CHEMISTRY LETTERS, pp. 17-20, 1980.

ENANTIOFACE-DIFFERENTIATING ADDITION OF A CHIRAL ARYLLITHIUM REAGENT TO ALDEHYDES

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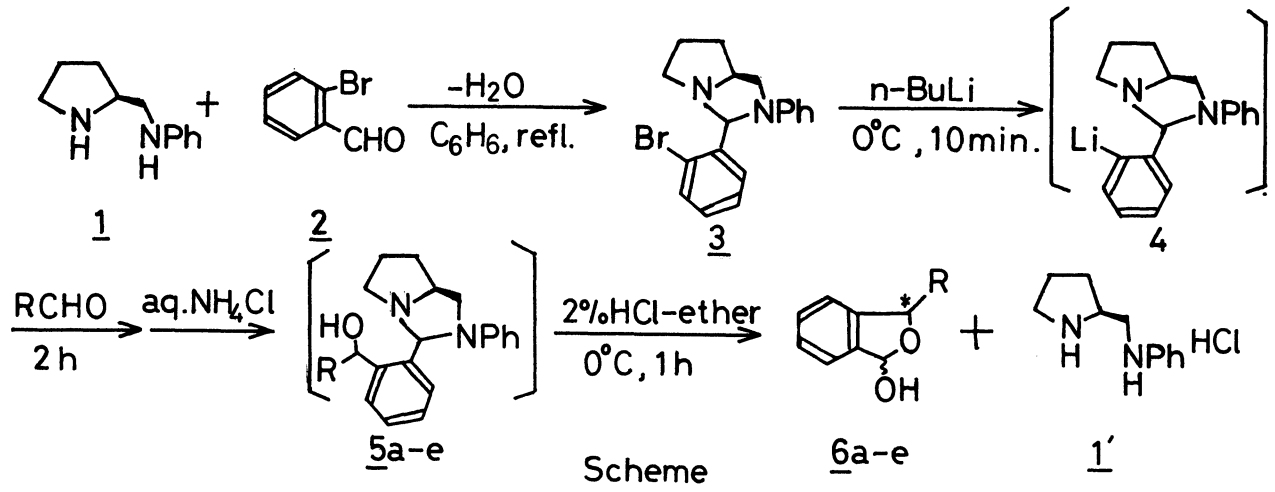
A chiral aryllithium reagent was prepared by treating a chiral aminal, derived from (S)-2-(anilinomethyl)pyrrolidine and o-bromobenzaldehyde, with n-butyl lithium. The chiral reagent reacted highly enantioface selectively with aliphatic aldehydes and, on hydrolysis of the resulting aminals, various 3-alkyl-1-hydroxy-2-oxaindanes with high enantiomeric excesses were obtained. The oxidation of 3-butyl-1-hydroxy-2-oxaindane with silver oxide afforded (S)-3-butylphthalide, an essential oil of celery, with 88% e.e..

Recently we reported the highly diastereoface-differentiating reactions of chiral aminals, derived from (S)-2-(anilinomethyl)pyrrolidine and functionalized aldehydes, with the Grignard reagent.[1] It was shown there that the chiral aminals are very effective for creating chiral environments.

Now we wish to report that the chiral aryllithium reagent possessing the aminal function added highly enantioface selectively to various aldehydes.

Many attempts have been reported on the enantioface-differentiating addition of the organometallic reagent to aldehydes by using various chiral ligands. However, the optical yields are generally not so high especially in the case of aliphatic aldehydes.[2]

The preparation of the chiral lithium reagent and the reaction of the chiral lithium reagent with aldehydes are represented in the following scheme.

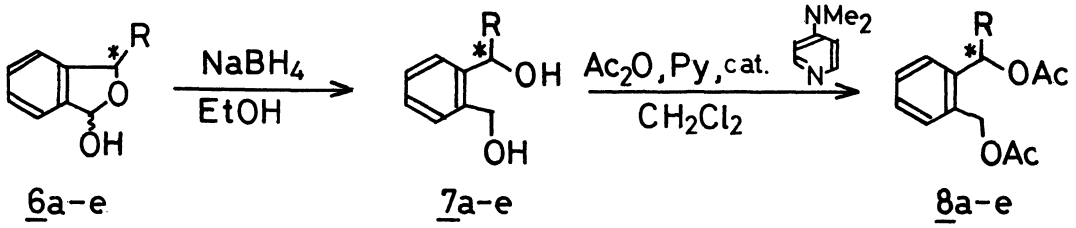


Scheme

Table The preparation of the chiral lactols 6a-e.

lactols 6	R	solvent	temp.	yield(%)	$[\alpha]_D$(c,C_6H_6)	e.e.(%)[a]
a	n-C_4H_9	toluene[b]	-78°C	73	-28.2°(5.53)	65
		ether	-78°C	63	-33.7°(3.80)	78
		ether	-100°C	62	-36.9°(3.47)	87
b	Et	ether	-100°C	51	-42.6°(5.35)	88
c	i-Pr	ether	-100°C	52	-65.8°(5.65)	>90[c]
d	n-C_8H_{17}	ether	-100°C	58	-24.6°(4.75)	90
e	CH_3CH=CH	toluene[b]	-78°C	70	+7.5°(3.73)	20

a) The enantiomeric excesses were determined by integration of one of the acetyl groups in diacetates 8a-e by 90 MHz ^{1}H-NMR using tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III) and tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]praceodymium(III) as chiral shift reagent.



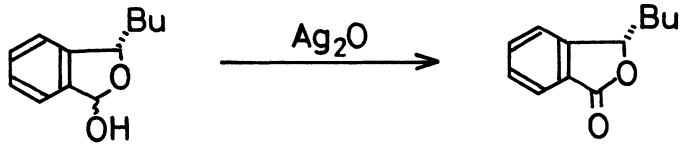
b) Two equivalents of n-butyl lithium and the aldehyde were used.

c) Only one enantiomer was detected by NMR.

The aminal 3 was prepared easily by mixing (S)-2-(anilinomethyl)pyrrolidine and o-bromobenzaldehyde in refluxing benzene and was recrystallized from cyclohexane: mp 169-170.5°C $[\alpha]_D^{23}$+125° (c 1.01, CH_2Cl_2).[3] Then the chiral lithium reagent 4 was prepared in situ by treating the aminal 3 with n-butyl lithium in ether or toluene. The aminals 5 a-e were obtained by the treatment with aldehydes and the chiral 3-alkyl-1-hydroxy-2-oxaindanes (lactols) 6 a-e[4] with high enantiomeric excesses were obtained. The results are summarized in a Table.

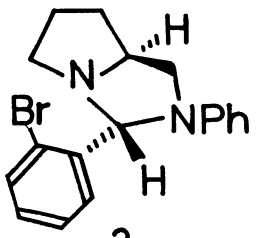
As shown in the Table, the high optical yields were attained by choosing ether as solvent and lowering the reaction temperature. Typical experimental procedure is as follows: The ethereal suspension (1 ml) of aminal 3 (172 mg, 0.5m mol) was added a hexane solution of n-butyl lithium (0.38 ml, 0.6m mol) at 0°C and stirred for ten minutes under an argon atmosphere. Then the reaction mixture was cooled to -100°C and pentanal (52 mg, 0.6m mol) was added. The reaction mixture was stirred for 2h at -100°C and quenched with saturated aqueous ammonium chloride solution. Then the ethereal layer was hydrolyzed with 5 ml of 2% HCl at 0°C for 1h. The ethereal layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resulting oily substance was separated by TLC to give the lactol 6a (61 mg, 62%), $[\alpha]_D^{23}$-36.9°, (c 3.47, C_6H_6), 87%e.e.. The diamine 1 was recovered from the aqueous layer by usual work up.

Next, the lactol 6a $[\alpha]_D^{23}$-36.9 (c 3.47, C_6H_6), was oxidised with silver oxide[5], without any racemization, to (S)-3-butylphthalide 9, the essential oil of celery, 88%; $[\alpha]_D^{24}$-50.0° (c 2.02, $CHCl_3$), 88%e.e..[6,7]



6a 9

Although a detailed mechanistic study was not yet made, the present asymmetric synthesis consists of two stereoselective steps, i) a formation of the aminal 3, ii) an addition of the lithium reagent 4 to aldehyde. In the first step aminal 3 is formed prefferentially; its diastereomer 3', would be more unstable because of its rather



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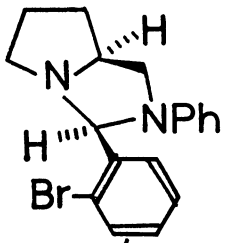

3'

Figure 1

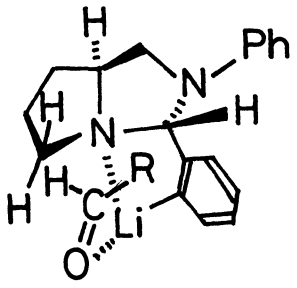

Figure 2

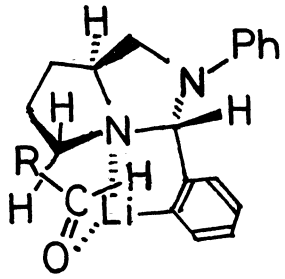

Figure 3

crowded structure (Figure 1). In the second step, an intramolecular coordination of the chiral aminal function to the lithium metal apparently plays an important role. Thus a rigid tricyclic five membered ring structure is postulated which would be effective for the differentiating of the enantioface of the approaching aldehydes. Namely the aldehyde approaches from the less hindered front side in the manner depicted in Figure 2. The opposite approach (Figure 3) would be less favorable because of the steric repulsion between the alkyl group of the aldehyde and the pyrrolidine ring. Thus the isolated lactols 6 have the S-configuration.

References and Notes

1) a) T. Mukaiyama, Y. Sakito, and M. Asami, Chem. Lett., 1978, 1253. b) M. Asami and T. Mukaiyama, ibid, 1979, 569. c) T. Mukaiyama, Y. Sakito, and M. Asami, ibid, 1979, 705.

2) a) T. Mukaiyama, K. Soai, T. Sato, H. Shimizu, and K. Suzuki., J. Am. Chem. Soc., 101, 1455 (1979) and references there in. b) Recently the preparation of α-methoxy aldehyde by condensation of a chiral acyl anion equivalent with benzaldehyde was reported. L. Colombo, C. Gennari, C. Scolastico, G. Guanti, and E. Narisano., J. Chem. Soc. Chem., Commun. 1979, 591.

3) IR(KBr) ν=3050 and 1600 cm^{-1}; NMR ($CDCl_3$) δ=1.43-4.13 (m, 9H), 5.50(s, 1H), and 6.05-7.60 (m, 9H); Found: C, 63.23; H, 5.48; N, 8.34; Br 23.60%; calcd for $C_{18}H_{19}N_2Br$: C, 62.98; H, 5.58; N. 8.16; Br, 23.28%.

4) Lactols 6 a-e showed satisfactory IR and NMR spectra.

5) M. Rosenberger, D. Andrews, F. DiMaria, A. J. Duggan, and G. Saucy, Helv. Chim. Acta., 55, 249 (1972).

6) D. H. R. Barton and J. X. de Vries., J. Chem. Soc., 1963, 1916.

7) An asymmetric synthesis of 3-alkylphthalide was reported by P. R. Jones and C. J. Jarboe, Tetrahedron Lett., 1969, 1849.

(Received September 29, 1979)