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Synthesis of 2-Aminoazoles from Thioesters via α-Heterosubstituted Ketones by Copper-mediated Cross-Coupling

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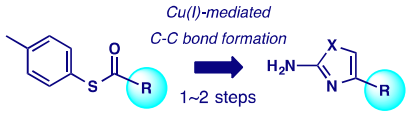
[TOC Graphic 

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‡ These authors contributed equally

ABSTRACT: Facile synthesis of a variety of α-heterosubstituted ketones under mild conditions was achieved by copper-mediated cross-coupling of thioesters with functionalized organostannanes. Application of this coupling methodology provided a concise pathway for the conversion of carboxylic acids to 2-aminoimidazoles, 2-aminothiazoles, and 2-aminooxazoles via thioesters in practical yields.

INTRODUCTION

α-Heterosubstituted methyl ketones are valuable intermediates in organic synthesis. Occasionally they constitute notable structural features of various bioactive compounds and natural products.[1] General methods for their preparation involve the intermediacy of α-bromomethyl ketones, where the bromide is substituted by a nucleophilic heteroatom. α-Aminomethyl ketones are typically prepared from α-bromomethyl ketones with hexamethylene tetraamine,[2] sodium diformylamide,[3] or potassium phthalimide.[4] α-Hydroxymethyl ketones and α-fluoromethyl ketones are obtained by the treatment with alkali formates[5] and tetrabutylammonium fluoride,[6] respectively. Importantly, α-bromomethyl ketones are used as precursors of heterocycles such as 2-aminoheteroazoles in medicinal chemistry.[7,8] However, the preparation of α-bromomethyl ketones require brominating reagents, diazomethane, and strict pH control over their multistep syntheses, and thus have limitations for the late-stage functionalization of complex molecules.

A mild synthesis of ketones from readily available thioesters and organostannanes has been reported by Liebeskind.[9] This reaction relies on the palladium-catalyzed, copper-mediated coupling under neutral conditions. Furthermore, a palladium-free, copper-mediated cross-coupling of thioesters with α-alkoxystannanes to give α-alkoxyketones has been developed.[10] In the synthesis of the agelastatin alkaloids, Movassaghi has capitalized on the cross-coupling of thioesters with aminostannanes and its application to azaheterocycle synthesis.[11]

RESULTS AND DISCUSSION

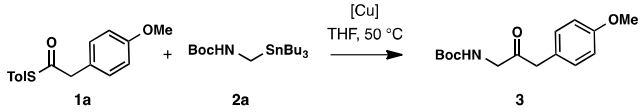
Herein, we describe our investigations utilizing mild, palladium-free cross-coupling for the synthesis of α-substituted methyl ketones and heterocycles from thioesters and functionalized organostannanes. Using Cu(I) additives with appropriate stannane coupling reagents, we achieved the synthesis of α-amino, α-oxy, α-thio, and α-fluoromethyl ketones. In addition, we developed the direct synthesis of 2-aminoimidazoles, 2-aminothiazoles, and 2-aminooxazoles from thioesters via the copper-mediated cross-coupling reaction.

In our initial assessment of copper sources to mediate the coupling of thioesters and α-heterosubstituted organostannanes, the reaction of thioester **1a** with (*N*-Boc-aminomethyl)tri-*n*-butylstannane **2a** was examined as a model system (Table 1). In the first attempt with 2 equivalents of CuTC (copper(I) thiophene-2-carboxylate) and 2 equivalents of the stannane in THF at 50 ºC (entry 1), the desired ketone **3** was obtained in nearly quantitative yield. Deprotection occurred readily with HCl to get α-aminomethyl ketone. Using 1 equivalent of CuTC (entry 2), the coupling reaction did not proceed to completion. All amounts of Cu(I) salts less than 2 equivalents lead to longer reaction times and decreased ketone yields with recovery of thioester. We observed that Cu(I) halides and CuCN (entries 3-6) produced only traces of the α-aminoketone derivative with the recovery of the starting thioester. Decomposition of the thioester occurred with CuOTf (entry 7). CuOAc and CuDPP (copper(I) diphenylphosphate) were effective in the coupling reaction of thioester **1a** and stannane **2a** (entries 8 and 10). Although the use of $Cu(OAc)_2$ gave some ketone product (entry 9), it clearly gave a substantially lower yield compared to CuTC, CuOAc, and CuDPP.

The coupling reaction of thioester **1a** with aminomethyl stannane **2a** using CuOAc effectively proceeded in THF under inert conditions. To determine the effective reaction parameters, we optimized the solvent and investigated the influence of the atmosphere (Table 2). Of the different solvents screened, THF, dioxane, toluene, DCE, and DMF were found to be suitable. Among the solvents investigated, THF and DMF produced high yields of ketone **3** and were chosen for further studies. To our surprise, no

ketone product was formed and no starting thioester recovered in MeCN as the solvent (entry 2). Addition of water to THF decreased the yield to 19% (entry 3). On exposure to air or oxygen, the reaction resulted in low or no yield, respectively (entries 4, 5).

Table 1. Optimization of copper reagent in the coupling of thioester 1a with aminomethylstannane 2a[a]



1a 2a 3

entry	[Cu]	equiv	time, h	**3**, %	**1a**, %
1	CuTC	2	2	99	0
2	CuTC	1	18	65	26
3	CuCl	2	2	trace	>90
4	CuBr•Me_2S	2	2	0	100
5	CuI	2	2	0	100
6	CuCN	2	2	0	100
7	CuOTf	2	1	0	0
8	CuOAc	2	2	97	0
9	$Cu(OAc)_2$	2	18	57	nd
10	CuDPP	2	2	92	0

[a] Standard Conditions: **1a** (0.1 mmol), **2a** (2.0 equiv), Cu source, THF (0.1 M) mixed under argon at 50 °C.

Table 2. Influence of solvent and atmosphere[a,b]

entry	solvent	atmosphere	**3**, %	**1a**, %
1	THF	argon	97	0
2	MeCN	argon	0	0
3	1% H_2O in THF	argon	19	78
4	THF	air	26	73
5	THF	oxygen	0	100

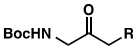
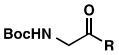
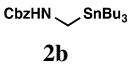
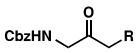
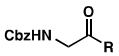
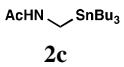
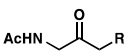
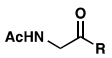
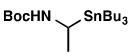
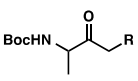
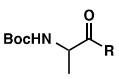
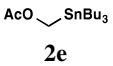
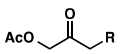
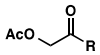
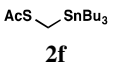
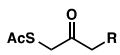
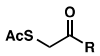
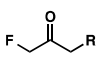
[a] Standard Conditions: **1a** (0.1 mmol), **2a** (2.0 equiv), CuOAc (2.0 equiv), THF (0.1 M) mixed under argon at 50 °C.

[b] Organic solvents were freshly distilled

Investigations were continued under the identified standard conditions to examine a variety of α-heterosubstituted methyl and ethyl stannanes in cross-coupling reactions with thioesters (Table 3). We selected CuOAc and CuDPP as the copper sources because the resulting tin byproducts, *n*-Bu_3SnOAc or *n*-$Bu_3SnOP(O)(Ph)_2$, were more easily separable from the reaction mixture by column chromatography compared to CuTC byproducts. The coupling reaction was effective for both aromatic and aliphatic thioesters. We chose *p*-toluenethioester derivatives over benzenethioester or *p*-nitrobenzenethioester due

to its easy of handling, generally increase in yields of ketones and reported lower toxicity of the thiol precursors.

Table 3. Scope of stannanes with thioesters 1a and 1b

entry	thioester	stannane	product[b]	yield
1	**1a**	**2a**	 **3**	97%
2	**1b**	**2a**	 **4**	95%
3	**1a**	 **2b**	 **5**	88%
4	**1b**	**2b**	 **6**	81%
5	**1a**	 **2c**	 **7**	96%
6	**1b**	**2c**	 **8**	89%
7	**1a**	 **2d**	 **9**	66%
8	**1b**	**2d**	 **10**	67%
9	**1a**	 **2e**	 **11**	81%
10	**1b**	**2e**	 **12**	78%
11	**1a**	 **2f**	 **13**	81%
12	**1b**	**2f**	 **14**	71%
13	**1a**	 **2g**	 **15**	78%
14	**1b**	**2g**	 **16**	72%

[a] Standard Conditions: **1** (0.1 mmol), **2** (2.0 equiv), CuOAc (2.0 equiv), THF (0.1 M) mixed under argon at 50 °C.

[b] R=4-MeOC$_6$H$_4$

Both 4-methoxyphenylacetothioate **1a** and 4-methoxybenzothioate **1b** underwent efficient cross-coupling with Boc-protected (**2a**), Cbz-protected (**2b**), and acetyl-protected (**2c**) aminomethyl stannanes in excellent yields (entries 1-6). In the case of *N*-Boc-α-aminoethyl stannane **2d**, the resulting ketones **9** and **10** were obtained in moderate yields after heating at 80 ºC for 24 h (entries 7 and 8). In the case of oxymethyl ketones, we initially examined acetoxymethyl stannane **2e**,[12] which underwent the coupling reaction to provide the desired α-acetoxymethyl ketones **11** and **12** in DMF at 80 ºC for 24 h (entries 9 and 10). On the other hand, no reaction occurred with the *tert*-butyldimethylsiloxymethyl-stannane even at elevated temperatures in DMF. Performing the cross-coupling with acetylthiomethylstannane **2f**,[13] CuDPP was found to be a more effective copper additive compared to CuOAc (entries 11 and 12). Although the coupling reaction with chloromethylstannane[14] or iodomethylstannane[15] did not take place, fluoromethylstannane **2g**[16] provided fluoromethyl ketones **15** and **16** (entries 13 and 14). Surprisingly, when CuOAc was used in this fluoromethylation reaction, the formation of the expected ketones (**15** and **16**) was accompanied by the formation of α-acetoxymethyl ketone byproducts (**11** and **12**). CuDPP suppressed the generation of byproducts and good yields of fluoromethyl ketones were achieved.

After accomplishing the synthesis of several of α-heterosubstituted ketones, we evaluated this approach as a method for the synthesis of a variety of 2-aminoazoles from thioesters. Movassaghi recently reported the synthesis of 2-aminoimdazoles using the coupling reaction of guanidinylmethylstannanes with thioesters followed by cyclization under acidic conditions.[11b] In our own studies, we also first evaluated and used this approach for the synthesis of 2-aminoimidazoles as a part of a program directed at the first enantioselective synthesis of dragmacidin D (Figure 1).[17]

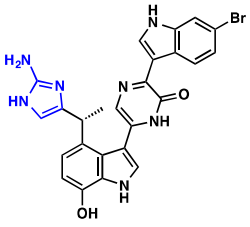
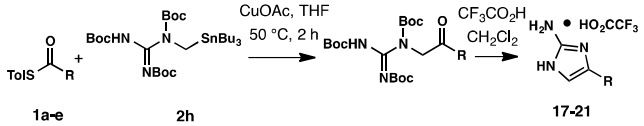


Figure 1. Structure of dragmacidin D.

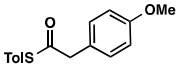
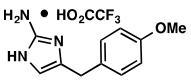
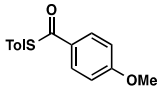
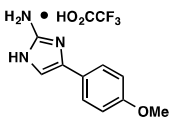
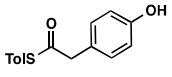
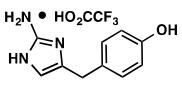
Initial investigations with variably protected guanidylmethylstannanes revealed that fully protected tris-*N*-Boc gunanidyl reagent **2h** is optimal in terms of coupling efficiency and overall yield of the heterocyclic product. The synthesis is best achieved by performing the cross-coupling first and then removing all Boc groups by treatment with trifluoroacetic acid in dichloromethane, which also accomplishes cyclocondensation of the intermediate ketone to 2-aminoimidazole in high yield. Cross-coupling of thioester **1a** and stannane **2h** was achieved in 95% yield, and subsequent cyclocondensation to 2-aminoimidazole **17** was performed in 88% isolated yield (Table 4, entry 1). This reaction was shown to be scalable; achieving 71% yield over the 2-step process starting with 1 gram (3.7 mmol) of thioester **1a**.

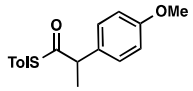
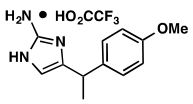
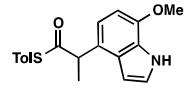
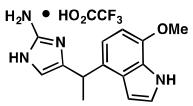
Table 4 provides additional thioesters tested in this approach to aminoimidazoles. Benzothioate **1b** and α-methyl phenylacetothioate **1d** provided the corresponding heterocyclic products **18** and **20** in very high yields (entries 2 and 4). Moreover, α-methyl-4-substituted indole containing 2-aminoimidazole **21**,[18] which is found in the marine natural product dragmacidin D[19] (Figure 1) could be synthesized from the thioester precursor **1e** in good yield (entry 5). The thioester **1c** containing a free phenol underwent the cross-coupling reaction and cyclization in 63% yield (entry 3).

Table 4. Two-step synthesis of 2-aminoimidazoles



1a-e 2h 17-21

entry	thioester	product	yield
1	 **1a**	 **17**	88%
2	 **1b**	 **18**	91%
3	 **1c**		63%

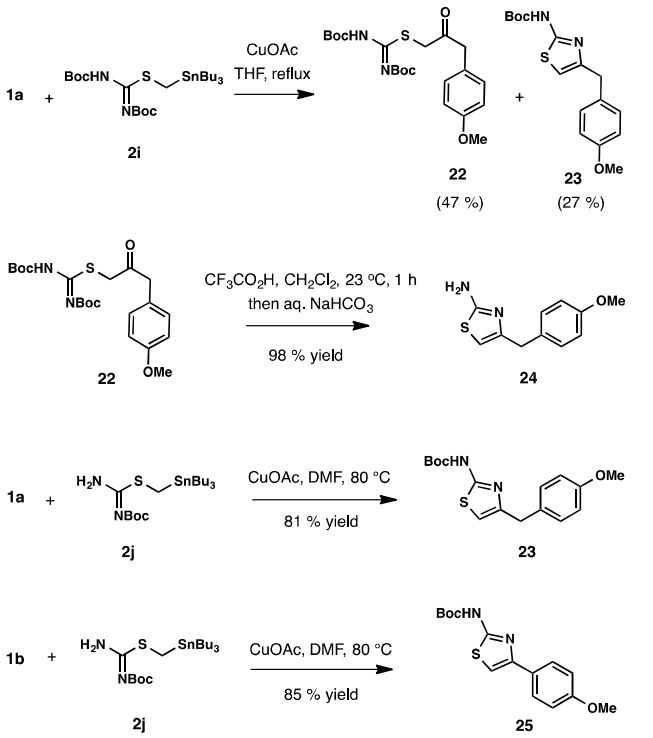
		19	
4	 **1d**	 **20**	88%
5	 **1e**	 **21**	71%

[a] Standard Conditions: Cross-coupling: **1** (0.1 mmol), **2h** (2.0 equiv), CuOAc (2.0 equiv), THF (0.1 M) mixed under argon at 50 °C. Cyclization: ketone (50 μmol), TFA (1 mL), DCM (1 mL) mix under argon at rt. Monitor by TLC.

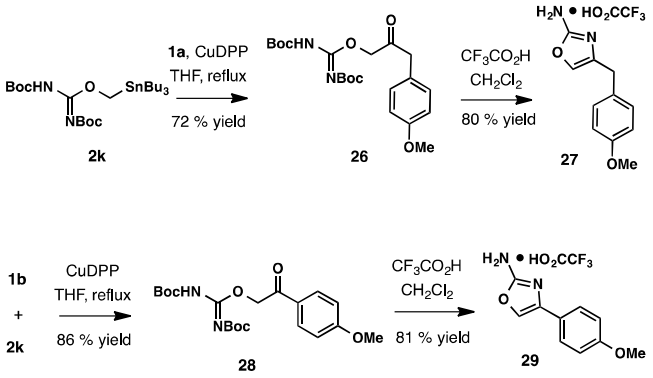
In a similar fashion, we assessed the formation of 2-aminothiazoles from aromatic and aliphatic thioesters (Scheme 1). For this class of products, we found that mono-Boc isothiourea reagent **2j**, easily prepared from iodomethyltributylstannane and Boc-protected thiourea,[15a,20] is the optimal choice compared to the bis-Boc reagent. Using DMF as the solvent at elevated temperatures, the heterocyclic product could be accessed *directly in one step* from the thioester precursor. Thus, upon treatment of **1a** and stannane **2j** with CuOAc in DMF at 80 °C, 2-aminothiazole derivative **23** was isolated in 81% yield. Similarly, **25** was prepared from aromatic thioester **1b** under identical reaction conditions in 85% isolated yield.

Finally, we investigated the synthesis of 2-aminooxazoles following the same blueprint (Scheme 2). After exploring several variants of the isourea-functionalized stannane reagent, bis-*N*-Boc-protected stannane **2k** emerged as the reagent of choice. Although the use of CuOAc led to the formation of a significant amount of byproducts, coupling of thioester **1a** with reagent **2k** in the presence of CuDPP under reflux in THF occurred in 72% isolated yield. Exposure of the product to trifluoroacetic acid in dichloromethane readily afforded 2-aminooxazole **27** in 80% isolated yield. Similarly, cross-coupling of aromatic thioester **1b** was efficient under identical conditions (86% yield). In the final step, aromatization of **28** under acidic conditions afforded 2-aminooxazole **29** in high yield. Longer reaction times were necessary in the cyclization toward **29** compared to the formation of similar heterocycles 2-aminooxazole **27** and 2-AI **18**. The slower reactivity of **28** is attributed to the lower nucleophilicity of the isourea-group.

Scheme 1. Synthesis of 2-aminothiazole from stannanes 2j and 2k



Scheme 2. Synthesis of 2-aminooxazole with stannane 2k



CONCLUSIONS

In conclusion, we provided our method in using neutral, palladium-free, copper-mediated cross-coupling conditions with thioates and organostannanes. We described how CuOAc and CuDPP were used to achieve the synthesis of a variety of α-heteroatomic methyl ketones, we also provided our findings on the operationally simple formation of 2-aminoimidazoles, 2-aminothiazoles, and 2-aminooxazoles in great yield.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and ether (diethyl ether) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, di-*iso*-propylamine and triethylamine were distilled from calcium hydride in a continuous still under and atmosphere of argon. Elevated reaction temperatures were controlled by thermo couples. Room temperature reactions were carried out between 22-24 °C. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F_{254} and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, and iodine staining. Flash column chromatography was performed using 40-63 μm silica gel as the stationary phase. Proton magnetic resonance spectra were recorded at 400, 500, and 600 MHz. Carbon magnetic resonance spectra were recorded at 126 MHz. All Chemical shifts were reported in δ units relative to tetramethylsilane. High-resolution mass spectra (HRMS) were obtained using electrospray ionization (ESI) with Q-TOF detection and electron ionization (EI) techniques.

General procedure 1.

S-4-Tolyl 4-methoxyphenylacetothioate 1a. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (10.0 g, 52.2 mmol) was added portionwise to a mixture of 2-(4-methoxyphenyl)acetic acid (8.0 g, 48.1 mmol) and 1-hydroxybenzotriazole monohydrate (8.0 g, 52.2 mmol) in dichloromethane (100 mL) at 0°C. After stirring for 30 min, 4-methylbenzenethiol (6.0 g, 48.3 mmol) was added to the solution and the mixture was allowed to warm to 23°C and stirred for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to afford S-4-tolyl 4-methoxyphenylacetothioate **1a** as a colorless solid (10.8 g, 39.8 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.25 (d, J = 7.5 Hz, 4H), 7.19 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 3.84 (s,

2H), 3.81 (s, 3H), 2.36 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 196.2, 159.0, 139.5, 134.3, 130.7, 129.9, 125.3, 124.3, 114.0, 55.2, 49.1, 21.2. HRMS (EI) $[M]^+$ calcd for $C_{16}H_{16}O_2S$: 272.0871; found 272.0870.

S-4-Tolyl 4-methoxybenzothioate 1b. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.9 g, 9.91 mmol) was added portionwise to a mixture of 4-methoxybenzoic acid (1.0 g, 6.57 mmol) and 1-hydroxybenzotriazole monohydrate (1.5 g, 9.80 mmol) in dichloromethane (20 mL) at 0°C. After stirring for 30 min, 4-methylbenzenethiol (1.2 g, 9.66 mmol) was added to the solution and the mixture was allowed to warm to 23°C and stirred for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to afford S-4-tolyl 4-methoxybenzothioate **1b** as a colorless solid (1.5 g, 5.88 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 8.00 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 3.88 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 188.9, 163.9, 139.5, 135.0, 130.0, 129.6, 129.4, 124.0, 113.8, 55.5, 21.3. HRMS (EI) $[M]^+$ calcd for $C_{15}H_{14}O_2S$: 258.0715; found 258.0714.

S-4-Tolyl 2-(4-hydroxyphenyl)ethanethioate 1c. Boron tribromide (2.0 mL, 1.0 M in dichloromethane, 2.00 mmol) was added dropwise to a solution of S-4-tolyl 4-methoxyphenylacetothioate **1a** (220 mg, 0.808 mmol) in dichloromethane (2.0 mL) at -78°C. The reaction mixture was allowed to warm at 23°C and stirred for 1 h. The reaction was quenched carefully with water at -78°C and extracted with dichloromethane. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (25% ethyl acetate in hexanes) to afford S-4-tolyl 2-(4-hydroxyphenyl)ethanethioate **1c** as a colorless solid (204 mg, 0.079 mmol, 98%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.25 (d, J = 7.8 Hz, 2H), 7.19 (d, J = 8.3 Hz, 4H),

6.80 (d, *J* = 8.5 Hz, 2H), 4.78 (s, 1H), 3.83 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 197.4, 155.1, 139.7, 134.3, 130.8, 130.0, 125.2, 124.1, 115.6, 49.1, 21.3. HRMS (EI) $[M]^+$ calcd for $C_{15}H_{14}O_2S$: 258.0715; found 258.0712.

S-4-Tolyl 2-(4-methoxyphenyl)propanethioate 1d. The title compound was prepared according to general procedure 1 using 2-(4-methoxyphenyl)propanoic acid (1.0 g, 5.72 mmol), 4-methylbenzenethiol (780 mg, 6.28 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.3 g, 6.78 mmol) and 1-hydroxybenzotriazole monohydrate (1.1 g, 7.18 mmol) in dichloromethane (20 mL) and purification by column chromatography on silica gel (5% ethyl acetate in hexanes) to obtain **1d** as a colorless solid (1.1 g, 3.95 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.31 – 7.14 (m, 6H), 6.89 (d, *J* = 8.7 Hz, 2H), 3.93 (q, *J* = 7.1 Hz, 1H), 3.81 (s, 3H), 2.35 (s, 3H), 1.54 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 199.6, 159.0, 139.3, 134.3, 131.6, 129.8, 129.0, 124.5, 114.0, 55.1, 53.1, 21.2, 18.6. HRMS (EI) $[M]^+$ calcd for $C_{17}H_{18}O_2S$: 286.1028; found 286.1026.

Ethyl 2-(2-bromo-4-methoxyphenyl)acetate S-1. Thionyl chloride (2.4 mL, 33.1 mmol) was added dropwise to a solution of 2-(2-bromo-4-methoxyphenyl)acetic acid (2.7 g, 10.9 mmol) in ethanol (40 mL) at 0°C. The reaction mixture was heated at reflux for 1 h. After cooling, the solvent was removed by evaporation and the residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford ethyl 2-(2-bromo-4-methoxyphenyl)acetate **S-1** as a colorless oil (2.7 g, 9.89 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.19 (d, *J* = 8.5 Hz, 1H), 7.12 (d, *J* = 2.6 Hz, 1H), 6.83 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.71 (s, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 170.8, 159.2, 131.7, 126.3, 125.1, 118.0, 113.6, 60.9, 55.5, 40.7, 14.2. HRMS (EI) $[M]^+$ calcd for $C_{11}H_{13}BrO_3$: 272.0048; found 272.0050.

Ethyl 2-(2-bromo-4-methoxyphenyl)propanoate S-2. Lithium hexamethyldisilazide (9.6 mL, 1.0 M in hexanes, 9.60 mmol) was added dropwise to a solution of ethyl 2-(2-bromo-4-methoxyphenyl)acetate **S-1** in THF (40 mL) at -78°C, the resulting solution was stirred at 0°C for 30 min. Methyl iodide (0.85 mL, 13.7 mmol) was added to the above solution at -78°C and the reaction mixture was allowed to warm at 23°C and stirred for 1 h. The reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to afford ethyl 2-(2-bromo-4-methoxyphenyl)propanoate **S-2** as a colorless oil (2.5 g, 8.71 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.22 (d, *J* = 8.7 Hz, 1H), 7.11 (d, *J* = 2.7 Hz, 1H), 6.85 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.20 – 4.07 (m, 3H), 3.78 (s, 3H), 1.45 (d, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $cdcl_3$) δ(ppm): 174.2, 158.8, 132.2, 128.6, 124.4, 118.0, 113.8, 60.8, 55.4, 43.8, 17.9, 14.1. HRMS (EI) $[M]^+$ calcd for $C_{12}H_{15}BrO_3$: 286.0205; found 286.0210.

tert-Butyl 2-(Boc-amino)-3-(2-(1-ethoxycarbonylethane-1-yl)-5-methoxyphenyl)acrylate S-3. A mixture of ethyl 2-(2-bromo-4-methoxyphenyl)propanoate **S-2** (3.9 g, 13.4 mmol), tert-butyl 2-(Boc-amino)acrylate (4.0 g, 16.4 mmol), palladium(*II*) acetate (150 mg, 0.668 mmol),tri- (*o-tolyl*)phosphine (410 mg, 1.35 mmol) and triethylamine (10 mL) in acetonitrile (40 mL) was heated at 90°C for 20 h. After cooling, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford tert-butyl 2-(Boc-amino)-3-(2-(1-ethoxycarbonylethane-1-yl)-5-methoxyphenyl)acrylate **S-3a** as a yellow oil (4.0 g, 8.79 mmol, 66%) and its geometric isomer **S-3b** as a yellow solid (0.5 g, 1.11 mmol, 8.3%). **S-3a :** ^{1}H NMR (400 MHz,$CDCl_3$) δ(ppm): 7.24 (d, *J* = 8.6 Hz, 1H), 7.17 (s, 1H), 6.88 (d, *J* = 2.8 Hz, 1H), 6.84 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.12 – 6.07 (s, 1H), 4.18 – 4.03 (m, 2H), 3.87 – 3.78 (m, 1H), 3.76 (s, 3H), 1.56 (s, 9H), 1.44 (d, *J* = 7.1 Hz, 3H), 1.39 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$)

δ(ppm): 174.5, 164.0, 158.2, 152.7, 134.3, 131.8, 129.5, 128.0, 125.3, 115.1, 113.0, 81.9, 80.5, 60.8, 55.2, 41.2, 28.1, 28.0, 18.0, 14.1. HRMS (ESI) $[M+Na]^+$ calcd for $C_{24}H_{35}NO_7Na$: 472.2311; found 472.2300. **S-3b** : ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.78 (s, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 6.98 (s, 1H), 6.78 (ddd, *J* = 8.6, 2.8, 0.8 Hz, 1H), 6.60 (dd, *J* = 2.8, 0.9 Hz, 1H), 4.18 – 4.02 (m, 2H), 3.84 (q, *J* = 7.1 Hz, 1H), 3.75 (s, 3H), 1.50 (s, 9H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.11 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 174.9, 163.6, 157.7, 152.7, 138.0, 130.7, 127.0, 120.5, 114.6, 113.1, 82.3, 80.5, 60.5, 55.2, 41.6, 28.3, 27.3, 18.4, 14.1. HRMS (ESI) $[M+Na]^+$ calcd for $C_{24}H_{35}NO_7Na$: 472.2311; found 472.2291.

Di-tert-butyl 4-(1-ethoxycarbonylethane-1-yl)-7-methoxy-1H-indole-1,2-dicarboxylate S-4. A mixture of tert-butyl 2-(Boc-amino)-3-(2-(1-ethoxycarbonylethane-1-yl)-5-methoxyphenyl)acrylate **S-3** (101 mg, 0.225 mmol), palladium(*II*) acetate (20 mg, 0.0891 mmol) and copper(II) acetate (122 mg, 0.672 mmol) in dimethyl sulfoxide (1.0 mL) was heated at 85°C for 4 h. After cooling, the reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford di-tert-butyl 4-(1-ethoxycarbonylethane-1-yl)-7-methoxy-1H-indole-1,2-dicarboxylate **S-4** as a colorless oil (85 mg, 0.184 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.15 (s, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H), 4.16 – 4.08 (m, 2H), 4.08 – 3.97 (m, 1H), 3.89 (s, 3H), 1.64 (s, 9H), 1.60 (s, 9H), 1.56 (d, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 174.5, 160.0, 150.6, 146.0, 129.1, 127.2, 126.8, 126.6, 119.7, 108.1, 105.9, 84.4, 81.8, 60.7, 55.5, 42.4, 28.2, 27.4, 17.9, 14.1. HRMS (ESI) $[M+Na]^+$ calcd for $C_{24}H_{33}NO_7Na$: 470.2155; found 470.2152.

4-(1-Ethoxycarbonylethane-1-yl)-7-methoxy-1H-indole-2-carboxylic acid S-5. Trifluoroacetic acid (30 mL) was added dropwise to 4-(1-ethoxycarbonylethane-1-yl)-7-methoxy-1H-indole-1,2-

dicarboxylate **S-4** (2.5 g, 5.32 mmol) in dichloromethane (30 ml) at 23°C. After stirring for 30 min, the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (100% ethyl acetate) to afford 4-(1-ethoxycarbonylethane-1-yl)-7-methoxy-1H-indole-2-carboxylic acid **S-5** as a yellow solid (1.5 g, 5.15 mmol, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 9.14 (s, 1H), 7.49 (d, *J* = 2.2 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 4.22 – 4.01 (m, 3H), 3.97 (s, 3H), 1.61 (dd, *J* = 7.2, 1.5 Hz, 3H), 1.20 (td, *J* = 7.1, 2.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 174.8, 166.5, 145.7, 128.8, 127.4, 127.0, 125.8, 119.3, 109.6, 104.7, 60.8, 55.5, 42.7, 17.8, 14.1. HRMS (ESI) $[M+Na]^+$ calcd for $C_{15}H_{17}NO_5Na$: 314.1003; found 314.1003.

4-(1-Ethoxycarbonylethane-1-yl)-7-methoxy-1H-indole S-6. A solution of 4-(1-ethoxycarbonylethane-1-yl)-7-methoxy-1H-indole-2-carboxylic acid **S-5** (1.5 g, 5.15 mmol) in quinoline (16 mL) was heated at 220°C using microwave irradiation for 40 min. After cooling, the reaction mixture was quenched with 1N HCl and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford 4-(1-ethoxycarbonylethane-1-yl)-7-methoxy-1H-indole **S-6** as a brown oil (1.1 g, 4.29 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.41 (s, 1H), 7.19 (t, *J* = 2.8 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 6.66 – 6.57 (m, 2H), 4.20 – 4.00 (m, 3H), 3.94 (s, 3H), 1.59 (d, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 175.1, 145.3, 127.7, 126.3, 125.3, 123.5, 117.9, 101.6, 101.3, 60.5, 55.2, 42.9, 17.8, 14.1. HRMS (EI) $[M]^+$ calcd for $C_{14}H_{17}NO_3$: 247.1208; found 247.1208.

4-(1-Carboxyethane-1-yl)-7-methoxy-1H-indole S-7. A solution of potassium hydroxide (210 mg, 3.74 mmol) in water (2.0 mL) was added dropwise to a solution of 4-(1-ethoxycarbonylethane-1-yl)-7-methoxy-1H-indole **S-6** (230 mg, 0.930 mmol) in THF-methanol (1 : 1, 4.0 mL) at 23°C. After stirring for 3 h, the reaction mixture was quenched with 1N HCl and extracted with ethyl acetate. The combined

organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (50% ethyl acetate in hexanes) to afford 4-(1-carboxyethane-1-yl)-7-methoxy-1H-indole **S-7** as a yellow solid (192 mg, 0.877 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.48 (s, 1H), 7.18 (t, *J* = 2.8 Hz, 1H), 6.98 (d, *J* = 7.9 Hz, 1H), 6.61 (m, 2H), 4.09 (q, *J* = 7.2 Hz, 1H), 3.94 (s, 3H), 1.61 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 181.0, 145.5, 127.8, 126.3, 124.4, 123.7, 118.2, 101.8, 101.3, 55.3, 42.6, 17.3. HRMS (EI) $[M]^+$ calcd for $C_{12}H_{13}NO_3$: 219.0895; found 219.0889.

7-Methoxy-4-(4-tolylsulfanyl-3-oxopropan-2-yl)-1H-indole 1e. The title compound was prepared according to general procedure 1 using 4-(1-carboxyethane-1-yl)-7-methoxy-1H-indole **S-7** (700 mg, 3.19 mmol) and 4-methylbenzenethiol (800 mg, 6.44 mmol) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.0 g, 5.22 mmol) and 1-hydroxybenzotriazole monohydrate (800 mg, 5.22 mmol) in dichloromethane (15 mL). The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to obtain 7-Methoxy-4-(4-tolylsulfanyl-3-oxopropan-2-yl)-1H-indole **1e** as a yellow oil (816 mg, 2.51 mmol, 79%) ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.47 (s, 1H), 7.25 – 7.12 (m, 5H), 7.04 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 8.0 Hz), 6.63 (t, *J* = 2.5 Hz), 4.32 (q, *J* = 7.1 Hz, 1H), 3.97 (s, 3H), 2.34 (s, 3H), 1.67 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 200.1, 145.8, 139.1, 134.4, 129.7, 128.0, 126.4, 124.8, 123.8, 119.3, 101.8, 101.3, 55.2, 51.6, 21.2, 17.7. HRMS (EI) $[M]^+$ calcd for $C_{19}H_{19}NO_2S$: 325.1136; found 325.1130.

N-(Tri-n-butylstannylmethyl)phthalimide S-9. Phthalimide potassium salt (1.8 g, 9.72 mmol) was added to a solution of tri-n-butylstannylmethyliodide (3.0 g, 6.96 mmol) in DMF (30 mL) at 23°C, and the mixture was stirred for 2 h. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford N-(tri-n-

butylstannylmethyl)phthalimide **S-9** as a colorless oil (2.9 g, 6.49 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.79 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.66 (dd, *J* = 5.4, 3.0 Hz, 2H), 3.23 (s, 2H), 1.62 – 1.36 (m, 6H), 1.32 – 1.23 (m, 6H), 1.02 – 0.89 (m, 6H), 0.85 (t, *J* = 7.3 Hz, 9H).^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 168.8, 133.5, 132.3, 122.7, 28.9, 27.3, 21.2, 13.6, 10.4. HRMS (ESI) $[M+Na]^+$ calcd for $C_{21}H_{33}NO_2NaSn$: 470.1426; found 470.1438.

***tert*-Butyl tri-n-butylstannylmethylcarbamate 2a.** Hydrazine monohydrate (4.0 mL, 81.8 mmol) was added dropwise to a solution of N-(tri-n-butylstannylmethyl)phthalimide **S-9** (1.0 g, 2.22 mmol) in ethanol (30 mL) at 80°C, and the reaction was stirred at 80°C for 1 h. After cooling, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was submitted to the next step without purification.

Di-tert-butyl dicarbonate (450 mg, 2.06 mmol) and triethylamine (620 μL, 4.45 mmol) were added sequentially to a solution of the crude substrate (2.22 mmol) in dichloromethane (10 mL) at 23°C. After stirring for 1 h, the reaction was quenched with water and extracted with dichloromethane. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel as a colorless oil (2% ethyl acetate in hexanes) to afford tert-butyl tri-n-butylstannylmethylcarbamate **2a**. (823 mg, 1.96 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 4.50 (s, 1H), 2.78 (d, *J* = 5.0 Hz, 2H), 1.55 – 1.45 (m, 6H), 1.42 (s, 9H), 1.29 (h, *J* = 7.3 Hz, 6H), 1.00 – 0.78 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 156.8, 78.7, 29.1, 28.4, 27.4, 24.4, 13.7, 9.7. HRMS (ESI) $[M+Na]^+$ calcd for $C_{18}H_{39}NO_2NaSn$: 440.1896; found 440.1893.

Benzyl tri-n-butylstannylmethylcarbamate 2b. Hydrazine monohydrate (4.0 mL, 81.8 mmol) was added dropwise to a solution of N-(tri-n-butylstannylmethyl)phthalimide **S-9** (1.0 g, 2.22 mmol) in ethanol (30 mL) at 80 °C, and the reaction was stirred at 80 °C for 1 h. After cooling, the reaction was

quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was submitted to the next step without purification.

Benzyl chloroformate (300 μL, 2.10 mmol) and triethylamine (620 μL, 4.45 mmol) were added sequentially to a solution of the crude substrate (2.22 mmol) in dichloromethane (10 mL) at 23°C. After stirring for 1 h, the reaction was quenched with water and extracted with dichloromethane. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to afford benzyl tri-n-butylstannylmethylcarbamate **2b** as a colorless oil (804 mg, 1.77 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.40 – 7.23 (m, 5H), 5.09 (s, 2H), 4.73 (s, 1H), 2.90 – 2.78 (m, 2H), 1.52-1.41 (m, 6H), 1.36 – 1.22 (m, 6H), 0.89 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 157.3, 136.8, 128.4, 128.0, 128.0, 66.6, 29.0, 27.3, 24.9, 13.7, 9.7. HRMS (ESI) $[M+Na]^+$ calcd for $C_{21}H_{37}NO_2NaSn$: 474.1739; found 474.1753.

N-(Tri-n-butylstannylmethyl)acetamide 2c. Hydrazine monohydrate (8.0 mL, 164 mmol) was added dropwise to a solution of N-(tri-n-butylstannylmethyl)phthalimide **S-9** (1.9 g, 4.27 mmol) in ethanol (50 mL) at 80°C, and the reaction was stirred at 80°C for 1 h. After cooling, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was submitted to the next step without purification.

Triethylamine (1.8 mL, 12.9 mmol) and acetyl chloride (600 μL, 8.45 mmol) were added sequentially to a solution of the crude substrate (4.27 mmol) in dichloromethane (30 mL) at 0°C. After stirring for 1 h, the reaction was quenched with water and extracted with dichloromethane. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (30% ethyl acetate in hexanes) to afford N-(tri-n-butylstannylmethyl)acetamide **2c** as a yellow oil (1.4 g, 3.84 mmol, 90%). ^{1}H NMR (500 MHz, $CDCl_3$)

δ(ppm): 5.66 (s, 1H), 2.82 – 2.69 (m, 2H), 1.94 (s, 3H), 1.57 – 1.39 (m, 6H), 1.33 – 1.28 (m, 6H), 0.95 – 0.81 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 169.9, 29.0, 27.3, 24.3, 22.7, 13.6, 10.2. HRMS (ESI) $[M+Na]^+$ calcd for $C_{15}H_{33}NONaSn$: 382.1477; found 382.1491.

N-(1-(Tri-n-butylstannyl)ethyl)phthalimide S-11. n-Butyllithium (1.6 mL, 2.4 M in hexanes, 3.84 mmol) was added dropwise to a solution of diisopropylamine (520 mL, 3.71 mmol) in THF (15 mL) at 0°C, the resulting solution was stirred at 0°C for 30 min. tri-n-butyltin hydride (1.0 mL, 3.72 mmol) was added to the above solution at 0°C. After stirring for 30 min at the same temperature, acetaldehyde (210 μL, 3.76 mmol) was added and the reaction mixture was allowed to warm at 23°C and stirred for 1 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexanes) to afford 1-(tri-n-butylstannyl)ethanol **S-10** as a colorless oil (796 mg, 2.37 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 4.16 (m, 1H), 1.69 – 1.43 (m, 9H), 1.43 – 1.19 (m, 3H), 1.01 – 0.79 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 63.7, 29.2, 27.5, 24.6, 13.6, 8.3. [MS was not attained due to decomposition upon analysis.]

Diisopropyl azodicarboxylate (480 μL, 2.44 mmol) was added to a mixture of 1-(tri-n-butylstannyl)ethanol **S-10** (820 mg, 2.45 mmol), phthalimide (440 mg, 2.99 mmol) and triphenylphosphine (640 mg, 2.44 mmol) in THF (10 mL) at 23°C, After stirring for 4 h, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to afford N-(1-(tri-n-butylstannyl)ethyl)phthalimide **S-11** as a yellow oil (847 mg, 1.83 mmol, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.81 (dd, J = 5.4, 3.0 Hz, 2H), 7.68 (dd, J = 5.4, 3.0 Hz, 2H), 3.94 (m, 1H), 1.53 – 1.41 (m, 9H), 1.33 – 1.21 (m, 6H), 1.05 – 0.90 (m,

6H), 0.85 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 169.0, 133.7, 132.2, 122.9, 31.4, 29.0, 27.4, 18.8, 13.6, 10.2. HRMS (ESI) $[M+Na]^+$ calcd for $C_{22}H_{35}NO_2NaSn$: 484.1583; found 484.1571.

tert-Butyl 1-(tri-n-butylstannyl)ethylcarbamate 2d. Hydrazine monohydrate (5.0 mL, 102.9 mmol) was added dropwise to a solution of N-(1-(tri-n-butylstannyl)ethyl)phthalimide **S-3** (1.2 g, 2.59 mmol) in ethanol (30 mL) at 80°C, and the reaction was stirred at 80°C for 1 h. After cooling, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was submitted to the next step without purification.

Di-tert-butyl dicarbonate (500 mg, 2.29 mmol) and triethylamine (720 μL, 5.17 mmol) were added sequentially to a solution of the crude substrate (2.59 mmol) in dichloromethane (12 mL) at 23°C. After stirring for 1 h, the reaction was quenched with water and extracted with dichloromethane. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (2% ethyl acetate in hexanes) to afford tert-butyl 1-(tri-n-butylstannyl)ethylcarbamate **2d** as a colorless oil (969 mg, 2.23 mmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm) : 4.60 (s, 1H), 3.26 (p, J = 7.9 Hz, 1H), 1.54 – 1.44 (m, 6H), 1.42 (s, 9H), 1.38 – 1.26 (m, 9H), 0.94 – 0.81 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 155.8, 78.7, 35.1, 29.2, 28.4, 27.5, 20.7, 13.7, 9.4. HRMS (ESI) $[M+Na]^+$ calcd for $C_{19}H_{41}NO_2NaSn$: 454.2052; found 454.2063

Tri-*n*-butylstannylmethyl acetate 2e. Triethylamine (650 μL, 4.66 mmol) and acetyl chloride (220 μL, 3.10 mmol) were added sequentially to a solution of tri-n-butylstannylmethanol (500 mg, 1.56 mmol) in dichloromethane (10 mL) at 23°C. After stirring for 2 h, the reaction was quenched with water and extracted with dichloromethane. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (20% dichloromethane in hexanes) to afford tri-*n*-butylstannylmethyl acetate **2e** as a colorless oil (414 mg, 1.14 mmol,

73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 4.15 (s, 2H), 2.02 (s, 3H), 1.60 – 1.40 (m, 6H), 1.30 (tq, *J* = 14.5, 7.3 Hz, 6H), 1.00 – 0.82 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 171.9, 55.8, 28.9, 27.3, 20.7, 13.7, 9.6. HRMS (ESI) $[M+Na]^+$ calcd for $C_{15}H_{32}O_2NaSn$: 383.1317; found 383.1335.

***S*-(Tri-n-butylstannylmethyl)ethanethioate 2f**. Potassium thioacetate (800 mg, 7.01 mmol) was added portionwise to a solution of tri-n-butylstannylmethyliodide (1.0 g, 2.32 mmol) in DMF (8.0 mL) at 23°C. After stirring for 15 min, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (1% ethyl acetate in hexanes) to afford *S*-(tri-n-butylstannylmethyl)ethanethioate **2f** as a colorless oil (864 mg, 2.28 mmol, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 2.31 (s, 3H), 2.06 (s, 2H), 1.59 – 1.39 (m, 6H), 1.30 (sex, *J* = 7.3 Hz, 6H), 0.99 – 0.84 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 198.9, 29.8, 28.9, 27.2, 13.6, 10.1, 4.9. HRMS (ESI) $[M+Na]^+$ calcd for $C_{15}H_{32}ONaSSn$: 399.1109; found 399.1099.

Tri-*n*-butylstannylmethylfluoride 2g. Deoxo-Fluor (50% in touluene, 1.2 mL, 3.25 mmol) was added dropwise to a solution of tri-n-butylstannylmethanol (466 mg, 1.45 mmol) in THF (8.0 mL) at 23°C. After stirring for 10 min, the reaction was quenched carefully with water at 0°C and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (100% hexanes) to afford tri-*n*-butylstannylmethylfluoride **2g** as a colorless oil (323 mg, 1.00 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 5.10 (dd, *J* = 47.3, 0.8 Hz, 2H), 1.65 – 1.39 (m, 6H), 1.39 – 1.24 (m, 6H), 1.00 – 0.85 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 81.6, 80.2, 29.0, 27.3, 13.7, 8.9. HRMS (EI) $[M-C_4H_9]^+$ calcd for $C_9H_{20}FSn$: 263.0556; found 263.0578.

N,N',N''-Tri-Boc-(tri-butylstannylmethyl)guanidine 2h. Di-tert-butyl azodicarboxylate (282 mg, 1.22 mmol) was added portionwise to a mixture of tri-n-butylstannylmethanol (393 mg, 1.22 mmol), tri-Boc-guanidine (440 mg, 1.22 mmol) and triphenylphosphine (321 mg, 1.22 mmol) in THF (5.0 mL) at 23°C, After stirring for 2 h, the reaction was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (2% ethyl acetate in hexanes) to afford N,N',N''-tri-Boc-(tri-n-butylstannylmethyl)guanidine **2h** as a colorless oil (623 mg, 0.941 mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 10.66 (s, 1H) 3.42 (s, 2H), 1.56 – 1.39 (m, 33H), 1.32 – 1.23 (m, 6H), 0.96 – 0.79 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 154.2, 151.2, 83.3, 34.2, 29.0, 28.1, 27.4, 13.7, 10.2. HRMS (ESI) $[M+Na]^+$ calcd for $C_{29}H_{57}N_3O_6NaSn$: 682.3163; found 682.3161.

N,N'-Di-Boc-(tri-n-butylstannylmethyl)carbamimidothioate 2i. A solution of tri-n-butylstannyliodide (980 mg, 2.27 mmol), N,N'-di-Boc thiourea (880 mg, 3.18 mmol) and triethylamine (800 μL, 5.74 mmol) in ethanol (10 mL) was heated at 80°C for 2 h. After cooling, the solvent was removed by evaporation and the residue was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (1% ethyl acetate in hexanes) to afford N,N'-di-Boc-(tri-n-butylstannylmethyl)carbamimidothioate **2i** as a colorless oil (1.1 g, 1.86 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 11.55 (s, 1H), 2.08 (s, 2H), 1.55 – 1.42 (m, 6H), 1.52 (s, 9H), 1.50 (s, 9H), 1.34 – 1.25 (m, 6H), 1.05 – 0.83 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 173.8, 160.8, 150.7, 82.9, 80.6, 29.0, 28.0, 27.3, 13.7, 10.3, 8.1. HRMS (ESI) $[M+Na]^+$ calcd for $C_{24}H_{48}N_2O_4NaSSn$: 599.2254; found 599.2252.

***N*-Boc-(tri-*n*-butylstannylmethyl)carbamimidothioate 2j**. A solution of tri-*n*-butylstannyliodide (1.8 g, 4.18 mmol), *N*-Boc thiourea (1.0 g, 5.67 mmol) and triethylamine (1.2 mL, 8.61 mmol) in ethanol (20

mL) was heated at 80°C for 2 h. After cooling, the solvent was removed by evaporation and the residue was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (2% ethyl acetate in hexanes) to afford *N*-Boc-(tri-n-butylstannylmethyl)carbamimidothioate **2j** as a colorless oil (1.6 g, 3.33 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 2.11 (s, 2H), 1.54 – 1.46 (m, 6H), 1.49 (s, 9H), 1.35 – 1.25 (m, 6H), 1.10 – 0.95 (m, 6H), 0.91 – 0.87 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 176.3, 161.5, 79.2, 28.8, 28.0, 27.1, 13.5, 10.1, 5.6. HRMS (ESI) $[M+Na]^+$ calcd for $C_{19}H_{40}N_2O_2NaSSn$: 499.1726; found 499.1730.

N,N'-Di-Boc-(tri-n-butylstannylmethyl)carbamimidate 2k. Mercury(II) chloride (1.25 g, 4.60 mmol) was added portionwise to a mixture of tri-n-butylstannylmethanol (1.0 g, 3.11 mmol), di-Boc-thiourea (1.3 g, 4.70 mmol) and triethylamine (2.0 mL, 14.4 mmol) in dichloromethane (20 mL) at 0°C, After stirring at 23°C for 2hr, the suspension was filtered through celite and washed with ethyl acetate. The filtrate was washed with water and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (20% dichloromethane in hexanes) to afford N,N'-di-Boc-(tri-n-butylstannylmethyl)carbamimidate **2k** as a colorless oil (818 mg, 1.45 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 10.55 (s, 1H), 4.39 (s, 2H), 1.54 – 1.42 (m, 6H), 1.49 (s, 9H), 1.48 (s, 9H), 1.32 – 1.23 (m, 6H), 0.96 – 0.81 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 162.0, 159.8, 148.5, 82.2, 80.1, 61.7, 28.9, 28.0, 27.9, 27.3, 13.6, 10.3. HRMS (ESI) $[M+Na]^+$ calcd for $C_{24}H_{48}N_2O_5NaSn$: 583.2478; found 583.2476.

General procedure 2.

***N*-Boc-amino-3-(4-methoxyphenyl)propan-2-one 3.** Copper(I) acetate (27 mg, 0.220 mmol) was added to a solution of *S*-4-tolyl-4-methoxyphenylacetothioate **1a** (30 mg, 0.110 mmol) and tert-butyl tri-*n*-butylstannylmethylcarbamate **2a** (93 mg, 0.220 mmol) in THF (1.0 mL). The reaction was heated at

50°C for 2 h. After cooling, the suspension was filtrated through Celite and washed with ethyl acetate. The filtrate was washed with water and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to afford *N*-Boc-amino-3-(4-methoxyphenyl)propan-2-one **3** as a colorless solid (30 mg, 0.108 mmol, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.15 – 7.09 (m, 2H), 6.89 – 6.83 (m, 2H), 5.19 (s, 1H), 4.03 (d, *J* = 4.8 Hz, 2H), 3.79 (s, 3H), 3.65 (s, 2H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 203.7, 158.9, 155.5, 130.3, 125.0, 114.3, 79.8, 55.2, 49.6, 46.6, 28.2. HRMS (EI) $[M]^+$ calcd for $C_{15}H_{21}NO_4$: 279.1471; found 279.1473.

2-Boc-amino-1-(4-methoxyphenyl)ethanone 4. The title compound was prepared according to general procedure 2 using copper(I) acetate (28 mg, 0.228 mmol), *S*-4-tolyl-4-methoxybenzothioate **1b** (30 mg, 0.116 mmol) and tert-butyl tri-n-butylstannylmethylcarbamate **2a** (97 mg, 0.231 mmol) in THF (1.0 mL) at 50°C for 2 h and obtained **4** as a colorless solid (30 mg, 0.114 mmol, 98%) after purification by column chromatography on silica gel (15% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.92 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 5.56 (s, 1H), 4.59 (d, *J* = 4.5 Hz, 2H), 3.86 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 192.8, 164.1, 155.8, 130.1, 127.6, 114.0, 79.7, 55.5, 47.1, 28.3. HRMS (ESI) $[M+Na]^+$ calcd for $C_{14}H_{19}NO_4Na$: 288.1212; found 288.1214.

1-Cbz-amino-3-(4-methoxyphenyl)propan-2-one 5. The title compound was prepared according to general procedure 2 using copper(I) acetate (27 mg, 0.220 mmol), *S*-4-tolyl 4-methoxyphenylacetothioate **1a** (30 mg, 0.110 mmol) and benzyl tri-*n*-butylstannylmethylcarbamate **2b** (100 mg, 0.220 mmol) in THF (1.0 mL) at 50°C for 2 h and obtained **5** as a colorless solid (31 mg, 0.097 mmol, 88%) after purification by column chromatography on silica gel (20% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.39 – 7.28 (m, 5H), 7.13 – 7.11 (m, 2H), 6.89 – 6.84 (m, 2H), 5.44 (s, 1H), 5.10 (s, 2H), 4.11 (d, *J* = 4.7 Hz, 2H), 3.79 (s, 3H), 3.66 (s, 2H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ(ppm): 203.2, 158.9, 156.0, 136.2, 130.3, 128.5, 128.0, 124.8, 114.3, 66.9, 55.2, 49.9, 46.5. HRMS (EI) $[M]^+$ calcd for $C_{18}H_{19}NO_4$: 313.1314; found 313.1312.

2-Cbz-amino-1-(4-methoxyphenyl)ethanone 6. The title compound was prepared according to general procedure 2 using copper(I) diphenylphosphinate (109 mg, 0.388 mmol), S-4-tolyl 4-methoxybenzothioate **1b** (50 mg, 0.194 mmol) and benzyl tri-n-butylstannylmethylcarbamate **2b** (176 mg, 0.388 mmol) in THF (1.5 mL) at 50°C for 2 h and obtained **6** as a colorless solid (47 mg, 0.156 mmol, 81%) after purification by column chromatography on silica gel (20% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.94 (d, J = 8.9 Hz, 2H), 7.42 – 7.30 (m, 5H), 6.96 (d, J = 8.9 Hz, 2H), 5.84 (s, 1H), 5.16 (s, 2H), 4.67 (d, J = 4.4 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 164.2, 156.2, 136.4, 130.1, 128.5, 128.1, 128.0, 127.4, 114.0, 66.9, 55.5, 47.4. HRMS (ESI) $[M+Na]^+$ calcd for $C_{17}H_{17}NO_4Na$: 322.1055; found 322.1063.

1-Acetylamino-3-(4-methoxyphenyl)propan-2-one 7. The title compound was prepared according to general procedure 2 using copper (I) acetate (42 mg, 0.343 mmol), S-4-tolyl 4-methoxyphenylacetothioate **1a** (46 mg, 0.169 mmol) and N-(tri-n-butylstannylmethyl)acetamide **2c** (122 mg, 0.337 mmol) im THF (1.0 mL) at 50°C for 2 h and obtained **7** as a colorless solid (36 mg, 0.162 mmol, 96%) after purification by column chromatography on silica gel (80% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.14 – 7.08 (m, 2H), 6.89 – 6.82 (m, 2H), 6.22 (s, 1H), 4.15 (s, 2H), 3.78 (s, 3H), 3.66 (s, 2H), 1.99 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 203.4, 170.1, 158.9, 130.3, 124.8, 114.4, 55.2, 48.6, 46.8, 22.8. HRMS (EI) $[M]^+$ calcd for $C_{12}H_{15}NO_3$: 221.1052; found 221.1049.

2-Acetylamino-1-(4-methoxyphenyl)ethanone 8. The title compound was prepared according to general procedure 2 using copper(I) diphenylphosphinate (109 mg, 0.388 mmol), S-4-tolyl 4-

methoxybenzothioate **1b** (50 mg, 0.194 mmol) and N-(tri-n-butylstannylmethyl)acetamide **2c** (140 mg, 0.387 mmol) in THF (1.5 mL) at 50°C for 2 h and obtained **8** as a colorless solid (36 mg, 0.173 mmol, 89%) after purification by column chromatography on silica gel (100% ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.94 (dd, *J* = 9.0, 1.1 Hz, 2H), 6.95 (dd, *J* = 9.0, 1.1 Hz, 2H), 6.63 (s, 1H), 4.69 (d, *J* = 4.2 Hz, 2H), 3.87 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 192.5, 170.2, 164.2, 130.2, 127.3, 114.1, 55.5, 46.1, 23.0. HRMS (ESI) $[M+Na]^+$ calcd for $C_{11}H_{13}NO_3Na$: 230.0793; found 230.0790.

3-Boc-amino-1-(4-methoxyphenyl)butan-2-one 9. The title compound was prepared according to general procedure 2 using copper(I) acetate (27 mg, 0.220 mmol), S-4-tolyl 4-methoxyphenylacetothioate **1a** (30 mg, 0.110 mmol) and tert-butyl 1-(tri-n-butylstannyl)ethylcarbamate **2d** (96 mg, 0.221 mmol) in THF (1.0 mL) at 65°C for 24 h and obtained **9** as a colorless solid (21 mg, 0.726 mmol, 66%) after purification by column chromatography on silica gel (15% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.26 (s, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.21 (s, 1H), 4.44 – 4.37 (m, 1H), 3.79 (s, 3H), 3.74 (d, *J* = 6.2 Hz, 2H), 1.31 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 207.3, 158.7, 155.1, 130.5, 125.3, 114.1, 79.7, 55.2, 54.5, 45.3, 28.3, 17.8. HRMS (EI) $[M]^+$ calcd for $C_{16}H_{23}NO_4$: 293.1627; found 293.1632.

2-Boc-amino-1-(4-methoxyphenyl)propanone 10. The title compound was prepared according to general procedure 2 using copper(I) acetate (47 mg, 0.383 mmol), S-4-tolyl 4-methoxybenzothioate **1b** (50 mg, 0.194 mmol) and tert-butyl 1-(tri-n-butylstannyl)ethylcarbamate **2d** (168 mg, 0.387 mmol) in THF (1.5 mL) at 65°C for 2 h and obtained **10** as a colorless solid (36 mg, 0.129 mmol, 67%) after purification by column chromatography on silica gel (15% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.96 (dd, *J* = 9.3, 2.3 Hz, 2H), 6.95 (dd, *J* = 9.0, 2.2 Hz, 2H), 5.59 (d, *J* = 7.7 Hz, 1H), 5.27 – 5.20 (m, 1H), 3.87 (s, 3H), 1.45 (s, 9H), 1.39 (dd, *J* = 7.2, 2.0 Hz, 3H). ^{13}C NMR (126 MHz,

$CDCl_3$) δ(ppm): 197.8, 164.0, 155.2, 131.0, 127.0, 114.0, 79.5, 55.5, 50.7, 28.4, 20.2. HRMS (ESI) $[M+Na]^+$ calcd for $C_{15}H_{21}NO_4Na$: 302.1368; found 302.1368.

1-Acetoxy-3-(4-methoxyphenyl)propan-2-one 11. The title compound was prepared according to general procedure 2 using copper(I) acetate (27 mg, 0.220 mmol), S-4-tolyl 4-methoxyphenylacetothioate **1a** (30 mg, 0.110 mmol) and tri-n-butylstannylmethyl acetate **2e** (80 mg, 0.220 mmol) in DMF (1.0 mL) at 80°C for 24 h and obtained **11** as a colorless solid (20 mg, 0.886 mmol, 81%) after purification by column chromatography on silica gel (25% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.13 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.68 (s, 2H), 3.79 (s, 3H), 3.67 (s, 2H), 2.15 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 201.6, 170.1, 158.9, 130.4, 124.7, 114.3, 67.4, 55.2, 45.5, 20.4. HRMS (EI) $[M]^+$ calcd for $C_{12}H_{14}O_4$: 222.0892; found 222.0896.

2-Acetoxy-1-(4-methoxyphenyl)ethanone 12. The title compound was prepared according to general procedure 2 using copper(I) acetate (28 mg, 0.228 mmol), S-4-tolyl 4-methoxybenzothioate **1b** (30 mg, 0.116 mmol) and tri-n-butylstannylmethyl acetate **2e** (84 mg, 0.231 mmol) in DMF (1.0 mL) at 80°C for 24 h and obtained **12** as a colorless solid (19 mg, 0.129 mmol, 78%) after purification by column chromatography on silica gel (20% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.89 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 5.29 (s, 2H), 3.87 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 190.6, 170.4, 164.0, 130.0, 127.2, 114.0, 65.7, 55.5, 20.6. HRMS (ESI) $[M+Na]^+$ calcd for $C_{11}H_{12}O_4Na$: 231.0633; found 231.0641.

1-Acetylsulfanyl-3-(4-methoxyphenyl)propan-2-one 13. The title compound was prepared according to general procedure 2 using copper(I) diphenylphosphinate (62 mg, 0.221 mmol), S-4-tolyl 4-methoxyphenylacetothioate **1a** (30 mg, 0.110 mmol) and *S*-(tri-n-Butylstannylmethyl)ethanethioate **2f** (84 mg, 0.222 mmol) in DMF (1.0 mL) at 80°C for 24 h and obtained **13** as a colorless solid (21 mg,

0.890 mmol, 81%) after purification by column chromatography on silica gel (15% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.14 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 2H), 3.76 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 201.7, 194.3, 158.8, 130.5, 125.4, 114.3, 55.2, 48.0, 38.4, 30.1. HRMS (EI) $[M]^+$ calcd for $C_{12}H_{14}O_3S$: 238.0664; found 238.0663.

2-Acetylsulfanyl-1-(4-methoxyphenyl)ethanone 14. The title compound was prepared according to general procedure 2 using copper(I) diphenylphosphinate (109 mg, 0.388 mmol), S-4-tolyl 4-methoxybenzothioate **1b** (50 mg, 0.194 mmol) and *S*-(tri-n-Butylstannylmethyl)ethanethioate **2f** (147 mg, 0.388 mmol) in DMF (1.5 mL) at 80°C for 24 h and obtained **14** as a colorless solid (31 mg, 0.137 mmol, 71%) after purification by column chromatography on silica gel (15% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.97 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 4.35 (s, 2H), 3.87 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 194.3, 191.7, 164.0, 130.8, 128.5, 113.9, 55.5, 36.3, 30.2. HRMS (EI) $[M]^+$ calcd for $C_{11}H_{12}O_3S$: 224.0507; found 224.0511.

1-Fluoro-3-(4-methoxyphenyl)propan-2-one 15. The title compound was prepared according to general procedure 2 using copper(I) diphenylphosphinate (103 mg, 0.367 mmol), S-4-tolyl 4-methoxyphenylacetothioate **1a** (50 mg, 0.184 mmol) and tri-n-butylstannylmethylfluoride **2g** (119 mg, 0.368 mmol) in DMF (1.0 mL) at 80°C for 24 h and obtained **15** as a yellow solid (26 mg, 0.142 mmol, 78%) after purification by column chromatography on silica gel (10% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.14 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.85 (d, *J* = 48 Hz, 2H), 3.80 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 204.4, 158.9, 130.5, 124.2, 114.3, 85.2, 83.7, 55.2, 44.6. HRMS (EI) $[M]^+$ calcd for $C_{10}H_{11}FO_2$: 182.0743; found 182.0746.

2-Fluoro-1-(4-methoxyphenyl)ethanone 16. The title compound was prepared according to general procedure 2 using copper(I) diphenylphosphinate (109 mg, 0.388 mmol), S-4-tolyl 4-methoxybenzothioate **1b** (50 mg, 0.194 mmol) and tri-n-butylstannylmethylfluoride **2g** (125 mg, 0.387 mmol) in DMF (1.5 mL) at 80°C for 24 h and obtained **16** as a colorless solid (23 mg, 0.139 mmol, 72%) after purification by column chromatography on silica gel (15% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.88 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 5.47 (dd, *J* = 50, 0.9 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 192.0, 164.2, 130.3, 126.8, 114.1, 84.2, 82.7, 55.5. HRMS (EI) $[M]^+$ calcd for $C_9H_9FO_2$: 168.0587; found 168.0593.

1-(N,N',N''-Tri-Boc-guanidinyl)-3-(4-methoxyphenyl)propan-2-one S-12. The title compound was prepared according to general procedure 2 using copper(I) diphenylphosphinate (62 mg, 0.221 mmol), S-4-tolyl 4-methoxyphenylacetothioate **1a** (30 mg, 0.110 mmol) and N,N',N''-tri-Boc-(tri-n-butylstannylmethyl)guanidine **2h** (146 mg, 0.220 mmol) in THF (1.0 mL) at 50°C for 2 h and obtained **S-12** as a colorless oil (52 mg, 0.0991 mmol, 90%) after purification by column chromatography on silica gel (15% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 10.63 (s, 1H), 7.15 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.59 (s, 2H), 3.78 (s, 3H), 3.71 (s, 2H), 1.48 (s, 18H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 202.0, 158.7, 153.0, 130.6, 125.5, 114.1, 84.1, 55.2, 55.1, 45.9, 28.0, 27.7. HRMS (ESI) $[M+Na]^+$ calcd for $C_{26}H_{39}N_3O_8Na$: 544.2635; found 544.2630.

2-(N,N',N''-Tri-Boc-guanidinyl)-1-(4-methoxyphenyl)ethanone S-13. The title compound was prepared according to general procedure 2 using copper(I) diphenylphosphinate (109 mg, 0.388 mmol), S-4-tolyl 4-methoxybenzothioate **1b** (50 mg, 0.194 mmol) and N,N',N''-tri-Boc-(tri-n-butylstannylmethyl)guanidine **2h** (256 mg, 0.386 mmol) in THF (1.5 mL) at 50°C for 2 h and obtained **S-13** as a colorless solid (95 mg, 0.187 mmol, 96%) after purification by column chromatography on silica gel (15% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 10.69 (s, 1H), 7.93 (d, *J*

= 8.8 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 5.24 (s, 2H), 3.87 (s, 3H), 1.47, (s, 18H), 1.41 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 191.4, 163.7, 153.3, 130.2, 128.1, 113.8, 84.0, 55.5, 52.7, 28.1, 27.7. HRMS (ESI) $[M+Na]^+$ calcd for $C_{25}H_{37}N_3O_8Na$: 530.2478; found 530.2467.

1-(N,N',N''-Tri-Boc-guanidinyl)-3-(4-hydroxyphenyl)propan-2-one S-14. The title compound was prepared according to general procedure 2 using copper(I) acetate (47 mg, 0.383 mmol), S-4-tolyl 2-(4-hydroxyphenyl)ethanethioate **1c** (50 mg, 0.194 mmol) and N,N',N''-tri-Boc-(tri-n-butylstannylmethyl)guanidine **2h** (256 mg, 0.386 mmol) in THF (1.5 mL) at 50°C for 2 h and obtained **S-14** as a colorless solid (67 mg, 0.133 mmol, 68%) after purification by column chromatography on silica gel (25% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 10.63 (s, 1H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 4.59 (s, 2H), 3.66 (s, 2H), 1.48 (s, 18H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 202.4, 155.4, 153.0, 148.8, 130.6, 130.3, 124.7, 115.7, 84.4, 55.0, 46.0, 28.0, 27.7. HRMS (ESI) $[M+Na]^+$ calcd for $C_{25}H_{37}N_3O_8Na$: 530.2478; found 530.2467.

1-(N,N',N''-Tri-Boc-guanidinyl)-3-(4-methoxyphenyl)butan-2-one S-15. The title compound was prepared according to general procedure 2 using copper(I) acetate (51 mg, 0.416 mmol), S-4-tolyl 2-(4-methoxyphenyl)propanethioate **1d** (60 mg, 0.210 mmol) and N,N',N''-tri-Boc-(tri-n-butylstannylmethyl)guanidine **2h** (278 mg, 0.420 mmol) in THF (1.5 mL) at 50°C for 2 h and obtained **S-15** as a colorless oil (101 mg, 0.189 mmol, 90%) after purification by column chromatography on silica gel (15% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 10.59 (s, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.56 (d, *J* = 17.8 Hz, 1H), 4.44 (d, *J* = 17.8 Hz, 1H), 3.81 (m, 1H), 3.77 (s, 3H), 1.47 (s, 18H), 1.39 (d, *J* = 13.7 Hz, 3H), 1.39 (s, 9H). ^{13}C NMR (126 MHz, $cdcl_3$) δ(ppm): 204.3, 158.8, 153.0, 131.9, 129.0, 114.3, 83.9, 82.3, 80.2, 55.2, 54.5, 49.1, 28.0, 27.6, 17.5. HRMS (ESI) $[M+Na]^+$ calcd for $C_{27}H_{41}N_3O_8Na$: 558.2791; found 558.2780.

4-(1-(N,N',N''-tri-Boc-guanidinyl)-2-oxo-butane-3-yl)-7-methoxy-1H-indole S-16. The title compound was prepared according to general procedure 2 using copper(I) acetate (48 mg, 0.392 mmol), 7-methoxy-4-(4-tolylsulfanyl-3-oxopropan-2-yl)-1H-indole **1e** (64 mg, 0.197 mmol) and N,N'.N''-tri-Boc-(tri-n-butylstannylmethyl)guanidine **2h** (260 mg, 0.393 mmol) in THF (1.5 mL) at 50°C for 2 h and obtained **S-16** as a colorless oil (111 mg, 0.193 mmol, 98%) after purification by column chromatography on silica gel (15% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 10.54 (s, 1H), 8.45 (s, 1H), 7.18 (dd, *J* = 3.1, 2.5 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 6.57 (dd, *J* = 3.1, 2.3 Hz, 1H), 4.51 (d, *J* = 17.8 Hz, 1H), 4.42 (d, *J* = 17.8 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 1H), 3.94 (s, 3H), 1.54 (d, *J* = 7.1 Hz, 3H), 1.48 (s, 18H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 204.8, 153.2, 145.5, 128.0, 126.4, 124.0, 123.8, 119.1, 102.0, 101.2, 83.7, 55.2, 54.4, 47.9, 28.0, 27.5, 16.3. HRMS (ESI) $[M+Na]^+$ calcd for $C_{29}H_{42}N_4O_8Na$: 597.2890; found 597.2890.

N,N'-Di-Boc-3-(4-methoxyphenyl)-2-oxopropylcarbamimidothioate 22. The title compound was prepared according to general procedure 2 using copper(I) acetate (27 mg, 0.220 mmol), S-4-tolyl 4-methoxyphenylacetothioate **1a** (30 mg, 0.110 mmol) and N,N'-di-Boc-(tri-n-butylstannylmethyl)carbamimidothioate **2i** (127 mg, 0.219 mmol) in THF (1.0 mL) at 50°C for 24 h and obtained **22** as a colorless solid (23 mg, 0.0513 mmol, 47%) after purification by column chromatography on silica gel (15% ethyl acetate in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 11.49 (s, 1H), 7.17 (s, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 3.96 (s, 2H), 3.80 (s, 3H), 3.62 (s, 2H), 1.50 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 202.8, 169.5, 160.0, 158.7, 150.6, 130.8, 126.2, 114.0, 83.7, 80.9, 55.2, 49.0, 39.6, 28.0. HRMS (ESI) $[M+Na]^+$ calcd for $C_{21}H_{30}N_2O_6NaS$: 461.1722; found 461.1711.

N,N'-Di-Boc-3-(4-methoxyphenyl)-2-oxopropylcarbamimidate 26. The title compound was prepared according to general procedure 2 using copper(I) diphenylphosphinate (103 mg, 0.367 mmol), S-4-tolyl 4-methoxyphenylacetothioate **1a** (50 mg, 0.184 mmol) and N,N'-di-Boc-(tri-n-

butylstannylmethyl)carbamimidate **2k** (207 mg, 0.367 mmol) in THF (1.5 mL) at 65°C for 24 h and obtained **26** as a colorless oil (56 mg, 0.132 mmol, 72%) after purification by column chromatography on silica gel (3% acetone in toluene). The NMR spectra of this compound showed keto and enol forms. ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): [keto form] 10.92 (s, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.85 (dd, *J* = 15.2, 8.6 Hz, 2H), 4.56 (s, 2H), 3.78 (s, *3*H), 3.65 (s, 2H), 1.49 (s, 9H), 1.38 (s, 9H). [enol form] 7.07 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 3.80 – 3.78 (m, 0.5 H), 3.51 (d, *J* = 11 Hz, 0.5 H), 3.39 (d, *J* = 14 Hz, 0.5 H), 3.15 (d, *J* = 14 Hz, 0.5 H), 1.60 (s, 9H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 201.3, 158.9, 158.8, 154.0, 151.8, 150.0, 149.6, 149.3, 147.5, 130.8, 130.4, 126.1, 125.1, 114.3, 114.1, 85.9, 85.1, 84.6, 83.3, 82.1, 55.2, 55.1, 51.6, 50.7, 46.2, 43.6, 28.1, 28.0, 27.9, 27.6. HRMS (ESI) $[M+Na]^+$ calcd for $C_{21}H_{30}N_2O_7Na$: 445.1951; found 445.1958.

N,N'-Di-Boc-2-(4-methoxyphenyl)-2-oxoethylcarbamimidate 28. The title compound was prepared according to general procedure 2 using copper(I) diphenylphosphinate (65 mg, 0.232 mmol), S-4-tolyl 4-methoxybenzothioate **1b** (30 mg, 0.116 mmol) and N,N'-di-Boc-(tri-n-butylstannylmethyl)carbamimidate **2k** (131 mg, 0.233 mmol) in THF (1.0 mL) at 65°C for 24 h and obtained **28** as a colorless solid (41 mg, 0.100 mmol, 86%) after purification by column chromatography on silica gel (25% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 11.04 (s, 1H), 7.92 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 5.13 (s, 2H), 3.87 (s, 3H), 1.50 (s, 9H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 191.3, 163.9, 154.4, 150.2, 149.4, 130.0, 127.9, 114.0, 85.0, 82.0, 55.5, 49.3, 28.0, 27.7. HRMS (ESI) $[M+Na]^+$ calcd for $C_{20}H_{28}N_2O_7Na$: 431.1794; found 431.1783.

2-Boc-amino-4-(4-methoxybenzyl)thiazole 23. The title compound was prepared according to general procedure 2 using copper(I) acetate (54 mg, 0.441 mmol), S-4-tolyl 4-methoxyphenylacetothioate **1a** (60 mg, 0.220 mmol) and N-Boc-(tri-n-butylstannylmethyl)carbamimidothioate **2j** (212 mg, 0.442 mmol) in DMF (1.5 mL) at 50°C for 24 h and obtained **23** as a colorless solid (57 mg, 0.179 mmol,

81%) after purification by column chromatography on silica gel (15% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.15 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.31 (s, 1H), 3.96 (s, 2H), 3.79 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 160.7, 158.2, 152.5, 151.6, 130.9, 130.0, 113.9, 107.5, 82.5, 55.2, 36.8, 28.3. HRMS (ESI) $[M+Na]^+$ calcd for $C_{16}H_{20}N_2O_3NaS$: 343.1092; found 343.1079.

2-(Boc-amino)-4-(4-methoxyphenyl)thiazole 25: The title compound was prepared according to general procedure 2 using copper(I) acetate (47 mg, 0.383 mmol), S-4-tolyl 4-methoxybenzothioate **1b** (50 mg, 0.194 mmol) and N-Boc-(tri-n-butylstannylmethyl)carbamimidothioate **2j** (186 mg, 0.388 mmol) in DMF (1.5 mL) at 80°C for 24 h and obtained **25** as a colorless solid (51 mg, 0.165 mmol, 85%) after purification by column chromatography on silica gel (10% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 10.17 (s, 1H), 7.75 (d, *J* = 8.8 Hz, 2H), 6.96 (s, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 160.8, 159.4, 152.6, 149.6, 127.4, 127.3, 114.0, 104.7, 82.1, 55.3, 27.8. HRMS (ESI) $[M+Na]^+$ calcd for $C_{15}H_{18}N_2O_3NaS$: 329.0936; found 329.0929.

2-Amino-4-(4-methoxybenzyl)-1H-imidazole TFA salt 17. Trifluoroacetic acid (2.0 mL) was added dropwise to a solution of 1-(N,N',N''-tri-Boc-guanidinyl)-3-(4-methoxyphenyl)propan-2-one **S-12** (83 mg, 0.159 mmol) in dichloromethane (2.0 ml). After stirring for 5 h, the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (10% methanol in dichloromethane) to afford 2-amino-4-(4-methoxybenzyl)-1H-imidazole TFA salt **17** as a yellow solid (44 mg, 0.148 mmol, 93%). ^{1}H NMR (500 MHz, Acetone-d_6) δ(ppm): 7.70 (s, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.52 (s, 1H), 3.78 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (126 MHz, Acetone-d_6) δ(ppm): 159.8, 149.9, 130.7, 130.5, 128.3, 115.0, 110.0, 55.7, 30.8. HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_{13}N_3O$: 204.1137; found 204.1133.

2-Amino-4-(4-methoxyphenyl)-1H-imidazole TFA salt 18. Trifluoroacetic acid (2.0 mL) was added dropwise to a solution of 2-(N,N',N''-tri-Boc-guanidinyl)-1-(4-methoxyphenyl)ethanone **S-13** (83 mg, 0.159 mmol) in dichloromethane (2.0 ml). After stirring for 5 h, the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (10% methanol in dichloromethane) to afford 2-amino-4-(4-methoxyphenyl)-1H-imidazole TFA salt **18** as a yellow solid (32 mg, 0.113 mmol, 91%). ^{1}H NMR (500 MHz, Acetone-d_6) δ(ppm): 11.87 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.14 (s, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, Acetone-d_6) δ(ppm): 160.9, 149.9, 128.7, 126.8, 121.6, 115.5, 108.1, 55.8. HRMS (ESI) $[M+H]^+$ calcd for $C_{10}H_{12}N_3O$: 190.0980; found 190.0969.

2-Amino-4-(4-hydroxybenzyl)-1H-imidazole TFA salt 19. Trifluoroacetic acid (1.0 mL) was added dropwise to a solution of 1-(N,N',N''-tri-Boc-guanidinyl)-3-(4-methoxyphenyl)propan-2-one **S-14** (39 mg, 0.077 mmol) in dichloromethane (1.0 ml). After stirring for 2 h, the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (10% methanol in dichloromethane with 0.5 % TFA) to afford 2-amino-4-(4-hydroxybenzyl)-1H-imidazole TFA salt **19** as a yellow solid (20 mg, 0.070 mmol, 92%). ^{1}H NMR (500 MHz, methanol-d_4) δ(ppm): 7.06 (m, 2H), 7.74 (m, 2H), 6.41 (m, 1H), 3.72 (s, 2H), 3.35 (s, 1H). ^{13}C NMR (126 MHz, methanol-d_4) δ(ppm): 157.4, 148.9, 130.6, 128.9, 128.8, 116.5, 110.2, 30.8. HRMS (EI) $[M]^+$ calcd for $C_{10}H_{11}N_3O$: 189.0902; found 189.0898.

2-Amino-4-(1-(4-methoxyphenyl)ethyl)-1H-imidazole TFA salt 20. Trifluoroacetic acid (2.0 mL) was added dropwise to a solution of 1-(N,N',N''-tri-Boc-guanidinyl)-3-(4-methoxyphenyl)butan-2-one **S-15** (101 mg, 0.189 mmol) and dichloromethane (2.0 mL) and obtained **20** as a brown oil (58 mg, 0.184 mmol, 98%) after purification by column chromatography on silica gel (10% methanol in dichloro-

methane). ^{1}H NMR (500 MHz, Acetone-d_6) δ(ppm): 7.71 (s, 1H), 7.24 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.54 (d, J = 1.2 Hz, 1H), 4.03 – 3.96 (m, 1H), 3.77 (s, 3H), 1.55 (d, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, Acetone-d_6) δ(ppm): 159.8, 149.7, 136.1, 133.2, 129.3, 115.0, 109.2, 55.7, 36.4, 20.9. HRMS (ESI) $[M+H]^+$ calcd for $C_{12}H_{16}N_3O$: 218.1293; found 218.1290.

2-Amino-4-(1-(7-methoxy-1H-indol-4-yl)ethyl)-1H-imidazole TFA salt 21. Trifluoroacetic acid (270 □L, 3.63 mmol) was added dropwise to a solution of 4-(1-(N,N',N''-tri-Boc-guanidinyl)-2-oxo-butane-3-yl)-7-methoxy-1H-indole **S-16** (103 mg, 0.179 mmol) in dichloromethane (2.0 mL) and obtained **21** as a purple solid (45 mg, 0.128 mmol, 72%) after purification by column chromatography on silica gel (10% methanol in dichloromethane). ^{1}H NMR (500 MHz, Acetone-d_6) δ(ppm): 10.31 (s, 1H), 7.65 (s, 2H), 7.26 (t, J = 2.8 Hz, 1H), 6.86 (dd, J = 7.9, 0.6 Hz, 1H), 6.60 (d, J = 7.9 Hz, 1H), 6.58 (d, J = 1.3 Hz, 1H), 6.53 (dd, J = 3.1, 2.1 Hz, 1H), 4.40 – 4.32 (m, 1H), 3.91 (s, 3H), 1.66 (d, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Acetone-d_6) δ(ppm): 149.7, 146.8, 132.9, 128.9, 127.9, 127.7, 125.2, 118.5, 109.4, 102.4, 101.3, 55.8, 34.7, 20.2. HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{16}N_4O$: 257.1402; found 257.1411.

2-Amino-4-(4-methoxybenzyl)thiazole 24. Trifluoroacetic acid (1.0 mL) was added dropwise to a solution of N,N'-di-Boc-3-(4-methoxyphenyl)-2-oxopropylcarbamimidothioate **22** (22 mg, 0.0490 mmol) in dichloromethane (1.0 ml). After stirring for 1 h, the solvent was removed by evaporation and the residue was quenched with saturated aqueous $NaHCO_3$ solution and extracted with dichloromethane. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (50% ethyl acetate in hexanes) to afford 2-amino-4-(4-methoxybenzyl)thiazole **24** as a yellow solid (11 mg, 0.0481 mmol, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ(ppm): 7.16 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.99 (s, 1H), 5.11 (s, 2H), 3.79 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ(ppm): 167.7, 158.1, 152.5, 131.1, 129.9, 113.8, 103.5, 55.2, 37.1. HRMS (ESI) $[M+H]^+$ calcd for $C_{11}H_{13}N_2OS$: 221.0749; found 221.0745.

2-Amino-4-(4-methoxybenzyl)oxazole TFA salt 27. Trifluoroacetic acid (2.0 mL) was added dropwise to a solution of N,N'-di-Boc-3-(4-methoxyphenyl)-2-oxopropylcarbamimidate **26** (55 mg, 0.129 mmol) in dichloromethane (2.0 ml). After stirring for 1 h, the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (10% methanol in dichloromethane) to afford 2-amino-4-(4-methoxybenzyl)oxazole TFA salt **27** as a orange solid (31 mg, 0.103 mmol, 80%). ^{1}H NMR (500 MHz, $CDCl_3$ (0.5% TFA)) δ(ppm): 7.14 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.21 (s, 1H), 3.85 (s, 3H), 3.73 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$ (0.5% TFA)) δ(ppm): 158.5, 154.1, 129.9, 128.5, 125.4, 114.8, 107.3, 55.8, 30.8. HRMS (ESI) $[M+Na]^+$ calcd for $C_{11}H_{12}N_2O_2Na$: 227.0796; found 227.0797.

2-Amino-4-(4-methoxyphenyl)-1H-imidazole TFA salt 29. Trifluoroacetic acid (1.0 mL) was added dropwise to a solution of N,N'-di-Boc-2-(4-methoxyphenyl)-2-oxoethylcarbamimidate **28** (43 mg, 0.105 mmol) in dichloromethane (1.0 ml). After stirring for 10 h, the reaction mixture was concentrated. Due to the substrates low solubility, the yellow solid was washed with cold DCM (x3) to afford 2-amino-4-(4-methoxyphenyl)-1H-imidazole TFA salt **29** as a white solid (22 mg, 0.076 mmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$ (0.5% TFA)) δ(ppm): 7.34 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.63 (s, 1H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$ (0.5% TFA)) δ(ppm): 159.9, 154.3, 125.74, 125.70, 120.4, 115.1, 104.7, 55.7. HRMS (EI) $[M]^+$ calcd for $C_{10}H_{12}N_3O$: 190.0980; found 190.0969.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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