Organolanthanide-Catalyzed Hydroamination/Cyclization. Efficient Allene-Based Transformations for the Syntheses of Naturally Occurring Alkaloids

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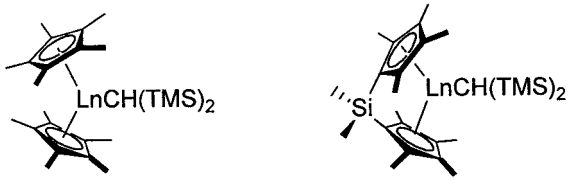
Abstract: The total syntheses of the pyrrolidine alkaloid (+)-197B (**1**) and pyrrolizidine alkaloid (+)-xenovenine (**2**) are described. The strategy involves enantioselective syntheses of the aminoallene, (5*S*,8*S*)-5-amino-trideca-8,9-diene (**3**), and the aminoallene-alkene, (5*S*)-5-amino-pentadeca-1,8,9-triene (**4**), which then undergo regio- and stereoselective cyclohydroamination catalyzed by the organolanthanide precatalysts $Cp'_2LnCH(TMS)_2$ and $Me_2SiCp''(^tBuN)LnN(TMS)_2$ ($Cp' = \eta^5$-Me_5C_5; $Cp'' = \eta^5$-Me_4C_5; Ln = lanthanide; TMS = Me_3Si). These reactive organolanthanide complexes efficiently mediate highly diastereoselective intramolecular hydroamination/cyclization (IHC) reactions under mild conditions. The turnover-limiting step in these catalytic cycles is proposed to be intramolecular insertion into the Ln−N bond of the proximal allenic C═C linkage, followed by rapid protonolytic cleavage of the resulting Ln−C bond. The rate and selectivity of the insertion process is highly sensitive to the steric demands of the substrate.

Introduction

The discovery and implementation of new synthetic reagents and transformations offers the opportunity to explore new, more efficient and selective synthetic strategies for the total synthesis of complex natural products. In the past decade, several broad classes of organolanthanide catalysts[1] were developed in this and other laboratories which effectively and selectively mediate a variety of transformations, including hydroamination,[2,3] hydrogenation,[4] oligomerization/polymerization,[5] silanolytic chain transfer in olefin polymerization,[6] hydrosilylation,[7] hydrophosphination,[8] hydroboration,[9] and reductive cyclization[10] of unsaturated C−C bonds. The regioselective, catalytic intramolecular hydroamination/cyclization (IHC) of aminoalkenes[2] and aminoalkynes[3] allows efficient construction of mono- and polycyclic organonitrogen frameworks (e.g., pyrrolidines, pyrrolizidines, indolizidines, and quinolizidines) using organolanthanide complexes of the type $Cp'_2LnCH(TMS)_2$ and $Me_2SiCp''_2LnCH(TMS)_2$ ($Cp' = \eta^5$-Me_5C_5, $Cp'' = \eta^5$-Me_4C_5; Ln = La, Sm, Y, Lu; TMS = Me_3Si; shown below)



as precatalysts in both single and sequentially coupled multistep processes. We recently reported the first organolanthanide-catalyzed regio- and diastereoselective IHC of disubstituted aminoallenes, which affords the corresponding mono- and disubstituted pyrrolidines and piperidines bearing an α-alkene functionality.[11] Such structures offer unique opportunities for

(1) For recent organolanthanide reviews, see: (a) Anwander, R.; Herrmann, W. A. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1996; Vol. 179, pp 1−32. (b) Edelmann, F. T. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1996; Vol. 179, pp 247−276. (c) Edelmann, F. T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2466−2488. (d) Schumann, H.; Meese-Marktscheffel, J. A.; Esser, L. *Chem. Rev.* **1995**, *95*, 865−986. (e) Schaverien, C. J. *Adv. Organomet. Chem.* **1994**, *36*, 283−362.

(2) (a) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1998**, *63*, 8983−8988. (b) Roesky, P. W.; Stern, C. L.; Marks, T. J. *Organometallics* **1997**, *16*, 4705−4711. (c) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241−10254. (d) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275−294. (e) Gagné, M. R.; Brard, L.; Conticello, V. P.; Giardello, M. A.; Stern, C. L.; Marks, T. J. *Organometallics* **1992**, *11*, 2003−2005. (f) Gagné, M. R.; Nolan, S P.; Marks, T. J. *Organometallics* **1990**, *9*, 1716−1718.

(3) (a) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757−1771. (b) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295−9306. (c) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770−3772. (d) Li, Y.; Marks, T. J. *J. Am. Chem. Soc*. **1996**, *118*, 707−708. (e) Li, Y.; Fu, P.-F.; Marks, T. J. *Organometallics* **1994**, *13*, 439−440.

(4) (a) Roesky, P. W.; Denninger, U.; Stern, C. L.; Marks, T. J. *Organometallics* **1997**, *16*, 4486-4492. (b) Molander, G. A.; Hoberg, J. O. *J. Org. Chem*. **1992**, *57*, 3266−3268. (c) Jeske, G.; Lauke, H.; Mauermann, H.; Swepston, P. N.; Schumann, H.; Marks, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 8111−8118. (d) Evans, W. J.; Bloom, I.; Hunter, W. E.; Atwood, J. L. *J. Am. Chem. Soc*. **1983**, *105*, 1401−1403.

(5) (a) Yang, X.; Seyam, A. M.; Fu, P.-F.; Marks, T. J. *Macromolecules* **1994**, *27*, 4625−4626. (b) Watson, P. L.; Parshall, G. W. *Acc. Chem. Res.* **1985**, *18*, 51−56. (c) Jeske, G.; Schock, L. E.; Swepston, P. N.; Schumann, H.; Marks, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 8103−8110.

(6) Fu, P.-F.; Marks, T. J. *J. Am. Chem. Soc.* **1995**, *117*, 10747−10748. (b) Koo, K.; Fu, P.-F.; Marks, T. J. *Macromolecules* **1999**, *32*, 981−988.

(7) (a) Molander, G. A.; Retsch, W. H. *Organometallics* **1995**, *14*, 4570−4575. (b) Fu, P.-F.; Brard, L.; Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1995**, *117*, 7157−7168. (c) Molander, G. A.; Julius, M. *J. Org. Chem.* **1992**, *57*, 6347−6351. (d) Sakakura, T.; Lautenschlager, H.-J.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1991**, 40−41.

(8) Giardello, M. A.; King, W. A.; Nolan, S. P.; Porchia, M.; Sishta, C.; Marks, T. J. In *Energetics of Organometallic Species*; Martinho Simoes, J. A., Ed.; Kluwer: Dordrecht, 1992; pp 35−51.

(9) (a) Harrison, K. N.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 9220−9221. (b) Bijpost, E. A.; Duchateau, R.; Teuben, J. H. *J. Mol. Catal.* **1995**, *95*, 121−129.

(10) (a) Molander, G. A.; Retsch, W. H. *J. Am. Chem. Soc.* **1997**, *119*, 8817−8825. (b) Molander, G. A.; Nichols, P. J. *J. Am. Chem. Soc.* **1995**, *117*, 4415−4416. (c) Molander, G. A.; Hoberg, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 3123−3125.

(11) Arredondo, V. M.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 4871−4872.

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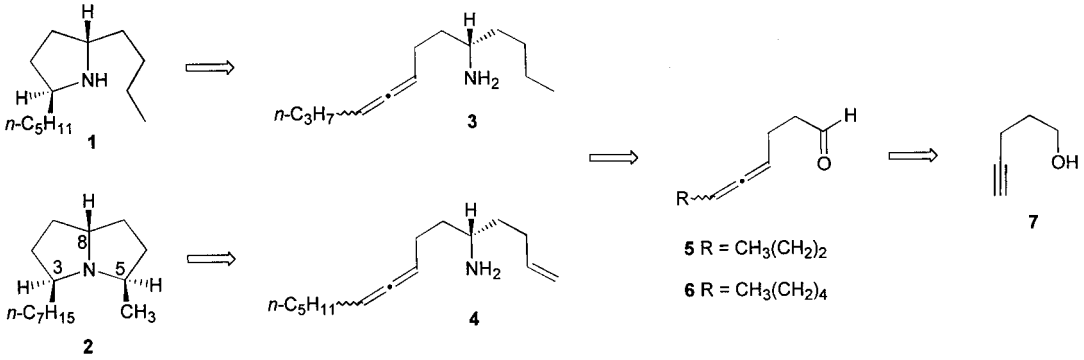
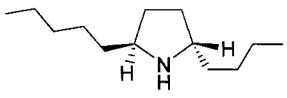
Scheme 1

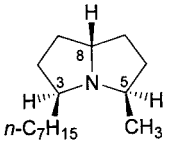


applying this methodology to natural product synthesis,[12] which will be described herein.

A variety of substituted pyrrolidines[13] and pyrrolizidines[14] are found in the venom of ants[15] of the genus *Solenopsis* and *Monomorium*, and play biological roles ranging from protective and pheromonal functions to necrotic, hemolytic, and allergenic reactions.[16] These alkaloids also occur in trace amounts in amphibian skins where they serve as a chemical defense.[17] However, the frogs themselves produce none of the alkaloids. Instead, they are taken up from dietary arthropods (including ants and beetles), and are sequestered unchanged into secretory skin glands.[18] Examples of these structures include (+)-pyrrolidine 197B (**1**), [(2*S*,5*S*)-*trans*-2-butyl-5-pentylpyrrolidine], which was detected in skin extracts of *Dendrobates histronicus*,[19] and (+)-xenovenine (**2**), [(3*S*,5*R*,8*S*)-3-heptyl-5-methylpyrrolizidine], isolated from *Solenopsis xenovenum* in 1980.[20]



(+)-Pyrrolidine 197B (**1**)



(+)-Xenovenine (**2**)

Previous asymmetric syntheses of these pyrrolidine and pyrrolizidine alkaloids were performed using chiral synthons derived from the natural chiral pool.[21] For example, Momose et al.[22] described the asymmetric synthesis of **1** by an intramolecular amidomercuration of α-butyl-4-pentenylcarbamate which was in turn prepared from L-norleucine, whereas Machinaga and Kibayashi[23] obtained **1** from C_2-symmetric diepoxides derived from D-mannitol. On the other hand, Lhommet et al.[24] and Momose et al.[25] reported the asymmetric synthesis of **2** from (*S*)-pyroglutamic acid and from D-alanine, respectively. Both syntheses relied on the reductive annulation of a cyclic aminocarbonyl compound.

On the basis of these reports, we decided to explore a completely different and potentially general stereoselective synthetic approach via organolanthanide-catalyzed ring closure processes involving N−H additions to C−C multiple bonds. We wish to report here the enantioselective total syntheses of (+)-pyrrolidine 197B[26] (**1**) and (+)-xenovenine[27] (**2**) implementing the IHC reaction as catalyzed by organolanthanide complexes.

Retrosynthesis. A retrosynthetic analysis is presented in Scheme 1. Our synthetic strategy includes three key stereogenic elements: (a) enantioselective formation of a primary amine adjacent to a chiral carbon center, (b) diastereoselective IHC of substrate **3**, and (c) tandem intramolecular hydroamination/bicyclization of substrate **4**. This overall strategy is based on our recent finding that the carbon atom bearing the amine functional group dictates the stereochemical course of this type of aminoallene cyclization process.[11]

Results and Discussion

Construction of Cyclization Substrates. The present synthetic strategy requires enantioselective construction of the cyclization precursors **3** and **4** (Scheme 1). As an entry point to aminoallene precursor **3**, we prepared enantiomerically pure

(12) For catalytic and synthetic organic applications of organolanthanide complexes, see: (a) Molander, G. A. *Chemtracts*: *Org. Chem.* **1998**, *11*, 237−263. (b) Taube, R. In *Applied Homogeneous Catalysis with Organometallic Complexes*; Cornils, B., Herrmann, W. A, Eds.; VCH: Weinheim, 1996; Vol. 2, pp 507−521. (c) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: San Diego, CA, 1994. (d) Molander, G. A. *Chem. Rev.* **1992**, *29*, 9−68.

(13) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 17−23.

(14) (a) Liddell, J. R. *Nat. Prod. Rep.* **1996**, *13*, 187−193. (b) Robins, D. J. *Nat. Prod. Rep.* **1994**, *11*, 613−619. (c) Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: Orlando, FL, 1986.

(15) Attygalle, A. B.; Morgan, D. E. *Chem. Soc. Rev.* **1984**, *13*, 245−278.

(16) Brown, K. S.; Trigo, J. R. in *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1995; Vol. 47, pp 227−354.

(17) (a) Daly, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 9−13. (b) Daly, J. W. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1998; Vol. 50, pp 141−169. (c) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1993; Vol. 44, pp 189−256.

(18) Daly, J. W.; Garraffo, H. M.; Spande, T. F.; Jaramillo, C.; Rand, A. S. *J. Chem. Ecol.* **1994**, *20*, 943−955.

(19) (a) Daly, J. W.; Spande, T. F.; Whittaker, N.; Highet, R. J.; Feigl, D.; Nishimori, N.; Tokuyama, T.; Myers, C. W. *J. Nat. Prod.* **1986**, *49*, 265−280. It has also been detected in the alkaloidal venoms of fire ants: (b) Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982**, *38*, 1949−1958. (c) Pedder, D. J.; Fales, H. M.; Jaouni, T.; Blum, M.; MacConnell, J.; Crewe, R. M. *Tetrahedron* **1976**, *32*, 2275−2279.

(20) Jones, T. H.; Blum, M. S.; Fales, H. M.; Thompson, C. R. *J. Org. Chem.* **1980**, *45*, 4778−4780.

(21) For discussion of the asymmetric synthesis of pyrrolizidine alkaloids, see: (a) Provot, O.; Lhommet, G.; Célerier, J.-P. *J. Heterocyclic Chem.* **1998**, *35*, 371−376. (b) Dai, W.-M.; Nagao, Y. *Heterocycles* **1990**, *30*, 1231−1261.

(22) Takahata, H.; Takehara, H.; Ohkubo, N.; Momose, T. *Tetrahedron: Asymmetry* **1990**, *1*, 561−566.

(23) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1991**, *56*, 1386-1393.

(24) Provot, O.; Célérier, P.; Petit, H.; Lhommet, G. *J. Org. Chem.* **1992**, *57*, 2163-2166.

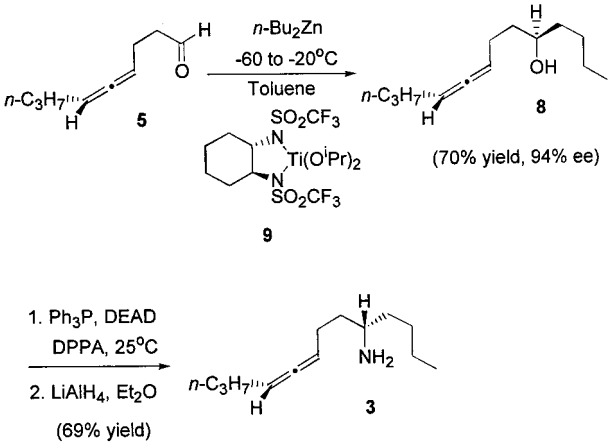
(25) Takahata, H.; Bandoh, H.; Momose, T. *J. Org. Chem.* **1992**, *57*, 4401−4404.

(26) For racemic syntheses, see: (a) Bäckvall, J.-E.; Schink, H. E.; Renko, Z. D. *J. Org. Chem.* **1990**, *55*, 826−831. (b) Gessner, W.; Takahashi, K.; Brossi, A.; Kowalski, M.; Kaliner, M. A. *Helv. Chim. Acta* **1987**, *70*, 2003−2010.

(27) For an asymmetric synthesis of **2** containing 12% of another diastereomeric product, see: (a) Arseniyadis, S.; Huang, P. Q.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 1391−1394. For racemic syntheses, see: ref 20 and (b) Vavrecka, M.; Janowitz, A.; Hesse, M. *Tetrahedron Lett.* **1991**, *32*, 5543−5546.

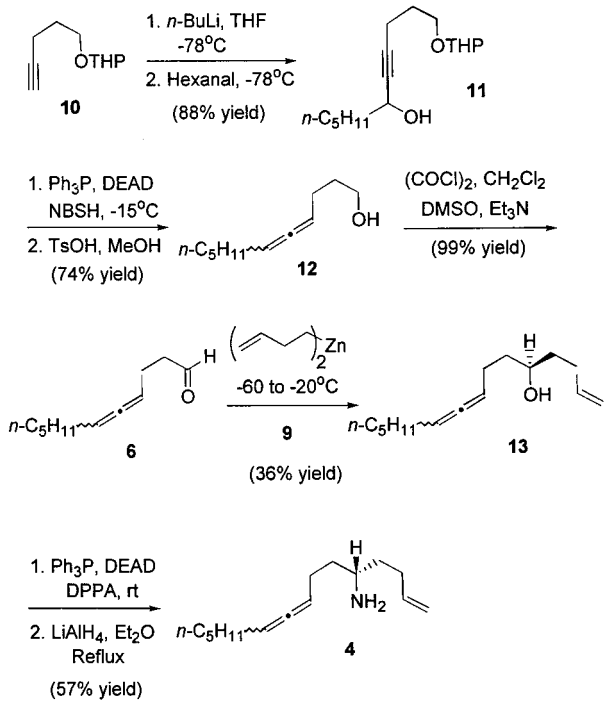
allene-aldehyde **5** from 4-pentyn-1-ol (**7**) in five steps.[11,28] Enantioselective addition of di-butylzinc[29] to **5** in the presence of bissulfonamide catalyst **9**[30] affords the (*R*)-secondary alcohol **8** in 70% yield (94% enantiomeric excess (ee), Scheme 2). Azide displacement of the free hydroxyl group under Mitsunobu conditions,[31] followed by LAH reduction to the amine, completes preparation of the desired aminoallene substrate **3** with inversion of configuration.

Scheme 2



The synthesis of aminoallene-alkene **4** is shown in Scheme 3. Treatment of **10** with *n*-butyllithium in tetrahydrofuran at −78 °C, followed by quenching with hexanal, provides the racemic propargylic alcohol **11**. Conversion of **11** to allenic alcohol **12** is accomplished in 74% yield (two steps) using the procedure of Myers and Zheng,[32] followed by Swern oxidation

Scheme 3

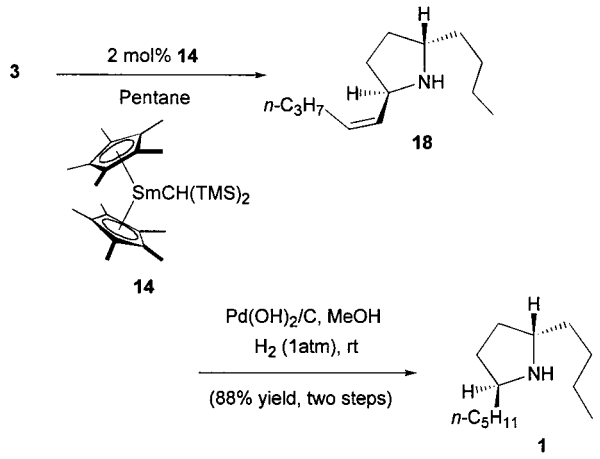


(28) See Supporting Information for experimental details.
(29) Noller, C. R. *Organic Syntheses*, 1942; Vol. II, pp 184−187.
(30) (a) Knochel, P. *Chemtracts: Org. Chem.* **1995**, *8*, 205−221. (b) Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095.
(31) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *18*, 1977−1980.

to afford aldehyde **6**. The sp^3-chiral center is set via the enantioselective addition of bis(3-butenyl)zinc[33] to aldehyde **6** in the presence of chiral catalyst **9** to furnish the hydroxy-eneallene **13**, which is stereospecifically converted to the (*S*)-amine substrate **4** in 57% yield as described above for **8**.

Cyclization and Synthesis Completion. The key step in the synthesis of **1** involves the regio- and diastereoselective IHC of **3** (Scheme 4). Thus, the catalytic ring closure of **3** is effected

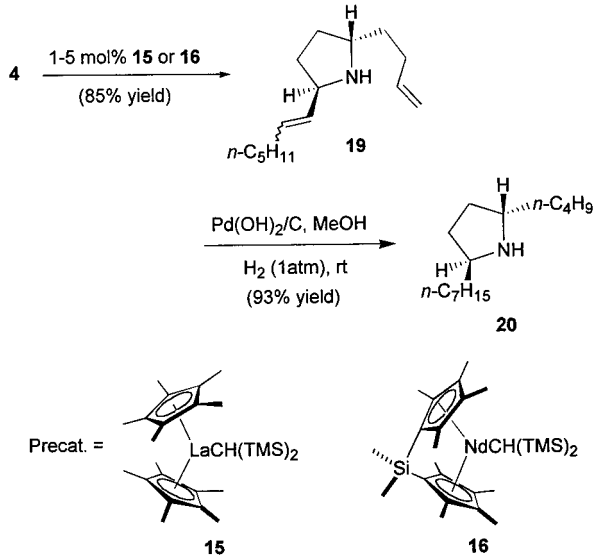
Scheme 4



by organolanthanide complex **14** in pentane solution at 23 °C, yielding the expected *trans*-pyrrolidine **18** bearing an exocyclic carbon−carbon double bond with excellent *Z* selectivity. Hydrogenation with $Pd(OH)_2/C$ led to pyrrolidine 197B (**1**) in 88% yield (two steps), $[\alpha]^{23}_D$ +6.1° (c 0.83, $CHCl_3$) [lit.[23] $[\alpha]^{27}_D$ +5.8° (c 0.79, $CHCl_3$)]. Comparison of the spectral properties of **1** to those reported in the literature[22,23] confirms the identity.

In contrast to the facile ring closure of **3** to form **18**, the stereoselective catalytic hydroamination/bicyclization of aminoallene-alkene **4** to (+)-xenovenine (**2**) proved more difficult to achieve (Scheme 5). For instance, **4** undergoes rapid reaction in the presence of precatalyst $Cp'_2LaCH(TMS)_2$ (**15**) at 23 °C yielding exclusively the corresponding *monocyclic* pyrrolidine

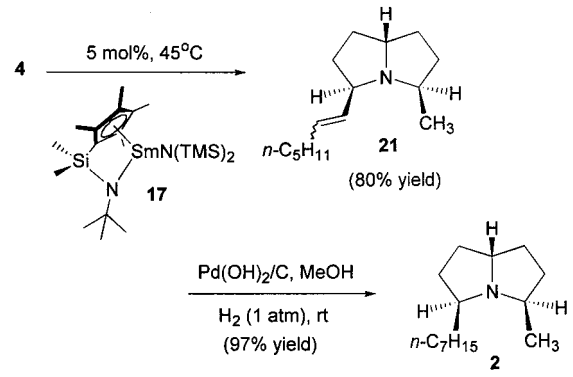
Scheme 5



(32) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492−4493.
(33) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363−4384.

19 via regioselective insertion−cyclization of the allene group into the Ln−N bond; no ^{1}H NMR indication of reaction with the alkene moiety was observed. Similar results were observed with the coordinatively more open[5c] organolanthanide complex $Me_2SiCp''_2NdCH(TMS)_2$ (**16**) at room temperature. Traces of a bicyclic intermediate are detected by ^{1}H NMR spectroscopy only in cases where the reactions are conducted at 60−80 °C.[34] Isolation of **19** by flash column chromatography and catalytic hydrogenation (1 atm) using $Pd(OH)_2$/C affords **20** in 79% yield (two steps).[35] In contrast, the "constrained geometry" organolanthanide complex $Me_2Si(Me_4C_5)(^tBuN)SmN(TMS)_2$ (**17**)[36] efficiently catalyzes the stereoselective tandem bicyclization of acyclic **4** to the bicyclic pyrrolizidine intermediate **21** under mild conditions (Scheme 6).[37] Finally, reduction of the exocyclic unsaturation using $Pd(OH)_2$/C and hydrogen (1 atm) furnishes (+)-xenovenine (**2**) in 78% yield (two steps). The spectroscopic properties of **2** (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]^{23}_D$, MS) agree in all respects with data reported in the literature.[24,25]

Scheme 6



Mechanistic Aspects of the IHC Reaction. On the basis of thermochemical considerations, substituent effects, metal ion effects, and kinetic studies of the organolanthanide-catalyzed IHC of aminoalkenes, aminoalkynes, and aminoallenes, we proposed a general mechanistic scenario for these transformations (e.g., Figure 1 for aminoallenes).[2,3,10] Kinetic and mechanistic data argue that the turnover-limiting step is intramolecular insertion of an unsaturated C−C linkage into the Ln−N bond (step i, Figure 1) of what is probably a labile amine−amido complex ($Cp'_2LnNHR(NH_2R)_x$).[2d] This insertion step is highly sensitive to modifications in the lanthanide coordination environment and/or to the steric demands that the unsaturated substrate moiety imposes. Thus, for the organolanthanide-catalyzed IHC of aminoalkenes, use of complexes with larger metal ionic radii and more open coordination spheres ($Cp'_2Ln \rightarrow Me_2SiCp''_2Ln$) results in increased reaction rates (increased turnover frequencies, N_t).[2d] However, the situation for aminoallene substrates is somewhat different, because the reaction exhibits maximum N_t values at metal ionic radii intermediate between the largest eight-coordinate lanthanide ionic radius, La^{3+} (1.160 Å) and the smallest, Lu^{3+} (0.977 Å).[10]

The rapid reaction of aminoallene **3** with precatalyst **14** cleanly generates *trans*-2-butyl-5-(1-pentenyl)pyrrolidine (**18**) as a 95:5 ratio of *Z*/*E* stereoisomers (Scheme 4). The observed

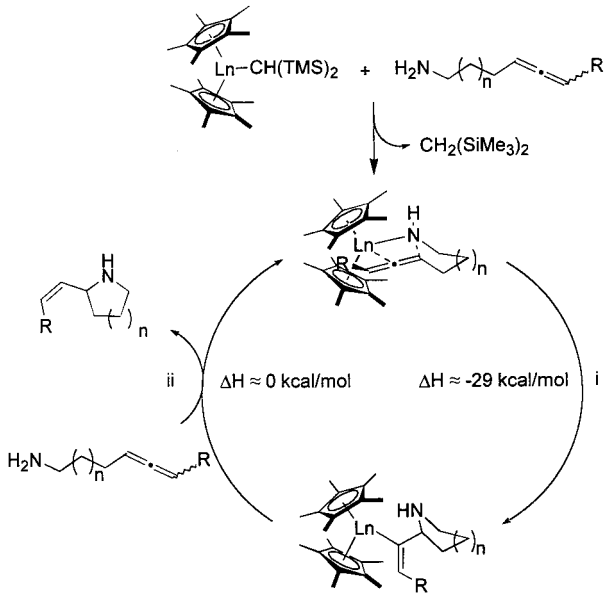


Figure 1. Simplified catalytic cycle for organolanthanide-catalyzed IHC of aminoallenes.

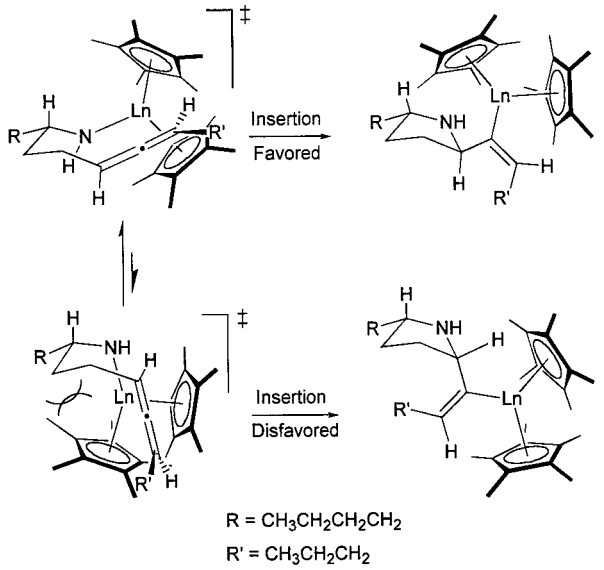


Figure 2. Plausible stereochemical pathway for the IHC of **3** to *trans*-2-butyl-5-(1-pentenyl)pyrrolidine (**18**) mediated by organolanthanide complex **14**.

trans-pyrrolidine diastereoselectivity can be rationalized by consideration of ligand−substrate nonbonded repulsions in the proposed transition-state structures shown in Figure 2. Interestingly, aminoallene-alkene substrate **4** undergoes *monocyclization* to the *trans*-2,5-disubstituted pyrrolidine **19** in the presence of lanthanocene precatalysts **15** and **16** (Scheme 5). The aborted insertion of the remaining terminal alkene moiety into the Ln−N bond (the organolanthanide hydroamination catalyst resting state)[2,3,11] is presumably due to repulsive interactions between the substrate alkyl substituents and the catalyst ancillary ligands. In contrast, the more open organolanthanide "constrained geometry" complex **17**[36] effects rapid, diastereoselective conversion to the desired bicyclic structure **21** (Scheme 6). The reaction of **4** with the diamagnetic precatalyst $Me_2Si(Me_4C_5)(^tBuN)YN(TMS)_2$ was closely monitored by ^{1}H NMR spectroscopy at 40 °C and at constant catalyst concentration (Figure 3).[38] The kinetic data clearly show that the allene moiety reacts significantly faster (~20 times) than its alkene counterpart. Thus, we

(34) Reactions are conveniently monitored by ^{1}H NMR spectroscopy.
(35) (*S*, *S*)-*trans*-2-Butyl-5-heptylpyrrolidine is an alkaloid isolated from *Solepnosis puctaticeps*, see ref 19c. For asymmetric syntheses, see: (a) Arseniyadis, S.; Huang, P. Q.; Piveteau, D.; Husson, H.-P. *Tetrahedron* **1988**, *44*, 2457−2470. (b) Shiosaki, K.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1229.
(36) Tian, S.; Arredondo, V. M.; Marks, T. J. *Organometallics*, in press.
(37) Identical results are obtained with $Me_2Si(Me_4C_5)(^tBuN)YN(TMS)_2$.

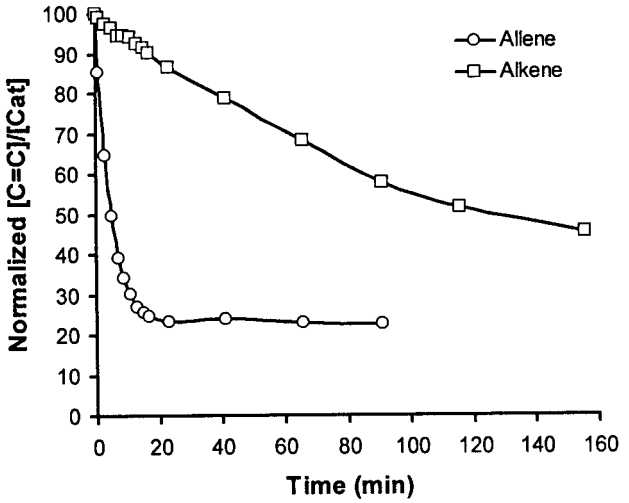


Figure 3. Normalized ratio of alkene and allene functionalities to precatalyst concentration as a function of time for the hydroamination/bicyclization of aminoallene−alkene (**4**) using $Me_2Si(Me_4C_5)(^tBuN)$-$YN(TMS)_2$ in benzene-d_6 at 40 °C. Lines through the data points are drawn as a guide to the eye.

propose that this bicyclization reaction proceeds as depicted in Figure 4. The first step is rapid protonolysis of the Ln−$N(TMS)_2$ bond to generate the catalytically active lanthanide−amido complex **I** and $HN(TMS)_2$. The latter species is observed immediately by NMR upon mixing of the substrate and precatalyst. In principle, complex **I** can exist in various energetically distinct conformations (such as **I**, **V**, and **VI**); however, on the basis of the present results, conformation **I** is favored for undergoing allene insertion to yield **II** (Figure 4). Intra- or intermolecular protonolysis of the Ln−C bond in **II** then provides the lanthanide−amido complex **III**, which undergoes further insertion of the alkene moiety into the Ln−N bond to yield **IV**. Finally, protonolysis of the Ln−C bond in **IV** completes the catalytic cycle and furnishes **21** with the desired observed stereochemistry.

Conclusions

The organolanthanide-catalyzed IHC reaction constitutes a valuable new tool for regio- and stereoselective construction of mono- and bicyclic alkaloid compounds, exemplified here by the total syntheses of pyrrolidine 197B (**1**) and (+)-xenovenine (**2**), respectively. The catalytic efficacy of the organolanthanide centers is highly sensitive to the electronic and steric characteristics of both the substrate and the catalyst. Thus, successful and general application of this methodology has benefited from the continued development of new, highly reactive, and selective organolanthanide complexes. The present results thus demonstrate that lanthanocenes are versatile precatalysts for the efficient insertion of unsaturated C−C linkages into Ln−N bonds, and thus for the construction of alkaloid natural products. Further studies of synthetic applications of this transformation are currently underway.

Experimental Section

Materials and Methods. All manipulations of air-sensitive materials were carried out with rigorous exclusion of oxygen and moisture in flame-dried Schlenk-type glassware on a dual-manifold Schlenk line interfaced to a high-vacuum line (10^{-6} Torr), or in a nitrogen-filled Vacuum Atmospheres glovebox with a high capacity recirculator (<1 ppm of O_2). Argon (Matheson, prepurified) was purified by passage through a MnO oxygen-removal column[39] and a Davison 4A molecular sieve column. All solvents were distilled before use under dry nitrogen over appropriate drying agents (sodium benzophenone ketyl, metal hydrides, Na/K alloy). Chloroform-*d*, benzene-d_6, and toluene-d_8 were purchased from Cambridge Isotope Laboratories. Benzene-d_6 and toluene-d_8 used for NMR reactions were stored in vacuo over Na/K alloy in resealable bulbs, and were vacuum transferred immediately prior to use. All organic starting materials were purchased from Aldrich Chemical Co., Farchan Laboratories Inc., or Lancaster Synthesis Inc., and were used without further purification unless otherwise stated. Cyclization substrates (5*S*,8*S*)-5-amino-trideca-8,9-diene (**3**), and (5*S*)-5-amino-pentadeca-1,8,9-triene (**4**) were used after purification by distillation (no drying step was required). Organolanthanide precatalysts $Cp'_2LnCH(TMS)_2$,[40] $Me_2SiCp''_2NdCH(TMS)_2$[5c] and $Me_2SiCp''(^tBuN)$-$LnN(TMS)_2$[36] (Ln = Sm, Lu, Y; Cp′= η^5-Me_5C_5; Cp″ = η^5-Me_4C_5; TMS = Me_3Si) were prepared by published procedures.

Physical and Analytical Measurements. NMR spectra were recorded on either a Varian Gemini, VXR 300 (FT, 300 MHz, ^{1}H; 75 MHz, ^{13}C), or Unity-400 (FT, 400 MHz, ^{1}H; 100 MHz, ^{13}C) instrument. Chemical shifts (δ) for ^{1}H and ^{13}C are referenced to internal solvent resonances and reported relative to $SiMe_4$. NMR experiments on air-sensitive samples were conducted in Teflon valve-sealed tubes (J. Young). Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN. Optical rotations were measured at 25 °C with an Optical Activity Ltd. AA-100 polarimeter (±0.001) using a 0.5 dm quartz cell. GC−MS analyses were performed using a Hewlett Packard HP6890 instrument with a HP-5MS (5% phenylmethylsiloxane, 30 m × 250 μm × 0.25 μm) capillary column and flame ionization detector (FID). The conditions were as follows: detector, 150 °C; injector, 250 °C; initial oven temperature, 55 °C for 3 min; 5° min^{-1} to 72 °C, hold for 0.1 min; 3° min^{-1} to 87 °C, hold for 0.1 min; then 40° min^{-1} to 270 °C. High-resolution mass spectrometry (HRMS) studies were conducted on a VG 70−250 SE instrument with 70 eV electron impact ionization. IR spectra were recorded using a BioRad FT S60 FTIR instrument. Boiling points are uncorrected.

(5*R*,8*S*)-Trideca-8,9-diene-5-ol (8). A 50 mL three-necked flask equipped with an argon inlet, a thermometer, and a septum cap was charged with dry toluene (19 mL), $Ti(O^iPr)_4$ (21.5 g, 75.5 mmol), and (1*S*,2*S*)-1,2-bis[(trifluoromethyl)sulfonamido]-cyclohexane (1.1 g, 3.0 mmol). The reaction mixture was heated to 40−45 °C for 0.5 h and then cooled to −60 °C; dibutylzinc[29] in toluene (17 mL) was then added, followed after 5 min by aldehyde **5**[28] (5.2 g, 37.8 mmol). The reaction mixture was stirred for 2 h at −60 °C and 4 h at −20 °C. The reaction mixture was then quenched with a 10% HCl solution and extracted with ether. The aqueous phase was extracted twice with ether, and the combined organic phase was washed successively with a saturated aqueous $NaHCO_3$ solution (2 × 100 mL) and brine (1 × 50 mL), and was dried over $MgSO_4$. After filtration and evaporation of the solvent, the residual oil was purified by flash column chromatography on silica gel (10% ether in pentane), affording 5.2 g (69% yield) of a light yellow oil (94% ee; Mosher ester analysis). $[\alpha]^{23}_D$ +64.9° (c 1.6, $CHCl_3$); IR (KBr, thin film): ν_{max} = 3342, 2958, 2930, 2870, 1962, 1457, 1378, 1127, 1053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08 (m, 2H), 3.63 (m, 1H), 2.14−2.02 (m, 2H), 1.98−1.89 (m, 2H), 1.59−1.26 (m, 11H), 0.92−0.86 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.8, 91.2, 90.4, 71.3, 37.1, 36.5, 31.0, 27.8, 25.1, 22.7, 22.3, 14.0, 13.6; HRMS (*m*/*z*): [M^+] calcd for $C_{13}H_{24}O$, 196.18271; found, 196.18263. Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.55; H, 12.49.

(5*S*,8*S*)-5-Amino-trideca-8,9-diene (3). To a solution of **8** (4.8 g, 24.3 mmol) in dry tetrahydrofuran (THF) (300 mL) was added PPh_3 (12.8 g, 48.7 mmol), diethyl azodicarboxylate (DEAD) (8.5 g, 48.7 mmol), and diphenylphosphoryl azide (13.4 g, 48.7 mmol). The reaction mixture was stirred for 30 min, then concentrated by rotary evaporation, and filtered through a plug of Celite, washing with 1:1 ether/pentane. The filtrate was concentrated by rotary evaporation and the residue

(38) Allene (CH=C=CH, $\delta \sim$ 5.2 ppm) and alkene (CH_2=CH, $\delta \sim$ 5.0 ppm) ^{1}H resonances were normalized to the signal of the stoichiometrically generated $HN(TMS)_2$ byproduct ($\delta \sim$ 0.1 ppm).

(39) (a) He, M. Y.; Toscano, P. J.; Burwell, R. L.; Marks, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 641−652. (b) McIlwrick, C. R.; Phillips, C. S. G. *J. Chem. Phys., E*. **1973**, *6*, 1208−1210.

(40) Jeske, G.; Lauke, H.; Mauermann, H.; Swepston, P. N.; Schumann, H.; Marks, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 8091−8103.

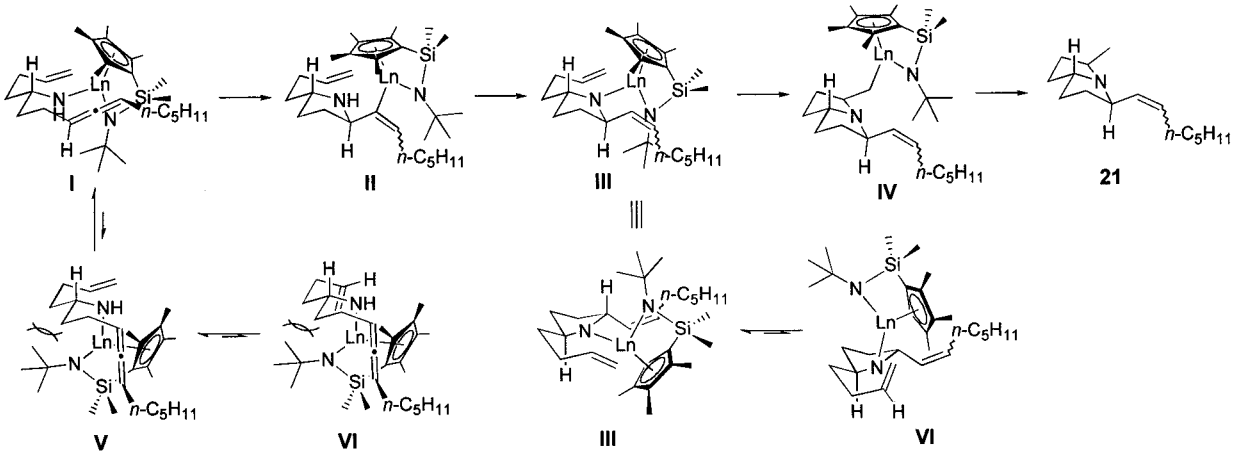


Figure 4. Probable reaction mechanism and stereochemical scenario for the bicyclization of aminoallene−alkene substrate **4** mediated by precatalyst **17**.

was purified by flash chromatography on silica gel (10% ether in pentane), yielding 4.1 g (75% yield) of the azide as a light yellow oil. $R_f = 0.88$ (20% ether in pentane). IR (KBr, thin film): $\nu_{max} = 2959$, 2932, 2865, 2097, 1963, 1465, 1258 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08 (m, 2H), 3.30 (quint, $J = 6.6$ Hz, 1H), 2.13−2.02 (m, 2H), 1.99−1.91 (m, 2H), 1.62−1.30 (m, 10H), 0.93−0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.1, 91.6, 89.7, 62.3, 34.1, 33.6, 31.0, 28.2, 25.3, 22.5, 22.4, 13.9, 13.6. A suspension of $LiAlH_4$ (1.4 g, 36.5 mmol) in ether (50 mL) was stirred while a solution of this azide (4.1 g, 18.8 mmol) in dry ether (25 mL) was added dropwise at a rate so as to maintain a gentle reflux. When addition was complete, reflux was continued for 24 h. The reaction mixture was then cooled to room temperature and quenched by the sequential addition of water (1.5 mL), a 15% solution of NaOH (1.5 mL), and water (4.5 mL). The white precipitate which formed was filtered off and washed with ether. The filtrate was dried over Na_2SO_4, filtered, the solvent evaporated, and the product purified by vacuum distillation (bp 135−136 °C/1 mmHg), yielding **3** as a colorless liquid (3.4 g, 92% yield). $[\alpha]^{23}_D$ +26.6° (c 2.0, $CHCl_3$); IR (KBr, thin film): $\nu_{max} = 3373$, 3303, 2958, 2929, 2859, 1962, 1465, 1378 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.05 (m, 2H), 2.73 (m, 1H), 2.15−1.90 (m, 4H), 1.58−1.25 (m, 12H), 0.92−0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.8, 91.0, 90.4, 50.5, 37.7, 37.3, 31.0, 28.3, 25.6, 22.8, 22.3, 14.0, 13.6; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{25}N$, 195.19870; found, 196.19874. Anal. Calcd for $C_{13}H_{25}N$: C, 79.93; H, 12.90; N, 7.17. Found: C, 79.73; H, 12.95; N, 7.13.

1-(Tetrahydropyran-2-yloxy)-undec-4-yn-6-ol (11). Compound **10** (21.1 g., 125.7 mmol) and THF (300 mL) were placed in a dried three-necked, round-bottom flask equipped with magnetic stirrer, addition funnel, low-temperature thermometer, and N_2 inlet. The stirring solution was cooled to −78 °C and a 1.6 M *n*-BuLi solution (86.4 mL, 138.3 mmol) was added dropwise while the temperature was maintained equal to or below −70 °C. The reaction mixture was stirred at −78 °C for 1 h. Hexanal (13.2 g, 132.0 mmol) was then added dropwise at −78 °C. After addition was complete, the mixture was stirred for an additional 15 min at −78 °C then was warmed slowly to room temperature, and the reaction was then quenched with saturated NH_4Cl solution. The aqueous layer was separated and extracted with ether (2 × 100 mL). The combined organic layer was dried over Na_2SO_4, filtered, and the solvent removed in vacuo yielding a yellow liquid. Flash column chromatography on silica gel (20% ether in pentane) afforded pure alcohol **11** (24.5 g, 88% yield). $R_f = 0.09$; IR (KBr, thin film): $\nu_{max} =$ 3427, 2930, 2854, 2236, 1441, 1322, 1138, 990 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.57 (t, $J = 3.4$ Hz, 1H), 4.31 (tt, $J = 6.5$, 1.9 Hz, 1H), 3.87−3.76 (m, 2H), 3.52−3.41 (m, 2H), 2.31 (dt, $J = 7.1$, 1.9 Hz, 2H), 1.77 (quintet, $J = 6.6$ Hz, 4H), 1.69−1.26 (m, 13H), 0.87 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.7, 84.5, 81.8, 65.8, 62.6, 62.1, 38.1, 31.4, 30.6, 28.8, 25.4, 24.9, 22.5, 19.4, 15.5, 14.0; HRMS (*m*/*z*): $[M-H]^+$ calcd for $C_{16}H_{28}O_3$, 267.1961; found, 267.1965.

4,5-Undecadien-1-ol (12). A 1 L Schlenk flask equipped with magnetic stirrer and low-temperature thermometer was charged with Ph_3P (30.9 g, 117.9 mmol), THF (450 mL), and **11** (24.3 g, 90.7 mmol). The solution was cooled to −15 °C and DEAD (20.5 g, 117.9 mmol) was added dropwise at −15 °C. After addition was complete, stirring was continued for 2.5 h. To the resulting yellow solution, nitrobenzenesulfonyl hydrazide (NBSH) (25.6 g, 117.9 mmol; dissolved in 200 mL of dry THF) was added dropwise at −15 °C. The reaction mixture was maintained at −15 °C and stirred for 4 h, then was allowed to warm to room temperature overnight. The resulting orange solution was concentrated, cooled to 0 °C, and the precipitated solid was filtered off and washed with cold ethyl acetate. Concentration of the filtrate and purification of the residue by flash column chromatography on silica gel (20% ether in pentane) afforded the protected allenic alcohol as a yellow liquid (16.9 g, 74% yield). $R_f = 0.76$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07 (m, 2H), 4.56 (t, $J = 3.6$ Hz, 1H), 3.88−3.81 (m, 1H), 3.79−3.71 (m, 1H), 3.51−3.36 (m, 2H), 2.08−2.01 (m, 2H), 1.99−1.91 (m, 2H), 1.82−1.64 (m, 4H), 1.40−1.25 (m, 6H), 0.86 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.8, 98.8, 98.7, 91.4, 90.3, 66.9, 66.8, 62.2, 31.3, 30.7, 29.1 (2C), 28.9, 28.8, 25.6, 25.5, 22.5, 19.6, 14.1; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{28}O_2$, 252.20892; found, 252.20839. To a solution of this product (16.9 g, 67.0 mmol) in MeOH (150 mL) was added TsOH (50 mg). The resulting mixture was stirred at room temperature until TLC analysis (50% ether in pentane) showed complete deprotection. Solvent was then removed in vacuo; the residue was then diluted with ether, washed with a 10% solution of Na_2CO_3, and dried over Na_2SO_4. Subsequent filtration and evaporation of the solvent yielded a yellowish liquid. Flash column chromatography on silica gel (30% ether in pentane) afforded **12** (11.1 g, 98% yield). $R_f =$ 0.29; IR (thin film): $\nu_{max} = 3331$, 2956, 2930, 2857, 1961, 1449, 1378, 1058 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.08 (apparent quintet, 2H), 3.67 (t, $J = 6.5$ Hz, 2H), 2.08−2.02 (m, 2H), 1.97−1.90 (m, 2H), 1.67 (quintet, $J = 7.1$ Hz, 2H), 1.40−1.25 (m, 7H), 0.87 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.7, 91.5, 90.1, 62.2, 31.9, 31.3, 28.8 (2C), 25.1, 22.4, 14.0; Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98; Found: C, 78.52; H, 11.91.

4,5-Undecadienal (6). While a solution of oxalyl chloride (37.3 mL, 74.5 mmol) dissolved in CH_2Cl_2 (150 mL) at −78 °C was stirred, dimethyl sulfoxide (DMSO) (10.6 mL, 149.0 mmol) dissolved in CH_2Cl_2 (20 mL) was added over a period of 20 min. After the solution was stirred for an additional 1 h, **12** (10.9 g, 64.8 mmol) dissolved in CH_2Cl_2 (30 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 1.5 h. Triethylamine (45.1 mL, 324.0 mmol) was then added dropwise at −78 °C, the reaction mixture was stirred for an additional 1 h, and then allowed to warm to 10 °C. Water (300 mL) was added and the two layers separated. The aqueous layer was acidified with 1% aqueous HCl (saturated with NaCl) and then back-extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with 1% aqueous HCl (saturated with NaCl, 6 × 100 mL) followed by 5% aqueous $NaHCO_3$ solution (2 × 50 mL). The aqueous extracts were back-extracted with CH_2Cl_2 (2 × 70 mL) and the combined organic extracts were washed with brine and dried over Na_2SO_4. After filtration, the solvent was removed by rotary evaporation to give the title

compound as a yellow liquid (10.6 g, 99% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.78 (t, J = 1.5 Hz, 1H), 5.14 (apparent quintet, 2H), 2.52 (t, J = 7.0 Hz, 2H), 2.33−2.25 (m, 2H), 1.96−1.90 (m, 2H), 1.38−1.29 (m, 6H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.7, 201.9, 92.9, 89.2, 42.3, 31.2, 28.7 (2C), 22.4, 21.2, 13.9; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{11}H_{18}O$, 166.13577; found, 166.13582.

(5*R*)-Pentadeca-1,8,9-triene-5-ol (13). From 2.1 g of **6**, 1.0 g of **13** was obtained (36% yield) after chromatographic separation (20% ether in pentane) using the same procedure as for **8**, but with bis(3-butenyl)zinc.[33] $[\alpha]^{23}_D$ +2.4° (c 0.41, $CHCl_3$); IR (KBr, thin film): ν_{max} = 3342, 2962, 2929, 2870, 1962, 1457, 1375, 1335, 1127, 876 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89−5.76 (m, 1H), 5.08 (m, 2H), 5.01−4.94 (m, 2H), 3.67 (m, 1H), 2.22−2.02 (m, 4H), 1.99−1.91 (m, 2H), 1.62−1.23 (m, 11H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.8, 138.6, 114.8, 91.6, 90.4, 70.9, 36.6, 36.4, 31.2, 30.1, 28.9 (2C), 25.1, 22.5, 14.1; HRMS (*m*/*z*): $[M-1]^+$ calcd for $C_{15}H_{26}O$, 221.19042; found, 221.19026.

(5*S*)-5-Amino-pentadeca-1,8,9-triene (4). From 942.4 mg of **13**, 538.7 mg of **4** was obtained (57% yield) after high-vacuum distillation using the same procedure as for **3**. $[\alpha]^{23}_D$ −49.4° (c 2.0, $CHCl_3$); IR (KBr, thin film): ν_{max} = 3373, 3303, 2957, 2926, 2871, 2855, 1961, 1641, 1467, 1451, 1378, 910 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87−5.73 (m, 1H), 5.06 (m, 2H), 4.99−4.91 (m, 2H), 2.76 (m, 1H), 2.18−1.91 (m, 6H), 1.58−1.44 (m, 2H), 1.41−1.21 (m, 10H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.7, 138.7, 114.5, 91.4, 90.5, 50.1, 37.3, 37.1, 31.3, 30.5, 28.9 (2C), 25.6, 22.5, 14.1; HRMS (*m*/*z*): $[M+1]^+$ calcd for $C_{15}H_{27}N$, 222.2222; found, 222.2226. Anal. Calcd for $C_{15}H_{27}N$: C, 81.38; H, 12.29; N, 6.33. Found: C, 80.68; H, 12.17; N, 6.05.

(2*S*,5*S*)-*trans*-2-Butyl-5-pentylpyrrolidine [(+)-Pyrrolidine 197B] (1). In the glovebox, **14** (15 mg, 25.8 μmol) was loaded into a storage tube equipped with magnetic stir bar and J. Young Teflon valve. At −78 °C, pentane (1.5 mL) was vacuum-transferred onto the catalyst, and **3** (264.5 mg, 1.35 mmol) was syringed in. The clear yellow solution was then stirred for 1 h at ambient temperature. The reaction mixture was next loaded onto a short column of silica gel and eluted with ether yielding (2*S*,5*S*)-*trans*-2-butyl-5-(1)-pentenylpyrrolidine (**18**) as a 95:5 mixture of *Z*/*E* isomers. ^{1}H NMR (300 MHz, $CDCl_3$) *Z*-isomer: δ 5.36 (m, 2H), 4.01 (m, 1H), 3.18 (m, 1H), 2.52 (br s, 1H), 2.06−1.92 (m, 4H), 1.48−1.23 (m, 10H), 0.87 (t, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.1, 130.5, 58.2 (2C), 36.5, 33.2, 32.5 (2C), 29.5, 22.9, 22.8, 14.1, 13.8; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{25}N$, 195.1987; found, 195.1983. A solution of this pyrrolidine in MeOH (3 mL) was hydrogenated over $Pd(OH)_2$/C (10 mg) for 2 h at 1 atm of H_2 pressure. The reaction mixture was then filtered through a short plug of Celite and washed with ether. The solvent was removed in vacuo to yield **1** (234.4 mg, 88%) as a pale yellow liquid. $[\alpha]^{23}_D$ +6.1° (c 0.83, $CHCl_3$); IR (KBr, thin film): ν_{max} = 3340, 2965, 2728, 1467, 1375 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27 (br s, 1H), 3.17 (m, 2H), 1.93 (m, 2H), 1.53 (m, 2H), 1.56−1.24 (m, 14H), 0.83 (t, J = 6.9 Hz, 3H), 0.81 (t, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 58.0, 57.9, 37.1, 36.8, 32.5 (2C), 32.0, 29.5, 27.0, 22.8, 22.6, 14.1, 14.0; HRMS (*m*/*z*): $[M-1]^+$ calcd for $C_{13}H_{27}N$, 196.2066; found, 196.20671.

(2*S*,5*S*)-2-Butyl-5-heptylpyrrolidine (20). In the glovebox, **15** (or **16**) (4.6 mg, 8.1 μmol) and C_6D_6 (~700 μL) were loaded into an NMR tube equipped with a Teflon valve. On the high-vacuum line, the tube was evacuated when the precatalyst solution was frozen. Under a stream of Ar gas, **4** (20 mg, 90.4 μmol) was then syringed in. The tube was sealed and the frozen reaction mixture was warmed to room temperature. After the mixture was shaken, the progress of the reaction in the clear, colorless solution was monitored by ^{1}H NMR spectroscopy. Upon reaction completion (<15 min), the reaction mixture was next loaded onto a short column of silica gel and eluted with ether affording **19** (17 mg, 85% yield) as a ~2.5:1 mixture of *Z*/*E* isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87−5.73 (m, 1H), 5.54−5.32 (m, 2H), 5.02−4.89 (m, 2H), 3.97 and 3.59 (m, 1H), 3.16 (m, 1H), 2.10−1.90 (m, 6H), 1.66 (br s, 1H), 1.52−1.21 (m, 10H), 0.85 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 133.1, 130.7, 114.4, 59.9, 57.4, 36.5, 33.1, 32.3, 32.2, 31.6, 31.4, 29.0, 22.5, 14.1 and 138.7, 133.5, 130.4, 114.4, 57.5, 54.1, 36.3, 33.4, 32.5, 31.4, 30.3, 29.5, 27.4, 14.1; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{27}N$, 221.21436; found, 221.21376. A solution of **19** in MeOH (2 mL) was hydrogenated over $Pd(OH)_2$/C (2 mg) for 2 h at 1 atm of H_2 pressure. The reaction mixture was then filtered through a short plug of Celite and washed with ether. The solvent was removed in vacuo to yield **20** (16 mg, 93%) as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.10 (m, 2H), 1.93 (m, 2H), 1.82 (br s, 1H), 1.34−1.21 (m, 20H), 0.89 (t, J = 6.5 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 58.0 (2C), 37.1, 36.9, 32.5, 31.8, 30.3, 29.8, 29.5, 29.3, 27.3, 22.9, 22.7, 14.1 (2C); HRMS (*m*/*z*): $[M-1]^+$ calcd for $C_{13}H_{31}N$, 224.23782; found, 224.23823.

(3*S*,5*R*,8*S*)-3-Heptyl-5-methylpyrrolizidine (2) [(+)-Xenovenine]. In the glovebox, **17** (4.7 mg, 8.8 μmol) and C_6D_6 (~700 μL) were loaded into an NMR tube equipped with a Teflon valve. On the high-vacuum line, the tube was evacuated after the precatalyst solution was frozen. Under a stream of Ar gas, **4** (50 mg, 226 μmol) was then syringed in. The tube was sealed and the frozen reaction mixture was warmed to room temperature. After the mixture was shaken, the clear yellow solution was then warmed to 45 °C. When the reaction was complete (overnight),[34] the contents were loaded onto a short column of silica gel and eluted with ether yielding **21** as a 1:1 mixture of *Z*/*E* isomers. A solution of **21** in MeOH (2 mL) was next hydrogenated over $Pd(OH)_2$/C (2 mg) for 2 h at 1 atm of H_2 pressure. The reaction mixture was filtered through a short plug of Celite and washed with ether. The solvent was removed in vacuo to yield **2** (39.3 mg, 78%) as a pale yellow liquid. $[\alpha]^{23}_D$ +10.9° (c 0.72, $CHCl_3$) [lit. $[\alpha]^{24}_D$ +11.7° (c 0.69, $CHCl_3$);[25] $[\alpha]^{22}_D$ +6.6° (c 2.35, $CHCl_3$)[24]]; IR (KBr, thin film): ν_{max} = 2963, 2932, 2872, 1462, 1370 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (m, 1H), 2.77 (m, 1H), 2.61 (m, 1H), 2.01−1.82 (m, 4H), 1.56−1.17 (m, 16H), 1.10 (d, J = 6.6 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.7, 65.1, 61.8, 36.9, 34.4, 32.4, 32.0, 31.9, 31.7, 29.8, 29.3, 27.2, 22.7, 21.7 14.1; HRMS (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{29}N$, 223.23000; found, 223.22950.

In Situ Kinetic Study of Hydroamination/Bicyclization Reaction. In the glovebox, the $Me_2SiCp''(^tBuN)YN(TMS)_2$ precatalyst (ca. 3.3 mg, 6.6 μmol) was weighed into an NMR tube equipped with a Teflon valve. On the high-vacuum line, the tube was evacuated, C_6D_6 (700 μL) was vacuum transferred into the tube, and (5*S*)-5-amino-pentadeca-1,8,9-triene (**4**) (18 mg, 81.3 μmol) was syringed in. The tube was then sealed and maintained at −78 °C until kinetic measurements were begun. The sample tube was inserted into the probe of the Unity-400 spectrometer which had been previously set to 40 °C temperature (T ± 0.2 °C; ethylene glycol temperature standard). Data were acquired using two scans per time interval with a long pulse delay (10 s) to avoid signal saturation. The kinetics were monitored from intensity changes in the substrate allenic and olefinic resonances. The relative concentration of either functional group was measured from the allenic and olefinic peak area, standardized to the area of the free $HN(TMS)_2$ formed as turnover commenced.

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Supporting Information Available: Detailed synthetic procedures and analytical data for aldehyde **5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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