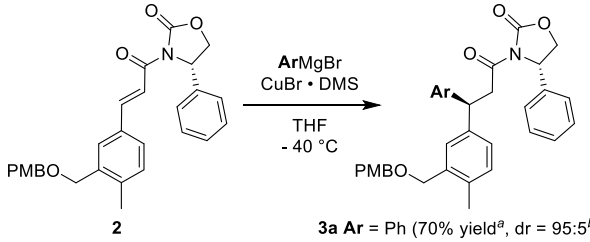


[a]Acryloyl chloride, DIPEA, THF, then (*S*)-(+)-4-phenyl-2-oxazolidinone, LiCl, 1 h, 81%. [b]Aryl bromide **A**, DIPEA, $Pd(OAc)_2/P(o\text{-tol})_3$, DMF, 120 °C, 7 h, 33%.

reported on simple systems employing Grignard reagents in the presence of copper(I) bromide dimethylsulfide complex (CuBr·DMS) and a 4-phenyl-2-oxazolidinone chiral auxiliary, and encouraged our attempts on a more complex, late-stage intermediate.[23−26] As a model system we chose to investigate Michael additions onto chiral *N*-enoyloxazolidin-2-one **2**, which was synthesized in two steps from acrylic acid (Scheme 2).

Treatment of acrylic acid with acryloyl chloride in the presence of DIPEA afforded the corresponding anhydride (not shown). Subsequent nucleophilic attack by (*S*)-(+)-4-phenyl-2-oxazolidinone in the presence of LiCl afforded chiral acryloyl-4-phenyloxazolidin-2-one **1** in 81% yield. Aryl bromide **A**, synthesized via a previously published procedure,[21] was coupled via a Heck reaction to afford **2** in 33% yield. To test whether conjugate addition chemistry would produce acceptable selectivity on the Nrf2 bisaryl scaffold, **2** was treated with cuprates generated from commercially available phenyl- and 2-methylphenylmagnesium bromide reagents and CuBr·DMS at −40 °C (Scheme 3).

Scheme 3. Asymmetric 1,4-Addition of Classic Organocuprates to Chiral *N*-Enoyloxazolidin-2-one 2



[a]Isolated yields after preparative HPLC. [b]Determined by chiral HPLC.

The reaction proceeded well in the presence or absence of the *o*-methyl group, and in fact, the steric bulk at the ortho position led to a notable improvement in diastereoselectivity (95:5 to 97:3 dr for products **3a** and **3b**, respectively). Since the Michael addition was successful on this model system, we sought to employ the approach on an advanced *N*-

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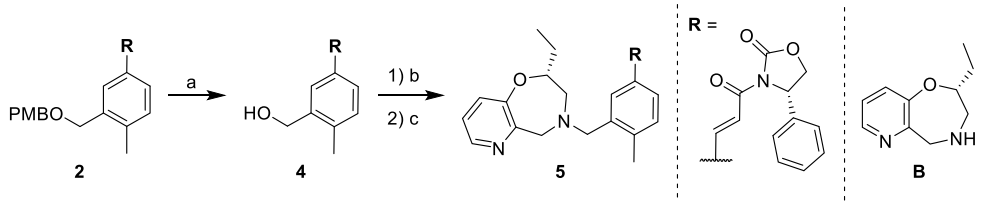
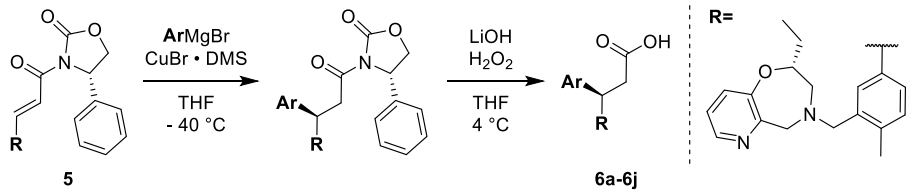
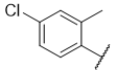
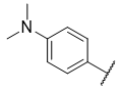
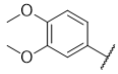
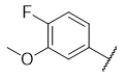
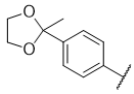
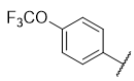
Scheme 4. Synthesis of Advanced *N*-Enoyloxazolidin-2-one 5



[a]DDQ, DCM/H_2O, 1 h, 94%. [b]$SOCl_2$, $CHCl_3$, 16 h, quant. [c]Oxazepine **B**, DIPEA, MeCN, 60 °C, 16 h, 82%.

Table 1. Substrate Scope of Conjugate Addition (CA) with Various Commercially Available Grignard Reagents and Subsequent Hydrolysis



entry	Ar	CA Yield (%)[a]	dr	COOH Product	COOH Yield (%)[d]
1		52	98:2[b]	**6a**	54
2		56	99:1[b]	**6b**	34
3		79	> 95:5[c]	**6c**	55
4		63	> 95:5[c]	**6d**	51
5		23	> 95:5[c]	**6e**	22
6		59	> 95:5[c]	**6f**	52
7		76	> 95:5[c]	**6g**	33
8		81	> 95:5[c]	**6h**	28
9		53	> 95:5[c]	**6i**[e]	55
10		61	> 95:5[c]	**6j**	66

[a]Isolated after flash chromatography. [b]Determined by chiral HPLC. [c]Determined by ^{1}H NMR. [d]Isolated yields after preparative HPLC. [e]Isolated as the benzophenone following aq HCl workup.

enoyloxazolidin-2-one **5** that would provide an ideal two-step route to prepare the desired analogues. For this purpose, benzylic oxazepine **5** was prepared in three steps from PMB ether **2** (Scheme 4).

The PMB protecting group was removed under oxidative conditions (DDQ) to afford benzyl alcohol **4** in 94% yield. Subsequent conversion to a benzyl chloride and its displacement with oxazepine **B**[21] afforded **5** in 82% yield over the two steps. Pleasingly, **5** proved to be a competent substrate for the cuprate-based 1,4-addition despite featuring complexing agents in the form of tertiary amine and pyridine nitrogen atoms.

We subjected **5** to Michael addition with cuprates prepared from various commercially available Grignard reagents and subsequently hydrolyzed the products to their corresponding carboxylic acids (Table 1). We were pleased to see that most CA products were isolated in high yields of 52−81% and

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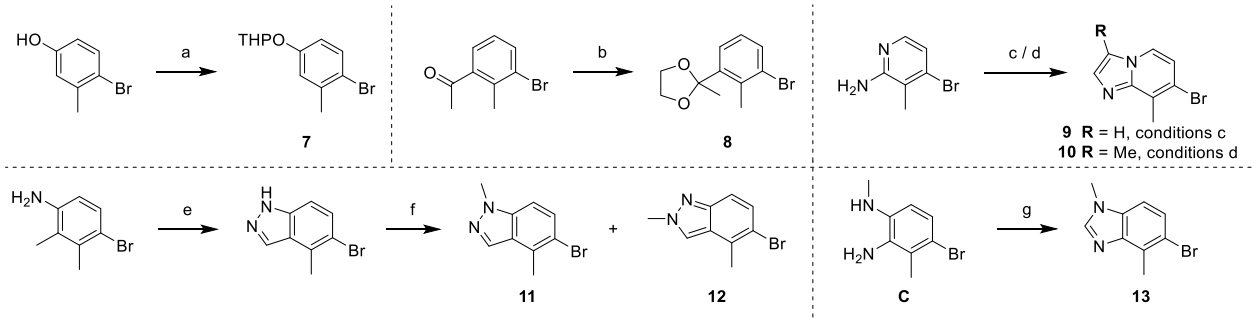
Scheme 5. Synthesis of Custom Aryl- and Heteroaryl Bromides



[a]3,4-Dihydro-2*H*-pyran, PTSA, DCM, 16 h, 93%. [b]Ethylene glycol, PTSA monohydrate, toluene, Dean−Stark apparatus, 56 h, 75%. [c]2-Bromo-1,1-diethoxyethane, 48% aq HBr, EtOH, 60 °C, 48 h, 77%. [d]2-Bromo-1,1-dimethoxypropane, 48% aq HBr, EtOH, 80 °C, 48 h, 51%. [e]Acetic anhydride, KOAc, 18-crown-6, *t*-BuONO, chloroform, 75 °C, 16 h, 90%. [f]NaH, MeI, DMF, room temperature, 16 h, 38 and 21% of **11** and **12**, respectively. [g]Formic acid, 37% aq HCl, 65 °C, 16 h, quantitative.

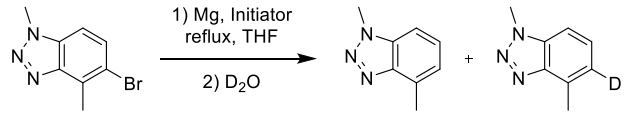
exhibited excellent diastereomeric ratios of >95:5 (Table 1, entries 1−10). The product of conjugate addition with (2-chlorophenyl)magnesium bromide suffered from a low yield of 23% which was attributed to side reactions due to generation of a benzyne intermediate (Table 1, entry 5). In this instance, several products were detected by LC/MS with masses corresponding to the desired product + phenyl ring suggesting electrophilic quenching with benzyne following Michael addition. The conjugate addition products were subsequently hydrolyzed using H_2O_2 and LiOH at low temperature to afford their corresponding carboxylic acids **6a−6j** in 22−66% yields.

Given the success of conjugate addition chemistry with commercially available Grignard reagents, we sought to prepare other organomagnesium reagents from aryl- and heteroaryl bromides that would further modulate physicochemical properties in the Nrf2 bisaryl series. While several of the necessary aromatic bromides were commercially available, we have synthesized additional custom aryl- and heteroaryl bromides as shown in Scheme 5.

Given the anionic character of the cuprate-mediated conjugate addition chemistry, the phenol and benzophenone substrates were protected with THP and ketal protecting groups to afford **7** and **8** in 93 and 75% yield, respectively. Condensation of a commercially available aminopyridine with either 2-bromo-1,1-diethoxyethane or 2-bromo-1,1-dimethoxypropane under acidic conditions (HBr) afforded the corresponding imidazopyridines **9** and **10**, respectively, in adequate yields. The indazole was prepared in one step from its corresponding aniline, and its methylation afforded separable regioisomeric methyl indazoles **11** and **12** in 38 and 21% yield, respectively. Phenylenediamine **C**[21] was condensed with formic acid to afford imidazole **13** in excellent yield.

To further expand the scope of the 1,4-addition reaction and access additional analogues of interest from the variety of aryl- and heteroaryl bromides, a robust method to generate other organomagnesium reagents was investigated. As a model system, we chose to resynthesize **419** using this newly developed 1,4-addition route beginning with the bromobenzotriazole **D**.[21] To generate the desired organomagnesium we first investigated known methods of Grignard reagent preparation from bromobenzotriazole **D** using catalytic amounts of initiators and magnesium metal at refluxing conditions (Table 2).[27−29] Aliquots of reaction mixtures were quenched with water-d_2 (D_2O) and analyzed by LC/MS to monitor for the formation of the deuterated product **14b**.

Table 2. Grignard Reagent Forming Conditions Using Mg and Different Initiators



D 14a 14b

entry	cat. initiator[a]	14a[b] (%)	14b[b] (%)
1	1,2-dibromoethane	0	0
2	iodine	23	0
3	DIBAL-H, LiCl	75	13

[a]Reactions performed under inert atmosphere over 2 h. [b]Conversions by LC/MS relative to % **D** remaining.

Overall, traditional approaches did not successfully promote the desired organomagnesium forming reaction. While 1,2-dibromoethane and iodine failed to produce any detectible **14b** (Table 2, entries 1 and 2), both iodine and DIBAL-H resulted in 23 and 75% conversion to the protodehalogenated product **14a** (Table 2, entries 2 and 3), which presumably arises through quench of a transient Grignard species by an in situ proton source.

In the case where catalytic iodine was used as initiator, protons could only be introduced from adventitious water or solvent; however, given the rigorous drying procedures as well as the measured 0.35% water content of the bromobenzotriazole **D** (coulometric Karl Fischer analysis), the 23% conversion to **14a** (Table 2, entry 2) was unlikely a result of residual water (water content of at least 1% would be needed to quench 25% of the desired Grignard reagent). Therefore, we postulated that one pathway for the formation of the **14a** could be through deprotonation of solvent (THF) following successful Grignard formation, which is analogous to THF decomposition by organolithium reagents.[30,31] To test this hypothesis, the Grignard reagent forming reaction employing iodine as initiator (entry 2) was repeated with THF-d_8 as the solvent (Scheme 6).

Following a quench with saturated ammonium chloride solution, a 1:2 mixture of products **14a** and **14b**, respectively, was isolated in 49% yield, confirming THF is a major source of protodehalogenation. We suspect that deprotonation of THF

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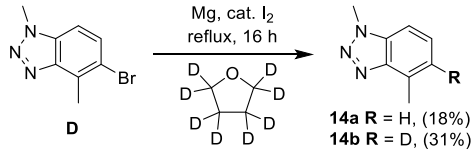
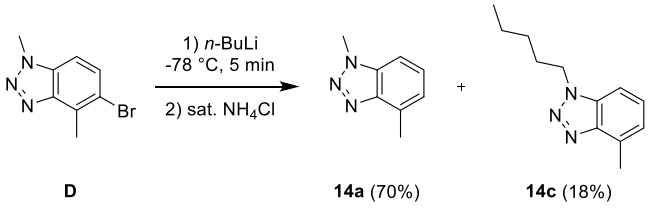
Scheme 6. Formation of an Organomagnesium of D with Mg and cat. Iodine in THF-d_8 at Reflux



observed for derivatives of **D** may be a feature of slowly forming Grignard reagents resulting from prolonged reaction times at reflux. To our knowledge, this observation has not been previously appreciated as shown by the lack of literature precedents for a reaction of this kind.

Given the inefficiency in Grignard reagent formation with magnesium metal under high temperatures, we investigated metal–halogen exchange with *n*-BuLi at low temperature (Scheme 7).

Scheme 7. Metal–Halogen Exchange of D with *n*-BuLi



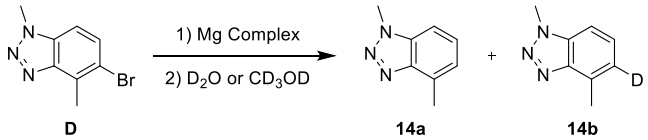
Complete consumption of starting material **D** was observed by LC/MS within 5 minutes following the addition of *n*-BuLi at −78 °C. However, the reaction produced a mixture of the desired **14a** and the alkylated side product **14c**. Given the 4:1 mixture of products **14a** and **14c**, it was postulated that the benzotriazole organolithium reagent deprotonated the *N*-methyl group, generating a highly nucleophilic species that was alkylated by the 1-bromobutane byproduct of metal–halogen exchange.

It was evident that metal–halogen exchange of bromobenzotriazole **D** must be carried out under milder conditions to suppress undesired reactions. Therefore, bromobenzotriazole **D** was subjected to various mono- and diorganomagnesium species as well as triorganomagnesiate complexes with additives that have been shown to be effective for metal–halogen exchange conditions (Table 3).[32−36]

Metal–halogen exchange of the bromobenzotriazole **D** proceeded at room temperature with all magnesium complexes, albeit with a high variability in yield. Monoorganomagnesium complexes caused decomposition with reaction times >4 h. Addition of stoichiometric LiCl to *i*PrMgBr improved the conversion to **14b** from 1 to 14% (Table 4, entries 1 and 2); however, the commercial Turbo Grignard (*i*PrMgCl·LiCl) afforded a greater conversion to **14b** and the undesired **14a** (Table 4, 26 and 14%, respectively, entry 5). Increasing the electron density around the metal center by utilizing a bulkier *s*-Bu group suppressed protodehalogenation and resulted in marginal improvement of the desired reaction over *i*PrMgCl·LiCl (Table 4, 30% **14b**, entry 3), while a *t*-Bu group showed only 4% conversion (Table 4, entry 4).

As demonstrated by Knochel et al., stochiometric chelators of $MgCl_2$ in the presence of *i*PrMgCl·LiCl enhanced the rate of metal–halogen exchange by shifting the Schlenk equilibrium toward production of diorganomagnesium species.[33] Accordingly, treatment of *i*PrMgCl·LiCl with TMEDA, 1,4-dioxane, or 15-crown-5 nearly doubled conversion to **14b** (Table 4, 48, 60, and 65%, entries 6–8) while direct use of commercially available $(s\text{-Bu})_2$Mg yielded similar results (Table 4, entry 9, 62% conversion).

Table 3. Metal–Halogen Exchange of D with Magnesium Complexes



entry	Mg complex	equiv	conditions[a]	14a[b] (%)	14b[b] (%)
1	*i*PrMgBr	1	rt, 4 h	3	1
2	*i*PrMgBr·LiCl	1	rt, 4 h	6	14
3	*s*-BuMgCl·LiCl	1	rt, 4 h	0	30
4	*t*-BuMgCl·LiCl	1	rt, 4 h	6	4
5	*i*PrMgCl·LiCl	1	rt, 4 h	14	26
6	*i*PrMgCl·LiCl	1	TMEDA, rt, 4 h	0	48
7	*i*PrMgCl·LiCl	1	1,4-dioxane, rt, 4 h	0	60
8	*i*PrMgCl·LiCl	1	15-crown-5, rt, 4 h	10	65
9	$(s\text{-Bu})_2$Mg	0.5	rt, 4 h	0	62
10	Me_3MgLi	0.35	−10 °C, 30 min	0	3
11	$(s\text{-Bu})_3$MgLi	0.35	−10 °C, 30 min	0	42
12	$(n\text{-Bu})_2$*i*PrMgLi	0.35	−10 °C, 30 min	0	51
13	$(n\text{-Bu})_3$MgLi	0.35	−10 °C, 30 min	0	63
14	$(n\text{-Bu})_3$MgLi	0.5	−10 °C, 5 min	0	100

[a]All reactions performed under inert atmosphere. [b]Conversions by LC/MS relative to % **D** remaining.

Triorganomagnesiate complexes are known to exhibit an increased reactivity due to the larger electron density on magnesium from the presence of an additional organic ligand. Similar results were observed with $(s\text{-Bu})_3$MgLi, $(n\text{-Bu})_2$*i*PrMgLi, and $(n\text{-Bu})_3$MgLi complexes, where the reaction times to reach peak conversion were drastically shortened from 4 h to 30 min, yielding 42, 51, and 63% **14b**, respectively (Table 4, entries 11–13). Only the Me_3MgLi complex performed poorly, with a 3% conversion to **14b** (Table 4, entry 10).

Since increasing reaction times for each of these complexes resulted in protodehalogenation and decomposition, modulation of reagent equivalents was explored. Triorganomagnesiate complexes feature three ligands, and thus, 0.35 equiv of each was used in an initial attempt to exchange all organic ligands to produce a triarylmagnesiate lithium complex upon complete metal–halogen exchange. However, this was not observed for any of the reagents investigated, and even in the case of the most reactive $(n\text{-Bu})_3$MgLi, 37% of bromobenzotriazole **D** remained, suggesting an exchange of only two *n*-Bu ligands and formation of an *n*-BuAr_2MgLi complex (Table 4, entry 13). Steric considerations do not explain this finding as the literature reports a $(2,4,6\text{-trimethylphenyl})_3$MgLi complex which been isolated and structurally confirmed by X-ray crystallography.[37] On the other hand, various procedures in the literature report using between 0.35 and 3 equiv of triorganomagnesiate lithium reagents in metal–halogen exchange reactions, presumably due to different energetic demands arising from a wide range of electronic properties of diverse aryl halides.[38,39] We found that by increasing the equivalents of $(n\text{-Bu})_3$MgLi from 0.35 to 0.5 complete metal–

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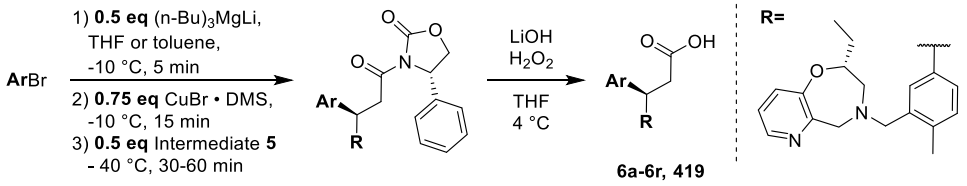
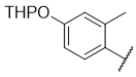
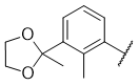
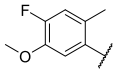
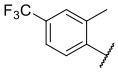
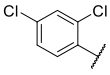
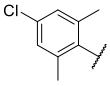
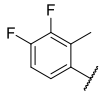
Table 4. Substrate Scope with Various Aryl and Heteroaryl Bromides and Subsequent Hydrolysis



entry	Ar	MHE (%)[a]	CA Yield (%)[b]	dr	COOH Product	COOH Yield (%)[e]
1		100	62	96:4[c]	**6a**	62
2		100	58	> 99:1[c]	**6b**	70
3		100	38	> 95:5[d]	**6k**[f]	53
4		100	39	> 95:5[d]	**6l**[f]	52
5		100	42	> 95:5[d]	**6m**	59
6		100	44	> 95:5[d]	**6n**	38
7		100	0	-	-	-
8		100	33	> 95:5[d]	**6o**	62
9		100	24	> 95:5[d]	**6p**	59
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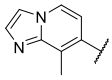
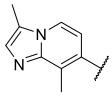
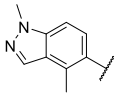
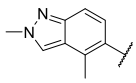
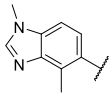
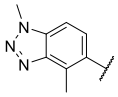
11		100	0	-	-	-
12		100	21	> 95:5[d]	**6q**	33
13		100	51	> 95:5[d]	**6r**	43
14		15	-	-	-	-
15		2	-	-	-	-
16		100	43	98:2[c]	**419**	38

[a]Metal−halogen exchange (MHE); percent conversions by LC/MS after quenching aliquots with D_2O or CD_3OD. [b]Conjugate addition (CA); isolated yields after flash chromatography (silica gel). [c]Determined by chiral HPLC. [d]Determined by ^1H NMR. [e]Isolated yields after preparative HPLC. [f]Isolated as the deprotected compound following aq HCl workup.

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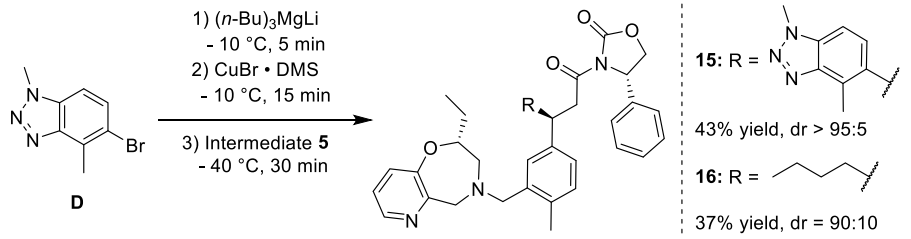
Scheme 8. Michael Addition of D onto Advanced *N*-Enoyloxazolidin-2-one 5



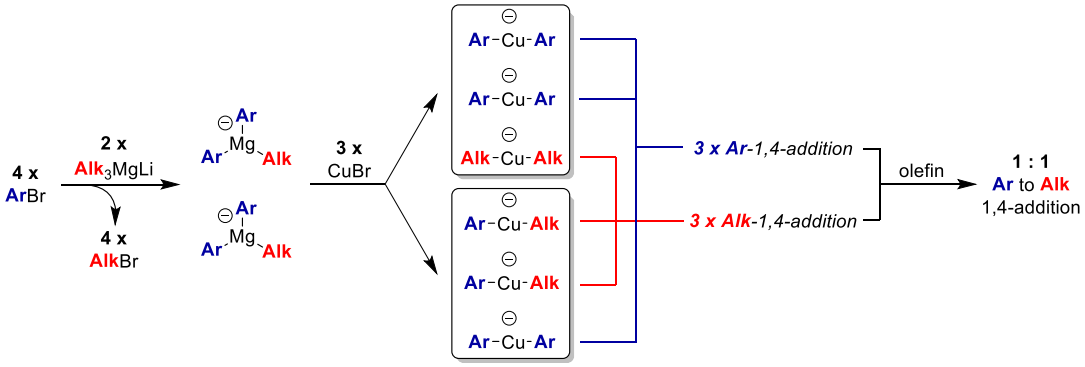


Figure 2. Proposed mechanism of the formation of homo- and heterocuprate reagents with the $Ar_2AlkMgLi$ complex.

halogen exchange and 100% conversion to **14b** was observed within 5 min (Table 4, entry 14). This procedure was adopted to test the full sequence of organomagnesiate formation followed by transmetalation with CuBr·DMS and conjugate addition (Scheme 8).

Gratifyingly, 1,4-addition of the cuprate of **D** to **5** was successful and afforded the desired product **15** in 43% yield and >95:5 dr. As expected, the *n*-Bu addition product **16**, which resulted from the presence of the residual *n*-Bu ligand in the magnesiate complex, was also isolated (37% yield, dr = 90:10). This procedure translated well on gram scale and afforded 611 mg of the desired product in a 43% yield. The chiral auxiliary was subsequently removed under previously described conditions to afford **419** in a 38% yield and 98:2 dr after reversed-phase HPLC, eliminating four steps and the need for chiral chromatography from the original synthesis.

Given the results obtained with the bromobenzotriazole **D**, the scope of this procedure was tested using various aryl and heteroaryl bromides to synthesize additional analogues (Table 4).

It was observed that a majority of both electron-rich and electron-deficient phenyl rings underwent full metal−halogen exchange and afforded their respective 1,4-addition products in 24−62% yields with excellent diastereoselectivity (dr >95:5). As noted previously with the model system which afforded **3a** and **3b** as well as conjugate addition products leading to **6a** and **6b** (Table 1, entries 1 and 2), the presence of the *o*-methyl group enhanced the diastereoselectivity under these conditions presumably due to increased steric bulk (Table 4, entries 1 and 2). As suspected, a substrate bearing a halogen at the ortho position (Table 4, entry 7) proved to be problematic and did not afford a Michael addition product, despite achieving complete metal−halogen exchange; again, benzyne intermediates are suspected. Interestingly, even the most sterically encumbered aryl bromide (Table 4, entry 8) underwent complete metal−halogen exchange and afforded its respective conjugate addition product in a 33% yield.

Heterocyclic aryl bromides proved to be difficult partners in this reaction sequence. Pyridyl bromide (Table 4, entry 10) did not afford its 1,4-addition product despite complete metal halogen exchange. We observed that the presence of a methyl group in the 5-membered ring of imidazopyridines improved the outcome of Michael addition from 0 to 21% (Table 4, entries 11 and 12), likely due to blocking a potential site of metalation. Interestingly, isomeric dimethyl indazoles showed remarkably different reactivity, as one regioisomer underwent full metal−halogen exchange and resulted in 51% yield of conjugate addition while the other regioisomer was resistant to metal−halogen exchange, with only 15% conversion (Table 4, entries 13 and 14). Similarly, benzimidazole **13** was found to be nearly inert to metal−halogen exchange under the magnesiate (Table 4, entry 15, 2% conversion) as well as traditional *n*-BuLi conditions (not shown).

It was noted that most substrates subjected to the newly developed two-step procedure afforded their products in <50% yield (Table 4). While limited studies have been done to elucidate the true mechanism of this reaction sequence, we surmise that upon transmetalation with 0.5 equiv of CuBr·DMS, the presence of a 2:1 ratio of Ar to *n*-Bu ligands results in formation of mixtures of homo- and heteroleptic organocuprates: the diaryl and dialkyl homocuprates as well as the mixed heterocuprate (Figure 2).

The homocuprates transfer one of their groups while retaining the other as a sacrificial ligand. On the other hand, the heterocuprate delivers the alkyl group preferentially and the aryl group is effectively lost. Upon metal−halogen exchange with $(n\text{-Bu})_3MgLi$ and transmetalation with the specified equivalents of CuBr, two possible mixtures of cuprates may be formed. If the transmetalation reaction proceeds at equal rates and leads to a random distribution of cuprate species, the net outcome results in an equal availability for aryl as well as alkyl 1,4-addition. The 1:1 ratio of the benzotriazole **15** and *n*-Bu addition **16** products supports this hypothesis, and the results of optimization of metal−halogen

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exchange on the bromobenzotriazole **D** substrate support the postulated formation of the *n*-BuAr$_2$MgLi complex as the active magnesiate species.

To complete the synthesis of Nrf2 analogs, the CA products were subsequently hydrolyzed using a previously described procedure to afford their corresponding carboxylic acids **6k−6r** in 33−62% yields (Table 4). Biological characterization of these analogues will be reported separately.

CONCLUSION

In conclusion, a shortened two-step synthesis of bisaryl Nrf2 activators was developed using late-stage functionalization via Michael addition of metalated aryl substituents. Asymmetric cuprate-based 1,4-addition was achieved on a complex system featuring both sp^2- and sp^3-hybridized basic nitrogen centers. Several methods for the preparation of a Grignard reagent of bromobenzotriazole **D** were investigated and led to utilization of a mild and rapid metal−halogen exchange procedure using (*n*-Bu)$_3$MgLi. This procedure allowed for a novel, accelerated synthesis of **419** as well as a number of diverse analogues with excellent diastereoselectivity. A mechanism involving formation of homo- and heterocuprate mixtures resulting in 1:1 aryl to alkyl conjugate addition products was postulated. It is hoped that these investigations will stimulate further exploration of high-valent organomagnesium species in organic synthesis.

EXPERIMENTAL SECTION

General Information. Compounds **A**, **B**, **C**, and **D** were prepared according to known procedures.[21] Grignard as well as other reagents were commercially available and were used without further purification. All reactions were monitored by liquid chromatography−mass spectrometry (LC/MS) using Waters Acquity UPLC and Waters QDa or thin layer chromatography (TLC). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker UltraShield Plus (101, 126, 400, 501 MHz) spectrometers, using DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. HRMS spectra were determined on an Orbitrap (QE Plus) or Waters Xevo G2-S (ESI-Tof) mass spectrometers in positive-ion mode. Compounds **6a−6r** and **419** were isolated via preparative mass directed auto purification (MDAP) system using XSELECT CSH C18 column with a mobile phase of 10 mM ammonium bicarbonate in H_2O and MeCN.

Synthesis. *4-Bromo-2-(((4-methoxybenzyl)oxy)methyl)-1-methylbenzene (**A**).*[21] ^{13}C NMR{^{1}H} (101 MHz, DMSO-d_6) δ = 158.80, 139.26, 135.32, 132.01, 130.08, 130.06, 130.00, 129.30, 118.50, 113.70, 71.54, 68.73, 55.04, 17.78. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{18}BrO_2$ 321.0485, found 321.0313.

*(R)-2-Ethyl-2,3,4,5-tetrahydropyrido[2,3-f][1,4]oxazepine dihydrochloride (**B**).*[21] ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 155.72, 144.34, 141.77, 132.45, 126.70, 80.80, 51.59, 48.46, 26.28, 10.14. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{10}H_{15}N_2O$ 178.1184, found 178.1183.

*4-Bromo-N-1,3-dimethylbenzene-1,2-diamine (**C**).*[21] ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 136.58, 134.92, 120.49, 118.99, 112.35, 108.82, 30.81, 17.78. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_8H_{12}BrN_2$ 215.0178, found 215.0178.

*5-Bromo-1,4-dimethyl-1H-benzo[d][1,2,3]triazole (**D**).*[21] ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 146.32, 132.80, 131.04, 129.39, 118.36, 110.01, 34.85, 17.01. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_8H_9BrN_3$ 225.9974, found 225.9975.

*(S)-3-Acryloyl-4-phenyloxazolidin-2-one (**1**).* A mixture of acrylic acid (5.46 mL, 80 mmol) in tetrahydrofuran (200 mL) at 25 °C was treated with DIPEA (32.1 mL, 184 mmol) and acryloyl chloride (7.47 mL, 92 mmol) and stirred for 1 h (off-white precipitate formed) before being treated with lithium chloride (2.86 g, 67.4 mmol) and (*S*)-4-phenyloxazolidin-2-one (10 g, 61.3 mmol). The mixture was stirred for an additional 1 h before being quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered, concentrated, and subjected to flash chromatography (30% EtOAc-heptane) to afford the desired product as a white, crystalline solid (10.8 g, 49.7 mmol, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.47−7.35 (m, 3H), 7.35−7.25 (m, 3H), 6.31 (dd, *J* = 2.0, 17.2 Hz, 1H), 5.95 (dd, *J* = 2.0, 10.6 Hz, 1H), 5.52 (dd, *J* = 3.9, 8.5 Hz, 1H), 4.78 (t,*J* = 8.7 Hz, 1H), 4.20 (dd, *J* = 3.9, 8.7 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 164.3, 154.2, 140.1, 131.8, 129.3, 128.5, 128.2, 126.3, 70.8, 57.6. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{12}H_{12}NO_3$ 218.0812, found 218.0812. $[\alpha]_D^{20}$ +170 (*c* 1.0, DCM). mp 87 °C.

*(S,E)-3-(3-(3-(((4-Methoxybenzyl)oxy)methyl)-4-methylphenyl)-acryloyl)-4-phenyloxazolidin-2-one (**2**).* A solution of **A** (20.70 g, 64.4 mmol) in *N*,*N*-dimethylformamide (200 mL) was purged with N_2 for 30 min, then tri-*o*-tolylphosphine (3.92 g, 12.89 mmol), palladium(II) acetate (1.447 g, 6.44 mmol), DIPEA (33.8 mL, 193 mmol), and **1** (14 g, 64.4 mmol) were added, and the mixture was stirred at 110 °C for 7 h before being cooled to room temperature. The mixture was diluted with EtOAc, washed (water, brine), dried (Na_2SO_4), filtered, concentrated, and subjected to flash chromatography (30% EtOAc-heptane) to give a yellow solid, which was triturated in Et_2O (200 mL) and collected by filtration to afford 12 g of a yellow solid which was subjected to flash chromatography (30% EtOAc-heptane) to afford the desired product as a pale yellow solid (9.7 g, 21.20 mmol, 32.9% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.81 (d, *J* = 16.0 Hz, 1H), 7.65 (d, *J* = 15.7 Hz, 1H), 7.62 (d, *J* = 1.5 Hz, 1H), 7.49 (dd, *J* = 1.8, 7.9 Hz, 1H), 7.43−7.36 (m, 2H), 7.36−7.22 (m, 6H), 6.97−6.89 (m, 2H), 5.58 (dd, *J* = 3.8, 8.6 Hz, 1H), 4.80 (t, *J* = 8.6 Hz, 1H), 4.57−4.43 (m, 4H), 4.21 (dd, *J* = 4.1, 8.9 Hz, 1H), 3.74 (s, 3H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 164.5, 159.2, 154.4, 145.3, 140.3, 140.0, 137.8, 132.2, 131.2, 130.6, 129.8, 129.3, 128.5, 128.2, 128.0, 126.3, 117.1, 114.2, 71.9, 70.7, 69.7, 57.7, 55.5, 18.9. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{28}H_{28}NO_5$ 458.1967, found 458.1965.

*(S)-3-((R)-3-(3-(((4-Methoxybenzyl)oxy)methyl)-4-methylphenyl)-3-phenylpropanoyl)-4-phenyloxazolidin-2-one (**3a**).* To an oven-dried glass vessel with a magnetic stirrer was transferred copper(I) bromide−dimethyl sulfide complex (0.063 g, 0.306 mmol) followed by dimethyl sulfide (0.162 mL, 2.186 mmol), and the mixture was stirred until dissolved. Next, anhydrous tetrahydrofuran (1.46 mL) was added, and the solution was cooled on a regular ice/water bath. A 3 M solution of phenylmagnesium bromide in diethyl ether (0.204 mL, 0.612 mmol) was added, and the reaction mixture was stirred over 10 min on the regular ice/water bath. Next, the reaction mixture was cooled to −40 °C on an MeCN/dry ice bath, solid **2** (0.100 g, 0.219 mmol) was added under a stream of nitrogen gas, and the reaction mixture was stirred over 1 h at −40 °C. The reaction was quenched with saturated NH_4Cl solution and combined with additional water and EtOAc. The aqueous layer was extracted three times with EtOAc, and the combined organic portions were dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture. The crude product mixture was purified via flash chromatography on silica gel (10−30% EtOAc/heptane, 12 g RediSep Rf Gold column) to the desired product as a white amorphous solid (86 mg, 0.153 mmol, 69.8% yield, 90% de by chiral HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.29−7.02 (m, 13H), 6.94−6.87 (m, 2H), 5.37 (dd, *J* = 3.7, 8.5 Hz, 1H), 4.68 (t, *J* = 8.6 Hz, 1H), 4.49−4.43 (m, 1H), 4.41 (s, 2H), 4.40 (s, 2H), 4.08 (dd, *J* = 3.8, 8.9 Hz, 1H), 3.86 (dd, *J* = 7.6, 16.7 Hz, 1H), 3.74 (s, 3H), 3.50 (dd, *J* = 8.0, 16.6 Hz, 1H), 2.57−2.43 (m, 2H), 2.17 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 170.6, 159.2, 154.3, 144.5, 141.6, 140.0, 136.8, 134.6, 130.7, 130.5, 129.8, 129.1, 128.8, 128.2, 128.1, 128.0, 127.0, 126.6, 125.9, 114.1, 71.7, 70.6, 70.1, 57.3, 55.5, 46.1, 40.7, 18.4. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{34}H_{33}NO_5Na$ 558.2256, found 558.2258. $[\alpha]_D^{20}$ +62 (*c* 1.0, DCM).

*(S)-3-((S)-3-(3-(((4-Methoxybenzyl)oxy)methyl)-4-methylphenyl)-3-(o-tolyl)propanoyl)-4-phenyloxazolidin-2-one (**3b**).* To an oven-dried glass vessel with a magnetic stirrer was transferred copper(I) bromide−dimethyl sulfide complex (0.063 g, 0.306 mmol) followed by dimethyl sulfide (0.162 mL, 2.186 mmol), and the mixture was stirred until dissolved. Next, anhydrous tetrahydrofuran (1.45 mL)

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was added, and the solution was cooled on a regular ice/water bath. *o*-Tolylmagnesium bromide (2 M, 0.306 mL, 0.612 mmol) was added, and the reaction mixture was stirred over 10 min on the regular ice/water bath. Next, the reaction mixture was cooled to −40 °C on an MeCN/dry ice bath, solid **2** (0.100 g, 0.219 mmol) was added under a stream of nitrogen gas, and the reaction mixture was stirred over 1 h at −40 °C. The reaction was quenched with saturated NH_4Cl solution and combined with additional water and EtOAc. The aqueous layer was extracted three times with EtOAc, and the combined organic portions were dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture. The crude product mixture was purified via flash chromatography on silica gel (10−30% EtOAc/heptane, 12 g RediSep Rf Gold column) to afford the desired product as a white amorphous solid (89 mg, 0.154 mmol, 70.4% yield, 94% de by chiral HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.36−7.16 (m, 7H), 7.15−7.00 (m, 7H), 6.93−6.87 (m, 2H), 5.38 (dd, J = 3.8, 8.6 Hz, 1H), 4.67 (t, J = 8.7 Hz, 1H), 4.62 (t, J = 7.7 Hz, 1H), 4.44−4.34 (m, 4H), 4.07 (dd, J = 3.8, 8.9 Hz, 1H), 3.91 (dd, J = 8.5, 16.9 Hz, 1H), 3.75 (s, 3H), 3.39 (dd, J = 7.1, 17.0 Hz, 1H), 2.17 (s, 3H), 2.16 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 170.7, 159.2, 154.3, 142.0, 141.0, 134.0, 136.8, 136.1, 134.5, 130.8, 130.7, 130.5, 129.7, 129.1, 128.2, 128.2, 127.4, 126.6, 126.5, 126.5, 125.8, 114.1, 71.6, 70.6, 70.0, 57.4, 55.5, 41.9, 41.3, 19.9, 18.4. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{35}H_{35}NO_5Na$ 572.2413, found 572.2419. $[\alpha]_D^{20}$ +98 (c 1.0, DCM).

*(S,E)-3-(3-(3-(Hydroxymethyl)-4-methylphenyl)acryloyl)-4-phenyloxazolidin-2-one (**4**).* To a biphasic mixture of **2** (5.827 g, 12.74 mmol) in dichloromethane (87 mL) and water (4.33 mL) was added DDQ (4.34 g, 19.10 mmol), and the resulting mixture was stirred over 1 h at room temperature. Next, the mixture was diluted with DCM and saturated $NaHCO_3$ solution, and the system was transferred to a separatory funnel. After the layers separated, the organic layer was drained. Over time, the aqueous layer showed formation of insoluble solids. The aqueous layer was filtered, and the leftover solids were washed with DCM. The filtrate was then placed back in the separatory funnel and extracted with DCM once again. The combined organic portions were washed once with brine, dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture was a yellow, brown, oil. The crude product mixture was purified via flash chromatography on silica gel (20−60% EtOAc/heptane, 330 g RediSep Rf Gold column) to afford the desired product as an amorphous solid (4.273 g, 12.03 mmol, 94% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.81 (d, J = 15.7 Hz, 1H), 7.65 (d, J = 15.7 Hz, 1H), 7.70−7.61 (m, 1H), 7.46−7.29 (m, 6H), 7.22 (d, J = 7.9 Hz, 1H), 5.58 (dd, J = 3.8, 8.6 Hz, 1H), 5.26−5.19 (m, 1H), 4.80 (t, J = 8.6 Hz, 1H), 4.51 (d, J = 5.6 Hz, 2H), 4.21 (dd, J = 3.8, 8.6 Hz, 1H), 2.26 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 164.5, 154.4, 145.7, 141.6, 140.3, 138.9, 132.1, 130.9, 129.3, 128.5, 127.7, 126.3, 126.0, 116.7, 70.7, 61.1, 57.7, 18.7. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{20}NO_4$ 338.1392, found 338.1391. $[\alpha]_D^{20}$ −20 (c 1.0, DCM).

*(S)-3-((E)-3-(3-(((R)-2-Ethyl-2,3-dihydropyrido[2,3-f][1,4]-oxazepin-4(5H)-yl)methyl)-4-methylphenyl)acryloyl)-4-phenyloxazolidin-2-one (**5**).* To a solution of **4** (4.273 g, 12.67 mmol) in anhydrous chloroform (63.3 mL) was added $SOCl_2$ (1.849 mL, 25.3 mmol) dropwise, and the resulting mixture was stirred at room temperature over 64 h. Next, the mixture was concentrated, and the resulting residue was reconcentrated from DCM three times and dried under high vacuum to afford the intermediate benzyl chloride as a sticky solid which was used directly without further purification. To this residue was added **B** (3.82 g, 15.20 mmol) followed by acetonitrile (63.3 mL) and DIPEA (11.06 mL, 63.3 mmol), and the resulting solution was stirred for 16 h at room temperature. The reaction was not complete at that time, and so the reaction mixture was heated to 60 °C (heating block) and stirred over an additional 4 h. Next, the reaction mixture was then cooled back to room temperature and quenched with saturated NH_4Cl solution. Water and EtOAc were added, and the biphasic system was transferred to a separatory funnel. The organic layer was removed, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed once with water and then once with brine, dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture. The crude product mixture was purified via flash chromatography on silica gel (30−55% EtOAc/heptane, 220 g RediSep Rf Gold column) to afford the desired product as a white, crystalline solid (5.441 g, 10.39 mmol, 82% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.18 (dd, J = 1.5, 4.9 Hz, 1H), 7.79 (d, J = 15.6 Hz, 1H), 7.63 (d, J = 15.6 Hz, 1H), 7.53−7.49 (m, 1H), 7.46 (dd, J = 2.0, 7.8 Hz, 1H), 7.42−7.29 (m, 6H), 7.28−7.21 (m, 2H), 5.58 (dd, J = 3.7, 8.6 Hz, 1H), 4.80 (t, J = 8.6 Hz, 1H), 4.20 (dd, J = 3.7, 8.6 Hz, 1H), 3.95 (d, J = 14.2 Hz, 1H), 3.92−3.87 (m, 1H), 3.84 (d, J = 14.2 Hz, 1H), 3.61 (s, 2H), 3.01 (d, J = 13.2 Hz, 1H), 2.89 (dd, J = 9.8, 13.7 Hz, 1H), 2.30 (s, 3H), 1.68−1.54 (m, 1H), 1.54−1.41 (m, 1H), 1.00 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 164.5, 1545.0, 154.3, 152.8, 145.5, 143.7, 141.3, 140.3, 137.9, 132.0, 131.4, 129.7, 129.3, 129.2, 128.5, 128.3, 127.9, 126.5, 126.3, 123.9, 116.9, 81.7, 70.7, 62.2, 60.0, 57.7, 56.8, 26.8, 19.3, 10.6. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{30}H_{32}N_3O_4$ 498.2393, found 498.2392. $[\alpha]_D^{20}$ −22 (c 1.0, DCM). Mp: 136 °C.

General Procedure 1 (Michael Addition Using Solutions of Commercially Available Grignard Reagents). To an oven-dried glass vessel with a magnetic stirrer was transferred copper(I) bromide−dimethyl sulfide complex (1.4 equiv) followed by dimethyl sulfide (10 equiv), and the mixture was stirred until dissolved. Next, anhydrous tetrahydrofuran (0.15 mol/L) was added, and the solution was cooled on a regular ice/water bath. A commercially available solution of Grignard reagent (2.8 equiv) was added and the reaction mixture was stirred over 10 min on the regular ice/water bath. Next, the reaction mixture was cooled to −40 °C on an MeCN/dry ice bath, **5** (1 equiv) was added under a stream of nitrogen gas, and the reaction mixture was stirred over 1 h at −40 °C. The reaction was quenched with saturated NH_4Cl solution and combined with additional water and EtOAc. The aqueous layer was extracted three times with EtOAc, and the combined organic portions were dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture. The crude product mixture was purified via flash chromatography on silica gel to afford the desired product.

General Procedure 2 (Hydrolysis of Chiral Auxiliary under Basic Conditions). To a solution of starting material in 3:1 tetrahydrofuran and water (0.025 mol/L) at 0 °C (water/ice) was added 30% aqueous H_2O_2 solution (5 equiv) followed by 2 M aqueous LiOH solution (3 equiv), and the reaction mixture was stirred until completion (15 min to 1 h) at 0 °C. The reaction mixture was quenched with 10% sodium metabisulfite solution and diluted with water. The resulting mixture was extracted with EtOAc three times, and the combined organic portions were dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture. The crude product was purified via preparative HPLC (MDAP), and the desired fractions were combined and lyophilized to afford the desired product as a white amorphous solid.

*(R)-3-(3-(((R)-2-Ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)-3-phenylpropanoic Acid (**6a**).* Michael addition was carried out according to according to general procedure 1 with **5** (100 mg, 0.165 mmol) and 3 M phenylmagnesium bromide in diethyl ether. The isolated product was purified additionally via MDAP to afford the conjugate addition product as a white amorphous solid (63 mg, 0.104 mmol, 51.7% yield); 96.00% de by chiral HPLC (CHIRALPAK IA column, 95/05 Ethanol/Heptane +0.1% isopropylamine, 15 min run). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.20 (dd, J = 1.5, 4.6 Hz, 1H), 7.39 (dd, J = 1.4, 8.0 Hz, 1H), 7.30−7.19 (m, 8H), 7.19−6.99 (m, 6H), 5.37 (dd, J = 3.7, 8.5 Hz, 1H), 4.63 (t, J = 8.6 Hz, 1H), 4.43 (t, J = 7.7 Hz, 1H), 4.07 (dd, J = 3.8, 8.9 Hz, 1H), 3.96 (d, J = 14.4 Hz, 1H), 3.90−3.76 (m, 3H), 3.60−3.46 (m, 3H), 2.88 (d, J = 13.2 Hz, 1H), 2.79 (dd, J = 9.4, 13.9 Hz, 1H), 2.19 (s, 3H), 1.61−1.45 (m, 1H), 1.44−1.30 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H). LC/MS (ESI) m/z: [M + H]$^+$ calcd for $C_{36}H_{38}N_3O_4$ 576.3, found 576.5. Hydrolysis was carried out according to general procedure 2 (63 mg, 0.104 mmol) to afford the desired product as a white amorphous solid (26 mg, 0.057 mmol, 52.4% yield). ^{1}H NMR (501 MHz, DMSO-d_6) δ = 8.20 (dd, J = 1.3, 4.7 Hz,

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1H), 7.40 (dd, J = 1.3, 8.2 Hz, 1H), 7.31−7.18 (m, 5H), 7.16−7.11 (m, 2H), 7.11−7.06 (m, 1H), 7.03 (d, J = 7.9 Hz, 1H), 4.34 (t, J = 7.9 Hz, 1H), 3.95 (d, J = 14.2 Hz, 1H), 3.86 (d, J = 14.5 Hz, 1H), 3.89−3.80 (m, 1H), 3.56−3.47 (m, 2H), 3.03−2.91 (m, 2H), 2.86 (d, J = 13.6 Hz, 1H), 2.77 (dd, J = 9.5, 13.6 Hz, 1H), 2.18 (s, 3H), 1.61−1.47 (m, 1H), 1.43−1.32 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ = 173.3, 155.0, 153.1, 144.9, 143.6, 141.8, 136.9, 135.4, 130.6, 129.2, 128.7, 128.4, 127.9, 126.6, 126.5, 123.9, 81.4, 61.5, 60.6, 57.0, 46.8, 26.8, 18.7, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{31}N_2O_3$ 431.2329, found 431.2327. $[\alpha]_D^{20}$ −7 (c 1.0, MeOH).

*(S)-3-(3-(((R)-2-Ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)-3-(o-tolyl)propanoic Acid (**6b**).* Michael addition was carried out according to according to general procedure 1 with **5** (100 mg, 0.165 mmol) and 2 M o-tolylmagnesium bromide in diethyl ether. The isolated product was purified additionally via MDAP to afford the conjugate addition product as a white amorphous solid (70 mg, 0.113 mmol, 56.1% yield); 97.34% de by chiral HPLC (CHIRALPAK IA column, 15/85 Ethanol/Heptane +0.1% isopropylamine, 15 min run). ^1H NMR (400 MHz, DMSO-d_6) δ = 8.20 (dd, J = 1.5, 4.8 Hz, 1H), 7.39 (dd, J = 1.4, 8.0 Hz, 1H), 7.34−7.20 (m, 5H), 7.19−6.92 (m, 8H), 5.38 (dd, J = 3.7, 8.5 Hz, 1H), 4.65 (t, J = 8.6 Hz, 1H), 4.59 (t, J = 7.7 Hz, 1H), 4.07 (dd, J = 3.8, 8.6 Hz, 1H), 3.98−3.86 (m, 2H), 3.83 (d, J = 14.4 Hz, 1H), 3.81−3.73 (m, 1H), 3.54−3.44 (m, 2H), 3.40 (dd, J = 7.4, 17.0 Hz, 1H), 2.85 (d, J = 13.2 Hz, 1H), 2.77 (dd, J = 9.1, 13.7 Hz, 1H), 2.19 (s, 3H), 2.16 (s, 3H), 1.59−1.44 (m, 1H), 1.42−1.27 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{37}H_{40}N_3O_4$ 590.3, found 590.6. Hydrolysis was carried out according to general procedure 2 (70 mg, 0.113 mmol) to afford the desired product as a white amorphous solid (19 mg, 0.041 mmol, 34.2% yield). ^1H NMR (501 MHz, DMSO-d_6) δ = 12.02 (br s, 1H), 8.20 (dd, J = 1.4, 4.6 Hz, 1H), 7.39 (dd, J = 1.4, 8.0 Hz, 1H), 7.30 (d, J = 7.3 Hz, 1H), 7.26 (dd, J = 4.6, 8.0 Hz, 1H), 7.16−6.99 (m, 6H), 4.53 (t, J = 7.9 Hz, 1H), 3.93 (d, J = 14.5 Hz, 1H), 3.84 (d, J = 14.2 Hz, 1H), 3.82−3.74 (m, 1H), 3.55−3.46 (m, 2H), 2.96 (dd, J = 8.2, 15.8 Hz, 1H), 2.92−2.83 (m, 2H), 2.78 (dd, J = 9.5, 13.9 Hz, 1H), 2.25 (s, 3H), 2.19 (s, 3H), 1.60−1.46 (m, 1H), 1.42−1.29 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6) δ = 173.3, 155.0, 153.1, 143.6, 142.4, 141.0, 136.8, 136.1, 135.3, 130.7, 130.5, 129.5, 128.3, 126.9, 126.6, 126.5, 126.3, 123.9, 81.4, 61.7, 60.4, 56.9, 42.6, 41.1, 26.8, 19.9, 18.7, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{33}N_2O_3$ 445.2486, found 445.2484. $[\alpha]_D^{20}$ +35 (c 1.0, MeOH).

*(S)-3-(4-Chloro-2-methylphenyl)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)propanoic Acid (**6c**).* Michael addition was carried out according to general procedure 1 with **5** (600 mg, 0.990 mmol) and 0.5 M (4-chloro-2-methylphenyl)magnesium bromide in THF to afford the conjugate addition product as an off-white amorphous solid (625 mg, 0.951 mmol, 79% yield). ^1H NMR (400 MHz, DMSO-d_6) δ = 8.20 (br d, J = 2.9 Hz, 1H), 7.39 (dd, J = 1.5, 8.3 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.30−7.22 (m, 4H), 7.21−7.14 (m, 1H), 7.14−7.08 (m, 3H), 7.03 (d, J = 7.8 Hz, 1H), 7.01−6.94 (m, 2H), 5.38 (dd, J = 3.9, 8.3 Hz, 1H), 4.66 (t, J = 8.6 Hz, 1H), 4.55 (t, J = 7.8 Hz, 1H), 4.07 (dd, J = 3.7, 8.6 Hz, 1H), 3.99−3.86 (m, 2H), 3.83 (d, J = 14.7 Hz, 1H), 3.81−3.72 (m, 1H), 3.54−3.43 (m, 2H), 3.36 (dd, J = 6.8, 17.1 Hz, 1H), 2.83 (d, J = 12.2 Hz, 1H), 2.76 (dd, J = 8.8, 13.7 Hz, 1H), 2.19 (s, 3H), 2.15 (s, 3H), 1.59−1.43 (m, 1H), 1.40−1.26 (m, 1H), 1.03−0.92 (m, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{37}H_{39}ClN_3O_4$ 624.3, found 624.4. Hydrolysis was carried out according to general procedure 2 (0.268 g, 0.429 mmol) to afford the desired product as a white amorphous solid (120 mg, 0.238 mmol, 55.4% yield). ^1H NMR (400 MHz, DMSO-d_6) δ = 11.76 (s, 1H), 8.20 (dd, J = 1.5, 4.9 Hz, 1H), 7.39 (dd, J = 1.5, 8.3 Hz, 1H), 7.32 (d, J = 8.3 Hz, 1H), 7.26 (dd, J = 4.6, 8.1 Hz, 1H), 7.21−7.13 (m, 2H), 7.08−6.97 (m, 3H), 4.49 (t, J = 7.8 Hz, 1H), 3.93 (d, J = 14.2 Hz, 1H), 3.82 (br d, J = 14.2 Hz, 1H), 3.80−3.73 (m, 1H), 3.49 (s, 2H), 2.96 (dd, J = 8.8, 16.1 Hz, 1H), 2.92−2.80 (m, 2H), 2.77 (dd, J = 8.8, 13.7 Hz, 1H), 2.24 (s, 3H), 2.19 (s, 3H), 1.59−1.43 (m, 1H), 1.40−1.26 (m, 1H), 0.98 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 173.1, 155.0, 153.1, 143.6, 141.5, 140.4, 138.8, 136.9, 135.5, 130.9, 130.6, 130.2, 129.5, 128.5, 128.3, 126.9, 126.1, 123.9, 81.4, 61.6, 60.4, 56.8, 42.2, 40.9, 26.8, 19.6, 18.7, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{32}N_2O_3Cl$ 479.2101, found 479.2103. $[\alpha]_D^{20}$ +34 (c 0.50, MeOH).

*(S)-3-(3-(((R)-2-Ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)-3-(2-methoxyphenyl)propanoic Acid (**6d**).* Michael addition was carried out according to general procedure 1 with **5** (250 mg, 0.413 mmol) and 1 M (2-methoxyphenyl)magnesium bromide in THF to afford the conjugate addition product an off-white amorphous solid (221 mg, 0.317 mmol, 63.2% yield). ^1H NMR (400 MHz, $DMSOd_6$) δ = 8.19 (dd, J = 1.5, 4.9 Hz, 1H), 7.39 (dd, J = 1.5, 8.3 Hz, 1H), 7.31−7.21 (m, 4H), 7.19−7.11 (m, 4H), 7.07 (s, 1H), 7.03−6.94 (m, 2H), 6.92−6.81 (m, 2H), 5.36 (dd, J = 3.7, 8.6 Hz, 1H), 4.77 (t, J = 7.8 Hz, 1H), 4.62 (t, J = 8.8 Hz, 1H), 4.08 (dd, J = 3.4, 8.8 Hz, 1H), 3.96 (d, J = 14.2 Hz, 1H), 3.85 (d, J = 14.7 Hz, 1H), 3.83−3.76 (m, 1H), 3.73−3.64 (m, 4H), 3.62−3.44 (m, 3H), 2.88 (d, J = 13.2 Hz, 1H), 2.79 (dd, J = 9.3, 13.7 Hz, 1H), 2.18 (s, 3H), 1.63−1.45 (m, 1H), 1.38 (s, 1H), 0.98 (t, J = 7.6 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ Calc for $C_{37}H_{40}N_3O_5$ 606.3, found 606.5. Hydrolysis was carried out according to general procedure 2 (0.221 g, 0.317 mmol, 87 wt %) to afford the desired product as a white amorphous solid (90 mg, 0.186 mmol, 58.5% yield). ^1H NMR (400 MHz, DMSO-d6) δ = 11.58 (br s, 1H), 8.18 (dd, J = 1.5, 4.9 Hz, 1H), 7.38 (dd, J = 1.5, 7.8 Hz, 1H), 7.29−7.23 (m, 1H), 7.20 (dd, J = 1.5, 7.3 Hz, 1H), 7.17−7.11 (m, 1H), 7.11−7.06 (m, 1H), 7.05−6.96 (m, 2H), 6.90 (d, J = 8.3 Hz, 1H), 6.84 (dt, J = 1.0, 7.8 Hz, 1H), 4.72 (t, J = 8.1 Hz, 1H), 3.95 (d, J = 14.2 Hz, 1H), 3.88 (d, J = 14.2 Hz, 1H), 3.85−3.77 (m, 1H), 3.73 (s, 3H), 3.51 (s, 2H), 2.96−2.82 (m, 3H), 2.77 (dd, J = 8.8, 13.7 Hz, 1H), 2.18 (s, 3H), 1.63−1.46 (m, 1H), 1.38 (s, 1H), 0.98 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 173.3, 156.8, 155.0, 153.0, 143.6, 141.2, 136.6, 135.1, 132.6, 130.3, 129.4, 128.3, 127.8, 127.6, 126.9, 123.9, 120.7, 111.4, 81.6, 61.6, 60.6, 57.2, 55.9, 39.6, 26.8, 18.7, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{33}N_2O_4$ 461.2440, found 461.2444. $[\alpha]_D^{20}$ −34 (c 1.0, MeOH).

*(S)-3-(2-Chlorophenyl)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)propanoic Acid (**6e**).* Michael addition was carried out according to general procedure 1 with **5** (250 mg, 0.413 mmol) and 0.5 M (2-chlorophenyl) magnesium bromide in 2-MeTHF to afford the conjugate addition product as an off-white amorphous solid (224 mg, 0.114 mmol, 22.65% yield) containing unreacted **5** (22% by weight by NMR) and a byproduct of mass 685.3 (desired mass + Ph, 44% by weight by NMR). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{36}H_{37}ClN_3O_4$ 610.3, found 610.3. Hydrolysis was carried out according to general procedure 2 (0.224 g, 0.114 mmol, 31% wt) to afford the desired product as a white amorphous solid (12 mg, 0.025 mmol, 21.5% yield). ^1H NMR (400 MHz, DMSO-d_6) δ = 12.14 (br s, 1H), 8.19 (dd, J = 1.2, 4.6 Hz, 1H), 7.47 (dd, J = 1.5, 7.8 Hz, 1H), 7.43−7.34 (m, 2H), 7.32−7.23 (m, 2H), 7.20 (dt, J = 1.5, 7.8 Hz, 1H), 7.09 (br s, 1H), 7.08−7.00 (m, 2H), 4.79 (t, J = 7.8 Hz, 1H), 3.95 (d, J = 14.7 Hz, 1H), 3.86 (d, J = 14.2 Hz, 1H), 3.83−3.75 (m, 1H), 3.51 (s, 2H), 3.02 (dd, J = 8.3, 16.1 Hz, 1H), 2.96 (dd, J = 8.3, 16.1 Hz, 1H), 2.85 (d, J = 13.2 Hz, 1H), 2.77 (dd, J = 9.3, 13.7 Hz, 1H), 2.19 (s, 3H), 1.61−1.45 (m, 1H), 1.43−1.30 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (176 MHz, DMSO-d_6) δ = 172.4, 154.4, 152.5, 143.1, 141.8, 139.2, 136.1, 134.7, 132.6, 129.9, 129.5, 129.3, 128.7, 128.1, 126.9, 125.9, 125.7, 123.4, 80.8, 60.7, 60.3, 56.5, 42.2, 40.4, 26.2, 18.2, 10.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{30}N_2O_3Cl$ 465.1945, found 465.1947. $[\alpha]_D^{20}$ −8 (c 0.20, MeOH).

*(R)-3-(4-(Dimethylamino)phenyl)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)propanoic Acid (**6f**).* Michael addition was carried out according to general procedure 1 with **5** (250 mg, 0.413 mmol) and 0.5 M (4- (dimethylamino)phenyl)magnesium bromide in THF to afford the conjugate addition product as an off-white solid (193 mg, 0.296 mmol, 59.0% yield). ^1H NMR (400 MHz, DMSO-d_6) δ = 8.21 (dd, J = 1.5, 4.9 Hz, 1H), 7.40 (dd, J = 1.5, 8.3 Hz, 1H), 7.29−7.22

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(m, 4H), 7.10−6.99 (m, 7H), 6.60 (d, J = 8.8 Hz, 2H), 5.38 (dd, J = 3.7, 8.6 Hz, 1H), 4.63 (t, J = 8.6 Hz, 1H), 4.31 (t, J = 7.6 Hz, 1H), 4.07 (dd, J = 3.4, 8.8 Hz, 1H), 3.97 (d, J = 14.2 Hz, 1H), 3.86 (d, J = 14.2 Hz, 1H), 3.84−3.75 (m, 1H), 3.80 (dd, J = 7.8, 16.6 Hz, 1H), 3.51 (s, 2H), 3.46 (dd, J = 7.8, 16.6 Hz, 1H), 2.89 (d, J = 13.7 Hz, 1H), 2.83 (s, 6H), 2.79 (dd, J = 9.3, 13.7 Hz, 1H), 2.20 (s, 3H), 1.61−1.47 (m, 1H), 1.39 (s, 1H), 0.99 (t, J = 7.3 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{38}H_{43}N_4O_4$ 619.3, found 619.3. Hydrolysis was carried out according to general procedure 2 (0.193 g, 0.312 mmol) to afford the desired product as a white amorphous solid (81 mg, 0.162 mmol, 52.1% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.95 (br s, 1H), 8.19 (dd, J = 1.5, 4.9 Hz, 1H), 7.39 (dd, J = 1.5, 7.8 Hz, 1H), 7.30−7.22 (m, 1H), 7.11−6.98 (m, 5H), 6.63−6.55 (m, 2H), 4.22 (t, J = 8.1 Hz, 1H), 3.95 (d, J = 14.2 Hz, 1H), 3.91−3.79 (m, 1H), 3.87 (d, J = 14.7 Hz, 1H), 3.59−3.47 (m, 2H), 2.93−2.84 (m, 3H), 2.84−2.73 (m, 7H), 2.19 (s, 3H), 1.62−1.47 (m, 1H), 1.46−1.31 (m, 1H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 173.3, 155.0, 153.1, 149.3, 143.6, 142.5, 136.7, 135.0, 132.5, 130.5, 129.1, 128.3, 128.3, 126.5, 123.9, 112.9, 81.5, 61.5, 60.6, 57.1, 45.9, 40.7, 26.8, 18.7, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{36}N_3O_3$ 474.2757, found 474.2758. $[\alpha]_D^{20}$ −13 (c 1.0, MeOH).

*(S)-3-(3,4-Dimethoxyphenyl)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)propanoic Acid (**6g**).* Michael addition was carried out according to general procedure 1 with **5** (250 mg, 0.413 mmol) and 0.5 M (3,4-dimethoxyphenyl)magnesium bromide in THF to afford the conjugate addition product as an off-white solid (254 mg, 0.380 mmol, 76% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.19 (dd, J = 1.5, 4.9 Hz, 1H), 7.39 (dd, J = 1.5, 8.3 Hz, 1H), 7.29−7.20 (m, 4H), 7.11 (s, 1H), 7.09−6.99 (m, 4H), 6.83 (d, J = 2.0 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.72 (dd, J = 2.0, 8.3 Hz, 1H), 5.38 (dd, J = 3.4, 8.3 Hz, 1H), 4.64 (t, J = 8.8 Hz, 1H), 4.36 (t, J = 7.8 Hz, 1H), 4.07 (dd, J = 3.7, 8.6 Hz, 1H), 3.94 (d, J = 14.7 Hz, 1H), 3.91−3.75 (m, 3H), 3.69 (s, 3H), 3.63 (s, 3H), 3.51 (s, 2H), 3.43 (dd, J = 7.6, 16.4 Hz, 1H), 2.90 (d, J = 13.2 Hz, 1H), 2.80 (dd, J = 9.3, 13.7 Hz, 1H), 2.19 (s, 3H), 1.61−1.46 (m, 1H), 1.45−1.31 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{38}H_{42}N_3O_6$ 636.3, found 636.4. Hydrolysis was carried out according to general procedure 2 (0.254 g, 0.400 mmol) to afford the desired product as a white amorphous solid (67 mg, 0.130 mmol, 32.5% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.63 (br s, 1H), 8.19 (dd, J = 1.5, 4.4 Hz, 1H), 7.39 (dd, J = 1.5, 7.8 Hz, 1H), 7.26 (dd, J = 4.6, 8.1 Hz, 1H), 7.13 (d, J = 1.5 Hz, 1H), 7.08 (dd, J = 1.5, 7.8 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 6.85 (d, J = 1.5 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.76 (dd, J = 2.0, 8.3 Hz, 1H), 4.28 (t, J = 7.8 Hz, 1H), 3.93 (d, J = 14.7 Hz, 1H), 3.86 (d, J = 14.2 Hz, 1H), 3.84−3.76 (m, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.58−3.47 (m, 2H), 3.01−2.91 (m, 2H), 2.89 (d, J = 13.7 Hz, 1H), 2.79 (dd, J = 9.3, 13.7 Hz, 1H), 2.19 (s, 3H), 1.63−1.46 (m, 1H), 1.46−1.31 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 173.3, 155.0, 153.1, 149.0, 147.6, 143.6, 142.0, 137.4, 136.8, 135.2, 130.5, 129.1, 128.3, 126.5, 123.9, 119.5, 112.2, 112.0, 81.7, 61.8, 60.4, 57.1, 55.9, 55.9, 46.4, 26.8, 18.7, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{35}N_2O_5$ 491.2546, found 491.2543. $[\alpha]_D^{20}$ −3 (c 1.0, MeOH).

*(S)-3-(3-(((R)-2-Ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)-3-(4-fluoro-3-methoxyphenyl)-propanoic Acid (**6h**).* Michael addition was carried out according to general procedure 1 with **5** (250 mg, 0.413 mmol) and 0.5 M (4-fluoro-3-methoxyphenyl)magnesium bromide in 2-MeTHF to afford the conjugate addition product as an off-white solid (272 mg, 0.406 mmol, 81% yield, 93 wt %) containing unreacted **5** and residual DCM (4 and 3% by weight by NMR, respectively). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.19 (dd, J = 1.5, 4.4 Hz, 1H), 7.39 (dd, J = 1.5, 7.8 Hz, 1H), 7.28−7.21 (m, 4H), 7.14−7.00 (m, 7H), 6.76 (ddd, J = 2.0, 4.3, 8.4 Hz, 1H), 5.38 (dd, J = 3.7, 8.6 Hz, 1H), 4.65 (t, J = 8.8 Hz, 1H), 4.42 (t, J = 7.8 Hz, 1H), 4.08 (dd, J = 3.4, 8.8 Hz, 1H), 3.94 (d, J = 14.2 Hz, 1H), 3.92−3.76 (m, 3H), 3.72 (s, 3H), 3.51 (s, 2H), 3.47 (dd, J = 7.3, 16.6 Hz, 1H), 2.88 (d, J = 12.7 Hz, 1H), 2.79 (dd, J = 9.3, 13.7 Hz, 1H), 2.19 (s, 3H), 1.53 (quind, J = 7.4, 14.8 Hz, 1H), 1.43−1.29 (m, 1H), 0.97 (t, J = 7.6 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{37}H_{39}FN_3O_5$ 624.3, found 624.3. Hydrolysis was carried out according to general procedure 2 (0.272 g, 0.406 mmol, 93 wt %) to afford the desired product as a white amorphous solid (57 mg, 0.113 mmol, 27.9% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.95 (br s, 1H), 8.18 (dd, J = 1.5, 4.9 Hz, 1H), 7.39 (dd, J = 1.5, 7.8 Hz, 1H), 7.29−7.22 (m, 1H), 7.17−7.00 (m, 5H), 6.81 (ddd, J = 2.0, 4.4, 8.3 Hz, 1H), 4.33 (t, J = 8.1 Hz, 1H), 3.93 (d, J = 14.2 Hz, 1H), 3.86 (d, J = 14.2 Hz, 1H), 3.83−3.79 (m, 1H), 3.76 (s, 3H), 3.58−3.47 (m, 2H), 3.04−2.93 (m, 2H), 2.88 (d, J = 13.2 Hz, 1H), 2.78 (dd, J = 9.3, 13.7 Hz, 1H), 2.19 (s, 3H), 1.61−1.45 (m, 1H), 1.45−1.31 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 173.2, 155.0, 153.0, 150.5 (d, J = 242.1 Hz, 1C), 147.22 (d, J = 10.3 Hz, 1C), 143.6, 141.7 (d, J = 2.9 Hz, 1C), 141.5, 136.9, 135.4, 130.6, 129.2, 128.3, 126.5, 123.9, 119.7 (d, J = 6.6 Hz, 1C), 115.8 (d, J = 17.6 Hz, 1C), 113.7, 81.6, 61.8, 60.5, 57.1, 56.4, 46.5, 26.8, 18.7, 10.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{32}N_2O_4F$ 479.2346, found 479.2346. $[\alpha]_D^{20}$ −3 (c 0.50, MeOH).

*(R)-3-(4-Acetylphenyl)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)propanoic Acid (**6i**).* Michael addition was carried out according to general procedure 1 with **5** (250 mg, 0.413 mmol) and 0.5 M (4-(2-methyl-1,3-dioxolan-2-yl)phenyl)magnesium bromide in 2-MeTHF to afford the conjugate addition product as a white solid (195 mg, 0.265 mmol, 52.8% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.20 (dd, J = 1.5, 4.9 Hz, 1H), 7.40 (dd, J = 1.5, 7.8 Hz, 1H), 7.30−7.19 (m, 8H), 7.15−7.08 (m, 3H), 7.07−6.99 (m, 2H), 5.37 (dd, J = 3.7, 8.6 Hz, 1H), 4.63 (t, J = 8.8 Hz, 1H), 4.42 (t, J = 7.8 Hz, 1H), 4.08 (dd, J = 3.9, 8.8 Hz, 1H), 3.99−3.89 (m, 3H), 3.89−3.75 (m, 3H), 3.67−3.60 (m, 2H), 3.60−3.53 (m, 1H), 3.53−3.45 (m, 2H), 2.88 (d, J = 13.2 Hz, 1H), 2.79 (dd, J = 9.3, 13.7 Hz, 1H), 2.19 (s, 3H), 1.49 (s, 3H), 1.60−1.45 (m, 1H), 1.45−1.32 (m, 1H), 0.98 (t, J = 7.3 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{40}H_{43}N_3O_6$ 662.3, found 662.4. Hydrolysis was carried out according to a modified general procedure 2: To a solution of (*S*)-3-((*R*)-3-(3-(((*R*)-2-ethyl-2,3-dihydropyrido[2,3-*f*]-[1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-3-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)propanoyl)-4-phenyloxazolidin-2-one (0.195 g, 0.295 mmol) in tetrahydrofuran (8.84 mL) and water (2.95 mL) at 0 °C (water/ice bath) was added 30% H_2O_2 aqueous solution (0.150 mL, 1.473 mmol) followed by 2 M LiOH aqueous solution (0.442 mL, 0.884 mmol), and the resulting mixture was stirred over 15 min at 0 °C. Next, the reaction mixture was quenched with 10% sodium metabisulfite solution and combined with additional water. The resulting mixture was treated with 6 M HCl and stirred over 2 h. Next, the mixture was basified to pH 5 with 5 M NaOH solution and then extracted with EtOAc three times. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture as a yellow oil. The crude product mixture was purified via preparative HPLC to afford the desired product as a white amorphous solid (80 mg, 0.161 mmol, 54.6% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.70 (br s, 1H), 8.20 (dd, J = 1.5, 4.4 Hz, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 7.39 (dd, J = 1.5, 7.8 Hz, 1H), 7.26 (dd, J = 4.6, 8.1 Hz, 1H), 7.16−7.08 (m, 2H), 7.04 (d, J = 7.8 Hz, 1H), 4.42 (t, J = 7.8 Hz, 1H), 3.94 (d, J = 14.2 Hz, 1H), 3.90−3.78 (m, 1H), 3.85 (d, J = 14.2 Hz, 1H), 3.57−3.47 (m, 2H), 2.98 (dd, J = 7.8, 16.1 Hz, 1H), 3.05 (dd, J = 7.8, 15.6 Hz, 1H), 2.84 (d, J = 13.2 Hz, 1H), 2.77 (dd, J = 8.8, 13.7 Hz, 1H), 2.52−2.51 (m, 3H), 2.19 (s, 3H), 1.60−1.44 (m, 1H), 1.42−1.27 (m, 1H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 197.8, 173.0, 155.0, 153.0, 150.3, 143.6, 141.0, 137.1, 135.7, 135.4, 130.7, 129.2, 128.8, 128.3, 128.2, 126.6, 123.9, 81.4, 61.5, 60.5, 56.9, 46.7, 39.9, 27.1, 26.8, 18.7, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{33}N_2O_4$ 473.2440, found 473.2439. $[\alpha]_D^{20}$ −4 (c 1.0, MeOH).

*(R)-3-(3-(((R)-2-Ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)-3-(4-(trifluoromethoxy)phenyl)-propanoic Acid (**6j**).* Michael addition was carried out according to general procedure 1 with **5** (250 mg, 0.413 mmol) and 0.5 M (4-(trifluoromethoxy)phenyl)magnesium bromide in THF to afford the conjugate addition product as an off-white solid (216 mg, 0.304 mmol, 60.6% yield, 93 wt %) containing unreacted **5** and residual

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DCM (6 and 1% by weight, by NMR). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.20 (br d, J = 3.9 Hz, 1H), 7.43−7.32 (m, 3H), 7.30−7.16 (m, 6H), 7.16−7.01 (m, 5H), 5.38 (dd, J = 3.7, 8.6 Hz, 1H), 4.65 (t, J = 8.6 Hz, 1H), 4.48 (t, J = 7.8 Hz, 1H), 4.08 (dd, J = 3.9, 8.8 Hz, 1H), 3.95 (d, J = 14.2 Hz, 1H), 3.90−3.75 (m, 3H), 3.59−3.46 (m, 3H), 2.86 (d, J = 12.7 Hz, 1H), 2.77 (dd, J = 9.3, 13.7 Hz, 1H), 2.19 (s, 3H), 1.59−1.44 (m, 1H), 1.42−1.28 (m, 1H), 0.96 (t, J = 7.3 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{37}H_{37}F_3N_3O_5$ 660.3, found 660.4. Hydrolysis was carried out according to general procedure 2 (0.216 g, 0.304 mmol) to afford the desired product as a white amorphous solid (106 mg, 0.200 mmol, 65.6% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.15 (br s, 1H), 8.19 (dd, J = 1.5, 4.9 Hz, 1H), 7.45−7.36 (m, 3H), 7.30−7.24 (m, 1H), 7.22 (d, J = 7.8 Hz, 2H), 7.16−7.08 (m, 2H), 7.05 (d, J = 7.8 Hz, 1H), 4.39 (t, J = 8.1 Hz, 1H), 3.94 (d, J = 14.2 Hz, 1H), 3.90−3.78 (m, 1H), 3.85 (d, J = 14.2 Hz, 1H), 3.59−3.47 (m, 2H), 3.08−2.93 (m, 2H), 2.85 (d, J = 13.2 Hz, 1H), 2.77 (dd, J = 9.3, 13.7 Hz, 1H), 2.19 (s, 3H), 1.60−1.45 (m, 1H), 1.43−1.29 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 173.1, 155.0, 153.1, 147.1, 147.1, 144.3, 143.6, 141.2, 137.1, 135.6, 130.7, 129.7, 129.2, 128.3, 126.5, 123.9, 121.3, 120.5 (q, J = 256.0 Hz, 1C), 81.4, 61.5, 60.6, 56.9, 46.1, 26.8, 18.7, 10.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{30}N_2O_4F_3$ 515.2158, found 515.2158. $[\alpha]_D^{20}$ −5 (c 1.0, MeOH).

*2-(4-Bromo-3-methylphenoxy)tetrahydro-2H-pyran (**7**).* To a solution of 4-bromo-3-methylphenol (1.669 g, 8.92 mmol) in anhydrous dichloromethane (29.7 mL) was added 3,4-dihydro-2*H*-pyran (1.224 mL, 13.39 mmol) followed by pyridinium *p*-toluenesulfonate (0.112 g, 0.446 mmol). The resulting mixture was stirred at room temperature for 16 h. Next, the mixture was washed with saturated $NaHCO_3$ solution three times and once with brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture as a light yellow oil. The crude product mixture was purified via chromatography on silica gel (0−10% EtOAc/petroleum ether, 40 g RediSep Rf Gold column) to afford the desired product (2.36 g, 8.27 mmol, 93% yield) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.45 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 2.9, 8.8 Hz, 1H), 5.46 (t, J = 3.4 Hz, 1H), 3.77−3.67 (m, 1H), 3.59−3.49 (m, 1H), 2.29 (s, 3H), 1.94−1.66 (m, 3H), 1.66−1.46 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 156.3, 138.7, 133.0, 119.7, 116.4, 116.0, 96.2, 61.9, 30.2, 25.1, 23.0, 18.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{12}H_{16}BrO_2$ 271.0328, found 271.0331.

*2-(3-Bromo-2-methylphenyl)-2-methyl-1,3-dioxolane (**8**).* To a solution of 1-(3-bromo-2-methylphenyl)ethan-1-one (3.045 g, 14.29 mmol) in anhydrous toluene (23.82 mL) was added ethylene glycol (4.78 mL, 86 mmol) followed by *p*-toluenesulfonic acid monohydrate (0.544 g, 2.86 mmol). A Dean−Stark apparatus was attached along with a condenser and the solution was heated (heating block) under reflux for 16 h. At 16 h, TLC (10% EtOAc/heptane) still indicated the presence of starting material. It was noted that a large amount of ethylene glycol was collected in the Dean−Stark apparatus and so additional fresh ethylene glycol (3.19 mL, 57.2 mmol) was added and the mixture was refluxed over another 40 h. The reaction mixture was then cooled to room temperature and quenched with saturated $NaHCO_3$ solution. The biphasic mixture was transferred to a separatory funnel and the aqueous layer was drained. The organic layer was then washed with saturated $NaHCO_3$ solution three times and once with brine, dried over $MgSO_4$, filtered and concentrated to afford the crude product mixture. The crude product mixture was purified via chromatography on silica gel (0−15% EtOAc/heptanes, 80g RediSep Rf Gold column) to afford the desired product as a yellow oil (2.918 g, 10.78 mmol, 75% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.56 (dd, J = 1.2, 8.1 Hz, 1H), 7.50 (dd, J = 1.5, 7.8 Hz, 1H), 7.11 (t, J = 7.8 Hz, 1H), 4.05−3.93 (m, 2H), 3.71−3.60 (m, 2H), 2.50 (s, 3H), 1.59 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 143.7, 135.0, 132.6, 127.7, 127.5, 125.6, 108.8, 64.3, 26.9, 20.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{11}H_{14}BrO_2$ 257.0172, found 257.0172.

*7-Bromo-8-methylimidazo[1,2-a]pyridine (**9**).* To a solution of 4-bromo-3-methylpyridin-2-amine (4.2 g, 22.46 mmol) in ethanol (30 mL) was added HBr (2.54 mL, 22.46 mmol, 48 wt %) and 2-bromo-1,1-diethoxyethane (13.28 g, 67.4 mmol) in one charge. The mixture was stirred at 60 °C over 48 h. After cooling, the mixture was treated with 0.5 M Na_2CO_3 (100 mL) and extracted with DCM (100 × 2). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford crude product mixture. The crude product was diluted with DCM (30 mL) and combined in a slurry with 100−200 silica gel mesh (10 g). The sample was purified by column chromatography (column size 5 × 25 cm, column volume: 200 mL, silica gel size (100−200 mesh) quantity: 80 g) and eluted with MeOH/DCM with a gradient from 3 to 5%. The desired fractions were combined and concentrated under reduced pressure to afford the product which was additionally treated with *n*-hexane to provide the desired product as a beige solid (3.684 g, 17.28 mmol, 77% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.35 (d, J = 7.3 Hz, 1H), 7.95 (d, J = 1.5 Hz, 1H), 7.54 (d, J = 1.0 Hz, 1H), 7.03 (d, J = 6.8 Hz, 1H), 2.56−2.52 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 145.4, 133.7, 126.3, 125.6, 118.1, 116.3, 114.7, 17.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_8H_8N_2Br$ 210.9871, found 210.9876.

*7-Bromo-3,8-dimethylimidazo[1,2-a]pyridine (**10**).* To a solution of 4-bromo-3-methylpyridin-2-amine (5 g, 26.7 mmol) in ethanol (50 mL) were added HBr (4.54 mL, 40.1 mmol, 48 wt %) and 2-bromo-1,1-dimethoxypropane (14.68 g, 80 mmol) in one charge. The mixture was stirred at 80 °C over 48 h. After cooling, the mixture was treated with 0.5 M Na_2CO_3 solution (100 mL) and extracted with DCM (100 × 2). The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford crude product mixture. The crude product was diluted with DCM (30 mL) and combined in a slurry with 100−200 silica gel mesh (10 g). The sample was purified by column chromatography (column size 5 × 25 cm, column volume: 200 mL, silica gel size (100−200 mesh) quantity: 80 g) and eluted with MeOH/DCM with a 3−5% gradient. The desired fractions were combined and concentrated under reduced pressure to afford the product that was additionally treated with *n*-hexane to afford the desired product as a beige solid (3.063 g, 13.54 mmol, 50.7% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.06 (d, J = 7.3 Hz, 1H), 7.33 (d, J = 1.0 Hz, 1H), 7.06 (d, J = 6.8 Hz, 1H), 2.53 (s, 3H), 2.42 (d, J = 1.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 145.0, 131.6, 126.2, 123.1, 121.9, 117.2, 116.0, 17.0, 9.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_9H_{10}N_2Br$ 225.0027, found 225.0027.

*5-Bromo-1,4-dimethyl-1H-indazole (**11**) and 5-Bromo-2,4-dimethyl-2H-indazole (**12**).* To a solution of 4-bromo-2,3-dimethylaniline (10 g, 50.0 mmol) in chloroform (100 mL) were added acetic anhydride (10.20 g, 100 mmol), potassium acetate (5.40 g, 55.0 mmol), and 18-crown-6 (2.64 g, 10.00 mmol), and then *tert*-butyl nitrite (10.31 g, 100 mmol) was added in one charge. The reaction mixture was stirred at 75 °C for 16 h. Next, the resulting solution was washed with saturated sodium bicarbonate (2 × 50 mL), and the combined organic layers were extracted with dichloromethane (2 × 50 mL) and then concentrated under reduced pressure. To the resulting residue were added methanol and hydrochloric acid. The reaction mixture was stirred at 50 °C for 2 h and concentrated under reduced pressure to afford the crude product which was carried on to the next step without further purification. To a solution of the intermediate 5-bromo-4-methyl-1*H*-indazole (13.6 g, 64.4 mmol) in *N*,*N*-dimethylformamide (100 mL) stirred at 0 °C was added NaH (5.15 g, 129 mmol) and MeI (4.83 mL, 77 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water (50 mL). The resulting solution was extracted with ethyl acetate (3 × 30 mL), and the organic layers were combined, washed with brine (2 × 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford crude product mixture. The crude product was diluted with dichloromethane (50 mL), made into a slurry with 100−200 silica gel mesh, and purified by column chromatography (column size 5 × 25 cm, column volume: 200 mL, silica gel size (100−200 mesh) quantity: 80 g) eluted with ethyl acetate/petroleum ether. The desired fractions were combined and concentrated under reduced

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pressure to afford **11** (5.509 g, 24.38 mmol, 37.8% yield) and **12** (3.178 g, 13.70 mmol, 21.3% yield) as beige solids. Analytical data for **11**: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.14 (d, J = 1.0 Hz, 1H), 7.51−7.45 (m, 1H), 7.44−7.38 (m, 1H), 4.02 (s, 3H), 2.55 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 138.9, 132.1, 130.3, 130.0, 125.7, 115.0, 109.6, 36.1, 19.1. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_9H_{10}N_2Br$ 225.0027, found 225.0033. Analytical data for **12**: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.47 (s, 1H), 7.42−7.36 (m, 1H), 7.34−7.29 (m, 1H), 4.16 (s, 3H), 2.51 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 147.2, 129.9, 129.6, 125.0, 124.4, 116.8, 115.1, 40.6, 19.7. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_9H_{10}N_2Br$ 225.0027, found 225.0031.

*5-Bromo-1,4-dimethyl-1H-benzo[d]imidazole (**13**).* A mixture of 4-bromo-*N*-1,3-dimethylbenzene-1,2-diamine (2.15 g, 10.00 mmol) in HCl (16.6 mL, 546 mmol) and formic acid (10 mL) was stirred for 16 h at 65 °C. Next, the reaction mixture was cooled in an ice−water bath, and the pH was slowly adjusted to 8−9 with 28% concentrated NH_4OH solution. The resulting mixture was then extracted with EtOAc (3 × 100 mL), and the organic layers were combined, washed with brine (2 × 100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford crude product mixture. The crude product was purified by reverse phase column chromatography (column: C18 spherical 20−35 um 100A 300 g; mobile phase A: water (0.05% TFA), mobile phase B: MeCN; flow rate: 65 mL/min; gradient: 12% B to 15% B in 30 min; 254 nm; t_R 5 min) to afford the desired product a dark brown solid (2.761 g, 11.78 mmol, quantitative) as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.19 (s, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.38 (d, J = 8.6 Hz, 1H), 3.83 (s, 3H), 2.58 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 145.4, 144.2, 133.7, 129.0, 126.0, 116.5, 109.8, 31.4, 17.0. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_9H_{10}N_2Br$ 225.0027, found 225.0029.

*1,4-Dimethyl-1H-benzo[d][1,2,3]triazole (**14a**) and 1,4-Dimethyl-1H-benzo[d][1,2,3]triazole-5-d (**14b**).* In an oven-dried microwave vial with a magnetic stirrer were placed magnesium metal turnings (0.016 g, 0.652 mmol) and iodine (6.62 mg, 0.026 mmol). The vial was capped under dry nitrogen gas, and the solids were heated at 79 °C (heating block) briefly to vaporize the iodine. Next, a solution of **D** (0.118 g, 0.522 mmol) in anhydrous tetrahydrofuran-d_8 (0.580 mL) was added slowly to the reaction vessel at 79 °C. The reaction was stirred under refluxing conditions for 16 h. At 16 h, the reaction mixture was allowed to cool to room temperature and was then quenched with saturated NH_4Cl solution. It was then combined with additional water and EtOAc, and the layers separated. The water layer was removed, and the organic layer was washed two additional times with water, once with 10% aq sodium thiosulfate solution, and once with brine. It was subsequently dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture as a dark amber oil. The crude product mixture was purified via chromatography con silica gel (15% EtOAc/heptane, isocratic, 12 g RediSep Rf Gold column) to afford a mixture of **14b** (38 mg, 0.159 mmol, 30.5% yield) containing **14a** (38% by weight by NMR) as a light yellow oil. Analytical data for the isotopic mixture of **14a** and **14b**: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.67−7.59 (m, 1H), 7.47−7.39 (m, 1H), 7.21−7.14 (m, 1H), 4.28 (s, 3H), 2.68 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ = 145.5, 133.7, 129.7, 127.5, 127.4, 127.4, 123.9, 123.6 (t, J = 24.5 Hz, 1C), 108.2, 34.6, 16.8, 16.7. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_8H_9N_3D$ 149.0937, found 149.0934.

*1,4-Dimethyl-1H-benzo[d][1,2,3]triazole (**14a**) and 4-Methyl-1-pentyl-1H-benzo[d][1,2,3]triazole (**14c**) (Scheme 7).* In an oven-dried microwave vial with a magnetic stirrer and an internal temperature probe was prepared a solution of **D** (0.133 g, 0.588 mmol) in anhydrous tetrahydrofuran (1.961 mL). This solution was cooled to −78 °C, and then 2.5 M solution of *n*-butyllithium in hexane (0.235 mL, 0.588 mmol) was added dropwise so that the temperature never increased above −70 °C. The resulting solution was stirred at −78 °C over 5 min. The reaction mixture was quenched with saturated NH_4Cl solution. Water and EtOAc were added and the layers separated. The aqueous layer was extracted with EtOAc three times, dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture as a yellow oil. The crude product mixture was purified via flash chromatography on silica gel (0−30% EtOAc/heptane, 4 g of RediSep Rf Gold column) to afford **14a** (61 mg, 0.39 mmol, 66.9% yield) and **14c** (23 mg, 0.107 mmol, 18.27% yield) as light yellow oils. Analytical data for **14a**: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.64 (d, J = 8.4 Hz, 1H), 7.44 (dd, J = 7.1, 8.4 Hz, 1H), 7.18 (d, J = 6.7 Hz, 1H), 4.29 (s, 3H), 2.69 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 145.5, 133.7, 129.8, 127.5, 123.9, 108.2, 34.6, 16.8. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_8H_{10}N_3$ 148.0875, found 148.0876. Analytical data for **14c**: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.66 (td, J = 0.8, 8.4 Hz, 1H), 7.42 (dd, J = 7.1, 8.4 Hz, 1H), 7.17 (td, J = 0.9, 7.0 Hz, 1H), 4.67 (t, J = 7.0 Hz, 2H), 2.68 (s, 3H), 1.95−1.83 (m, 2H), 1.36−1.13 (m, 4H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 145.6, 133.2, 129.9, 127.5, 123.9, 108.2, 47.9, 29.4, 28.7, 22.0, 16.8, 14.2. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{12}H_{18}N_3$ 204.1501, found 204.1502.

General Procedure 3 (In Situ formation of (n-Bu)$_3$MgLi). To 2.5 M solution of *n*-butyllithium in hexanes (2.05 equiv) in anhydrous toluene or THF (1.75 mL/mmol) at −10 °C (acetonitrile/dry ice) was added 2.0 M solution of *n*-BuMgCl in THF (1.03 equiv), and the resulting white suspension was stirred over 10 min at −10 °C. Next, a solution of aryl bromide (2.0 equiv) in anhydrous tetrahydrofuran (3.52 mL/mmol) was added dropwise. The reaction mixture was stirred over 5 min at −10 °C. A solution of copper(I) bromide−dimethyl sulfide complex (1.55 equiv) with DMS (10 equiv) in anhydrous tetrahydrofuran (0.44 mL/mmol) was added dropwise. The resulting solution was stirred at −10 °C over 15 min. Next, the reaction mixture was cooled to −40 °C (acetonitrile/dry ice), and then solid **5** was added under dry nitrogen protection. The resulting mixture was stirred at −40 °C over 1 h. Next, the reaction mixture was quenched with saturated NH_4Cl solution and then warmed to room temperature. The biphasic mixture was combined with extra water and EtOAc. The layers of the filtrate were then separated, and then the blue aqueous layer was extracted with EtOAc three times. The combined organic portions were dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture. The crude product mixture was purified via chromatography on silica gel to afford the desired product.

General Procedure 4 (Using Commercial (n-Bu)$_3$MgLi Solution). To a commercially available 0.7 M solution of tri-*n*-butyllithium magnesate in diethyl ether/hexanes (1.05 equiv) at −10 °C (acetonitrile/dry ice) was added a solution of aryl bromide (2.0 equiv) in anhydrous tetrahydrofuran (3.55 mL/mmol of **23**), and the resulting white suspension was stirred over 5 min at −10 °C. Next, a solution of copper(I) bromide−dimethyl sulfide complex (1.55 equiv) with DMS (10 equiv) in anhydrous tetrahydrofuran (0.44 mL/mmol) was added dropwise. The resulting suspension was stirred at −10 °C over 15 min. Next, the reaction mixture was cooled to −40 °C (acetonitrile/dry ice), and then solid **5** was added under dry nitrogen protection. The resulting mixture was stirred at −40 °C over 1 h. Next, the reaction mixture was quenched with saturated NH_4Cl solution and then warmed to room temperature. The biphasic mixture was combined with extra water and EtOAc. The biphasic mixture was extracted with EtOAc three times. The combined organic portions were dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture. The crude product mixture was purified via chromatography on silica gel to afford the desired product.

*(S)-3-((S)-3-(1,4-Dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)-methyl)-4-methylphenyl)propanoyl)-4-phenyloxazolidin-2-one (**15**) and (S)-3-((S)-3-(3-(((R)-2-Ethyl-2,3-dihydropyrido[2,3-f][1,4]-oxazepin-4(5H)-yl)methyl)-4-methylphenyl)heptanoyl)-4-phenyl-oxazolidin-2-one (**16**).* Prepared according to general procedure 3 with **5** (1.00 g, 1.65 mmol) and the magnesiate complex formed in toluene to afford **15** (611 mg, 0.862 mmol, 42.9% yield) as a light yellow solid and **16** (409 mg, 0.736 mmol, 36.6% yield, 90:10 dr by NMR) as a yellow amorphous glass. Analytical data for **15**: ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.20 (br d, J = 2.3 Hz, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.39 (dd, J = 1.1, 8.0 Hz, 1H), 7.27 (dd, J = 4.7, 8.0 Hz, 1H), 7.20−7.13 (m, 1H), 7.13−7.01 (m,

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5H), 7.00−6.92 (m, 2H), 5.38 (dd, J = 3.7, 8.5 Hz, 1H), 4.84 (t, J = 7.7 Hz, 1H), 4.66 (t, J = 8.6 Hz, 1H), 4.25 (s, 3H), 4.12−3.99 (m, 2H), 3.94 (d, J = 14.2 Hz, 1H), 3.85 (d, J = 14.4 Hz, 1H), 3.82−3.74 (m, 1H), 3.57−3.46 (m, 3H), 2.86 (d, J = 12.4 Hz, 1H), 2.77 (dd, J = 9.4, 13.7 Hz, 1H), 2.60 (s, 3H), 2.20 (s, 3H), 1.57−1.40 (m, 1H), 1.37−1.22 (m, 1H), 0.93 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 170.2, 153.7, 152.5, 145.8, 143.1, 140.4, 139.3, 136.4, 136.3, 134.9, 131.6, 130.2, 128.7, 128.4, 127.8, 127.6, 126.4, 126.2, 125.2, 123.4, 107.4, 80.9, 70.0, 61.2, 59.8, 56.8, 56.3, 40.7, 40.3, 34.0, 26.2, 18.2, 12.7, 10.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{38}H_{41}N_6O_4$ 645.3189, found 645.3187. $[\alpha]_D^{20}$ −27 (c 0.50, DCM). mp 107 °C. Analytical data for the mixture of diastereomers **16**: ^1H NMR (400 MHz, DMSO-d_6) δ = 8.20−8.11 (m, 1H), 7.42−7.18 (m, 7H), 7.06−6.90 (m, 3H), 5.43−5.30 (m, 1H), 4.74−4.55 (m, 1H), 4.14−4.04 (m, 1H), 4.00−3.92 (m, 1H), 3.91−3.79 (m, 2H), 3.57−3.47 (m, 2H), 3.27−3.17 (m, 1H), 3.17−3.07 (m, 1H), 3.03−2.86 (m, 2H), 2.84−2.73 (m, 1H), 2.26−2.16 (m, 3H), 1.64−1.35 (m, 4H), 1.26−0.88 (m, 7H), 0.80−0.70 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 171.3, 171.2, 155.0, 154.9, 154.2, 153.1, 143.6, 141.6, 140.3, 140.1, 136.7, 136.6, 135.3, 135.2, 130.5, 129.3, 129.2, 129.0, 128.3, 128.3, 126.8, 126.1, 125.9, 123.8, 81.5, 70.5, 61.6, 60.6, 57.4, 57.1, 55.4, 42.3, 40.9, 36.1, 29.5, 26.8, 22.5, 18.8, 14.3, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{34}H_{42}N_3O_4$ 556.3175, found 556.3181. $[\alpha]_D^{20}$ +72 (c 1.0, DCM).

*(S)-3-(1,4-Dimethyl-1H-benzo[d][1,2,3]triazol-5-yl)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)propanoic Acid (**419**).* Hydrolysis was carried out according to general procedure 2 with **15** (0.115 g, 0.178 mmol) to afford the desired product as a white solid (36 mg, 0.068 mmol, 38.4% yield, 98:2 dr). ^1H NMR (400 MHz, DMSO-d_6) δ = 8.17 (d, J = 3.9 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.41−7.35 (m, 1H), 7.25 (dd, J = 4.6, 8.1 Hz, 1H), 7.09 (br d, J = 4.9 Hz, 2H), 7.06−7.01 (m, 1H), 4.77 (br t, J = 7.6 Hz, 1H), 4.22 (s, 3H), 3.91 (d, J = 14.2 Hz, 1H), 3.86−3.75 (m, 1H), 3.83 (d, J = 14.7 Hz, 1H), 3.50 (s, 2H), 3.00 (br d, J = 7.8 Hz, 2H), 2.85 (d, J = 13.2 Hz, 1H), 2.76 (dd, J = 9.3, 13.7 Hz, 1H), 2.71 (s, 3H), 2.18 (s, 3H), 1.56−1.42 (m, 1H), 1.38−1.22 (m, 1H), 0.92 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 173.3, 155.0, 152.9, 146.4, 143.6, 141.2, 137.3, 136.9, 135.4, 132.1, 130.6, 129.3, 128.3, 126.9, 126.8, 126.6, 123.8, 107.9, 81.4, 61.7, 60.3, 57.0, 41.7, 40.9, 34.5, 26.7, 18.7, 13.3, 10.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{34}N_5O_3$ 500.2662, found 500.2663. $[\alpha]_D^{20}$ −60 (c 0.20, MeOH).

*(R)-3-(3-(((R)-2-Ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)-3-phenylpropanoic Acid (**6a**) (Table 4).* Prepared according to general procedure 3 with **5** (250 mg, 0.413 mmol) and the magnesiate complex formed in toluene to the conjugate addition product a white solid (188 mg, 0.310 mmol, 61.7% yield); 96:4 dr by chiral HPLC (CHIRALPAK IA column, 95/05 ethanol/heptane + 0.1% isopropylamine, 20 min run). ^1H NMR (400 MHz, DMSO-d_6) δ = 8.20 (dd, J = 1.5, 4.6 Hz, 1H), 7.39 (dd, J = 1.5, 8.1 Hz, 1H), 7.32−7.19 (m, 8H), 7.19−6.99 (m, 6H), 5.37 (dd, J = 3.7, 8.5 Hz, 1H), 4.63 (t, J = 8.6 Hz, 1H), 4.43 (t, J = 7.7 Hz, 1H), 4.07 (dd, J = 3.7, 8.7 Hz, 1H), 3.96 (d, J = 14.2 Hz, 1H), 3.90−3.75 (m, 3H), 3.61−3.45 (m, 3H), 2.88 (d, J = 13.4 Hz, 1H), 2.79 (dd, J = 9.4, 13.7 Hz, 1H), 2.19 (s, 3H), 1.61−1.45 (m, 1H), 1.44−1.30 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{36}H_{38}N_3O_4$ 576.3, found 576.5. Hydrolysis was carried out according to general procedure 2 (0.264 g, 0.408 mmol, 89 wt %) to afford the desired product a white amorphous solid (115 mg, 0.254 mmol, 62.2% yield).

*(S)-3-(3-(((R)-2-Ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)-3-(o-tolyl)propanoic Acid (**6b**) (Table 4).* Prepared according to general procedure 3 with **5** (250 mg, 0.413 mmol) and the magnesiate complex formed in toluene to the conjugate addition product as a white solid (180 mg, 0.290 mmol, 57.7% yield); >99:1 dr by chiral HPLC (CHIRALPAK IA column, 15/85 ethanol/heptane +0.1% isopropylamine, 15 min run). ^1H NMR (400 MHz, DMSO-d_6) δ = 8.20 (dd, J = 1.4, 4.7 Hz, 1H), 7.39 (dd, J = 1.4, 8.0 Hz, 1H), 7.35−7.21 (m, 5H), 7.19−6.99 (m, 7H), 6.97 (dd, J = 2.0, 7.9 Hz, 1H), 5.38 (dd, J = 3.7, 8.5 Hz, 1H), 4.65 (t, J = 8.7 Hz, 1H), 4.59 (t, J = 7.7 Hz, 1H), 4.07 (dd, J = 3.8, 8.6 Hz, 1H), 3.98−3.81 (m, 3H), 3.81−3.72 (m, 1H), 3.55−3.44 (m, 2H), 3.39 (dd, J = 7.2, 17.1 Hz, 1H), 2.85 (d, J = 13.2 Hz, 1H), 2.77 (dd, J = 9.1, 13.7 Hz, 1H), 2.19 (s, 3H), 2.16 (s, 3H), 1.59−1.44 (m, 1H), 1.42−1.28 (m, 1H), 0.98 (t, J = 7.4 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{37}H_{40}N_3O_4$ 590.3, found 590.6. Hydrolysis was carried out according to general procedure 2 (0.168 g, 0.248 mmol, 87 wt %) to afford the desired product a white amorphous solid (81 mg, 0.173 mmol, 69.8% yield).

*(S)-3-(3-(((R)-2-Ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)-3-(4-hydroxy-2-methylphenyl)-propanoic Acid (**6k**).* Prepared according to general procedure 4 with **5** (550 mg, 0.908 mmol) and **8** (0.559 g, 2.211 mmol) to afford the conjugate addition product as a white solid (307 mg, 0.423 mmol, 38.2% yield, 95 wt %). ^1H NMR (400 MHz, DMSO-d_6) δ = 8.23−8.17 (m, 1H), 7.42−7.37 (m, 1H), 7.29−7.17 (m, 5H), 7.14−7.05 (m, 2H), 7.01 (d, J = 8.3 Hz, 2H), 6.99−6.92 (m, 1H), 6.84−6.77 (m, 1H), 6.72 (dd, J = 2.7, 6.1 Hz, 1H), 5.44−5.32 (m, 2H), 4.65 (t, J = 8.8 Hz, 1H), 4.52 (t, J = 7.6 Hz, 1H), 4.11−4.04 (m, 1H), 3.98−3.69 (m, 5H), 3.62−3.43 (m, 3H), 3.39−3.33 (m, 1H), 2.92−2.83 (m, 1H), 2.83−2.73 (m, 1H), 2.18 (s, 3H), 2.12 (d, J = 1.5 Hz, 3H), 1.92−1.44 (m, 7H), 1.44−1.29 (m, 1H), 0.98 (t, J = 7.3 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{42}H_{48}N_3O_6$ 690.4, found 690.5. Hydrolysis was carried out according to a modified general procedure 2: To a solution of (4*S*)-3-((3*S*)-3-(3-(((*R*)-2-ethyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5*H*)-yl)methyl)-4-methylphenyl)-3-(2-methyl-4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)-propanoyl)-4-phenyloxazolidin-2-one (0.307 g, 0.423 mmol) in tetrahydrofuran (6.34 mL) and water (2.114 mL) at 0 °C (water/ice) was added 30% H_2O_2 aqueous solution (0.216 mL, 2.114 mmol) followed by 2 M LiOH aqueous solution (0.507 mL, 1.015 mmol), and the resulting mixture was stirred over 15 min at 0 °C. Next, the reaction mixture was quenched with 10% sodium metabisulfite solution and combined with additional water to produce a cloudy solution. To this mixture was added 6 M HCl until pH level of about 2 was reached; at that point the solution became transparent. This mixture was stirred over 20 min. Next, the pH of the reaction mixture was adjusted to 5 using 5 M NaOH solution. The resulting suspension was extracted with DCM three times. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture as a yellow oil. The crude product mixture was purified via MDAP to afford the desired product as a white amorphous solid (109 mg, 0.225 mmol, 53.2% yield). ^1H NMR (400 MHz, DMSO-d_6) δ = 11.39 (br s, 1H), 9.09 (br s, 1H), 8.19 (dd, J = 1.5, 4.4 Hz, 1H), 7.39 (dd, J = 1.5, 7.8 Hz, 1H), 7.26 (dd, J = 4.6, 8.1 Hz, 1H), 7.06 (d, J = 8.3 Hz, 1H), 7.03−6.94 (m, 3H), 6.55−6.46 (m, 2H), 4.41 (t, J = 7.8 Hz, 1H), 3.93 (d, J = 14.2 Hz, 1H), 3.84 (d, J = 14.2 Hz, 1H), 3.82−3.75 (m, 1H), 3.49 (s, 2H), 2.93−2.71 (m, 4H), 2.18 (s, 3H), 2.14 (s, 3H), 1.60−1.45 (m, 1H), 1.44−1.30 (m, 1H), 0.98 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 173.4, 155.7, 155.0, 153.1, 143.6, 141.8, 137.1, 136.7, 135.0, 132.8, 130.4, 129.5, 128.3, 127.5, 126.8, 123.9, 117.5, 113.0, 81.5, 61.6, 60.4, 57.0, 42.0, 41.6, 26.8, 20.0, 18.7, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{33}N_2O_4$ 461.2440, found 461.2441. $[\alpha]_D^{20}$ +32 (c 1.0, MeOH).

*(S)-3-(3-Acetyl-2-methylphenyl)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)propanoic Acid (**6l**).* Prepared according to a modified general procedure 4: To 0.7 M solution of tri-*n*-butyllithium magnesate in diethyl ether/hexanes (1.809 mL, 1.266 mmol) at −10 °C (acetonitrile/dry ice) was added a solution of **9** (0.620 g, 2.412 mmol) in anhydrous tetrahydrofuran (4.29 mL), and the resulting white suspension was stirred over 5 min at −10 °C; however, the reaction did not reach completion at that time. Additional 0.7 M solution of tri-*n*-butyllithium magnesate in diethyl ether/hexanes (0.568 mL, 0.398 mmol) was added, the reaction mixture was stirred over another 5 min at −10 °C, and the reaction reached completion. Next, a solution of copper(I) bromide−dimethyl sulfide complex (0.384 g, 1.869 mmol) with DMS (0.892 mL, 12.06 mmol) in anhydrous tetrahydrofuran (0.54 mL) was added dropwise. The

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resulting suspension was stirred at −10 °C over 15 min. Next, the reaction mixture was cooled to −40 °C (acetonitrile/dry ice) and then solid **5** (0.600 g, 1.206 mmol) were added under dry nitrogen protection. The resulting mixture was stirred at −40 °C over 1 h. Next, the reaction mixture was quenched with saturated NH_4Cl solution and then warmed to room temperature. The biphasic mixture was combined with extra water and EtOAc. The layers of the filtrate were then separated, and then the blue aqueous layer was extracted with EtOAc three times. The combined organic portions were dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture as a yellow oil. The crude product mixture was purified via chromatography on silica gel (35−65% EtOAc/heptane, 24 g RediSep Rf Gold column) to afford the conjugate addition product as an off-white solid (302 mg, 0.357 mmol, 29.6% yield, 80 wt %) containing unreacted **5** and residual DCM (15 and 5% by weight by NMR, respectively) and was advanced to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.20 (br s, 1H), 7.42−7.36 (m, 1H), 7.36−7.31 (m, 1H), 7.31−7.23 (m, 5H), 7.18−7.08 (m, 3H), 7.08−6.90 (m, 3H), 5.38 (dd, J = 3.7, 8.6 Hz, 1H), 4.74−4.59 (m, 2H), 4.07 (dd, J = 3.7, 8.6 Hz, 1H), 3.99−3.73 (m, 6H), 3.62−3.37 (m, 5H), 2.89−2.81 (m, 1H), 2.81−2.71 (m, 1H), 2.33 (s, 3H), 2.18 (s, 3H), 1.66−1.50 (m, 1H), 1.49 (s, 3H), 1.40−1.26 (m, 1H), 0.97 (br t, J = 7.3 Hz, 3H). LC/MS (ESI) m/z: [M + H]$^+$ calcd for $C_{41}H_{46}N_3O_6$ 676.3, found 676.5. Hydrolysis was carried out according to a modified general procedure 2: To a solution of (*S*)-3-((*S*)-3-(3-(((*R*)-2-ethyl-2,3-dihydropyrido[2,3-*f*][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)-3-(2-methyl-3-(2-methyl-1,3-dioxolan-2-yl)phenyl)propanoyl)-4-phenyloxazolidin-2-one (0.302 g, 0.357 mmol) in tetrahydrofuran (10.72 mL) and water (3.57 mL) at 0 °C (water/ice) was added 30% H_2O_2 aqueous solution (0.183 mL, 1.787 mmol) followed by 2 M LiOH aqueous solution (0.536 mL, 1.072 mmol) and the resulting mixture was stirred over 15 min at 0 °C. Next, the reaction mixture was quenched with 10% sodium metabisulfite solution. To hydrolyze the ketal protecting group, 6 M HCl solution was added until the solution turned transparent and the pH was about 1. This solution was stirred at room temperature over 4 h. Next, the mixture was basified with 2 M LiOH solution until pH of 5 was reached. The mixture was then extracted with EtOAc three times. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford the crude product mixture as a yellow oil. The crude product mixture was purified via preparative HPLC to afford a light blue solid. This light blue solid was further purified via chromatography on silica gel (0−80% 3:1 EtOAc:EtOH/Heptane, 12 g RediSep Rf Gold column) to afford desired product as a white amorphous solid (96 mg, 0.187 mmol, 52.4% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.15 (br s, 1H), 8.20 (dd, J = 1.2, 4.6 Hz, 1H), 7.52−7.42 (m, 2H), 7.39 (dd, J = 1.2, 8.1 Hz, 1H), 7.31−7.19 (m, 2H), 7.10−6.99 (m, 3H), 4.63 (t, J = 7.8 Hz, 1H), 3.92 (d, J = 14.2 Hz, 1H), 3.87−3.73 (m, 1H), 3.83 (d, J = 14.2 Hz, 1H), 3.55−3.45 (m, 2H), 3.00 (dd, J = 8.3, 16.1 Hz, 1H), 2.91 (dd, J = 7.3, 16.1 Hz, 1H), 2.88−2.83 (m, 1H), 2.79 (dd, J = 9.3, 13.7 Hz, 1H), 2.48 (s, 3H), 2.26 (s, 3H), 2.19 (s, 3H), 1.61−1.44 (m, 1H), 1.44−1.28 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 204.3, 173.1, 155.0, 153.1, 143.8, 143.6, 141.3, 140.6, 136.9, 135.5, 133.8, 130.6, 129.5, 129.2, 128.3, 126.9, 126.1, 125.9, 123.9, 81.5, 61.8, 60.4, 56.9, 42.4, 41.2, 31.1, 26.8, 18.7, 16.1, 10.6. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{30}H_{35}N_2O_4$ 487.2597, found 487.2594. $[\alpha]_D^{20}$ −28 (*c* 1.0, MeOH).

*(S)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)-3-(4-fluoro-5-methoxy-2-methylphenyl)propanoic acid (**6m**).* Prepared according to general procedure 4 with **5** (600 mg, 0.991 mmol) to afford the conjugate addition product as an off-white solid (351 mg, 0.501 mmol, 41.5% yield, 91 wt %) containing unreacted **5** (7% by weight by NMR). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.18 (dd, J = 1.2, 4.6 Hz, 1H), 7.39 (dd, J = 1.2, 8.1 Hz, 1H), 7.29−7.20 (m, 4H), 7.10−7.00 (m, 6H), 6.91 (d, J = 12.7 Hz, 1H), 5.40 (dd, J = 3.7, 8.6 Hz, 1H), 4.68 (t, J = 8.3 Hz, 1H), 4.52 (dd, J = 6.4, 9.3 Hz, 1H), 4.12−3.99 (m, 2H), 3.92 (d, J = 14.2 Hz, 1H), 3.83 (d, J = 14.2 Hz, 1H), 3.79−3.73 (m, 1H), 3.72 (s, 3H), 3.51 (s, 2H), 3.32 (dd, J = 6.4, 16.6 Hz, 1H), 2.85 (d, J = 13.2 Hz, 1H), 2.77 (dd, J = 9.3, 13.7 Hz, 1H), 2.19 (s, 3H), 2.06 (s, 3H), 1.57−1.45 (m, 1H), 1.40−1.27 (m, 1H), 0.96 (t, J = 7.3 Hz, 3H). LC/MS (ESI) m/z: [M + H]$^+$ calcd for $C_{38}H_{41}FN_3O_5$ 638.3, found 638.4. Hydrolysis was carried out according to general procedure 2 (0.351 g, 0.501 mmol, 91 wt %) to afford the desired product a white amorphous solid (153 mg, 0.295 mmol, 58.9% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.22 (br s, 1H), 8.18 (dd, J = 1.5, 4.9 Hz, 1H), 7.38 (dd, J = 1.2, 8.1 Hz, 1H), 7.25 (dd, J = 4.6, 8.1 Hz, 1H), 7.12−7.01 (m, 4H), 6.94 (d, J = 12.7 Hz, 1H), 4.46 (t, J = 7.8 Hz, 1H), 3.90 (d, J = 14.2 Hz, 1H), 3.83 (d, J = 14.2 Hz, 1H), 3.80−3.73 (m, 1H), 3.72 (s, 3H), 3.56−3.47 (m, 2H), 3.01 (dd, J = 8.3, 15.6 Hz, 1H), 2.86 (d, J = 12.7 Hz, 1H), 2.90 (dd, J = 7.3, 15.6 Hz, 1H), 2.77 (dd, J = 9.3, 13.7 Hz, 1H), 2.19 (s, 3H), 2.15 (s, 3H), 1.60−1.43 (m, 1H), 1.43−1.26 (m, 1H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 173.3, 155.0, 153.1, 145.0 (d, J = 242.1 Hz, 1C), 145.2 (d, J = 10.3 Hz, 1C), 143.6, 140.7, 138.7 (d, J = 3.7 Hz, 1C), 136.9, 135.3, 130.5, 129.3, 128.9 (d, J = 5.9 Hz, 1C), 128.3, 126.9, 123.9, 117.8 (d, J = 17.6 Hz, 1C), 112.9, 81.8, 61.9, 60.5, 57.2, 56.5, 42.6, 41.1, 26.8, 18.8, 18.7, 10.5. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{29}H_{34}FN_2O_4$ 493.2503, found 493.2505. $[\alpha]_D^{20}$ +84 (*c* 1.0, MeOH).

*(S)-3-(3-(((R)-2-Ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)-3-(2-methyl-4-(trifluoromethyl)-phenyl)propanoic Acid (**6n**).* Prepared according to general procedure 3 with **5** (650 mg, 1.073 mmol) and the magnesiate complex formed in THF to afford the conjugate addition product as a dark yellow solid (394 mg, 0.569 mmol, 43.6% yield, 95 wt %) containing unreacted **5** and DCM (4 and 1% by weight by NMR, respectively). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.20 (br d, J = 4.4 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.43−7.35 (m, 2H), 7.31−7.19 (m, 4H), 7.16−7.09 (m, 2H), 7.08−6.97 (m, 3H), 5.38 (dd, J = 3.9, 8.3 Hz, 1H), 4.67 (t, J = 8.8 Hz, 1H), 4.73−4.60 (m, 1H), 4.08 (dd, J = 3.9, 8.3 Hz, 1H), 3.98 (dd, J = 8.8, 17.1 Hz, 1H), 3.94 (d, J = 14.2 Hz, 1H), 3.83 (d, J = 14.2 Hz, 1H), 3.80−3.72 (m, 1H), 3.55−3.47 (m, 2H), 3.41 (dd, J = 6.6, 17.4 Hz, 1H), 2.83 (d, J = 12.2 Hz, 1H), 2.76 (dd, J = 8.8, 13.7 Hz, 1H), 2.25 (s, 3H), 2.20 (s, 3H), 1.58−1.43 (m, 1H), 1.39−1.25 (m, 1H), 0.95 (t, J = 7.3 Hz, 3H). LC/MS (ESI) m/z: [M + H]$^+$ calcd for $C_{38}H_{39}F_3N_3O_4$ 658.3, found 658.2. Hydrolysis was carried out according to general procedure 2 (0.394 g, 0.599 mmol) to afford the desired product a white amorphous solid (124 mg, 0.230 mmol, 38.4% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.32 (br s, 1H), 8.20 (dd, J = 1.5, 4.4 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.50−7.43 (m, 2H), 7.39 (dd, J = 1.5, 7.8 Hz, 1H), 7.26 (dd, J = 4.6, 8.1 Hz, 1H), 7.06 (s, 3H), 4.60 (t, J = 7.8 Hz, 1H), 3.93 (d, J = 14.2 Hz, 1H), 3.83 (d, J = 14.2 Hz, 1H), 3.80−3.74 (m, 1H), 3.50 (s, 2H), 3.05 (dd, J = 8.3, 16.1 Hz, 1H), 2.94 (dd, J = 7.3, 15.6 Hz, 1H), 2.84 (d, J = 12.7 Hz, 1H), 2.77 (dd, J = 8.8, 13.7 Hz, 1H), 2.35 (s, 3H), 2.20 (s, 3H), 1.59−1.43 (m, 1H), 1.41−1.26 (m, 1H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ = 173.0, 155.0, 153.0, 147.3, 143.6, 139.9, 137.7, 137.0, 135.7, 130.7, 129.5, 128.3, 127.5, 127.1 (q, J = 2.9 Hz, 1C), 127.1 (q, J = 31.5 Hz, 1C), 126.9, 123.9, 124.8 (q, J = 271.4 Hz, 1C), 123.0 (q, J = 4.4 Hz, 1C), 81.4, 61.6, 60.4, 56.8, 42.5, 40.7, 26.7, 19.8, 18.7, 10.5. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{29}H_{32}F_3N_2O_3$ 513.2365, found 513.2365. $[\alpha]_D^{20}$ +28 (*c* 1.0, MeOH).

*(S)-3-(4-Chloro-2,6-dimethylphenyl)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)propanoic Acid (**6o**).* Prepared according to general procedure 4 with **5** (550 mg, 0.908 mmol) to afford the conjugate addition product as an off-white solid (332 mg, 0.364 mmol, 32.9% yield, 70 wt %) containing unreacted **5**, **16**, and residual DCM (13, 15, and 2% by weight by NMR, respectively); advanced to the next step without further purification. LC/MS (ESI) m/z: [M + H]$^+$ calcd for $C_{38}H_{41}ClN_3O_4$ 638.3, found 638.4. Hydrolysis was carried out according to general procedure 2 (0.332 g, 0.364 mmol, 70 wt %) to afford the desired product a white amorphous solid (118 mg, 0.227 mmol, 62.4% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.19 (br s, 1H), 8.13 (dd, J = 1.5, 4.9 Hz, 1H), 7.37 (dd, J = 1.5, 7.8 Hz, 1H), 7.23 (dd, J = 4.9, 7.8 Hz, 1H), 7.16−6.92 (m, 3H), 6.91−6.81

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(m, 2H), 4.90 (t, J = 7.6 Hz, 1H), 3.90 (d, J = 14.7 Hz, 1H), 3.87−3.78 (m, 2H), 3.57−3.46 (m, 2H), 3.23 (dd, J = 7.8, 15.7 Hz, 1H), 2.87 (d, J = 12.7 Hz, 1H), 2.82−2.70 (m, 2H), 2.24−2.19 (m, 6H), 2.21 (s, 3H), 1.61−1.48 (m, 1H), 1.46−1.33 (m, 1H), 0.98 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 173.9, 154.8, 152.6, 143.5, 140.1, 139.6, 139.6, 136.8, 135.1, 130.8, 130.6, 128.2, 125.6, 123.7, 81.6, 61.5, 60.5, 57.4, 37.0, 26.7, 21.0, 18.7, 10.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{34}N_2O_3Cl$ 493.2258, found 493.2262. $[\alpha]_D^{20}$ −107 (c 1.0, MeOH).

*(S)-3-(3,4-Difluoro-2-methylphenyl)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)propanoic Acid (**6p**).* Prepared according to general procedure 3 with **5** (535 mg, 0.883 mmol) and the magnesiate complex formed in THF to afford the conjugate addition product as an off-white solid (288 mg, 0.276 mmol, 24.0% yield, 56 wt %) containing unreacted **5** (37% by weight by NMR); advanced to the next step without further purification. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.22−8.18 (m, 1H), 7.43−7.22 (m, 6H), 7.22−6.98 (m, 6H), 5.39 (dd, J = 3.9, 8.8 Hz, 1H), 4.68 (t, J = 8.8 Hz, 1H), 4.57 (dd, J = 6.8, 8.8 Hz, 1H), 4.09 (dd, J = 3.9, 8.8 Hz, 1H), 3.99−3.80 (m, 3H), 3.80−3.73 (m, 1H), 3.50 (s, 2H), 3.37 (dd, J = 6.4, 17.1 Hz, 1H), 2.85 (br d, J = 12.2 Hz, 1H), 2.78 (dd, J = 8.8, 13.7 Hz, 1H), 2.21 (s, 3H), 2.09 (d, J = 2.4 Hz, 3H), 1.68−1.42 (m, 1H), 1.38−1.26 (m, 1H), 0.97 (t, J = 7.3 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{37}H_{38}F_2N_3O_4$ 626.3, found 626.4. Hydrolysis was carried out according to general procedure 2 (0.288 g, 0.276 mmol, 60 wt %) to afford the desired product a white amorphous solid (82 mg, 0.162 mmol, 58.7% yield). ^1H NMR (400 MHz, DMSO-d6) δ = 8.19 (dd, J = 1.5, 4.4 Hz, 1H), 7.38 (dd, J = 1.5, 7.8 Hz, 1H), 7.26 (dd, J = 4.6, 8.1 Hz, 1H), 7.22−7.11 (m, 2H), 7.08−7.02 (m, 2H), 7.00 (s, 1H), 4.51 (t, J = 7.8 Hz, 1H), 3.92 (d, J = 14.2 Hz, 1H), 3.86−3.73 (m, 1H), 3.82 (d, J = 14.7 Hz, 1H), 3.50 (s, 2H), 2.96 (dd, J = 8.3, 16.1 Hz, 1H), 2.92−2.81 (m, 2H), 2.77 (dd, J = 8.8, 13.7 Hz, 1H), 2.20 (s, 3H), 2.18 (d, J = 2.4 Hz, 3H), 1.61−1.44 (m, 1H), 1.42−1.26 (m, 1H), 0.96 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 173.0, 155.0, 153.0, 150.5−146.6 (m, 1C), 148.6 (dd, J = 18.0, 250.2 Hz, 1C), 143.6, 140.3, 140.2−140.1 (m, 1C), 137.0, 135.7, 130.7, 129.4, 128.3, 126.8, 125.7 (d, J = 11.7 Hz, 1C), 123.9, 123.0−122.4 (m, 1C), 114.2 (d, J = 16.1 Hz, 1C), 81.4, 61.7, 60.4, 56.8, 42.2, 40.9, 26.7, 18.7, 11.1−10.8 (m, 1C), 10.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{31}F_2N_2O_3$ 481.2303, found 481.2306. $[\alpha]_D^{20}$ +42 (c 1.0, MeOH).

*(S)-3-(3,8-Dimethylimidazo[1,2-a]pyridin-7-yl)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)propanoic Acid (**6q**).* Prepared according to general procedure 4 with **5** (775 mg, 1.279 g) to afford the conjugate addition product as a light brown solid (238 mg, 0.325 mmol, 20.75% yield, 88 wt %) containing residual DCM, EtOAc, and heptane (12% by weight by NMR). ^1H NMR (400 MHz, DMSO-d_6) δ = 8.52−7.43 (m, 3H), 7.37 (d, J = 7.8 Hz, 1H), 7.30−6.94 (m, 11H), 5.39 (dd, J = 3.7, 8.6 Hz, 1H), 4.78 (br t, J = 7.3 Hz, 1H), 4.67 (t, J = 8.8 Hz, 1H), 4.08 (dd, J = 3.4, 8.8 Hz, 1H), 4.05−3.95 (m, 1H), 3.91 (d, J = 14.2 Hz, 1H), 3.86−3.75 (m, 2H), 3.56−3.44 (m, 3H), 2.88 (d, J = 13.2 Hz, 1H), 2.83−2.74 (m, 2H), 2.78 (br dd, J = 9.3, 13.7 Hz, 1H), 2.44 (s, 3H), 2.20 (s, 3H), 1.56−1.42 (m, 1H), 1.39−1.28 (m, 1H), 0.91 (t, J = 7.3 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{39}H_{42}N_5O_4$ 644.3, found 644.3. Hydrolysis was carried out according to general procedure 2 (0.225 g, 0.308 mmol, 88 wt %) to afford the desired product as a white amorphous solid (32 mg, 0.061 mmol, 19.82% yield). ^1H NMR (400 MHz, DMSO-d_6) δ = 8.15 (dd, J = 1.5, 4.9 Hz, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.37 (dd, J = 1.2, 8.1 Hz, 1H), 7.28−7.21 (m, 2H), 7.13−7.07 (m, 2H), 7.03 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 7.3 Hz, 1H), 4.69 (t, J = 7.8 Hz, 1H), 3.91 (d, J = 14.2 Hz, 1H), 3.88−3.76 (m, 1H), 3.83 (d, J = 14.7 Hz, 1H), 3.51 (s, 2H), 2.96−2.82 (m, 3H), 2.77 (dd, J = 9.3, 13.7 Hz, 1H), 2.53 (s, 3H), 2.38 (s, 3H), 2.19 (s, 3H), 1.57−1.42 (m, 1H), 1.40−1.27 (m, 1H), 0.92 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 173.6, 154.9, 152.9, 143.6, 141.1, 136.9, 136.4, 135.4, 130.8, 130.6, 129.4, 128.3, 126.5, 123.8, 123.1, 121.5, 120.2, 111.7, 81.5, 61.7, 60.4, 57.0, 41.8, 41.0, 26.7, 19.0, 12.9, 10.5, 9.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{35}N_4O_3$ 499.2704, found 499.2700.

*(S)-3-(1,4-Dimethyl-1H-indazol-5-yl)-3-(3-(((R)-2-ethyl-2,3-dihydropyrido[2,3-f][1,4]oxazepin-4(5H)-yl)methyl)-4-methylphenyl)propanoic Acid (**6r**).* Prepared according to general procedure 3 with **5** (500 mg, 0.825 mmol) and the magnesiate complex formed in THF to afford the conjugate addition product as an off-white solid (352 mg, 0.514 mmol, 51.1% yield, 94 wt %) containing residual EtOAc (6% by weight, by NMR); ^1H NMR (400 MHz, DMSO-d_6) δ = 8.19 (br d, J = 3.9 Hz, 1H), 8.01 (s, 1H), 7.42−7.29 (m, 3H), 7.29−7.11 (m, 2H), 7.11−6.97 (m, 5H), 6.96−6.88 (m, 2H), 5.37 (dd, J = 3.7, 8.6 Hz, 1H), 4.78 (t, J = 7.6 Hz, 1H), 4.64 (t, J = 8.6 Hz, 1H), 4.09−3.96 (m, 5H), 3.93 (d, J = 14.7 Hz, 1H), 3.84 (d, J = 14.2 Hz, 1H), 3.82−3.73 (m, 1H), 3.54−3.40 (m, 3H), 2.86 (d, J = 12.7 Hz, 1H), 2.77 (dd, J = 9.3, 13.7 Hz, 1H), 2.42 (s, 3H), 2.19 (s, 3H), 1.57−1.41 (m, 1H), 1.38−1.23 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H). LC/MS (ESI) m/z: $[M + H]^+$ calcd for $C_{39}H_{42}N_5O_4$ 644.3, found 644.3. Hydrolysis was carried out according to general procedure 2 (0.502 g, 0.733 mmol, 94 wt %) to afford the desired product as a white amorphous solid (165 mg, 0.314 mmol, 42.9% yield). ^1H NMR (400 MHz, DMSO-d_6) δ = 11.75 (br s, 1H), 8.18 (dd, J = 1.5, 4.4 Hz, 1H), 8.04 (s, 1H), 7.38 (dd, J = 1.5, 7.8 Hz, 1H), 7.36−7.29 (m, 2H), 7.26 (dd, J = 4.9, 7.8 Hz, 1H), 7.12−7.04 (m, 2H), 7.02 (d, J = 7.8 Hz, 1H), 4.71 (t, J = 8.1 Hz, 1H), 3.96 (s, 3H), 3.92 (d, J = 14.2 Hz, 1H), 3.84 (d, J = 14.2 Hz, 1H), 3.81−3.76 (m, 1H), 3.50 (s, 2H), 3.04−2.98 (m, 1H), 2.98−2.92 (m, 1H), 2.85 (d, J = 13.2 Hz, 1H), 2.76 (dd, J = 9.3, 13.7 Hz, 1H), 2.53 (s, 3H), 2.18 (s, 3H), 1.57−1.41 (m, 1H), 1.37−1.24 (m, 1H), 0.93 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ = 173.4, 155.0, 153.0, 143.6, 141.8, 138.6, 136.8, 135.1, 133.6, 132.0, 130.5, 129.3, 128.3, 127.9, 126.6, 125.9, 125.4, 123.8, 107.4, 81.5, 61.6, 60.4, 57.0, 41.6, 41.2, 35.7, 26.7, 18.7, 15.6, 10.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{35}N_4O_3$ 499.2709, found 499.2710. $[\alpha]_D^{20}$ −52 (c 1.0, MeOH).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02639.

^1H and ^{13}C NMR spectra, chiral HPLC chromatograms, CHN and water content (compound **D** only) (PDF)

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Notes

The authors declare no competing financial interest.

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