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ENANTIOSELECTIVE ADDITION OF N-BUTYLLITHIUM TO BENZALDEHYDE IN THE PRESENCE OF CHIRAL LITHIUM AMIDES

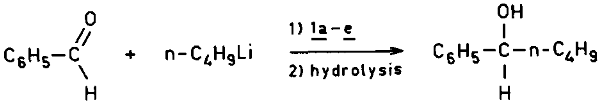
M.B. Eleveld and H. Hogeveen

Department of Organic Chemistry, University of Groningen
Nijenborgh 16, 9747 AG Groningen, The Netherlands

Abstract: The reaction of n-butyllithium with benzaldehyde in the presence of chiral lithium amides 1a-e gives 1-phenyl-1-pentanol with optical yields up to 90%.

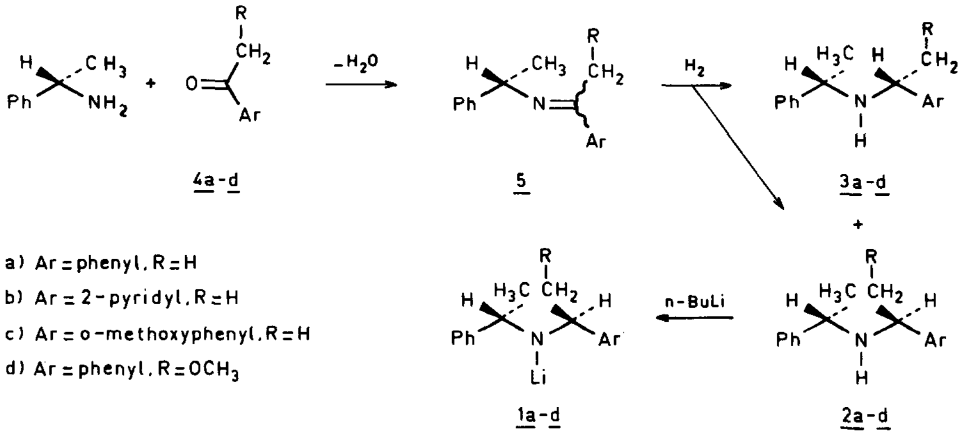
One of the most important reactions in organic synthesis is the carbon-carbon bond formation reaction.[1] With the current emphasis on asymmetric synthesis, much interest exists in the asymmetric variant of this reaction. A basic reaction of the latter type is the addition of organometallics to aldehydes in the presence of chiral ligands affording chiral alcohols.[2-9] In this area of stoichiometric asymmetric "catalysis" the three most successful methods have been described by Cram et al.,[5] Mukaiyama et al.[3] and Seebach et al.[8] (using a diamine, a lithium diamine alcoholate and a dialcoholate, respectively, as chiral ligands) which gave optical yields up to 92%.

We have investigated the potential of the lithium amides 1a-e to act as chiral catalyst in the addition of n-butyllithium to benzaldehyde.



$$C_6H_5-\overset{O}{\underset{H}{C}} + n\text{-}C_4H_9Li \xrightarrow[\text{2) hydrolysis}]{\text{1) 1a-e}} C_6H_5-\overset{OH}{\underset{H}{C}}-n\text{-}C_4H_9$$

The ligands 1a-d (which were recovered after the reaction as the corresponding amines 2a-d in 90-95% yield without loss of optical purity) were synthesized starting from the inexpensive S-α-methylbenzylamine.[11] Condensation of this amine with ketone 4 gave the imine mixture 5, which after hydrogenation yielded diastereomeric mixtures of secondary amines 2 and 3. Both 2a/3a and 2b/3b were formed in a 7 to 1 ratio, and from these mixtures 2a and 2b were obtained in pure form by recrystallization from water of the HCl- and D-tartaric acid salt, respectively. Starting with 4c only 2c was formed, while 4d gave a 2 to 1 mixture of 2d/3d, which after recrystallization of the HCl-salt from water/ethanol gave pure 2d. Compound 2d was also prepared by condensation of D-α-phenylglycinol and 4a followed by hydrogenation and methylation.[12,13]



a) Ar = phenyl, R = H
b) Ar = 2-pyridyl, R = H
c) Ar = o-methoxyphenyl, R = H
d) Ar = phenyl, R = OCH_3

Table: Chiral catalysis in addition of n-BuLi to benzaldehyde[a]

run	ligand	solvent[b]	reactiontemp.(°C)	yield (%)[c]	optical yield[d,e]
1	1a	THF	-90	72	14
2	1a	Et_2O	-100	65	12
3	1a	DMM	-100	82	7
4	1b	THF	-90	63	40
5	1b	Et_2O	-100	73	19[f]
6	1b	DMM	-100	62	37
7	1c	THF	-90	51	54
8	1c	DMM	-100	47	65
9	1d	THF	-90	77	68
10	1d	Et_2O	-100	83	74
11	1d	DMM	-100	90	83
12	1d	Et_2O	-120	80	81
13	1d	DMM/Me_2O (1:1)	-120	52[g]	38[f]
14	1d	DMM/Et_2O (1:1)	-120	83	90
15	1d	toluene	-100	95	18
16	1e	DMM	-100	74	14

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a) Molar ratio of benzaldehyde: n-BuLi:ligand 1.0:2.7:4.0.

b) All solvents distilled from sodium benzophenone; DMM≡ dimethoxymethane.

c) Yields are not optimized.

d) On the basis of the highest value in literature $[\alpha]_D^{26}$ = 35.7 (c=3, C_6H_6), ref. 5.

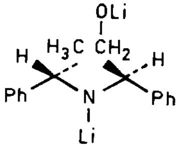
e) In all runs the product was enriched in the S-enantiomer.

f) Heterogenous reaction.

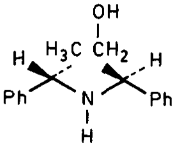
g) No complete reaction, 16% starting material was recovered.

The reaction of n-butyllithium with benzaldehyde in THF with 1a as chiral ligand yielded 1-phenyl-1-pentanol in an optical yield (o.y.) of 14% (run 1). The influence of an additional lithium-complexating group was investigated in the expectation that an additional internal ligation, implying a more rigid structure in the lithium amide, would cause a greater selectivity. Indeed replacement of one of the phenyl groups in 1a by a 2-pyridylgroup (1b) gave under the same reaction condition a greater selectivity (o.y. 37-40% (run 4-6)). The presence of a methoxy group on the ortho position of one of the phenyl groups (1c) gave an o.y. of 54-65%, while substitution of a hydrogen of one of the methylgroups by a methoxy group (1d) caused the o.y. to reach 83% (run 9-11). Changing the reactiontemperature also influenced the selectivity as shown in runs 10 and 12, where a decrease of the reactiontemperature from -100 to -120°C, increased the o.y. from 74 to 81%. The highest o.y. (90%) in this reaction was obtained by using a DMM/Et$_2$O (1:1, v/v) mixture as solvent, a reactiontemperature of -120°C and 1d as ligand (run 14). Using a DMM/Me$_2$O (1:1, v/v) mixture as solvent gave an o.y. of only 38% (run 13), probably because the n-butyllithium.1d complex is not (totally) soluble. The use of a non-ethereal solvent lowered the o.y. drastically as can be seen in run 15 where toluene was applied as solvent (o.y. 18%). With 1e as ligand, the o.y. is nearly as large as with 1a, indicating that the OLi-group has no capacity for complexation with the nitrogen-lithium moiety.[14]

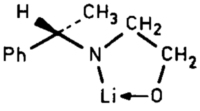
We have attempted to get some additional structural information of the effect of the chiral center at the lithium coordination side by using 6,[15] which has recently been described. However, the use of 6 as ligand did not lead to a complete reaction under the same conditions, and a comparison with 1d is therefore not yet possible.[16] Addition of other organometallics and complexation with other chiral lithium amides are presently under investigation.



1e



2e



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References and Notes

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9. Also a few enantioselective syntheses of homoallylic alcohols by addition of an allyl metallic species to an aldehyde are described. J. Otera, Y. Kawasaki, H. Mizuno and Y. Shimizu, Chem. Letters 1983, 1529 and refs. 3-5 therein.
10. The synthesis of 2a has been described before: C.G. Overberger, N.P. Marullo and R.G. Hiskey, J. Am. Chem. Soc. 83, 1374 (1961).
11. For example, the price of S- and of R-α-methylbenzylamine is $ 25.00/kg, $ 34.00/kg, respectively (Hexcel Chemical Products).
12. The absolute configuration of the compounds 2b and 2c were determined by X-ray analysis of their D-tartaric acid and HCl salts, respectively. The α-phenylethylmoiety of 3b and 3c has to be the S-configuration since S-α-methylbenzylamine was used as starting compound and because 3b and 3c are diastereomers of 2b and 2c, respectively, the other chiral center has to possess the R-configuration, which results in a S,R-configuration as indicated for 3b and 3c. The absolute configuration of 2d was determined by chemical correlation. Because in the first route was started with S-α-methylbenzylamine (and 4d), the α-phenylethyl moiety of 2a has to be the S-configuration, while by the second route is proven that the α-phenyl-β-methoxyethyl moiety has to be the R-configuration since in this route was started with D-α-phenylglycinol (which possesses the R-configuration). So 2d has to be the S,R-configuration as indicated. Using the same reasoning as for 3b and 3c, 3d has to be the S,S-configuration.
13. Methylation of 2e occurred exclusively on the hydroxyl and not on the amine function, probably for steric reasons.
14. The presence of 1d has a rate enhancing effect in the reaction of n-BuLi to benzaldehyde as shown by an experiment in which a mixture of n-BuLi/n-BuLi.1d complex (ratio 41:1) afforded the 1-phenyl-1-pentanol with an O.Y of 19% (reaction conditions as in run 11, Table).
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16. Even at 0°C, the addition is not complete.

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