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Synthesis of 5-Substituted 2-Pyrrolidinones by Coupling of Organozinc Reagents with Cyclic *N*-Acyliminium Ions

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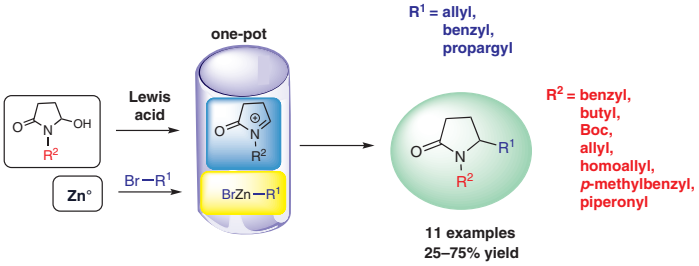

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Abstract A coupling reaction between cyclic *N*-acyliminium ions with organozinc reagents is described. The cyclic *N*-acyliminium ions, generated in situ from *N*-substituted-5-hydroxy-2-pyrrolidinones by treatment with boron trifluoride–diethyl ether complex or titanium tetrachloride, are trapped by the organozinc reagent, which is formed from an alkyl bromide in the presence of zinc in the same reaction medium. The *N*-substituted-5-allyl-2-pyrrolidinones generated using this method serve as versatile intermediates for the synthesis of azabicyclic systems with indolizidine and pyrroloazepinolizidine cores.

Key words *N*-acyliminium ions, organozinc reagents, coupling reactions, 5-allyl-2-pyrrolidinones, azabicyclic systems

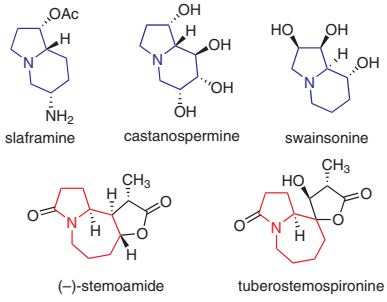

Figure 1 Indolizidine and pyrroloazepinolizidine cores in biologically active compounds

Indolizidine and pyrroloazepinolizidine alkaloids are present widely in Nature and are compounds of great interest due to their biological and pharmaceutical properties.[1] Representative examples of these azabicyclic alkaloids are castanospermine and swainsonine, which are prominent synthetic targets because of their potent glycosidase inhibitory activities, making them potential candidates for the treatment of various diseases, including cancer, malaria and obesity.[2] In addition, *Stemona* alkaloids, such as (–)-stemoamide and tuberostemospironine, are used for the treatment of respiratory diseases and as anthelmintics (Figure 1).[3]

A number of innovative methodologies for the synthesis of indolizidine and pyrroloazepinolizidine systems have been described in the literature.[4] Examples of these methods include *trans*-annular cyclization reactions,[5] reactions of cyclic nitrones,[6] reactions of α,β-unsaturated diazoketones,[7] imino Diels–Alder reactions,[8] and others.

N-Acyliminium ions, especially cyclic versions, are highly reactive intermediates, which is reflected in an impressive number of synthetic applications.[9] In this context, we envisaged that a very useful method for carbon–carbon bond formation would involve coupling reactions of iminium ions with organometallic compounds. In particular, intramolecular reactions have received considerable attention for the preparation of azabicyclic systems.[10] We therefore became interested in the generation of 5-allyl-2-pyrrolidinones, because the allyl moiety is a versatile functional group that is amenable to further synthetic transformations; for instance, via intramolecular reactions toward the synthesis of azabicyclic compounds by ring-closing metathesis (RCM).[11]

In view of their limited stability and high reactivity, *N*-acyliminium ions are generated in situ by treatment of a suitable precursor with protic or Lewis acids.[12] Typically, *N*-substituted-5-hydroxy-2-pyrrolidinones and their derivatives are used as precursors of cyclic *N*-acyliminium ions when the pyrrolidine moiety is involved in forming part of the azabicyclic system.[13] General methods to prepare precursors of cyclic *N*-acyliminium ions involve partial reduction of the corresponding *N*-substituted succinimides, for example, with $LiEt_3BH$,[14] sodium borohydride–$Mg(ClO_4)_2$,[15] lithium thexylborohydride (LTB) and diisobutylaluminum

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hydride (DIBAL-H).[16] The reduction with sodium borohydride in methanol solution at 0 °C in the presence of hydrochloric acid or potassium hydroxide is perhaps the most important method known for the preparation of these *N*-acyliminium ion precursors.[17] However, a large excess of sodium borohydride and long reaction times are required to obtain satisfactory yields, and in many cases the ring-opening product is observed due to over-reduction of the aldehyde group during the hydroxy–lactam equilibrium.[18]

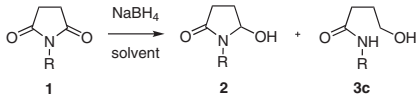
Although, the chemistry of *N*-acyliminium ions has been widely studied to date, there are few reports on coupling reactions with organometallic compounds. Those reports that do exist are based on the protocols of Pedregal[19] and Wistrand,[20] in which a cyclic *N*-acyliminium ion is coupled with an organocopper reagent, generated from the more readily available Grignard reagents.

In 1994, Kise reported the reactions of *N*-acyl-α-methoxyamines with organozinc reagents for the synthesis of homoallylamines.[21] Specifically, the 5-methoxy-*N*H-2-pyrrolidinone derived from *N*H-succinimide was reacted with allylzinc bromide to give the corresponding 5-allyl-*N*H-succinimide. Although this coupling reaction resulted in an acceptable yield, only one example has been examined so far. Additionally, this method has the disadvantage of requiring *N*-acyl-α-methoxyamines, which are very difficult to obtain in pure form. Mechanistically, an acid–base reaction is involved, resulting in an *N*-acylimine species during the coupling reaction with the organozinc reagent. However, the methodology was limited to the use of *N*H-acylamines to generate the corresponding *N*-acylimines. Therefore, it is reasonable to expect that *N*-acyliminium ions, generated from *N*-substituted-5-hydroxy-2-pyrrolidinones, would be better intermediates to carry out this coupling reaction with organozinc reagents, and might represent a useful tool for the conversion of *N*-substituted succinimides into 5-substituted-2-pyrrolidinone derivatives.

Our experimental work started with the synthesis of the *N*-acyliminium ion precursors. For this purpose, we selected *N*-benzyl **1a**, *N*-butyl **1b**, *N*-*tert*-butoxycarbonyl (Boc) **1c**, *N*-allyl **1d**, *N*-homoallyl **1e**, *N*-*p*-methylbenzyl **1f** and *N*-piperonyl **1g** succinimides as starting materials. We evaluated the partial reduction of these *N*-substituted succinimides with sodium borohydride in methanol solution.[17] When the reduction reaction of succinimides **1a–g** was carried out with only 3 equivalents of $NaBH_4$ in methanol (at –5 °C to rt) under neutral conditions, the corresponding *N*-substituted-5-hydroxy-2-pyrrolidinones **2a**,**b**,**d**–**g** were obtained in good to very good yields (Table 1, entries 1, 2 and 6–9).

Interestingly, when the *N*-Boc-succinimide **1c** was reduced under these conditions (Table 1, entry 3), the over-reduced amide-alcohol **3c** was obtained as the only product in 86% yield.

Table 1 Partial Reduction of *N*-Substituted Succinimides[a]



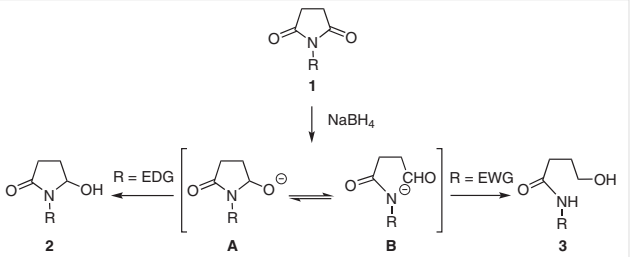
a: R = benzyl
b: R = butyl
c: R = Boc
d: R = allyl
e: R = homoallyl
f: R = *p*-methylbenzyl
g: R = piperonyl

Entry	1	$NaBH_4$ (equiv)	Solvent	Time (h)	Temp (°C)	Yield of **2** (%)	Yield of **3** (%)
1	**1a**	3	MeOH	1	–5 to rt	93	trace
2	**1b**	3	MeOH	3	–5 to rt	94	trace
3	**1c**	3	MeOH	1	–5 to rt	0	86
4	**1c**[b]	2	MeOH–THF	2	–50	24	30
5	**1c**	9[c]	MeOH	3	–78	86[d]	trace
6	**1d**	3	MeOH	3	–5 to rt	93	trace
7	**1e**	3	MeOH	3	–5 to rt	81	trace
8	**1f**	3	MeOH	1	–5 to rt	80	trace
9	**1g**	3	MeOH	1	–5 to rt	85	trace

[a] Reaction conditions: succinimide **1** (1.0 equiv), $NaBH_4$, MeOH (5.0 mL).
[b] Reaction carried out on gram scale.
[c] Reaction employing 5 M HCl solution.
[d] Based on 20% recovered starting material.

These results clearly show the considerable influence of the N-substituent present on the succinimide ring on the equilibrium of the oxy-anion A and amide-aldehyde B (Scheme 1). When the nitrogen atom of the succinimide ring contains an electron-donating substituent, the equilibrium in the reaction medium is displaced toward the oxy-anion A, which gives the corresponding N-substituted-5-hydroxy-2-pyrrolidinone **2** as the predominant product, even when the reduction is carried out at room temperature and over long reaction times. In contrast, when the nitrogen atom carries an electron-withdrawing group such as Boc, the equilibrium in the reaction medium shifts toward the amide-aldehyde **B**, which is reduced to the amide-alcohol derivative **3** in the presence of sodium borohydride.

The partial reduction of succinimide **1c** on milligram scale using $NaBH_4$ (2.0 equiv) in THF–methanol at –50 °C

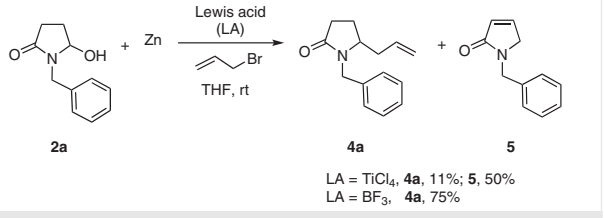


Scheme 1 Influence of the *N*-substituent on the formation of amide-alcohol **3**

has been previously reported in moderate yield.[22] However, when the reaction was carried out on gram scale, a mixture of *N*-Boc-5-hydroxy-2-pyrrolidinone (**2c**) (24%) along with the over-reduction product **3c** (30%) was obtained (Table 1, entry 4).

Fortunately, we found that when using $NaBH_4$ (9 equiv) in methanol at –78 °C and employing 5 M HCl solution, product **2c** was obtained as the major product in 86% yield (based on 20% the recovered starting material; this material was recycled until total consumption) (Table 1, entry 5). This result was attributed to the low temperature at which the reduction is carried out, since under these reaction conditions succinimide **1c** becomes partially insoluble offering a slower and therefore more selective reduction. Additionally, according to the report by D'Ulivo,[23] under acidic conditions, $NaBH_4$ is in equilibrium with a hydroboron species, which could be catalyzing the reduction reaction. This result was reproducible and significant variations in the yield were not detected when the reaction was performed on multigram scale.

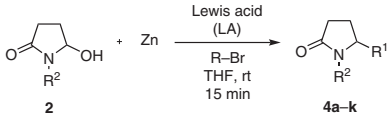
Having obtained *N*-benzyl-hydroxypyrrolidin-2-one **2a** using the optimized methodology, we next evaluated the conditions for the key coupling reaction of the allyl organozinc reagent with the corresponding *N*-acyliminium ion to obtain the 5-allyl-2-pyrrolidinone derivative **4a** (Scheme 2). Initially, a solution containing equimolar amounts of *N*-benzyl-hydroxypyrrolidin-2-one **2a** and $TiCl_4$ in anhydrous THF was added to a solution of freshly prepared allyl organozinc reagent, obtained by adding 5 equivalents of allyl bromide to 5 equivalents of Zn in THF. A mixture of 5-allyl-*N*-benzylpyrrolidin-2-one (**4a**) and *N*-benzyl-2-pyrrolinone (**5**) was obtained in a combined yield of 61%, with the yield of **4a** being very poor (11% of **4a** and 50% yield of **5**). Compound **5** is suggested to arise as a consequence of a proto-elimination reaction of the corresponding *N*-acyliminium ion, following a prototopic [1,3] rearrangement, an important and common side reaction in cyclic *N*-acyliminium ion chemistry.[11a,b] This result suggested that after formation of the iminium ion, the Lewis acid is possibly faster at promoting the formation of 2-pyrrolinone **5** than in mediating the coupling reaction with the organometallic compound.



Scheme 2 Synthesis of 5-allyl-*N*-benzylpyrrolidin-2-one (**4a**)

After considering a range of different experimental approaches, the reaction was optimized when 1 equivalent of boron trifluoride–diethyl ether complex (BF_3-etherate) and 3 equivalents of allyl bromide were added concurrently to a suspension containing 1 equivalent of *N*-benzyl-hydroxypyrrolidin-2-one **2a** and 3 equivalents of Zn in THF (1.5 mL/1.0 mmol of **2a**). This exothermic reaction gave the desired 5-allyl-2-pyrrolidinone **4a** in 75% yield (Table 2, entry 1).

Table 2 Synthesis of 5-Substituted-2-pyrrolidinone Derivatives[a]

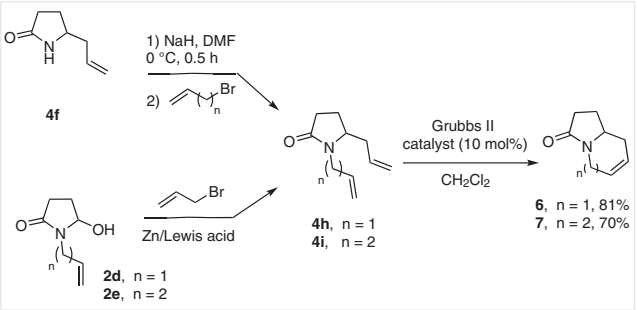


Entry	**2** (R^2)	LA	**4**	Yield (%)
1	**2a** (R^2 = Bn)	BF_3	**4a** (R^1 = allyl)	75
2	**2a** (R^2 = Bn)	BF_3	**4b** (R^1 = Bn)	50
3	**2a** (R^2 = Bn)	$TiCl_4$	**4c** (R^1 = propargyl)	60
4	**2b** (R^2 = *n*-Bu)	BF_3	**4d** (R^1 = allyl)	72
5	**2b** (R^2 = *n*-Bu)	BF_3	**4e** (R^1 = Bn)	53
6	**2c** (R^2 = Boc)	BF_3	**4f** (R^1 = allyl, R^2 = H)	25
7	**2c** (R^2 = Boc)	BF_3	**4g** (R^1 = Bn, R^2 = H)	34
8	**2d** (R^2 = allyl)	BF_3	**4h** (R^1 = allyl)	75
9	**2e** (R^2 = homoallyl)	BF_3	**4i** (R^1 = allyl)	75
10	**2f** (R^2 = *p*-$MeC_6H_4CH_2$)	BF_3	**4j** (R^1 = allyl)	73
11	**2g** (R^2 = piperonyl)	BF_3	**4k** (R^1 = allyl)	67

[a] Reaction conditions: hydroxypyrrolidin-2-one **2** (1.0 equiv), LA (1.0 equiv), Zn (3.0 equiv), R^1–Br (3.0 equiv), THF (1.5 mL/1.0 mmol of **2**), rt.

To demonstrate the generality of this methodology we performed this reaction with different *N*-substituted derivatives **2b–g**, using allyl, benzyl, and propargyl bromides as precursors of the organozinc reagents (Table 2, entries 2–11). Under these conditions, the 5-substituted 2-pyrrolidinones **4a**,**b**,**d**,**e**,**h–k** were obtained in acceptable yields (50–75%) (entries 1, 2, 4, 5 and 8–11). In contrast, the yields were lower when the *N*-substituent was Boc (entries 6 and 7). Interestingly, the Boc protecting group was cleaved under these conditions to give directly the *N*H-5-substituted pyrrolidinone derivatives **4f** and **4g**. Unfortunately, the application of this coupling process to propargyl bromide was less successful, affording the propargyl derivative **4c** in low yield. A better yield of **4c** (60%) was obtained when titanium tetrachloride was used as the Lewis acid to generate the *N*-acyliminium ion (entry 3). In stark contrast to allyl, propargyl and benzyl bromides, *n*-butyl bromide did not produce the corresponding coupling product. This can possibly be explained by the lower reactivity of this alkyl halide compared to the other examples used in this work. It is interesting to note that this methodology is the first report on the coupling reaction between cyclic *N*-acyliminium ions with organozinc reagents, both being generated in situ in the same reaction medium.

To show the utility of the 5-allyl pyrrolidinones **4h** and **4i**, we decided to carry out the synthesis of the indolizidine **6** and pyrroloazepinolizidine **7** cores through RCM (Scheme 3). It should be mentioned that 5-allyl pyrrolidinones **4h** and **4i** can also be prepared via *N*-alkylation of *N*H-pyrrolidinone **4f**.



Scheme 3 RCM of **4h** and **4i** for the synthesis of indolizidine **6** and pyrroloazepinolizidine **7**

To this end, pyrrolidinone **4f** was reacted with allyl bromide to give *N*-allyl pyrrolidinone **4h** in 55% yield, and with homoallyl bromide to give *N*-homoallyl pyrrolidinone **4i** in 63% yield under conditions reported by Boto.[24] Finally, 5-allyl pyrrolidinones **4h** and **4i** were reacted with Grubbs' catalyst using the RCM conditions reported by Meyers[25] to give the desired azabicyclic systems **6** and **7** in good yields of 81% and 70%, respectively.

In summary, the methodology outlined herein constitutes a convenient and easy means for the synthesis of 5-substituted-2-pyrrolidinones **4a–k** from precursors of *N*-acyliminium ions, which were coupled in a satisfactory manner with organozinc reagents. This is the first example in which a cyclic *N*-acyliminium ion and an organozinc reagent are generated in situ in the same reaction medium, followed by their spontaneous coupling to give the desired products. Although *N*-Boc-5-hydroxy-2-pyrrolidinone (**2c**) is reasonably stable, we found that under the reaction conditions described herein the Boc group was cleaved to give the coupling products **4f** and **4g**. Therefore, the use of this protecting group in 5-hydroxy-2-pyrrolidinones could be centered on logical *N*-unsubstituted congeners. Lastly, the usefulness of the *N*-alkenyl 5-allyl-2-pyrrolidinones was demonstrated by their use as precursors for the synthesis of indolizidine **6** and pyrroloazepinolizidine **7** cores in good yields.

All moisture-sensitive reactions were carried out in oven-dried glassware under a nitrogen atmosphere. Reagents were purchased from Aldrich and used without any further purification. All solvents were distilled over appropriate drying reagents (sodium or calcium hydride). All reactions were monitored by TLC on Merck precoated plates (silica gel 60 F254). Column chromatography was performed using Merck silica gel 60 (230–400 mesh). Melting points were measured using a Mel-Temp II apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured at 300 MHz and 75 MHz, respectively, on a Bruker Avance 300 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) relative to Me_4Si (δ = 0.0), with coupling constants (*J*) reported in hertz (Hz). Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad singlet (br s). ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) using the signal at δ = 77.0 ($CDCl_3$) as an internal reference.

1-*tert*-Butoxycarbonyl-5-hydroxypyrrolidin-2-one (2c)[22]

To a solution of *N*-*tert*-butoxycarbonyl succinimide (**1c**) (1.0 g, 5.0 mmol) in methanol (40.0 mL) at –78 °C was added sodium borohydride in 9 portions (0.20 g, 5.0 mmol, one portion each 40 min); after each addition of sodium borohydride a solution of 5 M hydrochloric acid was added until pH 2–3 was reached (0.4 mL). After 6 hours, the reaction mixture was quenched by the addition of crushed ice–water and the product was extracted thoroughly with CH_2Cl_2 (5 × 50.0 mL). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 6:4).

Yield: 640 mg (86%) based on 270 mg (20%) of recovered starting material; white solid; crystallization (hexanes–CH_2Cl_2); mp 78–79 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.67 (d, *J* = 6.3 Hz, 1 H), 4.03 (br s, 1 H), 2.76–2.64 (m, 1 H), 2.40–2.31 (m, 1 H), 2.21–2.08 (m, 1 H), 1.97–1.88 (m, 1 H), 1.49 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 150.5, 83.8, 82.0, 30.4, 27.09, 25.4.

2-Pyrrolidinone-5-substituted Derivatives 4a,b,d–k; General Procedure

To a suspension of the corresponding *N*-substituted-5-hydroxypyrrolidinone **2** (1.0 equiv) and Zn (3.0 equiv) in anhydrous THF (1.5 mL/1.0 mmol of **2**) at room temperature was added the Lewis acid ($TiCl_4$ or $BF_3{\cdot}Et_2O$, 1.0 equiv) and the alkyl bromide (3.0 equiv) at the same time. Caution! Exothermic reaction. After stirring for 15 min, the reaction was quenched by the addition of a saturated solution of $NaHCO_3$. The reaction mixture was filtered over Celite and the filter cake washed with EtOAc. The product was extracted with EtOAc and the combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using hexanes–EtOAc as the eluting solvent.

5-Allyl-1-benzylpyrrolidin-2-one (4a)[26]

Starting from **2a** (191 mg, 1.0 mmol), product **4a** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 6:4).

Yield: 160 mg (75%); pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.22 (m, 5 H), 5.65–5.59 (m, 1 H), 5.11–5.08 (m, 2 H), 5.01 (d, *J* = 15.0 Hz, 1 H), 3.98 (d, *J* = 15.0 Hz, 1 H), 3.52–3.48 (m, 1 H), 2.51–2.44 (m, 1 H), 2.41–2.34 (m, 2 H), 2.20–2.14 (m, 1 H), 2.08–2.00 (m, 1 H), 1.79–1.74 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.2, 136.6, 132.6, 128.6, 127.9, 127.4, 118.7, 56.2, 44.1, 37.1, 30.0, 23.2.

1,5-Dibenzylpyrrolidin-2-one (4b)[27]

Starting from **2a** (191 mg, 1.0 mmol), product **4b** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 7:3).

Yield: 132 mg (50%); pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–6.96 (m, 10 H), 5.04 (d, *J* = 15.0 Hz, 1 H), 3.95 (d, *J* = 15.0 Hz, 1 H), 3.62–3.54 (m, 1 H), 2.93 (dd, J_1 = 4.2 Hz, J_2 = 13.5 Hz, 1 H), 2.49 (dd, J_1 = 8.7 Hz, J_2 = 13.2 Hz, 1 H), 2.19 (t, *J* = 8.7 Hz, 2 H), 1.89–1.76 (m, 1 H), 1.72–1.61 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.2, 136.9, 136.6, 129.1, 128.7, 128.5, 128.0, 127.5, 126.7, 58.0, 44.4, 39.1, 29.8, 23.6.

5-Allyl-1-butylpyrrolidin-2-one (4d)[28]

Starting from **2b** (157 mg, 1.0 mmol), product **4d** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 7:3).

Yield: 130 mg (72%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.75–5.62 (m, 1 H), 5.14 (d, *J* = 6.3 Hz, 1 H), 5.10 (s, 1 H), 3.70–3.59 (m, 2 H), 2.93–2.86 (m, 1 H), 2.43–2.28 (m, 3 H), 2.22–2.03 (m, 2 H), 1.78–1.67 (m, 1 H), 1.55–1.40 (m, 2 H), 1.29 (sext, *J* = 7.5 Hz, 2 H), 0.91 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 132.8, 118.6, 56.7, 40.0, 37.4, 30.1, 29.3, 23.3, 20.1, 13.7.

5-Benzyl-1-butylpyrrolidin-2-one (4e)

Starting from **2b** (157 mg, 1.0 mmol), product **4d** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 7:3).

Yield: 123 mg (53%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.07 (m, 5 H), 3.82–3.74 (m, 1 H), 3.67–3.62 (m, 1 H), 3.34 (t, *J* = 6.3 Hz, 1 H), 2.95 (dd, J_1 = 4.2 Hz, J_2 = 13.8 Hz, 1 H), 2.89–2.84 (m, 1 H), 2.51 (dd, J_1 = 8.7 Hz, J_2 = 13.5 Hz, 1 H), 2.15–2.07 (m, 2 H), 1.94–1.81 (m, 1 H), 1.72–1.61 (m, 1 H), 1.55–1.40 (m, 1 H), 1.31–1.18 (m, 2 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 137.0, 129.2, 128.6, 126.7, 58.5, 40.1, 39.2, 29.9, 29.5, 23.7, 20.1, 13.8.

5-Allylpyrrolidin-2-one (4f)[29]

Starting from **2c** (200 mg, 1.0 mmol), product **4f** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 1:9).

Yield: 60 mg (25%); pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (br s, 1 H), 5.84–5.70 (m, 1 H), 5.15 (d, *J* = 3.3 Hz, 1 H), 5.11 (s, 1 H), 3.72 (quin, *J* = 6.6 Hz, 1 H), 2.37–2.20 (m, 5 H), 1.82–1.69 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.3, 133.5, 118.1, 53.8, 40.7, 30.1, 26.3.

5-Benzylpyrrolidin-2-one (4g)[30]

Starting from **2c** (200 mg, 1.0 mmol), product **4g** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 7:3).

Yield: 59 mg (34%); pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.09 (m, 5 H), 6.05 (br s, 1 H), 3.88–3.79 (m, 1 H), 2.71 (qd, J_1 = 5.7 Hz, J_2 = 13.5 Hz, 2 H), 2.27–2.13 (m, 3 H), 1.82–1.71 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.0, 137.4, 129.0, 128.7, 126.8, 55.7, 42.9, 30.0, 26.8.

1,5-Diallylpyrrolidin-2-one (4h)[31]

Starting from **2d** (141 mg, 1.0 mmol), product **4h** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 7:3).

Yield: 123 mg (75%); pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.82–5.63 (m, 2 H), 5.21 (qd, J_1 = 1.5 Hz, J_2 = 7.8 Hz, 1 H), 5.18–5.17 (m, 1 H), 5.16–5.15 (m, 1 H), 5.12–5.11 (m, 1 H), 4.33 (ddt, J_1 = 1.5 Hz, J_2 = 4.8 Hz, J_3 = 15.3 Hz, 1 H), 3.72–3.64 (m, 1 H), 3.52 (ddd, J_1 = 0.9 Hz, J_2 = 7.8 Hz, J_3 = 15.3 Hz, 1 H), 2.48–2.29 (m, 3 H), 2.27–2.06 (m, 2 H), 1.80–1.70 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 132.8, 132.7, 118.7, 117.7, 56.6, 43.1, 37.3, 30.0, 23.3.

5-Allyl-1-(but-3-enyl)pyrrolidin-2-one (4i)[31]

Starting from **2e** (310 mg, 2.0 mmol), product **4i** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 7:3).

Yield: 268 mg (75%); pale yellow oil.

^{1} H NMR (300 MHz, $CDCl_3$): δ = 5.82–5.67 (m, 2 H), 5.18–5.02 (m, 4 H), 3.81–3.65 (m, 2 H), 3.02–2.93 (m, 1 H), 2.47–2.02 (m, 7 H), 1.80–1.69 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0, 135.1, 132.7, 118.7, 116.8, 56.8, 39.5, 37.4, 31.8, 30.1, 23.3.

5-Allyl-1-(*p*-methylbenzyl)pyrrolidin-2-one (4j)

Starting from **2f** (205 mg, 1.0 mmol), product **4j** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 75:25).

Yield: 167 mg (75%); pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14 (s, 4 H), 5.71–5.66 (m, 1 H), 5.10 (d, *J* = 15.0 Hz, 2 H), 4.99 (d, *J* = 15.0 Hz, 1 H), 3.93 (d, *J* = 15.0 Hz, 1 H), 3.52–3.46 (m, 1 H), 2.50–2.36 (m, 3 H), 2.32 (s, 3 H), 2.28–2.12 (m, 1 H), 2.08–1.97 (m, 1 H), 1.83–1.69 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 137.1, 133.6, 132.7, 129.3, 128.0, 118.7, 56.1, 43.9, 37.2, 30.1, 23.2, 21.1.

5-Allyl-1-piperonylpyrrolidin-2-one (4k)

Starting from **2g** (235 mg, 1.0 mmol), product **4k** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 75:25).

Yield: 173 mg (67%); as pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.76–6.68 (m, 3 H), 5.94 (s, 2 H), 5.72–5.57 (m, 1 H), 5.10 (d, *J* = 15.0 Hz, 2 H), 4.90 (d, *J* = 15.0 Hz, 1 H), 3.89 (d, *J* = 15.0 Hz, 1 H), 3.57–3.48 (m, 1 H), 2.52–2.41 (m, 3 H), 2.22–2.16 (m, 1 H), 2.10–1.99 (m, 1 H), 1.82–1.72 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.1, 148.0, 147.0, 132.7, 130.6, 121.3, 118.8, 108.4, 108.2, 101.1, 56.1, 44.0, 37.2, 30.1, 23.2.

1-Benzyl-5-propargylpyrrolidin-2-one (4c)[32]

In a dry round-bottomed flask under nitrogen, *N*-benzyl-5-hydroxypyrrolidin-2-one (**2b**) (191 mg, 1.0 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) at room temperature. Titanium tetrachloride (0.21 mL, 1.1 mmol) was added dropwise and the resulting solution was allowed to stir for 10 min. In a separate round-bottomed flask under nitrogen, propargyl bromide (0.35 mL, 80% in toluene, 3.0 mmol) was dissolved in anhydrous THF (10 mL) at room temperature. Zn powder (197 mg, 3.0 mmol) was added in one portion and the resulting sus-

pension was stirred for 10 min and then cooled to 0 °C. The solution of **2b** from the first flask was added dropwise and the resulting mixture stirred overnight and then quenched with saturated NH_4Cl solution. The reaction mixture was filtered over Celite and the filter cake washed with CH_2Cl_2. The product was extracted with CH_2Cl_2 (3 × 50 mL) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (silica gel, hexanes–EtOAc, 7:3).

Yield: 127 mg (60%); pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H), 5.04 (d, *J* = 15 Hz, 1 H), 3.98 (d, *J* = 15 Hz, 1 H), 3.62–3.57 (m, 1 H), 2.68–2.47 (m, 1 H), 2.45–2.35 (m, 3 H), 2.22–2.12 (m, 1 H), 2.08–1.93 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.3, 136.3, 128.7, 128.6, 128.4, 128.0, 127.6, 79.2, 71.2, 55.3, 44.1, 30.1, 23.5, 23.1.

1,5,8,8a-Tetrahydroindolizin-3(2*H*)-one (6)[31]

To a solution of the bis-alkenylpyrrolidin-2-one **4h** (165 mg, 1.0 mmol) in dichloromethane (10 mL) at room temperature was added dropwise a solution of Grubbs II reagent (40 mg, 10% mol) in dichloromethane (5 mL). The reaction was heated at reflux temperature in a nitrogen atmosphere for 1.5 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography with hexanes–EtOAc (1:1) to give **6**. Starting from **4h** (165 mg, 1.0 mmol), product **6** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 1:1).

Yield: 115 mg (81%); pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.76–5.62 (m, 2 H), 4.19 (d, *J* = 18.9 Hz, 1 H), 3.57–3.45 (m, 2 H), 2.36–2.21 (m, 4 H), 2.00–1.90 (m, 1 H), 1.67–1.55 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1, 124.1, 123.4, 52.9, 40.3, 32.4, 29.9, 25.4.

1,2,5,6,9,9a-Hexahydro-3*H*-pyrrolo[1,2-*a*]azepin-3-one (7)[31]

Following the typical procedure from **4i** (100 mg, 0.55 mmol) in dichloromethane (7 mL) and Grubbs II reagent (30 mg) in dichloromethane (3 mL), **7** was obtained after purification by flash column chromatography (hexanes–EtOAc, 1:1). Starting from **4i** (100 mg, 0.55 mmol), product **7** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 1:1).

Yield: 61 mg (70%); pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.93–5.73 (m, 2 H), 3.96–3.88 (m, 1 H), 3.72–3.62 (m, 1 H), 3.09–3.01 (m, 1 H), 2.39–2.17 (m, 7 H), 1.71–1.59 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 131.6, 128.4, 58.5, 41.3, 36.3, 30.4, 27.8, 25.6.

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