Tetrahedron Letters, Vol.32, No.12, pp 1549-1552, 1991
Printed in Great Britain

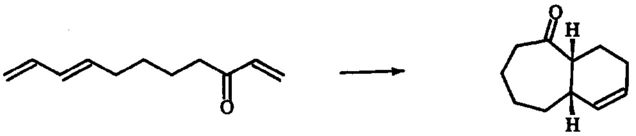
0040-4039/91 $3.00 + .00
Pergamon Press plc

$LiBF_4$: A Mild Lewis Acid for Intramolecular Diels-Alder Reactions.#

Douglas A. Smith*
Department of Chemistry, University of Toledo, Toledo, OH 43606
K. N. Houk
Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90024

Summary: The lithium salts, $LiClO_4$ and $LiBF_4$, have been investigated for their potential use as Lewis acid catalysts in the intramolecular Diels-Alder reaction. No cycloaddition of the trienone, 1, is observed when $LiClO_4$ is used. $LiBF_4$ provides quantitative yield of the *cis*-fused cycloadduct in 72 hours at room temperature. The catalysis is ascribed to the slow release of BF_3 rather than to the lithium cation.

A large number of Lewis acid catalyzed intramolecular Diels-Alder reactions have been reported. In addition to the classic Lewis acids such as $BF_3{\bullet}OEt_2$, $TiCl_4$, $SnCl_4$, and AlC13, several alkyl and alkoxy aluminum chlorides[1], WCl_4[1], $NbCl_5$[1], CF_3CO2H[2], H_2SO_4[3], HF[4], $HSbCl_6$[5], CF_3SO_3H[5], *p*-TsOH[5], and tris(*p*-bromophenyl)aminium hexachloroantimoniate[5] have been used with varying degrees of success. While the lithium cation is the archetypical Lewis acid for theoretical studies, no experimental reports of lithium salts as Lewis acid catalysts have appeared. A recent report by Grieco[6] suggests that 5M $LiClO_4$ in diethyl ether acts not as a Lewis acid, but rather provides a high internal solvent pressure which, due to the large negative volume of activation for intermolecular Diels-Alder reactions, results in increased rates and selectivities. Intramolecular Diels-Alder reactions involving tethers of less than six carbons typically have less negative activation entropies due to a reduction in the degrees of freedom available.[7] We have investigated the use of two lithium salts, $LiClO_4$ and $LiBF_4$, as catalysts for the intramolecular Diels-Alder reaction of trienone 1 (Equation 1). We have previously studied the cycloaddition of this substrate[8], and found that while the yield of cyclized product 2 is essentially the same from either the thermal or Lewis acid catalyzed reactions, the stereoselectivity for the *cis*-fused product changes from approximately 2:1 to 100%.



1

2

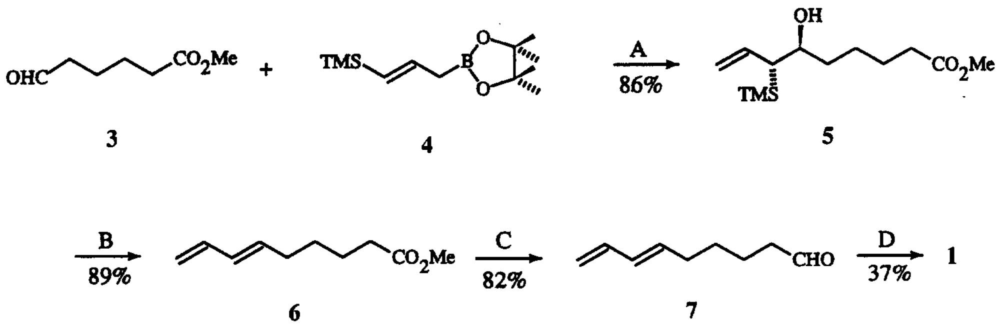
Equation 1

Trienone 1 was prepared in 5 steps and 26% yield from methyl 6-oxohexanoate, 3, as shown in Scheme 1.[9,10] Treatment with pinacol E-1-trimethylsilyl-1-propene-3-boronate[11], 4, followed by silica gel chromatography to cleave the boronate ester, gave silyl alcohol 5. Subsequent Peterson olefination gave

Dedicated to the memory of Professor Kunio Sakan.

exclusively the E diene ester, **6**. DIBAL reduction at -78 °C gave the aldehyde, **7**, which was treated with vinylmagnesium bromide to give the trienol. Swern oxidation[12] gave the cycloaddition substrate, **1**.

Scheme 1



A. 1) Ether, room temp.; 2) silica gel chromatography (4:1 pet. ether:ether). B. cat. conc. H_2SO_4, THF, room temp. C. 1.1 eq. DIBAL, CH_2Cl_2, -78 °C, 10 min. D. 1) $CH_2CHMgBr$, THF, -78°C 2) DMSO, $(CF_3CO)_2O$, CH_2Cl_2, -78 °C; 3) Et_3N, -78 °C → room temp.

The cycloaddition reactions were run in dry benzene under argon at room temperature, 1.1 equivalents of the lithium salt as a 1M solution in acetonitrile were added to the trienone and stirred for 48-72 hours. Use of $LiClO_4$ gave only quantitative recovery of starting material. $LiBF_4$, however, provided *cis*-fused bicyclo[5.4.0]undecenone, **2**, quantitatively after 72 hours.[13] No *trans*-fused product was detected by 300 MHz ^1H NMR. This represents the selectivity of the cyclization; the product has been shown to be configurationally stable in the presence of Lewis acid.[8] Treatment of **2** with NaOMe in methanol at 55 °C for 74 hours provided a 1:3 mixture of *cis*- to *trans*-bicyclo[5.4.0]undecenone. These results are impressive, when one considers that slow addition of a dilute solution of the trienone to 0.1M Me_2AlCl in benzene was required to maximize the yield of **2** by avoiding intermolecular reactions (cf. Table 1).[14]

Table 1. Intramolecular Diels-Alder Reaction of Trienone 1.

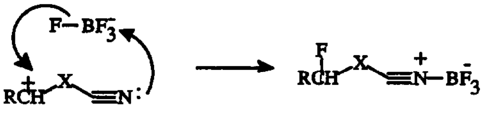
Conditions[a]	Time	Temp	Percent Yield	*cis*:*trans* Ratio
thermal	5 h	155 °C	90	62:38
0.02M **1** 0.1M Me_2AlCl[b]	3 h	25 °C	88	100:0
0.016M **1** 1.0M $LiBF_4$[c]	72 h	25 °C	100	100:0

[a] All reactions were run in dry benzene under argon. [b] 4 equivalents.
[c] 1.1 equivalents.

$LiBF_4$ has been used for the cleavage of silyl ethers[15] and the hydrolysis of acetals and ketals.[16] Lipshutz has suggested that $LiBF_4$ operates as a source of lithium, fluoride ion and BF_3 via a "push-pull" mechanism.[15b] Generation of some BF_3 for the pull was thought to be necessary. It was also noted that acetonitrile was the only solvent in which this dissociative mechanism was operative.[17] Since the substrate and all other solvents investigated contained oxygen, this was interpreted as due to a lack of competition between the nitrile and the substrate for association.

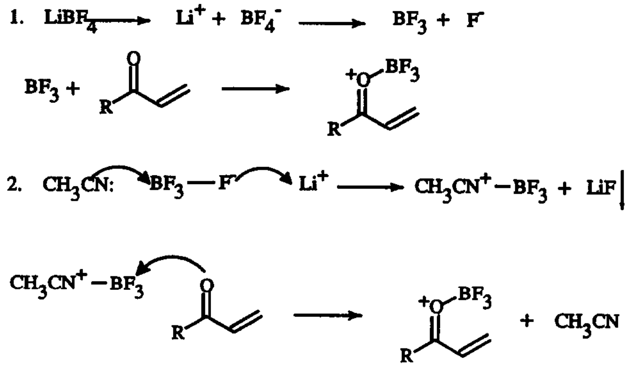
Three control experiments were conducted in order to provide further insight. A solution of 1 in benzene containing a small amount of acetonitrile (35 mL to 1 mL benzene) provided only quantitative recovery of starting material after 72 hours, as did the reaction with 1.1 equivalents of Me_4NBF_4 in the same solvent mixture. Equimolar $LiBF_4$ and dibenzo-18-crown-6 (precomplexed for 30 minutes) in acetonitrile-benzene gave the cycloadduct 2, although much more slowly than when the crown ether was absent (approximately 50% conversion after 72 hours).

It appears, therefore, that the lithium cation cannot be the Lewis acid species responsible for the observed catalysis. Rather, $LiBF_4$ functions as a slow releasing source of BF_3. This is most likely due to the inherent low stability of $LiBF_4$; the partial pressure of BF_3 above the solid salt is 30 torr at room temperature, the highest value for any tetrafluoroborate salt.[17] Alternatively, the acetonitrile may play a key role. Doyle has described the reaction of BF_4^- with nitriles in the presence of cations to produce the nitrile-boron trifluoride complex (Equation 2).[18] This would explain Lipshutz's observations of solvent dependance. Operation of both mechanisms (Scheme 2) is consistent with our observation of catalysis and the decreased rate of reaction in the presence of the crown ether.



Equation 2

Scheme 2



We conclude from these studies that the lithium cation derived from either $LiClO_4$ or $LiBF_4$ does not function as a Lewis acid for catalysis of the intramolecular Diels-Alder reaction in a nonpolar solvent such as

benzene. However, use of $LiBF_4$ as a slow releasing BF_3 source for catalysis negates the need for inverse addition and high dilution techniques. Exploitation of this method is currently under investigation in our labs.

References and Notes

1. Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* 1982, *104*, 2269.
2. Stork, G.; Clark, G.; Shiner, C. S. *J. Am. Chem. Soc.* 1981, *103*, 4948.
3. Snider, B. B; Duncia, J. V. *J. Org. Chem.* 1980, *45*, 3461.
4. Roush, W. R.; Gillis, H. R.; Essenfeld, A. P. *J. Org. Chem.* 1984, *49*, 4674.
5. Gassman, P. G.; Singleton, D. A. *J. Am. Chem. Soc.* 1984, *106*, 6085.
6. Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* 1990, *112*, 4595.
7. Ciganek, E. "The Intramolecular Diels-Alder Reaction" in *Organic Synthesis*, vol. 32, W. G. Dauben, Ed., 1984, p. 1.
8. Smith, D. A.; Sakan, K.; Houk, K. N. *Tetrahedron Lett.* 1986, *27*, 4877.
9. Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* 1982, *23*, 3867.
10. All compounds gave satisfactory ^{1}H and ^{13}C NMR, IR, and high resolution mass spectra data.
11. Tsai, D. J. S.; Matteson, D. S. *Tetrahedron Lett.* 1981, *22*, 2751.
12. Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* 1976, *41*, 957.
13. 2 was identical (^{1}H and ^{13}C NMR, IR, HRMS, and tlc) to an authentic sample.[3] Spectral data for *cis*-bicyclo[5.4.0]undec-5-ene-1-one, 2: ^{1}H NMR ($CDCl_3$) d 5.69 (dm, J = 9.1Hz, 1H) 5.59 (dm, J = 9.1Hz, 1H), 2.68 (ddd, 1H) 2.62 (bm, 1H), 2.53 (dddd, J = 11.3, 6.0, 3.0, 1.1Hz, 1H), 2.39 (ddd, 1H), 2.2-1.75 (m, 4H), 1.68-1.1 (m, 6H); ^{13}C NMR d 131.4 (d), 126.6 (d), 50.7 (d), 42.2 (t), 36.2 (d), 32.3 (t), 30.0 (t), 26.7 (t), 19.9 (t); IR ($CDCl_3$) 3020, 2940, 2860, 1695, 1445; HRMS (m/e) 164 (M^+, 70%), 146, 135, 121, 117, 107, 104, 94, 92, 79 (100%), 55; calc. for $C_{11}H_{16}O$: 164.1201, found 164.1200. Spectral data for *trans*-bicyclo[5.4.0]undec-5-ene-1-one: ^{1}H NMR (C_6D_6) d 5.61 (m, 1H), 5.31 (bd, J = 5Hz, 1H), 2.27-2.09 (m, H = 12.7, 10.3, 2.4Hz, 3H), 1.95-1.75 (m, 4H), 1.65-1.15 (m, 6H), 1.0-0.8 (m, 2H); IR ($CDCl_3$) 3025, 2940, 2855, 1695, 1625; HRMS (m/e) 164 (M^+, 35%), 146, 135, 120, 107, 93, 79, 67, 57 (100%)
14. Other cycloaddition substrates studied (cf. reference 8) gave qualitatively similar results.
15. a) Metclaf, B. W.; Burkhart, J. P.; Jund, K. *Tetrahedron Lett.* 1980, *21*, 35. b) Lipshutz, B. H.; Pegram, J. J.; Morey, M. C. *Tetrahedron Lett.* 1981, *22*, 4603.
16. Lipshutz, B. H.; Harvey, D. F. *Synth. Commun.* 1982, *12*, 267.
17. Complexes of CH_3CN and BF_3 are well known. See, for example: Greenwood, N. N. *Quart. Rev.* 1954, *8*, 1.
18. Doyle, M. P.; Whitefleet, J. L.; Zaleta, M. A. *Tetrahedron Lett.* 1975, 4201.

(Received in USA 4 December 1990)