Diastereoselective Addition of Prochiral Nucleophilic Alkenes to α-Chiral *N*-Sulfonyl Imines

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ABSTRACT: The Lewis acid catalyzed addition of prochiral *E* and *Z* allyl nucleophiles to chiral α-alkoxy *N*-tosyl imines is described. Alkene geometry is selectively transferred to the newly formed carbon-carbon bond, resulting in stereochemical control of C2, C3, and C4 of the resulting 2-alkoxy-3-*N*-tosyl-4-alkyl-5-hexenes. The C3 and C4 diastereoselectivity (dr) is influenced by the geometry of the alkene, size of *N*-sulfonyl substituent, and steric bulk of the substituted α-alkoxy ether group. This work demonstrates that three of the four possible diastereomers can be synthesized in high diastereoselectivity and high yields using the current methods. A mechanistic computational analysis to elucidate the high selectivity is also presented.

Introduction

Acyclic stereocontrol of carbon-carbon bond forming reactions is a longstanding challenge in organic synthesis. The addition of prochiral allylic nucleophiles to α-chiral sp^2 electrophiles creates a C-C bond under mild conditions while also producing two new stereogenic centers. While the crotylation of α-heteroatom-substituted electrophiles, particularly α-alkoxy aldehydes, has been studied extensively,[1] studies of crotylation and related nucleophilic additions to α-alkoxy imines yielding 1,2-amino alcohols are less explored. Amino alcohols are important structural targets that have been used as chiral auxiliaries for enantioselective catalysis.[2] Amino alcohols are present in natural products, such as veratramine, clausenamide, and isofebrifugine, and are important structural motifs in medicinal chemistry[3] (Figure 1a).

Investigations of acyclic stereocontrolled crotylation of α-chiral imines bearing polar heteroatoms were undertaken by Panek and Marek (Figure 1b).[4,5] Imine formation of alkyl aldehydes is often challenging, since these imines must be used immediately to avoid decomposition or enamine tautomerization.[6] To obviate this challenge Panek used a multicomponent reaction to generate α-alkoxy *N*-carbamoyl imines *in situ*.[7] In this case, Panek observed appreciable levels of selectivity with a chiral allylsilane, which provides the highest selectivity when matched with the appropriate chiral aldehyde. Marek demonstrated C2-C3 *syn* and C3-C4 *syn* stereocontrol by utilizing an amido sulfone imine precursor and a zinc nucleophile.[5]

Recently our group demonstrated a highly diastereoselective allylation of α-alkoxy *N*-tosyl imines producing either *anti* or *syn* homoallylic amino alcohols, depending on the reaction conditions.[8] Allyl BF_3K salts with BF_3•OEt_2 as a Lewis acid afford *anti* diastereoselectivity of the α-alkoxy and *N*-tosyl groups in the product. It was also demonstrated that $ZnBr_2$, as Lewis acid, and allyl trimethylsilanes selectively afford *syn* products. Although this study was limited to unsubstituted (non-prochiral) nucleophiles, it was the first comprehensive study of these addition reactions to electron-deficient imines.

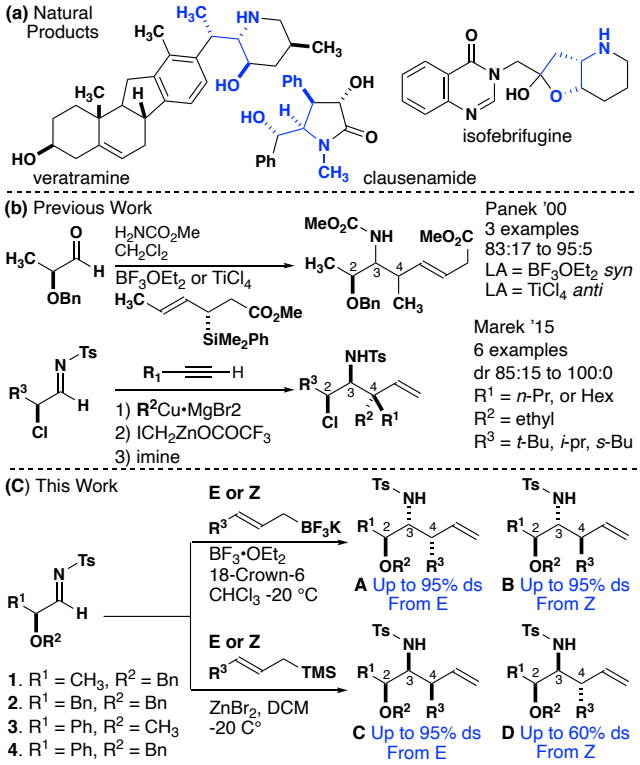


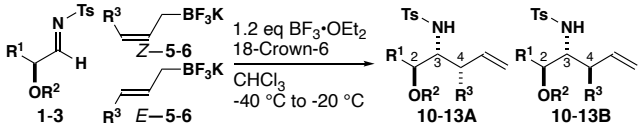
Figure 1. (a) Natural products containing 1,2-amino alcohol moiety. (b) Previous work involving crotylation of α-chiral heteroatom imines. (c) Studies described in this manuscript. ds = %major isomer of the four possible isomers.

We now describe the diastereoselective crotylation of α-alkoxy *N*-tosyl imines, where acyclic stereocontrol of carbons 2, 3, and 4 in a single step is achieved (Figure 1c). Transition

states of these reactions have been located and analyzed with density functional theory (B3LYP-D3/6-31G(d)) to explain the observed diastereoselectivity.

Results and Discussion

Our previous report demonstrating highly selective 1,2 asymmetric induction provided the basis for our study of the additions of prochiral alkene nucleophiles with *N*-tosyl imines. A series of *E* and *Z* substituted nucleophilic allyl BF_3K reagents were screened in order to develop an understanding of the stereochemical outcome at carbons 3 and 4. (*E*)-Hex-2-en-1-yl BF_3K *E*-**5** was added to *N*-tosyl imine **1** using BF_3•OEt_2 as a Lewis acid mediator to give product **10A** with >95:5 diastereoselectivity (entry 1, Table 1). Compound **10A** was isolated in 56% overall yield and had the expected *anti*-stereochemistry at C2 and C3 and *syn*-stereochemistry at C3 and C4. Changing the alkene geometry of the nucleophile produced the complementary major product. The addition of (*Z*)-hex-2-en-1-yl BF_3K nucleophile *Z*-**5** to imine **1** gave product **10B** in 62% with 90% diastereoselection (entry 2, Table 1). The same *anti* selectivity at C2 and C3 is observed, but now C3 and C4 have the *anti* stereochemistry. The sterically less demanding *E*-**6** and *Z*-**6** crotyl BF_3K reagents were also added to imine **1** and gave similar levels of stereocontrol. (*E*)-Crotyl BF_3K reagent *E*-**6** gave 95% selectivity for **11A**, and (*Z*)-Crotyl BF_3K reagent *Z*-**6** gave 91% selectivity for **11B** (entries 3 and 4, Table 1). These diastereomers were isolated in 76% and 53% yield, respectively. While the α-stereogenic center of the electrophile completely controls the facial approach of the nucleophile, the two new stereogenic centers at C3 and C4 are largely controlled by the alkene geometry of the nucleophile.

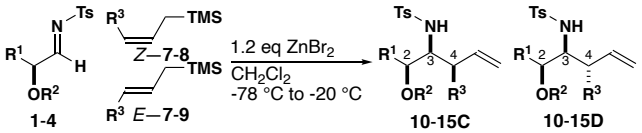


Entry	R^1	R^2	R^3	E/Z	Yield	A:B[a]
1	CH_3	Bn	*n*-Pr	*E*-**5**	**10A**[b] 56%	95:5
2	CH_3	Bn	*n*-Pr	*Z*-**5**	**10B** 62%	10:90
3	CH_3	Bn	CH_3	*E*-**6**	**11A** 76%	95:5
4	CH_3	Bn	CH_3	*Z*-**6**	**11B** 53%	9:91
5	Bn	Bn	CH_3	*E*-**6**	**12A**[b] 56%	95:5
6	Bn	Bn	CH_3	*Z*-**6**	**12B** 56%	5:95
7	Ph	CH_3	CH_3	*E*-**6**	**13A** 72%	95:5
8	Ph	CH_3	CH_3	*Z*-**6**	**13B**[b] 51%	5:95

Table 1. Addition of BF_3K prochiral nucleophilic alkenes to α-alkoxy *N*-tosyl imines. [a]dr was measured using ^1H NMR of the unpurified reaction mixture. *Syn* products **C** and **D** were not observed. [b]The structures were established by X-ray crystallography.

Imines **2** and **3** were screened to determine the effect of added substitution. The addition of *E*-**6** crotyl BF_3K to imine **2** gave a 95% diastereoselection for product **12A,** which was isolated in 56% yield (entry 5, Table 1). The crotylation of imine **2** with *Z*-**6**-crotyl BF_3K gave 95% diastereoselectivity of the opposite diastereomer product **12B** in 56% yield (entry 6, Table 1). The crotylation of *N*-tosyl imine **3** with *E*-**6** crotyl BF_3K gave a 95% diastereoselection and 72% yield of **13A** (entry 7, Table 1). The addition of *Z*-**6** crotyl BF_3K to imine **3** was 95% diastereoselective for **13B** (entry 8, Table 1). Overall, imine substituents with a range of steric influence all undergo highly stereoselective addition reactions with substituted allyl BF_3K reagents.

Substituted allylsilanes were examined next in order to achieve complementary selectivity with the goal of producing isomers **C** and **D** selectively. (*E*)-Hexy-2-en-1-trimethylsilane *E*-**7** was added to *N*-tosyl imines **1** using $ZnBr_2$ as Lewis acid mediator. This addition gave **10C** in 95% diastereoselection and 77% isolated yield. (entry 1, Table 2). To imine **1** was added *E*-**8** crotyl allyl TMS nucleophile giving an **11C** in 53% yield and 89% diastereoselectivity (entry 3, Table 2). Under similar conditions, *N*-tosyl imine **2**, with an α-benzyl group, provided **12C** with similar selectivity (88%) compared to the product from **1** and *E*-**8** (entry 5, Table 2). Imine **3**, with α-phenyl and α-methoxy groups, reacted with *E*-**8** crotyl allyl TMS and $ZnBr_2$ to give **13C** in 75% yield with 95% diastereoselectivity (entry 7, Table 2). This result demonstrates that the size of the α-alkoxy group plays a significant role in the *syn* diastereoselectivity of carbons 3 and 4. In order to investigate the effect of the α-alkoxy group further, *E*-cinnamyl trimethylsilane *E*-**9** was added to imines **3** and **4**. The addition of *E*-**9** to imine **3** bearing the α-methoxy was highly diastereoselective, yielding a single detectable diastereomer (entry 9, Table 2). Changing α-alkoxy group from methyl to benzyl (imine **4**) decreased the diastereoselectivity to 86 % with $ZnBr_2$ as the promoter and $ZnCl_2$ as the Lewis acid promoter increased the diastereoselectivity to 95:5 (entry 10, Table 2).



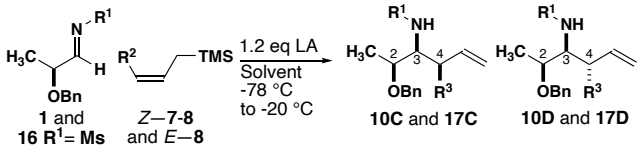
Entry	R^1	R^2	R^3	E/Z	Yield	C:D[a]
1	CH_3	Bn	*n*-Pr	*E*-**7**	**10C**[b] 77%	95:5
2	CH_3	Bn	*n*-Pr	*Z*-**7**	**10D** 11%	40:60
3	CH_3	Bn	CH_3	*E*-**8**	**11C** 53%	89:11
4	CH_3	Bn	CH_3	*Z*-**8**	**11C** --%	67:33
5	Bn	Bn	CH_3	*E*-**8**	**12C** 61%	88:12
6	Bn	Bn	CH_3	*Z*-**8**	**12C** --%	95:5
7	Ph	CH_3	CH_3	*E*-**8**	**13C** 75%	95:5
8	Ph	CH_3	CH_3	*Z*-**8**	**13C** --%	95:5
9	Ph	CH_3	Ph	*E*-**9**	**14C** 75%	95:5
10[c,d]	Ph	Bn	Ph	*E*-**9**	**15C** 85%	95:5

Table 2. Addition of TMS prochiral nucleophilic alkenes to α-alkoxy *N*-tosyl imine. [a]dr was measured using ^1H NMR of the unpurified reaction mixture. [b]The structures were established by X-ray crystallography . [c]Reaction yield on 1.5 mmol scale. [d]Reaction with $ZnCl_2$.

In all cases, excellent facial selectivity was observed in that only isomers **C** and **D** were formed, demonstrating that substituted allylic silanes complement the C2-C3 facial selectivity of allylic BF_3K reagents. (*Z*)-Substituted allyl trimethylsilanes react with lower diastereoselectivity than the (*E*)-substituted counterpart. The addition of (*Z*)-hex-2-en-1-yltrimethylsilane *Z*-**7** using $ZnBr_2$ was unselective, giving 60% diastereoselectivity for **10D** and 40% of **10C** (entry 2, Table 2). The addition of crotyl silane *Z*-**8** to imine **1** gave a small preference for the *syn* diastereomer, 67% of **11C** and 33%of **11D** (entry 4, Table 2). The addition of *Z*-**8** to imines **2** and **3** gave 95% diastere-

oselectivity for **12C** and **13C**, respectively (entries 6 and 8, Table 2), the same sense of induction as seen with *E*-**8** and imine **1**. In summary, **10-15C** is favored in all cases except entry 2 with the smallest imine substituent ($R^1 = CH_3$) and the larger allylsilane substituent (R^3=*n*-Pr).

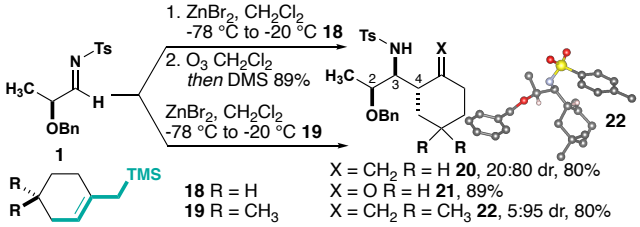
Several variables were changed in order to boost the selectivity for diastereomer **D** (Table 3). A series of other chelatable metals were screened in CH_2Cl_2 as solvent. Most Lewis acids gave no reaction, whereas other zinc halides also showed high reactivity. Reactions of *Z*-**7** and imine **1** using $ZnCl_2$ and ZnI_2 provided **10C** and **10D** in ratios of 47:53 and 75:25, respectively (entries 1 and 2, Table 3). Given the reduced selectivity of *Z*-allylsilanes for **10D**, solvent screening was undertaken. The use of $ZnBr_2$ in either α,α,α-trifluorotoluene or nitromethane also reduced the preference for **10D** (entries 3 and 4, Table 3). Changing the imine substituent from *p*-toluenesulfonyl (*N*-Ts) to methanesulfonyl (*N*-Ms) failed to reverse the preference for the **D** isomer, resulting in a ratio of 73:27 for **17C**:**17D** (entry 6, Table 3). As a point of direct comparison, addition using *E*-**8** to the *N*-Ms imine **16** gave an 81:19 ratio of **17C**:**17D** (Table 3, Entry 5), lower than the comparable reaction of the *N*-Ts imine (entry 1, Table 2, vide supra). Reactions with aldehydes and (*Z*) crotyl TMS reagents resulted is lower levels of diastereocontrol than with the *E*-configured nucleophile.[12]



Entry	R^1	R^2	E/Z	LA	Solvent	C:D[a]
1	Ts	*n*-Pr	*Z*-**7**	$ZnCl_2$	CH_2Cl_2	47:53
2	Ts	*n*-Pr	*Z*-**7**	ZnI_2	CH_2Cl_2	75:25
3	Ts	*n*-Pr	*Z*-**7**	$ZnBr_2$	$CF_3C_6H_5$	55:45
4	Ts	*n*-Pr	*Z*-**7**	$ZnBr_2$	NO_2CH_3	60:40
5	Ms	CH_3	*E*-**8**	$ZnBr_2$	CH_2Cl_2	81:19
6	Ms	CH_3	*Z*-**8**	$ZnBr_2$	CH_2Cl_2	73:27

Table 3. Optimization of (*Z*)-TMS nucleophilic alkene additions to α-alkoxy imines. [a]dr was measured using ^{1}H NMR of the unpurified reaction mixture

Cyclic allyl silanes were also added to **1** and gave interesting levels of diastereoselectivity. Silanes **18** and **19** have a similar (*E*)-geometric alkene configuration (cf. *E*-**8**). Based on observations with *E*-**8**, it was initially hypothesized that the major diastereomer would be analogous, *syn* between both C2-C3 and C3-C4. However, when **18** was added to **1**, product **20** was isolated in 80% yield and 20:80 dr, favoring the *syn* C2-C3, *anti* C3-C4 diastereomer. This is the opposite result to the addition of *E*-**8** to imine **1** under the analogous conditions. The exocyclic alkene was ozonolyzed to yield the *syn* C2-C3 *anti* C3-C4 substituted cyclohexanone **21**, (Scheme 1) for which the configuration was assigned by X-ray crystallography. The addition of the more sterically hindered trimethylsilyl nucleophile **19** gave the same stereochemical result with greater selectivity (5**:**95) for the formation of **22**. These results are significant in that they also diverge from the analogous additions to aldehydes. Cyclic allylsilanes add to aldehydes with poor selectivity or a preference for the *syn* configuration about the two newly- formed stereogenic centers.[13,14] *Syn* selectivity was also reported with silane **18** in an addition reaction with an ethyl glyoxylate-derived imine.[15] The origin of selectivity in reactions with aldehydes and imines is poorly understood, but could originate from facial selectivity that is unique to the cyclic allysilanes.[16] These results may eventually enable the design of other allylsilane nucleophiles that form isomer **D** selectively through Lewis acid-mediated additions to electron deficient imines.



Scheme 1. Addition of cyclohexyl allyl TMS to α-alkoxy *N*-tosyl imine **1**. dr was measured using ^{1}H NMR of the unpurified reaction mixture. The relative stereochemistry **21** and **22** were established by X-ray crystallography.

The addition reactions of allyl-BF_3K reagents and allylsilanes to aldehydes have been thoroughly investigated previously. Prior investigations have focused on the addition of substituted allyl BF_3K reagents to α-siloxy aldehydes as well as α-chiral alkyl and aryl imines.[17–23] After abstraction of a fluoride by BF_3•OEt_2, the resulting allyl-BF_2 species reacts with electrophiles through an organized Zimmerman-Traxler chair transition state, leading to predictable stereochemical outcome based on alkene geometry.[24]

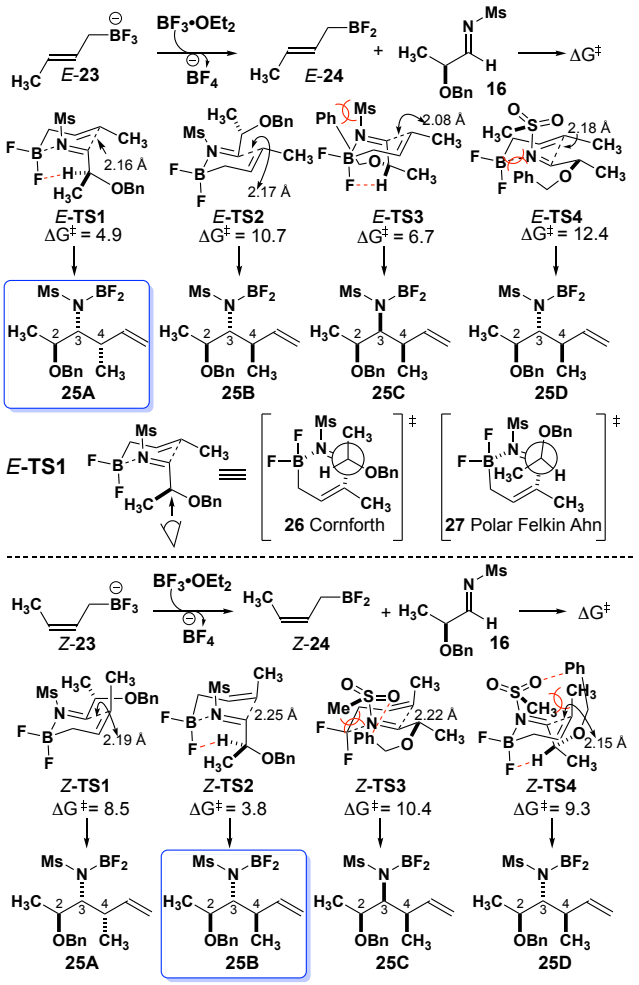
Our initial study on the addition of unsubstituted allyl-BF_3K reagents to imines **1-3** revealed a preference for Felkin/Cornforth facial selectivity of carbons 2 and 3. Allylsilanes, on the other hand, are presumed to react through an open transition state.[12] In that case, the product prediction is more complicated because each *E*/*Z* alkene isomer pair creates 12 possible reactive conformations in the transition state. There has been a considerable amount of work to elucidate the orientation of the aldehyde relative to the allyl silane in the transition state.[12,25] These reaction characteristics were used to develop stereochemical models for the observed selectivity of α-chiral alkoxy *N*-tosyl imines.

Computational Studies

Transition structures for the highly diastereoselective additions of *E*-**6** and *Z*-**6** crotyl BF_3K salts were computed to elucidate the origins of the stereoselectivity. First, a fluoride is abstracted by BF_3•OEt_2, generating the highly electrophilic crotyl BF_2 species *E*-**24** and *Z*-**24** (Scheme 2).[19] For the lowest energy reaction pathway, the lone pair of the (*E*)-imine coordinates to the electrophilic boron and a chair transition state structure. E-**TS1**. Based on the similar performance of *N*-methanesulfonyl (*N*-Ms) and *N*-toluenesulfonyl imines in our previous report, the former was used to simplify computational experiments.

The lowest energy pathway with *E*-**24** is *E*-**TS1** leading to the observed diastereomer **25A**. The transition states *E*-**TS2**, *E*-**TS3** and *E*-**TS4** are pathways for the other diastereomers **25B**, **25C**, and **25D**, respectively**.** In *E*-**TS1**, the methyl of the *E*-**24** crotyl is pseudo equatorial and thus imposes no 1,3 diaxial interactions with the *N*-mesyl. The C3, C4 *syn* stereochemistry is dictated by the (*E*)-geometry of the imine.[26–28] In each case where the imine has isomerized to the (*Z*)-geometry, *E*-

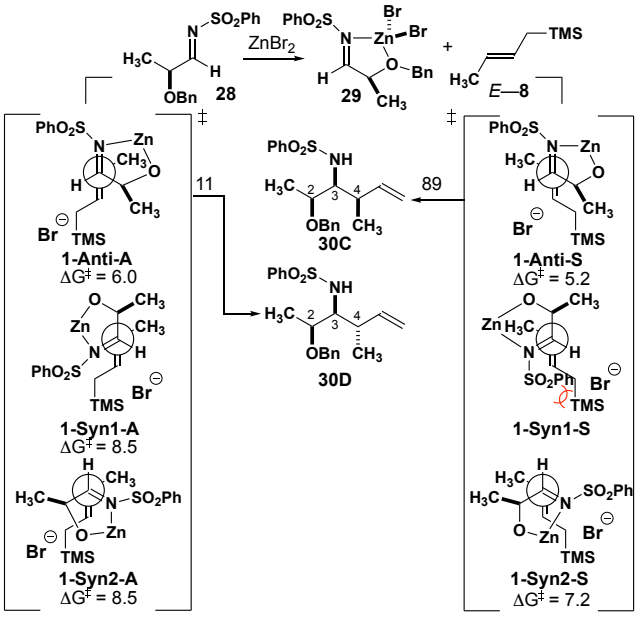
TS2 and *E*-**TS4**, C3, C4 are *anti*. The Szabo group has seen that (*Z*) imines derived from benzaldehyde give *anti* C3 C4 selective products.[26] *Z*-**TS2** is the lowest energy transition state for the imine reaction with *Z*-**24**.



Scheme 2. Computed relative ΔG transition state energies for *E* and *Z*-crotyl BF_3K and α-alkoxy *N*-mesyl imine in kcal/mol (B3LYP-D3/6-31G(d))

The *anti*-selectivity of C2 and C3 observed in **25A** and **25B** from *E*-**TS1** or *Z*-**TS2** is the result of a Cornforth orientation **26,** with the electronegative α-alkoxy group and the imine *anti*, following the dipole-dipole repulsion model proposed by Cornforth.[29] The stereoelectronically favored,[30] polar Felkin-Ahn conformer **27** induces a non-bonded interaction between the α-alkyl group of the imine and the developing chair transition state.[31] Analysis of the stereochemical handles in the transition state explicitly details the high diastereoselectivity using crotyl BF_3K reagents.

The transition states for the addition of crotyl silanes to **28** were computed as well. Additions of crotyl silanes are known to go through an open transition state. The high *syn* diastereoselectivity for the two new stereogenic centers (C3 and C4) resulting from the addition of *E*-**8** originates from the addition of a zinc-chelated imine **29** (Scheme 3). The structure of the zinc chelate was adapted from a similar structure computed previously.[8] The chelate positions the methyl group on the ring to create a more sterically hindered face. The prochiral crotyl *E*-**8** TMS then adds to the less sterically hindered face of the chelated imine, resulting in high selectivity for the C3-C4 *syn* configuration.

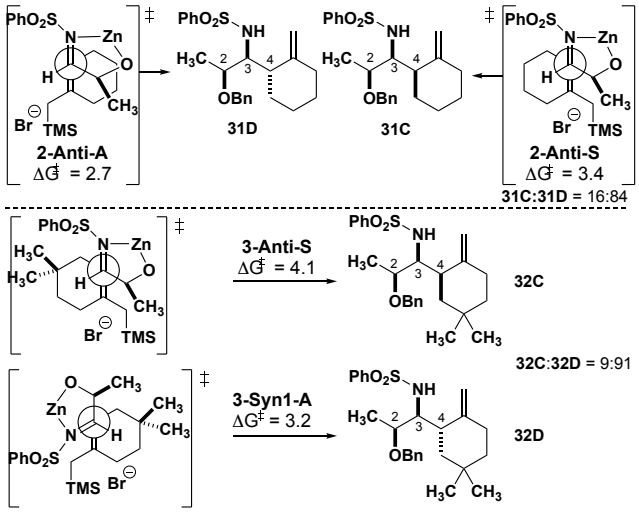


Scheme 3. Computed relative ΔG transition state energies for *E*-crotyl TMS and α-alkoxy *N*-phenylsulfonyl imine in kcal/mol (B3LYP-D3/6-31G(d)). Bromide ligands and benzyloxy substituents were omitted for clarity.

The chelate-induced facial selectivity of *E*-**8**-crotyl TMS gives rise to 6 possible transition states (Scheme 3). The C3-C4 *syn* addition is set via three alignments: one antiperiplanar and two synclinal orientations. Alternatively, opposite facial attack of the allyl silane results in the C3-C4 *anti* adduct and generates another set of antiperiplanar and synclinal conformations. The **1-Anti-S** (antiperiplanar-*syn* product) transition state is the lowest energy conformer (5.2 kcal/mol) of the possible six transition states and leads to the observed major diastereomer **30C**. This transition state arranges the crotyl trimethyl silane *E*-**8** in an antiperiplanar approach to the zinc-chelated imine, resulting in the C2-C3 *syn* and C3-4 *syn* configuration, **30C**. The lowest energy transition state for the minor diastereomer *syn* C2-C3 *anti* C3-C4 diastereomer is **1-Anti-A** (6.0 kcal/mol). The ΔΔG between the **1-Anti-A** and **1-Anti-S** is 0.8 kcal/mole in excellent agreement with the experimental results reported for **1** and *E*-**8** (Table 2, Entry 3). The **1-Syn1-S** (synclinal-*syn* product) transition state reorients to **1-Anti-S.** Therefore the **1-Syn1-S** transition state structure is too unstable to be a viable pathway. In all cases, synclinal orientations are higher energy than the two antiperiplanar ones.

The calculated transition states for the addition of cyclic allylsilanes **18** and **19** to chelate **29** show how a change in orientation leads to different selectivities from the acyclic cases. The two lowest energy transition states for the nucleophilic addition of silane **18** are **2-Anti-A** and **2-Anti-S,** leading to diastereomers **31D** and **31C**, respectively (Scheme 4). Although these two transition states are similar to those of *E*-**8** (Scheme 3), **2-Anti-A** is the lowest energy transition state and leads to the C3 C4 *anti* product **31D**. Analysis of the transition state for the nucleophile **19** with **29** shows that **3-Anti-S** and **3-Syn1-A** are the two lowest energy transition states. The experimentally observed *anti* product **32D** results from the syn-

clinal transition state **3-Syn1-A**. In this case, the **3-Anti-S** is the higher energy orientation.



Scheme 4. Computed relative ΔG transition state energies for cyclohexyl allyl TMS **18** and **19** and α-alkoxy *N*-phenylsulfonyl imine **29** at -78 °C in kcal/mol (B3LYP-D3/6-31G(d)). Bromide ligands and benzyloxy substituents were omitted for clarity.

Conclusion

In summary, we have conducted the first exhaustive study of the diastereochemical outcome of substituted nucleophilic alkenes to electron deficient imines derived from α-alkoxy aldehydes. In three out of four cases, one diastereomer out of four dominates and is formed in >90% selectivity. Although only 65% selectivity can be achieved for the last case, a constrained cyclic analog proceeds with higher selectivity (95%), suggesting that specific targets with this outcome may be accessed using this chemistry. In the case of the substituted borane nucleophiles, which are formed *in situ* from the allylic BF_3K precursors, calculations indicate that the major diastereomer is formed from a Cornforth-like transition state in which the alkoxy substituent to the imine-Lewis acid complex, providing ideal alignment of dipoles of these groups. With substituted allylic silanes, the high propensity for the imine substrates to form Lewis acid chelate complexes resulted in exclusive reactivity through the Cram chelate model. Although some level of Felkin/Cornforth selectivity was possible with unsubstituted allylic silanes[8], the reduced reactivity of the substituted allylic silanes required higher temperatures and prevented the use of a non-chelating Lewis acid (BF_3•OEt_2). The major isomers resulting from substituted allylic silanes emerge from anti-periplanar approach of the acyclic allyl silane nucleophile to the Lewis-acid-chelated imine.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge.

Experimental procedures, characterization data for all new compounds, copies of ^{1}H and ^{13}C NMR spectra, and .cif files for compounds **10A**, **10C**, **12A**, **13B**, **21, 22**.

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