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Organolithium Chemistry

Base-Catalyzed Intramolecular Hydroamination of Cyclohexa-2,5-dienes: Insights into the Mechanism through DFT Calculations and Application to the Total Synthesis of *epi*-Elwesine

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Abstract: The base-catalyzed intramolecular hydroamination of 1-ethylaminocyclohexa-2,5-dienes is described. The transformation proceeds through isomerization of the cyclohexa-1,4-dienyl fragment into the corresponding conjugated 1,3-diene prior to the hydroamination step. Attaching a chiral glycinol ether auxiliary on the amino group allows the protonation to occur with complete diastereocontrol. The resulting lithium amide then adds onto the 1,3-dienyl moiety, affording the desired fused pyrrolidine ring along with the corresponding lithium allylic anion. Protonation of the latter then proceeds with high regiocontrol to favor the resulting allylic amines. In contrast, when the reaction was performed on primary amines, fused pyrrolidines bearing a homoallylic amino group were obtained. The stereochemical course of the process and determination of the reaction pathways were established based on calculations performed at the DFT level. Finally, application of the methodology to the enantioselective synthesis of (+)-*epi*-elwesine, a crinane alkaloid, is described.

Introduction

Five- and six-membered ring nitrogen-containing heterocycles, which are ubiquitous in Nature and in biologically relevant targets, may be accessed through a wide range of methodologies.[1] Among them, hydroamination of olefins is particularly attractive because it is atom-economical and may be catalyzed through a plethora of achiral and chiral reagents.[2] Organolanthanides have received particular attention in this respect.[3] Transition-metal catalysts (Pd, Ru, Rh, Cu, and Fe), alkaline-earth (Mg, Ca) and rare-earth metals (Sc, Y) have also been shown to mediate inter- and intramolecular hydroamination processes.[4] More recently, gold complexes[5] and Brönsted acids[6] have also been revealed to be efficient catalysts for this transformation. Inter- and intramolecular based-catalyzed hydroamination, using lithium amides has also been reported, although less often.[7] Organolithium bases with chiral additives as well as homochiral lithium amide bases have been devised and shown to provide the expected amines, although the enantioselectivities remained modest compared with those obtained by using the metal-catalyzed processes mentioned above.[8] The addition of the alkali-amide moiety onto the olefin is generally more efficient with "activated olefins", including styrenes, dienes, or enynes. Hydroamination of "unactivated" olefins is also known but is generally more efficient if performed in an intramolecular manner. This important reaction has been incorporated with success in several synthesis of complex natural targets.[9] In the course of our studies on the reactivity and desymmetrization of 1-substituted cyclohexa-2,5-dienes,[10,11] we communicated on a highly diastereoselective intramolecular hydroamination of 1-ethylaminocyclohexa-2,5-dienes **1** by using a substoichiometric amount of *n*BuLi as a base.[12] We provide here a full description of this work, with experimental evidence supporting our preliminary mechanistic hypothesis. Calculations based on density functional theory (DFT) were carried out, affording a full picture of the outcome of this base-mediated cascade process. The study has also been extended to the hydroamination using primary amines, which surprisingly led to complementary regioselectivities. Finally, application of the methodology to the total synthesis of (*ent*)-*epi*-elwesine, a crinine-type alkaloid, is reported.

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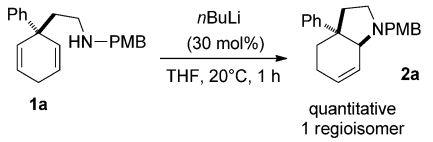
Results and Discussion

Base-catalyzed intramolecular hydroamination of a secondary 1-ethylaminocyclohexa-2,5-diene 1

We first tested the hydroamination process starting from the achiral N-PMB precursor **1a**,[13] which was readily available through Birch reduction of biphenyl.[14] Treatment of the latter

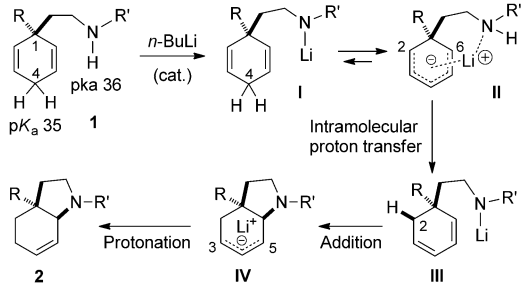


Scheme 1. Base-catalyzed desymmetrization of aminocyclohexa-2,5-diene **1**.

with a substoichiometric amount of *n*BuLi (30 mol%) as a base in tetrahydrofuran (THF) as solvent led to the expected fused pyrrolidine **2a** in essentially quantitative yield as a single regioisomer (Scheme 1).

Addition of the amino group onto the olefinic linkage was accompanied by isomerization of the remaining olefin. With a direct and totally diastereoselective addition of the amino group onto one of the nonconjugated olefin being unlikely under the reaction conditions, we proposed instead that a base-catalyzed isomerization of the 1,4-diene preceded the intramolecular proton transfer and hydroamination step onto a 1,3-diene, to lead to the observed allylic amine as a single regio- and diastereomer.

Examination of the pK_a of the secondary amine proton [ca. 36 in dimethyl sulfoxide (DMSO)] and that of allylic protons (ca. 35 in DMSO)[15] in dienes **1** suggest that treatment of the latter with a substoichiometric amount of *n*BuLi should lead to an equilibrium between the corresponding lithium amide **I** and a cyclohexadienyl lithium species **II** (Scheme 2).[11h,k] Depro-

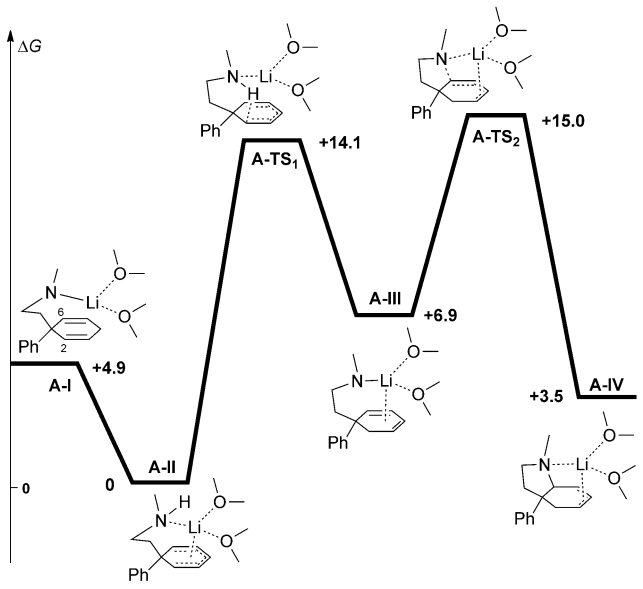


Scheme 2. Possible pathway for the deprotonation–protonation hydroamination cascade.

tonation at the nitrogen site is probably the fastest due to the higher kinetic acidity of the NH, but formation of the pentadienyl lithium moiety should be favored on thermodynamic grounds. The proton transfer between **II** and **III** is currently unknown but must occur intramolecularly. An alternative intermolecular protonation through a second equivalent of amine was ruled out because we observed that intermolecular reactions of related cyclohexadienyl anions with electrophiles (MeI, R_3SiCl, H^+) occurred exclusively at C4.[10e,16] We then envisioned that the transfer of a proton to C2 (or C6) would generate a 1,4 diene such as **III**. Addition of lithium amides to dienes is well documented and appears to be much more favorable than addition to nonconjugated olefins of the starting 1,4-dienes.[17] With hydroamination at C6 leading to an allyl-lithium intermediate **IV**, protonation of the latter would then occur on the least sterically hindered site (C3) to afford allylic amine **2**.

Theoretical studies of the mechanism of the base-catalyzed deprotonation–protonation–hydroamination cascade

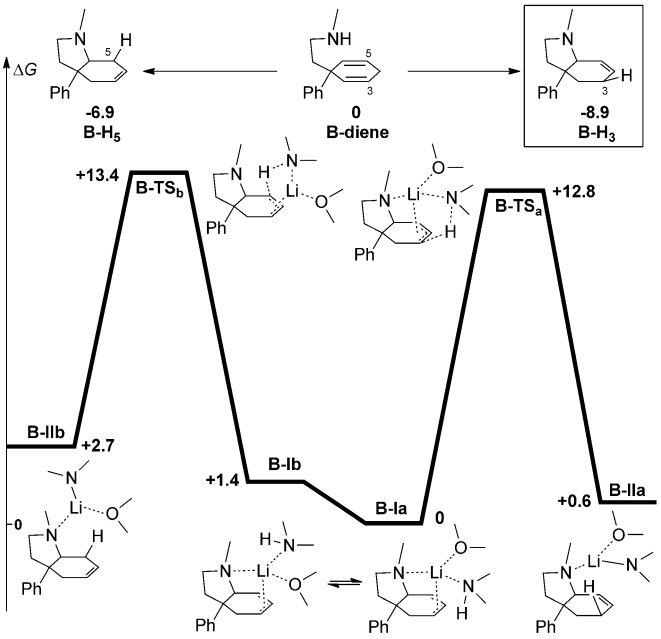
With the hypothesis described above in hand, we had an almost complete picture that could rationalize the course of the anionic cascade process. In the meantime, we started theoretical investigations at the DFT level to provide further elements that would support such assumptions and rationalize the position of the remaining double bond. DFT calculations were conducted at the B3LYP/6-31+G(d,p) level by using the Gaussian program package.[18] Explicit solvation being crucial for all calculations in which lithium is involved, two dimethyl ether ligands[19] [1,2-dimethoxyethane (DME), used commonly in place of "costly" THF, especially for large systems] coordinated to the lithium were added to keep the lithium adducts in a tetrahedral environment.[20] All the calculations were performed in the gas phase because with explicit ligands around lithium no significant differences were observed with calculations performed using a polarizable continuum solvation model.[10e] We started our calculations with the lithium amide **A-I**, which is likely produced in the first instance by reaction of the starting amine with *n*BuLi (the kinetic acidity of the N–H proton is certainly superior to that of a bisallylic C–H proton). **A-I** would also be regenerated at the end of the catalytic process because the starting amine **1** is believed to protonate the final lithium adduct **A-IV**. The lithium amide **A-I** could thus evolve toward the more stable pentadienyl lithium compound **A-II**. This complex is a plausible starting point for the process because dienyllithium species are expected to be monomeric.[21] The reaction pathway depicted in Scheme 3 showed two energetically low transition-states for the proton transfer at C2



Scheme 3. Free Gibbs energy profile [kcal mol^{-1}] for the deprotonation–protonation hydroamination cascade.

then hydroamination of the diene at C6, which should be easily attained at room temperature. The starting pentadienyl lithium **A-II** is the more stable form among all the computed lithiated species, with the reaction thus being driven by the exothermicity of the process (-8.9 kcal mol^{-1} was computed for the free Gibbs energy difference between the starting diene and the final allylic amine).

At the final allyl-lithium stage, a protonation should take place regioselectively. This has been modeled by replacing one of the two DME ligands by a dimethylamine ligand (used as a model for the starting secondary amine) (Scheme 4).[22] Two



Scheme 4. Free Gibbs energy profile [kcal mol^{-1}] for the protonation step.

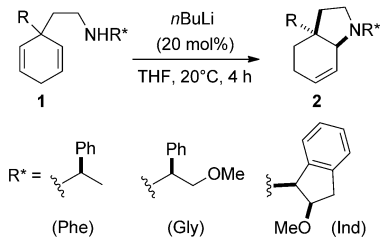
complexes may then be drawn, depending on which DME is replaced, one leading to the homoallylic amine after protonation at C5, the second to the observed allylic amine (protonation at C3). We considered the two complexes **B-Ia** and **B-Ib** to be in equilibrium because only ligand exchange is involved. From the calculations, it seems clear that the allylic product is favored. The transition states leading to the two products are quite similar in energy but the allylic amine–lithium complex **B-IIa** is more stable, which is in line with the stability of the final allylic (**B-H3**) and homoallylic (**B-H5**) amine products (Scheme 4).

Having rationalized the complete process, enantioselective and diastereoselective versions were then envisaged. Enantioselective protonation of lithiated species has received a lot of attention, and has been recognized to be an efficient way to deracemize chiral racemic compounds.[23] Our observations are relevant in this context and the use of chiral ligands around lithium was expected to open the way to a new enantioselective desymmetrization process. Unfortunately, all chiral amine-based ligands (sparteine, ephedrine, bis-oxazolines) we tried failed to afford satisfactory levels of enantioselectivities. We could nevertheless observe small enantiomeric excesses (less than 10%) when the reaction was run in toluene in the presence of 1,2-diphenylethane-1,2-diol dimethyl ether as chiral ligand around lithium.[24] These failures finally led us to consider instead a diastereoselective approach.

Diastereoselective intramolecular hydroaminations of chiral 1-ethylaminocyclohexa-2,5-dienes 1

Dienes **1** are readily available through Birch reduction of the corresponding arenes[13,14] followed by alkylation in situ with α-bromo esters or nitriles. Reduction of the ester or nitrile functions into the aldehyde, followed by introduction of the chiral auxiliary through reductive amination, provided the desired secondary amines **1b–f** in good overall yields (see the Supporting Information). Several chiral auxiliaries were selected, including α-methylbenzylamine (Phe), *cis*-1-amino-2-methoxyindanol (Ind), and the O-protected phenylglycinol (Gly) (Table 1). Preliminary attempts to cyclize amine **1b** provided

Table 1. Cyclization of amines **1b–f**.

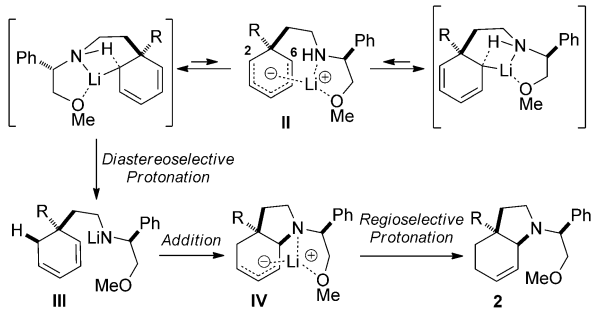


Diene	R*	R	2	Yield [%][a]	d.r.[b]
1b	Phe	Ph	**2b**	93	67:33[c]
1c	Ind	Ph	**2c**	26	90:10
1d	Gly	Ph	**2d**	95	>98:2
1e	Gly	3,5-$(OMe)_2$Ph	**2e**	46	>98:2
1f	Gly	CH_2OBn	**2f**	82	>98:2

[a] Isolated yield after chromatography. [b] Estimated through ^{1}H NMR analysis of the crude reaction mixture. [c] Mixture of unidentified regio- or diastereomers.

the bicyclic skeleton **2b** after 4 h at room temperature in excellent yield but as a mixture of isomers (regio- or diastereo) that could not be separated further. Introduction of an additional chelating group in precursors **1c–f** proved to be beneficial, leading to the bicyclic allylic amines **2c–f** in good to excellent yields and high levels of regio- and stereocontrol. The best results were obtained with the simple and flexible O-methyl protected phenylglycinol-derived chiral auxiliaries. Lower yield and selectivity were observed with the *cis*-indanol **1c**. The structure of the bicyclic amines was determined unequivocally through X-ray structure analysis of a crystal of **2e** (see the Supporting Information), confirming the position of the double bond.

In the proposed mechanism (Scheme 5), the proton transfer would then proceed quantitatively at C2 rather than at C6. This irreversible and stereochemically determining step, occur-



Scheme 5. Hydroaminations of chiral 1-ethylaminocyclohexa-2,5-dienes.

ring with complete diastereocontrol, would set up the stereochemistry of the quaternary center. The presence of a chelating amino-ether chiral auxiliary is highly beneficial here, providing sufficient rigidity to the lithium intermediate for efficient control of the selectivity during the stereochemically key proton transfer.[25]

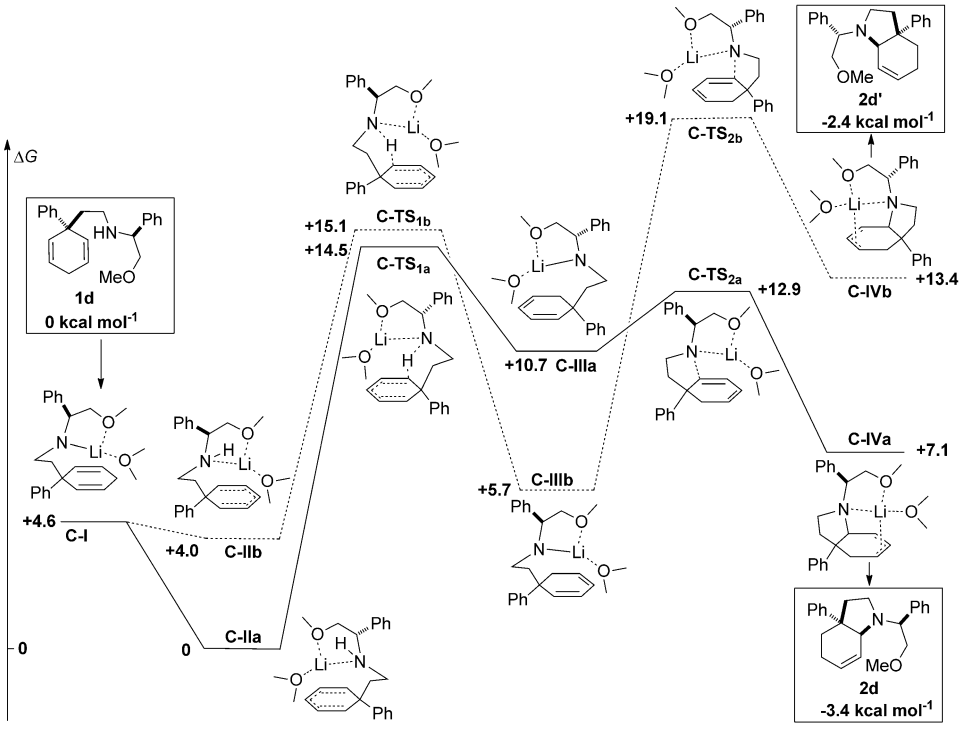
Computational studies on the asymmetric deprotonation–protonation–hydroamination cascade

DFT calculations were then extended to the chiral system, which introduced additional challenges. Apart from the chiral carbon on the ethylamino chain, the quaternary carbon center, but also nitrogen and silicon atoms become chiral at some point, thus multiplying the number of possible routes. Assuming that the chirality at the lithium center is labile and has a low energy barrier, and that its interconversion involves only solvent molecules, we could find two routes leading to the two possible diastereomers of **2d** (Scheme 6). The deprotonation of **C-I** would then lead to two possible pentadienyl complexes **C-IIa** and **C-IIb**, bearing a different chirality on the nitrogen center, which can both undergo hydrogen transfer, leading to **C-IIIa** and **C-IIIb**. The 5-exo hydroaminations then give rise to two possible allyllithium complexes **C-IVa** and **C-IVb**, which, upon protonation, give the two diastereomers **2d** and **2d′**. The most favorable path is clearly that leading to the only observable diastereomer **2d** because the two transition states, the final complex **C-IV** and final product are all energetically favored.

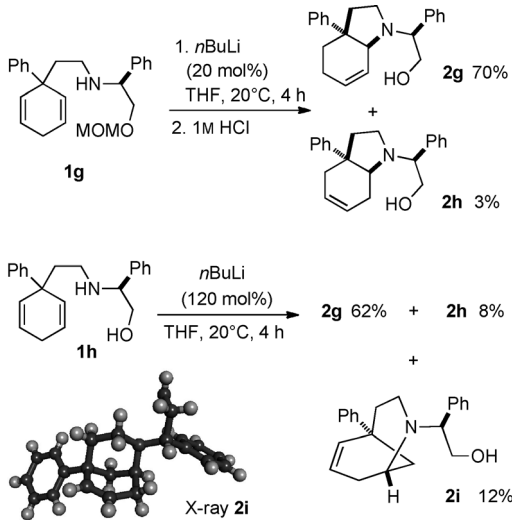
Hydroamination with protected phenylglycinols

Further experimental evidence that supported the proposed mechanism were obtained. For instance, repeating the reaction with precursor **1g**, having a MOM-protected phenylglycinol, led, as above, to the formation of the bicyclic structure (not shown) as a 95:5 mixture of two isomers that could not be separated at this stage (Scheme 7). Deprotection of the MOM group under acidic conditions, however, afforded allylic amine **2g** in 70% yield along with homoallylic isomer **2h** in 3% yield, proving that the final protonation could also take place at the 5-position with different lithium aggregates. More interestingly, when precursor **1h**, having an unprotected phenylglycinol moiety as a chiral auxiliary, was treated with 1.2 equivalent of *n*BuLi (1 equiv was used to deprotonate the free OH), allylic amine **2g** and homoallylic amine **2h** were formed along with bicyclic compound **2i**, as a single diastereomer, the structure of which was determined on the basis of X-ray diffraction studies. Only 8% of the starting amine **1h** was also recovered, showing that the process is high yielding.

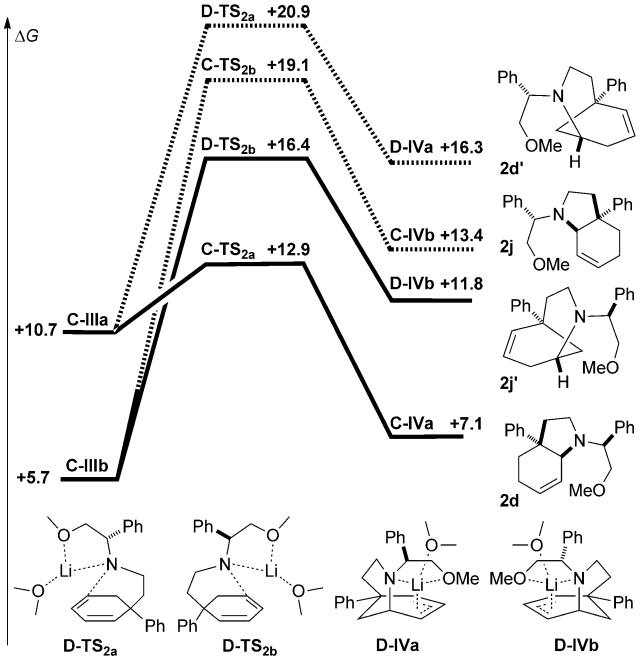
The presence of bicycle **2i** is intriguing and should result from a proton transfer at C6 instead of at C2, which would be followed by an exclusive 6-exo cyclization instead of 5-exo, to afford the bicyclo[3.3.1] system. Interestingly, the formation of **2i** also confirmed the presence of the putative diene **III** (Scheme 2) as an intermediate. Starting from the two computed dienes **C-IIIa** and **C-IIIb** (Scheme 6), the calculated reaction pathways for the 6-exo cyclization exhibited interesting profiles as depicted in Scheme 8.



Scheme 6. Free Gibbs energy profile [kcal mol^{-1}] for the asymmetric deprotonation–protonation–hydroamination cascade with phenylglycinol derivatives.

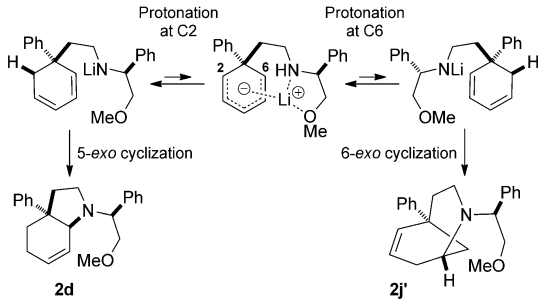


Scheme 7. Cyclizations of amines **1g** and **1h**. X-ray structure of **2i**.



Scheme 8. Free Gibbs energy profile [kcal mol^{-1}] for the 5-exo versus 6-exo aminations.

For diene **C-IIIa** (arising from protonation at C2), the 5-exo cyclization is kinetically favored (by 8 kcal mol^{-1}) over the 6-exo route, with the resulting **C-IVa** also being 9.2 kcal mol^{-1} more stable than **D-IVa**. With the other diene **C-IIIb**, the situation is reversed. Diene **C-IIIb**, resulting from protonation at C6, would cyclize preferentially in a 6-exo fashion, with **D-IVb** also being 1.6 kcal mol^{-1} more stable than **C-IVb**. Apart from the energy difference between **2d** and **2d′**, the different pathways followed by the intermediate dienes may be mainly responsible for the unique formation of **2d**. Starting from **C-II**, protonation at C2 would give the 5-exo product **2d**, whereas protonation

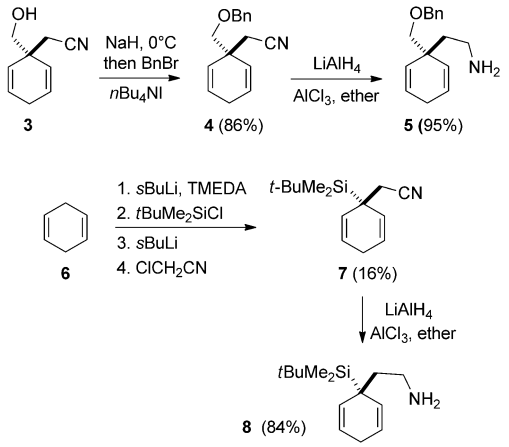


Scheme 9. Different reaction pathways depending on the protonation site.

at C6 would afford the 6-exo product, which has never been isolated for this methoxy-protected phenylglycinol (Scheme 9).

Base-catalyzed intramolecular hydroamination of cyclohexa-2,5-dienes bearing a primary amine

Having found that removing the chiral auxiliary was difficult because of the allylic nature of the tertiary amine (see below), the study was then extended to 1-substituted cyclohexyl-2,5-dienes possessing a primary amine. Base-catalyzed intramolecular hydroamination of primary unsaturated amines by using *n*BuLi to generate the starting lithium amide has been described.[7d,h] The precursors were prepared through Birch reductive alkylation of suitable arenes or metallation of cyclohexa-1,4-diene (Scheme 10).[11h,k,14] Cyclohexadienyl alcohol **3** was



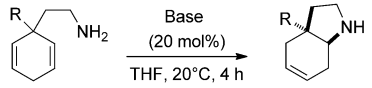
Scheme 10. Synthesis of dienes with primary amines.

obtained in two steps from benzoic acid (56%, see the Supporting Information).[26] Protection of the alcohol function was carried out by slow addition of NaH at 0 °C onto the substrate to avoid isomerization of the diene.[27] Under these conditions, **4** was obtained in good yield. This isomerization is notable and corroborates our hypothesis that these cyclohexadienes may be easily deprotonated in the presence of strong bases. The presence of the chelating CH_2OH substituent likely favors such a deprotonation as seen above with the amino-ether

moiety. Reduction of the nitrile was then performed with $LiAlH_4$ and $AlCl_3$, affording the amine in high yield.

The synthesis of the silylated precursor **8** proved to be more troublesome. By using Woerpel's procedure,[11h,j,k] cyclohexa-1,4-diene was metallated then silylated to afford the 1-silylcyclohexa-1,4-diene as an intermediate, which was not isolated, but instead metallated in situ with *s*BuLi and finally alkylated to give **7** in poor yield. Reduction as above gave **8** in good yield. The hydroamination process on precursor **9a**, carried out by using a substoichiometric amount of *n*BuLi (20 mol%), afforded the desired fused pyrrolidine as a 7:3 mixture of two regioisomers **12a** and **12b** (Table 2, entry 1 and Scheme 11), the structures of which were assigned as discussed below. Repeating the reaction by using 20 mol% lithium diisopropylamide [LDA; prepared from a 2:1 mixture of diisopropylamine (DIPA) and *n*BuLi] led to a deep orange-red coloration upon addition of **9a** at room temperature;[28] after workup, this reaction provided the secondary amine **12a** in quantitative yield as a single regioisomer. Interestingly, primary amines led to different regioisomers compared with those obtained from secondary amines discussed previously. This proved to be a general trend because other amines (**5**, **9b** and **9c**) led predominantly to the same regioisomers in generally high yields. Quantitative crude yields (based on ^{1}H NMR analysis) were generally obtained, suggesting that the lower isolated yields were due to a loss of the polar amine on silica gel. In contrast to other substrates, silylated diene **8** did not give the desired pyrrolidine because of extensive desilylation under the reaction conditions. The determination of the structure of regioisomers in the previous series, based solely on ^{1}H NMR experiments, proved to be inefficient; therefore, the position of the double bond in the six-membered ring of fused pyrrolidines **10**–**14** was established by first preparing all three regioisomers of **12** using independent routes.

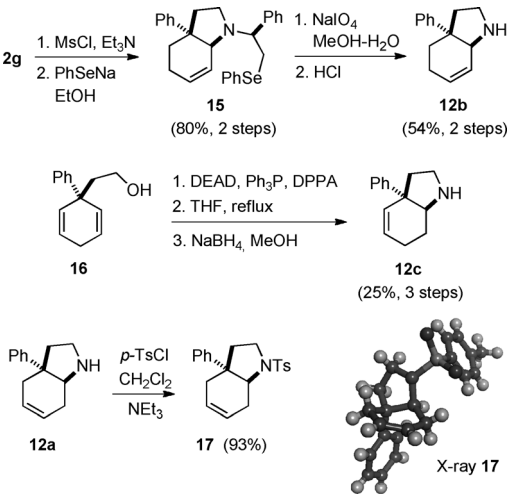
Table 2. Cyclization of amines **5**, **8**, and **9a–c**.



5, R = CH_2OBn **10**, R = CH_2OBn
8, R = $SiMe_2tBu$ **11**, R = $SiMe_2tBu$
9a, R = Ph **12**, R = Ph
9b, R = 3-(MeO)Ph **13**, R = 3-(MeO)Ph
9c, R = 3,5-$(MeO)_2$Ph **14**, R = 3,5-$(MeO)_2$Ph

Diene[a]	Base	Product[b]	Yield [%][a,b]	Regio[c]
9a	*n*BuLi[d]	**12a/12b**	95	67:33
9a	LDA[e]	**12a**	80	>98:2
5	LDA[e]	**10**	71	>98:2
8	LDA[e]	**11**	–	–
9b	LDA[e]	**13**	92	85:15
9c	LDA[e]	**14**	73	>98:2

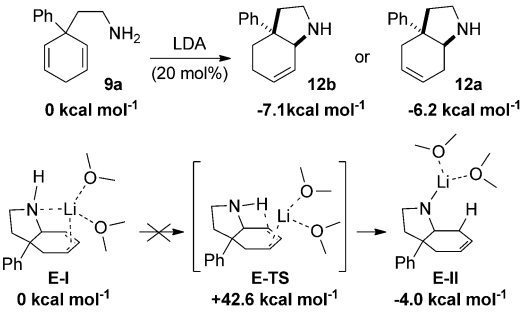
[a] Isolated yield after chromatography. [b] Quantitative crude yields were generally obtained before chromatography. [c] Homoallylic amine/allylic amine ratio estimated through ^{1}H NMR analysis of the crude reaction mixture. [d] 20 mol%. [e] 20 mol% of LDA prepared from a 2:1 mixture of DIPA and *n*BuLi.



Scheme 11. Preparation of pyrrolidine regioisomers **12b** and **12c** and tosylamide **17**.

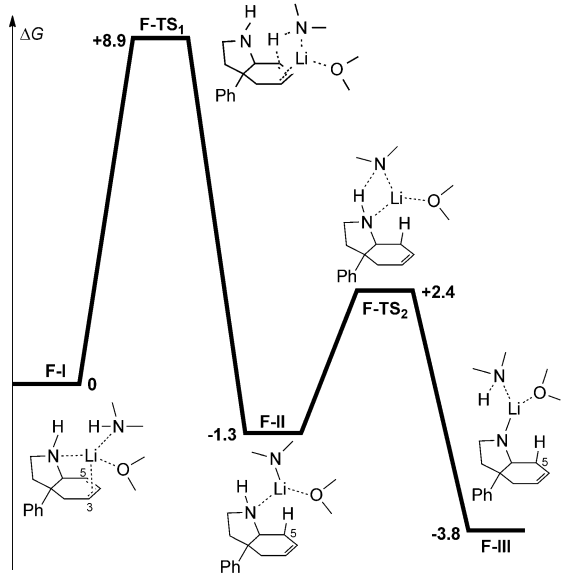
Fused pyrrolidines having an allylic secondary amine were obtained from compound **2g** by removing the chiral auxiliary (Scheme 11). Although numerous methods have been developed to cleave phenylglycinol auxiliaries, these generally rely on the unique reactivity of the benzylic amine moiety.[29] Unfortunately, in our case, the amine is both benzylic and allylic, thus restricting the number of methods available. After extensive studies, we found that substitution of the β-hydroxy group with a phenylselenyl substituent[30] allowed the removal of the glycinyl fragment after oxidation of the selenium and β-elimination, followed by hydrolysis of the enamine under acidic conditions to provide pyrrolidine **12b**. In parallel, the bishomoallylic amine was obtained by using a three-step procedure from alcohol **16**, involving a [3+2] cycloaddition of an azide intermediate onto one of the olefins of the cyclohexadienyl moiety.[31] The desired pyrrolidine **12c** was thus obtained in 25% overall yield from **16**.

Comparison of the ^{13}C NMR data of amines **10**–**14** with those of **12b** and **12c** showed unambiguously that the hydroamination of primary amines **5** and **9a–c** in the presence of LDA generates the corresponding homoallylamines, without traces of the corresponding allylic regioisomer. This assignment was later supported by X-ray diffraction studies of **17** prepared through tosylation of secondary amine **12a** (Scheme 11). The formation of the homoallylic amine as a unique regioisomer suggests a mechanism closely related to that proposed before for the cyclization of secondary amines, but with a final protonation step proceeding through a different pathway. Our calculations surprisingly showed that allylamine **12b** was the thermodynamic product (Scheme 12), indicating that the proton transfer likely proceeds through low transition-state barriers. A direct 1,3-proton transfer was envisioned: the close proximity of the amine proton with the allylic system perhaps explaining the reactivity difference between secondary and tertiary amines. However, this hypothesis was ruled out because of the very high computed transition state **E-TS** (+42.6 kcal mol^{-1}).



Scheme 12. Computed energies for the protonation–hydroamination of a primary amine and energy profile for the direct 1,3-proton transfer.

The cyclizations of primary amines were carried out in the presence of an excess of diisopropylamine. It was thus envisioned that regioselective protonation could result from a proton transfer from an amine complexed to the lithium,[32] in a fashion similar to that computed for tertiary amines (see Scheme 4). This difference in behavior would then arise from a chelation by hydrogen bonding between the secondary amine and DIPA that could direct the proton transfer towards C5 instead of C3. A computed reaction pathway involving a double proton transfer showed a much lower energetic profile than for the protonation of tertiary amines (Scheme 13).

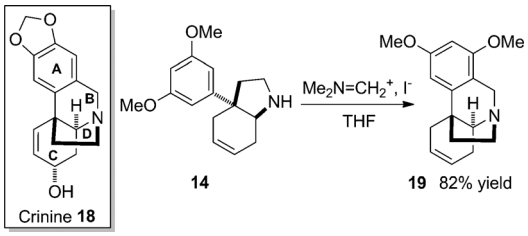


Scheme 13. Free Gibbs energy profile [kcal mol^{-1}] for the protonation step with hydrogen shuttle.

The occurrence of hydrogen bonding between the two amines in **F-II** and **F-TS$_2$** lowers the transition state for a proton transfer at C3 (compare +8.9 kcal mol^{-1} for **F-TS$_1$** in Scheme 13 with 13.4 kcal mol^{-1} for **B-TS$_b$** in Scheme 4). One can assume that a transition state for a protonation at C5 would be in the same range as for **B-TS$_a$** because of the absence of hydrogen bonding at this position.

Application of the protonation–hydroamination cascade to the synthesis of crinane-type alkaloids: total synthesis of (+)-*epi*-elwesine

The azabicyclo[4.3.0]nonane skeleton above (**2a**–**e** and **10**–**14**) is found in several classes of alkaloids, including those of *Amaryllidaceae* such as crinine **18** (Scheme 14),[33] but also in ter-

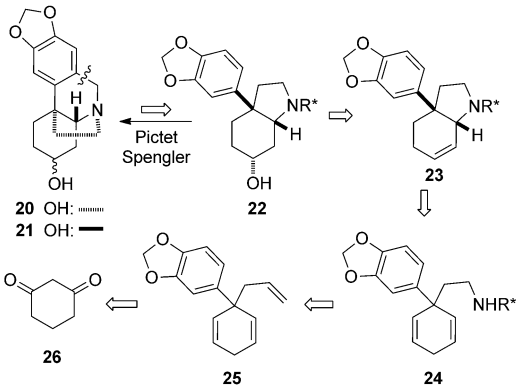


Scheme 14. Pictet–Spengler reaction on model substrate **14**.

pene indole alkaloids such as aspidospermine and more complex strychnine.[34] All these natural products have in common a quaternary center and a *cis*-ring junction, which still constitutes a challenging synthetic problem. Desymmetrization of cyclohexadienes flanked with an aryl substituent and an ethylamino group such as those described above offers an attractive and straightforward route through which to access the crinine-type alkaloid skeleton in a limited number of steps. This strategy, called "BRAD" (Birch reductive alkylation–desymmetrization) allows the preparation of simple building blocks, opening a unified access to several classes of alkaloids, including those mentioned above.[14a] For instance, with the azabicyclo-[4.3.0]nonene skeleton in hand, a simple Pictet–Spengler process should allow the formation of the B-ring and enable access to the complete skeleton of Amaryllidaceae alkaloids of the crinine family.[31,33] Several syntheses of alkaloids of this family have been reported in which the B-ring is formed through a Pictet–Spengler transformation.[31,33,35] This approach was tested on a simple model compound **14**, which, upon treatment with the Eschenmoser salt,[34b] effectively afforded the desired tetracyclic crinine skeleton **19** in good yield (Scheme 14).[36] Interestingly, the olefin was not affected under these conditions. When the same reaction was carried out with unsymmetrical analogue **13**, no trace of the desired tetracycle was observed, suggesting that in this case the arene is not sufficiently nucleophilic to react with the iminium intermediate. Under forcing conditions (formaldehyde, HCl, MeOH–H_2O, 60 °C, 15 h), the desired product was however observed but in a mixture of products that could not be separated further.

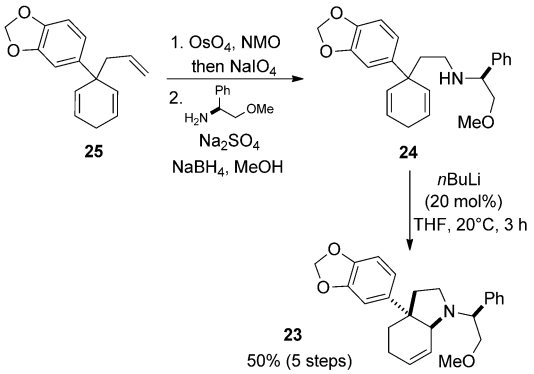
Based on these results, we embarked into the enantioselective synthesis of *epi*-elwesine **20**, which belongs to the broad family of crinine alkaloids. *epi*-Elwesine **20** and (+)-elwesine **21**, also called dihydrocrinine and dihydroepicrinine, respectively, have been isolated in small quantities from a giant snowdrop *Galanthus elwesii Hook*,[37] which also contains, as major component, galanthamine, which is used in the treatment of Alzheimer's disease. No enantioselective total synthesis of **20** and **21** has been reported to date.[38] However, both have been ob-

tained in enantiomerically pure form from dihydro-oxocrinine, a closely related alkaloid, through resolution with tartaric acid followed by reduction of the ketone function at C4.[39] We planned to rely, as a final step, on the Pictet–Spengler reaction of a suitably functionalized azabicyclo[4.3.0]nonene skeleton.[31,33] The latter was expected to be generated by applying the above diastereo- and regioselective hydroamination cascade, followed by introduction of the alcohol function to the C-ring. The required cyclohexadiene precursor **24** was not accessible by using our previously reported Birch reduction strategy[14] because of the low stability of the methylenedioxy group under these conditions. We therefore focused on the simple precursor **25**, which is available from cyclohexene-1,3-dione by using a high-yielding five-step sequence (Scheme 15).[40] Compound **25** would then deliver **24** through oxidation of the olefin into an aldehyde followed by a reductive amination to install the chiral auxiliary.



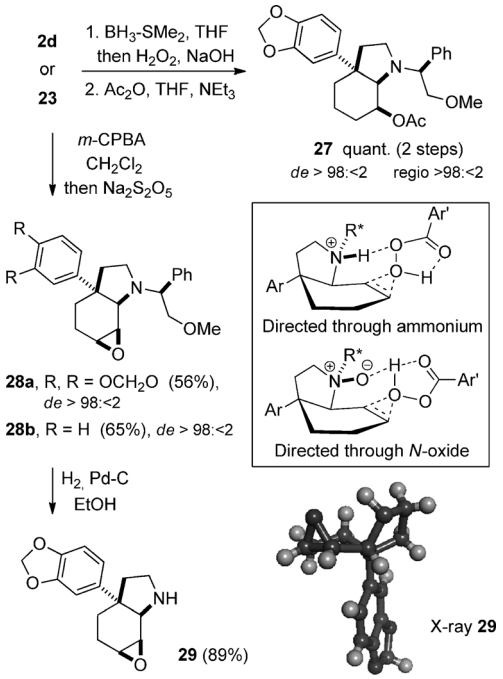
Scheme 15. Retrosynthetic analysis of crinine-type alkaloids.

Based on this disconnection, **25** was converted into **24** through a four-step, two-pot sequence involving a Lemieux–Johnson oxidation[41] followed by reductive amination (Scheme 16). Compound **24** was used directly in the hydroamination step without further purification to provide, using a substoichiometric amount of *n*BuLi, azabicyclo[4.3.0]nonene intermediate **23** (R* = Gly) in 50% overall yield from **25**.



Scheme 16. Synthesis of azabicyclo[4.3.0]nonene **23**.

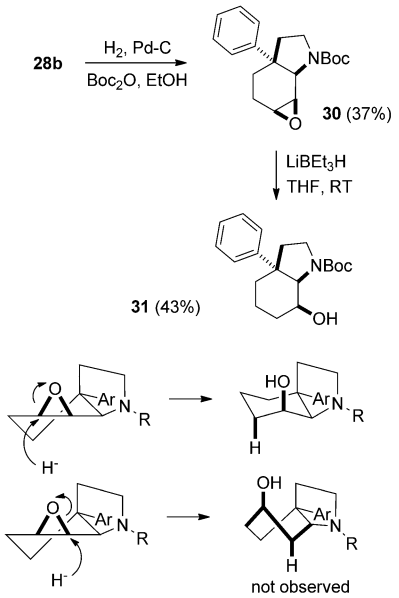
With **23** in hand, we then studied the functionalization of ring C through direct introduction of the hydroxyl group at C-3. Hydroboration was first tested by using various boranes. Whereas the use of 9-borabicyclo[3.3.1]nonane (9-BBN-H) or $(Cyclohex)_2BH$ led essentially to recovered starting material, BH_3-SMe_2 provided the undesired regioisomer as its acetate **27** in quantitative yield (Scheme 17). The complete regio- and stereocontrol suggests that the allylic amino group probably coordinates the boron center, directing the hydroboration onto the *syn* face and on the vicinal olefinic center. Attempts at reversing the regioselectivity through oxymercuration using $Hg(OAc)_2$ or $Hg(OCOCF_3)_2$ were also tested but this led essentially to starting compound **23**. We then turned our attention to a two-step alternative involving epoxidation followed by reductive opening of the epoxide. Epoxidation of **23** with *m*-chloroperoxybenzoic acid (*m*-CPBA) led to **28a** as a single stereoisomer, the *syn*-relative configuration of which was assigned based on X-ray diffraction studies of a derivative (i.e., **29**, see below). Similarly, model compound **2d** led to the corresponding epoxide **28b** with the same stereoselectivity. The high *syn*-stereocontrol could arise either through a directed epoxidation from the corresponding ammonium[42] or from the N-oxide formed in situ (Scheme 17).[43] The latter would be formed by oxidation of the amine before epoxidation and then reduction with $Na_2S_2O_5$, thus regenerating the tertiary amine. Epoxide **28a** was then treated with various hydride sources [$LiAlH_4$, diisobutylaluminum hydride (DIBAL-H), $LiBEt_3H$], but essentially no reaction or degradation of the starting material was observed. The results above indicate that the sterically hindered chiral auxiliary prevents reagents from approaching the olefinic moiety or the epoxide. Removal of the phenylglycinol methyl



Scheme 17. Functionalization of the C-ring olefin in **23**.

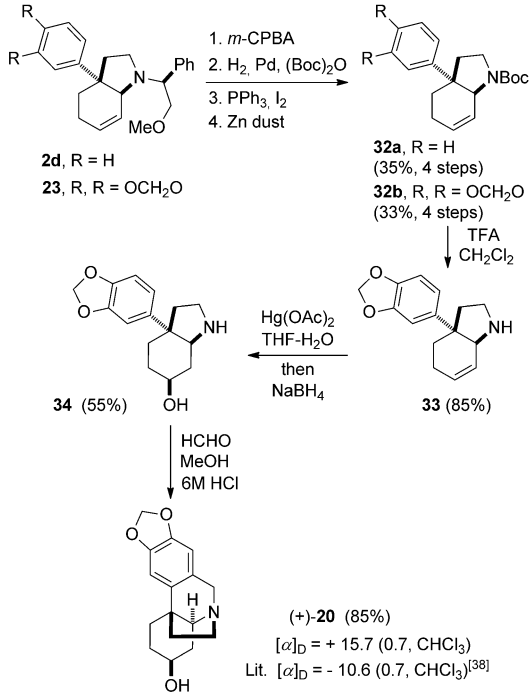
ether was thus carried out through hydrogenolysis, leading to the secondary amine **29** in good yield. X-ray diffraction studies on **29** secured its relative configuration and those of **28a**–**b**. All our efforts to open the epoxide of **29** met with failure, irrespective of the hydride source used.

Previous work by Overman et al.[38c] on the synthesis of racemic *epi*-elwesine showed that an intermediate such as **23**, devoid of chiral auxiliary, could be converted in two steps into the natural product. It was thus decided to employ the epoxide as an olefin protective group that could then be unmasked later in the synthesis. Epoxide ring opening to form the corresponding iodohydrin,[44] followed by zinc-mediated elimination[45] would thus be used, respectively, to protect then restore the olefinic appendage. Treatment of **29** with a mixture of PPh_3 and I_2 led effectively to epoxide ring opening and formation of the iodohydrin as a mixture of two regioisomers, albeit in 30% yield. Unfortunately, addition of zinc dust to this mixture led to unreproducible results, indicating that the free amino group reacted under these conditions. This was solved by removing the chiral auxiliary through hydrogenolysis with protection of the secondary amine in situ as a carbamate. By using this strategy, carbamate **30**, as a model compound, was obtained in moderate yield (the modest yield does not reflect the efficiency of the two-step, one-pot process, due to the loss of material upon purification; Scheme 18). Epoxide ring opening was tested with $LiBEt_3H$, but again this led to the undesired regioisomer **31**. The use of the Lewis acidic DIBAL-H also afforded **31** in 46% yield. The regioselectivity of the epoxide ring opening follows the Fürst–Plattner rules,[46] favoring a *trans*-diaxial mode and the formation of the isomer in a chair conformation instead of the other approach that leads to the more energetic twist-boat conformation.



Scheme 18. Attempts at opening the epoxide of **30**.

Although our efforts to restore the unsaturation on ring C in **29** were not successful (see above), the sequence was repeated with the Boc-protected amine **30**, and we were pleased to observe that treatment of the latter with Ph_3P-I_2 in *N*,*N*-dimethylformamide (DMF) led to the formation of the corresponding iodohydrins as a mixture of regioisomers, which were directly submitted to the elimination step using zinc dust. This afforded the desired olefin **32a** in a satisfactory 35% overall yield from **2d** (four steps; Scheme 19). The same strategy was applied to the *epi*-elwesine precursor **28a**, providing olefin **32b** in 33% yield from **23**. The Boc protective group was then removed under acidic conditions [trifluoroacetic acid (TFA)], leading to secondary amine **33**. Introduction of the hydroxyl group at C-3 was then performed through oxy-mercuration following Overman's precedent,[38c] giving rise to the alcohol **34** in 55% yield. Pictet–Spengler reaction onto **34** using formaldehyde finally afforded enantiomerically pure (+)-*epi*-elwesine **20**, the natural product enantiomer.



Scheme 19. Completion of the total synthesis of (+)-*epi*-elwesine **20**.

Conclusion

We provide here a full account on our research on lithium base-catalyzed intramolecular hydroamination of 1-substituted cyclohexa-2,5-dienes. When a secondary amine is present on the ethylamino substituent at C-1, azabicyclo[4.3.0]nonenes bearing an allylic amine are generated. In contrast, primary amines linked to the quaternary center provide the corresponding homoallylic amines. A mechanism has been proposed that rationalizes the different observations. Isomerization of the cyclohexa-2,5-diene system prior to the hydroami-

nation step was suggested, which is supported both by the isolation and the structure determination of minor byproducts, as well as by DFT calculations. These computational studies have also shed light on the origin of the enantioselectivity and have provided useful information on the organolithium intermediates involved in such processes. Finally, the value of the methodology was demonstrated by the facile access to crinane-type alkaloids and the completion of the first enantioselective synthesis of the enantiomer of naturally occurring *epi*-elwesine, an alkaloid of the crinine family.

Experimental Section

General procedure for hydroamination reactions

The amine (1.0 equiv.) was dissolved in THF (1 M), and *n*BuLi (2.5 M in hexane, 0.2 equiv) is added dropwise at RT. The reaction was stirred for 4 h during which the solution turned from orange to yellow. A drop of water was added and the organic layer was diluted with diethyl ether, washed with saturated Na_2CO_3 solution, and dried over sodium sulfate. After removal of the solvents, the product was obtained as a colorless oil in nearly quantitative yield.

3a-(Benzo[*d*][1,3]dioxol-5-yl)-1-((*S*)-2-methoxy-1-phenylethyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole (23): $[\alpha]_D = +120.6$ ($c = 0.02$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.23 (m, 5H), 6.75 (m, 1H), 6.70–6.66 (m, 2H), 6.09 (m, 1H), 5.96 (m, 1H), 5.90 (s, 2H), 4.19–4.10 (m, 1H), 3.78 (m, 2H), 3.34 (s, 3H), 3.10 (m, 1H), 2.96 (m, 1H), 2.56 (m, 1H), 2.06–1.85 (m, 4H), 1.65–1.57 ppm (m, 2H); ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 147.1$, 145.1, 142.3, 137.9, 137.9, 131.3, 128.7, 128.1, 126.0, 119.3, 107.4, 100.7, 75.1, 62.2, 61.1, 58.8, 46.3, 45.7, 34.6, 34.6, 23.5 ppm; IR (neat, NaCl): $\tilde{\nu} = 3024$, 2922, 1685, 1600, 1191, 1109 cm^{-1}; HRMS (LSIMS): *m/z*: calcd for $C_{24}H_{28}NO_3$: 378.2069 $[M+H]^+$; found: 378.2068;.

3a-Benzo[1,3]dioxol-5-yl-6-(2-methoxy-1-phenylethyl)octahydro-1-oxa-6-azacyclopropa[*e*]indene (28a): At 0 °C, *m*-CPBA (70%) (74 mg, 0.3 mmol, 3 equiv) was added to a solution of alkene **23** (38 mg, 0.1 mmol, 1 equiv) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at 0 °C for 3 h and at RT overnight, then washed three times with 10% $Na_2S_2O_5$ aqueous solution, three times with a 10% $NaHCO_3$ aqueous solution, and, finally, brine. The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel; petroleum ether/EtOAc, 9:1) gave epoxide **28a** (22 mg, 56%) as a yellow oil. $[\alpha]_D = +70.5$ ($c = 0.02$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.35$–7.25 (m, 5H), 6.70–6.51 (m, 3H), 5.90 (s, 2H), 4.38 (t, $J = 6.6$ Hz, 1H), 3.92 (dd, $J = 9.8$, 6.4 Hz, 1H), 3.80 (dd, $J = 9.8$, 7.2 Hz, 1H), 3.41–3.34 (m, 1H), 3.36 (s, 3H), 3.23 (br s, 1H), 3.19–3.17 (m, 1H), 2.96–2.89 (m, 1H), 2.50–2.43 (m, 1H), 1.97–1.75 (m, 4H), 1.34–1.14 ppm (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 147.4$, 145.2, 141.7, 138.0, 128.7, 128.2, 127.3, 119.5, 107.6, 107.5, 100.8, 75.1, 62.6, 61.0, 58.7, 52.7, 51.1, 45.7, 45.4, 39.0, 31.6, 21.5 ppm; IR (neat, NaCl): $\tilde{\nu} = 2924$, 1676, 1490, 1437, 1341, 1234, 1114, 1039 cm^{-1}; MS (EI): *m/z* (%): 348 (100) $[M-C_2H_5O]^+$; HRMS (LSIMS): *m/z*: calcd for $C_{24}H_{28}NO_4$: 394.2018 $[M+H]^+$; found: 394.2030.

3a-Benzo[1,3]dioxol-5-yl-2,3,3a,4,5,7a-hexahydroindole-1-carboxylic acid *tert*-butyl ester (32b): In a three-necked flask, Pd/C (430 mg, 0.41 mmol, 20 mol%) and $HClO_4$ (two drops) were added to a solution of epoxide **28a** (800 mg, 2.03 mmol, 1 equiv) and Boc_2O (1.33 g,6.1 mmol, 3 equiv) in EtOH/H_2O (2:1, 40 mL). The reaction mixture was degassed with three freeze-pump-thaw cycles and H_2 was introduced with a balloon (pump–H_2, 3×). After stirring at RT overnight, the solution was filtered twice through a pad of Celite and concentrated in vacuo. I_2 (1.02 g, 4 mmol, 2 equiv) was added to a solution of crude epoxide (2 mmol, 1 equiv) and PPh_3 (1.05 g, 4 mmol, 2 equiv) in DMF (15 mL). The reaction mixture was stirred at RT for 1.5 h. Zn dust (650 mg, 10 mmol, 5 equiv) was added and the resulting reaction mixture was stirred at RT for 2 h. Et_2O was added and the organic layer was washed with H_2O (3×), brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel; petroleum ether/EtOAc, 9:1) gave alkene **32b** (195 mg, 33% over four steps) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (two rotamers) = 6.78 (br s, 1H), 6.72 (br s, 2H), 6.23–6.21 (m, 0.5H), 6.24–6.21 (m, 0.5H), 5.93 (s, 2H), 5.86–5.83 (m, 1H), 4.39 (br s, 0.5H), 4.26 (br s, 0.5H), 3.46–3.32 (m, 2H), 2.18–1.85 (m, 6H), 1.50 (s, 4.5H), 1.45 ppm (s, 4.5H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (two rotamers) = 154.6, 147.6, 135.8, 140.4, 128.7, 128.24, 127.1, 126.8, 118.8, 107.9, 106.8, 100.9, 79.5, 58.9, 47.6, 47.0, 43.7, 34.7, 31.6, 28.6, 22.1 ppm; IR (neat, NaCl): $\tilde{\nu} =$ 3051, 2976, 2929, 1689, 1507, 1489, 1434, 1402, 1366 cm^{-1}; HRMS (LSIMS): *m/z*: calcd for $C_{20}H_{25}NO_4$: 343.1783 $[M]^+$; found: 343.1779.

3a-(Benzo[*d*][1,3]dioxol-5-yl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole (33): At 0 °C, TFA (5.4 mL, 72.7 mmol, 135 equiv) was added to a solution of protected amine **32b** (186 mg, 0.54 mmol, 1 equiv) in CH_2Cl_2 (27 mL) and the reaction mixture was stirred at this temperature for 30 min. Aq. NaOH (3 M) was added until the pH remained basic. The reaction mixture was then stirred at RT for 50 min. After separation of the two layers, the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel; CH_2Cl_2/MeOH/28% aq NH_4OH: 9:1:0.2) gave amine **33** (112 mg, 85%) as a white solid. Analytical data were in good agreement with those reported in the literature.[38] $[\alpha]_D +57.9$ ($c = 0.01$ in $CHCl_3$).

3a-Benzo[1,3]dioxol-5-yl-octahydroindol-6-ol (**34**). A solution of alkene **33** (112 mg, 0.46 mmol, 1 equiv) in THF (0.5 mL) was added to a mixture of mercuric acetate (291 mg, 0.91 mmol, 2 equiv) in H_2O (1.8 mL) and THF (0.5 mL). The reaction mixture was stirred for 24 h at RT before $NaBH_4$ (0.5 M in 3N NaOH, 1.8 mL, 0.46 mmol) and 3N NaOH (0.5 mL) were added. After 30 min, the mixture was quenched with solid potassium carbonate and extracted with Et_2O (2×12 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel; CH_2Cl_2/MeOH/28% aq NH_4OH, 9:1:0.2) gave alcohol **34** (66 mg, 55%) as a white solid. Mp 87–93 °C; $[\alpha]_D +63.4$ ($c = 0.009$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.84$–6.71 (m, 3H), 5.92 (s, 2H), 4.02 (br. s, 1H), 3.95 (br. s, 1H), 3.71 (br. s, 1H), 3.19–2.95 (m, 2H), 2.25 (td, $J = 14.3$, 3.4 Hz, 1H), 2.06–1.65 (m, 6H), 1.37 ppm (tt, $J = 13.1$, 2.4 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta =$ 147.7, 145.5, 139.2, 119.3, 107.8, 107.4, 100.9, 66.6, 60.5, 46.3, 42.7, 41.7, 31.4, 29.3, 26.5 ppm; IR (neat, NaCl): $\tilde{\nu} = 3308$, 1610, 1505, 1487, 1434, 1232 cm^{-1}; HRMS (LSIMS): *m/z*: calcd for $C_{15}H_{20}NO_3$: 262.1443 $[M+H]^+$; found: 262.1446.

(+)-*epi*-Elwesine (20):[38] Aqueous formaldehyde (37%, 0.5 mL, 2.7 mmol, 17 equiv) was added to a solution of **34** (43 mg, 0.16 mmol, 1 equiv) in MeOH (0.2 mL). The reaction mixture was stirred for 15 min, then poured into 6N HCl (7 mL). After stirring for 12 h, the reaction solution was basified with 28% aq NH_4OH and extracted with $CHCl_3$ (2×). The combined organic extracts were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (silica gel; CH_2Cl_2/MeOH/28% aq NH_4OH, 9:1:0.2) gave *epi*-Elwesine **20** (38 mg, 85%) as a white solid. $[\alpha]_D +15.7$ ($c = 0.7$ in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.68$ (s, 1H), 6.45 (s, 1H), 5.88 (s, 2H), 4.32 (d, $J =$ 16.8 Hz, 1H), 3.74 (d, $J = 16.8$ Hz, 1H), 3.67–3.55 (m, 1H), 3.39–3.29

(m, 1H), 2.94 (dd, $J=12.0$, 5.1 Hz, 1H), 2.87–2.76 (m, 1H), 2.64 (br. s, 1H), 2.40–2.35 (m, 1H), 2.25–2.13 (m, 1H), 2.09–1.93 (m, 2H), 1.79–1.46 (m, 3H), 1.30 ppm (q, $J=12.2$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=146.1$, 145.6, 141.1, 125.8, 106.1, 103.3, 100.6, 68.8, 66.4, 62.1, 51.9, 42.1, 37.8, 36.7, 30.8, 26.6 ppm; IR (neat, NaCl): $\tilde{\nu}=2390$, 1642, 1488, 1243 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{16}H_{20}NO_3$: 274.1437 $[M+H]^+$; found: 274.1444.

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Keywords: alkaloids · hydroamination · isomerization · reaction mechanisms · rearrangements

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