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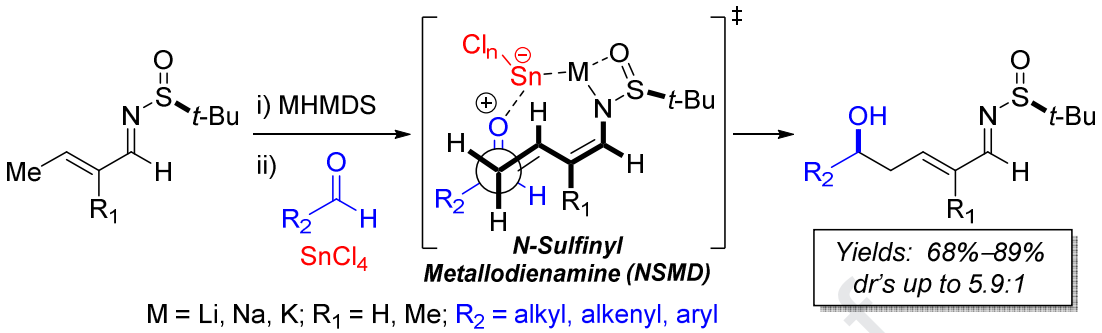
Graphical Abstract:



The Vinylogous Aldol Reaction of *N*-Sulfinyl Metallodienamines

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Abstract: The discovery and development of the vinylogous aldol reaction of *N*-sulfinyl metallodienamines with aldehydes and ketones is described. The diastereoselectivity of the reaction, first reported in 2017 as a key step in the total asymmetric synthesis of (–)-albocycline, has been corrected by Mosher ester analysis. The reaction has been optimized and the scope investigated, with yields ranging from 68–89% and diastereomeric ratios as high as 5.9:1. Extensive investigation into the mechanisms affecting stereoselectivity revealed that two stereochemical erosion pathways are operative when using LiHMDS and $SnCl_4$. A transition state supported by DFT calculations has been advanced to rationalize the stereochemical course of the reaction.

Key words: vinylogous aldol, *N*-sulfinyl metallodienamine, albocycline, methodology

1. Introduction

Structurally complex natural products are unrivaled in their ability to inspire novel synthetic strategies and/or tactics.[1-2] In 2017, we published a concise total synthesis of the macrolactone antibiotic albocycline (**1**) wherein we targeted the C6–C7 bond for disconnection in precursor **2** (Figure 1).[3] We envisioned this goal could be realized by the regio- and stereoselective addition of *N*-sulfinyl metallodienamine (NSMD) **3** derived from sulfinimine **5** to aldehyde **4**. While Ellman had demonstrated that *N*-sulfinyl metalloenamines stereoselectively add to aldehydes in analogy to the aldol reaction,[4-5] the vinylogous variant of this reaction had not been explored prior to our report.[3] In 2013, we first demonstrated the synthetic utility of 2,3-indole fused NSMDs in annulation reactions for the concise syntheses of *Aspidosperma* indole alkaloids.[6-7] Herein, we describe the optimization and scope of the vinylogous aldol reaction (VAR) of NSMDs. In addition, we correct and update the diastereoselectivity of the reaction as was previously reported and posit a stereochemical model to rationalize observed diastereoselectivity supported by DFT calculations.[3]

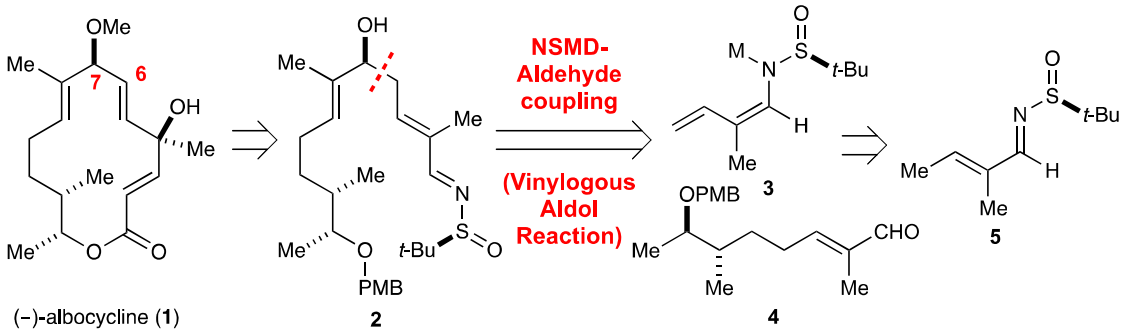


Figure 1. Inspiration for and discovery of the VAR of *N*-sulfinyl metallodienamines.

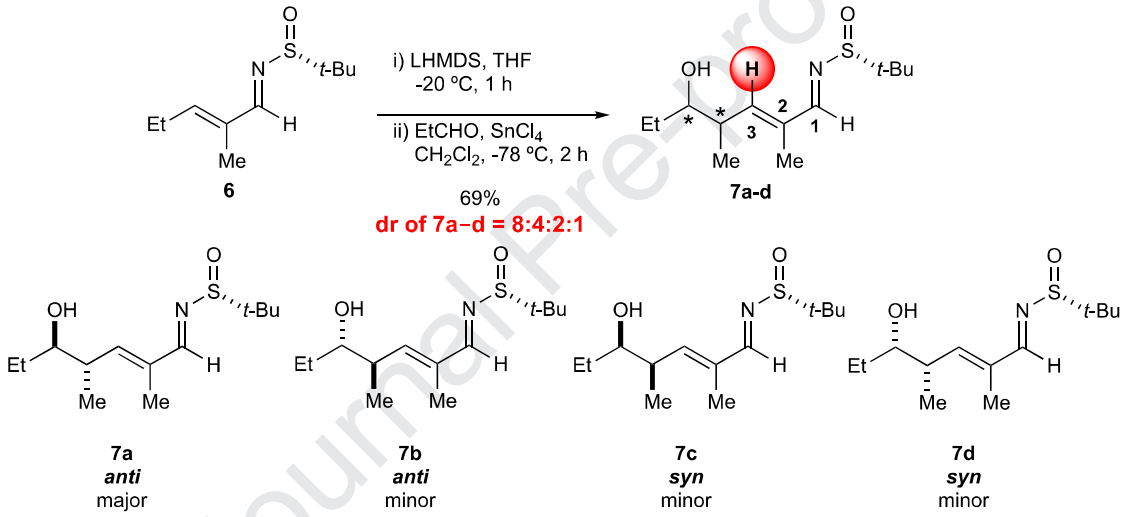
The vinylogous Mukaiyama aldol reaction (VMAR) has found widespread use in the chemical synthesis of polyketide natural products owing to its high regioselectivity (i.e., reaction at the γ- versus the α-position), stereoselectivity, and *a priori* inclusion of at least two additional carbons in the product vis-à-vis the standard aldol reaction, thus enhancing overall efficiency.[8-9] In 2004, Kobayashi reported that the VMAR of vinylketene silyl *N*,*O*-acetals bearing the Evans oxazolidinone auxiliary with aldehydes proceeds with high levels of remote 1,7- and 1,6,7-asymmetric induction under the agency of $TiCl_4$.[10] The Kalesse[11] and particularly Hosokawa[12-15] groups have made improvements to the Kobayashi aldol reaction that have been extensively employed in many total syntheses.[16]

Upon completion of our synthesis of albocycline enabled by new methodology, we turned our attention toward developing the scope of the VAR of *N*-sulfinyl metallodienamines with aldehydes.

2. Results and Discussion

Much like the reported reaction of NSMD **3** with aldehyde **4**, we found the former smoothly reacted with aliphatic, aromatic, and other α,β-unsaturated aldehydes in high yields (70–85%) and exclusive γ-regioselectivity to furnish what appeared to be a single diastereomer (dr > 95:5) of the vinylogous aldol product *as determined by ^{1}H and ^{13}C NMR analysis.*[17] However, when we employed the NSMD derived from *N*-sulfinyl imine **6** bearing a prochiral γ-carbon in the VAR with propionaldehyde, we were surprised to isolate what appeared to be a ~4:1 ratio of inseparable diastereomers. In principle, the VAR of prochiral NSMDs can produce up to four diastereomers (i.e., two *syn*- and two

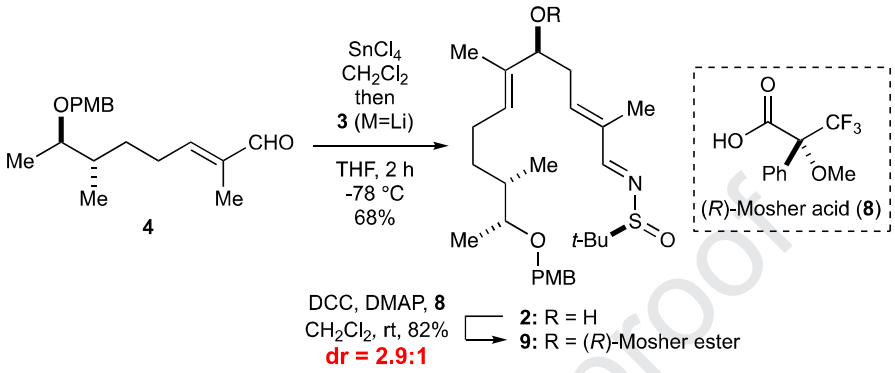
anti-stereoisomers). Protection of the newly formed carbinol as its TBS ether allowed for separation of the major isomer derived from **7a** (Scheme 1). Rigorous characterization of the relative and absolute stereochemistry of aldols **7a**–**d** was accomplished by correlation with known compounds (Scheme S1).[18-19] Moreover, the diastereomeric ratio (dr) of products **7a**–**d** as determined by integrating H-3 (Scheme 1, red sphere) in **7a–d** by ^{1}H NMR spectroscopy wherein the dr was found to be 8:4:2:1 (see Scheme S2 for details). In other words, the dr of major *anti*-**7a** aldol versus the sum of minor aldols **7b**–**d** was ~1:1.



Scheme 1. VAR of prochiral NSMD derived from **6** with propionaldehyde.

The results of the VAR prompted us to revisit the key step in our albocycline synthesis wherein NSMD **3** derived from *N*-sulfinyl imine **5** was reacted with aldehyde **4** complexed with $SnCl_4$ to furnish aldol **2** (Scheme 2). To confirm the dr of this reaction, we employed two methods. First, we prepared Mosher ester **9** in 82% yield by treating **2** with excess (*R*)-Mosher acid (**8**) in the presence of DCC and DMAP to ensure complete consumption of starting material. ^{1}H NMR analysis of **9** revealed a mixture of diastereomers in a 2.9:1 ratio (Figure S1). Second, we employed HPLC analysis, which

gave the same ratio, thus ultimately confirming the reported VAR did not proceed in >95:5 dr but rather a ~3:1 ratio (Figure S2).[3]

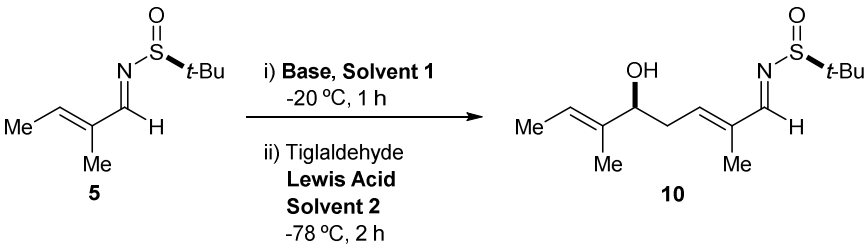


Scheme 2. Revisiting the diastereoselectivity of the VAR in the albocycline synthesis.

The absolute stereochemistry of the newly formed (7*S*)-chiral center in intermediate **2** was originally assigned by correlation with albocycline, whose structure had been unambiguously established by single crystal X-ray analysis.[20-21] Accordingly, Mosher ester analysis of the major diastereomer in **9** was fully consistent with an (*S*) configuration at the C7 stereocenter (Figure S1).[22] In retrospect, the minor (7*R*)-diastereomer unknowingly carried forward in the albocycline synthesis was therefore removed by iterative chromatography *en route* to the target, which required eight additional operations.[3]

Having corrected the diastereoselectivity of the VAR, we sought to optimize this reaction with the goal of increasing the modest dr. To that end, we screened a variety of conditions including the base (e.g., NaHMDS, KHMDS), additive (e.g., HMPA, LiCl), solvent (e.g., toluene, Et_2O, THF), and Lewis acid (e.g., BF_3•OEt_2, $TiCl_4$) to compare with the original procedure (entry 1) as determined by HPLC, and the results are shown

in Table 1. The use of HMPA and LiCl (entries 2–3) slightly decreased the yield; however, the former eroded dr. The requirement of a Lewis acid was demonstrated by a control experiment (entry 4) where no Lewis acid was used; accordingly, no reaction took place at -78 °C after 2 h. While the reaction proceeded in the presence of BF_3•OEt_2 (entry 5), no diastereoselectivity was observed. Replacing LiHMDS with NaHMDS (entry 6) led to an improvement in yield and dr, the latter of which went from 2.7:1 to 4.7:1. KHMDS (entry 7) proved to be the optimal base by providing the highest yield (89%) of VAR product while maintaining the same dr as NaHMDS (4.7:1). Entries 8–11 probed the role of solvent and Lewis acid when using KHMDS as the base, which were all inferior to the best conditions (entry 7).



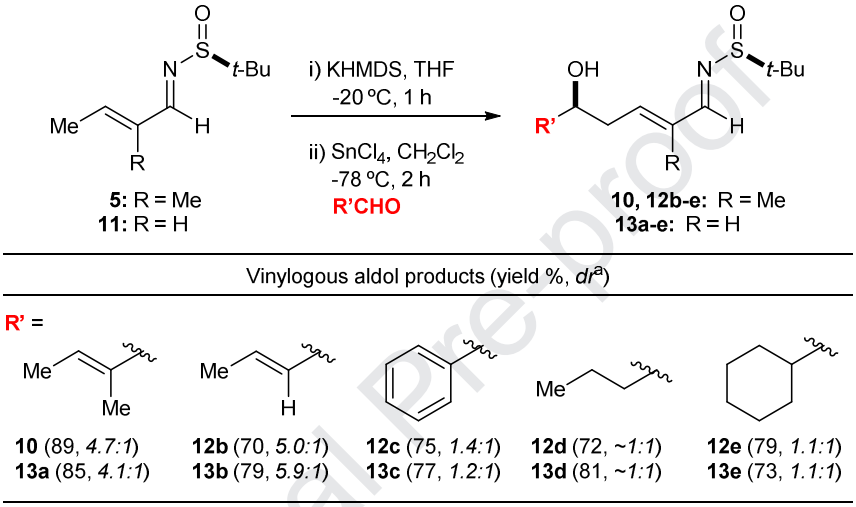
Entry	Base	Additive	Solvent 1	Solvent 2	Lewis acid	Yield (%)	dr[a]
1	LiHMDS	–	THF	CH_2Cl_2	$SnCl_4$	81	2.7:1[b]
2		HMPA	THF	CH_2Cl_2	$SnCl_4$	75	1.9:1
3		LiCl	THF	CH_2Cl_2	$SnCl_4$	77	2.6:1
4		–	THF	CH_2Cl_2	–	–	–
5		–	THF	CH_2Cl_2	BF_3•OEt_2	87	1:1
6	NaHMDS	–	THF	CH_2Cl_2	$SnCl_4$	85	4.7:1
7	KHMDS	–	THF	CH_2Cl_2	$SnCl_4$	89	4.7:1
8		–	THF	CH_2Cl_2	$TiCl_4$	43	4.0:1
9		–	THF	THF	$SnCl_4$	79	3.3:1
10		–	Toluene	CH_2Cl_2	$SnCl_4$	64	4.7:1
11		–	Et_2O	CH_2Cl_2	$SnCl_4$	63	4.1:1

[a] Diastereomeric ratio (dr) was determined by HPLC. [b] Absolute configuration of the new stereocenter was confirmed by Mosher analysis (see SI for details).

Table 1. Optimization of VAR of NSMD derived from **5** and tiglaldehyde.

With optimal reaction conditions for the VAR of NSMDs with aldehydes in hand, we turned our attention to determining the scope of this transformation. To this end, we investigated two NSMDs: one derived from tiglaldehyde **5**, which was used in the total synthesis of albocycline, and the other derived from crotonaldehyde **11**. Five aldehydes were selected including α,β-unsaturated, aromatic, aliphatic, and alicyclic. The results are shown in Table 2. Diastereomeric ratios and assignment of absolute stereochemistry were accomplished by Mosher ester analysis (Tables S1–2). Overall, yields for all VARs were very good (70–89%). Both NSMDs derived from **5** and **11** retained good diastereoselectivity when reacted with α,β-unsaturated aldehydes tiglaldehyde (**10**, **13a**) and crotonaldehyde (**12b**, **13b**), with aldol **13b** displaying the highest selectivity (dr =

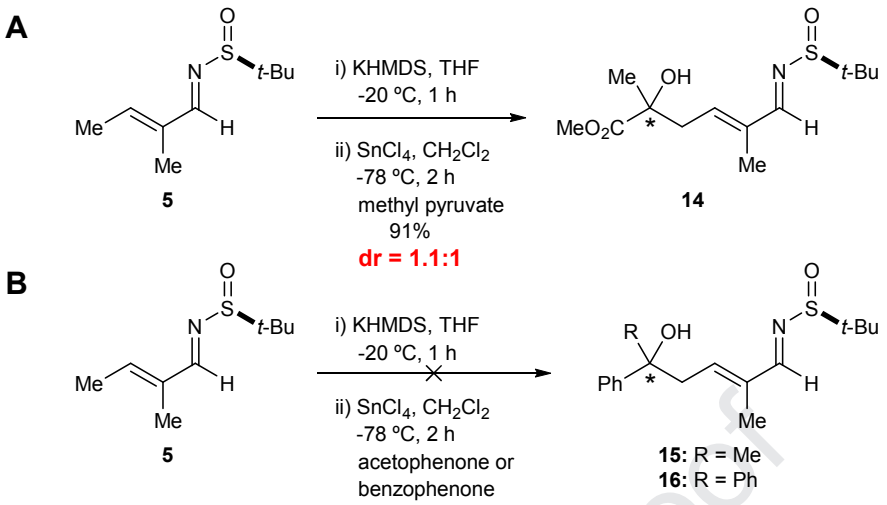
5.9:1). Erosion of diastereoselectivity was observed when benzaldehyde was employed (**12c**, **13c**) wherein the dr dropped to 1.4:1 for the NSMD derived from **5** and 1.2:1 for the NSMD derived from **11**. The VARs with aliphatic (**12d**, **13d**) and alicyclic (**12e**, **13e**) aldehydes showed little to no diastereoselectivity.



a Diastereomeric ratio (dr) was determined by Mosher analysis (see SI for details).

Table 2. Scope of VAR with NSMD derived from tiglaldehyde **5** or crotonaldehyde **11** and α,β-unsaturated, aromatic, aliphatic and alicyclic aldehydes.

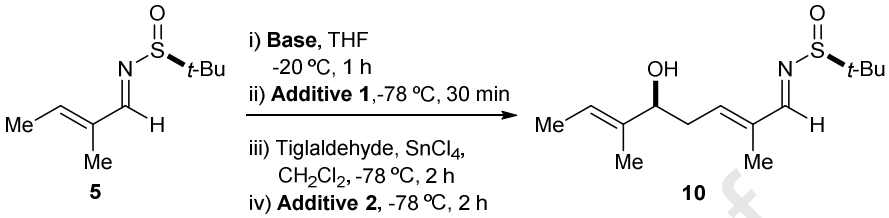
To probe nucleophilicity and expand the scope of the VAR, we reacted the NSMD derived from **5** with ketones. Specifically, we chose methyl pyruvate (Scheme 3A) in addition to acetophenone and benzophenone (Scheme 3B). While the reaction with the methyl pyruvate proceeded in high yield (91%), it was not particularly diastereoselective (dr = 1.1:1). Both aromatic ketones (Scheme 3B) failed to react in the VAR.



Scheme 3. Reaction of NSMD derived from **5** with (A) methyl pyruvate, (B) acetophenone, and benzophenone.

To better understand the difference in diastereoselectivity between Li- and K-derived *N*-sulfinyl metallodienamines in the vinylogous aldol reaction, we carried out additional experiments to identify the source of stereochemical erosion (Table 3). Entries 1–3 were performed under optimal reaction conditions (i.e., KHMDS); however, instead of quenching the reaction, an additional equivalent of HMDS base was added to the reaction mixture, followed by stirring at -78 °C for 2 h prior to quenching. Results from the experiment with LiHMDS (entry 1) revealed the dr eroded to 2.7:1, which was consistent with the original NSMD-mediated VAR conditions using LiHMDS (entry 1, Table 1). The use of NaHMDS (entry 2) and KHMDS (entry 3) had no effect on the dr, demonstrating the role of Li in the stereochemical erosion pathway. A plausible explanation for the erosion in dr is that Li promotes a retro-aldol reaction under thermodynamic control. To test this hypothesis, we carried out a crossover experiment with benzaldehyde (entry 4) and employed d_4-methanol (entry 5). In both cases, no evidence of reversibility was detected. To rule out the role of Li^+ in promoting a retro-

aldol pathway, 12-crown-4 was added to the reaction mixture following metalation with LiHMDS to sequester the cation. In the event, a dr of 2.7:1 was observed (entry 6).



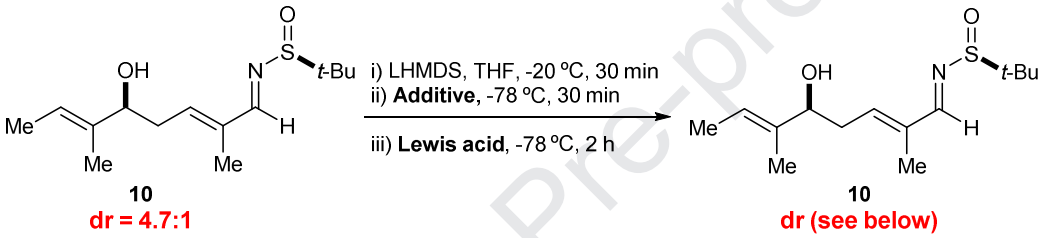
Entry	Base	Additive 1	Additive 2	dr[a]
1	KHMDS	–	LiHMDS	2.7:1
2	KHMDS	–	NaHMDS	4.7:1
3	KHMDS	–	KHMDS	4.7:1
4	LiHMDS	–	PhCHO, $SnCl_4$	2.7:1[b]
5	LiHMDS	–	CD_3OD	2.7:1[c]
6	LiHMDS	12-crown-4	–	2.7:1

[a] Diastereomeric ratio (dr) was determined by ^{13}C NMR analysis (see SI for details). [b] Crossover product with benzaldehyde **12c** was not detected. [c] γ-deutero *N*-sulfinyl imine **5** was not detected.

Table 3. Role of LiHMDS in the erosion of diastereoselectivity.

To probe the Li-mediated epimerization pathway further, we took vinylogous aldol product **10** prepared under optimized conditions (dr = 4.7:1) and subjected it to various reaction conditions (Table 4). Not surprisingly, stoichiometric deprotonation of **10** with LiHMDS to generate the lithium alkoxide and additional stirring at -78 °C for 2 h resulted in no change in dr (entry 1). Alternatively, the addition of $SnCl_4$ following the deprotonation event—conditions that recapitulate the previously observed LiHMDS-mediated epimerization pathway (entry 1, Table 3)—resulted in an erosion of dr to 2.7:1 (entry 2). Erosion was not observed when $BF_3{\bullet}OEt_2$ was added to the lithium alkoxide (entry 3), therefore strongly implicating the role of tin and lithium salts in combination.

Further evidence of this was obtained by sequestering Li^+ with 12-crown-4 prior to adding $SnCl_4$ (entry 4) wherein no erosion in dr was observed (Table 4, entry 4). Altogether, these results suggest the modest dr associated with LiHMDS-mediated vinylogous aldol reactions of NSMDs can arise either from C–C bond formation in the stereochemistry-determining VAR or an epimerization pathway, both of which are unique to Li vis-à-vis Na or K and reminiscent of the roles of alkali metal salts in determining the diastereoselectivity (i.e., *E/Z* ratios) in the venerable Wittig reaction.[23]



Entry	Additive	Lewis acid	dr[a]
1	–	–	4.7:1
2	–	$SnCl_4$	2.7:1
3	–	BF_3•OEt_2	4.7:1
4	12-crown-4	$SnCl_4$	4.7:1

[a] Diastereomeric ratio (dr) was determined by ^{13}C NMR analysis (see SI for details).

Table 4. Effects of Lewis acids and Li^+ on the dr of VAR product **10**.

To rationalize the stereochemical course of the NSMD-mediated VAR reaction, we employed DFT calculations at the B3LYP/6-31G(d) level of theory (see SI for details).[24] All NSMDs irrespective of metal counterion preferred the (*Z*)-NSMD geometry by approximately 1 kcal/mol (Figure 2A, see SI for details). Furthermore, we advance the *synclinal* transition state in Figure 2B as a stereochemical model for the observed diastereoselectivity wherein a tin species serves as a linchpin between the

aldehyde and the NSMD.[3,9-10] At this stage, it is unclear why α,β-unsaturated aldehydes emerged as the most stereoselective substrates in the vinylogous aldol reactions whereas aliphatic and aromatic aldehydes were not. Additional experiments are currently underway to explore this interesting transformation that despite its dr served admirably in the concise total asymmetric synthesis of macrolactone antibiotic (–)-albocycline.

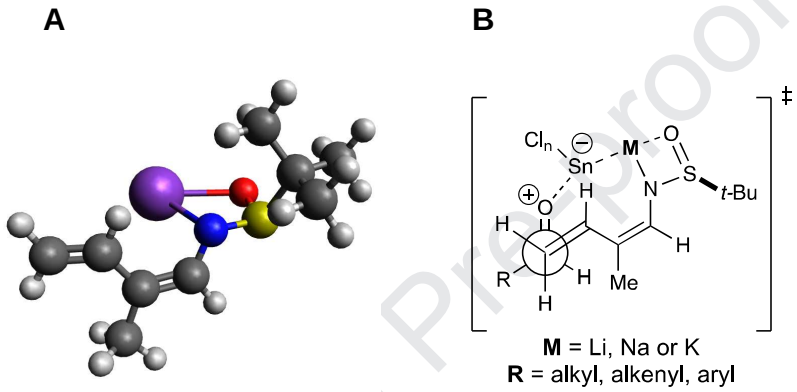


Figure 2. (A) Optimized structure of (*Z*)-NSMD **3** (M=K) from DFT calculations. (B) Stereochemical model for the $SnCl_4$-mediated VAR of NSMD **3** and aldehydes invoking a *synclinal* transition state.

3. Conclusion

Complex natural products offer unlimited sources of inspiration for the creation of novel synthetic methods. We have described the discovery and development of the vinylogous aldol reaction of *N*-sulfinyl metallodienamines (NSMDs) with aldehydes and ketones. Our first disclosure of this reaction in the total asymmetric synthesis of (–)-albocycline reported it proceeded with high diastereoselectivity (dr = >95:5). However, in the process of expanding reaction scope we found the dr was in fact ~3:1. Reaction optimization found that KHMDS was superior to LiHMDS. The reaction proceeded in synthetically useful yields (68–89%) with α,β-unsaturated aldehydes providing the

highest dr (5.9:1). While electrophilic methyl ketones (e.g., methyl pyruvate) reacted in high yields with KHMDS, no diastereoselectivity was observed. Owing to the modest natural of the VAR of NSMDs, we did not explore the reaction of these chiral synthons with chiral aldehydes to probe the diastereofacial preference of the former over the latter. Mechanistic invesigations revealed that two stereochemical erosion pathways are operative when using LiHMDS and $SnCl_4$ but not with NaHMDS or KHMDS. A transition state supported by DFT calculations has been advanced to rationalize the stereochemical course of the reaction.

4. Experimental Section

4.1. General information

All reactions containing moisture or air-sensitive reagents were performed in flame-dried glassware under nitrogen or argon. Tetrahydrofuran, toluene, diethyl ether and dichloromethane were passed through two columns of neutral alumina prior to use. Anhydrous dimethyl sulfoxide (DMSO) was purchased from Sigma-Aldrich and subjected to three cycles of freeze-pump-thaw before use. Diisopropylamine and trimethylamine were distilled from CaH_2 prior to use. Solutions of LiHMDS, NaHMDS, and KHMDS in THF (Sigma-Aldrich) were titrated with diphenylacetic acid (recrystallized from toluene and dried *in vacuo* prior to use) with the titre being the average of three runs. Tiglaldehyde-derived *N*-sulfinyl imine **5** and albocycline intermediates **2** and **4** were prepared by known methods.[3] Crotonaldehyde-derived *N*-sulfinyl imine **11** was prepared using the procedure of Ellman.[25] All other reagents were purchased from commercial sources and used without further purification. All solvents

for work-up procedures were used as received. Flash column chromatography was performed with ICN Silitech 32-63 D 60Å silica gel with the indicated solvents. Thin layer chromatography was performed on Merck 60 F254 silica gel plates. Detection was performed using UV light, $KMnO_4$ stain, iodine chamber, PMA stain and subsequent heating. ^{1}H and ^{13}C NMR spectra were recorded at the indicated field strength in $CDCl_3$ at rt. Chemical shifts are indicated in parts per million (ppm) downfield from tetramethylsilane (TMS, $\delta = 0.00$) and referenced to the $CDCl_3$. Splitting patterns are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Diastereomeric ratios and assignment of absolute stereochemistry for compounds **2**, **10**, **12b-e** and **13a-e** were accomplished by Mosher ester analysis (Figure S1, Tables S1–2).

4.2. General procedure

4.2.1. General procedure for N-sulfinyl imine aldol products

To a solution of *N*-sulfinyl imine (1.0 mmol) in anhydrous THF (3 mL) at -20 °C was added LiHMDS, NaHMDS, or KHMDS (1.2 mL, 1.2 mmol, 1.0 M in THF) dropwise and stirred for 1 h, and then cool to -78 °C. In a separate flask, $SnCl_4$ (1.1 mL, 1.1 mmol, 1.0 M in CH_2Cl_2) was added dropwise to a solution of aldehyde (1.1 mmol) in CH_2Cl_2 (3 mL) at -78 °C and stirred for 30 min. At this time, previously generated metallodienamine was cannulated to the Lewis acid-complexed aldehyde containing flask at -78 °C over 5 min and the reaction mixture was stirred for 2 h at -78 °C. The reaction was quenched with saturated NH_4Cl (3 mL) and extracted with EtOAc (3 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced

pressure. The residue was purified by flash column chromatography to afford aldol product as a viscous oil.

*4.2.2. (R)-N-((1E,2E)-2-methylpent-2-en-1-ylidene)-2-methylpropane-2-sulfinamide (**6**)*

To a solution of 2-methyl-2-pentenal (1.00 g, 10.2 mmol) and (*R*)-*tert*-butanesulfinamide (1.35 g, 11.22 mmol) in THF (5 mL) at rt were added $Ti(OEt)_4$ (4.28 mL, 20.4 mmol) dropwise with stirring overnight. The reaction was quenched with water (5 mL), and the resulting suspension was filtered through a short pad of Celite. The filter cake was washed with EtOAc (20 mL × 3). The aqueous layer was removed and the organic layer was washed with brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc/hexanes (2:8) to afford **6** as a clear oil (1.63 g, 79%). $[\alpha]_D^{20}$ **–**463 (*c* 1.0, $CHCl_3$); IR (neat) 2965, 2874, 1636, 1579, 1456, 1362, 1084, 1045, 729 cm^{-1}; ^1H NMR (500 MHz) δ 8.10 (s, 1H), 6.22 (t, *J* = 7.3 Hz, 1H), 2.30 (qd, *J* = 7.5, 7.5 Hz, 2H), 1.87 (s, 3H), 1.19 (s, 9H), 1.07 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz) δ 167.0, 150.1, 134.7, 57.4, 22.8, 22.6, 13.5, 11.5; HRMS (ESI) calcd for $C_{10}H_{19}NOSNa$ $[M + Na]^+$ 224.1085, found 224.1091.

*4.2.3. (R)-N-((1E,2E)-5-hydroxy-2,4-dimethylhept-2-en-1-ylidene)-2-methylpropane-2-sulfinamide (**7a–d**)*

Following general procedure *4.2.1* above, 179 mg (69% yield) of inseparable mixture **7a–d** were obtained as a yellowish oil after purification by flash column chromatography eluting with EtOAc/hexane (3:7). IR (neat) 3357, 2963, 2928, 2874, 1682, 1634, 1577, 1456, 1364, 1060, 974, 908, 731 cm^{-1}; ^1H NMR (500 MHz) δ 8.14 (s, 1H), 6.26–6.12 (*dq*, *J* = 10.0, 1.4 Hz, 0.53H,**7a**; *dq*, *J* = 10.0, 1.4 Hz, 0.27H, **7b**; *dq*, *J* =

10.1, 1.5 Hz, 0.13H, **7c**; *dq*, *J* = 10.1, 1.5 Hz, 0.07H, 7**d**), 3.48 (dt, *J* = 8.8, 4.7 Hz, 1H), 2.84–2.65 (m, 1H), 1.91 (s, 3H), 1.57–1.35 (m, 2H), 1.20 (s, 9H), 1.11–1.05 (m, 3H), 0.99–0.94 (m, 3H); ^{13}C NMR (126 MHz) δ 166.8, 149.5, 135.5, 76.6, 57.1, 39.1, 27.7, 22.5, 16.6, 11.7, 10.1; HRMS (ESI) calcd for $C_{13}H_{26}NO_2S$ $[M + H]^+$ 260.1684, found 260.1673.

*4.2.4. (S)-N-((S,1E,2E,6E)-5-hydroxy-2,6-dimethylocta-2,6-dien-1-ylidene)-2-methylpropane-2-sulfinamide (**10**)*

Following general procedure *4.2.1* above, 241 mg (89% yield) of inseparable diastereomers **10** were obtained as a yellowish oil after purification by flash column chromatography eluting with EtOAc/hexane (3:7). IR (neat) 3387, 2980, 2923, 1635, 1579, 1455, 1364, 1056, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 6.20 (t, *J* = 7.0 Hz, 1H), 5.49 (m, 1H), 4.13 (dd, *J* = 12.1, 6.0 Hz, 1H), 2.64–2.44 (m, 2H), 2.07 (s, 1H), 1.87 (s, 3H), 1.60 (s, 3H), 1.59 (d, *J* = 7.1 Hz, 3H), 1.17 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 144.1, 137.0, 136.2, 121.6, 76.6, 57.1, 34.5, 22.4, 13.1, 11.6, 11.1; HRMS (ESI) calcd for $C_{14}H_{25}NO_2SNa$ $[M + Na]^+$ 294.1504, found 294.1496.

4.2.5. *(S)-N-((S,1E,2E,6E)-5-hydroxy-2-methylocta-2,6-dien-1-ylidene)-2-methylpropane-2-sulfinamide (**12b**)*

Following general procedure *4.2.1* above, 180 mg (70% yield) of inseparable diastereomers **12b** were obtained as a yellowish oil after purification by flash column chromatography eluting with EtOAc/hexane (3:7). IR (neat) 3395, 2962, 2920, 1635, 1579, 1455, 1364, 1060, 966, 748 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 6.23 (t, *J* = 7.2 Hz, 1H), 5.66–5.58 (m, 1H), 5.44 (ddd, *J* = 15.3, 7.1, 1.6 Hz, 1H), 4.13 (q, *J* = 6.6 Hz, 1H), 2.90–2.63 (s, 1H), 2.57–2.39 (m, 2H), 1.82 (s, 3H), 1.62 (d, *J* = 6.3 Hz, 3H),

1.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 143.8, 136.2, 133.2, 127.2, 71.6, 57.0, 36.7, 22.3, 17.5, 11.5; HRMS (ESI) calcd for $C_{13}H_{23}NO_2SNa$ $[M + Na]^+$ 280.1347, found 280.1334.

*4.2.6. (S)-N-((S,1E,2E)-5-hydroxy-2-methyl-5-phenylpent-2-en-1-ylidene)-2-methylpropane-2-sulfinamide (**12c**)*

Following general procedure *4.2.1* above, 220 mg (75% yield) of inseparable diastereomers **12c** were obtained as a yellowish oil after purification by flash column chromatography eluting with EtOAc/hexane (2:8). IR (neat) 3389, 2960, 2923, 1635, 1580, 1454, 1364, 1052, 757, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.42–7.21 (m, 5H), 6.29 (m, 1H), 4.84 (dd, *J* = 12.7, 5.7 Hz, 1H), 2.90–2.67 (m, 3H), 1.82 (m, 3H), 1.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 143.8, 143.4, 136.8, 128.6, 127.8, 125.8, 73.3, 57.2, 38.7, 22.4, 11.5; HRMS (ESI) calcd for $C_{16}H_{23}NO_2SNa$ $[M + Na]^+$ 316.1347, found 316.1338.

*4.2.7. (S)-N-((R,1E,2E)-5-hydroxy-2-methylhept-2-en-1-ylidene)-2-methylpropane-2-sulfinamide (**12d**)*

Following general procedure *4.2.1* above, 176 mg (72% yield) of inseparable diastereomers **12d** were obtained as a yellowish oil after purification by flash column chromatography eluting with EtOAc/hexane (3:7). IR (neat) 3419, 2961, 2925, 1635, 1579, 1456, 1363, 1059, 981, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 6.29 (t, *J* = 7.4 Hz, 1H), 3.72–3.54 (m, 1H), 2.47–2.31 (m, 2H), 1.94 (s, 1H), 1.84 (s, 3H), 1.55–1.37 (m, 2H), 1.13 (s, 9H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 144.1, 136.7, 72.4, 57.1, 36.5, 30.1, 22.4, 11.6, 10.0; HRMS (ESI) calcd for $C_{12}H_{23}NO_2SNa$ $[M + Na]^+$ 268.1347, found 268.1338.

*4.2.8. (S)-N-((S,1E,2E)-5-cyclohexyl-5-hydroxy-2-methylpent-2-en-1-ylidene)-2-methylpropane-2-sulfinamide (**12e**)*

Following general procedure *4.2.1* above, 236 mg (79% yield) of inseparable diastereomers **12e** were obtained as a yellowish oil after purification by flash column chromatography eluting with EtOAc/hexane (3:7). IR (neat) 3423, 2970, 2925, 1634, 1575, 1456, 1363, 1060, 981, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 6.39–6.34 (m, 1H), 3.55–3.49 (m, 1H), 2.55–2.39 (m, 2H), 1.90 (s, 3H), 1.88–1.82 (m, 1H), 1.81–1.73 (m, 2H), 1.70–1.64 (m, 2H), 1.41–1.33 (m, 1H), 1.28–1.20 (m, 2H), 1.20 (m, 9H), 1.16–1.09 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 144.9, 136.5, 75.3, 57.1, 43.5, 33.9, 29.2, 27.8, 26.4, 26.2, 26.0, 22.4, 11.6; HRMS (ESI) calcd for $C_{16}H_{29}NO_2SNa$ $[M + Na]^+$ 322.1817, found 322.1806.

*4.2.9. (S)-N-((S,1E,2E,6E)-5-hydroxy-6-methylocta-2,6-dien-1-ylidene)-2-methylpropane-2-sulfinamide (**13a**)*

Following general procedure *4.2.1* above, 218 mg (85% yield) of inseparable diastereomers **13a** were obtained as a yellowish oil after purification by flash column chromatography eluting with EtOAc/hexane (3:7). IR (neat) 3394, 2923, 1639, 1581, 1363, 1056, 1000, 753, 720 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (m, 1H), 6.49 (d, *J* = 4.7 Hz, 2H), 5.53 (d, *J* = 6.4 Hz, 1H), 4.18 (t, *J* = 6.4 Hz, 1H), 2.65–2.46 (m, 2H), 1.87 (s, 1H), 1.64 (s, 3H), 1.63 (d, *J* = 7.7 Hz, 3H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 147.5, 136.9, 130.4, 121.6, 76.5, 57.3, 38.6, 22.4, 13.0, 11.2; HRMS (ESI) calcd for $C_{13}H_{23}NO_2SNa$ $[M + Na]^+$ 280.1347, found 280.1330.

*4.2.10. (S)-N-((S,1E,2E,6E)-5-hydroxyocta-2,6-dien-1-ylidene)-2-methylpropane-2-sulfinamide (**13b**)*

Following general procedure *4.2.1* above, 192 mg (79% yield) of inseparable diastereomers **13b** were obtained as a yellowish oil after purification by flash column chromatography eluting with EtOAc/hexane (3:7). IR (neat) 3393, 2980, 2921, 1639, 1581, 1456, 1364, 1060, 964, 752, 721 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.6 Hz, 1H), 6.51 (m, 2H), 5.70 (dd, *J* = 14.8, 6.7 Hz, 1H), 5.51 (dd, *J* = 15.0, 6.5 Hz, 1H), 4.22 (d, *J* = 6.3 Hz, 1H), 2.51 (d, *J* = 5.9 Hz, 2H), 2.48–2.25 (m, 1H), 1.70 (d, *J* = 6.1 Hz, 3H), 1.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 147.2, 133.0, 130.7, 127.8, 71.7, 57.3, 40.8, 22.4, 17.7; HRMS (ESI) calcd for $C_{12}H_{21}NO_2SNa$ $[M + Na]^+$ 266.1191, found 266.1179.

*4.2.11. (S)-N-((S,1E,2E)-5-hydroxy-5-phenylpent-2-en-1-ylidene)-2-methylpropane-2-sulfinamide (**13c**)*

Following general procedure *4.2.1* above, 215 mg (77% yield) of inseparable diastereomers **13c** were obtained as a yellowish oil after purification by flash column chromatography eluting with EtOAc/hexane (2:8). IR (neat) 3393, 2981, 2925, 2359, 1638, 1581, 1456, 1363, 1052, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (m, 1H), 7.41–7.24 (m, 5H), 6.58–6.39 (m, 2H), 4.84 (dd, *J* = 12.1, 5.1 Hz, 1H), 2.83–2.64 (m, 3H), 1.19 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 147.0, 143.6, 130.9, 128.6, 127.9, 125.8, 73.2, 57.3, 42.6, 22.4; HRMS (ESI) calcd for $C_{15}H_{21}NO_2SNa$ $[M + Na]^+$ 302.1191, found 302.1178.

*4.2.12. (S)-N-((R,1E,2E)-5-hydroxyhept-2-en-1-ylidene)-2-methylpropane-2-sulfinamide **13d***

Following general procedure *4.2.1* above, 187 mg (81% yield) of inseparable diastereomers **13d** were obtained as a yellowish oil after purification by flash column

chromatography eluting with EtOAc/hexane (3:7). IR (neat) 3419, 2962, 1640, 1581, 1458, 1363, 1081, 1062, 999, 719 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (m, 1H), 6.48 (dddd, *J* = 15.5, 9.9, 8.7, 2.6 Hz, 2H), 3.72–3.58 (m, 1H), 2.50–2.28 (m, 2H), 1.60 (s, 1H), 1.52–1.38 (m, 2H), 1.14 (s, 9H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 147.4, 130.9, 72.1, 57.3, 40.5, 30.1, 22.5, 9.8; HRMS (ESI) calcd for $C_{11}H_{21}NO_2SNa$ $[M + Na]^+$ 254.1191, found 254.1179.

*4.2.13. (S)-N-((S,1E,2E)-5-cyclohexyl-5-hydroxypent-2-en-1-ylidene)-2-methylpropane-2-sulfinamide (**13e**)*

Following general procedure *4.2.1* above, 208 mg (73% yield) of inseparable diastereomers **13d** were obtained as a yellowish oil after purification by flash column chromatography eluting with EtOAc/hexane (3:7). IR (neat) 3427, 2970, 2925, 1636, 1575, 1456, 1363, 1059, 981, 743 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.2 Hz, 1H), 6.73–6.41 (m, 2H), 3.56 (dd, *J* = 8.4, 3.6 Hz, 1H), 2.62–2.34 (m, 2H), 1.91–1.74 (m, 3H), 1.66 (dd, *J* = 37.3, 10.0 Hz, 3H), 1.47–1.33 (m, 1H), 1.27–1.24 (m, 2H), 1.21 (s, 9H), 1.11 (dddd, *J* = 25.1, 21.9, 15.5, 7.7 Hz, 3H);^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 148.5, 130.5, 74.8, 57.2, 43.4, 37.9, 29.0, 27.9, 27.8, 26.3, 26.0, 22.4; HRMS (ESI) calcd for $C_{15}H_{27}NO_2SNa$ $[M + Na]^+$ 308.1660, found 308.1650.

*4.2.14. (4E,6E)-methyl 6-(((S)-tert-butylsulfinyl)imino)-2-hydroxy-2,5-dimethylhex-4-enoate (**14**)*

Following general procedure *4.2.1* above, 263 mg (91% yield) of inseparable diastereomers **14** were obtained as a yellowish oil after purification by flash column chromatography eluting with EtOAc/hexane (3:7). IR (neat) 3395, 2980, 2954, 2925, 2869, 1737, 1636, 1581, 1455, 1364, 1083, 984 cm^{-1}; ^{1}H NMR (500 MHz) δ 8.12 (s, 1H),

6.23 (t, *J* = 7.4 Hz, 1H), 3.78 (s, 3H), 2.81–2.62 (m, 2H), 1.90 (s, 3H), 1.47 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (126 MHz) δ 176.6, 166.3, 140.8, 137.7, 74.3, 57.2, 53.0, 39.3, 25.9, 22.5, 11.6; HRMS (ESI) calcd for $C_{13}H_{24}NO_4S$ $[M + H]^+$ 290.1426, found 290.1417.

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Supporting Information

Stereochemical assignments by Mosher ester analysis and HPLC including experimental details, ^{1}H and ^{13}C NMR spectra for all new compounds, DFT calculations

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Highlights for "The Vinylogous Aldol Reaction of *N*-Sulfinyl Metallodienamines"

- development and optimization of the reaction of *N*-sulfinyl metallodienamines with aldehydes and ketones.
- key step employed in total synthesis of (–)-albocycline
- update and correct the diastereoselectivity of the reaction employing both HPLC and Mosher ester analysis
- yields ranging from 68–89% and diastereomeric ratios as high as 5.9:1.
- A transition state supported by DFT calculations has been advanced to rationalize the stereochemical course of the reaction.

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: