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# An Asymmetric Ugi Three-Component Reaction Induced by Chiral Cyclic Imines: Synthesis of Morpholin− or Piperazine−Keto-carboxamide Derivatives

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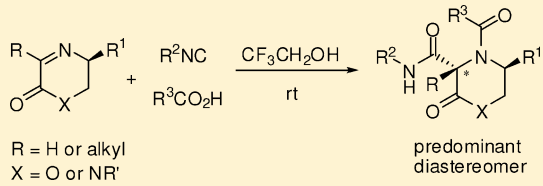
Supporting Information

**ABSTRACT:** A series of chiral 5,6-dihydro-1,4-oxazin-2-one substrates, as preformed cyclic aldimines and ketoimines, were employed to develop a new asymmetric Ugi three-component reaction for the first time. The Ugi reaction of the imines, isocyanides, and carboxylic acids opens an efficient access to novel morpholin-2-one-3-carboxamide compounds. The chiral imines showed promising stereoinduction for the new chiral center of the Ugi products, and predominant trans-isomers were obtained in the most cases. Addition of some Lewis acids or proton acids could improve the diastereoselectivity further but usually led to a drop in total yield. The Ugi-3CR could be extended to the stereoselective synthesis of ketopiperazine-2-carboxamide derivatives.

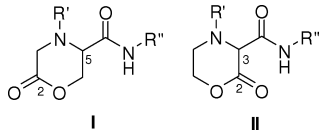



## INTRODUCTION

Multicomponent reactions (MCRs) refer to the reactions in which at least three materials assemble to form a product in one pot. MCRs showed high synthetic efficiency in forming complex structures and introducing molecular diversity by a simple operation.[1] The Ugi reaction is one of the most studied multicomponent reactions owing to its inherent potential in molecule creation and drug discovery and is widely applied in combinatorial and medical chemistry.[2] A classical Ugi four-component reaction (U-4CR) combines an amine, carbonyl compound, isocyanide, and carboxylic acid to $\alpha$-acylamino amides by a domino process involving formation of imine, $\alpha$-addition of isocyanide, and Mumm-type rearrangement. A preformed imine could be employed instead of amine and carbonyl components in Ugi three-component (U-3CR). Although in these reactions a new chiral center is created, most of them were reported as racemic cases or in low stereoselectivity.

With increasing application of the Ugi reaction in pharmaceutical and agricultural chemistry, development of asymmetric Ugi reactions[3] is in strong demand because of the possible different activities of various stereoisomers.[4] Until now, only one enantioselective version is achieved in a special Ugi-type reaction of aldehydes, anilines, and $\alpha$-isocyanoacetamides.[5] For common U-4R or U-3CR wherein a carboxylic acid component participates, diastereoselective approaches using chiral materials are possible solutions to stereocontrol. Chiral amines have been found to be more promising than chiral isocyanides,[6] carboxylic acids,[7] or carbonyl compounds[8] as stereochemical inductors in the reaction, but only limited examples with good selectivity were achieved when several amino acids,[9] ferrocenylamines,[10] aminosugars,[11] 1-phenylethylamines,[12] and acyclic and cyclic aldimines[13] were used as substrates. It is necessary to develop more asymmetric Ugi reactions to meet various requirements.

Chiral 5,6-dihydro-1,4-oxazin-2-one derivatives have demonstrated good diastereocontrol in Mannich-type reactions with some nucleophiles.[14] However, the potentiality of the cyclic imines for exploiting new asymmetric Ugi reactions, by which some interesting morpholinone derivatives could be synthesized quickly, has still not been studied. Morpholinone compounds have attracted much attention because of their biological and synthetic applications.[15] In 2001, Kim and coworkers described the synthesis of morpholin-2-one-5-carboxamide (Figure 1, I),[16] which showed potent and selective T-type $Ca^{2+}$ channel blocking activities in the subsequent study.[17] However, construction of the morpholin-2-one-3-carboxamide skeleton (Figure 1, II) is rarely reported. To the best of our knowledge, only the Wollf group has previously described a compound with structure II produced in 6% yield by a



I II

**Figure 1.** Structures of morpholin-2-one-5-carboxamide (**I**) and morpholin-2-one-3-carboxamide (**II**).

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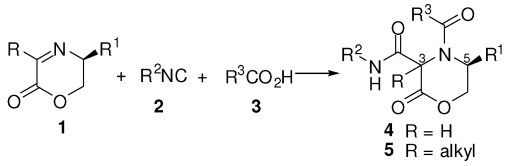
photoreaction of aminophenazone and ephedrine under UV irradiation.[18]

Herein we describe an asymmetric Ugi three-component reaction (U-3CR) of 5,6-dihydro-1,4-oxazin-2-one substrates **1** with isocyanides **2** and carboxylic acids **3** to effectively synthesize morpholin-2-one-3-carboxamide derivatives **4** and **5** (Scheme 1), in which the 2-amidomalonyl subunit is present in many bioactive and pharmacological compounds.[19]

**Scheme 1. Ugi Three-Component Reaction of 1−3**




**1a**: $R^1$ = $CH_2OTBDPS$, R = H
**1b**: $R^1$ = Ph, R = H
**1c**: $R^1$ = Bn, R = H
**1d**: $R^1$ = Ph, R = Me
**1e**: $R^1$ = Bn, R = Me
**1f**: $R^1$ = *i*-Pr, R = Me
**1g**: $R^1$ = Ph, R = Et

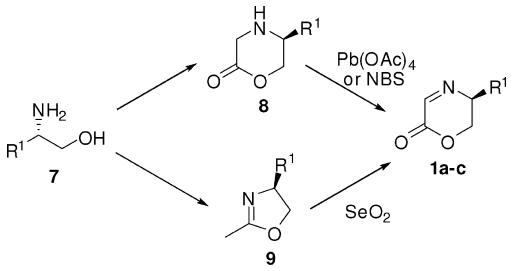
**2a**: $R^2$ = *t*-Bu
**2b**: $R^2$ = *n*-Bu
**2c**: $R^2$ = Bn
**2d**: $R^2$ = $CH_2CO_2Me$
**2e**: $R^2$ = Ph
**2f**: $R^2$ = Cy
**2g**: $R^2$ = $CH_2CH_2OCbz$
**2h**: $R^2$ = $CH_2CH_2OAc$

**3a**: $R^3$ = Me
**3b**: $R^3$ = H
**3c**: $R^3$ = Ph
**3d**: $R^3$ = Et

## RESULT AND DISCUSSION

Chiral 5,6-dihydro-1,4-oxazin-2-one **1a−c**, as preformed cyclic aldimines in the Ugi reaction, were conveniently prepared from the corresponding (*S*)-amino alcohols **7** in two steps by the literature procedures (Scheme 2).[20] In the initial study, imine

**Scheme 2. Preparation of imines 1a−c**




**1a**, *tert*-butyl isocyanide (**2a**), and acetic acid (**3a**) were employed to screen the conditions of the Ugi 3-CR. As shown in Table 1, the yield and velocity of the Ugi reaction remarkably depended on solvent. The reaction performed in 2,2,2-trifluoroethanol (TFE) proceeded much faster than in other solvents and finished in just about 4 h to afford **4a** in 70% yield (Table 1, entry 7). Usually $CH_2Cl_2$ was seldom chosen as solvent in normal U-4CR because of the possibility of Passerini-type products, but for this U-3CR, a similar good yield was obtained in $CH_2Cl_2$. Certainly, prolonged reaction times are necessary for full consumption of **1a** (Table 1, entry 5). In the presence of much excessive **3a**, the required reaction time in $CH_2Cl_2$ was efficiently shortened, whereas only a slight improvement in yield was observed (Table 1, entry 6). The reaction performed in other solvents including MeOH, which is the most common solvent in Ugi reactions, gave diminished yield. Lowering the reaction temperature (Table 1, entry 8) or decreasing the amount of **2a** and **3a** (Table 1, entry 4) led to a drop in yield. Higher reaction temperature did not show an

**Table 1. Optimization of the U-3CR with 1a, 2a, and 3a**[a]

| entry | solvent | time (h) | temp (°C) | yield of **4a** (%) |
|---|---|---|---|---|
| 1 | MeOH | 72 | rt | 39[b] |
| 2 | PhMe | 40 | rt | 58 |
| 3 | THF | 40 | rt | trace |
| 4 | $CH_2Cl_2$ | 50 | rt | 48[b] |
| 5 | $CH_2Cl_2$ | 50 | rt | 67 |
| 6 | $CH_2Cl_2$ | 5 | rt | 73[c] |
| 7 | TFE | 4 | rt | 70 |
| 8 | TFE | 6 | −30 | 51 |
| 9 | TFE | 4 | 60 | 68 |

[a]General conditions: the reaction was usually carried out in a ratio of **1a** (1 equiv)/**2a** (2 equiv)/**3a** (2.2 equiv). [b]**1a** (1 equiv)/**2a** (1.5 equiv)/**3a** (1.5 equiv) were used. [c]**1a** (1 equiv)/**2a** (2 equiv)/**3a** (20 equiv) were used.

improvement in the yield (Table 1, entry 9). Hence, the U-3CR is preferably carried out in TFE or $CH_2Cl_2$ at room temperature.

Subsequently, the generality of the Ugi-3CR was examined, and results are outlined in Table 2. Under the optimized conditions, various cyclic imines, isocyanides, and carboxylic acids reacted to provide morpholin-2-one-3-carboxamide derivatives **4** in moderate to good yield (Table 2). When formic acid (**3b**) was employed as a carboxylic acid component, the reactions were accelerated dramatically even using less acid (1.5 equiv) due to stronger acidity of **3b** (Table 2, entry 3 vs entry 2), and the reactions in $CH_2Cl_2$ completed at a similar rate to that in TFE (Table 2, entry 5 vs entry 6). The substituents in imines **1** ($R^1$) had no clear influence on the yield of the reaction (Table 2, entries 3, 6, and 10). Aliphatic and aromatic isocyanides were well tolerated in the reaction. In all cases, no Ugi product was obtained as two isolatable isomers on silica gel chromatography, which indicated potential good stereoselectivity of the reaction. However, amide functional groups in the products caused the paired signals from two rotamers in the most $^1H$ and $^{13}C$ NMR spectra.

One-pot protocols combining two or more reaction steps show higher efficiency because of simpler operation, lower costs, and shorter time.[21] As a mild versatile reagent, IBX has been employed in a wide array of chemical transformations,[22] including direct oxidation of benzyl amines to the corresponding imines.[23] On the basis of the methods, Zhu group developed an efficient IBX-mediated Ugi-type reaction of tetrahydroisoquinoline, isocyanides and carboxylic acids, in which formation of imine and Ugi-3CR were realized ingeniously in one-pot taking advantage of compatibility of IBX with the Ugi reaction conditions.[24] We found that secondary amines with an $\alpha$-carbonyl group such as **8** also could be oxidized to imine by IBX. Encouraged by the results, a one-pot IBX oxidation/Ugi-3CR procedure to synthesize **4b** was attempted preliminarily using **8a** ($R^1$ = $CH_2OTBDPS$), **2a**, and **3b** (Scheme 3). DMSO or THF is efficient reaction media for the oxidation stage, and complete conversion of **8a** to **1a** occurred in a short time. However, only a trace amount of **4b** was produced in the subsequent Ugi-3CR, whereas $CH_2Cl_2$ as an unfavorable solvent in the oxidation stage also gave a low yield of **4b**. The better common choice to both reaction stages is TFE, in which **4b** was obtained in a moderate yield from **8a** without further optimization. It indicated that the secondary amines with $\alpha$-carbonyl group were promising to develop a new IBX-mediate Ugi reaction.


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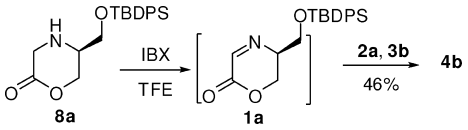
**Table 2. Synthesis of 5-Substituted Morpholin-2-one-3-carboxamide Derivatives 4a–l from Aldimines 1a–c**[a]

| entry | $R^1$ | $R^2$ | $R^3$ | solvent | time (h) | product | yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | $CH_2OTBDPS$ | *t*-Bu | Me | TFE | 4 | **4a** | 70 |
| 2 | $CH_2OTBDPS$ | *t*-Bu | Me | $CH_2Cl_2$ | 50 | **4a** | 67 |
| 3 | $CH_2OTBDPS$ | *t*-Bu | H | $CH_2Cl_2$ | 8 | **4b** | 74 |
| 4 | $CH_2OTBDPS$ | *n*-Bu | H | $CH_2Cl_2$ | 12 | **4c** | 66 |
| 5 | Ph | *t*-Bu | H | $CH_2Cl_2$ | 2.5 | **4d** | 71 |
| 6 | Ph | *t*-Bu | H | TFE | 2.5 | **4d** | 73 |
| 7 | Ph | $CH_2CO_2Me$ | Me | TFE | 4 | **4e** | 78 |
| 8 | Ph | Bn | H | $CH_2Cl_2$ | 4 | **4f** | 58 |
| 9 | Ph | $CH_2CO_2Me$ | H | $CH_2Cl_2$ | 4 | **4g** | 80 |
| 10 | Bn | *t*-Bu | H | $CH_2Cl_2$ | 7 | **4h** | 71 |
| 11 | Bn | *t*-Bu | Me | TFE | 4 | **4i** | 62 |
| 12 | Bn | Bn | Me | TFE | 4 | **4j** | 55 |
| 13 | Bn | $CH_2CO_2Me$ | Ph | TFE | 4.5 | **4k** | 67 |
| 14 | Bn | Ph | H | TFE | 5 | **4l** | 75 |

[a]General conditions: the reactions were carried out at room temperature, and **1**–**3** were used in a ratio of 1/1.5/1.5 (formic acid as acid component) or 1/2/2.2 (other acid as acid component).

**Scheme 3. Synthesis of 4b from 8a by a One-Pot Procedure**




Next, we prepared several ketoimines **1d**–**g** according to the literature[25] and moved our attention to the Ugi-3CR of ketoimines. Under the same reaction conditions as for aldimines, the Ugi reactions of ketoimine **1d**, **2a**, and **3b** proceed so sluggishly that the Ugi products **5a** ($5a_1$ + $5a_2$) were obtained in low yield even after a long span, together with considerable *N*-formamide byproduct from **2a** and remaining **1d** (Table 3, entry 1). It is attributed to the enhanced hindrance

**Table 3. Optimization of the U-3CR with 1d, 2a, and 3b**[a]

| entry | 1d:2a:3b | catalyst | time (h) | dr | yield of $5a_1$ + $5a_2$ (%) |
|---|---|---|---|---|---|
| 1 | 1:1.5:1.5 | | 48 | 3.4:1 | 50 |
| 2 | 1:1.5:2.2 | | 11 | 3.8:1 | 51 |
| 3 | 1:(1.5 + 0.5)[b]:2.2 | | 31 | 3.9:1 | 76 |
| 4 | 1:(2.0 + 0.5)[b]:10 | | 10 | 2.4:1 | 69 |
| 5 | 1:2:2.2 | 1 equiv of LiBr | 4 | 4.7:1 | 63 |
| 6 | 1:2:1.1 | 1 equiv of $ZnCl_2$ | 5 | 5.4:1 | 28 |
| 7 | 1:(1.5 + 0.5)[b]:2.2 | 0.25 equiv of phenylphosphinic acid | 24 | 7.3:1 | 58 |

[a]General conditions: the reactions were carried out at room temperature. [b]The two values in parentheses mean isocyanide **2a** was added in two portions.

of the ketoimines. When formic acid was increased to 2.2 equiv, velocity and yield were improved dramatically (Table 3, entry 2), but consumption of isocyanide was much faster than imine due to its conversion to formamide. Supplementing isocyanide is effective and necessary in the middle of the reaction, and the better result was brought about by the two-portion addition fashion (Table 3, entry 3). It is noteworthy that two diastereoisomers $5a_1$ and $5a_2$ (dr = 3.9:1) were obtained in the case. Excessive acid led to the dropped stereoselectivity (Table 3, entry 4). An improved dr value was obtained by addition of some Lewis acids or proton acids, particularly phenylphosphinic acid (dr up to 7:1), whereas the total yield of two diastereoisomers generally diminished in a different extent (Table 3, entries 5–7). Hence, the optimized conditions for the ketoimines were 1.5 + 0.5 equiv of isocyanides by two-portion addition, no catalyst, TFE, reaction time, and room temperature.

A variety of imines, isocyanides, and carboxylic acids were employed to construct the morpholin-2-one-3-carboxamide derivatives **5** containing a chiral quatenary carbon (Table 4). The Ugi-3CR formic acid participated usually showed relative good conversion and yield. When other carboxyl acids were used, the amount of remaining imine increased to different extent, though the acid loading was enhanced to 3 equiv to promote the reactions (Table 4, entries 2, 3, 5, 9, 11, and 13). However, in these cases, the yields based on recovered imines were very high. Gratifyingly, the most Ugi products were obtained in higher stereoselectivity than **5a**, and in some cases only a single diastereoisomer was obtained (Table 4, entries 2, 3, 6, 8, 10, and 13). In the presence of phenylphosphinic acid, similar positive effects on stereoselectivity and a negative effect on yield were verified again (Table 4, entry 14 vs entry 15). Diastereoisomers in these cases are easily separated through column chromatography, and each diastereoisomer of considerable Ugi products still contains two rotamers according to the paired signals in their NMR spectra. To further expand the scope of the approach, 5,6-dihydropyrazin-2(1*H*)-one **10** (**10a** and **10b**) instead of **1** were attempted in the Ugi-3CR to form the substituted piperazine scaffold, which is a pharmacologically important core found in many marketed drugs and bioactive compounds.[26] Gratifyingly, the reactions of **10a**/**2a**/**3b** and **10b**/**2d**/**3b** proceeded smoothly under similar conditions to give the desired products **11a** (74%) and **11b** (63%), respectively, as single isomer (Scheme 4). It opens a promising route to chiral 2-ketopiperazine-2-carboxamides with high stereoselectivity. The construction of the 2-ketopiperazine-2-carboxamide skeleton was achieved by several groups,[27] but asymmetric cases have not been reported. In general, the cyclic ketoimines could be served as good asymmetric inductors in the Ugi-3CR too.

The stereochemistry of the Ugi-3CR was then investigated via NOESY $^1$H NMR analysis. Among the Ugi products **4** from aldimines, **4a** was used to determine the configuration of the morpholin-2-one-3-carboxamide compounds because in its $^1$H


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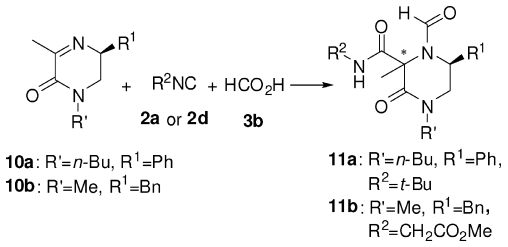
**Table 4. Synthesis of 5-Substituted Morpholin-2-one-3-carboxamide Derivatives 5a–o from Ketimines[a]**

| entry | $R^1$ | R | $R^2$ | $R^3$ | time (h) | product | dr | yield (%) | recovered **1** (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Ph | Me | *t*-Bu | H | 31 | $\mathbf{5a_1}$ + $\mathbf{5a_2}$ | 3.9:1 | 76 | 10 |
| 2 | Ph | Me | *t*-Bu | Me | 40 | **5b** | | 63 | 29 |
| 3 | Ph | Me | *t*-Bu | Et | 40 | **5c** | | 51 | 41 |
| 4 | Ph | Me | *n*-Bu | H | 36 | $\mathbf{5d_1}$ + $\mathbf{5d_2}$ | 8.2:1 | 81 | 8 |
| 5 | Ph | Me | *t*-Bu | Ph | 23 | $\mathbf{5e_1}$ + $\mathbf{5e_2}$ | 4.1:1 | 41 | 45 |
| 6 | Ph | Me | $CH_2CO_2CH_3$ | H | 34 | **5f** | | 63 | 18 |
| 7 | Ph | Me | Cy | H | 21 | $\mathbf{5g_1}$ + $\mathbf{5g_2}$ | 4.6:1 | 86 | 8 |
| 8 | Ph | Me | $CH_2CH_2OCbz$ | H | 25 | **5h** | | 68 | 17 |
| 9 | Bn | Me | *t*-Bu | Me | 24 | $\mathbf{5i_1}$ + $\mathbf{5i_2}$ | 5.5:1 | 59 | 36 |
| 10 | Ph | Me | $CH_2CH_2OAc$ | H | 29 | **5j** | | 72 | 16 |
| 11 | *i*-Pr | Me | *t*-Bu | Me | 38 | $\mathbf{5k_1}$ + $\mathbf{5k_2}$ | 4.3:1 | 48 | 40 |
| 12 | Ph | Et | *t*-Bu | H | 28 | $\mathbf{5l_1}$ + $\mathbf{5l_2}$ | 8.2:1 | 88 | 7 |
| 13 | Ph | Et | *t*-Bu | Me | 36 | **5m** | | 78 | 18 |
| 14 | Bn | Me | *t*-Bu | H | 24 | $\mathbf{5n_1}$ + $\mathbf{5n_2}$ | 3.5:1 | 71 | 11 |
| 15[b] | Bn | Me | *t*-Bu | H | 20 | $\mathbf{5n_1}$ + $\mathbf{5n_2}$ | 8.1:1 | 50 | 14 |
| 16 | *i*-Pr | Me | *t*-Bu | H | 24 | $\mathbf{5o_1}$ + $\mathbf{5o_2}$ | 6.0:1 | 87 | 9 |

[a]General conditions: the reactions were carried out at room temperature in TFE, and **1**, **2** and **3** were used in a ratio of 1/(1.5 + 0.5)/2.2 (formic acid as acid component) or 1/(1.5 + 0.5)/3 (other acid as acid component). [b]0.25 equiv phenyl phosphinic acid was added.

**Scheme 4. Synthesis of Piperazine-2-carboxamide 11a and 11b via the U-3CR**




NMR the paired H-3 (4.95 and 4.76 ppm) and H-5 (3.93 and 4.58 ppm) signals from two rotamers are easily distinguishable and not overlapped with other proton signals. The NOE correlation not between H-3 and H-5 signals but between H-3 and H-a signals, observed in each rotamer separately, reveal that both rotamers of **4a** have 3,5-*trans*-configurations, namely the (*S*)-configuration at $C_3$ (Figure 2). It is also further confirmed that the two rotamers are responsible for the paired signals in the NMR spectra. As two models of the Ugi products **5** from ketoimines for NOESY analysis, **5c** is obtained as a single isomer, and $\mathbf{5l_1}$ is the major one of two diastereoisomers. Obvious interaction between methyl (**5c**) or ethyl ($\mathbf{5l_1}$) and protons of the phenyl groups illustrates the trans-relationship between C-3 carboxamide and C-5 phenyl group in them. Furthermore, in combination with $^1$H NMR spectra analysis, their conformations were established as shown in Figure 2. In accordance with stereochemistry observed in other reactions of the similar cyclic imines,[14a,28] preferential access of isocyanide to imine from the side opposite to the C-5 alkyl group gives thermodynamically more stable trans-isomer as a major product.

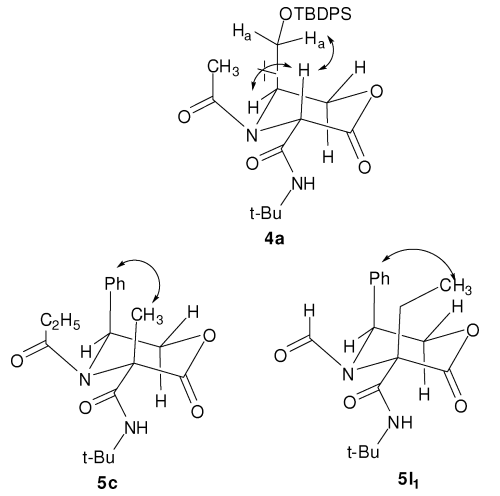
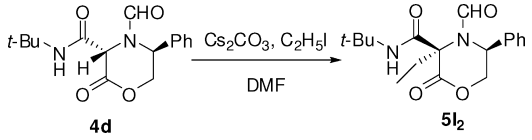



**Figure 2.** Configuration determination of Ugi products by NOESY analysis.

Combinations of Ugi reaction with other reactions are becoming highly efficient tools to create more complex structures.[29] Ugi products **4** from the aldimines are a kind of potential nucleophiles which would react with appropriate electrophiles at the C-3 activated by two carbonyl groups in alkylation, Michael addition, and so on. Compound **4d** was employed to test the possibility of C-alkylation primarily. After screening conditions, **4d** reacted smoothly with iodoethane to provide $\mathbf{5l_2}$ exclusively in 75% yield (Scheme 5). It is reasonable that halide approaches the resulting cyclic enolate from the less hindered face and is attacked to result in cis product with high stereoselectivity, which a owns complementary configuration with the predominant trans-isomer in the Ugi-3CR of ketoimines. Therefore, by a different synthetic method, stereochemistry of the quantanary center in **5** could be controlled to produce the trans- or cis-isomer.

**Scheme 5. Synthesis of *cis*-Isomer $\mathbf{5l_2}$ by Stereoselective Alkylation of 4d**





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## CONCLUSION

In summary, an asymmetric Ugi reaction of chiral cyclic imines **1**, isocyanides **2**, and carboxylic acids **3** was described first by which novel morpholin-2-one-3-carboxamide derivatives **4** and **5** were efficiently synthesized from both aldimines and ketoimines. Furthermore, the Ugi-3CR also showed potential in the synthesis of substituted ketopiperazine-2-carboxamide compounds such as **11**. Good diastereoselectivity of the new stereocenter at C-3 in the products was observed in most cases. In the primary extended studies, **4** could be obtained directly from the amines **8** by a new IBX-mediated Ugi-type reaction, and alkylation of **4** showed excellent but opposite stereoselectivity to give *cis*-**5**. The work will enrich asymmetric Ugi reactions, and further investigations on the employment of **4** as nucleophile in post-transformation with high stereoselectivity are underway.

## EXPERIMENTAL SECTION

**General Procedure for the Ugi Three-Component Reaction of Aldimines 1a–c.** To a 0.25 M solution of the imine **1a–c** (1 equiv) in solvent (TFE or $CH_2Cl_2$) were added carboxylic acid **3** (1.5 equiv for formic acid or 2.2 equiv for other acid) and isocyanide **2** (1.5 equiv when formic acid as acid component or 2 equiv when other acid as acid component) at room temperature. The resulting mixture was stirred until imine was consumed thoroughly and concentrated in vacuo. The product **4** was isolated by flash column chromatography using petroleum ether/ethyl acetate (3:1 to 1:1) as eluent.

*(3S,5R)-4-Acetyl-N-tert-butyl-5-(((tert-butyldiphenylsilyl)oxy)-methyl)-2-oxomorpholine-3-carboxamide (**4a**):* yield 70% (stirred in TFE for 4 h); colorless gel; $[\alpha]^{28}_D$ +4 ($c$ = 0.5, $CHCl_3$); IR (neat) 3337, 2963, 2932, 1752, 1666, 1539, 1463, 1391, 1289, 1108, 746, 705 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 4:1) $\delta$ = 7.66–7.61 (m, 4 H), 7.46–7.40 (m, 6 H), 5.98 (s, 1 H), 4.95 (s, 0.8 H), 4.82 (dd, $J$ = 2.7, 11.5 Hz, 1 H), 4.76 (s, 0.2 H), 4.71 (dd, $J$ = 1.3, 11.4 Hz, 0.8 H), 4.58 (m, 0.2 H), 4.47 (dd, $J$ = 2.8, 12.0 Hz, 0.2 H), 3.93 (m, 0.8 H), 3.86 (dd, $J$ = 4.0, 9.6 Hz, 0.2 H), 3.70 (t, $J$ = 10.6 Hz, 0.8 H), 3.59 (dd, $J$ = 5.3, 10.7 Hz, 0.8 H), 3.52 (t, $J$ = 9.6 Hz, 0.2 H), 1.89 (s, 0.6 H), 1.82 (s, 2.4 H), 1.36 (s, 1.8 H), 1.33 (s, 7.2 H), 1.06 (s, 7.2 H), 1.05 (s, 1.8 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 169.9, 169.8, 165.7, 163.3, 162.2, 162.1, 135.4, 135.3, 132.5, 131.9, 130.2, 130.1, 127.9, 127.7, 127.6, 66.7, 65.8, 62.7, 61.0, 60.7, 60.2, 52.9, 52.6, 52.2, 50.0, 29.6, 28.3, 26.6, 21.1, 20.4, 19.0 ppm; HRMS $m/z$ calcd for $C_{28}H_{38}N_2O_5SiNa$ $[M + Na]^+$ 533.2448, found 533.2437.

*(3S,5R)-N-tert-Butyl-5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-formyl-2-oxomorpholine-3-carboxamide (**4b**):* yield 74% (stirred in $CH_2Cl_2$ for 8 h); colorless gel; $[\alpha]^{28}_D$ +18 ($c$ = 0.7, $CHCl_3$); IR (neat) 3346, 2933, 2860, 1754, 1678, 1539, 1464, 1429, 1387, 1109, 704 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 4:1) $\delta$ = 8.14 (s, 0.2 H), 8.12 (s, 0.8 H), 7.62–7.58 (m, 4 H), 7.45–7.39, 6 H), 6.27 (s, 0.2 H), 6.10 (s, 0.8 H), 5.34 (s, 0.2 H), 4.90 (s, 0.8 H), 4.81 (dd, $J$ = 2.9, 11.8 Hz, 1 H), 4.57 (dd, $J$ = 5.0, 11.0 Hz, 0.2 H), 4.51 (dd, $J$ = 1.2, 11.7 Hz, 0.8 H), 3.94 (m, 1 H), 3.75 (dd, $J$ = 7.1, 10.8 Hz, 1 H), 3.61 (dd, $J$ = 7.3, 10.8 Hz, 1 H), 1.34 (s, 7.2 H), 1.27 (s, 1.8 H), 1.07 (s, 1.8 H), 1.06 (s, 7.2 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 165.0, 164.6, 162.8, 162.5, 162.4, 162.2, 135.5, 132.5, 132.2, 130.3, 130.2, 130.0, 128.1, 128.0, 127.8, 67.0, 66.1, 63.1, 62.8, 59.0, 56.7, 52.5, 52.2, 52.0, 51.8, 28.4, 26.8, 19.1 ppm; HRMS $m/z$ calcd for $C_{27}H_{37}N_2O_5Si$ $[M + H]^+$ 497.2472, found 497.2481.

*(3S,5R)-N-Butyl-5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-formyl-2-oxomorpholine-3-carboxamide (**4c**):* yield 66% (stirred in $CH_2Cl_2$ for 12 h); yellow gel; $[\alpha]^{28}_D$ +17 ($c$ = 0.9, $CHCl_3$); IR (neat) 3333, 2932, 2860, 1755, 1677, 1539, 1466, 1384, 1109, 741, 705 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 4:1) $\delta$ = 8.13 (s, 1 H), 7.63–7.59 (m, 4 H), 7.47–7.38 (m, 6 H), 6.46 (s, 0.2 H), 6.30 (s, 0.8 H), 5.39 (s, 0.2 H), 4.98 (s, 0.8 H), 4.82 (dd, $J$ = 3.0, 11.8 Hz, 0.8 H), 4.59 (dd, $J$ = 5.2, 11.6 Hz, 0.2 H), 4.52 (dd, $J$ = 1.4, 11.8 Hz), 4.46 (dd, $J$ = 4.0, 11.6 Hz, 0.2 H), 3.96 (m, 0.8 H), 3.87 (m, 0.6 H), 3.76 (dd, $J$ = 7.0, 10.8 Hz, 0.8 H), 3.62 (dd, $J$ = 7.3, 10.8 Hz, 0.8 H), 3.26 (dd, $J$ = 7.0, 12.9 Hz, 1.6 H), 3.19 (dd, $J$ = 3.6, 5.9 Hz, 0.4H), 1.48 (m, 2 H), 1.32 (m, 2 H), 1.06 (s, 8 H), 1.05(s, 1 H), 0.91 (t, $J$ = 7.3 Hz, 3H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, major rotamer) $\delta$ = 164.4, 163.7, 162.4, 135.5, 132.5, 132.2, 132.1, 130.3, 130.2, 128.1, 128.0, 66.1, 63.1, 58.3, 52.1, 40.1, 31.2, 26.8, 19.8, 19.1, 13.7 ppm; HRMS $m/z$ calcd for $C_{27}H_{36}N_2O_5Si$ $[M + H]^+$ 497.2472, found 497.2470.

*(3S,5S)-N-tert-Butyl-4-formyl-2-oxo-5-phenylmorpholine-3-carboxamide (**4d**):* yield 73% (stirred in $CH_2Cl_2$ for 2.5 h); yellow gel; $[\alpha]^{28}_D$ +16 ($c$ = 1.1, $CHCl_3$); IR (neat) 3347, 2971, 1757, 1671, 1537, 1457, 1366, 1255, 1203, 1046, 761, 702 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 2:1) $\delta$ = 8.18 (s, 0.33 H), 8.07 (s, 0.66 H), 7.55–7.52 (m, 1.4 H), 7.48–7.38 (m, 2.6 H), 7.23–7.18 (m, 1 H), 6.39 (s, 0.66 H), 6.25 (s, 0.33 H), 5.46 (s, 0.66 H), 5.41 (s, 0.33 H), 5.18 (t, $J$ = 3.0 Hz, 0.33 H), 5.02 (dd, $J$ = 3.2, 11.6 Hz, 0.33 H), 4.93 (dd, $J$ = 4.3, 11.6 Hz, 0.66 H), 4.76 (t, $J$ = 11.8 Hz, 0.66 H), 4.53 (dd, $J$ = 3.0, 11.6 Hz, 0.33 H), 4.29 (dd, $J$ = 4.3, 11.9 Hz, 0.66 H), 1.41 (s, 6 H), 1.38 (s, 3 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 165.0, 164.9, 163.9, 163.3, 162.8, 162.3, 137.0, 134.7, 129.5, 129.3, 128.8, 127.8, 126.3, 125.8, 70.6, 69.3, 59.2, 58.5, 56.7, 54.4, 52.4, 52.2, 28.3 ppm; HRMS $m/z$ calcd for $C_{16}H_{20}N_2O_4Na$ $[M + Na]^+$ 327.1321, found 327.1309.

*Methyl 2-((3S,5S)-4-acetyl-2-oxo-5-phenylmorpholine-3-carboxamido)acetate (**4e**):* yield 78% (stirred in TFE for 4 h); yellow oil; $[\alpha]^{28}_D$ +50 ($c$ = 1.0, $CHCl_3$); IR (neat) 3346, 2954, 2926, 2854, 1751, 1671, 1529, 1438, 1382, 1296, 1208, 1037, 758, 705 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 1.5:1) $\delta$ = 7.48–7.37 (m, 3 H), 7.16–7.13 (m, 2 H), 5.94 (s, 0.4 H), 5.77 (s, 0.6 H), 5.16 (s, 0.6 H), 5.05 (dd, $J$ = 2.9, 11.7 Hz, 0.6 H), 4.98 (dd, $J$ = 5.1, 11.6 Hz, 0.4 H), 4.55 (t, $J$ = 12.4 Hz, 0.6 H), 4.44 (dd, $J$ = 1.6, 11.8 Hz, 0.6 H), 4.33 (dd, $J$ = 5.1, 10.0 Hz, 0.4 H), 4.30 (s, 0.4 H), 4.27 (d, $J$ = 6.4 Hz, 0.4 H), 4.13 (dd, $J$ = 5.7, 14.9 Hz, 0.4 H), 4.10 (d, $J$ = 5.6 Hz, 0.6 H), 4.05 (d, $J$ = 5.3 Hz, 0.6 H), 4.01 (t, $J$ = 5.0 Hz, 0.4 H), 3.97 (d, $J$ = 5.1 Hz, 0.4 H), 3.79 (s, 1.2 H), 3.77 (s, 1.8 H), 1.98 (s, 1.8 H), 1.80 (s, 1.2 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 173.0, 171.3, 169.8, 169.3, 166.8, 165.5, 165.4, 165.0, 161.4, 137.6, 135.9, 129.4, 129.3, 128.9, 128.4, 126.7, 125.3, 70.5, 68.9, 59.8, 58.7, 58.1, 56.1, 52.3, 41.5, 41.2, 39.8, 22.9, 21.5 ppm; HRMS $m/z$ calcd for $C_{16}H_{18}N_2O_6Na$ $[M + Na]^+$ 357.1063, found 357.1040.

*(3S,5S)-N-Benzyl-4-formyl-2-oxo-5-phenylmorpholine-3-carboxamide (**4f**):* yield 58% (stirred in $CH_2Cl_2$ for 4 h); colorless gel; $[\alpha]^{28}_D$ +16 ($c$ = 0.6, $CHCl_3$); IR (neat) 3338, 3063, 2925, 1757, 1675, 1530, 1496, 1455, 1359, 1205, 756, 701 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 1.9:1) $\delta$ = 8.16 (s, 0.35 H), 8.04 (s, 0.65 H), 7.46–7.19 (m, 10 H), 6.99 (m, 0.65 H), 6.87 (m, 0.35 H), 5.56 (s, 0.65 H), 5.53 (s, 0.35 H), 5.19 (t, $J$ = 3.1 Hz, 0.35 H), 5.03 (dd, $J$ = 3.2, 11.6 Hz, 0.35 H), 4.92 (dd, $J$ = 4.2, 11.6 Hz, 0.65 H), 4.75 (t, $J$ = 11.8 Hz, 0.65 H), 4.63–4.40 (m, 2.35 H), 4.28 (dd, $J$ = 4.2, 11.9 Hz, 0.65 H) ppm; $^{13}C$ NMR (150 MHz, $CDCl_3$, two rotamers) $\delta$ = 164.9, 164.3, 164.6, 163.5, 163.3, 162.8, 137.0, 136.8, 134.4, 129.5, 129.3, 128.9, 128.7, 128.6, 127.8, 127.6, 127.5, 127.4, 126.3, 70.7, 69.5, 58.7, 57.8, 56.7, 54.5, 44.1, 44.0 ppm; HRMS $m/z$ calcd for $C_{19}H_{18}N_2O_4Na$ $[M + Na]^+$ 361.1159, found 361.1166.

*Methyl 2-((3S,5S)-4-formyl-2-oxo-5-phenylmorpholine-3-carboxamido)acetate (**4g**):* yield 80% (stirred in $CH_2Cl_2$ for 4 h); yellow gel; $[\alpha]^{28}_D$ +28 ($c$ = 0.6, $CHCl_3$); IR (neat) 3349, 3064, 2954, 1752, 1673, 1533, 1439, 1374, 1207, 1069, 1038, 762, 703 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 2:1) $\delta$ = 8.19 (s, 0.33 H), 8.10 (s, 0.66 H), 7.61–7.59 (m, 1 H), 7.45–7.40 (m, 4 H), 7.23–7.21 (m, 1 H), 7.15 (s, 0.66 H), 7.10 (s, 0.33 H), 5.66 (s, 0.66 H), 5.65 (s, 0.33 H), 5.19 (t, $J$ = 3.0 Hz, 0.33H), 4.97 (tt, $J$ = 3.4, 11.8 Hz, 1 H), 4.69 (t, $J$ = 11.9 Hz, 0.66 H), 4.55 (dd, $J$ = 3.0, 11.8 Hz, 0.33 H), 4.31 (dd, $J$ = 4.2, 12.0 Hz, 0.66 H), 4.19 (dd, $J$ = 5.9, 18.0 Hz, 1 H), 4.04 (dd, $J$ = 5.3, 18.0 Hz, 1 H), 3.78 (s, 2 H), 3.77 (s, 1 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 169.3, 169.1, 165.5, 164.5, 164.2, 164.1, 163.4, 163.0, 136.9, 134.4, 129.5, 129.3, 128.9, 128.0, 126.3, 125.8, 70.5, 69.5, 58.2, 57.5, 56.8, 54.5, 52.4, 52.3, 41.6, 41.5 ppm; HRMS $m/z$ calcd for $C_{15}H_{16}N_2O_6Na$ $[M + Na]^+$ 343.0906, found 343.0915.

*(3S,5S)-5-Benzyl-N-tert-butyl-4-formyl-2-oxomorpholine-3-carboxamide (**4h**):* yield 71% (stirred in $CH_2Cl_2$ for 7 h); yellow gel;


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$[\alpha]^{28}_D$ −41 ($c$ = 0.5, $CHCl_3$); IR (neat) 3280, 2969, 2927, 1654, 1565, 1446, 1384, 1221, 1169, 758, 701 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 2.3:1) $\delta$ = 8.11 (s, 0.3 H), 7.91 (s, 0.7 H), 7.36−7.28 (m, 4 H), 7.18−7.16 (m, 1 H), 6.40 (s, 0.3 H), 6.21 (s, 0.7 H), 5.42 (s, 0.3 H), 5.06 (s, 0.7 H), 4.82 (dd, $J$ = 2.6, 11.6 Hz, 1H), 4.37 (dd, $J$ = 5.8, 14.9 Hz, 0.3 H), 4.30 (dd, $J$ = 1.6, 11.6 Hz, 0.7 H), 4.22 (m, 0.7 H), 3.26 (m, 0.3 H), 2.99 (dd, $J$ = 8.3, 14.0 Hz, 1 H), 2.92 (dd, $J$ = 7.9, 13.8 Hz, 1 H), 1.35 (s, 2 H), 1.34 (s, 7 H) ppm; HRMS $m/z$ calcd for $C_{17}H_{23}N_2O_4$ $[M + H]^+$ 319.1658, found 319.1653.

*(3S,5S)-4-Acetyl-5-benzyl-N-tert-butyl-2-oxomorpholine-3-carboxamide (**4i**):* yield 62% (stirred in TFE for 4 h); yellow gel; $[\alpha]^{28}_D$ −31 ($c$ = 0.3, $CHCl_3$); IR (neat) 3334, 2950, 1751, 1695, 1530, 1455, 1390, 1219, 1090, 1044, 752, 702 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 2.3:1) $\delta$ = 7.37−7.30 (m, 3 H), 7.22−7.19 (m, 2 H), 6.14 (s, 0.7 H), 6.12 (s, 0.3 H), 5.10 (s, 0.7 H), 4.90 (s, 0.3 H), 4.77 (dd, $J$ = 2.2, 11.6 Hz, 0.7 H), 4.59 (d, $J$ = 11.2 Hz, 0.3 H), 4.19 (dd, $J$ = 1.4, 11.6 Hz, 1 H), 4.11 (m, 1 H), 3.16 (dd, $J$ = 3.4, 12.9 Hz, 0.3 H), 2.93 (m, 1.4 H), 2.61 (dd, $J$ = 11.4, 12.9 Hz, 0.3 H), 2.17 (s, 2.1 H), 2.00 (s, 0.9 H), 1.34 (s, 9 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 169.8, 169.7, 166.5, 165.9, 163.5, 162.3, 136.8, 135.5, 129.5, 129.2, 128.8, 127.6, 127.0, 67.0, 66.9, 62.6, 60.9, 54.2, 52.7, 52.3, 51.4, 37.8, 35.7, 28.4, 21.5, 21.0 ppm; HRMS $m/z$ calcd for $C_{18}H_{25}N_2O_4$ $[M + H]^+$ 333.1814, found 333.1806.

*(3S,5S)-4-Acetyl-N,5-dibenzyl-2-oxomorpholine-3-carboxamide (**4j**):* yield 55% (stirred in TFE for 4 h); yellow oil; $[\alpha]^{28}_D$ −33 ($c$ = 0.4, $CHCl_3$); IR (neat) 3322, 3029, 2927, 1748, 1654, 1534, 1456, 1389, 1287, 1210, 745, 701 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 3:1) $\delta$ = 7.35−7.31 (m, 7 H), 7.22−7.19 (m, 3 H), 6.98 (s, 0.25 H), 6.71 (s, 0.75 H), 5.51 (s, 0.25 H), 5.25 (s, 0.75 H), 4.80 (dd, $J$ = 2.0, 11.6 Hz, 0.75 H), 4.53 (m, 0.75 H), 4.44 (dd, $J$ = 3.0, 5.6 Hz, 1 H), 4.32 (dd, $J$ = 2.8, 11.7 Hz, 0.5 H), 4.21 (dd, $J$ = 1.3, 11.6 Hz, 1 H), 4.14 (m, 1 H), 3.17 (dd, $J$ = 3.6, 12.9 Hz, 0.25 H), 2.93 (m, 1.5 H), 2.61 (dd, $J$ = 11.4, 12.9 Hz, 0.25 H), 2.17 (s, 2.25 H), 2.15 (s, 0.75 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 169.8, 165.5, 164.7, 137.2, 137.0, 136.7, 129.5, 129.2, 129.1, 128.9, 128.8, 128.0, 127.6, 127.4, 127.0, 67.0, 66.9, 62.3, 60.3, 54.3, 51.5, 44.5, 44.2, 37.8, 35.7, 21.5, 21.0 ppm; HRMS $m/z$ calcd for $C_{21}H_{23}N_2O_4$ $[M + H]^+$ 367.1658, found 367.1651.

*Methyl 2-((3S,5S)-4-benzoyl-5-benzyl-2-oxomorpholine-3-carboxamido)acetate (**4k**):* yield 67% (stirred in TFE for 5 h); yellow oil; $[\alpha]^{28}_D$ −26 ($c$ = 0.8, $CHCl_3$); IR (neat) 3359, 3028, 2954, 1750, 1648, 1529, 1490, 1378, 1284, 1210, 1006, 733, 703 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 1.5:1) $\delta$ = 7.52−7.30 (m, 6 H), 7.18−7.06 (m, 4 H), 6.86 (s, 0.6 H), 6.60 (s, 1 H), 5.90 (s, 0.4 H), 5.67 (s, 0.4 H), 4.69 (d, $J$ = 11.5 Hz, 0.6 H), 4.23 (s, 2 H), 4.09 (s, 2 H), 3.78 (s, 1.8 H), 3.75 (s, 1.2 H), 2.78 (t, $J$ = 13.1 Hz, 2 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, major rotamers) $\delta$ = 171.1, 169.2, 164.7, 134.7, 128.7, 128.6, 126.3, 66.2, 59.0, 54.5, 52.2, 41.6, 36.0 ppm; HRMS $m/z$ calcd for $C_{22}H_{22}N_2O_6Na$ $[M + Na]^+$ 433.1376, found 433.1372.

*(3S,5S)-5-Benzyl-4-formyl-2-oxo-N-phenylmorpholine-3-carboxamide (**4l**):* yield 75% (stirred in TFE for 4.5 h); yellow gel; $[\alpha]^{28}_D$ −30 ($c$ = 0.6, $CHCl_3$); IR (neat) 3327, 2922, 1739, 1651, 1547, 1495, 1386, 1171, 1076, 750, 696 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two major rotamers 2:1) $\delta$ = 8.80 (s, 0.33 H), 8.78 (s, 0.67 H), 8.08 (s, 0.33 H), 7.97 (s, 0.47 H), 7.60−7.49 (m, 2 H), 7.47−7.27 (m, 6 H), 7.20−7.16 (m, 2 H), 5.59 (s, 0.33 H), 5.39 (s, 0.67 H), 4.82 (dd, $J$ = 2.5, 11.8 Hz, 0.67 H), 4.43 (dd, $J$ = 4.5, 11.8 Hz, 0.33 H), 4.39 (dd, $J$ = 4.0, 11.8 Hz, 0.33 H), 4.33 (d, $J$ = 10.6 Hz, 0.67 H), 4.17 (br t, $J$ = 7.8 Hz, 0.67 H), 4.07 (m, 0.33 H), 3.27 (dd, $J$ = 6.8, 14.0 Hz, 0.33 H), 3.00 (m, 1.67 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, two major rotamers) $\delta$ = 164.2, 164.1, 162.1, 161.8, 161.7, 136.9, 136.8, 135.5, 135.0, 129.2, 129.1, 129.0, 128.9, 128.8, 127.6, 127.3, 124.9, 124.8, 120.0, 119.9, 69.2, 67.8, 59.1, 57.2, 52.9, 52.6, 39.2. 37.5 ppm; HRMS $m/z$ calcd for $C_{19}H_{19}N_2O_4$ $[M + H]^+$ 339.1345, found 339.1355.

**One-Pot Procedure for the Synthesis of 4b from 8a.** The mixture of **8a** (37.6 mg, 0.102 mmol) and IBX (31.4 mg, 0.112 mmol) in TFE (1.0 mL) was stirred for 14 h at room temperature, and then **3b** (5.8 μL, 0.153 mmol) and **2a** (17.4 μL, 0.153 mmol) were added. After being stirred for an additional 4 h, the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography on silica gel column using petroleum ether/ethyl acetate (3:1 to 1:1) as the eluent to give product **4b** (23.3 mg, 46%) as a colorless gel.

**General Procedure for the Ugi Three-Component Reaction of Ketoimines 1d−g or 10a,b.** To a 0.25 M solution of the imine **1d−g** or **10a,b** (1 equiv) in TFE were added successively carboxylic acid **3** (2.2 equiv for formic acid or 3 equiv for other acid) and isonitrile **2** (1.5 equiv) under argon atmosphere. The resulting mixture was stirred at room temperature for about 12 h (**2** was exhausted), and then additional **2** (0.5 equiv) was added. The resulting mixture was stirred unceasingly until **2** was exhausted again and concentrated in vacuo. The residue was purified by flash chromatography on silica gel column using petroleum ether/ethyl acetate (3:1 to 1:2) as the eluent to give product **5** or **11**.

*(3S,5S)-N-tert-Butyl-4-formyl-3-methyl-2-oxo-5-phenylmorpholine-3-carboxamide (**5a$_1$**):* yield 61%; colorless gel; $[\alpha]^{26}_D$ +67 ($c$ = 1.9, $CHCl_3$); IR (neat) 3409, 2967, 2932, 1740, 1699, 1670, 1522, 1455, 1359, 1276, 1199, 1058, 742, 697 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 3:1) $\delta$ = 8.50 (s, 0.75 H), 8.28 (s, 0.25 H), 7.42−7.29 (m, 3.8 H), 7.22−7.19 (m, 1.2 H), 6.05 (s, 0.25 H), 5.77 (s, 0.75 H), 5.66 (s, 0.75 H), 5.20 (dd, $J$ = 2.6, 11.5 Hz, 0.25 H), 5.11 (s, 0.25 H), 4.88 (dd, $J$ = 2.2, 11.4 Hz, 0.25 H), 4.61 (dd, $J$ = 0.6, 11.6 Hz, 0.75 H), 4.56 (dd, $J$ = 2.8, 12.0 Hz, 0.75 H), 2.04 (s, 2.25 H), 1.87 (s, 0.75 H), 1.37 (s, 2.25 H), 1.36 (s, 6.75 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 168.9, 167.3, 166.1, 165.6, 162.8, 162.5, 137.5, 135.6, 129.3, 129.0, 128.7, 128.1, 126.9, 126.1, 69.9, 69.2, 67.2, 66.7, 54.9, 52.8, 52.3, 52.1, 28.3, 24.5, 20.6 ppm; HRMS $m/z$ calcd for $C_{17}H_{23}N_2O_4$ $[M + H]^+$ 319.1658, found 319.1651.

*(3R,5S)-N-tert-Butyl-4-formyl-3-methyl-2-oxo-5-phenylmorpholine-3-carboxamide (**5a$_2$**):* yield 15%; colorless gel; $[\alpha]^{26}_D$ +73 ($c$ = 1.6, $CHCl_3$); IR (neat) 3397, 2976, 2937, 1749, 1676, 1526, 1453, 1386, 1335, 1219, 1198, 757, 700 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 5.7:1) $\delta$ = 8.57 (s, 0.85 H), 7.93 (s, 0.15 H), 7.45−7.44 (m, 2 H), 7.31−7.29 (m, 3 H), 6.65 (s, 0.85 H), 6.06 (s, 0.15 H), 5.97 (s, 0.85 H), 5.93 (s, 0.15 H), 4.96 (dd, $J$ = 2.9, 11.8 Hz, 0.85 H), 4.88 (d, $J$ = 8.9 Hz, 0.258 H), 4.73 (dd, $J$ = 3.8, 11.8 Hz, 0.85 H), 4.35 (d, $J$ = 10.8 Hz, 0.25 H), 2.05 (s, 0.45 H), 1.96 (s, 2.55 H), 1.34 (s, 1.35 H), 1.05 (s, 7.65 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$, major rotamer) $\delta$ = 169.9, 165.3, 162.4, 134.4, 128.9, 128.6, 128.2, 70.2, 64.8, 51.6, 48.1, 28.0, 27.0 ppm; HRMS $m/z$ calcd for $C_{17}H_{23}N_2O_4$ $[M + H]^+$ 319.1658, found 319.1648.

*(3S,5S)-4-Acetyl-N-tert-butyl-3-methyl-2-oxo-5-phenylmorpholine-3-carboxamide (**5b**):* yield 63%; yellow gel; $[\alpha]^{26}_D$ +41 ($c$ = 1.7, $CHCl_3$); IR (neat) 3394, 2977, 2926, 1735, 1674, 1507, 1452, 1387, 1197, 1153, 751, 703 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 7.64−7.27 (m, 5 H), 6.13 (s, 1 H), 5.32 (d, $J$ = 11.4 Hz, 1 H), 5.22 (s, 1 H), 4.77 (d, $J$ = 11.3 Hz, 1 H), 2.17 (s, 3 H), 2.02 (s, 3 H), 1.36 (s, 9 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ = 170.5, 167.9, 167.0, 136.0, 129.3, 128.5, 126.5, 69.0, 68.5, 56.6, 52.1, 28.3, 22.9, 21.5 ppm; HRMS $m/z$ calcd for $C_{18}H_{25}N_2O_4$ $[M + H]^+$ 333.1814, found 333.1823.

*(3S,5S)-N-tert-Butyl-3-methyl-2-oxo-5-phenyl-4-propionylmorpholine-3-carboxamide (**5c**):* yield 51%; yellow gel; $[\alpha]^{26}_D$ +38 ($c$ = 0.9, $CHCl_3$); IR (neat) 3281, 1978, 2939, 1762, 1659, 1547, 1461, 1387, 1282, 1173, 1067, 756, 702 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 7.43−7.27 (m, 5 H), 6.14 (s, 1 H), 5.32 (dd, $J$ = 2.5, 11.4 Hz, 1 H), 5.25 (s, 1 H), 4.75 (d, $J$ = 11.1 Hz, 1 H), 2.49 (dt, $J$ = 7.6, 16.1 Hz, 1 H), 2.27 (dt, $J$ = 7.3, 16.0 Hz, 1 H), 2.03 (s, 3 H), 1.37 (s, 9 H), 1.12 (t, $J$ = 7.3 Hz, 3 H) ppm; $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ = 173.6, 168.0, 167.1, 136.4, 129.3, 128.4, 126.4, 69.1, 68.6, 55.6, 52.1, 28.3, 27.6, 21.7, 9.2 ppm; HRMS $m/z$ calcd for $C_{19}H_{27}N_2O_4$ $[M + H]^+$ 347.1971, found 347.1973.

*(3S,5S)-N-Butyl-4-formyl-3-methyl-2-oxo-5-phenylmorpholine-3-carboxamide (**5d$_1$**):* yield 72%; yellow oil; $[\alpha]^{26}_D$ +59 ($c$ = 0.6, $CHCl_3$); IR (neat) 3358, 2959, 2870, 1750, 1674, 1528, 1459, 1381, 1254, 1198, 1065, 749, 699 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$, two rotamers 2:1) $\delta$ = 8.52 (s, 0.68 H), 8.28 (s, 0.32 H), 7.44−7.20 (m, 5 H), 6.25 (s, 0.32 H), 6.05 (s, 0.68 H), 5.69 (s, 0.68 H), 5.22 (dd, $J$ = 2.7, 11.4 Hz, 0.32 H), 5.13 (s, 0.32 H), 4.89 (dd, $J$ = 2.2 11.5 Hz, 0.32 H), 4.63 (t, $J$ = 13.2 Hz, 1.36 H), 3.30 (m, 2 H), 2.05 (s, 2 H), 1.93 (s,


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1 H), 1.51 (m, 2 H), 1.33 (m, 2 H), 0.93 (t, $J$ = 7.3 Hz, 3 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 168.6, 167.1, 166.8, 166.7, 137.2, 135.5, 129.4, 129.0, 128.9, 128.2, 126.9, 126.2, 67.0, 69.2, 66.7, 66.3, 55.1, 51.9, 40.7, 40.4, 31.2, 24.9, 20.6, 20.0, 19.9, 13.7 ppm; HRMS $m/z$ calcd for $C_{17}H_{23}N_2O_4$ $[M + H]^+$ 319.1658, found 319.1662.

*(3R,5S)-N-Butyl-4-formyl-3-methyl-2-oxo-5-phenylmorpholine-3-carboxamide (**5d$_2$**):* yield 9%; yellow oil; $[\alpha]^{25}_D$ +57 ($c$ = 0.1, $CHCl_3$); IR (neat) 3342, 2926, 1749, 1677, 1533, 1458, 1377, 1225, 1126, 762, 701 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$, two rotamers 5.7:1) $\delta$ = 8.65 (s, 0.85 H), 7.90 (s, 0.15 H), 7.43−7.32 (m, 3 H), 7.29−7.26 (m, 2 H), 6.70 (s, 0.85 H), 6.25 (s, 0.15 H), 6.01 (br s, 1 H), 4.99 (d, $J$ = 11.6 Hz, 1 H), 4.87 (d, $J$ = 8.3 Hz, 0.15 H), 4.73 (dd, $J$ = 3.4, 11.8 Hz, 0.85 H), 4.33 (d, $J$ = 11.9 Hz, 0.15 H), 3.32 (m, 0.3 H), 2.92 (dd, $J$ = 6.1, 12.4 Hz, 1.7 H), 2.10 (s, 0.45 H), 1.99 (s, 2.55 H), 1.55−1.08 (m, 4 H), 0.93 (t, $J$ = 7.3 Hz, 0.45 H), 0.82 (t, $J$ = 6.8 Hz, 2.55 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, major rotamer) $\delta$ = 169.8, 166.7, 162.4, 134.1, 128.8, 128.6, 128.3, 70.3, 64.5, 48.2, 40.1, 31.0, 27.2, 19.8, 13.6 ppm; HRMS $m/z$ calcd for $C_{17}H_{23}N_2O_4$ $[M + H]^+$ 319.1658, found 319.1669.

*(3S,5S)-4-Benzoyl-N-tert-butyl-3-methyl-2-oxo-5-phenylmorpholine-3-carboxamide (**5e$_1$**):* yield 33%; yellow gel; $[\alpha]^{26}_D$ +60 ($c$ = 0.4, $CHCl_3$); IR (neat) 3412, 2970, 2922, 1745, 1651, 1518, 1455, 1374, 1292, 1197, 1110, 757, 701 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.41−7.33 (m, 8 H), 7.26−7.24 (m, 2 H), 5.95 (s, 1 H), 5.41 (dd, $J$ = 2.7, 11.2 Hz, 1 H), 5.21 (s, 1 H), 4.69 (dd, $J$ = 1.0, 11.1 Hz, 1 H), 2.05 (s, 3 H), 1.40 (s, 9 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 171.3, 167.9, 166.4, 136.7, 135.5, 130.2, 129.2, 128.6, 128.4, 126.8, 126.4, 69.7, 68.7, 57.1, 52.3, 28.3, 21.5 ppm; HRMS $m/z$ calcd for $C_{23}H_{26}N_2O_4Na$ $[M + Na]^+$ 417.1790, found 417.1788.

*(3R,5S)-4-Benzoyl-N-tert-butyl-3-methyl-2-oxo-5-phenylmorpholine-3-carboxamide (**5e$_2$**):* yield 8%; yellow gel; $[\alpha]^{26}_D$ +45 ($c$ = 0.3, $CHCl_3$); IR (neat) 3313, 2970, 2911, 1685, 1580, 1520, 1375, 1219, 1154, 1085, 1021, 812 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 8.09 (s, 1H), 7.38−6.95 (m, 10 H), 5.95 (s, 1 H), 5.01 (dd, $J$ = 4.2, 10.2 Hz, 1 H), 4.50 (dd, $J$ = 10.5, 12.4 Hz, 1 H), 4.21 (dd, $J$ = 4.2, 12.5 Hz, 1 H), 2.17 (s, 3 H), 1.50 (s, 9 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 175.1, 169.8, 167.4, 137.3, 136.5, 131.0, 128.9, 128.3, 128.2, 127.3, 126.8, 70.0, 68.7, 61.7, 51.9, 28.6, 21.7 ppm; HRMS $m/z$ calcd for $C_{23}H_{26}N_2O_4Na$ $[M + Na]^+$ 417.1790, found 417.1793.

*Methyl 2-((3S,5S)-4-formyl-3-methyl-2-oxo-5-phenylmorpholine-3-carboxamido)acetate (**5f**):* yield 63%; yellow oil; $[\alpha]^{27}_D$ +79 ($c$ = 0.7, $CHCl_3$); IR (neat) 3356, 3007, 2953, 1750, 1673, 1527, 1447, 1362, 1208, 1064, 754, 700 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$, two rotamers 2.3:1) $\delta$ = 8.52 (s, 0.7 H), 8.27 (s, 0.3 H), 7.43−7.29 (m, 3.5 H), 7.21−7.19 (m, 1.5 H), 7.02 (s, 0.3 H), 6.88 (t, $J$ = 5.5 Hz, 0.7 H), 5.63 (s, 0.7 H), 5.15 (s, 0.3 H), 5.13 (dd, $J$ = 2.7, 14.2 Hz, 0.3 H), 4.87 (dd, $J$ = 2.3, 11.4 Hz, 0.3 H), 4.75 (dd, $J$ = 3.0, 12.2 Hz, 0.7 H), 4.60 (d, $J$ = 12.1 Hz, 0.7 H), 4.05 (t, $J$ = 5.5 Hz, 0.6 H), 4.02 (dd, $J$ = 1.0, 5.9 Hz, 1.4 H), 3.76 (s, 0.9 H), 3.75 (s, 2.1 H), 2.10 (s, 2.1 H), 1.99 (s, 0.9 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 169.6, 169.3, 168.0, 167.9, 167.4, 166.6, 162.8, 162.7, 137.3, 135.4, 129.4, 129.0, 128.9, 128.2, 126.8, 126.1, 69.8, 69.2, 55.3, 52.6, 52.5, 52.3, 42.0, 24.3, 20.5 ppm; HRMS $m/z$ calcd for $C_{16}H_{19}N_2O_6$ $[M + H]^+$ 335.1243, found 335.1231.

*(3S,5S)-N-Cyclohexyl-4-formyl-3-methyl-2-oxo-5-phenylmorpholine-3-carboxamide (**5g$_1$**):* yield 71%; yellow oil; $[\alpha]^{27}_D$ +60 ($c$ = 0.7, $CHCl_3$); IR (neat) 3347, 2931, 2856, 1749, 1679, 1523, 1452, 1357, 1254, 1197, 1065, 743, 698 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$, two rotamers 2.3:1) $\delta$ = 8.52 (s, 0.7 H), 8.28 (s, 0.3 H), 7.41−7.30 (m, 3.5 H), 7.22−7.20 (m, 1.5 H), 6.08 (d, $J$ = 7.1 Hz, 0.3 H), 5.83 (d, $J$ = 7.1 Hz, 0.7 H), 5.68 (s, 0.7 H), 5.22 (dd, $J$ = 2.5, 11.4 Hz, 0.3 H), 5.12 (s, 0.3 H), 4.89 (dd, $J$ = 1.8, 11.4 Hz, 0.3 H), 4.64 (d, $J$ = 11.9 Hz, 0.7 H), 4.59 (dd, $J$ = 2.9, 12.3 Hz, 0.7 H), 3.76 (m, 1 H), 2.05 (s, 2.1 H), 1.93 (s, 0.9 H), 1.89 (m, 1 H), 1.71 (m, 2 H), 1.64 (m, 2 H), 1.36 (m, 2 H), 1.19 (m, 3 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 168.6, 167.1, 166.0, 165.8, 162.7, 162.5, 137.3, 135.6, 129.4, 129.0, 128.8, 128.1, 126.9, 126.2, 69.9, 69.2, 66.8, 66.3, 55.1, 52.0, 50.0, 49.6, 32.5, 32.4, 32.3, 25.5, 25.2, 24.8, 24.7, 24.6, 20.5 ppm; HRMS $m/z$ calcd for $C_{19}H_{25}N_2O_4$ $[M + H]^+$ 345.1814, found 345.1823.

*(3R,5S)-N-Cyclohexyl-4-formyl-3-methyl-2-oxo-5-phenylmorpholine-3-carboxamide (**5g$_2$**):* yield 15%; yellow oil; $[\alpha]^{27}_D$ +42 ($c$ = 0.2, $CHCl_3$); IR (neat) 3387, 2919, 2851, 1749, 1660, 1530, 1452, 1408, 1117, 753, 698 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$, two rotamers 4.9:1) $\delta$ = 8.63 (s, 0.83 H), 7.91 (s, 0.17 H), 7.44 −7.42 (m, 2 H), 7.32−7.30 (m, 3 H), 6.60 (d, $J$ = 6.4 Hz, 0.83 H), 6.13 (d, $J$ = 5.8 Hz, 0.17 H), 6.00 (m, 0.83 H), 4.98 (dd, $J$ = 2.3, 11.6 Hz, 0.83 H), 4.95 (m, 0.17 H), 4.88 (br d, $J$ = 7.4 Hz, 0.17 H), 4.73 (dd, $J$ = 3.5, 11.7 Hz, 0.83 H), 4.33 (br d, $J$ = 11 Hz, 0.17 H), 3.78 (m, 0.17 H), 3.37 (m, 0.83 H), 2.09 (s, 0.5 H), 1.98 (s, 2.5 H), 1.72−1.24 (m, 10 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, major rotamer) $\delta$ = 169.7, 165.6, 162.4, 134.1, 128.8, 128.6, 128.2, 70.2, 64.5, 49.1, 48.2, 32.2, 32.0, 27.1, 25.3, 24.4, 24.3 ppm; HRMS $m/z$ calcd for $C_{19}H_{25}N_2O_4$ $[M + H]^+$ 345.1814, found 345.1820.

*Benzyl (2-((3S,5S)-4-formyl-3-methyl-2-oxo-5-phenylmorpholine-3-carboxamido)ethyl)carbonate (**5h**):* yield 68%; yellow oil; $[\alpha]^{25}_D$ +44 ($c$ = 0.7, $CHCl_3$); IR (neat) 3343, 2935, 1743, 1689, 1530, 1455, 1393, 1261, 1065, 755, 699 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$, two rotamers 1.9:1) $\delta$ = 8.47 (s, 0.65 H), 8.20 (s, 0.35 H), 7.40−7.31 (m, 8.5 H), 7.20−7.18 (m, 1.5 H), 6.80 (s, 0.35 H), 6.53 (t, $J$ = 5.3 Hz, 0.65 H), 5.63 (s, 0.65 H), 5.17 (s, 0.7 H), 5.16 (s, 1.3 H), 5.13 (dd, $J$ = 2.7, 8.8 Hz, 0.35 H), 5.07 (s, 0.35 H), 4.84 (dd, $J$ = 2.4, 11.5 Hz, 0.35 H), 4.62 (dd, $J$ = 2.9, 12.1 Hz, 0.65 H), 4.54 (d, $J$ = 12.0 Hz, 0.65 H), 4.32−4.21 (m, 2 H), 3.60−3.57 (m, 2 H), 2.00 (s, 1.95 H), 1.90 (s, 1.05 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 168.1, 167.5, 166.7, 162.7, 162.6, 155.2, 155.1, 137.2, 135.4, 135.0, 134.9, 129.4, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.1, 126.9, 126.2, 70.1, 70.0, 69.9, 69.2, 66.6, 66.3, 66.1, 65.7, 55.1, 51.9, 40.1, 39.9, 24.7, 20.5 ppm; HRMS $m/z$ calcd for $C_{23}H_{25}N_2O_7$ $[M + H]^+$ 441.1662, found 441.1650.

*(3S,5S)-4-Acetyl-5-benzyl-N-tert-butyl-3-methyl-2-oxomorpholine-3-carboxamide (**5i$_1$**):* yield 50%; colorless gel; $[\alpha]^{27}_D$ −54 ($c$ = 1.4, $CHCl_3$); IR (neat) 3428, 2970, 2931, 1744, 1653, 1518, 1460, 1409, 1279, 1202, 1002, 753, 703 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.38−7.28 (m, 3 H), 7.23−7.21 (m, 2 H), 5.85 (s, 1 H), 4.98 (d, $J$ = 11.3 Hz, 1 H), 4.19 (d, $J$ = 11.0 Hz, 1 H), 4.08 (t, $J$ = 6.8 Hz, 1 H), 2.94 (m, 2 H), 2.06 (s, 3 H), 2.03 (s, 3 H), 1.36 (s, 9 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 168.7, 168.4, 166.8, 136.0, 129.2, 129.1, 127.5, 67.9, 67.4, 55.3, 52.1, 37.4, 28.3, 22.3, 21.8 ppm; HRMS $m/z$ calcd for $C_{19}H_{27}N_2O_4$ $[M + H]^+$ 347.1971, found 347.1961.

*(3R,5S)-4-Acetyl-5-benzyl-N-tert-butyl-3-methyl-2-oxomorpholine-3-carboxamide (**5i$_2$**):* yield 9%; yellow gel; $[\alpha]^{25}_D$ −7 ($c$ = 0.6, $CHCl_3$); IR (neat) 3343, 2973, 1735, 1677, 1453, 1385, 1274, 1136, 1088, 765 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.36−7.32 (m, 2H), 7.29−7.25 (m, 3 H), 5.69 (s, 1 H), 4.30 (dd, $J$ = 2.3, 11.8 Hz, 1 H), 4.23 (dd, $J$ = 1.7, 11.8 Hz, 1 H), 4.04 (s, 1 H), 3.16 (m, 2 H), 2.22 (s, 3 H), 1.92 (s, 3 H), 1.42 (s, 9 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 169.1, 167.7, 166.7, 136.4, 130.9, 129.3, 129.1, 128.8, 127.2, 71.8, 66.4, 66.3, 52.0, 36.5, 28.4, 27.7, 22.3, 19.2 ppm; HRMS $m/z$ calcd for $C_{19}H_{27}N_2O_4$ $[M + H]^+$ 347.1971, found 347.1975.

*2-((3S,5S)-4-Formyl-3-methyl-2-oxo-5-phenylmorpholine-3-carboxamido)ethyl acetate (**5j**):* yield 72%; yellow oil; $[\alpha]^{25}_D$ +54 ($c$ = 0.5, $CHCl_3$); IR (neat) 3362, 2925, 1743, 1676, 1528, 1453, 1364, 1231, 1062, 754, 700 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$, two rotamers 1.5:1) $\delta$ = 8.50 (s, 0.6 H), 8.25 (s, 0.4 H), 7.42−7.29 (m, 4 H), 7.22−7.21 (m, 1 H), 6.80 (t, $J$ = 4.9 Hz, 0.4 H), 6.57 (t, $J$ = 5.3 Hz, 0.6 H), 5.69 (s, 0.6 H), 5.16 (dd, $J$ = 2.7, 11.5 Hz, 0.4 H), 5.13 (s, 0.4 H), 4.88 (dd, $J$ = 2.3, 11.5 Hz, 0.4 H), 4.65 (d, $J$ = 1.6 Hz, 1.2 H), 4.27−4.15 (m, 2 H), 3.58−3.51 (m, 2 H), 2.09 (s, 1.2 H), 2.07 (s, 1.8 H), 2.04 (s, 1.8 H), 1.91 (s, 1.2 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 171.7, 171.1, 168.2, 167.3, 166.8, 162.7, 162.8, 137.1, 135.4, 129.4, 129.1, 128.9, 128.2, 126.9, 126.2, 69.9, 69.3, 66.7, 66.3, 62.3, 55.2, 51.8, 40.2, 40.1, 24.9, 20.9, 20.8, 20.5 ppm; HRMS $m/z$ calcd for $C_{17}H_{21}N_2O_6$ $[M + H]^+$ 349.1400, found 349.1406.

*(3S,5S)-4-Acetyl-N-tert-butyl-5-isopropyl-3-methyl-2-oxomorpholine-3-carboxamide (**5k$_1$**):* yield 39%; yellow gel; $[\alpha]^{25}_D$ −64 ($c$ = 1.0, $CHCl_3$); IR (neat) 3393, 2969, 2920, 1734, 1667, 1387, 1199, 1152 cm$^{-1}$; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ = 5.77 (s, 1 H), 5.07 (d, $J$ = 10.8 Hz, 1 H), 4.49 (d, $J$ = 10.9 Hz, 1 H), 3.57 (d, $J$ = 10.6 Hz, 1 H), 2.14 (s, 3 H), 1.90 (s, 3 H), 1.87 (m, 1 H), 1.35 (s, 9 H), 1.08 (d, $J$ =


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6.5 Hz, 6H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 168.9, 168.5, 166.8, 68.2, 67.9, 59.8, 52.0, 28.3, 22.7, 21.1, 19.8, 19.2 ppm; HRMS $m/z$ calcd for $C_{15}H_{27}N_2O_4$ $[M + H]^+$ 299.1971, found 299.1966.

*(3R,5S)-4-Acetyl-N-tert-butyl-5-isopropyl-3-methyl-2-oxomorpholine-3-carboxamide (**5k$_2$**):* yield 9%; yellow gel; $[\alpha]^{27}_D$ −39 ($c$ = 0.3, $CHCl_3$); IR (neat) 3445, 2921, 2852, 1747, 1657, 1385, 1257, 1127, 1066 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 5.62 (s, 1 H), 4.60 (d, $J$ = 10.8 Hz, 1 H), 4.42 (d, $J$ = 11.0 Hz, 1 H), 3.57 (bs, 1 H), 2.15 (s, 4 H), 1.91 (s, 3 H), 1.39 (s, 9 H), 1.16 (d, $J$ = 6.1 Hz, 3 H), 1.08 (d, $J$ = 6.6 Hz, 3 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 169.4, 169.2, 166.2, 67.3, 66.7, 51.8, 29.1, 28.4, 22.8, 20.7, 19.1 ppm; HRMS $m/z$ calcd for $C_{15}H_{27}N_2O_4$ $[M + H]^+$ 299.1971, found 299.1969.

*(3S,5S)-N-tert-Butyl-3-ethyl-4-formyl-2-oxo-5-phenylmorpholine-3-carboxamide (**5l$_1$**):* yield 78.5%; colorless gel; $[\alpha]^{27}_D$ +57 ($c$ = 0.6, $CHCl_3$); IR (neat) 3395, 2974, 2933, 1734, 1655, 1517, 1458, 1363, 1207, 1136, 728, 703 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$, two rotamers 5.7:1) $\delta$ = 8.38 (s, 0.85 H), 8.29 (s, 0.15 H), 7.41−7.30 (m, 5 H), 6.04 (s, 0.15 H), 5.79 (s, 0.85 H,), 5.66 (d, $J$ = 2.8 Hz, 0.85 H), 5.09 (s, 0.15 H), 4.85 (dd, $J$ = 2.6, 11.7 Hz, 0.15 H), 4.71 (d, $J$ = 5.4 Hz, 0.15 H), 4.66 (d, $J$ = 12.0 Hz, 0.85 H), 4.54 (dd, $J$ = 3.3, 12.1 Hz, 0.85 H), 2.87 (q, $J$ = 7.4 Hz, 0.15 H), 2.68 (q, $J$ = 7.3 Hz, 0.85 H), 2.33 (q, $J$ = 7.0 Hz, 0.15 H), 2.09 (q, $J$ = 7.3 Hz, 0.85 H), 1.36 (s, 9 H), 0.86 (t, $J$ = 7.2 Hz, 2.55 H), 0.70 (t, $J$ = 7.3 Hz, 0.45 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, major rotamer) $\delta$ = 168.5, 165.5, 163.4, 138.1, 128.8, 128.1, 127.1, 71.4, 69.3, 52.7, 51.2, 29.6, 28.4, 9.1 ppm; HRMS $m/z$ calcd for $C_{18}H_{25}N_2O_4$ $[M + H]^+$ 333.1814, found 333.1804.

*(3R,5S)-N-tert-Butyl-3-ethyl-4-formyl-2-oxo-5-phenylmorpholine-3-carboxamide (**5l$_2$**):* yield 9.5%; colorless gel; $[\alpha]^{26}_D$ +89 ($c$ = 0.7, $CHCl_3$); IR (neat) 3360, 2972, 1728, 1683, 1534, 1459, 1367, 1279, 1216, 1134, 728, 698 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$, major rotamer) $\delta$ = 8.56 (s, 1 H), 7.45−7.40 (m, 2.5 H), 7.30−7.26 (m, 2.5 H), 7.09 (s, 1 H), 6.15 (d, $J$ = 3.2 Hz, 1 H), 5.06 (d, $J$ = 11.6 Hz, 1 H), 4.73 (dd, $J$ = 3.6, 11.6 Hz, 1 H), 2.36 (q, $J$ = 7.4 Hz, 2 H), 1.06 (t, $J$ = 7.4 Hz, 3 H), 0.99 (s, 9 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, major rotamer) $\delta$ = 170.1, 164.9, 162.8, 134.2, 128.7, 128.6, 128.5, 70.6, 69.7, 51.4, 46.3, 33.6, 28.0, 8.4 ppm; HRMS $m/z$ calcd for $C_{18}H_{25}N_2O_4$ $[M + H]^+$ 333.1814, found 333.1808.

*(3S,5S)-4-Acetyl-N-tert-butyl-3-ethyl-2-oxo-5-phenylmorpholine-3-carboxamide (**5m**):* yield 78%; colorless gel; $[\alpha]^{24}_D$ +24 ($c$ = 0.3, $CHCl_3$); IR (neat) 3288, 2972, 2925, 1761, 1660, 1541, 1457, 1388, 1219, 1162, 763, 706 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.39−7.35 (m, 5 H), 6.62 (s, 1 H), 5.17 (bs, 1 H), 5.05 (bs, 1 H), 4.55 (bs, 1 H), 2.90 (bs, 1 H), 2.61 (q, $J$ = 6.6 Hz, 1 H), 2.18 (bs, 3 H), 1.36 (s, 9 H), 0.80 (bs, 3 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 172.8, 167.8, 167.1, 138.0, 129.2, 128.6, 127.0, 74.5, 68.6, 57.6, 52.2, 28.5, 27.5, 24.2, 10.7; HRMS $m/z$ calcd for $C_{19}H_{26}N_2O_4K$ $[M + K]^+$ 385.1530, found 385.1535.

*(3S,5S)-5-Benzyl-N-tert-butyl-4-formyl-3-methyl-2-oxomorpholine-3-carboxamide (**5n$_1$**):* yield 55%; yellow oil; $[\alpha]^{27}_D$ −7 ($c$ = 0.6, $CHCl_3$); IR (neat) 3395, 2931, 1734, 1687, 1517, 1452, 1386, 1307, 1253, 745, 701 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$, two rotamers 2:1) $\delta$ = 8.41 (s, 0.67 H), 7.86 (s, 0.33 H), 7.36−7.25 (m, 4 H), 7.21 - 7.18 (m, 1 H), 6.06 (s, 0.33 H), 5.75 (s, 0.67 H), 4.99 (dd, $J$ = 2.3, 11.0 Hz, 0.33 H), 4.63 (dd, $J$ = 2.8, 11.2 Hz, 0.67 H), 4.31 (d, $J$ = 10.5 Hz, 0.33 H), 4.19 (d, $J$ = 12.0 Hz, 0.67 H), 4.11 (dd, $J$ = 1.9, 12.1 Hz, 0.67 H), 4.04 (t, $J$ = 7.9 Hz, 0.33 H), 2.04 (s, 0.99 H), 1.96 (s, 2.01 H), 1.35 (s, 2.97 H), 1.33 (s, 6.03 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 169.3, 167.5, 165.9, 165.5, 162.6, 161.5, 136.3, 135.5, 129.5, 129.2, 128.9, 127.6, 127.1, 68.8, 66.6, 66.3, 66.0, 54.4, 52.7, 52.3, 50.4, 38.5, 36.4, 28.3, 25.2, 21.1 ppm; HRMS $m/z$ calcd for $C_{18}H_{25}N_2O_4$ $[M + H]^+$ 333.1814, found 333.1819.

*(3R,5S)-5-Benzyl-N-tert-butyl-4-formyl-3-methyl-2-oxomorpholine-3-carboxamide (**5n$_2$**):* yield 16%; yellow oil; $[\alpha]^{27}_D$ −26 ($c$ = 0.1, $CHCl_3$); IR (neat) 3427, 2976, 2923, 1740, 1703, 1676, 1511, 1460, 1374, 1254, 1189, 746, 701 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$, two rotamers 7.3:1) $\delta$ = 8.46 (s, 0.88 H), 7.97 (s, 0.12H), 7.33−7.31 (m, 3 H), 7.28−7.26 (m, 2 H), 7.12 (s, 0.88 H), 5.84 (s, 0.12 H), 4.78 (ddd, $J$ = 3.2, 3.3, 11.9 Hz, 0.88 H), 4.38 (br s, 0.24 H), 4.26 (d, $J$ = 3.0 Hz, 1.76 H), 3.96 (m, 0.12 H), 3.19 (m, 0.24 H), 3.08 (dd, $J$ = 3.6, 13.2 Hz, 0.88 H), 2.46 (t, $J$ = 12.6 Hz, 0.88 H), 1.99 (s, 2.64 H), 1.94 (s, 0.36 H), 1.43 (s, 1.08 H), 1.38 (s, 7.92H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, major rotamer) $\delta$ = 170.0, 166.0, 162.3, 136.6, 129.3, 128.9, 127.1, 68.6, 65.0, 52.1, 47.8, 34.0, 28.3, 26.6 ppm; HRMS $m/z$ calcd for $C_{18}H_{25}N_2O_4$ $[M + H]^+$ 333.1814, found 333.1812.

*(3S,5S)-N-tert-Butyl-4-formyl-5-isopropyl-3-methyl-2-oxomorpholine-3-carboxamide (**5o$_1$**):* yield 75%; yellow gel; $[\alpha]^{27}_D$ −29 ($c$ = 0.4, $CHCl_3$); IR (neat) 3379, 2972, 2929, 1740, 1679, 1521, 1389, 1367, 1266, 1199, 1118 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$, two rotamers 1.5:1) $\delta$ = 8.35 (s, 0.40 H), 8.03 (s, 0.60 H), 5.94 (s, 0.60 H), 5.82 (s, 0.40 H), 5.04 (dd, $J$ = 2.2, 11.2 Hz, 0.60 H), 4.56 (dd, $J$ = 1.1, 11.2 Hz, 0.60 H), 4.52 (d, $J$ = 10.9 Hz, 0.40 H), 4.35−4.30 (m, 0.80 H), 3.35 (d, $J$ = 10.6 Hz, 0.60 H), 1.93 (s, 3 H), 1.87 (m, 1 H), 1.36 (s, 5.40 H), 1.34 (s, 3.60 H), 1.08−0.98 (m, 6 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 169.2, 167.6, 165.8, 165.4, 163.1, 161.7, 68.1, 67.8, 66.8, 66.5, 59.3, 53.3, 52.7, 52.3, 29.0, 28.3, 27.9, 25.8, 20.5, 19.6, 19.5, 19.1 ppm; HRMS $m/z$ calcd for $C_{14}H_{25}N_2O_4$ $[M + H]^+$ 285.1814, found 285.1821.

*(3R,5S)-N-tert-Butyl-4-formyl-5-isopropyl-3-methyl-2-oxomorpholine-3-carboxamide (**5o$_2$**):* yield 12%; yellow gel; $[\alpha]^{27}_D$ −31 ($c$ = 0.2, $CHCl_3$); IR (neat) 3427, 2966, 2922, 1750, 1672, 1446, 1362, 1252, 1181, 1111, 1054 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$, two rotamers 5.7:1) $\delta$ = 8.54 (s, 0.85 H), 8.05 (s, 0.15 H), 7.51 (s, 0.85 H), 5.77 (s, 0.15 H), 4.67 (d, $J$ = 11.6 Hz, 0.15 H), 4.60 (d, $J$ = 11.3 Hz, 0.85 H), 4.43 (br d, $J$ = 10.4 Hz, 1 H), 4.35 (dd, $J$ = 2.7, 11.5 Hz, 0.85 H), 3.30 (br d, $J$ = 9.8 Hz, 0.15 H), 1.96 (s, 3 H), 1.63 (m, 1 H), 1.39 (s, 1.34 H), 1.36 (s, 7.66 H), 1.12 (d, $J$ = 6.6 Hz, 0.45 H),1.06 (d, $J$ = 6.8 Hz, 0.45 H), 1.02 (d, $J$ = 6.6 Hz, 2.55 H), 0.98 (d, $J$ = 6.6 Hz, 2.55 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, major rotamer) $\delta$ = 170.8, 165.9, 162.6, 70.1, 64.2, 51.8, 51.3, 28.3, 27.4, 19.9, 19.6 ppm; HRMS $m/z$ calcd for $C_{14}H_{25}N_2O_4$ $[M + H]^+$ 285.1814, found 285.1812.

*(2S,6S)-6-Phenyl-N-tert-butyl-4-butyl-1-formyl-2-methyl-3-oxopiperazine-2-carboxamide (**11a**):* yield 74%; yellow oil; $[\alpha]^{27}_D$ +33 ($c$ = 0.6, $CHCl_3$); IR (neat) 3384, 2962, 2928, 2870, 1662, 1524, 1453, 1365, 1303, 1206, 1088, 1026, 700; $^1$H NMR (400 MHz, $CDCl_3$, two rotamers 7.3:1) $\delta$ = 8.49 (s, 0.88 H), 8.22 (s, 0.12 H), 7.13−7.33 (m, 5 H), 5.96 (s, 0.88 H), 5.88 (s, 0.12 H), 5.65 (br s, 0.88 H), 5.11 (br s, 0.12 H), 4.27 (dd, $J$ = 3.4, 12.6 Hz, 0.12 H), 3.81 (dd, $J$ = 3.8, 13.5 Hz, 0.88 H), 3.66 (m, 0.12 H), 3.57 (m, 0.88 H), 3.35 (d, $J$ = 13.4 Hz, 1 H), 3.04 (m, 0.12 H), 2.78 (m, 0.88 H), 2.04 (s, 2.64 H), 1.96 (s, 0.36 H), 1.35 (s, 1.08 H), 1.34 (s, 7.92 H), 1.05−1.23 (m, 4 H), 0.85 (t, $J$ = 7.3 Hz, 0.36 H), 0.80 (t, $J$ = 7.3 Hz, 2.64 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 167.5, 167.2, 163.5, 139.7, 128.7, 127.6, 125.9, 67.1, 53.0, 52.0, 50.3, 48.4, 28.9, 28.4, 24.0, 19.8, 13.6 ppm; HRMS $m/z$ calcd for $C_{21}H_{32}N_3O_3$ $[M + H]^+$ 374.2444, found 374.2442.

*Methyl 2-((2S,6S)-6-benzyl-1-formyl-2,4-dimethyl-3-oxopiperazine-2-carboxamido)acetate (**11b**):* yield 63%; yellow oil; $[\alpha]^{10.6}_D$ −52 ($c$ = 0.9, $CH_2Cl_2$); IR (neat) 3358, 3059, 3027, 2949, 1751, 1672, 1522, 1439, 1402, 1366, 1208, 1095, 1051, 1021, 979, 737, 703; $^1$H NMR (400 MHz, $CDCl_3$, two rotamers 2.8:1) $\delta$ = 8.32 (s, 0.74 H), 7.86 (s, 0.26 H), 7.13−7.33 (m, 5 H), 6.80 (s, 0.74 H), 6.62 (s, 0.26 H), 4.71 (d, $J$ = 10.8 Hz, 0.74 H), 3.84−4.13 (m, 2.52 H), 3.69 (s, 0.78 H), 3.66 (s, 2.22 H), 3.40 (dd, $J$ = 2.7, 13.3 Hz, 0.74 H), 3.00 (s, 2.22 H), 2.99 (s, 0.78 H), 2.80−2.96 (m, 2.26 H), 2.54 (t, $J$ = 11.7 Hz, 0.74 H), 2.00 (s, 0.78 H), 1.95 (s, 2.22 H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, two rotamers) $\delta$ = 172.4, 169.8, 169.6, 169.2, 168.4, 166.6, 165.7, 163.4, 137.3, 136.4, 129.3, 129.2, 129.1, 129.0, 127.5, 127.1, 66.0, 65.9, 58.4, 55.0, 52.5, 52.5, 50.4, 50.1, 47.3, 42.1, 41.9, 39.5, 37.5, 36.6, 25.8, 20.2 ppm; HRMS $m/z$ calcd for $C_{21}H_{32}N_3O_3$ $[M + H]^+$ 362.1716, found 362.1720.

**Procedure for Synthesis of 5l$_2$ via Alkylation of 4d.** To a solution of **4d** (25.6 mg, 0.084 mmol) in DMF (0.84 mL) were added successively $Cs_2CO_3$ (27.4 mg, 0.084 mmol) and $C_2H_5I$ (67.3 $\mu$L, 0.84 mmol) under argon atmosphere. The resulting mixture was stirred at room temperature for 1.5 h and diluted with brine, and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with water, dried with $Na_2SO_4$, and concentrated under vacuum. The residue was further purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate


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(3:1 to 2:1) as the eluent to afford **5I$_2$** (21.0 mg, 75%) as a colorless gel.

## ■ ASSOCIATED CONTENT

### Supporting Information

Description of the general experimental procedures and NMR spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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