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Acyclic Stereocontrol in the Additions of Nucleophilic Alkenes to α-Chiral *N*-Sulfonyl Imines

Lucas C. Moore, Anna Lo, Jason S. Fell, Matthew R. Duong, Jose A. Moreno, Barry E. Rich, Martin Bravo, James C. Fettinger, Lucas W. Souza, Marilyn M. Olmstead, Kendall N. Houk,* and Jared T. Shaw*

Abstract: Diastereoselective Lewis acid-mediated additions of nucleophilic alkenes to *N*-sulfonyl imines are reported. The canonical Polar Felkin-Anh model describing additions to carbonyls does not adequately describe analogous additions to *N*-sulfonyl imines. Herein, we describe development of conditions to produce both syn and anti products with high diastereoselectivity and good yields. A stereoelectronic model consistent with experimental outcomes is also proposed.

Electrophilic imines are versatile substrates for the construction of nitrogen-bearing stereogenic centers. *N*-sulfonyl imines are of particular use, and have been used as electrophiles in natural product[1,2] and pharmaceutical target[3,4] syntheses. Acyclic stereocontrol in the additions of nucleophiles to chiral aldehydes and ketones has been extensively studied. Useful levels of predictability have emerged as the Cram chelation,[5,6] polar Felkin-Anh,[7,8] and Cornforth-Evans[9,10] models of carbonyl addition. Similar control has so far been absent for analogous imines.

Research into additions to alpha-chiral imines has been limited to a few notable cases (Figure 1). Chelate-controlled syn-additions to *N*-alkyl and *N*-aryl aldehyde-derived imines are well known. Anti-additions are only consistent achievable with auxiliary control[11,12] or β-chelate effects.[13,14] While the polar Felkin-Anh model is often used to rationalize these anti-selective results, a few examples of syn-selective additions using similar substrates demonstrate that the model is sometimes ineffective in predicting chiral imine addition outcomes.[15–17] Diastereoselective additions to *N*-sulfonyl imines are limited to six reports. Reetz has demonstrated anti-selective additions of Grignard reagents[18] and cyanide[19] to α-amino *N*-tosyl imines. Walsh has reported remarkable syn selectivity in the addition of organozinc reagents[20,21] to α-chloro *N*-sulfonyl imines, and a single occurrence[21] of an anti addition using alkynyllithium. Marek expanded Walsh's additions of organozincs to α-chloro *N*-tosyl imines to produce more stereochemically complex addition products through acyclic stereocontrol.[22]

With these few examples as a backdrop, there has been no systematic study of a-alkoxy imines that would provide similar insight to their extensively-studied carbonyl counterparts. Our interest in these additions was sparked during an investigation into the Brønsted base-mediated formation of δ-lactams from α-chiral *N*-sulfonyl imines and anhydride enolates.[23] We had difficulty rationalizing the syn, or Cram-predicted, major products as little had been reported on analogous additions using soft nucleophiles in the absence of chelatable metals. We set out to develop conditions that would enable complete stereocontrol in the formation of a new stereogenic center from α-chiral *N*-sulfonyl imines and soft nucleophiles alongside a stereoelectronic model that is consistent with our reaction outcomes and provides predictive power.

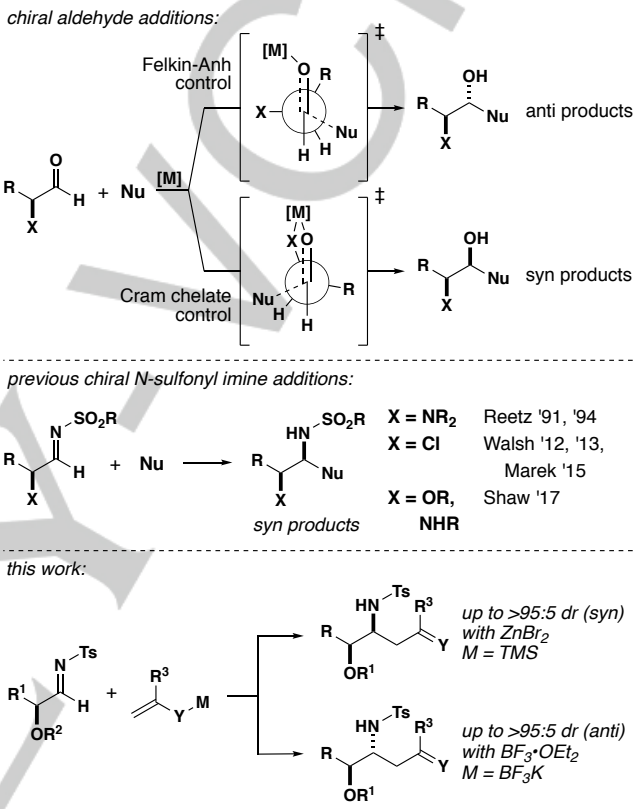

Figure 1. Imine acyclic stereocontrol summary.

Preliminary studies began with an exploration of additions of alkene nucleophiles to lactate-derived *N*-tosyl imine **1a** (Table 1). AllylTMS **3a** reacted with modest syn selectivity even in the presence of BF_3•OEt_2 (entry 2). This result was in stark contrast to similar additions to aldehydes, which give mostly anti products under the same conditions (entry 1).[24] Syn-selective additions to α-chiral imines using BF_3•OEt_2 are isolated to two reports, neither of which propose a mechanistic rationale or overcome this unexpected selectivity.[25,26] To further understand and reverse this selectivity, we manipulated nucleophile strength, reaction temperature, and Lewis acid mediator. Substitution of a stronger nucleophile (allylSnBu_3, entry 4) furnished product with nearly the same selectivity. An attempt to use TMSOTf as an anti selective mediator failed (entry 5). We later found that catalytic TfOH was sufficient to provide the same diastereomeric outcome in a comparatively fast reaction (entry 7) and that a nonnucleophilic base eliminated reactivity (entry 6). It is likely that partial TMSOTf hydrolysis produced the necessary catalytic TfOH. B3LYP calculations show that an *N*-sulfonyl imine chelates a proton much

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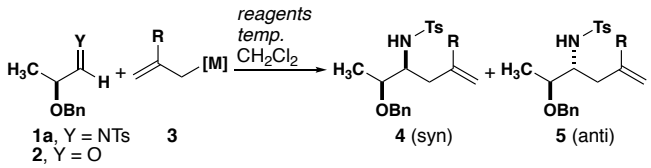
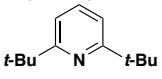
Table 1. Unexpected selectivity in nucleophilic additions to *N*-sulfonyl imines. Relative configuration established by X-ray crystallography (see SI).



entry	Y	[M]	R	reagents	temp	syn:anti
1	O	TMS	H	BF_3•OEt_2	-78 °C	40:60
2	NTs	TMS	H	BF_3•OEt_2	-78 °C to r.t.	70:30
3	NTs	TMS	H	BF_3•OEt_2	23 °C	56:44
4	NTs	$SnBu_3$	H	BF_3•OEt_2	-78 °C to r.t.	76:24
5	NTs	$SnBu_3$	H	TMSOTf	-78 °C to r.t.	85:15
6	NTs	$SnBu_3$	H	TMSOTf + **6**	-78 °C to r.t.	n.r.
7	NTs	$SnBu_3$	H	cat. TfOH	-78 °C	85:15
8	NTs	TMS	H	BF_3•OEt_2	-78 °C	80:20
9	NTs	TMS	H	BF_3•OEt_2	-20 °C	68:32
10	NTs	TMS	H	BF_3•OEt_2	0 °C	63:37
11	NTs	TMS	H	BF_3•OEt_2	25 °C	58:42
12	NTs	TMS	CH_3	BF_3•OEt_2	-20 °C	37:63
13	NTs	TMS	CH_3	BF_3•OEt_2	0 °C	27:73
14	NTs	TMS	CH_3	BF_3•OEt_2	25 °C	20:80
15	NTs	TMS	CH_3	BF_3•OEt_2	40 °C	18:82



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more strongly than the analogous aldehyde, favoring the syn addition (Figure 2).This result is consistent with a proposed proton-chelating intermediate in Mann's three-component reaction of aldehydes, allyltrimethylsilane, and benzyl carbamate.[27] A temperature screen demonstrated an unexpected selectivity inversion. With BF_3•OEt_2, allylTMS added to imine **1a** at –78 °C with high syn selectivity. Increasing the reaction temperature eroded this selectivity. Substitution of a higher-reactivity nucleophile (methallylTMS, **1b**) instead produced anti products at low temperature, and we observed better anti selectivity at higher temperatures. A similar effect has been reported in chiral *N*-silyl imines and was attributed to entropic factors.[28] We suspected that this temperature- and reactivity-dependent selectivity change could be due to a change in the dominant reaction mechanism.

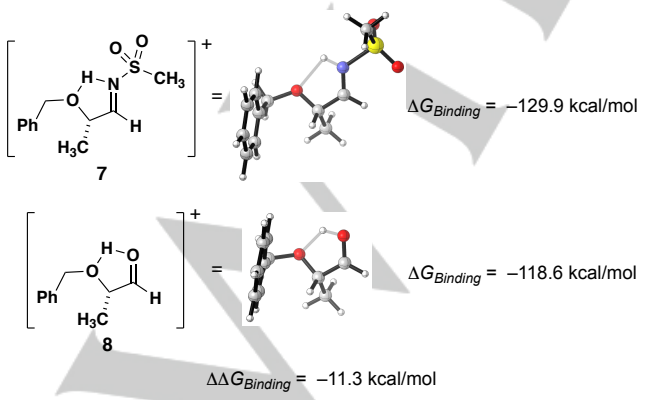
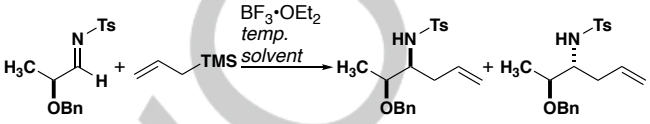


Figure 2. Proton binding energy differential between imine **7** and aldehyde **8**.

Solvent- and Lewis acid screens aided in optimization of anti selectivity. Although we found that catalytic amounts of BF_3•OEt_2 did not furnish full conversion, slightly over a full equivalent did. With optimal conditions (1.1 equivalents) in hand, we conducted a solvent screen (Table 2) and found that $CHCl_3$ facilitated somewhat higher anti selectivity compared to CH_2Cl_2. Finally, we reduced the temperature of the reaction, and we found –20 °C optimal for good levels of conversion and anti selectivity.

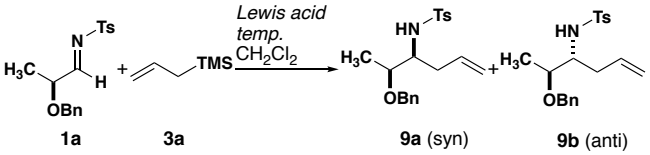
Table 2. Anti-selective condition optimizations.



entry	equiv BF_3•OEt_2	solvent	temp	syn:anti
1	1.1	CH_2Cl_2	23 °C	56:44
2	1.1	toluene	23 °C	38:62
3	1.1	Et_2O	23 °C	65:35
4	1.1	$CHCl_3$	23 °C	39:61
5	1.1	$CHCl_3$	-20 °C	30:70

We anticipated that reactions mediated by chelatable metals would be strongly syn selective. To that end, we screened a range of chelatable metal halides and triflates (Table 3). While several metal triflates enabled poor to modest anti selectivity, many chelatable Lewis acids provided good levels of syn selectivity. Our screen revealed that $ZnBr_2$ afforded a high level of chelation control consistent with Walsh's work with α-chloro *N*-sulfonyl imines.[20] Our calculations predict a highly organized zinc chelate structure that is consistent with the high degree of syn selectivity in analogous additions to both aldehydes and Walsh's α-chloro-*N*-tosyl imines (Figure 3).

Table 3. Chelatable Lewis acid screen.



entry	Lewis acid	temperature	syn:anti
1	$AlCl_3$	0	80:20
2	$AlCl_3$	-78	77:23
3	$Sc(OTf)_3$	0	62:38
4	$ZnBr_2$	-78	95:05
5	$Mg(OTf)_2$	0 to rt	31:69
6	$FeCl_3$	-78	81:19
7	$Ln(OTf)_3$	0 to rt	41:59
8	$La(OTf)_2$	-78	48:52
9	$Cu(OTf)_2$	0	36:64

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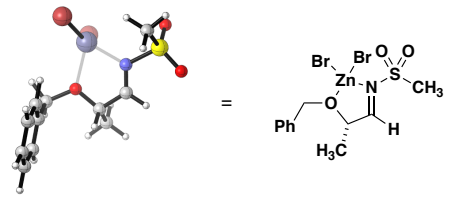


truncated **1a**–$ZnBr_2$ chelate $\Delta G_{Binding}$ = –32.5 kcal/mol

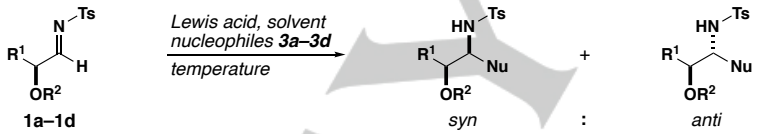
Figure 3. Calculated zinc chelate structure.

Our preliminary studies formed the basis of a more expansive study of *N*-sulfonyl imines and soft nucleophiles (Table 4). Alpha-alkoxy imines **1a**, **1b**, and **1c** reacted with alkenes **3a**, **3b**, and **3c** in the presence of $ZnBr_2$ to afford highly syn-selective products in moderate to good yield. Anti-selective products were similarly available when using BF_3•OEt_2, but selectivity when forming allyl adducts (**9b**, **12b**, and **15b**) was low despite use of optimal solvent and temperature. An attempt to use allylSnBu_3 as an alternate allylating agent did not result in an appreciable increase in selectivity compared to **3a**, so we explored less commonly-used allyl nucleophiles. Inspired by Batey's additions of allyltrifluoroborates to achiral aldehydes[29] and *N*-sulfonyl imines,[30] as well as diastereoselective additions to chiral aldehydes,[31,32] we substituted allylBF_3K for allylTMS. Under standard conditions, with 18-crown-6 added for solubility, allylBF_3K provided anti allyl adducts in good yield and excellent diastereoselectivity compared to allylTMS (Table 5). With $ZnBr_2$, allylBF_3K and imine **1a** did not provide anti selectivity. We surmise that liberated BF_3 outcompetes the sparingly soluble $ZnBr_2$ in the reaction mixture to favor anti products later in the course of the reaction, and so we did not attempt additions with the remaining imines.

In an effort to maximize anti selectivity, we synthesized α-silyloxy imine **1d**. Additions with nucleophiles **3b-d** provided anti products in moderate yield and excellent diastereoselectivity. Initial attempts to form syn products from imine **1d** and alkenes **3a** and **3b** resulted in poor selectivity, and so we did not attempt additions with the remaining nucleophiles.

The stereochemical outcome of these reactions was established by X-ray crystallography and NMR spectroscopy. The relative configurations of products **9a**, **11a**, **13b**, **14a, 16a**, and **17a** were established by X-ray crystallography. The stereochemistry for the remaining products were assigned by *J*-value or chemical correlation to those determined by X-ray crysta-

Table 4. Reaction scope.



conditions	$ZnBr_2$, CH_2Cl_2, –78 °C			BF_3•OEt_2, $CHCl_3$, –20 °C		
nucleophile	TMS (**3a**)	CH_3 TMS (**3b**)	OTMS Ph (**3c**)	BF_3K (**3d**)	CH_3 TMS (**3b**)	OTMS Ph (**3c**)
N Ts, H_3C, H, BnO (**1a**)	**9a**, 73% 95:05 d.r.	**10a**, 63% 94:06 d.r.	**11a**, 91% >95:05 d.r.	**9b**, 86% 11:89 d.r.	**10b**, 70% 10:90 d.r.	**11b**, 72% <05:95 d.r.
N Ts, Ph, H, H_3CO (**1b**)	**12a**, 77% 95:05 d.r.	**13a**, 74% >95:05 d.r.	**14a**, 50% >95:05 d.r.	**12b**, 90% <05:95 d.r.	**13b**, 78% 15:85 d.r.	**14b**, 61% 05:95 d.r.
N Ts, Bn, H, BnO (**1c**)	**15a**, 74% 93:07 d.r.	**16a**, 62% >95:05 d.r.	**17a**, 49% >95:05 d.r.	**15b**, 78% 08:92 d.r.	**16b**, 64% 10:90 d.r.	**17b**, 64% 10:90 d.r.
N Ts, H_3C, H, OTBDPS (**1d**)	**18a** 54:46 d.r.	**19a** 73:27 d.r.	**20a** n.d.	**18b**, 72% <05:95 d.r.	**19b**, 71% <05:95 d.r.	**20b**, 47% <05:95 d.r.

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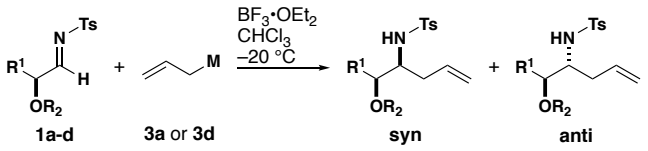
Table 5. Increase of anti selectivity with allylBF$_3$K compared to allylTMS.



entry	imine	product	syn:anti (3a)	yield (3a)	syn:anti (3d)	yield (3d)
1	**1a**	**9**	30:70	60%	11:89	86%
2	**1b**	**12**	26:74	30%	< 05:95	90%
3	**1c**	**15**	49:51	46%	08:92	78%
4	**1d**	**18**	31:69	53%	< 05:95	72%

-llography. Syn allyl adduct **9a** was synthesized in 97% ee from (–)-L-ethyl lactate (99% ee), confirming minimal erosion of enantiomeric purity through imine formation and nucleophilic addition (see supplemental information for complete details).

Our exploration of scope revealed general guidelines for these additions. $ZnBr_2$ can reliably be employed to form syn products using allylsilane and silyl enol ether nucleophiles. Synthetically useful anti-selectivity is possible, but greater care must be taken. Trace water in the reaction mixture may react with the Lewis acid to produce a Brønsted acid, which can be chelated and erode anti selectivity (see Table 1, entry 7). Additionally, more nucleophilic alkenes[33] appear to react with higher selectivity; trifluoroborates are preferable to trimethylsilanes, and more substitution or electron richness also increases selectivity. Silyloxy substitution also increases anti selectivity, possibly by the inactivation of the proton-chelated syn-selective pathway.

With an expanded reaction scope, we sought to determine the origins of the unexpected selectivity in BF_3-mediated reactions. Several reaction pathways and intermediates seemed possible (Figure 4). Although we first considered the Felkin-Anh model with a single BF_3 bound to the imine nitrogen as the active intermediate, we explored other possibilities. Given the optimal amount of BF_3 was slightly over one equivalent, we hypothesized that one equivalent of BF_3 could bind to the imine nitrogen while any excess BF_3 could bind to the alkoxy oxygen, similarly to Reetz's proposed intermediate for BF_3-mediated additions to β-chiral aldehydes.[34] We also hypothesized a disproportionation mechanism wherein a BF_3 bound to an imine nitrogen could lose a fluoride to another BF_3, forming BF_4^- anion and chelated BF_2. While not seen in aldehydes due to their lower Lewis basicity relative to imines, similar BF_2 chelates have been observed and isolated.[35,36] Furthermore, a similar process has been implicated in the exceptional chelate-based selectivity observed in Evans's additions to aldehydes mediated by $Al(CH_3)_2Cl$.[37]

To investigate the mechanism and stereoselectivity we have used the B3LYP[38,39] density functional, which has previously been shown to give reasonably accurate free energies and stereoselectivities for additions of this nature.[40,41] The 6-31G(d) basis set was used for geometry optimizations, and for heavy elements (Zn and Br) the LANL2DZ pseudopotential was utilized.[42] The *p*-tolSO_2 group has been truncated to a H_3CSO_2 group for computational fidelity. We have performed a conformational analysis of the initial imine reactants, BF_3-bound intermediates, and respective *syn*/*anti* transition structures, and herein we report the lowest energy conformers for each species.

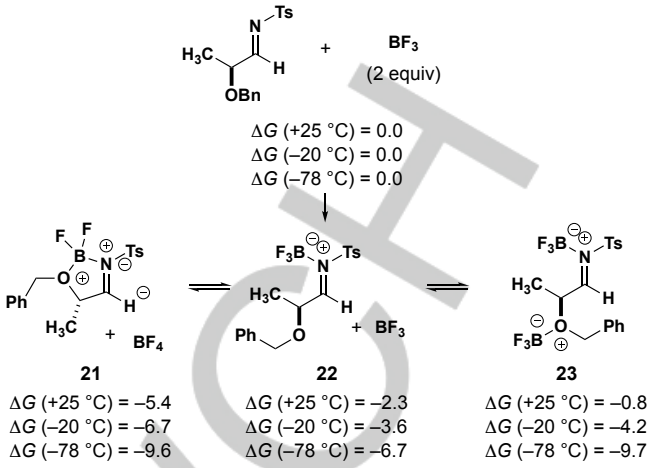


Figure 4. Energy and distribution of intermediates. Energy in kcal/mol relative to unbound imine.

We have calculated the free energy barriers from separated reactants and have included standard state solvation corrections.[43] See the Supporting Information for full computational methods.

We first examined the absolute free energies of the three proposed reactive intermediates. At ambient temperature we predict that the most common species is the BF_2 chelate intermediate **21**, and as the temperature shifts to cryogenic conditions, both the double BF_3 (**23**) and BF_2 chelate (**21**) intermediates are equally present. Given relatively low thermodynamic constraints at –20 and –78 °C, we explored the kinetic barriers from intermediates **21** and **23** and the *syn* or *anti* products that result. Using B3LYP, we calculated six transition structures (TS) that correspond to *anti* and *syn* additions to these three intermediates. Our earlier observation of temperature- and reactivity-dependent selectivity inversion (Table 1) prompted us to explore the effect of temperature on these calculated transition states.

A computational exploration of reasonable reactive intermediates and transition states revealed two competing pathways (Figure 5). We found that TS's arising from BF_2 chelate intermediate **21** favored *syn* additions at cryogenic temperatures (–20 and –78 °C), while the doubly bound BF_3 complex **23** favored *anti* additions at all temperatures. TS's that form from the single BF_3 intermediate **22** exclusively favor *anti* addition at all temperatures. The lowest energy *anti*- and *syn*-TS originate from intermediates **21** and **23** at all calculated temperatures, and TS's from intermediate **22** are generally higher in energy by up to 12 kcal mol^{-1} when compared to analogous TS from the other intermediates. These results indicate that mono-BF_3-coordinated intermediate **22** has a minor role in the mechanism due to being less favorable formation energy and leading to higher energy TS. At cryogenic temperatures, *syn*-selective **TS-1** from **21** is 2.6 kcal mol^{-1} lower in energy than *anti*-selective **TS-2** from **23**. As the temperature is increased to –20 °C, the free energy difference between these two TS narrows to 0.6 kcal mol^{-1} in favor of *syn* addition. At ambient temperatures, the *anti*-selective **TS-2** from **23** is 3.2 kcal mol^{-1} lower in energy than the lowest energy *syn*-selective TS which arises from **21**.

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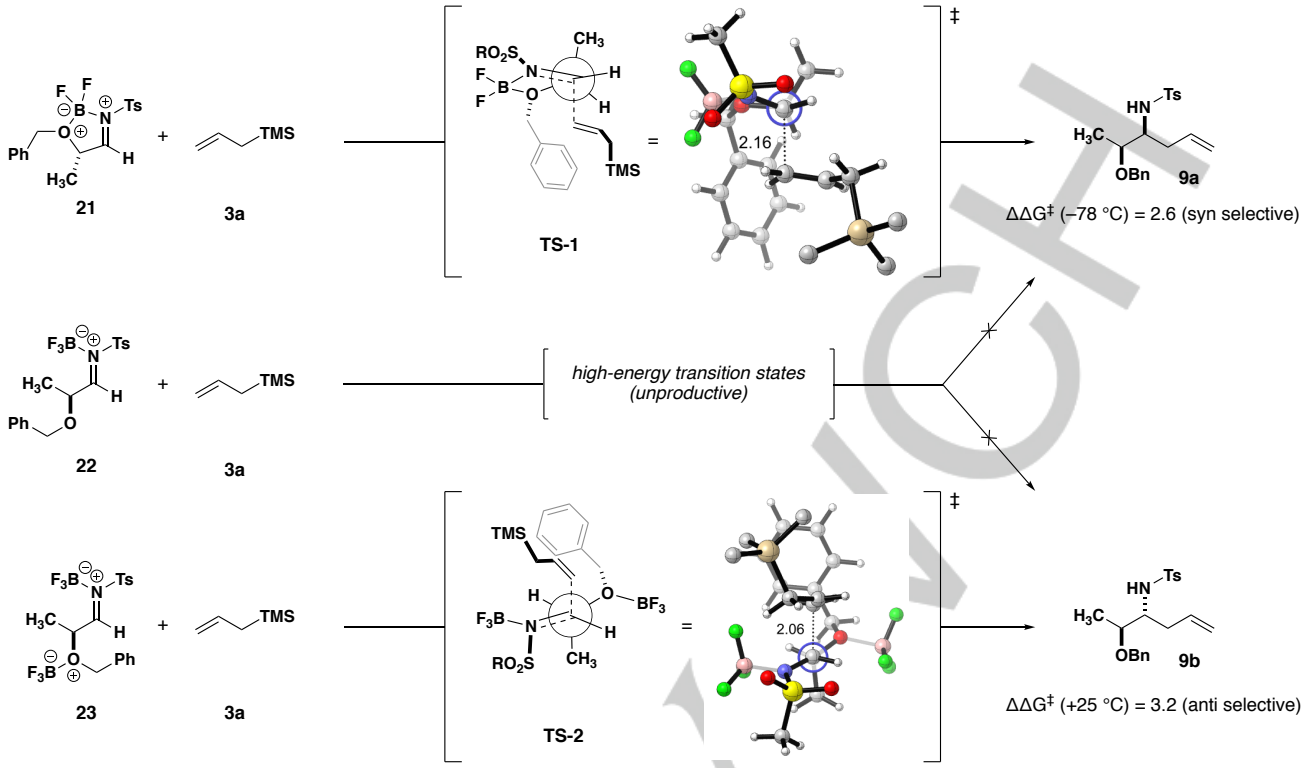

entry	TS	ΔG‡ (–78 °C)	ΔG‡ (–20 °C)	ΔG‡ (+25 °C)
1	**TS-1**	18.7	19.7	23.5
2	**TS-2**	21.3	20.3	20.3

Figure 5. Computed reaction kinetics at cryogenic and ambient temperatures. *p*-tol truncated to CH_3 to reduce calculation complexity. Energies in kcal mol^{-1} relative to separated imine **1a**, **3a**, and BF_3. Methyl hydrogens on TMS hidden for clarity.

These calculated transition state energies correlate well with observed reaction outcomes in CH_2Cl_2. At low temperatures, the reaction mainly proceeds through BF_2 chelate intermediate **21** and results in syn selectivity. At higher temperatures, the reaction proceeds through double BF_3 intermediate **23** and results in anti selectivity. To our surprise, the Felkin-Anh-like pathway arising from intermediate **22** is unproductive in the reaction. In fact, the transition states leading to major products appear to correlate to those proposed in the Cornforth-Evans model, with the imine and α-substituents arranged as to minimize the dipole of the intermediate.[9,10] Guided by these computational results, we hypothesized that additional BF_3•OEt_2 would not have a detrimental effect on the diastereoselectivity of the reaction, as any potential BF_2 chelate intermediate would be in equilibrium with the doubly-bound BF_3 intermediate. To that end, we reattempted several somewhat low-yielding reactions with 2 equivalents of BF_3•OEt_2 and found that yields increased while diastereoselectivity was unchanged.

The reactivity of doubly-BF_3-bound imine **21** and BF_2 chelate **23** hints at implications beyond the direct scope of this investigation. The syn-selective nucleophilic additions to other chiral imines using BF_3•OEt_2 at low temperature may have been due to a chelated BF_2 intermediate similar to **23**.[25,26] Additionally, although anti-selective additions to other chiral imines are reported to be consistent with predictions made using the Polar Felkin-Anh model, our findings that the monocoordinated imine-BF_3 adduct **22** is unreactive suggest that the model does not fully describe the underlying reactivity of systems other than additions to chiral carbonyl compounds. Other reactions that include substrates with multiple strong Lewis basic sites may also form similar BF_2 chelates that could lead to unexpected reactivity. Further investigation into the reactions of BF_3 and its Lewis base adducts are required.

In conclusion, we have demonstrated a practical method in achieving acyclic stereocontrol in the addition of nucleophilic alkenes to α-chiral *N*-sulfonyl imines. We developed a mechanistic rationale for the diastereoselectivity that is comparable to additions to analogous chiral carbonyl compounds. While syn-selective reactions can be favored using Cram chelation control, anti-selective reactions are not as straightforward. Computational evidence revealed an unexpected mode of reactivity compared to the commonly-understood monocoordinating nature of BF_3 as a Lewis acid. These considerations were crucial in anti-selective reaction optimization. Because the Polar Felkin-Anh model does not account for these deviations in reactivity, care must be taken in in its application to systems other than additions to chiral carbonyl compounds. Furthermore, nucleophilic additions using BF_3 as a Lewis acid mediator that produce unexpected diastereoselectivity should be reevaluated. Further applications of these methods to construct highly stereochemically complex products are under development.

Conflict of Interest

The authors declare no conflict of interest.

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Keywords: ab initio calculations • allylation • diastereoselectivity • Lewis acids • reaction mechanism

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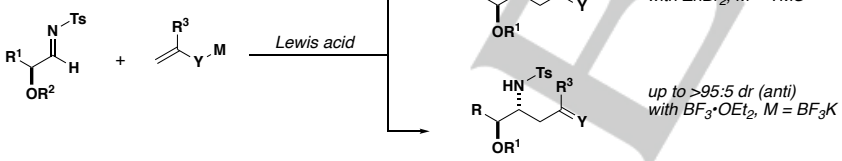

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