Recent Reviews:

Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600–3740.

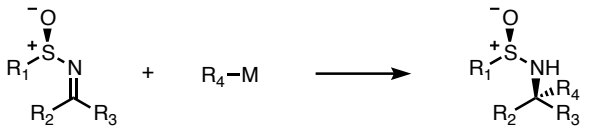
Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162–1186.

Zhou, P.; Chen. B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030.

- Davis first reported the synthesis of racemic *p*-toluenesulfinimines in 1974. Later, Davis demonstrated the 1,2-addition of organometallic reagents to enantioenriched *p*-toluenesulfinimines en route to enantioenriched amino acid derivatives and aziridines.

- In 1997, Ellman reported the enantioselective synthesis and application of *tert*-butanesulfinamide for the preparation of enantioenriched amines.

Generalized Reaction Scheme:

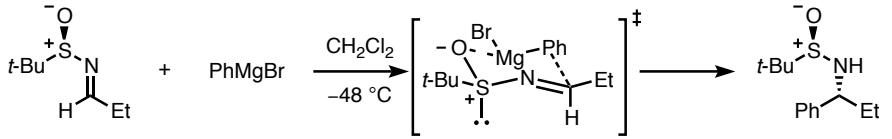


Typically:

- R_1 = *p*-tolyl (Davis), *tert*-butyl (Ellman).
- R_4 = alkyl, aryl, heteroaryl
- M = Li, MgBr
- R_2, R_3 = H, alkyl, aryl, heteroaryl

Mechanism:

- Coordination between oxygen and the metal center in a chair-like transition state has been invoked to explain the observed sense of stereochemical induction as seen in the example below:



100%, 92% de

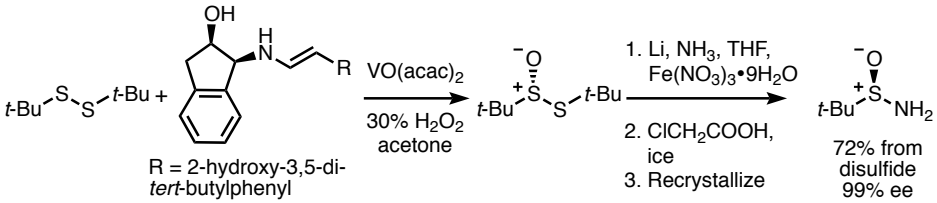
Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.

***tert*-Butylsulfinamide:**

- The advantages of *tert*-butylsulfinamide over related arenesulfinamides include ease of substrate synthesis, enhanced stereoselectivity, and reduction in side-reactions (e.g., addition at sulfur).

- Both enantiomers are readily available at reasonable prices (<$1/g in bulk quantities) and can be synthesized catalytically on 90-g scale in the laboratory in excellent yield and enantiopurity.

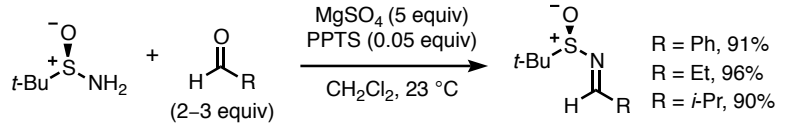
Sulfinimine Synthesis:



R = 2-hydroxy-3,5-di-*tert*-butylphenyl

- Condensation of *tert*-butylsulfinamide with a significant excess of an aldehyde in the presence of $MgSO_4$ and *p*-toluenesulfonate, as originaly reported, affords the corresponding *tert*-butylsulfinimine with no racemization at sulfur.

Weix, D. J.; Ellman, J. A. *Org. Synth.* **2005**, *82*, 157–165.



Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.

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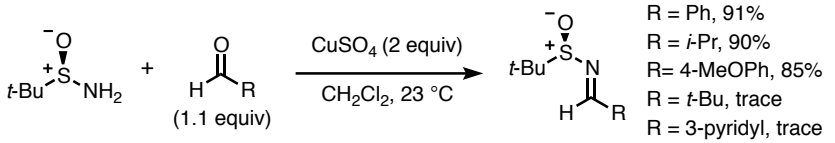
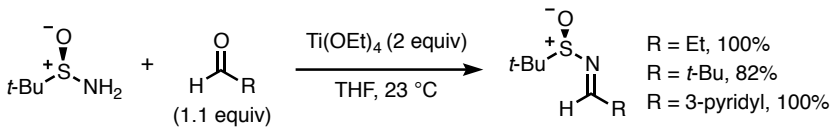
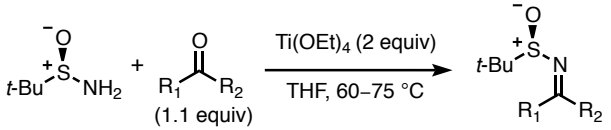
- The use of $CuSO_4$ as a Lewis acidic promoter gives a high yield of the *tert*-butylsulfinimine without the need for a large excess of aldehyde, and $Ti(OEt)_4$ leads to smooth condensation even in the case of highly recalcitrant aldehydes.





Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.

Ketimine Synthesis: The more challenging task of condensation of *tert*-butylsulfinamide with a ketone can be achieved using $Ti(OEt)_4$ at elevated temperatures. When R_1 and R_2 are similar in size, an equilibrating mixture of isomers is formed.



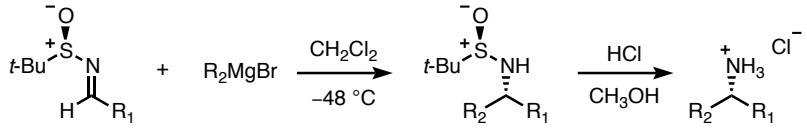
R^1 = Me, R^2 = Ph, 100%, single isomer
R^1 = *n*-Bu, R^2 = *i*-Pr, 77%, single isomer
R^1 = Me, R^2 = *t*-Bu, 82%, single isomer
R^1 = Me, R^2 = *i*-Bu, 88%, 6 : 1 E/Z
R^1 = Me, R^2 = *n*-Bu, 77%, 5 : 1 E/Z

- While *tert*-butanesulfinyl aldimines are generally robust, *tert*-butanesulfinyl ketimines are more sensitive to moisture. Though they can be handled in air and quickly chromatographed with hexanes/Et_2O as eluent, they should be stored dry at –5 °C.

Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.

Synthesis of enantioenriched primary amines:

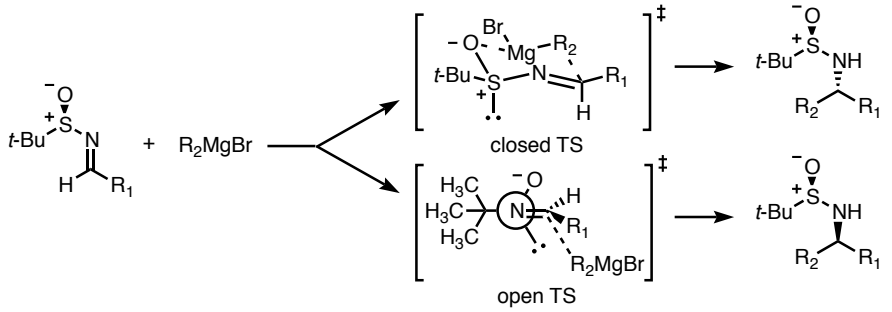
- Addition of Grignard reagents to enantioenriched *tert*-butanesulfinyl aldimines affords the corresponding sulfinamides typically in high yield and with high diastereoselectivity; subsequent HCl-promoted solvolysis in methanol and precipitation with Et_2O affords the corresponding primary amine•HCl salts.



R^1	R^2	sulfinamide yield (%)	dr	amine•HCl yield (%)
Et	CH_3	96	93:7	97
Et	Ph	100	96:4	90
i-Pr	Et	100	97:3	93 (85)[a]
i-Pr	Ph	98	89:11	91 (76)[a]
Ph	Et	98	92:8	94
Ph	H_2CCH	79	94:6	93
Bn	CH_3	89	95:5	95
Bn	Ph	81	95:5	99
4-MeOPh	Et	88	99:1	100

[a]isolated yield of enantiomerically pure material after a single recrystallization.

- The use of CH_2Cl_2 as solvent was found to be optimal, while the use of ethereal solvents such as Et_2O or THF gave reduced stereoselectivity, presumably due to binding to the magnesium ion to promote the open transition state as a competitive pathway.



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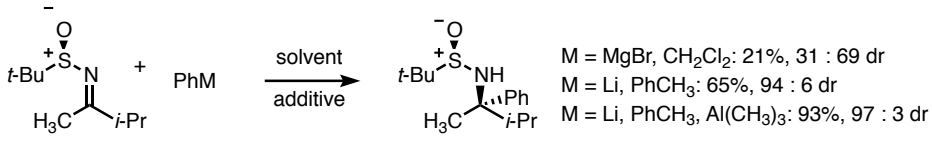
Use of Ketimine Electrophiles:

- While addition of phenyl Grignard to a ketimine substate in the example below proceeded with low stereoselectivity and with a reversed sense of addition, the use of PhLi in toluene gave excellent stereoselectivity.

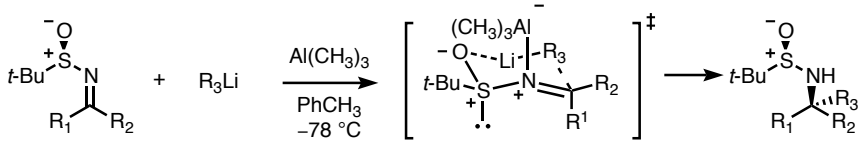
- Of several Lewis acid additives examined, $Al(CH_3)_3$ was found to provide optimal yield and dr:



M = MgBr, CH_2Cl_2: 21%, 31 : 69 dr
M = Li, $PhCH_3$: 65%, 94 : 6 dr
M = Li, $PhCH_3$, $Al(CH_3)_3$: 93%, 97 : 3 dr

- Optimized conditions were found to work well for a variety of ketimine and organolithium substrates.

- In the case of ketimines that were mixtures of geometric isomers, the product dr was found to exceed the substrate dr. It is proposed that the less stable, and less reactive, double bond stereoisomer is converted to the major isomer under the reaction conditions.



R^1	R^2	R^3	yield (%)	dr
CH_3	*i*-Pr	*n*-Bu	61	99:1
n-Bu	*i*-Pr	Ph	82	91:9
CH_3[a]	*n*-Bu	Ph	93	89:11
CH_3[b]	*i*-Bu	Ph	62	85:15
CH_3	2-Npth	Ph	62	99:1

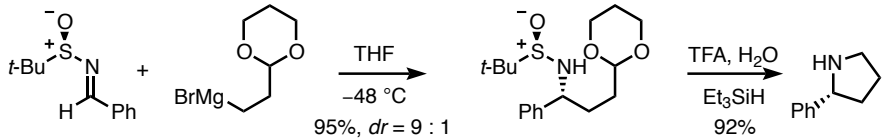
[a]This imine was used as a 5:1 mixture of double bond diastereomers.
[b]This imine was used as a 6:1 mixture of double bond diastereomers.

Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.
Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron*, **1999**, *55*, 8883–8904.

Additions to *tert*-Butylsulfinimines via Open Transition States:

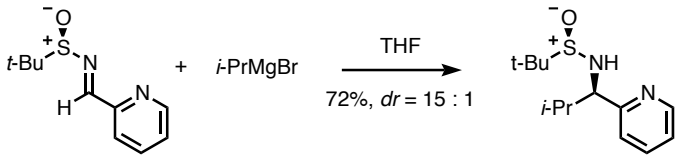
- The use of weakly coordinating metal counterions such as lithium, certain Lewis acid or base additives, or the presence of Lewis basic functional groups within the sulfinimine or organometallic reactant can disrupt chelation control, and can lead predominantly to products consistent with an open transition state.

- The Lewis basic acetal group promotes open transition states in the transformation below, part of a route to enantioenriched 2-substituted pyrrolidines.



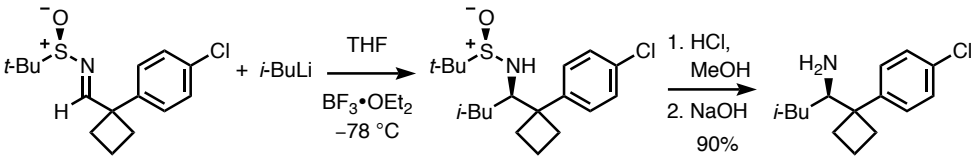
Brinner, K. M.; Ellman, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2109–2113.

- Coordinating groups within the sulfinimine substrate can also favor an open transition state.



Kuduk, S. D.; DiPardo, R. M.; Chang, R. K.; Ng, C.; Bock, M. G. *Tetrahedron Lett.* **2004**, *45*, 6641–6643.

- Lewis acid or base (TMEDA) additives favored an open transition state in this example from a synthesis of the CNS inhibitor (*R*)-DDMS.

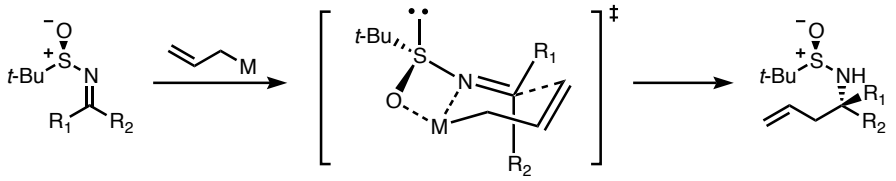


Han, Z.; Krishnamurthy, D.; Pflum, D.; Grover, P.; Wald, S. A.; Senanayake, C. H. *Org. Lett.* **2002**, *4*, 4025–4028.

Jonathan William Medley

Diastereoselective Allylations of Enantioenriched Sulfinimines:

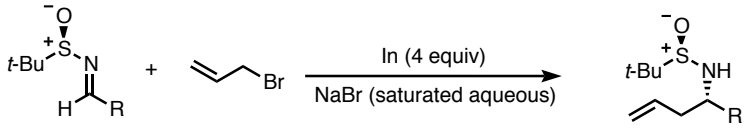
- The proposed transition state for allylation involves coordination of both imino nitrogen and sulfinyl oxygen to metal.
- Commonly used allylmetals for additions to sulfinyl imines include Mg, In, and Zn.



R_1	R_2	M	yield	dr
CH_3	Ph	MgBr	85%	>99:1
CH_3	*i*-Pr	MgBr	93%	>95:5
H	C_9H_{19}	MgBr	77%	91:9

Cogan, D. A.; Liu, G.; Ellman, J. *Tetrahedron* **1999**, *55*, 8883.
Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353.

Allylation of Imines in Aqueous Solution



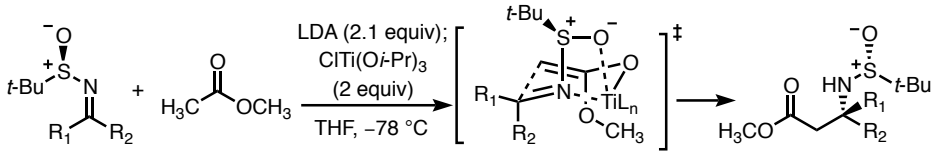
• The allylindium species, generated *in situ,* is an effective nucleophile in aqueous solution.

R	yield	dr
3,4-$(MeO)_2$-Ph	81%	98:2
3-furyl	90%	95:5
2-pyridyl	73%	95:5
i-Pr	82%	96:4

Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259.

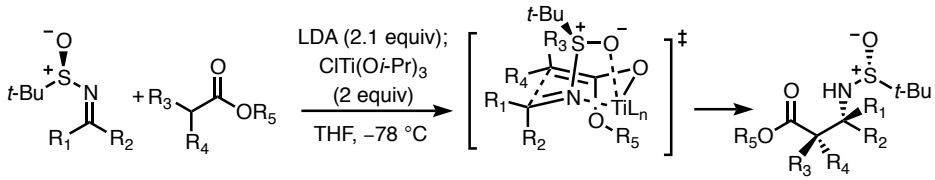
Additions of Enolates to *tert*-Butanesulfinimines:

- The addition of ester enolates to *tert*-butanesulfinimines provides ready access to enantioenriched β-amino acid derivatives.
- Optimized conditions involve *in situ* generation of the titanium enolate with an excess of chlorotitanium triisopropoxide, followed by addition of the sulfinimine.
- The stereochemical outcome can be rationalized by invoking a Zimmerman–Traxler transition state with chelation of the sulfinimine to titanium.



R^1	R^2	yield (%)	dr
i-Pr	H	85	98 : 2
3-pyr	H	70	95 : 5
i-Pr	CH_3	85	99 : 1
Ph	CH_3	89	98 : 2

- The use of α-subsituted esters as enolate precursors allows for the stereoselective synthesis of tri- and even tetrasubstituted β-amino acid derivatives.

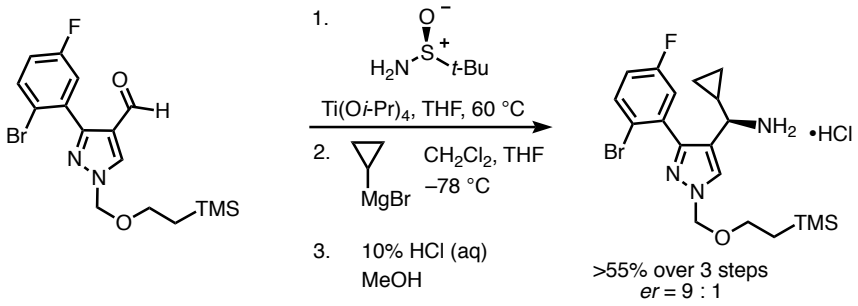


R^1	R^2	R^3	R^4	R^5	yield (%)	dr
H	*i*-Bu	H	CH_3	CH_3	85	96 : 4 : 0 : 0
H	CH_3	H	PMB	PMB	70	89 : 1 : 0 : 0
CH_3	Ph	CH_3	CH_3	CH_3	86	99 : 1
CH_3	Ph	$-(CH_2)_5-$		CH_3	65	99 : 1

Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12–13.
Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819–7832.

Jonathan William Medley, Daniel Schmitt

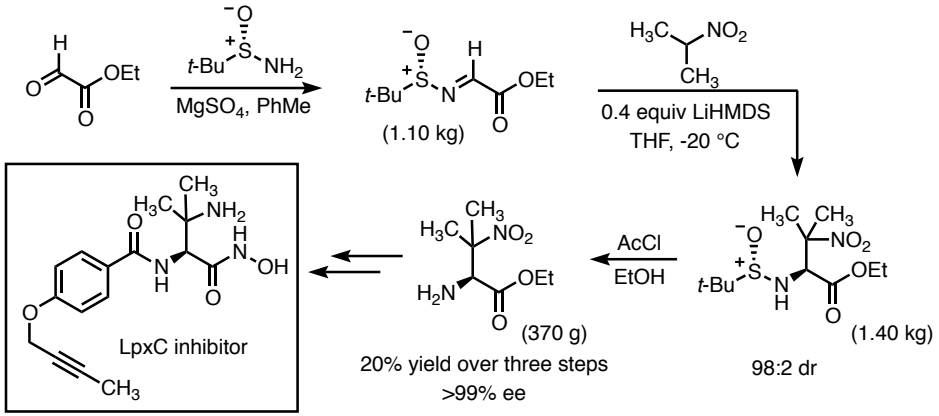
Additions to Enantioenriched Sulfinimines in the Pharmaceutical Industry:



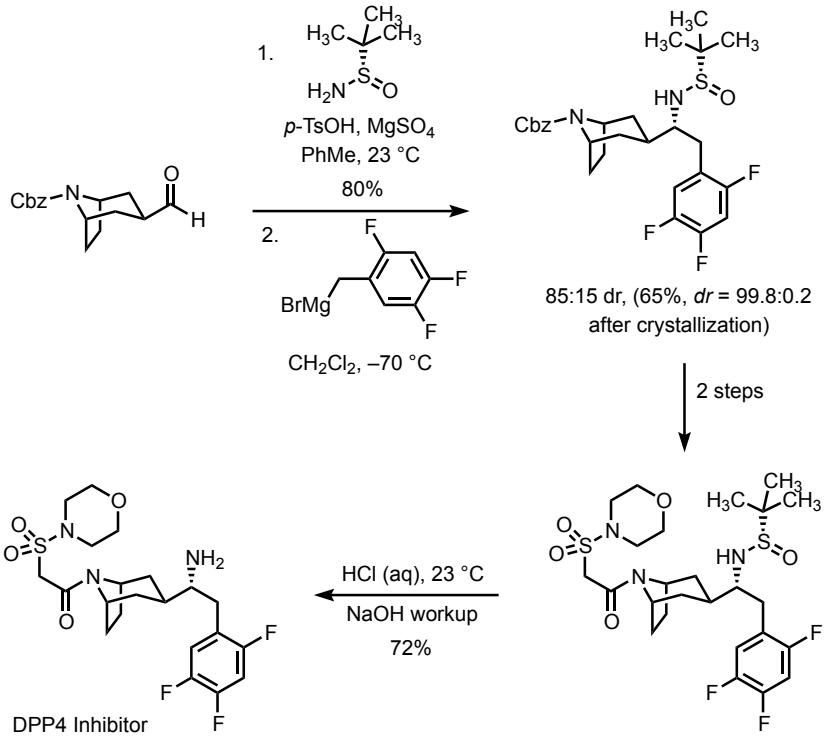
- An addition to a *tert*-butanesulfinimine was used in the synthesis of a γ-secretase inhibitor for the treatment of Alzheimer's Disease.
- The stereochemistry of Grignard addition is consistent with the standard chelated chair-like transition state.
- No chromatography was necessary over 3 steps.

Probst, G. *et al. J. Med. Chem.* **2013**, *56*, 5261–5274.

- The synthesis of an LpxC inhibitor for the treatment of bacterial infectious diseases employed a nitronate anion as nucleophile.
- The anion resulting from nitronate addition to the imine is sufficiently basic to deprotonate 2-nitropropane. Therefore, only catalytic LiHMDS is necessary.
- The stereochemical result is consistent with an open transition state.

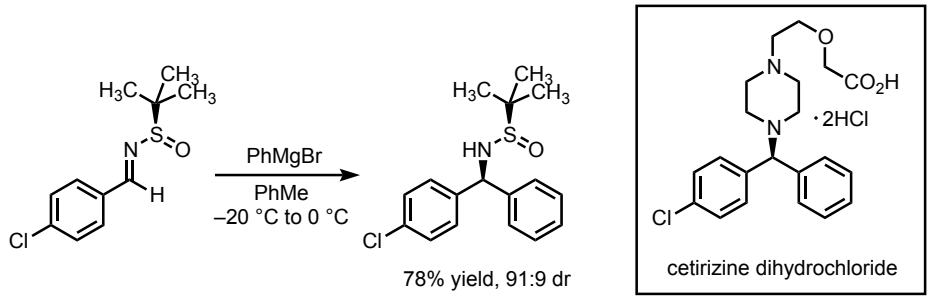


Fei, Z.; Kong, W.; Wang, H.; Peng, J.; Sun, F.; Yin, Y.; Bajwa, J.; Jiang, X. *Org. Process Res. Dev.* **2012**, *16*, 1436-1441.



- Synthesis of a DPP4 inhibitor for the treatment of diabetes.
- The imine addition proceeded with lower diastereoselectivity in ethereal solvents.

J. Org. Chem. **2008**, *73*, 9016–9021.



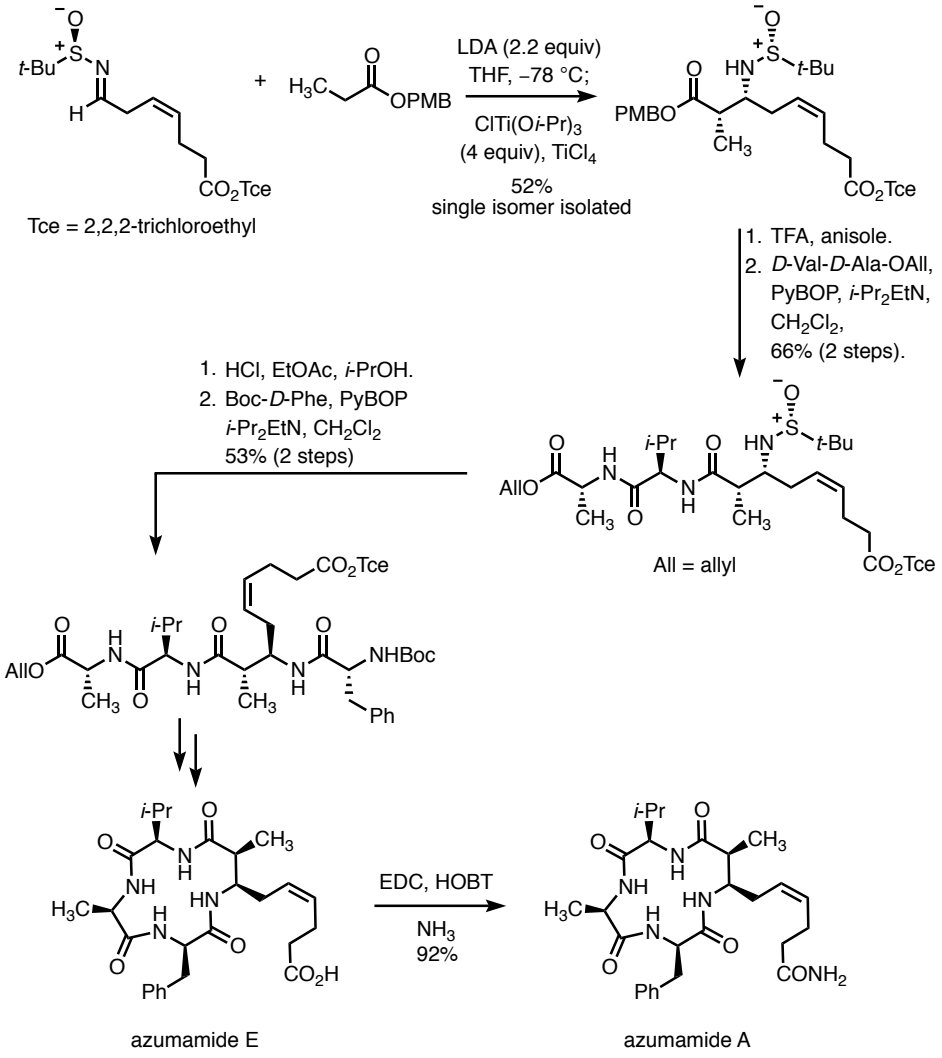
- Synthesis of an antihistamine sold under the brand name Xyzal. The racemic form of this compound is marketed as Zyrtec.
- A variety of Lewis acid additives were screened, but provided lower diastereoselectivity.

Pflum, D. A.; Krishnamurthy, D.; Han, Z.; Wald, S.; Senanayake, C. H. *Tetrahedron Lett.* **2002**, *43*, 923.

Jonathan William Medley, Daniel Schmitt

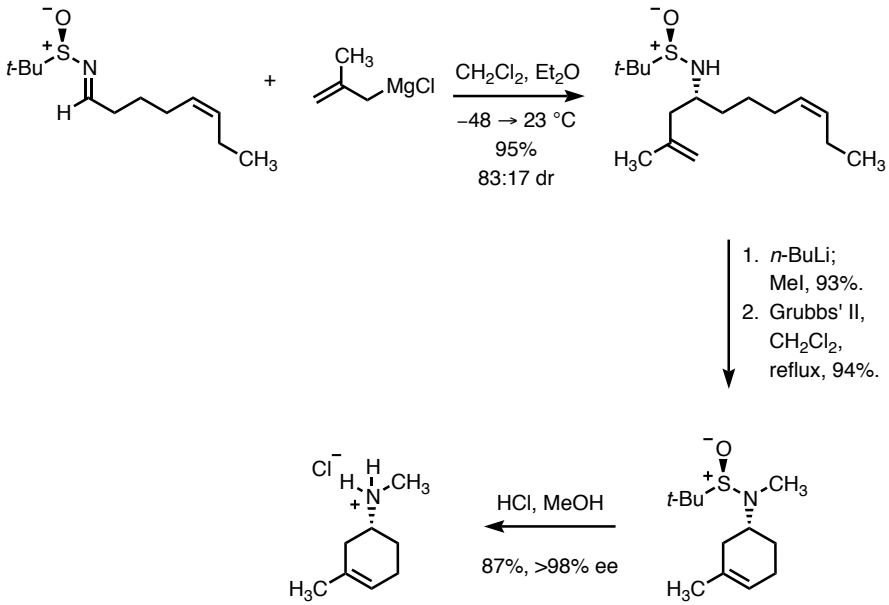
Examples in Syntheses of Natural Products:

- Ganesan and co-workers employed the addition of a titanium enolate to a sulfinimine in their total syntheses of the marine natural products azumamides A and E.



Wen, S.; Carey, K. L.; Nakao, Y.; Fusetani, N.; Packham, G.; Ganesan, A. *Org. Lett.* **2007**, *9*, 1105–1108.

- In their formal total synthesis of the natural product (–)-aphanorphine, Grainger and Welsh employed an asymmetric methallylation of an enantioenriched *tert*-butane sulfinimine.
- Although the methallylation proceeded with only moderate stereoselectivity to afford an inseparable mixture of diastereomers, recrystallization of the amine•HCl salt following ring-closing metathesis, *N*-methylation, and desulfinylation provided material with excellenet enantiopurity.



Grainger, R. S.; Welsh, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5377–5380.

Daniel Schmitt, Jonathan William Medley