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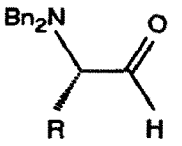
Stereoselective Synthesis of β-Amino Nitriles and 1,3-Diamines

Manfred T. Reetz[a)], Frank Kayser[b)] and Klaus Harms[b)]

[a)]Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim/Ruhr, Germany
[b)]Universität Marburg, Fachbereich Chemie, Hans-Meerwein-Strasse, 35043 Marburg, Germany

Abstract: *Chiral β-N,N-dibenzylamino nitriles $Bn_2NCH(R)CH_2CN$, prepared in enantiomerically pure form from α-amino acids, can be deprotonated and stereoselectively alkylated to afford β-amino nitriles $Bn_2NCH(R)CH(R')CN$ with two stereogenic centers. $LiAlH_4$-reduction leads to the corresponding 1,3-diamines.*

N,N-Dibenzylamino aldehydes **1**, accessible in enantiomerically pure form from amino acids, have emerged as useful building blocks in organic synthesis.[1,2] A wide variety of carbon nucleophiles add stereoselectively with non-chelation control (ds > 90%).[1,2] Although the explanation for this unusual stereochemical result is still a matter of debate,[1] it is clear that any stereogenic center bearing the *N,N*-dibenzylamino moiety exerts a strong influence on the neighboring *electrophilic* carbon center. We therefore posed the question whether *nucleophilic* or *radical* species (**2** and **3**, respectively) are also capable of stereoselective C-C bond formation. Here we present the first results in this endeavor.



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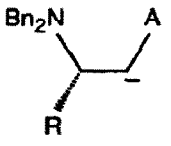

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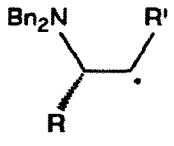
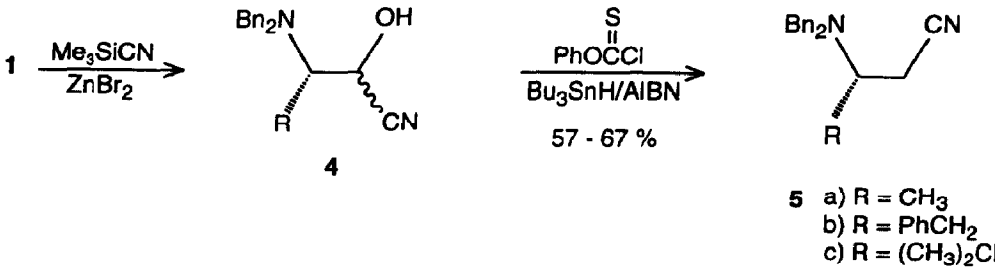


3

(A = stabilizing group)

Possible precursors for carbanions of the type **2** are the enantiomerically pure nitriles **5**,[3] prepared by Barton-deoxygenation[4] of the corresponding cyano hydrins[5] **4**.



Upon deprotonating the nitriles **5** with LDA and alkylating the intermediate carbanions **6**, products **7** were isolated in moderate to good yields (Table 1).[6] There are essentially no sideproducts; the crude reaction mixtures contain some starting material **5** which is readily separated and can be used again.[3] Table 1 shows that diastereoselectivity is in a synthetically acceptable range (exception: entry 1), and that it increases with increasing size of the groups R at the original stereogenic center.

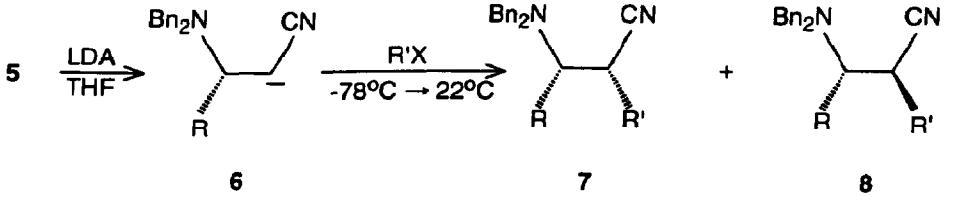
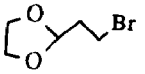


Table 1. Stereoselective Alkylation[6] of Nitriles **6**

R	R'-X	Yield (% isolated)	**7** : **8**
CH_3	CH_3I	53	60 : 40
CH_3	$PhCH_2Br$	45	80 : 20
CH_3	$(CH_3)_2CHCH_2Br$	39	75 : 25
$PhCH_2$	CH_3I	77	71 : 29
$PhCH_2$	$PhCH_2Br$	56	91 : 9
$PhCH_2$		62	86 : 14
$(CH_3)_2CH$	CH_3I	54	94 : 6
$(CH_3)_2CH$	$PhCH_2Br$	46	>95 : <5
$(CH_3)_2CH$	$(CH_3)_2CHBr$	40	87 : 13
$(CH_3)_2CH$	$(CH_3)_2CHCH_2Br$	42	93 : 7

The configurational assignment is based on an X-ray structural analysis[7] of the product **7** (R = $(CH_3)_2CH$; R' = $PhCH_2$ (Fig. 1). Correct CH-analyses (± 0.4) were obtained, and ^1H- and ^{13}C-NMR data are in line with these compounds.[3]

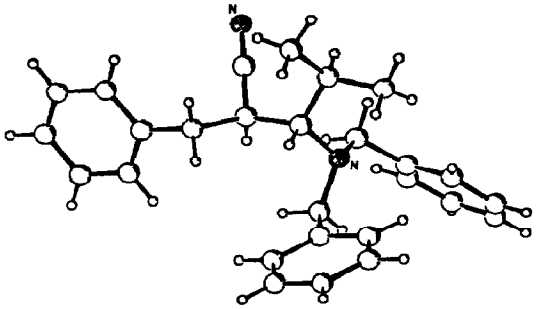
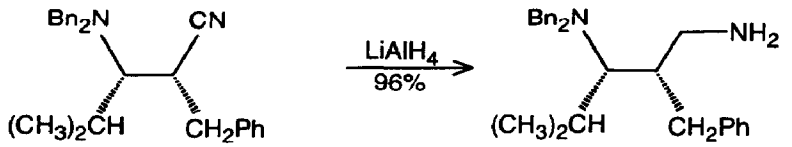


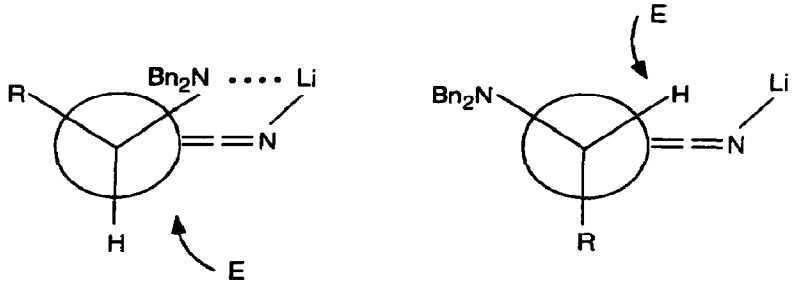
Fig. 1. X-ray crystal structure of **7** (R = $(CH_3)_2CH$; R' = $PhCH_2$)

In order to check whether any racemization occurs along the reaction sequence, compound **7** (R = $(CH_3)_2CH$; R' = $PhCH_2$) was reduced with $LiAlH_4$ to the diamine **9**. Treatment with the S- and R-configurated "Mosher chlorides"[8] afforded the corresponding MTPA-derivatives. In each case the ^1H-, ^{13}C- and ^{19}F-NMR spectra showed a single set of signals, proving enantiomeric purity (ee > 98%). The ready transformation **7** → **9** also demonstrates that 1,3-diamines of this kind are accessible in enantio- and diastereomerically pure form. Compounds **5** can also be reduced to the corresponding 1,3-diamines, e. g., **5b** (84% of the primary amine isolated).[3]



7 **9**

What is the origin of diastereoselectivity in the alkylation? Li-chelation according to **A** would lead to electrophilic attack from the "bottom" with preferential formation of the minor isomer **8**. A non-chelated form **B** is therefore more likely, attack from the "top" affording the observed major diastereomers **7**. However, this may be a simplification because 1) α-lithiated nitriles are often dimers[9] and 2) LDA transforms into $(iPr)_2NH$ which may form H-bonds with the nucleophile.[10]



Acknowledgement

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6. Proccdurc: To a solution of LDA (1.6 mmol in 10 ml of dry THF) is addcd at -78°C 1.5 mmol of a nitrile **5** in 5 ml THF. After stirring for 1h, an alkyl halide (~20 mmol) is added, and the mixture is allowed to come to room temperature overnight. H_2O (20 ml) is added followed by extraction with ether. After washing the combined org. phases with 1% HCl, sat. $NaHCO_3$ and sat. NaCl solutions and drying over $MgSO_4$, the solvent is stripped off and the residue is chromatographed over SiO_2 (pet ether/ether).
7. Crystal data have been deposited at the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.
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