272. Three New Chiral Aminoethers from Tartaric Acid for Improved Asymmetric Syntheses with Organolithium Reactions

Preliminary communication

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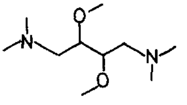
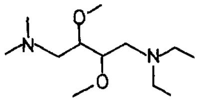
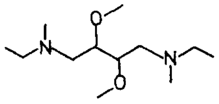
Summary

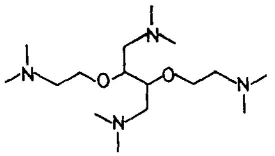
The chiral aminoethers **1–4**, accessible from tartaric acid, are tested as complexing ligands in organolithium reactions. The tetramine **4** turns out to cause highest inductions [see *Table 2* and Equations (1)–(4)].

In our continuing search for chiral solvents and complexing reagents which render reactions of polar organometallics enantioselective [1], we have recently taken four directions. One was to remove the C_2-axes of the previously employed aminoether DDB[1a] **1** as in **2**[1b]; the second was to make the N-atom a center of chirality when complexed to a metal, see **3**[2]. Thirdly, we increased the number of heteroatoms in order to get more stable complexes with multidentate ligands


(*S,S*)-**1** (DDB)
$[\alpha]_D = +14.7°$ (neat)


(*S,S*)-**2**
$[\alpha]_D = +23.4°$ ($c = 3$, C_6H_6)


(*S,S*)-**3**
$[\alpha]_D = +23.9°$ ($c = 2$, C_6H_6)


4 (DEB)
(*S,S*): $[\alpha]_D = -33.3°$ ($c = 2$, CH_3OH) (*R,R*): $[\alpha]_D = +34.5°$ ($c = 2$, CH_3OH)

[1a] DDB = 2,3-dimethoxy-1,4-bis(dimethylamino)-butane (following IUPAC-rules: 2,3-dimethoxy-butane-1,4-bis(dimethylamin).

[1b] From diacetoxy succinic anhydride [2] by reaction with diethylamine, esterification, reaction with dimethylamine, etherification and LAH reduction.

[2] From dimethoxy-*N,N'*-dimethylsuccinamide [1b] by reduction, acetylation, reduction.

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Table 1. *Results of the reaction of benzaldehyde with butyllithium at different ratios aldehyde: amino-ether and different concentration* (chiral auxiliary from (*R,R*)-tartrate, 10 mmol scale, $-78°$, pentane)

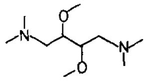
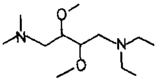
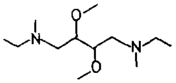
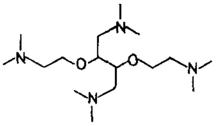
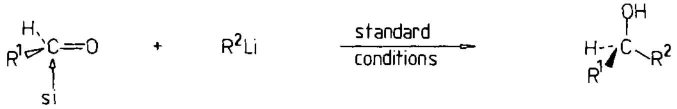
	Auxiliary mol-equiv.	Tot. volume (ml)	% e.e.	
 **1** (DDB)	10	40	19	*R*
	10	350	22	
	4	400	23	
 **2**	10	40	34	*R*
	4	400	29	
 **3**	5	40	30	*R*
	4	400	30	
 **4** (DEB)	1	100	38	*S*
	2	400	52	

Table 2. *Reactions of aldehydes with organolithium derivatives in the presence of 2 mol-equiv. of (S,S)-DEB in pentane; total volume 400 ml* (temperature $-78°$; 10 mmol scale; for determination of optical yields and sense of chirality (absolute configuration) see [1b] and [4])



R^1	R^2	% e.e.	R^1	R^2	% e.e.
CH_3	C_4H_9	46	p-CH_3–C_6H_4	C_4H_9	49
C_2H_5	C_4H_9	35	$(C_2H_5)_2CH$	C_4H_9	46
C_4H_9	CH_3	34	$(CH_3)_2CH$	C_4H_9	53
C_6H_5	C_4H_9	52	$(CH_3)_3C$	C_4H_9	18
C_4H_9	C_6H_5	15	cyclo-C_6H_{11}	C_4H_9	48
o-CH_3–C_6H_4	C_4H_9	56	$H_2C{=}CH$	C_4H_9	24

such as **4** (DEB)[3]. Finally, we found that working at higher dilutions in the cosolvent pentane is advantageous.

The results of these changes were first tested with the standard reaction between benzaldehyde and butyllithium (see *Table 1*). By far the highest enan-

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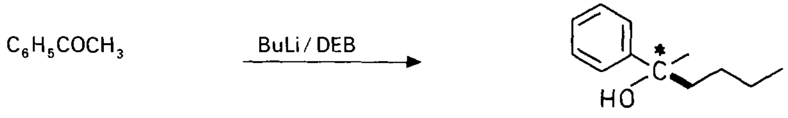
[3] From *N,N,N',N'*-tetramethyl-2,3-bis(carbethoxymethoxy)-succinamide [3] and dimethylamine, and subsequent reduction.

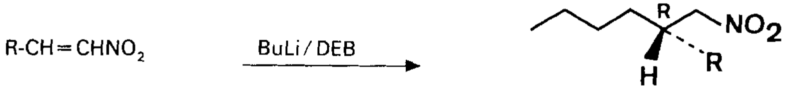
tiomeric excess was obtained with DEB which was also applied to a variety of other transformations, see *Table 2* and equations (1)-(4).

(1)



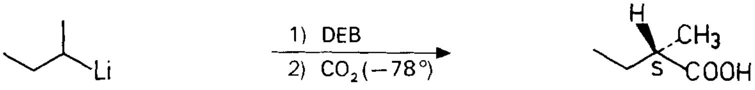
23% e.e.[4])

(2)



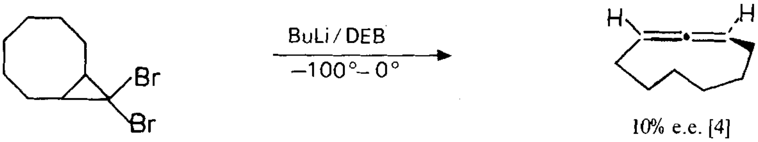
R = CH_3: 58% e.e.
R = C_6H_5: $[\alpha]_D = -4.6°$ (cf. [1d])

(3)



20% e.e. [4]

(4)



10% e.e. [4]

The following points about the use of DEB are noteworthy: (i) it is most efficient at a *2:1 ratio* and in *dilute* pentane solution; (ii) the optimum *temperature* appears to be *−80°* (−55°: 35% e.e., −130°: 49% e.e.); (iii) with only half the amount of chiral auxiliary, DEB gives an improvement of enantiomeric excess for the standard reaction by a factor of 2.5 as compared with DDB; (iv) in contrast to DDB, DEB reliably causes preferential attack from the Si-face with all aldehydes and lithiumcompounds tested; (v) DEB induces well even with simple aliphatic aldehydes and a ketone; (vi) the result obtained with DEB in the standard reaction is hardly altered in the presence of a tenfold excess of (+)-DDB [41.5% e.e. of (−)-phenylpentanol with (*S,S*)-DEB and 49.6% e.e. of (+)-phenylpentanol with (*R,R*)-DEB]; thus, a strong and well defined complex must be formed from DEB and butyllithium; (vii) we propose structure **5** as being responsible for the enantioselectivities observed; (viii) as with the chiral proline derived ate-complexes [5][5]), the induction is different in the beginning and at the end of the reaction: the first 20% of reaction produce phenylpentanol of *ca.* 45% e.e., the last 20% of only 17% e.e.

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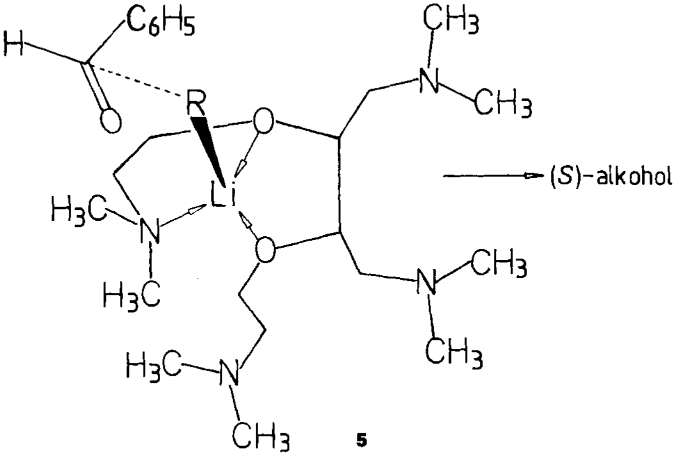
[4]) As determined by Eu(TFC)$_3$-^{1}H-NMR. shift measurements.

[5]) It must be concluded from the ratios employed (4.0 mol.-equiv. of proline derivative +6.7 mol-equiv. of butyllithium +1.0 mol-equiv. of benzaldehyde) that only the first 37% of the reaction give the high e.e. reported [5].



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[2] *F.D. Chattaway & G.D. Parkes,* J. chem. Soc. *123*, 663 (1923).

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