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Generation of Functional Diversity Via Nitroaldol Condensations of α-Aminoacid Aldehydes – A New and Stereocontrolled Route to Acyclic 1,3-Diamino-2-alcohols

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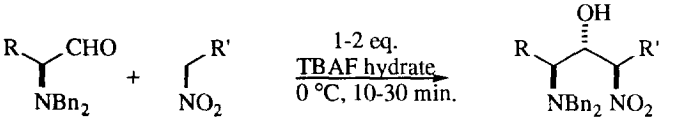
Abstract: *Condensations of N,N-dibenzyl α-amino aldehydes with nitroalkanes mediated by tetrabutylammonium fluoride proceed in excellent yields and selectivities. This affords rapid and stereoselective access to acyclic molecules containing differentiated nitrogen-containing functionality as well as diverse end groups.*

The Henry reaction[1] has seen extensive use in organic synthesis providing ready access to a wide variety of functionalities generated from the resulting nitroaldol products. Modifications of this reaction with the intent of improving diastereoselectivity through the use of α,α-doubly deprotonated nitroalkanes,[2] silylnitronates,[3] and a deprotonation-reprotonation protocol[4] have been introduced by Seebach and coworkers.

Previous studies in our laboratory[5] have shown that the reaction of α-benzyloxy aldehydes with methyl nitropropionate in the presence of neutral alumina[6] proceeds with excellent *anti-anti* diastereoselection. On the other hand, Gómez-Sánchez[7] and Jäger[8] have independently shown that TBAF-catalyzed condensations of α-alkoxy aldehydes with nitroacetaldehyde diethylacetal yield *anti-syn* diastereomers as predominant, thermodynamic products.

Herein we report an efficient method for the synthesis of nitroalcohols from chiral, non-racemic α-amino aldehydes with high *anti-anti* diastereoselectivity as exemplified in Scheme 1.

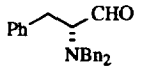
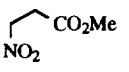
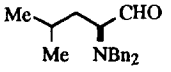
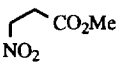
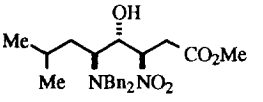
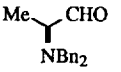
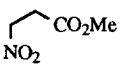
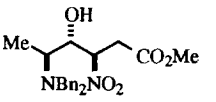
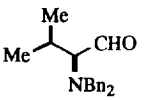
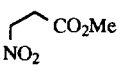
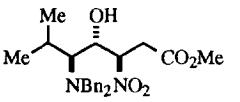
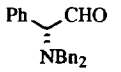
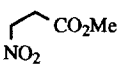
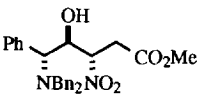
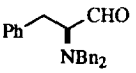
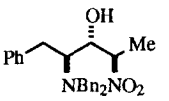
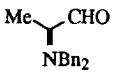
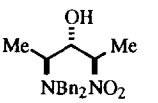
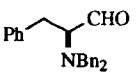
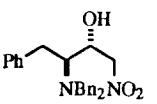
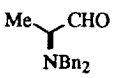
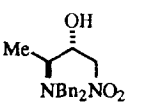
Scheme 1



N,N-Dibenzyl α-amino aldehydes were chosen as starting aldehydes as they were known to be relatively stable and less prone to epimerization.[9,10] Reaction of N,N-dibenzyl-L-phenylalaninal with methyl 3-nitropropionate in presence of neutral alumina[5,6] was unacceptably slow and low-yielding (45%, r.t., 10d).[11] However, in the presence of 1 or 2 equivalents of TBAF hydrate or 1M TBAF/THF solution and using methyl 3-nitropropionate, nitromethane, and nitroethane as representative nitroalkanes, reactions proceeded efficiently to give the corresponding nitroaldol products (*Table 1*).[12,13] The major diastereomers

Dedicated to Professor Dieter Seebach for his outstanding contributions in nitroalkane chemistry

Table 1. TBAF-Catalyzed Nitroaldol Reactions of α-Aminoacid Aldehydes.

Entry	Aldehyde	Nitroalkane	Major Product[a]		Yield[b]	Ratio[c]	Method[d]
1				**1a**	66 87 69	49:1[e] 8:1 49:1	A B C
2				**1b**	64	19:1[e]	A
3				**1c** **X-RAY**	59 84	12:1 19:1	A B
4				**1d** **X-RAY**	40 34	8:1[f] 99:1	A C
5				**1e**	22 55	21:3:1 13:3:1	A B
6				**1f**	86	5:2:1[f]	A
7				**1g**	68	10:1.5:1	A
8		$MeNO_2$		**1h**	63 97 63	8:1[e,g] 5:1 10:1[h]	A B C
9		$MeNO_2$		**1i**	88	4:1[e]	B

(a) For physical data, see note 13. (b) Isolated yields. (c) Ratio determined by ^1H NMR from integrations of nitromethine proton. (d) Method A: Using 1 eq. TBAF.xH_2O. Method B: 2 eq. TBAF.xH_2O. Method C: 1 eq. TBAF.xH_2O, 1 eq. TESOTf, 1 eq. Et_3N. (e) Separable by chromatography. (f) Major isomer crystallizes out. (g) Ratio determined by ^{13}C NMR and by weights of isolated diastereomers. (h) Method C with 50 mol% TBAF.xH_2O.

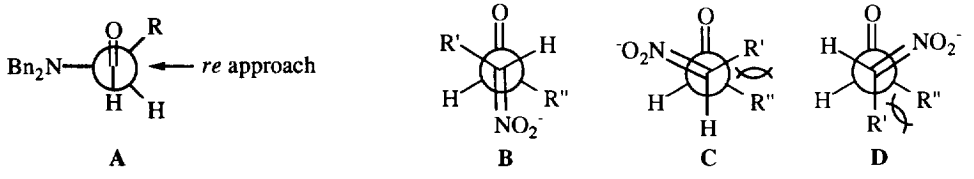
were shown to have an *anti-anti* disposition by analogy to structures **1c** and **1d** (entries 3, 4) which were unambiguously determined by single crystal X-ray analysis.[14,15]

In view of the diversity of the structures of α-amino acid aldehydes, optimal conditions for obtaining high yields and best selectivities varied with the method used. Thus, the use of two equivalents of TBAF.xH_2O gave the highest yields of diastereomeric mixtures with the major *anti-anti* isomer predominating in all cases. With one exception (entry 3, Table 1), selectivity was consistently better in the presence of one equivalent of TBAF.xH_2O, albeit giving modest to good yields. Thus, although reactions were more efficient, some equilibration of kinetically formed products took place in most instances when two equivalents of fluoride were used. Sterically encumbered aldehydes derived from valine and phenylglycine gave modest yields and selectivities (entries 4, 5, Table 1). However, utilizing a mixture of TBAF.xH_2O and triethylsilyl triflate in the presence of triethylamine resulted in the formation of virtually a single isomer from valine aldehyde (entry 4, Table 1).[16] Application of this triflate-mediated condensation (0 °C, 15 min) to phenylalanine aldehyde yielded 69% of a 98:2 mixture of products **1a**.

That the starting aldehydes do not epimerize under conditions of the reaction was shown by ^{1}H NMR studies of racemic and chiral, non-racemic **1a** in the presence of (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[17] A baseline splitting of NBn_2 and OCH_3 groups was seen in the ^{1}H NMR spectrum of racemic **1a**.

The kinetic, *anti-anti* diastereoselectivity is consistent with an antiperiplanar approach of the nitronate to the *re* face of the aldehyde in accordance with Felkin-Ahn rules (**A**, *Figure* 1).

Figure 1



Projections **B**, **C**, and **D** are consistent with the *anti-anti* diastereoselectivity observed. **B** appears to be most favorably disposed since it avoids unfavorable gauche (R' and R") and dipolar interactions in its transition state.[18] The products are kinetically controlled since the ratio in the reaction of valine aldehyde dropped from 8: 1 (*entry 4*) to 20: 12: 1 when the reaction was allowed to run overnight at r.t., suggesting a subsequent equilibration.

Thus, N,N-dibenzyl α-amino aldehydes, which are readily accessible from α-amino acids,[9,10] undergo facile TBAF-mediated condensations with nitroalkanes to give nitroaldol products in high yields and good stereoselectivities. These, in turn, provide ready access to 1,3-diamino-2-alcohols[19] which are important substructures in medicinally important compounds. The nitroaldol products shown here are also versatile chirons for further chemical manipulation with the intention of preparing acyclic and cyclic scaffolds and templates having functional diversity.

Acknowledgments

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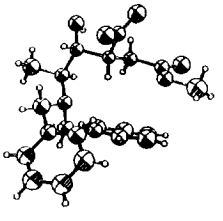
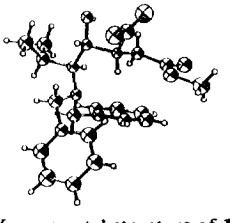
12. Typical Procedure: **Method A**: To a solution of tetrabutylammonium fluoride (1M in THF, 0.45 ml, 0.45 mmol) in dry THF (10 ml) at 0 °C was added a solution of methyl 3-nitropropionate (153 mg, 1.2 mmol) in THF (2 ml) dropwise. After stirring the pale yellow solution for 5 min. at 0 °C, a solution of N,N-dibenzyl-L-leucinal (147 mg, 0.5 mmol) in THF (4 ml) was added over 5 min. and stirring continued for a further 15 min. The reaction mixture was then poured into sat. aq. $NaHCO_3$ and extracted into ether and processed as usual. Flash chromatography (10% ethyl acetate-hexanes) yielded 12 mg of unreacted aldehyde and 137 mg (64%; 70% based on recovered aldehyde) of the nitroaldol product **1b**.
Method C: To a solution of tetrabutylammonium fluoride hydrate (55 mg, 0.21 mmol, 0.49 eq.) in dry THF (4 ml) at 0 °C was added nitromethane (0.2 ml, 3.7 mmol, 8.5 eq.). After stirring the solution for 5 min. at 0 °C, a solution of N,N-dibenzyl-L-alaninal (142 mg, 0.43 mmol) in THF (2 ml) followed immediately by TESOTf (0.1 ml, 0.44 mmol, 1 eq.) and Et_3N (0.06 ml, 0.43 mmol, 1 eq.) were added over 5 min. and stirring continued for a further 15 min. at 0 °C. The reaction mixture was then quenched with sat. aq. NH_4Cl, extracted into ether and processed as usual. Flash chromatography (10% ethyl acetate-hexanes) yielded 10 mg of the *syn* isomer and 95 mg of the *anti* isomer **1h** (63 % total).
13. All compounds gave satisfactory ^1H and ^{13}C NMR, IR, MS, and HRMS. Selected data:
$[\alpha]_D^{25}$ values in $CHCl_3$: **1a**: -0.13 °(0.115); **1b**: 24.4 °(c 0.36); **1c**: -30.0 °(0.09); **1d**: -40.0 °(0.25); **1e**: -7.4 ° (0.14); **1f**: +11.0 °(0.78); **1g**: +8.79 °(2.0); *anti*-**1h**: +10.8 °(1.14); *syn*-**1h**: +22.33 °(0.22).
melting points for crystalline products in °C: **1a**: 98-100; **1c**: 104-105; **1d**: 128-130; **1e**: 110-112; **1h** (*anti*): 109-111; **1h** (*syn*): 115-116.
14. Corresponding γ-lactone from **1a** ($BF_3.Et_2O/CH_2Cl_2$) showed a coupling constant of 2 *Hz* between H-3 and H-4, suggesting a *trans* relationship.
15. X-ray coordinates have been deposited at the Cambridge Crystallographic Data Centre.



X-ray crystal structure of **1c**



X-ray crystal structure of **1d**

16. Under conditions described in ref. 7, viz. TBAF/TBSCl/Et_3N, we obtained a 97:3 mixture in 22% yield.
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