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Determining the Scope of the Organolanthanide-Catalyzed, Sequential Intramolecular Amination/Cyclization Reaction: Formation of Substituted Quinolizidines, Indolizidines, and Pyrrolizidines

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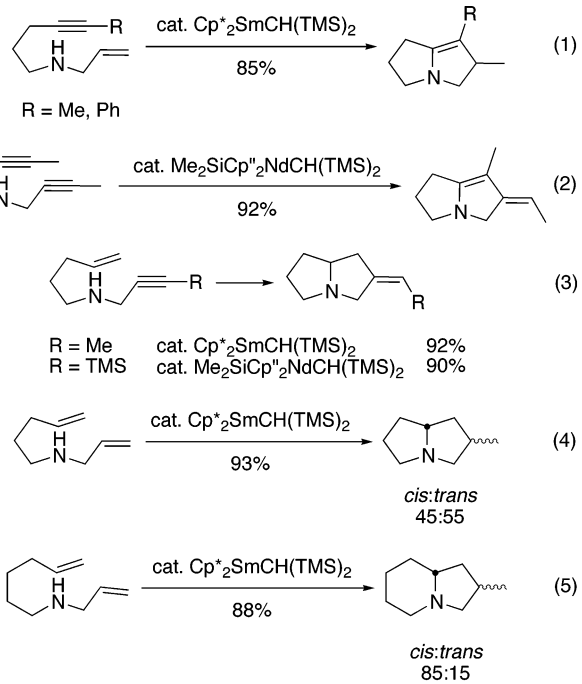
The scope of the lanthanide-mediated, intramolecular amination/cyclization reaction was determined for the formation of substituted quinolizidines, indolizidines, and pyrrolizidines. A methyl group was installed at diverse positions in the substrates to determine the sense and magnitude of diastereoselection. High diastereoselectivity (>20:1) was achieved for the formation of some quinolizidines and indolizidines. The sense of relative asymmetric induction was contrary to previously studied systems, and although some questions remain, a rationalization for these results is put forward.

Introduction

Cascade reactions involving the formation of multiple ring systems in a single operation have proven to be among the most powerful in the arsenal of synthetic organic chemists. However, the utility of these reactions cannot be fully realized until the scope of the reaction in question is outlined. The lanthanide-catalyzed sequential reaction of amino dienes is one such potentially useful transformation. Li and Marks first developed this elegant process.[1] In a thorough study, they have shown that lanthanide complexes possess a unique reactivity. Unlike other metal-catalyzed intramolecular amination reactions, the organometallic formed after the initial nitrogen−carbon bond-forming event can insert into a carbon−carbon multiple bond to form indolizidines and pyrrolizidines (Scheme 1).

Although a few reactions were performed that shed light on the stereochemical aspects of these reactions, much remained undone. Additionally, while the synthesis of pyrrolizidines and indolizidines was studied to a limited extent (eqs 1−5), bicyclic systems from the quinolizidine family were not examined.



Because numerous biologically active alkaloids contain the pyrrolizidine and indolizidine motif (Figure 1), the application of this method toward their synthesis would be very appealing.[2] From relatively simple starting

(1) (a) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757. For other aspects of the hydroamination reaction, see: (b) Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108. (c) Gagné, M. R.; Nolan, S. P.; Marks, T. J. *Organometallics* **1990**, *9*, 1716. (d) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275. (e) Gagné, M. R.; Brard, L.; Conticello, V. P.; Giardello, M. A.; Stern, C. L.; Marks, T. J. *Organometallics* **1992**, *11*, 2003. (f) Li, Y.; Fu, P.-F.; Marks, T. J. *Organometallics* **1994**, *13*, 439. (g) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 707. (h) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770. (i) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295. (j) Giardello, M. A.; Conticallo, V. P.; Brard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241. (k) Tian, S.; Arredondo, V. M.; Stern, C. L.; Marks, T. J. *Organometallics* **1999**, *18*, 2568. (l) Bürgstein, M. R.; Berberich, H.; Roesky, P. W. *Organometallics* **1998**, *17*, 1452. (m) Kim, Y. K.; Livinghouse, T.; Bercaw, J. E. *Tetrahedron Lett.* **2001**, *42*, 2933. (n) Gilbert, A. T.; Davis, B. L.; Emge, T. J.; Broene, R. D. *Organometallics* **1999**, *18*, 2125. (o) Kim, Y. K.; Livinghouse, T.; Horino, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9560 and references therein. For reviews on the application of lanthanocenes in organic synthesis, see: (p) Molander, G. A.; Dowdy, E. D. In *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer-Verlag: Berlin, 1999. (q) Molander, G. A.; Romero, J. A. C. *Chem. Rev.* **2002**, *102*, 2161.

(2) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; John Wiley & Sons Ltd.: Chichester, 1997.

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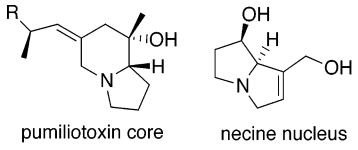
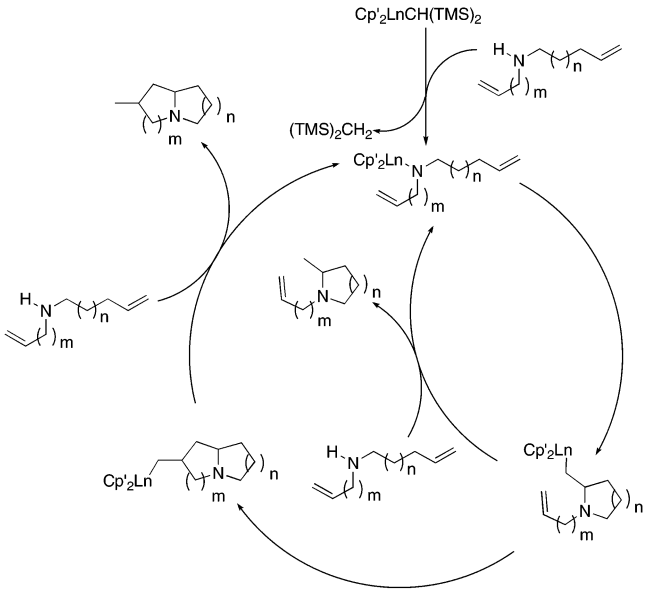


FIGURE 1. Representative indolizidine and pyrrolizidine alkaloids.

SCHEME 1



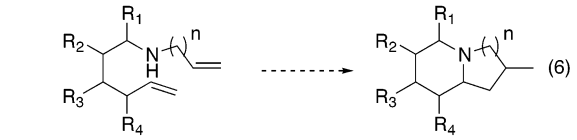
materials, one can form two fused rings in a single synthetic operation. However, to apply this method, its reliability and stereochemical outcomes given a diverse array of substrate substitution patterns needed to be determined. In addition, this potentially important method would further benefit by its application to the previously unexamined, but more prevalent, quinolizidine ring system.[2]

Herein, we describe our efforts to outline the scope and limitations of the Marks process as applied to the synthesis of a variety of nitrogen fused bicyclic systems, with particular focus on the stereochemical aspects of the reaction in the formation of diverse bicyclics.

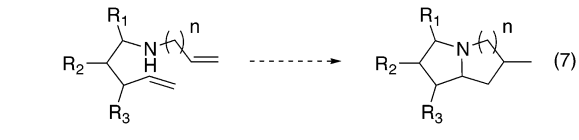
Results and Discussion

To initiate our studies, an extensive set of amino dienes was constructed to examine the scope of the process. A methyl group was installed at various positions in the cyclization substrates (eqs 6 and 7) to determine the diastereoselectivity of the sequential reaction. The methyl group was chosen because of the ease of preparation of the substrates. Furthermore, if steric effects proved to be the major factor in establishing the diastereoselectivity, the methyl group would provide a "worse case scenario" because of its relatively small size.

The synthesis of the HCl salts of substrates **10**−**13** and **15** (eq 8) was accomplished by modifying a procedure outlined by Fürstner.[3] The workup and yields of this method proved to be superior to the reported procedure used to make substrate **14**.[4] Purification by flash chromatography of the HCl salts, using 2-propanol/EtOAc as

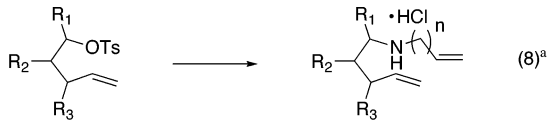


n = 2	n = 1	n = 2	n = 1
Methyl Position:	Methyl Position:	Methyl Position:	Methyl Position:
− = **1**	R_1 = **6**	− = **16**	R_1 = **21**
R_1 = **2**	R_2 = **7**	R_1 = **17**	R_2 = **22**
R_2 = **3**	R_3 = **8**	R_2 = **18**	R_3 = **23**
R_3 = **4**	R_4 = **9**	R_3 = **19**	R_4 = **24**
R_4 = **5**		R_4 = **20**	



n = 2	n = 1	n = 2	n = 1
Methyl Position:	Methyl Position:	Methyl Position:	Methyl Position:
R_1 = **10**	R_1 = **13**	R_1 = **25**	R_1 = **28**
R_2 = **11**	R_2 = **14**	R_2 = **26**	R_2 = **29**
R_3 = **12**	R_3 = **15**	R_3 = **27**	R_3 = **30**

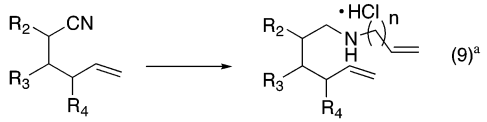
eluent, also allowed recovery of the allylamine or homoallylamine hydrochloride.



n = 2	n = 1	n = 2	n = 1
Methyl Position:	Methyl Position:	Methyl Position:	Methyl Position:
R_1 = **31**	R_1 = **10**	R_1 = **13**	
R_2 = **32**	R_2 = **11**	R_2 = **14**[b]	
R_3 = **33**	R_3 = **12**	R_3 = **15**	

[a](i) 3 equiv of allylamine (n=1) or homoallylamine (n=2), THF, 60 to 70 °C; (ii) HCl in Et_2O (70-72%).
[b](i) 2 equiv of allylamine, NaI, DMSO; (ii) HCl in Et_2O (17%).

One-carbon homologation of the tosylates with NaCN generated nitriles **36**−**38** (eq 9).[5] The known nitrile **35**



n = 2	n = 1	n = 2	n = 1
Methyl Position:	Methyl Position:	Methyl Position:	Methyl Position:
− = **35**	− = **1**	R_2 = **7**	
R_2 = **36**	R_2 = **3**	R_3 = **8**	
R_3 = **37**	R_3 = **4**	R_4 = **9**	
R_4 = **38**	R_4 = **5**		

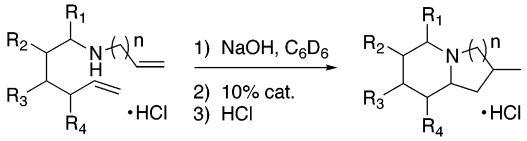
[a](i) DIBALH, Et_2O, -78 °C; (ii) allylamine (n=1) or homoallylamine (n=2) hydrochloride, Et_2O; (iii) LAH, -78 °C; (iv) HCl in Et_2O (20-80%).

was prepared via a literature procedure from the commercially available bromide.[6] A modified procedure out-

(3) Fürstner, A.; Langemann, K. *Synthesis* **1997**, *7*, 792.

(4) Martin, S. F.; Benage, B.; Williamson, S. A.; Brown, S. P. *Tetrahedron* **1986**, *42*, 2903.
(5) Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **1999**, *55*, 4583.
(6) Glover, S. A.; Hammond, G. P.; Harman, D. G.; Mills, J. G.; Rowbottom, C. A. *Aust. J. Chem.* **1993**, *46*, 1213.

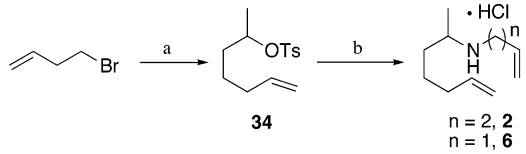
TABLE 1. Organolanthanide-Catalyzed Formation of Quinolizidines and Indolizidines



entry	substrate	product	methyl position	catalyst[a]	*T* (°C)	dr[b]	% isolated yield
	n = 2						
1	**1**	**16**		**I**	rt	>50:1	85[c]
2	**2**	**17**	R_1	**I**	70	nr	nr
3				**IV**	70	>50:1[d]	*d*
4				**III**	40	>2.5:1	91
5	**3**	**18**	R_2	**I**	50	>20:1	90
6				**I**	50	>20:1[e]	90[e]
7				**IV**	90	nr	nr
8	**4**	**19**	R_3	**I**	rt	1:1.3	86
9	**5**	**20**	R_4	**I**	rt	1:1.9	89
	n = 1						
10	**6**	**21**	R_1	**II**	50	8.3:1.3:1	87
11	**7**	**22**	R_2	**I**	40	27:1	86
12				**I**	40	27:1[e]	80[e]
13				**II**	40	23:1	*f*
14	**8**	**23**	R_3	**I**	rt	8.5:6.5:1	86
15				**II**	rt	2.8:2.3:1	*f*
16	**9**	**24**	R_4	**I**	rt	5:2.3:1:1	81
17				**II**	rt	4:3:1.4:1	*f*

[a] **I** = $Cp^*_2NdCH(TMS)_2$, **II** = $Cp^*_2SmCH(TMS)_2$, **III** = $Me_2SiCp^*_2NdCH(TMS)_2$, **IV** = $[Cp^{TMS}_2NdCH_3]_2$. [b] The diastereomeric ratio was determined by GC analysis of the filtered crude reaction mixture. [c] Isolated as the MeI monohydrate salt. [d] The reaction was 70% complete, and the product was not isolated. [e] 60−100 mg scale reaction. [f] Product was not isolated.

SCHEME 2 [a]



[a] Key: (a) (i) Mg, dibromoethane, 30−40 °C, THF, (ii) CuCN, propylene oxide, −60 to −50 °C, THF, (iii) TsCl, pyridine, CH_2Cl_2 (85%); (b) (i) equiv of allylamine (*n* = 1) or homoallylamine (*n* = 2), THF, 60−70 °C; (ii) HCl in diethyl ether (49−80%).

lined by Brussee[7] was used to prepare the HCl salts of substrates **1**, **3**−**5**, and **7**−**9**. The modification involved quenching the iminium solution into a slurry of the allylamine or homoallylamine hydrochloride followed by reduction with LAH at −78 °C. This modification simplified the quench and minimized an impurity formed in the reaction. Again, flash chromatography with 2-propanol/EtOAc not only purified the substrates but also allowed for recovery of the allylamine or homoallylamine hydrochlorides.

The HCl salts of substrates **2** and **6** were prepared from tosylate **34** (Scheme 2) as described above. The alcohol precursor to **34** was generated via a copper-promoted reaction of 3-butenylmagnesium bromide with propylene oxide.[8]

Several advantages were realized by isolating the HCl salts of the substrates. First, handling solids is much easier than handling liquids, especially in milligram quantities. Second, oxidation of the amines was greatly hindered, allowing for easy, prolonged storage. Last, the requisite purity for catalytic reactions could be achieved on a milligram scale. In comparison, gram quantities of material are desired to obtain comparably pure material by distillation.

Unfortunately, the HCl salt of the amine destroys the catalyst. Consequently, a simple free base protocol was required. An anhydrous, easily filtered, polymer base that is active enough to neutralize the HCl salt in a triphasic system (HCl salt, benzene, and polymer) would be ideal. However, to our knowledge, such a polymer does not exist. Several anhydrous bases such as the metal hydrides and metal carbonates were unsuccessful or the process too complicated. Eventually, the free amine was liberated with aqueous NaOH and extracted into benzene. Drying the benzene solution of the amine over activated molecular sieves proved, to our delight, adequate enough to remove the residual moisture without absorbing significant amounts of the free amine. The benzene solution was then degassed and taken into a glovebox where it was treated with the catalyst.

Formation of the quinolizidine ring system was best achieved at a concentration of 0.06 M with 10% $Cp^*_2NdCH(TMS)_2$ (Table 1). The monocyclic hydroamination side product was not observed by GC or by overnight carbon-13 NMR. The diastereoselectivity of the reaction ranged from 1.3:1 to greater than 50:1 with predominantly two diastereomers observed. It should be noted that with three stereogenic centers there are four possible diastereomers.

The high selectivity found in the formation of **16**, **18**, and **22** (Table 1, entries 1, 5, 6, and 11−13, respectively) was confirmed by carbon-13 NMR spectra taken of the reaction mixtures prior to workup. Formation of the HCl salts resulted in the isolation of two or more conformers. NMR analysis of the free base confirmed the diastereo-

(7) Zandbergen, P.; van den Niewendijk, A. M. C. H.; Brussee, J.; van der Gen, A.; Kruse, C. G. *Tetrahedron* **1992**, *48*, 3977.
(8) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998**, *63*, 7505.

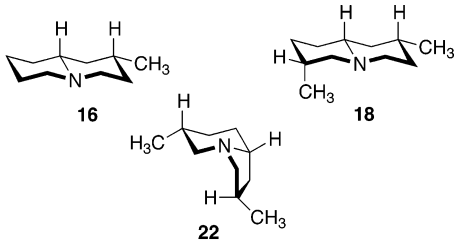


FIGURE 2. Stereochemistry of the major diastereomers as determined by single-crystal X-ray diffractometry.

meric purity. Further, the free base of **22** was converted back to the HCl salt, resulting in ^{1}H NMR spectra similar to that of the originally isolated product. The relative stereochemistry of the products was elucidated by X-ray diffraction analysis and is shown in Figure 2. X-ray quality crystals were obtained by the formation of the MeI (**16**), HCl (**18**), and picrate (**22**) salts, respectively, and GC analysis of the corresponding free bases confirmed the isolation of the major diastereomer.

Previous results from numerous laboratories[1] had established that lanthanide-mediated cyclization reactions (both intramolecular hydroamination and carbon−carbon bond formation via olefin insertion) transpired through chairlike transition structures. Consequently, isolation of **16** as the major diastereomer in the double cyclization of **1** was expected. In contrast, the formation **18** and **22**, wherein an axial substituent is established, was quite surprising. A further discussion of this interesting and unanticipated result is presented later.

In these preliminary studies, interesting features of the various catalysts were revealed. The low selectivity obtained with **2** and the ansa-bridged catalyst $Me_2SiCp^*_2NdCH(TMS)_2$ (entry 4) is most likely due to the more open coordination sphere of the catalyst.[9] As a consequence, this catalyst was not applied to any further systems. A higher diastereoselectivity was achieved with the $[Cp^{TMS}_2NdMe]_2$ catalyst that has a more restricted approach to the metal center (entry 3). However, in this case, the reaction could not be forced to completion. The difficulties encountered with this catalyst convinced us to drop it from broad application in our studies.

In terms of substrate control of stereochemistry, those starting materials with a methyl group at R_3 result in the lowest selectivity (entries 8, 14, and 15). A slight increase is observed by installing a substituent at the R_4 position (entries 9, 16, and 17). These results are an indication of the preorganization involved during the insertion of the Ln−N bond into the olefin, resulting in a significant steric influence by the substituted Cp rings.[10−14] The second clear trend is the decrease in selectivity in going from the quinolizidine ring system (n = 2, entries 1−9) to the indolizidine system (n = 1, entries 10−17), as evidenced by the appearance of a third diastereomer in the latter.

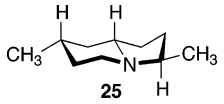


FIGURE 3. Stereochemistry of **25** as determined by single-crystal X-ray diffractometry.

A slight trend related to the catalyst is also observed in the formation of the indolizidine ring system. The $Cp^*_2NdCH(TMS)_2$ catalyst appears to provide better selectivity than the $Cp^*_2SmCH(TMS)_2$ catalyst for substrates **7** and **8** (entries 11−15). However, substrate **9** yielded a better selectivity with the samarium catalyst (entries 16−17). Although substrate **2** did not go to completion with the $[Cp^{TMS}_2NdCH_3]_2$ catalyst (entry 3), formation of the indolizidine ring system with the methyl at the R_1 position (entry 10**)** did proceed smoothly. The more rapid formation of the five-membered ring allowed for lower temperatures and a shorter reaction time. Unfortunately, the more accessible coordination sphere of the catalyst and/or the elevated temperature resulted in poorer selectivity. An apparent anomaly was observed for substrate **3** and the $[Cp^{TMS}_2NdCH_3]_2$ catalyst (entry 7). Even at 90 °C, no product was observed, again indicating the low reactivity in these systems of this particular catalyst.

The indolizidine ring system could also be generated by first forming the pyrrolidine ring followed by the piperidine portion (Table 2).

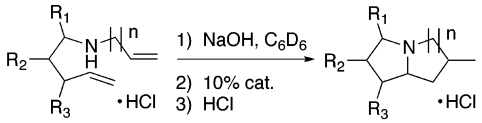
High selectivity was obtained with substrate **10** (Table 2, entries 1−3), and X-ray diffraction analysis of the HCl salt indicated the expected stereochemistry shown in Figure 3.

A reversal in catalyst selectivity was observed for substrate **10** where the neodymium catalyst was less selective than the samarium catalyst (compare entries 1−2 and 3). However, an increase in selectivity was observed for substrate **12** (entries 6 and 7). The opposite results were observed for substrates **6**−**9** as reported above (Table 1, entries 10−17). It should also be noted that substrates **8** (Table 1, entries 14 and 15) and **11** (Table 2, entries 4 and 5) generate the same indolizidine ring system with considerably different stereoselectivities. Substrates **13**−**15** (entries 9 and 10) formed only two diastereomers in the pyrrolizidine ring system, albeit in low ratios. Last, initial trials showed that the samarium catalyst was much less reactive than the neodymium catalyst for the formation of the quinolizidine ring system. Conversely, the neodymium catalyst did not perform as well as the samarium catalyst during the formation of the pyrrolizidine ring system. Stereoelectronic factors could play a role in this observation, wherein the larger ionic radius of the neodymium catalyst favors the formation of the larger six-membered ring and the smaller ionic radius of the samarium catalyst favors the formation of the smaller five-membered ring.

As alluded to previously, high diastereoselectivities in the formation of *cis*-2,6-disubstituted piperidines and *trans*-2,5-disubstituted pyrrolidines from primary amine precursors have been previously established (eqs 10 and

(9) (a) Molander, G. A.; Dowdy, E. D. *J. Org. Chem.* **1998**, *63*, 8983. (b) Ryu, J.; Marks, T. J.; McDonald, F. E. *Org. Lett.* **2001**, *3*, 3091.
(10) Casey, C. P.; Carpenetti, D. W., II.; Sakurai, H. *J. Am. Chem. Soc.* **1999**, *121*, 9483.
(11) Casey, C. P.; Klein, J. F.; Fagan, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 4320.
(12) Casey, C. P.; Lee, T.; Tunge, J. A.; Carpenetti, D. W., II. *J. Am. Chem. Soc.* **2001**, *123*, 10762.
(13) Casey, C. P.; Tunge, J. A.; Lee, T.; Carpenetti, D. W., II. *Organometallics* **2002**, *21*, 389.
(14) Casey, C. P.; Tunge, J. A.; Lee, T.; Fagan, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 2641.

TABLE 2. Organolanthanide-Catalyzed Formation of Indolizidines and Pyrrolizidines



entry	substrate	product	methyl position	catalyst[a]	*T* (°C)	dr[b]	% isolated yield
	n = 2						
1	**10**	**25**	R_1	**II**	50	25:1	91
2				**II**	50	25:1[c]	85[c]
3				**I**	50	10:1	*d*
4	**11**	**26**	R_2	**II**	rt	1:1	84
5				**I**	rt	1:1[e]	*d*
6	**12**	**27**	R_3	**II**	rt	6:1	91
7				**I**	rt	7:1	*d*
	n = 1						
8	**13**	**28**	R_1	**II**	50	2:1	83
9	**14**	**29**	R_2	**II**	rt	1.3:1	83
10	**15**	**30**	R_2	**II**	rt	1.5:1	88

[a] **I** = $Cp^*_2NdCH(TMS)_2$, **II** = $Cp^*_2SmCH(TMS)_2$. [b] The diastereomeric ratio was determined by GC of the filtered crude reaction mixture. [c] 80 mg scale reaction. [d] Product was not isolated.

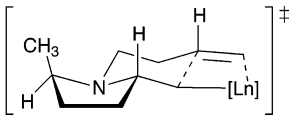
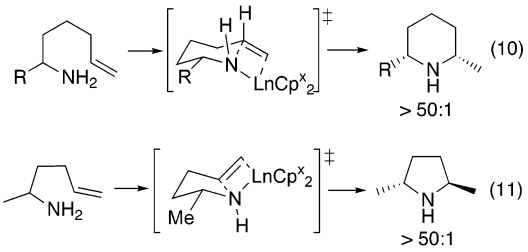


FIGURE 4. Transition structure leading to the formation of **25**.

11).[15,16] The diastereomers observed result from a transition structure wherein an energy-minimized chair conformation of the incipient ring places all of the substituents either equatorially or pseudoequatorially.



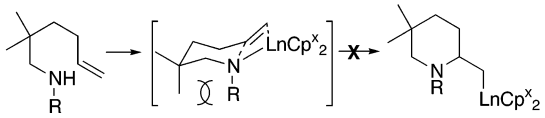
A priori, these results could be used to explain the sense and magnitude of diastereoselection in the formation of **16**. In addition, these results explain the high selectivity found in the construction of **25** (Figure 4). In this case, the initial intramolecular amination step leads to the formation of a *trans*-2,5-disubstituted pyrrolidine ring (eq 11). The transition structure of the subsequent olefin insertion step is similar to the formation of *cis*-2,6-disubstituted piperidines.

However, barring a boat transition structure, the relative stereochemistry found in **18** and **22** requires that either the methyl group on the incipient ring be oriented axially or the olefin engaged in ring formation must be situated pseudoaxially in the transition structure leading to the monocyclic intermediate. On the face of it, neither of these options is particularly appealing, and the latter appears contrary to all extant examples. However, closer inspection and molecular modeling studies offer a potential explanation.

In an attempt to approximate the transition structures by modeling the product geometries, the Merck Molecular Force Field[17] (substituting Cp^*_2Sc for Cp^*_2Nd) was employed to provide insight into the observed stereochemistry. Interestingly, this analysis in fact correctly predicts the sense of diastereoselection observed for all of these substrates (Figure 5). For the cyclization of a *primary* amine, e.g., 6-amino-1-hexene (**I**), reaction through a chair transition structure with the olefin oriented pseudoequatorially (**IA)** is predicted to be favored over the axial orientation (**IB**). The long carbon−lanthanide bonds (∼2.4−2.7 Å) aid the former in overcoming what would otherwise be a highly strained *trans*-bicyclo[4.2.0] ring system in the transition structure. The relatively normal chair conformation of the six-membered ring in **IA** attests to the relative lack of strain in the system. The increased strain in **IB** manifests itself in a greater degree of distortion in the six-membered ring.

Molecular modeling of the cyclization of 6-*N*-methylamino-1-hexene, a *secondary* amine, reveals a surprise. Here, cyclization through a transition structure with the olefin pseudoaxial (**IIB**) is predicted to be more favorable than the pseudoequatorial alternative (**IIA**), in line with our observations. The same issues concerning strain in the bicyclic ring system pertain to this system, but among other factors a severe $A^{1,3}$ interaction (closest contact 1.76 Å) between the axial *N*-methyl group and the developing metallomethyl group in **IIA** stands out in differentiating this structure from that of **IIB** as well as that of both des-methyl models **IA** and **IB**. This interaction may account for a significant fraction of the unfavorable interactions that mandate a switch in the transition structures leading to the observed products.

We sought further evidence for these observations. We reasoned that if the chair transition structure was correct, then reaction of a substrate with appropriately



(12)

(15) Molander, G. A.; Dowdy, E. D.; Pack, S. K. *J. Org. Chem* **2001**, *66*, 4344.
(16) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275.

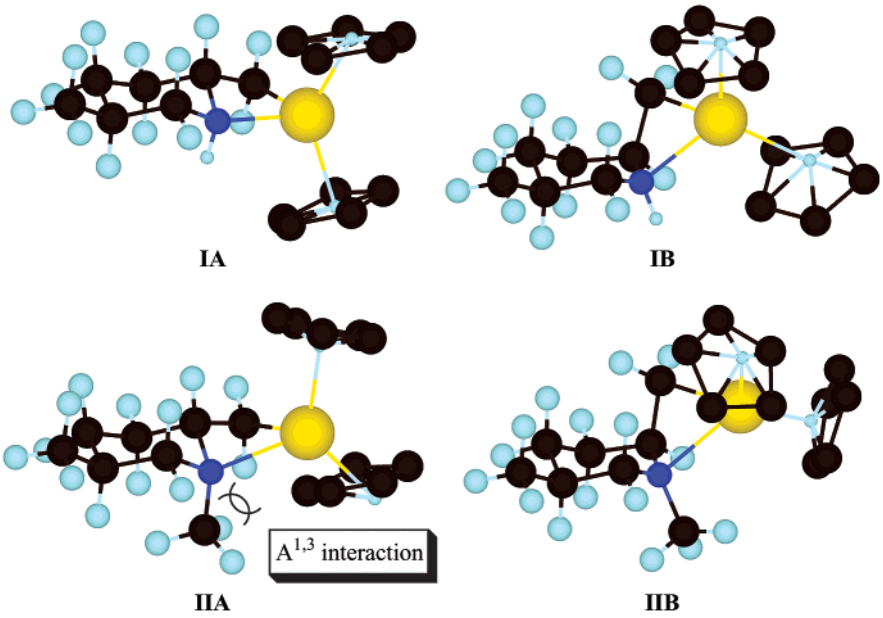
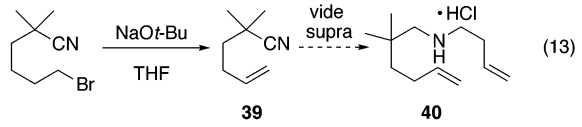


FIGURE 5. Calculated transition structure models for the lanthanide-catalyzed intramolecular amination reaction of primary (**I**) and secondary (**II**) aminoalkenes in which the alkene is oriented pseudoequatorially (**A**) and pseudoaxially (**B**). Methyl groups on the Cp* rings have been removed for visual clarity.

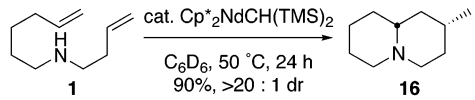
placed *gem*-dimethyl substituents should be slowed or inhibited altogether because of the unavoidable, additional 1,3-diaxial interaction (eq 12).

Substrate **40** was synthesized from the known nitrile **39** via the commercially available bromonitrile in ca. 55% overall yield using procedures described above (eq 13).[18]

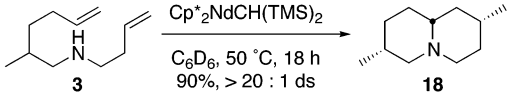


39 40 (13)

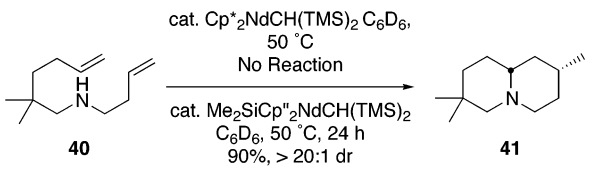
This substrate, along with substrates **1** and **3**, was treated with 8−9 mol % of catalyst in a 0.06 M benzene-d_6 solution, and the reactions, performed side-by-side, were monitored by NMR. The results are displayed in eqs 14−16.



1 16 (14)



3 18 (15)



40 41 (16)

Indeed, both substrates substrate **1** and **3** reacted faster than **40**, which was virtually unreactive using the Cp* catalyst. Substrate **40** did react with the ansa-bridged neodymium catalyst in which steric access to the metal is more facile. Curiously, this same catalyst did not react with substrates **1** and **3**. Another observation not readily explained by these models is the low diastereoselectivity seen in the conversion of **4** to **19**. Given the analysis provided above, high diastereoselectivity was anticipated. Thus, although some new light has been shed on the factors involved in lanthanocene catalyzed reactions, a truly comprehensive understanding of all the critical features involved in controlling reactivity and selectivity of this class of catalysts is obviously multivariate and not readily deconvoluted.

Conclusion

The stereoselectivity achieved during the formation of methyl-substituted quinolizidines, indolizidines, and pyrrolizidines via a sequential intramolecular amination/cyclization reaction was determined. A new stereocontrol element has been detected that appears to differentiate the transition structures of *N*-alkyl substituted (secondary) amino dienes from primary amino dienes. Additionally, a neodymium-based catalyst performed better for the initial formation of six-membered rings, and a samarium catalyst performed better for the initial formation of five-membered rings. Still, many questions remain concerning the reactivity and selectivity of this class of catalysts in sequential amination/cyclization reactions.

Experimental Section

***N*-3-Butenyl-5-hexen-1-amine, Hydrochloride (1). (Representative Procedure for the Formation of Secondary Amines from Their Corresponding Nitriles.)** Adapted from Brussee's procedure.[7] A 250 mL round-bottomed flask, equipped with a thermocouple, stir bar, and a nitrogen line, was charged with 890 mg (9.36 mmol) of nitrile (35) and 70 mL of HPLC-grade diethyl ether. The clear solution was cooled

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to −78 °C and charged with 22.5 mL (22.5 mmol) of 1 M DIBALH in hexane while maintaining an internal temperature less than −65 °C. The hazy white solution was allowed to stir at −78 °C for ca. 3 h. Meanwhile, a separate round-bottomed flask, equipped with a thermocouple, stir bar, and a nitrogen line, was charged with 2.45 g (22.8 mmol, 2.4 equiv) of the HCl salt of homoallylamine and 20 mL of HPLC grade diethyl ether. The cold iminium solution was then transferred, via cannula, to the HCl salt slurry over a period of ca. 30 min. The hazy white solution was allowed to stir at rt overnight. The mixture was then cooled to −78 °C and charged with 13.5 mL (13.5 mmol) of 1 M LAH in diethyl ether while maintaining an internal temperature less than −70 °C. The white solution was allowed to stir at −78 °C for ca. 2 h and quenched with 75 mL of 1 M aqueous HCl. The aqueous layer was separated, washed with 2 × 75 mL of diethyl ether and neutralized with 75 mL of 10 wt % aqueous NaOH. The free amine was extracted with 3 × 75 mL of diethyl ether and acidified with 16 mL of 2M HCl in diethyl ether. The solvents were removed under vacuum and the resulting mixture was separated by flash chromatography using 2-propanol/EtOAc as eluent. Crystallization was achieved by solvent exchanging the combined fractions into heptane. The white crystalline solids were filtered, providing 1.23 g (6.50 mmol, 69%) of the title compound. The HCl salt of homoallylamine was also recovered (1.0 g, 9.3 mmol, 1.0 equiv): mp 222−230 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 2H), 5.82−5.72 (m, 2H), 5.19−5.12 (d, J = 17.2 Hz, 1H), 5.19−5.12 (d, J = 10.3 Hz, 1H), 5.03−4.96 (d, J = 16.9 Hz, 1H), 5.03−4.96 (d, J = 10.3 Hz, 1H), 2.99−2.94 (m, 4H), 2.71−2.66 (dt, J = 7.9, 7.2 Hz, 2H), 2.11−2.06 (m, 2H), 1.94−1.88 (m, 2H), 1.51−1.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 132.7, 118. 6, 115.5, 47.8, 47.0, 33.2, 30.2, 26.2, 25.4; IR ($CDCl_3$) 3412.1, 3079.9, 2938.9, 2768.1, 2444.0, 2251.4, 2220.3, 1642.6, 1589.8, 1469.2, 1381.3, 1301.5 cm^{-1}; HRMS calcd for $C_{10}H_{20}N$ (M − Cl; CI$^+$) 154.1595, found 154.1600; LRMS (ESI$^+$) m/z 112 (30), 154 (100).

***N*-Methyl-2-methylquinolizidine, Iodide (16). (Representative Procedure for the Tandem Hydroamination/C−C Cyclization Reaction.)** A sealable NMR tube was charged with 380 mg (3.8 mg, 6.6 μmol) of a 1 wt % solution of $Cp^*_2NdCH(TMS)_2$ in C_6D_6. The catalyst solution was then layered with an additional 380 mg of C_6D_6 and 440 mg (12.9 mg, 68 μmol) of a 2.94 wt % solution of the free amine of **1** in C_6D_6. The layered mixture was allowed to sit at rt and monitored by NMR. Upon reaction completion, ca. 96 h, the green solution was charged with 2 mL of heptane and allowed to oxidize for ca. 2 h. The yellow slurry was filtered through Celite and the clear, pale yellow solution was analyzed by GC (>50:1 dr). The mixture was then treated with excess MeI, and the resulting solids were filtered and dried under high vacuum to yield 18.2 mg (58 μmol, 85%) of a pale yellow, monohydrate, crystalline solid. Recrystallization using acetone/heptane provided anhydrous crystals that were suitable for X-ray analysis: mp (monohydrate) 202−210 °C; ^{1}H NMR (monohydrate, 500 MHz, $CDCl_3$) δ 4.02−3.88 (m, 5H), 3.11 (s, 3H), 2.21−2.05 (m, 2H), 1.95−1.90 (m, 4H), 1.74−1.68 (m, 4H), 1.58 (s, 2H), 1.38−1.35 (dt, J = 15.1, 12.2 Hz, 1H), 1.03−1.02 (d, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.5, 64.9, 64.8, 38.3, 35.1, 29.2, 28.5, 26.8, 21.8, 21.3, 20.4; IR ($CDCl_3$) 2957.8, 2253.2, 2203.4, 1459.7, 1380.3, 1094.4 cm^{-1}; HRMS calcd for $C_{11}H_{22}N$ (M − I; ESI$^+$) 168.1752, found 168.1757; LRMS (ESI$^+$) m/z 168 (100).

Acknowledgment. We thank Dr. Pat Carroll for the X-ray structure determination of **16**, **18**, **22**, and **25**. Special thanks to Professor Marisa Kozlowski for performing the calculations, and both Professor Kozlowski and Professor Patrick Walsh for critical discussions concerning the stereochemical aspects of this study. We gratefully acknowledge the National Institutes of Health (Grant No. GM48580) and Merck Research Laboratories for their generous support of this research. S.K.P. thanks the Process R&D group of Bristol-Myers Squibb for their financial support and a study leave.

Supporting Information Available: Experimental procedures for all compounds not described within the text. HRMS, LRMS, and ^{1}H and ^{13}C NMR spectra of representative compounds. X-ray data for **16**, **18**, **22**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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