ALKENYL IMINIUM ION IN DIELS-ALDER REACTION: SYNTHESIS OF HIGHLY SUBSTITUTED *N*-HETEROCYCLES

by

Nihar R. Sarkar

MS, Indian Institute of Technology, 2001

MS, North Dakota State University, 2004

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FACULTY OF ARTS AND SCIENCES

This dissertation was presented

by

Nihar R. Sarkar

It was defended on

December 7th, 2009

and approved by

Craig S. Wilcox, Professor, Department of Chemistry

Paul E. Floreancig, Associate Professor, Department of Chemistry

Alexander S. Doemling, Associate Professor, Department of Pharmaceutical Sciences

Dissertation Advisor: Scott G. Nelson, Professor, Department of Chemistry

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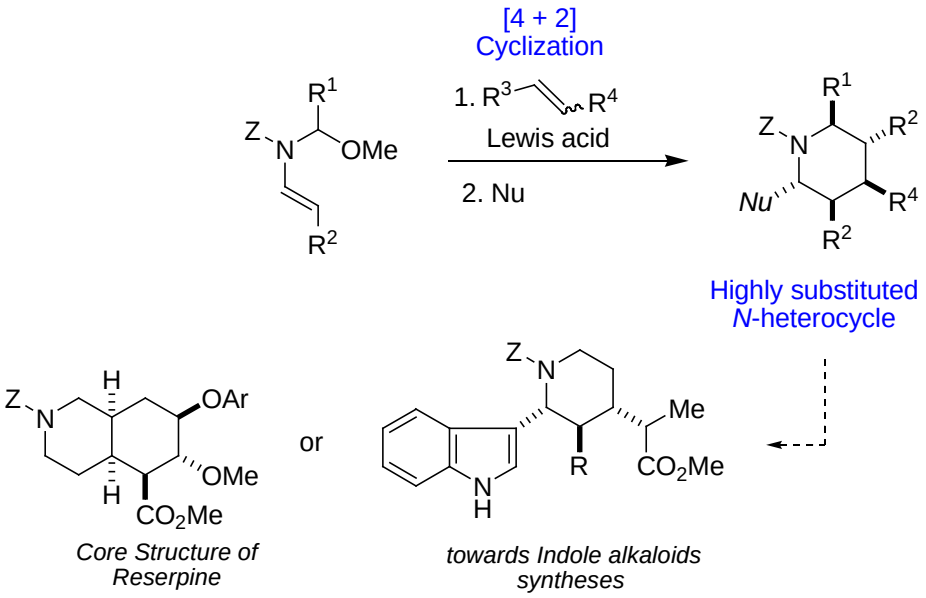
Nihar R. Sarkar, PhD

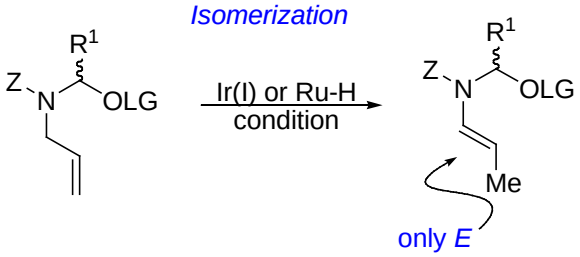
University of Pittsburgh, 2009



Heterocyclic structures are critical components of an extensive collection of chemotherapeutic agents, either in service or under development, for treating numerous human illnesses. As a result, reaction technologies for heterocycle construction, in the context of both target- and diversity-oriented synthesis, enjoy a particularly prominent role in medicinal chemistry. Amongst all the C-C bond forming reactions, the classic Diels-Alder cycloaddition remains one of the most powerful transformations in organic chemistry especially for the formation of heterocyclic structures. Herein, we report a new methodology based on inverse electron demand

Diels-Alder reaction utilizing reactive "*N*-alkenyl iminium ion" and a suitable dienophile for the stereoselective synthesis of substituted piperidine derivatives. In presence of a suitable Lewis acid, the "*N*-alkenyl iminium ion" is generated from the respective enamine-aminal derivative *in situ* and undergoes Diels-Alder reaction with a dienophile producing a highly substituted *N*-heterocycle (piperidine derivative) in one step.

An efficient transition metal catalyzed isomerization technique for the synthesis of a new enamine-aminal synthon from respective *N*-allylamine derivatives has been developed. Cationic Ir-(COE) complex, a potential catalyst for ICR chemistry, was used for the isomerization of tosyl protected *N*-allylamine derivatives to synthesize *N*-tosyl-alkenyl iminium ion precursor in high geometrical selectivity and quantitative yield whereas carbamate (or amide) protected *N*-allylamine derivatives were isomerized with good *E*/*Z* ratio using Grubbs II.



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LIST OF ABBREVIATIONS

BINOL	1,1′-bi-2-napthol
Boc	*tert*-butyloxycarbonyl
Bz	benzoyl
Cbz	carbobenzyloxy
COD	1,5-cyclooctodiene
COE	cyclooctene
DIBAL-H	di-*iso*-butylaluminum hydride
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
ICR	isomerization Claisen rearrangement
Moc	methoxycarbonyl
TBS	*tert*-butyldimethylsilyl
Th	thienyl (thiphene-2-sulfonyl)

THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl

PREFACE

I had a wonderful experience and very memorable time during these years and I am very thankful to everyone.

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1.0 DEVELOPMENT OF DIASTEREOSELECTIVE INTERMOLECULAR HETERO DIELS-ALDER REACTION: SYNTHESIS OF *N*-HETEROCYCLES

1.1 DIASTEREOSELECTIVE SYNTHESIS OF PIPERIDINES

1.1.1 Hetero Diels-Alder Reaction in Synthesis of Substituted Piperidines

Nitrogen-containing heterocycles (*N*-heterocycles) form an important part of the chemotherapeutic world.[1] Specifically, piperidines are found as common building blocks in large numbers of naturally/unnaturally occurring biologically active molecule[2] making them attractive targets for synthesis. The hetero-Diels-Alder cycloaddition[3] reaction is one of the most useful transformations for the synthesis of piperidines as it allows formation of the cyclic structures with high degrees of substitutions in a highly stereoselective fashion. For the synthesis of

[1] For selected reviews, see: (a) Sondhi, S. M.; Singhal, N.; Johar, M.; Reddy, B. S.; Lown, J. W. *Curr. Med. Chem.* **2002**, *9*, 1045-1074. (b) Newton, R. F. *PharmaChem* **2003**, *2*, 44-45. (c) Whitehouse, M. W. *Curr. Med. Chem.* **2005**, *12*, 2931-2942.

[2] For recent reviews, see: (a) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (b) Daly, J. W. *J. Med. Chem.* **2003**, *46*, 445. (c) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (d) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1349. (e) Escolano, C.; Amat, M.; Bosch, J. *Chem. Eur. J*. **2006**, *12*, 8198. (f) Sun, Z.;Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300-9301.

[3] For comprehensive reviews on asymmetric DA reaction see (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650-1667. (b) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668-1698. For an excellent introduction to heterodienophiles, see: (c) S. M. Weinreb in Comprehensive Organic Synthesis, Vol. 5 (Ed.: B. M. Trost, I. Flemming, L. A. Paquette), Pergamon, Oxford, 1991, chap. 4.2, pp. 401-449. For an overview of heterodiene Diels-Alder partners, see: (d) D. L. Boger in Comprehensive Organic Synthesis, Vol. 5 (Eds.: B. M. Trost, I. Flemming, L. A. Paquette), Pergamon, Oxford, 1991, chap. 4.3, pp. 451-512. For related overviews, see (e) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; Chapter 1. (f) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781-793.

piperidines, various possible combinations between dienes and dienophiles in hetero-Diels-Alder reactions are listed in Figure 1, showing both neutral (A, B and C) and ionic models (D) where either diene (A, B and D) or dienophile (C) is bearing the hetero atom. The resulting cycloadduct (piperidine) may be obtained from electron rich dienes (HOMO) and electron deficient dienophiles (LUMO) or *vice versa* (also known as Inverse-Electron-Demand cycloaddition).

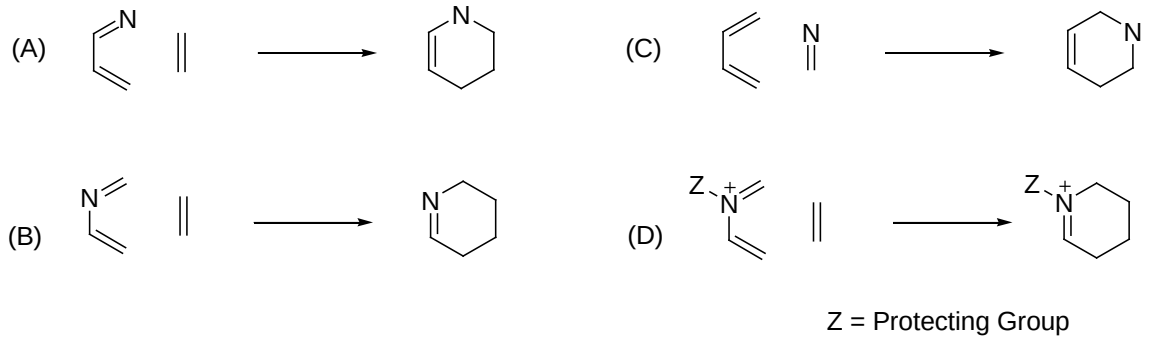
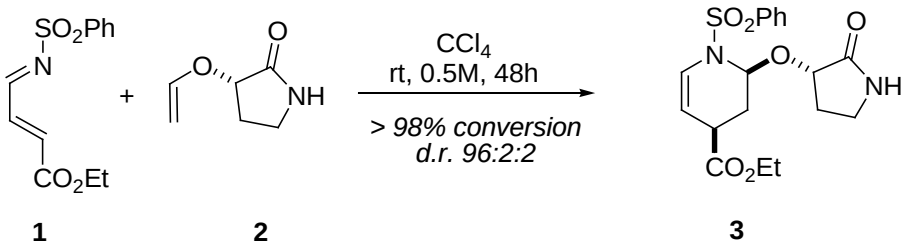


Figure 1. Various models for hetro Diels-Alder reaction

The model A is the most prevalent in the literature for the synthesis of piperidine derivatives. A few examples of asymmetric synthesis of piperidines utilizing model A are discussed. Boger and co-workers popularized *N*-sulfonyl-1-aza-1,3-dienes (**1)** as the 4π component in diastereoselective hetero-Diels-Alder reactions to access piperidine skeletons (Scheme 1).[4] When an optically active enol ether **2** was treated with *N*-sulfonyl-1-aza-1,3-diene (**1**), the respective cycloadduct **3** was obtained in high yield and high selectivity. Their studies showed that the reactions exhibited high endo selectivity and regiospecificity.

[4] Clark, R. C.; Pfeiffer, S. S.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 2587-2593.

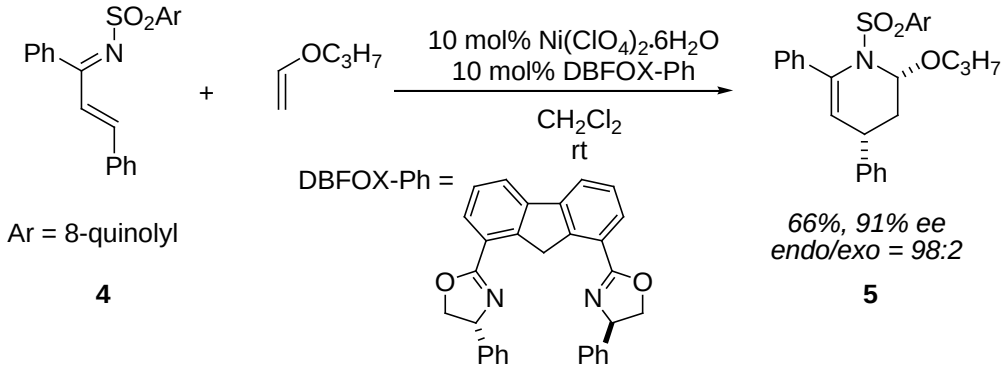
Scheme 1. Synthesis of substituted piperidines using chiral enol ether



1 **2** **3**

Carretero and co-workers reported [5] a chiral Lewis acid mediated catalytic and asymmetric cycloaddition protocol for the synthesis of enantiopure piperidine derivatives from *N*-sulfonyl-1-aza-1,3-dienes and simple vinyl ethers (Scheme 2). By choosing *N*-(8-quinolyl)-sulfonyl group in *N*-sulfonyl-1-aza-1,3-diene (**4**), both the reactivity and selectivity were improved dramatically. Kanemasa's chiral ligand, DBFOX-Ph, was found to provide the highest enantioselectivity.

Scheme 2. Lewis acid catalyzed substituted piperidine synthesis

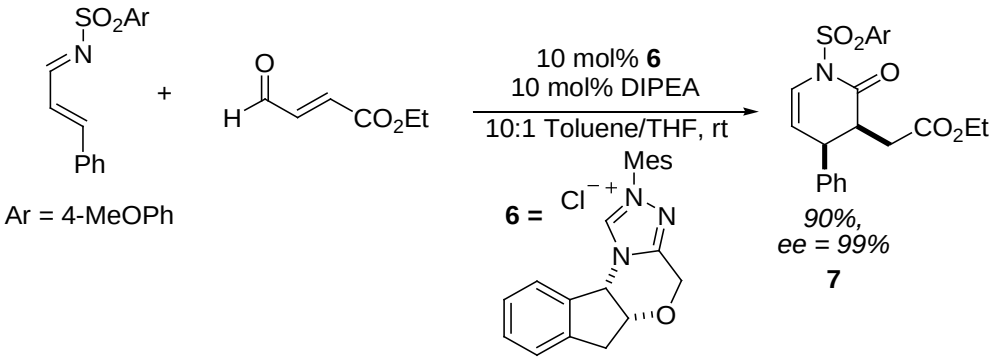


4 **5**

[5] Esquivias, J.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 1480-1481.

Heterocyclic chiral triazolium carbene catalyst **6** was used by Bode and co-workers[6] in the context of *N*-hereto Diels-Alder reactions using *N*-sulfonyl-1-aza-1,3-dienes and α,β-unsaturated aldehydes (Scheme 3). The triazolium carbene catalyst reacts with the aldehyde to generate a highly reactive dienophile that takes part in the Diels-Alder reaction producing highly enantioselective dihydropyridinone product **7**. This bears the significance that the organocatalyst mediated process can also be utilized in asymmetric preparations of piperidine derivatives.

Scheme 3. Chiral carbene catalyzed substituted piperidine synthesis

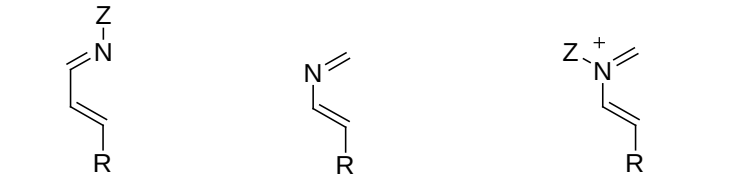


Aside from model A, the literature is also enriched with traditional hetero Diels-Alder cycloaddition models B and C[7], but the ionic model D is known to a much lesser extent. The models A and B involve neutral imine moieties **8** and **9** as the diene partner, whereas in model D, the diene partner is the alkenyl-iminium ion **10** (Figure 2). Surprisingly, these types of alkenyl-iminium ion dienes (**10**) are rarely known in the literature due to the fact that they are highly

[6] He, M.; Struble, J. R.; Bode J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418–8420.

[7] (a) i) For a review of Diels-Alder reactions with heteroaromatic compounds see: Needleman, S. B.; Kuo, M. C. C. *Chem. Rev.* **1962**, *62*, 405-431. ii) For a recent review of Diels-Alder reactions of aza dienes see: Boger, D. L. *Tetrahedron* **1983**, *39*, 2869-2939. (b) For examples of the use of 1-aza diene Diels-Alder cycloaddition readions in synthesis see: i) Cheng, Y. S.; Fowler, F. W.; Lupo, A. T. *J. Am. Chem. Soc*. **1981**, *103*, 2090-2091. ii) Cheng, Y. S.; Lupo, A. T.; Fowler, F. W. Ibid. **1983**, *105*, 7696-7703. (c) i) Sainte, F.; Serckx-Poncin, B.; Hesbain-Frisque, A. M.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428-1430. ii) Aue, D. H.; Thomas, D. *J. Org. Chem.* **1975**, *40*, 1349-1351.

reactive, and there is no easy way to generate them. However, considering the potential of alkenyl-iminium ion as a diene in the construction of highly substituted piperidine skeletons attracted us to pursue a detailed study of their preparations, reactivity, and application towards the synthesis of substituted piperidine derivatives.



8 1-azabutadiene **9** 2-azabutadiene **10** alkenyl-iminium ion

Figure 2. Aza dienes used in hetro-Diels-Alder reactions

1.1.2 Iminium Ion Intermediates in C-C Bond Forming Reactions

Iminium ions[8] are well known electrophilic intermediates, often used for C-C bond formation reactions for synthesizing cyclic and as well as acyclic nitrogen-containing structures. These intermediates are used widely in cyclization processes and exemplified by many famous reactions such as the Mannich reaction. Iminium ion mediated cyclization protocols offer many advantages over other methods. For example, iminium ions, in general, are very reactive intermediates and so a wide variety of nucleophiles can be used and they can easily be generated from available methods. The reactivity of the respective iminium ion depends on the substitution present at both C and N atom and on the associated counter ion (Figure 3). The presence of

[8] Royer, J.; Bonin, M.; Micoulin, L. *Chem. Rev.* **2004**, *104*, 2311-2352.

electron withdrawing group either at C or N enhances the electrophilicity, hence its reactivity. Acyl groups are often used as the protecting group on the N atom. The *intramolecular* addition of nucleophiles to *in situ* generated iminium ions is common in the literature. Several pathways have been used for generating these ions and among them, α-fragmentation methods, acylation/alkylation of imines and condensations with secondary amines are the most useful. The α-fragmentation method involved mainly the use of Lewis acids but electrochemical oxidation or metal catalyzed C-H activation (where LG = H) have also been employed. Among the Lewis acids, $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$ and TMSOTf are used most frequently.

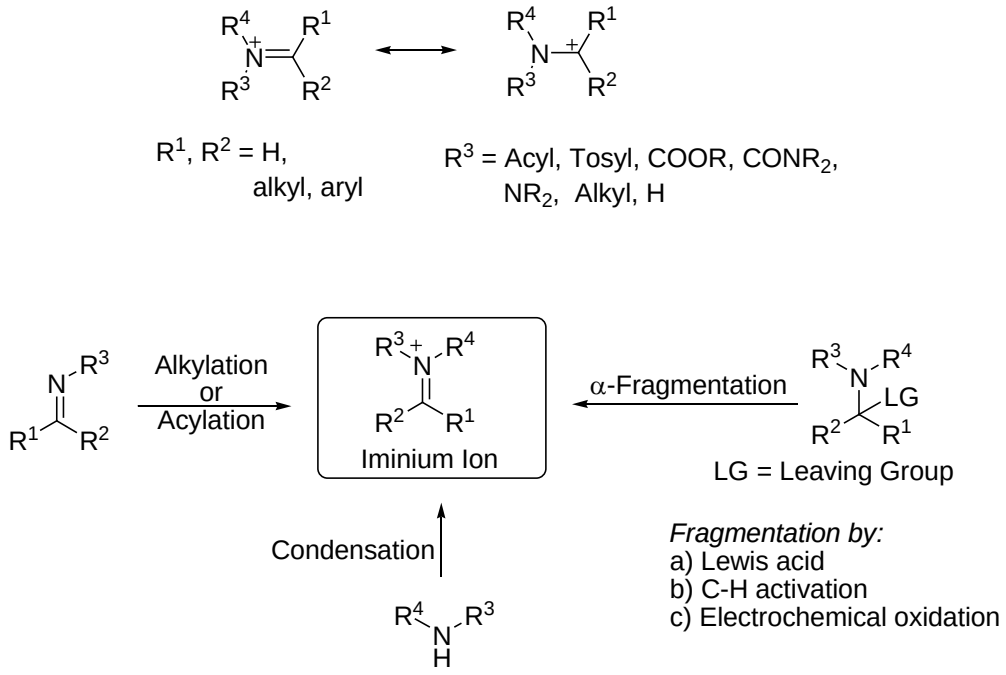
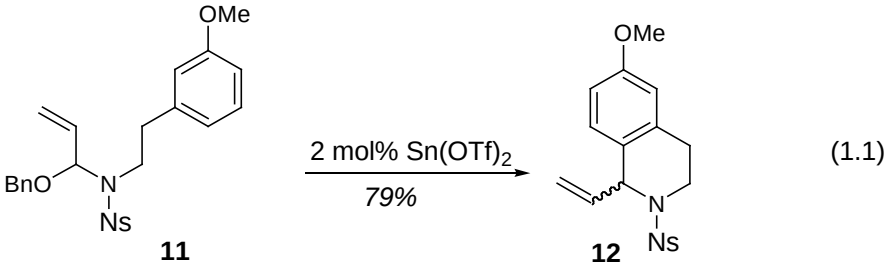


Figure 3. Iminium ions: General features

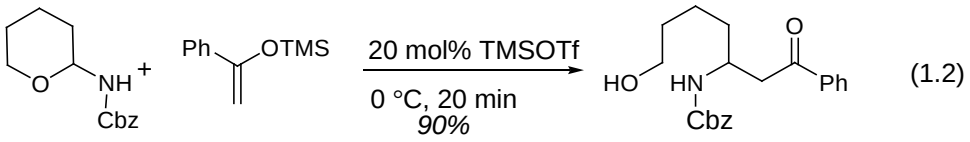
The chemistry associated with "*N*-acyl iminium"[8] and "*N*-alkyl iminium" ion intermediates[9] are well recognized in the chemical literature and are profoundly rich. These intermediates are normally generated by ionizing *N*,*O*-acetals using stoichiometric amount a of Lewis acid. Significant research efforts have been directed towards the development of suitable catalytic conditions so as to avoid the use of a full equivalent of the Lewis acid (Scheme 4). Recently, Rutjes[10] (eq 1.1) showed that 2 mol% $Sn(OTf)_2$ efficiently induced cyclization of aryl containing allylic *N*,*O*-acetal **11** to produce the substituted tetrahydroisoquinoline **12** in 79% yield. On a similar line, Kobayashi[11] reported Lewis acid catalyzed ring-opening of *N*,*O*-acetals possessing an exocyclic nitrogen atom to achieve acyclic structures. Benzyl (tetrahydropyran-2-yl) carbamate **13** formed the acyclic *N*-acyl iminium ion with 20 mol% TMSOTf, and was subsequently trapped with the reactive enolsilyl ether **14** to produce the ring-opened alcohol **15** in 90% yield (eq 1.2).

Scheme 4. Iminium ion mediated transformations catalyzed by Lewis acids



(1.1)

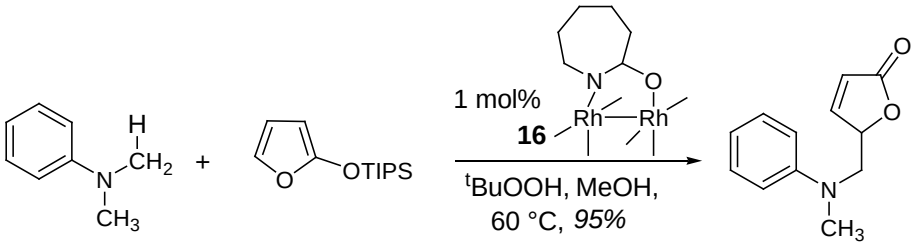
[9] For reviews on *N*-acyl iminium ions, see (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817-3856. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407-1438.
[10] Kinderman, S. S.; Wekking, M. M. T.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 5519-5527.
[11] Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510-12517.



13 **14** **15** (1.2)

In another experiment, Doyle [12] showed that the Rh-based catalyst, dirhodium caprolactamate (**16**), in the presence of methanol and hydrogen peroxide activates the α C-H bond of *N*,*N*-dimethyl aniline **17** and generated the respective *N*-alkyl iminium ion *in situ*, which was further intercepted by a reactive nucleophile, 2-triisopropoxysilylfuran (**18**) to produce the acyclic oxidative product **19** at 60 °C (Scheme 5).

Scheme 5. Transition metal catalyzed iminium ion formation



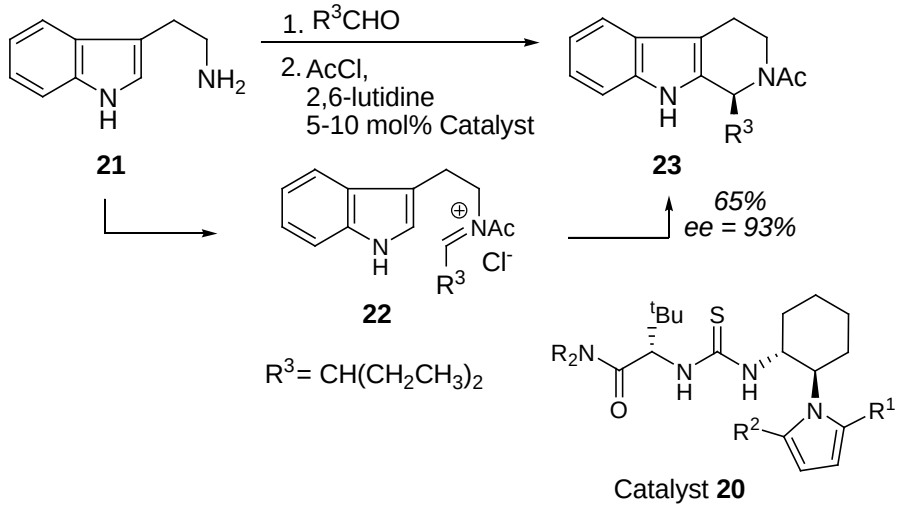
17 **18** **19**

Catalytic and asymmetric reactions utilizing iminium ion intermediates are still challenging and not well known in the literature. Recently, ingenious work in the Jacobsen group[13] has led to the identification of the thiourea based organo-catalyst **20** as the best catalyst to obtain highly enantioselective Pictet-Spengler reaction. Tryptamine derived imine formed from **21** and the aldehyde, produced the *N*-acyl iminium ion intermediate **22** in presence of an

[12] Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648-5649.
[13] Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558-10559.

acylating reagent like acylchloride, and the catalyst, which subsequently underwent intramolecular attack producing the enantiorich N_β-acyl-tetrahydro-β-carboline derivative **23** (Scheme 6).

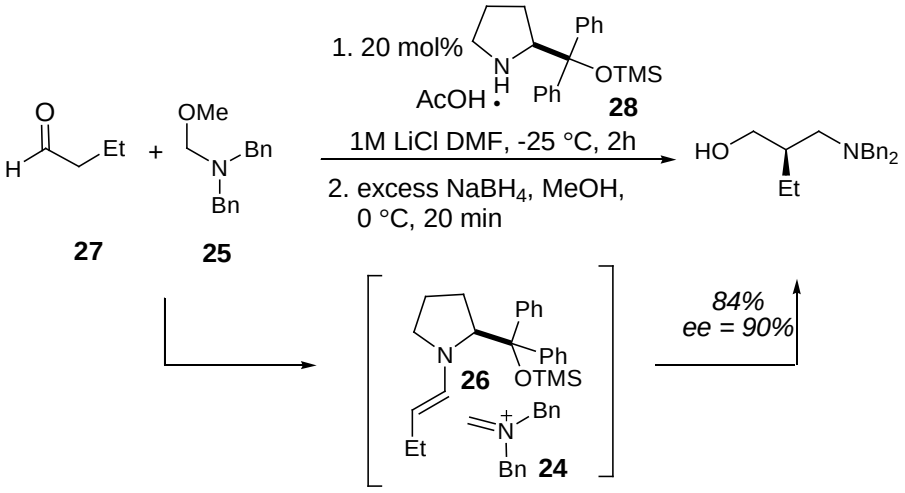
Scheme 6. Organocatalyzed cyclization via iminium ion formation



Gellman[14] in 2006 reported a highly enantioselective methodology for aminomethylation of aldehydes under organo-catalysis utilizing *N*-alkyl iminium ion intermediate, and this methodology could further be extended to produce β^2-amino acids. Less reactive *N*,*N*-dibenzyl-methylene iminium ion (**24**) was generated from aminal **25** under the reaction conditions, which got intercepted by reactive enamine **26** derived from the aldehyde **27** and organo-catalyst complex **28**. The selectivity of the nucleophilic addition to the iminium ion was rationalized from the sterics present on the catalyst (Scheme 7).

[14] Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804-6805.

Scheme 7. Bronsted acid mediated iminium ion formation followed by alkylation



It was evident that both Lewis and Bronsted acids were equally effective for the generation of iminium ions, and wide variety of nucleophiles could be applied to form the C-C bond. Strategically, both Lewis and Bronsted acid mediated cyclization processes would be valuable in the context of our approach towards the synthesis of substituted piperidines.

1.1.3 Alkenyl Iminium Ion as Diene in Hetero Diels-Alder Reaction

The existence of the "*N*-alkenyl iminium ion" (**29**) in the literature is not well known, but its related analogs derived from *N*-acyl iminium ion (**30**) are known (Figure 4). These intermediates are primarily involved in C-C bond construction and frequently utilized to introduce α-substitution to an amine. They also are well known in cyclization reactions for the formation of *N*-heterocycles. The lesser known part of *N*-acyl iminium ions is their ability to behave as diene partner in Diels-Alder cycloaddition reactions. Under certain conditions, the respective electron

deficient 4π system of *N*-acyl iminium ions can be exploited as diene partner in Diels-Alder reaction[15] with variety of electron rich alkenes producing stereoselective *N*-heterocycles.

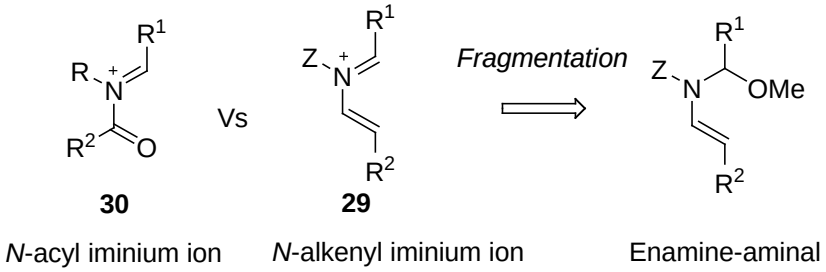


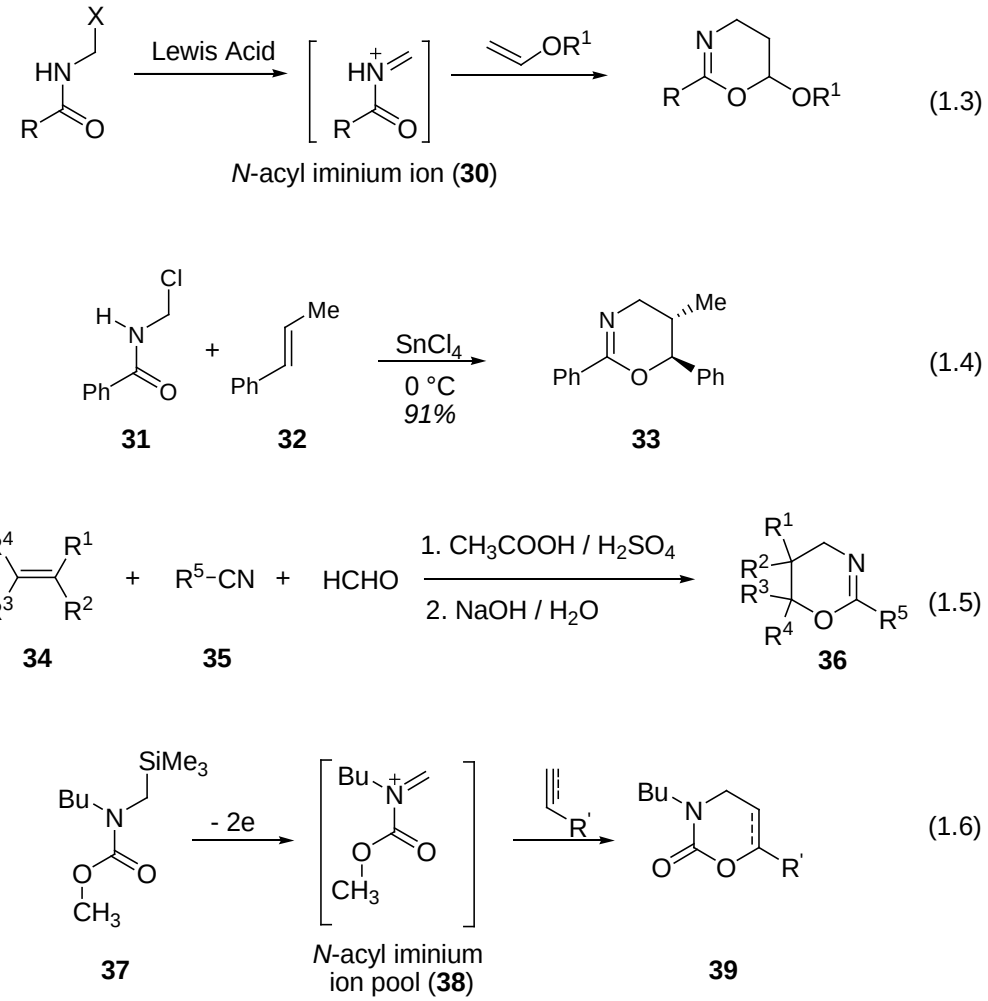
Figure 4. 4π systems of *N*-acyl and *N*-alkenyl iminium ion

Schmidt[16] in the late sixties used the electron deficient 4π system obtained from the *N*-acyl iminium ion **30** as a diene partner (Scheme 8), and using various dienophiles, was successfully able to form corresponding cycloadducts (eq 1.3). In presence of stoichiometric $SnCl_4$, the *N*-acyl iminium ion was produced from *N*-(chloromethyl)benzamide **31**, and the respective diene intermediate underwent [4+2] type cycloaddition with trans-β-methylstyrene (**32**) yielding the respective oxazine **33** in 91% yield (eq 1.4). Few years later, Borsotti[17] obtained similar results by utilizing a similar concept and was able to obtain cycloadduct **36** upon treating an olefin **34** with a solution of paraformaldehyde, nitrile **35**, and sulfuric acid (eq 1.5). In 2003, Yoshida[18] reported the irreversible generation of *N*-acyl iminium ion pool (**38**) by means electrochemical oxidation of **37** (to avoid Lewis acid) and obtained cycloadducts **39** with various dienophiles such as alkenes and alkynes (eq 1.6).

---

[15] For a review of *N*-acyl imines in Diels-Alder reactions: Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525-1534 and references therein.
[16] Schmidt, R. R. *Angew. Chem., Int. Ed.* **1969**, *8*, 312.
[17] Giordano, C.; Ribaldone, G.; Borosotti, G. S*ynthesis* **1971**, 92-95.
[18] Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J. *Org. Lett.* **2003**, *5*, 945-947.

Scheme 8. Examples of *N*-acyl iminium ion in cycloaddition reactions

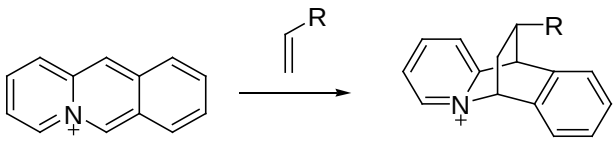


Relatively stable acridizinium salts have been known in the literature for a long time (Scheme 9). The electron deficient 4π system of acridizinium **40**[19] underwent cycloaddition with a variety of dienophiles to produce bicyclic pyridinium salt **41** (eq 1.7). In 1985, Shono[20] reported a new [3+3] type annulation to form piperidine skeletons using α,α′-dimethoxylated amide **43** and allyltrimethylsilane in presence of excess $TiCl_4$. One of the aminals of **43** was

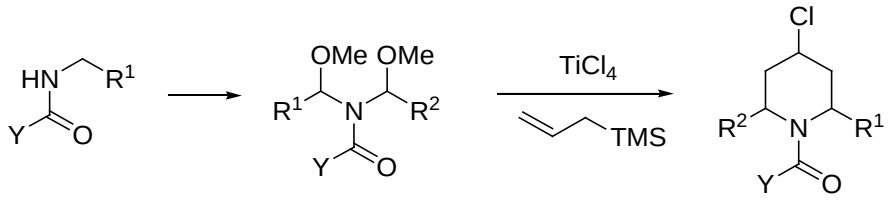
[19] Bradsher, C. K.; Solomons, T. W. G. *J. Am. Chem. Soc.* **1958**, *80*, 933-934.
[20] Shono, T.; Matsumura, Y.; Uchida, K.; Kobayashi, H. *J. Org. Chem.* **1985**, *50*, 3243-3245.

ionized first with $TiCl_4$ to produce an *N*-acyl iminium ion, which was subsequently trapped with allyltrimethylsilane to produce the homoallylic derivative via a stable β-silyl cation. Finally, under the reaction conditions, another iminium ion was generated, which underwent intramolecular cyclization with the homoallylic double bond, yielding the desired [3+3] cycloadduct **44** (eq 1.8).

Scheme 9. Iminium ion as diene in cycloaddition reactions



40 **41** (1.7)



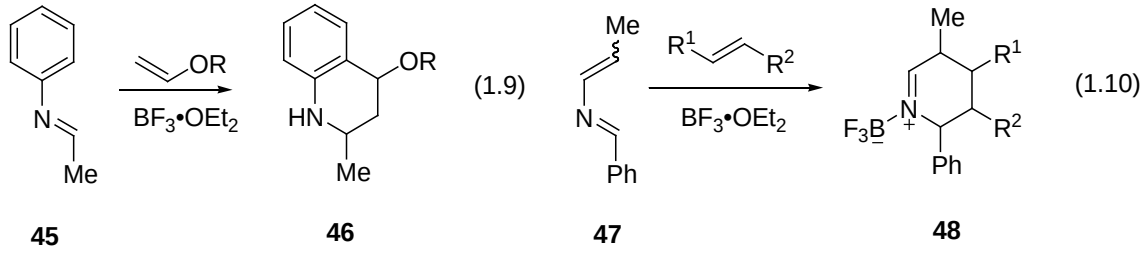
42 **43** **44** (1.8)

Based on the work of Povarov and Orahovats,[21] the aniline derived aldimine **45** in presence of $BF_3{\cdot}OEt_2$ underwent cycloaddition with electron rich dienophile (eq. 1.9) (Scheme 10). Upon activation by $BF_3{\cdot}OEt_2$, imine **45** generated an *N*-alkenyl iminium ion which underwent cycloaddition with enol ether and produced the tetrahydroquinoline derivative **46**. Mariano[22] reported a similar result utilizing the same concept. Instead of aldimine **45**, inactivated 2-aza 1,3-diene **47** was synthesized and treated with $BF_3{\cdot}OEt_2$ (eq. 1.10). Lewis acid activation of

[21] (a) i) Povarov, L. S.; Mikhailov, B. M. *Izu. Akad. Nauk SSSR, Ser. Khim.* **1964**, 2221. ii) Povarov, L. S., Grigos, V. I.; Karakhanov, R. A.; Mikhailov, B. M. *Ibid.* **1964**, 179; **1963**, 2039. (b) Trifonov, L. S.; Orahovats, A. S. *Heterocycles* **1984**, *22*, 355.
[22] Cheng, Y.; Ho, E.; Mariano, P. S.; Ammon, H. L. *J. Org. Chem.* **1985**, *50*, 5678-5686.

imine produced the *N*-alkenyl iminium ion, which upon cycloaddition with electron rich dienophiles, like vinyl ether, produced the respective cycloadduct **48**. The methodology described above proves that *N*-alkenyl iminium ion generation is possible under suitable Lewis acidic conditions, and they can be used as Diels-Alder reaction partners.

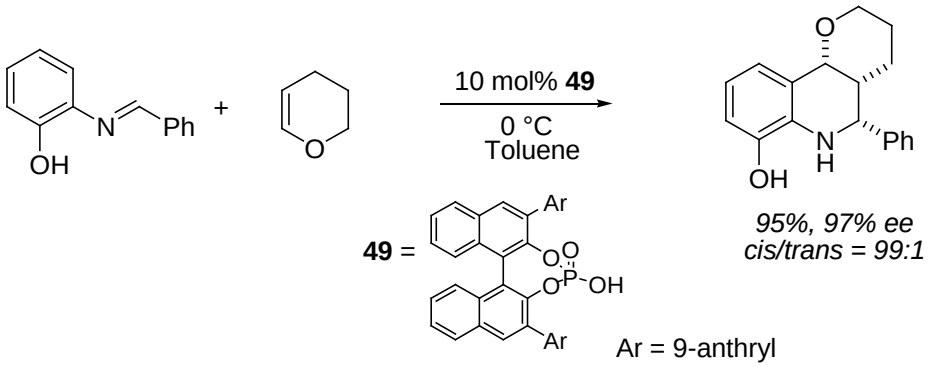
Scheme 10. Aza diene in cycloaddition reactions



45 **46** **47** **48**

Akiyama and co workers [23] reported a metal free cyclization protocol for tetrahydroquinoline derivatives synthesis. In the reaction protocol, chiral Bronsted acid (**49**) was used to produce the cycloadduct from azabutadiene and electron rich pyran. Overall, the reaction was cis stereoselective and exhibited high enantioselectivity (Scheme 11).

Scheme 11. Bronsted acid catalyzed tetrahydroquinoline synthesis



[23] Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070-13071.

Based on these literature evidences, we are confident that the respective *N*-alkenyl iminium ions, similarly, can also be engaged in cycloaddition reactions. They are less known in the literature because of the fact that azabutadiene synthesis is not well known. The only useful azabutadiene that can be generated easily is phenyl aldimine.

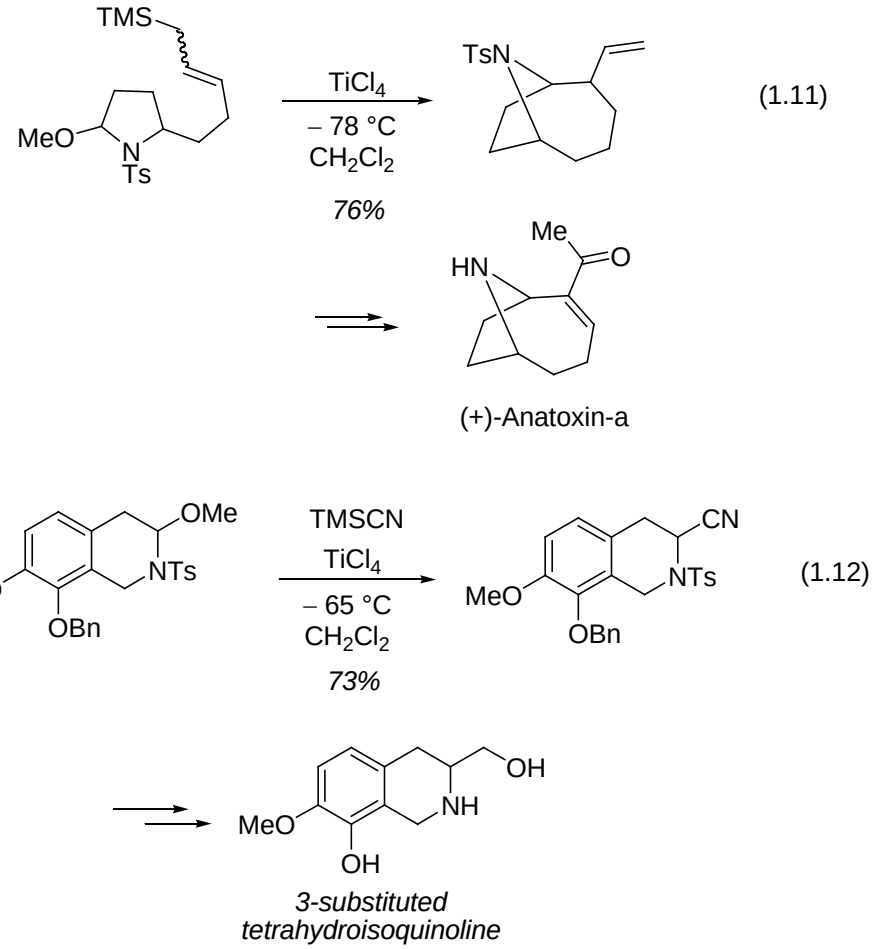
1.1.4 *N*-Tosyl Iminium Ion in C-C Bond Forming Reaction

N-Tosyl iminium ions mediated C-C bond forming reaction[24] strategies have received much less attention than the corresponding *N*-acyliminium ion mediated reactions. Limited synthesis of the respective aminals precursor prevents its use in C-C bond forming reactions. *N*-Tosyl iminium ion possesses similar characteristic properties as the *N*-acyliminium ion does, and in general, they are more reactive intermediate (Scheme 12). For example, Somafi and co-worker reported[25] the utility of such *N*-tosyl iminium ion in their methodology demonstrating by the synthesis of the powerful neurotoxin alkaloid (+)-Anatoxin-a via cyclic *N*-tosyl iminium ion intermediate (eq 1.11). In their tetrahydroisoquinolines synthesis methodology, Kaufman and co-workers[26] used cyclic *N*-tosyl iminium ion to introduce substitution at 3-position and synthesized a simplified analog of novel β-adrenergic receptor antagonist MY336-a (eq 1.12).

---

[24] (a) Ahman, J.; Somafi, P. *J. Chem. Soc. Perkin Trans.1* **1994**, *8*, 1079-1082. (b) Sisko, J.; Henry, J. R.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4945-4951. (c) Shono, T.; Matsumura, Y.; Katoh, S.; Takeuchi, K.; Sasaki, K.; Kamada, T.; Shimizu, R. *J. Am. Chem. Soc.* **1990**, *112*, 2368-2372.
[25] Ahman, J.; Somafi, P.*Tetrahedron* **1992**, *48*, 9537-9544.
[26] Ponzo, V. L.; Kaufman, T. S. *Synlett* **1995**, *11*, 1149-1150.

Scheme 12. *N*-Tosyl iminium ion mediated cyclization



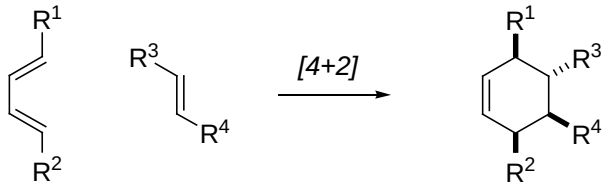
1.2 ALKENYL IMINIUM ION: REACTION DEVELOPMENT

1.2.1 *N*-Alkenyl Iminium Ion in Diels-Alder Reaction: A New Strategy for Piperidine Synthesis

Diels-Alder cycloadditions remain the standard by which most annulation methodologies are measured. The array of investigations devoted to developing new variants of the traditional Diels-Alder reaction attests to the critical role these cycloadditions continue to play in synthesis

activities.[3] Indeed, identifying Diels-Alder variants that are not extensively developed, or at least well investigated, is a challenging task. As discussed earlier, *N*-acyl iminium ions participate in a wide variety of transformations that have inspired remarkable creativity in methods development and synthesis enterprises. One family of these reactive intermediates that has received relatively little attention is *N*-alkenyl iminium ions **29** (Figure 5). We were, however, intrigued in the potential of *N*-alkenyl iminium ions **29** to function as diene and, simultaneously, cognizant of the limited information concerning these species' reactivity patterns. Cycloadditions with **29** as diene offered intriguing possibilities for tandem reaction development considering that these [4+2] cycloadditions would generate a new tetrahydropyridinium ion **51** suitable for further functionalization by nucleophilic addition. Therefore, we have envisioned that *N*-alkenyl iminium ion diene (**29**) would enable the stereoselective synthesis of fully-substituted piperidines **52** in Diels-Alder cycloadditions via a three component cycloaddition process. In the first step, the electron deficient diene **29** would undergo cycloaddition with dienophile **50** resulting in a new cyclic tetrahydropyridinium ion **51**; subsequent trapping of this intermediate with a suitable nucleophile would produce the fully substituted piperidine **52**. These cycloadditions offer the potential for constructing four new C−C bonds and five new stereocenters in a single step.

[4+2] Cycloaddition



- *High degree of substitution & stereoselective*

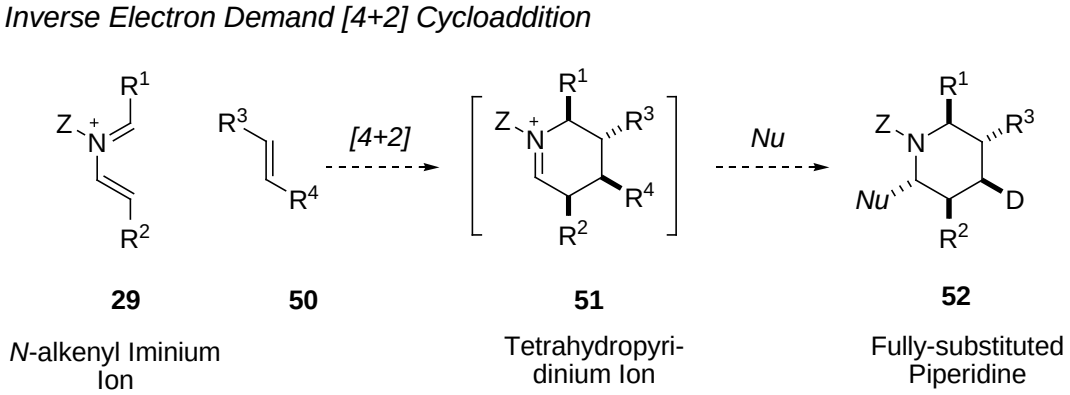


Figure 5. Strategy towards new Diels-Alder variant

The *N*-alkenyl iminium ion **29** can be obtained by ionization of an enamine-aminal derivative **53** under Lewis acid or Bronsted acid conditions (Figure 6). The respective enamine-aminal derivative **53** can in turn be synthesized by isomerization of a simple *N*-allylamine derivative **54**. We believed that the installing the aminal part in the enamine-aminal synthon could be done by direct alkylation using commercially available reagents like MOMCl or α-chloro nitrile. Having an electron withdrawing protecting group (**Z**) on the nitrogen atom would stabilize both of the aminal and enamine motifs and would provide us a practical and easy way of making such synthons. Upon ionization of the enamine-aminal **53** by a suitable Lewis acid, a highly electron deficient diene **29** would be produced.

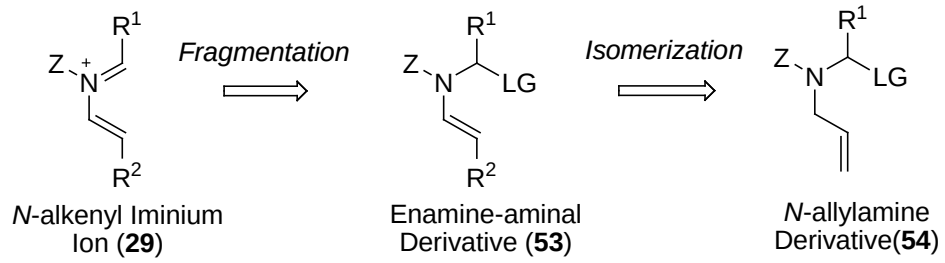


Figure 6. Strategy towards *N*-alkenyl iminium ion generation

1.3 CYCLOADDITION WITH ALLYLTRIMETHYLSILANE

1.3.1 Initial Reaction Conditions Optimization

To test our hypothesis, the *N*-tosyl enamine-aminal derivative, **55**, was synthesized by two high yielding steps from commercially available allylamine. *N*-Tosyl enamine (**55**) possessed OMe as a leaving group and Ts as a protecting group. As a result, strong Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ were considered for its ionization at low temperature and −78 °C was chosen as the initial operating reaction temperature considering the fact that the resulting electron deficient diene (**56**) might not be stable at higher temperatures. To exploit the resulting 4π system for [4+2] type addition, the electron rich dienophile, ethylvinyl ether, was used. A solution of **55** in dichloromethane was added to $TiCl_4$ (1.1 equiv) solution in dichloromethane at −78 °C followed by addition of ethylvinyl ether (10 equiv) (Figure 7). The progress of the reaction was monitored by TLC. Complete decomposition of the starting material **55** was observed. Similar observations were made when $BF_3{\cdot}OEt_2$ was used as the Lewis acid at room temperature. At −78 °C, no reaction was observed with $BF_3{\cdot}OEt_2$. In the reactions with $TiCl_4$ at −78 °C and $BF_3{\cdot}OEt_2$ at room temperature, extensive polymerization of the ethylvinyl ether was observed suggesting that the dienophile was not stable under these strong Lewis acid conditions. We then switched to milder Lewis acids such as $ZnCl_2$ and $MgBr_2{\cdot}OEt_2$, which failed to provide any reaction even at ambient temperature. This preliminary screening of the Lewis acids suggested that the aminal **55** was inactive with various Lewis acids at lower temperatures except $TiCl_4$ and therefore, led us to stay with the $TiCl_4$/ −78 °C condition.

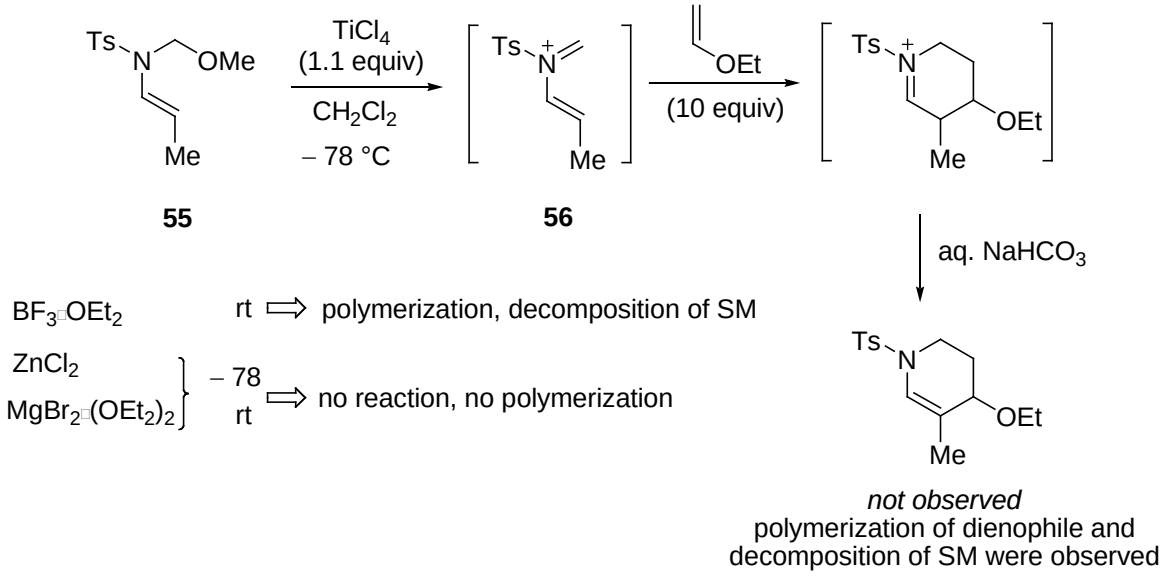


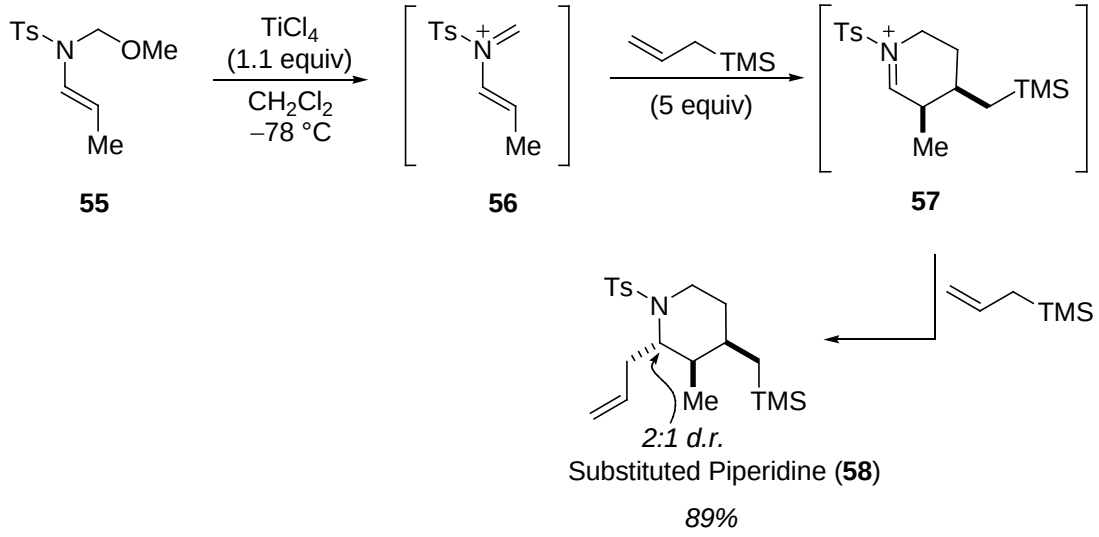
Figure 7. Preliminary reaction conditions development for the [4+2] cyclization reaction

At this point, to validate the cycloaddition process, a search for a suitable dienophile that could survive under the reaction condition ($TiCl_4$/ −78 °C) was made and allyltrimethylsilane was chosen. Allyltrimethylsilane is extensively used in nucleophilic addition reactions due to its reactivity and stability under strong Lewis acid such as $TiCl_4$.[27] Apart from being an electron-rich dienophile, allyltrimethylsilane would also offer an ancillary advantage of being the nucleophile with which the tetrahydropyridinium ion intermediate would be trapped. Treating **55** with $TiCl_4$ (1.1 equiv) at −78 °C in presence of allyltrimethylsilane (5 equiv) provided the cycloadduct **58 (**89% yield). This preliminary finding demonstrated well that the Lewis acid activated the leaving group (in this case OMe) generating an *N*-alkenyl iminium ion **56**, which then proceeded for the [4+2] cycloaddition resulting in the tetrahydropyridinium ion intermediate **57**. Finally, the tetrahydropyridinium ion **57** was trapped with excess allyltrimethylsilane present in the reaction system yielding the product **58** in 89% yield and as a 2:1 mixture of diastereomers

[27] Brocherieux-Lanoy, S.; Dhimane, H. ; Poupon, J-C. ; Vanucci, C.; Lhommet, G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2163-2165.

(determined fron ^{1}H NMR) (Scheme 14). The structure of the major diastereomer (as drawn in scheme 13) was deduced based on stereochemical proofs of cycloadditions performed later which suggested that the [4+2] cycloaddition itself was highly selective. The origin of the 2:1 dr in this case was the less selective addition of the nucleophile onto the tetrahydropyridinium ion **58**.

Scheme 13. Cycloaddition with allyltrimethylsilane via *N*-alkenyl iminium ion



1.3.2 Attempted Cyclization with Other Electron Rich Dienophiles

Due to the failure in getting cycloadducts from ethylvinyl ether and **55**, a different approach using a mild Lewis acid catalyst that would liberate the diene under the reaction conditions (and would not destroy the dienophile) was considered. It was realized that by making the enamine-aminal substrate more reactive, relatively milder Lewis acid could be used to generate the *N*-alkenyl iminium ion. The reactivity of the enamine **55** could be enhanced by changing the protecting group from tosyl to carbamate (-COOR) or acyl (-COR) and also by changing the

leaving group to –OAc or Cl^-. A carbamate (or acyl) moiety at the nitrogen would provide enough stability to the enamine, and at the same time, would make the nitrogen lone pair available to facilitate ionization. This might help to obtain ionization easily with relatively weaker Lewis acids. Hence, protecting group modified substrates **59** (methoxycarbamate protecting group) and **60** (benzyloxycarbamate protecting group) were synthesized and subjected to cycloaddition reaction with various vinylether type dienophiles as shown in figure 8. However, no reactivity was observed at −78 °C using $TiCl_4$, $Ti(^iOPr)_2Cl_2$ or $BF_3{\cdot}OEt_2$ as Lewis acids. At a low temperature (–78 °C), the catalysts were inactive, but upon increasing the temperature, polymerization was seen. The lack of reactivity of these carbamate protected dienes at −78 °C may be attributed to the carbonyl groups in the protecting groups which bind to the Lewis acids making them less reactive.

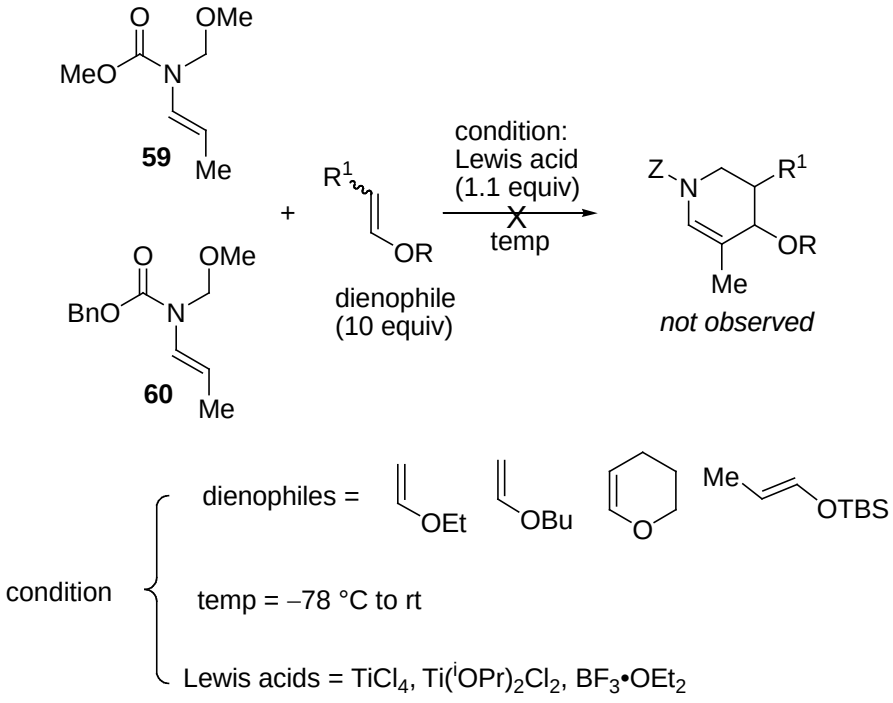


Figure 8. Cycloaddition with electronically rich dienophiles

Knowing that $TiCl_4$ was ineffective for the ionization of substrate **59** at −78 °C, a screen of higher temperatures was needed. Since vinyl ether type dienophiles underwent polymerization at higher temperatures, we switched to allyltrimethylsilane. To test the reactivity of the carbamate protected substrates in the cycloaddition, the carbamate **59** was subjected to excess allyltrimethylsilane and $TiCl_4$ at −78 °C and after 16 h, the starting material was recovered (Figure 9). In the next run, the reaction temperature was raised to −30 °C but again no conversion was observed. In a different reaction, we added $TiCl_4$, carbamate **59**, and allyltrimethylsilane at −78 °C, and then, the reaction temperature was increased gradually to room temperature. In this case, the desired cycloadduct **61** was obtained, but the yield (37%) and diastereoselection (1:1 d.r., determined fron ^{1}H NMR) both were poor. Thus the carbamate protected substrate **59** was found to be reactive only at room temperature in presence of $TiCl_4$, therefore less reactive than the tosyl-protected substrate **55**.

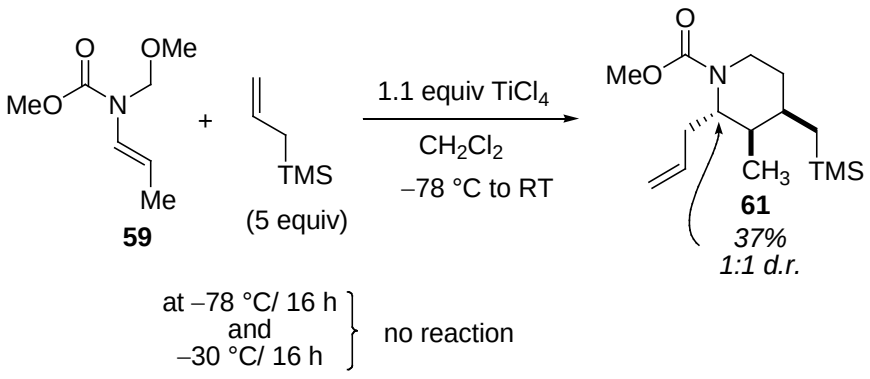
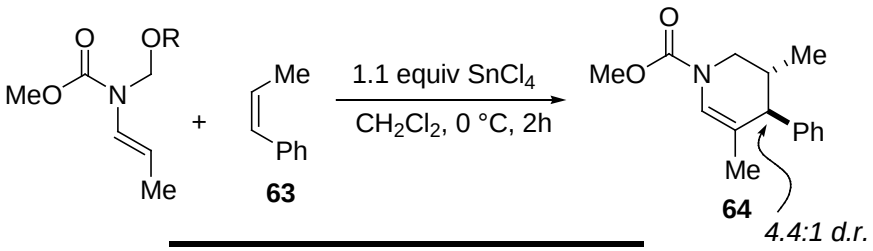


Figure 9. Cycloaddition with carbamate protected enamine derivative **59**

Reaction temperature, as high as room temperature for our cycloaddition reaction, was not desirable, as the intermediate tetrahydropyridinium ion would undergo facile deprotonation leading to the eliminated product at such temperatures. In order to enhance the reactivity of the

substrate to achieve reaction at lower temperature, the carbamate protected enamine-aminal derivative **62** with a better leaving group (OAc) was synthesized. Assuming that the binding of $TiCl_4$ to the carbonyl moiety was responsible for the low reactivity at low temperatures (< room temperature), we also looked for other weaker Lewis acid. $SnCl_4$ is often used for the ionization of *N,O*-acetals and most of these $SnCl_4$ mediated ionizations are done at 0 °C.[16] Thus, enamine **59** was treated with $SnCl_4$ (1.1 equiv) and β-methylstyrene (**63**) at 0 °C, and the eliminated cycloadduct **64** was obtained in good yield (67%, 4.4:1 d.r., determined fron ^{1}H NMR) (Table 1). Carbamate **62** was then subjected to similar reaction conditions (1.1 equiv $SnCl_4$, 0 °C) but the isolated yield was low (25%). The reaction with enamine **62** was much faster (starting material was disappeared after 1 h) than the reaction with enamine **59**, and it is because the OAc group is a better leaving group than OMe. The easy formation of *N*-alkenyl iminium ion from enamine **62** leads to the product along with decomposition.

Table 1. Cycloaddition with β-methylstyrene



substrate	OR	yield[a] (%)
59	OMe	67
62	OAc	25

[a] isolated yield. d.r. was determined from ^{1}H NMR

Upon analyzing the product **64**, it was concluded that $SnCl_4$ ionized the aminal to form the *N*-alkenyl iminium ion **65**, which immediately underwent cycloaddition and produced the cyclic iminium ion intermediate **66** (Figure 10). This intermediate being relatively unstable at the higher temperature (0 °C), underwent quick deprotonation to produce the respective cycloadduct **64** and none of the product **67** derived from nucleophile addition was observed. The 6:1 diastereoselection suggested that the cycloaddition proceeded via both synchronous and non-synchronous pathways via intermediates **68**, **69** or stable benzylic cation **70**. The preceding results clearly demonstrated that the carbamate protected system offered no advantage in terms of reactivity or diastereoselectivity and so we continued our investigations with the tosyl protected enamine-aminal **55**.

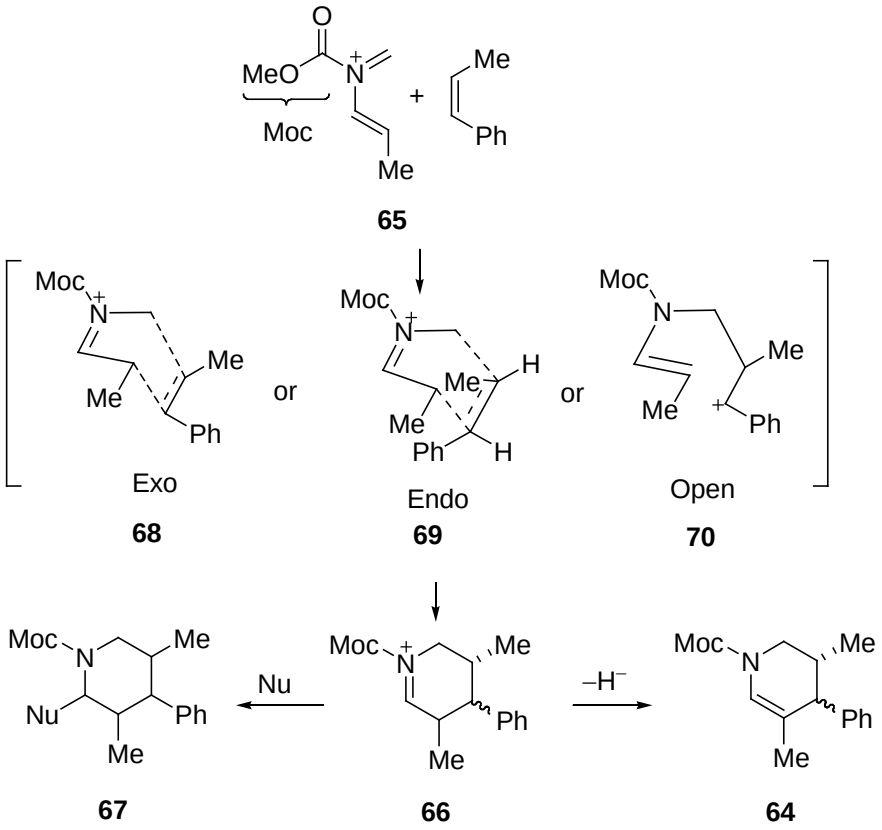


Figure 10. A plausible mechanism of cycloadduct **64**

1.4 CONCLUSION

A new strategy for the substituted piperidine derivatives synthesis in a three component coupling reaction manifold has been demonstrated. The Lewis acid mediated successful generation of new *N*-tosyl diene intermediate has been described, and subsequently, their engagement in cycloaddition process has been evaluated. *N*-tosyl enamine-aminal diene precursor showed higher reactivity over the carbamate protected diene precursors.

2.0 DIASTEREOSELECTIVE *N*-HETEROCYCLIC SCAFFOLD SYNTHESIS

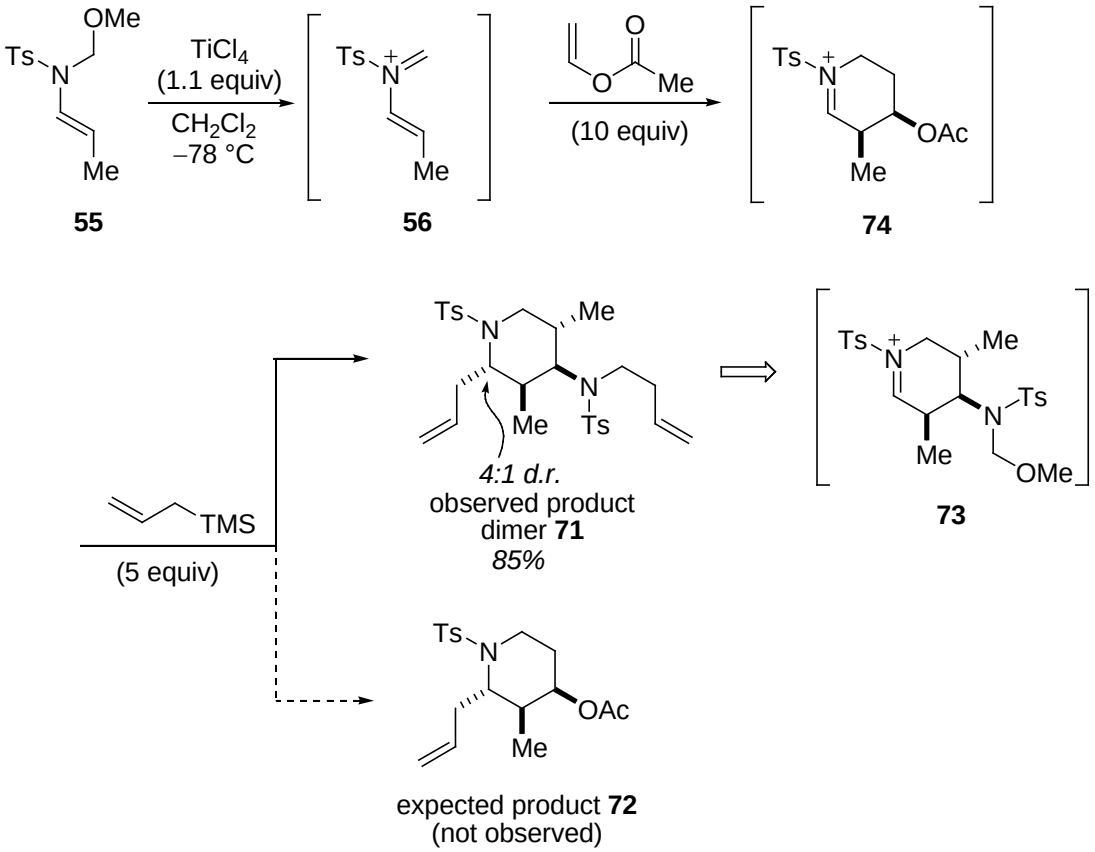
2.1 CYCLOADDITION WITH ENAMINE DIENOPHILES

2.1.1 Initial Observation: A Competitive Dimerization Reaction

So far allyltrimethylsilane has been engaged with the diene **56** as both the dienophile and nucleophile. The utility of this new diene in conjunction with other dienophiles has yet to be proved, but it is clear the *N*-alkenyl iminium ion expresses sufficient reactivity to engage electronically activated olefins as dienophiles in [4+2] cycloadditions. The resulting tetrahydropyridinium ion intermediate after the initial cycloaddition is also active and can be intercepted with various nucleophiles. In order to explore the reactivity of the diene toward other reaction partners, activated, unactivated, and neutral types of olefins were evaluated next. The enamine-aminal **55** was utilized for these studies, and the activation was done with $TiCl_4$ at −78 °C. It has been shown earlier that electron rich dienophiles such as vinyl ethers are prone to polymerization under the $TiCl_4$ conditions and so we were careful in choosing of electronically rich dienophiles. In our initial reaction, vinyl acetate was chosen as the dienophile partner and allyltrimethylsilane as the nucleophile (Scheme 14). Since vinyl acetate is not as reactive as allyltrimethylsilane, the nucleophile (allyltrimethylsilane) would have to be added at the end of the reaction to capture the cyclic intermediate formed after cycloaddition. A solution of vinyl

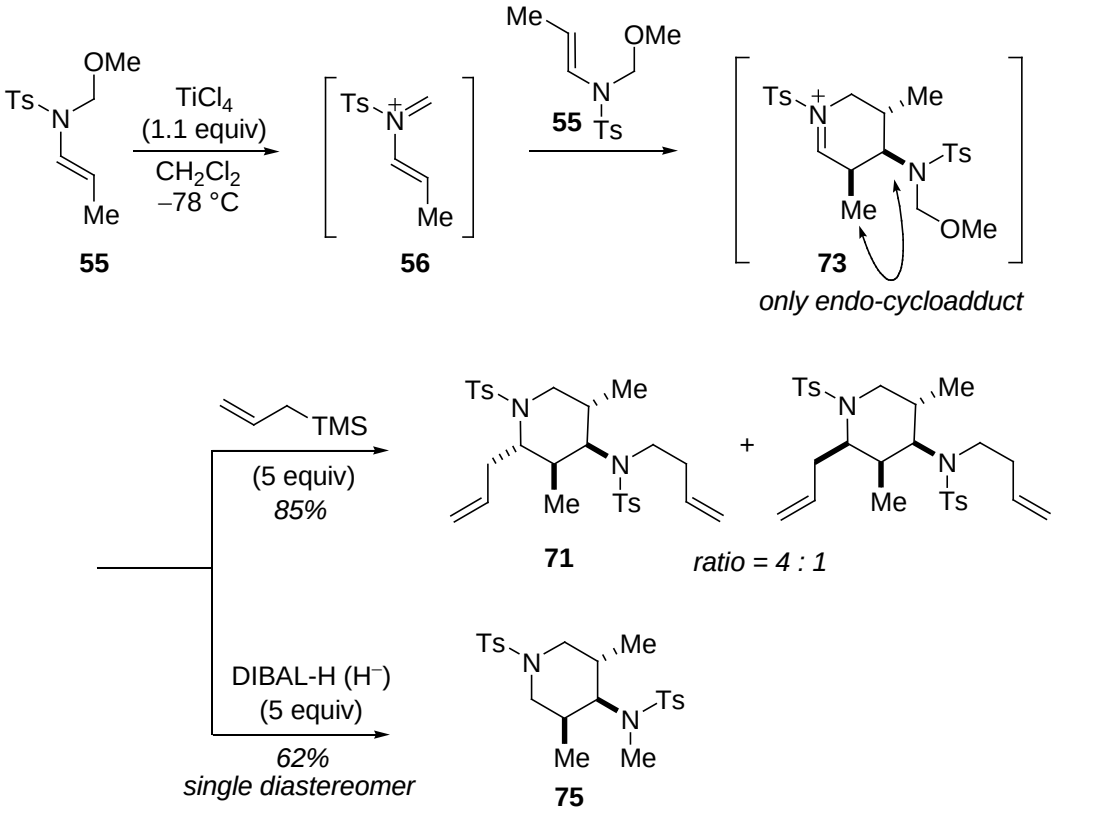
acetate was added to a solution of enamine **55** and $TiCl_4$ at −78 °C, and after disappearance of the starting material on TLC (3 h), a solution of excess allyltrimethylsilane was added. However, after isolation and characterization of the product, we were surprised to obtain the dimer **71** instead of the expected cycloadduct **72** in 85% yield. Thus in this reaction the enamine acted both as the diene and the dienophile partners and underwent cycloaddition reaction resulting in tetrahydropryridinium ion **73** instead of **74** which afforeded the dimer **71** after treating with allyltrimethylsilane. This suggested that vinyl acetate was less reactive than the enamine-aminal **55** itself as the dienophile. The deactivation of vinyl acetate could be due to its binding with the Lewis acid.

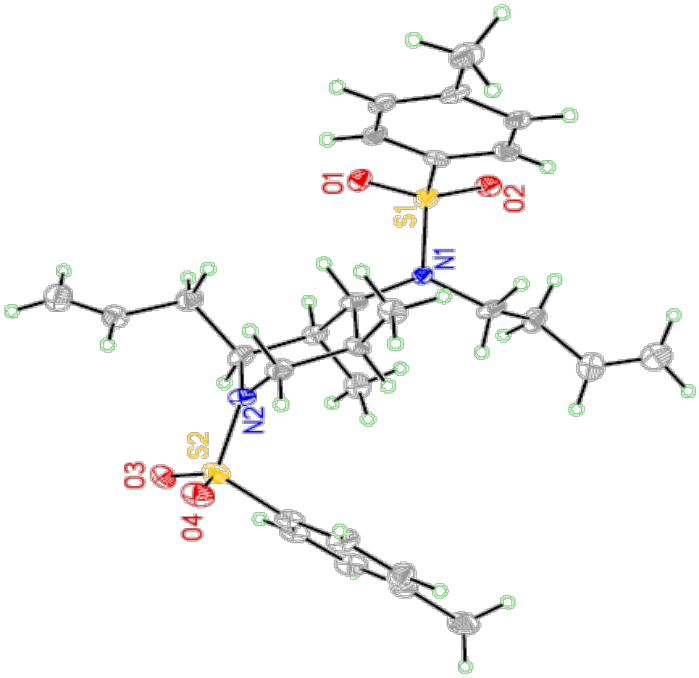
Scheme 14. An unexpected dimerization reaction

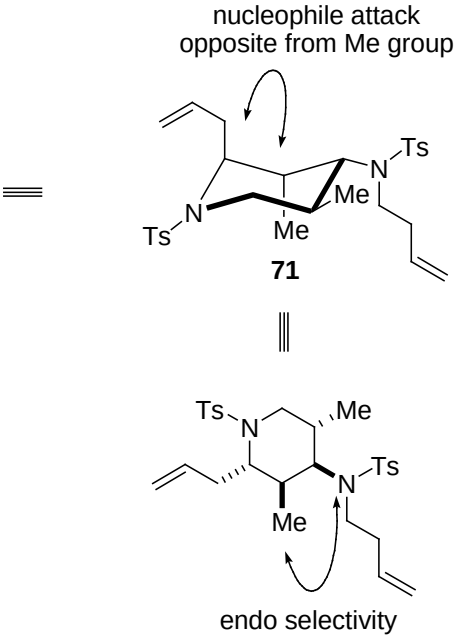


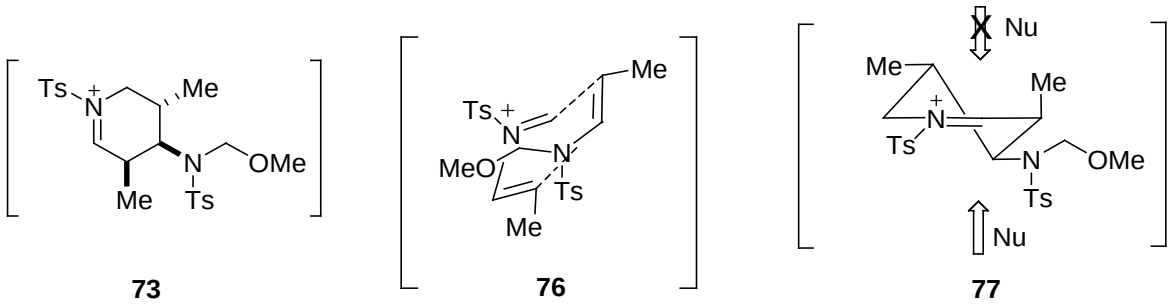
Knowing that the starting material could serve both as diene and dienophile, in the following reaction, we did not add any dienophile (Scheme 15). After disappearance of **55** (monitored by TLC), the resulting reaction mixture was quenched with two different nucleophiles, 1) allyltrimethylsilane and 2) DIBAL-H. In both cases, the respective dimers **71** and **75** were obtained in good yields (85 and 62% respectively). Trapping with allyltrimethylsilane produced the dimer **71** with similar yields (85%) as obtained in scheme 14, implying that vinyl acetate did not have any influence in the reaction. When DIBAL-H was used, the major product **75** was isolated in 62% yield but the diastereoselection obtained from this reaction was excellent (determined from ^{1}H NMR), producing a single diastereomer. The observation of a single diastereomer in case of the DIBAL-H reaction suggested two things. Firstly, the cycloaddition itself resulting in the tetrahydropyridinium intermediate **73** is highly stereoselective and secondly, the 4:1 diastereomer ratio obtained in case of the allytrimethylsilane reaction (determined from ^{1}H NMR) is caused by the less stereoselective addition of the nucleophile on to **73**. In order to determine the nature of stereoselectivity in the cycloaddition reaction, the dimer **71** which was a white crystalline solid, was submitted to X-ray crystallography (Figure 11). From its X-ray crystallographic structure, it was confirmed that the cycloaddition proceeded with endo selectivity. The intermediate **73** was formed from the cycloaddition reaction of **55** with **56** via the endo-transition state **76.** The subsequent nucleophilic addition of allyltrimethylsilane to the intermediate tetrahydropyridinium ion **73** proceeded selectively from one side of the cyclic iminium ion intermediate favoring the chair like transition state **77** to afford a 4:1 mixture of diastereomers.

Scheme 15. Cycloaddition with electron rich dienophile (enamine **55**)









73 **76** **77**

Figure 11. X-ray structure of dimer **71** and transition states

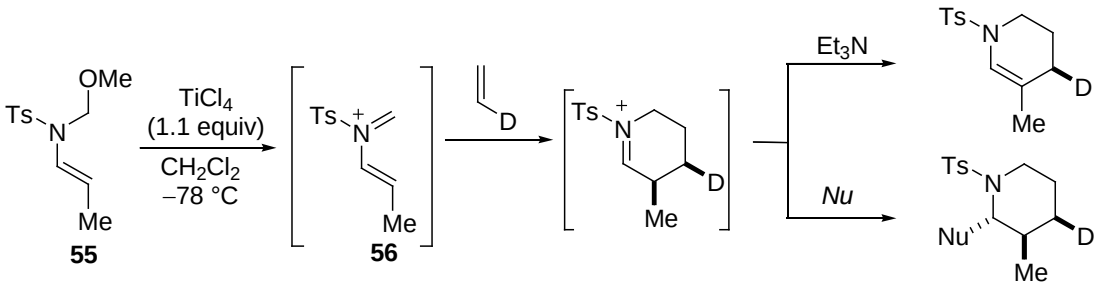
2.1.2 Reaction Scope with Enamine Dienophiles

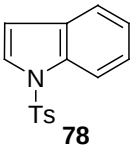
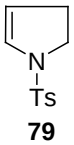
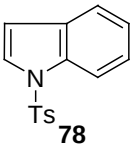
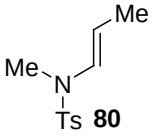
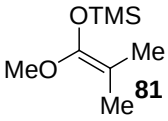
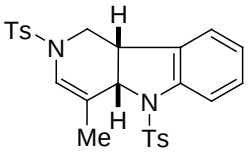
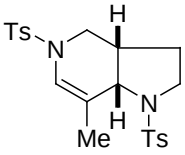
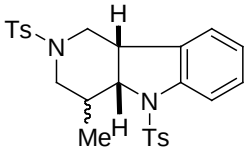
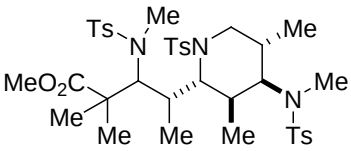
Based on the results of the dimerization reaction, it was clear that enamines could serve as effective dienophile partners in the cycloaddition reaction with the diene **56**. Enamines such as *N*-tosyl-indole **78**[28] and *N*-tosyl-2,3-dihydro-pyrrole **79**[29] are known in the literature and can be easily be prepared. [4+2] cycloaddition of diene **56** with such enamine types of dienophiles would allow construction of different complex piperidine structures very rapidly. Therefore, enamines **78**, **79** and (*E*)-*N*-methyl-*N*-(prop-1-enyl)-*p*-toluenesulfonamide (**80**) were chosen as dienophile partners in our subsequent cycloaddition reactions with **56**. The enamine dienophiles were subjected to the standard reaction conditions ($TiCl_4$, –78 °C) with enamine-aminal **55**, and the resulting tetrahydropyridinium ion intermediates were treated with either base such as triethylamine or nucleophiles such as ketene acetal **81** or DIBAL-H (Table 2). It was found that these enamine dienophiles were indeed reactive under the reaction conditions, as they formed the respective cycloadducts **82a-d** and suppressed the dimerization reaction. The eliminated

[28] Wagger, J.; Svete, J.; Stanovnik, B. *Synthesis* **2008**, *9*, 1436-1442.
[29] Fustero, S.; Sanchez-Rosello, M.; Jimenez, D.; Sanz-Cervera, J. F.; Del Pozo, C.; Acena, J. L. *J. Org. Chem.* **2006**, *71*, 2706-2714.

products **82a** and **82b** resulting via triethylamine promoted abstraction of C_3-H, were obtained as single diastereomers with good yield (79% and 76% respectively). When the resulting tetrahydropyridinium ion from *N*-tosyl-indole cycloaddition was reduced with DIBAL-H, a 1:1 mixture of diastereomers (determined from ^{1}H NMR) **82c** was isolated (71%). The 1:1 diastereoselectivity could be explained by considering the fact that the cycloaddition reaction was following an ionic pathway rather than a concerted pathway. When enamine **80** was used as the dienophile, the respective tetrahydropyridinium ion was formed which underwent nucleophilic addition with **80** itself to provide the product **82d** (43%, d.r. >97:3) after quenching with ketene acetal **81**. Thus the enamine **80** was found to be the most reactive among all of these enamine dienophiles. The above results suggest that enamine dienophiles are good dienophile partners in cycloaddition reactions with **56**.

Table 2. Reaction scopes: Synthesis of priperidine derivatives



= D	 **78**	 **79**	 **78**	 **80**
base/ Nu:	Et_3N	Et_3N	DIBAL-H	 **81**
product:	 **82a** *79% (d.r. > 97:3)*	 **82b** *76% (d.r. > 97:3)*	 **82c** *71% (d.r. 1:1)*	 **82d** *43% (d.r. > 97:3)*

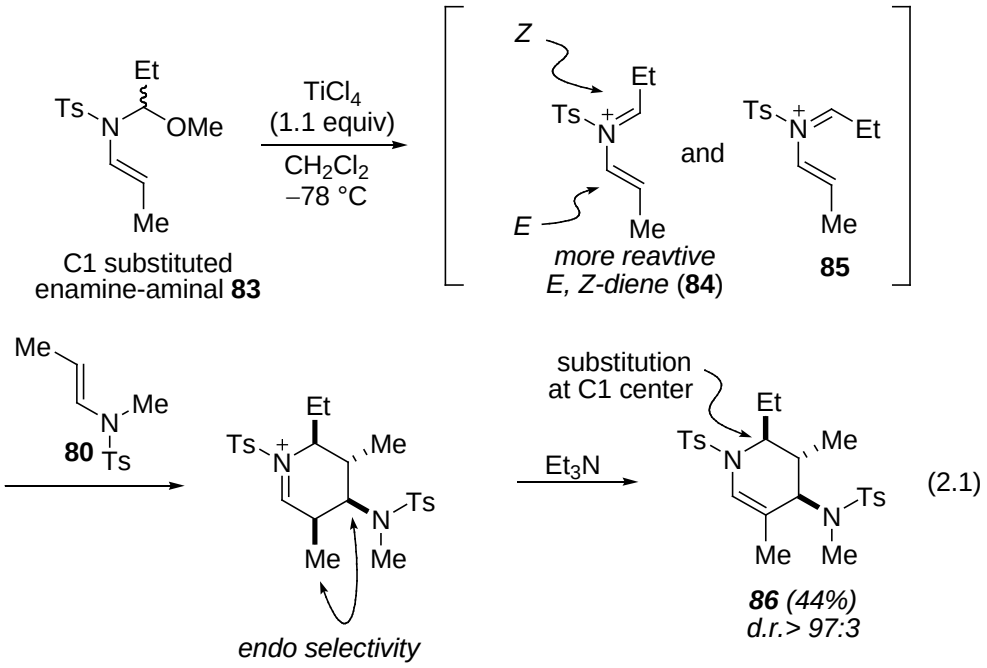
d.r. were determined from ^{1}H NMR

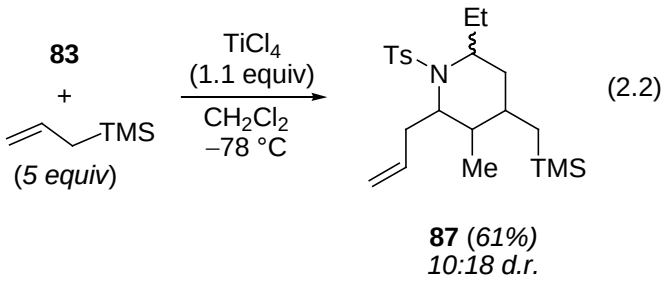
2.1.3 C1-Substituted Piperidine Synthesis

Substitution at the C1 position of enamine-aminal derivatives would provide access to azadienes possessing substitution at both terminal carbons. This substitution would allow us to construct fully substituted piperidine derivatives. Also from the reaction perspective, the substitution at the C1 position would change the reactivity of the resulting diene as the substitution would stabilize the incipient carbocation. For the same reason, milder Lewis acids could be effective for their generation. Considering these facts and the current progress in the enamine-aminal synthesis strategy, a C1-substituted *N*-alkoxymethyl enamine **83** was synthesized (discussed in Chapter 4).

Upon treating with Lewis acid, ionization of racemic **83** was obtained generating the anticipated mixture of (*Z*,*E*)- and (*E*,*E*)-dienes **84** and **85**, respectively (Scheme 16). In situ cycloaddition of the more reactive (*Z*,*E*)-diene **84** with enamine **80** afforded the tetrasubstituted piperidine **86** with high endo-selectivity (44%, 97:3 d.r. as d.r. determined from ^{1}H NMR) after quenching with triethylamine whereas the more stable (*E*,*E*)-diene **85** remained untouched and was recovered (eq 2.1). Instead of dienophile **80**, when more reactive dienophile allyltrimethylsilane was used, both of the (*Z*,*E*)- and (*E*,*E*)-dienes reacted with similar reactivity resulting in the cycloadduct **87** with 10:18 diasteomeric ratio (determined from ^{1}H NMR) (eq 2.2). Thus we have successfully added a degree of substitution to the cycloadducts by introducing a substitution at the C1 position. The introduction of the C1 substituent in the diene resulted in less reactive dienes **84** and **85** compared to **56** in the cycloaddition with enamine dienophile **80**. However allyltrimethylsilane was reactive enough to engage both dienes **84** and **85** in the cycloaddition reaction.

Scheme 16. Cycloaddition with C1-substituted enamine-aminal





2.2 CYCLOADDITION WITH NEUTRAL AND UNACTIVATED OLEFINS

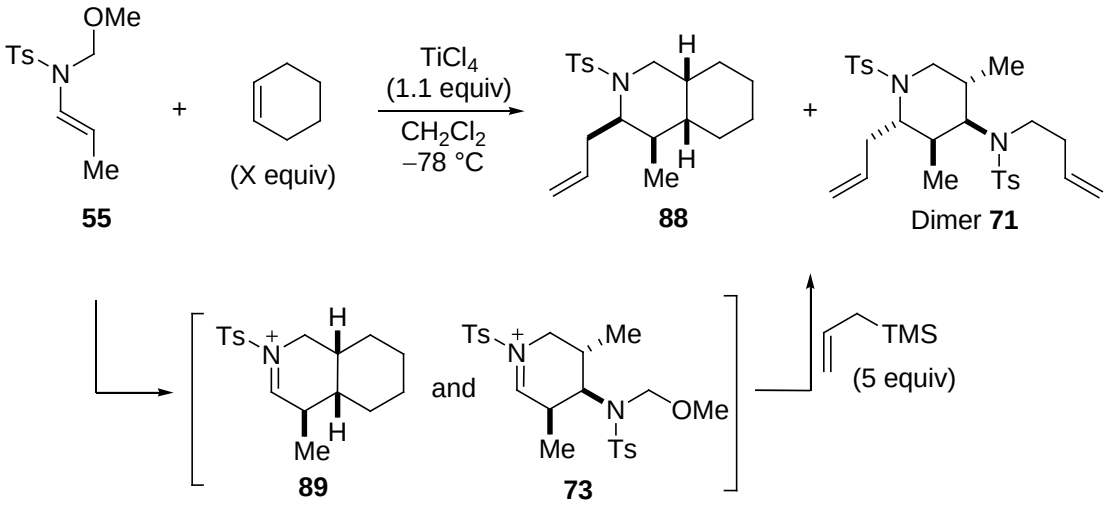
2.2.1 Reaction with Cyclohexene: Reaction Condition Development

The *N*-alkenyl iminium ion **56** has so far been found to engage in cycloadditions with electron rich dienophiles even at very low temperatures (–78 °C). Encouraged by these results, the reactivity of *N*-alkenyl iminium ion **56** was next evaluated with electronically neutral and unactivated olefins as dienophiles in the [4 + 2] cycloaddition reaction sequence to see if the electron-deficient nature of this diene would allow it to express sufficient reactivity in such cases. In this regard, cyclohexene (2.5 equiv) was subjected to the previously developed reaction conditions ($TiCl_4$, –78 °C) (Table 3). The reaction required a longer time (> 24 h) to complete (monitoring by TLC). Upon seeing the disappearance of the starting material on TLC, excess allyltrimethylsilane was added and the reaction was quenched with a saturated solution of $NaHCO_3$ after 3 h. The desired cycloadduct from cyclohexene, **88** (the perhydroisoquinoline derivative), as well as the dimer, **71**, were isolated (**88**:**71** = 2:1). Considering that non-reactive cyclohexene would not compete with the relatively reactive enamine **55**, a complete dimerization was expected. However, due to the extremely electron-deficient nature of the diene, reaction with cyclohexene was possible leading to formation of cycloadducts **71** and **88** in a 2:1 ratio. The

poorer reactivity of cyclohexene in comparison with electron-rich enamine dienophile (from the starting material itself) caused the poor yield of cyclohexene cycloadduct **88** (15%). For improving the reaction reactivity towards the desired pathway to generate more of the cycloadduct **88** we hypothesisized that increasing the quantity of cyclohexene in the reaction mixture, and decreasing the active concentraton of the enamine via slow addition of the enamine precursor might enhance the yield of the desired product **88**. Indeed, using 10 equivalents cyclohexene provided 48% of the desired product **88** and 20% of the dimer **71** after column purification. In the next experiment, a solution of enamine **55** was added slowly over a period of 3-4 hours to a mixture of cyclohexene with $TiCl_4$, a further enhancement in the yield of **88** (up to 54%, isolated yield) was obtained. The poorer reactivity of cyclohexene resulted in extended reaction times (36 hours at −78 °C). We assumed that a relatively higher temperature would enhance the rate of the cycloaddition step, and then the overall reaction time could be lowered. However the effect of an increase in temperature on the stability of the intermediate tetrahydropyridinium ion **89** was not known. In order to know upto what temperature the intermediate **89** was stable, a few control reactions at different temperatures were performed, and the products were analyzed (Table 4). It was observed that the tetrahydropyridinium ion intermediate was stable at −50 °C, and the reaction showed better reactivity as it took six-eight hours to complete providing **88** in a slightly better yield of 59%. Upon increasing the reaction temperature to −30 °C, deprotonation of the C_3-H occurred and the eliminated product **90** was isolated as the only product (yield not determined). Therefore the optimized condition for the cycloaddition reaction was found to be the slow addition of the diene precursor over three hours to cyclohexene (10 equiv) and $TiCl_4$ (1.1 equiv) in dichloromethane at −78 °C, followed by

warm up to −50 °C and stirring for six-eight hours, followed by nucleophile addition, and stirring for one-three hours. The results are tabulated below.

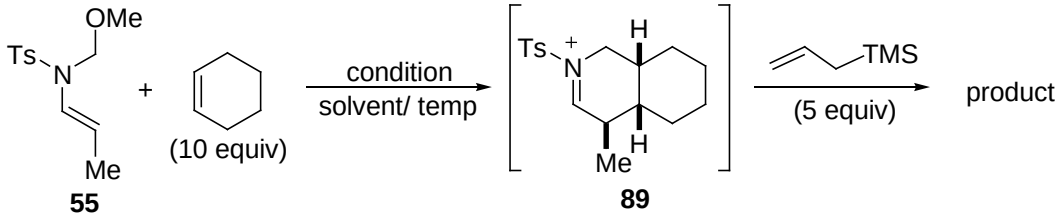
Table 3. Reaction with cyclohexene: Standard condition development

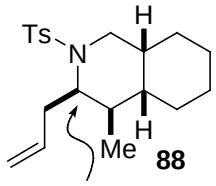
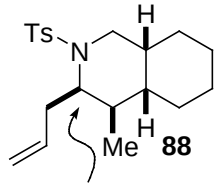
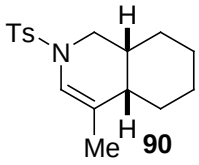


amount of cyclohexene	%yield of **88**	%yield of **71**
2.5 equiv	15	30
10 equiv	48	20
10 equiv	54	nd

nd = not determined

Table 4. Reaction with cyclohexene: Temperature scans



condition	solvent/ temp	Product[a]	yield[a] (%)
slow addition over 3h then 36 h	CH_2Cl_2 / – 78 °C	 30:1 d.r.	54
slow addition over 3h then 6 h	CH_2Cl_2 / – 78 °C at – 50 °C	 30:1 d.r.	59
slow addition over 3h then 6 h	CH_2Cl_2 / – 78 °C at –30 °C		nd

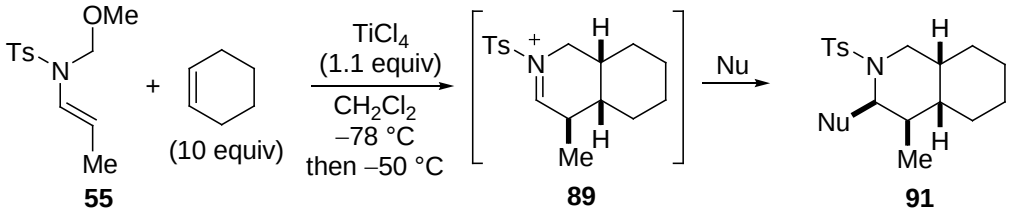
[a] isolated yields. d.r. was determined from ^{1}H NMR. nd = not determined

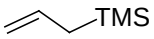
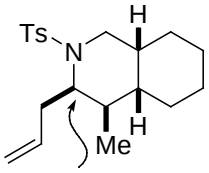
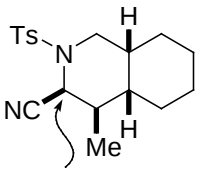
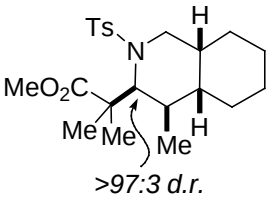
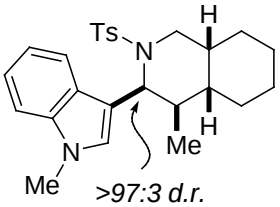
2.2.2 Reaction with Cyclohexene: Synthesis of Structurally Diverse *N*-Heterocycles

For the generation of structurally diverse piperidine derivatives, we proceeded to explore the scope of the cycloaddition reaction of diene **56** with cyclohexene with various nucleophiles, using the optimized reaction conditions [slow addition of **55** over three hours to a mixture of cyclohexene (10 equiv) and $TiCl_4$ (1.1 equiv) at –78 °C, then stirred at –50 °C for twelve hours]. Upon intercepting the cycloadduct **89** with different nucleophiles, the reaction delivered the

perhydroisoquinoline derivatives **88** (59%), **91a** (54%), **91b** (57%), and **91c** (53%) as single diastereomers (Table 5). From X-ray crystallographic analysis of the crystalline cycloadduct **88**, it was concluded that the reaction proceeded via an exo transition state **92**, presumably due to the seric bulk of the cyclohexene ring (Figure 12). The intermediate **89** when treated with allyltrimethylsilane, underwent selective nucleophilic attack from the top less hindered convex face of the cyclic intermediate affording excellent diastereoselection (d.r. = 30:1).

Table 5. Representative examples of synthesized piperidines with cyclohexene



Nu:		TMSCN	ketene acetal (**81**)	*N*-methyl indole
product:				
	30:1 d.r.	*>97:3 d.r.*	*>97:3 d.r.*	*>97:3 d.r.*
	88 *(59%)*	**91a** *(54%)*	**91b** (*57%)*	**91c** (*53%)*

d.r. were determined from ^{1}H NMR

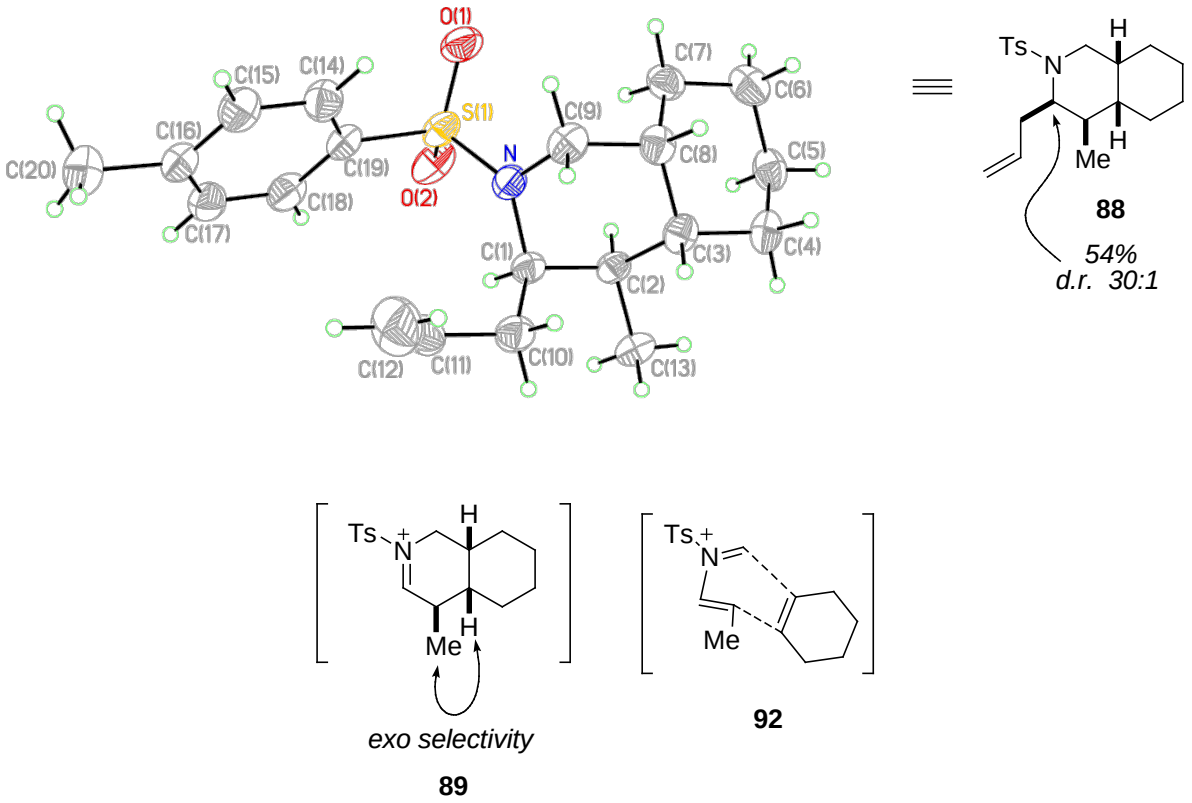
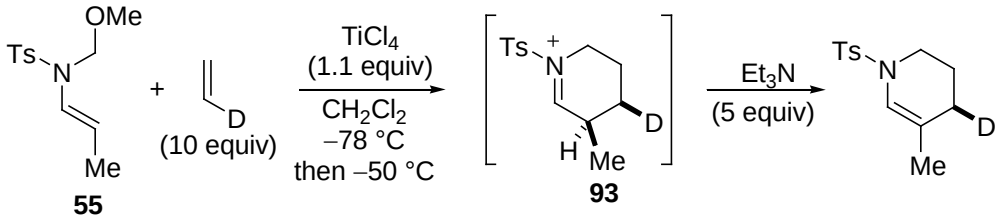


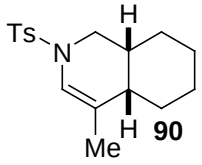
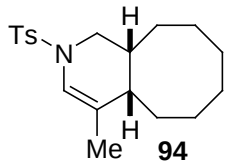
Figure 12. X-ray structure and transition state

Instead of treating with nucleophiles, the tetrahydropyridinium ion intermediate (**93**) was treated with base (Et_3N) to afford the [n.4.0] bicyclic heterocycles (Table 6). The amine-mediated deprotonation was used as an alternative method for further derivation of the cycloadducts providing an avenue to introduce diversity to the final structures. Cyclohexene and cyclooctene were employed as dienophiles in the reaction with **56** and the respective cycloadducts, **90** (53%) and **94** (69%), were isolated as single diastereomers. The results obtained from the cycloadditions between enamine **55** and neutral olefins where the non-reactive dienophiles underwent cycloaddition suggested that the *N*-alkenyl iminium ion is reactive with any type of dienophile, provided that the dienophile is stable under the reaction conditions. Upon establishing the reactivity towards neutral olefin dienophiles, simple *O*-allylic and *N*-allylic

olefins (electronically deactivated olefins) were evaluated next (Scheme 17). When subjected to excess **56** under the standard reaction conditions, decomposition of **55** was observed.

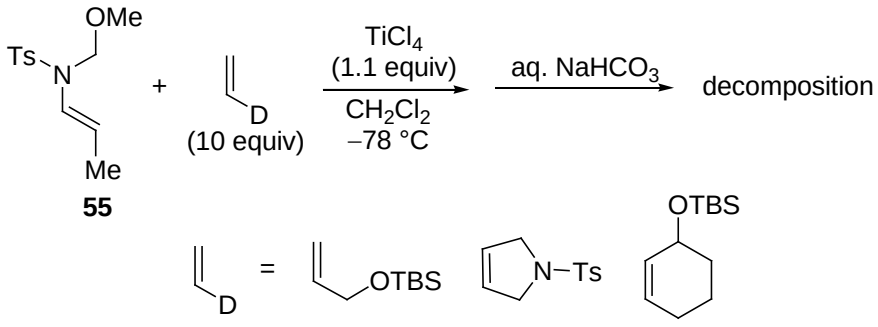
Table 6. Representative example of [n.4.0] bicyclic heterocycles



dienophile	product	yield[a] (%)	d.r.[b]
cyclohexene	 **90**	53	>97:3
cyclooctene	 **94**	69	>97:3

[a] isolated yields. [b] d.r. was determined from ^{1}H NMR

Scheme 17. Cycloaddition with electronically unactivated dienophiles



(eletronically deactivated dienophiles)

2.2.3 Trapping Tetrahydropyridinium Ion with Isonitriles

As mentioned above, the tetrahydropyridinium ion intermediate **89** was trapped with various reactive nucleophiles to introduce substitution at C2 position of the resulting piperidine such as **88**. Till this point, we did not evaluate the reactivity of the tetrahydropyridinium ion intermediate **89** with moderately reactive nuclophile. In this regard, we considered isonitriles (Figure 13) which were nucleophilic in nature, and we envisioned that these reagents might provide enough reactivity to trap the tetrahydropyridinium ion intermediate **89**. The addition of isonitriles would introduce diversity at C2 position by forming an amide type bond in the final cycloadducts.

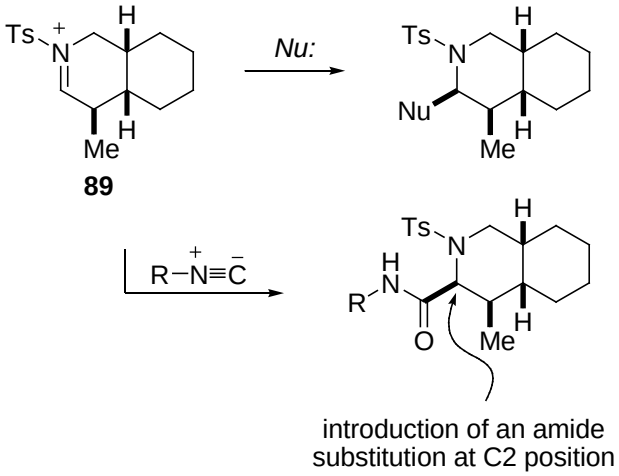


Figure 13. Isonitrile as nucleophile

Isonitriles are useful reagents in organic synthesis especially in several multicomponent processes, such as the Passerini [30] and Ugi [31] reactions. They are the active participant in

[30] (a) Andreana, P. R.; Liu, C. C.; Schreiber, S. L. *Org. Lett.* **2004**, *6*, 4231-4233. (b) Andrade, C. K. Z.; Takada, S. C. S.; Suarez, P. A. Z.; Alves, M. B. *Synlett.* **2006**, 1539-1541.
[31] (a) Kaim, L. E.; Grimaud, L.; Oble, J. *Angew. Chem., Int. Ed.*, **2005**, *44*, 7961-7964. (b) Tanaka, Y.; Hasui, T.; Suginome, M. *Org. Lett.* **2007**, *9*, 4407-4410.

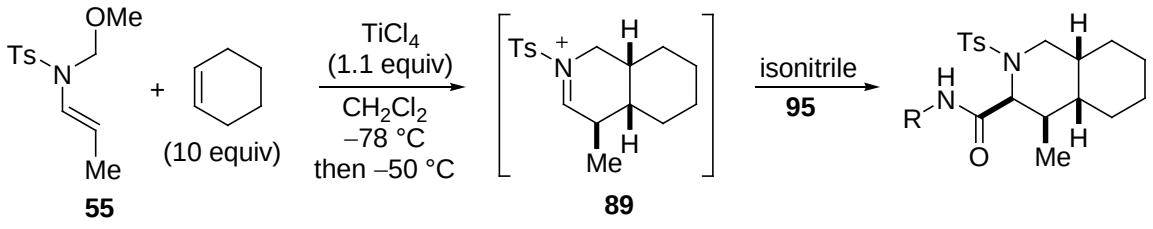
combinatorial and library syntheses of many methodologies.[32] Some of the isonitriles are commercially available, but they can also be easily prepared from readily available materials. We studied the addition of isonitriles as nucleophiles in the cycloaddition reaction of **56** with cyclohexene [slow addition of **55** over three hours to a mixture of cyclohexene (10 equiv) and $TiCl_4$ (1.1 equiv) at −78 °C, then stirred at −50 °C for twelve hours], and the tetrahydropyridinium ion intermediate **89** was intercepted with different isonitriles (**95a-c**) (Table 7). When *tert*-butylisonitrile (**95a**) was used, the corresponding cycloadduct was formed but the tertiary butyl group was found to be unstable under the reaction conditions affording **91a** (52% yield, single diastereomer) as the sole product. This result suggested that intermediate **89** was sufficiently reactive to undergo addition of moderate nucleophiles such as **95a**. When **95b** was used as the nucleophile, a complex mixture of products was isolated but it was evident from the crude ^{1}H NMR that product **96b** had been formed. Column purification followed by crystallization afforded analytically pure sample in 36% yield and as a single diastereomer. It was understood that **95b** was sufficiently reactive to trap **89**, but the work up led to formation of several other byproducts (unindentified). To solve this problem, the work up protocol was standardized where byproduct formation was minimized. It was highly possible that the aromatic substitution present in **95b** caused the isonitrile to be susceptible to work up conditions resulting in decomposition. Optically pure isonitrile **95c** was synthesized following literature protocol[33] and subjected to the reaction conditions which afforded the respective cycloadducts **96c** (50%, 1:1 d.r.) suggesting highly selective addition at C2 center.

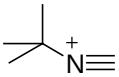
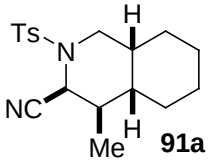
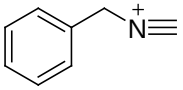
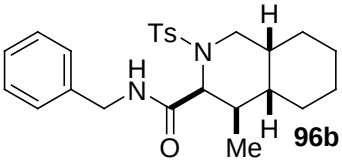
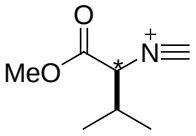
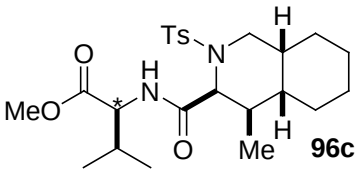
---

[32] (a) For review: Zhu, J. *Eur. J. Org. chem.* **2003**, 1133-1144. (b) Kennedy, A. L.; Fryer, A. M.; Josey, J. A. *Org. Lett.* **2002**, *4*, 1167-1170.

[33] (a) Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, *4*, 400-402. (b) Zhu, J.; Wu, X.; Danishefsky, S. J. *Tetrahedron Letters* **2009**, *50*, 577-579.

Table 7. Trapping the tetrahydropyridinium ion intermediate with isonitriles



isonitrile	product	yield[a] (%)
 **95a**	 **91a**	52 *d.r. > 97:3*
 **95b**	 **96b**	36 *d.r. > 97:3*
 **95c**	 **96c**	50 *d.r. = 1:1*

[a] isolated yield. d.r. was determined from ^{1}H NMR

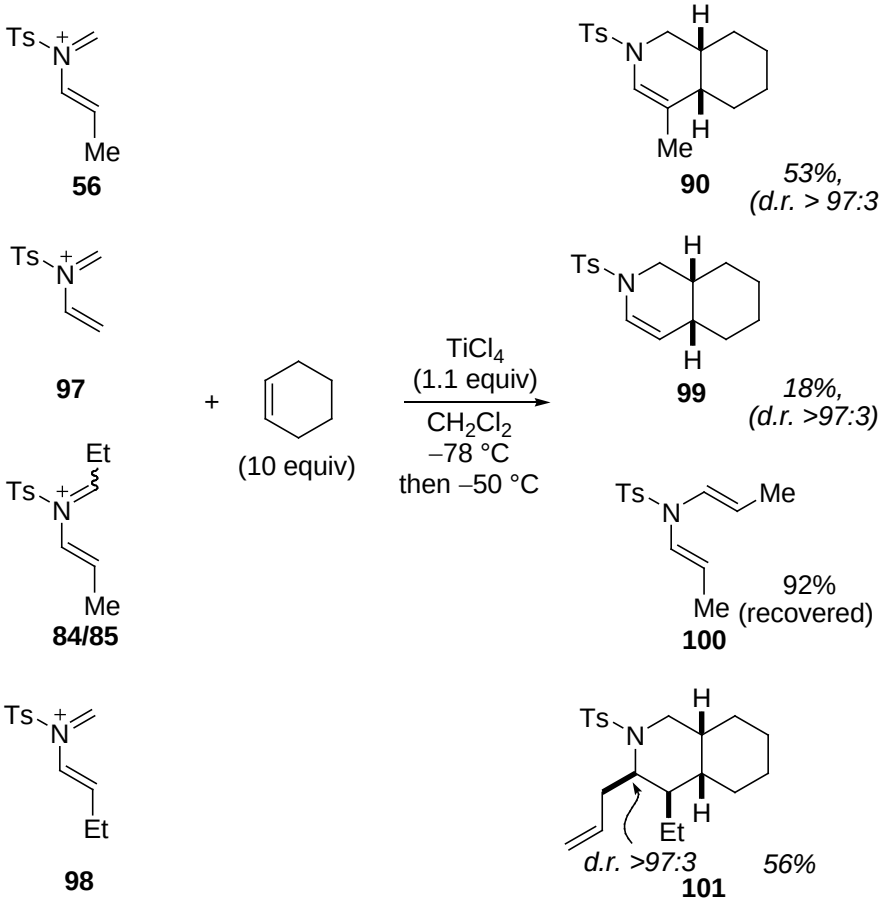
2.2.4 Reactivity of the *N*-Alkenyl Iminium Ion Diene

The current progress in enamine-aminal synthesis enabled us to have four different *N*-alkenyl iminium ion dienes, **56**, **97**, **84/85** and **98** which contained substitutions at either or both ends of the structure (Scheme 18). In order to determine and compare the reactivity of these dienes as cycloadition partners, the respective diene precursors were subjected to cycloaddition reactions with cyclohexene. The diene **56** provided the cycloadduct **90** in 53% yield and as a single diastereomer but the diene **97** with no substitution at either C1 and C3 provided **99** in 18% yield

and as a single diastereomer. Diene **84/85** was completely unreactive towards cyclohexene, and upon quenching the reaction, the eliminated product (*E*)-*N*,*N*-di-(prop-1-enyl)-*p*-toluenesulfonamide[34] **100** was obtained. The diene **98** provided the respective cycloadduct **101** (56% and > 97:3 d.r.) after the resulting tetrahydropyridinium ion intermediate was trapped by adding excess allyltrimethylsilane. The poor yield of cycloadduct (18%) from diene **97** and cyclohexene suggested that **97** was highly reactive in comparison to dienes **56** or **98**, preferentially decomposing at a faster rate than undergoing cycloaddition reaction**.** Dienes **56** and **98**, possessing substituents at C3, showed similar reactivities whereas diene **84/85** possessing substituents at both C1 and C3 was not sufficiently reactive and did not give any cycloadduct with cyclohexene. Therefore it could be concluded that substitution at C3 only was optimum for obtaining successful cycloaddition reaction with cyclohexene.

[34] Terada, Y.; Arisawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4063-4067.

Scheme 18. Reactivity comparison of the dienes



[a] isolated yield. d.r. was determined from ^{1}H NMR

2.2.5 Strategy to Remove Tosyl Protecting Group

In the context of our methodology, however, to make the piperidine derivatives useful, it was necessary to remove the tosyl group from the final piperidine structures. So far, the tosyl protected enamine-aminal **55,** provided better reactivity and was used throughout this

methodology as opposed to other carbamate protected enamine-aminals. Removal of the tosyl protecting group is usually carried out under harsh reductive conditions[35] using either sodium-naphthalenide or sodium-liquid ammonia, but some base mediated methods are known for the indole derived substrates.[36] As the utility of tosyl protected enamine-aminal **55** was well established in the synthesis of complex piperidines, efforts were made to find a different sulfonyl protecting group, which would provide similar reactivity and selectivity. The protecting group should offer a mild condition of its removal, which should be suitable for the piperidine derivatives. The group should be compatible with an isomerization reaction providing high yield and chemoselectivity. Considering all of these facts, we proceeded with both *tert*-butyl and thiophene containing sulfonyl groups (Figure 14). Both of the groups are known, can easily be removed, and are expected to not change reactivity greatly. Finally, we decided to synthesize thiophenesulfonyl (thienyl, Th) protected enamine-aminal **102** instead of the *tert*-butylsulfonyl protected enamine-aminal **103** because the latter might not be stable under the cycloaddition conditions.

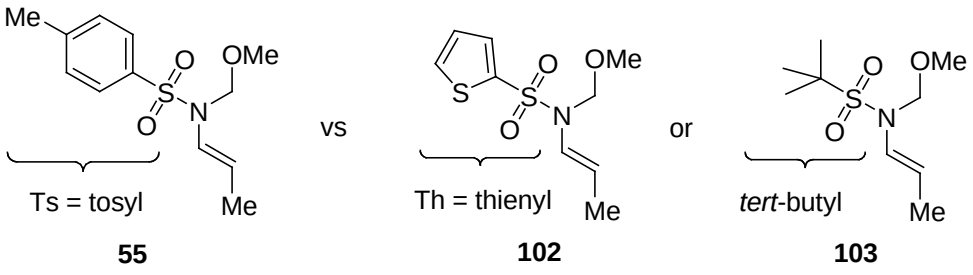
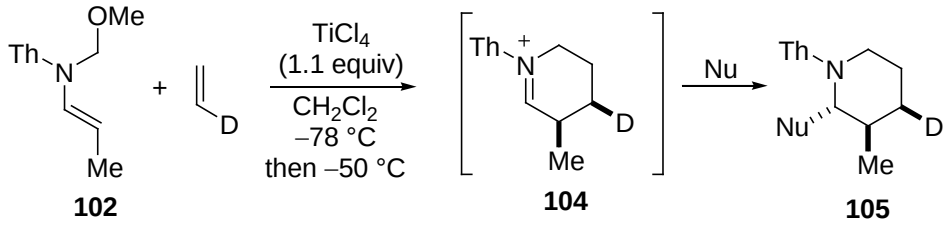


Figure 14. Tosyl vs thienyl protected enamine-aminal

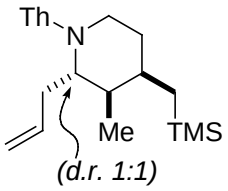
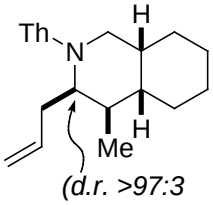
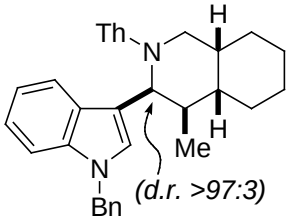
[35] (a) Moussa, Z.; Romo, D. *Synlett* **2006**, *19*, 3294-3298. (b) Gold, E. H.; Babad, E. *J. Org. Chem.* **1972**, *37*, 2208-2210.
[36] Bajwa, J. S.; Chen, G-P.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2006**, *47*, 6425-6427.

The diene precursor **102** was synthesized from commercially available thienyl-2-sulfonyl chloride following the same method as for the synthesis of **55** (details about their preparations are discussed in chapter 4). The reactivity pattern of the resulting dienophiles derived from **55** and **102** were supposed to be similar. Based on this assumption, **102** was subjected to the standard reaction conditions developed for reactive [slow addition of **102** over three hours to a mixture of allyltrimethylsilane (5 equiv) and $TiCl_4$ (1.1 equiv) at −78 °C] and non reactive dienophiles [slow addition of **102** over three hours to a mixture of cyclohexene (10 equiv) and $TiCl_4$ (1.1 equiv) at −78 °C, then stirred at −50 °C for twelve hours]. The resulting tetrahydropyridinium ion intermediates (**104**) were subsequently trapped with nucleophiles, and a few illustrative examples are shown in table 8. As expected, when treated with allyltrimethylsilane, the thienyl derived diene was found to be reactive and the respective cycloadduct **105a** was isolated (78%) as a 1:1 mixture of diastereomers at C2 center (determined from ^{1}H NMR). Cycloaddition with cyclohexene resulted in hydroisoquinoline products **105b** (49%, single diastereomer) and **105c** (52%, single diastereomer). The diastereoselectivity and yields were comparable to tosyl-diene derived products which suggested that both of the dienes possessed similar reactivity.

Table 8. Synthesis of thienyl-2-sulfonyl (Th) protected piperidines



102 **104** **105**

dienophile:	allylTMS	cyclohexene	cyclohexene
Nu:	allylTMS	allylTMS	*N*-benzyl Indole
product:			
	(d.r. 1:1)	*(d.r. >97:3*	*(d.r. >97:3)*
	105a (*78%)*	**105b** (*49%)*	**105c** *(52%)*

d.r. were determined from ^{1}H NMR

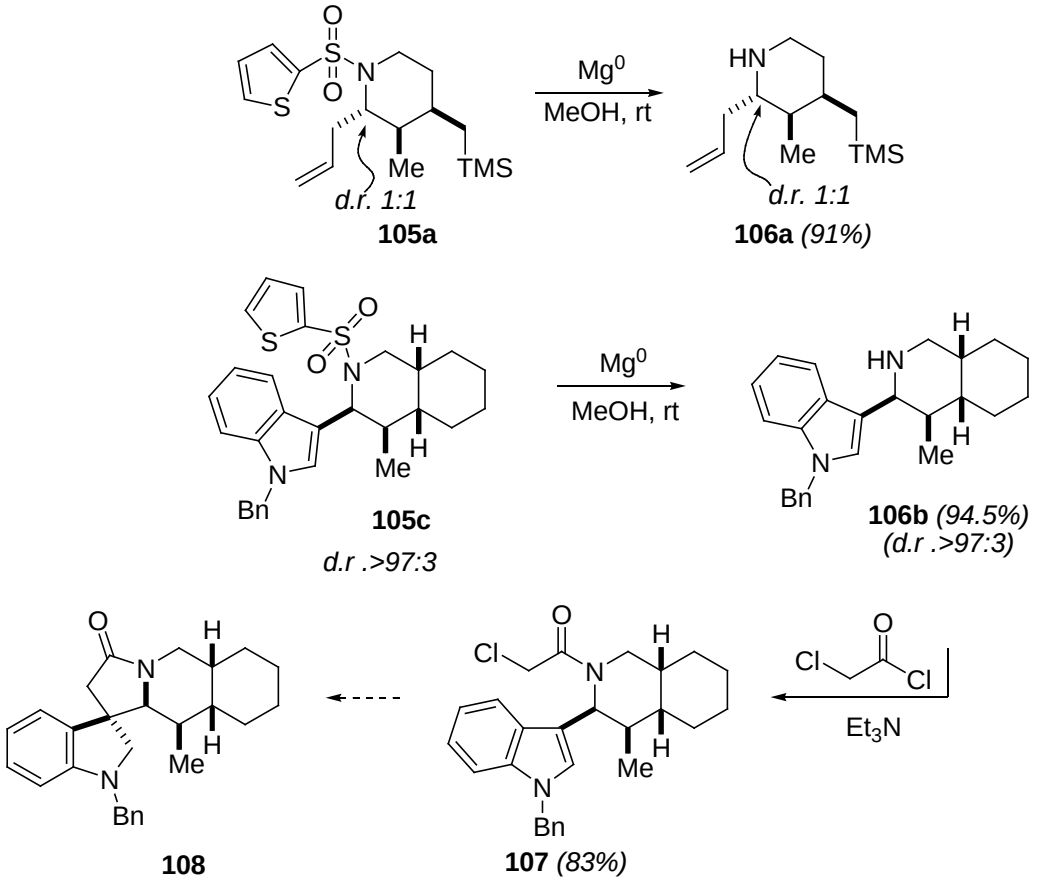
2.2.6 Removal of Thienyl Protecting Group and Derivatization of the Deprotected Piperidine

After establishing the utility of the thiophene-2-sulfonyl protecting group in cycloaddition reactions, we focused our attention towards its removal and further derivatization of the resulting piperidines. It is known in the literature[37] that the thienyl group can be cleaved reductively under mild condition using magnesium in methanol. For the desulfonylation reaction, the thienyl derived cycloadduct **105a** was subjected to magnesium-methanol condition at room temperature and the respective desulfonylated piperidine **106a** was isolated in 91% yield after two hours (Scheme 19). The indole derived cycloadduct **105c** was subjected next to the deprotection

[37] (a) Salvador Gonzalez, A.; Gomez Arrayas, R.; Rodriguez Rivero, M.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335-4337. (b) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 9588-9589.

conditions and the respective desulfonylated product **106b** was isolated in good yield (94.5%). The piperidine **106b** was subjected to further derivatization and subsequently was alkylated with chlorocaetyl chloride to afford **107** in good yield (83%). Further cyclization of **107** would lead to the complex spirocycle **108** (similar process is known in the literature[38]). Thus the removal of thienyl protecting group was easily achieved. Further derivatization at the N center would be possible and this would provide another degree of diversity in the piperidine structure.

Scheme 19. Reductive desulfonylation and further derivatization



[38] (a) Banwell, M. G.; Lupton, D. W.; Willis, A. C. *Aus. J. Chem.* **2005**, *58*, 722-737. (b) Banwell, M. G.; Lupton, D. W. *Org. & Biomol. Chem.* **2005**, *3*, 213-215.

2.3 CONCLUSION

The reactivity of *N*-tosyl diene intermediate with various olefins, such as electronically activated, neutral, and unactivated, has been evaluated. Finally, utilizing this reactive diene in a multicomponent cycloaddition reaction sequence, an efficient access to structurally diverse and stereochemically rich piperidine derivatives have been demonstrated. The diene was found to be highly reactive and reacted with even the neutral dienophile cyclohexene. Further functionalization of the cyclic tetrahydropyridinium ion either by different nucleophiles or by amine-mediated deprotonation strategies adds another degree of diversity to the final products. These attributes are expected to render this methodology generally useful in both target-directed and diversity-oriented synthetic activities.

3.0 DEVELOPMENT OF A CATALYTIC AND ASYMMETRIC REACTION

The direct production of enantioriched synthons by asymmetric catalysis is becoming a popular research strategy. Over the last two decades, chemists have discovered many asymmetric reactions to deliver enantiopure synthons by developing catalytic methods using either chiral Lewis acids or Bronsted acids. Towards this goal, we started to address those unsolved problems that we faced during our reaction development, and we focused our attention towards finding a catalytic and asymmetric method. We have observed a few facts during our reaction development using achiral Lewis acids catalysis and concluded that they are crucial in terms of finding a good catalytic and asymmetric method (Figure 15). Firstly, we realized that the *N*-protecting group and the leaving group of the diene should be complementary to each other so that the most reactive diene precursor could be prepared. The leaving group should not be too labile so that problems during the isolation and/or handing of the substrate could be avoided. On the other hand, it should be labile enough for the ionization to take place. Also the protecting group should not hold the nitrogen lone pair too strongly so that it requires a strong Lewis acid. Therefore, both the protecting group on N and the leaving group will determine the strength of Lewis acid required for successful ionization. Secondly, we observed that low temperature was needed in order to stabilize the tetrahydropyran intermediate to avoid significant decomposition. Finally, the dienophile should be reactive enough to react with the diene at low temperature and should be stable in presence of the Lewis acid.

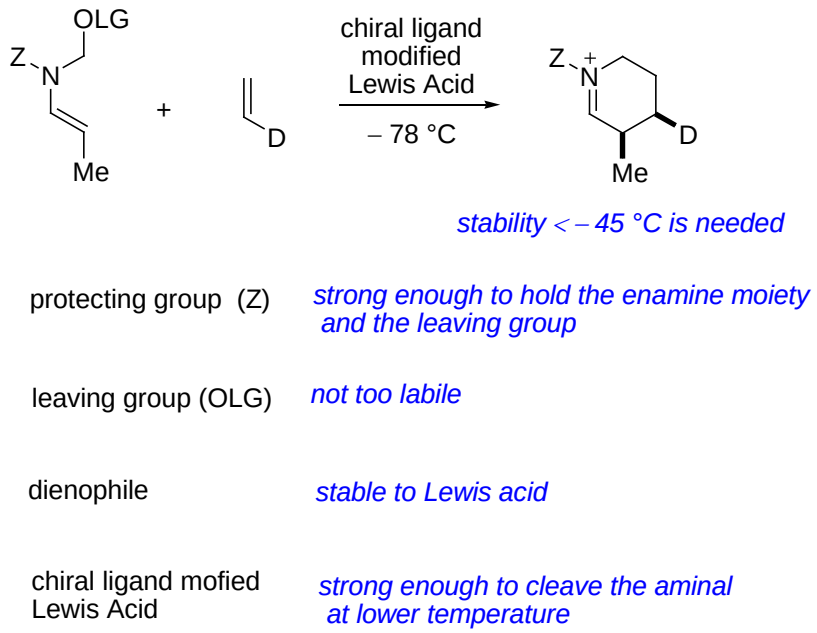


Figure 15. Evaluation of a catalytic and asymmetric reaction

Considering all of these facts, we started to design our reaction for a successful asymmetric method (Figure 16). We considered three possible strategies through which we could introduce asymmetric components to our reaction for the synthesis of enantioriched piperidines:

1) *Using chiral dienophiles:* The easiest and simplest way would be using simple chiral dienophiles, which are known in the literature and can easily be made while keeping the other parameters same.
2) *Using chiral diene:* Chiral *N*-protecting groups are known and by using them, a chiral component can be introduced to the reaction.
3) *Using chiral ligand modified Lewis acid complex:* Instead of using chiral auxiliary based approaches (1 and 2), a reagent controlled approach would be more attractive. The best and most desired way of introducing chirality would be using a chiral ligand modified Lewis acid complex.

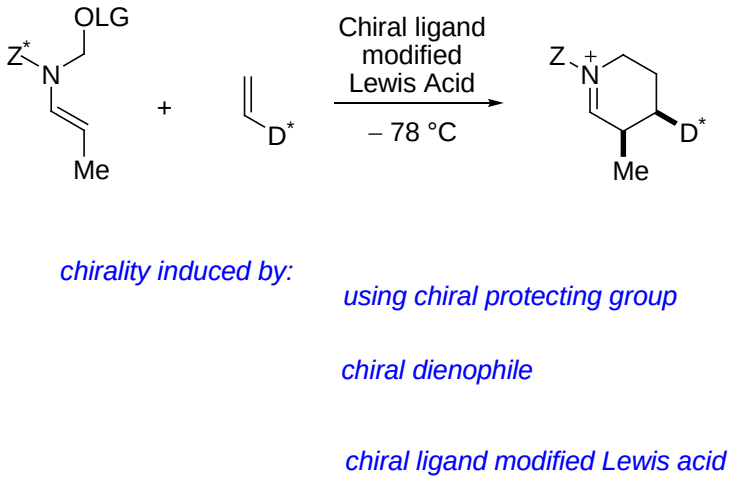


Figure 16. Introduction of chirality to the reaction via various components

3.1 REACTION DEVELOPMENT WITH CHIRAL AUXILIARIES

3.1.1 Reaction Development with Chiral Dienophiles

There are several chiral dienophiles often used in cycloaddition processes. For example, many diastereoselective Diels-Alder reactions were developed using enol ethers bearing chiral auxiliaries. Recently Boger and co-workers[39] reported an asymmetric variant of the 1-azadiene Diels-Alder reaction with high diastereoselectivity. Dujardin, Denmark, and many others[40] have successfully used different chiral enol ethers and showed that high diastereoselectivities could be

[39] Clark, R. C.; Pfeiffer, S. S.; Boger, D. L. *J. Am. Chem. Soc.*, **2006**, *128*, 2587–2593.
[40] (a) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1996**, *37*, 4007. (b) Dujardin, G.; Rossignol, S.; Brown, E. *Synthesis* **1998**, 763. (c) Gong, J.; Bonfand, E.; Brown, E.; Dujardin, G.; Michelet, V.; Geneˆt, J. *Tetrahedron Lett.* **2003**, *44*, 2141. (d) Gaulon, C.; Dhal, R.; Chapin, T.; Maisonneuve, V.; Dujardin, G. *J. Org. Chem.* **2003**, *68*, 4338. (e) Gizecki, P.; Dhal, R.; Poulard, C.; Gosselin, P.; Dujardin, G. *J. Org. Chem.* **2004**, *37*, 4007. (f) Review: Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (g) Pettus, T. R. R.; Selenski, C. *J. Org. Chem.* **2004**, *69*, 9196. (g) Gizecki,P.; Dhal, R.; Toupet, L.; Dujardin, G. *Org. Lett.*, **2000**, *2*, 585–588.

obtained. Representative examples of chiral auxiliary bearing dienophiles are shown in Figure 17.

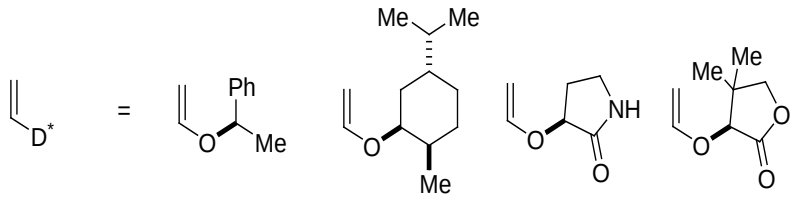
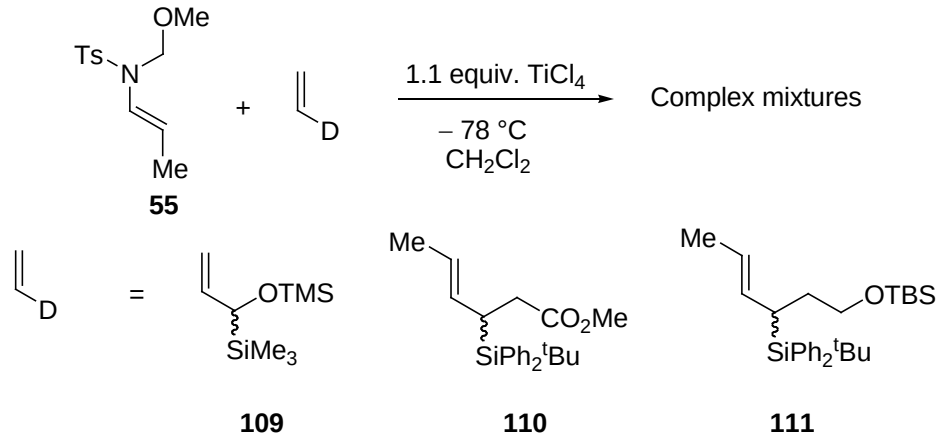


Figure 17. Commonly used vinyl ether derived chiral auxiliaries in Diels-Alder reactions

Initially, we thought that similar optically active enol ethers would be examined in our reaction methodology, but as mentioned previously, vinyl enol ethers were not compatible with titanium tetrachloride. Therefore we decided to use chiral silane based dienophiles rather than the chiral enol ethers. Several methods for the preparation of allylsilane derivatives are known in the literature. Racemic allylsilanes **109** [41], **110**, and **111** [42] were prepared according to known literature methods. Upon subjecting allylsilane **110** to the cycloaddition reaction with enamine **55**, the desired cycloadduct was not obtained (Scheme 20). Both the starting material and the allylsilanes disappeared leading to unindentified side-products. Similar observation was made with allylsilanes **109** and **111**. We concluded that the use of strong Lewis acid should be avoided, and hence, newer types of diene precursors were needed where efficient ionization could be achieved with milder Lewis acids.

[41] Hosomi, A.; Hashimoto, H.; Sakurai, H. *J. Org. Chem.*, **1978**, *43*, 2551-2552.
[42] Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1998**, *75*, 78-88.

Scheme 20. Cycloaddition: Attempts with racemic silanes



3.1.2 Reaction Development with *tert*-Butanesulfinyl Group

We envisioned that an optically active sulfinyl group, such as *tert*-butanesulfinyl group, could serve the purpose of both protecting group and chiral auxiliary at the same time (Figure 18). The optically active sulfinyl moiety is recognized as an efficient chiral auxiliary and often used as a nitrogen protecting group. High diastereoselectivities have been observed in reactions of chiral *tert*-butanesulfinyl-protected imines with various nucleophiles.[43] The *N*-sulfinyl group is readily cleaved from the addition products to provide amine hydrochlorides, and wide varieties of amine containing compounds have been prepared using this chemistry[44]. In this methodology, by using such sulfinyl derived chiral protecting group, chirality could be introduced in the diene precursor. Thus we decided to synthesize enamine-aminal **112** from *tert*-butanesulfonamide **113**.

[43] Fernandez, I.; Khiar, N. *Chem. Rev.*, **2003**, *103*, 3651–3706.
[44] (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.*, **2002**, *35*, 984–995. (b) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc.*, **2002**, *124*, 6518–6519.

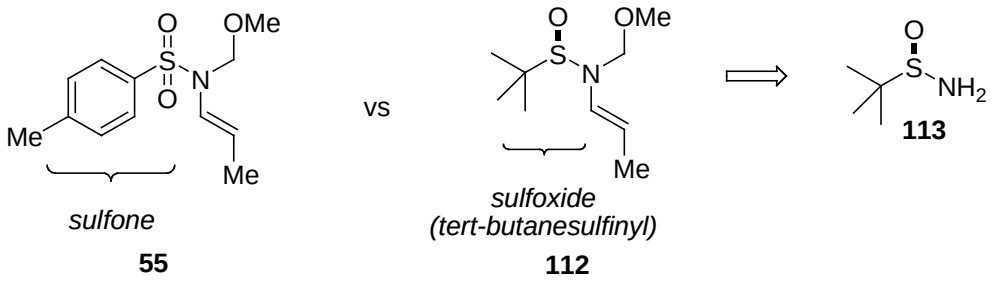
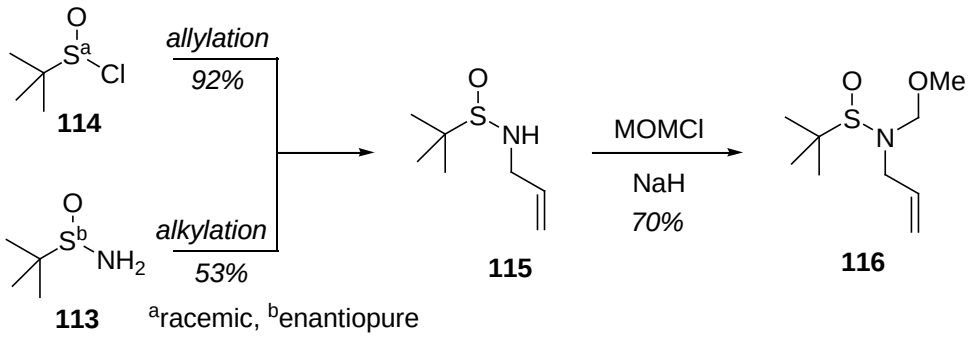


Figure 18. *tert*-Butanesulfinyl motif an effective chiral protecting group

The *tert*-butanesulfinamide **113** was prepared by following the procedure developed by Ellman and co-workers.[45] Subsequent allylation of **113** was screened under several mild basic conditions including K_2CO_3/CAN or Cs_2CO_3/CAN conditions at elevated temperatures and NaH/DMF conditions at ambient temperature (Scheme 21). The NaH/DMF condition was found to be the most reliable, yielding the desired product in moderate yield (53%). However, to expedite the synthesis of required enamine-aminal **112**, a racemic *tert*-butanesulfinyl chloride **114** was prepared quickly by following a known literature procedure[46] and upon treating with excess allylamine, *N*-allyl-*tert*-butanesulfinamide (**115**) was synthesized (92%). Having sufficient **115** in hand, the second alkylation reaction was performed with MOM-chloride and NaH, affording *N*-allylaminal **116** with good yield (70%).

[45] Weix, D. J.; Ellman, J. A.; Wang, X.; Curran, D. P. *Org. Synth.* **2005**, *82*, 157-165.
[46] (a) Gontcharov, A. V.; Liu, H.; Sharpless, K. B. *Org. Lett.*, **1999**, *1*, 783-786. (b) Netscher, T.; Prinzbach, H. *Synthesis*, **1987**, *8*, 683-688.

Scheme 21. Synthesis of *N*-allyl-*tert*-butanesulfinylaminal

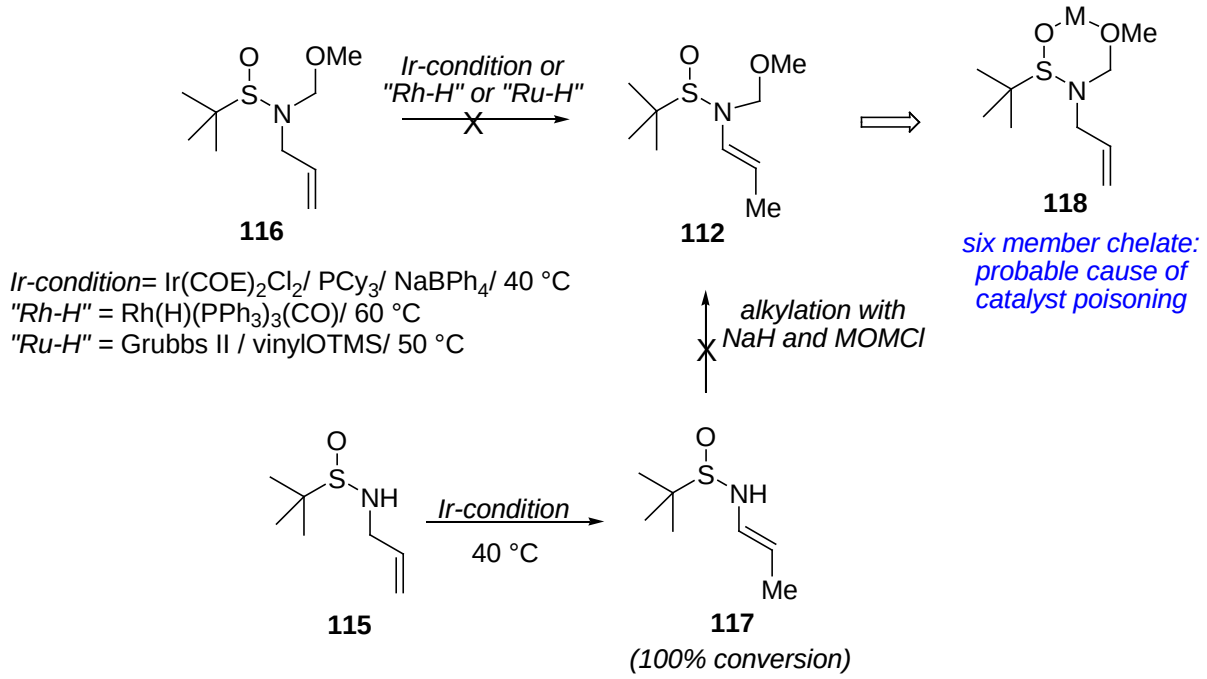


In order to synthesize the enamine-aminal **112**, isomerization of **116** was required next. The cationic iridium condition ($Ir_2(COE)_2Cl_2$, PCy_3, $NaBPh_4$, 40 ºC) developed in our group[47] was applied first, but only a partial conversion (<10%) was obtained (Scheme 22). Prolonging the reaction time at 40 ºC or raising the temperature to 80 ºC did not improve the conversion. It was also noticed that the conversion in the reaction was not reproducible. Isomerization reactions with other transitions metal catalyzed conditions, e.g. Rh(I) or Ru(I), were screened, but none of them led to product. In a control reaction, *N*-allyl-*tert*-butanesulfinamide (**115**) was subjected to isomerization with iridium catalyzed condition and a complete conversion to the corresponding isomerized product **117** was achieved providing the *E* isomer only. It was thought that the enamine-aminal **112** could also be prepared from **117** via alkylation with MOMCl. However, treating **117** with NaH and MOMCl did not afford the desired product. The observations resulting from the isomerization of **116** suggested that the catalyst was poisoned by the substrate as the sulfoxide functionality could bind with the transition metal[48] via its electron rich oxygen atom shutting down the isomerization process (**118**). Without investigating further to improve

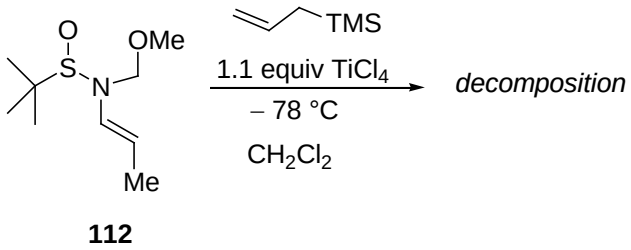
[47] Nelson, S. G.; Bungard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000-13001.
[48] (a) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188-8193. (b) Brunel, J. M.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1996**, *133*, 1109-1115.

the isomerization reaction yield and with the low amount of material in hand, the viability of the cycloaddition process was assessed. *tert*-Butylsulfoxide protected diene precursor (**112**) was subjected to cycloaddition with allyltrimethylsilane as the dienophile using $TiCl_4$ (1.1 equiv) at – 78 ºC, but a complete decomposition of **112** was observed (Scheme 23). The decomposition of **112** may be attributed to the instability of the ^{t}butyl group under the strong $TiCl_4$ conditions.

Scheme 22. Isomerization of *N*-allyl-*tert*-butanesulfinylaminal

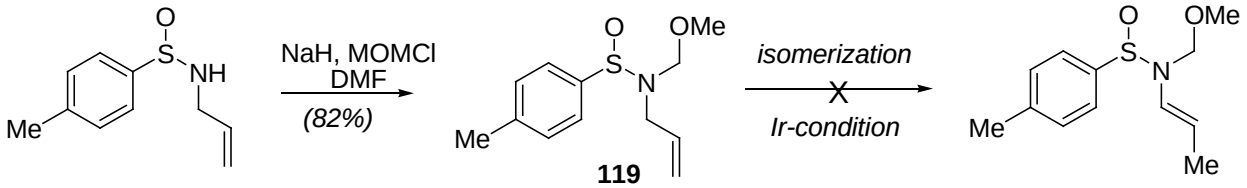


Scheme 23. Cycloaddition reaction with *N*-allyl-*tert*-butanesulfinylaminal



The instability of the *tert*-butylsulfoxide derived diene precursor **112** under the $TiCl_4$ reaction condition led us to construct more robust sulfinyl derived *N*-allylaminals. *p*-Tolylsulfinyl derived diene precursor **130** was synthesized,[49] but upon employing the iridium catalyzed isomerization condition, the catalyst was found to be completely inactive (Scheme 24). Chiral auxiliary based approaches for the asymmetric synthesis of piperidine derivatives were unsuccessful due to the inefficient isomerization techniques and incompatibility with $TiCl_4$. We proceeded for a Lewis acid catalyzed approach.

Scheme 24. Isomerization of *p*-tolylsulfinyl substrate **119**



Ir-condition= $Ir(COE)_2Cl_2$/ PCy_3/ $NaBPh_4$/ 40 °C

3.2 CATALYTIC AND ASYMMETRIC REACTION DEVELOPMENT WITH LEWIS ACID

So far in the cycloaddition reactions with diene **56**, stoichiometric amount of $TiCl_4$ has been used. For any Lewis acid mediated catalytic system, regeneration of the active catalyst is required at the end of the catalytic cycle. In our reaction, the Lewis acid binds to the substrate

[49] (a) Bravo, P.; Zanda, M.; Zappala, C. *Tetrahedron Lett.* **1996**, *37*, 6005-6006. (b) Cotton, H. K.; Huerta, F. F.; Baeckvall, J. *Eur. J. Org. Chem.* **2003**, *15*, 2756-2763. (c) Garcia R. J. L.; Aleman J.; Parra A. *J. Am. Chem. Soc.* **2005**, *127*, 13048-54.

120 in the first step providing the diene **121** and the Lewis acid-leaving group complex **122** (Figure 19). Next the diene would undergo a [4+2] cycloaddition with dienophile **123**, resulting in the formation of intermediate **124**. By choosing a suitable additive (in this case, excess allyltrimethylsilane), which will serve the purpose of both dienophile and nucleophile, the nucleophilic capture of tetrahydropyridinium ion intermediate (**124**) would produce the desired cycloadduct **125** and release a trimethylsilyl cation which would regenerate the active Lewis acid catalyst as described in the following mechanistic model. We were also aware of the fact that the electrophilic silicon species might activate the reaction itself, but we were hopeful that it would be trapped with the leaving group by forming a strong Si-O bond before it could start to behave as the catalyst under the reaction condition.

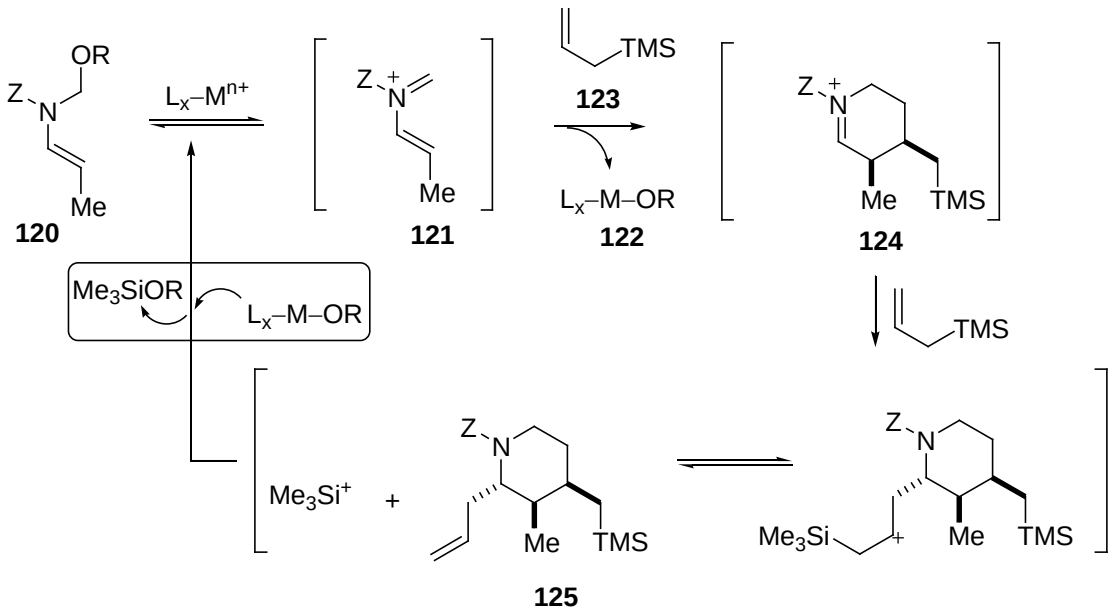


Figure 19. Mechanistic model for a Lewis acid catalyzed cycloaddition process

Lewis acid-substrate complexes often provide excellent stereoselectivity in presence of suitable chiral ligands[50] and numerous chiral ligand bound metal complexes are well known in the literatur.[51] We hypothesized that an enantiomerically enriched catalyst complex can effectively control cycloaddition facial selectivity exploiting fully the potential of this three-component cycloaddition process. In order to provide an effective binding site for the Lewis acid during the course of the reaction, carbonyl protected enamine-aminals such as **126** or **127** were considered. An asymmetric variant of this methodology would now be possible (Figure 20) as the chiral catalyst (**128**) would activate **126** affording the tight ion pair **129**, and the cycloaddition would proceed via the transition state ensemble **130**. Even if significant ion pairing were lost due to fast ionization, the fully developed diene intermediate would be in association with the catalyst, and the steric barrier from the ligand backbone would prevent the free rotation about the $N\text{-}C_{carbonyl}$ bond. The expectation was that the metal complex-diene intermediate assembly would be rigid enough and would dictate the metal complex to retain in one orientation relative to the diene plane defined by the initial chelate conformation. This reaction design implicated C_2-symmetric divalent metal complexes as suitable candidates. Divalent metals like Cu, Sn, Sc, Zn etc. would be considered due to their chelating ability. C_2-symmetric ligands like bisoxazoline (box), salen, and bispyridine derived were chosen for enantioselective cycloaddition catalysis.

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[50] (a) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8006-8007. (b) B. M. Trost, S. Shin, J. A. Sclafani, *J. Am. Chem. Soc.* **2005**, *127*, 8602-8603. (c) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998,** *120*, 4895-4896.

[51] (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669-685. (b) Walsh, P.J.; Lurain,A. E.; Balsells, J. *Chem. Rev.* **2003**, *103*, 3297-3344. (c) Sibi, M. P.; Manyem, S.; Zimmerman, Z. *Chem. Rev.* **2003**, *103*, 3263-3296. (d) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069-1094.

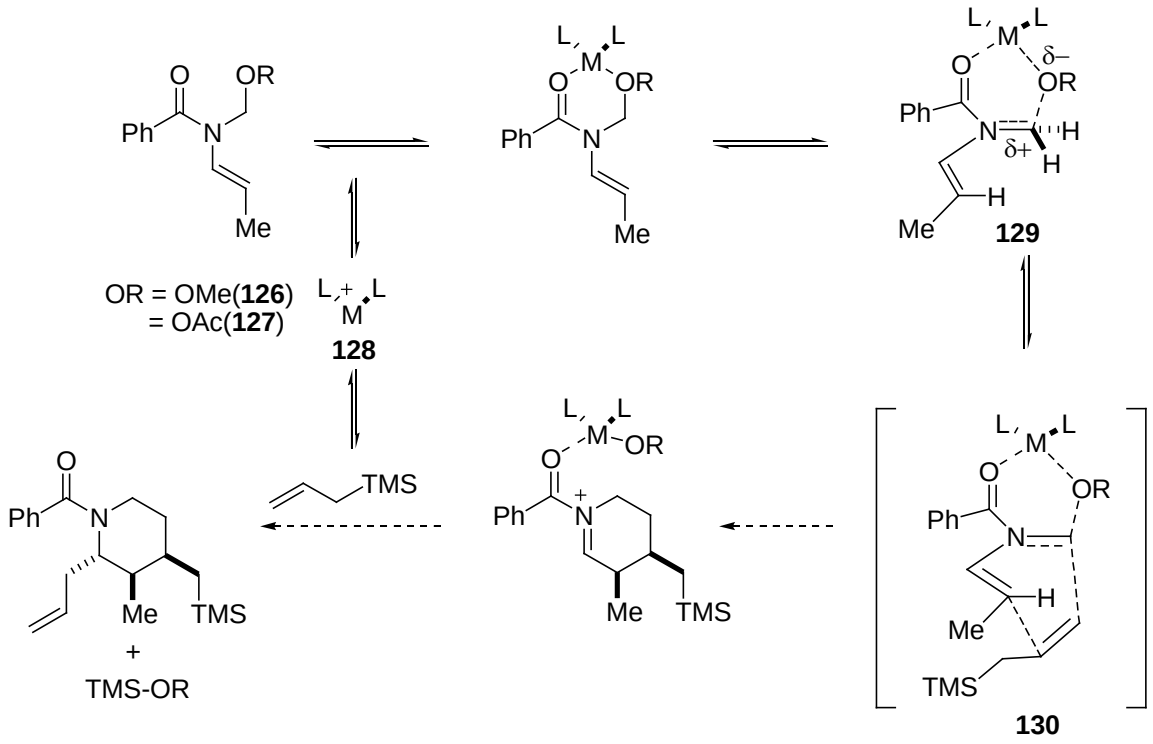
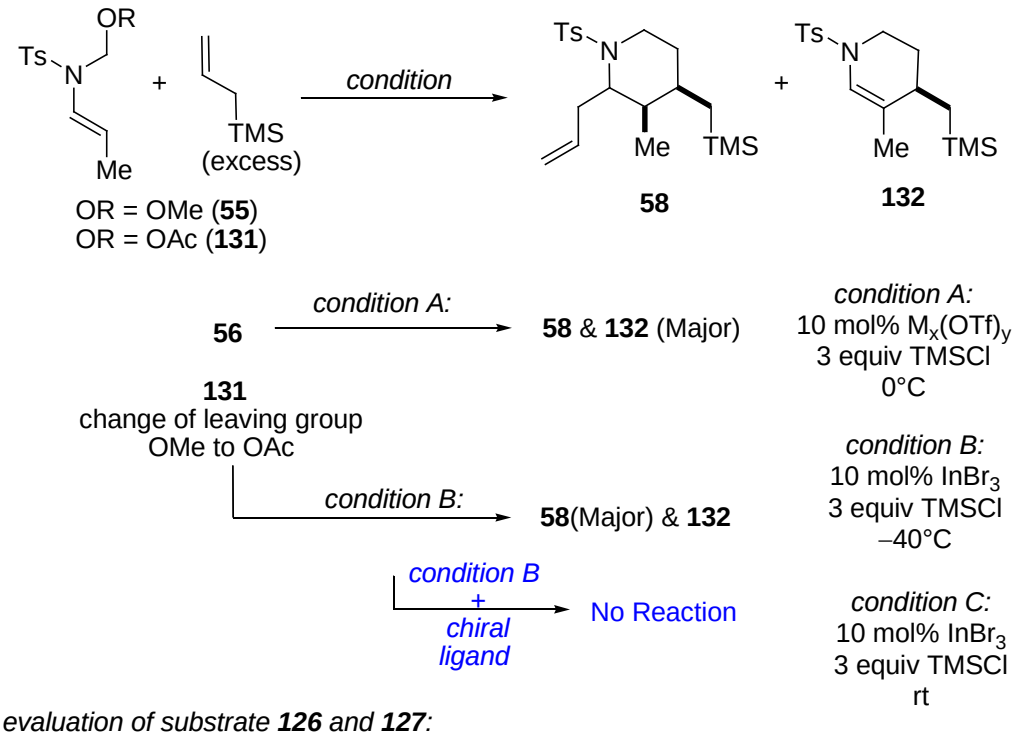


Figure 20. An asymmetric model for Lewis acid catalyzed cycloaddition reaction

In order to find the right Lewis acid for a catalytic system, a wide variety of metal salts, e.g. $Sn(OTf)_2$, $Cu(OTf)_2$, $MgBr_2$ etc. were screened. The tosyl protected enamine-aminal substrate **55** was evaluated first and subjected to 10 mol% $Sn(OTf)_2$ and excess of allyltrimethylsilane (Figure 21). The progress of the reaction (in this case formation of **58** and **132**) was measured either by running ^1H NMR of the reaction aliquot or performing TLC. It was observed that metal triflates could activate **55** and formed the respective products at ambient temperature. The reaction rate was slow and it took more than 12 h to complete the reaction. When excess of TMSCl was added as an activator at 0 °C, the reaction rate enhanced significantly and the reaction was completed within 2-3 h (condition A: 10 mol% metal triflate, 3 equiv TMSCl, 0 °C). Next, the reaction temperature of the cycloaddition reaction needed to be lowered (–40 °C or lower), where the intermediate tetrahydropyridinium ion would be stable.

Instead of **55**, when the more reactive substrate **131** (which had OAc as leaving group) was used, it was observed that catalytic $InBr_3$ with TMSCl could activate **131** affording the desired product **58** (condition B: 10 mol% $InBr_3$, 3 equiv TMSCl, –40 °C). After identifying $InBr_3$ as an effective catalyst, search for a chiral-ligand modified indium-complex was made and in situ generation of $InBr_3$-ligand complex with ligands **133**, **134**, and **135** were considered. Chiral ligand **135** modified In-complex was evaluated against substrate **131**, but was found to be completely inactive. The carbamate protected substrates **126** and **127** were screened next. It was found that both **126** and **127** were completely inactive under condition B (10 mol% $InBr_3$, 3 equiv TMSCl, –40 °C), but upon warming up the reaction mixture, **127** was found to react very slowly (<10% conversion over 24 h) at ambient temperature (condition C: 10 mol% $InBr_3$, 3 equiv TMSCl, 0 °C) which was not useful.

*Reactivity evaluation of substrate **55**and **131:***



*Reactivity evaluation of substrate **126** and **127**:*

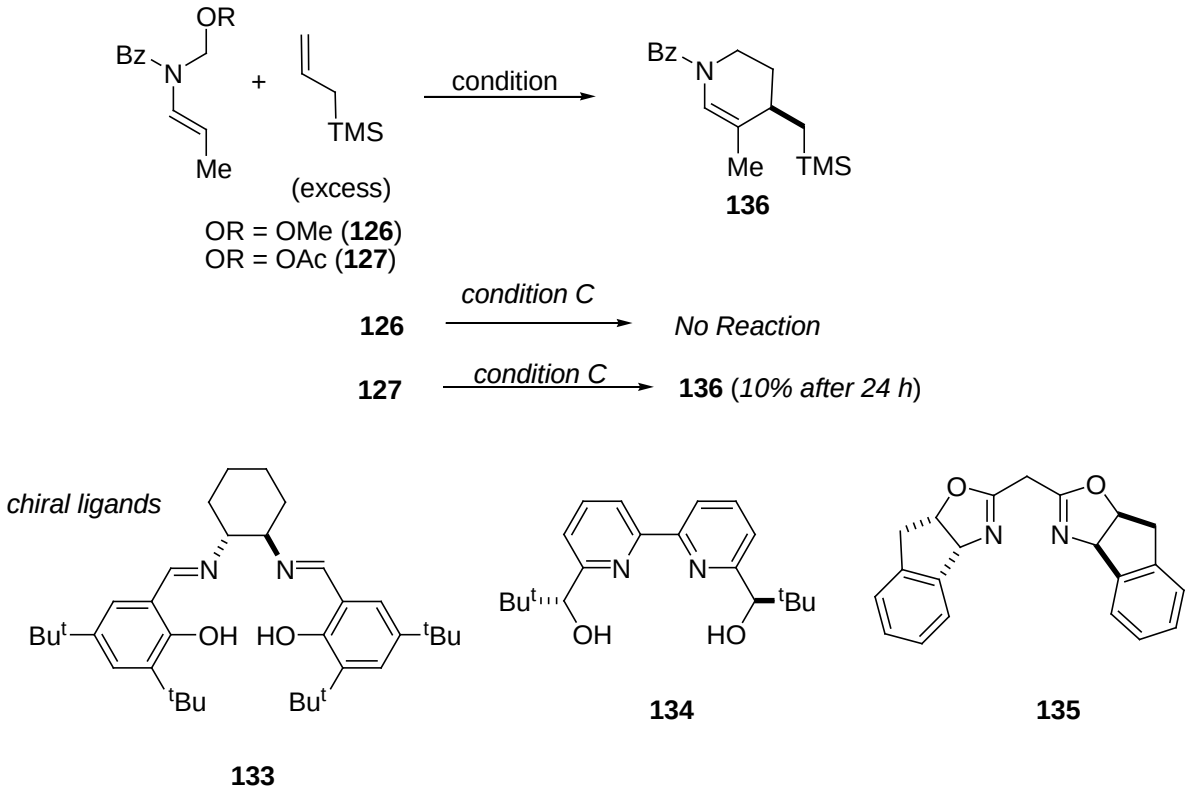


Figure 21. Chiral Lewis acid meditated approach towards catalytic reaction

3.3 CATALYTIC AND ASYMMETRIC REACTION DEVELOPMENT WITH BRONSTED ACIDS

Asymmetric catalysis with chiral Bronsted acids (or chiral H-bond donors) has emerged as an important paradigm for enantioselective catalysis[52]. Electrophile activation by these small-molecule chiral hydrogen-bond (H-bond) donors has provided new applications and developments in organic synthesis at a rapidly increasing pace. H-bonding plays crucial role in the biological world either by providing stable three-dimensional structures (e.g. three-dimensional structure of protein) or by catalyzing several transformations (e.g. Serine protease mediated amide hydrolysis). In trying to mimic enzyme catalyzed processes found in the biological world, small molecule catalysts have been designed in such a way that the new catalyst possesses H-bonding capability, several catalyst–substrate interactions sites, and is capable of simultaneous activation of nucleophile and electrophile behaving as bifunctional catalyst.

3.3.1 Thiourea Catalyzed Reaction Development

Enantioselective reaction development strategies by metal-free organocatalysts have recently attracted much attention from organic chemists. Organocatalysts[53] are environmentally benign, easy to handle and require low operational cost. Small organic molecules like ureas and thioureas are known for activating organic transformations from eighty's, and they feature the general properties that may be identified to characterize them as small-molecule chiral H-bond donors.

[52] For review see: Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520-1543 and references therein.
[53] MacMillan, D. W. C. *Nature* **2008**, *455*, 304-308.

Recent development in thiourea catalyzed enantioselective transformations[54] demonstrated well that the catalyst binds with substrate by H-bonding and excellent facial control is observed providing high enantioselectivities. Jacobsen and co-workers showed that the thiourea catalyst **137** forms an H-bond with the negative counterion in a zwitterionic ion pair with iminium or oxonium ion (Figure 22). The catalyst **137** was tuned in such a way that additional binding modes were possible making the catalyst bifunctional.

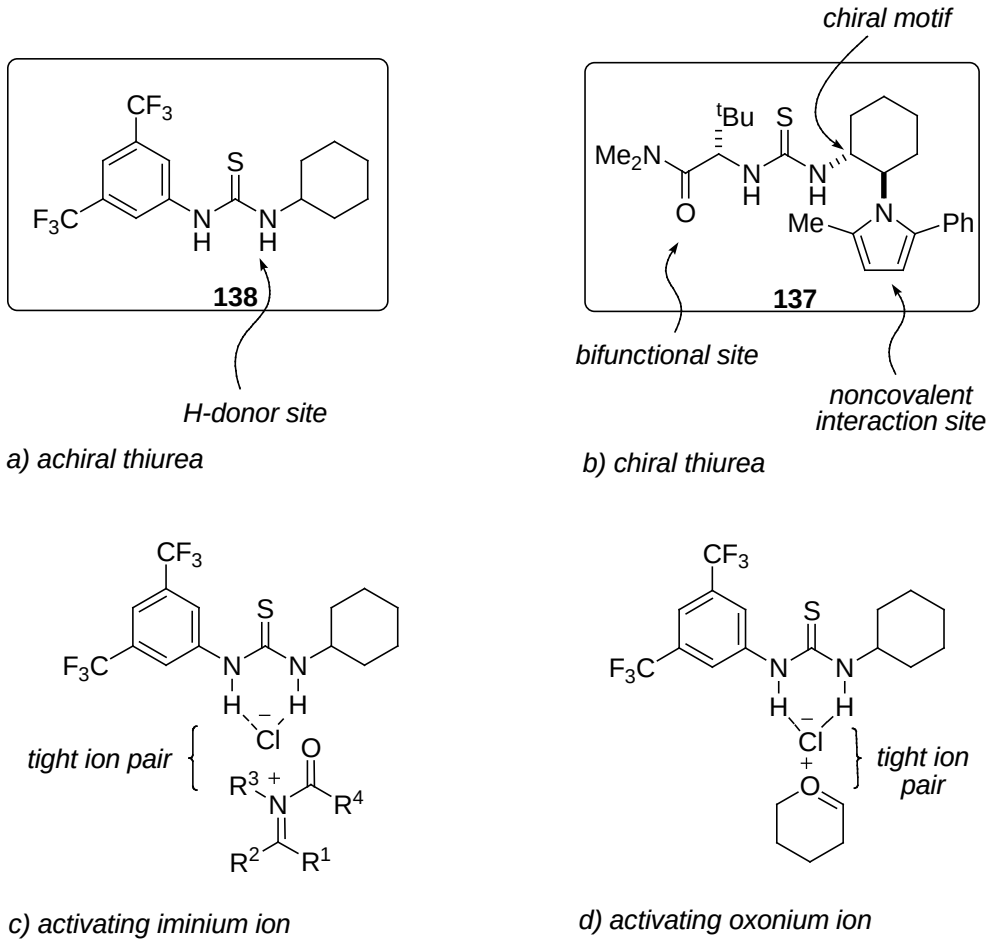


Figure 22. Chiral thiourea catalysts and their modes of binding

[54] (a) Raheem, I. T.; Thiara, P. V.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404-13405. (b) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198-7199.

Encouraged by these discoveries, we sought to synthesize catalysts **137** and **138** and evaluate their efficiency as acid catalysts for iminium ion generation. By following literature methods, both of the catalysts were synthesized.[13,55] Test reactions were run with substrates **55** and **131** using 10 mol% of catalyst **138** and excess allyltrimethylsilane (Figure 23). Generally ether (or toluene) type solvents were used considering the fact that less polar solvent would allow formation of a tight ion pair, which is the key to achieve high enantioselectivity. Both of the substrates **55** and **131** were inactive, and after extended reaction times (>24 h), only recovered starting material was observed. It was also known[54a] that additives like trimethylsilylchloride help in ionization and provide a relatively stabilized chloride-iminium ion pair. The addition of trimethylsilylchloride to the reaction mixture as an additive was also found to be inefficient, and most likely, an unknown complex with **131** was forming (disappearance of **131** was observed), which did not lead to the formation of products.

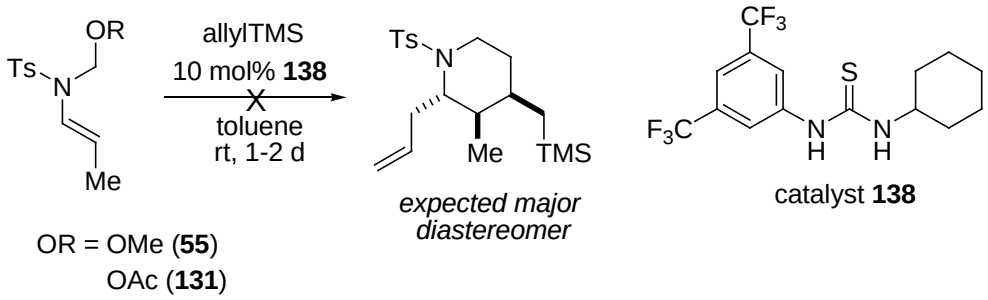


Figure 23. Screening with racemic thiourea catalyst **138**

The completed studies indicated that a more effective ionizable group would be necessary to facilitate the formation of iminium ions under the thiourea catalyzed reaction conditions. To gain the full advantage of bifunctional thiourea catalyst, an enantiopure catalyst would also be

[55] Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K.*Tetrahedron Lett.* **2004**, *45*, 5589-5592.

necessary where something other than H-bonding activation sites are present. The catalyst **137** was chosen (Figure 24). More reactive substrates **131** (OAc), **139** (*p*-nitrobenzoate), and **140** (*m*-nitrobenzoate) with more ionizable leaving groups were evaluated. Instead of allyltrimethylsilane, the enamine **80** was used as the dienophile. Upon subjecting to the cycloaddition reaction with 10 mol% catalyst **137** in *tert*-butyl methyl ether as solvent, no reaction was observed (>36 h). It was concluded that the inherent acidity of thiourea catalyst **137** was poor and not sufficient for the ionization of even the *m*-nitrobenzoate containing enamine aminal **140**, which had the most ionizable group (p*K*a of *m*-nitrobenzoic acid = 2.45). These results further impled that either a more ionizable group than *m*-nitrobenzoate, or a stronger acid than thiourea **137** would be required.

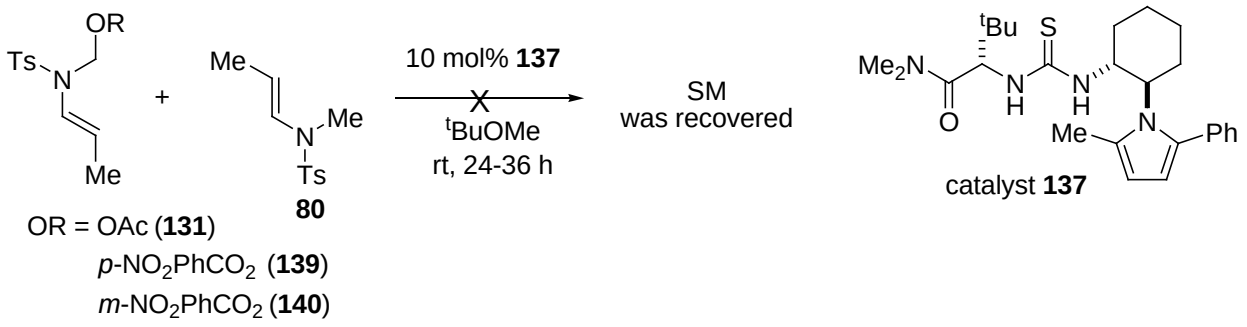


Figure 24. Screening with chiral thiourea catalyst **137**

3.3.2 Bronsted Acids Mediated Activation

Chiral Bronsted acid mediated organic reactions[56] have recently been successfully employed for the enantioselective preparations of many organic compounds, and this area of organocatalysis is progressing rapidly[57]. It is now well known that Bronsted acids can accelerate organic reactions by 1) specific acid catalysis and 2) general acid catalysis. However, considering its general mode of catalysis, many research efforts were made to develop synthetic Bronsted acid catalysts. Chiral phosphoric acids derived from binapthols constitute on of the most useful classes of Bronsted acids within the small molecule organocatalyst paradigm. The axial chirality from the binapthol backbone is utilized for enantio differentiation, and by varying sterically and/or electronically modified substituents at the 3 and 3' positions of the catalyst framework, a tuned catalyst can be generated for required reactivity and high enantioselectivity. In its mode of activation, catalytic protonation of the electrophile forms an intermediary ion pair composed of activated (or protonated) electrophile and a chiral phosphate counter ion. The observed high degree of enentioselectivity is induced from the chiral counter ion of the ion pair association.

Knowing that common Bronsted acids are much stronger than the thiourea catalyst, various common Bronsted acids such as CSA, acetic acid and, HCl in dioxane were screened against substrates **127** and **131** (Figure 25). Upon treating with 10 mol% acids either at 0 ˚C or at ambient temperature, none of these substrates were found to be active. Substrates **127**, **131**, **141** and **142** were screened with 10 mol% of phosphoric acid derived Bronsted acids **143** and **144**. However in all cases, no cycloaddition was observed. Different solvents (CH_2Cl_2 and toluene)

[56] (a)Terada,T.; Kyoko Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336-10337. (b) Guo, Q.; Liu, H.; Guo, C.; Luo, S.; Gu, Y.; Gong, L. *J. Am. Chem. Soc.* **2007**, *129*, 3790–3791. (c) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756-6764.
[57] (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744-5758. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569.

and temperatures (0 ˚C, 23 ˚C, 70 ˚C) were also screened, but without any reaction suggesting that the acidity of these phosphoric acid catalysts were not sufficient for aminal ionization.

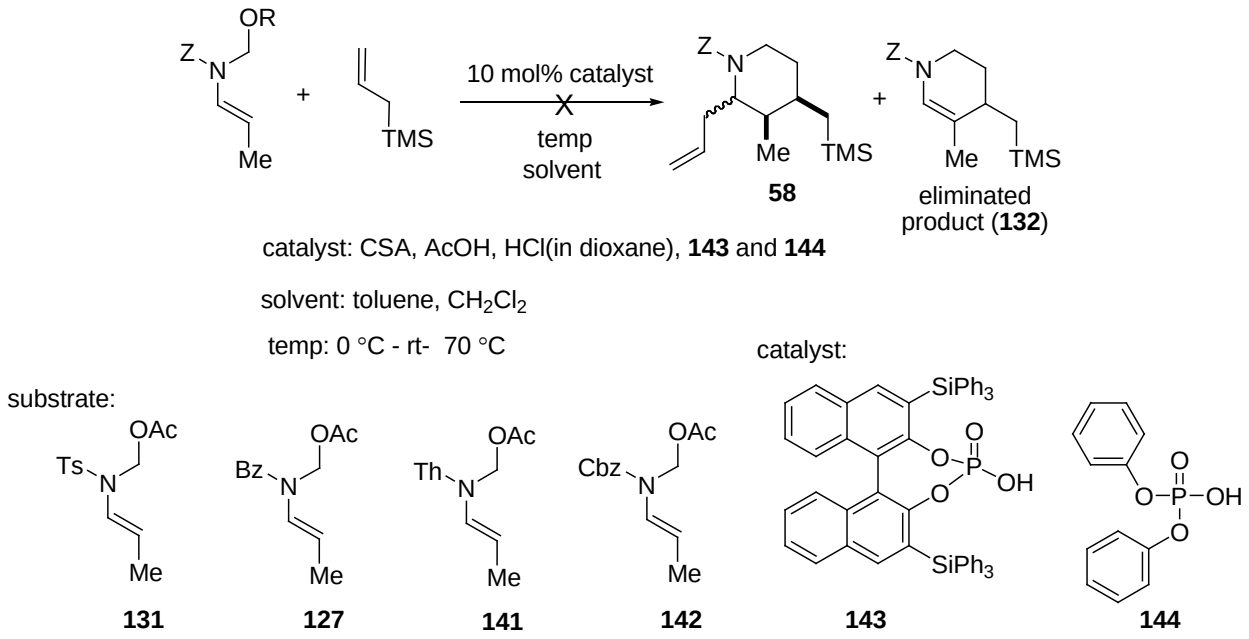


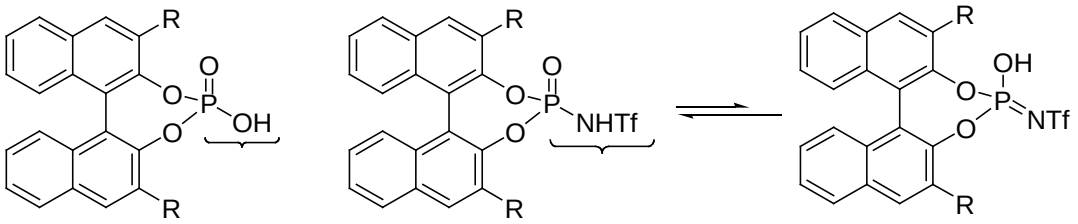
Figure 25. Screening with Bronsted acids

3.3.3 Reaction Development with *N*-Triflyl Phosphoramide

In search of more acidic chiral bronsted acid catalyst, we considered *N*-triflyl phosphoramide. *N*-Triflyl phosphoramides (**145**) comprise a new class of Bronsted acid catalysts capable of activating carbonyl compounds either in asymmetric Diels-Alder reactions [58] or in Nazarov reactions [59] providing enantio-rich compounds (Figure 26). They possess similar structural features as phosphoric acid (**146**) but provide stronger acids in solution. Introduction of the *N*-Tf

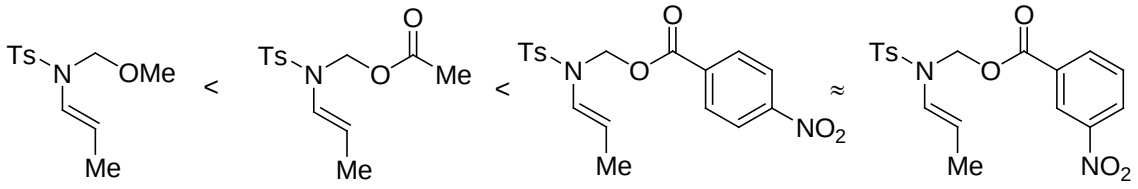
[58] Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626-9627.
[59] Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *119*, 2143-2146.

group make these phosphoramide catalysts highly reactive and capable of enabling transformations which were not achievable before with phosphoric acids. A modification in the diene precursor structure was further necessary as phosphoric acids were not strong enough even at higher temperatures (60-70 °C). In order to access more reactive diene precursors, different leaving groups in the order of decreasing p*K*a were incorporated using the standard *N*-allyl-chloroaminal protocol. A series of substrates as listed in figure 27 were synthesized and it was found that the *m*-nitrobenzoate group containing precursor **140** was the optimum substrate in terms of its isolation and handling (Figure 27).



phosphoric acid **146** *phosphoramide* **145**

Figure 26. Phosphoric acid and *N*-triflyl phosphoramide



55 **131** **139** **140**

increasing reactivity

Figure 27. Examples of p*K*a modified diene precursors

The modified diene precursor **140** was screened with a variety of Bronsted acids. Instead of allyltrimethylsilane, tertahydropyran was chosen as the dienophile partner. After few control reactions, it was found that when 10 mol% of the phosphoramide **147** was employed, successful

ionization of the aminal occurred at room temperature affording the desired cycloadduct **148** in 51% yield (Table 28). The choice of solvent was important as the dienophile itself was reactive towards the acid leading to polymerization. Tetrahydrofuran was found to be the best solvent in balancing the catalyst's activity towards cycloaddition over polymerization. The phosphoramide catalyst **147** thus provided the right acidity for the ionization of **140** whereas phosphoric acid **149** and *m*-nitrobenzoic acid were ineffective under the same reaction condition.

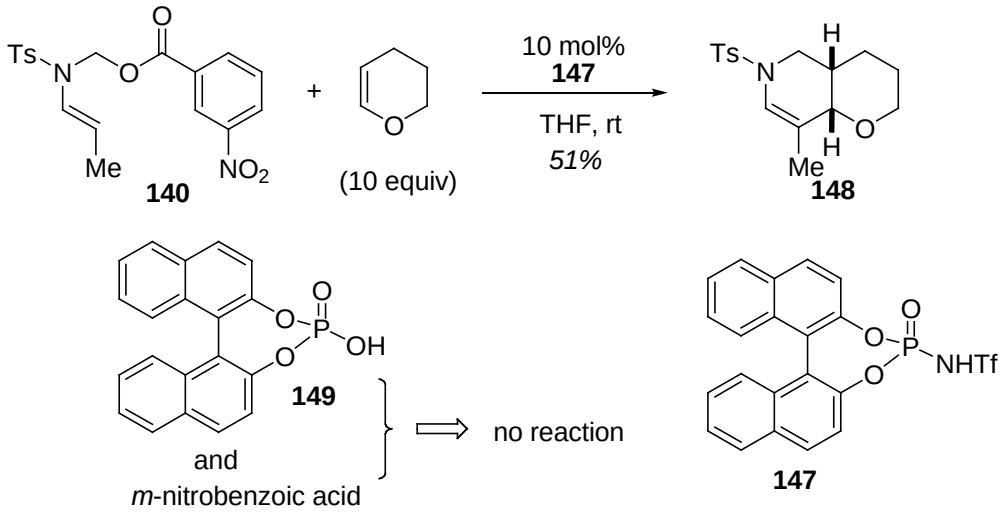
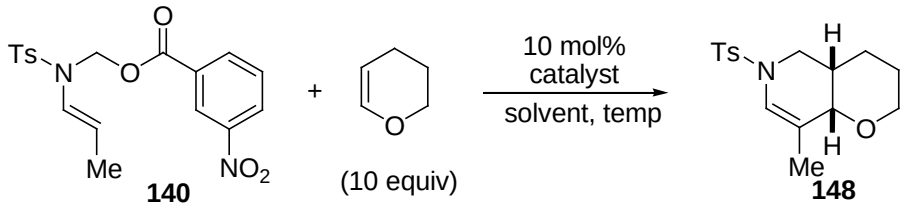


Figure 28. Screening of the aminal **140**

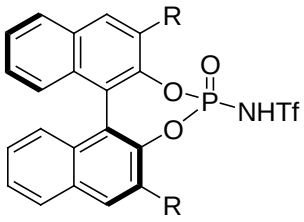
Encouraged by these results, chiral phosphoramide catalysts **150** and **151** were prepared, and the cycloaddition process was assessed (Table 9). The reaction conversion was dependent on solvent, and poor conversion was obtained at low temperature (30 °C). To fix this low turnover, the reactivity of **140** could be modified or the reaction could be run for a longer period. However, as we were more interested to see the enantioselectivity afforded in the reaction, the resulting products were analyzed by chiral HPLC with Chiral OD-H column (the yields were not determined). After extensive experimentation with varying catalysts, reaction temperatures and

solvents, we were unable to get any enantioselectivity. Surprisingly, even phosphoramide **151**, which had the large 9-anthryl group, was also ineffective in controlling the facial bias of the incipient diene. One possible reason could be that the *N*-tosyl dienes used in this study were too reactive, forming the product quickly once generated and not allowing enough time for forming the tight ion pair with the chiral counterion. Lowering the temperature might form the tight ion pair but the acidity of the phosphoramide was not sufficient for the ionization of **140** below −30 °C, implying that a more reactive substrate or a stronger chiral Bronsted acid was required. A second alternative would be to attenuate the reactivity of the *N*-tosyl iminium ion by replacing the tosyl group with carbamate protecting group. The introduction of different protecting group would introduce different degree of complication to the system (e.g. the aminal ionization might be too slow). However, to evaluate their reactivity, substrates **152** and **153** were synthesized but were both found to be inactive with catalyst **150** (Figure 29).

Table 9. Evaluation of the selectivity using chiral catalysts

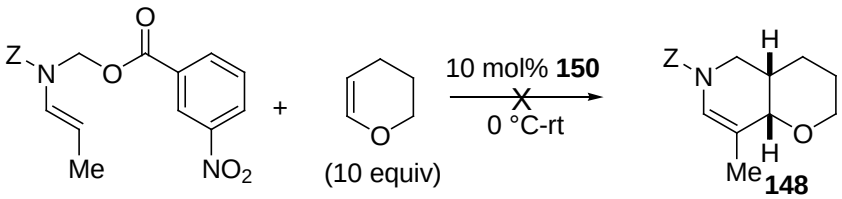


chiral catalyst	solvent	temp	conversion[a] (%)	ee[b] (%)
150	toluene	0 °C	100	0
150	toluene	– 30 °C	10[d]	0
151	THF	0 °C	60[c]	-
151	$CHCl_3$	– 30 °C	10[d]	-
151	toluene	– 30 °C	10[e]	0
151	toluene	0 °C	100[f]	0



R = 1-napthyl (*S*), **150**
= 9-anthryl (*R*), **151**

[a] conversions were based on ^{1}H NMR analysis of the crude reaction mixtures.
[b] analyzed in Chiral HPLC with OD-H column. [c] reaction time 12 h.
[d] reaction time 20 h. [e] reaction time 40 h. [f] reaction time 2 h



Z = Boc (**152**)
HCO (**153**)

Figure 29. Screening with substrates **152** and **153**

3.4 CONCLUSION

A systematic assessment of an asymmetric and catalytic cycloaddition reaction has been performed. An effective diene precursor has been synthesized from intermediate *N*-chloroaminal and successfully engaged in cycloaddition reactions with mild acids, thus providing a *catalytic* method for the preparation of piperidine derivatives. Unfortuntely, no chiral induction was found in the cyclization reaction with chiral Bronsted acid catalysts.

4.0 ENAMINE-AMINAL: A USEFUL SYNTHON FOR C-C BOND FORMING REACTION

4.1 ENAMINE-AMINAL SYNTHON

Enamine[60] and aminal (*N,O*-acetal) derivatives[61] are well known chemical literature and are found to be useful in numerous organic transformations (Figure 30). The *N,O*-acetals are often used to generate iminium ions and subsequently, used as electrophiles for C-C bond formation reactions. Enamines (or enamides) on the other hand, are often used as nucleophiles in C-C bond formation reactions. An enamine and an aminal together may form a highly reactive *enamine-aminal intermediate*, which combines the nucleophilic nature of enamine and the electrophilic nature of aminal. *N,O*-Aminals are widely used intermediates in organic synthesis and belong to the class of *X,Y*-acetals[62] where XR^1 and YR^2 are attached to a sp^3 carbon atom (X = Y = N, S, P, O) as shown in figure 31. X,Y-acetals can be a part of acyclic or cyclic structures, and depending on the nature of X, Y and the types of the substituent present, the acetals can be chemoselctively activated by Lewis or Bronsted acids. The resulting intermediate, which is an α-heteroatom substituted carbocation, is then trapped with various nucleophiles forming either linear or cyclic structures. The reactivity of an *X,Y*-acetal can be tuned properly by varying the substituents on

[60] For recent applications: (a) Bach, T.; Schroder, J. *J. Org. Chem.* **1999**, *64*, 1265-1273. (b) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045-2048.
[61] Sakai, N.; Hirasawa, M.; Hamajima, T.; Konakahara, T. *J. Org. Chem.* **2003**, *68*, 483-488 and references therein.
[62] Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 12510-12517.

either X or Y. As an example, for a given R, **154** is much more reactive towards ionization than **155**, so a milder acid is required. But the resulting iminium ion from **155** is much less reactive than iminium ion from **155**.

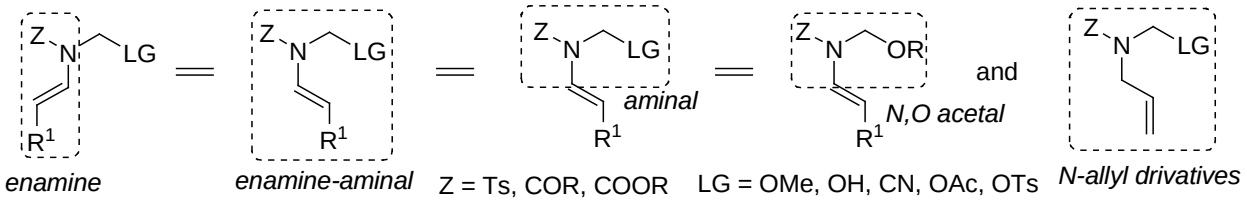


Figure 30. Various terminologies in enamine-aminal chemistry

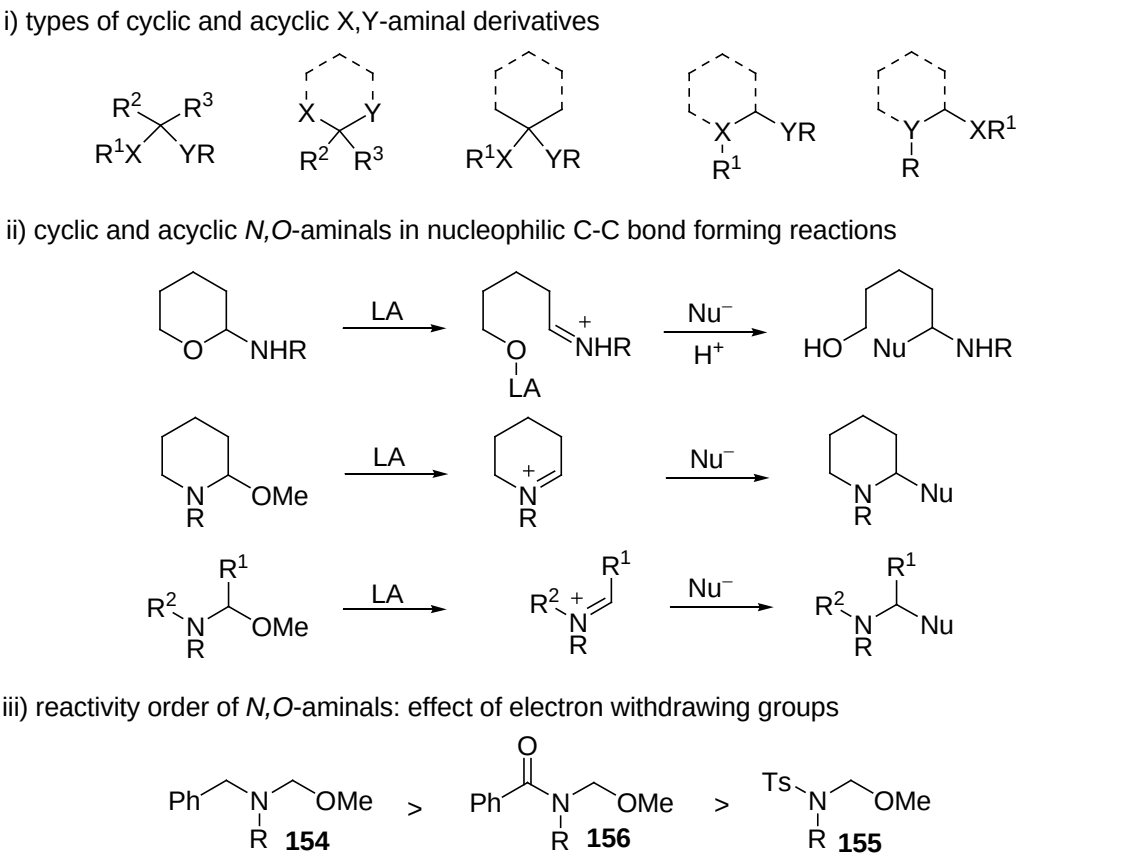


Figure 31. Types and reactivity of *N,O*-aminals

4.2 PROPOSED ENAMINE-AMINAL SYNTHESIS

After identifying the potential of enamine-aminal derivatives **157** towards the formation of *N*-alkenyl iminium ion and subsequently towards the formation of substituted piperidine skeleton, we focused our attention to the synthesis of enamine-aminal derivatives (Figure 32). The limited development of these intermediates is likely due to the difficulty associated with preparing the requisite precursors. However, applying traditional protocols for synthesizing the corresponding enamine-aminal derivatives would suffer from aminal incompatibility during acid-catalyzed condensation of α-alkoxy amine **158** with an aldehyde. Limited reactivity or poor regioselectivity causes the poor selectivity during attempted alkylation of enamine **159** because mostly *C*-alkylation would occur instead of *N*-alkylation. Conversely, *N*-allyl aminals **160** are readily obtained by *N*-alkylation of the corresponding *N*-allyl or *N*-alkyl carbamates or sulfonamides (**161** or **162** respectively). The *N*-alkyl carbamates or sulfonamides can easily be prepared from the condensation reaction of *N*-allylamine and the respective chloroformate or tosyl chloride. Thermodynamically-driven olefin isomerization will provide the *enamine-aminal* from the readily accessed *N*-allyl derivatives **160**. We proceeded for the synthesis of *N,O*-aminal **160**. The preparation of *N,O*- animals are well known in the chemical literature and are synthesized mainly from direct alkylation of amides[63], partial reduction of acylamides[64], addition of amides to aldehydes[65], electrochemical oxidation of amines[66] and Pd-catalyzed hydroamidation.[67] On the other hand, several traditional methods are known for the synthesis of enamines and enamides,

[63] Aurrecoechea, J. M.; Sureo, R.; Torres, E. *J. Org. Chem.* **2006**, *71*, 8767-8778.
[64] Suh, Y.; Shin, D.; Jung, J.; Kim, S. *Chem. Commun.* **2002**, 1064-1065.
[65] Kamatani, A.; Overman, L. E. *Org. Lett.* **2001**, *3*, 1229-1232.
[66] Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172-1176.
[67] Kinderman, S. S.; Wekking, M. M. T.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 5519-5527.

such as condensation of a secondary amine with a carbonyl compound followed by β-hydrogen elimination[68], copper mediated hydroamination of alkenes[69], and base[70] or transition metal catalyzed isomerization of *N*-allylamine derivatives. The first two of these approaches for enamine or enamide synthesis have limited substrate scope and typically require elevated temperatures, rigorous exclusion of water, and the use of excess base. Base (like *n*-BuLi, ^{t}BuLi, LDA, ^{t}BuOK and NaH) catalyzed isomerization techniques often suffer from low conversions and provide inseparable *E*/*Z* mixture of isomers. Considering all of these facts, we decided to use the *alkylation of amides* method for *N,O*-aminal preparation and *transition metal catalyzed isomerization* technique for their isomerization.

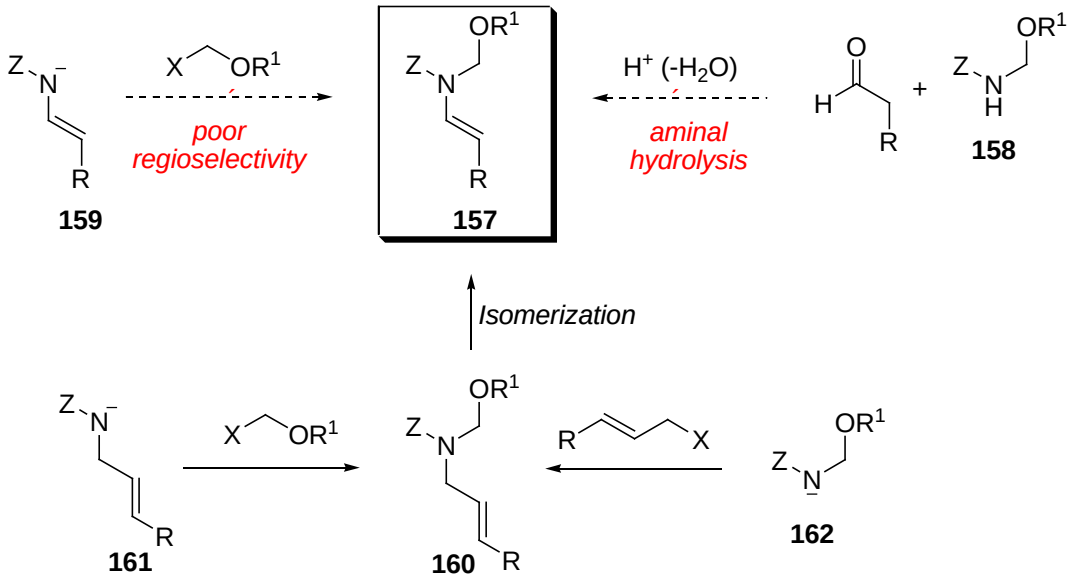


Figure 32. Proposed route for enamine-aminal synthon synthesis

[68] (a) Lenz, G. R. *Synthesis*, **1978**, 489-502. (b) Cook, G. R.; Barta, N. S.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 461-467.
[69] Bolshan, Y.; Batey, R. A. *Angew. Chem., Int. Ed.* **2008**, *120*, 2139-2142.
[70] (a) Ribereau, P.; Delamare, M.; Celanire, S.; Queguiner, G. *Tetrahedron Lett.* **2001**, *42*, 3571-3573. (b) Beak, P.; Lee, B. *J. Org. Chem.* **1989**, *54*, 458-464. (c) Tischler, A. N.; Tischler, M. H. *Tetrahedron Lett.* **1978**, *37*, 3407-3410. (d) Bortolussi, M.; Bloch, R.; Conia, J. M. *Tetrahedron Lett.* **1977**, *26*, 2289-2292.

4.3 ISOMERIZATION OF *N*-ALLYLAMINE DERIVATIVES: SYNTHESIS OF ENAMINE-AMINALS

4.3.1 Metal Catalyzed Isomerization of Allylic Double Bond

Metal catalyzed isomerization of an *N*-allyl derivative to the corresponding enamine is superior to the base catalyzed methods due to its mildness, catalytic usage and chemoselectivity (Figure 33). A wide variety of transition metals have been used, such as Ir, Ru, Rh, Ni, Fe, and Co etc. and among these Ir, Rh and Ru were found to be the most useful. The Nelson Group[71] in 2003, described the isomerization of diallyl ether **163** with a cationic iridium-phosphine complex obtained from $[Ir(COE)Cl]_2$ with excellent *E*/*Z* selectivity (eq 4.1) (Scheme 25). Neugnot[72] also reported that *N*-tosyl/amide allyl derivatives **164** could be isomerized by catalytic $[Ir(COD)Cl]_2$ to the respective enamides **165** with 97:3 *E*:*Z* selectivity (eq 4.2). It was believed that cationic Ir(I) was produced from $[Ir(COD)Cl]_2$ at elevated temperature and performed the isomerization.

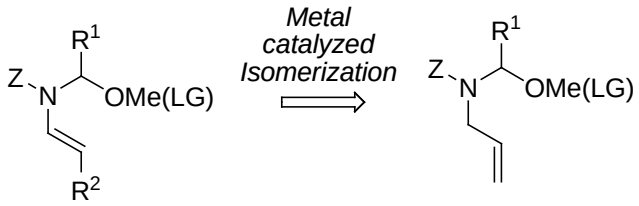
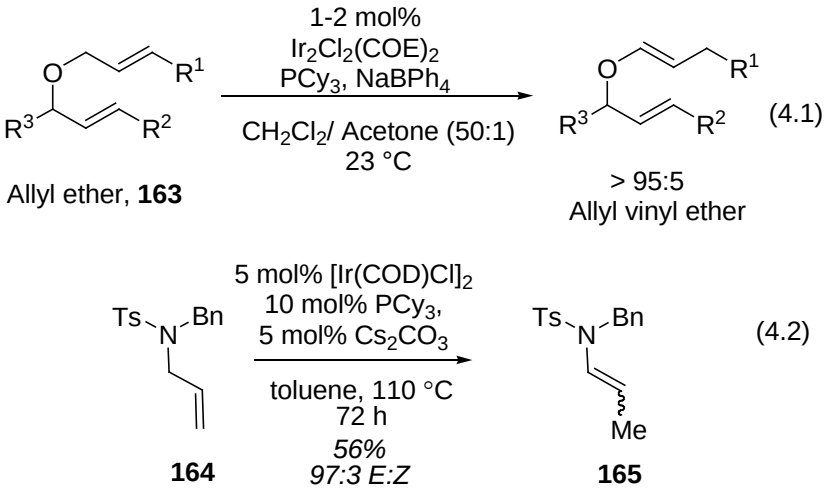


Figure 33. Metal catalyzed isomerization strategy for enamine synthesis

[71] Nelson, S. G.; Bungard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000-13001.
[72] Neugnot, B.; Cintrat, J.; Rousseau, B, *Tetrahedron* **2004**, *60*, 3575-3579.

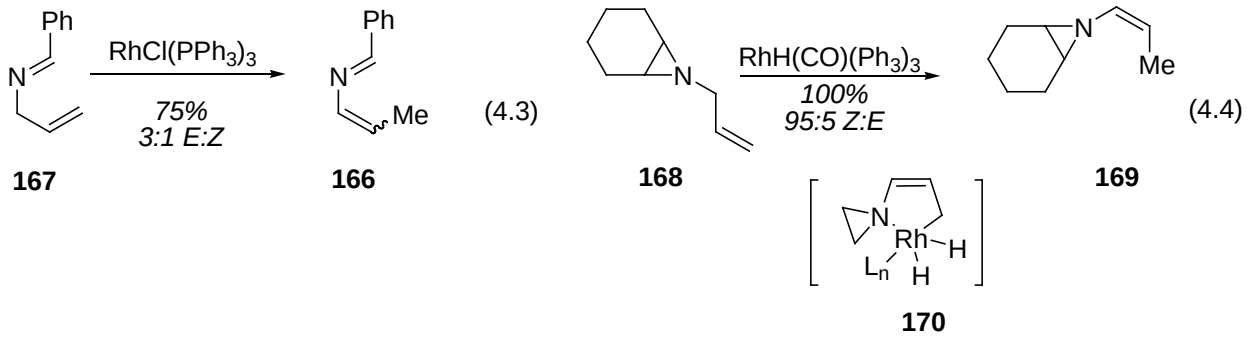
Scheme 25. Iridium catalyzed isomerization of allylic double bond



Another transition metal, Rh, is also known for olefin and *N*-allyl derivatives isomerization (Scheme 26). Grigg [73] reported in 1983 that the Wilkinson's catalyst, $[RhCl(PPh_3)_3]$, efficiently produced 2-aza-1,3-diene **166** with 75% yield (3:1 *E*:*Z*) at high temperature (140 °C) from respective *N*-allyl derivative **167** (eq 4.3). Noyori [74] reported that "cationic Rh" or "Rh-H" species could be used for *N*-allyl olefin isomerization to produce predominantly the thermodynamically favored *E*-isomer. Recently, Yudin [75] in 2006, utilizing cationic Rh(I), reported a condition to achieve the kinetically favored *Z*-isomer. *N*-allylaziridine derivative **168** formed the corresponding *Z*-enamine (**169**) in 100% conversion with cationic Rh(I) at −78 °C (eq 4.4). The higher selectivity (95:5 *Z:E*) was rationalized by proposing an *N*-coordinated intermediate **170**.

[73] Grigg, R.; Stevenson, P. J. *Synth. Commun.*. **1983**, 1009-1010l.
[74] Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008-2022.
[75] Alphonse, F.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 11754-11755.

Scheme 26. Rhodium catalyzed isomerization of *N*-allylanime derivatives



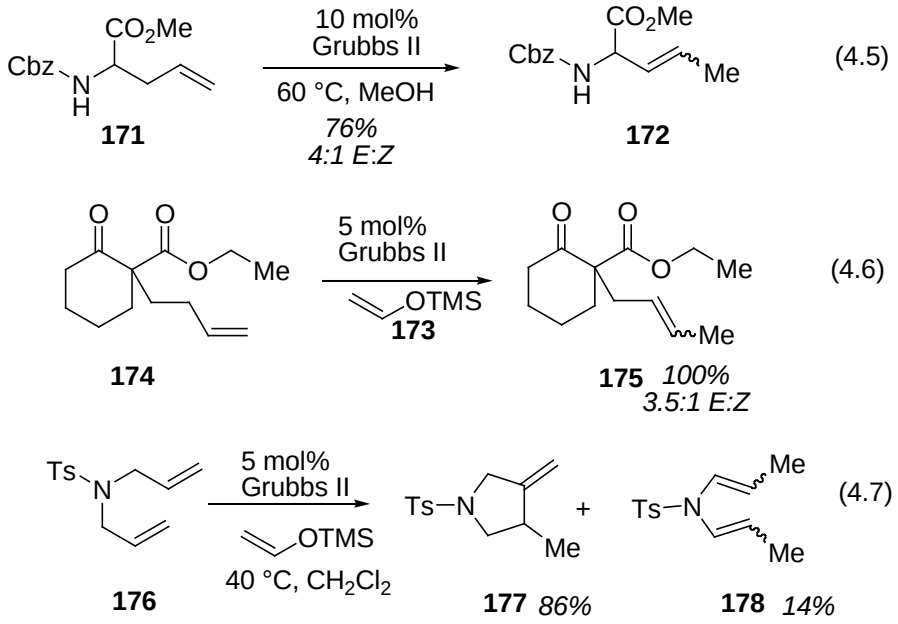
167 **166** **168** **169** **170**

Ru metal also possesses similar characteristics and under suitable reaction conditions, efficiently performs allylic isomerization.[76] It is believed that a "Ru-H species" is responsible for the olefin isomerization. Among the other Ru based catalysts, Grubbs II is well known and under normal circumstances, Grubbs II is popular for performing ring closing metathesis (RCM), cross metathesis (CM), and ring opening metathesis polymerization (ROMP) reactions. It is also believed that under certain conditions Grubbs II may perform olefin isomerization. Hanessian[77] reported that Grubbs II was used to isomerize the homoallylic derivative **171** in presence of methanol as solvent at 60 ˚C to produce **172** (75%, 4:1 *E*:*Z*) (eq 4.5, Scheme 27). Arisawa[78] observed that under vinyloxytrimethylsilane (**173**) condition, Grubbs II preferred isomerization over RCM. Terminal olefin **174** produced a single product **175** (3.5: *E*:*Z*) (eq 4.6) whereas **176** produced **177** (86%) and **178** (14%) (eq 4.7). Arisawa observed the formation of a new "Ru-species" under vinyloxytrimethylsilane condition and suggested formation of a Fischer type carbene. The new catalyst (Scheme 28, eq 4.8) then in its catalytic cycle, generated a "Ru-H"

[76] Krompiec, S.; Pigulla, M.; Szczepankiewicz, W.; Bieg, T.; Kuznik, N.; Leszcynska-Sejda, K.; Kubicki, M.; borowiak, T. *Tetrahedron Lett.* **2001**, *42*, 7095-7098.
[77] Hanessian, S.; Giroux, S.; Larson, A. *Org. Lett.* **2006**, *8*, 5481-5484.
[78] (a) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732-4734. (b) Terada, Y.; Arisawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4063-4067.

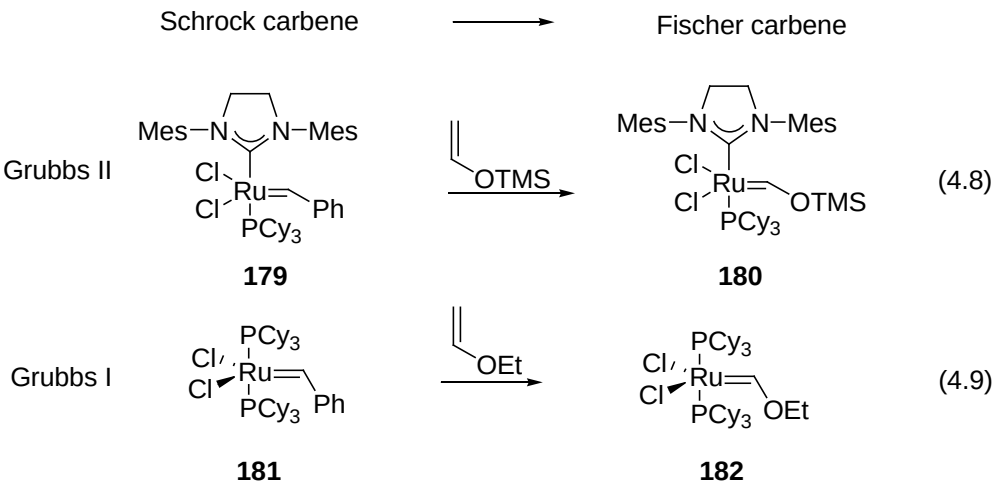
species, which was believed to be the active catalyst. Grubbs I[79] **181** can easily be converted to the respective Fischer type carbene (**182**, eq 4.9) with ethyl vinyl ether, which upon heating decomposes by forming a "Ru-H" species. The corresponding Ru Fischer carbene is also found to be a good catalyst for performing RCM under certain conditions. With the possibilities of having various species in the catalytic cycle, it is still unknown which species is actually responsible for the isomerization.

Scheme 27. Grubbs II mediated isomerization of *N*-allylanime derivatives



[79] Louie, J.; Grubbs, R. H. *Organometallics* **2000**, *21*, 2153-2164.

Scheme 28. Formation of Fischer carbene with vinyl ether

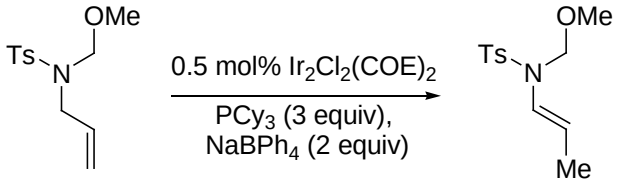


4.3.2 Cationic Ir-metal Catalyzed Isomerization: Reaction Development, Results and Discussions

Recognizing the usefulness of the cationic Ir(I)-phosphine complex generated from $Ir(COE)Cl]_2$/ PCy_3/ $NaBPh_4$ in the ICR reaction developed in our group, we started to explore the feasibility of using this complex in the isomerization of *N*-allylamine derivatives. Upon subjecting amine **183** to 0.5 mol % $[Ir(COE)Cl]_2$, PCy_3 (3 equiv) and $NaBPh_4$ (2 equiv)] at ambient temperature, partial conversion to the respective isomerized enamine-aminal **55** was obtained (Table 10). Upon increasing the reaction temperature to 40 °C, complete conversion with exclusive formation of the *E*-isomer was obtained. The enamine-aminal product was found to be stable under the given reaction conditions showing that the cationic Ir(I) present in the system was not Lewis acidic enough for the ionization of the aminal. The enamine-aminal was found to be stable to silica gel and was isolated in 95% yield. Only the *E* isomer was isolated, and this excellent selectivity can be accounted due to the thermodynamically biased C-H insertion by the catalyst. On the success of the above reaction, efforts were made to elaborate the substrate scope with different protecting

groups and leaving groups in the substrate. When a carbamate protected *N*-allylamine derivative **184** was subjected to similar isomerization conditions (45 °C), no conversion to the product was obtained (Figure 34). Increasing the temperature to 80 through 110 °C led to partial conversions, but higher temperatures compromised the isomer selectivity providing 1:1 mixture of *E*:*Z* isomers. The lack of reactivity of the carbamate substrate toward isomerization at 45 °C could be rationalized by considering binding of the Lewis acid to the carbonyl oxygen in the protecting group which would diminish the catalyst's ability toward activating the allylic C-H bond. This would explain why a high temperature was needed, and a poor selectivity was observed in comparison to the tosyl system.

Table 10. Isomerization of *N*-tosylaminal by cationic iridium catalyst



183 **55** *E isomer isolable*

catalyst	solvent	temp (°C)	time	conversion (%)	yield (100%)
1 mol% Ir^+	50:1 CH_2Cl_2/acetone	25	2 h	59	-
1 mol% Ir^+	50:1 CH_2Cl_2/acetone	40	30 min	100	95

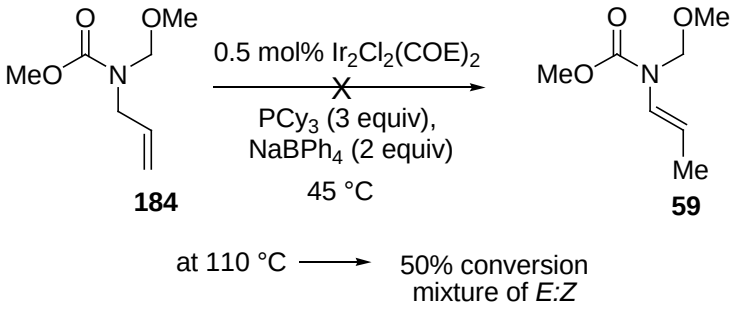
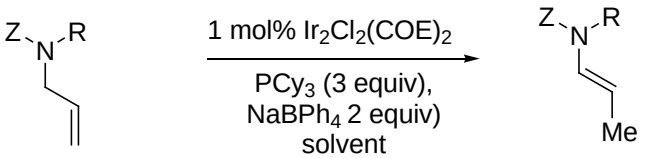


Figure 34. Isomerization of carbamate substrate **184**

To understand the interaction between the catalyst and carbamate protected substrate, a few control reactions were performed. Allylamine derivatives **185** and **186** were considered neither of which possessed any aminal moiety. Upon subjecting **185** to the isomerization reaction conditions with $Ir(COE)Cl]_2$/ PCy_3/ $NaBPh_4$ at 40 °C, the isomerized product **80** was isolated in 91% yield (*E* isomer only). Substrate **186** was subjected to $Ir(COE)Cl]_2$/ PCy_3/ $NaBPh_4$ at 80 °C affording **187** in 92% yield and as a 4:1 *E:Z* mixture of isomer (Table 11). These results confirmed that the Moc group in substrate **184** was definitely involved in the catalytic cycle and interfering with the iridium species. Both Moc and OMe groups on the substrate made the carbamate protected enamine-aminal to behave as a chelating ligand. Though there was no direct evidence, it was speculated that the cationic Ir(I) formed a stable six-membered ring **188** with the carbonyl oxygen atom of the carbamate and OMe before allylic C-H bond insertion occurrred thus, losing its catalytic activity (Figure 35).

Table 11. Isomerization of *N*-allyl anime substrates



Z	R	solvent	temp (°C)	time	conversion[a] (%)	yield (%)
Ts (**185**)	Me	CH_2Cl_2	40	30 min	100	91 (**80**) *E only*
Moc (**186**)	H	$ClCH_2CH_2Cl$	80	2 h	100	92 (**187**) *4:1 E:Z*

[a] E/Z ratio was measured by comparing the proton signal of alkene CH_3.

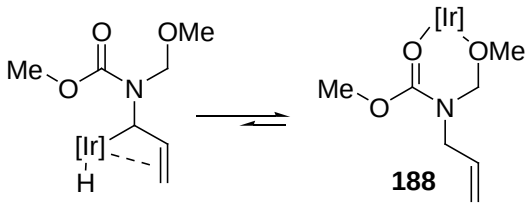


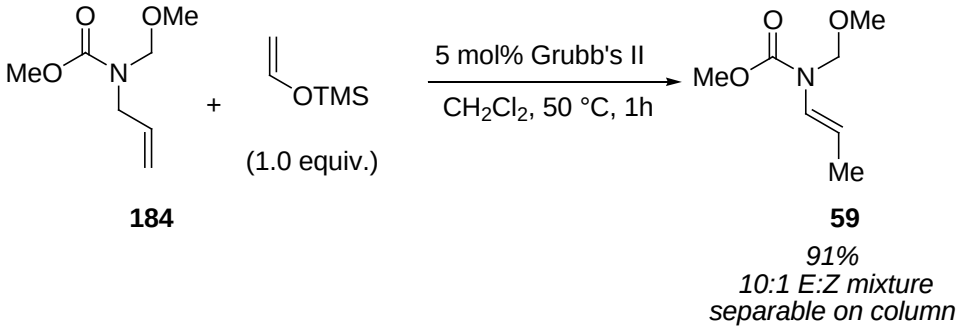
Figure 35. Rationale for catalyst poisoning

4.3.3 Grubbs II Catalyst: Ru-metal Catalyzed Isomerization

The 2nd generation Grubbs II catalyst is well known for performing cross metathesis (CM), ring closing metathesis (RCM), and ring opening polymerization (ROMP) reactions, but recent literature[77] reports suggest that the same catalyst can also perform isomerization of the terminal olefins under suitable conditions. Following Arisawa's protocol, we observed that Grubbs II, with reactive vinyloxytrimethylsilane, efficiently produced isomerized products with good selectivities from carbamate protected allylamine derivatives. In most cases, upon subjecting 5

mol % Grubb II catalyst to an equimolar solution of the respective *N*-allylamine derivative and vinyloxytrimethylsilane at 45 -50 °C, a complete conversion to product was observed within 1-2 hours. The methyl carbamate **184** was investigated first, and Grubbs II was found to produce the isomerized enamine-aminal **59** in 91% yield as a 10:1 mixture of *E*:*Z* isomers separable on column (Scheme 29).

Scheme 29. Grubbs II mediated isomerization of carbamate substrate **184**

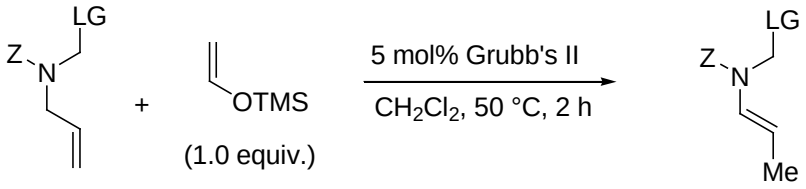


184 **59**

91%
10:1 E:Z mixture
separable on column

N-Allylamine **189** with a nitrile leaving group, was subjected next, and after isomerization the desired product **190** was obtained in 83% yield and 8:1 *E*:*Z* mixture of isomer (Table 12). Column purification afforded the pure *E* isomer. Substrate **189** which was tough to isomerize under cationic Ir(I) condition, now could easily be isomerized with the Grubbs II condition. This successful application led us to utilize this protocol for the isomerization of different challenging substrates in good yields and selectivities (shown in table 12). The respective carbamate and amide protected enamine-aminal products were found to be stable and the *E*/*Z* mixture could be separated through column chromatography.

Table 12. Grubbs II mediated isomerization of *N,O*-aminals



substrate	protecting group (Z)	leaving group (LG)	product yield[a](%)
189	Boc	CN	83, (**190)**
191	Bz	OMe	88, (**126**)
192	Cbz	OMe	90, (**60**)
193	Moc	OAc	80, (**62**)
194	Ts	"	92, (**131**)
195	Bz	"	85, (**127**)
196	Th	"	87, (**141**)
197	Ts	*p*-NO_2PhCO_2	83, (**139**)
198	Ts	*m*-NO_2PhCO_2	80, (**140**)
199	Boc	"	94, (**152**)
200	HCO	"	56, (**153**)

[a]isolated yields of *E*-isomer, after column chromatography

4.3.4 Isomerization of C1-Substituted Enamine-aminal

An effective synthetic protocol was required for the generation of C1-substituted enamine-aminal **201** as it allowed the use of mild Lewis acidic conditions for its ionization due to formation of secondary carbocation intermediate. The resulting C1-substituted iminium ion **202** would introduce a substitution in the piperidine structures **203** uopn cycloaddition and hence, introduce diversity in the synthesized *N*-heterocyclic scaffolds (Figure 36). With a limited choices of substrates, tosyl protected α-alkyl *N,OMe*-aminal **204** was subjected to the standard cationic Ir-catalyzed isomerization condition [$Ir(COE)Cl]_2$/ PCy_3/ $NaBPh_4$ at 40 °C] first, but the catalyst system was found to be ineffective at isomerizing the double bond. When the Grubbs II conditions (10 mol% Grubbs II, 100 mol% vinyloxytrimethylsilane at 50 °C) was used, the desired product **83** was isolated with high yield and high E/Z selectivity (Table 13). In summary, Grubbs II derived Ru-H catalyst successfully catalyzed the isomerization reaction to the product which was intriguing, whereas, the iridium condition was totally ineffective. The reason behind this fact was not exactly clear.

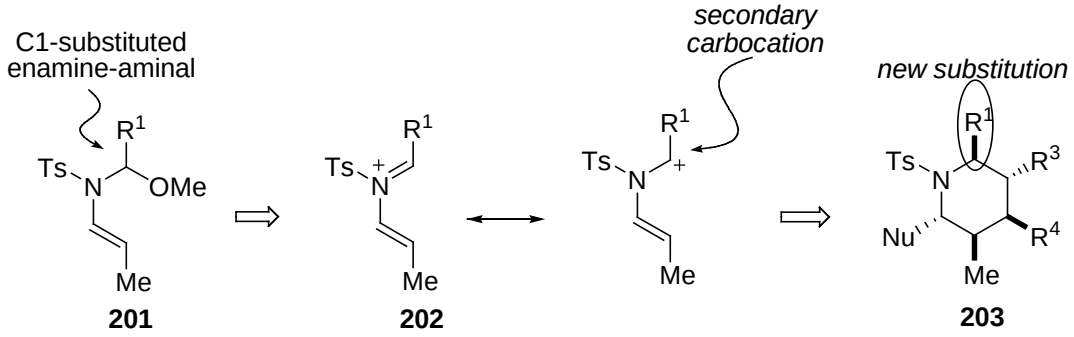
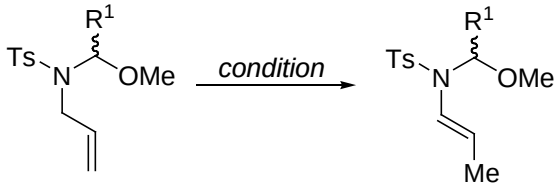


Figure 36. C1-Substituted enamie-aminal: Access to fully substituted piperidine scaffold

Table 13. Isomerization of C1-substituted enamie-aminal substrates



substrate	R^1	condition	conversion(%)	yield[a](%)
204	Et	cationic Ir, 40 °C	0	-
		cationic Ir, 80 °C	0	-
	Et	Grubb's II, 50 °C	100	94, (**83**)
205	Ph	"	100	91, (**206**)

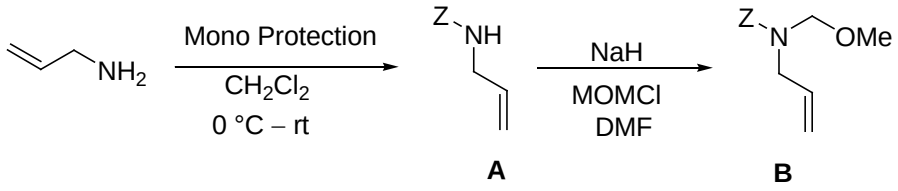
[a] isolated yield, only *E* isomer was observed

4.4 SYNTHESIS OF *N*-ALLYL *N,O* ACETALS/ AMINALS

4.4.1 Aminal Leaving Group: OMe

N-Allyl *N,O*-aminals were synthesized by following a two step protocol starting with allylamine (Table 14). The protecting groups were installed first and then the leaving groups. A series of *N*-protected allylamines series-**A** with different protecting groups were synthesized following common protocols with good yields. Then base mediated *N*-alkylations were performed with commercially available MOMCl. After exploring a few different bases and solvents, NaH mediated alkylation condition in DMF was found to be the best in terms of reactivity and isolated yields. *N*-alkylation with choloromethoxymethyl ether (MOMCl) produced compounds series-**B** with good yields, and they were found to be quite stable under silica gel purification.

Table 14. *N*-Allyl-*N,OMe*-aminal substrates synthesis



A **B**

#	Z	**A** yield(%)	**B** yield[b](%)
a	Ts	96	90, (**183**)
b	Moc[a]	93	72, (**184**)
c	Bz	95	87, (**191**)
d	Cbz	97	69, (**192**)

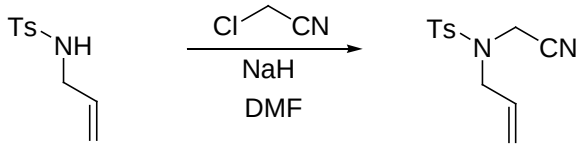
[a] methyloxycarbonyl. [b] isolated yield

4.4.2 Aminal Leaving Group: CN and OAc

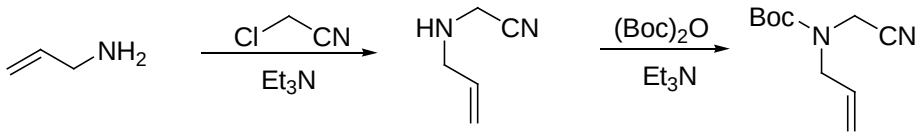
The nitrile group was incorporated as the leaving group via *N*-alkylation with commercially available chloroacetonitrile. Boc and Ts protected allylamines were subjected to alkylation, and the respective alkylated products **189** and **207** were isolated in moderate to good yields and both of the products were also found to be quite stable to silica gel purification (Table 15).

Table 15. Synthesis of *N*-allyl-*N,CN*-aminal substrates

method :1



method: 2

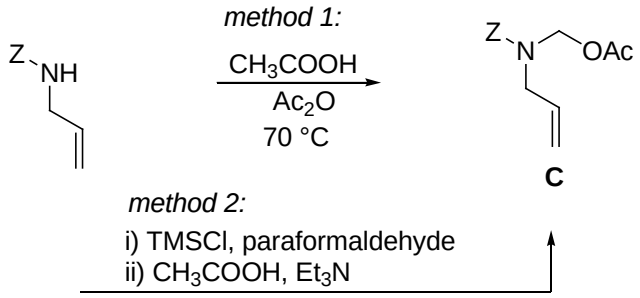


Method	Z	yield[a](%)
1	Ts	80, (**207**)
2	Boc	37, (**189**)

[a] isolated yield

N-Allylaminal with a better leaving group, such as OAc, was always desired. Making more labile aminal meant their stability during handling and silica gel purification could be an issue. However, heating a solution of acetic acid, acetic anhydride, paraformaldehyde, and protected *N*-allylamine produced the respective aminals series-**C** with moderate yields and the aminals were not susceptible to silica gel or to moisture (Table 16). The stability of the *N*-allylamine derivatives highly depended on the electron withdrawing capability of the protecting group. Electron withdrawing groups like tosyl, amide and even carbamates made the nitrogen lone pair less available for aminal hydrolysis, and the respective *N*-allylamine derivatives became stable towards moisture and could easily be purified, isolated, and stored for long times.

Table 16. Acetate containing *N*-allyl-*N,O*-aminal substrates synthesis



#	Method	Z	yield[b](%)
a	1	Ts	52, (**194**)
b	1	Moc	51, (**193**)
c	1	Bz	48, (**195**)
d	2	Th[a]	88, (**196**)

[a] thienylsulfone. [b] isolated yield

4.4.3 Common Routes to Generate *N,O*-Aminals

The most important remaining question at this point regarded the finding of common routes for the preparations of *N,O*-aminals. It was understood that more labile leaving groups could be incorporated as long as they were stabilized by the suitably chosen protecting groups. Labile leaving groups could introduce an intrinsic problem in their isomerization, they would definitely be beneficial in the cycloaddition process. It was known that the *N*-tosyl-α-chloroaminals (**208**) can be prepared from *N*-tosylallylamine upon treating with paraformaldehyde and chlorotrimethylsilane in quantitative yields.[80] The resulting reactive intermediate **208** was treated with carboxylate salts under basic conditions and allowed us to synthesize the OAc-series, the

[80] Iley, J.; Barroso, H.; Moreira, R.; Lopes, F.; Calheiros, T. *Bioorg. Med. Chem.* **2000**, *8*, 1629-1636.

m/p-NO_2PhCO_2- series, and, with MeOH/Et_3N condition, the OMe-series of *N,O*-aminals (Scheme 30). Among all of these substrates, *m*-nitrobenzoateaminals appeared to be appealing targets for cycloaddition due to their stability while still providing the most labile leaving group, which could be useful for iminium ion generation in the presence of various mild acids. Following the reaction protocol as described in the scheme 30, nitrobenzoate containing *N,O*-aminals (**197-198**) were synthesized (Table 17).

Scheme 30. Common routes for *N,O*-aminal substrates synthesis

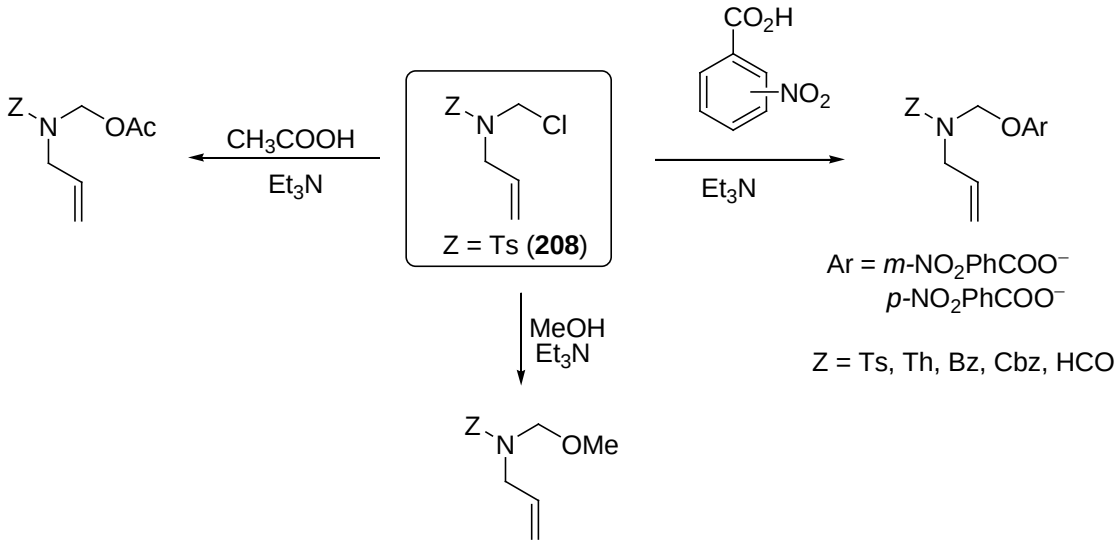


Table 17. Synthesis of nitrobenzoate containing *N,O*-aminals

protecting group	leaving group	yield[a](%)
Ts	*p*-NO_2PhCO_2	85, (**197**)
Ts	*m*-NO_2PhCO_2	82, (**198**)
Boc	"	77, (**199**)

[a] isolated yield

4.4.4 C1-Substituted Aminal Synthesis

Fully substituted piperidine derivatives could be obtained by using C1-substituted *N*-allylaminal substrates **209** as these substrates would introduce a new substitution in the final structure (Figure 37). Therefore, their convenient and scalable synthesis became an objective of this project. The preparation of C1-substituted *N*-allyl-*N,O*-aminal substrates was not straight forward and not known due to their instability (under work up condition). The direct *N*-alkylation as before was found to be problematic because substituted *N*-alkylating reagents are not known, and their in situ preparations were substrate dependant. Some examples were known, however, where a cyclic amide was reduced to the corresponding alcohol and was immediately used for the next reaction. The same idea was followed towards the synthesis of C1-substituted *N*-allyl-*N,O*-aminal, and **210** was prepared following literature methods.[81] After reduction, the isolation of the final alcohol **211** was unsuccessful, and the starting material was isolated instead (Scheme 31).

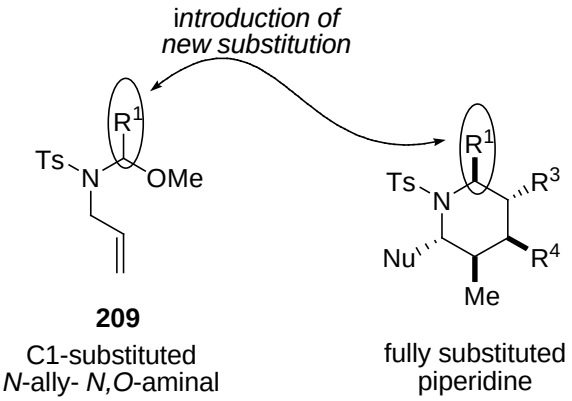
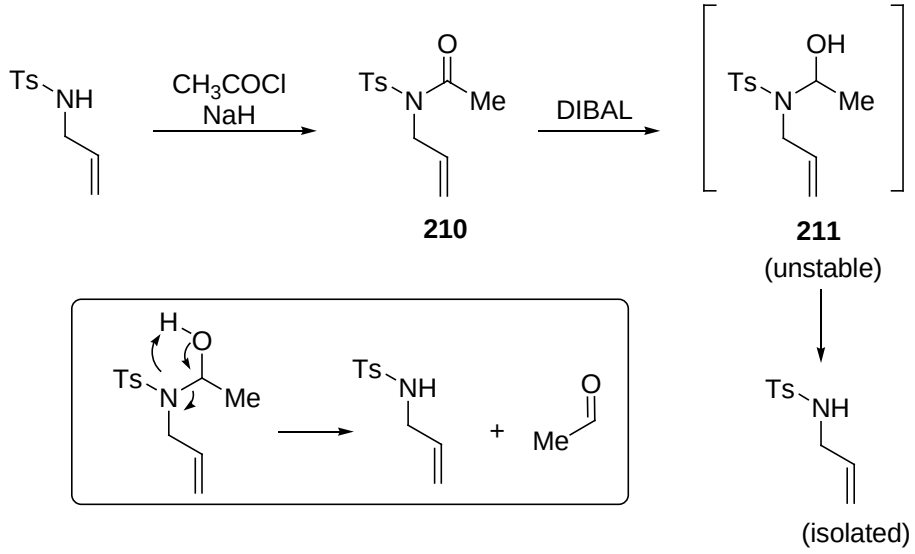


Figure 37. C1-Substituted *N*-allylaminal substrates towards fully substituted piperidines

[81] Gheorghe, A.; Quiclet-Sire, B.; Vila, X.; Zard, S. Z. *Tetrahedron* **2007**, *63*, 7187-7212.

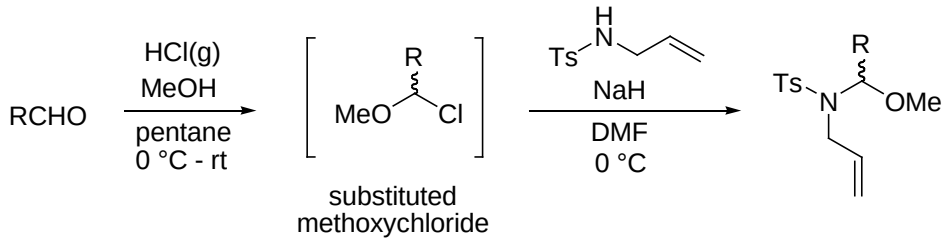
Scheme 31. Reduction of *N*-tosyl-allylamides **210**



The search for practical routes for the synthesis of C1-substituted *N*-allyl-*N*,*O*-aminal substrates were continued, and several different conditions were tried by keeping the Ts as protecting group and allyl as side chain. The use of substituted methoxychlorides could be a solution to this existing problem as their preparations were known[82] from late sixties. The same preparation protocol was followed for their synthesis in our studies. Starting from any commercially available alcohols and by treating with HCl gas in methanol/pentane mixtures, the corresponding substituted methoxychlorides were prepared successfully. Subsequently, they were used next for the *N*-alkylation of *N*-tosyl-allylamine with NaH and DMF. The end product was found to be stable during their work up, and column chromatography purification led the pure product in good yields (Scheme 32).

[82] Warner, H. R.; Lands, W. E. M. *J. Am. Chem. Soc.***1963**, *85*, 60–64.

Scheme 32. Successful route to C1-substituted *N*-allyl-*N*,*O*-aminal substrates



R	yield(%)
Et	64, (**204**)
Ph	72, (**205**)

4.5 CONCLUSION

The isomerization strategy has successfully, been applied to synthesize a wide variety of enamine-aminal derivatives. Various protecting and leaving groups have been incorporated to enamine-aminal structure, and a set of more reactive substrates has been identified. In general, it was concluded that Grubb II mediated isomerization protocol was found to more versatile and applicable to all sterically demanding and carbonyl containing substrates. A general method of synthesizing *N*-allyl amine derivatives has been developed, where different protecting and leaving groups can be incorporated following one reaction protocol.

5.0 EXPERIMENTAL

General Information: Unless otherwise stated, all reactions were performed in dry glassware under an atmosphere of oxygen-free nitrogen using standard inert atmosphere techniques for the manipulation of solvents and reagents. Proton NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm) for ^1H and $CDCl_3$ (77.00 ppm) for ^{13}C NMR spectra. Anhydrous solvents were obtained by passing through successive alumina and Q5 reactant-packed columns on a solvent purification system. $[(^cC_8H_{14})_2IrCl]_2$ was synthesized according to the literature procedure [83] and stored and weighed out in nitrogen-filled glove box. *N*-Allyl-4-methylbenzenesulfonamide, [84] *N*-tosylindole, [85] *N*-methylindole, and 1-chloro-1-methoxypropane[86] and (1-methoxy-2-methylprop-1-enyloxy)trimethylsilane[87] were prepared as described. *N*,*N*-Diisopropylethylamine and triethylamine were distilled under nitrogen from CaH_2. Acetone was purged with nitrogen prior to use. Other commercially available reagents were used as received from the suppliers. Flash chromatography was performed as previously described on Iatrobeads or 6RS-8060 (pH 7 silica gel), purchased from Sorbent-USA, or EM silica gel 60 (230-240 mesh).[88]

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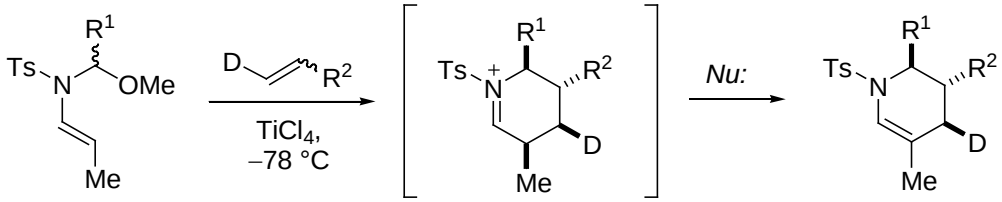
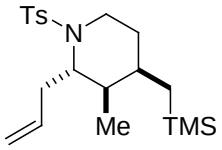
[83] Onderdelinden, A. L.; van der Ent, A. *Inorg. Chim. Acta* **1972**, *6*, 420.
[84] Brummond, K. M.; Chen, H.; Mitasev, B.; Casarez, A. D. *Org. Lett.* **2004**, *6*, 2161-2163.
[85] (a) Merlic, C. A.; You, Y.; McInnes, D. M.; Zechman, A. L.; Miller, M. M.; Deng, Q. *Tetrahedron* **2001**, *57*, 5199-5212. (b) Kikugawa, Y. *Synthesis* **1981**, 460-461.
[86] Warner, H. R.; Lands, W. E. M. *J. Am Chem. Soc.* **1963**, *85*, 60-64.
[87] Dong, S.; Parker, G. D.; Tei, T.; Paquette, L. A. *Org. Lett.* **2006**, *8*, 2429-2431.
[88] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

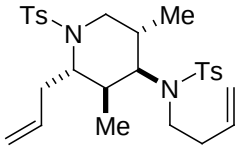


General Procedure A. $TiCl_4$-mediated Cycloadditions of Electron-rich Dienophiles: To a −78 °C solution of $TiCl_4$ (1.1 equiv) in 20 mL of CH_2Cl_2 was added a solution of the dienophile (1-10 equiv) in 2-3 mL of CH_2Cl_2 dropwise over 3-4 min. A solution enamine-aminal (1.0 mmol, 1 eq.) in CH_2Cl_2 (10 mL) was then added over 3-4 min. Once addition was complete, the reaction mixture was stirred for additional 6-8 h. A solution of the nucleophile (or Et_3N, 5 equiv) in CH_2Cl_2 (5 mL) was added dropwise and the reaction was stirred for an additional 60 min. A saturated aqueous solution of $NaHCO_3$ (10 mL) was added and the resulting solidified mass was warmed to ambient temperature (or in case of Et_3N quench, after 30 min of the addition of Et_3N the reaction mixture was warmed to ambient temperature and then saturated $NaHCO_3$ was added). The resulting mixture was stirred vigorously for 20 min and the homogeneous layers were separated. The aqueous portion was extracted with ether (10 mL) and the combined organic portions were washed with brine, dried ($MgSO_4$), and concentrated. The crude product mixture was purified by column chromatography on silica gel (10-25% ether in hexanes).



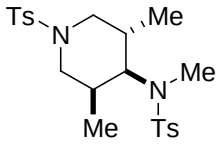
2-Allyl-3-methyl-1-tosyl-4-[(trimethylsilyl)methyl]piperidine (58): General Procedure A was followed employing enamine **55** (1.00 mmol, 255 mg) and allyltrimethylsilane (5.00 mmol, 572 mg) and a reaction time of 12 h. Purification by flash chromatography afforded 336 mg (89%, colorless oil) of the title compound as an inseparable 2:1 mixture of diastereomers (C2 epimers)

as determined by ^{1}H NMR analysis of the crude product mixture. IR (thin film): 2951, 1640, 1598, 1460, 1337, 1248, 1156, 1089, 985, 856 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$, both diastereomers): δ **7.70** (d, J = 9.6 Hz, 1.3H) & **7.69** (d, J = 8.4 Hz, 0.7H), 7.28 -7.25 (m, 2H), 5.71-5.62 (m, 1H), 5.10-4.91 (m, 2H), 4.00 (ddd, J = 15.0, 10.2, 4.8 Hz, 0.33H), 3.87 (dd, J = 10.2, 5.4 Hz, 0.66H), 3.70 (dd, J = 15.0, 3.6 Hz, 0.33H), 3.65 (dd, J = 12.6, 6.0 Hz, 0.66H), 2.94 (ddd, J = 27.6, 14.4, 2.4 Hz, 0.33H), 2.89 (ddd, J = 26.4, 13.2, 3.6 Hz, 0.66H), **2.41** (s, 2H) & **2.40** (s, 1H), 2.42-2.36 (m, 0.66H), 2.27-2.08 (m, 1.33H), 1.88 (dddd, J = 17.4, 13.8, 10.2, 6.0 Hz, 0.66H), 1.73-1.66 (m, 0.66H), 1.52 (dq, J = 13.2, 3.0 Hz, 0.33H), 1.46-1.34 (m, 1.33H), 1.28 (dq, J = 13.2, 2.4 Hz, 0.33H), 0.99 (ddd, J = 25.2, 13.2, 4.8 Hz, 0.66H), **0.85** (d, J = 6.6 Hz, 2H) & **0.84** (d, J = 6.6, 1H), 0.42 (dq, J = 14.4, 6.6 Hz, 1.33H), 0.08 (dd, J = 10.2, 15.0 Hz, 0.66H), −**0.02** (s, 6H) & −**0.05** (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6 at 70 °C, **major diastereomer in bold** where resolved): δ 142.1, 138.6 + **138.1** (1C), 135.6 + **134.8** (1C), 129.1, 126.3 + 126.2 (1C), **116.4** + 115.5 (1C), **58.7** + 57.4 (1C), **40.4** + 39.8 (1C), **33.9** + 32.0 (1C), **33.0** + 32.9 (1C), 28.7 + **28.2** (1C), 27.8, **20.8** + 20.2 (1C), 20.4, 15.6 + **11.6** (1C), – 0.90 + −**1.27** (3C); MS (EI, 70 V): *m/z* 364 $[(M-CH3)]^{\bullet+}$, 338, 224, 155, 139, 110; HRMS *m/z* calcd. For $C_{19}H_{30}NO_2SiS$ $[(M-CH_3)^{+}]$: 364.1766; found: 364.1758.



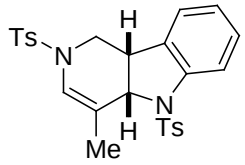
***N*-(2S,3S,4R,5S)-2-Allyl-3,5-dimethyl-1-tosylpiperidin-4-yl)-*N*-(but-3-enyl)-*p*-toluenesulfonamide (71):** General Procedure A was followed employing enamine **55** (1.00 mmol, 225 mg) and, after an initial reaction time of 5 h, allyltrimethylsilane (5.00 mmol, 572 mg) as the nucleophile. Purification by flash chromatography afforded 225 mg (85%, colorless solid) of the

title compound as an inseparable 4:1 mixture of diastereomers (C2 epimers) as determined by ^{1}H NMR analysis of the crude product mixture. Mp: 122-124 °C; IR (NaCl): 2928, 1641, 1598, 1460, 1338, 1156, 1089, 996, 918 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, both diastereomers): δ 7.72-7.63 (m, 4H), 7.32-7.22 (m, 4H), 5.79-5.46 (m, 2H), 5.14-4.92 (m, 4H), 4.14-4.07 (m, 0.2H) & 3.87-3.54 (m, 2.8H), 3.18 (ddd, J = 14.7, 11.1, 5.4 Hz, 1H), 2.99 (ddd, J = 15.9, 11.4, 4.8 Hz, 1H), 2.92-2.46 (m, 2H), 2.40 (s, 6H), 2.39-2.22 (m, 2H), 2.19-1.68 (m, 3H), 1.03 (d, J = 6.9 Hz, 2.4H) & 0.69 (d, J = 6.6 Hz, 0.6H), 0.65 (d, 7.2 Hz, 0.6H) & 0.56 (d, J = 6.3 Hz, 2.4H); ^{13}C NMR (75 MHz, CDCl3, **major diastereomer in bold** where resolved): δ 143.3, 143.2, 138.4 + **137.9** (1C), 137.8 + **137.7** (1C), **134.8** + 134.6 (1C), 134.5 + **134.1** (1C), 129.6, **129.5** + 129.4 (1C), 127.4 + **127.2** (1C), 127.1 + **127.0** (1C), 118.2, **117.0** + 116.9 (1C), 62.4 + **60.8** (1C), 60.2 + **58.2** (1C), **47.3** + 46.5 (1C), 45.1 + **42.1** (1C), 37.2 + **36.1** (1C), 35.5 + 34.8 (1C), 34.4 + **33.7** (1C), 29.5 + **28.6** (1C), 21.5 (2C), 16.1 + **15.9** (1C), 15.8 + **14.9** (1C); MS (EI, 70 V): *m/z* 310, 264, 250, 184, 155, 97, 91; HRMS (Q-TOF) *m/z* calcd. for $C_{28}H_{38}N_2O_4S_2Na$ $[(M+Na)^+]$: 553.2170; found: 553.1993.



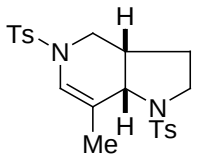
***N*-(3S,5S)-3,5-Dimethyl-1-tosylpiperidin-4-yl)-*N*-(methyl)-4-dimethylbenzenesulfonamide (75):** General Procedure A was followed employing enamine **55** (1 mmol, 255 mg), $TiCl_4$ (1.1 mmol, 1.1 mL), stirred for 12 hours and DIBAL-H (2.5 mmol, 5.0 mL, 0.5 M solution in CH_2Cl_2) was added and stirred for another 2 hours. Purification by flash chromatography with 20% ether in hexane afforded 140 mg (62%) of the title compound as a foamy white solid as a single diastereomer. Mp: 72-75 °C; IR (thin film): 2924, 2853, 1661, 1465, 1340, 1162, 1089,

968 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 3.74 (ddd, J = 11.4, 4.5, 2.7 Hz, 1H), 3.51 (dt, J = 11.7, 2.4 Hz, 1H), 3.36 (dd, J = 11.7, 4.8 Hz, 1H), 2.80 (s, 3H), 2.44 (s, 3H), 2.40 (dd, J = 12.0, 3.0 Hz, 1H), 2.39 (s, 3H), 2.26-2.08 (m, 1H), 2.08 (dq, J = 17.7, 4.8 Hz, 1H), 1.81 (t, J = 11.1 Hz, 1H), 1.10 (d, J = 6.9 Hz, 3H), 0.43 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 143.2, 136.8, 133.0, 129.7, 129.5, 127.5, 126.9, 62.9, 53.1, 52.9, 35.6, 30.8, 28.3, 21.5, 21.4, 16.0, 13.4; MS (EI, 70 V): *m/z* 309, 295, 267, 238, 224, 184, 155, 120, 91, 70; HRMS (Q-TOF) *m/z* calcd. for $C_{22}H_{30}N_2O_4S_2Na$ [$(M+Na)^+$]: 473.1545; found: 473.1536.

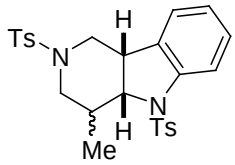


***R**-(4a*S*,9b*S*)-2,4a,5,9b-Tetrahydro-4-methyl-2,5-bis(*p*-toluenesulfonyl)-1H-pyrido[4,3-b] índole (82a):** General Procedure A was followed employing enamine **55** (1 mmol, 255 mg), *N*-tosylindole (2.00 mmol, 542 mg) as the dienophile and an initial reaction time of 12 h. Triethylamine (5.00 mmol, 506 mg) was used as the base. Purification by flash chromatography with 35% ether in hexane afforded 390 mg (79%) of the title compound as a colorless crystalline solid as a single diastereomer. Mp: 182-184 °C; IR (thin film): 3066, 2920, 1670, 1597, 1459, 1350, 1244, 1089, 962, 814 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.26-7.20 (m, 3H), 7.09 (d, J = 8.1 Hz, 2H), 6.99 (t, J = 7.5, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.45 (s, br, 1H), 4.57 (d, J = 7.8 Hz, 1H), 4.02 (d, J = 11.4 Hz, 1H), 2.95 (dd, J = 12.3, 3.0 Hz, 1H), 2.89-2.86 (m, 1H), 2.42 (s, 3H), 2.33 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.0, 143.9, 141.6, 135.3, 134.6, 133.6, 129.8, 129.6, 128.3, 127.1, 127.0, 125.9, 123.8, 123.3, 120.2, 113.4, 62.1, 41.7, 39.9, 21.5 (2C), 17.6; MS (EI,

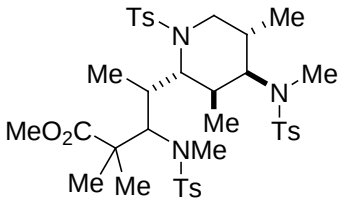
70 V): *m/z* 495 [$(M+H)^+$], 475, 443, 430, 365, 339, 212, 185; HRMS (Q-TOF) *m/z* calcd. for $C_{26}H_{26}N_2O_4S_2Na$ [$(M+Na)^+$]: 517.1232; found: 517.1248.



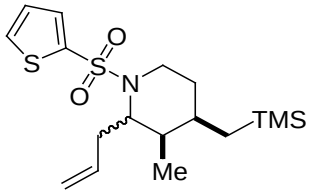
(3aS,7aS)-7-Methyl-1,5-ditosyl-2,3,3a,4,5,7a-hexahydro-1H-pyrrolo[3,2-c]pyridine (82b): General Procedure A was followed employing enamine **55** (0.250 mmol, 63.7 mg), $TiCl_4$ (0.27 mmol, 0.27 mL), 1-tosyl-2,3-dihydro-1H-pyrrole (0.500 mmol, 111 mg) as the dienophile and an initial reaction time of 12 h. Et_3N (1.25 mmol, 0.175 mL) was added and stirred for an additional 2 h. Purification by flash chromatography with 25% ether in hexane afforded 85 mg (76%) of the title compound. IR (thin film): 2923,1718, 1667, 1597, 1453, 1344, 1160, 1025, 815 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 7.5 Hz, 4H), 6.42 (d, J = 1.2 Hz, 1H), 4.12 (d, J = 6.6 Hz, 1H), 3.56 (d, J = 12 Hz, 1H), 3.39-3.21 (m, 2H), 2.83 (dd, J = 12, 2.4 Hz, 1H), 2.42 (s, 3H), 2.41 (s, 3H), 1.87-1.72 (m, 2H), 1.76 (s, 3H), 1.70-1.62 (m,1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144, 143.6, 135.1, 134.4, 129.8, 129.7, 127.4, 127, 121.4, 114.6, 58.5, 46.7, 43.5, 36.1, 26.4, 21.6, 21.5, 17.8; MS (EI, 70 V): *m/z* 446 ($M^{+\bullet}$), 368, 291, 264, 248, 224, 155, 135, 108; HRMS *m/z* calcd. for $C_{22}H_{26}N_2O_4S_2$: 446.1352; found: 446.1331.



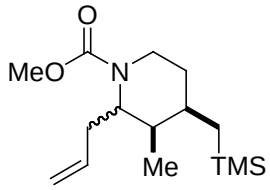
(4aR,9bS)-4-Methyl-2,5-bis(tosyl)-2,3,4,4a,5,9b-hexahydro-1H-pyrido[4,3-b]indole (82c): General Procedure A was followed employing enamine **55** (1 mmol, 255 mg), *N*-tosylindole (2 mmol, 542 mg) as the dienophile and an initial reaction time of 9 h. DIBAL-H (5 mmol) was added and stirred for another hour. Purification by flash chromatography (20% ethylacetate/hexane) afforded 352 mg (71%) of the title compound (colorless crystalline solid) as a 1:1 mixture of two diastereomers. Crystallization and re-column purification provided analytically pure sample of one diastereomer. Mp: 97-99 °C; IR (thin film): 3391, 2926, 1597, 1459, 1347, 1164, 1089, 1018, 814, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 6.98 (t, J = 7.5, 1H), 6.89 (d, J = 7.5 Hz, 1H), 4.33 (dd, J = 9.3, 6 Hz, 1H), 3.86 (dd, J = 12.6, 3 Hz, 1H), 3.09 (dt, J = 12, 3.9 Hz, 2H), 2.97 (dd, J = 12, 3.6 Hz, 1H), 2.86 (dd, J = 12, 8.7 Hz, 2H), 2.42 (s, 3H), 2.32 (s, 3H), 2.29-2.15 (m, 1H), 1.01 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.0, 143.3, 142.7, 134.9, 134.8, 134.0, 129.6, 129.5, 128.4, 127.2, 127.0, 125.5, 123.3, 118.1, 62.6, 46.7, 41.9, 40.3, 32.4, 21.5, 14.8; MS (EI, 70 V): *m/z* 496 ($M^{+\bullet}$), 341, 295, 224, 184, 158, 144, 130, 117, 91; HRMS *m/z* calcd. for $C_{26}H_{28}N_2O_4S_2$:496.1490; found: 496.1478.



Methyl 3-(*N*,4-dimethylphenylsulfonamido)-4-(4-(*N*,4-dimethylphenylsulfonamido)-3,5-dimethyl-1-tosylpiperidin-2-yl)-2,2-dimethylpentanoate (82d): General Procedure A was followed employing enamine **55** (0.500 mmol, 127 mg), (*E*)-*N*,4-dimethyl-*N*-(prop-1-enyl)-*p*-toluenesulfonamide (2.00 mmol, 450 mg) as the dienophile and an initial reaction time of 24 h. (1-Methoxy-2-methylprop-1-enyloxy)trimethylsilane (2.50 mmol, 435 mg) was added as the nucleophile 3 h. Purification by flash chromatography (20% ether/hexane) afforded 166 (43%) of the title compound (colorless crystalline solid) as a single diastereomer. Mp: 94-95 °C; IR (thin film): 2924, 1725, 1597, 1457, 1336, 1153, 1089, 1018, 958 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, J = 8.1 Hz, 2H), 7.69 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 4.43 (s, 1H), 4.06 (d, J = 10.8 Hz, 1H), 3.81 (dd, J = 12, 4.2 Hz, 2H), 3.68 (s, 3H), 2.61 (s, 3H), 2.65 (s, 3H), 2.64-2.52 (m, 2H), 2.44 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H), 1.88-1.71 (m, 2H), 1.47 (s, 3H), 1.23 (s, 3H), 0.85 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 6.9 Hz, 3H), 0.53 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3, 143.4, 143.1, 142.8, 138.8, 136.5, 135.6, 129.6, 129.5, 129.4, 128.7, 127.2, 127.1, 63.5, 62.4, 60.1, 52.2, 48.0, 47.3, 36.4, 34.3, 33.5, 31.1, 27.6, 26.6, 26.2, 21.5, 21.4, 16.1, 15.0, 13.2; HRMS (Q-TOF) *m/z* calcd. for $C_{38}H_{53}N_3O_8S_3Na$ [$(M+Na)^+$]: 798.2893; found: 798.2897.

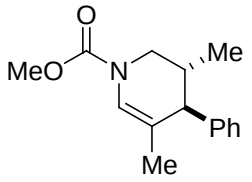


(3R,4R)-2-Allyl-3-methyl-1-(thiophen-2-sulfonyl)-4-((trimethylsilyl)methyl)piperidine (105a): General Procedure A was followed employing enamine **102** (0.500 mmol, 124 mg), allyltrimethylsilane (1.00 mmol, 228 mg) and titanium tetrachloride (0.55 mmol, 0.55 mL, 1 M solution in CH_2Cl_2). Purification by flash chromatography (10% ether/hexane) afforded 144 mg (78%) of the title compound as a 1:1 mixture of diastereomers (C2 epimers) as determined by ^{1}H NMR analysis of the crude product mixture. IR (thin film): 2950, 1641, 1407, 1342, 1248, 1151, 1013, 918, 856, 722 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (t, J = 5.1 Hz, 2H), 7.04 (dd, J = 5.1, 3.9 Hz, 1H), 5.99-5.58 (m, 1H), 4.99 (dd, J = 13.2, 13.2 Hz, 2H), 4.09-3.86 (m, 1H), 3.74 (dt, J = 18.9, 4.2 Hz, 1H), 2.96 (dq, J = 17.7, 3 Hz, 1H), 2.52-2.36 (m, 1H), 2.30-2.08 (m, 2H), 2.01-1.84 (m, 1H), 1.79-1.65 (m, 1H), 1.51-1.28 (m, 2H), 0.87 (t, 6.9 Hz, 3H), 0.46 (t, J = 6.3 Hz, 1H), -0.01 & -0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1 & 142.5, 135.2 & 134.8, 131.3, 131.0 & 130.9, 127.1 & 127.0, 117.4 & 116.6, 59.8 & 58.5, 41.2, 41.0 & 40.7, 34.5 & 33.6, 33.4 & 32.9, 28.8 & 28.6, 21.5 & 20.8, 16.5 & 12.2, -(0.47 & 0.78); HRMS (Q-TOF) *m/z* calcd. for $C_{17}H_{29}NO_2S_2SiNa$ [$(M+Na)^+$]: 394.1307; found: 394.1274.



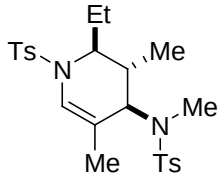
Methyl-2-allyl-3-methyl-4-[(trimethylsilyl)methyl]piperidine-1-carboxylate (61): To a stirred solution of $TiCl_4$ (0.55 mmol, 0.55 mL, 1M solution in CH_2Cl_2) in 1 mL CH_2Cl_2 at −78 °C a

solution of (*E*)-methyl methoxymethyl(prop-1-enyl)carbamate **59** (0.500 mmol, 79.5 mg) in 1 mL CH_2Cl_2 and allyTMS (2.00 mmol, 228 mg) were added. The reaction temperature was raised to ambient temperature over 3-4 hours and stirred for additional 3-4 hours. The reaction mixture was diluted with saturated $NaHCO_3$ (10 mL) and organic layer was separated. The organic phase was washed with water, dried ($MgSO_4$) and concentrated. Purification by column chromatography with 15% ether in hexane afforded 50 mg (37%) of the title compound as colorless oil as an inseparable 1:1 mixture of diastereomers (C2 epimers) as determined by ^1H NMR analysis of the crude product mixture. IR (thin film): 2952, 1701, 1641, 1448, 1248, 89 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, both diastereomers): δ 5.82-5.58 (m, 1H), 5.05-4.94 (m, 2H), 4.35-3.80 (m, 2H), 3.65 & 3.64 (s, 3H), 2.84-2.81 (m, 1H), 2.44-2.23 (m, 2H), 2.01-1.87 (m, 1H), 1.74-1.56 (m, 1H), 1.51-1.21 (m, 1H), 1.20-1.10 (m, 1H), 0.87 (dd, J = 6.3, 4.8 Hz, 3H), 0.45 (dd, J = 7.2, 6.9 Hz, 1H), 0.15 (dd, J = 9.9, 9.9 Hz, 0.5H), -0.002 & -0.008 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, for one diastereomer): δ 156.1, 135.2, 116.4, 57.5, 52.4, 39.4, 34.7, 33.2, 29.4, 21.6, 16.5, 12.2, −0.76; MS (EI, 70 eV): *m/z* 283 ($M^{+\bullet}$), 268, 242, 168, 154, 138, 128, 110, 95, 89; HRMS *m/z* calcd. for $C_{15}H_{29}NO_2Si$: 283.1967; found: 283.1973.



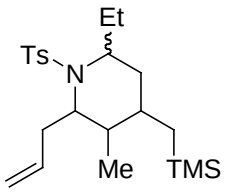
Methyl-3,5-dimethyl-4-phenyl-3,4-dihydropyridine-1(2H)-carboxylate (64): To an ice-cold solution of (*E*)-methylmethoxymethyl(prop-1-enyl)carbamate, **59** (0.33 mmol, 53 mg) and β-methylstyrene (0.500 mmol, 58.4 mg) in 3 mL CH_2Cl_2 was added a solution of $SnCl_4$ (0.400 mmol, 104 mg) in 0.5 mL CH_2Cl_2. After 2 hours, the reaction mixture was diluted with saturated

bicarbonate solution and organic layer was separated. The organic phase was washed with water, dried ($MgSO_4$) and concentrated. Purification by flash chromatography with 20% ether in hexane afforded 55 mg (67%) of the title compound as a colorless oil in 4.4:1 diastereomeric ratio. IR (thin film): 2957, 1709, 1674, 1444, 1394, 1207, 1191 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, minor diastereomer in bold where resolved): δ 7.28-7.13 (m, 5H), 6.95 & 6.81 (s, 1H), **6.90 & 6.77 (s, 0.2H),** 3.80 & 3.77 (s, 3H), **3.65 & 3.61 (s, 0.7H)**, 3.13 (d, J = 5.1 Hz, 1H), 2.86 (t, J = 12 Hz, 1H), 2.25-2.12 (m, 1H), 1.58 &1.57 (s, 3H), **1.49 &1.47 (s, 0.7H)**, 1.28-1.21 (m, 1H), **0.96 & 0.94 (s, 0.7H)**, 0.69 & 0.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, for both diastereomers): δ 154.1 + 153.6 (1C), 139.5, 129.7, 127.9, 126.6, 120.9 + 120.5 (1C), 116.2 + 115.9 (1C), 52.9 + 52.8 (1C), 48.5 + 48.3 (1C), 43.6 + 43.4 (1C), 31.1, 19.8 + 19.7 (1C), 16.2 + 16.1 (1C); MS (EI, 70 eV): *m/z* 245 ($M^{+\bullet}$), 230, 199, 183, 168, 155, 131, 109; HRMS *m/z* calcd. for $C_{15}H_{19}NO_2$: 245.1415; found: 245.1421.



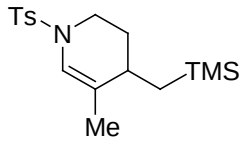
(2*S*,3*S*,4*R*)-2-Ethyl-1,2,3,4-tetrahydro-*N*,3,5-trimethyl-*N*,*N*′-bis(*p*-toluenesulfonyl)pyridine-4-amine (86): To a −78 °C solution of $TiCl_4$ (1.1 equiv, 0.55 mL) in 10 mL of CH_2Cl_2 was added a solution of enamine **83** (0.500 mmol, 141 mg) in CH_2Cl_2 (3 mL) and the reaction was stirred for 90 min. (*E*)-*N*,4-dimethyl-*N*-(prop-1-enyl)benzenesulfonamide **80** (0.600 mmol, 135 mg) was added and the reaction was stirred for 3 h at –78 °C prior to adding Et_3N (2.50 mmol, 250 mg). Once addition was complete, the reaction was warmed to ambient temperature whereupon a saturated aqueous solution of $NaHCO_3$ (5 mL) was added and resulting mixture

was stirred vigorously for 20 min. The resulting homogeneous layers were separated and the aqueous portion was extracted with ether (5 mL) and the combined organic portions were washed with brine, dried ($MgSO_4$), and concentrated. The crude product mixture was purified by flash chromatography on silica gel (25% ether in hexanes) affording 105 mg (44%) of the title compound as a white crystalline solid (single diastereomer). Mp: 176-178 °C; IR (thin film): 2969, 2932, 1659, 1597, 1453, 1339, 1219, 1187, 1163, 1084, 970, 947 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 6.41 (dd, J = 2.4, 1.2 Hz, 1H), 4.06 (d, J = 10.8 Hz, 1H), 3.67 (dt, J = 11.4, 2.7 Hz, 1H), 2.39 (s, 3H), 1.99 (s, 3H), 1.50 (ddd, J = 13.8, 7.5, 3.0 Hz, 1H), 1.41-1.32 (m, 1H), 1.30 (s, 3H), 1.03 (t, J = 7.2 Hz, 3H), 0.70 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 143.1, 137.3, 136.0, 129.6, 129.4, 127.1, 126.9, 123.3, 119.4, 60.9, 58.7, 31.6, 27.1, 21.5, 21.4, 18.7, 17.8, 15.8, 11.1; MS (EI, 70 V): *m/z* 476 ($M^{\bullet+}$), 447; HRMS (Q-TOF) *m/z* calcd. for $C_{24}H_{32}N_2O_4S_2Na$ [$(M+Na)^+$]: 499.1701; found: 499.1713.



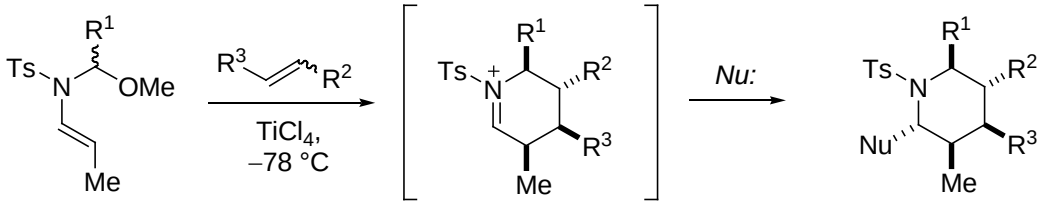
6-Ethyl-3-methyl-1-tosyl-4-((trimethylsilyl)methyl)-2-vinylpiperidine (87): To a −78 °C solution of $TiCl_4$ (1.1 equiv, 0.59 mL) in 10 mL of CH_2Cl_2 was added a solution of enamine **83** (0.540 mmol, 152 mg) and allyltrimetylsilane (2.15 mmol, 246 mg) in CH_2Cl_2 (3 mL) and the reaction was stirred for 3 hours. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) and the resulting residue was warmed to ambient temperature. The resulting homogeneous layers were separated and the aqueous portion was extracted with ether

(5 mL) and the combined organic portions were washed with brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography with 10% ether in hexane afforded 134 mg (61%) of the title compound in the form of a colorless oil as a 10:18 mixture of non-separable diastereomers as determined by ^{1}H NMR analysis of the crude product mixture. IR (thin film): 2957, 1640, 1460, 1340, 1248, 1162, 1088, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (dd, J = 8.1, 6 Hz, 2H), 7.26 (t, J = 6.9 Hz, 2H), 5.83 (ddd, J = 24.3, 14.1, 7.5 Hz, 1H), 5.05 (dd, J = 14.1, 3.9 Hz, 2H), 3.84-3.64 (m, 1.3 H), 3.63-3.42 (m, 0.7 H), 2.52-2.40 (m, 1H), 2.39 (s, 3H), 2.36-2.24 (m, 1H), 2.08-1.96 (m, 1H), 1.85 (ddd, J = 13.5, 10.5, 2.4 Hz, 1H), 1.75-1.59 (m, 1H), 1.58-1.42 (m, 1H), 1.39-1.14 (m, 1H), 1.05-0.94 (m,1H), 0.91 (t, J = 7.5 Hz, 3H), 0.86-0.74 (m, 1H), 0.68 (d, J = 6.9 Hz, 2H), 0.56 (dd, J = 14.7, 2.1 Hz, 1H), 0.46 (d, J = 9 Hz, 1H), 0.41-0.39 (m, 1H), 0.07 (dd. J = 14.4, 10.2, 1H) -0.17 & -0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8 & 142.5, 139.0 & 138.4, 136.2 & 135.5, 129.4 & 129.3, 127.3 & 127.0, 117.1& 117.0, 60.3 & 59.4, 56.7 & 55.4, 44.9, 43.7 & 40.3, 36.1 & 34.4, 33.9 & 29.3, 33.0 & 28.9, 23.5, 21.5 & 21.4, 20.55 & 20.51, 12.1 & 10.8, - (0.79 & 1.01); HRMS (Q-TOF) *m/z* calcd. for $C_{22}H_{37}NO2SSiNa$ [$(M+Na)^+$]: 430.2212; found: 430.2172.



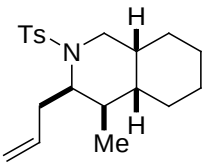
1,2,3,4-Tetrahydro-5-methyl-4-((trimethylsilyl)methyl)-1-tosylpyridine (132): General Procedure A was followed employing enamine **55** (0.500 mmol, 128 mg) and allyltrimethylsilane (2.50 mmol, 286 mg) in toluene and a reaction time of 12 h. Purification by flash chromatography afforded the title compound (13.5 mg, 8%) as minor product (along with the major product). IR (thin film): 2951, 1663, 1442, 1351, 1249, 1164, 1093, 859 cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$): δ 7.65 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 6.33 (s, 1 H), 3.40 (ddd, J = 9.6, 6, 3.3 Hz, 1H), 3.19 (ddd, J = 12.9, 10.2, 3.3 Hz, 1H), 2.42 (s, 3H), 1.91-1.87 (m, 1H), 1.62 (s, 3H), 1.48-1.32 (m, 2H), 0.76 (dd, J = 15, 2.7 Hz, 1H), 0.16 (dd, J = 15.3, 11.1 Hz, 1H), -0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 135.1, 129.6, 127.1, 122.9, 118.4, 40.3, 31.4, 28.3, 21.5, 21.1, 19.3, -0.87; MS (EI, 70 V): *m/z* 337 ($M^{\bullet+}$), 309, 249, 182, 155, 149, 139, 108, 91, 86; HRMS *m/z* calcd. For $C_{17}H_{27}NO_2SSi$: 337.1531; found: 337.1528.

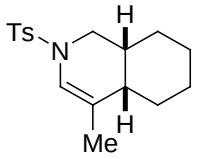


General Procedure B. $TiCl_4$-mediated Cycloadditions of Neutral Alkene Dienophiles: To a −78 °C solution of $TiCl_4$ (1.1 equiv) in 25 mL of CH_2Cl_2 was added a solution of the alkene dienophile (1-10 equiv) in 2-3 mL of CH_2Cl_2 dropwise over 3-4 min. A solution enamine- aminal (1.0 mmol, 1 eq.) in CH_2Cl_2 (10 mL) was then added over 3 h via syringe pump. Once addition was complete, the reaction mixture was warmed to −50 °C and stirred for additional 6-8 h. A solution of the nucleophile (or Et_3N, 5 equiv) in CH_2Cl_2 (5 mL) was added dropwise and the reaction was stirred for an additional 60 min. A saturated aqueous solution of $NaHCO_3$ (10 mL) was added and the resulting solidified mass was warmed to ambient temperature (or in case of Et_3N quench, after 30 min of the addition of Et_3N the reaction mixture was warmed to ambient temperature and then saturated $NaHCO_3$ was added). The resulting mixture was stirred vigorously for 20 min and the homogeneous layers were separated. The aqueous portion was extracted with ether (10 mL) and the combined organic portions were washed with brine, dried

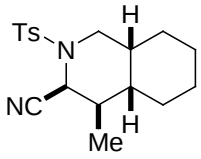
($MgSO_4$), and concentrated. The crude product mixture was purified by column chromatography on silica gel (10-25% ether in hexanes).



3-Allyl-4-methyl-2-tosyl-decahydroisoquinoline (88): General Procedure B was followed employing enamine **55** (1.00 mmol, 255 mg), cyclohexene (10.0 mmol, 820 mg) as the dienophile, and allyltrimethylsilane (5.00 mmol, 572 mg) as the nucleophile. Purification by flash chromatography afforded 203 mg (59%) of the title compound as a viscous oil that solidified upon standing (diastereomer ratio major:Σothers = 97:3 as determined by ^{1}H NMR analysis of the crude product mixture). Mp: 55-57 °C; IR (NaCl): 2929, 1640, 1448, 1333, 1153, 1089, 1005, 915 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 5.37 (dddd, J = 17.0, 10.0, 7.5, 7.2 Hz, 1H), 4.85 (dd, J = 17.1, 1.2 Hz, 1H), 4.70 (dd, J = 10.2, 1.2 Hz, 1H), 3.96 (dd, J = 13.2, 5.7 Hz, 1H), 3.50 (d, J = 13.8 Hz, 1H), 3.12 (dd, J = 13.5, 2.7 Hz, 1H), 2.40 (s, 3H), 2.25 (dddd, J = 18.6, 13.8, 11.7, 6.9 Hz, 1H), 2.18-2.13 (m, 2H), 1.81-1.48 (m, 5H), 1.41-1.18 (m, 5H), 0.83 (d, J = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.5, 139.0, 135.8, 129.2, 127.2, 116.2, 58.4, 46.1, 36.6, 34.7, 30.6, 29.6, 27.6, 26.2, 25.6, 21.5, 19.7, 16.1; MS (EI, 70 V): *m/z* 306 [$(M-41)^{\bullet+}$], 231, 215, 177, 155, 117, 97, 91; HRMS *m/z* calcd. For $C_{17}H_{24}NO_2S$ [$(M-C_3H_5)^{\bullet+}$]: 306.1527; found: 306.1534.

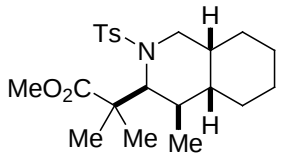


***R**-(4a*S*,8a*R*)-1,2,4a,5,6,7,8,8a-Octahydro-4-methyl-2-(*p*-toluenesulfonyl)isoquinoline (90):** General Procedure B was followed employing enamine **55** (1.00 mmol, 255 mg), cyclohexene (10.0 mmol, 820 mg) as the dienophile, and Et_3N (5.00 mmol, 506 mg) as the base. Purification by flash chromatography (15% ether/hexane) afforded 162 mg (53%) of the title compound as a viscous oil (single diastereomer as determined by ^1H NMR analysis of the crude product mixture). IR (thin film): 2924, 2854, 1662, 1597, 1450, 1346, 1162, 1091, 1055, 948, 812 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 6.37 (s, 1H), 3.25-3.19 (m, 2H), 2.42 (s, 3H), 1.89-1.79 (m, 2H), 1.62 (s, 3H), 1.55-1.15 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 135.4, 129.6, 127.0, 119.5, 118.8, 45.3, 37.1, 31.9, 27.9, 27.6, 24.5, 22.7, 21.5, 18.7; MS (EI, 70 V): *m/z* 305 ($M^{\bullet+}$), 290, 276, 224, 155, 123, 91, 81, 67; HRMS *m/z* calcd. for $C_{17}H_{23}NO_2S$: 305.1449; found: 305.1438.

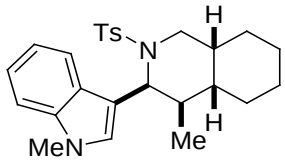


(3S,4R,4aS,8aR)-4-Methyl-2-tosyl-(3-nitrile)decahydroisoquinoline (91a): General Procedure B was followed employing enamine **55** (0.500 mmol, 127 mg), cyclohexene (5.00 mmol, 410 mg) as dienophile, and trimethylsilylnitrile (2.50 mmol, 248 mg) as the nucleophile. Purification by flash chromatography (10% ether/hexane) afforded 88 mg (53%) of the title compound as a single diastereomer. IR (thin film): 2930, 2861, 1597, 1451, 1350, 1163, 1026, 931, 813, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 4.82 (d, J =

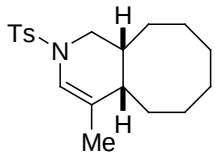
3.9 Hz, 1H), 3.54 (d, J = 12.6 Hz, 1H), 2.88 (dd, J = 12.3, 2.1 Hz, 1H), 2.43 (s, 3H), 2.41-2.31 (m, 1H), 1.92-1.71 (m, 4H), 1.66-1.59 (m, 1H), 1.51-1.12 (m, 5H), 1.02 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.4, 133.6, 129.8, 127.7, 113.8, 52.5, 48.8, 36.6, 35.5, 30.2, 27.0, 25.8, 25.3, 21.6, 19.6, 15.0; HRMS (Q-TOF) *m/z* calcd. for $C_{18}H_{24}N_2O_2SNa$ $[(M+Na)^+]$: 355.1456; found: 355.1443.



***R**-(3'*S*,4'*R*,4a'*S*,8a'*R*)-Methyl 2-(decahydro-4'-methyl-2'-(*p*-toluenesulfonyl)isoquinolin-3'-yl)-2,2-dimethylpropanoate (91b):** General Procedure B was followed employing enamine **55** (1.00 mmol, 255 mg), cyclohexene (10.0 mmol, 820 mg) as dienophile, and (1-methoxy-2-methylprop-1-enyloxy)trimethylsilane (5.00 mmol, 870 mg) as the nucleophile. Purification by flash chromatography (15% ether/hexane) afforded 232 mg (57%) of the title compound as a single diastereomer as determined by ^{1}H NMR analysis of the crude product mixture. IR (thin film): 2926, 2855, 1728, 1597, 1450, 1339, 1257, 1158, 11116, 1022, 810 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 7.8 Hz, 2H), 3.93 (dd, J = 7.5, 1.5 Hz, 1H), 3.81 (ddd, J = 15.6, 9.3, 1.5 Hz, 1H), 3.66 (s, 3H), 2.74 (dd, J = 15.6, 8.7 Hz, 1H), 2.41 (s, 3H), 1.82 (ddd, J = 16.8, 13.2, 6.0 Hz, 1H), 1.68-1.64 (m, 2H), 1.53-1.52 (m, 1H), 1.33 (s, 3H), 1.31-1.27 (m, 3H), 1.25 (s, 3H), 1.11-1.05 (m, 3H), 0.93-0.89 (m, 1H), 0.83 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.5, 143.0, 138.0, 129.4, 127.5, 67.4, 51.8, 48.0, 47.6, 36.0, 32.2, 28.4, 27.4, 26.4 (2C), 24.8, 23.0, 21.5, 21.1, 19.6; MS (EI, 70 V): *m/z* 408 $[(M+H)^{\bullet+}]$, 306; HRMS (Q-TOF) *m/z* calcd. for $C_{22}H_{33}NO_4SNa$ $[(M+Na)^+]$: 430.2028; found: 430.2035.

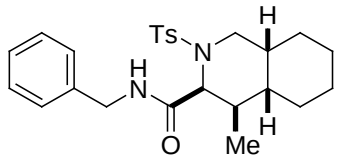


***R**-(3*S*,4*R*,4a*S*,8a*R*)-Decahydro-4-methyl-3-(*N*-methyl-1H-indol-3-yl)-2-(*p*-toluenesulfonyl) isoquinoline (91c):** General Procedure B was followed employing enamine **55** (1.00 mmol, 255 mg), cyclohexene (10.0 mmol, 820 mg) as the dienophile, and *N*-methylindole (1.300 mmol, 170.5 mg) as the nucleophile. Purification by flash chromatography (15% ether/hexane) afforded 230 mg (53%) of the title compound as a colorless crystalline solid (single diastereomer as determined by ^{1}H NMR analysis of the crude product mixture). Mp: 73-75 °C; IR (thin film): 3051, 2926, 1597, 1466, 1374, 1331, 1159, 1022, 969, 950, 912, 808, 736 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, J = 7.5 Hz, 1H), 7.25-7.14 (m, 3H), 6.89 (d, J = 8.1, 2H), 6.62-6.60 (m, 3H), 5.55 (d, J = 5.1 Hz, 1H), 3. 57 (dd, J = 24.3, 12.0 Hz, 1H), 3.50 (s, 3H), 3.12 (dd, J = 12, 3.3 Hz, 1H), 2.62 (septet, J = 6.3 Hz, 1H), 2.18 (s, 3H), 2.11-2.03 (m, 1H), 1.87-1.77 (m, 4H), 1.57-1.50 (m, 1H), 1.43-1.32 (m, 4H), 0.58 (d, J = 6.6, 3H); 13C NMR (75 MHz, CDCl3): δ 141.4, 136.0, 135.2, 130.0, 127.9, 126.9, 125.8, 121.8, 119.4, 119.3, 109.5, 108.5, 53.7, 48.0, 36.5, 34.5, 32.4, 30.9, 27.5, 26.2, 25.5, 21.2, 19.7, 15.4; MS (EI, 70 V): *m/z* 436 ($M^{\bullet+}$), 305, 281, 265, 198, 171, 157, 144, 131, 91; HRMS *m/z* calcd. for $C_{26}H_{32}N_2O_2S$: 436.2184; found: 436.2185.



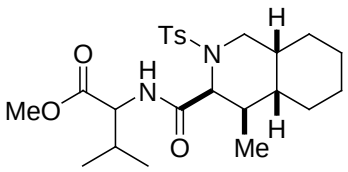
***R**-(4a*S*,10a*R*)-1,2,4a,5,6,7,8,9,10,10a-Decahydro-4-methyl-2-(*p*-toluenesulfonyl)cycloocta [c]pyridine (94):** General Procedure B was followed employing enamine **55** (1.00 mmol, 255 mg), cyclooctene (10 mmol, 1.1 g) as the dienophile, and Et_3N (5.00 mmol, 506 mg) as the base.

Purification by flash chromatography (15% ether/hexane) afforded 230 mg (69%) of the title compound as viscous oil (single diastereomer as determined by ^{1}H NMR analysis of the crude product mixture. IR (thin film): 2920, 1671, 1597, 1468, 1342, 1186, 1163, 1092, 1044, 980, 813 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 6.38 (s, 1H), 3.43 (d, J = 11.4 Hz, 1H), 2.56 (t, J = 11.8 Hz, 1H), 2.45 (s, 3H), 2.10-1.95 (m, 1H), 1.71 (s, 3H), 1.65-1.60 (m, 6H), 1.42-1.32 (m, 6H), 1.15-1.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1, 134.8, 129.4, 126.7, 121.3, 117.5, 45.2, 37.9, 35.8, 29.6, 28.5, 26.8, 26.7, 26.0, 25.3, 21.3, 19.4; MS (EI, 70 V): *m/z* 333 ($M^{\bullet+}$), 318, 248, 236, 178, 155, 91, 80, 68; HRMS *m/z* calcd. for $C_{19}H_{27}NO_2S$: 333.1762; found: 333.1758.

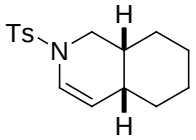


(3S,4R,4aS,8aR)-*N*-Benzyl-4-methyl-2-tosyl-decahydroisoquinoline-3-carboxamide (96b): General Procedure B was followed employing enamine **55** (0.500 mmol, 128 mg), cyclohexene (5.00 mmol, 410 mg) as dienophile, and benzylisonitrile (1.500 mmol, 175.5 mg) as the nucleophile. Purification by flash chromatography (25% ether/hexane) afforded 80 mg (36%) of the title compound (white solid) as a single diastereomer. MP: 160-161 °C; IR (thin film): 3398, 2924, 1656, 1576, 1498, 1450, 1334, 1159, 1027, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J = 8.4 Hz, 2H), 7.38-7.21 (m, 7H), 6.15 (t, J = 6.3 Hz, 1H), 4.38 (dd, J = 14.7, 6.3 Hz, 1H), 4.25 (d, J = 4.8 Hz, 1H), 4.09 (dd, J = 9.9, 4.8 Hz, 1H), 3.66 (dd, J = 12.6, 3.6 Hz, 1H), 3.37 (d, J = 13.8 Hz, 1H), 2.41 (s, 3H), 2.33-2.15 (m, 2H), 1.84-1.61 (m, 3H), 1.38-1.14 (m, 6H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 143.2, 137.7, 136.5, 129.5, 128.7, 127.8,

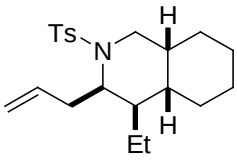
127.5, 127.0, 59.7, 48.3, 43.2, 35.9, 33.4, 29.3, 27.3, 26.0, 25.1, 21.5, 19.3, 15.2; HRMS (Q-TOF) *m/z* calcd. for $C_{25}H_{32}N_2O_3SNa$ [$(M+Na)^+$]: 463.2031; found: 463.1991.



(S)-Methyl 3-methyl-2-((3S,4R,4aS,8aR)-4-methyl-2-tosyl-decahydroisoquinoline-3-carboxamido)butanoate (96c): General Procedure B was followed employing enamine **55** (0.500 mmol, 128 mg), cyclohexene (5.00 mmol, 410 mg) as dienophile, and (S)-methyl 2-isocyano-3-methylbutanoate (1.60 mmol, 225 mg) as the nucleophile. Purification by flash chromatography (25% ether/hexane) afforded 116 mg (50%) of the title compound as an oil (diastereomeric ratio = 1:1 as determined by ^{1}H NMR analysis of the crude product mixture). IR (thin film): 3373, 2930, 1743, 1679, 1522, 1450, 1450, 1333, 1156, 1027, 814 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J = 8.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.20 (d, J = 8.1 Hz, 1H), 6.50 (d, J = 7.8 Hz, 0.5H), 6.42 (d, J = 8.1 Hz, 0.5H), 4.33 (dt, J = 7.8, 4.8 Hz, 1.5H), 4.22 (dd, J = 8.1, 4.5 Hz, 0.5H), 3.79 (s, 1.5 H), 3.72 (s, 1.5 H), 3.68 (t J = 3.3 Hz, 0.5H), 3.64 (d, J = 3.6 Hz, 0.5H), 3.42 (d, J = 12.3 Hz, 0.5H), 3.34 (d, J = 12.6 Hz, 0.5H), 2.41 (s, 1.5H), 2.39 (s, 1.5H), 2.28-2.02 (m, 3H), 1.82-1.61 (m, 4H), 1.41-1.05 (m, 4H), 0.97 (t, J = 7.2 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.86 (dd, J = 6.9, 3.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, for both diastereomer): δ 171.9 & 171.8, 169.2 & 168.8, 143.1 & 143.0, 137.0 & 136.5, 129.4 & 129.3, 127.1 & 127.0, 59.6 & 59.2, 57.1 & 56.9, 52.0 & 51.9, 48.2 & 48.16, 35.9 & 35.8, 33.6 & 33.4, 31.2 & 30.8, 29.36 & 29.33, 27.32 & 27.26, 25.9, 25.2 & 25.1, 21.4, 19.3 & 19.2, 18.9 & 18.8, 17.88 & 17.82, 15.4 & 14.9; HRMS (Q-TOF) *m/z* calcd. for $C_{24}H_{36}N_2O_5SNa$ [$(M+Na)^+$]: 487.2243; found: 487.2213.

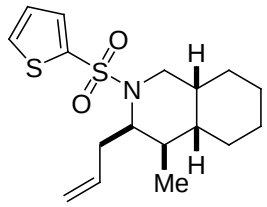


***R**-(4a*S*,8a*R*)-1,2,4a,5,6,7,8,8a-Octahydro-2-(*p*-toluenesulfonyl) isoquinoline (99):** General Procedure B was followed employing enamine *N*-(methoxymethyl)-*N*-vinyl-*p*-toluenesulfonamide **212** (1.00 mmol, 241 mg), cyclohexene (10.0 mmol, 820 mg) as the dienophile, and Et_3N (5 mmol, 506 mg) as the base. Purification by flash chromatography (10% ether/hexane) afforded 52 mg (18%) of the title compound as viscous oil (single diastereomer as determined by ^1H NMR analysis of the crude product mixture). IR (thin film): 2928, 1686, 1597, 1449, 1378, 1165, 1092, 935, 815, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.59 (dd, J = 8.4, 2.4 Hz, 1H), 4.23 (dd, J = 8.4, 3 Hz, 1H), 3.39 (dd, J = 11.4, 6 Hz, 1H), 3.14 (dd, J = 11.7, 3.3 Hz, 1H), 2.42 (s, 3H), 2.27-2.18 (m, 1H), 190-1.78 (m, 1H), 1.52-1.44 (m, 4H), 1.43-1.25 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.5, 135.2, 129.6, 127.0, 124.0, 111.5, 47.4, 31.9, 31.8, 30.8, 29.7, 26.4, 24.0, 21.5; MS (EI, 70 V): *m/z* 291 ($M^{\bullet+}$), 278, 264, 184, 155, 150, 136, 124, 111, 95, 91; HRMS *m/z* calcd. for $C_{16}H_{21}NO_2S$: 291.1293; found: 291.1285.



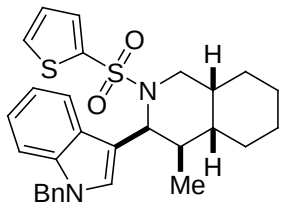
3-Allyl-4-ethyl-2-tosyl-decahydro-isoquinoline (101): General Procedure B was followed employing (*E*)-*N*-(but-1-enyl)-*N*-(methoxymethyl)-*p*-toluenesulfonamide **213** (0.250 mmol, 67.3 mg), cyclohexene (2.50 mmol, 205 mg) as the dienophile, and allyltrimethylsilane (1.25 mmol, 143 mg) as the nucleophile. Purification by flash chromatography afforded 49 mg (56%) of the

title compound as viscous oil (single diastereomer as determined by ^{1}H NMR analysis of the crude product mixture). IR (NaCl): 2926, 1640, 1455, 1332, 1153, 1090, 1024, 949 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 5.41 (dddd, J = 14.1, 9.9, 9.9, 6.6 Hz, 1H), 4.87 (dd, J = 17.1, 1.8 Hz, 1H), 4.71 (dd, J = 9.9, 1.2 Hz, 1H), 3.48 (d, J = 13.8 Hz, 1H), 3.15 (dd, J = 13.8, 3.8 Hz, 1H), 2.41 (s, 3H), 2.32-2.17 (m, 1H), 2.09-1.87 (m, 2H), 1.83 (d, J = 12.3 Hz, 1H), 1.75-1.57 (m, 3H), 1.43 (dd, J = 13.2, 3.9 Hz, 1H), 1.42-1.08 (m, 7H), 0.94 (d, J = 4.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.4, 139.0, 135.6, 129.1, 127.1, 116.2, 54.8, 45.8, 36.9, 33.8, 29, 27.6, 26.1, 25.7, 21.5, 21.4, 19.7, 11.4; HRMS(Q-Tof) *m/z* calcd. For $C_{21}H_{31}NO_2SNa$ [(M+ Na)$^+$]: 384.1973; found: 384.1940.

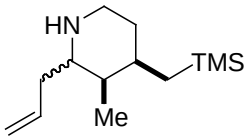


(3R,4R,4aS,8aR)-3-Allyl-4-methyl-2-(thiophen-2-ylsulfonyl)-decahydroisoquinoline (105b): General Procedure B was followed employing enamine **102** (0.250 mmol, 61.8 mg), cyclohexene (2.50 mmol, 205 mg) as dienophile, and allyltrimethylsilane (1.40 mmol, 159 mg) as the nucleophile. Purification by flash chromatography (10% ether/hexane) afforded 41 mg (49%) of the title compound as a single diastereomer as determined by ^{1}H NMR analysis of the crude product mixture. IR (thin film): 2928, 1642, 1450, 1337, 1149, 1029, 915 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.49 (d, J = 1.2 Hz, 1H), 7.02 (dd, J = 4.5, 3.6 Hz, 1H), 5.50 (dddd, J = 16.8, 9.9, 6.9, 6.9 Hz, 1H), 4.89 (dd, J = 16.8, 1.5 Hz, 1H), 4.77 (d, J = 10.5 Hz, 1H), 4.04 (q, J = 5.7 Hz, 1H), 3.53 (d, J = 13.8 Hz, 1H), 3.15 (dd, J 13.8, 3.3 Hz, 1H), 2.33-2.14 (m, 2H), 1.79 ()d, J = 11.1 Hz, 1H), 1.74-1.57 (m, 3H), 1.46 (dd, J = 12.6, 3.6 Hz, 1H), 1.41-1.12 (m, 6H),

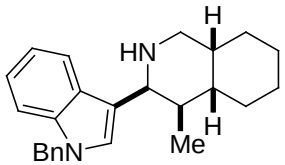
0.85 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1, 135.3, 131.2, 130.6, 126.8, 116.3, 58.6, 46.2, 36.5, 34.5, 30.5, 29.5, 27.5, 26.1, 25.4, 19.6, 16.0; HRMS (Q-TOF) *m/z* calcd. for $C_{17}H_{25}NO_2S_2Na$ [$(M+Na)^+$]: 362.1224; found: 362.1213.



(3S,4R,4aS,8aR)-3-(1-Benzyl-1H-indol-3-yl)-4-methyl-2-(thiophen-2-ylsulfonyl) decahydro isoquinoline (105c): General Procedure B was followed employing enamine **102** (0.500 mmol, 124 mg), cyclohexene (5.00 mmol, 410 mg) as dienophile, and *N*-benzylindole (1.30 mmol, 135 mg) as the nucleophile. Purification by flash chromatography (15% ether/hexane) afforded 131 mg (52%) of the title compound as a single diastereomer as determined by ^{1}H NMR analysis of the crude product mixture. Mp: 165-166 °C; IR (thin film): 2924, 1609, 1466, 1451, 1334, 1143, 1018, 915 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91-7.86 (m, 1H), 7.31-7.24 (m, 3H), 7.22-7.14 (0m, 3H), 7.05 (dd, J = 5.1, 1.5 Hz, 1H), 6.94 (s, 1H), 6.91 (dd, J = 7.2, 3.9 Hz, 2H), 6.60 (dd, J = 3.6, 1.2 Hz, 1H), 6.39 (dd, J = 5.1, 3.9 Hz, 1H), 3.52 (d, J = 12.3 Hz, 1H), 3.17 (dd, J = 12.3, 3 Hz, 1H), 2.66 (sep, J = 6.6 Hz, 1H), 2.17-1.95 (m, 1H), 1.92-1.78 (m, 4H), 1.52 (d, J = 13.2 Hz, 1H), 1.45-1.27 (m, 4H), 0.62 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ139.8, 137.3, 134.9, 131.4, 130.22, 130.2, 128.7, 127.6, 126.5, 122.2, 119.74, 119.7, 109.7, 109.2, 53.6, 49.9, 47.5, 36.3, 34.9, 31.1, 27.5, 26.2, 25.4, 19.7, 15.5; MS (EI, 70 V): *m/z* 504 [$(M)^{\bullet+}$], 357, 304, 256, 247, 220, 123, 95, 91, 81, 69; HRMS *m/z* calcd. for $C_{29}H_{32}N_2O_2S_2$: 504.1905; found: 504.1892.

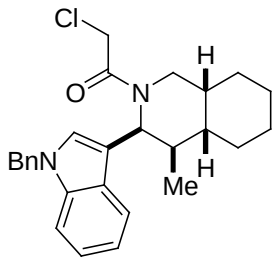


(3R,4R)-2-Allyl-3-methyl-4-((trimethylsilyl)methyl)piperidine (106a): Piperidine **105a** (78 mg, 0.21 mmol) was added to a stirred solution of magnesium (25.0 mg, 1.05 mmol) and methanol (3 mL) at room temperature. The resulting solution was stirred vigorously until completion (~2 h, monitored by TLC). The solvent was removed and the resulting solid residue was suspended in water. The resulting slurry was extracted with ether (3 ×). The combined organic phase was dried ($MgSO_4$), and concentrated affording 43 mg (91%) of the title compound as an yellowish oil with > 90% purity. IR (thin film): 3336, 2951, 1640, 1439, 1334, 1248, 1140, 913, 859, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.85-5.69 (m, 1H), 5.15-5.05 (m, 2H), 3.74 (q, J = 7.2 Hz, 1H), 2.94-2.76 (m, 2H), 2.54 (dt, J = 8.4, 3.9 Hz, 0.4H) & 2.41-2.26 (m, 0.6H), 2.26-1.98 (m, 1H), 1.96-1.81 (m, 1H), 1.59-1.41 (m, 2H), 1.31-1.12 (m, 2H), 0.96 & 0.87 (d, J = 6.9 Hz, 3H), 0.82-0.55 (m, 1H), 0.54-0.50 (m, 1H), -0.017 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.2 &135.8, 117.5 & 117.0, 55.5 & 53.8, 41.0 & 39.2, 40.6 & 39.4, 37.6 & 34.8, 33.4 & 32.0, 29.6, 20.7 & 15.6, 14.5 & 14.2, -(0.79 & 0.87, 3C); HRMS (Q-TOF) *m/z* calcd. for $C_{13}H_{28}NSi$ [$(M+H)^+$]: 226.1991; found: 226.1988.



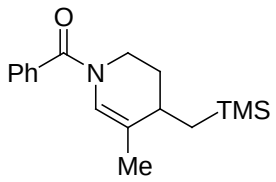
(3S,4R,4aS,8aR)-3-(1-Benzyl-1H-indol-3-yl)-4-methyldecahydroisoquinoline (106b): Piperidine **105c** (130 mg, 0.250 mmol) was added to a stirred solution of magnesium (60 mg, 2.5 mmol, added 3 ×) and methanol/ THF (10 : 2 mL) at room temperature. The resulting solution

was stirred vigorously until completion. The solvent was removed and the resulting solid residue was suspended in water. The resulting slurry was extracted with ether (3 ×). The combined organic phase was dried ($MgSO_4$), and concentrated. Purification by flash chromatography (5% methanol/dichloromethane) afforded 87 mg (94.5%) of the title compound as an yellowish oil. IR (thin film): 3332, 2924, 2854, 1611, 1466, 1377, 1176, 1075, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, J = 7.5 Hz, 1H), 7.31-7.22 (m, 5H), 7.18 (dd, J = 6.9, 1.2 Hz, 1H), 7.1 (dd, J = 6, 1.2 Hz, 1H), 7.11-7.05 (m, 2H), 5.23 (s, 2H), 4.60 (, J = 3.3 Hz, 1H), 3.17 (t, J = 12.3 Hz, 1H), 2.87 (dd, J = 12, 4.2 Hz, 1H), 2.33-2.21 (m, 1H), 2.09-1.91 (m, 2H),1.87-1.43 (m, 4H), 1.38-1.23 (m, 4H), 0.90 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 136.4, 128.6, 127.4, 126.6, 126.4, 125.3, 121.7, 119.0, 118.9, 116.1, 109.8, 51.9, 50.0, 46.4, 41.2, 38.3, 29.7 & 29.6 (1C), 29.3, 27.1, 26.7, 21.7, 14.2; MS (EI, 70 V): *m/z* 358 [$(M+H)^{\bullet+}$], 287, 275, 261, 247, 234, 220, 157, 91, 65; HRMS *m/z* calcd. for $C_{25}H_{30}N_2$: 358.2408; found: 358.2392.



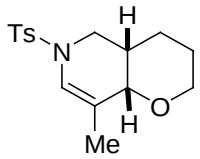
1-((3S,4R,4aS,8aR)-3-(1-Benzyl-1H-indol-3-yl)-octahydro-4-methylisoquinolin-2(1H)-yl)-2-chloroethanone (107): To a stirred solution of amine **106b** (60.0 mg, 1.67 mmmol) and Et_3N (203 mg, 2.01 mmol) in 8 mL CH_2Cl_2 at 0 °C was added chloroacetyl chloride (208 mg, 1.84 mmol). The resulting dark colored solution was stirred for 2 h after which the reaction was quenched with a saturated aqueous solution of ammonium chloride. The organic layer was separated, washed with water and brine, dried ($MgSO_4$) and concentrated. Purification by flash

chromatography (50% ether/hexane) afforded 61 mg (83%) of the title compound as yellow oil. IR (thin film): 3058, 2926, 2241, 1639, 1465, 1449, 1370, 1017, 910, 735, 693 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers were obtained): δ 7.92 (dd, J = 6.6, 1.5 Hz, 1H) & 7.66 (dd, J = 11.4, 7.2 Hz, 0.4H), 7.36-7.24 (m, 5H), 7.22-7.16 (m, 1H), 7.16 (dd, J = 7.5, 2.4 Hz, 1H), 7.07 (d, J = 6.3 Hz, 2H), 6.34 (d, J = 5.4 Hz, 1H), & 5.51 (d, J = 5.4 Hz, 0.3H), 5.34 (s, 3H) 5.29 (s, 0.2H), 4.44 (d, J = 9.9 Hz, 0.3H), 4.33 (d, J = 13.8 Hz, 0.3H), 4.15-3.97 (m, 1H), 4.09 (d, J = 3 Hz, 3H), 3.49 (dd, J = 14.1, 3.3 Hz, 1H), 3.26 (d, J = 13.8 Hz, 1H) & 3.18 (dd, J = 14.1, 3.9 Hz, 0.5H), 2.69-2.58 (m, 0.3H), 2.57-2.44 (m, 1H), 2.31-2.15 (m, 1H), 2.05-1.91 (m, 1H), 1.90-1.21 (m, 8H), 0.94 (d, J = 6.9 Hz, 3H) & 0.74 (d, J = 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, for major roramer): δ 164.5, 137.5, 135.8, 129.2, 128.8, 127.5, 127.2, 126.4, 122.3, 120.5, 119.8, 110.9, 109.2, 50.4, 50.0, 47.4, 41.7, 37.4, 36.3, 30.0, 27.5, 26.0, 25.3, 19.3, 16.1; MS (EI, 70 V): *m/z* 434 $[(M)^{\bullet+}]$, 399, 357, 307, 274, 247, 220, 152, 91; HRMS (Q-TOF) *m/z* calcd. for $C_{27}H_{31}N_2OCl$: 434.2129; found: 434.2119.



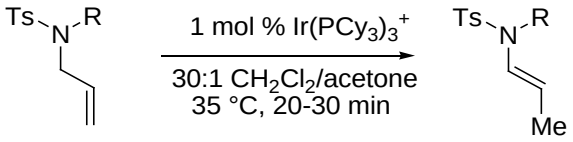
5-Methyl-4-((trimethylsilyl)methyl)-3,4-dihydropyridin-1(2H)-yl)(phenyl)methanone (136): To a 0 °C stirred solution of indium bromide (0.250 mmol, 88.5 mg)) in 1.5 mL CH_2Cl_2, a mixture of enamine **127** (0.25 mmol, 58 mg) and allyltrimethylsilane (0.50 mmol, 72 mg) in 1 mL CH_2Cl_2 was added dropwise. After stirring for 16 h at ambient temperature, the reaction was diluted with brine and the layers were separated. The organics were washed with brine and dried over $MgSO_4$. The crude product mixture was purified by column chromatography on silica gel

using 15% ether/hexanes as eluent affording 22 mg (32%) of the title compound as yellow oil. IR (thin film): 2950, 1712, 1638, 1405, 1248, 1134, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53-7.28 (m, 5H), 7.02 (s, 0.3 H) & 6.15 (s, 0.7 H), 3.90 (ddd, J = 10.2, 6.3, 3.6 Hz, 0.7H), 3.65 (ddd, J = 12.9, 9.6, 3.3 Hz, 0.7H), 3.49 (dd, J = 8.1, 3.3 Hz, 0.6H), 2.22-2.11 (m, 1H), 2.07-1.92 (m, 1H), 1.76 (s, 1H) & 1.56 (s, 2H), 1.74-1.66 (m, 1H), 0.91 (dd, J = 15, 2.4 Hz, 1H), 0.48 (dd, J = 15, 11.1 Hz, 1H), 0.6(s, 6H) & 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.4, 129.7, 128.3, 128.1, 127.4, 124.8+121.6 (1C),121.1+118.7 (1C), 37.9, 32.5, 29.9+29.0 (1C), 20.8, 19.2, -0.76; MS (EI, 70 V): *m/z* 287 ($M^{\bullet+}$), 272, 214, 200, 105, 73; HRMS *m/z* calcd. For $C_{17}H_{25}NOSi$: 287.1705; found: 287.1715.

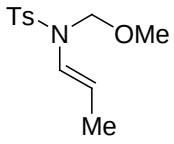


3,4,4a,5,6,8a-Hexahydro-8-methyl-6-tosyl-2H-pyrano[3,2-c]pyridine (148): To a stirred solution of pyran (0.50 mmol, 42 mg) and **140** (0.10 mmol, 39 mg) in 1 mL THF, rac-1,1'-binaphthyl-2,2'-diyl-*N*-triflylphosphoramidates (0.010 mmol, 4.8 mg) was added. After stirring for 1 hour, the reaction was diluted with a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The organics were combined, dried ($MgSO_4$) and concentrated. The crude product mixture was purified by column chromatography on silica gel (15% ether/hexanes) affording 16 mg (51%) of the title compound as oil. IR (thin film): 2929, 1726, 1668, 1454, 1349, 1164, 1052, 949, 812 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 6.54 (s, 1 H), 3.79 (d, J = 11.4 Hz, 2H), 3.60 (d, J = 2.1 Hz, 1H), 3.43 (dt, J = 11.1, 2.4 Hz, 2H), 3.17 (t, J = 11.1 Hz, 1H), 2.42 (s, 3H), 1.92-1.31 (m, 4H), 1.72 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 143.7, 135.2, 129.8, 127, 122.7, 115.2, 72.4, 67.4, 43.3, 31.9, 25.1, 22.3, 21.5, 18; HRMS (Q-TOF) *m/z* calcd. For $C_{16}7H_{22}NO_3S$ [$(M+H)^+$]: 308.1320; found: 308.1329.



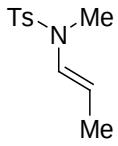
General Procedure C. Iridium(I)-catalyzed isomerization of *N*-alkyl-*N*-tosylallylamines:[89] A solution of $[(^cC_8H_{14})_2IrCl]_2$ (0.5 mol%, 0.01 equiv Ir, 4.5 mg) and PCy_3 (1.5 mol%, 0.03 equiv, 8.5 mg), and $NaBPh_4$ (0.01 mol%, 0.01 equiv, 3.4 mg, 0.01 mmol) were dissolved in 3.1 mL of CH_2Cl_2/acetone (30:1). The resulting mixture was stirred at ambient temperature until a clear yellow solution resulted (~30 min). The reaction flask was placed in a 35 °C oil bath and stirred an additional 10 min, whereupon the allylic sulfonamides (1 mmol) were added via syringe. The reaction was stirred 30 min then cooled to ambient temperature and concentrated. The resulting residue was purified by flash chromatography on silica gel (10% ether in hexanes eluent).



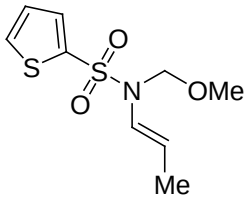
(*E*)-*N*-(Methoxymethyl)-*N*-(prop-1-enyl)-*p*-toluenesulfonamide (55): General Procedure C was followed employing *N*-allyl-*N*-(methoxymethyl)-4-methylbenzenesulfonamide **183** (5.60 mmol, 1.43 g). Purification by column chromatography afforded 1.33 g (93%) of the title

[89] Nelson, S. G.; Bungard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000-13001. Slightly modified procedure was followed. Tosyl protected allylamine derivatives are especially good substrate for Ir(I)-catalyzed isomerization. Small to large scale (3 g of substrate loading) can be performed with as low as 1 mol % to Ir(I) catalyst loading. Reaction is sluggish at room temperature but proceeds to completion at slightly elevated temperature (35-40 °C). Typical ratio of Ir^+:$NaBPh_4$:PCy_3 is 1:2:3 and CH_2Cl_2: CH_3COCH_3 is 30:1.

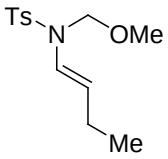
compound as a viscous oil that solidified upon storage at 4 °C. Mp: 29-32 °C; IR (thin film): 2936, 2887, 1662, 1453, 1399, 1290, 1058, 912 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 6.39 (dd, J = 14.1, 1.6 Hz, 1H), 5.28 (ddd, J = 20.7, 13.5, 6.7 Hz, 1H), 4.85 (s, 2H), 3.31 (s, 3H), 2.41 (s, 3H), 1.64 (dd, J = 6.6, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 137.0, 129.7, 126.9, 125.9, 110.8, 79.0, 55.7, 21.5, 15.3; MS (EI, 70 V): *m/z* 255 ($M^{\bullet+}$), 224, 155, 119, 91, 68; HRMS: *m/z* calcd. for $C_{12}H_{17}NO_3S$: 255.0929; found: 255.0940.



(*E*)-*N*,4-Dimethyl-*N*-(prop-1-enyl)-*p*-toluenesulfonamide (80): General Procedure C was followed employing *N*-allyl-*N*,4-dimethylbenzenesulfonamide **185** (2.0 mmol, 0.45 g). Purification by column chromatography afforded 0.41 g (91%) of the title compound as a colorless solid. Mp: 47-50 °C; IR (thin film): 2922, 2866, 1658, 1597, 1453, 1382, 1198, 992 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 7.8 Hz, 2H), 6.70 (dd, J = 14.1, 1.2 Hz, 1H), 4.73 (ddd, J = 20.4, 13.2, 6.6 Hz, 1H), 2.82 (s, 3H), 2.42 (s, 3H), 1.67 (dd, J = 6.6, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.5, 134.6, 129.6, 128.2, 127.0, 106.3, 32.2, 21.5, 15.1; MS (EI, 70 V): *m/z* 225 ($M^{\bullet+}$), 161, 155, 139, 120, 105, 91, 89; HRMS *m/z* calcd. for $C_{11}H_{15}NO_2S$: 225.0823; found: 225.0823.

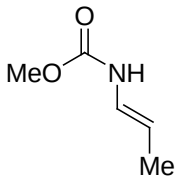


(*E*)-*N*-(Methoxymethyl)-*N*-(prop-1-enyl)-thiophene-2-sulfonamide (102): General Procedure C was followed employing *N*-allyl-*N*-(methoxymethyl)-thiophene-2-sulfonamide **214** (1.00 mmol, 247 mg). Purification by column chromatography afforded 230 mg (93%) of the title compound as a viscous oil. IR (thin film): 3107, 2939, 1662, 1403, 1359, 1227, 1174, 1058, 912 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64-7.53 (m, 2H), 7.08 (t, J = 4.2 Hz, 1H), 6.39 (dd, J = 13.8, 1.5 Hz, 1H), 5.36 (dq, J = 13.5, 6.6 Hz, 1H), 4.88 (s, 2H), 3.34 (s, 3H), 1.68 (dd, J = 6.6, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.4, 132.2, 132.1, 127.3, 125.5, 112.6, 79.4, 55.9, 15.4; MS (EI, 70 V): *m/z* 247 ($M^{\bullet+}$), 216, 156, 147, 131, 111, 99, 83, 68, 57; HRMS: *m/z* calcd. for $C_9H_{13}NO_3S_2$: 247.0337; found: 247.0332.

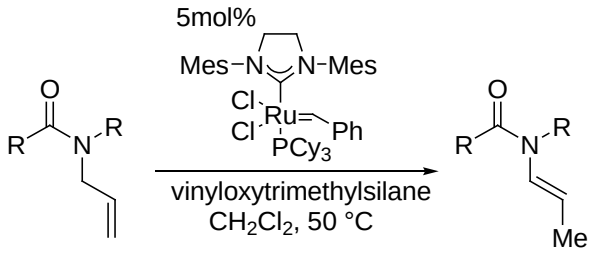


(*E*)-*N*-(but-1-enyl)-*N*-(methoxymethyl)-*p*-toluenesulfonamide (213): General Procedure C was followed employing (*E*)-*N*-(but-2-enyl)-*N*-(methoxymethyl)-*p*-toluenesulfonamide **215** (2.00 mmol, 538 mg). The conversion was found to be poor (~16% after 3h). Purification by column chromatography afforded 80 mg (94%, brsm) of the title compound as a viscous oil. IR (thin film): 2961, 1658, 1458, 1351, 1173, 1062, 949, 812 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 6.38 (d, J = 14.1 Hz, 1H), 5.28 (ddd, J = 13.8, 6.9, 69 Hz, 1H), 4.85 (s, 2H), 3.30 (s, 3H), 2.40 (s, 3H), 2.00 (dpent, J = 7.2, 1.2 Hz, 2H), 0.95 (t, J =

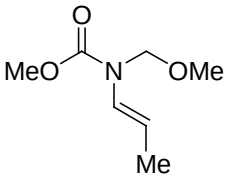
7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 136.9, 129.6, 126.9, 124.5, 117.4, 78.8, 55.7, 23.4, 21.5, 14.1; HRMS (Q-Tof): *m/z* calcd. for $C_{13}H_{19}NO_3SNa$ [$(M + Na)^+$]: 292.0983; found: 292.0963.



(*E*)-Methyl prop-1-enylcarbamate (187): $[(^cC_8H_{14})_2IrCl]_2$ (0.28 mol%×3, 8.8 mg), PCy_3 (0.84 mol%×3, 0.03 equiv, 14.28 mg), and $NaBPh_4$ (0.56 mol%×3, 5.7 mg) were dissolved in 9 mL of BTF/acetone (30:1). The resulting mixture was stirred at ambient temperature until a clear yellow solution resulted (~10 min). The reaction flask was placed in a 80 °C oil bath and stirred an addition 10 min, whereupon methyl *N*-allylcarbamate **186** (3.5 mmol, 0.42 g) was added. The reaction was stirred for 60 min then cooled to ambient temperature and concentrated. The resulting residue was purified by flash chromatography on silica gel (10% ether in hexanes eluent) which afforded 0.36 g (91%) of the title compound (colorless solid) as a non separable 4:1 mixture of *E*/*Z* isomers. Mp: 47-49 °C; IR (thin film): 3294, 2958, 1704, 1528, 1242, 1041, 952 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, for major isomer): δ 6.55-6.34 (m, 1H), 5.00 (dq, J = 13.2, 6.6 Hz, 1H), 3.67 (s, 3H), 1.62 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, for major isomer): δ 154.2, 124.1, 105.5, 52.3, 14.6; MS (EI, 70 V): *m/z* 115 ($M^{\bullet+}$), 100, 86, 84, 70, 59, 56; HRMS *m/z* calcd. for $C_5H_9NO_2$: 115.0633; found: 115.0637.



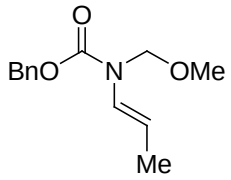
General Procedure D. Ru(II)-catalyzed Isomerization of Allylamine Derivatives:[90] A two-necked roundbottomed flask was fitted with a condenser and charged with *N*-(1-methoxypropyl)-*N*-tosylprop-2-en-1-amine (1 equiv), vinyloxytrimethylsilane (1 equiv), and 12 mL of CH_2Cl_2. The resulting solution was placed in a preheated 50 °C oil bath and a solution of the Grubbs 2nd generation catalyst (Grubbs II, 5 mol%, 0.05 equiv) in 2 mL CH_2Cl_2 was added and the resulting solution was stirred at 45-50 °C until the reaction was complete (determined by ^{1}H NMR analysis of reaction aliquots). The reaction was cooled to ambient temperature, the reaction mixture was concentrated and purified by column chromatography (10-20% ether in hexanes eluents).



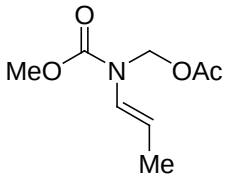
(*E*)-Methyl methoxymethyl(prop-1-enyl)carbamate (59): General Procedure D was followed employing methyl allyl(methoxymethyl)carbamate **184** (2.80 mmol, 0.445 g), vinyloxytrimethyl -silane (2.8 mmol, 0.33 g) and Grubbs II (0.056 mmol, 47.5 mg) in 10 mL CH_2Cl_2. Purification

[90] (a) Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732-4734. (b) Terada, Y.; Arisawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4063-4067. Benzylidene[1,3-bis(12,4,6 trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium [CAS 246047-72-3]. The isomerization can be performed in small to large scale (1 g of substrate loading) using as low as 1.6 mol % catalyst loading at 45-50 °C for 2 h in CH_2Cl_2. A complete conversion was obtained and longer time enhanced the *E*/*Z* ratio (typical *E/Z* ratio was 8 to 1).

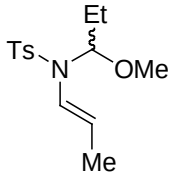
by flash chromatography afforded 0.4 g (91%) of the title compound as a yellowish oil. IR (thin film): 2956, 1720, 1666, 1444, 1394, 1282, 1146, 1083 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (m, 1H), 5.31-5.19 (m, 1H), 4.96 (br s, 2H), 3.78 (s, 3H), 3.31 (s, 3H), 1.68 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.7, 127.0, 107.3, 76.8, 53.5, 53.1, 15.3; MS (EI, 70 eV): *m/z* 159 ($M^{\bullet+}$), 144, 128, 97, 84, 69, 57; HRMS *m/z* calcd. for $C_7H_{13}NO_3$: 159.0895; found: 159.0891.



(*E*)-Benzylmethoxymethyl(prop-1-enyl)carbamate (60): General Procedure D was followed employing benzyl allyl(methoxymethyl)carbamate **192** (1.00 mmol, 0.235 g), vinyloxytrimethylsilane (1.00 mmol, 0.116 g) and Grubbs II (5 mol %, 0.050 mmol, 42 mg) in 3 mL CH_2Cl_2. Purification by flash chromatography afforded 0.21 g (90%) of the title compound as a yellowish liquid. IR (thin film): 2936, 1983, 1718, 1667, 1456, 1278, 1140, 946 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.30 (m, 5H), 6.77 (d, J= 13.2 Hz, 1H), 5.29 (dq, J = 13.2, 6.6 Hz, 1H), 5.22 (s, 2H), 5.0 (s, 2H), 3.31 (s, 3H), 1.68 (dd, J = 6.6, 0.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 136.0, 128.6, 128.3, 128.1, 126.9, 107.5, 77.2, 67.9, 55.7, 15.6; MS (EI, 70 eV): *m/z* 235 ($M^{\bullet+}$), 204, 160, 144, 107; HRMS *m/z* calcd. for $C_{13}H_{17}NO_3$: 235.1208; found: 235.1206.

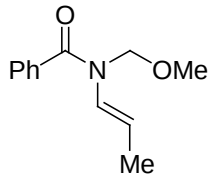


(*E*)-Methyl acetoxymethyl(prop-1-enyl)carbamate (62): General Procedure D was followed employing methyl allyl(acetyloxymethyl)carbamate **193** (2.00 mmol, 0.375 g), vinyloxytrimethyl -silane (2.00 mmol, 0.232 g) and Grubbs II (0.04 mmol, 34 mg) in 12 mL CH_2Cl_2. Purification by flash chromatography afforded 0.3 g (80%) of the title compound as a yellowish liquid. IR (thin film): 2959, 1742, 1726, 1669, 1445, 1373, 1221, 950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.68-6.58 (m, 1H), 5.58 (br s, 2H), 5.13 (dq, J = 13.3, 6.6 Hz, 1H), 3.76 (s, 3H), 2.07 (s, 3H), 1.69 (dd, J = 6.6, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 154.2, 126.7, 107.4, 70.1, 53.5, 20.8, 15.2; MS (EI, 70 eV): *m/z* 187 ($M^{\bullet+}$), 128, 115, 100, 83, 68, 59; HRMS *m/z* calcd. for $C_8H_{13}NO_4$: 187.0844; found: 187.0847.

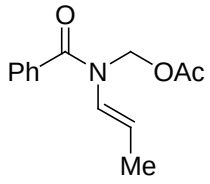


(+/−)-*N*-(1-Methoxypropyl)-*N*-(prop-1-enyl)-*p*-toluenesulfonamide (83): General procedure D was followed employing *N*-(1-methoxypropyl)-*N*-tosylprop-2-en-1-amine **204** (4.00 mmol, 1.13 g), vinyloxytrimethylsilane (4.00 mmol, 0.465 g), and 50 mL of CH_2Cl_2. A solution of the Grubbs 2nd generation catalyst (Grubbs II) (0.200 mmol, 170 mg) was added. After completion (determined by ^1H NMR analysis of reaction aliquots), the reaction was cooled to ambient temperature, the reaction mixture was concentrated and purified by column chromatography (SiO_2, 10% ether in hexanes) to afford the title compound as a brown oil (94% yield). IR (thin

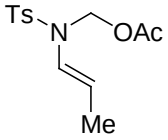
film): 3033, 2937, 1659, 1597, 1494, 1460, 1345, 1165, 1081, 989, 814 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 10.2 Hz, 2H), 5.80 (dd, J = 14.0, 0.9 Hz, 1H), 5.65 (dq, J = 14.1, 6.6 Hz, 1H), 5.04 (t, J = 6.6 Hz, 1H), 3.23 (s, 3H), 2.42 (s, 3H), 1.73 (ddq, J = 21.3, 14.4, 7.5 Hz, 1H), 1.67 (dd, J = 6.6, 1.2 Hz, 3H), 1.50 (ddq, J = 21.3, 14.4, 7.2 Hz, 1H), 0.83 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 137.8, 129.4, 127.4, 124.9, 121.5, 91.7, 56.0, 26.1, 21.5, 15.8, 9.5; MS (EI, 70 V): *m/z* 283 ($M^{\bullet+}$), 252, 211, 155, 147, 120, 96, 91, 73; HRMS *m/z* calcd. for $C_{14}H_{21}NO_3S$: 283.1242; found: 283.1236.



(*E*)-*N*-(Methoxymethyl)-*N*-(prop-1-enyl)benzamide (126): General Procedure D was followed employing *N*-allyl-*N*-(methoxymethyl)benzamide **191** (1.00 mmol, 0.205 g), vinyloxytrimethylsilane (1.00 mmol, 0.116 g) and Grubbs II (1.8 mol %, 0.018 mmol, 15 mg) in 3 mL CH_2Cl_2. Purification by flash chromatography afforded 0.18 g (88%) of the title compound as a pale yellowish liquid. IR (thin film): 3418, 2254, 2128, 1652, 1026, 825 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, calibrated at 2.49 ppm at 65 °C): δ 7.50-7.47 (m, 5H), 6.63 (d, J = 13.8 Hz, 1H), 5.39 (dq, J = 14.1, 7.2 Hz, 1H), 4.93 (s, 2H), 3.22 (s, 3H), 1.63 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, calibrated at 39.5 ppm at room temperature): δ 169.8, 135.2, 130.5, 128.5, 127.8, 127.5, 108.9, 76.8, 55.1, 15.3; MS (EI, 70 eV): *m/z* 205 ($M^{\bullet+}$), 175, 173, 164, 105; HRMS *m/z* calcd. for $C_{12}H_{15}NO_2$: 205.1103; found: 205.1098.

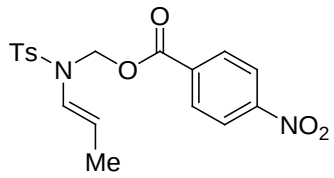


(*E*)-(*N*-(Prop-1-enyl)methylacetate)benzamide (127): General Procedure D was followed employing *N*-allyl-*N*-(methoxyacetate)benzamide **195** (5.58 mmol, 1.30 g). Purification by flash chromatography afforded 1.12g (85%) of the title compound as a pale yellowish liquid. IR (thin film): 2922, 1744, 1685, 1446, 1396, 1369, 1219, 1020, 951 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.48 (m, 2H), 7.46-7.37 (m, 3H), 6.71 (s, br, 1H), 5.64 (s, br, 2H), 5.26 (dq, J = 13.5, 6.6 Hz, 1H), 2.10 (s, 3H), 1.63 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.3, 134.4, 130.8, 128.4, 127.8, 109.4, 20.8, 15.3; MS (EI, 70 eV): *m/z* 233 ($M^{\bullet+}$), 174, 161, 106, 78, 56; HRMS *m/z* calcd. for $C_{13}H_{15}NO_3$: 233.1052; found: 233.1058.

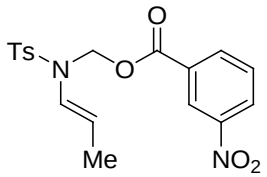


(*E*)-*N*-Methylacetate-*N*-(prop-1-enyl)-*p*-toluenesulfonamide (131): General Procedure D was followed employing *N*-allyl-*N*-(methylacetate)-*p*- toluenesulfonamide **194** (2.47 mmol, 700 mg). Purification by flash chromatography (20% ether in hexanes) afforded 645 mg (92%) of the title compound as a yellowish oil that solidified upon storage at 4 °C. Mp: 43-44 °C. IR (thin film): 3036, 2923, 1745, 1664, 1453, 1361, 1216, 1171, 1090, 1018, 994, 811 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J = 8.1 Hz, 2H), 7.30 (dd, J = 8.4, 0.6 Hz, 2H), 6.42 (dq, J = 13.8, 1.5 Hz, 1H), 5.60 (s, 2H), 5.18 (dq, J = 13.5, 6.6 Hz, 1H), 1.86 (s, 3H), 1.66 (dd, J = 6.9, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 144, 136.4, 129.5, 127.3, 125.5, 111.8, 71.3, 21.5,

20.5, 15.2; MS (EI, 70 eV): *m/z* 283 ($M^{\bullet+}$), 225, 219, 211, 184, 156, 146, 140, 132, 105, 90, 88, 63; HRMS *m/z* calcd. for $C_{13}H_{17}NO_4S$: 283.0878; found: 283.0879.

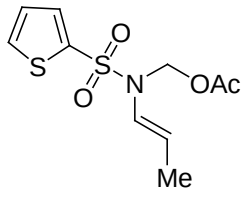


(*E*)-*N*-4-Nitrobenzylmethyl-*N*-(prop-1-enyl)-*p*-toluenesulfonamide (139): General Procedure D was followed employing *N*-allyl-*N*-(4-nitrobenzoatemethyl)-*p*-toluenesulfonamide **197** (0.660 mmol, 310 mg). Purification by flash chromatography (20% ether in hexanes) afforded 260 mg (83%) of the title compound as a brownish oil that solidified upon storage at 4 °C. Mp: 90-91 °C. IR (thin film): 2922, 1728, 1528, 1357, 1270, 1171, 1089, 996, 718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, J = 9 Hz, 2H), 7.75 (d, J = 9.3, 2H), 7.72 (d, J = 9 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.56 (dd, J = 14.1, 1.8 Hz, 1H), 5.88 (s, 2H), 5.25 (dq, J = 14.1, 6.9 Hz, 1H), 2.38 (s, 3H), 1.70 (dd, J = 3.6, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 150.6, 144.2, 136.7, 134.4, 130.7, 129.7, 127.3, 125.7, 123.3, 112.3, 72.8, 21.5, 15.3; MS (EI, 70 eV): *m/z* 390 ($M^{\bullet+}$), 326, 269, 235, 224, 205, 171, 155, 150, 119, 92, 84, 68, 65; HRMS *m/z* calcd. for $C_{18}H_{18}N_2O_6S$: 390.0885; found: 390.0874.

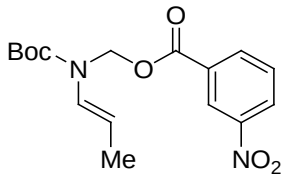


(*E*)-*N*-3-Nitrobenzylmethyl-*N*-(prop-1-enyl)-*p*-toluenesulfonamide (140): General Procedure D was followed employing *N*-allyl-*N*-(3-nitrobenzoatemethyl)-*p*-toluenesulfonamide **198** (5.00 mmol, 1.95 g). Purification by flash chromatography (20% ether in hexanes) afforded 1.56 g

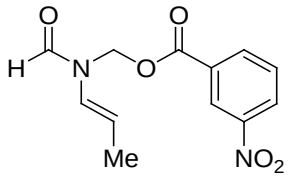
(80%) of the title compound as a brownish oil that solidified upon storage at 4 °C. Mp: 93-95 °C. IR (thin film): 3086, 2922, 1728, 1534, 1352, 1228, 1172, 1122, 995, 717 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), 8.33 (t, J = 1.8, 1H), 8.04 (dt, J = 7.8, 1.2 Hz, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.58 (t, J = 8.1 Hz, 1H), 7.26 (d, J = 7.5 Hz, 2H), 6.56 (dq, J = 14.1, 1.5 Hz, 1H), 5.92 (s, 2H), 5.25 (dq, J = 13.5, 6.6 Hz, 1H), 2.36 (s, 3H), 1.69 (dd, J = 6.9, 1.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3, 148.1, 144.4, 136.4, 135.3, 130.8, 129.8, 129.6, 127.7, 127.2, 125.6, 124.2, 112.2, 72.9, 21.5, 15.3; MS (EI, 70 eV): *m/z* 390 ($M^{\bullet+}$), 326, 235, 224, 205, 151, 139, 88, 75, 63; HRMS *m/z* calcd. for $C_{18}H_{18}N_2O6S$: 390.0886; found: 390.0894.



(*E*)-*N*-Methylacetate-*N*-(prop-1-enyl)-thiophene-2-sulfonamide (141): General Procedure D was followed employing *N*-allyl-*N*-(methylacetate)-thiophene-2-sulfonamide **196** (1.00 mmol, 275 mg). Purification by flash chromatography (25% ether in hexanes) afforded 240 mg (87%) of the title compound as a yellowish oil. IR (thin film): 3100, 2921, 1744, 1664, 1365, 1213, 1167, 1018, 993, 949 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (dt, J = 3.9, 1.2 Hz, 2H), 7.10 (dt, J = 4.8, 0.9 Hz, 1H), 6.40 (dd, J = 14.1, 1.5 Hz, 1H), 5.62 (s, 1H), 5.30 (dq, J = 13.5, 6.9 Hz, 1H), 1.93 (s, 3H), 1.70 (dd, J = 6.9, 1.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 139.8, 133.0, 132.7, 127.2, 125.1, 113.7, 71.6, 20.6, 15.2; MS (EI, 70 eV): *m/z* 275 ($M^{\bullet+}$), 223, 203, 155, 147, 139, 112, 91, 65; HRMS *m/z* calcd. for $C_{10}H_{13}NO_4S_2$: 275.0286; found: 275. 0279.

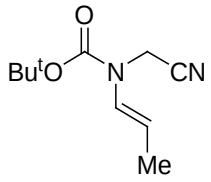


(*E*)-*N*-(3-Nitrobenzylmethyl)-*N*-(prop-1-enyl)-*tert*-butoxycarbmide (152): General Procedure D was followed employing *N*-allyl-*N*-(3-nitrobenzoatemethyl)-*tert*-butyloxy carbamide **199** (0.660 mmol, 224 mg). Purification by flash chromatography (15% ether in hexanes) afforded 211 mg (94%) of the title compound as a brownish oil. IR (thin film): 2977, 1720, 1670, 1533, 1395, 1253, 1124, 947 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.84 (t, J = 1.8 Hz, 1H), 8.43 (ddd, J = 8.1, 2.1, 0.9, 1H), 8.35 (d, J = 7.8 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 6.75 (d, J = 12.6 Hz, 1H), 5.87 (s, 2H), 5.16 (dd, J = 14.1, 6.9 Hz, 1H), 1.71 (dd, J = 6.6, 1.5 Hz, 3H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9, 152.2, 148.3, 135.4, 131.5, 129.7, 127.6, 127.0, 124.7, 106.5, 82.5, 71.3, 28.1, 15.3; MS (EI, 70 eV): *m/z* 336 ($M^{\bullet+}$), 236, 219, 170, 151, 104, 76, 70, 57; HRMS *m/z* calcd. for $C_{16}H_{20}N_2O_6$: 336.1321; found: 336.1337.

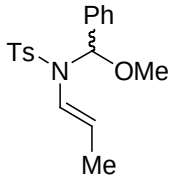


(*E*)-*N*-(Prop-1-enyl)-*N*-(3-nitrobenzylmethyl)-formamide (153): General Procedure D was followed employing *N*-allyl-*N*-(3-nitrobenzylmethyl)-formamide **200** (3.59 mmol, 940 mg). Purification by flash chromatography (40% ether in hexanes) afforded 526 mg (56%, 80% brsm) of the title compound (2:1 mixture of non convertible rotamers) as a brownish oil. IR (thin film): 3087, 2922, 1730, 1697, 1670, 1533, 1397, 1352, 1258, 1122, 951, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, for both of the rotamers): δ 8.80 (t, J = 2.1 Hz, 1.5H), 8.47-8.28 (m, 4.5H), 7.68 (t, J = 8.1 Hz, 1H) &7.65 (t, J = 8.1 Hz, 0.5H), 6.90 (dd, J = 14.7, 1.5 1H) & 6.37 (dd, J = 14.7, 1.5

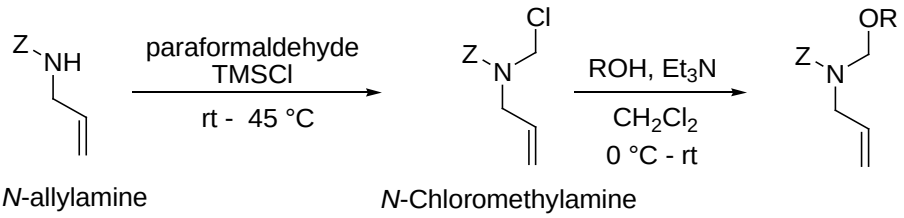
Hz, 0.5H), 5.85 (s, 2H) & 5.76 (s, 1H), 5.57 (dq, J = 14.4, 6.9 Hz, 1H) & 5.43 (dq, J = 14.4, 6.9 Hz, 0.5H), 1.76 (dd, J = 6.9, 1.8 Hz, 3H) & 1.74 (dd, J = 6, 1.5 Hz, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164 & 163.7, 162.1 & 161.6, 148.3, 135.4 & 135.3, 131 & 130.8, 129.9 & 127.7, 128 & 127.8, 126.4, 124.7 & 123.1, 111.1 & 109.9, 71.7 & 66.6, 15.4 & 15.1; MS (EI, 70 eV): *m/z* 264 ($M^{\bullet+}$), 236, 206, 167, 150, 134, 121, 104, 97, 92, 77, 74, 65; HRMS *m/z* calcd. for $C_{12}H_{12}N_2O_5$: 264.0746; found: 264.0750.



(*E*)-*tert*-Butyl cyanomethyl(prop-1-enyl)carbamate (190): General Procedure D was followed employing *tert*-butyl allyl(cyanomethyl)carbamate **189** (0.51 mmol, 0.10 g), vinyloxytrimethylsilane (0.51 mmol, 60 mg) and Grubbs II (0.024 mmol, 20 mg) in 3 mL CH_2Cl_2. Purification by flash chromatography afforded 83 mg (83%) of the title compound as a pale yellowish liquid. IR (thin film): 2979, 2934, 2246, 1711, 1667, 1397, 1373, 1163, 969 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.82-6.66 (m, 1H), 4.95 (dq, J = 13.1, 9 Hz, 1H), 4.44+4.34 (2 S, 2H), 1.74 (dd, J = 6.6, 1.5 Hz, 3H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8, 126.4, 115.1, 105.5, 83.0, 32.0, 28.1, 15.2; MS (EI, 70 eV): *m/z* 196 ($M^{\bullet+}$), 181, 140, 123, 96, 84; HRMS *m/z* calcd. for $C_{10}H_{16}N_2O_2$: 196.1211; found: 196.1209.



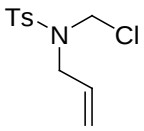
(+/−)-*N*-(1-Methoxyphenyl)-*N*-(prop-1-enyl)-*p*-toluenesulfonamide (206): General procedure D was followed employing *N*-(1-methoxybenzyl)-*N*-tosylprop-2-en-1-amine **205** (0.500 mmol, 165 mg), vinyloxytrimethylsilane (0.50 mmol, 58 mg), and 5 mL of CH_2Cl_2. A solution of the Grubbs 2nd generation catalyst (Grubbs II) (0.025 mmol, 21 mg) was added. After completion (determined by ^{1}H NMR analysis of reaction aliquots), the reaction was cooled to ambient temperature, the reaction mixture was concentrated and purified by column chromatography (SiO_2, 10% ether in hexanes) to afford 150 mg (91%) of the title compound as a brown oil. IR (thin film): 2924, 1597, 1451, 1340, 1165, 1096, 1005, 814, 666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, J = 8.1 Hz, 2H), 7.32 - 7.26 (m, 7H), 6.28 (s, 1H), 5.66 (dq, J = 13.8, 1.5 Hz, 1H), 5.45 (dq, J = 13.8, 6.6 Hz, 1H), 3.39 (s, 3H), 2.44 (s, 3H), 1.49 (dd, J = 6.9, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 137.2, 137.1, 129.5, 128.1, 128.0, 127.5, 126.7, 124.1, 121.5, 89.6, 56.3, 21.6, 15.7; MS (EI, 70 V): *m/z* 331 ($M^{\bullet+}$), 300, 224, 155, 147, 121, 105, 91, 77; HRMS *m/z* calcd. for $C_{18}H_{21}NO_3S$: 331.1242; found: 331.1239.



General Procedure E. *N*-(Methyl)-benzoate preparation via *N*-Chloromethylation of *N*-allylamine: To a mixture of paraformaldehyde (2 equiv) and *N*-allylamine (1 mmol, 1 equiv) was added 0.5 mL of TMSCl and the resulting mixture was stirred at room temperature (or

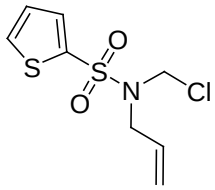
warmed to 45 °C) until completed (determined by ^{1}H NMR analysis of reaction aliquots). The reaction was diluted with CH_2Cl_2 and the resulting mixture was passed through celite. Combined organics were concentrated and used for the next reaction.[91]

To a 0 °C solution of triethylamine (3 equiv) and ROH (1 mmol, 1 equiv) in 5 mL CH_2Cl_2, *N*-(chloromethyl)-allylamine was added (in 1 mL CH_2Cl_2). The resulting mixture was stirred at room temperature until completion (~ 1h). The reaction was diluted with a saturated aqueous solution of $NaHCO_3$ and the layers were separated. The organics were combined and washed with water, dried over $MgSO_4$ and concentrated. The resulting residue was purified by flash chromatography on silica gel (15-25% ether in hexanes eluent).

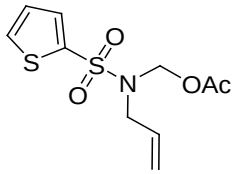


***N*-Allyl-*N*-(chloromethyl)-*p*-toluenesulfonamide (208):** General Procedure E was followed employing *N*-allyl-*N*,4-methylbenzenesulfonamide (23.7 mmol, 5.00 g) and paraformaldehyde (47.4 mmol, 1.33 g) in 12 mL TMSCl under nitrogen atmosphere at room temperature. The resulting heterogeneous mixture was stirred vigorously for 2 h. Filtration and removal of the solvent afforded the title compound (quantitative) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 5.76 (dddd, J = 16.8, 10.2, 6.6, 6.6 1H), 5.44 (s, 2H), 5.33 (ddd, J = 9, 2.4, 0.6 Hz, 2H), 3.80 (d, J = 6.3 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.4, 135.2, 131, 129.7, 128.3, 121, 59.5, 48.1, 21.6.

[91] The products contained small amount of paraformaldehyde.

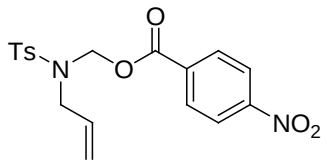


***N*-Allyl-*N*-(chloromethyl)-thiophene-2-sulfonamide:** General Procedure E was followed employing *N*-allyl-*N*,thiophene-2-sulfonamide (2.46 mmol, 0.500 g) and paraformaldehyde (3.0 mmol, 90 mg) in 2 mL TMSCl. Filtration and removal of the solvent afforded the title compound (0.59 g, 95 %) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (dd, J = 3.9, 1.5 Hz, 1H), 7.67 (dd, J = 5.9, 1.5 Hz, 1H), 7.13 (dd, J = 5.1, 3.9 Hz, 1H), 5.79 (dddd, J = 16.5, 10.8, 6.6, 6.6 Hz, 1H), 5.42 (s, 2H), 5.38 (dd, J = 13.8, 1.2 Hz, 1H), 5.34 (dd, J = 6.9, 1.2 Hz, 1H), 3.90 (d, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 133.8, 133.3, 130.8, 127.6, 121.2, 59.2, 48.3.

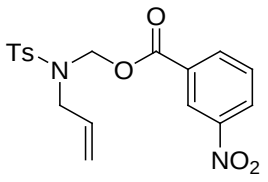


***N*-Allyl-*N*-(methylacetate)-thiophene-2-sulfonamide (196):** General Procedure E was followed employing *N*-allyl-*N*-(chloromethyl)-thiophene-2-sulfonamide (0.50 mmol, 0.13 g), acetic acid (0.60 mmol, 36 mg), and triethylamine (2.0 mmol, 0.28 mL) in 5 mL CH_2Cl_2. Purification by flash chromatography (15% ether/hexanes) afforded the title compound (0.44 g, 88%) as colorless oil. IR (thin film): 3097, 2983, 1745, 1403, 1345, 1232, 1157, 1016, 945 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (d, J = 1.8 Hz, 1H), 7.63 (d, J = 1.8 Hz, 1H), 7.10 (dd, J = 4.8, 3.9 Hz, 1H), 5.74 (dddd, J = 12.6, 9.9, 6.3, 6.3 Hz, 1H), 5.28 (dd, J = 11.21, 1.2 Hz, 1H), 5.24 (dd, J = 3.9, 1.2 Hz, 1H), 3.88 (d, J = 6.3, 2H), 1.93 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 169.9, 140.1, 132.8, 132.5, 131.6, 127.1, 119.7, 70.9, 49.4, 20.4; HRMS (QTof): *m/z* calcd. for $C_{10}H_{13}NO_4S_2Na$; [$(M+Na)^+$],: 298.0184; found: 298.0180.

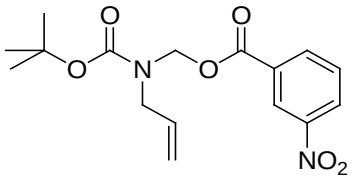


***N*-Allyl-*N*-(4-nitrobenzoatemethyl))-*p*-toluenesulfonamide (197):** General Procedure E was followed employing *N*-allyl-*N*-(chloromethyl)-*p*- toluenesulfonamide (4.81 mmol, 1.25 g), *p*-nitrobenzoic acid (5.77 mmol, 0.800 g), and triethylamine (7.11 mmol, 0.990 mL) in 15 mL CH_2Cl_2. Purification by flash chromatography (25% ether/hexanes) afforded 1.6 g (85%) of the title compound as oil which solidified upon standing. Mp: 84-85 °C; IR (thin film): 3112, 2981, 1727, 1604, 1528, 1348, 1266, 1162, 1082, 900, 718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, J = 9.3 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 6.84(d, J = 9.3 Hz, 2H), 5.76 (dddd, J = 16.5, 10.2, 6.3, 6.3 Hz, 1H), 5,41 (s, 2H), 5.22 (ddq, J = 9.3, 9.3, 1.2 Hz, 2H), 3.89 (d, J = 6.6 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 144, 142, 136.4, 131.7, 129.6, 127.7, 125.9, 120.1, 115.1, 75.4, 49.0, 21.5; HRMS (Q-Tof): *m/z* calcd. for $C_{18}H_{18}N_2O_6SNa$ [$(M+Na)^+$]: 390.0783; found: 390.0797.



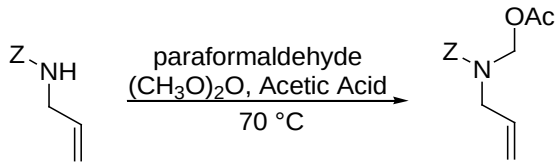
***N*-Allyl-*N*-(3-nitrobenzoatemethyl)-*p*-toluenesulfonamide (198):** General Procedure E was followed employing *N*-allyl-*N*-(chloromethyl)-*p*- toluenesulfonamide (10.0 mmol, 2.95 g), *m*-nitrobenzoic acid (15 mmol, 1.7 g), and triethylamine (20 mmol, 2.8 mL) in 30 mL CH_2Cl_2.

Purification by column chromatography (20% ether/hexanes) afforded 3.2 g (82%) of the title compound as oil which solidified upon standing. Mp: 64-65 °C; IR (thin film): 3088, 2925, 1727, 1616, 1534, 1351, 1258, 1163, 1120, 904 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.44-8.38 (m, 2H), 8.12 (dt, J = 7.8, 1.2 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.60 (dd, J = 9, 7.8 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 5.80 (dddd, J = 16.5, 10.2, 6.6, 6.6 Hz, 1H) 3.95 (d, J = 6.3 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5, 148.1, 144.2, 136.9, 135.3, 131.8, 131.0, 129.8, 129.6, 127.7, 127.4, 124.2, 120.1, 72.8, 49.7, 21.4; MS (EI, 70 V): *m/z* 390 ($M^{\bullet+}$), 235, 226, 139, 134, 121, 107, 90, 77, 69, 64; HRMS: *m/z* calcd. for $C_{18}H_{18}N_2O_6S$: 390.0886; found: 390.0868.

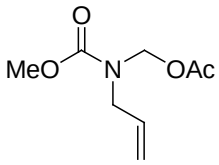


***N*-Allyl-*N*-(3-nitrobenzoatemethyl)-*tert*- butyloxycarbamide (199):** General Procedure E was followed employing *N*-allyl-*N*-(chloromethyl)-*tert*- butyloxycarbamide[92] (4.25 mmol, 0.875 g), m-nitrobenzoic acid (5.32 mmol, 0.890 g), and triethylamine (8.5 mmol, 1.9 mL) in 20 mL CH_2Cl_2. Purification by flash chromatography (20% ether in hexanes) afforded 1.1 g (77%) of the title compound as oil. IR (thin film): 3084, 2978, 1700, 1535, 1350, 1160, 921, 847 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.85 (t, J = 1.8 Hz, 1H), 8.43 (d, J = 8.1 Hz, 1H), 8.35 (d, J = 7.5 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 5.85 (dddd, J = 16.2, 11.1, 5.7, 5.7 Hz, 1H), 5.64 (s, br, 2H), 5.27-5.06 (m, 2H), 4.03 (s, br, 2H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 148.2, 135.2, 131.7, 129.6, 127.5, 124.6, 117.5, 81.4, 73.5, 55.8, 28.2; HRMS (Q-Tof): *m/z* calcd. for $C_{16}H_{20}N_2O_6Na$ [$(M+Na)^+$]: 359.1219; found: 359.1206.

[92] *N*-Allyl-*N*-(chloromethyl)-*tert*- butyloxycarbamide was prepared from *N*-allyl-*tert*-butyloxycarbamide, paraformaldehyde and TMSCl.

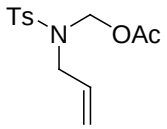


General Procedure F. *N*-Acetoxymethylation of *N*-(*p*-toluenesulfonyl)-1-amino-2-propene: To a mixture of paraformaldehyde (5 equiv) and *N*-allylamine (1 mmol, 1 equiv) was added 1 mL of $(CH_3O)_2O$ and 1 mL of acetic acid. The resulting mixture was stirred at 70-80 °C for 3-4 hours. The reaction was cooled to room temperature; the reaction mixture was diluted with CH_2Cl_2 and washed with water. Column purification afforded the desired product as colorless oil.

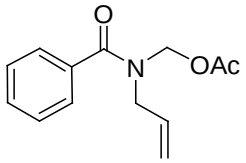


Methyl-*N*-allyl(acetyloxymethyl)carbamate (193): [93] General Procedure F was followed employing paraformaldehyde (4.34 mmol, 0.130 g) and methyl *N*-allylcarbamate (4.34 mmol, 0.500 g) in a 1: 1 v/v mixture of acetic anhydride and acetic acid (2 mL). The resulting mixture was stirred at 70 °C for 2 h. Purification by flash chromatography (20% ether in hexane) afforded 0.42 g (51%) of the title compound as a colorless oil. IR (thin film): 2988, 2959, 1746, 1721, 1645, 1476, 1214, 1205, 1017, 944 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.77-5.64 (m, 1H), 5.26 (br s, 2H), 5.11-5.05 (m, 2H), 3.89 (br s, 2H), 3.67 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, for two rotamers): δ 170.5, 156.4 + 155.8 (1C), 133.1, 117.1 + 116.6 (1C), 71.9 + 77.2 (1C), 52.9, 49.5, 20.7; MS (EI, 70 eV): *m/z* 187 ($M^{\bullet+}$), 160, 144, 129, 144, 114, 73, 57, 54; HRMS: m/*z* calcd. for $C_8H_{13}NO_4$: 187.0844; found: 187.0851.

[93] Oleksyszyn, J.; Subotkowska, L. *Synthesis* **1980**, 906.

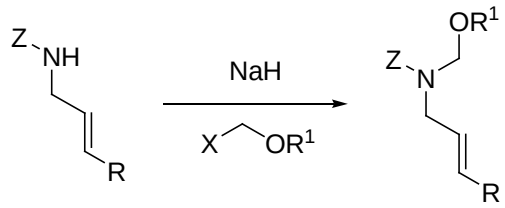


***N*-Allyl-*N*-(methylacetate)-*p*-toluenesulfonamide (194):** General Procedure F was followed employing *N*-allyl-4-methylbenzenesulfonamide (2.46 mmol, 0.520 g) and paraformaldehyde (12.3 mmol, 0.370 g) in 2 mL of a 1:1 v/v mixture of $(CH_3O)_2O$ and acetic acid. Column purification (15% ethyl acetate/hexanes) afforded 0.36 g (52%) of the title compound as a pale yellow oil. IR (thin film): 2982, 1745, 1597, 1495, 1347, 1233, 1161, 1016, 943, 816, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.72 (dddd, J = 16.5, 9, 6, 6 Hz, 1H), 5.42 (s, 2H), 5.22 (ddd, J = 18, 18, 9 Hz, 2H), 3.81 (d, J = 6.3, 2H), 2.44 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 143.8, 137, 132.1, 129.5, 127.6, 119.6, 71.1, 49.5, 21.5, 20.6; MS (EI, 70 V): *m/z* 224 $[(M-C_2H_3O_2)^{\bullet+}]$, 155, 91, 68; HRMS: *m/z* calcd. for $C_{10}H_{14}NO_2S$: 224.0740; found: 224.0741.

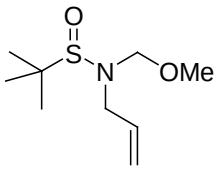


Phenyl-*N*-allyl(acetyloxymethyl)carbamate (195): General Procedure F was followed employing *N*-allyl-*N*-benzamide (21.4 mmol, 3.45 g) and paraformaldehyde (36.7 mmol, 1.10 g) in a 1: 1 v/v mixture of acetic anhydride and acetic acid (12 mL). The resulting mixture was stirred at 95 °C. Purification by flash chromatography (20% ether/hexanes) afforded 2.4 g (48%) of the title compound as colorless oil. IR (thin film): 2984, 1743, 1658, 1443, 1409, 1238, 1202, 1018, 947 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.52-7.46 (m, 2H), 7.45-7.36 (m, 3H), 5.86 (s, br, 1H), 5.38-5.18 (m, 4H), 4.17 (s, br, 2H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, for two

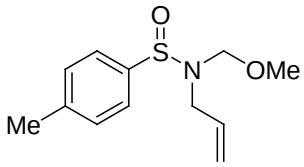
rotamers): δ 172.3, 170.4 + 170.2 (1C), 134.9, 132.6, 130.3, 128.5, 127.1, 118, 86.8, 48.8, 21; MS (EI, 70 eV): *m/z* 233 ($M^{\bullet+}$), 190, 173, 150, 106, 103, 77, 73, 68; HRMS: m/*z* calcd. for $C_{13}H_{15}NO_3$: 233.1052; found: 233.1053.



General Procedure G. *N*-Alkylation of *N*-(*p*-toluenesulfonyl)-1-amino-2-propene: To a 0 °C suspension of NaH (60% in mineral oil, 1.2 equiv) in 5 mL of DMF was added a solution of *N*-tosylallylamine (1 mmol, 1 equiv) in 1 mL of DMF (CAUTION: H_2 gas evolution). Once addition was complete, the resulting thick mixture was warmed to ambient temperature and stirred for 30 min. The reaction mixture was cooled to 0 °C and a solution of chloro(methoxy)methane or iodomethane (1.5 equiv) in 1 mL DMF was added dropwise by syringe. After warming to ambient temperature, the reaction was stirred until complete as monitored by TLC (~1-2 h). The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ and the resulting mixture was extracted with ether (3×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product mixture was purified by column chromatography on silica gel using 10-15% ether/hexanes as eluent.

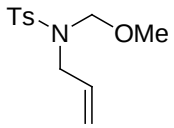


***N*-Allyl-*N*-(methoxymethyl)-2-methylpropane-2-sulfinamide (116):** General Procedure G was followed employing NaH (7.44 mmol, 0.300 g), *N*-allyl-2-methylpropane-2-sulfinamide **115** (6.2 mmol, 1.0 g) and chloro(methoxy)methane (8.68 mmol, 0.700 g) in 30 mL DMF. Purification by flash chromatography (15% ether/hexanes as eluent) afforded 0.89g (70%) of the title compound as yellow oil. IR (thin film): 3486, 2953, 1455, 1361, 1077, 902 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76 (dddd, J = 15.6, 10.2, 6.9, 5.4 Hz, 1H), 4.48 (d, J = 10.8 Hz, 1H), 4.40 (dd, J = 10.5, 0.6 Hz, 1H), 3.86 (dd, J = 5.4, 0.9 Hz, 1H), 3.47 (dd, J = 6.9, 0.9 Hz, 2H), 3.28 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.6, 118.3, 80.7, 58, 55.4, 45, 22.7 (3C); MS (EI, 70 V): *m/z* 205 ($M^{\bullet+}$), 191, 174, 149, 119, 99, 84, 69, 55; HRMS *m/z* calcd. for $C_9H_{19}NO_2S$: 205.1136; found: 205.1130.

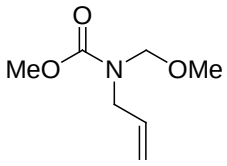


***N*-Allyl-*N*-(methoxymethyl)-4-methylbenzenesulfinamide (119):** General Procedure G was followed employing NaH (11.7 mmol, 0.468 g), *N*-allyl-4-methylbenzenesulfinamide (9.74 mmol, 1.90 g) and chloro(methoxy)methane (14.6 mmol, 1.18 g) in 50 mL DMF. Purification by flash chromatography (20% ether/hexanes as eluent) afforded 1.9 g (82%) of the title compound as yellow oil. IR (thin film): 3488, 2924, 1491, 1449, 1210, 1156, 1090, 1068, 925, 897 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 8.1 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 5.52 (dddd, J = 16.5, 9.9, 6.6, 6.6 Hz, 1H), 5.14-5.05 (m, 2H), 4.73 (d, J = 10.5 Hz, 1H), 4.63 (d,

J = 10.8 Hz, 1H), 3.52 (d, J = 6.3Hz, 2H), 3.38 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4, 140.6, 133.4, 129.5, 126.0, 118.8, 82.2, 55.8, 45.4, 21.3; HRMS (Q-TOF) *m/z* calcd. for $C_{12}H_{17}NO2SNa$ [$(M+Na)^+$]: 262.0878; found: 262.0888.

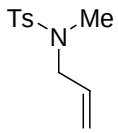


***N*-Allyl-*N*-(methoxymethyl)-*p*-toluenesulfonamide (183):** General Procedure G was followed employing NaH (2.85 mmol, 0.113 g), *N*-allyl-4-methylbenzenesulfonamide (2.36 mmol, 0.500 g) and chloro(methoxy)methane (3.54 mmol, 0.284 g) in 12 mL DMF. Purification by flash chromatography afforded 0.54 g (90%) of the title compound as viscous oil. IR (thin film): 2928, 1678, 1455, 1344, 1161 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 7.8 Hz, 2H), 5.63 (dddd, J = 16.9, 10.2, 6.41, 6.4 Hz, 1H), 5.17 (dd, J = 13.6, 1.4 Hz, 1H), 5.13 (dd, 5.2, 1.4 Hz, 1H), 4.69 (s, 2H), 3.80 (d, J = 6.3 Hz, 2H), 3.27 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 137.5, 132.4, 129.6, 127.3, 119.1, 78.4, 55.7, 48.6, 21.5; MS (EI, 70 eV): *m/z* 255 ($M^{\bullet+}$), 224, 184, 155, 100, 91, 68; HRMS *m/z* calcd. for $C_{12}H_{17}NO_3S$: 255.0929; found: 255.0938.

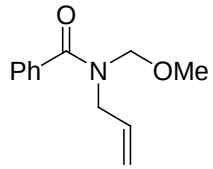


Methylallyl(methoxymethyl)carbamate (184): General Procedure G was followed employing NaH (5.22 mmol, 0.200 g), *N*-allylmethylcarbamate (4.35 mmol, 0.500 g) and chloro(methoxy)methane (6.52 mmol, 0.523 g) in 15 mL DMF. Purification by flash

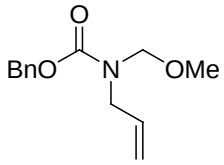
chromatography afforded 0.498 g (72%) of the title compound as yellow viscous oil. IR (thin film): 2954, 2821, 1717, 1644, 1473, 1258, 1085, 980 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.73-5.71 (m, 1H), 5.07-5.04 (m, 2H), 4.65-4.63 (m, 2H), 3.83-3.81 (m, 2H), 3.21 (s, 3H), 3.65 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, for two rotamers): δ 156.9 + 156.2 (1C), 133.3, 116.9 + 116.4 (1C), 77.9 + 77.6 (1C), 55.3, 53.3 + 52.6 (1C), 48.2 + 47.6 (1C); MS (EI, 70 eV): *m/z* 159 ($M^{\bullet+}$), 144, 128, 100, 84, 59; HRMS *m/z* calcd for $C_7H_{13}NO_3$: 159.0895; found: 159.0901.



***N*-Allyl-*N*-methyl-*p*-toluenesulfonamide (185):** General Procedure G was followed employing NaH (5.68 mmol, 0.227 g), *N*-allyl-4-methylbenzenesulfonamide (4.73 mmol, 1.00 g), and methyl iodide (7.10 mmol, 1.01 g) in 25 mL DMF. Purification by flash chromatography afforded 1.0 g (94%) of the title compound as viscous oil. IR (thin film): 2978, 1644, 1597, 1454, 1381, 1184, 985 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.70 (ddt, J = 17.1, 9.9, 6.3 Hz, 1H), 5.20 (dq, J = 3.9, 1.5 Hz, 1H), 5.15 (dt, J = 3.6, 1.5 Hz, 1H), 3.61 (d, J = 6.3 Hz, 2H), 2.65 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 134.4, 132.5, 129.6, 127.4, 119.0, 53.0, 34.1, 21.4; MS (EI, 70 V): *m/z* 225 ($M^{\bullet+}$), 198, 155, 91; HRMS *m/z* calcd. for $C_{11}H_{15}NO_2S$: 225.0823; found: 225.0825.

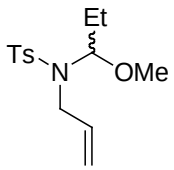


***N*-Allyl-*N*-(methoxymethyl)benzamide (191):** General Procedure G was followed employing NaH (8.06 mmol, 0.322 g), *N*-allylbenzamide (6.2 mmol, 1.0 g) and chloro(methoxy)methane (9.3 mmol, 0.749 g) in 15 mL DMF. Purification by flash chromatography afforded 1.11 g (87%) of the title compound as viscous yellow oil. IR (thin film): 3081, 2985, 2933, 1652, 1602, 1446, 1412, 1266, 1086, 916 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, calibrated at 2.49 ppm at 70 °C): δ 7.44-7.42 (m, 5H), 5.93-5.80 (m, 1H), 5.22-5.14 (m, 2H), 4.61 (s, 2H), 4.04 (d, J = 5.7 Hz, 2H), 3.17 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, calibrated at 39.5 ppm at 70 °C): δ 171.0, 135.5, 133.3, 129.2, 127.8, 126.3, 116.4, 78.4, 54.7, 47.3. MS (EI, 70 eV): *m/z* 205 ($M^{\bullet+}$), 175, 164, 105; HRMS *m/z* calcd. for $C_{12}H_{15}NO_2$: 205.1102; found: 205.1094.



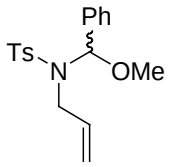
Benzylallyl(methoxymethyl)carbamate (192): General Procedure G was followed employing NaH (6.28 mmol, 0.252 g), *N*-allylbenzylcarbamate (5.23 mmol, 1.00 g) and chloro(methoxy)methane (7.85 mmol, 0.632 g) in 10 mL DMF. Purification by flash chromatography afforded 0.85 g (69%) of the title compound as colorless oil. IR (thin film): 3066, 2942, 1709, 1645, 1455, 1414, 1283, 1256, 1229, 915 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6, calibrated at 2.49 ppm at 70 °C): δ 7.43-7.27 (m, 5H), 5.88-5.72 (m, 1H), 5.20-5.06 (m, 4H), 4.66 (s, 2H), 3.90 (d, J = 5.7 Hz, 2H), 3.20 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, calibrated at 39.5 ppm at 70 °C): δ 155.0, 136.3, 133.6, 127.8, 127.3, 127.0, 116.0, 78.0, 66.2, 54.7, 47.8; MS

(EI, 70 eV): *m/z* 235 ($M^{\bullet+}$), 203, 160, 144, 130, 121, 113, 107, 104; HRMS *m/z* calcd. for $C_{13}H_{17}NO_3$: 235.1208; found: 235.1210.



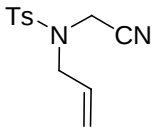
(+/−)-*N*-Allyl-*N*-(1-methoxypropyl)-*p*-toluenesulfonamide (204): General Procedure G was followed employing NaH (6.00 mmol, 240 mg), *N*-allyl-*N*,4-methylbenzenesulfonamide (5.00 mmol, 1.05 g) in 25 mL DMF at 0°C. The resulting slurry was stirred vigorously for 20-30 min at ambient temperature. The reaction mixture was cooled to 0 °C and 1-chloro-1-methoxypropane (12.5 mmol, 1.35 g)[94] was added slowly. The resulting mixture was stirred at ambient temperature for additional 1 hour (complete by TLC). Purification by flash chromatography (10% ether/hexanes) afforded 0.91 g (64%) of the title compound as colorless oil. IR (thin film): 2935, 1598, 1495, 1464, 1339, 1170, 1149, 1069, 925, 873 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 9.0 Hz, 2H), 5.74 (dddd, J = 16.9, 10.3, 6.6, 6.4 1H), 5.15 (dd, J = 17.4, 1.5 Hz, 1H), 5.03 (dd, J = 9.9, 0.9 Hz, 1H), 4.91 (dd, J = 7.2, 6.0 Hz, 1H), 3.78 (ddd, J = 5.5, 3.3, 1.5 Hz, 2H), 3.20 (s, 3H), 2.42 (s, 3H), 1.70 (ddq, J = 21.6, 14.7, 7.5 Hz, 1H), 1.43 (ddq, J = 21.0, 13.8, 7.5 Hz, 1H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 138.3, 135.5, 129.5, 127.3, 117.1, 91.1, 56.0, 44.4, 27.4, 21.5, 10.0; MS (EI, 70 V): *m/z* 252, 155, 91; Q-TOF *m/z* calcd. for $C_{14}H_{21}NO_3SNa$ [$(M+Na)^+$]: 306.1140; found: 306.1145.

[94] 1-Chloro-1-methoxypropane was freshly prepared as a solution in pentane and used directly in the reaction, see: Berliner, M. A.; Belecki, K. *J. Org. Chem.* **2005**, *70*, 9618-9621.

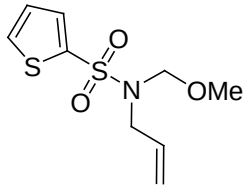


(+/−)-*N*-Allyl-*N*-(1-methoxybenzyl)-*p*-toluenesulfonamide (205): General Procedure G was followed employing NaH (2.84 mmol, 113 mg.), *N*-allyl-*N*,4-methylbenzenesulfonamide (2.37 mmol, 0.5 g) in 10 mL DMF under nitrogen atmosphere at 0°C a slurry was obtained and stirred vigorously for 20-30 min. The reaction mixture was cooled down to 0 °C and 1-(chloro(methoxy)methyl)benzene (5.92 mmol, 927 mg)[95] was added slowly. The resulting mixture was stirred at ambient temperature for additional 1 hour (complete by TLC). Purification by flash chromatography (10% ether/hexanes) afforded 0.57 g (72%) of the title compound as colorless oil. IR (thin film): 3065, 2932, 1597, 1493, 1452, 1342, 1096, 1028, 923, 889, 814, 745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 8.4 Hz, 2H), 7.25 - 7.26 (m, 7H), 6.15 (s, 1H), 5.43 (dddd, J = 16.5, 10.2, 6.6, 6.6 Hz, 1H), 4.85 (ddq, J = 17.4, 14.1, 1.2 Hz, 2H), 3.75 (dt, J = 16.5, 1.5 Hz, 1H), 3.50 (dt, J = 16.2, 1.2 Hz, 1H), 3.38 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 138.0, 137.4, 134.7, 129.5, 128.3, 128.2, 127.6, 126.7, 116.9, 89.1, 56.1, 45.5, 21.5; MS (EI, 70 V): *m/z* 331, 300, 224, 176, 155, 144, 122, 104, 89, 78; Q-TOF *m/z* calcd. for $C_{18}H_{21}NO_3S$ [$(M+Na)^+$]: 331.1142; found: 331.12409.

[95] 1-(Chloro(methoxy)methyl)benzene was freshly prepared as a solution in pentane and used directly in the reaction, see: Berliner, M. A.; Belecki, K. *J. Org. Chem.* **2005**, *70*, 9618-9621.

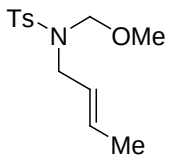


***N*-Allyl-*N*-(cyanomethyl)-*p*-toluenesulfonamide (207):** General Procedure G was followed employing NaH (5.67 mmol, 0.227 g), chloroacetonitrile (7.10 mmol, 0.535 g) and *N*-allyl-4-methylbenzenesulfonamide (4.73 mmol, 1.00 g) in 15 mL DMF. Purification by flash chromatography afforded 0.96 g (80%) of the title compound as viscous oil. IR (thin film): 2986, 2249, 1644, 1597, 1353, 1186, 1092 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 5.79-5.66 (m, 1H), 5.39-5.29 (m, 2H), 4.21 (s, 2H), 3.82 (d, J = 6.6 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.8, 134.3, 130.7, 130.1, 127.6, 121.8, 113.4, 50.2, 34.4, 21.6; MS (EI, 70 eV): *m/z* 250 ($M^{\bullet+}$), 155, 91; HRMS *m/z* calcd. for $C_{12}H_{14}N_2O_2S$: 250.0776; found: 250.0767.

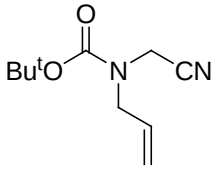


***N*-Allyl-*N*-(methoxymethyl)-thiophene-2-sulfonamide (214):** General Procedure G was followed employing NaH (2.95 mmol, 0.12 g), *N*-allyl-2-thiophenesulfonamide (2.46 mmol, 0.50 g) and chloro(methoxy)methane (3.69 mmol, 0.296 g) in 12 mL DMF. Purification by flash chromatography afforded 0.44 g (72%) of the title compound as viscous oil. IR (thin film): 3093, 2934, 1446, 1404, 1348, 1156, 1080, 915 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 3.6 Hz, 1H), 7.58 (d, J = 5.1 Hz, 1H), 7.07 (t, J = 4.5 Hz, 1H), 5.70 (dddd, J = 16.8, 12.9, 6.6, 6.6 Hz, 1H), 5.19 (dd, J = 12.9, 4.2, 2H), 4.71 (s, 2H), 3.88 (d, J = 6.3 Hz, 2H), 3.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 132.3, 132.2, 131.8, 127.2, 119.3, 78.8, 55.9, 48.9; MS (EI, 70

eV): *m/z* 247 ($M^{\bullet+}$), 216, 147, 100, 68; HRMS *m/z* calcd. for [$C_9H_{13}NO_3S_2$ – CH_3O]: 216.0147; found: 216.0151.



(*E*)-*N*-(But-2-enyl)-*N*-(methoxymethyl)-*p*-toluenesulfonamide (215): General Procedure G was followed employing NaH (2.60 mmol, 0.106 g), *N*-(but-2-enyl)-*p*-toluenesulfonamide (2.22 mmol, 0.500 g) and chloro(methoxy)methane (3.33 mmol, 0.268 g) in 10 mL DMF. Purification by flash chromatography afforded 0.57 g (96%) of the title compound as colorless oil. IR (thin film): 2934, 1598, 1449, 1340, 1164, 1076, 929, 815, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 7.8 Hz, 2H), 5.30-5.17 (m, 2H), 4.67 & 4.66 (s, 2H), 3.72 (d, J = 6.9 Hz, 2H), 3.27 & 3.25 (s, 2H), 2,40 (s, 3H), 1.61 (dd, J = 6.3, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2, 137.6, 130.8, 129.5, 127.2, 124.8, 77.9, 55.5, 47.7, 21.4, 17.6; MS (EI, 70 V): *m/z* 269 ($M^{\bullet+}$), 254, 238, 224, 184, 155, 139, 114, 91; HRMS *m/z* calcd. for $C_{13}H_{19}NO_3S$: 269.1089; found: 269.1093.

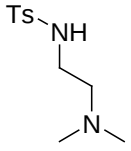


***tert*-Butyl-allyl(cyanomethyl)carbamate (189):**[96] To a suspension of allylamine (24.9 mmol, 1.42 g), K_2CO_3 (51 mmol, 7.1 g), NaI (50 mmol, 7.5 g) and Et_3N (100 mmol, 10.2 g) in

[96] Gensini, M.; Kozhushkov, S. I.; Yufit, D. S.;Howard, J. A. K.; Es-Sayed, M.; Meijere, A. D**.** *Eur. J. Org. Chem.* **2002,** 2499-2507.

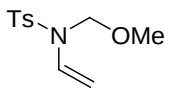
anhydrous DMF (50 mL) was added chloromethylnitrile (25.1 mmol, 1.90 g) and the resulting mixture was stirred for 24 h. The mixture was filtered through celite and the solid filter cake was washed with ether (30 mL). The filtrates were combined and washed with water (30 mL) and brine (30 mL). The aqueous portions were combined and extracted with EtOAc (3 ×). The organic extracts were combined, dried ($MgSO_4$) and concentrated to afford a brown oil of (*N*-allylamino)acetonitrile (confirmed by NMR) and used directly for the next reaction.

To an ice cold solution of $(Boc)_2O$ (27.5 mmol, 6.00 g) in 50 mL MeOH and Et_3N (36.0 mmol, 3.64 g) was added a solution of (*N*-allylamino)acetonitrile (prepared above) in MeOH (50 mL) and the resulting mixture was stirred at 60 °C for 3 h. The solvent was evaporated and the resulting mixture was dissolved in water (60 mL). The aqueous phase was extracted with CH_2Cl_2 (3 ×) and the combined organic extracts were dried ($MgSO_4$) and concentrated. Purification by flash chromatography (1:2 ether in hexane) afforded 1.8 g (37% overall yield) the title compound as a colorless oil. IR (thin film): 2981, 2249, 1703, 1645, 1456, 1402, 1369, 1250, 1072, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.82-5.69 (m, 1H), 5.26-5.20 (m, 2H), 4.11 (m, 2H), 3.94-3.92 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.7, 132.1, 118.8, 115.9, 81.8, 49.7, 34.4, 28.1; MS (EI, 70 eV): *m/z* 196 ($M^{\bullet+}$), 181, 140, 123, 114, 95, 86, 69, 58,56; HRMS: m/*z* calcd. for $C_{10}H_{16}N_2O_2$: 196.1211; found: 196.1209.



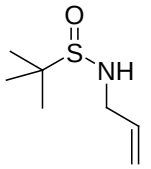
***N*-(2-(Dimethylamino)ethyl)-*p*-toluenesulfonamide:** To a 0 °C solution of tosylchloride (0.95 equiv, 10.5 mmol, 2.00 g) and Et_3N (3 equiv, 33.2 mmol, 4.60 mL) in 30 mL of CH_2Cl_2 was added *N*,*N*-dimethylethane-1,2-diamine (1 equiv, 11.1 mmol, 1.20 mL) in 3 mL of CH_2Cl_2

dropwise over 3-4 min. The reaction mixture was brought to ambient temperature and stirred for additional 30 min. The reaction was diluted with CH_2Cl_2 and a saturated aqueous solution of $NaHCO_3$ was added. The organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated. Removal of the solvent afforded 2.44 g (96%) of the title compound as yellow oil. IR (thin film): 3566, 3275, 2948, 1598, 1457, 1331, 1160, 1096, 816, 661 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 5.22 (t, J = 3.6 Hz, NH), 2.97 (dd, J = 6.9, 5.7 Hz, 2H), 2.43 (s, 3H), 2.34 (dd, J = 6, 4.5 Hz, 2H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1, 136.4, 129.4, 126.9, 56.8, 44.5, 39.9, 21.3; MS (EI, 70 V): *m/z* 242 ($M^{\bullet+}$), 213, 155, 105, 91, 65, 59; HRMS: *m/z* calcd. for $C_{11}H_{18}N_2O_2S$: 242.1089; found: 242.1085.



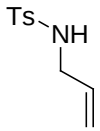
***N*-Vinyl-*N*-(methoxymethyl)-*p*-toluenesulfonamide (212):** To a 0 °C solution of NaH (65%, 9.07 mmol, 0.360 g) in 55 mL of THF was added *N*-(2-(dimethylamino)ethyl)-*p*-toluenesulfonamide (1 equiv, 7.56 mmol, 1.83 g) in 3 mL of THF dropwise over 3 min. The reaction mixture was brought to ambient temperature and stirred for one hour. The reaction mixture was cooled to 0 °C and MOMCl (18.9 mmmol, 1.43 mL) in 2 mL THF was added. The reaction temperature was raised to ambient temperature and stirred for additional 2 h. The reaction was quenched by adding 10M NaOH solution (caution: caustic!) and the resulting mixture was stirred for 14 h, then diluted with ether. The organic part was separated, washed with water and brine, dried over $MgSO_4$, and concentrated. Column purification afforded 1.34 g (95%) of the title compound as yellow oil. IR (thin film): 2946, 1630, 1597, 1449, 1354, 1172, 1089, 941, 661 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4

Hz, 2H), 6.75 (dd, J = 15.6, 9.3 Hz, 1H), 4.92 (s, 2H), 4.65 (dd, J = 15.9, 1.2, 1H), 4.42 (dd, J = 9.3, 1.2, 1H), 3.32 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 136.9, 131.6, 129.8, 126.8, 95.7, 77.7, 55.8, 21.5; MS (EI, 70 V): *m/z* 241 ($M^{\bullet+}$), 210, 155, 145, 105, 91, 65, 58; HRMS: *m/z* calcd. for $C_{11}H_{15}NO_3S$: 241.0773; found: 241.0780.

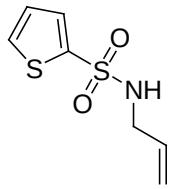


***N*-Allyl-2-methylpropane-2-sulfinamide (115):** To a stirred solution of allylamine (0.1779 mol, 10.14 g) in 30 mL CH_2Cl_2 at 0 °C was added 2-methylpropane-2-sulfinic chloride (**114**)[97] (35.6 mmol, 5.00 g) slowly over 10 minutes. The resulting mixture was stirred at room temperature for 1 h. The reaction was diluted with brine and the layers were separated. The organics were combined and washed with water, and dried over $MgSO_4$. Upon concentration and passing through silica gel with ether as eluent, the title compound (5.27 g, 92%) was isolated as yellow oil. IR (thin film): 3479, 2978, 1640, 1476, 1418, 1361, 1078, 922 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (dddd, J = 15.9, 10.2, 5.7, 5.7 Hz, 1H), 5.23 (dq, J = 17.1, 1.5 Hz, 1H), 5.12 (dq, J = 10.2, 1.2 Hz, 1H), 3.83-3.61 (m, 2H), 3.26 (t, J = 5.7 Hz, N<u>H</u>), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.2, 117, 55.6, 48.1, 22.5 (3C); MS (EI, 70 V): *m/z* 162 [$(M+H)^{\bullet+}$], 145, 105, 86, 56; HRMS *m/z* calcd. for $C_7H_{16}NOS$ (M+H): 162.0953; found: 162.0954.

[97] (a) Weix, D.J.; Ellman, J. A.;Wang, X.; Curran, D.P. *Org. Synth.* **2005**, *82*, 157-162. (b) Gontcharov, A. V.; Liu, H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 783-786. (c) Netscher, T.; Prinzbach, H. *Synthesis* **1987**, 683-688.

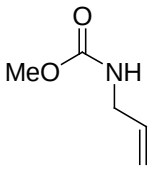


***N*-Allyl-*p*-toluenesulfonamide (186):**[84] 4-Methylbenzenesulfonyl chloride (26.2 mmol, 5.00 g) was dissolved in 100 mL dry CH_2Cl_2 at 0°C and allylamine (92.8 mmol, 7.00 mL) was introduced. The resulting mixture was stirred at ambient temperature for 1 h. The solvent was removed and the residue was dissolved in ether. The organic layer was washed with water (2 ×), brine and dried ($MgSO_4$). Purification by flash chromatography with ether as eluent afforded 5.32 g (96%) of the title compound as a white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 5.76-5.64 (m, 2H), 5.18-5.04 (m, 2H), 4.89 (br s, N<u>H</u>), 3.58-3.53 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.4, 136.9, 132.9, 129.6, 127.1, 117.5, 45.6, 21.4.

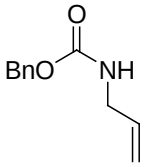


***N*-Allylthiophene-2-sulfonamide:** Thiophene-2-sulfonyl chloride (5.47 mmol, 1.00 g) was dissolved in 10 mL dry CH_2Cl_2 at 0°C and allylamine (27.3 mmol, 1.56 g) was added. The resulting mixture was stirred at ambient temperature for 1 h. The solvent was removed and the residue was purified by flash chromatography with ether as eluent affording 1.0 g (90%) of the title compound as a white crystalline solid. IR (thin film): 3286, 3094, 1646, 1405, 1327, 1156, 925, 855 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (dd, J = 3.9, 1.5 Hz, 1H), 7.59 (dd, J = 5.1, 1.2 Hz, 1H), 7.09 (dd, J = 4.8, 3.6 Hz, 1H), 5.75 (dddd, J = 16.2, 10.5, 5.7, 5.7 Hz, 1H), 5.20 (dd, 17.1, 1.2 Hz, 1H), 5.13 (dt, J = 10.2, 0.9 Hz, 1H), 4.8 (br s, N<u>H</u>), 3.68 (t, J = 5.7 Hz, 2H); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 140.9, 132.6, 132.2, 131.9, 127.4, 117.9, 45.9; MS (EI, 70 eV): *m/z* 225 (M^+ + Na),; HRMS *m/z* calcd. for $C_7H_9NO_2S_2Na$: 225.9972; found: 225.9961.



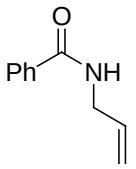
Methyl *N*-allylcarbamate:[98] Methylchloroformate (40.0 mmol, 3.78 g) was added over 5 min to an ice cold solution of allylamine (88 mmol, 5.0 g) in 60 mL CH_2Cl_2. After addition was complete, the reaction mixture was allowed to warm to ambient temperature and stirred for additional 2 h. The reaction mixture was diluted with 2 M HCl solution (25 mL) and the organic layer was separated. The organic layer was washed with saturated $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated to afford 4.3 g (93%) of the title compound as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 5.78-5.65 (m, 1H), 5.26-5.15 (m, 1H, NH), 5.09-4.96 (m,2H), 3.66-3.60 (m, 2H), 3.59 (br s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 134.4, 115.4, 51.7, 43.1.



Benzyl allylcarbamate:[99] Benzylchloroformate (42.2 mmol, 7.20 g, 95%) was added over 30 min to a 1:1 mixture of water and EtOAc (75 mL each), K_2CO_3 (130 mmol, 18.0 g) and allylamine (38.0 mmol, 2.17 g) at 0 °C with vigorous stirring. After addition, the reaction

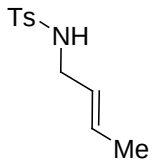
[98] Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628 -4641.
[99] Bischofberger, N.; Waldmann, H.; Saito, T.; Simon, E. S.; Lees, W.; Bednarski, M. D.; Whitesides, G. M. *J. Org. Chem.* **1988**, *53*, 3457-3465.

mixture was brought to ambient temperature and stirred for additional 2 h. Upon completion, the reaction mixture was diluted with 2 M HCl solution (40 mL) and the organic layer was separated. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated to afford 7.0 g (97%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.34 (m, 5H), 5.87-5.78 (m, 1H), 5.22-5.11 (m, 4H), 4.58 (br s, 1H, NH), 3.80 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 136.4, 134.3, 128.2, 127.8, 115.6, 66.4, 43.3.

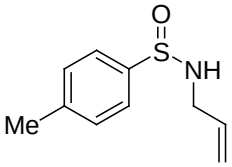


***N*-Allylbenzamide:**[100] To a stirred solution of allylamine (86.16 mmol, 4.920 g) in 50 mL CH_2Cl_2 at 0°C, benzoyl chloride (17.2 mmol, 2.42 g) was added over 30 min. After addition, the resulting solution was stirred at ambient temperature for additional 2 h and diluted with saturated $NaHCO_3$ solution. The organic layer was separated and washed with brine, dried ($MgSO_4$) and concentrated to afford 2.64 g (95%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.8-7.76 (m, 2H), 7.51-7.37 (m, 3H), 6.39 (br s, 1H, NH), 5.99-5.86 (m, 1H), 5.27-5.14 (m, 2H), 4.09-4.03 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 134.1, 131.4, 128.5, 126.9, 116.6, 42.4.

[100] Castagnolo, D.; Armaroli, S.; Corelli, F.; Botta, M. *Tetrahedron: Asymmetry* **2004**, *15*, 941-949.



***N*-(But-2-enyl)-*p*-toluenesulfonamide:**[101] To a stirred solution of tosylamine (6.92 mmol, 1.18 g) and K_2CO_3 (14.8 mmol, 2.04 g) in 20 mL CH_3CN, crotyl bromide (85%, 7.4 mmol, 1.0 g) was added and the resulting mixture was refluxed for 5-6 hours. The reaction was cooled down to ambient temperature and diluted with water. Excess of ether was added to the reaction mixture and extracted. The organic layer was separated and washed with brine, dried ($MgSO_4$) and concentrated. Column purification afforded 1.1 g (71%) of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 6.6 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 5.67- 5.52 (m, 1H), 5.35-5.27 (m, 1H), 4.52 (s, br, 1H, NH), 3.52- 3.47 (m, 2H), 2.43 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.3, 129.7, 129.6, 127.1, 125.6, 45.3, 21.4, 17.5.



***N*-Allyl-4-methylbenzenesulfinamide:**[102] To a 0 °C solution of *p*-toluenesulfinic acid sodium salt (16.8 mmol, 3.00 g) in 15 mL toluene, oxalyl chloride (17.9 mmol, 2.26 g) was added dropwise. After stirring the reaction for 1 h at room temperature, allylamine (84.18 mmol, 6.3 mL) was added and the reaction was stirred for another hour. The reaction mixture was diluted with brine and the layers were separated. The aqueous layer was extracted with ether. The combined organics were washed with brine and dried over $MgSO_4$. The crude product mixture

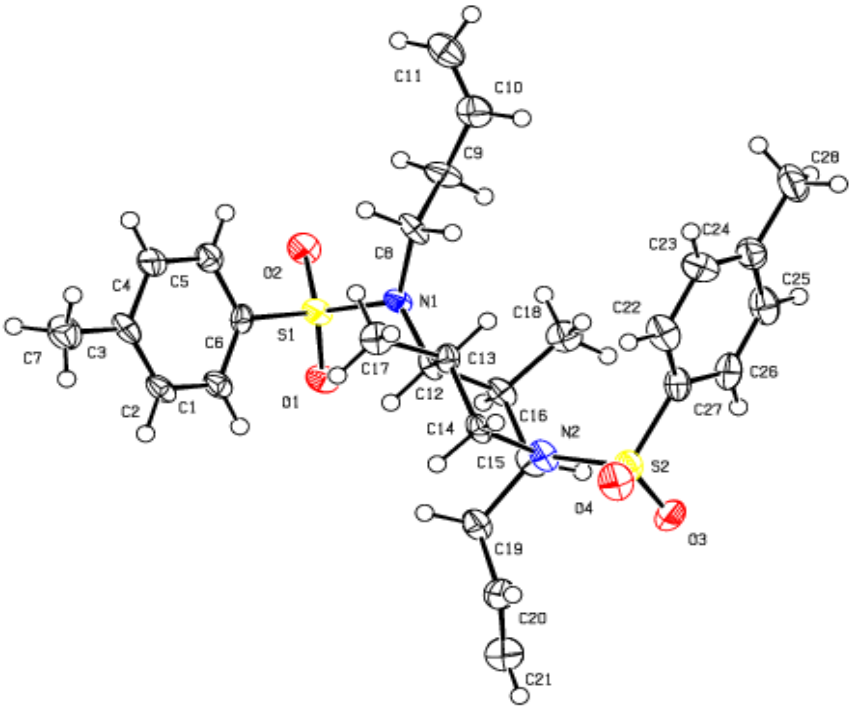
[101] Aggarwal, V. K.; Fang, G. Y.; Charmant, J. P. H.; Meek, G. *Org. Lett.* **2003**, *5*, 1757-1760.
[102] (a) Savilea, C. K.; Kazlauskas, R. J. *Adv. Synth. Catal.* **2006**, *348*, 1183-1192. (b) Ruano, J.L. G.; Parra, A.; Yuste, F.; Mastranzo, V. M. *Synthesis* **2008**, *2*, 311-319.

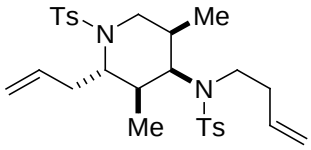
was purified by column chromatography on silica gel using 20% ether/hexanes as eluent affording 2.25 g (69%) of the title compound as yellow oil.

APPENDIX A

X-RAY DATA

Table 18. Crystal data for **71**

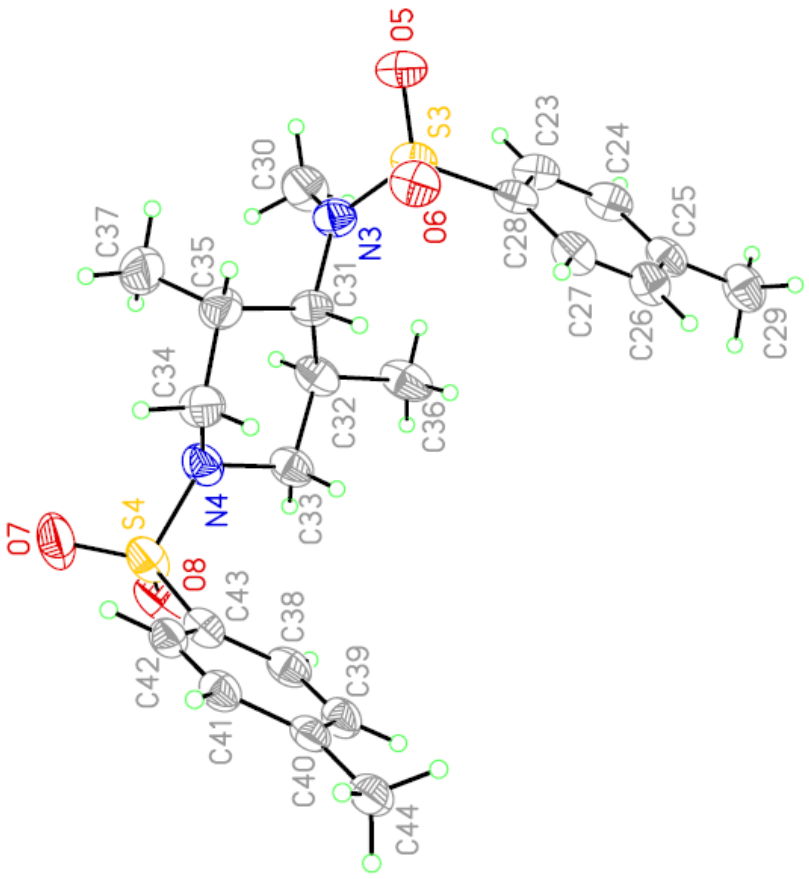


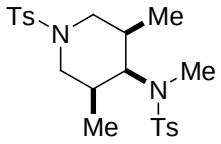


Identification code	nihar6
Empirical formula	C28 H38 N2 O4 S2
Formula weight	530.72
Temperature	150(2) K
Wavelength	0.71073 Å

Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.186(3) Å	α= 90°.
	b = 7.968(2) Å	β= 97.626(5)°.
	c = 16.756(4) Å	γ = 90°.
Volume	1347.9(6) $Å^3$	
Z	2	
Density (calculated)	1.308 Mg/m^3	
Absorption coefficient	0.234 mm^{-1}	
F(000)	568	
Crystal size	,0.18 x 0.23 x 0.26 mm^3	
Theta range for data collection	2.02 to 24.99°.	
Index ranges	-12<=h<=12, -9<=k<=9, -19<=l<=19	
Reflections collected	10604	
Independent reflections	4720 [R(int) = 0.1187]	
Completeness to theta = 24.99°	100.0 %	
Absorption correction	multi-scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4720 / 1 / 327	
Goodness-of-fit on F^2	0.794	
Final R indices [I>2sigma(I)]	R1 = 0.0653, wR2 = 0.1304	
R indices (all data)	R1 = 0.1339, wR2 = 0.1590	
Absolute structure parameter	0.23(14)	
Extinction coefficient	0.0000(15)	
Largest diff. peak and hole	0.274 and -0.257 $e.Å^{-3}$	

Table 19. Crystal data **75**

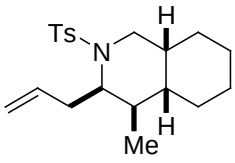


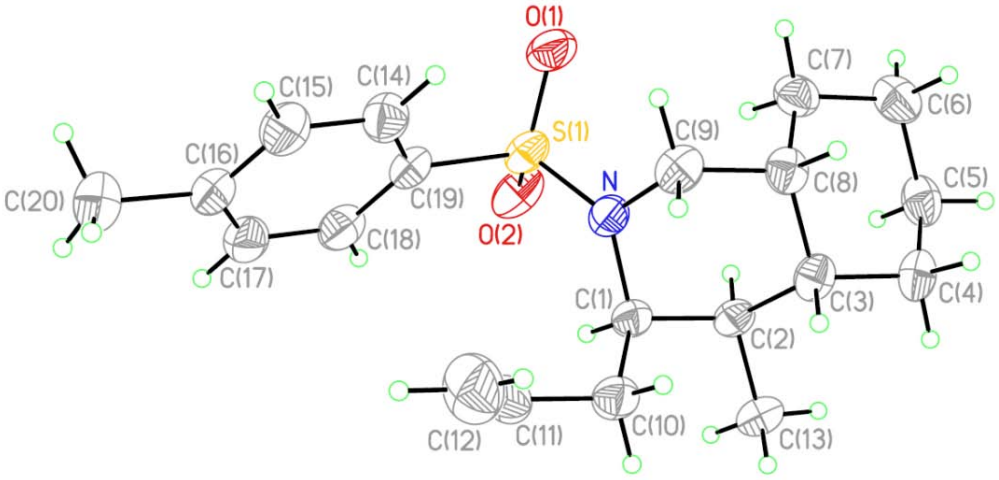


Identification code	ns112006	
Empirical formula	C22 H30 N2 O4 S2	
Formula weight	450.60	
Temperature	373(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 16.5309(11) Å	α= 90°.
	b = 8.3946(5) Å	β= 95.5840(10)°.
	c = 33.062(2) Å	γ = 90°.
Volume	4566.2(5) Å^3	
Z	8	
Density (calculated)	1.311 Mg/m^3	

Absorption coefficient	0.264 mm^{-1}
F(000)	1920
Crystal size	0.28 x 0.23 x 0.22 mm^3
Theta range for data collection	1.66 to 25.00°.
Index ranges	-19<=h<=19, -9<=k<=9, -39<=l<=39
Reflections collected	35433
Independent reflections	8018 [R(int) = 0.0495]
Completeness to theta = 25.00°	99.9 %
Absorption correction	None
Max. and min. transmission	0.9443 and 0.9298
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8018 / 0 / 551
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0620, wR2 = 0.1549
R indices (all data)	R1 = 0.0869, wR2 = 0.1664
Largest diff. peak and hole	0.690 and -0.556 $e.Å^{-3}$

Table 20. Crystal data for **88**

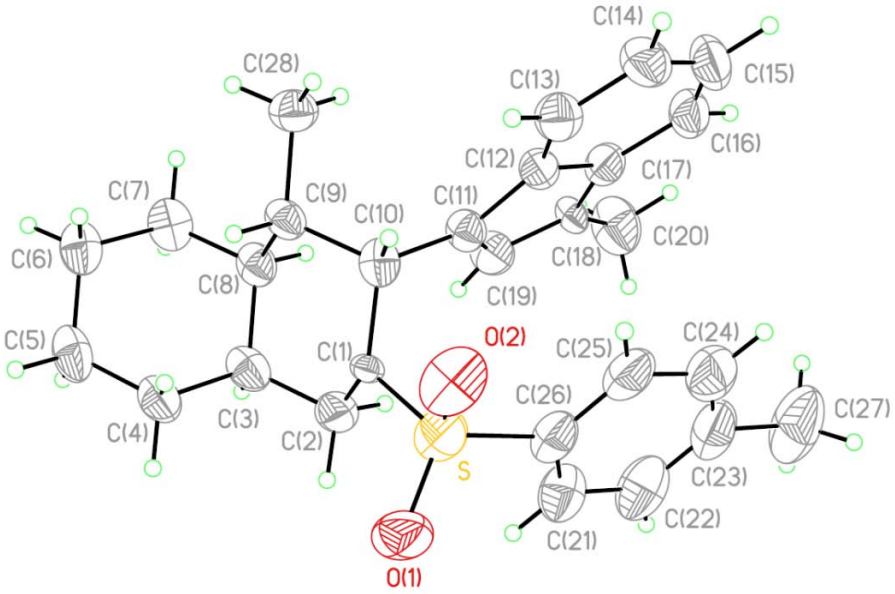


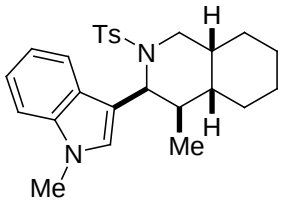


Identification code	ns92906s
Empirical formula	C20 H29 N O2 S

Formula weight	347.50	
Temperature	473(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 7.6629(8) Å	α= 90°.
	b = 10.9011(11) Å	β= 90.215(2)°.
	c = 22.370(2) Å	γ = 90°.
Volume	1868.7(3) $Å^3$	
Z	4	
Density (calculated)	1.235 Mg/m^3	
Absorption coefficient	0.185 mm^{-1}	
F(000)	752	
Crystal size	0.27 x 0.22 x 0.21 mm^3	
Theta range for data collection	1.82 to 27.50°.	
Index ranges	-9<=h<=9, -14<=k<=14, -29<=l<=28	
Reflections collected	17888	
Independent reflections	4286 [R(int) = 0.0643]	
Completeness to theta = 27.50°	100.0 %	
Absorption correction	multi-scan (Sadabs)	
Max. and min. transmission	0.9622 and 0.9517	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4286 / 0 / 217	
Goodness-of-fit on F^2	0.955	
Final R indices [I>2sigma(I)]	R1 = 0.0562, wR2 = 0.1287	
R indices (all data)	R1 = 0.0954, wR2 = 0.1454	
Largest diff. peak and hole	0.385 and -0.228 $e.Å^{-3}$	

Table 21. Crystal data for **91c**

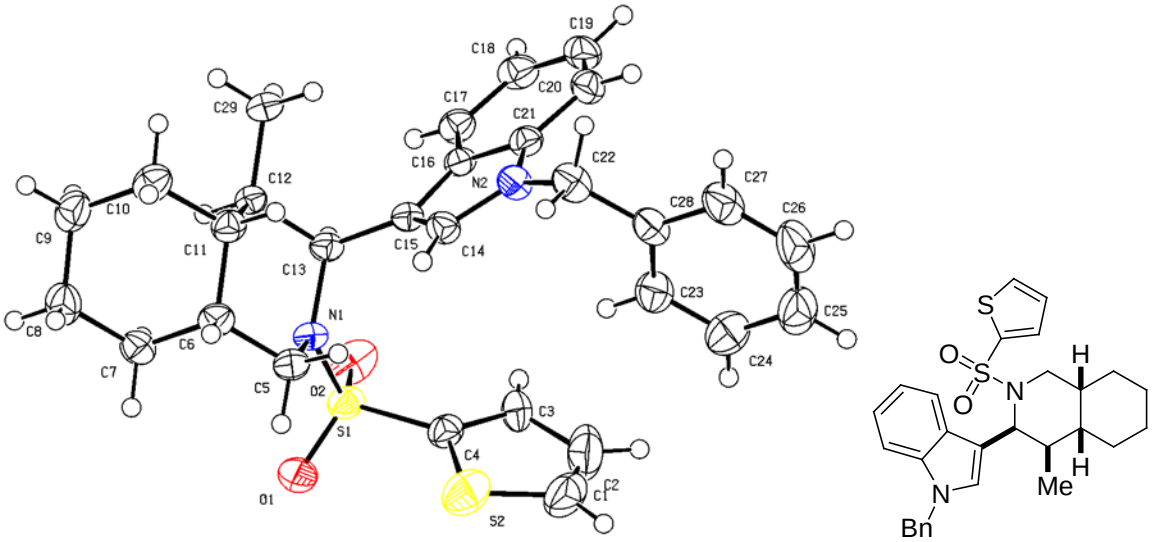




Identification code	ns1206	
Empirical formula	C26 H32 N2 O2 S	
Formula weight	436.60	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 16.566(11) Å	α= 90°.
	b = 14.871(12) Å	β= 106.885(14)°.
	c = 10.019(8) Å	γ = 90°.
Volume	2362(3) $Å^3$	
Z	4	
Density (calculated)	1.228 Mg/m^3	
Absorption coefficient	0.162 mm^{-1}	
F(000)	936	
Crystal size	0.28 x 0.14 x 0.08 mm^3	
Theta range for data collection	1.28 to 24.99°.	
Index ranges	-19<=h<=19, -17<=k<=17, -11<=l<=11	
Reflections collected	16172	
Independent reflections	4156 [R(int) = 0.1503]	
Completeness to theta = 24.99°	100.0 %	

Absorption correction	Multi-scan
Max. and min. transmission	0.9872 and 0.9561
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4156 / 0 / 280
Goodness-of-fit on F^2	0.846
Final R indices [I>2sigma(I)]	R1 = 0.0657, wR2 = 0.1425
R indices (all data)	R1 = 0.1994, wR2 = 0.2018
Largest diff. peak and hole	0.203 and -0.195 e.Å^{-3}

Table 22. Crystal data for **105c**



Identification code	ns825s	
Empirical formula	C29 H32 N2 O2 S2	
Formula weight	504.69	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.8077(13) Å	α= 90°.
	b = 9.9740(10) Å	β= 96.093(2)°.
	c = 19.981(2) Å	γ = 90°.
Volume	2538.1(4) Å^3	

Z	4
Density (calculated)	1.321 Mg/m^3
Absorption coefficient	0.240 mm^{-1}
F(000)	1072
Crystal size	0.38 x 0.36 x 0.23 mm^3
Theta range for data collection	1.60 to 32.34°.
Index ranges	-18<=h<=19, -14<=k<=14, -29<=l<=29
Reflections collected	30858
Independent reflections	8517 [R(int) = 0.0346]
Completeness to theta = 32.34°	94.0 %
Absorption correction	None
Max. and min. transmission	0.9469 and 0.9144
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8517 / 0 / 316
Goodness-of-fit on F^2	1.539
Final R indices [I>2sigma(I)]	R1 = 0.0698, wR2 = 0.1895
R indices (all data)	R1 = 0.0935, wR2 = 0.2018
Largest diff. peak and hole	1.027 and -0.698 $e.Å^{-3}$

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