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Synthesis of Tetrazole-Derived Organocatalysts via Azido-Ugi Reaction with Cyclic Ketimines

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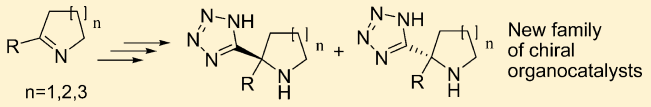
Supporting Information

ABSTRACT: A new route to tetrazole-derived cyclic amines based on the $TMSN_3$-modified Ugi reaction with 2-substituted cyclic imines was elaborated. The reaction allows the direct preparation of five-, six-, and seven-membered cyclic amines substituted with a tetrazole ring, which are important types of organocatalysts. The scope and limitations of this method are discussed. In the case of the Ugi reaction with benzyl isocyanide, the N-substituted tetrazoles can be easily debenzylated under catalytic hydrogenation conditions to form NH-tetrazoles in quantitative yields. It was demonstrated that both enantiomers of tetrazole-derived cyclic amines can be prepared by resolution with tartaric acid, thereby initiating a simple route to chiral derivatives. One of the obtained chiral tetrazoles was efficiently used as an organocatalyst in the amination reaction.



INTRODUCTION

Tetrazoles have found broad applications in medicinal chemistry and pharmacology,[1] materials chemistry (e.g., as highly energetic compounds[2]), organometallic and coordination chemistry,[3] and organocatalysis.[4] To date, many drugs containing a tetrazole moiety have been marketed. These drugs exhibit a very broad range of biological activity to be used in various branches of medicine. Some of the modern drugs containing tetrazole rings are presented in Figure 1; they include diuretic agents (azosemide), angiotensin II receptor antagonists (candensartan, irbesartan, losartan, valsartan), antiallergic drugs (pranlukast, tazanolast, pemiroplast), cephalosporin antibiotics (cefazoline, ceftezole), thrombogenesis inhibitors (cilostazol), and circulatory and respiratory stimulants (pentylenetetrazole).

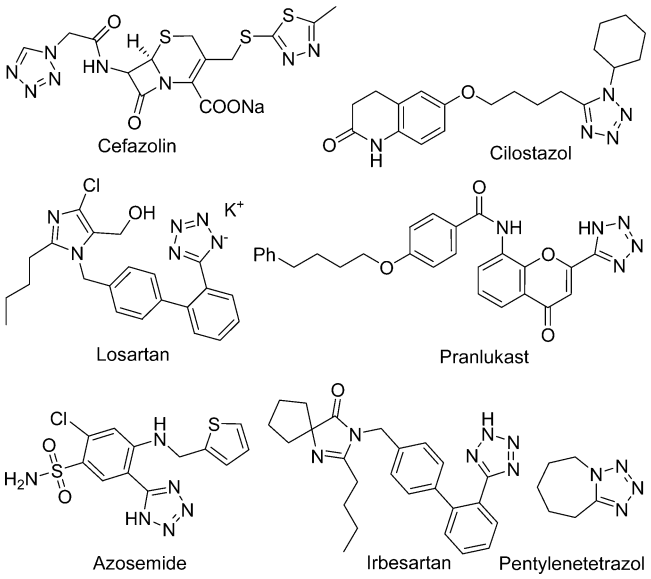


Figure 1. Some modern tetrazole-containing drugs.

It is commonly known that 5-substituted-1*H*-tetrazoles serve as nonclassical metabolism-resistant isosteres of the carboxylic group. The tetrazole anion is 10 times more lipophilic than the carboxylate ion and demonstrates similar basicity. At the same time, it is larger and its charge is more delocalized compared with the carboxylic functional group.[5] It was shown that these properties of tetrazolic rings may increase the substrate–receptor interaction. Thus, synthetic strategies leading to the replacement of carboxylate groups by tetrazole moieties in biologically active molecules are of current interest.

At the same time, 1,5-disubstituted tetrazoles have been found to mimic *cis*-amide bonds of peptides.[6] It was shown that tetrazole-containing compounds can adopt almost the same steric conformations as the initial peptides. Among publications concerning the use of 1,5-disubstituted tetrazoles as isosteric replacements of the *cis*-amide bonds of peptides, the synthesis of HIV-protease inhibitors[7] and anti-inflammatory preparations based on phenothiazine[8] are also included.

During the past decade, the interest in tetrazoles has increased because of the successful application of tetrazole derivatives in organocatalysis. Proline-derived tetrazoles were found to be effective catalysts in asymmetric Mannich, nitro-Michael, aldol, amination, and nitrosoaldol reactions, etc.[4] These compounds were designed to overcome the main drawback of proline, namely, its insolubility in conventional organic solvents. In spite of significant success in this field, the tetrazole-derived catalysts have been prepared from proline and its commercially available derivatives. These structural limitations restrict the diversity of such compounds. Therefore, the design and synthesis of novel efficient catalysts possessing good solubility and high selectivity is still of high interest. To date,

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only one α-substituted proline-derived tetrazole has been described in the literature (compound C in Figure 2).[9]

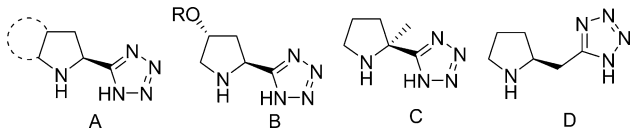


Figure 2. Some tetrazole-containing chiral proline-based organocatalysts.

It is known that the application of isocyanide-based multicomponent reactions is a very efficient approach for the synthesis of various kinds of complex molecules.[10] For example, the Ugi reaction is a very powerful tool for preparing peptides and peptide mimics.[11] Replacement of the carboxylic acid (used in the classical version of the Ugi reaction) with hydrazoic acid[12] opens a direct and efficient route to various 1,5-substituted tetrazole derivatives. Recent advances in this field have been reviewed by El Kaim and Grimaud.[13]

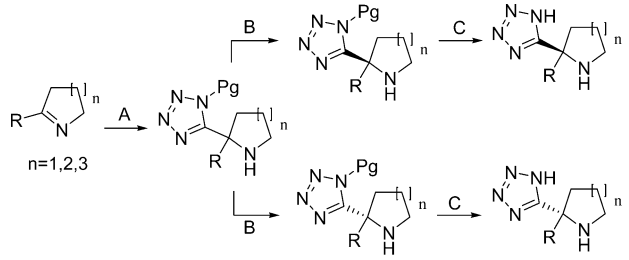
Cyclic ketimines are very valuable building blocks for the incorporation of cyclic amine fragments into various molecules.[11a,b,14] These substances can be also used for the synthesis of useful compounds with aminoalkyl fragments, which are analogues of natural molecules.[15] We recently reported that 2-substituted cyclic imines can be used as substrates for the three-component Ugi reaction, opening a direct pathway to α-substituted proline peptides.[11a,b] The application of cyclic ketimines in the $TMSN_3$-modified Ugi reaction is still unknown. However, this approach could open attractive pathways to cyclic amines connected to tetrazole rings. These compounds would be engaging targets as a new family of tetrazole organocatalysts. Such an approach would be a very flexible method for the synthesis of target derivatives because it opens access to tetrazole-substituted cyclic amines with the possibility of varying the cycle size (five-, six-, and seven-membered) and α-substituents (diverse electronic nature and steric hindrance) of the cyclic amine. Quite important also is the possibility of having access to both enantiomers of tetrazole-substituted cyclic amines because their synthesis starting from natural amino acids (proline and its derivatives) provides only one enantiomeric form.

Herein we report the $TMSN_3$-modified Ugi reaction of α-substituted cyclic imines as a novel approach to tetrazole-derived cyclic amines. The aims of this study were to investigate the possibility of using 2-substituted cyclic imines in the $TMSN_3$-modified Ugi reaction, to develop subsequent N-deprotection to prepare 1*H*-tetrazoles, to show the possibility of obtaining these compounds in enatiomerically pure form, and to demonstrate the application of these compounds as new efficient organocatalysts (Scheme 1).

RESULTS AND DISCUSSION

To study the scope and limitations of the azido-Ugi reaction with cyclic imines, we decided to focus our attention mostly on the influence of the cyclic imine structure on the reaction. There is a considerable difference in the conformational peculiarities of five-, six-, and seven-membered nitrogen heterocycles. For example, five-membered rings are more flat and rigid, in contrast to quite flexible seven-membered cycles. Moreover, the α-substituents of the imine component can affect the reaction path significantly. Starting cyclic imines with various aliphatic, aromatic, or heteroaromatic substituents at

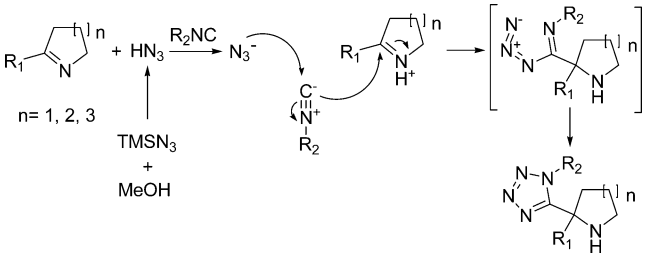
Scheme 1. Tetrazole-Containing Chiral Organocatalysts via 2-Substituted Cyclic Imines: (A) Azido-Ugi Reaction; (B) Chiral Resolution; (C) Deprotection



the α-position can be easily prepared from commercially accessible materials.[16] In all experiments, $TMSN_3$ in methanol was used as a convenient source of HN_3.

We started our study using the model reaction of 2-substituted cyclic imines with benzyl isocyanide and $TMSN_3$ (Scheme 2). The application of cleavable benzyl isonitrile could

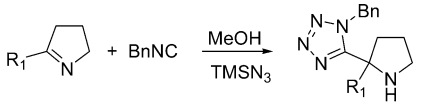
Scheme 2. Mechanism of the $TMSN_3$-Modified Ugi Reaction with Cyclic Imines



provide an efficient synthetic route to 1*H*-tetrazoles by subsequent removal of the benzyl group under appropriate conditions. For example, this protective group can be removed cleanly by hydrogenolysis.[17] As a result, α-substituted proline-derived tetrazoles and their six- and seven-membered analogues could be prepared, opening a straightforward route to a family of tetrazole-derived organocatalysts. Some other cleavable isocyanides were developed recently for the azido-Ugi reaction,[18] but benzyl isocyanide is one of cheapest commercially available isocyanides.

First we studied the influence of the α-substituent of pyrrolines **1a−j** on the $TMSN_3$-modified Ugi reaction (Scheme 3) with benzyl isocyanide **2a**. The reaction with five-membered

Scheme 3. $TMSN_3$-Modified Ugi Reaction with Five-Membered Cyclic Imines



imines with primary alkyl groups (Me, Et, Bu; **1a−c**) proceeded in 51−66% isolated yield (Table 1). Pyrrolines with secondary (cyclopentyl; **1e**) and tertiary (*tert*-butyl; **1f**) substituents reacted smoothly as well (75% and 64% yield, respectively). Even in the case of sterically hindered 2-(1-adamantyl)pyrroline **1g**, the target tetrazole **3g** was prepared in reasonably high yield (50%). Benzyl-derived pyrroline **1d** afforded the corresponding tetrazole **3d** in 72% yield. It is interesting to note that

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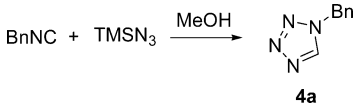
Table 1. Synthesis of Tetrazole-Derived Pyrrolidines

Entry	R_1	Product	Yield, %
1	Me	**3a**	51
2	Et	**3b**	66
3	Bu	**3c**	56
4	3-$MeC_6H_4CH_2$	**3d**	72
5	cyclopentyl	**3e**	75
6	*t*Bu	**3f**	64
7	1-Ad	**3g**	50
8	Ph	-	0
9	CH_2SMe	**3i**	80
10		**3j**	61

functional groups such as methylthio or an additional amine group on the pyrroline did not prevent the azido-Ugi reaction, as these substrates provided the corresponding products in 80 and 61% yield, respectively. Therefore, the reaction is quite tolerant of the presence of additional functional groups.

The only restriction was found in an attempt to perform the reaction with 2-phenylpyrroline (**1h**) and other aryl-substituted five-membered imines (not shown in Table 1). The failure with these substrates is most probably due to the lower electrophilicity of intermediate iminium salts as well as structural peculiarities of the five-membered fings. After several days, the initial 2-arylimines were isolated from reaction mixture without change in the azido-Ugi reaction, and *N*-benzyltetrazole (**4a**) was the only product of the reaction (Scheme 4).

Scheme 4. Formation of Byproduct 4a

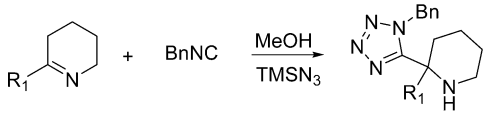


4a

It should be noted that these results are in perfect agreement with the behavior of such five-membered ketimines in the classical Ugi reaction with carboxylic acids.[11a] Therefore, we believe that the azido-Ugi reaction is very general and that almost any 2-substituted pyrroline bearing aliphatic substituents can be used to prepare tetrazole derivatives **3** by this approach.

The next step of our investigation was to study the behavior of six-membered imines **5a–i** in this reaction and the influence of substituents at the α-position of the imine on the reaction yield (Scheme 5). Benzyl isonitrile **2a** was used again as a model isocyanide. In general, the reaction proceeded smoothly

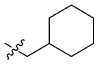
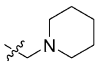
Scheme 5. $TMSN_3$-Modified Ugi Reaction with Six-Membered Cyclic Imines



5a-i **2a** **6a-i**

to give target compounds **6a–i** in high yields (Table 2). No limitation on the nature of the substituents was observed.

Table 2. Synthesis of Tetrazole-Derived Piperidines

Entry	R_1	Product	Yield, %
1	Cyclohexyl	**6a**	65
2	3,5-diMeC_6H_3	**6b**	69
3	3-$CF_3C_6H_4$	**6c**	69
4	2-$MeC_6H_4CH_2$	**6d**	46
5		**6e**	68
6	*t*Bu	**6f**	44
7	2-Furyl	**6g**	73
8		**6h**	63
9	$CH(Ph)_2$	**6i**	77

Tetrahydropyridines with primary and secondary alkyl groups afforded the target products in good yields (up to 77%). Only the sterically hindered 2-*tert*-butyl-substituted imine **5f** was found to be less reactive, giving the final product **6f** in 44% yield. Quite important was the successful participation of aryl-substituted six-membered imines in the azido-Ugi reaction. In contrast to 2-arylpyrrolines, tetrahydropyridines **5b** and **5c** gave the desired products **6b** and **6c** in high yields (69% for both imines). Even the 2-furyl-substituted product **6g** was isolated in 73% yield. Subsequent oxidative transformation of the furyl moiety to the carboxyl group makes this compound an important precursor for the synthesis of tetrazolyl-substituted homoprolines.[14b]

Thus, almost any six-membered imine can participate successfully to afford target tetrazole-substituted piperidines in high yields. As a result, there is no structural restriction on obtaining 1,5-disubstituted tetrazoles with the piperidine moiety (**6a–i**) using the $TMSN_3$-modified Ugi reaction. We believe that the observed difference in reactivity can be explained in terms of conformational differences of five- and six-membered rings. It is known that the formation of the double bond is more favorable for five-membered cycles.

To have a complete picture of the effect of ring size on the outcome of the reaction, we studied the transformation with seven-membered imines **7a–g** (Scheme 6). It has been demonstrated previously that seven-membered imines bearing aliphatic and aromatic substituents do not participate in the classical Ugi reaction with carboxylic acids.[11a] To our delight, seven-membered imines **7a–g** were found to be reactive in the

Scheme 6. $TMSN_3$-Modified Ugi Reaction with Seven-Membered Cyclic Imines

7a-g **2a** **8a-g**

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azido-Ugi reaction to afford the desired tetrazoles **8a–g** in good to moderate yields (Table 3). Both aliphatic and aromatic

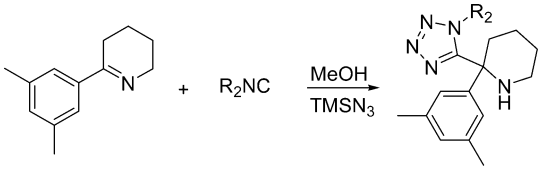
Table 3. Synthesis of Tetrazole-Substituted Azepanes

Entry	R_1	Product	Yield, %
1	Bu	**8a**	63
2	2-Thiophenyl	**8b**	29
3	Ph	**8c**	52
4	*t*Bu	**8d**	45
5	2-Furyl	**8e**	20
6		**8f**	57
7	3-$MeOC_6H_4$	**8g**	49

tetrahydroazepines reacted well. For example 2-*n*-butyl-substituted imine **7a** gave the target tetrazole **8a** in 63% yield. In the case of the sterically demanding 2-*tert*-butyl-substituted tetrahydroazepine **7d**, the desired tetrazole **8d** was isolated in moderate yield (45%). A quite reasonable outcome was observed in the reaction with 2-phenyltetrahydroazepine **7c**, which formed product **8c** in 52% yield. Only modest yields were observed for 2-furyl-substituted (**7e**) and 2-thiophenyl-substituted (**7b**) seven-membered imines (**8e**, 20%; **8b**, 29%). As mentioned above, an additional tertiary amino group in the imine did not inhibit the Ugi reaction, as imine **7f** afforded the target tetrazole **8f** in 57% yield.

Next we studied the influence of the isocyanide component on the azido-Ugi reaction. 2-(3,5-Dimethylphenyl)-tetrahydropyridine (**5b**) was chosen as the model imine (Scheme 7). In general, we found no restrictions on the

Scheme 7. Variation of the Isocyanide Component in the Azido-Ugi Reaction with Imine 5b

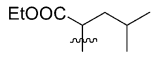
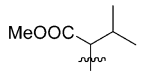
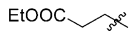
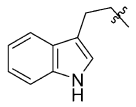


5b **2a-i** **6b, 9b-i**

structure of the isocyanide component. The isolated yields for the reaction are given in Table 4. One can see that, as a rule, the target tetrazoles **6b** and **9b–i** were prepared in good yields. Isocyanides **2f–h** prepared from natural amino acids (valine, leucine, and *β*-alanine) were also employed to demonstrate the generality of the method. As we expected in the case of **2f** and **2g**, two pairs of diastereomers in a 1:1 ratio were obtained because the starting isocyanides were in racemic form. The compounds obtained from isonitriles **9f–h** can be considered as tetrazole surrogates of dipeptides containing a 2-substituted pipecolinic acid fragment.

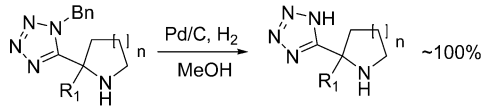
Having in hand a set of tetrazole-substituted cyclic amines, we decided to employ hydrogenolysis of the benzyl group to prepare NH-tetrazoles. Various 1-benzyltetrazoles connected to cyclic amines with different ring sizes were studied in the debenzylation process (Scheme 8). We found the optimal

Table 4. Influence of the Isocyanide Component

Entry	R_2	Isonitrile	Product	Yield, %
1	Bn	**2a**	**6b**	69
2	*t*Bu	**2b**	**9b**	61
3	CH_2COOEt	**2c**	**9c**	47
4	Allyl	**2d**	**9d**	67
5	Bu	**2e**	**9e**	70
6		**2f**	**9f**[a]	70
7		**2g**	**9g**[a]	84
8		**2h**	**9h**	53
9		**2i**	**9i**	50

[a]Two pairs of diastereomers in a 1:1 ratio were isolated.

Scheme 8. Synthesis of N-Unsubstituted Tetrazoles 10a–e



3e, 6a-b, 8a, 8c **10a-e**

conditions for deprotection to provide quantitative yields of the target NH-tetrazoles **10a–e** to be a catalytic amount of 10% palladium on carbon and hydrogen (1 atm) in methanol (Table 5). The benzyl group was cleanly removed, and almost

Table 5. Removal of the Benzyl Group by Hydrogenolysis

Entry	R_1	*N*-benzyltetrazole	Product	Yield, %
1	Cyclopentyl	**3e**	**10a**	97
2	Cyclohexyl	**6a**	**10b**	94
3	3,5-diMeC_6H_3	**6b**	**10c**	95
4	Bu	**8a**	**10d**	98
5	Ph	**8c**	**10e**	90

quantitative yields of tetrazoles **10a–e** were observed. After filtration of the catalyst and evaporation of the solvent, no further purification of the obtained substances was required.

The structure of the products **10a–e** resembles the structure of tetrazole–proline analogues having various substituents at the *α*-position. Our approach opens a short and efficient route to a family of such molecules with broad possibilities for changing not only the electronic and steric properties of the substituent at the *α*-position but also the ring size and therefore the C–N–C angle in the cyclic amine, providing an opportunity for the efficient construction of new organo-catalysts.

Interest in tetrazole-containing compounds has increased after the work of Hartikka and Arvidsson.[19] They elaborated a new proline-derived catalyst by substitution of the carboxylic group of proline with a 1*H*-tetrazole fragment. This

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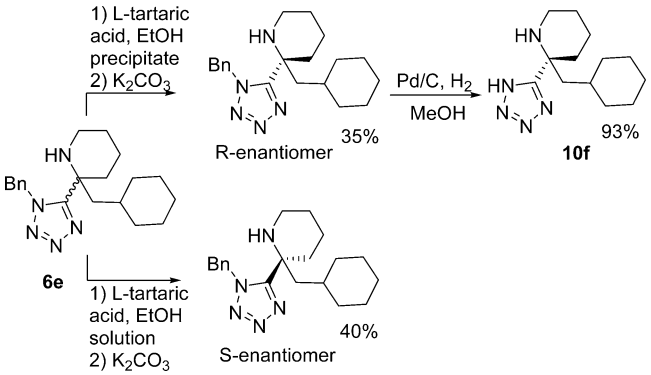
replacement improved the solubility of the organocatalysts and reduced the aldol reaction times from 1−2 days to less than half a day. Brimble and co-workers showed that an α-methyl substituent in proline and "proline tetrazole" could improve the stereoselectivity of the reactions.[9] However, the α-methylated organocatalyst was prepared in six steps from the α-methyl proline ester, which is not commercially available. To the best of our knowledge, no examples of other tetrazoles linked with α-substituted cyclic amines have been published to date. Therefore, such compounds are still very desirable targets for modern organocatalysis.

We applied resolution to demonstrate a simple route to new chiral tetrazole organocatalysts. L-Tartaric acid was chosen as an abundantly used resolving agent[20] to prepare diastereomeric salts of amine and L-tartaric acid in a 1:1 ratio (Scheme 9). The

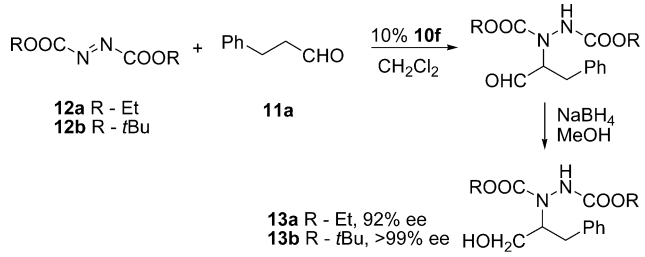
Scheme 9. Resolution of 6e into Enantiomers



tartrate salt of Ugi product **6e** was crystallized from ethanol. The precipitate formed was filtered off, and part of it was converted into the free base, which was studied by optical rotation. After recrystallization of the precipitate, the optical rotation of the amine became constant ($[\alpha]_D^{25}$ = +30.0° (*c* 1, CH_2Cl_2)). The melting point of the tartrate salt after recrystallization also became constant (193−195 °C). By this means, the *R* enantiomer of compound **6e** was isolated in 35% yield. The liquor obtained after filtration was evaporated, and after conversion into the free base, the *S* enantiomer was isolated in 40% yield ($[\alpha]_D^{25}$ = −30.0° (*c* 1, CH_2Cl_2)). The melting point of tartrate is 152−154 °C. We believe that both enantiomeric forms were very pure (>99% ee) because the rotation angles were the same and the X-ray data (see below) showed that the pure diastereomeric salt of (*R*)-**6e** was formed. One of the obtained enantiomers of **6e** was debenzylated (Scheme 9), and the target product **10f** was prepared in excellent yield (93%). The absolute configuration of the enantiomer isolated as the precipitated tartrate was determined by X-ray analysis. According to the X-ray data, the *R* enantiomer formed the less-soluble salt.

Finally, we demonstrated the utility of the new tetrazoles in organocatalysis. The aminations of 3-phenylpropanal (**11a**) with diethyl and di-*tert*-butyl azodicarboxylate (**12a** and **12b**, respectively) were chosen as model reactions (Scheme 10). The use of compound **10f** as an organocatalyst in this reaction demonstrated high effectiveness of amination to give target products **13a** and **13b** in high chemical yields with high ee. Only one enantiomer was detected by chiral HPLC for the reaction of di-*tert*-butyl azodicarboxylate with 3-phenylpropanal (>99% ee). In the case of the reaction of diethyl

Scheme 10. Model Aminations Using 10f as the Organocatalyst



azodicarboxylate, 92% ee was observed. Therefore, our expectation about the effective use of this new family of organocatalysts was confirmed, opening a fruitful path for their subsequent application in organocatalysis.

CONCLUSIONS

We have investigated the $TMSN_3$-modified Ugi reaction with 2-substituted cyclic imines. It has been shown that the influence of the imine structure on the reaction is more important than the nature of the isonitrile. The reaction allows the preparation of 1,5-disubstituted tetrazole derivatives bearing a cyclic amine fragment in good to high yields. Subsequent debenzylation opens an efficient way to a series of 1*H*-tetrazoles connected to cyclic amines. The possibility of simple resolution of such tetrazoles via tartrate salts was demonstrated, allowing both enantiomers of tetrazole-substituted cyclic amines bearing substituents in α-position to be obtained effectively. Efficient application of the prepared tetrazole-derived cyclic amines was demonstrated in the chiral organocatalytic reaction between diethyl or di-*tert*-butyl azodicarboxylate and 3-phenylpropanal, which gave the target product with up to >99% ee.

EXPERIMENTAL SECTION

1D NMR (^1H, ^{19}F, and ^{13}C) spectra were obtained on 400 MHz spectrometers. Chemical shifts are reported in parts per million downfield from TMS. Deuterated solvent peaks were used as internal references: deuterochloroform at 7.27 and 77.00 ppm, deutero-DMSO at 2.50 and 39.50 ppm, and deuteromethanol at 3.31 and 49.00 ppm. Chemical shifts for ^{19}F NMR data are referenced to $CFCl_3$ (0.0 ppm) or $PhCF_3$ (−63.90 ppm). High-resolution mass spectrometry (HRMS) was performed using a MicroTOF-Q instrument. Electrospray ionization (ESI) mass spectrometry (MS) was performed using methanol or acetonitrile solutions. Melting points are uncorrected. The silica gel used for flash chromatography was 230−400 mesh. The starting cyclic imines were prepared by described methods.[16]

General Procedure for the Ugi Reaction. The appropriate imine (**1a−j**, **5a−i**, **7a−g**) (1 mmol) was dissolved in dry MeOH (2 mL). The isocyanide (**2a−i**) (1.1 mmol) and $TMSN_3$ (1.1 mmol) were added, and the solution was stirred for several days (TLC control) at room temperature. In cases where solid products were formed, the product was purified by filtration and washing with cold methanol. For products soluble in methanol, the solvent was evaporated and the product was purified by column chromatography (hexane/ethyl acetate or dichloromethane).

*1-Benzyl-5-(2-methylpyrrolidin-2-yl)-1H-tetrazole (**3a**).* Yield: 0.124 g (51%). Yellowish solid, mp 73−74 °C. ^1H NMR ($CDCl_3$): δ 1.40 (s, 3H), 1.62 (br, 1H), 1.67−1.92 (m, 3H), 2.66−2.73 (m, 2H), 3.11−3.17 (m, 1H), 5.93 and 6.02 (both d, 2H, *J* = 14.8 Hz), 7.23−7.36 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 25.6, 27.7, 40.1, 46.8, 52.0, 61.5, 127.7, 128.3, 128.9, 135.4, 159.3. IR (ν, cm^{-1}): 3313, 3288 (**NH**). Anal. Calcd for $C_{13}H_{17}N_5$: C, 64.17; H, 7.04; N, 28.78. Found: C, 64.20; H, 6.99; N, 28.68.

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*1-Benzyl-5-(2-ethylpyrrolidin-2-yl)-1H-tetrazole (**3b**).* Yield: 0.170 g (66%). White solid, mp 62−64 °C. ^{1}H NMR ($CDCl_3$): δ 0.60 (t, 3H, J = 7.5 Hz), 1.56−1.77 (m, 5H), 1.82 (br, 1H), 2.52−2.52 (m, 1H), 2.64−2.68 (m, 1H), 2.99−3.05 (m, 1H), 5.89 and 5.93 (both d, 2H, J = 14.97 Hz), 7.16−7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 9.0, 25.1, 33.1, 37.6, 46.4, 51.6, 65.5, 127.3, 127.9, 128.4, 135.2, 158.0. IR (ν, cm^{-1}): 3284 (**NH**). HRMS (ESI) m/z: calcd for $C_{14}H_{20}N_5$ [M + H]$^+$, 258.1713; found, 258.1718.

*1-Benzyl-5-(2-butylpyrrolidin-2-yl)-1H-tetrazole (**3c**).* Yield: 0.160 g (56%). White solid, mp 51−53 °C. ^{1}H NMR ($CDCl_3$): δ 0.67 (t, 3H, J = 7.1 Hz), 0.77−1.10 (m, 4H), 1.54−1.61 (m, 2H), 1.65−1.85 (m, 4H), 2.56−2.64 (m, 1H), 2.77−2.82 (m, 1H), 3.05−3.11 (m, 1H), 5.92 and 6.03 (both d, 2H, J = 14.9 Hz), 7.22−7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.7, 22.5, 25.4, 27.1, 38.2, 40.3, 46.5, 51.8, 65.3, 127.5, 128.2, 128.7, 135.4, 158.3. IR (ν, cm^{-1}): 3295 (**NH**). Anal. Calcd for $C_{16}H_{23}N_5$: C, 67.34; H, 8.12; N, 24.54. Found: C, 67.20; H, 8.04; N, 24.33.

*1-Benzyl-5-[2-(2-methylbenzyl)pyrrolidin-2-yl]-1H-tetrazole (**3d**).* Yield: 0.240 g (72%). White solid, mp 137−138 °C. ^{1}H NMR ($CDCl_3$): δ 1.54−1.63 (m, 1H), 1.71−1.81 (m, 1H), 1.87−1.94 (m, 2H), 2.04 (s, 3H), 2.43−2.50 (m, 1H), 2.83−2.89 (m, 1H), 2.96−3.01 (m, 1H), 3.05 and 3.15 (both d, 2H, J = 14.1 Hz), 5.51 and 5.36 (both d, 2H, J = 14.8 Hz), 6.87−6.89 (m, 1H), 7.09−7.18 (m, 5H), 7.25−7.32 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 19.5, 23.9, 38.4, 42.3, 46.3, 51.5, 66.4, 125.9, 127.4, 127.8, 128.1, 128.6, 131.0, 134.0, 135.2, 137.4, 158.5. IR (ν, cm^{-1}): 3315 (**NH**). Anal. Calcd for $C_{20}H_{23}N_5$: C, 72.04; H, 6.95; N, 21.00. Found: C, 72.21; H, 6.91; N, 20.93.

*1-Benzyl-5-(2-cyclopentylpyrrolidin-2-yl)-1H-tetrazole (**3e**).* Yield: 0.223 g (75%). White solid, mp 95−97 °C. ^{1}H NMR ($CDCl_3$): δ 1.10−1.17 (m, 1H), 1.22−1.47 (m, 7H), 1.49−1.58 (m, 1H), 1.63−1.73 (m, 1H), 1.79−1.86 (m, 2H), 2.06−2.15 (m, 1H), 2.39−2.45 (m, 1H), 2.63−2.69 (m, 1H), 2.96−3.02 (m, 1H), 5.87 and 6.02 (both d, 2H, J = 14.68 Hz), 7.18−7.28 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): δ 25.1, 25.3, 25.7, 27.1, 28.4, 35.2, 47.0, 48.2, 52.1, 67.9, 127.6, 128.0, 128.5, 135.5, 159.2. IR (ν, cm^{-1}): 3313 (**NH**). Anal. Calcd for $C_{17}H_{23}N_5$: C, 68.66; H, 7.80; N, 23.55. Found: C, 68.57; H, 7.74; N, 23.43.

*1-Benzyl-5-(2-tert-butylpyrrolidin-2-yl)-1H-tetrazole (**3f**).* Yield: 0.182 g (64%). White solid, mp 109−110 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (s, 9H), 1.22−1.36 (m, 1H), 1.57−1.67 (m, 1H), 1.83 (br, 1H), 1.93−2.01 (m, 1H), 2.22−2.28 (m, 1H), 2.62−2.68 (m, 1H), 2.86−2.92 (m, 1H), 5.70 and 6.26 (both d, 2H, J = 14.4 Hz), 7.23−7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 25.7, 26.3, 35.6, 37.8, 47.4, 53.0, 72.6, 127.9, 128.5, 135.7, 158.2. IR (ν, cm^{-1}): 3388 (**NH**). Anal. Calcd for $C_{16}H_{23}N_5$: C, 67.34; H, 8.12; N, 24.54. Found: C, 67.17; H, 7.94; N, 24.48.

*5-[2-(2-Adamantyl)pyrrolidin-2-yl]-1-benzyl-1H-tetrazole (**3g**).* Yield: 0.182 g (50%). White solid, mp 142−143 °C. ^{1}H NMR ($CDCl_3$): δ 1.39−1.35 (m, 1H), 1.40−1.74 (m, 13H), 1.96−2.08 (m, 5H), 2.19−2.25 (m, 1H), 2.55−2.61 (m, 1H), 2.81−22.87 (m, 1H), 5.68 and 6.25 (both d, 2H, J = 14.4 Hz), 7.25−7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 25.3, 28.2, 33.8, 36.5, 37.3, 39.1, 47.0, 52.9, 72.8, 127.7, 127.8, 128.3, 135.6, 157.8. IR (ν, cm^{-1}): 3398 (**NH**). HRMS (ESI) m/z: calcd for $C_{22}H_{30}N_5$ [M + H]$^+$, 364.2496; found, 364.2488.

*1-Benzyl-5-{2-[(methylthio)methyl]pyrrolidin-2-yl}-1H-tetrazole (**3i**).* Yield: 0.231 g (80%). White solid, mp 90−92 °C. ^{1}H NMR ($CDCl_3$): δ 1.56−1.64 (m, 1H), 1.74−1.83 (m, 4H inc. 1.81 (s, 3H)), 1.90−1.97 (m, 1H), 2.31 (br, 1H), 2.37−2.43 (m, 1H), 2.66−2.73 (m, 1H), 2.79 and 2.90 (both d, 2H, J = 13.5 Hz), 3.04−3.10 (m, 1H), 5.95 and 6.00 (both d, 2H, J = 14.8 Hz), 7.20−7.31 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): δ 17.0, 24.9, 38.1, 44.1, 46.3, 52.1, 65.0, 127.5, 128.1, 128.6, 135.2, 158.0. IR (ν, cm^{-1}): 3271 (**NH**). HRMS (ESI) m/z: calcd for $C_{14}H_{20}N_5S$ [M + H]$^+$, 290.1434; found, 290.1448.

*1-{[2-(1-Benzyl-1H-tetrazol-5-yl)pyrrolidin-2-yl]methyl}piperidine (**3j**).* Yield: 0.199 g (61%). Yellow solid, mp 62−64 °C. ^{1}H NMR ($CDCl_3$): δ 1.25−1.29 (m, 2H), 1.31−1.39 (m, 4H), 1.52−1.58 (m, 1H), 1.66−1.74 (m, 1H), 1.81−1.88 (m, 1H), 2.15−2.28 (m, 5H), 2.48 and 2.75 (both d, 2H, J = 13.7 Hz), 2.57−2.64 (m, 1H), 2.99−3.05 (m, 1H), 3.62 (br, 1H), 5.94 and 6.02 (both d, 2H, J = 14.7 Hz), 7.20−7.29 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): δ 23.5, 24.8, 25.8, 37.2, 46.2, 51.9, 56.0, 65.2, 65.5, 127.6, 127.9, 128.4, 135.4, 158.7. IR (ν, cm^{-1}): 3296 (**NH**). HRMS (ESI) m/z: calcd for $C_{18}H_{27}N_6$ [M + H]$^+$, 327.2292; found, 327.2296.

*1-Benzyl-1H-tetrazole (**4a**).* White solid; mp 59 °C. ^{1}H NMR ($CDCl_3$): δ 5.6 (s, 2H, CH_2), 7.27−7.33 (m, 2H, Ar), 7.39−7.42 (m, 3H, Ar), 8.54 (s, 1H, Ar). The spectroscopic data are in agreement with those in the literature.[21]

*2-(1-Benzyl-1H-tetrazol-5-yl)-2-cyclohexylpiperidine (**6a**).* Yield: 0.369 (65%). White solid, mp 161−162 °C. ^{1}H NMR ($CDCl_3$): δ 0.40−0.50 (m, 1H), 0.78−1.05 (m, 5H), 1.14−1.27 (m, 2H), 1.38−1.48 (m, 5H), 1.55−1.72 (m, 4H), 1.99−2.06 (m, 1H), 2.51−2.56 (m, 1H), 2.81−2.86 (m, 1H), 5.92 and 6.04 (both d, 2H, J = 14.9 Hz), 7.24−7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 21.1, 26.1, 26.2, 26.4, 26.5, 26.9, 27.3, 29.7, 43.2, 47.1, 52.1, 60.1, 127.9, 128.1, 128.7, 135.3, 158.8. IR (ν, cm^{-1}): 3333 (**NH**). HRMS (ESI) m/z: calcd for $C_{19}H_{28}N_5$ [M + H]$^+$, 326.2339; found, 326.2331.

*2-(1-Benzyl-1H-tetrazol-5-yl)-2-(3,5-dimethylphenyl)piperidine (**6b**).* Yield: 0.239 g (69%). White solid, mp 110−112 °C. ^{1}H NMR ($CDCl_3$): δ 1.34−1.44 (m, 1H), 1.50−1.55 (m, 1H), 1.64−1.71 (m, 1H), 1.35−1.80 (m, 2H), 2.08−2.14 (m, 2H), 2.23 (s, 6H), 2.77−2.76 (m, 1H), 2.91−2.97 (m, 1H), 5.25 and 5.59 (both d, 2H, J = 15.1 Hz), 6.81−6.86 (m, 3H), 6.93−6.96 (m, 2H), 7.21−7.23 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 21.4, 21.8, 26.1, 39.1, 42.8, 51.5, 58.6, 122.6, 127.6, 128.1, 128.5, 129.3, 134.1, 138.4, 143.5, 157.4. IR (ν, cm^{-1}): 3305 (**NH**). Anal. Calcd for $C_{21}H_{25}N_5$: C, 72.59; H, 7.25; N, 20.16. Found: C, 72.69; H, 7.20; N, 20.10.

*2-(1-Benzyl-1H-tetrazol-5-yl)-2-[3-(trifluoromethyl)phenyl]-piperidine (**6c**).* Yield: 0.267 g (69%). Yellow solid, mp 105−106 °C. ^{1}H NMR ($CDCl_3$): δ 1.37−1.48 (m, 1H), 1.53−1.59 (m, 1H), 1.65−1.84 (m, 3H), 2.04−2.23 (m, 2H), 2.84−2.89 (m, 1H), 2.97−3.03 (m, 1H), 5.31 and 5.67 (both d, 2H, J = 15.2 Hz), 6.84−6.88 (m, 2H), 7.13−7.20 (m, 3H), 7.28−7.35 (m, 2H), 7.43−7.47 (m, 1H), 7.57−7.60 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 21.6, 25.8, 39.2, 42.8, 51.7, 58.8, 121.3 (q, J = 3.7 Hz), 123.8 (q, J = 272.6 Hz), 124.5 (q, J = 3.3 Hz), 127.2, 128.2, 128.7, 128.9, 129.4, 131.1 (q, J = 31.8 Hz), 133.6, 144.4, 156.5. ^{19}F NMR ($CDCl_3$): δ −63.4 (s). IR (ν, cm^{-1}): 3302, 3270 (**NH**). Anal. Calcd for $C_{20}H_{20}F_3N_5$: C, 62.01; H, 5.20; N, 18.08. Found: C, 61.97; H, 5.21; N, 18.00.

*2-(1-Benzyl-1H-tetrazol-5-yl)-2-(2-methylbenzyl)piperidine (**6d**).* Yield: 0.160 g (46%). White solid, mp 126−128 °C. ^{1}H NMR ($CDCl_3$): δ 1.12−1.23 (m, 1H), 1.32−1.39 (m, 1H), 1.41−1.61 (m, 3H), 1.65−1.72 (m, 1H), 1.90−1.97 (m, 1H), 1.99 (s, 3H), 2.67−2.74 (m, 1H), 2.78−2.83 (m, 1H), 2.90 and 2.86 (both d, 2H, J = 13.9 Hz), 5.13 and 5.42 (both d, 2H, J = 14.9 Hz), 6.90−6.92 (m, 1H), 7.10−7.21 (m, 3H), 7.24−7.32 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 19.4, 21.0, 26.0, 35.5, 43.0, 45.5, 51.3, 58.9, 125.6, 127.3, 128.1, 128.1, 128.4, 130.8, 131.6, 133.3, 134.4, 137.5, 156.7. IR (ν, cm^{-1}): 3298 (**NH**). Anal. Calcd for $C_{21}H_{25}N_5$: C, 72.59; H, 7.25; N, 20.16. Found: C, 72.80; H, 7.33; N, 20.01.

*2-(1-Benzyl-1H-tetrazol-5-yl)-2-(cyclohexylmethyl)piperidine (**6e**).* Yield: 0.231 g (68%). White solid, mp 100−101 °C. ^{1}H NMR ($CDCl_3$): δ 0.27−0.37 (m, 1H), 0.64−0.67 (m, 1H), 0.71−0.80 (m, 1H), 0.88−0.97 (m, 2H), 1.03−1.12 (m, 2H), 1.21−1.74 (m, 12H), 2.01−2.08 (m, 1H), 2.75−2.80 (m, 2H), 5.91 and 5.95 (both d, 2H, J = 14.6 Hz), 7.28−7.36 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$): δ 21.0, 25.8, 26.0, 26.5, 32.4, 33.9, 35.0, 35.7, 42.7, 50.0, 51.9, 56.6, 128.2, 128.3, 128.5, 134.7, 156.7. IR (ν, cm^{-1}): 3305 (**NH**). Anal. Calcd for $C_{20}H_{29}N_5$: C, 70.76; H, 8.61; N, 20.63. Found: C, 70.85; H, 8.41; N, 20.58.

*2-(1-Benzyl-1H-tetrazol-5-yl)-2-tert-butylpiperidine (**6f**).* Yield: 0.132 g (44%). Yellowish solid, mp 134−135 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (s, 9H), 1.12−1.25 (m, 2H), 1.33−1.45 (m, 2H), 1.56−1.65 (m, 1H), 1.72 (br, 1H), 2.02−2.12 (m, 1H), 2.75−2.80 (m, 1H), 2.85−2.89 (m, 1H), 5.83 and 6.31 (both d, 2H, J = 14.8 Hz), 7.29−7.36 (m, 3H), 7.40−7.42 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 21.5, 25.7, 26.5, 31.0, 39.5, 43.7, 52.9, 63.9, 128.0, 128.5, 128.5, 134.7, 155.7. IR (ν, cm^{-1}): 3348 (**NH**). Anal. Calcd for $C_{17}H_{25}N_5$: C, 68.19; H, 8.42; N, 23.39. Found: C, 68.25; H, 8.51; N, 23.20.

*2-(1-Benzyl-1H-tetrazol-5-yl)-2-(2-furyl)piperidine (**6g**).* Yield: 0.226 g (73%). White solid, mp 94−95 °C. ^{1}H NMR ($CDCl_3$): δ 1.33−1.46 (m, 2H), 1.66−1.82 (m, 2H), 1.93−2.00 (m, 1H), 2.04 (br,

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1H), 2.23−2.30 (m, 1H), 2.61−2.74 (m, 2H), 5.67 and 5.71 (both d, 2H, J = 15.2 Hz), 6.02−6.03 (m, 1H), 6.20−6.21 (m, 1H), 7.10−7.13 (m, 2H), 7.19−7.24 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 20.7, 25.5, 34.6, 42.1, 51.7, 56.1, 106.4, 110.1, 127.7, 127.8, 128.3, 134.2, 141.9, 154.2, 155.6. IR (ν, cm^{-1}): 3309 (**NH**). Anal. Calcd for $C_{17}H_{19}N_5O$: C, 66.00; H, 6.19; N, 22.64. Found: C, 66.12; H, 6.18; N, 22.67.

2-(1-Benzyl-1H-tetrazol-5-yl)-2-(piperidin-1-ylmethyl)piperidine ***(6h)***. Yield: 0.214 g (63%). White solid, mp 130−132 °C. ^{1}H NMR ($CDCl_3$): δ 1.22−1.50 (m, 9H), 1.59−1.67 (m, 2H), 1.94 (br, 1H), 2.01−2.08 (m, 1H), 2.19−2.36 (m, 6H), 2.41−2.45 (m, 1H), 2.72−2.76 (m, 1H), 5.97 and 6.08 (both d, 2H, J = 14.7 Hz), 7.27−7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 21.0, 23.6, 26.0, 26.1, 32.7, 42.7, 52.2, 56.9, 59.3, 67.4, 128.0, 128.1, 128.5, 134.9, 156.9. IR (ν, cm^{-1}): 3302 (**NH**). HRMS (ESI) m/z: calcd for $C_{19}H_{29}N_6$ $[M + H]^+$, 341.2448; found, 341.2452.

2-(1-Benzyl-1H-tetrazol-5-yl)-2-(diphenylmethyl)piperidine ***(6i)***. Yield: 0.295 g (77%). White solid, mp 72−74 °C. ^{1}H NMR ($CDCl_3$): δ 1.17−1.41 (m, 3H), 1.64−1.85 (m, 3H), 1.98−2.04 (m, 1H), 2.72−2.75 (m, 1H), 2.83−2.86 (m, 1H), 4.07 (s, 1H), 5.10 and 5.31 (both d, 2H, J = 15.1 Hz), 7.18−7.37 (m, 15H). ^{13}C NMR ($CDCl_3$): δ 21.2, 25.8, 34.0, 43.1, 51.6, 61.5, 63.3, 127.0, 127.3, 128.3, 128.5, 128.6, 129.7, 130.0, 134.2, 139.0, 139.2, 156.2. IR (ν, cm^{-1}): 3311 (**NH**). HRMS (ESI) m/z: calcd for $C_{26}H_{27}N_5Na$ $[M + Na]^+$, 432.2159; found, 432.2149.

2-(1-Benzyl-1H-tetrazol-5-yl)-2-butylazepane ***(8a)***. Yield: 0.197 g (63%). White solid, mp 74−75 °C. ^{1}H NMR ($CDCl_3$): δ 0.34−0.40 (m, 1H), 0.55 (t, 3H, J = 7.2 Hz), 0.70−0.75 (m, 1H), 0.85−0.91 (m, 2H), 1.21−1.48 (m, 6H), 1.58−1.72 (m, 3H), 2.16−2.36 (m, 3H), 2.67−2.74 (m, 1H), 5.88 and 6.05 (both d, 2H, J = 14.9 Hz), 7.14−7.17 (m, 2H), 7.21−7.28 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 13.4, 22.0, 22.2, 26.0, 29.4, 33.3, 37.2, 39.6, 43.1, 51.7, 60.1, 127.1, 127.8, 128.4, 135.3, 159.1. IR (ν, cm^{-1}): 3330 (**NH**). HRMS (ESI) m/z: calcd for $C_{18}H_{28}N_5$ $[M + H]^+$, 314.2339; found, 314.2340.

2-(1-Benzyl-1H-tetrazol-5-yl)-2-(2-thienyl)azepane ***(8b)***. Yield: 0.098 g (29%). White solid, mp 147−148 °C. ^{1}H NMR ($CDCl_3$): δ 1.45−1.82 (m, 7H), 2.41−2.53 (m, 3H), 3.00−3.08 (m, 1H), 5.24 and 5.60 (both d, 2H, J = 15.4 Hz), 6.72−6.74 (m, 1H), 6.91−7.00 (m, 3H), 7.20−7.31 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 22.1, 29.3, 32.6, 42.3, 42.8, 51.6, 60.5, 123.9, 124.8, 127.1, 127.3, 128.1, 128.7, 134.2, 149.5, 158.8. IR (ν, cm^{-1}): 3278 (**NH**). Anal. Calcd for $C_{18}H_{21}N_5S$: C, 63.69; H, 6.24; N, 20.63. Found: C, 63.55; H, 6.04; N, 20.53.

2-(1-Benzyl-1H-tetrazol-5-yl)-2-phenylazepane ***(8c)***. Yield: 0.173 g (52%). White solid, mp 149−150 °C. ^{1}H NMR ($CDCl_3$): δ 1.48−1.65 (m, 7H), 2.25−2.32 (m, 1H), 2.45−2.52 (m, 1H), 2.60−2.66 (m, 1H), 3.12−3.19 (m, 1H), 4.92 and 5.43 (both d, 2H, J = 15.3 Hz), 6.82−6.84 (m, 2H), 7.21−7.33 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 22.1, 29.3, 32.8, 41.7, 42.7, 51.3, 61.8, 125.8, 127.3, 127.5, 128.1, 128.6, 128.7, 133.9, 143.7, 159.4. IR (ν, cm^{-1}): 3289 (**NH**). Anal. Calcd for $C_{20}H_{23}N_5$: C, 72.04; H, 6.95; N, 21.00. Found: C, 72.12; H, 6.97; N, 20.98.

2-(1-Benzyl-1H-tetrazol-5-yl)-2-tert-butylazepane ***(8d)***. Yield: 0.141 g (45%). White solid, mp 166−167 °C. ^{1}H NMR ($CDCl_3$): δ 0.85 (s, 9H), 0.95−1.05 (m, 1H), 1.17−1.78 (m, 6H), 2.09−2.15 (m, 1H), 2.52−2.64 (m, 2H), 2.84−2.92 (m, 1H), 6.03 (br, 2H), 7.17−7.23 (m, 2H), 7.28−7.34 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 24.7, 26.0, 29.6, 32.5, 34.6, 41.3, 45.1, 53.4, 68.1, 127.4, 127.9, 128.6, 135.8, 159.2. IR (ν, cm^{-1}): 3373 (**NH**). Anal. Calcd for $C_{18}H_{27}N_5$: C, 68.97; H, 8.68; N, 22.34. Found: C, 68.87; H, 8.50; N, 22.34.

2-(1-Benzyl-1H-tetrazol-5-yl)-2-(2-furyl)azepane ***(8e)***. Yield: 0.065 g (20%). White solid, mp 101−103 °C. ^{1}H NMR ($CDCl_3$): δ 1.40−1.53 (m, 3H), 1.64−1.76 (m, 3H), 1.87 (br, 1H), 2.44−2.62 (m, 3H), 2.72−2.78 (m, 1H), 5.35 and 5.58 (both d, 2H, J = 15.2 Hz), 6.20−6.21 (m, 1H), 6.29−6.30 (m, 1H), 7.00−7.02 (m, 2H), 7.25−7.31 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 21.9, 29.4, 32.9, 38.4, 42.4, 51.3, 59.3, 106.9, 110.2, 127.1, 127.9, 128.5, 134.5, 142.2, 154.8, 157.7. IR (ν, cm^{-1}): 3338 (**NH**). Anal. Calcd for $C_{18}H_{21}N_5O$: C, 66.85; H, 6.55; N, 21.66. Found: C, 67.03; H, 6.69; N, 21.49.

2-(1-Benzyl-1H-tetrazol-5-yl)-2-(piperidin-1-ylmethyl)azepane ***(8f)***. Yield: 0.202 g (57%). White solid. ^{1}H NMR ($CDCl_3$): δ 1.20−1.35 (m, 6H), 1.38−1.90 (m, 6H), 1.99−2.05 (m, 1H), 2.08−2.31 (m, 6H), 2.39−2.43 (m, 2H), 2.62−2.72 (m, 2H), 5.99 and 6.22 (both d, 2H, J = 14.8 Hz), 7.18−7.32 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 22.7, 23.6, 26.1, 29.9, 32.8, 38.4, 42.5, 52.6, 56.5, 62.34, 67.3, 127.3, 127.8, 128.6, 136.0, 159.9. IR (ν, cm^{-1}): 3325 (**NH**). HRMS (ESI) m/z: calcd for $C_{20}H_{31}N_6$ $[M + H]^+$, 355.2605; found, 355.2605.

2-(3-Methoxyphenyl)-2-(1-benzyl-1H-tetrazol-5-yl)azepane ***(8g)***. Yield: 0.178 g (49%). White solid. ^{1}H NMR ($CDCl_3$): δ 1.53−1.57 (m, 7H), 2.20−2.25 (m, 1H), 2.43−2.46 (m, 1H), 2.57−2.61 (m, 1H), 3.06−3.11 (m, 1H), 3.69 (s, 3H), 4.94 and 5.42 (both d, 2H, J = 15.4 Hz), 6.80−6.85 (m, 2H), 7.18−7.22 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 22.1, 29.3, 32.8, 41.5, 42.7, 51.3, 55.1, 61.8, 112.2, 112.3, 127.2, 128.1, 128.6, 129.7, 134.0, 145.4, 159.3, 159.8. IR (ν, cm^{-1}): 3338 (**NH**). HRMS (ESI) m/z: calcd for $C_{21}H_{26}N_5O$ $[M + H]^+$, 364.2132; found, 364.2143.

2-(1-tert-Butyl-1H-tetrazol-5-yl)-2-(3,5-dimethylphenyl)piperidine ***(9b)***. Yield: 0.191 g (61%). White solid, mp 183−184 °C. ^{1}H NMR ($CDCl_3$): δ 1.38−1.49 (m, 10H, incl. 1.45 (s, 9H)), 1.53−1.61 (m, 2H), 1.73−1.80 (m, 1H), 2.04−2.26 (m, 9H), 2.92−2.99 (m, 1H), 3.00−3.06 (m, 1H), 6.59−6.61 (m, 2H), 6.81−6.81 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 21.3, 22.1, 26.3, 30.1, 43.1, 43.4, 60.4, 63.9, 122.0, 128.5, 137.9, 146.0, 157.1. IR (ν, cm^{-1}): 3342 (**NH**). Anal. Calcd for $C_{18}H_{27}N_5$: C, 68.97; H, 8.68; N, 22.34. Found: C, 68.81; H, 8.57; N, 22.27.

Ethyl {5-[2-(3,5-Dimethylphenyl)piperidin-2-yl]-1H-tetrazol-1-yl}-acetate ***(9c)***. Yield: 0.161 g (47%). White solid, mp 133−134 °C. ^{1}H NMR ($CDCl_3$): δ 1.13 (t, 3H, J = 7.2 Hz), 1.30−1.40 (m, 1H), 1.54−1.58 (m, 1H), 1.64−1.85 (m, 3H), 2.05−2.15 (m, 1H), 2.24−2.36 (m, 7H), 2.94−3.03 (m, 2H), 3.90−4.07 (m, 2H), 5.01 and 5.27 (both d, 2H, J = 17.2 Hz), 6.84−6.87 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 13.8, 21.4, 21.5, 26.4, 38.6, 42.9, 49.0, 58.0, 61.9, 122.4, 129.2, 138.4, 142.3, 157.4, 165.7. IR (ν, cm^{-1}): 3332 (**NH**), 1751 (**CO**). Anal. Calcd for $C_{18}H_{25}N_5O_2$: C, 62.95; H, 7.34; N, 20.39. Found: C, 63.13; H, 7.39; N, 20.19.

2-(1-Allyl-1H-tetrazol-5-yl)-2-(3,5-dimethylphenyl)piperidine ***(9d)***. Yield: 0.199 g (67%). White solid, mp 142−144 °C. ^{1}H NMR ($CDCl_3$): δ 1.36−1.47 (m, 1H), 1.53−1.60 (m, 1H), 1.65−1.72 (m, 1H), 1.78−1.85 (m, 2H), 2.04−2.16 (m, 1H), 2.24 (s, 6H), 2.27−2.34 (m, 1H), 2.92−2.97 (m, 1H), 2.99−3.05 (m, 1H), 4.78−4.86 (m, 1H), 4.88−4.95 (m, 1H), 4.98−5.02 (m, 1H), 5.08−5.11 (m, 1H), 5.57−5.67 (m, 1H), 6.84−6.86 (m, 3H, Ar). ^{13}C NMR ($CDCl_3$): δ 21.4, 21.7, 26.2, 38.9, 43.0, 50.4, 58.4, 119.1, 122.5, 129.2, 130.7, 138.3, 143.4, 157.0. IR (ν, cm^{-1}): 3288 (**NH**). Anal. Calcd for $C_{17}H_{23}N_5$: C, 68.66; H, 7.80; N, 23.55. Found: C, 68.76; H, 7.77; N, 23.59.

2-(1-Butyl-1H-tetrazol-5-yl)-2-(3,5-dimethylphenyl)piperidine ***(9e)***. Yield: 0.219 g (70%). White solid, mp 75−77 °C. ^{1}H NMR ($CDCl_3$): δ 0.77 (t, 3H, J = 7.3 Hz), 1.09−1.18 (m, 2H), 1.11−1.29 (m, 1H), 1.36−1.46 (m, 1H), 1.50−1.60 (m, 2H), 1.66−1.73 (m, 1H), 1.76−1.85 (m, 2H), 2.09−2.19 (m, 1H), 2.25 (s, 6H), 2.29−2.36 (m, 1H), 2.95−3.00 (m, 1H), 3.04−3.10 (m, 1H), 4.16−4.31 (m, 2H), 6.85−6.87 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 13.4, 19.6, 21.4, 21.7, 26.4, 30.9, 39.0, 43.0, 48.1, 58.3, 122.5, 129.1, 138.3, 143.5, 156.8. IR (ν, cm^{-1}): 3323 (**NH**). Anal. Calcd for $C_{18}H_{27}N_5$: C, 68.97; H, 8.68; N, 22.34. Found: C, 68.90; H, 8.64; N, 22.19.

Ethyl 2-{5-[2-(3,5-Dimethylphenyl)piperidin-2-yl]-1H-tetrazol-1-yl}-4-methylpentanoate ***(9f)***. Mixture of diastereomers, 1:1 ratio. Yield: 0.279 g (70%). White solid, mp 95−97 °C. ^{1}H NMR ($CDCl_3$): δ 0.06 and 0.47 (d, 3H, J = 6.7 Hz, J = 6.5 Hz), 0.80 and 0.89 (d, 3H, J = 6.5 Hz, J = 6.7 Hz), 0.75 and 1.14 (t, 3H, J = 7.1 Hz), 1.21−1.82 (m, 7H), 2.03−2.36 (m, 9H), 2.75−2.85 (m, 1H), 2.92−3.02 (m, 1H), 3.43−3.50 (m, 1H), 4.01−4.13 (m, 1H), 5.04 and 6.00 (dd, 1H, J = 10.8 Hz and J = 4.1 Hz, J = 10.3 Hz and J = 4.7 Hz), 6.67−6.76 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 13.3, 13.9, 20.3, 21.1, 21.1, 21.2, 21.4, 21.6, 22.2, 22.7, 24.4, 24.7, 26.1, 26.3, 38.7, 39.5, 39.9, 40.4, 42.7, 43.0, 57.7, 58.9, 59.0, 59.7, 61.2, 61.6, 122.1, 122.3, 128.7, 129.1, 138.0, 138.4, 142.2, 142.9, 157.0, 157.5, 168.0, 169.0. IR (ν, cm^{-1}): 3309 (**NH**), 1753 (**CO**). Anal. Calcd for $C_{22}H_{33}N_5O_2$: C, 66.14; H, 8.33; N, 17.53. Found: C, 66.04; H, 8.30; N, 17.54.

Methyl 2-{5-[2-(3,5-Dimethylphenyl)piperidin-2-yl]-1H-tetrazol-1-yl}-3-methylbutanoate ***(9g)***. Mixture of diastereomers, 1:1 ratio. Yield: 0.312 g (84%). White solid, mp 90−92 °C. ^{1}H NMR ($CDCl_3$):

δ 0.46 (dd, 3H, *J* = 6.8 Hz, *J* = 0.3 Hz), 0.93−0.94 (m, 3H), 1.23−1.38 (m, 1H), 1.43−1.58 (m, 2H), 1.71−1.83 (m, 2H), 2.03−2.45 (m, 9H), 2.64−2.73 (m, 1H), 2.84−2.99 (m, 1H), 3.03 and 3.66 (s, 3H), 5.06 and 5.83 (d, 1H, *J* = 8.0 Hz, *J* = 8.3 Hz), 6.69−6.81 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 18.6, 18.9, 18.9, 18.7, 21.1, 21.2, 21.6, 26.1, 26.3, 30.6, 30.9, 39.0, 39.1, 42.6, 42.9, 51.6, 52.3, 58.0 (C_q), 65.5, 66.2, 122.3, 128.7, 129.0, 138.0, 138.2, 142.3, 143.0, 157.2, 157.7, 168.4, 168.5. IR (ν, cm^{-1}): 3311 (**NH**), 1753 (**CO**). Anal. Calcd for $C_{20}H_{29}N_5O_2$: C, 64.66; H, 7.87; N, 18.85. Found: C, 64.64; H, 7.70; N, 18.68.

*Ethyl 3-{5-[2-(3,5-Dimethylphenyl)piperidin-2-yl]-1H-tetrazol-1-yl}propanoate (**9h**).* Yield: 0.189 g (53%). White solid, mp 91−93 °C. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, 3H, *J* = 7.2 Hz), 1.30−1.43 (m, 1H), 1.50−1.57 (m, 1H), 1.63−1.71 (m, 1H), 1.74−1.81 (m, 1H), 1.93 (br, 1H, NH), 2.03−2.15 (m, 1H), 2.20−2.31 (m, 3H), 2.62−2.70 (m, 1H), 2.90−2.96 (m, 1H), 3.03−3.09 (m, 1H), 4.06 (q, 2H, *J* = 7.2 Hz), 4.44−4.57 (m, 2H), 6.83 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 13.9, 21.2, 21.5, 26.2, 33.1, 38.6, 42.8, 43.7, 58.1, 60.7, 122.3, 129.1, 138.3, 142.9, 156.9, 169.9. IR (ν, cm^{-1}): 3300 and 3288 (**NH**), 1730 (**CO**). Anal. Calcd for $C_{19}H_{27}N_5O_2$: C, 63.84; H, 7.61; N, 19.59. Found: C, 63.70; H, 7.48; N, 19.41.

*3-(2-{5-[2-(3,5-Dimethylphenyl)piperidin-2-yl]-1H-tetrazol-1-yl}ethyl)-1H-indole (**9i**).* Yield: 0.200 g (50%). Yellow solid, mp 82−84 °C. ^{1}H NMR ($CDCl_3$): δ 1.33−1.44 (m, 1H), 1.48−1.55 (m, 1H), 1.66−1.83 (m, 3H), 2.10−2.19 (m, 2H), 2.26 (s, 6H), 2.77−2.83 (m, 1H), 2.86−2.93 (m, 2H), 3.21−3.29 (m, 1H), 4.44−4.56 (m, 2H), 6.86−6.90 (m, 4H), 7.13−7.17 (m, 1H), 7.20−7.24 (m, 1H), 7.37−7.39 (m, 1H), 7.45−7.47 (m, 1H), 8.50 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 21.4, 21.6, 25.3, 26.1, 39.0, 42.5, 48.8, 58.4, 110.9, 111.3, 188.2, 119.4, 122.2, 122.4, 122.6, 126.7, 129.2, 136.2, 138.4, 143.6, 157.3. IR (ν, cm^{-1}): 3305 (**NH**), 3411 (**NH**). Anal. Calcd for $C_{24}H_{28}N_6 \cdot {}^1/_2H_2O$: C, 70.39; H, 7.14; N, 20.52. Found: C, 70.43; H, 6.92; N, 20.27.

General Procedure for Debenzylation. The solution of the appropriate tetrazole (**3e**, **6a−b**, **8a**, **8c**) (1 mmol) in 10 mL of absolute MeOH was treated with 10% palladium on carbon (50 mg, 5 mol %) and placed under hydrogen (1 atm). Stirring was continued at room temperature for a few hours (TLC control), after which the mixture was filtered through Celite, washed with methanol, and concentrated to give the product (**10a−f**) as a white solid.

*5-(2-Cyclopentylpyrrolidin-2-yl)-1H-tetrazole (**10a**).* Yield: 0.201 g (97%). White solid, mp 253−255 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.07−1.41 (m, 5H), 1.48−1.69 (m, 4H), 1.85−1.99 (m, 2H), 2.36−2.44 (m, 1H), 2.61−2.66 (m, 1H), 2.99−3.05 (m, 1H), 3.15−3.22 (m, 1H), 3.80 (br, 2H). ^{13}C NMR (DMSO-d_6): δ 22.5, 24.9, 25.0, 27.3, 27.5, 35.9, 44.3, 46.6, 70.6, 159.4. IR (ν, cm^{-1}): (br) 3390 (**NH**). Anal. Calcd for $C_{10}H_{17}N_5$: C, 57.95; H, 8.27; N, 33.79. Found: C, 58.06; H, 8.11; N, 33.87.

*2-Cyclohexyl-2-(1H-tetrazol-5-yl)piperidine (**10b**).* Yield: 0.221 g (94%). White solid, mp 280−281 °C (dec). ^{1}H NMR (DMSO-d_6): δ 0.53−0.88 (m, 2H), 1.04−1.22 (m, 2H), 1.49−1.79 (m, 7H), 2.61−2.71 (m, 1H), 3.00−3.04 (m, 1H), 3.10−4.20 (br, 6H). ^{13}C NMR (DMSO-d_6): δ 19.1, 21.7, 25.5, 25.6, 25.7, 25.9, 26.1, 30.6, 46.6, 62.3, 157.8. IR (ν, cm^{-1}): (br) 3455 (**NH**). HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{22}N_5$ $[M + H]^+$, 236.1870; found, 236.1874.

*2-(3,5-Dimethylphenyl)-2-(1H-tetrazol-5-yl)piperidine (**10c**).* Yield: 0.244 g (95%). White solid, mp 232−233 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.39−1.47 (m, 1H), 1.55−1.67 (m, 3H), 2.15−2.28 (m, 7H, incl. 2.17 (s, 6H)), 2.74−2.80 (m, 1H), 2.86−2.93 (m, 1H), 2.98−3.05 (m, 1H), 6.87 (m, 1H), 7.03 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 19.7, 21.0, 21.8, 33.4, 41.8, 60.9, 123.5, 128.9, 137.3, 142.2, 160.9. IR (ν, cm^{-1}): (br) 3400 (**NH**). HRMS (ESI) *m*/*z*: calcd for $C_{14}H_{20}N_5$ $[M + H]^+$, 258.1713; found, 258.1704.

*2-Butyl-2-(1H-tetrazol-5-yl)azepane (**10d**).* Yield: 0.220 g (98%). White solid, mp 198−200 °C (dec). ^{1}H NMR (DMSO-d_6): δ 0.74 (t, 3H, *J* = 7.3 Hz), 0.92−0.98 (m, 2H), 1.08−1.16 (m, 2H), 1.44−1.82 (m, 6H), 1.86−2.07 (m, 3H), 2.40−2.47 (m, 1H), 2.98−3.04 (m, 1H), 3.15−3.21 (m, 1H), 4.00 (br, 2H). ^{13}C NMR (DMSO-d_6): δ 13.8, 21.3, 22.2, 25.1, 25.3, 27.3, 35.3, 39.2, 42.7, 62.9, 161.3. IR (ν, cm^{-1}): (br) 3400 (**NH**). HRMS (ESI) *m*/*z*: calcd for $C_{11}H_{22}N_5$ $[M + H]^+$, 224.1870; found, 224.1874.

*2-Phenyl-2-(1H-tetrazol-5-yl)azepane (**10e**).* Yield: 0.219 g (90%). White solid, mp 195−197 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.48−1.75 (m, 5H), 2.48−2.51 (m, 1H), 2.54−2.62 (m, 1H), 2.66−2.73 (m, 1H), 3.03−3.07 (m, 2H), 7.23−7.38 (m, 5H). ^{13}C NMR (DMSO-d_6): δ 22.1, 26.8, 27.3, 37.8, 43.3, 64.3, 126.3, 127.5, 128.3, 142.8, 162.8. IR (ν, cm^{-1}): (br) 3400 (**NH**). Anal. Calcd for $C_{13}H_{17}N_5 \cdot {}^1/_3H_2O$: C, 62.63; H, 7.14; N, 28.09. Found: C, 62.73; H, 6.99; N, 27.83.

Enantiomeric Resolution of 6e. Compound **6e** (1.645 g, 4.85 mmol) was dissolved in ethanol (10 mL). Tartaric acid (0.727 g, 4.85 mmol) was dissolved in ethanol (10 mL). The obtained solutions were mixed, and the precipitate was filtered off. The precipitate was recrystallized from 50 mL of ethanol. The salt obtained was converted into the free base by shaking with aqueous potassium carbonate and dichloromethane, and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. In this way, the *R* isomer of **6e** ($[\alpha]_D^{25}$ = +30.0° (*c* 1, CH_2Cl_2)) was isolated in 35% yield (0.58 g); mp 193−195 °C (tartrate). The liquor obtained after mixing amine **6e** with tartaric acid was evaporated and also converted into the free base by the procedure described above. By this means, the *S* isomer of **6e** ($[\alpha]_D^{25}$ = −30.0° (*c* 1, CH_2Cl_2)) was isolated in 40% yield (0.65 g); mp 152−154 °C (tartrate). The ^{1}H NMR spectra of diastereomeric salts were identical: ^{1}H NMR (DMSO-d_6): δ 0.25−0.36 (m, 1H), 0.57−1.07 (m, 6H), 1.28−1.33 (m, 3H), 1.40−1.51 (m, 6H), 1.64−1.67 (m, 1H), 1.97−2.04 (m, 1H), 2.58−2.61 (m, 1H), 2.73−2.76 (m, 1H), 3.53 (br, 8H inc. 4.29 (2H, s)), 5.95 and 6.03 (both d, 2H, *J* = 14.9 Hz), 7.30−7.40 (m, 5H).

*X-ray Diffraction Analysis of (R)-**6e** Tartrate Salt.* Crystals of the tartrate salt of (*R*)-**6e** ($C_{24}H_{35}N_5O_6$, *M* = 489.57 Da) at 100 K were monoclinic (space group $P2_1$) at 100 K: Crystal data: *a* = 7.5027(2) Å, *b* = 20.0377(6) Å, *c* = 8.6994(3) Å, β = 104.1532(5)°, *V* = 1268.14(7) $Å^3$, *Z* = 2 (*Z*′ = 1), d_{calc} = 1.282 g cm^{-3}, μ(Mo Kα) = 0.93 cm^{-1}, *F*(000) = 524. The intensities of 16 782 reflections were measured with a diffractometer [λ(Mo Kα) = 0.71072 Å, ω-scans, 2θ < 60°], and 3806 independent reflections (R_{int} = 0.0247) were used in further refinement. The structure was solved by direct methods and refined using the full-matrix least-squares technique against F^2 in the anisotropic/isotropic approximation. Hydrogen atoms were located from the Fourier synthesis of the electron density and refined in the isotropic approximation. For the tartrate salt of (*R*)-**6e**, the refinement converged to wR_2 = 0.0755 and GOF = 1.035 for all independent reflections [R_1 = 0.0330 was calculated against *F* for 3635 observed reflections with $I > 2\sigma(I)$]. All of the calculations were performed using SHELXTL PLUS 5.0. CCDC 933178 contains supplementary crystallographic data. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html.

(*R*)-2-(Cyclohexylmethyl)-2-(1*H*-tetrazol-5-yl)piperidine (10f). Compound **10f** was obtained from (*R*)-**6e** by the general procedure for debenzylation. Yield: 0.232 g (93%). White solid, mp 263−264 °C (dec). ^{1}H NMR (MeOD): δ 0.71−0.85 (m, 2H), 1.03−1.15 (m, 4H), 1.21−1.39 (m, 2H), 1.47−1.55 (m, 4H), 1.71−1.80 (m, 3H), 1.89−1.96 (m, 3H), 2.73−2.77 (m, 1H), 2.95−3.02 (m, 1H), 3.27−3.31 (m, 1H), 5.01(br, 2H). ^{13}C NMR (MeOD): δ 20.2, 23.2, 26.9, 27.0, 27.1, 33.4, 34.0, 35.5, 35.7, 42.8, 50.1, 61.0, 161.4. IR (ν, cm^{-1}): (b) 3370 (**NH**). $[\alpha]_D^{25}$ = +8.5° (*c* 1, methanol). HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{24}N_5$ $[M + H]^+$, 250.2026; found, 250.2029.

General Procedure for Organocatalytic Amination. Azodicarboxylate (**12a**, **12b**) (0.216 mmol) was added to a stirred solution of **10f** (5 mg, 0.02 mmol, 9 mol %) and 3-phenylpropanal (**11a**) (0.029 mL, 0.219 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at room temperature for 5 days. Next, the mixture was filtered through Celite, evaporated, and dissolved in MeOH (5 mL). The solution was cooled to 0 °C and treated with sodium borohydride (18 mg, 0.240 mmol). After 20 min, the reaction was quenched with aqueous NH_4Cl (10 mL), and the mixture was extracted with CH_2Cl_2, dried under anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate) to afford the pure α-aminated product (**13a**, **13b**), which was studied by chiral HPLC [Chiralpak AD-H column, 4.6 mm × 250 mm (95:5 hexane/*i*-PrOH, flow rate = 1.0 mL/min, λ = 210 nm)].

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*Diethyl 1-(1-Benzyl-2-hydroxyethyl)hydrazine-1,2-dicarboxylate (**13a**).* Yield: 0.058g (87%). 92% ee. White solid. ^{1}H NMR ($CDCl_3$): δ 1.25 (s, 3H), 1.39−1.91 (m, 3H), 2.69 (s, 2H), 3.58 (s, 2H), 3.86−4.45 (m, 5H), 4.45−4.97 (m, 2H), 6.38 (d, 1H), 7.04−7.37 (m, 5H). The spectroscopic data were in agreement with those in the literature.[22]

*Di-tert-butyl 1-(1-Benzyl-2-hydroxyethyl)hydrazine-1,2-dicarboxylate (**13b**).* Yield: 0.066 g (84%). >99% ee. White solid. ^{1}H NMR ($CDCl_3$): δ 1.28 and 1.37 (both s, 9H), 1.54 (s, 9H), 2.50−2.80 (m, 2H), 3.43−3.70 (m, 2H), 4.50−4.91 (m, 1H), 5.95 and 6.07 (both s, 1H), 7.09−7.40 (m, 5H). The spectroscopic data were in agreement with those in the literature.[23]

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all compounds, HPLC analysis of **13a** and **13b**, and X-ray data for the tartrate salt of (*R*)-**6e** (CIF). 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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