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Exceptionally High Felkin-Anh Control for the Addition of Nucleophiles to a β-Aminocyclopropylcarbaldehyde

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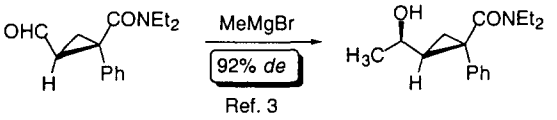
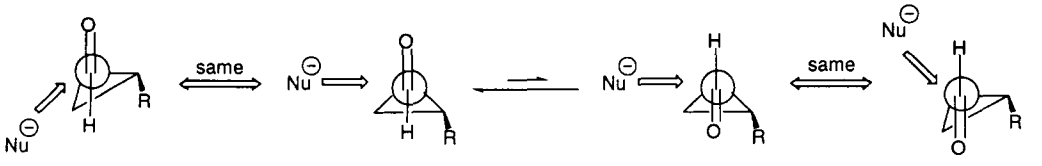
Abstract: Exceptionally high diastereocontrol in agreement with the Felkin-Anh model was observed for the addition of nucleophiles to the β-aminocyclopropylcarbaldehyde **5** in nitroaldol, cyanohydrin, Mukaiyama aldol, and Sakurai reactions, contrasting the low diastereoselectivities generally observed in additions to cyclopropylcarbaldehydes.

The stereochemical course of the addition of nucleophiles to acyclic α-chiral aldehydes has been extensively studied, and predictions can be made on the basis of the Felkin-Anh and Cram-chelate model and its variations.[1] In general, selectivities obtained by Felkin-Anh, i.e. non chelation, control are moderate, while high selectivities are observed if a preorganization of the substrate by chelation can be accomplished.
The nucleophilic addition to cyclopropyl carbonyls has found considerable attention,[2] but very few cases for cyclopropylcarbaldehydes have been reported to proceed with high diastereocontrol.[2e] In a recent study, however, it was elegantly demonstrated that the addition of methylmagnesium bromide to the cyclopropylcarbaldehyde **1** proceeds highly selectively to yield the carbinol **2** with 92% *de*.[3]



1 **2**

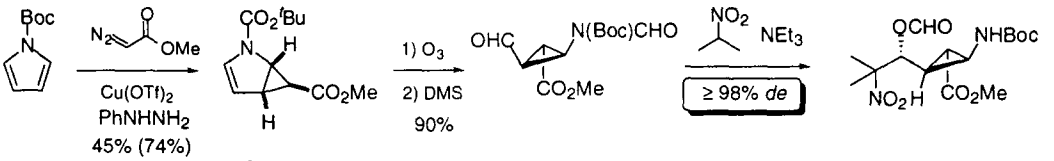
This result was explained by a model which is based on the fact that cyclopropylcarbaldehydes exist due to stereoelectronical reasons preferentially in a bisected conformation. Of the two possibilities, the *s-trans* conformation is preferred rather than the *s-cis* conformation, because in the latter the carbonyl group is oriented into the cyclopropyl moiety leading to increased steric repulsion. Nucleophilic attack would then occur in the *s-trans*-conformation from the sterically less hindered side.[3]



Anti-Felkin-Anh *s-trans* *s-cis* Felkin-Anh

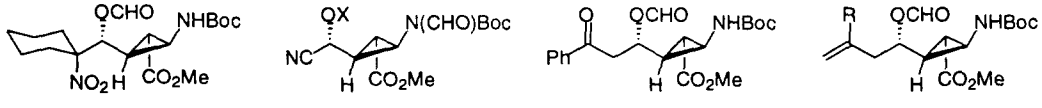
However, an analysis concurrent with the Felkin-Anh paradigm must lead to the conclusion that attack takes place over the medium sized group, thus almost complete Anti-Felkin-Anh control has occurred in the transformation of **1** to **2**.

Cyclopropylamino acids are of considerable interest because of their biological activity[4] as well as their rigidity which makes them attractive building blocks for peptide mimetics.[5] As part of our studies toward conformationally constrained β-amino acids[6] we developed an efficient and highly diastereoselective synthetic route to the β-aminocyclopropylcarbaldehyde **5** starting from N-Boc-pyrrole (**3**):[7] cyclopropanation with diazoacetate yields selectively the *exo*-adduct **2**, as has been already demonstrated by Fowler.[8] In difference to the procedure reported there, we have found that if CuBr is replaced with $Cu(OTf)_2$ / $PhNHNH_2$ as the catalyst the reaction proceeds already at room temperature in considerable improved yield, giving rise to **4** on a 20 g scale in 45% yield (74% after recovered **3**). Ozonolysis followed by reductive work up results in the amino aldehyde **5** as a single diastereomer, which is completely stable toward ring opening or condensation reactions because of the two electron withdrawing protecting groups at nitrogen. Due to the general interest in amino-nitro carboxylic acids[9] and especially in the ability of the nitro group to act as a good mimic for a carboxylic acid in γ-amino butyric acid derivatives which was used to develop new GABA receptor antagonists[10], we carried out a nitroaldol reaction of **5** and 2-nitropropane catalyzed by triethylamine at 0°C. To our delight the reaction proceeded completely diastereoselectively to yield **6a**,[11] however, attack of the nucleophile onto the aldehyde must have taken place from the opposite side compared to the addition mode of methylmagnesium bromide to **1**. Since the conditions used in our nitroaldol reaction rule out any chelation and the nucleophile used is extremely bulky, we concluded that the reaction proceeded *in agreement* with the Felkin-Ahn model, even though this requires that the reaction takes place from the *s-cis* conformation of the aldehyde **5**. Finally, it should be noted that in the nitroaldol reaction a shift of the N-formyl group to the hydroxyl group has taken place. This behavior has been observed in some other additions as well (*vide infra*).



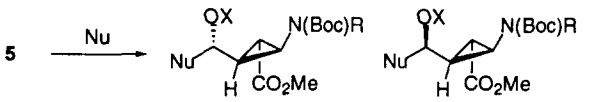
3 **4** **5** **6a** (Felkin-Anh)

We subsequently studied the addition of other nucleophiles to the aldehyde **5** (Table 1). Only secondary nitro compounds could be used for the nitroaldol reaction, nitromethane or nitroethane resulted in a mixture of products probably due to elimination of formic acid and subsequent side reactions of the primary formed nitroaldol adduct. Nevertheless, nitrocyclohexane reacts again with perfect diastereoselectivity in favor of the Felkin-Anh product **6b**[11] (entry 2). The addition of trimethylsilylcyanide (TMSCN) could be carried out at room temperature in the absence of a catalyst (entry 3), or at –78°C in the presence of the non chelating Lewis acid boron trifluoride (BF_3•OEt_2) (entry 4). In both cases, the Felkin Anh diastereomer was preferred with a ratio of about 9:1. The latter result was particular remarkable since coordination of a Lewis acid to the aldehyde should even stronger disfavor the s-*cis* conformation of **5** for steric reasons. Even more strikingly, the Mukaiyama aldol reaction with 1-phenyl-1-(trimethylsiloxy)-ethene (entry 5) or Sakurai reactions with allyl silanes (entries 6-7) all resulted in the exclusive formation of the Felkin-Anh product **6**.[11] Other Lewis acids ($ZnBr_2$, $TiCl_4$, $SnCl_4$) were also examined, however, the reactions proceeded less cleanly due to decomposition of the substrate.

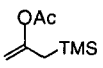


6b **6c**: X = H; **6d**: X = $SiMe_3$ **6e** **6f**: R = H; **6g**: R = OAc

Table 1. Additions of Nucleophiles to 5[a]



6 (Felkin-Anh) **7** (Anti-Felkin-Anh)

Entry	Nucleophile	Catalyst	Time [h]	Temp [°C]	Product	X	R	6 : 7[b]	Yield[c] [%]
1[d]		NEt_3	6	0	**6a/7a**	CHO	H	≥ 99:01	91
2[e]		NEt_3	12	0	**6b/7b**	CHO	H	≥ 99:01	84
3[f]	TMSCN	–	24	25	**6c/7c**	TMS	CHO	91:09	100
4[g]	TMSCN	$BF_3 \cdot OEt_2$	4	–78	**6d/7d**	H	CHO	89:11	94
5		$BF_3 \cdot OEt_2$	1	–78	**6e/7e**	CHO[h]	H	≥ 99:01	71
6		$BF_3 \cdot OEt_2$	8	–78	**6f/7f**	CHO	H	≥ 99:01	92
7		$BF_3 \cdot OEt_2$	4	–78	**6g/7g**	CHO	H	≥ 99:01	93

[a] **5** (1.0 mmol), nucleophile (1.0 mmol), catalyst (1.0 mmol) in CH_2Cl_2 (10 ml). [b] Determined from the crude product by ^1H NMR.[12] [c] Isolated Yield. [d] 2-nitropropane (2ml) as the solvent. [e] nitrocyclohexane (2 ml) as the solvent. [f] **5** (0.25 mmol), TMSCN (1.0 mmol). [g] **5** (1.0 mmol), TMSCN (1.5 mmol). [h] Formyl shift only occurs on chromatographic work up with silica gel. The initial aldol product was obtained in pure form by direct crystallization of the crude from CH_2Cl_2 / hexanes.

We were able to obtain the X-ray structure analysis[13] of the aldehyde **5**, which sheds further light on the remarkable Felkin-Anh-selectivity observed, although one must be aware of the inadequacy in drawing conclusions from a ground state structure in the solid state to a reactive conformation in solution. Nevertheless, it was most surprising and unprecedented to find that the *s-cis* conformation in **5** is being preferred despite the obvious steric interactions of the aldehyde carbonyl group and the cyclopropyl moiety. However, the carbonyl group does not exactly bisect the cyclopropyl moiety, but rather points toward its neighbored cyclopropyl hydrogen.

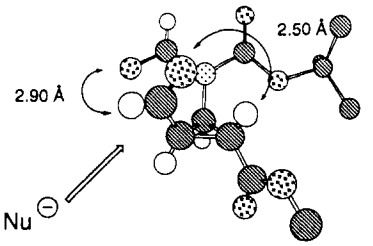


Fig. 1. X-ray structure of **5**

Moreover, there might be a conformational lock established by the oxygen of the N-formyl group and the hydrogen of the aldehyde, although the distance (2.90Å) is rather large. Since β-amino aldehydes, being N-Boc-N-formyl protected are readily available,[14] we are currently investigating if by such interactions one might be able to generally control the diastereoselectivity in nucleophilic additions to β-amino aldehydes.

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7. All products are racemic, for clarity only one enantiomer is shown. **4** can also be obtained enantiomerically pure by enzymatic resolution: C. Cabrele, T. Stauch, O. Vielhauer, M. Pietsch, O. Reiser, *unpublished results*.
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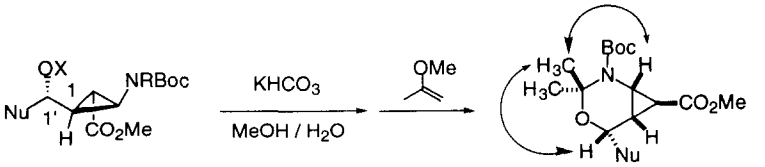
11. All new compounds were fully characterized by spectroscopical methods and gave correct elemental analyses. The relative stereochemistry of **6a-g** was unambiguously proven by X-ray structure analyses of an analog of **6a** (N-CO_2Me instead of N-CO_2^{t}Bu) and of **6c** and by NOE experiments on **8** which was readily obtained from **6a,b** and **6e-g** by deformylation and cyclization with 2-methoxypropene. The stereochemistry of **6d** was confirmed by its transformation to **6c**.



6 **8**

12. Selected ^{1}H NMR data (250 MHz, $CDCl_3$): **6a**: 5.55 (d, 10.0 Hz, 1'-H), 8.02 (s, OCHO); **6b**: 5.21 (d, 9.2 Hz, 1'-H), 8.07 (s, OCHO); **6c**: 4.76 (d, J = 2.5 Hz, 1'-H), 9.03 (s, NCHO); **7c**: 4.82 (d, J = 3.8 Hz, 1'-H), 9.11 (NCHO); **6d**: 9.18(NCHO); **7d**: 9.16 (NCHO); **6e**: 5.40 (m_c, 1'H), 8.03 (s, OCHO), **6f**: 4.85 (m_c, 1'-H), 8.04 (s, OCHO); **6g**: 1.89 (dd, J = 5.4, 3.7 Hz, 1-H), 8.00 (s, OCHO).
13. Atomic coordinates, bond lengths and angels, and thermal parameters of **5** can be obtained on request from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ (UK).
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