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Effective, Selective Hydroalkoxylation/Cyclization of Alkynyl and Allenyl Alcohols Mediated by Lanthanide Catalysts

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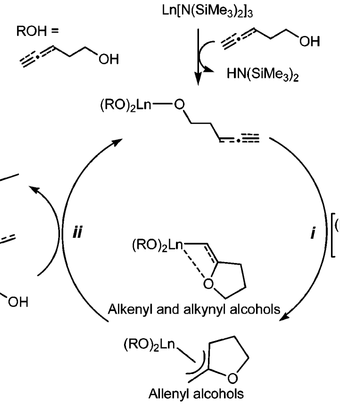
Nitrogen- and oxygen-containing heterocycles are important structural components of a vast array of naturally occurring and pharmacologically active molecules.[1] The limitations of traditional heterocycle synthetic methodologies have stimulated considerable interest in developing of new, efficient catalytic methods for the synthesis of heterocyclic compounds.[2] Catalytic formal addition of an X−H bond, where X = O, N, across C−C unsaturation is in principle an attractive, atom-economical route for the synthesis of functionalized heterocycles.[3] However, due to a number of factors, including the relatively high bond enthalpies of most X−H σ-bonds and the modest reactivity of electron-rich olefins with nucleophiles, efficient catalytic intramolecular hydrofunctionalization remains a challenge. Olefin hydroalkoxylation (HO) is an area with limited numbers of catalysts and is relatively unexplored.[3−6] Only a few alkali and transition metal HO catalysts have been studied, with limited reported reaction yields and scope. Organolanthanide complexes are known to be highly active hydrofunctionalization catalysts.[7,8] Their versatility in hydroamination and hydrophosphination raises the intriguing question of whether or not these efficient catalysts could mediate hydroalkoxylation. Bond energetic considerations[9] for unexplored alkene−, alkyne−, and allene−lanthanide alkoxide cycles (Scheme 1) predict net exothermic processes for all alcohols; however, the very large Ln−O bond enthalpy[9a] renders insertive step *i* very endothermic for alkenyl alcohols. Here we report the effective and selective intramolecular HO/cyclization of alkynyl and allenyl alcohols mediated by homogeneous lanthanide catalysts.

In the present study, homoleptic lanthanide amides, Ln$[N(SiMe_3)_2]_3$, are found to undergo instantaneous protonolysis with C−C unsaturated alcohols (substrates **2**−**7** in Table 1) at room temperature to form the corresponding alkoxides and free $HN(SiMe_3)_2$. At 60 °C, substrate **2** undergoes conversion to cyclic methylenetetrahydrofuran **8** within 5 h with 5 mol % of La$[N(SiMe_3)_2]_3$ (**1a**) precatalyst. Conversion is clean and quantitative as monitored by ^{1}H NMR spectroscopy. The regioselective *exo* hydroalkoxyl addition to the alkyne here differs markedly from that of most transition metal catalysts with similar substrates, where *endo* addition is commonly observed.[3a,5]

Such different regiochemistries suggest that very different mechanisms are operative.[5b] A similar selectivity is observed with Ag_2CO_3 as the catalyst; however, only trace amounts of product are detected unless stoichiometric substrate/catalyst ratios are employed.[5e] The **2** → **8** conversion is found to be first-order in [catalyst] and zero-order in [substrate], similar to lanthanide-catalyzed hydroamination/cyclization processes.[7] An −OH versus −OD labeling study (entry 2, Table 1), assayed by ^{1}H and ^{2}H NMR spectroscopy, indicates that deuterium is transferred to both terminal methylene positions (products **9** and **10**). The measured **2-D** turnover frequency is only slightly smaller than that for **2** (KIE = 0.95), suggesting a nonprimary isotopic effect and consistent with the alkyne insertion being the turnover-limiting step in the catalytic cycle. These data are consistent with the pathway in Scheme 1, where slow alkyne insertion is followed by rapid substrate protonolysis. This scenario would then be followed by ligand substitution by another substrate molecule. Kinetic analysis of the **2** → **8** conversion between 40 and 80 °C yields $\Delta H^{\ddagger} = 20.2(1.0)$ kcal/mol, $\Delta S^{\ddagger} = -11.8(0.3)$ eu, and $E_a = 20.9(0.3)$ kcal/mol, with the negative $\Delta S^{\ddagger}$ suggesting a rather organized transition state.[7] The formation of **10** (**9**/**10** ratio = 54:46) suggests that any coordination

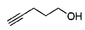
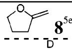
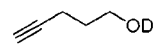
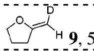
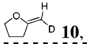
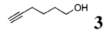
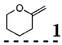
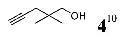
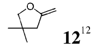
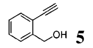
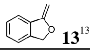
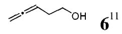
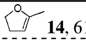
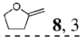
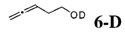
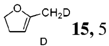
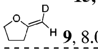
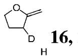
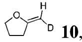
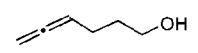
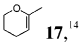
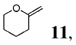
Scheme 1. Proposed Catalytic Cycle for Lanthanide-Mediated Hydroalkoxylation/Cyclization of Alkenyl, Allenyl, and Alkynyl Alcohols



Estimated ΔH's (kcal/mol)

Alcohols	Step *i*	Step *ii*
Alkenyl	+22	-36
Alkynyl	-13	-26
Allenyl	+6	-19

Table 1. Catalytic Hydroalkoxylation/Cyclization by Precatalyst La$[N(SiMe_3)_2]_3$ (5 mol %) in Benzene-d_6

Entry	Substrate (ref)	Product (ref, yield[a])		N_t (h^{-1}, °C)
1	 **2**	 **8**[5e]		4.3 (60)
2	 **2-D**	 **9**, 54%	 **10**, 46%	4.1 (60)
3	 **3**	 **11**[5e]		1.1 (130)
4	 **4**[10]	 **12**[12]		18.0 (60)
5	 **5**	 **13**[13]		9.8 (60)
6	 **6**[11]	 **14**, 61%	 **8**, 39%	0.51 (60)
7	 **6-D**	 **15**, 51%  **9**, 8.0%	 **16**, 34%  **10**, 7.0%	0.50 (60)
8	 **7**[11]	 **17**,[14] 79%	 **11**, 21%	0.28 (130)

[a] Yields determined by NMR integration with methyltriphenylsilane as the internal standard.

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of the furan oxygen to the Ln^{3+} ion may be weak, likely due to the abundant concentrations of free alcohol and product furan. Other homoleptic lanthanide amide complexes {$Ln[N(SiMe_3)_2]_3$, Ln = Nd (**1b**), Sm (**1c**), Y (**1d**), and Lu (**1e**)} similarly catalyze this reaction, with decreasing turnover frequency accompanying declining ionic radius [$N_t = 4.2$ (**1b**), 2.1 (**1c**), 0.13 (**1d**), and 0.20 h^{-1} (**1e**)]. This pattern parallels that of organolanthanide-catalyzed aminoalkene hydroamination/cyclization but not that for aminoalkynes.[7a] Longer chain alkynol **3** (entry 3) undergoes quantitative HO/cyclization to methylenepyran **11** at a significantly diminished N_t, while substituted alkynyl alcohols **4** and **5** proceed more rapidly (entries 4 and 5), consistent with previous hydroamination/cyclization trends.[7a,f] In marked contrast to **2**, pent-4-en-1-ol, the olefinic analogue of **2**, undergoes negligible reaction in the presence of **1a**, even at 120 °C, in accord with bonding energetic expectations (Scheme 1).

Allenyl alcohol penta-3,4-dien-1-ol (**6**) also undergoes catalytic HO/cyclization, however at a diminished rate versus the alkynyl alcohols (Table 1, entry 6) at 60 °C. Conversion also proceeds cleanly and quantitatively as monitored by ^{1}H NMR spectroscopy. In addition to the formation of methylenetetrahydrofuran (**8**) as in entry 1, a second product, methyldihydrofuran (**14**), is also observed with a ratio of **8**/**14** = 39:61. Of the few reported examples of catalytic allenyl alcohol HO/cyclization, most additions are either *endo* or *exo*,[2a,6] with HO delivery to the central allene carbon being rare, but not for lanthanide-mediated aminoallene hydroamination.[7c] Both conversions $\mathbf{6} \rightarrow \mathbf{8}$ and $\mathbf{6} \rightarrow \mathbf{14}$ are also found to be first-order in [catalyst] and zero-order in [substrate]. Labeling studies show that, for **6-D**, deuterium is transferred to either the furan 3 skeletal position or to the terminal methyl/methylene group (Table 1). The proposed mechanism (Scheme 1) thus invokes terminal C=C insertion into the Ln−O bond and η^3-allyl lanthanide complex formation. Protonolysis of either external allyl position then affords two different products, **8** and **14**. Exposure of either **8** or **14** to $La[N(SiMe_3)_2]_3$ under the same reaction conditions does not generate new **14** or **8**, respectively, on the reaction time scale, ruling out formation of significant **8** or **14** via product isomerization. Furthermore, introducing additional **14** to the **6** HO/cyclization process does not affect N_t nor the ratio of newly formed **8**/**14**. Kinetic studies of conversion $\mathbf{6} \rightarrow \mathbf{8} + \mathbf{14}$ between 70 and 110 °C yield $\Delta H^\ddagger = 20(2)$ kcal/mol, $\Delta S^\ddagger = -17.6(0.7)$ eu, and $E_a = 20.9(0.7)$ kcal/mol. Allenyl alcohol **7** undergoes HO/cyclization, but also at a slower rate, even at 130 °C (entry 6). Slower cyclization rates with longer chain substrates are also observed in aminoallene hydroamination/cyclizations with lanthanide catalysts.[7a,e]

In contrast to thermal HO/cyclization pathways found in typical transition metal catalytic systems, which are generally thought to involve either nucleophilic attack on an activated π-system or vinylidene intermediates, the present results represent, to our knowledge, the first observation of catalytically significant C=C/C≡C insertion into Ln−O bonds.[15] In summary, we have demonstrated efficient catalytic hydroalkoxylation/cyclization of alkynyl and allenyl alcohols mediated by lanthanide catalysts. The conversions are remarkably clean and proceed via a different pathway than conventional transition metal catalysts. Further studies of mechanism and synthetic applications are in progress.

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Supporting Information Available: Experimental details and kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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