Iodoacetic Acid is an Efficient Reagent for the Synthesis of Amino Acid Derived 2-Aminobenzimidazoles

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Abstract: Chiral, nonracemic, N-unprotected amino acids were converted into the corresponding *N*-benzimidazol-2-yl derivatives by a sequential procedure involving initial formation of isothiocyanates, their reaction with arene-1,2-diamines, and cyclization–desulfurization of the intermediate thioureas with iodoacetic acid. The simplified workup and the lack of volatile or toxic byproducts in the key desulfurization step renders iodoacetic acid a superior reagent to the usual reagent, iodomethane.

Key words: amino acids, cyclization, desulfurization, green chemistry, heterocycles

2-Aminobenzimidazoles are important pharmacophores and are useful as scaffolds in the development of new drugs.[1] A number of medicines, such as mebendazole, astemizole, and the drug candidate maribavir, contain a 2-aminobenzimidazole subunit (Figure 1). As part of our drug-discovery efforts, we became interested in an efficient approach to L-cysteine derivatives **1** containing 2-(alkylamino)benzimidazole residues (Figure 1). Related amino acid-containing 2-(alkylamino)benzimidazoles have been developed as integrin α4β1 antagonists,[2] inhibitors of peptidylprolyl isomerase,[3] antagonists of fibrinogen gpIIb/IIIa,[4] and modulators of melanocortin MC4 receptors.[5]

Although a number of methods have been reported for the preparation of 2-aminobenzimidazoles,[1a,6] the presence of a chiral nonracemic L-cysteine moiety in benzimidazole **1** limits the choice of suitable synthetic approaches. Introduction of an amine moiety at the 2-position of benzimidazole by nucleophilic substitution of a suitable leaving group[7] (Figure 2, route A) requires the presence of a strong base and high temperature, which might cause racemization of the L-cysteine moiety. Likewise, the synthesis of 2-aminobenzimidazoles by a palladium-

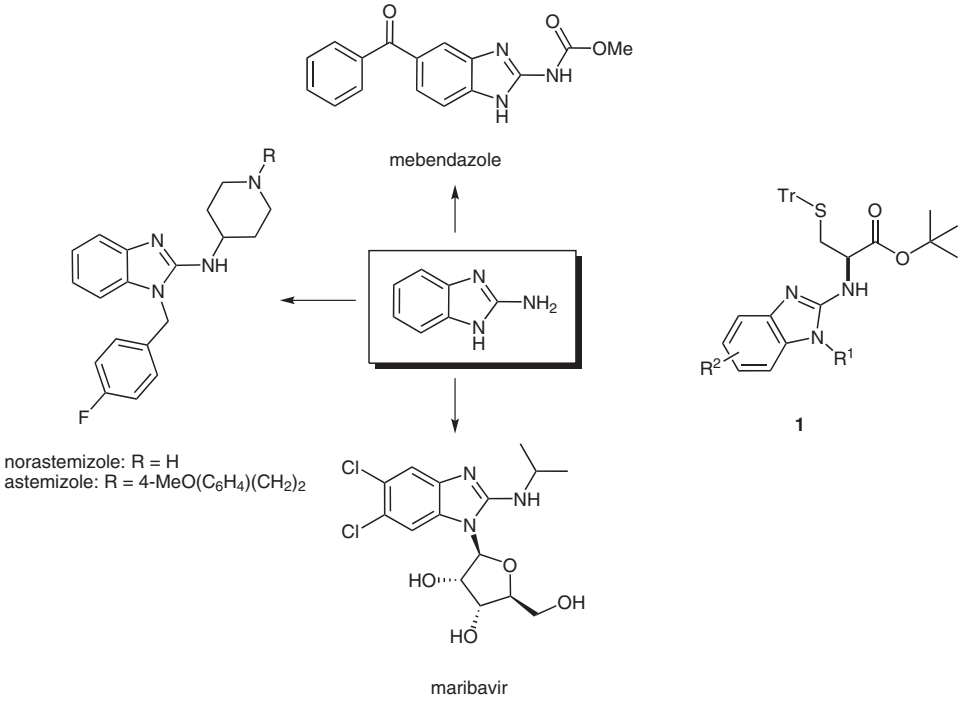

Figure 1 Pharmacologically active 2-aminobenzimidazoles

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catalyzed C–H activation reaction,[8] in a Buchwald–Hartwig C–N bond-forming process[9] (Figure 2, route A) or by an intramolecular copper-catalyzed arylation of guanidines[10] (Figure 2, route B) requires harsh conditions that would not appear to be compatible with the fragile L-cysteine moiety.[11] We therefore required an approach that would involve considerably milder conditions for the preparation of the desired benzimidazole **1**, so we chose a method based on desulfurization and cyclization of the corresponding substituted thiourea (Figure 2, route C).

We obtained the required thiourea as an inseparable mixture of regioisomers **5bA** and **5bB** by a two-step procedure involving treatment of L-cysteine (**2**) with thiophosgene,[12] followed by reaction of the intermediate isothiocyanate **3** with *N*-methylbenzene-1,2-diamine (**4b**) (Scheme 1). We attempted the subsequent conversion of the thioureas **5bA** and **5bB** into the target benzimidazole **1b** under various published conditions. The use of metal salts such as mercury(II) oxide[13] or copper(I) oxide[14] afforded poor yields (<20%) of the desired product **1**, as did the use of carbodiimides[15] or diacetyl(phenyl)-λ^3-iodane[16] (Table 1, entries 1–3 and 6). The use of tosyl chloride and sodium hydroxide[17] or of 2-chloro-1,3-dimethyl-1*H*-imidazol-3-ium chloride (DMC) was also unsuccessful, giving a ~40% yield of **1b** in each case (entries 4 and 5, respectively).[18]

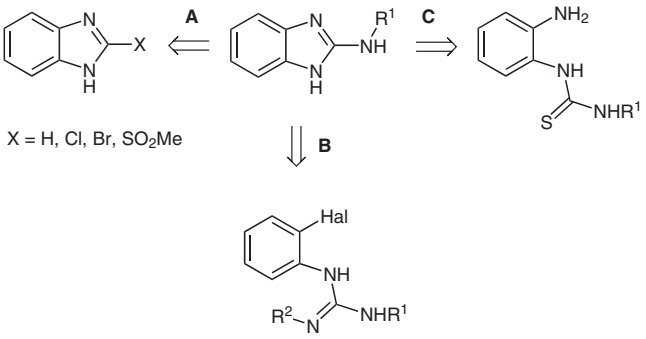
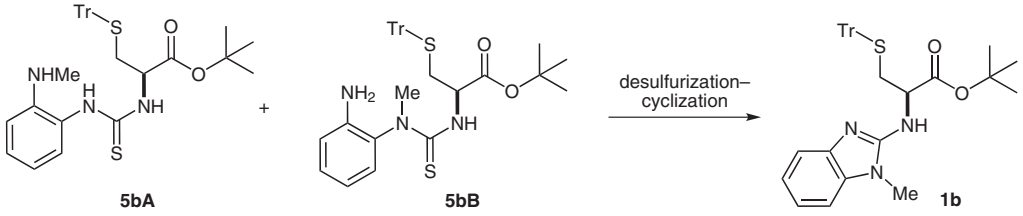


Figure 2 Options for the synthesis of 2-aminobenzimidazoles

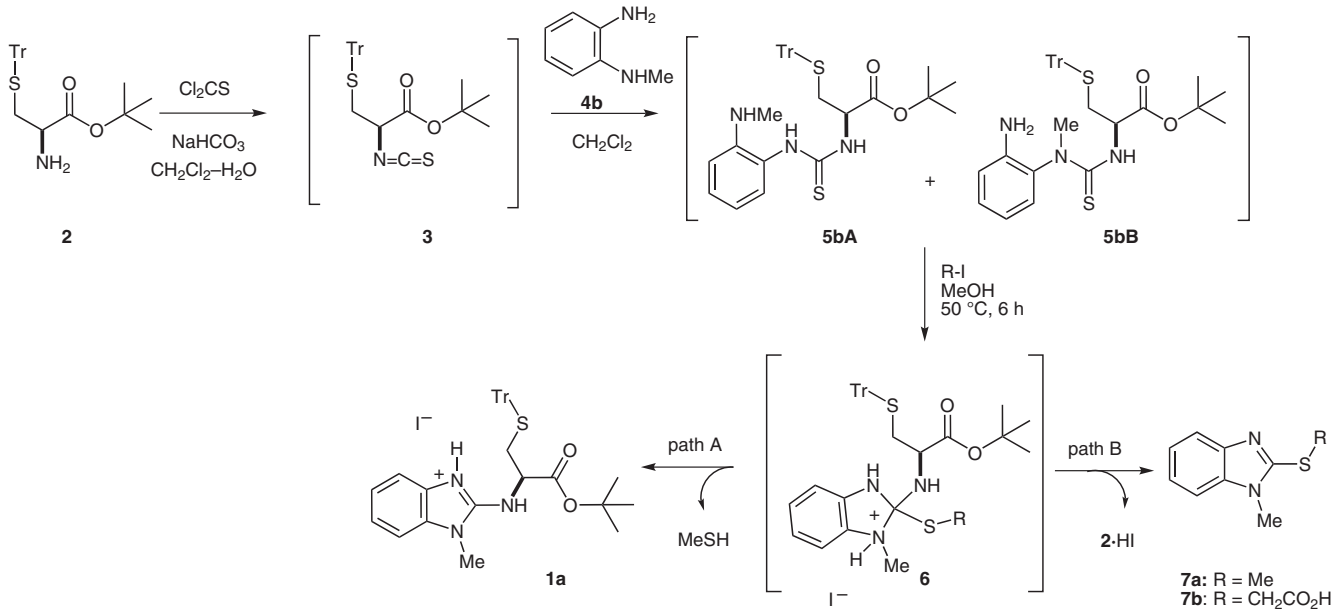
The best results among the literature methods were obtained by using iodomethane[19] in methanol or *N*,*N*-dimethylformamide (entries 7 and 8). However, the *S*-methylbenzimidazole **7a** (3–10%) was obtained as a by-product in these cases. Presumably, **7a** is formed through decomposition of a transient tetrahedral intermediate **6** (Scheme 1, path B).[20]

Table 1 Optimization of Conditions for the Desulfurization–Cyclization Reaction



Entry	Reaction conditions	Conversion (%)[a]	Yield (%) of **1b**[a]
1	HgO, S, EtOH, reflux, 2 h	99	18
2	$PhI(OAc)_2$, Et_3N, MeCN, 0.5 h, r.t.	61	<1
3	EDC, DMF, 3 h 80 °C	33	19
4	TsCl, THF, NaOH, 72 h, r.t.	58	36
5	DMC[b], Et_3N, CH_2Cl_2, 4 h, r.t.	65	43
6	CuCl, DIPEA, toluene–MeCN (4:1), 1 h, 80 °C	96	10
7	MeI, DMF, 3 h, r.t.	75	58
8	MeI, EtOH, 50 °C, 7 h	93	88
9	ICH_2CO_2H, EtOH, 50 °C, 7 h	97	92
10	$ClCH_2CO_2H$, EtOH, 50 °C, 7 h	21	18

[a] Yields and conversion were determined by an HPLC method (for details, see below).
[b] DMC = 2-chloro-1,3-dimethyl-1*H*-imidazol-3-ium chloride.



Scheme 1 Formation of the *S*-methylbenzimidazole **7a**

Because the desired product **1a** and the byproduct **7a** have similar solubility profiles and comparable chromatographic properties, the removal of the byproduct **7a** required laborious column chromatography. We reasoned that the separation of **7a** might be simplified by replacing the methyl group on the sulfur atom of benzimidazole **7a** by a functional group that would change the solubility profile of the resulting byproduct. A carboxylic acid moiety was considered to be the most suitable candidate, so we examined the use of haloacetic acids as desulfurization agents instead of iodomethane.[21] We were pleased to find that the undesired byproduct **7b** (3–5%) that was formed in the cyclization of **5bA**/**B** with iodoacetic acid (entry 9) could be efficiently removed from the reaction mixture by simple extraction with an aqueous base. Chloroacetic acid was considerably less efficient than iodoacetic acid (entry 10). Furthermore, iodoacetic acid is a more benign reagent than iodomethane, as desulfurization by the iodoacetic acid does not generate volatile, foul-smelling, toxic methanethiol as a byproduct.

To establish the scope of the reaction, we then synthesized a series of L-cysteine residue-containing benzimidazoles **1a**–**j** by using iodoacetic acid in the desulfurization–cyclization step (Table 2).

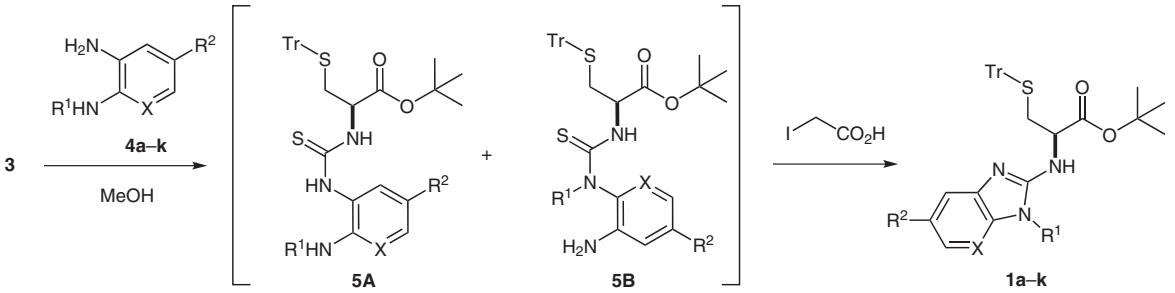
N-Unsubstituted benzimidazoles **1a** (Table 2, entry 1) and N-substituted benzimidazoles **1b**–**d** (entries 2–4) were obtained in good yields.[22] The formation of a mixture of intermediate thioureas **5A** and **5B** has usually been observed in the case of N-substituted diamines **4b**–**d** (Table 2). However, regioisomers **5A** and **5B** were both converted into the desired benzimidazole **1** in the reaction with iodoacetic acid, and therefore no attempt was made to separate the two regioisomers.

Thioureas possessing either electron-donating (entry 5) or electron-withdrawing substituents (entries 6–10) at the 4-position of the arene-1,2-diamine moiety were efficiently transformed into the corresponding benzimidazoles **1f**–**j** (Table 2). However, thiourea **5k**, which contains a strongly electron-deficient 2,3-diaminopyridine moiety, was not compatible with the cyclization conditions, because it formed thiazolidinone **8k** in the reaction with iodoacetic acid. Thiazolidinone **8j** was similarly formed as a byproduct from the electron-deficient thiourea **5j**. In fact, haloacetic acids have been routinely used in the synthesis of thiazolidinones from thioureas under base-free conditions[23] or in the presence of base.[24] Interestingly, thiazolidinones such as **8j** and **8k** were only obtained from the strongly electron-deficient thioureas **5j** and **5k** (entries 10 and 11), and they were not formed in the case of the other thioureas **5a**–**i** (entries 1–9). Apparently, the lower nucleophilicity of the aromatic amine group in **5k** slows down the conversion of the transient *S*-alkylthiouronium iodide **9k** into the key tetrahedral intermediate **6k** *en route* to the target benzimidazole (Scheme 2).[25] In the meantime, a competitive intramolecular amide-bond formation reaction occurs, leading to thiazolidinone **8k**; similar considerations apply in the case of the conversion of amine **5j** into the thiazolidinone **8**j.

The structures of benzimidazole **1b** and thiazolidinone **8k** (as its hydroiodide salt) were established by X-ray crystallography (Figure 3).

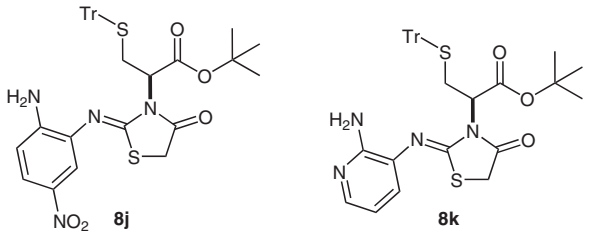
Note that the iodoacetic acid-based cyclization–desulfurization conditions do not cause detectable levels of racemization at the chiral center of L-cysteine, as evidenced by HPLC analysis on a chiral stationary phase of the products of conversion of (*R*)-**3** into (*R*)-**1a** and (*R*)-**1b** (Table 2, entries 1 and 2).[27]

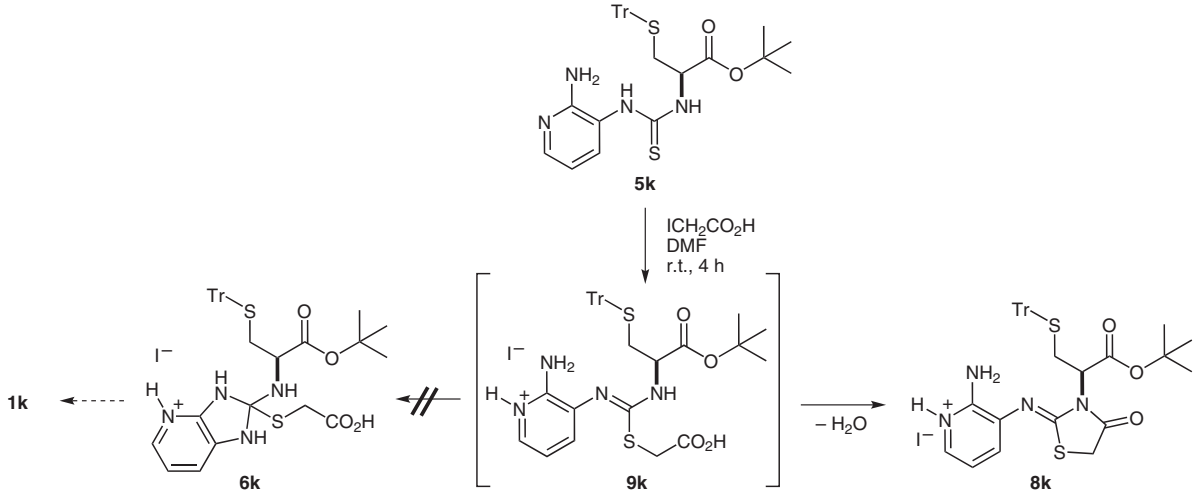
Table 2 Scope of Aryldiamines Used in Synthesis of L-Cysteine-Derived Benzimidazoles **1**



Entry[a]	Product	R^1	R^2	X	Yield (%)[b]
1	**1a**	H	H	CH	51
2	**1b**	Me	H	CH	64
3	**1c**	Bn	H	CH	67
4	**1d**		H	CH	60
5	**1e**	H	OMe	CH	63
6	**1f**	H	Cl	CH	60
7	**1g**	H	CF_3	CH	50
8	**1h**	H	CO_2Me	CH	61
9	**1i**	H	CN	CH	59
10	**1j**	H	NO_2	CH	62 (14%)[c]
11	**1k**	H	H	N	0 (72%)[d]

[a] *Reaction conditions*: ICH_2CO_2H (1.2 equiv), MeOH, 50 °C, 6 h.
[b] Isolated yields of the >95% pure product determined by HPLC with UV detection at 254 nm.
[c] Isolated yield of thiazolidinone **8j**.
[d] Isolated yield of thiazolidinone **8k**.





Scheme 2 Formation of thiazolidinone **8k**

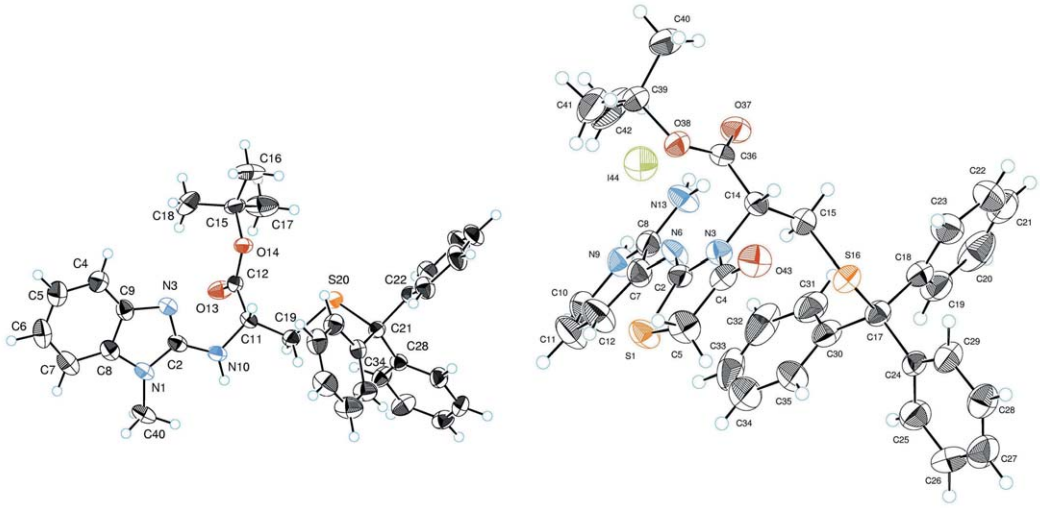


Figure 3 Single-crystal X-ray structures of **1b** (left) and **8k** (right).[26] Thermal ellipsoids are drawn at the 50% probability level.

We performed additional experiments to examine the suitability of our procedure for the synthesis of various amino acid-derived benzimidazoles (Table 3). Accordingly, esters of glycine **10a**, L-phenylglycine **10b**, L-phenylalanine **10c**, protected L-serine **10d**, protected L-lysine **10e** and L-glutamic acid **10f** were readily converted into the corresponding benzimidazol-2-yl derivatives **11a–f** and **12a–f** in good-to-excellent yields in a reaction sequence involving initial formation of the amino acid isothiocyanate, subsequent reaction with a benzene-1,2-diamine and, finally, cyclization–desulfurization of the intermediate thiourea by iodoacetic acid (Table 3). The conversion of the amino acids into **11a–f** and **12a–f** was performed in a sequential manner without isolation and purification of the intermediate isothiocyanates and thioureas. In most cases, a byproduct **7b** was formed (3–5%), and this was separated by simple extraction with an aqueous base. Iodoacetic acid-mediated synthesis of benzimidazoles is compatible with various protecting groups in the amino acid residue, for example, acid-sensitive *S*-trityl and *O*-*tert*-butyl moieties, as well as *O*-benzyl or *N*-benzyloxycarbonyl groups.[28]

In conclusion, we have demonstrated that iodoacetic acid is an efficient reagent for cyclization–desulfurization of amino acid-derived thioureas to give 2-aminobenzimidazoles. Iodoacetic acid is superior to the usual reagent, iodomethane, in that the product workup is simpler and there is no production of the volatile toxic byproduct methanethiol. All the sulfur-containing byproducts, such as 2-sulfanylacetic acid and (1*H*-imidazol-2-ylsulfanyl)acetic acid, are nonvolatile, soluble in basic aqueous media, and can be readily removed by simple extraction with an aqueous base. The conversion of N-unprotected amino acids into the corresponding *N*-benzimidazol-2-yl-derivatives can be performed in a sequential manner without isolation and purification of the intermediate isothiocyanates and thioureas.

In the reaction with iodoacetic acid, intermediate thioureas can be transformed into 2-aminobenzimidazoles or thiazolidinones, depending on the electronic properties of the aryl moiety. Formation of thiazolidinones was observed only for certain electron-deficient thioureas. The developed approach is sufficiently mild to preserve the stereogenic center of the α-amino acid, permitting the preparation of the corresponding *N*-benzimidazol-2-yl derivatives in enantiomerically pure forms.

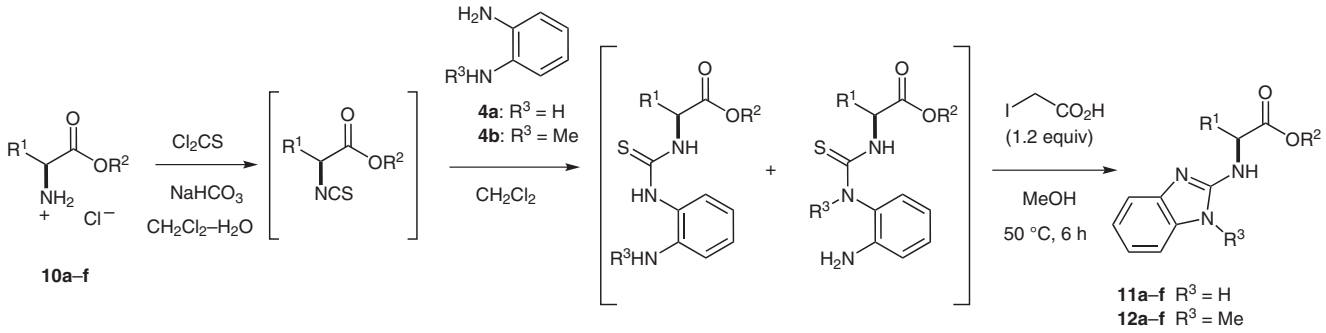
The formation of 2-(1*H*-imidazol-2-ylsulfanyl)acetic acid as a byproduct is presumably the result of a side-track decomposition of the transient tetrahedral thiol intermediate formed by cyclization of the S-alkylated thiourea, which subsequently undergoes decomposition to give the desired benzimidazoles. This suggests that the alternative mechanism for the formation of the 2-aminobenzimidazole through initial desulfurization of the S-alkylated thiourea to form a carbodiimide, followed by cyclization to the benzimidazole, is less likely to have occurred.[29]

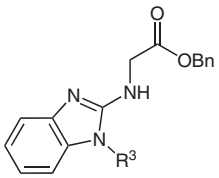
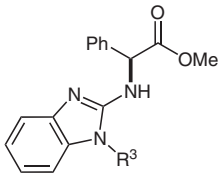
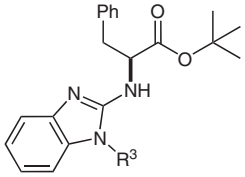
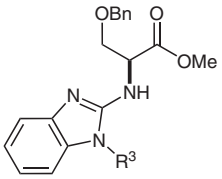
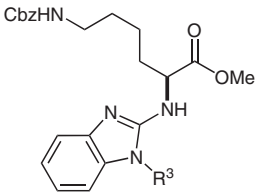
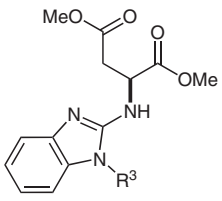
All reactions were carried out under an argon atmosphere. TLC was performed on Merck Kieselgel 60_{F254} plates. Melting points were determined by using an OptimMelt automated melting point system and are uncorrected. NMR spectra were recorded on a Varian Inova 400 MHz spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to Me_4Si or with the residual solvent peak as an internal reference. HRMS were obtained with a Micromass AutoSpec Ultima Magnetic sector mass spectrometer. Elemental analyses were performed on a Carlo-Erba CHNS-0 EA1108 combustion analysis system.

HPLC Method for Determining the Conversion of 5b and the Yields of 1b (Table 1)

All the reactions listed in Table 1 were run on a 0.043-mmol scale of **5b**. HPLC analyses were performed on an Alltech Apollo C18 column (5 μm; 4.6 × 150 mm) (Alltech Associates, Inc.) with elution by a linear gradient from 50% MeOH in 0.01 M aq KH_2PO_4 (pH 2.5) to 95% MeOH in 0.01 M aq KH_2PO_4 (pH 2.5) over 24 min. The flow rate was 0.8 mL/min, and UV-detection was carried out at 254 nm. Compounds **5bA** and **5bB** co-eluted in a single peak after

Table 3 Scope for Amino Acids in the Synthesis of Benzimidazoles



Entry	Products		Yield (%)
1		**11a** **12a**	88 85
2		**11b** **12b**	58 75
3		**11c** **12c**	84 82
4		**11d** **12d**	74 91
5		**11e** **12e**	85 80
6		**11f** **12f**	63 59

19.0 min and **1b** was eluted after 16.4 min. To compensate for loss of material during HPLC sample preparation, PhOMe (24 μL, 0.22 mmol) was added to the reaction mixture as an internal standard (retention time: 12.0 min). The conversion of **5b** and the yield of **1b** were determined by using three-point calibration curves.

Benzimidazoles 1a–j; General Procedure

Sat. aq $NaHCO_3$ (3 mL) was added to a soln of cysteine derivative **2** (200 mg, 0.48 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the mixture was stirred for 10 min. $Cl_2C{=}S$ (40 μL, 0.53 mmol, 1.1 equiv) was added and the mixture was stirred for a further 45 min at 0 °C. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The organic extracts were combined, washed with H_2O (10 mL) and dried (Na_2SO_4). Removal of the solvent gave the crude isothiocyanate **3**, which was dissolved in dry MeOH (3 mL). The soln was purged with argon, and diamine **4** (0.48 mmol, 1 equiv) was added. The mixture was stirred at r.t. (diamines **4a–e)** or at 50 °C (diamines **4f–h**) for 2–20 h until the isothiocyanate **3** was completely consumed [TLC; R_f = 0.58 (EtOAc–PE, 9:1)]. ICH_2CO_2H (107 mg, 0.58 mmol, 1.2 equiv) was added and the mixture was heated at 50 °C for 7 h. All volatiles were evaporated, sat. aq $NaHCO_3$ (10 mL) was added, and the resulting suspension was extracted with EtOAc (3 × 5 mL). The organic extracts were combined, washed with brine (10 mL), dried (Na_2SO_4), and concentrated, and the residue was purified by flash column chromatography.

***tert*-Butyl *N*-1*H*-Benzimidazol-2-yl-*S*-trityl-L-cysteinate (1a)**

This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 14–20% EtOAc–PE) to give a white solid; yield: 130 mg (51%; 98% ee by chiral HPLC); mp 78–81 °C; $[\alpha]_D^{20}$ –17.5 (*c* 1.36, acetone); R_f = 0.31 (EtOAc–PE, 1:3).

IR (film): 3365 (NH), 1739 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.43–8.10 (s, 1 H), 7.38–7.34 (m, 6 H), 7.22–7.12 (m, 10 H), 7.06–6.97 (m, 3 H), 5.40–5.25 (m, 1 H), 4.54–4.44 (m, 1 H), 2.83 (dd, *J* = 12.2, 4.8 Hz, 1 H), 2.73 (dd, *J* = 12.2, 5.4 Hz, 1 H), 1.43 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.6, 152.9, 144.4, 129.5, 127.9, 126.7, 120.6, 82.9, 66.6, 55.2, 34.4, 27.9.

Anal. Calcd for $C_{33}H_{33}N_3O_2S$: C, 73.99; H, 6.21; N, 7.84. Found: C, 73.61; H, 6.14; N, 7.75.

HPLC: Daicel CHIRALPAK IA, 25 cm × 4.6 mm i.d.; mobile phase: 20% *i*-PrOH–80% hexane; flow rate: 0.9 mL/min; detection: UV, 254 nm; retention times: 7.9 min [(*S*)–**1a**] and 21.3 min [(*R*)–**1a**].

***tert*-Butyl *N*-(1-Methyl-1*H*-benzimidazol-2-yl)-*S*-trityl-L-cysteinate (1b)**

This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 5–15% EtOAc–PE) to give a white powder; yield: 170 mg (64%; 96% ee by chiral HPLC); mp 86–88 °C (MeOH); $[\alpha]_D^{20}$ –5.3 (*c* 0.42, acetone); R_f = 0.41 (EtOAc–PE, 1:3).

IR (film): 3319 (NH), 1724 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 1 H), 7.38–7.34 (m, 6 H), 7.21–7.07 (m, 12 H), 4.91 (d, *J* = 7.4 Hz, 1 H), 4.84 (dt, *J* = 7.4, 4.5 Hz, 1 H), 3.51 (s, 3 H), 2.81 (dd, *J* = 11.8, 4.5 Hz, 1 H), 2.77 (dd, *J* = 11.8, 4.5 Hz, 1 H), 1.47 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.4, 152.6, 144.4, 134.8, 129.4, 127.8, 126.6, 121.1, 119.6, 116.6, 107.1, 82.7, 66.3, 54.8, 34.3, 28.3, 27.9.

Anal. Calcd for $C_{34}H_{35}N_3O_2S$: C, 74.29; H, 6.42; N, 7.64. Found: C, 73.96; H, 6.30; N, 7.56.

HPLC: Daicel CHIRALPAK IA, 25 cm × 4.6 mm i.d.; mobile phase: 20% *i*-PrOH–80% hexane, flow rate: 0.9 mL/min; detection: UV, 254 nm; retention times: 8.4 min [(*S*)–**1b**] and 14.2 min [(*R*)–**1b**].

***tert*-Butyl *N*-(1-Benzyl-1*H*-benzimidazol-2-yl)-*S*-trityl-L-cysteinate (1c)**

This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 10–15% EtOAc–PE) to give a white powder; yield: 201 mg (67%); mp 98–101 °C; $[\alpha]_D^{20}$ –36.8 (*c* 0.37, acetone); R_f = 0.46 (EtOAc–PE, 1:3).

IR (film): 3328 (NH), 1721 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 7.8 Hz, 1 H), 7.28–7.21 (m, 11 H), 7.21–7.07 (m, 11 H), 7.06–7.01 (m, 1 H), 5.09 (s, 2 H), 4.91 (d, *J* = 7.4 Hz, 1 H), 4.74 (dt, *J* = 7.4, 4.5 Hz, 1 H), 2.86 (dd, *J* = 11.8, 4.5 Hz, 1 H), 2.61 (dd, *J* = 11.8, 4.5 Hz, 1 H), 1.39 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.1, 152.4, 144.4, 142.2, 135.4, 134.7, 129.4, 129.1, 128.0, 127.8, 126.9, 126.6, 121.3, 119.8, 116.8, 107.5, 82.6, 66.1, 54.6, 34.2, 27.9, 16.0.

Anal. Calcd for $C_{40}H_{39}N_3O_2S$: C, 76.77; H, 6.28; N, 6.71. Found: C, 76.37; H, 6.18; N, 6.66.

***tert*-Butyl *N*-[1-(Cyclopropylmethyl)-1*H*-benzimidazol-2-yl]-*S*-trityl-L-cysteinate (1d)**

This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 10–15% EtOAc–PE) to give a white powder; yield: 170 mg (60%); mp 141–144 °C; $[\alpha]_D^{20}$ –36.5 (*c* 0.23, acetone); R_f = 0.42 (EtOAc–PE. 1:3).

IR (film): 3325 (NH), 1722 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 1 H), 7.37–7.32 (m, 6 H), 7.19–7.04 (m, 12 H), 5.08 (d, *J* = 7.4 Hz, 1 H), 4.88 (dt, *J* = 7.4, 4.5 Hz, 1 H), 3.88 (dd, *J* = 15.4, 6.4 Hz, 1 H), 3.81 (dd, *J* = 15.4, 6.4 Hz, 1 H), 2.93 (dd, *J* = 11.8, 4.5 Hz, 1 H), 2.70 (dd, *J* = 11.8, 4.5 Hz, 1 H), 1.47 (s, 9 H), 0.90–0.83 (m, 1 H), 0.66–0.60 (m, 2 H), 0.48–0.42 (m, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.4, 152.3, 144.4, 142.2, 134.7 129.4, 127.8, 126.6, 121.0, 119.5, 116.6, 107.4, 82.7, 66.1, 54.7, 46.4, 34.4, 28.0, 10.5, 4.1, 4.0.

Anal. Calcd for $C_{37}H_{39}N_3O_2S$: C, 75.35; H, 6.67; N, 7.12. Found: C, 75.07; H, 6.93; N, 6.80.

***tert*-Butyl *N*-(5-Methoxy-1*H*-benzimidazol-2-yl)-*S*-trityl-L-cysteinate (1e)**

This was prepared by following the general procedure with purification of the crude product by column chromatography (silica gel, 25% EtOAc–PE) to give a white powder; yield: 172 mg (63%); mp 111–113 °C; $[\alpha]_D^{20}$ –14.6 (*c* 1.07, acetone); R_f = 0.48 (EtOAc–PE, 50:50).

IR (film): 3376 (NH), 1733 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.8–8.0 (br s, 1 H), 7.41–7.31 (m, 6 H), 7.24–7.11 (m, 9 H), 7.09–6.91 (m, 1 H), 6.87–6.67 (m, 1 H), 6.65–6.55 (m, 1 H), 5.50 (br s, 1 H), 4.59–4.44 (m, 1 H), 3.76 (s, 3 H), 2.80–2.70 (m, 2 H), 1.42 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.9, 155.1, 153.2, 144.4, 129.5, 127.9, 126.7, 108.2, 82.9, 66.6, 55.8, 55.3, 34.4, 27.9.

Anal. Calcd for $C_{34}H_{35}N_3O_3S$: C, 72.19; H, 6.24; N, 7.43. Found: C, 71.95; H, 6.14; N, 7.24.

***tert*-Butyl *N*-(5-Chloro-1*H*-benzimidazol-2-yl)-*S*-trityl-L-cysteinate (1f)**

This was prepared by following the general procedure with purification of the crude product by column chromatography (silica gel, gradient 1–15% EtOAc–PE) to give a white powder; yield: 164 mg (60%); mp 122–124 °C; $[\alpha]_D^{20}$ –14.7 (*c* 0.47, acetone); R_f = 0.37 (EtOAc–PE, 1:3).

IR (film): 3382 (NH), 1733 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.32 (m, 6 H), 7.22–7.15 (m, 7 H), 7.15–7.11 (m, 4 H), 6.98 (dd, *J* = 8.4, 2.0 Hz, 1 H), 4.50–4.44 (m, 1 H), 2.85 (dd, *J* = 12.6, 5.6 Hz, 1 H), 2.73 (dd, *J* = 12.6, 5.0 Hz, 1 H), 1.41 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.3, 153.8, 144.3, 129.4, 127.9, 126.8, 120.6, 83.3, 66.8, 55.2, 34.3, 27.9.

Anal. Calcd for $C_{33}H_{32}ClN_3O_2S$: C, 69.52; H, 5.66; N, 7.37. Found: C, 69.31; H, 5.81; N, 7.09.

***tert*-Butyl *N*-[5-(Trifluoromethyl)-1*H*-benzimidazol-2-yl]-*S*-trityl-L-cysteinate (1g)**

This was prepared by following the general procedure with purification of the crude product by column chromatography (silica gel, gradient 10–20% EtOAc–PE) to give a white powder; yield: 144 mg (50%); mp 115–118 °C; $[\alpha]_D^{20}$ –12.5 (*c* 0.41, acetone); R_f = 0.46 (EtOAc–PE, 1:3).

IR (film): 3389 (NH), 3342 (NH), 1717 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (s, 1 H), 7.58–7.45 (m, 0.5 H), 7.42–7.28 (m, 6.5 H), 7.22–7.05 (m, 10 H), 6.94–6.72 (m, 1 H), 5.80–5.66 (m, 1 H), 4.58–4.50 (m, 1 H), 2.84 (dd, *J* = 12.2, 5.6 Hz, 1 H), 2.73 (dd, *J* = 12.2, 4.6 Hz, 1 H), 1.45 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.7, 154.5, 144.2, 129.4, 127.9, 126.8, 125.0 (d, J_{C-F} = 270 Hz), 83.5, 66.9, 55.1, 34.3, 27.9

Anal. Calcd for $C_{34}H_{32}F_3N_3O_2S$: C, 67.64; H, 5.34; N, 6.96. Found: C, 67.82; H, 5.25; N, 6.79.

Methyl 2-({(1*R*)-2-*tert*-Butoxy-2-oxo-1-[(tritylsulfanyl)methyl]ethyl}amino)-1*H*-benzimidazole-5-carboxylate (1h)

This was prepared by following the general procedure with purification of the crude product by column chromatography (silica gel, gradient 10–20% EtOAc–PE) to give a white powder; yield: 174 mg (61%); mp 116–119 °C; $[\alpha]_D^{20}$ –30.8 (*c* 0.82, acetone); R_f = 0.23 (EtOAc–PE, 25:75).

IR (film): 3351 (NH), 1715 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (s, 0.3 H), 8.56 (s, 0.7 H), 8.04 (s, 0.3 H), 7.83–7.69 (m, 0.7 H), 7.60 (s, 1 H), 7.38–7.32 (m, 6.7 H), 7.22–7.11 (m, 9 H), 6.91–6.81 (m, 0.3 H), 5.85–5.60 (m, 1 H), 4.61–4.50 (m, 1 H), 3.89 (s, 3 H), 2.82 (dd, *J* = 12.4, 5.4 Hz, 1 H), 2.74 (dd, *J* = 12.4, 4.6 Hz, 1 H), 1.44 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.2, 167.9, 144.2, 129.4, 127.9, 126.8, 83.3, 66.8, 55.1, 51.8, 34.3, 27.9.

Anal. Calcd for $C_{35}H_{35}N_3O_4S$: C, 70.80; H, 5.94; N, 7.08. Found: C, 70.57; H, 5.88; N, 6.79.

***tert*-Butyl *N*-(5-Cyano-1*H*-benzimidazol-2-yl)-*S*-trityl-L-cysteinate (1i)**

This was prepared by following the general procedure with purification of the crude product by column chromatography (silica gel, gradient CH_2Cl_2 to 1% EtOH–CH_2Cl_2) to give a white powder; yield: 159 mg (59%); mp 138–140 °C; $[\alpha]_D^{20}$ –5.8 (*c* 1.86, acetone); R_f = 0.27 (EtOAc–PE, 25:75).

IR (film): 3324 (NH), 2219 (C≡N), 1739 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.05–8.74 (m, 1 H), 7.61–7.24 (m, 8 H), 7.22–6.74 (m, 10 H), 6.12–5.80 (m, 1 H), 4.61–4.50 (m, 1 H), 2.85 (dd, *J* = 12.4, 5.8 Hz, 1 H), 2.69 (dd, *J* = 12.4, 4.6 Hz, 1 H), 1.45 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.5, 155.1, 144.1, 129.4, 128.0, 126.9, 118.3, 115.1, 105.0, 83.9, 67.0, 55.1, 34.2, 27.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{34}H_{33}N_4O_2S$: 561.2324; found: 561.2313.

***tert*-Butyl *N*-(5-Nitro-1*H*-benzimidazol-2-yl)-*S*-trityl-L-cysteinate (1j)**

This was prepared by following the general procedure with purification of the crude product by column chromatography (silica gel, gradient CH_2Cl_2 to 1% EtOH–CH_2Cl_2) to give a yellow powder; yield: 174 mg (62%); mp 177–180 °C; $[\alpha]_D^{20}$ –9.4 (*c* 2.57, acetone); R_f = 0.30 (EtOAc–PE, 25:75).

IR (film): 3365 (NH), 1729 (C=O), 1516 (NO_2) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.9–8.6 (m, 1 H), 8.2–7.6 (m, 2 H), 7.43–7.29 (m, 6 H), 7.27–7.11 (m, 9 H), 6.92–6.78 (m, 1 H), 6.05–5.72 (m, 1 H), 4.60–4.50 (m, 1 H), 2.88 (dd, *J* = 12.4, 5.8 Hz, 1 H), 2.71 (dd, *J* = 12.4, 4.6 Hz, 1 H), 1.47 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.3, 144.1, 129.4, 128, 126.9, 83.9, 67.0, 55.1, 34.2, 27.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{33}N_4O_4S$: 581.2223; found: 581.2191.

***tert*-Butyl 2-{(2*Z*)-2-[(2-Amino-4-nitrophenyl)imino]-4-oxo-1,3-thiazolidin-3-yl}-3-(tritylsulfanyl)propanoate (8j)**

This was prepared by following the general procedure with purification of the crude product by column chromatography (silica gel, gradient CH_2Cl_2 to 1% EtOH–CH_2Cl_2) to give a yellow foam; yield: 45 mg (14%); R_f = 0.56 (MeOH–CH_2Cl_2, 5:95).

IR (film): 3476 (NH), 3368 (NH), 1732 (C=O), 1494 (NO_2) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (dd, *J* = 9.0, 2.6 Hz, 1 H), 7.83 (d, *J* = 2.6 Hz, 1 H), 7.41–7.36 (m, 6 H), 7.32–7.20 (m, 9 H) 6.60 (d, *J* = 9.0 Hz, 1 H), 4.91 (dd, *J* = 11.2, 4.0 Hz, 1 H), 4.46 (s, 2 H), 3.87 (ABq, J_{AB} = 17.2 Hz, 2 H), 3.35 (dd, *J* = 13.2, 11.2 Hz, 1 H), 2.92 (dd, *J* = 13.2, 4.0 Hz, 1 H), 1.35 (s, 9 H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 170.6, 166.4, 156.5, 146.5, 144.2, 138.0, 131.2, 129.6, 128.0, 127.0, 123.0, 116.1, 113.0, 83.3, 67.5, 56.3, 32.6, 30.2, 27.8.

***tert*-Butyl 2-{2-[(2-Aminopyridin-3-yl)amino]-4-oxo-1,3-thiazolidin-3-yl}-3-(tritylsulfanyl)propanoate (8k)**

This was prepared by following the general procedure. The product was isolated as hydroiodide salt; yield: 63 mg (72%). The pure material was obtained by crystallization (MeOH); mp 163–165 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 14.0–13.0 (br s, 1 H), 7.80 (dd, *J* = 6.3, 1.2 Hz, 1 H), 7.62 (dd, *J* = 7.7, 1.2 Hz, 1 H), 7.36–7.18 (m, 15 H), 6.96 (dd, *J* = 7.7, 6.3 Hz, 1 H), 5.19 (dd, *J* = 10.2, 4.7 Hz, 1 H), 4.35 (ABq, J_{AB} = 17.8 Hz, 2 H), 3.76–3.31 (m, 2 H), 2.91 (dd, *J* = 12.8, 10.2 Hz, 1 H), 2.82 (dd, *J* = 12.8, 4.7 Hz, 1 H), 1.28 (s, 9 H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 171.5, 166.8, 159.7, 150.2, 144.4, 131.2, 130.6, 129.5, 128.5, 127.3, 113.0, 82.9, 66.9, 55.6, 33.1, 33.0, 27.8.

Benzimidazoles 11a–f and 12a–f; General Procedure

CAUTION: *Thiophosgene is toxic and causes severe irritation of the skin, eyes, and respiratory tract.*

Sat. aq $NaHCO_3$ (5 mL) was added to a suspension of an amino acid hydrochloride **10** (1.00 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred for 10 min then Cl_2C=S (100 μL, 1.05 mmol) was added and the mixture was stirred at 0 °C for 45 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The organic extracts were combined, washed with H_2O (10 mL), and dried (Na_2SO_4). Removal of the solvent gave the crude isothiocyanate **3**, which was used in the next step without purification.

Benzene-1,2 diamine **4** (1.00 mmol) was added to a soln of the isothiocyanate in CH_2Cl_2 (15 mL), and the mixture was stirred at r.t. for 2 h. The solvent was evaporated to afford the crude thiourea **5**. This was dissolved in MeOH (7 mL) and treated with ICH_2CO_2H (223 mg, 1.20 mmol), and the mixture was heated at 50 °C for 5 h. Volatiles were evaporated, and then sat. aq $NaHCO_3$ (10 mL) was added. The resulting suspension was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined, washed with H_2O (10 mL), dried (Na_2SO_4), and concentrated. The crude product was purified by flash column chromatography.

Benzyl *N*-1*H*-Benzimidazol-2-ylglycinate (11a)
This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 1–7% EtOH–CH_2Cl_2) to give a white foam; yield: 248 mg (88%); R_f = 0.29 (EtOAc).

IR (film): 3366 (NH), 1742 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.5–7.8 (br s, 1 H), 7.37–7.23 (m, 7 H), 7.07–7.02 (m, 2 H), 5.53–5.24 (m, 1 H), 5.16 (s, 2 H), 4.30 (s, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.2, 154.1, 135.0, 128.6, 128.5, 128.2, 120.9, 112.6, 67.3, 44.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{16}N_3O_2$: 282.1243; found: 282.1233.

Benzyl *N*-(1-Methyl-1*H*-benzimidazol-2-yl)glycinate (12a)
This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 1–3% EtOH–CH_2Cl_2) to give a white foam; yield: 252 mg (85%); R_f = 0.25 (EtOAc–PE, 50:50).

IR (film): 3280 (NH), 1731 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.45 (m, 1 H), 7.39–7.30 (m, 5 H), 7.15–7.06 (m, 3 H), 5.24 (s, 2 H), 4.85–4.77 (m, 1 H), 4.41 (d, *J* = 4.6 Hz, 2 H), 3.53 (s, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.0, 153.4, 141.5, 135.2, 134.9, 128.6, 128.4, 128.2, 121.4, 119.9, 116.5, 107.3, 67.3, 44.9, 28.2.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}N_3O_2$: 296.1399; found: 296.1393.

Methyl (2*S*)-(1*H*-Benzimidazol-2-ylamino)(phenyl)acetate (11b)
This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 10–50% EtOAc–PE) to give a white powder; yield: 162 mg (58%; 91% ee, chiral HPLC); mp 170–172 °C; $[\alpha]_D^{20}$ +108.8 (*c* 1.02, acetone); R_f = 0.32 (EtOAc–PE, 50:50).

IR (film): 3359 (NH), 1743 (C=O) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.56 (br s, 1 H), 7.55 (d, *J* = 8.2 Hz, 1 H), 7.52–7.47 (m, 2 H), 7.43–7.32 (m, 3 H), 7.21–7.15 (m, 2 H), 6.94–6.85 (m, 2 H), 5.59 (d, *J* = 8.0 Hz, 1 H), 3.65 (s, 3 H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 172.6, 154.5, 137.6, 129.1, 128.6, 128.0, 119.9, 59.6, 52.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{16}N_3O_2$: 282.1243; found: 282.1243.

HPLC: Daicel CHIRALPAK IA, 25 cm × 4.6 mm i.d.; mobile phase: *i*-PrOH–hexane–Et_2NH (10:90:0.1), flow rate: 0.9 mL/min; detection: UV, 228 nm; retention times: 17.0 min [(*R*)-**11b**] and 27.7 min [(*S*)-**11b**].

Methyl (2*S*)-[(1-Methyl-1*H*-benzimidazol-2-yl)amino](phenyl)-acetate (12b)
This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 10–50% EtOAc–PE) to give a white powder; yield: 221 mg (75%; 87% ee by chiral HPLC); mp 143–146 °C; R_f = 0.35 (EtOAc–PE, 50:50); $[\alpha]_D^{20}$ +76.8 (*c* 1.32, acetone).

IR (film): 3349 (NH), 1742 (C=O) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.56–7.53 (m, 2 H), 7.45–7.34 (m, 4 H), 7.26–7.18 (m, 2 H), 7.02–6.94 (m, 2 H), 5.65 (d, *J* = 8.0 Hz, 1 H), 3.66 (s, 3 H), 3.60 (s, 3 H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 172.6, 154.6, 142.2, 137.2, 135.8, 129.0, 128.6, 128.5, 120.9, 119.4, 116.0, 108.2, 60.2, 52.6, 29.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{18}N_3O_2$: 296.1399; found: 296.1403.

HPLC: Daicel CHIRALPAK IA, 25 cm × 4.6 mm i.d.; mobile phase: *i*-PrOH–hexane–Et_2NH 92:8:0.1%, flow rate: 0.9 mL/min; detection: UV, 228 nm; retention times: 13.1 min [(*R*)–**12b**] and 21.4 min [(*S*)–**12b**].

***tert*-Butyl *N*-1*H*-Benzimidazol-2-yl-L-phenylalaninate (11c)**
This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 1–5% EtOH–CH_2Cl_2) to give a yellow powder; yield: 283 mg (84%); $[\alpha]_D^{20}$ +34.4 (*c* 0.25, acetone); R_f = 0.48 EtOAc–PE (50:50).

IR (film): 3345 (NH), 1729 (C=O) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.8–10.6 (br s, 1 H), 7.33–7.25 (m, 4 H), 7.24–7.18 (m, 1 H), 7.17–7.11 (m, 2 H), 6.93–6.84 (m, 3 H), 4.62–4.51 (m, 1 H), 3.11 (dd, *J* = 13.7, 6.2 Hz, 1 H), 3.05 (dd, *J* = 13.7, 8.0 Hz, 1 H), 1.33 (s, 9 H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 172.1, 154.7, 137.9, 129.7, 128.6, 126.9, 119.8, 81.1, 57.4, 37.9, 28.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{24}N_3O_2$: 338.1869; found: 338.1869.

***tert*-Butyl *N*-(1-Methyl-1*H*-benzimidazol-2-yl)-L-phenylalaninate (12c)**
This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 1–3% EtOH–CH_2Cl_2) to give a foam; yield: 266 mg (85%). The analytically pure compound was obtained by column chromatography (silica gel, 20–40% EtOAc–petroleum ether); $[\alpha]_D^{20}$ +4.2 (*c* 0.86, acetone); R_f = 0.48 (EtOAc–PE, 25:75).

IR (film): 3324 (NH), 1714 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.47 (m, 1 H), 7.30–7.20 (m, 3 H), 7.19–7.15 (m, 2 H), 7.15–7.09 (m, 1 H), 7.09–7.05 (m, 2 H), 5.04–4.98 (m, 1 H), 4.73 (d, *J* = 7.5 Hz, 1 H), 3.45 (s, 3 H), 3.36 (dd, *J* = 13.8, 6.1 Hz, 1 H), 3.26 (dd, *J* = 13.8, 4.9 Hz, 1 H), 1.44 (s, 9 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.2, 153.0, 141.8, 136.4, 134.8, 129.6, 128.2, 126.9, 121.2, 119.7, 116.4, 107.3, 82.5, 56.7, 37.9, 28.0, 27.9.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{26}N_3O_2$: 352.2025; found: 352.2033.

Methyl *N*-1*H*-Benzimidazol-2-yl-*O*-benzyl-L-serinate (11d)
This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 1–5% EtOH–CH_2Cl_2) to give a foam; yield: 240 mg (74%). The pure compound was obtained by crystallization (CCl_4); $[\alpha]_D^{20}$ –2.0 (*c* 0.27, MeOH); R_f = 0.21 (EtOAc–PE, 50:50).

IR (film): 3350 (NH), 1744 (C=O) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.63 (s, 1 H) 7.38–7.26 (m, 5 H), 7.20–7.14 (m, 2 H), 6.97 (d, *J* = 8.5 Hz, 1 H), 6.92–6.86 (m, 2 H), 4.77–4.70 (m, 1 H), 4.57 (d, *J* = 12.2 Hz, 1 H), 4.51 (d, *J* = 12.2 Hz, 1 H), 3.88 (dd, *J* = 9.6, 4.3 Hz, 1 H), 3.81 (dd, *J* = 9.6, 4.0 Hz, 1 H), 3.66 (s, 3 H).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 172.1, 154.8, 138.3, 128.7, 128.0, 127.9, 119.9, 72.6, 70.2, 56.0, 52.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{20}N_3O_3$: 326.1505; found: 326.1487.

Methyl *O*-Benzyl-*N*-(1-methyl-1*H*-benzimidazol-2-yl)-L-serinate (12d)
This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 1–3% EtOH–CH_2Cl_2) to give a white foam; yield: 310 mg (91%); $[\alpha]_D^{20}$ –6.5 (*c* 1.09, acetone); R_f = 0.39 (EtOAc–PE, 50:50).

IR (film): 3342 (NH), 1744 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.43 (m, 1 H), 7.36–7.25 (m, 5 H), 7.15–7.04 (m, 3 H), 5.11 (d, *J* = 8.5 Hz, 1 H), 4.98 (dt, *J* = 8.5, 3.0 Hz, 1 H), 4.59 (d, *J* = 12.2 Hz, 1 H), 4.51 (d, *J* = 12.2 Hz, 1 H), 4.03 (dd, *J* = 9.5, 3.0 Hz, 1 H), 3.96 (dd, *J* = 9.5, 3.0 Hz, 1 H), 3.77 (s, 3 H), 3.53 (s, 3 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 171.7, 153.2, 141.9, 137.6, 135.0, 128.4, 127.8, 127.6, 121.2, 119.7, 116.5, 107.2, 73.3, 69.9, 56.2, 52.6, 28.3.

Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.02; H, 6.16; N, 12.33.

Methyl N^2-1*H*-Benzimidazol-2-yl-N^6-[(phenylacetyl)oxy]-L-lysinate (11e)

This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 1–3% EtOH–CH_2Cl_2) to give a foam; yield: 350 mg (85%). The analytically pure compound was obtained by column chromatography (silica gel, 40% EtOAc–petroleum ether); $[\alpha]_D^{20}$ –10.3 (*c* 0.54, acetone); R_f = 0.32 (EtOAc).

IR (film): 3332 (NH), 1696 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.60 (s, 1 H) 7.34–7.17 (m, 4 H) 7.13–7.06 (m, 2 H) 6.94 (d, J = 8.7 Hz, 1 H) 6.90–6.77 (m, 2 H) 4.96 (s, 2 H) 4.35 (td, J = 8.7, 5.2 Hz, 1 H) 3.60 (s, 3 H) 2.99–2.91 (m, 2 H) 1.82–1.62 (m, 2 H) 1.47–1.30 (m, 4 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.1, 156.8, 154.1, 136.5, 128.6, 128.2, 128.0, 120.8, 66.7, 55.4, 52.4, 40.4, 31.8, 29.3, 22.2.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{27}N_4O_4$: 411.2032; found: 411.2007.

Methyl N^2-(1-Methyl-1*H*-benzimidazol-2-yl)-N^6-[(phenylacetyl)oxy]-L-lysinate (12e)

This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 1–3% EtOH–CH_2Cl_2) to give a foam; yield: 365 mg (80%); $[\alpha]_D^{20}$ –26.5 (*c* 0.58, acetone); , R_f = 0.16 (EtOAc–PE, 50:50).

IR (film): 3335 (NH), 1724 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.44 (m, 1 H), 7.37–7.26 (m, 5 H), 7.12–7.04 (m, 3 H), 5.09–5.06 (m, 2 H), 4.89–4.76 (m, 3 H), 3.77 (s, 3 H), 3.53 (s, 3 H), 3.24–3.15 (m, 2 H), 2.09–1.98 (m, 1 H), 1.93–1.80 (m, 1 H), 1.65–1.37 (m, 4 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.4, 156.5, 153.4, 141.9, 136.5, 134.9, 128.5, 128.1, 128.0, 121.2, 119.7, 116.6, 107.2, 66.5, 55.4, 52.5, 40.5, 32.2, 29.5, 28.2, 22.3.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{29}N_4O_4$: 425.2189; found: 425.2137.

Dimethyl *N*-1*H*-Benzimidazol-2-yl-L-glutamate (11f)

This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 10–25% EtOAc–PE) to give a foam; yield: 172 mg (59%); $[\alpha]_D^{20}$ –24.6 (*c* 0.86, acetone); R_f = 0.16 (EtOAc–PE, 50:50).

IR (film): 3355 (NH), 1739 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.6–8.6 (br s, 1 H), 7.36–7.24 (m, 2 H), 7.08–7.01 (m, 2 H), 5.8–5.4 (br s, 1 H), 4.71–4.65 (m, 1 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 2.54 (t, *J* = 7.0 Hz, 2 H), 2.35–2.24 (m, 1 H), 2.19–2.08 (m, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.9, 173.5, 154.1, 120.7, 55.1, 52.6, 51.9, 30.1, 27.7.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}N_3O_4$: 292.1297; found: 292.1285.

Dimethyl *N*-(1-Methyl-1*H*-benzimidazol-2-yl)-L-glutamate (12f)

This was prepared by following the general procedure with purification by column chromatography (silica gel, gradient 10–25% EtOAc–PE) to give a foam; yield: 193 mg (63%); $[\alpha]_D^{20}$ –48.4 (*c* 1.12, acetone); R_f = 0.19 (EtOAc–PE, 50:50).

IR (film): 3342 (NH), 1739 (C=O), 1733 (C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.44 (m, 1 H), 7.13–7.03 (m, 3 H), 5.08 (d, *J* = 7.9 Hz, 1 H), 4.85 (td, *J* = 7.9, 5.0 Hz, 1 H), 3.78 (s, 3 H), 3.66 (s, 3 H), 3.51 (s, 3 H), 2.60–2.34 (m, 3 H), 2.24–2.13 (m, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.7, 173.7, 153.3, 141.9, 134.9, 121.2, 119.8, 116.7, 107.3, 55.2, 52.6, 51.8, 30.3, 28.2, 27.4.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{20}N_3O_4$: 306.1454; found: 306.1442.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) Alamgir, M.; Black, D. St. C.; Kumar, N. *Top. Heterocycl. Chem* **2007**, *9*, 87. (b) Boiani, M.; Gonzalez, M. *Mini-Rev. Med. Chem.* **2005**, *5*, 409. (c) Wang, J.; Hou, T. *J. Chem. Inf. Model.* **2010**, *50*, 55.

(2) Grant, F. S.; Konradi, A. W.; Pleiss, M. A.; Thorsett, E. D. US 6,545,003, **2003**.

(3) Wythes, M. J.; Palmer, M. J.; Kemp, M. I.; Mackenny, M. C.; Maguire, R. J.; Blake, J. F. WO 0005231, **2000**.

(4) Keenan, R. M.; Miller, W. H. WO 9412478 **1994**.

(5) Poitout, L.; Brault, V.; Sackur, V.; Pierre, C. R.; Pascale, P. US 20090270372, **2009**.

(6) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(7) For selected recent examples of nucleophilic replacements of Cl, see: (a) Sun, A.; Ndungu, J. M.; Krumm, S. A.; Yoon, J.-J.; Thepchatri, P.; Natchus, M.; Plemper, R. K.; Snyder, J. P. *ACS Med. Chem. Lett.* **2011**, *2*, 798. (b) Peddibhotla, S.; Shi, R.; Khan, P.; Smith, L. H.; Mangravita-Novo, A.; Vicchiarelli, M.; Su, Y.; Okolotowicz, K. J.; Cashman, J. R.; Reed, J. C.; Roth, G. P. *J. Med. Chem.* **2010**, *53*, 4793. (c) Almasi, D.; Alonso, D. A.; Gómez-Bengoa, E.; Nájera, C. *J. Org. Chem.* **2009**, *74*, 6163. (d) Lahue, B. R.; Ma, Y.; Shipps, G. W.; Seghezzi, W.; Herbst, R. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3405. (e) Moriya, M.; Kishino, H.; Sakuraba, S.; Sakamoto, T.; Suga, T.; Takahashi, H.; Suzuki, T.; Ito, M.; Ito, J.; Moriya, R.; Takenaga, N.; Iwaasa, H.; Ishihara, A.; Kanatani, A.; Fukami, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3568. (f) Bonfanti, J-F.; Meyer, C.; Doublet, F.; Fortin, J.; Muller, P.; Queguiner, L.; Gevers, T.; Janssens, P.; Szel, H.; Willebrords, R.; Timmerman, P.; Wuyts, K.; van Remoortere, P.; Janssens, F.; Wigerinck, P.; Andries, K. *J. Med. Chem.* **2008**, *51*, 875. (g) Arienzo, R.; Cramp, S.; Dyke, H. J.; Lockey, P. M.; Norman, D.; Roach, A. G.; Smith, P.; Wong, M.; Wren, S. P. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1403. (h) Martin, R. E.; Green, L. G.; Guba, W.; Kratochwil, N.; Christ, A. *J. Med. Chem.* **2007**, *50*, 6291. (i) Ognyanov, V. I.; Balan, C.; Bannon, A. W.; Bo, Y.; Dominguez, C.; Fotsch, C.; Gore, V. K.; Klionsky, L.; Ma, V. V.; Qian, Y.-X.; Tamir, R.; Wang, X.; Xi, N.; Xu, S.; Zhu, D.; Gavva, N. R.; Treanor, J. J. S.; Norman, M. H. *J. Med. Chem.* **2006**, *49*, 3719. For replacement of a methylsulfonyl

group, see: (j) Lan, P.; Romero, F. A.; Malcolm, T. S.; Stevens, B. D.; Wodka, D.; Makara, G. M. *Tetrahedron Lett.* **2008**, *49*, 1910.
(8) (a) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (b) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607.
(9) (a) Hong, Y.; Tanoury, G. J.; Wilkinson, H. S.; Bakale, R. P.; Wald, S. A.; Senanayake, C. H. *Tetrahedron Lett.* **1997**, *38*, 5607. (b) Hong, Y. P.; Senanayake, C. H.; Xiang, T. J.; Vandenbossche, C. P.; Tanoury, G. J.; Bakale, R. P.; Wald, S. A. *Tetrahedron Lett.* **1998**, *39*, 3121. (c) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861. (d) Wang, X.; Bhatia, P. A.; Daanen, J. F.; Latsaw, S. P.; Rohde, J.; Kolasa, T.; Hakeem, A. A.; Matulenko, M. A.; Nakane, M.; Uchic, M. E.; Miller, L. N.; Chang, R.; Moreland, R. B.; Brioni, J. D.; Steward, A. O. *Bioorg. Med. Chem.* **2005**, *13*, 4667.
(10) (a) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133. (b) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719. (c) Deng, X.; McAllister, H.; Mani, N. S. *J. Org. Chem.* **2009**, *74*, 5742. (d) Lv, X.; Bao, W. *J. Org. Chem.* **2009**, *74*, 5618.
(11) L-Cysteine is especially susceptible to racemization in solution-phase peptide synthesis, see: (a) Barber, M.; Jones, J. H.; Witty, M. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2425. It is also susceptible to racemization in solid-phase peptide synthesis, see: (b) Han, Y.; Albericio, F.; Barany, G. *J. Org. Chem.* **1997**, *62*, 4307.
(12) Kokotos, C. G.; Kokotos, G. *Adv. Synth. Catal.* **2009**, *351*, 1355.
(13) (a) Floch, L.; Uher, M.; Leško, J. *Collect. Czech. Chem. Commun.* **1989**, *54*, 206. (b) Perkins, J. L.; Zartman, A. E.; Meissner, R. S. *Tetrahedron Lett.* **1999**, *40*, 1103.
(14) (a) Wang, X.; Zhang, L.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Tetrahedron Lett.* **2004**, *45*, 7167.
(15) (a) Carpenter, R. D.; Andrei, M.; Lau, E. Y.; Lightstone, F. C.; Liu, R.; Lam, K. S.; Kurth, M. J. *J. Med. Chem.* **2007**, *50*, 5863. (b) Carpenter, R. D.; DeBredt, P. B.; Lam, K. S.; Kurth, M. J. *J. Comb. Chem.* **2006**, *8*, 907. (c) Cee, V. J.; Downing, N. S. *Tetrahedron Lett.* **2006**, *47*, 3747. (d) Krchňák, V.; Smith, J.; Vágner, J. *Tetrahedron Lett.* **2001**, *42*, 1627.
(16) (a) Ghosh, H.; Yella, R.; Nath, J.; Patel, B. K. *Eur. J. Org. Chem.* **2008**, 6189.
(17) (a) Heinelt, U.; Schulthesis, D.; Jäger, J.; Lindenmaier, M.; Pollex, A.; Beckmann, H. G. S. *Tetrahedron* **2004**, *60*, 9883.
(18) Artman, G. D. III; Solovay, C. F.; Adams, C. M.; Diaz, B.; Dimitroff, M.; Ehara, T.; Gu, D.; Ma, F.; Liu, D.; Miller, B. R.; Pick, T. E.; Poon, D. J.; Ryckman, D.; Siesel, D. A.; Stillwell, B. S.; Swiftney, T.; van Dyck, J. P.; Zhang, C.; Ji, N. *Tetrahedron Lett.* **2010**, *51*, 5319.
(19) (a) Hamley, P.; Tinker, A. C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1573. (b) Taniguchi, K.; Shigenaga, S.; Ogahara, T.; Fujitsu, T.; Matsuo, M. *Chem. Pharm. Bull.* **1993**, *41*, 301.
(20) A tetrahedral intermediate in the formation of 2-aminobenzimidazoles has been proposed: see ref. 15c.
(21) To the best of our knowledge, iodoacetic acid has never been used as desulfurizing agent in the synthesis of benzimidazoles.
(22) The structure of **1b** was supported by a single-crystal X-ray analysis.
(23) Meng, G.; Zheng, M.; Dong, M.; Qu, Q. *Org. Prep. Proced. Int.* **2012**, *44*, 184.
(24) For selected examples of the use of NaOAc as a base, see: (a) Erol, S.; Dogan, I. *J. Org. Chem.* **2007**, *72*, 2494. (b) Obushak, N. D.; Matiichuk, V. S.; Martyak, R. L. *Chem. Heterocycl. Comp.* **2003**, *39*, 878. (c) Choubey, V. N.; Singh, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2233.
(25) (a) Presumably, the proton of the **9k·HI** salt resides mainly on the 2-aminopyridine moiety, thereby further decreasing its nucleophilicity [pK_a (DMSO) = 27.72 for 2-aminopyridine (ref. 25a) and pK_a (DMSO) = 21.0 for thiourea (ref. 25b)]: (b) Bordwell, F. G.; Algrim, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 2964. (c) Bordwell, F. G.; Ji, G. Z. *J. Am. Chem. Soc.* **1991**, *113*, 8398; Note, however, that in the crystal lattice, the proton of 8k•HI is located on the pyridine nitrogen, as evidenced by single-crystal X-ray analysis.
(26) Crystallographic data for compounds **1b** and **8k** have been deposited with the accession numbers CCDC 912871 and 912872, respectively, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.
(27) Determined by HPLC on a chiral stationary phase; see the experimental section for details. *tert*-Butyl *S*-trityl-l-cysteinate of 98% ee optical purity was used as the starting material in all experiments.
(28) Partial racemization of an asymmetric center occurred in the l-phenylglycine-derived benzimidazoles **11b** (91% ee) and **12b** (87% ee), as evidenced by chiral HPLC assay (see the experimental section for details).
(29) Omar, A.-M. M. E.; Habib, N. S.; Aboulwafa, O. M. *Synthesis* **1977**, 864.