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CHIRAL LEWIS ACIDS FOR ENANTIOSELECTIVE C-C BOND FORMATION

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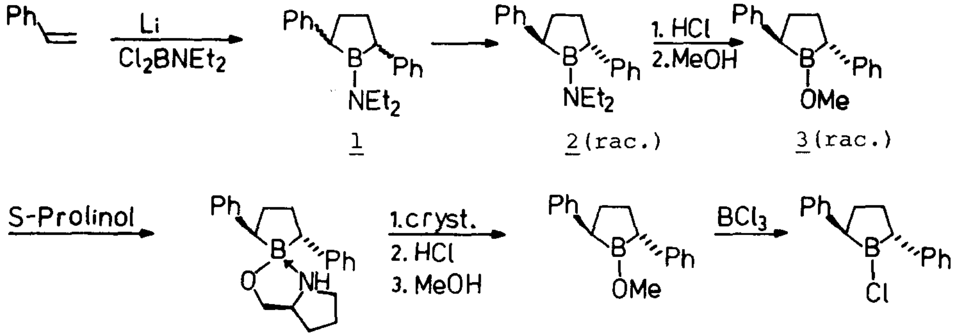
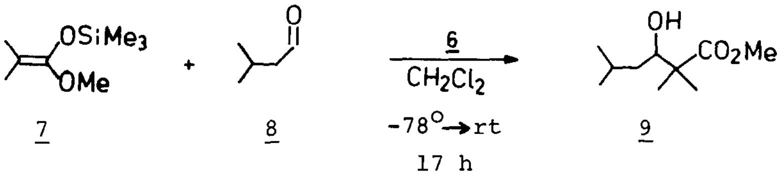
Summary: The optically active Lewis acid 6 has been prepared and used in the enantioselective addition of enolsilanes and Me_3SiCN to aldehydes.

Lewis acids have been used to perform a variety of C-C bond forming reactions, including carbonyl addition reactions of enolsilanes, cyanotrimethylsilane and other silylated C-nucleophiles[1)]. Stoichiometric amounts of Lewis acids are often employed, but exceptions are known. An attractive strategy for enantioselective reactions would be the use of chiral Lewis acids[2,3)]. This Letter describes one of the approaches that we are taking in this endeavor.

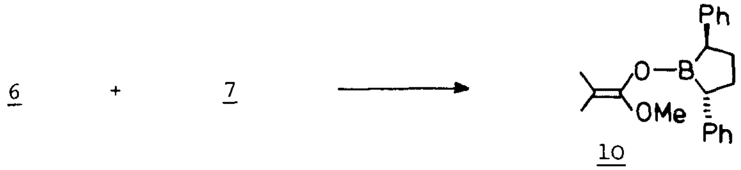
We speculated some time ago that the chiral boron compound 6 could be a useful candidate[3)]. Of the several different approaches to its synthesis, the following was best. Reductive dimerization of styrene in the presence of Cl_2BNEt_2 gave a cis/trans mixture of 1. Crystallization afforded a 45% yield of 2 (>99% purity; one enantiomer arbitrarily shown). Addition of HCl and methanol followed by crystallization yielded >99% pure 3 (98%), which was converted into the diastereomers 4[4,5]. The diastereomer that crystallized first (83 % yield) was treated with HCl/MeOH, forming optically active 5[4]. Treatment with BCl_3 led to the optically active 6[4] (98% yield; ee ≥95%)[6].



We first tested the aldol addition of 7 to 8 in the presence an equivalent amount of 6. Aqueous workup and chromatography led to a 57% yield of 9 having an ee value of 90%[7]. Use of less than one equivalent of 6 reduced conversion.



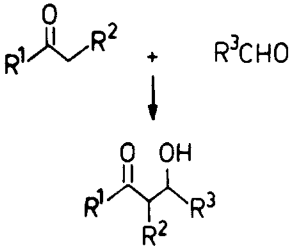
In order to shed light on the mechanism of the reaction, 7 was treated with 6 in the absence of an aldehyde. H, ^{13}C and ^{11}B NMR spectroscopy revealed that under the reaction conditions a Si/B exchange to 10 sets in, showing that it is the reacting species in the aldol addition.



Since ketones can be O-borylated directly in the presence of Hünig bases[8], we performed the following aldol additions (Table 1):

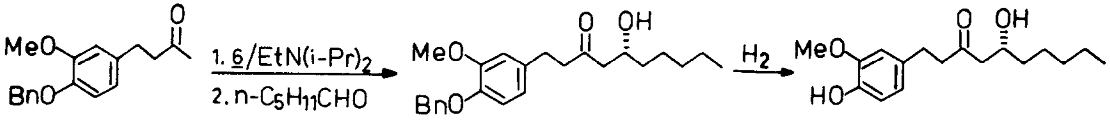
Table 1 Enantioselective Aldol Additions(-78°C/1 h)

R^1	R^2	R^3	Yield[a)] (%)	ee[b)] (%)
Me_2C	H	Me_3C	55	84
Me_2C	H	Ph	60	32
Me_3C	H	$n\text{-}C_5H_{11}$	67	81
$-(CH_2)_3$	-	Ph	65	92[c)]



a) Non-optimized isolated yield; b) values determined by the Mosher method; absolute configurations presently unknown; c) syn/anti diastereomer ratio is 13:87; ee value pertains to the anti diastereomer.

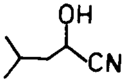
Using 11 and n-hexanal, the aldol 12 was obtained (58% yield; ee=66%). Hydrogenolysis afforded (-)-13 having the R-configuration. This is the enantiomer of natural S-(+)-gingerol[9)]. We are currently attempting to determine the absolute configuration of 6 via an X-ray structural analysis of 4, so that a discussion of the detailed mechanism of aldol addition becomes meaningful.



11 12 13

The optically active Lewis acids 5 and 6 can also be used as catalysts, e.g., in the addition of Me_3SiCN to 8 . After aqueous workup (and deprotection), the cyanohydrin 14 of unknown absolute configuration was obtained (45-55% yield) having an ee-value of 12-16% (Mosher method). This is the first example of a Lewis acid catalyzed enantioselective addition of Me_3SiCN to a carbonyl compound.

$$\underline{8} \quad + \quad Me_3SiCN \quad \xrightarrow[\underline{6}(20\ \text{mol-}\%)\ -78^\circ C/140\ h]{\underline{5}(10\ \text{mol-}\%)\ \text{or}}$$



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It remains to be seen whether more efficient chiral Lewis acid catalysts can be developed for these and other C-C bond forming reactions.

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References and Notes

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6. The ee value was determined by oxidative cleavage to the 1,4-diol which was analyzed by the Mosher method (R-MTPA-Cl). ^{11}B NMR (CDCl$_3$) of 6: δ = 79 ppm (upfield from BF$_3$·OEt$_2$); ^{13}C NMR (CD$_2$Cl$_2$): δ = 50.8 (C2, broad due to boron) 32.6 (C3) and 128.5, 128.7, 128.8, 141.9 for the aromatic C-atoms.
7. Determined by NMR shift experiments using Eu(tfc)$_3$; absolute configuration currently unknown.
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