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

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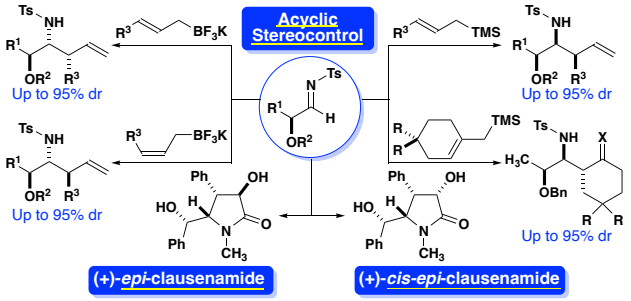
Supporting Information Placeholder



ABSTRACT: The Lewis acid promoted 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 C1, C2, and C3 of the resulting 2-alkoxy-3-*N*-tosyl-4-alkyl-5-hexene products. A computational analysis to elucidate the high selectivity is also presented. This methodology was employed in the synthesis of two naturally occurring isomers of clausenamide.

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 under explored.

Investigations of acyclic stereocontrolled crotylation of α-chiral imines bearing polar heteroatoms were undertaken by Panek and Marek (Figure 1a).[2,3] Imine formation of alkyl aldehydes is often challenging, since these imines must be used immediately to avoid decomposition or enamine tautomerization.[4] To obviate this challenge Panek used a multicomponent reaction to generate α-alkoxy *N*-carbamoyl imines *in situ*. In this case, appreciable levels of selectivity were observed with a chiral allylsilane, providing the highest selectivity when matched with the appropriate chiral aldehyde. Marek demonstrated C1-C2 *syn* and C2-C3 *syn* stereocontrol by utilizing an amido sulfone imine precursor and a zinc nucleophile.[3]

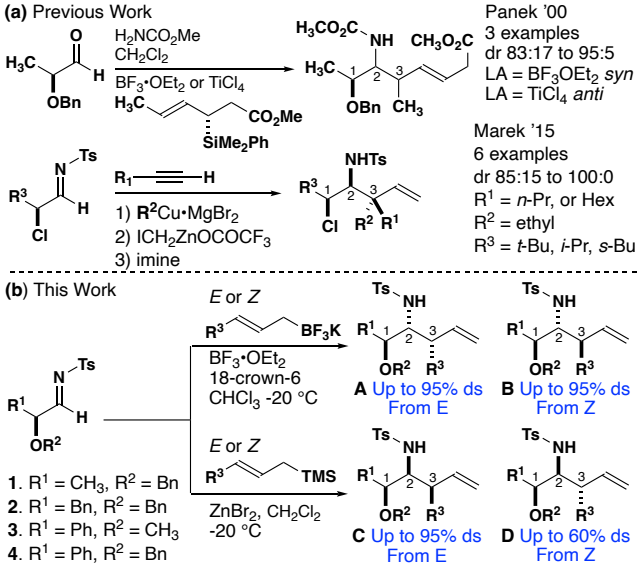


Figure 1. (a) Previous work involving crotylation of α-chiral heteroatom imines. (b) Studies described in this manuscript. ds = % major isomer of the four possible isomers.

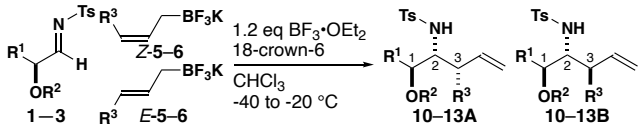
Recently our group demonstrated a highly diastereoselective allylation of α-alkoxy *N*-tosyl imines producing either C1-C2 *anti* or *syn* homoallylic amino alcohols, depending on the reac-

tion conditions.[5] Allyl BF_3K with BF_3•OEt_2 as a Lewis acid affords *anti* diastereoselectivity and $ZnBr_2$, as Lewis acid, and allyl trimethylsilanes selectively afford *syn* products.

We now describe the diastereoselective crotylation of α-alkoxy *N*-tosyl imines, where acyclic stereocontrol of carbons 1, 2, and 3 is achieved in a single step (Figure 1b). Transition states have been located and analyzed with density functional theory (B3LYP-D3/6-31G(d)) to explain the observed diastereoselectivity. The stereocontrolled reaction was employed in a divergent synthesis of two epimers of clausenamide: (+)-epiclausenamide and, (+)-*cis*-epi-clausenamide.[6–8]

Our previous report 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 2 and 3. Nucleophile *E*-**5** was added to *N*-tosyl imine **1** to give product **10A** with >95:5 diastereoselectivity (entry 1, Table 1). Compound **10A** had the expected *anti*-stereochemistry at C1 and C2 and *syn*-stereochemistry at C2 and C3. Changing the alkene geometry of the nucleophile to the *Z* configuration produced the complementary major product **10B** in 62% yield with 90% diastereoselection (entry 2, Table 1). The same *anti* selectivity at C1 and C2 is observed, but now C2 and C3 have *anti* stereochemistry. Crotyl BF_3K nucleophiles *E*-**6** and *Z*-**6** were also added to imine **1** and gave similar levels of stereocontrol, 95% diastereoselection for **11A**, and 91% diastereoselection for **11B** (entries 3 and 4, Table 1). While the α-stereogenic center of the electrophile completely controls the facial approach of the nucleophile, the two new stereogenic centers at C2 and C3 are largely controlled by the geometry of the alkene nucleophile.

Table 1. Addition of BF_3K prochiral nucleophilic alkenes to α-alkoxy *N*-tosyl imines.



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[c]	Bn	Bn	CH_3	*E*-**6**	**12A**[b] 47%	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

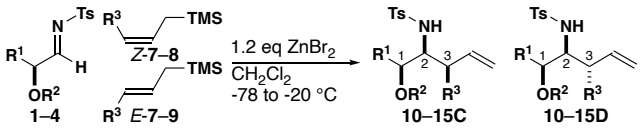
[a]dr was measured using ^{1}H NMR of the unpurified reaction mixture. *Syn* products **C** and **D** were not observed. [b]Structures were established by X-ray crystallography. [c]Reaction yield on 1.2 mmol scale.

Imines **2** and **3** were screened to determine the effect of added substitution. The addition of *E*-**6** crotyl BF_3K to imines **2** and **3** gave 95% diastereoselection for products **12A** and **13A** respectively (entries 5 and 7, Table 1). The crotylation of imines **2** and **3** with *Z*-**6**-crotyl BF_3K gave 95% diastereoselectivity for products **12B** and **13B** respectively (entries 6 and 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. Nucleophile *E*-**7** was added to *N*-tosyl imine **1** using $ZnBr_2$ as Lewis acid mediator, giving **10C** in 95% diastereoselection. (entry 1, Table 2). To imine **1** was added crotyl TMS *E*-**8** giving **11C** in 89% diastereoselectivity (entry 3, Table 2). Nucleophilic addition of *E*-**8** to imine **2**, provided **12C** with similar diastereoselectivity 88% (entry 5, Table 2). Imine **3**, reacted with *E*-**8** crotyl allyl TMS and $ZnBr_2$ to give **13C** in 95% diastereoselection (entry 7, Table 2). The addition of *E*-cinnamyl trimethylsilane *E*-**9** to imine **3** bearing an α-methoxy was highly diastereoselective, yielding a single detectable diastereomer (entry 9, Table 2). However, addition of *E*-**9** to imine **4** decreased the diastereoselectivity to 86% with $ZnBr_2$ as the promoter. Substituting $ZnCl_2$ as the Lewis acid promoter increased the diastereoselectivity to 95:5 (entry 10, Table 2). In all cases, excellent facial selectivity was observed in that only isomers **C** and **D** were formed. These results are complementary to the C1-C2 facial selectivity of allylic BF_3K reagents.

In contrast (*Z*)-Substituted allyl trimethylsilanes react with lower diastereoselectivity than the (*E*)-substituted counterpart. The addition of *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% diastereoselectivity for **12C** and **13C**, respectively (entries 6 and 8, Table 2), the same sense of induction is seen with *E*-**8** and imine **1**. In summary, **10**-**15C** is favored in all cases except entry 2 in Table 2.

Table 2. Addition of TMS prochiral nucleophilic alkenes to α-alkoxy *N*-tosyl imines.



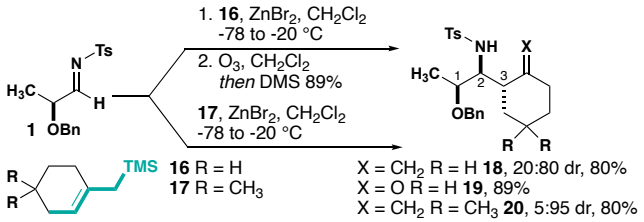
Entry	R^1	R^2	R^3	E/Z	Yield	C:D[a]
1	CH_3	Bn	*n*-Pr	*E*-**7**	**10C**[b] 77%	95:5
2	CH_3	Bn	*n*-Pr	*Z*-**7**	**10D** 11%	40:60
3	CH_3	Bn	CH_3	*E*-**8**	**11C** 53%	89:11
4	CH_3	Bn	CH_3	*Z*-**8**	**11C** nd[e]	67:33
5	Bn	Bn	CH_3	*E*-**8**	**12C** 61%	88:12
6	Bn	Bn	CH_3	*Z*-**8**	**12C** nd[e]	95:5
7	Ph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

[a]dr was measured using ^{1}H NMR of the unpurified reaction mixture. *Anti* products **A** and **B** were not observed. [b]The structures were established by X-ray crystallography. [c]Reaction yield on 1.2 mmol scale. [d]Reaction with $ZnCl_2$.[e]Yields not determined

Cyclic allyl silanes**16** and **17** were added to imine **1** and gave interesting levels of diastereoselectivity. Silanes **16** and **17** have a similar (*E*)-geometric alkene configuration to *E*-**8**. Based on

observations with *E*-**8**, it was hypothesized that the major diastereomer would be analogous. That is *syn* between both C1-C2 and C2-C3. However, addition of silane **16** to imine **1**, yielded product **18** in 20:80 dr, favoring the *syn* C1-C2, *anti* C2-C3 diastereomer (Scheme 1). This is the opposite result to the addition of silane *E*-**8** to imine **1** under the identical conditions. The exocyclic alkene was ozonolyzed to yield the crystalline ketone **19**. The addition of the more sterically hindered nucleophilic silane **17** gave the same stereochemical result with greater selectivity (5:95) for the formation of **20**. These results may eventually enable the design of other allylsilane nucleophiles that form isomer **D** selectively.

Scheme 1. Addition of cyclohexyl allyl TMS to α-alkoxy *N*-tosyl imine 1.[a,b]

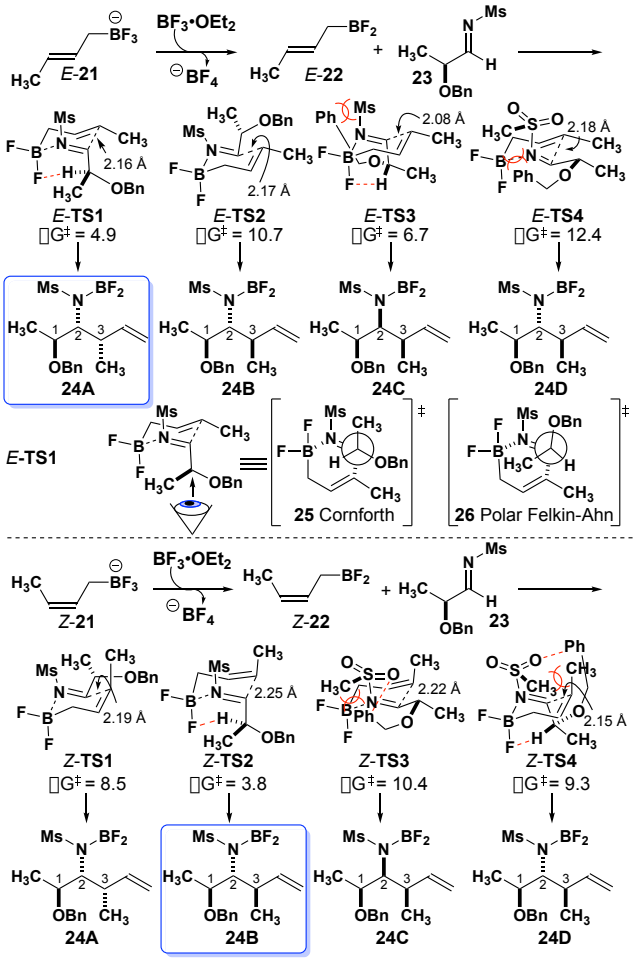


[a]dr was measured using ^{1}H NMR of the unpurified reaction mixture. [b]The relative stereochemistry **19** and **20** were established by X-ray crystallography.

The reaction characteristics of crotyl-BF_3K[9–16] and crotyl trimethyl silane[17,18] were used to develop stereochemical models for the observed selectivity in the nucleophilic additions to α-chiral alkoxy *N*-tosyl imines. In the case of highly diastereoselective additions of *E*-**6** and *Z*-**6** crotyl BF_3K salts; first, a fluoride is abstracted by BF_3•OEt_2, generating the highly electrophilic crotyl BF_2 species *E*-**22** and *Z*-**22** (Scheme 2).[11] The lone pair of the (*E*)-imine coordinates to the electrophilic boron generating a chair transition state structure. The lowest energy pathway with *E*-**22** is *E*-**TS1**, leading to the observed diastereomer **24A**. In *E*-**TS1**, the methyl of *E*-**22** is pseudo equatorial and thus imposes no 1,3 diaxial interactions with the *N*-mesyl. The C2, C3 *syn* stereochemistry is dictated by the (*E*)-geometry of the imine.[19–21] In each case where the imine has isomerized to the (*Z*)-geometry, *E*-**TS2** and *E*-**TS4**, C2-C3 are *anti*.[19]

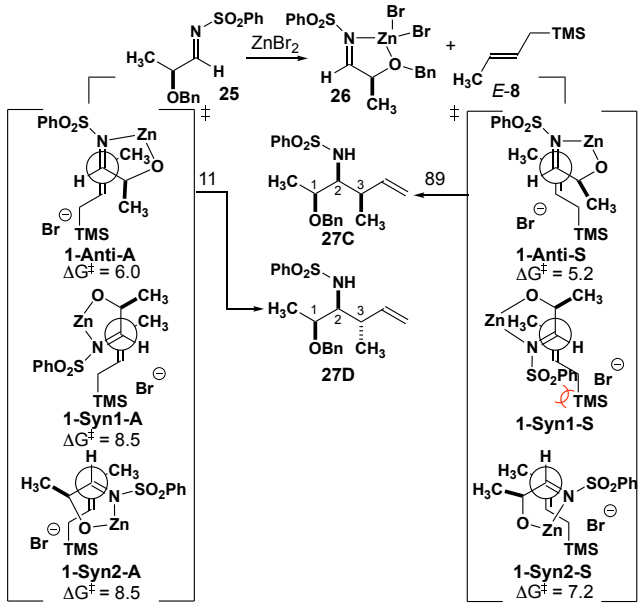
The *anti*-selectivity of C1 and C2 observed in **24A** and **24B** from *E*-**TS1** and *Z*-**TS2** is the result of a Cornforth orientation **25,** with the electronegative α-alkoxy group and the imine *anti*, following the dipole-dipole repulsion model proposed by Cornforth.[22] The stereoelectronically favored,[23] polar Felkin-Ahn conformer **26** induces a non-bonded interaction between the α-alkyl group of the imine and the developing chair transition state.[24] Analysis of the stereochemical elements in the transition state explicitly details the high diastereoselectivity using crotyl BF_3K reagents.

Scheme 2. Computed relative ΔG transition state energies for E and Z-crotyl BF3K and α-alkoxy *N*-mesyl imine in kcal/mol (B3LYP-D3/6-31G(d))



The transition states for the addition of crotyl silanes to **25** were computed as well. The zinc-chelated imine **26** positions the methyl group on the ring to create a more sterically hindered face resulting in high *syn* diastereoselectivity for C1 and C2 (Scheme 3). The C2-C3 *syn* addition is set via three alignments: one antiperiplanar and two synclinal orientations. Alternatively, opposite facial attack of the allyl silane results in the C2-C3 *anti* adduct via 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 experimentally observed major diastereomer **27C**. This transition state arranges the crotyl trimethyl silane *E*-**8** in an antiperiplanar approach to the zinc-chelated imine. The lowest energy transition state for the minor diastereomer, **27D**, 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.

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))[a].



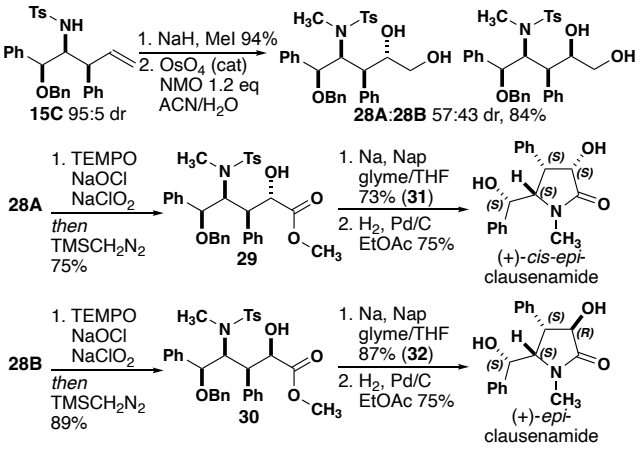
[a]Bromide ligands and benzyloxy substituents are omitted for clarity.

The calculated transition states for the addition silanes **16** and **17** to chelate **26** show a change in the orientation of the prochiral nucleophile leading to opposite selectivity from the acyclic cases.[25]

The diastereoselective addition of allylsilanes to imines provides an efficient route to access clausenamides, a family of isomeric alkaloid natural products. The parent compound, clausenamide, is isolated from the seeds of *Clausena lansium*, an evergreen tree native to southeast Asia. Leaf extracts of this plant have been investigated for a variety of medicinal uses, including the treatment of dementia.[6,26–30]

We selected a route employing acyclic stereocontrol for a divergent synthesis of *epi*- and *cis-epi*-clausenamide, the latter of which has not previously been synthesized. Sulfonamide **15C** (Table 2, entry 10, vide supra) was methylated before dihydroxylating the terminal alkene providing diols **28A** and **28B** in 57:43 diastereomeric ratio. The epimeric alcohols were separated and oxidized to their corresponding methyl esters **29** and **30**. Cleavage of the toluenesulfonyl group and cyclization was achieved in a single step with sodium naphthalide. Finally, hydrogenation of the benzyl protecting group gives (+)-*cis-epi*-clausenamide and (+)-*epi*-clausenamide (Scheme 4).

Scheme 4. Total synthesis of *cis-epi*-clausenamide and *epi*-clausenamide.[a,b]



[a]dr was measured using ^{1}H NMR of the unpurified reaction mixture. [b]The structures of **29** and **32** were established by X-ray crystallography.

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%). In the case of the substituted borane nucleophiles, calculations indicate that the major diastereomer is formed through a Zimmerman Traxler like transition state. The major isomers resulting from substituted allylic silanes emerge from anti-periplanar approach of the acyclic allyl silane nucleophile to the zinc Lewis-acid-chelated imine. The observations of selectivity in the addition of substituted alkene nucleophiles to chiral α-alkoxy imines enabled a short, stereoselective synthesis of two diastereomers of clausenamide.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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**, **19, 20**, **29** and **32**.

The Supporting Information is available free of charge on the ACS Publications website.

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