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Diastereoselective Aldol Additions to α-Amino-β-silyloxy Aldehydes. Divergent Synthesis of Aminodiols

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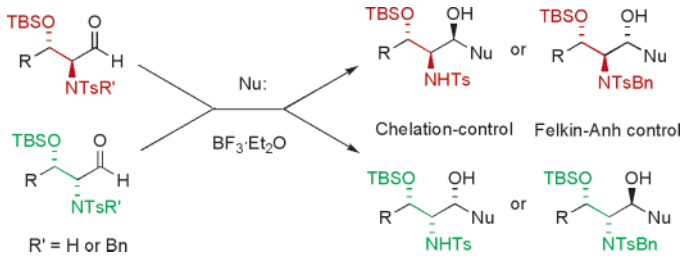
ABSTRACT



A divergent protocol for substrate-controlled diastereoselective synthesis of aminodiols has been developed using nucleophilic Mukaiyama aldol additions to α-amino-β-silyloxy aldehydes. The merged stereochemical impact on the diastereoselectivity of the polar α- and β-substituents is highlighted.

Nucleophilic carbonyl addition reactions can be ranked among the premier transformations in organic synthesis for stereoselective C−C bond formation. Asymmetric induction can in general be realized in the presence of proximal stereogenic centers, which can provide a diastereofacial discrimination at the C=O π-faces, and much work has been devoted toward elucidating the underlying factors. The influence of α- or β-substituents on the stereochemical outcome of additions to C=O bonds have been well studied and can be rationalized by steric and electronic effects[1] or chelation to adjacent heteroatoms.[2] However, the stereochemical outcome in additions to more complex systems, containing multiple adjacent stereocenters, is more difficult to predict and has only received scarce attention. Recently, Evans et al. reported that the stereochemical outcome of nucleophilic additions to β-alkoxy-α-methyl aldehydes are influenced by the stereochemistry of both stereocenters and that their stereodirecting effects can be mutually reinforcing or attenuating.[3] This study showed that in *anti*-β-alkoxy-α-methyl aldehydes the stereocenters operate in concert and nucleophilic additions afford uniformly high diastereoselectivities in favor of the Felkin−Anh products. In contrast, additions to *syn*-β-alkoxy-α-methyl aldehydes proceed with variable levels of aldehyde π-facial selectivity depending on the steric demands of the nucleophile and solvent polarity. These findings were qualitatively rationalized by using an integrated stereoinduction model,[3] based on the Felkin−Anh[4] and the 1,3-polar induction models,[5] that correctly accounts for the combined effects of both the α-methyl and β-alkoxy substituents. This methodology has successfully been implemented in the synthesis of complex organic structures.[6]

(1) Nógradí, M. In *Stereoselective Synthesis*; VCH: New York, 1986. (b) Mander, L. N. In *Stereochemistry of Organic Compounds*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1994; pp 875−894. (c) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223.

(2) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468. (b) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833−4835. (c) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840−10852.

(3) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619−6620. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322−4343.

(4) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828−5835. (b) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145−162. (c) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199−2204.

(5) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729−732. (b) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537−8540.

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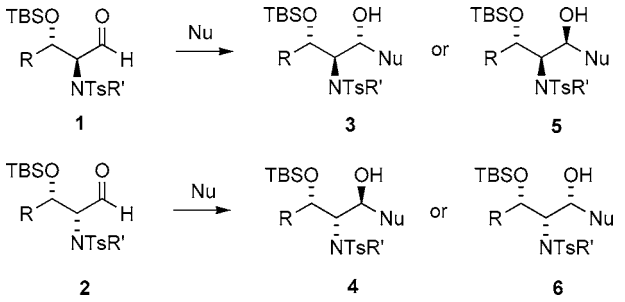
Scheme 1. Stereodivergent Synthesis of Aminodiols[a]

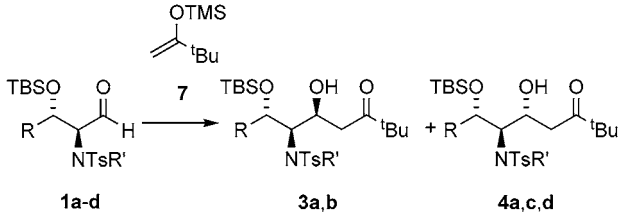


[a] R′ = Bn or H.

The aminodiol subunit is a common structural feature in several aza-sugars, polyhydroxylated indolizidine and pyrrolizidine alkaloids, many of which have interesting biological properties.[7] An interesting approach toward these densely functionalized compounds would be a divergent, diastereoselective addition of nucleophiles to β-alkoxy-α-amino aldehydes using the inherent diastereoselectivity of the aldehyde to control the stereochemical outcome (Scheme 1). For this approach to be attractive, however, the stereochemical impact of the α- and β-substituents must be understood, and herein is reported initial results from a study directed toward elucidating these factors using $BF_3{\cdot}OEt_2$-promoted Mukaiyama aldol additions[8] to aldehydes **1** and **2**[9] as model reactions.

In nucleophilic additions to aldehydes **1** and **2** (R′ = Bn) it was anticipated that the α-*N*TsBn moiety would act as the large substituent, for both steric and electronic reasons, and exert the major stereodirecting effect. Consequently, these reactions were expected to give the Felkin−Anh products *anti*,*anti*-**3** and *syn*,*anti*-**4**, respectively as the major products.[10] Additionally, these additions would also demonstrate the influence, if any, of the polar β-substituent on the stereoselectivity. The aminodiols *anti*,*syn*-**5** and *syn*,*syn*-**6** would be accessed from **1** and **2** (R′ = H) in a chelation-controlled reaction.[10] In the present study the silyl enol ether, solvent and the protecting groups employed have been held constant. Our initial focus was directed toward investigating the stereochemical outcome in the Mukaiyama aldol addition of silyl enol ether **7** to *N*HTs protected *anti*-substituted aldehydes **1a** and **1b** using either a monodentate (Table 1, entries 1, 3) or a chelating Lewis acid (entry 2). In all cases the reactions proceeded in excellent yields and stereoselectivities in favor of the chelation-controlled products, *anti*,*syn*-aminodiols **3a** and **3b**.[11] This outcome can be rationalized by invoking an intramolecular hydrogen bond between the *N*-H and the C═O oxygen, followed by nucleophilic attack on the sterically more accessible carbonyl *Si*-face.[12]

Table 1. Diastereoselective Mukaiyama Additions to *Anti*-α,β-Substituted Aldehydes **1a**−**d**[a]



1a R=$PhCH_2CH_2$, R'=H
1b R=c-C_6H_{11}, R'=H
1c R=$PhCH_2CH_2$, R'=Bn
1d R=c-C_6H_{11}, R'=Bn

entry	subst	Lewis acid	yield[b] (%)	dr (**3**/**4**)[c]	products
1	**1a**	$BF_3{\cdot}OEt_2$	91	92:8	**3a**, **4a**
2	**1a**	$TiCl_4$	85	90:10	**3a**, **4a**
3	**1b**	$BF_3{\cdot}OEt_2$	94	>98:2	**3b**
4	**1c**	$BF_3{\cdot}OEt_2$	92	<2:98	**4c**
5[d]	**1d**	$BF_3{\cdot}OEt_2$	81	<2:98	**4d**

[a] Reaction conditions: To **1** (1 equiv) in CH_2Cl_2 at −60 °C were added Lewis acid (3 equiv) and **7** (2 equiv), and the mixture was stirred for 18 h. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] The reaction time was 24 h.

Addition to *N*BnTs-protected *anti*-amino aldehyde **1c** resulted in *anti*,*anti*-aminodiol **4c** as a single detectable isomer in excellent yield (entry 4).[11] The diastereoselectivity was not affected by increasing the steric demands of the R-substituent, but a slight decrease in reaction rate was observed (entry 5). With these results at hand, we turned our attention to the nucleophilic additions of **7** to *syn*-aldehydes **2a**−**d** (Table 2). Addition to *N*HTs-protected *syn*-amino aldehydes **2a** and **2b** afforded the chelation-controlled products *syn*,*syn*-aminodiols **5a** and **5b**, respectively, in good yields and diastereoselectivities (entries 1, 2). This outcome is in analogy to the additions to aldehydes **1a** and **1b**.

In contrast, addition to *N*BnTs-protected *syn*-amino aldehyde **2c** under Felkin−Anh conditions gave a considerably lower reaction rate and, more interestingly, no diastereofacial selectivity was observed (entry 3). Increasing the temperature to −40 °C resulted in complete conversion but equally low selectivity (entry 4). With bulkier R-substituents even lower reaction rates and similar stereoselectivities were obtained

(6) Keck, G. E.; Knutson, C. E.; Wiles, S. A. *Org. Lett.* **2001**, *3*, 707−710. (b) Roush, W. R.; Newcom, S. N. *Org. Lett.* **2002**, *4*, 4739−4742.

(7) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045−4066. (b) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520−542.

(8) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503−7509.

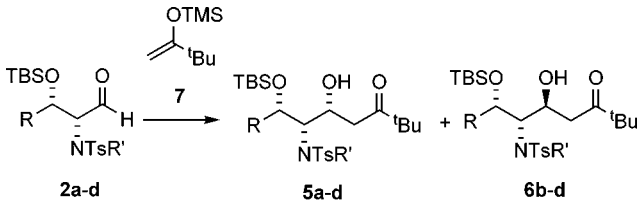
(9) Aldehydes **1** and **2** were prepared from the corresponding *vic*-vinylic amino alcohols, see; Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574−8583.

(10) Similar strategies have been developed for stereoselective additions of nucleophiles to α-amino aldehydes, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531−1546; Gryko, D.; Prokopowicz, P.; Jurczak, J. *Tetrahedron: Asymmetry* **2002**, *13*, 1103−1113.

(11) The relative stereochemistry of **3a** was assigned by desilylation of **3a** followed by intramolecular acetalization. The chelation-controlled major products **5a** and **5b** were assigned in analogy to this result. Felkin−Anh adducts **4c** and **9** were converted to the corresponding oxazolidinones by an Evans−Saksena reduction (Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578), detosylation and formation of the oxazolidinone. Felkin−Anh adduct **4d** was assigned in analogy with these results.

(12) Kiyooka, S.; Shiomi, Y.; Kira, H.; Kaneko, Y.; Tanimori, S. *J. Org. Chem.* **1994**, *59*, 1958−1960. (b) Vara Prasad, J. V. N.; Rich, D. H. *Tetrahedron Lett.* **1990**, *31*, 1803−1806. (c) Yamada, Y.; Shirakawa, E.; Ando, K.; Shibata, S.; Uchida, I. *Tetrahedron: Asymmetry* **1999**, *10*, 3443−3448.

Table 2. Diastereoselective Mukaiyama Additions to *Syn*-α,*β*-Substituted Aldehydes **2a**−**d**[a]



2a-d **5a-d** **6b-d**

2a R=$PhCH_2CH_2$, R'=H
2b R=c-C_6H_{11}, R'=H
2c R=$PhCH_2CH_2$, R'=Bn
2d R=c-C_6H_{11}, R'=Bn

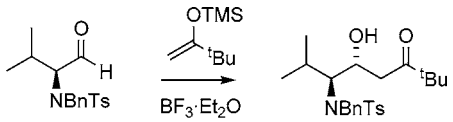
entry	subst	Lewis acid	yield[b] (%)	dr (**5**/**6**)[c]	products
1	**2a**	$BF_3{\cdot}OEt_2$	88	>98:2	**5a**
2	**2b**	$BF_3{\cdot}OEt_2$	89	88:12	**5b**,**6b**
3	**2c**	$BF_3{\cdot}OEt_2$	26[d]	49:51	**5c**, **6c**
4[e]	**2c**	$BF_3{\cdot}OEt_2$	91	47:53	**5c**, **6c**
5	**2d**	$BF_3{\cdot}OEt_2$	*f*		
6[e]	**2d**	$BF_3{\cdot}OEt_2$	49[g]	44:56	**5d**, **6d**

[a] Reaction condition: To **2** (1 equiv) in CH_2Cl_2 at −60 °C were added $BF_3{\cdot}OEt_2$ (3 equiv) and **7** (2 equiv), and the mixture was stirred for 18 h. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Conversion after 18 h at −60 °C according to ^1H NMR analysis. [e] Reaction carried out at −40 °C for 40 h. [f] No reaction; **2d** was recovered. [g] Conversion after 40 h at −40 °C according to ^1H NMR analysis.

(entries 5, 6). Apparently, the polar *β*-OTBS substituent influences the stereoselectivity of the nucleophilic addition, since the diastereoselectivities observed in the additions to *syn*- and *anti*-disubstituted aldehydes differ significantly.[13] To determine the inherent stereodirecting effect of the α-amino substituent in the absence of a polar *β*-substituent *N*BnTs amino aldehyde **8** was subjected to the same reaction conditions (Scheme 2). This gave *anti*-amino alcohol **9** as a single diastereomer,[11] showing that the diastereofacial bias imposed on the carbonyl moiety by the α-*N*BnTs substituent

(13) A similar observation has been reported before; see: Ohfune, Y.; Nishio, H. *Tetrahedron Lett.* **1984**, *25*, 4133−4136.

Scheme 2. Felkin−Anh Addition to *N*,*N*-Diprotected Amino Aldehyde **8**



8 85% *anti*:*syn* >98:2 **9**

is sufficiently strong to direct the approaching nucleophile according to the Felkin−Anh model.

Consequently, in the Felkin−Anh additions to *anti*-aldehydes **1c** and **1d** the polar *β*-OTBS substituent exerts an insignificant or cumulative stereodirecting effect, affording *anti*,*anti*-aminodiols **4c** and **4d**, respectively. It should be noted that **4c** and **4d** are not the predicted products by the Evans merged 1,2- and 1,3-stereoinduction model. In the Felkin−Anh additions to *syn*-aldehydes **2c** or **2d** a diminished diastereoselectivity is obtained, due to strongly opposing α- and *β*-stereocenters. We are currently developing a stereochemical rationale for these observations.

In conclusion, we have developed a divergent protocol for diastereoselective synthesis of aminodiols by nucleophilic additions to α,*β*-disubstituted aldehydes. Furthermore, we report that the merged stereochemical impact of the *β*-OTBS and α-*N*BnTs substituents are mutually reinforcing in *anti*-disubstituted aldehydes and opposing in *syn*-disubstituted aldehydes.

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Supporting Information Available: General experimental procedure for the aldol reaction and spectral data characterization for compounds **1**-**6**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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