Coupled Organolanthanide-Catalyzed C−N/C−C Bond Formation Processes. Efficient Regiospecific Assembly of Pyrrolizidine and Indolizidine Skeletons in a Single Catalytic Reaction

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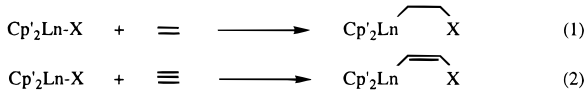
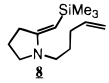
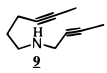
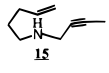
The remarkable kinetic facility with which early lanthanide−alkyl and −heteroatom bonds undergo insertion of unactivated alkene[1,2] and alkyne[3,4] functionalities within bis(pentamethylcyclopentadienyl)metal environments[1] (e.g., eqs 1 and 2; Cp′ = η^5-Me_5C_5; X = alkyl, NR_2, PR_2) has recently been documented, as has the susceptibility of the resulting Ln−C bonds to protonolysis.[2,3] These results raise the interesting question



of whether lanthanide-mediated C−N/C−C fusions could be coupled in sequence to assemble, in conjunction with protonolysis, complex polycyclic, heteroatom-containing skeletons (e.g., pyrrolizidine, indolizidine, and other alkaloid frameworks)[5,6] in a single catalytic reaction. We report here the facile, regiospecific organolanthanide-catalyzed bicyclization of aminodiolefins, aminodialkynes, and aminoalkenalkynes to access a variety of such architectures, as well as initial observations regarding scope and mechanism.[7]

Table 1. Intramolecular Hydroamination/Bicyclization Results

Entry	Substrate	Product	N_t, h^{-1}(°C)	Yield (%)
1.	 1	 2	17(21)[a,c] 12(21)[b]	68[d]
2.	 3	 4	777(21)[a,c] 124(21)[b]	75[d]
3.	 5	 6	2.6(60)[a] 1.7(60)[b]	91[e,f]
4.	 7	 8	129(21)[a]	90[e,f]
5.	 9	 10	74(21)[a] 132(21)[b]	95[e]
6.	 11	 12	55(21)[a,c] 1(60)[b]	93[d]
7.	 13	 14	5(21)[a,c]	88[d]
8.	 15	 16	2(21)[a] 14(60)[a] 10(21)[b]	92[e]

[a] $Cp'_2SmCH(TMS)_2$ as precatalyst. [b] $Me_2SiCp''_2NdCH(TMS)_2$ as precatalyst. [c] NMR and preparative scale reactions. [d] Isolated yield. [e] Yield determined by ^1H NMR and GC/MS after vacuum transfer of the volatile products. [f] Traces of other isomers present; see text.

The unsaturated difunctional amine substrates shown in Table 1 were straightforwardly synthesized, purified, and characterized by standard methodologies.[8] Reactions with precatalysts $Cp'_2SmCH(TMS)_2$[1b] and $Me_2SiCp''_2NdCH(TMS)_2$ (Cp″ = η^5-Me_4C_5)[9] were carried out in C_6H_6/C_6D_6 under rigorously anhydrous/anaerobic conditions ([catalyst] = 7.5−15 mM; substrate:catalyst ≈ 50:1).[8] Isolated yields in Table 1 refer to products isolated by distillation or column chromatography. With the exception of entries 3 and 4 (vide infra), bicyclizations proceed with ≥95% regioselectivity, as ascertained by ^1H NMR and GC/MS, and at the turnover frequencies (N_t) indicated. Product structure and stereochemistry were established by 1-D and 2-D $^1H/^{13}C$ NMR, HRMS, and other standard techniques.[8] It can be seen that alkyne, alkene; alkyne, alkyne; and alkene, alkene bicyclizations can all be effected to yield a variety of pyrrolizidine and indolizidine skeletons.[5,6] Thus, entries 1 and 2 demonstrate clean and rapid (N_t as high as 777 h^{-1} at 21 °C) sequential alkyne, alkene insertive bicyclization. That alkyne insertion into Ln−N bonds is expected to be more rapid and exothermic than that of olefins[4] (which in this case would also yield strained three-membered rings) suggests the representative mechanistic scenario portrayed in Scheme 1. Further evidence for this pathway derives from entries 3 and 4, in which the second (olefinic) insertion into the α-silylvinyl−lanthanide linkage is arrested (slow, precedented catalytic[1b] double bond

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(2) Alkene insertions involving heteroatoms: (a) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241−10254. (b) 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. (c) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275−294. (d) Gagné, M. R.; Nolan, S. P.; Marks, T. J. *Organometallics* **1990**, *9*, 1716−1718.

(3) Alkyne insertions involving alkyls: (a) Heeres, H. J.; Teuben, J. H. *Organometallics* **1991**, *10*, 1980−1986 and references therein. (b) Heeres, H. J.; Meetsma, A.; Teuben, J. H.; Rogers, R. D. *Organometallics* **1989**, *8*, 2637−2646.

(4) Alkyne insertions involving heteroatoms: (a) Li, Y.; Fu, P.-F.; Marks, T. J. *Organometallics* **1994**, *13*, 439−440. (b) Li, Y.; Marks, T. J. *Abstracts of Papers*, 34th National Organic Symposium, ACS Division of Organic Chemistry, Williamsburg, VA, June 1995; American Chemical Society: Washington, DC, 1995; Abstract 44.

(5) For some leading reviews, see: (a) Robins, D. J. *Nat. Prod. Rep.* **1994**, *11*, 613−619 and references therein. (b) Michael, J. P. *Nat. Prod. Rep.* **1994**, *11*, 639−657 and references therein. (c) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1. (d) Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: Orlando, 1986. (e) Robins, D. J. *Adv. Heterocycl. Chem.* **1979**, *24*, 247−291.

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(7) Communicated in part: Li, Y., Marks, T. J. *Abstracts of Papers*, 209th National Meeting of the American Chemical Society, Anaheim, CA, Spring 1995; American Chemical Society: Washington, DC, 1995; INOR012.

(8) See supporting information for full synthetic details and characterization data for new compounds.

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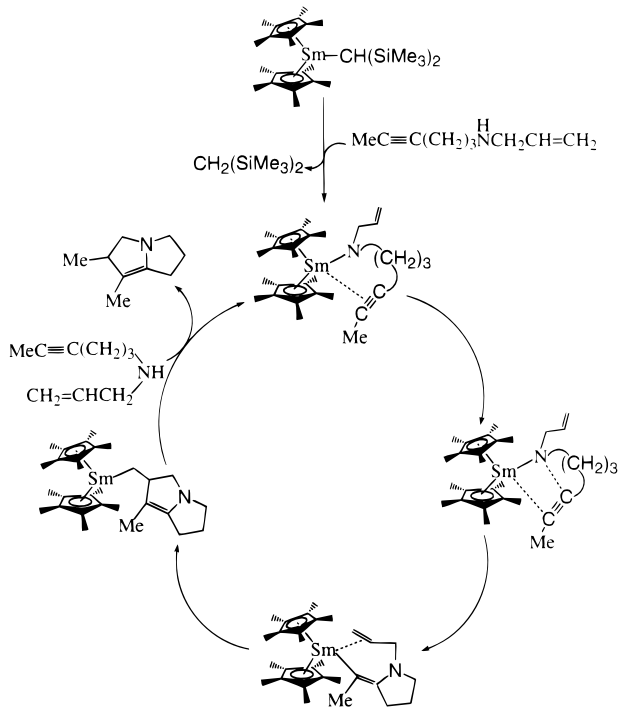
Scheme 1. Proposed Pathway for Organolanthanide-Catalyzed Sequential C−N and C−C Bond Formation



migration occurs in entry 3 instead), presumably due to a combination of electronic[10] and steric impediments. The two products indicated each contain ∼10% of other uncyclized double bond positional isomers. Entry 5 illustrates rapid sequential alkyne, alkyne insertive bicyclization to introduce two regions of heterocyclic unsaturation. The stereochemistry of **10** is assigned from NOE difference spectroscopy. Entries 6 and 7 illustrate alkene, alkene bicyclization to yield the saturated (known) pyrrolizidine **12**[11] and indolizidine **14** (*cis: trans* = 45:55 and 85:15,[12] respectively). Entry 8 further illustrates that alkene, alkyne bicyclization can be employed to produce an *exo*-alkene-functionalized pyrrolizidine. In this case, initial olefinic insertion into the Ln−N bond[2a,c] is favored, doubtless due to the short alkyne connecting linkage. The stereochemistry of **16** is assigned by analogy to that of **10**, by NOE difference spectroscopy, and by the expected[3,4] *cis* course of the alkyne insertion process.

In regard to reaction mechanism, an ^{1}H NMR kinetic analysis of the Cp′$_2$Sm-catalyzed **11** → **12** transformation indicates zero-order behavior in [substrate] over a 20-fold concentration range and first-order behavior in [Sm] over a 15-fold concentration range (eq 3), implicating an intramolecular, insertive process as the turnover-limiting step. Further support for a turnover-limiting insertion scenario is found in the pronounced correlation of **1** → **2** turnover frequencies (at constant [Cp′$_2$Ln], [substrate], and temperature) with decreasing eight-coordinate Ln^{3+} ionic radius[13] (Ln (ionic radius, Å), N_t): La (1.16), 148; Nd (1.11), 45; Sm (1.08), 17; Lu (0.977), <0.2 h^{-1}). Similar trends obtain in a variety of Cp′$_2$Ln-catalyzed processes, where the turnover-limiting step is olefin insertion.[1b,2a,c,14]

$$\nu = k[\mathrm{Sm}]^1[\mathrm{substrate}]^0 \qquad (3)$$

In summary, these results demonstrate that organolanthanide centers can mediate unusual tandem sequences of insertive C−N and C−C bond-forming processes and that such transformations can be readily integrated into novel and regioselective catalytic cycles. Of note is the attraction of assembling pyrrolizidine and indolizidine skeletons having varying degrees of unsaturation, hence points for subsequent functionalization, in a single catalytic cycle. Additional applications are currently under investigation.

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Supporting Information Available: Details of the syntheses and characterization data for new compounds (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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