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General Solid-Phase Method for the Preparation of Mechanism-Based Cysteine Protease Inhibitors

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Abstract: The first general method has been developed for the expedient solid-phase synthesis of ketone-based cysteine protease inhibitors. The synthesis approach was designed to allow the introduction of diverse functionality at *all* variable sites about the ketone carbonyl using readily available precursors. The chloromethyl ketone scaffold **7** is attached to the solid support through the newly developed hydrazine linker **6**. Successful nucleophilic displacement of the support-bound α-chloro hydrazones **8** with carboxylates, thiolates, and amines provides entry to the acyloxymethyl, mercaptomethyl, and amidomethyl ketone classes of cysteine protease inhibitors. Further transformations followed by cleavage from support provides the fully substituted ketone products in 40−100% overall yields after release from support. Significantly, racemization of the α-stereocenter does not occur during loading onto support, nucleophilic displacement, or cleavage from support.

Introduction

Cysteine proteases are important pharmaceutical targets because of their role in the pathogenesis of many diseases.[1] Characterized by a conserved cysteine residue in the active site, this class of proteases include the calpains,[2] which have been implicated in neurodegenerative disorders, cathepsin K,[3] which has been linked to osteoporosis, and the caspase family of proteases,[4] recently shown to be involved in programmed cell death.

Cysteine proteases produce a biological response by catalyzing the hydrolysis of amide bonds in peptides and proteins through nucleophilic attack of the active site cysteine residue upon the amide carbonyl (Figure 1). A common feature of virtually all cysteine protease inhibitors is an electrophilic
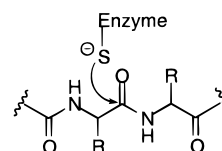

Figure 1. Attack of active-site cysteine upon scissile amide carbonyl.

functionality, such as a carbonyl or a Michael acceptor, that can react with the nucleophilic cysteine residue.[1,5] Peptidyl aldehydes were the first class of reversible inhibitors to be reported.[1] However, the inherent reactivity of the aldehyde pharmacophore to nucleophilic attack and oxidation is a considerable liability for attaining good pharmacokinetics. Additionally, aldehyde-based inhibitors are limited since functionality can only be displayed on one side of the carbonyl. In contrast, the ketone-based pharmacophore is more chemically stable, and the display of functionality on both sides of the carbonyl provides the potential to achieve enhanced specificity through multiple interactions with the active site. Indeed, Veber and co-workers recently have reported several examples of reversible peptidyl ketones with nanomolar inhibition toward cathepsin K,[6] and

(1) For a review on cysteine proteases and their inhibitors, see: Otto, H.-H.; Schirmeister, T. *Chem. Rev.* **1997**, *97*, 133−171.

(2) Suzuki, K.; Sorimachi, H. *FEBS Lett.* **1998**, *433*, 1−4.

(3) Bossard, M. J.; Tomaszek, T. A.; Thompson, S. K.; Amegadzie, B. Y.; Hanning, C. R.; Jones, C.; Kurdyla, J. T.; McNulty, D. E.; Drake, F. H.; Gowen, M.; Levy, M. A. *J. Biol. Chem.* **1996**, *271*, 12517−12524.

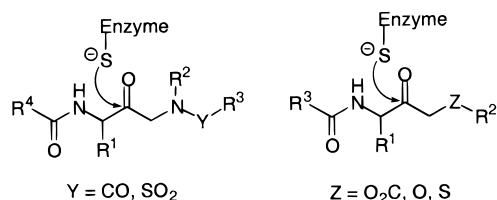(4) Thornberry, N. A. *Chem. Biol.* **1998**, *5*, R97−R103.

Figure 2. Ketone-based inhibitors.

Thornberry and co-workers have identified ketone-based inhibitors that target caspase-1.[7] A number of researchers have developed irreversible ketone-based inhibitors targeting several different cysteine proteases.[8]

The recent development of synthesis methods to prepare mechanism-based inhibitor libraries targeting metalloproteases and aspartyl proteases have enabled the rapid and efficient identification of potent small-molecule inhibitors.[9] We developed the first general method to prepare libraries of mechanism-based inhibitors that target the aspartyl class of proteases by the display of functionality at all sites about a support-bound secondary alcohol, which represents the minimal pharmacophore required to achieve inhibition. Using this method we have identified single-digit nanomolar and high-picomolar small-molecule inhibitors to the aspartyl proteases plasmepsin II and cathepsin D, respectively.[10]

The ketone carbonyl serves as a minimal pharmacophore required to achieve inhibition of cysteine proteases. A general solid-phase synthesis approach to display diverse functionality about a ketone carbonyl would therefore enable the preparation of libraries of potential inhibitors targeting the cysteine protease class (Figure 2). In previous efforts toward the solid-phase synthesis of ketone-based caspase inhibitors, Chapman attached the starting scaffold to the support through a carboxylic acid side chain at the P1 position, clearly limiting diversity at this site.[11] In very recent work, Veber and co-workers described a method for the solid-phase synthesis of α-amidoketones. In their approach, the ketone was protected as a dimethoxy ketal. Deprotection resulted in extensive racemization.[12] Herein we

Scheme 1

report the first general method for the solid-phase preparation of small-molecule cysteine protease inhibitors where diverse functionality can be displayed at all sites about a support-bound ketone carbonyl.[13]

Results

Synthetic Strategy. A chloromethyl ketone, prepared in one pot from an *N*-protected amino acid, introduces the P1 side chain and provides sites for further functionalization on both sides of the ketone carbonyl (Scheme 1). Linking to support through the ketone carbonyl is ideal because the carbonyl functionality is the only invariant part of a ketone-based inhibitor regardless of the cysteine protease that is targeted. A hydrazone linkage would allow for nucleophilic substitution at the α-position while simultaneously preventing nucleophilic attack at the carbonyl. The hydrazone should also prevent racemization, which is problematic for the corresponding enolizable α-acylamino substituted chiral ketone. The fully functionalized ketone inhibitor would be released from the support by a final acidic cleavage of the hydrazone linkage. A key challenge in the synthesis effort was the identification of the appropriate hydrazone linkage that would meet the aforementioned objectives. Precedent did not exist for performing this series of transformations on α-halo-hydrazones, and the known conversion of α-halohydrazones to azodienes provided significant potential for complications.[14] Hydrazine linkers previously have been employed to couple peptidyl aldehydes and trifluoromethyl ketones to solid supports; however, these preformed handle strategies required the preparation of the hydrazone derivative in solution before loading onto solid support.[15] To enable the rapid introduction of diverse functionality at the P1 site, direct loading of the halomethyl ketone onto a support-bound hydrazine would be required.

Model Studies. To identify the optimal hydrazone linker, solution studies were performed for hydrazone formation, halide displacement, subsequent functionalization, and hydrazone cleavage. L-Cbz-phenylalanine was selected as the initial starting material and was converted to the desired halomethyl ketone according to a one-pot literature procedure.[16]

Investigation of functionalized hydrazines as potential linkers revealed that *N*-alkyl-, *N,N*-dialkyl-, and *N*-arylhydrazines did not form stable adducts with halomethyl ketones, but hydrazine derivatives substituted with electron-withdrawing groups did

(5) See also the Symposium-in-Print on cysteine protease inhibitors featured in *Bioorg. Med. Chem.* **1999**, *7*, 571−644.

(6) (a) Marquis, R. W.; Ru, Y.; Yamashita, D. S.; Oh, H.-J.; Yen, J.; Thompson, S. K.; Carr, T. J.; Levy, M. A.; Tomaszek, T. A.; Ijames, C. F.; Smith, W. W.; Zhao, B.; Janson, C. A.; Abdel-Meguid, S. S.; D'Alessio, K. J.; McQueney, M. S.; Veber, D. F. *Bioorg. Med. Chem.* **1999**, *7*, 581−588. (b) Yamashita, D. S.; Smith, W. W.; Zhao, B.; Janson, C. A.; Tomaszek, T. A.; Bossard, M. J.; Levy, M. A.; Oh, H.; Carr, T. J.; Thompson, S. K.; Ijames, C. F.; Carr, S. A.; McQueney, M.; D'Alessio, K. J.; Amegadzie, B. Y.; Hanning, C. R.; Abdel-Meguid, S.; DesJarlais, R. L.; Gleason, J. G.; Veber, D. F. *J. Am. Chem. Soc.* **1997**, *119*, 11351−11352.

(7) (a) Mjalli, A. M.; Chapman, K. T.; Zhao, J. J.; Thornberry, N. A.; Peterson, E. P.; MacCoss, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1405−1408. (b) Mjalli, A. M.; Chapman, K. T.; MacCoss, M.; Thornberry, N. A.; Peterson, E. P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1965−1968.

(8) (a) Krantz, A.; Copp, L. J.; Coles, P. J.; Smith, R. A.; Heard, S. B. *Biochemistry* **1991**, *30*, 4678−4687. (b) Pliura, D. H.; Bonaventura, B. J.; Smith, R. A.; Coles, P. J.; Krantz, A. *Biochem. J.* **1992**, *288*, 759−762. (c) Graybill, T. L.; Prouty, C. P.; Speier, G. J.; Hoyer, D.; Dolle, R. E.; Helaszek, C. T.; Ator, M. A.; Uhl, J.; Strasters, J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 41−46.
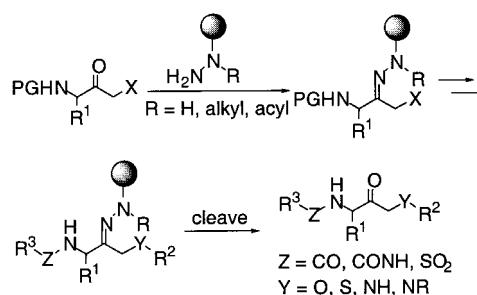
(9) Whittaker, M. *Curr. Opin. Chem. Biol.* **1998**, *2*, 386−396.

(10) (a) Lee, C. E.; Kick, E. K.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 9735−9747. (b) Kick, E. K.; Roe, D. C.; Skillman, A. G.; Liu, G.; Ewing, T. J. A.; Sun, Y.; Kuntz, I. D.; Ellman, J. A. *Chem. Biol.* **1997**, *4*, 297−307.

(11) Rano, T. A.; Timkey, T.; Peterson, E. P.; Rotonda, J.; Nicholson, D. W.; Becker, J. W.; Chapman, K. T.; Thornberry, N. A. *Chem. Biol.* **1997**, *4*, 149−155.

(12) Yamashita, D. S.; Dong, X.; Oh, H.-J.; Brook, C. S.; Tomaszek, T. A.; Szewcsuk, L.; Tew, D. G.; Veber, D. F. *J. Comb. Chem.* **1999**, *1*, 207−215.

(13) See also: Lee, A.; Huang, L.; Ellman, J. A. Presented at the 217th National Meeting of the American Chemical Society, Anaheim, CA, March 1999; poster ORGN 213.

(14) For a review on azodiene chemistry, see: Attanasi, O. A.; Filippone, P. *Synlett* **1997**, 1128−1140.

(15) Murphy, A. M.; Dagnino, R.; Vallar, P. L.; Trippe, A. J.; Sherman, S. L.; Lumpkin, R. H.; Tamura, S. Y.; Webb, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 3156−3157.

(16) (a) Krantz, A.; Copp, L. J.; Smith, R. A.; Heard, S. B. *Biochemistry* **1991**, *30*, 4678−4687. (b) Dolle, R. E.; Hoyer, D.; Prasad, C. V. C.; Schmidt, S. J.; Helaszek, C. T.; Miller, R. E.; Ator, M. A. *J. Med. Chem.* **1994**, *37*, 563−564.
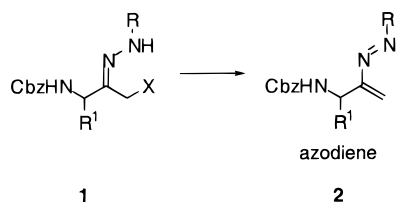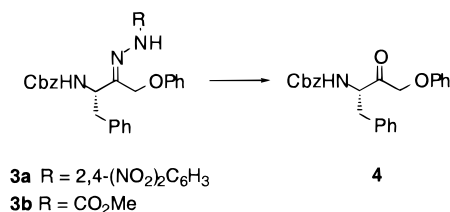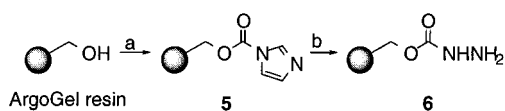
Figure 3. Azodiene formation.

Scheme 2

3a R = 2,4-(NO$_2$)$_2$C$_6$H$_3$ **4**
3b R = CO$_2$Me

Scheme 3[a]

ArgoGel resin   **5**   **6**

[a] (a) CDI, CH$_2$Cl$_2$, 3 h; (b) NH$_2$NH$_2$, DMF, 1 h.

Table 1. Effect of R^1 on Scaffold Loading

ketone	R^1	R	rxn condns	yield (%)[a]
7a	CH$_2$—C$_6$H$_5$	H	4 h, rt	100
7b	CH$_3$	H	4 h, rt	92
7c	CH$_2$-(thiophene)	H	4 h, rt	91
7d	H	H	30 min, rt	90
7e	CH(CH$_3$)$_2$	H	6 h, 45-50 °C	88
7f	CH$_2$CO$_2$C(CH$_3$)$_3$	H	9 h, 45-50 °C	91
7g	CH$_3$	CH$_3$	24h, 45-50 °C	61

[a] Yields for loading the chloromethyl ketone were based on either the loading level of the commercial resin or by comparison to the loading and cleavage of the stable ketone **12d**.

produce stable hydrazones. An electron-withdrawing group on the hydrazone presumably minimizes azodiene formation (Figure 3). Furthermore, azodienes formed from the corresponding electron-deficient hydrazones appeared to be less prone to decomposition, an observation that coincides with the few known azodienes reported in the literature.[14] Of the electron-deficient hydrazines investigated, only 2,4-dinitrophenylhydrazine and methyl carbazate (R = CO$_2$Me) provided hydrazones in high yield and successfully underwent halide displacement with a thiol nucleophile.

Cleavage conditions were determined by formation and hydrolysis of hydrazones prepared from the more stable phenoxymethyl ketone derived from L-Cbz-phenylalanine (Scheme 2). Although the dinitrophenylhydrazone did not hydrolyze upon exposure to a variety of cleavage conditions, the complete hydrolysis of the hydrazone derived from methyl carbazate could be accomplished using 1:4:4:15 TFA/H$_2$O/acetaldehyde/THF, in which acetaldehyde is utilized as a hydrazine scavenger. Cleavage was similarly accomplished with trifluoroethanol (TFE) in place of THF, providing conditions which are compatible with a polypropylene-based parallel synthesis apparatus. Thus, we chose to base our linker on methyl carbazate.

Linker Synthesis. Initial work on solid support focused on linker formation using gel-form polystyrene-poly(ethylene glycol) resin (ArgoGel-OH, Argonaut Technologies), because of its compatibility with both the protic and aprotic solvents that are required in the synthetic sequence. Linker loading was measured through loading and cleavage of the phenoxymethyl ketone prepared from L-Cbz-phenylalanine. Activation of the alcohol moiety on the resin with carbonyldiimidazole (CDI) followed by reaction with anhydrous hydrazine for 1 h provided near-quantitative loading levels (0.3−0.4 mmol/g) of linker **6** (Scheme 3).[17] The reaction should be stopped after the 1 h time period required for reaction completion since prolonged reactions times result in lower loading levels due to the attack of hydrazine upon the carbazate linker as evidenced by the production of carbohydrazide.

(17) An analogous procedure with 4-nitrophenylchloroformate provided lower loading of the linker on support.

Scaffold Loading. Hydrazone formation was first investigated by comparing the loading efficiencies of α-bromomethyl and α-chloromethyl ketones (eq 1). The loading levels of the ketone scaffolds were measured through subsequent quantitative halide displacement by thiophenol followed by cleavage from support. The chloromethyl ketone gave higher resin loading due to the greater stability of the chloromethyl hydrazone to azodiene formation and subsequent decomposition.

Scaffold-loading reaction times varied depending on the R^1 group (Table 1). For the phenylalanine-based ketone **7a**, 4 h was necessary for complete loading. However, glycine-based ketone **7d** loaded within 30 min, but the resultant product decomposed under the reaction conditions during longer time periods. In contrast, for complete loading to be achieved with ketones containing bulkier side chains, as seen with ketones prepared from Cbz-valine, **7e**, and *N*-Cbz β-O-*t*-Bu aspartic acid, **7f**, moderate heating (45−50 °C) as well as a reaction time of 6−9 h was required. For ketones derived from α,α-disubstituted amino acids, such as aminoisobutyric acid, **7g**, modest loading was obtained by heating for 24 h. Thus, although the reaction time for hydrazone formation varied with respect to the steric bulk of the side chain, all scaffolds were accessible.

Halide Displacement. Since little work has been reported on nucleophilic displacement of α-halo hydrazones,[14] an investigation of nucleophiles was undertaken. When carboxylates were employed as the nucleophiles, high yields of the desired acyloxymethyl ketone product were observed upon cleavage from resin (Table 2). The more basic thiol nucleophiles also led to quantitative reaction at room temperature (Table 3). The crude acyloxymethyl and thiomethyl ketone products were of high purity and uncontaminated with byproducts as determined by NMR analysis (>90% purity). In contrast, phenoxides proved to be poor nucleophiles, furnishing desired material in optimized yields of only 30% after considerable experimentation with different bases, solvents, reaction temperatures, and reaction times (Table 3).

For completely general access to amidomethyl ketones, we employed a two-step procedure: halide displacement with primary amines, followed by acylation of the resulting secondary

Table 2. Carboxylate Nucleophiles

product	R^2CO_2H	overall yield (%)[a]
10a		80
10b		80
10c		87
10d		90

[a] Yields were obtained by *p*-xylene calibration in NMR analysis.

Table 3. Thiol and Phenol Nucleophiles

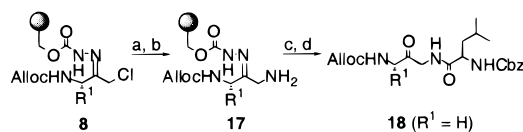| product	R^2XH	overall yield (%)[a]
12a	HSPh	quantitative
12b	Ph⌒⌒SH	97
12c	Ph⌒⌒⌒SH	97
12d[b]		37
12e	O_2N⌬OH	33
12f		31

[a] Yields were obtained by *p*-xylene calibration in NMR analysis.
[b] Best results obtained using *i*-Pr$_2$NEt, CH$_2$Cl$_2$ at room temperature for 4 h.
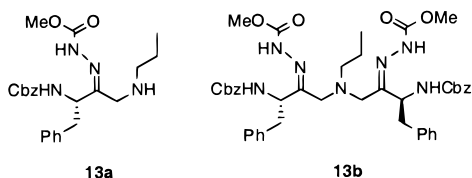
Figure 4. Products from halide displacement with propylamine in solution-phase studies.

amine (eq 4). Initial solution-phase studies of halide displacement showed a pronounced solvent dependence, with dimethylformamide providing the highest yield of the secondary amine product **13a** (Figure 4). The over-alkylated tertiary amine **13b** also was observed as a byproduct of the displacement reaction. Investigations of the same reaction on solid support revealed the presence of the over-alkylated tertiary amine which led to a decreased yield of the desired product.[18] Fortunately, this byproduct was not cleaved under the acidic cleavage conditions

(18) Site−site interactions on solid support have been well-documented in literature. (a) Bhargava, K. K.; Sarin, V. K.; Trang, N. L.; Cerami, A.; Merrifield, R. B. *J. Am. Chem. Soc.* **1983**, *105*, 3247−3251. (b) Scott, L. T.; Rebek, J.; Ovsyanko, L.; Sims, C. L. *J. Am. Chem. Soc.* **1977**, *99*, 625−626.

Table 4. Amidomethyl Ketones

PG = Cbz or Alloc

product	R^2NH_2	R^3CO_2H	overall yield (%)[a]
16a	⌒NH$_2$		53
16b	⌇NH$_2$		55
16c			61
16d	⌒NH$_2$	H$_3$CO⌬⌒OH	59
16e	⌒NH$_2$		50

[a] Yields were obtained by *p*-xylene calibration in NMR analysis.
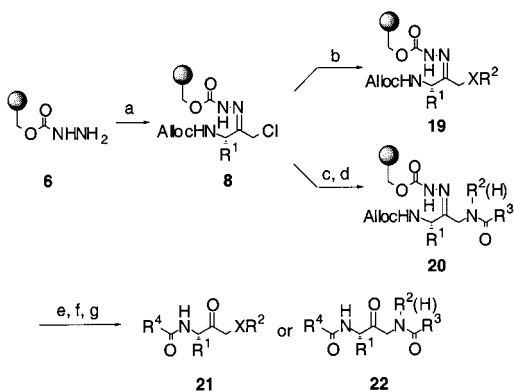
Scheme 4[a]

[a] (a) NaN$_3$, MeOH; (b) SnCl$_2$, PhSH, *i*-Pr$_2$NEt, THF; (c) Cbz-Leu-OH, PyBOP, HOAt, *i*-Pr$_2$NEt, DMF; (d) 1:4:4:15 TFA/H$_2$O/CH$_3$CHO/TFE.

used (1:4:4:15 TFA/H$_2$O/acetaldehyde/TFE), an observation that coincided with solution-phase studies where hydrazones displaying a tertiary amine at the α-position failed to hydrolyze to the ketone products under acidic conditions. Acylation of the secondary amine with standard coupling reagents followed by cleavage from support provided the amidomethyl ketones in 50−61% yield (Table 4). Minimal amounts of impurities were observed as determined by NMR analysis; however, the presence of amide rotamers complicated accurate measurement.

An alternative route toward secondary amidomethyl ketones **18** was also developed (Scheme 4). To this end, chloride displacement with sodium azide, followed by tin(II) chloride-mediated reduction, acylation of the resultant primary amine, and acidic cleavage of the hydrazone afforded the ketone product **18** ($R_1 = H$) in 93% overall yield.

Racemization Studies. In addition to demonstrating the viability of the chemistry using a hydrazone-bound scaffold, we wanted to verify that racemization does not occur during the synthetic sequence regardless of the type of nucleophilic substitution performed. Acyloxymethyl ketone **10a** (Table 2), mercaptomethyl ketone **12b** (Table 3), and amidomethyl ketone **16a** (Table 4) were each synthesized on solid support from the (*R*) and (*S*) chloromethyl ketones derived from both D- and L-Cbz-phenylalanine, respectively. As determined by chiral HPLC analysis, no racemization occurred during the synthesis of ketones **10a**, **12b**, or **16a** to the limits of detection (<1%).

Complete Functionalization of Scaffold. It remained for us to establish methods to introduce functionality on the other side of the masked ketone to display functionality at all sites about the carbonyl. This was accomplished by using the allyloxycarbonyl (Alloc)-protecting group, which was removed under mild Pd(0)-mediated conditions. Subsequent acylation of the resulting amine followed by cleavage would provide the desired fully functionalized product **21** or **22** (Scheme 5). While Pd(PPh$_3$)$_4$

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Scheme 5[a]

[a] (a) Chloromethyl ketone derivative of *N*-Alloc amino acid, THF, 4 h, rt; (b) R_2CO_2H or R_2SH, *i*-Pr$_2$NEt, DMF; (c) R_2NH_2, DMF or (1) NaN$_3$, MeOH (2) SnCl$_2$, PhSH, *i*-Pr$_2$NEt, THF; (d) R_3CO_2H, PyBOP, HOAt, *i*-Pr$_2$NEt, DMF; (e) Pd(PPh$_3$)$_4$, CH$_2$Cl$_2$, TMSN$_3$, TBAF·3H$_2$O; (f) R_4CO_2H, PyBOP, HOAt, *i*-Pr$_2$NEt, DMF; (g) 1:4:4:15 TFA/H$_2$O/CH$_3$CHO/TFE.

with acetic acid and *N*-methyl morpholine resulted in successful Alloc-deprotection of the amidomethyl hydrazones, the acyloxymethyl hydrazones decomposed under these conditions. Clean deprotection was observed for the amidomethyl hydrazones and for most of the acyloxymethyl hydrazones using an alternative procedure reported by Shapiro and co-workers[19] where trimethylsilyl azide and tetrabutylammonium fluoride hydrate were used to scavenge the allyl group. These conditions were successful because the Alloc cleavage provides the TMS-protected carbamic acid rather than the free amine,[20] which can participate in acyl transfer reactions. Presumably, breakdown to the free amine occurs during the subsequent acylation step where the amine is rapidly trapped. It should be noted that competitive hydrolysis of highly activated esters was problematic. For example, a dichlorobenzoate derivative did not completely survive the latter half of the synthetic sequence, producing a 1:1 mixture of the desired acyloxymethyl ketone and the α-hydroxyketone.

Amidomethyl, mercaptomethyl, and most acyloxymethyl ketones were obtained in moderate to high yields for the full synthetic sequence (Scheme 5). These classes of compounds each have been identified previously as inhibitors against cysteine protease targets. Acyloxymethyl and amidomethyl ketones have exhibited potent inhibition against cathepsins B[8a] and K[12] respectively, and mercaptomethyl ketones have demonstrated strong activity against caspase-1[7] and cathepsin K.[6a] Representative ketone products prepared by our solid-phase methodology are shown in Table 5. The solid-phase synthetic sequence developed here will enable the rapid parallel synthesis of libraries of small-molecule, ketone-based inhibitors targeting cysteine proteases.

Conclusions

We have developed a general synthetic strategy to access mechanism-based cysteine protease inhibitors by linking a minimal scaffold element to solid support through the invariant ketone carbonyl. A newly developed carbazate linker enables the straightforward and direct loading of chloromethyl ketone scaffolds. A variety of nucleophiles may be used to displace the chloride without racemization. Additional functionality can then be introduced about both sides of the carbonyl such that

Table 5. Full-Sequence Products

product	compound	overall yield (%)[a]
21a		quantitative
21b		78
21c		91
21d		75
21e		85
21f		48
22a		61
22b		40

[a] Yields were obtained by *p*-xylene calibration in NMR analysis.

the display of diverse functionality at all sites about the ketone carbonyl may be accomplished in as few as five solid-phase synthesis steps in high yield. Using this synthesis strategy, library preparation and evaluation against cysteine proteases is currently in progress and will be reported in due course.

Experimental Section

General Methods. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. THF was distilled under N$_2$ from sodium/benzophenone and CH$_2$Cl$_2$ and DIEA were distilled over CaH$_2$ immediately prior to use. Diazomethane was generated in situ using the following procedure.[21] To a 0.7 M solution of *p*-toluenesulfonylmethylnitrosamide (Diazald) in absolute ethanol was added small aliquots of 1.5 N KOH until the Diazald solution became white. Diazomethane gas was produced and transferred by cannula (two fire-polished pipets connected by rubber tubing) under positive N$_2$ flow into the stirring THF solution of the second reagent. Dry phenol crystals were prepared through azeotropic distillation of a benzene solution of phenol, using a Dean–Stark trap, followed by concentration and drying in vacuo in the presence of phosphorus pentoxide. Pd(PPh$_3$)$_4$ was prepared according to literature procedure.[22] ArgoGel-OH resin was purchased from Argonaut Technologies (San Carlos, CA).

Reaction progress was monitored through thin-layer chromatography on Merck 60 F$_{254}$ 0.25 μm silica plates. Unless otherwise specified, extracts were dried over MgSO$_4$ and solvents were removed with a rotary evaporator at aspirator pressure. Flash chromatography was carried out with Merck 60 230–400 mesh silica gel according to the

(19) Shapiro, G.; Buechler, D. *Tetrahedron Lett.* **1994**, *35*, 5421–5424.
(20) Guibé, F. *Tetrahedron* **1998**, *54*, 2967–3042.

(21) Lombardi, P. *Chem. Ind.* **1990**, 708.
(22) Coulson, D. R. *Inorg. Synth.* **1972**, 121–124.

procedure described by Still.[23] Infrared spectra were recorded with a Perkin-Elmer 1600 Series Fourier transform spectrometer as thin films on NaCl plates or as KBr pellets, and only partial data are listed. ^{1}H and ^{13}C NMR spectra were obtained with Bruker AMX-300, AMX-400, AM-400, and DRX-500 spectrometers. Unless otherwise specified, all spectra were obtained in CDCl$_3$; chemical shifts are reported in parts per million relative to TMS, and coupling constants are reported in hertz. Melting points were determined on a MelTemp apparatus and are reported uncorrected. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ).

General Methods for Solid-Phase Synthesis. Solvents were distilled for resin reactions. Unless otherwise stated, reactions were conducted in 12-mL polypropylene cartridges with 70-mm PE frits attached to Teflon stopcocks. Cartridges and stopcocks were obtained from Applied Separations (Allentown, PA). Syringe barrels from 10-mL disposable syringes were used as stoppers for the cartridges. Resin was gently rocked on an orbital shaker table during solid-phase reactions. Solvents were removed by taking off the syringe barrel and opening the stopcock. Resin was washed for a duration of 2−5 min unless otherwise stated.

General Methods for Cleavage of Compounds from Resin and for Yield Quantitation. To 0.2 g of derivatized resin was added a 5 mL solution of 1:4:4:15 TFA/H$_2$O/acetaldehyde/trifluoroethanol. After sitting at room temperature for 4 h with gentle stirring, the solution was removed. The resin was washed with THF (3 × 5 mL), and the washings were combined and concentrated. Toluene was added to form an azeotrope with the residual water and TFA. The resultant crude oil or solid was quantitated for yield calculation by NMR calibration with *p*-xylene (0.02 mmol), and analytically pure samples were obtained by purification by column chromatography or recrystallization.

For aspartic acid derivatives with the side chain protected as the *tert*-butyl ester, the ester functionality was removed first with 1.1 mL of a 9% solution of ethanedithiol in 1:1 TFA/CH$_2$Cl$_2$ for 4 h. To this reaction mixture, was added a 5 mL solution of 1:1:3 water/acetaldehyde/trifluoroethanol for another 4 h. The resin was washed with THF (3 × 5 mL), and the washings were combined, concentrated, and analyzed following the procedure described above.

Synthesis of Carbazate Linker (6). Ten grams of ArgoGel-OH (4.8 mmol, loading 0.48 mmol/g) was dried overnight in vacuo. After pre-solvation with anhydrous CH$_2$Cl$_2$, a solution of 4.67 g of carbonyldiimidazole (28.8 mmol, 6 equiv) in 60 mL of CH$_2$Cl$_2$ was added to the resin. An additional 10 mL of CH$_2$Cl$_2$ was added to rinse the sides of the flask. The reaction flask was purged under N$_2$ for 5 min. The reaction flask was placed on a shaker table and slowly shaken for 3 h. Following several rinses with CH$_2$Cl$_2$, a solution of hydrazine (9.0 mL, 290 mmol, 60 equiv) in 50 mL of DMF was added to the resin. After reacting for 1 h with slow shaking under N$_2$, the resin was rinsed with DMF (6 × 20 mL) and THF (4 × 20 mL). The resin was pumped overnight in vacuo and stored at −4 °C.

Quantitation of Carbazate Linker Loading Levels. The loading level of the carbazate linker was quantitated by loading the linker resin with the phenoxymethyl ketone derivative of *N*-benzyloxycarbonyl-L-phenylalanine (**4**). To 0.15 g of linker pre-solvated in THF, a solution of 0.112 g (0.288 mmol, 4 equiv) of **4** was added. After heating at 45 °C for 10 h, the resin was cleaved using 1:4:4:15 TFA/H$_2$O/acetaldehyde/trifluoroethanol. Amount of final product was quantitated by NMR calibration with *p*-xylene (0.02 mmol) or through purification by column chromatography. Cleavage afforded loading levels of 0.33−0.40 mmol/g (theoretical 0.41 mmol/g).

Loading of Halomethyl Ketone Derivatives of Phenylalanine, Alanine, and Thienylalanine. A solution of *N*-allyloxycarbonyl or *N*-benzyloxycarbonyl chloromethyl ketone (**7a**, **7b**, or **7c**, 4 equiv) in 0.2 M of THF was added to carbazate linker **6** pre-solvated in THF. After 4 h of gentle rocking on the shaker table, the solution was removed, and the resin was rinsed with THF (5×). This support-bound ketone was used immediately in order to prevent decomposition through azodiene formation.

Loading of Halomethyl Ketone Derivative of Glycine. A solution of *N*-allyloxycarbonyl glycine chloromethyl ketone (**7d**, 4 equiv) in

0.2 M of THF was added to carbazate linker **6** pre-solvated in THF. After 30 min of gentle rocking on the shaker table, the solution was removed, and the resin was rinsed with THF (5×). This support-bound ketone was used immediately in order to prevent decomposition through azodiene formation.

Loading of Halomethyl Ketone Derivative of Valine. A solution of *N*-allyloxycarbonyl valine chloromethyl ketone (**7e**, 4 equiv) in 0.2 M of THF was added to carbazate linker **6** pre-solvated in THF in a capped vial. After 9 h at 45−50 °C, the solution was removed, and the resin was rinsed with THF (5×). This support-bound ketone was used immediately in order to prevent decomposition through azodiene formation.

Loading of Halomethyl Ketone Derivative of Aspartic Acid (β-*tert*-butyl ester). A solution of *N*-allyloxycarbonyl aspartic acid (β-*tert*-butyl ester) chloromethyl ketone (**7f**, 4 equiv) in 0.2 M of THF was added to carbazate linker **6** pre-solvated in THF in a capped vial. After 6 h at 45−50 °C, the solution was removed, and the resin was rinsed with THF (5×). This support-bound ketone was used immediately in order to prevent decomposition through azodiene formation.

Loading of Halomethyl Ketone Derivative of Aminoisobutyric Acid. A solution of *N*-allyloxycarbonyl aminoisobutyric acid chloromethyl ketone (**7g**, 4 equiv) in 0.2 M of THF was added to carbazate linker **6** pre-solvated in THF in a capped vial. After 24 h at 45−50 °C, the solution was removed, and the resin was rinsed with THF (5×). This support-bound ketone was used immediately in order to prevent decomposition through azodiene formation.

General Procedure for Synthesis of Acyloxymethyl ketones. Loading of the halomethyl ketone onto the carbazate linker was performed as previously described. A solution of the carboxylic acid (4.0 mmol, 50 equiv) and *i*-Pr$_2$EtN (4.8 mmol, 60 equiv) in a 4 M solution of DMF was added to the resin. The cartridge was gently rocked on the shaker table for 7 h. After the solution was removed, the resin was rinsed with DMF (5 × 5 mL) and THF (5 × 5 mL) and dried overnight in vacuo. After cleavage of the resin, the desired acyloxymethyl ketone was formed in 80−90% yield as determined by NMR calibration with *p*-xylene (0.02 mmol).

10a: 80% yield, mp 106−107 °C. IR: 1718, 1724, 1734 cm^{-1}. ^{1}H NMR (300 MHz): δ 3.05 (dd, 1, *J* = 7.0, 13.9), 3.19 (dd, 1, *J* = 6.4, 14.1), 4.77 (app q, 1, *J* = 7.0), 4.89 (d, 1, *J* = 17.2), 4.98 (d, 1, *J* = 17.2), 5.09 (s, 2), 5.36 (d, 1, *J* = 7.4), 7.19 (d, 2, *J* = 6.4), 7.26−7.36 (m, 8), 7.46 (t, 2, *J* = 7.8), 7.60 (m, 1), 8.08 (d, 2, *J* = 8.0). ^{13}C NMR (125 MHz): δ 37.4, 58.3, 67.2, 67.3, 127.3, 128.1, 128.2, 128.5, 128.5, 128.8, 128.9, 129.3, 129.9, 133.5, 135.4, 136.0, 155.8, 165.7, 202.1. Anal. Calcd for C$_{25}$H$_{23}$NO$_5$: C, 71.93; H, 5.55; N, 3.36. Found: C, 71.99; H, 5.67; N, 3.21.

10b: 80% yield. IR: 1717, 1736 cm^{-1}. ^{1}H NMR (300 MHz): δ 2.15 (s, 3), 3.00 (dd, 1, *J* = 6.7, 14.0), 3.12 (dd, 1, *J* = 6.6, 14.3), 4.83−4.61 (m, 3), 5.08 (s, 2), 5.29 (d, 1, *J* = 7.5), 7.16 (d, 2, *J* = 6.4), 7.23−7.38 (m, 8). ^{13}C NMR (125 MHz): δ 20.4, 37.4, 58.1, 66.4, 67.2, 127.3, 128.1, 128.2, 128.5, 128.8, 129.2, 135.3, 136.0, 155.7, 170.0, 202.2. Anal. Calcd for C$_{20}$H$_{21}$NO$_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.64; H, 6.13; N, 4.11.

10c: 87% yield. IR: 1700, 1716, 1732 cm^{-1}. ^{1}H NMR (400 MHz): δ 2.73 (m, 2), 2.94−2.99 (m, 3), 3.11 (dd, 1, *J* = 6.5, 14.0), 4.61−4.74 (m, 3), 5.06 (s, 2), 5.32 (d, 1, *J* = 7.6), 7.13−7.34 (m, 15). ^{13}C NMR (101 MHz): δ 30.3, 30.7, 35.2, 37.2, 40.2, 58.1, 66.9, 67.1, 126.3, 127.2, 128.0, 128.2, 128.5, 128.8, 129.2, 135.4, 136.0, 140.1, 155.7, 172.0, 202.1. Anal. Calcd for C$_{27}$H$_{27}$NO$_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.55; H, 5.92; N, 3.21.

10d: 90% yield. IR: 1700, 1718, 1735 cm^{-1}. ^{1}H NMR (500 MHz): δ 3.06 (dd, 1, *J* = 6.8, 14.1), 3.21 (dd, 1, *J* = 6.8, 14.1), 4.79 (m, 1), 4.93 (d, 1, *J* = 17.0), 5.02 (d, 1, *J* = 17.0), 5.09 (s, 2), 5.36 (d, 1, *J* = 7.4), 7.17−7.37 (m, 13). ^{13}C NMR (125 MHz): δ 37.2, 58.3, 67.2, 68.0, 125.5, 127.3, 128.0, 128.1, 128.2, 128.5, 128.8, 129.2, 131.3, 132.2, 135.3, 136.0, 155.7, 163.9, 201.1. Anal. Calcd for C$_{25}$H$_{21}$NCl$_2$O$_5$: C, 61.74; H, 4.35; N, 2.88; Cl, 14.58. Found: C, 61.65; H, 4.48; N, 2.97; Cl, 14.37.

General Procedure for Synthesis of Mercaptomethyl Ketones. Loading of the halomethyl ketone onto the carbazate linker was performed as previously described. A solution of the thiol (4 mmol,

(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2927.

50 equiv) and *i*-Pr$_2$EtN (4.8 mmol, 60 equiv) in a 4 M solution of DMF was added to the resin. The cartridge was gently rocked on the shaker table for 2 h. After filtration of the solution, the resin was rinsed with DMF (5 × 5 mL) and THF (5 × 5 mL) and dried overnight in vacuo. Cleavage of the resin afforded the desired mercaptomethyl ketone in quantitative or near-quantitative yields as determined by NMR calibration with *p*-xylene (0.02 mmol).

12a: Quantitative yield, mp 74 °C. IR: 1694, 1720 cm^{-1}. ^{1}H NMR (300 MHz): δ 3.0 (dd, 1, J = 7.0, 13.9), 3.1 (dd, 1, J = 6.7, 13.9), 3.7 (s, 2), 4.9 (app q, 1, J = 7.0), 5.1 (s, 2), 5.4 (d, 1, J = 7.7), 7.1–7.4 (m, 15). ^{13}C NMR (125 MHz): δ 37.9, 42.7, 58.9, 67.0, 127.2, 128.0, 128.2, 128.5, 128.8, 129.1, 129.2, 130.2, 134.2, 135.7, 136.1, 155.7, 203.1. Anal. Calcd for C$_{24}$H$_{23}$NO$_3$S: C, 71.08; H, 5.72; N, 3.45. Found: C, 70.96; H, 5.67; N, 3.50.

12b: 97% yield. IR: 1709, 1722 cm^{-1}. ^{1}H NMR (400 MHz): δ 2.70 (t, 2, J = 7.6), 2.82–2.87 (m, 2), 3.04 (dd, 1, J = 6.9, 13.9), 3.14 (dd, 1, J = 6.7, 13.9), 3.23 (s, 2), 4.93 (m, 1), 5.12 (s, 2), 5.44 (d, 1, J = 7.9), 7.11–7.37 (m, 15). ^{13}C NMR (125 MHz): δ 33.4, 35.3, 38.1, 39.0, 58.6, 67.0, 126.5, 127.2, 128.1, 128.2, 128.5, 128.5, 128.5, 128.8, 129.2, 135.9, 136.1, 139.9, 155.7, 203.0. Anal. Calcd for C$_{26}$H$_{27}$NO$_3$S: C, 72.03; H, 6.28; N, 3.23. Found: C, 71.85; H, 6.45; N, 3.05.

12c: 97% yield. IR: 1708, 1722 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.80–1.84 (m, 2), 2.40 (t, 2, J = 7.3), 2.64–2.67 (m, 2), 3.01–3.05 (dd, 1, J = 6.8, 13.9), 3.08–3.13 (dd, 1, J = 6.8, 13.9), 3.17–3.18 (m, 2), 4.91 (m, 1), 5.05–5.11 (m, 2), 5.35 (d, 1, J = 7.8), 7.13–7.35 (m, 15). ^{13}C NMR (125 MHz): δ 30.3, 31.4, 34.6, 38.1, 38.9, 58.5, 67.0, 126.0, 127.1, 128.1, 128.2, 128.3, 128.4, 128.5, 128.7, 129.2, 135.9, 136.1, 141.1, 155.6, 203.1. Anal. Calcd for C$_{27}$H$_{29}$NO$_3$S: C, 72.45; H, 6.53; N, 3.13. Found: C, 72.26; H, 6.77; N, 3.23.

General Procedure for Synthesis of Phenoxymethyl Ketones. Loading of the halomethyl ketone onto the carbazate linker was performed as previously described. A solution of the desired phenol (4 mmol, 50 equiv) and *i*-Pr$_2$EtN (4.8 mmol, 60 equiv) in a 2 M solution of CH$_2$Cl$_2$ was added to the resin. The cartridge was gently rocked on the shaker table for 4 h. After the solution was removed, the resin was rinsed with CH$_2$Cl$_2$ and dried overnight in vacuo. Cleavage of the resin as previously described produced the desired phenoxymethyl ketone in yields that were determined by NMR calibration with *p*-xylene (0.02 mmol).

12d: 37% yield, mp 97–98 °C. IR: 1737, 1697 cm^{-1}. ^{1}H NMR (400 MHz): δ 3.04 (dd, 1, J = 6.6, 14.0), 3.21 (dd, 1, J = 6.2, 13.9), 4.55 (d, 1, J = 17.0), 4.67 (d, 1, J = 17.0), 4.96–5.00 (app q, 1, J = 6.8), 5.08 (s, 2), 5.33 (d, 1, J = 7.5), 6.84 (d, 2, J = 7.9), 7.00 (t, 1, J = 7.4), 7.15 (d, 2, J = 6.9), 7.24–7.35 (m, 10). ^{13}C NMR (101 MHz): δ 37.3, 58.0, 67.1, 71.9, 114.6, 121.9, 127.2, 128.1, 128.2, 128.5, 128.8, 129.2, 129.6, 135.5, 136.1, 155.7, 157.4, 204.9. Anal. Calcd for C$_{24}$H$_{23}$NO$_4$: C, 74.01; H, 5.96; N, 3.60. Found: C, 74.26; H, 6.17; N, 3.55.

General Procedure for Synthesis of Amidomethyl Ketones. Loading of the halomethyl ketone onto the carbazate linker was performed as previously described. A solution of the amine (4.0 mmol, 50 equiv) in a 4 M solution of DMF was added to the resin. The cartridge was gently rocked on the shaker table for 30 min. The solution was removed, and the resin was rinsed with DMF (5 × 5 mL). An acylation solution of the desired carboxylic acid (0.40 mmol, 5 equiv), *i*-Pr$_2$EtN (0.80 mmol, 10 equiv), HOAt (0.40 mmol, 5 equiv), and PyBOP (0.40 mmol, 5 equiv) in 0.2 M of DMF was made immediately before addition. The acylation solution was added to the support-bound amine, and the cartridge was gently shaken for 4 h. After removal of the solution, the resin was rinsed with DMF (5 × 5 mL) and resubjected to the same acylation conditions. Following this, the solution was removed, and the resin was rinsed with DMF (5 × 5 mL) and THF (5 × 5 mL) and dried overnight in vacuo. The resin was cleaved, and the desired amidomethyl ketone was formed in 50–61% yield as determined by NMR calibration with *p*-xylene (0.02 mmol).

16a: 53% yield. IR: 1635, 1717, 1734 cm^{-1}. ^{1}H NMR (500 MHz) [major rotamer]: δ 0.84 (t, 3, J = 7.3), 1.42 (app sextet, 2, J = 7.4), 2.61 (m, 2), 2.88 (m, 2), 2.98 (dd, 1, J = 7.8, 14.2), 3.13–3.23 (m, 3), 4.05 (d, 1, J = 17.5), 4.18 (m, 1), 4.58 (dd, 1, J = 7.4, 13.8), 5.06 (s, 2), 5.43 (d, 1, J = 7.3), 5.91 (s, 2), 6.64–6.73 (m, 3), 7.19–7.35 (m, 10). ^{13}C NMR (125 MHz): δ 11.1, 21.9, 31.0, 34.8, 37.3, 50.9, 53.8,

59.0, 67.0, 100.8, 108.3, 108.9, 121.1, 127.0, 128.0, 128.2, 128.5, 128.7, 129.1, 129.3, 135.0, 136.2, 145.9, 147.6, 155.9, 172.3, 203.9. Anal. Calcd for C$_{31}$H$_{34}$N$_2$O$_6$: C, 70.17; H, 6.46; N, 5.28. Found: C, 70.08; H, 6.64; N, 5.18.

16b: 55% yield. IR: 1628, 1715, 1734 cm^{-1}. ^{1}H NMR (500 MHz) [major rotamer]: δ 1.04 (t, 6, J = 6.0), 2.63 (m, 2), 2.87 (m, 2), 2.98 (dd, 1, J = 8.2, 14.4), 3.28 (dd, 1, J = 5.7, 14.3), 4.06–4.14 (m, 1), 3.93 (d, 1, J = 17.3), 4.02 (d, 1, J = 17.4), 4.61 (m, 1), 5.06 (s, 2), 5.45 (d, 1, J = 7.27), 5.90 (s, 2), 6.65–6.74 (m, 3), 7.21–7.33 (m, 10). ^{13}C NMR (125 MHz): δ 21.0, 21.0, 31.1, 35.2, 37.2, 47.9, 48.1, 59.4, 66.9, 100.8, 108.3, 108.9, 121.1, 127.0, 128.0, 128.1, 128.5, 128.7, 129.1, 129.3, 135.0, 136.5, 145.9, 147.6, 156.0, 171.4, 203.5. Anal. Calcd for C$_{31}$H$_{34}$N$_2$O$_6$: C, 70.17; H, 6.46; N, 5.28. Found: C, 70.20; H, 6.50; N, 5.13.

16c: 61% yield. IR: 1635, 1718, 1734 cm^{-1}. ^{1}H NMR (500 MHz): δ 2.69 (m, 2), 2.85–2.97 (m, 3), 3.17 (m, 1), 4.16 (m, 2), 4.49 (s, 2), 4.55 (m, 1), 5.03 (s, 2), 5.31 (d, 1, J = 7.3), 5.90 (s, 2), 6.65–6.71 (m, 3), 7.05–7.33 (m, 15). ^{13}C NMR (125 MHz): δ 31.0, 34.8, 37.2, 52.2, 53.2, 58.9, 67.0, 100.8, 108.2, 108.9, 121.1, 126.6, 127.0, 127.8, 128.0, 128.1, 128.2, 128.5, 128.7, 128.9, 129.0, 129.2, 134.7, 135.9, 145.8, 147.6, 155.8, 172.9, 203.7. Anal. Calcd for C$_{35}$H$_{34}$N$_2$O$_6$: C, 72.65; H, 5.92; N, 4.84. Found: C, 72.90; H, 6.08; N, 4.60.

16d: 59% yield. IR: 1645, 1716, 1732 cm^{-1}. ^{1}H NMR (500 MHz) [major rotamer]: δ 0.81 (t, 3, J = 7.4), 1.38 (app sextet, 2, J = 7.5), 2.98 (dd, 1, J = 7.8, 14.3), 3.18–3.22 (m, 3), 3.75 (m, 2), 3.79 (s, 3), 4.09 (d, 1, J = 17.5), 4.18 (d, 1, J = 17.5), 4.58 (m, 1), 5.05 (s, 2), 5.42 (d, 1, J = 7.4), 6.72–6.84 (m, 3), 7.17–7.34 (m, 11). ^{13}C NMR (125 MHz): δ 11.1, 21.9, 37.2, 40.2, 51.4, 53.6, 55.2, 59.0, 67.0, 112.6, 114.1, 121.1, 127.0, 128.0, 128.2, 128.5, 128.7, 129.1, 129.3, 129.6, 136.1, 136.3, 155.9, 159.8, 171.2, 203.5. Anal. Calcd for C$_{30}$H$_{34}$N$_2$O$_5$: C, 71.69; H, 6.82; N, 5.57. Found: C, 71.58; H, 6.70; N, 5.62.

16e: 50% yield. IR: 1635, 1716, 1733 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.75–0.82 (m, 3), 1.37–1.43 (m, 2), 1.98 (app quintet, 2, J = 7.4), 2.35 (m, 2), 2.67 (t, 2, J = 7.5), 2.97 (dd, 1, J = 7.7, 14.2), 3.11 (app sextet, 2, J = 7.3), 3.20 (dd, 1, J = 6.0, 14.2), 4.05 (d, 1, J = 17.5), 4.17 (d, 1, J = 17.5), 4.58 (m, 1), 5.05 (s, 2), 5.41 (d, 1, J = 7.4), 7.18–7.34 (m, 15). ^{13}C NMR (101 MHz): δ 11.0, 21.9, 26.6, 31.5, 35.0, 37.2, 50.9, 53.6, 58.9, 66.9, 125.8, 127.0, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6, 129.0, 129.2, 155.8, 173.1, 203.7. Anal. Calcd for C$_{31}$H$_{36}$N$_2$O$_4$: C, 74.37; H, 7.25; N, 5.60. Found: C, 74.22; H, 7.07; N, 5.64.

General Procedure for Synthesis of Unsubstituted Amidomethyl Ketones. Loading of the halomethyl ketone onto the carbazate linker was performed as previously described. A solution of sodium azide (0.8 mmol, 10 equiv) in a 0.2 *M* solution of MeOH was added to the resin. The cartridge was gently rocked on the shaker table for 4 h, and the solution was removed. The resin was rinsed with MeOH (5 × 5 mL) and THF (5 × 5 mL). The azide was reduced using a solution of SnCl$_2$ (1.6 mmol, 20 equiv), thiophenol (6.4 mmol, 80 equiv), and triethylamine (8 mmol, 100 equiv) in 6.2 mL of THF. After gentle shaking for 4 h, the solution was removed. The resin was rinsed with THF (2 × 5 mL), 1:1 THF:H$_2$O (2 × 5 mL), THF (2 × 5 mL), DMF (2 × 5 mL), MeOH (2 × 5 mL), and THF (2 × 5 mL).

An acylation solution composed of the desired carboxylic acid (0.40 mmol, 5 equiv), *i*-Pr$_2$EtN (0.80 mmol, 10 equiv), HOAt (0.40 mmol, 5 equiv), and PyBOP (0.40 mmol, 5 equiv) in 0.2 M of DMF was made immediately before addition. This solution was added to the support-bound amine, and the cartridge was gently shaken for 4 h. After the solution was removed, the resin was rinsed with DMF (5 × 5 mL) and resubjected to the same acylation conditions. Upon filtration of the acylation solution, the resin was rinsed with DMF (5 × 5 mL) and THF (5 × 5 mL) and dried overnight in vacuo. Cleavage of the resin produced the desired amidomethyl ketone in 62–93% yield as determined by NMR calibration with *p*-xylene (0.02 mmol).

18: 93% yield. IR: 1665, 1708 cm^{-1}. ^{1}H NMR (300 MHz): δ 0.93 (m, 6), 1.42–1.70 (m, 3), 4.07–4.14 (m, 4), 4.27 (m, 1), 4.56 (t, 1, J = 1.3), 4.58 (t, 1, J = 1.3), 5.09 (m, 2), 5.42 (d, 1, J = 7.9), 5.55 (s, 1), 5.90 (m, 1), 6.99 (s, 1), 7.33 (m, 5). ^{13}C NMR (101 MHz): δ 21.9, 22.9, 24.7, 41.2, 47.1, 48.7, 53.4, 67.1, 67.2, 118.0, 128.1, 128.3, 128.6, 132.5, 136.1, 156.3, 156.4, 172.9, 201.5. Anal. Calcd for C$_{21}$H$_{29}$N$_3$O$_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.33; H, 6.77; N, 9.88.

Racemization Studies. To determine the enantiomeric purity of the ketone products, acyloxymethyl ketone **10a**, mercaptomethyl ketone **12b**, and amidomethyl ketone **16a** were prepared form both D- and L-Cbz-phenylalanine. No racemization was detected (<1%). Retention times for both isomers are reported. An amidomethyl ketone **16a** was analyzed using a Chiralcel OD column (Daicel Chemical Industries). Solvent: 90:10 hexanes/2-propanol. Flow rate: 1 mL/min. Retention times: 4.3 min (*S*-isomer); 8.0 min (*R*-isomer). A mercaptomethyl ketone **12b** and an acyloxymethyl ketone **10a** were analyzed using a Chiralcel AD column (Daicel Chemical Industries). Solvent: 90:10 hexanes/2-propanol. Flow rate: 1 mL/min. Retention times (mercaptomethyl ketone): 13.9 min (*R*-isomer); 16.8 min (*S*-isomer). Retention times (acyloxymethyl ketone): 19.6 min (*R*-isomer); 31.1 min (*S*-isomer).

General Procedure for Synthesis of Fully Functionalized Ketones. The *N*-allyloxycarbonyl chloromethyl ketone derivative of the desired L-amino acid was loaded onto the carbazate linker, and nucleophilic displacement of the chloride and subsequent functionalization were performed as previously described. Following these steps, the resin was rinsed with CH_2Cl_2 (3 × 5 mL). A solution of trimethylsilyl azide (0.09 mL, 0.7 mmol, 8 equiv), tetrabutylammonium fluoride (0.063 g, 0.24 mmol, 3 equiv), Pd(PPh$_3$)$_4$ (0.018 g, 0.16 mmol, 0.2 equiv) in 5 mL of CH_2Cl_2 was added to the resin in a N_2 glovebag. The resin was gently rocked for 4 h, protected from light. After removal of the solution, the resin was rinsed with CH_2Cl_2 (5 × 5 mL) and DMF (5 × 5 mL).

An acylation solution of the desired carboxylic acid (0.40 mmol, 5 equiv), *i*-Pr$_2$EtN (0.8 mmol, 10 equiv), HOAt (0.40 mmol, 5 equiv), and PyBOP (0.40 mmol, 5 equiv) in 0.2 M of DMF was made immediately before addition. The acylation solution was added to the resin, and the cartridge was gently rocked for 4 h. Upon removal of this solution, the resin was rinsed with DMF (5 × 5 mL) and resubjected to the same acylation conditions. After excess reagents were filtered, the resin was rinsed with DMF (5 × 5 mL) and THF (5 × 5 mL) and dried overnight in vacuo. The material was cleaved from resin as previously described. Yields were determined by NMR calibration with *p*-xylene (0.02 mmol).

21a: Quantitative yield. IR: 1645, 1717, 1741, 1773 cm^{-1}. ^{1}H NMR (400 MHz): δ 2.62 (m, 2), 3.03 (dd, 1, J = 7.0, 14.1), 3.16 (dd, 1, J = 6.8, 14.1), 3.95 (m, 2), 4.84 (d, 1, J = 17.2), 4.96 (d, 1, J = 17.2), 5.00 (app q, 1, J = 7.0), 6.49 (d, 1, J = 7.5), 7.17−7.27 (m, 5), 7.44 (m, 2), 7.58 (t, 1, J = 6.2), 7.67 (dd, 2, J = 3.0, 5.5), 7.80 (dd, 2, J = 3.0, 5.5), 8.03 (d, 2, J = 8.3). ^{13}C NMR (101 MHz): δ 34.1, 34.5, 37.0, 56.4, 67.5, 123.4, 127.2, 128.5, 128.8, 129.0, 129.2, 129.9, 132.0, 133.5, 134.0, 135.6, 165.7, 168.1, 169.9, 202.1 Anal. Calcd for C$_{28}$H$_{24}$N$_2$O$_6$: C, 69.41; H, 4.99; N, 5.78. Found: C, 69.60; H, 5.08; N, 5.89.

21b: 78% yield. IR: 1683, 1719, 1732 cm^{-1}. ^{1}H NMR (500 MHz): δ 3.36−3.40 (dd, 1, J = 6.2, 15.2), 3.44−3.49 (dd, 1, J = 5.9, 15.2), 3.87 (s, 3), 3.88 (s, 3), 4.47−4.54 (app s, 2), 4.84−4.87 (d, 1, J = 17.1), 4.89−4.92 (d, 1, J = 17.1), 5.01−5.05 (m 1), 6.56−6.59 (d, 1, J = 16.2), 6.83−7.26 (m, 10), 8.07−8.11 (d, 1, J = 16.2). ^{13}C NMR (125 MHz): δ 31.0, 55.9, 56.1, 61.3, 66.8, 67.3, 112.9, 114.4, 115.5, 117.6, 119.4, 122.5, 124.2, 125.2, 127.1, 127.2, 128.2, 130.6, 135.2, 136.7, 141.4, 148.7, 153.1, 157.7, 166.1, 167.8, 201.1. Anal. Calcd for C$_{27}$H$_{26}$ClNO$_7$S: C, 59.61; H, 4.82; N, 2.57. Found: C, 59.44; H, 5.02; N, 2.60.

21c: 91% yield. IR: 1652, 1700, 1715 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.43 (s, 9), 2.88−3.09 (m, 6), 3.48 (d, 1, J = 13.4), 3.53 (d, 1, J = 13.4), 4.38 (m, 1), 4.98 (m, 1), 5.06 (s, 2), 5.20 (m, 1), 6.40 (d, 1, J = 7.2), 6.98−7.33 (m, 19). ^{13}C NMR (125 MHz): δ 30.3, 31.3, 34.5.

35.4. 37.6. 37.6. 38.2. 56.1. 57.3. 67.1. 125.5. 127.1. 127.1. 128.1. 128.2. 128.5. 128.6. 128.8. 128.8. 129.2. 129.2. 133.7. 135.8. 135.9. 136.0. 150.3. 155.8. 170.4. 202.1. Anal. Calcd for C$_{38}$H$_{42}$N$_2$O$_4$S: C, 73.28; H, 6.80; N, 4.50. Found: C, 73.00; H, 6.81; N, 4.38.

21d: 75% yield. IR: 1655, 1705 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.45−1.49 (m, 1), 1.60−1.66 (m, 2), 1.84−1.93 (m, 3), 2.26−2.32 (m, 1), 2.47 (m, 2), 2.61−2.68 (m, 4), 3.23 (d, 1, J = 14.1), 3.33 (d, 1, J = 14.3), 4.19 (m, 1), 4.22 (t, 2, J = 6.8), 4.87 (m, 1), 5.03 (d, 1, J = 8.4), 6.61 (d, 1, J = 7.6), 7.12−7.31 (m, 12), 7.40 (m, 2), 7.58 (m, 2), 7.77 (dd, 2, J = 3.7, 7.5). ^{13}C NMR (125 MHz): δ 21.9, 22.9, 24.7, 30.3, 31.5, 31.6, 33.1, 34.6, 37.9, 41.1, 47.1, 53.6, 56.4, 67.0, 126.2, 120.0, 120.0, 124.9, 126.0, 127.1, 127.7, 128.4, 128.6, 140.7, 141.1, 141.3, 143.6, 143.8, 156.2, 172.0, 203.0. Anal. Calcd for C$_{41}$H$_{46}$N$_2$O$_4$S: C, 74.29; H, 6.99; N, 4.23. Found: C, 74.10; H, 7.02; N, 4.11.

21e: 85% yield of the mixture of two diastereomers. IR: 1648, 1716, 1730 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.26−1.28 (m, 3), 1.31−1.33 (m, 3), 3.40−3.74 (m, 5), 4.14−4.20 (m, 2), 5.21−5.30 (m, 1), 6.86 (d, 1, J = 3.4), 6.93−6.95 (m, 1), 7.00−7.04 (m, 1), 7.18−7.19 (m, 1), 7.59−7.61 (m, 2), 7.80−7.83 (m, 2), 7.92−7.94 (m, 2), 7.96−7.98 (m, 2). ^{13}C NMR (125 MHz): δ 14.1, 14.1, 16.7, 16.8, 31.2, 31.3, 38.3, 38.4, 41.2, 41.2, 58.0, 58.3, 61.4, 61.5, 123.9, 125.0, 125.0, 126.2, 126.3, 126.9, 126.9, 127.1, 127.1, 127.9, 127.9, 131.5, 132.7, 132.7, 134.6, 135.0, 135.0, 137.3, 137.3, 166.0, 166.0, 166.8, 172.3, 172.4, 202.2, 202.5. Anal. Calcd for C$_{27}$H$_{26}$N$_2$O$_5$S$_2$: C, 62.05; H, 5.01; N, 5.36. Found: C, 62.10; H, 5.02; N, 5.38.

21f: 48% yield. IR: 1713 cm^{-1}. ^{1}H NMR (300 MHz): δ 1.86 (m, 2), 2.50 (m, 2), 2.67 (m, 2), 2.87−3.13 (m, 2), 3.41 (s, 2), 5.22 (m, 1), 6.65 (d, 1, J = 16.2), 7.05−7.34 (m, 8), 7.77 (d, 1, J = 16.0). ^{13}C NMR (125 MHz): δ 30.3, 31.5, 34.6, 35.2, 37.5, 53.1, 126.0, 127.7, 128.4, 128.5, 128.8, 129.7, 131.9, 135.0, 136.2, 141.2, 165.2, 175.3, 201.7. Anal. Calcd for C$_{23}$H$_{23}$Cl$_2$NO$_4$S: C, 57.50; H, 4.83; N, 2.92. Found: C, 57.50; H, 4.66; N, 2.88.

22a: 61% yield. IR: 1634, 1646, 1713, 1771 cm^{-1}. ^{1}H NMR (400 MHz) [major rotamer]: δ 0.84 (t, 3, J = 7.3), 1.43 (app sextet, 2, J = 7.5), 2.59 (m, 4), 2.74−2.78 (m, 2), 2.92−3.02 (m, 2), 3.13−3.20 (m, 2), 3.90−3.96 (m, 2), 4.03 (d, 1, J = 17.5), 4.18 (d, 1, J = 17.5), 4.79 (m, 1), 5.91 (s, 2), 6.59 (d, 1, J = 8.1), 6.64−6.73 (m, 3), 7.18−7.28 (m, 5), 7.69−7.72 (m, 2), 7.80−7.82 (m, 2). ^{13}C NMR (101 MHz): δ 11.1, 21.9, 31.0, 34.1, 34.4, 34.8, 36.8, 51.0, 54.0, 57.4, 100.8, 108.3, 108.9, 121.1, 123.3, 127.0, 128.7, 129.2, 132.0, 134.0, 135.0, 136.3, 145.9, 147.6, 168.1, 169.9, 172.4, 203.7. Anal. Calcd for C$_{34}$H$_{35}$N$_3$O$_7$: C, 68.33; H, 5.90; N, 7.03. Found: C, 68.13; H, 6.05; N, 7.01.

22b: 40% yield. IR: 1527, 1643, 1733 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.89 (t, 3, J = 7.4), 0.99 (d, 3, J = 6.8), 1.11 (d, 3, J = 6.8), 1.54 (app sextet, 2, J = 7.2), 2.40−2.46 (m, 1), 2.63−2.67 (m, 2), 2.87−2.91 (m, 2), 3.18−3.65 (m, 2), 4.18 (d, 1, J = 17.4), 4.39 (d, 1, J = 17.4), 4.86 (m, 1), 5.92 (s, 2), 6.65−6.74 (m, 3), 7.19 (d, 1, J = 8.3), 7.65 (t, 1, J = 8.0), 8.16 (d, 1, J = 7.7), 8.37 (ddd, 1, J = 0.9, 2.2, 8.2), 8.67, (t, 1, J = 1.9). ^{13}C NMR (125 MHz): δ 11.1, 17.3, 20.0, 22.1, 30.5, 31.0, 34.8, 51.1, 54.4, 61.6, 100.8, 108.3, 108.9, 121.1, 122.3, 126.3, 129.9, 133.1, 134.9, 135.6, 145.9, 147.6, 148.3, 165.3, 172.6, 204.1. Anal. Calcd for C$_{26}$H$_{31}$N$_3$O$_7$: C, 62.76; H, 6.28; N, 8.45. Found: C, 62.52; H, 6.28; N, 8.34.

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