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Investigation of the Configurational Stabilities of Chiral Isocyanoacetates in Multicomponent Reactions

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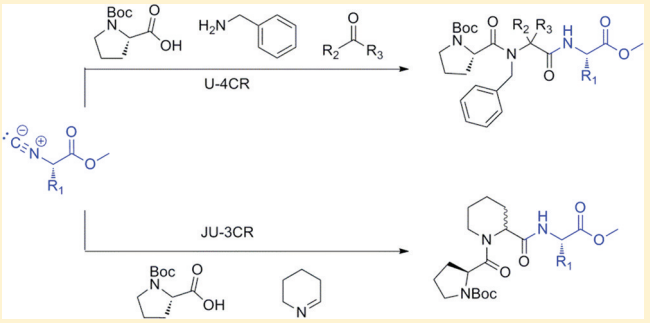
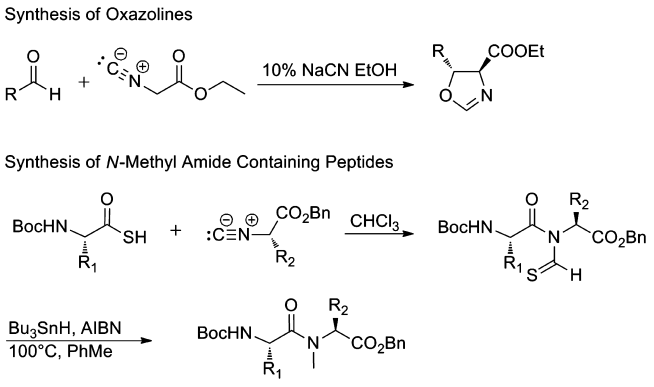
Supporting Information

ABSTRACT: Isocyanoacetates are uniquely reactive compounds characterized by an ambivalent isocyano functional group and an enolizable α-carbon. It is widely believed that chiral α-substituted isocyanoacetates are configurationally unstable in some synthetically useful isocyanide-based multicomponent reactions. Herein, we demonstrate that chiral isocyanoacetates can be used with minimal to negligible epimerization in a variety of canonical Ugi four-component condensations as well as Joullié–Ugi three-component condensations, reactions that are particularly useful for constructing complex peptide structures in a single synthetic operation.



Isocyanoacetates are synthons of growing utility in synthetic organic chemistry.[1] In addition to the intriguing reactivity of their isocyano functional group, the α-carbon of an isocyanoacetate is acidic and as such can act as a nucleophile. These peculiar compounds have been used as substrates in the synthesis of functionalized heterocycles wherein the nucleophilicity of their α-carbon is essential (Scheme 1).[1−3] More recently, Danishefsky and co-workers used these compounds as chiral substrates in the preparation of *N*-methyl peptides containing α-amino acids of prescribed configurations (Scheme 1).[4] Unlike the heterocycle-forming reactions, the α-acidity of isocyanoacetates is a potential liability in peptide synthesis due to the possibility of racemization. Even under mildly basic conditions, reversible enolization of chiral α-substituted isocyanoacetates can occur.[1,5] Indeed, in the aforementioned synthesis of *N*-methyl peptides, a racemization-free, dehydrative method was used to prepare the enantiomerically pure isocyanoacetate substrates from chiral *N*-formylamino acid esters, and the reactions were performed under mildly acidic conditions.[4,5]

Scheme 1. Reactions of Isocyanoacetates



Despite their utility as substrates in the reactions described in Scheme 1, chiral isocyanoacetates[6] are thought to be unsuitable substrates in two reactions for which isocyanides are best known, specifically, the Ugi four-component condensation (U-4CR) and Joullié–Ugi three-component condensation (JU-3CR).[1,7] The inherent lack of stereoselectivity in these multicomponent reactions is often tolerated because of their high yield and simple execution;[8] however, the inclusion of epimerizable isocyanoacetate substrates has been avoided because it could yield an unacceptably complex mixture of diastereomers. In our survey of the literature, we found that widely held notions about the configurational instability of isocyanoacetates are based on two U-4CRs[7a,9] and one JU-3CR.[10] It seemed that such a small number of examples did not justify this broad generalization. Clarification of this issue is warranted by the utility of these substrates and multicomponent reactions in the facile preparation of complex peptide-like structures.

The reported epimerization of chiral isocyanoacetates in U-4CR and JU-3CRs could be explained by two distinct mechanisms (Scheme 2). In one mechanism, the reactants and/or intermediates promote epimerization by abstraction of a proton from the isocyanoacetate α-carbon, which has an estimated pK_a of 9–11.[7b] Alternatively, epimerization could occur via the reversible formation of an oxazole intermediate.[3,11] Either or both of these mechanisms is feasible, but the

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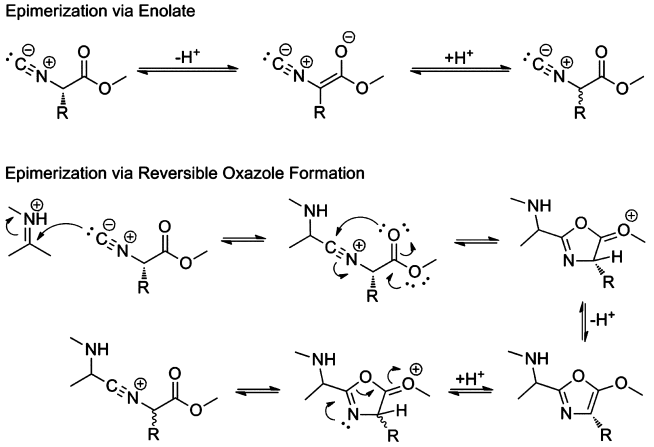
Scheme 2. Hypothetical Mechanisms for Isocyanoacetate Epimerization



complexities of these multicomponent reactions preclude unambiguous elucidation of the operative mechanism(s) for epimerization. Nevertheless, we assessed the influence of reagents and reaction conditions over the configurational stability of chiral isocyanoacetates. To the best of our knowledge, this is the first comprehensive study of the configurational stability of chiral isocyanoacetates in U-4CR and JU-3CRs.

We first conducted a series of epimerization experiments wherein enantiomerically pure isocyanoacetate derived from (*S*)-*N*-formylalanine methyl ester was incubated with substrates of the U-4CR reaction. After incubation for the indicated time, the enantiomeric purity of the isocyanoacetate was determined by chiral GC−MS analysis (Table 1). While the isocyanoacetate was configurationally stable alone and in the presence of Boc-proline, it racemized quickly when incubated with benzylamine, a typical U-4CR reaction substrate. We found that racemization was nearly instantaneous in methanol but took a few hours in dichloromethane. The relative rates of racemization are consistent with differences in the polarities of the two solvents commonly used in U-4CRs. Our data clearly indicate that a typical amine substrate in an U-4CR reaction can promote epimerization of the isocyanoacetate.

Table 1. Effect of U-4CR Reactants on the Stereochemical Configuration of a Chiral Isocyanoacetate[a]

	enantiomeric ratio (*S*:*R*) in methanol/dichloromethane		
reactant(s)	0 h	2 h	20 h
none	99:1/98:2	99:1/97:3	99:1/97:3
Boc-proline	99:1/98:2	99:1/97:3	99:1/98:2
benzylamine	51:49/93:7	52:48/67:36	racemic/racemic
isobutyraldehyde + benzylamine	99:1/99:1	52:48/99:1	racemic/66:34
benzaldehyde + benzylamine	97:3/98:2	90:10/98:2	61:39/97:3
cyclohexanone + benzylamine	73:27/99:1	54:46/81:19	racemic/racemic
Boc-proline + benzylamine	99:1/99:1	79:21/91:9	racemic/racemic

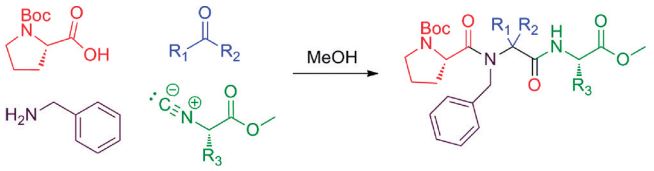
[a]Enantiomeric ratios were determined by chiral GC−MS. Incubations were conducted at 0.5 M concentration. Samples were analyzed at the indicated time points.

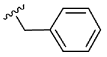
We hypothesized that the ability of the amine to promote epimerization should be compromised by the oxo-compound and carboxylic acid substrates of the U-4CR. The oxo-compound undergoes a reversible reaction with the amine forming an imine and thus limits the availability of free amine for epimerization. On this basis, the enantiomerically pure isocyanoacetate was incubated with benzylamine that had been allowed to react for 2 h with benzaldehyde, isobutyraldehyde, or cyclohexanone. Consistent with our hypothesis, the rates of epimerization were suppressed relative to those observed in incubations with benzylamine alone. Additionally, there was a correlation between the reactivity of the oxo-compound and the relative rates of isocyanoacetate epimerization. Specifically, the addition of the ketone had a smaller effect on the rate of epimerization than did either aldehyde (Table 1). Indeed, the condensation equilibria for aldimines generally lies further in favor of products than do those for ketimines.[12] We also suspected that the carboxylic acid component should limit the availability of the basic amine species via proton transfer. Accordingly, when the enantiomerically pure isocyanoacetate was added to a solution of Boc-proline and benzylamine, the rates of epimerization were suppressed relative to those of the incubations with benzylamine alone (Table 1).

Since the carbonyl compound and the carboxylic acid reactants individually suppress isocyanoacetate epimerization by the amine, one would expect these reactants to synergistically suppress epimerization in an U-4CR. We assessed epimerization in U-4CRs using model reactions of Boc-proline, benzylamine, and enantiomerically pure isocyanoacetate derived from (*S*)-*N*-formylalanine methyl ester and five different oxo-compounds, including three aldehydes and two symmetric ketones. Moreover, Boc-proline, benzylamine, and isobutyraldehyde were reacted with three additional isocyanoacetates derived from *N*-formylamino acid esters (Table 2). Epimerization could be inferred from either measurement of the enantiomeric ratio of the isocyanoacetate-derived amino acid in the U-4CR product or of the diastereomeric ratios of the products. In reactions with aldehydes and cyclobutanone, the enantiomeric ratios of the isocyanoacetate-derived amino acids in the reaction products were determined by "advanced Marfey analysis".[13,14] Isocyanoacetate epimerization in the reaction with cyclohexanone was assessed by measuring the relative ratios of the two possible diastereomeric products using LC−MS.[15] In reactions with cyclohexanone and all three aldehydes, we deduced that epimerization of all four isocyanoacetates was negligible. Unexpectedly, in the case of cyclobutanone, an appreciable amount of epimerization was observed. In any case, the apparent stability of the chiral isocyanides in these model reactions raised the possibility that this approach could be used in the preparation of *N*-methyl peptides, an important class of biomolecules. Indeed, the U-4CR of Boc-proline, methylamine, isobutyraldehyde, and the isocyanoacetate derived from (*S*)-*N*-formylleucine methyl ester yielded the expected *N*-methyl tripeptide in 68% yield with 4.2% epimerization of the isocyanoacetate (as determined by Marfey analysis).

Since our preliminary results showed that reaction of the amine and the oxo-compound significantly reduced isocyanoacetate epimerization, we systematically analyzed the effect of their precondensation time on the reaction outcome. With isobutyraldehyde, isocyanoacetate epimerization was minimal with a precondensation time of seconds and undetectable with a precondensation time of 1 h or longer. In contrast, epimerization was significant in reactions with cyclohexanone

Table 2. Ugi Four-Component Condensations with Chiral Isocyanoacetates[a]



Entry	R_1/R_2	R_3	Yield%	Isocyanoacetate Epimerization %
1	H/Ph	CH_3	86	<5.0[b]
2	H/CH_2CH_2Ph	CH_3	58	<5.0[b]
3	H/*i*Pr	CH_3	96	<5.0[b]
4	H/*i*Pr		95	2.3
5	H/*i*Pr		98	3.7
6	H/*i*Pr		96	3.6
7	-$CH_2CH_2CH_2$-	-CH_3	81	30
8	-$CH_2(CH_2)_3CH_2$-	-CH_3	90	5.6

[a]Reported yields are the average of two trials. Isocyanide epimerization was inferred from Marfey analysis of products in all cases except entry 8, for which epimerization was inferred from LC–MS analysis of the reaction product. Reactions were carried out at 2 M concentration. Aldehyde reactions ran for 24 h, and ketone reactions ran for 48 h after a 2 h precondensation of benzylamine and the indicated oxo-compound. All components were combined in an equimolar ratio. [b]In reactions with the isocyanoacetate derived from (*S*)-*N*-formylalanine methyl ester, epimerization in quantities less than 5% could not be reliably quantified.

when the precondensation time was less than 2 h (Table 3). These observations are consistent with the relative suppression

Table 3. Effect of Benzylamine–Cyclohexanone Precondensation Time on Isocyanoacetate Epimerization[a]

precondensation time	0 min	30 min	60 min	120 min
isocyanoacetate epimerization %	9.1	6.5	6.4	5.6

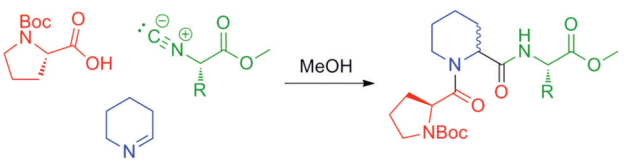
[a]Isocyanoacetate epimerization inferred from LC–MS analysis of the products. Reactions were carried out at 2 M concentration for 48 h after the indicated precondensation time.

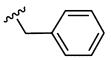
of amine-promoted isocyanoacetate epimerization by aldehydes and ketones as described above (see Table 1). Collectively, these observations indicate in most cases the isocyanoacetates are configurationally stable in U-4CRs.

Chiral isocyanoacetates can also serve as useful substrates for Joullié–Ugi three-component condensations, in which an isocyanide and carboxylic acid react with a cyclic imine.[16] The use of this reaction with isocyanoacetates and *N*-protected amino acids is particularly useful for the preparation of tripeptides containing cyclic amino acids such as proline and pipecolic acid.[16] There is controversy about the configurational stability of chiral isocyanoacetates in JU-3CR. Whereas Joullié and co-workers reported the use of an optically active isocyanoacetate without racemization,[16b] Riva and co-workers reported a reaction product with a mixture of configurations at the stereogenic center originating from their chiral isocyanoacetate.[10] Our group recently reported that a JU-3CR utilizing the isocyanoacetate derived from (*S*)-*N*-formylalanine methyl ester was diastereoselective on the basis of the observation of two peaks in the HPLC chromoatogram.[17] Subsequent Marfey analyses of the resolved peaks indicated that the major peak was in fact a mixture of three diastereomers rather than a single diastereomer. These observations were indicative of epimerization of the isocyanoacetate in the JU-3CR.

In light of our studies of U-4CRs (*vide supra*), isocyanoacetate epimerization in the JU-3CR is especially curious, as there is no basic amine substrate. In our observations, we suspected that the apparent isocyanoacetate epimerization was a consequence of the manner in which the cyclic imine was prepared. The cyclic imine, Δ^1-piperideine, was prepared by base-promoted dehydrohalogenation of *N*-chloropiperidine and used without purification because of its instability. We proposed that residual base from the dehydrohalogenation was effecting epimerization of the isocyanoacetate. To circumvent the use of a crude reactant, the Δ^1-piperideine was induced to undergo a reversible trimerization yielding crystalline and easily isolated tripiperideine.[18] JU-3CR reactions of four different chiral isocyanoacetates with Boc-proline and a molar excess of tripiperideine (containing 1.5 equiv of Δ^1-piperideine) yielded the expected peptides in moderate to good yields (Table 4).[19] Advanced

Table 4. Joullié–Ugi Three-Component Condensations with Isocyanoacetates[a]



Entry	R	Yield%	Isocyanoacetate Epimerization %
1	CH_3	70	20.3
2		54 (31)	18.4 (3.4)
3		58	16.8
4		54	28.1

[a]Reported yields are the average of two trials. Isocyanide epimerization was inferred from Marfey analysis. Reactions were carried out at 1 M concentration for 48 h with a 0.5 molar excess of Δ^1-piperideine. The yields and epimerizations of reactions with equimolar reactants are shown in parentheses.

Marfey analyses of these products revealed 17–28% epimerization of the isocyanoacetate substrates. In the JU-3CR with the isocyanoacetate derived from (*S*)-*N*-formylleucine methyl ester, we found that epimerization could be reduced to 3.4% by using 1 equiv of Δ^1-piperideine, in the form of tripiperideine. The reaction with this stoichiometry provided the product in only 31% yield, which compares unfavorably to the reaction with an excess of tripiperideine (Table 4, entry 2).

Although chiral isocyanoacetates have previously been shown to be configurationally stable in the Passerini three-component condensation,[20,21] they have seldom been used as substrates in U-4CRs and JU-3CRs because of concerns about their potential

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for racemization in the course of the reaction. Indeed, several groups have used elaborate protecting groups and cumbersome reaction conditions to avoid isocyanoacetate epimerization.[7] Our observations suggest that these strategies may only be necessary in select cases. Here, we show that isocyanoacetate epimerization does not take place in canonical Ugi four-component reactions with aldehydes and can be significantly suppressed in those with ketone substrates by increasing the precondensation time. Further, we report a procedure for racemization-free Joullié–Ugi reactions with chiral isocyanoacetates and tripiperideine. These findings should prompt reconsideration of multicomponent reactions for the diversity- and target-oriented synthesis of structurally complex peptides as alternatives to the classical synthetic methods that are labor-intensive and require expensive coupling reagents.

■ EXPERIMENTAL SECTION

All commercially available reagents were used without further purification. NMR spectra were obtained at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts were referenced on residual solvent peaks: $CDCl_3$ (δ = 7.27 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR).

Direct Measurement of Chiral Isocyanoacetate Epimerization. As described in Table 1, epimerization of a chiral isocyanoacetate was assessed by GC–MS analysis. Aliquots (100 μL) of 1 M stock solutions of the enantiomerically pure isocyanoacetate derived from (*S*)-*N*-formylalanine in either methanol or dichloromethane were treated with substrates of the U-4CR. Negative control experiments in which the isocyanoacetate solution was not treated with any substrate were carried out in parallel. At the indicated time points, 3 μL samples were removed from the isocyanoacetate solutions and dissolved in 1 mL of dichloromethane. From the resulting solution, splitless injections of 1 μL were made onto a Varian CP Chirasil-DEX 25 m × 0.32 mm column with an inlet temperature of 150 °C and a detector temperature of 220 °C. Initial column temperature of 50 °C was held for 4 min, followed by a 12 °C/min ramp to 150 °C, and then holding for 2 min. Enantiomeric ratios were determined by integration of the total ion chromatogram.

Indirect Measurement of Chiral Isocyanoacetate Epimerization. As described in Tables 2–4, epimerization was inferred from either measurement of the enantiomeric ratio of the isocyanoacetate-derived amino acid in the U-4CR product or of the diastereomeric ratios of the products. In the former, a published procedure for advanced Marfey analysis was used.[14] The derivatized amino acids were separated on a Higgins Analytical-Hasil C18 column (100 mm × 1.8 mm) using a binary mobile phase: A = H_2O/0.1% formic acid and B = acetonitrile. Solvent gradient: 20–60% B over 20 min at 0.250 mL/min. UV Detection: 350 nm. Negative ion mode was used for mass detection. Epimerization was quantified directly by integration of the Marfey analysis UV chromatograms. As determined in limits of detection experiments, the ratio of derivatized (*R*)- and (*S*)-alanine could not be measured in quantities less than 5%.

Alternatively, isocyanoacetate epimerization in reactions with symmetric ketones (e.g., cyclohexanone) was assessed by measuring the relative ratios of the two possible diastereomeric U-4CR products using LC–MS. After flash chromatography, the MCR products were dissolved in methanol to a concentration of 1 mg/mL. Samples (3 μL) were separated on a Higgins Analytical-Hasil C18 column (100 mm × 1.8 mm). The compounds were separated using a binary mobile phase: A = H_2O/0.1% formic acid and B = acetonitrile. Solvent gradient: 20–60% B over 20 min at 0.250 mL/min. UV Detection: 214 nm. Positive ion mode was used for mass detection.

General Amino Acid Ester Formylation Procedure. Dicyclohexylcarbodiimide (DCC) (6.5 mmol, 1.34 g) was dissolved in dichloromethane (DCM) (20 mL), and the mixture was cooled to 0 °C. To this solution, 98% formic acid (6.5 mmol, 0.25 mL) was added, and the mixture was allowed to stir for 10 min, over the course of which a white precipitate formed. The amino acid methyl ester hydrochloride (5 mmol, 0.908 g) and dimethylaminopyridine (DMAP) (1.0 mmol, 123 mg) were added directly to the solution of the *O*-formylisourea. Five microliters of DCM was used to rinse residual reagent from the neck of the flask into the reaction. Finally, *N*-methylmorpholine (NMM) (8 mmol, 0.88 mL) was added, and the reaction was allowed to stir for 16 h. Upon completion, the reaction was concentrated in vacuo to near dryness and then suspended with cold ethyl acetate and filtered through a short silica gel column (0.5 in. × 1 in.). The filtrate was concentrated in vacuo, and the residue was applied directly to a silica gel column (5 in. × 2 in. column). The *N*-formylamino acid methyl ester product was eluted using an ethyl acetate/hexanes mobile phase. Often times, the product was contaminated with dicyclohexylurea (DCU) after flash chromatography. To remove this impurity, the concentrated residue was dissolved in ethyl acetate (0.5–1 mL) and stored at −20 °C overnight, during which time the contaminating DCU precipitated. The precipitate was filtered and washed with −20 °C ethyl acetate. The filtrate was concentrated yielding a colorless oil.

(*S*)-*N*-Formylalanine Methyl Ester. Yield 1.162 g (89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (1 H, s), 6.20 (1 H, broad s), 4.71 (1 H, dt, J = 7.2 Hz, 7.2 Hz), 3.78 (3 H, s), 1.46 (3 H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 160.4, 52.6, 46.8, 18.5; HRMS (FAB) calcd for $[C_5H_9NO_3 + Na]^+$ 154.0480, found 154.0483.

(*S*)-*N*-Formylleucine Methyl Ester. Yield 801 mg (82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (1 H, s), 6.01 (1 H, broad s), 4.76 (1 H, td, J = 8.8, 3.5 Hz), 3.76 (3 H, s), 1.68 (2 H, m), 1.59 (1 H, m), 0.97 (3 H, d, J = 6.1 Hz), 0.95 (3 H, d, J = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 180.6, 52.5, 49.3, 41.7, 24.8, 22.9, 21.9; HRMS (FAB) [M + Na]$^+$ calcd for $[C_8H_{15}NO_3 + Na]^+$ 196.0950, found 196.0955.

(*S*)-*N*-Formylphenylalanine Methyl Ester. Yield 869 mg (84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (1 H, s), 7.28 (3 H, m), 7.11 (2 H, dd, J = 7.9 1.0 Hz), 6.05 (1 H, broad s), 4.99 (1 H, dt, J = 7.9, 6.10 Hz), 3.76 (3 H, s), 3.18 (1 H, d, J = 5.3 Hz), 3.16 (1H, d, J = 5.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 180.4, 129.3, 128.9, 127.3, 52.5, 51.8, 37.7; HRMS (FAB) calcd for $[C_{11}H_{13}NO_3 + Na]^+$ 230.0793, found 230.0785.

(*S*)-*N*-Formylmethionine Methyl Ester. Yield 939 mg (98%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (1 H, s), 6.35 (1 H d, J = 5.3 Hz), 4.82 (1 H, td, J = 7.85.3 Hz), 3.79 (1 H, s), 2.53 (2 H, t, J = 7.10 Hz), 2.21 (1 H, m), 2.10 (1 H, s), 2.04 (1 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 160.7, 52.8, 50.2, 31.6, 29.8, 15.5; HRMS (FAB) calcd for $[C_7H_{13}NO_3S + Na]^+$ 214.0514, found 214.0508.

General Procedure for *N*-Formylamino Acid Ester Dehydration. The *N*-formylamino acid ester was dissolved in dry DCM (20 mL) under nitrogen and cooled to −78 °C. Triphosgene (0.35 equiv) was dissolved separately in dry DCM (5 mL). The triphosgene solution was added dropwise to the cold *N*-formylamino acid ester solution. After the mixture was stirred for 5 min, neat NMM (2 equiv) was added slowly over the course of 10 min. With all reagents added, the reaction was stirred at −78 °C for 2 h and quenched by the addition of water (10 mL). The heterogeneous mixture was allowed to warm until all of the ice had melted and the two phases were partitioned. The aqueous phase was extracted with an additional 20 mL DCM, which was pooled and dried over magnesium sulfate. The dried solution was then filtered through a short silica gel column (1.5 in. × 1 in.) and concentrated in vacuo.

Isocyanoacetate Derived from (*S*)-*N*-Formylalanine Methyl Ester. Yield 723.9 mg (71.2%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35 (1 H, quart, J = 7.3 Hz), 3.84 (3 H, s), 1.67 (3 H, d, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 159.5, 53.4, 51.6, 19.4; LRMS (EI) [M]$^+$ 113, [M − 45]$^+$ 68, [M − 54]$^+$ 59, [M − 59]$^+$ 54.

Isocyanoacetate Derived from (*S*)-*N*-Formylleucine Methyl Ester. Yield 506 mg (80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (1 H, dd, J = 10.1, 4.8 Hz), 3.83 (3 H, s), 1.87 (2 H, m), 1.70 (1 H, m), 0.99 (6 H, t, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 160.1, 55.1, 53.3, 41.3, 24.8, 22.6, 20.9; LRMS (EI) [M − 15]$^+$ 140, [M − 43]$^+$ 112, [M − 59]$^+$ 96, [M − 87]$^+$ 68, [M − 100]$^+$ 55.

Isocyanoacetate Derived from (*S*)-*N*-Formylphenylalanine Methyl Ester. Yield 596 mg (80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.34 (3 H, m), 7.27 (2H, m), 4.48 (2 H, dd, J = 8.28, 4.88 Hz), 3.82 (3 H, s), 3.28 (1 H, dd, J = 14.03, 4.82 Hz), 3.15 (1 H, dd, J = 13.81, 8.33 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 160.9, 134.3, 129.3, 128.89, 127.9, 58.0, 53.4, 38.9; LRMS (EI) $[M - 32]^+$ 157, $[M - 59]^+$ 130, $[M - 98]^+$ 91.

Isocyanoacetate Derived from (*S*)-*N*-Formylmethionine Methyl Ester. Yield 563 mg (81%): ^{1}H NMR(400 MHz, $CDCl_3$) δ 4.57 (1 H, dd, J = 7.89, 6.14 Hz), 3.85 (3 H, s), 2.60−2.81 (2 H, m), 2.21 (2 H, dd, J = 14.03, 7.00 Hz), 2.12 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 160.7, 54.8, 53.5, 31.8, 26.6, 15.4; LRMS (EI) $[M]^+$ 173, $[M - 59]^+$ 114, $[M - 86]^+$ 87, $[M - 99]^+$ 74, $[M - 112]^+$ 61.

***N*-Chloropiperidine.** Piperidine (5.8 mmol, 1.39 mL) and *tert*-butanol (5.8, 0.55 mL) were added to methyl *tert*-butyl ether (MTBE) (30 mL), and the mixture was cooled to 0 °C. Acetic acid (11.8 mmol, 0.68 mL) and commercial grade cleaning bleach (11.8 mmol, 23.5 mL) were added simultaneously with stirring. The reaction was stirred for 30 min, after which water (15 mL) was added. The phases were partitioned, and the organic phase washed with brine (15 mL). The organic material was dried over magnesium sulfate and then concentrated. Yield 1.17 g (84.0%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14 (4 H, s broad), 1.72 (4 H, quint, J = 5.7 Hz), 1.46 (2 H, s broad); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.9, 27.6, 22.9; LRMS (EI) $[M]^+$ 119.3.

Tripiperideine. *N*-Chloropiperidine (0.915 g, 7.65 mmol) was dissolved in diethylether (5 mL) and treated with 25% sodium methoxide in methanol (2.28 mL, 9.95 mmol). After refluxing for 45 min, a white precipitate formed. The reaction was allowed to cool to room temperature, after which water (7 mL) added, resulting in solvation of the white precipitate. The phases were partitioned, and the aqueous phase was washed with diethylether (4 × 10 mL). All of the organic phases were pooled and dried over $MgSO_4$. The ether layer was then filtered and concentrated, yielding a pale, yellow oil. The oil was dissolved in a minimum volume of acetone from which crystals began to form at 0 °C. Either a seed crystal or scratching the inside of the flask with a glass stirring rod was required to induce crystallization. Once crystals were visible at 0 °C, the solution was stored at −20 °C for 2−3 days, after which the large white tripiperideine crystals were filtered and washed with −20 °C acetone. Yield 0.4086 g (64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (3 H dt, J = 10.64, 5.04 Hz), 2.80 (3 H, dd, J = 6.8, 1.9 Hz), 2.02 (3 H dt, J = 11.2, 5.9 Hz), 1.72 (9 H, m), 1.57 (6 H, m), 1.31 (3 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.9, 46.4, 29.2, 25.8, 22.3.

Ugi Reaction General Procedure. To a 1 dram glass vial containing the prescribed volume of methanol, oxo-compound (0.5 mmol) and benzylamine (0.5 mmol, 54.6 μL) were added. After a precondensation time of 0−2 h, Boc-proline (0.5 mmol, 107.6 mg) and the isocyanoacetate (0.52 mmol) were added. With all reactants added, the solution was allowed to stir for either 24 h in reactions with aldehydes or 48 h in reactions with ketones. The reactions were concentrated in vacuo and subsequently dissolved in 1:1 hexanes/ethyl acetate. The solution was then applied to a silica gel column (4 in. × 0.75 in.). Unreacted isocyanide was eluted with 3:1 hexanes/ethyl acetate, and the product was eluted with 1:1 to 1:2 hexane/ethyl acetate.

Ugi Product Derived from Boc-Proline, Benzylamine, Isocyanoacetate Derived from (*S*)-*N*-Formylalanine Methyl Ester, and Benzaldehyde (Table 2, Entry 1). Mixture of diastereomers and rotamers. Yield 234 mg (86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11, 7.69, 6.36, 6.10 (2 H, 4 doublets, J = 7.0 Hz), 6.95−7.56 (20 H, m), 6.68 (1H, m), 6.57 (1 H, s), 6.27, 6.16, 5.96, (1 H, 3 singlets), 1.29, 5.24, 5.21, 5.14 (1H, 4 singlets), 4.35−4.78 (4.5 H, m), 4.18−4.30 (1 H, m), 3.96−4.10 (0.5 H m), 3.80, 3.74, 3.73, 3.69 (6 H, 4 singlets), 3.56−3.67 (1 H, m), 3.21−3.56 (3 H, m), 1.99−2.40 (2 H, m), 1.59−1.99 (4 H, m), 1.33−1.58 (23 H, m), 1.25 (1.5 H, d), 0.95, (1.5 H, d, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 174.9, 174.7, 173.6, 173.2, 173.0, 169.2, 167.7, 154.7, 138.0, 137.8, 135.5, 135.3, 130.6, 130.4, 129.8, 129.6, 129.4, 129.0, 128.8, 128.7, 128.6, 128.3, 128.2, 127.9, 127.8, 127.1, 126.9, 126.7, 126.7, 126.6, 126.3, 80.3, 79.9, 77.2, 63.3, 62.3, 56.5, 54.8, 52.4, 52.2, 52.1, 50.1, 48.6, 48.4, 47.4, 47.2, 30.6, 29.8, 28.6, 28.5, 28.4, 28.4, 25.1, 24.8, 17.3; HRMS (FAB) calcd for $[C_{29}H_{37}N_3O_6 + Na]^+$ 546.2580, found 546.2588.

Ugi Product Derived from Boc-Proline, Benzylamine, Isocyanoacetate Derived from (*S*)-*N*-Formylalanine Methyl Ester, and Hydrocinnamaldehyde (Table 2, Entry 2). Mixture of diastereomers and rotamers. Yield 167 mg (58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27, 6.70 (1 H, 2 doublets, J = 6.1 Hz), 7.77, 6.80 (1 H 2 doublets, J = 7.3 Hz, 1 H), 7.07−7.40 (20 H, m), 7.03 (2 H, d, J = 7.0 Hz), 5.45 (0.5 H, dd, J = 7.9, 5.0 Hz), 5.20, 5.15 (1 H, 2 singlets), 4.74−4.83 (0.5 H, m), 4.47−4.73 (3 H, m), 4.46, 4.42, 4.38 (1.5 H, 3 singlets), 4.28 (1 H, t, J = 7.1 Hz), 3.95 (0.5 H, dd, J = 7.3, 6.3 Hz), 3.67 (3 H, s), 3.70 (3 H, s) 3.56−3.64 (1 H, m), 3.34−3.55 (3 H, m), 2.66−2.95 (2 H, m), 2.39−2.64, (3 H, m), 2.11−2.29 (1 H, m), 1.71−2.03, (6 H, m) 1.52−1.71 (2 H, m), 1.49 (2 H, d, J = 7.4 Hz), 1.29−1.47 (20 H, m), 1.27 (2 H, s), 1.14 (2H, d, J = 7.4 Hz), 1.34, 1.14 (6 H, 3 doublets, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 174.3, 173.5, 173.4, 170.5, 168.9, 154.6, 154.5, 145.7, 141.6, 140.7, 138.3, 138.2, 130.6, 128.7, 128.5, 128.4, 128.4, 128.3, 128.3, 128.0, 127.5, 126.9, 126.5, 126.1, 125.8, 83.6, 80.2, 79.9, 77.2, 62.2, 59.3, 58.0, 56.4, 55.0, 52.1, 50.3, 48.5, 48.5, 47.4, 47.0, 46.1, 33.3, 32.4, 30.6, 30.4, 30.3, 30.2, 28.6, 28.4, 28.3, 25.0, 24.8, 17.2, 16.5; HRMS (FAB) calcd for $[C_{31}H_{41}N_3O_6 + Na]^+$ 574.2893, found 574.2876.

Ugi Product Derived from Boc-Proline, Benzylamine, Isocyanoacetate Derived from (*S*)-*N*-Formylalanine Methyl Ester, and Isobutyraldehyde (Table 2, Entry 3). Mixture of diastereomers and rotamers. Yield 246 mg (96%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (1 H, d, J = 5.3 Hz), 7.80 (1 H, d, J = 5.3 Hz), 7.09−7.42 (10 H, m), 4.79−5.03 (2 H, m), 4.25−4.60 (4 H, m), 4.13, 4.08 (1 H, 2 singlets), 3.74, 3.72, 3.65 (6 H, singlets), 3.58−3.75 (1 H, m), 3.43−3.57 (2 H, m), 3.30−3.43 (1 H, m), 2.43−2.67 (1 H, m), 2.24−2.43 (1 H, m), 2.02−2.21 (2 H. m), 1.79−1.99 (2 H, m), 1.54−1.78 (2 H, m), 1.22−1.53 (21 H, m), 0.69−1.08 (17 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 174.8, 173.4, 173.1, 170.3, 168.0, 154.6, 154.5, 137.9, 137.3, 128.6, 128.2, 127.7, 127.5, 127.4, 126.6, 80.3, 79.7, 77.5, 77.2, 77.0, 76.6, 65.8, 57.0, 54.5, 52.1, 52.0, 48.3, 48.1, 47.3, 47.3, 46.0, 30.7, 30.2, 28.6, 28.4, 28.3, 28.1, 26.4, 25.1, 24.5, 20.2, 19.9, 19.5, 19.1, 17.6, 16.7; HRMS (FAB) calcd for $[C_{26}H_{39}N_3O_6 + Na]^+$ 512.2737, found 512.2752.

Ugi Product Derived from Boc-Proline, Benzylamine, Isocyanoacetate Derived from (*S*)-*N*-Formylleucine Methyl Ester, and Isobutyraldehyde (Table 2, Entry 4). Mixture of diastereomers and rotamers. Yield 263 mg (95%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (1H, 2 doublets, J = 5.6 Hz), 7.86 (1 H, br s), 7.15−7.43 (10 H, m), 4.58−5.12 (1 H, m), 4.60−4.73 (1 H, m), 4.45−4.60 (3 H, m), 4.41, 4.38, 4.37, 4.33 (2 H, 4 singlets), 3.79−3.89 (1 H, m), 3.73, 3.72, 3.71, 4.67 (6 H, 4 singlets), 3.69−3.74 (0.5 H, m), 3.58−3.69 (0.5 H, m) 3.45−3.60 (2 H, m), 3.35−3.45 (1 H, m), 2.66−2.92 (1 H, m), 2.27−2.55 (1 H, m), 2.04−2.19 (2 H, m), 1.82−2.04 (2 H, m), 1.82−2.04 (2 H, m), 1.52−1.81 (7 H, m), 1.51, 1.49, 1.46, 1.44 (18 H, 4 singlets), 1.12−1.35 (3 H, m), 0.88−1.03, (16 H, m), 0.73−0.87 (8 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 174.8, 173.3, 173.0, 172.7, 170.8, 168.2, 154.6, 154.3, 138.0, 137.0, 128.6, 128.3, 127.8, 127.6, 127.5, 126.7, 108.4, 80.2, 79.6, 77.4, 76.6, 66.1, 63.8, 57.2, 54.5, 52.0, 51.8, 51.4, 50.6, 47.3, 47.1, 46.1, 40.6, 40.4, 31.3, 30.8, 29.9, 28.6, 28.4, 28.3, 27.9, 27.6, 26.7, 25.0, 24.8, 24.6, 24.3, 22.9, 22.8, 21.9, 21.4, 20.2, 19.8, 19.4, 19.1; HRMS (FAB) calcd for $[C_{29}H_{45}N_3O_6 + Na]^+$ 554.3206, found 554.3220.

Ugi Product Derived from Boc-Proline, Methylamine, Isocyanoacetate Derived from (*S*)-*N*-Formylleucine Methyl Ester, and Isobutyraldehyde. Mixture of diastereomers and rotamers. Yield 155 mg (68%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38, 6.97, 6.57, 6.31 (2 H, 4 doublets, J = 7.9 Hz), 4.75−4.81 (1 H, m), 4.42−4.76 (4 H, m), 4.29 (1 H, d, J = 10.7 Hz), 3.71, 3.70 (6 H, 2 singlets), 4.42−4.76 (4 H, m), 3.04, 3.00, 2.98, 2.74 (6 H, 4 singlets), 2.10−2.46 (4 H, m), 2.00−2.10 (2 H, m), 1.79−1.99 (4 H, m), 1.54−1.74 (6 H, m), 1.44, 1.43, 1.40, 1.37 (18 H, 4 singlets), 1.00−1.09 (4 H, m), 0.86−0.97 (15 H, m), 0.77−0.84 (5 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 173.4, 173.3, 170.5, 169.7, 168.8, 154.6, 154.5, 80.2, 79.6, 79.5, 77.2, 66.1, 56.2, 54.2, 52.0, 51.9, 51.0, 50.9, 50.3, 47.3, 47.0, 40.3, 40.2, 30.9, 29.4, 29.0, 28.4, 28.2, 26.1, 26.0, 24.9, 24.7, 24.6,

24.6, 22.8, 22.8, 22.6, 21.8, 21.4, 20.7, 20.4, 19.0, 18.5; HRMS (FAB) calcd for $[C_{23}H_{41}N_3O_6 + Na]^+$ 478.2893, found 478.2878.

Ugi Product Derived from Boc-Proline, Benzylamine, Isocyanoacetate Derived from (*S*)-*N*-Formylphenylalanine Methyl Ester, and Isobutyraldehyde (Table 2, Entry 5). Mixture of diastereomers and rotamers. Yield 238 mg (98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (1 H, d, J = 6.5 Hz), 7.78 (1 H, br s), 6.92–7.40 (20 H, m), 7.85 (0.5 H, dd, J = 7.2, 5.1 Hz), 4.76, 4.72, (0.5 H, 2 singlets), 4.49–4.69 (2 H, m), 4.31–4.48 (2 H, m), 4.23, (1 H, s), 4.09–4.21 (1 H, m), 3.61–3.75, (4 H, m), 3.43–3.60, (4 H, m), 3.27–3.43 (1 H, m), 3.05–3.28 (1 H, m), 2.91–3.04 (1 H, m), 2.87 (1 H, dd, J = 13.4, 8.6 Hz), 2.53–2.72 (1.5 H, m), 2.22–2.44 (1.5 H, m), 1.97–2.15 (2 H, m), 1.83–1.95 (1 H, m), 1.56–1.80 (2H, m), 1.49, 1.45, 1.44, 1.41 (18 H, 4 singlets), 0.95 (2 H, d, J = 6.3 Hz), 0.79–0.91 (8 H, m), 0.68, (2 H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 174.7, 174.1, 172.3, 171.7, 168.1, 154.6, 154.3, 153.8, 145.2, 138.2, 136.6, 136.4, 129.0, 128.8, 128.6, 128.5, 128.4, 128.3, 127.8, 127.4, 127.2, 126.9, 126.7, 126.6, 126.3, 80.3, 80.1, 79.4, 66.3, 57.7, 57.1, 54.5, 54.2, 53.2, 52.9, 52.1, 52.0, 51.6, 47.3, 47.0, 45.9, 37.6, 37.6, 31.1, 30.8, 29.8, 28.5, 28.3, 27.6, 26.5, 25.0, 24.4, 22.6, 20.2, 19.7, 19.6, 19.2, 19.1; HRMS (FAB) calcd for $[C_{32}H_{43}N_3O_6 + Na]^+$ 485.2264, found 485.2288.

Ugi Product Derived from Boc-Proline, Benzylamine, Isocyanoacetate Derived from (*S*)-*N*-Formylmethionine Methyl Ester, and Isobutyraldehyde (Table 2, Entry 6). Mixture of diastereomers and rotamers. Yield 274 mg (96%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (1 H, d, J = 6.1 Hz), 7.92 (1 H, br s), 7.09–7.45 (10 H, m), 4.81–5.10 (2 H, m), 4.66–4.78 (1 H, m), 4.46–4.66 (3 H, m), 4.37–4.45 (1 H, m), 4.32, 4.29 (1 H, 2 singlets), 3.89 (1 H, q, J = 7.0 Hz), 3.74, 3.73, 3.67 (6 H, 3 singlets), 3.59–3.65 (1 H, m), 3.44–3.57 (2 H, m), 3.31–3.44 (1 H, m), 2.40–2.53 (3 H, m), 2.20–2.38 (3 H, m), 2.06 (3 H, s), 2.01 (3 H, s), 1.61–1.17 (12 H, m), 1.49, 1.48, 1.45, 1.42 (18 H, 4 singlets), 4.84–1.06 (9 H, m), 0.75 (3 H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 174.8, 174.4, 172.3, 172.0, 171.7, 170.5, 168.4, 154.7, 154.4, 137.9, 136.8, 128.6, 128.5, 128.4, 127.8, 127.5, 127.3, 127.1, 126.7, 126.5, 83.6, 80.3, 79.6, 79.4, 77.2, 66.1, 57.8, 57.2, 56.5, 54.5, 52.3, 52.2, 52.2, 52.0, 51.3, 51.2, 51.2, 47.4, 47.1, 46.1, 31.3, 31.0, 30.8, 30.1, 30.1, 29.8, 29.6, 28.5, 28.4, 27.7, 27.6, 27.5, 26.6, 25.0, 24.5, 24.4, 22.7, 20.2, 19.8, 19.7, 19.4, 19.2, 19.1, 18.8, 15.3; HRMS (FAB) $[C_{28}H_{43}N_3O_6S + Na]^+$calcd 572.2770, found 572.2780.

Ugi Product Derived from Boc-Proline, Benzylamine, Isocyanoacetate Derived from (*S*)-*N*-Formylalanine Methyl Ester, and Cyclobutanone (Table 2, Entry 7). Mixture of rotamers. Yield 207 mg (81%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81, 7.75 (1 H, 2 doublets, J = 7.0 Hz), 7.29–7.49 (5 H, m), 5.20, 5.14, (1 H, 2 singlets), 4.43–4.63 (1 H, m), 4.41, 4.35 (1 H, 2 singlets), 4.10–4.31 (1H, m), 3.75, 3.73, 3.71, 3.65, (3 H, 4 singlets), 3.29–3.56, (2 H, m), 2.55–2.94 (1 H, m), 2.00–2.54 (4 H, m), 1.59–1.99 (5 H, m), 1.49–1.57 (1 H, m), 1.32–1.45 (11 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 173.7, 173.3, 154.7, 138.6, 128.9, 128.8, 127.3, 126.1, 125.9, 79.7, 77.2, 66.1, 56.8, 52.1, 49.5, 48.5, 47.4, 30.7, 28.7, 28.5, 28.4, 24.6, 17.5, 15.1; HRMS (FAB) calcd for $[C_{26}H_{37}N_3O_6 + Na]^+$ 510.2580, found 510.2595.

Ugi Product Derived from Boc-Proline, Benzylamine, Isocyanoacetate Derived from (*S*)-*N*-Formylalanine Methyl Ester, and Cyclohexanone (Table 2, Entry 8). Mixture of rotamers. Yield 242 mg (90%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.18–7.61 (5 H, m), 7.65, 7.56 (1 H, 2 doublets, 7.0 Hz), 5.05, 4.99, 4.84, 4.78 (1 H, 4 singlets), 4.33–4.72, (3 H, m), 3.75, 3.73, 3.71, (3 H, 3 singlets), 3.47–3.65 (1 H, m), 3.28–3.47 (1 H, m), 2.13–2.56, (2 H, m), 1.54–1.99 (10 H, m), 1.37–1.54 (14 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 173.8, 173.4, 154.5, 139.3, 138.9, 129.0, 128.9, 127.3, 126.3, 126.2, 80.1, 79.4, 72.5, 66.3, 57.8, 52.1, 48.4, 48.3, 47.9, 47.3, 32.8, 30.5, 28.7, 28.5, 25.4, 24.3, 23.1, 22.7, 22.5, 17.8; HRMS (FAB) calcd for $[C_{28}H_{41}N_3O_6 + Na]^+$ 538.2893, found 538.2876.

Joullié–Ugi Reaction General Procedure. Tripiperideine (either 0.17 or 0.25 mmol) and Boc-proline (0.5 mmol, 108 mg) were dissolved in methanol and stirred until the solution was homogeneous. Subsequently, the isocyanoacetate (0.52 mmol) was added to the reaction. After stirring for 48 h at room temperature, the reaction solvent was removed in vacuo. The oily residue was applied to a silica gel column, and the product was eluted with hexanes:ethyl acetate.

Boc-(*S*)-Pro-Pip-(*S*)-Ala-Ome (Table 4, Entry 1). Mixture of diastereomers and rotamers. Yield 158 mg (73%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.45, 7.37, 6.62, 6.59 (2 H, 4 doublets, J = 7.0 Hz), 5.14–5.55 (1 H, m), 4.37–4.90 (5 H, m), 3.89, 3.86 (2 H, 2 singlets), 3.71, 3.68 (6H, 2 singlets), 3.52–3.61 (2H, m), 3.39–3.51 (2H, m), 2.43–2.65 (2 H, m), 2.03–2.30 (5 H, m), 1.80–2.03 (6 H, m), 1.55–1.79 (7 H, m), 1.22–1.55 (26 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 172.0, 171.5, 170.1, 169.8, 154.6, 79.9, 79.7, 56.3, 55.7, 55.6, 52.1, 52.1, 48.8, 48.3, 47.0, 46.8, 43.7, 39.7, 29.6, 29.5, 28.4, 26.1, 26.0, 24.8, 24.7, 20.6, 16.9, 16.5; HRMS (FAB) calcd for $[C_{20}H_{33}N_3O_6 + Na]^+$ 434.2267, found 434.2262.

Boc-(*S*)-Pro-Pip-(*S*)-Leu-Ome (Table 4, Entry 2). Mixture of diastereomers and rotamers. Yield 129 mg (54%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33 (1 H, d, J = 7.9 Hz), 7.13 (1 H, d, J = 7.5 Hz), 5.08–5.47 (1 H, m), 4.29–4.75 (4 H, m), 3.84 (0.5 H, d, J = 12.4 Hz), 3.67, 3.65 (6 H, 2 singlets), 3.47–3.60 (2.5 H, m), 3.29–3.47 (3H, m), 2.31–2.60 (2 H, m), 1.97–2.23 (3 H, m), 1.76–1.95 (4 H, m), 1.54–1.76 (10 H, m), 1.17–1.54 (29 H, m), 0.75–0.99 (12 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ173.5, 173.3, 171.8, 170.2, 170.0, 154.5, 79.8, 79.5, 56.2, 55.7, 55.5, 51.9, 51.8, 51.6, 50.9, 46.9, 46.7, 43.5, 40.1, 39.6, 38.7, 29.5, 28.3, 28.2, 26.1, 25.9, 24.8, 24.7, 24.6, 22.9, 22.7, 22.5, 21.8, 20.9, 20.6; HRMS (FAB) calcd for $[C_{23}H_{39}N_3O_6 + Na]^+$ 476.2737, found 476.2720.

Boc-(*S*)-Pro-Pip-(*S*)-Phe-Ome (Table 4, Entry 3). Mixture of diastereomers and rotamers. Yield 148 mg (58%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.50 (1 H, d, J = 8.3 Hz), 7.46 (1 H, J = 7.7 Hz), 7.05–7.38 (10 H, m), 5.04–5.41 (1 H, m), 4.78–4.04 (0.5 H, m), 4.54–4.78 (3 H, m), 4.36–4.54 (1 H, m), 4.33, 4.30 (0.5 H, 2 singlets), 3.86, 1.83 (1 H, 2 singlets), 3.63–3.78 (6 H, m), 3.52–3.63 (2 H, m), 3.53 −5.52 (2 H, m), 3.15–3.43 (3 H, m), 2.98–3.15 (2 H, m), 2.34–2.57 (1 H, m), 1.99–2.28 (5 H, m), 1.80–1.99 (4 H, m), 1.58–1.80, (4 H, m), 1.00–1.58 (26 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 172.1, 171.9, 171.3, 169.9, 169.7, 154.7, 137.5, 137.1, 129.2, 129.2, 128.4, 128.3, 127.0, 126.5, 126.5, 80.0, 79.7, 57.0, 56.2, 55.9, 55.6, 54.4, 54.2, 53.3, 52.1, 51.9, 47.0, 46.9, 43.5, 39.3, 37.4, 36.2, 29.6, 29.5, 28.4, 25.9, 25.9, 25.7, 24.8, 24.8, 24.7, 24.4, 20.5, 20.4; HRMS (FAB) calcd for $[C_{26}H_{37}N_3O_6 + Na]^+$ 510.2580, found 510.2566.

Boc-(*S*)-Pro-Pip-(*S*)-Met-Ome (Table 4, Entry 4). Mixture of diastereomers and rotamers. Yield 135 mg (54%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.46 (1 H, d, J = 7.7 Hz), 7.30 (1 H, d, 8.2 Hz), 5.14–5.44 (1 H, m), 4.74 (1 H, td, J = 8.6, 5.4 Hz), 4.52–4.67 (4 H, m), 3.89, 3.86 (1 H, 2 singlets), 3.72, 3.69, 3.65, (6 H, 3 singlets), 3.51–3.63 (2 H, m), 3.33–3.51 (3 H, m), 2.42–2.63 (6 H, m), 2.08, 2.06 (6 H, 2 singlets), 2.02–2.29 (8 H, m), 1.79–2.02 (6 H, m), 1.52–1.79 (4 H, m), 1.30–1.52 (24 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ172.7, 171.9, 171.4, 170.4, 170.3, 154.7, 83.6, 80.0, 79.7, 56.3, 55.8, 55.6, 52.1, 51.5, 47.0, 46.9, 43.6, 39.7, 30.7, 30.0, 29.7, 29.6, 28.5, 28.4, 26.1, 26.0, 24.8, 20.6, 15.5, 15.3; HRMS (FAB) calcd for $[C_{22}H_{37}N_3O_6S + Na]^+$ 494.2301, found 494.2311.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Passerini three-component reaction results, ^{1}H and ^{13}C NMR spectra, epimerization measurement chromatograms, advanced Marfey analysis chromatograms, and LC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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