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Highly Stereoselective Synthesis of *anti,anti*-Dipropionate Stereotriads: A Solution to the Long-Standing Problem of Challenging Mismatched Double Asymmetric Crotylboration Reactions

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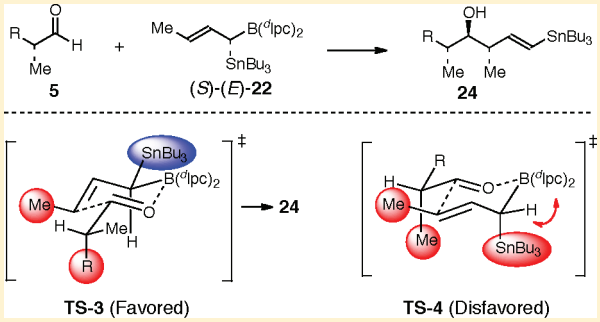
Supporting Information

ABSTRACT: The stereocontrolled synthesis of the β-branched *anti,anti*-dipropionate stereotriad **4** via aldol or crotylmetal chemistry represents a historical challenge to the organic synthesis community. Here we describe a general solution to the long-standing problem associated with the synthesis of **4** by utilizing mismatched double asymmetric crotylboration reactions of enantioenriched α-methyl substituted aldehydes with the chiral, nonracemic crotylborane reagent (*S*)-(*E*)-**22** (or its enantiomer). This method not only provides direct access to *anti,anti*-dipropionate stereotriads **24** [a synthetic equivalent of **4**] with very good (5−8:1) if not excellent (≥15:1) diastereoselectivity from β-branched chiral aldehydes with ≤50:1 intrinsic diastereofacial selectivity preferences but also provides a vinylstannane unit in the products that is properly functionalized for use in subsequent C−C bond-forming events. We anticipate that this method will be widely applicable and will lead to substantial simplification of strategies for synthesis of polyketide natural products.



INTRODUCTION

Polyketide natural products are structurally diverse secondary metabolites isolated from sponges, bacteria and fungi that display a wide variety of biological activities.[1] The exquisite molecular architectures coupled with the diverse biological activities of the polyketides makes them attractive targets for the synthetic organic, medicinal chemistry and chemical biology communities.[2] One characteristic structural feature of polyketide natural products is the frequent occurrence of the dipropionate stereotriads **1**−**4** embedded in the carbon skeleton (Figure 1).[3] While stereotriad isomers **1**−**3** can be readily synthesized with high selectivities via aldol or crotylmetal chemistry,[4,5] the *anti,anti*-isomer **4** remains notoriously challenging to synthesize with acceptable diastereoselectivities using these reactions, especially for β-branched chiral aldehydes **5**.[3]

As depicted in Figure 2, *anti,anti*-stereotriads **8** can be prepared, in principle, directly from an enantioenriched aldehyde **5** by using a chiral crotylmetal reagent such as **6**. These reactions are mismatched double asymmetric reactions[6] owing to the intrinsic diastereofacial bias of aldehyde **5**. (The intrinsic diastereofacial bias of the aldehyde substrate is defined by the ratio of products obtained in its reaction with an appropriate achiral reagent.)[5a,7,8] Although **TS-2** incorporates the proper sense of asymmetric induction by the di(isopinocampheyl)boryl unit of reagent **6** with addition of the crotyl reagent to the *si* face of aldehyde **5**,[9] the conformation of the aldehyde α-stereocenter in **TS-2** is opposite to that typically invoked in the Felkin-Anh model for diastereoselective carbonyl addition.[8] An unfavorable gauche-pentane interaction between the R group of aldehyde **5** and the methyl group of reagent **6** occurs in this transition state.[5a,7] When the R substituent is more sterically demanding than a methyl group, **TS-2** is destabilized relative to **TS-1**. In contrast, the competing transition state **TS-1**, in which addition of crotylborane **6** occurs to the *re* face of aldehyde **5**, operates under favorable Felkin-Anh control[8] and minimal gauche-pentane interactions.[5a,7] However, **TS-1** is disfavored with respect to the enantiofacial selectivity preferences of the di(isopinocampheyl)boryl group of crotylborane **6**.[9] Consequently, a mixture of homoallylic alcohols **7** and **8** are usually generated from these two competing transition states in mismatched crotylboration reactions of chiral aldehydes **5**, with the ratio of the two products depending on the interplay between the inherent diastereofacial bias of the aldehyde and the enantioselectivity of the chiral reagent.[5a,7] In some cases, the diastereofacial selectivity bias of the chiral aldehyde can completely override the asymmetric induction of the reagent such that the crotylation proceeds under substrate control to give the undesired stereotriad **7**.

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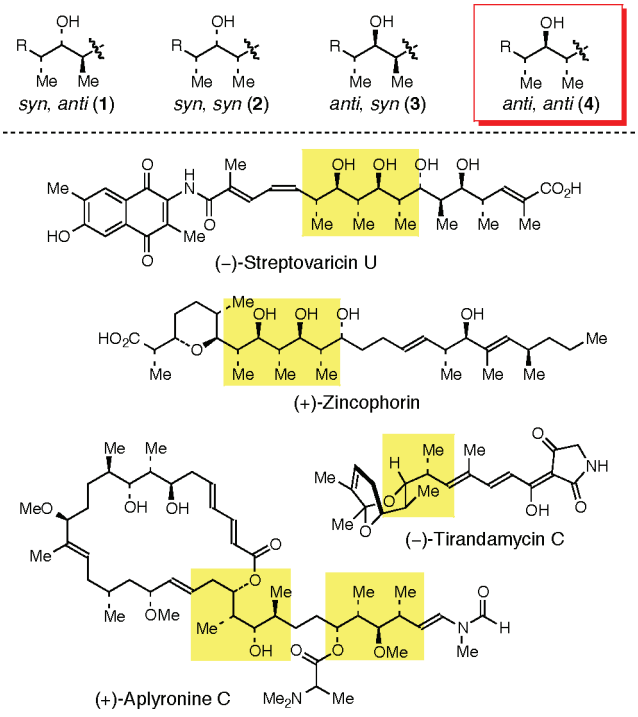

Figure 1. Structure of stereotriads and representative *anti,anti*-stereotriad containing polyketide natural products.

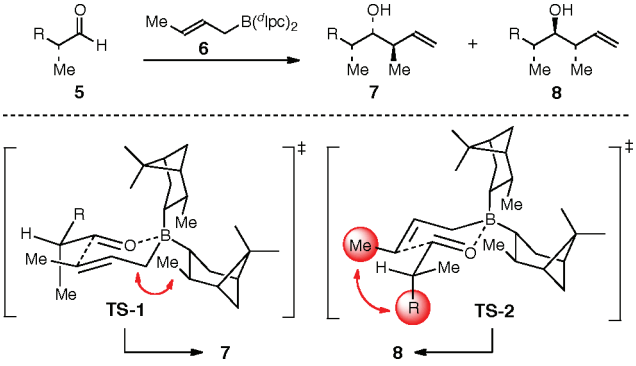

Figure 2. Transition states analysis of mismatched double asymmetric crotylboration reactions.

For example, in work on the total synthesis of (−)-calyculin C,[10a] Armstrong attempted the synthesis of intermediate **10** with *anti,anti* stereochemistry (Figure 3). However, in this instance, the intrinsic diastereofacial selectivity of the chiral aldehyde **9** completely overrode the enantioselectivity of the chiral crotylborane reagent *ent*-**6**, such that the only observed product (**11**) derived from substrate control via transition state *ent*-**TS-1**.

A second example derives from work published from our laboratory on the synthesis of the ansa chain of rifamycin S.[10b] In this case, the tartrate ester modified (*E*)-crotylboronate reagent **13** was incapable of overriding the intrinsic diastereofacial preference of the chiral aldehyde **12**, such that the undesired 3,4-*anti*-4,5-*syn* diastereomer **15** predominated by a 73:27 preference (Figure 4).

A third example, taken from the asymmetric aldol literature, demonstrates that some chiral reagents, when faced with an exceedingly large intrinsic face selectivity on the part of the chiral aldehyde substrate, will follow a reaction pathway not

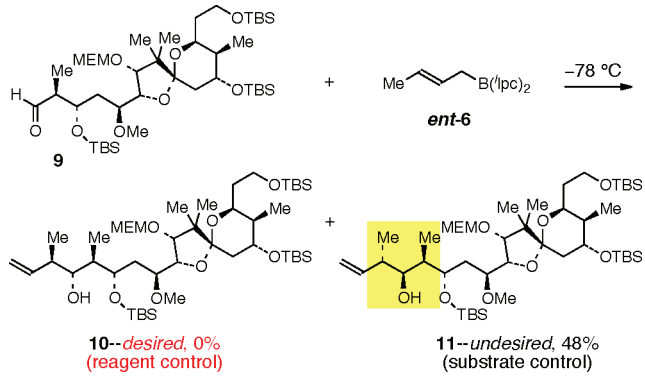

Figure 3. Attempted mismatched double asymmetric crotylboration of aldehyde **9** with crotylborane *ent*-**6** in the synthesis of (−)-calyculin C.

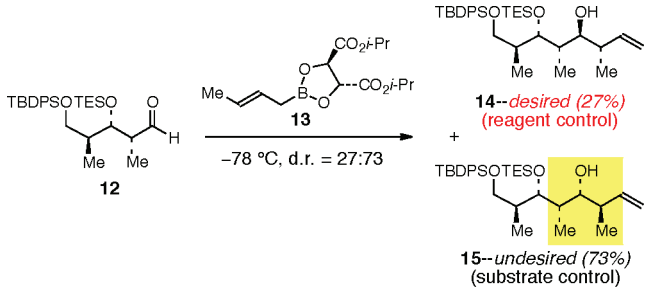

Figure 4. Attempted mismatched double asymmetric crotylboration of aldehyde **12** with crotylboronate reagent **13** in the synthesis of the *ansa* chain of rifamycin S.

normally associated with the chiral reagent. In the specific example illustrated below,[10c] Evans found that the enantioselective aldol reaction of the stereochemically demanding chiral aldehyde **18** proceeded preferentially by way of a boat-like transition state **TS-B** to provide **20** as the exclusive product. The anticipated aldol adduct **19** derived from the typical chairlike transition state **TS-A** was not observed (Figure 5).

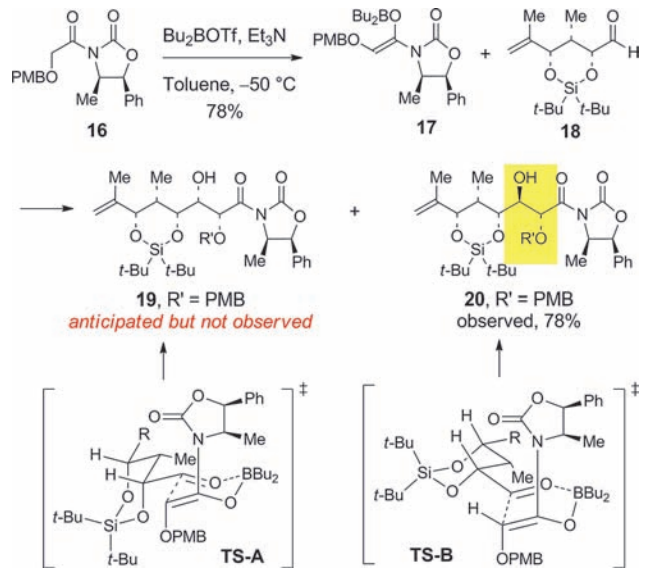

Figure 5. Attempted asymmetric aldol reaction of aldehyde **18** with reagent **16** in the synthesis of cytovaricin.

Thus, in this case, the exceptional enantioselectivity of the chiral oxazolidinone auxiliary was incapable of overriding the

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inherent diastereofacial selectivity of aldehyde **18**, and the reaction proceeded under substrate control via a transition state not normally associated with chiral oxazolidinone aldol reactions.

Because of the historical failure to achieve synthetically useful selectivity in the synthesis of *anti,anti*-stereotriads via aldol or crotylmetal reactions, especially for *β*-branched chiral aldehydes **5** that have a significant intrinsic diastereofacial bias (e.g., ≥ 5:1)[3], indirect methods involving multistep sequences are often employed to synthesize *anti,anti*-stereotriads **4**.[3a,b] To achieve a much more general and direct solution to this problem, a crotylating reagent with much higher enantioselectivity than **6** is required. We report herein our studies that address this problem, specifically focusing on the synthesis of *anti,anti*-stereotriad **8** via mismatched double asymmetric crotylboration reaction of enantioenriched aldehydes **5** with significant (≥8:1) inherent diastereofacial selectivities.

RESULTS AND DISCUSSION

We recently described the synthesis of a new chiral, nonracemic crotylborane reagent, (*S*)-(*E*)-**22** (Figure 6).[11] Reagent (*S*)-

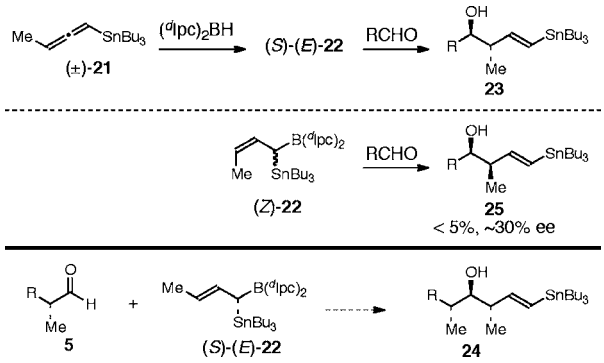
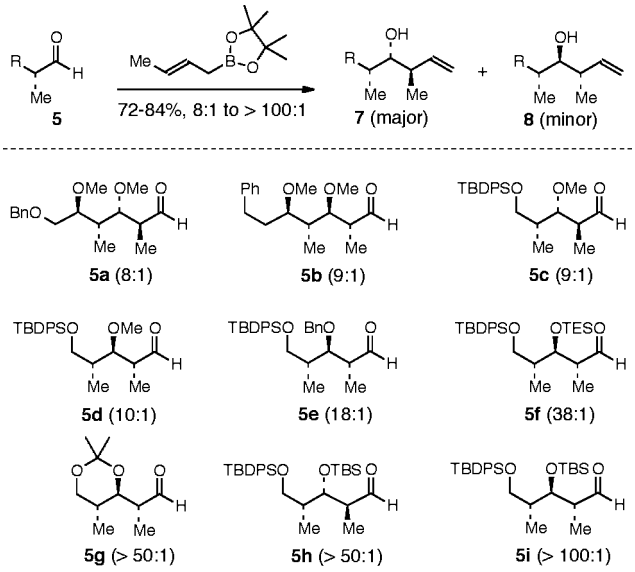


Figure 6. Proposed mismatched double asymmetric *γ*-stannylcrotylboration reactions.

(*E*)-**22** is easily generated from the enantioconvergent and enantioselective hydroboration of racemic allenylstannane (±)-**21**[11] with the chiral nonracemic hydroborating reagent, di(isopinocampheyl)borane [(^{d}Ipc)$_2$BH]. In this reaction, both enantiomers of (±)-**21** are converted into the same enantiomer of the reagent, (*S*)-(*E*)-**22**. Crotylboration reactions of aldehydes with (*S*)-(*E*)-**22** provided (*E*)-*δ*-stannyl-*anti*-homoallylic alcohols **23** in good yields and excellent enantioselectivities. In these experiments, small amounts of the 3,4-*syn*-isomer **25** were also produced (almost racemic), deriving from small amounts of the (*Z*)-crotylborane reagent (*Z*)-**22** generated as the minor product of the enantioconvergent allene hydroboration reaction. Owing to the high enantioselectivity of (*S*)-(*E*)-**22**, we were intrigued by the potential for use of this reagent in mismatched double asymmetric crotylboration reactions with enantioenriched aldehydes **5**, thereby providing access to the *anti,anti*-stereotriads **24** (Figure 6).[12]

Toward this end, a series of enantioenriched aldehydes **5a**−**i** with different stereochemical patterns and protecting groups were synthesized. We intentionally sought chiral aldehydes with high intrinsic diastereofacial selectivity preference. The intrinsic diastereofacial bias of these aldehydes was assessed by performing crotylboration reactions with achiral pinacol (*E*)-crotylboronate (Scheme 1). These results indicate that the inherent diastereofacial selectivities of aldehydes **5** vary from

Scheme 1. Crotylboration of Aldehydes 5 with Achiral Pinacol (*E*)-Crotylboronate[a]



[a]The ratios of **7**:**8** (in parentheses) define the intrinsic diastereofacial selectivity bias of aldehydes **5**.

8:1 to >100:1, in all cases favoring formation of the 3,4-*anti*-4,5-*syn*-stereotriads **7**. It is worth mentioning that the choice of protecting group for the aldehyde *β*-hydroxyl group has significant impact on the inherent diastereofacial selectivities of aldehydes **5** (e.g., **5c** vs **5h**; **5d** and **5e** vs **5f** and **5i**).

Mismatched double asymmetric crotylboration reactions of these chrial aldehydes with (*S*)-(*E*)-**22** [deriving from (^{d}Ipc$_2$BH)] or the enantiomeric reagent (*R*)-(*E*)-**22** [deriving from (^{l}Ipc$_2$BH)] were then carried out. Addition of aldehyde **5a** to the crotylborane (*R*)-(*E*)-**22** (generated as described previously[11]) at −78 °C followed by warming the reaction mixture to ambient temperature provided *anti-anti-stereotriad* ***24a*** *in 72% yield and with >15:1 diastereoselectivity* (entry 1, Table 1). Application of this procedure to chiral aldehydes **5b**−**e** (entries 2−5, Table 1), which have intrinsic diatereofacial selectivity preferences ranging from 8:1 to 18:1, similarly provided *anti,anti*-stereotriads **24b-e** in 72−84% yield with >15:1 diastereoselectivity. Other diastereomeric products were not observed in these reactions. Stereochemical assignments for these compounds are summarized in the Supporting Information.

The mismatched crotylboration of the much more highly stereochemically demanding aldehyde **5f** (with a 38:1 inherent diastereofacial selectivity preference) provided a 5:1:1 mixture of diastereomers, favoring the *anti,anti*-stereotriad **24f** as the major product (Scheme 2a). The mismatched crotylboration of another highly stereochemically demanding aldehyde **5g** (with a >50:1 inherent facial selectivity preference) provided an 8:1 mixture of diastereomers, favoring again the *anti,anti*-stereotriad **24g** (Scheme 2b). In the case of aldehyde **5h** (with again a >50:1 inherent facial selectivity), a 16:1 mixture of diastereomers was obtained, favoring the *anti,anti*-stereotriad **24h** (Scheme 2c). Finally, when an extremely stereochemically demanding aldehyde **5i** (with a >100:1 inherent facial selectivity preference) was subjected to the mismatched double asymmetric crotylboration, a 3:2:1 mixture of diastereomers was obtained, with the *anti,anti*-stereotriad **24i** as the major

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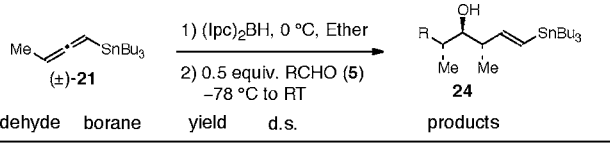
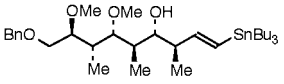
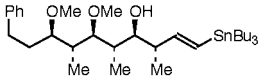
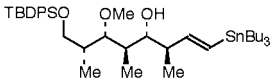
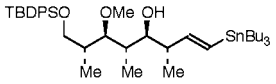
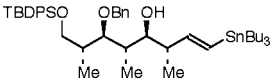
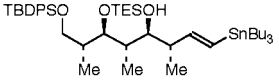
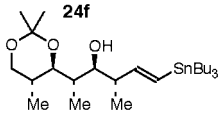
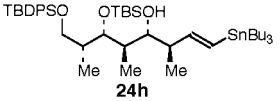
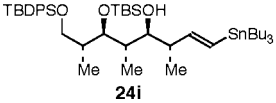
Table 1. Mismatched Double Asymmetric Crotylboration of Aldehydes 5

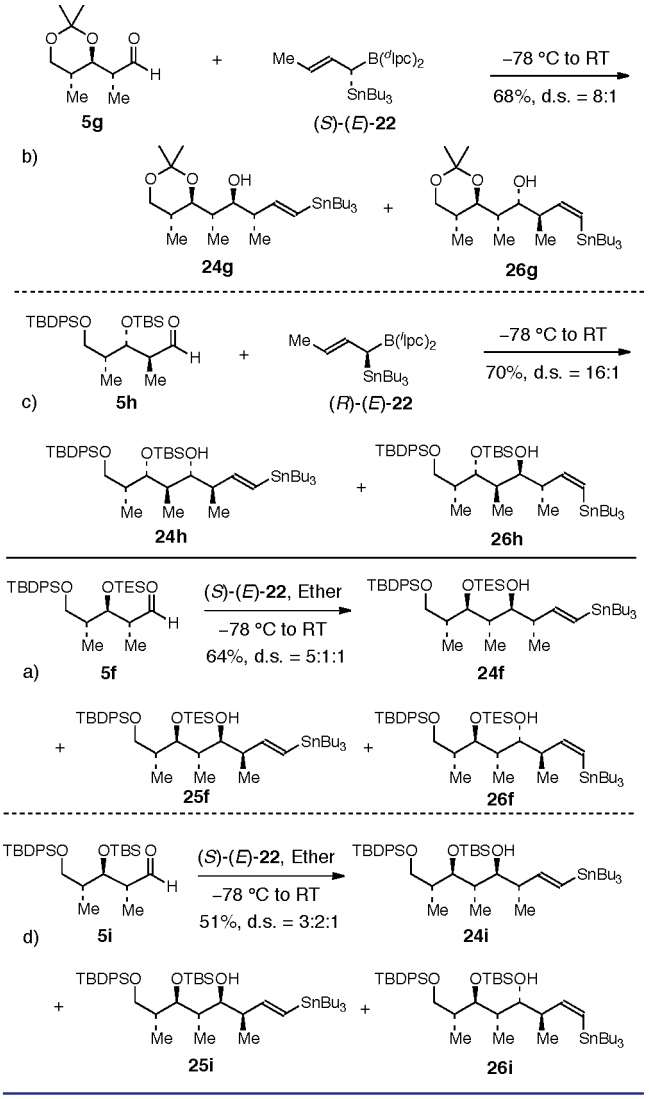


aldehyde	borane	yield	d.s.	products
5a	(^{l}Ipc)$_2$BH	72%	> 15:1	 24a
5b	(^{d}Ipc)$_2$BH	72%	> 15:1	 24b
5c	(^{l}Ipc)$_2$BH	84%	> 15:1	 24c
5d	(^{d}Ipc)$_2$BH	77%	> 15:1	 24d
5e	(^{d}Ipc)$_2$BH	78%	> 15:1	 24e
5f	(^{d}Ipc)$_2$BH	64%	5:1:1	 24f
5g	(^{d}Ipc)$_2$BH	68%	8:1	 24g
5h	(^{l}Ipc)$_2$BH	70%	16:1	 24h
5i	(^{d}Ipc)$_2$BH	51%	3:2:1	 24i

component (Scheme 2d). The minor products **26f–i** in the above reactions were identified[13] as the (*Z*)-3,4-*anti*-4,5-*syn*-stereotriad isomers derived from **TS-4** (Figure 7a). In the cases of **5f** and **5i** (parts a and d of Scheme 2), the third products **25f** and **25i** were identified as the (*E*)-3,4-*syn*-4,5-*anti*-stereotriad isomers derived from reaction of the chiral aldehydes with reagent (*Z*)-**22** (Figure 6).[13]

Assuming that the crotylboration proceeds through a chairlike transition state,[5] the results obtained from the mismatched double asymmetric crotylboration reactions in Table 1 indicate that transition state **TS-3**, with the α-stannyl unit of reagent (*S*)-(*E*)-**22** in a pseudo-equatorial position, is highly favored (Figure 7a). The competing transition state **TS-4** with pseudo-axial placement of the α-stannyl unit, which leads to the (*Z*)-3,4-*anti*-4,5-*syn* diastereomer **26**, is highly disfavored (as **26** is observed only in several exceptional cases, Scheme 2). The origin of the remarkable diastereoselectivity of these mismatched double asymmetric crotylboration reactions is intriguing; it appears that the pseudo-equatorial placement of

Scheme 2. Mismatched Double Asymmetric Crotylboration of Aldehydes 5g–i



the α-stannyl unit in **TS-3** (shown in blue) contributes significantly to the observed diastereoselectivity (vide infra).

In our recent report on enantioselective synthesis of (*E*)-δ-stannyl-homoallylic alcohols **29** (Figure 7b), we demonstrated that allylboration of aldehydes with α-stannylallylborane reagent **28a**, generated by hydroboration of **27** with (^{d}Ipc)$_2$BH at −40 °C, gave homoallylic alcohols **29** with excellent enantioselectivities.[14] However, when the hydroboration was performed at 0 °C, a thermodynamic mixture of allylboranes **28a** and **28b** was generated from a reversible 1,3-boratropic shift.[15] The homoallylic alcohols **29** obtained under these conditions have much lower enantiomeric excess (~30% ee). As shown in Figure 7b, **28a** reacts with aldehydes, as expected, via **TS-5** to give alcohols **29**. Intriguingly, **28b** reacts with aldehydes via **TS-7** to give alcohols ***ent*-29**, which indicates that *pseudo-equatorial placement of the α-stannyl unit in* **TS-7** *overrides the enantiofacial selectivity of the* −B(^{d}Ipc)$_2$ *group*. The latter, if dominant, would have dictated the formation of (*Z*)-δ-stannyl-homoallylic alcohols **30** via **TS-6**. *However, the (Z)-vinylstannyl homoallylic alcohols* **30** *were not observed in these reactions.* Consequently, these data show that the stereodirecting influence of the α-stannylboryl stereocenter and that of the −B(^{d}Ipc)$_2$ group are *dissonantly paired* in **28b**, and that the α-

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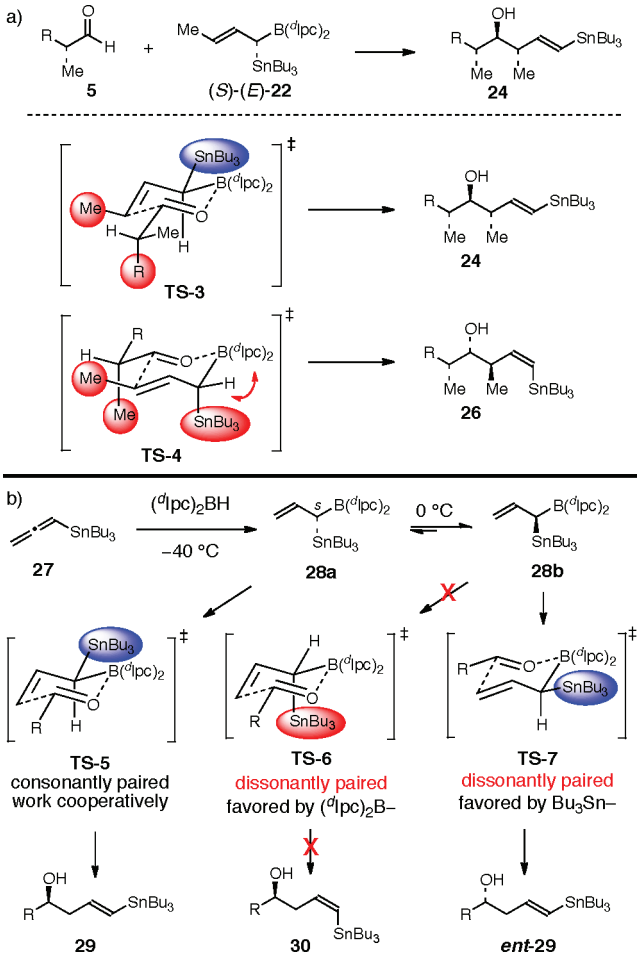

Figure 7. (a) Transition state analysis of mismatched double asymmetric stannylcrotylboration. (b) Transition state analysis of stannylallylboration reactions of **28**.

stannylboryl stereocenter is the more dominant of the two. Results of enantioselective reactions of Brown's crotylborane reagent **6** with achiral aldehydes (enantioselectivities are typically 88−92% ee)[5,9] indicate that the energy difference ($\Delta\Delta G^{\ddagger}$) between the two competing crotylboration transition states (e.g., **TS-1**, **TS-2** in Figure 1 with achiral aldehydes for reactions with **6**) is ∼1.2 kcal/mol at −78 °C. In transition structure **TS-7** (Figure 7b), where the stereodirecting influence of the α-stannylboryl stereocenter and that of the $(^{d}Ipc)_2B$ are dissonantly paired (i.e., mismatched), the $\Delta\Delta G^{\ddagger}$ contribution deriving from the α-stannylboryl stereocenter is estimated to be at least 2.0 kcal/mol at −78 °C (in order to generate a product distribution of ***ent*-29**:**30** >10:1). Consequently, if these two stereodirecting factors work synergistically, as is the case in **TS-5**, it is reasonable to expect that the enantioselectivity ($\Delta\Delta G^{\ddagger}$) associated with crotylborane reagent (*S*)-(*E*)-**22** (Figure 7a) would be ≥3.2 kcal/mol at −78 °C. *This corresponds to a significantly greater level of enantioselectivity than for all other known chiral crotylmetal reagents.*

As illustrated in Figure 7a, **TS-3** incorporates the proper sense of asymmetric induction deriving from the $(^{d}Ipc)_2B$− unit and more importantly, the pseudo-equatorial placement of the α-stannyl unit. *The additive stereodirecting effects of these two factors combine to override the intrinsic aldehyde diastereofacial bias, even for extremely stereochemically demanding substrates such as* ***5f−i***. In contrast, the competing crotylation transition state **TS-4** is strongly disfavored owing to the unfavorable mismatched facial selectivity of the borane reagent and the pseudo-axial placement of the Bu_3Sn− group (shown in red). Consequently, mismatched double asymmetric crotylboration reactions of (*S*)-(*E*)-**22** with enantioenriched aldehydes **5** proceed preferentially via transition state **TS-3** to provide the requisite *anti,anti*-stereotriads with excellent selectivities. Even in the reactions with the very stereochemically demanding aldehydes **5f−i**, the *anti,anti*-stereotriads were obtained with good selectivities. On the basis of the results of the mismatched crotylboration of aldehydes **5f−i**, the enantioselectivity ($\Delta\Delta G^{\ddagger}$) associated with reagent (*S*)-(*E*)-**22** can be calculated to be >3.0 kcal/mol (at 25 °C). The examples shown in Table 1 and Scheme 1 provide a powerful demonstration of the high enantiofacial selectivity of reagents (*S*)-(*E*)-**22** and its enantiomer (*R*)-(*E*)-**22**. Notably, the all-*anti*-stereopentads embedded in **24d−g**, which proved to be a significant challenge in syntheses of (+)-zincophorin[16] and (−)-streptovaricin U,[17] can be obtained in good yields and with excellent selectivities (>15:1 ds in the case of **24e**). Furthermore, the vinylstannane unit in the products is properly functionalized to permit fragment assembly via a variety of subsequent transformations.[12,18]

It is well documented[3] that for the enantioenriched aldehydes **5** with modest (e.g., <5:1) intrinsic diastereofacial bias (e.g., for aldehyde **5** without β-branches, and specifically for **5** with R = CH_2OTBS, the intrinsic diastereofacial bias is only ∼1.5:1), many crotylmetal reagents have demonstrated ability to overcome the modest intrinsic facial bias. Virtually all synthetic methods papers focusing on mismatched double asymmetric crotylation and aldol reactions published to date have focused on substrates with such very modest (e.g., <5:1 and most frequently <3:1) intrinsic diastereofacial selectivity preferences. Thus, in such cases the *anti,anti*-stereotriads can be prepared with acceptable diastereoselectivities via mismatched double asymmetric crotylation reactions using many different reagents, such as those cited in references 3−5.

However, when the enantioenriched aldehydes **5** have much higher (e.g., >5:1) intrinsic diastereofacial preferences, the relative (and dissonantly paired) contributions from the enantioselectivity of the enantioenriched crotylmetal reagents and the intrinsic diastereofacial bias of aldehydes **5** are crucial to the product distribution realized (e.g., the ratio of **7** vs **8**). In many cases, attempted mismatched double asymmetric crotylation of such stereochemically demanding aldehydes provide the undesired 3,4-*anti*-4,5-*syn*-stereotriads as the major isomer (e.g., see the examples in Figures 3 and 4 above). Therefore, in order to put the remarkable enantioselectivity of (*S*)-(*E*)-**22** (and its enantiomer) into proper perspective, we performed comparative mismatched double asymmetric crotylation reactions of enantioenriched aldehyde **5j**[12c] with a collection of highly regarded contemporaneous chiral, nonracemic crotylmetal reagents. The results of this study are summarized in Scheme 3.

The intrinsic diastereofacial selectivity of aldehyde **5j** (an intermediate in our recent synthesis of (−)-tirandamycin C)[12c] was determined by its crotylboration reaction with achiral pinacol (*E*)-crotylboronate **31**. This experiment provided an 11:89 mixture of homoallylic alcohols **8j** and **7j**, indicating a ∼8:1 intrinsic diastereofacial bias favoring formation of the 3,4-*anti*-4,5-*syn*-stereotriad **7j**. The reaction of aldehyde **5j** with the tartrate based crotylboronate reagent *ent*-**13** developed in our laboratory[19] gave a 27:73 mixture of alcohols **8j** and **7j** favoring,

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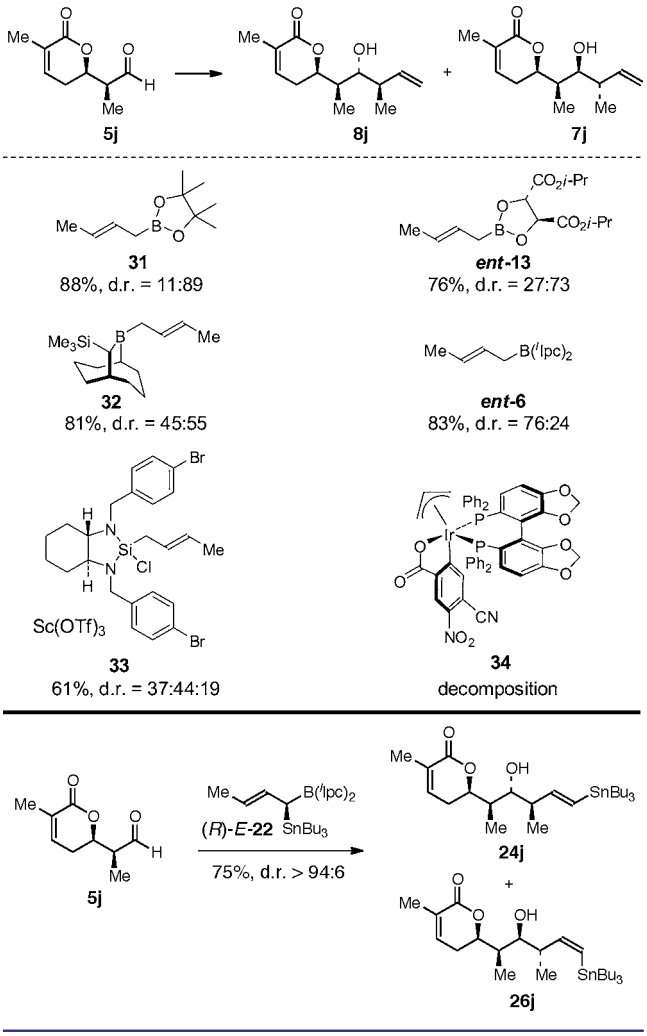
Scheme 3. Comparative Mismatched Double Asymmetric Crotylboration Studies of Aldehyde 5j with Crotylmetal Reagents *ent*-6, *ent*-13, and 31−34



again, the undesired 3,4-*anti*-4,5-*syn*-stereotriad **7j**. The reaction of **5j** with crotylborane reagent **32**, developed by Soderquist and co-workers,[20] provided a 45:55 mixture of **8j** and **7j**. Crotylboration of **5j** using Brown's reagent *ent*-**6**[9b] gave a 76:24 mixture of alcohols **8j** and **7j**, with the *anti*,*anti*-stereotriad **8j** as the major diastereomer in this instance. Use of other highly enantioselective crotylmetal reagents were also examined. Crotylation of **5j** using the commercially available *EZ*-CrotylMix **33** developed in Leighton's laboratory[3h] gave a 37:44:19 mixture of three products, among which **7j** (44%) and **8j** (37%) predominated. The 3,4-*syn*-4,5-*anti*-isomer (19%) was also identified as the third (minor) product from this reaction (see SI). Finally, attempted catalytic asymmetric crotylation of aldehyde **5j** using the Ir-based reagent **34** led only to the decomposition of the chiral aldehyde using the reaction conditions reported by Krische and co-workers.[3i]

These results indicate that the enantioselectivity of these chiral reagents is insufficient to overcome the intrinsic diastereofacial bias of aldehyde **5j**. In contrast, the mismatched double asymmetric crotylboration of aldehyde **5j** with crotylborane (*R*)-(*E*)-**22** provided *a* > 94:6 mixture of stereotriads **24j** and **26j** (Scheme 3).[12c] The remarkable selectivity realized in this transformation, particularly in view of the inability of other reagents to provide access to **8j** with synthetically useful stereochemical control, augurs well for further applications of (*S*)-(*E*)-**22** and its enantiomer (*R*)-(*E*)-**22** in mismatched double stereoselective transformations.

Comparative mismatched double asymmetric reactions of aldehyde **5i** (with a significant >100:1 intrinsic diastereofacial selectivity preference) with reagents *ent*-**33** and *ent*-**34** were also carried out. These studies are summarized in the Supporting Information. *We were unable to detect even trace quantities of the targeted anti,anti-stereotriad* ***8i.*** This is in contrast to our results, summarized in Table 1, for the reaction of **5i** with (*S*)-(*E*)-**22** that provided a 3:2:1 mixture of diastereomers, with the *anti*,*anti*-stereotriad **24i** as the major one. Therefore, all available evidence indicates that our new reagent **22** is significantly more enantioselective than all other contemporaneous chiral (*E*)-crotylmetal reagents, and that **22** is correspondingly uniquely useful in demanding examples of mismatched double asymmetric *anti*-crotylboration reactions such as those summarized in Table 1 and Scheme 3.

Finally, to illustrate the synthetic utility of the mismatched double asymmetric crotylboration reactions of (*S*)-(*E*)-**22**, studies toward the synthesis of the all-*anti*-stereopentad fragment of (+)-zincophorin were carried out. It has been demonstrated that the highly diastereoselective synthesis the all-*anti*-stereopentad of (+)-zincophorin via crotylmetal or aldol chemistry is a significant challenge. Consequently, several creative (and generally multistep, indirect) approaches have been developed to access the requisite all-*anti*-stereopentad.[3c,d,16] We envisioned that this unit could be obtained via a mismatched double asymmetric crotylboration of aldehyde **40** with crotylborane (*S*)-(*E*)-**22**, although selection of the protecting group for the β-hydroxyl group might be crucial for achieving high diastereoselectivity as suggested by the results summarized in Table 1.

Indeed, crotylboration of aldehyde **5k** with achiral pinacol (*E*)-crotylboronate gave the substrate controlled 3,4-*anti*-4,5-*syn* stereoisomer **7k** with >50:1 selectivity (Scheme 4). On the other hand, the mismatched double asymmetric crotylboration of **5k** with crotylborane (*S*)-(*E*)-**22** followed by protodestannylation under acidic conditions ($TsOH{\cdot}H_2O$) provided a 1:18 mixture of **7k** and **8k**, with the desired isomer **8k** as the major isomer. This experiment again demonstrated the power of reagent (*S*)-(*E*)-**22** in mismatched double asymmetric stannylcrotylboration reactions with stereochemically challenging substrates.

In conclusion, we have developed a highly stereoselective solution to the long-standing problem associated with the synthesis of the *anti*,*anti*-stereotriad **4**, specifically involving the diastereoselective mismatched double asymmetric stannylcrotylboration of enantioenriched aldehydes with crotylborane reagents (*S*)-(*E*)-**22** or (*R*)-(*E*)-**22**. *Anti, anti*-stereotriads **24a-j** are obtained in good yields and with high diastereoselectivities from a broad range of aldehyde substrates using these reagents (Table 1). The synthetic utility of this method is illustrated in the highly diastereoselective synthesis of the all *anti*-stereopentad fragment of (+)-zincophorin (Scheme 4). The comparative results described in Scheme 3 and in the Supporting Information provide convincing evidence that *crotylborane reagents (S)-(E)-22 and (R)-(E)-22 demonstrate significantly greater enantiofacial selectivity than for all other currently known chiral crotylmetal reagents.*

Additional applications and further extensions of this methodology to other problem in organic synthesis will be reported in due course.

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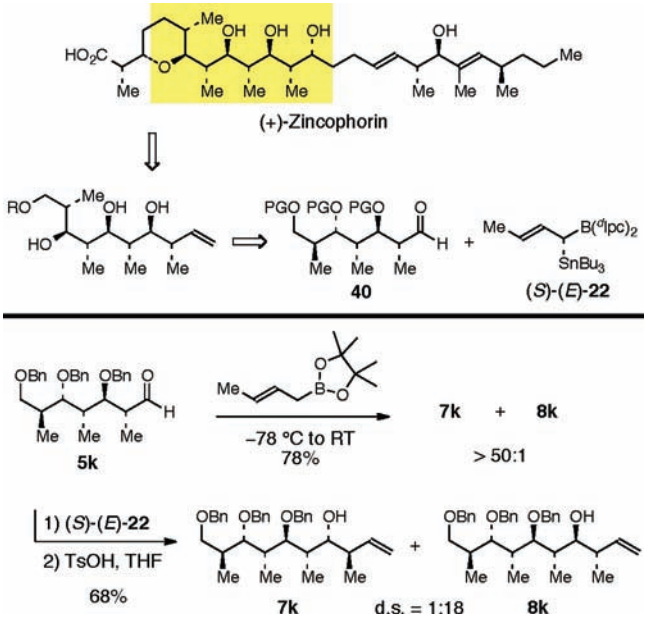
Scheme 4. Highly Diastereoselective Synthesis of the all-*anti*-Stereopentad Fragment of (+)-Zincophorin Using Mismatched Double Asymmetric Crotylboration of Aldehyde 5k with Crotylmetal Reagent (*S*)-(*E*)-22



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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