Confinement-Controlled, Either syn- or anti-Selective Catalytic
Asymmetric Mukaiyama Aldolizations of Propionaldehyde
Enolsilanes

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ABSTRACT: Protected aldols (i.e., truealdols derived from aldehydes) with either syn- or anti- stereochemistry are versatile intermediates in many oligopropionate syntheses. Traditional stereoselective approaches to such aldols typically require several nonstrategic operations. Here we report two highly enantioselective and diastereoselective catalytic Mukaiyama aldol reactions of the TBS- or TES- enolsilanes of propionaldehyde with aromatic aldehydes. Our reactions directly deliver valuable silyl protected propionaldehyde aldols in a catalyst controlled manner, either as syn- or anti- isomer. We have identified a privileged IDPi catalyst motif that is tailored for controlling these aldolizations with exceptional selectivities. We demonstrate how a single atom modification in the inner core of the IDPi catalyst, replacing a CF3-group with a CF2H-group, leads to a dramatic switch in enantiofacial differentiation of the aldehyde. The origin of this remarkable effect was attributed to tightening of the catalytic cavity via unconventional C–H hydrogen bonding of the CF2H group.

Polyketides are pharmaceutically important secondary metabolites. Erythromycin is a prototypical example, which as a synthetic target was declared by Woodward as “hopelessly complex ... in view of its plethora of asymmetric centers”. This statement encouraged the beginning of several decades of intense and highly innovative method development in acyclic stereocontrol. Generations of chemists have contributed approaches to overcoming the synthetic challenges posed by oligopropionates, typically bearing linear stereopolyads with alternating methyl and hydroxyl groups. Nonetheless, only few truly reliable methods have found general utility in numerous syntheses of complex oligopropionates. Widely used approaches, based on chiral auxiliaries, rely on diastereoselective asymmetric propionate aldolizations or crotylation reactions (Figure 1). Very often, both approaches converge after several steps: following the critical diastereoselective C–C bond-formation, protecting group installation and redox manipulations lead to stable protected aldol intermediates of a general structure I, which are ideal for downstream functionalization to construct various polyketide motifs. Catalytic asymmetric crotylation methods developed more recently by Krische et al. provide an attractive alternative but feature a moderate step-economy when protected aldols of type I are needed. Direct stereoselective cross-aldol reactions of aldehydes have also been described, but an additional protection step is often unavoidable. A truly practical approach, from a total synthesis chemist’s perspective, would directly deliver the protected aldols in a predictable catalytic manner, with full control over diastereoselectivity and enantioselectivity. In this regard, arguably the most useful variant of the Mukaiyama aldol reaction, the aldolization of propionaldehyde-derived enolsilanes with aldehydes, has been...
remained elusive. In addition to directly delivering the protected aldehydes, such a reaction would favorably meet all of the metrics used to evaluate synthetic methods, such as atom-10, redox-11, and especially step-economy.12

Yamamoto reported nonenantioselective examples using the bulky tris(trimethylsilyl)silyl (TTMSS, supersilyl) group to control selectivity toward single addition of aldehyde-derived enolisilanes.13 The first diastereo- and enantioselective examples by Denmark utilized trichlorosilyl enolisilanes under Lewis base catalysis.14 This approach is poorly atom-economic, as the silyl group is not retained in the final product and several steps are required to obtain aldehydes suitable for chain elongations. Kanai and Matsunaga reported an asymmetric Cu-catalyzed aldolization using in situ generated boron enulates of propionaldehyde, which gives mainly syn-aldehydes.15 Although up to quadruple aldolizations were achieved, the existence of unprotected oligoaldehydes in various cyclic hemiacetals forms limits their selective elaboration to useful oligopropionate motifs. Recently we reported the first, highly enantioselective Mukaiyama cross-aldol reaction with simple triethylsilyl (TES) and tert-butyldimethylsilyl (TBS) enolisilanes of acetaldehyde and aliphatic and aromatic aldehydes using confined and strongly acidic imidodiphosphorimidate (IPi) catalysts developed here.16 Enzyme-like discrimination of the small substrate aldehyde over the larger product goal.20 Catalysts provides a powerful solution to this long-standing aldolization challenge.

Our investigations commenced with an exploration of different IDPi catalysts in the aldolization of benzaldehyde in (E)-enolisilanes 2a–b or (Z)-enolisilanes 4a–c (Table 1). At the onset we found that the diastereoselectivity was dependent on the nucleophile geometry, with (E)-enolisilanes providing syn-aldols and (Z)-enolisilanes giving anti-aldols, with varying degrees of diastereoselectivity, depending on the silyl group and the catalyst. IDPi 6, which was a preferred catalyst in our acetaldehyde-derived enolisilane additions, was tested in the reaction of (E)-enolisilane 2a with benzaldehyde at 20 °C. Single aldolization product 3 was indeed formed in high yield, excellent diastereoselectivity (d.r. 97.5:2.5) in favor of the syn-aldol 3a ([Si] = TES), and with a promising enantiomeric ratio (e.r.) of 10.5:89.5 (Table 1A, entry 1). Given that fluorenesubstituted IDPi catalysts were especially privileged in our recent silylum-ion asymmetric counteranion-directed catalysis (Si-ACDC)21 methodologies,22a–d we turned our attention to catalysts 7a–d (and 8a–c in the Supporting Information). Indeed, these IDPis emerged as preferred catalysts for our reactions. Spirocyclobutane-substituted IDPi 7a markedly stood out in terms of enantioselectivity, providing aldol 3a with a 95.5:4.5 e.r. (Table 1A, entry 2). Modification of the inner core of the IDPi from the Tf-group to a Nf-group further increased diastereoselectivity and enantioselectivity. Lowering the temperature to −40 °C led to a d.r. of 99:1 and a 98:2 e.r. (Table 1A, entry 5). Variation of the silyl group was well-tolerated when the TBS-enolisilane 2b was used instead of the TES-enolisilane 2a (Table 1A, entry 6). An opposite trend was observed in the anti-selective Mukaiyama aldol addition of (Z)-enolisilanes (Table 1B). Both the size of the perfluorinated sulfonamide in the inner core of IDPi and the silyl group had tremendous effects on the selectivity. Longer perfluorinated groups gave poorer d.r. and e.r. At −60 °C, the addition of

| Table 1. Reaction Development |

| A. syn-Selective Mukaiyama aldol addition |
|---|---|---|---|---|---|
| entry | IDPi | [Si] | T (°C) | yield (%) | syn/anti | e.r. | |
| 1 | 6 | TES | −20 | 98 | 97.5:2.5 | 10.5:89.5 | |
| 2a | 7a | TES | −20 | 99 | 95.5:4.5 | 95.5:4.5 | |
| 3 | 7b | TES | −20 | 99 | 96:4 | 96:4 | |
| 4c | 7c | TES | −20 | 99 | 97:3 | 97:3 | |
| 5 | 7c | TBS | −50 | 99 | 99:1 | 99:1 | |
| 6 | 7c | TBS | −50 | 99 | 99:1 | 99:1 | |

| B. anti-Selective Mukaiyama aldol addition |
|---|---|---|---|---|---|
| entry | IDPi | [Si] | T (°C) | yield (%) | anti/syn | e.r. | |
| 1a | 7a | TES | −60 | 99 | 96:14 | 75:25 | |
| 2a | 7a | TBS | −60 | 99 | 94:6 | 89:11 | |
| 3a | 7a | TIPS | −60 | 99 | 90:10 | 83:17 | |
| 4 | 7b | TES | −60 | 96 | 63:37 | 39:61 | |
| 5 | 7c | TES | −60 | 84 | 62:38 | 38:62 | |
| 6 | 7d | TES | −60 | 99 | 96:4 | 87:13 | |
| 7 | 7d | TBS | −60 | 99 | 99:1 | 97.5:2.5 | |
| 8 | 7d | TBS | −78 | 99 | >99:1 | 98:2 | |
(Z)-enolsilane 4a ([Si] = TES) to benzaldehyde proceeded with modest d.r. and e.r. using catalysts 7b and 7c, which performed exceptionally well previously in the syn-aldolization (Table 1B, entries 4−5). In contrast, IDPi 7a with the shortest trifluoromethylsulfonamide core performed far better, but to our surprise, with inverted benzaldehyde enantiofacial preference. Among (Z)-enolsilanes 4a−4c with different silyl-groups (Table 1B, entries 1−3), enolsilane 4b with the TBS-group performed best, albeit only in 89:11 e.r. Hypothesizing that replacing one of the F atoms in the CF3-group to an H atom may help in positively influencing the selectivity without introducing significant steric changes,23 IDPi 7d containing a CF2H-group was designed and synthesized. Specifically, we envisioned that CF2H···heteroatom interactions could lead to a modulation of the active site of the IDPi catalyst.24 Strikingly, the single-atom modification of the inner core of the catalyst, replacing the CF3-groups with CF2H-groups, indeed resulted in a spectacular enhancement of both the d.r. (99:1) and e.r. (98:2) in the addition of enolsilane 4b (Table 1B, entries 7 and 8).

With these results in hand, the scope of our syn-selective Mukaiyama aldol reaction with various aromatic aldehydes was explored, using catalyst 7c (Table 2A). Aromatic aldehydes with o-, m-, and p-substituents and heteroaromatic aldehydes (3a−3j) gave the corresponding products in excellent yields and stereoselectivity. Multisubstituted aromatic aldehydes provided products 3k−3m, which contain substructures of complex polyketides.25,26 The catalyst loading could be reduced to 0.5 mol % without compromising the reaction time and stereoselectivity as shown with the gram scale synthesis of aldols 3h and 3k. A diastereoselective and enantioselective single aldolization of a dialdehyde substrate gave product 3m.

Essentially the same set of aromatic aldehydes performed equally well in our anti-aldolization process furnishing products 5b−k and 5m (Table 2B). Electron-rich aromatic aldehydes also delivered anti-aldols 5l and 5n with good diastereoselectivity and enantioselectivity. Only furfural gave somewhat lower yield of product 5i.

Furthermore, butyraldehyde-derived enolsilanes 8 and 9 also readily reacted to either syn- or anti-products 10 and 11 (Scheme 1A). Moreover, both enantiomers of our IDPi catalysts enabled access to all four possible stereoisomers of aldols as shown in Scheme 1B.

Our stereodivergent aldolization method is especially valuable in the context of the rapid generation of complex polyketide motifs (Scheme 1C). For example, when syn-aldol 3h was subjected to a follow-up propionate aldolization using in situ generated chiral boron enolates 12,27 either the all-syn-stereotetrad 13 or its syn, anti, syn stereoisomer 14 were obtained as single diastereomers. The structure of the polyketide-like molecule 13 was unambiguously confirmed by

| Table 2. Substrate Scope for the syn- and anti-Mukaiyama Aldol Additions |
|-----------------------------|-----------------------------|
| A. syn-Selective Mukaiyama aldol addition | B. anti-Selective Mukaiyama aldol addition |
| ![Reaction](image.png) | ![Reaction](image.png) |
| ![Molecule](image.png) | ![Molecule](image.png) |
| ![Molecule](image.png) | ![Molecule](image.png) |

"Reaction scale: 0.2−5 mmol. See the Supporting Information for full reaction conditions and the determination of e.r."
Scheme 1. Further Applications of the Diastereoselective and Enantioselective Aldol Reactions

A. Catalysis with Tf$_2$NH

B. Control experiment rules out matched/mismatched scenario

C. Acetaldehyde enolisilane additions and the origin of switch in enantioselectivity

D. Transition state structures leading to 3a and 5b

E. C–H hydrogen bondings tighten the catalytic pocket

Figure 2. Mechanistic studies. (A–C) Control experiments. (D) Computed transition-state structures of major enantiomer of 3a (syn-selective addition) with 7a (left) and 5b (anti-selective addition) with 7d (right) at B3LYP-D3(BJ)/def2TZVP+CPCM(Chloroform)//ONIOM(PBE-D3/6-31G(d):PBE-D3/3-21G) level of theory. Distances between centroids of the two inner spirocyclobutyl-2-fluorenyle groups are shown. *Energies in kcal/mol (see the Supporting Information for details). (E) Effect of C–H hydrogen bondings on the cavity size. Angles represent centroids of the two inner spirocyclobutyl-2-fluorenyle groups and the central nitrogen.
X-ray crystallography. Alternatively, iterative aldolization using the proline-catalyzed cross-aldol addition with propionaldehyde delivered the \textit{syn, syn, anti}-stereotetrad 15 with excellent diastereoselectivity. Further, \textit{anti-}aldol 5d was converted to a fully protected double aldol adduct 16, containing the key \textit{anti, syn}-stereotriad of antarlide A, when our method was coupled with Yamamoto’s supersilyl enolate technology. Stereo triad 16 is fully suited for further aldol addition toward antar lides. 1,3-Dienyl-6-oxy polyketide motif 17, an intermediate from a reported total synthesis of nanocystin \textit{A}, was also obtained in only two steps starting from benzaldehyde (via \textit{ent-3b}). The previous synthesis of 17 involved five steps, including an Evans-aldolization.\textsuperscript{20} It is noteworthy that all of the polyketide motives 13–17 were obtained in just two steps from commercially available aldehydes such as furfural, m-anis aldehyde, and benzaldehyde.

To gain insight into the mechanism of our stereoselective aldol additions, experimental and computational studies were performed. Experiments were directed at probing aspects of our aldol reactions such as the origin of single aldolization and the unexpected change of facial selectivity during \textit{anti-}aldolization using IDPi 7d. Initially, we confirmed that our IDPi catalysts were indeed unique in promoting the single aldolization of propionaldehyde enol silanes: the well-established Mukaiyama aldol addition catalyst triflimide did not give even a trace of the desired single aldolization products because of complete enol silane oligomerization (Figure 2A, see the Supporting Information, Figure S2 for details), \textit{syn-Aldol} 3c, which was obtained using IDPi (S,S)-7c at \textdegree40, underwent less than 10% conversion under the same conditions using the opposite enantiomer of the catalyst \textit{(R,R)-7c}, excluding a potential matched–mismatched scenario (Figure 2B). The change in facial selectivity of aldol hyde attack upon switching from the \textit{n-CF3F}- and CF3-groups to the CF2H-group was also manifested when simple acetaldehyde-derived enol silanes 19a–b were used (Figure 2C). With catalysts 7a and 7c, acetaldehyde-derived enol silane additions to benzaldehyde proceeded with \textit{re}-selectivity, giving \textit{ent-20} irrespective of the silyl groups. In contrast, IDPi 7d, having a difluoromethanesulfonyl group in the core, reacted with \textit{si}-selectivity.

In order to probe the origin of stereoselectivity and the switch of enantiofacial selectivity, an extensive DFT study was conducted for both \textit{syn-} and \textit{anti-}selective additions with IDPis 7a and 7d. Computed e.r.s and d.r.s were in good agreement with experimental observations in both cases (Figure 2D; see the Supporting Information, Figures S6–S10 for more details). When the optimized major transition-state structures of \textit{syn-} and \textit{anti-}selective aldolizations are compared, one of the most prominent differences appears to be the catalyst pocket size.\textsuperscript{20} While catalyst 7a with CF3-cores has a relatively open cavity, the CF3 groups in catalyst 7d engage in intramolecular hydrogen bonding interactions resulting in a more compact catalytic pocket (Figure 2D and 2E). Accordingly, for the \textit{syn-}selective addition with 7a, the bulky \textit{(E)}-enol silane 2a bearing a smaller TES group would approach from the less hindered \textit{re}-face (Figure 2B, left). In contrast, for the case of \textit{anti-}selective addition with 7d, the sterically less hindered \textit{(Z)}-enol silane 4b, with a slightly bulkier TBS group, provides a perfect fit into the narrower cavity, resulting in the complete switch of the facial selectivity (Figure 2D, right). The outcome of the acetaldehyde-derived enol silane additions using catalysts 7a and 7d is also in good agreement with this model (Figures 2C, S12, and S13).

Additionally, our study has identified the involvement of CH/\pi interactions, indicated in Figure 2D,\textsuperscript{31} between the spirocyclic methylene groups of the catalyst counteranion and the aromatic ring of the aldehyde substrate, which contribute to the high enantioselectivities in both transition states.\textsuperscript{32} This is in agreement with our experimental observations, showing a strong effect of the spirocycle on the enantioselectivity (Figure S1).

Our highly stereoselective Mukaiyama aldol additions of propionaldehyde enol silanes give access to all stereoisomers of the stable and versatile protected aldehyds in a predictable manner and can be used in rapid syntheses of complex polyketide motifs. Ultimately, our approach could aid in streamlining the synthesis of complex oligopropionates. We also uncovered an unusual enantioreversal effect by modifying a CF3-group to a CF2H-group. The origin of stereoselectivities and enantiofacial switch was rationalized through computational studies, revealing the cooperation of C–H hydrogen bonds and CH/\pi interactions to govern catalyst structure and transition states.

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c07447.

Experimental details and analytical data for all new compounds (PDF)

### Accession Codes

CCDC 2097850–2097853 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes
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