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Stereocontrolled Disruption of the Ugi Reaction toward the Production of Chiral Piperazinones: Substrate Scope and Process Development

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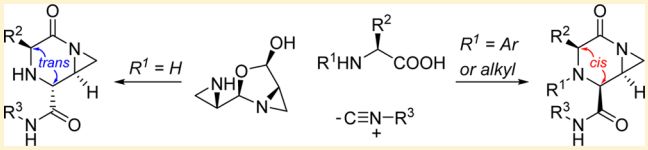
Supporting Information

ABSTRACT: The factors determining diastereoselectivity observed in the multicomponent conversion of amino acids, aziridine aldehyde dimers, and isocyanides into chiral piperazinones have been investigated. Amino acid-dependent selectivity for either *trans*- or *cis*-substituted piperazinone products has been achieved. An experimentally determined diastereoselectivity model for the three-component reaction driven by aziridine aldehyde dimers has predictive value for different substrate classes. Moreover, this model is useful in reconciling the previously reported observations in multicomponent reactions between isocyanides, α-amino acids, and monofunctional aldehydes.



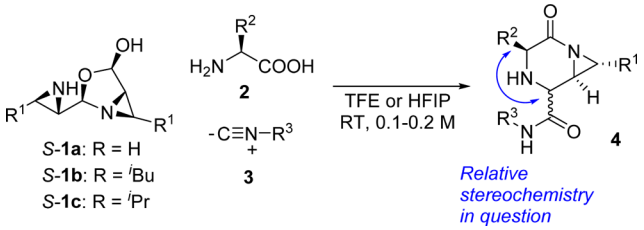
INTRODUCTION

By linking several different starting materials into a densely functionalized product, multicomponent reactions facilitate convergent assembly of medicinally relevant chemotypes.[1] The impact of this chemistry has been particularly profound in the synthesis of small-to-medium ring heterocycles. When it comes to sp^3-rich rings, controlling both relative and absolute stereochemistry of their chiral centers is an additional challenge.[2] Here we investigate how amphoteric aziridine aldehyde dimers interfere with one of the pivotal intermediates in the Ugi reaction pathway, thereby enabling rapid construction of biologically significant piperazinones.[3]

The Ugi reaction is a multicomponent process that produces α-acylaminoamides from primary amines, aldehydes or ketones, carboxylic acids, and isocyanides.[4] Unless formaldehyde or a symmetrical ketone is employed, a chiral center is produced during the course of the reaction. While this reaction has been widely applied in both diversity-[5] and target-oriented synthesis,[6] as well as in preparation of interesting biological probes,[7] stereocontrol remains a challenge.[8] For example, a practical and diastereoselective synthesis of polypeptides using the Ugi reaction has proven elusive due to limited understanding of the origins of diastereoselectivity in these reactions.[9]

In 2010, we reported a *trans*-diastereoselective cyclization of amino acids and peptides using a "disrupted" Ugi reaction (Scheme 1).[10] In this reaction, a reversibly autoprotected aziridine aldehyde dimer **1** is involved in iminium ion formation prior to the selectivity-determining isocyanide addition. The exocyclic aziridine intercepts the well-established course of the reaction by attacking the carbonyl group of the mixed anhydride, which otherwise undergoes solvolysis. In addition to the stereocontrol, the "disrupted" Ugi reaction afforded piperazinone rings from three readily available components in a single step, thereby simplifying access to these products,[11] while adding significant molecular complexity.

Scheme 1. Aziridine Aldehyde Dimers (1), Amino Acids (2), and Isocyanides (3) Undergo a "Disrupted" Ugi Reaction To Yield Piperazinone Rings (4)



Recently, we reported evidence of *cis*-products from the three-component cyclization reaction.[12] Using X-ray crystallography, we confirmed this configuration for an 18-membered peptide macrocycle. This prompted us to undertake a detailed assessment of the stereochemical outcome of the three-component cyclization process in the formation of piperazinones (**4**, Scheme 1). In this paper, we report on the X-ray crystallography and through-space NOESY NMR studies which shed light on the diastereoselectivity of aziridine aldehyde-

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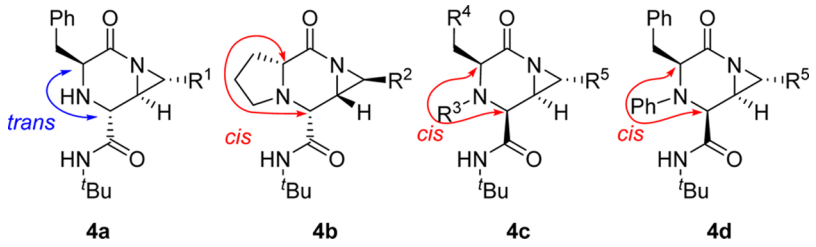

Figure 1. Stereochemistry as determined by X-ray structures of phenylalanine-derived piperazinone (**4a**), proline-derived piperazinone (**4b**), *N*-alkylated amino acid-derived piperazinone (**4c**), and *N*-phenylphenylalanine-derived piperazinone (**4d**). (R^1 = $CH_2OTBDMS$, R^2 = ^{i}Pr, R^3 = CH_2-4-biphenyl, R^4 = 2-naphthyl, R^5 = H)

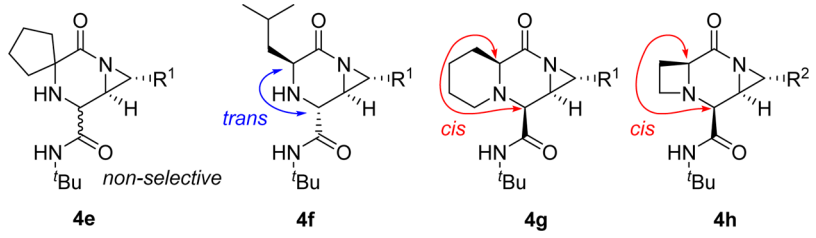

Figure 2. Stereochemical structure determination from 1D and 2D NOESY NMR of major products in the formation of cycloleucine-derived piperazinone (**4e**), leucine-derived piperazinone (**4f**), pipecolic acid-derived piperazinone (**4g**), and azetidine-2-carboxylic acid-derived piperazinone (**4h**). (R^1 = H, R^2 = ^{i}Bu)

induced cyclization of amino acids. Primary and secondary amino acids participated in the reaction with opposite diastereoselectivity. We also compare the diastereoselectivity of the "disrupted" Ugi reaction with the previously published variants of the Ugi reaction.

RESULTS

A detailed analysis of piperazinones derived from α-amino acids (Scheme 1) revealed amino acid-dependent diastereoselectivity. As confirmed by X-ray crystallography and 2D NOESY data, piperazinones derived from phenylalanine or other chiral primary α-amino acids have a *trans* orientation of the newly formed stereocenter relative to the α-stereocenter of the amino acid (**4a**, Figure 1). In contrast, when proline serves as the amino acid component, the major diastereomer formed has *cis* relative orientation of substituents (**4b**, Figure 1). Cyclization of an *N*-substituted amino acid gave the same relative stereochemistry as proline (**4c**, Figure 1). Similarly, an *N*-phenyl-substituted phenylalanine also resulted in *cis* stereochemistry (**4d**, Figure 1).

Low diastereoselectivity was observed when achiral amino acids were used. This trend was observed for piperazinones derived from both substituted and unsubstituted aziridine aldehyde dimers. For instance, cycloleucine, devoid of a chiral center, led to the corresponding piperazinone with little diastereoselectivity (**4e**, Figure 2).

For substrates where a crystal was not generated, stereochemistry of the newly formed methine center was confirmed by 1D and 2D NOESY NMR. The proximity of the new methine to both the amino acid C_α–H and the aziridine C_α–H would depend greatly on whether the diastereomer is *cis* or *trans*. For example, the diastereomeric products of cyclization using L-leucine with aziridine aldehyde dimer *S*-**1a** were characterized by NMR of the crude reaction mixture (Figure 3). Major isomer *trans*-**4f** was identified by NOESY crosspeaks between the C–H signal of the newly incorporated methine (δ 3.52 ppm) and the signal of one of the exocyclic aziridine CH_2s (δ 1.67 ppm) and by NOESY crosspeaks between the C_α–H

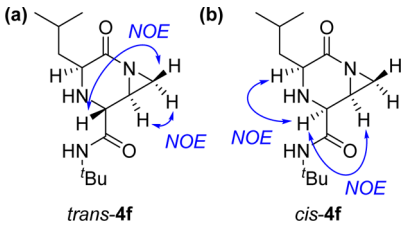

Figure 3. NOEs observed for *trans*-**4f** (a) and *cis*-**4f** (b).

signal of the aziridine (δ 3.49 ppm) and the signal of the other exocyclic aziridine CH_2 (δ 2.52 ppm). Conversely, the *cis*-**4f** isomer was identified by NOESY crosspeaks from the C–H signal of the newly incorporated methine (δ 4.08 ppm) to both the C_α–H signal of the aziridine (δ 2.96 ppm) and the L-leucine C_α–H (δ 3.21 ppm).

In an effort to determine the diastereoselectivity with greater detail, we monitored crude reactions by NMR. The selectivity for the *trans*/*cis* products was determined by evaporating the mixture and taking ^{1}H and ^{13}C NMR in $CDCl_3$ or by using ^{13}C-labeled amino acids and following the conversion and selectivity of the reaction by ^{13}C NMR in 10% TFE-d_3/TFE.

Piperazinone formation with primary L-amino acids (phenylalanine and leucine) indicated moderate *trans* selectivity of approximately 3:1 (*trans*/*cis*). In contrast, secondary amino acids were selective for the *cis* isomer with over 9:1 (*cis*/*trans*) selectivity for L-proline. For L-pipecolic acid and L-azetidine-2-carboxylic acid, the selectivity was also high (Table 1: entry 10 and 11). Interestingly, when the primary amino acid L-phenylalanine was used in an *N*-alkylated form, piperazinone products **4c**′ and **4d** were formed in a *cis*-selective fashion with >95:5 (*cis*/*trans*) selectivity. In the case of primary or secondary amino acids, the aziridine aldehyde side chain size (*S*-**1a** vs *S*-**1b**) did not significantly affect the diastereoselectivity. As diastereoselectivity was mostly absent from cycloleucine-derived products, it was clear that the aziridine aldehyde chirality does not alone cause a diastereoselective reaction.

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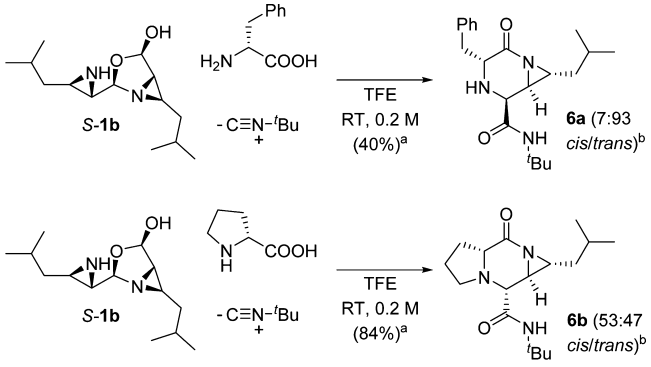
Table 1. Amino Acid–Based Diastereoselectivity of the Ugi Three-Component Reaction with Aziridine Aldehydes

				selectivity (%)		
entry	aziridine aldehyde	amino acid	product	*cis*	*trans*	yield (%)
1	*S*-**1a**	L-Phe	**4a′**	27,[a] 28[b]	73,[a] 72[b]	81[c]
2	*S*-**1b**	L-Phe	**4a″**	19,[a] 20[b]	81,[a] 80[b]	60 (*trans*)[d]
3	*S*-**1a**	L-Pro	**4b′**	93,[ab]	7,[ab]	84 (*cis*)[d]
4	*S*-**1b**	L-Pro	**4b″**	92,[a] 90[b]	8,[a] 10[b]	73[c]
5	*S*-**1a**	L-*N*-Bn-Phe	**4c′**	>95[a]	<5[a]	54 (*cis*)[d]
6	*S*-**1a**	L-*N*-Ph-Phe	**4d**	>95[a]	<5[a]	70 (*cis*)[d]
7	*S*-**1a**	cyclo-Leu	**4e**	59 (*S*)[a]	41 (*R*)[a]	81[c]
8	*S*-**1a**	L-Leu	**4f**	28[b]	72[b]	74[c]
9	*S*-**1b**	L-Leu	**4f′**	27,[a] 31[b]	73,[a] 69[b]	87[c]
10	*S*-**1a**	L-pipecolic acid	**4g**	>95[a]	<5[a]	71 (*cis*)[d]
11	*S*-**1b**	L-Aze[e]	**4h**	93[a]	7[a]	70 (*cis*)[d]

[a]Based on crude NMR after 15 min. [b]Selectivity based on ^{13}C NMR with ^{13}C-labeled amino acid after 15 min. [c]Combined yield for both diastereomers. [d]Yield of one diastereomer. [e]Azetidine-2-carboxylic acid.

Having established that the substitution of the amine drives selectivity for one isomer over the other, we next turned to varying the stereochemistry of the aziridine aldehyde component with respect to the amino acid stereochemistry. The pairing of an amino acid with identical stereochemistry to the aziridine aldehyde was termed "match" (Scheme 1 and Table 1), while pairing reagents of opposite stereochemistry was termed "mismatch" (Scheme 2).

Scheme 2. Mismatch Conditions of *S*-1b with D-Phenylalanine and D-Proline[a,b]



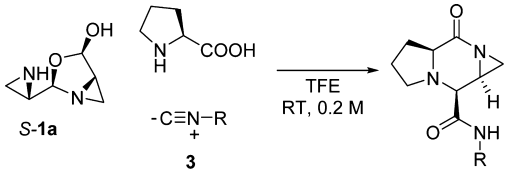
[a]Combined yield for both diastereomers. [b]Based on crude NMR after 15 min.

In the mismatch cases, D-phenylalanine was still selective for the *trans* isomer; however, increased selectivity was observed (Scheme 2). Whereas in the match case the diastereoselectivity was 3:1 (*trans*/*cis*), for the mismatch case the dr was 93:7 (*trans*/*cis*). Piperazinone formation from the secondary amino acid D-proline was the opposite of primary amino acids, and while the major product was still the *cis* isomer, the selectivity was much lower and approached that of cyclo-Leu (59:41).

Lastly, we turned to varying the isocyanide substitution and studying the effects on diastereoselectivity (Scheme 3). Using *n*-pentyl isocyanide or benzyl isocyanide, 75:25 (*cis*/*trans*) and 76:24 (*cis*/*trans*) diastereoselectivity was observed, respectively.

During the course of the diastereoselectivity studies, we noted, in certain cases, formation of a byproduct and a change in the apparent diastereoselectivity if reactions were allowed to stir for extended periods of time.[13] The byproducts did not contain a downfield aziridine amide, and instead, a new peak

Scheme 3. Effects of Isocyanide Substitution on the Formation of Piperazinones from *S*-1a and L-Pro[a,b]

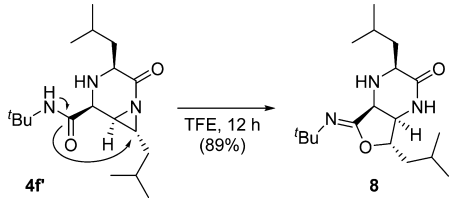


7a, R = *n*-pentyl, 44%[a] (75:25 *cis*/*trans*)[b]
7b, R = Bn, 51%[a] (76:24 *cis*/*trans*)[b]

[a]Combined yield for both diastereomers. [b]Selectivity based on ^{13}C NMR with ^{13}C-labeled amino acid after 15 min.

was found in the conventional amide region of the ^{1}H NMR. In our previous report on the homo-Ugi four-component-five-centered reaction, we observed acid-catalyzed aziridine ring-opening by the neighboring amide group.[14] We were able to confirm a similar rearrangement within the piperazinone rings that led to bicyclic imidates (Scheme 4). When both

Scheme 4. Imidate Formation by Attack of the Exocyclic Amide onto the Aziridine



diastereomers of **4f′** were dissolved in TFE and left to stir for 12 h, only the minor *cis* product formed imidate **8**. It was apparent that a *cis* relationship between the protons of the neighboring methines of the exocyclic amide and aziridine was required to afford nucleophilic attack.

DISCUSSION

Our results indicate that there is a substantial difference in reactivity between secondary and primary amino acids in the context of aziridine aldehyde "disrupted" Ugi reactions. When reacted with an *S*-aziridine aldehyde dimer, amino acids such as L-phenylalanine lead to *R*-stereochemistry of the newly formed methine center of the piperazinone (*S*,*R*,*S* relative stereo-

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chemistry). At first glance, it is reasonable to ascribe the observed reactivity difference to the known difference in conformation between proline-derived iminium ions and their primary amine-derived counterparts (Figure 4). For an *S*-primary amino acid, the allylic strain would bias the isocyanide to attack from the *si*-face, whereas L-proline is expected to favor the *re*-attack.

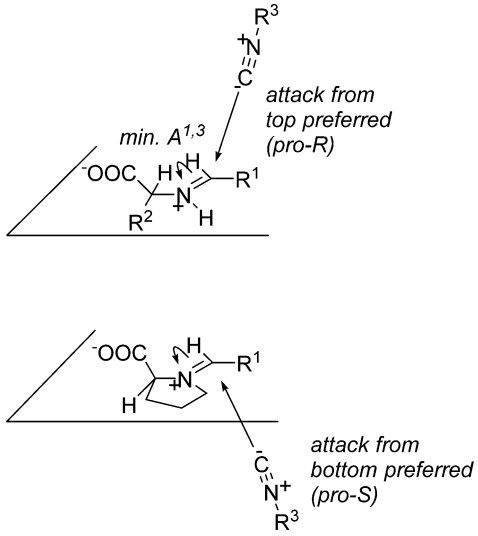

Figure 4. Preliminary rationale for difference in reactivity between proline and other amino acids during cyclization.

In contrast to the three-component cyclizations using aziridine aldehydes, the homo-Ugi four-component reaction exhibits poor control over formation of the α-aziridinyl stereocenter.[14] The diastereomeric ratios of products of the four-component reaction were no greater than 4:1 and the use of chiral amines along with chiral aldehydes did not lead to more selective reactions. These results reinforce the notion that the chirality of aziridine aldehydes alone cannot control the stereochemical outcomes of isocyanide-based multicomponent reactions, and suggest that intramolecular pairing of iminium ion and carboxylic acid is crucial to achieving high facial selectivity of isocyanide attack (Figure 5).

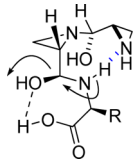

Figure 5. Carboxylate-assisted iminium ion formation with primary amino acids.

The amine-dependent stereoselectivity prompted us to compare our data to previous contributions in the literature. Ugi's 1996 paper[15] documents the same sense of stereoinduction with proline, whereas Kim's,[16] Dyker's,[17] and Ciufolini's[18] subsequent studies are at odds with Ugi's seminal work, documenting the opposite stereochemistry (Figure 6). However, Kim, Dyker, and Ciufolini considered primary amine-containing amino acids in their investigations. Ciufolini also observed (*S*,*S*) stereochemical outcomes but only in specific combinations of aromatic aldehydes and isocyanides.[18,19] We suggest that the disagreement in the Ugi three-component

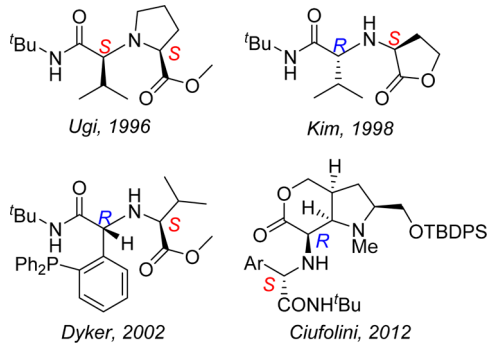

Figure 6. Stereochemical outcomes of Ugi multicomponent reactions with amino acids.

condensation with amino acid substrates is readily resolved if one acknowledges the fundamental differences in reactivity between a proline-derived iminium ion and a primary amine-derived congener. To the best of our knowledge, this important aspect of reactivity difference has not been illuminated thus far.

The dimeric nature of aziridine aldehydes was previously shown to play an important role in several processes. The relevance of higher order intermediates to the reaction comes to light when the match/mismatch behavior described above is subjected to further scrutiny. The key to reconciling the difference in behavior of the matched pairs lies in the open dimer intermediates. In our previous studies, open dimers were found to be kinetically important in indium-promoted aldehyde allylation[20] (Figure 7a) and a rerouted aza-Michael reaction[21] (Figure 7b). Importantly, the open dimer scaffold has been successfully captured within seven-membered rings (Figure 7c).[22]

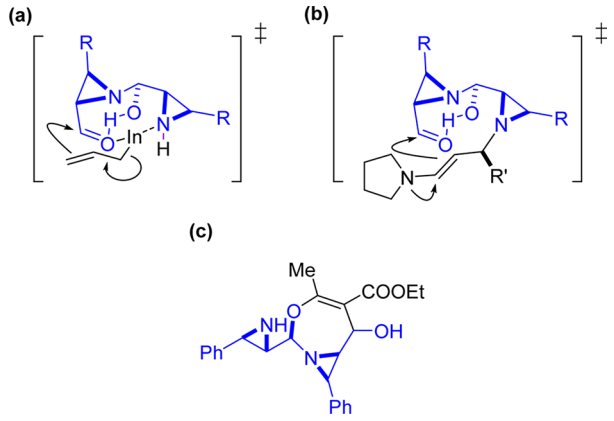

Figure 7. Open dimers are key to the reactivity of aziridine aldehyde dimers.

In the case of proline, a set of kinetics experiments and a computational study have provided justification for *cis* selectivity.[23] *Re*-attack to furnish *cis* products can be achieved through attack of either *trans*-**9** or *cis*-**9** iminium ions (Figure 8). While thermodynamically a *trans* arrangement is expected, structures of iminium ions calculated at the MPWPW91/6-31G(d) level showed *cis* iminium ion formation to be energetically favoured (difference of 1.0 kcal/mol). Additionally, either ion could be sequestered as the corresponding oxazolidinone, such as oxazolidinone **10** arising from the *cis* iminium ion (Figure 9).

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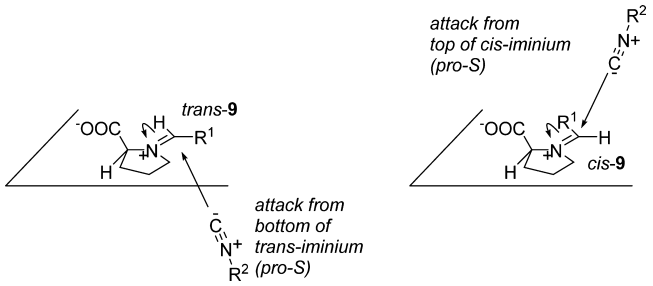

Figure 8. Two trajectories and assemblies of iminium ions that lead to *cis* products.

Subsequently, the governing principles for the trajectory of attack were found to be the proximity of the carboxylate to the nucleophile and a Cieplak model of nucleophilic addition to carbonyls.[24] Pro-*S* attack from the bottom face of the *trans*-**9** iminium ion would not allow the carboxylate to participate and cause a disfavored stepwise mechanism (Figure 8).[25] Conversely, the *cis*-**9** iminium ion would allow carboxylate participation and it would also be a good fit for the Cieplak model with the electron rich C−C aziridine σ bond positioned antiperiplanar to the σ^* of the forming C−C bond. On the basis of these factors, attack of iminium ion **12** was justified as the most favored pathway (Figure 9).

In the mismatch case (**14**), the expected *cis* iminium ion would not engender a favorable trajectory of attack for the isocyanide (Figure 9). Pro-*S* (**16**) attack would be disadvantaged by a lack of carboxylate participation, while pro-*R* (**18**) attack would not conform to the Cieplak model and would also be disadvantaged. The lack of a defined trajectory of attack is in line with the low diastereoselectivity observed in mismatch scenarios with proline (see Results).

Primary amine-containing amino acids present an altogether different story. In order to minimize $A^{1,2}$ and $A^{1,3}$ strain, the iminium ion would adopt a *trans* geometry **19** and **21** (Figure 10). We expect the same principles of carboxylate participation

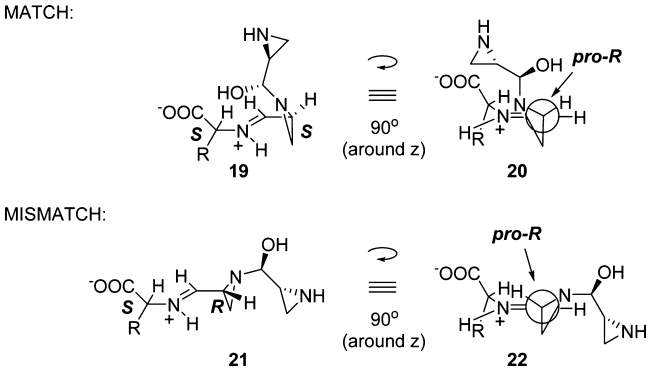

Figure 10. Proposed mechanism for aziridine aldehyde dimer mediated Ugi three-component condensation of primary amine-containing amino acids.

and Cieplak model of carbonyl attack to govern the trajectory of the nucleophilic isocyanide. In the match case, **20**, pro-*R* attack suffers from steric clash of the dimeric aziridine aldehyde portion and the iminium ion. Experimentally, much higher diastereoselectivity for pro-*R* attack was observed in the mismatch case. The proposed model, **22**, justifies this by fulfilling both the carboxylate participation and the Cieplak model requirements without the steric clash seen in the match case.

Finally, this model also explains the excellent diastereoselectivity observed with other secondary amino acids. The favored geometry of the iminium ion would minimize the allylic strain and adopt *cis* iminium geometry (Figure 11). Attack from the *re*-face would then proceed with the same governing principles as isocyanide addition to the proline iminium **12**.

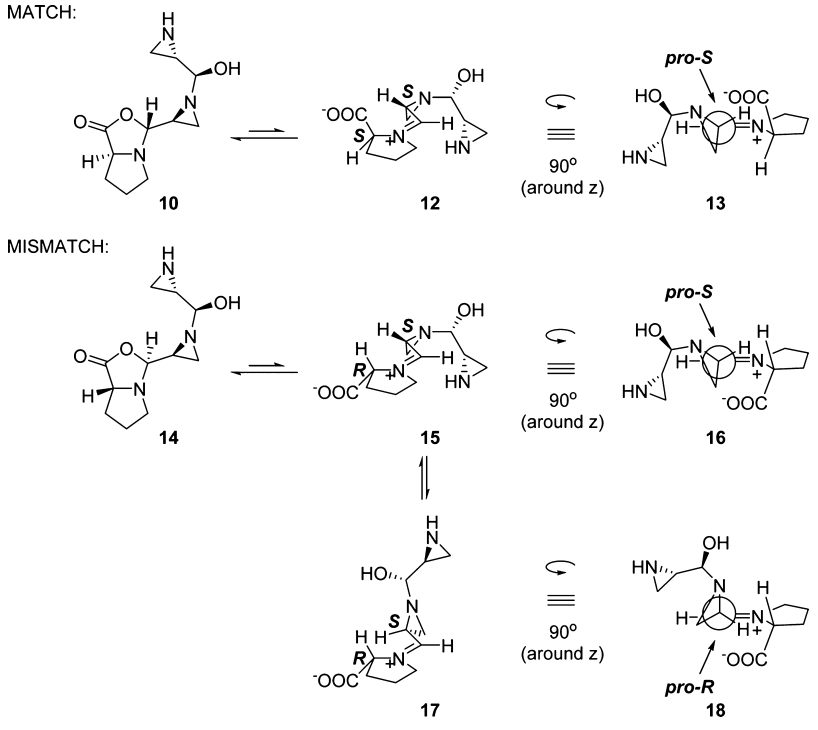

Figure 9. Stereochemistry matched (*S*,*S*) and mismatched (*S*,*R*) cases for reactions involving proline.

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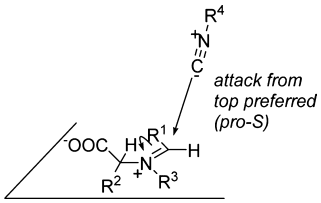

Figure 11. Minimizing allylic strain for the iminium ion leads to a similar mechanism as for proline.

In the "disrupted" Ugi reaction with aziridine aldehydes, we found that the nature of the isocyanide is not greatly significant, and the reaction with benzyl isocyanide formed the expected *cis* (*S*,*S*) products. Yet, when the Ley team employed benzyl isocyanide, a reversal of selectivity was observed, to produce the (*R*,*S*) product.[26] A possible explanation for the departure in diastereoselectivity observed by Ley *et al.*, can be attributed to their choice of an α-amino tetrazole as a surrogate for α-amino acids, which may impact the transition state assembly for isocyanide attack. If the Ley case is considered as operating on different principles, then the diastereoselectivity with the "disrupted" Ugi reaction behaves in a similar manner to other Ugi reactions.

CONCLUSIONS

In summary, we have performed a close analysis of the diastereoselectivity of amino acid cyclizations using aziridine aldehyde dimers and isocyanides. The diastereoselectivity for piperazinone formation from primary and secondary amino acids was determined by using NMR and X-ray crystallography. Our study shows that the relative stereochemistry of the newly formed methine center is controlled by both the amino acid and the aziridine aldehyde dimer. Achiral amino acids did not engender significant diastereoselectivity in these reactions. In the case of chiral secondary amino acids such as proline, *cis* relative stereochemistry of the methine carbon was observed. Conversely, chiral primary amino acids were selective for the *trans*-substituted products. Since the aziridine aldehyde component is chiral, a match/mismatch scenario is operative. In the case of L-proline, the aziridine aldehyde dimer with the *S*-stereocenter at the α position relative to the aldehyde produced high diastereoselectivity, whereas the *R*-aziridine aldehyde dimer led to mismatch and low diastereoselectivity. For primary amino acids this trend was reversed, and higher diastereoselectivity was observed in the mismatch case.

The aziridine aldehyde dimer-driven cyclization offered us a model to investigate diastereoselectivity in the Ugi three-component condensation. These observations are consistent with literature precedent, and contribute to a resolution of a long-standing controversy concerning five-centered Ugi reactions. Our results for diastereoselectivity in the "disrupted" Ugi reaction with aziridine aldehydes parallel the findings of Ugi, Kim, Dyker, and Ciufolini. By looking at a simple model of proline-derived iminium ions versus primary amine-derived iminium ions (Figures 9 and 10), a stereochemical model emerges that explains the formation of *cis* products derived from secondary amino acids and *trans* products from primary amino acids. Furthermore, the stereochemistry match/mismatch scenarios that arise between amino acid and aziridine aldehyde partners are readily explained when one considers the Cieplak model of carbonyl addition and the importance of carboxylate participation in Ugi reactions. It is our belief that these results will elucidate a more complete understanding of Ugi reactions and a fuller view of their mechanisms. Finally, in light of the importance of heterocycles as therapeutic chemotypes, the ability to create piperazinone rings in a stereocontrolled fashion will be of use to medicinal chemistry efforts.

EXPERIMENTAL SECTION

General Information. All solvents (except HPLC solvents) and reagents were of reagent-grade quality. ^{13}C-labeled amino acids were sourced from Cambridge Isotope Laboratories, Inc. (Tewksbury). Aziridine aldehyde dimers *S*-**1a**, *S*-**1b**, and *R*-**1c** were prepared as per literature procedures.[14,27]

Chromatography. Flash column chromatography was carried out using 230−400 mesh silica gel. Thin-layer chromatography (TLC) was performed on precoated glass backed TLC plates and visualized using a UV lamp (254 nm), iodine stain, or ninhydrin stain.

Nuclear Magnetic Resonance Spectra. ^{1}H and ^{13}C NMR spectra were recorded on 400, 500, 600, and 700 MHz spectrometers. ^{1}H NMR spectra were referenced to $CDCl_3$ (δ 7.26 ppm), CD_3OD (δ 3.30 ppm), DMSO-d_6 (δ 2.50 ppm), acetone-d_6 (δ 2.05 ppm), and TFE-d_3 (δ 5.02 ppm), and ^{13}C NMR spectra were referenced to $CDCl_3$ (δ 77.2 ppm), CD_3OD (δ 49.0 ppm), DMSO-d_6 (δ 39.52 ppm), acetone-d_6 (δ 29.84 ppm), and TFE-d_3 (δ 126.28 ppm). Peak multiplicities are designated by the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; ds, doublet of singlets; dd, doublet of doublets; ddd, doublet of doublet of doublets; bt, broad triplet; td, triplet of doublets; tdd, triplet of doublets of doublets.

Mass Spectrometry. High-resolution mass spectra were obtained on mass spectrometers with electrospray ionization (ESI) or direct analysis in real time (DART) sources and TOF analyzers.

RP-HPLC/MS. Low-resolution mass spectra (ESI) were collected on an HPLC paired to a single-quad mass spectrometer. Compounds were resolved on an Agilent Poroshell 120 EC-C_{18}, 2.7 μm, 4.6 × 50 mm^2 column at room temperature with a flow of 1 mL/min. The gradient consisted of eluents A (0.1% formic acid in double distilled water) and B (0.1% formic acid in HPLC-grade acetonitrile). The gradient method started at 5% of B for the first 1.0 min, followed by a linear gradient from 5% to 95% B in 8.0 min. The column was then washed with 95% B for 1.0 min and equilibrated at 5% B for 1.5 min.

(3*R*,5*S*,6*R*,7*S*)-3-Benzyl-*N*-(*tert*-butyl)-7-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamide (4a). Previously reported.[10]

(3*S*,5*R*,6*S*)-3-Benzyl-*N*-*tert*-butyl-2-oxo-1,4-diazabicyclo-[4.1.0]heptane-5-carboxamide (4a′). In a 1 dram vial equipped with a magnetic stirring bar were added L-phenylalanine (0.114 mmol), 0.6 mL of HFIP, *S*-**1a** (0.057 mmol), and *tert*-butyl isocyanide (0.136 mmol), and the resulting mixture was stirred for 100 min. The mixture was concentrated under reduced pressure and purified by silica gel chromatography (hexanes to 50% EtOAc) to yield both diastereomers. Yield: 28 mg, 81%; crude dr 72:28 (*anti*/*syn*); HRMS (DART) calcd for $[C_{17}H_{23}N_3O_2 + H]^+$ 302.1863, found 302.1875.

Major diastereomer: TLC EtOAc R_f = 0.71; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 3.54 (ddd, J = 4.8, 4.1, 1.7 Hz, 1H), 3.45 (d, J = 1.7 Hz, 1H), 3.25 (dd, J = 14.4, 3.5 Hz, 1H), 3.17 (dd, J = 10.5, 3.5 Hz, 1H), 2.59 (d, J = 4.7 Hz, 1H), 2.54 (dd, J = 14.5, 10.5 Hz, 1H), 2.01 (d, J = 4.1 Hz, 1H), 1.03 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 185.3, 169.0, 138.3, 129.7, 128.9, 127.0, 57.8, 54.0, 50.7, 35.5, 34.8, 31.5, 28.4.

Minor diastereomer: TLC EtOAc R_f = 0.52; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (s, 1H), 3.94 (d, J = 5.9 Hz, 1H), 3.49−3.46 (m, 1H), 3.31 (dd, J = 14.5, 4.3 Hz, 1H), 2.96 (ddd, J = 5.9, 4.6, 4.1 Hz, 1H), 2.66 (dd, J = 14.5, 9.6 Hz, 1H), 2.39 (d, J = 4.7 Hz, 1H), 2.23 (dd, J = 4.1, 0.6 Hz, 1H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 183.4, 169.0, 137.3, 129.2, 129.1, 127.2, 58.6, 56.2, 51.5, 35.4, 35.4, 29.8, 28.9, 28.8.

(3*S*,5*R*,6*R*,7*R*)-3-Benzyl-*N*-*tert*-butyl-7-isobutyl-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamide (4a″). In a 2 dram vial

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equipped with a magnetic stirring bar were added L-phenylalanine (0.05 mmol) and 0.25 mL of TFE, and the mixture was stirred until a homogeneous solution was obtained. *S*-**1b** (0.025 mmol) and *tert*-butyl isocyanide (0.05 mmol) were then added sequentially, and the resulting mixture was stirred for 1 h. The mixture was concentrated by N_2 purge and purified by silica gel chromatography (EtOAc/hexanes 10% to EtOAc/hexanes 30%) to yield the major diastereomer: yield 11 mg, 60%; crude dr 81:19 (*anti*/*syn*).

Major diastereomer: TLC EtOAc/hexanes 30% R_f = 0.75; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.18 (m, 5H), 6.77 (bs, 1H), 3.45 (bs, 1H), 3.28 (dd, J = 3.5, 1.5 Hz, 1H), 3.25 (dd, J = 14.5, 3.5 Hz, 1H), 3.11 (bs, 1H), 2.53 (dd, J = 14.0, 10.0 Hz, 1H), 2.23 (m, 1H), 1.88 (m, 1H), 1.79 (bs NH, 0.9H), 1.63 (bs NH, 0.6H), 1.56 (m, 1H), 1.43 (m, 1H), 1.04 (s, 9H), 1.02 (d, J = 5.0 Hz, 3H), 1.00 (d, J = 4.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 185.1, 169.0, 138.3, 129.5, 128.7, 126.8, 57.4, 53.7, 50.5, 43.3, 41.3, 41.0 35.4, 28.3, 26.9, 22.7, 22.3; HRMS (DART) calcd for $[C_{21}H_{31}N_3O_2 + H]^+$ 358.2495, found 358.2482.

(1*S*,3a*R*,8*R*,8a*R*)-*N*-*tert*-Butyl-1-isopropyl-3-oxooctahydroazirino[1,2-*a*]pyrrolo[1,2-*d*]pyrazine-8-carboxamide (4b). In a 2 dram vial equipped with a magnetic stirring bar were added D-proline (0.20 mmol), 1.0 mL of TFE, *R*-**1c** (0.10 mmol), and *tert*-butyl isocyanide (0.20 mmol), the resulting mixture was stirred for 1 h. The mixture was concentrated under reduced pressure and purified by silica gel chromatography (hexanes to 50% EtOAc) to yield the major diastereomer as a white solid: yield 48 mg, 82%.

Major diastereomer: TLC EtOAc/hexanes 50% R_f = 0.52; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H), 6.32 (bs, 1H), 3.86 (m, 1H), 3.73 (dd, J = 11.5, 4.2 Hz, 1H), 3.59 (bs, 1H), 3.05 (m, 3H), 2.65 (dd, J = 14.4, 10.4 Hz, 1H), 2.40 (m, 1H), 1.80 (bs, 1H), 1.31 (s, 9H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 183.0, 168.7, 64.7, 62.8, 54.5, 51.1, 49.2, 42.4, 31.0, 28.9, 22.0, 21.7, 19.8, 18.7; HRMS (DART) calcd for $[C_{16}H_{27}N_3O_2 + H]^+$ 294.2182, found 294.2176.

(3a*S*,8*R*,8a*S*)-*N*-*tert*-Butyl-3-oxooctahydroazirino[1,2-*a*]-pyrrolo[1,2-*d*]pyrazine-8-carboxamide (4b′).[23] In a two-dram vial equipped with a magnetic stirring bar were added L-proline (0.20 mmol) and 1.0 mL of TFE. *S*-**1a** (0.10 mmol) and isocyanide (0.20 mmol) were then added sequentially, and the resulting mixture was stirred for 30 min (reaction was monitored by RP-HPLC/MS). The solvent was then evaporated under a stream of nitrogen. The mixture was then immediately purified by flash column chromatography (hexanes to EtOAc) to yield the major piperazinone product as a white solid. Major diastereomer yield: 42 mg, 84%; crude dr 93:7 (*syn*/*anti*).

Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (bs, 1H), 3.42 (d, J = 6.2 Hz, 1H), 3.13 (dd, J = 9.5, 5.2 Hz, 1H), 3.05 (dd, J = 10.7, 4.6 Hz, 1H), 2.98 (t, J = 8.6 Hz, 1H), 2.41 (d, J = 4.8 Hz, 1H), 2.23 (d, J = 3.9 Hz, 1H), 2.21 (m, 1H), 2.13 (m, 2H), 1.86 (m, 2H), 1.35 (s, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 183.4, 169.0, 64.5, 63.2, 54.5, 51.4, 37.0, 30.5, 28.9, 22.0, 21.9; HRMS (ESI) calcd for $[C_{13}H_{21}N_3O_2 + H]^+$ calcd 252.1707, found 252.1712.

(1*R*,3a*S*,8*S*,8a*S*)-*N*-*tert*-Butyl-1-isobutyl-3-oxohexahydro-1*H*,3*H*-azirino[1,2-*a*]pyrrolo[1,2-*d*]pyrazine-8-carboxamide (4b″). In a 2 dram vial equipped with a magnetic stirring bar were added L-proline (0.10 mmol) and 0.50 mL of TFE, and the mixture was stirred until a homogeneous solution was obtained. *S*-**1b** (0.050 mmol) and *tert*-butyl isocyanide (0.10 mmol) were then added sequentially, and the resulting mixture was stirred for 1 h. The mixture was concentrated by N_2 purge and purified by silica gel chromatography (EtOAc/hexanes 30% to EtOAc/hexanes 50%) to yield both diastereomers. Yield: 22 mg, 73%; crude dr 92:8 (*syn*/*anti*), isolated dr 87:13 (*syn*/*anti*).

Major diastereomer: TLC EtOAc/hexanes 40% R_f = 0.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (bs, 1H), 3.37 (d, J = 6.0 Hz, 1H), 3.11 (m, 1H), 2.90 (m, 1H), 2.79 (dd, J = 6.0, 3.5 Hz, 1H), 2.46 (m, 1H), 2.21−2.09 (m, 2H), 1.89−1.75 (m, 4H), 1.56 (dt, J = 14, 6.5 Hz, 1H), 1.35 (s, 9H), 1.24 (m, 1H), 0.98 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 183.2, 168.8, 65.2, 63.1, 54.6, 51.3, 43.8, 42.3, 41.9, 29.0, 26.8, 23.1, 22.6, 22.1, 21.9; HRMS (DART) calcd for $[C_{17}H_{29}N_3O_2 + H]^+$ 308.2338, found 308.2333.

Minor diastereomer: TLC EtOAc/hexanes 40% R_f = 0.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (bs, 1H), 3.86 (t, J = 7.5 Hz, 1H), 3.02 (m, 1H), 2.58 (dd, J = 7.0, 2.5 Hz, 1H), 2.45−2.42 (m, 2H), 2.26 (m, 1H), 2.16 (m, 1H), 1.93−1.73 (m, 4H), 1.51−1.40 (m, 2H), 1.39 (s, 9H), 1.00 (d, J = 1.5 Hz, 3H), 0.98 (d, J = 2.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 187.4, 169.3, 66.7, 60.8, 54.9, 51.0, 46.4, 44.3, 40.6, 28.9, 27.1, 25.2, 24.6, 22.8, 22.3; HRMS (DART) calcd for $[C_{17}H_{29}N_3O_2 + H]^+$ 308.2338, found 308.2330.

(3*S*,5*S*,6*S*)-4-([1,1′-Biphenyl]-4-ylmethyl)-*N*-*tert*-butyl-3-(naphthalen-2-ylmethyl)-2-oxo-1,4-diazabicyclo[4.1.0]-heptane-5-carboxamide (4c). In a two-dram vial equipped with a magnetic stir bar were added *S*-**1a** (0.32 mmol), (*S*)-2-(([1,1′-biphenyl]-4-ylmethyl)amino)-3-(naphthalen-2-yl)propanoic acid (0.63 mmol), and 10 mol % of $Yb(OTf)_3$ (0.032 mmol) followed by 1.6 mL of HFIP. The suspension was sonicated for 5 min to break up the solid material and followed by the addition of *N*,*N*-diisopropyl-*N*-ethylamine (1.26 mmol). The reaction mixture was stirred for 30 min at room temperature, at which time *tert*-butyl isocyanide (0.633 mmol) was added. The mixture was subsequently stirred overnight, at which time RP-HPLC/MS examination of the reaction showed complete consumption of the starting material. The solvent was then removed under reduced pressure and the mixture was purified by silica gel chromatography (EtOAc/hexanes 50%) to yield the major diastereomer as an off-white solid. X-ray quality crystals were grown from the slow diffusion of hexanes into a solution of **4c** in acetone: yield 186 mg, 57%.

Major diastereomer: TLC EtOAc/hexanes 50% R_f = 0.44; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83−7.75 (m, 4H), 7.57−7.51 (m, 3H), 7.49−7.41 (m, 5H), 7.38−7.33 (m, 1H), 7.32−7.28 (m, 2H), 7.21 (d, J = 6.6 Hz, 1H), 4.09−3.98 (m, 2H), 3.83 (dd, J = 7.7, 4.7 Hz, 1H), 3.74 (d, J = 7.1 Hz, 1H), 3.67 (dd, J = 13.9, 7.6 Hz, 1H), 3.20 (ddd, J = 7.1, 4.5, 3.1 Hz, 1H), 3.09 (dd, J = 13.9, 4.7 Hz, 1H), 2.36 (dd, J = 4.5, 0.6 Hz, 1H), 2.32 (dd, J = 3.1, 0.6 Hz, 1H), 1.30 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 184.8, 168.1, 141.1, 140.4, 135.9, 135.7, 133.4, 132.2, 129.2, 128.8, 128.3, 128.0, 127.6, 127.6, 127.5, 127.5, 127.4, 127.0, 126.1, 125.6, 64.4, 60.1, 58.1, 51.2, 37.1, 35.7, 30.3, 28.4; HRMS (DART) calcd for $[C_{34}H_{35}N_3O_2 + H]^+$ 518.2807, found 518.2806.

(3*S*,5*S*,6*S*)-3,4-Dibenzyl-*N*-*tert*-butyl-2-oxo-1,4-diazabicyclo-[4.1.0]heptane-5-carboxamide (4c′). *N*-Benzyl-L-phenylalanine (0.16 mmol) was weighed into a half-dram vial with *S*-**1a** (0.094 mmol) and dissolved in HFIP (0.80 mL). The reaction was stirred gently for 10 minutes before DIPEA (0.32 mmol) and *tert*-butyl isocyanide (0.20 mmol) were added. Stirring speed was maximized, and the reaction was allowed to proceed until converted by RP-HPLC/MS (4 h). The solvent was removed under N_2 stream, and the residue was suspended in methyl *tert*-butyl ether (MTBE, 1 mL), which extracted the piperazinone. The residue was washed twice more with MTBE (2 × 1 mL), added to the first extract, and evaporated. The residue was purified by silica gel chromatography (EtOAc/hexanes 50% followed by EtOAc) to yield the major diastereomer as an off-white solid: yield 34 mg, 54%; crude dr >95:5 (*syn*/*anti*).

Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.14 (m, 10H), 7.10 (s, 1H), 3.97−3.84 (m, 2H), 3.66 (dd, J = 7.6, 4.9 Hz, 1H), 3.61 (d, J = 7.1 Hz, 1H), 3.43 (dd, J = 13.9, 7.7 Hz, 1H), 3.10 (ddd, J = 7.1, 4.5, 3.1 Hz, 1H), 2.85 (dd, J = 13.9, 4.9 Hz, 1H), 2.28 (dd, J = 4.5, 0.6 Hz, 1H), 2.23 (dd, J = 3.1, 0.6 Hz, 1H), 1.21 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 185.0, 168.3, 138.5, 137.2, 129.6, 129.0, 129.0, 128.7, 128.3, 126.8, 64.7, 60.5, 58.1, 51.3, 37.1, 35.8, 30.4, 28.6; HRMS (ESI) calcd for $[C_{24}H_{29}N_3O_2 + H]^+$ 392.2333, found 392.2331.

(5*S*,5a*S*,8a*R*)-*N*-*tert*-Butyl-8-oxotetrahydro-1*H*,3*H*,5*H*-azirino-[1,2-*a*]thiazolo[3,4-*d*]pyrazine-5-carboxamide (4d). *N*-Phenyl-L-phenylalanine[28] (0.21 mmol), *S*-**1a** (0.12 mmol), and a stir bar were added to a small vial. HFIP (1.8 mL) and *tert*-butyl isocyanide (0.25 mmol) were added, and a pale yellow suspension resulted. The reaction was monitored by RP-HPLC/MS and after 2 h, the reaction was concentrated to an oil and purified by silica gel chromatography (EtOAc/hexanes 50%) to yield an off-white solid: yield 55 mg, 70%;

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crude dr >95:5 (*syn*/*anti*). The white solid was dissolved in minimal acetone and slow vapor diffusion of hexanes gave white needle-like crystals. Analysis by X-ray crystallography indicated syn stereochemistry.

Major diastereomer: TLC EtOAc/hexanes 50% R_f = 0.65; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.39−7.35 (m, 2H), 7.33 (s, 1H), 7.30−7.24 (m, 4H), 7.19−7.15 (m, 1H), 6.92−6.84 (m, 3H), 4.74 (d, J = 7.4 Hz, 1H), 4.56 (dd, J = 8.6, 2.0 Hz, 1H), 3.59 (dd, J = 14.6, 8.5 Hz, 1H), 3.25 (ddd, J = 7.5, 4.3, 3.2 Hz, 1H), 2.71 (dd, J = 14.5, 2.1 Hz, 1H), 2.38 (d, J = 4.3 Hz, 1H), 2.27 (d, J = 3.2 Hz, 1H), 1.35 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, acetone-d_6) δ 184.0, 169.5, 148.8, 141.5, 130.2, 130.1, 129.0, 126.8, 120.4, 117.6, 61.7, 57.8, 51.9, 37.1, 36.9, 30.9, 28.8; HRMS (ESI) calcd for $[C_{23}H_{27}N_3O_2 + H]^+$ 378.2176, found 378.2188.

(5*S*,6*R*,7*R*)-*N*-*tert*-Butyl-7-isobutyl-2-oxo-1,4-diazaspiro-[bicyclo[4.1.0]heptane-3,1′-cyclopentane]-5-carboxamide (4e). In a 2 dram vial equipped with a magnetic stirring bar were added cycloleucine (0.050 mmol) and 0.50 mL of TFE. The mixture was stirred until a homogeneous solution was obtained. *S*-**1b** (0.025 mmol) and *tert*-butyl isocyanide (0.050 mmol) were then added sequentially, and the resulting mixture was stirred for 1 h. The mixture was concentrated by N_2 purge and purified by silica gel chromatography (EtOAc/hexanes 10% to EtOAc/hexanes 40%) to yield both diastereomers. Yield: 13 mg, 81%; crude dr 59:41 (*S*/*R*), isolated dr 57:43 (*S*/*R*).

Major diastereomer: TLC EtOAc/hexanes 50% R_f = 0.60; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (bs, 1H), 4.07 (d, J = 1.0 Hz, 1H), 2.69 (dd, J = 6.0, 3.5 Hz, 1H), 2.49 (m, 1H), 2.40 (m, 1H), 2.06 (m, 1H), 1.88−1.52 (m, 9H), 1.35 (s, 9H), 1.29 (m, 1H), 0.98 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 186.3, 169.5, 66.2, 52.9, 51.6, 42.5, 41.7, 40.3, 34.3, 34.2, 28.9, 27.0, 24.2, 23.7, 22.9, 22.7; HRMS (DART) calcd for $[C_{18}H_{31}N_3O_2 + H]^+$ 322.2495, found 322.2506.

Minor diastereomer: TLC EtOAc/hexanes 50% R_f = 0.90; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (bs, 1H), 3.09 (dd, J = 5.0, 3.0 Hz, 1H), 3.06 (m, 1H), 2.31 (m, 1H), 2.24 (m, 1H), 2.00−1.94 (m, 2H), 1.87 (m, 1H), 1.83−1.73 (m, 5H), 1.54−1.41 (m, 3H), 1.39 (s, 9H), 1.02 (d, J = 2.0 Hz, 3H), 1.00 (d, J = 2.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 189.6, 170.1, 68.1, 55.3, 51.1, 45.1, 43.9, 41.0, 36.3, 36.1, 28.9, 27.1, 25.1, 24.4, 22.9, 22.5; HRMS (DART) calcd for $[C_{18}H_{31}N_3O_2 + H]^+$ 322.2495, found 322.2495.

(3*S*,5*R*,6*S*)-*N*-*tert*-Butyl-3-isobutyl-2-oxo-1,4-diazabicyclo-[4.1.0]heptane-5-carboxamide (4f). In a 1 dram vial equipped with a magnetic stirring bar were added L-leucine (0.11 mmol), 0.60 mL of HFIP, *S*-**1a** (0.057 mmol), and *tert*-butyl isocyanide (0.14 mmol), and the resulting mixture was stirred for 2 h. The mixture was concentrated under reduced pressure and purified by silica gel chromatography (hexanes to 50% EtOAc) to yield both diastereomers. Yield: 22 mg, 74%; crude dr 72:28 (*anti*/*syn*); HRMS (DART) calcd for $[C_{14}H_{25}N_3O_2 + H]^+$ 268.2020, found 268.2027.

Major diastereomer: TLC EtOAc R_f = 0.44; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (bs, 1H), 3.57 (ddd, J = 4.7, 4.0, 1.5 Hz, 1H), 3.54 (s, 1H), 2.99 (bs, 1H), 2.56 (d, J = 4.7 Hz, 1H), 1.97 (d, J = 4.0 Hz, 1H), 1.86−1.79 (m, 1H), 1.71 (ddd, J = 14.2, 8.9, 4.8 Hz, 1H), 1.40 (s, 9H), 1.33−1.27 (m, 1H), 0.97 (dd, J = 8.7, 6.6 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 185.8, 169.5, 54.1, 53.9, 38.0, 34.7, 31.3, 29.8, 28.8, 24.7, 23.6, 22.4.

Minor diastereomer: TLC EtOAc R_f = 0.63; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 (s, 1H), 4.10 (d, J = 5.8 Hz, 1H), 3.23 (dd, J = 7.6, 5.3 Hz, 1H), 2.95 (ddd, J = 5.8, 4.7, 4.1 Hz, 1H), 2.36 (d, J = 4.6 Hz, 1H), 2.16 (dd, J = 4.0, 0.6 Hz, 1H), 1.81−1.72 (m, 2H), 1.35 (s, 9H), 1.28−1.26 (m, 1H), 0.93 (dd, J = 10.8, 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 184.2, 169.0, 56.4, 55.7, 38.0, 35.5, 32.1, 29.8, 28.9, 28.5, 24.8, 23.1, 22.4.

(3*S*,5*R*,6*R*,7*R*)-*N*-*tert*-Butyl-3,7-diisobutyl-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamide (4f′). In a 1 dram vial equipped with a magnetic stirring bar were added L-leucine (0.11 mmol) and 1.2 mL of TFE. Then, *S*-**1b** (0.057 mmol) and *tert*-butyl isocyanide (0.14 mmol) were added sequentially, and the resulting mixture was stirred for 2 h. The mixture was concentrated by N_2 purge and purified by silica gel chromatography (EtOAc/hexanes 10% to EtOAc/hexanes 30%) to yield both diastereomers. Yield: 31 mg, 87%; crude dr 69:31 (*anti*/*syn*), isolated dr 69:31 (*syn*/*anti*).

Major diastereomer: TLC EtOAc/hexanes 50% R_f = 0.79; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 3.53 (d, J = 1.5 Hz, 1H), 3.30 (dd, J = 3.6, 1.6 Hz, 1H), 2.93 (dd, J = 8.8, 5.0 Hz, 1H), 2.18 (ddd, J = 6.9, 5.7, 3.6 Hz, 1H), 1.91−1.83 (m, 1H), 1.85−1.75 (m, 1H), 1.70 (ddd, J = 14.2, 8.7, 5.0 Hz, 1H), 1.58−1.51 (m, 1H), 1.46−1.41 (m, 1H), 1.39 (s, 9H), 1.28−1.24 (m, 1H), 1.00 (dd, J = 6.7, 4.1 Hz, 6H), 0.96 (dd, J = 8.2, 6.6 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 185.8, 169.7, 53.9, 53.6, 51.0, 43.2, 41.3, 41.2, 38.1, 28.8, 27.1, 24.8, 23.5, 22.8, 22.5, 22.5; HRMS (ESI) calcd for $[C_{18}H_{33}N_3O_2 + H]^+$ 324.2646, found 324.2636.

Minor diastereomer: TLC EtOAc/hexanes 50% R_f = 0.59; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (s, 1H), 4.04 (d, J = 5.9 Hz, 1H), 3.18 (dd, J = 7.4, 5.9 Hz, 1H), 2.69 (dd, J = 5.9, 3.6 Hz, 1H), 2.45−2.39 (m, 1H), 1.83−1.69 (m, 3H), 1.54 (dt, J = 13.5, 6.6 Hz, 1H), 1.35 (s, 9H), 1.27−1.23 (m, 2H), 0.96 (dd, J = 9.7, 6.7 Hz, 6H), 0.92 (dd, J = 9.6, 6.5 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 184.0, 169.1, 56.9, 55.5, 51.5, 42.3, 41.5, 40.2, 38.1, 29.9, 28.9, 26.9, 24.9, 23.1, 22.8, 22.6, 22.4; HRMS (ESI) calcd for $[C_{18}H_{33}N_3O_2 + H]^+$ 324.2646, found 324.2641.

(3a*S*,9*S*,9a*S*)-*N*-*tert*-Butyl-3-oxooctahydro-1*H*-azirino[1,2-*a*]-pyrido[1,2-*d*]pyrazine-9-carboxamide. (4g). In a 2 dram vial equipped with a magnetic stirring bar were added L-pipecolic acid (0.20 mmol) and 1.0 mL of TFE, and the mixture was stirred until a homogeneous solution was obtained. *S*-**1a** (0.20 mmol) and *tert*-butyl isocyanide (0.24 mmol) were then added sequentially, and the resulting mixture was stirred for 22 h. The mixture was concentrated by N_2 purge and purified by silica gel chromatography (EtOAc/hexanes 30% to EtOAc/hexanes 50%) to yield the major diastereomer: yield 38 mg, 71%; crude dr >95:5 (*syn*/*anti*).

Major diastereomer: TLC EtOAc/hexanes 50% R_f = 0.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (bs, 1H), 3.31 (d, J = 7.0 Hz, 1H), 3.01 (m, 1H), 2.89 (m, 1H), 2.84 (dd, J = 11.5, 3.5 Hz, 1H), 2.39 (d, J = 4.5 Hz, 1H), 2.17 (dt, J = 12.0, 2.5 Hz, 1H), 2.11 (d, J = 4.0 Hz, 1H), 1.98 (m, 1H), 1.86 (m, 1H), 1.70−1.57 (m, 2H), 1.46−1.25 (m, 11H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 183.5, 169.5, 63.3, 60.0, 57.1, 51.1, 33.9, 30.3, 28.9, 26.2, 25.5, 23.5; HRMS (DART) calcd for $[C_{14}H_{23}N_3O_2 + H]^+$ 266.1869, found 266.1859.

(2*S*,3*S*,4*R*,7*S*)-*N*-*tert*-Butyl-4-isobutyl-6-oxo-1,5-diazatricyclo[5.2.0.03,5]nonane-2-carboxamide. (4h). In a 2 dram vial equipped with a magnetic stirring bar were added L-azetidine-2-carboxylic acid (0.10 mmol) and 0.50 mL of TFE, and the mixture was stirred until a homogeneous solution was obtained. *S*-**1b** (0.050 mmol) and *tert*-butyl isocyanide (0.10 mmol) were then added sequentially, and the resulting mixture was stirred for 1 h. The mixture was concentrated by N_2 purge and purified by silica gel chromatography (EtOAc/hexanes 50% to EtOAc 100%, and MeOH/EtOAc 9%) to yield the major diastereomer: yield 21 mg, 70%; crude dr 93:7 (*syn*/*anti*).

Major diastereomer: TLC MeOH/EtOAc 9% R_f = 0.30; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (bs, 1H), 3.70 (m, 1H), 3.53 (d, J = 6.0 Hz, 1H), 3.24 (m, 1H), 3.17 (m, 1H), 2.72 (dd, J = 6.0, 3.5 Hz, 1H), 2.59 (m, 1H), 2.51 (dt, J = 6.5, 4.0 Hz, 1H), 2.08 (m, 1H), 1.75 (m, 1H), 1.56 (m, 1H), 1.35 (s, 9H), 1.20 (m, 1H), 0.97 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 181.6, 168.0, 63.2, 62.6, 51.6, 51.5, 43.7, 41.78, 47.76, 29.1, 26.9, 23.3, 23.0, 22.6; HRMS (DART) calcd for $[C_{16}H_{27}N_3O_2 + H]^+$ 294.2182, found 294.2189.

(3*R*,5*S*,6*R*,7*R*)-3-Benzyl-*N*-*tert*-butyl-7-isobutyl-2-oxo-1,4-diazabicyclo[4.1.0]heptane-5-carboxamide. (6a). In a 2 dram vial equipped with a magnetic stirring bar were added D-phenylalanine (0.10 mmol) and 0.50 mL of TFE, and the mixture was stirred until a homogeneous solution was obtained. *S*-**1b** (0.050 mmol) and *tert*-butyl isocyanide (0.10 mmol) were then added sequentially, and the resulting mixture was stirred for 3 h. The mixture was concentrated by N_2 purge and purified by silica gel chromatography (EtOAc/hexanes 35% to EtOAc/hexanes 50%) to yield both diastereomers. Yield: 14 mg, 40%; crude dr: 93:7 (*anti*/*syn*), isolated dr 85:15 (*anti*/*syn*).

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Major diastereomer: TLC EtOAc/hexanes 50% R_f = 0.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.23 (m, 5H), 6.41 (bs, 1H), 4.07 (d, J = 6.0 Hz, 1H), 3.58 (dd, J = 10.0, 5.0 Hz, 1H), 3.10 (dd, J = 14.0, 5.5 Hz, 1H), 3.00 (dd, J = 14.0, 10.5 Hz, 1H), 2.87 (dd, J = 6.5, 3.5 Hz, 1H), 2.45 (dt, J = 7.0, 4.0 Hz, 1H), 1.81 (m, 1H), 1.58 (m, 1H), 1.33 (m, 1H), 1.31 (s, 9H), 0.99 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 184.3, 169.4, 136.2, 129.3, 129.2, 127.4, 59.5, 51.4, 49.9, 41.69, 41.65, 41.22, 36.1, 28.9, 26.9, 23.0, 22.6; HRMS (DART) calcd for $[C_{21}H_{31}N_3O_2 + H]^+$ 358.2495, found 358.2503.

(1*R*,3a*R*,8*R*,8a*S*)-*N*-*tert*-Butyl-1-isobutyl-3-oxohexahydro-1*H*,3*H*-azirino[1,2-*a*]pyrrolo[1,2-*d*]pyrazine-8-carboxamide. (6b). In a 2 dram vial equipped with a magnetic stirring bar were added D-proline (0.10 mmol) and 0.50 mL of TFE, and the mixture was stirred until a homogeneous solution was obtained. *S*-**1b** (0.050 mmol) and *tert*-butyl isocyanide (0.10 mmol) were then added sequentially, and the resulting mixture was stirred for 1 h. The mixture was concentrated by N_2 purge and purified by silica gel chromatography (EtOAc/hexanes 30% to EtOAc/hexanes 50%) to yield both diastereomers. Yield: 26 mg, 84%; crude dr 53:47 (*syn*/*anti*), isolated dr 58:42 (*syn*/*anti*).

Major diastereomer: TLC EtOAc/hexanes 40% R_f = 0.45; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (bs, 1H), 3.80 (dd, J = 9.5, 5.5 Hz, 1H), 3.12 (dd, J = 8.5, 3.0 Hz, 1H), 3.05−2.98 (m, 2H), 2.88 (d, J = 9.0 Hz, 1H), 2.37−2.29 (m, 1H), 2.21 (dt, J = 6.0, 3.0 Hz, 1H), 2.05−1.97 (m, 2H), 1.92−1.80 (m, 2H), 1.50 (m, 2H), 1.38 (s, 9H), 1.02 (d, J = 4.5 Hz, 3H), 1.01 (d, J = 4.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 189.8, 167.5, 65.9, 62.5, 51.3, 47.6, 45.6, 40.79, 40.76, 30.5, 29.0, 27.2, 25.7, 22.9, 22.6; HRMS (DART) calcd for $[C_{17}H_{29}N_3O_2 + H]^+$ 308.2338, found 308.2338.

Minor diastereomer: TLC EtOAc/hexanes 40% R_f = 0.20; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (bs, 1H), 3.73 (d, J = 6.5 Hz, 1H), 3.56 (m, 1H), 3.24 (m, 1H), 3.17 (m, 1H), 3.01 (dd, J = 7.0, 3.0 Hz, 1H), 2.53 (dt, J = 6.5, 3.5 Hz, 1H), 2.36 (m, 1H), 2.05−1.96 (m, 2H), 1.90−1.78 (m, 2H), 1.52 (m, 1H), 1.39 (m, 1H), 1.30 (s, 9H), 1.02 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 188.1, 167.7, 60.9, 56.9, 54.3, 51.2, 42.4, 41.9, 41.4, 32.1, 28.8, 27.2, 25.6, 22.8, 22.6; HRMS (DART) calcd for $[C_{17}H_{29}N_3O_2 + H]^+$ 308.2338, found 308.2339.

(3a*S*,8*R*,8a*S*)-3-Oxo-*N*-pentylhexahydro-1*H*,3*H*-azirino[1,2-*a*]pyrrolo[1,2-*d*]pyrazine-8-carboxamide (7a). In a 2 dram vial equipped with a magnetic stirring bar were added L-proline (0.050 mmol) and 0.25 mL of TFE, and the mixture was stirred until a homogeneous solution was obtained. *S*-**1a** (0.030 mmol) and pentyl isocyanide (0.060 mmol) were then added sequentially, and the resulting mixture was stirred for 1.5 h. The mixture was concentrated by N_2 purge and purified by silica gel chromatography (EtOAc/hexanes 50% to EtOAc 100%) to yield both diastereomers. Yield: 5.8 mg, 44%; crude dr 75:25 (*syn*/*anti*), isolated dr: 81:19 (*syn*/*anti*).

Mixture of diastereomers (A: syn, B: anti): TLC EtOAc R_f = 0.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (bs, 1H of B), 6.40 (bs, 1H of A), 3.93 (t, J = 7.0 Hz, 1H of B), 3.55 (d, J = 6.0 Hz, 1H of A), 3.35 (m, 2H of B), 3.27 (m, 2H of A), 3.14 (m, 1H of A), 3.09−3.02 (m, 1H of A and 1H of B), 2.99 (m, 1H of A), 2.86 (m, 1H of B), 2.57−2.52 (m, 2H of B), 2.40 (m, 1H of A), 2.30−2.18 (m, 3H of A and 2H of B), 1.95−1.67 (m, 3H of A and 4H of B), 1.56 (m, 2H of B), 1.50 (m, 2H of A), 1.39−1.25 (m, 4H of A and 4H of B), 0.90 (m, 3H of A and 3H of B); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 187.3 (B), 183.2 (A), 169.9 (B), 169.6 (A), 66.5 (B), 64.2 (A), 63.4 (A), 61.0 (B), 55.0 (B), 54.7 (A), 39.33 (B), 39.25 (A), 37.9 (B), 37.1 (A), 34.4 (B), 30.8 (A), 29.6 (A), 29.5 (B), 29.28 (B), 29.27 (A), 24.9 (B), 24.7 (B), 22.52 (B), 22.47 (A), 22.1 (A), 21.9 (A), 14.19 (B), 14.16 (A); HRMS (DART) calcd for $[C_{14}H_{23}N_3O_2 + H]^+$ 266.1869, found 266.1860.

(3a*S*,8*S*,8a*S*)-*N*-Benzyl-3-oxohexahydro-1*H*,3*H*-azirino[1,2-*a*]pyrrolo[1,2-*d*]pyrazine-8-carboxamide (7b). In a 2 dram vial equipped with a magnetic stirring bar were added L-proline (0.050 mmol) and 0.25 mL of TFE, and the mixture was stirred until a homogeneous solution was obtained. *S*-**1a** (0.030 mmol) and benzyl isocyanide (0.10 mmol) were then added sequentially, and the resulting mixture was stirred for 1.5 h. The mixture was concentrated by N_2 purge and purified by silica gel chromatography (EtOAc/hexanes 30% to EtOAc 100%) to yield both diastereomers. Yield: 7.3 mg, 51%; crude dr 74:26 (*syn*/*anti*), isolated dr 74:26 (*syn*/*anti*).

Mixture of diastereomers (A: syn, B: anti): TLC EtOAc R_f = 0.45; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (bs, 1H of B), 7.38−7.22 (m, 5H of A and 5H of B), 6.69 (bs, 1H of A), 4.53−4.41 (m, 2H of A and 2H of B), 3.90 (t, J = 8.0 Hz, 1H of B), 3.61 (d, J = 6.5 Hz, 1H of A), 3.13−3.08 (m, 2H of A), 3.02 (m, 1H of B), 2.99 (m, 1H of A), 2.90 (m, 1H of B), 2.64 (d, J = 6.5 Hz, 1H of B), 2.55 (d, J = 4.5 Hz, 1H of B), 2.37 (d, J = 4.5 Hz, 1H of A), 2.31 (d, J = 3.0 Hz, 1H of B), 2.29−2.16 (m, 2H of A and 2H of B), 2.08 (m, 1H of A), 1.91−1.75 (m, 3H of A and 3H of B); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 187.2 (B), 183.0 (A), 187.0 (B), 169.7 (A), 138.2 (B), 138.0 (A), 129.08 (A), 129.06 (B), 128.0 (A), 127.94 (A), 127.92 (B), 127.89 (B), 66.4 (B), 64.2 (A), 63.4 (A), 61.0 (B), 55.0 (B), 54.6 (A), 43.41 (B), 43.37 (A), 37.9 (B), 37.1 (A), 34.4 (B), 30.8 (A), 24.8 (B), 24.7 (B), 22.1 (A), 21.9 (A); HRMS (DART) calcd for $[C_{16}H_{19}N_3O_2 + H]^+$ 286.1556, found 286.1550.

(3*S*,4a*S*,7*S*,7a*R*,*Z*)-3-Benzyl-5-(*tert*-butylimino)-7-isobutylhexahydrofuro[3,4-*b*]pyrazin-2(1*H*)-one (8). In a 1 dram vial equipped with a magnetic stirring bar were added **4f′-minor product** (0.030 mmol) and 0.50 mL of TFE, and the mixture was stirred for 14 h. The mixture was then concentrated by N_2 purge and purified by silica gel chromatography (EtOAc/hexanes 50% to EtOAc to MeOH/EtOAc 10%) to yield the imidate product as a white powder: yield 8.6 mg, 89%; TLC EtOAc R_f = 0.15; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.01 (s, 1H), 4.53−4.42 (m, 1H), 3.72 (d, J = 5.7 Hz, 1H), 3.39 (ddd, J = 9.0, 5.7, 3.7 Hz, 1H), 3.35 (dd, J = 9.1, 3.6 Hz, 1H), 1.91 (ddd, J = 13.9, 10.0, 3.7 Hz, 1H), 1.89−1.80 (m, 1H), 1.79−1.68 (m, 1H), 1.61−1.53 (m, 1H), 1.53−1.47 (m, 2H), 1.27 (s, 9H), 0.98 (dd, J = 14.2, 6.7 Hz, 6H), 0.93 (dd, J = 27.4, 6.5 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.9, 158.0, 84.2, 57.7, 57.0, 55.8, 53.9, 42.0, 40.6, 29.7, 26.1, 24.5, 23.7, 23.4, 22.3, 21.5; HRMS (DART) calcd for $[C_{18}H_{33}N_3O_2 + H]^+$ 324.2646, found 324.2660.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of piperazinone compounds and X-ray crystallography information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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