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Article

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Reductive Alkylation of Tertiary Lactams via Addition of Organocopper (RCu) Reagents to Thioiminium Ions

Pierre Mateo,[†] Joséphine E. Cinqualbre,[†] Melinda Meyer Mojzes,[†] Kurt Schenk,[§] Philippe Renaud[†]*

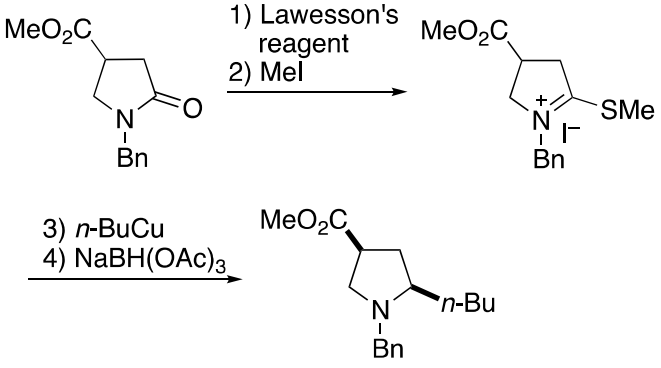
[†]University of Bern, Department of Chemistry and Biochemistry, Freiestrasse 3, 3012 Bern, Switzerland

[§]Ecole Polytechnique Fédérale de Lausanne, Laboratoire de Magnétisme Quantique, BSP 314, Rte de la Sorge, CH-1015 Lausanne, Switzerland

philippe.renaud@dcb.unibe.ch

Abstract

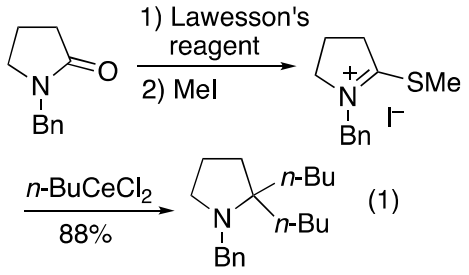
A simple procedure for the conversion of tertiary lactams to 2-monoalkylated cyclic amines is described. The reaction sequence involves conversion of a lactam to a thioiminium ion followed by reaction with an organocopper (RCu) reagent and final reduction with triacetoxyborohydride. The reaction is high yielding and shows an excellent functional group tolerance. Its utility is demonstrated by a rapid synthesis of indolizidine 167B. The excellent chemoselectivity of the process, only monoalkylation products are formed, is rationalized by a mechanism involving the formation of a transient enamine.



Introduction

Lactams are attractive building blocks for the preparation of a wide range of substituted *N*-heterocycles. For instance, addition of organometallic nucleophiles to the activated carbonyl of amides or lactams has emerged as a useful tool for the preparation of 2-mono- and 2,2-disubtituted cyclic amines.[1-3] Tertiary amides and lactams are quite poor electrophiles, however, their reactivity can be dramatically enhanced by converting them into the corresponding trifluoromethanesulfonyloxyiminium ions.[4-5] This approach proved to be good for the preparation of 2-monoalkylated as well as unsymmetrical 2,2-dialkylated cyclic tertiary amines but significant amounts of side products arising from the bis-addition of the second nucleophile are usually observed in this reaction.[6-7] In term of cost and experimental ease, conversion of tertiary amides and lactams into thioiminium ions is more attractive. Our initial work on the reaction of thioiminium ions with organometallic reagents has shown that moderately basic species such as allylic and benzylic Grignard reagents as well as organocerium compounds react efficiently and provide exclusively the *gem*-disubstituted compounds (Scheme 1).[8]

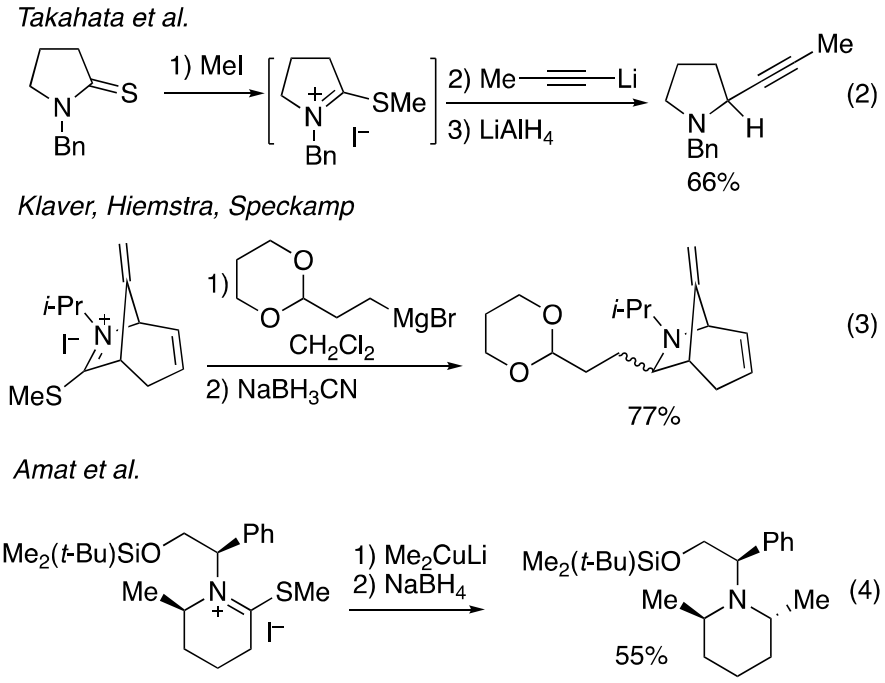
Scheme 1. Synthesis of *gem*-2,2-disubstituted amines.



The preparation of monoalkylated products from thioiminium ions is more challenging. Takahata *et al.* reported that sequential use of lithium acetylides and $LiAlH_4$ afford product of monoalkylation (Scheme 2, eq. 2).[9] Murai and co-workers extended this method for the sequential addition of two different nucleophiles to an *in situ* generated thioiminium salt.[10-11] In these two approaches, the first nucleophile has to be a lithium acetylide to avoid bis-alkylation processes. Klaver et al. reported an isolated example where a thioiminium ion derived from a bicyclic amide reacts with an alkyl Grignard reagent to afford, after treatment with $NaBH_3CN$, the monoalkylated product when the reaction was run in dichloromethane (Scheme 2, eq. 3).[12] Amat *et al.* have reported the reaction of Gilman cuprates with a

methylthioiminium ion derived from *N*-alkylated 6-methylpiperidin-2-one.[13] No product of bis-alkylation was observed but reported yields were moderate (55%) (Scheme 2, eq. 4).

Scheme 2. Preparation of monoalkylated amides from thioiminium ions.

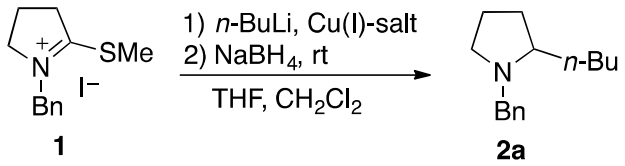


Herein, we report that clean and selective monoalkylation products can be obtained by treating methylthioiminium ions successively with a simple organocopper reagent and sodium triacetoxyborohydride.

Results

n-Butylation of the thioiminium ion **1**, prepared in 87% yield from *N*-benzylpyrrolidinone, was investigated first to optimize the reaction. A rapid screening of the conditions with the cuprate $Bu_2Cu{\cdot}LiI$ showed that a good 89% yield of **2a** was obtained when 3 equivalents of the cuprate were added at –30 °C (Table 1, entry 1). The corresponding higher order cyanocuprate led to a similar yield (Table 1, entry 2). In order to enhance the atom efficiency of the process, the use of organocuprous reagent BuCu (3 equiv) was tested. It afforded the desired product in 83% yield (Table 1, entry 3). To our delight, by using Me_2S as an additive (10 equiv), the monoalkylated product **2a** was obtained in 95% yield (Table 1, entry 4). Me_2S is known to solubilize copper iodide[14] and to stabilize organocopper reagents.[15] Attempt to use a smaller excess of the organocuprous reagent (1.5 equiv) led to a clear drop of the yield (Table 1, entry 5).

Table 1. Optimization of the reaction conditions with the model compound **1**.



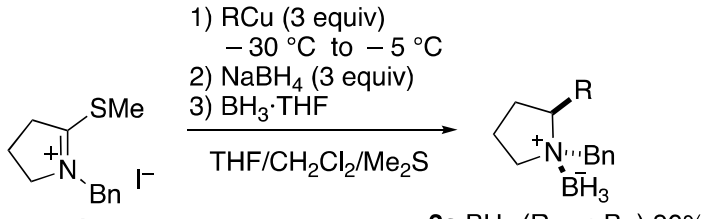
1 **2a**

	Organocopper	Equiv	Additive	Yield[a,b]
1	*n*-$Bu_2CuLi{\cdot}LiI$	3	–	89%
2	*n*-$Bu_2Cu(CN)Li_2$	3	–	81%
3	*n*-BuCu·LiI	3	–	83%
4	*n*-BuCu·LiI	3	Me_2S	95%
5	*n*-BuCu·LiI	1.5	Me_2S	66%

a) For practical convenience, a CH_2Cl_2 solution of the thioiminium ion **1** was added to the –78 °C cooled organocopper solution in THF. Identical results were obtained when the cooled organocopper reagent was added to a cooled solution of **1**. b) Yields determined from the NMR of the crude product using 1,4-dimethoxybenzene as an internal standard. Yields refer to the sum of **2a** and **2a**·BH_3 that are formed as mixtures under these reaction conditions.

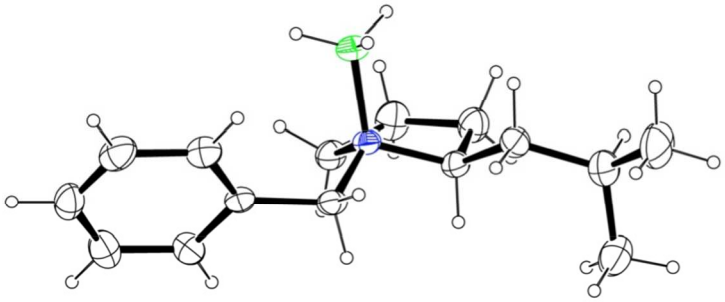
When the reaction was run with $NaBH_4$ as a reducing agent, the tertiary amines were isolated as a mixture of free amine and amine·BH_3 complex. Since the complexes are less polar and easier to purify than the free amines, addition of an excess of BH_3·THF to the crude product was performed to furnish the amine·BH_3 complexes.[16] *n*-BuCu and *i*-BuCu afforded the amine **2a** and **2b** as amine·BH_3 complexes. Both complexes were obtained as single diastereoisomers and in high yields (Scheme 3). The relative configuration of the **2b**·BH_3 complex has been unambiguously assigned by X-ray single crystal structure analysis (Scheme 3).[17]

Scheme 3. Formation of the amine·borane complexes via reductive alkylation of the thioiminium ion **1** and X-ray single crystal structure of **2b**·BH_3 complex (20% probability ellipsoids).



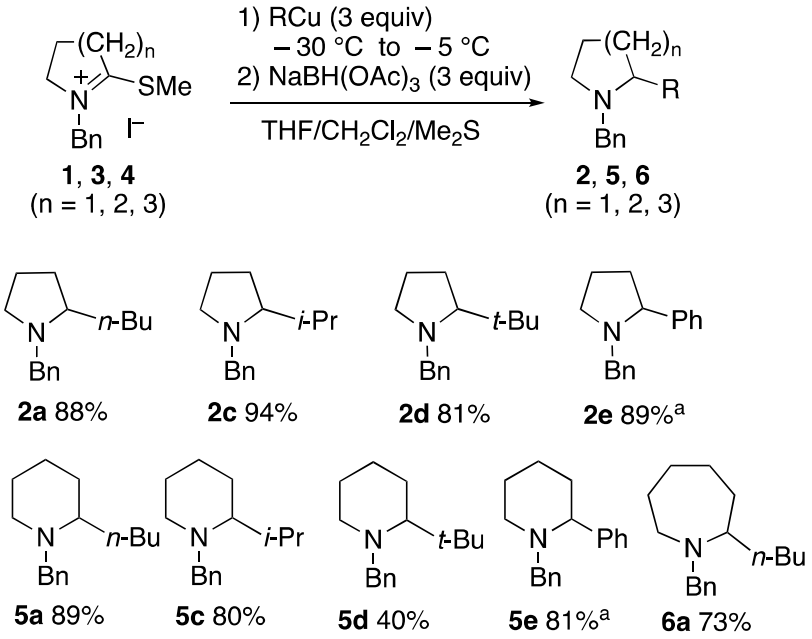
1

2a·BH_3 (R = *n*-Bu) 90%
2b·BH_3 (R = *i*-Bu) 90%



By using sodium triacetoxyborohydride ($NaBH(OAc)_3$), the formation of the borane complex is suppressed and the free amine is isolated. A simple filtration of the crude product over basic aluminum oxide ensures the removal of inorganic by-products and affords the pure tertiary amines. The reaction was performed with different substrates and various organocuprous species in order to evaluate the scope and limitations of the process (Scheme 4).

Scheme 4. Reaction of thioiminium ions **1**, **3** and **4** with organocopper reagents.



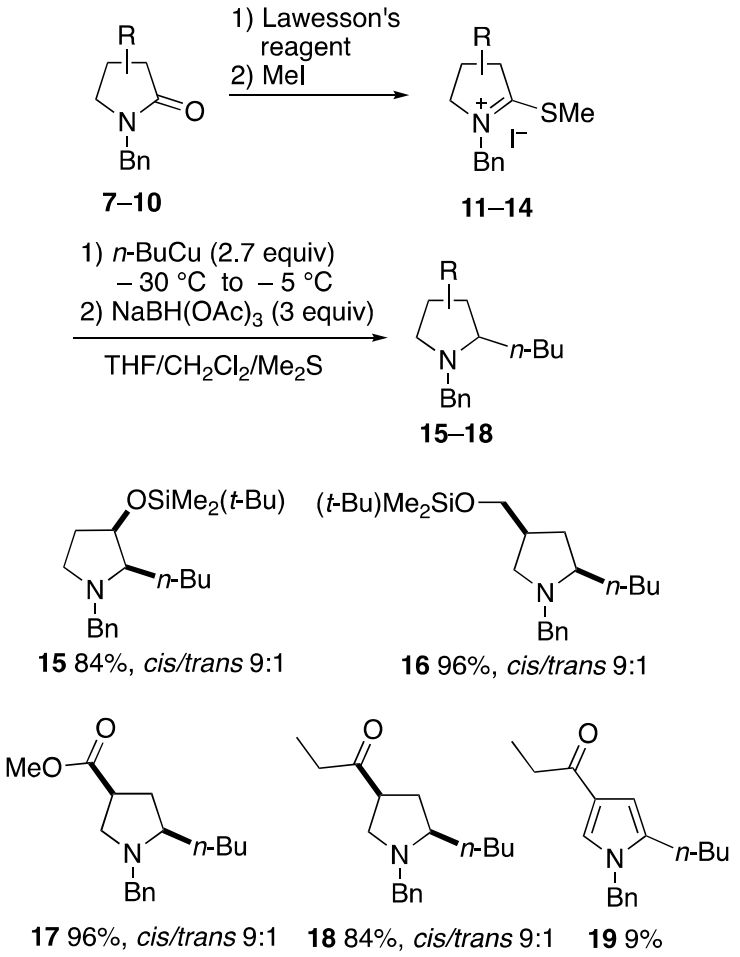
a) Using $NaBH_4$ instead of $NaBH(OAc)_3$

Reaction of the 5-membered-ring thioiminium **1** with primary, secondary and tertiary alkylcopper reagents gave, after reduction, the 2-alkyl *N*-benzylpyrrolidines **2a**, **2c**–**2e** in 81–94% yield. In these examples, the only side-product detected in trace amount is the parent lactam that was easily separated by chromatography. The reaction with PhCu·LiI gave mainly biphenyl. However, the desired amine **2e** was obtained in 89% yield when the reaction was run in THF only (no CH_2Cl_2) with $NaBH_4$ as a

hydride source. The piperidine derivative **3** obtained in 93% by thionation of *N*-benzylvalerolactam followed by methylation with methyl iodide was examined next. The products **5a**, **5c** and **5e** were obtained in good yields (80–89%). Amine **5d** (R = *tert*-butyl) was obtained in lower yield (40%). Finally, the 7-membered ring **6a** was obtained in 73% yield from **4** demonstrating the generality of the reaction.

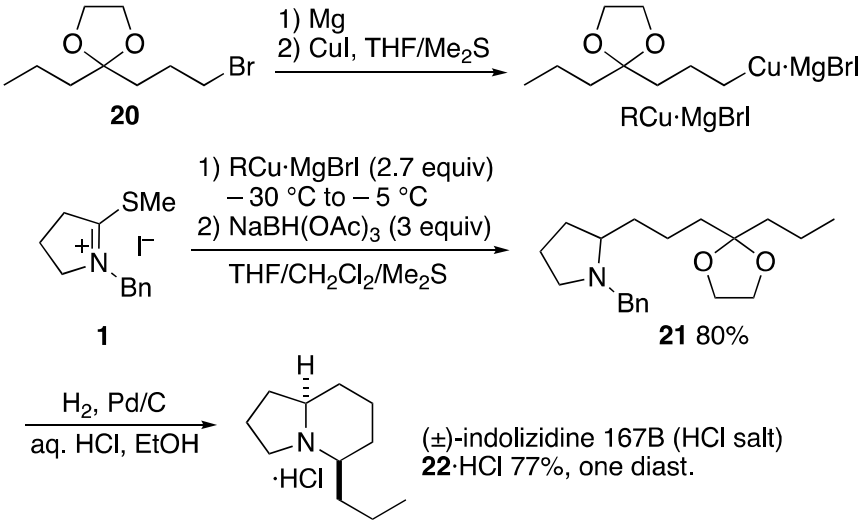
The reaction was further examined starting from substituted lactams **7**–**10** in order to test the stereochemical outcome of the process as well as the functional group tolerance (Scheme 5). The four thioiminiums **11**–**14** were prepared in >90% yield. The thioiminium **9** and **10** containing either an ester or ketone moiety are easily prepared due to the remarkable chemoselectivity of the Lawesson's reagent.[18-20] Moreover, the four thioiminiums were converted into the 2,3- and 2,4-disubstituted pyrrolidines **15**–**18** in 84–96% yield and good *cis* stereoselectivity. The relative configuration of the products has been attributed based on n.O.e. difference spectra and by analogy to literature precedents.[6-7, 21-22] In case of **18**, the corresponding substituted pyrrole side-product **19** was also isolated.

Scheme 5. Diastereoselectivity and chemoselectivity of the reductive alkylation.



Application of the developed method for the synthesis of (±)-indolizidine 167B, a natural product isolated from the skin of the frog *Dendrobates speciosus*,[23,24-25] was examined next (Scheme 6).[26-47] Reaction of the thioiminium **1** with the organocopper reagent derived from the protected bromoketone **20**, easily prepared from commercial 4-bromobutanoyl chloride in two steps,[41, 48] afforded the desired 2-substituted pyrrolidine **21** in 80% yield. Remarkably, the use of an organocopper species derived from an organomagnesium reagent is fully compatible with our reaction sequence. The pyrrolidine **21** was converted to (±)-indolizidine 167B by *N*-debenzylation, hydrolysis of the dioxolane acetal and intramolecular reductive amination. This sequence of reaction could be performed in a single operation by running the hydrogenation under aqueous acidic condition (H_2, Pd/C, aq. HCl in EtOH). The reaction afforded the hydrochloride form of (±)-indolizidine 167B (**22**·HCl) as a single diastereomer in 77% yield.[49] Starting from commercially available *N*-benzylpyrrolidinone, (±)-indolizidine 167B was synthesized in four step and 54% overall yield.

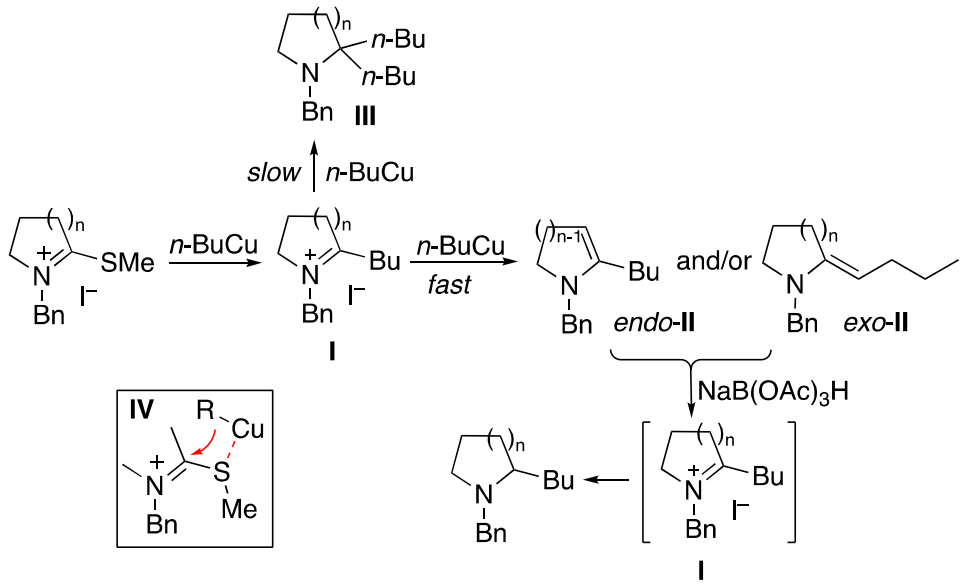
Scheme 6. Synthesis of (±)-indolizidine 167B.



Discussion

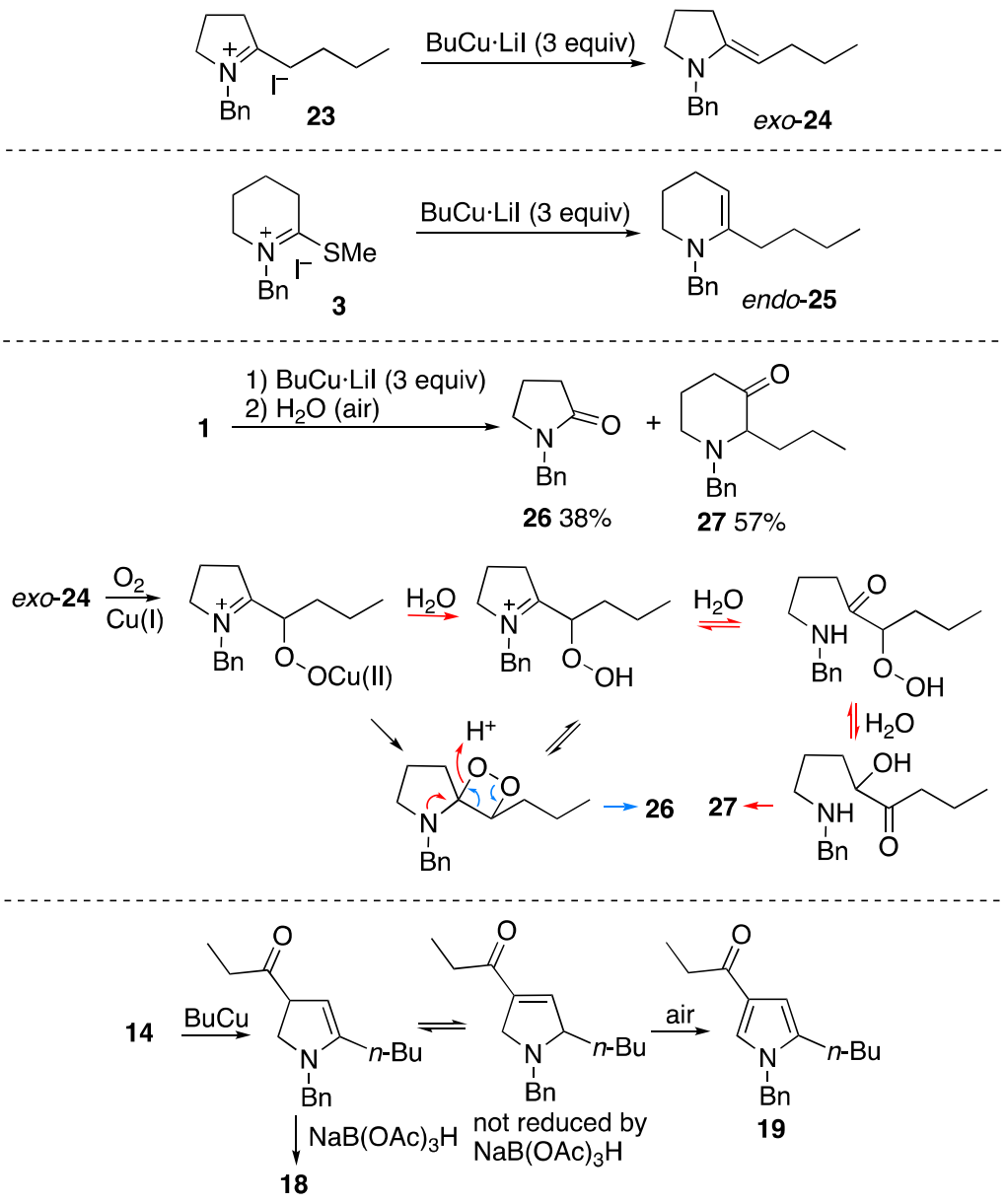
The highly selective monoalkylation process results from a delicate balance between the nucleophilic character of the organocopper species and its basic character. A plausible mechanism for this transformation is the reaction of the organocopper reagent with the thioiminium ion to afford the intermediate iminium **I** that is deprotonated by a second equivalent of the organocopper species to afford the enamine **II**. Finally, reduction of the enamine **II** by $NaBH(OAc)_3$ affords the amine via the transient iminium **I** (Scheme 7). Formation of enamine **II** prevents the formation of a *gem*-disubstituted product **III**. Interestingly, the less electrophilic thioiminium ion reacts efficiently with the organocopper species while the iminium ion **I** is deprotonated by the same reagent. This may simply be a consequence of the difference of their acidity (the thioiminium is expected to be less acidic) or of the complexation of the organocopper species to the sulfur atom of the thioiminium ion (complex **IV**) that favors the nucleophilic addition. An oxidative addition of the copper(I) species leading to a copper(III) intermediate cannot be totally ruled out.

Scheme 7. Proposed mechanism.



This mechanism involving an intermediate enamine **II** is supported by several experimental observations: 1) The iminium ion **23** was prepared independently by *N*-benzylation of 5-butyl-3,4-dihydro-2*H*-pyrrole. When treated with BuCu·LiI, it produces quantitatively the enamine *exo*-**24**. 2) Reaction of the thioiminium **3** with BuCu·LiI followed by evaporation of the solvent afford the enamine *endo*-**25**. 3) When the thioiminium ion **1** is treated with BuCu·LiI followed by hydrolysis, a mixture of the pyrrolidone **26** and the ring expanded ketone **27** resulting both from the oxidation of the enamine by oxygen were isolated. A plausible mechanism for the formation of **26** and **27** is given in Scheme 8. Interestingly, such oxidations of enamines have been reported but they require, when performed in the absence of copper salts, the use of singlet oxygen.[50-53] 4) The reaction involving the thioiminium **14** (Scheme 5) afforded, beside the expected **18**, a small amount of the pyrrole **19**. The formation of this product is expected to derive from the competitive isomerization of the enamine to an α,β-unsaturated ketone (= dihydropyrrole) that cannot be reduced by $NaB(OAc)_3$. This isomerization is followed by an oxygen mediated aromatization of the dihydropyrrole either during the $NaB(OAc)_3H$ reduction step (solvent not degassed) or during the workup procedure.

Scheme 8. Observations supporting the formation of an enamine intermediate.



Conclusions

The reductive alkylation of lactams leading to 2-monoalkylated cyclic amines can be performed in two steps via formation of a thioiminium salt followed by treatment successively with an organocopper reagent and with sodium triacetoxyborohydride. This procedure shows an amazing functional group tolerance and a high level of diastereocontrol. The highly selective monoalkylation results from the formation of an intermediate enamine. Based on this mechanism, this reaction might be extended to

polyfunctionalization of cyclic amines at position 2 using iminium chemistry and at position 3 using enamine chemistry. Progress towards this goal will be reported soon.

EXPERIMENTAL SECTION

Materials and Method. For flash and simple column chromatography (FC and CC, respectively) silica gel 60 Å (40–63 μm), neutral aluminum oxide (40–160 μm) and basic aluminum oxide (40–160 μm) were used. TLC analyses were performed on silica gel 60 F_{254} and on neutral aluminum oxide N/UV_{254} analytical plates. The melting points (m.p.) are corrected. Infrared spectra were recorded neat on a FT-IR spectrometer equipped with a single reflection diamond ATR System and are reported in wave numbers (cm^{-1}). The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on a 300 MHz spectrometer (^{1}H: 300.18 MHz, ^{13}C: 75.48 MHz). ^{11}B NMR and some ^{1}H NMR spectra were recorded on 400 MHZ spectrometer (^{1}H: 400.12 MHz, ^{11}B: 128.38 MHz). Chemical shifts are reported in units of δ (ppm) using the internal standard residual signal of solvent. ^{1}H NMR: $CHCl_3$ δ = 7.26 ppm, C_6H_6 δ = 7.16 ppm and CD_2Cl_2 δ = 5.32 ppm. $^{13}C\{^{1}H\}$ NMR: $CDCl_3$ δ = 77.16 ppm, C_6D_6 δ = 128.06 ppm and CD_2Cl_2 δ = 54.0 ppm for ^{1} spectra).[54] B NMR: Et_2OBF_3 as an external standard (δ = 0 ppm). The following abbreviations were used to describe the multiplicities: app (apparent), s (singlet), d (doublet), t (triplet), q (quadruplet), quint (quintet), sext (sextet), sept (septuplet), m (multiplet), br (broad). Coupling constants, *J*, are reported in Hz with a precision of one unit on the last digit. The number of carbon atoms for each signal is indicated only when superior to 1. GC-MS analyses were performed on a quadrupole mass analyzer using electron impact (70 eV) fitted with a 0.25 mm capillary column (20 m, 0.25 mm); gas carrier: He 1.4 mL/min; injector: 220°C split mode. HRMS analyses were recorded on a hybrid quadrupole time-of-flight mass spectrometer using positive electrospray ionization. Unless otherwise stated, all reagents were obtained from commercial sources and used without further purification. Solvents for reactions (THF, Et_2O, CH_2Cl_2, benzene, toluene and CH_3NO_2) were filtered over columns of dried alumina under a positive pressure of argon. Solvents for extractions and flash column chromatography were of technical grade and were distilled prior to use. The solutions of Grignard and organolithium reagents were titrated on a regular basis or just prior to use.[55-58]

Preparation of the thioiminium salts 1, 3 and 4

1-Benzylpyrrolidine-2-thione. Lawesson's reagent (9.9 g, 24.5 mmol) was added at rt to a solution of 1-benzylpyrrolidin-2-one (8.0 mL, 48.5 mmol) in CH_2Cl_2 (100 mL). Vigorous stirring was maintained for 3-12 h (TLC monitoring). Filtration of the reaction mixture over neutral aluminium oxide (CH_2Cl_2) afforded the thiolactam (8.80 g, 95% yield) as a colorless solid after concentration under reduced pressure. M.p. 71–72 °C (lit.[59] 70–72 °C). Physical and spectral data in accordance with the literature.[59]

1-Benzyl-5-methylsulfanyl-3,4-dihydro-2H-pyrrolium iodide **(1).** Methyl iodide (1.8 mL, 29.2 mmol) was added at rt to a solution of 1-benzylpyrrolidine-2-thione (4.30 g, 22.5 mmol) in THF (75 mL). The flask was wrapped in aluminum foil and the reaction mixture was stirred at rt for 8-12 h (TLC monitoring). Et_2O was added and the suspension was cooled with an ice bath to ensure full precipitation of the thioiminium. The supernatant was removed and the remaining solid was repeatedly washed with Et_2O. Drying under reduced pressure furnished **1** (6.86 g, 92% yield) as a pale brownish solid. Mp = 98-99 °C (lit.[8] 94-95 °C). Physical and spectral data in accordance with the literature.[8]

1-Benzylpiperidine-2-thione. Prepared from 1-benzylpiperidin-2-one (1.8 mL, 10.2 mmol) according to the procedure for 1-benzylpyrrolidine-2-thione. The thiolactam (2.13 g, quantitative) was obtained as colorless crystals. Mp = 69-71 °C (lit.[59] 68-69 °C). Physical and spectral data in accordance with the literature.[59-60]

1-Benzyl-6-methylsulfanyl-2,3,4,5-tetrahydropyridinium iodide **(3).** Prepared from 1-benzylpiperidine-2-thione (2.33 g, 11.3 mmol) according to the procedure for **1**. The thioiminium **3** (3.67 g, 93% yield) was obtained as a pale brownish solid. Mp = 116-118 °C (lit.[8] 103-106 °C). Physical and spectral data in accordance with the literature.[8]

1-Benzylazepane-2-thione. Prepared from 1-benzylazepane-2-one[61] (6.35 g, 31.2 mmol) according to the procedure for 1-benzylpyrrolidine-2-thione. The thiolactam (6.76 g, 99% yield) was obtained as a colorless solid. Mp = 71-72 °C (lit.[62] 76 °C). Physical and spectral data in accordance with the literature.[62]

1-Benzyl-7-methylsulfanyl-3,4,5,6-tetrahydro-2H-azepinium iodide **(4).** Prepared from 1-benzylazepane-2-thione (6.64 g, 30.3 mmol) according to the procedure for **1**, with CH_3NO_2 instead of THF. The thioiminium **4** (9.37 g, 94% yield) was obtained as a yellow solid. Mp = 111–112 °C (lit.[8] 124 °C, decomposition). Physical and spectral data in accordance with the literature.[8]

Preparation of the amine-borane complexes 2a·BH_3 and 2b·BH_3

1-Benzyl-2-butylpyrrolidinium trihydroborate (**2a**·BH_3). Me_2S (0.40 mL, 5.45 mmol) was added to a suspension of CuI (333 mg, 1.75 mmol) in THF (5 mL) at rt. The colorless solution obtained was cooled with a dry-ice/acetone bath and the suitable organometallic lithium or magnesium derivative was added dropwise (1.60 mmol). The temperature was maintained below –65 °C during the addition. The resulting suspension was allowed to warm up to –20/–15 °C and was immediately cooled back to –78 °C. 1-Benzyl-5-methylsulfanyl-3,4-dihydro-2H-pyrrolium iodide **1** (199 mg, 0.60 mmol) was then added as a CH_2Cl_2 solution (4 mL). The stirring was maintained at –35/–30 °C for 0.5 h. An ice-brine bath was put in place and the stirring maintained for an additional 0.5 h. $NaBH_4$ (57mg, 1.51 mmol) was then added neat and allowed to react for 5 min at rt. Sat. aq. NH_4Cl was added, followed by EtOAc, H_2O and solid Na_2CO_3. The mixture was allowed to decant and filtered over a pad of Celite. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was dissolved in THF (5 mL), and BH_3·THF was added (0.5 mL, 1 M in THF) at 0 °C. The solution was allowed to warm gently to rt over a 45 min period. After concentration under reduced pressure, FC (silica gel, pentane/CH_2Cl_2 1:1) afforded the pure amine-borane **2a**·BH_3 (125 mg, 90% yield) as a colorless solid. Mp = 86-87 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.36 (m, 3H), 7.31-7.25 (m, 2H), 4.12 (A part of an AB system, J = 13.8 Hz, 1H), 4.06 (B part of an AB system, J = 13.8 Hz, 1H), 3.06 (ddd, J = 9.8, 8.4, 1.4 Hz, 1H), 2.74 (app q, J = 9.9 Hz, 1H), 2.58 (ddd, J = 18.7, 10.2, 3.5 Hz, 1H), 2.18-2.02 (m, 1H), 1.99-1.79 (m, 5H), 1.64-1.51 (m, 1H), 1.49-1.09 (m, 6H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 132.7 (2C), 131.2, 128.9, 128.4 (2C), 65.9, 62.5, 59.1, 29.6, 29.5, 27.8, 23.0, 19.7, 14.2. IR (cm^{-1}): 2376, 2337, 1174, 1146. HRMS calcd. for $C_{15}H_{26}BNNa$ $[M+Na]^+$: 254.2056, found: 254.2051.

1-Benzyl-2-isobutylpyrrolidinium trihydroborate (**2b**·BH_3). Prepared from the 1-benzyl-5-methylsulfanyl-3,4-dihydro-2*H*-pyrrolium iodide **1** (200 mg, 0.60 mmol) according to the procedure for **2a**·BH_3. FC (silica gel, pentane/EtOAc 97:3) afforded the complex **2b**·BH_3 as a colorless solid (125 mg, 90% yield). Suitable crystals for X-ray single crystal structure analysis were obtained by recrystallization from a mixture of ethyl acetate and pentane. Mp = 113-114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5H), 4.12 (A part of an AB system, J = 13.8 Hz, 1H), 4.03 (B part of an AB system, J = 13.8 Hz, 1H), 3.07 (ddd, J = 9.8, 8.4, 1.4 Hz, 1H), 2.81-2.62 (m, 2H), 2.20-2.00 (m, 1H), 2.00-1.81 (m, 3H), 1.74-1.48 (m, 3H), 1.01 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 132.8 (2C), 131.2, 129.0, 128.4 (2C), 64.4, 62.5, 59.2, 38.3, 27.8, 26.4, 24.5, 21.7,

19.8. ^{11}B NMR (128 MHz, $CDCl_3$) δ -14.7. IR (cm^{-1}): 2371, 2330, 1173, 1069. HRMS calcd. for $C_{15}H_{26}BNNa$ $[M+Na]^+$: 254.2056, found: 254.2051.

Preparation of the monoalkylated amines 2a, 2c–2e, 5a, 5c–5e and 6a

1-Benzyl-2-butylpyrrolidine **(2a)**. Me_2S (0.40 mL, 5.45 mmol) was added to a suspension of CuI (333 mg, 1.75 mmol) in THF (5 mL), at rt. The colorless solution obtained was cooled with a dry-ice/acetone bath and the suitable organometallic lithium or magnesium derivative was added dropwise (1.70 mmol). The temperature was maintained below –65 °C during the addition. The resulting suspension was allowed to warm up to –20/–15 °C and was immediately cooled back to –78 °C. The thioiminium (0.60 mmol) was then added as a CH_2Cl_2 solution (4 mL). The stirring was maintained at –35/–30 °C for 0.5 h. An ice-brine bath was put in place and the stirring maintained for an additional 0.5 h. $Na(AcO)_3BH$ (360 mg, 1.70 mmol) was then added neat and allowed to react for 1 h at rt. Sat. aq. NH_4Cl was added, followed by EtOAc, H_2O and solid Na_2CO_3. The mixture was allowed to decant and filtered over a pad of Celite. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to furnish the crude product. Filtration with CH_2Cl_2 over basic aluminum oxide afforded the pure substituted amine **2a** (114 mg, 88% yield) as a colorless oil after concentration under reduced pressure. Physical and spectral data in accordance with the literature.[7]

1-Benzyl-2-isopropylpyrrolidine **(2c)**. Prepared from the 1-benzyl-5-methylsulfanyl-3,4-dihydro-2*H*-pyrrolium iodide **1** (199 mg, 0.60 mmol) according to the procedure for **2a**. The amine **2c** (114 mg, 94% yield) was obtained as a colorless oil. Physical and spectral data in accordance with the literature.[63]

1-Benzyl-2-(tert-butyl)pyrrolidine **(2d)**. Prepared from the 1-benzyl-5-methylsulfanyl-3,4-dihydro-2*H*-pyrrolium iodide **1** (333 mg, 1.00 mmol) according to the procedure for **2a**. The amine **2d** (176 mg, 81% yield) was obtained as a colorless oil after filtration over neutral aluminum oxide (pentane/EtOAc 96:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.18 (m, 5H), 4.07 (A part of an AB system, J = 14.0 Hz, 1H), 3.49 (B part of an AB system, J = 14.0 Hz, 1H), 2.90-2.78 (m, 1H), 2.53 (dd, J = 9.1, 4.2 Hz, 1H), 2.29 (app dt, J = 9.7, 6.9 Hz, 1H), 1.88-1.74 (m, 1H), 1.72-1.58 (m, 3H), 0.92 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 141.8, 128.24 (2C), 128.17 (2C), 126.6, 73.5, 63.4, 55.7, 36.2, 27.9, 27.0 (3C), 25.4. IR (cm^{-1}): 3026, 1495, 1452, 1028, 733, 696. EI-MS, *m/z* (%): 202 (2), 160 (95), 91 (100), 89 (2), 70 (2), 68 (2), 65 (13). HRMS calcd. for $C_{15}H_{24}N$ $[M+H]^+$: 218.1903, found: 218.1896.

1-Benzyl-2-phenylpyrrolidine **(2e).** To CuI (334 mg, 1.75 mmol) in Et_2O (7 mL) were added Me_2S (1.0 mL, 13.6 mmol) and THF (3 mL). PhMgBr (2.4 mL, 0.7 M in THF) was added dropwise at –78 °C. The resulting yellow suspension was allowed to warm up to –7 °C and was cooled back to –78 °C. 1-Benzyl-5-methylsulfanyl-3,4-dihydro-2*H*-pyrrolium iodide **1** (200 mg, 0.60 mmol) was added neat, followed by 2 mL of THF. The stirring was maintained at –35/–30 °C for 0.5 h. An ice-brine bath was put in place and the stirring maintained for an additional 0.5 h. $NaBH_4$ (70 mg, 1.85 mmol) was added neat and allowed to react for 5 min at rt. Sat. aq. NH_4Cl was added, followed by EtOAc, H_2O and solid Na_2CO_3. The mixture was allowed to decant and filtered over a pad of Celite. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Acid-base extraction afforded **2e** as a colorless oil that crystallized on standing (127 mg, 89% yield). Mp = 41-42 °C (lit.[64] 44-45 °C). Physical and spectral data in accordance with the literature.[64-65]

1-Benzyl-2-butylpiperidine **(5a)**. Prepared from the 1-benzyl-6-methylsulfanyl-2,3,4,5-tetrahydro pyridinium iodide **3** (339 mg, 0.98 mmol) according to the procedure for **2a**. The amine **5a** (216 mg, 96% yield) was obtained as a pale-orange liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 -7.20 (m, 5H), 3.98 (A part of an AB system, J = 13.4 Hz, 1H), 3.22 (B part of an AB system, J = 13.4 Hz, 1H), 2.81-2.64 (m, 1H), 2.35-2.18 (m, 1H), 2.10-1.93 (m, 1H), 1.75-1.17 (m, 12H), 0.91 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 140.1, 129.0 (2C), 128.2 (2C), 126.6, 60.9, 57.7, 51.8, 31.6, 30.4, 27.8, 25.3, 23.9, 23.3, 14.3. IR (cm^{-1}): 3026, 1495, 1452, 1028, 731, 696. EI-MS, *m/z* (%): 174 (99), 132 (2), 104 (2), 91 (100), 89 (2), 82 (5), 65 (9). HRMS calcd. for $C_{16}H_{26}N$ $[M+H]^+$: 232.2060, found: 232.2064.

1-Benzyl-2-isopropylpiperidine **(5c).** Prepared from the 1-benzyl-6-methylsulfanyl-2,3,4,5-tetrahydropyridinium iodide **3** (348 mg, 1.00 mmol) according to the procedure for **2a**. The amine **5c** (174 mg, 80% yield) was obtained as a pale-yellow solid. Physical and spectral data in accordance with the literature.[63]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 -7.18 (m, 5H), 4.11 (A part of an AB system, J = 13.5 Hz, 1H), 3.08 (B part of an AB system, J = 13.5 Hz, 1H), 2.86-2.79 (m, 1H), 2.26 (septd, J = 6.8, 1.7 Hz, 1H), 2.05-1.90 (m, 2H), 1.76-1.71 (m, 1H), 1.64-1.56 (m, 1H), 1.50-1.21 (m, 4H), 0.94 (d, J = 2.4 Hz, 3H), 0.93 (d, J = 2.4 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 140.5, 128.9 (2C), 128.2 (2C), 126.6, 66.6, 56.7, 52.8, 27.7, 24.9, 24.7, 23.6, 20.3, 16.2.

1-Benzyl-2-(tert-butyl)piperidine **(5d).** Prepared from the 1-benzyl-6-methylsulfanyl-2,3,4,5-tetrahydropyridinium iodide **3** (345 mg, 0.99 mmol) according to the procedure for **2a**. The amine **5d** (91 mg, 40% yield) was obtained as a colorless liquid. CC (neutral aluminum oxide, pentane/EtOAc 98:2 then 90:10). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 -7.37 (m, 2H), 7.34 -7.27 (m, 2H), 7.25 -7.18 (m, 1H), 3.91 (A part of an AB system, J = 13.6 Hz, 1H), 3.75 (B part of an AB system, J = 13.6 Hz, 1H), 2.76-2.68 (m, 1H), 2.50 (app dt, J = 14.2, 5.1 Hz, 1H), 2.41-2.36 (m, 1H), 1.89-1.76 (m, 1H), 1.59-1.38 (m, 5H), 0.98 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 141.3, 128.6 (2C), 128.3 (2C), 126.7, 70.3, 56.9, 45.3, 36.1, 27.8 (3C), 22.4, 20.8, 18.0. IR (cm^{-1}): 3026, 1494, 1451, 1018, 730, 696. EI-MS, *m/z* (%): 216 (7), 174 (98), 91 (100), 82 (12), 65 (19), 55 (16). HRMS calcd. for $C_{16}H_{26}N$ $[M+H]^+$: 232.2060, found: 232.2057.

1-Benzyl-2-phenylpiperidine **(5e).** To CuI (556 mg, 2.92 mmol) in Et_2O (8 mL) were added Me_2S (1.5 mL, 20.4 mmol) and THF (4 mL). PhMgBr (2.9 mL, 1.0 M in THF) was added dropwise at –78 °C. The resulting yellow suspension was allowed to warm up to –7 °C and was cooled back to –78 °C. 1-Benzyl-6-methylsulfanyl-2,3,4,5-tetrahydropyridinium iodide **3** (338 mg, 0.97 mmol) was added neat, followed by 3 mL of THF. The stirring was maintained at –35/–30 °C for 0.5 h. An ice-brine bath was put in place and the stirring maintained for an additional 0.5 h. $NaBH_4$ (115 mg, 2.89 mmol) was added neat and allowed to react for 5 min at rt. Sat. aq. NH_4Cl was added, followed by EtOAc, H_2O and solid Na_2CO_3. The mixture was allowed to decant and filtered over a pad of Celite. The aqueous phase was separated and extracted with EtOAc. Acid-base extraction of the combined organic layers afforded the crude amine that crystallized upon trituration with EtOH to give **5e** (199 mg, 81% yield). M.p. = 89-90 °C (lit.[64] 90-91 °C, EtOH/H_2O). Physical and spectral data in accordance with the literature.[64, 66-67]

1-Benzyl-2-butylazepane **(6a).** Prepared from the 1-benzyl-7-methylsulfanyl-3,4,5,6-tetrahydro-2*H*-azepinium iodide **4** (361 mg, 1.00 mmol) according to the procedure for **2a**. The amine **6a** (178 mg, 73% yield) was obtained as a pale-yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 -7.17 (m, 5H), 3.78 (A part of an AB system, J = 14.1 Hz, 1H), 3.68 (B part of an AB system, J = 14.1 Hz, 1H), 2.81 (A part of an ABXY system, J = 14.6, 6.0, 4.2 Hz, 1H), 2.76-2.65 (m, 1H), 2.58 (B part of an ABXY system, J = 14.6, 7.1, 3.8 Hz, 1H), 1.85-1.72 (m, 1H), 1.71-1.41 (m, 8H), 1.41-1.22 (m, 5H), 0.89 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 141.5, 128.7 (2C), 128.2 (2C), 126.6, 62.6, 55.2, 49.8, 34.3, 33.4, 29.5, 28.6, 27.3, 26.1, 23.1, 14.4. IR (cm^{-1}): 3025, 1451, 1028, 728, 695. EI-MS, *m/z* (%): 216 (4), 188 (100), 160 (6), 154 (13), 132 (4), 96 (11), 91 (92), 65 (9). HRMS calcd. for $C_{17}H_{28}N$ $[M+H]^+$: 246.2216, found: 246.2213.

Preparation of the substituted lactams 7-10

1-Benzyl-3-(tert-butyldimethylsilyloxy)pyrrolidin-2-one **(7)**. To 1-benzyl-3-hydroxypyrrolidin-2-one[68] (0.57 g, 2.98 mmol) in DMF were successively added imidazole (0.29 g, 4.26 mmol), DMAP (10 mg, 0.08 mmol), and TBDMSCl (0.62 g, 3.91 mmol). The stirring was then maintained overnight at rt. The reaction mixture was diluted with ethyl acetate (a colorless precipitate formed) and poured into a separatory funnel with brine. The organic layer was further washed, once with water and twice with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to furnish the crude lactam. FC (silica gel, pentane/EtOAc 80:20) afforded **7** (0.88 g, 97% yield) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.22 (m, 5H), 4.44 (s, 2H), 4.35 (app t, J = 7.6 Hz, 1H), 3.24 (ddd, J = 9.6, 8.8, 3.2 Hz, 1H), 3.09 (app dt, J = 9.6, 7.4 Hz, 1H), 2.28 (dddd, J = 12.7, 7.6, 7.4, 3.2 Hz, 1H), 1.89 (dddd, J = 12.7, 8.8, 7.6, 7.4 Hz, 1H), 0.93 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.1, 136.1, 128.5 (2C), 128.0 (2C), 127.5, 71.0, 46.8, 42.6, 29.1, 25.7 (3C), 18.2, -4.5, -5.1. IR (cm^{-1}): 1699, 1254, 1143. EI-MS, *m/z* (%): 290 (10), 248 (100), 156 (3), 101 (3), 91 (74), 73 (10), 65 (9). HRMS calcd. for $C_{17}H_{28}NO_2Si$ $[M+H]^+$: 306.1884, found: 306.1884.

1-Benzyl-4-[(tert-butyldiphenylsilyloxy)methyl]pyrrolidin-2-one **(8)**. To 1-benzyl-4-(hydroxymethyl)pyrrolidin-2-one[69] (1.50 g, 7.31 mmol) in DMF were successively added imidazole (0.75 g, 11.0 mmol) and (*t*-Bu)Ph_2SiCl (2.2 mL, 8.60 mmol). The stirring was then maintained overnight at rt. The reaction mixture was diluted with EtOAc, washed twice with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure to furnish the crude lactam. FC (silica gel, pentane then pentane/EtOAc 1:1) afforded **8** (2.99 g, 92% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62-7.54 (m, 4H), 7.47-7.18 (m, 11H), 4.44 (A part of an AB system, J = 14.7 Hz, 1H), 4.41 (B part of an AB system, J = 14.7 Hz, 1H), 3.58 (A part of an ABX system, J = 10.4, 5.6 Hz, 1H), 3.55 (B part of an ABX system, J = 10.4, 6.4 Hz, 1H), 3.31 (A part of an ABX system, J = 9.9, 8.0 Hz, 1H), 3.13 (B part of an ABX system, J = 9.9, 4.9 Hz, 1H), 2.61-2.47 (m, 2H), 2.40-2.26 (m, 1H), 1.01 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 174.2, 136.7, 135.75 (2C), 135.74 (2C), 133.53, 133.47, 130.0 (2C), 128.9 (2C), 128.3 (2C), 128.0 (4C), 127.7, 65.5, 49.2, 46.8, 34.1, 33.5, 27.0 (3C), 19.5. IR (cm^{-1}): 1684, 1256, 1110. EI-MS, *m/z* (%): 386 (100), 308 (15), 218 (30), 199 (6), 183 (29), 181 (8), 135 (8), 91 (57). HRMS calcd. for $C_{28}H_{34}NO_2Si$ $[M+H]^+$: 444.2359, found: 444.2346.

Methyl 1-benzyl-5-oxopyrrolidine-3-carboxylate **(9)**. Prepared from 1-benzyl-5-oxopyrrolidine-3-carboxylic acid [18] (46.7 g, 213 mmol) according to a known procedure.[69] The lactam **9** (36.4 g, 73% yield) was obtained as a colorless solid. Physical and spectral data in accordance with the literature.[18]

1-Benzyl-4-propionylpyrrolidin-2-one **(10)**. To 1-benzyl-5-oxopyrrolidine-3-carboxylic acid (3.00 g, 13.7 mmol) in CH_2Cl_2 (20 mL) was added 1,1'-carbonyldiimidazole (2.88 g, 17.8 mmol). The stirring was maintained at rt for 30 min, at which time *N,O*-dimethylhydroxylamine hydrochloride (1.73 g, 17.7 mmol) was added. After an additional 3 h water was added. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Repeated washings with aqueous 1 N HCl and drying in the usual manner afforded a viscous oil (3.42 g, 95% yield), pure enough to be used directly in the next step.

The Weinreb amide (1.80 g, 6.86 mmol) was dissolved in THF (30 mL) at rt and cooled down to –78 °C. EtMgBr (5.5 mL, 2.8 M in Et_2O) was then added, the temperature being maintained below –60 °C. The reaction mixture was allowed to warm up slowly to –10 °C (30 min) and aq. 1 N HCl was added followed by Et_2O. The aq. layer was separated and extracted 3 times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. FC (silica gel, pentane/EtOAc 1:2 then EtOAc) afforded **10** as a liquid that crystallized on standing (1.45 g, 91% yield). Pale brownish solid. M.p. = 45-47 °C. ^{1}H NMR[70] (300 MHz, $CDCl_3$) δ 7.37-7.20 (m, 5H), 4.52 (A part of an AB system, J = 14.9 Hz, 1H), 4.39 (B part of an AB system, J = 14.9 Hz, 1H), 3.48-3.24 (m, 3H), 2.68 (app d, J = 8.5 Hz, 2H), 2.48 (A part of an ABX_3 system, J = 17.9, 7.3 Hz, 1H), 2.43 (B part of an ABX_3 system, 17.9, 7.3 Hz, 1H), 1.06 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.8, 172.1, 135.9, 128.7 (2C), 128.0 (2C), 127.6, 47.4, 46.4, 42.1, 34.6, 33.3, 7.5. IR (cm^{-1}): 1710, 1683. EI-MS, *m/z* (%): 231 (60), 202 (21), 174 (18), 146 (50), 132 (21), 106 (22), 91 (100), 84 (21), 65 (19), 57 (25). HRMS calcd. for $C_{14}H_{18}NO_2$ $[M+H]^+$: 232.1332, found: 232.1328.

Preparation of the substituted thioiminiums 11-14

1-Benzyl-3-(tert-butyldimethylsilyloxy)pyrrolidine-2-thione. Prepared from the 1-benzyl-3-(*tert*-butyldimethylsilyloxy)pyrrolidin-2-one **7** (0.80 g, 2.62 mmol) according to the procedure for 1-benzylpyrrolidine-2-thione with THF instead of CH_2Cl_2. The thiolactam (0.84 g, quantitative) was obtained as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 4.99 (A part of an AB system, J = 14.4 Hz, 1H), 4.94 (B part of an AB system, J = 14.4 Hz, 1H), 4.62 (t, J = 6.7 Hz, 1H), 3.57

(ddd, *J* = 11.2, 8.3, 4.3 Hz, 1H), 3.38 (ddd, *J* = 11.2, 7.2, 6.3 Hz, 1H), 2.32 (dddd, *J* = 12.5, 7.2, 6.7, 4.3 Hz, 1H), 1.91 (dddd, *J* = 12.5, 8.3, 6.7, 6.3 Hz 1H), 0.93 (s, 9H), 0.25 (s, 3H), 0.22 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 202.4, 134.8, 128.7 (2C), 128.2 (2C), 127.9, 80.7, 51.8, 50.3, 30.6, 25.8 (3C), 18.3, -4.0, -5.0. IR (cm^{-1}): 1505, 1251, 1158. EI-MS, *m/z* (%): 306 (7), 264 (100), 188 (8), 174 (11), 91 (80), 75 (9), 73 (12), 65 (8). HRMS calcd. for $C_{17}H_{28}NOSSi$ $[M+H]^+$: 322.1655, found: 322.1649.

1-Benzyl-4-(tert-butyldimethylsilyloxy)-5-methylsulfanyl-3,4-dihydro-2H-pyrrolium iodide **(11)**. Prepared from 1-benzyl-3-(*tert*-butyldimethylsilyloxy)pyrrolidine-2-thione (0.69 g, 2.15 mmol) according to the procedure for **1** using CH_3NO_2 instead of THF. The thioiminium **11** (0.94 g, 95% yield) was obtained as a colorless solid. M.p. = 135-136 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.35 (m, 5H), 6.11-6.07 (m, 1H), 4.99 (A part of an AB system, *J* = 15.2 Hz, 1H), 4.86 (B part of an AB system, *J* = 15.2 Hz, 1H), 4.25 (ddd, *J* = 12.8, 8.5, 5.9 Hz, 1H), 3.89 (ddd, *J* = 12.8, 8.6, 5.0 Hz, 1H), 3.09 (dddd, *J* = 13.2, 8.5, 7.4, 5.0 Hz, 1H), 3.05 (s, 3H), 1.97 (dddd, *J* = 13.2, 8.6, 5.9, 4.5 Hz, 1H), 0.91 (s, 9H), 0.22 (s, 3H), 0.17 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 193.8, 130.0, 129.8, 129.7 (2C), 129.0 (2C), 80.4, 58.6, 56.2, 30.6, 25.6 (3C), 17.9, 15.9, -3.6, -4.6. IR (cm^{-1}): 1599, 1583, 1086. HRMS calcd. for $C_{18}H_{30}NOSSi$ $[M-I]^+$: 336.1812, found: 336.1801.

1-Benzyl-4-[(tert-butyldiphenylsilyloxy)methyl]pyrrolidine-2-thione. Prepared from the 1-benzyl-4-[(*tert*-butyldiphenylsilyloxy)methyl] pyrrolidin-2-one **8** (2.57 g, 5.79 mmol) according to the procedure for 1-benzylpyrrolidine-2-thione. The thiolactam (2.64 g, 97%, corrected yield; contains 10 mol% residual CH_2Cl_2) was obtained as a colorless sticky oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.63 (m, 4H), 7.46-7.26 (m, 11H), 4.95 (s, 2H), 3.61 (A part of an ABX system, *J* = 11.4, 8.2 Hz, 1H), 3.56 (A part of an ABX system, *J* = 10.1, 5.6 Hz, 1H), 3.51 (B part of an ABX system, *J* = 10.1, 7.1 Hz, 1H), 3.47 (B part of an ABX system, *J* = 11.4, 4.9 Hz, 1H), 3.18 (A part of an ABX system, *J* = 18.0, 8.9 Hz, 1H), 2.94 (B part of an ABX system, *J* = 18.0, 5.8 Hz, 1H), 2.64-2.50 (m, 1H), 1.00 (s, 9H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 201.1, 135.65 (2C), 135.63 (2C), 135.2, 133.3, 133.2, 129.99, 129.97, 129.0 (2C), 128.4 (2C), 128.2, 127.92 (2C), 127.91 (2C), 64.8, 56.3, 51.7, 47.5, 35.1, 26.9 (3C), 19.3. IR (cm^{-1}): 1505, 1248, 1105. EI-MS, *m/z* (%): 402 (94), 324 (25), 234 (7), 199 (8), 190 (8), 183 (42), 135 (6), 105 (9), 91 (100). HRMS calcd. for $C_{28}H_{34}NOSSi$ $[M+H]^+$: 460.2125, found: 460.2118.

1-Benzyl-3-[(tert-butyldiphenylsilyloxy)methyl]-5-methylsulfanyl-3,4-dihydro-2H-pyrrolium iodide **(12)**. Prepared from 1-benzyl-4-[(*tert*-butyldiphenylsilyloxy)methyl]pyrrolidine-2-thione (2.37 g, 5.16 mmol) according to the procedure for **1** using CH_3NO_2 instead of THF. The thioiminium **12** (2.96 g, 95% yield)

was obtained as a colorless solid. M.p. = 144-146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.30 (m, 15H), 4.86 (A part of an AB system, J = 14.9 Hz, 1H), 4.81 (B part of an AB system, J = 14.9 Hz, 1H), 4.37 (app t, J = 12 Hz, 1H), 4.11 (dd, J = 19, 9 Hz, 1H), 3.77 (dd, J = 12, 4 Hz, 1H), 3.61 (d, J = 4 Hz, 2H), 3.12 (dd, J = 19, 3 Hz, 1H), 3.12-3.00 (m, 1H), 2.87 (s, 3H), 0.95 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 193.0, 135.5 (2C), 135.4 (2C), 132.6, 132.5, 130.2, 130.1, 130.0, 129.7, 129.5 (2C), 129.3 (2C), 128.0 (2C), 127.9 (2C), 64.2, 62.5, 55.6, 43.6, 34.6, 26.9 (3C), 19.2, 17.4. IR (cm^{-1}): 1601, 1585, 1094. HRMS calcd. for $C_{29}H_{36}NOSSi$ $[M\text{-}I]^+$: 474.2281, found: 474.2276.

Methyl 1-benzyl-5-thioxopyrrolidine-3-carboxylate. Prepared from the methyl 1-benzyl-5-oxopyrrolidine-3-carboxylate **9** (4.90 g, 21.0 mmol) according to a known procedure.[18] The thiolactam (4.24 g, 80% yield) was obtained as a colorless liquid. n_D^{20} = 1.5920 (lit. n_D^{20} 1.5880).[18] Physical and spectral data in accordance with the literature.[18]

1-Benzyl-3-methoxycarbonyl-5-methylsulfanyl-3,4-dihydro-2H-pyrrolium iodide **(13)**. Prepared from methyl 1-benzyl-5-thioxopyrrolidine-3-carboxylate (0.69 g, 2.15 mmol) according to the procedure for **1** using CH_3NO_2 instead of THF. The thioiminium **13** (2.20 g, 81% yield) was obtained as a colorless solid. M.p. = 108-109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.42 (m, 3H), 7.40-7.35 (m, 2H), 4.93 (A part of an AB system, J = 15.2 Hz, 1H), 4.86 (B part of an AB system, J = 15.2 Hz, 1H), 4.65 (A part of an ABC system, J = 12.5, 9.3 Hz, 1H), 4.47 (A part of an ABC system, J = 18.8, 10.4 Hz, 1H), 4.13 (B part of an ABC system, J = 12.5, 4.5 Hz, 1H), 3.95 (app tt, J = 10, 5 Hz, 1H), 3.73 (s, 3H), 3.58 (B part of an ABC system, J = 18.8, 3.9 Hz, 1H), 2.94 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 192.4, 170.8, 129.6, 129.5, 129.3 (2C), 129.1 (2C), 61.5, 55.2, 53.0, 43.7, 37.2, 17.5. IR (cm^{-1}): 1722, 1608. HRMS calcd. for $C_{14}H_{18}NO_2S$ $[M\text{-}I]^+$: 264.1053, found: 264.1053.

1-Benzyl-4-propionylpyrrolidine-2-thione. Prepared from the 1-benzyl-4-propionylpyrrolidin-2-one **10** (1.45 g, 6.27 mmol) according to the procedure for 1-benzylpyrrolidine-2-thione. The thiolactam (1.35 g, 87% yield) was obtained as a colorless solid. M.p. = 64-65 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 5.08 (A part of an AB system, J = 14.4 Hz, 1H), 4.86 (B part of an AB system, J = 14.4 Hz, 1H), 3.94-3.88 (m, 1H), 3.66-3.60 (m, 1H), 3.45-3.16 (m, 3H), 2.50 (A part of an ABX_3 system, J = 17.7, 7.3 Hz, 1H), 2.40 (B part of an ABX_3 system, J = 17.7, 7.3 Hz, 1H), 1.06 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 208.2, 198.7, 134.8, 129.1 (2C), 128.5 (2C), 128.4, 54.6, 51.8, 47.3, 44.0, 34.9, 7.7. IR (cm^{-1}): 1711, 1506. EI-MS, *m/z* (%): 247 (86), 214 (15), 190 (23), 162 (14), 156 (15),

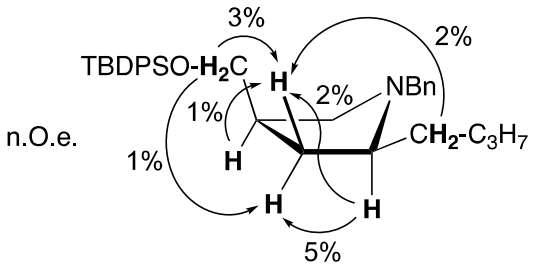
148 (17), 123 (17), 106 (62), 103 (20), 99(34), 91 (100), 85 (19), 65 (22). HRMS calcd. for $C_{14}H_{18}NOS$ $[M+H]^+$: 248.1104, found: 248.1096.

1-Benzyl-3-propionyl-5-methylsulfanyl-3,4-dihydro-2H-pyrrolium iodide **(14)**. Prepared from 1-benzyl-4-propionylpyrrolidine-2-thione (1.31 g, 5.30 mmol) according to the procedure for **1**. The thioiminium **14** (1.82 g, 88% yield) was obtained as a pale brownish solid. M.p. = 126-127 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-741 (m, 3H), 7.38-7.30 (m, 2H), 4.91 (A part of an AB system, J = 15.0 Hz, 1H), 4.86 (B part of an AB system, J = 15.0 Hz, 1H), 4.64 (dd, J = 12.2, 10.0 Hz, 1H), 4.47 (dd, J = 18.7, 10.0 Hz, 1H), 4.13 (app tdd, J = 10.0, 5.0, 4.5 Hz, 1H), 4.00 (dd, J = 12.2, 4.5 Hz, 1H), 3.46 (dd, J = 18.7, 5.0 Hz, 1H), 2.96 (s, 3H), 2.58 (A part of an ABX_3 system, J = 18.9, 7.2 Hz, 1H), 2.51 (B part of an ABX_3 system, J = 18.9, 7.2 Hz, 1H), 1.05 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 207.1, 192.4, 129.7, 129.6, 129.5 (2C), 129.0 (2C), 61.1, 55.3, 43.5, 43.3, 35.3, 17.7, 7.5. IR (cm^{-1}): 1704, 1596, 1582. HRMS calcd. for $C_{15}H_{20}NOS$ $[M-I]^+$: 262.1260, found: 262.1253.

Preparation of the substituted amines 15-19

1-Benzyl-2-butyl-3-(tert-butyldimethylsilyloxy)pyrrolidine **(15)**. Prepared from the 1-benzyl-4-(*tert*-butyldimethylsilyloxy)-5-methylsulfanyl-3,4-dihydro-2*H*-pyrrolium iodide **11** (400 mg, 0.86 mmol) according to the procedure for **2a** (dr 91:9 by GC). CC (neutral aluminum oxide, pentane/Et_2O 95:5 then Et_2O) afforded **15** (253 mg, 84% yield, dr 89:11) as a pale-yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) *Cis* derivative, major isomer, δ 7.33-7.19 (m, 5H), 4.27 (dd, J = 11.7, 6.0 Hz, 1H), 3.98 (A part of an AB system, J = 13.2 Hz, 1H), 3.26 (B part of an AB system, J = 13.2 Hz, 1H), 2.91 (app t, J = 7.5 Hz, 1H), 2.34-2.20 (m, 1H), 2.10-1.92 (m, 2H), 1.77-1.59 (m, 2H), 1.52-1.26 (m, 5H), 0.97-0.85 (m, 12H), 0.06 (br s, 6H). *Trans* derivative, minor isomer (characteristic signals), δ 2.81 (app t, J = 8.3 Hz, 1H), 2.44-2.34 (m, 2H). ^{13}C{^{1}H} NMR (75MHz, $CDCl_3$) Major, δ 139.5, 129.1 (2C), 128.2 (2C), 126.8, 73.0, 68.6, 59.0, 51.4, 34.4, 29.2, 27.8, 26.0 (3C), 23.5, 18.2, 14.3, -4.1, -4.9; Minor, δ 140.0, 129.0 (2C), 128.3 (2C), 126.9, 76.7, 72.6, 59.5, 51.9, 33.5, 32.0, 27.8, 26.0 (3C), 23.3, 18.1, 14.3, -4.2, -4.6. IR (cm^{-1}): 3026, 1115, 1073, 1057, 732, 697. EI-MS, *m/z* (%): Major, 290 (97), 188 (13), 160 (40), 147 (27), 98 (20), 91 (100), 73 (18); Minor, 290 (96), 188 (6), 160 (16), 147 (11), 98 (10), 91 (100), 73 (10). HRMS calcd. for $C_{21}H_{38}NOSi$ $[M+H]^+$: 348.2717, found: 348.2706. The relative *cis* configuration of the major diastereomer was tentatively attributed based on mechanistic considerations and by analogy to the work of Huang and co-worker.[6-7, 22]

1-Benzyl-2-butyl-4-[(tert-butyldiphenylsilyloxy)methyl]pyrrolidine **(16).** Prepared from the 1-Benzyl-3-[(*tert*-butyldiphenylsilyloxy)methyl]-5-methylsulfanyl-3,4-dihydro-2*H*-pyrrolium iodide **12** (602 mg, 1.00 mmol) according to the procedure for **2a**. The amine **16** (465 mg, 96%, dr 89:11 by GC) was obtained as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) *Cis* derivative, major isomer, δ 7.70-7.60 (m, 4H), 7.46-7.20 (m, 11H), 4.05 (A part of an AB system, J = 13.3 Hz, 1H), 3.61 (A part of an ABX system, J = 9.3, 7.7 Hz, 1H), 3.52 (B part of an ABX system, J = 9.3, 6.6 Hz, 1H), 3.14 (B part of an AB system, J = 13.3 Hz, 1H), 2.88 (dd, J = 8.7, 1.8 Hz, 1H), 2.42-2.17 (m, 3H), 2.06 (ddd, J = 12.6, 8.4, 7.1 Hz, 1H), 1.80-1.64 (m, 1H), 1.41-1.09 (m, 6H), 1.03 (s, 9H), 0.93 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) Major, δ 140.2, 135.7 (4C), 134.4, 134.2, 129.6 (2C), 128.8 (2C), 128.2 (2C), 127.7 (4C), 126.7, 67.9, 64.6, 58.1, 56.6, 38.1, 34.3, 33.6, 28.5, 27.0 (3C), 23.3, 19.4, 14.3; Minor, δ 139.7, 135.7 (4C), 134.2, 134.1, 129.7 (2C), 129.2 (2C), 128.3 (2C), 127.7 (4C), 126.9, 66.9, 64.1, 58.8, 57.9, 38.2, 34.1, 33.9, 28.7, 27.0 (3C), 23.3, 19.4, 14.3. IR (cm^{-1}): 3026, 1111, 1087, 738, 697. EI-MS, *m/z* (%): Major, 428 (100), 280 (4), 199 (7), 183 (9), 172 (15), 135 (6), 91 (63); Minor 428 (100), 280(3), 199 (6), 183 (7), 172 (13), 135 (5), 91 (55). HRMS calcd. for $C_{32}H_{44}NOSi$ $[M+H]^+$: 486.3187, found: 486.3176. The relative *cis* configuration of the major diastereomer was assigned based on analysis of n.O.e. difference spectra and by analogy to the work of Huang and co-worker.[6-7, 22]



Methyl 1-benzyl-5-butylpyrrolidine-3-carboxylate **(17)**. Prepared from the 1-benzyl-3-methoxycarbonyl-5-methylsulfanyl-3,4-dihydro-2*H*-pyrrolium iodide **13** (390 mg, 1.00 mmol) according to the procedure for **2a**. The amine **17** (279 mg, 96% yield, dr 88:12 by GC) was obtained as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) *Cis* derivative, major isomer, δ 7.33-7.20 (m, 5H), 4.04 (A part of an AB system, J = 13.4 Hz, 1H), 3.65 (s, 3H), 3.21 (A part of an ABC system, J = 9.8, 3.6 Hz, 1H), 3.18 (B part of an AB system, J = 13.4 Hz, 1H), 2.86 (app tdd, J = 9.2, 7.2, 3.6 Hz, 1H), 2.47-2.31 (m, 1H), 2.36 (B part of an ABC system, J = 9.8, 9.2 Hz, 1H), 2.21 (ddd, J = 12.7, 9.3, 6.7 Hz, 1H), 1.86 (ddd, J = 12.7, 9.1, 7.2 Hz, 1H), 1.80-1.70 (m, 1H), 1.43-1.23 (m, 5H), 0.91 (t, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) Major, δ 175.6, 139.3, 128.7 (2C), 128.2 (2C), 126.8, 64.3, 57.6, 56.1, 51.8, 40.3, 34.3, 33.0, 28.4, 23.2,

14.2; Minor, δ 175.6, 139.3, 128.9 (2C), 128.3 (2C), 127.0, 64.0, 58.3, 57.1, 51.8, 40.5, 34.2, 33.6, 28.3, 23.1, 14.2. IR (cm^{-1}): 3026, 1737, 1195, 1172, 738, 698. EI-MS, *m/z* (%): Major, 244 (18), 218 (95), 158 (8), 91 (100), 65 (14); Minor, 244 (6), 218 (91), 158 (3), 91 (100), 65 (7). HRMS calcd. for $C_{17}H_{26}NO_2$ $[M+H]^+$: 276.1958, found: 276.1958. The relative *cis* configuration of the major diastereomer was tentatively attributed by analogy with compound **16** and by analogy to the work of Huang and co-worker.[6-7, 22]

1-Benzyl-2-butyl-4-propionylpyrrolidine **(18)**. Prepared from the 1-Benzyl-3-propionyl-5-methylsulfanyl-3,4-dihydro-2*H*-pyrrolium iodide **14** (392 mg, 1.01 mmol) according to the procedure for **2a** (dr 88:12 by GC). CC (neutral aluminum oxide, pentane/EtOAc 95:5 then 85:15) afforded **18** as a colorless liquid and as an unseparable mixture of diastereoisomers with inversion of the diastereoisomeric ratio (232 mg, 84% yield, dr 33:67). ^{1}H NMR (300 MHz, $CDCl_3$) *Trans* derivative, major isomer after column, δ 7.33-7.20 (m, 5H), 4.05 (A part of an AB system, J = 13.4 Hz, 1H), 3.15-3.05 (m, 2H), 2.88 (app tdd, J = 9.2, 7.1, 3.3 Hz, 1H), 2.46-2.10 (m, 5H), 1.81-1.63 (m, 2H), 1.41-1.23 (m, 5H), 1.02 (t, J = 7.3 Hz, 3H), 0.91 (t, J = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) *Trans* isomer, δ 212.0, 139.6, 129.0 (2C), 128.4 (2C), 127.0, 64.2, 58.4, 56.6, 47.8, 35.4, 33.7, 33.2, 28.4, 23.2, 14.3, 7.9; *Cis* isomer, δ 212.1, 139.5, 128.7 (2C), 128.3 (2C), 126.9, 64.5, 57.7, 55.3, 47.8, 33.7, 33.4, 33.1, 28.4, 23.2, 14.2, 8.1. IR (cm^{-1}): 3031, 1712, 1144, 1119, 738, 697. EI-MS, *m/z* (%): *Trans* isomer, 244 (2), 216 (96), 182 (19), 158 (14), 91 (100), 68 (4), 65 (10); *Cis* isomer, 273 (2), 216 (88), 182 (2), 158 (11), 91 (100), 68 (3), 65 (8). HRMS calcd. for $C_{18}H_{28}NO$ $[M+H]^+$: 274.2165, found: 274.2160. The relative *cis* configuration of the major diastereomer was tentatively attributed by analogy with compound **16** and by analogy to the work of Huang and co-worker.[6-7, 22]

1-Benzyl-2-butyl-4-propionyl-1H-pyrrole **(19)**. Isolated as a side product in the synthesis of 1-benzyl-2-butyl-4-propionylpyrrolidine **18**. The pyrrole **19** (25 mg, 9% yield) was obtained as a pale-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.340-7.22 (m, 4H), 7.05-6.98 (m, 2H), 6.42-6.37 (m, 1H), 5.04 (s, 2H), 2.73 (q, J = 7.4 Hz, 2H), 2.41 (t, J = 7.4 Hz, 2H), 1.55 (quint, J = 7.4 Hz, 2H), 1.34 (sext, J = 7.4 Hz, 2H), 1.17 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 196.8, 137.1, 135.6, 129.0 (2C), 127.9, 126.6 (2C), 125.9, 124.5, 106.6, 50.9, 32.5, 30.6, 25.8, 22.5, 13.9, 9.1. IR (cm^{-1}): 3120, 3031, 1653, 1516, 1453, 730, 700. EI-MS, *m/z* (%): 269 (14), 240 (74), 226 (12), 170 (5), 106 (4), 91 (100), 65 (5). HRMS calcd. for $C_{18}H_{24}NO$ $[M+H]^+$: 270.1852, found: 270.1857.

Synthesis of (±)-indolizidine 167B

(3-(2- Propyl-1,3-dioxolan-2-yl)propyl)magnesium bromide. Prepared from the 2-(3- bromopropyl)-2-propyl-1,3-dioxolane **20**[48] (1.26 g, 4.99 mmol) and magnesium turnings (0.25g, 10.3 mmol) in 5.0 mL THF according to a known procedure.[41] The Grignard reagent (0.51 M, 50% yield) was obtained as a clear solution and was used directly in the following step.

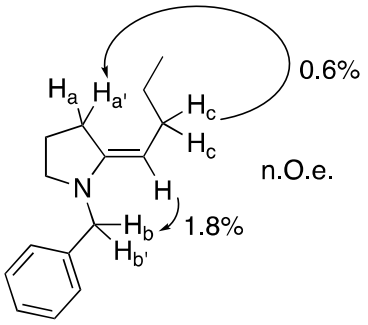
1-Benzyl-2-[3-(2-propyl-1,3-dioxolan-2-yl)propyl]pyrrolidine **(21)**. Prepared from the 1-benzyl-5-methylsulfanyl-3,4-dihydro-2*H*-pyrrolium iodide **1** (202 mg, 0.61 mmol) and (3-(2- propyl-1,3-dioxolan-2-yl)propyl)magnesium bromide according to the procedure for **2a**. CC (neutral aluminum oxide, CH_2Cl_2/MeOH 99:1 then cyclohexane/EtOAc 80:20) afforded **21** (154 mg, 80% yield) as a pale-yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.18 (m, 5H), 4.03 (A part of an AB system, J = 12.9 Hz, 1H), 3.92 (s, 4H), 3.13 (B part of an AB system, J = 12.9 Hz, 1H), 2.94-2.85 (m, 1H), 2.38-2.26 (m, 1H), 2.08 (app q, J = 9 Hz, 1H), 2.01-1.86 (m, 1H), 1.78-1.26 (m, 13H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 139.9, 129.0 (2C), 128.1 (2C), 126.7, 111.7, 64.9 (2C), 64.4, 58.8, 54.3, 39.5, 37.6, 34.6, 30.5, 22.0, 20.7, 17.2, 14.5. IR (cm^{-1}): 3025, 1073, 1051, 1028, 737, 698. EI-MS, *m/z* (%): 274 (11), 186 (4), 160 (100), 115 (21), 91 (97), 86 (3), 71 (3), 65 (3). HRMS calcd. for $C_{20}H_{32}NO_2$ $[M+H]^+$: 318.2428, found: 318.2422.

(±)-Indolizidine 167B, hydrochloric salt **(22**·HCl**)**. To the 1-benzyl-2-[3-(2-propyl-1,3-dioxolan-2-yl)propyl] pyrrolidine **21** (265 mg, 0.83 mmol) in EtOH (15 mL) were added HCl (2.0 mL, 1 N in H_2O) and 10% Pd/C (107 mg, 0.10 mmol). H_2 was bubbled through the vigorously stirred reaction mixture for 10 min and atmospheric pressure was then maintained for 48 h. The black suspension was filtered over a pad of Celite and concentrated under reduced pressure. The residue was diluted with H_2O and Et_2O. The aqueous phase was separated, basified with solid Na_2CO_3 and extracted twice with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. An etheral solution of HCl (3 mL, 1 M in Et_2O) was added to the residue and the solvent was removed under reduced pressure. Trituration of the residue with Et_2O afforded **22**·HCl (131 mg, 77% yield) as a pale brownish solid. M.p. = 166–169 °C (lit.[71] 167–169 °C). Given the limited solubility of **22**·HCl in $CDCl_3$, the NMR spectra were also recorded with the corresponding free amine **22**. Physical and spectral data in accordance with the literature.[27, 36, 41, 71]

Formation and reactivity of the enamines

1-Benzyl-5-butyl-3,4-dihydro-2H-pyrrolium iodide **(23)**. To 5-butyl-3,4-dihydro-2*H*-pyrrole[72] (215 mg, 1.72 mmol) in CH_3NO_2 (2.5 mL) was added benzyl iodide (0.23 mL, 1.84 mmol). The flask was wrapped in aluminum foil and the reaction mixture was stirred at rt for 8-12 h. The volatiles were removed under reduced pressure. After precipitation/crystallization with Et_2O, the supernatant was removed and the remaining solid was repeatedly washed with Et_2O. Drying under reduced pressure afforded the iminium salt **23** (513 mg, 87% yield) as a yellow solid. M.p. = 64-68 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.38 (m, 5H), 5.08 (s, 2H), 4.18 (app t, J = 7.9 Hz, 2H), 3.49 (app t, J = 8.0 Hz, 2H), 3.04 (app t, J = 8.1 Hz, 2H), 2.29 (app quint, J = 8 Hz, 2H), 1.78 (app quint, J = 8 Hz, 2H), 1.48 (sext, J = 7.3 Hz, 2H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 195.2, 130.1, 129.6, 129.5 (2C), 129.0, 60.7, 55.2, 40.1, 32.2, 27.9, 22.9, 18.1, 13.6. IR (cm^{-1}): 2957, 2930, 2871, 1659, 1455, 1373, 727, 696. HRMS calcd. for $C_{15}H_{22}N$ $[M\text{-}I]^+$: 216.1747, found: 216.1749.

1-Benzyl-2-butylidenepyrrolidine **(24)**. Me_2S (0.40 mL, 5.45 mmol) was added to a suspension of CuI (333 mg, 1.75 mmol) in THF (5 mL), at rt. The colorless solution obtained was cooled with a dry-ice/acetone bath and *n*-BuLi (0.85 mL, 2.5 M in hexanes, 1.7 mmol) was added dropwise. The temperature was maintained below –65 °C during the addition. The resulting suspension was allowed to warm up to –20/–15 °C and was immediately cooled back to –78 °C. 1-Benzyl-5-butyl-3,4-dihydro-2*H*-pyrrolium iodide **23**. (309 mg, 0.90 mmol) was then added as a CH_2Cl_2 solution (4 mL). The stirring was maintained at –35/–30 °C for 0.5 h. An ice-brine bath was put in place and the stirring maintained for an additional 0.5 h. After decantation, an aliquot of the solution was evaporated and submitted to ^{1}H NMR showing *exo*-**24** as sole product. ^{1}H NMR (300 MHz, C_6D_6) δ 7.23-7.07 (m, 5H), 4.17 (t, J = 7.2 Hz, 1H), 3.98 (s, 2H), 2.76 (t, J = 6.5 Hz, 2H), 2.33 (t, J = 7.6 Hz, 2H), 2.08 (q, J = 7.2 Hz, 2H), 1.50-1.45 (m, 4H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2) δ 147.5, 140.0, 128.8 (2C), 128.3 (2C), 127.1, 90.1, 53.0, 52.3, 31.3, 29.0, 25.1, 22.5, 14.1. IR (cm^{-1}): 3032, 1617, 1453, 1329, 732, 699. HRMS calcd. for $C_{15}H_{22}N$ $[M+H]^+$: 216.1741, found: 216.1747. The exocyclic nature and the geometry of the enamine was assigned from n.O.e. difference spectra.



1-Benzyl-6-butyl-1,2,3,4-tetrahydropyridine **(25)**. Me_2S (0.40 mL, 5.45 mmol) was added to a suspension of CuI (333 mg, 1.75 mmol) in THF (5 mL), at rt. The colorless solution obtained was cooled with a dry-ice/acetone bath and *n*-BuLi (0.85 mL, 2.5 M in hexanes, 1.7 mmol) was added dropwise. The temperature was maintained below –65 °C during the addition. The resulting suspension was allowed to warm up to –20/–15 °C and was immediately cooled back to –78 °C. 1-benzyl-6-methylsulfanyl-2,3,4,5-tetrahydro pyridinium iodide **3** (208 mg, 0.60 mmol) was then added as a CH_2Cl_2 solution (4 mL). The stirring was maintained at –35/–30 °C for 0.5 h. An ice-brine bath was put in place and the stirring maintained for an additional 0.5 h. After decantation, an aliquot of the solution was evaporated and submitted to ^{1}H NMR showing *endo*-**25** as sole product. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.37-7.23 (m, 5H), 4.45 (app s, 1H), 4.11 (s, 2H), 2.93-2.90 (m, 2H), 2.17 (t, J = 7.4 Hz, 2H), 2.04 (t, J = 5.9 Hz, 2H), 1.72-1.65 (m, 2H), 1.56-1.46 (m, 2H), 1.42-1.32 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2) δ 145.5, 141.2, 128.9 (2C), 128.1 (2C), 127.2, 97.8, 54.5, 48.9, 34.2, 31.6, 23.7, 23.0, 22.3, 14.4. IR (cm^{-1}): 3059, 1640, 1451, 728, 696. HRMS calcd. for $C_{16}H_{24}N$ $[M+H]^+$: 230.1903, found: 230.1903.

1-Benzyl-2-propylpiperidin-3-one **(27)**. To CuI (571 mg, 3.00 mmol) in THF (6 mL) was added Me_2S (0.66 mL, 9.00 mmol) at rt. The colorless solution obtained was cooled with a dry-ice/acetone bath and *n*-BuLi (1.2 mL, 2.5 M in hexanes) was added dropwise with the temperature being maintained below –65 °C. The resulting suspension was allowed to warm up to –15 °C and was cooled back to –78 °C. 1-Benzyl-5-methylsulfanyl-3,4-dihydro-2*H*-pyrrolium iodide (334 mg, 1.00 mmol) in CH_2Cl_2 (4.5 mL) was added. The stirring was maintained at –35/–30 °C for 0.5 h. An ice-brine bath was put in place and the stirring was maintained for an additional 0.5 h. H_2O (5 mL) was added and the stirring was maintained at rt overnight. EtOAc and solid Na_2CO_3 were added. The mixture was allowed to decant and filtered over a pad of Celite. The aqueous phase was separated and extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure.

Filtration (neutral aluminum oxide, CH_2Cl_2) afforded **27** (133 mg, 57% yield) as a yellow oil along with 1-benzyl-2-pyrrolidinone **26** (69 mg, 39% yield) upon elution with EtOAc. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 3.77 (A part of an AB system, J = 13.5 Hz, 1H), 3.61 (B part of an AB system, J = 13.5 Hz, 1H), 3.07 (br t, J = 7 Hz, 1H), 3.02 (ddd, J = 13, 9, 5 Hz, 1H), 2.59 (app dt, J = 13, 6 Hz, 1H), 2.53 (ddd, J = 15, 9, 6 Hz, 1H), 2.35 (ddd, J = 15, 6, 5 Hz, 1H), 2.11-1.91 (m, 2H), 1.86-1.60 (m, 2H), 1.34 (app sext, J = 7 Hz, 2H), 0.89 (t, J = 7 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 212.0, 139.0, 128.8 (2C), 128.4 (2C), 127.2, 70.7, 57.4, 46.0, 37.9, 29.4, 24.2, 19.2, 14.2. IR (cm^{-1}): 2955, 1712, 1495, 1452, 730, 697. EI-MS, *m/z* (%): 203 (15), 188 (10), 174 (12), 160 (72), 91 (100), 84 (9), 65 (11). HRMS calcd. for $C_{15}H_{22}NO$ $[M+H]^+$: 232.1696, found: 232.1696.

AUTHOR INFORMATION

Corresponding Author

*E-mail: philippe.renaud@dcb.unibe.ch

ORCID

Philippe Renaud: 0000-0002-9069-7109

Notes

The authors declare no competing financial interest.

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ASSOCIATED CONTENT

Supporting Information

NMR spectra of all compounds and X-ray crystallographic data (CIF file) for compounds **2b**·BH_3. This material is available free of charge via the Internet at http://pubs.acs.org.

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