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On the role of β-silyloxy- and β-alkoxyaldehyde protecting groups in Mukaiyama aldol 1,3-diastereocontrol

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ABSTRACT

Longstanding paradigmatic studies have noted anti-1,3-diastereocontrol in Mukaiyama aldol reactions with β-silyloxy- and β-alkoxyaldehydes. In our efforts to exploit this stereocontrol, we found that an aldehyde of this type that lacks branching at the γ-carbon led to eroded diastereoselectivity that was restored upon changing the β-protecting group. This suggested the hypothesis that 1,3-anti selectivity in these cases is inversely dependent on the size of the β-protecting group. In testing this hypothesis, Mukaiyama aldol reactions of several analogs of unbranched β-silyloxy- and β-alkoxyaldehydes, varying only the protecting group, showed improved selectivity with smaller silyl and alkyl groups. These results will aid synthetic design as well as provide experimental benchmarks for computational studies.

Introduction

The venerable Mukaiyama aldol reaction has been an essential tool in total synthesis of polyketide natural products, allowing carbon–carbon bond-constructive coupling of complex multifunctional components with both 1,2- and 1,3-diastereocontrol of the product β-hydroxycarbonyl motif [1]. Stereochemical models for the 1,3-diastereocontrol event were proposed by Reetz [2] and further developed by Evans [3], recognizing dipole repulsion as a key contributing factor. The generally accepted Evans model can often explain the 1,3-diastereocontrol observed in Mukaiyama aldol reactions, but the best predictive outcomes involve examples that contain branched substituents adjacent to the enol silane, or at the β -carbon of the aldehyde, or both. Our recent synthetic objectives in 1,5-polyol synthesis [4] required the use of unbranched precursors for polyacetate-type targets, and the results raised questions of whether the aforementioned models would require further refinement [5]. Specifically, we found that a BF_3-mediated Mukaiyama aldol reaction of enolsilane **1** (Fig. 1) with unbranched β -silyloxyaldehyde acceptor **2** gave poor selectivity when the β-protecting group was *tert*-butyldiphenylsilyl, but selectivity improved with an apparently smaller *tert*-butyldimethylsilyl [5a]. This counterintuitive observation is not addressed by the typical 1,3-diastereocontrol models. Similar observations have appeared sporadically in related enolsilane additions, for example, in syntheses of aculeatins [6] and bryostatins [7], as well as in the development of iterative Mukaiyama aldol cascade processes [8]. Taken together, our findings and these related precedents warrant further data for refinement of the 1,3-diastereocontrol models.

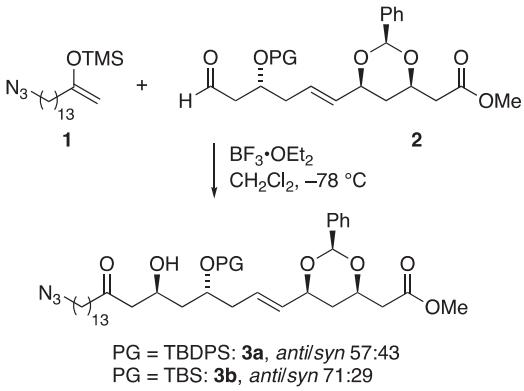

Fig. 1. Improved *anti*-1,3-diastereocontrol in Mukaiyama aldol with β -silyloxyaldehyde acceptor upon switch from TBDPS to TBS.

Notably, the Evans model is justified through experimental and theoretical results involving electrophiles bearing branched alkyl groups at the aldehyde β -carbon (Fig. 2). Stereocontrol models **A**–**F** (Fig. 2b, R = *t*-Bu, PG = Me), generated via AM1 computation, led to the conclusion that stereocontrol model **A** benefits from minimized electrostatic repulsion and torsional strain components.

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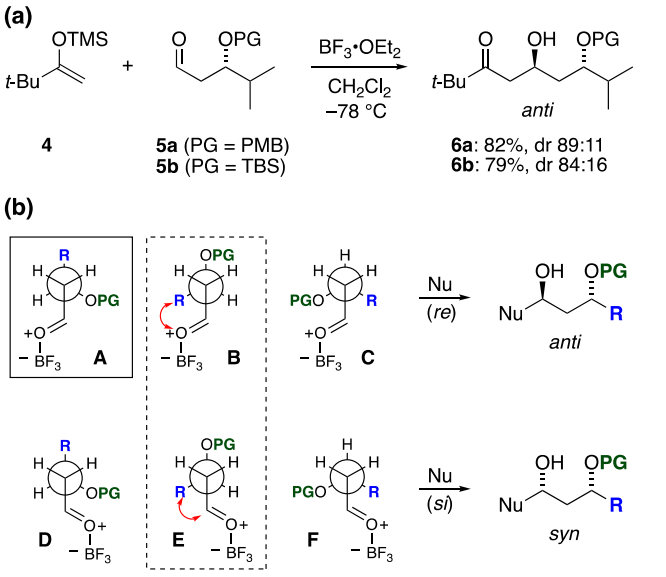


Fig. 2. (a) Evans experimental results showing *anti*-1,3-diastereocontrol. (b) Evans rationale for *anti* selectivity via addition via conformer **A**.

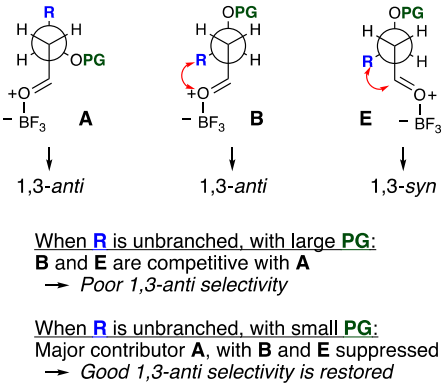


Fig. 3. Restoring 1,3-*anti* selectivity in Mukaiyama aldol reactions with unbranched β -silyloxy- or β -alkoxyaldehydes.

In contrast, aldehyde substrate **2** (Fig. 1), the alkyl group attached to the β carbon is unbranched at the point of attachment (R = CH_2–alkyl), and we suggested that models **B** and **E** become competitive with **A** because steric repulsions in **B** and **E** (indicated by red arrows in Fig. 2b) are diminished when R is small. Reaction via **E** affords the *syn* diastereomer, eroding the 1,3-*anti* selectivity, an effect which may be further magnified with the larger TBDPS protecting groups. From this reasoning, we suggested that the smaller TBS protecting group had returned the reaction to a preferred pathway through conformer **A**. Thus our working hypothesis is that protecting groups with less steric demand afford higher 1,3-*anti* selectivity by favoring reaction through conformer **A**. An expanded set of protecting groups could test this hypothesis. Here we describe a series of Mukaiyama aldol reactions designed specifically to probe the role of the protecting group in 1,3-diastereocontrol with β -silyloxy and β -alkoxyaldehyde acceptors.

Results and discussion

Preparation of β-silyloxy- and β-alkoxyaldehydes

We began by installing a series of silyl and alkyl groups on the hydroxyl of homoallylic alcohol **7** [9], synthesized via Grignard addition to hexanal (Table 1). These ranged from trimethylsilyl to *tert*-butyldiphenylsilyl in the silyl series **8a**–**8e**, while the alkyl series **8f**–**8i** consisted of benzyl, *p*-methoxybenzyl (PMB), methyl, and *tert*-butyl. Subjection of **8a**–**8i** to a modified Lemieux-Johnson oxidative cleavage [10] furnished racemic β-silyloxy- and β-alkoxyaldehydes **9a**–**9i**.

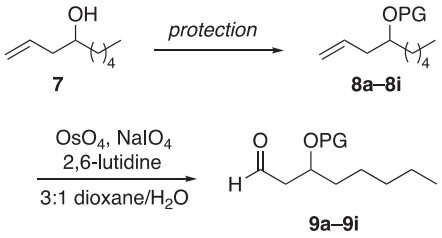
Mukaiyama aldol reactions

As a nucleophilic partner in the Mukaiyama aldol reaction, enolsilane nucleophile **10** was prepared from the corresponding ketone [11]. This reactant was chosen to mimic the unbranched nucleophiles anticipated in applications to synthesis of polyacetate structures. Also, for focusing on the 1,3-diastereocontrol question, its lack of a stereocontrol element would be advantageous. Aldehydes **9a**–**9i** were subjected to Mukaiyama aldol conditions to enolsilane **10** in CH_2Cl_2 with BF_3•OEt_2 at low temperature, and after aqueous workup the crude aldol products **11b** and **11d**–**11i** were obtained in 70–85 % yield as diastereomer mixtures. To obtain aldol products **11a** (PG = TMS) and **11c** (PG = TES), a modified procedure was used to avoid material loss through partial desilylation [12]. Diastereomer ratios (Table 2) were recorded for these crude products by integration of their ^{1}H NMR spectra, in which resonances for the R_2CHOH methine at the new stereogenic center were well-resolved for the *anti* and *syn* diastereomers.

Configurational assignments

The pure major diastereomers of **11**, with the exception of **11d** and **11h**, were separated via flash chromatography. Configurational assignment entailed a sequence involving directed *anti*-reduction with $Me_4NBH(OAc)_3$ and deprotection for **11a, 11c, 11e, 11g, and 11i** (Scheme 1); in all cases this furnished the same triol **12**, which

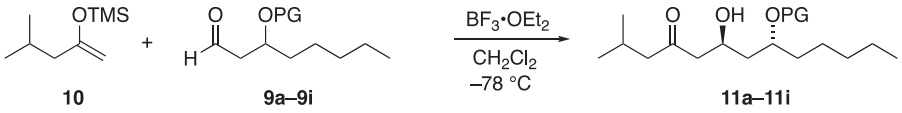
Table 1
Preparation of β -silyloxy- and β -alkoxyaldehydes[a].



Entry	PG	Ether, yield	Aldehyde, yield
1	Me_3Si (TMS)	**8a**, na	**9a**, 77 %[b]
2	*t*-$BuMe_2Si$ (TBS)	**8b**, 83 %	**9b**, 78 %
3	Et_3Si (TES)	**8c**, 100 %	**9c**, 75 %
4	*i*-Pr_3Si (TIPS)	**8d**, 65 %	**9d**, 100 %
5	*t*-$BuPh_2Si$ (TBDPS)	**8e**, 89 %	**9e**, 93 %
6	Bn	**8f**, 93 %	**9f**, 70 %
7	PMB	**8g**, 83 %	**9g**, 99 %
9	Me	**8h**, 75 %	**9h**, 48 %
10	*t*-Bu	**8i**, 50 %	**9i**, 47 %

[a] Conditions: Typical conditions were employed for protection. See supporting information for details. Oxidative cleavage: OsO_4 (2 mol%), 2,6-lutidine (2 equiv), $NaIO_4$ (5 equiv) in 3:1 dioxane:H_2O.
[b] Upjohn conditions were adopted (OsO_4, NMO acetone; then $NaIO_4$).

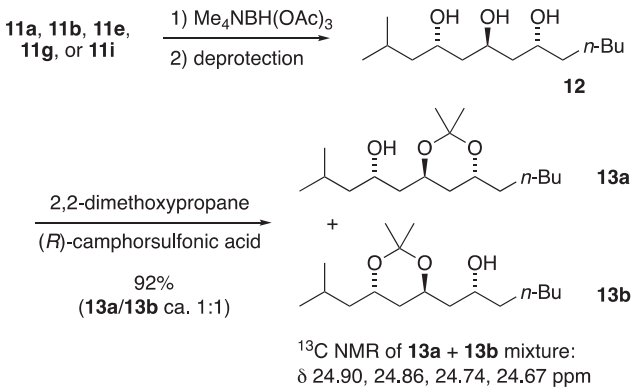
Table 2
Diastereoselectivity of Mukaiyama aldol reactions.



10 **9a–9i** **11a–11i**

Entry	Aldehyde	PG	Product, dr (*anti*:*syn*)[a]
1	**9a**	Me_3Si (TMS)	**11a**, 82:18
2	**9b**	*t*-BuMe_2Si (TBS)	**11b** 79:21
3	**9c**	Et_3Si (TES)	**11c** 68:32
4	**9d**	*i*-Pr_3Si (TIPS)	**11d** 63:37
5	**9e**	*t*-BuPh_2Si (TBDPS)	**11e**, 60:40
6	**9f**	Bn	**11f**, 84:16
7	**9g**	PMB	**11g**, 83:17
8	**9g**	PMB	**11g**, 85:15[b]
9	**9h**	Me	**11h**, 83:17
10	**9i**	*t*-Bu	**11i**, 73:27

[a] Conditions: To a mixture of **9** and **10** in CH_2Cl_2 at −78 °C was added BF_3•OEt_2. Diastereomer ratios were measured on the crude product by ^{1}H NMR integration of CHOH peaks.
[b] Toluene was used in place of CH_2Cl_2.



Scheme 1. Configurational assignment.

in turn gave a mixture of regioisomeric acetonide derivatives **13a** and **13b**, as expected for an *anti*,*anti* 1,3,5-triol. An *anti*,*syn* diastereomer would afford thermodynamically controlled regioselectivity for the *syn*-diol acetonide as a consequence of its more stable chairlike conformation. The ^{13}C NMR DEPT-135 spectrum of the observed mixture of acetonides exhibited four CH_3 peaks between 24.7 and 24.9 ppm, and none at 19 and 30 ppm, confirming that no *syn* relationship was present. This established the *anti*, *anti* configuration of triol **12**, and the *anti* configurations of **11** [13].

Evaluation of protecting group impact on 1,3-diastereocontrol

Our working hypothesis, that smaller protecting groups lead to increased 1,3-*anti* selectivity by favoring reaction through conformer **A** (Fig. 2b), seems to be supported within the separate types of protecting groups we tested, silyl and alkyl. First, selectivities among additions to β -silyloxyaldehydes **9a**–**9e** appeared inversely related, from a qualitative standpoint, to the apparent size of silyl protecting groups [14,15]. Aldehydes **9d** and **9e** with the bulkiest β -silyloxy groups (OTBDPS and OTIPS) led to the poorest 1,3-*anti* selectivities, OTES (**9c**) is slightly better. The smaller silyl groups bearing two or three methyl groups, TMS (**9a**) and TBS (**9b**), afforded the best 1,3-*anti* selectivities (ca. 4:1). While its *tert*-butyl group clearly makes the overall structure of TBS larger than TMS, a freely rotating Si–O bond allows the *tert*-butyl of the TBS group to occupy space that is distant from repulsive interactions within the transition state. For 1,3-diastereocontrol in Mukaiyama aldol reactions of these unbranched β -silyloxyaldehydes, the TMS and TBS groups are optimal. From a practical standpoint, the lability of the TMS group could be troublesome, and therefore the TBS is preferred.

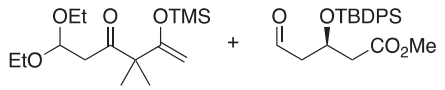
Among the alkyl groups, selectivities were quite similar among aldehydes **9f**–**9h** bearing OBn, OPMB, and OMe in the β -position. As noted above for the TBS group, conformational freedom within the arylmethyl groups may allow for C—O rotamers in which the arene avoids repulsive interactions so it is unsurprising that OBn and OMe lead to quite similar 1,3-*anti* selectivities. In the β -*tert*-butoxyaldehyde **9i**, the *tert*-butoxy group would not avoid repulsive interactions in this way, as the alternative C—O rotamers would be degenerate. Thus the lower selectivity with aldehyde **9i** is in line with expectations for a larger protecting group. For 1,3-diastereocontrol in Mukaiyama aldol reactions of these unbranched β -alkoxyaldehydes, the Me, Bn and PMB groups are optimal, but given the deprotection difficulties with a methyl group, the Bn and PMB are preferred.

Comparison across the silyl and alkyl classes is available with β -trimethylsilyloxyaldehyde **9a** and β -*tert*-butoxyaldehyde **9i**; the latter gives lower selectivity. These are nearly identical groups, except for replacement of the Si atom in **9a** with a C atom in **9i**. Longer bondlengths (C—Si > C—C) allow the TMS group to behave as a smaller protecting group than *tert*-butyl, yielding higher 1,3-*anti*-selectivity.

Conclusion

In Mukaiyama aldol reactions of β -silyloxyaldehydes, across a series of different silyl protecting groups, smaller protecting groups lead to better 1,3-*anti*-selectivity. In the alkyl series, the evidence is not as clear because steric demands are not as diverse throughout the series. However, the comparison of *tert*-butyl versus methyl clearly fits the same trend noted for the silyl groups. Taken together, all these results are qualitatively consistent with the working hypothesis; smaller protecting groups yield better 1,3-diasterecontrol in Mukaiyama aldol reactions of unbranched β -silyloxy and β -alkoxyaldehydes by favoring reaction through conformer **A** (Fig. 3), whereas larger protecting groups compromise the selectivity by making a pathway through conformer **E** more competitive.

The results reported here will aid in design of more selective Mukaiyama aldol reactions. For example, in Wender's impressive synthetic route to bryostatin [16], an attempted Mukaiyama aldol



Mukaiyama aldol in bryostatin synthesis (dr ~1:1)

Fig. 4. Potential for improved selectivity.

reaction of an unbranched β -silyloxyaldehyde was replaced in the sequence due to negligible 1,3-*anti* selectivity; the silyl group was TBDPS (Fig. 4). Our results suggest that simply switching the TBDPS group with TBS could significantly improve this reaction.

Aside from synthetic studies, there are further impacts to be expected: Computational work continues to shed light on anomalous conformational and steric effects of silyloxy groups [14], and we hope that the experimental data herein will help to inform such theoretical studies.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Synthetic procedures and characterization data for all new compounds, including configurational assignments. Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2022.154203.

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