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Rhodium-catalyzed intramolecular conjugate addition of vinylstannanes to dihydro-4-pyridones: a simple method for stereoselective construction of 1-azabicyclic alkaloids

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Abstract

A straightforward route for the stereoselective synthesis of unsaturated quinolizidines and related higher homologs has been developed. Our results revealed that the rhodium complex $[RhCl(cod)]_2$ is an effective catalyst for the intramolecular conjugate addition of vinylstannanes to the dihydropyridones leading to the corresponding 1-azabicyclo[*m.n*.0]alkenes in a moderate to good yield and an excellent diastereoselectivity under neutral conditions at room temperature. This methodology has been successfully applied to the stereoselective synthesis of the racemic lasubine I.

Keywords: Vinylstannanes; Dihydropyridones; Rhodium complexes; Quinolizidines

1. Introduction

Vinylstannanes are extremely versatile reagents for the preparation of complex organic and organometallic compounds, since they are sources of alkenyl units with a defined stereochemistry. They are most often used for the C–C bond forming reactions, during which they are converted into the corresponding lithium,[1] copper,[2] or palladium[3] derivatives. The palladium-catalyzed coupling with carbon electrophiles is the most common application of vinylstannanes in organic synthesis.[3] This procedure has been widely used in the synthesis of biologically active and pharmaceutically relevant compounds.[4] In 1998, Inoue and Oi reported that rhodium complexes catalyze the conjugate addition of organostannanes to the α,β-unsaturated compounds.[5] During the course of the reaction, carried out in the presence of $[Rh(cod)(MeCN)_2]BF_4$ in THF at 60 °C, a variety of α,β-unsaturated ketones and esters were transformed into the corresponding conjugate addition products. However, the observed high yield of this process is highly dependent on the substitution pattern of the substrates. During these reactions, the alkenyl–rhodium complex, which is generated by the transmetallation from the organometallic precursors, is considered to be the catalytically active species.[5] At the same time Li has reported a similar rhodium-catalyzed conjugate addition of organostannanes in water,[6] where the electronic nature of the substituents on the tin atom was demonstrated to have a significant impact on the reactivity.[7]

Numerous natural and biologically active products contain an azabicyclic skeleton as a structural element.[8] Therefore, the stereoselective synthesis of the fused nitrogen-containing bicyclic alkaloids became an important goal for synthetic chemists during recent years.[9] Indeed, a number of syntheses of such compounds have been published.[8b] Most of the reported methodologies are restricted, however, to the preparation of a limited range of derivatives. In order to test novel therapeutic agents it is desirable to develop a general synthetic route to various azabicyclic alkaloids. Recently, we have demonstrated that the dihydropyridones of type **1** containing the vinylstannane in the side-chain are excellent substrates for the rhodium-catalyzed

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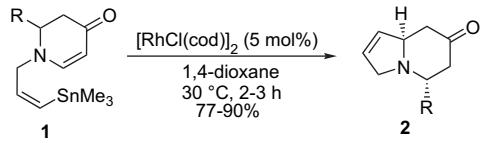
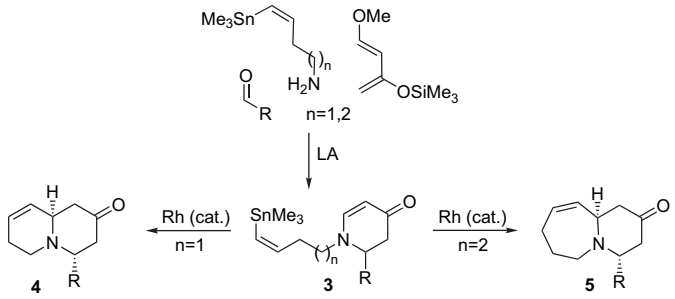
intramolecular conjugate addition, yielding corresponding unsaturated indolizidines **2** in a high yield. Typically, only a single detectable diastereomer is formed (Scheme 1).[10]



Scheme 1.

During the course of these studies, we became interested if the homologated compounds of the type **3** undergo cyclization in a similar fashion (Scheme 2).



Scheme 2. Synthetic strategy.

In this paper, we report that such rhodium-catalyzed cyclocondensation does readily occur and provides a useful method for the stereocontrolled assembly of unsaturated quinolizidines (1-azabicyclo[4.4.0]decenes) **4** and 1-azabicyclo[5.4.0]undecenes **5**.

2. Results and discussion

The starting alkenylstannanes **14** and **15** were prepared as shown in Scheme 3.

The commercially available 3-butyn-1-ol (**6**) and 4-pentyn-1-ol (**7**) were converted into the corresponding silyl ethers **8** and **9**, which upon deprotonation with MeLi and the reaction of resultant lithium acetylides with Me_3SnCl afforded the alkynylstannanes **10** and **11**. The hydrozirconation of **10** and **11** followed by the protonation and fluoride-induced cleavage of the silyl ethers led to the required (*Z*)-alkenylstannanes **12** and **13**. Finally, the alkenylstannanes **12** and **13** were transformed into amines **14** and **15** by the conversion of alcohol functionalities into the corresponding alkyl azides and subsequent reduction.

The amines **14** and **15** were converted into the required Schiff bases **16** by the treatment with selected aldehydes in CH_2Cl_2 in the presence of 4 Å molecular sieves. These reactive intermediates were not isolated and after exchange of the solvent were immediately subjected to the Lewis acid-mediated reaction with Danishefsky's diene **17**. We found that for aromatic and aliphatic imines of the type **16** the highest yield of dihydropyridones **3** is obtained when about 10 mol % of $Yb(OTf)_3$ was used as Lewis acid and CH_3CN was employed as a solvent (Table 1).

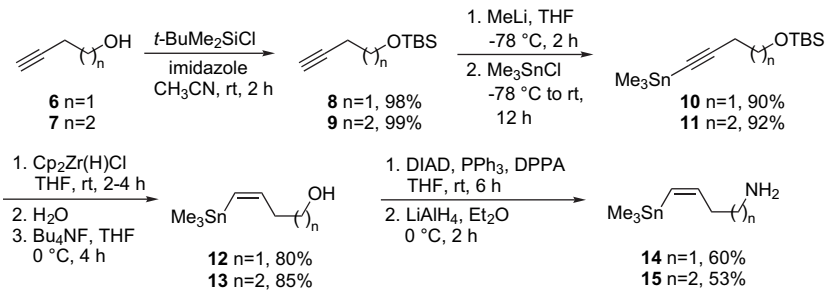
As shown in Table 1, a variety of imines can be employed in the cycloaddition process. It is important to note that the overall yield of this reaction showed no dependence on the nature of the starting imine.

With a series of structurally diverse 2,3-dihydro-4-pyridones **3** in hand we initiated the study of the cyclization reaction using conditions that were successfully applied in our earlier work (Table 2).[10]

In most cases, a good chemical yield and high diastereoselectivity were obtained in the presence of 5 mol % of catalyst. No remarkable difference between the electron-donating and electron-withdrawing groups was observed with respect to the reaction yield (entries 1–4). It should be noted that the rhodium-catalyzed cyclization of **3g** led to the corresponding quinolizidine carboxylic ester **18g**. Such a unique heterocyclic framework could become a useful synthetic building block in the synthesis of peptidomimetics.[11] The relative stereochemistry at C4 and C9a was established with an aid of NOE experiments. Furthermore, the structure of **18a** was unambiguously determined by the X-ray diffraction study (Fig. 1).[12]

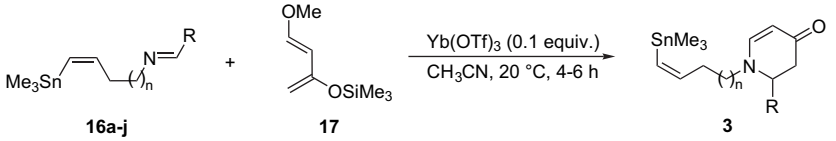
To illustrate the general nature of this transformation we synthesized a series of 1-azabicyclo[5.4.0]undecenes (entries 8–10). Although the bicyclic structures with a seven-membered ring annulated to a six-membered ring occur frequently in alkaloids,[13] only a small number of synthetic strategies applicable to the preparation of such alkaloids are known.[14] For compounds with a longer side-chain the intramolecular 1,4-addition, under standard cyclization conditions, led to the 1-azabicyclo[5.4.0]undecenes **18h–j**, obtained as single diastereomers in a moderate yield.

To demonstrate the applicability of the presented methodology to the synthesis of azabicyclic alkaloids we carried out the



Scheme 3.

Table 1
Lewis acid-mediated synthesis of 2-substituted dihydropyridones

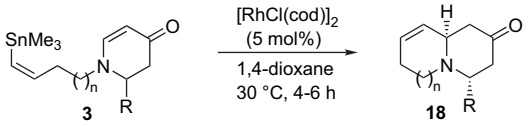


16a-j 17 3

Entry	*n*	R	Product	Yield of **3**[a] (%)
1	1	C_6H_5	**3a**	81
2	1	4-MeC_6H_4	**3b**	89
3	1	4-FC_6H_4	**3c**	79
4	1	3,4-$(MeO)_2C_6H_3$	**3d**	84
5	1	$C_6H_5CH_2OCH_2$	**3e**	82
6	1	*c*-C_6H_{11}	**3f**	84
7	1	COOEt	**3g**	75
8	2	C_6H_5	**3h**	82
9	2	4-$NO_2C_6H_4$	**3i**	81
10	2	COOEt	**3j**	79

[a] All yields are based on isolated product after purification by column chromatography.

Table 2
Rhodium-catalyzed cyclizations of 2,3-dihydro-4-pyridones **3**



3 18

Entry	*n*	R	Product	Yield of **18**[a] (%)
1	1	C_6H_5	**18a**	72
2	1	4-MeC_6H_4	**18b**	80
3	1	4-FC_6H_4	**18c**	76
4	1	3,4-$(MeO)_2C_6H_3$	**18d**	78
5	1	$C_6H_5CH_2OCH_2$	**18e**	80
6	1	*c*-C_6H_{11}	**18f**	82
7	1	COOEt	**18g**	79
8	2	C_6H_5	**18h**	32
9	2	4-$NO_2C_6H_4$	**18i**	22
10	2	COOEt	**18j**	26

[a] All yields are based on isolated product after purification by column chromatography.

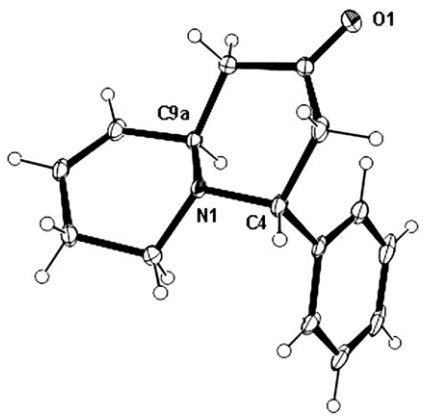
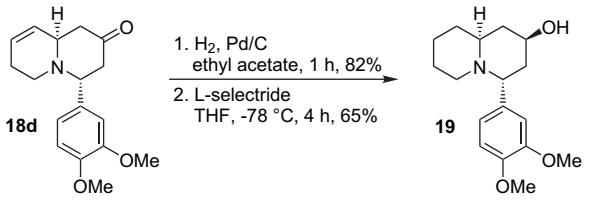


Figure 1. The X-ray structure of **18a**.

concise synthesis of racemic lasubine I (**19**).[15] Lasubine I (**19**) is an interesting quinolizidine alkaloid isolated from plants of *Lythraceae* family, that possesses two hydrogen atoms at C4 and C9a oriented trans to each other (Scheme 4).



Scheme 4.

The hydrogenation of **18d** in the presence of a catalytic amount of Pd/C in ethyl acetate followed by subsequent stereoselective reduction with L-Selectride in THF at −78 °C provided racemic lasubine I (**19**) in 53% overall yield.[16]

3. Conclusions

In summary, we have described a general preparation of 1-azabicycloalkanes by the rhodium-catalyzed intramolecular conjugate addition of vinylstannanes to the 2,3-dihydro-4-pyridones. The utility of this methodology was illustrated by the stereoselective synthesis of racemic lasubine I. An additional demonstration of the utility of these annulation reactions, including the asymmetric synthesis of 1-azabicycloalkanes, is in progress and will be reported in due course.

4. Experimental section

4.1. General

Column chromatography was performed on Merck silica gel, grade 60 (230–400 mesh). TLC plates were visualized with UV and/or staining with phosphomolybdic acid. ^1H and ^{13}C NMR spectra were recorded on Bruker AM500 (500 MHz) and Varian

(400 MHz) spectrometers and the chemical shifts are reported in parts per million with TMS as an internal standard (δ=0 ppm). Infrared (IR) spectra were recorded using Perkin Elmer FT-IR-1600 infrared spectrophotometer. High-resolution mass spectra were recorded using Mariner PerSeptive Biosystems mass spectrometer with time-of-flight (TOF) detector. Unless stated otherwise, all reagents and solvents were purchased from commercial sources and used without additional purification. Alkenylstannanes **12** and **13** were prepared according to Ref. 17.

4.1.1. (Z)-5-(Trimethylstannyl)but-4-en-1-amine (**14**)

DIAD (1.2 mmol) was added dropwise to a cooled solution (0 °C) of PPh_3 (1.2 mmol) in THF (20 mL). After 10 min a solution of alcohol **12** (1.0 mmol) in THF (5 mL) was added to the ylide, followed by diphenylphosphoryl azide (1.2 mmol). The reaction was stirred for 0.5 h at 0 °C and then 6 h at room temperature. The reaction was concentrated and purified by flash chromatography (hexane) to give azide as a yellow oil (0.8 mmol). This oil was redissolved in Et_2O (10 mL), cooled to 0 °C and 1 M solution of $LiAlH_4$ in Et_2O (1 mL) was added. After the addition, the reaction mixture was stirred at 0 °C for 1 h and quenched by careful addition of water (0.1 mL). The reaction mixture was then warmed to room temperature and filtered. Evaporation of the solvent gave crude amine **14** (0.6 mmol, 60% for two steps): IR (neat) 3377, 2809, 1456, 1573, 1483 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.18 (s, 9H), 2.20–2.26 (m, 2H), 2.78 (t, J=7.1 Hz, 2H), 5.96 (dt, J=1.1, 12.5 Hz, 1H), 6.45 (dt, J=7.1, 12.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −8.5, 40.1, 41.8, 132.1, 145.8; HRMS (ESI) calcd for $C_7H_{18}N^{120}Sn$ ($M+H^+$) 236.0456, found 236.0449.

4.1.2. (Z)-5-(Trimethylstannyl)pent-4-en-1-amine (**15**)

Compound **15** was obtained according to the procedure described above (53%): IR (neat) 3339, 2968, 2825, 1598, 1573, 1483, 768, 526 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.17 (s, 9H), 1.46–1.66 (m, 4H), 2.00–2.25 (m, 2H), 2.71 (t, J=7.2 Hz, 2H), 5.96 (dt, J=1.1, 12.4 Hz, 1H), 6.45 (dt, J=7.2, 12.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −8.6, 33.7, 33.8, 41.8, 129.5, 148.4; HRMS (ESI) calcd for $C_8H_{20}N^{120}Sn$ ($M+H^+$) 250.0612, found 250.0620.

4.2. General procedure for the synthesis of imines

To a solution of amine **14** or **15** (0.5 mmol) in CH_2Cl_2 (5 mL) the corresponding aldehyde (0.5 mmol) and activated 4 Å molecular sieves (200 mg) were added. The mixture was stirred for 12 h at ambient temperature, filtered through a Celite pad, and solvent was evaporated in vacuo. The resulting imines were used in subsequent reactions without further purification.

4.3. General procedure for the aza-Diels–Alder reaction of Danishefsky's diene with imines

To a solution of respective imine (0.5 mmol) in MeCN (5 mL) was added $Yb(OTf)_3$ (0.05 mmol) followed by diene **17** (0.6 mmol, 1.2 equiv). The reaction mixture was stirred for 3–5 h at room temperature. The saturated $NaHCO_3$ (10 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL), combined organic phases were dried over $MgSO_4$, and the solvent was evaporated in vacuo. The crude material was purified by flash column chromatography on silica gel.

4.3.1. (Z)-2-Phenyl-1-(4-(trimethylstannyl)but-3-enyl)-2,3-dihydro-1H-pyridin-4-one (**3a**)

Chromatography (50:50 AcOEt/hexane) afforded 0.158 g (81%) of a yellow oil: IR (neat) 2955, 2920, 1640, 1594, 767, 526 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.15 (s, 9H), 2.19–2.33 (m, 2H), 2.60 (dd, J=8.2, 16.4 Hz, 1H), 2.62 (dd, J=7.4, 16.2 Hz, 1H), 2.80 (dd, J=6.9, 16.2 Hz, 1H), 3.08–3.18 (m, 2H), 4.58 (t, J=7.1 Hz, 1H), 5.06 (d, J=7.6 Hz, 1H), 5.99 (d, J=12.5 Hz, 1H), 6.33 (dt, J=7.1, 12.5 Hz, 1H), 7.14 (d, J=7.6 Hz, 1H), 7.12–7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −8.6, 35.6, 43.6, 52.0, 61.7, 99.2, 127.1, 129.3, 133.0, 135.2, 138.1, 143.7, 154.2, 190.6. Anal. Calcd for $C_{18}H_{25}NOSn$: C, 55.42; H, 6.46; N, 3.59. Found: C, 55.28; H, 6.23; N, 3.78.

4.3.2. (Z)-2-p-Tolyl-1-(4-(trimethylstannyl)but-3-enyl)-2,3-dihydro-1H-pyridin-4-one (**3b**)

Chromatography (50:50 AcOEt/hexane) afforded 0.180 g (89%) of a yellow oil: IR (neat) 2965, 2918, 1643, 1591, 767, 526 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.15 (s, 9H), 2.23–2.28 (m, 2H), 2.34 (s, 3H), 2.65 (dd, J=8.3, 16.4 Hz, 1H), 2.61 (dd, J=7.4, 16.3 Hz, 1H), 2.82 (dd, J=6.9, 16.4 Hz, 1H), 3.10–3.15 (m, 2H), 4.58 (t, J=7.1 Hz, 1H), 5.02 (d, J=7.6 Hz, 1H), 5.97 (d, J=12.6 Hz, 1H), 6.32 (dt, J=7.1, 12.6 Hz, 1H), 7.12 (d, J=7.6 Hz, 1H), 7.18–7.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −8.6, 21.1, 35.6, 44.0, 53.0, 61.2, 98.6, 126.9, 129.7, 133.5, 135.7, 138.1, 143.7, 153.8, 190.3; HRMS (ESI) calcd for $C_{19}H_{27}NNaO^{120}Sn$ ($M+Na^+$) 428.1007, found 428.1022.

4.3.3. (Z)-2-(4-Fluorophenyl)-1-(4-(trimethylstannyl)but-3-enyl)-2,3-dihydro-1H-pyridin-4-one (**3c**)

Chromatography (40:60 AcOEt/hexane) afforded 0.161 g (79%) of a yellow oil: IR (neat) 2960, 2931, 1653, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.17 (s, 9H), 2.28 (ddd, J=1.1, 7.2, 14.3 Hz, 2H), 2.61 (dd, J=7.4, 16.3 Hz, 1H), 2.88 (dd, J=7.1, 16.4 Hz, 1H), 3.15 (td, J=1.9, 7.2 Hz, 2H), 4.61 (t, J=7.2 Hz, 1H), 5.04 (d, J=7.6 Hz, 1H), 6.01 (dt, J=1.1, 12.6 Hz, 1H), 6.33 (dt, J=7.0, 12.6 Hz, 1H), 7.03–7.07 (m, 2H), 7.14 (d, J=7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −8.6, 30.3, 35.6, 43.8, 53.5, 60.6, 98.8, 116.0, 116.1, 128.5, 128.6, 133.8, 134.6, 143.4, 153.6, 161.6, 163.5, 189.8; HRMS (ESI) calcd for $C_{18}H_{24}FNNaO^{120}Sn$ ($M+Na^+$) 432.0756, found 432.0779.

4.3.4. (Z)-2-(3,4-Dimethoxyphenyl)-1-(4-(trimethylstannyl)-but-3-enyl)-2,3-dihydro-1H-pyridin-4-one (**3d**)

Chromatography (40:60 AcOEt/hexane) afforded 0.189 g (84%) of a yellow oil: IR (neat) 2959, 2921, 2851, 1639, 1594, 1585, 1516 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.13 (s, 9H), 1.93–2.03 (m, 2H), 2.69 (dd, J=9.0, 16.4 Hz, 1H),

2.81 (dd, J=6.7, 16.4 Hz, 1H), 3.00–3.10 (m, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 4.53 (dd, J=6.7, 9.0 Hz, 1H), 5.04 (d, J=7.6 Hz, 1H), 5.85 (dt, J=1.1, 12.4 Hz, 1H), 6.33 (dt, J=7.0, 12.4 Hz, 1H), 6.83 (br s, 3H), 7.12 (d, J=7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −8.6, 33.2, 44.1, 52.9, 56.0, 61.2, 98.5, 109.9, 111.4, 119.6, 131.1, 131.3, 146.7, 149.1, 149.2, 153.9, 190.5; HRMS (ESI) calcd for $C_{21}H_{32}NO_3^{120}Sn$ (M+H$^+$) 466.1399, found 466.1433.

4.3.5. (Z)-2-(Benzyloxymethyl)-1-(4-(trimethylstannyl)but-3-enyl)-2,3-dihydro-1H-pyridin-4-one (**3e**)

Chromatography (40:60 AcOEt/hexane) afforded 0.178 g (82%) of a yellow oil: IR (neat) 2965, 2920, 2859, 1641, 1588, 1180, 768, 736, 527 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.19 (s, 9H), 2.30–2.45 (m, 3H), 2.65 (dd, J=7.2, 16.7 Hz, 1H), 3.25–3.29 (m, 1H), 3.44–3.54 (m, 2H), 3.74–3.79 (m, 1H), 3.80 (dd, J=7.7, 9.4 Hz, 1H), 4.50 (s, 2H), 4.87 (dd, J=0.9, 7.5 Hz, 1H), 6.02 (dt, J=1.0, 12.6 Hz, 1H), 6.41 (dt, J=7.1, 12.6 Hz, 1H), 6.91 (dd, J=1.0, 7.4 Hz, 1H), 7.27–7.37 (m, 5H); HRMS (ESI) calcd for $C_{20}H_{29}NNaO_2^{120}Sn$ (M+Na$^+$) 458.1112, found 458.1128.

4.3.6. (Z)-2-(Cyclohexyl)-1-(4-(trimethylstannyl)but-3-enyl)-2,3-dihydro-1H-pyridin-4-one (**3f**)

Chromatography (40:60 AcOEt/hexane) afforded 0.166 g (84%) of a yellow oil: IR (neat) 2850, 1630, 1590, 1575, 1516 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.19 (s, 9H), 0.88–1.02 (m, 1H), 1.04–1.28 (m, 4H), 1.60–1.70 (m, 2H), 1.71–1.81 (m, 3H), 1.81–1.92 (m, 1H), 2.37 (m, 2H), 2.42 (ddd, J=1.1, 2.7, 16.5 Hz, 1H), 2.70 (dd, J=7.5, 16.5 Hz, 1H), 3.10–3.20 (m, 1H), 3.26–3.35 (m, 2H), 4.87 (dd, J=1.1, 7.3 Hz, 1H), 6.03 (dt, J=1.1, 12.7 Hz, 1H), 6.43 (dt, J=7.0, 12.7 Hz, 1H), 6.97 (dd, J=1.1, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −8.5, 26.1, 26.3, 28.8, 30.1, 30.4, 37.1, 37.6, 38.8, 55.4, 61.8, 97.3, 133.7, 143.6, 152.5, 191.0; HRMS (ESI) calcd for $C_{18}H_{32}NO_2^{120}Sn$ (M+H$^+$) 398.1500, found 398.1522.

4.3.7. Ethyl 1,2,3,4-tetrahydro-1-((Z)-4-(trimethylstannyl)-but-3-enyl)-4-oxopyridine-2-carboxylate (**3g**)

Chromatography (50:50 AcOEt/hexane) afforded 0.145 g (75%) of a yellow oil: IR (neat) 2976, 2915, 1738, 1644, 1591, 1218, 1184 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.19 (s, 9H), 1.27 (t, J=7.0 Hz, 3H), 2.30–2.89 (m, 4H), 3.28–3.46 (m, 2H), 4.13 (ddd, J=1.0, 3.8, 6.6 Hz, 1H), 4.22 (ddd, J=0.6, 7.1, 14.3 Hz, 1H), 4.98 (d, J=7.6 Hz, 1H), 6.05 (d, J=12.6 Hz, 1H), 6.42 (dt, J=7.0, 12.6 Hz, 1H), 7.05 (dd, J=1.1, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −8.6, 14.1, 36.1, 37.9, 55.3, 59.4, 62.1, 99.1, 133.9, 143.5, 153.4, 169.9, 188.6; HRMS (ESI) calcd for $C_{15}H_{25}NNaO_3^{120}Sn$ (M+Na$^+$) 410.0749, found 410.0732.

4.3.8. (Z)-2-Phenyl-1-(5-(trimethylstannyl)pent-4-enyl)-2,3-dihydro-1H-pyridin-4-one (**3h**)

Chromatography (50:50 AcOEt/hexane) afforded 0.166 g (82%) of a yellow oil: IR (neat) 2963, 2923, 1640, 1593, 1579, 1177, 768, 700, 526 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.15 (s, 9H), 1.58–1.68 (m, 2H), 1.94–2.08 (m, 2H), 2.70 (dd, J=8.3, 16.4 Hz, 1H), 2.88 (dd, J=6.9, 16.4 Hz, 1H), 3.08 (t, J=7.7 Hz, 1H), 4.58 (t, J=7.4 Hz, 1H), 5.05 (d, J=7.6 Hz, 1H), 5.86 (br d, J=12.4 Hz, 1H), 6.32 (dt, J=7.0, 12.4 Hz, 1H), 7.15 (d, J=7.6 Hz, 1H), 7.29–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −8.6, 28.8, 33.1, 43.8, 53.1, 61.3, 98.5, 125.5, 127.0, 128.3, 129.0, 129.1, 131.1, 138.7, 146.6, 153.9, 190.2; HRMS (ESI) calcd for $C_{19}H_{28}NO^{120}Sn$ (M+H$^+$) 406.1187, found 406.1205.

4.3.9. (Z)-2-(4-Nitrophenyl)-1-(5-(trimethylstannyl)pent-4-enyl)-2,3-dihydro-1H-pyridin-4-one (**3i**)

Chromatography (40:60 AcOEt/hexane) afforded 0.182 g (81%) of a yellow oil: IR (neat) 2966, 2916, 1640, 1586, 1520, 1346, 1176, 855, 770, 749, 527 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.14 (s, 9H), 1.61–1.72 (m, 2H), 1.98–2.11 (m, 2H), 2.61 (br dd, J=6.2, 16.4 Hz, 1H), 2.99 (dd, J=7.4, 16.4 Hz, 1H), 3.02–3.09 (m, 1H), 3.13–3.21 (m, 1H), 4.72 (br t, J=6.8 Hz, 1H), 5.07 (br d, J=7.7 Hz, 1H), 5.88 (dt, J=1.1, 12.4 Hz, 1H), 6.35 (dt, J=7.0, 12.4 Hz, 1H), 7.15 (d, J=7.7 Hz, 1H), 7.48–8.23 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −8.6, 28.9, 33.0, 43.1, 53.6, 60.4, 99.3, 124.4, 127.7, 131.6, 146.1, 146.2, 153.4, 188.7; HRMS (EI) calcd for $C_{19}H_{26}N_2O_3^{120}Sn$ (M$^+$) 450.0965, found 450.0973.

4.3.10. Ethyl 1,2,3,4-tetrahydro-1-((Z)-5-(trimethylstannyl)-pent-4-enyl)-4-oxopyridine-2-carboxylate (**3j**)

Chromatography (50:50 AcOEt/hexane) afforded 0.158 g (79%) of a yellow oil: IR (neat) 2965, 2927, 1736, 1642, 1591, 1212, 1180, 1029, 768, 526 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.17 (s, 9H), 1.27 (t, J=7.1 Hz, 3H), 1.70–1.79 (m, 2H), 2.09–2.17 (m, 2H), 2.74–2.94 (m, 2H), 3.20–3.27 (m, 1H), 3.29–3.36 (m, 1H), 4.12 (ddd, J=1.0, 3.8, 6.6 Hz, 1H), 4.11–4.31 (m, 2H), 5.05 (br d, J=7.6 Hz, 1H), 5.91 (dt, J=1.0, 12.5 Hz, 1H), 6.43 (dt, J=7.0, 12.5 Hz, 1H), 7.05 (dd, J=1.1, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −8.6, 14.1, 29.2, 33.1, 38.1, 55.0, 59.3, 62.1, 99.0, 131.3, 146.7, 153.5, 169.9, 188.6; HRMS (EI) calcd for $C_{16}H_{27}NO_3^{120}Sn$ (M$^+$) 401.1013, found 401.1024.

4.4. General procedure for the catalytic intramolecular conjugate addition of vinylstannanes to 2,3-dihydro-4-pyridones

To a solution 0.5 mmol of the respective 2,3-dihydro-4-pyridone in 1,4-dioxane (5 mL) was added (0.025 mmol) $[RhCl(cod)]_2$. After stirring for 2–3 h at room temperature the reaction mixture was concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with AcOEt–hexane mixtures as eluents.

4.4.1. (4R*,9aR*)-4-Phenyl-1,3,4,6,7,9a-hexahydro-2H-quinolizin-2-one (**18a**)

Chromatography (30:70 AcOEt/hexane) afforded 0.082 g (72%) of light yellow needles: mp 128–129 °C; IR (CH_2Cl_2) 2867, 1723 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.00–2.07

(m, 1H), 2.29–2.43 (m, 2H), 2.48–2.57 (m, 2H), 2.74 (dd, J=2.0, 15.0 Hz, 1H), 2.90 (dd, J=6.4, 15.0 Hz, 1H), 2.98 (ddd, J=2.9, 5.6, 11.7 Hz, 1H), 3.52–3.56 (m, 1H), 4.33 (dd, J=3.9, 6.4 Hz, 1H), 5.43 (ddd, J=2.1, 4.0, 9.9 Hz, 1H), 5.70–5.82 (m, 1H), 7.20–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.2, 46.0, 46.5, 47.3, 52.0, 63.7, 125.5, 127.6, 128.2, 128.4, 128.5, 138.6, 209.4; HRMS (ESI) calcd for $C_{17}H_{22}NO_2$ ($M+H^+$) 228.1383, found 228.1388.

4.4.2. (4R,9aR*)-4-p-Tolyl-1,3,4,6,7,9a-hexahydro-2H-quinolizin-2-one (**18b**)*

Chromatography (30:70 AcOEt/hexane) afforded 0.097 g (80%) of a yellow oil: IR (neat) 3027, 2917, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.05–1.97 (m, 1H), 2.33 (s, 3H), 2.38 (ddd, J=1.2, 10.4, 15.0 Hz, 1H), 2.46 (ddd, J=4.5, 9.4, 11.7 Hz, 1H), 2.55 (ddd, J=1.9, 4.0, 15.0 Hz, 1H), 2.71 (ddd, J=1.9, 3.7, 15.0 Hz, 1H), 2.90 (ddd, J=1.2, 6.6, 15.0 Hz, 1H), 2.96 (ddd, J=2.6, 5.6, 11.5 Hz, 1H), 3.48–3.52 (m, 1H), 4.30 (dd, J=3.7, 6.5 Hz, 1H), 5.41 (ddd, J=2.1, 4.0, 9.9 Hz, 1H), 5.72–5.78 (m, 1H), 7.01–7.26 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0, 25.3, 46.1, 46.6, 47.4, 51.9, 63.4, 125.4, 128.4, 128.6, 128.9, 135.5, 137.3, 209.6; HRMS (EI) calcd for $C_{16}H_{19}NO$ (M^+) 241.1467, found 241.1458.

4.4.3. (4R,9aR*)-4-(Fluorophenyl)-1,3,4,6,7,9a-hexahydro-2H-quinolizin-2-one (**18c**)*

Chromatography (30:70 AcOEt/hexane) afforded 0.093 g (76%) of a yellow oil: IR (neat) 3020, 2915, 1724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.00–2.09 (m, 1H), 2.31–2.36 (m, 1H), 2.40 (ddd, J=1.1, 10.2, 14.9 Hz, 1H), 2.47 (ddd, J=4.7, 9.4, 11.7 Hz, 1H), 2.55 (ddd, J=1.8, 4.0, 15.0 Hz, 1H), 2.71 (ddd, J=1.8, 4.0, 15 Hz, 1H), 2.90 (ddd, J=1.2, 6.5, 15.0 Hz, 1H), 2.97 (ddd, J=3.2, 5.5, 11.6 Hz, 1H), 3.46–3.52 (m, 1H), 4.33 (dd, J=4.0, 6.5 Hz, 1H), 5.44 (ddd, J=2.2, 4.1, 10.0 Hz, 1H), 5.75–5.79 (m, 1H), 6.98–7.05 (m, 2H), 7.11–7.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1, 45.9, 46.4, 47.1, 52.0, 63.0, 115.0, 115.2, 125.6, 128.6, 128.4, 129.8, 129.9, 134.5, 160.9, 163.4, 209.3; HRMS (ESI) calcd for $C_{15}H_{17}NOF$ ($M+H^+$) 246.1289, found 246.1303.

4.4.4. (4R,9aR*)-4-(3,4-Dimethoxyphenyl)-1,3,4,6,7,9a-hexahydro-2H-quinolizin-2-one (**18d**)*

Chromatography (30:70 AcOEt/hexane) afforded 0.112 g (78%) of an orange oil; IR (neat) 3017, 2913, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.99–2.07 (m, 1H), 2.27–2.36 (m, 1H), 2.39 (ddd, J=1.2, 10.0, 14.8 Hz, 1H), 2.50–2.58 (m, 2H), 2.73 (ddd, J=1.9, 4.1, 14.9 Hz, 1H), 2.88 (ddd, J=1.3, 6.3, 14.9 Hz, 1H), 2.98 (ddd, J=3.0, 5.6, 11.8 Hz, 1H), 3.55 (m, 1H), 3.86 (2×s, 6H), 4.28 (dd, J=4.1, 6.4 Hz, 1H), 5.44 (ddd, J=2.1, 4.1, 9.9 Hz, 1H), 5.75–5.79 (m, 1H), 6.73–6.82 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.1, 46.3, 46.5, 47.2, 52.2, 55.9, 63.3, 110.7, 111.6, 120.6, 125.5, 128.5, 131.5, 148.5, 148.7, 209.6; HRMS (EI) calcd for $C_{17}H_{21}NO_3$ (M^+) 287.1521, found 287.1525.

4.4.5. (4R,9aR*)-4-(Benzyloxymethyl)-1,3,4,6,7,9a-hexahydro-2H-quinolizin-2-one (**18e**)*

Chromatography (30:70 AcOEt/hexane) afforded 0.109 g (80%) of a yellow oil: IR (neat) 3029, 2906, 1716, 1131 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.08–2.16 (m, 1H), 2.24 (dd, J=11.5, 14.6 Hz, 1H), 2.30–2.38 (m, 2H), 2.48 (dt, J=2.1, 14.5 Hz, 1H), 2.70 (dd, J=7.23, 14.5 Hz, 1H), 2.86 (ddd, J=4.4, 8.9, 11.3 Hz, 1H), 2.93 (ddd, J=3.4, 5.7, 11.3 Hz, 1H), 3.38–3.46 (m, 1H), 3.53 (dd, J=4.6, 9.8 Hz, 1H), 3.63 (dd, J=4.8, 9.8 Hz, 1H), 3.70–3.72 (m, 1H), 4.87 (d, J=1.3 Hz, 2H), 5.45 (ddd, J=2.2, 4.1, 9.9 Hz, 1H), 5.75–5.77 (m, 1H), 7.27–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.6, 43.5, 46.1, 47.2, 53.5, 61.3, 69.1, 73.5, 124.9, 127.5, 127.6, 128.4, 129.4, 138.0, 208.5; HRMS (ESI) calcd for $C_{17}H_{22}NO_2$ ($M+H^+$) 272.1645, found 272.1641.

4.4.6. (4R,9aR*)-4-Cyclohexyl-1,3,4,6,7,9a-hexahydro-2H-quinolizin-2-one (**18f**)*

Chromatography (20:80 AcOEt/hexane) afforded 0.096 g (82%) of a colorless oil: IR (neat) 3072, 2915, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.78–0.92 (m, 2H), 1.05–1.25 (m, 3H), 1.30–2.11 (m, 6H), 2.21 (ddd, J=2.0, 3.5, 14.1 Hz, 1H), 2.34–2.46 (m, 3H), 2.55 (dd, J=6.1, 13.5 Hz, 1H), 2.66 (dd, J=2.6, 6.0, 11.2 Hz, 1H), 2.80 (ddd, J=2.7, 6.1, 9.6 Hz, 1H), 3.09–3.11 (m, 1H), 3.55–3.60 (m, 1H), 5.57–5.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1, 26.2, 26.5, 26.7, 30.3, 30.4, 38.5, 39.6, 43.9, 45.5, 53.0, 68.7, 125.4, 128.8, 209.9; HRMS (ESI) calcd for $C_{15}H_{24}NO_2$ ($M+H^+$) 234.1852, found 234.1856.

4.4.7. (4R,9aR*)-Ethyl 2,3,4,6,7,9a-hexahydro-2-oxo-2H-quinolizine-4-carboxylate (**18g**)*

Chromatography (20:80 AcOEt/hexane) afforded 0.088 g (79%) of a colorless oil: IR (neat) 2916, 1736, 1727, 1181 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.27 (t, J=7.1 Hz, 2H), 2.03–2.11 (m, 1H), 2.21 (ddd, J=0.6, 11.8, 14.8 Hz, 1H), 2.38–2.46 (m, 2H), 2.55 (dt, J=2.0, 15.0 Hz, 1H), 2.71 (ddd, J=0.8, 6.8, 15.0 Hz, 1H), 2.81 (dt, J=11.1, 15.2 Hz, 1H), 2.99 (dd, J=6.0, 11.6 Hz, 1H), 3.63–3.67 (m, 1H), 3.88 (dd, J=1.6, 6.8 Hz, 1H), 4.16–4.19 (m, 1H), 5.42–5.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.4, 26.6, 42.9, 46.5, 48.7, 53.0, 60.8, 63.8, 124.8, 128.9, 170.4, 206.2; HRMS (EI) calcd for $C_{12}H_{18}NO_3$ ($M+H^+$) 224.1281, found 224.1289.

4.4.8. (4R,10aR*)-1,3,4,7,8,10a-Hexahydro-4-phenyl-pyrido[1,2-a]azepin-2-one (**18h**)*

Chromatography (30:70 AcOEt/hexane) afforded 0.021 g (32%) of a yellow oil: IR (neat) 2920, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05–1.15 (m, 1H), 1.48–1.58 (m, 1H), 2.23–2.31 (m, 2H), 2.41 (dt, J=2.6, 13.4 Hz, 1H), 2.46 (ddd, J=2.4, 4.0, 14.5 Hz, 1H), 2.55 (dd, J=10.2, 14.4 Hz, 1H), 2.86 (ddd, J=2.2, 11.9, 14.8 Hz, 1H), 2.93 (dd, J=5.5, 13.4 Hz, 1H), 3.12–3.17 (m, 1H), 4.21 (dd, J=3.9, 10.1 Hz, 1H), 5.51 (ddd, J=2.3, 4.5, 11.0 Hz, 1H), 6.03–6.07 (m, 1H), 7.25–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz)

δ 21.2, 29.0, 48.7, 50.5, 54.6, 58.8, 58.9, 127.6, 127.8, 128.8, 132.7, 135.0, 141.9, 208.9; HRMS (ESI) calcd for $C_{16}H_{20}NO$ ($M+H^+$) 242.1539, found 242.1547.

4.4.9. (4R*,10aR*)-1,3,4,7,8,10a-Hexahydro-4-(4-nitrophenyl)pyrido[1,2-a]azepin-2-one (**18i**)

Chromatography (20:80 AcOEt/hexane) afforded 0.032 g (22%) of a yellow oil: IR (neat) 2917, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.12–1.54 (m, 2H), 2.26–2.32 (m, 2H), 2.41–2.48 (m, 3H), 2.89–2.96 (m, 2H), 3.07–3.09 (m, 1H), 4.30–4.37 (m, 2H), 5.50 (ddd, *J*=2.4, 4.5, 11.1 Hz, 1H), 6.04–6.11 (m, 1H), 7.56–8.22 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0, 28.9, 48.5, 49.8, 54.6, 58.4, 58.8, 124.2, 128.6, 132.2, 135.3, 147.5, 149.5, 207.4; HRMS (ESI) calcd for $C_{16}H_{19}N_2O_3$ ($M+H^+$) 287.1390, found 287.1382.

4.4.10. (4R*,10aR*)-Ethyl-2-oxo-1,2,3,4,6,7,8,10a-octahydropyrido[1,2-a]azepine-4-carboxylate (**18j**)

Chromatography (20:80 AcOEt/hexane) afforded 0.008 g (26%) of a colorless oil: IR (neat) 2920, 1737, 1725, 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.27 (t, *J*=7.1 Hz, 2H), 1.42–2.13 (m, 3H), 2.21 (dd, *J*=11.7, 15.0 Hz, 1H), 2.38–2.46 (m, 2H), 2.55 (dt, *J*=2.0, 15.0 Hz, 1H), 2.71 (dd, *J*=6.8, 15.0 Hz, 1H), 2.80–2.86 (m, 1H), 2.99 (dd, *J*=6.0, 11.6 Hz, 1H), 3.62–3.68 (m, 1H), 3.88 (dd, *J*=1.6, 6.8 Hz, 1H), 4.16–4.20 (m, 1H), 5.43–5.49 (m, 1H), 5.64–5.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.6, 27.6, 31.0, 41.9, 46.3, 49.3, 53.1, 60.8, 63.8, 124.8, 128.9, 170.8, 208.3; HRMS (EI) calcd for $C_{13}H_{19}NO_3$ (M^+) 237.1365, found 237.1372.

4.4.11. (2R*,4R*,9aS*)-4-(3,4-Dimethoxyphenyl)octahydro-1H-quinolizin-2-ol (**19**)

A solution of **18d** (112 mg, 0.38 mmol) and Pd/C (10%) in ethyl acetate (5 mL) was hydrogenated (balloon) at room temperature for 1 h. The catalyst was removed by filtration and the solution concentrated in vacuo to give a colorless oil. This was dissolved in THF (5 mL) and a 1.0 M solution of L-Selectride in THF (0.50 mL, 0.50 mmol) was added dropwise at −78 °C. The reaction mixture was stirred for 4 h at −78 °C and saturated aqueous ammonium chloride (1.0 mL) was added. The aqueous layer was extracted with ether and the combined organic extracts were dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (EtOAc/MeOH 70:30) afforded **19** (60 mg, 53%) as a white wax: IR (neat) 3369, 2932, 2854, 1603, 1590, 1515, 1463, 1451, 1260, 1234, 1144, 1028, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22–1.31 (m, 2H), 1.43–1.72 (m, 10H), 1.93–2.02 (m, 2H), 2.06–2.10 (m, 1H), 2.25 (td, *J*=3.1, 11.6 Hz, 1H), 2.72 (dt, *J*=3.6, 12.1 Hz, 1H), 2.94–2.99 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 4.08 (t, *J*=4.8 Hz, 1H), 4.17–4.20 (m, 1H), 6.79–6.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.1, 24.7, 29.1, 32.6, 40.1, 40.3, 51.2, 53.9, 55.9, 62.1, 65.2, 110.5, 110.8, 120.5, 135.6, 147.8, 148.8; HRMS (EI) calcd for $C_{17}H_{25}NO_3$ (M^+) 291.1834, found 291.1831.

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