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Peptide-Catalyzed Conversion of Racemic Oxazol-5(4*H*)-ones into Enantiomerically Enriched α-Amino Acid Derivatives

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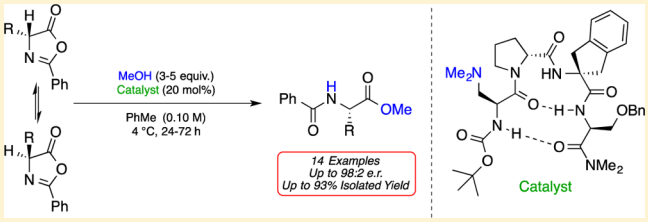
Supporting Information

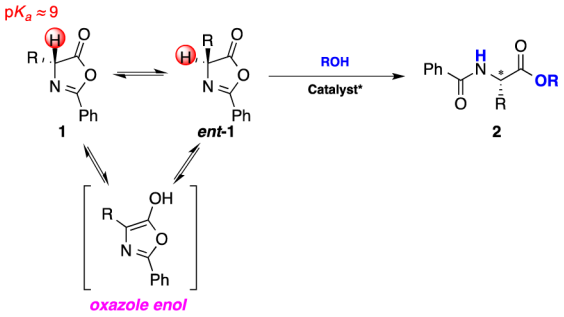
ABSTRACT: We report the development and optimization of a tetrapeptide that catalyzes the methanolytic dynamic kinetic resolution of oxazol-5(4*H*)-ones (azlactones) with high levels of enantioinduction. Oxazolones possessing benzylic-type substituents were found to perform better than others, providing methyl ester products in 88:12 to 98:2 er. The mechanism of this peptide-catalyzed process was investigated through truncation studies and competition experiments. High-field NOESY analysis was performed to elucidate the solution-phase structure of the peptide, and we present a plausible model for catalysis.



INTRODUCTION

The alcoholytic dynamic kinetic resolution[1] (DKR) of oxazol-5(4*H*)-ones[2] (**1**) has proven to be an important method for the preparation of a wide variety of enantiomerically enriched α-amino acid derivatives (**2**), including many that are non-proteinogenic (Scheme 1). This process takes advantage of the

Scheme 1



anomalously acidic oxazolone α-proton ($pK_a \approx 9$),[3] which allows for facile epimerization, and therefore rapid equilibration of enantiomers, through the aromatic oxazole enol intermediate.[4] Design of a chiral catalyst that preferentially reacts with one enantiomer of **1** over the other establishes a Curtin–Hammett scenario, wherein the product distribution is governed by the difference in diastereomeric transition state energies. This process has been used to explore an array of asymmetric catalyst types (Figure 1).[5] It is noteworthy that both transition metal complexes[6,7] (**3** and **4**) and low molecular weight organic scaffolds[8−11] (**5**, **6**, and **7**), as well as hydrolytic enzymes[12] (e.g., **8**), have been demonstrated to be effective catalysts for the DKR of **1**. Of particular interest is the diversity of reaction mechanisms—from Lewis acid[6] and nucleophilic catalysis[7,8] to bifunctional activation,[8−11] through the operation

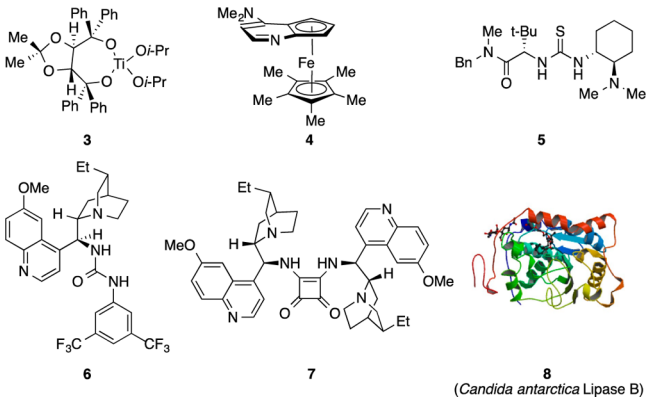


Figure 1. Several catalyst types that have been employed in the ring-opening DKR of oxazolones (**1**).[6,7,9−11,12a]

of intricate catalytic triads[12]—that have been harnessed to control this intriguing process. We were drawn to this particular reaction as an inquiry into whether a purely peptide-based scaffold might be an effective catalyst for a DKR of this type. Stimulated by potential analogies between peptides and their enzymatic counterparts,[13] we embarked on an investigation that has culminated in state-of-the-art levels of selectivity over a rather broad substrate scope for these intriguing reactions.

We began our study with scaffolds that likely take advantage of a well-defined, β-hairpin-like secondary structure.[14] We,[13,15] and others,[16] have shown previously that a number of reactions may be catalyzed with significant selectivity when functional groups are disposed proximally to one another within such a framework. Catalyst scaffold **9** (Scheme 2), which contains a β-dimethylaminoalanine (Dmaa) residue at the *N*-terminal (*i*)

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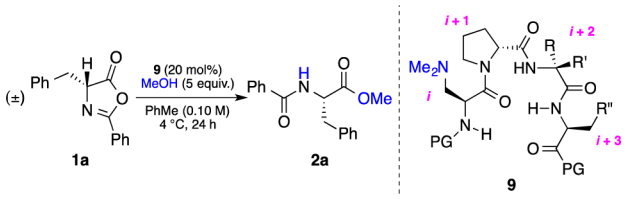
Scheme 2



position,[15a,17] presented the possibility for general base-mediated catalysis through the action of a side chain tertiary amine. In cases where the β-hairpin conformation is adopted, the backbone amides also provide the possibility for nominal bifunctional catalysis, wherein the amide O or NH may contribute as hydrogen bond acceptors or donors, respectively.[13,15−17] Thus, we evaluated families of catalysts structurally related to scaffold **9** for their ability to effect the DKR of oxazolones **1** to provide optically enriched methyl esters **2**.

RESULTS AND DISCUSSION

Table 1 summarizes the results of our efforts to optimize a peptidic catalyst for the methanolytic DKR of **1a** (Scheme 2). In the absence of catalyst, no conversion into methyl ester **2a** was observed under the reaction conditions described in Scheme 2 (entry 1). We were pleased to discover that catalyst **9a**, an archetypal β-hairpin that we had investigated previously in an unrelated transformation,[15a] provided **2a** with 67:33 er, albeit with low conversion (entry 2). This promising initial result spurred a full optimization of scaffold **9**. Replacing the *C*-terminal methyl ester with a dimethyl amide protecting group was advantageous, providing **2a** in 47% conversion and 76:24 er (entry 3). This is presumably due to a strengthing of the NH_i to O_{i+3} hydrogen bond,[18] perhaps providing a more defined secondary structure.

We next proceeded to optimize the $i + 2$ position of **9**, and in so doing we ultimately discovered a rather uncommon $i + 2$ residue that proved to be crucial to catalyst performance. Replacing Aib with cyclopentyl-substituted Cle provided a modest increase in conversion and er (entry 4), while both cyclopropyl-substituted Acpc (entry 5) and the mono-α-substituted Phe[19] (entry 6) were found to be deleterious relative to Cle. However, catalyst **9f**, possessing an indane-substituted Aic residue at the $i + 2$ position, provided **2a** in 84% conversion and 93:7 er (entry 7), a significant improvement over the other residues examined in this position. The reason for this improvement is not fully understood. However, in order to investigate its possible origins, we compared the ^{1}H NMR spectra of peptides **9b**, **9c**, and Aic-containing **9f** (Figure 2).[20] The signal corresponding to NH_{Phe} of **9f** is shifted downfield by 0.10 ppm relative to that of **9c** and by 0.18 ppm relative to that of **9b**. Similarly, the NH_{Aic} signal in **9f** is downfield-shifted by 0.19 ppm relative to NH_{Cle} of **9c** and by 0.27 ppm relative to NH_{Aib} of **9c**. These rather dramatic downfield shifts suggest that the Aic-residue of **9f** may influence the catalyst conformation, perhaps through a strengthening of intramolecular hydrogen bonds. Additional studies of the solution conformation of the catalyst are presented below.

Optimization of the $i + 3$ position allowed us to fine-tune the reactivity and selectivity of the catalyst. Using D-Phe in place of L-Phe decreased the conversion to 75% and the er to 91:9 (entry 8), while substitution with Gly, having no substitutents, was even more deleterious (entry 9). Catalyst **9i**, with its ethyl-substituted Abu residue, provided **2a** in 94% conversion and 96:4 er (entry 10). Both *S*-methyl cysteine (entry 11) and *O*-benzyl serine (entry 12) in the $i + 3$ position provided modest increases in conversion to 97% with no observable effect on the selectivity. Substitution with Leu provided a nearly 30% decrease in conversion and a decrease in er to 91:9 (entry 13). While Gly-containing **9h** is a competent catalyst, these results show that an $i + 3$ side chain in the L-configuration and of appropriate size is required to achieve the highest levels of

Table 1. Catalyst Optimization[a,d]

entry	catalyst	i	$i + 1$	$i + 2$	$i + 3$	conversion[b] (%)	er[c]
1	none	–	–	–	–	0	n/a
2	**9a**	Boc-Dmaa	D-Pro	Aib	Phe-OMe	37	67:33
3	**9b**	Boc-Dmaa	D-Pro	Aib	Phe-NMe_2	47	76:24
4	**9c**	Boc-Dmaa	D-Pro	Cle	Phe-NMe_2	55	79:21
5	**9d**	Boc-Dmaa	D-Pro	Acpc	Phe-NMe_2	37	75:25
6	**9e**	Boc-Dmaa	D-Pro	Phe	Phe-NMe_2	50	78:22
7	**9f**	Boc-Dmaa	D-Pro	Aic	Phe-NMe_2	84	93:7
8	**9g**	Boc-Dmaa	D-Pro	Aic	D-Phe-NMe_2	75	91:9
9	**9h**	Boc-Dmaa	D-Pro	Aic	Gly-NMe_2	62	89:11
10	**9i**	Boc-Dmaa	D-Pro	Aic	Abu-NMe_2	94	96:4
11	**9j**	Boc-Dmaa	D-Pro	Aic	Cys(Me)-NMe_2	97	95:5
12	**9k**	Boc-Dmaa	D-Pro	Aic	Ser(Bn)-NMe_2	97	96:4
13	**9l**	Boc-Dmaa	D-Pro	Aic	Leu-NMe_2	70	91:9
14	**9m**	Ac-Dmaa	D-Pro	Aic	Leu-NMe_2	51	87:13
15	**9n**	Ts-Dmaa	D-Pro	Aic	Leu-NMe_2	31	84:16
16	**9o**	Boc-D-Dmaa	Hyp(Bn)	Aic	D-Ser(Bn)-NMe_2	95	4:96
17	**9p**	Boc-Leu	D-Pro	Aic	Cys(Me)-NMe_2	0	n/a

[a]Reported results are the average of two trials. [b]Conversion is defined as the ^{1}H NMR integration of the product alpha signal relative to an internal standard in the crude reaction mixture. [c]Enantiomer ratios (*S*:*R*) were determined using chiral HPLC. [d]Abbreviations: Boc, *tert*-butoxycarbonyl; Dmaa, β-dimethylaminoalanine; Aib, α-aminoisobutyric acid; Cle, cycloleucine (1-aminocyclopentane-1-carboxylic acid); Acpc, 1-amino-cyclopropane-1-carboxylic acid; Aic, 2-aminoindane-2-carboxylic acid; Abu, 2-aminobutyric acid (ethylglycine); Hyp, *trans*-4-hydroxyproline; Ac, acetyl; Ts, *para*-toluenesulfonyl (tosyl).

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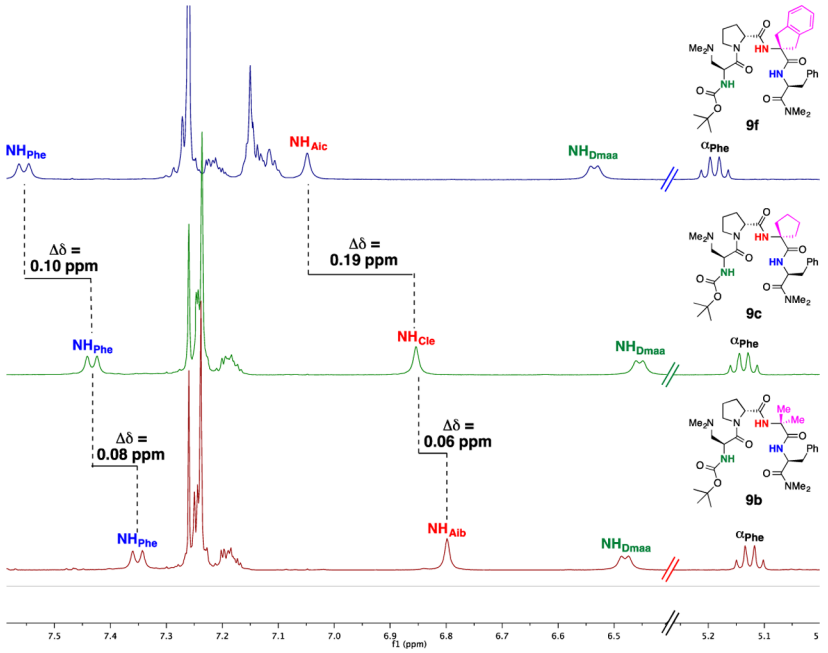

Figure 2. A comparison of the ^{1}H NMR spectra of peptides **9b**, **9c**, and **9f** (500 MHz, 0.02 M in $CDCl_3$). Compared to the other two peptides, the NH_{Phe} and NH_{i+2} signals of **9f** are significantly downfield-shifted. This behavior is consistent with a stronger intramolecular NH_{i+3} to O_i hydrogen bond in the Aic-substituted peptide, which may correlate to a more rigid secondary structure. The NH_{Dmaa} is also downfield-shifted in **9f**, which is consistent with a tighter NH_{Dmaa} to O_{Phe} hydrogen bond.

selectivity and conversion. In an attempt to further rigidify the secondary structure of **9**, catalysts **9m** and **9n** were synthesized possessing acetyl and tosyl *N*-terminal protecting groups, respectively. We expected these groups to acidify the amide NH of the *i* position, providing a stronger NH_i to O_{i+3} intramolecular hydrogen bond. However, both peptides performed worse than the analogous **9l** (entries 14 and 15[21]). Finally, *O*-benzyl-Hyp was substituted for Pro at the *i* + 1 position with no noticeable effect on reactivity or selectivity (entry 16). The *C*-isostere of **9j**, with Leu at the *i* position, provided no conversion into **2a**, suggesting that the tertiary amine moiety of Dmaa was required for catalysis (entry 17).

Having identified peptide **9k** as an effective catalyst for the DKR of **1a**, we proceeded to optimize the reaction conditions. The selectivity of the **9k**-catalyzed DKR of **1a** remained fairly constant over a survey of 10 solvents, only fluctuating between 91:9 and 96:4 (Table 2, entries 1−10). Aromatic solvents (entries 4−7) provided the best results overall, while chlorinated solvents (entries 1−3) delivered comparable selectivities with significantly reduced conversion. Ethereal solvents (entries 8−10) provided the lowest conversions (10−44%), but the selectivity remained high (91:9 to 96:4 er). This was interesting given the ability of these ethereal solvents, especially THF, to compete for hydrogen bonds. Even methanol (entry 11), a highly competitive hydrogen-bonding solvent, furnished **2a** with some selectivity (64:36 er).

Additional studies evaluating reaction conditions are presented in Table 3. Fortuitously, the conditions that we had already chosen for the catalyst optimization study above (Scheme 2) proved to be the most suitable. Taken together, the data presented in Tables 2 and 3 suggest the following: (1) the enantioselectivity of the **9k**-catalyzed reaction is not conversion dependent, as low-conversion reactions also exhibit high ers; and (2) the catalytic system is robust, in that it can provide high ers under a broad range of conditions.

Table 2. Effect of Solvent on Reactivity and Conversion[a,b]

entry	solvent[c]	conversion[d] (%)	er[e]
1	CH_2Cl_2	59	94:6
2	$Cl(CH_2)_2Cl$	80	95:5
3	$CHCl_3$	76	96:4
4	C_6H_6	89	95:5
5	C_6F_6	98	95:5
6	$PhCF_3$	>99	96:4
7	PhCl	94	95:5
8	THF	40	95:5
9	Et_2O	10	91:9
10	*t*-BuOMe	44	96:4
11	MeOH	>99	64:36

[a]Reaction conditions: oxazolone **1a** (1 equiv, 0.05 mmol), peptide **9k** (20 mol %, 0.01 mmol), MeOH (5 equiv, 0.25 mmol), solvent (0.50 mL, 0.10 M), 4 °C, 24 h. [b]Reported results are the average of two trials. [c]All solvents were dried over 4 Å molecular sieves 48 h before use. [d]Conversion is defined as the ^{1}H NMR integration of the product alpha signal relative to an internal standard in the crude reaction mixture. [e]Enantiomer ratios (*S*:*R*) were determined using chiral HPLC.

Table 4 describes our exploration of the substrate scope. Each substrate was analyzed on a small (0.05−0.07 mmol) and large (0.30−0.58 mmol) scale. The small-scale reaction was always quenched in the vicinity of 24 h, and the conversion measured was used to assess whether the larger scale reaction should be allowed to stir longer. Enantioselectivities were consistent between the two scales in every case. We were pleased to discover that **9k** performed well in the methanolytic DKR of 14 different oxazolones **1a**−**n**.[22] Of particular note, oxazolones possessing benzylic substitution at the 4-position were found to provide the best results in terms of selectivity (entries 1−16). It has been noted previously that oxazolones of this type racemize with an accelerated rate over alkyl-

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Table 3. Optimization of Reaction Conditions[a]

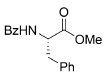
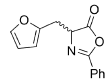
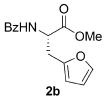
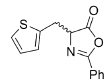
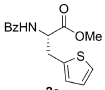
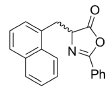
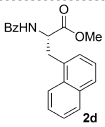
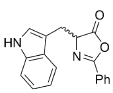
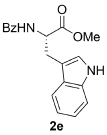
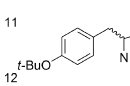
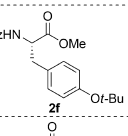
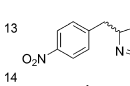
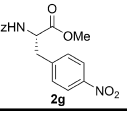
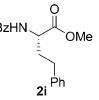
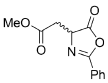
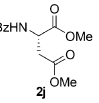
entry	x	loading (mol %)	conc (M)[b]	temp (°C)	time (h)	conversion[c] (%)	er[d]
1	4	20	0.10	4	24	96	96:4
2	3	20	0.10	4	24	96	96:4
3	2	20	0.10	4	24	83	96:4
4	3	20	0.05	4	24	44	96:4
5	3	20	0.20	4	24	>99	95:5
6	3	10	0.05	4	24	27	95:5
7	3	10	0.10	4	24	54	94:6
8	3	10	0.20	4	24	82	94:6
9	2	20	0.10	21	24	64	92:8
10	3	20	0.05	21	24	50	92:8
11	5	20	0.10	−40	24	16	96:4
12	3	20	0.20	−40	24	18	95:5
13	3	20	0.10	4	12	75	96:4

[a]Reaction conditions: oxazolone **1a** (1 equiv, 0.05 mmol), peptide **9k** (20 mol %, 0.01 mmol), MeOH (x equiv, 0.25 mmol), PhMe (conc), temp, time. [b]Concentration with respect to **1a**. [c]Conversion is defined as the ^{1}H NMR integration of the product alpha signal relative to an internal standard in the crude reaction mixture. [d]Enantiomer ratios (*S*:*R*) were determined using chiral HPLC.

substituted oxazolones.[4b] It is possible that this observation partially accounts for their increased conversion and selectivity, though interaction with the catalyst likely plays an important role, as well. Further evidence for this hypothesis is provided by oxazolone **1j**, derived from aspartic acid, which also provides high conversion and er (entries 19−20). In general, alkyl-substituted oxazolones provided **2** in the lowest conversion and er (entries 17−18 and 23−28), though the leucine-derived oxazolone (**1k**) is a notable exception (entries 21−22). The structure−activity relationship highlighted with oxazolones **1k**−**n** may provide insight into the reaction mechanism. While γ-disubstituted **1k** performed well, γ-trisubstituted **1m** provided **2m** with significantly reduced er and conversion (entries 21 vs 25). Similarly, valine-derived **1l** performed better than its β-trisubstituted analogue (**1n**), though neither is particularly impressive in terms of conversion. It appears that β-disubstitution and β/γ-trisubstitution is not well-tolerated by **9k**. It is plausible that destabilizing *syn*-pentane type interactions in the tetrahedral intermediate of methanolysis, or even in the transition state leading to that intermediate, may account for this observation. However, oxazolone **1h** provided **2h** in upward of 90:10 er, despite its β-disubstitution (entries 15−16). This may be due to the presumably increased acidity of the α-proton or to the presence of aryl groups for interaction with **9k**.

The high selectivity exhibited by catalyst **9k** across a wide range of substrate types stimulated a desire to understand its mode of action. These issues were probed with an analysis of additional catalyst analogues, including several that were truncated to explore the influence of peptide miniaturization (Table 5). Dmaa monomers **10a** and **10b** provided very low

Table 4. Substrate Scope[a]

Entry	Oxazolone	Product	Scale (mmol)	Time (h)	Conversion[b]	Yield[c]	er[d]
1			0.05	24	94%	-	96:4
2	**1a**	**2a**	0.50	24	90%	86%	96:4
3			0.05	23	96%	-	96:4
4	**1b**	**2b**	0.50	26	99%	78%	96:4
5			0.05	22	99%	-	96:4
6	**1c**	**2c**	0.50	24	95%	84%	97:3
7			0.05	23	93%	-	94:6
8	**1d**	**2d**	0.50	25	93%	84%	93:7
9			0.05	23	94%	-	98:2
10	**1e**	**2e**	0.50	26	99%	93%	97:3
11			0.05	24	69%	-	93:7
12	**1f**	**2f**	0.50	45	92%	78%	93:7
13			0.05	22	88%	-	88:12
14	**1g**	**2g**	0.50	30	94%	88%	88:12
15			0.05	24	49%	-	91:9[e]
16	**1h**	**2h**	0.30	48	26%	19%	90:10[e]
17			0.05	23	36%	-	81:19
18	**1i**	**2i**	0.50	48	50%	47%	81:19
19			0.05	22	94%	-	90:10
20	**1j**	**2j**	0.47	25	99%	79%	90:10
21[f]			0.05	24	57%	-	91:9
22[f]	**1k**	**2k**	0.50	48	60%	58%	93:7
23[f]			0.05	24	20%	-	80:20
24[f]	**1l**	**2l**	0.58	48	30%	27%	83:17
25[f]			0.05	23	15%	-	79:21
26[f]	**1m**	**2m**	0.50	69	46%	33%	80:20
27[f]			0.07	24	5%	-	72:28
28[f]	**1n**	**2n**	0.50	62	9%	5%	71:29

[a]Substrate scope examined using optimized conditions: peptide **9k** (20 mol %), MeOH (3 equiv), PhMe (0.10 M wrt **1**), 4 °C, unless otherwise specified. [b]Conversion is defined as the ratio of ^{1}H NMR alpha signals (product to total alpha) in the crude reaction mixture. [c]Isolated yield after flash chromatography. [d]Enantiomer ratios were determined by chiral HPLC using an AD-H column, unless otherwise noted. [e]Enantiomer ratios were determined by chiral HPLC using an OD-H column. [f]5 equiv of MeOH were used to promote conversion.

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Table 5. Truncation Study[a,b]

entry	catalyst	*i*	*i* + 1	*i* + 2	conversion[c] (%)	er[d]
1	**10a**	Boc-Dmaa-NMe_2	–	–	9	46:54
2	**10b**	Boc-Dmaa-Pyr[e]	–	–	10	44:56
3	**10c**	Boc-Dmaa	D-Pro-NMe_2	–	32	54:46
4	**10d**	Boc-Dmaa	D-Pro-NHMe	–	24	56:44
5	**10e**	Boc-Dmaa	D-Pro	Aic-NMe_2	32	66:34
6	**10f**	Boc-Dmaa	D-Pro	Aic-NHMe	62	86:14

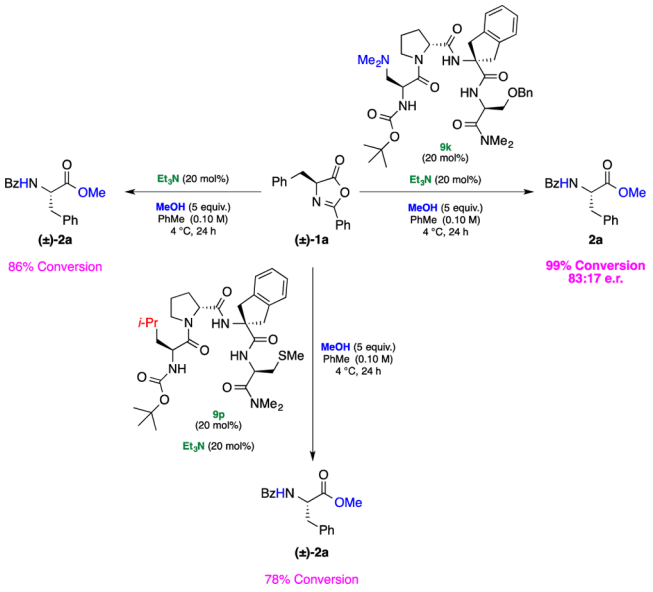
[a]Reaction conditions: oxazolone **1a** (1 equiv, 0.05 mmol), peptide **10** (20 mol %, 0.01 mmol), MeOH (5 equiv, 0.25 mmol), PhMe (0.50 mL, 0.10 M), 4 °C, 24 h. [b]Reported results are the average of two trials. [c]Conversion is defined as the ^{1}H NMR integration of the product alpha signal relative to an internal standard in the crude reaction mixture. [d]Enantiomer ratios (*S*:*R*) were determined using chiral HPLC. [e]Pyr, 1-pyrrolidinyl.

conversion of **1a** to **2a**, but the er was nonracemic in favor of the opposite enantiomer provided by the tetramers examined previously (entries 1 and 2). Dimers **10c** and **10d** more than doubled the conversion, and interestingly provided equal and opposite enantioinduction compared with **10a** and **10b** (entries 3 and 4). To this point, there had been no noticeable effect of the *C*-terminal protecting group on reactivity and selectivity (entries 1–4). Trimer **10e**, possessing a dimethyl amide protecting group, provided **2a** in the same conversion as dimer **10c** with slightly elevated enantioinduction (entry 5). However, trimer **10f**, possessing a *C*-terminal *N*-methyl amide protecting group, nearly doubled the conversion relative to **10e** and provided **2a** in 86:14 er (entry 6). These levels of conversion and enantioselectivity are comparable to those obtained with certain tetramers (Table 1). This suggests that the ability to form an NH_{i+3} to O_i hydrogen bond is important to enantioinduction and conversion. These observations also lend credence to our hypothesized β-hairpin structure and reinforce the notion that secondary structure is important to enantioselective catalysis in this system.

In order to gain further insight into the mechanism of action, we next subjected **9k** to a competition experiment (Scheme 3). When triethylamine (20 mol %) was used to catalyze the DKR of **1a** under the same conditions described in Scheme 2, racemic **2a** was produced in 86% conversion. However, when **9k** and triethylamine were used together (20 mol % of each), the reaction proceeded to quantitative conversion and an 83:17 er was observed in the product. These results suggest that **9k** is able to out-compete triethylamine in the DKR of **1a**. When peptide **9p** (20 mol %), lacking the pendant tertiary amine base, was used with an equimolar amount of triethylamine, racemic **2a** was formed in 78% conversion, suggesting that the pendant tertiary amine of **9k** is important for organizing the transition state in the selective reaction.

Our mechanistic inquiry was extended to include an NMR study of the solution-phase conformation of **9k**. Using high-field ^{1}H–^{1}H-NOESY experiments, the correlations summarized in Figure 3a were observed. Of particular interest are the NOEs observed between β_{Ser} and β_{Dmaa}, NH_{Ser} and NH_{Dmaa}, NH_{Aic} and $\alpha_{D\text{-}Pro}$, and between *trans*-NMe_{Ser} and NH_{Dmaa}. These NOEs are consistent with a β-hairpin-type structure,[23] as shown

Scheme 3



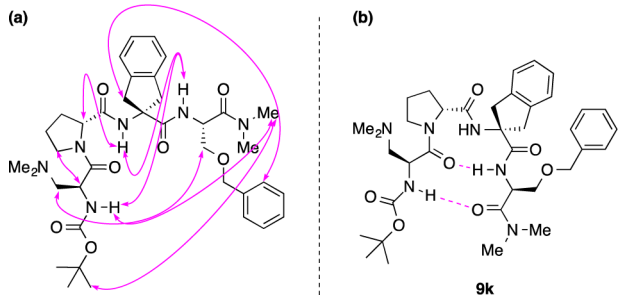


Figure 3. (a) Representative NOEs observed in a 0.02 M solution of **9k** in C_6D_6. (b) The NOESY data are consistent with a hydrogen-bonded, β-hairpin structure.

in Figure 3b. Furthermore, in the ^{1}H NMR spectrum of **9k**, the NH_{Ser} and NH_{Dmaa} signals are shifted significantly downfield at 7.93 and 6.92 ppm, respectively (in C_6D_6), consistent with intramolecular hydrogen bonds involving these protons. While we cannot be certain that the active catalyst adopts such a conformation, the data that we have accumulated herein show that the efficacy of this catalytic system improves as NMR signatures of β-turn-like character become more pronounced.

Figure 4 presents a plausible model for the interaction between peptide **9k** and the substrate that is able to account for the absolute stereochemistry of the products. The β-turn structure of **9k** in Figure 4b is adapted from a previously reported X-ray structure of a related peptide (Figure 4a).[23] Given the results of previous theoretical and mechanistic studies on analogous systems,[24] it is possible that **9k** acts to bind and stabilize the zwitterionic, tetrahedral intermediate of methanolysis.[25,26] In a preliminary NMR complexation study, no change in the chemical shifts of **9k** or oxazolone **1a** were observed in a 1:1 solution relative to individual spectra acquired at the same concentration and temperature. This result is consistent with the hypothesized model, as it suggests that the catalyst does not dock with the oxazolone itself to any appreciable degree. Furthermore, it seems as though a bifunctional catalyst such as **9k** would be well-poised to accelerate the formation of a zwitterionic intermediate through backbone hydrogen bonding[26,27] and general base catalysis.

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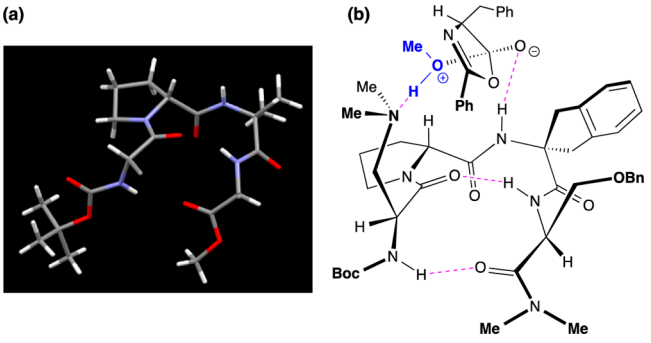

Figure 4. (a) A previously reported X-ray crystal structure showing a D-Pro-Aib-containing β-hairpin structure (ref 23). Side chains were omitted for clarity. (b) Plausible model that accounts for the absolute stereochemistry of products **2**.

Mechanistically, it is plausible that the tertiary amine moiety of **9k** directs methanol to **1** and stabilizes charge as it develops in the tetrahedral intermediate (Figure 4b). The catalyst interacts preferentially with (*S*)-**1**, which may benefit from a minimization of destabilizing *syn*-interactions between the base-delivered methoxy group and the side chain. Furthermore, the side-chain of (*S*)-**1** points away from the Dmaa-residue, leaving the site of catalysis sterically unencumbered. Tertiary amine-catalyzed proton transfer to the oxazole N, followed by ring-opening, provides (*S*)-**2** as observed.

CONCLUSION

In summary, we have developed a simple tetrapeptide that catalyzes the enantioselective ring-opening DKR of oxazolones **1** with state-of-the-art levels of selectivity. The substrate scope addressed by the catalyst is also rather broad. Structural analysis of the catalyst allows for the derivation of a self-consistent mechanistic model that accounts for the absolute sense of asymmetric induction. The culmination of these concepts allows analogies to be drawn between the low molecular weight peptide and far more complex enzymes, which seem to operate through multifunctional mechanisms that often exploit non-covalent interactions to stabilize charge development in transition states.[26] In this sense, the presently reported system may mimic an important aspect of enzymatic chemistry.[28]

EXPERIMENTAL SECTION

Solution Phase Synthesis of Peptides 9a–p and 10a–f. The solution phase synthesis of peptides **9a–p** was accomplished using the *N-tert*-butoxycarbonyl (Boc) protecting group strategy (see Scheme S1 in the Supporting Information).[4c,29] Boc-L-β-Dimethylaminoalanine (Boc-Dmaa-OH) was synthesized according to a literature procedure.[30] All other amino acid residues and coupling reagents were purchased from commercial suppliers. Yields are not optimized. Once synthesized, peptides were stored at 0 °C to prevent epimerization and other adverse side-reactivity. Peptide **9k** was characterized fully (*vide infra*). Peptides **9a–j**, **9l–p**, and **10a–f** were characterized by HRMS (see Supporting Information).

Representative Synthesis and Characterization of Peptide 9k. *Installation of C-Terminal Protecting Group.* Boc-Ser(Bn)-OH (2.00 g, 6.77 mmol), dimethylamine hydrochloride (690 mg, 8.46 mmol), EDC·HCl (1.62 g, 8.46 mmol), and HOBt·H_2O (1.30 g, 8.46 mmol) were added to a round-bottom flask. The solid mixture was dissolved in CH_2Cl_2 (33.8 mL, 0.20 M), and the resulting solution was allowed to stir at rt as *i*-Pr_2NEt (2.94 mL, 16.9 mmol) was added slowly. The pale yellow solution was allowed to stir at rt overnight. After 14 h, the solution was poured into a separatory funnel and washed with approximately 100 mL of 10% aqueous (w/v) citric acid. The organic layer was separated and subsequently washed with 100 mL each of saturated aqueous $NaHCO_3$, water, and brine. The organics were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to provide a clear, yellow oil (2.23 g, > 99% crude yield). The identity of Boc-Ser(Bn)-NMe_2 was confirmed by UPLC–MS. MS exact mass calculated for $[C_{17}H_{26}N_2O_4 + H]^+$ requires m/z = 323.19, found 323.29 (ESI+).

Deprotection 1. Crude Boc-Ser(Bn)-NMe_2 was then treated with 10 mL of 4 M HCl in 1,4-dioxane to cleave the Boc group. The resulting yellow solution was allowed to stir at rt for 1 h, before HCl and 1,4-dioxane were removed in vacuo. Residual 1,4-dioxane was removed by coevaporation with CH_2Cl_2 to provide 1.75 g (99% crude yield) of H-Ser(Bn)-NMe_2·HCl as a white foam, which was dried thoroughly under reduced pressure before being carried forward to the next coupling step.

Peptide Coupling 1. H-Ser(Bn)-NMe_2·HCl (1.75 g, 6.77 mmol) was added to a round-bottom flask, along with Boc-Aic-OH (2.15 g, 7.74 mmol), EDC·HCl (1.62 g, 8.46 mmol), and HOBt·H_2O (1.30 g, 8.46 mmol). The solid mixture was dissolved in CH_2Cl_2 (33.8 mL, 0.20 M), and the resulting solution was allowed to stir at rt as *i*-Pr_2NEt (2.94 mL, 16.9 mmol) was added slowly. The deep yellow solution was allowed to stir at rt for 42 h, after which the solution was poured into a separatory funnel and washed with 100 mL of 10% aqueous (w/v) citric acid. The organic layer was separated and subsequently washed with 100 mL each of saturated aqueous $NaHCO_3$, water, and brine. The organics were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to provide an off-white foam (3.13 g, 96% crude yield). The identity of Boc-Aic-Ser(Bn)-NMe_2 was confirmed by UPLC–MS. MS exact mass calculated for $[C_{27}H_{35}N_3O_5 + H]^+$ requires m/z = 482.26, found 482.39 (ESI+).

Deprotection 2. Deprotection of the crude dipeptide Boc-Aic-Ser(Bn)-NMe_2 was accomplished in the same manner as described in Deprotection 1 (vide supra) to provide H-Aic-Ser(Bn)-NMe_2·HCl (2.72 g, 6.50 mmol) as a white foam.

Peptide Coupling 2. The coupling of H-Aic-Ser(Bn)-NMe_2·HCl (2.72 g, 6.50 mmol) to Boc-D-Pro-OH (2.15 g, 9.97 mmol) was performed using the procedure detailed in Peptide Coupling 1, above. Boc-D-Pro-Aic-Ser(Bn)-NMe_2 was isolated as a white foam (3.39 g, 90% crude yield), the identity of which was confirmed by UPLC–MS. MS exact mass calculated for $[C_{32}H_{42}N_4O_6 + H]^+$ requires m/z = 579.31, found 579.52 (ESI+).

Deprotection 3. Deprotection of the crude tripeptide Boc-D-Pro-Aic-Ser(Bn)-NMe_2 was accomplished in the same manner as described in Deprotection 1 (vide supra) to provide H-D-Pro-Aic-Ser(Bn)-NMe_2·HCl (3.02 g, 5.86 mmol) as a pale yellow foam.

Peptide Coupling 3. H-D-Pro-Aic-Ser(Bn)-NMe_2·HCl (3.02 g, 5.86 mmol), Boc-Dmaa-OH (1.70 g, 7.33 mmol), and HBTU (2.78 g, 7.33 mmol) were added to a round-bottom flask. The solid mixture was dissolved in CH_2Cl_2 (29.3 mL, 0.20 M), and the resulting solution was allowed to stir at rt as *i*-Pr_2NEt (2.55 mL, 14.7 mmol) was added slowly. The yellow solution was allowed to stir at rt for 38 h, after which the solution was poured into a separatory funnel and washed with about 100 mL of saturated aqueous $NaHCO_3$. The organic layer was separated and subsequently washed with 100 mL each of water and brine. The organics were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to provide a deep yellow oil. The crude product was loaded onto a flash purification system for reverse-phase column chromatography (120 g column, 30–100% MeOH/H_2O over 16 column volumes with 3 column volume pre- and postrun equilibrations, 45 mL min^{-1} flow, collection λ = 210 nm, monitored λ = 245 nm, 16 × 150 mm test tubes with 21 mL fractions). Fractions were pooled, concentrated in vacuo, and dried by coevaporation thrice with CH_2Cl_2 to provide Boc-Dmaa-D-Pro-Aic-Ser(Bn)-NMe_2 (**9k**, 2.18 g, 54% yield) as white foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.9 Hz, 1H), 7.35–7.20 (m, 5H), 7.19–7.09 (m, 4H), 6.25 (d, J = 6.0 Hz, 1H), 5.26 (td, J = 8.2, 5.8 Hz, 1H), 4.51 (q, J = 12.0 Hz, 2H), 4.40–4.33 (m, 2H), 3.89 (d, J = 16.8, 1H), 3.84–3.80 (m, 1H), 3.72 (AMX, J_{AX} = 6.2 Hz, J_{MX} = 5.9 Hz, J_{AM} = 16.3 Hz, ν_{AM} = 56.1 Hz, 2H), 3.52 (m, 2H), 3.33 (d, J = 16.7, Hz, 1H), 3.12 (d, J = 17.8 Hz, 1H), 3.10 (s, 3H), 2.94 (s, 3H), 2.53 (AMX, J_{AX} = 6.7 Hz, J_{MX} = 7.5 Hz, J_{AM}

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= 12.4 Hz, ν_{AM} = 130.7 Hz, 2H), 2.26 (s, 6H), 2.22−2.18 (m, 1H), 2.08−1.99 (m, 2H), 1.91−1.81 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 171.5, 171.4, 170.4, 155.9, 141.4, 139.3, 138.3, 128.4, 127.6, 127.5, 127.0, 126.7, 124.8, 124.4, 79.6, 77.4, 77.2, 76.9, 73.3, 70.8, 67.2, 60.8, 60.0, 50.8, 48.5, 47.3, 45.8, 45.5, 42.6, 37.6, 36.0, 28.5, 27.8, 25.0; IR (film, cm^{-1}) 3296, 3243, 3213, 3184, 2929, 2860, 2773, 2250, 1684, 1632, 1522, 1453, 1404, 1366, 1307, 1274, 1165, 1098, 1051, 1025; HRMS exact mass calculated for $[C_{37}H_{52}N_6O_7 + H]^+$ requires m/z = 693.3976, found 693.3971 (ESI+); $[\alpha]_D^{20}$ = +38.8 (c = 1.0, $CHCl_3$).

_N_-Terminal Modification in Peptides 9m−n. *Deprotection 4.* Following Peptide Coupling 3, Boc-Dmaa-D-Pro-Aib-Leu-NMe_2 (**9l**, 100 mg, 0.16 mmol) was dissolved in 3 mL of 4 M HCl in 1,4-dioxane solution and allowed to stir at ambient temperature for 1 h, after which HCl and 1,4-dioxane were removed in vacuo. The resulting salt was carried forward assuming quantitative yield (96 mg, 0.16 mmol).

*Acetylation (**9m**).* H-Dmaa-D-Pro-Aic-Leu-NMe_2·2HCl (96 mg, 0.16 mmol) was suspended in 0.80 mL of dry CH_2Cl_2 and treated with *i*-Pr_2NEt (0.11 mL, 0.64 mmol). The resulting solution was cooled to 0 °C over an ice bath and allowed to stir vigorously as Ac_2O (19 μL, 0.20 mmol) was added slowly. The flask was sealed with a septum and purged with N_2. The reaction solution was allowed to warm to rt over 2 h, after which the solution was poured into a separatory funnel, diluted to 10 mL with additional CH_2Cl_2, and washed once with 20 mL of saturated aqueous $NaHCO_3$ and once with 20 mL of H_2O. The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to provide a clear, colorless oil. The crude product was loaded onto a flash purification system for reverse-phase column chromatography using the same method described above in Peptide Coupling 3. The appropriate fractions were pooled, concentrated in vacuo, and dried by coevaporation with CH_2Cl_2 to provide **9m** (54 mg, 0.095 mmol, 59% yield) as a white foam.

*Tosylation (**9n**).* H-Dmaa-D-Pro-Aic-Leu-NMe_2·2HCl (96 mg, 0.16 mmol) was tosylated following the above acetylation procedure using TsCl (45 mg, 0.20 mmol) in place of Ac_2O. Workup and purification by the same method provided **9n** (81 mg, 0.12 mmol, 74% yield) as an off-white foam.

Synthesis of Boc-L-*β*-Dimethylaminoalanine (Boc-Dmaa-OH). *Boc-L-β-Aminoalanine.*[30] Boc-L-Asn-OH (10.0 g, 43.1 mmol) was added to a 500 mL round-bottom flask equipped with a large stir bar. The white solid was suspended in 120 mL of a 2:2:1 (v/v/v) solution of MeCN, EtOAc, and water and allowed to stir at 0 °C over an ice bath. $PhI(OAc)_2$ (16.7 g, 51.7 mmol) was added slowly to the cloudy, white suspension at 0 °C. The flask was sealed with a septum, and the reaction was allowed to warm to rt over 4 h under an atmosphere of N_2. Within a few minutes, the white suspension became a clear, pale yellow solution. Within an hour, a white solid precipitate began to form. After 4 h, the white suspension was cooled to 0 °C over an ice bath for an additional 30 min to promote precipitation. The white solid was collected by vacuum filtration through a Büchner funnel, washing with 200 mL of EtOAc. The product was allowed to dry on high vacuum for multiple hours, providing Boc-L-*β*-aminoalanine (5.58 g, 63% yield) as a white powdery solid: ^{1}H NMR (500 MHz, CD_3OD) δ 4.06 (t, J = 6.5 Hz, 1H), 3.15 (ABX, J_{AX} = 6.8 Hz, J_{BX} = 6.2 Hz, J_{AB} = 12.4 Hz, ν_{AB} = 19.2 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$):δ 174.7, 158.0, 80.9, 53.9, 43.1, 28.7; MS exact mass calculated for $[C_8H_{16}N_2O_4 + H]^+$ requires m/z = 205.12, found 205.13 (ESI+).

Boc-L-β-Dimethylaminoalanine. Boc-L-*β*-Aminoalanine (1.88 g, 9.19 mmol) was added to a round-bottom flask containing a magnetic stir bar. Palladium (10% on activated charcoal, 188 mg, 10 mass%) was added to the flask, and the solid mixture was carefully treated with formaldehyde (37% aq, 1.71 mL, 23.0 mmol). The flask was filled with N_2, and methanol (40 mL) was added slowly to the slurry. The resulting black suspension was allowed to stir vigorously. The flask was sealed with a septum, evacuated, and filled with H_2 from a balloon. Five rounds of filling and evacuating were performed. After the final evacuation, the flask was again filled with H_2, and the reaction was allowed to stir 48 h at rt under positive H_2 pressure (from a balloon). After 48 h, the heterogeneous reaction mixture was vacuum filtered through a plug of Celite to remove Pd/C, washing with MeOH. The filtrate was concentrated in vacuo, and residual solvent was removed by coevaporation with CH_2Cl_2 to provide a flaky, white solid. ^{1}H NMR analysis confirmed the structure of the crude product. The white solid product was triturated thrice with Et_2O and dried under reduced pressure, providing clean Boc-Dmaa-OH (1.90 g, 89% yield) to be used in peptide synthesis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.0 (bs, 1H), 5.78 (d, J = 4.7 Hz, 1H), 4.13 (q, J = 6.5 Hz, 1H), 3.26 (m, 2H), 2.85 (s, 6H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 155.7, 79.7, 58.6, 50.9, 44.2, 28.5; MS exact mass calculated for $[C_{10}H_{20}N_2O_4 + H]^+$ requires m/z = 233.15, found 233.13 (ESI+).

Synthesis of Oxazolones 1. All oxazolone substrates **1** were previously known compounds. They were synthesized from commercially available amino acids in a precedented two-step sequence. The amino acids were first acylated with benzoyl chloride using the Schötten-Baumann conditions.[7,31] The resulting *N*-benzoyl amino acids were cyclodehydrated to oxazolones **1** with acetic anhydride in refluxing CH_2Cl_2[9a,32] or with EDC·HCl at 0 °C in CH_2Cl_2.[33] Please consult the Supporting Information for additional synthetic details and characterization.

Synthesis of _N_-Benzoyl Amino Acids 1a′−n′. *General Procedure A.*[7,31] Amino acid (1.0 equiv) was added to a round-bottom flask equipped with a magnetic stir bar and was suspended in 2 M aqueous NaOH (0.20 M solution). The resulting mixture was allowed to stir vigorously at 0 °C over an ice bath. Benzoyl chloride (1.05 equiv) was then added dropwise with a syringe. The mixture was allowed to warm to rt over 1−3 h, after which the reaction was again cooled to 0 °C and quenched by acidification to pH < 2 with 1 M aqueous HCl. A white/off-white precipitate formed instantly upon acidification. The mixture was allowed to stand at 0 °C for 15 min before the precipitate was collected by vacuum filtration and subsequently recrystallized from hot EtOH/H_2O. The resulting crystalline solid was collected by vacuum filtration, rinsed with H_2O, and dried on high vacuum for multiple hours to provide *N*-benzoyl amino acids **1′**.

General Procedure B.[7,31] The reaction was performed in the same manner as in General Procedure A, except an extractive workup was performed. After acidification with 1 M aqueous HCl to pH < 2, the organics were extracted thrice with Et_2O. The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to provide a white/off-white solid, which was subsequently recrystallized from hot EtOH/H_2O. The resulting crystalline solid was collected by vacuum filtration, rinsed with H_2O, and dried on high vacuum for multiple hours to provide *N*-benzoyl amino acids **1′**.

General Procedure C.[7,31] Amino acid (1.0 equiv) was added to a round-bottom flask equipped with a magnetic stir bar and was suspended in 2 M aqueous Na_2CO_3 (0.25 M solution). The resulting mixture was allowed to stir vigorously at 0 °C over an ice bath. Benzoyl chloride (1.05 equiv) was then added dropwise with a syringe. The mixture was allowed to warm to rt overnight, after which the reaction was again cooled to 0 °C and quenched by acidification to pH < 2 with 1 M aqueous HCl. No precipitate formed. The aqueous solution was extracted thrice with CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to provide a white solid, which was dissolved in a minimal amount of MeOH and loaded onto a reverse-phase flash purification system (120g C18 column, 0 to 60% MeOH/H_2O linear gradient, 50 mL min^{-1} flow rate). The appropriate fractions were pooled and concentrated in vacuo, and adventitious water was removed by coevaporation with CH_2Cl_2, providing *N*-benzoyl amino acids **1′**.

*N-Benzoyl-DL-phenylalanine (**1a′**).* Title compound was synthesized from DL-phenylalanine (10.00 g, 60.5 mmol) according to General Procedure A above. Yield: 40% (fine, white powder); ^{1}H NMR (500 MHz, CD_3OD) δ 7.77−7.59 (m, 2H), 7.56−7.44 (m, 1H), 7.45−7.37 (m, 2H), 7.30−7.20 (m, 4H), 7.19−7.12 (m 1H), 4.78 (dd, J = 8.2, 5.0 Hz, 1H), 3.24 (AMX, J_{AX} = 5.0 Hz, J_{MX} = 8.2 Hz, J_{AM} = 13.8 Hz, ν_{AM} = 105.7 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.4, 169.6, 139.1, 135.7, 132.6, 130.5, 129.5, 129.3, 128.2, 127.5, 56.7, 38.7; MS exact mass calculated for $[C_{16}H_{15}NO_3 + H]^+$ requires m/z = 270.11, found 270.11 (ESI+).

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*N-Benzoyl-D-β-(2-furyl)alanine (**1b′**).* Title compound was synthesized from D-β-(2-furyl)alanine (750 mg, 4.83 mmol) according to General Procedure B above with the following modifications: (1) the reaction concentration was 0.24 M wrt the amino acid. Yield: 42% (fluffy white solid); ^{1}H NMR (500 MHz, CD_3OD) δ 7.81−7.69 (m, 2H), 7.56−7.49 (m, 1H), 7.47−7.41 (m, 2H), 7.38 (d, J = 1.8 Hz, 1H), 6.30 (dd, J = 3.0, 1.9 Hz, 1H), 6.17 (d, J = 3.1 Hz, 1H), 4.97−4.74 (m, 1H), 3.28 (AMX, J_{AX} = 4.8 Hz, J_{MX} = 9.3 Hz, J_{AM} = 15.5 Hz, ν_{AM} = 59.7 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.4, 170.1, 152.6, 143.1, 135.2, 132.8, 129.5, 128.3, 111.3, 108.4, 53.4, 30.7; MS exact mass calculated for $[C_{14}H_{13}NO_4 + H]^+$ requires m/z = 260.09, found 260.10 (ESI+).

*N-Benzoyl-L-β-(2-thienyl)alanine (**1c′**).* Title compound was synthesized from L-β-(2-thienyl)alanine (1.00 g, 65.84 mmol) according to General Procedure B above with the following modifications: (1) 1.1 equiv of benzoyl chloride were used; (2) the reaction concentration was 0.97 M wrt the amino acid; (3) the reaction was allowed to run overnight (12−14 h). Yield: 62% (flaky white solid); ^{1}H NMR (500 MHz, CD_3OD) δ 7.82−7.75 (m, 2H), 7.56−7.50 (m, 1H), 7.49−7.40 (m, 2H), 7.22 (dd J = 4.6, 1.8 Hz, 1H), 6.96−6.88 (m, 2H), 4.89−4.76 (m, 1H), 3.48 (AMX, J_{AX} = 4.4 Hz, J_{MX} = 9.1 Hz, J_{AM} = 15.0 Hz, ν_{AM} = 79.7 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.2, 170.0, 140.4, 135.4, 132.8, 129.5, 128.4, 127.8, 127.4, 125.4, 55.7, 32.3; MS exact mass calculated for $[C_{14}H_{13}NO_3S + H]^+$ requires m/z = 276.07, found 276.06 (ESI+).

*N-Benzoyl-L-β-(1-naphthyl)alanine (**1d′**).* Title compound was synthesized from L-β-(1-naphthyl)alanine (1.00 g. 4.65 mmol) according to General Procedure B above with the following modifications: (1) 1.1 equiv of benzoyl chloride were used; (2) the reaction concentration was 0.93 M wrt the amino acid; (3) the reaction was allowed to run overnight (12−14 h). Yield: 67% (white solid); ^{1}H NMR (500 MHz, CD_3OD) δ 8.23 (dd, J = 8.5, 1.1 Hz, 1H), 7.89−7.84 (m, 1H), 7.76 (d, J = 8.1, 1H), 7.69−7.64 (m, 2H), 7.55 (ddd, J = 8.5, 6.8, 1.4 Hz, 1H), 7.52−7.45 (m, 2H), 7.46−7.29 (m, 4H), 5.01 (dd, J = 9.7, 4.7 Hz, 1H), 3.71 (AMX, J_{AX} = 4.7 Hz, J_{MX} = 9.7 Hz, J_{AM} = 14.3 Hz, ν_{AM} = 196.3 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 175.3, 170.7, 135.9, 135.7, 135.2, 133.8, 133.1, 130.3, 129.8, 129.1, 129.0, 128.8, 127.7, 127.1, 126.7, 124.9, 55.5, 35.9; MS exact mass calculated for $[C_{20}H_{17}NO_3 + H]^+$ requires m/z = 320.13, found 320.13 (ESI+).

*N-Benzoyl-O-tert-butyl-L-tyrosine (**1f′**).* Title compound was synthesized from *O-tert*-butyl-L-tyrosine (712 mg, 3.00 mmol) according to General Procedure A above with the following modifications: (1) the reaction concentration was 0.41 M wrt the amino acid; (2) after 1 h, the aqueous solution was acidified with 1 M HCl until pH 4; (3) recrystallized from EtOH/H_2O at 0 °C overnight. Yield: 68% (colorless needle-like crystals); ^{1}H NMR (500 MHz, CD_3OD) δ 7.72−7.68 (m, 2H), 7.53−7.48 (m, 1H), 7.44−7.39 (m, 2H), 7.21−7.17 (m, 2H), 6.93−6.87 (m, 2H), 4.88−4.81 (m, 1H), 3.20 (AMX, J_{AX} = 5.1 Hz, J_{MX} = 9.7 Hz, J_{AM} = 13.9 Hz, ν_{AM} = 118.8 Hz, 2H), 1.28 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.8, 170.2, 155.3, 135.4, 133.9, 132.7, 130.8, 129.5, 128.3, 125.2, 79.5, 55.6, 37.6, 29.1; MS exact mass calculated for $[C_{21}H_{25}NO_4 + H]^+$ requires m/z = 342.17 Found 342.17 (ESI+).

*N-Benzoyl-L-(4-nitro)phenylalanine (**1g′**).* Title compound was synthesized from L-(4-nitro)phenylalanine (1.00 g, 4.76 mmol) according to General Procedure A with the following modifications: (1) the reaction concentration was 0.24 M wrt the amino acid. Yield: 68% (white, flaky solid); ^{1}H NMR (400 MHz, CD_3OD) δ 8.18−8.12 (m, 2H), 7.75−7.70 (m, 2H), 7.56−7.48 (m, 3H), 7.46−7.39 (m, 2H), 4.95 (dd, J = 9.8, 5.0 Hz, 1H), 3.37 (AMX, J_{AX} = 5.0 Hz, J_{MX} = 9.9 Hz, J_{AM} = 14.0 Hz, ν_{AM} = 93.9 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.1, 170.2, 148.3, 147.0, 135.1, 132.9, 131.4, 129.5, 128.3, 124.4, 55.0, 38.0; MS exact mass calculated for $[C_{16}H_{14}N_2O_5 + H]^+$ requires m/z = 315.10, found 315.10 (ESI+).

*N-Benzoyl-L-β,β-diphenylalanine (**1h′**).* Title compound was synthesized from L-β,β-diphenylalanine (1.00 g, 4.14 mmol) according to General Procedure A with the following modifications: (1) the reaction concentration was 0.41 M wrt the amino acid. Yield: 60% (fluffy, white solid); ^{1}H NMR (500 MHz, CD_3OD) δ 7.55−7.51 (m, 2H), 7.48−7.42 (m, 1H), 7.42−7.37 (m, 4H), 7.37−7.31 (m, 2H), 7.30−7.23 (m, 4H), 7.22−7.11 (m, 2H), 5.53 (d, J = 11.4 Hz, 1H), 4.61 (d, J = 11.3 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.3, 170.2, 142.3, 142.3, 135.4, 132.6, 129.5, 129.5, 129.5, 129.4, 129.4, 128.3, 128.0, 127.8, 57.5, 54.6; MS exact mass calculated for $[C_{22}H_{19}NO_3 + H]^+$ requires m/z = 346.14, found 346.15 (ESI+).

*N-Benzoyl-L-homophenylalanine (**1i′**).* Title compound was synthesized from L-homophenylalanine (896 mg, 5.00 mmol) according to General Procedure A with the following modifications: (1) the reaction concentration was 0.50 M wrt the amino acid. Yield: 59% (white, granular solid); ^{1}H NMR (500 MHz, CD_3OD) δ 7.87−7.82 (m, 2H), 7.58−7.51 (m, 1H), 7.50−7.44 (m, 2H), 7.36−7.19 (m, 4H), 7.20−7.10 (m, 1H), 4.58 (dd, J = 9.6, 4.7 Hz, 1H), 2.86−2.69 (m, 2H), 2.32−2.23 (m, 1H), 2.21−2.11 (m, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 175.5, 170.5, 142.3, 135.4, 132.8, 129.6, 129.5, 128.5, 127.1, 117.3, 53.9, 34.3, 33.4; MS exact mass calculated for $[C_{17}H_{17}NO_3 + H]^+$ requires m/z = 284.13, found 284.13 (ESI+).

*N-Benzoyl-L-aspartic acid β-methyl ester (**1j′**).* Title compound was synthesized from L-aspartic acid β-methyl ester (1.03 g, 6.97 mmol) was synthesized using General Procedure C. Yield: 16% (white, flaky solid); ^{1}H NMR (500 MHz, CD_3OD) δ 7.86−7.79 (m, 2H), 7.61−7.51 (m, 1H), 7.50−7.43 (m, 2H), 4.98 (dd, J = 7.5, 5.5 Hz, 1H), 3.70 (s, 3H), 2.98 (AMX, J_{AX} = 7.0 Hz, J_{MX} = 9.3 Hz, J_{AM} = 20.5 Hz, ν_{AM} = 57.8 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 172.8, 170.0, 135.1, 132.9, 129.6, 128.4, 52.4, 52.4, 36.9; MS exact mass calculated for $[C_{12}H_{13}NO_5 + H]^+$ requires m/z = 252.09, found 252.17 (ESI+).

*N-Benzoyl-DL-leucine (**1k′**).* Title compound was synthesized from DL-leucine (5.00 g, 38.1 mmol) according to General Procedure B with the following modifications: (1) 0.95 equiv of benzoyl chloride was used; (2) the reaction concentration was 1.66 M wrt the amino acid; (3) EtOAc was used to extract the aqueous layer after acidification. Yield: 61% (white powder); ^{1}H NMR (400 MHz, CD_3OD) δ 7.88−7.80 (m, 2H), 7.57−7.50 (m, 1H), 7.49−7.41 (m, 2H), 4.67 (dd, J = 10.4, 4.2 Hz, 1H), 1.91−1.63 (m, 3H), 0.99 (dd, J = 8.4, 5.7 Hz, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.2, 170.5, 135.4, 132.8, 129.5, 128.5, 52.6, 41.4, 26.3, 23.4, 21.8; MS exact mass calculated for $[C_{13}H_{17}NO_3 + H]^+$ requires m/z = 236.13, found 236.13 (ESI+).

*N-Benzoyl-DL-valine (**1l′**).* Title compound was synthesized from DL-valine (5.00 g, 42.7 mmol) using General Procedure A with the following modifications: (1) the product was recrystallized from hot H_2O instead of EtOH/H_2O. Yield: 72% (white, granular solid); ^{1}H NMR (400 MHz, CD_3OD) δ 7.87−7.81 (m, 2H), 7.58−7.51 (m, 1H), 7.50−7.42 (m, 2H), 4.51 (d, J = 6.3 Hz, 1H), 2.29 (o, J = 6.7 Hz, 1H), 1.05 (d, J = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.9, 170.7, 135.5, 132.8, 129.5, 128.5, 59.8, 31.8, 19.7, 18.9; MS exact mass calculated for $[C_{12}H_{15}NO_3 + H]^+$ requires m/z = 222.11, found 222.11 (ESI+).

*N-Benzoyl-L-β-tert-butylalanine (**1m′**).* Title compound was synthesized from L-β-*tert*-butylalanine (500 mg, 3.44 mmol) according to General Procedure B with the following modifications: (1) 1.1 equiv of benzoyl chloride was used; (2) the reaction concentration was 1.0 M wrt the amino acid. Yield: 63% (white, flaky solid); ^{1}H NMR (500 MHz, CD_3OD) δ 7.87−7.81 (m, 2H), 7.57−7.48 (m, 1H), 7.49−7.42 (m, 2H), 4.73 (dd, J = 9.4, 2.8 Hz, 1H), 1.87 (ABX, J_{AX} = 2.5 Hz, J_{BX} = 9.8 Hz, J_{AB} = 14.5 Hz, ν_{AB} = 30.7 Hz, 2H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.5, 170.1, 135.5, 132.7, 129.5, 128.4, 51.7, 45.7, 31.6, 30.0; MS exact mass calculated for $[C_{14}H_{19}NO_3 + H]^+$ requires m/z = 250.14, found 250.14 (ESI+).

*N-Benzoyl-DL-tert-leucine (**1n′**).* Title compound was synthesized from DL-*tert*-leucine (5.00 g, 38.1 mmol) according to General Procedure B with the following modifications: (1) the reaction concentration was 1.59 M. Yield: 49% (white, flaky solid); ^{1}H NMR (500 MHz, CD_3OD) δ 7.84−7.79 (m, 2H), 7.57−7.52 (m, 1H), 7.50−7.42 (m, 2H), 4.56 (s, 1H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.2, 170.5, 135.6, 132.8, 129.6, 128.5, 62.4, 35.3, 27.3; MS exact mass calculated for $[C_{13}H_{17}NO_3 + H]^+$ requires m/z = 236.13, found 236.13 (ESI+).

Synthesis of Oxazolones 1a−n. *General Procedure A.*[9a,32] *N*-Benzoyl amino acid **1′** (1.0 equiv) was added to a round-bottom flask

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equipped with a magnetic stir bar and subsequently suspended in dry CH_2Cl_2 (0.10 M solution). The suspension was allowed to stir vigorously at rt as Ac_2O (2.0 equiv wrt **1′**) was added slowly with a syringe. A reflux condenser was affixed to the flask, and the suspension was stirred at reflux overnight under an atmosphere of N_2. After 12−14 h, the suspension had often become a clear, colorless or pale yellow solution. The solution was allowed to cool to rt before solvent was removed in vacuo. Acetic acid byproduct was removed by coevaporation three times each with PhMe and CH_2Cl_2. The resulting crude product was loaded onto a silica column in CH_2Cl_2 and purified by flash chromatography using a suitable EtOAc/hexanes gradient (as determined by TLC). The appropriate fractions were pooled, concentrated under reduced pressure, and dried on high vacuum to afford oxazolone **1**.

General Procedure B.[33] *N*-Benzoyl amino acid **1′** (1.0 equiv) was added to a round-bottom flask equipped with a magnetic stir bar and subsequently suspended in dry CH_2Cl_2 (0.10 M solution wrt **1′**). The suspension was cooled to 0 °C over an ice bath as EDC·HCl (1.1 equiv wrt **1′**) was added portionwise. The flask was sealed, and the reaction mixture was allowed to warm to rt overnight under an atmosphere of N_2. After 12−14 h, the suspension had often become a clear, colorless or pale yellow solution. The solution was diluted to double the initial volume with CH_2Cl_2 and poured into a separatory funnel containing an approximately equal volume of H_2O. The layers were separated, and the organic layer was washed sequentially with saturated aqueous $NaHCO_3$ and H_2O (equal volume of each relative to the organics). The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to provide a white solid. The crude product was loaded onto a silica column in CH_2Cl_2 and purified by flash chromatography using a suitable EtOAc/hexanes gradient (as determined by TLC). The appropriate fractions were pooled, concentrated under reduced pressure, and dried on high vacuum to afford oxazolone **1**.

4-Benzyl-2-phenyloxazol-5(4H)-one (***1a***). Title compound was synthesized from *N*-benzoyl-DL-phenylalanine (**1a′**, 6.567 g, 24.4 mmol) according to General Procedure A above. Yield: 89% (white solid); TLC R_f = 0.48 (20% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95−7.86 (m, 2H), 7.51−7.47 (m, 1H), 7.45−7.38 (m, 2H), 7.29−7.22 (m, 4H), 7.22−7.15 (m, 1H), 4.66 (dd, J = 6.8, 5.0 Hz, 1H), 3.26 (AMX, J_{AX} = 5.0 Hz, J_{MX} = 6.8 Hz, J_{AM} = 14.0 Hz, ν_{AM} = 92.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 161.7, 135.4, 132.7, 129.6, 128.7, 128.4, 127.9, 127.2, 125.8, 66.5, 37.3; MS exact mass calculated for $[C_{16}H_{13}NO_2 + H]^+$ requires m/z = 252.10, found 252.11 (ESI+).

4-(2-Furylmethyl)-2-phenyloxazol-5(4H)-one (***1b***). Title compound was synthesized from *N*-benzoyl-D-β-(2-furyl)alanine (**1b′**, 520 mg, 2.01 mmol) according to General Procedure A above. Yield: 88% (pale yellow solid); TLC R_f = 0.41 (20% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99−7.93 (m, 2H), 7.60−7.53 (m, 1H), 7.50−7.42 (m, 2H), 7.29 (dd, J = 1.9. 0.8 Hz, 1H), 6.26 (dd, J = 3.2, 1.9 Hz, 1H), 6.17 (dd, J = 3.2, 0.9 Hz, 1H), 4.70 (dd, J = 6.3, 5.5 Hz, 1H), 3.35 (AMX, J_{AX} = 5.4 Hz, J_{MX} = 6.4 Hz, J_{AM} = 15.3 Hz, ν_{AM} = 58.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 162.5, 149.8, 142.3, 133.1, 129.0, 128.22, 126.0, 110.7, 108.2, 64.7, 30.3; MS exact mass calculated for $[C_{14}H_{11}NO_3 + H]^+$ requires m/z = 242.08, found 242.08 (ESI+).

2-Phenyl-4-(2-thiophenylmethyl)oxazol-j5(4H)-one (***1c***). Title compound was synthesized from *N*-benzoyl-L-β-(2-thienyl)alanine (**1c′**, 600 mg, 2.18 mmol) according to General Procedure A above. Yield: 61% (pale yellow oil); TLC R_f = 0.43 (20% EtOAc/hexanes, UV); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.92 (m, 2H), 7.62−7.52 (m, 1H), 7.52−7.41 (m, 2H), 7.12 (dd, J = 5.1, 1.3 Hz, 1H), 6.97−6.90 (m, 1H), 6.90 (dd, J = 5.1, 3.5 Hz, 1H), 4.70 (dd, J = 6.0, 4.7 Hz, 1H), 3.54 (AMX, J_{AX} = 4.7 Hz, J_{MX} = 6.0 Hz, J_{AM} = 15.0 Hz, ν_{AM} = 44.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 162.3, 136.5, 132.8, 128.8, 128.0, 127.1, 126.8, 125.7, 125.2, 66.2, 31.3; MS exact mass calculated for $[C_{14}H_{11}NO_2S + H]^+$ requires m/z = 258.06, found 258.06 (ESI+).

4-(1-Naphthalenylmethyl)-2-phenyloxazol-5(4H)-one (***1d***). Title compound was synthesized from *N*-benzoyl-L-β-(1-naphthyl)alanine (**1d′**, 600 mg, 1.88 mmol) according to General Procedure A above. Yield: 76% (yellow oily solid); TLC R_f = 0.44 (20% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22−8.14 (m, 2H), 7.93−7.89 (m, 2H), 7.86 (dd, J = 8.3, 1.5 Hz, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.61−7.48 (m, 4H), 7.47−7.40 (m, 3H), 4.83 (dd, J = 7.9, 5.1 Hz, 1H), 3.70 (AMX, J_{AX} = 5.1 Hz, J_{MX} = 7.9 Hz, J_{AM} = 14.5 Hz, ν_{AM} = 156.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 161.8, 134.0, 132.8, 132.0, 132.0, 128.9, 128.8, 128.2, 128.1, 128.0, 126.2, 125.9, 125.8, 125.5, 123.9, 66.3, 34.8; MS exact mass calculated for $[C_{20}H_{15}NO_2 + H]^+$ requires m/z = 302.12, found 302.12 (ESI+).

4-((1H-3-Indolyl)methyl)-2-phenyloxazol-5(4H)-one (***1e***). Title compound was synthesized from *N*-benzoyl-L-tryptophan (**1e′**, 1.00 g, 3.24 mmol) according to General Procedure A above. Yield: 66% (off-white solid); TLC R_f = 0.20 (20% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.05−8.00 (m, 2H), 7.89−7.81 (m, 1H), 7.68−7.60 (m, 1H), 7.58−7.51 (m, 2H), 7.45−7.37 (m, 1H), 7.30−7.24 (m, 2H), 7.22 (d, J = 2.5 Hz, 1H), 4.89 (dd, J = 6.3, 4.9 Hz, 1H), 3.60 (AMX, J_{AX} = 4.8 Hz, J_{MX} = 6.2 Hz, J_{AM} = 14.8 Hz, ν_{AM} = 61.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 161.9, 136.1, 132.7, 128.8, 128.0, 127.5, 126.0, 123.5, 122.2, 119.7, 119.3, 111.1, 109.8, 66.7, 27.4; MS exact mass calculated for $[C_{18}H_{14}N_2O_2 + H]^+$ requires m/z = 291.11, found 291.12 (ESI+).

4-(4-(tert-Butoxy)benzyl)-2-phenyloxazol-5(4H)-one (***1f***). Title compound was synthesized from *N*-benzoyl-*O*-*tert*-butyl-L-tyrosine (**1f′**, 600 mg, 1.76 mmol) according to General Procedure A above. Yield: 97% (clear, pale yellow oil); TLC R_f = 0.42 (20% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91−7.85 (m, 2H), 7.55−7.48 (m, 1H), 7.45−7.38 (m, 2H), 7.18−7.10 (m, 2H), 6.88−7.81 (m, 2H), 4.66 (t, J = 5.5 Hz, 1H), 3.25 (AMX, J_{AX} = 4.9 Hz, J_{MX} = 6.1 Hz, J_{AM} = 14.0 Hz, ν_{AM} = 79.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 161.7, 154.6, 132.7, 130.2, 130.0, 128.8, 127.9, 125.9, 124.1, 78.5, 66.7, 36.8, 28.9; MS exact mass calculated for $[C_{20}H_{21}NO_3 + H]^+$ requires m/z = 324.16, found 324.16 (ESI+).

4-(4-Nitrobenzyl)-2-phenyloxazol-5(4H)-one (***1g***). Title compound was synthesized from *N*-benzoyl-L-(4-nitro)phenylalanine (**1g′**, 600 mg, 1.91 mmol) according to General Procedure A above. Yield: 78% (off-white solid); TLC R_f = 0.24 (20% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20−8.08 (m, 2H), 7.96−7.85 (m 2H), 7.62−7.54 (m, 1H), 7.53−7.42 (m, 4H), 4.73 (dd, J = 6.9, 5.0 Hz, 1H), 3.38 (AMX, J_{AX} = 5.0 Hz, J_{MX} = 7.0 Hz, J_{AM} = 14.0 Hz, ν_{AM} = 101.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 162.4, 147.5, 143.1, 133.3, 130.7, 129.0, 128.1, 125.5, 123.8, 66.0, 37.0; MS exact mass calculated for $[C_{16}H_{12}N_2O_4 + H]^+$ requires m/z = 297.09, found 297.09 (ESI+).

4-Benzhydryl-2-phenyloxazol-5(4H)-one (***1h***). Title compound was synthesized from *N*-benzoyl-L-diphenylalanine (**1h′**) according to General Procedure B above. Yield: undetermined (off-white powder); TLC R_f = 0.50 (20% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02−7.96 (m, 2H), 7.75−7.69 (m, 2H), 7.65−7.56 (m, 1H), 7.57−7.47 (m, 2H), 7.49−4.71 (m, 2H), 7.40−7.30 (m, 3H), 7.30−7.22 (m, 2H), 7.25−7.16 (m, 1H), 5.24 (d, J = 3.2 Hz, 1H), 4.88 (d, J = 3.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 161.8, 141.1, 138.3, 132.8, 129.5, 128.8, 128.7, 128.3, 128.0, 127.4, 127.1, 125.9, 69.5, 52.7; MS exact mass calculated for $[C_{22}H_{17}NO_2 + H]^+$ requires m/z = 328.13, found 328.14 (ESI+).

4-Phenethyl-2-phenyloxazol-5(4H)-one (***1i***). Title compound was synthesized from *N*-benzoyl-L-homophenyl-alanine (**1i′**, 800 mg, 2.80 mmol) according to General Procedure A above. Yield: 76% (clear, colorless oil); TLC R_f = 0.44 (20% EtOAc/hexanes, UV); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−7.93 (m, 2H), 7.69−7.54 (m, 1H), 7.54−7.44 (m, 2H), 7.40−7.07 (m, 5H), 4.40 (dd, J = 7.6, 5.8 Hz, 1H), 2.88 (t, J = 7.8 Hz, 2H), 2.47−2.33 (m, 1H), 2.24−2.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 161.9, 140.3, 132.9, 128.9, 128.7, 128.7, 128.0, 126.5, 126.0, 64.6, 33.3, 31.6; MS exact mass calculated for $[C_{17}H_{15}NO_2 + H]^+$ requires m/z = 266.12, found 266.12 (ESI+).

Methyl 2-(5-oxo-2-phenyl-(4H)oxazolyl)acetate (***1j***). Title compound was synthesized from *N*-benzoyl-L-aspartic acid β-methyl ester (**1j′**, 278 mg, 1.11 mmol) according to General Procedure A above. Yield: 63% (clear, colorless oil); TLC R_f = 0.19 (20% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J = 7.5 Hz, 2H), 7.56 (t,

J = 7.4 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 4.61 (t, J = 5.0 Hz, 1H), 3.66 (s, 3H), 3.08 (AMX, J_{AX} = 4.5 Hz, J_{MX} = 5.6 Hz, J_{AM} = 17.3 Hz, ν_{AM} = 47.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 169.8, 163.1, 133.0, 128.9, 128.1, 125.8, 61.8, 52.4, 35.1; MS exact mass calculated for $[C_{12}H_{11}NO_4 + H]^+$ requires m/z = 234.08, found 234.08 (ESI+).

*4-Isobutyl-2-phenyloxazol-5(4H)-one (**1k**).* Title compound was synthesized from *N*-benzoyl-DL-leucine (**1k**′, 1.00g, 4.25 mmol) according to General Procedure B above. Yield: 66% (white solid); TLC R_f = 0.44 (10% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03−7.96 (m, 2H), 7.59−7.52 (m, 1H), 7.50−7.43 (m, 2H), 4.40 (dd, J = 8.9, 5.7 Hz, 1H), 2.14−1.98 (m, 1H), 1.83 (ddd, J = 13.6, 7.8, 5.7 Hz, 1H), 1.67 (ddd, J = 13.7, 9.0, 6.3 Hz, 1H), 1.02 (dd, J = 11.4, 6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 161.5, 132.7, 128.8, 127.9, 126.1, 64.0, 40.9, 25.3, 22.8, 22.2; MS exact mass calculated for $[C_{13}H_{15}NO_2 + H]^+$ requires m/z = 218.12, found 218.12 (ESI+).

*4-Isopropyl-2-phenyloxazol-5(4H)-one (**1l**).* Title compound was synthesized from *N*-benzoyl-DL-valine (**1l**′, 1.00 g, 4.52 mmol) according to General Procedure B above. Yield: 72% (clear, colorless oil); TLC R_f = 0.40 (10% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04−7.98 (m, 2H), 7.61−7.54 (m, 1H), 7.51−7.45 (m, 2H), 4.29 (dd, J = 4.36, 1.1 Hz, 1H), 2.39 (m, 1H), 1.15 (dd, J = 6.8, 0.9 Hz, 3H), 1.02 (dd, J = 6.8, 0.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.9, 161.8, 132.8, 128.9, 128.0, 126.1, 70.9, 31.4, 18.9, 17.7; MS exact mass calculated for $[C_{12}H_{13}NO_2 + H]^+$ requires m/z = 204.10, found 204.11 (ESI+).

*4-Neopentyl-2-phenyloxazol-5(4H)-one (**1m**).* Title compound was synthesized from *N*-benzoyl-L-*tert*-butylalanine (**1m**′, 250 mg, 1.00 mmol) according to General Procedure B above. Yield: 94% (white solid); TLC R_f = 0.65 (20% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03−7.95 (m, 2H), 7.59−7.52 (m, 1H), 7.50−7.42 (m, 2H), 4.39 (dd, J = 9.8, 3.3 Hz, 1H), 1.77 (AMX, J_{AX} = 3.3 Hz, J_{MX} = 9.8 Hz, J_{AM} = 14.1 Hz, ν_{AM} = 144.4 Hz, 2H), 1.10 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 160.9, 132.6, 128.8, 127.9, 126.3, 63.6, 45.9, 31.0, 29.8; MS exact mass calculated for $[C_{14}H_{17}NO_2 + H]^+$ requires m/z = 232.13, found 232.14 (ESI+).

*4-tert-Butyl-2-phenyloxazol-5(4H)-one (**1n**).* Title compound was synthesized from *N*-benzoyl-DL-*tert*-leucine (**1n**′, 1.00 g, 4.25 mmol) according to General Procedure B above. Yield: 88% (white solid); TLC R_f = 0.62 (20% EtOAc/hexanes, UV); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07−7.96 (m, 2H), 7.59−7.52 (m, 1H), 7.50−7.43 (m, 2H), 4.07 (s, 1H), 1.14 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 161.3, 132.7, 128.8, 128.0, 126.1, 74.1, 36.0, 26.3; MS exact mass calculated for $[C_{13}H_{15}NO_2 + H]^+$ requires m/z = 218.12, found 218.12 (ESI+).

General Procedures for the DKR of Oxazolones 1. All vials, flasks, and magnetic stir bars were oven-dried overnight before use in DKR experiments. Peptides **9** (and truncated peptides **10**) and reaction conditions were screened using the small-scale procedure detailed below (0.05 mmol of **1a**). 2,3-Dimethylnaphthalene (3.9 mg, 0.025 mmol) was used as an internal standard. Competition experiments (Scheme 3) were also performed using the small-scale procedure, with triethylamine (20 mol % wrt **1a**) added to the reaction mixture along with peptide **9k** or **9p**. The substrate scope was examined on small scale (0.05 mmol of **1**), as well as on a larger scale (0.50 mmol of **1**). The 0.05 mmol scale reactions were quenched after 22−24 h. Conversion was determined by ^{1}H NMR of the crude reaction mixture and is defined as the ratio of product α-signal integration (α_{pdt}) to the total α-signal integration (α_{sm} + α_{pdt}). The 0.50 mmol scale reactions were allowed to stir longer than 24 h if the conversion of the small-scale counterparts (which were started at the same time) was low at the 24 h mark. Additional MeOH (5 equiv) was used for less reactive, alkyl-substituted substrates (**1k**−**n**). Results were consistent between the two scales in every case. Isolated yields are only reported for the scale-up reactions.

Small (0.05 mmol) Scale Procedure. Peptide **9k** (6.9 mg, 0.01 mmol, 20 mol %) was added to a 4 mL vial, followed by oxazolone **1** (0.05 mmol, 1.0 equiv). The solid mixture was dissolved in PhMe (0.50 mL, 0.10 M solution). The resulting clear colorless solution was allowed to stir at 4 °C (cold room) as MeOH (6.1 μL, 0.15 mmol, 3 equiv) was added to the solution. The PTFE-lined vial cap was replaced and tightened, and the solution was allowed to stir at 4 °C. The reaction was quenched after 22−24 h by concentration in vacuo to remove excess MeOH and solvent. Conversion was determined by ^{1}H NMR as described above. The crude reaction mixture was then purified by filtration through a pipet silica plug (1 × 7 cm, 50% EtOAc/hexanes). The fractions containing both starting material and product were pooled together and concentrated in vacuo to provide a clear, colorless oil. Analytical HPLC analysis was performed to assess the er of both the starting material and product.

Scale-Up (0.50 mmol) Procedure. Peptide **9k** (69.3 mg, 0.10 mmol, 20 mol %) was first added to an oven-dried round-bottom flask equipped with a magnetic stir bar. Oxazolone **1** (0.50 mmol, 1.0 equiv) was added next, and the solid mixture was dissolved in PhMe (5.0 mL, 0.10 M solution). The resulting solution was allowed to stir at 4 °C (cold room) as MeOH (61 μL, 1.5 mmol, 3 equiv) was added to the solution with a syringe. The flask was sealed, and the solution was allowed to stir at 4 °C for 24−70 h depending on the substrate. The reaction was quenched by concentration in vacuo, and conversion was assessed by crude ^{1}H NMR (vide supra). The crude reaction mixture was then loaded onto a silica column in CH_2Cl_2 and purified by flash chromatography using an appropriate EtOAc/hexanes gradient chosen on the basis of TLC. The fractions containing product were pooled and concentrated in vacuo. Adventitious solvent was removed by coevaporation with CH_2Cl_2 before the product was allowed to dry under a vacuum overnight. ^{1}H and ^{13}C NMR confirmed the structure of the methyl ester product. Analytical HPLC was performed to assess the er of both the remaining starting material and product.

Racemic Standard Procedure A. Oxazolone **1** (1 equiv, 0.050 mmol) was added to an oven-dried vial equipped with a magnetic stir bar. The substrate was dissolved in a 0.02 M solution of Et_3N in PhMe (0.50 mL, 0.10 M solution). The resulting solution was allowed to stir at 4 °C (cold room) as MeOH (10.1 μL, 0.25 mmol) was added to the solution. The PTFE-lined vial cap was replaced and tightened, and the solution was allowed to stir at 4 °C for 24 h. The reaction was quenched by concentration in vacuo to remove excess MeOH, Et_3N, and PhMe. The crude reaction mixture was then purified by filtration through a pipet silica plug (1 × 7 cm, 50% EtOAc/hexanes, isocratic). The fractions containing starting material and product were pooled together and concentrated in vacuo. Analytical HPLC analysis was performed to assess the er of both the remaining starting material and product to ensure that both were indeed racemic (vide infra for substrate-specific HPLC methods). Note: In a number of cases, an unidentified side product was present in the HPLC trace, eluting just before the first product peak.[34]

Racemic Standard Procedure B.[35] Racemic *N*-benzoyl amino acid **1**′ (1 equiv) was added to an oven-dried round-bottom flask equipped with a magnetic stir bar. The white solid was dissolved in a 3:1 (v/v) PhMe/MeOH solution (0.15 M wrt **1**′), and the resulting clear, colorless solution was allowed to stir at rt. The flask was sealed with a septum, and a N_2 inlet was added. (Trimethylsilyl)diazomethane ($TMSCHN_2$, 2.0 M in hexanes, 1.1 equiv) was added dropwise to the stirring solution at rt, causing evolution of a gas. Additional $TMSCHN_2$ was added until the pale yellow color persisted. The solution was allowed to stir 20 min at rt before the reaction was quenched by addition of excess silica. The pale yellow solution became clear and colorless. The reaction mixture was filtered to remove silica, and the filtrate was concentrated in vacuo to provide white granular solid. Analytical HPLC analysis was performed to assess the er of the product (vide infra for substrate-specific HPLC methods).

*N-Benzoyl-L-phenylalanine methyl ester (**2a**).* Title compound was synthesized from oxazolone **1a** (126 mg, 0.50 mmol) according to the Scale-Up Procedure above. TLC R_f = 0.22 (20% EtOAc/hexanes, UV). Conversion: 94% (0.050 mmol scale, 24 h); 90% (0.50 mmol scale, 24 h). Yield: 86% isolated (white solid), 97% brsm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.69 (m, 2H), 7.56−7.48 (m, 1H), 7.47−7.38 (m, 2H), 7.35−7.24 (m, 3H), 7.20−7.11 (m, 2H), 6.71 (d, J = 7.6 Hz, 1H), 5.12 (dt, J = 7.7, 5.6 Hz, 1H), 3.78 (s, 3H), 3.29 (ABX, J_{AX} = 5.7 Hz, J_{BX} = 5.6 Hz, J_{AB} = 13.8 Hz, ν_{AB} = 27.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 166.9, 136.0, 134.0, 131.8, 129.4, 128.7,

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128.7, 127.2, 127.1, 53.6, 52.5, 38.0; HRMS exact mass calculated for $[C_{17}H_{17}NO_3 + H]^+$ requires m/z = 284.1287, found 284.1261 (ESI+); HPLC (Chiralpak AD-H column, 10% *i*-PrOH/hexanes eluent, 1.0 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 96:4 er (0.050 mmol scale, minor t_R = 12.6 min, major t_R = 15.4 min); 96:4 er (0.50 mmol scale, minor t_R = 12.5 min, major t_R = 15.4 min).

*N-Benzoyl-L-β-(2-furyl)alanine methyl ester (**2b**).* Title compound was synthesized from oxazolone **1b** (121 mg, 0.50 mmol) according to the Scale-Up Procedure above. TLC R_f = 0.16 (20% EtOAc/hexanes, UV). Conversion: 96% (0.050 mmol scale, 23 h); 99% (0.50 mmol scale, 26 h). Yield: 78% isolated (white solid); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79−7.68 (m, 2H), 7.54−7.48 (m, 1H), 7.46−7.39 (m, 2H), 7.33 (dd, J = 1.9, 0.8 Hz, 1H), 6.79 (d, J = 7.4 Hz, 1H), 6.29 (dd, J = 3.2, 1.9 Hz, 1H), 6.10 (dd, J = 3.1, 0.8 Hz, 1H), 5.05 (dt, J = 7.6, 5.2 Hz, 1H), 3.78 (s, 3H), 3.31 (ABX, J_{AX} = 5.0 Hz, J_{BX} = 4.8 Hz, J_{AB} = 15.3 Hz, ν_{AB} = 17.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 167.0, 150.5, 142.4, 134.1, 131.9, 128.7, 127.2, 110.5, 108.2, 52.8, 52.1, 30.8; HRMS exact mass calculated for $[C_{15}H_{15}NO_4 + H]^+$ requires m/z = 274.1079, found 274.1044 (ESI+); HPLC (Chiralpak AD-H column, 10% *i*-PrOH/hexanes eluent, 1.0 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 96:4 er (0.050 mmol scale, minor t_R = 12.5 min, major t_R = 15.9 min); 96:4 er (0.50 mmol scale, minor t_R = 12.5 min, major t_R = 15.8 min).

*N-Benzoyl-L-β-(2-thienyl)alanine methyl ester (**2c**).* Title compound was synthesized from oxazolone **1c** (129 mg, 0.50 mmol) according to the Scale-Up Procedure above. TLC R_f = 0.17 (20% EtOAc/hexanes, UV). Conversion: 99% (0.050 mmol scale, 22 h); 95% (0.50 mmol scale, 24 h). Yield: 84% isolated (yellow oily solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.73 (m, 2H), 7.55−7.48 (m, 1H), 7.47−7.39 (m, 2H), 7.17 (dd, J = 5.1, 1.2 Hz, 1H), 6.94 (dd, J = 5.2, 3.4 Hz, 1H), 6.80 (dd, J = 3.4, 1.2 Hz, 1H), 6.79 (bs, 1H), 5.09 (dt, J = 7.5, 4.8 Hz, 1H), 3.79 (s, 3H), 3.52 (ABX, J_{AX} = 5.0 Hz, J_{BX} = 4.8 Hz, J_{AB} = 14.9 Hz, ν_{AB} = 16.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 167.0, 137.3, 133.9, 131.9, 128.7, 127.2, 127.2, 127.0, 125.1, 53.5, 52.7, 32.2; HRMS exact mass calculated for $[C_{15}H_{15}NO_3S + H]^+$ requires m/z = 290.0851, found 290.0881 (ESI+); HPLC (Chiralpak AD-H column, 10% *i*-PrOH/hexanes eluent, 1.0 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 96:4 er (0.050 mmol scale, minor t_R = 13.2 min, major t_R = 16.6 min); 97:3 er (0.50 mmol scale, minor t_R = 13.0 min, major t_R = 16.4 min).

*N-Benzoyl-L-β-(1-napthyl)alanine methyl ester (**2d**).* Title compound was synthesized from oxazolone **1d** (151 mg, 0.50 mmol) according to the Scale-Up Procedure above. TLC R_f = 0.14 (20% EtOAc/hexanes, UV). Conversion: 93% (0.050 mmol scale, 23 h); 93% (0.50 mmol scale, 25 h). Yield: 84% isolated (off-white, foamy solid), 90% brsm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.2 Hz, 1H), 7.86 (dd, J = 7.6, 2.1 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.72−7.63 (m, 2H), 7.58−7.21 (m, 7H), 6.93 (d, J = 7.9 H, 1H), 5.24 (q, J = 6.9 Hz, 1H), 3.71 (ABX, J_{AX} = 6.4 Hz, J_{BX} = 6.5 Hz, J_{AB} = 14.8 Hz, ν_{AB} = 13.0 Hz, 2H), 3.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 167.1, 133.9, 133.7, 132.4, 132.2, 131.6, 128.8, 128.4, 128.0, 127.4, 127.0, 126.3, 125.7, 125.2, 123.5, 53.6, 52.2, 35.0; HRMS exact mass calculated for $[C_{21}H_{19}NO_3 + H]^+$ requires m/z = 334.1443, found 334.1473 (ESI+); HPLC (Chiralpak AD-H column, 10% *i*-PrOH/hexanes eluent, 1.0 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 94:6 er (0.050 mmol scale, minor t_R = 14.2 min, major t_R = 18.1 min); 93:7 er (0.50 mmol scale, minor t_R = 14.2 min, major t_R = 18.1 min).

*N-Benzoyl-L-tryptophan methyl ester (**2e**).* Title compound was synthesized from oxazolone **1e** (145 mg, 0.50 mmol) according to the Scale-Up Procedure above. TLC R_f = 0.05 (20% EtOAc/hexanes, UV). Conversion: 94% (0.050 mmol scale, 23 h); 99% (0.50 mmol scale, 26 h). Yield: 93% isolated (off-white, foamy solid); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.71−7.65 (m, 2H), 7.56 (dt, J = 8.0, 0.9 Hz, 1H), 7.50−7.45 (m, 1H), 7.41−7.33 (m, 3H), 7.19 (ddd, J = 8.2, 7.0, 1.1 Hz, 1H), 7.08 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.68 (d, J = 7.9 Hz, 1H), 5.16 (dt, J = 7.7, 5.2 Hz, 1H), 3.72 (s, 3H), 3.46 (ABX, J_{AX} = 5.2 Hz, J_{BX} = 4.7 Hz, J_{AB} = 14.8 Hz, ν_{AB} = 13.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 167.1, 136.3, 134.0, 131.8, 128.7, 127.8, 127.2, 122.9, 122.4, 119.9, 118.8, 111.4, 110.2, 53.6, 52.6, 27.8; HRMS exact mass calculated for $[C_{19}H_{18}N_2O_3 + H]^+$ requires m/z = 323.1396, found 323.1375 (ESI+); HPLC (Chiralpak AD-H column, 10% EtOH/hexanes eluent, 0.70 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 98:2 er (0.050 mmol scale, minor t_R = 49.2 min, major t_R = 61.3 min); 97:3 er (0.50 mmol scale, minor t_R = 50.2 min, major t_R = 61.5 min).

*N-Benzoyl-O-tert-butyl-L-tyrosine methyl ester (**2f**).* Title compound was synthesized from oxazolone **1f** (162 mg, 0.50 mmol) according to the Scale-Up Procedure above. TLC R_f = 0.11 (20% EtOAc/hexanes, UV). Conversion: 69% (0.050 mmol scale, 24 h); 92% (0.50 mmol scale, 45 h). Yield: 78% isolated (white solid), 85% brsm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75−7.63 (m, 2H), 7.56−7.46 (m, 1H), 7.45−7.36 (m, 2H), 7.10−6.99 (m, 2H), 6.97−6.88 (m, 2H), 6.54 (d, J = 7.7 Hz, 1H), 5.05 (dt, J = 7.6, 5.7 Hz, 1H), 3.74 (s, 3H), 3.21 (ABX, J_{AX} = 6.0 Hz, J_{BX} = 5.5 Hz, J_{AB} = 13.9 Hz, ν_{AB} = 23.4 Hz, 2H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 166.9, 134.1, 131.9, 130.7, 129.9, 128.8, 127.1, 124.4, 78.6, 53.7, 52.5, 37.4, 29.0; HRMS exact mass calculated for $[C_{21}H_{25}NO_4 + H]^+$ requires m/z = 356.1862, found 356.1821 (ESI+); HPLC (Chiralpak AD-H column, 10% *i*-PrOH/hexanes eluent, 1.0 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 93:7 er (0.050 mmol scale, minor t_R = 10.1 min, major t_R = 13.2 min); 93:7 er (0.50 mmol scale, minor t_R = 10.2 min, major t_R = 13.5 min).

*N-Benzoyl-L-(4-nitro)phenylalanine methyl ester (**2g**).* Title compound was synthesized from oxazolone **1g** (148 mg, 0.50 mmol) according to the Scale-Up Procedure above. The oxazolone substrate was difficult to dissolve, so the reaction solution was prestirred at RT before addition of MeOH at 4 °C. Addition of MeOH helped to dissolve the reactants. TLC R_f = 0.33 (50% EtOAc/hexanes, UV). Conversion: 88% (0.050 mmol scale, 22 h); 94% (0.50 mmol scale, 30 h). Yield: 88% isolated (off-white, flaky solid); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15−7.99 (m, 2H), 7.74−7.60 (m, 2H), 7.50−7.41 (m, 1H), 7.40−7.32 (m, 2H), 7.30−7.20 (m, 2H), 6.64 (d, J = 7.2 Hz, 1H), 5.05 (dt, J = 7.1, 5.7 Hz, 1H), 3.72 (s, 3H), 3.31 (AMX, J_{AX} = 6.0 Hz, J_{BX} = 5.5 Hz, J_{AM} = 13.8 Hz, ν_{AM} = 68.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 167.0, 147.4, 144.0, 133.6, 132.2, 130.4, 128.9, 127.1, 123.8, 53.5, 52.9, 37.9; HRMS exact mass calculated for $[C_{17}H_{16}N_2O_5 + H]^+$ requires m/z = 329.1137, found 329.1128 (ESI+); HPLC (Chiralpak AD-H column, 10% EtOH/hexanes eluent, 0.70 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 88:12 er (0.050 mmol scale, major t_R = 68.6 min, minor t_R = 81.7 min); 88:12 er (0.50 mmol scale, major t_R = 69.6 min, major t_R = 82.7 min).

*N-Benzoyl-L-β,β-diphenylalanine methyl ester (**2h**).* Title compound was synthesized from oxazolone **1h** (96 mg, 0.30 mmol) according to the Scale-Up Procedure above. The oxazolone substrate was difficult to dissolve, so the reaction solution was prestirred with gentle heating before addition of MeOH at 4 °C. Even so, the solution was largely heterogeneous (cloudy, pale-yellow solution). TLC R_f = 0.16 (20% EtOAc/hexanes, UV). Conversion: 49% (0.050 mmol scale, 24 h); 26% (0.30 mmol scale, 38 h). Yield: 19% isolated (white, foamy solid), 75% brsm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.49 (m, 2H), 7.43−7.36 (m, 1H), 7.33−7.11 (m, 12H), 6.37 (d, J = 8.8 Hz, 1H), 5.55 (t, J = 8.6 Hz, 1H), 4.55 (d, J = 8.4 H, 1H), 3.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 167.3, 140.1, 139.6, 133.9, 131.9, 129.0, 128.7, 128.7, 128.6, 128.3, 127.5, 127.3, 127.1, 127.1, 55.7, 53.7, 52.3; HRMS exact mass calculated for $[C_{23}H_{21}NO_3 + H]^+$ requires m/z = 360.1600, found 360.1570 (ESI+); HPLC (Chiralcel OD-H column, 10% *i*-PrOH/hexanes eluent, 1.00 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 91:9 er (0.050 mmol scale, minor t_R = 9.2 min, major t_R = 18.6 min); 90:10 er (0.30 mmol scale, minor t_R = 9.0 min, major t_R = 17.9 min).

*N-Benzoyl-L-homophenylalanine methyl ester (**2i**).* Title compound was synthesized from oxazolone **1i** (133 mg, 0.50 mmol) according to the Scale-Up Procedure above. The reaction solution was no longer homogeneous after 48 h at 4 °C. The cloudy, white suspension became a clear solution again upon warming to rt. TLC R_f = 0.12 (20% EtOAc/hexanes, UV). Conversion: 40% (0.050 mmol scale, 22 h); 50% (0.50 mmol scale, 48 h). Yield: 47% isolated (white solid), 76% brsm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.68 (m, 2H), 7.55−7.47 (m, 1H), 7.47−7.39 (m, 2H), 7.33−7.24 (m, 2H), 7.24−

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7.17 (m, 3H), 6.71 (d, J = 7.7 Hz, 1H), 4.91 (td, J = 7.4, 5.0 Hz, 1H), 3.77 (s, 3H), 2.75 (m, 1H), 2.35 (m, 1H), 2.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 167.1, 140.8, 134.0, 131.9, 128.7, 128.7, 128.5, 127.2, 126.3, 52.7, 52.6, 34.1, 31.9; HRMS exact mass calculated for $[C_{18}H_{19}NO_3 + H]^+$ requires m/z = 298.1443, found 298.1422 (ESI+); HPLC (Chiralpak AD-H column, 10% i-PrOH/hexanes eluent, 1.00 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 81:19 er (0.050 mmol scale, minor t_R = 11.5 min, major t_R = 14.1 min); 81:19 er (0.50 mmol scale, minor t_R = 11.7 min, major t_R = 14.4 min).

*N-Benzoyl-dimethyl-L-aspartate (**2j**).* Title compound was synthesized from oxazolone **1j** (109 mg, 0.47 mmol) according to the Scale-Up Procedure above. TLC R_f = 0.19 (40% EtOAc/hexanes, UV). Conversion: 94% (0.050 mmol scale, 22 h); 99% (0.47 mmol scale, 25 h). Yield: 79% isolated (white solid); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.77 (m, 2H), 7.54–7.48 (m, 1H), 7.47–7.40 (m, 2H), 7.24 (d, J = 8.0 Hz, 1H), 5.06 (dt, J = 8.3, 4.5 Hz, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.06 (AMX, J_{AX} = 4.2 Hz, J_{BX} = 4.5 Hz, J_{AM} = 17.3 Hz, ν_{AM} = 75.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 171.4, 167.0, 133.7, 132.0, 128.8, 127.3, 53.0, 52.2, 49.0, 36.2; HRMS exact mass calculated for $[C_{13}H_{15}NO_5 + H]^+$ requires m/z = 266.1028, found 266.1022 (ESI+); HPLC (Chiralpak AD-H column, 10% EtOH/hexanes eluent, 0.70 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 90:10 er (0.050 mmol scale, major t_R = 45.4 min, minor t_R = 67.8 min); 90:10 er (0.47 mmol scale, major t_R = 45.4 min, minor t_R = 68.9 min).

*N-Benzoyl-L-leucine methyl ester (**2k**).* Title compound was synthesized from oxazolone **1k** (109 mg, 0.50 mmol) according to the Scale-Up Procedure above. TLC R_f = 0.08 (10% EtOAc/hexanes, UV). Conversion: 57% (0.050 mmol scale, 24 h); 60% (0.50 mmol scale, 48 h). Yield: 58% isolated (white solid), 95% brsm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.74 (m, 2H), 7.50–7.43 (m, 1H), 7.41–7.35 (m, 2H), 6.73 (d, J = 8.4 Hz, 1H), 4.84 (td, J = 8.6, 4.8 Hz, 1H), 3.73 (s, 3H), 1.78–1.60 (m, 3H), 0.95 (dd, J = 8.8, 5.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 167.2, 134.0, 131.7, 128.6, 127.2, 52.4, 51.2, 41.8, 25.1, 22.9, 22.1; HRMS exact mass calculated for $[C_{14}H_{19}NO_3 + H]^+$ requires m/z = 250.1443, found 250.1428 (ESI+); HPLC (Chiralpak AD-H column, 10% i-PrOH/hexanes eluent, 1.00 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 91:9 er (0.050 mmol scale, minor t_R = 7.2 min, major t_R = 9.5 min); 93:7 er (0.50 mmol scale, minor t_R = 7.2 min, major t_R = 9.5 min).

*N-Benzoyl-L-valine methyl ester (**2l**).* Title compound was synthesized from oxazolone **1l** (118 mg, 0.58 mmol) according to the Scale-Up Procedure above. TLC R_f = 0.22 (20% EtOAc/hexanes, UV). Conversion: 20% (0.050 mmol scale, 24 h); 30% (0.58 mmol scale, 48 h). Yield: 27% isolated (white solid), 86% brsm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.76 (m, 2H), 7.55–7.49 (m, 1H), 7.48–7.40 (m, 2H), 6.63 (d, J = 8.4 Hz, 1H), 4.79 (dd, J = 8.7, 4.9 Hz, 1H), 3.77 (s, 3H), 2.34–2.22 (m, 1H), 1.00 (dd, J = 11.8, 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 167.4, 134.3, 131.8, 128.7, 127.1, 57.6, 52.4, 31.8, 19.1, 18.1; HRMS exact mass calculated for $[C_{13}H_{17}NO_3 + H]^+$ requires m/z = 236.1287, found 236.1295 (ESI+); HPLC (Chiralpak AD-H column, 10% i-PrOH/hexanes eluent, 1.00 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 80:20 er (0.050 mmol scale, minor t_R = 7.1 min, major t_R = 9.2 min); 83:17 er (0.58 mmol scale, minor t_R = 7.2 min, major t_R = 9.4 min).

*N-Benzoyl-L-β-tert-butylalanine methyl ester (**2m**).* Title compound was synthesized from oxazolone **1m** (116 mg, 0.50 mmol) according to the Scale-Up Procedure above. TLC R_f = 0.20 (20% EtOAc/hexanes, UV). Conversion: 15% (0.050 mmol scale, 46 h); 30% (0.58 mmol scale, 69 h). Yield: 33% isolated (white solid), 79% brsm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.72 (m, 2H), 7.55–7.47 (m, 1H), 7.46–7.39 (m, 2H), 6.45 (d, J = 8.6 Hz, 1H), 4.88 (td, J = 8.8, 3.5 Hz, 1H), 3.75 (s, 3H), 1.75 (AMX, J_{AX} = 3.8 Hz, J_{BX} = 9.0 Hz, J_{AM} = 14.4 Hz, ν_{AM} = 122.4 Hz, 2H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 167.0, 134.2, 131.9, 128.7, 127.1, 52.5, 50.5, 46.5, 31.0, 29.8; HRMS exact mass calculated for $[C_{15}H_{21}NO_3 + H]^+$ requires m/z = 264.1600, found 264.1572 (ESI+); HPLC (Chiralpak AD-H column, 10% i-PrOH/hexanes eluent, 1.00 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 79:21 er (0.050 mmol scale, minor t_R = 6.6 min, major t_R = 9.8 min); 80:20 er (0.50 mmol scale, minor t_R = 6.7 min, major t_R = 9.9 min).

*N-Benzoyl-L-tert-leucine methyl ester (**2n**).* Title compound was synthesized from oxazolone **1n** (109 mg, 0.50 mmol) according to the Scale-Up Procedure above. TLC R_f = 0.29 (20% EtOAc/hexanes, UV). Conversion: 5% (0.070 mmol scale, 24 h); 9% (0.50 mmol scale, 62 h). Yield: 5% isolated (yellow oil), 92% brsm; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.77 (m, 2H), 7.55–7.50 (m, 1H), 7.48–7.42 (m, 2H), 6.64 (d, J = 9.3 Hz, 1H), 4.71 (d, 9.3 Hz, 1H), 3.76 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 167.5, 134.7, 132.1, 129.0, 127.4, 60.2, 52.3, 35.6, 27.1; HRMS exact mass calculated for $[C_{14}H_{19}NO_3 + H]^+$ requires m/z = 250.1443, found 250.1442 (ESI+); HPLC (Chiralpak AD-H column, 10% i-PrOH/hexanes eluent, 1.00 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 72:28 er (0.070 mmol scale, minor t_R = 5.9 min, major t_R = 7.9 min); 71:29 er (0.50 mmol scale, minor t_R = 5.8 min, major t_R = 7.7 min).

Assignment of Absolute Stereochemistry of 1a. *N-Benzoyl-L-phenylalanine methyl ester.* N-Benzoyl-L-phenylalanine (500 mg, 1.86 mmol) was added to an oven-dried round-bottom flask equipped with a magnetic stir bar. The white solid was dissolved in a 3:1 (v/v) PhMe/MeOH solution (12.4 mL, 0.15 M wrt Bz-L-Phe-OH), and the resulting clear, colorless solution was allowed to stir at ambient temperature. The flask was sealed with a septum, and a N_2 inlet was added. (Trimethylsilyl)diazomethane ($TMSCHN_2$, 1.02 mL, 2.05 mmol) was added dropwise to the stirring solution at rt, causing evolution of a gas. Additional $TMSCHN_2$ was added until the pale yellow color persisted. The solution was allowed to stir 20 min at rt before the reaction was quenched by addition of excess silica. The pale yellow solution became clear and colorless. The reaction mixture was filtered to remove silica, and the filtrate was concentrated in vacuo to provide white granular solid (488 mg, 93% yield). The product was shown to be spectroscopically consistent with **2a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.71 (m, 2H), 7.55–7.48 (m, 1H), 7.46–7.40 (m, 2H), 7.34–7.24 (m, 3H), 7.19–7.12 (m, 2H), 6.61 (d, J = 7.8 Hz, 1H), 5.11 (dt, J = 7.5, 5.6 Hz, 1H), 3.78 (s, 3H), 3.28 (ABX, J_{AX} = 5.8 Hz, J_{BX} = 5.5 Hz, J_{AB} = 13.9 Hz, ν_{AB} = 32.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 166.9, 136.0, 134.0, 131.9, 129.5, 128.7, 128.7, 127.3, 127.1, 53.7, 52.5, 38.0; HRMS exact mass calculated for $[C_{17}H_{17}NO_3 + H]^+$ requires m/z = 284.1287, found 284.1273 (ESI+); HPLC (Chiralpak AD-H column, 10% i-PrOH/hexanes eluent, 1.0 mL min^{-1} flow, 20 °C uniform column temperature, 230 nm) 100:0 er (t_R = 15.6 min); $[\alpha]_D^{20}$ = +90.9 (c = 1.0, $CHCl_3$); literature $[\alpha]_D^{24}$ = +98.1 (c = 1.0, $CHCl_3$).[36]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

HRMS data for peptides **9a–p** and **10a–f**, ^{1}H and ^{13}C NMR spectra of compounds **9k** and **2a–n**, HPLC traces of **2a–n**, and high-field (2D-)NMR characterization of **9k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For relevant reviews, see: (a) Faber, K. *Chem.—Eur. J.* **2001**, *7*, 5004−5010. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5−26. (c) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475−1490. (d) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 659−676. (e) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563−1601.

(2) Referred to simply as oxazolones from here forward. Also known as azlactones.

(3) de Jersey, J.; Zerner, B. *Biochemistry* **1969**, *8*, 1967−1974.

(4) For discussions on oxazolone racemization, see: (a) Goodman, M.; Levine, L. *J. Am. Chem. Soc.* **1964**, *86*, 2918−2922. (b) Slebioda, M.; St-Amand, M. A.; Chen, F. M. F.; Benoiton, N. L. *Can. J. Chem.* **1988**, *66*, 2540−2544. (c) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827−10852.

(5) For a relevant review, see: Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432−1440 and references therein.

(6) (a) Seebach, D.; Jaeschke, G.; Gottwald, K.; Matsuda, K.; Formisano, R.; Chaplin, D. A.; Breuning, M.; Bringmann, G. *Tetrahedron* **1997**, *53*, 7539−7556. (b) Gottwald, K.; Seebach, D. *Tetrahedron* **1999**, *55*, 723−738.

(7) Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154−3155.

(8) (a) Yang, X.; Lu, G.; Birman, V. B. *Org. Lett.* **2010**, *12*, 892−895. (b) Xie, L.; Hua, W.; Chan, A. C. S.; Leung, Y.-C. *Tetrahedron: Asymmetry* **1999**, *10*, 4715−4728.

(9) (a) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 807−811. (b) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun.* **2005**, 1898−1900.

(10) (a) Hang, J.; Li, H.; Deng, L. *Org. Lett.* **2002**, *4*, 3321−3324. (b) Peschiulli, A.; Quigley, C.; Tallon, S.; Gun'ko, Y. K.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 6409−6412.

(11) (a) Oh, J. S.; Lee, J. W.; Ryu, T. H.; Lee, J. H.; Song, C. E. *Org. Biomol. Chem.* **2012**, *10*, 1052−1055. (b) Lee, J. W.; Ryu, T. H.; Oh, J. S.; Bae, H. Y.; Jang, H. B.; Song, C. E. *Chem. Commun.* **2009**, 7224−7226.

(12) For examples, see: (a) Brown, S. A.; Parker, M.-C.; Turner, N. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1687−1690. (b) Turner, N. J.; Winterman, R.; McCague, R.; Parratt, J. S.; Taylor, S. J. C. *Tetrahedron Lett.* **1995**, *36*, 1113−1116. (c) Podea, P. V.; Toşa, M. I.; Paizs, C.; Irimie, F. D. *Tetrahedron: Asymmetry* **2008**, *19*, 500−511. (d) Crich, J. Z.; Brieva, R.; Marquart, P.; Gu, R.-L.; Flemming, S.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 3252−3258. (e) Gu, R.-L.; Lee, I.-S.; Sih, C. J. *Tetrahedron Lett.* **1992**, *33*, 1953−1956. (f) Daffe, V.; Fastrez, J. *J. Am. Chem. Soc.* **1980**, *102*, 3601−3605. (g) For the crystal structure of *Candida antarctica* Lipase B (**8**), see: Uppenberg, J.; Hansen, M. T.; Patkar, S.; Jones, T. A. *Structure* **1994**, *2*, 293−308.

(13) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601−610.

(14) (a) Haque, T. S.; Little, J. C.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 6975−6985. (b) Wilmot, C. M.; Thornton, J. M. *J. Mol. Biol.* **1988**, *203*, 221−232.

(15) For examples, see: (a) Barrett, K. T.; Miller, S. J. *J. Am. Chem. Soc.* **2013**, *135*, 2963−2966. (b) Cowen, B. J.; Saunders, L. B.; Miller, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 6105−6107. (c) Fowler, B. S.; Mikochik, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **2009**, *132*, 2870−2871. (d) Peris, G.; Jakobsche, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 8710−8711.

(16) For examples, see: (a) Kastl, R.; Wennemers, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7228−7232. (b) Müller, C. E.; Hrinda, R.; Wende, R. C.; Schreiner, P. R. *Chem.—Eur. J.* **2011**, *17*, 6309−6314. For relevant reviews, see: (c) Wennemers, H. *Chem. Commun.* **2011**, *47*, 12036−12041. (d) Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759−5812. (e) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481−2495.

(17) For an example of a Dmaa-containing peptide, see: Gustafson, J.; Lim, D.; Miller, S. J. *Science* **2010**, *328*, 1251−1255. See also ref 15a.

(18) Gilli, P.; Pretto, L.; Bertolasi, V.; Gilli, G. *Acc. Chem. Res.* **2009**, *42*, 33−44.

(19) Other chiral, monosubstituted residues were substituted at the *i* + 2 position in other scaffolds, and none were as successful as Phe.

(20) ^{1}H NMR spectra of peptides **9b**, **9c**, and **9f** were acquired on the same 500 MHz spectrometer at ambient temperature. Samples were freshly prepared, each with the same concentration (0.02 M in $CDCl_3$).

(21) It was later observed that tosylated **9n** had epimerized, which may partially account for its low selectivity.

(22) The absolute configuration of methyl esters **2** was assigned by analogy to Bz-L-Phe-OMe (see the Experimental Section for details).

(23) For a crystal structure of a *β*-hairpin peptide, see: Blank, J. T.; Miller, S. J. *Biopolymers* **2006**, *84*, 38−47.

(24) (a) Oh, S. H.; Rho, H. S.; Lee, J. W.; Lee, J. E.; Youk, S. H.; Chin, J.; Song, C. E. *Angew. Chem.* **2008**, *120*, 7990−7993. (b) Li, H. M.; Liu, X. F.; Wu, F. H.; Tang, L. A.; Deng, L. *Proc. Nat. Acad. Sci. U. S. A.* **2010**, *107*, 20625−20629.

(25) For a discussion on the mechanism of ester hydrolysis, see: Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley: New York, 2007; Chapter 16.

(26) For discussions on the stabilizing effects of oxyanion holes, see: (a) Pihko, P. M., Ed.; *Hydrogen Bonding in Organic Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2009; pp 43−72. (b) Etzenbach-Effers, K.; Berkessel, A. *Top. Curr. Chem.* **2010**, *291*, 1−27. (c) Kamerlin, S. C. L.; Chu, Z. T.; Warshel, A. *J. Org. Chem.* **2010**, *75*, 6391−6401. (d) Simón, L.; Goodman, J. M. *J. Org. Chem.* **2010**, *75*, 1831−1840.

(27) For a binding model in a similar system, see: Garand, E.; Kamrath, M. Z.; Jordan, P. A.; Wolk, A. B.; McCoy, A. B.; Miller, S. J.; Johnson, M. A. *Science* **2012**, *335*, 694−698. See also refs 15a and 17.

(28) Knowles, R. R.; Jacobsen, E. N. *Proc. Nat. Acad. Sci. U. S. A.* **2010**, *107*, 20678−20685.

(29) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557−6602.

(30) Zhang, L.-h.; Kauffman, G. S.; Pesti, J. A.; Yin, J. *J. Org. Chem.* **1997**, *62*, 6918−6920. See also ref 17.

(31) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: Boston, 2005; pp 398−399 and references therein.

(32) Goodman, M.; Glaser, C. B. *J. Org. Chem.* **1970**, *35*, 1954−1962.

(33) (a) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638−12639. (b) Frébault, F.; Luparia, M.; Oliveira, M. T.; Goddard, R.; Maulide, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 5672−5676.

(34) The unidentified side-product may be a cyclodimer that has been observed when oxazolones are treated with tertiary amine bases. See: Kobayashi, K.; Bryant, L. L.; Tsukamoto, Y.; Saegusa, T. *Macromolecules* **1986**, *19*, 1547−1551.

(35) Kühnel, E.; Laffan, D. D. P.; Lloyd-Jones, G. C.; del Campo, T. M.; Shepperson, I. R.; Slaughter, J. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7075−7078.

(36) Ghosh, S. C.; Ngiam, J. S. Y.; Seayad, A. M.; Tuan, D. T.; Chai, C. L. L.; Chin, A. *J. Org. Chem.* **2012**, *77*, 8007−8015.