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LANTHANIDES IN ORGANIC SYNTHESIS. SYNTHESIS OF BICYCLIC ALCOHOLS.

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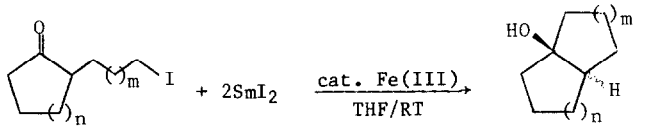
Abstract: Lanthanide reducing agents have been found to effectively promote intramolecular alkylation reactions to provide the corresponding bicyclic alcohols in excellent yields.

Ever since the Barbier reaction was first introduced, efforts have been made to apply conceptually similar methodologies towards the construction of cycloalkanols.[1] While some success has been achieved in the synthesis of three-, four-, and five-membered rings utilizing a variety of reducing agents and substrates, few attempts to prepare the corresponding six-membered carbocyclic rings have succeeded. Thus, attempted cyclization of 2-(4-halobutyl)cyclohexanones to the corresponding six-membered ring carbocycles has failed when magnesium[1q] as well as alkali metals[1d] were used as the reducing agents. The use of a reduced nickel species has proven successful,[1i] although only one example has been attempted and thus the scope of this particular reaction is not clear. Our interest in the use of lanthanides in organic synthesis led us to consider the utilization of these reagents to solve this very fundamental problem.

The application of lanthanide metals and derivatives in organic synthesis is a relatively new development within the field.[2] That organosamarium (II)- and organoytterbium (II) halides could be synthesized directly from the metals and organic halides was first recognized in 1970.[3] Subsequent studies showed that they possess some of the same reactivity patterns as organomagnesium reagents.[3,4] Even more recently, the application of lanthanide (II) salts as reducing agents to effect carbon-carbon bond formation as well as functional group reduction has been explored.[5] We have recently found that many of the problems encountered in intramolecular Barbier-type syntheses, particularly the inability to form six-membered rings, can be nicely solved by utilizing lanthanide reagents to effect the cyclization. We report here the preliminary results of our study.

Several 2-(n-iodoalkyl)cycloalkanones were prepared by standard procedures.[6] Treatment of these substrates with SmI_2 (prepared by the method of Kagan[5b]) in tetrahydrofuran (THF) in the presence of a catalytic amount of iron tris(dibenzoylmethane) [$Fe(DBM)_3$][7] afforded excellent isolated yields of the bicyclic alcohols (Table I).

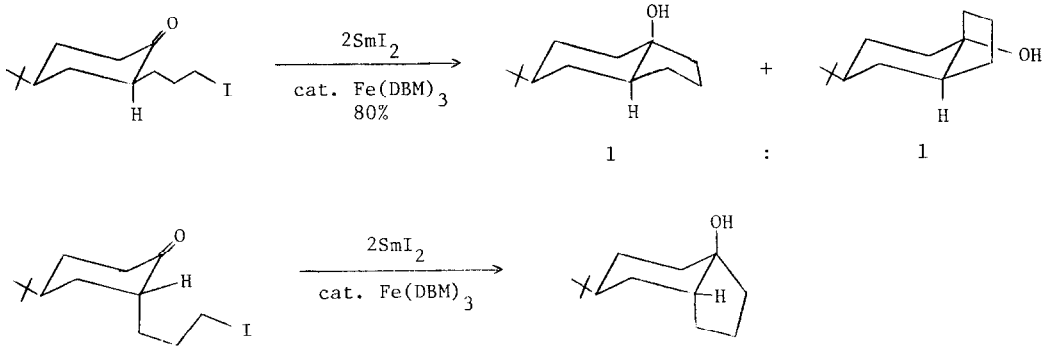
Table I. 

Entry	n	m	% GC Yield(Isolated)[a]	cis:trans ratio[b]
1	1	1	90(60)[8]	>99.5 < 0.5
2	2	1	100(75)[1q,9]	1.3 : 1
3	3	1	85(77)[8b,10]	2.0 : 1
4	1	2	67[1q,9]	18 : 1
5	2	2	95(75)[8b,9a,11]	1 : 1.5

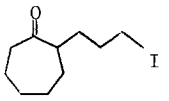
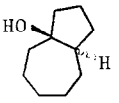
[a]Satisfactory ^{1}H NMR, ^{13}C NMR, IR and mass spectral data were obtained for all compounds.
[b]Determined by gas chromatography.

In two cases, the process was found to be highly stereoselective, resulting in nearly exclusive formation of a single stereoisomer (Entries 1 and 4. Table I). Modest stereoselectivity was observed in the other systems studied. Under a variety of conditions (change of solvent, temperature, mode of addition, in the presence of halide additives[5b,12] and in the absence of the Fe(III) catalyst) the stereochemical outcome of the reaction did not change to a great degree. We imply from these preliminary data that the bicyclic alcohols formed by the use of SmI_2 are the kinetic products of the reaction (compare Entries 2 and 4, Table I).

The lack of stereoselectivity in the synthesis of the bicyclo[4.3.0]decan-9-ol (Entry 2, Table I) has been demonstrated to result from attack of an equatorial side chain on the carbonyl intermediate with comparable ease from both the equatorial and axial direction. Thus cis-2-(3-iodopropyl)-4-t-butylcyclohexanone provides a 1:1 mixture of ring-fused stereoisomers. The trans-2-(3-iodopropyl)-4-t-butylcyclohexanone yields only the cis ring-fused isomer, indicating that under the reaction conditions no epimerization takes place.

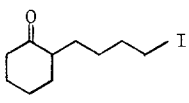
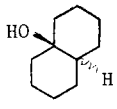


We have had some success in increasing the stereoselectivity of the reaction by changing the nature of the reducing agent itself. Thus we have discovered that use of ytterbium metal and YbI_2 as reducing agents results in predominant formation of a single ring-fused isomer (Tables II and III).

Table II.  reducing agent, THF 

Entry	Reducing Agent	% GC Yield	cis:trans ratio[a]
1	SmI_2/cat. Fe(III)	85	2.0:1
2	SmI_2	77	3.1:1
3	YbI_2/cat. Fe(III)	59	6.1:1
4	Sm	71	4.1:1
5	Yb	77	6.7:1

[a]Determined by gas chromatography.

Table III.  reducing agent, THF 

Entry	Reducing Agent	% GC Yield	cis:trans ratio[a]
1	SmI_2/cat. Fe(III)	95	1:1.5
2	SmI_2	71	1:3.0
3	YbI_2	68	1:5.6

[a]Determined by gas chromatography.

It is interesting to note that YbI_2 was found to be ineffective in inducing intermolecular alkylations,[5b] yet performs quite efficiently in these intramolecular reactions (Entry 3, Tables II and III). Even more fascinating is the effect of Yb and YbI_2 on the stereoselectivity of the process. While the shorter metal-oxygen bond as well as the greater solvated radius of the Yb(III) ion relative to the somewhat larger, and therefore less polarizing, Sm(III) ion might be implicated,[13] it is not clear at this point how these factors may manifest themselves in the transition state.

Further studies to elucidate these and other features of the reaction are currently in progress.

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