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An unusual 1,2-N→C acyl migration in urea derivatives of α-aminoorganolithiums

Kevin W. Kells, Adela Ncube and J. Michael Chong*

Department of Chemistry, Guelph-Waterloo Centre for Graduate Work in Chemistry and Biochemistry, University of Waterloo, 200 University Ave W, Waterloo, Ontario, Canada N2L 3G1

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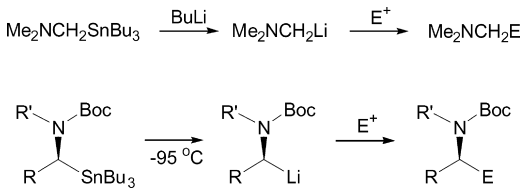
Abstract—Transmetalation of urea derivatives of α-aminoorganostannanes with alkyllithiums provides α-aminoorganolithiums which undergo rapid N to C acyl migration to afford α-aminocarboxamides. The stereochemical course of the transmetalation/migration process depends on the substituents on the urea and varies from complete retention of configuration to complete racemization.

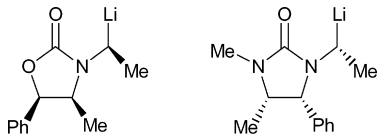
1. Introduction

α-Aminoorganostannanes are useful precursors of α-aminoorganolithiums.[1] The first example of this type of transformation was reported by Peterson using *N*,*N*-dimethylaminomethyltributylstannane (Scheme 1).[2] It has subsequently been shown that Sn–Li exchange with other dimethylaminoorganostannanes gives organolithiums which are too unstable to be trapped with electrophiles.[3] However, use of other nitrogen-protecting groups, particularly carbamates, allows for the preparation of synthetically useful α-aminoorganolithiums.[4–6]



Scheme 1.

The configurational stability of *N*-Boc α-aminoorganolithiums is such that trapping with complete retention of configuration is possible at −95 °C but slow racemization occurs even at −78 °C.[1,5] Pearson has shown that with oxazolidinone and imidazolidinone-protected α-aminoorganolithiums **1** and **2**, the imidazolidinone **2** was more configurationally stable.[7] This increased stability was attributed to the better donor properties of the imidazolidinone carbonyl oxygen compared to the oxazolidinone carbonyl. Further evidence for the importance of coordination on the configurational stability of α-aminoorganolithiums has been provided by Meyers who showed that certain formamidines (featuring Li–N coordination) are more resistant to racemization than their Boc counterparts (which presumably have Li–O complexation).[8]



1 **2**

To investigate whether this observation is general, we decided to prepare urea-protected α-aminoorganostannanes and study their transmetalation chemistry, with the intent of developing α-aminoorganolithiums which are more configurationally stable. We now report that the acyclic urea-protected α-aminoorganolithiums formed by Sn–Li exchange undergo an unusual 1,2-acyl migration with unexpected stereochemical consequences.

2. Results and discussions

We have previously shown that *N*-methyl-*N*-Boc-protected α-aminoorganostannanes such as **4** could be prepared by sequential treatment of primary amines $RCH(NH_2)SnBu_3$ (**3**) with $(Boc)_2O$ followed by NaH/MeI. By analogy, we prepared urea derivative **6a** by treatment of **3a** with dimethylcarbamoyl chloride followed by NaH/MeI

Keywords: Acyl migration; Urea; α-Aminoorganostannanes; α-Aminoorganolithiums.
* Corresponding author. Tel.: +1-519-888-4567x6643; fax: +1-519-746-0435; e-mail address: jmchong@uwaterloo.ca

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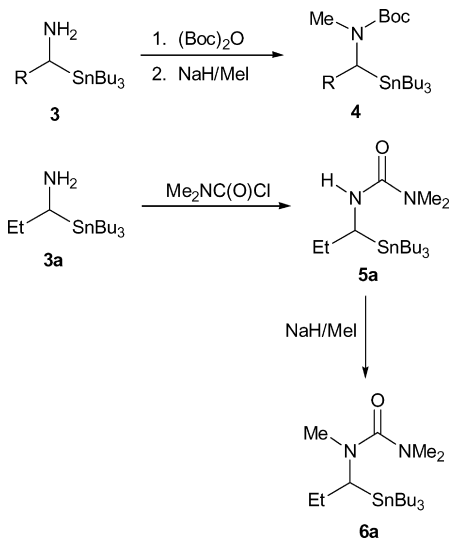
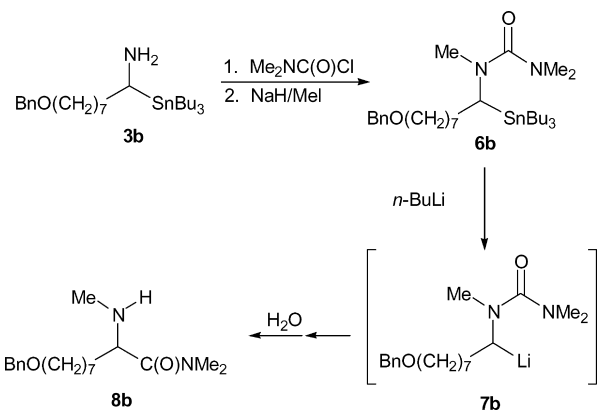


Scheme 2.

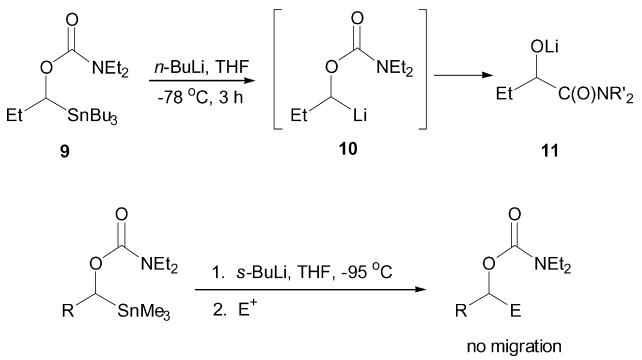
(Scheme 2). With Boc derivatives **4**, transmetalation/trapping (*n*-BuLi, THF, −78 °C then E^+) proceeded routinely to provide the expected products in high yields. However, reactions of urea **6a** under essentially the same conditions were anything but routine. Indeed, Bu_4Sn was isolated in high yields but no other products were detected. None of the expected products from a variety of electrophilic quenches could be isolated.

These results suggested that the expected Sn–Li exchange was occurring but the intermediate organolithium generated undergoes further chemistry to produce materials which are not easily detected (e.g., volatile or polar/water soluble). In order to possibly isolate and identify these materials, urea **6b**, containing a large, non-polar side-chain, was prepared. Synthesis of **6b** was straightforward using previously developed methodology (Scheme 3). When **6b** was subjected to the usual transmetalation conditions (*n*-BuLi, THF, −78 °C), Bu_4Sn was produced along with an extremely polar compound which was subsequently identified as amino amide **8b**.

Amide **8b** was completely unexpected as ureas are usually stable to organolithiums and we have previously shown that similar *t*-Boc carbamates form reasonably stable α-aminoorganolithiums. One would anticipate, based on simple



Scheme 3.

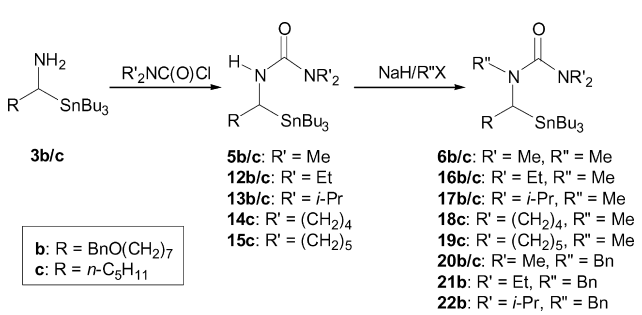


Scheme 4.

electronegativity arguments, that the carbonyl of a urea would be much less electrophilic than that of a carbamate just as amides are usually much less electrophilic than esters. Amide **8b** formally arises from a 1,2-acyl migration from nitrogen to carbon. Gawley has reported a similar migration from oxygen to carbon (Scheme 4).[9] In Gawley's example, the intermediate α-alkoxyorganolithium rearranged to the more stable alkoxide over a period of 3 h at −78 °C. We have previously shown that this migration in carbamate-protected α-alkoxyorganolithiums can be suppressed by cooling to −95 °C.[10] With the organolithium derived from **6b**, migration occurred rapidly at −78 °C. The difference in reaction rates is counter-intuitive as the amide anion formed should be much less stable than an alkoxide. In other words, one might expect acyl migration to occur with organolithium **10** (especially given what is known about similar rearrangements—anionic Fries—in *ortho*-lithiated *O*-phenylcarbamates[11] and similar compounds[12]) but not with organolithium **7b**. While rearrangement of **7b** was not expected, it should be noted that structurally related lithiated phosphoramidates undergo rapid migration of the dialkoxyphosphinyl group.[13]

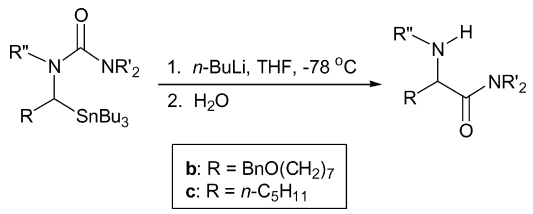
To probe the generality of this unexpected rearrangement and to possibly develop it as a useful synthetic method, other urea derivatives were prepared (Scheme 5). These were all prepared routinely from primary α-aminoorganostannanes by treatment with a carbamoyl chloride followed by alkylation.

For a series of *N*-methyl ureas, transmetalation/migration occurred smoothly to give α-amino amides (Table 1, entries 1–8). Reactions were typically very clean with Bu_4Sn and the amino amides as the only products detected. Isolated yields increased as the size of the *N*,*N*-dialkyl substituent increased from Me to Et to *i*-Pr. This may be because the



Scheme 5.

Table 1. Rearrangement of urea-protected α-aminoorganostannanes to α-amino amides



Entry	Stannane	R′	R″	% Yield[a] (#)
1	**6b**	Me	Me	69 (**8b**)
2	**6c**	Me	Me	77 (**8c**)
3	**16b**	Et	Me	73 (**23b**)
4	**16c**	Et	Me	85 (**23c**)
5	**17b**	*i*-Pr	Me	85 (**24b**)
6	**17c**	*i*-Pr	Me	96 (**24c**)
7	**18c**	$(CH_2)_4$	Me	69 (**25c**)
8	**19c**	$(CH_2)_5$	Me	70 (**26c**)
9	**20b**	Me	Bn	56 (**27b**)
10	**20c**	Me	Bn	50 (**27c**)
11	**21b**	Et	Bn	0
12	**22b**	*i*-Pr	Bn	0

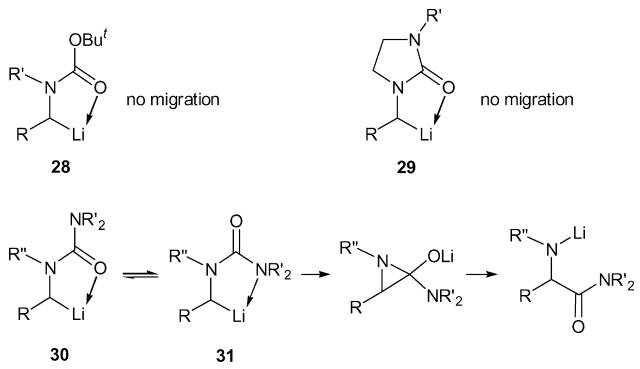
[a] Isolated yields of amino amides after flash chromatography.

polar amino amides were difficult to isolate and larger groups made the products effectively less polar. Particularly impressive are the results with **17b** and **17c** where an *N*,*N*-diisopropylcarbamoyl group, which is very robust in amides and carbamates, migrates with very high efficiency.

When the *N*-alkyl group was a benzyl group (Table 1, entries 9–12), transmetalation and migration occurred only with dimethylureas, and then only in modest yields. We have previously observed inhibition of transmetalation by *N*-benzyl groups, particularly with sterically encumbered stannanes.[1] Thus it was not surprising to find that stannanes **20b** and **20c** underwent only partial transmetalation (starting material was recovered in high yield) while **21b** and **22b**, containing diethyl- and diisopropylureas, respectively, showed no reaction with *n*-BuLi.

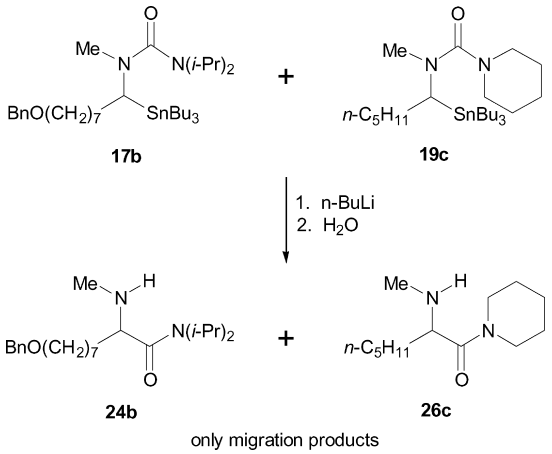
These results indicate that urea derivatives of α-aminoorganolithums undergo rapid 1,2-N→C acyl migration, even at −78 °C. While N→C acyl migrations are known,[14] these are usually thermal reactions and there are no previous reports of 1,2-N→C acyl migrations. The most closely related transformation is a recently reported anionic 1,4-N→C acyl migration (also at −78 °C) in a conformationally constrained system.[15]

In contrast to their urea counterparts, *t*-Boc-protected α-aminoorganolithiums are quite stable at −78 °C. There is no obvious explanation for this difference in reactivity. However, if one speculates that the acyl migration occurs via a carbinolamine-type intermediate, then the conformational preferences of the different carbonyl groups may be important. Specifically, one would not expect organolithium **28** to undergo an intramolecular reaction whereas conformer **31** is stereoelectronically poised to undergo acyl migration (Scheme 6).[16] With cyclic ureas such as those used by Pearson, such a conformation is not feasible and thus organolithiums **29** do not undergo acyl migration.



Scheme 6.

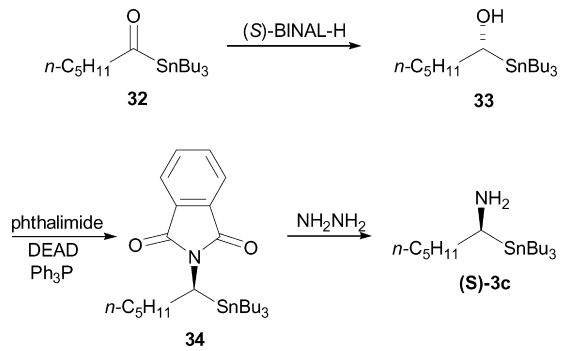
To establish the intramolecularity of the migration, a crossover experiment was carried out. Thus a mixture of **17b** and **19c** was treated with *n*-BuLi and the resulting product mixture was carefully analyzed for the presence of crossover products (Scheme 7). Specifically, the amines formed were converted to Cbz derivatives and analyzed by HPLC. Only the products of intramolecular migration, **24b** and **26c** were detected. Thus it is highly likely that the 1,2-acyl migrations observed proceed intramolecularly.



Scheme 7.

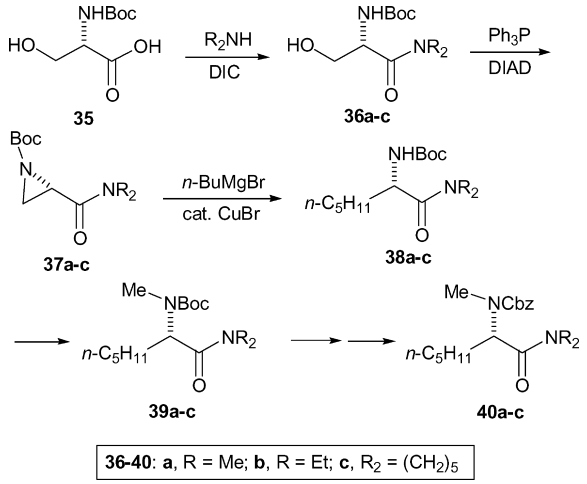
In order to explore the stereochemistry of the migration, enantiomerically-enriched materials were required. Thus acylstannane **32** was reduced with (*S*)-BINAL-H to give (*R*)-hydroxystannane **33**[17,18] which was subsequently converted, under Mitsunobu conditions, to (*S*)-phthalimide **34** (Scheme 8).[5] Hydrazinolysis of (*S*)-**34** then provided (*S*)-**3c** which was converted to ureas (*S*)-**6c**, (*S*)-**16c**, (*S*)-**17c**, (*S*)-**18c**, and (*S*)-**19c** (see Scheme 5). Analysis of (*S*)-**3c** showed an er=89:11, so the enantiomeric purities of derived ureas should be the same.

Stereochemically defined samples of some of the anticipated migration products were prepared from (*S*)-Boc-serine in order to establish the stereochemistry of the acyl migration (Scheme 9). Thus, (*S*)-Boc-serine (**35**) was converted to a series of amides **36** which were cyclized to the corresponding aziridines **37** under Mitsunobu conditions. Copper catalyzed opening of the aziridines with *n*-BuMgBr[19] gave Boc-protected amino amides **38** that could be easily manipulated into *N*-Cbz-*N*-methyl amino amides **40**, compounds amenable to chiral HPLC analysis.



Scheme 8.

When (*S*)-**6c** (er=89:11) was treated with *n*-BuLi followed by aqueous extractive workup, the anticipated amino amide was isolated in good yield (Table 2, entry 1). Analysis by chiral HPLC of the derived *N*-Cbz-*N*-methyl amino amide **40a** showed er=88:12 with the minor isomer co-eluting with (*S*)-**40a** prepared from (*S*)-serine. Thus the major isomer had *R* configuration and the transmetalation/migration proceeded with complete retention of configuration.

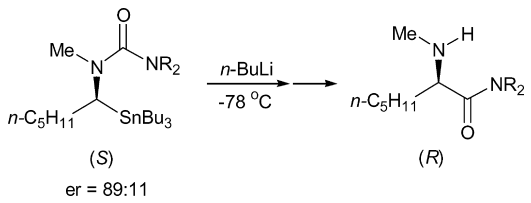


Scheme 9.

Other ureas were treated similarly but gave dissimilar results (Table 2). Very surprisingly, diethylurea **16c** and diisopropylurea **17c** gave results quite different from the dimethylurea. Where the dimethylcarbamoyl group migrated with complete retention of configuration, the diethylcarbamoyl group migrated with only partial retention (entry 2). When the reaction was conducted at −95 °C, the enantiomeric purity of the product did not change significantly (entry 3). For migration of the diisopropylcarbamoyl group, essentially racemic α-amino amide was isolated. In ether, transmetalation was incomplete so there was only a low conversion to amino amide **24c**. Unfortunately, the amino amide formed in ether was also nearly racemic (entries 4 and 5).

Taken together, these results suggest that the bulk of the alkyl groups on the migrating unit plays a major role in the stereochemistry of the migration. With small methyl groups, retention of configuration is observed whereas large isopropyl groups lead to racemization and intermediate

Table 2. Conversion of enantiomerically enriched α-aminostannanes to α-amino amides



Entry	Stannane	R	Amide	Yield[a]	er[b]
1	**6c**	Me	**8c**	77	88:12
2	**16c**	Et	**23c**	85	64:36
3[c]	**16c**	Et	**23c**	81	66:34
4	**17c**	*i*-Pr	**24c**	96	52:48
5[d]	**17c**	*i*-Pr	**24c**	29	56:44
6	**18c**	$(CH_2)_4$	**25c**	69	89:11
7	**19c**	$(CH_2)_5$	**26c**	70	72:28

[a] Isolated yields of amino amides.
[b] Determined by HPLC (4.6 mm×250 mm Chiralcel OD) analysis of Cbz derivatives.
[c] Reaction was carried out at −95 °C.
[d] Reaction was carried out in ether; low yield due to incomplete transmetalation.

sized ethyl groups give partial racemization. There is no obvious mechanistic rationale for these observed differences. To add to the mystery, the very similar pyrrolidine and piperidine derivatives **18c** and **19c**, respectively, showed complete retention in one case and partial racemization in the other. It is not clear why the stereochemical outcome in the migration of such similar urea derivatives should be so different.

3. Conclusions

We have shown that urea derivatives of α-aminoorganostannanes undergo efficient transmetalation with *n*-BuLi to organolithiums which undergo rapid acyl migration to afford α-amino amides. This constitutes the first report of 1,2-N→C acyl migrations and is an unprecedented route to α-amino amides. Such migrations do not occur with cyclic ureas or carbamate protected α-aminoorganolithiums. These intramolecular migrations occur with retention of configuration in some cases and varying degrees of racemization in others.

4. Experimental

4.1. General

All reactions were carried out under argon using flame-dried glassware. NMR data were recorded on a 300 MHz instrument in $CDCl_3$ unless otherwise noted. THF was distilled from Na/benzophenone. Hexanes, acetonitrile, diisopropylamine, and pyridine were distilled from CaH_2. Enantiomerically enriched α-hydroxystannanes were prepared by BINAL-H reduction of acylstannanes as previously described[17] and converted to phthalimides as described in Section 4.2 below. Reagents were purchased from Aldrich Chemical Co. and used without further

purification. Silica gel 60 (40–63 μm) from EM Science was used for flash chromatography.

4.2. General procedure A: preparation of α-phthalimidotributylstannanes (precursors of α-aminostannanes 3)

To a cooled (0 °C) 0.5 M solution of diisopropylamine (1 mmol, 1 equiv.) in THF was added *n*-BuLi (1 mmol, 1 equiv.) dropwise, and the resulting solution stirred for 15 min. Bu_3SnH (1 mmol, 1 equiv.) was then added dropwise, and the solution stirred another 15 min. The resulting slightly yellowish solution was then cooled to −78 °C and the appropriate aldehyde (1 mmol, 1 equiv.) was added dropwise. The reaction was stirred at −78 °C for 30 min., quenched with saturated aqueous NH_4Cl (20 mL), and allowed to warm to room temperature. The solution was diluted with 50 mL of Et_2O, the layers separated, and the aqueous layer washed with 20 mL of Et_2O. The organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo (room temperature water bath).

The crude hydroxystannane was made as a 0.5 M solution in THF, and cooled to 0 °C. To the cooled solution was added phthalimide (1.3 mmol, 1.3 equiv.), and triphenylphosphine (1.3 mmol, 1.3 equiv.). A 3 M solution of DEAD (1.3 mmol, 1.3 equiv.) in THF was then added dropwise slowly to the stirring solution through a dropping funnel. The cooling bath was removed and the solution stirred at room temperature for 30 min. The THF was removed in vacuo and the resulting yellow oil extracted four times with 30 mL each of hexanes. The combined hexanes extracts were washed with a small amount (10 mL) of acetonitrile and then concentrated in vacuo to give a yellow oil which was purified via flash column chromatography (20 g silica/g substrate, 2–10% diethyl ether/hexanes).

4.2.1. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)phthalimide (3b precursor). This compound was prepared according to General procedure A in 45% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, m), 7.64 (2H, m), 7.33–7.28 (5H, m), 4.46 (2H, s), 3.93 (1H, dd, *J*=6.8, 9.2 Hz), 3.41 (2H, t, *J*=6.6 Hz), 2.05–1.65 (2H, m), 1.65–1.17 (22H, m), 1.05–0.78 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 138.6, 133.6, 132.0, 128.2, 127.5, 127.3, 122.7, 72.7, 70.3, 37.3, 32.8, 29.6, 29.2, 29.1, 28.9, 28.1, 27.3, 26.0, 13.5, 10.3; IR (neat) 1771, 1710, 1466 cm^{-1}; MS (CI) *m*/*z* 598 (M+H−C_4H_{10}), 656 (M+H). Anal. calcd for $C_{35}H_{53}NO_3Sn$: C, 64.23; H, 8.16; N, 2.14. Found: C, 64.12; H, 7.95; N, 2.10. The phthalimide precursors to amines **3a** and **3c** have been described previously.[1,5]

4.3. General procedure B: synthesis of *N*,*N*-dialkylureas

The appropriate phthalimide (0.30 mmol) was weighed into a round bottom flask equipped with a stir bar and argon line, and dissolved in ethanol (7 mL). Water (3 drops) was added to the solution, followed by hydrazine monohydrate (9.0 mmol, 30 equiv.), and the solution was refluxed for 4 h. The ethanol was evaporated under reduced pressure and the residue dissolved in diethyl ether (40 mL). The ether layer was washed with brine (10 mL), dried with sodium sulfate, filtered through a pad of Celite® and evaporated under reduced pressure to afford the crude α-aminostannane as a clear colorless oil.

The crude α-aminostannane **3** was dissolved in dry CH_2Cl_2 (5 mL) and added to a dry round bottom flask equipped with a stir bar and argon line. The solution was cooled to 0 °C and Et_3N (0.60 mmol, 2 equiv.) was added, followed by the appropriate dialkyl carbamoyl chloride (0.45 mmol, 1.5 equiv.), and finally DMAP (0.03 mmol, 0.1 equiv.). The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (5 mL) and the solution was diluted with CH_2Cl_2 (20 mL). The CH_2Cl_2 layer was washed with brine (10 mL), dried with sodium sulfate, and filtered through a pad of Celite®. The CH_2Cl_2 was evaporated under reduced pressure to afford a clear oil which was purified via flash column chromatography (30 g of silica/g of crude material, 5:1 to 10:1 hexane/diethyl ether) to afford a clear colorless oil.

4.3.1. *N*-(1-Tributylstannyl-1-propyl)-*N*′,*N*′-dimethylurea (5a). This compound was prepared from amine **3a** according to General procedure B in 75% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.66 (1H, d), 3.20 (1H, q), 2.91 (6H, s), 1.81–1.60 (2H, m), 1.54–1.01 (12H, m), 0.97–0.75 (18H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.7, 43.4, 36.3, 29.3 (^2J=20 Hz), 28.1, 27.6 (^1J=55 Hz), 13.7, 12.7, 10.1 (^1J=317, 304 Hz); IR (neat) 3337, 1624, 1528 cm^{-1}; MS (FAB) *m*/*z* 363 (M$^+$−C_4H_9), 207, 129. Anal. calcd for $C_{18}H_{40}N_2OSn$: C, 51.57; H, 9.62; N, 6.68. Found: C, 51.74; H, 9.59; N, 6.69.

4.3.2. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N*′,*N*′-dimethylurea (5b). This compound was prepared from amine **3b** according to General procedure B in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (5H, m), 4.58 (1H, d, *J*=6.6 Hz), 4.47 (2H, s), 3.43 (2H, t, *J*=6.6 Hz), 3.26–3.12 (1H, m), 2.84 (6H, s), 1.80–1.19 (24H, m), 0.93–0.78 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 138.6, 128.3, 127.6, 127.4, 72.8, 70.5, 41.5, 36.2, 35.1, 29.7, 29.4, 29.3, 29.1, 28.1, 27.9, 27.6, 26.2, 13.7, 10.0; IR (neat) 3339, 1630, 1529 cm^{-1}; MS (CI) *m*/*z* 539 (M+H−C_4H_{10}), 597 (M+H). Anal. calcd for $C_{28}H_{56}N_2O_2Sn$: C, 60.51; H, 9.48; N, 4.70. Found: C, 60.80; H, 9.30; N, 4.61.

4.3.3. *N*-(1-Tributylstannyl-1-hexyl)-*N*′,*N*′-dimethylurea (5c). This compound was prepared from amine **3c**[5] according to General procedure B in 67% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.58 (1H, d, *J*=6.5 Hz), 3.18 (1H, m), 2.84 (6H, s), 1.65–1.24 (20H, m), 0.89–0.77 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 41.4, 36.0, 34.9, 31.5, 29.1, 27.7, 27.4, 22.4, 13.8, 13.5, 9.9; IR (neat) 3332, 1620, 1531 cm^{-1}; MS (CI) *m*/*z* 405 (M+H−C_4H_{10}), 463 (M+H). Anal. calcd for $C_{21}H_{46}N_2OSn$: C, 54.68; H, 10.05; N, 6.07. Found: C, 54.90; H, 9.96; N, 6.24.

4.3.4. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N*′,*N*′-diethylurea (12b). This compound was prepared from amine **3b** according to General procedure B in 58% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (5H, m), 4.52 (1H, d, *J*=6.4 Hz), 4.47 (2H, s), 3.43 (2H, t, *J*=6.5 Hz), 3.30–3.10 (5H, m), 1.80–1.20 (24H, m), 1.12–1.05 (6H, t, *J*=7.0 Hz), 0.90–0.75 (15H, m); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 157.3, 138.7, 128.3, 127.6, 127.4, 72.8, 70.5, 41.4, 41.1, 35.1, 29.7, 29.5, 29.4, 29.3, 29.2, 28.3, 27.8, 27.6, 26.8, 26.2, 13.7, 10.1; IR (neat) 3339, 1582 cm^{-1}; MS (CI) *m/z* 625 (M+H). Anal. calcd for $C_{32}H_{60}N_2O_2Sn$: C, 61.64; H, 9.70; N, 4.49. Found: C, 61.56; H, 9.54; N, 4.10.

4.3.5. *N*-(1-Tributylstannyl-1-hexyl)-*N′*,*N′*-diethylurea (12c). This compound was prepared from amine **3c**[5] according to General procedure B in 61% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (1H, d, *J*=6.5 Hz), 3.20 (5H, m), 1.65 (2H, m), 1.55–1.38 (6H, m), 1.35–1.22 (12H, m), 1.09 (6H, t, *J*=7.1 Hz), 0.90–0.77 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 41.4, 41.1, 35.1, 31.7, 29.3, 28.0, 27.6, 22.6, 14.0, 13.9, 13.7, 10.1; IR (neat) 3352, 1624, 1523 cm^{-1}; MS (EI) *m/z* 433 (M−C_4H_9). Anal. calcd for $C_{23}H_{50}N_2OSn$: C, 56.45; H, 10.30; N, 5.72. Found: C, 56.34; H, 10.13; N, 5.58.

4.3.6. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N′*,*N′*-diisopropylurea (13b). This compound was prepared from amine **3b** according to General procedure B in 66% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.23 (5H, m), 4.48 (2H, s), 4.39 (1H, d, *J*=6.4 Hz), 3.91 (2H, sept, *J*=6.9 Hz), 3.43 (2H, t, *J*=6.6 Hz), 3.23 (1H, m), 1.70–1.23 (24H, m), 1.18 (12H, d, *J*=6.9 Hz), 0.90–0.75 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 138.6, 128.3, 127.6, 127.4, 72.8, 70.4, 44.4, 41.2, 35.0, 31.5, 29.7, 29.5, 29.4, 28.5, 27.3, 26.1, 21.5, 21.4, 13.7, 10.1; IR (neat) 1626, 1509 cm^{-1}; MS (CI) *m/z* 590 (M+H−C_4H_{10}), 653 (M+H); HRMS Calcd for $C_{34}H_{64}N_2O_2Sn$: 653.4068. Found: 653.4066.

4.3.7. *N*-(1-Tributylstannyl-1-hexyl)-*N′*,*N′*-diisopropylurea (13c). This compound was prepared from amine **3c**[5] according to General procedure B in 53% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (1H, d, *J*=6.5 Hz), 3.91 (2H, sept, *J*=6.9 Hz), 3.25 (1H, dt, *J*=6.6, 8.0 Hz), 1.75–1.60 (2H, m), 1.55–1.38 (6H, m), 1.35–1.22 (12H, m), 1.17 (6H, d, *J*=7.0 Hz), 1.17 (6H, d, *J*=6.9 Hz), 0.90–0.77 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 44.3, 41.2, 34.9, 31.6, 29.2, 28.1, 27.6, 22.5, 21.4, 21.3, 13.9, 13.6, 10.1; IR (neat) 3370, 1628, 1509 cm^{-1}; MS (CI) *m/z* 461 (M+H−C_4H_{10}), 519 (M+H). Anal. calcd for $C_{25}H_{54}N_2OSn$: C, 58.03; H, 10.52; N, 5.41. Found: C, 58.14; H, 10.40; N, 5.24.

4.3.8. Pyrrolidine-1-carboxylic acid (1-tributylstannyl-1-hexyl)amide (14c). This compound was prepared from amine **3c**[5] according to General procedure B in 75% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.40 (1H, d, *J*=6.3 Hz), 3.26 (4H, m), 3.15 (1H, m), 1.85 (4H, m), 1.55–1.35 (6H, m), 1.32–1.15 (14H, m), 0.90–0.73 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 45.4, 41.1, 35.2, 31.6, 29.2, 27.8, 27.5, 25.5, 22.6, 14.0, 13.6, 10.0; IR (neat) 3307, 1615, 1531 cm^{-1}; MS (CI) *m/z* 431 (M+H−C_4H_{10}), 489 (M+H). Anal. calcd for $C_{23}H_{48}N_2OSn$: C, 56.68; H, 9.93; N, 5.75. Found: C, 56.80; H, 9.96; N, 5.75.

4.3.9. Piperidine-1-carboxylic acid (1-tributylstannyl-1-hexyl)amide (15c). This compound was prepared from amine **3c**[5] according to General procedure B in 77% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (1H, d, *J*=6.3 Hz), 3.32–3.05 (5H, m), 1.85–1.15 (26H, m), 0.95–0.67 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 45.0, 41.5, 35.0, 31.7, 29.3, 27.9, 27.6, 25.6, 24.5, 22.6, 14.0, 13.7, 10.1; IR (neat) 3331, 1606, 1531 cm^{-1}; MS (CI) *m/z* 445 (M+H−C_4H_{10}), 503 (M+H). Anal. calcd for $C_{24}H_{50}N_2OSn$: C, 57.49; H, 10.05; N, 5.59. Found: C, 57.72; H, 10.18; N, 5.45.

4.4. General procedure C: synthesis of *N*,*N*-dialkyl-*N′*-alkylureas

The appropriate dialkylurea (0.30 mmol) was weighed into a round bottom flask equipped with a stir bar and kept under argon. The oil was dissolved in DMF, and the solution cooled to 0 °C. The appropriate alkylating agent (MeI or BnBr, 0.60 mmol, 2 equiv.) was added to the solution, followed by sodium hydride (0.60 mmol, 2 equiv.). The cooling bath was removed and the solution was allowed to stir at room temperature overnight. The reaction was quenched with saturated aqueous ammonium chloride (5 mL), and diluted with ether (50 mL). The ether layer was washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure to afford a clear oil which could be purified by flash column chromatography (30 g silica/g substrate, 2–10% diethyl ether/hexane).

4.4.1. *N*-(1-Tributylstannyl-1-propyl)-*N*,*N′*,*N′*-trimethylurea (6a). This compound was prepared from urea **5a** according to General procedure C in 70% yield. ^1H NMR (200 MHz, $CDCl_3$) δ 3.00 (1H, t, *J*=8.1 Hz, CHN), 2.84 (3H, s), 2.74 (6H, s), 1.88–1.59 (2H, m), 1.55–1.21 (12H, m), 0.99–0.69 (18H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.2, 54.1, 38.9, 38.3, 29.2 (^2J=29 Hz), 27.6 (^3J=55 Hz), 25.3, 13.6, 12.8, 10.1 (^1J=309, 297 Hz); IR (neat) 1631, 1459 cm^{-1}; MS (FAB) *m/z* 377 (M^+−C_4H_9), 291, 221, 177, 143. Anal. calcd for $C_{19}H_{42}N_2OSn$: C, 52.67; H, 9.77; N, 6.46. Found: C, 52.46; H, 9.69; N, 6.22.

4.4.2. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N*,*N′*,*N′*-trimethylurea (6b). This compound was prepared from urea **5b** according to General procedure C in 86% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (5H, m), 4.48 (2H, s), 3.43 (2H, t, *J*=6.6 Hz), 3.02 (1H, t, *J*=8.1 Hz), 2.80 (3H, s), 2.70 (6H, s), 1.80–1.15 (24H, m), 0.90–0.75 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 138.7, 128.3, 127.6, 127.4, 72.8, 70.5, 52.1, 38.9, 38.5, 32.3, 29.7, 29.4, 29.3, 29.1, 28.1, 28.0, 27.6, 26.2, 13.7, 10.1; IR (neat) 1631, 1497 cm^{-1}; MS (CI) *m/z* 553 (M+H−C_4H_{10}), 611 (M+H). Anal. calcd for $C_{31}H_{58}N_2O_2Sn$: C, 61.09; H, 9.59; N, 4.60. Found: C, 60.95; H, 9.33; N, 4.50.

4.4.3. *N*-(1-Tributylstannyl-1-hexyl)-*N*,*N′*,*N′*-trimethylurea (6c). This compound was prepared from urea **5c** according to General procedure C in 50% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.04 (1H, t, *J*=8.0 Hz), 2.80 (3H, s), 2.71 (6H, s), 1.55–1.35 (6H, m), 1.32–1.15 (14H, m), 0.90–0.73 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 52.0, 38.8, 38.4, 32.2, 31.6, 29.2, 27.7, 27.5, 22.6, 13.9, 13.6, 10.0; IR (neat) 1632, 1498 cm^{-1}; MS (CI) *m/z* 419 (M+H−C_4H_{10}), 477 (M+H). Anal. calcd for $C_{22}H_{48}N_2OSn$: C, 55.59; H, 10.18; N, 5.89. Found: C, 55.80; H, 10.25; N, 5.66.

4.4.4. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N*-methyl-*N′*,*N′*-diethylurea (16b). This compound was prepared from urea **12b** according to General procedure C

in 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (5H, m), 4.48 (2H, s), 3.43 (2H, t, J=6.6 Hz), 3.15–2.97 (4H, m), 2.79 (3H, s), 1.80–1.15 (24H, m), 1.10–1.03 (6H, t, J=7.1 Hz), 0.90–0.75 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 138.7, 128.3, 127.6, 127.4, 72.8, 70.5, 52.0, 42.5, 38.4, 32.4, 29.7, 29.4, 29.3, 29.1, 28.1, 27.6, 26.2, 13.7, 13.4, 10.0; IR (neat) 1625, 1485 cm^{-1}; MS (CI) m/z 581 (M+H–C_4H_{10}), 639 (M+H). Anal. calcd for $C_{33}H_{62}N_2O_2Sn$: C, 62.17; H, 9.80; N, 4.39. Found: C, 61.92; H, 9.70; N, 4.24.

4.4.5. *N*-(1-Tributylstannyl-1-hexyl)-*N*-methyl-*N′*,*N′*-diethylurea (16c). This compound was prepared from urea **12c** according to General procedure C in 43% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06 (5H, m), 2.80 (3H, s), 1.52–1.37 (6H, m), 1.35–1.15 (14H, m), 1.06 (6H, t, J=7.0 Hz), 0.90–0.75 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 52.0, 42.5, 38.4, 32.4, 31.6, 29.2, 28.0, 27.8, 22.6, 14.0, 13.7, 13.4, 10.0; IR (neat) 1627, 1486 cm^{-1}; MS (CI) m/z 477 (M+H–C_4H_{10}), 505 (M+H). Anal. calcd for $C_{24}H_{52}N_2OSn$: C, 57.26; H, 10.41; N, 5.56. Found: C, 57.47; H, 10.44; N, 5.80.

4.4.6. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N*-methyl-*N′*,*N′*-diisopropylurea (17b). This compound was prepared from urea **13b** according to General procedure C in 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (5H, m), 4.48 (2H, s), 3.46 (2H, m), 3.43 (2H, t, J=6.6 Hz), 3.20 (1H, dd, J=7.2, 9.0 Hz), 2.69 (3H, s), 1.80–1.15 (36H, m), 0.90–0.75 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 138.6, 128.3, 127.6, 127.4, 72.8, 70.5, 65.8, 52.1, 47.4, 38.1, 32.6, 29.7, 29.5, 29.4, 29.3, 29.2, 28.0, 27.6, 26.1, 22.1, 21.8, 13.7, 10.0; IR (neat) 1621, 1454 cm^{-1}; MS (CI) m/z 609 (M+H–C_4H_{10}), 667 (M+H). Anal. calcd for $C_{35}H_{66}N_2O_2Sn$: C, 63.16; H, 9.99; N, 4.21. Found: C, 63.24; H, 9.77; N, 4.03.

4.4.7. *N*-(1-Tributylstannyl-1-hexyl)-*N*-methyl-*N′*,*N′*-diisopropylurea (17c). This compound was prepared from urea **13c** according to General procedure C in 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.45 (2H, sept, J=6.7 Hz), 3.21 (1H, dd, J=9.2, 6.9 Hz), 2.69 (3H, s), 1.55–1.35 (6H, m), 1.35–1.15 (26H, m), 0.90–0.77 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 52.1, 47.4, 38.0, 32.6, 31.6, 29.3, 28.0, 27.9, 22.7, 22.2, 21.8, 14.0, 13.7, 10.0; IR (neat) 1622, 1446 cm^{-1}; MS (CI) m/z 475 (M+H–C_4H_{10}), 533 (M+H); HRMS Calcd for $C_{26}H_{56}N_2OSn$: 533.3520. Found: 533.3493.

4.4.8. Pyrrolidine-1-carboxylic acid (*N*-1-tributylstannyl-1-hexyl-*N*-methyl)amide (18c). This compound was prepared from urea **14c** according to General procedure C in 83% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (4H, m), 3.04 (1H, t, J=8.0 Hz), 2.79 (3H, s), 1.80–1.60 (4H, m), 1.55–1.35 (6H, m), 1.32–1.15 (14H, m), 0.90–0.73 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 52.1, 48.5, 37.8, 32.2, 31.7, 31.5, 29.2, 27.7, 27.6, 25.5, 22.6, 14.0, 13.6, 10.1; IR (neat) 1619, 1454 cm^{-1}; MS (CI) m/z 445 (M+H–C_4H_{10}), 503 (M+H). Anal. calcd for $C_{24}H_{50}N_2OSn$: C, 57.49; H, 10.05; N, 5.59. Found: C, 57.60; H, 10.20; N, 5.72.

4.4.9. Piperidine-1-carboxylic acid (*N*-1-tributylstannyl-1-hexyl-*N*-methyl)amide (19c). This compound was prepared from urea **15c** according to General procedure C in 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09–3.00 (5H, m), 2.78 (3H, s), 1.85–1.15 (26H, m), 0.95–0.67 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 51.7, 48.2, 38.1, 32.1, 31.6, 29.2, 27.6, 27.5, 25.7, 24.7, 22.6, 14.0, 13.6, 10.0; IR (neat) 1628, 1484 cm^{-1}; MS (CI) m/z 459 (M+H–C_4H_{10}), 517 (M+H). Anal. calcd for $C_{25}H_{52}N_2OSn$: C, 58.26; H, 10.17; N, 5.44. Found: C, 58.40; H, 9.90; N, 5.60.

4.4.10. *N*-(1-Tributylstannyl-8-benzyloxy-1-octyl)-*N*-benzyl-*N′*,*N′*-dimethylurea (20b). This compound was prepared from urea **5b** according to General procedure C in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.23 (10H, m), 4.50 (2H, s), 4.41 (2H, s), 3.47 (2H, t, J=6.6 Hz), 2.75 (6H, s), 2.62 (1H, dd, J=10.2, 9.9 Hz), 1.80–1.15 (24H, m), 0.96–0.75 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 138.5, 138.1, 128.4, 128.1, 127.3, 127.2, 126.8, 126.5, 72.6, 70.2, 54.6, 50.1, 38.9, 31.9, 29.5, 29.4, 29.2, 29.1, 27.9, 27.5, 26.0, 13.6, 10.5; IR (neat) 1629, 1494 cm^{-1}; MS (CI) m/z 629 (M+H–C_4H_{10}), 687 (M+H). Anal. calcd for $C_{37}H_{62}N_2O_2Sn$: C, 64.82; H, 9.11; N, 4.09. Found: C, 65.02; H, 9.23; N, 4.04.

4.4.11. *N*-(1-Tributylstannyl-1-hexyl)-*N*-benzyl-*N′*,*N′*-dimethylurea (20c). This compound was prepared from urea **5c** according to General procedure C in 63% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.21 (5H, m), 4.36 (2H, s), 2.72 (6H, s), 2.57 (1H, dd, J=10.4, 10.3 Hz), 2.05–1.65 (2H, m), 1.52–1.05 (18H, m), 0.90–0.73 (18H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 138.4, 128.5, 126.9, 126.7, 54.7, 50.4, 39.1, 32.1, 31.8, 29.2, 27.8, 27.6, 22.6, 14.0, 13.7, 10.6; IR (neat) 1631, 1489 cm^{-1}; MS (CI) m/z 495 (M+H–C_4H_{10}), 553 (M+H); HRMS Calcd for $C_{28}H_{52}N_2OSn$: 553.3184. Found: 553.3180.

4.5. General procedure D: transmetalation of trialkylureas with *n*-BuLi to form α-amino amides

The appropriate trialkylurea (0.50 mmol) was weighed into a flame dried round bottomed flask equipped with a stir bar and argon inlet. The oil was dissolved in THF (3 mL) and the solution cooled to −78 °C while kept under argon. *n*-BuLi (0.55 mmol, 1.1 equiv., 1.6 M) was added dropwise slowly to the solution, which acquires a light yellow color almost immediately. Once this addition was complete, the solution was allowed to stir for 30 min at −78 °C, at which point the reaction was quenched cold with methanol (1 mL), followed by saturated aqueous ammonium chloride (5 mL). The solution was allowed to warm to room temperature and was diluted with water (5 mL) and ether (30 mL). The aqueous layer was extracted three times with 10 mL ether. The combined ether extracts were washed with brine, dried with sodium sulfate, filtered, and concentrated under reduced pressure to afford a clear oil which could be purified via flash column chromatography (30 g silica/g substrate, 5–10% MeOH/CH_2Cl_2).

4.5.1. 9-Benzyloxy-2-(*N*-methylamino)-*N*,*N*-dimethylnon-amide (8b). This compound was prepared from urea **6b** according to General procedure D in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.20 (5H, m), 4.45 (2H, s), 3.41 (2H, t, J=6.6 Hz), 3.37 (1H, m), 3.00 (3H, s), 2.95 (3H, s), 2.25, (3H, s), 2.22 (1H, s), 1.60–1.20 (12H, m); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 174.7, 138.6, 128.2, 127.5, 127.4, 72.8, 70.3, 59.5, 53.4, 36.8, 35.6, 34.9, 33.5, 29.6, 29.2, 26.0, 25.8; IR (neat) 3503, 1644, 1103 cm^{-1}; MS (CI) *m/z* 321 (M+H). Anal. calcd for $C_{19}H_{32}N_2O_2$: C, 71.21; H, 10.06; N, 8.74. Found: C, 71.37; H, 9.96; N, 8.89.

4.5.2. 2-(*N*-Methylamino)-*N*,*N*-dimethylheptanamide (8c). This compound was prepared from urea **6c** according to General procedure D in 77% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.26 (1H, t, *J*=6.1 Hz), 2.93 (3H, s), 2.87 (3H, s), 2.15 (3H, s), 1.99 (1H, s), 1.51–1.13 (8H, m), 0.80–0.68 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 59.4, 36.6, 35.4, 34.9, 33.5, 31.7, 25.4, 22.3, 13.8; IR (neat) 3491, 1644, 1457 cm^{-1}; MS (CI) *m/z* 187 (M+H). Anal. calcd for $C_{10}H_{22}N_2O$: C, 64.47; H, 11.90; N, 15.04. Found: C, 64.61; H, 12.12; N, 15.03.

4.5.3. 9-Benzyloxy-2-(*N*-methylamino)-*N*,*N*-diethylnonamide (23b). This compound was prepared from urea **16b** according to General procedure D in 73% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.20 (5H, m), 4.43 (2H, s), 3.57–3.13 (5H, m), 3.40 (2H, t, *J*=6.6 Hz), 2.25 (3H, s), 2.23 (1H, s), 1.60–1.20 (12H, m), 1.16 (3H, t, *J*=7.1 Hz), 1.08 (3H, t, *J*=7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 138.5, 128.2, 127.5, 127.3, 72.7, 70.3, 59.5, 41.3, 40.3, 34.8, 34.1, 29.6, 29.2, 26.0, 25.9, 14.8, 13.1; IR (neat) 3494, 1639, 1454 cm^{-1}; MS (CI) *m/z* 349 (M+H). Anal. calcd for $C_{21}H_{36}N_2O_2$: C, 72.37; H, 10.41; N, 8.04. Found: C, 72.28; H, 10.29; N, 7.91.

4.5.4. 2-(*N*-Methylamino)-*N*,*N*-diethylheptanamide (23c). This compound was prepared from urea **16c** according to General procedure D in 73% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.52 (1H, m), 3.36 (1H, m), 3.27–3.15 (3H, m), 2.24 (3H, s), 2.04 (1H, s), 1.51–1.35 (2H, m), 1.31–1.20 (6H, m), 1.17 (3H, t, *J*=7.2 Hz), 1.08 (3H, t, *J*=7.1 Hz), 0.83 (3H, t, *J*=6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 59.6, 41.3, 40.4, 34.9, 34.2, 31.9, 25.7, 22.5, 14.8, 14.0, 13.1; IR (neat) 3439, 1632, 755 cm^{-1}; MS (CI) *m/z* 215 (M+H). Anal. calcd for $C_{12}H_{26}N_2O$: C, 67.24; H, 12.23; N, 13.07. Found: C, 67.44; H, 12.48; N, 13.18.

4.5.5. 9-Benzyloxy-2-(*N*-methylamino)-*N*,*N*-diisopropylnonamide (24b). This compound was prepared from urea **17b** according to General procedure D in 85% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.20 (5H, m), 4.43 (2H, s), 3.97 (2H, sept, *J*=6.7 Hz), 3.39 (2H, t, *J*=6.6 Hz), 3.23 (1H, dd, *J*=5.7, 6.4 Hz), 2.32 (1H, s), 2.23 (3H, s), 1.60–1.20 (12H, m), 1.38 (3H, d, *J*=8.7 Hz), 1.35 (3H, d, *J*=8.7 Hz), 1.17 (3H, d, *J*=6.6 Hz), 1.15 (3H, d, *J*=6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 138.5, 128.2, 127.5, 127.3, 72.7, 70.3, 60.5, 47.6, 46.1, 34.9, 33.9, 29.6, 29.2, 26.0, 25.8, 21.2, 20.7, 20.5; IR (neat) 3318, 1633, 1118 cm^{-1}; MS (CI) *m/z* 377 (M+H). Anal. calcd for $C_{35}H_{66}N_2O_2Sn$: C, 63.16; H, 9.99; N, 4.21. Found: C, 63.24; H, 9.77; N, 4.03.

4.5.6. 2-(*N*-Methylamino)-*N*,*N*-diisopropylheptanamide (24c). This compound was prepared from urea **17c** according to General procedure D in 96% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.00 (1H, sept, *J*=6.6 Hz), 3.43 (1H, m), 3.23 (1H, dd, *J*=5.9, 6.0 Hz), 2.24 (3H, s), 2.17 (1H, s), 1.50–1.12 (20H, m), 0.88–0.77 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 60.8, 47.8, 46.3, 35.1, 34.2, 32.0, 25.7, 22.6, 21.4, 20.9 (2C), 20.7, 14.1; IR (neat) 3436, 1628, 755 cm^{-1}; MS (CI) *m/z* 243 (M+H); HRMS Calcd for $C_{14}H_{30}N_2O$: 243.2430. Found: 243.2436.

4.5.7. 2-Methylamino-1-pyrrolidin-1-yl-heptan-1-one (25c). This compound was prepared from urea **18c** according to General procedure D in 69% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.55–3.32 (4H, m), 3.15 (1H, t, *J*=6.4 Hz), 2.24 (3H, s), 2.08 (1H, s), 1.97–1.75 (4H, m), 1.52–1.15 (8H, m), 0.81 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 61.8, 46.3, 45.7, 35.0, 33.6, 32.0, 26.2, 25.8, 24.2, 22.6, 14.1; IR (neat) 3486, 1634, 1426 cm^{-1}; MS (CI) *m/z* 213 (M+H). Anal. calcd for $C_{12}H_{24}N_2O$: C, 67.88; H, 11.39; N, 13.19. Found: C, 67.80; H, 11.32; N, 12.72.

4.5.8. 2-Methylamino-1-piperidin-1-yl-heptan-1-one (26c). This compound was prepared from urea **19c** according to General procedure D in 70% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 3.66–3.28 (5H, m), 3.36 (1H, m), 3.27–3.15 (3H, m), 2.23 (3H, s), 2.02 (1H, s), 1.67–1.14 (14H, m), 1.31–1.20 (6H, m), 0.82 (3H, t, *J*=6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 59.6, 41.3, 40.4, 34.9, 34.2, 31.9, 25.7, 22.5, 14.8, 14.0, 13.1; IR (neat) 3430, 1640, 1441 cm^{-1}; MS (CI) *m/z* 227 (M+H). Anal. calcd for $C_{13}H_{26}N_2O$: C, 68.98; H, 11.58; N, 12.38. Found: C, 68.69; H, 11.38; N, 12.36.

4.5.9. 9-Benzyloxy-2-(*N*-benzylamino)-*N*,*N*-dimethylnonamide (27b). This compound was prepared from urea **20b** according to General procedure D in 56% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.15 (10H, m), 5.22 (1H, s), 4.45 (2H, s), 3.63 (2H, AB_q), 3.42 (2H, t, *J*=6.3 Hz), 2.94 (3H, s), 2.85 (3H, s), 2.26 (1H, s), 1.65–1.15 (12H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 140.0, 138.5, 128.1 (2C), 127.4, 127.2 (2C), 126.7, 72.6, 70.2, 65.6, 56.4, 53.3, 52.0, 36.5, 35.4, 33.6, 29.3, 25.9, 15.1; IR (neat) 3314, 1644 cm^{-1}; MS (CI) *m/z* 397 (M+H). Anal. calcd for $C_{25}H_{36}N_2O_2$: C, 75.72; H, 9.15; N, 7.06. Found: C, 75.57; H, 9.00; N, 7.18.

4.5.10. 2-(*N*-Benzylamino)-*N*,*N*-dimethylheptanamide (27c). This compound was prepared from urea **20c** according to General procedure D in 50% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.17 (5H, m), 3.63 (2H, AB_q), 3.42 (1H, t, *J*=6.1 Hz), 2.97 (3H, s), 2.89 (3H, s), 2.11 (1H, s), 1.55–1.15 (8H, m), 0.84 (3H, t, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 140.3, 128.3, 128.2, 126.8, 56.6, 52.1, 36.7, 35.6, 33.8, 31.8, 25.6, 22.5, 14.0; IR (neat) cm^{-1}.

4.6. General procedure E: coupling of Boc-serine with dialkylamines

Into a dry round bottom flask equipped with a stir bar and argon inlet was added THF (100 mL) and the appropriate dialkylamine (30 mmol, 3 equiv.). The solution was then cooled to 0 °C (when dimethylamine was used, it was first condensed at −78 °C, then diluted with THF and warmed to 0 °C). Boc-serine (10 mmol) was added to the solution, followed by HOBT (1 mmol, 0.1 equiv.) and DIC (10.5 mmol, 1.05 equiv.). The solution was stirred overnight, warming to room temperature. The bulk of the THF was removed under reduced pressure, and the residue dissolved in a small amount of CH_2Cl_2 prior to purification via flash column chromatography (30 g silica/g crude

material, EtOAc). The *N*,*N*′-diisopropylurea remaining after the column was removed by dissolving the product in CH_2Cl_2 and then filtering (two times).

4.6.1. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-3-hydroxy-*N*,*N*-dimethylpropanamide (36a). This compound was prepared from Boc-serine and Me_2NH according to General procedure E in 39% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (1H, d, J=8.5 Hz), 4.58 (1H, m), 3.61 (2H, m), 3.00 (3H, s), 2.83 (3H, s), 1.30 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 155.5, 79.6, 63.4, 51.6, 37.0, 35.6, 28.0; IR (neat) 3426, 1704, 1640, 1170 cm^{-1}; MS (CI) m/z 233 (M+H). Anal. calcd for $C_{10}H_{20}N_2O_4$: C, 51.71; H, 8.68; N, 12.06. Found: C, 51.95; H, 8.47; N, 12.18.

4.6.2. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-*N*,*N*-diethyl-3-hydroxypropanamide (36b). This compound was prepared from Boc-serine and Et_2NH according to General procedure E in 44% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (1H, d, J=8.3 Hz), 4.57 (1H, m), 3.73 (2H, m), 3.50–3.23 (4H, m), 1.41 (9H, s), 1.18 (3H, t, J=7.2 Hz), 1.08 (3H, t, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 155.7, 80.1, 64.6, 51.3, 42.0, 40.4, 28.3, 14.5, 12.8; IR (neat) 3419, 1715, 1650, 1061 cm^{-1}; MS (CI) m/z 261 (M+H). Anal. calcd for $C_{12}H_{24}N_2O_4$: C, 55.36; H, 9.29; N, 10.76. Found: C, 55.47; H, 9.06; N, 10.71.

4.6.3. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-3-hydroxy-1-piperidin-1-yl-propan-1-one (36c). This compound was prepared from Boc-serine and piperidine according to General procedure E in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (1H, d, J=8.0 Hz), 4.60 (1H, m), 3.75–3.32 (7H, m), 1.65–1.43 (6H, m), 1.38 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 155.7, 80.0, 64.4, 51.6, 46.7, 43.2, 28.2, 26.3, 25.4, 24.3; IR (neat) 3415, 1694, 1650, 1065 cm^{-1}; MS (EI) m/z 272 (M). Anal. calcd for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29. Found: C, 57.50; H, 8.62; N, 10.12.

4.7. General procedure F: synthesis of Boc-protected aziridines

The appropriate Boc-protected amino alcohol (2.20 mmol) was weighed into a dry round bottom flask equipped with a stir bar and argon inlet. The flask was charged with 30 mL of dry THF and the solution cooled to 0 °C. PPh_3 (2.31 mmol, 1.05 equiv.) was added to the solution, followed by DIAD (2.31 mmol, 1.05 equiv.). The reaction was stirred overnight, warming to room temperature. The THF was removed under reduced pressure, and the residue dissolved in CH_2Cl_2 before purifying via flash column chromatography (30 g silica/g crude material, 1:1 to 2:1 hexane/ethyl acetate).

4.7.1. 2-Dimethylcarbamoyl-aziridine-1-carboxylic acid tert-butyl ester (37a). This compound was prepared from **36a** according to General procedure F in 84% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.21 (3H, s), 3.16 (1H, dd, J=5.4, 3.4 Hz), 2.93 (3H, s), 2.60 (1H, dd, J=3.3, 1.0 Hz), 2.30 (1H, dd, J=5.4, 1.0 Hz), 1.39 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 160.7, 81.7, 37.0, 35.8, 34.4, 30.8, 27.8; IR (neat) 3497, 1724, 1659 cm^{-1}; MS (CI) m/z 215 (M+H); HRMS Calcd for $C_{10}H_{18}N_2O_3$: 215.1410. Found: 215.1396.

4.7.2. 2-Diethylcarbamoyl-aziridine-1-carboxylic acid tert-butyl ester (37b). This compound was prepared from **36b** according to General procedure F in 67% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67–3.42 (2H, m), 3.35 (2H, m), 3.10 (1H, dd), 2.61 (1H, dd), 2.26 (1H, dd, J=5.3, 1.4 Hz), 1.39 (9H, s), 1.23 (3H, t, J=7.2 Hz), 1.08 (3H, t, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 160.6, 81.6, 42.0, 41.2, 34.1, 30.7, 27.8, 14.8, 13.0; IR (neat) 3292, 1728, 1650 cm^{-1}; MS (ESI) m/z 243 (M+H), 265 (M+Na). Anal. calcd for $C_{12}H_{22}N_2O_3$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.47; H, 8.94; N, 11.66.

4.7.3. 2-(Piperidine-1-carbonyl)-aziridine-1-carboxylic acid tert-butyl ester (37c). This compound was prepared from **36c** according to General procedure F in 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75–3.37 (4H, m), 3.15 (1H, dd, J=5.5, 3.4 Hz), 2.57 (1H, dd, J=3.3, 0.8 Hz), 2.27 (1H, dd, J=5.8, 0.7 Hz), 1.65–1.44 (6H, m), 1.38 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 160.8, 81.6, 46.5, 43.4, 34.6, 30.6, 27.8, 26.4, 25.3, 24.3; IR (neat) 3285, 1732, 1650 cm^{-1}; MS (ESI) m/z 255 (M+H), 277 (M+Na). Anal. calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.18; H, 8.58; N, 10.81.

4.8. General procedure G: ring opening of aziridines with *n*-BuMgBr

Into a flame dried round bottom flask equipped with a stir bar and argon inlet was suspended CuBr·DMS (1.15 mmol, 0.3 equiv.) in THF (30 mL). The suspension was cooled to −78 °C, and *n*-butylmagnesium bromide (11.65 mmol, 2.79 M, 3 equiv.) was added. The appropriate aziridine **37** was dissolved in THF (5 mL) and added to the solution. The reaction was stirred overnight, warming to −40 °C. The reaction was then allowed to warm to room temperature and was quenched with 10% NH_4OH/NH_4Cl (30 mL). The aqueous phase was extracted three times with ether (50 mL), washed with water (10 mL), dried with sodium sulfate, filtered, and concentrated to provide a colorless oil. The crude oil was purified by flash column chromatography (30 g silica/g substrate, 2:1 to 4:1 hexane/ethyl acetate).

4.8.1. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-*N*,*N*-dimethylheptanamide (38a). This compound was prepared from **37a** according to General procedure G in 19% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.33 (1H, d, J=8.6 Hz), 4.53 (1H, dt, J=4.9, 8.3 Hz), 3.02 (3H, s), 2.90 (3H, s), 1.65–1.13 (8H, m), 1.37 (9H, s), 0.85–0.77 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 155.5, 79.3, 50.0, 37.0, 35.6, 33.3, 31.5, 28.3, 24.8, 22.4, 13.9; IR (neat) 3306, 1713, 1650 cm^{-1}; MS (CI) m/z 273 (M+H). Anal. calcd for $C_{14}H_{28}N_2O_3$: C, 61.73; H, 10.36; N, 10.28. Found: C, 62.00; H, 10.44; N, 10.07.

4.8.2. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-*N*,*N*-diethylheptanamide (38b). This compound was prepared from **37b** according to General procedure G in 43% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (1H, d, J=8.8 Hz), 4.47 (1H, dt, J=5.2, 8.3 Hz), 3.47 (1H, m), 3.32 (1H, m), 3.18 (1H, m), 1.65–1.20 (8H, m), 1.37 (9H, s), 1.17 (3H, t, J=7.2 Hz), 1.06 (3H, t, J=7.1 Hz), 0.85–0.77 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 155.4, 79.2, 50.0, 41.8, 40.2, 33.9, 31.5, 28.3, 24.9, 22.4, 14.5, 13.9, 12.9; IR (neat)

3303, 1713, 1644 cm^{-1}; MS (CI) *m/z* 301 (M+H). Anal. calcd for $C_{16}H_{32}N_2O_3$: C, 63.96; H, 10.74; N, 9.32. Found: C, 64.18; H, 10.59; N, 9.43.

4.8.3. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino)-1-piperidin-1-yl-heptan-1-one (38c). This compound was prepared from **36c** according to General procedure G in 41% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (1H, d, *J*=8.4 Hz), 4.55 (1H, dt, *J*=4.5, 7.9 Hz), 3.51 (2H, t, *J*=5.4 Hz), 3.40 (2H, m), 1.66–1.15 (8H, m), 1.39 (9H, s), 0.85–0.79 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 155.5, 79.2, 49.9, 46.5, 43.1, 33.6, 31.5, 28.3, 26.4, 25.5, 24.7, 24.4, 22.4, 13.9; IR (neat) 3299, 1714, 1652 cm^{-1}; MS (CI) *m/z* 313 (M+H). Anal. calcd for $C_{17}H_{32}N_2O_3$: C, 65.35; H, 10.32; N, 8.97. Found: C, 65.50; H, 10.18; N, 9.11.

4.9. General procedure H: methylation of Boc-protected α-amino amides

Into a dry round bottom flask was weighed the amino amide (0.30 mmol), which was then dissolved in dry THF (10 mL) and cooled to 0 °C while kept under argon. Methyl iodide (0.33 mmol, 1.1 equiv.) was added followed by sodium hydride (60% in oil, 0.33 mmol, 1.1 equiv.). The stirring solution was allowed to warm to room temperature, and monitored by TLC. When the reaction was complete, the reaction was quenched with saturated aqueous NH_4Cl (10 mL). The aqeous layer was extracted with diethyl ether (10 mL) and the combined ether layers were washed with brine (10 mL). The solution was dried, filtered, and concentrated under reduced pressure to afford a colorless oil which could be purified by flash column chromatography (30 g silica/g crude material, 4:1 hexane/ethyl acetate).

4.9.1. (*S*)-2-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-*N*,*N*-dimethylheptanamide (39a). This compound was prepared from **38a** according to General procedure H in 82% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.95 (1H, dd, *J*=6.7, 8.3 Hz), 3.01 (3H, s), 2.91 (3H, s), 2.69 (3H, s), 1.77–1.50 (2H, m), 1.42 (9H, s), 1.35–1.12 (6H, m), 0.90–0.78 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 155.8, 80.2, 53.9, 36.8, 35.7, 31.6, 29.3, 28.9, 28.3, 25.4, 22.5, 13.9; IR (neat) 3487, 1732, 1650 cm^{-1}; MS (CI) *m/z* 287 (M+H). Anal. calcd for $C_{15}H_{30}N_2O_3$: C, 62.90; H, 10.56; N, 9.78. Found: C, 62.99; H, 10.48; N, 9.52.

4.9.2. (*S*)-2-(*N*-*tert*-Butoxycarbonyl-*N*-methylamino)-*N*,*N*-diethylheptanamide (39b). This compound was prepared from **38b** according to General procedure H in 90% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.88 (1H, dd, *J*=6.8, 8.1 Hz), 3.45–3.13 (4H, m), 2.66 (3H, s), 1.75–1.53 (2H, m), 1.39 (9H, s), 1.32–1.12 (6H, m), 1.10–1.01 (6H, m), 0.85–0.77 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 155.5, 80.1, 53.8, 41.4, 40.2, 31.5, 29.0, 28.5, 28.3, 25.3, 22.5, 14.3, 13.9, 12.8; IR (neat) 3584, 1694, 1651 cm^{-1}; MS (CI) *m/z* 315 (M+H). Anal. calcd for $C_{17}H_{34}N_2O_3$: C, 64.93; H, 10.90; N, 8.91. Found: C, 64.76; H, 10.74; N, 8.79.

4.9.3. (*S*)-2-(*N*-*tert*-Butoxycarbonylamino-*N*-methyl)-1-piperidin-1-yl-heptan-1-one (39c). This compound was prepared from **38c** according to General procedure H in 83% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 4.91 (1H, dd, *J*=6.8, 8.0 Hz), 3.83 (1H, m), 3.65–3.51 (1H, m), 3.30–3.10 (2H, m), 2.67 (3H, s), 1.78–1.08 (14H, m), 1.41 (9H, s), 0.88–0.77 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 155.4, 79.7, 53.8, 46.3, 43.3, 31.6, 29.1, 28.9, 28.3, 26.6, 26.0, 25.3, 24.7, 22.5, 13.9; IR (neat) 3584, 1690, 1648 cm^{-1}; MS (CI) *m/z* 327 (M+H). Anal. calcd for $C_{18}H_{34}N_2O_3$: C, 66.22; H, 10.50; N, 8.58. Found: C, 66.44; H, 10.32; N, 8.74.

4.10. General procedure for the deprotection of *N*-Boc α-amino amides

The amino amide (0.61 mmol) was weighed into a dry round bottom flask equipped with a stir bar and argon line. The flask was charged with 6 mL of CH_2Cl_2. The solution was cooled to 0 °C and trifluoroacetic acid (18.3 mmol, 30 equiv.), diluted 1:1 with CH_2Cl_2, was added dropwise. The ice bath was removed and the solution stirred at room temperature for 2–2.5 h (monitored by TLC). Once the reaction was complete, the solvent was removed in vacuo and the residue dissolved in CH_2Cl_2. The CH_2Cl_2 was washed with saturated aqueous $NaHCO_3$, dried, filtered, and concentrated in vacuo to afford a colorless oil which could be purified by flash column chromatography (30 g silica/g crude material, 5% MeOH/CH_2Cl_2). These compounds were converted to CBz derivatives for analysis by HPLC.

4.11. General procedure for the CBz-protection of α-amino amides

Into a dry round bottom flask was weighed the amino amide (0.34 mmol), which was then dissolved in $CH-_2Cl_2$ (30 mL) and cooled to 0 °C while kept under argon. Sodium bicarbonate was added (0.41 mmol, 1.2 equiv.) followed by benzyl chloroformate (0.41 mmol, 1.2 equiv.) and DMAP (0.034 mmol, 0.1 equiv.). The stirring solution was allowed to warm to room temperature, and monitored by TLC. After 2 h, when the reaction was complete, the solution was washed with water (10 mL), dried, filtered, and concentrated under reduced pressure to afford a colorless oil which could be purified by flash column chromatography (30 g silica/g crude material, 4:1 hexane/ethyl acetate).

The enantiomeric purity of the CBz-protected α-amino amides was determined by chiral HPLC analysis (2.5–10% *i*PrOH/hexanes, 1.0 mL/min, 4.6×250 mm ChiralCel OD).

4.12. General procedure for the determination of optical purity of enantiomerically enriched phthalimides

The phthalimide (0.43 mmol) was weighed into a round bottom flask equipped with a stir bar and argon line, and dissolved in ethanol (10 mL). Water (3 drops) was added to the solution, followed by hydrazine monohydrate (21.5 mmol, 50 equiv.), and the solution was refluxed for 4 h. The ethanol was evaporated under reduced pressure and the residue dissolved in diethyl ether (40 mL). The ether layer was washed with brine (10 mL), dried with sodium sulfate, filtered through a pad of Celite® and evaporated under reduced pressure to afford the crude α-aminostannane as a clear colorless oil.

The crude α-aminostannane was dissolved in dry CH_2Cl_2 (5 mL) and added to a dry round bottom flask equipped with

a stir bar and argon line. The solution was cooled to 0 °C and triethylamine (2.15 mmol, 5 equiv.) was added, followed by (*S*)-(+)-MTPA chloride (0.47 mmol, 1.1 equiv.) and finally DMAP (0.43 mmol, 1 equiv.). The solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (5 mL) and the solution was diluted with CH_2Cl_2 (20 mL). The CH_2Cl_2 layer was washed with brine (10 mL), dried with sodium sulfate, and filtered through a pad of Celite®. The CH_2Cl_2 was evaporated under reduced pressure to afford a clear yellowish oil which was purified via flash column chromatography (30 g of silica/g of crude material, 8:1 hexane/ethyl acetate) to afford a clear colorless oil.

The purified oil was subjected to HPLC analysis (20% CH_2Cl_2/hexanes, 2.0 mL/min, Waters Resolve™ silica (5 μm, 8×100 mm) Radial-Pak column.

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