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Development and Applications of Hydrazone-Based Transformations for the Synthesis of Allenes

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Abstract

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The diverse reactivity patterns, unique structural features imparted by the cumulated double bonds, and possibility of axial chirality have garnered allenes considerable attention in organic synthesis. Numerous methods have been described in the literature to afford optically active allenes starting from chiral starting materials, yet catalytic and asymmetric methods to directly synthesize chiral allenes from achiral precursors remain underdeveloped. Furthermore, few methods exist that can directly generate aliphatic allenes through mild fragment-coupling reactions. Herein we describe two elaborations of a Petasis reaction of N-sulfonylhydrazones to enable the direct synthesis of allenes. The first involves the alkynylation of aliphatic N-sulfonyl hydrazones to generate aliphatic allenes. This reaction was optimized in a high-throughput fashion by SAMDI mass spectrometry. The second project presents an organocatalytic, asymmetric boronate addition to N-sulfonyl hydrazones enabled by chiral binaphthols to access enantioenriched 2,3-allenols or 1,3-alkynyl allenes. The application of the latter methodology to the synthesis of chiral natural products is also described, in particular the exploitation of the known ability of 2,3-allenol to undergo gold-mediated cycloisomerization to enable the convergent stereocontrolled synthesis of potent anticancer and antimalarial annonaceus acetogenin natural products (+)-solamin and (+)-*cis*-solamin.

Thesis Advisor: Prof. Regan J. Thomson

Acknowledgments

I am very honored and grateful to have worked under the guidance of Prof. Regan Thomson during my doctoral studies. His sheer brilliance as an organic chemist was quite intimidating early in my career, but my goal of emulating him to the best of my ability allowed me to grow tremendously as a scientist, employing fastidious care in my experiments and rationally working through any problems I encountered. Regan fostered a welcoming and congenial atmosphere in the laboratory and treated his students with tremendous respect, which allowed us to maximize our success. I would also like to acknowledge the significant role that my thesis committee members Profs. Karl Scheidt and Richard Silverman played to that end, as they provided constant intellectual and logistical support for my research. Most notably, I made heavy use of Prof. Silverman's cold room for one of my projects.

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laboratory. I am happy to say that I have learned just as much from them as they have from me, as they allowed me to significantly improve my leadership and management skills, which will undoubtedly serve me well in the future. I wish them continued success in their chosen career paths.

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List of Abbreviations

Ac	acetyl
acac	acetonyl acetate
Ac_2O	acetic anhydride
AcOH	acetic acid
ADR	allylic diazine rearrangment
AIBN	2,2´-azobisisobutyronitrile
Alloc	allyloxycarbonyl
amu	atomic mass units
aq	aqueous
Ar	aryl
ATR	attenuated total reflectance
BINOL	1,1´-bi-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
Bu	butyl
BuLi	butyl lithium
Bu_4NOAC	tetrabutylammonium acetate
Bz	benzoyl

$CHCl_3$	chloroform
cod	1,4-cyclooctadiene
$C(O)Me_2$	acetone
CSA	camphorsulfonic acid
d.r.	diastereomeric ratio
dba	dibenzylideneacetone
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
e.e.	enantiomeric excess

e.r.	enantiomeric ratio
EI	electron impact
ESI	electrospray ionization
Et	ethyl
$EtAlCl_2$	ethylaluminum dichloride
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
Et_3SiH	triethylsilane
Et_2NH	diethylamine
Et_3N	triethylamine
eq.	equivalents
FT	Fourier transform
GC	gas chromatography
H_2NNH_2/N_2H_4	anhydrous hydrazine
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
HTS	high-throughput screening
IBX	2-iodoxybenzoic acid

IPNBSH	N-isopropylidene-N′-2-nitrobenzenesulfonyl hydrazine
IR	infrared spectroscopy
J	coupling constant
LA	Lewis acid
$LiAlH_4$	lithium aluminum hydride
Me	methyl
$MeAlCl_2$	methylaluminum dichloride
MeCN	acetonitrile
MeOH	methanol
Ms	methanesulfonyl
MsCl	methanesulfonyl chloride
MS	molecular sieves
N_2	nitrogen gas
$NaBH_4$	sodium borohydride
$NaBH_3CN$	sodium cyanoborohydride
Na_2CO_3	sodium carbonate
NaH	sodium hydride
NaOAc	sodium acetate
NBSH	2-nitrobenzenesulfonyl hydrazine

NMM	N-methyl morpholine
NMR	nuclear magnetic resonance spectroscopy
nOe	nuclear Overhauser effect
Ns	2-nitrobenzenesulfonyl
NsH	2-nitrobenzenesulfinic acid
(m/z)	mass to charge ratio
$^{-}$OH	hydroxide
PG	protecting group
Ph	phenyl
$PhI(OAc)_2$	(diacetoxyiodo)benzene
PhMe	toluene
$Ph(Me)_3$	mesitylene
PPh_3	triphenylphosphine
Pr	propyl
P.T.	proton transfer
pTsOH	4-toluenesulfonic acid
pybox	pyridine bis(oxazoline)
r.t.	room temperature
SAM	self-assembled monolayer

SAR	structure-activity relationship
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Tf	(trifluoromethyl)sulfonyl
TFE	trifluoroethanol
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
tr	retention time
Ts	4-toluenesulfonyl
TsH	4-toluenesulfinic acid
$TsNHNH_2$	4-toluenesulfonyl hydrazine
ZnI_2	zinc (II) iodide

Table of Contents

List of Figures

List of Schemes

List of Tables

CHAPTER 1

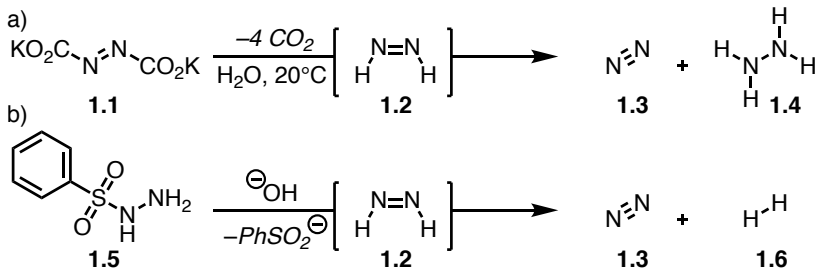
An Introduction to the Allylic Diazine Rearrangement in Organic Synthesis

Chapter 1

Hydrazones are an extremely useful functional handle in organic synthesis, capable of undergoing a myriad of powerful transformations. They have been featured in capital reaction modes for decades since their emergence in the late 19th century,[1] such as the classic Fischer indole synthesis,[2] the Wolff-Kishner reduction of carbonyls,[3] the Piloty-Robinson pyrrole synthesis,[4] the Bamford-Stevens olefination reaction[5] and its variants,[6] as well as several diverse alkylation[7] and halogenation reactions.[8] The synthetic utility of hydrazones stems primarily from their ease of synthesis—a simple condensation reaction between a carbonyl species and a hydrazine—and the expansive mutability of the parent hydrazine, which can be grafted either with labile groups or non-labile, reactive groups. A wide collection of powerful transformations ensues from both of these types of hydrazones. Their commonality is the liberation of dinitrogen and the concomitant generation of a reactive charged or neutral species that can engage in either an additional fragment coupling reactions, or a sigmatropic rearrangement. The products generated from these reactions lack the hydrazine moiety present in the starting material, and fundamentally these reactions are deemed to be traceless, as do not present clearly obvious retrons in a retrosynthetic analysis of a bond construction.[9] It is therefore important to expand the existing toolkit provided by hydrazones to further facilitate the rapid and efficacious assembly of complex molecules and architectures. What follows in this thesis is the development of traceless N-sulfonylhydrazone-based fragment coupling reactions for the efficient and mild construction of allenes, and their application toward the synthesis of biologically relevant natural products.

1.1 Early History of Diazine

Like that of many important functional groups, the history of diazine goes back to the late 19th century during the early experiments of Thiele. In 1892, he observed that the decarboxylation reaction of azodicarboxylate salt **1.1** resulted in the formation of carbon dioxide, nitrogen gas, and hydrazine, and he posited that the latter two products must have emerged from the disproportionation of a putative transient diazine species **1.2** (Scheme 1.1).[10] A couple of decades later, Raschig posited that **1.2** is produced as a transient intermediate in the cleavage of benzenesulfonyl hydrazide **1.5** in hot alkali, a species that further decomposes into dinitrogen and hydrogen gas (Scheme 1.1).[11]

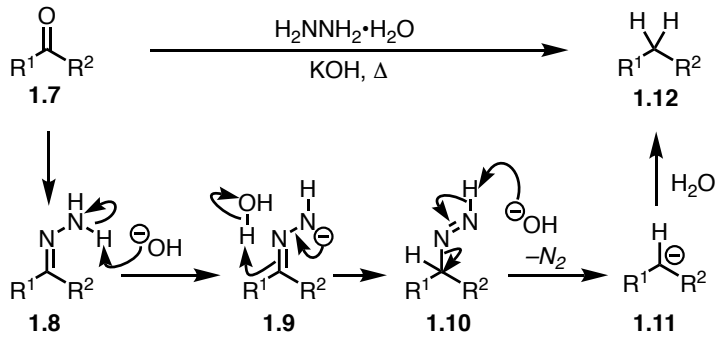


Scheme 1.1 Early propositions of putative diazine intermediates

Neither of these examples could conclusively prove the existence of diazine, and it was not until the 1960s that concrete evidence was presented for its formation.[12] Eckhardt and Hünig discovered that the Wolff-Kishner reduction of long chain ω-unsaturated ketocarboxylic acids would result in the concomitant hydrogenation of the double bond, but this side reaction did not occur in the absence of molecular oxygen, indicating that the hydrogenation of the double bond is performed by a dehydrogenated variant of hydrazine.[13] These findings were independently confirmed by Corey,[14] van Tamelen[15] and Aylward.[16] In the intervening years since these important studies, diazine has found widespread use as a mild reducing agent for a wide variety of substrates, including alkenes, alkynes, allenes, and carbonyl compounds.[17]

1.2 History of Monoalkyldiazines

The chemical reactivity of free diazine was long suspected before being systematically validated in the early 1960s, and much of the same can be said for monoalkyldiazines. Their existence has been surmised as early as 1895, and especially in the 1910s, during the independent discovery of the hydrazine-based carbonyl deletion reaction by Kishner[3a] and Wolff.[3b] The kinetics of this important reaction were arguably not decisively established for another 40 years by Szmant and coworkers,[18] though other mechanistic proposals were advanced earlier. The Wolff-Kishner reaction is now understood to proceed by the following mechanism (Scheme 1.2).[18-19]



Scheme 1.2 The Wolff-Kishner reduction

Under strongly alkaline conditions, the hydrazone **1.8** decomposes to form the monoalkyldiazine **1.10**. This intermediate extrudes dinitrogen via the polar pathway to generate carbanion **1.11**, which is then protonated to afford the deoxygenated product **1.12**. Although monoalkyldiazines are known to fragment via a polar pathway under alkaline conditions to form reactive carbanions,[20] other nonpolar decomposition pathways are possible, and they are summarized in Figure 1.1.

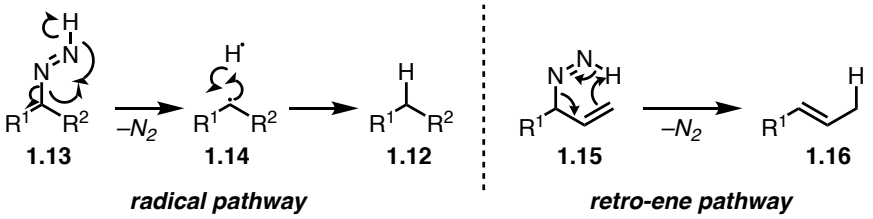
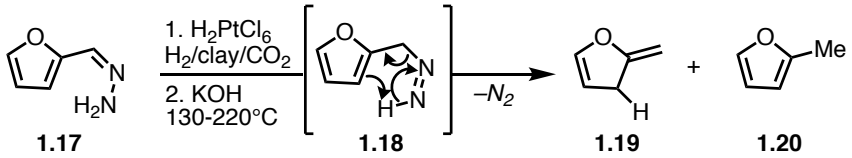


Figure 1.1. Nonpolar decomposition pathways of monoalkyldiazines

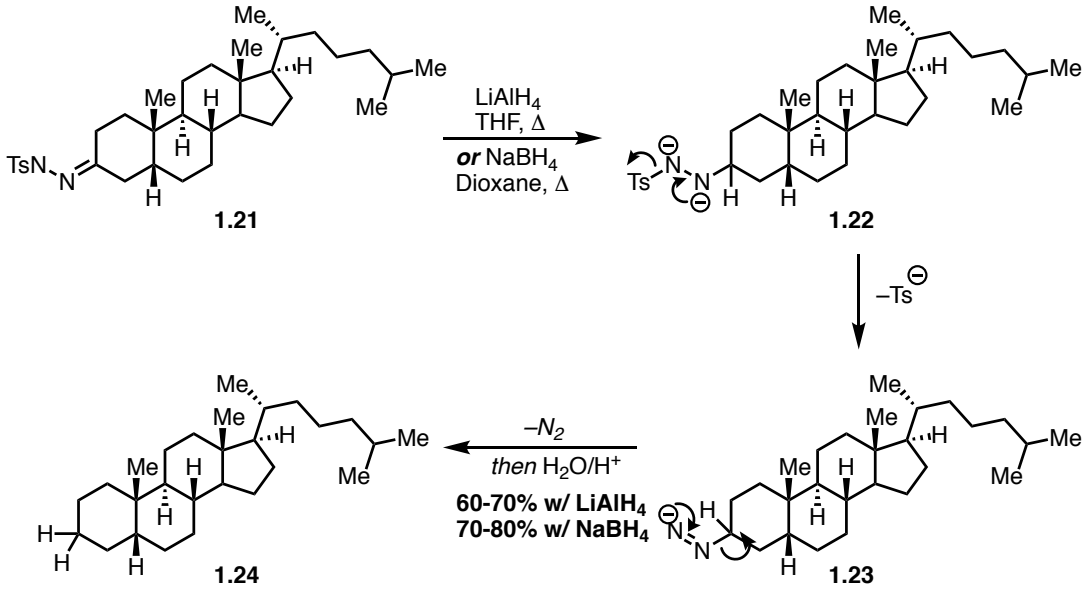
The pioneering work to elucidate the radical decomposition pathway of monoalkyldiazines was accomplished by Kosower and coworkers,[21] who were inspired by the earlier work of Cram.[22] They isolated and characterized a number of stable monoalkyldiazine derivatives, and determined that both aromatic and saturated alkyl diazines extrude dinitrogen via a bimolecular radical pathway to generate the reduction products. These decompositions occur rapidly and under mild conditions.[23] On the other hand, the first known instance of the retro-ene decomposition of monoalkyldiazines was reported in 1931 by Kishner in his attempted deoxygenation of furfural.[24] Subjecting 2-furyl hydrazone **1.17** first to platinized clay, then to Kishner's strong alkaline conditions, resulted in the formation of 2-methylene-2,3-dihydrofuran **1.19** as the major product, presumably via the retro-ene decomposition of 2-furyldiazine **1.18** (Scheme 1.3). This reaction mode is known as the allylic diazine rearrangement (ADR), or more colloquially the "alkene walk."[25] Over the course of many decades that ensued, the induction of the ADR has been realized under increasingly mild conditions, for a wide variety of transformations.[26] It will be further discussed in Section 1.5.



Scheme 1.3. ADR reaction of 2-furyl hydrazone

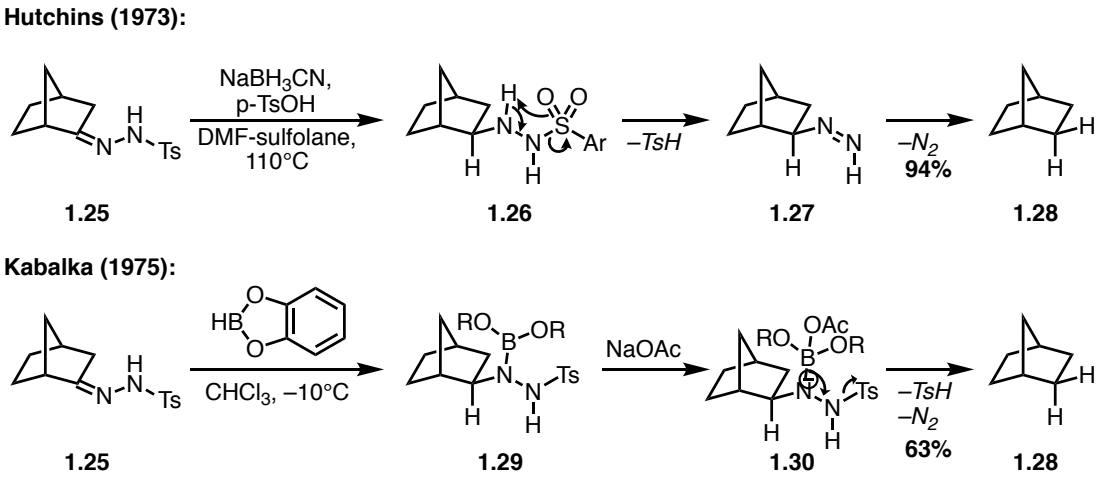
1.3 Anionic Decomposition: Reactions of Tosylhydrazones

The Wolff-Kishner reaction for the deoxygenation of aldehydes and ketones necessitates harsh alkaline and pyrolysis conditions, rendering it unsuitable for base-sensitive substrates, and especially molecules containing α-stereogenic centers to the carbonyls. As a result, milder conditions were continuously sought to effect this important transformation. An important breakthrough was achieved when Magi and Caglioti reported the complete reduction of aldehydes and ketones to their parent alkanes via the lithium aluminum hydride ($LiAlH_4$) reduction of the corresponding tosylhydrazones.[27] Caglioti later developed even milder conditions for the reduction of tosylhydrazones, utilizing the more functional group-tolerant $NaBH_4$.[28] The tosylhydrazones of coprostan-3-one **1.21** was easily reduced to coprostane **1.24** under both reaction conditions (Scheme 1.4). These advances increased the operational simplicity and specificity of the reaction by precluding the *in situ* generation of the free hydrazone, which could easily form unproductive azines.



Scheme 1.4 Caglioti's hydride-based reductions of tosylhydrazones

Once the hydride-based reduction of tosylhydrazones was established as a viable method to perform carbonyl deletion reactions, continued research yielded reaction conditions that were tolerant of a wider scope of substrates. In the 1970s, Hutchins,[29] then Kabalka[30] reported highly-yielding tosylhydrazone reduction protocols that made use of the weak reducing agents sodium cyanoborohydride ($NaBH_3CN$) and catechol borane, respectively (Scheme 1.5).

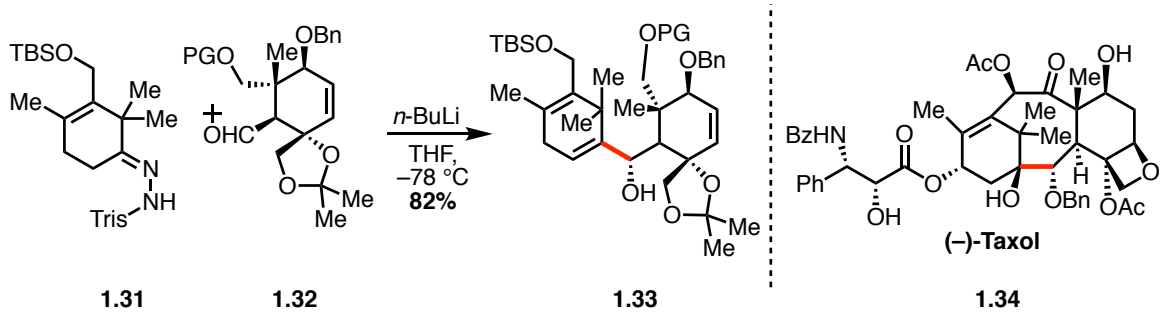


Scheme 1.5 Mild hydride-based reductions of tosylhydrazones

Hutchins reduced 2-norbornanone-derived tosylhydrazone **1.25** using $NaBH_3CN$ to furnish intermediate **1.26**, which eliminates *p*-toluenesulfinic acid to generate the unstable monoalkyldiazine **1.27** that immediately extrudes dinitrogen via the radical pathway to generate afford alkane **1.28** in 94% yield. In Kabalka's system, **1.25** is reduced by catechol borane at subzero temperatures to generate the organoborane addition adduct **1.29**. Complexation of the acetate anion generates "–ate" species **1.30** and induces the elimination of *p*-toluenesulfinic acid to generate monoalkyldiazine **1.27** and eventually **1.28** after loss of N_2. In both of these publications, the authors reported that substrates containing an α,δ-unsaturated ketone underwent the reduction smoothly, albeit with concomitant alkene migration, a phenomenon that will be further discussed in Section 1.5.

1.4 Traceless Fragment-coupling Reactions of Tosylhydrazones

The previous section showcased the ability of tosylhydrazones to undergo smooth reactions upon treatment with hydride nucleophiles to generate monoalkyldiazines that decompose either via the anionic or radical pathway, in a process that forms two new carbon-hydrogen bonds. The full synthetic potential of this nucleophilic addition would not be realized unless carbon-carbon bonds were capable of being formed through this process. The addition of two equivalents of organolithium reagents to tosylhydrazones with acidic protons at the α-position generally result in the Shapiro olefination,[31] a highly important reaction that produces, after anionic extrusion of dinitrogen, an intermediate vinyl lithium that can be further engaged in a variety of fragment-coupling reactions.[6,32] The Shapiro olefination has notably been utilized as a key step in the Nicolaou synthesis of (–)-Taxol (Scheme 1.6), albeit requiring a 2,4,6-triisopropylbenzenesulfonyl hydrazone.[33]

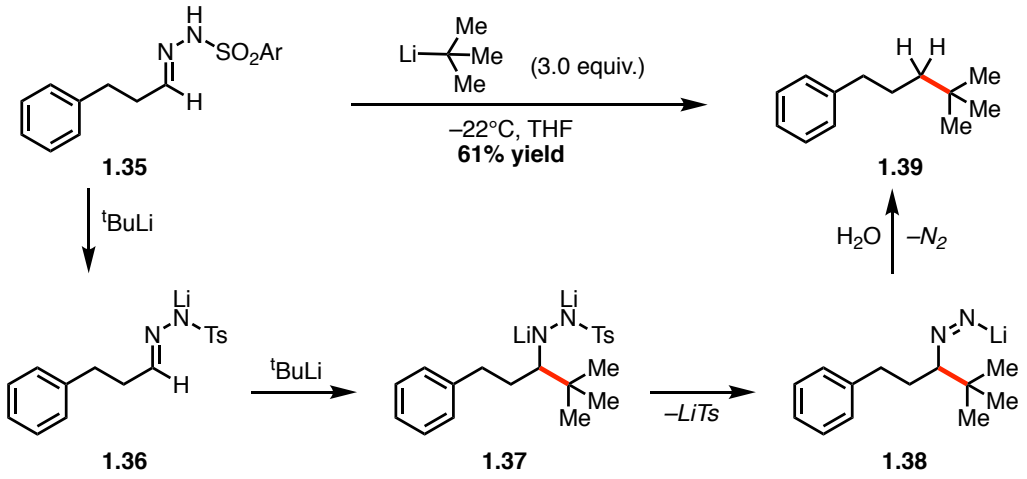


1.31 **1.32** **1.33** **1.34**

Scheme 1.6 Shapiro olefination in Nicolaou's synthesis of (–)-Taxol

The first example of a reliable reductive alkylation of aldehyde-derived tosylhydrazones with organolithium reagents to form a new Csp^3–Csp^3 bond was reported by Vedejs and Stolle in 1977,[34] albeit with low to moderate yields. The corresponding Shapiro olefination was not possible in these substrates, due to the lack of formation of a dianion prior to the alkylation of the monoanionic hydrazone. Unfortunately, the main decomposition pathway, which involves the

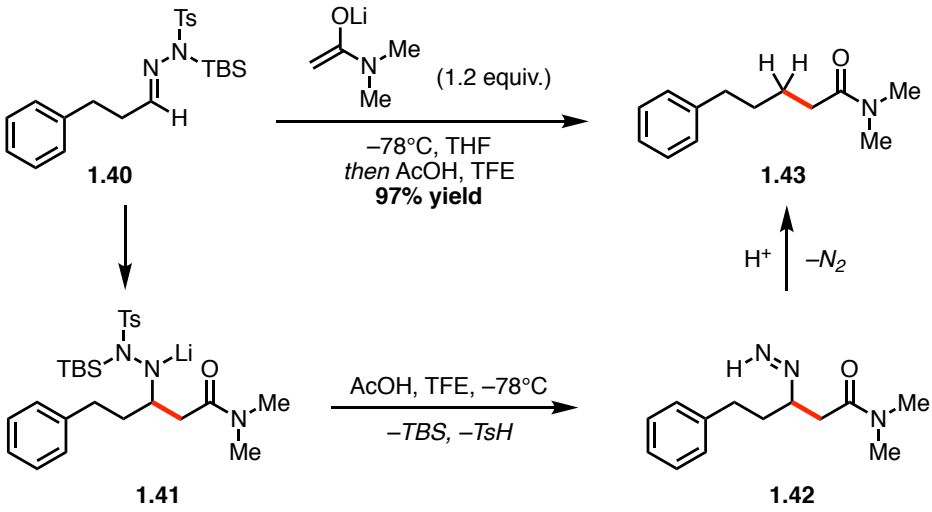
base-induced transformation of the monoanionic tosylhydrazone into a nitrile and the lithium salt of *p*-toluenesulfonamide, could not be completely suppressed. Nevertheless, this reaction permitted the reductive alkylation of the three isomeric forms of butyllithium, with only the temperature profile of the reaction being changed across the disparate nucleophiles. An example is illustrated in Scheme 1.7. Vedejs was later able make this new reaction mode amenable to olefin synthesis, by utilizing an organolithium reagent equipped with a labile stabilizing group for the anion, which could be eliminated as a leaving group during the anionic extrusion of dinitrogen to produce an alkene.[35]



Scheme 1.7 Reductive alkylation of aldehyde-derived tosylhydrazones

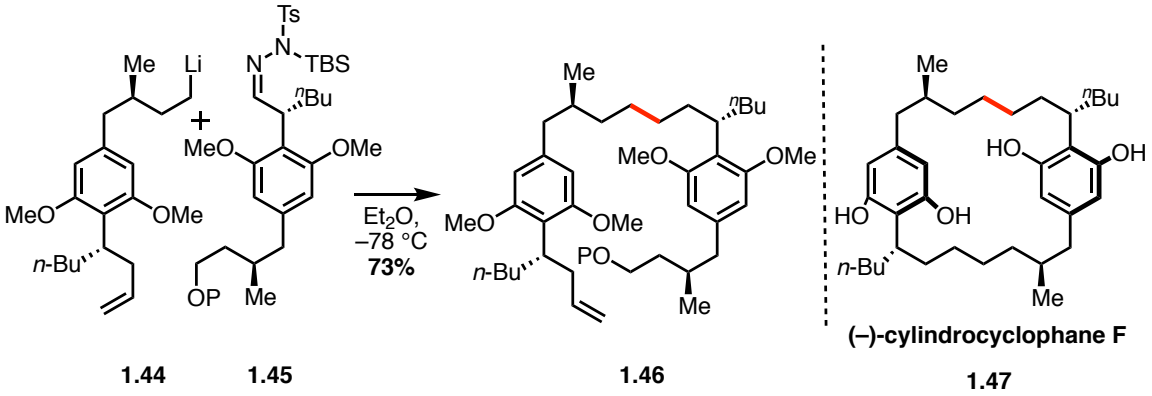
Myers and coworkers sought to remediate the problematic side reaction identified in Vedejs' reductive alkylation protocol, which arises during the decomposition of the monolithiated tosylhydrazone. They found in an earlier study that aldehyde tosylhydrazones can be quantitatively N-TBS-silylated, and the resulting derivatives can readily undergo 1,2-addition of vinyllithium reagents.[36] Myers and Movassaghi showed that the same N-*tert*-butyldimethylsilyl aldehyde tosylhydrazones akin to **1.40** react with 1.2 equivalents of sp^3-hybrided alkyllithium reagents at –78°C, producing stable intermediate addition adducts like **1.41** that only reveal the

unstable monoalkyldiazine **1.42** upon treatment with acetic acid in TFE (Scheme 1.8).[37] Dinitrogen is expelled under radical conditions to generate the final product **1.43**.



Scheme 1.8 Improved reductive alkylation of aldehyde tosylhydrazones

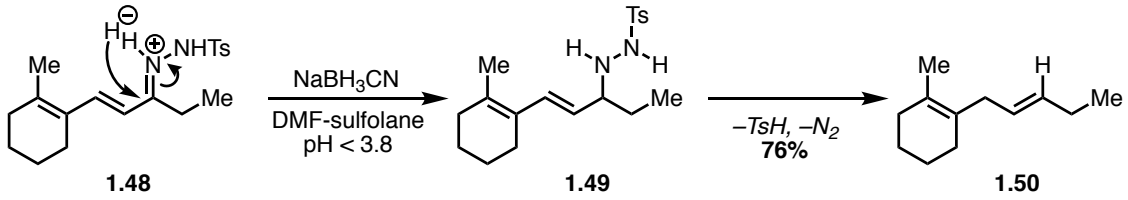
The afore-mentioned reductive alkylation reactions of aldehyde tosylhydrazones are representative examples of very powerful traceless reactions,[38] wherein the afforded products with the new C–C σ-bonds do not contain any trace of the tosylhydrazone functionality that permitted their formation.[39] As such, they can feature unifications of complex fragments that do not have obvious retrons,[9] thereby enabling highly convergent yet versatile syntheses of natural products. The reductive alkylation conditions developed by Myers have been elegantly employed in the key convergent fragment-coupling step in the synthesis of (–)-cylindrocyclophane F **1.47** by Smith and coworkers (Scheme 1.9).[40] Alkyllitihum reagent **1.44** adds into N-silylated aldehyde-derived tosylhydrazone **1.45** to produce an addition adduct that then forms the corresponding monoalkyldiazine upon treatment with AcOH and TFE at –78°C. Nitrogen is then extruded under radical conditions to generate product **1.46**, a fully aliphatic system that does not present obvious disconnections in a retrosynthetic sense.



Scheme 1.9 Reductive coupling step in the total synthesis of (–)-cylindrocyclophane F

1.5 Reduction of α,β-Unsaturated Tosylhydrazones

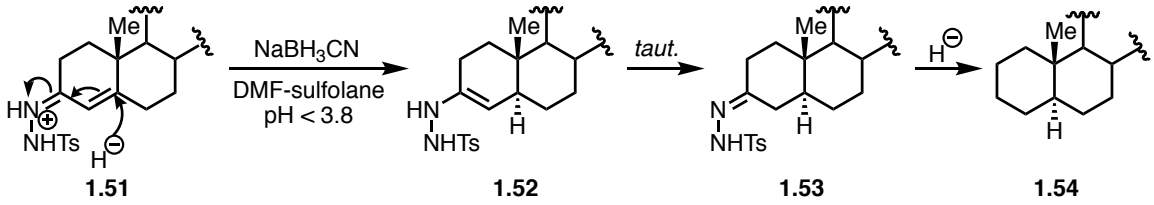
Both Hutchins[29] and Kabalka,[30] in their seminal publications describing mild hydride reducing agents for carbonyl deletions, related that the reduction of α,β-unsaturated tosylhydrazones under their respective reaction conditions resulted in complete removal of the hydrazone functionality and simultaneous migration of the double bond. Hutchins reported several examples of that unexpected phenomenon. In their follow up work to validate these observations, Hutchins and coworkers described general and high yielding conditions for the $NaBH_3CN$ reduction of unsaturated tosylhydrazones, all of them resulting in double bond migration (Scheme 1.10).[41] Treatment of α,β-unsaturated tosylhydrazone **1.48** results in the formation of addition adduct **1.49** that loses sulfinic acid to generate the corresponding monoalkyldiazine, which Hutchins averred to "transfer its hydrogen to the β-carbon with concomitant π-bond migration via a 1,5-sigmatropic rearrangement" to afford product **1.50**, wherein the olefin and the added hydride occupy the position previously occupied by the hydrazone. Kabalka also extended the scope of his even milder and operationally simple methodology to effect the same transformation.[42] The reductive transposition of olefins, having now been firmly established, was dubbed the "alkene walk."[25]



1.48 **1.49** **1.50**

Scheme 1.10 Reduction of α,β-unsaturated tosylhydrazones

Questions lingered as to its true mechanism. Djerassi and coworkers in 1976 accomplished extensive deuterium labeling studies to confirm Hutchins' mechanistic hypotheses that the reductive transposition occurs in three phases: i) the 1,2-reduction of the tosylhydrazone, ii) formation of the monoalkyldiazine intermediate by loss of sulfinic acid, and iii) retro-ene rearrangement.[43] Moreover, they found that this particular mechanism is not always general, and in sterically congested substrates, the hydride performs a conjugate reduction in the first step, instead producing to a fully saturated alkane rather than a transposed alkene (Scheme 1.11).



1.51 **1.52** **1.53** **1.54**

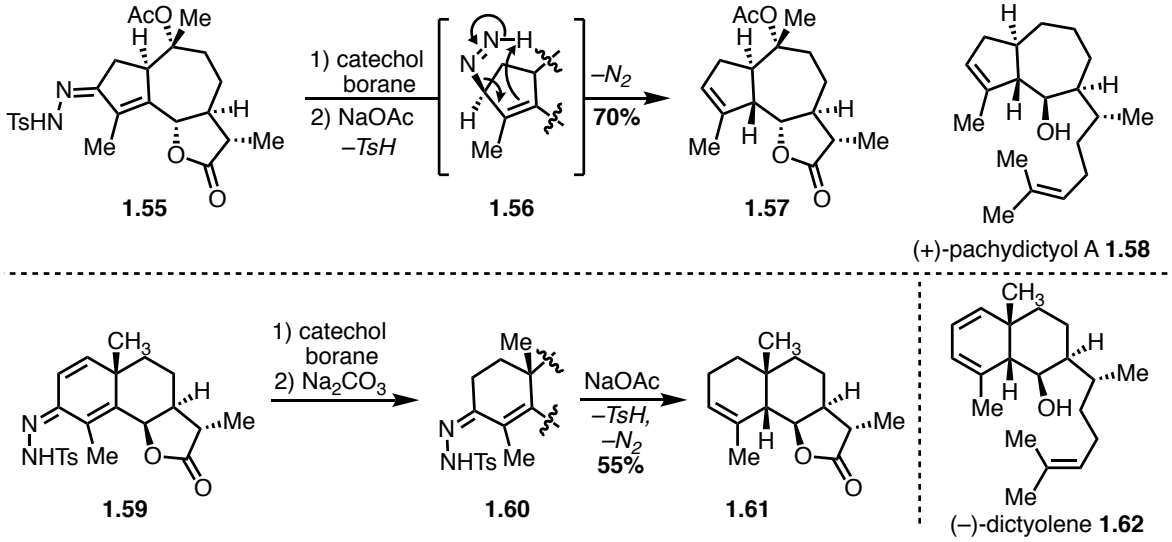
Scheme 1.11 Reduction of sterically congested α,β-unsaturated tosylhydrazones

The tosylhydrazone derived from 5α-cholest-1-en-3-one **1.51** is reduced by the hydride in a conjugate addition to produce intermediate **1.52**, which tautomerizes to the saturated tosylhydrazone **1.53**, the further reduction of which results in an alkane as previously noted.[29] Liu and coworkers later corroborated Djerassi's results and mechanistic proposals.[44] For all systems that proceed with an initial 1,2-reduction of the hydrazone moiety, the alkene walk proceeds through a retro-ene rearrangement, which Houk later validated with computational studies.[45]

1.6 Synthetic Applications of the Reduction of α,β-Unsaturated Tosylhydrazones

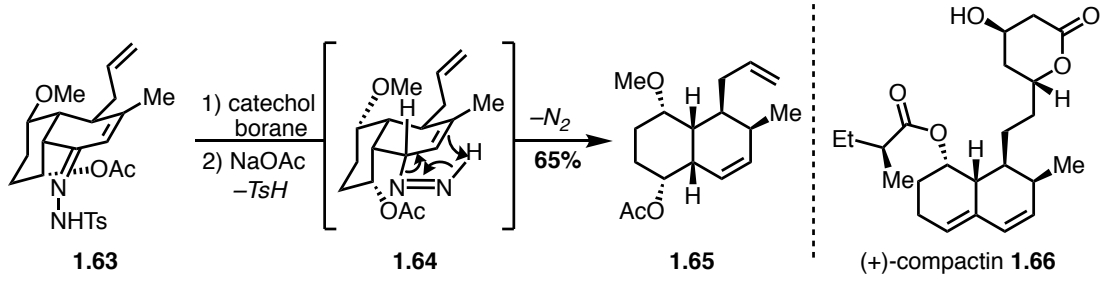
The allylic diazine rearrangement of olefins induced by hydride reduction of α,β-unsaturated tosylhydrazones, since the pioneering fundamental science of the 1970s,[25,41-42] has become a reliable and oft-used reaction to carry out a number of useful transformations in the context of complex molecule synthesis.[46] Kabalka's catechol borane-based procedure has especially endured, a testament to its wide functional group tolerance and operational simplicity. Some of the more compelling examples will be highlighted next.

One of the most appealing advantages offered by the allylic diazine rearrangement is its ability to form new stereogenic centers within complex cyclic systems, the standard retron[9] being a double bond with an α-stereogenic center. Greene featured this rearrangement as a key step in his stereocontrolled synthesis of marine diterpenes (+)-pachydictyol A **1.58** and (–)-dictyolene **1.62** (Scheme 1.12).[46a] The tosylhydrazone derived from O-acetylisophotosantonic lactone **1.55** was subjected to Kabalka reduction conditions, with the hydride being delivered from the more hindered side of the molecule to diastereoselectively generate monoalkyldiazine **1.56**, from which the retro-ene decomposition results in formation with 70% yield of the *trans* ring juncture in product **1.57**, an advanced intermediate toward (+)-pachydictyol **1.58**. The reduction of cross-conjugated tosylhydrazone **1.59** occurred in two stages, an outcome that was validated by judicious control experiments. The first equivalent of catechol borane results in the net reduction of the disubstituted olefin to produce **1.60** after basic workup of the borane intermediate. The second equivalent of the reducing agent, after addition of NaOAc, engenders the alkene walk to produce **1.61** in 55% yield as a single diastereomer.



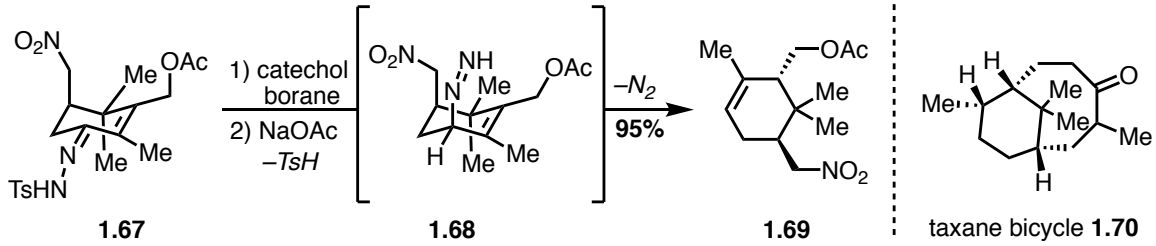
Scheme 1.12 Alkene walk reaction in Greene's syntheses of marine diterpenes

Wendler later parlayed these promising results to a new system to great effect.[46c] In his enantioselective formal synthesis of hypolipidemic agent (+)-compactin **1.66**, he performs the Kabalka reduction of enantioenriched *cis*-decalin tosylhydrazone **1.63**, which proceeds with complete stereoselectivity from the *exo*-face of the molecule due to the steric hindrance provided by the pendant acetate group (Scheme 1.13). The intermediate *endo*-monoalkyldiazine **1.64** then delivers the hydrogen to the β-carbon from the bottom face of the molecule, resulting in completely selective formation of the new methyl stereogenic center in **1.65** in 65% overall yield. The stereochemical bias of the starting material was adequately utilized to install a new stereogenic center.



Scheme 1.13 Alkene walk reaction in Wendler's formal synthesis of (+)-compactin

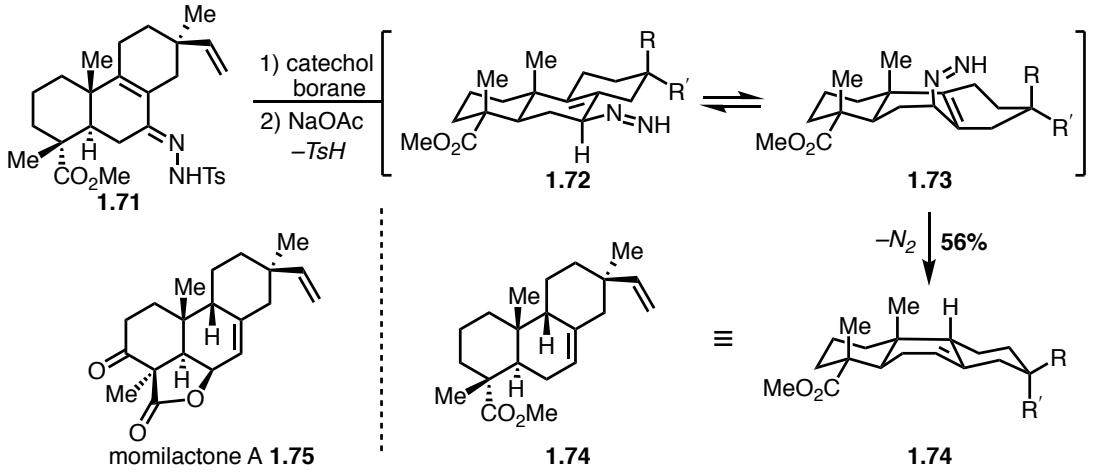
Oishi later took advantage of this precedent and applied it to the generation of cyclohexene derivatives that could easily be elaborated into the bicyclic core of taxane natural products.[46f] The Kabalka reduction of unsaturated tosylhydrazone **1.67** results in equatorial hydride delivery across the less hindered α-side of the molecule, which does not feature an axially substituted nitro group (Scheme 1.14). The resulting monoalkyldiazine **1.68** then delivers the hydrogen across the top face of the molecule, leading to the completely diastereoselective formation of *trans* cyclohexene **1.69** in 95% yield, a product that can be easily elaborated into taxane bicyclic systems like **1.70**.



Scheme 1.14 Alkene walk reaction in Oishi's synthesis of the taxane core

A powerful illustration of the ADR's broad applicability to the generation of stereogenic centers within ring junctures of complex polycyclic molecules is Coates' synthesis of 9,10-*syn*-diterpenes.[46h] Coates targeted the compound (9*β*)-pimara-7,15-diene, a putative intermediate in the biosynthesis of momilactone phytoalexins such as momilactone A **1.76** (Scheme 1.15). α,β-unsaturated tosylhydrazone **1.71** was therefore subjected to the Kabalka reduction, resulting in the initial axial delivery of the hydride, followed by boro-sulfinate elimination to generate equitorial monoalkyldiazine **1.72**. As this conformation was not conducive to a retro-ene decomposition of the diazine, structural inversion of the B ring to half-boat configuration **1.73** was necessary for the proper orbital overlap. The allylic diazine rearrangement then resulted in the diastereoselective formation of product **1.74** in 56% overall yield, and completely precluded the formation of the thermodynamically more favored 9,10-*anti* diastereomer that would have

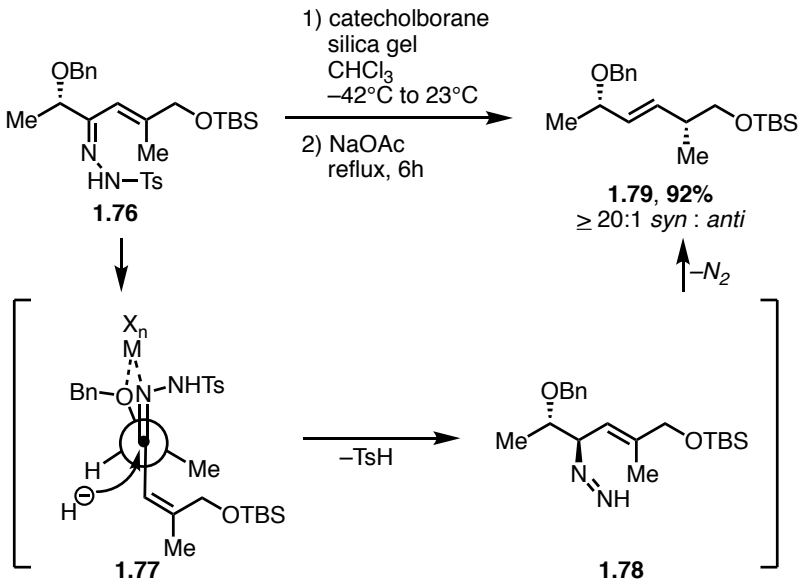
been produced through the standard conjugate reduction of the parent enone of **1.71**. This reaction also remarkably overcame the unfavorable *syn*-pentane interactions between the axial monoalkyldiazine and the methyl group in conformer **1.73**.



Scheme 1.15 Alkene walk reaction in Coates' partial synthesis of 9,10-*syn*-diterpenes

The above examples illustrate the extensive utility of the allylic diazine rearrangement in the generation of stereogenic centers within cyclic systems, and such reports became par for the course in the 1980s and 1990s (see ref. 46). The work of McIntosh and coworkers in the 2000s therefore represented a major advancement in this reaction, as it allowed the formation of sp^3 stereogenic centers within acyclic systems for the first time.[46t] They hypothesized that a prochiral α,β-unsaturated tosylhydrazone containing an α-alkoxy stereocenter could engage in a Cram chelation-controlled reduction of the hydrazone imine and perform a allylic diazine rearrangement that would produce a new stereogenic center and a 1,4-*syn* stereodiad. They identified modified Kabalka reduction conditions that diastereoselectively reduced hydrazone **1.76** via the chelate-controlled hydride transfer illustrated by **1.77** to generate monoalkyldiazine **1.78**. Suprafacial ADR generated product **1.79** in 92% yield as a single diastereomer and geometric isomer (Scheme 1.16). Subjection of the *Z*-isomer of **1.76** to the identical reaction

conditions produced the 1,4-*anti* diastereomer of **1.79** with equally impressive stereocontrol and efficiency. McIntosh and coworkers quickly realized the synthetic potential of this useful transformation by employing it towards the synthesis of complex immunosuppressant polyketide (–)-antascomicin B.[46s,46v]

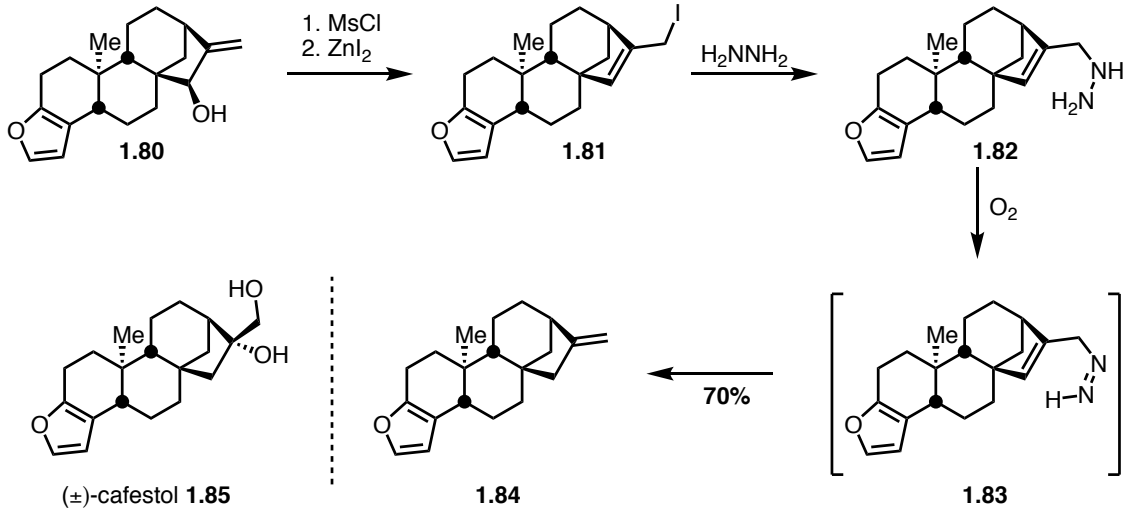


Scheme 1.16 Acyclic 1,4-stereocontrol via reductive 1,3-transpositions

1.7 Alternative Generation of Monoalkyldiazines

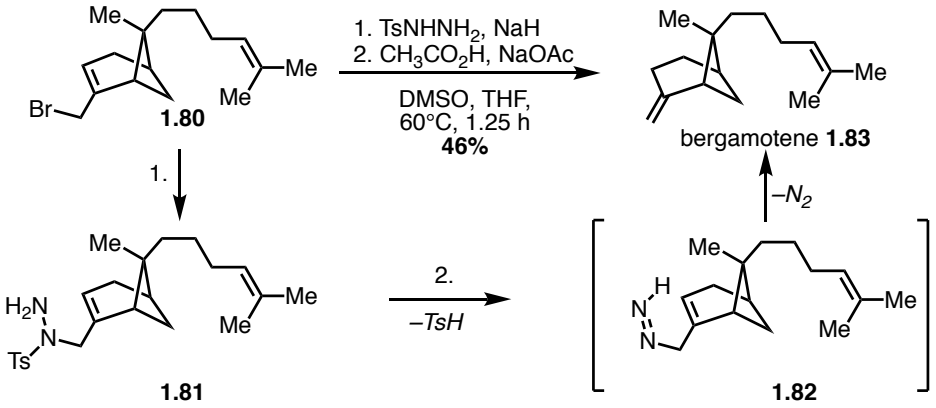
The previous section delineated a plethora of examples wherein allylic diazine rearrangement was induced by the mild reduction of α,β-unsaturated hydrazones. Although it has experienced widespread use in the 1980s and 1990s, there were other reports that showcased alternative methods of generating allylic monoalkyldiazines, whether by direct oxidation of allylic hydrazines,[47] by nucleophilic substitutions with arylsulfonyl hydrazides and subsequent elimination of the corresponding arylsulfinic acid,[48] or through by methods.[49] Some elegant syntheses of complex molecules enabled by alternatively induced ADR transformations will be highlighted next.

A capital example of a natural product synthesis featuring the ADR as a key step that avoided the use of reducing agents was the total synthesis of (±)-cafestol by EJ Corey.[47a] Scheme 1.17 illustrates a sequence of reactions that ostensibly serve as a formal deoxygenation of allylic alcohol **1.80**. Formation of the mesylate, followed by nucleophilic conjugate substitution with a stoichiometric amount of ZnI_2 produced allylic iodide **1.81**, which was then displaced with anhydrous hydrazine to form hydrazide **1.82**. Atmospheric oxidation produced monoalkyldiazine **1.83**, whose retro-ene rearrangement afforded the alkene **1.84** in 70% overall yield, an advanced intermediate towards (±)-cafestol **1.85**.



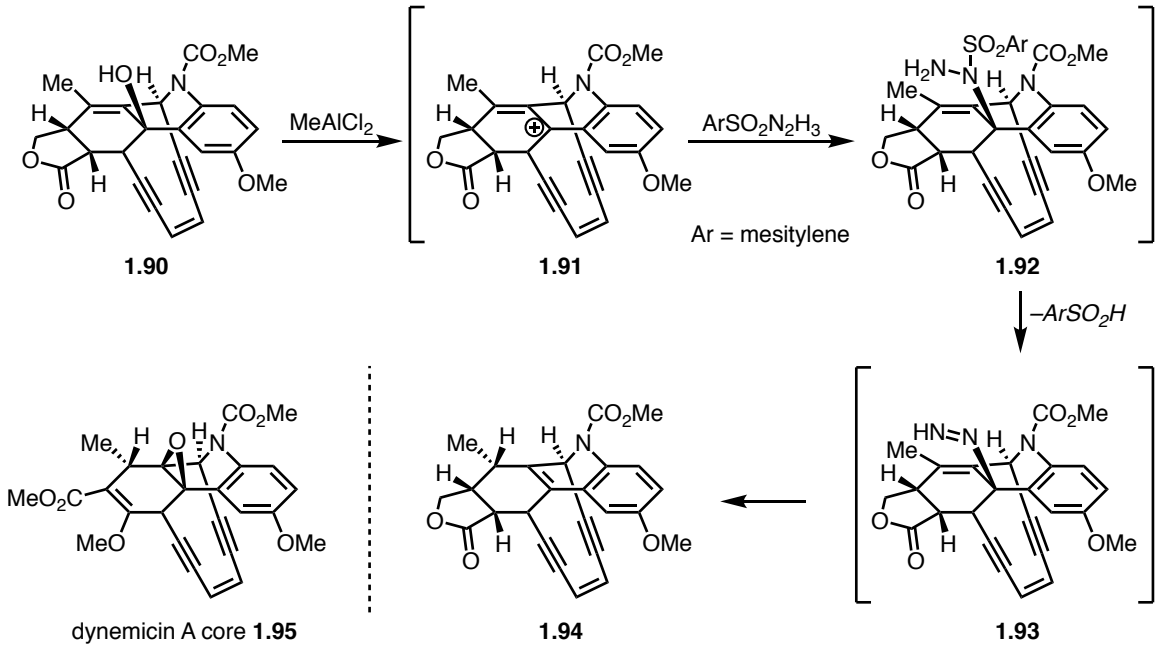
Scheme 1.17 ADR in Corey's synthesis of (±)-cafestol

One of the first known example of the allylic diazine rearrangement being utilized in the context of natural product synthesis was during Corey's synthesis of bergamotene, in which it was conducted as the final step in the synthetic strategy (Scheme 1.18).[48a] The allylic bromide **1.80** derived from the corresponding allylic alcohol was first displaced with the sodium salt of tosylhydrazine to generate hydrazide **1.82**. Upon treatment with acetic acid (buffered by a small amount of sodium acetate), *p*-toluenesulfinic acid was eliminated to generate monoalkyldiazine **1.82**, which decomposed to afford bergamotene **1.83** in 46% overall yield.



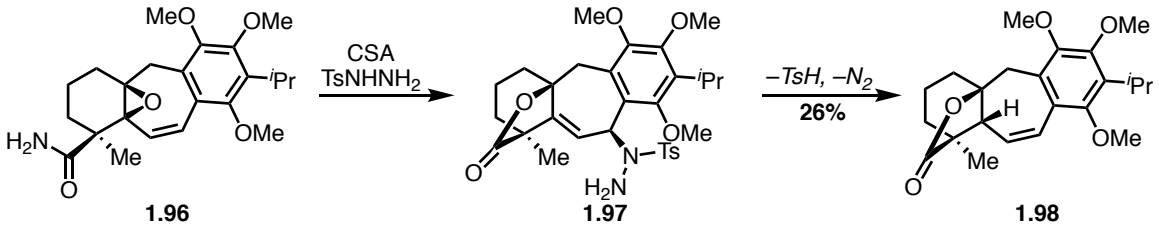
Scheme 1.18 ADR in Corey's synthesis of bergamotene

Several other natural product syntheses featured a similar nucleophilic displacement of a good leaving group to generate allylic hydrazides such as **1.81**. For instance, Schreiber and coworkers accomplished the Lewis-acid promoted formation of allylic hydrazide **1.92** during their synthesis of the dynemacin A core in 1992 (Scheme 1.19).[48b] In their previous attempt[50] towards the synthesis of this molecule, they established that the application of a ceric ammonium nitrate oxidation, followed by $EtAlCl_2/Et_3SiH$ reduction sequence to the deoxygenated analog of alcohol **1.90** led to a transposed olefin, but installed the incorrect methyl stereochemistry. In their subsequent studies, they therefore turned to the ADR as an alternative method of conducting the olefin transposition and simultaneously forming the methyl stereogenic center. They eventually determined that allylic alcohol **1.90** could be effectively ionized by treatment with $MeAlCl_2$ to form benzylic carbocation **1.91**, which is trapped with mesitylenesulfonylhydrazide to form allylic hydrazide **1.92**. Formation of the monoalkyldiazine **1.93** and stereospecific retro-ene rearrangement resulted in product **1.94**, with the transposed olefin and the correct methyl stereochemistry.



Scheme 1.19 ADR in Schreiber's synthesis of the dynemicin A core

In 2010, Sarpong and Cortez reported the use of a late-stage ADR to furnish advanced intermediate **1.98** towards the formal synthesis of icetexane diterpenoid icetexone (Scheme 1.20).[48d] Epoxide **1.96**, upon treatment with CSA, opened to reveal the corresponding allylic carbocation, and the resulting hydroxyl moiety performed a lactonization reaction with the pendant amide to form the tricyclic lactone.

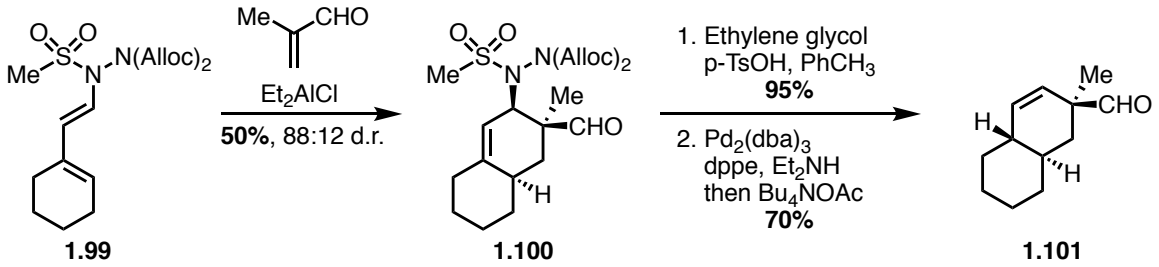


Scheme 1.20 Late stage ADR in Sarpong's formal synthesis of icetexone

Nucleophilic conjugate addition of tosylhydrazine from the convex face of the rigid bicycle formed intermediate **1.97**, which, upon loss of sulfinic acid and diazine rearrangement, formed lactone **1.98** as the major product in >10 : 1 d.r. It is interesting to note that in the cascade

reaction illustrated in Scheme **1.20**, the net result was a stereoretentive opening of an epoxide with a hydride, and subsequent lactonization of the resulting hydroxyl group. The double bond is transposed twice between **1.96** and **1.98** and therefore resumed its incipient position within the molecule. There are no complementary reactions that could achieve a similar stereochemical outcome. This is a remarkable illustration of the synthetic utility of the allylic diazine rearrangement in complex molecule synthesis, especially if the diazine moiety is introduced in a nucleophilic displacement reaction.

Another elegant, non-traditional induction of the ADR was accomplished by Sorensen and coworkers in 2005.[51] They synthesized a series of 1-hydrazinodienes akin to **1.99** that could be engaged in Lewis acid-catalyzed, highly diastereoselective Diels-Alder cycloadditions with acrylate derived dienophiles to generate allylic diazine cycloadducts like **1.100**, which in particular was obtained in 50% yield and 88 : 12 d.r. (Scheme 1.21).



Scheme 1.21 Diels-Alder cycloaddition/alkene walk sequence in decalin synthesis

Conversion of the aldehyde to a dioxolane, followed by a one-pot palladium-mediated deprotection of the hydrazine and Bu_4NOAc-promoted desulfonylation/diazine rearrangement cascade afforded *trans*-decalin **1.101** in excellent overall yield and diastereoselectivity. It is important to note that this Diels-Alder cycloaddition/alkene walk sequence is effectively a traceless route for the synthesis of cyclohexenes containing a 1,4-stereochemical relationship.[52] Sorensen significantly expanded the synthetic utility of this reaction sequence by making it

enantioselective through the use of chiral Pybox ligands in a copper-mediated Diels-Alder cycloaddition step.[53] The intriguing possibility remains of imparting chirality to the hydrazine itself and performing a substrate-controlled enantioselective Diels-Alder cycloaddition/alkene walk sequence.

1.8 Generation of Monoalkyldiazines from NBSH

The previous several sections have established *N*-arylsulfonylhydrazones as convenient sources of diazine derivatives, due to their propensity to easily eliminate their corresponding arylsulfinic acids. In fact, this ability was described as early as 1898 by Curtius and Lorenzen, who reported that benzenesulfonylhydrazine undergoes thermal decomposition at elevated temperatures to produce diazine.[54] In 1929, Dann and Davies reported the important synthesis of *o*-nitrobenzenesulfonyl hydrazine (NBSH),[55] whose enhanced electron deficiency—and consequently increased lability—relative to benzenesulfonylhydrazine makes it capable of generating diazine at room temperature.[12] Although this means that NBSH-derived hydrazones would be more convenient sources of monoalkyldiazines than their tosylhydrazone counterparts, the latter would remain more synthetically useful as they would have superior stability, and could more easily be purified and isolated.

The group of Myers, who have nurtured a long-term interest in the synthesis of allenes through a reductive transposition of allylic monoalkyldiazines,[47b,47c] resolved this issue when they reported a general, high-yielding, one-pot synthesis of allenes by a stereospecific transposition of propargyl alcohols (Figure 1.2b).[56] This transformation features innovative elements that represented a significant departure from the established precedent in the ADR: the allylic hydrazide **1.106** is directly generated at low temperatures from propargyl alcohol **1.102** via a Mitsunobu displacement[57] with NBSH[58] as a nucleophile, and the monoalkyldiazine retro-

ene decomposition is easily engendered by simple warming of the reaction mixture to room temperature. The entire transformation was thus carried out as a single operation as opposed to three in the previous iteration (Figure 1.2a),[47b] and as illustrated in Figure 1.2b, the entire sequence to produce **1.105** is stereospecific and results in the successful transposition of the diazine with complete conservation of optical purity. This is an important facet because it allows for the straightforward formation of the highly desired optically active di- or trisubstituted allenes from readily accessed chiral propargylic alcohols.

Myers later extended the scope of the reaction to include both the reductive transposition of allylic alcohols (Figure 1.2c),[56b] and the reductive deoxygenation of unhindered alcohols (Figure 1.2d).[59] In the former reaction, the solvent was changed to N-methylmorpholine (NMM) due to its enhanced ability to solubilize the reactants and to accommodate higher reaction concentrations, thereby increasing the efficiency of the Mitsunobu reaction. This transposition was shown to be highly selective for *E* olefins, and both primary and secondary alcohols were well tolerated. In the latter transformation, aliphatic NBSH hydrazides were produced, and they were unequivocally shown to decompose by first forming the aliphatic monoalkyldiazines, which extrude dinitrogen through the radical pathway.[60] Myers and coworkers shrewdly leveraged this property to their benefit by employing substrates that are prone to rearrangements (**1.113)** or additional carbon-carbon bond forming steps (**1.117)** (Figure 1.2d). The deoxygenation of substrate **1.113** leads to a ring-opening of the epoxide to afford terminal olefin **1.116**, while the deoxygenation of alcohol **1.117** leads to intermediate radical **1.118** that reacts with the remaining olefin in the molecule to produce a new ring within alkane **1.119**.

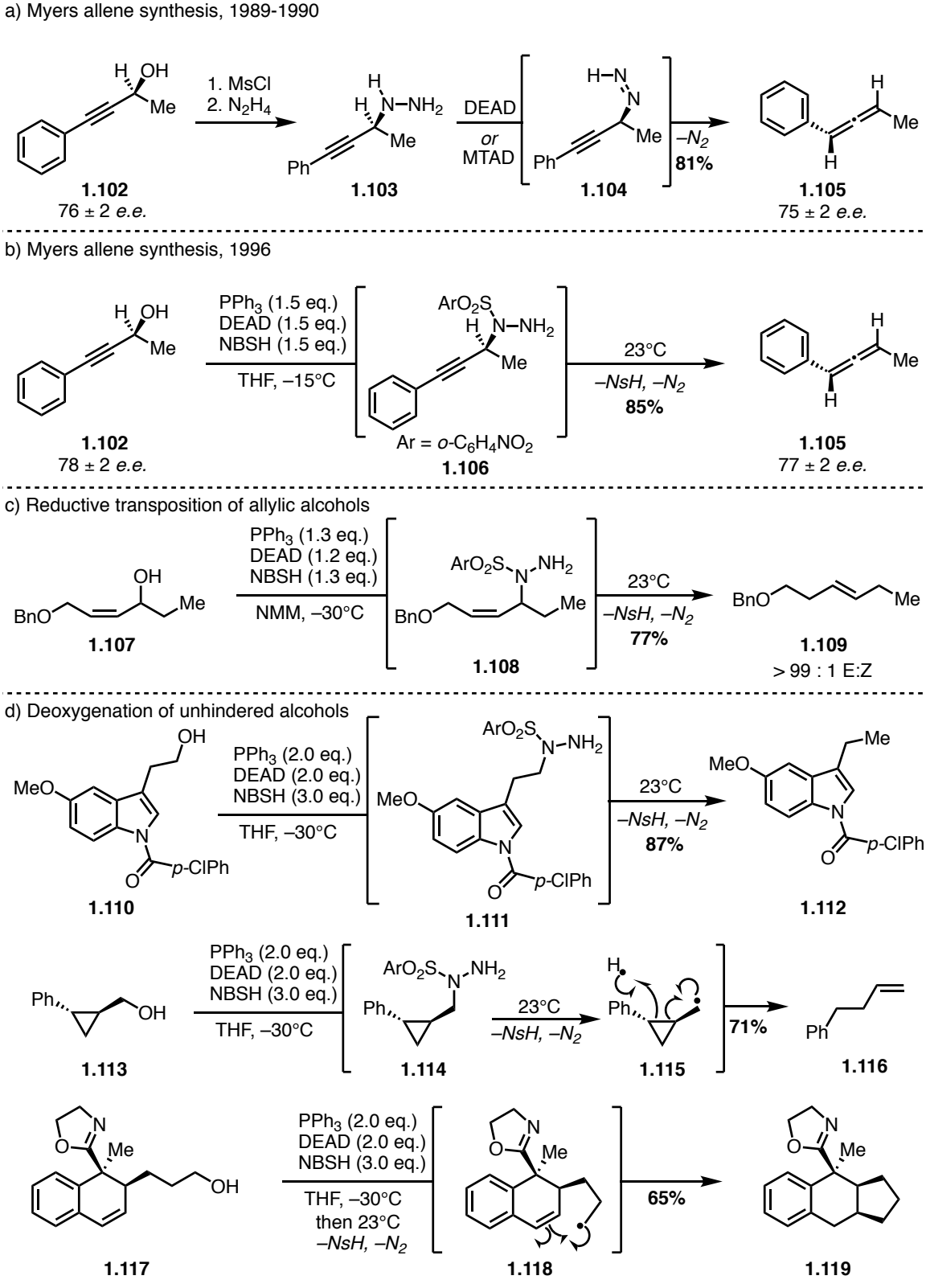
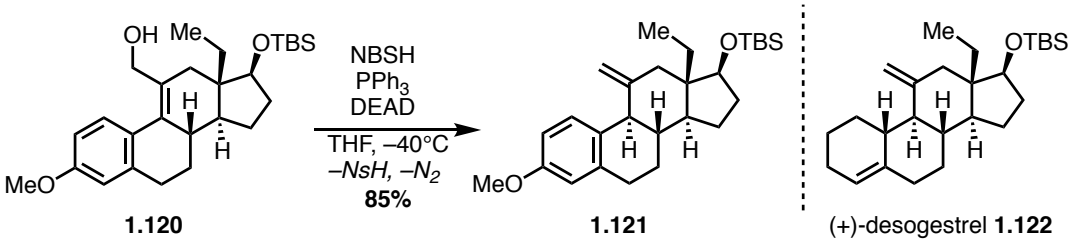


Figure 1.2 Scope of Myers' NBSH-mediated transformations

Since the seminal publication in 1996, the Myers reductive transposition of unsaturated alcohols has undergone widespread utilization in the context of complex molecule synthesis,[61] especially because of its ability to produce optically active allenes from easily obtained chiral propargylic alcohols. Some of the more remarkable applications are highlighted below.



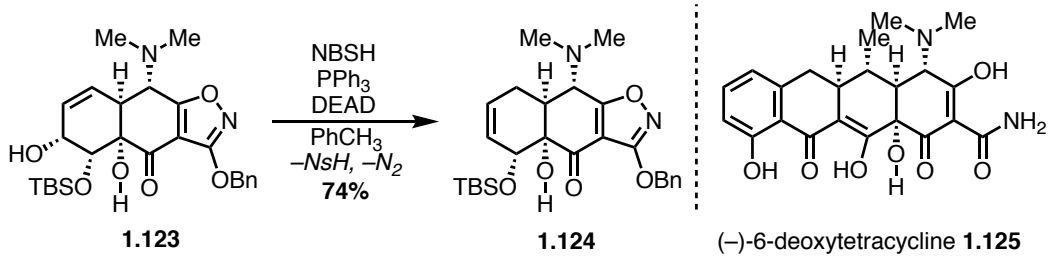
1.120 **1.121** (+)-desogestrel **1.122**

Scheme 1.22 Allylic alcohol transposition in Corey's synthesis of (+)-desogestrel

Corey and coworkers showcased the Myers reductive transposition of allylic alcohols in his enantioselective and concise synthesis of third generation oral contraceptive desogestrel **1.122** (Scheme 1.22).[61c] Previous convergent iterations of this synthesis could not install the correct stereochemistry at the ring juncture while forging the exocyclic olefin, therefore the authors turned to the reductive transposition. Subjection of allylic alcohol **1.120** to a modified version of Myers' protocol smoothly afforded product **1.121** in 85% yield as a single diastereomer, and with the correct stereochemical relationship. The monoalkyldiazine retro-ene decomposition occurred from the bottom face of the molecule in order to avoid developing *syn* pentane interactions with the axial ethyl group. The Myers reductive transposition of allylic alcohols was used to great effect in this concise synthesis of an important pharmaceutical agent.

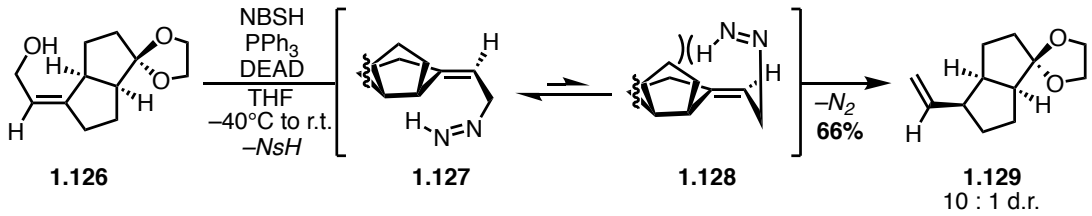
In 2005 Myers and coworkers reported a brief, enantioselective synthetic route to structurally varied 6-deoxytetracycline antibiotics,[61h] which are composed of a synthetically challenging scaffold of four linearly fused rings. Enantiopure allylic alcohol **1.123** served as the common intermediate for all of the targeted 6-deoxytetracycline molecules (Scheme 1.23). Transformation

of **1.123** to cyclohexene **1.124** required migration of the olefin in the B-ring with concomitant deoxygenation of the free hydroxyl group, which was achieved by Myers' NBSH-mediated transformation to generate the product in 74% yield. As a testament to the broad synthetic utility of the reaction, the numerous functional groups within **1.123** were tolerated under the reaction conditions, especially the tertiary hydroxyl at the AB ring juncture, which is unreactive under the Mitsunobu conditions.



Scheme 1.23 Reductive transposition in Myers' synthesis of (–)-6-deoxytetracyclines

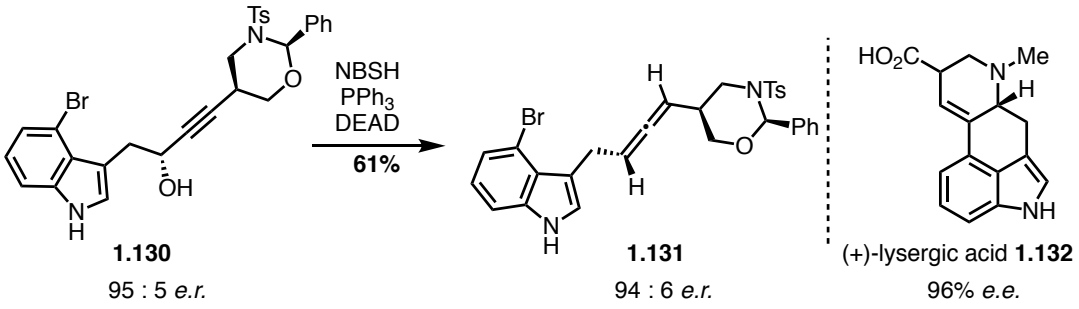
The NBSH-mediated reductive transposition of olefins was prominently featured as a key step in the total syntheses of (+)-echiopine A and B by Tiefenbacher, who attempted to determine the absolute configuration of those natural products.[61u]



Scheme 1.24 Olefin transposition in Tiefenbacher's synthesis of (+)-echiopine A and B

It was therefore important to establish the correct stereochemistry from the reduction of the exocyclic olefin within diquinane **1.126**, and this was achieved by making use of Myers' olefin transposition reaction (Scheme 1.24). The stereochemical outcome of the transformation of the (*Z*)-isomer of **1.126** into **1.129** is rationalized by the development of unfavorable steric

interactions between the monoalkyldiazine and the adjacent cyclopentene ring in conformer **1.127**, which equilibrates to the more stable conformation **1.128**. Retro-ene decomposition of the monoalkyldiazine therefore results in isoprenyl product **1.129** in 66% yield and high diastereoselectivity.

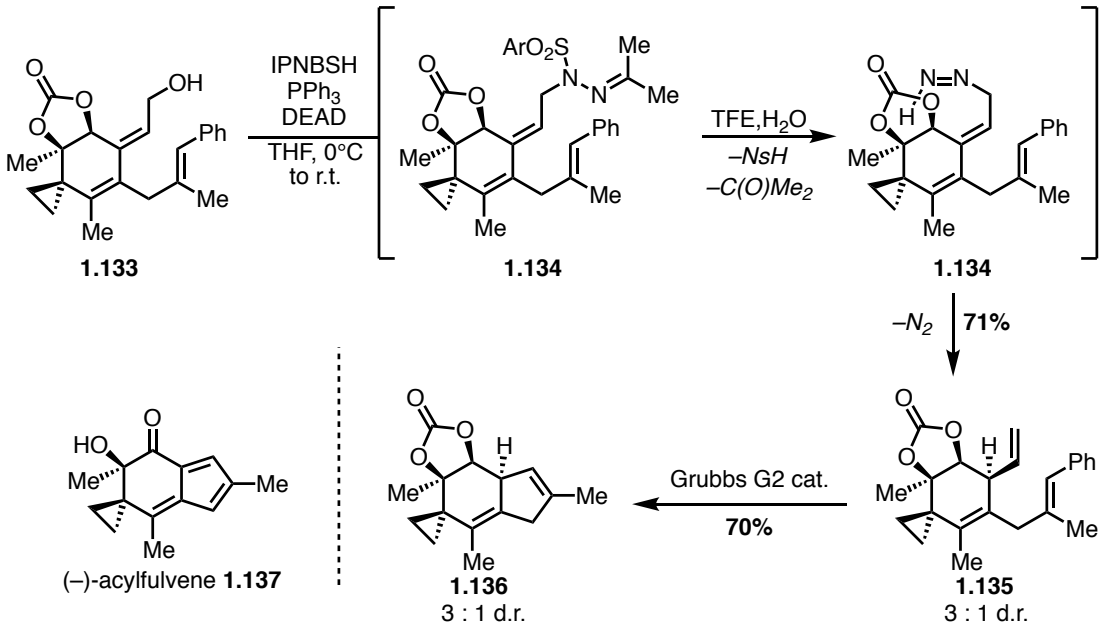


Scheme 1.25 Olefin transposition in Ohno's synthesis of (+)-lysergic acid

Ohno and coworkers reported the enantioselective total synthesis of the ergot alkaloid (+)-lysergic acid **1.132** in 2011,[61x] a synthetic sequence marked by the Pd^0-catalyzed cascade cyclization of an enantioenriched allene bearing bromoindolyl and amino groups. This domino sequence permitted the stereocontrolled construction of the C/D ring system of the natural product, with concurrent formation of a C5-stereogenic center resulting from the transfer of stereochemical information from an axially chiral allene to the centrally chiral ring juncture. In order for this synthetic sequence to be realized, the Myers reductive transposition was utilized to effectively convert enantioenriched propargylic alcohol **1.130** to optically enriched allene **1.131** with near perfect point-to-axial chirality transfer in 61% yield. This report showcased the high synthetic potential of the NSBH-mediated allylic diazine rearrangement, which easily enables the formation of optically enriched allenes that can be engaged in a wide variety of useful transformations to access diverse architectures.

1.9 Generation of Monoalkyldiazines from IPNBSH

The latest significant breakthrough regarding the ADR in organic synthesis is the introduction of the reagent N-isopropylidene-N′-2-nitrobenzenesulfonyl hydrazine (IPNBSH) by Movassaghi as a component in Myers' reductive transposition reaction.[62] The planned reductive transposition of allylic alcohol **1.133** under Myers' original conditions proceeded in unsatisfactory and highly variable yields. The use of the more stable IPNBSH derivative achieved an efficient Mitsunobu reaction to provide hydrazone **1.134**, which, upon exposure to TFE and H_2O, eliminated nosylsulfinic acid and acetone to generate monoalkyldiazine **1.134**, which extrudes dinitrogen to form product **1.135** in 71% yield, with formation of a new stereogenic center in an eventually inconsequential 3 : 1 ratio of diastereomers (Scheme 1.26). Importantly, the use of NBSH allowed for a more efficient and reproducible reaction. **1.135** was quickly elaborated to (–)-acylfulvene **1.137** via olefin metathesis product **1.136**.



Scheme 1.26 IPNBSH-mediated ADR in Movassaghi's synthesis of (–)-acylfulvene

In his follow up publication, Movassaghi explored the wide scope of reactions enabled by the use of IPNBSH.[63] The reductive transposition of allylic alcohols occurs smoothly for substrates

1.138, **1.140**, **1.142** and **1.144**, affording the respective transposed olefin **1.139**, silylated allene **1.141**, steroid **1.143**, and terminal olefin **1.145** in good yields (Figure 1.3). The internal olefin **1.139** was obtained with high selectivity for the thermodynamically favored *E* constitutional isomer. Steroid **1.143** contains a new stereogenic center at the decalin ring juncture as a result of the stereoselective reductive transposition. Finally, Movassaghi also illustrated the complementary introduction of the IPNBSH hydrazone to various substrates.

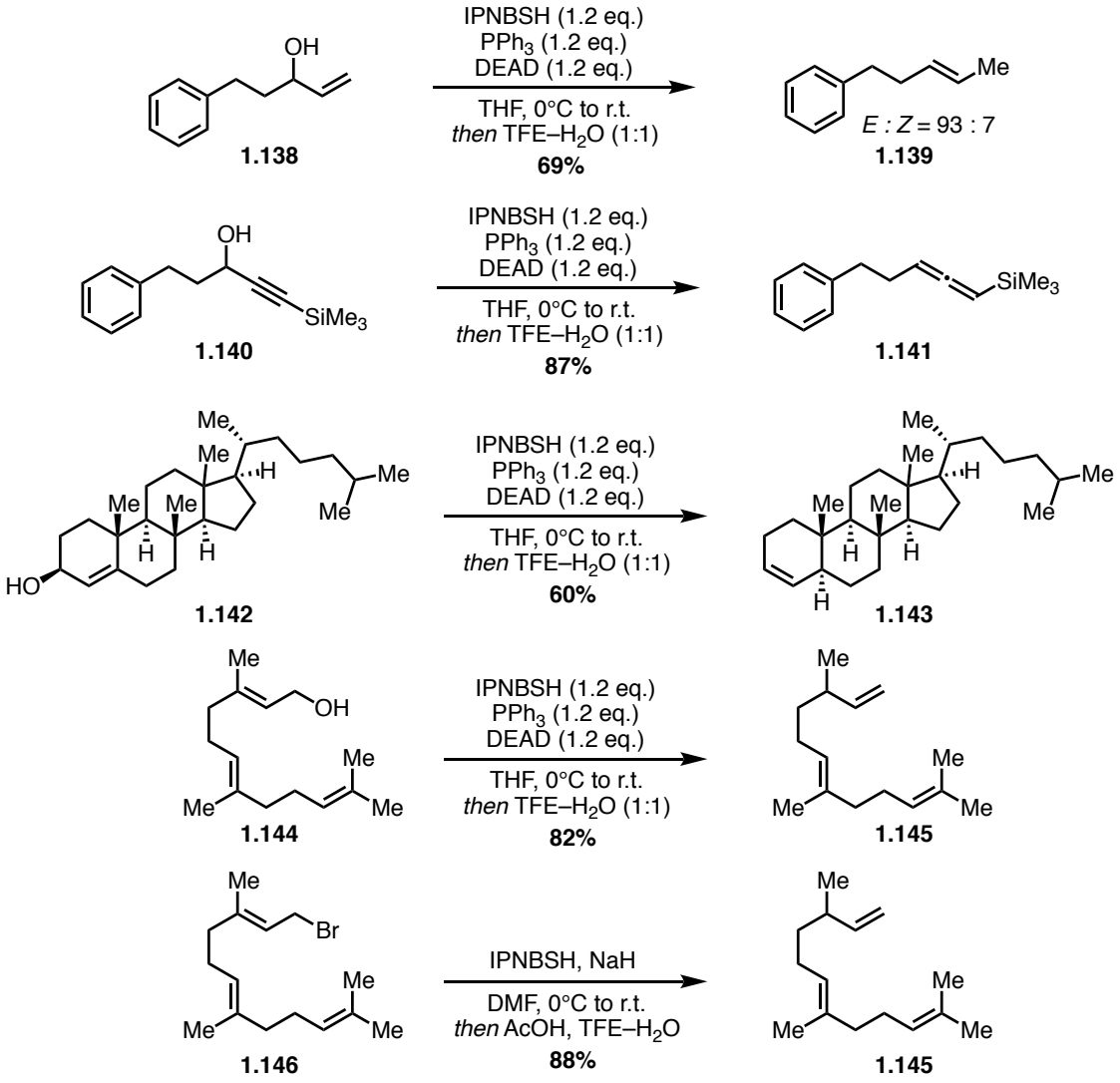
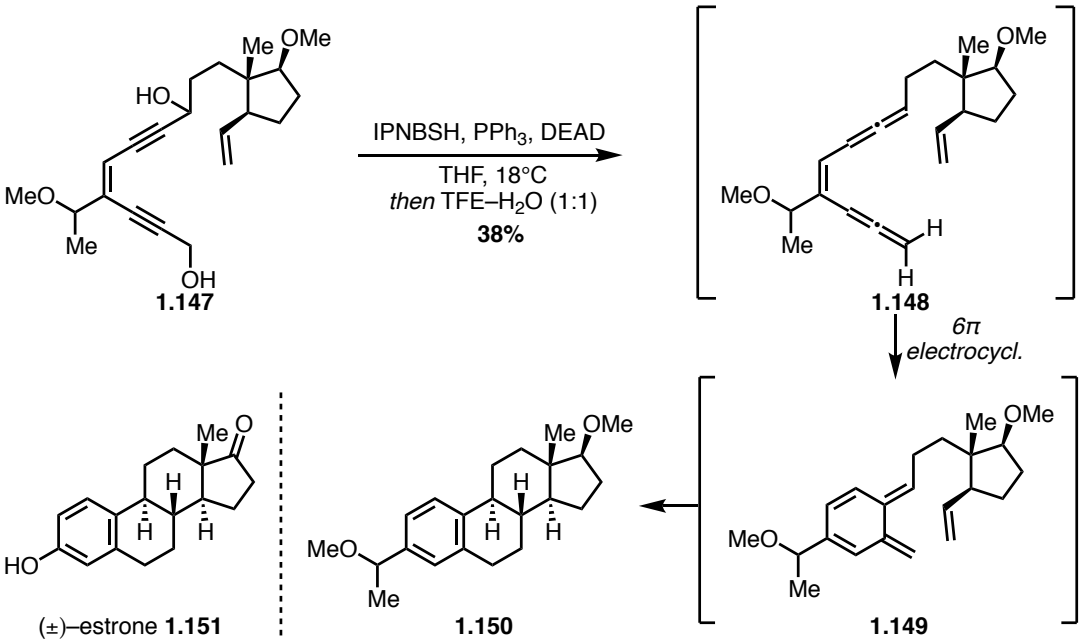


Figure 1.3 Scope of Movassaghi's IPNBSH-mediated transformations

IPNBSH is affixed to allylic alcohol **1.144** through the Mitsunobu reaction, while it is affixed to allylic bromide **1.148** by a nucleophilic displacement of the bromide, with both reactions producing the olefin **1.145** in similarly good yields. Overall, the wide scope of the IPNBSH-mediated allylic diazine rearrangement, in conjunction with the reagent's increased stability and the enhanced operational simplicity of the reaction, has resulted its numerous applications in the context of complex molecule synthesis,[64] some of which will be highlighted next.

In 2007, Mukai and coworkers reported the synthesis of racemic estrone, which featured an ambitious pericyclic cascade, consisting of a 6π electrocyclization of an ene-diallene, followed by the [4+2] cycloaddition of the resulting diene with a pendant olefin to rapidly assemble the tetracyclic core.[64a] Bis-propargyl alcohol **1.147** was envisioned as the precursor to the ene-diallene species and was therefore subjected to a variety of reductive transposition conditions, of which the IPNBSH-mediated variant emerged as the superior set, relative to those employing NBSH or even tosylhydrazine (Scheme 1.27).



Scheme 1.27 IPNBSH-mediated ADR in Mukai's synthesis of (±)-estrone

The reaction produced the transient ene-diallene **1.148** that then underwent 6π electrocyclization to form diene **1.149**, which finally performed a Diels-Alder cycloaddition with the pendant olefin to produce advanced intermediate **1.150** with high diastereoselectivity and an impressive 38% overall yield from **1.147**. The authors explicitly cited the operational simplicity of the IPNBSH-mediated ADR as a major reason for its employment. The reported synthetic route could easily be employed for the enantioselective synthesis of (+)-estrone if enantioenriched compound **1.147** is utilized.

In 2008 Movassaghi reported the first transition-metal catalyzed, stereospecific conversion of allylic electrophiles into their corresponding monoalkyldiazines for a one-pot ADR.[64b] The palladium-catalyzed displacement of a wide variety of allylic carbonates proceeded smoothly, affording the reductively transposed products in good yields. Importantly, this palladium metal-catalyzed variant enabled the reductive transposition of doubly activated allylic carbonates (i.e. featuring unsaturation on both sides of the carbonate) in reasonable yields, whereas the analogous transformation using the Mitsunobu reaction of the corresponding allylic alcohols resulted in major decomposition. The most important facet of this report was the application of this reaction to asymmetric synthesis. Enantioenriched vinyl epoxide **1.152** underwent ring-opening under the reaction conditions to generate π-allyl species **1.153**, which eventually forms chiral monoalkyldiazine **1.155**, whose stereospecific sigmatropic decomposition produced the chiral homoallylic alcohol **1.156** in 79% yield, with complete conservation of stereochemical information and generation of a new methyl stereogenic center (Figure 1.4). The olefin was stereoselectively obtained as the *E* geometric isomer. In addition to this important transformation, Movassaghi and coworkers showed that *meso* substrate **1.157** can undergo the reaction in the presence of the chiral Trost ligand[65] to enantioselectively produce hydrazone

1.158 in 93% *e.e.*, whose hydrolysis and sigmatropic rearrangement results in enantioenriched homoallylic benzoate **1.159**. This publication showcased one of the few examples in the literature of the catalyst-controlled, enantioselective generation of monoalkyldiazines directly from achiral starting materials until the work performed in this thesis, delineated in Chapter 3.

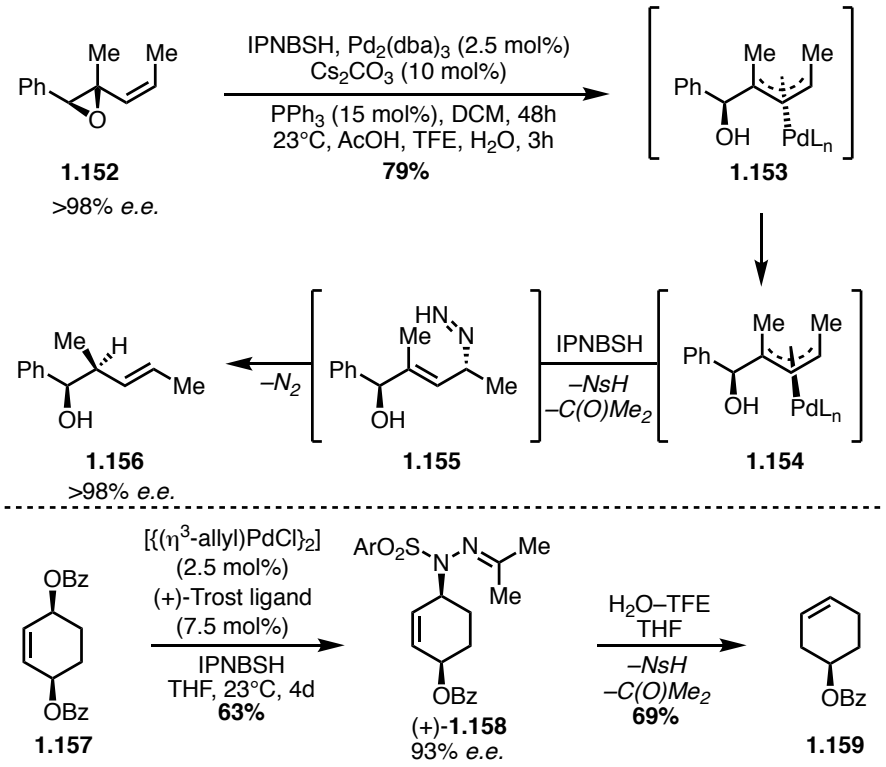
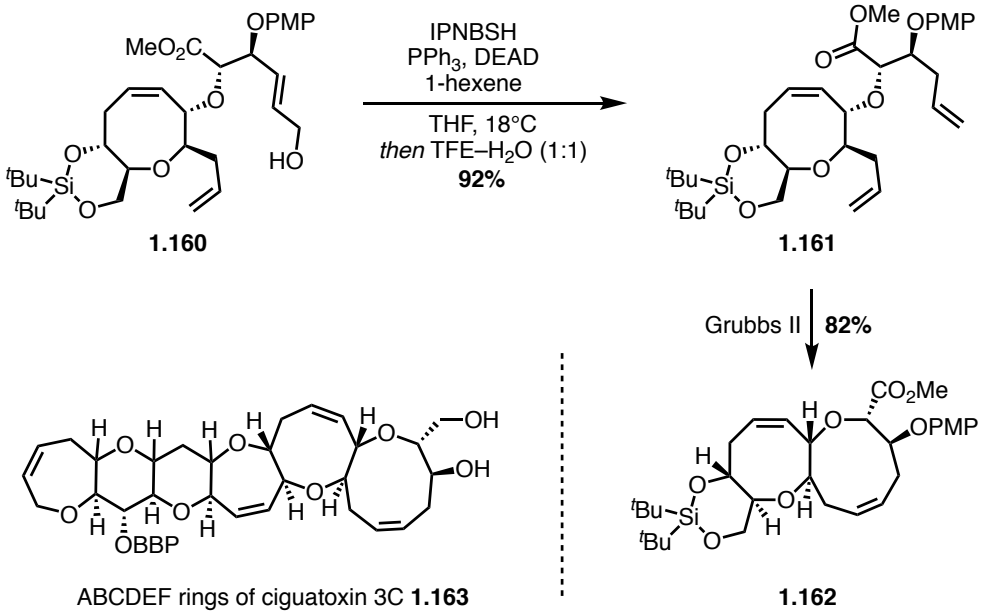


Figure 1.4 Pd-catalyzed allylic diazine rearrangements featuring IPNBSH

A final illustration of the synthetic utility of the IPNBSH-mediated ADR in the context of complex natural product synthesis is Suzuki's synthesis of the ABCDEF hexacyclic portion of the causative toxin of ciguatera fish poisoning, ciguatoxin 3C in 2017 (Scheme 1.28).[64h] Application of a modified version of Movassaghi's procedure to allylic alcohol **1.160** furnished terminal olefin **1.161** in an excellent 92% yield. Remarkably, none of the numerous functional groups present within **1.160** were adversely affected by the mild reaction conditions. Olefin **1.161** was effectively elaborated into bicycle **1.162** in 82% yield after ring-closing metathesis

using Grubbs II catalyst. Successful application of the IPNBSH-mediated ADR therefore allowed the synthesis of complex intermediate **1.163** towards ciguatoxin 3C.



Scheme 1.28 IPNBSH-mediated ADR towards Suzuki's synthesis of ciguatoxin 3C

1.10 Summary and Outlook

In the half century since the detailed investigations of the allylic diazine rearrangement, there have been numerous innovations accomplished to enable the rapid and stereocontrolled synthesis of complex molecules. There remains significant room for the continued development of mild and broadly applicable methods to engender allylic diazine rearrangements in the synthesis of interesting architectures. In the rest of this thesis are described two novel N-sulfonylhydrazone-based fragment-coupling methods to enable the synthesis of allenes, both of which featuring innovative applications of the Petasis Borono-Mannich reaction.

CHAPTER 2

SAMDI Mass Spectrometry-Enabled High-Throughput Optimization of a *Traceless* Petasis Reaction

Portions of this chapter appear in the following publication:

Diagne, A. B.; Li, S.; Mrksich, M.; Thomson, R. J. "SAMDI Mass Spectrometry-Enabled High-Throughput Optimization of a Traceless Petasis Reaction." *ACS Combi. Sci.* **2015**, *17*, 658–662[66]

Chapter 2

The generation of monoalkyldiazines in organic synthesis has long been a very powerful tool to enable a wide range of transformations. These include the rapid and straightforward deoxygenation of aliphatic alcohols through the radical or anionic decomposition pathway, and the reductive transpositions of unsaturated alcohols or carbonyl species through the retro-ene decomposition pathways. The latter transformation, the allylic diazine rearrangement (ADR) or "alkene walk", has permitted the stereocontrolled synthesis of a number of natural products (see Chapter 1). Significant advances were made in the last two decades with the introduction of the sulfonyl hydrazines NBSH and IPNBSH, which enable the ADR to proceed under extremely mild conditions (i.e. obviating a strong base or elevated temperatures) due to the enhanced lability of the nosyl appendage at room temperature. The retro-ene decomposition of propargylic nosyl hydrazides—which Myers innovatively generated from the Mitsunobu displacement of the corresponding propargylic alcohols—produces allenes under unprecedentedly mild conditions from readily available starting materials. Movassaghi's modification of the Myers allene synthesis further increased its versatility and operational simplicity. The considerable synthetic utility of allenes, and the opportunity to produce them with high optical activity, invite increased attention and innovations towards this important transformation, namely the propargylic diazine rearrangement.

2.1 Allenes in Organic Synthesis

Allenes have attracted considerable attention in recent years due to their unique structural features and properties related to the presence of two cumulated double bonds.[67] The latter impart the rare characteristic of axial chirality, rendering allenes highly useful as building blocks in the fields of organic synthesis, natural product biochemistry, and materials sciences.[68]

Examples of allenes in these fields are illustrated in Figure 2.1. They can undergo a myriad of useful transformations such as intramolecular cyclizations to afford disparate architectures,[69] and are highly amenable to intermolecular fragment-coupling reactions.[70] Moreover, the introduction of an allenic moiety onto an existing molecular scaffold has been shown to improve a compound's biological and pharmacological properties.[71]

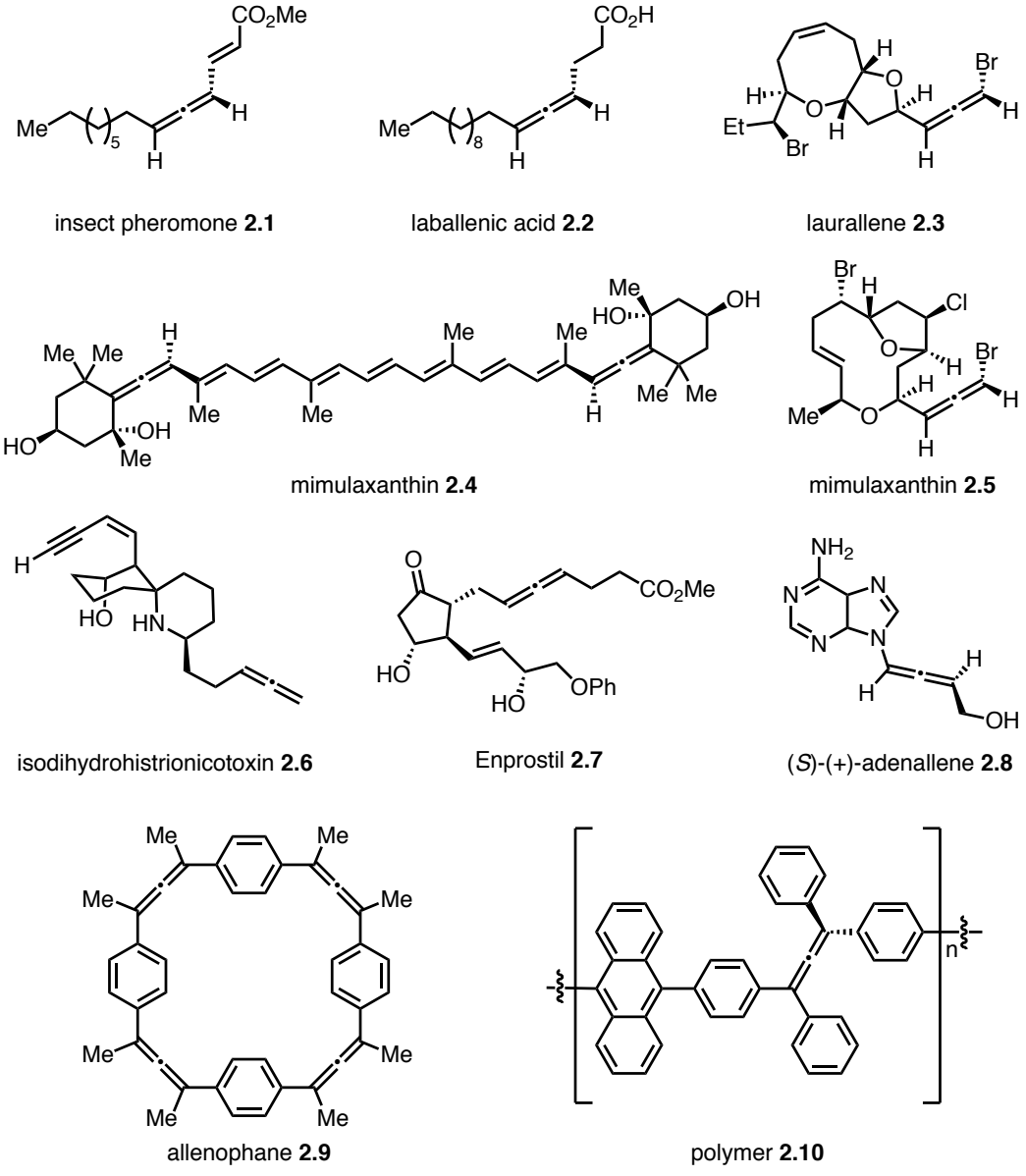


Figure 2.1 Allenic natural products, drugs, and materials

Allenes have been frequently implicated as reactive intermediates that enable the efficient synthesis of complex natural products[70e,72] (also see Schemes 1.25 and 1.27). For this collection of reasons, numerous recent synthetic endeavors have focused on accessing these important compounds.[73] The majority of reports in the literature rely on the efficient and well-known generation of allenes from the conjugate displacement of a propargylic leaving group. The degree of convergence and efficiency of these allene-based syntheses will indubitably be improved given the continued development of direct, multicomponent fragment-coupling methods to synthesize allenes from readily available substrates.

2.2 Allene Synthesis by the Allenylation of Terminal Alkynes (ATA) Reaction

So far, the most widely investigated aforesaid strategy is the allenylation of terminal alkynes (ATA) reaction, which features the copper (I)-mediated three-component fragment coupling reaction of a terminal alkyne, a secondary amine and formaldehyde to afford a terminal allene, a reaction denoted the Crabbé homologation (Figure 2.2a).[74] It proceeds mechanistically by the rapid addition of the copper acetylide of **2.11** into the imminium ion derived from **2.12** to form an intermediate propargylic amine that undergoes a retro-ene-type decomposition at high temperatures in dioxane to produce the allene **2.13**.[75] This reaction is generally beset by low yields and a severely limited substrate scope, and its subsequent modification by Kuang and Ma in 2009 partially resolved these issues.[76] The next breakthrough in the ATA was the development of conditions that enable the participation of aldehydes **2.14** within the reaction to produce 1,3-disubstituted allenes **2.15** (Figure 2.2b),[77] including a method that mechanistically involves the copper acetylide migratory insertion into a diazo species derived from tosylhydrazones.[78] These methods still employed metallic reagents and high reaction temperatures, and generally suffered

from mediocre yields; nevertheless, the opportunity to employ chiral amines enabled these methods to be asymmetric.

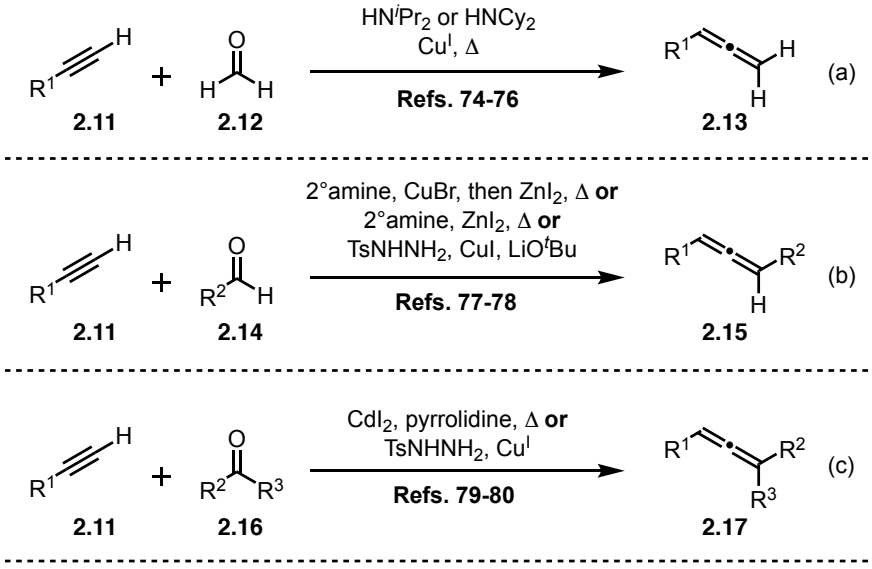


Figure 2.2 Allene synthesis by allenylation of terminal alkynes

Because of the relative inertness of ketones towards the ATA, a significant breakthrough was achieved when Wang reported a copper(I)-catalyzed cross-coupling reaction of N-tosylhydrazones derived from ketones **2.16** and terminal alkynes **2.11** to afford trisubstituted allenes **2.17**.[79] The previously recalcitrant ketone substrates easily formed diazo species with which copper acetylides can perform migratory insertions. Ma and coworkers subsequently reported a CdI_2-mediated allenylation of terminal alkynes with unactivated ketones, thereby permitting the direct formation of trisubstituted allenes from readily available starting materials.[80] Despite these reports representing the peak of the ATA (by definition this reaction cannot be used to forge tetra-substituted allenes), the reactions featured in Figure 2.2c remain limited by the requirement of high reaction temperatures and of exotic transition metals. Innovation within this reaction mode would lead to mild and operationally simple syntheses of allenes.

2.3 Direct Synthesis of Allenes by the *Traceless* Petasis Reaction

The opportunity to develop an innovative solution to the deficiencies of allene synthesis spurred the Thomson group to investigations within this chemical space. Our group has long nurtured an interest in developing fragment-coupling or rearrangement reactions via hydrazone intermediates.[81] The reductive alkylation reactions reported by Vedejs in 1976[34] and Myers in 1998[37] informed the possibility of engaging aliphatic hydrazones like **1.40** in traceless fragment-coupling reactions (Figure 2.3a). Additionally, the Myers allene synthesis[56b] revealed that propargylic N-sulfonylhydrazides like **1.106** can decompose through a retro-ene rearrangement to generate allenes **1.105** (Figure 2.3b). It was thus hypothesized that the addition of an alkynyl nucleophile **2.20** into an aliphatic N-sulfonylhydrazone **2.19** would form a propargylic monoalkyldiazine **2.22**, whose retro-ene decomposition would produce allene **2.23** (Figure 2.3c).

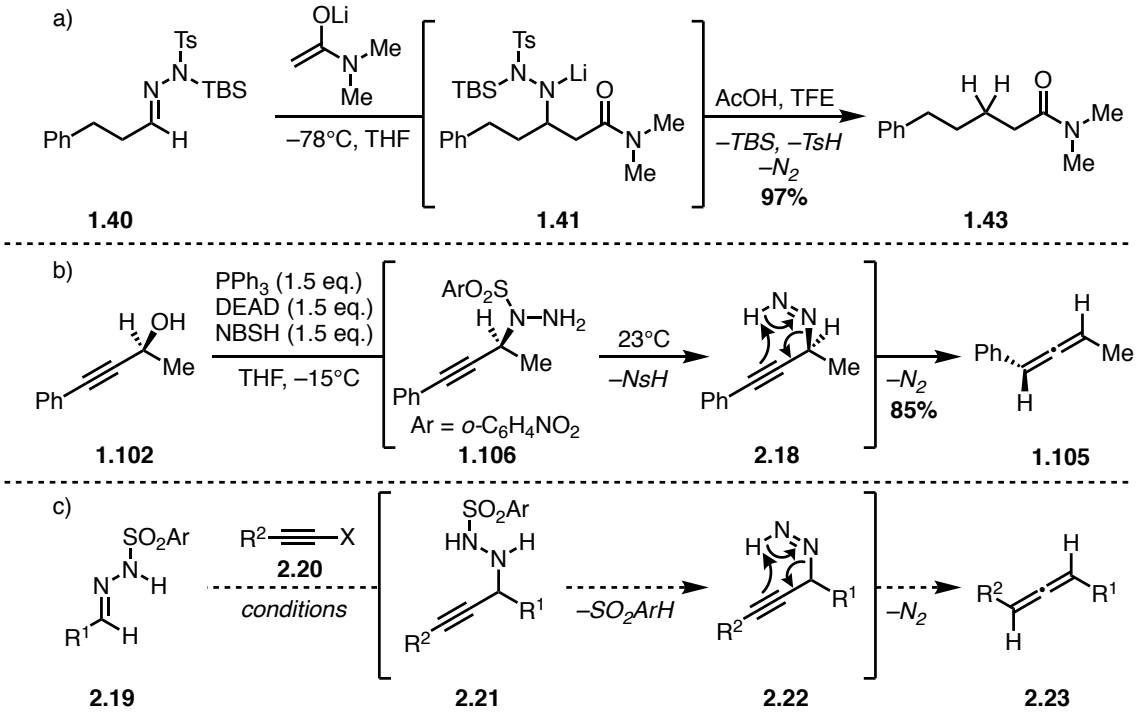
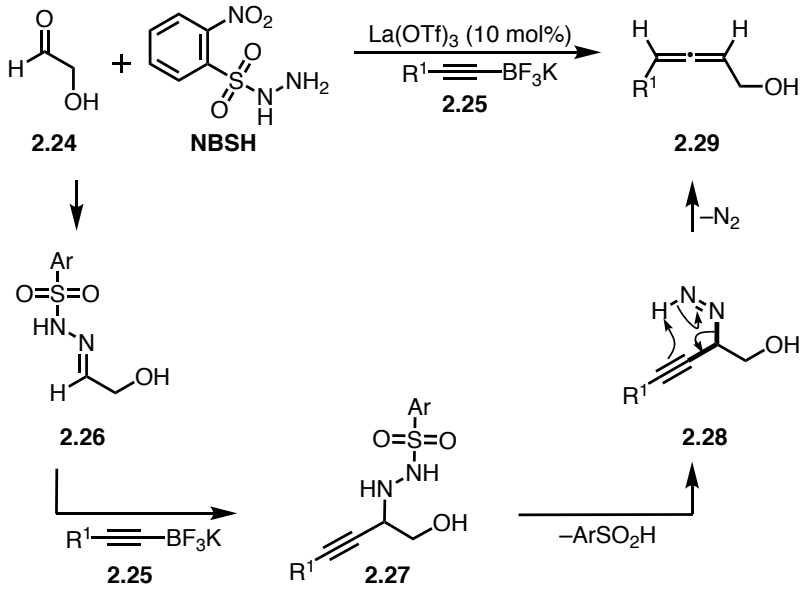


Figure 2.3 Strategy for a traceless direct synthesis of allenes

The realization of the synthetic strategy illustrated in Figure 2.3c would enable the direct

synthesis of allenes through a fragment coupling reaction, whose scope would be comparative to the reactions featured in Figure 2.2. The full idealization[82] of this reaction would denote three additional requirements: i) the ability of the reaction to proceed at room temperature; ii) the use of stable, cheap and easily handled reagents, especially regarding the activated alkyne **2.20**; and iii) the high operational simplicity of the synthetic operations. We turned to the Petasis Borono-Mannich reaction[83] as the preferred method to deliver the alkyne into the hydrazone, due to its status as an extremely efficient, mild and modular three-component fragment-coupling reaction that can incorporate a wide variety of nucleophiles and imine derivatives.[84] Despite all of the useful transformations it spurred, its application to the chemistry of hydrazones remains severely underexplored. In the fully actualized synthetic strategy we disclosed in 2012, N-sulfonylhydrazone **2.26** reacted with alkynyl trifluoroborates **2.25** to generate transient propargylic hydrazides **2.27**, which decomposed via intermediate monoalkyldiazines **2.28** to produce 2,3-allenols **2.29** through an alkene walk pathway (Scheme 2.1).[85]



Scheme 2.1 Traceless Petasis reaction for the synthesis of allenes

The reaction proved to be widely tolerant of numerous functional groups within the alkynyl trifluoroborates, and gratifyingly was tolerant of cyclic and acyclic α-hydroxy ketones to afford trisubstituted allenes (Table 2.1). At the time of publication, the titular reaction was one of the mildest and operationally simple syntheses of allenes via the ATA reaction in the literature, able to proceed at room temperature, using only substoichiometric amounts of a Lewis acid, and consisting of the simple combination of three easily handled, air- and moisture-stable reagents.

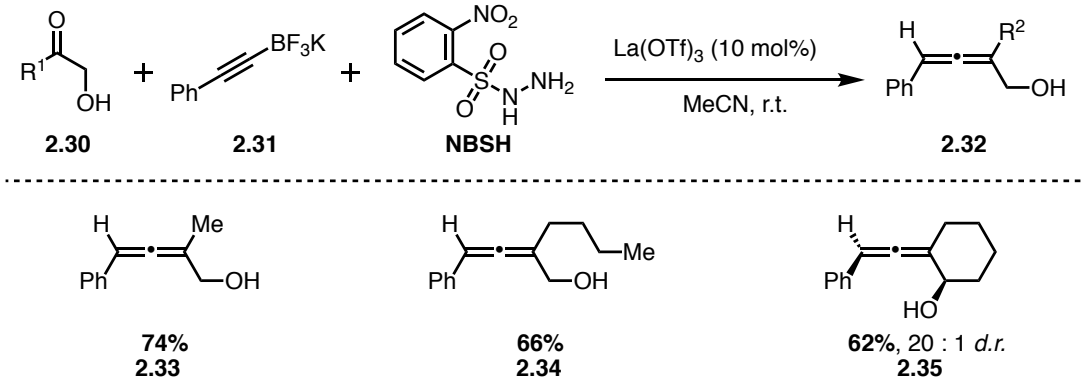


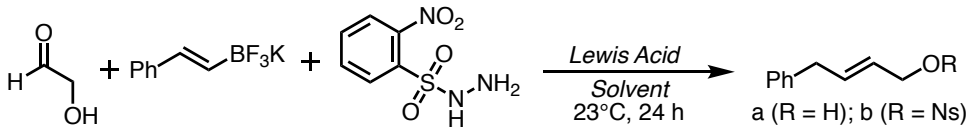
Table 2.1 Traceless Petasis reaction of ketones

Despite the wide success of this traceless Petasis reaction in enabling the unprecedentedly mild synthesis of allenes by the ATA, it suffered from two major drawbacks. The reaction required an α- or β-activating hydroxyl group on the carbonyl moiety to activate the trifluoroborate and deliver the alkyne into the hydrazone, and it was also poorly diastereoselective, with approximately a 2:1 mixture of diastereomers resulting from the alkynylation of acyclic, enantioenriched α-hydroxy aldehydes.[85] These two drawbacks severely limited the substrate scope and synthetic utility of this important reaction, and therefore spurred further investigation. We first wanted to see whether this reaction would proceed when less nucleophilic organotrifluoroborates were employed, such as α,β-unsaturated or even aliphatic

ones, and also whether the activating group can be obviated under alternative conditions to enable the synthesis of aliphatic products. Those results are summarized next.

2.4 Traceless Petasis Reaction for the Synthesis of Allylic Alcohols

We initially sought to expand the scope of our *traceless* Petasis reaction by employing α,β-unsaturated organotrifluoroborates in order to form α,β-unsaturated hydrazides analogous to **2.27**, which would produce monoalkyldiazines whose retro-ene decomposition would afford an allylic alcohol as opposed to a 2,3-allenol. The attenuated reactivity of alkenyl trifluoroborates relative to alkynyl trifluoroborates would make this transformation more challenging, and therefore a large variety of conditions were screened. The preliminary optimization studies are summarized in Table 2.2.



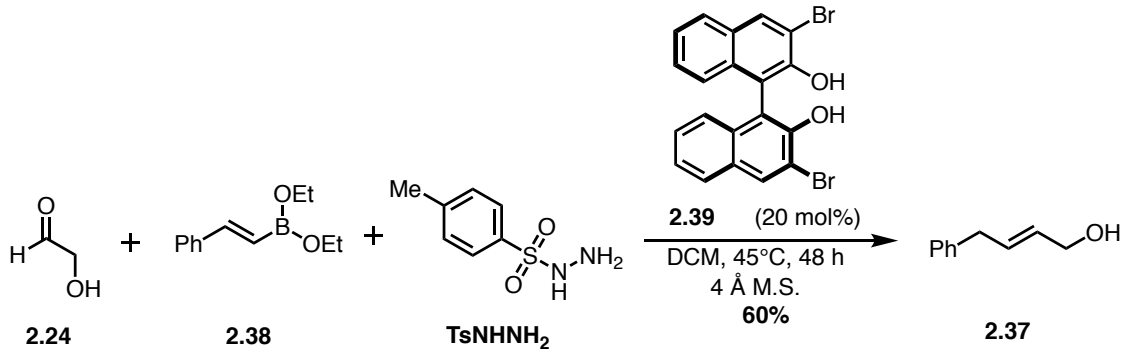
2.24 **2.36** **NBSH** **2.37**

Entry	Solvent	Eq. 2.36	Eq. NBSH	Lewis Acid (mol%)	Yield
1	MeCN	2.0	2.0	$Sc(OTf)_3$ (10 mol %)	38%[a]
2	THF	2.0	2.0	$Sc(OTf)_3$ (10 mol %)	5%[a]
3	EtOAc	2.0	2.0	$Sc(OTf)_3$ (10 mol %)	11%[a]
4	Diglyme	2.0	2.0	$Sc(OTf)_3$ (10 mol %)	10%[a]
5	MeCN	3.0	2.0	no L.A., heat (70°C)	21%[a], 9%[b]
6	MeCN	3.0	2.0	no L.A., 23°C	21%[a], 8%[b]
7	MeCN	3.0	2.0	$La(OTf)_3$ (10 mol %)	31%[a]
8	MeCN	3.0	2.0	$Zn(OTf)_3$ (10 mol %)	21%[a]
9	MeCN	3.0	2.0	$Cu(OTf)_2$ (10 mol %)	35%[a]
10	MeCN	3.0	2.0	$Yb(OTf)_3$ (10 mol %)	32%[a], 11%[b]
11	MeCN	3.0	2.0	$AlCl_3$ (50 mol %)	26%[a], 8%[b]
12	MeCN	3.0	2.0	AgOTf (20 mol %)	6%[a]
13	MeCN	3.0	2.0	$FeCl_3$ (100 mol %)	47%[a]

Table 2.2 Optimization of the traceless Petasis reaction of styryl trifluoroborate

An exploratory solvent screen revealed that the Petasis reaction could be performed in a diverse array of polar aprotic solvents or chlorinated solvents; however, yields suffered as a

result of the limited solubility of the reagents, and the commensurately higher propensity of unproductive protodeboronation of trifluoroborate **2.36** in most solvents. Acetonitrile ultimately emerged as the best solvent for this traceless Petasis reaction, affording the desired allylic alcohol **2.37** in 38% isolated yield in the presence of $Sc(OTf)_3$ (Entry 1). Encouraged by this result, we decided to screen more Lewis acids, especially those with triflate counterions, which were found to efficiently promote Petasis reactions.[86] Of these, $Cu(OTf)_2$ furnished the best result (Entry 9), although $Yb(OTf)_3$ demonstrated comparable reactivity, yet additionally furnished the nosyl-protected allylic alcohol in 11% yield (Entry 10). This side-product was also observed in the absence of a Lewis acid (Entries 5-6), and the mechanism of its formation is not quite well understood. Employing a stoichiometric amount of iron (III) chloride afforded **2.37** in a respectable 47% isolated yield (Entry 13). This promising result indicated that the expensive catalysts such as $Sc(OTf)_3$ or $La(OTf)_3$ could be substituted with a much cheaper Lewis acid. However, given the mediocre yield, and the requirement of large equivalents of the trifluoroborate and NBSH, these optimizations studies were abandoned. Current graduate student Weiwei Wang began re-investigating this transformation three years later, employing BINOL-derived organocatalyst **2.39** as a promoter, and substituting the styryl trifluoroborate **2.36** with boronic ester **2.38**. The current optimal conditions are illustrated in Scheme 2.2.



Scheme 2.2 Organocatalytic traceless Petasis reaction for the synthesis of allenes

2.5 Development of a Petasis Reaction for the Synthesis of Aliphatic Allenes

The optimization studies described above did not lead to synthetically useful results, therefore we turned out attention to developing an analogous traceless Petasis reaction that obviates the hydroxyl activating group within **2.24** in order to afford fully aliphatic allenes. The Petasis reaction mechanistically requires a Lewis base to complex with the boronic reagent to form the active "–ate" species that undergoes an irreversible Mannich reaction with the imine-derived electrophile.[83e] In the absence of an internally activating hydroxyl group, trifluoroborate **2.25** would be activated via fluoride abstraction by an external reagent to form a Lewis acidic organodifluoroborane, which could then accept electron density from the imine's lone pair to form the "–ate" species. This "external activation" pathway has precedent in the literature in the context of a Petasis reaction featuring organotrifluoroborates.[87] Tehrani and coworkers published two examples wherein aliphatic imines **2.40** and **2.44** were treated with an organotrifluoroborate in the presence of the Lewis acid BF_3•OEt_2 to generate "–ate" species **2.41** or **2.45**, which can undergo the Borono-Mannich reaction to form carbinamines **2.43** and **2.47** (Figure 2.4).

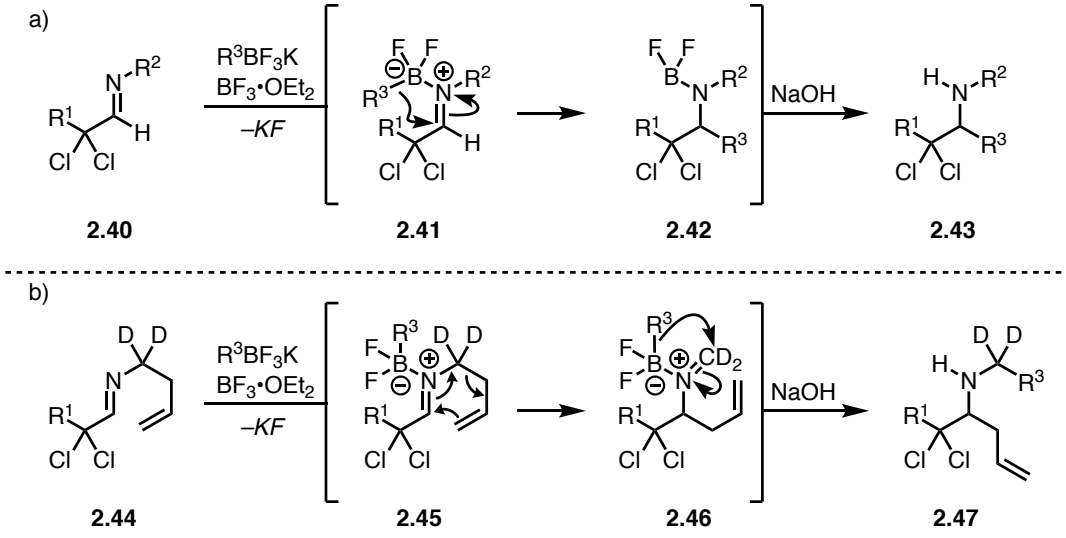


Figure 2.4 Precedent of external activation mechanism

Successful application of the above methodology to the traceless Petasis alkynylation of aliphatic N-sulfonylhydrazones should therefore enable the mild synthesis of aliphatic allenes. Subsequent optimization studies would entail a three-dimensional survey of hydrazides, solvents and activators for the reaction. This prospect constituted a wonderful opportunity to collaborate with the Mrksich group at Northwestern University to develop a platform that can effect a high-throughput optimization of this potentially mild and operationally simple transformation. The successful achievement of this collaborative effort will be discussed next.

2.5.1 SAMDI Mass Spectrometry as a High-Throughput Screening (HTS) Platform

The thorough investigation of a wide set of a chemical reaction's optimal parameters can be a very laborious and cost-ineffective endeavor with regards to time and the amount of material used. Fundamentally new approaches have therefore been adopted to comply with the current research climate's requirements of utter minimization of the costs and environmental impact of new synthetic endeavors.[82e] To this end, numerous platforms have been recently developed that perform high-throughput screens in order to elucidate productive combinations of reagents that promote novel transformations,[88] methods that have been extensively reviewed.[89] Despite these significant breakthroughs, it is rare to find a platform that can: i) rapidly and efficiently screen thousands of reactions; ii) miniaturize reaction scales to sub-micromolar quantities; iii) avoid a time-consuming purification step; iv) semi-quantitatively determine reaction yields. The latter quality specifically allows for an HTS platform to go beyond simple reaction discovery, as it additionally permits a high-throughput optimization of a novel reaction. Combining these four factors would therefore make for a powerful high-throughput optimization platform with general applicability.

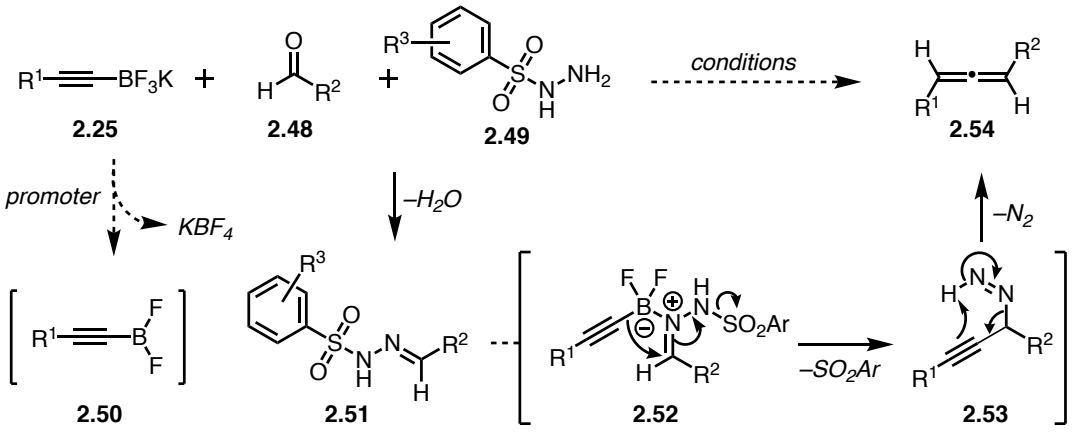
In 2002, Su and Mrksich described the application of MALDI-TOF mass spectrometry to the

characterization of self-assembled monolayers (SAMs) of alkanethiolates on gold.[90] This analytical technique[91] supersedes the classical tools of X-ray photoelectron spectroscopy, ellipsometry, surface plasmon resonance, and scanning tunneling microscopy in characterizing SAMs,[92] because it enables the unambiguous assessment of molecular change in the SAMs in an appreciably non-invasive and straightforward manner. This new method, denoted SAMDI, has proven to be widely advantageous for a wide variety of chemical biology applications.[93] Of particular significance was the employment of the SAMDI technology towards the quantitative characterization of organic interfacial reactions,[94] which later informed its adaptation as a reaction discovery platform that revealed new multicomponent fragment-coupling reactions involving siloxyalkynes.[95] The HTS provided early insight into the catalysts that would enable these unexpected transformations to proceed; nevertheless, all of the optimization studies were conducting in the solution phase, eventually yielding optimal promoters that were not initially tested on the surface. The full potential of the SAMDI technology was therefore not realized. SAMDI could prevent significant solution-phase experimentation, provided it incorporates a quantitative analysis tool that can directly compare successful reactions within the HTS. It was with this goal in mind that we decided to leverage this platform to optimize our traceless Petasis reaction for the synthesis of aliphatic allenes, whereupon a HTS of thousands of unique reaction conditions would reveal a targeted set of reactions (i.e. <10) to perform in the solution phase, strictly as a validation tool.

2.5.2 SAMDI-Enabled High-Throughput Optimization: Conceptual Framework

The hypothesized traceless Petasis reaction for the synthesis of aliphatic allenes is illustrated in Scheme 2.3. Alkynyl trifluoroborate **2.25**, upon treatment with a suitable promoter, would lose a fluoride ion to form intermediate difluoroborane **2.50**, which can complex with the Lewis basic

aliphatic hydrazone **2.51** to form "–ate" species **2.52**. The latter would perform a Borono-Mannich reaction with concomitant loss of sulfinic acid to produce the monoalkyldiazine **2.53**, whose retro-ene decomposition would afford aliphatic allene **2.54**. The performance of this reaction on a self-assembled monolayer would occur in three stages: i) immobilization of an aliphatic aldehyde on the SAM; ii) formation of a hydrazone; iii) addition of trifluoroborate **2.25** and a promoter to perform the Borono-Mannich reaction to form the allene. The SAM would be monitored by MALDI-TOF mass spectrometry after each phase to ensure successful reactivity. At the end of the third phase, the extent of each reaction can be determined by examining the ratio of the formed product relative to an internal standard. The high-throughput readout of the thousands of reactions to be screened can be performed through an automated process within a one-hour time frame, which compares very favorably to state-of-the-art platforms in industry.



Scheme 2.3 The traceless Petasis reaction for the synthesis of aliphatic allenes

The workflow regarding the HTS is illustrated in Figure 2.5. Part a) visually represents the interfacial reactions performed on the monolayer, which also gives us an appreciation of how the mass would change given each step. Figure 2.5b illustrates the mechanism by which the functionalized SAM, upon laser irradiation, desorbs from the surface, and the resulting disulfides travel intact towards the detector and their masses are accurately measured. It is important to

note that while SAMDI allows for the precise measurement of both the desorbed thiols and disulfides, the disulfide region of the spectra generally is much cleaner, and free from the interference of peaks resulting from the matrix molecules and other contaminants. The resulting spectra of the disulfides can easily determine successful reactions based on the presence of a new peak corresponding to the expected allene product.

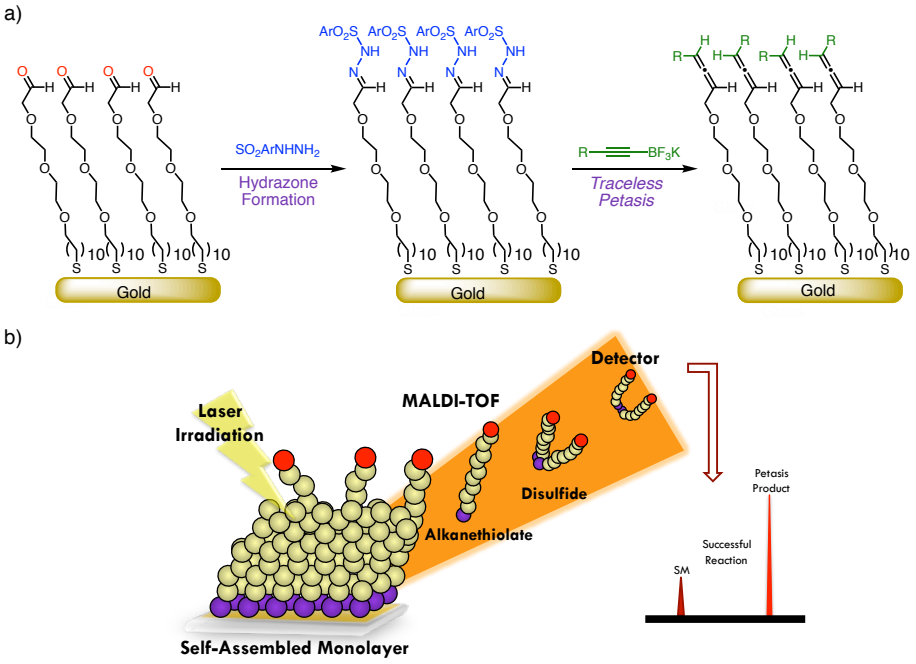


Figure 2.5 Workflow of the high-throughput screening of the traceless Petasis reaction

2.5.3 Optimization of the Aldehyde Immobilization

Former Mrksich group graduate student Dr. Shuheng Li and I initially set out to determine conditions that could reliably and reproducibly affix the reactive aldehyde moiety onto the tri(ethylene glycol)-terminated monolayer (see Figure 2.5a).[91] Our initial plan was to perform a S_N2 etherification by treating monolayer **2.55** with acetal protected tosylate **2.56** in the presence of NaH, and then to subject the monolayer to acidic conditions in order to unveil the aldehyde group. This strategy was ultimately successful, as illustrated in Figure 2.6.

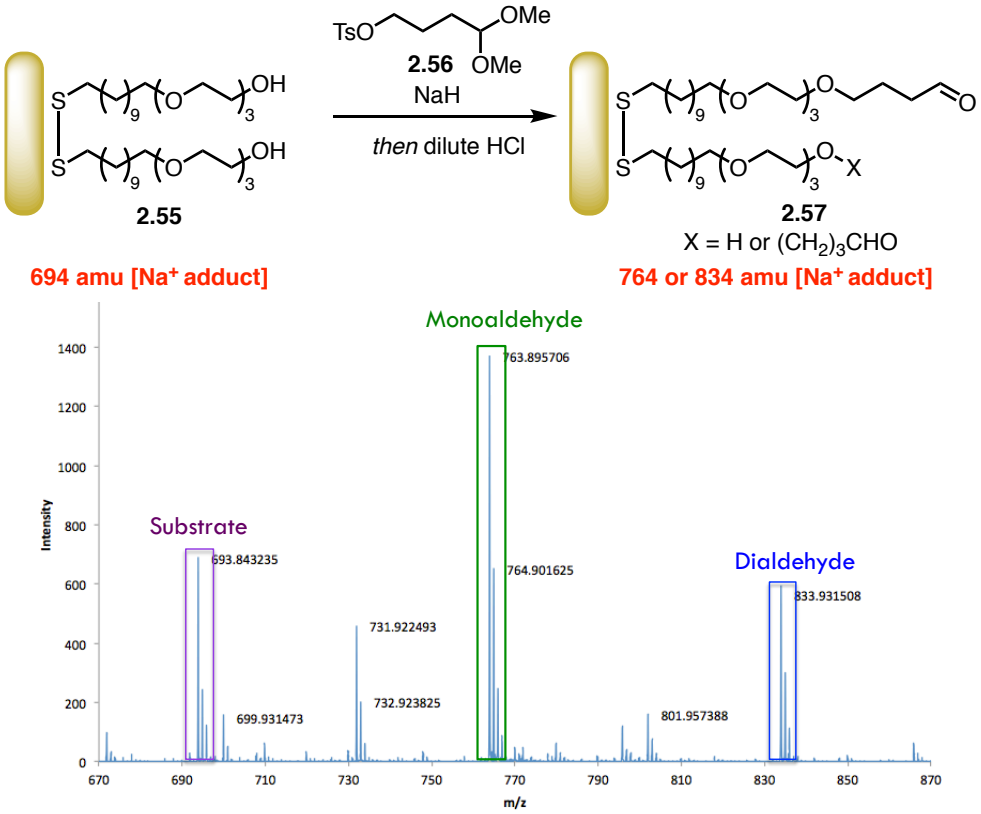


Figure 2.6 S_N2 etherification for aldehyde immobilization on the SAM (w/ Dr. Li)

After reacting for 30 minutes, the monolayer formed a significant amount of the unsymmetrical monoaldehyde (764 amu) and symmetrical dialdehyde products (834 amu) whose sodium adducts are easily detected by MALDI-TOF mass spectrometry. Unfortunately, the harshly basic sodium hydride conditions appreciably degraded the monolayer, such that subsequent reactions were impossible to conduct reliably and reproducibly. This reaction mode therefore had to be abandoned in favor of a milder method to functionalize the monolayer with an aldehyde.

We therefore turned to the direct oxidation of the terminal hydroxyl group to form the aldehyde. Because of the sensitivity of the monolayer to basic conditions, and because of our desire to greatly increase the operational simplicity and cost efficiency of interfacial reactions,

we settled on using hypervalent iodides to effect this oxidation. The gold plates containing the monolayer could simply be soaked in solutions of hypervalent iodide reagents in a suitable solvent to perform the oxidation step. We tested three reagents: a) a combination of $PhI(OAc)_2$ and TEMPO; b) 2-iodoxybenzoic acid (IBX); c) Dess-Martin periodinane (DMP). A 50 mM solution of each reagent in DCM was prepared and stored in a scintillation vial, and 6 individual glass slides containing the gold-adsorbed monolayer were added to these vials, and removed in 5 minute increments for 30 minutes as a way to monitor the kinetics of the oxidation. These glass slides were rinsed with water, acetone and ethanol, dried under a stream of N_2, and analyzed by SAMDI mass spectrometry. The resulting spectra showed three sets of peaks: the purple-coded peaks at (m/z) 693.6 and 709.6 amu correspond to the Na^+ and K^+ adducts of the symmetrical alcohol-terminated disulfide **2.55**; the green-coded peaks at (m/z) 691.7 and 707.7 belong to the unsymmetrical disulfide with one alcohol and one aldehyde terminus **2.58**; the blue-coded peaks at (m/z) 689.7 and 705.7 indicate the symmetrical disulfide with two aldehyde termini **2.59** (Figure 2.7). Dr. Li then semi-quantitatively calculated the extent of the reaction using the following equation, where the I values denote the intensities of the respective peaks of the substrate **2.55**, the intermediate **2.58** and the desired product **2.59**.

$$\text{Yield} = \frac{\frac{1}{2}\text{I(intermediate)} + \text{I(product)}}{\text{I(substrate)} + \text{I(intermediate)} + \text{I(product)}} \qquad (1)$$

The calculations revealed that the DMP oxidation conditions worked best, with 80% yield after 30 minutes. Moreover these conditions were very operationally simple, highly reproducible, and provided the cleanest spectra. We later determined that, within the context of a HTS, soaking the 384 well plates containing the monolayer into a sealed plastic bag containing 20 mL of a 50

mM solution of DMP for 30 minutes leads to nearly quantitative oxidation of the alcohol monolayer.

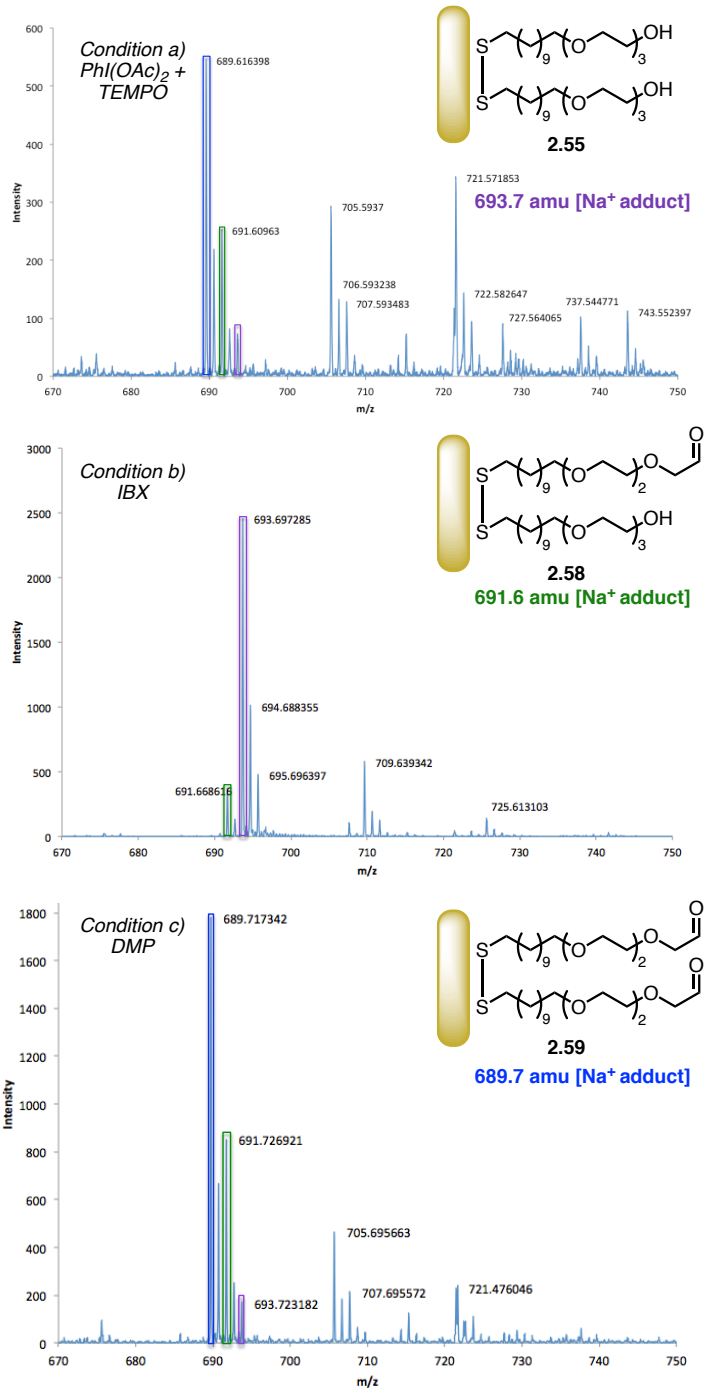


Figure 2.7 Spectra for the hypervalent iodide-mediated oxidations after 30 minutes, along with the corresponding disulfides for each color-coded highlighted peak (w/ Dr. Li)

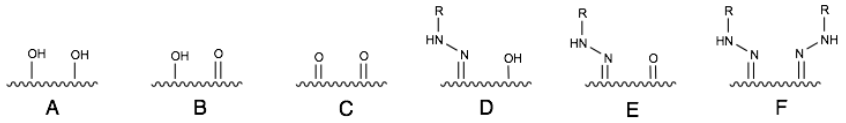
2.5.4 Optimization of the Hydrazone Formation

Once the first phase of the interfacial traceless Petasis reaction was optimized, we turned our attention towards the second phase, the formation of a hydrazone on the self-assembled monolayer. NBSH was the hydrazide of choice for these experiments, and its condensation with the aldehyde-terminated monolayer was optimized using a two-dimensional screen, wherein the solvents and reaction concentrations were varied. In an initial screen, we chose 5 polar aprotic solvents in which NBSH was highly soluble: DMSO, DMF, propionitrile, propionyl carbonate and 1,3-dimethyl-2-imidazolidinone, and 4 different concentrations: 25, 50, 100, and 200 mM. There were thus a total of 20 scintillation vials representing 20 unique reaction conditions, and four glass slides containing the gold-adsorbed, aldehyde-functionalized monolayer were added to each scintillation vial and allowed to soak for one hour. They were then removed, rinsed and subjected to SAMDI analysis. The experiment was conducted in triplicate, thus providing 12 data points for each of the 20 unique conditions, in order to account for the disparities provided by the variable quality of the monolayer on each glass slide. The yields of the reaction were calculated according to the equation presented in Figure 2.8, and the numerical values obtained were visualized through conditional formatting, wherein the highest yields appear more green, and the lowest yields appear more red.

It is immediately visually clear that propionitrile was the solvent that provided the highest yield of the hydrazone on the surface, and the reaction did not seem sufficiently sensitive to the reaction concentration, so we eventually settled on an optimized concentration of 50 mM of hydrazides. A secondary screen (not shown here) revealed that acetonitrile caused the formation of all hydrazones screened in higher yields on the surface than propionitrile. This factor, in combination with acetonitrile's availability as an anhydrous solvent dispensed from the solvent

system, facilitated the adoption of 50 mM solutions of hydrazides in acetonitrile as the optimal protocol to reliably functionalize the monolayers with hydrazones. Representative spectra of different hydrazones on the surface are shown in Figure 2.9.

$$\text{Yield of Product} = \frac{\text{Product}}{\text{Reactant + Product}} \quad \therefore \quad \text{Yield of Hydrazone} = \frac{2F + E + D}{B + 2C + D + 2E + 2F}$$



	Dimethyl Sulfoxide				Propionitrile				Dimethyl Formamide				Propionyl Carbonate				1,3-dimethyl-2-imidazolidionone			
Concentration (μM)	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
25	0.428	0.387	0.432	0.410	0.698	0.693	0.643	0.705	0.438	0.471	0.462	0.472	0.465	0.457	0.513	0.497	0.588	0.557	0.523	0.448
50	0.305	0.420	0.419	0.474	0.658	0.636	0.636	0.607	0.413	0.351	0.468	0.472	0.344	0.493	0.486	0.509	0.369	0.521	0.511	0.552
100	0.429	0.458	0.520	0.523	0.656	0.603	0.642	0.677	0.414	0.487	0.482	0.475	0.520	0.492	0.490	0.388	0.537	0.526	0.488	0.408
200	0.628	0.493	0.574	0.570	0.618	0.605	0.630	0.673	0.436	0.295	0.491	0.510	0.517	0.537	0.511	0.560	0.512	0.552	0.513	0.516
25	0.572	0.511	0.460	0.472	0.613	0.580	0.604	0.666	0.470	0.419	0.370	0.361	0.441	0.463	0.498	0.470	0.562	0.590	0.551	0.502
50	0.554	0.554	0.502	0.453	0.647	0.634	0.592	0.638	0.456	0.434	0.448	0.406	0.394	0.483	0.483	0.459	0.553	0.558	0.524	0.536
100	0.528	0.577	0.491	0.452	0.627	0.591	0.651	0.614	0.419	0.458	0.418	0.372	0.474	0.494	0.503	0.471	0.462	0.489	0.497	0.498
200	0.510	0.497	0.511	0.491	0.592	0.642	0.631	0.640	0.443	0.438	0.456	0.466	0.569	0.536	0.532	0.524	0.435	0.527	0.497	0.476
25	0.546	0.485	0.462	0.493	0.599	0.655	0.528	0.555	0.415	0.433	0.461	0.502	0.401	0.442	0.421	0.461	0.396	0.499	0.694	0.619
50	0.523	0.516	0.500	0.497	0.672	0.599	0.646	0.609	0.346	0.391	0.336	0.425	0.460	0.461	0.483	0.451	0.411	0.467	0.580	0.548
100	0.573	0.492	0.484	0.454	0.595	0.609	0.611	0.620	0.384	0.390	0.362	0.423	0.438	0.447	0.441	0.444	0.398	0.476	0.483	0.524
200	0.488	0.486	0.495	0.517	0.531	0.642	0.662	0.671	0.368	0.373	0.381	0.418	0.507	0.486	0.521	0.577	0.339	0.561	0.558	0.510

Figure 2.8 Optimization of the hydrazone formation on the surface (w/ Dr. Li)

2.5.5 High-Throughput Screening of the Traceless Petasis Reaction

Once the first two phases of the interfacial reactions were fully optimized, we finally focused on realizing the high-throughput screening of the traceless Petasis reaction for the synthesis of aliphatic allenes. Preliminary individual experiments conducted on glass slides containing the gold-adsorbed monolayer revealed that the traceless Petasis reaction could indeed be performed on the surface, as Dr. Li was able to detect a wide variety of allene peaks by SAMDI mass spectrometry. The next phase was to move to a high-throughput platform. As per the workflow illustrated in Figure 2.5a, the hydrazone-functionalized monolayers were to be treated with a combination of alkynyl trifluoroborates **2.25** and a number of different reaction promoters.

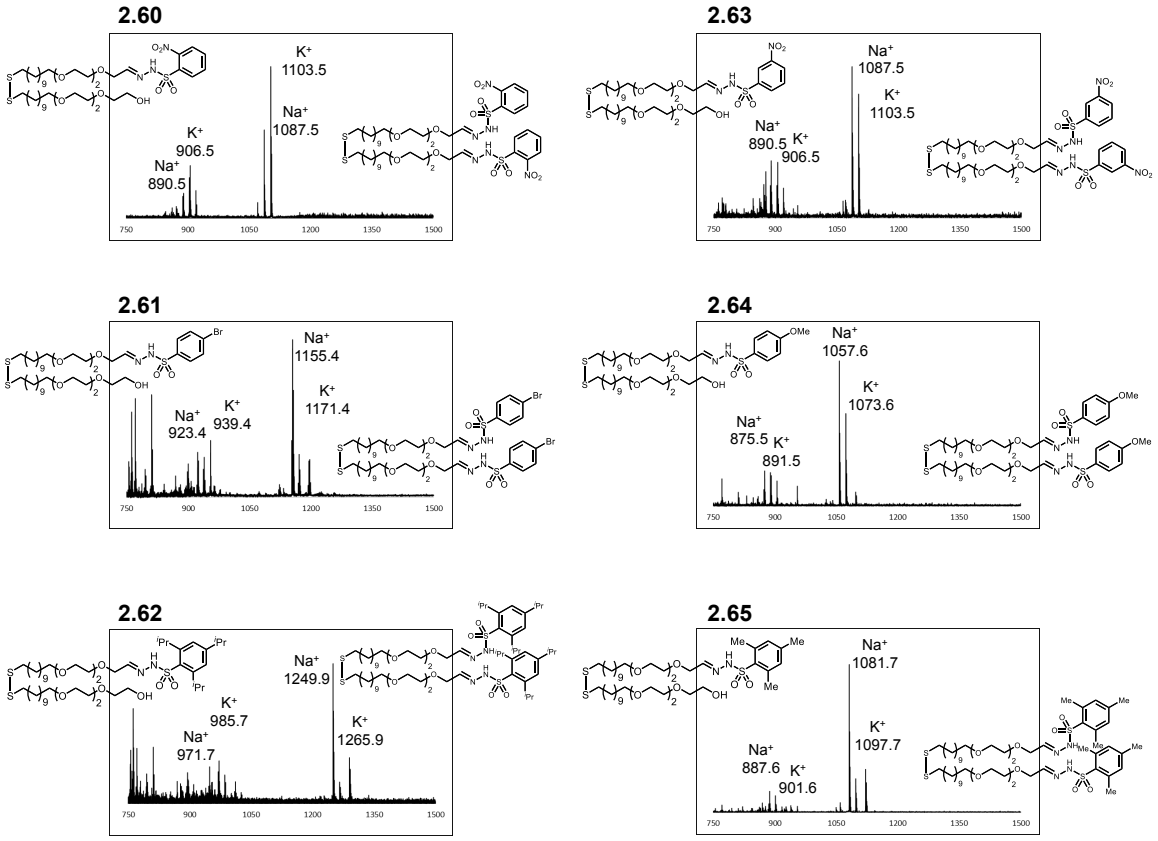


Figure 2.9 Representative spectra of hydrazones on the surface (Dr. Li)

The latter were judiciously chosen based either on literature precedent in their ability to facilitate Petasis reactions, such as the metal triflate reagents,[86] or due to their hypothesized ability to abstract fluoride ions from organotrifluoroborate **2.25**. For this first proof-of-concept illustration of the power of the SAMDI MS method to effect a high-throughput optimization of a novel reaction, we settled on a smaller, targeted screening of 1800 unique reaction conditions, consisting of the combination of 20 promoters, 15 alkynyl trifluoroborates, and 6 N-sulfonylhydrazides. Because it has been shown that the success of SAMDI is highly dependent on the solubility of all species, acetonitrile was the only solvent we screened, yet it must be noted that the decision to employ 6 different solvents would have easily increased the scale of the HTS to more than 10,000 reactions.

The transition to the high-throughput format meant replacing the gold-coated glass slides with a stainless steel plate containing 384 gold spots with a 1 mm diameter. 6 gold-coated steel plates were thus prepared that were then soaked in sealed plastic bag containing 20 mL of a 50 mM solution of DMP in DCM for 30 minutes to near quantitatively oxidize the monolayer to afford the aldehyde monolayer **2.59** (Figure 2.10). The next step in the workflow utilized automated liquid-handling robots to deliver one unique arene-N-sulfonyl hydrazide **2.66−2.71** (0.5 μL of a 50 mM solution in MeCN) to 300 gold spots on each plate, leading to hydrazone formation after 1 h. The six disparate hydrazone-functionalized plates were then rinsed with acetone and the robot was further used to sequentially deliver each alkynyl trifluoroborate **2.31**, **2.73-2.86** (0.5 μL of a 50 mM solution in MeCN) to 20 spots across 2 rows and 10 columns, and a unique promoter (0.5 μL of a 50 mM solution in MeCN) to each spot. The reactions were allowed to proceed for another hour, and the plates were rinsed sequentially with water, acetone, and ethanol, followed by treatment with a THP matrix containing a known amount of an 11-amino acid peptide (Ac-AIYpENPFARKC-NH_2, (m/z) 1432.5 amu) that served as the internal standard. The resulting allene-functionalized plates were finally analyzed by SAMDI mass spectrometry in a high-throughput fashion. Automated software was utilized to extract the intensities of the expected allene product peaks for each reaction as well as of the internal standard, and their ratio was computed and visualized through conditional formatting in a heat map (Figure 2.11). An immediate qualitative analysis reveals that hydrazide **2.66** was the best performer, although the sterically congested electron-rich hydrazides **2.70-2.71** were also reasonably effective.

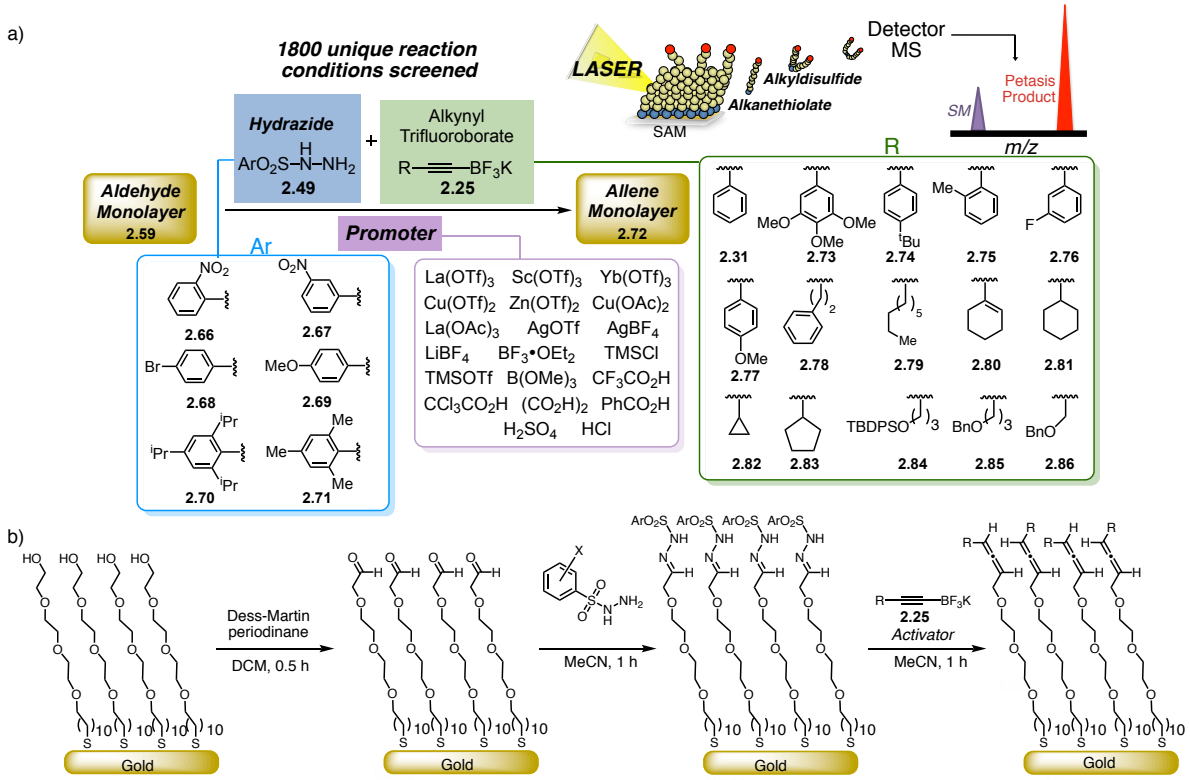


Figure 2.10 Workflow of the HTS of the *traceless* Petasis reaction (w/ Dr. Li)

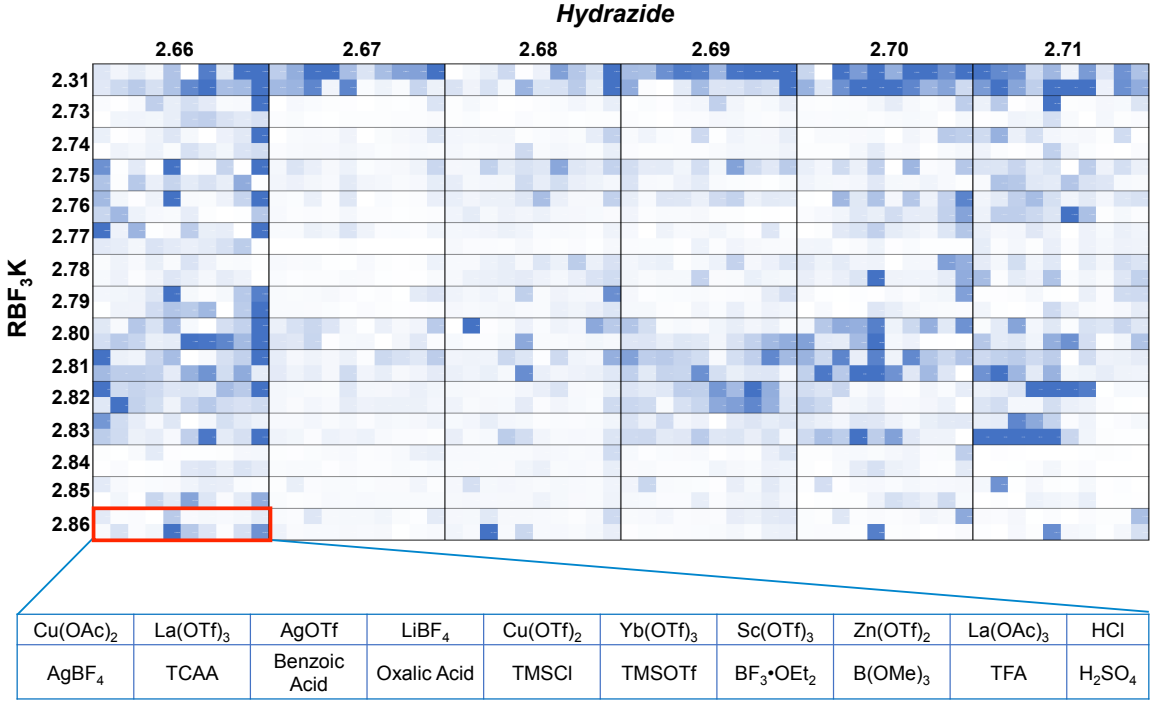
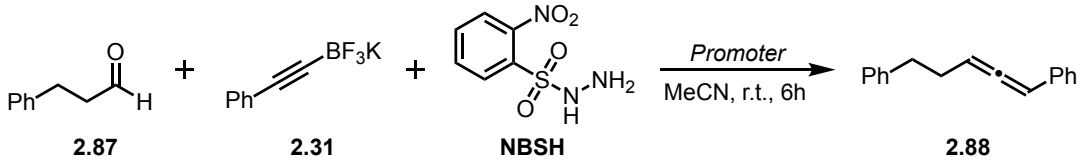


Figure 2.11 Heat map of the traceless Petasis reaction on the SAM (w/ Dr. Li)

Trifluoroborate **2.31** provided the highest yields of allenes across the widest range of conditions, followed by the saturated and unsaturated cyclohexane derivatives **2.81** and **2.80**, then other aliphatic alkynyl trifluoroborates **2.79**, and **2.82-2.83**. Other aryl substituted alkynyl trifluoroborates **2.73-2.77** showed attenuated reactivity, though they were effective in the presence of HCl as the promoter. Based on the consistently high-yielding surface reaction between alkynyl trifluoroborate **2.66** and hydrazide **2.31**, we identified the six most efficient activators in the interfacial traceless Petasis reaction to be HCl, $La(OAc)_3$, $Sc(OTf)_3$, BF_3•OEt_2, TMSOTf, and TMSCl.

2.5.6 Solution Phase Validation Studies

The application of the optimal interfacial reactions to the solution phase yielded some interesting results. In general, we found a reasonable correlation of reactivity between the two phases, but there were some noted differences. For instance, the Lewis acids $Sc(OTf)_3$ and $La(OAc)_3$ were good performers on the surface, but gave very low yields of the allene **2.88** in the solution phase (Table 2.3, Entries 2 and 4), unlike HCl and BF_3•OEt_2, each of which showed good reactivity on both the surface and the solution phase (Entries 1 and 3). TMSCl, in contrast, gave better yields in solution than did several activators that performed better on the surface (Entry 6). Certain discrepancies between the surface and solution phases can be rationalized by invoking the disparate solvation and diffusion properties within each phase, along with the fact that the promoters were presented in million-fold excess relative to the hydrazone-functionalized SAM in our HTS. For certain promoters like $La(OAc)_3$, this super-stoichiometric ratio may be needed to promote the reaction in the solution phase, but this recourse is synthetically impractical.



Entry	Promoter	Loading	Yield	Surface Ranking	Solution Ranking	Difference
1	HCl	100 mol%	46%	1	2	–1
2	$La(OAc)_3$	10 mol%	0%	2	6	–4
3	BF_3•OEt_2	100 mol%	58%	3	1	+2
4	$Sc(OTf)_3$	10 mol%	10%	4	5	–1
5	TMSOTf	100 mol%	20%	5	4	+1
6	TMSCl	100 mol%	35%	6	3	+3

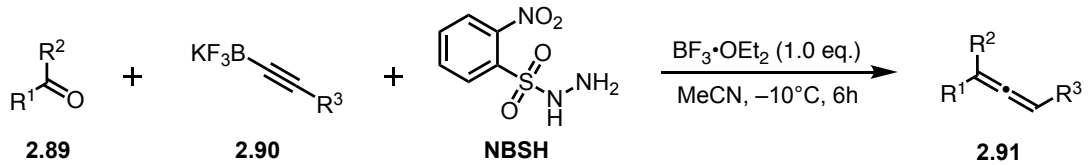
Table 2.3 Comparison between surface and solution phase reactions

Ultimately, we found that BF_3•OEt_2 was the most effective promoter for the solution reaction, furnishing the allene **2.88** in 58% yield using 1.5 equivalents of alkyne **2.31** and 1.0 equivalent of NBSH. This result is consistent with the reactions reported by Tehrani and coworkers, outlined in Figure 2.4,[87] and lends credence to the hypothesized external activation mechanism delineated in Scheme 2.3. Subsequent targeted optimization studies featuring BF_3•OEt_2 as the promoter revealed that by increasing the amount of NBSH to 1.5 equivalents and lowering the reaction temperature to –10°C upon addition of BF_3•OEt_2, the yield can be augmented from 58% to 69%. Thus, the high-throughput investigation enabled by SAMDI, conducted on significantly miniaturized scales, allowed for the rapid discovery of effective reaction conditions, thereby significantly reducing the necessary amount of solution phase optimization studies to only a few focused reactions.

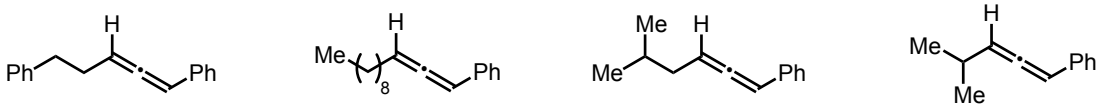
2.5.7 Evaluation of the Substrate Scope of the Traceless Petasis Reaction

Under these newly optimized conditions, a number allenes could be accessed from a variety of cyclic and acyclic aliphatic aldehydes and ketones (Table 2.4). A range of linear, branched and cyclic aldehydes delivered disubstituted allenes in good to excellent yield upon reaction with

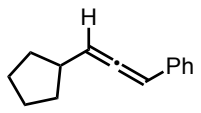
phenylacetylene trifluoroborate **2.31** (Table 2.4, **2.91 a**–**f**). Benzyl ether, alkene and alkyne functionalized aldehydes proved to be tolerant of the reaction conditions (Table 2.4, **2.91g**–**i**), with the interesting note that an unactivated terminal alkyne does not participate in the reaction (Table 2.4, **2.91h**). For aldehydes possessing a-stereocenters, the reaction proved to be poorly diastereoselective (Table 2.4, **2.91i** and **2.91j**). The alkynyl trifluoroborate partner could also be readily changed, allowing access to a diverse set of aryl and alkyl substituted products using dihydrocinnamaldehyde **2.87** as a standard aldehyde partner (Table 2.4, **2.91k**–**s**). The oxygenated derivatives **2.91t** and **2.91u** were accessed in reasonable yields when the reactions were conducted at lower concentrations. Their parent alkynyl trifluoroborates showed attenuated solubility in acetonitrile, and a commensurately increased propensity towards protodeboronation under the standard reaction conditions. Finally, we demonstrated that the traceless allene synthesis is also tolerant of ketones as reaction partners, allowing the generation of trisubstituted allenes in modest to high yields (Table 2.4, **2.91v**–**x**). The relatively mild reaction conditions, low reaction temperature and operational simplicity of this allene synthesis are particularly noteworthy, especially in the context of trisubstituted allenes, as many of the previously established ATA methods require relatively harsh conditions and elevated temperatures.[79a,80]



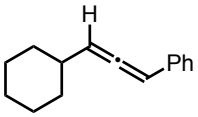
2.89 **2.90** **NBSH** **2.91**



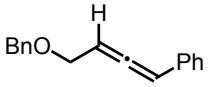
2.91a (69%) **2.91b** (91%) **2.91c** (80%) **2.91d** (78%)



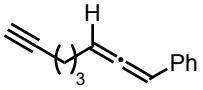
2.91e (80%)



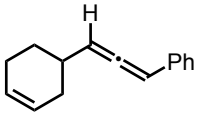
2.91f (91%)



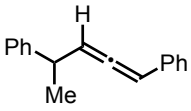
2.91g (70%)



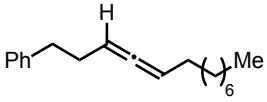
2.91h (50%)



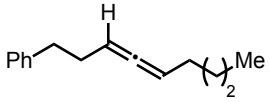
2.91i (66%.1:1 dr)



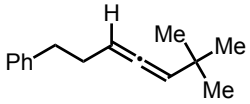
2.91j (53%, 2:1 dr)



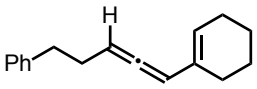
2.91k (70%)



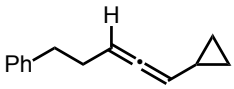
2.91l (69%)



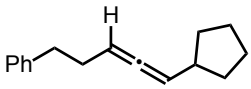
2.91m (84%)



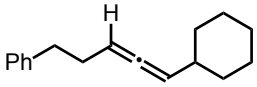
2.91n (80%)



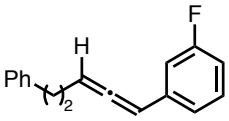
2.91o (87%)



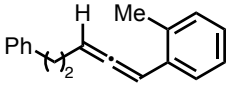
2.91p (63%)



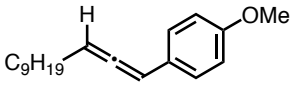
2.91q (65%)



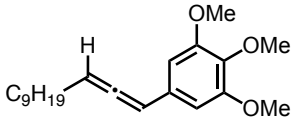
2.91r (59%)



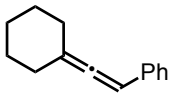
2.91s (72%)



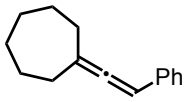
2.91t (53%)[b]



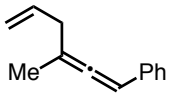
2.91u (63%)[b]



2.91v (66%)



2.91w (45%)



2.91x (89%)

Table 2.4 Substrate scope of the *traceless* Petasis reaction

2.6 Conclusions and Outlook

In summary, we have demonstrated the application of SAMDI mass spectrometry for the high–throughput development and optimization of organic reaction parameters. By using the automated ability of the SAMDI mass spectrometry platform to rapidly conduct and analyze sequential reactions at miniaturized scale, we were able to conduct and analyze 1800 unique variations of a *traceless* Petasis reaction in order to provide early insight into productive reaction conditions and into the substrate scope of the reaction. Translation of the most efficient surface–based conditions to the solution phase rapidly established an optimal set of reaction conditions to

allow for preparative scale reactions to be run with minimal additional optimization necessary. Ultimately, an operationally simple and high yielding allene synthesis was established that displays a significantly broadened substrate scope in comparison to the originally devised traceless Petasis coupling,[85] as it obviates the presence of a hydroxyl activating group. The results of this study set the stage for the further refinement of the SAMDI mass spectrometry-based methods for future applications to reaction discovery and optimization. Current work with the SAMDI platform makes a significant amendment to this established protocol, whereupon disparate reactions are conducted in miniaturized scales in the solution phase, then tethered onto a self-assembled monolayer via photoexcitation of a reactive diazirine moiety. This "pull-down" method is the natural expansion of the SAMDI technology for reaction discovery, as it may avoid disparate reactivity between the surface and the solution phase. The results of this ongoing work will be reported in due course.

2.7 HTE Reaction Optimization on SAMDI Platform

2.7.1 Materials and General Methods

Acetonitrile (HPLC grade) was obtained from VWR International and used without further purification. Tri(ethylene glycol)-terminated alkyl disulfide was prepared as previously reported.[91] The external standard (Ac–AIYpENPFARKC–NH_2) was synthesized using standard FMOC solid phase peptide synthesis protocols. All of the requisite amino acids and peptide synthesis reagents were purchased from Anaspec.

2.7.2 Preparation of Monolayers

384-format steel plates coated with a 5 nm layer of titanium and a 30 nm layer of gold were prepared as reported.[93i] These gold-coated array plates were immersed in an ethanolic solution of the tri(ethylene glycol)-terminated alkyl disulfide (0.2 mM) for 18 h at room temperature. The

arrayed substrates were then rinsed with ethanol and immersed into an ethanolic solution of 10 mM hexadecyl phosphonic acid for 15 minutes. The arrays were then washed with ethanol, deionized ultra-filtered water, with ethanol again, and then were dried under a stream of nitrogen for later use.

2.7.3 SAMDI Screen and Data Analysis

After their use in SAMDI-based reaction screenings, the array plates were treated with 2,4,6-trihydroxyacetophenone (10 mg/mL solution in acetone; for the Petasis screening, the peptide used as external standard was dissolved in the matrix solution at a final concentration of 0.3 μM), and allowed to dry. SAMDI arrays were analyzed using an Applied Biosystems 4800 MALDI TOF/TOF instrument with 20kV accelerating voltage in positive reflector mode using 200 laser shots to each spot. The 1800 spectra were acquired in approximately 3 hours. The obtained spectra were analyzed in an automated fashion using the Applied Biosystems Data Explorer Software® to retrieve the peak intensities that correspond to the substrate (I_S), the product (I_P) and external peptide standard (I_E). For the screening of the Dess–Martin Periodinane (DMP)-mediated oxidation of the monolayer and the subsequent hydrazone formation steps, a parameter representing the extent of reaction was calculated using the relation $I_P/(I_P + I_S)$ for each spectrum. For the screening of the Petasis reaction, this parameter was based on the relation I_P/I_E for each spectrum.

2.7.4 High-Throughput Screening of the Traceless Petasis Reaction on the SAM

Six array plates immobilized with tri(ethylene glycol)-terminated alkanethiolates were sealed inside three plastic bags each containing 20 mL solution of 25 mM DMP in dichloromethane at room temperature for 30 minutes. The plates were rinsed with acetone, DIUF water, ethanol and dried. Then every gold spot on each plate was treated with 0.5 μL solution of 50mM hydrazide

(**2.66-2.71**) in MeCN using a Multidrop™ Combi reagent dispenser. The plates were kept in a chamber saturated with MeCN vapor at room temperature for 1 hour. The plates were then rinsed following the usual method, and analyzed by SAMDI MS. An automated liquid handling robot was utilized to sequentially deliver 0.5 μL of 50 mM alkynyl trifluoroborates (**2.31**, **2.73-2.86**) solutions in MeCN and 0.5 μL of 50 mM promoter solutions in MeCN to each spot, in the setup described in Figure 2.11. The reactions were kept in a chamber saturated with MeCN vapor at room temperature for 1 hour, and the plates were rinsed with acetonitrile, acetone, DIUF water, ethanol again, and then were treated with the 2,4,6-trihydroxyacetophenone matrix solution containing the external peptide standard, and analyzed by SAMDI mass spectrometry. Representative spectra are shown in Figure 2.12 (note the updated legend: **5a = NBSH**; **6a** = **2.31**; **6d** = **2.76**; **6e** = **2.77**; **6f** = **2.78**; **6k** = **2.82**; **6l** = **2.83**.

2.8 Solution Phase Experiments

2.8.1 General Information

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring unless otherwise stated. Methanol, diethyl ether, THF and acetonitrile were purified by passage through a bed of activated alumina.[96] Reagents were purified prior to use unless otherwise stated following the guidelines of Armarego and Chai.[97] Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates.

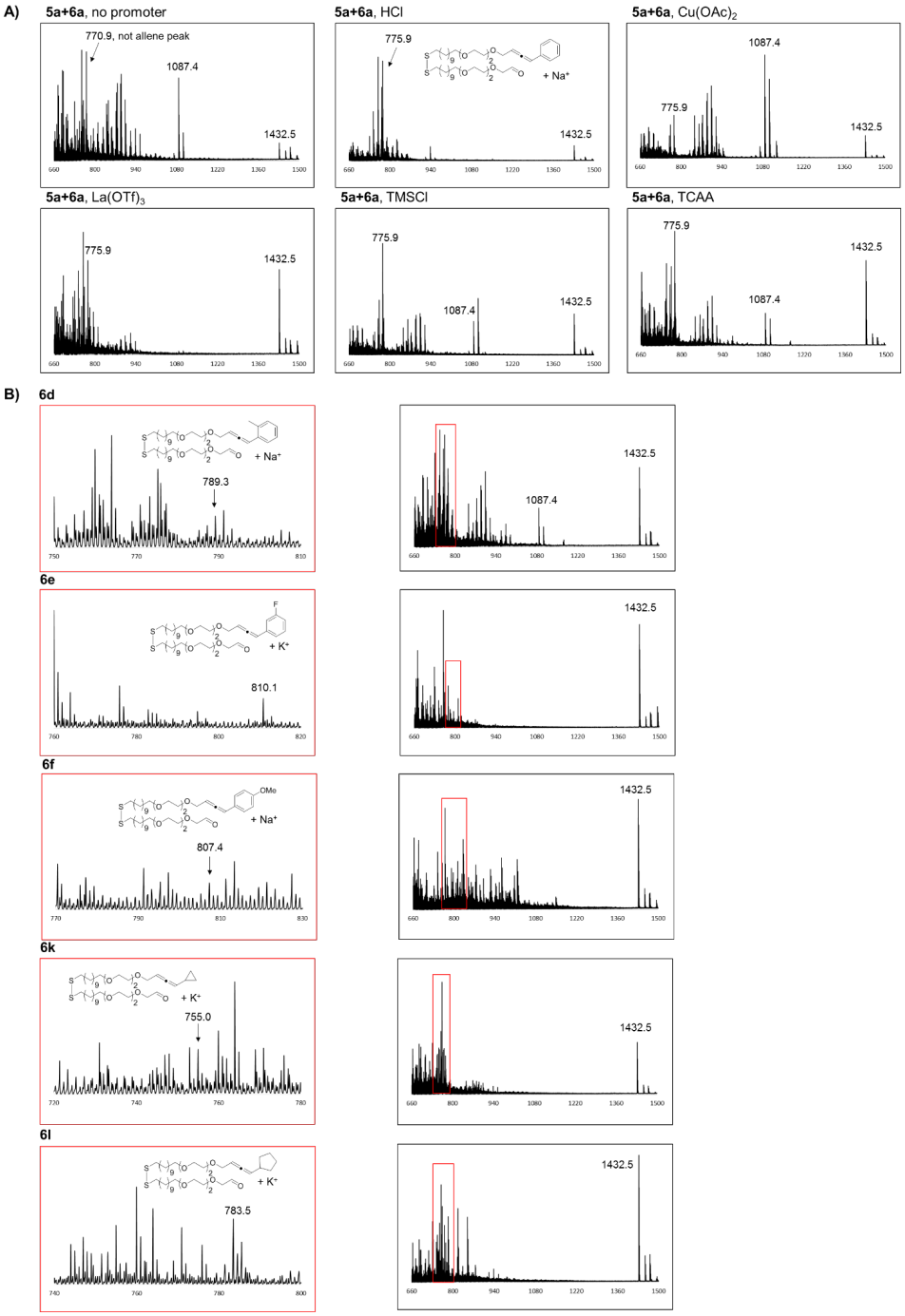
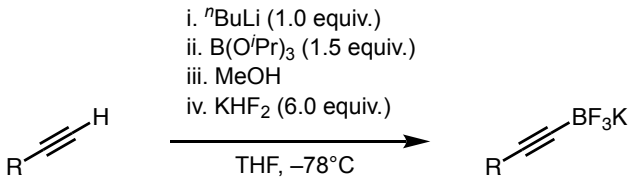


Figure 2.12. Representative spectra of successful "hits" of the traceless Petasis reaction, often identified as unsymmetrical disulfides (Dr. Li)

Visualization was accomplished with UV light, *p*-anisaldehyde or $KMnO_4$ stain. Germanium ATR infrared spectra were recorded using a Bruker Tensor 37. ^1H NMR spectra were recorded

on a Varian Inova 500 (500 MHz), or Bruker Advance III 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, m = multiplet; integration; coupling constant(s) in Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker Advance III 500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.00 ppm). Mass spectra data were obtained on an Agilent 6210 Time-of-Flight LC/MS and a Thermo Finnegan Mat 900 XL High Resolution Magnetic Sector.

2.8.2 General Procedure for the Synthesis of Potassium Alkynyl trifluoroborates

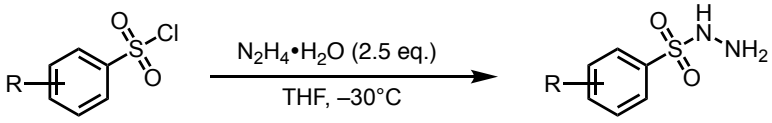


2.73–2.86

To a solution of the alkyne in dry THF (30 mL/mmol) at –78 °C under N_2 atmosphere was added *n*-BuLi (1.0 equiv.) dropwise. After stirring for 1 h 45 min at –78 °C, triisopropylborate (1.5 equiv.) was added quickly by syringe. After 10 min, the reaction was allowed to warm to room temperature over 2 h. The reaction was then cooled to 0 °C and MeOH (1 mL/mmol of alkyne) was added in one portion, followed by a slurry of potassium hydrogen difluoride (KHF_2) (6.0 equiv.) in H_2O (0.45 mL/mmol KHF_2). The reaction was then allowed to warm to room temperature over 1.5 h. The solvent was removed under reduced pressure and the resulting white solid dried under high vacuum for 14 h. The dry solid was taken up in acetone (80 mL), and the solution was heated to 45°C for 45 min and filtered over celite (2x), taking care to only decant the liquid the first time. The combined filtrates were concentrated under reduced pressure to afford an amorphous solid, which was re-dissolved in a minimal amount of hot acetone. Et_2O

(200 mL) was then added, causing a white solid to crash out of solution. TNhe solid was collected by vacuum filtration using a medium gauge fritted filter. The resulting solid was dried under high vacuum for 20 h, affording the desired potassium alkynyl trifluoroborate **2.73-2.86** as a white powder.

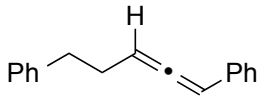
2.8.3 General Procedure for the Synthesis of Sulfonyl Hydrazides



2.66–2.71

To a solution of the aryl sulfonyl chloride in THF (1.4 mL/mmol) under N_2 atmosphere at –30°C was added hydrazine hydrate (2.5 equiv.) dropwise. The reaction was allowed to stir at this temperature for 2 h, at which time it was diluted with EtOAc (10 mL). The mixture was transferred to a separatory funnel with the aid of EtOAc, where it was washed with chilled brine (6 x 50 mL) until the organic layer was completely clear. The organic layer was then dried over $MgSO_4$ and poured into a rapidly stirring solution of hexanes (200 mL), causing a solid to crash out. This solid was then dried over high vacuum for 16 h, affording the desired hydrazides **2.66-2.71** as an off-white solid (**2.66, 2.67**) and as a white solid (**2.68-2.71**).

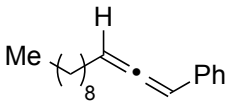
2.8.4 Synthesis of Aliphatic Allenes



Penta–1,2–diene–1,5–diyldibenzene (2.91a): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 3-phenylpropionaldehyde (67 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol) was added in

one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent as the eluent to afford the title compound (76 mg, 69%) as a clear and colorless oil. The product was in good agreement by ^{1}H NMR spectroscopy with the reported values in the literature.[98]

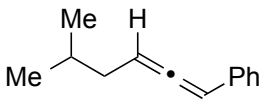
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.15 (m, 10H), 6.12 (dt, J = 6.2, 3.0 Hz, 1H), 5.59 (q, J = 6.6 Hz, 1H), 2.87 – 2.76 (m, 2H), 2.54 – 2.40 (m, 2H).



Dodeca–1,2–dienyl benzene (2.91b): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). Decanal (94 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent as the eluent to

afford the title compound (110 mg, 91%) as a clear and colorless oil.

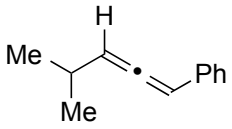
IR (neat): 2924, 2853, 1949, 1496, 1459, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$,) δ 7.30 – 7.27 (m, 4H), 7.19 (dd, J = 4.5, 4.0 Hz, 1H), 6.12 (dt, J = 6.1, 3.0 Hz, 1H), 5.56 (q, J = 6.7 Hz, 1H), 2.15 – 2.10 (m, 2H), 1.53 – 1.45 (m, 14H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 135.3, 128.7, 126.7, 126.7, 95.3, 94.7, 32.1, 29.8, 29.6, 29.5, 29.4, 29.3, 28.9 22.8, 22.8, 14.1; HRMS (EI) Calcd. for $C_{18}H_{26}$ $[M]^+$: 242.2035. Found : 242.2043.



(5–Methylhexa–1,2–dienyl)benzene (2.91c): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). Isovaleraldehyde (55 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (55 mg, 64%) as a clear and colorless oil.

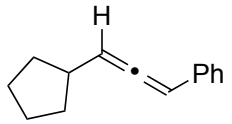
IR (neat): 2956, 2869, 2833, 1942, 1496, 1459, 906, 883 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.30 – 7.27 (m, 4H), 7.19 (dd, J = 6.0, 3.2 Hz, 1H), 6.15 (dt, J = .3, 3.1 Hz, 1H), 5.58 (q, J = 6.5 Hz, 1H), 2.29 – 2.23 (m, 4H), 1.96 (t, J = 2.7 Hz, 1H), 1.77 – 1.69 (pd, J = 7.5, 7.3, 2.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 135.3, 128.7, 126.7, 126.7, 94.1, 93.8, 38.3, 28.7, 22.5,

22.5; HRMS (EI) Calcd. for $C_{13}H_{16}$ $[M]^+$: 172.1252. Found : 172.1224.



(4–Methylpenta–1,2–dienyl)benzene (2.91d): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). Isobutyraldehyde (46 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (62 mg, 78%) as a clear and colorless oil. The product was in good agreement by ^{1}H NMR spectroscopy with the reported values in the literature.[99]

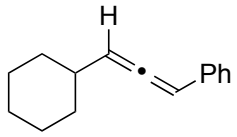
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.28 (d, J = 4.5 Hz, 4H), 7.21 – 7.16 (m, 1H), 6.18 (dd, J = 6.4, 3.1 Hz, 1H), 5.60 (q, J = 6.1 Hz, 1H), 2.49 – 2.41 (m, 1H), 1.10 (dd, J = 6.8, 3.9 Hz, 6H).



(3–Cyclopentylpropa–1,2-dienyl)benzene (2.91e): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). Cyclopentane carboxaldehyde (53 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol)

was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (74 mg, 80%) as a clear and colorless oil. The product was in good agreement by ^{1}H NMR spectroscopy with the reported values in the literature.[99]

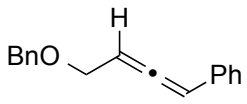
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30 – 7.27 (m, 4H), 7.19 (m, 1H), 6.15 (dt, J = 6.4, 2.8 Hz, 1H), 5.62 (q, J = 6.4, 1H), 2.64 – 2.56 (m, 1H), 1.89 – 1.82 (m, 2H), 1.74 – 1.64 (m, 2H), 1.63 – 1.55 (m, 2H), 1.52 – 1.40 (m, 2H).



(3–Cyclohexylpropa–1,2–dienyl)benzene (2.91f): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). Cyclohexane carboxaldehyde (61 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over

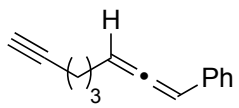
reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (90 mg, 91%) as a clear and colorless oil. The product was in good agreement by ^{1}H NMR spectroscopy with the reported values in the literature.[98]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.28 (m, 4H), 7.20 – 7.15 (m, 1H), 6.15 (dd, J = 6.4, 3.0 Hz, 1H), 5.56 (t, J = 6.2, 1H), 2.16 – 2.09 (m, 1H), 1.87 – 1.60 (m, 5H), 1.35 – 1.13 (m, 5H).



(4–(Benzyloxy)buta–1,2–dienyl)benzene (2.91g): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). Benzyloxyacetaldehyde (70 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (82 mg, 70%) as a pale yellow oil. The product was in good agreement by ^{1}H NMR spectroscopy with the reported values in the literature.[77h]

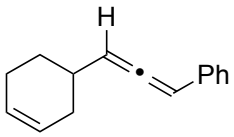
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 9H), 7.25 – 7.20 (m, 1H), 6.27 (dt, J = 6.4, 2.4 Hz, 1H), 5.72 (q, J = 6.7 Hz, 1H), 4.59 (d, J = 4.3 Hz, 2H), 4.18 (dd, J = 6.8, 2.4 Hz, 2H).



Octa–1,2–dien–7–yn–1–ylbenzene (2.91h): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl

hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 5-hexynal (48 mg, 0.50 mmol) was then added, and the mixture was then allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (46 mg, 50%) as a clear and colorless oil. The product was in good agreement by ^{1}H NMR spectroscopy with the reported values in the literature.[100]

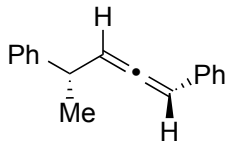
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 4H), 7.19 (m, 1H), 7.19 (dd, J = 3.2, 6.0 Hz, 1H), 6.15 (dt, J = 6.3, 3.1 Hz, 1H), 5.58 (q, J = 6.5 Hz, 1H), 2.29 – 2.23 (m, 4H), 1.96 (t, J = 2.7 Hz, 1H), 1.77 – 1.69 (pd, J = 7.5, 7.3, 2.1 Hz, 2H).



(3–(Cyclohex–3–en–1–yl)propa–1,2–dienyl)benzene (2.91i): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 3-cyclohexene-1-carboxaldehyde (59 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to

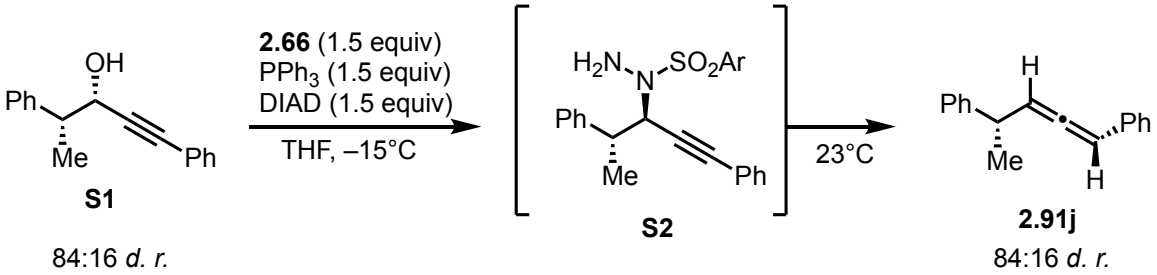
proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (65 mg, 66%) as a clear and colorless oil.

IR (neat): 3023, 2911, 2834, 1948, 1597, 1493, 1434, 909, 876; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 4H), 7.21 – 7.15 (m, 1H), 6.19 (ddd, J = 6.4, 4.5, 3.0 Hz, 1H), 5.71 – 5.62 (m, 3H), 2.44 (ddp, J = 16.9, 8.5, 2.8, 1H), 2.27 – 2.19 (m, 1H), 2.15 – 2.07 (m, 2H), 2.03 – 1.88 (m, 2H), 1.55 – 1.43 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ **Major** 204.4, 135.2, 128.7, 126.9, 126.7, 126.2, 100.4, 95.9, 33.7, 31.4, 29.1, 25.0; **Minor** 204.3, 135.2, 128.7, 127.0, 126.8, 126.7, 126.1, 100.4, 95.9, 33.7, 31.5, 29.0, 25.0; HRMS (APPI) Calcd. for $C_{15}H_{17}$ $[M+H]^+$: 197.1325 Found : 197.1335.



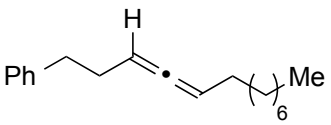
Penta–1,2–diene–1,4–diyldibenzene (2.91j): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 2-phenylpropionaldehyde (67 µL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 µL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5

M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (58 mg, 53%, 2: 1 d.r.) as a clear and colorless oil. The stereochemical outcome of this reaction was verified by subjecting the known propargyl alcohol **S1**[101] to the conditions developed by the Myers group for the stereospecific NBSH-enabled reductive transposition of propargyl alcohols.[56a]



Scheme 2.4 Verification of the stereochemical outcome of the traceless Petasis reaction on a prochiral substrate

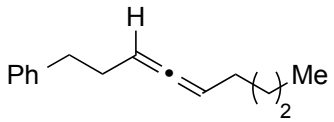
IR (neat): 3029, 2968, 2928, 1949, 1598, 1494, 1451, 905, 726, 692 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 8H), 7.26 – 7.18 (m, 1H), 6.27 (ddd, J = 6.2, 3.1, 2.3 Hz, 1H), 5.80 (td, J = 6.2, 6.2, 4.0 Hz, 1H), 3.68 – 3.57 (m, 1H), 1.42 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) **Major** δ 204.5, 146.0, 135.0 128.8, 128.7, 127.0, 126.8, 126.6, 100.9, 96.6, 39.8, 21.7; **Minor** δ 204.7, 145.9, 134.9, 128.7, 128.6, 127.3, 127.0, 126.8, 126.5, 100.9, 96.5, 39.6, 21.6**;** HRMS (EI) Calcd. for $C_{17}H_{16}$ $[M]^+$: 220.1252. Found : 220.1238.



Trideca–3,4–dienylbenzene (2.91k): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 3-phenylpropionaldehyde (67 µL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone.

At this time, the 1-decyne-derived trifluoroborate **2.79** (0.183 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (89 mg, 69%) as a clear and colorless oil.

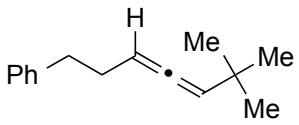
IR (neat): 2924, 2854, 1962, 1604, 1496, 1454, 906, 872 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.21 – 7.16 (m, 3H), 5.14 – 5.06 (m, 2H), 2.72 (t, J = 7.7 Hz, 2H), 2.34 – 2.27 (m, 2H), 1.97 – 1.91 (m, 2H), 1.42 – 1.21 (m, 16H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 142.1, 128.6, 128.4, 125.9, 91.7, 90.4, 35.7, 32.1, 30.9, 29.6, 29.5, 29.3, 29.3, 29.1, 22.8, 14.3; HRMS (EI) Calcd. for $C_{19}H_{28}$ $[M]^+$: 256.2191. Found : 256.2209.



Nona–3,4–dienylbenzene (2.91l): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 3-phenylpropionaldehyde (67 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, potassium trifluoro(hex–1-yn–1–yl)borate (0.141 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The

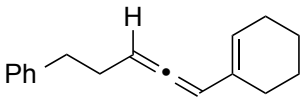
organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (70 mg, 70%) as a clear and colorless oil.

IR (neat): 2957, 2856, 1962, 1604, 1956, 1453, 908, 868 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.22 – 7.16 (m, 3H), 5.11 (dtp, J = 13.1, 6.5, 3.3, 3.1 Hz, 2H), 2.72 (t, J = 7.8 Hz, 2H), 2.34 – 2.27 (m, 2H), 1.96 – 1.91 (m, 2H), 1.38 – 1.30 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 142.1, 128.7, 125.9, 91.7, 90.4, 35.7, 31.5, 30.9, 28.8, 22.3, 14.1; HRMS (EI) Calcd. for $C_{15}H_{20}$ $[M]^+$: 200.1565. Found : 200.1576.



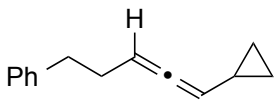
(6,6–Dimethylhepta–3,4–dienyl)benzene (2.91m): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 3-phenylpropionaldehyde (67 µL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, potassium trifluoro(3,3–dimethylbut–1–yn–1–yl)borate (0.141 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 µL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (85 mg, 84%) as a clear and colorless oil. The product was in good agreement by ^1H NMR spectroscopy with the reported values in the literature.[102]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.21 – 7.16 (m, 3H), 5.20 (q, J = 6.4 Hz, 1H), 5.11 (dt, J = 6.2, 3.1 Hz, 1H), 2.72 (t, J = 7.9 Hz, 2H), 2.34 – 2.28 (m, 2H), 1.01 (s, 9H).



(5–(Cyclohex–1–en–1–yl)penta–3,4–dienyl)benzene (2.91n): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 3-phenylpropionaldehyde (67 µL, 0.50 mmol) was then added, and the mixture was then allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the 1-ethynylcyclohexene-derived trifluoroborate **2.80** (0.161 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 µL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (89 mg, 80%) as a clear and colorless oil.

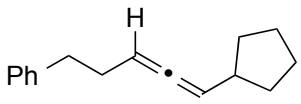
IR (neat): 2926, 2857, 2833, 1942, 1496, 1953, 906, 880 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.21 – 7.16 (m, 3H), 5.82 (dt, J = 6.2, 3.0 Hz, 1H), 5.63 (td, J = 3.7, 2.3 Hz, 1H), 5.40 (m, 1H), 2.75 – 2.72 (m, 2H), 2.39 – 2.32 (m, 2H), 2.11 – 2.07 (m, 2H), 2.00 – 1.78 (m, 2H), 1.65 – 1.55 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 141.9, 132.5, 128.7, 128.4, 126.0, 125.7, 98.4, 93.5, 35.6, 31.1, 26.0, 22.7, 22.6; HRMS (APPI) Calcd. for $C_{17}H_{21}$ $[M+H]^+$: 225.1638. Found : 225.1646.



(5–Cyclopropylpenta–3,4–dienyl)benzene (2.91o): To a flame-dried

round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 3-phenylpropionaldehyde (67 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, potassium trifluoro(cyclopropylethynyl)borate (0.129 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (80 mg, 87%) as a clear and colorless oil. The product was in good agreement by ^{1}H NMR spectroscopy with the reported values in the literature.[98]

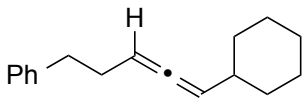
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.22 – 7.16 (m, 3H), 5.23 (dq, J = 6.4, 1.0 Hz, 1H), 4.97 (ddd, J = 9.3, 6.1, 2.9 Hz, 1H), 2.72 (t, J = 7.8 Hz, 2H), 2.34 – 2.28 (m, 2H), 1.22 – 1.14 (m, 1H), 0.69 – 0.62 (m, 2H), 0.35 – 0.26 (m, 2H).



(5–(Cyclopentyl)penta–3,4–dienyl)benzene (2.91p): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 3-phenylpropionaldehyde (67 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the cyclopentylacetylene-derived trifluoroborate **2.83** (0.155 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL,

0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (67 mg, 63%) as a clear and colorless oil.

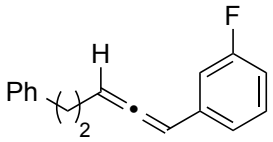
IR (neat): 3027, 2951, 2863, 1960, 1603, 1496, 1453, 907, 872 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.22 – 7.16 (m, 3H), 5.18 – 5.12 (m, 2H), 2.72 (t, J = 7.6 Hz, 2H), 2.45 – 2.36 (m, 1H), 2.34 – 2.27 (m, 2H), 1.78 – 1.70 (m, 2H), 1.66 – 1.48 (m, 4H), 1.38 – 1.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 142.1, 128.6, 128.4, 125.9, 96.7, 91.2, 39.4, 35.7, 32.9 (d, J = 11.3 Hz), 31.0, 25.0; HRMS (EI) Calcd. for $C_{16}H_{20}$ $[M]^+$: 212.1565. Found : 212.1566.



(**5–Cyclohexylpenta–3,4–dienyl)benzene (2.91q):** To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 3-phenylpropionaldehyde (67 µL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the cyclohexylacetylene-derived trifluoroborate **2.81** (0.161 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 µL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic

layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (73 mg, 65%) as a clear and colorless oil. The product was in good agreement by ^{1}H NMR spectroscopy with the reported values in the literature.[98]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.23 – 7.15 (m, 3H), 5.16 (qd, J = 6.4, 3.0 Hz, 1H), 5.08 (dq, J = 9.2, 3.0 Hz, 1H), 2.77 – 2.67 (m, 2H), 2.37 – 2.25 (m, 2H), 1.96 – 1.87 (m, 1H), 1.74 – 1.60 (m, 5H), 1.35 – 0.98 (m, 5H).

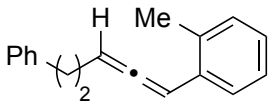


1–Fluoro–3–(5–phenylpenta–1,2–dienyl)benzene (2.91r): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 3-phenylpropionaldehyde (67 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the 3-fluorophenylacetylene-derived trifluoroborate **2.76** (0.170 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes/DCM (9/1) to afford the title compound (70 mg, 59%) as a clear and colorless oil.

IR (neat): 3027, 2919, 2850, 1949, 1611, 1585, 1487, 1451, 1263, 1140, 878, 786, 741, 678 cm^{-1};

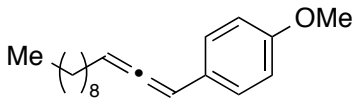
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.23 – 7.18 (m, 4H), 6.91 (d, J = 7.6 Hz,

1H), 6.88 –6.83 (m, 2H), 6.09 (dt, J = 6.3, 3.1 Hz, 1H), 5.61 (q, J = 6.7 Hz, 1H), 2.84 – 2.78 (m, 2H), 2.55 – 2.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 163.3 (d, J = 245 Hz), 141.5, 137.6 (d, J = 7.7 Hz), 130.0 (d, J = 8.5 Hz), 128.5, 128.4, 126.2, 122.5 (d, J = 2.8 Hz), 113.7 (d, J = 21.5 Hz), 113.2 (d, J = 22.2 Hz), 94.9, 94.5 (d, J = 2.8 Hz), 35.4, 30.5; HRMS (EI) Calcd. for $C_{17}H_{15}F$ $[M]^+$: 238.1158. Found : 238.1166.



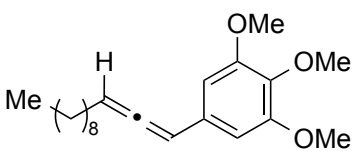
1–Methyl–2–(5–phenylpenta–1,2–dienyl)benzene (2.91s): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 3-phenylpropionaldehyde (67 µL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the 2-methylphenylacetylene-derived trifluoroborate **2.76** (0.167 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 µL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (84 mg, 72%) as a clear and colorless oil.

IR (neat): 3025, 2921, 2853, 1947, 1602, 1494, 1452, 874, 734, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.23 – 7.17 (m, 4H), 7.13 – 7.05 (m, 3H), 6.30 (dt, J = 6.3, 3.0 Hz, 1H), 5.55 (q, J = 6.6 Hz, 1H), 2.83 – 2.78 (m, 2H), 2.50 –2.40 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 141.7, 134.9, 133.1, 130.5, 128.7, 128.5, 127.2, 126.7, 126.2, 126.1, 93.5, 92.3, 35.6, 30.8, 20.0; HRMS (EI) Calcd. for $C_{18}H_{18}$ $[M]^+$: 234.1409. Found : 234.1428.



1–(Dodeca–1,2–dienyl)–4–methoxybenzene (2.91t): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). Decanal (94 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the 4-methoxyphenylacetylene-derived trifluoroborate **2.77** (0.179 g, 0.75 mmol) was added in one portion. 3 more mL of acetonitrile was added to aid the dissolution of the trifluoroborate, followed by 5 minutes of sonication. At this time the reaction was cooled to –10°C and BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes/DCM (9/1) to afford the title compound (73 mg, 53%) as a pale yellow oil.

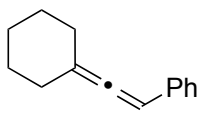
IR (neat): 2924, 2852, 1945, 1607, 1510, 1464, 1245, 1171, 1036, 832, 683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.08 (dt, J = 6.2, 3.0 Hz, 1H), 5.53 (q, J = 6.7 Hz, 1H), 3.80 (s, 3H), 2.11 (ddt, J = 7.5, 7.0, 3.0 Hz, 2H), 1.51 – 1.43 (m, 2H), 1.38 – 1.20 (m, 12H), 0.88 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6, 158.7, 127.8, 127.6, 114.2, 95.2, 94.1, 55.5, 32.1, 29.9, 29.8, 29.6, 29.5, 29.3, 29.1, 22.8, 14.3; HRMS (ESI) Calcd. for $C_{19}H_{28}O$ $[M+H]^+$: 273.2213. Found : 273.2217.



5–(Dodeca–1,2–dienyl)–1,2,3-trimethoxybenzene (2.91u): To a flame-dried round bottom flask equipped with a stir bar was added

o-nitrobenzenesulfonyl hydrazine **2.66** (0.224 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). Decanal (67 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the 3,4,5-trimethoxyphenylacetylene-derived trifluoroborate **2.73** (0.179 g, 0.75 mmol) was added in one portion. 3 more mL of acetonitrile was added before the trifluoroborate completely dissolved. At this time the reaction was cooled to –10°C and BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes/EtOAc (17/3) to afford the title compound (105 mg, 63%) as a pale yellow oil.

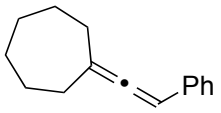
IR (neat): 2920, 2851, 1948, 1586, 1505, 1464, 1396, 1324, 1232, 1128, 1007, 836, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.52 (s, 2H), 6.04 (dt, J = 6.1, 2.9 Hz, 1H), 5.58 (q, J = 6.7 Hz, 1H), 3.86 (s, 6H), 3.82 (s, 3H), 2.17 – 2.09 (ddt, J = 10.4, 7.1, 3.2 Hz, 2H), 1.52 – 1.20 (m, 14H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1, 153.5, 137.1, 130.9, 103.7, 95.7, 94.8, 61.1, 56.2, 30.0, 29.7, 29.7, 29.5, 29.4, 29.4, 29.0, 22.8, 12.2; HRMS (ESI) Calcd. for $C_{21}H_{32}O_3$ $[M+H]^+$: 333.2424. Found : 333.2422.



(2-Cyclohexylidenevinyl)benzene (2.91v): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). Cyclohexanone (52 μL, 0.50 mmol) was then added, and the mixture was then allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the

phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (61 mg, 66%) as a clear and colorless oil. The product was in good agreement by ^{1}H NMR spectroscopy with the reported values in the literature.[103]

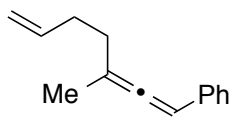
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.25 (m, 4H), 7.18 – 7.11 (m, 1H), 2.30 – 2.14 (m, 4H), 1.73 – 1.49 (m, 6H).



(2–Phenylvinylidene)cycloheptane (2.91w): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). Cycloheptanone (59 μL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 μL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was transferred to a separatory funnel using Et_2O (10 mL), where it was washed with aqueous NaOH (2 x 10 mL, 0.5 M). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the

eluent to afford the title compound (44 mg, 45%) as a clear and colorless oil.

IR (neat): 3028, 2922, 2850, 1944, 1598, 1495, 1443, 1214, 815, 745, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 4H), 7.19 – 7.14 (m, 1H), 5.99 (p, J = 2.4 Hz, 1H), 2.47 – 2.25 (m, 5H), 1.75 – 1.59 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.5, 136.3, 128.7, 126.6, 126.4, 108.6, 92.4, 32.4, 29.6, 28.9; HRMS (EI) Calcd. for $C_{15}H_{18}$ $[M]^+$: 198.1409. Found : 198.1388.



(3–Methylhepta–1,2,6–trienyl)benzene (2.91x): To a flame-dried round bottom flask equipped with a stir bar was added o-nitrobenzenesulfonyl hydrazine **2.66** (0.163 g, 0.75 mmol) and anhydrous acetonitrile (2 mL). 5-hexen-2-one (58 µL, 0.50 mmol) was then added, and the mixture was allowed to stir at room temperature until TLC analysis showed full conversion of the aldehyde to the hydrazone. At this time, the phenylacetylene-derived trifluoroborate **2.31** (0.156 g, 0.75 mmol) was added in one portion, and the reaction was cooled to –10°C. After 5 minutes, BF_3•OEt_2 (63 µL, 0.50 mmol) was added dropwise, and the reaction was allowed to proceed at –10°C for 1 h, then allowed to slowly warm to room temperature over the next 5 h. The reaction was diluted with 10 mL of diethyl ether and transferred to a separatory funnel, where it was washed two times with 10 mL of 0.5 M NaOH. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed over reduced pressure. The crude residue was purified by silica gel chromatography using hexanes as the eluent to afford the title compound (82 mg, 89%) as a colorless oil.

IR (neat): 3029, 2979, 1951, 1641, 1598, 1496, 909 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 4H), 7.18 – 7.13 (m, 1H), 6.06 (m*, 1H), 5.84 (ddt, J = 16.9, 10.3, 6.3 Hz, 1H), 1.81 (d, J = 2.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8, 138.4, 136.0, 128.6, 126.7, 126.6, 114.9, 103.3, 94.4, 33.6, 31.9, 19.1; HRMS (APPI) Calcd. for $C_{14}H_{17}$ $[M+H]^+$: 185.1325. Found : 185.1337.

CHAPTER 3

Organocatalytic Asymmetric Traceless Petasis Reactions for the Synthesis of Allenes: Development and Applications

Portions of this chapter appear in the following publication:

Jiang, Y.; Diagne, A. B.; Thomson, R. J.; Schaus, S. E. "Enantioselective Synthesis of Allenes by Catalytic Traceless Petasis Reactions." *J. Am. Chem. Soc.* **2017**, *139*, 1998–2005[104]

Chapter 3

The previous Chapter highlighted two important contributions from the Thomson group vis-à-vis the allenylation of terminal alkynes (ATA). These reactions utilized the Petasis Borono-Mannich reaction to perform mild and operationally simple alkynylation reactions on N-sulfonylhydrazones to furnish 2,3-allenols[85] or aliphatic allenes.[66] Despite these significant breakthroughs that permitted the unprecedentedly mild syntheses of allenes through the ATA, both reactions suffered from poor inherent asymmetric induction, and as such did not prove to be synthetically useful methods to synthesize enantioenriched allenes. In fact, few reactions exist that can directly produce optically active allenes with high levels of enantio- and diastereomic purity through a fragment-coupling reaction. The vast majority of established methods leverage the reliable point-to-axial chirality transfer[105] to produce optically active allenes from enantioenriched propargyl alcohol derivatives. The most effective strategies for the synthesis of allenes would therefore allow for convergent C–C bond formation with simultaneous introduction of stereogenic elements. The following chapter describes—as an extension of the original research illustrated in Chapter 2—the development of two distinct reaction modes featuring the generation of enantioenriched propargylic monoalkyldiazines by way of organocatalytic asymmetric *traceless* Petasis reactions of N-sulfonylhydrazones, and their applications towards natural product total synthesis.

3.1 Introduction to the Asymmetric Synthesis of Allenes by the ATA

Methods to synthesize disubstituted allenes by the ATA have proliferated rapidly in the last decade (see Chapter 2, reference 77). Nearly all methods involve the copper (I)-mediated alkynylation of an imine derivative to form a propargylic amine, which is

decomposed at elevated temperatures by another transition metal like zinc or cadmium. Because this decomposition is stereospecific, this reaction mode can enable access to nonracemic allenes via the intermediacy of enantioenriched propargylic amines. The latter can be generated either by i) enantioselective alkynylation of imine derivatives enabled by chiral transition metal complexes[77e] or ii) diastereoselective alkynylation of enantiopure imine derivatives.[77f-j,77l-r] In Ma's report in 2012,[77e] Propargylic alcohol **3.1** reacts with copper (I) in the presence of (*R*,*R*)-N-PINAP to form the chiral acetylide **3.5** that reacts with iminium **3.6** to afford enantioenriched propargyl amine **3.7** (Figure 3.1a). This species decomposes to allene **3.4** via intermediates **3.8** and **3.9** upon reaction with ZnI_2 at elevated temperatures. Ma later employed a single transition metal catalyst ($CuBr_2$) to effect both the formation and decomposition of enantioenriched propargyl amine **3.11**, thereby streamlining the synthesis of allene **3.4** to a single operation (Figure 3.1b).[77p] Figures 3.1c and d showcase two disparate syntheses of allene **3.14** by the groups of Che[106] and Periasamy,[77h] which both employ chiral amines **3.12** and **3.15** and necessitate two distinct operations to form and decompose the respective propargyl amines **3.13** and **3.16**.

The synthetic utility of the asymmetric ATA will be broadened if new reactions are developed that can obviate stoichiometric amounts of expensive chiral amines or chiral ligands for metals. Novel methods that enable the direct catalytic asymmetric synthesis of allenes, by means of convergent fragment coupling reactions of readily accessible and racemic starting materials, are especially attractive. As such, the ATA could become fully complementary or even superior to the existing methods to produce optically active allenes,[73c,107] which make use of transition metal catalysis[73a,108] or organocatalysis.[109]

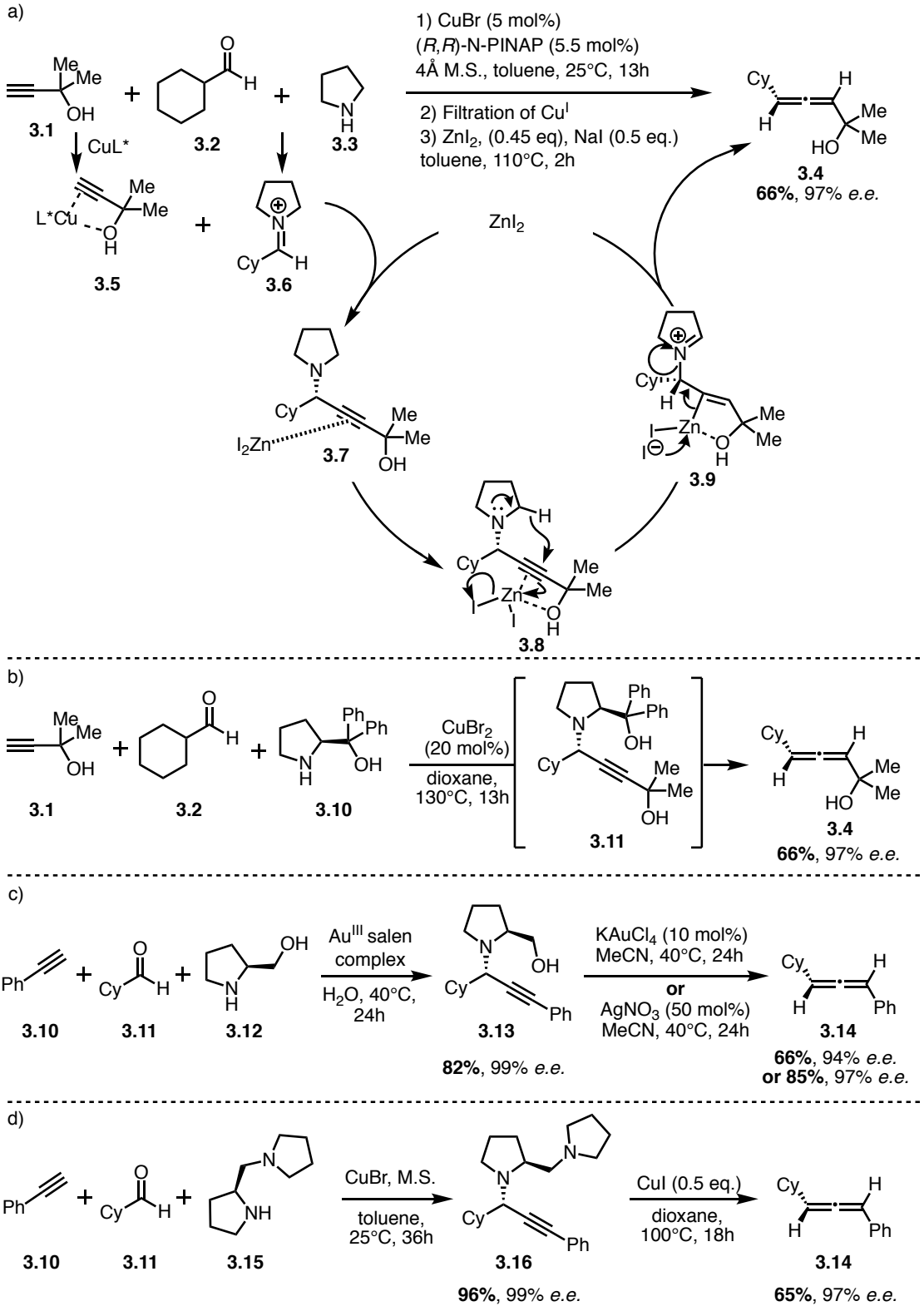


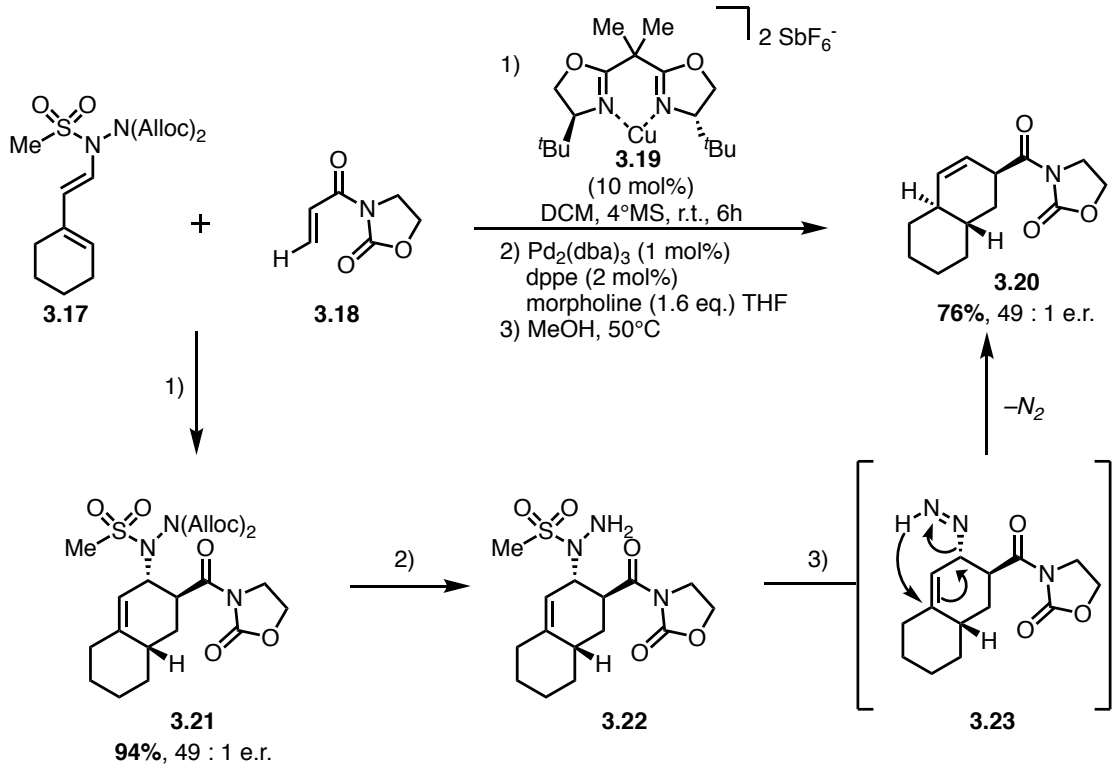
Figure 3.1 Asymmetric syntheses of allenes by the ATA

3.2 Asymmetric Generation of Monoalkyldiazines

Strategies that take advantage of the 1,3-chirality transfer by the allylic diazine rearrangement (ADR) are regularly encountered in the literature, and have been elegantly featured in the total synthesis of complex natural products, many examples of which were highlighted in Chapter 1. These monoalkyldiazines are often generated diastereoselectively as a result of the conformational bias of the substrate, such as a puckered polycyclic molecule that only permits the hydride reduction of the α,β-unsaturated hydrazone to proceed from the β-face. McIntosh reported the first example of a diastereoselective formation of a monoalkyldiazine from an acyclic substrate (see Scheme 1.16) and has since utilized this reaction in the context of natural product synthesis. Nevertheless, the synthetic utility of this reaction is contingent upon the employment of chiral substrates with oxygenated stereogenic centers, and as such the substrate scope remains severely limited.

The catalytic and enantioselective generation of chiral transient monoalkyldiazine intermediates from achiral starting materials is a reaction mode that remains severely underexplored. It had been previously reported in the literature in only two occasions, both of which make use of chiral transition metal complexes: i) the Movassaghi group's palladium-catalyzed asymmetric alkylation of π-allyl cations using IPNBSH (see Figure 1.4) and ii) the Sorensen group's asymmetric Diels-Alder reaction and subsequent retro-ene decomposition of 1-hydrazinodienes.[53] In the latter reaction, 1-hydrazinodiene **3.17** underwent a Diels-Alder cycloaddition with N-acryloyl oxazolidinone **3.18** in the presence of a substoichiometric amount of chiral copper complex **3.19** to form cyclohexene adduct **3.21** as a single diastereomer, with a 49 : 1 e.r. (Scheme 3.1).

Palladium-mediated deprotection of this product furnished hydrazide **3.22** which, upon gentle heating in methanol, unmasked the monoalkyldiazine **3.23**, whose retro-ene decomposition afforded the desired *trans*-decalin **3.20** in 76% yield, and with complete 1,3-transfer of stereochemical information. This report greatly enhances the synthetic utility of 1-hydrazinodienes and shows that they can be judiciously engaged in the traceless, stereocontrolled syntheses of decalin systems.



Scheme 3.1 Sorensen's asymmetric Diels-Alder reaction/alkene walk sequence

Reports of the 1,3-chirality transfer from chiral propargylic monoalkyldiazines are much rarer than those featuring their α,β-unsaturated counterparts. Myers and coworkers were the first to disclose two distinct methods to effect the retro-ene rearrangement of nonracemic propargylic monoalkyldiazines to enable the synthesis of optically active allenes (see Figure 1.2a-b). Of higher synthetic utility is the method that employs the

Mitsunobu reaction to form an NBSH-derived chiral propargyl hydrazide, which fragments with loss of sulfinic acid and dinitrogen to form the corresponding axially chiral allene. As illustrated in sections 1.8 and 1.9, this methodology has found widespread use to enable the synthesis of complex molecules. Nevertheless, since Myers' seminal report in 1996, there have been no examples of the direct generation of an enantioenriched propargylic monoalkyldiazine by means of a catalytic, asymmetric fragment-coupling reaction of achiral substrates. Such a reaction would be a welcome addition to the toolkit of the ATA, which has traditionally only encompassed the transition metal-mediated, stereospecific decomposition of enantioenriched propargylic secondary amines akin to **3.7** (Figure 3.1).

This particular fragmentation is not formally dissimilar to the retro-ene rearrangement of propargylic monoalkyldiazines. The most consequential disparity between these two decomposition modes is that propargylic monoalkyldiazines are both formed and fragmented under mild reaction conditions at or below room temperature, while propargylic amines always necessitate transition metals and high reaction temperatures to decompose into their corresponding allenes. We therefore hypothesized that the development of a catalyst-controlled, asymmetric variant of our traceless Petasis reaction[85] would represent a general, convergent methodology to access optically active allenes that would obviate the use of precious transition metals or harsh reaction conditions. This transformation would furthermore represent an uncommon example of the achievement of acyclic stereocontrol in the synthesis of monoalkyldiazines, for which only the afore-mentioned works of Movassaghi and McIntosh provide any precedent. During the rate-determining step of the sequence, we postulate that the chiral

environment imparted by the catalyst would engender an asymmetric alkyne transfer into the hydrazone, which would lead to enantioenriched propargylic monoalkyldiazines. Retro-ene fragmentation of this transient intermediate would afford optically active 2,3-allenols.

Successful implementation of this strategy would require numerous factors: i) the judicious choice of a boronic reagent amenable to asymmetric catalysis; ii) the inertness of this boronic reagent towards an uncatalyzed background reaction with the α-hydroxy hydrazone akin to **2.26**; iii) the complete and independent catalyst-control of the stereochemical outcome of the alkyne transfer reaction; iv) for added ideality[82e] of this transformation, the avoidance of transition metal-mediated asymmetric catalysis. The remainder of this chapter details the successful actualization of this formulated approach towards axially chiral allenes.

3.3 Development of Organocatalytic Asymmetric Traceless Petasis Reactions

Catalytic and asymmetric variants of the Petasis Borono-Mannich reaction have become increasingly prevalent over the years since its discovery in 1993, with the stereochemical information within the products being imparted by either enantioenriched substrates, or chiral catalysts.[110] Armed with the desire to maximize its potential in the synthesis of many useful chiral building blocks, many research groups over the last few years have developed or extensively studied chiral catalysts that facilitate asymmetric Petasis-type reactions,[111] including chiral thioureas[110b] and chiral diols. The Schaus group in particular has been responsible for many of the advances concerning the latter,[86,112] some of which are illustrated in Figure 3.2. All of these cases employ vinyl boronic esters that readily undergo ligand exchange with axially chiral diols **3.30**, **3.26** or **2.39** to carry

out asymmetric vinylations of imine derivatives. The three-component fragment-coupling reaction between enantiopure protected α-hydroxy aldehyde **3.32**, L-leucine methyl ester **3.33** and vinyl boronic ester **2.38** showcased in Figure 3.2c produced Petasis product **3.34** as a 7.5 : 1 mixture of *syn* and *anti* diastereomers.[112d] It is one of only two examples in the literature where the inherent *anti* selectivity of the Petasis reaction is overcome to produce *syn* diastereomers as the major product, the other being reported by Yudin.[111d]

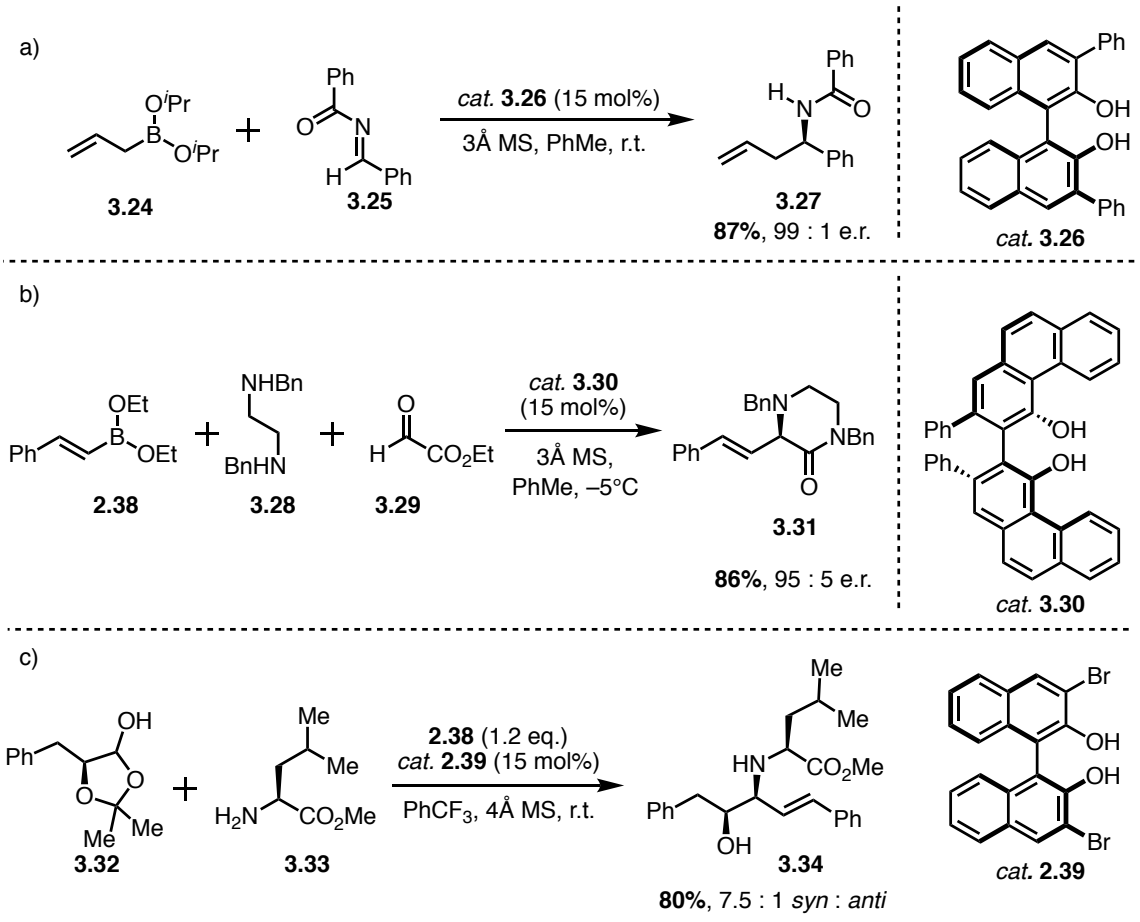
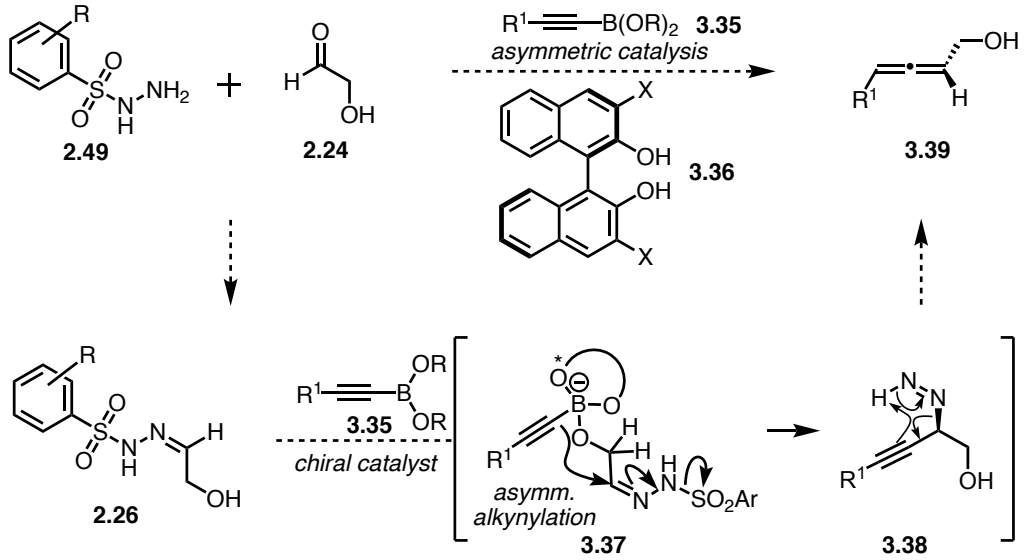


Figure 3.2 Asymmetric Petasis reactions catalyzed by chiral diols

3.3.1 Optimization of the Asymmetric Alkynylation of Glycoaldehyde-derived N-sulfonyl Hydrazones

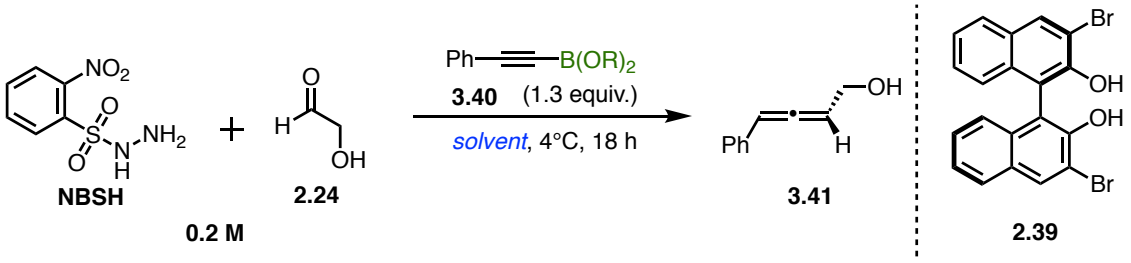
The prospect of developing an asymmetric variant of our traceless Petasis reaction presented a wonderful opportunity to establish a formal collaboration with the Schaus group, as they had decisively established the ability of chiral biphenols to catalyze regular Petasis-type reactions with high levels of asymmetric induction. In our collectively devised strategy for the asymmetric variant of the traceless Petasis reaction, the α-hydroxy hydrazone **2.26** would coordinate with alkynyl boronate species **3.35** in the presence of a chiral catalyst to generate the chiral "–ate" species **3.37** (Scheme 3.2). The configuration of the catalyst would direct the stereoselective alkyne transfer to produce enantioenriched monoalkyldiazine **3.38** after fragmentation with loss of sulfinic acid. Retro-ene decomposition of **3.38** would extrude dinitrogen and generate optically active 2,3-allenol **3.39**.



Scheme 3.2 Organocatalytic enantioselective traceless Petasis reaction

In order to maximize the success of this reaction, it was crucial to not only suppress

the rate of the unproductive background reaction, but also to augment the stereochemical induction of the alkynylation step. Our comprehensive optimization studies therefore comprised a four-dimensional screening of four different variables: the identity of i) the solvent; ii) the alkynyl boronate **3.35**; iii) the arene-N-sulfonyl hydrazide **2.49**; and iv) the structure of the biphenol catalyst **3.36**. The first two factors were collectively posited to have the most significant impact on the relative rates of the background vs. catalyzed reactions, and by extension the stereochemical outcome of the asymmetric alkynylation, so they were examined first, using NBSH as the hydrazide and 3,3′-Br_2-BINOL **2.39**. A selection of the initial optimization results is summarized in Table 3.1.



Solvent	Polarity Index	Selectivity
PhMe	2.4	88:12 e.r.
$PhMe_3$		88: 12 e.r.
Benzene	2.7	77: 23 e.r.
$PhCF_3$		78:22 e.r.
DCM	3.1	74: 26 e.r.
THF	4.0	54: 46 e.r.
EtOAc	4.4	50: 50 e.r.

Yields: 50-70%

Boronate	A-Value (kcal/mol)	Yield	Selectivity
R = Me	1.70	78%	88:12 e.r.
R = Et	1.75	95%	86: 14 e.r.
R = ^{n}Pr	*~1.80*	68%	83: 17 e.r.
R = ^{n}Bu	*~1.85*	70%	82: 18 e.r.
R = ^{i}Pr	2.15	71%	80: 18 e.r.
R = $SiMe_3$	2.50	61%	76: 24 e.r.

Table 3.1 Optimization of the solvent and boronic ester (Dr. Jiang)

The results of these early optimization studies, performed by former Schaus group graduate student Dr. Yao Jiang, underscore that the selectivity of the reaction is directly correlated to both the polarity of the solvent and the steric bulk of the boronic ester. Indeed, relatively nonpolar solvents such as toluene or mesitylene lead to a promising 88 : 12 ratio of allene enantiomers, while the extremely polar ethyl acetate affords a racemic mixture. The aromatic character of toluene or mesitylene presumably reinforces a more optimal organization of the transition state structure during the asymmetric alkyne transfer, i.e. a structure akin to **3.37**. Moreover, the larger the steric bulk of the boronic reagent, the poorer the asymmetric induction. This result can be ascribed to the increased aptitude of smaller boronates such as methyl or ethyl boronates to perform ligand exchange with chiral catalyst **2.39**, and their consequent attenuated participation in an unproductive background reaction. Given the significant difference in yield between the ethyl and methyl boronate (95% vs. 78%), the ethyl boronate was adopted as the reagent of choice for further optimization studies that systematically evaluated the identity of the hydrazide reagent and of the catalyst. Dr. Jiang conducted these reactions in toluene. Selected results are presented in Table 3.2.

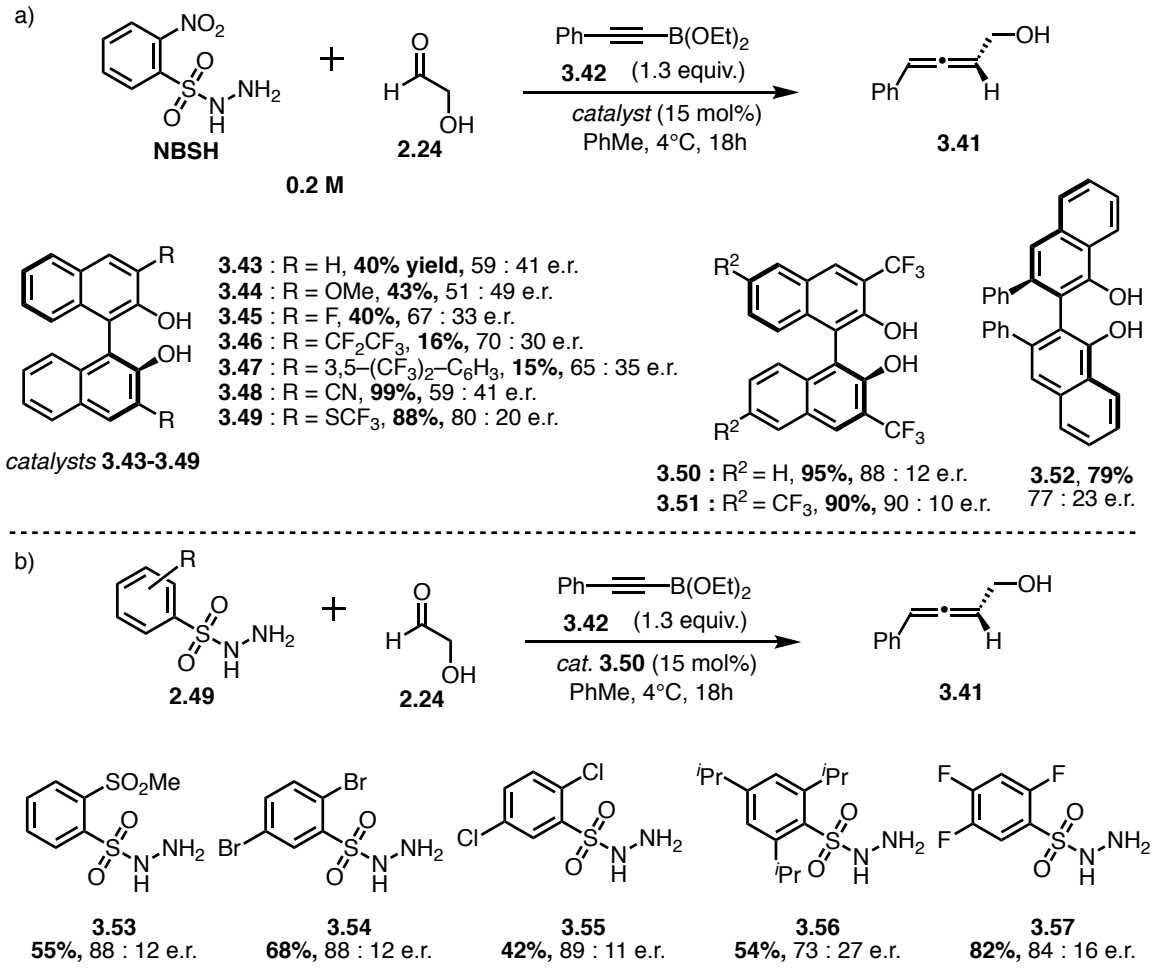
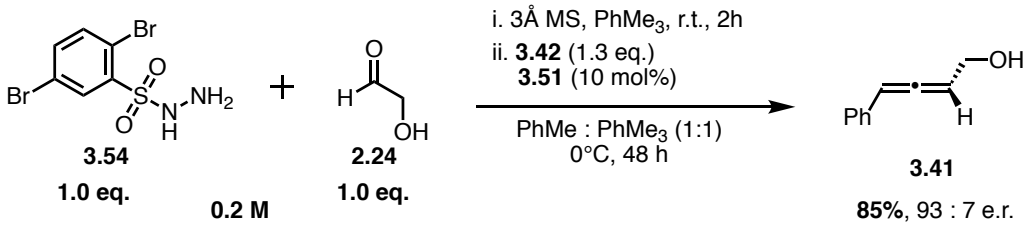


Table 3.2 Optimization of the hydrazide and the biphenol catalyst (Dr. Jiang)

The results in Table 3.2a underline a correlation between the electron-deficiency of the biphenol catalyst, and the stereoselectivity of the reaction. The native selectivity of the parent BINOL **3.43** is 59 : 41 e.r., while the only catalyst that is more electron rich, the methoxy-functionalized BINOL **3.44**, essentially affords a racemic mixture of allene products. This trend denotes that the more electron-deficient—and thus acidic—biphenol catalysts are more apt to perform ligand exchange with boronate **3.42**, and hence mitigate the uncatalyzed background reaction. Following that logic, it is not altogether surprising that the highly acidic catalysts **3.50** and **3.51** provide the highest yielding and most

selective reactions, with the 3,3′,6,6′-$(CF_3)_4$-BINOL **3.51** providing the first selectivity ratio above 90 : 10 e.r. The simultaneous optimization studies regarding the identity of the hydrazide, which were performed with catalyst **3.50**, revealed that 2,5-dibromobenzenesulfonyl hydrazide **3.54** produces the most useful mix of high yield and stereoselectivity.

The results in Table 3.2b emphasize, in a non-obvious way, that the selectivity and yield of the reaction are dependent on both the electron-withdrawing nature of the hydrazide, which directly correlates with yields of the allene—consistent with our observations from previous iterations of the traceless Petasis reaction[66,85]—and the steric bulk of the arene moiety. **3.54** offers the best amalgamation of these steric and electronic factors. Overall, as a result of the four-dimensional screen, we identified toluene/mesitylene, 2,5-dibromobenzenesulfonyl hydrazide **3.54**, 3,3′,6,6′-$(CF_3)_4$-BINOL **3.51**, and ethyl boronate **3.42** as the optimal combination of reagents to carry out the enantioselective traceless Petasis reaction. What remained is a final targeted optimization of reaction conditions and operational procedures, which is summarized in Scheme 3.3.



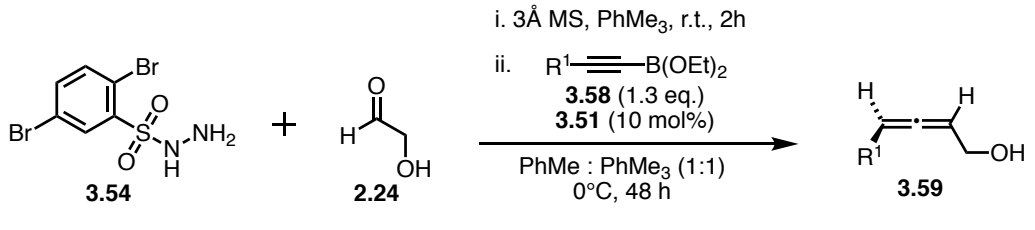
Scheme 3.3 Optimized conditions for the enantioselective traceless Petasis reaction

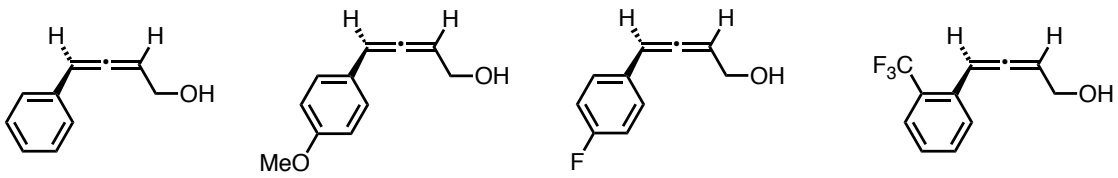
The initial condensation of hydrazide **3.54** and α-hydroxy aldehyde **2.24** is performed in mesitylene at r.t. over 2 hours in the presence of molecular sieves. At this time the catalyst is added, followed by the alkynyl boronate **3.42** as a 1.0 M solution in toluene.

The reaction is then allowed to stir at 0 °C over 48 hours. It was discovered that the reaction temperature needs to be lowered to 0°C to slow down the rate of the unproductive background reaction relative to the catalyzed asymmetric reaction for optimal stereoselectivity, and the reaction time was consequently elongated to allow for full conversion. Furthermore, the reaction is quenched with aqueous sodium hydroxide and allowed to warm up to room temperature in order to fully fragment the intermediate chiral propargylic hydrazide to form the allene **3.41**. This procedural modification would have been unnecessary with NBSH as the hydrazide, as the hydrazide fragmentation with concomitant loss of *o*-nitrobenzenesulfinic acid proceeds spontaneously at 0 °C. The intermediate enantioenriched propargylic hydrazide was actually isolated and fully characterized, which allowed us to confirm the mechanism postulated in Scheme 3.2.

3.3.2 Evaluation of the Substrate Scope of the Asymmetric Traceless Petasis Reaction

With the operational protocol of this transformation fully elucidated, we proceeded to evaluate the substrate scope of the enantioselective traceless Petasis reaction with regards to alkynyl boronate partners. The results are listed in Table 3.3.





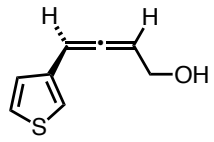
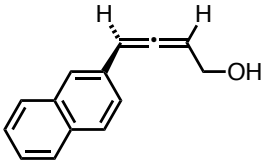
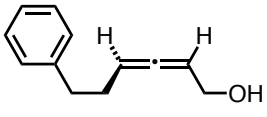
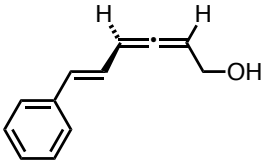
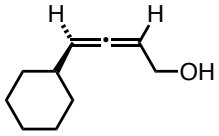
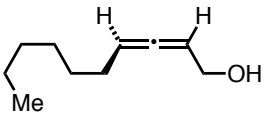
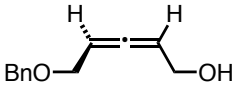
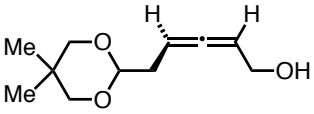
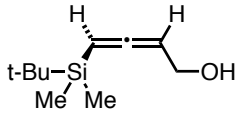
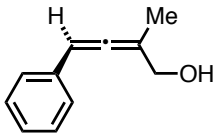
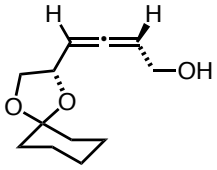
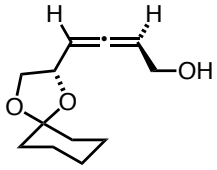
3.41, 85% yield 93 : 7 e.r.	**3.59b**, 80% yield 91 : 9 e.r.	**3.59c**, 78% yield 93 : 7 e.r.	**3.59d**, 71% yield 93 : 7 e.r.
			
3.59e, 70% yield 92 : 8 e.r.	**3.59f**, 85% yield 90 : 10 e.r.	**3.59g**, 72% yield 92 : 8 e.r.	**3.59h**, 71% yield 90 : 10 e.r.
			
3.59i, 63% yield 90 : 10 e.r.	**3.59j**, 73% yield 90 : 10 e.r.	**3.59k**, 60% yield 90 : 10 e.r.	**3.59l**, 70% yield 85 : 15 e.r.
			
3.59m, 62% yield 95 : 5 e.r.	**3.59n**, 91% yield 90 : 10 e.r.	**3.59o**, 71% yield 93 : 7 d.r.	**3.59p**, 68% yield 91 : 9 d.r.

Table 3.3 Substrate scope of the enantioselective traceless Petasis reaction (w/ Dr. Jiang)

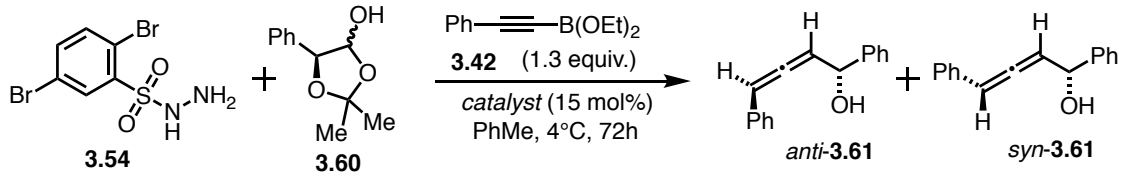
A number of electron-rich and electron-deficient aromatic alkynyl boronates were well tolerated under the reaction conditions, furnishing the desired axially chiral allenes **3.41** and **3.59b-f** in consistently good yields and enantioselectivities, ranging from 90 : 10 to 93 : 7 e.r. Aliphatic and α,β-unsaturated boronates furnished the corresponding allenes **3.59g-k** in commensurately good yields and enantioselectivities. A TBS-protected alkynyl boronate furnished allene **3.59m** in moderate yield, but with the highest enantioselectivity of 95 : 5 e.r., potentially owing to the increased steric bulk of the alkyne. Encouragingly, an α-hydroxy ketone such as hydroxyacetone was tolerated under

the reaction conditions, and its reaction with phenylacetylene derived boronate **3.42** afforded trisubstituted allene **3.59n** in excellent yield and reasonable enantioselectivity of 90 : 10 e.r. As such, this is the first example of a catalyst-controlled, asymmetric synthesis of a trisubstituted allene through the ATA, since this particular reaction is mechanistically distinct from the report of Jianbo Wang and coworkers, whose reaction proceeds via the intermediacy of diazo species derived from tosylhydrazones.[108p] Alkynyl boronates containing reactive handles for post-synthetic modifications of the chiral allenes can also be fruitfully engaged in the reaction. Acetal **3.59l** is produced in good yield, albeit with the reduced enantioselectivity of 85 : 15 e.r. Most importantly, chiral alkynyl boronates can be engaged in the catalyst-controlled, diastereoselective traceless Petasis reaction, wherein both enantiomers of catalyst **3.51** can be used to furnish the diastereomeric pair of allenes **3.59o** and **3.59p** in nearly identical yields and selectivity.

3.3.3 Diastereoselective Variant of the Traceless Petasis Reaction

The successful application of a catalyst-controlled, stereodivergent traceless Petasis reaction to afford diastereomeric pair **3.59o** and **3.59p** was an exciting achievement, as it illustrated that stereochemical information can be adequately introduced through the alkynyl reaction partner. We were intrigued by the prospect of developing a complementary diastereoselective traceless Petasis reaction featuring the coupling of an achiral alkynyl boronate with a chiral α-hydroxy hydrazone, wherein the stereochemical outcome would be entirely controlled by the catalyst rather than the substrate. Because both enantiomers of chiral α-hydroxy aldehydes and catalyst **3.51** are readily available, this devised reaction offered the exciting possibility of performing stereodivergent syntheses of all possible diastereomers of a given allene, or its post-synthetically

accessed derivatives. We therefore began these optimization studies by examining the level of asymmetric induction imparted by various catalysts in the traceless Petasis reaction of (+)-mandelic acid-derived, protected α-hydroxy aldehyde **3.60** (Table 3.4).



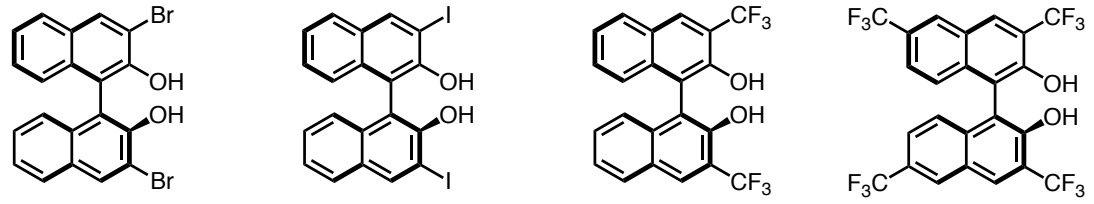


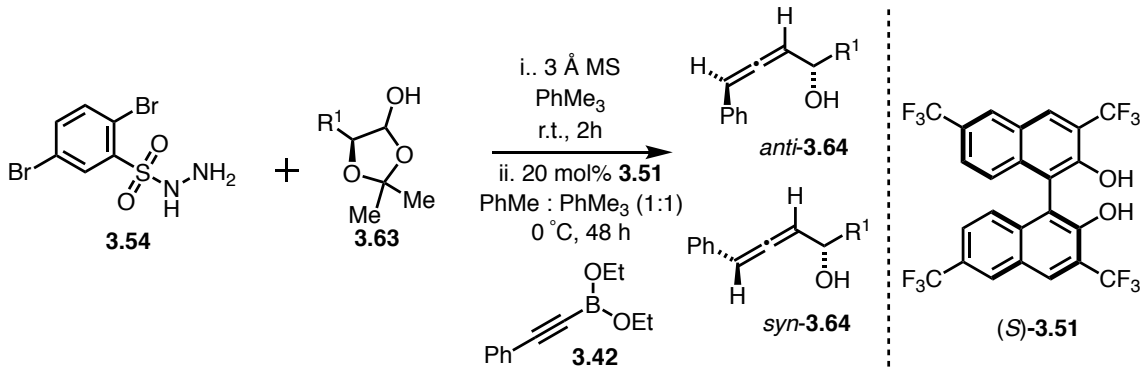
Table 3.4 Optimization of the diastereoselective traceless Petasis reaction

All four different catalysts screened afforded the *anti* diastereomer **3.61** as the major product of the diastereoselective traceless Petasis reaction, in accordance with the established mechanism of the Petasis Borono-Mannich reaction, as well as our own previous observations.[66,85,112d] The electron-deficiency of each catalyst is once again found to be the major factor in the level of asymmetric induction it imparts in the reaction. Halogenated binaphthols **2.39** and **3.62** both provided the major *anti* diastereomer in nearly 4 : 1 d.r., albeit with poor yields. Trifluoromethylated catalysts **3.50** and **3.51** furnished much better results, both with yields above 87%, and selectivities of 9 : 1 and >20 : 1 d.r. respectively.

Subsequent experiments summarized in Table 3.5 were devoted to determining the selectivity imparted by the configuration of the catalyst, while also examining the scope of the reaction vis-à-vis the α-hydroxy aldehydes. One catalyst enantiomer, (*S*)-**3.51**, gives rise to enhanced selectivity in the formation of the *anti* diastereomers of all chiral α-hydroxy aldehydes surveyed, with selectivities as high as >20 : 1 for products **3.61** and **3.64b**, and in excellent yields. However, the use of the (*R*)-**3.51** catalyst only results in a 1 : 1 mixture of diastereomers in nearly all cases, with correspondingly reduced yields. Evidently, the catalyst is not able to completely overturn the inherent selectivity imparted by the chiral substrate. In the diastereomeric transition state structures akin to **3.37** (Scheme 3.2), the helicity of the axially chiral (*S*)-**3.51** is reinforced by the (*S*)-configuration of the α-hydroxy aldehyde **3.63** in the matched case, while the helicity is destabilized in (*R*)-**3.51** in the mismatched case. This effect is even more pronounced when employing an enantiopure α-hydroxy ketone such as **3.65.** The *anti*-**3.64e** product is obtained in >20 : 1 selectivity and 70% yield in the matched case, while the enantiomeric (*R*)-catalyst results in a 9:1 diastereomeric ratio still favoring the *anti*-diastereomer.

These moderately disappointing results underscore the synthetic challenge of overcoming the inherent *anti* selectivity of the Petasis reaction by a catalyst-controlled process. The previous successful realization of this strategy featured an additional element of stereocontrol beyond what is presented here, notably a stereocenter within the amine component.[112d] In that particular reaction, the matched combination of an L-amine and (*S*)-configured catalyst favored the production of the *syn* diastereomers, together overcoming the inherent *anti* selectivity bias imparted by the aldehyde. Overall, while we

were unable to achieve our desired goal of developing a completely catalyst-controlled diastereoselective variant of the traceless Petasis reaction, we still uncovered a very synthetically useful method to selectively synthesize *anti* 2,3-allenols.



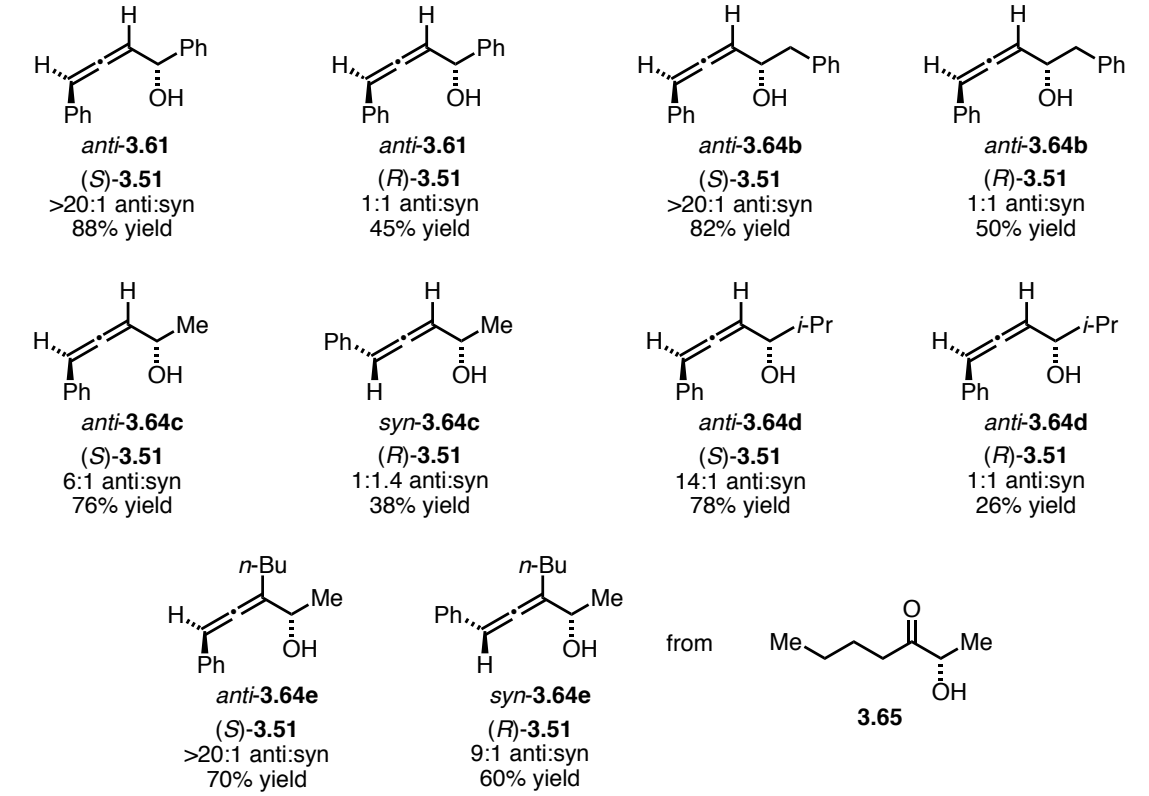


Table 3.5 Diastereoselective allene synthesis

3.3.4 Traceless Petasis Reactions of Alkynyl Aldehydes

The previous sections decisively underscore the ability of enantioenriched propargylic hydrazides akin to **3.66** to stereospecifically form optically active allenes via the retro-ene decomposition of the corresponding monoalkyldiazines. These propargylic hydrazides were generated by the asymmetric alkynylation of α-hydroxy hydrazones **2.26** with boronates **3.35**, corresponding to disconnection A Figure 3.3. This reaction proceeded with a remarkable level of acyclic stereocontrol. The alternative disconnection B of propargylic hydrazide **3.66**—where R^2 = vinyl—leads back to propargylic N-sulfonyl hydrazone **3.67** as the electrophile and allyl boronate **3.68** as the nucleophile. We turned to the nucleophilic allylation reaction as a fruitful reaction to survey, given the well-established precedent in the literature regarding the chiral biphenol-catalyzed asymmetric reactions of allyl boronate reagents.[111f,112a,113]

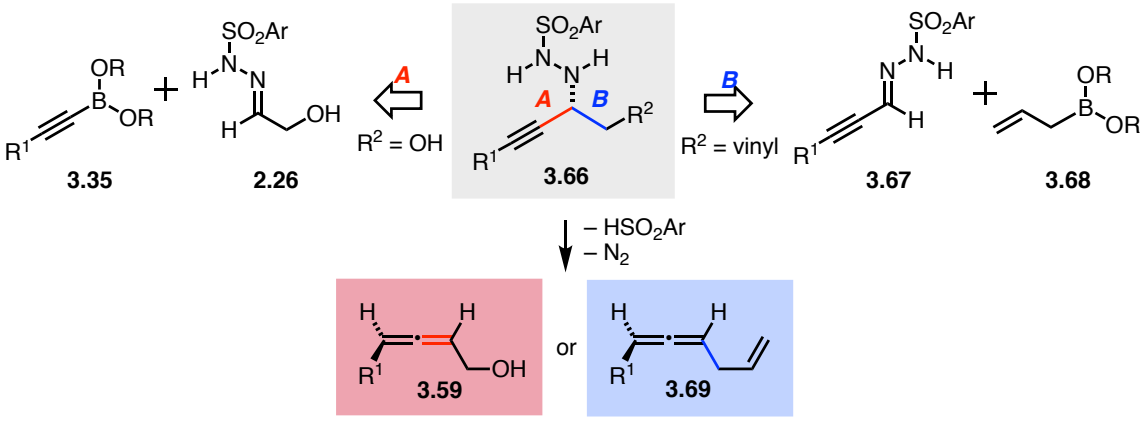


Figure 3.3 Asymmetric routes to chiral allenes using traceless Petasis reactions

The Schaus group in particular has significantly explored this chemical space, leading to the disclosure of a highly stereoselective allylation of hindered ketones such as **3.70** with acyclic allyldiisopropoxyboronate reagent **3.24** to generate homoallylic alcohol **3.72**

in 95 : 5 e.r. via the closed transition state depicted in **3.71** (Figure 3.4a).[113a] They subsequently reported improved reaction conditions to effect the same transformation, employing cyclic allyl boronate reagent **3.24a** in the presence of a reduced loading of the same catalyst, with *tert*-butanol as the solvent, to generate product **3.72** in higher yield and enantioselectivity (Figure 3.4b).[113b]

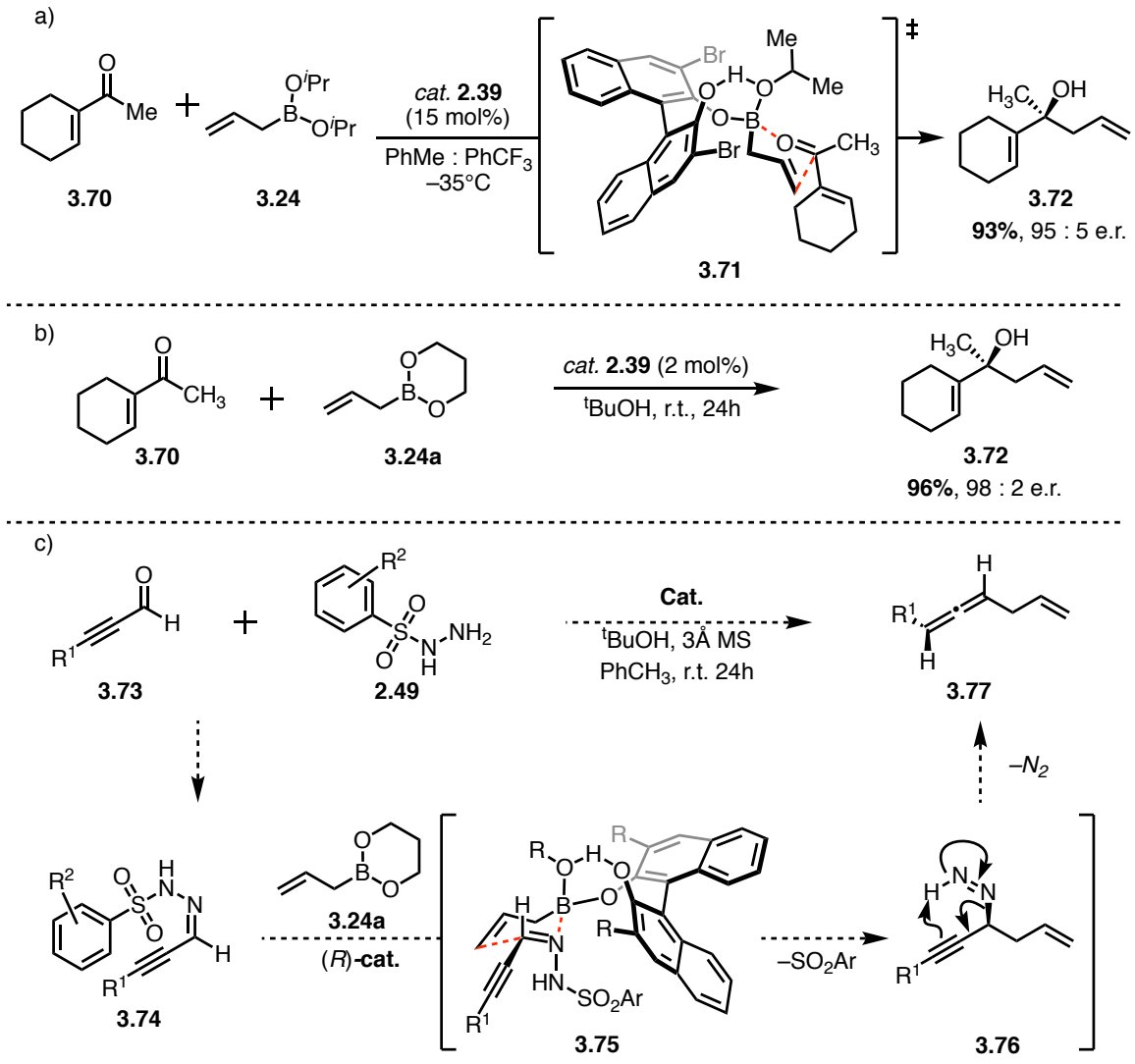
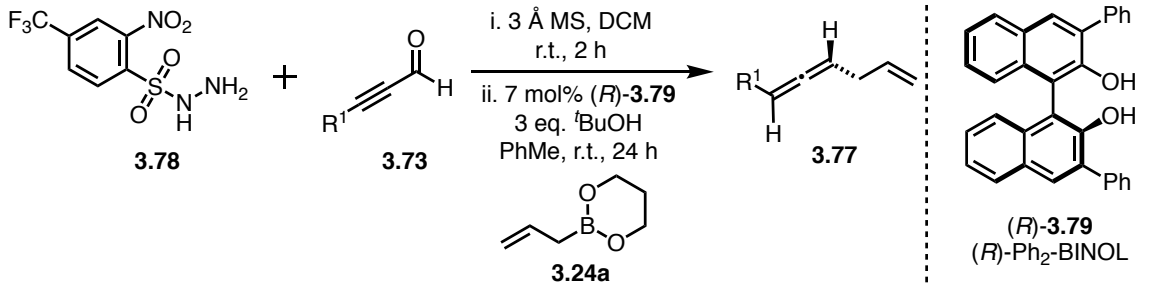
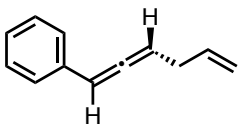


Figure 3.4 Chiral binaphthol-catalyzed asymmetric allylation reactions

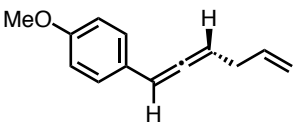
We therefore surmised that it would be possible to engage propargylic N-sulfonyl hydrazone **3.74** in the same reaction, via intermediate **3.75** to generate the enantioenriched propargylic monoalkyldiazine **3.76**, whose retro-ene decomposition produces the desired allyl allene **3.77** (Figure 3.4c). Once again the identity of the hydrazide reaction partner **2.49** and the chiral biphenol catalyst proved to be capital for optimal results of this new asymmetric Petasis allylation reaction.

Following targeted optimization studies, Dr. Yao Jiang ultimately determined that the combination of 2-nitro-4-trifluoromethylbenzene sulfonyl hydrazide **3.78**, the cyclic allyl boronate **3.24a** and the 3,3′-Ph_2-BINOL catalyst **3.79** afforded the desired allenes **3.77** in the highest yields and enantioselectivities. Furthermore, the Petasis Borono-Mannich reactions could be effectively carried out in toluene—after an initial condensation reaction in DCM—in the presence of 3 equivalents of *tert*-butanol, which serve to accelerate the catalyzed reaction by facilitating ligand exchange and catalyst turnover.[113b] The full scope of the transformation is presented in Table 3.6.

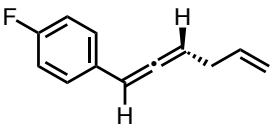




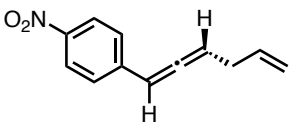
3.77a, 83% yield
99 : 1 e.r.



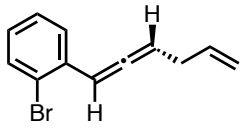
3.77b, 88% yield
98 : 2 e.r.



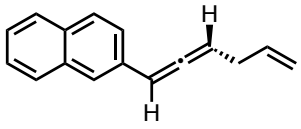
3.77c, 87% yield
99 : 1 e.r.



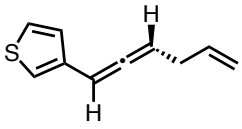
3.77d, 87% yield
98 : 2 e.r.



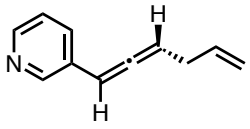
3.77e, 60% yield
99 : 1 e.r.



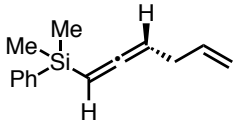
3.77f, 89% yield
98 : 2 e.r.



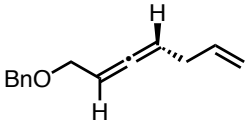
3.77g, 87% yield
99 : 1 e.r.



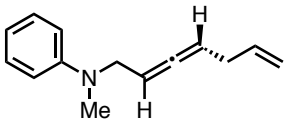
3.77h, 27% yield
98 : 2 e.r.



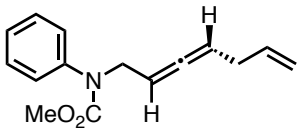
3.77i, 73% yield
98 : 2 e.r.



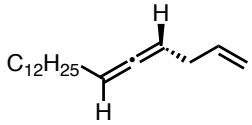
3.77j, 90% yield
98 : 2 e.r.



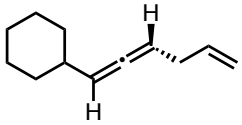
3.77k, 50% yield
99 : 1 e.r.



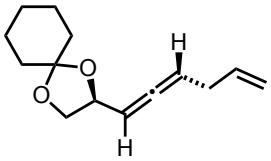
3.77l, 85% yield
99 : 1 e.r.



3.77m, 98% yield
98 : 2 e.r.



3.77n, 62% yield
99 : 1 e.r.



3.77o, 79% yield
99 : 1 d.r.

Table 3.6 Scope of the enantioselective allylation of alkynyl aldehydes (w/ Dr. Jiang)

The fact that this reaction proceeds mechanistically through a closed transition state as opposed to the acyclic transition state of the asymmetric alkynylation reaction signifies that the desired products are generally accessed with much better asymmetric induction. Notably, this reaction was tolerant of a series of electron-rich and electron-deficient aromatic alkynyl aldehyde, affording allenes **3.77a-f** in excellent yields and enantioselectivities of up to 99 : 1. Heterocyclic propiolaldehydes were also good substrates for the reaction, with products **3.77g** and **3.77h** being produced in >98 : 2 e.r., although the yield of **3.77h** was a low 27%, presumably owing to the ability of the pyridine moiety to act as a Lewis basic coordinator to boronate **3.73**, thereby appreciably inhibiting the reaction. Silyl propiolaldehyde (**3.77i**, 73% yield, 98 : 2 e.r.) and

propargylic heteroatom-bearing propiolaldehydes proved to be good substrates, as evidenced by the production of allenes **3.77j-l** in good yields and excellent enantioselectivities. Finally, both acyclic and cyclic aliphatic propiolaldehydes were also effectively converted to the corresponding enantioenriched allenes **3.77m-n**, with allene **3.77o** being produced in good yield and excellent diastereoselectivity of 99 : 1.

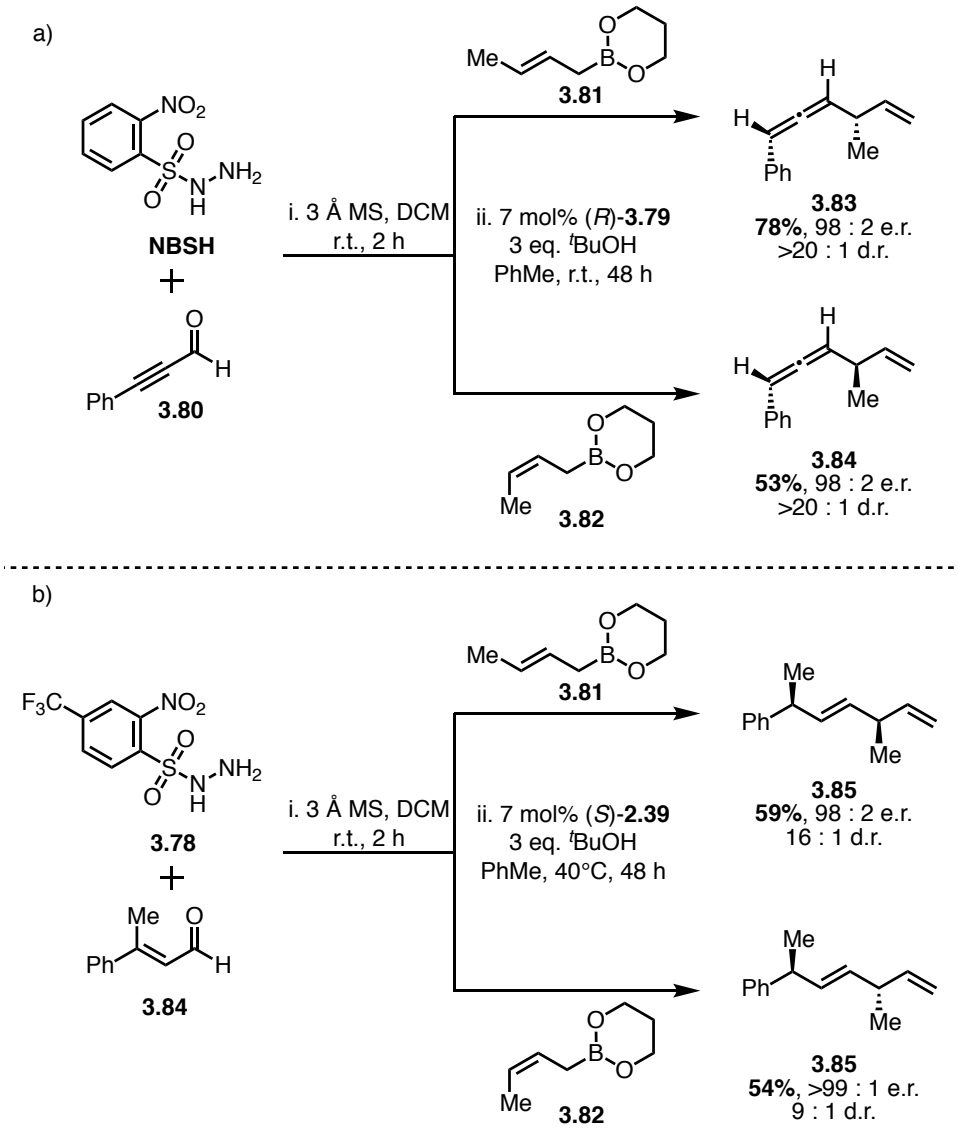


Figure 3.5 Diastereoselective crotyllations of unsaturated aldehydes (Dr. Jiang)

3.4 Synthetic Applications of the Enantioenriched Allene Products

3.4.1 Cycloisomerization Reactions of Enantioenriched 2,3-allenols

The enantioenriched 2,3-allenols **3.59** or allylic allenes **3.77** obtained as the result of the novel synthetic methodology developed herein are versatile intermediates that can be further elaborated into a number of useful architectures. Notably, optically active 2,3-allenols undergo stereospecific cycloisomerization reactions in the presence of Au(III) or Ag(I) catalysts to afford enantioenriched 2,5-dihydrofurans.[115] In particular, diastereomic allenol pair **3.59o** and **3.59p** cyclize in a stereodivergent manner to afford diastereomeric 2,5-dihydrofurans **3.87** and **3.88**, and single diastereomer *anti*-**3.64b** produces *trans*-dihydrofuran **3.89**, all with complete retention of stereochemical information. The attempted cyclization of phenyl-substituted allene **3.41** using $AuCl_3$ produced dihydrofuran **3.86** in a low 25% yield, and with significant erosion of the enantiopurity, while $AgNO_3$ (10 mol%) on silica gel induced the cyclization to produce **3.86** in 67% yield, and with no change in the enantiomeric ratio. This discrepancy in results could be potentially rationalized by a non-negligible propensity for a slow gold-mediated racemization of aromatic allenes via an isomerization pathway to the corresponding alkyne. This pathway could be conceivably responsible for the commensurate depreciation of the reaction yield. This tendency for the racemization of allenic species containing unsaturated groups at the α-position was also observed during our attempted stereocontrolled synthesis of the pheromone of the dried-bean beetle[116] from the enantioenriched allenol derived from 1-decyne. MnO_2-mediated oxidation produced an intermediate allenyl aldehyde that was found to slowly racemize, with its enantiopurity eroding from 93 : 7 e.r. to ~60 : 40 e.r. within a 16 hour period of storage at 0°C.

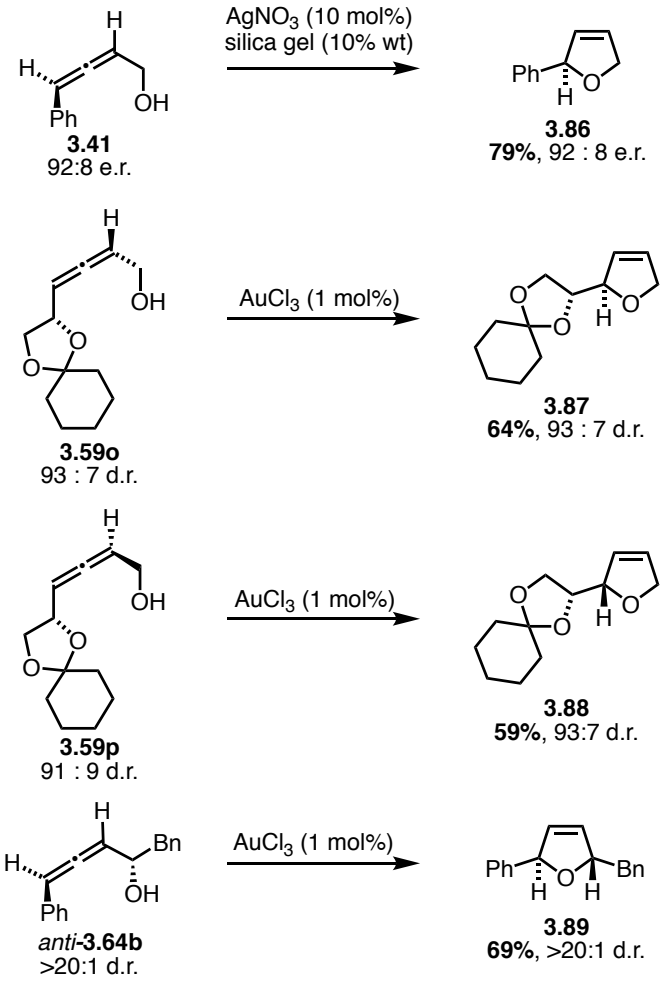
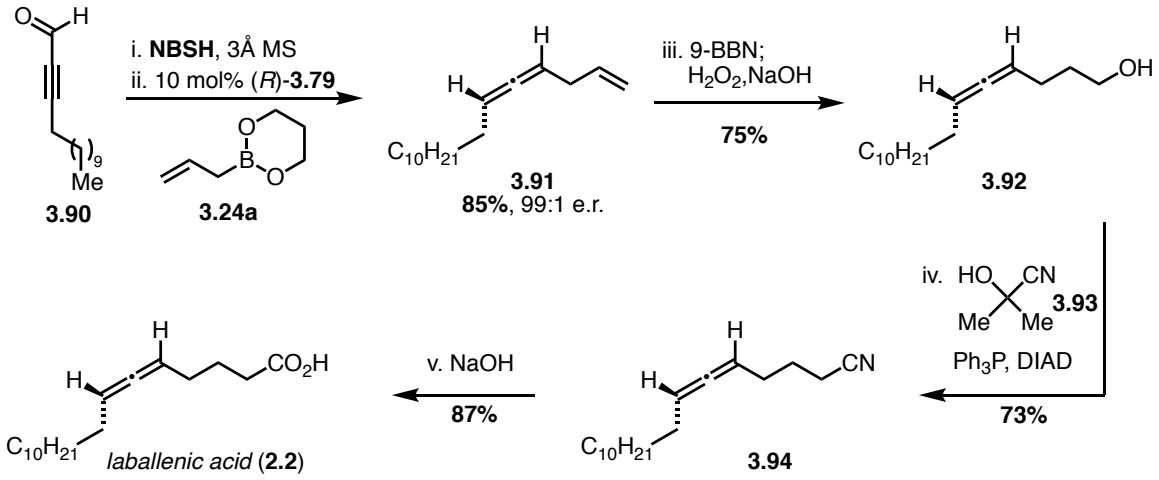


Figure 3.6 Selected cycloisomerization reactions of optically active 2,3-allenols

3.4.2 Application to the Stereocontrolled Total Synthesis of Laballenic Acid

As an illustration of the synthetic utility of the traceless Petasis allylation of alkynyl aldehydes, Dr. Yao Jiang completed the stereocontrolled synthesis of allenic natural product laballenic acid **2.2**, which is a major constituent of *Leonotis nepetafolia* seed oil. The synthetic sequence is illustrated in Scheme 3.3. The enantioselective allylation of the hydrazone derived from propiolaldehyde **3.90** with boronate **3.24a** afforded allene **3.91** in 85% yield and 99 : 1 e.r. This product was then remarkably chemoselectively hydroborated with 9-BBN and oxidized with H_2O_2 in the presence of aq. NaOH to

furnish alcohol **3.92** in 75% yield. Mitsunobu displacement with reagent **3.93** produced nitrile **3.94**, which was readily saponified to afford the natural product **2.2**. Our observed optical rotation of the synthetic sample of **2.2** compared very favorably with that of the natural sample, allowing us to determine that the entire synthetic sequence delineated in Scheme 3.3 proceeded without any erosion of stereochemical information. Dr. Jiang also applied a similar sequence to complete the formal synthesis of an odor-active lactone component of oranges and wasabi. Overall, the methodologies developed in this chapter are broadly useful in enabling the synthesis of optically active molecules. The disclosed chemoselective hydroboration/oxidation of allylic allenes **3.77** and **3.90** greatly expands the synthetic utility of these molecules, given the diverse opportunities for post-synthetic modifications of highly versatile alcohol functionalities.



Scheme 3.4 Enantioselective synthesis of laballenic acid (Dr. Jiang)

3.5 Application to the Stereocontrolled Total Synthesis of Annonaceus Acetogenins

3.5.1 Introduction to Annonaceus Acetogenin Natural Products

Section 3.4.2 illustrates the relative ease with which optically enriched 2,3-allenols can be effectively cycloisomerized by Au(III) or Ag(I) complexes to produce

stereodefined 2,5-dihydrofurans. The latter, along with their saturated derivatives, constitute a privileged structural motif found in numerous biologically active natural products and pharmaceuticals, including ionophore antibiotics,[117] amphidinolides,[118] lignans,[119] toxins,[120] and other macrolides.[121] As a result, stereodefined dihydrofurans and tetrahydrofurans have attracted considerable attention in the synthetic community and have been the inspiration of a number of capital reaction modes.[122] One particular family of tetrahydrofuran-containing natural products that has commanded outsized interest since its discovery in the early 1980s[123] is that of the annonaceus acetogenins, mostly due to their broad scope of remarkable antifungal, herbicidal, antiviral, and anticancer biological properties, and their prominent use as therapeutic agents in traditional medicine.[124] Annonaceus acetogenins are potent cytotoxic compounds that inhibit the NADH: ubiquinone oxidoreductase[124c,125]—also know as complex I—which is the first enzyme of the mitochondrial electron transport chain. Inhibition of complex I results in ATP deprivation, which leads to apoptosis of tumor cells.[126]

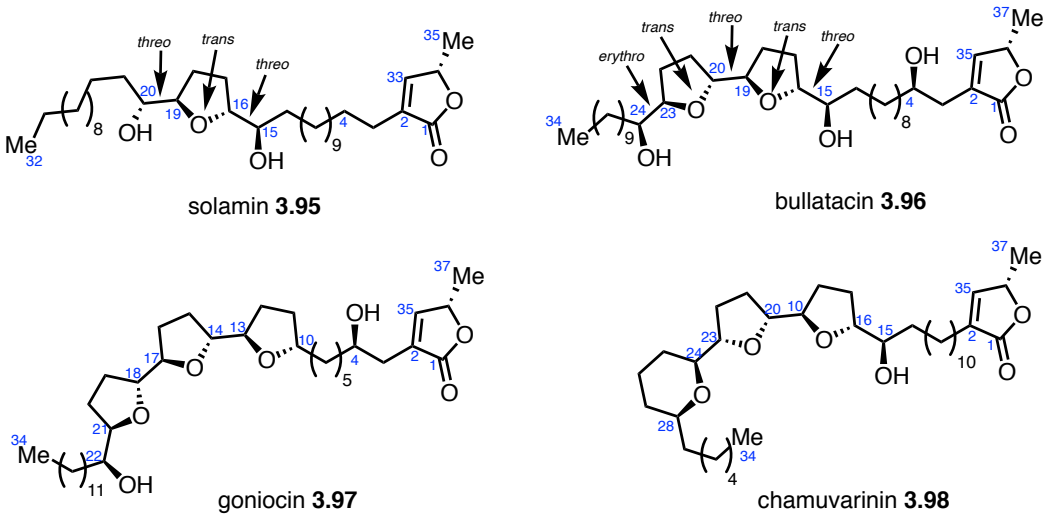


Figure 3.7 Representative annonaceus acetogenin natural products

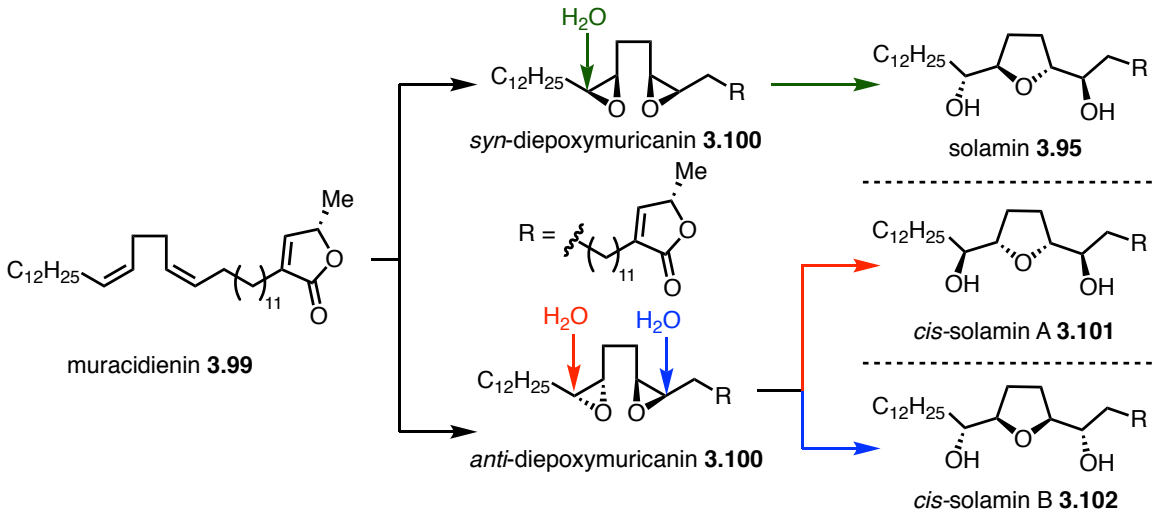
As a result of this property, many members of the annonaceus acetogenins routinely exhibit strong antitumor activity in the low nanomolar range.[127] Annonaceus acetogenins have thus been the subjects of more than 100 total synthesis efforts.[128] Representative targets are illustrated in Fig. 3.7. Archetypal annonaceus acetogenins **3.95**-**3.98** underscore the wide variability of structures within this family of more than 420 members. Solamin **3.95** is a highly sought-after C35 member, while the other illustrated ones are C37 compounds, which possess variable oxygenation patterns within their backbone, including a disparate number of stereodefined THF rings ranging from one to three. Unusual variants such as chamuvarinin **3.98** can also incorporate stereodefined tetrahydropyran moieties within their backbone. Furthermore, the relative stereochemistry of the oxygenated stereocenters may differ across molecules, which seemingly negligibly impacts the biological activity of the molecules. One salient commonality within molecules **3.95**-**3.98** is their terminal chiral butenolide functionality, which previous studies have shown to directly interact with the hydrophobic domain of complex I, thereby allowing the precise positioning of the hydrophilic components of the acetogenin within the enzyme's active site for successful inhibition.[129] In all, previously reported asymmetric syntheses of these molecules tend to be long, albeit convergent, and usually feature well-known reactions that can reliably produce oxygenated stereogenic centers, such as the Sharpless asymmetric epoxidation[130] and dihydroxylation[131] reactions. Alternatively, a number of approaches also rely on the chiral pool to introduce stereodefined carbinols, or on novel methodologies that are analogous to those afore-mentioned Sharpless asymmetric transformations. Because these powerful and modular reactions are readily amenable to the synthesis of a number of diastereomerically pure

compounds, they easily enabled the unambiguous determination of the absolute configurations of a number of acetogenins. Overall, annonaceus acetogenins remain a highly desired set of natural products that inspire creative and novel methodologies to access privileged motifs in organic synthesis.

3.5.2 Introduction to Solamin and its *cis* Congeners

Solamin (**3.95**) is a C35 mono-THF acetogenin first isolated from the extracts of the seeds of *Annona muricata* by Myint *et al.* in 1991.[132] It possesses the characteristic chiral butenolide terminus, along with only two hydroxyl groups, one at each of the two α-positions on the tetrahydrofuran ring, with an overall *threo/trans/threo* stereochemical configuration. Its absolute configuration could not be conclusively determined on the basis of spectroscopic studies at the time of isolation, hence the stereochemical assignment was only confirmed by total synthesis.[133] Its congener *cis*-solamin was first isolated from the roots of *Annona muricata* in 1998 by Laurens and coworkers;[134] the authors determined in the same publication that the relative stereochemistry of the THF-diol component is *threo/cis/threo*. Once again, the absolute stereochemistry of this natural product could not be assigned at the time of isolation, therefore subsequent synthetic efforts focused on synthesizing both possible tetra-epimeric diastereomers *cis*-solamin A **3.101** and *cis*-solamin B **3.102** (Scheme 3.5) and decisively establishing one of them as the natural isomer. These efforts were not ultimately successful, given that both compounds display nearly identical NMR data and optical rotations; however, they were easily differentiable by chiral HPLC analysis.[135] Finally, in 2006 Brown and coworkers determined that natural *cis*-solamin is indeed composed of the two tetra-epimeric

diastereomers, and reasoned that the biosynthesis of the solamins must incorporate the stereodivergent enzymatic hydrolytic cyclization of previously devised precursor *anti*-diepomuricanin A2 **3.100** (see Scheme 3.5).[123,136] The putative tetra-epimeric diastereomer of solamin **3.95** is proposed to arise from the complementary hydrolytic cyclization of *syn*-diepoxymuricanin **3.100**, but it has yet to be isolated from natural sources.



Scheme 3.5 Proposed biosynthetic pathway towards solamin natural product congeners

All three known diastereomers of solamin **3.95**, **3.101** and **3.102** were shown to be highly potent inhibitors of mitochondrial complex I, with IC_{50} values of 3.9,[126b] 2.2, and 2.1 nM[135c] respectively. As a result, they have served as highly desired synthetic targets, and have been accessed by means of total or formal synthesis more than 20 times, efforts that additionally included incorporation of various heterocyclic moieties for SAR studies.[133,135a,135b,137] The syntheses of optically enriched solamin isomers reported to date either make use of the Sharpless asymmetric epoxidation,[137b,137c,137e] the Sharpless asymmetric dihydroxylation,[133,137c,137f] chiral pool starting materials,[137d] and chiral

auxiliaries,[135b,135d,137l] or they begin from other acetogenin natural products such as muricatacin.[135a,135c,137a,137j,137k,137m,137o] A selection of approaches towards these natural products is illustrated in Figure 3.8.

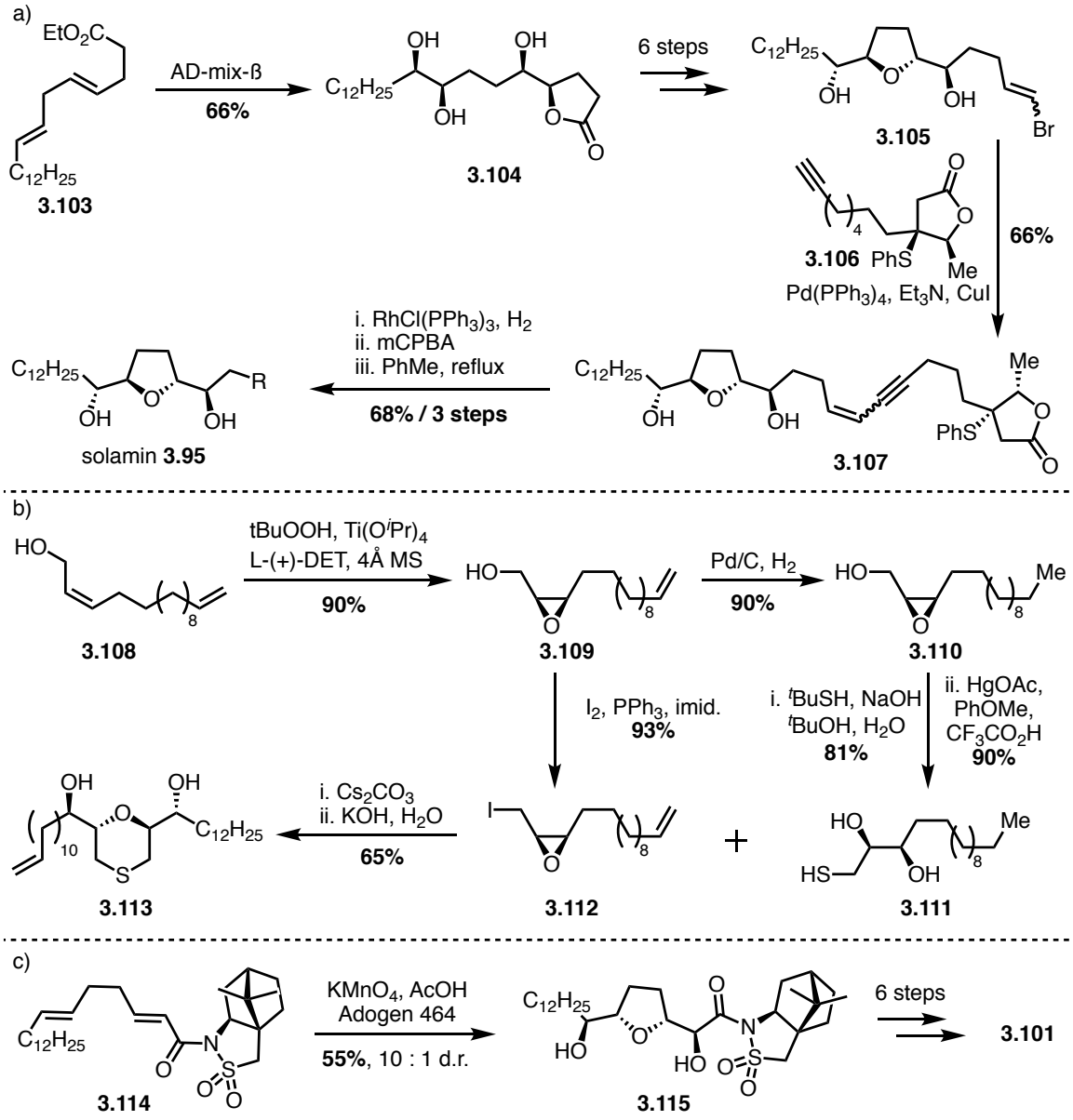


Figure 3.8 Selected syntheses of solamin natural products

Keinan's first total synthesis of solamin in 1993[133] (Figure 3.8a) commenced with the Sharpless asymmetric dihydroxylation of diene **3.103** to form lactone **3.104** as a single

enantiomer after recrystallization. After a 6-step sequence, the THF-diol **3.105** was produced as a single enantiomer with the desired *threo/trans/threo* configuration. Sonogashira coupling of vinyl bromide **3.105** with enantiopure alkyne **3.106** afforded enyne **3.107**, which was elaborated to the desired natural product in three steps. The modularity of the Sharpless asymmetric dihydroxylation permitted the unambiguous assignment of the absolute stereochemistry of the natural product for the first time.

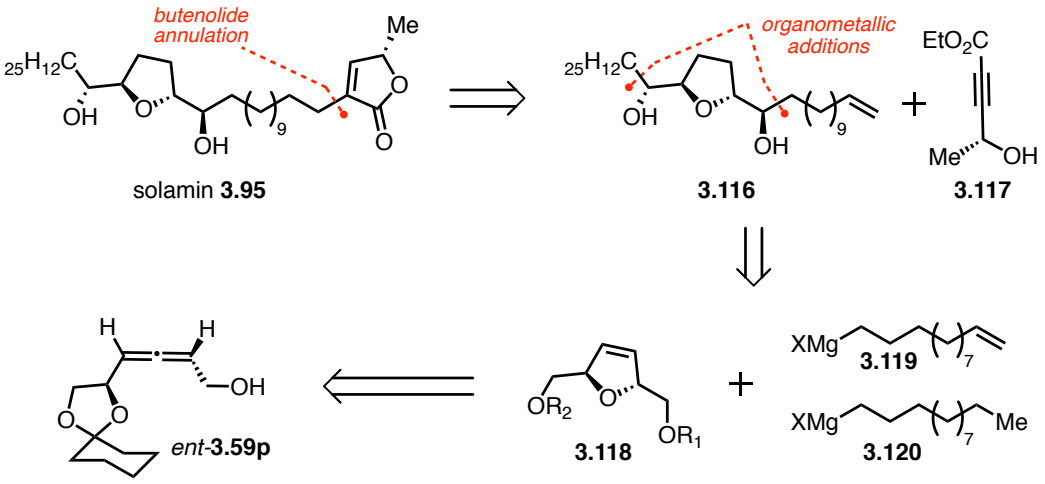
Trost's synthesis in 1994[137b] (Figure 3.8b) constituted the first use of the Ramberg-Bäcklund olefination as a key step to synthesize 2,5-dihydrofurans. The Sharpless asymmetric epoxidation of allylic alcohol **3.108** formed enantiopure allylic epoxide **3.109** after recrystallization. The synthesis then bifurcated from this epoxide to produce iodide **3.112** after an Appel reaction, and diol **3.111** after a tandem Payne rearrangement and nucleophilic opening of the rearranged epoxide from **3.110**. These two halves were united under basic conditions to form enantiopure oxathiane **3.113**, which subsequently underwent the Ramberg- Bäcklund olefination to produce the desired 2,5-dihydrofuran intermediate that is then elaborated to the natural product in four additional reactions. The final convergent step featured the ruthenium-catalyzed butenolide annulation of the terminal olefin with the ethyl ynoate derived from L-(+)-lactic acid (see Scheme 6), a transformation that has been replicated numerous subsequent times to install the butenolide functionality within annonaceus acetogenin natural products.

Finally, in 2002, Brown's group reported the total synthesis of *cis*-solamin A **3.101**, starting with chiral sulfonamide-affixed 1,5-diene **3.114**. Subjecting the latter to the key diastereoselective permanganate-promoted oxidative cyclization under phase-transfer conditions directly afforded the THF-diol moiety in its *threo/cis/threo* stereochemical

motif in 10 : 1 d.r. This powerful example denotes a unique case in which the entire stereotetrad of solamin was constructed with high diastereoselectivity in a single operation. This chiral auxiliary-mediated methodology is additionally very modular, as it enables the stereoselective synthesis of both diastereomers of *cis*-solamin by changing the absolute configuration of the chiral auxiliary. Overall, the syntheses of solamin diastereomers have been fruitful vehicles for innovation within organic chemistry, as they notably enabled the development of novel asymmetric oxidative cyclization methodologies, and refined the elegant use of fragment-coupling reactions to effect convergent syntheses.

3.5.3 Retrosynthetic Analysis of Solamin

We viewed the synthesis of annonaceus acetogenin natural products as an excellent opportunity to showcase the full utility of our asymmetric traceless Petasis reaction for the synthesis of optically active 2,3-allenols. Section 3.4.1 manifested the relative ease with which they can be cycloisomerized to 2,5-dihydrofurans in good yields and with no loss of stereochemical information. Given this precedent, we were intrigued by the possibility of accessing the THF-diol moiety of the solamins by means of a straightforward synthetic manipulation of diastereomeric allenes **3.59o** and **3.59p** (Table 3.3), which already possess the requisite three oxygen atoms of the THF-diol, and two stereogenic centers of the THF ring. The stereochemistry of the free hydroxyls would then be installed by careful chelate-controlled organometallic addition of the appropriate aliphatic groups. The full retrosynthetic analysis of solamin is illustrated in Scheme 3.5.



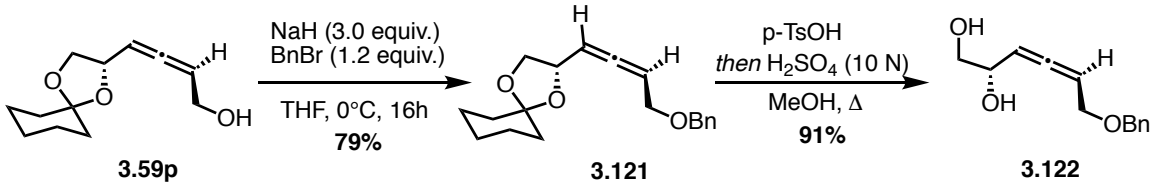
Scheme 3.6 Retrosynthetic analysis of solamin

We envisioned a late-stage application of Trost's ruthenium-catalyzed annulation reaction between a terminal alkene and lactic acid-derived alkyne **3.117** to install the terminal butenolide functionality.[137b] This transform leads back to olefin **3.116**, which can be accessed through the sequential chelate-controlled organometallic addition of Grignard reagents **3.119** and **3.120** on *trans*-dihydrofuran **3.118**, which features disparately protected hydroxyl groups. This particular dihydrofuran leads back to the enantiomer of product **3.59p** as a starting material. The forward synthesis of *epi*-solamin would first be attempted with **3.59p**, which is much more readily accessible, as the corresponding alkyne can be obtained in good overall yields from D-mannitol. The results of the enantiomeric set of compounds could then easily be translated to the desired natural product **3.95**.

3.5.4 Total Synthesis of *epi*-Solamin

The forward synthesis began with a survey of several protecting group strategies to be able to access dihydrofuran **3.118** in good yields. Silyl protecting groups such as TBS and TIPS ultimately proved to be fruitless because of the unexpected recalcitrance of the

cyclohexylidene protecting group to mild acids such as CSA and AcOH. Such conditions typically afforded unreacted starting material, and harsher conditions led to concomitant deprotection of the silyl group with the cyclohexylidene. The protecting group was then changed to a benzyl group, which is inert to acidic conditions and can be judiciously removed at a later stage in the synthesis. Subjecting an optically pure sample of **3.59p** to standard benzylation conditions thus furnished product **3.121** in 79% yield. Acid-mediated deprotection provided the free diol **3.122** in 91% yield.



Scheme 3.7 Synthesis of the cycloisomerization precursor

We were then ready to attempt the regioselective cycloisomerization reaction. We envisaged that the 5-*endo*-dig cyclization would be kinetically favored over the corresponding six-*endo*-dig cyclization, and therefore the 2,5-dihydrofuran would be preferentially formed over the dihydropyran. Since the cycloisomerization reaction is not reversible, the reaction would not necessarily require cryogenic temperatures to avoid thermodynamic control, and could potentially be performed at room temperature. This hypothesis was substantiated by precedent in the literature for regioselective gold-mediated cycloisomerization reactions in the context of natural product total synthesis, as illustrated in Figure 3.9.[138] In all cases, which include Krause's (–)-isochrysoticine, Kocienski's synthesis of the ionomycin calcium complex, and Murakami's synthesis of boivinianin B, the 2,5-dihydrofuran was exclusively the only product formed.

The application of this precedent to our system proceeded gratifyingly well. Upon treatment with 5 mol% of $AuCl_3$ at room temperature in THF, the starting diol **3.122** was fully consumed within 5 minutes to produce the cycloisomerized dihydrofuran **3.132** in 74% isolated yield (Scheme 3.7). The next step in the devised sequence would be to oxidize this alcohol and then effect the chelate-controlled organometallic addition of Grignard reagent **3.120**; however, we hypothesized that the diastereoselectivity of the addition would be improved by increasing the steric bulk of the dihydrofuran moiety, so it needed to be chemoselectively reduced in the presence of the benzyl protecting group.

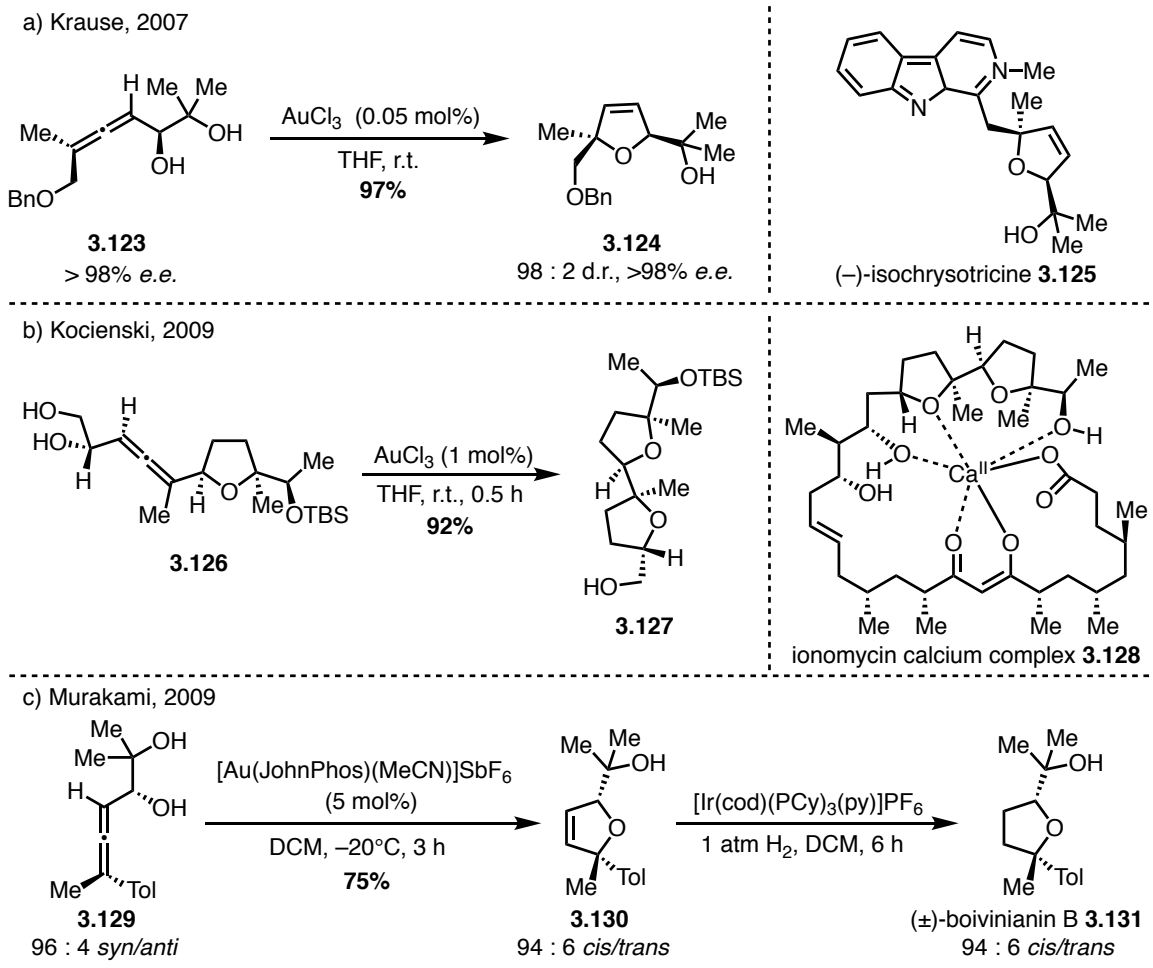
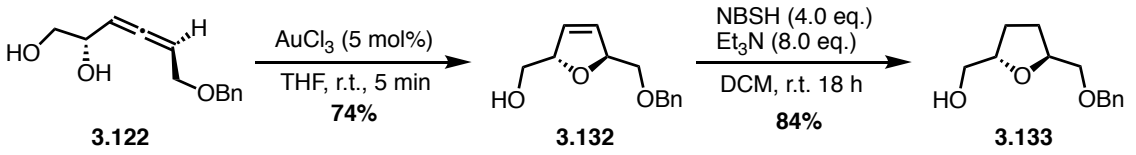
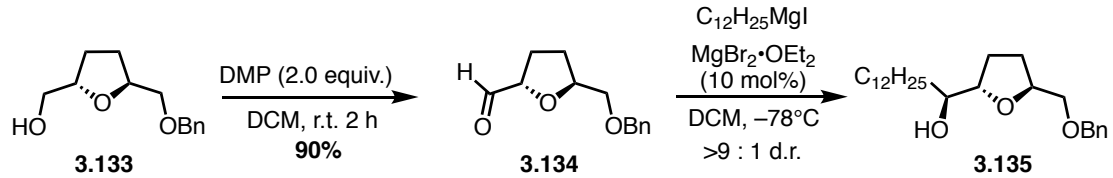


Figure 3.9 Regioselective allenol cyclizations for the synthesis of 2,5-dihydrofurans



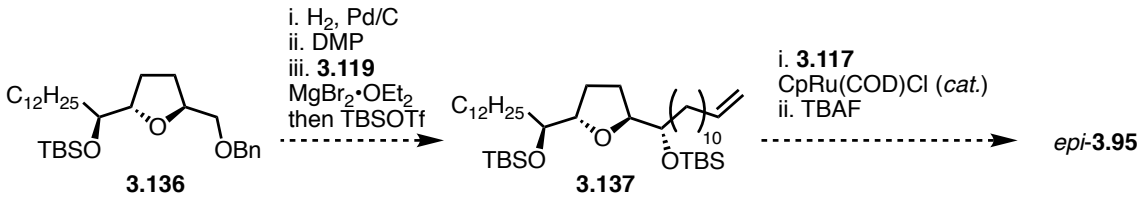
Scheme 3.8 Regioselective cycloisomerization of the allenic diol

The latter reaction was accomplished with a NBSH-based diimide reduction to furnish the saturated tetrahydrofuran **3.133** in 84% yield, a reaction that importantly did not remove the benzyl protecting group. The stage was then set for the key chelate-controlled Grignard addition. The addition of organometallic reagents to aldehydes with an α-tetrahydrofuran ring has a long history in organic synthesis, with mixed degrees of success.[139] The diastereoselectivity of the transformation generally tends to be substrate dependent, yet the reactions are often successful in polar solvents. The alcohol was first oxidized to the aldehyde with DMP to furnish aldehyde **3.134** in 90% yield (Scheme 3.9). Finally, the addition of Grignard reagent **3.120** furnished the desired alcohol **3.135** in good selectivity on a small ~5 mg test scale. Preliminary optimization studies showed that the combination of DCM as the solvent, and $MgBr_2 \bullet OEt_2$ as the chelating Lewis acid gave very good selectivity. A scaled up reaction, conjugated with an *in situ* protection of the intermediate alkoxide with *tert*-butyldimethylsilyl triflate would furnish the protected alcohol **3.136** (Scheme 3.10) in one pot.



Scheme 3.9 Preliminary result of the chelate-controlled organometallic addition

The remainder of the synthesis has yet to be completed, but it will proceed according to the plan delineated in Scheme 3.10. Hydrogenolysis of THF **3.136** would unveil the alcohol, which can be oxidized to the aldehyde. Re-iteration of the organometallic addition with Grignard reagent **3.119**, followed by *in situ* TBS-protection would provide intermediate olefin **3.137**. Finally, application of Trost's ruthenium mediated butenolide annulation reaction, followed by global desilylation would afford *epi*-solamin **3.95**.



Scheme 3.10 Synthetic end game

The diastereomerically correct natural product solamin can be obtained via application of the entire synthetic sequence to the starting material *ent*-**3.59p**—synthesized in 8 steps from L-ascorbic acid—(Scheme 3.6). Importantly, all three known diastereomers of solamin (in addition to putative *epi*-**3.95**) can be obtained through our synthetic sequence, given that two enantiomers of the alkynyl boronate are available, and both enantiomers of the catalyst can be used to furnish each diastereomer of the corresponding allenol.

3.6 Conclusions and Outlook

In summary, we have developed two unique asymmetric transformations that furnish, as a result of a convergent fragment coupling reaction, intermediate enantioenriched propargylic monoalkyldiazines that readily decompose via a stereospecific retro-ene rearrangement with perfect point-to-axial chirality transfer to furnish optically active

allenes. The chiral binaphthol-catalyzed enantioselective Petasis alkynylation of α-hydroxy N-sulfonylhydrazones affords optically active 2,3-allenols in good yields and with up to 95 : 5 e.r., while the complementary Petasis allylation or crotyllation of propargylic N-sulfonylhydrazones produces optically active allylic allenes in excellent enantioselectivity and diastereoselectivity. These novel reactions represent rare examples of organocatalytic fragment-coupling reactions that facilitate the efficient asymmetric synthesis of chiral allenes from achiral starting materials. Furthermore, we have illustrated the broad synthetic utility of these transformations by applying them in the context of natural product total synthesis. Specifically, the asymmetric allylation reaction permitted the concise, stereocontrolled synthesis of chiral allenic natural product (–)-laballenic acid, while the asymmetric alkynylation reaction permitted the stereocontrolled and stereodivergent synthesis of diastereomers of the highly potent antitumor annonaceus acetogenin solamin. The collection of novel traceless Petasis reactions described in this thesis represents the successful realization of mild and broadly applicable synthesis of allenes, which are very important intermediates in organic synthesis that can be leveraged to access a wide variety of cyclic and acyclic architectures. This collection also presents wonderful opportunities for continued exploration within this chemical space, which may eventually lead to stereocontrolled traceless reactions featuring sp^3–sp^2 or even sp^3–sp^3 coupling, which remain severely underdeveloped.

3.7 Experimental Section

3.7.1 General Information

All ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Unity Plus 500 MHz

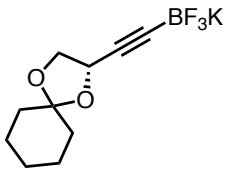
spectrometer at ambient temperature in $CDCl_3$ (Cambridge Isotope Laboratories, Inc.). Chemical shifts in ^1H NMR spectra are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (app = apparent, br = broad, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Chemical shifts in ^{13}C NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 77.0 ppm). All ^{13}C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR ESP spectrophotometer. High-resolution mass spectra were obtained using a Waters Q-TOF mass spectrometer. LC-MS experiments were performed using an Agilent Single-Quad LC/MSD VL with single-quad low resolution (1 decimal place) capable of both ESI positive and negative modes using flow injection analysis. GC-MS experiments were performed using an Agilent GC-MS 6890N equipped with a MS detector up to 800 m/z. The ionization is electron impact (EI) and software is ChemStation. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and were reported as $[\alpha]^{T\ ^\circ C}_D$ (concentration in grams/100 mL solvent). Chiral HPLC analysis was performed using an Agilent 1100 series HPLC System with a diode array detector. Chiral columns include Chiralcel®OD (Chiral Technologies Inc., 25cm×4.6mm I.D.), Chiralpak®AD-H (Chiral Technologies Inc., 25cm × 4.6 mm I.D.) and Chiralpak®IA-H (Chiral Technologies Inc., 25cm × 4.6 mm I.D.). Analytical thin layer chromatography was performed using EMD 0.25 mm silica gel 60-F plates. Flash column chromatography was performed on Sorbent Technologies 60 Å silica gel. Yields

refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Catalyst loadings were calculated with respect to the amount of boronates. All reactions were carried out in oven-dried glassware under an argon or nitrogen atmosphere unless otherwise noted. HPLC grade THF, dichloromethane, Et_2O and toluene were purchased from Fisher and VWR and were purified and dried by passing through as PURE SOLV® solvent purification system (Innovative Technology Inc.). Triethyl borate was distilled over CaH_2 before use in the preparation of alkynyl boronates. Mesitylene was dried by and stored with 3 Å molecular sieves beads. The previously reported chiral biphenol catalysts were prepared according to known literature procedures.[140] All other reagents were purchased from commercial suppliers and used without further purification.

3.7.2 Experimental Procedures for the Synthesis of N-sulfonyl Hydrazides

2-Nitrobenzenesulfonylhydrazide (NBSH) was synthesized according to the procedure reported by Myers and coworkers.[58] The syntheses of hydrazides **3.54** and **3.78** were reported by Dr. Jiang.

3.7.3 Synthesis of the Cyclic Alkynyl Boronate



Potassium *(S)*-((1,4-dioxaspiro[4.5]decan-2-yl)ethynyl)trifluoroborate (S1)

The title trifluoroborate salt was synthesized according to the procedure reported by Thomson and coworkers.[85] To a solution of (S)-2-ethynyl-1,4-dioxaspiro[4.5]decane[141] (4.00 g, 24.1 mmol) in dry THF (75 mL) at –78 °C under N_2 atmosphere was added *n*-BuLi (13.75 mL, 24.1 mmol, 1.75 M in hexanes) dropwise over 10 minutes. After stirring

at –78 °C for 1 h, triisopropyl borate (8.33 mL, 36.1 mmol) was quickly added by syringe. The reaction was maintained at –78 °C for 10 minutes, and removed from the bath and allowed to warm up to room temperature over 2 h. The reaction was then cooled to 0 °C and dry MeOH (25 mL) was then added by syringe, followed by a slurry of potassium hydrogen difluoride (KHF_2) (11.28 g, 144.4 mmol) in H_2O (60 mL + 2 x 5 mL rinses) via addition funnel. The reaction was then allowed to warm to room temperature over 1.5 h. The solvent was removed under reduced pressure, and the resulting suspension was allowed to dry over high vacuum overnight. The residual solids were broken up using a spatula and dissolved in 75 mL of acetone. The resulting mixture was placed on a rotary evaporator and rotated rapidly at atmospheric pressure with the bath set at 45 °C for 45 minutes. The mixture was decanted over Celite® under vacuum, and the residual solids were once again taken up in 75 mL of acetone and the mixture was heated at 45 °C for 15 minutes. The mixture was filtered over Celite®, washing with acetone. The filtrate was concentrated to ~ 10 mL, and Et_2O (100 mL) was added, causing a gel to crash out. The flask was chilled in the freezer at –30 °C for 6 h, and the gel was collected by vacuum filtration using a medium gauge fritted filter, then further dried over high vacuum overnight to afford **S12** (2.51 g, 9.22 mmol, 38%) as an off-white solid.

mp (decomp) 327 °C

$[\alpha]_D^{22}$ = +268.5 (c = 0.94, CH_3CN).

^{1}H NMR (500 MHz, DMSO-d_6) δ 4.58 (dd, J = 7.5, 6.1 Hz, 1H), 4.05 (dd, J = 7.5, 6.1 Hz, 1H), 3.60 (dd, J = 7.5, 7.5 Hz, 1H), 1.65 – 1.48 (m, 8H), 1.40 – 1.34 (m, 2H).

^{13}C NMR (126 MHz, DMSO-d_6) (relaxation time d_1 = 3 seconds, increasing to d_1 = 7

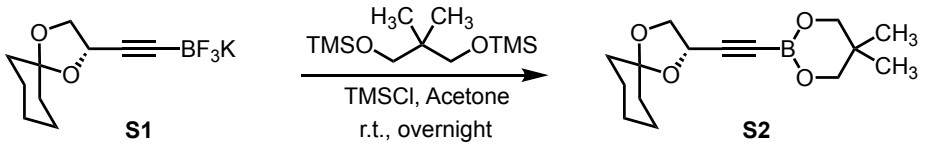
seconds does not reveal clear signal for the second acetylenic carbon atom) δ 109.0, 69.2, 65.5, 35.6, 35.1, 24.6, 23.5.

^{11}B NMR (128.4 MHz, DMSO-d_6) δ –2.10.

^{19}F NMR (376.5 MHz, DMSO-d_6) δ –127.3.

ESI-HRMS found 233.1054 (calculated for $C_{10}H_{13}BF_3O_2$ [M–K]$^-$: 233.1075.)

IR (thin film, cm^{-1}): 2935, 2861, 1449, 1365, 1345, 1279, 1236, 979.



***(S)*-2-((1,4-Dioxaspiro[4.5]decan-2-yl)ethynyl)-5,5-dimethyl-1,3-2-dioxaborinane (S2)**

To a flame-dried round bottom flask equipped with a stir bar was added potassium trifluoroborate **S1** (1.00 g, 3.67 mmol) and dry acetone (3.70 mL). 1,3-Bis(trimethylsilyloxy)-2,2-dimethylpropane[142] (1.10 mL, 3.67 mmol) was then added quickly, followed by trimethyl silyl chloride (0.933 mL, 7.35 mmol). The reaction was allowed to stir at room temperature for 24 h, at which time it was filtered over a pad of neutral alumina, washing with hexanes. The filtrate was then concentrated to afford the title compound (0.762 g) with some impurities as a yellow oil. It was then stored as a 1M solution in toluene.

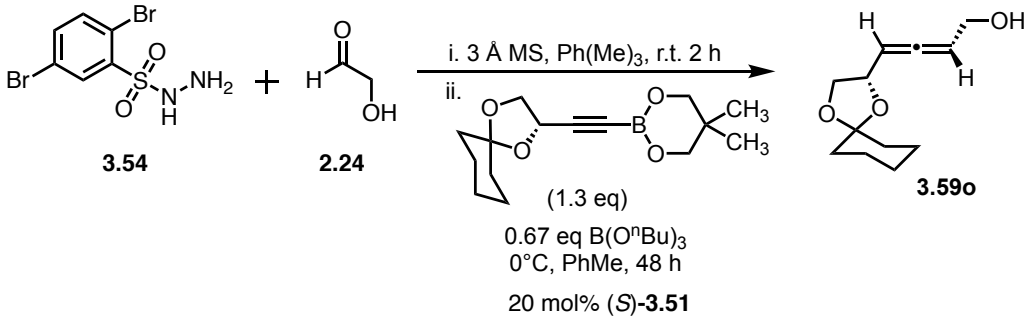
^{1}H NMR (500 MHz, $CDCl_3$) *δ* 4.71 (td, J = 6.3, 2.1 Hz, 1H), 4.17 (ddd, J = 8.0, 6.1, 0.6 Hz, 1H), 3.94 (dddd, J = 8.0, 6.2, 4.8, 0.6 Hz, 1H), 3.59 (d, J = 0.6 Hz, 3H), 3.50 (dd, J = 1.8, 0.6 Hz, 1H), 1.77 – 1.54 (m, 10 H), 0.95 (d, J = 0.6 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) *δ* 111.2, 81.6, 73.7, 72.0, 69.8, 69.5, 64.9, 35.6, 35.4, 25.0,

23.9, 22.8, 22.6, 21.8.

^{11}B NMR (128.4 MHz, $CDCl_3$) δ 31.57.

3.7.4 Asymmetric Traceless Petasis Reaction of the Cyclic Alkynyl Boronate



(*S*)-4-((*S*)-1,4-Dioxaspiro[4.5]decan-2-yl)buta-2,3-dien-1-ol (3.59o)

2,5-Dibromobenzenesulfonohydrazide **3.54** (132 mg, 0.4 mmol), glycolaldehyde **2.24** (24 mg of dimer, 0.2 mmol), and oven-dried 3 Å powdered molecular sieves (400 mg) were added to a 10 mL oven-dried reaction vial equipped with a magnet stir bar. Dry mesitylene (1.0 mL) was added to the vial and the reaction mixture was stirred at room temperature for 2 h, at which time (*S*)-$(CF_3)_4$-BINOL catalyst **3.51** (58 mg, 0.104 mmol, 20 mol%) was added and rinsed into the solution with tributyl borate (60 mg, 0.26 mmol) and dry toluene (0.48 mL). The mixture was cooled to 4 °C for 10 min, at which moment to it was subjected **S2** (0.52 mmol, 1 M solution in toluene). The reaction was allowed to stir at 4 °C for 48 h and then quenched by 1 ml aqueous 10% NaOH solution and allowed to warm up to room temperature overnight. The reaction mixture was transferred to a separatory funnel using EtOAc (5 mL) and H_2O (5 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 X 5 ml). The combined organic layers were dried with Na_2SO_4. Concentration under reduced pressure followed by flash column chromatography on silica gel with hexanes/EtOAc (19:1) afforded the product as

a colorless oil. The single diastereomer can be isolated by the same chromatography conditions using silver-impregnated ($AgNO_3$) silica gel.

Yield: 56 mg, 68%

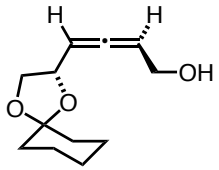
$[\alpha]_D^{24}$ = +108.6 (c = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (qd, J = 6.0, 1.5 Hz, 1H), 5.36 (tt, J = 6.3, 3.0 Hz, 1H), 4.60 (dd, J = 6.4, 1.5 Hz, 1H), 4.14 (dd, J = 5.9, 2.8 Hz, 2H), 4.10 (dd, J = 8.2, 6.0 Hz, 1H), 3.75 (dd, J = 8.3, 6.3 Hz, 1H), 1.93 – 1.50 (m, 8H), 1.45 – 1.32 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 110.3, 94.3, 93.9, 73.7, 73.7, 69.8, 60.1, 36.4, 35.3, 25.1, 23.9, 23.8.

HRMS (EI) found 210.1248 (calculated for $C_{12}H_{18}O_3$: 210.1256.)

IR (thin film, cm^{-1}): 3326, 2936, 2862, 1962, 1448, 1366, 1278, 1162, 1099, 1041.



***(R)*-4-((*S*)-1,4-Dioxaspiro[4.5]decan-2-yl)buta-2,3-dien-1-ol (3.59p)**

Prepared from glycolaldehyde **2.24** (0.2 mmol) and the corresponding alkynyl boronate **S7** (0.52 mmol) according to the General Procedure outlined above for **3.59o**, using (*R*)-**3.51** catalyst. The crude mixture was purified by flash column chromatography with hexanes/EtOAc (19:1) to afford the pure product as a colorless oil. The single diastereomer can be isolated by the same chromatography conditions using silver-impregnated ($AgNO_3$) silica gel.

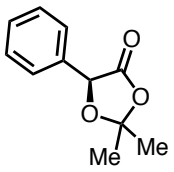
Yield: 60 mg, 71%

$[\alpha]_D^{24}$ = +41.2 (c = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (qd, J = 6.0, 1.6 Hz, 1H), 5.38 (tt, J = 9.6, 3.0 Hz, 1H), 4.60 (dd, J = 6.4, 1.5 Hz, 1H), 4.16 (ddd, J = 11.5, 6.0, 3.1 Hz, 2H), 4.11 (dd, J = 8.3, 6.0 Hz, 1H), 3.70 (dd, J = 8.2, 6.8 Hz, 1H), 1.68 – 1.48 (m, 8H), 1.45 – 1.32 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.6, 110.2, 94.3, 94.0, 73.9, 73.7, 69.0, 60.1, 36.3, 35.3, 25.1, 23.9, 23.8.

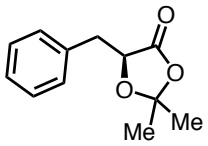
3.7.5 Synthesis of α-Hydroxy Lactones



(*S*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-one (S3a)

To a flame-dried round bottom flask equipped with a stir bar was added S-(+)-mandelic acid (3.00 g, 19.7 mmol) and acetone (30 mL). 2,2-dimethoxypropane (7.19 g, 69.0 mmol) was then added, followed by p-toluenesulfonic acid (0.150 g, 0.789 mmol). The reaction was allowed to stir at room temperature for 14 h. The solvent was then evaporated under reduced pressure, and the residue was taken up in EtOAc (40 mL) and transferred to a separatory funnel, where it was washed with 25 mL of sat. $NaHCO_3$ and 35 mL of brine. The organic layer was dried over $MgSO_4$ and concentrated to afford the title compound (3.60 g, 18.7 mmol, 95%) as a white solid that required no further purification. Spectral data matched those previously reported in the literature.[143]

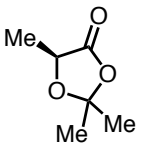
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.35 (m, 5H), 5.39 (s, 1H), 1.73 (s, 3H), 1.68 (s, 3H).



(*S*)-5-Benzyl-2,2-dimethyl-1,3-dioxolan-4-one (S3b)

To a flame-dried round bottom flask equipped with a stir bar was added L-(–)-3-phenyllactic acid (3.00 g, 18.1 mmol) and acetone (30 mL). 2,2-dimethoxypropane (6.58 g, 63.2 mmol) was then added, followed by p-toluenesulfonic acid (0.137 g, 0.722 mmol). The reaction was allowed to stir at room temperature for 18 h. The solvent was then evaporated under reduced pressure, and the residue was taken up in EtOAc (40 mL) and transferred to a separatory funnel, where it was washed with 25 mL of sat. $NaHCO_3$ and 25 mL of brine. The organic layer was dried over $MgSO_4$ and concentrated to afford the title compound (3.63 g, 17.6 mmol, 98%) as a clear and colorless liquid that solidified into a white solid upon refrigeration. Spectral data matched those previously reported in the literature.[144]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 5H), 4.66 (dd, J = 6.6, 4.1 Hz, 1H), 3.20 (dd, J = 14.5, 4.1 Hz, 1H), 3.05 (dd, J = 14.5, 6.5 Hz, 1H), 1.50 (s, 3H), 1.37 (s, 3H).



(*S*)-2,2,5-Trimethyl-1,3-dioxolan-4-one (S3c)

To a flame-dried round bottom flask equipped with a stir bar was added L–(+)–lactic acid (5.00 g, 55.5 mmol) and anhydrous benzene (35 mL). 2,2-dimethoxypropane (10.2 mL, 83.3 mmol) was then added, and the reaction was allowed to stir under reflux with a Dean-Stark apparatus for 4 h with azeotropic removal of methanol. The reaction was then

concentrated to afford the title compound (4.05 g, 31.1 mmol, 56%) as a clear and colorless oil that required no further purification.

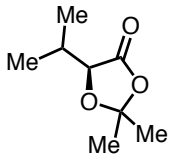
$[\alpha]_D^{22}$ = +42.9 (c = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.48 (q, J = 6.8 Hz, 1H), 1.61 (s, 3H), 1.58 (s, 3H), 1.48 (d, J = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 110.3, 70.4, 27.4, 25.6, 17.4.

HRMS (ESI) found 131.0708. (Calculated for $C_6H_{10}O_3$ $[M+H]^+$ 131.0706.)

IR (neat, cm^{-1}): 2992, 2941, 2876, 1799, 1447, 1346, 1267, 1146, 1126, 1051, 935, 844.

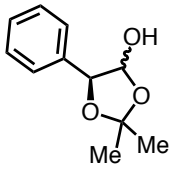


(*S*)-5-Isopropyl-2,2-dimethyl-1,3-dioxolan-4-one (S3d)

To a flame-dried round bottom flask equipped with a stir bar was added (S)-(+)-2-hydroxy-3-methyl-butyric acid (2.30 g, 19.5 mmol) and acetone (50 mL). 2,2-dimethoxypropane (7.10 g, 68.1 mmol) was then added, followed by p-toluenesulfonic acid (0.129 g, 0.677 mmol). The reaction was allowed to stir at room temperature for 18 h. The solvent was then evaporated under reduced pressure, and the residue was taken up in EtOAc (100 mL) and transferred to a separatory funnel, where it was washed with 50 mL of sat. $NaHCO_3$ and 50 mL of brine. The organic layer was dried over $MgSO_4$ and concentrated to afford the title compound (2.82 g, 17.8 mmol, 92%) as a pale yellow liquid. Spectral data matched those previously reported in the literature.[144]

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 (d, J = 3.9 Hz, 1H), 2.20 – 2.09 (m, 1H), 1.60 (s, 3H), 1.53 (s, 3H), 1.07 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H).

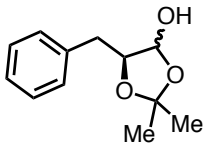
3.7.6 Synthesis of α-Hydroxy Lactols



(5*S*)-2,2-Dimethyl-5-phenyl-1,3-dioxolan-4-ol (3.63a)

To a flame-dried round bottom flask equipped with a stir bar was added the acetonide **S3a** (1.26 g, 6.57 mmol) and anhydrous toluene (20 mL). The reaction was cooled to –78°C, and DIBAL (10.95 mL, 10.95 mmol, 1.0 M in hexanes) was then added dropwise. The mixture was allowed to stir at –78°C for 50 minutes, at which time 15 mL of 1M HCl was added carefully to quench the reaction. The cooling bath was removed, and the flask was allowed to warm slowly to room temperature. After the clear formation of two layers, the mixture was transferred to a separatory funnel using EtOAc (25 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with 3 x 25 mL of EtOAc. The combined organic layers were filtered through a pad of silica gel, washing with EtOAc, then were dried over $MgSO_4$ and concentrated to afford the title compound (1.19 g, 6.13 mmol, 93%) as a clear and colorless oil that was directly used in the next step without further purification.

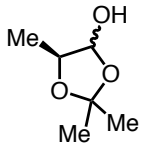
^{1}H NMR (500 MHz, CDCl3) δ 7.42 – 7.29 (m, 5H), 5.32 (t, J = 3.9 Hz, 1H), 4.99 (d, J = 3.7 Hz, 1H), 2.94 (br s, 1H), 1.64 (s, 3H), 1.59 (s, 3H), major diastereomer.



(5*S*)-5-Benzyl-2,2-dimethyl-1,3-dioxolan-4-ol (3.63b)

To a flame-dried round bottom flask equipped with a stir bar was added the acetonide **S3b** (1.50 g, 7.27 mmol) and anhydrous toluene (20 mL). The reaction was cooled to –78°C, and DIBAL (6.86 mL, 10.2 mmol, 25 wt% in toluene) was then added dropwise. The mixture was allowed to stir at –78°C for 60 minutes, at which time 6 mL of 3M HCl was added carefully to quench the reaction. The cooling bath was removed, and the flask was allowed to warm slowly to room temperature. After the clear formation of two layers, the mixture was transferred to a separatory funnel using EtOAc (25 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with 3 x 25 mL of EtOAc. The combined organic layers were filtered through a pad of silica gel, washing with EtOAc, then were dried over $MgSO_4$ and concentrated to afford the title compound (1.28 g, 6.15 mmol, 85%) as a clear and colorless oil that was directly used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 5H), 5.11 (dd, J = 4.0, 3.0 Hz, 1H), 4.28 (td, J = 6.7, 3.0 Hz, 1H), 3.04 (dd, J = 7.0, 1.2 Hz, 1H), 2.97 (dd, J = 14.0, 7.0 Hz, 1H0, 2.89 (dd, J = 14.0, 6.5 Hz, 1H), 1.52 (s, 3H), 1.46 (s, 3H), major diastereomer.

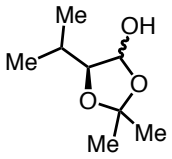


(5*S*)-2,2,5-Trimethyl-1,3-dioxolan-4-ol (3.63c)

To a flame-dried round bottom flask equipped with a stir bar was added the acetonide **S3c** (0.335 g, 2.57 mmol) and anhydrous toluene (20 mL). The reaction was cooled to –78°C, and DIBAL (2.08 mL, 3.09 mmol, 25 wt% in toluene) was then added dropwise. The mixture was allowed to stir at –78°C for 60 minutes, at which time 5 mL of

anhydrous MeOH was added carefully to quench the reaction. The flask was allowed to warm to room temperature, and a saturated solution of Rochelle's salt (10 mL) was then added, causing a gel to form immediately. This gel was filtered over Celite® to form a biphasic solution that was transferred to a separatory funnel with the aid of EtOAc (10 mL). The layers were separated, and the aq. Layer was extracted with 50 mL of EtOAc. The combined organic layers were washed with 50 mL of sat. $NaHCO_3$ followed by 50 mL of brine, then dried over $MgSO_4$ and concentrated to afford the title compound (68 mg, 0.51 mmol, 20%) that was directly used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (t, J = 3.7 Hz, 1H), 3.72 (dd, J = 7.1, 3.4 Hz, 1H), 2.90 (br s, 1H), 1.53 (s, 3H), 1.43 (s, 3H), 0.98 (d, J = 6.7 Hz, 3H), major diastereomer.



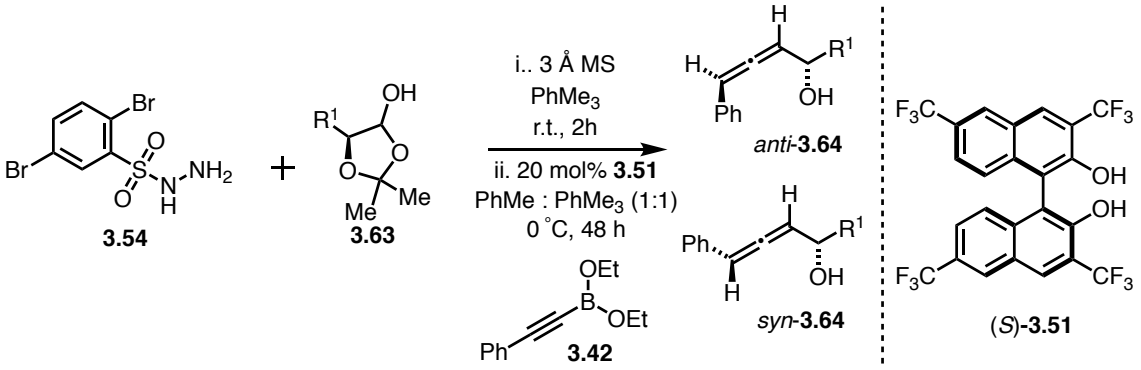
(5*S*)-5-Isopropyl-2,2-dimethyl-1,3-dioxolan-4-ol (3.63d)

To a flame-dried round bottom flask equipped with a stir bar was added the acetonide **S3d** (1.00 g, 6.32 mmol) and anhydrous toluene (20 mL). The reaction was cooled to –78°C, and DIBAL (5.05 mL, 7.59 mmol, 25 wt% in toluene) was then added dropwise. The mixture was allowed to stir at –78°C for 60 minutes, at which time 15 mL of 1M HCl was added carefully to quench the reaction. The cooling bath was removed, and the flask was allowed to warm slowly to room temperature for 1h. After the clear formation of two layers, the mixture was transferred to a separatory funnel using EtOAc (25 mL) and water (10 mL). The layers were separated, and the aqueous layer was extracted with 3 x 25 mL of EtOAc. The combined organic layers were filtered through a pad of silica

gel, washing with EtOAc, then were dried over $MgSO_4$ and concentrated to afford the title compound (0.785 g, 4.90 mmol, 78%) as a clear and colorless oil that was directly used in the next step without further purification.

^{1}H NMR (500 MHz, CDCl3) δ 5.11 (dd, *J* = 4.3, 3.5 Hz, 1H), 4.14 (dqd, *J* = 19.2, 6.3, 3.4 Hz, 1H), 2.73 (dd, J = 4.4, 0.9 Hz, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.32 (d, J = 6.5 Hz, 6H), major diastereomer.

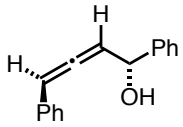
3.7.7 General Procedure for the Diastereoselective Traceless Petasis Alkynylations



2,5-Dibromobenzenesulfonohydrazide **3.64** (132 mg, 0.4 mmol), α-hydroxy lactol **3.63** (0.4 mmol), and oven-dried 3 Å powdered molecular sieves (250 mg) were added to a 4 dram flame-dried reaction vial equipped with a magnetic stir bar. Dry mesitylene (1.0 mL) was added to the vial and the reaction mixture was stirred at room temperature for 2 h, at which time (*S*)-$(CF_3)_4$-BINOL catalyst **3.51** (44 mg, 0.078 mmol, 15 mol%) was added and rinsed into the solution with dry toluene (0.48 mL). The mixture was cooled to 0 °C for 10 min under nitrogen, at which time the alkynyl boronate **3.42** (0.52 mmol, 1 M solution in toluene) was added. The reaction was allowed to stir at 0 °C for 48 h and then quenched by 1 ml aqueous 10% NaOH solution. The reaction was then diluted with 5 mL Et_2O and transferred to a separatory funnel with the aid of additional NaOH (5 mL). The

layers were separated, and the aqueous layer was extracted with 3 x 5 mL Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash column chromatography on silica gel afforded the desired compound.

3.7.8 Analytical Data for the Allenol Diastereomers



(1*R*, 3*S*)-1,4-Diphenylbuta-2,3-dien-1-ol (*anti*-3.64a)

Prepared from the corresponding α-hydroxy lactol **3.63a** (0.4 mmol) and alkynyl boronate **3.42** (0.52 mmol) according to the General Procedure. The product was purified by flash column chromatography with elution by hexanes/EtOAc (9:1) to afford the pure product as a pale yellow oil.

Yield: 80 mg, 90%.

d.r.: 20:1.

$[\alpha]_D^{22}$ = +158.9 (c = 1.0, $CHCl_3$). In lit:[77o] $[\alpha]_D^{22}$ = +168.6 (c = 1.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.39 (t, J = 7.7 Hz, 2H), 7.34 – 7.29 (m, 2H), 7.27 – 7.12 (m, 6H), 6.31 (dd, J = 6.4, 2.2 Hz, 1H), 5.81 (app t, J = 6.4 Hz, 1H), 5.31 (dd, J = 6.4, 2.3 Hz, 1H), 2.10 (br s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.8, 142.8, 133.6, 128.7, 128.6, 127.9, 126.9, 126.0, 100.0, 97.9, 72.4.

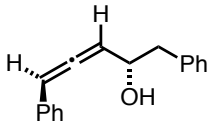
All spectra were in agreement with reported data.[77o] Thus, the major diastereomer was assigned as *anti*-**3.64a**.

Carrying out the reaction under identical conditions with catalyst (*R*)-**3.51** afforded the

title compound (0.040 g, 0.17 mmol, 45%, 1.2 : 1 d.r.) as a pale yellow oil. The minor *syn*-**3.64a** isomer was not separable from its *anti*-**3.64a** isomer through chromatography. The following signals are discernible:

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (dd, J = 6.4, 2.3 Hz, 1H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 142.7, 127.8, 126.0, 99.9, 97.9, 72.1.



(2*S*, 4*S*)-1,5-Diphenylpenta-3,4-dien-2-ol (*anti*-3.64b)

Prepared from the corresponding α-hydroxy lactol **3.63b** (0.4 mmol) and alkynyl boronate **3.42** (0.52 mmol) according to the General Procedure. The product was purified by flash column chromatography with elution by hexanes/EtOAc (19:1) to afford the pure product as a clear and colorless oil.

Yield: 77 mg, 85%.

d.r.: 20:1.

$[\alpha]_D^{22}$ = –343.9 (c = 0.5, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.10 (m, 8H), 7.08 – 7.05 (m, 2H), 6.26 (d, J = 6.4, 1.9 Hz, 1H), 5.69 (app t, J = 6.5 Hz, 1H), 4.53 (m, 1H), 3.02 (dd, J = 13.4, 7.0 Hz, 1H), 2.94 (dd, J = 13.5, 6.5 Hz, 1H), 1.86 (d, J = 4.1 Hz, 1H).

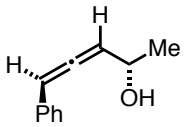
^{13}C NMR (126 MHz, $CDCl_3$) δ 204.0, 137.5, 133.6, 129.7, 128.6, 127.1, 126.8, 126.6, 98.6, 97.1, 71.4, 44.1.

The spectral data matched those of an authentic sample previously reported in the literature.[85] Thus, the major diastereomer was assigned *anti*-**3.64b**.

Carrying out the reaction under identical conditions with catalyst (*R*)-**3.51** afforded the title compound (0.044 g, 0.187 mmol, 47%, 1.1 : 1 d.r.) as a clear and colorless oil. Partial separation of the minor *syn*-**3.64b** isomer was possible under the chromatography conditions. The spectral data matched those of an authentic sample previously reported in the literature.[85]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 2H); 7.26 (m, 5H), 7.19 (m, 1H), 7.12 (m, 2H), 6.29 (dd, J = 6.4, 2.9 Hz, 1H), 5.73 (app t, J = 5.8 Hz, 1H), 4.53 (m, 1H), 3.01 (dd, J = 13.6, 5.2 Hz, 1H), 2.91 (dd, J = 13.7, 6.9 Hz, 1H), 1.87 (d, J = 4.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.1, 137.3, 133.6, 129.8, 128.6, 128.5, 127.2, 126.8, 126.6, 99.2, 98.0, 70.0, 43.8.



(2*S*,4*S*)-5-Phenylpenta-3,4-dien-2-ol (*anti*-3.64c)

Prepared from the corresponding α-hydroxy lactol **3.63c** (0.2 mmol) and alkynyl boronate **3.42** (0.26 mmol) according to the General Procedure. The product was purified by flash column chromatography with elution by hexanes/EtOAc (19:1) to afford the pure product as a clear and colorless oil.

Yield: 24.6 mg, 76%.

d.r.: 6:1.

$[\alpha]_D^{22}$ = +70.7 (c = 0.15, $CHCl_3$).

^{1}H NMR (500 MHz, C_6D_6) δ 7.51 – 7.48 (m, 1H), 7.22 (dd, J = 8.0, 1.4 Hz, 1H), 7.13 – 7.08 (m, 1H), 7.05 –6.93 (m, 2H), 6.14 (dd, J = 6.4, 2.5 Hz, 1H), 5.49 (app t, J = 6.0 Hz,

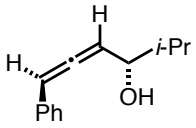
1H), 4.17 (app pd, J = 6.1, 2.4 Hz, 1H), 1.35 (br s, 1H), 1.15 (d, J = 6.3 Hz, 3H).

^{13}C NMR (126 MHz, C_6D_6) δ 203.4, 129.6, 129.0, 127.4, 127.1, 101.5, 97.5, 23.8.

This compound was previously reported in the literature.[145]

Carrying out the reaction under identical conditions with catalyst (*R*)-**3.51** afforded the title compound (12.2 mg, 0.076 mmol, 36%, 1 : 1.4 d.r.) as a clear and colorless oil. Partial separation of the *syn*-**3.64c** isomer was not possible under the chromatography conditions. The following peaks are discernible:

^{13}C NMR (125 MHz, C_6D_6) δ 203.5, 130.4, 128.9, 101.4, 97.6, 23.1.



(3*S*,5*S*)-2-Methyl-6-phenylhexa-4,5-dien-3-ol (*anti*-3.64d)

Prepared from the corresponding α-hydroxy lactol **3.63d** (0.4 mmol) and alkynyl boronate **3.42** (0.52 mmol) according to the General Procedure. The product was purified by flash column chromatography with elution by hexanes/EtOAc (19:1) to afford the pure product as a clear and colorless oil.

Yield: 59 mg, 78%.

d.r.: 12:1.

$[\alpha]_D^{22}$ = +7.1 (c = 0.25, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.30 (m, 4H), 7.22 (app h, J = 4.0 Hz, 1H), 6.34 (dd, J = 6.5, 2.7 Hz, 1H), 5.68 (app t, J = 6.1 Hz, 1H), 4.07 (td, J = 5.6, 2.7 Hz, 1H), 1.86 (dq, J = 13.0, 6.5, 6.1 Hz, 1H), 1.72 (br s, 1H), 1.01 (d, J = 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.5, 134.0, 128.7, 127.2, 126.8, 98.1, 97.6, 74.6, 34.3,

18.2, 17.7.

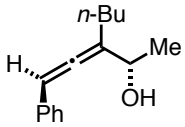
HRMS (ESI) found 188.1208 (calculated for $C_{13}H_{16}O$ $[M]^+$: 188.1201.)

IR (neat, cm^{-1}): 3410, 2961, 2926, 2873, 1951, 1598, 1459, 1386, 1261, 1168, 1027.

Carrying out the reaction under identical conditions with catalyst (*R*)-**3.51** afforded the title compound (0.035 g, 0.187 mmol, 47%, 1.2 : 1 d.r.) as a clear and colorless oil. Partial separation of the minor *syn*-**3.64d** isomer was possible under the chromatography conditions.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.29 (m, 4H), 7.22 (app h, J = 4.0 Hz, 1H), 6.32 (dd, J = 6.4, 2.1 Hz, 1H), 5.66 (app t, J = 6.4 Hz, 1H), 4.07 (td, J = 5.6, 2.7 Hz, 1H), 1.86 (dq, J = 13.0, 6.5, 6.1 Hz, 1H), 1.69 (br s, 1H), 1.02 (d, J = 6.8 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.0, 134.0, 128.7, 127.2, 126.8, 97.7, 97.0, 75.2, 34.2, 18.3, 17.9.



(*S*)-3-((*S*)-2-Phenylvinylidene)heptan-2-ol (*anti*-3.64e)

Prepared from the corresponding α-hydroxy ketone **3.65** (0.4 mmol) and alkynyl boronate **3.42** (0.52 mmol) according to the General Procedure. The product was purified by flash column chromatography with elution by hexanes/EtOAc (9:1) to afford the pure product as a clear and colorless oil.

Yield: 61 mg, 70%.

d.r.: 20:1.

$[\alpha]_D^{22}$ = –23.1 (c = 1.5, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 4H), 7.17 (ddd, J = 6.1, 2.7 Hz, 1H), 6.30 (app q, J = 3.0 Hz, 1H), 4.32 (ddt, J = 10.0, 6.4, 3.2 Hz, 1H), 2.12 (ddt, J = 7.8, 5.7, 3.0 Hz, 2H), 1.59 (d, J = 5.4 Hz, 1H), 1.45 (ddt, J = 13.2, 8.5, 6.6 Hz, 2H), 1.39 – 1.30 (m, 2H), 1.34 (d, J = 6.3 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.1, 135.0, 128.6, 126.9, 126.5, 114.4, 98.7, 68.5, 30.0, 28.5, 22.6, 22.5, 13.9.

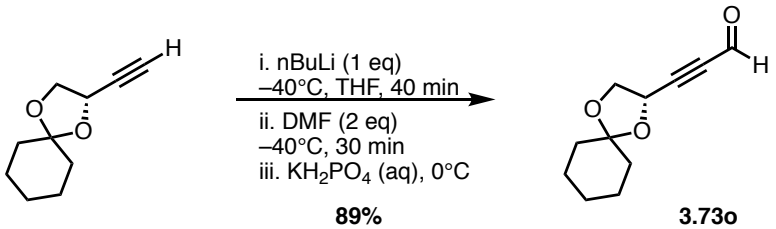
HRMS (ESI) found 216.1506 (calculated for $C_{15}H_{20}O$ $[M]^+$: 216.1514.

IR (neat, cm^{-1}): 3384, 2959, 2929, 2873, 2858, 1952, 1598, 1496, 1460, 1377, 1216, 1081.

Carrying out the reaction under identical conditions with catalyst (*R*)-**3.51** afforded the title compound (50 mg, 0.23 mmol, 58%, 9 : 1 d.r.) as a clear and colorless oil. Partial separation of the *syn*-**3.64e** isomer was not possible under the chromatography conditions. The following peaks are discernible:

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.31 (app q, J = 3.0 Hz, 1H), 4.27 (ddt, J = 10.0, 6.4, 3.2 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 200.4, 135.1, 99.0, 68.5, 30.2, 29.1, 22.9, 21.2, 14.4.

3.7.9 Synthesis of Ynal 3.73o



(*S*)-3-(1,4-dioxaspiro[4.5[decan-2-yl)propiolaldehyde (3.73o)

To a solution of (*S*)-2-ethynyl-1-4,-dioxaspiro[4.5]decane (1.00 g, 6.02 mmol, 1.0 eq)

in dry THF (16.5 mL) at –40°C under N_2 atmosphere was added *n*-BuLi (2.4 mL, 6.02 mmol, 2.50 M in hexanes, 1.0 eq) dropwise over 3 minutes. The reaction was maintained at –40°C for 40 minutes, at which point *N,N*-dimethyl formamide (0.93 mL, 12.04 mmol, 2 eq) was added, and the reaction was allowed to stir at the same temperature for an additional 30 minutes. The solution was then poured into an Erlenmeyer flask containing a stirring mixture of KH_2PO_4 (0.90 g, 6.62 mmol, 1.1 eq), Et_2O (66 mL) and H_2O (66 mL) at 0°C. After stirring for 5 min at that temperature, the mixture was transferred to a separatory funnel with the aid of Et_2O and H_2O (10 mL each). The layers were separated, and the organic layer was washed with H_2O (30 mL), dried over anhydrous $MgSO_4$, and concentrated. The crude residue was purified by silica gel chromatography with hexanes/EtOAc (19:1) to afford the title compound (1.04 g, 5.35 mmol, 89%) as a pale yellow oil.

$[\alpha]_D^{22}$ = +48.5 (c = 1.1, $CHCl_3$).

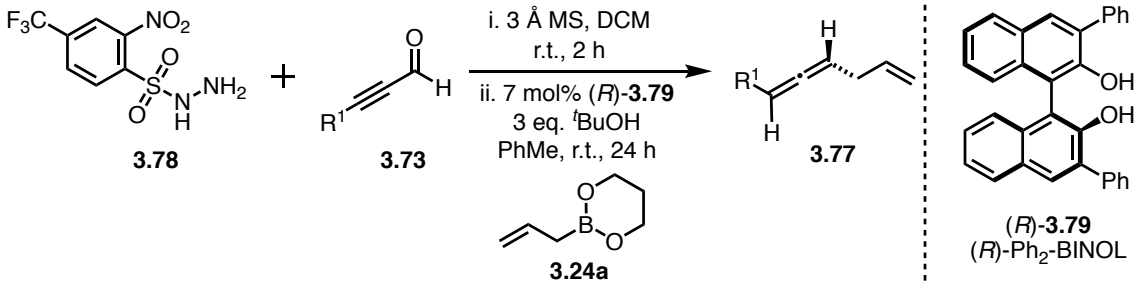
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (d, J = 0.7 Hz, 1H), 4.89 (ddd, J = 6.5, 5.4 0.6 Hz, 1H), 4.22 (dd, J = 8.3, 6.6 Hz, 1H), 4.05 (dd, J = 8.3, 5.4 Hz, 1H), 1.69 – 1.58 (m, 8H), 1.47 – 1.35 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 112.1, 93.4, 84.1, 68.9, 64.7, 35.6, 35.2, 24.9, 23.8, 23.8.

ESI-HRMS found 194.0952 (calculated for $[C_{11}H_{14}O_3]^+$: 194.0943.)

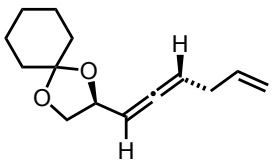
IR (neat, cm^{-1}): 2935, 2861, 2262, 1713, 1449, 1366, 1333, 1160, 1094.

3.7.10 General Procedure for the Asymmetric Traceless Petasis Allylation



2-Nitro-4-(trifluoromethyl)benzenesulfonohydrazide **3.78** (114 mg, 0.4 mmol), ynal **3.73** (0.4 mmol), and oven-dried 3 Å powdered molecular sieves (200 mg) were added to a 10 mL oven dried reaction vial equipped with a magnet stir bar. Dichloromethane (1.0 mL) was added to the vial and the reaction mixture was stirred at room temperature for 2 h. After this, the solvent was evaporated off and vacuumed by a high-vac pump for 10 min. (*R*)-Ph_2-BINOL catalyst **3.79** (18 mg, 0.04 mmol, 7 mol%), *tert*-butanol (89 mg, 1.2 mmol) and allylboronate **3.24a** (76 mg, 0.6 mmol) was added and rinsed into the solution with dry toluene (0.2 mL). The reaction was applied to sonication for 10 min to facilitate dissolution. The vial was sealed with a rubber septum and attached to a balloon filled with argon. The mixture was allowed to stir at room temperature for 24 h, at which time the crude mixture was chromatographed on silica gel to afford the desired product.

3.7.11 Analytical Data for Allyl Allenes



(*S*)-2-((*R*)-Hexa-1,2-5-trien-1-yl)-1,4-dioxaspiro[4.5]decane (3.77o)

Prepared from the corresponding ynal **3.73o** (0.4 mmol) and allyl boronate **3.24a** (0.6 mmol) according to the General Procedure. The crude mixture was purified by flash

column chromatography with hexanes to afford the pure product as a pale yellow oil.

Yield: 70 mg, 79%

e.r.: 98:2

$[\alpha]_D^{22}$ = +69.0 (c = 1.0, $CHCl_3$).

HPLC Analysis tr major: 4.25 min., tr minor: 6.69 min., [Chiralcel®OD column, 24 cm × 4.6 mm I.D., Hexanes: ^{i}PrOH = 99.0 : 1.0, 1.0 mL/min, 250 nm].

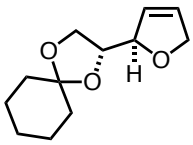
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, J = 16.6, 10.1, 6.4 Hz, 1H), 5.31 (qd, J = 6.8, 1.4 Hz, 1H), 5.21 (ddt, J = 7.5, 6.0, 2.9 Hz, 1H), 5.08 (dq, J = 17.1, 1.7 Hz, 1H), 5.03 (dq, J = 10.1, 1.5 Hz, 1H), 4.55 (tdd, J = 7.4, 6.1, 1.4 Hz, 1H), 4.09 (dd, J = 8.2, 6.1 Hz, 1H) 3.69 (dd, J = 8.2, 7.0 Hz, 1H), 2.76 (tdt, J = 6.6, 2.9, 1.5 Hz, 2H), 1.68 – 1.55 (m, 8H), 1.45 – 1.34 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.9, 135.9, 115.6, 110.0, 91.5, 91.4, 74.4, 69.3, 36.4, 35.4, 32.7, 25.1, 23.9, 23.9.

HRMS (EI) found 221.1467 (calculated for $C_{14}H_{20}O_2$ $[M+H]^+$ 221.1463)

IR (thin film, cm^{-1}): 2936, 2862, 2002, 1586, 1586, 1448, 1366, 1278, 1162, 1099, 1041.

3.7.12 Cycloisomerizations of Enantioenriched Allenols



(*R*)-2-((*R*)-2,5-Dihydrofuran-2-yl)-1,4-dioxaspiro[4.5]decane (3.87)

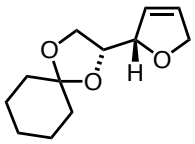
To a solution of $AuCl_3$ (0.6 mg, 0.0020 mmol) in THF (0.5 mL) in a flame-dried vial equipped with a magnetic stir bar was added a solution of the allenol **3.59o** (30 mg, 0.14 mmol) in THF (1 mL) via cannula, followed by a 1 mL rinse. The reaction was allowed

to stir at r.t. for 2 h, at which time TLC indicated full consumption of the starting material. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography with hexanes (39 : 1) to afford the title compound as a pale yellow oil and a single diastereomer.

Yield: 19 mg, 64%.

$[\alpha]_D^{24}$ = +41.3 (c = 0.40, CH_2Cl_2). In lit[146]: $[\alpha]_D^{24}$ = +51 (c = 0.9, CH_2Cl_2).

All spectra were in agreement with reported data.[146]



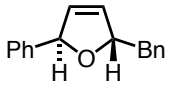
(*R*)-2-((*S*)-2,5-Dihydrofuran-2-yl)-1,4-dioxaspiro[4.5]decane (3.88)

To a solution of $AuCl_3$ (0.6 mg, 0.0020 mmol) in THF (0.5 mL) in a flame-dried vial equipped with a magnetic stir bar was added a solution of the allenol **3.59p** (30 mg, 0.14 mmol) in THF (1 mL) via cannula, followed by a 1 mL rinse. The reaction was allowed to stir at r.t. for 2 h, at which time TLC indicated full consumption of the starting material. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography with hexanes (39 : 1) to afford the title compound as a pale yellow oil and a single diastereomer.

Yield: 18 mg, 59%.

$[\alpha]_D^{24}$ = +26.1 (c = 0.40, CH_2Cl_3).

All spectra were in agreement with reported data.[146]



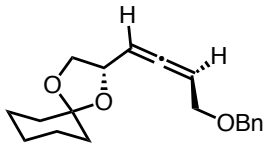
(2*S*, 5*R*)-2-Benzyl-5-phenyl-2,5-dihydrofuran (3.89)

A solution of the allenol *anti*-**3.64b** (0.046 g, 0.19 mmol) in THF (2.0 mL) was added by cannula to a solution of $AuCl_3$ (~0.6 mg, 0.002 mmol) in THF (0.5 mL). The reaction was allowed to stir at room temperature over 2h, at which time TLC indicated full consumption of the starting material. The reaction was then concentrated under reduced pressure, and the residue was purified by flash column chromatography with 0% → 2% EtOAc/Hexanes to afford the title compound as a clear and colorless oil.

Yield: (0.027 g, 0.16 mmol, 59%) as a clear oil.

All spectra were in agreement with reported data.[85]

3.7.13 Synthesis of *epi*-solamin



(*S*)-2-((*R*)-4-(benzyloxy)buta-1,2-dien-1-yl)-1,4-dioxaspiro[4,5]decane (3.121)

NaH (212 mg, 8.82 mmol, 3.0 equiv.) was suspended in 15 mL of THF and the suspension was brought to 0°C. A solution of alcohol **3.59p** (618 mg, 2.94 mmol, 1.0 equiv.) in 10 mL of THF was then added dropwise via cannula over 5 minutes, followed by 2 x 2.5 mL rinses with THF. The reaction was maintained at 0°C for 25 minutes, at which time neat benzyl bromide (603 mg, 3.53 mmol, 1.2 equiv.) was added dropwise via syringe. The resulting orange suspension was then allowed to slowly warm to r.t. and stirred overnight. After 16 hours, the reaction was quenched with 10 mL of sat. NH_4Cl at room temperature, and the biphasic mixture was transferred to a separatory funnel with the aid of H_2O. The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried and concentrated under reduced

pressure. The crude mixture was purified by silica gel column chromatography with hexanes/EtOAc (19 : 1 to 9 : 1 gradient) to afford the pure product as a pale yellow oil.

Yield: 700 mg, 79%

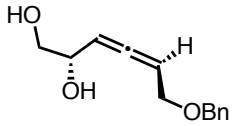
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 5H), 5.37 (qd, J = 6.5, 4.1 Hz, 1H), 5.23 (m, 1H), 4.51 (dd, J = 6.8, 1.5 Hz, 1H), 4.46 (s, 2H), 4.04 – 4.00 (m, 2H), 3.98 (dd, J = 6.7, 2.4 Hz, 1H), 3.62 (dd, J = 8.2, 6.8 Hz, 1H), 1.60 – 1.45 (m, 8H), 1.40 – 1.25 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 205.2, 138.0, 128.4, 127.9, 127.7, 110.2, 92.2, 90.8, 73.9, 72.0, 69.1, 67.7, 36.3, 35.4, 25.1, 23.9.

Analytical data for the benzyl-protected allenol derived from **3.59o**, **(*S*)-2-((*S*)-4-(benzyloxy)buta-1,2-dien-1-yl)-1,4-dioxaspiro[4,5]decane**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 5H), 5.33 (qd, J = 7.3, 6.8, 1.4 Hz, 1H), 5.23 (m, 1H), 4.51 (dd, J = 6.8, 1.5 Hz, 1H), 4.45 (s, 2H), 4.04 – 4.00 (m, 2H), 3.98 (dd, J = 6.7, 2.4 Hz, 1H), 3.62 (dd, J = 8.2, 6.8 Hz, 1H), 1.60 – 1.45 (m, 8H), 1.40 – 1.25 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 205.1, 138.0, 128.4, 127.9, 127.8, 110.2, 92.2, 90.8, 73.9, 71.9, 69.1, 67.6, 36.3, 35.4, 25.1, 23.9.



(2*S*,4*R*)-6-(benzyloxy)hexa-3,4-diene-1,2-diol (3.122)

To a solution of cyclohexylidene-protected diol **3.121** (700 mg, 2.33 mmol, 1.0 equiv.) in 10 mL of MeOH was added p-TsOH•H_2O (89 mg, 0.466 mmol, 0.2 equiv.). The reaction was allowed to stir at reflux for 4 hours, at which time TLC analysis

revealed a very low conversion of the starting material. The amount of p-TsOH•H_2O was then increased (added 354 mg, 0.8 equiv.), and the reaction was allowed to continue stirring at reflux for 2 h, and then at r.t. overnight. After 18 h, the starting material was not fully consumed, therefore the amount of p-TsOH•H_2O in the reaction was doubled, and the reaction was allowed to stir at r.t. for 1 h. At this time, 5 mL of a 2M aqueous solution of sulfuric acid was added, and the reaction was allowed to stir at r.t. for 2 h, whereupon TLC analysis finally revealed the full consumption of the starting material. The reaction was then diluted with EtOAc (15 mL) and transferred to a separatory funnel with the aid of additional EtOAc (15 mL) and brine (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with $NaHCO_3$ (2 x 50 mL), dried, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography with hexanes/EtOAc (8 : 2 to 3 : 7 gradient) to afford the title compound as a pale yellow oil.

Yield: 466 mg, 91%

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 5H), 5.40 (dqd, J = 12.2, 6.1, 2.6 Hz, 1H), 5.29 (dtt, J = 14.3, 5.8, 2.7 Hz, 1H), 4.48 (s, 2H), 4.19 (m, 1H), 3.97 (ddd, J = 12.5, 6.2, 2.7 Hz, 2H), 3.56 (m, 1H), 3.46 (dd, J = 11.3, 6.1 Hz, 1H), 2.40 – 2.10 (br s, 2H).

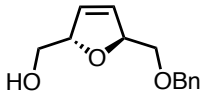
^{13}C NMR (126 MHz, $CDCl_3$) δ 203.7, 137.7, 128.5, 127.9, 127.8, 93.8, 92.1, 72.4, 69.6, 67.2, 65.7.

Analytical data for the diastereomer of benzyl-protected diol derived from **3.59o**, **(2*S*,4*S*)-6-(benzyloxy)hexa-3,4-diene-1,2-diol**:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 5H), 5.40 (dqd, J = 12.2, 6.1, 2.6 Hz, 1H), 5.29 (dtt, J = 14.3, 5.8, 2.7 Hz, 1H), 4.47 (s, 2H), 4.19 (m, 1H), 3.97 (ddd, J = 12.5, 6.2,

2.7 Hz, 2H), 3.61 (dd, J = 11.3 Hz, 3.8 Hz, 1H), 3.56 (m, 1H), 2.40 – 2.10 (br s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 203.4, 137.6, 128.5, 127.9, 127.8, 93.5, 91.8, 72.3, 69.8, 67.1, 66.1.

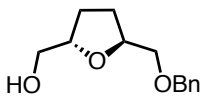


((2S,5S)-5-((benzyloxy)methyl)-2,5-dihydrofuran-2-yl)methanol 3.132

To a solution of $AuCl_3$ (3.2 mg, 0.106 mmol, ~5 mol%) in 1 mL of THF was added a solution of diol **3.122** (466 mg, 2.12 mmol, 1.0 equiv.) in 0.5 mL THF via cannula, followed by 2 x 0.25 mL rinses. The reaction was allowed to stir at r.t. for 5 minutes, at whereupon TLC analysis indicated full consumption of the starting material. The reaction was then concentrated under reduced pressure, and the crude mixture was purified by silica gel column chromatography with DCM/MeOH (99 : 1 to 97 : 3 gradient) to afford the title compound as a pale yellow oil.

Yield: 344 mg, 74%

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 5.92 (d, J = 6.5 Hz, 1H), 5.86 (d, J = 6.5 Hz, 1H), 5.07 (d, J = 5.7 Hz, 1H), 5.01 – 4.93 (m, 1H), 4.65 – 4.53 (m, 2H), 3.79 – 3.73 (m, 2H), 3.60 – 3.50 (m, 2H), 1.86 (br s, 1H).



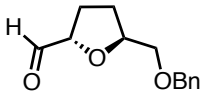
((2S,5S)-5-((benzyloxy)methyl)tetrahydrofuran-2-yl)methanol 3.133

Dihydrofuran **3.132** (344 mg, 1.56 mmol, 1.0 equiv.) was dissolved in 3 mL of DCM, and then NBSH (1.356g, 6.25 mmol, 4.0 equiv.) was added at r.t. to form a pale yellow suspension. To this suspension was added Et_3N (1.264 g, 12.49 mmol, 8.0 equiv.), and

the increasingly dark yellow suspension was allowed to continue stirring at room temperature. After 4 hours the suspension became homogeneous, and the reaction was allowed to stir overnight, whereupon it turned a dark red and clear color. After 18 hours, the reaction was diluted with Et_2O and DCM (5 mL of each) and transferred to a separatory funnel. The organic solution was washed with 30 mL of $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with Et_2O (2 x 25 mL). The combined organic layers were washed with 50 mL of brine, dried, and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography with Hexanes/EtOAc (9 : 1 to 7 : 3 gradient) to produce the title compound as a pale yellow oil.

Yield: 290 mg, 84%

All spectra were in agreement with reported data.[147]



((2S,5S)-5-((benzyloxy)methyl)tetrahydrofuran-2-carbaldehyde 3.134

A solution of alcohol **3.133** (30 mg, 0.135 mmol, 1.0 equiv.) in 0.5 mL of THF was added via cannula to a suspension of DMP (115 mg, 0.270 mmol, 2.0 equiv.) in 0.5 mL of DCM, followed by 2 x 0.25 mL rinses. The reaction was allowed to stir at r.t. for 2 h, at which time TLC analysis indicated full consumption of the starting material. The reaction was diluted with 5 mL of DCM, and the resulting suspension was filtered over a pad of Celite®. The filtrate was transferred to a separatory funnel, where it was washed with 2 x 5 mL of brine. The organic layer was then collected, dried, and concentrated under reduced pressure. The crude mixture was purified by silica gel column

chromatography with Hexanes/EtOAc (19 : 1) to produce the title compound as a yellow oil.

Yield: 27 mg, 90%

All spectra were in agreement with reported data.[147]

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