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The First Example of a Diastereoselective Thio-Ugi Reaction: A New Synthetic Approach to Chiral Imidazole Derivatives

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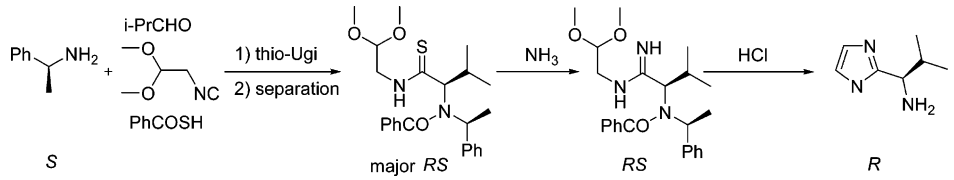

The first example of a diastereoselective thio-Ugi reaction with chiral α-methylbenzylamine is described. The reaction results in formation of two diastereomers of thioamides, the major of which was isolated. We have found that under similar conditions stereochemical results of the thio-Ugi reaction are opposite to stereochemical results of the Ugi reaction. Several chiral thioamides were synthesized. The reaction of thioamides with ammonia results in substituted amidines, which can be cyclized to imidazole derivatives in aqueous HCl. The synthesis of chiral imidazole derivatives was elaborated. Using certain approaches, both isomers of a key synthon in the synthesis of SB203386 (an orally bioactive HIV-1 protease inhibitor) were prepared. The scope, limitations, and stereochemistry of the approach are discussed.

Introduction

Imidazole is a common heterocyclic fragment of many biologically important small molecules, such as histidine, histamine, adenine, etc. There are also many effective pharmaceutical compounds and drugs containing the imidazole residue (Scheme 1).[1] Imidazoles containing a 2-aminoalkyl residue (for example **B** or **C**) are important building blocks for the synthesis of different natural products such as SB203386 (**A**) is an orally bioactive HIV-1 protease inhibitor.[2] 2-Arylaminoalkylimidazoles **D** (benzhydrylamine derivatives) containing an imidazole residue are interesting drug-like substances for medicinal chemistry.

There is no general method for the synthesis of different functionalized imidazole derivatives. Several protected 2-aminoalkylimidazoles have been prepared by reaction of imidazolium ylides (generated from N-substituted imidazole and Boc_2O) with imines.[3] Another method is based on reaction of imines with lithiated imidazoles.[4] Several imidazoles can be obtained starting from amino acids.[2,5] Several MCR approaches to imidazoles based on the TosMIC were described recently.[6] Consequently, new, efficient methodology for the preparation of imidazole derivatives would provide a valuable tool to synthetic organic chemists. This research is concerned with the development of a new synthetic approach to imidazole derivatives, based on the Ugi reaction.

The four-component Ugi reaction belongs to the most interesting diversity-generating reactions of modern organic and combinatorial chemistry. One of the most important applications of the Ugi reaction is the synthesis of the different type of heterocycles.[7] The thio-Ugi reaction (the Ugi MCR with thioacids) is an important approach to various thioamides[8] which have been used as amide bond surrogates in a number of

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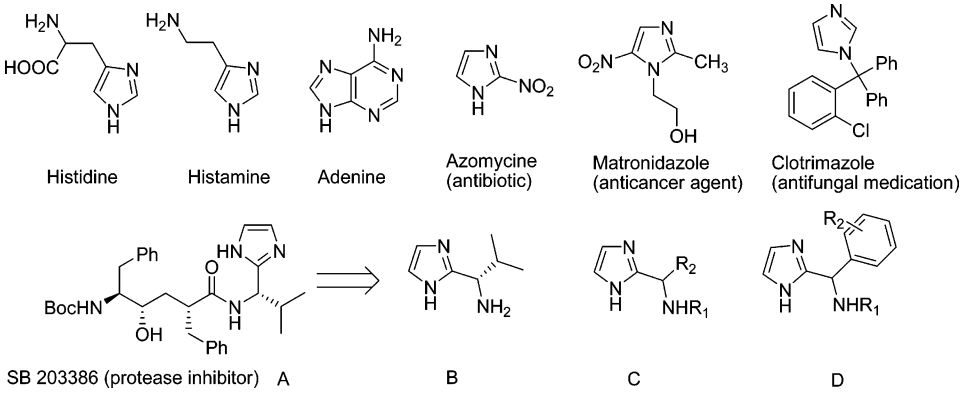
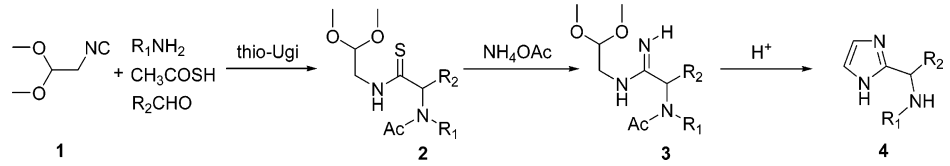
SCHEME 1. Imidazole Derivatives in Nature and Medicine



SCHEME 2. New Synthetic Approach to Imidazole Derivatives



biologically active peptides and incorporated into different natural molecules.[9] Asymmetric multicomponent reactions (AMCR) have a great importance and interest for chemists.[10] The thio-Ugi reaction has various synthetic applications, but no diastereoselectivity of the reactions has been investigated. However, development of diastereoselective thio-Ugi MCR can open new possibilities for organic and medicinal chemistry.

Results and Discussion

It has been demonstrated that the Ugi reaction with thioacids is an important approach to various thioamides. Thioamides are valuable precursors for many synthetic purposes. It is known that thioamides react with ammonia,[11] amines,[12] hydroxylamine,[13] acetamide,[14] hydrazine,[15] and other nucleophiles. Recently, Kazmaier developed an effective method for synthesis of the thiazole derivatives. The approach is based on the Ugi reaction with thioacids and 2,2-dimethoxyethylisocyanide, followed by cyclization under microwave irradiation using TMSI.[16] In this paper, we elaborate a new effective method for the synthesis of imidazoles bearing an aminoalkyl fragment in the 2-position. The synthesis is based on high reactivity of the thioamide bond in thiopeptides toward nucleophiles. We proposed that the thiopeptides prepared by the Ugi reaction using 2,2-dimethoxyethylisocyanide can be converted to amidines by treatment with ammonia.[11] Subsequent heterocyclization and deprotection of nitrogen can open an effective synthetic way to imidazole derivatives (Scheme 2).[17]

First, we decided to investigate the synthetic scope and limitations of the thio-Ugi reaction to prepare thioamides **2**. The influence of the amine and aldehyde components on the yield of the target thiopeptides was studied for this aim (Scheme 3).

We have investigated the influence of the amine component on the reaction using model 4-chlorobenzaldehyde or the isobutyraldehyde, isocyanide **1**, and thioacetic acid (Table 1). We found that target thioamides **2a**−**g** could be prepared

SCHEME 3. Synthesis of the Thiopeptides

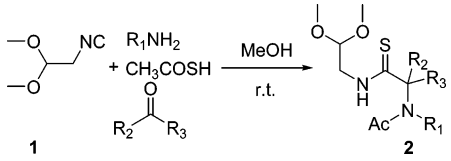
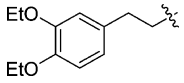


TABLE 1. Influence of Amine Component

entry	R_1	R_2	product	yield, %
1	Bn	4-ClPh	**2a**	45
2	$PhCH_2CH_2$	4-ClPh	**2b**	53
3	3,5-Me_2Ph	4-ClPh	**2c**	50
4	3-indolylCH_2CH_2	*i*-Pr	**2d**	64
5	cyclohexyl	*i*-Pr	**2e**	66
6	Me[a]	*i*-Pr	**2f**	65
7		*i*-Pr	**2g**	83

[a] Hydrochloride was used.

generally in good yield with alkyl amines and electron-rich anilines. Anilines bearing electron-withdrawing groups (for example, 4-F-aniline and 4-NO_2-aniline) and sterically hindered alkyl amines (*t*-$BuNH_2$) were almost unreactive in this process.

Second, using a model benzylamine, isocyanide **1**, and thioacetic acid, we investigated the relationship between the

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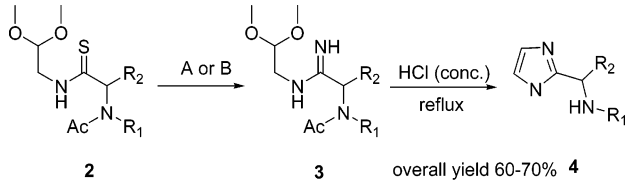
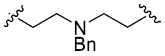
SCHEME 4. Synthesis of Imidazoles[a]



[a] **A** R_2 = Ar, NH_4OAc/EtOH, reflux; **B** R_2 = Alk, NH_4OAc/EtOH/NH_3(aq), reflux.

TABLE 2. Influence of Carbonyl Component, R_1 = Bn

entry	R_2	R_3	product	yield, %
8	4-ClPh	H	**2a**	45
9	Ph	H	**2h**	52
10	3-MePh	H	**2i**	57
11	4-MeOPh	H	**2j**	60
12	4-NO_2Ph	H	**2k**	15
13	2-thienyl	H	**2l**	25
14	*i*-Pr	H	**2m**	75
15	$-(CH_2)_5-$		**2n**	55
16	$-(CH_2)_4-$		**2o**	53
17			**2p**	48

structure of carbonyl compounds and the yield of the thiopeptides (Table 2). It was found that the effect of the structure of the carbonyl component on the reaction was very important. Benzaldehydes without an electron-withdrawing group (entries 8−11) and aliphatic aldehydes and ketones (entries 14−17) reacted smoothly. In general, the thio-Ugi reaction is a common and effective approach to different thioamides. However, in the case of electron-poor and heteroaromatic aldehydes, yields were lower (entries 12 and 13). Owing to steric sensitivity of the thio-Ugi reaction, acetophenone and diphenylketone did not give any Ugi products.

With these endothiopeptides **2** in hand, we began our investigations toward the imidazole synthesis. Transformation of thioamides in amidines is a well-known process.[13] We tested several reagents, such as NH_3(gas), NH_3(aq), NH_4Cl/EtOH, NH_3(aq)/HgO, NH_3(aq)/($Hg(OAc)_2$), and NH_4OAc/EtOH, and found that NH_4OAc in ethanol was the most effective reagent for such amidine **3** synthesis (Method A). If a thiopeptide contained alkyl residue (**2f**, **2g**, **2m**), addition of aqueous ammonia in the reaction mixture was necessary (Method B). Amidine **3** (R_1 = Bn, R_2 = 4-ClPh) was isolated in a yield of 82% and was characterized by ^{1}H NMR and ^{13}C NMR spectra. Using **3**, we have investigated several reagents for cyclization (AcOH, CF_3-COOH, NH_4Cl, HCl, and others) and found that HCl (concd) was the reagent of choice.

Amidines are not very stable compounds, and they can be transformed without isolation directly to imidazole derivatives by reflux in aqueous HCl. This permitted the development of short and straightforward syntheses of imidazoles directly from thio-Ugi products (Scheme 4). Reactions of the thioamides with NH_4Cl followed by cyclization of the amidines by reflux in concentrated HCl was accomplished by cleavage of the acetyl group and gave directly unprotected 2-aminoalkylimidazoles **4** in good yield (Table 3). A few thioamides, such as the α,α-disubstituted thioamides **2n**−**p**, prepared from ketones or labile in acidic conditions, and compounds **2d** and **2l** were not stable and decomposed completely. In general, this method allows synthesis of 2-aminoalkylimidazoles with different alkyl or aryl substitutes.

The thio-Ugi reaction has various synthetic applications, but no diastereoselective modification of the reaction has been investigated. A major obstacle to provide stereoinduction by the Ugi reaction is that it consequently follows sometimes different mechanisms under specific conditions.[18] Chiral amines

SCHEME 5. Investigation of the Stereoselectivity

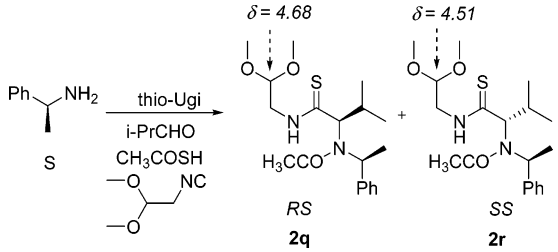


TABLE 3. Imidazoles, Obtained by Acidic Cyclization

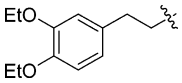
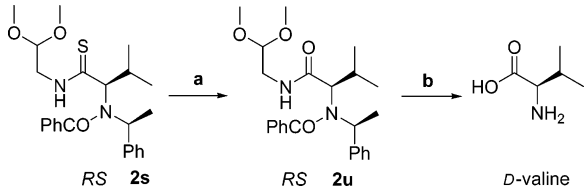
entry	thioamide	R_1	R_2	method	product	yield, %
18	**2a**	Bn	4-ClPh	A	**4a**	61
19	**2b**	$PhCH_2CH_2$	4-Cl−Ph	A	**4b**	72
20	**2f**	Me	*i*-Pr	B	**4f**	63
21	**2g**		*i*-Pr	B	**4g**	64
22	**2h**	Bn	Ph	A	**4h**	67
23	**2i**	Bn	3-MePh	A	**4i**	61
24	**2j**	Bn	4-MeOPh	A	**4j**	59
25	**2m**	Bn	*i*-Pr	B	**4m**	69

TABLE 4. Investigation of the Diastereoselectivity (*R*,*S*/S,S)

	0.01 mol/L	0.1 mol/L	1 mol/L
−22 °C	1.42	**2.56**	2.02
0 °C	1.78	1.14	1.72
20 °C	1.54	1.53	1.69

SCHEME 6. Determination of the Absolute Stereochemistry[a]



[a] Conditions: (a) $Hg(OAc)_2$/EtOH; (b) HCl (6 M), reflux, 12 h.

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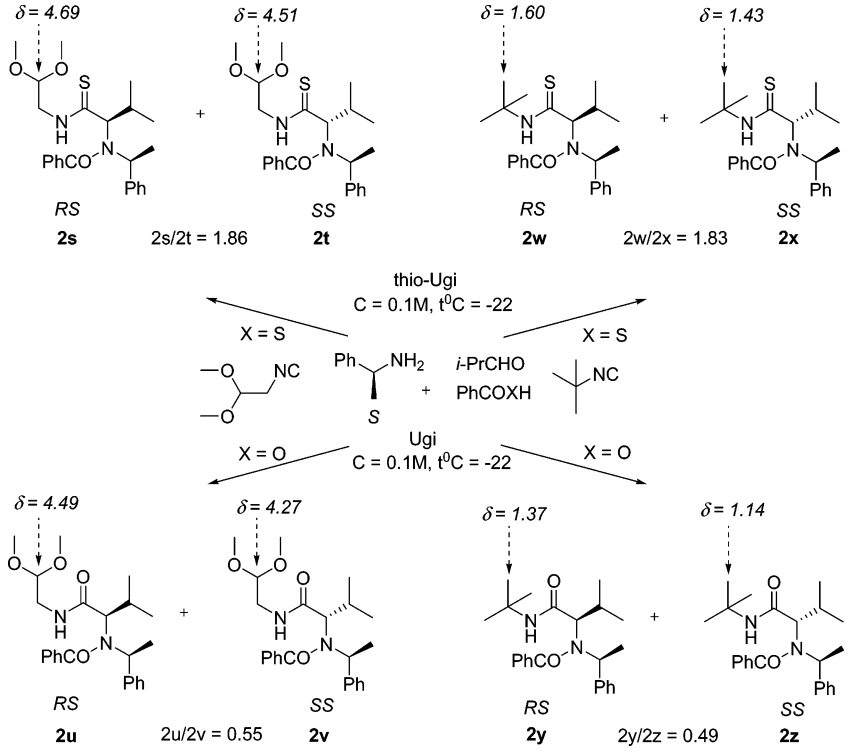
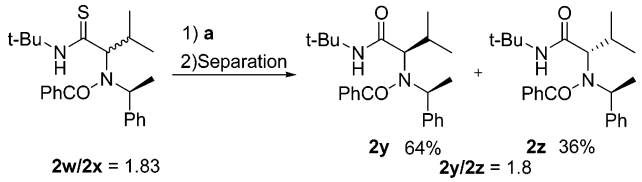
SCHEME 7. Stereoselectivity of the Ugi and Thio-Ugi Reaction[a]



[a] Isolated yields: **2s** (the less polar) 35%; **2u** (the less polar) 26%; **2v** (the more polar) 54%; **2y** (the less polar) 28%; and **2z** (the more polar) 50%.

SCHEME 8[a]



[a] Conditions: (a) $Hg(OAc)_2$, $EtOH/H_2O$, rt.

have been used several times to control the formation of a new stereogenic center in Ugi-4CR.[19] The most common amine for this aim was chiral α-methylbenzylamine, both enantiomers of which were commercially available substances. Therefore, we decided to investigate the stereochemistry of the thio-Ugi reaction to develop a new diastereoselective approach toward imidazole synthesis. Using (*S*)-α-methylbenzylamine as a model amine (Scheme 5), we investigated the dependence of stereoselectivity of the model reaction by temperature and concentrations of the reagents (all components were mixed in equimolar amounts). We found that the ratio of diastereoisomers depends significantly an both from temperature and concentrations of the reagents. It should be noted that the dependence is not linear. The best ratio of diastereomers (**2q**/**2r** 2.56) was observed in 0.1 M MeOH solution at −22 °C (Table 4). The ratio of the isomers was determined by GCMS analysis of the reaction mixtures. According to the ^{1}H NMR spectrum, we assigned the configuration of **2q** and **2r** by chemical shift of the C**H**$(OMe)_2$ proton. *R*,*S*- and *S*,*R*-diastereomers have δ 4.68, and *S*,*S*- and *R*,*R*-diastereomers have δ 4.51 (see below). Unfortunately, the diastereomers could not be separated by column chromatography. We postulated that replacement of thioacetic acid by thiobenzoic acid would permit us to isolate pure diastereomers.

Fortunately, the reaction with thiobenzoic acid under the particular conditions resulted in two isomers (2:1 according GCMS). The major isomer **2s** (the more polar product) was isolated by column chromatography in a yield of 35%. To confirm the stereochemistry, the major product **2s** was converted to D-valine by transformation of the thioamide to an amide, followed by acidic hydrolysis, giving this amino acid with $[\alpha]_D$ −26.04 (*c* 0.42 M, 6 M HCl), in agreement with the literature data (Scheme 6).[20]

Consequently, the major product **2s** of the thio-Ugi reaction is the *R*,*S*-diastereomer. This result did not correlate with the usual stereochemical result of the Ugi reaction, the major product of which is the *S*,*S*-diastereomer (under the same conditions, $T = -20$ °C, $c = 0.1$ M, MeOH).[21]

We decided to study the stereochemistry of the Ugi reaction and thio-Ugi under the same conditions (Scheme 7) to compare

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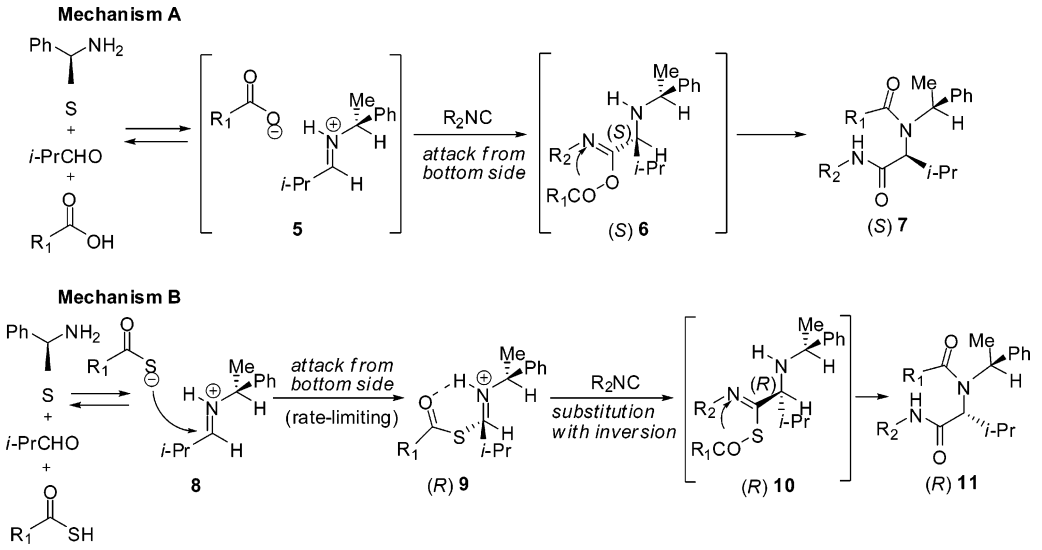
(20) See for example: Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176−185.

(21) (a) Ugi, I.; Offerman, K.; Herlinger, H.; Marquarding, D. *L. Ann. Der Chemie* **1967**, *709*, 1−10. (b) Kelly, C. L.; Lawrie, W. M. K.; Morgan, P.; Willis, C. L. *Tetrahedron Lett.* **2000**, *41*, 8001−8005.

SCHEME 9. Possible Mechanisms of the Ugi and Thio-Ugi Reactions

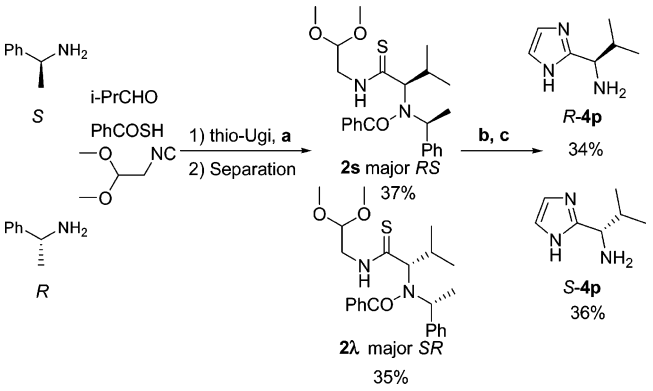


the stereochemical results. Unexpectedly, we observed inversion of the stereoselectivity upon replacement of benzoic acid by thiobenzoic acid. Specific chemical shift of the C**H**$(OMe)_2$ proton could be used for assignment of the absolute stereochemistry of **2s**−**v** by ^{1}H NMR analysis and characterization of the absolute stereochemistry of the products of Ugi and thio-Ugi reactions. Specific δ values of the thio product are 4.69 for *R*,*S*- and *S*,*R*- (**2s**) and 4.51 for *R*,*R*- and *S*,*S*-diastereomers (**2t**), while for similar Ugi products, they are 4.49 (**2u**) and 4.27 (**2v**), respectively. These δ values can be used for assignment of the absolute stereochemistry in cases of thioamides with other substituents on the asymmetric center.

Additional verification of these unexpected results was done using *tert*-butyl isocyanide (Scheme 7). To examine the ratio of diastereomers, we transformed the crude mixture of thioamides **2w** and **2x** to the mixture of oxo compounds **2y** and **2z**, which could be isolated by column chromatography (Scheme 8). The major isomer in the mixture of amides was **2y**, and the major isomer in the mixture of thioamides was **2w**. This result confirms again the inversion of stereochemical preference in the thio-Ugi reaction. The assignment of the absolute stereochemistry of **2y** and **2z** was based on ^{1}H NMR chemical shift values for *tert*-butyl groups. Empirically, the chemical shift values for the *tert*-butyl groups of *R*,*S*- and *S*,*R*-forms of this compounds were in the range of δ 1.3−1.4, whereas chemical shifts for *R*,*R*- and *S*,*S*-diastereomers were δ 1.1.[22] We detected by ^{1}H NMR spectra of the mixture of **2w** and **2x** (predominance **2w**) that *tert*-butyl groups in thioamides also have specific δ values, namely, δ 1.60 for *R*,*S*- and *S*,*R*- (**2w**) and δ 1.43 for *R*,*R*- and *S*,*S*-diastereomers (**2x**). This NMR data can be used for further configuration assignment.

We propose that preferable formation of the *R*-diastereomer in the thio-Ugi reaction with (*S*)-α-methylbenzylamine can be explained in the detailed view of mechanism of the reaction. There are a number of mechanisms of the Ugi reaction described.[17] We believe that the mechanisms of Ugi and thio-Ugi reactions are different (Scheme 9). Carboxylic acids form salts with the imine **5** (Mechanism A) without further nucleophilic addition to the iminium center. Thereafter, an isocyanide attack occurs from the less sterically hindered side, and product **7** having the *S* configuration is formed. In the case of the thio-Ugi reaction (Mechanism B), the much more nucleophilic thiocarboxylate attacks **8** from the less sterically hindered side, and intermediate (*R*)-**9** is formed. Furthermore, an S_N2-type nucleophilic substitution with inversion of configuration of the formed stereocenter results in **10** as the *R*-isomer. Therefore, thioamide (*R*)-**11** is formed as the major diastereomer.

SCHEME 10. Synthesis of Chiral Imidazole Derivatives[a]



[a] Conditions: (a) $T = -22$ °C; $C = 0.1$ M in MeOH; (b) NH_4OAc, NH_3, EtOH, reflux; (c) HCl (concd), reflux.

Using a diastereoselective method for the synthesis of chiral thioamides **2s** (-*R*,*S*) and **2**λ (-*S*,*R*), we were successful in obtaining both isomers of **4p**, the key synthon in the synthesis of SB203386 (an orally bioactive HIV-1 protease inhibitor; Scheme 10). During acidic cyclization (6 M aq HCl, reflux), the α-methylbenzyl group, unlike the benzyl group, was removed, and the reaction led directly to the target imidazole in moderate yield. It should be noted that the proposed method of synthesis of the **4p** is rather short, simple, and very competitive compared to literature approaches. Starting from both enantiomers of α-methylbenzylamine, both *R*- and *S*-enantiomers of **4p** can be prepared very easily.

(22) (a) Marquarding, D.; Hoffman, P.; Heitzer, H.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 1969−1971. (b) Semple, J. E.; Wang, P. S.; Lysenko, Z.; Joullié, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505−7510.

Conclusion

In conclusion, we have studied for the first time a diastereoselective thio-Ugi reaction and investigated the influence of reaction conditions on the stereoselectivity. Chiral thioamides were prepared, and their absolute stereochemistry was determined. It was found that stereochemistry of the thio-Ugi reaction was opposite to the Ugi reaction. On the basis of one method of synthesis of the thioamides, we developed a new effective synthetic approach to imidazole derivatives. Starting from chiral thioamides, both isomers of chiral imidazole **4p**, a key synthon in the synthesis of SB203386, were synthesized. The scope, limitations, and stereochemistry of the approach were discussed.

Experimental Section

Preparation of Isocyanide 1. Isocyanide **1** was obtained by a literature procedure from aminoacetaldehyde dimethylacetal as a colorless liquid: yield 64%; bp 30 °C (1 Torr). *Attention, heating isocyanide 1 at a temperature higher than 60 °C can provoke an explosion.* Spectroscopic data correlated with literature data.[15]

General Procedure for Thio-Ugi Reaction. An aldehyde (1 mmol) and an amine (1 mmol) were dissolved in methanol (5 mL) and stirred for 15 min at rt. Then the reaction mixture was cooled to 0 °C, and the thioacetic acid (1 mmol) and isocyanide **1** (1 mmol) were added. The mixture stood overnight at room temperature. The solvent was removed in vacuo, and the crude product was purified by column chromatography.

Investigation of the Stereoselectivity. Investigation of the stereoselectivity was carried out according to a general procedure for a thio-Ugi reaction using (*S*)-α-methylbenzylamine with different temperatures and concentration. Crude mixtures were analyzed by GCMS.

***N*-Benzyl-*N*-{1-(4-chlorophenyl)-2-[(2,2-dimethoxyethyl)amino]-2-thioxoethyl}acetamide (2a):** yield 45%; yellow oil; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 3.35 (s, 3H), 3.38 (s, 3H), 3.80−3.85 (m, 2H), 4.5−4.8 (m, 3H), 6.04 (s, 1H), 7.03−7.08 (m, 2H), and 7.15−7.28 (m, 7 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 47.0, 52.3, 54.2, 69.8, 100.7, 126.3, 127.1, 128.2, 128.3, 130.2, 133.7, 134.0, 136.8, 172.8, 201.1. Anal. Calcd for $C_{21}H_{25}ClN_2O_3S$: C, 59.92; H, 5.99. Found: C, 59.97; H, 5.84.

***N*-{1-(4-Chlorophenyl)-2-[(2,2-dimethoxyethyl)amino]-2-thioxoethyl}-*N*-(2-phenylethyl)acetamide (2b):** yield 53%; white solid; mp 89−90 °C; R_f 0.50 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 3H), 2.45−2.55 (m, 1H), 2.75−2.85 (m, 1H), 3.34 (s, 3H), 3.36 (s, 3H), 3.54−3.65 (m, 1H), 3.70−3.90 (m, 3H), 4.57 (t, J = 5.3 Hz, 1 H), 6.04 (s, 1H), 7.03−7.08 (m, 2c), 7.14−7.37 (m, 7c), 9.0 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 36.0, 47.4, 52.5, 54.3, 72.4, 100.9, 126.7, 128.6, 128.7, 128.8, 129.4, 134.4, 137.6, 138.8, 172.2, 201.0. Anal. Calcd for $C_{22}H_{27}ClN_2O_3S$: C, 60.75; H, 6.26. Found: C, 60.70; H, 6.24.

***N*-Benzyl-*N*-[2-[(2,2-dimethoxyethyl)amino]-1-(3,5-dimethylphenyl)-2-thioxoethyl]acetamide (2c):** yield 50%; colorless oil; R_f 0.60 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1740 H cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 2.25 (s, 6H), 3.37 (s, 3H), 3.38 (s, 3H), 3.80−3.90 (m, 2H), 4.60 (t, J = 4.7 Hz, 1 H), 5.88 (s, 1H), 7.14−7.37 (m, 7H), 9.0 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 23.7, 47.3, 54.3, 76.2, 100.9, 117.6, 125.9, 128.5, 129.7, 130.1, 134.0, 139.4, 142.6, 172.2, 200.4. Anal. Calcd for $C_{22}H_{27}ClN_2O_3S$: C, 60.75; H, 6.26. Found: C, 60.50; H, 6.04.

***N*-(1-{[(2,2-Dimethoxyethyl)amino]carbonothioyl}-2-methylpropyl)-*N*-[2-(1*H*-indol-3-yl)ethyl]acetamide (2d):** yield 64%; yellow oil; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 3450, 2950, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H), 2.01 (s, 3H), 2.82−3.20 (m, 3H), 3.39 (s, 6H), 3.45−3.55 (m, 2H), 3.67−3.80 (m, 2H), 3.85−3.97 (m, 1H), 4.62 (t, J = 5.6 Hz, 1H), 7.01 (s, 1H), 7.10−7.22 (m, 2H), 7.35 (d, J = 8.1 Hz, 2H), 8.2 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 20.3, 22.5, 25.2, 28.0, 47.2, 54.1, 77.2, 100.9, 111.3, 111.8, 118.4, 119.5, 122.1, 122.5, 127.0, 136.2, 173.2, 202.7. Anal. Calcd for $C_{21}H_{31}N_3O_3S$: C, 62.19; H, 7.70. Found: C, 62.40; H, 7.64.

***N*-Cyclohexyl-*N*-(1-{[(2,2-dimethoxyethyl)amino]carbonothioyl}-2-methylpropyl)acetamide (2e):** yield 66%; yellow oil; R_f 0.50 (2:1 hexanes/ethyl acetate); IR (film) 3430, 2950, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (d, J = 6.5 Hz, 3H), 1.03 (d, J = 6.5 Hz, 3H), 1.10−1.33 (m, 4H), 1.47−1.75 (m, 4H), 1.82−1.92 (m, 2H), 2.15 (s, 3H), 2.87−2.99 (m, 1H), 3.35 (s, 3H), 3.36 (s, 3H), 3.42−3.50 (m, 1H), 3.69−3.69 (m, 1H), 3.77−3.87 (m, 2H), 4.57 (t, J = 5.56, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 21.0, 23.3, 24.7, 25.8, 26.0, 27.7, 31.1, 32.7, 47.1, 53.5, 53.8, 60.9, 76.2, 100.6, 173.1, 204.4. Anal. Calcd for $C_{17}H_{32}N_2O_3S$: C, 59.27; H, 9.36. Found: C, 59.04; H, 9.46.

***N*-(1-{[(2,2-Dimethoxyethyl)amino]carbonothioyl}-2-methylpropyl)-*N*-methylacetamide (2f):** yield 71%; colorless oil; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3 H), 2.07 (s, 3H), 2.47−2.60 (m, 1H), 3.04 (s, 3H), 3.34 (s, 3H), 3.35 (s, 3H), 3.75−3.85 (m, 2 H), 3.82−3.90 (m, 1H), 4.52 (t, J = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 19.7, 22.2, 27.6, 46.4, 54.1, 77.4, 100.8, 172.6, 201.4. Anal. Calcd for $C_{12}H_{24}N_2O_3S$: C, 52.15; H, 8.75. Found: C, 52.17; H, 8.54.

***N*-[2-(3,4-Diethoxyphenyl)ethyl]-*N*-(1-{[(2,2-dimethoxyethyl)amino]carbonothioyl}-2-methylpropyl)acetamide (2g):** yield 83%; yellow oil; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, J = 6.5 Hz, 3H), 1.04 (d, J = 6.5 Hz, 3H), 1.36−1.45 (m, 6H), 2.00 (s, 3H), 2.70−3.00 (m, 3H), 3.36 (s, 3H), 3.37 (s, 3H), 3.55−3.75 (m, 1H), 3.83−3.92 (m, 3H), 4.00−4.07 (m, 4H), 4.58 (t, J = 5.5 Hz, 1H), 6.65−6.80 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 20.2, 25.3, 28.0, 35.2, 44.4, 47.1, 54.0, 54.6, 64.6, 64.7, 77.3, 100.8, 113.7, 114.4, 121.0, 130.7, 147.5, 148.8, 173.1, 202.5. Anal. Calcd for $C_{23}H_{38}N_2O_5S$: C, 60.76; H, 8.42. Found: C, 60.40; H, 8.64.

***N*-Benzyl-*N*-{2-[(2,2-dimethoxyethyl)amino]-1-phenyl-2-thioxoethyl}acetamide (2h):** yield 52%; colorless oil; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 2960, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.34 (s, 3H), 3.36 (s, 3H), 3.75−3.90 (m, 2H), 4.42−4.46 (m, 1H), 6.02 (s, 1H), 7.0−7.09 (m, 2H), 7.12−7.35 (m, 8H), 8.5 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 47.2, 52.7, 54.3, 54.3, 70.6, 100.9, 126.6, 127.4, 127.7, 128.4, 128.5, 130.1, 133.7, 138.2, 172.8, 201.0. Anal. Calcd for $C_{21}H_{26}N_2O_3S$: C, 65.26; H, 6.78. Found: C, 65.36; H, 6.49.

***N*-Benzyl-*N*-[2-[(2,2-dimethoxyethyl)amino]-1-(3-methylphenyl)-2-thioxoethyl]acetamide (2i):** yield 57%; colorless oil; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 2960, 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.18 (s, 3H), 3.32 (s, 3H), 3.35 (s, 3H), 3.82 (s, 2H), 4.45−4.80 (m, 3H), 6.17 (s, 1H), 6.90−7.20 (m, 9H), 8.2 (br s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.3, 22.7, 47.2, 52.7, 54.4, 70.6, 101.0, 126.1, 126.5, 127.0, 128.3, 129.2, 130.1, 135.0, 138.2, 145.9, 157.9, 172.9, 202.5. Anal. Calcd for $C_{22}H_{28}N_2O_3S$: C, 65.97; H, 7.05. Found: C, 65.90, H, 6.95.

***N*-Benzyl-*N*-{2-[(2,2-dimethoxyethyl)amino]-1-(4-methoxyphenyl)-2-thioxoethyl}acetamide (2j):** yield 60%; colorless oil; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.32 (s, 3H), 3.34 (s, 3H), 3.71 (s, 3H), 3.77−3.85 (m, 2H), 4.50−4.80 (m, 3H), 6.17 (s, 1H), 6.67 (d, J = 7.6, 2H), 6.95 (d, J = 7.6, 2H), 7.10−7.20 (m, 5H), 8.11 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 47.2, 52.0, 54.4, 55.2, 70.1, 101.0, 113.8, 126.4, 127.0, 128.3, 130.7, 159.5, 172.8, 202.2. Anal. Calcd for $C_{22}H_{28}N_2O_4S$: C, 63.44; H, 6.78. Found: C, 63.38; H, 6.66.

***N*-Benzyl-*N*-{2-[(2,2-dimethoxyethyl)amino]-1-(4-nitrophenyl)-2-thioxoethyl}acetamide (2k):** yield 15%; colorless oil; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.37 (s, 3H), 3.38 (s, 3H), 3.70−

3.90 (m, 2H), 4.55−4.60 (m, 1H), 4.75 (s, 2H), 5.90 (s, 1H), 7.12−7.34 (m, 7H), 8.03 (d, J = 8.9, 2H), 9.1 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 47.4, 54.2, 54.3, 72.6, 100.7, 123.4, 127.4, 128.2, 128.3, 128.9, 142.8, 147.2, 172.8, 199.4. Anal. Calcd for $C_{21}H_{25}N_3O_5S$: C, 58.45; H, 5.84. Found: C, 58.58; H, 5.76.

***N*-Benzyl-*N*-{2-[(2,2-dimethoxyethyl)amino]-1-(2-thienyl)-2-thioxoethyl}acetamide (2l):** yield 25%; colorless oil; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 2970, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.34 (s, 3H), 3.35 (s, 3H), 3.70−3.90 (m, 2H), 4.48−4.57 (m, 1H), 4.70−4.81 (m, 2H), 6.17 (s, 1H), 6.83 (m, 1H), 6.93 (m, 1H), 7.03−7.08 (m, 2H), 7.15−7.25 (m, 4H), 8.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 47.3, 54.2, 54.3, 66.8, 101.0, 126.4, 126.6, 127.3, 127.4, 128.5, 129.4, 137.1, 140.1, 172.5, 200.5. Anal. Calcd for $C_{19}H_{24}N_2O_3S_2$: C, 58.14; H, 6.16. Found: C, 58.04; H, 6.26.

***N*-Benzyl-*N*-(1-{[(2,2-dimethoxyethyl)amino]carbonothioyl}-2-methylpropyl)acetamide (2m):** yield 75%; colorless oil; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.3 Hz, 3H), 2.11 (s, 3H), 2.70−2.90 (m, 1H), 3.42 (s, 6H), 3.77−3.83 (m, 2H), 3.82−3.90 (m, 1H), 4.55−4.65 (m, 3H), 7.20−7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 23.0, 23.1, 28.2, 30.9, 44.4, 46.9, 54.0, 100.8, 127.1, 172.6, 128.6, 135.1, 173.5, 201.8. Anal. Calcd for $C_{18}H_{28}N_2O_3S$: C, 61.33; H, 8.01. Found: C, 61.17; H, 8.04.

***N*-Benzyl-*N*-(1-{[(2,2-dimethoxyethyl)amino]carbonothioyl}-cyclohexyl)acetamide (2n):** yield 55%; white solid; mp 112−113 °C (lit.[15] 115 °C); R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10−1.22 (m, 1H), 1.35−1.60 (m, 5H), 1.85−1.93 (m, 2H), 2.06 (s, 3H), 2.83−2.92 (m, 2H), 3.40 (s, 6H), 3.83 (t, J = 5.3 Hz, 2H), 4.60 (t, J = 5.3 Hz, 1H), 4.73 (s, 2H), 7.20−7.35 (m, 5H), 9.0 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 24.7, 25.2, 35.1, 47.3, 49.8, 54.1, 69.3, 101.1, 125.9, 127.1, 128.8, 138.8, 174.5, 205.5. Anal. Calcd for $C_{20}H_{30}N_2O_3S$: C, 63.46; H, 7.99. Found: C, 63.31; H, 7.82.

***N*-Benzyl-*N*-(1-{[(2,2-dimethoxyethyl)amino]carbonothioyl}-cyclopentyl)acetamide (2o):** yield 53%; colorless oil, crystallized on standing; mp 96−97 °C; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52−1.63 (m, 4H), 1.87−1.98 (m, 2H), 1.99 (s, 3H), 2.87−2.97 (m, 2H), 3.36 (s, 6H), 3.79 (t, J = 5.3 Hz, 2H), 4.55 (t, J = 5.3 Hz, 1H), 4.72 (s, 2H), 7.15−7.35 (m, 5H), 8.8 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 22.0, 37.9, 47.3, 52.0, 53.9, 77.3, 100.7, 125.3, 126.9, 128.7, 138.6, 174.0, 205.9. Anal. Calcd for $C_{19}H_{28}N_2O_3S$: C, 62.61; H, 7.74. Found: C, 62.41; H, 7.65.

***N*-Benzyl-*N*-(1-benzyl-4-{[(2,2-dimethoxyethyl)amino]-carbonothioyl}piperidin-4-yl)acetamide (2p):** yield 48%; colorless oil; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02 (s, 3H), 2.05−2.20 (m, 4H), 2.67 (d, J = 11.6 Hz, 2H), 3.13 (d, J = 11.6 Hz, 2H), 3.35 (s, 2H), 3.41 (s, 6H), 3.86 (t, J = 5.3 Hz, 2H), 4.62 (t, J = 5.3 Hz, 1H), 4.71 (s, 2H), 7.20−7.35 (m, 10H), 9.2 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 30.9, 34.6, 47.4, 50.0, 58.2, 62.4, 77.2, 105.8, 121.8, 125.9, 128.0, 128.5, 128.7, 128.8, 135.3, 136.4, 167.3, 203.4. Anal. Calcd for $C_{26}H_{35}N_3O_3S$: C, 66.49; H, 7.51. Found: C, 66.31; H, 7.52.

***N*-((1*R*)-1-{[(2,2-Dimethoxyethyl)amino]carbonothioyl}-2-methylpropyl)-*N*-[(1*S*)-1-phenylethyl]benzamide (2s):** yield 37%; colorless oil; R_f 0.4 (3:1 hexanes/ethyl acetate); IR (film) 2940, 1750 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.37 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H), 1.69 (d, J = 7.1, 3H), 2.90−3.00 (m, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 3.77−3.82 (m, 1H), 3.97−4.05 (m, 2H), 4.70 (t, J = 5.6 Hz, 1H), 5.12 (q, J = 7.1 Hz, 1H), 7.20−7.55 (m, 10H), 10.4 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 20.3, 20.6, 28.3, 47.2, 53.5, 54.0, 60.2, 75.2, 100.6, 128.5, 128.6, 128.9, 129.0, 129.5, 137.5, 138.23, 174.42, 205.42; $[\alpha]^{20}_D$ −174.16 (*c* 0.05 M, MeOH). Anal. Calcd for $C_{24}H_{32}N_2O_3S$: C, 67.26; H, 7.53. Found: C, 67.26; H, 7.33.

***N*-((1*R*)-1-{[(2,2-Dimethoxyethyl)amino]carbonyl}-2-methylpropyl)-*N*-[(1*S*)-1-phenylethyl]benzamide (2u):** yield 26%; colorless oil; R_f 0.6 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1740 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.31 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H), 1.55 (d, J = 7.1 Hz, 3H), 2.87−3.00 (m, 1H), 3.20−3.40 (m, 2H), 3.37 (s, 3H), 3.36 (s, 3H), 3.50−3.60 (m, 1H), 4.49 (t, J = 5.6 Hz, 1H), 5.06 (q, J = 7.1 Hz, 1H), 7.27−7.35 (m, 5H), 7.42−7.52 (m, 5H), 8.4 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 19.7, 19.8, 24.3, 53.0, 53.7, 59.1, 68.7, 101.9, 125.5, 128.4, 128.4, 128.9, 129.3, 137.7, 138.4, 173.4, 173.8; $[\alpha]^{20}_D$ −87.48 (*c* 0.05 M, MeOH). Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82. Found: C, 69.70; H, 7.53.

***N*-((1*S*)-1-{[(2,2-Dimethoxyethyl)amino]carbonyl}-2-methylpropyl)-*N*-[(1*S*)-1-phenylethyl]benzamide (2v):** yield 54%; colorless oil, crystallizes on standing; mp 110−112 °C; R_f 0.4 (2:1 hexanes/ethyl acetate); IR (film) 2950, 1740 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.00 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H), 1.65 (d, J = 6.8 Hz, 3H), 3.00−3.15 (m, 2H), 3.39 (s, 3H), 3.40 (s, 3H), 4.27 (t, J = 5.8 Hz, 1H), 5.13 (q, J = 6.8 Hz, 1H), 7.7−7.35 (m, 5H), 7.48−7.60 (m, 5H), 8.4 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 19.8, 20.7, 26.6, 40.2, 52.8, 54.0, 58.1, 69.5, 101.8, 126.3, 127.5, 128.3, 128.9, 130.0, 137.3, 138.5, 173.6, 179.9; $[\alpha]^{20}_D$ −12.77 (*c* 0.05 M, MeOH). Anal. Calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82. Found: C, 69.80; H, 7.77.

***N*-{(1*R*)-1-[(*tert*-Butylamino)carbonyl]-2-methylpropyl}-*N*-[(1*S*)-1-phenylethyl]benzamide (2y):** yield 28%; colorless oil; R_f 0.6 (2:1 hexanes/ethyl acetate); IR (film) 2960, 1760 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.30 (d, J = 6.5 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H), 1.37 (s, 9H), 1.57 (d, J = 7.1 Hz, 3H), 2.85−2.95 (m, 1H), 3.05 (d, J = 10.9 Hz, 1H), 5.11 (q, J = 7.1 Hz, 1H), 7.23−7 35 (m, 5H), 7.42−7.55 (m, 5H), 8.2 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 19.7, 19.8, 27.5, 28.7, 50.5, 59.3, 70.2, 125.4, 128.4, 128.7, 129.1, 129.3, 137.8, 138.5, 172.4, 173.1. Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48. Found: C, 75.55; H, 8.28 (lit.[22]).

***N*-((1*S*)-1-{[(2,2-Dimethylpropyl)amino]carbonyl}-2-methylpropyl)-*N*-[(1*S*)-1-phenylethyl]benzamide (2z):** yield 50%, colorless oil; R_f 0.5 (2:1 hexanes/ethyl acetate); IR (film) 2960, 1760 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.00 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H), 1.15 (s, 9H), 1.62 (d, J = 6.8 Hz, 3H), 2.95−3.20 (m, 2H), 5.11 (q, J = 6.8 Hz, 1H), 7.15−7 30 (m, 5H), 7.45−7.60 (m, 5H), 8.3 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 19.7, 19.8, 20.6, 27.5, 28.6, 50.4, 59.2, 70.1, 125.4, 128.3, 128.6, 129.0, 129.3, 137.8, 138.4, 172.4, 173.1. Anal. Calcd for $C_{24}H_{32}N_2O_2$: C, 75.75; H, 8.48. Found: C, 76.00; H, 8.69 (lit.[22]).

***N*-((1*S*)-1-{[(2,2-Dimethoxyethyl)amino]carbonothioyl}-2-methylpropyl)-*N*-[(1*R*)-1-phenylethyl]benzamide (2λ):** yield 35%; colorless oil; R_f 0.4 (3:1 hexanes/ethyl acetate); IR (film) 2940, 1750 cm^{-1}; ^{1}H NMR (400 MHz) δ 0.37 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H), 1.69 (d, J = 7.1, 3H), 2.90−3.00 (m, 1H), 3.43 (s, 3H), 3.42 (s, 3H), 3.77−3.82 (m, 1H), 3.97−4.05 (m, 2H), 4.69 (t, J = 5.6 Hz, 1H), 5.12 (q, J = 7.1 Hz, 1H), 7.20−7.55 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 20.3, 20.6, 28.3, 47.2, 53.5, 54.0, 60.2, 75.2, 100.6, 128.5, 128.6, 128.9, 129.0, 129.5, 137.5, 138.23, 174.42, 205.42; $[\alpha]^{20}_D$ +177.02 (*c* 0.05 M, MeOH). Anal. Calcd for $C_{24}H_{32}N_2O_3S$: C, 67.26; H, 7.53. Found: C, 67.33; H, 7.66.

General Procedure for Hydrolysis of Thioamides: To the solution of thioamide **2s** (1 mmol) in ethanol was added a solution of the $Hg(OAc)_2$ (318 mg, 1 mmol) in water (1 mL). The reaction mixture was stirred overnight, black precipitate was filtered off, and filtrate was evaporated and purified by column chromatography. The yield of amide **2u** was about 60%.

A suspension of amide **2u** (1 mmol) was refluxed in 6 M HCl (3 mL) for 6 h. A precipitate was filtered off. The reaction mixture was evaporated, and the residue was dissolved in H_2O (5 mL) and extracted with CH_2Cl_2 (2 × 5 mL). After evaporation of the aqueous phase, recrystallization of the residue (H_2O) afforded D-valine: yield 11%; $[\alpha]^{20}_D$ −26.04 (*c* 0.42 M, 6 M HCl). The ^{1}H NMR spectrum and melting point correlated with literature data.[19]

***N*-Benzyl-*N*-{1-(4-chlorophenyl)-2-[(2,2-dimethoxyethyl)amino]-2-iminoethyl}acetamide 3:** Thioamide **2a** (1 mmol) was dissolved in ethanol (10 mL). Then NH_4OAc (2 g) was added. The reaction mixture was refluxed overnight. The solvent was removed in vacuo above 40 °C. The solid residue was treated with 1 M aq K_2CO_3. The mixture was extracted with 1 M aq H_2Cl_2, dried over K_2CO_3, and the solvent was removed in vacuo. The amidine **3** was obtained (82%) as a gray solid: mp 160−165 °C; R_f 0.55 (2:1 hexanes/ethyl acetate); IR (Nujol) 2950, 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.34 (d, $J = 6.2$ Hz, 1H), 3.50 (s, 6H), 4.43 (d, $J = 5.3$ Hz, 2H), 4.95 (t, $J = 5.5$ Hz, 1H), 5.12 (s, 2H), 6.87−6.95 (m, 2H), 7.30−7.35 (m, 5**H**), 7.46 (d, $J = 8.6$, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 47.3, 48.9, 56.6, 77.0, 103.1, 125.37, 128.4, 128.8, 129.3, 131.7, 133.9, 134.3, 139.2, 147.0, 172.7. Anal. Calcd for $C_{21}H_{26}ClN_3O_3$: C, 62.45; H, 6.49. Found: C, 62.38; H, 6.56.

General Procedure for Imidazole Synthesis. Method A: A thiopeptide (1 mmol) was dissolved in ethanol (10 mL). Then NH_4OAc (2 g) was added. The reaction mixture was held at reflux overnight, and the solvent was removed in vacuo above 40 °C. The solid residue was dissolved in concd HCl (10 mL). The reaction mixture was held at reflux overnight, and the solvent was removed in vacuo. The residue was made alkaline with saturated K_2CO_3 solution (10%), and the product was extracted with CH_2Cl_2 (3 × 10 mL). After drying the organic layer over K_2CO_3, the solvent was removed in vacuo, and the crude product was purified by column chromatography.

Method B: A thiopeptide (1 mmol) was dissolved in ethanol (10 mL). Then NH_4OAc (2 g) and aq NH_3 (2 mL) were added. The reaction mixture was refluxed for 40 h, and the solvent was removed in vacuo above 40 °C. Further treatment was according to Method A.

***N*-Benzyl-*N*-[(4-chlorophenyl)(1*H*-imidazol-2-yl)methyl]-amine (4a):** Method A; yield 61%; gray solid; mp 115−117 °C; R_f 0.5 (4:1:0.1 acetonitrile/methanol/NH_3(aq)); IR (Nujol) 3130 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.3 (br s, NH), 5.60 (s, 2H), 6.87−7.03 (m, 2H), 7.25−7.45 (m, 7H), 7.56 (s, 2H), 9.0 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.7, 77.2, 120.3, 121.9, 123.6, 126.2, 128.7, 129.4, 130.0, 130.5, 133.2, 136.8, 136.8. Anal. Calcd for $C_{17}H_{16}ClN_3$: C, 68.57; H, 5.32. Found: C, 68.40; H, 5.05.

***N*-[(4-Chlorophenyl)(1*H*-imidazol-2-yl)methyl]-2-phenylethanamine (4b):** Method A; yield 72%; gray solid; mp 130−131°C; R_f 0.5 (4:1:0.1 acetonitrile/methanol/NH_3(aq)); IR (Nujol) 3110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.84 (t, $J = 6.1$ Hz, 2H), 3.03 (br s, NH), 4.72 (t, $J = 6.1$ Hz, 2H), 6.75−6.80 (m, 2H), 7.10−7.20 (m, 3H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.35−7.40 (m, 2H), 7.46 (d, $J = 8.4$ Hz, 2H), 8.9 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.5, 49.0, 77.2, 120.3, 121.5, 123.8, 127.6, 129.0, 130.1, 130.6, 135.5, 136.3, 36.8. Anal. Calcd for $C_{18}H_{18}ClN_3$: C, 69.34; H, 5.82. Found: C, 69.50; H, 5.63.

***N*-[1-(1*H*-Imidazol-2-yl)-2-methylpropyl]-*N*-methylamine (4f):** Method B; yield 63%; white solid; mp 130−131°C; R_f 0.5 (4:1:0.1 acetonitrile/methanol/NH_3(aq)); IR (Nujol) 3140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, $J = 7.1$ Hz, 6H), 3.10−3.25 (m, 3H), 4.01 (s, 3H), 7.35 (s, 2H), 8.8 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 24.4, 33.5, 77.2, 119.6, 121.3, 128.9. Anal. Calcd for $C_8H_{15}N_3$: C, 62.71; H, 9.87. Found: C, 63.00; H, 10.12.

***N*-[2-(3,4-Diethoxyphenyl)ethyl]-*N*-[1-(1*H*-imidazol-2-yl)-2-methylpropyl]amine (4g):** Method B; yield 64%; gray solid; mp 123−124°C; R_f 0.5 (4:1:0.1 acetonitrile/methanol/NH_3(aq)); IR (Nujol) 3140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, $J = 6.9$ Hz, 6H), 1.33 (t, $J = 7.1$ Hz, 3H), 1.38 (t, $J = 7.1$ Hz, 3H), 2.75−2.85 (m, 2H), 2.90 (s, 1H), 3.00 (t, $J = 6.9$ Hz, 2H), 3.92 (q, $J = 7.1$ Hz, 2H), 4.05 (q, $J = 7.1$ Hz, 2H), 4.57 (t, $J = 6.9$ Hz, 2H), 6.42 (d, $J = 8.0$ Hz, 1H), 6.51 (s, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 7.35 (s, 2H), 8.6 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7, 21.2, 24.3, 35.8, 48.4, 64.5, 64.7, 77.3, 113.7, 114.1, 121.0, 121.7, 128.2, 129.0, 134.6, 148.3, 149.1. Anal. Calcd for $C_{19}H_{29}N_3O_2$: C, 68.85; H, 8.82. Found: C, 68.80; H, 8.60.

***N*-Benzyl-*N*-[1*H*-imidazol-2-yl(phenyl)methyl]amine (4h):** Method A; yield 67%; gray solid; mp 119−120°C; R_f 0.5 (4:1:0.1 acetonitrile/methanol/NH_3(aq)); IR (Nujol) 3120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.3 (br s, NH), 5.74 (s, 2H), 6.94−7.02 (m, 2H), 7.23−7.30 (m, 3H), 7.37−7.50 (m, 7H), 9.1 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.5, 77.2, 120.4, 121.8, 125.2, 126.3, 128.6, 129.3, 129.8, 130.5, 133.4, 136.6. Anal. Calcd for $C_{17}H_{17}N_3$: C, 77.54; H, 6.51. Found: C, 77.16; H, 6.15.

***N*-Benzyl-*N*-[1*H*-imidazol-2-yl(3-methylphenyl)methyl]-amine (4i):** Method A; yield 61%; gray crystals; mp 130−131°C; R_f 0.5 (4:1:0.1 acetonitrile/methanol/NH_3(aq)); IR (Nujol) 3110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.3 (br s, NH), 5.70 (s, 2H), 6.97−6.99 (m, 2H), 7.14−7.33 (m, 5H), 7.52 (s, 2H), 9.1 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 50.5, 77.2, 120.2, 122.0, 124.0, 125.1, 126.2, 126.4, 128.7, 129.3, 129.6, 131.3, 133.5, 136.3, 139.9. Anal. Calcd for $C_{18}H_{18}ClN_3$: C, 69.34; H, 5.82. Found: C, 69.50; H, 5.63.

***N*-Benzyl-*N*-[1*H*-imidazol-2-yl(4-methoxyphenyl)methyl]-amine (4j):** Method A; yield 59%; white solid; mp 114−115 °C; R_f 0.5 (4:1:0.1 acetonitrile/methanol/NH_3(aq)); IR (Nujol) 3110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.24 (s, 3H), 5.77 (s, 2H), 6.91−7.00 (m, 2H), 7.20−7.30 (m, 3H), 7.36−7.49 (m, 6H), 9.1 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.5, 77.2, 120.2, 121.8, 123.0, 126.2, 128.7, 129.4, 129.5, 130.0, 133.1, 135.8, 136.4. Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53. Found: C, 73.79; H, 6.20.

***N*-Benzyl-*N*-[1-(1*H*-imidazol-2-yl)-2-methylpropyl]amine (4m):** Method B; yield 69%; white solid; mp 127−130 °C; R_f 0.5 (4:1:0.1 acetonitrile/methanol/NH_3(aq)); IR (Nujol) 3130 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, $J = 6.9$ Hz, 6H), 3.05−3.15 (m, 3H), 5.69 (s, 2H), 6.97−7.03 (m, 2H), 7.25−7.35 (m, 3H), 7.40 (s, 2H), 8.9 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 24.5, 49.8, 77.2, 119.9, 121.8, 125.9, 128.7, 129.4, 133.0, 135.2. Anal. Calcd for $C_{14}H_{19}N_3$: C, 73.33; H, 8.35. Found: C, 73.07; H, 8.25.

[(1*R*)-1-(1*H*-Imidazol-2-yl)-2-methylpropyl]amine (*R*)-4p: Method B; yield 34%; yellow oil; R_f 0.5 (4:1:0.1 acetonitrile/methanol/NH_3(aq)); IR (Nujol) 3140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, $J = 6.8$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H), 1.9 (br s, 2H), 2.15−2.25 (m, 1H), 4.10 (d, $J = 5.3$ Hz, 1H), 7.22 (d, $J = 3.0$ Hz, 1H), 7.70 (d, $J = 3.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 19.4, 34.8, 59.6, 118.3, 142.3, 176.7; $[\alpha]^{20}_D$ −2.4 (*c* 0.027 M, MeOH). Anal. Calcd for $C_7H_{13}N_3$: C, 60.40; H, 9.41. Found: C, 60.80; H, 9.67.

[(1*S*)-1-(1*H*-Imidazol-2-yl)-2-methylpropyl]amine (*S*)-4p: Method B; yield 36%; yellow oil; R_f 0.5 (4:1:0.1 acetonitrile/methanol/NH_3(aq)); IR (Nujol) 3140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, $J = 6.8$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H), 1.9 (br s, 2H), 2.15−2.25 (m, 1H), 4.10 (d, $J = 5.3$ Hz, 1H), 7.22 (d, $J = 3.3$ Hz, 1H), 7.70 (d, $J = 3.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 19.4, 34.8, 59.6, 118.3, 142.3, 176.7; $[\alpha]^{20}_D$ +2.8 (*c* 0.03 M, MeOH). Anal. Calcd for $C_7H_{13}N_3$: C, 60.40; H, 9.41. Found: C, 60.74; H, 9.57.

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Supporting Information Available: ^1H and ^{13}C NMR spectral data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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