Lewis Acids in Organic Synthesis

Alkyl Aluminum Halide Promoted Intramolecular Cyclization of ω-Allyl-cycloalk-2-enones: Access to Bridged Bi- and Tricyclic Compounds

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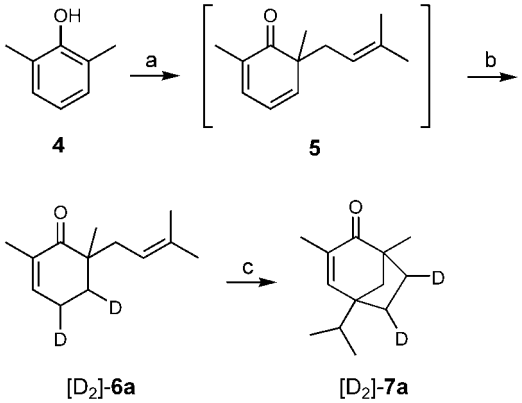
Dedicated to Professor Günter Helmchen

The cationic cyclization of olefins has been developed as an important methodology in organic synthesis.[1] Since Stork and Burgstahler and Eschenmoser et al. rationalized the proton-catalyzed biological cyclization of polyprenoids,[2] a variety of different initiators of this and related reactions have been developed.[3] Intramolecular Lewis acid promoted conjugate additions of olefins to α,β-unsaturated ketones or aldehydes belong to this category,[4] although, depending on the Lewis acid, the course of such cyclizations can be different. Snider et al. demonstrated that cyclohexenone **1** reacted in the presence of $SnCl_4$ to compound **2** which is the product of a concerted Lewis acid induced ene reaction,[5] while treatment of **1** with two equivalents of $MeAlCl_2$ (or $EtAlCl_2$) resulted in naphthalenone **3** (Scheme 1).[6] It was deduced that this compound was generated by two consecutive 1,2-H shifts of zwitterionic intermediates **A** and **B** rather than by one 1,3-H shift as the relative configuration of the stereogenic centers C4a and C8 was determined to be *anti*.

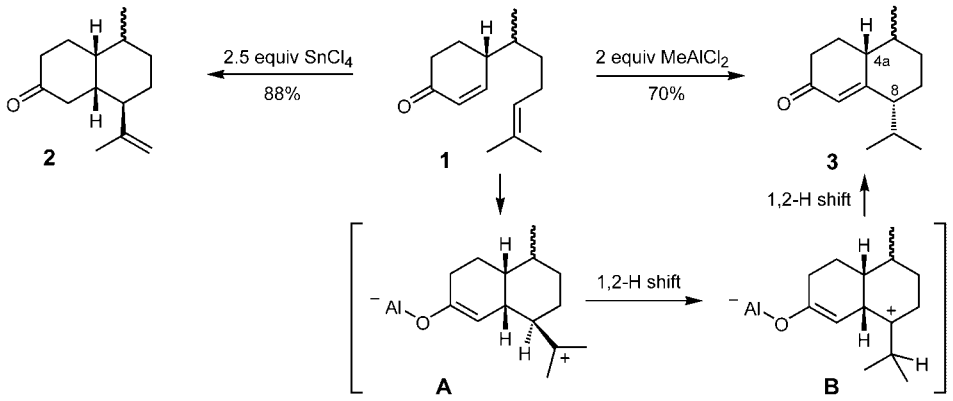
This unique behavior of alkyl aluminum halides as Lewis acids was partially explained by their Brønsted base-like character: Any adventitious water will be scavenged by forming an alkane and a new Lewis acid.[7]

While investigating novel syntheses of functionalized odorants,[8] we observed a novel and unexpected $EtAlCl_2$ promoted cyclization of cyclohexenone **6a** to bicyclo[3.2.1]octenone **7a** (see Table 1, entry 1) which displays a pleasant woody vetiver-like odor.[9] To better understand this reaction, labeled substrate [D_2]-**6a** was prepared by a selective deuteration of unstable trienone **5**[10] which was accessible by C-alkylation of phenol **4** (Scheme 2).[11] After cyclization,



Scheme 2. Synthesis of [D_2]-**7a** by deuteration of trienone **5**. Conditions: a) NaH, toluene, prenyl chloride; b) MeOH, Pd/C, D_2; c) 1.5 equiv $EtAlCl_2$, toluene.

the overall deuterium incorporation of [D_2]-**6a** was retained in [D_2]-**7a**, which indicates a) the methylene-bridge in **7a** stems from the prenyl group and b) the deuterated positions of the cyclohexenone unit of **6a** are not the locations of intermediate zwitterions.



Scheme 1. Ene reaction versus cationic cyclization of **1**.[6]

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Further investigation (Table 1) revealed that the cyclization tolerates cycloalkenones of different substitution at R^1–R^6 and also of different ring sizes, although yields decrease with increasing steric strain (entries 3,4) and increasing ring size (entries 8,9). Additional unsaturation in substituents R^2,R^4, and R^6 (entries 5,6,7) neither disturbed the cationic cyclization, nor was a competitive or subsequent cyclization observed in these cases.[12] The yields dramatically decreased

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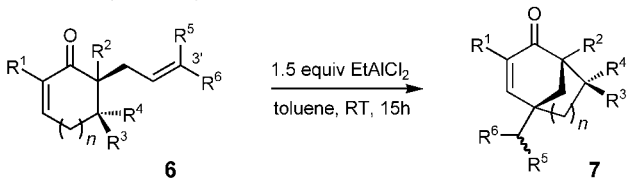
Table 1: Cyclization of allyl cycloalkenones **6** to bicyclic compounds **7**.



6 **7**

Entry	R^1	R^2	R^3	R^4	R^5	R^6	*n*	d.r.	Product [%][a]
1	Me	Me	H	H	Me	Me	1	-	**7a** 95
2	Me	H	H	H	Me	Me	1	-	**7b** 86
3	Me	H	Me	Me	Me	Me	1	-	**7c** 67
4	Me	Me	H	H	Me	*c*-C_6H_{13}	1	-	**7d** 54
5	Me	Me	H	H	Me	$CHC(CH_3)_2$	1	1.6:1	**7e** 90
6	Me	prenyl	H	H	Me	Me	1	-	**7f** 75
7	Me	H	H	$C(CH_2)CH_3$	Me	Me	1	7:3[b]	**7g** 71
8	H	H	H	H	Me	Me	2	-	**7h** 64
9	H	H	H	H	Me	Me	3	-	**7i** 45
10	Me	Me	H	H	H	Me	1	-	**7j** 30[c]
11	Me	Me	H	H	Me	$(CH_2)_2CO_2Me$	1	1.5:1	**7k** 86[c,d]

[a] Products isolated by chromatography. [b] *Endo:exo*-isomers at 7-position. [c] Reaction was carried out at 80 °C. [d] 3 equiv $EtAlCl_2$, 8 h.

with R^5 or $R^6 = H$, which reflects the necessity of cation stabilization at the 3′ position of the allylic substituent in ketone **6** (Table 1, entry 10). Entry 11 shows that an additional ester group in substrate **6k** consumes at least one equivalent of the Lewis acid by a competitive complexation, although esters were shown to be less basic than ketones.[13]

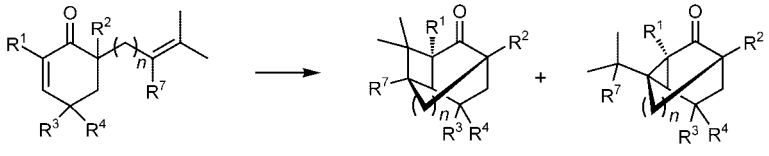
The outcome of the cyclization does change completely with different substitution patterns of ketones **8**[10] (Table 2). In these cases, mixtures of tricyclic compounds **9** and **10** were usually obtained, in ratios not very much influenced by varying steric demand of the substituents R^3 and R^4. However, cyclization of compound **8a** (R^3, $R^4 = H$) led to a mixture of **9a** and **11a** (see Scheme 3) while the transformation of homoallylic derivative **8f** provided compound **10f** exclusively.

These observations are in accordance with the proposed mechanism in Scheme 3. It can be explained by a sequence of 1,2-H and alkyl shifts that were proposed by Snider et al.[6,7]

The conversion of compounds **6** (and **8a**) follows path A. The initially formed zwitterion results from cyclization of the enone–$EtAlCl_2$ complex with the allyl side chain being in an *s-trans* conformation. Subsequent 1,2-H (or methyl) shift followed by intramolecular alkyl migration generates compounds **7** (**11a**). In path B, the allyl side chain of compounds **8** may be sterically (R^3,R^4 = alkyl, $R^7 = Me$) pushed into a *s-cis* conformation which gives, after the initial cyclization, the cation close to the enolate. This effect may also be caused by angular strain that occurs during the cyclization of homoallylic derivative **8f**. The quenching of charges in the zwitterionic intermediate at this stage results in compounds **9**. However, the 1,2-R^7 shift is rapid enough to allow path B to be partially terminated by the formation of compounds **10**.

In summary, the novel $EtAlCl_2$-induced cyclization of 6-allyl cyclohexenones is a flexible tool for the synthesis of bi- and tricyclic compounds. The scope and limitations were investigated with respect to substitution patterns.

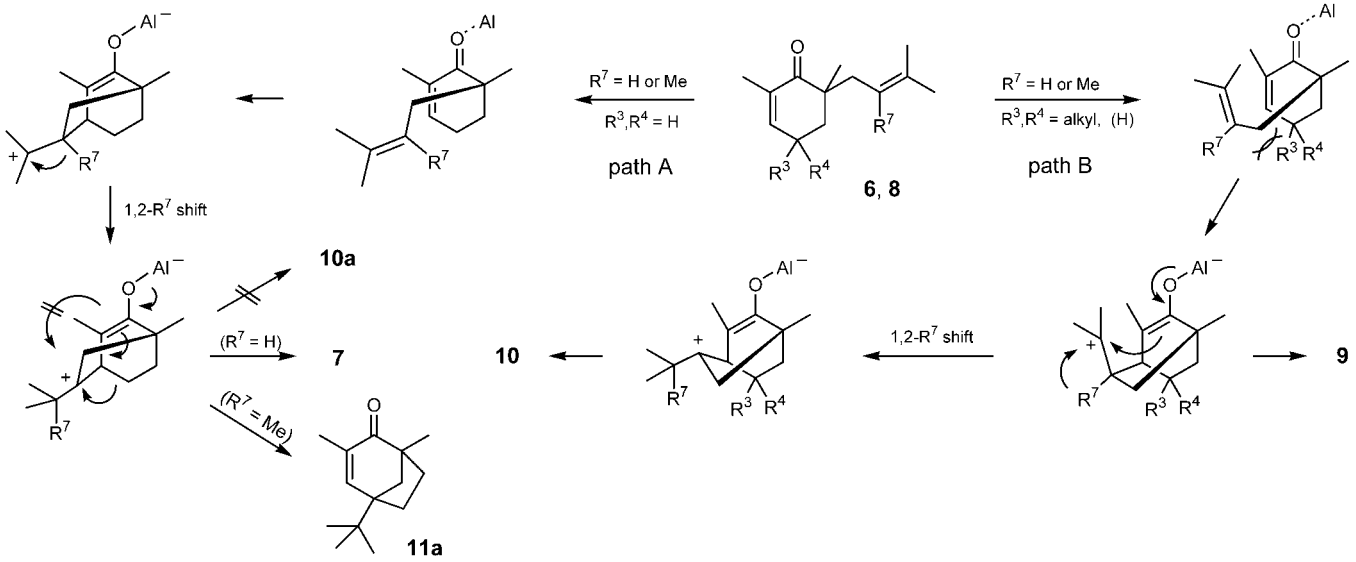
Table 2: Cyclization of cyclohexenones **8** to tricyclic compounds **9**, **10**, and **11**.



8 **9** **10**

Entry	Compound	R^1	R^2	R^3	R^4	R^7	*n*	Ratio	Yield [%][a]
1	**8a**	Me	Me	H	H	Me	1	**9a**:**11a**[b] (1:1)	61
2	**8b**	H	Me	Me	Me	H	1	**9b**:**10b** (1.4:1)	74
3	**8c**	Me	Me	Me	Me	Me	1	**9c**:**10c** (1:1.4)	52
4	**8d**	H	Me	$CH_2(CH_2)_3CH_2$		H	1	**9d**:**10d** (1.1:1)	78
5	**8e**	Me	Me	$CH_2(CH_2)_2CH_2$		H	1	**9e**:**10e** (1.5:1)	86
6	**8f**	Me	Me	H	H	H	2	only **10f**	60

[a] Products isolated by chromatography. [b] For compound **11a** see Scheme 3; **10a** was not detected.



Scheme 3. Mechanistic considerations.

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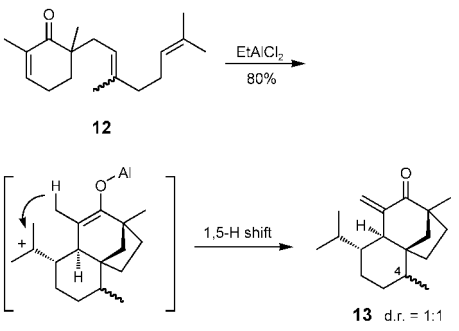

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