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Expanding the Scope of the Acyl-Type Radical Addition Reactions Promoted by SmI_2

Jakob Karaffa, Karl B. Lindsay, 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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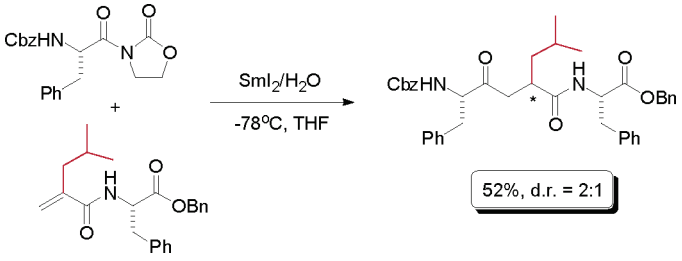

N-Acyl oxazolidinones of simple carboxylic acids and amino acids were observed to undergo successful SmI_2-promoted couplings with substituted acrylamides and acrylates, affording a variety of functionalized γ-ketoamides and -esters with yields attaining 85%. As many of these reductive couplings were previously found to be ineffective employing the corresponding 4-pyridylthio esters, the applicability of this methodology has been substantially improved. The methodology has been adapted to prepare structures related to two potent aspartate protease inhibitors, the renin inhibitor aliskiren, and the γ-secretase inhibitor L-685,458. Finally, a convenient two-step procedure for the preparation of *N*-acyl oxazolidinones of *N*-protected amino acids, which provides consistently good yields of the corresponding imide, has been devised.

Introduction

In 2003, we disclosed the ability of thiopyridyl esters of amino acids to participate in a SmI_2-promoted radical addition to acrylamides and acrylates, providing a convenient route to the corresponding γ-keto ester/amides.[1,2] Some of these structures revealed a close similarity to a class of important aspartate protease inhibitors containing a hydroxyethylene dipeptide isostere.[3] Unfortunately, this methodology proved to be quite sensitive to the substitution pattern of both the radical donor and the radical acceptor, as attempts to expand this reaction to either (a) α-substituted acrylates or acrylamides,[4] (b) thioesters of amino acids containing sterically demanding side chains (e.g., valine) or an *N*-Boc protecting group,[2b] or (c) thiopyridyl esters of carboxylic acids other than amino acids were all met with limited success (Scheme 1).[5] A solution to the latter problem was found when the acyl thioester unit was exchanged with an *N*-acyl oxazolidinone, and the SmI_2-promoted coupling reactions were run in the presence of H_2O.[6,7] In this way, a series of radical addition reactions were performed successfully with a wide variety of *N*-acyl substituents.

In this paper, we report on the use of *N*-acyl oxazolidinones as a viable solution for promoting acyl-like radical couplings[8] with both problematic amino acids and α-substituted acrylates and acrylamides. This methodology is applied to prepare

(1) Blakskjær, P.; Høj, B.; Riber, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2003**, *125*, 4030.

(2) See also: (a) Mikkelsen, L. M.; Jensen, C. M.; Høj, B.; Blakskjær, P.; Skrydstrup, T. *Tetrahedron* **2003**, *59*, 10541. (b) Jensen, C. M.; Lindsay, K. B.; Andreasen, P.; Skrydstrup, T. *J. Org. Chem.* **2005**, *70*, 7512.

(3) (a) Leung, D.; Abbenante, G.; Fairlie, D. P. *J. Med. Chem.* **2000**, *43*, 305. (b) Bursavich, M. G.; Rich, D. H. *J. Med. Chem.* **2002**, *45*, 541.

(4) Lindsay, K. B.; Skrydstrup, T. *J. Org Chem.* **2006**, *71*, 4766.

(5) Blakskjær, P.; Høj, B.; Skrydstrup, T. Unpublished results.

(6) (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.

(7) 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.

(8) For a comprehensive review on acyl radical chemistry, see: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

10.1021/jo061299s CCC: $33.50
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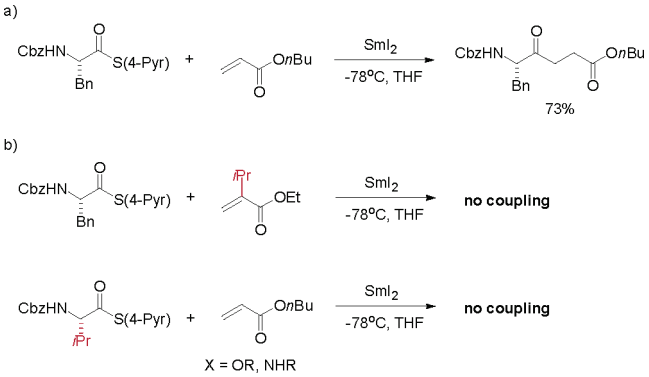
SCHEME 1. Examples of Successful (a) and Unsuccessful (b) Acyl-like Radical Addition Reactions with Thiopyridyl Esters



structures related to two potent aspartate protease inhibitors, namely, aliskiren[9] and L-685,458,[10] as depicted in Figure 1. In addition, we disclose a convenient two-step procedure for the preparation of *N*-acyl oxazolidinones of *N*-protected amino acids, which provides consistently good yields of the corresponding imide.

Results and Discussion

Table 1 summarizes reactions carried out with simple *N*-acyl oxazolidinones in the presence of α- and *β*-substituted acrylates and acrylamides.[11] When 1 equiv of α-substituted acrylamide and 1.5 equiv of the *N*-acyl oxazolidinone were reacted at −78 °C with samarium diiodide (4 equiv) in the presence of water (8 equiv, entries 1, 3, 5, and 6) for 20 h, good yields of the *γ*-keto amides **1**, **3**, **5**, and **6** were obtained. A slight excess of the oxazolidinone was desirable, as separation of the starting acrylamide and product was frequently not possible. Particularly noteworthy is the successful result obtained for the example in entry 6, as previous attempts to couple the thiopyridyl ester of Cbz-protected phenylalanine to the same acrylamide were nonrewarding.[4] α-Substituted acrylates (entries 2 and 4) were also well tolerated by the reaction providing **2** and **4** in acceptable yields; however, in these cases, excess acrylate was used (2 equiv), as product separation was not an issue, and the reaction was run at −40 °C to ensure good conversion. It was interesting to note that *β*-methyl acrylates can be applied to these C−C bond forming reactions, but only in less hindered cases. For example, the reaction of ethyl crotonate with the *N*-phenylacetyl oxazolidinone provided the ketone **7** in satisfactory yield (entry 7); however, when the *N*-pivaloyl oxazolidinone was applied under identical conditions (entry 8), there was no detectable product formation.

With the successful initial results using simple substrates, we next turned our attention to amino acid substrates, in keeping with an interest within the group to prepare hydroxyethylene dipeptide isosteres.[2b,4,12] Prior to beginning this study, we required an efficient method for accessing *N*-acyl oxazolidinones directly from *N*-protected amino acids, as existing methods were incompatible, such as the use of acid chlorides as earlier employed for the preparation of simpler oxazolidinone substrates.[6] Our initial approach to these oxazolidinones encompassed the reaction between the pivaloyl-mixed anhydride of Cbz-protected phenylalanine **8** and the *N*-lithiated derivative of 2-oxazolidinone as shown in Table 2 (entry 1).[13] There were several major impediments to this reaction that contributed to the low yields of **17** (20−40%). The lithium salt of 2-oxazolidinone is not soluble in THF at either −78 °C or at room temperature and, therefore, was only poorly reactive to electrophiles. The anhydride electrophile has two possible sites of attack, and indeed, both Cbz−Phe−OH and the pivaloyl derivative of 2-oxazolidinone were detectable in the product mixture. Alternative methods for activating the carboxylic acid were also examined, as shown in entries 2 and 3, although without any progress. A clear improvement was found when using $AlMe_3$ to activate the 2-oxazolidinone, as the resulting aluminum salt was highly soluble in organic solvents and strongly nucleophilic. When this was used with the pivaloyl mixed anhydride **8**, a much cleaner reaction was observed (entry 4); however, the yield remained modest (30%). Other activated (and one nonactivated) esters were, therefore, tried in order to

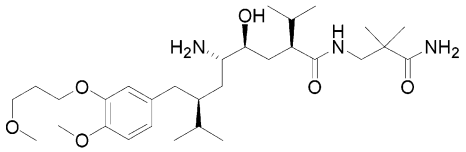
(9) Rahuel, J.; Rasetti, V.; Maibaum, J.; Rueger, H.; Goschke, R.; Cohen, N. C.; Stutz, S.; Cumin, F.; Fuhrer, W.; Wood, J. M.; Grutter, M. G. *Chem. Biol.* **2000**, *7*, 493.

(10) Wolfe, M. S. *J. Med. Chem.* **2001**, *44*, 2039.

(11) α-Substituted acrylates were prepared according to: Lee, H. S.; Park, J. S.; Kim, B. M.; Gellman, S. H. *J. Org. Chem.* **2003**, *68*, 1575. These were transformed into the corresponding acrylamides via standard methods.

(12) For some examples on the synthesis and application of other hydroxyethylene isosteres for the inhibition of a variety of proteases, see ref 19 and: (a) Holladay, M. W.; Rich, D. H. *Tetrahedron Lett.* **1983**, *24*, 4401. (b) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615. (c) Bradbury, R. H.; Major, J. S.; Oldham, A. A.; Rivett, J. E.; Roberts, D. A.; Slater, A. M.; Timms, D.; Waterson, D. *J. Med. Chem.* **1990**, *33*, 2335. (d) Poss, M. A.; Reid, J. A. *Tetrahedron Lett.* **1992**, *33*, 1411. (e) Baker, W. R.; Pratt, J. K. *Tetrahedron* **1993**, *49*, 8739. (f) Myers, A. G.; Barbay, J. K.; Zhong, B. *J. Am. Chem. Soc.* **2001**, *123*, 7207. (g) Ghosh, A. K.; Shin, D.; Downs, D.; Koelsch, G.; Lin, X.; Ermolieff, J.; Tang, J. *J. Am. Chem. Soc.* **2000**, *122*, 3522. (h) Brewer M.; Rich, D. H. *Org. Lett.* **2001**, *3*, 945. (i) Nadin, A.; Sánchez Lopéz, J. M.; Neduvelil, J. G.; Thomas, S. R. *Tetrahedron* **2001**, *57*, 1861. (j) Tossi, A.; Benedetti, F.; Norbedo, S.; Skrbec, D.; Berti, F.; Romeo, D. *Bioorg. Med. Chem.* **2003**, *11*, 4719. (k) Brewer M.; James, C. A.; Rich, D. H. *Org. Lett.* **2004**, *6*, 4779. (l) Haug, B. E.; Rich, D. H. *Org. Lett.* **2004**, *6*, 4783. (m) Hom, R. K.; Gailunas, A. F.; Mamo, S.; Fang, L. Y.; Tung, J. S.; Walker, D. E.; Davis, D.; Thorsett, E. D.; Jewett, N. E.; Moon, J. B.; John, V. *J. Med. Chem.* **2004**, *47*, 158. (n) Våbenø, J.; Lejon, T.; Nielsen, C. U.; Steffansen, B.; Chen, W.; Ouyang, H.; Borchardt, R. T.; Luthman, K. *J. Med. Chem.* **2004**, *47*, 1060. (o) Brady, S. F.; Singh, S.; Crouthamel, M.-C.; Holloway, M. K.; Coburn, C. A.; Garsky, V. M.; Bogusky, M.; Pennington, M. W.; Vacca, J. P.; Hazuda, D.; Lai, M.-T. *Bioorg. Med. Chem.* **2004**, *14*, 601. (p) Hanessian, S.; Hou, Y.; Bayrakdarian, M.; Tintelnot-Blomely, M. *J. Org. Chem.* **2005**, *70*, 6735. (q) Hanessian, S.; Yun, H.; Hou, Y.; Tintelnot-Blomely, M. *J. Org. Chem.* **2005**, *70*, 6746. (r) Hanessian, S.; Yun, H.; Hou, Y.; Yang, G.; Bayrakdarian, M.; Therrien, E.; Moitessier, N.; Roggo, S.; Veenstra, S.; Tintelnot-Blomely, M.; Rondeau, J.-M.; Ostermeier, C.; Strauss, A.; Ramage, P.; Paganetti, P.; Neumann, U.; Betschart, C. *J. Med. Chem.* **2005**, *48*, 5175. (s) Specker, E.; Böttcher, J.; Heine, A.; Sotriffer, C. A.; Lilie, H.; Schoop, A.; Müller, G.; Griebenow, N.; Klebe, G. *J. Med. Chem.* **2005**, *48*, 6607.

(13) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.



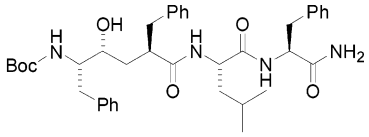


FIGURE 1. Structures of two potent aspartate protease inhibitors.

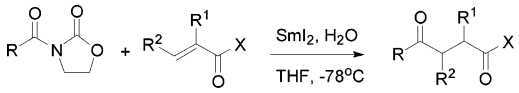
further improve the reaction. While the Weinreb amide **10** (entry 5) and methyl ester **11** (entry 6) were completely unreactive toward the aluminum salt, both the pentafluorophenol (PFP) ester **12** (entry 7) and the 4-mercaptopyridine thioester **13** (entry 8) gave smooth (albeit slow) conversions to the desired oxazolidinone **17** after 2 days (81% yield in both cases). Subjection of the PFP esters of other amino acids, as illustrated in entries 9−11, to the same conditions also afforded the desired oxazolidinones **18**−**20** of Boc-Phe (83%), Boc-Leu (73%), and Cbz-Val (62%), respectively. It was noted, however, that excessively prolonged reaction times can result in carbamate cleavage when using Cbz-protected amino acids, and we, therefore, recommend either tracking the reaction closely by TLC or the use of Boc-protected amino acids.

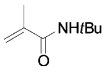
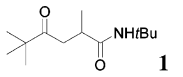
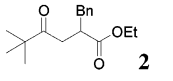
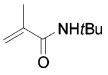
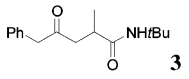
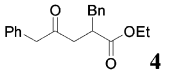
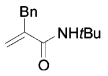
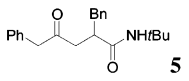
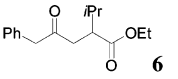
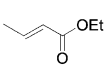
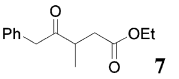
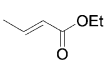
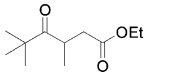
Further work was then carried out to examine the suitability of the oxazolidinones derived from amino acids as coupling partners with the α,*β*-unsaturated esters and amides. As can be seen in Table 3, these compounds react in a well-behaved manner with α-substituted acrylamides (entries 1, 2, and 6) and acrylates (entries 3, 4, 5, 7, 8, and 9) when using the standard coupling conditions described above. The olefin substituents examined were methyl, isopropyl, isobutyl, and benzyl, intended to mimic the amino acids alanine, valine, leucine, and phenylalanine, respectively. Earlier, we had observed that the 4-thiopyridine esters of Boc-protected amino acids were less reactive in the addition reactions compared to their Cbz-counterparts.[1,2] As illustrated in entries 4, 5, and 7, the *N*-acyl oxazolidinone derivates of the Boc-protected amino acids were just as effective as the Cbz-derivatives as coupling partners. The dipeptide mimic **25** prepared by the coupling of the Boc-phenylalanine derivative **17** to ethyl α-benzyl acrylate (entry 5) represents a key fragment of the potent *γ*-secretase inhibitor, L-685,458.[10]

Selectivities in these reactions were nevertheless generally low (as determined by ^{1}H NMR of the isolated products), with the exception of entry 2, where a 5:1 ratio of isomers **22** was observed. The lack of selectivity is not unexpected when considering the fact that the configuration about this center is expected to arise upon protonation of the surmised samarium enolate intermediate with water. Attempts to influence this selectivity with bulky chiral proton sources complexed to the divalent lanthanide reagent under anhydrous conditions as previously reported by Takeuchi and Mikami[14] were unsuccessful. Finally, it is interesting to note the good reactivity exhibited by the Cbz-valine derivative **20** when coupled to two α-substituted acrylates (entries 8 and 10). In both cases, a 69% yield of the *γ*-keto esters **28** and **30** was obtained along with unreacted starting materials, which could be recovered almost quantitatively. In contrast, performing a similar reaction with the corresponding 4-thiopyridyl derivative led to none of the desired coupling product.[2b]

(14) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Yamaoka, M.; Yoshida, A.; Mikami, K. *Tetrahedron* **1999**, *55*, 4595.

TABLE 1. SmI_2-Promoted Coupling of *N*-Acyl Oxazolidinones with α- and *β*-Substituted Acrylates and Acrylamides

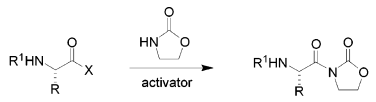


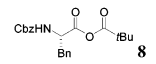
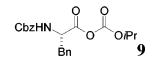
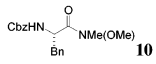
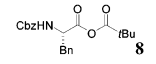
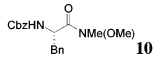
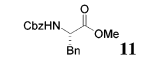
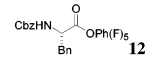
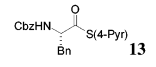
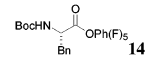
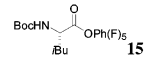
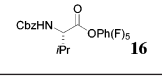
entry	R	Olefin	Product	Yield[a]
1	*t*Bu		 **1**	63 %
2	*t*Bu		 **2**	60 %
3	$PhCH_2$		 **3**	60 %[b]
4	$PhCH_2$		 **4**	65 %
5	$PhCH_2$		 **5**	44 %
6	$PhCH_2$		 **6**	55 %
7	$PhCH_2$		 **7**	60 %
8	*t*Bu			0 %

[a] All yields are based on chromatographically pure compounds. [b] Yield calculated from ^{1}H NMR of an inseparable mixture of product and starting oxazolidinone.

Our recent interest in the total synthesis of aliskiren[4] prompted a short study regarding the applicability of the above reactions to its synthesis. Earlier work in a model study had revealed the inability of the 4-thiopyridine ester of Cbz-phenylalanine to couple to ethyl α-isopropyl acrylate, forcing us to choose an alternative, but longer, route for the introduction of the isopropyl side chain.[4] However, the successful coupling noted between the *N*-acyl oxazoldinone **17** and the same acrylate (Table 3, entry 9) encouraged us to examine this protocol as a more direct

TABLE 2. *N*-Acyl Oxazolidinone Synthesis Studies



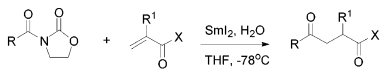
Entry	Activated amino acid	Solvent	Activator	Time	Temp.	*N*-Acyl oxazolidinone (yield)
1	 **8**	THF	*n*-BuLi	2-4 h	-78 °C	**17** (20-40 %)
2	 **9**	THF	*n*-BuLi	4 h	0 °C	**17** (<10 %)
3	 **10**	THF	*n*-BuLi	24 h	20 °C	recovered **10**
4	 **8**	CH_2Cl_2	$AlMe_3$	5 h	20 °C	**17** (33 %)
5	 **10**	CH_2Cl_2	$AlMe_3$	24 h	20 °C	recovered **10**
6	 **11**	CH_2Cl_2	$AlMe_3$	5 d	20 °C	recovered **11**
7	 **12**	CH_2Cl_2	$AlMe_3$	2 d	20 °C	**17** (81 %)
8	 **13**	CH_2Cl_2	$AlMe_3$	2 d	20 °C	**17** (81 %)
9	 **14**	CH_2Cl_2	$AlMe_3$	2 d	20 °C	**18** (83 %)
10	 **15**	CH_2Cl_2	$AlMe_3$	2 d	20 °C	**19** (73 %)
11	 **16**	CH_2Cl_2	$AlMe_3$	2 d	20 °C	**20** (62 %)

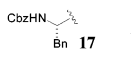
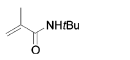
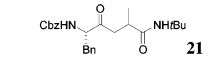
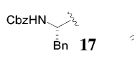
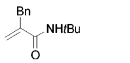
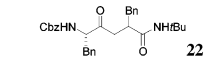
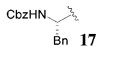
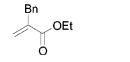
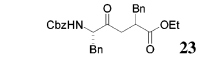
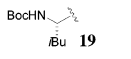
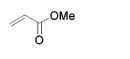
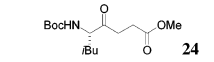
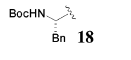
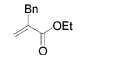
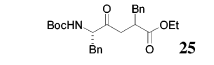
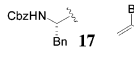
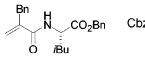
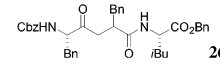
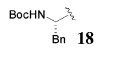
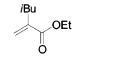
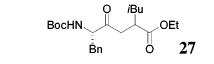
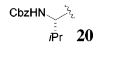
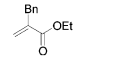
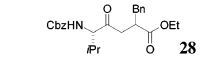
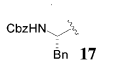
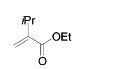
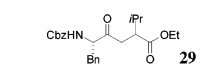
route to the renin inhibitor. Acid **31**[4,15] was first transformed into the PFP ester **32** in an excellent yield of 98% via an EDCI-promoted coupling with pentafluorophenol (Scheme 2). After purification, **32** was then reacted with 2-oxazolidinone previously treated with $AlMe_3$. Displacement of pentafluorophenoxide was slow at room temperature; however, the desired *N*-acyl oxazolidinone **33** could be obtained in good yield after 4 days without detectable α-epimerization. With the oxazolidinone in hand, the coupling reaction with ethyl α-isopropyl acrylate was finally carried out as described for the simple derivative **17** (Table 3, entry 9). To our delight, the radical reaction proceeded, affording the coupling product **34** in a 52% yield after a reaction time of 2 days (95% yield based on 43% recovered **33**). Although the diastereomeric ratio in this reaction was merely 5:4 and no attempt was made to assign the two inseparable diastereomers, this example represents a highly promising and convergent approach to the basic carbon framework of aliskiren.

(15) Goeschke, R.; Stutz, S.; Heinzelmann, W.; Maibaum, J. *Helv. Chim. Acta* **2003**, *86*, 2848.

(16) Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045.

TABLE 3. SmI_2-Promoted Coupling of Amino Acid Oxazolidinones with Substituted Acrylates and Acrylamides[a]



entry	R	Olefin	Product	Yield (d.r.)
1	 **17**		 **21**	85 % (1:1)
2	 **17**		 **22**	56 % (5:1)
3	 **17**		 **23**	71 % (2:1)
4	 **19**		 **24**	60 %
5	 **18**		 **25**	71 % (2:1)
6	 **17**		 **26**	52 % (2:1)
7	 **18**		 **27**	68 % (2:1)
8	 **20**		 **28**	69 % (2:1)
9	 **17**		 **29**	45 % (2:1)
10	**20**		**30**	69 % (2:1)

[a] All yields are based on chromatographically pure compounds.

Conclusions

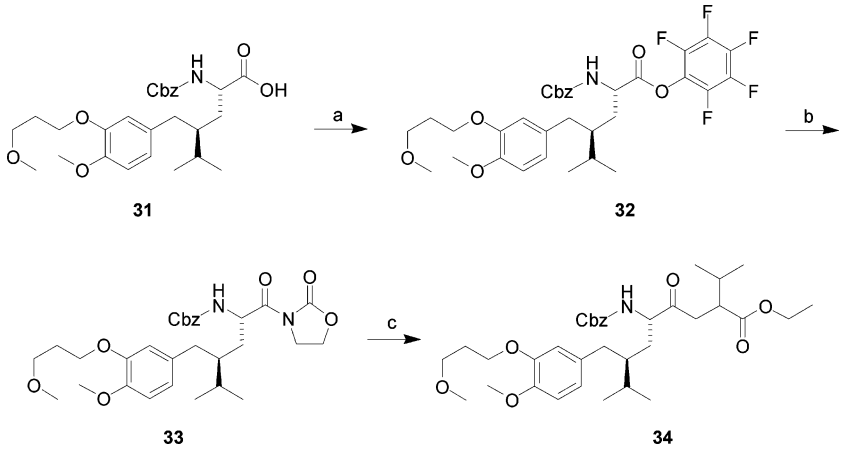
We have successfully demonstrated the suitability of both simple *N*-acyl oxazoldinones and amino acid derivates thereof to undergo SmI_2-promoted additions to substituted acrylates and acrylamides. These results expand considerably the applicability of these reactions for the synthesis of functionalized γ-keto amides and esters. Efforts are underway to improve the stereochemical issues of these radical coupling reactions with substituted acrylates and acrylamides by means of functionalized acrylates possessing chiral auxiliaries. With the known ability to stereoselectively reduce α-aminoketones to either the *syn*- or *anti*-vicinal amino alcohol in mind,[16,17] success in such studies would provide a rapid and general approach to the important class of hydroxyethylene dipeptide isosteres.

Experimental Section

***N-tert*-Butyl-2,5,5-trimethyl-4-oxohexanamide (1). General Procedure for Coupling with Acrylamides.** To a solution of 3-pivaloyloxazolidin-2-one (96 mg, 0.561 mmol, 1.5 equiv) and *N-tert*-butylmethacrylamide (53 mg, 0.375 mmol, 1 equiv) in THF (5.0 mL) was added H_2O (54 μL, 3.00 mmol, 8 equiv), and then

(17) Våbenø, J.; Brisander, M.; Lejon, T.; Luthman, K. *J. Org. Chem.* **2002**, *67*, 9186.

SCHEME 2. Potential Application to the Synthesis of Aliskiren[a]



[a] Reagents and conditions: (a) EDCI, DMAP, pentafluorophenol, 0 °C, CH_2Cl_2, 98%; (b) 2-oxazolidinone, $AlMe_3$, CH_2Cl_2, 30 min, then **32**, 20 °C, 4 days, 77%; (c) $H_2C{=}C(i\text{Pr})CO_2Et$, SmI_2, H_2O, −78 °C, THF, 52%, dr = 5:4.

the solution was cooled to −78 °C. To this a solution of SmI_2 (0.1 M, 15 mL, 1.5 mmol, 4 equiv), at room temperature (rt), was added dropwise over 1 h. The solution was left stirring at −78 °C for 24 h. Excess SmI_2 was oxidized by flushing the mixture with oxygen from a balloon. To the resulting yellow solution was added saturated NH_4Cl (4 mL) at −78 °C followed by warming to rt. HCl(aq) (1 M, 5 mL) was added followed by extraction with EtOAc (3 × 10 mL). The combined organic phases were washed with NaS_2O_3(aq) (10 mL), dried over $MgSO_4$, and then evaporated *in vacuo*. The pure product was then obtained by gradient flash chromatography on silica gel using 2−6% acetone in DCM as eluant, which gave compound **1** (54 mg, 0.238 mmol, 63%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.53 (br s, 1H), 2.93 (dd, J = 18.1, 8.7 Hz, 1H), 2.62 (m, 1H), 2.39 (dd, J = 18.1, 4.5 Hz, 1H), 1.28 (s, 9H), 1.10 (s, 9H), 1.08 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 215.4, 175.2, 51.0, 44.1, 41.5, 36.6, 28.9 (3C), 26.5 (3C), 18.0. HRMS $C_{13}H_{25}NO_2$ [M + Na^+]: calcd, 250.1783; found, 250.1779.

***N*-*tert*-Butyl-2-methyl-4-oxo-5-phenylpentanamide (3).** This was prepared using the general method for coupling with acrylamides, with 3-(2-phenylacetyl)oxazolidin-2-one (114 mg, 0.555 mmol) and *N*-*tert*-butylmethacrylamide (53 mg, 0.375 mmol). EtOAc (10%) in pentane was used as eluant for flash chromatography, which gave an inseparable 1:0.08 mixture of product **3** and starting oxazolidinone (67 mg) (mass of product 61 mg, 0.232 mmol, 62%). The yield has been calculated from the ^{1}H NMR of this mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.33−7.18 (m, 5H), 5.62 (br s, 1H), 3.67 (s, 2H), 2.94 (dd, J = 18.0, 8.8 Hz, 1H), 2.65−2.60 (m, 1H), 2.42 (dd, J = 18.0, 4.5 Hz, 1H), 1.10 (s, 9H), 1.07 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 207.8, 175.0, 134.1, 129.6 (2C), 128.9 (2C), 127.2, 51.2, 50.5, 46.2, 36.8, 28.9 (3C), 18.0. HRMS $C_{16}H_{23}NO_2$ [M + Na^+]: calcd, 284.1626; found, 284.1626.

***N*-*tert*-Butyl-2-benzyl-4-oxo-5-phenylpentanamide (5).** This was prepared using the general method for coupling with acrylamides, with 3-(2-phenylacetyl)oxazolidin-2-one (114 mg, 0.555 mmol) and 2-benzyl-*N*-*tert*-butylacrylamide (82 mg, 0.377 mmol). EtOAc (15%) in pentane was used as eluant for flash chromatography, which gave compound **5** (56 mg, 0.166 mmol, 44%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31−7.13 (m, 5H), 5.09 (br s, 1H), 3.67 (s, 2H), 3.01 (dd, J = 17.9, 8.6 Hz, 1H), 2.81−2.71 (m, 2H), 2.63 (dd, J = 11.9, 5.1 Hz, 1H), 2.49 (dd, J = 17.9, 3.9 Hz, 1H), 1.13 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 207.5, 173.0, 139.4, 134.1, 129.6 (2C), 129.3 (2C), 128.9 (2C), 128.6 (2C), 127.2, 126.6, 51.1, 50.5, 44.9, 44.5, 38.8, 28.7 (3C). HRMS $C_{22}H_{27}NO_2$ [M + Na^+]: calcd, 360.1939; found, 360.1938.

Benzyl (2*S*)-5-(*tert*-Butylcarbamoyl)-3-oxo-1-phenylhexan-2-ylcarbamate (21). This was prepared using the general method for coupling with acrylamides, with oxazolidinone **17** (206 mg, 0.559 mmol) and *N*-*tert*-butylmethacrylamide (53 mg, 0.375 mmol). EtOAc (10%) in pentane was used as eluant for flash chromatography, which gave compound **21** (135 mg, 0.318 mmol, 85%) as a colorless solid and recovered acrylamide. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35−7.10 (m, 10H), 5.50 (br s, 1H), 5.27 (br s, 1H), 5.06−5.00 (m, 2H), 4.57−4.52 (m, 1H), 3.20−2.28 (m, 5H), 1.32 (s, 9H), 1.12 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 207.8, 174.7, 156.0, 136.0, 136.4, 129.6 (2C), 129.4 (2C), 129.3 (2C), 128.8 (2C), 128.2, 127.2, 68.1, 67.0, 51.1, 44.2, 37.5, 36.8, 28.9 (3C), 18.4. HRMS $C_{25}H_{32}N_2O_4$ [M + Na^+]: calcd, 447.2260; found, 447.2273.

Benzyl (2*S*)-5-(*tert*-Butylcarbamoyl)-3-oxo-1,6-diphenylhexan-2-ylcarbamate (22). This was prepared using the general method for coupling with acrylamides, with oxazolidinone **17** (206 mg, 0.559 mmol) and 2-benzyl-*N*-*tert*-butylacrylamide (81 mg, 0.373 mmol). EtOAc (increasing polarity, 10 to 20%) in pentane was used as eluant for flash chromatography, which gave compound **22** (105 mg, 0.210 mmol, 56%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *major isomer* 7.36−7.05 (m, 15H), 5.35 (br s, 1H), 5.27 (br s, 1H), 4.58−4.51 (m, 1H), 3.22−2.40 (m, 7H), 1.17 (s, 9H); *minor isomer inter alia* 2.42 (dd, J = 17.9, 3.3 Hz, 1H), 1.13 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) *major isomer* 207.5, 172.8, 156.0, 139.2, 136.4, 135.9, 129.6 (2C), 129.4 (2C), 129.3 (2C), 128.8 (2C), 128.7 (2C), 128.5 (2C), 127.3, 127.2, 126.8, 67.1, 60.5, 51.2, 44.7, 42.8, 39.2, 36.9, 28.7 (3C); *minor isomer inter alia* 136.4, 61.1, 45.0. HRMS $C_{31}H_{36}N_2O_4$ [M + Na^+]: calcd, 523.2573; found, 523.2571.

Benzyl 2-(2-Benzyl-5-(benzyloxycarbonylamino)-4-oxo-6-phenylhexanamido)-4-methylpentanoate (26). This was prepared using the general method for coupling with acrylamides, with oxazolidinone **17** (276 mg, 0.75 mmol) and (S)-benzyl 2-(2-benzylacrylamido)-3-phenylpropanoate (137 mg, 0.375 mmol). EtOAc (30%) in pentane was used as eluant for column chromatography, which gave compound **26** (126 mg, 0.195 mmol, 52%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39−7.05 (m, 21H), 5.96 (d, J = 7.1 Hz, 1H), 5.12 (s, 2H), 5.03 (s, 2H), 4.62−4.45 (m, 2H), 3.15−2.46 (m, 7H), 1.61−1.15 (m, 3H), 0.90−0.86 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) *major isomer* 203.3, 169.6, 168.6, 151.9, 134.7, 132.4, 132.0, 131.7, 125.5 (2C), 125.2 (2C), 124.9 (2C), 124.8 (2C), 124.6 (2C), 124.5 (2C), 124.4 (2C), 124.3 (2C), 123.2 (2C), 122.9 (2C), 63.2, 63.1 (2C), 55.5, 47.1, 39.6, 37.8, 34.6, 33.3, 20.9, 19.0, 18.2; *minor isomer*

inter alia 203.6, 169.9, 168.8, 152.1, 56.8, 39.8, 38.7, 38.3, 37.7, 34.4, 33.5. HRMS $C_{40}H_{44}N_2O_6$ [M + Na^+]: calcd, 671.3097; found, 671.3099.

Ethyl 2-Benzyl-5,5-dimethyl-4-oxohexanoate (2). General Procedure for Coupling with Acrylates. To a solution of 3-pivaloyloxazolidin-2-one (64 mg, 0.374 mmol, 1 equiv) and ethyl 2-benzylacrylate (143 mg, 0.752 mmol, 2 equiv) in THF (5.0 mL) was added H_2O (54 μL, 3.00 mmol, 8 equiv), and then the solution was cooled to −40 °C. To this a solution of SmI_2 (0.1 M, 15.0 mL, 1.50 mmol, 4 equiv), at rt, was added dropwise over 1 h. The solution was left stirring at −40 °C for 24 h. Excess SmI_2 was oxidized by flushing the mixture with oxygen from a balloon. To the resulting yellow solution was added saturated NH_4Cl (4 mL) at −40 °C followed by warming to rt. HCl(aq) (1 M, 5 mL) was added followed by extraction with EtOAc (3 × 10 mL). The combined organic phases were washed with NaS_2O_3(aq) (10 mL), dried over $MgSO_4$, and then evaporated *in vacuo*. The pure product was then obtained by gradient flash chromatography on silica gel using 10% EtOAc in pentane as eluant, which gave compound **2** (62 mg, 0.224 mmol, 60%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.29−7.14 (m, 5H), 4.07 (q, J = 7.1 Hz, 2H), 3.15−3.09 (m, 1H), 2.99 (dd, J = 13.5, 6.7 Hz, 1H), 2.92 (dd, J = 18.1, 8.9 Hz, 1H), 2.72 (dd, J = 13.5, 8.2 Hz, 1H), 2.51 (dd, J = 18.1, 4.5 Hz, 1H), 1.15 (t, J = 7.1 Hz, 3H), 1.09 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 214.1, 175.1, 138.9, 129.1 (2C), 128.6 (2C), 126.7, 60.7, 44.1, 42.2, 38.0, 26.6 (3C), 14.2. HRMS $C_{17}H_{24}O_3$ [M + Na^+]: calcd, 299.1623; found, 299.1631.

Ethyl 2-Benzyl-4-oxo-5-phenylpentanoate (4). This was prepared using the general method for coupling with acrylates, with 3-(2-phenylacetyl)oxazolidin-2-one (77 mg, 0.375 mmol) and ethyl 2-benzylacrylate (143 mg, 0.752 mmol). EtOAc (increasing polarity, 5 to 8%) in pentane was used as eluant for flash chromatography, which gave compound **4** (76 mg, 0.245 mmol, 65%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34−7.09 (m, 10H), 4.06 (q, J = 7.1 Hz, 2H), 3.64 (s, 2H), 3.66−3.18 (m, 1H), 2.96 (dd, J = 13.5, 6.5 Hz, 1H), 2.85 (dd, J = 18.0, 8.8 Hz, 1H), 2.70 (dd, J = 13.5, 8.3 Hz, 1H), 2.48 (dd, J = 18.0, 4.7 Hz, 1H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 206.4, 174.7, 138.6, 134.1, 129.6, 129.2 (2C), 128.9 (2C), 128.6 (2C), 127.2 (2C), 126.8, 60.8, 50.2, 42.8, 42.2, 37.8, 14.2. HRMS $C_{20}H_{22}O_3$ [M + Na^+]: calcd, 333.1467; found, 333.1469.

Ethyl 2-Isopropyl-4-oxo-5-phenylpentanoate (6). This was prepared using the general method for coupling with acrylates, with 3-(2-phenylacetyl)oxazolidin-2-one (77 mg, 0.375 mmol) and ethyl 3-methyl-2-methylenebutanoate (106 mg, 0.745 mmol). EtOAc (increasing polarity, 5 to 8%) in pentane was used as eluant for flash chromatography, which gave compound **6** (54 mg, 0.206 mmol, 55%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34−7.18 (m, 5H), 4.11 (q, J = 7.1 Hz, 2H), 3.72 (s, 2H), 2.93 (dd, J = 17.6, 10.5 Hz, 1H), 2.75 (dd, J = 5.3, 3.5 Hz, 1H), 2.44 (dd, J = 17.6, 3.5 Hz, 1H), 1.95−1.91 (m, 1H), 1.22 (t, J = 7.1 Hz, 3H), 0.87 (dd, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 207.1, 174.7, 134.3, 129.6 (2C), 128.9 (2C), 127.2, 60.5, 50.3, 46.5, 40.6, 30.1, 20.2, 19.8, 14.4. HRMS $C_{16}H_{22}O_3$ [M + Na^+]: calcd, 285.1467; found, 285.1468.

Ethyl 3-Methyl-4-oxo-5-phenylpentanoate (7). This was prepared using the general method for coupling with acrylates, with 3-(2-phenylacetyl)oxazolidin-2-one (77 mg, 0.375 mmol) and (*E*)-ethyl but-2-enoate (86 mg, 0.753 mmol). EtOAc (10%) in pentane was used as eluant for column chromatography, which gave compound **7** (53 mg, 0.226 mmol, 60%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34−7.18 (m, 5H), 4.10 (q, J = 7.1 Hz, 2H), 3.70 (s, 2H), 2.92−2.89 (m, 2H), 2.50−2.45 (m, 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.12 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 206.4, 175.8, 134.2, 129.6 (2C), 128.9 (2C), 127.2, 60.7, 50.4, 45.2, 35.0, 17.2, 14.3. HRMS $C_{14}H_{18}O_3$ [M + Na^+]: calcd, 257.1154; found, 257.1158.

Benzyl (2*S*)-5-(Ethoxycarbonyl)-3-oxo-1,6-diphenylhexan-2-ylcarbamate (23). This was prepared using the general method for coupling with acrylates, with oxazolidinone **17** (138 mg, 0.375 mmol) and ethyl 2-benzylacrylate (143 mg, 0.752 mmol). EtOAc (10%) in pentane was used as eluant for column chromatography, which gave compound **23** (126 mg, 0.266 mmol, 71%) as a colorless solid and recovered **17** (37 mg, 0.101 mmol, 27%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *major isomer* 7.35−7.01 (m, 15H), 5.24 (d, J = 7.2 Hz, 1H), 5.05 (s, 2H), 4.51−4.43 (m, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.16−2.32 (m, 7H), 1.18 (t, J = 7.1 Hz, 3H); *minor isomer inter alia* 5.32 (d, J = 7.5 Hz, 1H), 5.12 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) *major isomer* 207.0, 174.5, 155.9, 138.4, 136.5, 136.1, 129.5 (2C), 129.3 (2C), 129.2 (2C), 128.8 (2C), 128.7 (2C), 128.3 (2C), 128.2, 127.2, 126.9, 67.1, 60.9, 60.6, 42.2, 41.5, 41.3, 37.9, 37.4, 14.3; *minor isomer inter alia* 206.6, 67.7, 60.5, 41.9, 41.5, 41.3, 37.8. HRMS $C_{29}H_{31}NO_5$ [M + Na^+]: calcd, 496.2100; found, 496.2094.

Ethyl (2*S*)-5-(*tert*-Butoxycarbonyl)-7-methyl-4-oxooctanoate (24). This was prepared using the general method for coupling with acrylates, with oxazolidinone **19** (108 mg, 0.375 mmol) and methyl acrylate (65 mg, 0.755 mmol). EtOAc (10−50%) in pentane was used as eluant for column chromatography, which gave compound **24** (68 mg, 0.226 mmol, 60%) as an oil and recovered **19** (51 mg, 0.177 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.98 (d, J = 8.4 Hz, 1H), 4.29 (ddd, J = 10.0, 8.0, 4.4 Hz, 1H), 3.64 (s, 3H), 2.88 (dt, J = 18.8, 6.8 Hz, 1H), 2.77 (dt, J = 18.4, 6.0 Hz, 1H), 2.52−2.69 (m, 2H), 1.54−1.77 (m, 2H), 1.43 (s, 9H), 1.35 (ddd, J = 14.4, 10.0, 4.8 Hz, 1H), 0.96 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 208.6, 177.0, 155.6, 79.7, 57.7, 51.8, 40.4, 34.2, 28.2, 27.4, 24.8, 23.2, 21.6. HRMS $C_{15}H_{27}NO_5$ [M + Na^+]: calcd, 324.1786; found, 324.1787.

***tert*-Butyl (2*S*)-5-(Ethoxycarbonyl)-3-oxo-1,6-diphenylhexan-2-ylcarbamate (25).** This was prepared using the general method for coupling with acrylates, with oxazolidinone **18** (125 mg, 0.374 mmol) and ethyl 2-benzylacrylate (143 mg, 0.752 mmol). EtOAc (10%) in pentane was used as eluant for column chromatography, which gave compound **25** (134 mg, 0.305 mmol, 81%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *major isomer* 7.29−7.04 (m, 10H), 4.95 (d, J = 6.6 Hz, 1H), 4.48−4.44 (m, 1H), 4.13−4.05 (m, 2H), 3.18−2.31 (m, 7H), 1.36 (s, 9H), 1.19−1.17 (m, 3H); *minor isomer inter alia* 5.12 (d, J = 7.2 Hz, 1H), 2.34 (dd, J = 18.0, 4.3 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) *major isomer* 207.2, 174.6, 155.3, 138.5, 136.5, 129.5 (2C), 129.2 (2C), 128.8 (2C), 128.7 (2C), 127.1 (2C), 126.9, 80.0, 60.9, 41.9, 41.4, 38.0, 28.4 (3C), 14.3; *minor isomer inter alia* 207.6, 138.4, 136.6, 60.9, 60.5, 42.1, 41.2, 37.9. HRMS $C_{26}H_{33}NO_5$ [M + Na^+]: calcd, 462.2256; found, 462.2245.

***tert*-Butyl (2*S*)-5-(Ethoxycarbonyl)-7-methyl-3-oxo-1-phenyloctan-2-ylcarbamate (27).** This was prepared using the general method for coupling with acrylates**,** with oxazolidinone **18** (125 mg, 0.374 mmol) and ethyl 4-methyl-2-methylenepentanoate (116 mg, 0.743 mmol). EtOAc (10%) in pentane was used as eluant for column chromatography, which gave compound **27** (103 mg, 0.254 mmol, 68%) as a colorless solid and recovered **18** (24 mg, 0.072 mmol, 19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *major isomer* 7.30−7.14 (m, 5H), 5.01 (d, J = 7.7 Hz, 1H), 4.59−4.40 (m, 1H), 4.11 (q, J = 7.1 Hz, 1H), 3.16−2.30 (m, 5H), 1.58−1.49 (m, 2H), 1.37 (s, 9H), 1.23 (t, J = 7.0 Hz, 3H), 0.90 (dd, J = 21.0, 6.3 Hz, 6H); *minor isomer inter alia* 5.12 (d, J = 7.6 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (200 MHz, $CDCl_3$) δ (ppm) *major isomer* 207.5, 175.8, 155.4, 136.5, 129.5 (2C), 128.9 (2C), 127.2, 80.0, 60.7, 60.1, 42.9, 41.4, 38.2, 37.4, 28.4 (3C), 26.0, 22.5, 14.4; *minor isomer inter alia* 208.0, 136.4, 60.4, 60.1, 42.9, 41.3, 38.2, 25.9, 22.6, 22.5. HRMS $C_{23}H_{35}NO_5$ [M + Na^+]: calcd, 428.2413; found, 428.2424.

Benzyl (3*S*)-6-(Ethoxycarbonyl)-2-methyl-4-oxo-7-phenylheptan-3-ylcarbamate (28). This was prepared using the general method for coupling with acrylates, with oxazolidinone **20** (120 mg, 0.375 mmol) and ethyl 2-benzylacrylate (143 mg, 0.752 mmol). EtOAc (10%) in pentane was used as eluant for column chromatography, which gave compound **28** (110 mg, 0.259 mmol, 69%)

as a colorless solid and recovered **20** (24 mg, 0.075 mmol, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *major isomer* 7.35−7.13 (m, 10H), 5.35 (d, J = 8.2 Hz, 1H), 5.09 (s, 2H), 4.33−4.28 (m, 1H), 4.10−4.04 (m, 2H), 3.15−2.09 (m, 6H), 1.19−1.13 (m, 3H), 0.99 (dd, J = 20.6, 6.8 Hz, 3H), 0.72 (dd, J = 15.3, 6.8 Hz, 3H); *minor isomer inter alia* 5.06 (s, 2H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) *major isomer* 207.5, 174.6, 155.6, 138.5, 136.5, 129.1 (2C), 128.8 (2C), 128.7 (2C), 128.3 (2C), 128.2, 126.9, 67.2, 64.7, 60.9, 42.2, 41.3, 38.0, 37.4, 28.9, 20.2, 14.2; *minor isomer inter alia* 207.0, 174.3, 155.6, 138.4, 136.1, 60.5, 42.2, 41.3, 37.8. HRMS $C_{25}H_{31}NO_5$ [M + Na^+]: calcd, 448.2100; found, 448.2108.

(5*S*)-Ethyl 5-(Benzyloxycarbonyl)-2-isopropyl-4-oxo-6-phenylhexanoate (29). This was prepared using the general method for coupling with acrylates, with oxazolidinone **17** (138 mg, 0.375 mmol) and ethyl 3-methyl-2-methylenebutanoate (107 mg, 0.752 mmol). EtOAc (10−80%) in pentane was used as eluant for flash chromatography, which gave compound **29** (52 mg, 0.122 mmol, 45%) as a colorless gum and recovered **17** (51 mg, 0.138 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *major isomer* 7.10−7.40 (m, 10H), 5.29 (d, J = 8.0 Hz, 1H), 5.05 (s, 2H), 4.57−4.68 (m, 1H), 4.06−4.18 (m, 2H), 3.19 (dd, J = 14.0, 6.0 Hz, 1H), 2.74−3.08 (m, 3H), 2.47 (dd, J = 17.6, 3.2 Hz, 1H), 1.86−2.03 (m, 1H), 1.26 (t, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); *minor isomer inter alia* 5.09 (s, 2H), 2.66 (ddd, J = 8.4, 5.2, 3.2 Hz, 1H), 2.24 (dd, J = 17.6, 3.2 Hz, 1H), 1.23 (t, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 207.0/207.6, 174.3/174.4, 156.0/155.7, 136.1, 136.1, 129.3 (2C), 129.2 (2C), 128.7 (2C), 128.5/128.6 (2C), 128.0/128.1, 127.0/127.1, 66.9, 60.4/63.0, 60.4/60.8, 45.8/46.3, 38.9/39.2, 37.2/38.0, 29.8/29.9, 20.7, 14.2/14.2. HRMS $C_{25}H_{31}NO_5$ [M + Na^+]: calcd, 448.2100; found, 448.2098.

Benzyl (3*S*)-6-(Ethoxycarbonyl)-2,8-dimethyl-4-oxononan-3-ylcarbamate (30). This was prepared using the general method for coupling with acrylates, with oxazolidinone **20** (120 mg, 0.375 mmol) and ethyl 4-methyl-2-methylenepentanoate (116 mg, 0.743 mmol). EtOAc (10%) in pentane was used as eluant for column chromatography, which gave compound **30** (100 mg, 0.255 mmol, 68%) as a colorless solid and recovered **20** (24 mg, 0.075 mmol, 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) *major isomer* 7.37−7.26 (m, 5H), 5.35 (s, 1H), 5.10 (s, 2H), 4.35 (m, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.14−2.22 (m, 4H), 1.59−1.49 (m, 1H), 1.23 (q, J = 7.1 Hz, 3H), 1.01 (t, J = 7.0 Hz, 3H), 0.90 (dd, J = 21.1, 6.3 Hz, 6H), 0.77 (dd, J = 6.7, 3.8 Hz, 3H); *minor isomer inter alia* 5.10 (s, 2H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) *major isomer* 207.6, 175.6, 156.6, 136.5, 128.6 (2C), 128.3 (2C), 128.2, 67.1, 64.3, 60.6, 43.2, 41.3, 38.0, 30.3, 25.9, 22.6 (2C), 20.0, 16.2 (2C), 14.2; *minor isomer inter alia* 207.4, 175.3, 155.5, 136.4, 64.7, 60.6, 42.7, 41.3, 38.5, 26.0, 22.4, 19.9, 16.2, 14.2. HRMS $C_{22}H_{33}NO_5$ [M + Na^+]: calcd, 414.2256; found, 414.2268.

Phenylmethyl [(1*S*)-2-Oxo-2-(2-oxo-3-oxazolidinyl)-1-(phenylmethyl)ethyl]carbamate (17). 2-Oxazolidinone (175 mg, 2.00 mmol) was dissolved in dry CH_2Cl_2 (5 mL), and then $AlMe_3$ (1.0 mL, 2.00 mmol, 2 M in toluene) was added dropwise. The mixture was stirred at rt for 30 min and then added via syringe to a solution of PFP ester **12** (310 mg, 0.666 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at rt for 2 days and then poured directly into 1 M HCl (40 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The pure product was obtained by column chromatography (40−70% EtOAc in pentane as eluant), which gave compound **17** (199 mg, 0.540 mmol, 81%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.17−7.40 (m, 10H), 5.76 (td, J = 8.0, 4.8 Hz, 1H), 5.36 (d, J = 8.0 Hz, 1H), 5.03 (AB system, J = 12.0 Hz, 2H), 4.30−4.47 (m, 2H), 4.05 (dd, J = 16.4, 9.6 Hz, 1H), 3.92 (dd, J = 16.4, 8.4 Hz, 1H), 3.23 (dd, J = 13.6, 4.0 Hz, 1H), 2.84 (dd, J = 13.2, 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 155.8, 152.8, 136.2, 135.6, 129.3 (2C), 128.5 (2C), 128.4 (2C), 128.1, 128.0 (2C), 127.1, 66.9, 62.4, 54.3, 42.5, 38.5. HRMS $C_{20}H_{20}N_2O_5$ [M + Na^+]: calcd, 391.1270; found, 391.1271.

***tert*-Butyl [(1*S*)-2-Oxo-2-(2-oxo-3-oxazolidinyl)-1-(phenylmethyl)ethyl]carbamate (18).** 2-Oxazolidinone (740 mg, 8.46 mmol) was dissolved in dry CH_2Cl_2 (21 mL) and then cooled to 0 °C before $AlMe_3$ (4.2 mL, 8.40 mmol, 2 M in toluene) was added dropwise. The mixture was stirred at rt for 30 min and then added via syringe to a solution of PFP ester **14** (1.60 g, 4.027 mmol) in CH_2Cl_2 (21 mL). The mixture was stirred at rt for 20 h and then poured directly into 1 M HCl (80 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The pure product was obtained by column chromatography (20−70% EtOAc in pentane as eluant), which gave compound **18** (779 mg, 2.330 mmol, 83%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.20−7.34 (m, 5H), 5.68 (dt, J = 8.8, 4.8 Hz, 1H), 5.07 (br d, J = 7.6 Hz, 1H), 4.32−4.46 (m, 2H), 4.04 (ddd, J = 10.8, 9.2, 6.8 Hz, 1H), 3.87−3.97 (m, 1H), 3.18 (br d, J = 12.8 Hz, 1H), 2.78 (br t, J = 8.8 Hz, 1H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.8, 155.0, 153.0, 136.0, 129.5, 128.5 (2C), 127.1 (2C), 80.0, 62.5, 53.9, 42.6, 38.5, 28.2 (3C). HRMS $C_{17}H_{22}N_2O_5$ [M + Na^+]: calcd, 357.1426; found, 357.1422.

(*S*)-*tert*-Butyl 4-Methyl-1-oxo-1-(2-oxooxazolidin-3-yl)pentan-2-ylcarbamate (19). 2-Oxazolidinone (1.052 g, 12.08 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and then cooled to 0 °C before $AlMe_3$ (6.0 mL, 12.00 mmol, 2 M in toluene) was added dropwise. The mixture was stirred at rt for 30 min and then added via syringe to a solution of PFP ester **15** (1.60 g, 4.027 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at rt for 18 h and then poured directly into 1 M HCl (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The pure product was obtained by column chromatography (20−70% EtOAc in pentane as eluant), which gave compound **19** (847 mg, 2.937 mmol, 73%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.41 (ddd, J = 11.2, 8.8, 2.4 Hz, 1H), 5.01 (d, J = 8.4 Hz, 1H), 4.42 (ddd, J = 9.2, 7.2, 2.4 Hz, 2H), 4.05 (ddd, 10.8, 8.8, 7.2 Hz, 1H), 3.90−3.98 (m, 1H), 1.72−1.82 (m, 1H), 1.48−1.59 (m, 1H), 1.41 (s, 9H), 1.32−1.41 (m, 1H), 0.99 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.3, 155.6, 152.7, 79.7, 62.3, 51.6, 42.5, 41.1, 28.2 (3C), 24.9, 23.4, 20.8. HRMS $C_{14}H_{27}N_2O_5$ [M + Na^+]: calcd, 323.1582; found, 323.1581.

(*S*)-Benzyl 3-Methyl-1-oxo-1-(2-oxooxazolidin-3-yl)butan-2-ylcarbamate (20). 2-Oxazolidinone (386 mg, 3.90 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and then cooled to 0 °C before $AlMe_3$ (1.95 mL, 3.90 mmol, 2 M in toluene) was added dropwise. The mixture was stirred at rt for 30 min and then added via syringe to a solution of PFP ester **16** (540 mg, 1.30 mmol) in CH_2Cl_2 (3.0 mL). The mixture was stirred at rt for 48 h and then poured directly into 1 M HCl (100 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The pure product was obtained by column chromatography (30−50% EtOAc in pentane as eluant), which gave compound **20** (258 mg, 0.806 mmol, 62%) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25−7.40 (m, 5H), 5.43−5.50 (m, 2H), 5.08 (AB system, J = 14.4 Hz, 2H), 4.38 (t, J = 8.4 Hz, 2H), 3.85−4.07 (m, 2H), 2.10−2.22 (m, 1H), 1.04 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.6, 156.2, 152.8, 136.2, 128.4 (3C), 128.0 (2C), 66.9, 62.2, 57.5, 42.4, 30.6, 19.6, 16.1. HRMS $C_{16}H_{20}N_2O_5$ [M + Na^+]: calcd, 343.1270; found, 343.1267.

(2*S*,4*S*)-Perfluorophenyl 4-(4-Methoxy-3-(3-methoxypropoxy)benzyl)-2-(benzyloxycarbonylamino)-5-methylhexanoate (32). Acid **31**[4] (284 mg, 0.582 mmol) was dissolved in CH_2Cl_2 (5 mL), and then the mixture was cooled to 0 °C. PFP (150 mg, 0.814 mmol), EDCI (191 mg, 1.000 mmol), and DMAP (20 mg, 0.169 mmol) were added, and then the mixture was stirred for 30 min at 0 °C and at rt for a further 30 min. It was then 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 (10−25% EtOAc in pentane as eluant), which gave compound **32** (371 mg, 0.568 mmol, 97%) as a colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27−7.37 (m, 5H), 6.73−6.80 (m, 2H), 6.68 (d, J = 8.0 Hz, 1H), 5.19 (d, J = 8.8 Hz, 1H), 5.14 (s, 2H), 4.68 (br q, J = 4.8 Hz, 1H), 4.08 (t, J = 6.0 Hz, 2H), 3.82 (s, 3H), 3.56 (t, J = 6.0 Hz, 2H), 3.33 (s, 3H), 2.59 (d, J = 5.6 Hz, 1H), 2.07 (quin, J = 6.0 Hz, 2H), 1.70−1.88 (m, 4H), 0.91 (d, J = 6.8 Hz, 3H), 0.88 (s, J = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.2, 168.0 (br), 155.9, 148.4, 147.8, 142.2 (br), 139.7 (br), 136.7 (br), 136.0 (br), 135.9, 133.0, 128.5 (2C), 128.2, 128.0 (2C), 121.2, 114.3, 111.8, 69.4, 67.3, 65.9, 58.5, 56.0, 52.3, 42.1, 36.3, 33.2, 29.5, 28.2, 19.3, 17.1. HRMS $C_{33}H_{36}F_5NO_7$ [M + Na^+]: calcd, 676.2310; found, 676.2253.

Benzyl (2*S*,4*S*)-4-(4-Methoxy-3-(3-methoxypropoxy)benzyl)-5-methyl-1-oxo-1-(2-oxooxazolidin-3-yl)hexan-2-ylcarbamate (33). 2-Oxazolidinone (175 mg, 2.00 mmol) was dissolved in dry CH_2Cl_2 (5 mL), and then $AlMe_3$ (1.0 mL, 2.00 mmol, 2 M in toluene) was added dropwise. The mixture was stirred at rt for 30 min and then added via syringe to a solution of PFP ester **32** (370 mg, 0.566 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at rt for 4 days and then poured directly into 1 M HCl (40 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The pure product was obtained by column chromatography (20−100% EtOAc in pentane as eluant), which gave compound **33** (242 mg, 0.435 mmol, 77%) as a colorless gum and recovered **32** (40 mg, 0.061 mmol, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26−7.36 (m, 5H), 6.79 (s, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 5.60 (br t, J = 8.4 Hz, 1H), 5.40 (br t, J = 8.8 Hz, 1H), 5.10 (s, 2H), 4.41 (t, J = 7.6 Hz, 2H), 4.08 (t, J = 6.0 Hz, 2H), 3.88−4.06 (m, 2H), 3.81 (s, 3H), 3.55 (t, J = 6.0 Hz, 2H), 3.13 (s, 3H), 2.97 (br d, J = 11.2 Hz, 1H), 2.37 (dd, J = 13.6, 10.0 Hz, 1H), 2.06 (quin, J = 6.4 Hz, 2H), 1.45−1.74 (m, 4H), 0.78 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.6, 156.0, 152.7, 148.1, 147.4, 136.3, 134.1, 128.4 (2C), 128.0, 127.9 (2C), 121.2, 114.4, 111.6, 69.4, 66.8, 65.9, 62.4, 58.5, 56.0, 51.9, 42.5, 41.9, 36.1, 32.7, 29.6, 27.4, 20.6, 16.1. HRMS $C_{30}H_{40}N_2O_8$ [M + Na^+]: calcd, 579.2682; found, 579.2692.

(5*S*,7*S*)-Ethyl 7-(4-Methoxy-3-(3-methoxypropoxy)benzyl)-5-(benzyloxycarbonylamino)-2-isopropyl-8-methyl-4-oxononanoate (34). Oxazolidinone **33** (37 mg, 0.0664 mmol) was dissolved in THF (5 mL), and then ethyl α-isopropyl acrylate (150 mg, 1.055 mmol) and water (100 mg, 5.55 mmol) were added. The mixture was cooled to −78 °C before a 0.1 M solution of SmI_2 (15 mL, 1.50 mmol) was added dropwise over 15 min. The mixture was stirred at −78 °C for 2 days, and then the flask was flushed with O_2. The mixture was poured into 0.5 M HCl (40 mL) and extracted with EtOAc (5 × 15 mL). The combined organic portions were washed with saturated $Na_2S_2O_3$, dried ($MgSO_4$), filtered, and evaporated. The pure product was obtained by column chromatography (10−100% EtOAc in pentane as eluant), which gave compound **34** (21 mg, 0.0342 mmol, 52%) as a colorless gum and a 5:4 mixture of isomers and recovered **33** (16 mg, 0.0287 mmol, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.20−7.30 (m, 5H), 6.60−6.78 (m, 3H), 5.12/5.21 (br d, J = 8.0 Hz, 1H), 5.03/5.05 (s/AB system, J = 12.0 Hz, 2H), 4.23/4.32 (br t, J = 8.0 Hz, 1H), 3.96−4.10 (m, 4H), 3.76 (s, 3H), 3.49 (t, J = 6.0 Hz, 2H), 3.26 (s, 3H), 2.72−2.90 (m, 1H), 2.56−2.70 (m, 2H), 2.22−2.50 (m, 2H), 2.02 (quin, J = 6.4 Hz, 2H), 1.84−1.96 (m, 1H), 1.43−1.68 (m, 3H), 1.10−1.27 (m, 4H), 0.68−0.90 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 208.4/208.8, 174.3/174.5, 156.3/156.4, 148.4, 147.7, 133.5, 128.6 (2C), 128.2, 128.0 (2C), 121.3, 114.4, 111.6, 69.6, 66.0/66.9, 60.5/60.6, 58.7, 58.3/58.6, 56.1, 45.8/46.3, 42.1/42.2, 37.8/38.7, 32.4, 30.0, 29.7, 28.2/28.8, 20.3/20.4, 20.1/20.4, 19.7, 16.9/17.0, 14.3/14.4. HRMS $C_{35}H_{51}NO_8$ [M + Na^+]: calcd, 636.3512; found, 636.3510.

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Supporting Information Available: Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1**−**7**, **17**−**30**, and **32**−**34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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