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Direct Entry to Peptidyl Ketones via SmI_2-Mediated C−C Bond Formation with Readily Accessible *N*-Peptidyl Oxazolidinones

Tina Mittag, Kasper L. Christensen, Karl B. Lindsay, Niels Christian Nielsen, and Troels Skrydstrup*

Center for Insoluble Protein Structures, Department of Chemistry and Interdisciplinary Nanoscience Center, University of Aarhus, Langelandsgade 140, 8000 Aarhus C, Denmark

ts@chem.au.dk

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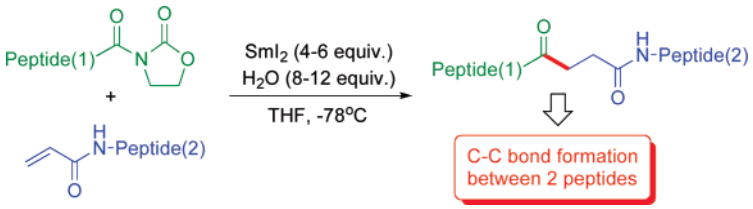

In this work, a new method for the preparation of peptidyl ketones is presented employing a SmI_2/H_2O-mediated coupling of *N*-peptidyl oxazolidinones with electron-deficient alkenes. The requisite peptide imides were easily prepared by solution-phase peptide synthesis starting from an *N*-acyl oxazolidinone derivative of an amino acid. Importantly, they could be used directly in the C−C bond-forming step without the need for further functionalization. Coupling of these peptide derivatives with a second peptide possessing an *N*-terminal acryloyl group leads to ketomethylene isosteres of glycine-containing peptides. This method represents an alternative means for ligating two small peptides through a C−C bond-forming step.

Introduction

Peptidyl ketones represent an important class of nonhydrolyzable peptide isosteres, exhibiting a broad range of biological activities. For example, such peptide mimics have been exploited as effective inhibitors of numerous metabolic proteases,[1] as well as being stable analogue substrates for the di- and tripeptide transporters,[2] and inhibitors of the peptidylglycine α-amidating monooxygenase (PAM).[3] Synthetic routes to peptidyl ketones generally involve lengthy syntheses, including installation of the ketone functionality onto an *N*-protected amino acid derivative via the addition of carbon nucleophiles, followed by *N*-deprotection and peptide chain construction.[4] On the other hand, the possibility for accessing the peptide mimics directly from a suitably functionalized peptide would provide access to numerous ketone derivatives without the need for synthesizing the peptide strand for each modification. In a recent paper by Liebeskind and co-workers, this goal was reached by Pd-mediated cross coupling of peptidyl thioesters with aryl and alkenyl boronic acids.[5,6]

Previously, we have demonstrated the capacity of 4-pyridyl thioester derivatives of amino acids to undergo a samarium diiodide-mediated coupling with electron-deficient alkenes generating enantiomerically pure α-amino ketones in good yields (Scheme 1).[7,8] These reactions were also found to be adaptable to the synthesis of methylene isosteres of small glycine-containing peptides. However, attempts to expand the methodology to the use of 4-pyridyl thioesters of small peptides from

(1) For some recent reviews, see: (a) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305. (b) Powers, J. C.; Asgian, J. L.; Ekici, Ö. D.; James, K. E. *Chem. Rev.* **2002**, *102*, 4639.

(2) See: Våbenø, J.; Nielsen, U.; Ingebrigtsten, T.; Lejon, T.; Steffansen, B.; Luthman, K. *J. Med. Chem.* **2004**, *47*, 4755 and references cited therein.

(3) Baratt, B. J. W.; Easton, C. J.; Henry, J. D.; Li, I. H. W.; Random, L.; Simpson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 13306.

(4) For a few representative examples see: (a) DeGraw, J. I.; Almquist, R. G.; Hiebert, C. K.; Colwell, W. T.; Crase, J.; Hayano, T.; Judd, A. K.; Dousman, L.; Smith, R. L.; Waud, W. R.; Uchida, I. *J. Med. Chem.* **1997**, *40*, 2386. (b) Eda, M.; Ashimori, A.; Akahoshi, F.; Yoshimura, T.; Inoue, Y.; Fukaya, C.; Nakajima, M.; Fukuyama, H.; Imada, T.; Nakamura, N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 913. (c) Dragovich, P. S.; Zhou, R.; Webber, S. E.; Prins, T. J.; Kwok, A. K.; Okano, K.; Fuhrman, S. A.; Zalman, L. S.; Maldonado, F. C.; Brown, E. L.; Meador, J. W., III; Patick, A. K.; Ford, C. E.; Brothers, M. A.; Binford, S. L.; Matthews, D. A.; Ferre, R. A.; Worland, S. T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 45.

(5) Yang, H.; Li. H.; Wittenberg, R.; Egi. M.; Huang, W.; Liebeskind, L. *J. Am. Chem. Soc.* **2007**, *129*, 1132.

(6) For an interesting partial approach to peptidyl ketones, see: Lin, W.; Tryder, N.; Su, F.; Zercher, C. K.; Jasinski, J. P.; Butcher, R. J. *J. Org. Chem.* **2006**, *71*, 8140.

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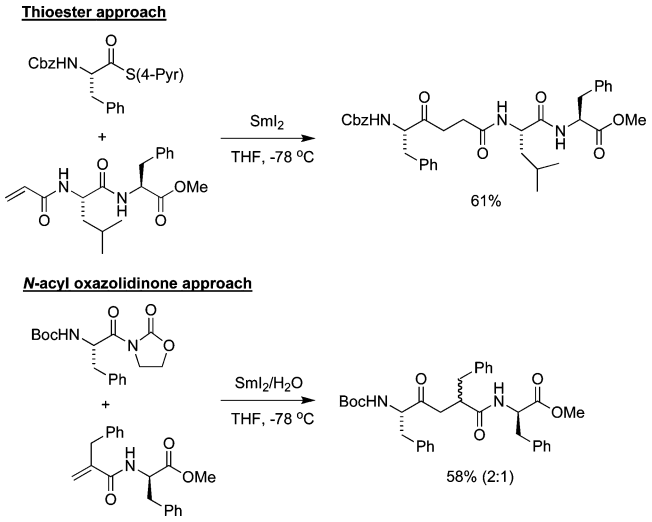
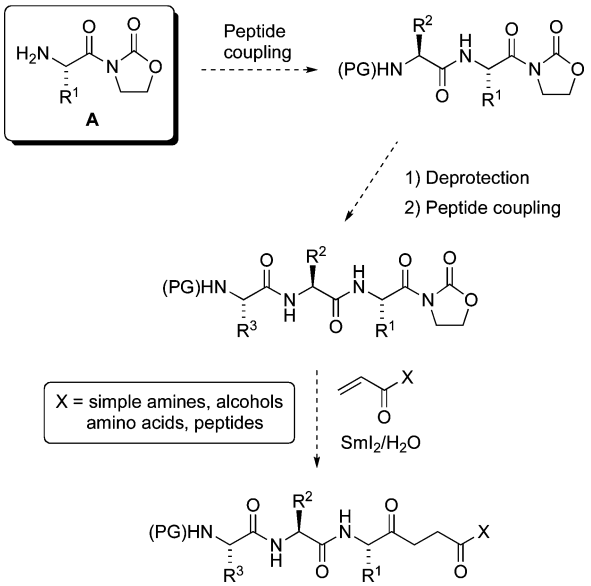
SCHEME 1. Examples of the Synthesis of α-Aminoketones via SmI_2-Promoted Coupling of 4-Pyridyl Thioesters and *N*-Acyl Oxazolidinones of Amino Acids with Electron-Deficient Alkenes.

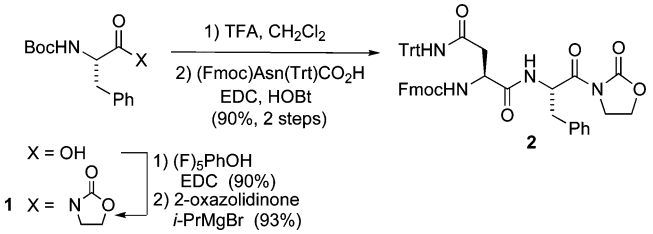


the corresponding terminal carboxylic acids were hampered by the desire of the thioesters to undergo intramolecular cyclization with the adjacent amide group. In later work, we discovered the possibility of replacing the thiopyridyl esters of amino acids with their corresponding *N*-acyl oxazolidinone derivatives, as illustrated with the example in Scheme 1.[9,10] Although the mechanisms of the C−C bond-forming step with these two classes of substrates were found to be different,[9b] the reactions performed with the *N*-acyl oxazolidinone derivatives of amino acids proved to be less sensitive to steric effects with respect to the substitution pattern of the amino acid and the acrylate/acrylamide used. As these *N*-acyl oxazolidinone derivatives of amino acids, as represented by structure **A**, were expected to display greater stability than the corresponding thioesters, we speculated whether such compounds could be amenable to a peptide-coupling sequence (Scheme 2). Indeed peptide-coupling reactions of this type have been demonstrated previously.[11] With this as the case, then without the need for further transformation, the treatment of this peptide imide with SmI_2 and a suitable alkene could possibly lead directly to a peptidyl ketone.

SCHEME 2. Proposed Strategy for the Synthesis of Peptidyl Ketones Starting from an *N*-Acyl Oxazolidinone Derivative of an Amino Acid



SCHEME 3. Synthesis of the Dipeptidyl Oxazolidinone 2



In this paper, we confirm the ability of such *N*-acyl oxazolidinone derivatives of amino acids to be sufficiently stable and hence to be suitable substrates for peptide-coupling sequences. In addition, such peptide derivatives not only allow for a novel access to peptidyl ketones through their coupling with an electron-deficient olefin under mild conditions, but also provide for an alternative means of ligating two small peptides via C−C bond formation.

Results and Discussion

To examine the viability of the synthetic strategy as represented in Scheme 2, we prepared the *N*-acyl oxazolidinone of phenylalanine **1** exploiting a modification of our previously published two-step protocol for accessing these amino acid derivatives (Scheme 3).[10a,12] Gratifyingly, its deprotection and peptide coupling with the partially protected asparagine provided in good yields the *N*-dipeptidyl oxazolidinone **2**.

The reactivity of the peptide derivative **2** was investigated in SmI_2-mediated coupling experiments with a variety of electron-deficient alkenes as illustrated in Table 1. The reactions were performed by adding a solution of SmI_2 (0.1 M in THF) over a period of 30 min to a cold THF solution (−78 °C) of the alkene and *N*-acyl oxazolidinone in the presence of water (SmI_2:H_2O ratio, 1:2), followed by stirring for approximately 18 h.[13] The C−C bond formation proved to proceed well with the

(7) For previous work featuring SmI_2-promoted coupling reactions of amino acid thioesters see: (a) Blakskjær, P.; Høj, B.; Riber, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2003**, *125*, 4030. (b) Mikkelsen, L. M.; Jensen, C. M.; Høj, B.; Blakskjær, P.; Skrydstrup, T. *Tetrahedron* **2003**, *59*, 10541. (c) Jensen, C. M.; Lindsay, K. B.; Andreasen, P.; Skrydstrup, T. *J. Org. Chem.* **2005**, *70*, 7512. (d) Lindsay, K. B.; Skrydstrup, T. *J. Org. Chem.* **2006**, *71*, 4766.

(8) For some recent reviews on the use of SmI_2 in organic synthesis, see: (a) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (b) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351. (c) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727. (d) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (e) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (f) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

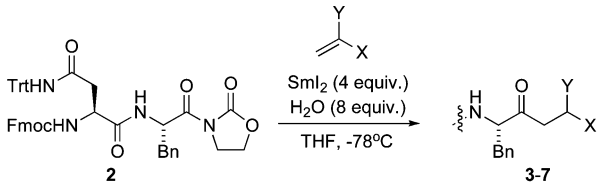
(9) For development of SmI_2-promoted *N*-acyloxazolidinone coupling reactions see: (a) Jensen, C. M.; Lindsay, K. B.; Taaning, R. H.; Karaffa, J.; Hansen, A. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2005**, *127*, 6544. (b) Hansen, A. M.; Lindsay, K. B.; Sudhadevi Antharjanam, P. K.; Karaffa, J.; Daasbjerg, K.; Flowers, R. A., II; Skrydstrup, T. *J. Am. Chem. Soc.* **2006**, *128*, 9616.

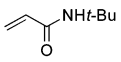
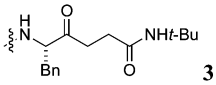
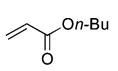
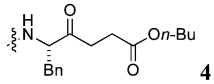
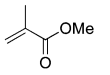
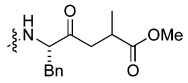
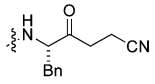
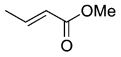
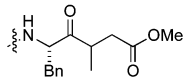
(10) (a) Karaffa, J.; Lindsay, K. B.; Skrydstrup, T. *J. Org. Chem.* **2006**, *71*, 8219. (b) Lindsay, B. K.; Ferrando, F.; Christensen, K. L.; Overgaard, J.; Roca, T.; Bennasar, M.-L.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 4181.

(11) (a) Bänteli, R.; Brun, I.; Hall, P.; Metternich, R. *Tetrahedron Lett.* **1999**, *40*, 2109−2112. (b) Luppi, G.; Soffre, C.; Tomasini, C. *Tetrahedron*: *Asymmetry* **2004**, *15*, 1645−1650.

(12) Cardillo, G.; Gentilucci, L.; De Matteis, V. *J. Org. Chem.* **2002**, *67*, 5957.

TABLE 1. Scope of the SmI_2-Promoted Radical Addition Reaction with the *N*-Dipeptidyl Oxazolidinone 2



Entry	Olefin	Product	Yield[a]
1		 **3**	85%
2		 **4**	55%
3		 **5**	58%[b]
4		 **6**	75%
5		 **7**	47%[c]

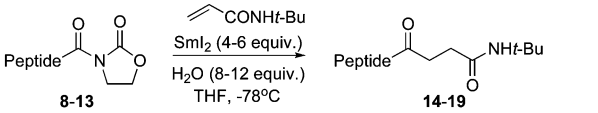
[a] Isolated yields after column chromatography. [b] An approximate 1:1 diastereomeric mixture. [c] 3:1 diastereomeric mixture.

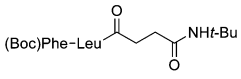
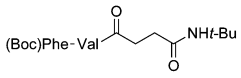
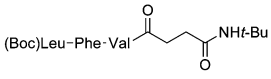
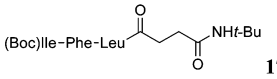
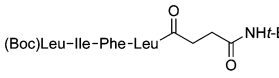
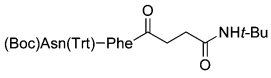
acrylamide and the three acrylates providing the ketones **3**−**5** and **7** in good yields (entries 1−3 and 5). Couplings were also possible with acrylonitrile (entry 4), leading to the nitrile derivative **6** in a 75% yield.

Further examination of this coupling protocol was carried out with other *N*-peptidyl oxazolidinones ranging from dipeptides to a tetrapeptide derivative (Table 2). As with **2**, all the *N*-peptidyl oxazolidinones were prepared by solution-phase peptide synthesis starting from the easily accessible amino acid imide derivatives.[10a] The SmI_2-mediated coupling of **8**−**13** with *N*-*tert*-butyl acrylamide proved again feasible, where in most cases the yields were not significantly affected by the size of the starting peptide as shown by the 45% yield obtained with the tetrapeptide **12** (entry 5). The valine-containing peptides were slightly less effective, which was attributed to the greater sterical bulk at the reacting center.[7d,10a] Equally interesting was the observation that both the Fmoc and Boc protecting groups were compatible for the peptidyl ketone syntheses (entry 6 compared to entry 1 from Table 1).

Finally, the methodology was examined for its suitability in the coupling of *N*-peptidyl oxazolidinones with *N*-acryloyl

TABLE 2. Radical Addition of *N*-Peptidyl Oxazolidinones to *N*-*tert*-Butyl Acrylamides Promoted by SmI_2/H_2O.



Entry	Peptide	Product	Yield[a]
1	(Boc)Phe–Leu **8**	 **14**	72%
2	(Boc)Phe–Val **9**	 **15**	68%
3	(Boc)Leu–Phe–Val **10**	 **16**	40%
4	(Boc)Ile–Phe–Leu **11**	 **17**	61%
5	(Boc)Leu–Ile–Phe–Leu **12**	 **18**	45%
6	(Boc)Asn(Trt)–Phe **13**	 **19**	94%

[a] Isolated yields after column chromatography.

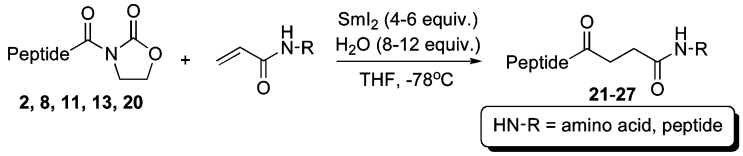
derivatives of a second peptide, thereby representing a novel peptide ligating technique via C−C bond formation. As shown in Table 3, these couplings proved successful with yields ranging from 20% to 82%. It is important to emphasize that the C−C bond formation leads directly to a ketomethylene isostere of a glycine-containing peptide. For example, product **23** (entry 4) represents a ketomethylene analogue of the fibrillating peptide NFGAIL.[14] Compounds such as this can provide important information on the role of the individual amide functional groups in the fibrillation process. Although the coupling yield for the preparation of the hexapeptide mimic was low, it is important to note that considerable amounts of the starting acrylamide were recovered due to its low solubility in the reaction conditions used. Further work is now in progress to provide solutions to these solubility issues in order to improve the coupling yields.

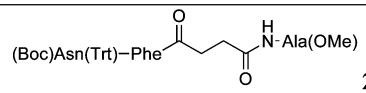
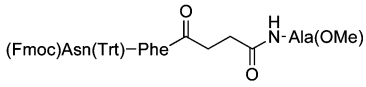
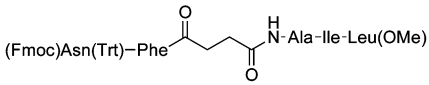
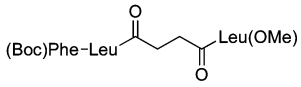
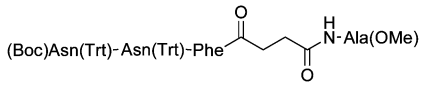
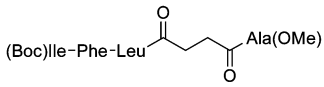
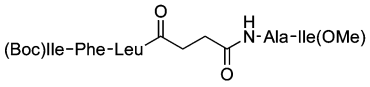
In conclusion, we have disclosed a novel approach to peptidyl ketones, which can also be applied to the synthesis of ketomethylene isosteres of peptides. Importantly, the starting *N*-peptidyl oxazolidinones are easily prepared by simple solution peptide synthesis and are directly amenable to the C−C bond-forming step.

(13) Flowers and Prasad have demonstrated the ability of water to increase the reducing powers of samarium diiodide, thus facilitating the electron-transfer step from the divalent lanthanide to the substrate. Furthermore, the addition of water can also lead to the formation of a dimer complex of SmI_2 and H_2O. Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2005**, *127*, 18093.

(14) Wu, C.; Lei, H.; Duan, Y. *J. Am. Chem. Soc.* **2005**, *127*, 13530 and references cited therein.

TABLE 3. Coupling of *N*-Peptidyl Oxazolidinones and Acrylamides of Amino Acids and Peptides.



Entry	Peptide	R	Product	Yield[a]
1	(Boc)Asn(Trt)–Phe (**13**)	Ala(OMe)	 **21**	66%
2	(Fmoc)Asn(Trt)–Phe (**2**)	Ala(OMe)	 **22**	82%
3	(Fmoc)Asn(Trt)–Phe (**2**)	Ala–Ile–Leu(OMe)	 **23**	20%
4	(Boc)Phe–Leu (**8**)	Leu(OMe)	 **24**	48%
5	(Boc)Asn(Trt)–Asn(Trt)–Phe (**20**)	Ala(OMe)	 **25**	62%
6	(Boc)Ile–Phe–Leu (**11**)	Ala(OMe)	 **26**	60%
7	(Boc)Ile–Phe–Leu (**11**)	Ala–Ile(OMe)	 **27**	38%

[a] Isolated yields after column chromatography.

Experimental Section

1,1-Dimethylethyl [(1*S*)-2-Oxo-2-(2-oxo-3-oxazolidinyl)-1-(phenylmethyl)ethyl]carbamate (1):[10a] General Procedure for the Preparation of *N*-Acyl Oxazolidinone Derivatives of Amino Acids. 2-Oxazolidinone (393 mg, 4.52 mmol) was dissolved in dry THF (20 mL) and then the solution was cooled to −10 °C, before *i*PrMgCl (2 M in toluene, 2.25 mL, 4.50 mmol) was added dropwise. The mixture was stirred at −10 °C for 30 min under an atmosphere of argon. The mixture was then added via syringe to a solution of *N*-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine pentafluorophenyl ester[2] (1.50 g, 3.48 mmol) in THF (25 mL). The mixture was stirred at −5 °C for 2.5 h under an atmosphere of argon and then water (20 mL) was added and the solvent was evaporated in vacuo. The remaining aqueous suspension was then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 40% to 80% EtOAc in pentane as eluant), which gave the title compound (1.08 g, 3.22 mmol, 93%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.21−7.30 (m, 5H), 5.68 (td, J = 8.8, 4.8 Hz, 1H), 5.08 (br d, J = 6.4 Hz, 1H), 4.32−4.44 (m, 2H), 4.04 (dt, J = 10.8, 6.8 Hz, 1H), 3.92 (dt, J = 10.0, 7.6 Hz, 1H), 3.18 (dd, J = 9.6, 4.0 Hz, 1H), 2.78 (dd, J = 9.2, 3.6 Hz, 1H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.9, 155.3, 153.0, 136.1, 129.5, 128.6 (2C), 127.2 (2C), 80.0, 62.6, 54.0, 42.7, 38.6, 28.4 (3C). HRMS $C_{17}H_{22}N_2O_5$ [M + Na^+] calcd 357.1426, found 357.1424.

(9*H*-Fluoren-9-yl)methyl (*S*)-1,4-Dioxo-1-[(*S*)-1-oxo-1-(2-oxo-3-oxazolidinyl)-3-phenylpropan-2-ylamino]-4-(triphenylmethylamino)butan-2-ylcarbamate (2): General Method for *N*-Terminal Extension of *N*-Boc Protected Amino Acid-Oxazolidinones. Oxazolidinone **1** (300 mg, 0.898 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2 and TFA (10 mL). The mixture was stirred at rt for 1 h and then all volatiles were removed in vacuo. The crude oil was redissolved in CH_2Cl_2 and the solvent was removed in vacuo. This step was repeated three times, to give the crude TFA salt as a pale yellow syrup. This was redissolved in CH_2Cl_2 (20 mL) and NMM (0.50 mL, 4.49 mmol) was added dropwise. Fmoc-L-Asn-(Trt)-OH (535 mg, 0.898 mmol), HOBt (281 mg, 1.79 mmol), and EDC·HCl (344 mg, 1.80 mmol) were added and the

reaction was stirred at rt for 2 d. The mixture was poured into water (40 mL) and extracted with CH_2Cl_2 (3 × 20 mL), and then the combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 40% to 90% EtOAc in pentane as eluant), which gave the title compound (657 mg, 0.809 mmol, 90%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.2 Hz, 2H), 7.57 (d, J = 7.2 Hz, 2H), 7.50 (d, J = 6.4 Hz, 1H), 7.40 (t, J = 7.2 Hz, 2H), 7.30−7.12 (m, 23H), 6.37 (d, J = 8.0 Hz, 1H), 5.74−5.79 (m, 1H), 4.55−4.51 (m, 1H), 4.32−4.17 (m, 5H), 3.89 (dt, J = 9.6, 7.2 Hz, 1H), 3.80 (dt, J = 9.2, 7.6 Hz, 1H), 3.14 (dd, J = 14.0, 5.6 Hz, 1H), 2.99 (br d, J = 14.4 Hz, 1H), 2.83 (dd, J = 13.2, 8.4 Hz, 1H), 2.66 (dd, J = 15.2, 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.6, 171.0, 170.5, 156.3, 153.1, 144.4 (3C), 143.9 (2C), 141.3 (2C), 135.8, 129.4 (2C), 128.8 (8C), 128.6 (2C), 128.1 (6C), 127.8 (2C), 127.2 (5C), 125.3, 120.1 (2C), 71.0, 67.4, 62.5, 53.6, 51.2, 47.2, 42.6, 38.4, 37.4. HRMS $C_{50}H_{44}N_4O_7$ [M + Na^+] calcd 835.3102, found 835.3116.

Butyl (*S*)-5-[(*S*)-2-{[(9*H*-Fluoren-9-yl)methoxy]carbonyl}-4-oxo-4-(triphenylmethylamino)butanamido]-4-oxo-6-phenylhexanoate (4): General Method for the SmI_2-Promoted Coupling of *N*-Peptidyl Oxazolidinones with Acrylates and Acrylonitrile. The oxazolidinone **2** (203 mg, 0.25 mmol) and *n*-butyl acrylate (128 mg, 1.00 mmol) were dissolved in THF (5 mL) and then water (36 μL, 2.00 mmol) was added. The mixture was cooled to −78 °C under a strict argon atmosphere, before a solution of SmI_2 (0.1 M in THF, 10 mL, 1.00 mmol)[15] was added dropwise over 30 min. The solution was stirred at −78 °C for 18 h, and then the flask was flushed with O_2 to quench excess SmI_2. The mixture was poured into sat aq $Na_2S_2O_3$ (40 mL) and extracted with EtOAc (3 × 20 mL). The combined organic portions were dried over $MgSO_4$, filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 10% to 60% EtOAc in pentane as eluant), which gave the title compound (118 mg, 0.138 mmol, 55%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 7.6 Hz, 2H), 7.45−7.37 (m, 3H), 7.34−7.10 (m, 22H), 7.06 (br s, 1H), 6.37 (d, J = 7.6 Hz, 1H), 4.67 (q, J = 6.8 Hz, 1H), 4.59−4.51 (m, 1H), 4.39−4.28 (m, 2H), 4.18 (t, J = 6.8 Hz, 1H), 4.06 (t, J = 6.8 Hz, 2H), 3.10−2.97 (m, 2H), 2.89 (dd, J = 14.0, 7.2 Hz, 1H), 2.72−2.60 (m, 3H), 2.60−2.48 (m, 2H), 1.60 (quin, J = 6.8 Hz, 2H), 1.37 (hex, J = 7.2 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 206.6, 172.6, 170.9, 170.4, 156.3, 144.4 (2C), 143.8, 143.8, 141.3, 136.3, 129.2 (2C), 128.8 (10C), 128.1 (6C), 127.8 (2C), 127.2 (5C), 127.1, 125.2 (2C), 120.1 (2C), 70.9, 67.4, 64.7, 59.8, 51.3, 47.1, 38.2, 36.9, 35.3, 30.7, 27.8, 19.2, 13.8. HRMS $C_{54}H_{53}N_3O_7$ [M + Na^+] calcd 878.3776, found 878.3703.

(9*H*-Fluoren-9-yl)methyl (*S*)-1-[(*S*)-6-(1,1-Dimethylethan-1-ylamino)-3,6-dioxo-1-phenylhexan-2-ylamino]-1,4-dioxo-4-(triphenylmethylamino)butan-2-ylcarbamate (3): General Method for the SmI_2-Promoted Coupling of *N*-Peptidyl Oxazolidinones with Acrylamides. The oxazolidinone **2** (102 mg, 0.125 mmol) and *N-tert*-butyl acrylamide (11 mg, 0.083 mmol) were dissolved in THF (3 mL) and then water (18 μL, 1.00 mmol) was added. The mixture was cooled to −78 °C under a strict argon atmosphere, before a solution of SmI_2 (0.1 M solution in THF, 5 mL, 0.50 mmol)[15] was added dropwise over 30 min. The solution was stirred at −78 °C for 2 d and then the flask was flushed with O_2 to quench excess SmI_2, before sat aq NH_4Cl (2.5 mL) was added. The mixture was allowed to warm to rt and then poured into 0.5 M HCl (20 mL). The mixture was extracted with EtOAc (3 × 15 mL), then the combined organic portions were washed with sat aq $Na_2S_2O_3$ (10 mL), dried over $MgSO_4$, filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (increasing polarity from 10% to 60% EtOAc in CH_2Cl_2 as eluant), which gave the title compound (60 mg, 0.071 mmol, 85%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.2 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.2 Hz, 3H), 7.29−7.06 (m, 22H), 6.95 (br s, 1H), 6.30 (d, J = 6.4 Hz, 1H), 5.36 (br s, 1H), 4.61 (q, J = 6.8 Hz, 1H), 4.53−4.48 (m, 1H), 4.35−4.27 (m, 2H), 4.16 (t, J = 7.6 Hz, 1H), 3.06−2.97 (m, 2H), 2.82 (dd, J = 14.0, 7.6 Hz, 1H), 2.73−2.62 (m, 3H), 2.33−2.24 (m, 2H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 207.5, 170.9, 170.8, 170.5, 156.4, 144.4 (3C), 143.9, 143.8, 141.4 (2C), 136.2, 129.3 (2C), 128.8 (6C), 128.8 (2C), 128.1 (6C), 127.9 (2C), 127.3 (5C), 127.1, 125.3 (2C), 120.1 (2C), 71.0, 67.5, 59.9, 51.3 (2C), 47.2, 38.3, 36.9, 35.7, 30.7, 28.9 (3C). HRMS $C_{54}H_{54}N_4O_6$ [M + Na^+] calcd 877.3936, found 877.3946.

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Supporting Information Available: Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1**−**29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Samarium(II) diiodide was prepared according to a literature procedure. Girard, P.; Namy, J.-L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.