Note

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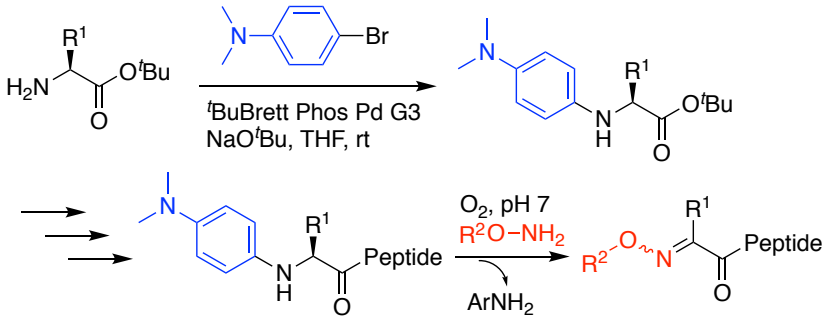
N-Arylation of Amino Acid Esters to Expand Side Chain Diversity in Ketoxime Peptide Ligations

Hailey A. Young, Quibria A. E. Guthrie, and Caroline Proulx*

Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204, USA.



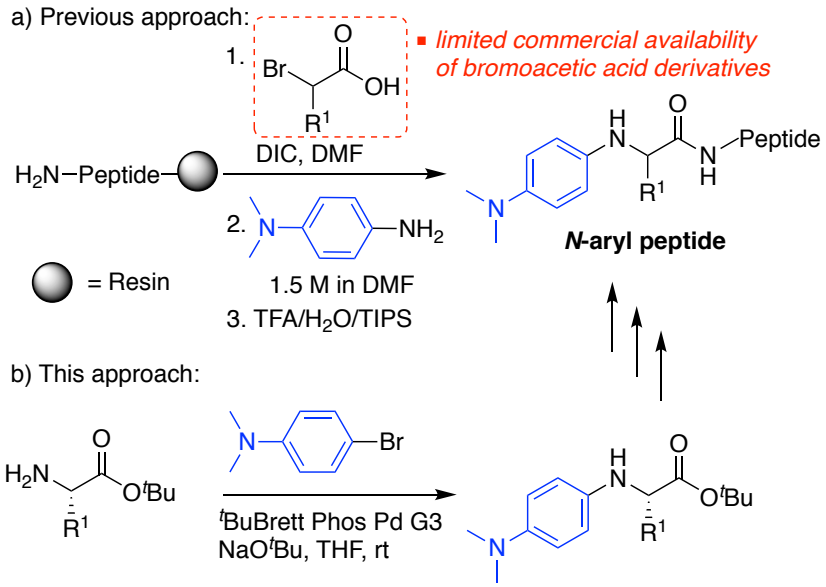
ABSTRACT

Palladium-catalyzed *N*-arylations of amino acid *tert*-butyl esters using 4-bromo-*N*,*N*-dimethylaniline as a coupling partner are reported. The resulting *N*-aryl amino acid esters are suitable building blocks for the synthesis of electron-rich *N*-aryl peptides, which undergo oxidative couplings to aminooxy groups to afford ketoxime peptides under mild conditions. *N*-aryl amino acid *tert*-butyl esters possessing unnatural side chains were also accessed *via* glycine Schiff base alkylation, further increasing the scope of Cα-substitution in ketoxime peptides.

Methods that allow the chemoselective functionalization of common amino acid building blocks streamline the synthesis and structure-activity relationship (SAR) studies of bioactive compounds, and enable site-specific bioconjugation reactions of functionally-dense biomolecules.[1] For example, *N*-arylation of amino acids has been used as a key step to furnish protein kinase modulators,[2,3,4] and conditions for amino acid side-chain

arylation (*e.g.* of Cys, Lys, Tyr, Trp residues) have been developed for macrocyclization and labeling of peptide and protein substrates.[5] Conversely, *N*-aryl glycine derivatives have emerged as valuable precursors to create libraries of unnatural amino acids *via* site-selective αC–H backbone functionalization reactions, presumably proceeding through an α-imino amide intermediate.[6] Recently, *N*-phenylglycinyl peptides were found to undergo oxidative couplings with alkoxyamines to afford oxime ligation products *via* formation of similar aniline Schiff base intermediates[7] under mild aqueous conditions.[8] Beyond glycine derivatives, this method has allowed the chemoselective oxidation of Cα-substituted *N*-aryl peptides into reactive α-ketimino amide intermediates,[9] allowing expansion of side chain diversity at the site of oxime ligation.

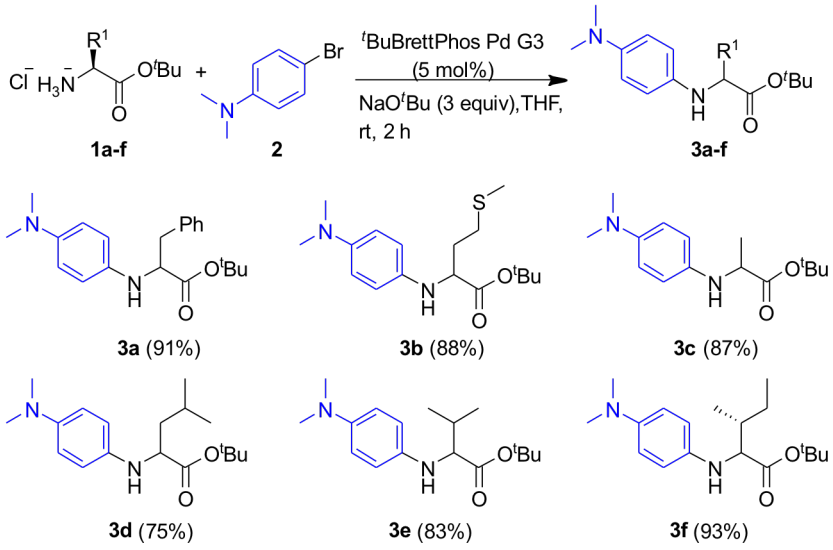
To proceed under oxygen atmosphere and at neutral pH, ketoxime ligations using *N*-aryl peptide substrates require very electron rich aryl rings.[9] Specifically, while analogs with a dimethylamino group (σ = –0.83)[10] at the *para* position of the aryl ring readily undergo oxidation, similar compounds with a methoxy substituent instead (σ = –0.27)[10] do not afford ketoxime peptides.[9] Previously, the required *N*-aryl peptide substrates were prepared using a two-step submonomer peptoid synthesis procedures,[11] where racemic α-substituted bromoacetic acid derivatives were coupled to resin-bound peptides, followed by an S_N2 displacement using 4-dimethylamino aniline as the nucleophile (Scheme 1a). However, extensive exploration of functionalized ketoxime peptides has been hampered by the limited commercial availability of bromoacetic acid derivatives. Here, we expand the scope of side chain diversity in ketoxime peptides *via* access to *N*-(4-Me_2N-Ph) amino acid *tert*-butyl ester building blocks using an *N*-arylation of more widely accessible amino acid esters (Scheme 1b).



Scheme 1. Synthesis of *N*-aryl peptides *via* a) submonomer peptoid synthesis procedure (previous method) and b) *N*-arylation of amino acid *tert*-butyl esters (this approach).

N-arylation of amino acids and amino acid esters has previously been accomplished using both copper-catalyzed[2,3,4,12] and palladium-catalyzed[13] cross-coupling reaction procedures. In particular, Buchwald *et al.* recently reported mild conditions for the epimerization-free *N*-arylation of amino acid esters with aryl triflate as coupling partners, using palladacycle precatalysts and cesium carbonate as base.[13e] However, the use of electron-rich 4-bromo-*N*,*N*-dimethylaniline as a coupling partner has not been reported under these conditions, and would be highly relevant in the context of bioconjugation. Thus, our initial evaluations employed *t*-BuBrettPhos Pd G3 as the precatalyst in 2-Me THF with Cs_2CO_3 as base, closely mimicking the previously optimized procedure with aryl triflates.[13e] While we were initially successful using HCl · L-Phe-O*t*Bu as a test substrate, the use of cesium carbonate caused reproducibility issues in our hands, which were ultimately relieved by changing the base to sodium *tert*-butoxide.[14] NaO*t*Bu was previously shown to lead to decreased functional group tolerance[15] and increased epimerization using amino acid esters as substrates;[13e] however, our

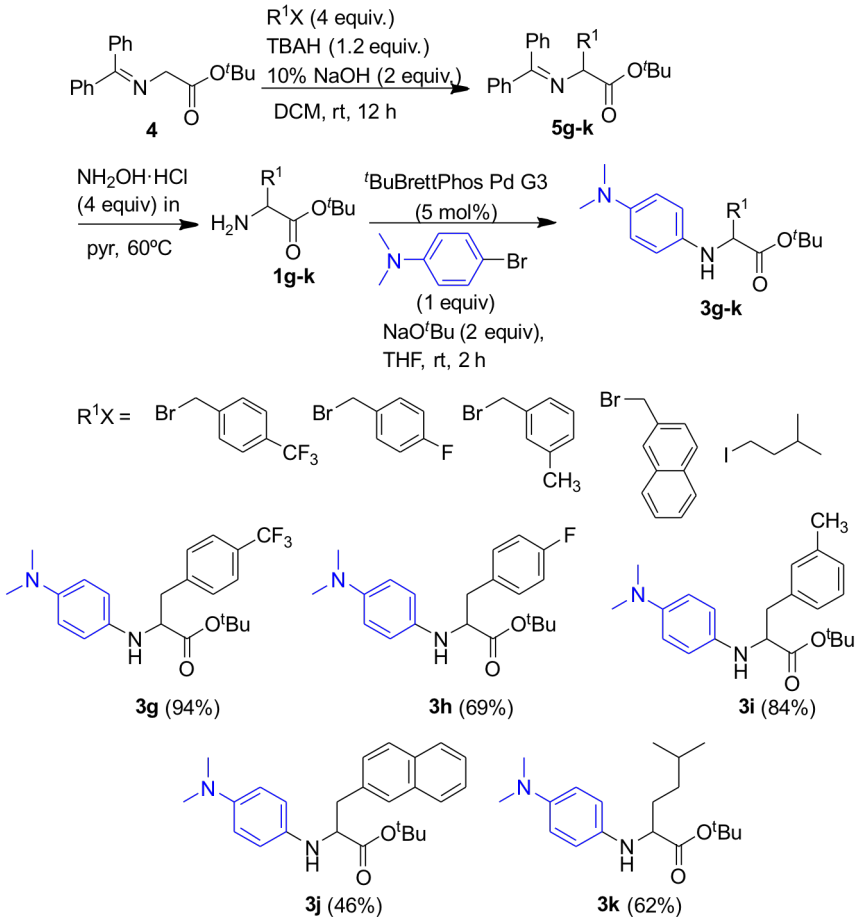
downstream application in ketoxime ligations eliminated the need to isolate enantiopure material. Gratifyingly, treating amino acid *tert*-butyl esters **1a-f** with NaO*t*Bu (3 equiv), *t*-BuBrettPhos Pd G3 (5 mol%), and 4-bromo-*N*,*N*-dimethylaniline (1 equiv) at room temperature afforded *N*-aryl amino acid *tert*-butyl esters **3a-f**, possessing a variety of hydrophobic side-chains, in 75-93% yields after 2 hours (Scheme 2). Importantly, these analogs can be purified by column chromatography,[16] and do not undergo oxidation to



Scheme 2. Pd-catalyzed *N*-arylation of amino acid *tert*-butyl esters using 4-bromo-*N*,*N*-dimethylaniline as the aryl halide.

the α-ketimino amide until exposed to phosphate buffer at neutral pH.[9] In contrast, *N*-arylation of *glycine tert*-butyl ester with 4-bromo-*N*,*N*-dimethylaniline provided variable results, which may be due to the ease of oxidation of the resulting *N*-aryl glycine *tert*-butyl ester product in organic solvent[9] and exacerbated by the palladium catalyst. It should also be mentioned that despite extensive optimization attempts, *N*-arylations of amino acid methyl esters proved unsuccessful, likely due to the use of NaO*t*Bu as the base. To expand our scope, analogs **3g-k** were pursued to include unnatural side chain diversity (Scheme 3). The required amino ester substrates **1g-k** were accessed in racemic form

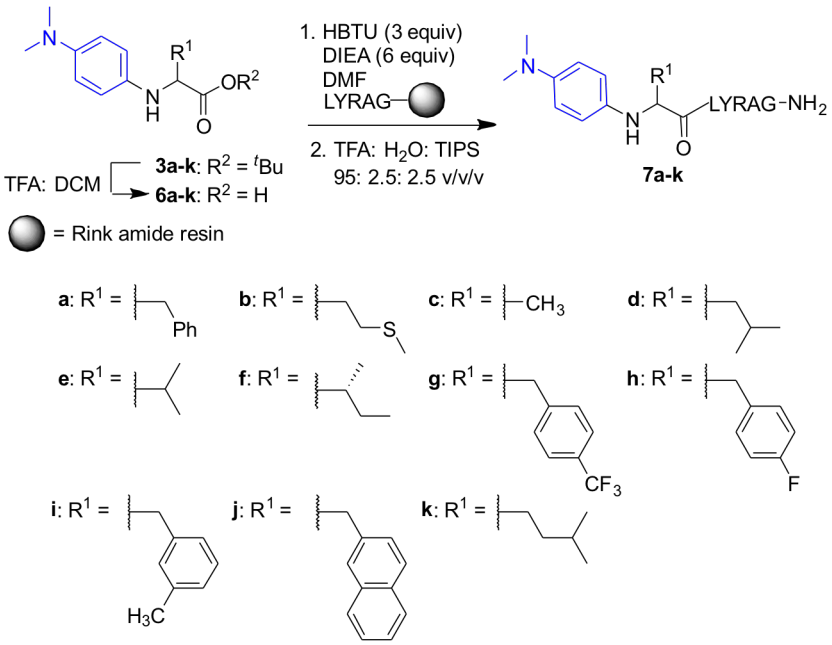
from known glycine Schiff base alkylation procedures,[17] using benzyl bromide derivatives and 1-iodo-3-methyl butane as the electrophiles. Orthogonal deprotection of the benzophenone imine was next accomplished using hydroxylamine hydrochloride in pyridine.[18] Using two equivalents of base instead of three in the *N*-arylation procedure, the desired *N*-aryl amino acid esters **3g-k** products were obtained in 46 to 94% yields.



Scheme 3. Synthesis and *N*-arylation of unnatural amino acid *tert*-butyl esters **1g-k**.

We next sought to optimize conditions for the activation and coupling of the *N*-aryl amino acids onto a resin-bound peptide, using LYRAG as a representative example. Initially, protection of the secondary amine with a *tert*-butoxycarbonyl (Boc) or fluorenylmethyloxycarbonyl (Fmoc) group was thought to be required. However,

difficulties in performing these protection reactions prompted us to investigate the coupling of these substrates without protecting the amino group, with the hope that the



Scheme 4. Synthesis of *N*-aryl peptides *via* the activation of protecting-group free *N*-aryl amino acids.

poor nucleophilicity of the *N*-aryl amino acids[19] would prevent unwanted oligomerization upon activation of the carboxylic acid with HBTU/DIEA (Scheme 4). Conveniently, this was found to be the case, with most analogs providing the desired *N*-aryl peptides as the major product with little to no byproduct observed by LCMS analysis (Table 1). Cleavage of the *N*-aryl peptides from the solid support and purification by reverse-phase HPLC afforded **7a-k** in 10-44% isolated yield (Table 1).

Table 1. Characterization data for *N*-aryl peptides **7a-k**.

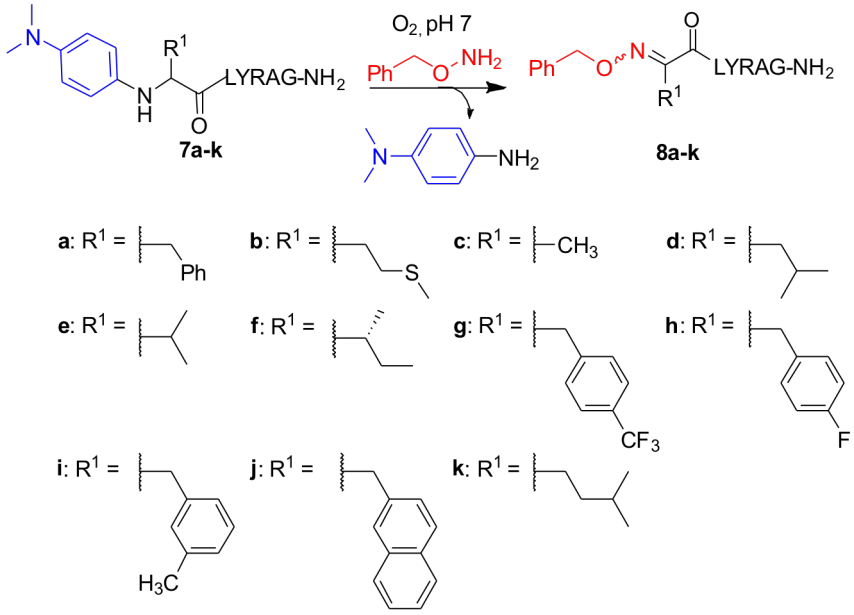
entry	peptide	crude purity (%)[a]	yield (%)[b]
1	**7a**	97	21
2	**7b**	79	10
3	**7c**	77	23
4	**7d**	85	18
5	**7e**	92	35
6	**7f**	74	18

7	**7g**	88	25
8	**7h**	88	28
9	**7i**	92	38
10	**7j**	94	44
11	**7k**	84	26

[a]The purity at 214 nm wavelength is reported in all cases. [b]Yields after purification by RP-HPLC are based on initial resin loading.

With *N*-aryl peptides **7a-k** in hand, we next assessed their ability to undergo ketoxime ligation reactions in phosphate buffer (pH 7) under an O_2 atmosphere, using *O*-benzylhydroxylamine hydrochloride as a model α-nucleophile (Scheme 5, Table 2). Most analogs afforded the desired *E/Z* ketoxime peptides as the major products after 24 h, albeit some reacted more slowly. The majority of ketoxime peptides in our current study were observed as ~1:1 mixtures of *E* and *Z* isomers, with the exception of those obtained from oxidative couplings to *N*-aryl-Met-LYRAG **7b** and *N*-aryl-Ala-LYRAG **7c** (Table 2, entries 2-3)**.** While situated relatively far from the α-carbon, electron-withdrawing groups at the *para* position of the benzyl side chain in *N*-aryl phenylalanine analogs **7g-h** appear to slow down oxidation (Table 2, entries 7 and 8). Conversely, in the case of analog **7j**, which possesses a bulky 2-naphthyl substituent, steric hindrance is likely responsible for the observed decrease in reactivity (Table 2, entry 10). Moreover, in agreement with our previous findings,[9] β-branched substitution in amino acids (*i.e.* Val and Ile) was found to be detrimental, giving ketoximes **8e-f** as minor products with appearance of other side products (Table 2, entries 5-6). Methionine side chain oxidation was not detected in analog **7b** under these mild conditions (Table 2, entry 2). Overall, in addition to the mild procedure, fewer limitations are encountered using this approach compared to methods starting from less reactive α-keto amide substrates. For example, while we note slower reactivity with *N*-aryl amino acids possessing electron-poor benzyl side-chains, the

desired ketoxime peptides are produced cleanly nonetheless after 24 to 72 h when starting from *N*-aryl peptide substrates. As a comparison, other methods have failed to produce similar ketoximes in high yields.[20]



Scheme 5. Ketoxime ligation reactions between *N*-aryl peptides **7a-k** and *O*-benzylhydroxylamine hydrochloride.

Table 2. Characterization data for ketoxime peptides **8a-k**.

entry	*N*-aryl peptide	% ketoxime[a]
1	**7a**	90
2	**7b**	82
3	**7c**	98
4	**7d**	99
5	**7e**	38[b]
6	**7f**	24[b]
7	**7g**	36(75)[c]
8	**7h**	65(90)[c]
9	**7i**	85
10	**7j**	40(89)[d]
11	**7k**	85

[a]Unless noted otherwise, % ketoxime is at t = 24 h and ketoxime conversions were calculated using areas obtained from the two peaks corresponding to the *E* and *Z* isomers on LCMS traces at 214 nm. [b]% ketoxime at t = 24 h showed 50% oxidation, where ~20% of an α-keto

amide byproduct was detected. [c] % ketoxime after 48 hours. [d]% ketoxime after 72 hours.

In summary, a Pd-catalyzed *N*-arylation reaction using 4-bromo-*N*,*N*-dimethylaniline as the aryl halide and amino acid *tert*-butyl ester substrates is reported in high yield, expanding the scope of electron-rich *N*-(*p*-Me_2N-Ph)-peptide substrates available for ketoxime peptide ligation reactions. The efficiency of the *N*-arylation reaction procedure described here, combined with the simplicity of existing glycine Schiff base alkylation procedures and the breadth of commercially available electrophiles, will contribute to expand side chain diversity even further in ketoxime peptide ligations.

Experimental Section

General. All glycine Schiff base alkylations and deprotections were performed in round-bottom flasks. All *N*-arylation reactions were performed in oven-dried microwave vials sealed with microwave caps and stirred using teflon-coated magnetic stir bars. *Tert*-butyl deprotections were performed in 20-mL scintillation vials. Tetrahydrofuran (THF) was dried by passage over a column of activated alumina (JC Meyers Solvent System). Thin layer chromatography (TLC) was performed using Silicycle silica gel 60 F-254 precoated plates (0.25 mm) that were visualized by exposure to ultraviolet (UV) light and/ or submersion in aqueous potassium permanganate or ninhydrin solutions. Samples were purified using a Biotage® Isolera One, employing polypropylene cartridges preloaded with silica gel (25 micron) and were eluted with UV detection (254, 280 nm). Nuclear magnetic resonance (NMR) spectra (^{1}H, ^{13}C) were recorded on a 600 and 700 MHz Bruker spectrometer at 24 ^{o}C. Chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26 ppm or

CD_3OD, δ 3.31). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant in Hertz, and integration. Chemical shits for ^{13}C NMR spectra are recorded in parts per million (ppm, δ scale) and are referenced to the central peak of deuterochloroform (δ 77.16 ppm) or methanol (δ 49.00 ppm). All spectra were obtained with complete proton decoupling. Infrared (IR) spectra were collected on a Thermo Scientific Nicolet iS5 FTIR instrument using attenuated total reflectance (ATR) mode and signals are reported in reciprocal centimeters (cm^{-1}). Only selected IR frequencies are reported. Melting points were obtained on a Mettler Toledo MP50 One Click Melting Point System. Optical rotation data was obtained using a Jasco P-2000 polarimeter equipped with a sodium (589 nm, D) lamp. The corresponding data are presented as follows: specific rotation ($[\alpha]_D^T$), concentration (1 g/ 100 mL), and solvent.

Polystyrene Rink Amide resin (0.61 mmol/ g) was purchased from Protein Technology, Inc™, and the manufacturer's reported loading of the resin was used in the calculation of the yields. Solid phase peptide synthesis (SPPS) was performed using an automated Biotage Syro Wave™ peptide synthesizer in 10 mL parallel reactors with PTFE frits. Incorporation of the *N*-aryl amino acids were performed manually in disposable filter columns with 20 μM PE frit filters and caps purchased from Applied Separations (catalog # 2413 for 3-mL filter columns) with gentle agitation on a Thermo Fisher vortex mixer equipped with a microplate tray. Solution draining and washing of the resin was done by connecting the filter columns to a water aspirator vacuum *via* a waste trap. Analytical LC-MS analyses were performed using an Agilent Technologies 1260 Infinity II series LCMS Single Quad instrument with ESI ion-source and positive mode ionization, equipped with

either a 5 μM, 150 x 4.6 mm C18 Vydac column purchased from Mac-Mod Analytical, Inc. (catalog # 218TP5415) or a 5 μM, 150 x 4.6 mm C18 Luna column purchased from Phenomenex (catalog # 00F-4252-E0). A flow rate of 0.5 mL/ min. and 5-95% or 20-80% gradient of CH_3CN [0.1% trifluoroacetic acid (TFA)] in water (0.1% TFA) over 12 minutes (total run time = 22 minutes) were used for all LC-MS analyses. Peptides were purified on a preparative HPLC (Agilent 218 purification system) using a preparative column (10-20 μM, 250 mm x 22 mm, C18 Vydac column, catalog # 218TP101522 or 10 μM, 250 mm x 21.2 mm, C18 Luna column, catalog # 00G-4253-P0-AX) at a flow rate of 10 mL/ min. with gradients of CH_3CN (0.1% TFA) in water (0.1% TFA) over 30 minutes (total run time = 60 minutes).

General Procedure for the *N*-arylation of Amino Acid *tert*-Butyl Esters 1a-f with 4-Bromo-*N,N*-dimethylaniline

The amino acid *t*-butyl ester hydrochloride (1.0 mmol, 1.0 equiv), 4-bromo-*N,N*-dimethylaniline (1.0 mmol, 1.0 equiv), *t*-Bu BrettPhos Pd G3 (0.05 mmol, 0.05 equiv), and sodium *t*-butoxide (3.0 mmol, 3.0 equiv) were added to an oven-dried 5-mL microwave vial. The vial was capped and flushed with argon. Dry tetrahydrofuran (2.0 mL) was added to the vial, and the reaction mixture was stirred at room temperature for two hours. The reaction mixture was filtered through a small plug of celite and rinsed with dichloromethane (2 x 10 mL), evaporated to dryness on a rotary evaporator, and purified by automated flash-column chromatography.

4-(*p*-dimethylamino-phenyl) phenylalanine *tert*-butyl ester (3a). This was synthesized according to the general procedure described above, using HCl · L-Phe-O*t*Bu (100.0 mg, 0.39 mmol). The product was purified by silica gel column chromatography using 5-40%

ethyl acetate in hexanes to afford a red-brown solid (120.7 mg, 91% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.31 - 7.28 (m, 2H), 7.25 - 7.23 (m, 3H), 6.72 (s, 2H), 6.62 (s, 2H), 4.16 (s (br), 1H), 3.84 (s (br), 1H), 3.11 - 3.06 (m, 2H), 2.83 (s, 6H), 1.34 (s, 9H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 172.8, 144.5, 139.0, 137.0, 129.6, 128.3, 126.8, 115.7, 115.5, 81.5, 59.6, 42.2, 39.0, 28.0. **IR** (neat) 3407, 2976, 2928, 2791, 1710, 1519, 1475, 1255, 1146. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{29}N_2O_2$ 341.2224; Found 341.2217. **$[\alpha]_D^{23}$** + 0.081 (*c* 1.0, $CHCl_3$). **R_f** = 0.18 (20% ethyl acetate in hexanes). **MP** = 75.3 – 77.4 ºC.

4-(*p*-dimethylamino-phenyl)methionine *tert*-butyl ester (3b). This was synthesized according to the general procedure described above, using HCl · L-Met-O*t*Bu (100.0 mg, 0.41 mmol). The product was purified by silica gel column chromatography using 5-40% ethyl acetate in hexanes to afford a dark yellow solid (117.5 mg, 88% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.70 (d, *J* = 8.4 Hz, 2H), 6.63 (d, *J* = 8.4 Hz, 2H), 4.00 (s (br), 1H), 3.82 (s (br), 1H), 2.81 (s, 6H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.10 (s, 3H), 2.08 – 2.04 (m, 1H), 1.98 – 1.92 (m, 1H), 1.42 (s, 9H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 173.4, 144.7, 139.2, 115.6, 115.5, 81.5, 57.7, 42.1, 32.8, 30.4, 28.1, 15.5. **IR** (neat) 3350, 2973, 2779, 1727, 1520, 1443, 1327, 1254, 1145, 1116. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{29}N_2O_2S$ 325.1944; Found 325.1938. **$[\alpha]_D^{23}$** –0.906 (*c* 1.0, $CHCl_3$). **R_f** = 0.21 (20% ethyl acetate in hexanes). **MP** = 76.5 – 78.1 ºC.

4-(*p*-dimethylamino-phenyl)alanine *tert*-butyl ester (3c). This was synthesized according to the general procedure described above, using HCl · L-Ala-O*t*Bu (100.0 mg, 0.55 mmol). The product was purified by silica gel column chromatography using 10-60% ethyl acetate in hexanes to afford a yellow-brown solid (126.4 mg, 87% yield). **^{1}H NMR**

(600 MHz, $CDCl_3$): δ 6.71 (s (br), 2H), 6.61 (s (br), 2H), 3.94 (s (br), 1H), 3.78 (s (br), 1H), 2.82 (s, 6H), 1.43 (s, 9H), 1.41 (d, *J* = 6.8 Hz, 3H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 174.3, 144.6, 139.1, 115.5, 115.3, 81.0, 53.8, 42.0, 28.0, 19.0. **IR** (neat) 3385, 2973, 2932, 2788, 1705, 1518, 1445, 1288, 1259. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{25}N_2O_2$ 265.1911; Found 265.1906. **$[\alpha]_D^{23}$** –0.008 (*c* 1.0, $CHCl_3$). **R_f** = 0.38 (35% ethyl acetate in hexanes). **MP** = 47.5 – 50.3 ºC.

4-(*p*-dimethylamino-phenyl)leucine *tert*-butyl ester (3d). This was synthesized according to the general procedure described above, using HCl · L-Leu-O*t*Bu (100.0 mg, 0.45 mmol). The product was purified by silica gel column chromatography using 2-15% ethyl acetate in hexanes to afford a yellow-brown solid (103.2 mg, 75% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.71 (d, *J* = 7.2 Hz, 2H), 6.63 (d, *J* = 6.3 Hz, 2H), 3.88 (s (br), 1H), 3.64 (s (br), 1H), 2.82 (s, 6H), 1.87 – 1.80 (m, 1H), 1.63 – 1.55 (m, 2H), 1.41 (s, 9H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 174.5, 144.6, 139.6, 115.6, 115.4, 81.0, 57.2, 42.6, 42.2, 28.1, 25.0, 22.8, 22.5. **IR** (neat) 3374, 3344, 2956, 2867, 2791, 1722, 1517, 1368, 1269, 1145. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{31}N_2O_2$ 307.2380; Found 307.2372. **$[\alpha]_D^{23}$** –1.25 (*c* 1.0, $CHCl_3$). **R_f** = 0.21 (10% ethyl acetate in hexanes). **MP** = 64.7 – 67.8 ºC.

4-(*p*-dimethylamino-phenyl)valine *tert*-butyl ester (3e). This was synthesized according to the general procedure described above, using HCl · L-Val-O*t*Bu (100.0 mg, 0.55 mmol). The product was purified by silica gel column chromatography using 10-35% ethyl acetate in hexanes to afford an orange-brown solid (133.9 mg, 83% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.72 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 3.80 (s(br), 1H), 3.66 (d, *J* = 5.4 Hz, 1H), 2.82 (s, 6H), 2.10 – 2.05 (m, 1H), 1.43 (s, 9H), 1.04 (t, *J* = 6.5

Hz, 6H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 173.3, 144.5, 140.1, 115.7, 81.2, 64.4, 42.2, 31.6, 28.1, 19.2, 18.8. **IR** (neat) 3383, 2970, 2931, 2875, 2786, 1705, 1519, 1471, 1274, 1156. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{29}N_2O_2$ 293.2224; Found 293.2217. **$[\alpha]_D^{23}$** –2.28 (*c* 1.0, $CHCl_3$). **R_f** = 0.27 (20% ethyl acetate in hexanes). **MP** = 84.1 – 87.2 ºC.

4-(*p*-dimethylamino-phenyl)isoleucine *tert*-butyl ester (3f). This was synthesized according to the general procedure described above, using HCl · L-Ile-O^{t}Bu (100.0 mg, 0.47 mmol). The product was purified by silica gel column chromatography using 5-35% ethyl acetate in hexanes gradient to afford a red-brown oil (127.2 mg, 93% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.71 (s (br), 2H), 6.63 (s (br), 2H), 3.74 (s (br), 1H), 2.82 (s, 6H), 1.85 – 1.78 (m, 1H), 1.68 – 1.63 (m, 1H), 1.42 (s, 9H), 1.35 – 1.29 (m, 1H), 0.99 – 0.96 (m, 6H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 173.2, 144.5, 139.9, 115.7, 115.4, 81.2, 62.9, 42.2, 38.1, 28.1, 25.9, 15.5, 11.7. **IR** (neat) 3390, 2969, 2877, 2787, 1703, 1519, 1477, 1275, 1155. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{31}N_2O_2$ 307.2380; Found 307.2375. **$[\alpha]_D^{23}$** –3.74 (*c* 1.0, $CHCl_3$). **R_f** = 0.27 (20% ethyl acetate in hexanes).

General Procedure for the Glycine Schiff Base Alkylation

5g-k were prepared following literature procedures.[17] Briefly, *N*-(diphenylmethylene)glycine *tert*-butyl ester (1.0 mmol, 1.0 equiv) and the corresponding electrophile (4.0 mmol, 4.0 equiv) (if solid) were transferred to a 10-mL round bottom flask. DCM (6.67 mL) was added, followed by tetrabutylammonium hydroxide (TBAH, 1.5 M in H_2O, 1.2 mmol, 1.2 equiv) and 10% aq. NaOH (2.5 mmol, 2.5 equiv). The reaction mixture was allowed to stir at room temperature overnight. The crude solution was transferred to a separatory funnel and the organic layer was washed with saturated brine

(3 x 15 mL). The organic layer was dried over Na_2SO_4, evaporated to dryness using a rotary evaporator, and purified by automated flash-column chromatography. *Note: due to the lack of ionization sites on these molecules, HRMS data could not be obtained for this series of compounds.*

***Tert*-butyl 2-((diphenylmethylene)amino)-3-(4-(trifluoromethyl)phenyl)propanoate (5g).** This was synthesized according to the general procedure described above, using *N*-(diphenylmethylene)glycine *tert*-butyl ester (295.4 mg, 1.0 mmol). The product was purified by silica gel column chromatography using 5-15% diethyl ether in hexanes to afford a white solid (362.1 mg, 80% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.60 – 7.59 (m, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.28 (m, 6H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.64 (s(br), 2H), 4.15 (q, *J* = 9.2, 4.1 Hz, 1H), 3.30 – 3.28 (m, 1H), 3.25 – 3.21 (m, 1H), 1.46 (s, 9H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 170.8, 170.5, 142.8, 139.4, 136.2, 132.5, 130.4, 130.3, 130.2, 128.9, 128.8, 128.6, 128.5, 128.4 128.3, 128.2, 127.6, 125.1 (q, *J* = 3.6 Hz), 124.3 (q, *J* = 271.8 Hz), 81.6, 67.6, 39.5, 28.2. **IR** (neat) 2976, 2932, 1726, 1616, 1448, 1188, 1151, 1064. **R_f** = 0.25 (10% diethyl ether in hexanes). **MP** = 106.6 – 112.7 ºC.

***Tert*-butyl 2-((diphenylmethylene)amino)-3-(4-fluorophenyl)propanoate (5h).** This was synthesized according to the general procedure described above, using *N*-(diphenylmethylene)glycine *tert*-butyl ester (886.1 mg, 3.0 mmol). The product was purified by silica gel column chromatography using 10% diethyl ether in hexanes to afford a white crystalline solid (1.03 g, 85% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.2 Hz, 2H), 7.29 – 7.27 (m, 2H), 7.25 – 7.24 (m, 4H), 6.99 – 6.96 (m, 2H), 6.83 (t, *J* = 8.7 Hz, 2H), 6.65 (s (br), 2H), 4.08 (d of d, *J* = 9.1, 4.3 Hz, 1H), 3.19 – 3.16 (m, 1H), 3.13 – 3.10 (m, 1H), 1.40 (s, 9H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 170.6, 170.4, 162.3, 160.7

139.4, 136.3, 134.1, 134.1, 131.3 (d, *J* = 7.8 Hz), 130.0, 129.1 (d, *J* = 280.2 Hz), 128.7, 128.3, 128.1, 128.0, 127.6, 114.8, 114.7, 81.1, 67.8, 38.8, 28.0. **IR** (neat) 2976, 2928, 1725, 1626, 1507, 1446, 1369, 1283, 1220, 1143, 1039. $\mathbf{R_f}$ = 0.22 (10% diethyl ether in hexanes). **MP** = 69.3 – 77.5 ºC.

***Tert*-butyl 2-((diphenylmethylene)amino)-3-(*m*-tolyl)propanoate (5i).** This was synthesized according to the general procedure described above, using *N*-(diphenylmethylene)glycine *tert*-butyl ester (886.1 mg, 3.0 mmol). The product was purified by silica gel column chromatography using 10% diethyl ether in hexanes to afford a light yellow oil (718.3 mg, 60% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.59 – 7.58 (m, 2H), 7.35 – 7.31 (m, 2H), 7.29 – 7.27 (m, 3H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.88 – 6.85 (m, 2H), 6.62 (s (br), 1H), 4.13 (d of d, *J* = 9.4, 4.2 Hz, 1H), 3.23 – 3.20 (m, 1H), 3.16 – 3.13 (m, 1H), 2.22 (s, 3H), 1.46 (s, 9H).**^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 171.0, 170.3, 139.7, 138.3, 137.7, 137.6, 136.5, 132.5, 130.8, 130.2, 128.8, 128.4, 128.3, 128.1, 128.0, 127.8, 127.0, 126.9, 81.2, 68.0, 39.6, 28.2, 28.1, 21.3. **IR** (neat) 2977, 2928, 1726, 1626, 1507, 1446, 1368, 1283, 1220, 1144, 1039. $\mathbf{R_f}$ = 0.29 (10% diethyl ether in hexanes).

***Tert*-butyl 2-((diphenylmethylene)amino)-3-(napthalen-2-yl)propanoate (5j).** This was synthesized according to the general procedure described above, using *N*-(diphenylmethylene)glycine *tert*-butyl ester (295.4 mg, 1.0 mmol). The product was purified by silica gel column chromatography using 5% ethyl acetate in hexanes to afford a yellow solid (349.8 mg, 80% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.76 – 7.74 (m, 1H), 7.68 – 7.65 (m, 1H), 7.62 – 7.60 (m, 1H), 7.54 (s, 1H), 7.41 – 7.36 (m, 2H), 7.34 – 7.31 (m, 1H), 7.29 – 7.27 (m, 3H), 7.23 – 7.22 (m, 1H), 7.17 (t, *J* = 7.7 Hz, 2H), 6.57 (s (br),

1H), 4.30 (d of d, *J* = 9.3, 4.3 Hz, 1H), 3.46 (d of d, *J* = 13.5, 4.2 Hz, 1H), 3.38 (d of d, *J* = 13.4, 9.4 Hz, 1H), 1.47 (s, 9H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 196.8, 170.9, 170.6, 139.6, 137.7, 136.4, 136.0, 133.5, 132.5, 132.2, 130.2, 130.2, 128.8, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.6, 127.6, 125.9, 125.3, 81.3, 68.0, 39.9, 28.6, 28.2. **IR** (neat) 3061, 2969, 2844, 1734, 1658, 1624, 1286, 1147. **R_f** = 0.51 (5% ethyl acetate in hexanes). **MP** = 86.4 – 93.2 ºC.

***Tert*-butyl 2-((diphenylmethylene)amino)-5-methylhexanoate (5k).** This was synthesized according to the general procedure described above, using *N*-(diphenylmethylene)glycine *tert*-butyl ester (886.1 mg, 3.0 mmol). The product was purified by silica gel column chromatography using 10% diethyl ether in hexanes to afford a yellow oil (986.0 mg, 90% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.70 – 7.69 (m, 2H), 7.47 – 7.42 (m, 3H), 7.38 – 7.36 (m, 1H), 7.33 – 7.31 (m, 2H), 7.21 – 7.20 (m, 2H), 3.95 (q, *J* = 7.9, 5.1 Hz, 1H), 1.98 - 1.88 (m, 2H), 1.53 – 1.50 (m, 1H), 1.48 (s, 9H), 1.25 – 1.20 (m, 1H), 1.19 – 1.14 (m, 1H), 0.89 (q, *J* = 6.7, 3.9 Hz, 6H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 171.7, 169.8, 139.9, 136.9, 132.5, 130.2, 130.1, 128.9, 128.5, 128.5, 128.4, 128.1, 128.0, 80.8, 66.5, 35.3, 31.7, 28.2, 28.0, 22.7, 22.6. **IR** (neat) 2976, 1725, 1626, 1508, 1446, 1368, 1284, 1144, 1039. **R_f** = 0.36 (10% diethyl ether in hexanes).

General Procedure for Benzophenone Imine Deprotection.

Following literature procedures,[21] the desired benzophenone imine protected unnatural amino acid ester (0.34 mmol, 1.0 equiv) and hydroxylamine hydrochloride (1.38 mmol, 4.0 equiv) were transferred to an oven-dried round-bottom flask. The compounds were dissolved in pyridine (8.01 mL) and allowed to stir at 60 ºC overnight. Pyridine was evaporated using a rotary evaporator, followed by co-evaporation with DCM (x 3) to

remove trace amounts of pyridine. The residue was digested with 5% MeOH in DCM for 2 hours to remove the insoluble excess hydroxylamine hydrochloride salt. The solution was filtered through a plug of cotton and evaporated to dryness on a rotary evaporator. The crude was re-dissolved in DCM and concentrated using a rotary evaporator (x 3), then placed under high vacuum for several hours prior to flash column chromatography. *Note: thorough removal of pyridine and methanol from the reaction and digestion procedures, respectively, was found to be critical for effective separation.*

***Tert*-butyl 2-amino-3-(4-(trifluoromethyl)phenyl)propanoate (1g).** This was synthesized according to the general procedure described above, using **5g** (1.34 g, 3.0 mmol). The crude product was purified by silica gel column chromatography using a step gradient from 5% methanol in dichloromethane to 10% methanol in dichloromethane to afford a beige crystalline solid (567.6 mg, 66% yield). **^{1}H NMR** (600 MHz, CD_3OD): δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 4.17 (t, *J* = 7.3 Hz, 1H), 3.27 – 3.24 (m, 1H), 3.21 – 3.17 (m, 1H), 1.36 (s, 9H). **^{13}C {^{1}H} NMR** (150 MHz, CD_3OD): δ 169.5, 140.8, 130.8 (q, *J* = 32.4 Hz), 126.7 (q, *J* = 3.7 Hz), 125.6 (q, *J* = 271.2 Hz), 85.0, 55.4, 37.8, 28.0. **IR** (neat) 2983, 2864, 2630, 1731, 1621, 1565, 1502, 1372, 1325, 1245, 1128, 1108, 1019. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{19}F_3NO_2$ 290.1362; Found 290.1364. **R_f** = 0.28 (5% methanol in dichloromethane). **MP** = 168.3 – 176.1 ºC.

***Tert*-butyl 2-amino-3-(4-fluorophenyl)propanoate (1h).** This was synthesized according to the general procedure described above, using **5h** (670.6 mg, 1.7 mmol). The product was purified by silica gel column chromatography using a step gradient from 3% methanol in dichloromethane to 10% methanol in dichloromethane to afford a yellow oil (235.9 mg, 59% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.13 (q, *J* = 8.3, 5.5 Hz, 2H), 6.92

(t, *J* = 8.6 Hz, 2H), 3.54 (s (br), 1H), 2.94 (d of d, *J* = 13.4, 4.6 Hz, 1H), 2.79 (d of d, *J* = 13.5, 6.8 Hz, 1H), 1.83 (s (br), 2H), 1.36 (s, 9H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 174.0, 161.7 (d, *J* = 244.6 Hz), 133.1, 130.8 (d, *J* = 7.8 Hz), 115.1 (d, *J* = 21.2 Hz), 81.3, 56.2, 40.2, 27.9. **IR** (neat) 3607, 3555, 2982, 2850, 2631, 1732, 1617, 1509, 1397, 1243, 1144, 1096, 1054. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{19}FNO_2$ 240.1394; Found 240.1391. $\mathbf{R_f}$ = 0.32 (5% methanol in dichloromethane).

***Tert*-butyl 2-amino-3-(*m*-tolyl)propanoate (1i).** This was synthesized according to the general procedure described above, using **5i** (718.3 mg, 1.8 mmol). The product was purified by silica gel column chromatography using a step gradient from 3% methanol in dichloromethane to 10% methanol in dichloromethane to afford a yellow oil (186.9 mg, 44% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.17 (t, *J* = 7.4 Hz, 1H), 7.03 – 6.99 (m, 3H), 3.60 (s (br), 1H), 3.00 (d of d, *J* = 13.5, 5.3 Hz, 1H), 2.81 (d of d, *J* = 13.5, 7.6 Hz, 1H), 2.31 (s, 3H), 1.76 (s (br), 1H), 1.42 (s, 9H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 172.7, 138.3, 136.6, 130.5, 128.7, 127.9, 126.8, 82.2, 55.9, 40.0, 28.2, 21.6. **IR** (neat) 2977, 2928, 1726, 1626, 1508, 1447, 1393, 1284, 1144, 1039. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{22}NO_2$ 236.1645; Found 236.1642. $\mathbf{R_f}$ = 0.33 (5% methanol in dichloromethane).

***Tert*-butyl 2-amino-3-(naphthalen-2-yl)propanoate (1j).** This was synthesized according to the general procedure described above, using **5j** (150.0 mg, 0.34 mmol). The product was purified by silica gel column chromatography using a step gradient from 50% ethyl acetate in hexanes to 100% ethyl acetate to afford a yellow oil (57.3 mg, 61% yield). **^{1}H NMR** (600 MHz, CD_3OD): δ 7.82 – 7.77 (m, 3H), 7.70 (s, 1H), 7.46 – 7.41 (m, 2H), 7.37 (d of d, *J* = 8.4, 1.8 Hz, 1H), 4.07 (t, *J* = 7.0 Hz, 1H), 3.28 – 3.20 (m, 2H), 1.31

(s, 9H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 170.9, 134.9, 134.1, 133.9, 129.5, 129.5, 128.7, 128.6, 128.3, 127.4, 127.0, 84.3, 55.9, 39.2, 28.1. **IR** (neat) 2977, 2929, 2632, 1727, 1623, 1507, 1446, 1507, 1368, 1247, 1148, 1067, 1020. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{22}NO_2$ 272.1645; Found 272.1638. **R_f** = 0.22 (100% ethyl acetate).

***Tert*-butyl 2-amino-5-methylhexanoate (1k).** This was synthesized according to the general procedure described above, using **5k** (986.0 g, 2.7 mmol). The product was purified by silica gel column chromatography using a step gradient from 1% methanol in dichloromethane to 10% methanol in dichloromethane to afford a yellow oil (282.7 mg, 52% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 5.95 (s (br), 2H), 3.78 (t, *J* = 5.9 Hz, 1H), 1.87 – 1.82 (m, 2H), 1.56 – 1.51 (m, 1H), 1.44 (s, 9H), 1.36 – 1.31 (m, 1H), 1.22 – 1.16 (m, 1H), 0.85 (t, *J* = 6.9 Hz, 6H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 171.1, 83.1, 54.3, 33.9, 30.1, 28.1, 27.7, 22.5, 22.3. **IR** (neat) 2963, 2868, 1718, 1596, 1449, 1366, 1296, 1249, 1149, 1089, 1028. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{24}NO_2$ 202.1802; Found 202.1802. **R_f** = 0.20 (5% methanol in dichloromethane).

General Procedure for *N*-arylations of Unnatural Amino Acid *t*-Butyl Esters 1g-k with 4-Bromo-*N,N*-dimethylaniline

The amino acid *t*-butyl ester hydrochloride (1.0 mmol, 1.0 equiv), 4-Bromo-*N,N*-dimethylaniline (1.0 mmol, 1.0 equiv), *t*-Bu BrettPhos Pd G3 (0.05 mmol, 0.05 equiv), and sodium *t*-butoxide (2.0 mmol, 2.0 equiv) were added to the oven-dried 5-mL microwave vial. The vial was immediately capped and flushed with argon. Dry tetrahydrofuran (2.0 mL) was added to the vial and the reaction mixture was stirred at room temperature for two hours. The crude solution was filtered through a small plug of celite, rinsed with

dichloromethane, evaporated to dryness on a rotary evaporator, and purified by flash-column chromatography.

***Tert*-butyl2-((4-dimethylamino)phenyl)amino)-3-(4-(trifluoromethyl)phenyl) propanoate (3g).** This was synthesized according to the general procedure described above, using **1g** (50.0 mg, 0.17 mmol). The product was purified by silica gel column chromatography using 5-40% ethyl acetate in hexanes to afford a red oil (66.6 mg, 94% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 6.79 (d, *J* = 7.7 Hz, 2H), 6.62 (d, *J* = 8.3 Hz, 2H), 4.18 (s (br), 1H), 3.13 (d, J = 6.2 Hz, 2H), 2.85 (s, 6H), 1.34 (s, 9H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 172.4, 144.2, 141.4, 139.3, 130.0, 129.6, 129.2 (q, *J* = 32.3 Hz), 125.4 (q, *J* = 3.6 Hz), 124.2 (q, *J* = 271.9 Hz), 116.2, 115.6, 82.1, 59.3, 42.6, 38.8, 28.1. **IR** (neat) 2978, 1725, 1517, 1322, 1151, 1118, 1065. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{28}F_3N_2O_2$ 409.2097; Found 409.2103. $\mathbf{R_f}$ = 0.18 (20% ethyl acetate in hexanes).

***Tert*-butyl 2-((4-(dimethylamino)phenyl)amino)-3-(4-fluorophenyl)propanoate (3h).** This was synthesized according to the general procedure described above, using **1h** (100.0 mg, 0.42 mmol). The desired compound was purified by silica gel column chromatography using 5-40% ethyl acetate in hexanes to afford a yellow oil (103.0 mg, 69% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.20 – 7.19 (m, 2H), 7.00 – 6.99 (m, 2H), 6.72 (s (br), 2H), 6.63 (s (br), 2H), 4.14 (s (br), 1H), 3.85 (s (br), 1H), 3.06 – 3.05 (m, 2H), 2.84 (s, 6H), 1.36 (s, 9H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 172.6, 161.8 (d, *J* = 244.6 Hz), 144.8, 138.7, 132.8 (d, *J* = 3.1 Hz), 131.1 (d, *J* = 7.9 Hz), 115.6, 115.5, 115.1 (d, *J* = 21.2 Hz), 81.6, 59.6, 42.0, 38.1, 28.0. **IR** (neat) 2976, 2790, 1725, 1601, 1509, 1367, 1220,

1150. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{28}FN_2O_2$ 359.2129; Found 359.2132. $\mathbf{R_f}$ = 0.16 (20% ethyl acetate in hexanes).

***Tert*-butyl 2-((4-dimethylamino)phenyl)amino)-3-(*m*-tolyl)propanoate (3i).** This was synthesized according to the general procedure described above, using **1i** (100.0 mg, 0.43 mmol). The product was purified by silica gel column chromatography using 5-40% ethyl acetate in hexanes to afford a yellow oil (126.5 mg, 84% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.20 – 7.17 (m, 1H), 7.06 – 7.03 (m, 3H), 6.72 (d, *J* = 8.3 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 4.15 (s (br), 1H), 3.83 (s, (br), 1H), 3.09 – 3.05 (m, 1H), 3.03 – 3.00 (m, 1H), 2.83 (s, 6H), 2.33 (s, 3H), 1.34 (s, 9H). **^{13}C {^{1}H} NMR** (600 MHz, $CDCl_3$): δ 172.9, 144.7, 139.0, 137.9, 136.9, 130.4, 128.3, 127.5, 126.6, 115.6, 115.6, 81.5, 59.6, 42.2, 39.0, 28.0, 21.5. **IR** (neat) 2954, 1728, 1520, 1458, 1368, 1257, 1151. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{31}N_2O_2$ 355.2380; Found 355.2385. $\mathbf{R_f}$ = 0.21 (20% ethyl acetate in hexanes).

***Tert*-butyl 2-((4-(dimethylamino)phenyl)amino)-3-(naphthalen-2-yl)propanoate (3j).** This was synthesized according to the general procedure described above, using **1j** (25.0 mg, 0.09 mmol). The product was purified by silica gel column chromatography using 5-40% ethyl acetate in hexanes to afford a red oil (16.7 mg, 46% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.84 – 7.82 (m, 1H), 7.80 – 7.79 (m, 2H), 7.96 (s, 1H), 7.49 – 7.45 (m, 2H), 7.41 – 7.39 (m, 1H), 6.74 (d, *J* = 8.3 Hz, 2H), 6.65 (d, *J* = 8.6 Hz, 2H), 4.28 (t, *J* = 6.4 Hz, 1H), 3.89 (s (br), 1H), 3.30 – 3.23 (m, 2H), 2.84 (s, 6H), 1.33 (s, 9H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 172.9, 144.8, 138.9, 134.7, 133.5, 132.5, 128.2, 128.0, 127.9, 127.7, 127.6, 126.1, 125.6, 115.6, 115.6, 81.6, 59.7, 42.1, 39.2, 28.0. **IR** (neat) 2975, 2788, 1723, 1601,

1516, 1477, 1367, 1253, 1147, 1055. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{31}N_2O_2$ 391.2380; Found 391.2365. $\mathbf{R_f}$ = 0.18 (20% ethyl acetate in hexanes).

***Tert*-butyl 2-((4-(dimethylamino)phenyl)amino)-5-methylhexanoate (3k).** This was synthesized according to the general procedure described above, using **1k** (100.0 mg, 0.50 mmol). The product was purified by silica gel column chromatography using 5-40% ethyl acetate in hexanes to afford a red oil (98.8 mg, 62% yield). **^{1}H NMR** (600 MHz, $CDCl_3$): 6.71 (s (br), 2H), 6.62 (s (br), 2H), 3.83 (s (br), 1H), 2.82 (s, 6H), 1.81 – 1.69 (m, 2H), 1.61 – 1.54 (m, 1H), 1.43 (s, 9H), 1.35 – 1.31 (m, 2H), 0.91 (d of d, *J* = 6.6, 4.4 Hz, 6H). **^{13}C {^{1}H} NMR** (150 MHz, $CDCl_3$): δ 173.0, 137.9, 136.9, 130.4, 128.3, 127.5, 126.6, 115.8, 115.6, 81.5, 59.6, 42.3, 39.0, 28.0, 21.5. **IR** (neat) 2976, 1727, 1610, 1519, 1478, 1367, 1257, 1154. **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{33}N_2O_2$ 321.2537; Found 321.2542. $\mathbf{R_f}$ = 0.28 (20% ethyl acetate in hexanes).

General Procedure for *N*-aryl Amino Acid Coupling to Resin-Bound Peptide

The amino acid *tert*-butyl ester (100.0 mg, 0.061 mmol, 1.0 equiv) was transferred to a new 20-mL scintillation vial, dissolved in 1:1 TFA/ DCM (2 mL), and allowed to stir at room temperature for two hours. The reaction mixture was evaporated to dryness using a Biotage V10 evaporator (volatile setting), followed by co-evaporation (x 5) with dichloromethane to remove residual TFA. The resulting oil was used in the next step without further purification.

Dimethylformamide (DMF) was added to resin-bound LYRAG peptide (100.0 mg, 0.061 mmol, 1.0 equiv) in a 3-mL disposable filter column with a 20 μM PE frit filter and allowed to swell on a shaker for approximately twenty-five minutes. DMF was drained from the

cartridge. The *N*-aryl amino acid (0.183 mmol, 3.0 equiv) dissolved in DMF (1.0 mL) was added to the cartridge, followed by 2-(1H-benzotriazol-1-yl)-1,2,3,3-tetramethyluronium hexafluorophosphate (HBTU) (0.183 mmol, 3.0 equiv) and diisopropylethylamine (DIEA) (0.366 mmol, 6 equiv). The resin was allowed to shake for two hours, after which the reagents were drained and the resin was washed with DMF, MeOH, and DCM (x3).

Test cleavage of resin-bound peptides

A small aliquot of resin (1-5 mg) was transferred to a 1-mL disposable filter column with a 20 μM PE frit filter. A freshly made solution of TFA/TIPS/H_2O (95:2.5:2.5, v/v/v, 0.2 mL) was added to the cartridge and allowed to shake at room temperature for two hours. The resin was filtered through the PE frit and the filtrate was collected in a 20-mL scintillation vial and evaporated to dryness on a Biotage V10 evaporator (volatile setting). Addition of cold ether (1 mL) to the crude oil caused a precipitate to form, which was redissolved in 1:1 MeCN/ H_2O v/v (1 mg/ mL) prior to LCMS analysis.

Full cleavage of resin-bound peptides

The resin-bound peptide was transferred to a 20-mL scintillation vial and treated with a freshly made solution of TFA/TIPS/H_2O (95:2.5:2.5, v/v/v, 4.0 mL). The vial was capped and allowed to shake at room temperature for two hours. The cleavage mixture was filtered through a 3-mL disposable filter column with a 20 μM PE frit filter into a 50-mL falcon tube containing cold ether (25-30 mL). The falcon tube was centrifuged for 5 minutes at 7000 RPM, the ether was decanted, and the precipitate was redissolved in 1:1 MeCN/ H_2O v/v before freeze-drying.

Analysis and purification of peptides 7a-k

Crude peptides **7a-k** were analyzed and characterized by LCMS as described in the General Methods. Following gradient optimization, the peptides were purified by preparative HPLC as described in the General Methods. Peptides **7a, 7d** and **7f** were purified using a 25-80% MeCN (0.1% TFA) in water (0.1% TFA) gradient. Peptide **7b** was purified using 20-70% MeCN (0.1% TFA) in water (0.1% TFA) gradient. Peptide **7c** was purified using 10-70% MeCN (0.1% TFA) in water (0.1% TFA) gradient. Peptides **7e** was purified using a 20-80% MeCN (0.1% TFA) in water (0.1% TFA) gradient. Peptides **7g-k** was purified using a 30-90% MeCN (0.1% TFA) in water (0.1% TFA) gradient. The contents of the HPLC fractions were analyzed using LC-MS. The fractions containing the desired peptide were collected, frozen immediately, and lyophilized. **7a**: HPLC (5−95% MeCN, 12 min) retention time = 9.12 min; **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{43}H_{62}N_{11}O_7$ 844.4828; Found 844.4832; **7b**: HPLC (5−95% MeCN, 12 min) retention time = 8.48 min; **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{39}H_{62}N_{11}O_7S$ 828.4549; Found 828.4556; **7c**: HPLC (5−95% MeCN, 12 min) retention time = 7.91 min; **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{37}H_{58}N_{11}O_7$ 768.4515; Found 768.4528; **7d**: HPLC (5−95% MeCN, 12 min) retention time = 8.96, 9.10 min; **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{40}H_{64}N_{11}O_7$ 810.4985; Found 810.4997; **7e**: HPLC (5−95% MeCN, 12 min) retention time = 8.92 min; **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{39}H_{62}N_{11}O_7$ 796.4828; Found 796.4839; **7f**: HPLC (5−95% MeCN, 12 min) retention time = 8.99 min; **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{40}H_{64}N_{11}O_7$ 810.4985; Found 810.4998; **7g**: HPLC (5−95% MeCN, 12 min) retention time = 10.08 min; **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{44}H_{61}F_3N_{11}O_7$ 912.4702; Found 912.4724; **7h**: HPLC (5−95% MeCN, 12 min) retention time = 9.53 min; **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$

Calcd for $C_{43}H_{61}FN_{11}O_7$ 862.4734; Found 862.4732; **7i**: HPLC (5−95% MeCN, 12 min) retention time = 9.73 min; **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{44}H_{64}N_{11}O_7$ 858.4985; Found 858.4985; **7j**: HPLC (5−95% MeCN, 12 min) retention time = 10.00 min; **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{47}H_{64}N_{11}O_7$ 894.4985; Found 894.4991; **7k**: HPLC (5−95% MeCN, 12 min) retention time = 9.70 min; **HRMS** (HESI/ orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{41}H_{66}N_{11}O_7$ 824.5141; Found 824.5145.

General procedure for ketoxime ligation reactions

All ligation reactions were performed using previously reported reaction conditions.[8,9] Briefly, stock solutions of the peptide (2 mM) and *O*-benzylhydroxylamine hydrochloride (10 mM) were prepared in phosphate buffer pH 7. 1 mL of each reagents were combined in a 4 mL vial, and the solution was sparged with O_2 for thirty seconds. The reaction was allowed to stir at room temperature for twenty-four hours under O_2 atmosphere, after which a small aliquot (100 µL) of the reaction mixture was analyzed by LCMS. Oxime conversions were calculated using peak areas at 214 nm, where % oxime conversion = [(area of oxime **8a-k**)/(area of **7a-k** + **8a-k**)] x 100. Ketoximes **8a-k** were analyzed and characterized by LCMS as described in the General Methods. **8a**: HPLC (5−95% MeCN, 12 min) retention time = 11.22, 11.76 min; LCMS (ESI) calcd for $C_{42}H_{57}N_{10}O_8$ $[M + H]^+$ m/z 829.4, m/z (obs) 829.7; **8b**: HPLC (5−95% MeCN, 12 min) retention time = 10.86, 11.35 min; LCMS (ESI) calcd for $C_{38}H_{57}N_{10}O_8S$ $[M + H]^+$ m/z 813.4, m/z (obs) 813.6; **8c**: HPLC (20-80% MeCN, 12 min) retention time = 10.06, 10.86 min; LCMS (ESI) calcd for

$C_{36}H_{53}N_{10}O_8$ $[M + H]^+$ m/z 753.4, m/z (obs) 753.6; **8d**: HPLC (5−95% MeCN, 12 min) retention time = 11.21, 11.83 min; LCMS (ESI) calcd for $C_{39}H_{59}N_{10}O_8$ $[M + H]^+$ m/z 795.4, m/z (obs) 795.7; **8e**: HPLC (5−95% MeCN, 12 min) retention time = 11.18, 11.75 min; LCMS (ESI) calcd for $C_{38}H_{57}N_{10}O_8$ $[M + H]^+$ m/z 781.4, m/z (obs) 781.6; **8f**: HPLC (5−95% MeCN, 12 min) retention time = 11.28, 11.89 min; LCMS (ESI) calcd for $C_{39}H_{59}N_{10}O_8$ $[M + H]^+$ m/z 795.4, m/z (obs) 795.6; **8g**: HPLC (5−95% MeCN, 12 min) retention time = 12.28, 12.76 min; LCMS (ESI) calcd for $C_{43}H_{56}F_3N_{10}O_8$ $[M + H]^+$ m/z 897.4, m/z (obs) 897.6; **8h**: HPLC (5−95% MeCN, 12 min) retention time = 11.68, 12.18 min; LCMS (ESI) calcd for $C_{42}H_{56}FN_{10}O_8$ $[M + H]^+$ m/z 847.4, m/z (obs) 847.7; **8i**: HPLC (5−95% MeCN, 12 min) retention time = 11.91, 12.39 min; LCMS (ESI) calcd for $C_{43}H_{59}N_{10}O_8$ $[M + H]^+$ m/z 843.4 m/z (obs) 843.7; **8j**: HPLC (5−95% MeCN, 12 min) retention time = 12.20, 12.69 min; LCMS (ESI) calcd for $C_{46}H_{59}N_{10}O_8$ $[M + H]^+$ m/z 879.4, m/z (obs) 879.6; **8k**: HPLC (5−95% MeCN, 12 min) retention time = 11.93, 12.50 min; LCMS (ESI) calcd for $C_{40}H_{61}N_{10}O_8$ $[M + H]^+$ m/z (cald) 809.5, m/z (obs) 809.7.

ASSOCIATED CONTENT

Supporting Information. ^1H and ^{13}C NMR spectra for compounds **1g-k**, **3a-k**, and **5g-k**. LCMS traces for peptides **7a−k** and ketoxime peptides **8a-k**. The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

* cproulx@ncsu.edu

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